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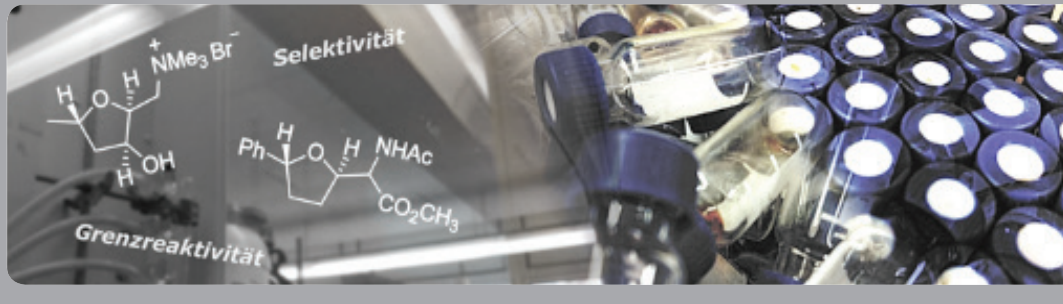

Untersuchung polarer Substituenteneffekte in Alkenoxylradikal-Cyclisierungen

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TECHNISCHE UNIVERSITÄT
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Untersuchung polarer Substituenteneffekte in Alkenoxylradikal-Cyclisierungen

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vorgelegt von

Dipl.-Chem. Irina Kempter

Betreuer: Professor Dr.-Ing. Jens Hartung

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meiner Familie

„Am Ende wird alles gut. Und wenn es nicht gut ist,

ist es noch nicht zu Ende.“

Oscar Wilde

Die vorliegende Arbeit wurde in der Zeit von Februar 2009 bis Dezember 2016 im Fachbereich Chemie (Fachrichtung Organische Chemie) an der Technischen Universität Kaiserslautern durchgeführt.

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Zweitgutachter: Prof. Dr. Stefan Kubik

Die Ergebnisse der vorliegenden Dissertation wurden in den folgenden begutachteten Arbeiten veröffentlicht oder sind zur Veröffentlichung vorgesehen.

- *Hindered rotation in N-acyloxy-4-methylthiazole-2(3H)-thiones*. J. Hartung, C. Schur, I. Kempter, S. Altermann, G. Stapf, U. Bergsträßer, T. Gottwald, M. Heubes, *Tetrahedron* **2009**, *65*, 7527–7532.

- *Lessons of 3-Alkoxy-4-(p-chlorophenyl)-1,3-thiazole-2(3H)-thione Chemistry Learned from Structural Investigations*. J. Hartung, K. Daniel, U. Bergsträßer, I. Kempter, N. Schneiders, S. Danner, P. Schmidt, I. Svoboda, H. Fuess, *Eur. J. Org. Chem.* **2009**, 4135–4142.

- *Efficiency of alkoxyl radical product formation from 5-substituted 3-alkoxy-4-methylthiazole-2(3H)-thiones*. J. Hartung, C. Schur, I. Kempter, T. Gottwald, *Tetrahedron* **2010**, *66*, 1365–1374.

- *Discussion Addendum for: N-Hydroxy-4-(p-chlorophenyl)thiazole-2(3H)-thione*. C. Schur, I. Kempter, J. Hartung, *Org. Synth.* **2012**, *89*, 409–419.

- *Alkoxyl radical addition to acceptor-substituted carbon−carbon double bonds*. I. Kempter, A. Groß, J. Hartung, *Tetrahedron* **2012**, *68*, 10378−10390.

- *Synthesis and Structural Characterization of the Isomuscarines.* I. Kempter, B. Frensch, T. Kopf, R. Kluge, R. Csuk, I. Svoboda, H. Fuess, J. Hartung, *Tetrahedron* **2014**, *70*, 1918−1927.

- *2,3-cis-Cyclization of 4-Pentenoxyl Radicals.* I. Kempter, C. Schur, K. Huttenlochner, R.-M. Bergsträßer, B. Wolff, T. Kopf, J. Hartung, *Tetrahedron* **2016**, *72*, 7699−7714.

- *Controlling Stereoselectivity in 4-Pentenoxyl Radical Cyclization by the Allylic Substituent*. I. Kempter, T. Schick, J. Hartung, *Manuskript in Vorbereitung*.

Eidesstattliche Erklärung

Hiermit erkläre ich ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig angefertigt und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt habe.

Ich erkläre außerdem, dass diese Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat und ich, außer den mit dem Zulassungsgesuch urkundlich vorgelegten Graden, keine weiteren akademischen Grade erworben habe oder zu erwerben versucht habe.

Kaiserslautern, den 22.12.2016

Irina Kempter

Erläuterungen

Die vorliegende Dissertation ist in eine Zusammenfassung, eine Einleitung (Kapitel 1), einen Kenntnisstand inklusive Aufgabenstellung, vier Ergebnisteile (Kapitel 3–6) und einen Anhang gegliedert. Jedem Ergebnisteil ist als Unterpunkt der jeweilige Forschungsartikel sowie die Zusatzinformationen (*Supporting Information*), wie experimentelle Daten, angewandte Methoden, sowie die verwendeten Arbeits- und Messgeräte angefügt und besitzen eine eigene Gliederung. Für jedes Kapitel wurde ein separates Literaturverzeichnis erstellt, wobei mehrfach zitierte Referenzen in jedem Kapitel berücksichtigt wurden.

Abbildungen, Tabellen und Schemata sind im jeweiligen Kapitel fortlaufend nummeriert. Die Nummerierung der Strukturformeln beginnt in jedem Ergebnisteil neu und stimmt nicht zwingend mit der Nummerierung in den Forschungsartikeln überein. Die in Strukturformeln mit Keilschreibweise angezeigte Stereochemie bezeichnet, wenn nicht anders angegeben, relative und nicht absolute Konfigurationen.

Die Hierarchie von Substituenten zur Benennung von Molekülen folgt in einigen Fällen nicht den IUPAC-Regeln, falls somit die Nachvollziehbarkeit einfacher wird.

Inhaltsverzeichnis

Zusammenfassung

Die vorliegende Arbeit fasst Erkenntnisse zum Einfluss polarer Alken-Substituenten auf Selektivitäten intramolekularer Alkoxylradikal-Additionen zusammen. Ergänzend zu den eigenen mechanistisch-synthetischen Studien flossen in die Bewertung der Reaktionsverläufe thermodynamische Daten und molekularorbital-theoretische Erkenntnisse ein, die in Kooperation mit Jens Hartung aus Dichtefunktional-Rechnungen abgeleitet wurden.

Die existierende Lehrmeinung beschreibt Sauerstoffradikale in Additionen und Substitutionen als Elektrophile, deren Selektivitäten durch sterische Effekte gesteuert werden. Auf Grundlage dieser Einteilung lassen sich atmosphärische und physiologische Sauerstoffradikal-Reaktionen und das komplementäre Reaktionsverhalten zu ionischen Cyclisierungen von Alkenolen deuten.

Vorläufermoleküle, die Sauerstoffradikale in unverzweigten Kettenreaktionen unter pH-neutralen nicht oxidativen Bedingungen freisetzen, erlaubten in der vorliegenden Arbeit strukturell komplexere Sauerstoffradikale mit hoher Spezifität zu erzeugen und aus den isolierten Produkten ein differenzierteres Bild zur Radikalselektivität abzuleiten. In diesem Bild besitzen Sauerstoffradikale Grenzreaktivität. Gegenüber Akzeptor-substituierten Alkenen treten Sauerstoffradikale als Nucleophile und gegenüber Donor-substituierten Alkenen als Elektrophile auf. Elektrophilie bildet darüber hinaus die Grundlage für einen neuen 2,3-cis-dirigierenden Effekt Allyl-ständiger Akzeptor-Gruppen, in denen der polare Einfluss über den sterischen dominiert.

In einem Projekt zur Synthese von Isomuscarinen, die sich durch Positionierung einer endocyclischen Hydroxy-Gruppe von den Glutamat-abgeleiteten Muscarin-Alkaloiden unterscheiden, fiel eine unerwartete 2,3-cis-Selektivität der 5-Hexen-2-oxylradikal-Cyclisierung auf. Aus sterischen Gründen wäre das 2,3-trans-konfigurierte Produkt favorisiert. 2,3-cis-Selektivität, die sich sowohl bei thermisch als auch photochemisch durchgeführten homolytischen Bromcyclisierungen zum Aufbau von Isomuscarin-Gerüsten zeigte, lässt sich in einem der diastereomeren Radikale durch den konformellen Effekt einer Methylgruppe zu 2,3-trans übersteuern. Die Befunde legen nahe, dass die 2,3-cis-Selektivität aus der kinetischen Reaktionskontrolle der Cyclisierungsreaktion resultiert. Kristallographische Untersuchungen der vier racemischen Isomuscarine und umfangreiche NMR-Studien aus denen sogar $^{1}J(^{14}N,^{13}C)$ offenkund wurden, stützten die stereochemische Analyse zur Radikalselektivität.

Um die Ursache 2,3-cis-selektiver Radikalcyclisierungen einzugrenzen, wurde in einem zweiten Projekt das Untersuchungssystem auf das Allyl-ständig Hydroxy-substituierte 4-Pentenoxylradikal reduziert. Letzteres liefert in Gegenwart von Bromtrichlormethan das 2,3-cis-Cyclisierungsprodukt in einer Selektivität von 74:26. Da das 2,3-cis- und das 2,3-trans-Stereoisomer des (3-Hydroxytetrahydrofuran-2-yl)methyl-Radikals unter den Reaktionsbedingungen nicht ringöffnen, liegt der 2,3-cis-Selektiviät ein kinetischer Einfluss der Allyl-ständigen Hydroxy-Gruppe zugrunde. Auch Acyloxy-Gruppen in allylischer Position ermöglichen 2,3-cis-selektive 4-Pentenoxylradikal-Cyclisierungen, jedoch mit abweichender Selektivität. Den polaren Effekt überlagert demzufolge der sterische des eingesetzten Substituenten.

Das Zusammenspiel zwischen polarem und sterischem Effekt eines Allyl-ständigen Substituenten gelang es in einem dritten Projekt zu separieren. In diesem Projekt variierte der Allyl-ständige Substituent von Hydroxy, Methoxy, Trifluoracetoxy, Chlor, Benzamido, Benzolsulfonamido, *N*-Phthalimido zu Benzoylsulfanyl. Entlang dieser Reihe fiel der Anteil 2,3-cis-bromcyclisierter Produkte bei thermisch induzierter Umsetzung der synthetisierten Allyl-substituierten 4-Pentenylthiohydroxamate mit Bromtrichlormethan. In einer Korrelationsanalyse folgt der cis-Anteil an 5-*exo*-trig-Cyclisierungsprodukt der Stabilisierung der HOMO-Energie, wobei 2-substituierte But-3-ene als Modell-Verbindungen zur Korrelation eingesetzt wurden. Mit zunehmendem sterischen Substituenteneinfluss, ausgedrückt anhand des entsprechenden Winstein-Holness-Parameters, steigt der Anteil 2,3-trans-konfigurierter Cyclisierungsprodukte. 2,3-cis-Selektivität resultiert in dem Modell aus einer Verlangsamung der 2,3-trans-Reaktion durch den stabilisierenden Einfluss eines sterisch möglichst kleinen stark elektronenziehenden Substituenten. Mit zunehmender Stabilisierung des Alkenteils sinkt die Geschwindigkeit der Radikaladdition. Mit zunehmender Raumerfüllung des Allyl-Substituenten wird jedoch das Konformer aus dem die 2,3-cis-Reaktion erreicht werden kann zu energiereich, um nennenswert eine Rolle zu spielen.

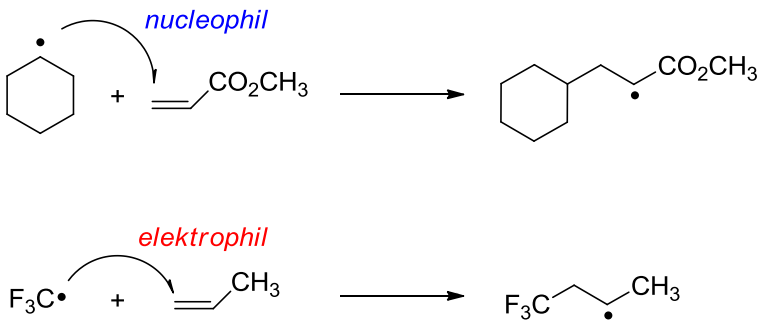
Direkt an der Doppelbindung gebundene Substituenten haben einen noch deutlicheren Einfluss auf die Radikalselektivitäten, da sie die Energien von π-Typ-Orbitalen direkt beeinflussen. Alkoxylradikale addieren dabei rascher an eine terminal Cyano-substituierte Doppelbindung als an eine unsubstituierte. Kontrollreaktionen mit einer Radikaluhr zeigten, dass alle Intermediate auf Radikale zurückzuführen sind. Anwenden ließ sich die unerwartete nucleophile Reaktivität in der Synthese einer neuen Tetrahydrofuran-abgeleiteten Aminosäure.

1 Einleitung

1.1 Bedeutung von Radikalen

Radikale sind elektrisch neutrale, reaktive Zwischenstufen[1], die ein ungepaartes Elektron besitzen und spielen aufgrund ihrer hohen Reaktivität als Intermediate[2–5] in biochemischen[6–9] und atmosphärischen[10,11] Prozessen eine wichtige Rolle. Mit Hilfe von experimentell und theoretisch fundierten Reaktionsmodellen konnten in den letzten Jahren Radikalreaktionen analysiert werden. Die Kontrollierbarkeit von Radikalreaktionen führte zur Vergrößerung ihrer Anwendungsbreite in der organischen Synthese.[12,13] Die Radikalchemie eröffnet aufgrund ihrer komplementären Reaktivität und Selektivität im Vergleich zu ionischen Reaktionen[14] neue Synthesestrategien.

Vor allem die C-Radikalchemie[15] wurde intensiv untersucht und wird in der Synthesechemie genutzt. C-Radikalreaktionen können mit Hilfe von sterischen und polaren Effekten gesteuert werden. Besonders interessant sind hierbei die polaren Effekte, da dadurch die Reaktivität der Reaktanden beeinflusst werden kann und somit die Reaktionsbreite vervielfältigt wird. C-Radikale zeigen eine Grenzreaktivität[15], das heißt sie können sowohl als Elektrophile als auch als Nucleophile reagieren. Das Cyclohexyl-Radikal besitzt in einer Additionsreaktion mit einem Ester-substituierten Alken nucleophilen Charakter[16], wohingegen die Fluor-Substituenten im Trifluormethyl-Radikal eine elektrophile Reaktivität[17] des Radikals bewirken (Schema 1.1).



Schema 1.1 Polare Effekte zur nucleophilen und elektrophilen Reaktivitätssteuerung von C-Radikalen in Additionsreaktionen an substituierte C,C-Doppelbindungen.[16,17]

Radikalische Additionsreaktionen verlaufen kinetisch kontrolliert, weshalb die Reaktivitäts- und Selektivitätssteuerung durch polare Effekte mit Hilfe der Grenzorbitaltheorie[18–20] beschrieben werden können. Die Reaktionen verlaufen stark exotherm und ihr Übergangszustand liegt somit früh auf der Reaktionskoordinate. Dem Hammond-Postulat[21] zufolge sind die Geometrie und demzufolge auch die Orbitale des Übergangszustandes der Ausgangverbindung ähnlicher. Bei einer Annäherung der Reaktanden kommt es zu einer günstigen Wechselwirkung zwischen dem einfach besetzten Orbital des Radikals (SOMO, *engl. Single Occupied Molecular Orbital*) entweder mit dem höchsten besetzten (HOMO, *engl. Highest Occupied Molecular Orbital*) oder dem tiefsten unbesetzten (LUMO, engl. *Lowest Unoccupied Molecular Orbital*) Orbital eines Alkens. Nucleophile Radikale weisen eine ausgeprägte SOMO/LUMO-Wechselwirkung auf (Abb. 1.1, links), wohingegen eine SOMO/HOMO-Wechselwirkung für eine elektrophile Reaktivität des Radikals spricht (Abb. 1.1, rechts).[15]

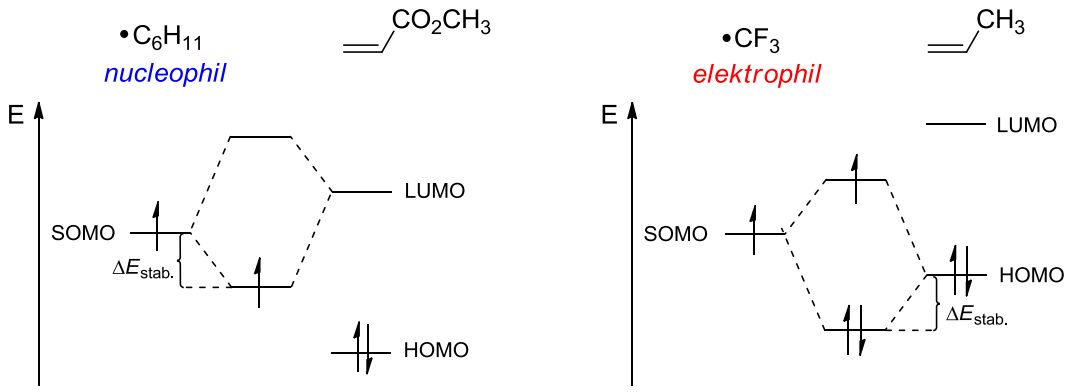


Abbildung 1.1 Grenzorbitalwechselwirkungen zur Erklärung polarer Effekte in Additionsreaktionen von nucleophilen (links) und elektrophilen (rechts) C-Radikalen.[15]

Neben den C-Radikalen spielen auch Heteroatom-Radikale in der Naturstoff-Synthese eine zentrale Rolle. Im Gegensatz zu den C-Radikalen ist bei Heteroatom-Radikalen[22] über ein Grenzreaktivitäts-Verhalten bislang wenig bekannt und somit auch über polare Effekte. Die Reaktivitäts- und Selektivitätssteuerung dieser Radikale beschränkt sich zum jetzigen Zeitpunkt ausschließlich auf sterische Substituenteneffekte. Zu einem wichtigen Vertreter zählen die Sauerstoffradikale, die zum Aufbau von substituierten Tetrahydrofuranen und

-pyranen genutzt werden können.[23] Alkoxylradikale besitzen elektrophile Eigenschaften und zu ihren typischen Reaktionskanälen gehören die Addition an C,C-Doppelbindungen[14,24], die H-Abstraktion[25], die β-C,C-Fragmentierung[26] sowie Umlagerungsreaktionen[27]. Die Reaktionsgeschwindigkeiten der bekannten Elementarreaktionen von O-Radikalen liegen zwischen $k \sim 10^4$ bis 10^9 s^{-1}.[28,29] Vor allem die Addition ist aufgrund ihrer geringen Aktivierungsenergie und der stark exothermen Reaktionsenthalpie mit einer hohen Geschwindigkeitskonstante verbunden, wodurch sie zu einem der wichtigsten Reaktionskanäle von Alkoxylradikalen gehört.

Im Vergleich zu den C-Radikalen ist die Reaktivität und Selektivität von O-Radikalen noch nicht vollständig verstanden. Ein Grund hierfür ist, dass Alkoxylradikale lange Zeit nur in Anwesenheit von Metallionen[30,31] oder starken Oxidationsmitteln[32] erzeugt werden konnten. Ein großer Fortschritt wurde mit den von Beckwith und Hay erstmals hergestellten *N*-Alkoxypyridin-2(1*H*)-thionen[33,34] erreicht, die eine homolytische N,O-Bindungsspaltung unter pH-neutralen und nicht oxidativen Bedingungen ermöglichen (Abb. 1.2, links). Die O-Ester dieser cyclischen Thiohydroxamsäuren sind in der Lage Sauerstoffradikale in einer unverzweigten Kettenreaktion zu generieren, wodurch die Radikalkonzentrationen niedrig bleiben und unerwünschte Nebenreaktionen unterdrückt werden.[16]

Nachteile von *N*-Alkoxypyridin-2(1*H*)-thionen sind ihre hohe Lichtempfindlichkeit und die daraus resultierende schlechte Lagerbarkeit. Aufgrund dessen eigneten sich in den letzten Jahren die in unserer Arbeitsgruppe entwickelten *N*-Alkoxythiazol-2(3*H*)-thione zur Untersuchung der Reaktivität von Alkoxylradikalen (Abb. 1.2, rechts).[35] Diese sind weniger lichtempfindlich und in der Regel über einen Zeitraum von mehreren Jahren ohne Zersetzung lagerbar. *N*-Alkoxythiazol-2(3*H*)-thione besitzen eine günstige Balance zwischen einer ausreichenden Stabilität für die praktische Anwendung und einer niedrigen N,O-Bindungsdissoziationsenergie für den Radikalkettenstart. Dies macht intramolekulare Additionsreaktionen von Alkoxylradikalen für die Darstellung von substituierten Tetrahydrofuranen attraktiv.

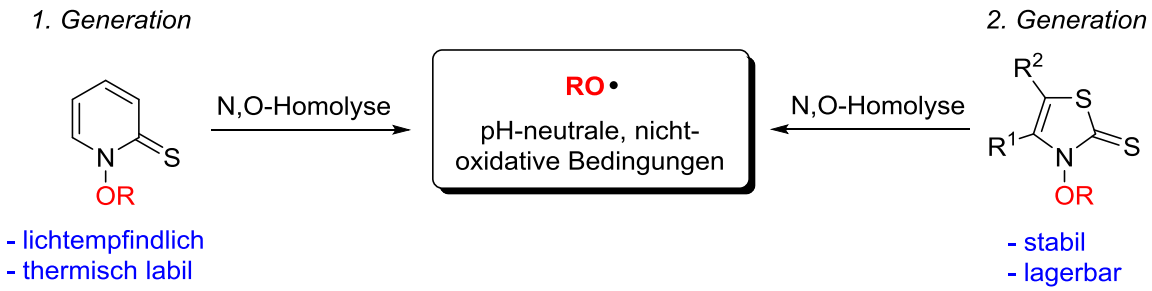
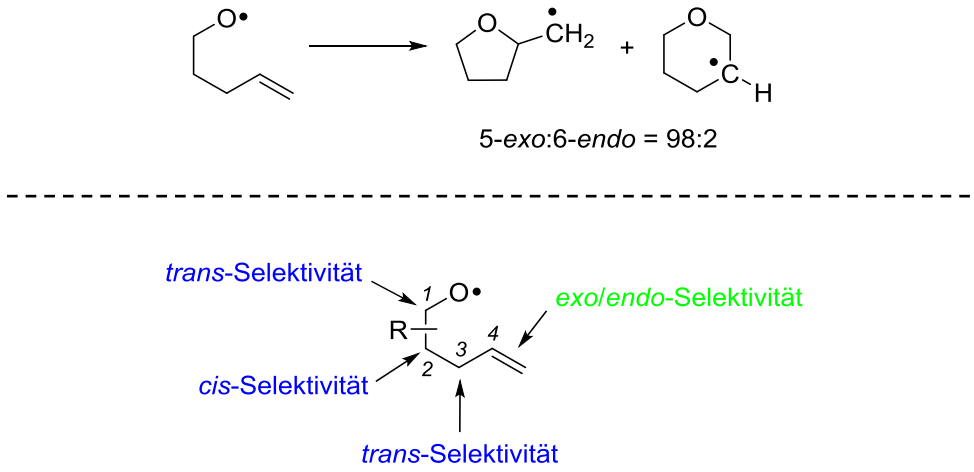


Abbildung 1.2 Alkoxylradikalerzeugung aus cyclischen Thiohydroxamsäuren. R = Alkyl, Aryl; R^1, R^2 = H, Alkyl, Aryl.[33–35]

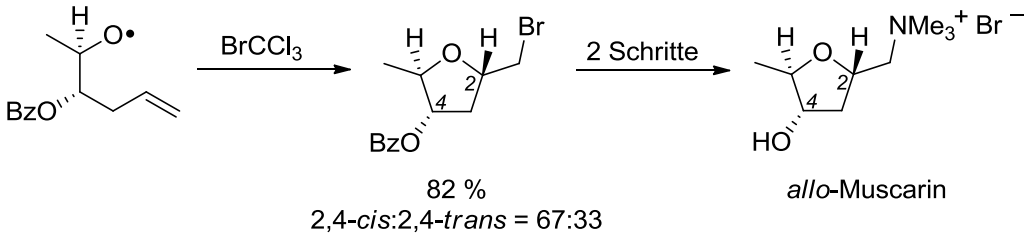
1.2 Anwendung von Alkoxylradikal-Additionen

In intramolekularen Additionsreaktionen nutzt man die hohe Reaktivität von elektrophilen O-Radikalen gegenüber C,C-Doppelbindungen ohne zusätzliche Aktivierung. Darin besteht der wesentliche Unterschied zu einer ionischen Cyclisierungsreaktion, bei der ein nucleophiler Sauerstoff an eine Elektrophil-aktivierte C,C-Doppelbindung addiert.[36] Mit Hilfe von O-Radikalreaktionen können Regio- und Stereoselektivitäten erreicht werden, die mit anderen Methoden nicht möglich sind. Radikalische Ringschlussreaktionen von 4-Penten-1-oxylradikalen verlaufen 5-*exo*-trig-selektiv (5-*exo*:6-*endo*-Verhältnis = 98:2) und liefern in sehr guten Ausbeuten substituierte Tetrahydrofurane (Schema 1.4).[29,37] Neben der hohen Regioselektivität weisen O-Radikalcyclisierungen zusätzlich synthetisch wertvolle Stereoselektivitäten auf (Schema 1.2). Mit Hilfe von Alkyl- und Aryl-Substituenten entlang der Pentenoxyl-Kette können Stereoselektivitäten in intramolekularen Additionsreaktionen gesteuert werden. 4-Penten-1-oxylradikale mit einem Alkyl-Substituent in Position 1 oder 3 reagieren in einer 5-*exo*-trig-Cyclisierung bevorzugt zum trans-konfigurierten Tetrahydrofuran. In Position 2 dirigiert ein Alkyl- oder Aryl-Substituent die Cyclisierungsreaktion cis-selektiv (Schema 1.2).[38]



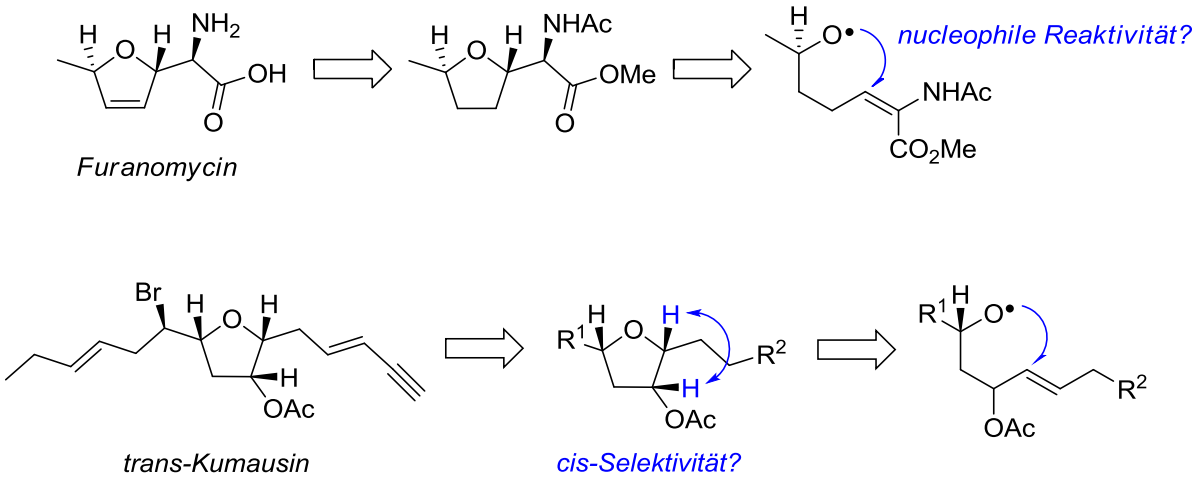
Schema 1.2 Substituenteneinfluss in verschiedenen Positionen auf die Regio- und Stereoselektivitäten intramolekularer Additionen von 4-Penten-1-oxylradikalen. R = Alkyl, Aryl.[38]

Die gebildeten Tetrahydrofuryl-Radikale können durch verschiedene Abfangreagenzien beispielweise bromierend, chlorierend oder iodierend abgefangen und in darauffolgenden Reaktionssequenzen weiter funktionalisiert werden.[39] Aufgrund dieser Eigenschaften finden radikalische Cyclisierungsreaktionen immer größere Anwendung zum Aufbau von Naturstoffen, wie beispielweise den stereoselektiven Aufbau des Alkaloids *allo*-Muscarin (Schema 1.3).[40]



Schema 1.3 Anwendung einer radikalischen Bromcyclisierung zur stereoselektiven Darstellung von *allo*-Muscarin.[40]

Bislang beschränkt sich die Reaktivität von O-Radikalen in Additionsreaktionen auf deren elektrophilen Charakter, wodurch das zugängliche Produktspektrum begrenzt wird. Die Stereoselektivitätssteuerung bezieht sich im Wesentlichen auf sterische Effekte, der Einfluss polarer Effekte ist nur wenig untersucht. Durch polare Substituenten an der C,C-Doppelbindung könnte der Charakter des O-Radikals beeinflusst und eine nucleophile Reaktivität synthetisch genutzt werden (Schema 1.4, oben). Polare Effekte könnten in allylischer Position im Vergleich zu Alkyl- und Aryl-Substituenten eine cis-selektive Cyclisierung bewirken (Schema 1.4, unten). Dies würde den Zugang zu pharmazeutisch interessanten Naturstoffen über O-Radikalcyclisierungen ermöglichen.[41,42]



Schema 1.4 Retrosynthese zum selektiven Aufbau Tetrahydrofuran-abgeleiteter Naturstoffe via O-Radikalcyclisierung.[41,42] R^1, R^2 = H, Alkyl, Aryl, Halogen.

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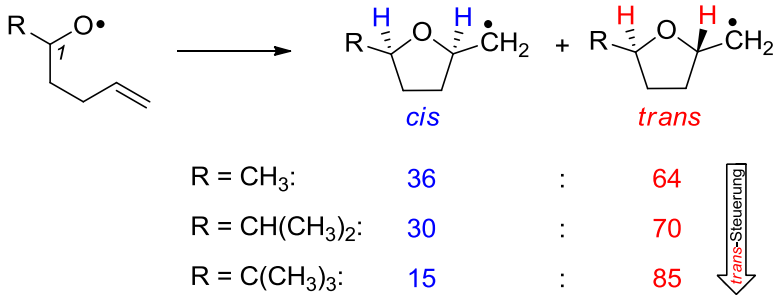
2 Kenntnisstand und Aufgabenstellung

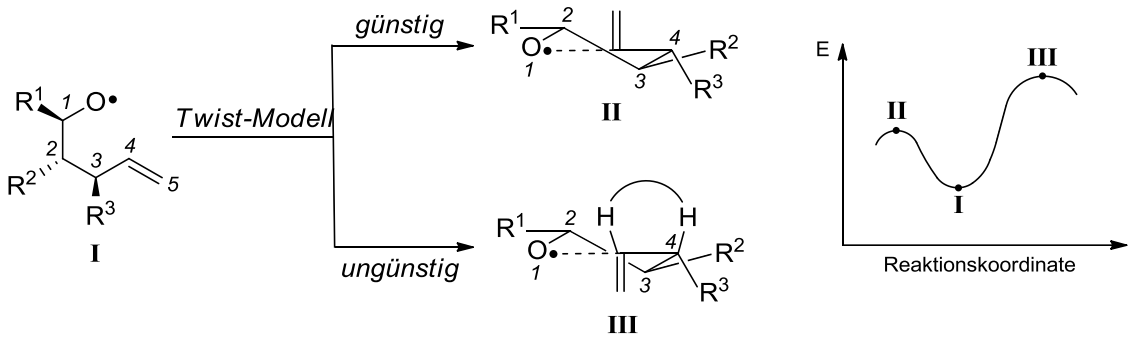
2.1 Sterische Selektivitätssteuerung in Additionsreaktionen

Sterische Substituenten in Position 1, 2 und 3 entlang der Pentenoxyl-Kette steuern Stereoselektivitäten in 5-*exo*-trig-Cyclisierungen.[1] Dabei ist das Ausmaß der Stereoselektivität vom sterischen Anspruch des Substituenten abhängig.[2] Eine Alkyl-Gruppe in Position 1 steigert die trans-Selektivität der gebildeten Tetrahydrofurane entlang der Reihe $CH_3 < CH(CH_3)_2 < C(CH_3)_3$ (Schema 2.1).[3]



Schema 2.1 Selektivitätssteuerung in 4-Penten-1-oxylradikal-Cyclisierungen durch sterische Substituenteneffekte.[3]

Die beobachteten Stereoselektivitäten können anhand des stereochemischen Modells, dem sogenannten Twist-Modell, beschrieben werden.[4] Das Modell basiert auf einem fünfgliedrigen Übergangszustand, der einem verzerrten Tetrahydrofuran-Konformer ähnelt. Bei der intramolekularen O-Radikaladdition ordnen sich das O-Atom (O1) und die Doppelbindung (C5=C6) im Übergangszustand in einer Bürgi-Dunitz-ähnlichen Trajektorie an. Daraus ergeben sich für eine 5-*exo*-trig-Cyclisierung zwei relevante Übergangszustände **II** und **III** (Schema 2.2).[5,6] Die Substituenten im System ordnen sich hierbei aufgrund von sterischen Effekten bevorzugt äquatorial oder *pseudo*-äquatorial an. Diese Wechselwirkungen führen dazu, dass die Anordnung in Übergangszustand **II** gegenüber der in Übergangszustand **III** energetisch günstiger wird. Aus dem energetisch günstigeren Übergangszustand **II** ergibt sich für Alkyl- und Aryl-Substituenten eine 2,5-trans-, 2,4-cis- und 2,3-trans-selektive 5-*exo*-trig-Cyclisierung.[7] Diese stereochemischen Richtlinien werden in der Synthesechemie genutzt, um Selektivität vorherzusagen.



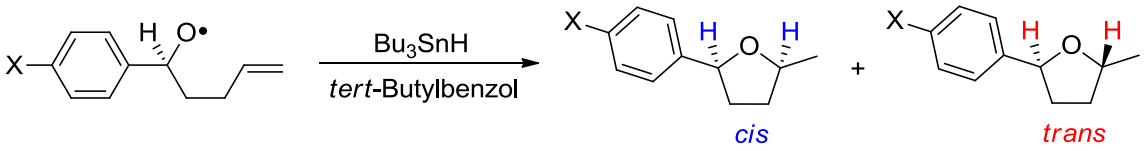
Schema 2.2 Übergangsstrukturen des Twist-Modells zur Erläuterung von Selektivitäten in 5-*exo*-trig-Cyclisierungen von substituierten 4-Penten-1-oxylradikalen. R^1, R^2, R^3 = Alkyl, Aryl; der Bogen symbolisiert sterische Wechselwirkungen.[6]

2.2 Polare Substituenteneffekte in Alkoxylradikalreaktionen

Die bislang existierenden Reaktionsmodelle zur Selektivitätssteuerung von intramolekularen Additionen von O-Radikalen berücksichtigen weitestgehend den Einfluss sterischer Effekte. Bei Sauerstoffradikalen gibt es jedoch bereits Beispiele, die zeigen, dass auch polare Effekte Reaktivitäten und Selektivitäten steuern können.

Aus den Ringschlussreaktionen Aryl-substituierter 4-Penten-1-oxylradikalen wurde ersichtlich, dass polare *para*-Substituenten am Aryl-Rest in der Lage sind die relative Reaktionsgeschwindigkeit der 5-*exo*-trig-Cyclisierung signifikant zu beeinflussen (Tabelle 2.1).[8] Dies wird auf eine elektronische Wechselwirkung zwischen der Aryl-Gruppe und dem ungepaarten Elektron des O-Radikals, die im Übergangszustand eine koplanare Anordnung einnehmen, zurückgeführt. Diese koplanare Anordnung ermöglicht, dass das aromatische π-System Elektronendichte an das O-Radikal abgeben kann.[8,9] Durch verschiedene polare *para*-Substituenten am Aryl-Gerüst kann diese Wechselwirkung verändert werden, wodurch die Reaktivität beeinflusst wird, jedoch nicht die Stereoselektivität der Reaktion (*cis*:*trans* = 50:50). Die genauen Details dieser Wechselwirkung sind bislang noch ungeklärt.

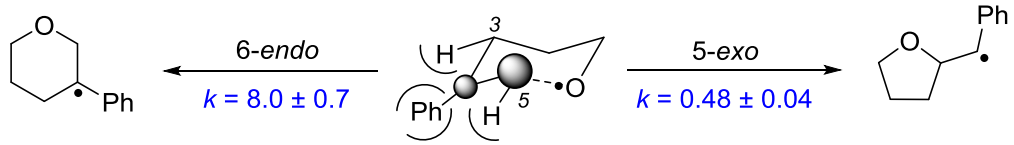
Tabelle 2.1 Experimentell bestimmte relative Geschwindigkeitskontanten für 5-*exo*-trig-Cyclisierungen 1-*para*-Aryl-substituierter 4-Penten-1-oxylradikale[8]



Eintrag	X	$k^{rel} = k^{cis} : k^{trans}$
1	OCH_3	4.3±0.4 : 4.3±0.4
2	Cl	2.8±0.3 : 2.5±0.2
3	*i*Pr	1.55±0.14 : 1.45±0.13
4	OCF_3	1.28±0.12 : 1.05±0.09
5	CF_3	1.09±0.10 : 0.90±0.08
6	H	0.86±0.08 : 0.77±0.07
7	CN	0.83±0.08 : 0.67±0.07
8	CH_3	0.50±0.05 : 0.46±0.04

Reaktivitätssteigerung

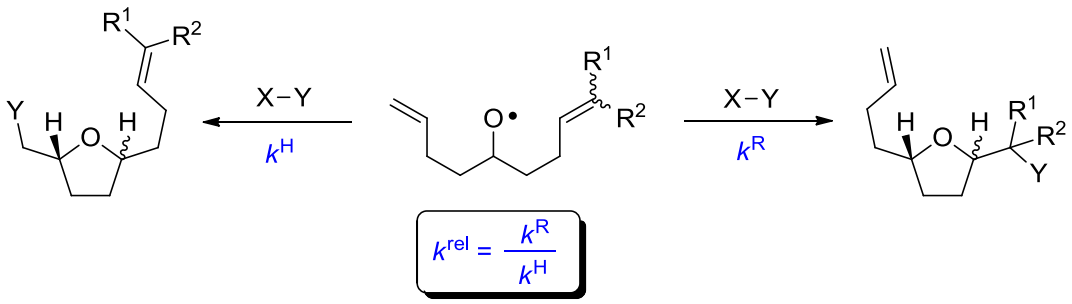
Die typische Regioselektivität von Pent-4-en-1-oxylradikalen beträgt für 5-*exo*:6-*endo* = 98:2.[10] Der Grund hierfür sind Torsionsspannungen im 6-*endo*-Übergangszustand, da es aufgrund struktureller Änderungen zu van-der-Waals-Abstoßungen kommt. Durch die Einführung eines Phenyl-Substituenten in Position 4 kann die Regioselektivität zugunsten der 6-*endo*-Cyclisierung (5-*exo*:6-*endo* = 7:93) beeinflusst werden.[11] Dies wird auf einen polaren Einfluss der Phenyl-Gruppe zurückgeführt, der aufgrund von stereoelektronischen Effekten den HOMO-Orbitalkoeffizienten am terminalen C5-Atom gegenüber dem des C4-Atoms vergrößert. Hierdurch wird die SOMO/HOMO-Wechselwirkung[12] zwischen dem C5-Atom und dem O-Radikal so attraktiv, dass die ungünstigen Torsionsspannungen im 6-*endo*-Übergangszustand kompensiert werden und somit die 6-*endo*- gegenüber der 5-*exo*-Cyclisierung um den Faktor 8 beschleunigt wird (Schema 2.3).[13]



Schema 2.3 Relative Geschwindigkeitskonstanten der Cyclisierungsreaktion des 4-Phenyl-4-penten-1-oxylradikals. Bogen symbolisiert Torsionsspannung.[11,13]

C-Radikale weisen eine Grenzreaktivität auf und können je nach Reaktionspartner sowohl nucleophil als auch elektrophil reagieren.[14,15] Bei O-Radikalen ist bislang nur bekannt, dass Donorgruppen, wie Methyl oder Phenyl, am terminalen C-Atom der C,C-Doppelbindung die intramolekulare Addition beschleunigen. Terminale Donorgruppen erhöhen die Elektronendichte der π-Bindung und begünstigen somit den elektrophilen Angriff des O-Radikals.[16,17] Erste Hinweise auf eine Grenzreaktivität bei Alkoxylradikalen zeigten die Untersuchungen von A. Groß zu relativen Reaktivitäten von O-Radikalen (Tabelle 2.2).[18]

Tabelle 2.2 Relative Geschwindigkeitskonstanten aus konkurrenzkinetischen Untersuchungen substituierter Alkenoxylradikalen[18]

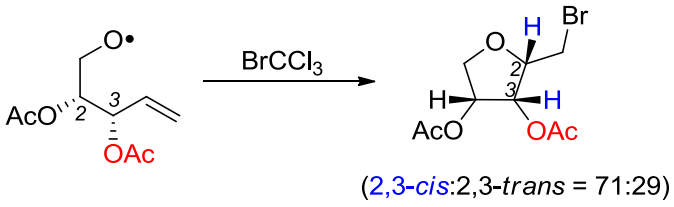


Eintrag	R^1	R^2	X−Y	k^{rel}
1	H	CN	Bu_3SnD	1.1 ± 0.1
2	H	$COOCH_3$	Bu_3SnD	0.6 ± 0.1
3	CH_3	CH_3	Bu_3SnH	≥19 ± 2
4	H	OCH_3	Bu_3SnH	≥49 ± 5

Bei intramolekularen Konkurrenzreaktionen zur Bestimmung relativer Geschwindigkeitskonstanten von Alkenoxylradikal-Cyclisierungen an substituierte C,C-Doppelbindungen wurde gezeigt, dass eine Addition von O-Radikalen nicht nur an Donor- sondern auch an Akzeptor-substituierte Doppelbindungen möglich ist. Hierbei stellte sich heraus, dass ein terminaler Cyano-Substituent mit einer vergleichbaren Reaktivität wie ein Wasserstoffatom in dieser Position reagiert und eine überraschend hohe relative Geschwindigkeitskonstante liefert (Tabelle 2.2, Eintrag 1). Die Ergebnisse zeigen, dass eine Reaktivitätssteigerung nicht nur mit Hilfe von terminalen Donor-Gruppen, wie Methyl und Methoxy (Tabelle 2.2, Eintrag 3 und 4), sondern auch durch Akzeptor-Gruppen[19], wie Cyano, erreicht werden kann. Diese Befunde deuten auf eine Grenzreaktivität von Alkoxylradikalen hin. Um eine fundamentale Aussage treffen zu können, bedarf es einer

detaillierten Analyse der Grenzreaktivität, die Aufgabe der vorliegenden Arbeit war. Eine nucleophile Reaktivität von O-Radikalen würde Additionen von Alkoxylradikalen an Michael-ähnliche Akzeptoren ermöglichen und die strukturelle Vielfalt an Verbindungen vergrößern.[20]

Die Beeinflussung der Stereoselektivität durch polare Substituenten zeigt eine Studie von T. Kopf, in der das (2*R*,3*S*)-Isomer des zweifach Acetyloxy-substituierten 4-Penten-1-oxylradikals bevorzugt das 2,3-cis-konfigurierte Tetrahydrofuran liefert (Schema 2.4).[21,22] Diese 2,3-cis-Selektivität war bislang unbekannt und widerspricht der bekannten 2,3-trans-Selektivität von 4-Penten-1-oxylradikal-Cyclisierungen mit Alkyl- oder Aryl-Substituenten in Position 3. Diese Beobachtung kann nicht mit dem existierenden Reaktionsmodell für Alkenoxylradikal-Cyclisierungen erklärt werden. Aufgrund dessen wird in der vorliegenden Arbeit geprüft, ob diese neue 2,3-cis-Selektivität aus einem Zusammenspiel der Substituenten in Position 2 und 3 resultiert oder ob ein polarer Substituenteneffekt zur 2,3-cis-Selektivitätssteuerung existiert.



Schema 2.4 2,3-cis-Selektive 5-*exo*-trig-Cyclisierung des zweifach Acetyloxy-substitiuierten 4-Penten-1-oxylradikals.[22]

2.3 Aufgabenstellung

Aufgrund des dargelegten Hintergrunds liegt das Ziel der vorliegenden Arbeit in folgende Themengebieten:

- Polarer Effekt des allylischen Substituenten zur 2,3-cis-Selektivitätssteuerung.
- Variation terminaler Alken-Substituenten zur Untersuchung der Grenzreaktivität von Alkoxylradikalen.
- Richtlinien zur Beschreibung polarer Substituenteneffekte.

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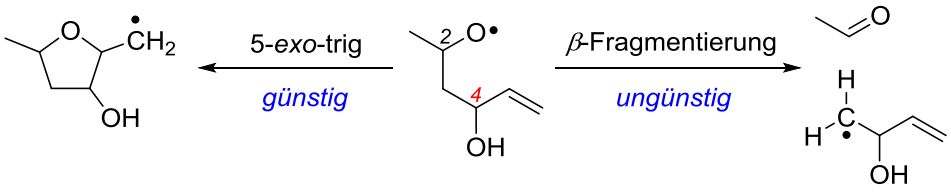
3 Darstellung und Charakterisierung der Isomuscarine

3.1 Zusammenfassung

Die vier Diastereomere Isomuscarin, *allo*-, *epi*- und *epiallo*-Isomuscarin können ausgehend von 2,4-*like*- und 2,4-*unlike*-konfigurierten 3-(4-Hydroxyhex-5-en-2-oxy)-4-methylthiazol-2(3*H*)-thionen über eine stereoselektive Alkenoxylradikal-Cyclisierung dargestellt werden. Die 5-*exo*-trig-Bromcyclisierung verläuft für das 2,4-*unlike*-Diastereomer 2,3-trans-selektiv, wohingegen das 2,4-*like*-Diastereomer eine 2,3-cis-Selektivität liefert. Dieser neue 2,3-cis-dirigierende Effekt einer allylischen Hydroxy-Gruppe ist auf eine polare Wechselwirkung zurückzuführen. Die gebildeten Brommethyltetrahydrofurane wurden in Kooperation mit T. Kopf als Grundbausteine zur Kristallisation der Isomuscarin-Bromide genutzt.

3.2 Wissenschaftlicher Hintergrund, Zielsetzung und Strategie

Ein Hydroxy-Substituent in 4-Position des 4-Pentenoxylradikals bewirkt, dass die 5-*exo*-trig-Cyclisierung gegenüber der *β*-Fragmentierung bevorzugt wird.[1] Die Triebkraft von *β*-C,C-Fragmentierungen liegt in der Entropie der Reaktion, der Stärke der gebildeten C,O-Doppelbindung sowie der Stabilisierung des gebildeten C-Radikals.[2] Im Fall des allylischen Hydroxy-Substituenten ist die Stabilisierung des C-Radikals gering und führt dazu, dass die gewünschte Cyclisierungsreaktion den Hauptreaktionskanal darstellt (Schema 3.1).



Schema 3.1 Bevorzugter Reaktionskanal Hydroxy-substituierter Alkoxylradikale.

Diese 5-*exo*-trig-Cyclisierung eröffnet einen neuen synthetischen Zugang zu den vier Diastereomeren des Isomuscarins (Abb. 3.1). Diese sind aufgrund ihrer strukturellen Ähnlichkeit zu den aus dem Fliegenpilz *Amanita muscaria* bekannten Muscarinen[3,4]

hinsichtlich ihrer möglichen pharmakologischen Wirksamkeit interessant. Bislang ist lediglich das *epiallo*-Isomuscarin bekannt, welches von Jouilliée *et. al* in einer neunstufigen Synthese ausgehend von einem D-Glucose-Derivat dargestellt wurde.[5,6]

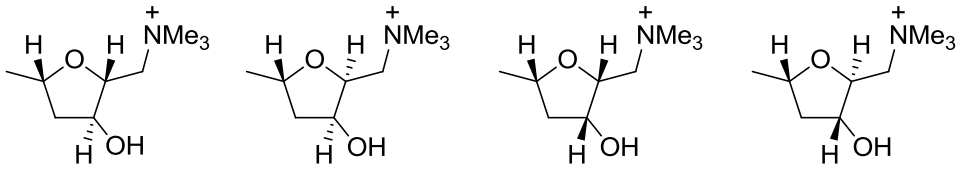


Abbildung 3.1 Strukturfomeln der vier Diastereomere des Isomuscarins.

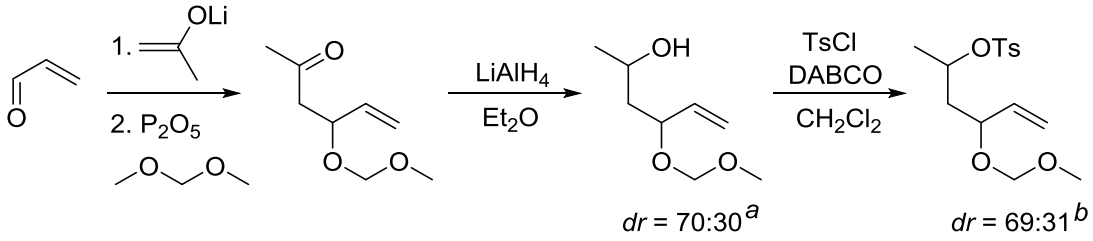
Der dargelegte Hintergrund lieferte die Grundlage für ein Forschungsprojekt mit folgender Aufgabenstellung:

- Stereoselektive 5-*exo*-trig-Cyclisierung zur Darstellung von Isomuscarinen und deren vollständige Charakterisierung.
- Untersuchung des Einflusses eines Allyl-ständigen Hydroxy-Substituenten auf den stereochemischen Verlauf der Alkenoxylradikal-Cyclisierung.

3.3 Ergebnisse und Diskussion

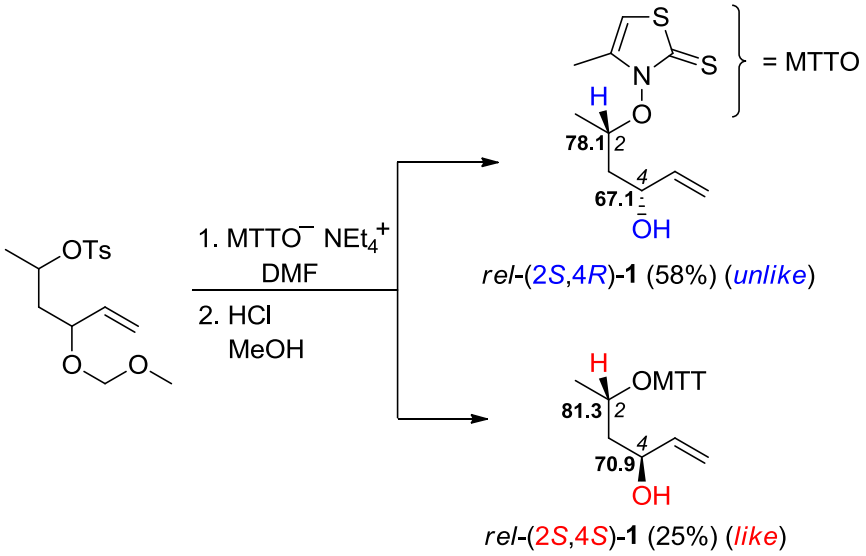
3.3.1 Synthese diastereomerenreiner 3-(4-Hydroxyhex-5-en-2-oxy)-4-methylthiazol-2(3*H*)-thione

Die beiden Diastereomere des 3-(4-Hydroxyhex-5-en-2-oxy)-4-methylthiazol-2(3*H*)-thions (**1**) stellen Schlüsselbausteine zur Synthese der vier Isomuscarin-Isomere dar. Die Verbindungen *rel*-(2*S*,4*R*)- und *rel*-(2*S*,4*S*)-**1** werden in einer sechsstufigen Synthese ausgehend von 2-Propenal dargestellt (Schema 3.2).[7,8] Der Vorteil dieser Synthesesequenz liegt darin, dass diese für die beiden Konfigurationsisomere *like*- und *unlike*-**1** identisch ist.



Schema 3.2 Syntheseroute zur Darstellung von 4-(Methoxymethyloxy)hex-5-en-2-yl *p*-Toluolsulfonat ausgehend von 2-Propenal. [a] Bestimmung des Diastereomeren-Verhältnisses über die Intensität der ^{13}C-NMR-Signale. [b] Bestimmung des Diastereomeren-Verhältnisses über ^{1}H-NMR-Integrale.

Die Trennung der *rel*-(2*S*,4*S*)- und *rel*-(2*S*,4*R*)-Stereoisomere **1** erfolgt im letzen Syntheseschritt nach der Kopplung des Tosylats mit dem *N*-Hydroxy-4-methylthiazol-2(3*H*)-thion-Tetraethylammoniumsalz (Schema 3.3).[9,10] Nach säulenchromatographischer Aufreinigung werden die beiden Diastereomere separat isoliert und charakterisiert. Aus den dargestellten Molekülen erhält man nach homolytischer Spaltung der N,O-Bindung effektiv Alkenoxylradikale, die 5-*exo*-trig-selektiv cyclisieren.[11]

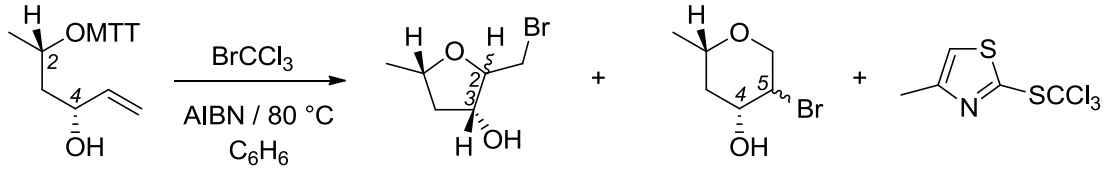


Schema 3.3 Synthese der Thiohydroxamsäure-*O*-Ester *like*- und *unlike*-**1** mit signifikanten ^{13}C-NMR-Resonanzen in ppm der C-Atome C2 und C4. MTTO$^-$ NEt$_4^+$ = *N*-Hydroxy-4-methylthiazol-2(3*H*)-thion-Tetraethylammoniumsalz.

3.3.2 Homolytische Bromcyclisierungen

(A) *rel*-(2*S*,4*R*)-Stereoisomer

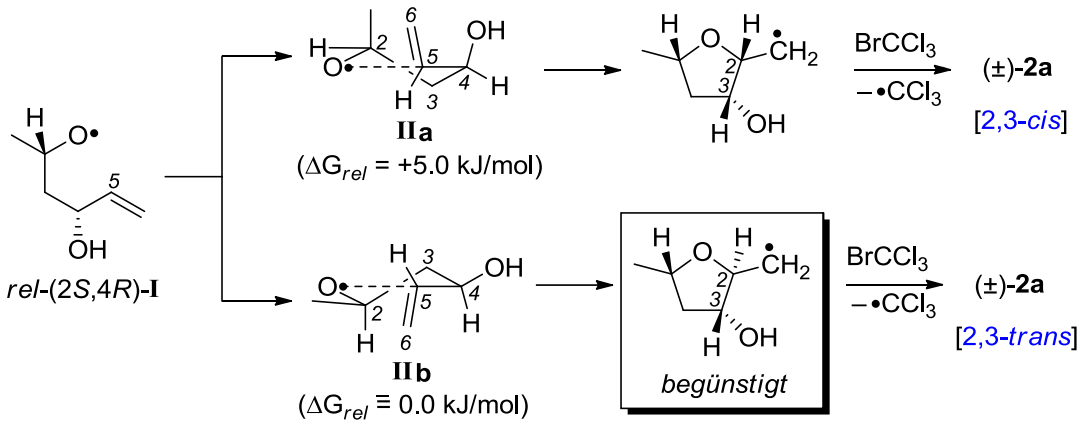
Die Reaktion von *unlike*-1 bei 80 °C mit Bromtrichlormethan und in Anwesenheit des Initiators AIBN [2,2′-Azobis(2-methylpropionitril)] lieferte 62% des bromierten Tetrahydrofurans **2a** in einem 2,3-*cis*:2,3-*trans*-Verhältnis von 37:63.[12] Zusätzlich wurde das 6-*endo*-Cyclisierungsprodukt **3a** in 10% und das Abfangprodukt 2-Trichlormethylsulfanylthiazol **4** in 96% gebildet (Schema 3.4).[13] Ein Experiment in C_6D_6, welches direkt NMR-analytisch untersucht wurde, ergab keinen Hinweis auf weitere Produkte zur Verbesserung der Massenbilanz. Eine Variation der Reaktionstemperatur, sowohl eine Erhöhung (130 °C) als auch eine Erniedrigung (22 °C), führt zu keiner Ausbeutesteigerung an Cyclisierungsprodukten **2a** und **3a**.



rel-(2*S*,4*R*)-**1** **2a** (62%) (2,3-*cis*:*trans* = 37:63) **3a** (10%) (4,5-*cis*:*trans* = 40:60) **4** (96%)

Schema 3.4 Produktspektrum der radikalischen Bromcyclisierung von *unlike*-**1**.

Anhand der NMR-spektroskopischen Daten der Cyclsierungsprodukte **2a** und **3a** ist eine Konfigurationszuordnung der cis/trans-Isomere möglich. Die Reaktion verläuft 2,3-trans-selektiv in einem Verhältnis von 37:63. Das beobachtete 2,3-cis/2,3-trans-Verhälntis ist jedoch geringer verglichen mit einem Methyl-Substituenten in allylischer Position (2,3-*cis*:2,3-*trans* = 14:86).[14] Somit leistet der Hydroxy-Substituent in Position 4 des *unlike*-Stereoisomers **1** im Vergleich zu einem Alkyl-Substituenten einen geringeren Beitrag zur 2,3-trans-Selektivität. Dementsprechend kommen beim Hydroxy-Substituenten Wechselwirkungen zum Tragen, die den sterischen Effekten von Alkyl-Substituenten entgegenwirken. Die Methyl-Gruppe in Position 2 des O-Radikals **I** besitzt einen trans-dirigierenden Effekt[15], dem der stereochemische Effekt der Hydroxyl-Gruppe entgegenwirkt. Anhand der Übergangszustände kann der bevorzugte stereochemische Verlauf der Reaktion erklärt werden (Schema 3.5).[16]



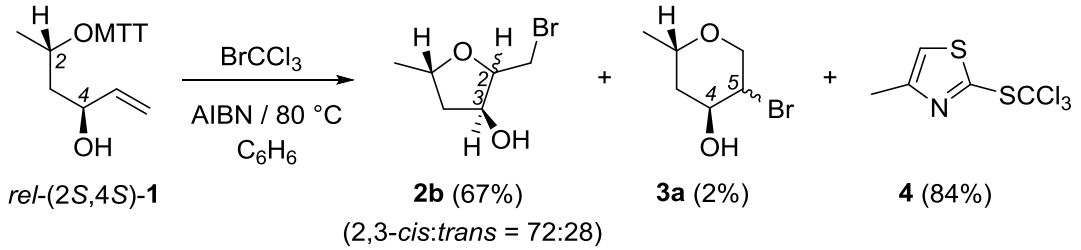
Schema 3.5 Übergangszustände zur Erklärung der cis/trans-Selektivität bei der 5-*exo*-trig-Cylisierung von *unlike*-**1**. ΔG_{rel}-Werte aus B3LYP/6-31+G** Dichtefunktional-Rechnungen.[17,18]

Berechnungen ergeben, dass die Übergangszustände **II** jeweils die energetisch günstigsten für die 2,3-cis- und 2,3-trans-selektive 5-*exo*-trig-Cyclisierung sind. Die Übergangszustände **IIa** und **IIb** sind als Twist-Konformer angeordnet und der energetische Unterschied resultiert aus der Anordnung der Substituenten.[19] Der Übergangszustand **IIb** wird bevorzugt gebildet, da aufgrund der äquatorialen bzw. *pseudo*-äquatorialen Anordnung der Substituenten die sterische Wechselwirkung geringer ist als im Vergleich zu Übergangszustand **IIa**, in dem die Substituenten axial bzw. *pseudo*-axial angeordnet sind (Schema 3.5). Im Übergangszustand **IIa** ist ein Effekt der Hydroxy-Gruppe vorhanden, der einen höheren Anteil an 2,3-cis-Produkt im Vergleich zu einem Alkyl-Substituenten in allylischer Position bewirkt. Ein Einfluss der allylischen Hydroxy-Gruppe zeigt nicht nur in den Stereoselektivitäten sondern auch in der Regioselektivtät der Reaktion. Das Nebenprodukt Tetrahydropyran **3a** wird im Vergleich zum typischen 5-*exo*:6-*endo*-Verhältnis von 98:2 für 4-Penten-1-oxylradikale[20] in einem Verhältnis von 5-*exo*:6-*endo* = 86:14 gebildet.

(B) *rel*-(2*S*,4*S*)-Stereoisomer

Das bromierte Tetrahydrofuran **3b** wurde bei der thermischen Umsetzung des *like*-Stereoisomers **1** in einer Ausbeute von 67% mit einem 2,3-*cis*:2,3-*trans*-Verhältnis von 72:28 gebildet (Schema 3.6). Das entsprechende Produkt **4** wurde dabei in 84% isoliert. Zusätzlich wurde im GC/MS-Chromatogramm Spuren des 6-*endo*-trig-Cyclisierungsproduktes detektiert,

aufgrund der geringen Ausbeute konnte jedoch keine vollständige stereochemische Analyse des Produktes durchgeführt werden. Ein Experiment in C_6D_6 mit direkter NMR-analytischer Untersuchung zeigte auch hier keine zusätzlichen Produkte.

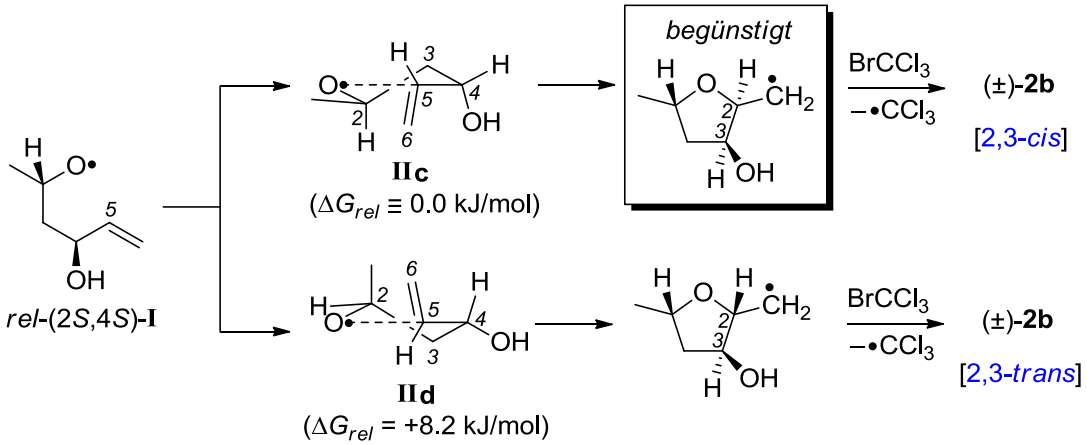


rel-(2*S*,4*S*)-**1** **2b** (67%) **3a** (2%) **4** (84%)

(2,3-*cis*:*trans* = 72:28)

Schema 3.6 Produktspektrum der radikalischen Bromcyclisierung von *like*-**1**.

Das 5-*exo*:6-*endo*-Verhältnis der Reaktion liegt im typischen Fingerprint-Bereich von 98:2 für radikalische Cyclisierungsreaktionen.[20] Bemerkenswert ist die 2,3-cis-selektiv verlaufende 5-*exo*-trig-Cyclisierung, die bislang in Alkenoxylradikal-Cyclisierungen nicht beobachtet wurde.[21] Die Berechnungen der Freien Energiedifferenzen (ΔG_{rel}) der Übergangszustände **IIc** und **IId** verdeutlichen, dass der Übergangszustand **IIc** energetisch günstiger ist und somit der Reaktionsweg zum 2,3-cis-konfigurierten Produkt bevorzugt wird (Schema 3.7).



rel-(2*S*,4*S*)-**I** **IIc** (ΔG_{rel} ≡ 0.0 kJ/mol) **IId** (ΔG_{rel} = +8.2 kJ/mol)

Schema 3.7 Übergangszustände zur Erklärung der cis/trans-Selektivität bei der 5-*exo*-trig-Cylisierung von *like*-**1**. ΔG_{rel}-Werte aus B3LYP/6-31+G** Dichtefunktional-Rechnungen.[17,18]

3.3.3 Darstellung der Isomuscarine

Die vier diastereomerenreinen 2-Brommethyl-5-methyltetrahydrofuranole **2** wurden im letzten Syntheseschritt mit Hilfe einer Substitution von Brom gegen Trimethylamin in die Bromide der Isomuscarine umgesetzt. Die erhaltenen Bromide lassen sich aus einem Dichlormethan/Pentan-Gemisch kristallisieren, wodurch eine Zuordnung der Stereozentren möglich wird (Abb. 3.2).[22] Die diastereotopen Protonen am C4-Atom des 3,5-trans-substituierten Tetrahydrofurans zeigen im ^{1}H-NMR eine Aufspaltung der beiden Signale von 0.19−0.31 ppm, wohingegen die Protonen bei einer 3,5-cis-Konfiguration einen signifikanten Abstand von 0.84−1.00 ppm besitzen.

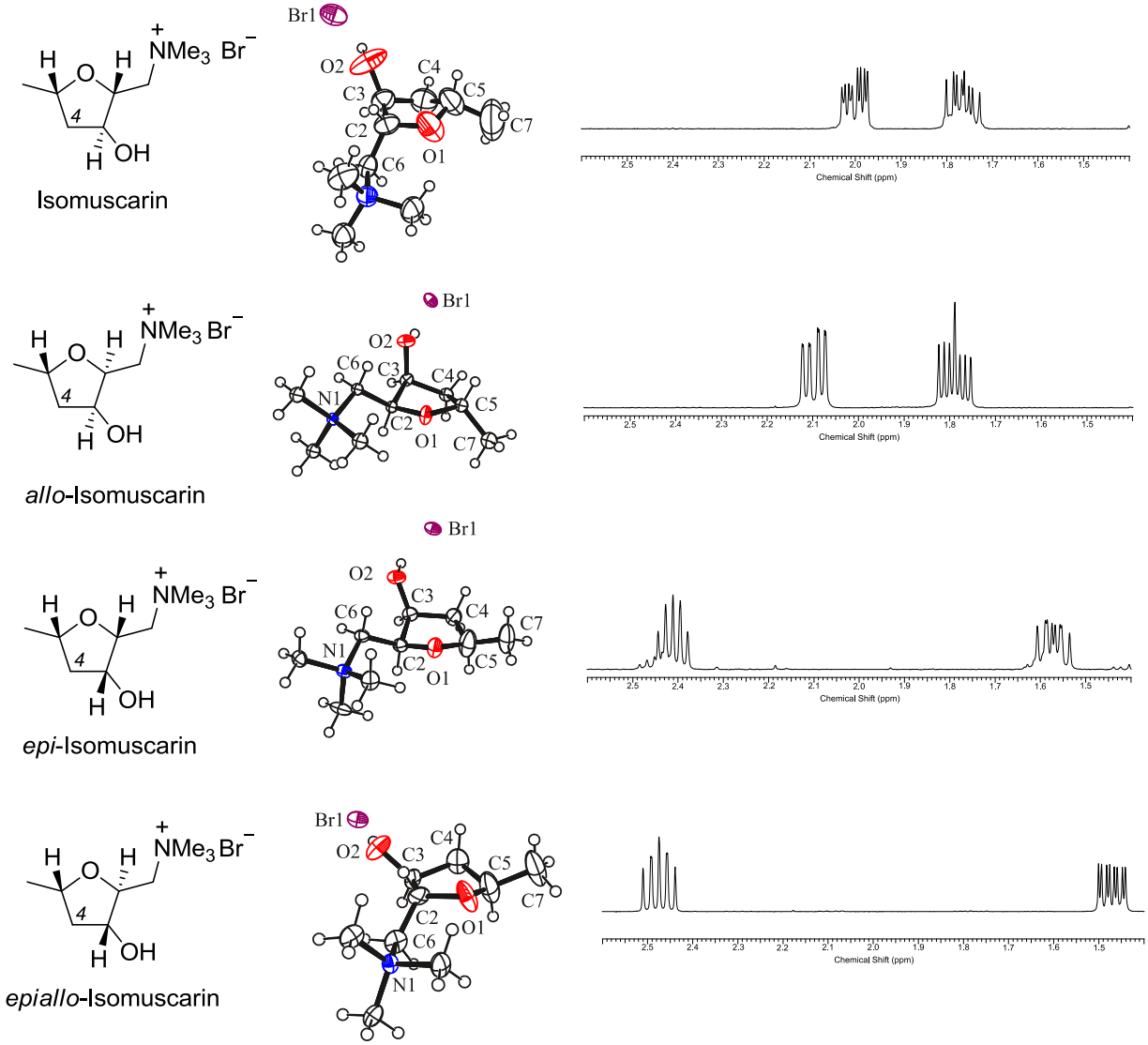


Abbildung 3.2 Kristallstrukturen der Isomuscarin-Bromide (Mitte) und ^{1}H-NMR-Verschiebungen der diastereotopen Protonen am C4-Atom (rechts).[23]

Eine charakteristische Aufspaltung der Signale ist auch im ^{13}C-NMR-Spektrum sichtbar. Die ^{13}C-Signale in Nachbarschaft des Stickstoff-Atoms zeigen bei einer Temperatur von 80 °C eine ^{13}C-^{14}N-Kopplung von 6−8 Hz und werden somit in 1/1/1-Tripletts aufgespalten (Abb. 3.3). Bei Ammoniumsalzen bewirkt die quartäre Ammoniumgruppe eine Verlangsamung der Quadrupol-Relaxation, wodurch die ^{13}C-^{14}N-Kopplungen in manchen Fällen im ^{13}C-NMR-Spektrum detektierbar werden.[24]

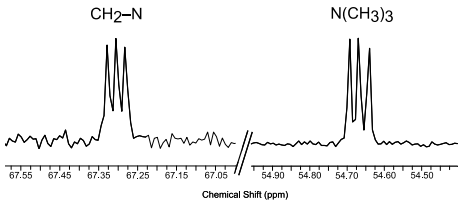


Abbildung 3.3 ^{13}C-^{14}N-Aufspaltung im ^{13}C-NMR-Spekrum von *epi*-Isomuscarin-Bromid in D_2O bei 80 °C.

3.4 Ausblick

Die 5-*exo*-trig-Cyclisierung stellt einen neuen, kurzen synthetischen Zugang zu den vier Isomuscarin-Diastereomeren dar. Über den Syntheseweg ist es möglich die Diastereomere in ausreichenden Mengen darzustellen, um somit die Verbindungen auf ihre mögliche Wirksamkeit in biochemischen Prozessen zu untersuchen. Die Alkenoxylradikal-Cyclisierung könnte in Zukunft den Aufbau von enantiomerenreinen Isomuscarinen ermöglichen. Die Studie zeigt erste Hinweise auf eine 2,3-cis-selektive Steuerung von O-Radikalcyclisierungen. Im Fall des *allo*-Isomuscarins ist der allylische Hydroxy-Substituent in der Lage, im Gegensatz zum sterischen Einfluss einer Alkyl-Gruppe, die 5-*exo*-trig-Cyclisierung 2,3-cis-selektiv zu steuern. Dies wird auf eine stereoelektronische Wechselwirkung der Hydroxy-Gruppe mit der Vinyl-Einheit zurückgeführt. Zur Klärung der Ursache gilt es zu prüfen, ob dieser 2,3-cis-dirigierende Effekt des Hydroxy-Substituenten auch ohne Beeinflussung einer zusätzlichen Methyl-Gruppe auf weitere polare Substituenten ausweitbar ist. Diese polare Selektivitätssteuerung würde die Anwendungsbreite der radikalischen Cyclisierungsreaktion deutlich erweitern.[25]

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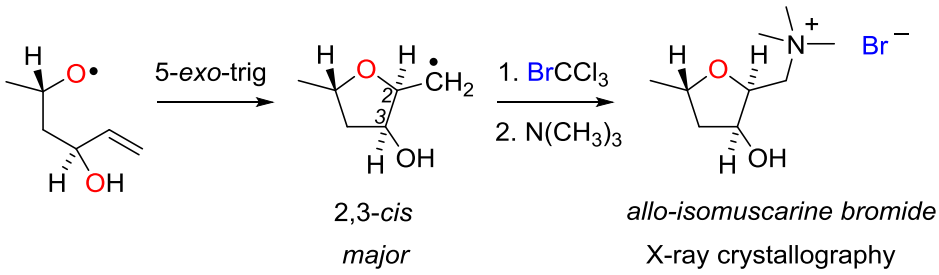
3.6 Forschungsartikel

Synthesis and Structural Characterization of the Isomuscarines

Irina Kempter, Britta Frensch, Thomas Kopf, Ralph Kluge, René Csuk, Ingrid Svoboda, Hartmut Fuess, Jens Hartung, *Tetrahedron* **2014**, *70*, 1918−1927.



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Synthesis and structural characterization of the isomuscarines

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ABSTRACT

Four diastereomers of 2-[(trimethylammonium)-methyl]-5-methyltetrahydrofuran-3-ol, trivially named isomuscarine, *allo*-isomuscarine, *epi*-isomuscarine, and *epiallo*-isomuscarine, were prepared as bromide salts from 2,4-*like* and 2,4-*unlike* diastereomers of 3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione. The strategy for constructing the tetrahydrofuran nucleus of the isomuscarines uses alkenoxyl radical 5-*exo*-bromocyclization, occurring 2,3-cis-selectively for the 2,4-*like*-4-hydroxyhex-5-en-2-oxyl radical, and 2,3-trans-selectively for the 2,4-*unlike* diastereomer. A fraction of 4-hydroxyhex-5-en-2-oxyl radicals cyclizes 6-*endo*-selectively providing 5-bromo-2-methyltetrahydropyran-4-ols in yields between 3 and 15%. Substituting trimethylamine for bromide in 5-*exo*-bromocyclized products furnishes isomuscarine bromides, which were structurally characterized by X-ray diffraction and NMR-spectroscopy.

1. Introduction

Isomuscarines are tetrahydrofuran-derived quaternary ammonium cations structurally related to the muscarines,[1] by changing position of the hydroxyl substituent (Fig. 1).[2] In extension to the muscarines,[3,4] isomuscarine diastereomers are specified by prefices *allo*, *epi*, and *epiallo* for distinguishing relative configuration at the three stereocenters. The only isomuscarine prepared and structurally characterized so far is the *epiallo*-isomer, obtained by Joulliée and co-workers from a D-glucose-derived building block in nine synthetic steps.[2,5]

Our interest in muscarine- and isomuscarine-chemistry started with the quest for selectivity control in polar and free radical bromocyclizations.[6–9] From an enantioselective synthesis of (+)-muscarine we learned that the hydroxyl group in position 3 of (2*S*,3*R*)-hex-5-ene-2,3-diol directs polar 5-*exo*-bromocyclization by the *gauche* effect 2,5-cis-selectively.[10–13] Reversing this intrinsic stereoselectivity is feasible by changing the mechanism from polar to radical addition, converting the hydroxyl oxygen involved in C,O-bond formation into a radical oxygen. Oxygen radicals add to carbon–carbon double bonds via early transition states in kinetically controlled reactions with selectivity being controlled by orbital effects, torsional strain, temperature, and steric repulsion between the reaction centers.[14–17]

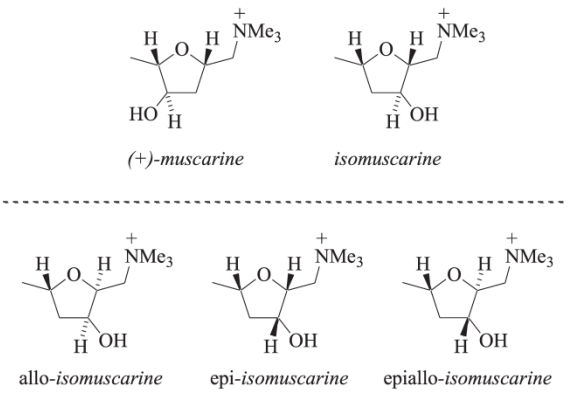

Fig. 1. Structure formulas of muscarine (top left) and isomuscarine (top right), and descriptors for specifying isomuscarine stereoisomers (bottom).

From a study on synthesis of *allo*-muscarine via 3-hydroxyhex-5-en-2-oxyl radical cyclization we learned that a hydroxyl group in β-position to the radical oxygen induces rapid β-fragmentation to

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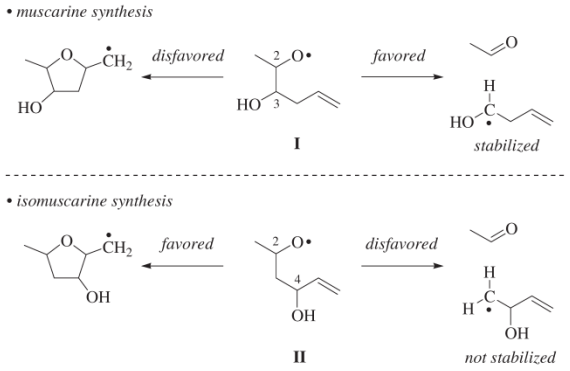
the aliphatic chain (Scheme 1, top).[18,19] Driving forces for breaking the β-carbon–carbon bond in alkenoxyl radical **I** are entropy, strength of the newly formed carbon–oxygen double bond, and stabilization of the liberated carbon radical by an α-hydroxyl substituent.



Scheme 1. Chemistry of the 3-hydroxyhex-5-en-2-oxyl radical (**I**) (top) and proposed selectivity of the 4-hydroxyhex-5-en-2-oxyl radical (**II**) (bottom).

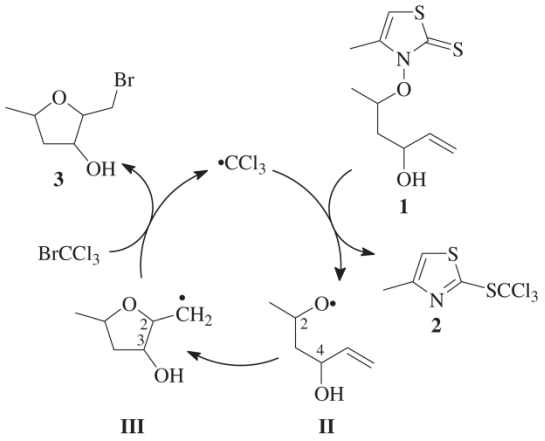
From the information gained by the *allo*-muscarine project we predicted that a hydroxyl substituent in γ-position to the radical oxygen exerts no similar rate enhancing effect for β-carbon–carbon breaking, as in regioisomer **I** (Scheme 1, bottom). We therefore reasoned that alkenoxyl radical **II** cyclizes 5-*exo*-selectively with stereoselectivity being guided by an interplay between polar and steric effects of the allylic hydroxyl group and the methyl substituent.[20,21]

The major result from the isomuscarine project shows that diastereomers of the 4-hydroxyhex-5-en-2-oxyl radical **II** undergo in solutions of bromotrichloromethane rapid, regio- and stereoselective 5-*exo*-bromocyclizations. The isomer described as *rel*-(2*S*,4*S*)-**II**, hereafter specified as *like*-**II**, cyclizes 2,3-cis-selectively, whereas the *rel*-(2*S*,4*R*)-stereoisomer of **II**, abbreviated as *unlike*-**II**, prefers the 2,3-trans mode of 5-*exo*-cyclization. Substituting trimethylamine for bromide in 5-*exo*-bromocyclized products gives the isomuscarines as bromide salts, which were structurally characterized by X-ray diffraction and NMR-spectroscopy.

2. Results and interpretation

2.1. Concept and general mechanistic considerations

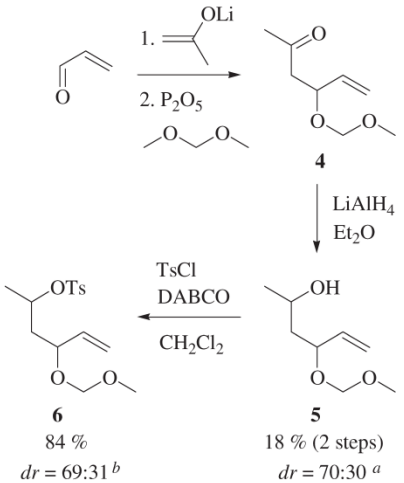
In extension to previous mechanistic and synthetic studies,[6,22,23] we used 3-alkenoxy-4-methylthiazole-2(3*H*)-thiones (MTTORs) **1** as progenitors for generating oxygen radicals under non-oxidative and pH-neutral conditions. Derivatives of compound **1** liberate alkenoxyl radicals in a propagating step of a radical chain reaction, by adding the trichloromethyl radical to the thione sulfur and subsequently breaking the nitrogen–oxygen bond homolytically (Scheme 2).[17] Alkenoxyl radical **II**, in extension to the general mechanism, cyclizes with a predicted 5-*exo*/6-*endo*-regioselectivity of 98:2, leading to carbon radical **III** as major product.[24] Nucleophilic carbon radicals similar to **III** homolytically displace bromine from bromotrichloromethane with bimolecular rate constants in the order of 10^8 M^{-1} s^{-1} at ambient temperature, providing 2-bromomethyl-5-methyltetrahydrofuran-3-ol (**3**) presumably as mixture of 2,3-cis/trans-stereoisomers. Bromine atom abstraction from the mediator gives the trichloromethyl radical for continuing the chain reaction.



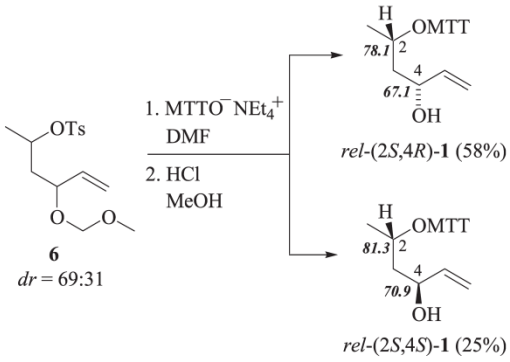
Scheme 2. Strategy for constructing the isomuscarine nucleus from 3-alkenoxythiazole-2(3*H*)-thione **1** and bromotrichloromethane in a radical chain reaction.

2.2. Stereoisomers of 3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione (1)

For preparing *like* and *unlike* stereoisomers of 3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione (**1**) we devised a six-step synthesis beginning with a mixed aldol addition of lithium propenolate to 2-propenal. The aldol addition yields 4-hydroxyhex-5-en-2-one.[25] The product rapidly eliminates water on standing and was therefore immediately converted into methoxymethyl derivative **4**.[26] Reducing the carbonyl group of *O*-protected hydroxyketone **4** by lithium aluminum hydride afforded a 30:70-mixture of *like*/*unlike*-4-methoxymethyloxyhex-5-en-2-ol (**5**), which was esterified by *p*-toluenesulfonyl chloride in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to furnish derived tosylate **6**. Treating *O*-alkenyl tosylate **6** in a solution of dimethylformamide with *N*-hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt gives after acid-catalyzed methanolysis of the methoxymethyl protecting group and chromatographic purification MTTORs *like*- and *unlike*-**1** as single diastereomers (Schemes 3 and 4).[27,28]



Scheme 3. Synthesis of 4-(methoxymethyloxy)-hex-5-en-2-yl tosylate (**6**) from 2-propenal. [a] Diastereomeric ratio (dr) derived from intensities of carbon-13 NMR-resonances. [b] dr derived from proton-NMR-integrals.

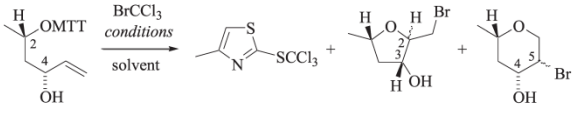


Scheme 4. Synthesis of *O*-alkenyl thiohydroxamates *rel*-(2*S*,4*R*)-**1** (*unlike*-**1**) and *rel*-(2*S*,4*S*)-**1** (*like*-**1**). MTTO$^-$NEt$_4^+$=*N*-hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt. Figures printed in bold and italics refer to carbon-13 NMR-resoncances of carbons 2 and 4.

2.3. Alkenoxyl radical bromocyclizations

*2.3.1. Conversion of rel-(2S,4R)-3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3H)-thione unlike-(**1**).* From a screening of parameters we found that MTTOR *unlike*-**1** furnishes a 86:14-mixture of 5-*exo*-bromocyclized compounds **3a**,**b** and 6-*endo*-bromocyclization products **7a**,**b** in up to 72%, when heated for 120 min at 80 °C in a 1.5-M solution of bromotrichloromethane in benzene, containing ~25 mol% of azo-α,α-bis-(isobutyronitrile) (AIBN) as initiator (Table 1, entry 1). The reaction mixture furthermore provides up to 96% of 2-trichloromethylsulfanylthiazole **2**, the product of trichloromethyl radical trapping by *unlike*-**1** (cf. Scheme 2). In a control, performed in perdeuterobenzene and directly analyzed by NMR and GC–MS, we identified a total yield of 86% for bromocyclization products **3a**,**b** and **7a**,**b** taken together, but no supplementary products for improving the mass balance (Table 1, entry 2).

Table 1
Products formed from 3-(4-hydroxyhex-5-en-2-oxy)-thiazolethione *unlike*-**1** and bromotrichloromethane



rel-(2*S*,4*R*)-**1** **2** **3a–b** **7a–b**

Entry	Conditions	Solvent	**2**/%	**3a** and **3b**/% (2,3-cis/trans=**3a**:**3b**)	**7a** and **7b**/% (4,5-cis/trans=**7a**:**7b**)
1	AIBN/80 °C	C_6H_6	96[a]	62 (37:63)[a]	10 (40:60)[a]
2	AIBN/80 °C	C_6D_6	81[b]	71 (37:63)[b]	15 (40:60)[b]
3	AIBN/130 °C	C_6H_5Cl	—[c]	59 (37:63)[d]	13 (46:54)[d]
4	hν[e]/22 °C	C_6H_6	86[a]	44 (34:66)[a]	7 (43:57)[a]
5	hν[e]/22 °C	C_6D_6	50[b]	54 (39:61)[b]	12 (47:53)[b]

[a] Yields of isolated products.
[b] Yields of **2**, **3a**, and **3b** were determined via proton-NMR, using pentachlorobenzene as internal standard. Yields of **7a** and **7b** were estimated by quantitative GC, using yields determined for **3a**,**b** by NMR-spectroscopy as standard, assuming identical response factor for bromocyclization products **3** and **7**.
[c] Not determined.
[d] Yields of **3a** and **3b** refer to quantitative GC-analysis performed with the aid of calibration curves. Yields of **7a** and **7b** were estimated from integrals of GC-signals, based on identical response factors for **3** and **7**.
[e] Chamber photoreactor equipped with 350 nm light sources.

To explore, whether alternative bromine atom donors improve yields of target products **3** and **7**, we replaced bromotrichloromethane by diethyl dibromomalonate and 2,2-dibromodimedone. 2,2-Dibromodimedone was completely ineffective and diethyl dibromomalonate provided 35% of bromocyclization products **3a** and **3b** as 39:61-mixture of 2,3-cis/trans-isomers (Supplementary data).

For investigating temperature effects we heated MTTOR *unlike*-**1** and bromotrichloromethane in the presence of AIBN to 130 °C and photolyzed a similarly prepared reaction mixture in the absence of AIBN with 350 nm light at 22 °C (Table 1, entries 3–5).[29,30] The ratio of 5-*exo*- to 6-*endo*-cyclized products **3** versus **7** and stereoselectivities of the underlying ring closures remained approximately unchanged by varying temperature in the given range. The yields obtained from photochemical experiments were up to 21% lower than from thermally initiated reactions.

According to our interpretation of NMR-spectroscopic data, the major tetrahydrofuran obtained from alkenoxythiazolethione *unlike*-**1** and bromotrichloromethane is the 2,3-trans-2,5-trans stereoisomer **3b**. This assignment is based on low field shifts of resonances for carbons 2 and 3 by 1.3–2.1 ppm compared to the 2,3-cis isomer **3a**, and NOESY-cross signals between cis-oriented protons at carbons 2 and 5 in **3a**, which were not present in the spectrum of 2,5-trans isomer **3b**. Both 5-*exo*-bromocyclization products show large shift dispersion for diastereotopic protons bound to carbon 4 (0.85 ppm for **3a** and 0.74 ppm for **3b**).

The 2,3-trans-2,5-trans configuration of major bromocyclization product **3b** is in line with predictions made by stereochemical guidelines, stating that 1- and 3-alkyl-substituted 4-pentenoxyl radicals provide trans-disubstituted tetrahydrofurans as major 5-*exo*-cyclization products.[14,17] The degree of stereoinduction according to the guidelines increases as the distance between the stereoinducing alkyl substituent and the π-bond shortens, for example, from 31:69-2,5-cis/trans-ratio for the 5-hexen-2-oxyl radical to 14:86-2,3-cis/trans-selectivity for the 3-methyl-4-penten-1-oxyl radical.[31] A 2,5-cis/trans-selectivity of 34:66 is smaller than the reference value, pointing to a stereochemical mismatching effect of the 4-hydroxyl group for controlling stereoselectivity in 5-*exo*-cyclization of alkenoxyl radical *unlike*-**II**.

To rationalize the stereodirecting effect of the 4-hydroxyl group we turned from stereochemical guidelines to transition state theory.[32] Since oxygen radicals add to terminal alkenes in kinetically controlled reactions, we modeled the two lowest in energy transition structures (*TS*) for the 2,3-cis- and the 2,3-trans 5-*exo*-cyclization of alkenoxyl radical *unlike*-**II** using Becke's three parameter Lee–Young–Parr hybrid functional (B3LYP)[33,34] in combination with the 6-31+G**-basis set,[35] based on previous method assessment.[14]

The wavefunctions of computed transition structures for 5-*exo*-cyclization of alkenoxyl radical *unlike*-**II**, *TS*-**IIIa**, and *TS*-**IIIb**, show one negative mode of vibration (*i*) referring to the trajectory of oxygen radical addition to alkene carbon C5.[36] Carbon–oxygen distances of 2.030–2.040 Å (Table 2) point to early transition structures, as predicted for fast and exothermic reactions on the basis of the Hammond postulate.[37]

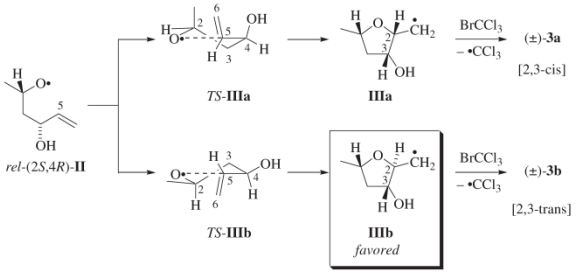
Table 2
Energies and diagnostic parameter of computed transition structures (B3LYP/6-31+G**) associated with in 5-*exo*-cyclization of 4-hydroxyhex-5-en-2-oxyl radical *unlike*-**II**

Entry	*TS*-**III**	E^a/a.u.	ΔG^{298}/kJ mol^{-1}	i^b/cm^{-1}	O1–C5/Å	O–C4–C5=C6/°
1	**a**	−385.474178	+5.0	−397	2.031	−1.8
2	**b**	−385.475671	≡0.0	−390	2.030	−114.1

[a] Zero-point vibrational energy-corrected heat of formation at 0 K; 1 atom unit (a.u.)=1 Hartree=2625.5 kJ mol^{-1}.
[b] *i*=imaginary stretching mode of vibration.

Transition structures *TS*-**IIIa** and *TS*-**IIIb** are best described as twist (T)-conformers of tetrahydrofuran comprising one regular and one extended carbon–oxygen bond (Scheme 5, Supplementary

data). The radical oxygen, the inner alkene carbon (C5), and the allylic carbon (C4) align for stereoelectronic reasons collinearly, defining a plane. Carbon atoms 2 and 3 are for steric reasons offset into opposite directions from the plane, leading to $^{2}T_{3}$- (for *TS*-**IIIa**) or $_{2}T^{3}$-conformers (for *TS*-**IIIb**), with the superscript describing the carbon offset above the plane, the subscript indicating the carbon underneath the twist plane. The projection required to assign tetrahydrofuran conformers places the center atom of the twist plane in front of the paper plane toward the viewer, and the atoms displaced from the plane into the back. Atom numbering in this projecting increases in a clockwise manner, with the oxygen being position 1 (Hantzsch–Widman convention).[38–40] Substituents in twist conformers of tetrahydrofuran prefer equatorial and pseudo-equatorial positions, for keeping steric repulsion with the tetrahydrofuran core to a minimum.[24] The vinyl group and carbon 3 are located on opposite sides of the twist plane for preventing an eclipsing of hydrogens at carbons 4 and 5 (Scheme 5).



Scheme 5. Transition structure models for explaining stereoselectivity in 5-*exo*-cyclization of 4-hydroxyhex-5-en-2-oxyl radical *unlike*-**II** (Supplementary data).

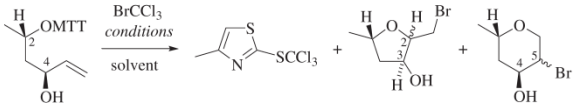
According to theory, transition structure *TS*-**IIIa**, leading to 2,3-cis-cyclized product **IIIa**, is by 5.0 kJ mol^{-1} higher in Gibbs free energy than transition structure *TS*-**IIIb**, affording 2,3-trans-cyclized product **IIIb**. The computed free energy difference translates into a 2,3-cis/trans-selectivity of 12:88 at 298 K (Table 2). Assuming identical rates of bromine atom-trapping by carbon radicals **IIIa** and **IIIb**, the experimental **3a**/**3b**-selectivity of 34:66 (Table 1, entry 4) qualitatively agrees with the value derived from theory.

In favored transition structure *TS*-**IIIb** the methyl group adopts an equatorial and the hydroxyl group a pseudo-equatorial position, with the latter being in anticlinal orientation to the carbon–carbon double bond. In disfavored transition structure *TS*-**IIIa**, the methyl group is axially oriented and the hydroxyl group pseudo-axially. This arrangement of substituents leads to close contacts, increasing the conformational free energy of *TS*-**IIIa**.

To sum up, *N*-(4-hydroxyhex-5-en-2-oxy)-thiazole-2(3*H*)-thione *unlike*-**1** furnishes bromocyclized tetrahydrofuran **3b** as major product from the radical reaction with bromotrichloromethane. The stereochemical outcome qualitatively agrees with guidelines for tetrahydrofuran synthesis from monoalkyl-substituted 4-pentenoxyl radicals.[14,17] Quantitatively, the allylic hydroxyl group in relative *unlike*-configuration with respect to the methyl substituent is an instance of stereochemically mismatching arrangement, given the low 2,5-cis/trans selectivity of 34:66. A second aspect deserving to be mentioned is the 86:14-ratio of 5-*exo*/6-*endo*-bromocyclized products **3a**,**b** versus **7a**,**b**, which is by almost one order of magnitude smaller than the value obtained for the 5-hexen-2-oxyl radical.[31]

*2.3.2. Conversion of rel-(2S,4S)-3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3H)-thione like-(**1**).* *N*-Alkenoxythiazolethione *like*-**1** provides 67% of bromomethyltetrahydrofurans **3c** and **3d** as 72:28-mixture of stereoisomers, when heated in a solution of benzene containing bromotrichloromethane and AIBN. The reaction affords 84% of trichloromethylsulfanylthiazole **2** as co-product from the radical chain reaction (Table 3, entry 1). By GC–MS-analysis we detected two additional products showing 5-bromo-2-methyltetrahydropyran-3-ol-type fragmentation pattern in electron impact mass spectra. From replicated runs we collected a sufficient quantity of this material for clarifying that the minor products are 6-*endo*-bromocyclized products **7c** and **7d**, without being able to present a full stereochemical analysis. In a control performed by heating *like*-**1**, bromotrichloromethane, and AIBN in perdeuterobenzene we obtained 84% of bromocyclization products **3c**,**d**, and 3% of tetrahydropyrans **7c**,**d** (Table 3, entry 2). A supplementary photochemical experiment conducted at 22 °C showed similar yields of bromocyclized products **3c**,**d** and **7c**,**d**, and stereoselectivity for synthesis of tetrahydrofurans **3c** and **3d** (Table 3, entry 3).

Table 3
Products formed from 3-(4-hydroxyhex-5-en-2-oxy)-thiazolethione *like*-**1** and bromotrichloromethane



rel-(2*S*,4*S*)-**1** **2** **3c–d** **7c–d**

Entry	Conditions	Solvent	**2**/%	**3c** and **3d**/% (2,3-cis/trans=**3c**:**3d**)	**7c** and **7d**%
1	AIBN/80 °C	C_6H_6	84[a]	67 (72:28)[a]	[2][b]
2	AIBN/80 °C	C_6D_6	80[c]	84 (70:30)[c]	3[c]
3	hν[d]/22 °C	C_6D_6	53[c]	68 (73:27)[c]	2[c]

[a] Yields of isolated products.
[b] Yields determined via proton-NMR from methyl doublet integral intensities, using pentachlorobenzene as internal standard.
[c] Yields of **2**, **3c**, and **3d** were determined via proton-NMR, using pentachlorobenzene as internal standard. Yields of **7c** and **7d** were approximated from quantitative GC-analysis, using yields determined for **3c** and **3d** from proton-NMR as reference, and assuming identical response factors for bromocyclization products **3** and **7**.
[d] Chamber photoreactor equipped with 350 nm light sources.

From proton- and carbon-13 NMR data, we assigned 2,3-cis-2,5-trans-configuration to the major product **3c** formed from MTTOR *like*-**1** and bromotrichloromethane. The resonances of diastereotopic protons attached to carbon 4 for 3,5-trans-substituted tetrahydrofurans **3c**,**d** ($\Delta\delta$=0.40 for **3c** and 0.25 for **3d**) are less dispersed than for 3,5-cis-substituted derivatives **3a** and **3b** (vide supra).

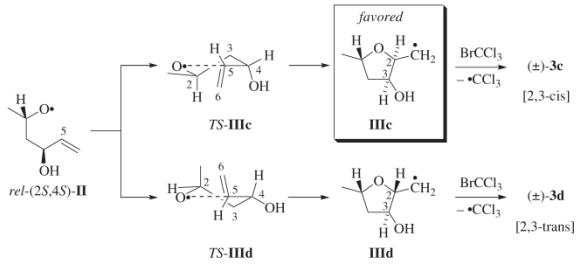
A 2,3-cis-selective 5-*exo*-cyclization would not have been predicted on the basis of stereochemical guidelines[14,17] summarized in the previous section.[14] Using density functional calculations on a B3LYP/6-31+G**-level of theory we found that transition structure *TS*-**IIIc** leading to 2,3-cis-cyclized tetrahydrofuryl-2-methyl radical **IIIc**, is by 8.2 kJ mol^{-1} lower in Gibbs free energy (298 K) than intermediate *TS*-**IIId**, cyclizing to 2,3-trans-configured radical **IIId**. The computed free energy difference translates into a 2,3-cis/trans-selectivity of 96:4, which qualitatively agrees with the 73:27-ratio found for bromides **3c** and **3d** in the experiment (Table 4).

Table 4
Energies and diagnostic parameter for computed transition structures (B3LYP/6-31+G**) associated with 5-*exo*-cyclization of 4-hydroxyhex-5-en-2-oxyl radical *like*-**II**

Entry	*TS*-**III**	E^{a}/a.u.	ΔG^{298}/kJ mol^{-1}	i^{b}/cm^{-1}	O1–C5/ Å	O–C4–C5=C6/°
1	**c**	−385.476128	≡0.0	−384	2.038	3.6
2	**d**	−385.475671	+8.2	−382	2.040	110.9

[a] Zero-point vibrational energy-corrected heat of formation at 0 K; 1 atom unit (a.u.)=1 Hartree=2625.5 kJ mol^{-1}.
[b] i=imaginary stretching mode of vibration.

In energetically favored intermediate *TS*-**IIIc**, the methyl group is bound equatorially and the hydroxyl group pseudo-axially to the distorted $_2T^3$-conformer of tetrahydrofuran (Scheme 6, top). A 27:73-selectivity for 2,5-cis/trans-cyclized products obtained from alkenoxyl radical *like*-**II** is higher than the value obtained for the 5-hexen-2-oxyl radical (31:69). From this information we concluded that synclinal orientation between the vinyl and the hydroxyl group, as computed for *TS*-**IIIc**, poses a stereochemically matching arrangement. In stereoisomeric transition structure *TS*-**IIId**, the methyl group adopts an axial position, and the hydroxyl substituent an anticlinal arrangement with respect to the carbon–carbon double bond, which we consider by the aforementioned arguments as disfavored.



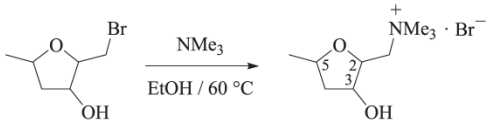
Scheme 6. Transition structure models for explaining stereoselectivity in 5-*exo*-cyclization of 4-hydroxyhex-5-en-2-oxyl radical *like*-**II** (Supplementary data).

4-Hydroxyhex-5-en-2-oxyl radical *like*-**II**, in summary, poses a rare example of an aliphatic unsaturated radical, preferring the 2,3-cis-mode of 5-*exo*-cyclization. The experimental 97:3-ratio of 5-*exo*- versus 6-*endo*-bromocyclized products agrees with the fingerprint 98:2-regioselectivity observed for the 5-hexen-2-oxyl radical[17,24,31].

2.4. Isomuscarines

2.4.1. Synthesis and mass spectrometry. From larger scale batches we obtained diastereomerically pure 2-bromomethyl-5-methyl-tetrahydrofuranols **3a**–**d** in a sufficient quantity for finalizing syntheses of isomuscarine bromides by substituting trimethylamine for bromide (Table 5). *epiallo*-Isomuscarine bromide formed in this procedure in comparatively low yields (Table 5, entry 2), leaving unspent bromomethyltetrahydrofuran **3b** in the mother liquor after filtrating off the target compound.

Table 5
Formation of isomuscarine bromides from bromocyclization products **3a**–**d**, and synopsis of endocyclic carbon-13 NMR resonances of the isomuscarines



3 *isomuscarine bromide*

Entry	3	Isomuscarine bromide	Yield/%	C2[a]/ppm	C3[a]/ppm	C4[a]/ppm	C5[a]/ppm
1	**a**	*epi*-	72	76.5	73.9	41.9	76.1
2	**b**	*epiallo*-	36	78.9	75.9	40.9	75.1
3	**c**	*allo*-	69	76.1	74.5	42.2	75.6
4	**d**	no prefix	79	80.4	77.4	40.9	75.4

[a] In D_2O, 25 °C, referenced versus 1,4-dioxane as internal standard.

Isomuscarine bromides are colorless, hygroscopic, crystalline solids, dissolving in water, lower alkanols, and moderately polar solvents, such as dichloromethane. From solutions in methanol we determined molecular masses via electrospray ionization (ESI)-mass spectrometry. Spectra recorded in the positive ion polarity mode show for all compounds strong signals at *m*/*z* 174.2 from non-fragmented ammonium cations $[C_9H_{20}NO_2]^+$ (calculated 174.15). A weaker signal at *m*/*z* 427 originates from clusters composed of two non-fragmented ammonium cations and one bromide ion, as derived from the experimental isotopic envelope. To secure the chemical nature of the counter anion we used the negative ion mode of the mass spectrometer, revealing signals at *m*/*z* 79/81 in a 50:50-ratio of intensity.

Collision-induced dissociation (CID)-mass spectra show for all isomuscarines molecular ions at *m*/*z* 174 [MSMS experiments, isolation width of 5 atomic mass units (amu)] and main product ions at *m*/*z* 115 and 97 of similar relative intensity (70±5% for *m*/*z* 115 and 100% for *m*/*z* 97), which we related to successive loss of trimethylamine (Δ*m*=59 amu) and water (Δ*m*=18 amu).

2.4.2. Solid state structures. Isomuscarine bromides crystallize from dichloromethane/pentane-mixtures in centrosymmetric space groups comprising racemic mixtures of the title compounds at crystallographically independent sites. Distances between bromide and oxygen of 3.22(3) Å fall short of the sum of bromine- (1.85 Å) and oxygen-van der Waals-radii (1.52 Å)[41] pointing to O–H···Br hydrogen bonds (Figs. 2 and 3).[42] Close contacts furthermore exist between trimethylammonium carbons and bromide, leading in the models used for refining structures to mono-, di-, and tridentate C–H···Br interactions. Except of isomuscarine bromide, which shows exclusively bidentate binding between methyl C,H-bonds and bromide, all isomuscarines show combinations of mono- and bidentate interactions. In the crystal structure of *allo*-isomuscarine bromide, a tridentate contact exists as third mode methyl-bromide interaction. The coordination number attained for bromide by hydrogen bonding with methyl and hydroxyl groups is five for isomuscarine bromide, six for *epiallo*-isomuscarine bromide, and seven for *allo*- and *epi*-isomuscarine bromide.

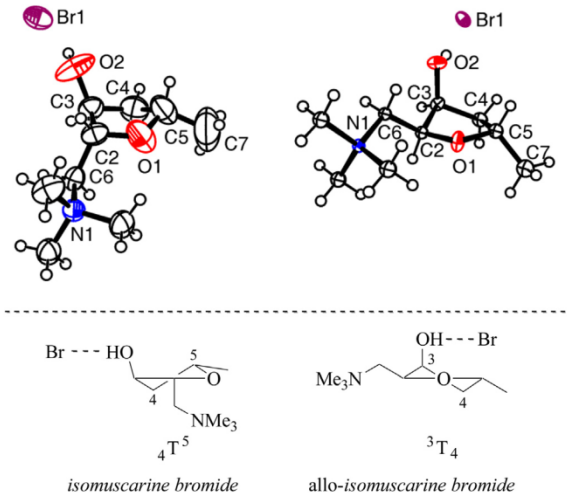


Fig. 2. Ellipsoid graphics (50% probability) and structure formulas depicting conformational characteristics of isomuscarine bromide at 301 K and *allo*-isomuscarine bromide at 100–105 K (top). For presentation, (3*S*)-enantiomers were arbitrarily chosen from the racemate in the unit cell. Hydrogen atoms are drawn as circles of an arbitrary radius. Charges were omitted for the sake of clarity.

The tetrahydrofuran conformation in the crystal structures is $_4T^5$ for isomuscarine bromide, $^3T_4$ for *allo*-isomuscarine bromide, $^1T_2$ for *epi*-isomuscarine bromide, and $^4T_5$ for *epiallo*-isomuscarine

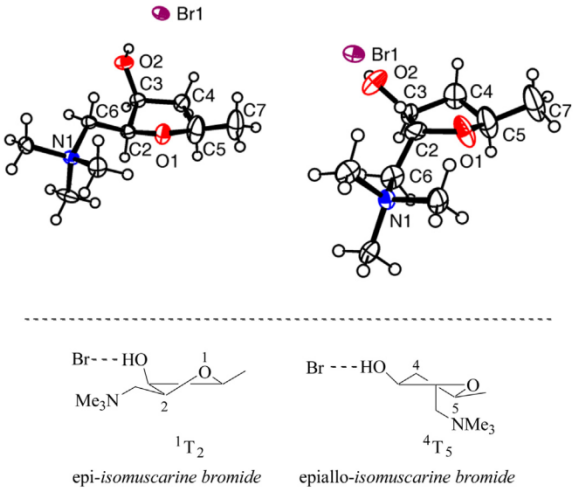


Fig. 3. Ellipsoid graphics (50% probability) and structure formulas depicting conformational characteristics of *epi*-isomuscarine bromide and *epiallo*-isomuscarine bromide at 100–105 K (top) in the solid state. For presentation, (3*S*)-enantiomers were arbitrarily chosen from the racemate in the unit cell. Hydrogen atoms are drawn as circles of an arbitrary radius. Charges were omitted for the sake of clarity.

bromide (Figs. 2 and 3). Different conformers arise from steric and polar interplay of substituents with the heterocyclic core and packing of anions and cations in the unit cell. Both effects energetically are more relevant than preferences of the underlying heterocycle, because conformers of tetrahydrofuran almost freely interconvert in the gas phase between high in energy conformers [E_2 (E=envelope) and $_2T^3$] to low in energy conformers ($_3T^4$ and E_1), being separated by only 0.8–2.1 kJ mol^{-1}.[43–45]

In crystal structures of isomuscarines, the 2-methyl substituent is equatorially arranged (isomuscarine bromide and *epi-allo*-isomuscarine bromide) or pseudo-equatorially (*allo*-isomuscarine bromide and *epi*-isomuscarine bromide). The (trimethylammonium)-methyl group adopts equatorial or bisectional positions, with the latter being a borderline position in terms of tolerating steric encroachment (Figs. 2 and 3). The hydroxyl group is axially oriented in the crystal structure of *allo*-isomuscarine bromide, pseudo-axially in *epi*-isomuscarine- and in isomuscarine bromide, and pseudo-equatorially in *epiallo*-isomuscarine bromide, showing in summary an inconsistent conformational behavior.

2.4.3. Gas phase structures of the isomuscarines from density functional calculations. For investigating conformational preferences in the gas phase, we computed equilibrium structures of the isomuscarines on the B3LYP/6-31+G**-level of theory, without taking effects of bromide and solvent molecules into account. The favored spatial position of the conformationally flexible (trimethylammonium)-methyl side chain was located from potential energy surface scans. Computed and experimental bond lengths match within reasonable precision, considering the experimental accuracy of X-ray diffraction analysis (Supplementary data).

According to theory, the isomuscarines are very close in zero-point vibrational energy-corrected heats of formation, with the 2,5-trans-2,3-cis-configured tetrahydrofuran *allo*-isomuscarine being favored by 3.5–4.3 kJ mol^{-1} over the three other diastereomers. This energy difference, however, is close to the precision for reproducing relative energies by the chosen computational method (Table 6, entries 1 and 2).

Theory predicts for the gas phase equilibrium structure of *allo*-isomuscarine $^3T_4$ conformation, which is identical to the solid state

Table 6
Calculated energies and equilibrium conformers of isomuscarine cations

Entry	Parameter	Isomuscarine			
		—	*allo-*	*epi-*	*epiallo-*
1	E^a/a.u.	−559.709427	−559.711054	−559.709726	−559.709580
2	ΔE^b/kJ mol^{-1}	4.3	≡0.0	3.5	3.9
3	Conformer (theor.)	$^5T_1$	$^3T_4$	$^5T_1$	$^3T_4$
4	Conformer (exptl.)	$_4T^5$	$^3T_4$	$^1T_2$	$_4T^5$

[a] 1 atom unit (a.u.)=2625.5 kJ mol^{-1}.
[b] ΔE=relative heat of formation (B3LYP/6-31+G**//B3LYP/6-31+G**), referring to energy differences at 0 K (zero-point vibrational energy corrected).

structure (cf. Fig. 2). For the remaining isomuscarines computed gas phase structures of the cations and experimental solid state structures of derived bromide salts differ (Table 6, entry 3; Figs. 2 and 3). We think that the majority of conformational deviations arise from packing and counter ion effects.

Substituents in computed structures adopt similar sites as experimentally found in crystal structures. The 2-methyl substituent is located equatorially in equilibrium structures of isomuscarine and *epi*-isomuscarine, and pseudo-equatorially in *allo*- and *epiallo*-isomuscarine. The hydroxyl group adopts an equatorial position in *epiallo*-isomuscarine, an isoclinal position in isomuscarine and *epi*-isomuscarine, and an axial position in *allo*-isomuscarine. For the (trimethylammonium)-methyl substituent theory consistently predicts pseudo-equatorial orientation, showing a *gauche* torsion angle between heteroatoms in the O–C2–C6–N-fragment, extending from the tetrahydrofuran oxygen to the ammonium nitrogen.[46] According to natural bond orbital (NBO)-calculations[47] on the B3LYP/6-31G**//B3LYP/6-31+G**-level of theory, transferring $\sigma_{C2,C3}$-electrons into the σ^*-orbital of the C6,N-bond in the *gauche*-arranged O–C2–C6–N-segment stabilizes equilibrium structures of the isomuscarines by 17.1–19.3 kJ mol^{-1} (Supplementary data). Delocalizing $\sigma_{C6,H}$-electrons into the σ^*-orbital of the C2,O1-bond further stabilizes the isomuscarines by 18.9–19.7 kJ mol^{-1}. Similar stabilization, according to theory, is not available from the glycol ether fragment involving the hydroxyl substituent, since this entity for all calculated equilibrium structures is not *gauche* arranged (Supplementary data).

2.4.4. NMR-spectroscopy. Proton-NMR spectra of isomuscarine bromides in heavy water (D_2O) show baseline-separated resonances, split by up to four doublet couplings in the range of 1–14 Hz. Proton resonances of diastereotopic hydrogens bound to carbon 4 are separated by 0.19–0.31 ppm for 3,5-trans-substituted tetrahydrofurans isomuscarine and *allo*-isomuscarine, and by 0.84–1.00 ppm for the 3,5-cis-stereoisomers *epi*- and *epiallo*-isomuscarine bromide (Fig. 4). In carbon-13 NMR spectra, resonances of the side chain carbon C6 and endocyclic carbon C3 of 2,3-cis-configured tetrahydrofurans *allo*- and *epi*-isomuscarine are upfield-shifted due to steric compression known as the γ-effect (Table 5, entries 1 and 3).

Resonances of carbons bound to nitrogen are split by coupling with nitrogen-14. Broad signals change to 1/1/1-triplets showing 6–8 Hz couplings, by heating samples of isomuscarines from ambient temperature to 80 °C (for *epi*-isomuscarine, see Fig. 5).

Couplings between nitrogen and carbon are more often observed for ammonium salts than for amines, since quaternization causes quadrupole relaxation at nitrogen to become less effective.[48,49] The magnitude of scalar coupling correlates in a Fermi-contact model with probability density of electrons at a nucleus, which in a localized bond model is proportional to the *s*-character of the orbital at nitrogen (S_N) involved in bonding to carbon. The s-orbital contribution to bonding orbitals at nitrogen in the

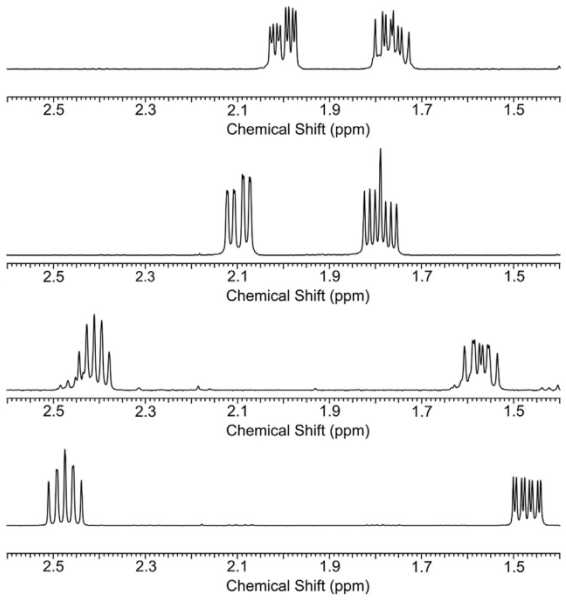


Fig. 4. Excerpts from proton-NMR spectra of (from top to bottom) isomuscarine bromide, *allo*-isomuscarine bromide, *epiallo*-isomuscarine bromide, and *epi*-isomuscarine bromide showing resonances of diastereotopic protons attached to C4 (400 MHz, D_2O, referenced versus 1,4-dioxane, 25 °C).

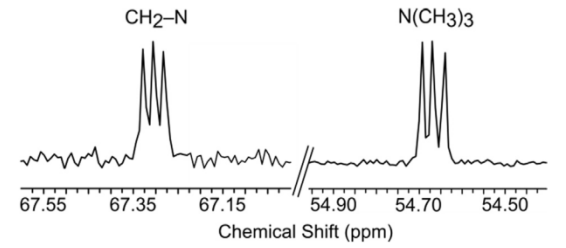


Fig. 5. Excerpt from the carbon-13 NMR spectrum of *epi*-isomuscarine bromide, recorded in D_2O at 80 °C, showing fine structures from coupling with nitrogen-14.

isomuscarines, according to NBO-calculations is 25%, leading to a factor of P=3.4±0.4 for correlating scalar $^1J(^{14}N,^{13}C)$-coupling to hybridization (Eq. 1, Table 7, entries 3 and 4).

$$\frac{S_N \times J^*}{^1J(^{13}C,\ ^{14}N)} \qquad (1)$$

Table 7
Coupling constants between carbon-13 and nitrogen-14 in isomuscarine bromides, and correlation factor P for approximating the s-character at nitrogen in bonding orbitals to carbon

Entry	Parameter	Isomuscarine			
		—	*allo-*	*epi-*	*epiallo-*
1	$^1J(^{13}CH_2,^{14}N)$/Hz[a]	(5.7)[b]	6.8	6.8	6.7
2	$^1J(^{13}CH_3,^{14}N)$/Hz[a]	8.0	8.0	8.0	7.6
3	$P(^{13}CH_2,^{14}N)$[c]	(4.5)	3.8	3.8	3.8
4	$P(^{13}CH_2,^{14}N)$[c]	3.1	3.1	3.1	3.3

[a] 150 MHz; coupling constants refer to 80 °C for bromide salts in solutions of D_2O.
[b] Poor spectral resolution, broad signal.
[c] Dimensionless correlation factor P, calculated according to Eq. 1, by inserting the percent value for S_N, for example, 25 for 25% in an sp^3-hybride; J^*=1 Hz.

3. Concluding remarks

Bromocyclization of the 4-hydroxyhex-5-en-2-oxyl radical (**II**) occurs stereoselectively providing access to diastereomeric pure 2-[(trimethylammonium)-methyl]-5-methyltetrahydrofuran-3-ols, trivially named isomuscarine, *allo*-isomuscarine, *epi*-isomuscarine, and *epiallo*-isomuscarine. Since alkenoxyl radical reactions occur without racemization, we consider the approach also valid for preparing enantiomerically pure isomuscarines.

Isomuscarines so far have neither been described as natural products nor characterized in terms of biochemical properties. The configuration of substituents required for attaining selectivity in biochemical modes of action by an isomuscarine is therefore completely unknown. From information summarized in this article and from results obtained by oxidizing structurally related alkenols[20,21] it is clear that methods for preparing 2,3-trans-stereoisomers of the isomuscarines from 5-*exo*-cyclization in notable diastereomeric excess have to overrule an inherent driving force for the 2,3-cis ring closure.

2,3-Cis-stereocontrol in 5-*exo*-radical-cyclizations until then was restricted to synthesis of bicyclic compounds.[50] The polar effect exerted by an allylic hydroxyl group therefore adds a component to stereocontrol in oxygen radical cyclization, which is not available from alkyl and phenyl substituents. Since alkyl groups control stereoselectivity by steric effects, we think that the new 2,3-cis-directing effect of the allylic hydroxyl group is polar in origin. The polar effect exerted by oxygen arises from σ-electron accepting and π-type lone pair-donating contributions. According to this interpretation we expect other substituents to exist for directing 4-pentenoxyl radical cyclization in a similar or even in a more pronounced manner 2,3-cis-selectively, which is being investigated at the moment in our laboratory.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see Ref. 51 and Supplementary data. Carbon-13 NMR-shifts of the isomuscarines (Section 4.6) refer to a temperature of 20 °C, $^1J(^{13}C,^{14}N)$-couplings to a temperature of 80 °C. Carbons bound to nitrogen show uncharacteristic broad resonances in isomuscarine NMR spectra recorded at 20 °C in D_2O.

4.2. 4-(Methoxymethyloxy)-hex-5-en-2-one (4)

Phosphorous pentoxide (222 g) was added at 0 °C to a solution of dimethoxymethane (433 mL) in chloroform (360 mL) in an atmosphere of dry nitrogen. A solution of 4-hydroxyhex-5-en-2-one (12.5 g, 109 mmol; see Supplementary data) in chloroform (80 mL) was added at 0 °C. The mixture was stirred at 22 °C for 3.5 h. The precipitate was filtrated off and washed with chloroform (2×100 mL). The filtrate and combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure (250 mbar) without allowing the water bath temperature at the rotary evaporator to exceed 40 °C. 4-(Methoxymethyloxy)-hex-5-en-2-one (**4**) prepared accordingly was used for the transformation described in section 4.3 without further purification. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H, CH_3), 2.52 (dd, 1H, J=16, 4.7 Hz), 2.79 (dd, 1H, J=15.8, 8.4 Hz), 3.33 (s, 3H, CH_3), 4.49–4.54 (m, 2H), 4.66 (d, 1H, J=6.7 Hz), 5.19–5.21 (m, 1H), 5.25–5.30 (m, 1H), 5.66–5.75 (m, 1H).

4.3. 4-(Methoxymethyloxy)-hex-5-en-2-yl *p*-toluenesulfonate (6)

In an atmosphere of dry nitrogen, a solution of 4-(methoxymethyloxy)-hex-5-en-2-one (**4**) (109 mmol) in dry diethyl ether

(120 mL) was added in a dropwise manner to a suspension of $LiAlH_4$ (4.58 g, 121 mmol) in dry diethyl ether (150 mL) at 0 °C. The mixture was stirred for 16 h at 22 °C and then treated in intervals of 20 min successively with water (4.60 mL), aq NaOH [4.60 mL, 10% (w/w)], and water (13.6 mL), while stirring is continued at a temperature of 22 °C. The colorless precipitate, which formed was removed by filtration, and subsequently washed with diethyl ether (2×50 mL). Combined filtrate and washings were dried ($MgSO_4$) and concentrated under reduced pressure (600 mbar, 40 °C). The remaining oil was purified by column chromatography [SiO_2, diethyl ether/pentane=1:2 (v/v)]. Yield: 3.12 g (19.5 mmol, 18% over two steps), pale yellow oil, 30:70 mixture of diastereomers, R_f=0.12 [diethyl ether/pentane=1:2 (v/v)]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.17–1.21 (m, 3H, CH_3), 1.54–1.85 (m, 2H, CH_2), 2.91 (s, 1H, OH), 3.39 (s, 3H), 3.97–4.09 (m, 1H), 4.20–4.31 (m, 1H), 4.51–4.58 (m, 1H), 4.66–4.75 (m, 1H), 5.16–5.27 (m, 2H), 5.57–5.84 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3, 23.5, 43.9, 44.1, 55.7 (2C), 64.3, 67.0, 75.4, 77.5, 93.4, 94.3, 116.8, 117.9, 137.5, 137.7. MS (EI) *m/z* 159 (1) [M^+], 101 (92), 84 (22), 73 (20), 55 (49), 45 (100). *p*-Toluenesulfonyl chloride (5.57 g, 29.2 mmol) was added to a solution of 4-(methoxymethyloxy)-hex-5-en-2-ol (**5**) (3.12 g, 19.5 mmol) and DABCO (4.37 g, 38.9 mmol) in dichloromethane (60 mL) at 0 °C. The mixture was stirred for 13 h at 22 °C. Solids were removed by filtration and washed with dichloromethane (2×20 mL). Combined filtrate and organic washings were treated with aq hydrochloric acid (2 N, 2×40 mL), a satd aq solution of $NaHCO_3$ (40 mL), and brine (40 mL). The organic solution containing the title compound was dried ($MgSO_4$) and concentrated under reduced pressure (600 mbar, 40 °C) to leave an oil, which was purified by chromatography [SiO_2, diethyl ether/pentane=1:2 (v/v)]. Yield: 5.13 g (16.3 mmol, 84%), pale yellow oil, 31:69 mixture of diastereomers A and B, R_f=0.27 [diethyl ether/pentane=1:2 (v/v)]. *Diastereomer A*: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, 3H, *J*=6.4 Hz), 1.72–1.82 (m, 2H), 2.44 (s, 3H), 3.37 (s, 3H), 3.93–4.15 (m, 1H), 4.43–4.49 (m, 1H), 4.58–4.63 (m, 1H), 4.84–4.97 (m, 1H), 5.06–5.19 (m, 2H), 5.47–5.71 (m, 1H), 7.33 (d, 2H, *J*=8.2 Hz), 7.77–7.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.8, 21.4, 43.0, 55.9, 74.4, 77.3, 94.6, 117.5, 127.6, 129.8, 134.7, 137.8, 144.5. *Diastereomer B*: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (d, 3H, *J*=6.3 Hz), 1.58–1.68 (m, 1H), 2.03 (dt, 1H, J_t=14.0 Hz, J_d=7.0 Hz), 2.44 (s, 3H), 3.31 (s, 3H), 3.93–4.15 (m, 1H), 4.43–4.49 (m, 1H), 4.58–4.63 (m, 1H), 4.76 (q, 1H, *J*=6.4 Hz), 5.06–5.19 (m, 2H), 5.47–5.71 (m, 1H), 7.33 (d, 2H, *J*=8.2 Hz), 7.77–7.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.8, 21.6, 42.2, 55.6, 73.8, 77.4, 93.6, 118.6, 127.7, 129.7, 134.5, 136.9, 144.5. Anal. calcd. for $C_{15}H_{22}O_5S$ (314.40): C, 57.30; H, 7.05; S, 10.20. Found: C, 57.20; H, 6.92; S, 10.20.

4.4. 3-(4-Hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione (1)

To a solution of 3-hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt[6] (7.58 g, 27.4 mmol) in anhydrous DMF (20 mL) was added at 22 °C 4-(methoxymethyloxy)-hex-5-en-2-yl tosylate (**6**) (5.13 g, 16.3 mmol) in anhydrous DMF (20 mL). The mixture was stirred for 4 days at 22 °C in the dark. Water (80 mL) was added and the resulting mixture was extracted with diethyl ether (100 mL and 2×50 mL). Combined organic extracts were washed with aq sodium hydroxide (2 N, 2×50 mL) and brine (50 mL). The organic solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C) to leave an oil, which was purified by chromatography (SiO_2, diethyl ether). Yield: 3.98 g (13.8 mmol, 84%), yellow oil, 32:68 mixture of diastereomers A and B, R_f=0.50 (diethyl ether). *Diastereomer A*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.34 (d, 3H, *J*=6.4 Hz, CH_3), 1.71–1.78 (m, 1H, CH_2), 2.14–2.20 (m, 1H, CH_2), 2.23 (s, 3H, CH_3), 3.36 (s, 3H, CH_3), 4.18–4.28 (m, 1H), 4.50 (d, 1H, *J*=6.7 Hz), 4.66 (d, 1H, *J*=7.0 Hz), 5.20–5.32 (m, 2H), 5.48–5.57 (m, 1H), 5.67–5.79 (m, 1H), 6.16 (d, 1H, *J*=0.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.3, 40.7, 55.8, 74.1, 79.1, 93.8, 102.7, 118.1, 137.5, 138.9, 180.9. *Diastereomer B*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 3H, *J*=6.3 Hz, CH_3), 1.84–1.91 (m, 1H, CH_2), 1.98–2.05 (m, 1H, CH_2), 2.23 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 4.18–4.28 (m, 1H), 4.63 (d, 1H, *J*=6.7 Hz), 4.72 (d, 1H, *J*=6.3 Hz), 5.20–5.32 (m, 2H), 5.48–5.57 (m, 1H), 5.67–5.79 (m, 1H), 6.16 (d, 1H, *J*=0.9 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.0, 41.1, 55.9, 74.7, 78.8, 94.6, 102.7, 117.7, 137.9, 138.9, 180.9. Anal. calcd. for $C_{12}H_{19}NO_3S_2$ (289.41): C, 49.80; H, 6.62; N, 4.84; S, 22.16. Found: C, 49.48; H, 6.45; N, 4.73; S, 22.10.

3-(4-Methoxymethyloxyhex-5-en-2-oxy)-4-methylthiazole-2(3*H*)-thione (3.98 g, 13.8 mmol) was dissolved in methanol (30 mL) and treated at 22 °C with aq concentrated hydrochloric acid [2.5 mL, 37% (w/w)]. The reaction mixture was stirred for 20.5 h at 22 °C and treated thereafter with water (40 mL). The mixture was extracted with diethyl ether (3×30 mL). Combined organic extracts were washed with a satd aq solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure (600 mbar, 40 °C) to afford a residue, which was purified by chromatography [SiO_2, diethyl ether/dichloromethane/pentane=1:1:2 (v/v/v)]. *rel-(2S,4R)-3-(4-Hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3H)-thione rel-(2S,4R)-(**1**)*. Yield: 1.94 g (7.91 mmol, 58%), pale yellow oil, R_f=0.25 [diethyl ether/dichloromethane/pentane=1:1:2 (v/v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 3H, *J*=6.1 Hz), 1.67–1.74 (m, 1H, CH_2), 1.85–1.92 (m, 1H, CH_2), 2.26 (s, 3H, CH_3), 4.00 (br s, 1H, OH), 4.69–4.72 (m, 1H), 5.11 (d, 1H, *J*=10.5 Hz), 5.32 (d, 1H, *J*=17.1 Hz), 5.46–5.54 (m, 1H), 5.91 (ddd, 1H, *J*=17.2, 10.6, 5.3 Hz), 6.26 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.5, 42.9, 67.1, 78.1, 103.5, 114.2, 139.3, 139.8, 180.8. Anal. calcd. for $C_{10}H_{15}NO_2S_2$ (245.35): C, 48.95; H, 6.16; N, 5.71; S, 26.13. Found: C, 48.90; H, 6.09; N, 5.80; S, 26.04. *rel-(2S,4S)-3-(4-Hydroxyhex-5-en-2-oxy)-4-methylthiazole-2(3H)-thione rel-(2S,4S)-(**1**)*. Yield: 826 mg (3.37 mmol, 25%), pale yellow oil, R_f=0.15 [diethyl ether/dichloromethane/pentane=1:1:2 (v/v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, 3H, *J*=6.2 Hz), 1.78–1.83 (m, 1H), 2.00 (dt, 1H, J_d=15.1 Hz, J_t=8.9 Hz), 2.26 (d, 3H, *J*=1.0), 3.34 (br s, 1H, OH), 4.59–4.61 (m, 1H), 5.11 (dt, 1H, J_d=10.5 Hz, J_t=1.6 Hz), 5.32 (dt, 1H, J_d=17.1 Hz, J_t=1.7 Hz), 5.52–5.60 (m, 1H), 5.91–6.00 (m, 1H), 6.22 (d, 1H, *J*=1.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.8, 42.6, 70.9, 81.3, 103.2, 114.6, 139.1, 140.0, 180.8. Anal. calcd. for $C_{10}H_{15}NO_2S_2$ (245.35): C, 48.95; H, 6.16; N, 5.71; S, 26.13. Found: C, 49.25; H, 6.34; N, 5.52; S, 25.94.

4.5. Bromocyclizations

4.5.1. General method for thermally initiated radical reactions. Bromotrichloromethane (8 equiv) and 2,2′-azobis(2-methylpropionitrile) (0.25 equiv) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv, c^0=175 mM) in benzene. The solution was refluxed for 2 h. The solvent was removed under reduced pressure (200 mbar, 40 °C) and the residue purified by chromatography [SiO_2, diethyl ether/pentane=1:1 (v/v)].

4.5.2. General method for photochemically initiated reactions. Bromotrichloromethane (10 equiv) was added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv, c^0=175 mM) in benzene and the solution was photolyzed (350 nm) for 1.5 h. The solvent was removed under reduced pressure (200 mbar, 40 °C) and the residue purified by chromatography [SiO_2, diethyl ether/pentane=1:1 (v/v)].

*4.5.3. Thermally induced bromocyclization of rel-(2S,4R)-3-(4-hydroxyhex-5-en-2-oxy)-thiazolethione rel-(2S,4R)-**1**.* From bromotrichloromethane (3.17 g, 16.0 mmol), 2,2′-azobis(2-

methylpropionitrile) (83 mg, 0.50 mmol), and thiazolethione *rel*-(2*S*,4*R*)-**1** (494 mg, 2.01 mmol) in benzene (11.5 mL) according to procedure 4.5.1. *4-Methyl-2-(trichloromethylsulfanyl)-thiazole* (**2**). Yield: 478 mg (1.92 mmol, 96%), orange oil, R_f=0.55 [diethyl ether/pentane=1:1 (v/v)]. NMR data agreed with reference values from an authentic sample.[6] *rel-(2S,4R,5R)-5-Bromo-2-methyltetrahydropyran-4-ol rel-(2S,4R,5R)-(**7b**)*. Yield (determined versus bromobenzaldehyde as internal NMR-standard): 21 mg (0.11 mmol, 6%), yellow oil, R_f=0.27 [diethyl ether/pentane=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (d, 3H, J=6.1 Hz, CH_3), 1.40–1.49 (m, 1H, CH_2), 2.13 (ddd, 1H, J=13.2, 4.8, 2.0 Hz, CH_2), 3.46–3.52 (m, 1H), 3.56–3.64 (m, 1H), 3.71–3.85 (m, 2H), 4.09 (dd, 1H, J=11.5, 4.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 42.1, 55.0, 70.5, 73.1, 73.3. HRMS (EI$^+$) *m*/*z* 193.9957/195.9928 [M$^+$]; calculated mass for $C_6H_{11}O_2Br^+$: 193.9942/195.9922. *rel-(2S,3R,5S)-2-Bromomethyl-5-methyltetrahydrofuran-3-ol rel-(2S,3R,5S)-(**3a**)*. Yield: 92 mg (0.47 mmol, 23%), yellow oil, R_f=0.23 [diethyl ether/pentane=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (d, 3H, J=5.9 Hz, CH_3), 1.57 (ddd, 1H, J=13.7, 6.7, 2.7 Hz), 2.08 (br s, 1H, OH), 2.38–2.46 (m, 1H), 3.48–3.58 (m, 2H), 3.87–3.93 (m, 1H), 4.00–4.07 (m, 1H), 4.41–4.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 29.2, 42.5, 72.6, 74.7, 82.2. MS (EI) *m*/*z* 181/179 (1/1), 137/135 (6/8), 114 (21), 101 (22), 71 (60), 57 (100). HRMS (EI$^+$) *m*/*z* 193.9948/195.9925 [M$^+$]; calculated mass for $C_6H_{11}O_2Br^+$: 193.9942/195.9922. *rel-(2R,3R,5S)-2-Bromomethyl-5-methyltetrahydrofuran-3-ol rel-(2R,3R,5S)-(**3b**)*. Yield: 154 mg (0.79 mmol, 39%), yellow oil, R_f=0.18 [diethyl ether/pentane=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 3H, J=6.3 Hz, CH_3), 1.66 (dt, 1H, J_d=12.7 Hz, J_t=7.5 Hz), 2.12 (br s, 1H, OH), 2.40 (dt, 1H, J_d=12.8 Hz, J_t=6.3 Hz), 3.37–3.41 (m, 1H), 3.45–3.49 (m, 1H), 4.02–4.06 (m, 1H), 4.19–4.27 (m, 1H), 4.33–4.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.7, 33.5, 42.3, 74.7, 76.0, 83.5. MS (EI) *m*/*z* 181/179 (3/3), 137/135 (5/6), 114 (18), 101 (46), 71 (50), 57 (100). Anal. calcd. for $C_6H_{11}BrO_2$ (195.06): C, 36.95; H, 5.68. Found: C, 36.95; H, 5.62. *rel-(2S,4R,5S)-5-Bromo-2-methyltetrahydropyran-4-ol rel-(2S,4R,5S)-(**7a**)*. Yield (determined versus bromobenzaldehyde as internal NMR-standard): 18 mg (0.09 mmol, 4%), yellow oil, R_f=0.08 [diethyl ether/pentane=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, J=6.1 Hz, CH_3), 1.60–1.70 (m, 1H), 1.74–1.79 (m, 1H), 2.02 (br s, 1H, OH), 3.46–3.52 (m, 1H), 3.54–3.62 (m, 1H), 3.82 (dd, 1H, J=13.4, 1.6 Hz), 4.20 (dd, 1H, J=13.4, 1.9 Hz), 4.40–4.42 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 38.1, 58.7, 68.3, 70.5, 73.1. HRMS (EI$^+$) *m*/*z* 193.9962/195.9943 [M$^+$]; calculated mass for $C_6H_{11}O_2Br^+$: 193.9942/195.9922.

*4.5.4. Photochemically initiated bromocyclization of rel-(2S,4R)-3-(4-hydroxyhex-5-en-2-oxy)-thiazolethione rel-(2S,4R)-**1***. From bromotrichloromethane (3.97 g, 20.0 mmol) and 3-alkenoxythiazole-2(3*H*)-thione *rel*-(2*S*,4*R*)-**1** (498 mg, 2.03 mmol) in benzene (11.5 mL) according to procedure 4.5.2. *4-Methyl-2-(trichloromethylsulfanyl)-thiazole* (**2**). Yield: 433 mg (1.74 mmol, 86%), orange oil, R_f=0.58 [diethyl ether/pentane=1:1 (v/v)]. NMR data agreed with values from an authentic sample.[6] *rel-(2S,4R,5R)-5-Bromo-2-methyltetrahydropyran-4-ol rel-(2S,4R,5R)-(**7b**)*. Yield (determined versus bromobenzaldehyde as internal NMR-standard): 14 mg (0.07 mmol, 4%), yellow oil, R_f=0.37 [diethyl ether/pentane=1:1 (v/v)]. NMR data agreed with values from an authentic sample. *rel-(2S,3R,5S)-2-Bromomethyl-5-methyltetrahydrofuran-3-ol rel-(2S,3R,5S)-(**3a**)*. Yield: 68 mg (0.35 mmol, 15%), yellow oil, R_f=0.28 [diethyl ether/pentane=1:1 (v/v)]. NMR data agreed with values from an authentic sample. *rel-(2R,3R,5S)-2-Bromomethyl-5-methyltetrahydrofuran-3-ol rel-(2R,3R,5S)-(**3b**)*. Yield: 113 mg (0.58 mmol, 29%), yellow oil, R_f=0.15 [diethyl ether/pentane=1:1 (v/v)]. NMR data agreed with values from an authentic sample. *rel-(2S,4R,5S)-5-Bromo-2-methyltetrahydropyran-4-ol rel-(2S,4R,5S)-(**7a**)*. Yield (determined versus bromobenzaldehyde as internal NMR-standard): 12 mg (0.06 mmol, 3%), yellow oil, R_f=0.12 [diethyl ether/pentane=1:1 (v/v)]. NMR data agreed with values from an authentic sample. *rel-(2S,4R)-3-(4-Hydroxyhex-5-en-2-oxy)-thiazole-2(3H)-thione rel-(2S,4R)-(**1**)*. Yield: 32 mg (0.13 mmol, 6%), yellow oil, R_f=0.12 [diethyl ether/pentane=1:1 (v/v)]. NMR data agreed with values from an authentic sample.

*4.5.5. Thermally initiated bromocyclization of rel-(2S,4S)-3-(4-hydroxyhex-5-en-2-oxy)-thiazolethione rel-(2S,4S)-**1***. From bromotrichloromethane (3.06 g, 15.4 mmol), 2,2′-azobis(2-methylpropionitrile) (83 mg, 0.51 mmol), and 3-alkenoxythiazole-2(3*H*)-thione *rel*-(2*S*,4*S*)-**1** (474 mg, 1.93 mmol) in benzene (11 mL) according to procedure 4.5.1. *4-Methyl-2-(trichloromethylsulfanyl)-thiazole* (**2**). Yield: 318 mg (1.63 mmol, 84%), orange oil, R_f=0.46 [diethyl ether/pentane=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53 (s, 3H), 7.29 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.0, 96.7, 122.6, 153.1, 155.3. *rel-(2R,3S,5S)-2-Bromomethyl-5-methyltetrahydrofuran-3-ol rel-(2R,3S,5S)-(**3c**)*. Yield: 181 mg (0.93 mmol, 48%), yellow oil, R_f=0.18 [diethyl ether/pentane=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, 3H, J=5.9 Hz, CH_3), 1.74 (ddd, 1H, J=13.4, 10.1, 4.7 Hz), 1.96 (br s, 1H, OH), 2.14 (dd, 1H, J=13.3, 5.5 Hz), 3.44–3.53 (m, 2H), 4.21 (ddd, 1H, J=9.1, 5.6, 3.3 Hz), 4.38–4.47 (m, 1H), 4.53 (t, 1H, J=3.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 29.2, 43.1, 72.9, 75.0, 81.6. Anal. calcd. for $C_6H_{11}BrO_2$ (195.06): C, 36.95; H, 5.68. Found: C, 37.01; H, 5.47. MS (EI) *m*/*z* 181/179 (1/1), 137/135 (4/5), 114 (21), 101 (20), 71 (58), 57 (100). *rel-(2S,3S,5S)-2-Bromomethyl-5-methyltetrahydrofuran-3-ol rel-(2S,3S,5S)-(**3d**)*. Yield: 72.0 mg (0.37 mmol, 19%), yellow oil, R_f=0.15 [diethyl ether/pentane=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, 3H, J=6.3 Hz, CH_3), 1.73 (ddd, 1H, J=13.3, 10.0, 6.5 Hz), 1.98 (ddd, 1H, J=13.3, 5.3, 1.8 Hz), 2.08 (br s, 1H, OH), 3.30 (dd, 1H, J=10.4, 7.2 Hz), 3.47 (dd, 1H, J=10.4, 4.5 Hz), 3.96–4.00 (m, 1H), 4.27–4.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 33.2, 42.6, 75.2, 76.0, 85.9. Anal. calcd. for $C_6H_{11}BrO_2$ (195.06): C, 36.95; H, 5.68. Found: C, 36.78; H, 5.72. MS (EI) *m*/*z* 181/179 (1/1), 137/135 (4/4), 114 (14), 101 (43), 71 (49), 57 (100). The yields for the tetrahydropyrans **7c**,**d** were determined via proton-NMR, based on integral intensity of the methyl doublets, using pentachlorobenzene as internal standard. Yield (**7c** and **7d**): 2%. The tetrahydropyran with the smaller retention time is arbitrarily abbreviated as **7c** and the compound with the higher retention time **7d**. High resolution mass spectra were recorded from the experiment outlined in Table 3, entry 2. HRMS (**7c**) (EI$^+$) *m*/*z* 193.9956/195.9931 [M$^+$]; calculated mass for $C_6H_{11}O_2Br^+$: 193.9942/195.9922. HRMS (**7d**) (EI$^+$) *m*/*z* 193.9941/195.9931 [M$^+$]; calculated mass for $C_6H_{11}O_2Br^+$: 193.9942/195.9922.

4.6. Isomuscarines

4.6.1. General method. In a pressure-proof-screw-cooped Schlenk-tube, 2-bromomethyl-5-methyltetrahydrofuran-3-ol was dissolved in a solution of trimethylamine in ethanol (4.2 M, 10 mL/mmol of **3**) and heated for 10 days at 60 °C. The solvent was removed under reduced pressure (150 mbar, 40 °C). The oily products were crystallized by slowly allowing diethyl ether to diffuse into a satd solution of isomuscarine bromides in ethanol. Crystals suitable for X-ray diffraction were grown from satd solutions of isomuscarine bromides in dichloromethane/pentane=1:3 (v/v).

4.6.2. N-[rel-(2R,3S,5S)-3-Hydroxy-5-methyltetrahydrofur-2-ylmethyl]-N,N,N-trimethylammonium bromide (isomuscarine bromide). From tetrahydrofuran *rel-(2S,3S,5S)-(**3d**)* (219 mg, 1.12 mmol). Yield: 224 mg (0.88 mmol, 79%), colorless needles. Mp 82 °C. ^{1}H NMR (D_2O, 400 MHz) δ 1.24 (d, 3H, J=6.1 Hz), 1.81 (ddd, 1H, J=13.6, 9.2, 6.4 Hz), 2.00 (ddd, 1H, J=13.6, 6.0, 2.7 Hz), 3.16 (s, 9H), 3.40 (dd, 1H, J=13.8, 9.7 Hz), 3.57 (dd, 1H, J=13.9, 1.2 Hz), 4.14–4.17 (m, 2H), 4.29–4.37 (m, 1H). ^{13}C NMR (D_2O, 150 MHz) δ 20.9, 40.9, 54.7 [^1J (N,CH_3)=8.0 Hz], 69.3 [^1J (N,CH_2)=5.7 Hz], 75.4, 77.4, 80.4. X-ray crystallography: $C_9H_{20}BrNO_2$ (254.17), T=301(2) K, λ=0.71073 Å, monoclinic, $P2_1/n$, a=6.412(2) Å, b=23.486(5) Å, c=8.465(2) Å,

β=102.69(2)°, Z=4, μ=3.281 mm^{-1}, completeness 98.2%, (2θ=52.72°), goodness-of-fit on F^2=0.923; final R indices [$I>2\sigma(I)$]: $R1$=0.0429, $wR2$=0.0535.

4.6.3. N-[rel-(2S,3S,5S)-3-Hydroxy-5-methyltetrahydrofur-2-ylmethyl]-N,N,N-trimethylammonium bromide (allo-isomuscarine bromide). From tetrahydrofuran *rel-(2R,3S,5S)*-(**3c**) (605 mg, 3.10 mmol). Yield: 544 mg (2.18 mmol, 70%), colorless needles. Mp 84 °C. ^{1}H NMR (D_2O, 400 MHz) δ 1.23 (d, 3H, J=6.4 Hz), 1.79 (ddd, 1H, J=13.8, 9.3, 4.8 Hz), 2.10 (ddd, 1H, J=13.7, 6.1, 1.0 Hz), 3.17 (s, 9H), 3.44 (dd, 1H, J=14.2, 8.8 Hz), 3.61–3.65 (m, 1H), 4.39–4.48 (m, 3H). ^{13}C NMR (D_2O, 150 MHz) δ 21.1, 42.2, 54.6 [^1J (N,CH_3)=8.0 Hz], 67.5 [^1J (N,CH_2)=6.8 Hz], 74.5, 75.6, 76.1. X-ray crystallography: $C_9H_{20}BrNO_2$ (254.17), T=100(2) K, λ=0.71073 Å, monoclinic, $P2_1/n$, a=6.3612(4) Å, b=22.843(1) Å, c=8.5539(5) Å, β=98.579(6)°, Z=4, μ=3.320 mm^{-1}, completeness 98.1% (2θ=52.74°), goodness-of-fit on F^2=1.067; final R indices [$I>2\sigma(I)$]: $R1$=0.0380, $wR2$=0.0926.

4.6.4. N-[rel-(2R,3R,5S)-3-Hydroxy-5-methyltetrahydrofur-2-ylmethyl]-N,N,N-trimethylammonium bromide (epi-isomuscarine bromide). From tetrahydrofuran *rel-(2S,3R,5S)*-(**3a**) (507 mg, 2.60 mmol). Yield: 476 mg (1.87 mmol, 72%), colorless needles. Mp 80 °C. ^{1}H NMR (D_2O, 400 MHz) δ 1.29 (d, 3H, J=6.1 Hz), 1.47 (ddd, 1H, J=13.9, 7.1, 2.7 Hz), 2.47 (ddd, 1H, J=14.1, 7.6, 6.8 Hz), 3.17 (s, 9H), 3.46 (dd, 1H, J=14.3, 8.9 Hz), 3.68 (dd, 1H, J=14.2, 1.2 Hz), 4.00–4.09 (m, 1H), 4.12 (dd, 1H, J=8.9, 3.1 Hz), 4.42 (ddd, 1H, J=6.7, 3.9, 2.8 Hz). ^{13}C NMR (D_2O, 150 MHz) δ 21.3, 41.9, 54.7 [^1J (N,CH_3)=8.0 Hz], 67.3 [^1J (N,CH_2)=6.8 Hz], 73.9, 76.1, 76.5. X-ray crystallography: $C_9H_{10}Br_2N_2O_3$ (354.00), T=103(2) K, λ=0.71073 Å, triclinic, $P1$, a=9.151(1) Å, b=11.564(1) Å, c=12.355(2) Å, α=98.41(1)°, β=99.31(1)°, γ=91.27(1)°, Z=4, μ=6.352 mm^{-1}, completeness to 2θ=85.5%, goodness-of-fit on F^2=0.979; final R indices [$I>2\sigma(I)$]: $R1$=0.0517, $wR2$=0.1459.

4.6.5. N-[rel-(2S,3R,5S)-3-Hydroxy-5-methyltetrahydrofur-2-ylmethyl]-N,N,N-trimethylammonium bromide (epiallo-isomuscarine bromide). From tetrahydrofuran *rel-(2R,3R,5S)*-(**3b**) (1.05 g, 5.38 mmol). Yield: 499 mg (1.96 mmol, 36%), colorless needles. Mp 84 °C. ^{1}H NMR (D_2O, 400 MHz) δ 1.27 (d, 3H, J=6.1 Hz), 1.57 (ddd, 1H, J=12.8, 8.6, 7.2 Hz), 2.41 (dt, 1H, J_d=12.8 Hz, J_t=6.5 Hz), 3.16 (s, 9H), 3.43–3.53 (m, 2H), 4.20 (td, 1H, J_t=7.0 Hz, J_d=5.0 Hz), 4.25–4.32 (m, 2H). ^{13}C NMR (D_2O, 150 MHz) δ 21.2, 40.9, 54.5 [^1J (N,CH_3)=7.6 Hz], 67.8 [^1J (N,CH_2)=6.7 Hz], 75.1, 75.9, 78.9. X-ray crystallography: $C_9H_{10}Br_2N_2O_3$ (354.00), T=105(2) K, λ=0.71073 Å, monoclinic, $P2_1/n$, a=6.180(2) Å, b=23.718(7) Å, c=8.567(2) Å, β=101.48(2)°, Z=4, μ=3.320 mm^{-1}, completeness 98.1%, (2θ=52.74), goodness-of-fit on F^2=1.067; final R indices [$I>2\sigma(I)$]: $R1$=0.0380, $wR2$=0.0926.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication [CCDC 912839 (isomuscarine bromide), CCDC 912840 (*allo*-isomuscarine bromide), CCDC 912841 (*epi*-isomuscarine bromide), CCDC 912842 (*epiallo*-isomuscarine bromide)]. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary data

Instrumentation, synthesis of 4-hydroxyhex-5-en-2-one, ^{13}C NMR spectra of 4-hydroxyhex-5-en-2-one, 4-(methoxymethyloxy)-hex-5-en-2-ol, bromocyclization products **3a, 7a** and **7b**, isomuscarine bromides, atomic coordinates, and energies of calculated (B3LYP/6-31+G**) transition structures *TS*-**IIIa**–**d**, atomic coordinates, energies, and NBO-analysis of isomuscarine equilibrium structures, and summary of geometric parameter from crystal structures and computed equilibrium structures of isomuscarines. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.085.

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3.7 Anhang

Supplementary Data for

Synthesis and Structural Charactererization of the Isomuscarines

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Contents

1 General Remarks

(i) The compound numbering in the Supplementary data is consistent with the accompanying article. (ii) Numbering of references refers exclusively to the Supplementary data. (iii) Oxygen atoms in B3LYP/6-31+G**-calculated structures (section 7) are depicted in red, carbons in gray, hydrogens in white, and nitrogens in blue.

2 Instrumentation and Solvent Purification

2.1 NMR-spectroscopy

^{1}H- and ^{13}C NMR spectra were recorded with FT-NMR DPX 200, DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale. The resonances of residual $CHCl_3$ and of the carbon in $CDCl_3$ (δ_H 7.26, δ_C 77.0) were used as internal standards. NMR shift values of isomuscarine bromides in solutions of D_2O were referenced versus 1,4-dioxane as internal standard (δ_H 3.17, δ_C 67.1).

2.2 Electron impact mass spectrometry

Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*).

2.3 High resolution mass spectrometry

Mass spectroscopy (EI, 70 eV), GCT Premier Micromass (*Waters*).

2.4 Electrospray mass spectrometry

ESI mass spectra were obtained using a Finnigan LCQ spectrometer (Thermo Electron) under the following conditions: solvent flow, 8 µL/min; ESI spray voltage, 4.1 kV; capillary temperature, 200 °C; capillary voltage, –34 or +34 V; tube lens offset, –10 or +10 V; sheath gas N_2; damping gas He. The CID-experiments were carried out in the mass analyzer region using He as collision gas and applying a resonance excitation RF-voltage (475 mV, peak to peak). Masses, charge states and isotopic envelopes were derived from the zoom scan mode [high resolution scan, resolution < 0.2 atomic mass units (amu) at 10 amu width].

2.5 Combustion analysis

Combustion analyses were performed with a vario Micro cube CHNS (*Elementar Analysentechnik / Hanau*).

2.6 Thin layer chromatography

Reaction progress was monitored via thin layer chromatography (tlc) on aluminium sheets coated with silica gel (60 F_{254}, *Merck*). Compounds on developed tlc-sheets were detected with the aid of the UV-VIS indicator commercially disposed on the sheets, becoming apparent for example by a hand lamp emitting 254 nm light. As alternative method for detecting compounds on developed tlc-sheets is staining by Ekkert´s reagent and subsequently heating, leading to blue-green spots for organobromines, blue spots for alcohols and yellow spots for radical precursors.

2.7 Gas chromatography coupled to mass spectrometry

GC/MS Analysis was performed with a HP 6890 Series (*Hewlett Packard*) system and mass detector with a HP-5MS column (*Agilent*, 30 m × 0.25 mm, 0.25 μm). Temperature program: 40 °C (3 min), 10 °C min^{-1} → 280 °C, 280 °C (10 min).

2.8 Melting points

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*) and are not corrected.

2.9 Purification of solvents

Petroleum ether refers to the fraction boiling between 40–55°C. All solvents were purified according to standard procedures.[1]

3 4-Hydroxy-5-hexen-2-one

In an atmosphere of dry nitrogen, a solution of diisopropylamine (24.5 g, 240 mmol) in dry tetrahydrofuran (175 mL) was added at –78 °C to a solution of *n*-butyl lithium in hexane (150 mL, 240 mmol, 1.6 M) over a period of 15 min. Stirring of the reaction mixture was continued for 15 min at –78 °C. To this mixture, a solution of acetone (12.8 g, 220 mmol) in dry tetrahydrofuran (70 mL) was added in a dropwise manner over a period of 10 min at –78 °C. The reaction mixture was stirred at –78 °C for additional 60 minutes and treated within 10 min in a dropwise manner at that temperature with a solution of acrolein (13.6 g, 242 mmol) in dry tetrahydrofuran (70 mL). The solution was stirred for 5 min at –78 °C and treated with a solution of satd. aq. NH_4Cl (100 mL) at –78 °C. The resulting reaction mixture was allowed to warm to 22 °C while being stirred. The layers were separated and the organic layer was washed with a solution of satd. aq. KH_2PO_4 (50 mL). The aqueous layer was extracted with diethyl ether (2 × 100 mL) and ethyl acetate (100 mL). The organic solution obtained by combining the layer from the reaction mixture and the organic washings was dried ($MgSO_4$) and concentrated under reduced pressure (600–150 mbar, 40 °C) leaving an oil which was distilled at a pressure of 16 mbar. Yield: 12.5 g (109 mmol, 50%), yellow oil. Bp 82–86 °C/16 mbar. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3 H, CH_3), 2.64 (d, 1 H, J = 2.0 Hz), 2.66 (s, 1 H), 3.09 (s, 1 H, OH), 4.53–4.57 (m, 1 H), 5.11 (d, 1 H, J = 10.6 Hz), 5.27 (d, 1 H, J = 17.2 Hz), 5.84 (ddd, 1 H, J = 16.9, 10.9, 5.5 Hz). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 30.8, 49.6, 68.5, 115.0, 138.9, 208.9.

4 Bromocyclizations Analyzed by NMR-Spectroscopy

4.1 General method for thermally initiated radical reactions: Bromotrichloromethane (10 equiv.) and 2,2′-azobis(2-methylpropionitrile) (0.25 equiv.) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv., c^0 = 82 mM) in perdeuterobenzene. The solution was refluxed for 2 hours. The yields for 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**) and 2-bromomethyl-5-methyltetrahydrofuran-3-ol (**3a**–**d**) were determined via proton-NMR using pentachlorobenzene as internal standard. The yields for 5-bromo-2-methyltetrahydropyran-4-ol (**7a**–**d**) were determined via GC using 2-bromomethyl-5-methyltetrahydrofuran-3-ol **3a**/**3b** and **3c**/**3d** as internal standard, assuming the identical response factor for bromocyclization products **3** and **7**.

4.2 General method for photochemically initiated radical reactions: Bromotrichloromethane (10 equiv.) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv., c^0 = 82 mM) in perdeuterobenzene. The solution was photolyzed (350 nm) for 1 hour. The yields for 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**) and 2-bromomethyl-5-methyltetrahydrofuran-3-ol (**3a**–**d**) were determined via proton-NMR using pentachlorobenzene as internal standard. The yields for 5-bromo-2-methyltetrahydropyran-4-ol (**7a**–**d**) were determined via GC using 2-bromomethyl-5-methyltetrahydrofuran-3-ol **3a**/**3b** and **3c**/**3d** as internal standard, assuming the identical response factor for bromocyclization products **3** and **7**.

4.3 General method for thermally initiated radical reaction with diethyl dibromomalonate: Diethyl dibromomalonate (8 equiv.) and 2,2′-azobis(2-methylpropionitrile) (0.25 equiv.) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione *unlike*-**1** (1 equiv., c^0 = 180 mM) in perdeuterobenzene. The solution was refluxed for 2 hours. The yields for 2-bromomethyl-5-methyltetrahydrofuran-3-ol (**3a**–**b**) were determined via proton-NMR using bromobenzaldehyd as internal standard.

5 Bromocyclizations Analyzed by GC/MS-Spectrometry

5.1 General method for thermally initiated radical reactions: Bromotrichloromethane (8 equiv.) and 2,2′-azobis(2-methylpropionitrile) (0.25 equiv.) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione *unlike*-**1** (1 equiv., c^0 = 180 mM) in chlorobenzene. The solution was refluxed for 2 hours. The yields of **3a** and **3b** were determined via quantitative GC-anaylsis performed with the aid of calibration curves. The yields of **7a** and **7b** were estimated from integrals of GC-signals, based on identical response factors for **3** and **7**.

6 Carbon-13 NMR-Spectra

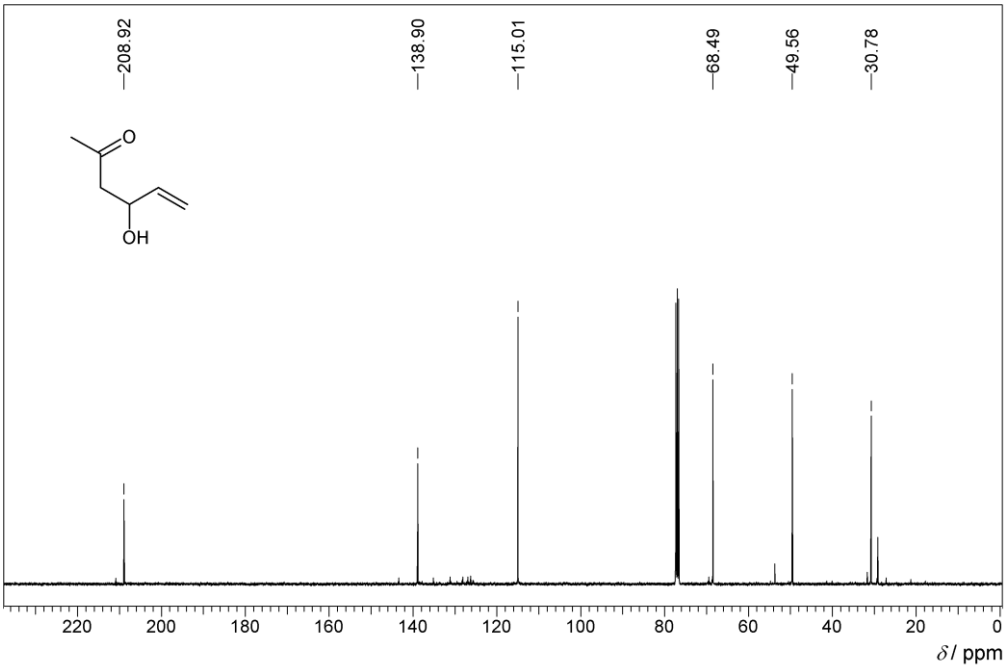

Figure S1. Carbon-13 NMR-spectrum of 4-hydroxyhex-5-en-2-one ($CDCl_3$, 20 °C, 100 MHz).

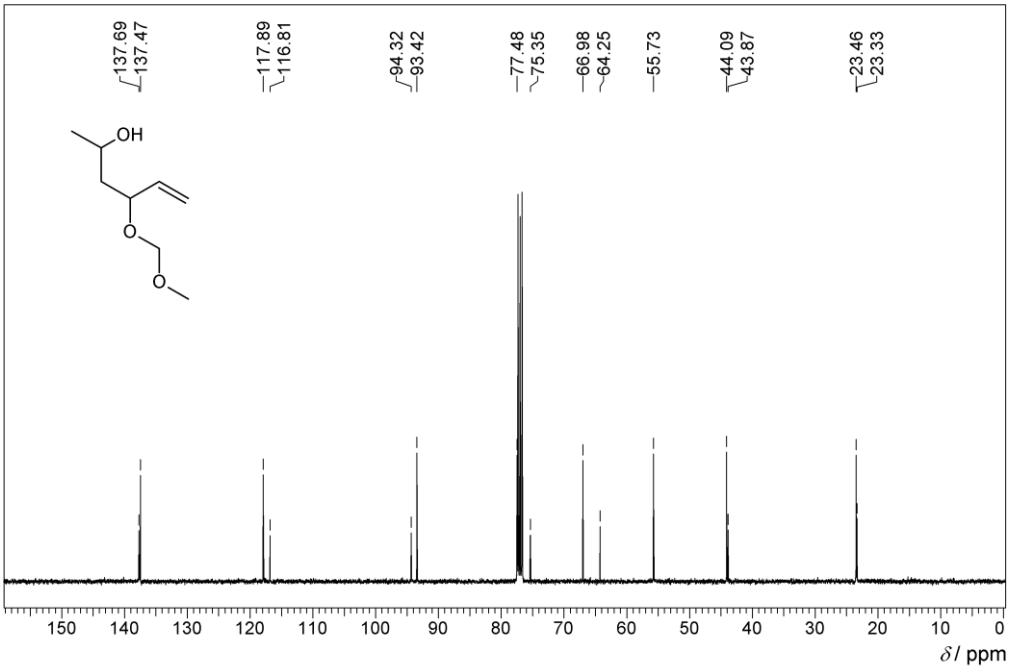

Figure S2. Carbon-13 NMR-spectrum of 4-(methoxymethyloxy)hex-5-en-2-ol ($CDCl_3$, 20 °C, 100 MHz).

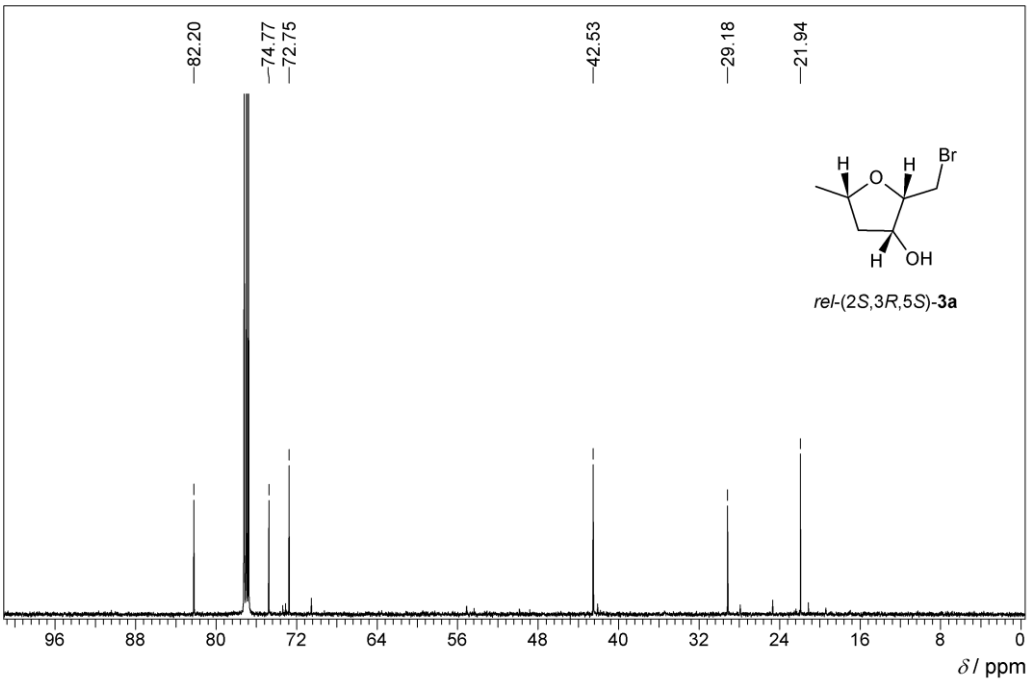

Figure S3. Carbon-13 NMR-spectrum of *rel*-(2*S*,3*R*,5*S*)-2-bromomethyl-5-methyl-tetrahydrofuran-3-ol *rel*-(2*S*,3*R*,5*S*)-(**3a**) ($CDCl_3$, 20 °C, 150 MHz).

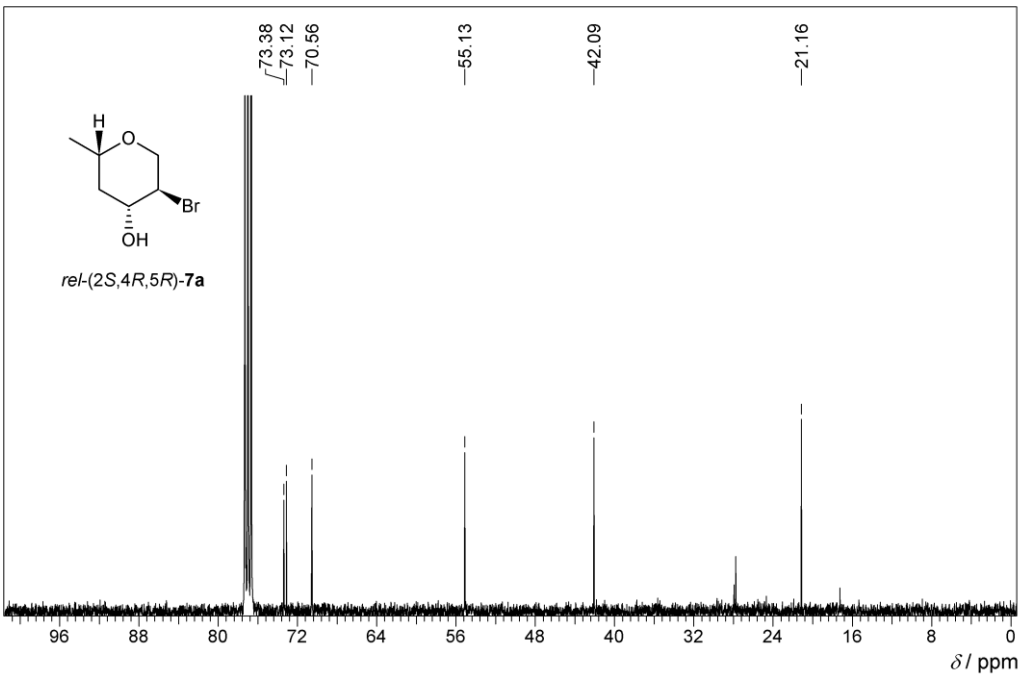

Figure S4. Carbon-13 NMR-spectrum of *rel*-(2*S*,4*R*,5*R*)-5-bromo-2-methyl-tetrahydropyran-4-ol *rel*-(2*S*,4*R*,5*R*)-(**7a**) ($CDCl_3$, 20 °C, 100 MHz).

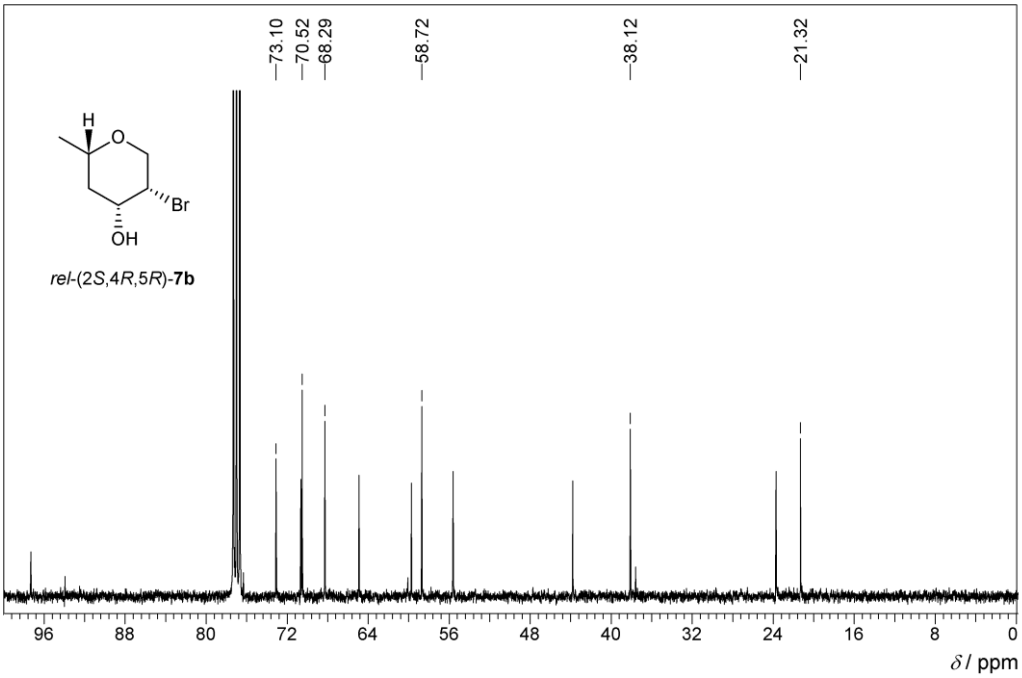

Figure S5. Carbon-13 NMR-spectrum of *rel*-(2*S*,4*R*,5*S*)-5-bromo-2-methyl-tetrahydropyran-4-ol *rel*-(2*S*,4*R*,5*S*)-(**7b**) ($CDCl_3$, 20 °C, 100 MHz).

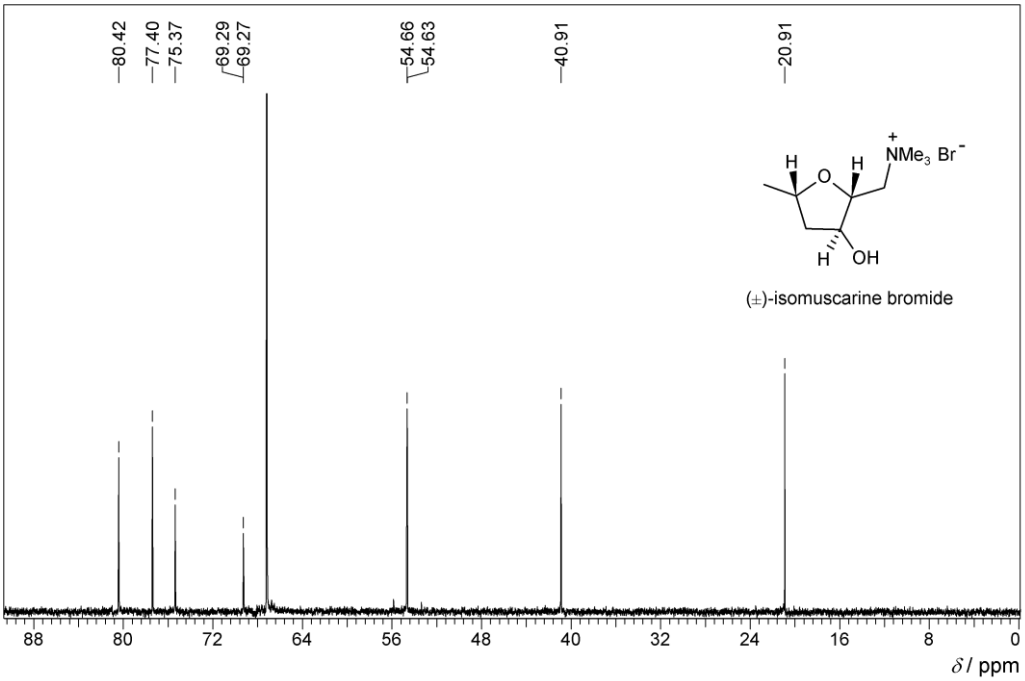

Figure S6. Carbon-13 NMR-spectrum of (±)-isomuscarine bromide (D_2O, 20 °C, 150 MHz; δ_C 67.19 = 1,4-dioxane).

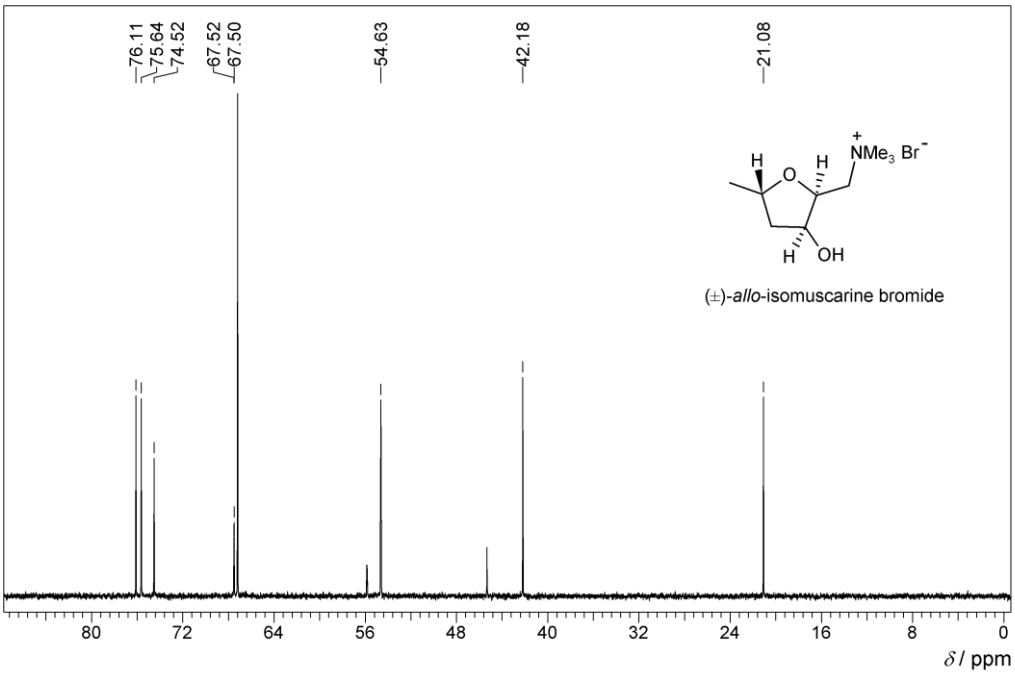

Figure S7. Carbon-13 NMR-spectrum of (±)-*allo*-isomuscarine bromide (D_2O, 20 °C, 150 MHz; δ_C 67.19 = 1,4-dioxane; δ_C 45.3 = $NHMe_3^+$).

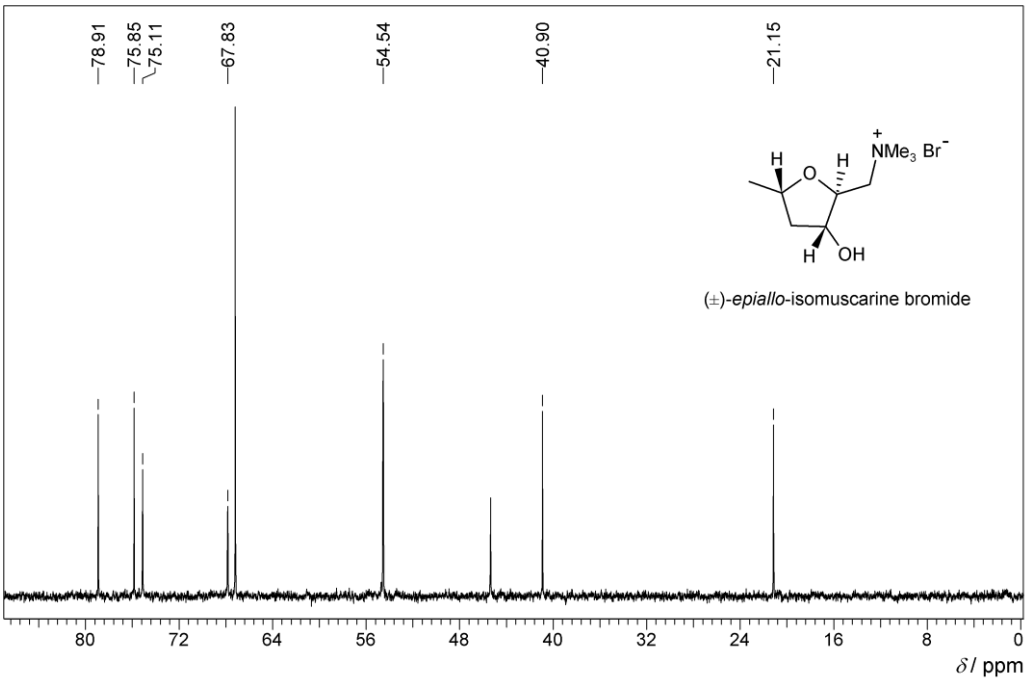

Figure S8. Carbon-13 NMR-spectrum of (±)-*epiallo*-isomuscarine bromide (D_2O, 20 °C, 150 MHz; δ_C 67.19 = 1,4-dioxane; δ_C 45.3 = $NHMe_3^+$).

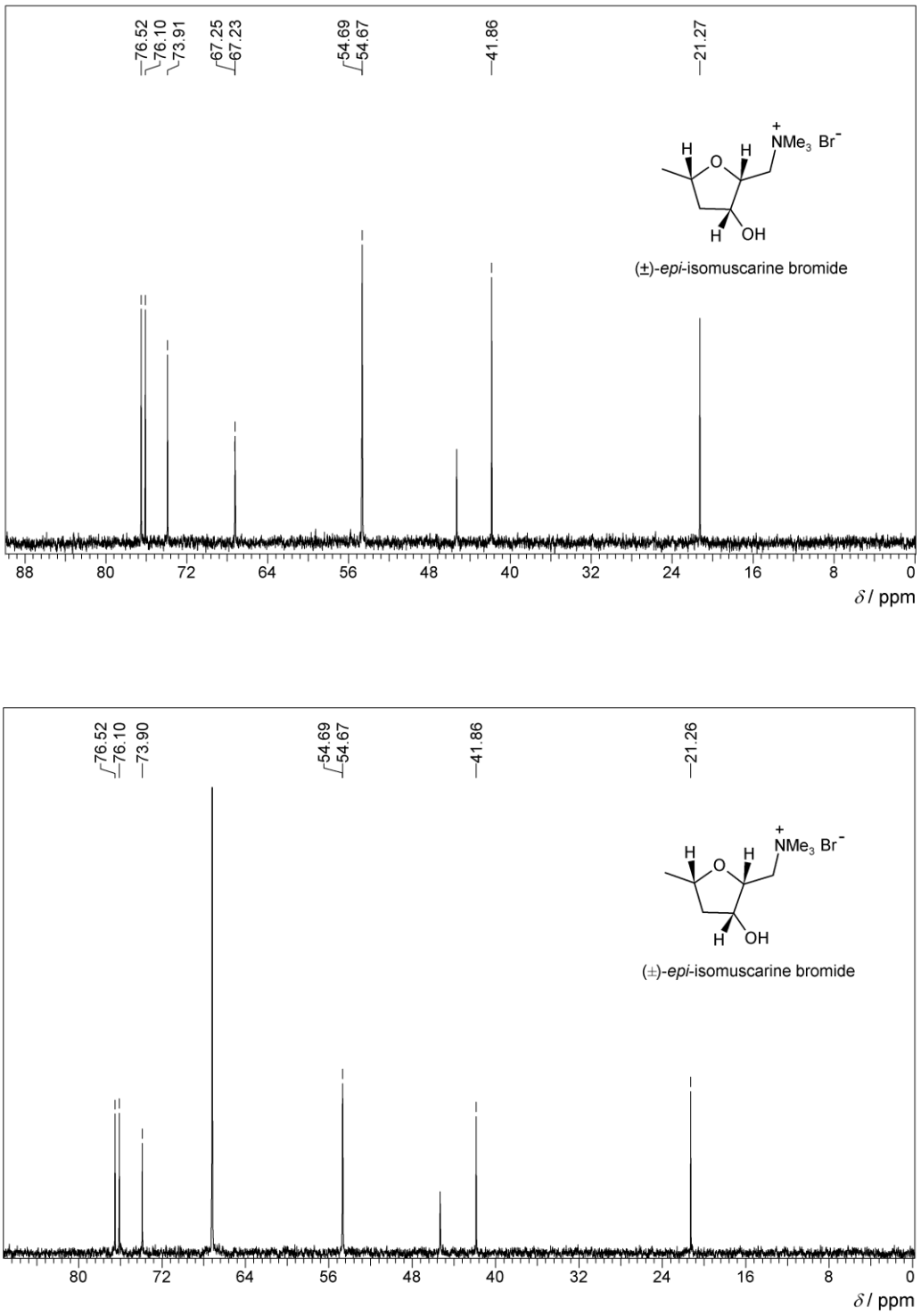

Figure S9. Carbon-13 NMR-spectrum of (±)-*epi*-isomuscarine bromide (D_2O, 20 °C, 150 MHz; spectrum on top: without 1,4-dioxane; spectrum on bottom: δ_C 67.19 = 1,4-dioxane, δ_C 45.3 = $NHMe_3^+$).

7 Computational Chemistry

All calculations were carried out with Gaussian03[2], using the density functional/Hartee-Fock hybrid model B3LYP and split valence double-ζ basis set 6-31+G(d,p). No symmetry or internal coordinate constraints were applied during energy function minimization. The ultrafine grid in combination with the tight option for energy function minimization were used.

Transition structures *TS*-**IIIa**–**d** were located with the Berny algorithm. Hessian matrices of transition structures had exactly one negative stretching mode (*i*). Animations of eigenvector coordinates using Molden[3] were performed to verify that the imaginary mode correlates with the trajectory of C,O bond formation.

Approximate Gibbs free energies ($G_{298.15}$) were obtained through thermochemical analysis for 298.15 K by unscaled frequency calculation from the thermal correction reported by Gaussian03. Likewise obtained Gibbs free energies took zero-point correction, thermal correction, and entropy into account. All transition structures were maxima on electronic potential energy hypersurface, which may not correspond to maxima on the free energy surface.

Equilibrium structures of isomuscarine cations were located with the Berny algorithm on potential hypersurfaces. Input structures were obtained from low minimum conformations calculated from a grid search (15-degree steps) for the torsional movement of the trimethylammoniummethyl side chain with respect to the tetrahydrofuran nucleus, using the modredundant option.

7.1 Transition structure *TS*-IIIa (from *unlike*-II)

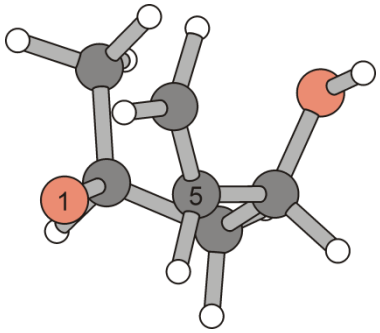

Figure S10. Depiction of transition structure *TS*-**IIIa** for the 2,3-cis-selective 5-*exo*-trig-ring closure of 4-hydroxyhex-5-en-2-oxyl radical *unlike*-**II** ($d_{O1–C5}$ = 2.031 Å).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.834289	-0.043883	1.148780
2	6	0	-1.418968	-0.259843	-0.311420
3	6	0	-0.671851	0.923069	-0.961291
4	6	0	0.801255	0.852608	-0.527023
5	6	0	1.236142	-0.603208	-0.493522
6	6	0	1.737812	-1.216096	0.630140
7	8	0	-0.631487	-1.401569	-0.509506
8	8	0	0.926769	1.513099	0.734062
9	1	0	-2.333142	-0.451339	-0.905421
10	1	0	1.418259	1.375938	-1.273964
11	1	0	-2.320151	-0.947813	1.528490
12	1	0	-0.965941	0.180972	1.772851
13	1	0	-2.538639	0.792464	1.233034
14	1	0	-0.712813	0.801435	-2.049183
15	1	0	-1.091991	1.902084	-0.708815
16	1	0	1.439909	-1.046081	-1.463575
17	1	0	2.138939	-2.222097	0.578761
18	1	0	1.639588	-0.761379	1.610005
19	1	0	1.863119	1.567694	0.967394

Zero-point correction= 0.161004 (Hartree/Particle)
Thermal correction to Energy= 0.169390
Thermal correction to Enthalpy= 0.170334
Thermal correction to Gibbs Free Energy= 0.127977
Sum of electronic and zero-point Energies= -385.474178
Sum of electronic and thermal Energies= -385.465792
Sum of electronic and thermal Enthalpies= -385.464848
Sum of electronic and thermal Free Energies= -385.507206

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7.2 Transition structure *TS*-IIIb (from *unlike*-II)

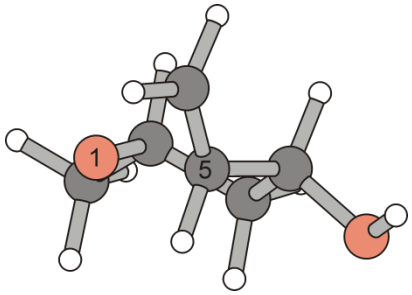

Figure S11. Depiction of transition structure *TS*-**IIIb** for the 2,3-trans-selective 5-*exo*-trig-ring closure of 4-hydroxyhex-5-en-2-oxyl radical *unlike*-**II** ($d_{O1–C5}$ = 2.030 Å).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.802782	-0.153460	-0.081628
2	6	0	-1.347555	0.068484	0.356528
3	6	0	-0.440364	-1.138307	0.107811
4	6	0	0.990894	-0.635997	0.301294
5	6	0	1.144173	0.714222	-0.379983
6	6	0	1.617721	1.818933	0.284668
7	8	0	-0.840068	1.142843	-0.398797
8	8	0	1.886353	-1.605110	-0.251664
9	1	0	-1.347541	0.317382	1.433637
10	1	0	1.191874	-0.512418	1.376748
11	1	0	-3.395832	0.748504	0.091881
12	1	0	-2.847116	-0.401554	-1.146513
13	1	0	-3.241624	-0.976300	0.493956
14	1	0	-0.656985	-1.982639	0.771684
15	1	0	-0.551887	-1.477340	-0.929233
16	1	0	1.185641	0.685491	-1.464883
17	1	0	1.833666	2.744041	-0.239202
18	1	0	1.691254	1.832432	1.369024
19	1	0	2.795751	-1.322709	-0.085538

```
 Zero-point correction=                           0.161089 (Hartree/Particle)
 Thermal correction to Energy=                    0.169656
 Thermal correction to Enthalpy=                  0.170600
 Thermal correction to Gibbs Free Energy=         0.127660
 Sum of electronic and zero-point Energies=           -385.475671
 Sum of electronic and thermal Energies=              -385.467104
 Sum of electronic and thermal Enthalpies=            -385.466160
 Sum of electronic and thermal Free Energies=         -385.509100
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7.3 Transition structure *TS*-IIIc (from *like*-II)

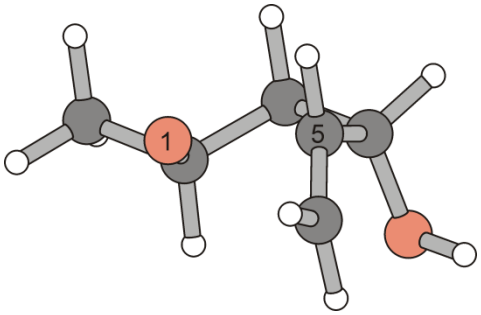

Figure S12. Depiction of transition structure *TS*-**IIIc** for the 2,3-trans-selective 5-*exo*-trig-ring closure of 4-hydroxyhex-5-en-2-oxyl radical *like*-**II** ($d_{O1–C5}$ = 2.038 Å).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.738455	0.115058	-0.223454
2	6	0	1.209769	0.030793	-0.352979
3	6	0	0.585020	-1.057087	0.529121
4	6	0	-0.930304	-0.822669	0.502490
5	6	0	-1.193248	0.671119	0.615374
6	6	0	-1.904227	1.388409	-0.315510
7	8	0	0.680006	1.261041	0.070875
8	8	0	-1.426055	-1.392627	-0.709109
9	1	0	0.957322	-0.161584	-1.408475
10	1	0	-1.399132	-1.321204	1.365295
11	1	0	3.130678	0.923241	-0.846541
12	1	0	3.026107	0.305278	0.815595
13	1	0	3.190161	-0.828258	-0.550631
14	1	0	0.814504	-2.075038	0.196537
15	1	0	0.949762	-0.932707	1.556024
16	1	0	-1.065657	1.087692	1.610094
17	1	0	-2.162549	2.425920	-0.135392
18	1	0	-2.117326	0.979565	-1.297551
19	1	0	-2.388269	-1.303955	-0.729331

Zero-point correction= 0.161233 (Hartree/Particle)
Thermal correction to Energy= 0.169691
Thermal correction to Enthalpy= 0.170635
Thermal correction to Gibbs Free Energy= 0.128048
Sum of electronic and zero-point Energies= -385.476128
Sum of electronic and thermal Energies= -385.467670
Sum of electronic and thermal Enthalpies= -385.466726
Sum of electronic and thermal Free Energies= -385.509312

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0.5732767\PG=C01 [X(C6H11O2]\NImag=1(i=-384.4266)\\@

7.4 Transition structure *TS*-IIId (from *like*-II)

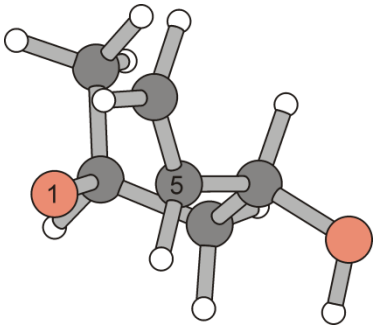

Figure S13. Depiction of transition structure *TS*-**IIId** for the 2,3-trans-selective 5-*exo*-trig-ring closure of 4-hydroxyhex-5-en-2-oxyl radical *like*-**II** ($d_{O1–C5}$ = 2.040 Å).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.199036	-0.192640	0.866067
2	6	0	1.402833	-0.434502	-0.423485
3	6	0	0.167465	-1.332011	-0.248480
4	6	0	-0.949657	-0.459754	0.350629
5	6	0	-0.922286	0.911972	-0.304266
6	6	0	-0.802388	2.070680	0.421764
7	8	0	0.971792	0.749062	-1.043670
8	8	0	-2.238752	-1.069955	0.246121
9	1	0	2.080664	-0.904999	-1.159799
10	1	0	-0.796668	-0.339382	1.427420
11	1	0	3.028785	0.490897	0.664593
12	1	0	1.574210	0.260000	1.643299
13	1	0	2.607664	-1.131616	1.258188
14	1	0	-0.156422	-1.675677	-1.240528
15	1	0	0.352803	-2.217128	0.369719
16	1	0	-1.326006	0.965588	-1.312018
17	1	0	-0.898959	3.043702	-0.047805
18	1	0	-0.523745	2.050036	1.471574
19	1	0	-2.376665	-1.356752	-0.667624

Zero-point correction= 0.160717 (Hartree/Particle)
Thermal correction to Energy= 0.169331
Thermal correction to Enthalpy= 0.170275
Thermal correction to Gibbs Free Energy= 0.127236
Sum of electronic and zero-point Energies= -385.472726
Sum of electronic and thermal Energies= -385.464112
Sum of electronic and thermal Enthalpies= -385.463168
Sum of electronic and thermal Free Energies= -385.506207

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7.5 Equilibrium structure of the isomuscarine cation

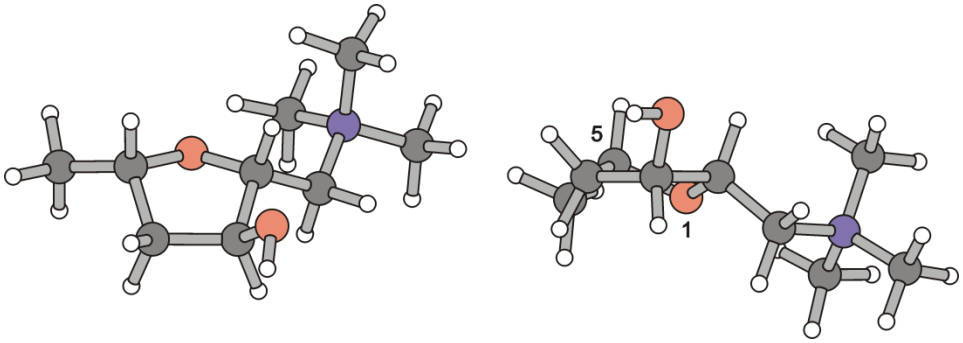
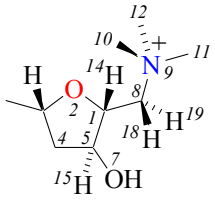


Figure S14. Projections of the calculated (B3LYP/6-31+G**) equilibrium structure of the isomuscarine cation in the gas phase (0 K).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.746573	-0.871303	0.114939
2	6	0	2.182524	-0.840561	0.368976
3	6	0	2.650877	0.390745	-0.424501
4	6	0	1.435014	1.348280	-0.427245
5	6	0	0.302890	0.471538	0.178897
6	6	0	-1.013567	0.652965	-0.559537
7	7	0	-2.211638	-0.145012	-0.027512
8	6	0	-3.462183	0.431779	-0.644354
9	6	0	-2.102350	-1.602155	-0.423978
10	6	0	-2.316638	-0.045552	1.473449
11	6	0	2.787134	-2.170537	-0.031657
12	8	0	1.541138	2.486870	0.417366
13	1	0	2.323366	-0.668259	1.446081
14	1	0	0.206845	0.799405	1.224850
15	1	0	1.192807	1.663674	-1.451804
16	1	0	2.907261	0.098578	-1.448159
17	1	0	3.525687	0.868208	0.025065
18	1	0	-1.297525	1.706818	-0.499688
19	1	0	-0.911574	0.369072	-1.609961
20	1	0	-4.315733	-0.178331	-0.347037
21	1	0	-3.595032	1.455393	-0.292564
22	1	0	-3.358825	0.419977	-1.729944
23	1	0	-2.957222	-2.135068	-0.005919
24	1	0	-2.119149	-1.666885	-1.512408
25	1	0	-1.162821	-1.996225	-0.042608
26	1	0	-3.253501	-0.509702	1.783190
27	1	0	-1.477266	-0.571470	1.925187
28	1	0	-2.308510	1.005790	1.763660
29	1	0	2.625561	-2.366517	-1.096398
30	1	0	3.864938	-2.161034	0.157913
31	1	0	2.351368	-2.989393	0.547877
32	1	0	2.156897	3.127502	0.036517

NATURAL BOND ORBITALS (Summary - atom numbering for nbo-analysis):

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==========================================================================
No. (Occupancy) Bond orbital/ Coefficients/ Hybrids
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18. (1.98240) BD ( 1) C  8- N  9
           ( 33.73%)   0.5808* C  8 s( 19.83%)p 4.04( 80.02%)d 0.01( 0.16%)
                                     0.0002  0.4445  0.0268  0.0016 -0.6708
                                    -0.0236 -0.4813 -0.0113  0.3433  0.0070
                                     0.0275 -0.0197 -0.0130  0.0109 -0.0121
           ( 66.27%)   0.8140* N  9 s( 25.38%)p 2.94( 74.58%)d 0.00( 0.04%)
                                     0.0000  0.5038 -0.0002 -0.0004  0.6884
                                    -0.0037  0.4384 -0.0010 -0.2825 -0.0005
                                     0.0149 -0.0092 -0.0065  0.0060 -0.0068
21. (1.98479) BD ( 1) N  9- C 10
           ( 66.08%)   0.8129* N  9 s( 25.06%)p 2.99( 74.89%)d 0.00( 0.05%)
                                     0.0000  0.5006  0.0023  0.0001 -0.0513
                                     0.0005  0.0609 -0.0005  0.8617  0.0013
                                    -0.0004 -0.0035  0.0027  0.0000  0.0212
           ( 33.92%)   0.5824* C 10 s( 20.70%)p 3.82( 79.12%)d 0.01( 0.18%)
                                     0.0003  0.4544  0.0226 -0.0037  0.0674
                                     0.0012 -0.0541 -0.0038 -0.8845 -0.0369
                                     0.0001 -0.0050  0.0047  0.0002  0.0413
22. (1.98503) BD ( 1) N  9- C 11
           ( 65.95%)   0.8121* N  9 s( 24.56%)p 3.07( 75.39%)d 0.00( 0.05%)
                                     0.0000 -0.4956  0.0003 -0.0004  0.7196
                                     0.0024 -0.3327  0.0017  0.3540 -0.0015
                                     0.0121 -0.0127  0.0060 -0.0108  0.0058
           ( 34.05%)   0.5835* C 11 s( 21.02%)p 3.75( 78.81%)d 0.01( 0.17%)
                                    -0.0003 -0.4580 -0.0203  0.0039 -0.7354
                                    -0.0266  0.3375  0.0152 -0.3637 -0.0153
                                     0.0229 -0.0244  0.0115 -0.0195  0.0104
23. (1.98405) BD ( 1) N  9- C 12
           ( 66.64%)   0.8163* N  9 s( 25.00%)p 3.00( 74.95%)d 0.00( 0.04%)
                                     0.0000 -0.5000 -0.0012 -0.0001 -0.0711
                                    -0.0013  0.8323  0.0004  0.2273 -0.0012
                                     0.0015  0.0003 -0.0090  0.0169  0.0081
           ( 33.36%)   0.5776* C 12 s( 20.20%)p 3.94( 79.62%)d 0.01( 0.18%)
                                    -0.0003 -0.4489 -0.0218  0.0036  0.0639
                                     0.0034 -0.8587 -0.0349 -0.2313 -0.0105
                                     0.0056  0.0019 -0.0182  0.0337  0.0168
==========================================================================
```

SECOND ORDER PERTURBATION THEORY ANALYSIS OF FOCK MATRIX IN NBO BASIS

Donor NBO (i)	Acceptor NBO (j)	kcal/mol	a.u.	a.u.
1. BD (1) C 1- O 2	260. BD*(1) C 5- O 7	0.74	1.12	0.026
2. BD (1) C 1- C 5	266. BD*(1) C 8- N 9	4.64	0.79	0.054
4. BD (1) C 1- H14	260. BD*(1) C 5- O 7	1.61	0.82	0.032
12. BD (1) C 5- O 7	249. BD*(1) C 1- O 2	0.96	1.11	0.029
19. BD (1) C 8- H18	249. BD*(1) C 1- O 2	4.60	0.86	0.056

Zero-point correction= 0.294121
(Hartree/Particle)
Thermal correction to Energy= 0.307765
Thermal correction to Enthalpy= 0.308709
Thermal correction to Gibbs Free Energy= 0.253984
Sum of electronic and zero-point Energies= -559.709427
Sum of electronic and thermal Energies= -559.695783
Sum of electronic and thermal Enthalpies= -559.694839
Sum of electronic and thermal Free Energies= -559.749564

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7.6 Equilibrium structure of the *allo*-isomuscarine cation

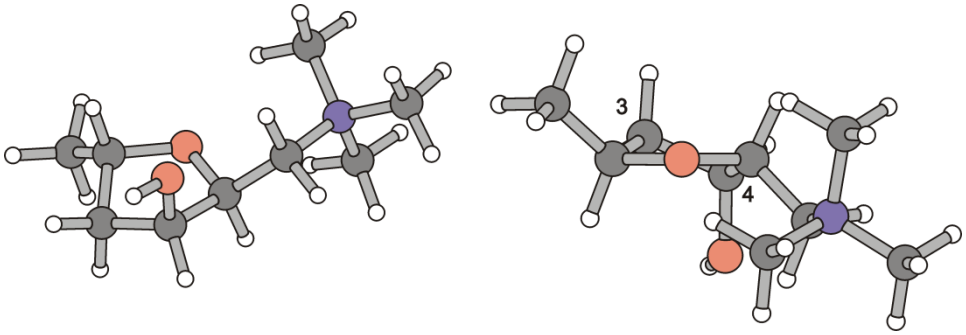
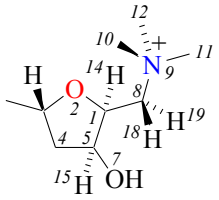


Figure S15. Projections of the calculated (B3LYP/6-31+G**) equilibrium structure of the *allo*-isomuscarine cation in the gas phase (0 K).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.757958	-0.808667	-0.051005
2	6	0	-2.176461	-0.682855	-0.404640
3	6	0	-2.656836	0.518591	0.416332
4	6	0	-1.419320	1.421289	0.482881
5	6	0	-0.296783	0.366028	0.612667
6	6	0	1.027148	0.860373	0.031615
7	7	0	2.163191	-0.170521	-0.015920
8	6	0	3.458438	0.582255	-0.195044
9	6	0	2.238676	-0.981895	1.251818
10	6	0	1.985450	-1.105463	-1.194098
11	6	0	-2.880976	-1.998663	-0.132169
12	8	0	-1.199259	2.151295	-0.723566
13	1	0	-2.216634	-0.445365	-1.474683
14	1	0	-0.171660	0.143794	1.682187
15	1	0	-1.428165	2.098577	1.345907
16	1	0	-2.943363	0.204541	1.427421
17	1	0	-3.514298	1.025133	-0.035725
18	1	0	0.890223	1.215770	-0.989319
19	1	0	1.391791	1.689643	0.643622
20	1	0	4.268203	-0.135682	-0.329917
21	1	0	3.376615	1.219908	-1.075869
22	1	0	3.643747	1.191392	0.690261
23	1	0	3.129697	-1.609065	1.206702
24	1	0	2.307162	-0.305632	2.104945
25	1	0	1.348996	-1.605487	1.326769
26	1	0	2.804094	-1.826264	-1.184753
27	1	0	1.020168	-1.597131	-1.099060
28	1	0	2.018440	-0.514941	-2.110192
29	1	0	-2.832492	-2.257709	0.930343
30	1	0	-3.933735	-1.925511	-0.424317
31	1	0	-2.429423	-2.809916	-0.710279
32	1	0	-1.889984	2.818610	-0.832217

NATURAL BOND ORBITALS (Summary - atom numbering for nbo-analysis):




```
==========================================================================
No. (Occupancy) Bond orbital/ Coefficients/ Hybrids
==========================================================================
18. (1.98220) BD ( 1) C  8- N  9
           ( 33.54%)   0.5792* C  8 s( 19.83%)p 4.04( 80.01%)d 0.01( 0.16%)
                                    -0.0002 -0.4445 -0.0268 -0.0017 -0.6328
                                    -0.0234  0.6315  0.0160  0.0047  0.0015
                                     0.0345 -0.0001 -0.0004 -0.0022  0.0203
           ( 66.46%)   0.8152* N  9 s( 25.50%)p 2.92( 74.46%)d 0.00( 0.04%)
                                     0.0000 -0.5050  0.0005  0.0005  0.6550
                                    -0.0038 -0.5604  0.0014 -0.0387  0.0011
                                      0.0176  0.0016 -0.0011 -0.0016  0.010
21. (1.98387) BD ( 1) N  9- C 10
           ( 66.65%)   0.8164* N  9 s( 24.94%)p 3.01( 75.01%)d 0.00( 0.04%)
                                     0.0000 -0.4994 -0.0012 -0.0001  0.1114
                                     0.0018  0.5336  0.0009  0.6731 -0.0008
                                    -0.0020 -0.0022 -0.0174  0.0071 -0.0086
           ( 33.35%)   0.5775* C 10 s( 20.16%)p 3.95( 79.66%)d 0.01( 0.18%)
                                    -0.0003 -0.4485 -0.0215  0.0036 -0.1049
                                    -0.0046 -0.5520 -0.0218 -0.6925 -0.0286
                                    -0.0055 -0.0074 -0.0350  0.0134 -0.0171
22. (1.98511) BD ( 1) N  9- C 11
           ( 65.91%)   0.8118* N  9 s( 24.48%)p 3.08( 75.47%)d 0.00( 0.05%)
                                     0.0000  0.4948 -0.0004  0.0004  0.7461
                                     0.0026  0.4335 -0.0021 -0.1003  0.0004
                                     0.0162 -0.0037 -0.0022  0.0100 -0.0109
           ( 34.09%)   0.5839* C 11 s( 21.06%)p 3.74( 78.76%)d 0.01( 0.17%)
                                     0.0003  0.4585  0.0200 -0.0039 -0.7611
                                    -0.0277 -0.4422 -0.0193  0.1079  0.0041
                                     0.0310 -0.0074 -0.0044  0.0175 -0.0201
23. (1.98518) BD ( 1) N  9- C 12
           ( 65.97%)   0.8122* N  9 s( 25.08%)p 2.99( 74.88%)d 0.00( 0.05%)
                                     0.0000 -0.5008 -0.0028 -0.0002 -0.0345
                                     0.0012  0.4612  0.0010 -0.7313 -0.0011
                                     0.0014 -0.0027  0.0169  0.0053 -0.0123
           ( 34.03%)   0.5834* C 12 s( 20.75%)p 3.81( 79.08%)d 0.01( 0.17%)
                                    -0.0003 -0.4549 -0.0225  0.0037  0.0486
                                     0.0006 -0.4827 -0.0189  0.7443  0.0320
                                     0.0023 -0.0027  0.0329  0.0105 -0.0233
==========================================================================
```

SECOND ORDER PERTURBATION THEORY ANALYSIS OF FOCK MATRIX IN NBO BASIS

Donor NBO (i)	Acceptor NBO (j)	kcal/mol	a.u.	a.u.
2. BD (1) C 1- C 5	266. BD*(1) C 8- N 9	4.09	0.81	0.051
4. BD (1) C 1- H14	260. BD*(1) C 5- O 7	3.21	0.81	0.046
9. BD (1) C 4- C 5	249. BD*(1) C 1- O 2	1.72	0.89	0.035
13. BD (1) C 5- H15	249. BD*(1) C 1- O 2	2.40	0.81	0.039
20. BD (1) C 8- H19	249. BD*(1) C 1- O 2	4.54	0.84	0.055

Zero-point correction= (Hartree/Particle)	0.294159
Thermal correction to Energy=	0.307714
Thermal correction to Enthalpy=	0.308659
Thermal correction to Gibbs Free Energy=	0.254796
Sum of electronic and zero-point Energies=	-559.711054
Sum of electronic and thermal Energies=	-559.697499
Sum of electronic and thermal Enthalpies=	-559.696555
Sum of electronic and thermal Free Energies=	-559.750418

Version=AM64L-G03RevE.01\State=1-A\HF=-560.0052136\ RMSD=9.556e-10\
RMSF=5.522e-07\Dipole=0.3721781,0.3360245,-2.0357603\PG=C01[X(C9H20N1O2)]\
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7.7 Equilibrium structure of the *epi*-isomuscarine cation

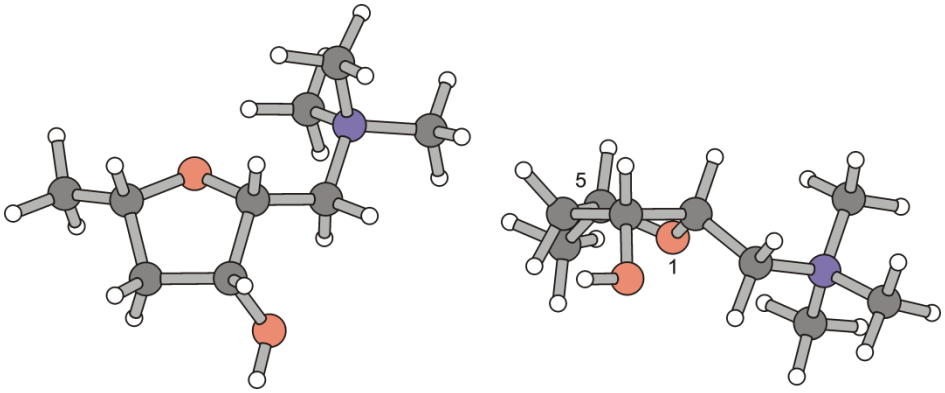
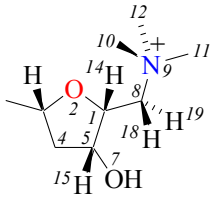


Figure S16. Projections for the (B3LYP/6-31+G**) equilibrium structure of the *epi*-isomuscarine cation in the gas phase (0 K).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.771336	-0.820101	0.039588
2	6	0	2.186424	-0.899619	0.363581
3	6	0	2.681458	0.545916	0.177407
4	6	0	1.439730	1.439272	0.417369
5	6	0	0.297276	0.394360	0.600299
6	6	0	-1.000880	0.834676	-0.065510
7	7	0	-2.151582	-0.179560	-0.035540
8	6	0	-3.423756	0.565034	-0.359139
9	6	0	-1.945031	-1.253074	-1.083744
10	6	0	-2.294243	-0.827775	1.316800
11	6	0	2.842143	-1.947809	-0.513289
12	8	0	1.117134	2.275284	-0.692652
13	1	0	2.266862	-1.191776	1.422259
14	1	0	0.143779	0.259387	1.683152
15	1	0	1.533761	2.050200	1.323286
16	1	0	3.017674	0.694587	-0.853891
17	1	0	3.509512	0.785642	0.849565
18	1	0	-1.366407	1.732714	0.437397
19	1	0	-0.830070	1.075676	-1.114228
20	1	0	-4.241684	-0.151799	-0.439054
21	1	0	-3.631448	1.281045	0.436646
22	1	0	-3.294100	1.088613	-1.306847
23	1	0	-2.778991	-1.953601	-1.024052
24	1	0	-1.926470	-0.777506	-2.064745
25	1	0	-0.996156	-1.747708	-0.890587
26	1	0	-3.195457	-1.441830	1.311775
27	1	0	-1.421869	-1.451846	1.503894
28	1	0	-2.381434	-0.051068	2.077661
29	1	0	2.739029	-1.686899	-1.571158
30	1	0	3.908287	-2.017517	-0.276391
31	1	0	2.396090	-2.932409	-0.346512
32	1	0	1.803679	2.945655	-0.807526

NATURAL BOND ORBITALS (Summary – atom numbering for nbo-analysis):




```
==========================================================================
No. (Occupancy) Bond orbital/ Coefficients/ Hybrids
==========================================================================
18. (1.98215) BD ( 1) C  8- N  9
           ( 33.57%)   0.5794* C  8 s( 19.84%)p 4.03( 80.00%)d 0.01( 0.16%)
                                     0.0002  0.4447  0.0268  0.0015 -0.6421
                                    -0.0236 -0.6203 -0.0155  0.0454 -0.0006
                                     0.0342 -0.0027 -0.0021  0.0030 -0.0203
           ( 66.43%)   0.8151* N  9 s( 25.54%)p 2.91( 74.42%)d 0.00( 0.04%)
                                     0.0000  0.5053 -0.0006 -0.0005  0.6634
                                    -0.0039  0.5514 -0.0015 -0.0019 -0.0011
                                     0.0177  0.0003 -0.0002  0.0021 -0.0104
21. (1.98516) BD ( 1) N  9- C 10
           ( 65.95%)   0.8121* N  9 s( 25.09%)p 2.98( 74.87%)d 0.00( 0.05%)
                                     0.0000  0.5008  0.0029  0.0002 -0.0731
                                     0.0011 -0.3681 -0.0011  0.7796  0.0013
                                     0.0018 -0.0043 -0.0144 -0.0032  0.0154
           ( 34.05%)   0.5836* C 10 s( 20.78%)p 3.80( 79.05%)d 0.01( 0.17%)
                                     0.0003  0.4553  0.0225 -0.0037  0.0880
                                     0.0024  0.3866  0.0147 -0.7949 -0.0338
                                     0.0034 -0.0059 -0.0281 -0.0064  0.0295
22. (1.98491) BD ( 1) N  9- C 11
           ( 65.94%)   0.8120* N  9 s( 24.45%)p 3.09( 75.50%)d 0.00( 0.05%)
                                     0.0000 -0.4944  0.0005 -0.0004  0.7332
                                     0.0026 -0.4286  0.0022  0.1838 -0.0005
                                     0.0157 -0.0067  0.0040 -0.0096  0.0099
           ( 34.06%)   0.5836* C 11 s( 21.03%)p 3.75( 78.79%)d 0.01( 0.17%)
                                    -0.0003 -0.4582 -0.0200  0.0039 -0.7473
                                    -0.0270  0.4372  0.0193 -0.1927 -0.0075
                                     0.0301 -0.0131  0.0078 -0.0167  0.0181
23. (1.98387) BD ( 1) N  9- C 12
           ( 66.64%)   0.8163* N  9 s( 24.93%)p 3.01( 75.02%)d 0.00( 0.04%)
                                     0.0000 -0.4993 -0.0012 -0.0001 -0.1279
                                    -0.0017  0.6133  0.0009  0.5981 -0.0009
                                     0.0028  0.0025 -0.0177  0.0093 -0.0047
           ( 33.36%)   0.5776* C 12 s( 20.18%)p 3.95( 79.64%)d 0.01( 0.18%)
                                    -0.0003 -0.4487 -0.0215  0.0036  0.1211
                                     0.0054 -0.6331 -0.0250 -0.6161 -0.0257
                                     0.0073  0.0076 -0.0358  0.0176 -0.0091
==========================================================================
```

SECOND ORDER PERTURBATION THEORY ANALYSIS OF FOCK MATRIX IN NBO BASIS

Donor NBO (i)	Acceptor NBO (j)	kcal/mol	a.u.	a.u.
2. BD (1) C 1- C 5	266. BD*(1) C 8- N 9	4.19	0.80	0.052
4. BD (1) C 1- H14	260. BD*(1) C 5- O 7	2.48	0.82	0.040
9. BD (1) C 4- C 5	249. BD*(1) C 1- O 2	1.72	0.88	0.035
13. BD (1) C 5- H15	249. BD*(1) C 1- O 2	1.94	0.81	0.036
19. BD (1) C 8- H18	249. BD*(1) C 1- O 2	4.51	0.85	0.055

Zero-point correction= 0.294234
(Hartree/Particle)
Thermal correction to Energy= 0.307854
Thermal correction to Enthalpy= 0.308798
Thermal correction to Gibbs Free Energy= 0.254244
Sum of electronic and zero-point Energies= -559.709726
Sum of electronic and thermal Energies= -559.696106
Sum of electronic and thermal Enthalpies= -559.695162
Sum of electronic and thermal Free Energies= -559.749716

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2.0564791\PG=C01[X(C9H20N1O2)]\NImag=0\\@

7.8 Equilibrium structure of the *epiallo*-isomuscarine cation

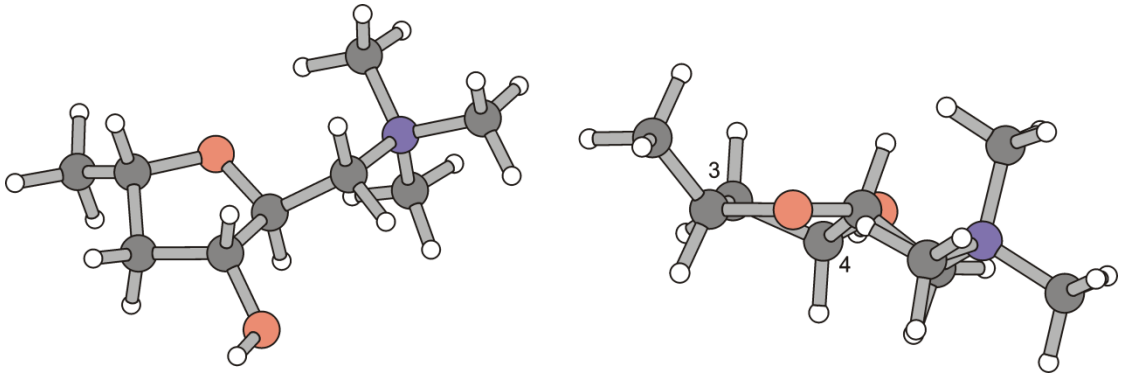
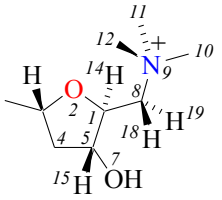


Figure S17. Projections for the calculated (B3LYP/6-31+G**) equilibrium structure of the *epiallo*-isomuscarine cation in the gas phase (0 K).

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.778881	-0.925134	-0.172624
2	6	0	-2.233077	-0.917366	-0.419879
3	6	0	-2.679491	0.514153	-0.090915
4	6	0	-1.416315	1.344995	-0.351472
5	6	0	-0.329235	0.379853	0.155575
6	6	0	1.025709	0.684957	-0.466931
7	7	0	2.205371	-0.172941	0.007205
8	6	0	2.249658	-0.265403	1.511660
9	6	0	2.122691	-1.567665	-0.575037
10	6	0	3.475923	0.480871	-0.477824
11	6	0	-2.894526	-2.016793	0.390902
12	8	0	-1.287713	2.556200	0.370766
13	1	0	-2.355777	-1.121087	-1.490760
14	1	0	-0.280282	0.514665	1.246271
15	1	0	-1.291782	1.521838	-1.431266
16	1	0	-2.952292	0.607759	0.966688
17	1	0	-3.532966	0.828288	-0.697816
18	1	0	0.987554	0.562808	-1.552259
19	1	0	1.283364	1.720575	-0.229021
20	1	0	3.180580	-0.755785	1.798027
21	1	0	2.213492	0.740081	1.932768
22	1	0	1.402373	-0.853661	1.859990
23	1	0	2.962748	-2.148430	-0.192092
24	1	0	1.169828	-2.008508	-0.289608
25	1	0	2.185050	-1.493524	-1.661188
26	1	0	4.321420	-0.158885	-0.222650
27	1	0	3.418608	0.605388	-1.559667
28	1	0	3.584178	1.452781	0.004677
29	1	0	-2.758450	-1.849134	1.464065
30	1	0	-3.968596	-2.043189	0.178724
31	1	0	-2.476799	-2.994009	0.132510
32	1	0	-1.925108	3.208470	0.050555

NATURAL BOND ORBITALS (Summary - atom numbering for nbo-analysis):




```
==========================================================================
No. (Occupancy) Bond orbital/ Coefficients/ Hybrids
==========================================================================
18. (1.98240) BD ( 1) C  8- N  9
           ( 33.64%)   0.5800* C  8 s( 19.85%)p 4.03( 79.99%)d 0.01( 0.16%)
                                    -0.0002 -0.4447 -0.0271 -0.0017 -0.6585
                                    -0.0234  0.5218  0.0125 -0.3052 -0.0066
                                     0.0294 -0.0173  0.0125 -0.0087  0.0136
           ( 66.36%)   0.8146* N  9 s( 25.45%)p 2.93( 74.51%)d 0.00( 0.04%)
                                     0.0000 -0.5045  0.0003  0.0004  0.6791
                                    -0.0039 -0.4694  0.0009  0.2522  0.0004
                                     0.0156 -0.0079  0.0062 -0.0049  0.0076
21. (1.98489) BD ( 1) N  9- C 10
           ( 65.96%)   0.8121* N  9 s( 24.55%)p 3.07( 75.40%)d 0.00( 0.05%)
                                     0.0000  0.4955 -0.0003  0.0004  0.7314
                                     0.0023  0.3764 -0.0020 -0.2783  0.0012
                                     0.0139 -0.0100 -0.0053  0.0105 -0.0079
           ( 34.04%)   0.5835* C 10 s( 21.02%)p 3.75( 78.81%)d 0.01( 0.17%)
                                     0.0003  0.4580  0.0202 -0.0039 -0.7471
                                    -0.0270 -0.3832 -0.0172  0.2863  0.0120
                                     0.0264 -0.0195 -0.0103  0.0187 -0.0144
22. (1.98471) BD ( 1) N  9- C 11
           ( 66.03%)   0.8126* N  9 s( 25.00%)p 3.00( 74.95%)d 0.00( 0.05%)
                                     0.0000  0.5000  0.0023  0.0001  0.0159
                                    -0.0006 -0.0497 -0.0006  0.8642  0.0014
                                     0.0001  0.0020 -0.0021  0.0000  0.0215
           ( 33.97%)   0.5828* C 11 s( 20.75%)p 3.81( 79.08%)d 0.01( 0.18%)
                                     0.0003  0.4549  0.0225 -0.0037 -0.0322
                                     0.0001  0.0583  0.0009 -0.8860 -0.0368
                                    -0.0006  0.0021 -0.0045  0.0001  0.0416
23. (1.98407) BD ( 1) N  9- C 12
           ( 66.61%)   0.8161* N  9 s( 25.00%)p 3.00( 74.95%)d 0.00( 0.04%)
                                     0.0000 -0.5000 -0.0013 -0.0001  0.0554
                                     0.0014  0.7968  0.0005  0.3340 -0.0008
                                    -0.0008 -0.0002 -0.0126  0.0157  0.0057
           ( 33.39%)   0.5778* C 12 s( 20.23%)p 3.93( 79.59%)d 0.01( 0.18%)
                                    -0.0003 -0.4492 -0.0218  0.0036 -0.0481
                                    -0.0028 -0.8222 -0.0332 -0.3410 -0.0149
                                    -0.0041 -0.0021 -0.0258  0.0310  0.0118
==========================================================================
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SECOND ORDER PERTURBATION THEORY ANALYSIS OF FOCK MATRIX IN NBO BASIS

Donor NBO (i)	Acceptor NBO (j)	kcal/mol	a.u.	a.u.
1. BD (1) C 1- O 2	260. BD*(1) C 5- O 7	1.28	1.12	0.034
2. BD (1) C 1- C 5	266. BD*(1) C 8- N 9	4.60	0.80	0.054
4. BD (1) C 1- H14	260. BD*(1) C 5- O 7	0.98	0.82	0.025
9. BD (1) C 4- C 5	249. BD*(1) C 1- O 2	1.31	0.90	0.031
12. BD (1) C 5- O 7	249. BD*(1) C 1- O 2	1.34	1.13	0.035
20. BD (1) C 8- H19	249. BD*(1) C 1- O 2	4.71	0.86	0.057

Zero-point correction= 0.293911
(Hartree/Particle)
Thermal correction to Energy= 0.307636
Thermal correction to Enthalpy= 0.308580
Thermal correction to Gibbs Free Energy= 0.253827
Sum of electronic and zero-point Energies= -559.709580
Sum of electronic and thermal Energies= -559.695856
Sum of electronic and thermal Enthalpies= -559.694912
Sum of electronic and thermal Free Energies= -559.749664

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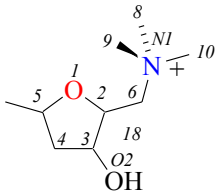
8 Solid state and computed structural data of isomuscarine cations

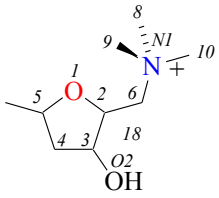
8.1 Bond lengths



parameter	isomuscarine							
	–		*allo*		*epi*		*epiallo*	
	exp. [a]	calc. [b]	exp. [a]	calc. [b]	exp. [a]	calc. [b]	exp. [a]	calc. [b]
T / K	301(2)	0	100(2)	0	103(/2)	0	105(2)	0
conformation	$_4T^5$	$^5T_1$	$^3T_4$	$^3T_4$	$^1T_2$	$^5T_1$	$^4T_5$	$^3T_4$
O1–C2 / Å	1.398(5)	1.416	1.436(4)	1.426	1.420(5)	1.419	1.392(8)	1.419
C2–C3 / Å	1.533(6	1.555	1.526(4)	1.546	1.527(6)	1.559	1.547(9)	1.540
C3–C4 / Å	1.479(7)	1.548	1.521(4)	1.533	1.531(6)	1.548	1.51(1)	1.534
C4–C5 / Å	1.511(8)	1.538	1.517(5)	1.532	1.488(7)	1.539	1.45(1)	1.535
C5–O1 / Å	1.404(6)	1.459	1.452(4)	1.467	1.429(6)	1.454	1.46(1)	1.475
C6–N1 / Å	1.510(5)	1.535	1.516(4)	1.528	1.514(5)	1.534	1.540(7)	1.534
N1–C8 / Å	1.495(6)	1.514	1.499(4)	1.507	1.493(5)	1.514	1.480(8)	1.508
N1–C9 / Å	1.486(6)	1.508	1.506(4)	1.515	1.494(5)	1.506	1.497(8)	1.514
N1–C10 / Å	1.485(6)	1.509	1.499(4)	1.509	1.512(5)	1.509	1.482(8)	1.509
C3–O2 / Å	1.384(5)	1.459	1.428(4)	1.467	1.424(5)	1.454	1.401(8)	1.475

[a] Single crystal X-ray diffraction analysis. [b] B3LYP/6-31+G**

8.2 Bond- and dihedral angles



parameter	isomuscarine							
	–		*allo*		*epi*		*epiallo*	
	exp. [a]	calc. [b]	exp. [a]	calc. [b]	exp. [a]	calc. [b]	exp. [a]	calc. [b]
T / K	301(2)	0	100(2)	0	103(/2)	0	105(2)	0
conformation	$_4T^5$	$^5T_1$	$^3T_4$	$^3T_4$	$^1T_2$	$^5T_1$	$^4T_5$	$^3T_4$
C2-O1-C5 / °	110.0(4)	106.3	109.8(2)	110.7	105.4(3)	106.5	110.4(6)	110.3
O1-C2-C3 / °	108.1(4)	106.8	105.5(2)	106.8	105.9(3)	106.4	106.5(6)	106.1
C2-C3-C4 / °	101.8(4)	102.9	100.7(2)	100.8	101.6(3)	102.7	101.9(6)	100.7
C3-C4-C5 / °	104.5(5)	104.9	103.3(2)	103.4	106.3(4)	105.4	105.1(6)	103.2
C4-C5-O1 / °	104.0(5)	103.1	105.4(3)	104.0	106.9(4)	103.6	104.0(7)	104.8
C6-N1-C8 / °	112.3(4)	110.7	116.2(2)	110.6	111.1(3)	111.9	113.0(5)	111.4
C6-N1-C9 / °	111.1(4)	111.4	111.9(2)	111.9	111.7(3)	110.7	111.2(5)	110.8
C6-N1-C10 / °	107.1(3)	107.8	107.8(2)	107.7	107.7(3)	107.6	106.4(5)	107.8
O1-C2-C3-N1 / °	63.3(5)	61.8	–73.5(3)	–54.2	71.5(4)	56.3	–70.0(8)	–63.9
O1-C2-C3-O2 / °	–106.3(5)	–138.0	–83.2(3)	–89.3	91.1(4)	101.4	135.5(6)	158.1

[a] Single crystal X-ray diffraction analysis. [b] B3LYP/6-31+G**

9 References

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[2] Gaussian 03, Revision C.01, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, Jr., J.A.; Vreven, T.; Kudin, K.N.; Burant, J.C.; Millam, J.M.; Iyengar, S.S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J.E.; Hratchian, H.P.; Cross, J.B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Ayala, P.Y.; Morokuma, K.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V.G.; Dapprich, S.; Daniels, A.D.; Strain, M.C.; Farkas, O.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Ortiz, J.V.; Cui, Q.; Baboul, A.G.; Clifford, S.; Cioslowski, J.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y. Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Gonzalez, C.; Pople, J.A., Gaussian, Inc., Wallingford CT, **2004**.

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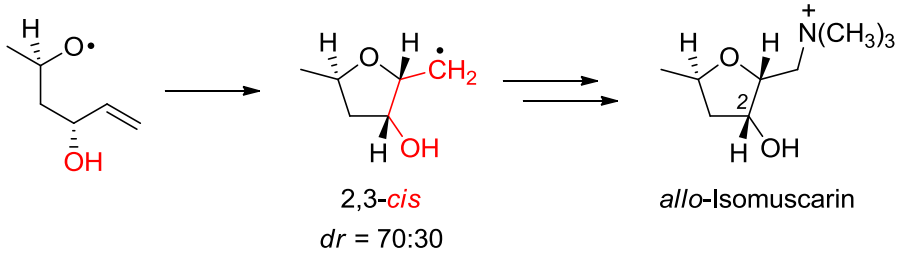
4 2,3-cis-Selektivität in 4-Pentenoxylradikal-Cyclisierungen

4.1 Zusammenfassung

Akzeptor-Substituenten, wie Hydroxy, Acetyloxy oder Benzoyloxy, dirigieren in allylischer Position eine 5-*exo*-trig-Cyclisierung von 4-Pentenoxylradikalen 2,3-cis-selektiv. Zusätzliche Substituenten entlang der Alkenoxyl-Kette bewirken eine Erhöhung oder Erniedrigung der 2,3-cis-Selektivität abhängig von der Position, der Konfiguration sowie deren chemischen Struktur. Untersuchungen zur Reversibilität der Cyclisierungsreaktion zeigen, dass die Reaktion kinetisch kontrolliert verläuft und somit der 2,3-cis-Selektivität ein kinetischer Effekt zugrunde liegt. Aus der Grenzorbitaltheorie wird ersichtlich, dass im Übergangszustand des 2,3-trans-konfigurierten Cyclisierungsprodukt sekundäre Orbital-Wechselwirkungen zwischen der C,C-Doppelbindung und dem Allyl-Substituenten stattfinden. Die daraus resultierende Delokalisierung der π-Elektronen in das σ^*(C,O)-Orbital führt zu einer verringerten Reaktivität der C,C-Doppelbindung gegenüber dem elektrophilen Angriff des O-Radikals. Eine solche Wechselwirkung ist im Übergangszustand des 2,3-cis-konfigurierten Produkts aufgrund der räumlichen Anordnung nicht möglich und somit ist der Reaktionskanal zum 2,3-cis-konfigurierten Tetrahydrofuran begünstigt.

4.2 Wissenschaftlicher Hintergrund, Zielsetzung und Strategie

4-Pentenoxylradikale mit allylischen Kohlenstoff-Substituenten, wie Phenyl oder Alkyl, cyclisieren aufgrund von sterischen Effekten 2,3-trans-selektiv.[1] Bei der Darstellung von *allo*-Isomuscarin über eine 5-*exo*-trig-Cyclisierung gibt es Hinweise, dass durch einen Hydroxy-Substituent in allylischer Position eine 2,3-cis-Selektivität bewirkt werden kann (Schema 4.1).[2] Mit Hilfe des bekannten stereochemischen Modells zur Beschreibung sterischer Effekte in Cyclisierungsreaktionen,[3] kann dieser 2,3-cis-dirigierende Einfluss nicht erklärt werden. Aufgrund dessen wird die Ursache auf eine stereoelektronische Wechselwirkung des Allyl-Substituenten zurückgeführt.[4] Untersuchungen sollen zeigen, ob ein polarer Substituenteneffekt zur Steuerung von Selektivitäten existiert, der auf weitere Akzeptor-Gruppen erweitert werden kann und somit das Synthesespektrum homolytischer Cyclisierungen deutlich vergrößert.



Schema 4.1 2,3-cis-Selektive 4-Pentenoxyl-Cyclisierung zur Darstellung von *allo*-Isomuscarin.[2]

Zur Aufklärung des 2,3-cis-Effektes bei Alkenoxylradikal-Cyclisierungen ergab sich ein Forschungsbedarf mit folgender Aufgabenstellung:

- Untersuchung von 4-Pentenoxylradikalen mit unterschiedlichen allylischen O-Akzeptor-Substituenten hinsichtlich ihrer Reaktivität und Selektiviät in 5-*exo*-trig-Cyclisierungen.
- Entwicklung eines stereochemischen Modells zur Erklärung des 2,3-cis-dirigierenden Effektes durch polare Substituenten.

4.3 Ergebnisse und Diskussion

4.3.1 Darstellung Allyl-substituierter Thiohydroxamate

Um ausschließlich den Einfluss des allylischen Substituenten auf die 2,3-cis-Selektivität zu untersuchen, wurden monosubstituierte Pentenoxylradikale mit verschiedenen allylischen O-Akzeptor-Substituenten dargestellt (Abb. 4.1, **1a**–**c**). Das Hydroxy-substituierte Thiohydroxamat **1a** wurde ausgehend von Ethylacetat und Arcolein in einer sechsstufigen Synthese dargestellt.[5] Die Hydroxy-Gruppe wurde dann zum entsprechenden Acetat **1b** und Benzoat **1c** verestert.

Die Einführung weiterer Substituenten in proximaler Position soll zeigen, ob dies zu einer Verstärkung oder Abschwächung des 2,3-cis-Effektes führt (Abb. 4.1, **1d**–**e**). Im Fall der zweifach Acetyloxy-substituierten Alkenoxylradikale **1d** wird zusätzlich geprüft, ob die Konfiguration der beiden Gruppen einen Einfluss hat. Die Darstellung des *erythro*-konfigurierten Thiohydroxamats *erythro*-**1d** erfolgte ausgehend von D-Isoascorbinsäure in einer achtstufigen Synthesesequenz.[6] L-Weinsäure-dimethylester diente als Startmaterial zur Synthese des *threo*-konfigurierten Produktes **1d**.[7] Das trisubstituierte O-Pentenyl-

thiohydroxamat **1e**, das eine zusätzliche Methyl-Gruppe in Position 1 besitzt, wurde durch die Umsetzung von D-Ribose in einer siebenstufigen Sequenz erhalten.[8]

Der Effekt einer O-Akzeptor-Gruppe auf die Regioselektivität in 5-*exo*-trig-Cyclisierungen wird anhand der bevorzugten Reaktivität des O-Radikals im Dienol **1f** ersichtlich. Das Kohlenstoff-Gerüst wurde durch die Kopplung von But-3-en-1-yl-magnesiumbromid mit 3-(Methoxymethyloxy)pent-4-enal in einer Grignard-Reaktion aufgebaut. Das erhaltene Zwischenprodukt wurde anschließend in drei Stufen zum Thiohydroxamat **1f** umgesetzt.

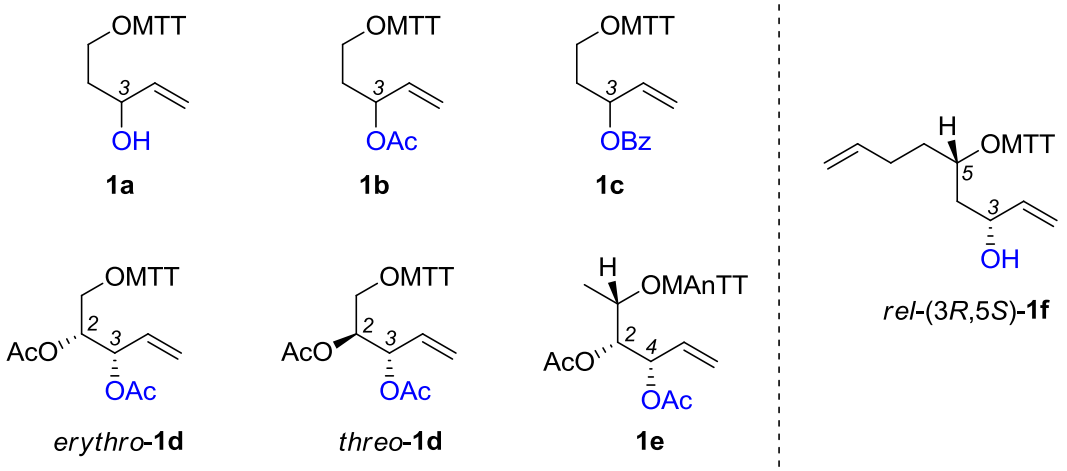


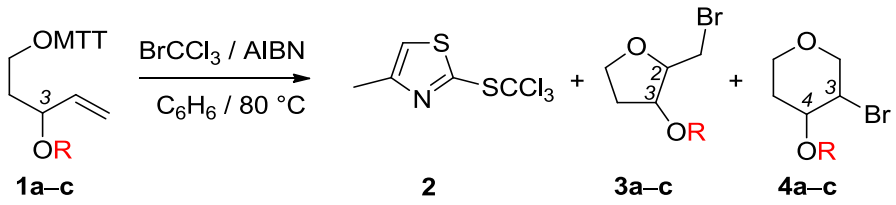
Abbildung 4.1 Mono-, di- und trisubstituierte Pentenoxylradikale **1a–e** (links) und konkurrenzkinetisches Dienol **1f** (rechts) zur Untersuchung des allylischen O-Akzeptor-Einflusses auf die 2,3-cis-Selektivität in 5-*exo*-trig-Cyclisierungen. MTTO = 4-Methyl-2-thiooxo-1,3-thiazyl-3-oxy; MAnTTO = 4-Methyl-5-(4-methoxyphenyl)-2-thiooxo-1,3-thiazyl-3-oxy.

4.3.2 Intramolekulare Additionsreaktionen

(A) 2,3-cis-Selektive Cyclisierung monosubstituierter Thiohydroxamate

Die thermisch induzierten Reaktionen der Thiohydroxamate **1a–c** lieferten als Hauptprodukt das bromierte 5-*exo*-Cyclisierungsprodukt **3** in Ausbeuten von 56–71%. In allen Fällen wurde das 2,3-cis-konfigurierte Tetrahydrofuran **3** in einem Verhältnis von 70:30 bevorzugt gebildet (Tabelle 4.1). Als Nebenprodukt wurde das 6-*endo*-Produkt **4** in Ausbeuten von 4–12% gebildet. Diese Tetrahydropyran-Ausbeuten überschreiten das für allylische Alkyl- oder Phenyl-substituierte Pentenoxyle bekannte 5-*exo*:6-*endo*-Verhältnis von 98:2.[9]

Tabelle 4.1 Cyclisierungsprodukte bei der Umsetzung der Radikalvorläufer **1a–c** in Anwesenheit von Bromtrichlormethan



1a–c **2** **3a–c** **4a–c**

Eintrag	**1** / R	**2** / %	**3** / % (*cis*:*trans*)	**4** / % (*cis*:*trans*)
1	**1a** / H	84	**3a**: 56 (74:26)	**4a**: 4 (65:35)
2	**1b** / Ac	94	**3b**: 71 (68:32)	**4b**: 11 (57:43)
3	**1c** / Bz	75	**3c**: 69 (68:32)	**4c**: 12 (50:50)

Die beobachteten 2,3-cis-Selektivitäten, die durch den Einfluss polarer Substituenten in allylischer Position gesteuert werden, können mit Hilfe der Grenzorbitaltheorie (FMO-Theorie)[10,11] erklärt werden. Alkoxylradikal-Additionen sind schnelle, exotherme Reaktionen, deshalb können die Übergangszustände zur Erklärung von Selektivitäten herangezogen werden. Der trans- und der cis-Übergangszustand unterscheiden sich in der räumlichen Anordnung des allylischen Substituenten X zur C,C-Doppelbindung. Im Fall der 2,3-trans-Additionsreaktion sind der Substituent X und die Alken-Einheit antiklinal angeordnet. Substituenten, wie *tert*-Butyl oder Phenyl, bevorzugen aus sterischen Gründen diese Anordnung.[12] Bei polaren Gruppen findet eine Wechselwirkung zwischen der π(C,C)- und der σ^*(C,O)-Bindung statt, wodurch eine Delokalisierung der π-Elektronen eintritt (Abb. 4.2, rechts). Dies bewirkt eine Absenkung der Doppelbindungsenergie und reduziert somit die 2,3-trans-Cyclisierungsrate. In der synperiplanaren Anordnung im 2,3-cis-Übergangszustand ist diese Wechselwirkung nicht möglich (Abb. 4.2, links).[13] Aus diesem Grund bewirken polare Akzeptor-Substituenten eine 2,3-cis-selektive Alkenoxylradikal-Cyclisierung.

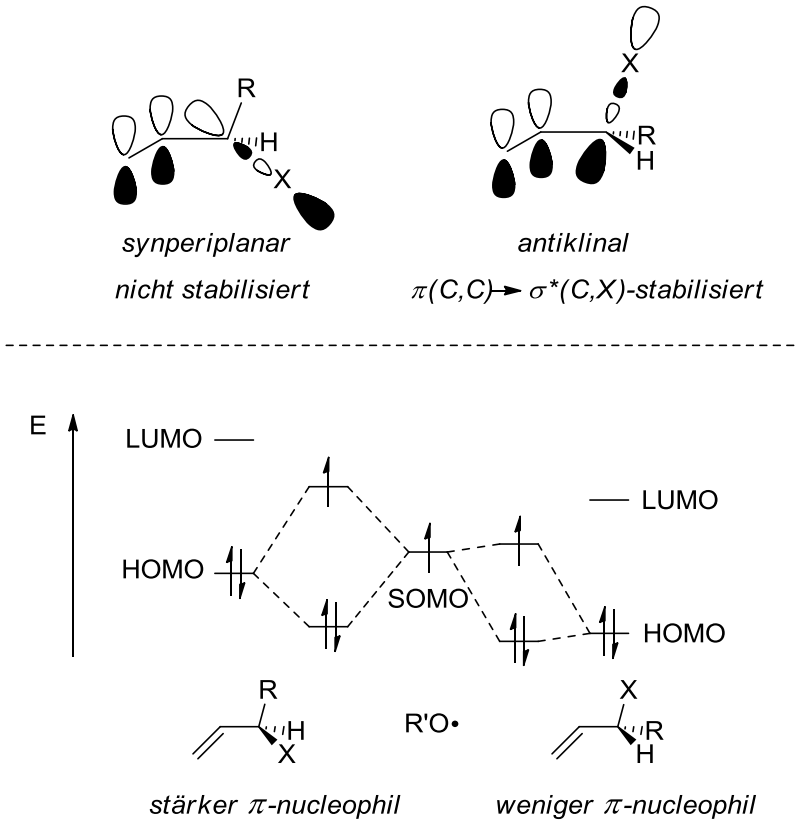
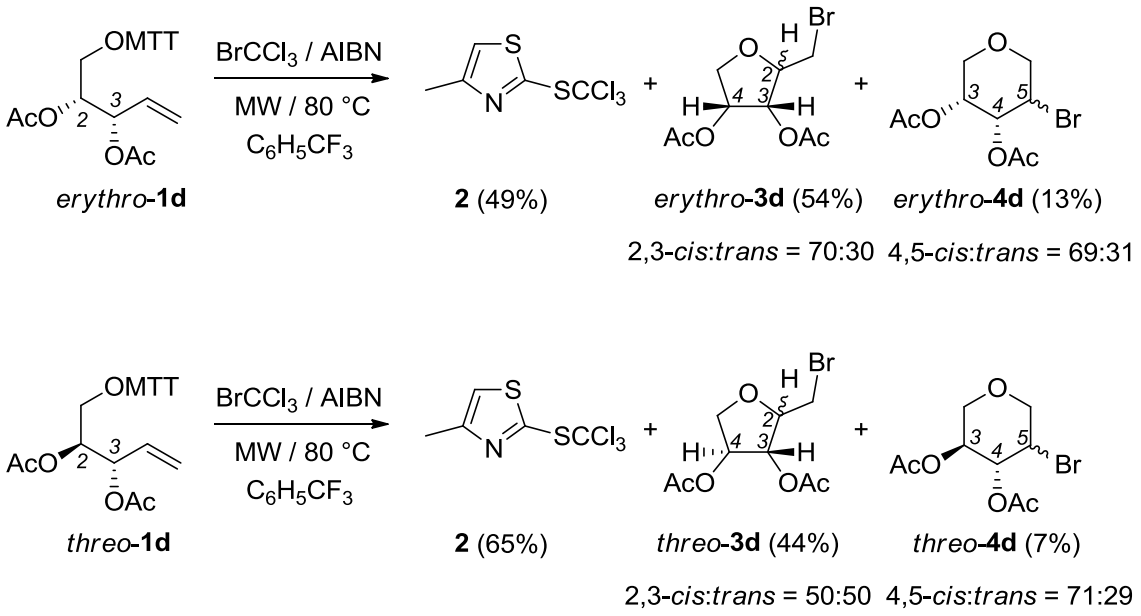


Abbildung 4.2 Mechanistisches Modell zur 2,3-cis-selektiven Cyclisierungungsreaktion von Akzeptor-substituierten Butenen anhand von Grenzorbitalwechselwirkungen in den cis- und trans-Übergangszuständen. R = z. B. CH_3 oder CH_2CH_2O•; R' = z. B. primär, sekundär oder tertiär Alkyl; X = z. B. OH, OAc, OBz.

(B) 5-*exo*-trig-Cyclisierung disubstituierter O-Pentenyl Thiohydroxamate

Die thermisch induzierte Reaktion von *erythro*-**1d** in Anwesenheit von Bromtrichlormethan lieferte 54% trisubstituiertes Tetrahydrofuran *erythro*-**3d**, 13% des 6-*endo*-Produktes *erythro*-**4d** und 49% des Thiazols **2** (Schema 4.2, oben). Das 5-*exo*-Produkt *erythro*-**3d** wird in einem 2,3-*cis*:*trans*-Verhältnis von 70:30 gebildet und somit bewirkt der zusätzliche Substituent im Vergleich zu den monosubstituierten O-Radikalen keine Änderung der Selektivität. Die Umsetzung des *threo*-konfigurierten Radikalvorläufers *threo*-**1d** ergab folgendes Produktbild: 44% bromcyclisiertes Produkt *threo*-**3d**, 7% Tetrahydropyran *threo*-**4d** und 65% Produkt **2** (Schema 4.2, unten). Bei der Bildung des Tetrahydrofurans *threo*-**3d** wird das cis- und trans-Isomer in gleichem Maße favorisiert.



Schema 4.2 Produktspektrum der Radikalreaktionen von *erythro*- und *threo*-**1d** mit Bromtrichlormethan unter thermischen Bedingungen. MW = Mikrowelle.[14,15]

Mit Hilfe der FMO-Theorie kann auch hier die Stereoselektivität der 5-*exo*-trig-Cyclisierung begründet werden. Die räumliche Anordnung der zweiten Acetyloxy-Gruppe in Position 2 spielt hierbei eine entscheidende Rolle. Im cis-Übergangszustand des Tetrahydrofurans *erythro*-**3d** liegen der allylische Acetyloxy-Substituent und die C,C-Doppelbindung synperiplanar zueinander, der zweite Acteyloxy-Substituent ist dabei äquatorial angeordnet (Abb. 4.3, oben). Beide Substituenten nehmen in diesem Übergangszustand günstige Positionen ein, in allylischer Position aufgrund polarer und in Position 2 aufgrund sterischer Effekte. Im trans-Übergangszustand hingegen nehmen beide Substituenten die ungünstigere Position ein. Der polare Allyl-Substituent steht antiklinal zur C,C-Doppelbindung und die benachbarte Acetyloxy-Gruppe axial. Hiermit lässt sich die Bevorzugung der 2,3-cis-Cyclisierung erklären.

Bei der Cyclisierung des *threo*-konfigurierten Alkoxylradikals *threo*-**Id** besteht zwischen beiden Übergangszuständen kein energetischer Unterschied, wodurch beide gleich favorisiert werden. Dies ist darin begründet, dass im cis-Übergangszustand die allylische Gruppe die synperiplanare Anordnung einnimmt, die für polare Substituenten bevorzugt ist. Der Substituent in Position 2 hingegen nimmt die sterisch ungünstige axiale Stellung ein. Im trans-Übergangszustand liegt der umgekehrte Fall vor, hier ist die Positionierung der Substituenten elektronisch ungünstig und sterisch günstig (Abb. 4.3, unten).

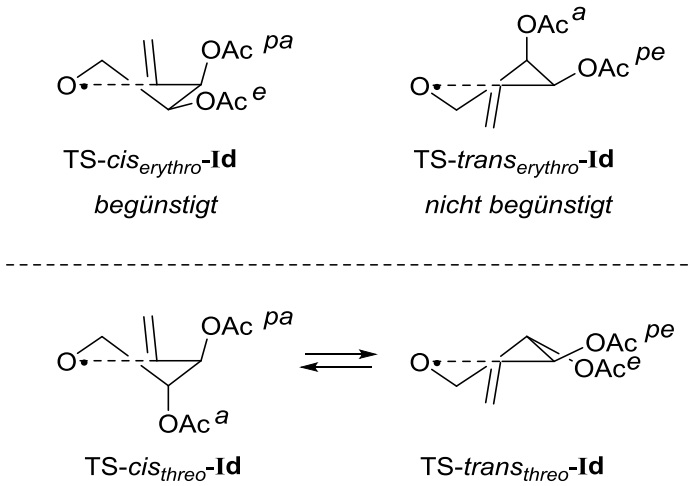
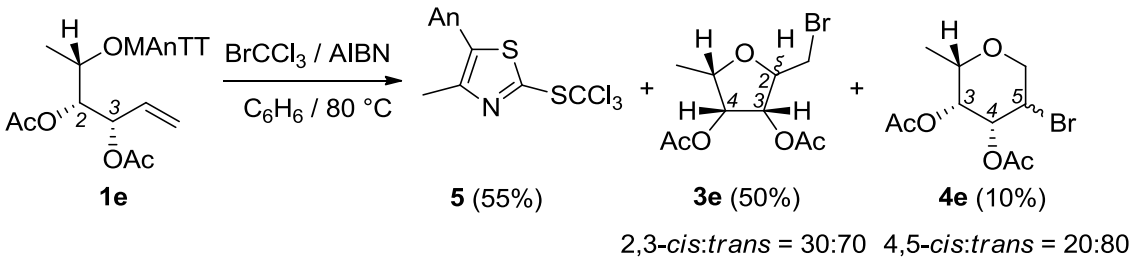


Abbildung 4.3 Polare und sterische Substituenteneffekte in den Übergangszuständen der 5-*exo*-trig-Cyclisierung der Alkoxylradikale *erythro*- und *threo*-**Id**. a = axial; pa = *pseudo*-axial; e = äquatorial; pe = *pseudo*-äquatorial.

(C) 2,3-trans-Selektive Cyclisierung trisubstituierter Thiohydroxamate

Das vierfach-substituierte Tetrahydrofuran **3e** wurde bei der Umsetzung des *arabino*-konfigurierten Thiohydroxamats **1e** in 50% Ausbeute mit einem Selektivitätsverhältnis von 2,3-*cis*:*trans* = 30:70 isoliert. Die zusätzliche Methyl-Gruppe in Position 1 bewirkt eine bvorzugte 2,3-trans-Selektivität.[16] Als weitere Verbindungen wurden das Tetrahydropyran **4e** (10%) und das Thiazol **5** (55%) erhalten (Schema 4.3).



Schema 4.3 Radikalische Bromcyclisierung des Radikalvorläufers *arabino*-**1e** unter thermischen Bedingungen in Anwesenheit des Initiator AIBN.[17]

Im cis-Übergangszustand bewirkt die zusätzliche Methyl-Gruppe in Position 1 sterische Wechselwirkungen, die dazu führen, dass der trans-Übergangszustand **Ie** energetisch günstiger ist. Die Methyl-Gruppe ist der bestimmende Stereoinduktor, der die 5-*exo*-Cyclisierung 2,3-trans-selektiv steuert. Die sterische Abstoßung überwiegt gegenüber dem polaren Effekt der allylischen Acetyloxy-Gruppe (Abb. 4.4).

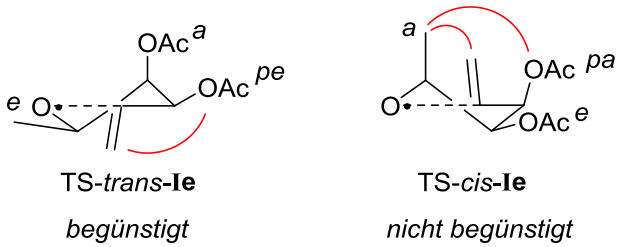
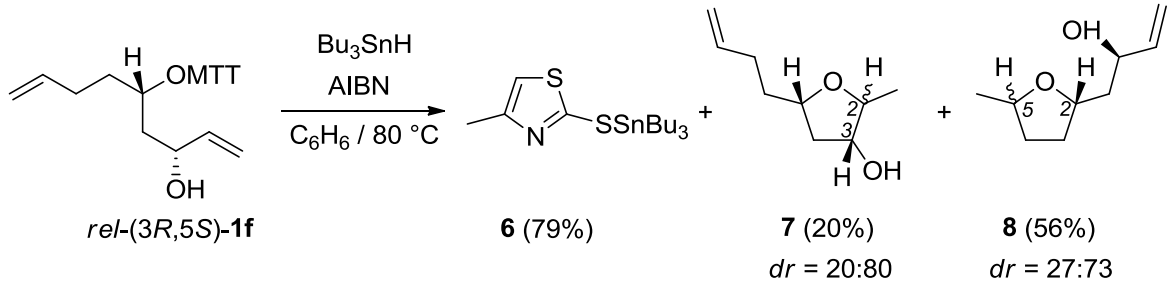


Abbildung 4.4 Übergangsstrukturen der Cyclisierungsreaktion des O-Radikals **Ie** zur Erklärung der 2,3-trans-Selektivität. a = axial; pa = *pseudo*-axial; e = äquatorial; pe = *pseudo*-äquatorial; der Bogen symbolisiert sterische Abstoßung.

(D) Relative Reaktivität eines allylischen O-Akzeptor-Substituenten

Der kinetische Effekt einer allylischen O-Akzeptor-Gruppe zeigt die Cyclisierung des Dienols *rel*-(3*R*,5*S*)-**1f**, welches eine unsubstituierte und eine Hydroxy-substituierte Doppelbindung als Konkurrenzsysteme enthält. Da aus der Karasch-Reaktion[18] bekannt ist, dass Bromtrichlormethan an C,C-Doppelbindungen addiert, wird in diesem Fall auf das Tributylstannan als Abfangreagenz zurückgegriffen. Bei der thermischen Umsetzung von *rel*-(3*R*,5*S*)-**1f** wurden die Tetrahydrofurane **7** und **8** in einer Gesamtausbeute von 76% (**7**:**8** = 26:74) erhalten (Schema 4.4). Das substituierte Produkt **6** wurde in 79% Ausbeute gebildet, wobei dessen Ausbeute aus der Reaktionsmischung vor der säulenchromatographischen Aufreinigung über ^{1}H-NMR bestimmt wurde, da sich die Verbindung auf Kieselgel zersetzt.

Anhand der unterschiedlichen chemischen Verschiebungen und Feinstrukturen der ^{1}H-NMR-Signale konnte das Cyclisierungsprodukt **8** als Hauptprodukt identifiziert werden. Die intramolekulare Addition an die unsubstituierte Doppelbindung wird um einen Faktor drei gegenüber der Addition an die Allyl-substituierte Doppelbindung bevorzugt. Dies dient zur ersten Abschätzung des kinetischen Effektes einer polaren O-Akzeptor-Gruppe.

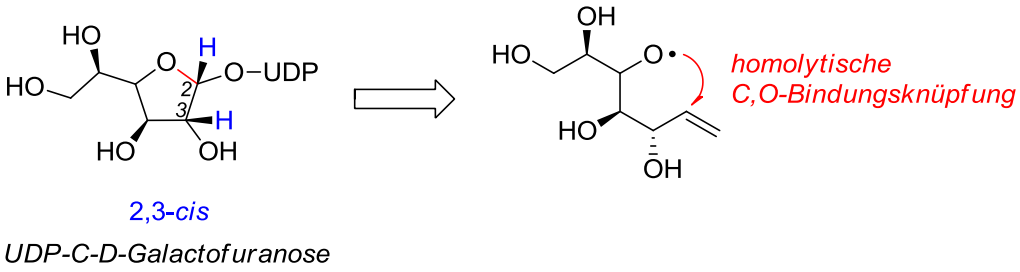


rel-(3*R*,5*S*)-**1f** **6** (79%) **7** (20%) *dr* = 20:80 **8** (56%) *dr* = 27:73

Schema 4.4 Produktverhältnisse bei der Reaktion von 3-[*rel*-(3*R*,5*S*)-3-hydroxynona-1,8-dien-5-oxy]-4-methyl-1,3-thiazol-2(3*H*)-thion **1f** in Anwesenheit von AIBN und Tributylstannan.[19]

4.4 Ausblick

O-Akzeptor-Substituenten in allylischer Position bewirken eine 2,3-cis-selektive Cyclisierung von Pentenoxylradikalen. Die Selektivitätssteuerung durch polare Effekte ergänzt das bislang auf Sterik beruhende stereochemische Modell für 5-*exo*-trig-Cyclisierungen. Viele biologisch aktive Naturstoffe besitzen 2,3-cis-substituierte Tetrahydrofurane als Grundstruktur.[20] Die 2,3-cis-Stereokontrolle durch O-Akzeptor-Gruppen ermöglicht den Aufbau dieser Zielmoleküle durch homolytische O-Radikalcyclisierungen und erweitert somit deren Anwendungsgebiet in der organischen Synthese (Schema 4.5).[21]



Schema 4.5 Homolytische Cyclisierungsreaktion zum Aufbau 2,3-cis-substituierter Tetrahydrofuran-Gerüste. UDP = Uridindiphosphat.[21]

Dieser Effekt sollte auf weitere Akzeptor-Heteroatome, wie Stickstoff, Schwefel oder Halogene, ausdehnbar sein. Dabei ist es wichtig, die richtige Balance zwischen elektronenziehenden und sterischen Eigenschaften zu finden, wobei die 2,3-cis-Selektivität durch sterisch anspruchslose und stark elektronegative Gruppen verstärkt werden sollte.[22]

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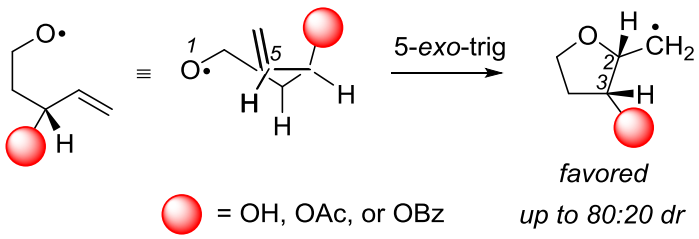
4.6 Forschungsartikel

2,3-cis-Cyclization of 4-Pentenoxyl Radicals

Irina Kempter, Christine Schur, Katharina Huttenlochner, Ruth-Maria Bergsträßer, Benjamin Wolff, Thomas Kopf, Jens Hartung, *Tetrahedron* **2016**, *72*, 7699−7714.



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2,3-*cis*-Cyclization of 4-pentenoxyl radicals

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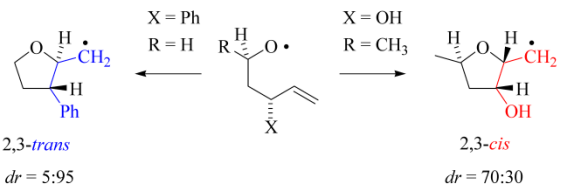
ABSTRACT

4-Pentenoxyl radicals cyclize 2,3-*cis*-selectively, when substituted by an allylic hydroxy, acetyloxy, or benzoyloxy group. Additional substituents increase or decrease the fraction of 2,3-*cis*-cyclized product, depending on relative configuration, positioning, and their chemical nature. The preference for 3-acceptor-subsituted pentenoxyl radicals to furnish products of 2,3-*cis*-ring closure arises from a secondary orbital interaction between the allylic oxygen substituent and the alkene entity, kinetically disfavoring the 2,3-*trans*-mode of 5-*exo*-cyclization. Aligning the β-C,O-bond in anticline orientation to the plane of the alkene, which is the preferred conformation for transition structures for 2,3-*trans*-cyclization, stabilizes the double bond by delocalizing π-electrons into the σ*(C,O)-orbital. Along with energy decreases the affinity of π-electrons for forming a σ (C,O)-bond with the oxygen radical. In 2,3-*cis*-cyclization, a similar stabilizing effect cannot occur, because the allylic oxygen substituent and the alkene align synperiplanar. The kinetic effect of an allylic oxygen substituent becomes furthermore apparent in cyclization of the 3-hydroxynona-1,8-dien-5-oxyl radical, favoring intramolecular addition to the unsubstituted allylic double bond by a factor three.

1. Introduction

4-Pentenoxyl radicals cyclize 2,3-*trans*-selectively when substituted with an allylic alkyl or a phenyl group (Scheme 1).[1] The fraction of 2,3-*trans*-product increases with the size of the allylic substituent, from 80/20 for methyl to above 99/1 for *tert*-butyl.[2,3] Transition state theory[4] explains 2,3-*trans*-selectivity on the basis of cumulative 1,2- and 1,3-repulsion, progressively disfavoring 2,3-*cis*-addition as steric demand of the allylic substituent grows.[5,6]



Scheme 1. Stereoselectivity in 5-*exo*-cyclization of allyl-substituted 4-pentenoxyl radicals.[2,3,7]

Steric effects controlling selectivity in synthesis of 2,3-*trans*-substituted heterocycles by intramolecularly adding polar reactands[11,12] or radicals[13–17] to double bonds are well documented in the scientific literature. In the past decades, however, more and more reports appeared describing selectivity not fitting into this stereochemical scheme. Alkenols bearing an allylic oxygen substituent, for example, show a marked propensity for cyclizing 2,3-*cis*-selectively, when treated with molecular iodine. A theory explaining this phenomenon starts to evolve, but is not yet consistent.[18–21]

The affinity of the allylic hydroxy group to direct cyclizations 2,3-*cis*-selectively also extends to oxygen radical additions, as recently outlined in synthesis of *allo*-isomuscarine (Scheme 1, Fig. 1).[8] The alkene in this example poses the nucleophilic component and the radical oxygen the electrophilic, which is exactly opposed to the situation in electrophile-induced alkenol cyclization. A theory explaining 2,3-*cis*-selectivity in radical cyclization so far does not exist.

For uncovering the principles leading to 2,3-*cis*-selective ring closures, we investigated in the study summarized below, reactivity and selectivity of 4-pentenoxyl radicals, differing in substitution at the allylic carbon and at proximal positions (Fig. 2). The results from this effort show that an allylic oxygen substituent reduces the rate of intramolecular 2,3-*trans*-addition, and leave the rate of the 2,3-*cis*-pathway largely unaffected. The rate effect of the allylic oxygen

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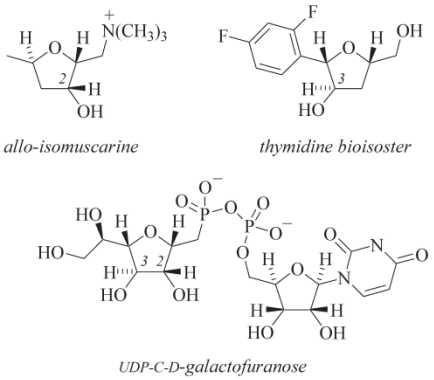
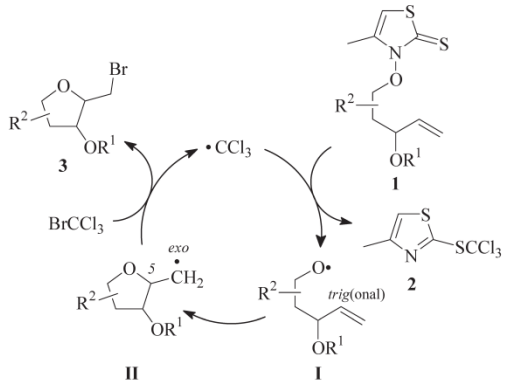
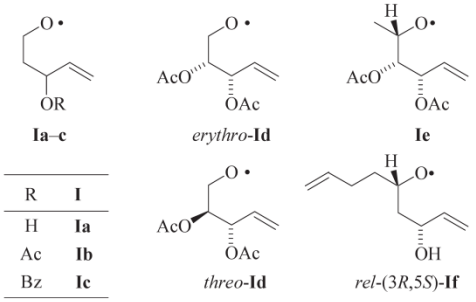


Fig. 1. Structure formulas of bio-inspired 2- and 3-hydroxy-substituted tetrahydrofurans as targets in organic synthesis.[8–10]



Scheme 2. Chain reaction for bromomethyltetrahydrofuran synthesis from 3-alkenoxy-4-methylthiazole-2(3*H*)-thione **1** and $BrCCl_3$ (R^1=H, Ac, Bz; R^2=H, OAc, CH_3).[8,24]

substituent is not restricted to stereocontrol but also controls selectivity in intramolecular addition of an oxyl radical to two chemically different C,C-double bonds. The 3-hydroxynona-1,8-dien-5-oxyl radical thus prefers adding to the unsubstituted allylic double bond by a partial rate factor three.



R	I
H	**Ia**
Ac	**Ib**
Bz	**Ic**

Fig. 2. Structure formulas of 4-pentenoxyl radicals **Ia**–**f** conceived for uncovering the origin of 2,3-*cis*-selectivity in homolytic 5-*exo*-cyclization.

2. Results and interpretation

2.1. Alkenoxyl radical generation, chain reaction, and design of alkenoxyl radicals for conducting the study

Based on the expertise from preceding mechanistic studies,[8,22] we used *O*-pentenyl esters of 1,3-thiazole-derived heterocyclic thiohydroxamic acids[23] as progenitors for generating oxygen radicals. Heating compounds of this kind, for example the 3-alkoxy-1,3-thiazole-2(3*H*)-thiones,[1] in the presence of a chemical initiator, or photoexciting the molecules with 350 nm-light, almost specifically breaks the N,O-bond, allowing to liberate oxygen radicals under pH-neutral and non oxidative conditions from otherwise stable compounds.

The mechanism operating for converting 3-alkoxy-1,3-thiazole-2(3*H*)-thiones into alkoxyl radicals is a chain reaction. The sequence starts by adding a chain propagating radical to the thione sulfur of the thiohydroxamate used as progenitor, providing oxygen radical **I** and substituted thiazole **2** (Scheme 2).[24] By extrapolating known kinetic data,[2,25,26] we expect allyl-substituted derivatives to intramolecularly add with a rate constant between 10^8 s^{-1} and 10^9 s^{-1} to the C,C-double bond. In terms of regioselectivity the intramolecular addition should lead to a 5-*exo*/6-*endo*-distribution ranging from 98:2 (for X=CH_3) to 90:10 (for X=OH).[27] For terminating the sequence, cyclized radical **II** needs to be trapped by a mediator. In the present study, we used bromotrichloromethane for this purpose, providing 2-bromomethyltetrahydrofuran **3** as major oxygen radical-derived product.[8] The requested information on stereocontrolling effects of oxygen substituents in cyclizations then is stored in the *cis*/*trans*-ratio of bromocyclization product **3**. The second product of bromine atom transfer from bromotrichloromethane to carbon radical **II** is the trichloromethylradical, being essential for resuming the chain reaction.

For clarifying the role of the allylic oxygen substituent in stereoselectivity control for alkenoxyl radical 5-*exo*-cyclization, we conceived a set of six alkenoxyl radicals: three monosubstituted 4-pentenoxyl radicals (**Ia**–**c**), two homologues bearing acetyloxy groups in different relative configuration (*erythro*/*threo*-**Id**), and a third (**Ie**) having an allylic acyloxy group positioned next to two additional substituents (Fig. 2). As we became aware of the kinetic role of the allylic oxygen substituent, we included nonadienyloxyl radical **If** into the study, for exploring regioselectivity effects.

2.2. Convention used for numbering atom positions

Oxygen and carbon differ in priority for systematically naming aliphatic and heterocyclic compounds. For carbons in the aliphatic side chain of *O*-alkenyl ester **1**, and for the carbons of radical **I**, we adhered to the IUPAC-recommendation for aliphatic compounds.[28] A transition structure TS-**I** associated with 5-*exo*-cyclization, in the chosen stereochemical model, derives from tetrahydrofuran (cf. Section 2.5.3). Numbering atoms in intermediate TS-**I**, similar to tetrahydrofuran core of cyclized carbon radical **II**, and bromocyclization product **3** thus follows the Hantzsch and Widman convention (Fig. 3).[29,30]

For assigning configuration of vicinal stereocenters, we adhered in this article to descriptors *erythro* and *threo*. By this approach we feel, that the reader may easier follow differences in chemical selectivity, as configuration at one of the stereocenters changes.

2.3. 3-Alkenoxy-4-methylthiazole-2(3*H*)-thiones

2.3.1. Monosubstituted O-pentenyl thiohydroxamates. For constructing the alkenoxy group of thiohydroxamate **1a**, we connected in the initial step ethyl acetate to acrolein by a mixed aldol addition (Scheme 3).[31,32] The product formed in the addition, ethyl 3-

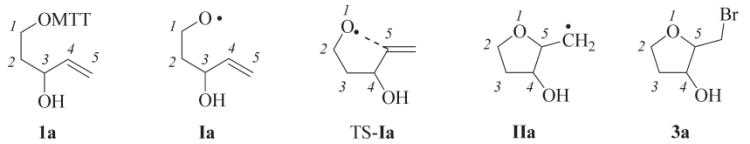
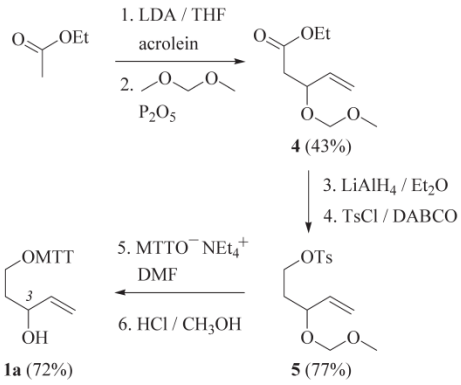
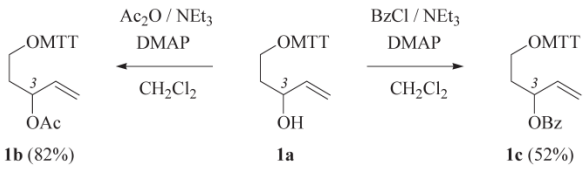


Fig. 3. Convention used in this article for numbering atoms in product classes associated with alkenoxyl radical cyclization, as exemplified for alkenoxythiazolethione **1a**, derived 4-alkenoxyl radical **Ia**, transition structure for 5-*exo*-cyclization TS-**Ia**, 5-*exo*-cyclized carbon radical **IIa**, and bromocyclization product **3a** (MTT=4-methyl-2-thiooxo-1,3-thiaz-3-yl).

hydroxypentenoate, eliminates water on standing. For preventing this elimination to occur, we converted the reactive hydroxy group into a methoxymethyloxy (MOMO)-group.[32,33] Subsequently, we transformed the ethoxycarbonyl group in ester **4** into primary alkyl sulfonate group in tosylate **5** by standard procedures.[32,34] Displacing the sulfonate group in tosylate **5** by the 4-methyl-2-thiooxo-(3*H*)-1,3-thiazyl-1-oxide anion furnishes a MOM-protected *O*-alkenyl thiohydroxamate, which was treated with hot acidic methanol for solvolytically cleaving off the acetal-protecting group. Esterifying the hydroxy group in alcohol **1a** with acetic anhydride gives acetate **1b**. Using benzoyl chloride as acylation reagent provides benzoate **1c** (Scheme 4).

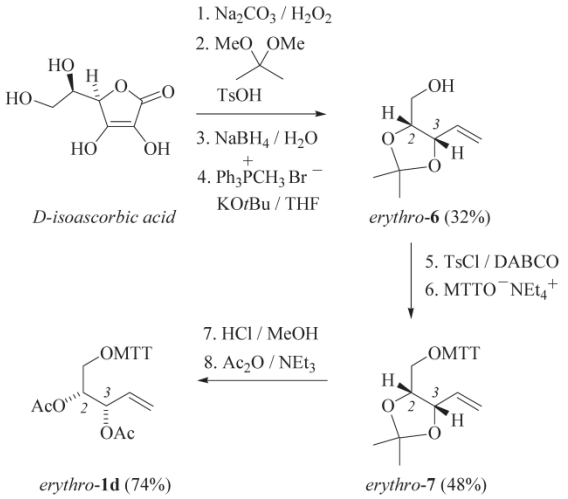


Scheme 3. Summary of functional group transformation for preparing 3-(3-hydroxypent-4-enyloxy)thiazolethione **1a** from ethyl acetate (MTTO=4-methyl-2-thiooxo-1,3-thiazyl-3-oxy; cf. Fig. 3).



Scheme 4. *O*-Acylation of 3-(3-hydroxypent-4-enyloxy)thiazolethione **1a**.

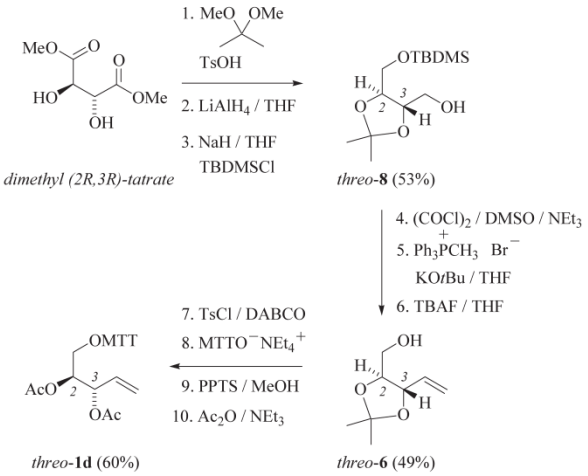
2.3.2. Disubstituted O-pentenyl thiohydroxamates. For preparing the *erythro*-configured side chain of *O*-(2,3-*erythro*-bisacetyloxypentenyl) thiohydroxamate *erythro*-**1d**, we started from D-erythronolactone. The lactone is synthetically available from D-isoascorbic acid by oxidatively removing two carbon atoms (Scheme 5). For preventing oxidative side reactions, we protected the two hydroxy groups of the lactone with 2,2-dimethoxypropane in acidic solution under kinetic control, leading to the derived acetonide.[35] Reducing the protected D-erythronolactone with sodium borohydride affords a lactol, which was treated with methanediyltriphenylphosphorous ylide to furnish alkenol *erythro*-**6**.[35–37] For converting alkenol *erythro*-**6** into *O*-alkenyl thiohydroxamate *erythro*-**7**, we adhered to methods already summarized in Scheme 3.[24,38,39] At the final stage, we again changed protecting groups at oxygen from acetonide, required for synthesis, to acyl required for alkenoxyl radical cyclization.[40]



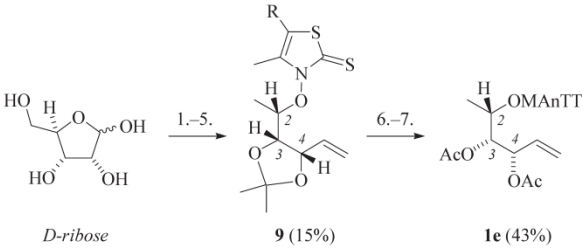
Scheme 5. Preparing of 3-[2,3-*erythro*-2,3-bis-(acetyloxy)pent-4-en-1-oxy]thiazolethione *erythro*-**1d** from D-isoascorbic acid.

For preparing *O*-(*threo*-2,3-bisacetyloxypentenyl) thiohydroxamate *threo*-**1d**, we used dimethyl (2*R*,3*R*)-tartrate as starting material. The ester comprises two stereocenters in the required configuration and two functional groups for building the carbon skeleton of target compound *threo*-**1d**. One of the ester groups served in a sequence adapted from synthesis of diastereomer *erythro*-**1d** for introducing the thiohydroxamate functional group at a primary carbon. The second ester group was used for constructing the alkene entity needed for conducting the alkenoxyl radical cyclization. By this strategy, we obtained monosilyl-protected diol *threo*-**8** as first key intermediate, acetonide-protected 4-pentenetriol *threo*-**6** as second and *O*-alkenyl thiohydroxamate *threo*-**1d** as final product[41–45](Scheme 6).

*2.3.3. Trisubstituted O-pentenyl thiohydroxamate **1e**.* For accomplishing synthesis of D-*arabino*-configured thiohydroxamate **1e** we extended the five carbon chain from D-ribose by one carbon in a Wittig-alkenylation, and inverted configuration at carbon C2 in the thiohydroxamate O-alkylation step (Scheme 7). For simplifying work-up procedures we, again, used the acetonide protecting group for the glycol segment. The thiohydroxamic acid we changed to 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione,



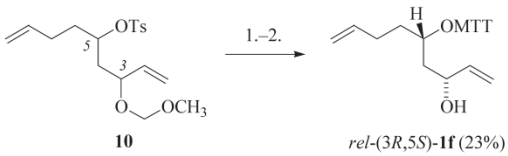
Scheme 6. Synthesis of 3-[2,3-*threo*-2,3-bis-(acetyloxy)pent-4-en-1-oxy]thiazolethione *threo*-**1d** from dimethyl (2*R*,3*R*)-tartrate.



Scheme 7. Synthesis of 2,3,4-*arabino*-configured 3-(hexenoxy)thiazolethione **1e** from D-ribose [R=4-methoxyphenyl; reagents and conditions – 1. step: acetone, concentrated sulfuric acid (81% yield);[47] 2. step: iodine, imidazole, triphenylphosphine, toluene/acetonitrile (54% yield);[48,49] 3. step: palladium on charcoal, hydrogen, ethanol (97% yield);[50,51] 4. step: methyl triphenylphosphonium bromide, potassium *tert*-butoxide, tetrahydrofuran (67% yield); 5. step: 3-hydroxy-4-methyl-5-(4-methoxyphenyl)-1,3-thiazole-2(3*H*)-thione (MAnTTOH), diethyl azodicarboxylate, triphenylphosphine, benzene (54% yield); 6. step: hydrogen chloride, methanol (96% yield); 7. step: acetic anhydride, 4-(*N*,*N*-dimethylamino)pyridine, dichloromethane (45% yield)].

providing a crystalline target compound **1e**, for purifying the ester in the final step by crystallization.[46]

2.3.4. O-(3-Hydroxy-5-nona-1,8-dienyl) thiohydroxamate ***1f****.* For preparing the C9-carbon skeleton of dienyl tosylate **10** we added but-3-en-1-yl magnesium bromide to 3-(methoxymethyloxy)pent-4-enal and esterified the resulting product, 3-(methoxymethyloxy) nona-1,8-dien-5-ol, with *p*-toluenesulfonyl chloride. Heating tosylate **10** with 3-hydroxy-4-methyl-1,3-thiazole-2(3*H*)-thione



Scheme 8. Preparing 3-(3-hydroxynona-1,8-dien-5-yl)thiazolethione *rel*-(3*R*,5*S*)-**1f** from dienyl tosylate **10** (Supplementary data) [reagents and conditions – 1. step: 3-hydroxy-4-methyl-1,3-thiazole-2(3*H*)-thione tetraethylammonium salt, DMF, 40 °C (67% yield); 2. step: hydrogen chloride, methanol, and column chromatography for separating diastereomers {*rel*-(3*R*,5*S*)-**1f**: 35% yield}].

tetraethylammonium salt in DMF yields a MOM-protected *O*-dienyl thiohydroxamate as 50/50-mixture of stereoisomers. The diastereomers separate on the silica gel column, used for purifying the 3-(3-hydroxynona-1,8-dien-5-yl)thiazolethione **1f** after having solvolytically cleaved off the MOM-protecting group (Scheme 8). Only isomer *rel*-(3*R*,5*S*)-**1f** provided a correct combustion analysis and was therefore considered in the subsequent alkenoxyl radical study.

2.3.5. Stereochemical analysis. All stereocenters of *O*-alkenyl thiohydroxamates *erythro*-**1d**, *threo*-**1d**, and **1e** derive from enantiopure natural products. All synthetic manipulations used for transforming the starting materials into the target compounds occurred stereospecifically, as concluded from single sets of resonances in proton- and carbon-13 NMR-spectra (Experimental, Table 1). For unknown reasons, optical rotations recorded for *erythro*-**1d** and *threo*-**1d** scattered from batch to batch, and in one instance even changed sign. Since stereochemical information obtained by transforming single diastereomers suffice to answer all relevant question associated with the study, we refrained from emphasizing absolute configuration of *O*-alkenyl thiohydroxamates *erythro*/*threo*-**1d** and **1e** hereafter.

2.4. Homolytic bromocyclization

2.4.1. Parameters for conducting alkenoxyl radical reactions. For studying the chemistry of 4-pentenoxyl radicals **1a**–**f**, we adhered to a standardized protocol derived from preceding mechanistic investigations.[8,22,24] Operational standards thereby relate to (i) the experimental set-up, (ii) methods for quantifying products, and (iii) structure analysis.

(i) *Experimental set-up.* For securing that yields and selectivity are not flawed by technical details associated with the initiating step, we used photochemical and thermal activation for initiating radical chain reactions. In the following, we assessed yields and product manifolds obtained from *O*-esters **1a** and **1b** under both conditions, for deciding which of the methods to use as standard.

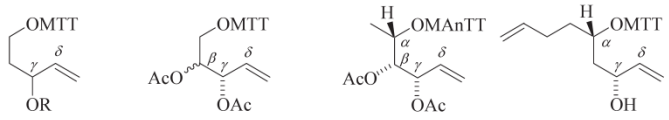
The most effective way for initiating a radical reaction photochemically started from a 83-millimolar solution of **1a** in perdeuterobenzene containing bromotrichloromethane. The solution was irradiated in a Rayonet®-chamber reactor equipped with twelve 350-nm light bulbs. This set-up gave 2-methylsulfanylthiazole **2** in 59% and bromoethers **3a**/**11a** in 71% yield. For initiating the radical reaction thermally, we heated a likewise prepared solution of **1a** in the presence of azobisisobutyronitrile (AIBN) as chemical initiator. The thermal version of the radical reaction gave 88% of bromoethers **3a**/**11a** in total, and co-product **2** in 81% yield.

The same trend for providing elevated yields under thermal conditions was seen for reactions between *O*-acetyl-substituted ester **1b** and bromotrichloromethane. For example, heating **1b** in a 83-millimolar solution of perdeuterobenzene and bromotrichlormethane gave *O*-acetyloxybromoethers **3b**/**11b** in 89% combined yield, and 90% of thiazole **2**. The photochemical reaction provided 77% of bromocyclization products **3b**/**11b** and 71% of co-product **2**. By comparing yields we finally decided to use the thermal method as standard for conducting alkenoxyl radical bromocyclizations of *O*-alkenylthio-hydroxamates **1a**–**f**. Benzoate **1c**, under thermal conditions, gave 95% of thiazole **2** and a combined yield of 94% for brominated ethers **3c**/**11c**.

Regarding reaction times, thermally initiated conversions of *O*-alkenyl esters **1a**–**c** took no longer than two hours for completion. Extending reaction times diminishes yields and causes side-products to appear.

Photoreactions of standardized solutions of esters **1a**–**b** were complete within one hour. In some of the experiments the

Table 1
Chemical shifts of oxygen-bound carbons and the inner alkene proton of *O*-alkenyl thiohydroxamates **1a**–**f** (in $CDCl_3$, ambient temperature)



1a–c *erythro*/*threo*-**1d** **1e** (±)-**1f**

Entry	1/R	C^{α}/ppm	C^{β}/ppm	C^{γ}/ppm	H^{δ}/ppm
1	**1a**/H	73.1	35.1	68.5	5.94 (ddd)
2	**1b**/Ac	72.0	32.5	71.1	5.85 (ddd)
3	**1c**/Bz	72.0	32.6	71.7	5.97 (ddd)
4	*erythro*-**1d**	72.5	71.2	73.3	5.83 (ddd)
5	*threo*-**1d**	73.8	70.8	72.0	5.90 (ddd)
6	**1e**	74.0	72.1	76.9	5.79 (ddd)
7	(±)-**1f**	84.5	—[a]	71.0	5.94 (ddd)

[a] Not assigned; for entire sets of chemical shifts, see the Experimental.

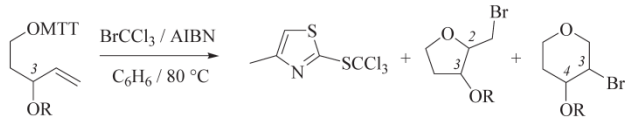
reaction mixture turned in an unpredictable manner yellowish or turbid with some of the starting material still present. Extending the reaction time quantitatively causes substrate **1** to quantitative turn over, however, by also leading to a higher product manifold.[22,52]

(ii) *Methods for quantifying products.* For obtaining the original stereochemical information from bromocyclization product **3**, information on chemoselectivity for the reaction between thiohydroxamate **1** and $BrCCl_3$, and maximum yields of products, we

*2.4.2. Bromocyclization of monosubstituted O-(4-pentenyl) thiohydroxamates **1a**–**c**.*

(i) *Products.* In a larger scale-up experiment, conducted under thermal conditions, 1.12 mmol monosubstituted *O*-alkenyl thiohydroxamate **1a** gave 56% of 2-bromomethyl-tetrahydrofuran-3-ol (**3a**), 4% of 4-bromotetrahydropyran-3-ol (**11a**), and 84% of disubstituted thiazole **2** (Table 2, entry 1). Tetrahydrofuran **3a** was formed under such conditions as 74/26-mixture of 2,3-*cis*/*trans*-isomers.

Table 2
Products formed from *O*-(4-pentenoxy)thiazolethiones **1a**–**c** and bromotrichloromethane



1a–c **2** **3a–c** **11a–c**

Entry	**1**/R	**2**/%	**3**/% (*cis*:*trans*)[a]	**11**/% (*cis*:*trans*)[b]
1	**1a**/H	84	**3a**: 56 (74:26)	**11a**: 4 (65:35)
2	**1b**/Ac	94	**3b**: 71 (68:32)	**11b**: 11 (57:43)
3	**1c**/Bz	75	**3c**: 69 (68:32)	**11c**: 12 (50:50)

[a] Stereodescriptors refer to configuration at carbons C2 and C3.
[b] Stereodescriptors refer to configuration at carbons C3 and C4.

injected samples taken directly from solutions of products in perdeuterobenzene into a gas chromatograph equipped with a flame ionization detector and coupled to a mass spectrometer. For cross-checking structural assignments, we analyzed samples from the same mixture by NMR-spectroscopy (proton and carbon-13).

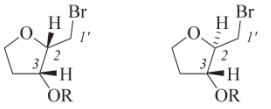
(iii) *Structure analysis.* All products described in this article were characterized by high resolution mass spectrometry, combustion analysis, and NMR-spectroscopy for constitution analysis. For assigning relative configuration of bromocyclization products (i.e., **3**), we relied on shift differences of carbon-13 resonances between *cis*/*trans*-isomers (vide infra). For deducing constitution and, wherever possible, relative configuration of brominated tetrahydropyrans, being formed in 13% yield and less (cf. Section 2.5.2), we used mass spectrometry in combination with NMR-spectroscopy. In one instance (for **11a**), we independently prepared a bromotetrahydropyran for securing our interpretation.

O-Acetyl-substituted ester **1b** yielded 71% of tetrahydrofuran **3b** as 68/32-mixture of 2,3-*cis*/*trans*-isomers, 11% of tetrahydropyran **11b** and 94% of thiazole **2** under standard conditions (Table 2, entry 2).

O-Benzoyl-substituted thiohydroxamate **1c** provided 69% of disubstituted tetrahydrofuran **3c** as 68/32-mixture of 2,3-*cis*/*trans*-isomers, 12% of tetrahydropyran isomer **11c** and 75% of thiazole **2**, when heated with bromotrichloromethane (Table 2, entry 3).

(ii) *Stereochemical analysis.* For assigning relative configuration of 5-*exo*-bromocyclization product **3** we relied on a systematic highfield shift of resonances for carbons C2, C3, and for exocyclic bromomethyl carbon C1′ in 2,3-*cis*-isomers. This guideline derives from a combined NMR-spectroscopy/X-ray-diffraction study on di- and trisubstituted tetrahydrofurans.[8,12] Highfield shifts of resonances in cis-isomers arise from steric deshielding of interacting nuclei (Table 3).[53]

Table 3
Carbon-13 NMR-chemical shifts for *cis*/*trans*-isomers of 2,3-substituted tetrahydrofurans **3a**–**c** (in $CDCl_3$, ambient temperature)



(±)-*cis*-**3a**–**c** (±)-*trans*-**3a**–**c**

Entry	**3**/R	C2/ppm	C3/ppm	C1′/ppm
1	*cis*-**3a**/H	82.2	71.9	29.0
2	*cis*-**3b**/Ac	80.8	73.7	28.4
3	*cis*-**3c**/Bz	81.2	74.5	28.7
4	*trans*-**3a**/H	85.1	75.1	32.8
5	*trans*-**3b**/Ac	83.2	77.4	33.1
6	*trans*-**3c**/Bz	83.3	78.0	33.2

2.4.3. Products from erythro/threo-isomers of 3-[2,3-bis-(acetyloxy) pent-4-enyloxy]-4-methyl-1,3-thiazole-2(3H)-thione ***1d****.*

(i) *Products.* *O*-(2,3-Bisacetyloxypentenyl) thiohydroxamate *erythro*-**1d** furnished 67% of bromoethers *erythro*-**3d** and *erythro*-**11d** taken together, and 49% of disubstituted thiazole **2**, when heated in a laboratory microwave to 80 °C in a solution of α,α,α-trifluorotoluene under otherwise standard conditions (Scheme 9, top).

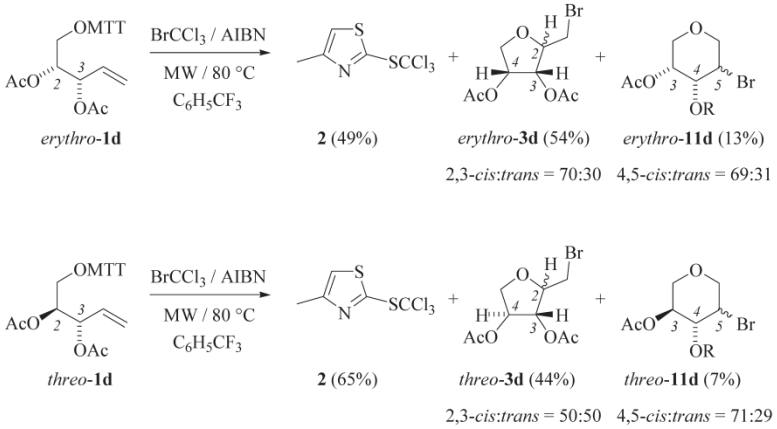
spectrometer, having one proton chelated by two vicinal acetyloxy groups.

Heating stereoisomer *threo*-**1d** in a solution of α,α,α-trifluorotoluene (80 °C) containing bromotrichloromethane and AIBN gave 65% of thiazole **2**, and a combined yield of 51% for bromocyclization products *threo*-**3d** and *threo*-**11d** (Scheme 9, bottom). For assigning constitution and configuration, we, again, relied on information gained from analyzing sets of *threo*-**3d**/**11d**-mixtures containing differing isomer ratios.

(ii) *Stereochemical analysis of tetrahydrofurans.* According to the stereochemical guideline for interpreting carbon-13 NMR-spectra described in Section 2.4.2, the major stereoisomer formed from *O*-pentenyl ester *erythro*-**1d** is the all-*cis*-configured tetrahydrofuran $cis_{erythro}$-**3d**. This guideline in a similar manner allows to assigning spectral data of cis_{threo}-**3d** from the equimolar mixture of diastereoisomers (Table 4).

2.4.4. Products from 3-[arabino-3,4-bis-(acetyloxy)hex-5-enoxy]-1,3-thiazole-2(3H)-thione ***1e****.*

(i) *Products.* *Arabino*-configured *O*-(3,4-bisacetyloxyhexenyl) thiohydroxamate **1e** reacted with bromotrichloromethane in boiling benzene containing AIBN to give 50% bromomethyltetrahydrofuran **3e**, and 10% of bromotetrahydropyran **11e**, and 55% of trisubstituted thiazole **12** (Scheme 10). Chromatography on silica gel allows to separate tetrahydropyran 4,5-*trans*-**11e** from



Scheme 9. Products formed from radical reactions between bromotrichloromethane and 3-[*erythro*-2,3-bis-(acetyloxy)pent-4-enoxy]thiazolethione *erythro*-**1d** [top; yields for experiment conducted via photochemical activation (λ=350 nm, 22 °C, 30 min) on a 196-millimolar scale of **1d** in C_6D_6 containing 9.6 equivalents of $BrCCl_3$: 77% of **2**, 68% of *erythro*-**3d** and *erythro*-**11d** taken together] and stereoisomer *threo*-**1d** [bottom; yields for experiment conducted via photochemical activation (λ=350 nm, 22 °C, 30 min) on a 196-millimolar scale of **1d** in C_6D_6, containing 9.0 equivalents of $BrCCl_3$: 53% of **2**, 72% of *threo*-**3d** and *threo*-**11d** taken together]; MW=microwave.

All attempts to chromatographically separate 2,3-*cis*/*trans*-isomers of bromoethers **3d** and **11d** gave in our hands product mixtures in differing ratios. Superimposing information gained from such mixtures allowed to characterize all products by chemical shifts and fine structures of proton resonances. In high resolution mass spectrometra bisacetates *erythro*-**3d**/**11d** showed the peculiar phenomenon of being by one proton heavier than calculated for the molecular formula $C_9H_{13}O_5Br$. This excess mass-per-charge unit is retained throughout the fragmentation of *erythro*-**3d**/**11d**, until one of the acetyl groups dissociates off. Given consistent proton integrals and fine structures in underlying NMR-spectra, we assigned molecular ions $C_9H_{14}O_5Br^+$ to derivatives of *erythro*-**3d**/**11d**, generated in the mass

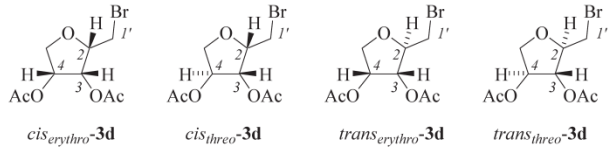
all-*cis*-configured tetrahydropyran 4,5-*cis*-**11e**, and a 2,3-*cis*/*trans*-mixture of bromomethyltetrahydrofuran **3e**.

(ii) *Stereochemical analysis.* From low field-shifted resonances of carbons C2–C4 and carbon C1′ we concluded that the major 5-*exo*-bromocyclization product obtained from *arabino*-configured *O*-hexenoxyl radical **Ie** is the 2,3-*trans*-stereoisomer of tetrahydrofuran **3e** (Table 5).

2.4.5. Products from 3-[rel-(3R,5S)-3-hydroxynona-1,8-dien-5-oxy]-4-methyl-1,3-thiazole-2(3H)-thione ***1f****.*

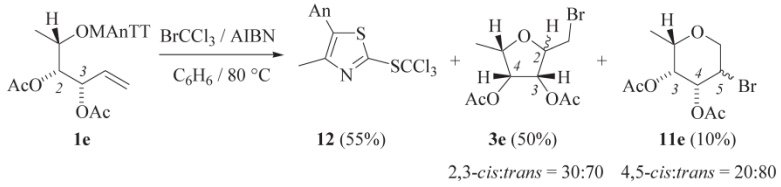
(i) *Products.* Heating or photolyzing *O*-nonadienyl thiohydroxamate **1f** in benzene/bromotrichloromethane-solutions

Table 4
Selected carbon-13 NMR-chemical shifts of 3,4-bisacetyloxy-2-bromomethyl-tetrahydrofurans *erythro*/*threo*-**3d** (in C_6D_6, ambient temperature)



cis$_{erythro}$-**3d** *cis*$_{threo}$-**3d** *trans*$_{erythro}$-**3d** *trans*$_{threo}$-**3d**

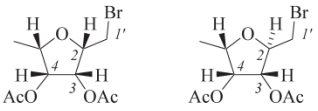
Entry	**3d**	C2/ppm	C3/ppm	C4/ppm	C1′/ppm
1	*cis*$_{erythro}$	79.2	71.9	72.2	29.2
2	*cis*$_{threo}$	80.2	76.4	77.9	28.0
3	*trans*$_{erythro}$	79.6	74.5	72.3	33.3
4	*trans*$_{threo}$	83.9	80.2	78.4	32.2



1e **12** (55%) **3e** (50%) **11e** (10%)
2,3-*cis*:*trans* = 30:70 4,5-*cis*:*trans* = 20:80

Scheme 10. Products formed from 3-[*arabino*-3,4-bis-(acetyloxy)hex-5-enoxy]-1,3-thiazole-2(3*H*)-thione **1e** and bromotrichloromethane.

Table 5
Proton and carbon-13 chemical shift values used for distinguishing tetrasubstituted tetrahydrofuran *cis*-**3e** from isomer *trans*-**3e** ($CDCl_3$, ambient temperature)



cis-**3e** *trans*-**3e**

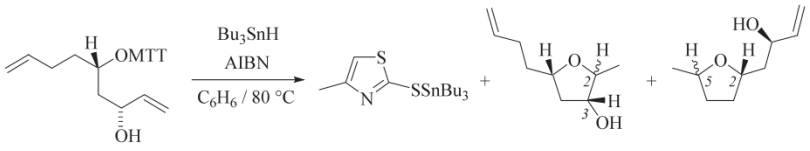
Entry	**3**	C2/ppm	C3/ppm	C4/ppm	C1′/ppm
1	*cis*-**3e**	77.9	72.9	72.4	29.4
2	*trans*-**3e**	78.1	74.9	73.6	33.7

gives products of sequential alkoxyl radical cyclization *and* bromotrichloromethane addition across the remaining carbon-carbon double bond.[52,54] For preventing such side reactions to occur, we changed the mediator from bromotrichloromethane to tributylstannane. This modification, in all instances studied so far, never changed stereo- and regioselectivity of alkenoxyl radical additions.[1,8]

Boiling a solution of *O*-nonadienyl ester **1f** in benzene in the presence of a 3.7-fold excess of tributylstannane, provided a 26/74-mixture of tetrahydrofurans **14** and **15** in a total yield of 76%, besides 79% of thiazole **13** (Scheme 11). Tin compound **13** fragments into 2-methylthiazole-2(3*H*)-thione and yet unidentified organotin derivatives when being contacted with silica gel, and therefore was characterized and quantified from the reaction mixture by proton-NMR spectroscopy.[24]

2,5-Substituted tetrahydrofuran **15** formed from *O*-nonadienyl ester **1f** and tributylstannane as 27/73-mixture of *cis*/*trans*-isomers, which we used for stereochemical analysis. Based on a model developed from theory for predicting selectivity in 5-*exo*-cyclization of monosubstituted 4-pentenoxyl radicals, we think that the major stereoisomer is disubstituted tetrahydrofuran *trans*-**15**.[1] Since most resonances of *cis*/*trans*-**15** overlap, we unfortunately could not conduct a more sophisticated stereochemical analysis at this point.

From the reaction mixture we furthermore separated trisubstituted tetrahydrofuran **14** as 20/80-mixture of 2,3-*cis*/*trans*-isomers in a total yield of 20%. This mixture, however, was contaminated by 13 percent by weight with a third product, showing in high resolution mass spectra identical molecular masses to tetrahydrofurans **14** and **15**. From supplementary NMR-spectroscopic information we concluded that the third product is a tetrahydropyran formed from 6-*endo*-cyclization. Since the yield of the product was rather low (3%), we were not able to provide at this point a complete structure analysis (see also Section 2.5.2). Given the propensity of hydroxyl-substituted alkoxyl radicals to afford a higher fraction of 6-*endo*-cyclized products, we propose that the third product arises from 6-*endo*-addition of **1f** to the allylic alcohol segment.



rel-(3*R*,5*S*)-**1f** **13** (79%) **14** (20%) **15** (56%)
dr = 20:80 *dr* = 27:73

Scheme 11. Products formed from 3-[*rel*-(3*R*,5*S*)-3-hydroxynona-1,8-dien-5-oxy]-4-methyl-1,3-thiazole-2(3*H*)-thione **1f** and tributylstannane.

(ii) *Analyzing regioselectivity in 5-exo-cyclization.* From a doublet of double-doublet fine structure for the inner alkene proton and larger shift dispersion for the two terminal protons, we concluded that the major cyclization product obtained from nonadien-5-yl ester **1f** is disubstituted tetrahydrofuran **15** (Fig. 4, top and bottom). In tetrahydrofuranol **14**, the resonance of the inner alkene proton is split into a triplet of double-doublet and the terminal protons are less shift-dispersed (Fig. 4, center).

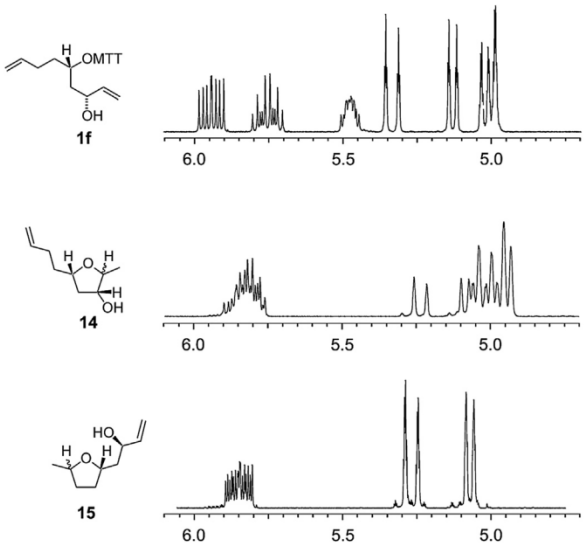


Fig. 4. Section of proton NMR-spectra displaying resonances of inner and terminal alkene protons of tetrahydrofurans **14** and **15**, and *O*-[*rel*-(3*R*,5*S*)-3-hydroxynona-1,8-dien-5-yl] thiohydroxamate **1f** for comparison.

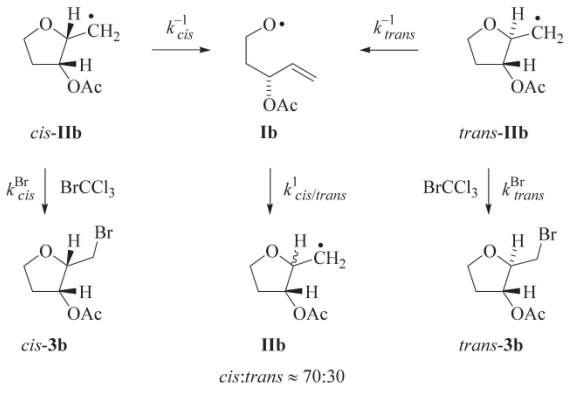
2.5. Mechanistic and stereochemical aspects

To find out what causes 3-substitued-4-pentenoxyl radicals **Ia**–**c** to cyclize 2,3-*cis*-selectively, we at first verified that the intramolecular addition follows kinetic control. For this purpose, we monitored stereochemical integrity of diastereomerically pure cyclized radicals *cis*-**IIb** and *trans*-**IIb** under conditions that extended their life-times by a factor 100.

2.5.1. On reversibility of 3-acyloxypent-4-en-1-oxyl radical 5-exo-cyclization.

(i) *Kinetic approach.* In a kinetically controlled reaction a notable barrier would prevent tetrahydrofuranyl-2-methyl radical *cis*-**IIb** or stereoisomer *trans*-**IIb** from ring opening to alkenoxyl radical **I** in a β-fragmentation. If the oxygen radical formed, a de-novo-cyclization would become apparent by altering stereochemical integrity of previously pure *cis*-**IIb** and *trans*-**IIb** towards an equilibrium mixture presumably of 68/32 (Scheme 12 and eq. 1). By extending the life-time of radicals *cis*-**IIb** and *trans*-**IIb** by, for example, a factor 100 compared to conditions applied in bromocyclization, the stereochemical fingerprint from a possible ring-opening should become apparent by stereochemical scrambling.

The kinetic life-time of carbon radical **IIb** in bromocyclization is defined as inverse pseudo-first order rate constant for homolytic substitution for brominative trapping. This rate constant numerically derives from the product between the rate constant k^{Br} and concentration of bromotrichloromethane (eq. 2).[55] In bromocyclization starting from a 0.2 molar solution of *O*-alkyl



$$\frac{d[\mathbf{3b}]}{dt} = k^{Br}[BrCCl_3][\mathbf{IIb}] \quad \text{(eq. 1)}$$

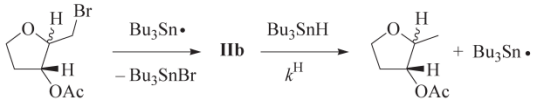
$$\textit{life-time for } \mathbf{IIb}\text{: } \tau = \frac{1}{k^{Br}[BrCCl_3]} \quad \text{(eq. 2)}$$

$$k^{Br}_{cis} = k^{Br}_{trans} \quad \text{(app. 1)}$$

Scheme 12. Scheme of elementary reactions, kinetic equations (eqs. 1–2) and approximation (app. 1) set up for identifying thermochemical contributions to 2,3-*cis*-selectivity in 5-*exo*-cyclization of 3-acetyloxypentenoxyl radical **Ib** (see also text).

thiohydroxamate **1b**, as used in the standard operational procedure, the concentration of bromotrichloromethane declines from 1.49±0.01 M at the beginning towards 0.91±0.01 M by the end. The rate constant k^{Br} for trapping primary carbon radicals *cis*-**IIb** and *trans*-**IIb**, is approximately 3.9×10^7 $M^{-1}s^{-1}$. This value derives from the experimental rate constant for hept-6-en-2-yl radical-trapping with bromotrichloromethane ($k^{Br}=1.2\times10^8$ $M^{-1}s^{-1}$ at 26 °C in benzene) divided by three.[56] The factor three corrects for a polar rate effect arising from alkyl substitution at the radical center.[57] Since rate effects of β-substituents are in general small, we assumed that $k^{Br}{}_{cis}$ and $k^{Br}{}_{trans}$ are identical (approximation 1).[58] Based on these approximations, life-times of *cis*/*trans*-**IIb** in standard bromocyclizations are 1.7×10^{-8} s at the beginning of the reaction, and 2.8×10^{-8} s by the end.

For experimentally extending tetrahydrofuran-2-methyl radicals life-times, we changed the mediator to tributylstannane. The tin compound traps, primary carbon radicals, for example the 1-butyl radical with a rate constant of $k^H=2.4\times10^6$ M^{-1} s^{-1} at 300 Kelvin in benzene, which is 16-times slower than the reaction with bromotrichloromethane (Scheme 13). The ratio k^{Br}/k^H remains constant, if activation parameters for the two processes respond

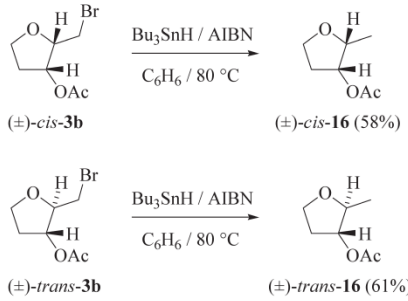


$$\frac{d[\mathbf{16}]}{dt} = k^H[\mathbf{IIb}][Bu_3SnH] \quad \text{(eq. 3)}$$

Scheme 13. Elementary reactions (top) and differential equation (bottom) for comparing rates and life-time of alkyl radical trapping under reductive conditions (eq. is short for equation).

similar to a change in reaction temperature. On the basis of this assumption, we extrapolated that the life-time of primary alkyl radicals *cis*/*trans*-**IIb** in a 0.17 molar solution of tributylstannane, as used for conducting the controls, extends to 2.5×10^{-6} s.

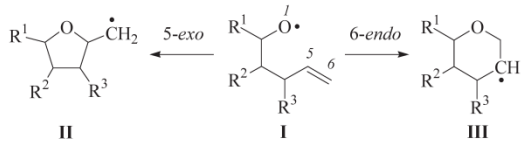
(ii) *Stereochemical study.* For putting our theoretical considerations on radical life-times into practice, we heated a 0.07 molar solution of 2-bromomethyltetrahydrofuran-3-yl acetate *cis*-**3b** in benzene with an excess of tributylstannane (c_0=0.17 M). The reduction furnishes diastereomerically pure 2-methyltetrahydrofuranyl acetate *cis*-**16**. Stereoisomer *trans*-**3b** reacts with tributylstannane under identical conditions to 3-acetyl-2-methyltetrahydrofuran *trans*-**16**. From gas chromatograms, we concluded that 2-methyltetrahydrofurans *cis*/*trans*-**16** form in essentially quantitative yield. The amount of products obtained after removing organotin compounds declined to 58–61% (Scheme 14). Since no stereochemical scrambling occurs upon reducing the two diastereomers of 2-bromomethyltetrahydrofuryl acetates **3b** we concluded that carbon radicals *cis*/*trans*-**IIb** retain configuration in the environment used for conducting homolytic bromocyclization.



Scheme 14. Reducing 2-bromomethyltetrahydrofurans *cis*/*trans*-**3b** with tributylstannane (diastereomeric purity of all products >98:2, according to information from GC-MS in combination with proton NMR-spectroscopy; for reactand concentrations, refer to the text).

2.5.2. On 6-endo-cyclization. Bromotetrahydropyrans **11a**–**e** are by-products in homolytic bromocyclization of *O*-alkenyl thiohydroxamates **1a**–**e**. From arguments summarized in Section 2.5.1, we expect 6-*endo*-cyclizations proceed kinetically controlled as well. The experimental tetrahydropyran/tetrahydrofuran-ratio exceeds in most instances the expectation value of 2/98, derived from cyclizations of allylic carbon-substituted 4-pentenoxyl radicals, by a factor 6–7 (Table 6).[2] We think that declining regioselectivity and

Table 6
Survey of selectivity data for cyclization of substituted 4-penten-1-oxyl radicals **Ia**–**e** (80 °C)



Entry	I	R^1	R^2	R^3	II:III[a]	2,3-*cis*:*trans*-II[b]
1	**Ia**	H	H	OH	94:6	74:26
2	**Ib**	H	H	OAc	87:13	68:32
3	**Ic**	H	H	OBz	85:15	68:32
4	*erythro*-**Id**	H	OAc	OAc	81:19	70:30
5	*threo*-**Id**	H	OAc	OAc	86:14	50:50
6	**Ie**	CH_3	OAc	OAc	83:17	30:70

[a] Approximated from ratio of bromine atom-trapping.
[b] Relative configuration of substituents at alkenoxyl radical carbons C2 and C3.

2,3-*cis*-selectivity in tetrahydrofuran synthesis have the same origin.

For elucidating constitution and configuration of minor cyclization products **11a**–**e**, we analyzed fragmentation pattern from electron impact mass spectra and carbon-13 NMR-chemical shift differences. A diagnostic tool for distinguishing a 2-bromomethyltetrahydrofuran from a 3-bromotetrahydropyran is the chemical shift of endocyclic ether carbons, which are high field-shifted by 1.7–14.0 ppm for the six-membered ring. For distinguishing *cis*-from *trans*-stereoisomers, we translated absolute values of vicinal coupling constants with the aid of the Karplus-relationship into dihedral angles, and assigned substituent positions accordingly to axial and equatorial locations in the chair conformation of tetrahydropyran.[59,60]

2.5.3. On the origin of 2,3-cis-selective pent-4-en-1-oxyl radical cyclization.

(i) *Transition structures.* In transition structures associated with 5-*exo*-C,O-cyclization, the radical oxygen, the inner alkene carbon (C5), and the allylic carbon (C4) lie for stereoelectronic reason in a plane. Carbons C2 and C3 are offset into opposite directions from this plane, leading to distorted twist (T)-conformers $^2T_3$ (Fig. 5, left) or $_2T^3$.

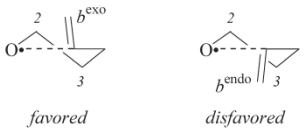


Fig. 5. Twist-model for predicting lowest in energy transition structures of the 4-pentenoxyl radical in 5-*exo*-trig-cyclization, having the terminal vinyl group located in *exo*-bisectional position (b^{exo}, favored), or *endo*-bisectional orientation (b^{endo}, disfavored).

(ii) *Preferred sites for placing substituents.* 2,3-*cis*-Cyclization, in the twist-model, proceeds via transition structures having the substituent at carbon C4 located pseudo-axially, forming a plane with the alkene carbons (Fig. 6, left). Rotating the vinyl substituent by 180° causes atoms C2 and C3, for arguments summarized in Fig. 5, to interchange positions with respect to the twist plane. This conformational change causes carbon C2 to flip underneath, and carbon C3 above the twist plane, transforming a $^2T_3$-into a $_2T^3$-conformer. The allylic substituent thereby changes position in the twist-conformer from pseudo-axial to pseudo-equatorial. In pseudo-equatorial orientation, a sterically demanding group at carbon C4, for instance methyl, *tert*-butyl, or phenyl, experiences less strain from other substituents and the heterocyclic core (Fig. 6, right).[2,7]

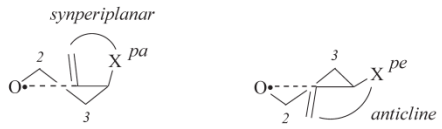


Fig. 6. Twist-models for transition structures leading to 2,3-*cis*- (left; *pa*=pseudo-axial) or 2,3-*trans*-5-*exo*-cyclized products (right; *pe*=pseudo-equatorial) from 4-pentenoxyl radicals.

(iii) *Theory of reactive conformers.* Substituents favoring 2,3-*cis*-cyclization are able to overcompensate repulsion from synperiplanar orientation of the vinyl group and pseudo-axially

orientation of the substituent. Opponents to steric effects in chemical reactivity are polar effects. Alkoxyl radical additions to carbon–carbon double bonds are fast and exothermic reactions having, according to Hammond's postulate, transition structures located early on the reaction coordinate. A valid theory for interpreting selectivity based on polar effects in transition structures located early on a reaction coordinate is frontier molecular orbital (FMO)-theory.

The major difference between transition structures leading to 2,3-*cis*- and 2,3-*trans*-cyclization of a 3-substituted 4-pentenoxyl radical arises from relative orientation between allylic substituent X and the plane of the carbon–carbon double bond, which, in turn, effects the π(C,C)-bond energy. In transition structures associated with 2,3-*trans*-cyclization the alkene and the allylic oxygen substituent adopt an anticline conformation, allowing π-electrons to delocalize into the σ*(C,O)-orbital (for X=O: Fig. 7, right). In transition structures associated with 2,3-*cis*-cyclization, the alkene entity is not similarly stabilized and therefore a better electron donor for the singly occupied molecular orbital (SOMO) of the oxygen radical (for X=O: Fig. 7, left).

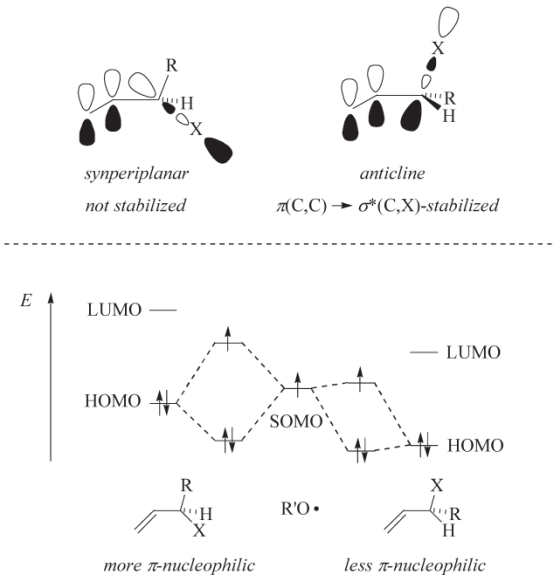


Fig. 7. Correlation diagram describing angle dependency of frontier molecular orbital (FMO)-interactions in acceptor-substituted butenes used for explaining the kinetic origin of 2,3-*cis*-selectivity in oxygen radical additions (R=e.g., CH_3 or $CH_2CH_2O^{\bullet}$, R'=e.g., primary, secondary, and tertiary alkyl; X=e.g., OH, OAc, OBz).

In a kinetically controlled reaction, differences in transition structure energies translate into free activation energy differences for competing reaction pathways, as expressible in a selectivity parameter, for example, a relative rate constant. From this argument we concluded that the π(C,C)→σ*(C,O)-interaction reduces the rate constant for 2,3-*trans*-cyclization, allowing 2,3-*cis*-cyclization to become the more effective pathway for 5-*exo*-cyclization. Experimentally, the rate effect of an allylic hydroxy group becomes apparent in cyclization of the 3-hydroxynona-1,8-dien-5-oxyl radical **1f**, which favors addition to the unsubstituted terminal double bond by a factor three.

Stabilizing FMO-interactions between an allylic hydroxy group and the alkene have been put forward earlier for explaining anticline conformation of but-3-en-2-ol in the ground state.[61] Rotating the hydroxy and the vinyl group about the σ(C2,C3)-bond uncouples π(C,C)→σ*(C,O)-electron delocalization, raising the HOMO-energy of but-3-en-2-ol, until the hydroxy group and the alkene align coplanar in the energetic maximum.

(iv) *2,3-cis-Directing effect in multiply substituted 4-pentenoxyl radicals.* In proposed transition structure TS-$cis_{erythro}$-**Id**, the allylic acetyloxy group and the π(C,C)-bond align synperiplanar. The second acetyloxy group adopts an equatorial position, which is the preferred position for steric reasons. Changing orientation of the underlying twist conformation directs both acetyloxy substituents in transition structure TS-$trans_{erythro}$-**Id** into unfavorable positions – pseudo-equatorial for the allylic group and axial for the substituent at carbon C2 (Fig. 8, top). By favoring intermediate TS-$cis_{erythro}$-**Id** the reaction leads to all-*cis*-configured tetrahydrofuran $cis_{erythro}$-**3d** as major product from *O*-alkenyl thiohydroxamate *erythro*-**1d**.

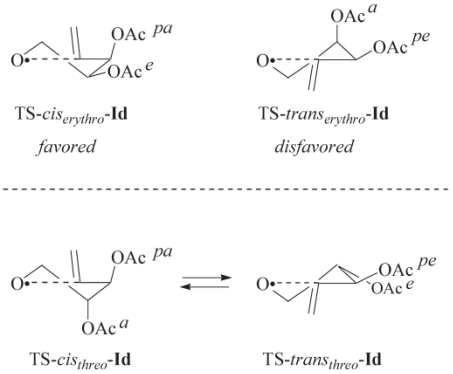


Fig. 8. Transition structure models for explaining stereoselectivity in 5-*exo*-trig-cyclization on the basis of cumulative polar and steric substituent effects in 2,3-diacetyloxy-4-pentenoxyl radicals *erythro*-**Id** and *threo*-**Id** (*a*=axial, *pa*=pseudo-axial, *pe*=pseudo-equatorial, *e*=equatorial).

In transition structure TS-cis_{threo}-**Id**, the allylic acetyloxy group aligns synperiplanar to the π-bond and the second axial. In diastereomorphic transition structure TS-$trans_{threo}$-**Id**, the situation for the two acetyloxy groups reverses – being electronically disfavored for the substituent in position 3 and sterically favored for position 2 (Fig. 8, bottom). Polar and steric effects in both of the proposed transition structures seem to counterbalance, offering no obvious preference for either pathway and explaining a 50/50-stereoselectivity for homolytic bromocyclization of *O*-alkenyl thiohydroxamate *threo*-**1d**. *arabino*-Configured 4-pentenoxyl radical **Ie** cyclizes 2,3-*trans*-selectively. The methyl substituent becomes the principal stereoinductor, guiding 5-*exo*-cyclization by steric effects (Fig. 9). Density functional theory predicts the transition structure for 2,5-*trans*-cyclization of the 5-hexen-2-oxyl radical to be 3 kJ mol^{-1} lower in free activation energy than the transition structure leading to 2,5-*cis*-cyclization. This value poses an

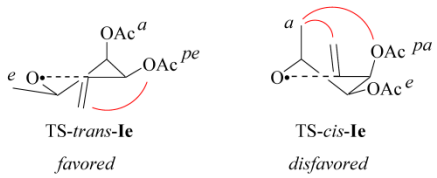


Fig. 9. Transition structure models for explaining 2,5-*trans*-selectivity in 5-*exo*-trig-cyclisation of *arabino*-configured 3,4-bis(acetyloxy)-5-hex-2-oxyl radical **Ie** (*a*=axial, *pa*=pseudo-axial, *pe*=pseudo-equatorial, *e*=equatorial; arcs symbolize steric repulsion between interconnected substituents).

approximate upper limit for the 2,3-*cis*-directing effect of the acetyloxy group.

3. Concluding remarks

2,3-*cis*-Selectivity arises from electrophilicity at oxygen in homolytic addition to non-activated double bonds on one side and a stereoelectronic effect exerted by an allylic hydroxy, acetyloxy or benzoyloxy substituent on the other. This combination kinetically disfavors 2,3-*trans*-ring closures of 3-acceptor-subsituted 4-pentenoxyl radicals, allowing the a 2,3-*cis*-stereoisomer of a substituted tetrahydrofuran to become principal cyclization product.

According to theory, 2,3-*cis*-selectivity should extend to other acceptor groups X in allylic position and to other electrophilic radicals. The stronger X withdraws π-electrons toward the σ*(C,X)-orbital, the more pronounced 2,3-*cis*-stereocontrol shall be. At some point, we expect steric repulsion between the vinyl group and X to counteract the polar 2,3-*cis*-directing effect. Using Winstein-Holness *A*-parameters[62,63] and electronegativity of atoms, we expect allylic halogens to be potential 2,3-*cis*-directing substituents. Nitrogen and sulfur groups, on the other hand possibly are borderline cases.

Addressing questions of this kind will help to expand our knowledge about polar effects in oxygen radical chemistry and the role such effects play for controlling selectivity in homolytic carbon–oxygen bond formation.[8,64–66] This is particularly interesting because 2,3-*cis*-selectivity adds a component to synthesis of tetrahydrofurans in pH-neutral non-oxidative environment, not available so far from carbon substitution. The key for refining the existing reaction model, as far as we understand the mechanism, lies in the interplay between steric and polar substituent effects acting on transition structures. We will report in an upcoming article on this topic.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see the Supplementary data.

4.2. 3-Alkenoxythiazole-2(3*H*)-thiones

4.2.1. General method for hydroxy group O-acetylation. A solution of 3-alkenoxythiazole-2(3*H*)-thione MTTOR **1b** or **1d**–**e** (1 equiv), triethylamine (0.5–3.8 equiv), *N*,*N*-dimethylaminopyridine (DMAP, 0.1–0.35 equiv) in dichloromethane (6–25 mL/mmol MTTOR) was treated at 0 °C with acetic anhydride (2.4–5.0 equiv). The mixture was stirred for 12–22 h at 22 °C and treated afterwards with water (7.5 mL/mmol MTTOR). Extracting the reaction mixture with diethyl ether (3×10 mL/mmol MTTOR) furnishes an organic solution, which was successively washed with water, an aqueous saturated solution of $NaHCO_3$, and brine (je 15 mL/mmol MTTOR). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure (600 mbar, 40 °C) to leave a residue, which was crystallized from the solvent specified below, or purified by chromatography on silica gel (SiO_2) as stationary phase.

*4.2.2. 3-(3-Hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1a**).* A solution of 3-[3-(methoxymethyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (2.51 g, 9.11 mmol; Supplementary data) in methanol (57 mL) was treated with aqueous hydrochloric acid [4.7 mL, 37% (*w*/*w*)]. Stirring at 22 °C was continued for 3 days and 30 min. Water (60 mL) was afterwards added to furnish a mixture, which was extracted with diethyl ether (3×70 mL). Combined organic extracts were washed with an aqueous saturated solution of $NaHCO_3$ (70 mL) and brine (70 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C) to afford a residue that was purified by chromatography (diethyl ether). Yield: 1.81 g (7.82 mmol, 86%), pale yellow oil. R_f=0.36 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (dddd, 1 H, *J*=14.8, 9.8, 5.0, 3.7 Hz), 2.07 (dddd, 1 H, *J*=14.7, 9.8, 4.4, 3.4 Hz), 2.31 (d, 3 H, *J*=1.0 Hz), 3.54 (s, 1 H, OH), 4.39–4.43 (m, 1 H), 4.59–4.64 (m, 2 H), 5.14 (dt, 1 H, J_d=10.5 Hz, J_t=1.5 Hz), 5.33 (dt, 1 H, J_d=17.2 Hz, J_t=1.6 Hz), 5.94 (ddd, 1 H, *J*=17.2, 10.6, 5.5 Hz), 6.21 (d, 1 H, *J*=1.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 35.1, 68.5, 73.1, 103.2, 114.7, 137.8, 139.9, 180.4. Anal. Calcd for $C_9H_{13}NO_2S_2$ (231.34): C, 46.73; H, 5.66; N, 6.05; S, 27.72; found: C, 46.71; H, 5.76; N, 6.13; S, 27.89.

*4.2.3. 3-(3-Acetyloxypent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1b**).* From 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (462 mg, 2.00 mmol), triethylamine (486 mg, 4.80 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 24 mg, 0.20 mmol) and acetic anhydride (490 mg, 4.80 mmol) in dichloromethane (12 mL) according to procedure 4.2.1. Yield: 447 mg (1.64 mmol, 82%), colorless crystalline solid, mp 63–64 °C (from diethyl ether/pentane). R_f=0.30 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 3 H, CH_3), 2.16–2.22 (m, 2 H), 2.26 (d, 3 H, *J*=1.2 Hz), 4.39–4.45 (m, 1 H), 4.48–4.53 (m, 1 H), 5.24 (dt, 1 H, J_d=10.5 Hz, J_t=1.1 Hz), 5.33 (dt, 1 H, J_d=17.2 Hz, J_t=1.2 Hz), 5.47–5.52 (m, 1 H), 5.85 (ddd, 1 H, *J*=17.2, 10.6, 6.3 Hz), 6.15 (d, 1 H, *J*=1.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 21.2, 32.5, 71.1, 72.0, 102.7, 117.6, 135.5, 137.5, 170.1, 180.4. Anal. Calcd for $C_{11}H_{15}NO_3S_2$ (273.38): C, 48.33; H, 5.53; N, 5.12; S, 23.46; found: C, 48.39; H, 5.58; N, 5.17; S, 23.38.

*4.2.4. 3-(3-Benzoyloxypent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1c**).* Pyridine (0.35 mL, 4.30 mmol) was added at room temperature to a solution of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (500 mg, 2.15 mmol) in dichloromethane (38 mL). The reaction mixture was cooled to 0 °C and treated at this temperature in a dropwise manner with benzoyl chloride (604 mg, 4.30 mmol). The resulting mixture was stirred for 20 h at 22 °C and treated afterwards with water (20 mL). Extracting the reaction mixture with dichloromethane (3×20 mL) furnishes an organic solution which was washed with brine (2×10 mL), dried ($MgSO_4$), and concentrated under reduced pressure (600 mbar, 40 °C). The remaining residue was purified by chromatography [SiO_2, diethyl ether/pentane=1:1(*v*/*v*)]. Yield: 374 mg (1.11 mmol, 52%), pale yellow oil. R_f=0.29 [diethyl ether/pentane=1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (d, 3 H, *J*=1.4 Hz), 2.33–2.36 (m, 2 H), 4.42–4.47 (m, 1 H), 4.60–4.65 (m, 1 H), 5.28 (dt, 1 H, J_d=10.5 Hz, J_t=1.2 Hz), 5.42 (dt, 1 H, J_d=17.2 Hz, J_t=1.3 Hz), 5.75–5.79 (m, 1 H), 5.97 (ddd, 1 H, *J*=17.1, 10.7, 6.1 Hz), 6.12 (d, 1 H, *J*=1.3 Hz), 7.43–7.47 (m, 2 H), 7.56–7.59 (m, 1 H), 8.05–8.07 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 32.6, 71.7, 72.0, 102.7, 117.7, 128.5, 129.6, 130.0, 133.2, 135.5, 137.6, 165.6, 180.4. Anal. Calcd for $C_{16}H_{17}NO_3S_2$ (335.44): C, 57.29; H, 5.11; N, 4.18; S, 19.12; found: C, 57.21; H, 5.22; N, 4.05; S, 19.05.

*4.2.5. 3-[(2R,3S)-2,3-Bis(acetyloxy)-pent-4-en-1-oxy]-4-methylthiazole-2(3H)-thione erythro-(**1d**).* A solution of 3-[(2*R*,3*S*)-isopropylidendioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(**7**) (980 mg, 3.41 mmol) in methanol (70 mL) was treated with aqueous hydrochloric acid [2.76 mL, 37% (*w*/*w*)]. The reaction mixture was stirred for 8 h at 22 °C. Diethyl ether (20 mL) was added and the mixture was extracted with diethyl ether/petroleum ether=2:1 (*v*/*v*) (3×30 mL). Combined organic solutions were concentrated under reduced pressure (370 mbar, 40 °C) to leave 3-[(2*R*,3*S*)-dihydroxypent-4-en-1-oxy]-4-methylthiazole-

2(3*H*)-thione as product, which was used as obtained in the succeeding step. Yield: 669 mg (2.73 mmol, 80%), colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.32 (d, 3 H, J=1.2 Hz), 3.06 (br s, 1 H), 3.94 (d, 1 H, J=1.2 Hz), 4.05 (br s, 1 H), 4.33 (br s, 1 H), 4.36 (dd, 1 H, J=9.4, 6.8 Hz), 4.49 (dd, 1 H, J=9.4, 3.8 Hz), 5.28 (d, 1 H, J=10.6 Hz), 5.38–5.45 (m, 1 H), 5.95 (ddd, 1 H, J=17.0, 10.8, 5.7 Hz), 6.23 (d, 1 H, J=1.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 71.7, 72.9, 78.7, 103.4, 117.3, 136.1, 138.0, 180.6. 3-[(2*R*,3*S*)-2,3-dihydroxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (524 mg, 2.12 mmol), triethylamine (818 mg, 8.08 mmol, 1.12 mL), *N*,*N*-dimethylaminopyridine (DMAP, 26.0 mg, 0.21 mmol) and acetic anhydride (821 mg, 8.04 mmol, 0.76 mL) were dissolved in dichloromethane (50 mL) according to general procedure 4.2.1. Eluent used for chromatographic purification: ethyl acetate/pentane=2:1 (*v*/*v*). Yield: 655 mg (1.98 mmol, 93%), yellow oil. R_f=0.40 [petroleum ether/diethyl ether=1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3 H), 2.11 (s, 3 H), 2.24 (d, 3 H, J=1.2 Hz), 4.46 (dd, 1 H, J=9.6, 7.0 Hz), 4.78 (dd, 1 H, J=9.6, 2.5 Hz), 5.33–5.42 (m, 3 H), 5.57 (ddt, 1 H, J_d=6.1, 4.8 Hz, J_t=1.2 Hz), 5.83 (ddd, 1 H, J=17.1, 10.6, 6.4 Hz), 6.15 (d, 1 H, J=1.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2, 20.9, 21.0, 71.2, 72.5, 73.3, 102.7, 120.1, 131.3, 137.3, 169.6, 170.0, 180.4. Anal. Calcd for $C_{13}H_{17}NO_5S_2$ (331.41): C, 47.11; H, 5.17; N, 4.23; S, 19.35; found: C, 47.02; H, 5.21; N, 4.28; S 19.53.

*4.2.6. 3-[(2S,3S)-Bis(acetyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3H)-thione threo-(**1d**).* Pyridinium *p*-toluenesulfonate (434 mg, 1.73 mmol) was added to a solution of 3-[(2*R*,3*R*)-isopropylidenedioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (451 mg, 1.57 mmol; Supplementary data) in methanol (20 mL) to furnish a solution which was boiled under reflux for 2 days and 2 h. Adding water (20 mL) at room temperature to the mixture affords a suspension, which was extracted with dichloromethane (3×50 mL). Combined organic solutions were concentrated under reduced pressure (370 mbar, 40 °C) to leave 3-[(2*S*,3*S*)-dihydroxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione as crude product, which was used as obtained in the succeeding step. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.32 (d, 3 H, J=1.2 Hz), 3.06 (br s, 1 H), 3.91–3.98 (m, 1 H), 4.05 (br s, 1 H), 4.31–4.39 (m, 2 H), 4.49 (dd, 1 H, J=9.4, 3.8 Hz), 5.28 (d, 1 H, J=10.6 Hz), 5.38–5.44 (m, 1 H), 5.95 (ddd, 1 H, J=17.0, 10.8, 5.7 Hz), 6.23 (d, 1 H, J=1.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.3, 71.2, 72.3, 79.0, 103.4, 117.5, 136.5, 137.9, 180.6. Crude 3-[(2*S*,3*S*)-dihydroxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (477 mg), triethylamine (730 mg, 7.21 mmol, 1 mL), *N*,*N*-dimethylaminopyridine (DMAP, 22.0 mg, 0.18 mmol) and acetic anhydride (735 mg, 7.19 mmol, 0.68 mL) were dissolved in dichloromethane (50 mL) and treated as described in general procedure 4.2.1, to leave a crude product, which was purified by chromatography using ethyl acetate/pentane=2:1 (*v*/*v*) as eluent. Yield: 431 mg (1.30 mmol, 83% for both steps), yellow oil. R_f=0.21 [petroleum ether/diethyl ether=1:1 (*v*/*v*)]. ^{1}H NMR (C_6D_6, 600 MHz) δ 1.52 (d, 3 H, J=1.2 Hz), 1.68 (s, 3 H), 1.76 (s, 3 H), 4.27 (dd, 1 H, J=9.1, 6.2 Hz), 4.41 (dd, 1 H, J=9.1, 2.6 Hz), 5.05–5.09 (m, 1 H), 5.12 (d, 1 H, J=1.2 Hz), 5.27 (dt, 1 H, J_d=17.2 Hz, J_t=1.2 Hz), 5.41 (td, 1 H, J_t=5.9 Hz, J_d=3.4 Hz), 5.67–5.70 (m, 1 H), 5.78 (ddd, 1 H, J=17.0, 10.7, 6.0 Hz). ^{13}C NMR (C_6D_6, 150 MHz) δ 13.1, 20.77, 20.79, 71.5, 72.5, 74.0, 102.2, 119.7, 132.6, 137.5, 169.3, 169.8, 181.0. Anal. Calcd for $C_{13}H_{17}NO_5S_2$ (331.41): C, 47.11; H, 5.17; N, 4.23; S, 19.35; found: C, 46.95; H, 5.19; N, 4.02; S 18.68.

*4.2.7. 3-[(2S,3S,4S)-3,4-O-Bis(acetyloxy)hex-5-en-2-oxy]-4-methyl-5-(p-methoxyphenyl)thiazole-2(3H)-thione (**1e**).* From 3-[(2*S*,3*S*,4*S*)-3,4-*O*-bishydroxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (880 mg, 2.39 mmol; Supplementary data), triethylamine (121 mg, 1.19 mmol, 167 μL), *N*,*N*-dimethylaminopyridine (DMAP, 35.0 mg, 287 μmol) and acetic anhydride (1.22 g, 12.0 mmol) in dichloromethane (28 mL) according to general procedure 4.2.1. Eluent used for chromatographic purification: diethyl ether/pentane=1:1 (*v*/*v*). Yield: 480 mg (1.06 mmol, 45%), colorless solid. R_f=0.16 [diethyl ether/pentane=1:1 (*v*/*v*)]. $[\alpha]_{25}^{D}$=35.0 (*c*=1.93 g/100 mL dichloromethane). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.22 (d, 3 H, J=6.4 Hz), 2.08 (s, 3 H), 2.09 (s, 3 H), 2.26 (s, 3 H), 3.80 (s, 3 H), 5.26 (dd, 2 H, J=4.1, 11.1 Hz), 5.30 (d, 1 H, J=10.5 Hz), 5.38 (d, 1 H, J=17.4 Hz), 5.53 (t, 1 H, J=7.3 Hz), 5.79 (ddd, 1 H, J=17.4, 10.2, 7.6 Hz), 5.93–5.98 (m, 1 H), 6.95 (d, 2 H, J=8.6 Hz), 7.24 (d, 2 H, J=8.5 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.6, 14.5, 20.9, 21.5, 55.5, 72.1, 74.0, 76.9, 114.7, 119.4, 120.9, 122.6, 129.9, 132.4, 133.5, 160.0, 169.8, 170.2, 178.9. Anal. Calcd for $C_{21}H_{25}NO_6S_2$ (451.55): C, 55.86; H, 5.58; N, 3.10; found: C, 56.06; H, 5.70; N, 3.03.

*4.2.8. 3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3H)-thione (**1f**).* A solution of 3-[3-(methoxymethyloxy)nona-1,8-dien-5-oxy]-4-methylthiazole-2(3*H*)-thione (1.36 g, 4.12 mmol; Supplementary data) in methanol (27 mL) was treated with aqueous hydrochloric acid [37% (*w*/*w*), 0.92 mL, 9.45 mmol]. The reaction mixture was allowed to stir for 18 h at 22 °C. Adding water (20 mL) and diethyl ether (20 mL) provided a two-phase system. The aqueous layer was extracted with diethyl ether (3×10 mL). Organic washings were combined with the organic layer from the reaction mixture and washed with an aqueous saturated solution of $NaHCO_3$ (30 mL) and brine (30 mL). After drying ($MgSO_4$), the organic solvent was removed under reduced pressure (600 mbar, 30 °C) to leave a residue, which was purified by chromatography [diethyl ether/pentane=1:2 (*v*/*v*)]. *rel-(3S,5S)-3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3H)-thione*. Yield: 457 mg (1.60 mmol, 39%), pale yellow liquid. R_f=0.35 [diethyl ether/pentane=1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63–1.75 (m, 2 H), 1.78–1.84 (m, 2 H), 1.94–2.14 (m, 2 H), 2.27 (d, 3 H, J=1.1 Hz), 4.71–4.77 (m, 1 H), 4.98–5.03 (m, 2 H), 5.14 (dt, 1 H, J_d=10.5 Hz, J_t=1.5 Hz), 5.34 (dt, 1 H, J_d=17.2 Hz, J_t=1.6 Hz), 5.40–5.47 (m, 1 H), 5.74 (ddt, 1 H, J_d=16.9, 10.4 Hz, J_t=6.5 Hz), 5.93 (ddd, 1 H, J=17.2, 10.5, 5.3 Hz), 6.26 (d, 1 H, J=1.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 29.2, 32.2, 40.4, 67.0, 81.3, 103.6, 114.3, 115.7, 136.7, 139.4, 139.9, 180.9. *rel-(3R,5S)-3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3H)-thione (**1f**)*. Yield: 418 mg (1.46 mmol, 35%), pale yellow liquid. R_f=0.16 [diethyl ether/pentane=1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67–1.73 (m, 2 H), 1.84–1.92 (m, 2 H), 2.02–2.20 (m, 2 H), 2.25 (d, 3 H, J=1.3 Hz), 4.56–4.60 (m, 1 H), 4.98–5.04 (m, 2 H), 5.13 (dt, 1 H, J_d=10.5 Hz, J_t=1.4 Hz), 5.33 (dt, 1 H, J_d=17.2 Hz, J_t=1.5 Hz), 5.45–5.51 (m, 1 H), 5.76 (ddt, 1 H, J_d=17.0, 10.4 Hz, J_t=6.5 Hz), 5.94 (ddd, 1 H, J=17.2, 10.5, 5.5 Hz), 6.22 (d, 1 H, J=1.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 29.1, 32.1, 39.9, 71.0, 84.5, 103.3, 114.7, 115.6, 136.8, 139.2, 140.0, 180.8. Anal. Calcd for $C_{13}H_{21}NO_2S_2$ (285.43): C, 54.70; H, 6.71; N, 4.91; S, 22.47; found: C, 54.57; H, 6.92; N, 4.91; S, 22.19.

4.3. Radical bromocyclizations

4.3.1. General method for thermally initiated radical reactions. Azobisisobutyronitrile (AIBN) (0.25 equiv) was added to a solution of *N*-(alkenoxy)-4-methylthiazole-2(3*H*)-thione **1a**–**e** (1 equiv) in benzene (5–10 mL/mmol MTTOR) and bromotrichloromethane (8–10 equiv). The mixture is heated under reflux for 1–2.5 h. The solution is allowed to cool to 22 °C and concentrated under reduced pressure (200 mbar, 40 °C). The residual oil is purified by chromatography using silica gel (SiO_2) as stationary phase.

4.3.2. General method for thermally initiated radical reaction in a laboratory microwave. A solution of *N*-(alkenoxy)-4-methylthiazole-2(3*H*)-thione **1d** (1 equiv) and bromotrichloromethane (8.6–9.25 equiv) in α,α,α-trifluorotoluene (3 mL/mmol

MTTOR) was treated with AIBN (0.25 equiv) and heated for 30 min at 80 °C in a laboratory microwave (see Supplementary data). The reaction mixture is allowed to cool to room temperature and concentrated under reduced pressure (70 mbar, 40 °C). The remaining residue is purified by chromatography [pentane/diethyl ether=1:2 (*v*/*v*)].

*4.3.3. Conversion of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1a**).* Reactants: MTTOR **1a** (260 mg, 1.12 mmol), bromotrichloromethane (1.78 g, 0.89 mL, 9.00 mmol), and AIBN (46.0 mg, 0.28 mmol) in benzene (6.1 mL) according to procedure 4.3.1. Reaction time: 2 h. Eluent used for chromatographic purification: diethyl ether/pentane=1:1 (*v*/*v*). 4-*Methyl*-2-*(trichloromethylsulfanyl)thiazole* (**2**). Yield: 234 mg (0.94 mmol, 84%), yellow oil. R_f=0.60 [diethyl ether/pentane=1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.59 (s, 3 H), 7.33 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.2, 96.8, 122.6, 153.5, 155.6.[40] 3-*Bromotetrahydropyran-4-ol* (**11*a***). Yield: 7.1 mg (39.3 μmol, 3.5%, *cis*:*trans* = 65:35) isolated as a mixture of tetrahydropyranol **11a** and tetrahydrofuranol *cis*-**3a** (**11a**/**3a**=8/92), yellow oil. R_f=0.19 [diethyl ether/pentane=1:1 (*v*/*v*)]. *cis*-(**11*a***): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92–2.06 (m, 2 H), 3.62 (dt, 1 H, J_d=11.5 Hz, J_t=4.7 Hz), 3.79 (dd, 1 H, J=11.8, 3.8 Hz), 3.83–3.96 (m, 3 H), 4.35 (dt, 1 H, J_d=8.3 Hz, J_t=3.4 Hz). Retention time (t_r)=11.40 min (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 121 (35), 108 (44), 101 (26), 100 (70), 83 (100), 73 (59), 55 (37). HRMS (EI$^+$) *m*/*z* 179.9775/181.9759 [M$^+$]; calculated mass for $C_5H_9O_2Br^+$: 179.9786/181.9765. *trans*-(**11*a***): t_r=11.28 min: 122 (37), 108 (49), 106 (51), 101 (38), 83 (79), 73 (100), 57 (32). HRMS (EI$^+$) *m*/*z* 181.9772/179.9778 [M$^+$]; calculated mass for $C_5H_9O_2Br^+$: 181.9765/179.9786. *rel*-(2*S*,3*R*)-2-*Bromomethyltetrahydrofuran*-3-*ol cis*-(**3*a***). Yield: 81.9 mg (0.45 mmol, 40%), yellow oil. R_f=0.16 [diethyl ether/pentane=1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85 (br s, 1 H, OH), 2.02 (dddd, 1 H, J=13.4, 6.9, 3.7, 1.4 Hz), 2.16–2.25 (m, 1 H), 3.47–3.55 (m, 2 H), 3.92 (td, 1 H, J_t=8.6 Hz, J_d=3.6 Hz), 4.01 (ddd, 1 H, J=8.3, 6.1, 3.5 Hz), 4.09 (td, 1 H, J_t=8.7 Hz, J_d=7.0 Hz), 4.50 (td, 1 H, J_t=4.3 Hz, J_d=1.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0, 35.4, 67.2, 71.9, 82.2. HRMS (EI$^+$) *m*/*z* 181.9772/179.9778 [M$^+$]; calculated mass for $C_5H_9O_2Br^+$: 181.9765/179.9786; *m*/*z* 87.0443 [M$^+$–CH_2Br]; calculated mass for $C_4H_7O_2^+$: 87.0446. From a 92:8-mixture of tetrahydrofuranol *cis*-**3a** and tetrahydropyranol **11a**: Anal. Calcd for $C_5H_9O_2Br$ (181.03): C, 33.17; H, 5.01; found: C, 33.22; H, 5.07. 2-*Bromomethyltetrahydrofuran*-3-*ol* (**3*a***). Yield (determined vs *para*-bromobenzaldehyde as internal NMR-standard): 17.3 mg (95.7 μmol, 9%, *cis*:*trans*=15:85), yellow oil. R_f=0.14 [diethyl ether/pentane=1:1 (*v*/*v*)]. *cis*-**3a**: NMR data agreed with values from an authentic sample. *trans*-**3a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76 (br s, 1 H, OH), 1.94 (dddd, 1 H, J=13.2, 6.3, 4.2, 3.2 Hz), 2.14–2.23 (m, 1 H), 3.32 (dd, 1 H, J=10.4, 7.3 Hz), 3.45 (dd, 1 H, J=10.5, 4.8 Hz), 3.96–4.03 (m, 3 H), 4.36 (dt, 1 H, J_d=6.3 Hz, J_t=3.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.8, 34.9, 67.5, 75.1, 85.1. HRMS (EI$^+$) *m*/*z* 87.0447 [M$^+$–CH_2Br]; calculated mass for $C_4H_7O_2^+$: 87.0446. *rel*-(2*R*,3*R*)-2-*Bromomethyltetrahydrofuran*-3-*ol trans*-(**3*a***). Yield (determined vs *para*-bromobenzaldehyde as internal NMR-standard): 13.8 mg (76.0 μmol, 7%), yellow oil. R_f=0.11 [diethyl ether/pentane=1:1 (*v*/*v*)]. NMR data agreed with values from an authentic sample.

*4.3.4. Conversion of 3-(3-acetyloxypent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1b**).* Reactants: MTTOR **1b** (334 mg, 1.22 mmol), bromotrichloromethane (1.94 g, 0.96 mL, 9.76 mmol), AIBN (51.0 mg, 0.31 mmol) in benzene (6.8 mL) according to procedure 4.3.1. Reaction time: 2 h. Eluent used for chromatographic purification: diethyl ether/pentane=1:1 (*v*/*v*). 4-*Methyl*-2-*(trichloromethylsulfanyl)thiazole* (**2**). Yield (determined vs pentachlorobenzene as internal NMR-standard): 250 mg (1.15 mmol, 94%), yellow oil. R_f=0.61 [diethyl ether/pentane=1:1 (*v*/*v*)]. NMR data agreed with values from an authentic sample. *rel*-(3*R*,4*R*)-3-*Bromotetrahydropyran*-4-*yl acetate trans*-(**11*b***). Yield (determined vs pentachlorobenzene as internal NMR-standard): 12.4 mg (55.5 μmol, 4.5%), orange oil. R_f=0.51 [diethyl ether/pentane=1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68–1.75 (m, 1 H), 2.11 (s, 3 H), 2.19 (ddt, 1 H, J_d=13.2, 5.0 Hz, J_t=2.6 Hz), 3.52–3.58 (m, 2 H), 3.90–4.01 (m, 2 H), 4.15 (dd, 1 H, J=12.0, 4.3 Hz), 4.98 (td, 1 H, J_t=9.8 Hz, J_d=4.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 32.6, 47.8, 66.0, 71.3, 73.7, 170.0. HRMS (EI$^+$) *m*/*z* 143.0711 [M$^+$–Br]; calculated mass for $C_7H_{11}O_3^+$: 143.0708. 2-*Bromomethyltetrahydrofuran*-3-*yl acetate* (**3*b***). Yield (determined vs pentachlorobenzene as internal NMR-standard): 194 mg (0.87 mmol, 71%, *cis*:*trans*=68:32), yellow oil. R_f=0.45 [diethyl ether/pentane=1:1 (*v*/*v*)]. *cis*-**3b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94–2.04 (m, 1 H), 2.07 (s, 3 H), 2.18–2.34 (m, 1 H), 3.41–3.55 (m, 2 H), 3.86–3.95 (m, 1 H), 4.00–4.15 (m, 2 H), 5.39 (ddd, 1 H, J=5.5, 4.0, 1.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 28.4, 33.5, 66.9, 73.7, 80.8, 170.1. HRMS (EI$^+$) *m*/*z* 223.9880/221.9887 [M$^+$]; calculated mass for $C_7H_{11}O_3Br^+$: 223.9871/221.9892. *trans*-**3b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94–2.04 (m, 1 H), 2.05 (s, 3 H), 2.18–2.34 (m, 1 H), 3.41–3.55 (m, 2 H), 3.86–3.95 (m, 1 H), 4.00–4.15 (m, 2 H), 5.09 (dt, 1 H, J_d=6.7 Hz, J_t=2.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.94, 32.6, 33.1, 67.7, 77.4, 83.2, 170.6. HRMS (EI$^+$) *m*/*z* 129.0551 [M$^+$–CH_2Br]; calculated mass for $C_6H_9O_3^+$: 129.0552. *rel*-(3*S*,4*R*)-3-*Bromotetrahydropyran*-4-*yl acetate cis*-(**11*b***). Yield (determined vs pentachlorobenzene as internal NMR-standard): 15.3 mg (68.4 μmol, 6%), yellow oil. R_f=0.43 [diethyl ether/pentane=1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.85–1.91 (m, 1 H), 1.95–2.00 (m, 1 H), 2.13 (s, 3 H), 3.62–3.68 (m, 1 H), 3.83–3.89 (m, 2 H), 3.94–3.97 (m, 1 H), 4.30–4.33 (m, 1 H), 5.08 (dt, 1 H, J_d=7.0 Hz, J_t=3.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.99, 32.6, 49.1, 64.2, 69.1, 69.3, 170.0. HRMS (EI$^+$) *m*/*z* 223.9885/221.9902 [M$^+$]; calculated mass for $C_7H_{11}O_3Br^+$: 223.9871/221.9892.

*4.3.5. Conversion of 3-(3-benzyloxypent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1c**).* Reactants: MTTOR **1c** (324 mg, 0.97 mmol), bromotrichloromethane (1.54 g, 0.77 mL, 7.76 mmol), AIBN (39.0 mg, 0.24 mmol) in benzene (5.3 mL) according to procedure 4.3.1. Reaction time: 2 h. Eluent used for chromatographic purification: diethyl ether/pentane=1:2 (*v*/*v*). 4-*Methyl*-2-*(trichloromethylsulfanyl)thiazole* (**2**). Yield: 181 mg (0.73 mmol, 75%), yellow oil. R_f=0.55 [diethyl ether/pentane=1:2 (*v*/*v*)]. NMR data agreed with values from an authentic sample. *rel*-(2*R*,3*R*)-2-*Bromomethyltetrahydrofuran*-3-*yl benzoate trans*-(**3*c***) [Yield (determined vs *para*-bromobenzaldehyde as internal NMR-standard): 54.7 mg (0.21 mmol, 22%)] and *rel*-(3*R*,4*R*)-3-*bromotetrahydropyran*-4-*bezoate trans*-(**11*c***) [Yield (determined vs *para*-bromobenzaldehyde as internal NMR-standard): 16.2 mg (57 μmol, 6%)], yellow oil. R_f=0.46 [diethyl ether/pentane=1:2 (*v*/*v*)]. *rel*-(2*R*,3*R*)-2-*bromomethyltetrahydrofuran*-3-*yl benzoate trans*-(**3*c***): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14–2.20 (m, 1 H), 2.33–2.41 (m, 1 H), 3.54–3.58 (m, 1 H), 3.61–3.67 (m, 1 H), 3.99–4.07 (m, 1 H), 4.15–4.22 (m, 1 H), 4.26 (td, 1 H, J_t=5.0 Hz, J_d=2.5 Hz), 5.38 (dt, 1 H, J_d=6.6 Hz, J_t=2.2 Hz), 7.44–7.49 (m, 2 H), 7.57–7.61 (m, 1 H), 8.02–8.09 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.8, 33.2, 68.0, 78.0, 83.3, 128.5, 129.7, 133.3, 166.2. HRMS (EI$^+$) *m*/*z* 286.0042/284.0068 [M$^+$]; calculated mass for $C_{12}H_{13}O_3Br^+$: 286.0028/284.0048. *rel*-(3*R*,4*R*)-3-*Bromotetrahydropyran*-4-*yl benzoate trans*-(**11*c***): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80–1.91 (m, 1 H), 2.33–2.41 (m, 1 H), 3.61–3.67 (m, 2 H), 3.99–4.07 (m, 1 H), 4.09–4.14 (m, 1 H), 4.15–4.22 (m, 1 H), 5.22 (td, 1 H, J_t=9.6 Hz, J_d=4.8 Hz), 7.44–7.49 (m, 2 H), 7.57–7.61 (m, 1 H), 8.02–8.09 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.8, 47.7, 66.0, 71.3, 74.3, 128.5, 129.6, 129.7, 133.3, 166.2. HRMS (EI$^+$) *m*/*z* 286.0065/284.0062 [M$^+$]; calculated mass

for $C_{12}H_{13}O_3Br^+$: 286.0028/284.0048. *rel*-(2*S*,3*R*)-2-*Bromomethyltetrahydrofuran*-3-*yl benzoate cis*-(**3c**). Yield: 122 mg (0.46 mmol, 47%), yellow oil. R_f=0.38 [diethyl ether/pentane=1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18–2.24 (m, 1 H), 2.43 (dtd, 1 H, J_d=14.1, 5.5 Hz, J_t=8.6 Hz), 3.52–3.61 (m, 2 H), 4.01 (td, 1 H, J_t=8.6 Hz, J_d=4.3 Hz), 4.12–4.18 (m, 1 H), 4.27 (td, 1 H, J_t=6.9 Hz, J_d=4.0 Hz), 5.67 (ddd, 1 H, J=5.5, 3.9, 1.8 Hz), 7.45–7.48 (m, 2 H), 7.57–7.61 (m, 1 H), 8.02–8.05 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7, 33.7, 67.1, 74.5, 81.2, 128.5, 129.6, 129.7, 133.4, 165.6. HRMS (EI$^+$) *m*/*z* 286.0028/284.0063 [M$^+$]; calculated mass for $C_{12}H_{13}O_3Br^+$: 286.0028/284.0048. Anal. Calcd for $C_{12}H_{13}O_2Br$ (285.13): C, 50.55; H, 4.60; found: C, 50.20; H, 4.65. *rel*-(3*S*,4*R*)-3-*Bromotetrahydropyran*-4-*yl benzoate cis*-(**11c**). Yield (determined vs *para*-bromobenzaldehyde as internal NMR-standard): 16.5 mg (58 µmol, 6%), orange oil. R_f=0.33 [diethyl ether/pentane=1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00–2.07 (m, 1 H), 2.17–2.30 (m, 1 H), 3.74 (ddd, 1 H, J=11.7, 6.3, 4.0 Hz), 3.91–3.96 (m, 1 H), 3.98–4.04 (m, 1 H), 4.05–4.10 (m, 1 H), 4.43 (dt, 1 H, J_d=7.0 Hz, J_t=3.3 Hz), 5.35 (dt, 1 H, J_d=6.9 Hz, J_t=3.3 Hz), 7.45–7.50 (m, 2 H), 7.58–7.62 (m, 1 H), 8.09–8.12 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0, 49.1, 64.2, 69.5, 69.6, 128.5, 129.67, 129.74, 133.3, 165.4. HRMS (EI$^+$) *m*/*z* 205.0870 [M$^+$–Br]; calculated mass for $C_{12}H_{13}O_3^+$: 205.0865.

*4.3.6. Conversion of 3-[(2R,3S)-2,3-bis-(acetyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3H)-thione erythro-(**1d**).* Reactants: 3-[(2*R*,3*S*)-2,3-bis-(acetyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(**1d**) (320 mg, 966 µmol), bromotrichloromethane (0.82 mL, 8.32 mmol), AIBN (40 mg, 0.24 mmol) in α,α,α-trifluorotoluene (3 mL) according to procedure 4.3.2. 4-*Methyl*-2-(*trichloromethylsulfanyl*)*thiazole* (**2**). Yield: 119 mg (478 µmol, 49%), yellow oil. R_f=0.55 [pentane/diethyl ether=1:2 (*v*/*v*)]. NMR data agreed with values from an authentic sample. (2*S*,3*R*,4*R*)-2-*Bromomethyltetrahydrofuran*-3,4-*diyl bisacetate cis*$_{erythro}$-(**3d**). Yield: 103 mg (365 µmol, 38%), yellow oil. R_f=0.55 [petroleum ether/diethyl ether=1:2 (*v*/*v*)]. ^{1}H NMR (400 MHz, C_6D_6) δ 1.56 (s, 3 H), 1.65 (s, 3 H), 3.19 (d, 2 H, J=7.0 Hz), 3.58–3.65 (m, 2 H), 3.80 (td, 1 H, J_t=7.0 Hz, J_d=4.8 Hz), 5.09 (td, 1 H, J_t=6.2 Hz, J_d=5.1 Hz), 5.29 (t, 1 H, J=4.9 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 20.28, 20.33, 29.2, 69.7, 71.9, 72.2, 79.2, 169.2, 169.5. MS (EI) *m*/*z* 283 (1), 281 (1), 201 (26), 187 (76), 178 (5), 158 (17), 141 (42), 127 (37), 115 (100), 99 (20), 85 (45), 81 (77). (2*R*,3*R*,4*R*)-2-*Bromomethyltetrahydrofuran*-3,4-*diyl bisacetate trans*$_{erythro}$-(**3d**). Yield: 43.3 mg (154 µmol, 16%), yellow oil. R_f=0.55 [petroleum ether/diethyl ether=1:2 (*v*/*v*)]. ^{1}H NMR (400 MHz, C_6D_6) δ 1.62 (s, 3 H), 1.63 (s, 3 H), 3.03–3.14 (m, 2 H), 3.57–3.65 (m, 1 H), 3.74 (dd, 1 H, J=10.2, 4.8 Hz), 3.98 (dt, 1 H, J_d=6.6 Hz, J_t=4.5 Hz), 5.14 (dd, 1 H, J=6.6, 5.3 Hz), 5.23 (td, 1 H, J_t=5.0 Hz, J_d=3.5 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 20.4, 20.5, 33.3, 71.1, 72.3, 74.5, 79.6, 169.5, 169.6. MS (EI) *m*/*z* 283(1), 281(1), 201(14), 187(33), 141(50), 127(21), 115 (100), 99(12), 85(24), 81(41). Mixture of *cis*$_{erythro}$- and *trans*$_{erythro}$-(**3d**): HRMS (EI$^+$) *m*/*z* 283.0065/281.0023 [M+H]$^+$; calculated mass for $C_9H_{14}O_5Br^+$: 283.0004/281.0025; *m*/*z* 201.0767 [M+H]$^+$–Br; calculated mass for $C_9H_{13}O_5^+$: 201.0763. Anal. Calcd for $C_9H_{13}BrO_5$ (281.17): C, 38.66; H, 4.66; found: C, 38.64; H, 4.96. (3*R*,4*R*,5*R*)-3-*Bromotetrahydropyran*-4,5-*diyl bisacetate trans*$_{erythro}$-(**11d**). Yield: 24.6 mg (87.5 µmol, 9%), yellow oil. R_f=0.55 [petroleum ether/diethyl ether=1:2 (*v*/*v*)]. ^{1}H NMR (400 MHz, C_6D_6) δ 1.65 (s, 3 H), 1.73 (s, 3 H), 2.80 (dd, 1 H, J=13.1, 1.1 Hz), 3.07 (t, 1 H, J=11.2 Hz), 3.50–3.54 (m, 1 H), 3.85 (ddd, 1 H, J=11.6, 4.9, 1.1 Hz), 4.12 (td, 1 H, J_t=10.8 Hz, J_d=5.0 Hz), 5.03 (dd, 1 H, J=10.6, 3.5 Hz), 5.21–5.22 (m, 1 H). ^{13}C NMR (100 MHz, C_6D_6) δ 20.57, 20.65, 45.3, 68.7, 70.0, 71.6, 74.1, 169.6, 169.9. MS (EI) *m*/*z* 283 (1), 281 (1), 237 (5), 195 (17), 179 (5), 159 (5), 141 (100), 140 (29), 115 (4), 103 (12), 99 (66), 98 (58), 81 (17). (3*S*,4*R*,5*R*)-3-*Bromotetrahydropyran*-4,5-*diyl bisacetate cis*$_{erythro}$-(**11d**). Yield: 10.6 mg (37.9 µmol, 4%), yellow oil. R_f=0.55 [petroleum ether/diethyl ether=1:2 (*v*/*v*)]. ^{1}H NMR (400 MHz, C_6D_6) δ 1.60 (s, 3 H), 1.72 (s, 3 H), 3.32–3.37 (m, 1 H), 3.38–3.44 (m, 1 H), 3.47–3.49 (m, 2 H), 3.51–3.55 (m, 1 H), 4.82 (ddd, 1 H, J=10.7, 5.3, 2.8 Hz), 5.62–5.64 (m, 1 H). ^{13}C NMR (100 MHz, C_6D_6) δ 20.48, 20.50, 44.3, 63.9, 67.5, 68.1, 69.5, 169.2, 169.6. MS (EI) *m*/*z* 283 (1), 281 (1), 222 (1), 209 (4), 207 (4), 195 (3), 178 (7), 177 (7), 159 (15), 141 (100), 140 (56), 103 (38), 99 (90), 98 (59), 81 (20). Mixture of *cis*$_{erythro}$- and *trans*$_{erythro}$-(**11d**): HRMS (EI$^+$) *m*/*z* 283.0043/281.0040 [M+H]$^+$; calculated mass for $C_9H_{14}O_5Br^+$: 283.0004/281.0025; *m*/*z* 238.9760/236.9976 [M$^+$–C_2H_3O]; calculated mass for $C_7H_{10}O_4Br^+$: 238.9742/236.9762.

*4.3.7. Conversion of 3-[(2S,3S)-bis(acetyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3H)-thione threo-(**1d**).* Reactants: 3-[(2*S*,3*S*)-Bis(acetyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *threo*-(**1d**) (200 mg, 603 µmol), bromotrichloromethane (0.55 mL, 5.58 mmol), AIBN (25 mg, 0.15 mmol) in α,α,α-trifluorotoluene (2 mL) according to procedure 4.3.2. 4-*Methyl*-2-(*trichloromethylsulfanyl*)*thiazole* (**2**). Yield: 97.0 mg (390 µmol, 65%), yellow oil. R_f=0.55 [pentane/diethyl ether=1:2 (*v*/*v*)]. NMR data agreed with values from an authentic sample. (2*S*,3*R*,4*S*)-2-*Bromomethyltetrahydrofuran*-3,4-*diyl bisacetate cis*$_{threo}$-(**3d**). Yield: 38.3 mg (136 µmol, 22%), yellow oil. R_f=0.56 [petroleum ether/methyl *tert*-butyl ether=1:4 (*v*/*v*)]. ^{1}H NMR (400 MHz, C_6D_6) δ 1.48 (s, 3 H), 1.50 (s, 3 H), 3.16 (d, 2 H, J=7.3 Hz), 3.58 (dd, 1 H, J=10.5, 2.3 Hz), 4.00 (dd, 1 H, J=10.7, 4.9 Hz), 4.14 (td, 1 H, J_t=7.0 Hz, J_d=3.8 Hz), 5.07–5.09 (m, 1 H), 5.37 (dd, 1 H, J=3.7, 1.0 Hz). ^{13}C NMR (100 MHz, C_6D_6) δ 20.3, 20.5, 28.0, 72.7, 76.4, 77.9, 80.2, 169.1, 169.4. MS (EI) *m*/*z* 283 (1), 281 (1), 201 (10), 187 (8), 178 (2), 158 (3), 141 (18), 127 (10), 115 (100), 99 (8), 85 (17), 81 (58). (2*R*,3*R*,4*S*)-2-*Bromomethyltetrahydrofuran*-3,4-*diyl bisacetate trans*$_{threo}$-(**3d**). Yield: 38.2 mg (136 µmol, 22%), yellow oil. R_f=0.56 [petroleum ether/methyl *tert*-butyl ether=1:4 (*v*/*v*)]. ^{1}H NMR (400 MHz, C_6D_6) δ 1.49 (s, 3 H), 1.50 (s, 3 H), 3.27–3.36 (m, 2 H), 3.69–3.72 (m, 1 H), 3.78–3.81 (m, 1 H), 3.86 (td, 1 H, J_t=5.9 Hz, J_d=3.5 Hz), 5.07 (dt, 1 H, J_d=4.3 Hz, J_t=1.6 Hz), 5.17–5.19 (m, 1 H). ^{13}C NMR (100 MHz, C_6D_6) δ 20.4, 20.5, 32.2, 72.5, 78.4, 80.2, 83.9, 169.5, 169.7. Mixture of *cis*$_{threo}$- and *trans*$_{threo}$-**3d**: HRMS (EI$^+$) *m*/*z* 283.0000/281.0010 [M+H]$^+$; calculated mass for $C_9H_{14}O_5Br^+$: 283.0004/281.0025; *m*/*z* 187.0623 [M$^+$–CH_3Br]; calculated mass for $C_8H_{11}O_3^+$: 187.0606. Anal. Calcd for $C_9H_{13}BrO_5$ (281.17): C, 38.66; H, 4.66; found: C, 38.66; H, 4.90. (3*R*,4*R*,5*S*)-4,5-*Bis*(*acetyloxy*)-3-*bromomethyltetrahydropyran trans*$_{threo}$-(**11d**). Yield: 8.09 mg (28.8 µmol, 2%), yellow oil. R_f=0.56 [petroleum ether/methyl *tert*-butyl ether=1:4 (*v*/*v*)]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11 (s, 3 H), 2.12 (s, 3 H), 3.31 (t, 1 H, J=10.7 Hz), 3.50 (t, 1 H, J=11.4 Hz), 3.83–3.91 (m, 1 H), 4.08–4.11 (m, 1 H), 4.14 (dd, 1 H, J=11.6, 5.0 Hz), 4.89 (ddd, 1 H, J=10.3, 9.2, 5.5 Hz), 5.21 (t, 1 H, J=9.6 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.8, 20.9, 44.7, 67.8, 69.9, 71.2, 75.2, 169.4, 169.5. (3*R*,4*R*,5*S*)-4,5-*Bisacetyloxy*-3-*bromomethyltetrahydropyran cis*$_{threo}$-(**11d**). Yield: 3.75 mg (13.3 µmol, 5%), yellow oil. R_f=0.56 [petroleum ether/methyl *tert*-butyl ether=1:4 (*v*/*v*)]. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.11 (s, 3 H), 2.12 (s, 3 H), 3.70 (dd, 1 H, J=12.7, 3.9 Hz), 3.83–3.91 (m, 3 H), 4.47 (ddd, 1 H, J=8.2, 4.3, 3.5 Hz), 4.95–4.97 (m, 1 H), 5.13–5.15 (m, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.8, 20.9, 45.3, 65.8, 68.2, 68.7, 69.1, 169.4, 169.5.

*4.3.8. Conversion of 3-[(2S,3S,4S)-3,4-O-bis(acetyloxy)hex-5-en-2-oxy]-4-methyl-5-(p-methoxyphenyl)thiazole-2(3H)-thione (**1e**).* Reactants: 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Bis(acetyloxy)hex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (**1e**) (222 mg, 0.49 mmol), bromotrichloromethane (488 µL, 4.9 mmol), AIBN (20 mg, 0.12 mmol) in benzene (5 mL) according to procedure 4.3.1. Reaction time: 2.5 h. Eluent used for chromatographic purification: diethyl ether/pentane=1/1 (*v*/*v*). 4-*Methyl*-5-(*p*-*methoxyphenyl*)-2-(*trichloromethylsulfanyl*)*thiazole* (**12**). Yield: 96.9 mg (0.27 mmol, 55%), yellow crystals. R_f=0.48 [diethyl ether/pentane=1/1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3 H), 3.85 (s, 3 H), 6.97 (d, 2 H, J=8.6 Hz), 7.24 (d, J=8.6 Hz). ^{13}C NMR (150 MHz, C_6D_6) δ 16.3, 54.9, 97.9, 114.6, 123.4, 129.9, 130.7, 141.6,

150.1, 150.8, 160.4. MS (EI) *m/z* 355 [M^+], 248 (8), 236 (100), 203 (28), 192 (17), 177 (38), 160 (22), 145 (27), 134 (8), 119 (5), 108 (9), 77 (8).[24] (2*S*,3*R*,4*R*,5*R*)-5-*Bromo*-2-*methyltetrahydropyran*-3,4-*diyl bisacetate trans*-(**11e**). Yield: 12.0 mg (40.8 μmol, 8%), yellow crystals. R_f=0.36 [diethyl ether/pentane=1/1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, 3 H, *J*=6.4 Hz), 2.05 (s, 3 H), 2.16 (s, 3 H), 3.57–3.64 (m, 1 H), 3.74–3.79 (q, 1 H, *J*=6.7 Hz), 4.14–4.21 (m, 2 H), 5.03 (dd, 1 H, *J*=3.5, 10.8 Hz), 5.22 (dd, 1 H, *J*=1.0, 3.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6, 20.6, 20.7, 44.0, 71.3, 71.9, 74.0, 74.7, 169.8, 170.4. MS (EI) *m/z* 207/209 (4), 152/154 (24), 129 (22), 113 (75), 103 (14), 95 (16), 85 (16), 69 (100), 57 (13). 2-*Brommethyl*-5-*methyltetrahydrofuran*-3,4-*diyl bisacetate* (**3e**). Yield: 72.7 mg (247 μmol, 50%, 2,5-*cis*:2,5-*trans* = 30:70), yellow oil. R_f=0.24 [diethyl ether/pentane=1/1 (*v*/*v*)]. *cis*-**3e**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.21 (d, 3 H, *J*=6.9 Hz), 2.09 (d, 6 H, *J*=2.2 Hz), 3.41–3.45 (m, 2 H), 4.17–4.29 (m, 2 H), 4.37–4.42 (m, 1 H), 5.36–5.40 (m, 1 H), 5.51 (t, 1 H, *J*=5.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 20.5, 20.9, 29.4, 72.4, 72.9, 75.3, 77.9, 169.6, 169.8. MS (EI) *m/z* 201 (15), 175/177 (19), 155 (93), 129 (58), 113 (18), 99 (100), 95 (60), 87 (16), 69 (39), 57 (17). *trans*-**3e**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.23 (d, 3 H, *J*=1.9 Hz), 2.04 (s, 3 H), 2.12 (s, 3 H), 3.49 (dd, 1 H, *J*=4.4, 11.1 Hz), 3.59 (dd, 1 H, *J*=4.4, 11.1 Hz), 4.17–4.29 (m, 1 H), 4.37–4.42 (m, 1 H), 5.29–5.32 (m, 1 H), 5.36–5.40 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 20.6 (2C), 33.7, 73.6, 74.9, 76.1, 78.1, 169.8, 170.4. MS (EI) *m/z* 201 (15), 175/177 (19), 155 (93), 129 (58), 113 (18), 99 (100), 95 (60), 87 (16), 69 (39), 57 (17). Mixture of *cis*- and *trans*-**3e**: Anal. Calcd for $C_{10}H_{15}BrO_5$ (295.13): C, 40.70; H, 5.12; found: C, 41.02; H, 5.13. (2*S*,3*R*,4*R*,5*S*)-5-*Bromo*-2-*methyltetrahydropyran*-3,4-*diyl bisacetate cis*-(**11e**). Yield: 3.03 mg (10.3 μmol, 2%), yellow oil. R_f=0.12 [diethyl ether/pentane=1/1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3 H, *J*=6.7 Hz), 2.10 (s, 3 H), 2.17 (s, 3 H), 3.74–3.79 (m, 1 H), 3.93–3.98 (m, 1 H), 4.24–4.28 (m, 2 H), 5.09 (t, 1 H, *J*=4.0 Hz), 5.15 (t, 1 H, *J*=2.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.3, 20.9 (2C), 44.6, 68.9, 69.1, 70.3, 73.6, 170.0, 170.7. MS (EI) *m/z* 207/209 (4), 152/154 (24), 129 (22), 113 (75), 103 (14), 95 (16), 85 (16), 69 (100), 57 (13).

*4.3.9. Conversion of rel-(3R,5S)-3-(3-hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3H)-thione (**1f**) with Bu_3SnH.* A solution of *rel*-(3*R*,5*S*)-3-(3-hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3*H*)-thione (**1f**) (418 mg, 1.46 mmol) in benzene (17.0 mL) containing tributylstannane (1.57 g, 5.40 mmol) and AIBN (59.9 mg, 0.37 mmol) was boiled under reflux for 2 h, while being heated in an oil bath (bath temperature 100 °C). The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure (200 mbar, 40 °C), to leave a residue which was purified by chromatography [SiO_2, diethyl ether/pentane=1:2 (*v*/*v*)]. 4-*Methyl*-2-(*tributylstannylsulfanyl*)*thiazole* (**13**). Yield: 1.15 mmol (79%, yield was determined via ^{1}H NMR with pentachlorobenzene as internal standard before the chromatography). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.87–0.94 (m, 9 H), 1.24–1.68 (m, 18 H), 2.28 (s, 3 H), 6.54 (s, 1 H). *rel*-(2′*S*,2*R*)-1-(5′-*methyltetrahydrofuran*-2′-*yl*)*but*-3-*ene*-2-*ol* (**15**). Yield: 127 mg (815 μmol, 56%), as a mixture of *cis*- and *trans*-isomers (A:B=27:73), colorless liquid. R_f=0.23 [diethyl ether/pentane=1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (dd, 3 H, *J*=6.1, 0.7 Hz, B), 1.24 (dd, 3 H, *J*=6.1, 0.7 Hz, A), 1.40–1.70 (m, 4 H, A/B), 1.91–2.07 (m, 2 H, B), 2.09–2.16 (m, 2 H, A), 4.00–4.07 (m, 1 H, B), 4.11–4.18 (m, 1 H, B), 4.21–4.27 (m, 2 H, A), 4.31–4.35 (m, 1 H, A/B), 5.07 (d, 1 H, *J*=10.4 Hz, A/B), 5.27 (d, 1 H, *J*=17.2 Hz, A/B), 5.80–5.89 (m, 1 H, A/B). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 21.4, 32.1, 32.2, 33.0, 33.2, 42.6, 43.2, 72.8, 72.9, 75.1, 76.2, 79.0, 79.6, 114.0 (2C), 140.5 (2C). Retention time (t_r)=12.2 min (for GC/MS conditions see Supplementary data): MS (EI) *m/z* 138 (10), 127 (5), 111 (5), 98 (14), 85 (100), 79 (110), 67 (33), 57 (52). HRMS (EI^+) *m/z* 156.1146 [M^+]; calculated mass for $C_9H_{16}O_2^+$: 156.1150. t_r=12.3 min: MS (EI) *m/z* 138 (10), 127 (5), 111 (5), 98 (14), 85 (100), 79 (110), 67 (33), 57 (52). HRMS (EI^+) *m/z* 156.1135 [M^+]; calculated mass for $C_9H_{16}O_2^+$: 156.1150. *rel*-(3*R*,5*S*)-5-(*But*-3-*en*-1-*yl*)-2-*methyltetrahydrofuran*-3-*ol* (**14**) and *Tetrahydropyran-derivative* as a 86/14-mixture. Yield: 53 mg (340 μmol, 23%), colorless liquid. R_f=0.15 [diethyl ether/pentane=1:1 (*v*/*v*)]. *rel*-(3*R*,5*S*)-5-(*But*-3-*en*-1-*yl*)-2-*methyltetrahydrofuran*-3-*ol* (**14**) as a mixture of *cis*- and *trans*-isomers (A:B=20:80). *Main isomer B*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, 3 H, *J*=6.3 Hz), 1.46–1.78 (m, 4 H), 2.02–2.20 (m, 2 H), 3.95–4.00 (m, 1 H), 4.14–4.17 (m, 1 H), 4.19–4.24 (m, 1 H), 4.93–5.10 (m, 2 H), 5.76–5.90 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 30.2, 35.4, 41.6, 74.1, 76.5, 77.3, 114.6, 138.2. Retention time (t_r)=12.8 min: MS (EI) *m/z* 138 (1), 127 (14), 114 (57), 101 (57), 79 (29), 70 (29), 57 (100), 53 (10). HRMS (EI^+) *m/z* 156.1151 [M^+]; calculated mass for $C_9H_{16}O_2^+$: 156.1150; *m/z* 138.1042 [M^+-H_2O]; calculated mass for $C_9H_{14}O_1^+$: 138.1045. *Minor isomer A*: t_r=12.6 min: MS (EI) *m/z* 138 (1), 127 (14), 114 (57), 101 (57), 79 (29), 70 (29), 57 (100), 53 (10). HRMS (EI^+) *m/z* 138.1036 [M^+-H_2O]; calculated mass for $C_9H_{14}O_1^+$: 138.1045. *Tetrahydropyran-derivative*. Retention time (t_r)=13.6 min: MS (EI) *m/z* 137 (0.9), 114 (10), 101 (14), 83 (28), 79 (19), 67 (48), 55 (100), 51 (10). HRMS (EI^+) *m/z* 138.1042 [M^+-H_2O]; calculated mass for $C_9H_{14}O_1^+$: 138.1045.

4.4. Reduction of bromomethyletrahydrofurans

4.4.1. General method. Tributylstannane (1.03 g, 3.40 mmol) and AIBN (25.0 mg, 0.15 mmol) were added to a solution of 2-bromomethyltetrahydrofuran-3-yl acetate (**3b**) (303 mg, 1.36 mmol) in dry benzene (20 mL). The reaction mixture was boiled under reflux for 1.5 h and treated afterwards at room temperature with potassium fluoride (2.5 g, 43.0 mmol) and water (2 mL). Stirring was continued for 30 min at room temperature. The slurry was dried ($MgSO_4$) and filtrated. The solids were washed with methyl *tert*-butyl ether (3×30 mL). Organic washings were combined with the filtrate from potassium fluoride-treatment and concentrated under reduced pressure (300 mbar, 40 °C). The remaining oil was purified by chromatography [SiO_2, diethyl ether/pentane=2:1 (*v*/*v*)].

*4.4.2. cis-2-Methyltetrahydrofuran-3-yl acetate cis-(**16**).* From *cis*-2-bromomethyltetrahydrofuran-3-yl acetate *cis*-(**3b**) according to procedure 4.4.1. Yield: 114 mg (790 μmol, 58%), yellowish oil. R_f=0.52 [diethyl ether/pentane=2:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, 3 H, *J*=6.5 Hz), 1.90–2.01 (m, 1 H), 2.08 (s, 3 H), 2.25–2.36 (m, 1 H), 3.75 (td, 1 H, J_t=8.7 Hz, J_d=6.5 Hz), 3.83–3.96 (m, 1 H), 4.02 (q, 1 H, *J*=8.2 Hz), 5.26 (ddd, 1 H, *J*=6.0, 4.0, 1.9 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 20.9, 33.4, 65.8, 75.2, 77.3, 170.6.[67]

*4.4.3. trans-2-Methyltetrahydrofuran-3-yl acetate trans-(**16**).* From *trans*-2-bromomethyltetrahydrofuran-3-yl acetate *trans*-(**3b**) according to procedure 4.4.1. Yield: 120 mg (830 μmol, 61%), yellowish oil. R_f=0.55 [diethyl ether/pentane=2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, 3 H, *J*=6.5 Hz), 1.85–1.98 (m, 1 H), 2.06 (s, 3 H), 2.16–2.27 (m, 1 H), 3.79–4.04 (m, 3 H), 4.86 (dt, 1 H, J_d=6.5 Hz, J_t=2.4 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.0, 21.1, 32.0, 66.5, 79.6, 80.0, 170.3.[67]

Supplementary data

Supplementary data (Instrumentation, precursors for the synthesis of 3-alkenoxythiazole-2(3*H*)-thiones **1a**–**f** (alkenols and alkenyl *p*-toluenesulfonates), ^{1}H NMR- and ^{13}C NMR spectra of selected 3-alkenoxythiazole-2(3*H*)-thiones, tetrahydrofurans and tetrahydropyrans (30 pages).) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2016.07.001.

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4.7 Anhang

Supplementary Data for

2,3-*cis*-Cyclization of 4-Pentenoxyl Radicals

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Contents

1 General Remarks

(i) Numbering of compounds in the Supplementary data is consistent with the accompanying article. (ii) Numbering of references refers exclusively to the Supplementary data.

2 Instrumentation and Solvent Purification

2.1 Nuclear magnetic resonance spectroscopy

Proton- and carbon-13 nuclear magnetic reonance (NMR)-spectra were recorded with FT-NMR DPX 200, DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale. The resonances of residual $CHCl_3$ and of the carbon atom of $CDCl_3$ (δ_H 7.26, δ_C 77.0) were used as internal standards. NMR shift values of isomuscarine bromides in solutions of D_2O were referenced versus 1,4-dioxane as internal standard (δ_H 3.17, δ_C 67.1).

2.2 Electron impact mass spectrometry

Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*).

2.3 High resolution mass spectrometry

Mass spectroscopy (EI, 70 eV), GCT Premier Micromass (*Waters*).

2.4 Combustion analysis

Combustion analysis was performed with a vario Micro cube CHNS (*Elementar Analysentechnik/Hanau*).

2.5 Thin layer chromatography

Reaction progress was monitored via thin layer chromatography (tlc) on aluminium sheets coated with silica gel (60 F_{254}, *Merck*). Compounds on developed tlc-sheets were detected with the aid of the UV/VIS indicator commercially disposed on the sheets, becoming apparent, for example, by a hand lamp emitting 254 nm light. As alternative method for detecting compounds on developed tlc-sheets is staining by Ekkert´s reagent, and subsequent heating, leading to blue-green spots for organobromines, blue spots for alcohols and yellow spots for radical precursors.

2.6 Gas chromatography coupled to mass spectrometry

GC/MS-analysis was performed with a HP 6890 Series (*Hewlett Packard*) system and mass detector with a HP-5MS column (*Agilent*, 30 m × 0.25 mm, 0.25 μm). Temperature program: 40 °C (3 min), 10 °C min^{-1} → 280 °C, 280 °C (10 min).

2.7 Melting points

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*) and are not corrected.

2.8 Photoreactor

Photochemically initiated reactions were performed in a Rayonet®-chamber reactor equipped with 350-nm light bulbs from the *Southern New England Ultraviolet* company.

2.9 Laboratory microwave

Microwave heating solutions in α,α,α-trifluorotoluene was performed in a Biotage Initiator 2.5 microwave, using a preselected temperature of 80 °C and using absorption settings for toluene available from the instrument menu.

2.10 Purification of solvents

The term “petroleum ether” refers to the fraction of hydrocarbons boiling between 40–55 °C. All solvents were purified according to standard procedures.[1]

3 *O*-Alkenylthiohydroxamate Syntheses

3.1 General method for acid-catalyzed hydrolysis of di-*O*-isopropylidene protecting groups. A solution of a di-*O*-isopropylidene-protected 3-alkenoxythiazole-2(3*H*)-thione in methanol was treated with aqueous hydrochloric acid [37 % (*w*/*w*)] and stirred for 8 hours at 22 °C. Water or diethyl ether was added at this temperature, and the product was extracted from this mixture with diethyl ether or dichloromethane. Combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure (600 mbar, 40 °C) to furnish a residue, which was purified by chromatography (SiO_2).

3.2 3-[3-(methoxymethyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione

3.2.1 Ethyl 3-hydroxypent-4-enoate[2,3] In an atmosphere of dry nitrogen, a solution of diisopropylamine (9.71 g, 96.0 mmol, 13.6 mL) in dry tetrahydrofuran (80 mL) was cooled to −78 °C and treated in a dropwise manner with *n*-butyllithium (88.0 mmol, 35.2 mL, 2.5 M in hexane) over a period of 30 minutes. At this temperature ethyl acetate (7.05 g, 80.0 mmol) dissolved in dry tetrahydrofuran (35 mL) and afterwards acrolein (4.93 g, 88.0 mmol) dissloved in dry tetrahydrofuran (25 mL) were added in a dropwise manner. The reaction mixture was stirred for 15 minutes at −78 °C and then treated with an aqueous saturated solution of NH_4Cl (50 mL). The reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 80 mL). Combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (600−300 mbar, 40 °C) to afford a residue, which was distilled under reduced pressure (5.0×10^{-1} mbar). Yield: 8.89 g (61.7 mmol, 77%), colorless liquid, b.p. 67 °C (5.0×10^{-1} mbar). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3 H, J = 7.1 Hz), 2.47−2.59 (m, 2 H), 3.05 (brs, 1 H, OH), 4.16 (q, 2 H, J = 7.3 Hz), 4.52 (brs, 1 H), 5.14 (dt, 1 H, J_d = 10.5 Hz, J_t = 1.3 Hz), 5.30 (dt, 1 H, J_d = 17.3 Hz, J_t = 1.4 Hz), 5.87 (ddd, 1 H, J = 17.1, 10.5, 5.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 41.1, 60.7, 68.9, 115.3, 138.8, 172.2.

3.2.2 Ethyl 3-(methoxymethyloxy)pent-4-enoate (4).[3,4] Phosphorous pentoxide (14.0 g, 98.7 mmol) was added at 0 °C to a stirred solution of dimethoxymethane (34 mL) in chloroform (13 mL) in an atmosphere of dry nitrogen at such rate that no clumping occurs. To this slurry, a solution of ethyl 3-hydroxypent-4-enoate (2.04 g, 14.2 mmol) in chloroform (13 mL) was added in a dropwise manner at 0 °C. The reaction mixture was allowed to warm

to 22 °C and stirred for 1 hour at this temperature. Additional phosphorus pentoxide (14.0 g, 98.7 mmol) was added and the mixture was stirred for 2 hours at 22 °C. Solids were filtered off and washed with chloroform (3 × 30 mL). The solvent was removed under reduced pressure (200 mbar, 30 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1:2 (*v*/*v*)]. Yield: 1.49 g (7.90 mmol, 56%), colorless liquid. R_f = 0.47 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, 3 H, J = 7.2 Hz), 2.47−2.66 (m, 2 H), 3.35 (s, 1 H), 4.11−4.19 (m, 2 H), 4.49 (td, 1 H, J_t = 7.9 Hz, J_d = 5.4 Hz), 4.55 (d, 1 H, J = 6.8 Hz), 4.69 (d, 1 H, J = 6.8 Hz), 5.23 (dt, 1 H, J_d = 10.3 Hz, J_t = 1.1 Hz), 5.30 (dt, 1 H, J_d = 17.3 Hz, J_t = 1.3 Hz), 5.73 (ddd, 1 H, J = 17.5, 10.1, 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 41.0, 55.5, 60.5, 73.8, 93.9, 118.1, 136.7, 170.7.

3.2.3 3-(Methoxymethyloxy)pent-4-en-1-ol.[3,5] In an atmosphere of dry nitrogen, a solution of ethyl 3-(methoxymethyloxy)pent-4-enoate (**4**) (3.47 g, 18.44 mmol) in dry diethyl ether (78 mL) was cooled in an ice bath and treated with lithium aluminium hydride (700 mg, 18.44 mmol) at such a rate that the temperature of 0 °C is maintained. The reaction mixture was allowed to warm to 22 °C and stirred for 1.5 hours at this temperature. Water (0.72 mL) was added at room temperature and the suspension was stirred for 5 minutes, afterwards aqueous sodium hydroxide (2 M, 0.95 mL) was added and the suspension was stirred for 5 minutes. The reaction mixture was treated with additional water (2.20 mL) and stirred for 5 minutes, while solids were precipitated. The solids were filtered off and washed with diethyl ether (30 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C) to leave a residue that was purified by chromatography (SiO_2, diethyl ether). Yield: 2.37g (16.21 mmol, 88%), colorless liquid. R_f = 0.38 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80−1.85 (m, 2 H), 2.35 (brs, 1 H, OH), 3.39 (s, 1 H), 3.71−3.84 (m, 2 H), 4.23−4.28 (m, 1 H), 4.55 (d, 1 H, J = 6.6 Hz), 4.70 (d, 1 H, J = 6.8 Hz), 5.19−5.27 (m, 2 H), 5.72 (ddd, 1 H, J = 17.4, 10.1, 7.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.7, 55.6, 60.0, 76.3, 93.9, 117.4, 137.6.

3.2.4 3-(Methoxymethyloxy)pent-4-en-1-yl *p*-toluenesulfonate (5).[5] 3-(Methoxymethyloxy)pent-4-en-1-ol (3.67 g, 25.11 mmol) was dissolved in dichloromethane (120 mL) and treated with 1,4-diazabicyclo[2.2.2]octane (5.63 g, 50.22 mmol) at room temperature. The reaction mixture was cooled in an ice bath and treated in portions with *p*-toluenesulfonyl chloride (7.18 g, 37.67 mmol) at such at rate that the temperature is kept at 0 °C. The reaction

mixture was allowed to warm to 22 °C. Stirring at this temperature was continued for 16 hours, leading to a colorless deposit. Solids were filtered off and washed with dichloromethane (50 mL). The solution was washed with aqueous hydrochloric acid (2 M, 2 × 50 mL), an aqueous saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL). Combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 6.54 g (21.76 mmol, 87%), colorless oil. R_f = 0.44 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81−1.94 (m, 2 H), 2.45 (s, 3 H), 3.29 (s, 1 H), 4.07−4.12 (m, 2 H), 4.16−4.22 (m, 1 H), 4.46 (d, 1 H, J = 6.6 Hz), 4.63 (d, 1 H, J = 6.8 Hz), 5.15−5.19 (m, 2 H), 5.55−6.64 (m, 1 H), 7.34 (d, 2 H, J = 8.1 Hz), 7.79 (d, 2 H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 34.6, 55.5, 67.0, 73.4, 93.9, 118.3, 127.9, 129.8, 133.1, 137.0, 144.7. Anal. Calcd. for $C_{14}H_{20}O_5S$ (300.37): C, 55.98; H, 6.71; S, 10.68; found: C, 56.12; H, 6.62; S, 10.50.

3.2.5 3-[3-(Methoxymethyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione. To a solution of 3-hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (2.14 g, 7.74 mmol) in anhydrous dimethylformamide (8 mL) was added at 22 °C 3-(methoxymethyloxy)pent-4-en-1-yl *p*-toluenesulfonate (**5**) (2.12 g, 7.04 mmol) in anhydrous dimethylformamide (5.5 mL). The reaction mixture was stirred at 50 °C (oil bath temperature) for 2.5 hours. Water (50 mL) was added and the resulting suspension was extracted with dichloromethane (3 × 20 mL). Combined organic extracts were washed with aqueous sodium hydroxide (2 M, 3 × 20 mL) and brine (20 mL). The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2:1 (*v*/*v*)]. Yield: 1.63 g (5.92 mmol, 84%), pale yellow oil. R_f = 0.33 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03−2.18 (m, 2 H), 2.28 (d, 3 H, J = 1.4 Hz), 3.37 (s, 1 H), 4.23−4.29 (m, 1 H), 4.44−4.55 (m, 2 H), 4.58 (d, 1 H, J = 6.6 Hz), 4.71 (d, 1 H, J = 6.6 Hz), 5.24−5.32 (m, 2 H), 5.74 (ddd, 1 H, J = 17.4, 10.1, 7.4 Hz), 6.15 (d, 1 H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 33.7, 55.7, 72.9, 74.2, 94.1, 102.7, 118.2, 137.4, 137.6, 180.4. Anal. Calcd. for $C_{11}H_{17}NO_3S_2$ (275.39): C, 47.98; H, 6.22; N, 5.09; S, 23.29; found: C, 48.18; H, 6.17; N, 5.14; S, 23.48.

3.3 3-[(2*R*,3*S*)-Isopropylidendioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *erythro*-(7). 3-Hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (575 mg, 2.08 mmol) and [(*2R*,*3S*)-isopropylidendioxypent-4-en-1-yl] *p*-toluenesulfonate were dissolved in dimethylformamide (5 mL). The resulting clear solution was stirred for 16 hours at 40 °C. Afterwards water (50 mL) was added and the resulting mixture was extracted with diethyl ether (4 × 50 mL). Combined organic extracts were washed with aqueous sodium hydroxide (2 M, 50 mL). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2.5/1 (*v*/*v*)]. Yield: 361 mg (1.26 mmol, 78%), yellow oil. R_f = 0.65 [petroleum ether/diethyl ether = 1/3 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 3 H), 1.52 (s, 3 H), 2.31 (d, 3 H, J = 1.17 Hz), 4.12 (dd, 1 H, J = 9.3, 8.3 Hz), 4.58–4.74 (m, 3 H), 5.28 (dt, 1 H, J_d = 10.4 Hz, J_t = 1.1 Hz), 5.41 (dt, 1 H, J_d = 17.1 Hz, J_t = 1.3 Hz), 5.83 (ddd, 1 H, J = 17.2, 10.2, 7.1 Hz), 6.15 (d, 1 H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.5, 25.2, 27.8, 75.0, 75.7, 77.9, 102.6, 109.5, 119.4, 132.3, 138.0, 180.3. Anal. Calcd. for $C_{12}H_{17}NO_3S_2$ (287.39): C, 50.15; H, 5.96; N, 4.87; S, 22.31; found: C, 50.26; H, 6.21; N, 4.97; S, 22.45.

3.4 3-[(2*S*,3*S*)-Isopropylidendioxypent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione. 3-Hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (2.07 g, 7.49 mmol) and [(2*R*,3*R*)-isopropylidendioxypent-4-en-1-yl] *p*-toluenesulfonate (1.80 g, 5.76 mmol) were dissolved in dimethylformamide (10 mL). The solution was stirred at 40 °C for 16 hours and then added to water (50 mL). The mixture was extracted with diethyl ether (4 × 50 mL). Combined organic extracts were washed with aqueous sodium hydroxide (2 M, 50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2.5/1 (*v*/*v*)]. Yield: 1.40 g (4.87 mmol, 85%), yellow oil. R_f = 0.63 [petroleum ether/diethyl ether = 1/3 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.43 (d, 6 H, J = 6.2 Hz), 2.30 (d, 3 H, J = 1.2 Hz), 4.03 (ddd, 1 H, J = 8.5, 5.1, 3.4 Hz), 4.45 (t, 1 H, J = 7.8 Hz), 4.52–4.58 (m, 2 H), 5.30 (d, 1 H, J = 10.3 Hz), 5.49 (d, 1 H, J = 10.3 Hz), 5.86 (ddd, 1 H, J = 17.2, 10.3, 7.0 Hz), 6.16 (d, 1 H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.3, 26.7, 26.9, 74.3, 78.0, 78.3, 102.6, 109.9, 119.7, 134.2, 137.9, 180.2. Anal. Calcd. for $C_{12}H_{17}NO_5S_2$ (287.39): C, 50.15; H, 5.96; N, 4.87; S, 22.31; found: C, 50.23; H, 5.82; N, 4.82; S, 21.93.

3.5 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Bishydroxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione

3.5.1 (2*R*,3*R*,4*S*)-3,4-*O*-Isopropylidendioxyhex-5-en-2-ol. Potassium *tert*-butoxide (1.88 g, 16.8 mmol) and methyltriphenylphosphonium bromide (5.77 g, 16.2 mmol) were dissolved in dry tetrahydrofuran (80 mL). The reaction mixture was stirred 2 hours at 25 °C. 2,3-*O*-Isopropyliden-5-*O*-desoxy-D-ribofuranose (1.10 g, 6.46 mmol) in tetrahydrofuran (20 mL) was added and the mixture was stirred 6 hours while being refluxed. The reaction mixture was treated with water (20 mL) at room temperature and the layers were separated. The aqueous layer was extracted with diethyl ether (5 × 20 mL). Combined organic extracts were washed with water (20 mL) and brine (20 mL). The solution was dried (Na_2SO_4) and the solvent was removed under reduced pressure (800 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1/1 (*v*/*v*)]. Yield: 755 mg (4.37 mmol, 67%), colorless oil. R_f = 0.47 [diethyl ether/pentane = 1/1 (*v*/*v*)]. $[\alpha]^D_{25}$ = −21.3 (*c* = 1.00 g/100 mL/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 3 H, *J* = 6.2 Hz), 1.37 (s, 3 H), 1.48 (s, 3 H), 1.74 (d, 1 H, *J* = 4.4 Hz, OH), 3.79–3.86 (m, 1 H), 3.93 (dd, 1 H, *J* = 7.9, 6.2Hz), 4.66 (dd, 1 H, *J* = 7.3, 6.4 Hz), 5.31 (ddd, 1 H, *J* = 17.3, 2.9, 1.7 Hz), 5.44 (ddd, 1 H, *J* = 12.0, 2.9, 1.4 Hz), 5.98−6.05 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 25.3, 27.7, 66.4, 78.8, 82.0, 108.7, 118.5, 134.6. Anal. Calcd. for $C_9H_{16}O_3$ (172.22): C, 62.77; H, 9.36; found: C, 62.46; H, 9.58.

3.5.2 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Isopropylidendioxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (9). In an atmosphere of dry nitrogen, (2*R*,3*R*,4*S*)-3,4-*O*-isopropylidendioxyhex-5-en-2-ol (750 mg, 4.36 mmol), 3-hydroxy-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (1.66 g, 6.54 mmol) and triphenylphosphine (2.29 g, 8.72 mmol) were dissolved in benzene (50 mL). The solution was cooled to 0 °C and diethyl azodicarboxylate (3.04 g, 17.4 mmol) was added in a dropwise manner. The reaction mixture was stirred 48 hours at 25 °C and then treated with with aqueous sodium hydroxide (2 M, 15 mL). The resulting layers were separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). Combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure (600 mbar, 40 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1/1 (*v*/*v*)]. Yield: 953 mg (2.35 mmol, 54%), yellow solid. R_f = 0.26 [diethyl ether/pentane = 1/1 (*v*/*v*)]. $[\alpha]^D_{25}$ = 28.9 (*c* = 11.2 g/100 mL/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (d, 6 H, *J* = 6.7 Hz), 1.43 (s,

3 H), 2.32 (s, 3 H), 3.83 (s, 3 H), 4.34 (dd, 2 H, J = 7.8, 6.2 Hz), 4.53 (dd, 1 H, J = 8.6, 6.2 Hz), 5.34 (t, 2 H, J = 8.3, Hz), 5.41−5.47 (m, 1 H), 5.97−6.05 (m, 1 H), 6.94 (d, 2 H, J = 8.0 Hz), 7.21 (d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.8, 15.2, 25.7, 28.0, 55.6, 79.8, 80.0, 80.8, 109.7, 114.7, 118.6, 120.4, 123.1, 130.0, 133.7, 134.3, 160.0, 178.7. Anal. Calcd. for $C_{20}H_{25}NO_4S_2$ (407.54): C, 58.94; H, 6.18; N, 3.44; found: C, 58.75; H, 6.21; N, 3.63.

3.5.3 3-[(2*S*,3*S*,4*S*)-3,4-*O*-Bishydroxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione. From 3-[(2*S*,3*S*,4*S*)-3,4-*O*-isopropylidendioxyhex-5-en-2-oxy]-4-methyl-5-(*p*-methoxyphenyl)thiazole-2(3*H*)-thione (**9**) (1.14 g, 2.8 mmol), methanol (48 mL) and aqueous hydrochloric acid [2.96 mL, 37 % (*w*/*w*)] according to procedure 3.1. Water (60 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). This product was used as obtained in the succeeding step. Yield: 1.00 g (2.75 mmol, 96%), yellow oil. R_f = 0.0 [diethyl ether/pentane = 1/1 (*v*/*v*)]. $[\alpha]^D_{25}$ = 21.7 (c = 8.84 g/100 mL/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, 3 H, J = 6.7 Hz), 2.34 (s, 3 H), 3.58 (d, 1 H, J = 4.7 Hz), 3.83 (s, 3 H,), 4.42 (t, 1 H, J = 6.6 Hz), 5.32 (d, 1 H, J = 10.6 Hz), 5.43 (d, 1 H, J = 17.2 Hz), 5.49 (dd, 1 H, J = 9.4, 3.1 Hz), 6.10−6.01 (m, 1 H), 6.95 (d, 2 H, J = 9.0 Hz), 7.24 (d, J = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9, 15.4, 55.5, 72.8, 76.2, 80.8, 114.6, 117.7, 120.1, 122.1, 129.9, 133.8, 137.2, 160.0, 178.8. Anal. Calcd. for $C_{17}H_{21}NO_4S_2$ (367.48): C, 55.56; H, 5.76; N, 3.81; found: C, 55.31; H, 5.75; N, 4.04.

3.6 Synthesis of 3-(3-Hydroxynona-1,8-dien-5-oxy)-4-methylthiazole-2(3*H*)-thione (1f)

3.6.1 3-(Methoxymethyloxy)pent-4-enal. In an atmosphere of dry nitrogen, a solution of ethyl 3-(methoxymethyloxy)pent-4-enoate (9.49 g, 50.4 mmol) in dichloromethane (125 mL) was cooled to −78 °C, and treated in a dropwise manner at −78 °C with diisobutylaluminium hydride (50.4 mL, 1 M solution in hexane) and afterwards with methanol (99.5 mL). The reaction mixture was allowed to 22 °C and solids were filtered off over celite. The filtrate was concentrated under reduced pressure (650 mbar, 30 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 3.00 g (20.80 mmol, 41%), colorless liquid. R_f = 0.41 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53–2.59 (m, 1 H), 2.67–2.70 (m, 1 H), 3.34 (s, 3 H), 4.53 (d, 1 H, J = 6.9 Hz), 4.57 (m, 1 H), 4.70 (d, 1 H, J = 6.9 Hz,), 5.23–5.26 (m, 1 H), 5.28–5.33 (m, 1 H), 5.70–5.78 (m, 1 H), 9.77–9.78 (dd, 1 H, J = 2.6, 1.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.9, 55.7, 72.2, 93.9, 118.2, 136.5, 200.5.

3.6.2 3-(Methoxymethyloxy)nona-1,8-dien-5-ol. In an atmosphere of dry nitrogen, a suspension of magnesium (450 mg, 18.5 mmol) in dry tetrahydrofuran (18.5 mL) was treated in a dropwise manner with bromobut-2-ene (2.50 g, 18.5 mmol) and afterwards with 3-(methoxymethyloxy)pent-4-enal (2.06 g, 14.20 mmol) at room temperature. The reaction mixture was stirred for 1 hour at 22 °C and then cooled to 0 °C. At 0 °C the reaction mixture was treated with an aqueous saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). Combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (650 mbar, 30 °C) and the residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 2.08 g (10.2 mmol, 70%), colorless liquid, as a 50/50-mixture of diastereomers. R_f = 0.53 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49–1.80 (m, 4 H), 2.10–2.24 (m, 2 H), 3.41 (s, 3 H), 3.83–3.92 (m, 1 H), 4.27–4.36 (m, 1 H), 4.54–4.59 (dd, 1 H, *J* = 13.6, 6.7 Hz), 4.68–4.75 (m, 1 H), 4.96–4.98 (m, 2 H), 5.18–5.28 (m, 2 H), 5.63–5.75 (m, 1 H), 5.77–5.90 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.7, 30.0, 36.4, 36.6, 42.2, 42.3, 55.8, 67.5, 70.3, 75.4, 77.6, 93.4, 94.4, 114.7, 116.8, 118.1, 137.4 (2C), 137.7 (2C), 138.5 (2C), 138.5 (2C). Retention time (t_r) = 14.8 minutes (for GC/MS conditions see section 2.7): MS (EI) *m*/*z* 138 (<1), 113 (24), 101 (28), 83 (57), 67 (57), 55 (100). HRMS (EI$^+$) *m*/*z* 168.1142 [M^+−OCH_3−H]; calculated mass for $C_{10}H_{16}O_2^+$: 168.1150. t_r = 14.9 minutes: MS (EI) *m*/*z* 138 (<1), 113 (24), 101 (28), 83 (57), 67 (57), 55 (100). HRMS (EI$^+$) *m*/*z* 168.1133 [M^+−OCH_3−H]; calculated mass for $C_{10}H_{16}O_2^+$: 168.1150.

3.6.3 3-(Methoxymethyloxy)nona-1,8-dien-5-yl-4-methyl *p*-toluenesulfonate (10). In an atmosphere of dry nitrogen, a solution of 3-(methoxymethyloxy)nona-1,8-dien-5-ol (1.30 g, 6.50 mmol) in dry dichloromethane (32 mL) was treated with 1,4-diazabicyclo[2.2.2]octane (1.46 g, 13.00 mmol) and the mixture was cooled in an ice bath. *p*-Toluenesulfonyl chloride (1.86 g, 9.75 mmol) was added in portions that the temperature does not exceed 0 °C. The resulting reaction mixture was allowed to warm to 22 °C and stirred for 19 hours at this temperature. The precipitate formed was filtered off and washed with diethyl ether (3 × 30 mL). Filtrate and organic washings were washed with aqueous hydrochloric acid (2 M, 30 mL), an aqueous saturated solution of $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 30 °C) to leave a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1:3 (*v*/*v*)]. Yield: 1.85 g (5.20 mmol, 80%), pale yellow liquid, as a 50/50-mixture of diastereomers. R_f = 0.26 [diethyl ether/pentane = 1:3 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ

1.71–1.84 (m, 4 H), 1.99–2.06 (m, 2 H), 2.45 (s, 3 H), 3.33–3.39 (m, 3 H), 3.98–4.03 (m, 1 H), 4.47–4.51 (m, 1 H), 4.62–4.64 (m, 1 H), 4.80–4.86 (m, 1 H), 4.93–4.98 (m, 2 H), 5.15–5.21 (m, 2 H), 5.58–5.72 (m, 2 H), 7.35 (d, 2 H, J = 8.2 Hz), 7.80–7.83 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 28.5, 28.8, 33.3, 34.1, 39.9, 40.6, 55.7, 55.9, 73.8, 74.5, 80.4, 80.5, 93.6, 94.5, 115.3, 115.3, 117.6, 118.6, 127.7, 127.8, 129.7, 134.5, 134.7, 137.0, 137.1, 137.1, 137.8, 144.5.

3.6.4 3-[3-(Methoxymethyloxy)nona-1,8-diene-5-oxy]-4-methylthiazole-2(3*H*)-thione.

3-Hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (0.87 g, 5.90 mmol) was dissolved in anhydrous dimethylformamide (3.5 mL) and treated with 3-(methoxymethyloxy)nona-1,8-diene-5-yl-4-methyl *p*-toluenesulfonate (**10**) (1.85 g, 5.20 mmol) in anhydrous dimethylformamide (7 mL). The solution was stirred at 40 °C (oil bath temperature) for 2 hours and then allowed to cool to 22 °C. The mixture was treated with water (10 mL) and dichlormethane (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). Combined organic layers were washed with aqueous sodium hydroxide (2 M, 3 × 10 mL) and brine (3 × 25 mL). The organic solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The residue was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 1.16 g (3.50 mmol, 67%), pale yellow liquid, as a 50/50-mixture of diastereomers. R_f = 0.35 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78–2.00 (m, 4 H), 2.20–2.27 (m, 5 H), 3.37–3.39 (m, 3 H), 4.17–4.20 (m, 1 H), 4.51–4.68 (m, 2 H), 4.98–5.07 (m, 2 H), 5.23–5.31 (m 2 H), 5.45–5.50 (m, 1 H), 5.67–5.83 (m, 2 H), 6.16–6.18 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 29.1, 31.7, 32.1, 38.4, 38.7, 55.8, 55.9, 74.0, 74.7, 81.9, 93.7, 94.5, 102.8, 115.2, 118.3, 137.3, 137.6, 137.8, 138.9, 181.0.

4 Synthesis of *rel*-(3*S*,4*R*)-3-bromotetrahydropyran-4-ol *cis*-(11a)

3-Bromotetrahydropyran-4-one (180 mg, 1.00 mmol) was dissolved in methanol (4 mL) and treated with sodium borohydride (46 mg, 1.20 mmol) at 22 °C.[6,7] The reaction mixture was stirred at 22 °C for 3 hours. The solvent was removed under reduced pressure (300 mbar, 40 °C). Ethyl acetate (20 mL) was added and the resulting solution was washed with brine (20 mL). The layers were separated and the organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure (200 mbar, 40 °C) and the residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2:1 (*v*/*v*)]. Yield: 95.0 mg (0.52 mmol, 52%), pale yellow oil. R_f = 0.30 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91–2.04 (m, 2 H), 3.62 (dt, 1 H, J_d = 11.7 Hz, J_t = 4.7 Hz), 3.79 (dd, 1 H, J = 11.9, 3.8 Hz), 3.89 (ddd, 1 H, J = 11.8, 8.5, 3.7 Hz), 3.95–3.99 (m, 2 H), 4.35 (dt, 1 H, J_d = 8.3 Hz, J_t = 3.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.6, 55.7, 63.3, 67.0, 68.1. MS (EI) *m*/*z* 124/122, 108/106, 101, 100, 83 (100), 73, 61, 55.

5 Bromocyclizations

5.1 General method for thermally initiated radical reactions. Bromotrichloromethane (10 equiv.) and azobisisobutyronitrile (AIBN) (0.25 equiv) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv, c_0 = 83 mM) in perdeuterobenzene. The solution was heated to reflux for 2 hours. For yields of 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**), tetrahydrofuran **3** and tetrahydropyran **11**, determined via proton-NMR using pentachlorobenzene or bromobenzaldehyde as internal standard, refer to section 2.4.1 of the associated publication.

5.2 General method for photochemically initiated radical reactions. Bromotrichloromethane (9−10 equiv) was added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv., c_0 = 83 or 196 mM) in perdeuterobenzene. The solution was photolyzed (350 nm) for 30−60 minutes. For yields of 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**), tetrahydrofuran **3** and tetrahydropyran **11**, determined via proton-NMR using pentachlorobenzene or bromobenzaldehyde as internal standard, refer to section 2.4.1 and Scheme 9 of the associated publication.

6 NMR Spectra

6.1 *O*-Alkenylthiohydroxamate

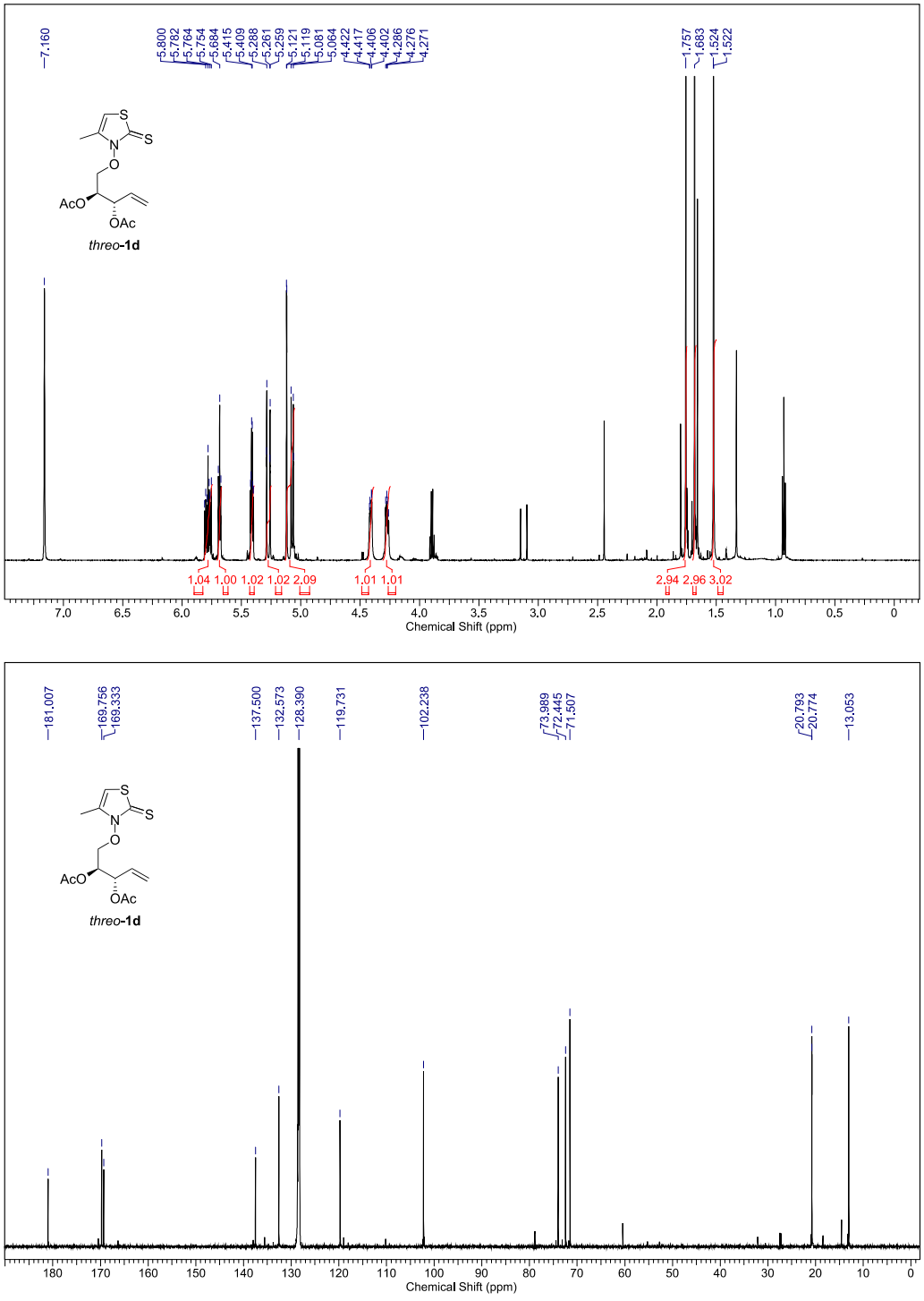

Figure 6.1 ^{1}H-NMR-spectrum (C_6D_6, 600 MHz, top) and ^{13}C-NMR-spectrum (C_6D_6, 150 MHz, bottom) of 3-[(2*S*,3*S*)-bis(acetyloxy)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione *threo*-(**1d**).

6.2 Bromocyclization products of 1a

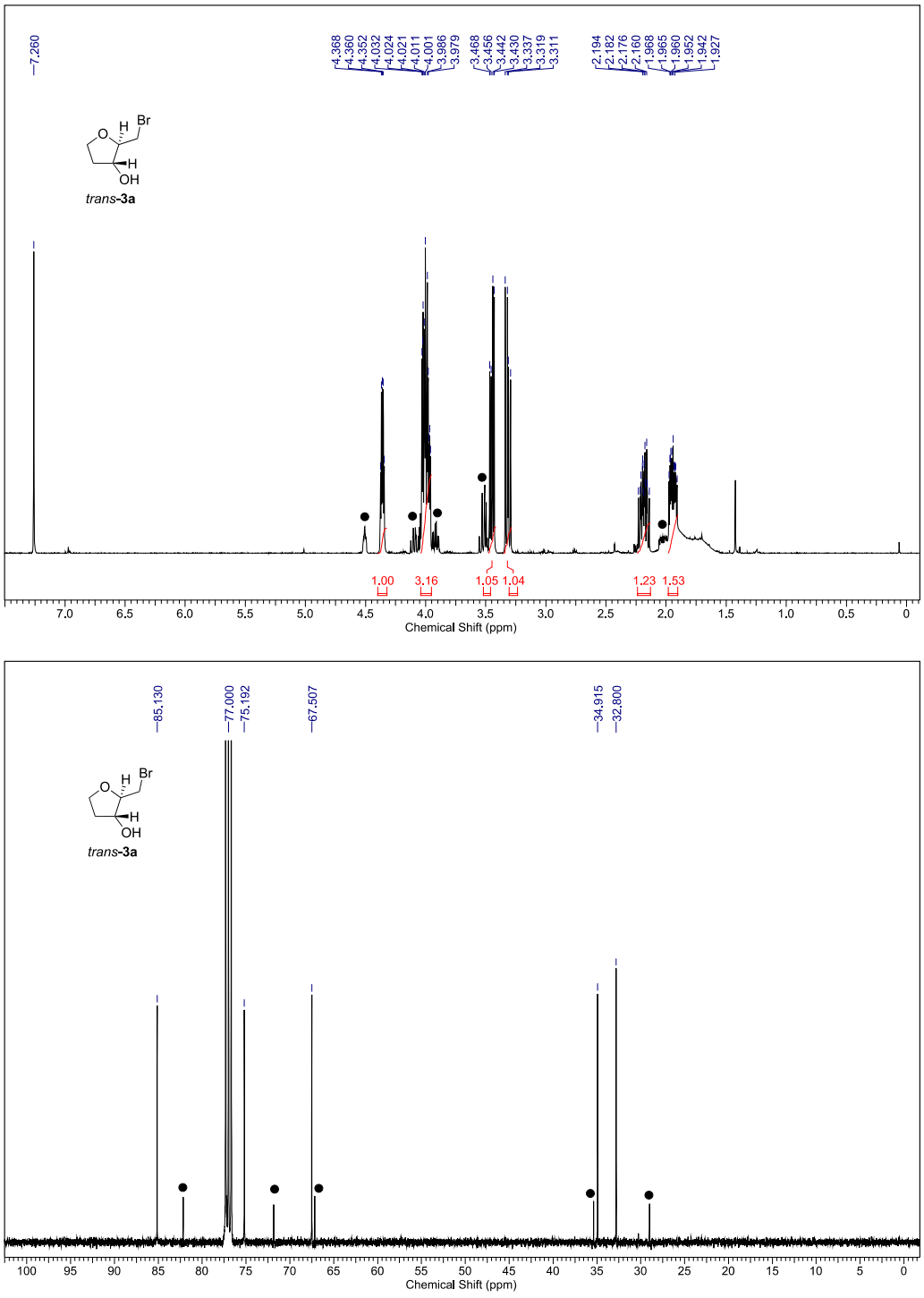

Figure 6.2 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(2*R*,3*R*)-2-bromomethyltetrahydrofuran-3-ol *trans*-(**3a**). Labeling (●) refer to *rel*-(2*S*,3*R*)-2-bromomethyltetrahydrofuran-3-ol *cis*-(**3a**).

6.3 Bromocyclization products of 1b

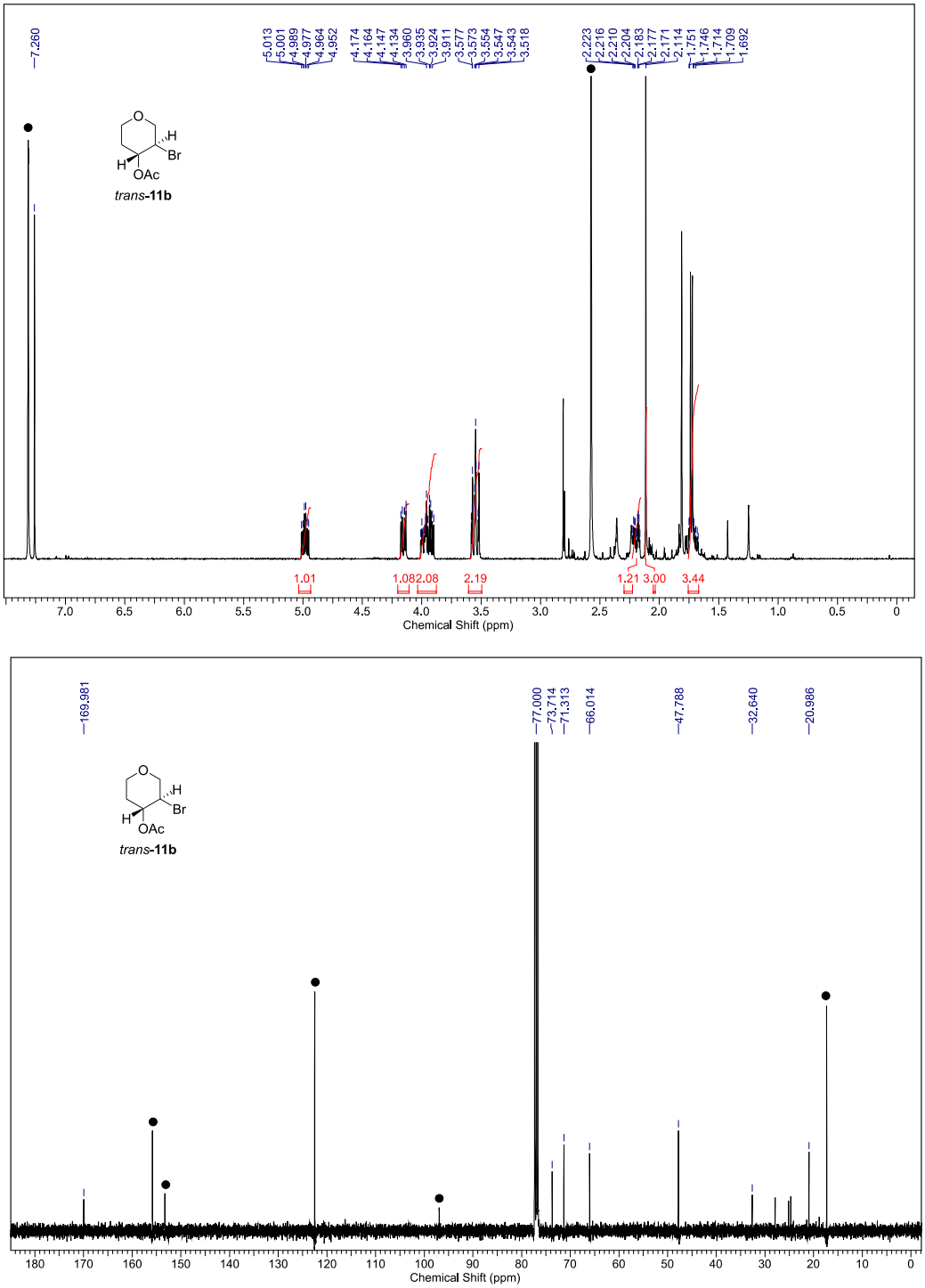

Figure 6.3 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(3*R*,4*R*)-3-bromotetrahydropyran-4-yl acetate *trans*-(**11b**). Labeling (●) refer to 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**).

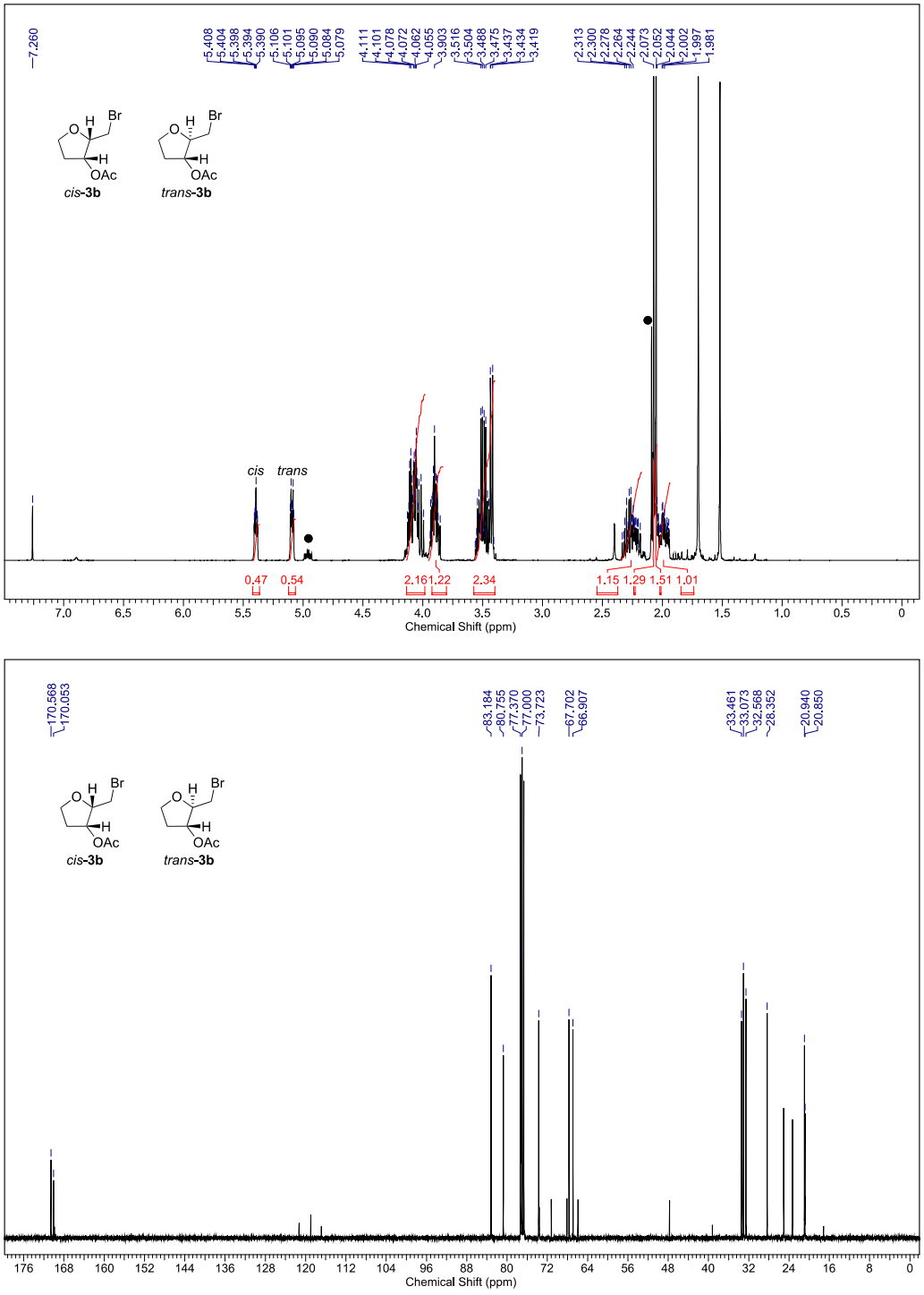

Figure 6.4 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of 2-bromomethyltetrahydrofuran-3-yl acetate (**3b**) (47/53-mixture of *cis*/*trans*-isomers). Labeling (●) refer to assignable resonances for *rel*-(3*R*,4*R*)-3-bromotetrahydropyran-4-yl acetate *trans*-(**11b**).

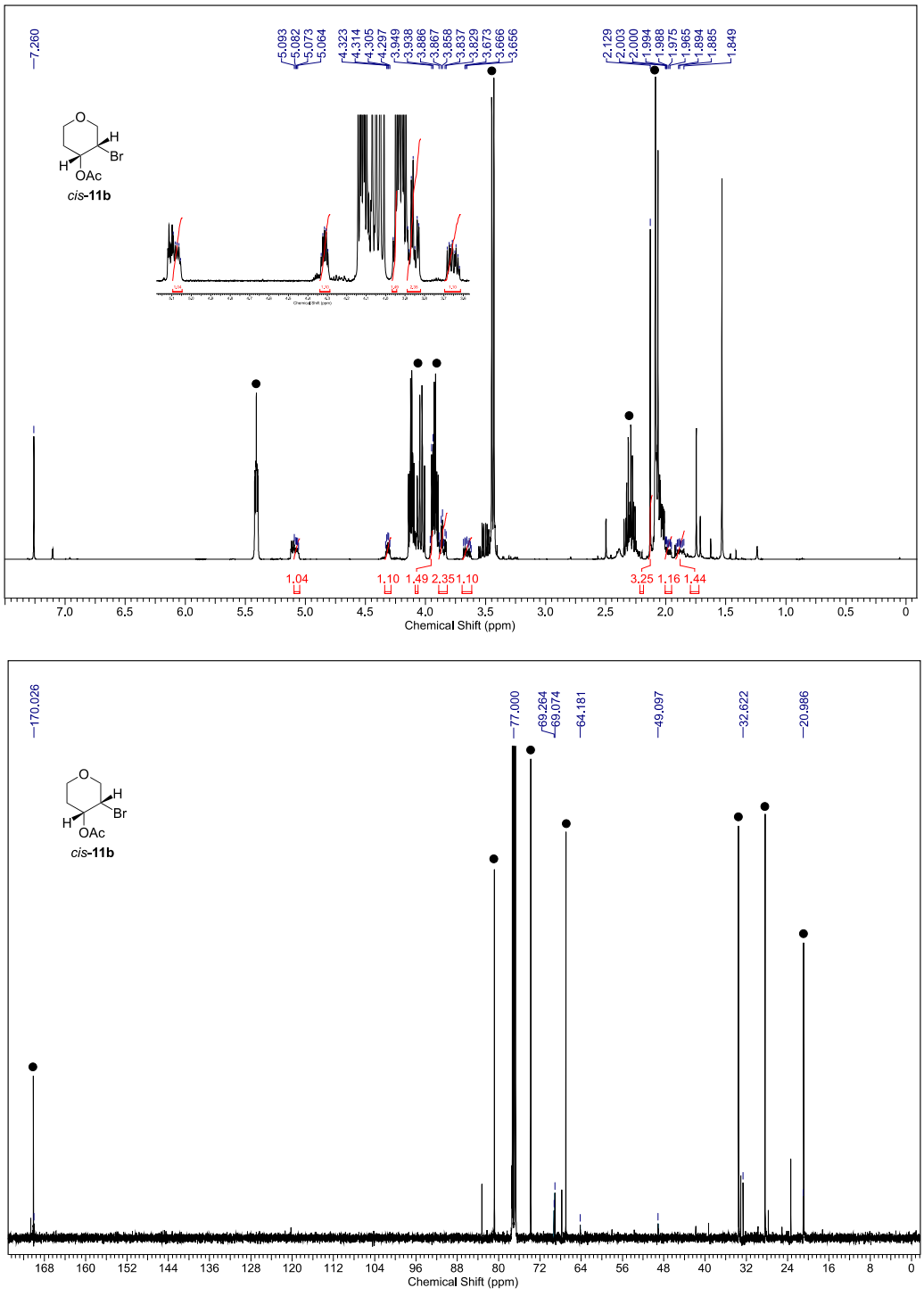

Figure 6.5 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(3*S*,4*R*)-3-bromotetrahydropyran-4-yl acetate *cis*-(**11b**). Labeling (●) refer to *rel*-(2*S*,3*R*)-2-bromomethyltetrahydrofuran-3-yl acetate *cis*-(**3b**).

6.4 Bromocyclization products of 1c

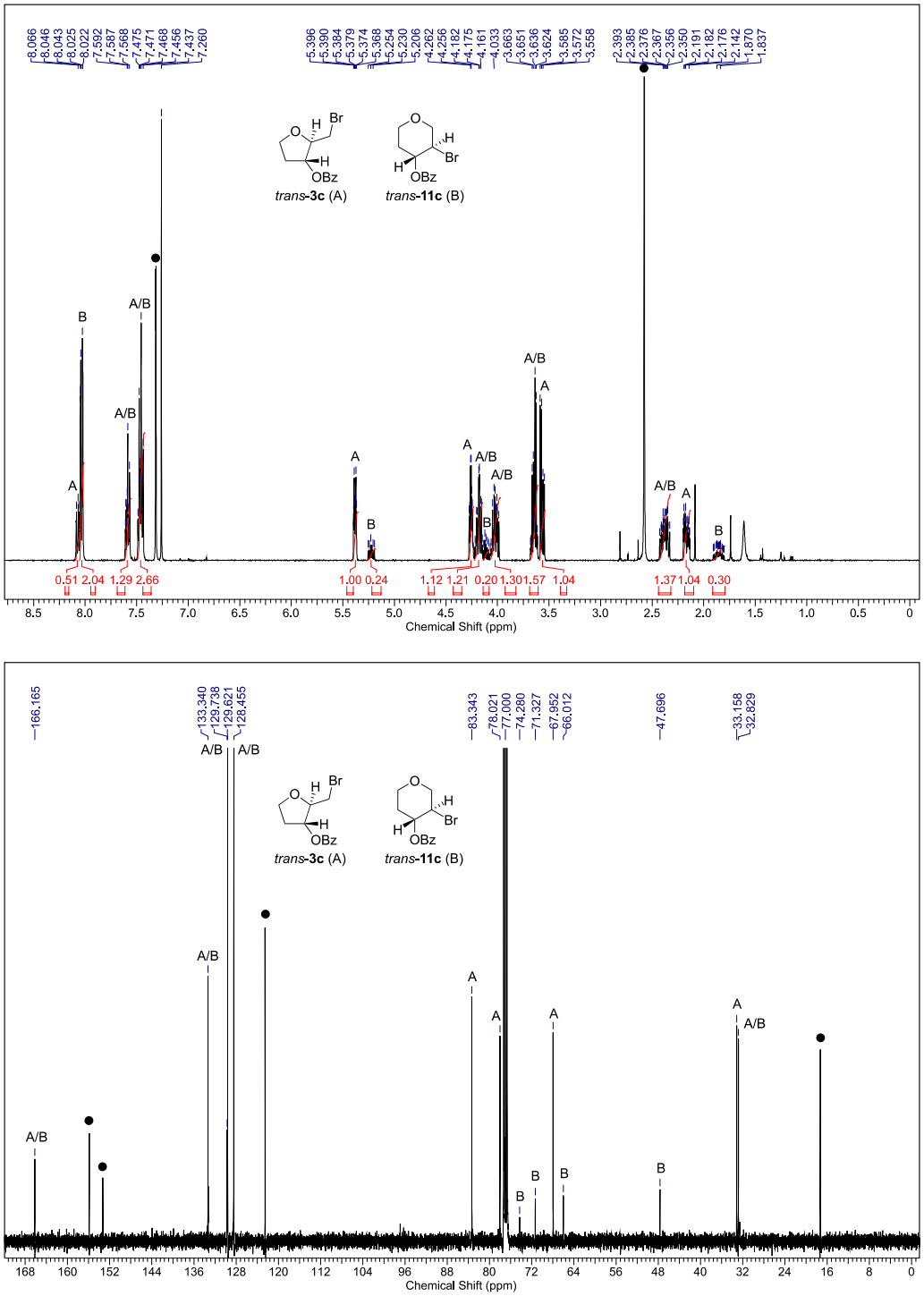

Figure 6.6 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(2*R*,3*R*)-2-bromomethyltetrahydrofuran-3-yl benzoate *trans*-(**3c**) and *rel*-(3*R*,4*R*)-3-bromotetrahydropyran-4-yl benzoate *trans*-(**11c**) (81/9-mixture of **3c**/**11c**-isomers). Labeling (●) refer to 4-methyl-2-(trichloromethylsulfanyl)thiazole (**2**).

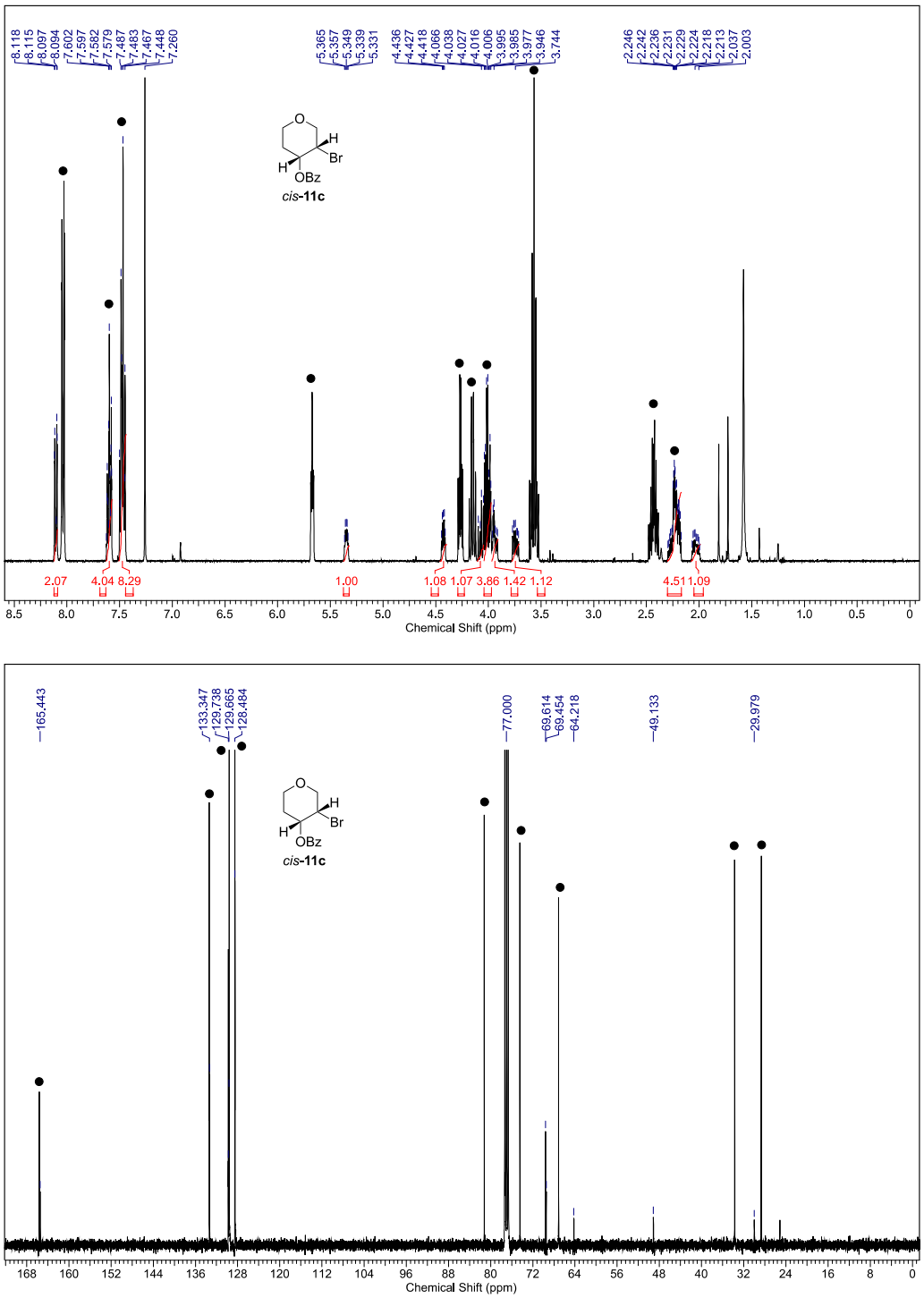

Figure 6.7 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(3*S*,4*R*)-3-bromotetrahydropyran-4-yl benzoate *cis*-(**11c**). Labeling (●) refer to *rel*-(2*S*,3*R*)-2-bromomethyltetrahydrofuran-3-yl benzoate *cis*-(**3c**).

6.5 Bromocyclization products of *erythro*-1d

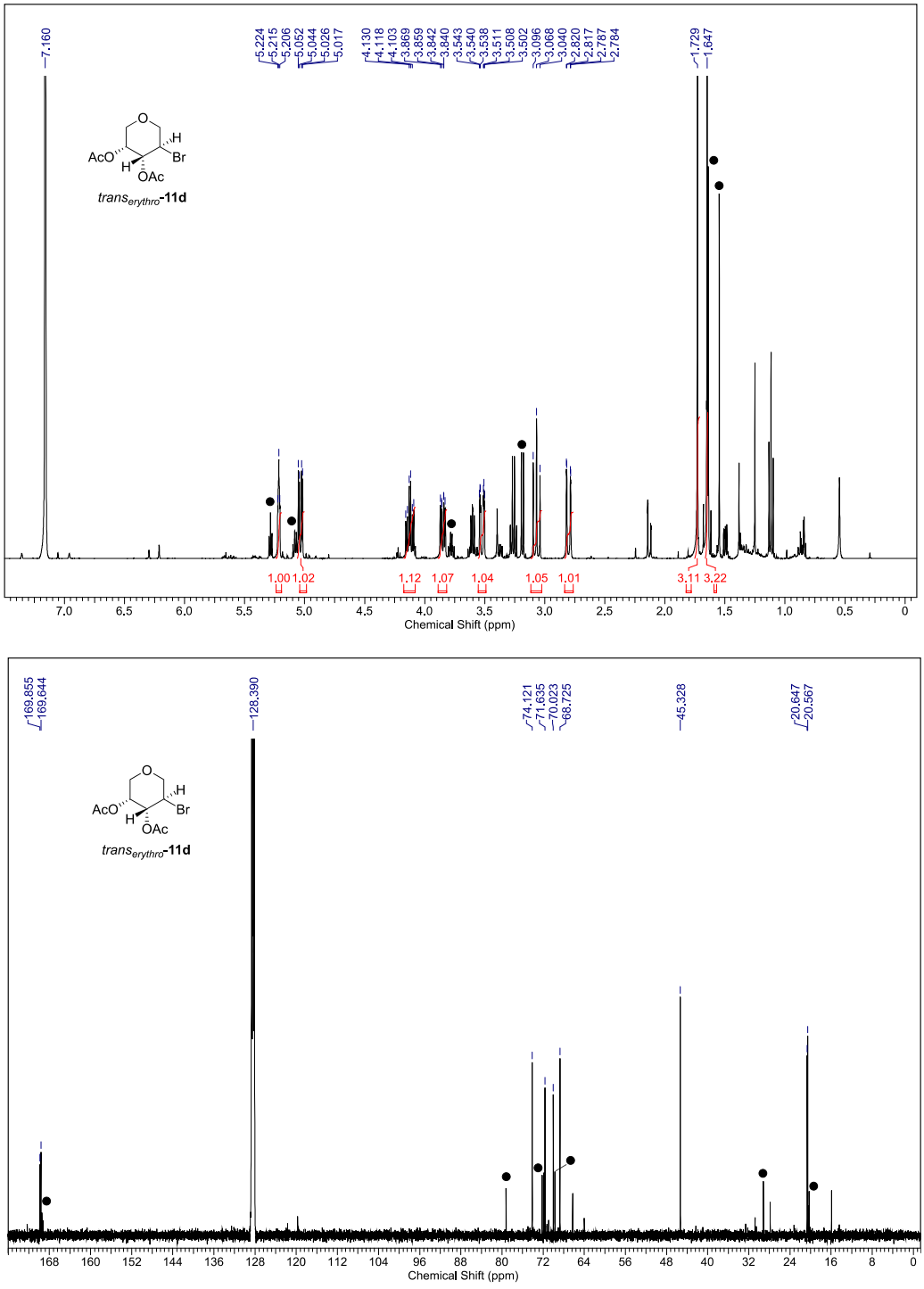

Figure 6.8 ^{1}H-NMR-spectrum (C_6D_6, 400 MHz, top) and ^{13}C-NMR-spectrum (C_6D_6, 100 MHz, bottom) of (3*R*,4*R*,5*R*)-3-bromotetrahydropyran-4,5-diyl bisacetate *trans*$_{erythro}$-(**11d**). Labeling (●) refer to (2*S*,3*R*,4*R*)-2-bromomethyltetrahydrofuran-3,4-diyl bisacetate *cis*$_{erythro}$-(**3d**).

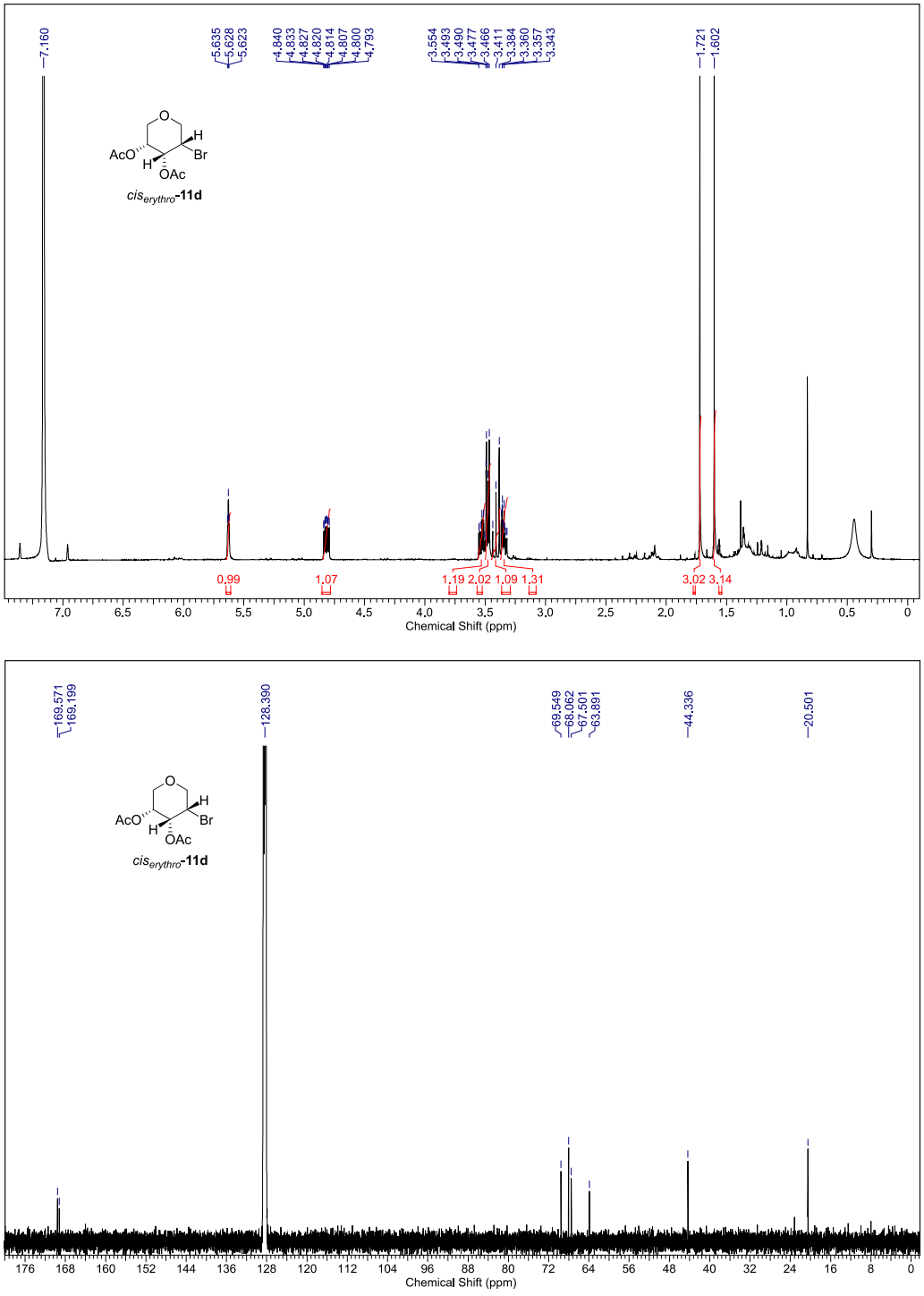

Figure 6.9 ^{1}H-NMR-spectrum (C_6D_6, 400 MHz, top) and ^{13}C-NMR-spectrum (C_6D_6, 100 MHz, bottom) of (3*S*,4*R*,5*R*)-3-bromotetrahydropyran-4,5-diyl bisacetate *cis*$_{erythro}$-(**11d**).

6.6 Bromocyclization products of *threo*-1d

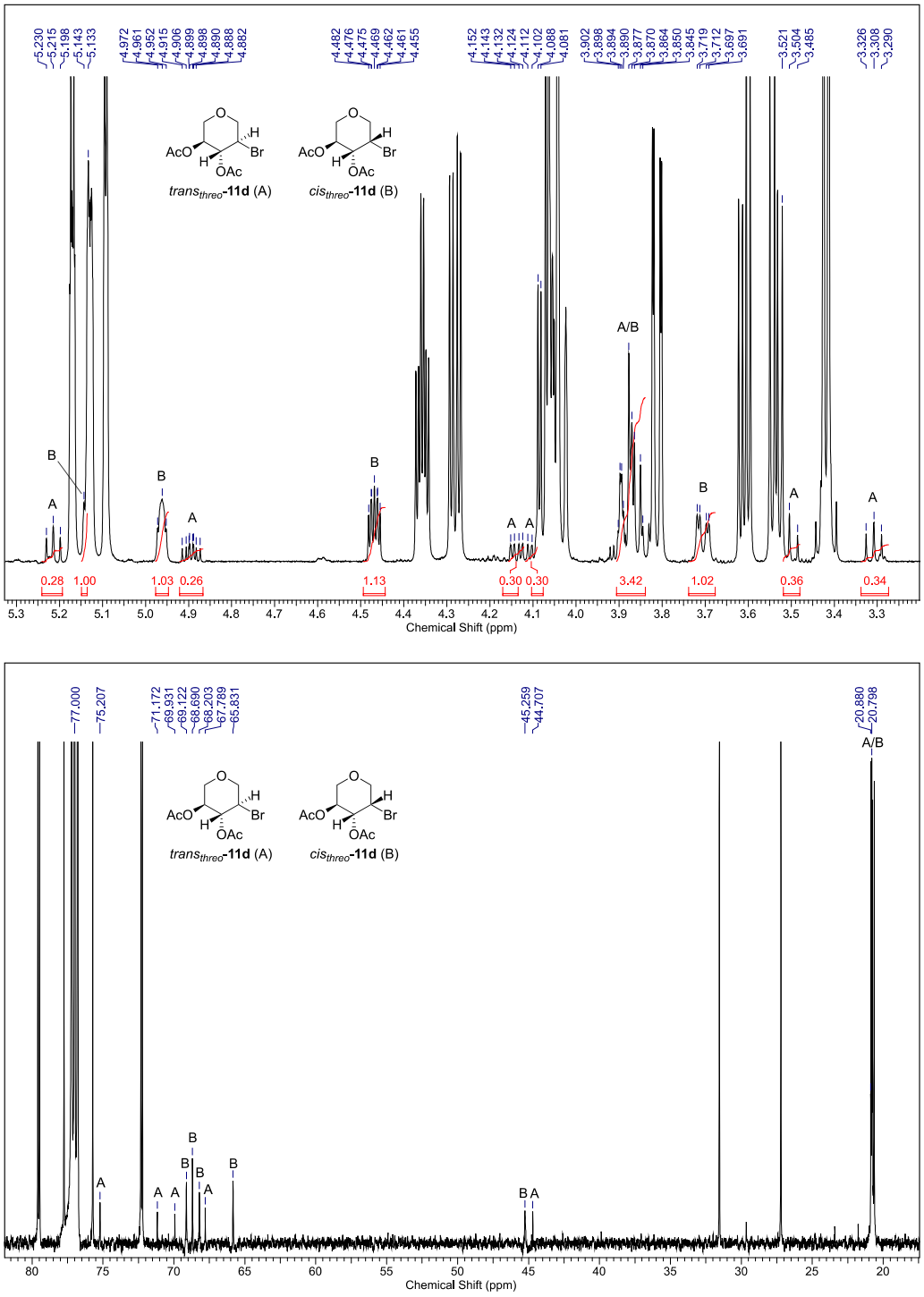

Figure 6.10 Expert of ^{1}H-NMR-spectrum ($CDCl_3$, 600 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 150 MHz, bottom) of (3*R*,4*R*,5*S*)-4,5-bis(acetyloxy)-3-bromomethyltetrahydropyran *trans*$_{threo}$-(**11d**) and (3*R*,4*R*,5*S*)-4,5-bisacetyloxy-3-bromomethyltetrahydropyran *cis*$_{threo}$-(**11d**) (80/20-mixture of *cis*/*trans*-isomers).

6.7 Bromocyclization products of 1f

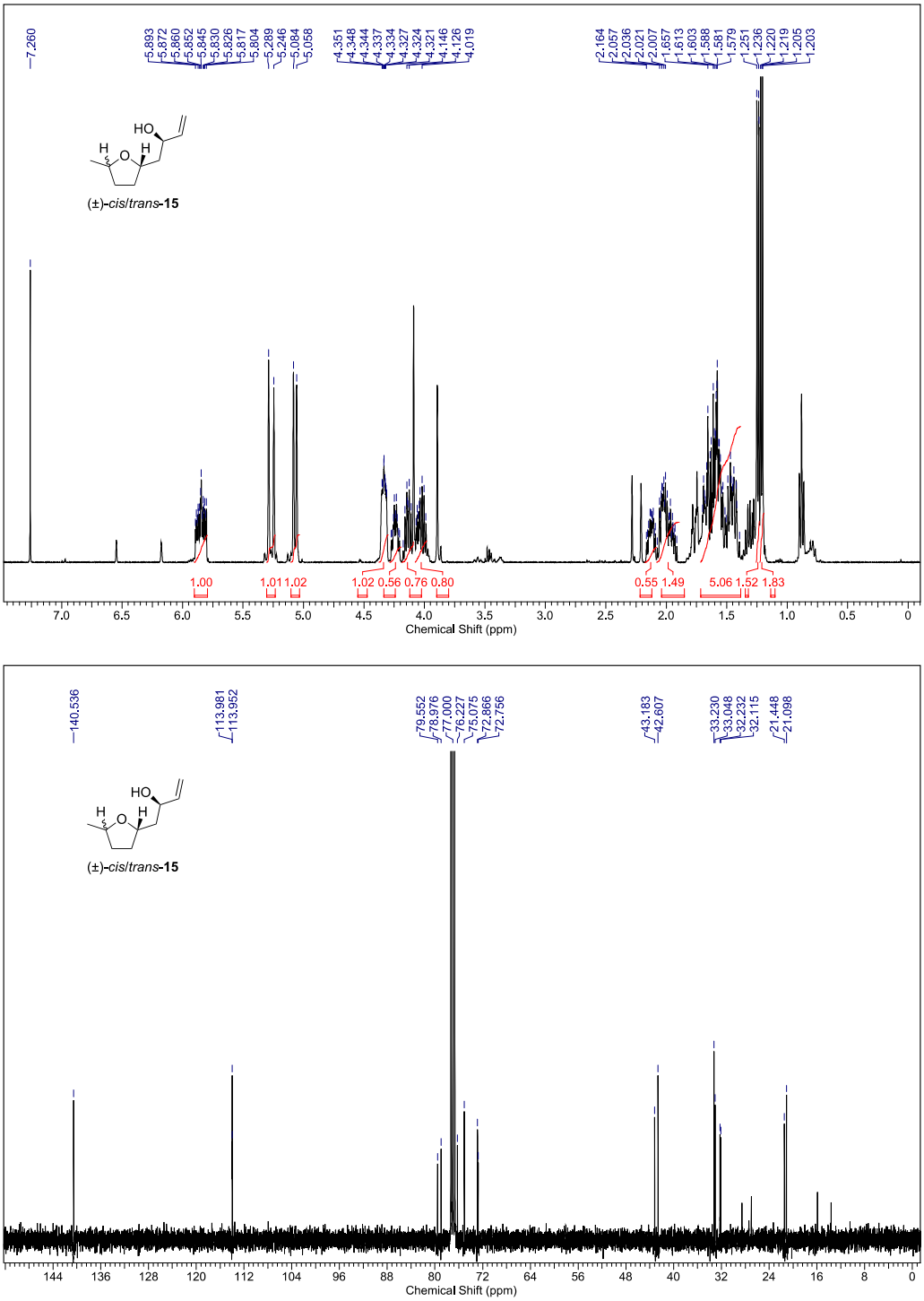

Figure 6.11 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) of *rel*-(2'*S*,2*R*)-1-(5'-methyltetrahydrofuran-2'-yl)but-3-ene-2-ol (**15**) (27/73-mixture of diastereomers).

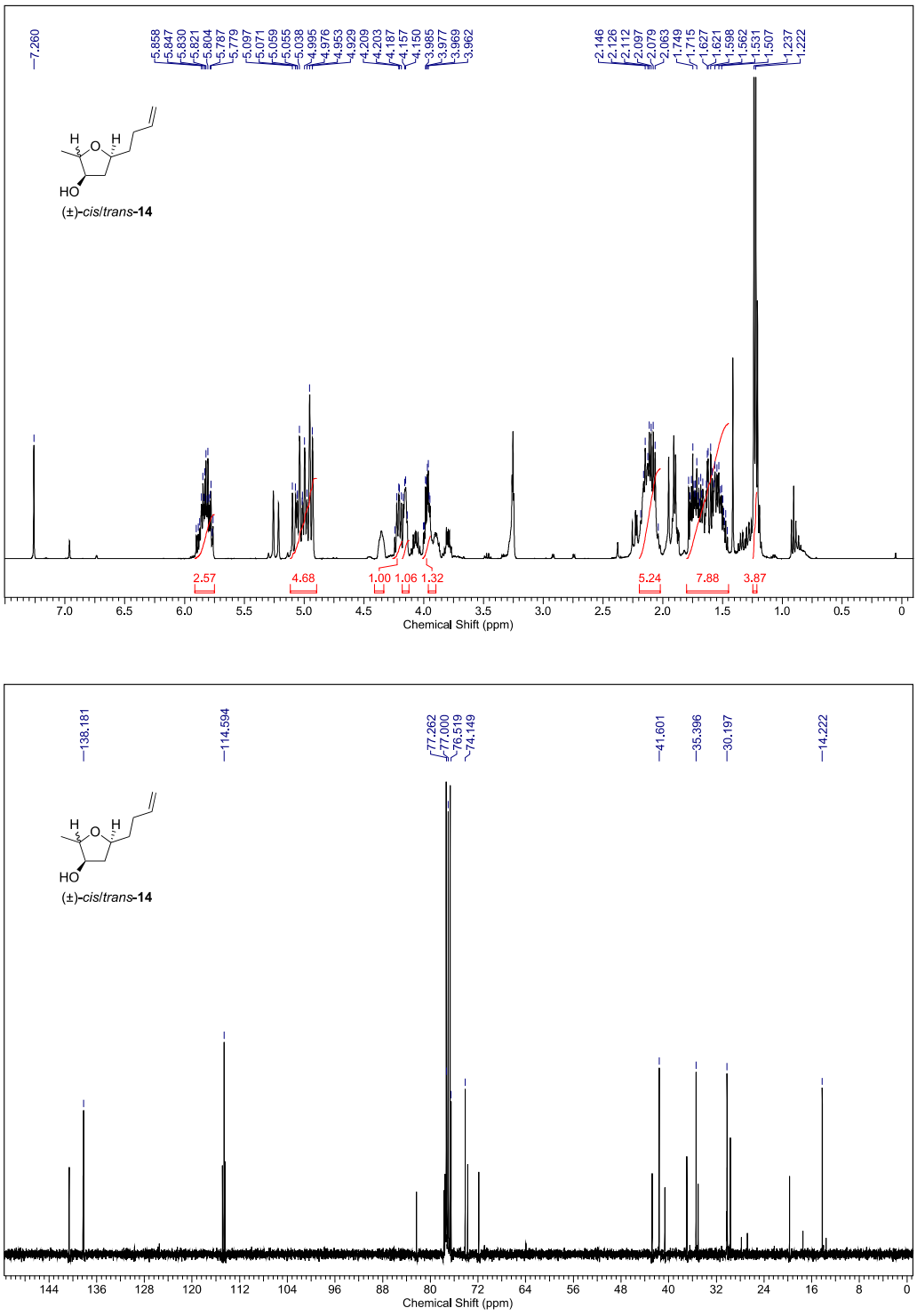

Figure 6.12 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz, top) and ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz, bottom) from the main isomer B of *rel*-(3*R*,5*S*)-5-(but-3-en-1-yl)-2-methyltetrahydrofuran-3-ol (**14**) (20/80-mixture of diastereomers).

7 References

[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, The Bath Press, Oxford, 4th Edition, **1996**.

[2] Smith, A. B.; Levenberg, P. A. *Synthesis* **1981**, 567−570.

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[4] Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276−277.

[5] White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129−9142.

[6] In extension to: Hofmann, H.; Salbeck, G. *Chem. Ber.* **1970**, *103*, 2768−2774.

[7] Tata, J. R.; Chapman, K. T.; Duffy, J. L.; Kevin, N. J.; Cheng, Y.; Rano, T. A.; Zhang, F.; Huening, T.; Kirk, B. A.; Lu, Z.; Raghavan, S.; Fleitz, F. J.; Petrillo, D. E.; Amstrong, J. D.; Varsolona, R. J.; Askin, D.; Hoerrner, R. S.; Purick, R. US Patent US6642237 B1, **2003**.

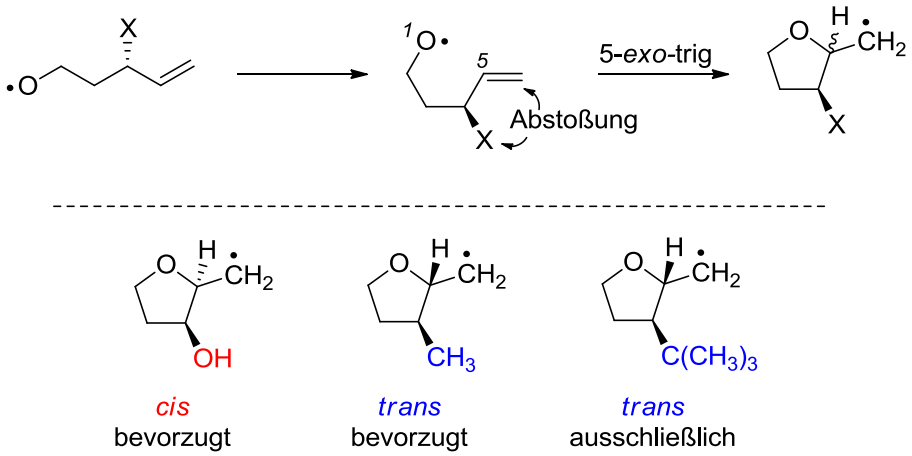
5 Selektivitätswechsel von 2,3-trans zu 2,3-cis in O-Radikalcyclisierungen

5.1 Zusammenfassung

Radikalische Additionsreaktionen von Allyl-substituierten 4-Pentenoxylradikalen können durch polare und sterische Effekte beeinflusst werden. Elektronenziehende Substituenten, wie Fluor, Hydroxy oder Benzoyloxy steuern eine 5-*exo*-trig-Cyclisierung 2,3-cis-selektiv, wobei Fluor das höchste *cis*:*trans*-Verhältnis von 82:18 erzielte. Alkyl-, Sticksoff- und Schwefel-Gruppen bewirken hingegen aufgrund ihres sterischen Einflusses einen Selektivtätswechsel zu 2,3-trans. Die gebildeten Radikale wurden in Ausbeuten von 13–72% zu den bromierten Tetrahydrofuranen abgefangen. Bei polaren Substituenten wird der aus sterischen Gründen bevorzugte 2,3-trans-Übergangszustand aufgrund von π(C,C)→σ*(C,X)-Wechselwirkungen stabilisiert und somit die Geschwindigkeit der Reaktion verlangsamt. Hierdurch wird die 2,3-cis-Cyclisierung zum bevorzugten Reaktionspfad. Die experimentellen Untersuchungen konnten durch theoretische Berechnungen bestätigt werden und erweitern das Reaktionsmodell für 5-*exo*-trig-Cyclisierungen um einen polaren Effekt.

5.2 Wissenschaftlicher Hintergrund, Zielsetzung und Strategie

Im stereochemischen Twist-Modell für radikalische 5-*exo*-trig-Cyclisierungen ordnen sich benachbarte Substituenten aufgrund der sterischen Abstoßung bevorzugt äquatorial an. Somit verlaufen radikalische Cyclisierungsreaktionen mit Alkyl-Substituenten in allylischer Position 2,3-trans-selektiv (Schema 5.1).[1] Eine vorangegangene Studie zeigte, dass polare Effekte existieren, die eine 2,3-cis-Selektivtät bewirken. Allylische O-Akzeptor-Gruppen führen zu einer stabilisierenden π(C,C)→σ*(C,X)-Wechselwirkungen im 2,3-trans Übergangszustand. Die Stabilisierung senkt die Reaktivität und verlangsamt dadurch die 2,3-trans-Ringschlussreaktion. Die 2,3-cis-Cyclisierungsreaktion wird von dieser Stabilisierung nicht beeinflusst und liefert das Hauptprodukt der Reaktion (Schema 5.1).[2] Dieses Konzept sollte auf weitere Heteroatome übertragbar sein und somit die Selektivität durch die Wahl eines geeigneten Substituenten sowohl 2,3-trans- als auch 2,3-cis-selektiv gesteuert werden können. Je stärker der Akzeptor-Substituent ist, desto ausgeprägter sollte der polare Effekt sein. Die Selektivitätssteuerung folgt aus einem Zusammenspiel von polarem und sterischem Effekt.



Schema 5.1 Polare und sterische Selektivitätssteuerung in 5-*exo*-trig-Cyclisierungen Allyl-substituierter 4-Pentenoxylradikale.[1]

Aus dem dargelegten wissenschaftlichen Hintergrund eröffnete sich folgender Forschungsbedarf:

- Korrelation der Selektivität bei homolytischen Cyclisierungsreaktionen Heteroatom-substituierter 4-Pentenoxylradikale mit sterischen und polaren Substitutionsparametern.
- Mechanistisch-synthetische Studie zum Reaktionsverlauf begleitet von thermodynamischen Daten und molekularorbital-theoretischen Erkenntnissen aus Dichtefunktional-Rechnungen in Kooperation mit J. Hartung.

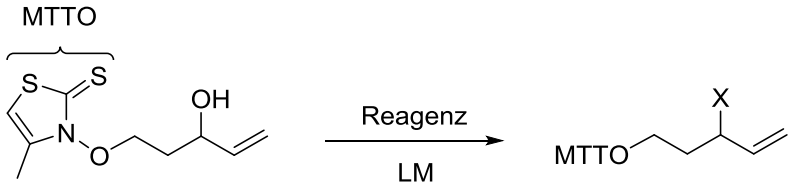
5.3 Ergebnisse und Diskussion

5.3.1 Synthese Akzeptor-substituierter Thiohydroxamate

Zur Untersuchung der 2,3-Selektivität in Cyclisierungsreaktionen von 4-Pentenoxylradikalen wurde die allylische Hydroxy-Gruppe der Ausgangsverbindung 3-(3-Hydroxypent-4-en-1-oxy)-4-methylthiazol-2(3*H*)-thion (**1a**) durch Substitutionsreaktionen in verschiedene Heteroatom-substituierte Thiohydroxamate **1d**, **1g**, **1i**, **1m**–**n** überführt (Tabelle 5.1). Die eingeführten Substituenten besitzen unterschiedliche elektronische und sterische Eigenschaften mit denen die Selektivität gesteuert werden kann.[3,4,5]

Die Verbindungen **1a**, **1e** und **1f** waren bereits aus einer vorherigen Studie bekannt. Die aus der homolytischen Bromcyclisierung erhaltenen Daten wurden in dieser Arbeit zur Vervollständigung der stereochemischen Informationen aufgenommen (Tabelle 5.3).

Tabelle 5.1 Rektionsbedingungen zur Modifikation der Hydroxy-Gruppe in Thiohydroxamat **1a**. MTTO = 4-Methyl-2-thiooxo-1,3-thiazyl-3-oxy; HN(Phth) = Phthalimid; Tfac = Trifluoracetyl; Bz = Benzoyl; LM = Lösungsmittel

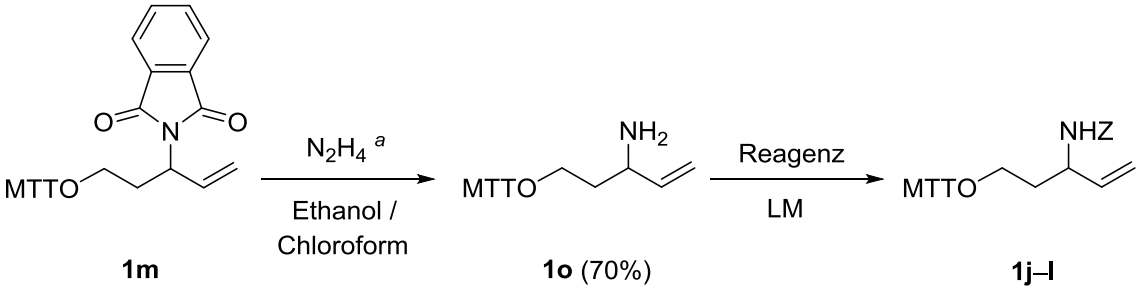


1a **1d**,**1g**,**1i**,**1m–n**

Eintrag	Reagenz	LM	X	**1** / %
1	$(Tfac)_2O$ / DABCO	CH_2Cl_2	O(Tfac)	**1d** / 90
2	CH_3OTs / NaH	THF	OCH_3	**1g** / 85
3	CCl_4 / PPh_3	CH_2Cl_2	Cl	**1i** / 83
4	HN(Phth) / PPh_3 / DIAD	THF	N(Phth)	**1m** / 79
5	BzSH / PPh_3 / DIAD	THF	SBz	**1n** / 25

Die Einführung weiterer Stickstoff-Akzeptoren erfolgte über das Amin **1o**, welches aus der Hydrazinolyse des Phthalimids **1m** erhalten wurde. Die anschließende Umsetzung mit verschiedenen Substitutionsreagenzien lieferten die Thiohydroxamate **1j–l** in Ausbeuten von 67–82% (Tabelle 5.2).[6]

Tabelle 5.2 Synthese Stickstoff-substituierter Thiohydroxamate **1j–l**

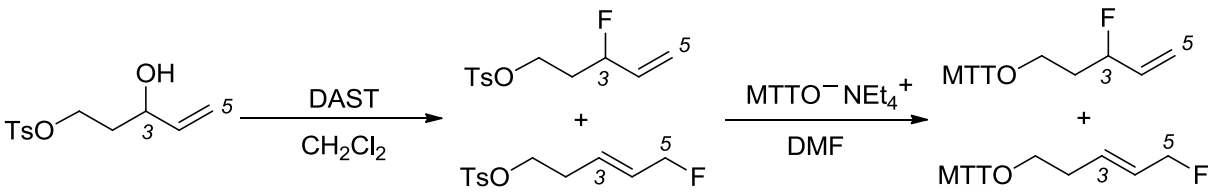


1m **1o** (70%) **1j–l**

Eintrag	Reagenz	LM	Z	**1** / %
1	$(Tfac)_2O$ / DABCO	CH_2Cl_2	Tfac	**1j** / 67
2	$PhSO_2Cl$ / NEt_3	CH_2Cl_2	$PhSO_2$	**1k** / 82
3	BzCl / NaOH	CH_2Cl_2	Bz	**1l** / 67

[a] Hydrazin-Hydrat.

Die Fluorierung von allylischen Hydroxy-Gruppen konnte mit dem Reagenz Dimethylaminoschwefeltrifluorid (DAST) realisiert werden.[7] Die Umsetzung des Thiohydroxamates **1a** mit DAST enthielt Nebenprodukte, die nicht abgetrennt werden konnten. In einem Folgeprojekt von T. Schick[8] wurde die Hydroxy-Gruppe im Tosylat **2** in das fluorierte Produkt **3** überführt. Das erhaltene Produkt **3** enthielt zu 19% die terminal fluorierte Verbindung *iso*-**3**, welche durch keine Methode abgetrennt werden konnte. Die Isomerenmischung wurde weiter umgesetzt und das Thiohydroxamat **1h** ebenfalls als 66/34-Mischung der beiden Isomere **1h** und *iso*-**1h** erhalten (Schema 5.2). Die Verbindung *iso*-**1h** konnte der Nebenverbindung aus der Fluorierung von **1a** zugeordnet werden.



2 **3** (89%) **3**:*iso*-**3** = 81:19 **1h** (79%) **1h**:*iso*-**1h** =66:34

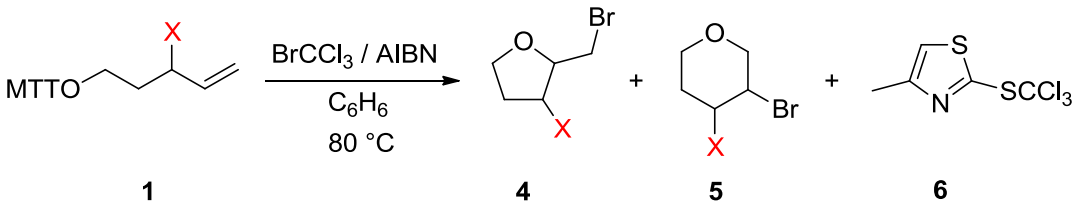
Schema 5.2 Darstellung von *O*-(3-Fluor-4-pentenyl)thiohydroxamat **1h** (isoliert als 66:34-Mischung der Isomere **1h** und *iso*-**1h**). $MTTO^- NEt_4^+$ = *N*-Hydroxy-4-methylthiazol-2(3*H*)-thion-Tetraethylammoniumsalz; Ts = *p*-Toluolsulfonyl.

5.3.2 Homolytische Bromcyclisierungen

Die Thiohydroxamate **1d**, **1g–1n** wurden unter thermischen Bedingungen in Anwesenheit von Bromtrichlormethan umgesetzt und lieferten die bromierten Tetrahydrofurane **4** in Ausbeuten von 13–72% als 2,3-cis/trans-Mischungen (Tabelle 5.3). Zusätzlich wurden die Tetrahydropyrane **5** (3–16%) und das Produkt **6** (54–94%) gebildet (Tabelle 5.3). Die niedrigen Ausbeuten an Tetrahydrofuranen **4** lassen sich auf die Flüchtigkeit der erhaltenen Produkte zurückgeführt. Die Durchführung von *in situ* Analysen, durch NMR- und GC/MS, zeigte vollständigen Umsatz und höhere Ausbeuten aller Cyclisierungsprodukten.

Die experimentellen Untersuchungen zeigen, dass Fluor- und O-Akzeptor-Substituenten 4-Pentenoxylradikal-Cyclisierungen 2,3-cis-selektiv steuern. Fluor als das elektronegativste Atom in der Reihe liefert das höchste 2,3-*cis*:2,3-*trans*-Verhältnis von 82:18. Das Halogen Chlor hingegen bewirkt eine 50:50-Selektivität der gebildeten Tetrahydrofurane. Schwefel- und Stickstoff-Gruppen in allylischer Position lenken die Cyclisierungsreaktion der 4-Pentenoxylradikale zum 2,3-trans-Produkt. Diese Ergebnisse verdeutlichen, dass die Selektivitätssteuerung sowohl von polaren als auch sterischen Effekten der Allyl-Substituenten abhängig ist. Der stereochemische Verlauf der Reaktion besteht aus einem Zusammenspiel dieser beiden Einflussgrößen. Ergänzend zu den experimentellen Daten wurden hierzu Dichtefunktional-Rechnungen durchgeführt.

Tabelle 5.3 Produkte bei der homolytischen Bromcyclisierung der Allyl-substituierten Thiohydroxamate **1d**, **1g**–**1n**



1 **4** **5** **6**

Eintrag	**1** / X	**4** / % (*cis*:*trans*)	**5** / (*dr*) [a]	**6** / %
1	**1a** / OH	**4a**: 56 (74:26)	**5a**: 4 (65:35)	84
2	**1d** / O(Tfac)	**4d**: 13 (68:32)	**5d**: 3 (73:27)	72
3	**1e** / OBz	**4e**: 69 (68:32)	**5e**: 12 (50:50)	75
4	**1f** / OAc	**4f**: 71 (68:32)	**5f**: 11 (57:43)	94
5	**1g** / OCH_3	**4g**: 62 (58:42)	**5g**: 11 (85:15)	83
6	**1h** / F [b]	**4h**: – [c] (82:18)	**5h**: – [d]	– [e]
7	**1i** / Cl	**4i**: 37 (47:53)	**5i**: – [d]	54
8	**1j** / NH(Tfac)	**4j**: 59 (36:64)	**5j**: 11 (24:76)	76
9	**1k** / $NH(SO_2Ph)$	**4k**: 65 (39:61)	**5k**: 8 (44:56)	66
10	**1l** / NH(Bz)	**4l**: 61 (38:62)	**5l**: 7 [f]	89
11	**1m** / N(Phth)	**4m**: 52 (5:95)	**5m**: 16 [f]	90
12	**1n** / SBz	**4n**: 72 (25:75)	**5n**: – [d]	70

[a] Diastereomerenverhältnis (diastereomeric ratio, *dr*) 3,4-cis/trans-isomerer Produkte; Haupt- und Minderisomer wurde nicht zugeordnet. [b] Die Produkte der homolytischen Bromcyclisierung von Thiohydroxamat **1h** wurden *in situ* durch NMR-Spektroskopie charakterisiert. [c] Die bestimmten Ausbeuten an **4h** über ^{1}H- und ^{19}F-NMR mit internem Standard stimmten nicht überein, weshalb nur das relative Verhältnis der Isomere angeben ist. [d] 6-*endo*-Cyclisierugnsprodukt wurde nicht detektiert (NMR- und GC-analytisch). [e] Die Ausbeute an Koppelprodukt **4** konnte aufgrund von Überlagerungen im ^{1}H-NMR nicht bestimmt werden. [f] Ausschließlich ein Isomer des 6-*endo*-Cyclisierungsproduktes gefunden.

5.3.3 Berechnungen polarer und sterischer Einflussgrößen

Der polare Effekt wurde durch die Korrelation der HOMO-Energien mit den Elektronegativitäten des allylischen Substituenten X in Butenen ermittelt. Die HOMO-Energien wurden aufgrund der höheren Präzision gegenüber den Dichtefunktional-Rechnungen mit der Hybrid-Methode G3 berechnet.[9] Hierbei besitzt das antiklinal angeordnete Konformer die niedrigste Energie. Die angegebenen Pauling-Elektronegativitäten wurden mit Hilfe der Sanderson-Gleichung berechnet.[10] Die Korrelation zeigt, dass mit zunehmender Elektronegativität des Substituenten X die HOMO-Energien des antiklinalen Konformers sinken (Abb. 5.1).[11]

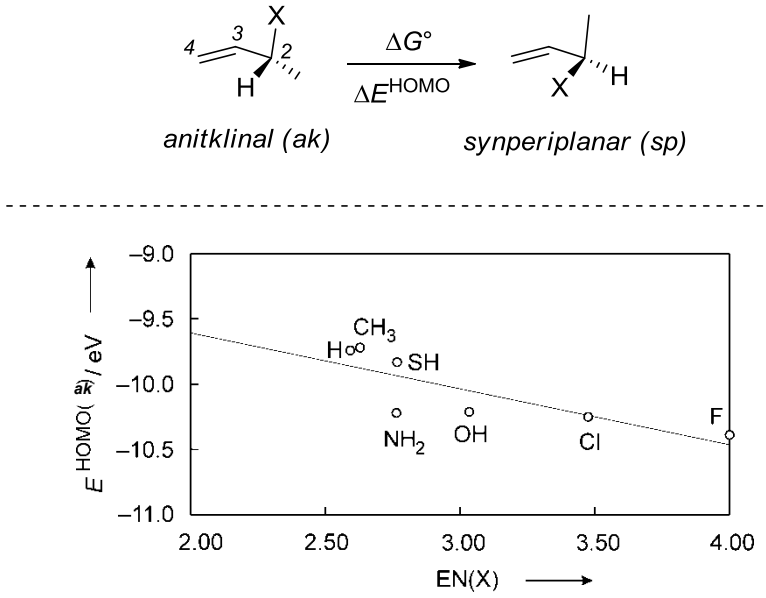
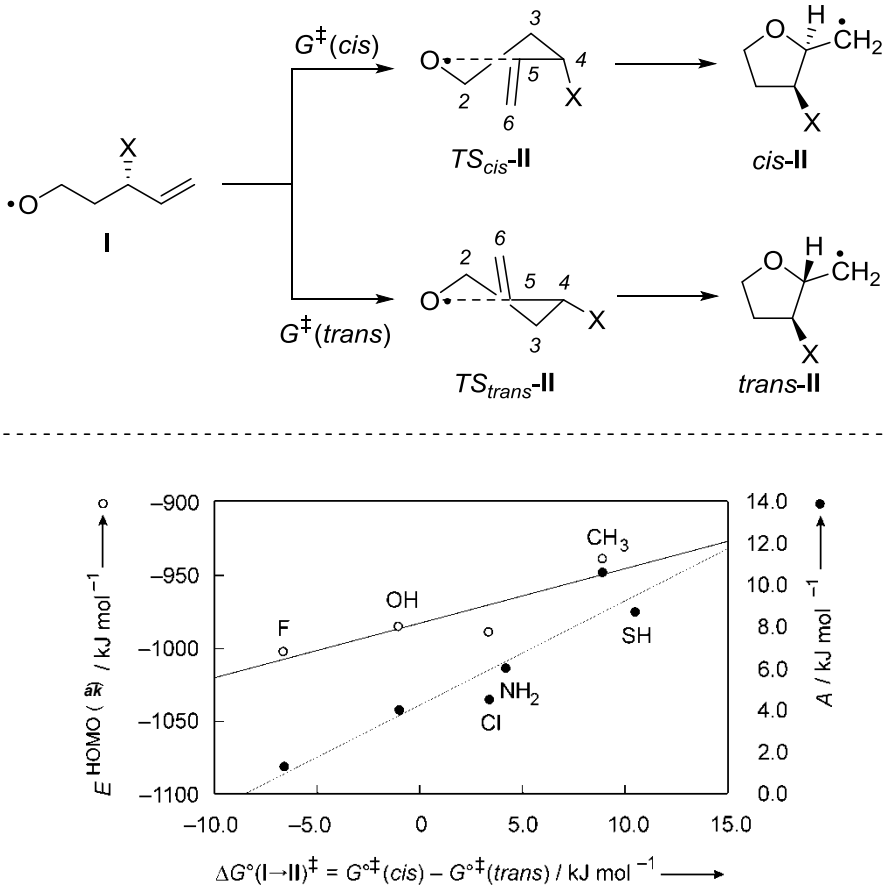


Abbildung 5.1 Korrelation der berechneten HOMO-Energien des antiklinalen Konformers 2-substituierter Butene mit der Pauling-Eleketronegativität (EN) der Substituenten X.[12]

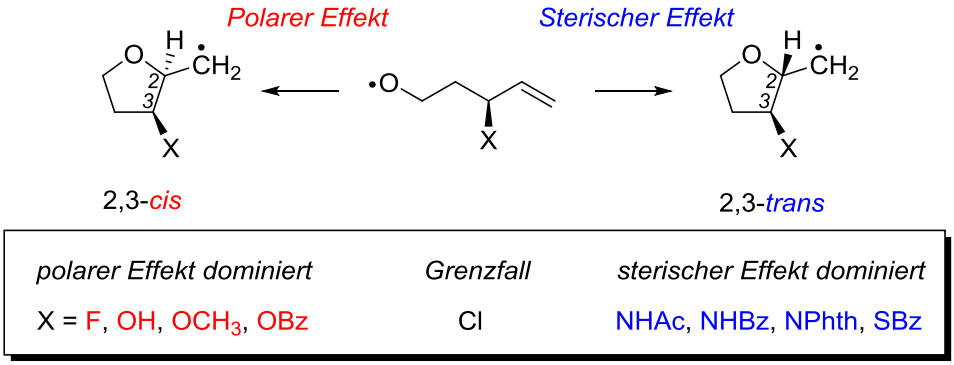
Der sterische Einfluss auf frühe Übergangszustände bei der Cyclisierung von 4-Pentenoxylradikalen wird mit dem Winstein-Holness-Parameter *A* wiedergegeben.[13] Hierzu wurden die freien Gibbs-Energien zwischen axialen und äquatorialen Substituenten X in Cyclohexan Dichtefunktional-theoretisch (B3LYP/6-31+G**) berechnet. Die Größe des *A*-Wertes gibt die Präferenz des Substitutenen X für die äquatoriale Position an. Die Berechnungen zeigen, dass der *A*-Wert entlang der Reihe F < OH < Cl < NH_2 < SH < CH_3 zunimmt.

Die intramolekulare Addition von 3-substituierten 4-Pentenoxylradikalen an C,C-Doppelbindungen verlaufen kinetisch kontrolliert und somit lassen sich deren Selektivitäten mit Hilfe der freien Gibbs-Energien der Übergangszustände ($G^{\ddagger}$) vorhersagen. Für die Substituenten X = OH, CH_3, F, Cl, NH_2 und SH wurden die relativen Gibbs-Energien für die vier möglichen Übergangszustände Dichtfunktional-theoretisch berechnet. Die Korrelation der ΔG-Werte der Übergangszustände gegen die polaren (E^{HOMO}) und sterischen (A-Werte) Effekte zeigt das Zusammenspiel beider Einflussgrößen auf die Selektivitätssteuerung (Schema 5.4).



Schema 5.4 Korrelation der berechneten Gibbs-Energien ($G^{\ddagger}$) der bevorzugten Übergangszustände der 5-*exo*-trig-Cyclisierung Allyl-substituierter 4-Pentenoxylradikale gegen polare (E^{HOMO}) und sterische (A-Wert) Einflussgrößen auf die cis/trans-Selektivitäten.

Diese Interpretation erweitert das bestehende Reaktionsmodell für die Steuerung von 5-*exo*-trig-Cyclisierungen und zeigt den Einfluss polarer und sterischer Effekte auf die 2,3-cis/2,3-trans-Selektivität (Schema 5.5). Bei kleinen, polaren Substituenten dominiert der polare Effekt und steuert die Reaktion 2,3-cis-selektiv. Mit zunehmendem sterischen Anspruch der Substituenten wirkt dieser Effekt dem polaren entgegen und bewirkt eine 2,3-trans-Selektivität. Die Möglichkeit eines Selektivitätswechsels zwischen 2,3-trans und 2,3-cis durch die Variation der allylischen Substituenten eröffnet neue Optionen in der diastereodivergenten Tetrahydrofuran-Syntheseplanung.



Schema 5.5 Übersicht über Substituenteneffekte zur Steuerung der 2,3-Selektivität in 4-Pentenoxylradikal-Cyclisierungen.

5.4 Ausblick

Das Zusammenspiel aus polaren und sterischen Effekten zur Steuerung von Selektivitäten sollte nicht nur auf radikalische Cyclisierungen beschränkt sein. Um eine allgemeingültige Interpretation zur Selektivitätssteuerung in Tetrahydrofuran-Synthesen zu erreichen, wäre eine mechanistische Studie über den Substituenteneinfluss in ionischen Alkenolcyclisierungen hilfreich. In ionischen Reaktionen ist die Polarität der Reaktionszentren diametral zu denen in Alkenoxylradikal-Cyclisierungen, wodurch ein polarer Effekt in ionischen Reaktionen zu einer Verstärkung der 2,3-trans-Selektivität führen sollte.

Die gezeigte Systematik von polaren und sterischen Effekten könnte auch Beiträge zu bislang ungeklärten Fragen im mechanistischen Reaktionsverlauf bei aeroben Cobalt-katalysierten Alkenoloxidationen leisten.[14] Mit Hilfe der Oxidationen Akzeptor-substituierter Alkenole (X = OH, Cl, F) könnte aus der Bildung des bevorzugten Stereoisomers die Polarität an den beteiligten Reaktionszentren geklärt werden.

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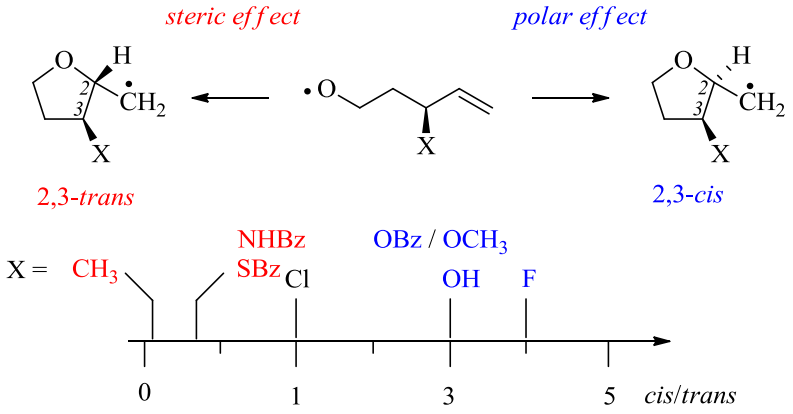
5.6 Forschungsartikel

Controlling Stereoselectivity in 4-Pentenoxyl Radical Cyclization by the Allylic Substituent

Irina Kempter, Tobias Schick, Jens Hartung, *Manuskript in Vorbereitung*.



Controlling Stereoselectivity in 4-Pentenoxyl Radical Cyclization by the Allylic Substituent

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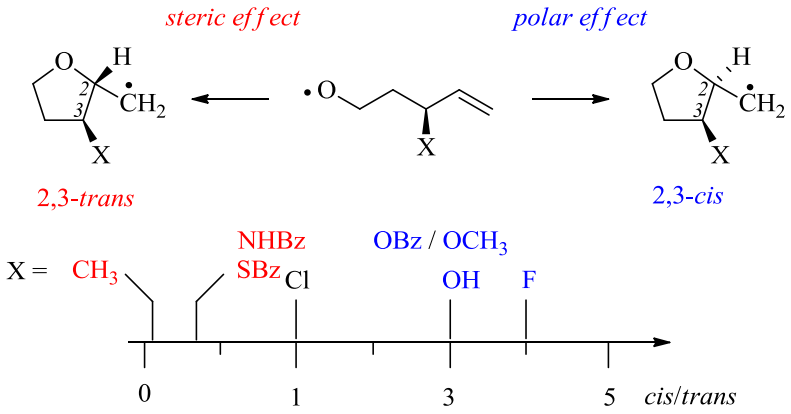
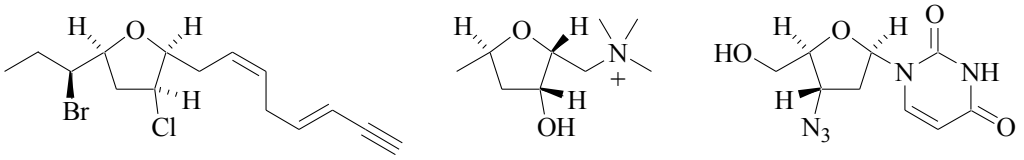


Keywords: Alkoxyl radical, Bromocyclization, Polar effect, Stereoselective synthesis, Tetrahydrofuran.

Summary: Fluor, Hydroxy, und Benzoyloxy steuern 5-*exo*-trig-Cyclisierungen 3-substituierter 4-Pentenoxylradikale 2,3-cis-selektiv, *S*-Benzoylthiyl, *N*-Benzoylamin und Ptthalimidoyl 2,3-trans-selektiv. Die höchste 2,3-cis-Selektivität bei Raumtemperatur liefert das 3-Fluor-4-pentenoxylradikal mit einem Wert von 82:18, und mit 15:85 die höchste 2,3-trans-Selektivität für das 3-Ptthalimidoyl-4-pentenoxylradikals. Die cyclisierten Radikale werden mit Bromtrichlormethan in Ausbeuten von 13–72% zu 3-substituierten Tetrahydrofuran-2-ylmethylbromiden abgefangen, und stehen somit als Synthesebausteine für weiterführende Anwendungen zur Verfügung. 3-Bromtetrahydropyrane entstehen aus parallel zum Tetrahydrofuran-Ringschluss verlaufenden 6-*endo*-Cyclisierungen in Ausbeuten zwischen 3 und 16%. Dichtefunktional-theoretische Rechnungen sagen einen vergleichbaren Selektivitätswechsel von 2,3-cis zu 2,3-trans entlang der Reihe Allyl-ständiger Substituenten Fluor, Hydroxy, Chlor, Amino, Thiyl und Methyl voraus. Die experimentell beobachtete Selektivität spiegelt die Summe polarer und sterischer Allyl-Substituenteneffekte wider. Der sterische Einfluss einer Allyl-ständigen Methyl-, Thiyl-, und Amino-Gruppe begünstigt Übergangsstrukturen für 2,3-trans-Reaktionen. Fluor stabilisiert als starker Elektronenakzeptor in der sterisch favorisierten Übergangsstruktur des 2,3-trans-Ringschlusses das benötigte Donororbital der Alkenteilstruktur für die C,O-Addition durch eine π(C,C)$\rightarrow\sigma^*$(C,F)-Wechselwirkung. Die Geschwindigkeit der 2,3-trans-Reaktion fällt für starke Elektronenakzeptoren hinter die der 2,3-cis-Cyclisierung zurück.

Introduction

Tetrahydrofurane, die benachbart zu anspruchsvollen Gruppen beiderseits des Ether-Sauerstoffatoms einen Heteroatom-Substituenten in Position 3 tragen, sind als Wirkstoffe ebenso interessant wie als Syntheseziele herausfordernd. 2,5-Substituierte Tetrahydrofurane mit einem zusätzlichen polare Substituenten in Position 3 kommen in Sekundärmetaboliten natürlich vor (Figure 1). Biosynthetisch ist davon auszugehen, dass die meisten Naturstoffe dieses Typs auf Acetogenin- oder Terpen-abgeleitete konstitutionell dissymmetrische Alkenole zurückgehen, die Enzym-katalysiert zu funktionalisierten Tetrahydrofuranen oxidiert werden.[1]



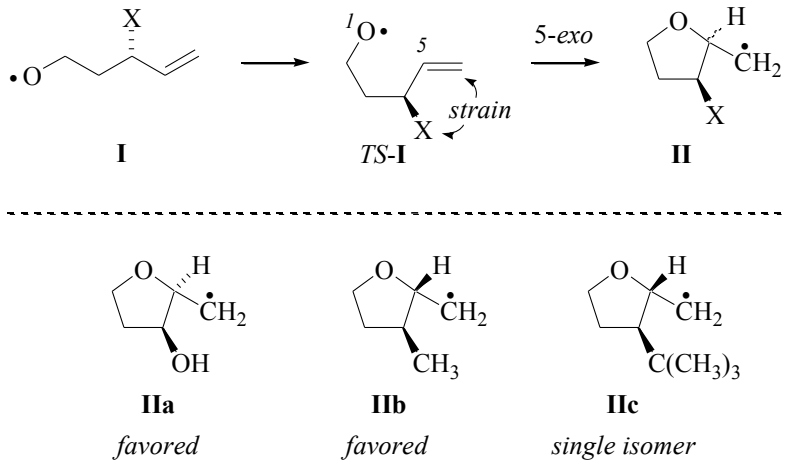
from Laurencia bisezakynes *allo*-isomuscarine azidothymidin

Figure 1. Examples for secondary metabolite[2] and bio-inspired target products[3,4] comprising a 3-acceptor-substituted tetrahydrofuran core.

In der Synthesechemie verlaufen Ringschlussreaktionen zum Aufbau 2,3-substituierter Tetrahydrofurane aus Alkenolen oder aus Alkenoxylradikalen in der Regel trans-selektiv, da die benachbarten Substituenten im Übergangszustand von 2,3-cis-Cyclisisierungen beginnen sich abzustoßen und diese Abstoßung mit kürzer werdendem C,O-Abstand zunimmt.[5,6,7] Um Stereoselektivitäten in Alkenolcyclisierungen zu steuern begannen wir vor einigen Jahren Reaktivitäten an Sauerstoff und Methoden zur Aktivierung der C,C-Doppelbindung zu variieren.[8]

Die deutlichsten Änderungen hinsichtlich Reaktivität und Selektivität intramolekularer Additionen treten beim Übergang von polaren zu homolytischen Reaktionen ein. 4-Pentenoxylradikale addieren an nicht aktivierte Doppelbindungen mit Geschwindigkeitskonstanten, die Werte bis 10^9 s^{-1} bei Raumtemperatur erreichen.[6] In diesem Reaktionstyp besitzt der Radikalsauerstoff Grenzreaktivität, die ihm erlaubt an Akzeptor- und an Donor-substituierte Doppelbindungen rascher als an terminale zu addieren. Gegenüber terminalen π(C,C)-Bindungen tritt der Radikalsauerstoff als Elektrophil auf.[9] π-Bindungsenergie-steigernde Substituenteneinflüsse beschleunigen 4-Pentenoxylradikal-Cyclisierungen und senkende verlangsamen sie.

Beim Aufbau des *allo*-Isomuscarin-Rings durch Alkenoxylradikal-Cyclisierung fiel uns mit dem 2,3-cis-dirigierenden Einfluss einer Allyl-positionierten Hydroxy-Gruppe ein Effekt auf (in **Ia**), der dem bekannten 2,3-trans-dirigierenden sterischen Einfluss von Methyl (in **Ib**) und *tert*-Butyl (in **Ic**) in Nachbarschaft zur C,C-Doppelbindung entgegen wirkt.[3,8]



Scheme 1. Summary of known stereoselectivity controlling effects in 5-*exo*-C,O-cyclization of allyl-substituted 4-pentenoxyl radicals [X = OH for **I**/**IIa**, CH_3 for **I**/**IIb**, and **I**/**IIc** for $C(CH_3)_3$].[7,10]

In einer zweiten Studie klärten wir, dass der 2,3-cis-steuernde Einfluss einer Allyl-positionierten Hydroxy-Gruppe mit einer Verlangsamung der 4-Pentenoxylradikal-Reaktion korreliert. Eine Allyl-positionierte Hydroxy-Gruppe senkt im Besonderen die Geschwindigkeit des 2,3-trans-Tetrahydrofuran-Ringschlusses, bedingt durch eine stabilisierende π(C,C)$\rightarrow\sigma^*$(C,O)-Wechselwirkung. Mit abnehmender π(C,C)-Energie sinkt die Stärke der stabilisierende Wechselwirkung zwischen Sauerstoffradikal und der Alken-Teilstruktur bei Annäherung der Reaktionszentren in dem frühen Übergangszustand der schnellen, exothermen, kinetisch kontrollierten Addition. In frühen Übergangszuständen spielen sterische Substituenteneinflüsse eine geringere Rolle, so dass die 2,3-cis-Reaktion neben Torsionsspannungen zwischen synklinaler Vinyl-Gruppe und dem Sauerstoff-Substituenten keinen weiteren destabilisierenden Einfluss erfahren.[10]

Stärkere Akzeptor-Gruppen sollten dem mechanistischen Modell folgend den Anteil an 2,3-cis-Produkt über den Wert von 74/26 für Hydroxy steigern. Schwächere Akzeptoren mit größeren van-der-Waals-Radien des Kohlenstoff-gebundenen Heteroatoms sollten den polaren Einfluss zugunsten des sterischen in den Hintergrund treten lassen. Da Heteroatom-Substituenten durch andere Gruppen nucleophil oder homolytisch ausgetauscht werden

können,[11] ließen sich bei adäquater Wahl eines Allyl-Substituenten gezielt 2,3-trans- oder 2,3-cis-konfigurierte Tetrahydrofurane als Synthesebausteine darstellen.

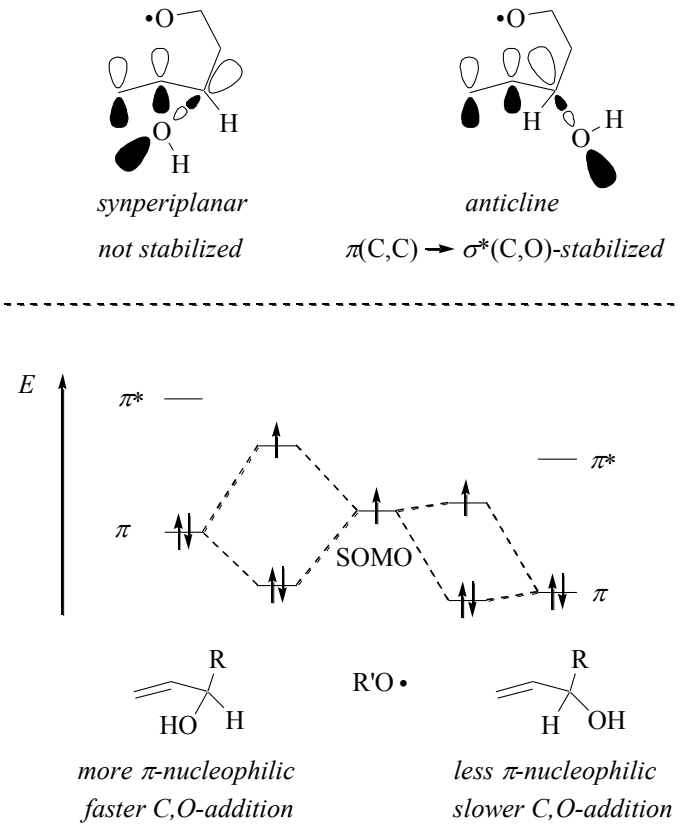


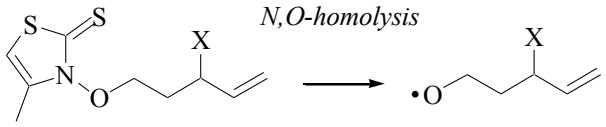
Figure 2. Summary of FMO-model for explaining 2,3-cis-selectivity in 3-hydroxypent-4-enoxyl radical 5-*exo*-cyclization.[10]

Da die vorhandene wissenschaftliche Literatur keine Antworten auf unsere Fragen lieferte, synthetisierten wir neun *O*-Alkenylthiohydroxamate (**1d**, **1g**–**n**) und untersuchten Selektivitäten der zugrundeliegenden 4-Pentenoxylradikale (**Id**, **Ig**–**n**). Die gewonnenen Daten vervollständigten einen bereits existierenden Datensatz (aus **1a**, **1e**–**f**),[10] um ein stereochemisches Model zur Erklärung des polaren Effektes von Allyl-Substituenten auf Grundlage eines möglich breiten Datensatzes zu entwickeln.

Die durchgeführten Experimente zeigen, dass der Anteil an 2,3-cis-cyclisiertem Alkoxyl-Radikalprodukt entlang der Allylsubstituenten Fluor (82:18 für **Ih**), Sauerstoff (74:26 für **Ia**), Chlor (47:53 für **Ii**), während bei Stickstoff- und Schwefel-Gruppen 2,3-trans-Cyclisierungsprodukte überwiegen (36:64 für **Ij** und 25:75 für **In**). Die stereochemische Reihe bildet sterische und polare Einflüsse der Substituenten ab. Sterische Faktoren favorisieren den 2,3-trans-Reaktionsverlauf, polare die 2,3-cis-Cyclisierung. Den sterischen

Einfluss erfassten wir mit Hilfe von Dichtefunktional-Rechnungen (B3LYP/6-31+G**) auf Grundlage des Winstein-Holness-Parameters[12] (*A*-Wert). Als polaren Substituentenparameter wählten wir den Wert der Ausgleichselektronegativität nach Sanderson[13,14] und berechneten HOMO-Energien Allyl-substituierter Butene. Der Wechsel zwischen cis- und trans-Selektivität ist ein Tribut an die elektrophile Reaktivität von Sauerstoffradikalen gegenüber terminalen π(C,C)-Bindungen und bietet neue Optionen zur Planung diastereodivergenter Tetrahydrofuran-Syntheseplanungen mit Anwendungspotential in der Wirkstoff-Forschung.

Table 1. Indexing of 4-pentenoxyl radicals **Ia** and **Id**–**n** and *O*-(4-pentenyl) thiohydroxamate progenitors for investigating stereochemical principles of 5-*exo*-cyclization controlled by allyl



1 MTTOR [a] **I**

X [b]	**1** / **I**	X [b]	**1** / **I**
OH	**a**	Cl	**i**
O(Tfac)	**d**	NH(Tfac)	**j**
OBz	**e**	NH(SO_2Ph)	**k**
OAc	**f**	NH(Bz)	**l**
OCH_3	**g**	N(Phthalimide)	**m**
F	**h**	SBz	**n**

[a] MTT = 4-methyl-2-thiooxo-1,3-thiaz-3-yl. [b] Abbreviations: Tfac = trifluoroacetyl; Bz = benzoyl; Ac = acetyl.

Results and interpretation

1 *O*-Alkenyl thiohydroxamates

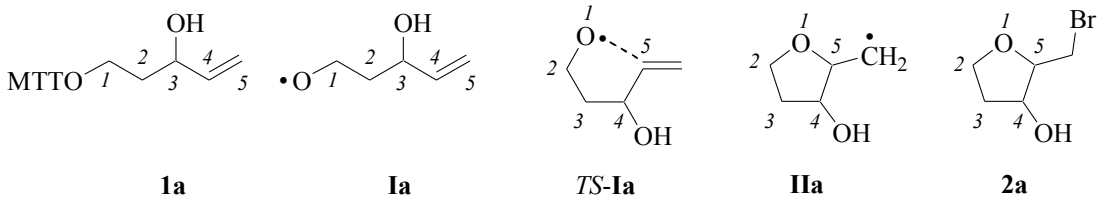
1.1 On numbering of structurally related molecules

Um dem Leser einfacher zu ermöglichen, Änderungen von Selektivitäten bei Wechsel eines Substituenten zu erfassen, tragen Moleküle innerhalb einer Versuchsserie gleiche arabische Buchstaben als Indices. Strukturelle Zusammenhänge bestehen zwischen *O*-Alkenoxylthiohydroxamat **1**, daraus hervorgehendes Alkenoxylradikal **I**,

selektivitätsbestimmende Übergangsstruktur *TS*-**I**, 5-*exo*-Cyclisierungsprodukt **II**, Bromatomeinfangsprodukt **2** und im späteren Verlauf der Untersuchung 6-*endo*-Bromcyclisierungsprodukt **3**. Moleküle mit gleichem Substituenten X erhalten den gleichen Index, beispielsweise **a** für Hydroxy und **b** für Methyl.

Für die Zählweise der Atome tritt ein Wechsel beim Übergang von offenkettigen zu cyclischen Molekülen ein. In offenkettigen Molekülen ist der Hydroxy-Sauerstoff Teil eines Substituenten. Entsprechend besitzt in offenkettigen Molekülen der Sauerstoff-bindende 4-Kohlenstoff die Positionsnummer 1. In Heterocyclen liegt die Hierarchie von Sauerstoff zur Vergabe von Positionsziffern über Kohlenstoff. Übergangsstrukturen von 4-Pentenoxylradikal-Cyclisierungen sind Tetrahydrofuran-Derivate, so dass der Sauerstoff der Heterocyclen-Zählweise folgend die Positionsnummer 1 erhält (Figure 3).[15]

Die Antworten auf die eingangs gestellten wissenschaftlichen Fragen lassen sich aus relativen Stereoselektivitäten ableiten. Daher setzten wir durchgehend racemische Ausgangverbindungen als Startmaterialien ein, aus denen racemische Produkte hervorgehen.

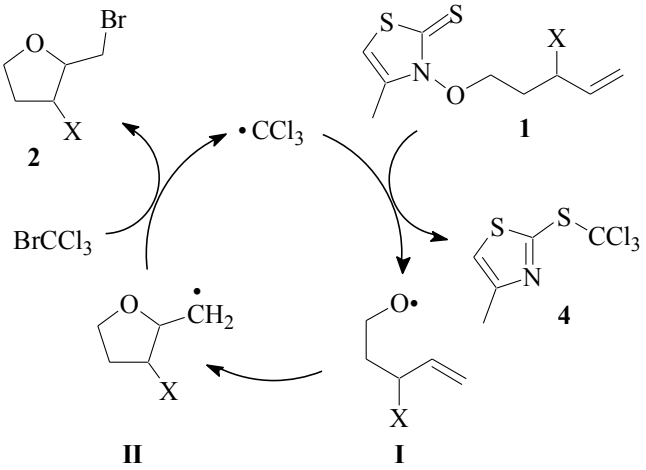


1a **Ia** *TS*-**Ia** **IIa** **2a**

Figure 3. Convention used in this article for numbering atoms in product classes associated with alkenoxyl radical chemistry, exemplified for alkenoxythiazolethione **1a**, derived 4-alkenoxyl radical **Ia**, transition structure for 5-*exo*-cyclization *TS*-**Ia**, 5-*exo*-cyclized carbon radical **IIa**, and product of bromine atom trapping **2a** (for MTT, refer to Table 1).

1.2 Preparation of acceptor-substituted 4-pentenyl thiohydroxamates

Alkenoxyl-Radikale entstehen unter pH-neutralen, nicht oxidativen Bedingungen aus *O*-Alkenylthiohydroxamaten. Der homolytische N,O-Bindungsbruch ist Teilschritt einer Kettenreaktion und erfordert chemoselektive Addition eines kettenfortführenden Mediator-Radikals, das wiederum aus einem Abfangreagenz durch homolytische Substitution hervorgeht. Die experimentellen Befunde, die der Formulierung des dargelegten Reaktionsverlaufs zugrundeliegen, haben wir in früheren Arbeiten ausführlich zusammengefasst.[3,16,17]



Scheme 2. Mechansim for homolytic bromocyclization of allyl-substituted *O*-alkenyl thiohydroxamate **1** (for X, refer to Tables 4 and 5).[3,16,17]

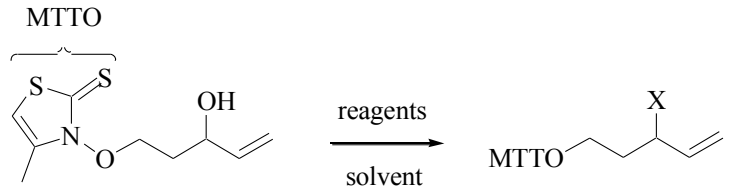
Heterocyclische *O*-Alkylthiohydroxamate entstehen durch Veresterung heterocyclischer Thiohydroxamsäuren mit Alkoholen.[18,19] Eine Besonderheit dieser Chemie ist die bislang vorherrschende Einschränkung, dass der Ester-Sauerstoff aus der Säure stammt. Thiohydroxamat-Synthesen, in denen der Hydroxy-Sauerstoff durch Knüpfen einer N,O-Bindung Teil des Zielmoleküls wird, sind bislang wenig untersucht. *O*-Alkylthiohydroxamate reagieren mit redoxaktiven Metallen, starken Basen, Oxidantien und Hydriddonoren, sind aber durch anderweitige Transformationen derivatisierbar.[19,20]

Aufbauend auf Vorarbeiten[10] wählten wir 3-(3-Hydroxypent-4-en-1-oxy)-4-methylthiazol-2(3*H*)-thion (**1a**) als Ausgangsverbindungen um Ester **1d**, **1g**, **1i** und **1m**–**n** nach Standardverfahren darzustellen (Tabelle 2). Benzoat **1e** und Acetat **1f** waren zu Beginn der Studie bereits dargestellt und in Alkenoxylradikal-Cyclisierungen untersucht worden.[10] Die Ergebnisse dieser Untersuchung sind in dieser Arbeit aufgenommen, um alle verfügbaren Aussagen zur Vervollständigung des mechanistischen Modells zu berücksichtigen. Akzeptor-substituierte Aminogruppen erhielten wir durch Hydrazinolyse von *N*-Alkylphthalimid **1m** und Umsetzen des erhaltenen Amins **1o** mit Trifluormethansulfonsäureanhydrid (für **1j**) oder passenden Säurechloriden (für **1k** und **1l**; Table 3).[21,22,23]

Allylalkohol **1a** reagiert mit Diethylaminoschwefeltrifluorid (DAST) zu Allylfluorid **1h**. Da jedoch nicht abtrennbare Nebenprodukte entstanden, führten wir Fluor in das Tosylat **5** ein.[24] Das erhaltene Produkt bestand aus einer 81/19-Mischung von internem und terminalem Allylfluorid **6** und *iso*-**6**. Da wir keinen Weg zur wirksamen Trennung fanden, setzten wir die

81/19-Isomerenmischung **6**/*iso*-**6** zur Synthese von Zielverbindung **1h** ein, die entsprechend mit Isomer *iso*-**1h** verunreinigt war und blieb (Scheme 3).

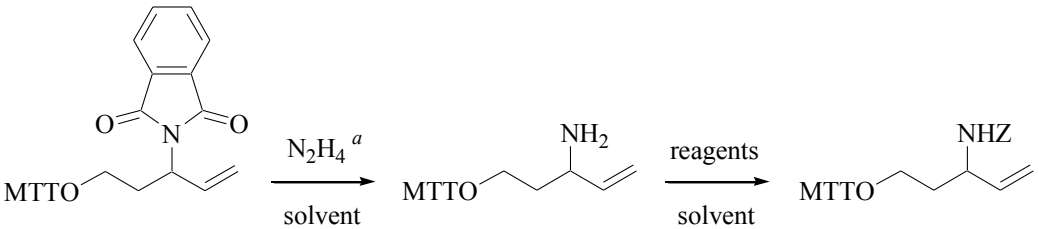
Table 2. Products obtained from hydroxy group modification in *O*-(3-hydroxypent-4-en-1-yl) thiohydroxamate **1a**



1a **1d**, **1g**, **1i**, **1m–n**

entry	reagents [a]	solvent	X	**1** / %
1	$(Tfac)_2O$ / DABCO	CH_2Cl_2	OTfac	**1d** / 90
2	CH_3OTs / NaH	THF	OCH_3	**1g** / 85
3	CCl_4 / PPh_3	CH_2Cl_2	Cl	**1i** / 83
4	HNR_2 / PPh_3 / DIAD	THF	NR_2	**1m** / 79
5	BzSH / PPh_3 / DIAD	THF	SBz	**1n** / 25

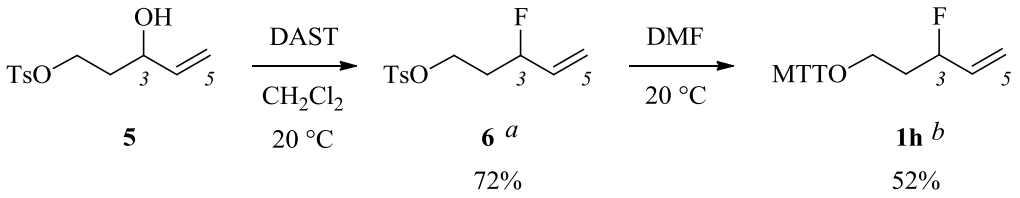
Table 3. Preparing side chain nitrogen-substituted *O*-(4-pentyl) thiohydroxamates



1m **1o** **1j–l**

entry	reagents	solvent	Z	**1** / %
1	$(Tfac)_2O$ / DABCO	CH_2Cl_2	Tfac	**1j** / 67
2	$PhSO_2Cl$ / NEt_3	CH_2Cl_2	Ts	**1k** / 67
3	BzCl / NaOH	CH_2Cl_2	Bz	**1l** / 82

[a] Used as hydrate.



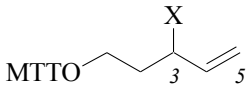
5 **6** [a] **1h** [b]

72% 52%

Scheme 3. Synthesis of *O*-(3-fluoro-4-pentyl) thiohydroxamate **1h**. [a] Total yield: 89% as 81/19-mixture of isomers bearing fluorine at carbons C3 (major, **6**) and C5 (minor, *iso*-**6**). [b] Total yield: 79% as 66/34-mixture of **1h** (major, fluorine at C3) and *iso*-**1h** (minor, fluorine at C5).

Nach säulenchromatischer Reinigung lagen die Zielmoleküle als gelbliche Öle (**1d**, **1g**–**i**, **1k**–**1l**, **1n**) oder gelbliche Feststoffe (**1j**, **1m**) vor, die über mehrere Monate im Kühlschrank bei 6 °C ohne nachweisliche (^{1}H-NMR) Zersetzung gelagert werden können.

Table 4. Characteristics of allyl-substituted *O*-alkenyl thiohydroxamates **1a**, **1d**–**1n**.



1

entry	X / **1**	3-H [a] / ppm	C3 / ppm	C4 / ppm	C5 / ppm
1	OH / **1a**	4.59–4.64	68.5	139.9	114.7
2	OTfac / **1d**	5.71–5.76	75.8	133.1	120.4
3	OBz / **1e**	5.75–5.79	71.7	135.5	117.7
4	OAc / **1f**	5.47–5.52	71.1	135.5	117.6
5	OCH_3 / **1g**	3.84–3.90	78.8	137.7	118.2
6	F / **1h**	5.12–5.30	89.0	135.6	117.8
7	Cl / **1i**	4.66–4.75	58.7	137.5	117.5
8	NH(Tfac) / **1j**	4.85–4.91	50.1	135.1	117.6
9	$NH(SO_2Ph)$ / **1k**	4.15–4.22	53.9	136.5	116.8
10	NH(Bz) / **1l**	5.04–5.11	49.6	137.2	116.2
11	N(Phth) / **1m**	5.04–5.11	50.5	134.7	118.5
12	SBz / **1n**	4.47–4.59	42.9	136.8	117.3

[a] Multiplet fine structure

1.3 Homolytic bromocyclization

Die Thiohydroxamate **1d**, **1g–1n** wurden unter dem bekannten, standardisierten Protokoll für Alkoxyl-Radikalcyclisierungen umgesetzt.[17] Aus einer vorherigen Studie wurden die Verbindungen **1a**, **1e–f** bereits untersucht und die Ergebnisse werden zur Vervollständigung der stereochemischen Daten in dieser Arbeit verwendet. Dieses Projekt zeigte, dass die Umsetzung unter thermischen Bedingungen eine höhere Ausbeute an Cyclisierungsprodukten **2** und **3** (für **1a**: 88%) liefert im Vergleich zur photochemischen Reaktionsführung (für **1a**: 71%). Aufgrund dessen wurde sich in dieser Arbeit ebenfalls für die thermischen Reaktionsbedingungen unter Zusatz von AIBN als Initiator und Bromtrichlormethan als Abfangreagenz entschieden, um eine Vergleichbarkeit der Ausbeuten und Selektivitäten zu gewährleisten.[10]

(i) *Methoden zur Quantifizierung von Ausbeuten und Selektivitäten*. Um eventuelle Ausbeuteverluste durch Aufarbeitungsschritte der Reaktionslösungen oder durch die Flüchtigkeit der gebildeten Cyclisierungsprodukte ausschließen zu können, wurden die Thiohydroxamate **1d**, **1g–1n** in Benzol-d_6 umgesetzt und direkt GC- sowie NMR-analytisch untersucht. Hierzu wurde eine 83-millimolare Lösung von **1d**, **1g–1n** in Benzol-d_6 in Anwesenheit von AIBN (0.25 Äquiv.) und Bromtrichlormethan (10 Äquiv) für 2 Stunden bei 80 °C erhitzt. Die Reaktionsmischung wurde anschließend mit einem Standard (Pentachlorbenzol oder *p*-Brombenzaldehyd) versetzt. Aus den ^{1}H-NMR-Spektren konnten somit die Ausbeuten an Cyclisierungsprodukten **2** und **3** sowie das Verhältnis der cis/trans-Isomere bestimmt werden. Mit Hilfe der GC/MS-Chromatogramme konnte durch Integration der einzelnen Signalflächen die cis/trans-Verhältnisse bestätigt werden. Die Umsätze der Thiohydroxamate **1d**, **1g–1n** waren in allen Fällen quantitativ, so dass eine zuverlässige Aussage über Radikalselektivitäten getroffen werden kann.

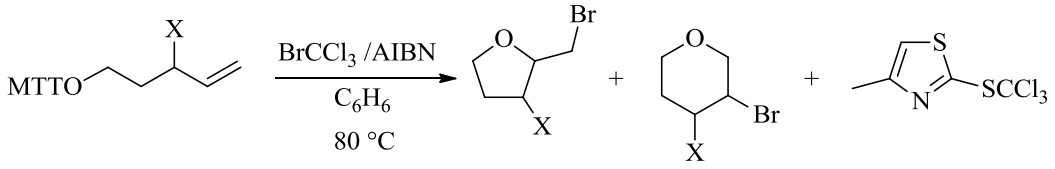
(ii) *Separierung und Charakterisierung der Produkte*. Zur Verifizierung der Daten und unabhängigen Charakterisierung von Reaktionsprodukten wurden Thiohydroxamat-Bromcyclisierungen in einem präparativen Maßstab durchgeführt. Hierzu wurde eine Lösung von *O*-Estern **1d**, **1g, 1i–1n** in Benzol (c_0 = 179–184 mM) mit AIBN (0.25 Äquiv.) und Bromtrichlormethan (8 Äquiv.) versetzt. Bei einer Reaktionstemperatur von 80 °C trat nach zwei Stunden vollständiger Umsatz ein. Höhere Reaktionszeiten führen zu niedrigeren Ausbeuten und zu Zersetzungsprodukten. Das Reaktionsgemisch wurde anschließend säulenchromatographisch gereinigt und die Produkte isoliert. Die Tetrahydrofurane **2** wurden als Hauptprodukte in Ausbeuten von 13–72% als 2,3-cis/trans-Mischungen

erhalten (Tabelle 5). Zusätzlich wurden die 6-*endo*-Cyclisierungsprodukte **3** in Ausbeuten von 3–16% gebildet (Tabelle 5).

(iii) *Konstitution und Konfiguration der bromcyclisierten Produkte*. Die Konstitutionsanalyse aller gebildeten Tetrahydrofurane **2** wurde mittels HRMS oder Verbrennungsanalyse und NMR-Spektroskopie vorgenommen. Die Zuordnung der relativen Konfiguration bezogen auf die Atome C2 und C3 erfolgte anhand der unterschiedlichen ^{13}C-Verschiebungen der cis/trans-Isomere (Tabelle 6). Die ^{13}C-NMR-Verschiebungen der Atome C2 und C3 der O-substituierten Tetrahydrofurane **2a–g** liegen im Bereich von 71.9–85.1 ppm, wobei die Signale der trans-konfigurierten Tetrahydrofurane einen systematischen Tieffeld-Shift im Vergleich zu den cis-konfigurierten aufweisen. Diese Richtlinie erlaubte in früheren Studien zuverlässig Strukturen 2,3-cis/trans-isomerer Tetrahydrofurane zuzuordnen.[3,10] Im Fall der Tetrahydrofurane **2i–l**, **2n** ist eine deutliche Hochfeld-Verschiebung der C3-Signale (44.2–60.8 ppm) zu erkennen. Hier ist ebenfalls aufgrund der höheren Verschiebungen am trans-C2-Atom eine Zuordnung der Konfigurationsisomere möglich. Eine Ausnahme stellt das *N*-Phthalimidoyl-substituierte Tetrahydrofuran **2m** dar, dies konnte aufgrund von Literaturdaten zugeordnet werden.[23]

Die Tetrahydropyrane **3** wurden in deutlich geringeren Ausbeuten von 3–16% gebildet. Ihre Konstitution ließ sich mit Hilfe von HMRS, GC/MS-Daten und diagnostischer NMR-Resonanzen sichern. cis/trans-Isomere von Tetrahydropyran **3a** dienten als Referenz, die uns aus einer unabhängigen Synthese zur Verfügung stand. Aufgrund der geringen Stoffmenge konnten wir nicht in allen Fällen die relative Konfigurationen von Haupt- und Minderisomer eindeutig zuordnen und ließen diese Angaben in den Einträgen von Tabelle 5 daher offen.

Table 5. Products from homolytic bromocyclization of allyl-substituted *O*-alkenyl thiohydroxamates **1**

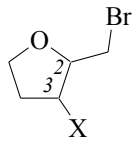


1 **2** **3** **4**

entry	**1** / X	**2** / % (*cis*:*trans*)	**3** / % (*dr*) [a]	**4** / %
1	**1a** / OH	**2a**: 56 (74:26)	**3a**: 4 (65:35)	84
2	**1d** / OTfac	**2d**: 13 (68:32)	**3d**: 3 (73:27)	72
3	**1e** / OBz	**2e**: 69 (68:32)	**3e**: 12 (50:50)	75
4	**1f** / OAc	**2f**: 71 (68:32)	**3f**: 11 (57:43)	94
5	**1g** / OCH_3	**2g**: 62 (58:42)	**3g**: 11 (85:15)	83
6	**1h** / F [b]	**2h**: – [c] (82:18)	– [d]	– [e]
7	**1i** / Cl	**2i**: 37 (47:53)	– [d]	54
8	**1j** / NH(Tfac)	**2j**: 59 (36:64)	**3j**: 11 (24:76)	76
9	**1k** / $NH(SO_2Ph)$	**2k**: 65 (39:61)	**3k**: 8 (44:56)	66
10	**1l** / NH(Bz)	**2l**: 61 (38:62)	**3l**: 7 [f]	89
11	**1m** / NH(Phth)	**2m**: 52 (5:95)	**3m**: 16 [f]	90
12	**1n** / SBz	**2n**: 72 (25:75)	– [d]	70

[a] Diastereomerenverhältnis (diastereomeric ratio, *dr*) 3,4-cis/trans-isomerer Produkte; Haupt- und Minderisomer nicht zugeordnet. [b] Die Produkte der homolytischen Bromcyclisierung von Thiohydroxamat **1h** wurden *in situ* durch NMR-Spektroskopie charakterisiert. [c] Die bestimmte Ausbeute an **2h** über ^{1}H- und ^{19}F-NMR mit internem Standard stimmten nicht überein, weshalb nur das relative Verhältnis der Isomere angeben ist. [d] 6-*endo*-Cyclisierungsprodukt **3** wurde nicht detektiert (NMR- und GC-analytisch). [e] Die Ausbeute an Koppelprodukt **4** konnte aufgrund von Überlagerungen im ^{1}H-NMR nicht bestimmt werden. [f] Ausschließlich ein Isomer des 6-*endo*-Cyclisierungsproduktes gefunden.

Table 6. Diagnostic shifts for distinguishing 2,3-cis/trans-substituted tetrahydrofurans



2

entry	**2** / X	*cis*-C2 / ppm	*trans*-C2 / ppm	*cis*-C3 / ppm	*trans*-C3 / ppm
1	**2a** / OH	82.2	85.1	71.9	75.1
2	**2d** / OTfac	80.8	82.6	77.9	81.5
3	**2e** / OBz	81.2	83.3	74.5	78.0
4	**2f** / OAc	80.8	83.2	73.7	77.4
5	**2g** / OCH_3	80.4 or 82.0 [a]	82.8 or 83.9 [a]	80.4 or 82.0 [a]	82.8 or 83.9 [a]
6	**2h** / F	82.1	83.4	92.7	96.0
7	**2i** / Cl	82.0	85.6	60.8	58.5
8	**2j** / NH(Tfac)	79.3	82.8	51.9	54.2
9	**2k** / $NH(SO_2Ph)$	79.8	82.9	55.3	56.7
10	**2l** / NH(Bz)	79.5	84.0	51.8	54.3
11	**2m** / N(Phth)	80.3	78.7	52.1	53.3
12	**2n** / SBz	80.1	83.7	44.9	44.2

[a] Chemische Verschiebung von C2 und C3 nicht eindeutig differenzierbar (Messung in $CDCl_3$).

2 On 2,3-stereocontrol in 4-pentenoxyl radical cyclization

2.1 Approach and methods

Fluor und monovalente Sauerstoff-Substituenten begünstigen 2,3-cis-selektive 4-Pentenoxylradikal-Cyclisierungen, Stickstoff-haltige Substituenten und Phenylthioxomethoxy 2,3-trans-selektive Reaktionen, Chlor ist ein Grenzfall (Tabelle 5). Der Unterschied zwischen den Halogenen Chlor und Fluor auf der einen Seite und der Chalkogene Schwefel und Sauerstoff auf der anderen verifizierten die formulierte Hypothese gegenläufiger Substituenteneinflüsse im selektivitätsbestimmenden Schritt.

Stereodifferenzierend in der intramolekularen Addition von 3-Hydroxypent-4-en-1-oxylradikal **Ia** sind die relativen Energien der Übergangsstrukturen, da die Rückreaktion von cyclisierten Radikalen *cis*/*trans*-**IIa** zu Ausgangsverbindung **Ia** unter den Bedingungen

homolytischer Bromcyclisierung keine Rolle spielt. Neben dem 2,3-cis-dirigierenden polaren Effekt besitzt Hydroxy auch einen sterischen Effekt und dieser steuert beispielsweise im Methyl-Derivat **Ib** 4-Pentenoxylradikal-Cyclisierungen wirkungsvoll 2,3-trans-selektiv.[6]

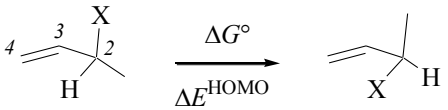
Um gegenläufige polare und sterische Substituenteneinflüsse unabhängig voneinander zu erfassen, berechneten wir π-Orbitalenergien X-substituierter Butene (Verbindungen des Typs **IV**) und konformelle Präferenzen X-substituierter Cyclohexane auf Grundlage des Winstein-Holness-Parameters A.[12] Die Stickstoff-Substituenten der experimentellen Studie verkleinerten wir im theoretisch-chemischen Teil der Studie auf Amin (Index **o**), und Benzoylthio zu Thiol (Index **p**). Innerhalb theoretisch-chemischer Korrelationen sind die Vereinfachungen stimmig, im Vergleich zu experimentellen Daten sind sie in den korrekten Kontext zu stellen.

2.2 Polar effect of allyl substituents in butenes

Zur Berechnung konsistenter Datensätze evaluierten wir Dichtefunktional-Methoden und sogenannte Hybrid-Methoden. Das Becke's Drei-Parameter-Lee-Yang-Parr-Hybrid-Funktional (B3LYP)[25,26] in Kombination mit dem 6-31+G**-Basissatz[27] erlaubt, Bindungslängen der C,O-Einfach- und der C,C-Doppelbindung in But-3-en-2-ol (**IVa**) mit einer Genauigkeit von 99% und dem Diederwinkel zwischen Alken-Teilstruktur und Hydroxy-Sauerstoff mit einer Präzision von 98% im Vergleich zur mikrowellenspektroskopischen Analyse in der Gasphase[28] widerzugeben. G3-Rechnungen liegen RHF/6-31G*-Rechnungen zugrunde, die Feinheiten organischer Strukturen weniger präzise reproduzieren.[29]

Im energetisch niedrigsten Konformer der theoretisch-chemisch untersuchter (2*S*)-substituierter Butene **IVa**–**b**, **IVh**–**i**, und **IVo**–**p** ist in Übereinstimmung mit experimentellen Daten die σ(C,X)-Bindung antiklinal (*ac*) zur Ebene der Kohlenstoff-Kohlenstoff-Doppelbindung angeordnet. Synperiplanare (*sp*)-Konformere besitzen unter Standardbedingungen, dem thermochemischen Modell von Gaussian03 folgend, zwischen 2.0 kJ mol^{-1} (Fluorbuten **IVa**) und 9.5 kJ mol^{-1} (Butenthiol **IVp**) höhere freie Gibbs-Energien $\Delta G°$ (Tabelle 7). Antiklinale Buten-Konformere besitzen niedrigere HOMO-Energie als synperiplanare.[30] Für den Methyl-Substituenten ist der Unterschied vernachlässigbar gering (0.6 kJ mol^{-1}) und für Fluor in der berechneten Reihe maximal (29.9 kJ mol^{-1}).

Table 7. Calculated dihedral angle ω for the minimal conformation energy, alterations of free Gibbs-energy and increase of HOMO-energy with change of conformation *ac*-**IV** → *sp*-**IV**



ac-**IV** *sp*-**IV**

entry	**IV** / X	EN [a]	ω [b] / deg	$\Delta G°$ [c] / kJ mol^{-1}	$E(\pi)$ [d] (*ac*-**IV**) / eV	$E(\pi)$ [d] (*sp*-**IV**) / eV
1	**IVh** / F	4.000	120.8	2.0	–10.39	–10.09
2	**IVi** / Cl	3.475	115.7	6.8	–10.25	–10.17
3	**IVa** / OH	3.033	119.4	4.6	–10.21	–10.98
4	**IVo** / NH_2	2.766	115.4	3.7	–9.83	–9.93
5	**IVp** / SH	2.763	116.6	9.5	–10.22	–10.12
6	**IVb** / CH_3	2.629	118.3	4.5	–9.73	–9.72

[a] Recommended Pauling-Electronegativity (EN) for atoms;[13] group electronegativities were calculated from Pauling-values of atoms according to the Sanderson-equation.[14] [b] Dihedral angle X,C2,C3,C4 for minimum conformation *ac*-**IV** (B3LYP/6-31+G**). [c] $\Delta G° = G°$(*sp*-**IV**) – $G°$(*ac*-**IV**), for 298.15 K and 1 atm; B3LYP/6-31+G**. [d] $\Delta E^{HOMO} = E^{HOMO}$(*sp*-**IV**) – E^{HOMO}(*ac*-**IV**); G3; π(C,C) is equivalent to the HOMO for entries 1–4 and 6, and for the HOMO–1 for entry 5.

Zur Berechnung von π-Orbitalenergien nutzten wir das G3-Verfahren aus Gaussian03. Für das gewählte Referenzmolekül But-1-en beträgt die HOMO-Energie auf Grundlage der G3-Theorie 9.74 eV und liegt damit nur 0.02 eV über dem Vertrauensbereich des experimentell bestimmten Ionisationspotentials von 9.64±0.08 eV.[31]

Mit zunehmender Elektronegativität (EN) des Substituenten X sinken G3-berechnete HOMO-Energien (Figure 4). B3LYP/6-31+G**-berechnete HOMO-Energien zeigen einen ähnlichen, jedoch einen schwächer korrelierten Verlauf (*Supplementary data*). Elektronegativitäten von Gruppen berechneten wir auf Grundlage von Pauling-Elektronegativitäten mit Hilfe der Sanderson-Gleichung.[32]

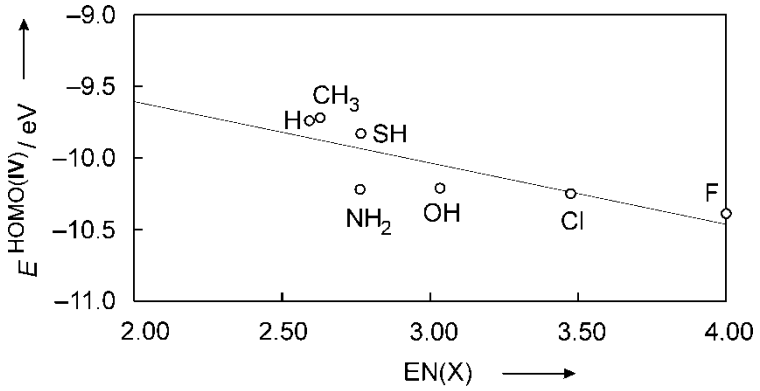


Figure 4.Correlating G3-calculated HOMO-energies for anticlinal conformers of 2-butenes with electronegativity of X [EN(X)] on the Pauling-scale for atoms and equilibrated electronegativities for groups based according to Sanderson, using electronegativities of atoms on the Pauling-scale (E = –0.541EN – 8.313; $R2$ = 0.876).[32]

2.3 Steric substituent parameter *A*

Differenzen freier Gibbs-Energien für axial- und äquatorial-substituierte Cyclohexane (*A*-Werte) gibt das B3LYP/6-31+G**-Verfahren in Genauigkeiten bis zu ±40% wider. G3-berechnete *A*-Werte divergierten zwischen –9% (X = CH_3) bis 100% (F). Die absoluten Werte für Fluorcyclohexan 0.9 kJ mol^{-1} (G3, 25 °C), 1.3 (B3LYP, 25° C) zu 1.8 (experimentell, –25 °C) zeigen, dass alle drei Methoden hinsichtlich der Größenordnung des *A*-Wertes näher zusammenliegen, als die relativen Werte den Anschein haben. Einen Großteil der Differenz zwischen Theorie und Praxis führen wir auf Temperaturunterschiede zurück.[33] Um konsistent innerhalb der Methoden zu bleiben, entschieden wir uns Dichtefunktional-berechnete *A*-Werte weiterzuverfolgen, da die gleiche Methode (B3LYP/6-31+G**) zur Berechnung von Radikalselektivitäten in dieser Studie zentral ist.

Für Dichtefunktional-berechnete Cyclohexan-Strukturen steigt der *A*-Wert entlang der Reihe F < OH < Cl < NH_2 < SH < CH_3 von 1.3 auf 10.6 kJ mol^{-1}. In der experimentellen sterischen Reihe F < Cl < OH < SH < NH_2 < CH_3 tauschen Chlor (2.7 kJ mol^{-1}, 25 °C) und Hydroxy (4.8 kJ mol^{-1}, 25 °C), sowie Amin (5.2 kJ mol^{-1}, –80 °C) und Thiol (5.1 kJ mol^{-1}, –80°C) die Plätze. Die Energieunterschiede sind jedoch klein verschwimmen im Toleranzbereich der experimentellen Methoden. Auch hier bleibt festzuhalten, dass Dichtefunktional-berechnete *A*-Werte gleiche Größenordnungen wie experimentelle erreichen.

Auf Grundlage des Substituentenparameter *A* besitzen Fluor, Chlor und Hydroxy einen geringeren sterischen Effekt als Methyl, Amin und Thiol.

2.4 Selectivity in 4-pentenoxyl radical cyclization

2.4.1 Model and Theory

Homolytische Bromcyclisierungen von 3-Hydroxy-4-pentenoxylradikal **Ia** und 3-Methyl-4-pentenoxylradikal **Ib** unterliegen kinetischer Reaktionskontrolle, da die cyclisierten Radikale 2,3-*cis*/*trans*-**IIa**–**b** unter den Reaktionsbedingungen konfigurativ stabil sind.[10] Selektivitäten von Radikaladditionen liegen daher Differenzen freier Gibbs-Energien für Übergangsstrukturen für den 2,3-cis- und den 2,3-trans-Ringschluss zugrunde.[34]

Das Modell zur Beschreibung stereoselektiver 4-Pentenoxylradikal-Cyclisierungen begrenzt das Ensemble möglicher Konformere auf die zwei Reaktionswege für den 2,3-cis-Ringschluss und zwei für die 2,3-trans-Reaktion.[7] Unter Annahme freier Äquilibrierung, wovon bei Vergleich von Geschwindigkeitskonstanten intramolekularer Rotationen um σ(C,C)-Bindungen von 10^{10}–10^{11} s^{-1} zur intramolekularen C,O-Addition von 10^{8}–10^{9} s^{-1} gewährleistet sein sollte,[8,35] bilden dem Curtin-Hammett-Prinzip[36] folgend Boltzmann-gewichtete relative Gibbs-Energien $\Delta G°$ von Übergangsstrukturen ein Maß für die relative Häufigkeit, mit der die vier Reaktionswege durchlaufen werden (Gleichungen 1–2).[37] Auf Grundlage dieser Überlegungen lässt sich der prozentuale Anteil von Reaktanden p_i für die cis-Reaktion und derjenige für die trans-Reaktion und damit Stereoselektivitäten von 4-Pentenoxylradikal-Cyclisierungen vorhersagen (eq 3).[38]

$$\frac{N_i}{N_0} = e^{-\left(\frac{\Delta G°}{RT}\right)} \qquad \text{(eq. 1)}$$

$$x_0 = \sum_{i=1}^{4} \left(\frac{N_i}{N_0}\right) \qquad \text{(eq. 2)}$$

$$p_i = 100\ \frac{x_i}{x_0} \qquad \text{(eq. 3)}$$

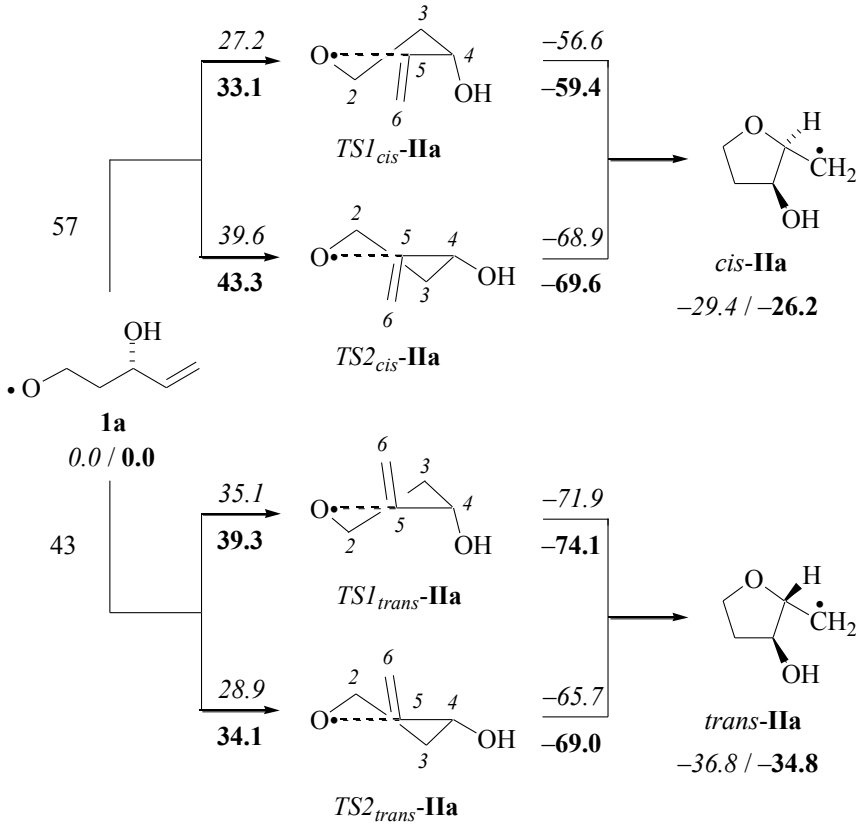
Das Kernstück der Berechnung von Radikalselektivitäten auf Grundlage des Reaktionsmodells ist eine Methode zur Berechnung freier Gibbs-Energie, aus denen experimentelle Selektivitäten innerhalb tolerabler Grenzen reproduziert werden können. Da Selektivitäten auf Energiedifferenzen basieren genügen zur Widergabe stereochemischer

Präferenzen in Sauerstoffradikal-Additionen in der Regel Dichtefunktional-Verfahren. In eigenen Arbeiten erlaubten B3LYP/6-31+G**-berechnete Gibbs Energien Stereoselektivitäten in 5-*exo*-Cyclisierungen Methyl-, *tert*-Butyl- und Phenyl-substituierter 4-Pentenoxylradikale innerhalb von Genauigkeiten zu reproduzieren, die der Präzision der Methoden nahekommt aus denen die experimentellen Daten abgeleitet sind. Auf Empfehlungen aus der chemischen Literatur ergänzten wir die Rechnung bei der Untersuchung intermolekularer Radikaladditionen und der Synthese bicyclischer Verbindungen durch die BHandHLYP/6-31+G**- und BHandHLYP/6-311G**-Theorien.[39,40,41] Die Ergebnisse der Theorien stützen sich und erlauben Trends sicherer einzuordnen als mit nur einer Methode alleine.[42] In dieser Arbeit setzten wir die drei Dichtefunktional-Verfahren erstmals ein um zu prüfen, in wie weit sie in der Lage sind den Übergang von 2,3-cis- zu 2,3-trans-selektiver 4-Pentenoxylradikal-Cyclisierung in Abhängigkeit eines Allyl-ständigen Substituenten X widerzugeben.

2.4.2 Validating Theory

Zur Validierung der Dichtefunktional-Theorien berechneten wir dem Reaktionsmodell folgend Selektivitäten der 3-Hydroxy-4-pentenoxylradikal-Cyclisierung **Ia**→*cis*/*trans*-**IIa**. Kernstück des Modells sind die Übergangsstrukturen *TS1/2* für den cis- und für den trans-Ringschluss (Scheme 4).

Die energieärmsten Übergangsstrukturen in 4-Pentenoxylradikal-Cyclisierungen leiten sich strukturell von einem Tetrahydrofuran-Twist-Konfomer ab, in dem der angreifende Sauerstoff (O1), der innere Alken-Kohlenstoff (C5) und der Allyl-ständige Kohlenstoff (C4) eine Ebene bilden. Die verbleibenden Kohlenstoffatome der cyclisierenden 4-Pentenoxylradikal-Kette (C2, C3) sind in entgegengesetzter Richtung aus der Ringebene versetzt, woraus diastereomorphe ${}_2T^3$- oder ${}^2T_3$-Konformere resultieren, welches der beiden diastereomorphen Twist-Konformer energetisch bevorzugt wird hängt von der Konfiguration des Substituenten-gebundenen Kohlenstoffs ab. Stereodifferenzierung basiert in dem Twist-Modell auf Rotation des Vinyl-Substituenten, aus der dem angreifenden Sauerstoffradikal je eine der diastereotopen Seiten von 4-Pentenoxylradikal **I** zur Bindungsknüpfung angeboten wird. Aus sterischen Gründen weichen der terminale Alken-Kohlenstoff C6 und der innere Alkylkohlenstoff C3 sich maximal aus.



Scheme 4. Calculated (B3LYP/6-31+G**) preferred transition structures for 2,3-cis-5-*exo*-cyclization of the (3*R*)-3-hydroxypent-4-en-1-oxyl radical (**Ia**) (top) and the 2,3-trans-pathway (bottom; numbers printed in italics refer to zero-point vibrational energy-corrected energies at 0 K, numbers printed in bold are Gibbs free energy differences, referring to a temperature of 298.15 K and a pressure of 1 atm, based on the thermochemical model implemented in the Gaussian03-suite of program[27]).

Der energieärmste Reaktionsweg der 5-*exo*-Cyclisierung von (3*S*)-konfiguriertem 3-Hydroxypent-4-enyl-1-oxylradikal (**Ia**) führt in allen drei Theorien über Übergangsstruktur *TS1*$_{cis}$-**IIa**, die nach vollzogener C,O-Bindungsknüpfung zu Tetrahydrofuranyl-2-methyl-Radikal *cis*-**IIa** führt. Der nächst energiereichere Reaktionsweg führt über Intermediat *TS2*$_{trans}$-**IIa** zum Produkt *trans*-**IIa** (Scheme 4, Table 9). Die 2,3-trans-Cyclisierung ist in allen drei Theorien die exergonere Reaktion. Alle Theorien liefern für Übergangsstrukturen akzeptable ($\langle S^2 \rangle$ = 0.77–0.79) aber nicht perfekte ($\langle S^2 \rangle$ = 0.75) Erwartungswerte für den Spinoperator.[43]

Der Abstand zwischen Radikalsauerstoff O1 und Alken-Kohlenstoff C5 beträgt in Intermediat *TS1*$_{cis}$-**IIa** 2.028 Ångström. Gegenüber Ausgangsradikal **Ia** ist die C5,C6-Doppelbindung um 0.039 Ångström verlängert. Auf Grundlage der Marcus-Theorie kann aus

Aktivierungsenergie ($E^{\ddagger}$) und Reaktionsenergie (ΔE) eine ungefähre Position $x^{\ddagger}$ von Übergangstruktur *TS1*$_{cis}$-**IIa** auf der Reaktionskoordinate abgeschätzt werden (eq 4).[44,45] Mit $x^{\ddagger}$ = 0.4 (B3LYP/6-31+G**) liegt *TS1*$_{cis}$-**IIa** später auf der Reaktionskoordinate als die Übergangstruktur des 3-Desoxy-Derivats von **I**, dem 4-Penten-1-oxylradikal ($x^{\ddagger}$ = 0.2; für X = H). Diesem Unterschied liegt eine 7.4 kJ mol–1 (B3LYP/6-31+G**) höhere Aktivierungsenergie für die Reaktion *TS1*$_{cis}$-**IIa** verglichen mit der 4-Penten-1-oxylradikal-Cyclisierung zugrunde. BHandHLYP-Rechnungen sagen sowohl für die Intermediate *TS1/2*-**IIa** der cis- und trans-Reaktionswege als auch für die günstigste 5-*exo*-Übergangstruktur des 4-Penten-1-oxylradikals (**I**, X = H) vergleichbare Positionierung von $x^{\ddagger}$ = 0.4 auf der Reaktionskoordinate voraus (Table 8 and ESI).

Die Differenzen freier Gibbs Energien zwischen den vier Intermediaten *TS1/2*$_{cis}$-**IIa** und *TS1/2*$_{trans}$-**IIa** liefern bei Anwendung der Gleichungen 1–3 2,3-cis/trans-Selektivitäten für den Ringschluss **Ia**→**IIa** von 57:47 (B3LYP/6-31+G**), 60:40 (BHandHLYP/6-31+G**) und 83:17 (BHandHLYP/6-31+G**). Das cis/trans-Verhältnis von 2-Brommethyltetrahydrofuran-3-ol (**2a**) bei 80 °C durchgeführter Bromcyclisierung beträgt 74:26.[10]

Auf Grundlage der Marcus-Theorie lässt sich die Aktivierungsenergie $E^{\ddagger}$ in einen Term separieren, der sterische Effekte ($E^{\ddagger}_{S}$; S für Sterik) abbildet und in einen der den Proporz von Bindungslösung und Bindungsknüpfung widergibt ($E^{\ddagger}_{TD}$; TD für Thermodynamik; Gleichungen 5–6). Positive $E^{\ddagger}_{S}$-Werte stehen für Repulsion, negative $E^{\ddagger}_{TD}$-Werte für Dominanz von Bindungsknüpfung über Bindungslösung.

$$x^{\ddagger} = \frac{1}{2}\left(1 + \frac{\Delta E}{4\,E^{\ddagger}}\right) \qquad \text{(eq. 5)}$$

$$E^{\ddagger}_{S} = \frac{E^{\ddagger} - \frac{\Delta E}{2} + \sqrt{(E^{\ddagger})^2 - (\Delta E)(E^{\ddagger})}}{2} \qquad \text{(eq. 4)}$$

$$E^{\ddagger} = E^{\ddagger}_{S} + E^{\ddagger}_{TD} \qquad \text{(eq. 6)}$$

Die intrinsische, sterische Barriere für die Reaktion über Intermediat *TS1*$_{cis}$-**IIa** ist mit Abstand die niedrigste. Mit einem Wert von 40.6 kJ mol^{-1} liegt dieser Wert immer noch 3.3 kJ mol^{-1} über dem berechneten für die 4-Penten-1-oxylradikal-Cyclisieurng (37.3 kJ mol^{-1} für X = H in **I**). Der stabilisierende thermodynamische Beitrag der Barriere ist für die stärker exergonen 2,3-trans-Cyclisierungen über Intermediate *TS1/2*$_{trans}$-**IIa** (–16.5 bis –16.8 kJ mol^{-1}) niedriger als für *TS1/2*$_{cis}$-**IIa**, aber immer noch leicht über dem der analogen 4-Penten-1-oxylradikal-Cyclisierung (–17.5 kJ mol^{-1} für X = H in **I**).

Aus der Marcus-Analyse folgerten wir, dass eine Allyl-ständige Hydroxy-Gruppe auf eine 4-Pentenoxylradikal-Cyclisierung **I→II** ungünstige sterische und polare Beiträge ausübt. Experimentell bestätigt ist eine Verlangsamung der Reaktivität beim Austausch von H gegen OH in Allyl-Position von 4-Pentenoxylradikalen.

Ein zweites Radikal, dessen Selektivitäten wir auf Grundlage Dichtefunktional-Theorie-berechneter Gibbs Energiedifferenzen validierten, ist (3*S*)-Methyl-4-pentenoxylradikal (**Ib**). Das energieärmste Intermediat *TS2*$_{trans}$-**IIb** der Reaktion von 4-Pentenoxylradikal **Ib** führt zum Produkt *trans*-**IIb** und besitzt $^{2}T_{3}$-Konformation. Das energieärmste Intermediat der 2,3-cis-Reaktion ist *TS1*$_{cis}$-**IIb** und besitzt $_{2}T^{3}$-Konformation. Die energiereicheren Intermediate beider Reaktionswege nehmen eine $_{3}T^{4}$- (*TS2*$_{cis}$-**IIb**) und eine $^{3}T_{4}$-Konformation (*TS1*$_{trans}$-**IIb**) ein (ESI). Der Wechsel von $_{2}T^{3}$ zu $_{3}T^{4}$ tritt ein, sobald die sterischen Effekte des Allyl-Substituenten X, auf Grundlage des *A*-Wertes bewertet, signifikanter werden. Ein Allyl-ständiger Methyl-Substituent führt auf der anderen Seite zu den durchweg niedrigsten Aktivierungsenergien $E^{‡}$. Mit 34.3 kJ mol^{-1} erreicht $E^{‡}_{TD}$ für *TS2*$_{trans}$-**IIb** in der untersuchten Reaktionsserie ein Minimum. Methyl führt in Radikal **Ib** zu Rückseitenspannung, die eine Annäherung der reaktiven Gruppen statistisch begünstigt.

Auf Grundlage der Gleichungen 1–3 führen die Dichtefunktional-berechneten Differenzen freier Gibbs Energien für eine Temperatur von 25 °C zu 2,3-cis/trans-Selektivitäten für die Reaktion **Ib→IIb** von 4:96 (B3LYP/6-31+G**), 3:97 (BHandHLYP/6-31+G**) und 4:96 (BHandHLYP/6-311G**). Das cis/trans-Verhältnis für 2,3-Dimethyltetrahydrofuran (**2b**) aus homolytischer reduktiver Cyclisierung in Gegenwart von Naphtalin-2-thiol bei 15 °C beträgt 14:86.[6,7]

Zusammenfassend ermöglichen Dichtefunktional-theoretisch berechnete Differenzen freier Gibbs Energiedifferenzen Selektivitäten von Radikalcyclisierung qualitativ (cis/trans-Präferenz) und mit kleiner Streuung auch quantitativ vorherzusagen.

2.4.3 Exploring Selectivity

Auf Grundlage des vorgestellten Reaktionsmodells lassen sich Differenzen freier Gibbs-Energien nutzen, um Selektivitäten für 5-*exo*-Cyclisierungen von 3-Fluor-4-pentenoxyl-Radikal **Ih**, Chlor-Derivat **Ii**, Amin **Io** und Thiol **Ip** vorherzusagen.

Bei einer Reaktionstemperatur von 25 °C beträgt die 2,3-cis/trans-Selektivität für den Ringschluss **Ih→IIh** 88:12 (B3LYP/6-31+G** und BHandHLYP/6-31+G**) und 95:5

(BHandHLYP/6-311G**). Das experimentell bestimmte cis/trans-Verhältnis für 2-Brommethyl-3-fluortetrahydrofuran (**2h**) aus homolytischer Bromcyclisierung bei 80 °C beträgt 82:18.

Für die Chlorpentenoxylradikal-Cyclisierung **Ii→IIi** betragen die berechneten Selektivitäten 20:80 (B3LYP/6-31+G**), 18:82 (BHandHLYP/6-31+G**) und 19:81 (BHandHLYP/6-311G**). Das experimentell bestimmte cis/trans-Verhältnis für 2-Brommethyl-3-chlortetrahydrofuran (**2i**) aus homolytischer Bromcyclisierung bei 80 °C beträgt 47:53.

Für die Aminopentenoxylradikal-Cyclisierung **Io→IIo** betragen die berechneten Selektivitäten 15:85 (B3LYP/6-31+G**), 14:86 (BHandHLYP/6-31+G**) und 27:73 (BHandHLYP/6-311G**). Das experimentell bestimmte cis/trans-Verhältnis für 2-Brommethyl-3-benzamidotetrahydrofuran (**2l**) aus homolytischer Bromcyclisierung bei 80 °C beträgt 38:62. Aufgrund des geringen stereoinduzierenden Unterschieds zwischen Hydroxy (74:26) und Benzoyloxy (68:32) schlagen wir vor, die experimentellen Daten für das Benzamid-substituierte 4-Pentenoxyl-Radikal **Ia** als Referenz zum Vergleich der berechneten Selektivitäten **Io→IIo** zu nutzen. Entsprechende Logik liegt dem Vergleich des experimentellen cis/trans-Verhältnisses für 2-Brommethyl-3-(benzoylthio)tetrahydrofuran (**2n**) von 25:75 für eine Temperatur von 80 °C mit den berechneten Selektivitäten der Cyclisierung **Ip→IIp** von 2:98 (B3LYP/6-31+G**, BHandHLYP/6-31+G** und BHandHLYP/6-311G**) zugrunde.

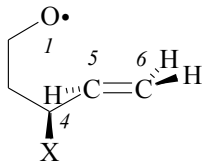
Table 8. Thermochemical data for 5-*exo*-cyclization of 3-substiuted 4-pentenoxyl radicals from B3LYP/6-31+G**-theory

I → **II** / X	*cis*-**II**		*trans*-**II**	
	ΔE / kJ mol^{-1}	$\Delta G°$ / kJ mol^{-1}	ΔE / kJ mol^{-1}	$\Delta G°$ / kJ mol^{-1}
Ia → **IIa** / OH	–29.4	–26.2	–36.8	–34.8
Ib → **IIb** / CH_3	–42.7	–39.4	–49.8	46.0
Ih → **IIh** / F	–38.0	–34.6	–43.1	–39.8
Ii → **IIi** / Cl	–35.0	–31.0	–38.8	–32.9
Io → **IIo** / NH_2	–34.5	–30.2	–37.8	–35.3
Ip → **IIp** / SH	–33.8	–29.7	–38.8	–36.8

Table 9. Free activation energy ($\Delta G°$), activation energy ($E^{‡}$) intrinsic ($E_i^{‡}$) and thermodynamic ($E_{TD}^{‡}$) barriers for reactions **I** → *cis*/*trans*-**II** (B3LYP/6-31+G** and eqs. I–V)

I → *cis*/*trans*-**II** / X	energy / kJ mol^{-1}	*TS1*$_{cis}$-**II**	*TS2*$_{cis}$-**II**	*TS1*$_{trans}$-**II**	*TS2*$_{trans}$-**II**
Ia → **IIa** / OH	$\Delta G°$ / kJ mol^{-1}	≡ 0.00	10.2	6.1	1.0
	$E^{‡}$ / kJ mol^{-1}	27.2	39.6	35.1	28.9
	$E_S^{‡}$ / kJ mol^{-1}	40.6	53.3	51.9	45.4
	$E_{TD}^{‡}$ / kJ mol^{-1}	–13.4	–13.7	–16.8	–16.5
Ib → **IIb** / CH_3	$\Delta G°$ / kJ mol^{-1}	8.9	11.5	9.7	≡ 0.00
	$E^{‡}$ / kJ mol^{-1}	22.2	25.9	24.4	13.9
	$E_S^{‡}$ / kJ mol^{-1}	40.8	44.7	45.9	34.3
	$E_{TD}^{‡}$ / kJ mol^{-1}	–18.6	–18.8	–21.5	–20.4
Ih → **IIh** / F	$\Delta G°$ / kJ mol^{-1}	≡ 0.00	13.6	6.6	6.6
	$E^{‡}$ / kJ mol^{-1}	21.9	38.4	30.0	29.0
	$E_S^{‡}$ / kJ mol^{-1}	38.6	55.8	49.2	48.1
	$E_{TD}^{‡}$ / kJ mol^{-1}	–16.7	–17.4	–19.2	–19.1
Ii → **IIi** / Cl	$\Delta G°$ / kJ mol^{-1}	3.4	10.4	7.3	≡ 0.00
	$E^{‡}$ / kJ mol^{-1}	28.4	37.1	34.0	25.7
	$E_S^{‡}$ / kJ mol^{-1}	44.2	53.2	51.6	42.9
	$E_{TD}^{‡}$ / kJ mol^{-1}	–19.0	–19.2	–20.9	–20.7
Io → **IIo** / NH_2	$\Delta G°$ / kJ mol^{-1}	4.2	12.4	6.5	≡ 0.00
	$E^{‡}$ / kJ mol^{-1}	29.3	39.2	33.2	25.7
	$E_S^{‡}$ / kJ mol^{-1}	44.9	55.1	50.3	42.5
	$E_{TD}^{‡}$ / kJ mol^{-1}	–15.6	–15.9	–17.1	–16.8
Ip → **IIp** / SH	$\Delta G°$ / kJ mol^{-1}	10.5	12.5	12.1	≡ 0.00
	$E^{‡}$ / kJ mol^{-1}	30.7	34.1	35.3	20.5
	$E_S^{‡}$ / kJ mol^{-1}	46.0	49.6	53.1	37.4
	$E_{TD}^{‡}$ / kJ mol^{-1}	–15.3	–15.5	–17.6	–16.9

Table 10. Distance (*d*), lengthening of C5,C6 (Δd), dihedral angle (α, ω), approximated transition structure location ($x^{\ddagger}$), imaginary O1,C5-stretching vibration (*i*), and expectation value of spin operator ($\langle S^2 \rangle$) characterizing calculated (B3LYP/6-31+G**), lowest in energy transition structures in 5-*exo*-cyclization of 3-substituted 4-pentenoxyl radicals



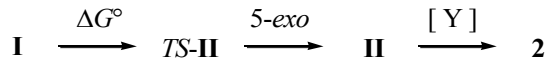
TS-**II** / X	*d*(O1,C5) / Å	Δd(C5,C6) [a] / Å	ω [b] / degrees	$x^{\ddagger}$ [c]	*i* [d] / cm^{-1}	$\langle S^2 \rangle$ [e] / cm^{-1}
$TS1_{cis}$-**IIa** / OH	2.028	0.039	–4.0	0.4	-404	0.7779
$TS2_{trans}$-**IIb** / CH_3	2.046	0.039	110.5	0.1	-374	0.7782
$TS1_{cis}$-**IIh** / F	2.037	0.040	–5.2	0.3	-394	0.7786
$TS2_{trans}$-**IIi** / Cl	2.023	0.040	109.7	0.3	-407	0.7801
$TS2_{trans}$-**IIo** / NH_2	2.033	0.039	111.0	0.3	-390	0.7785
$TS2_{trans}$-**IIp** / SH	2.030	0.040	111.1	0.3	-393	0.7796

[a] $\Delta d(C5,C6) = d^{TS\text{-}II}(C5,C6) - d^{I}(C5,C6)$. [b] ω = X,C4,C5,C6. [c] Relative position on the reaction coordinate; $x = 0$ for I, $x = 1$ for *cis*/*trans*-**II**. [d] Wave number of the imaginary stretching vibration associated with O1,C5-bond formation. [e] Expectation value of spin operator; $\langle S^2 \rangle = 0.7500$ for the doublet state.

Dem stereochemischen Modell zufolge verlaufen 2,3-cis-selektive 4-Pentenoxylradikal-Cyclisierungen (aus **Ia** und **Ih**) über $TS1_{cis}$-**I**, in dem Allyl-Substituent X und die Vinyl-Gruppe koplanar zueinander angeordnet sind. Für die gewählte (3*S*)-Konfiguration von **I** besitzt $TS1_{cis}$-$\mathbf{I}_2T^3$-Konformation (Tables 9 und 10).

2,3-trans-Selektive 4-Pentenoxylradikal-Cyclisierungen favorisieren Intermediat $TS2_{trans}$-**II**. Für (3*S*)-konfigurierte 4-Pentenoxylradikale liegt Intermediat $TS2_{trans}$-**II** in der $^2T_3$-Konformation vor. Allyl-Substituent X und terminale Vinyl-Gruppe sind in $TS2_{trans}$-**II** antiklinal zueinander angeordnet.

Table 11. Correlating polar (EN) and steric (*A*) effects of substituents X versus calculated (B3LYP/6-31+G** and eqs. 1–3) and experimental selectivity data (Table 5)



I / X	EN [a]	*A* [b] / kJ mol^{-1}	Δ*G*° [c] / kJ mol^{-1}	*cis*/*trans*-**II** [d] B3LYP	*cis*/*trans*-**2** [e] experimental
Ia / OH	4.000	4.0	–1.0	57:43	74:26 (68:32)
Ib / CH_3	3.475	10.6	8.9	4:96	18:82
Ih / F	3.033	1.3	–6.6	84:16	80:20
Ii / Cl	2.766	4.5	3.4	20:80	52:48
Io / NH_2	2.763	6.0	4.2	15:85	(38:62)
Ip / SH	2.629	8.7	10.5	2:98	(25:75)

[a] Electronegativity of atoms on the Pauling-scale and for equilibrated electronegativities of groups based on the Sanderson-approximation. [b] Calculated (B3LYP-6-31+G**) Winstein-Holness-parameter *A* for X in monosubstituted cyclohexanes. [c] $\Delta G° = G°_{cis} - G°_{trans}$ (B3LYP/6-31+G**). [d] Calculated from Δ*G*°-values listed in Table 9 and equations 1–3. [e] Experimental selectivities: X = Br from $BrCCl_3$ for **2a**, **2h**, and **2h**; X = H from naphthalene-2-thiol for **2b**;[6] numbers in brackets refer to selectivity of X-benzoyl derivatives **2e** (OBz), **2l** (NHBz), and **2n** (SBz).

2.4.4 On steric and polar effects

Analyse von Reaktionsenergien und Aktivierungsenergien für 4-Pentenoxylradikal-Cyclisierungen **I→II** erlauben die Signifikanz von sterischen und polaren Einflüssen eines Allyl-Substituenten gegeneinander zu bewerten. Der thermodynamische Beitrag $E_{TD}^{\ddagger}$ zur Energiebarriere $E^{\ddagger}$ ist für 2,3-trans-Cyclisierungen durchweg niedriger als für 2,3-cis-Reaktionen. Dieser Befund bildet den geringeren Energieinhalt des 2,3-trans-Stereoisomers von **II** ab. Die relative intrinsische Barriere $E_S^{\ddagger}$ ist für die Hauptreaktion am niedrigsten und dient als zuverlässiger Marker des Hauptprodukts.

In einem Korrelationsdiagramm, in dem die berechnete Differenz $\Delta G°(\ \mathbf{I}\rightarrow\mathbf{II})^{\ddagger}$ zwischen *TS1*$_{cis}$-**II** und *TS2trans*-**II** einer Radikalreaktion als Selektivitätsparameter in Bezug zum *A*-Wert des vorhandenen Allylsubstituenten X zueinander gesetzt werden, folgt die 2,3-trans-Selektivität nahezu linear dem sterischen Effekt. Der Selektivitätsparameter $\Delta G°(\ \mathbf{I}\rightarrow\mathbf{II})^{\ddagger}$ korreliert linear mit dem Einfluss eines Allylsubstituenten auf die HOMO-

Energie des antiklinalen Konformer von Buten **IV**.

Aus der Gegenüberstellung von polarem und sterischem Einfluss folgt, dass Allylsubstituenten X mit *A*-Werten von 4 kJ mol^{-1} und kleiner, 2,3-cis-selektive 4-Pentenoxyladikal-Cyclisierungen begünstigen, falls sie das π-Typ-MO vergleichbar wie Fluor oder Hydroxy stabilisieren.

Reaktionstheoretisch erweitert diese Einteilung die auf Hydroxy begrenzte, um Stickstoff- und Schwefel-Substituenten, in denen sterische Einflüsse überwiegen und Fluor mit dominierendem polarem Effekt. Methyl war vorab aufgrund seines sterischen Effekts als 2,3-trans-steuerender Substituent im Kontext zu Phenyl[46] und *tert*-Butyl[7] eingeteilt worden, diese Einteilung hat Bestand. Chlor gibt uns Rätsel auf. Ob der sterische Einfluss im Radikalexperiment unter dem der *A*-Wert-Analyse für Cyclohexane liegt, oder ob der elektronische im Übergangszustand $TS1_{cis}$-**IIi** durch die eingesetzten Theorien unterbewertet wird, wird in künftigen Studien zu klären sein. Ergänzend möchten wir hinzufügen, dass Versuche, Brom als ergänzenden Allylsubstituenten in die Studie aufzunehmen aufgrund experimenteller Schwierigkeiten der gewählten Allylfunktionalisierung[47] ausgehen von 3-Hydroxypentenylthiohydroxamat **1a** vorerst beiseitegelegt wurden und künftig vor dem Hintergrund unbeantworteter Fragen noch einmal verfolgt werden sollte.

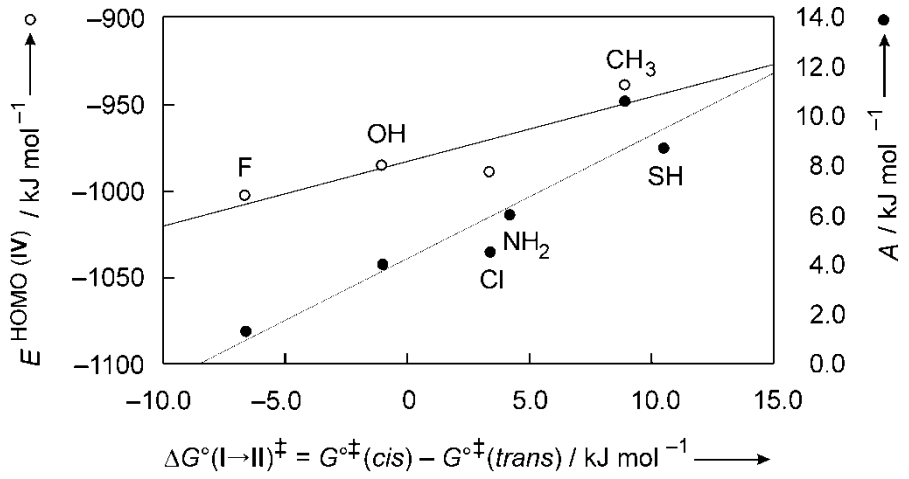
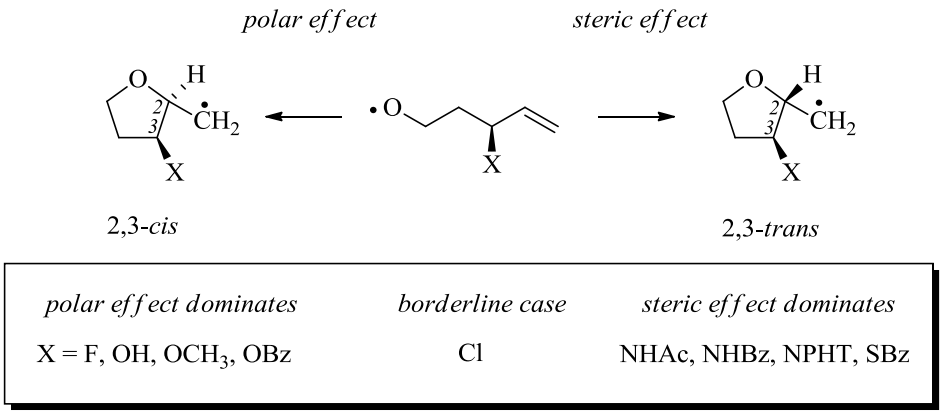


Figure 5. Correlating calculated (B3LYP/6-31+G**) selectivity for cyclization of X-substituted 4-pentenoxyl radical **I** based on lowest in energy transition structures for the 2,3-cis- and the trans-5-exo ring closure to calculated (G3) HOMO-energy of corresponding X-substituted butene [left *y*-axis: E^{HOMO} (**IV**) = –3.732($\Delta G°$) –982.9 (R^2 = 0.885)] and calculated (B3LYP/6-31+G**) Winstein-Holness parameter *A* for X-substituted cyclohexanes [right y-axis: *A* = 0.500($\Delta G°$) + 4.235 (R^2 = 0.939); cf. Table 11 and the *Supplementary data*].



polar effect dominates	*borderline case*	*steric effect dominates*
X = F, OH, OCH_3, OBz	Cl	NHAc, NHBz, NPHT, SBz

Scheme 5. Synopsis of substituent effects controlling 2,3-cis-selectivity in 4-pentenoxy radical cyclization

4. Concluding Remarks

Stark elektronenziehende Allyl-Subsituenten von geringem sterischen Anspruch, beispielsweise Fluor und Hydroxy, begünstigen 2,3-cis-selektive Tetrahydrofuran-Synthesen durch intramolekulare Alkenoxylradikal-Cyclisierung. Mit sinkender Akzeptorwirkung tritt der 2,3-cis-begünstigende Einfluss des Allyl-Substituenten in den Hintergrund. Akzeptor-substituierte Amine und Thiole treten daher als 2,3-trans-steuerende Allyl-Substituenten in 4-Pentenoxylradikal-5-*exo*-Cyclisierungen in Erscheinung, deren Wirkung auf einen dominierenden sterischen Einfluss schließen lässt.

Beim Übergang von elektrophilen Radikalen zu nukleophilen sollte der 2,3-cis-steuerende polare Einfluss nicht wirksam sein. Aminyl-Radikale sind Grenzfälle.[48,49] Da für Sauerstoffradikale 2,3-cis-Selektivität mit Fluor und monovalenten Sauerstoff-Gruppen auf die stärksten Akzeptoren begrenzt ist, gehen wir davon aus, dass für Aminyl-Radikale der cis-Effekt eines Allyl-Substituenten eher klein ist, für Aminyl-Radikalkationen hingegen signifikant sein sollte.[50]

Dem mechanistischen Modell liegt als auslösender Effekt eine Donor-Akzeptor-Wechselwirkung zwischen σ^*(C,X)-Orbital des Allyl-Subsituenten und π(C,C)-Orbital der Alken-Teilstruktur zugrunde. Die resultierende Stabilisierung des π(C,C)-Orbitals tritt besonders deutlich bei antiklinaler Konformation der wechselwirkenden Einheiten auf und wirkt selektivitätskontrollierend, da Sauerstoffradikale gegenüber terminalen Alkene elektrophile Reaktivität besitzen. In Elektrophil-induzierten polaren Cyclisierungen sollten die Allyl-Substituenten X dieser Studie nicht in analoger Reihung und Wirkung

selektivitätssteuernd in Erscheinung treten.[51] Einen ausgewählten Satz Allyl-substituierter 4-Pentenole planen wir auf diagnostische Weise Oxidationen zu unterwerfen, um aus resultierenden Selektivitäten eine vereinheitlichende mechanistische Interpretation zur 2,3-cis-selektiven Tetrahydrofuran-Synthesen in ionischen Reaktionen zu erreichen.

Experimental

1. General

For general laboratory practice and instrumentation see ref.[10] and the ESI.

4.2 3-Alkenoxythiazole-2(3*H*)-thiones

4.2.1 3-(3-Trifluoroacetyloxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1d). A solution of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (174 mg, 0.75 mmol) in dry dichloromethane (1 mL) was treated with 1,4-diazabicyclo[2.2.2]octane (168 mg, 1.50 mmol) at room temperature. The reaction mixture was cooled to 0 °C and trifluoroacetic anhydride (235 mg, 0.16 mL, 1.12 mmol) was added. The resulting solution was stirred for 20 minutes at 0 °C and then was allowed to warm to room temperature. The reaction mixture was stirred 16.5 hours at 22 °C in the dark and afterwards diethyl ether (10 mL) and aqueous hydrochloric acid (2 M, 10 mL) were added. The resulting layers were separated and the organic layer was washed with an aqueous saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL). Combined aqueous washings were extracted with diethyl ether (1 × 10 mL). The organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C). The resulting residue was purified by chromatography (SiO_2, diethyl ether). Yield: 221 mg (0.67 mmol, 90%), yellow oil. R_f = 0.53 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (d, 3 H, J = 1.1 Hz), 2.28−2.34 (m, 2 H), 4.41−4.53 (m, 2 H), 5.39 (d, 1 H, J = 10.4 Hz), 5.48 (d, 1 H, J = 17.2 Hz), 5.71−5.76 (m, 1 H), 5.85−5.93 (m, 1 H), 6.17 (d, 1 H, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 32.3, 71.1, 75.8, 102.8, 114.6 (q, $^1J_{C,F}$ = 268 Hz), 120.4, 133.1, 137.3, 156.5 (q, $^2J_{C,F}$ = 42.0 Hz), 180.4. Anal. Calcd. for $C_{11}H_{12}F_3NO_3S_2$ (327.34): C, 40.36; H, 3.69; N, 4.28; S, 19.59; found: C, 40.35; H, 3.67; N, 4.30; S, 19.37.

4.2.2 3-(3-Methoxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1g). In an atmosphere of dry nitrogen, a suspension of sodium hydride (120 mg, 60% dispersion in mineral oil) in dry tetrahydrofuran (10 mL) was cooled to 0 °C and treated with a solution of

3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (347 mg, 1.50 mmol) in dry tetrahydrofuran (15.5 mL). The reaction mixture was stirred for 5 minutes at this temperature and afterwards methyl *p*-toluenesulfonate (1.40 g, 7.5 mmol) in dry tetrahydrofuran (3 mL) was added. The suspension was allowed to warm to room temperature and was stirred for 21 hours at this temperature in the dark. An aqueous saturated solution of NH_4Cl (10 mL) was added and the resulting mixture was extracted with diethyl ether (3 × 50 mL). Combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (600−300 mbar, 40 °C) to afford a residue, which was purified by chromatography [SiO_2, diethyl ether/pentane = 1:1 (*v*/*v*)]. Yield: 315 mg (1.28 mmol, 85%), pale yellow oil. R_f = 0.28 [diethyl ether/pentane = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96−2.10 (m, 2 H), 2.28 (d, 3 H, J = 1.1 Hz), 3.30 (s, 3 H), 3.87 (td, 1 H, J_t = 7.8 Hz, J_d = 5.2 Hz), 4.48 (t, 2 H, J = 6.3 Hz), 5.25−5.32 (m, 2 H), 5.69 (ddd, 1 H, J = 17.4, 10.1, 7.8 Hz), 6.15 (d, 1 H, J = 1.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 33.8, 56.2, 72.6, 78.8, 102.7, 118.2, 137.7, 180.4. Anal. Calcd. for $C_{10}H_{15}NO_2S_2$ (245.36): C, 48.95; H, 6.16; N, 5.71; S, 26.14; found: C, 49.11; H, 6.29; N, 5.58; S, 26.03.

4.2.3 3-(3-Fluoropent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1h). In an atmosphere of dry nitrogen 3-hydroxy-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (99.2 mg, 0.35 mmol) and a 81/19-mixture of 3-fluoropent-4-enyl *p*-toluenesulfonate and 5-fluoropent-3-enyl *p*-toluenesulfonate (**6**) (86.0 mg, 0.33 mmol) were dissolved in anhydrous dimethylformamide (720 µL). The resulting solution was stirred at 35 °C (oil bath) for 5 hours. The reactions mixture was cooled to 22 °C and stirred for 19 hours. Afterwards water (5 mL) was added to the solution. After stirring the solution for 5 minutes, the layers were separated and the aqueous layer was extracted with diethyl ether (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure (200 mbar, 40 °C). *3-(3-Fluoropent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1h**)* [Yield: 39.6 mg (0.17 mmol, 52%)] and *3-(5-fluoropent-3-en-1-oxy)-4-methylthiazole-2(3H)-thione iso-(**1h**)* [Yield: 21.0 mg (0.09 mmol, 27%)], yellow liquid. *3-(3-Fluoropent-4-en-1-oxy)-4-methylthiazole-2(3H)-thione (**1h**)*. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06–2.22 (m, 2 H), 2.28 (s, 1 H), 4.34–4.49 (m, 1 H), 4.56–4.65 (m, 1 H), 5.12–5.30 (m, 1 H), 5.24–5.43 (m, 2 H), 6.18 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 33.7 (d, $^2J_{C,F}$ = 22.0 Hz), 71.5 (d, $^3J_{C,F}$ = 4.40 Hz), 89.0 (d, $^1J_{C,F}$ = 168.7 Hz), 102.8, 117.8 (d, $^3J_{C,F}$ = 12.5 Hz), 135.6 (d, $^2J_{C,F}$ = 19.0 Hz), 137.6. ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ –182.0. *3-(5-fluoropent-3-en-1-oxy)-4-*

*methylthiazole-2(3H)-thione iso-(**1h**)*. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3 H), 2.54–2.54 (m, 2 H), 4.46–4.37 (m, 2 H), 4.78 (dd, 2 H, J = 47.0, 4.2 Hz), 5.80–5.96 (m, 2 H), 6.18 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 30.6 (d, $^{4}J_{C,F}$ = 2.2 Hz), 74.6 (d, $^{5}J_{C,F}$ = 2.9 Hz), 82.9 (d, $^{1}J_{C,F}$ = 162.1 Hz), 102.7, 128.0 (d, $^{2}J_{C,F}$ = 16.9 Hz), 130.1 (d, $^{3}J_{C,F}$ = 11.7 Hz), 137.7, 180.2.^{19}F NMR ($C_6H_5CF_3$, 376.5 MHz) δ –212.3. From a 81/19-mixture of **1h** and *iso*-**1h**: Anal. Calcd. for $C_9H_{12}FNOS_2$ (233.03): C, 46.33; H, 5.18; N, 6.00; S, 27.49; found: C, 46.52; H, 5.19; N, 6.01; S, 27.46.

4.2.4 3-(3-Chloropent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1i). To a solution of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (694 mg, 3.00 mmol) in tetrachloromethane/dichloromethane [8 mL, 5:3 (*v*/*v*)] was added triphenylphosphine (1.02 g, 3.9 mmol). The solution was stirred 2 days and 21.5 hours at 22 °C in the dark. Afterwards the solution was stirred at 45 °C (oil bath temperature) for 3 hours and then was allowed to cool to room temperature. The mixture was stirred for additional 30 minutes at room temperature. The solvent was removed under reduced pressure (600−250 mbar, 40 °C) to afford a residue that was purified by chromatography (SiO_2, diethyl ether). Yield: 620 mg (2.48 mmol, 83%), yellow oil. R_f = 0.60 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17−2.56 (m, 2 H), 2.32 (d, 3 H, J = 1.3 Hz), 2.41−2.50 (m, 1 H), 4.46 (td, 1 H, J_t = 8.3 Hz, J_d = 4.6 Hz), 4.66−4.75 (m, 2 H), 5.23 (dt, 1 H, J_d = 10.2 Hz, J_t = 0.7 Hz), 5.39 (dt, 1 H, J_d = 16.9 Hz, J_t = 0.9 Hz), 5.96 (ddd, 1 H, J = 16.9, 10.2, 7.8 Hz), 6.17 (q, 1 H, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 36.2, 58.7, 72.4, 102.8, 117.5, 137.5, 137.6, 180.4. Anal. Calcd. for $C_9H_{12}ClNOS_2$ (249.78): C, 43.28; H, 4.84; N, 5.61; S, 25.67; found: C, 43.38; H, 4.99; N, 5.60; S, 25.59.

4.2.5 3-(3-Trifluoroacetamidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1j). A solution of 3-(3-aminopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1o**) (173 mg, 0.75 mmol) in dry dichloromethane (1.5 mL) was treated with 1,4-diazabicyclo[2.2.2]octane (168 mg, 1.50 mmol) and cooled to 0 °C. Afterwards trifluoroacetic anhydride (237 mg, 0.16 mL, 1.13 mmol) was added in a dropwise manner and the reaction mixture was stirred for 15 minutes at 0 °C. The solution was allowed to warm to room temperature and stirred for 23.5 hours in the dark. Dichloromethane (10 mL) and aqueous hydrochloric acid (2 M, 10 mL) were added and the resulting layers were separated. The aqueous layer was extracted with dichloromethane (2 × 10 mL). Combined organic extracts were washed with an aqueous

saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (600 mbar, 40 °C) to leave a residue that was purified by chromatography [SiO_2, diethyl ether/pentane = 2:1 (*v*/*v*)]. Yield: 164 mg (0.50 mmol, 67%), pale yellow solid, mp 90–92 °C (dec.). R_f = 0.16 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09−2.17 (m, 1 H), 2.24−2.32 (m, 1 H), 2.29 (d, 3 H, J = 1.1 Hz), 4.31−4.36 (m, 1 H), 4.60 (td, 1 H, J_t = 8.7 Hz, J_d = 2.5 Hz), 4.85−4.91 (m, 1 H), 5.28 (dd, 1 H, J = 10.4, 0.8 Hz), 5.33 (dd, 1 H, J = 17.2, 1.0 Hz), 6.02 (ddd, 1 H, J = 17.0, 10.6, 5.9 Hz), 6.22 (d, 1 H, J = 1.3 Hz), 8.14 (d, 1 H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 31.7, 50.1, 72.8, 103.4, 115.9 (q, $^1J_{C,F}$ = 285 Hz), 117.6, 135.1, 137.4, 156.9 (q, $^2J_{C,F}$ = 37.2 Hz), 180.5. Anal. Calcd. for $C_{11}H_{13}F_3N_2O_2S_2$ (326.36): C, 40.48; H, 4.01; N, 8.58; S, 19.65; found: C, 40.42; H, 4.12; N, 8.53; S, 19.57.

4.2.6 3-(3-Benzenesulfonamidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1k). In an atmosphere of dry nitrogen, a solution of 3-(3-aminopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1o**) (404 mg, 1.75 mmol) in dichloromethane (8 mL) was treated with triethylamine (354 mg, 0.49 mL, 3.50 mmol). Benzenesulfonyl chloride (371 mg, 0.27 mL, 2.10 mmol) dissolved in dichloromethane (10 mL) was added in a dropwise manner at room temperature. The resulting solution was stirred for 24 hours in the dark at 22 °C. The reaction mixture was washed with an aqueous saturated solution of $NaHCO_3$ (5 mL) and brine (2 × 10 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure (600 mbar, 40 °C) and the resulting oil was purified by chromatography [SiO_2, diethyl ether/pentane = 10:2 (*v*/*v*)]. Yield: 435 mg (1.17 mmol, 67%), yellow resin. R_f = 0.16 [diethyl ether/pentane = 10:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93−2.01 (m, 1 H), 2.13−2.21 (m, 1 H), 2.28 (d, 3 H, J = 1.3 Hz), 4.15−4.22 (m, 1 H), 4.35−4.39 (m, 1 H), 4.48 (td, 1 H, J_t = 8.1 Hz, J_d = 3.8 Hz), 4.95–4.98 (m, 1 H), 5.00–5.06 (m, 1 H), 5.71 (ddd, 1 H, J = 17.1, 10.5, 6.5 Hz), 6.04 (d, 1 H, J = 8.9 Hz), 6.19 (q, 1 H, J = 1.3 Hz), 7.45−7.56 (m, 3 H), 7.86−7.89 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 33.6, 53.9, 72.8, 103.2, 116.8, 127.2, 128.9, 132.4, 136.5, 137.7, 141.1, 180.4. Anal. Calcd. for $C_{15}H_{18}N_2O_3S_3$ (370.51): C, 48.63; H, 4.90; N, 7.56; S, 25.96; found: C, 48.72; H, 5.14; N, 7.40; S, 26.06.

4.2.7 3-(3-Benzamidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1l). A solution of 3-(3-aminopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1o**) (314 mg, 1.36 mmol) in dichloromethane (24 mL) was treated with aqueous sodium hydroxide (2 M, 24 mL). The

reaction mixture was cooled to 0 °C and then benzoylchloride (382 mg, 0.32 mL, 2.72 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 20 hours and 45 minutes in the dark. Water (12 mL) was added and the resulting layers were separated. The organic layer was washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure (600 mbar, 40 °C) to afford a residue, which was purified by chromatography (SiO_2, diethyl ether). Yield: 376 mg (1.12 mmol, 82%), pale yellow oil. R_f = 0.16 (diethyl ether). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14−2.21 (m, 1 H), 2.27 (d, 3 H, J = 1.3 Hz), 2.29−2.37 (m, 1 H), 4.37−4.42 (m, 1 H), 4.63 (td, 1 H, J_t = 8.3 Hz, J_d = 3.3 Hz), 5.04−5.11 (m, 1 H), 5.21–5.25 (m, 1 H), 5.32–5.37 (m, 1 H), 6.09 (ddd, 1 H, J = 17.2, 10.4, 5.6 Hz), 6.19 (q, 1 H, J = 1.1 Hz), 7.40−7.50 (m, 3 H), 7.53 (d, 1 H, J = 8.6 Hz), 7.91−7.94 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3, 32.3, 49.6, 73.5, 103.2, 116.2, 127.4, 128.4, 131.4, 134.2, 137.2, 137.6, 166.9, 180.3. Anal. Calcd. for $C_{16}H_{18}N_2O_3S_2$ (334.46): C, 57.46; H, 5.42; N, 8.38; S, 19.17; found: C, 57.32; H, 5.54; N, 8.16; S, 18.88.

4.2.8 3-(2-Phthalimidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1m). In an atmosphere of dry nitrogen, a solution of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (694 mg, 3.00 mmol) in dry tetrahydrofuran (15 mL) was treated with triphenylphosphine (866 mg, 3.30 mmol) and phthalimide (486 mg, 3.30 mmol). The reaction mixture was cooled to 0 °C and stirred for 10 minutes. Afterwards a solution of diisopropyl azodicarboxylate (667 mg, 0.65 mL, 3.30 mmol) in dry tetrahydrofuran (8 mL) was added in a dropwise manner. The resulting solution was stirred for 5 minutes at 0 °C, then was allowed to warm to room temperature and stirred for 4 hours at this temperature in the dark. The solvent was removed under reduced pressure (300 mbar, 40 °C) and the resulting residue was purified by chromatography [SiO_2, diethyl ether/pentane = 2:1 (*v*/*v*)]. Yield: 852 mg (2.36 mmol, 79%), pale yellow solid, mp 110–111 °C (dec.). R_f = 0.27 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (d, 3 H, J = 0.8 Hz), 2.48−2.57 (m, 1 H), 2.67−2.76 (m, 1 H), 4.39−4.48 (m, 2 H), 5.03−5.09 (m, 1 H), 5.25 (d, 1 H, J = 10.1 Hz), 5.34 (d, 1 H, J = 17.2 Hz), 6.11 (d, 1 H, J = 1.2 Hz), 6.20 (ddd, 1 H, J = 17.3, 10.0, 7.4 Hz), 7.70−7.74 (m, 2 H), 7.82−7.86 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 30.3, 50.5, 72.6, 102.5, 118.5, 123.3, 131.9, 134.1, 134.7, 137.6, 168.0, 180.3. Anal. Calcd. for $C_{17}H_{16}N_2O_3S_2$ (360.45): C, 56.65; H, 4.47; N, 7.77; S, 17.79; found: C, 56.52; H, 4.55; N, 7.81; S, 17.95.

4.2.9 3-[3-(Benzoylthio)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (1n). In an atmosphere of dry nitrogen, a solution of 3-(3-hydroxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1a**) (695 mg, 3.00 mmol) in dry tetrahydrofuran (16.5 mL) was treated with triphenylphosphine (866 mg, 3.30 mmol) and thiobenzoic acid (456 mg, 0.40 mL, 3.30 mmol). The reaction mixture was cooled to 0 °C and a solution of diisopropyl azodicarboxylate (667 mg, 0.65 mL, 3.30 mmol) in dry tetrahydrofuran (8.5 mL) was added. The solution was stirred for 5 minutes at 0 °C, then was allowed to warm to room temperature and stirred for 5 hours and 15 minutes in the dark. Afterwards diethyl ether (20 mL) was added and the reaction mixture was washed with aqueous sodium hydroxide (2 M, 2 × 15 mL) and brine (15 mL). Impurities of triphenylphosphine and diisopropyl azodicarboxylate reaction by-products were crystallized from ethyl acetate/hexane in the refrigerator. The solvent from the resulting solution was removed under reduced pressure (400 mbar, 40 °C) to leave a residue, which was purified by chromatography [SiO_2, dichloromethane/pentane = 1:1 (*v*/*v*) → 2:1 (*v*/*v*)]. Yield: 260 mg (0.74 mmol, 25%, conversion of the reaction 60%), yellow oil. R_f = 0.25 [dichloromethane/pentane = 2:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (d, 3 H, J = 1.3 Hz), 2.28−2.44 (m, 2 H), 4.47−4.59 (m, 3 H), 5.20 (dt, 1 H, J_d = 10.2 Hz, J_t = 1.0 Hz), 5.41 (dt, 1 H, J_d = 16.9 Hz, J_t = 1.0 Hz), 5.95 (ddd, 1 H, J = 17.0, 10.2, 8.0 Hz), 6.14 (q, 1 H, J = 1.3 Hz), 7.43−7.48 (m, 2 H), 7.56−7.60 (m, 1 H), 7.93−7.96 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.5, 32.1, 42.9, 73.4, 102.6, 117.3, 127.3, 128.7, 133.6, 136.7, 136.8, 137.6, 180.4, 190.4. Anal. Calcd. for $C_{16}H_{17}NO_2S_3$ (351.51): C, 54.67; H, 4.87; N, 3.98; S, 27.37; found: C, 54.71; H, 5.07; N, 3.93; S, 27.33.

4.2.10 3-(3-Aminopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1o). A solution of 3-(3-phthalimidoylpent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (**1m**) (867 mg, 2.41 mmol) dissolved in ethanol/chloroform [28 mL, 1:1 (*v*/*v*)] was treated with hydrazine hydrate (604 mg, 0.59 mL, 12.05 mmol). The reaction mixture was stirred for 17 hours at room temperature in the dark, while solids were precipitated. The solids were filtered off and washed with chloroform (30 mL). The solvent was removed under reduced pressure (450−150 mbar, 40 °C) to afford an oil, which was purified by chromatography [SiO_2, ethyl acetate/methanol = 10:1 (*v*/*v*) and 6 mL triethylamine/300 mL eluent]. Yield: 387 mg (1.68 mmol, 70%), yellow oil. R_f = 0.18 [ethyl acetate/methanol = 10:1 (*v*/*v*) and 6 mL triethylamine/300 mL eluent]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78−1.87 (m, 1 H), 1.96−2.05 (m, 1 H), 2.29 (d, 3 H, J = 1.3 Hz), 3.66−3.71 (m, 1 H), 4.40−4.44 (m, 1 H), 4.52−4.57 (m, 1 H), 5.07 (dt, 1 H, J_d = 10.4 Hz, J_t = 1.2 Hz), 5.20 (dt, 1 H, J_d = 17.2 Hz, J_t = 1.3 Hz), 5.87

(ddd, 1 H, J = 17.1, 10.4, 6.7 Hz), 6.16 (d, 1 H, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.4, 35.5, 51.0, 73.5, 102.8, 114.2, 137.7, 142.4, 180.3. Anal. Calcd. for $C_9H_{14}N_2OS_2$ (230.35): C, 46.93; H, 6.13; N, 12.16; S, 27.84; found: C, 46.68; H, 6.30; N, 12.28; S, 27.62.

4.3 Radical Bromocyclizations

4.3.1 General method for thermally initiated radical reactions. Azobisisobutyronitrile (AIBN) (0.25 equiv.) was added to a solution of *N*-(alkenoxy)-4-methylthiazole-2(3*H*)-thione **1d–n** (1 equiv.) in benzene (5.4–5.6 mL/mmol MTTOR) and bromotrichloromethane (8 equiv.). The mixture is heated under reflux for 2 hours. The solution is allowed to cool to 22 °C and concentrated under reduced pressure (200 mbar, 40 °C). The residual oil is purified by chromatography using silica gel (SiO_2) as stationary phase.

4.3.2 Conversion of 3-(3-trifluoroacetyloxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1d). Reactants: MTTOR **1d** (371 mg, 1.13 mmol), bromotrichloromethane (1.80 g, 0.89 mL, 9.07 mmol), and AIBN (47.0 mg, 0.28 mmol) in benzene (6.3 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:2 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**4**)*. Yield: 201 mg (0.81 mmol, 72%), orange oil. R_f = 0.57 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (d, 3 H, J = 0.8 Hz), 7.31 (d, 1 H, J = 0.9 Hz).[52] *rel*-(2*S*,3*S*)-*2-Bromomethyl-3-trifluoroacetyloxytetrahydrofuran trans-(**2d**)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 13.7 mg (49.6 µmol, 4%)] and *3-Bromo-4-trifluoroacetyloxytetrahydropyran (**3d**, isomer 1)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 8.4 mg (30.4 µmol, 2%)], yellow oil. R_f = 0.56 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *rel*-(2*R*,3*R*)-*2-Bromomethyl-3-trifluoroacetyloxytetrahydrofuran trans-(**2d**)*. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.10−2.15 (m, 1 H), 2.34−2.41 (m, 1 H), 3.44−3.61 (m, 2 H), 3.93−4.08 (m, 1 H), 4.15−4.22 (m, 2 H), 5.37 (dt, 1 H, J_d = 6.5 Hz, J_t = 1.8 Hz). *Assignable shifts*: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.7, 81.5, 82.6. Retention time (t_r) = 11.04 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 183 (100), 164 (12), 162 (13), 123 (5), 85 (5), 83 (5), 69 (67), 55 (11). HRMS (EI$^+$) *m*/*z* 183.0266 [M^+–CH_2Br]; calculated mass for $C_6H_6O_3F_3^+$: 183.0269. *3-Bromo-4-trifluoroacetyloxytetrahydropyran (**3d**, isomer 1)*. *Assignable shifts*: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.22–2.28 (m, 1 H), 5.17 (td, 1 H, J_t = 9.9 Hz, J_d = 4.9 Hz). t_r = 10.88 minutes: MS (EI) *m*/*z* 167 (4), 157 (9), 139 (10), 134 (12), 132 (12), 127 (10), 122 (10), 108 (11),

106 (11), 101 (9), 83 (100), 73 (31), 69 (34), 53 (39). HRMS (EI^+) *m*/*z* 197.0430 [M^+–Br]; calculated mass for $C_7H_8O_3F_3^+$: 197.0426. *rel*-(2*R*,3*S*)-*2-Bromomethyl-3-trifluoroacetyloxytetra-hydrofuran cis-(**2d**)*. Yield (determined versus pentachlorobenzene as internal NMR-standard): 29.4 mg (106 µmol, 9%), yellow oil. R_f = 0.42 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.15 (dddd, 1 H, J = 14.4, 7.1, 4.2, 1.4 Hz), 2.38–2.47 (m, 1 H), 3.39–3.54 (m, 2 H), 3.99 (td, 1 H, J_t = 8.7 Hz, J_d = 4.3 Hz), 4.11 (td, 1 H, J_t = 8.7 Hz, J_d = 7.3 Hz), 4.20 (ddd, 1 H, J = 8.6, 6.0, 3.6 Hz), 5.63 (ddd, 1 H, J = 5.2, 3.8, 1.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8, 33.2, 67.1, 77.9, 80.8, 114.4 (q, $^1J_{C,F}$ = 284 Hz), 156.6 (q, $^2J_{C,F}$ = 42 Hz). t_r = 11.12 minutes: MS (EI) *m*/*z* 235 (0.5), 227 (0.5), 183 (100), 163 (11), 162 (12), 123 (12), 85 (12), 69 (65), 57 (15). HRMS (EI^+) *m*/*z* 183.0266 [M^+–CH_2Br]; calculated mass for $C_6H_6O_3F_3^+$: 183.0269. *3-Bromo-4-trifluoroacetyloxytetrahydropyran (**3d**, isomer 2)*. Yield: 3.1 mg (11.2 µmol, 1%), yellow oil. R_f = 0.35 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *Assignable shifts*: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.97–4.03 (m, 1 H), 4.05–4.11 (m, 1 H), 4.29–4.33 (m, 1 H), 4.49 (ddd, 1 H, J = 5.1, 3.5, 1.4 Hz), 5.37 (dt, 1 H, J_d = 5.8 Hz, J_t = 3.1 Hz). t_r = 11.31 minutes: MS (EI) *m*/*z* 227 (1), 196 (4), 167 (6), 157 (12), 139 (17), 134 (15), 132 (16), 127 (12), 83 (100), 69 (66), 53 (40). HRMS (EI^+) *m*/*z* 197.0437 [M^+–Br]; calculated mass for $C_6H_6O_3F_3^+$: 197.0426.

4.3.3 Conversion of 3-(3-methoxypent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1g). Reactants: MTTOR **1g** (308 mg, 1.25 mmol), bromotrichloromethane (1.99 g, 0.99 mL, 10.0 mmol), and AIBN (51.0 mg, 0.31 mmol) in benzene (7 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:2 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**4**)*. Yield: 258 mg (1.04 mmol, 83%), orange oil. R_f = 0.51 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.56 (d, 3 H, J = 0.9 Hz), 7.30 (d, 1 H, J = 0.9 Hz).[52] *2-Bromomethyl-3-methoxytetrahydrofuran (**2g**)* [Yield: 150 mg (0.77 mmol, 62%, *cis*/*trans* = 58:42)] and *3-Bromo-4-methoxytetrahydropyran (**3g**, isomer 1)* [Yield: 21.5 mg (0.11 mmol, 9%)], orange oil. R_f = 0.35 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *cis*-**2g**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.94−2.04 (m, 1 H), 2.07−2.13 (m, 1 H), 3.34 (s, 3 H), 3.40−3.42 (m, 1 H), 3.54 (ddd, 1 H, J = 9.9, 7.2, 1.0 Hz), 3.88−3.95 (m, 2 H), 3.97−4.00 (m, 1 H), 4.01−4.06 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.6, 31.2, 57.2, 66.9, 80.4, 82.0. Retention time (t_r) = 11.42 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 196/294 [M^+] (0.4), 165 (0.4) 151/149 (0.9), 123/121 (4), 115 (21), 83 (100), 71 (39), 57 (32). HRMS (EI^+) *m*/*z*

195.9934/193.9913 [M^+]; calculated mass for $C_6H_{11}O_2Br^+$: 195.9922/193.9942; *m/z* 115.0765 [M^+−Br]; calculated mass for $C_6H_{11}O_2^+$: 115.0759; *m/z* 101.0609 [M^+−CH_2Br]; calculated mass for $C_5H_9O_2^+$: 101.0603. *trans*-**2g**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.95−2.05 (m, 2 H), 3.30−3.33 (m, 1 H), 3.35 (s, 3 H), 3.41−3.44 (m, 1 H), 3.85−3.88 (m, 1 H), 3.89−3.94 (m, 1 H), 4.01 (dd, 1 H, *J* = 8.0, 3.6 Hz), 4.03−4.07 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.7, 33.2, 56.9, 67.8, 82.8, 83.9. t_r = 11.34 minutes: MS (EI) *m/z* 165 (0.5), 151 (0.5), 123/121 (4), 115 (20), 83 (100), 71 (38), 57 (28). HRMS (EI^+) *m/z* 195.9930/193.9945 [M^+]; calculated mass for $C_6H_{11}O_2Br^+$: 195.9922/193.9942; *m/z* 115.0766 [M^+−Br]; calculated mass for $C_6H_{11}O_2^+$: 115.0759; *m/z* 101.0608 [M^+−CH_2Br]; calculated mass for $C_5H_9O_2^+$: 101.0603. (**3g**, *isomer 1*): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.57−1.66 (m, 1 H), 2.20−2.26 (m, 1 H), 3.45 (s, 3 H), 3.47−3.49 (m, 1 H), 3.50−3.52 (m, 1 H), 3.85−3.95 (m, 2 H), 4.03−4.07 (m, 1 H), 4.11 (ddd, 1 H, *J* = 11.8, 4.5, 0.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.5, 50.1, 56.9, 66.0, 71.1, 80.8. t_r = 11.27 minutes: MS (EI) *m/z* 195/193 (2), 165/163 (6), 138/136 (15), 121 (3), 108/106 (12/13), 83 (100), 71 (18), 58 (57). HRMS (EI^+) *m/z* 195.9934/193.9950 [M^+]; calculated mass for $C_6H_{11}O_2Br^+$: 195.9922/193.9942; *m/z* 164.9745/162.9763 [M^+−OCH_3]; calculated mass for $C_5H_8O_1Br^+$: 164.9738/162.9759; *m/z* 115.0756 [M^+−Br]; calculated mass for $C_6H_{11}O_2^+$: 115.0759. *3-Bromo-4-methoxytetrahydropyran (**3g**, isomer 2)*. Yield (determined versus pentachlorobenzene as internal NMR-standard): 3.7 mg (19 µmol, 1.5%), orange oil. R_f = 0.27 [diethyl ether/pentane = 1:2 (*v/v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.77−1.83 (m, 1 H), 2.01−2.10 (m, 1 H), 3.42 (s, 3 H), 3.43−3.45 (m, 1 H), 3.55 (ddd, 1 H, *J* = 11.6, 7.9, 3.5 Hz), 3.77 (dd, 1 H, *J* = 12.2, 3.0 Hz), 3.89−3.95 (m, 1 H), 4.02 (dd, 1 H, *J* = 12.2, 6.1 Hz), 4.30−4.33 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.0, 51.2, 56.2, 64.6, 69.5, 76.2. t_r = 11.71 minutes: MS (EI) *m/z* 195/193 (1), 165/163 (4), 138/136 (11), 121 (2), 108/106 (11), 83 (100), 71 (16), 58 (54). HRMS (EI^+) *m/z* 195.9933/193.9946 [M^+]; calculated mass for $C_6H_{11}O_2Br^+$: 195.9922/193.9942; *m/z* 164.9748/162.9762 [M^+−OCH_3]; calculated mass for $C_5H_8O_1Br^+$: 164.9738/162.9759; *m/z* 115.0758 [M^+−Br]; calculated mass for $C_6H_{11}O_2^+$: 115.0759.

4.3.4 3-(3-Fluoropent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1h).

Azobisisobutyronitrile (ABIN) (0.31 mg, 1.84 µmol) was added to a solution of 3-(3-fluoropent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione **1h** as a mixture of **1h**:*iso*-**1h** (1.71 mg, 7.35 µmol) in perdeuterobenzene (90 µL) and bromotrichloromethane (14.6 mg, 73.5 µmol). The mixture was heated to reflux for 1 hour. Afterwards bromotrichloromethane (14.6 mg,

73.5 µmol) in perdeuterobenzene (90 µL) and AIBN (0.31 mg, 1.84 µmol) was added to the solution which then was stirred under reflux for 1 hour. The solution was cooled to 22 °C and directly investigated via NMR spectroscopy. The ratio of the cis/trans-isomers of 2-bromomethyl-3-fluorotetrahydrofuran (*cis*:*trans* = 81:19) was determined via ^{19}F-NMR using fluorophenol as internal standard.

4.3.5 Conversion of 3-(3-Chloropent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1i). Reactants: MTTOR **1i** (346 mg, 1.38 mmol), bromotrichloromethane (2.19 g, 1.09 mL, 11.0 mmol), and AIBN (57.0 mg, 0.35 mmol) in benzene (7.6 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:3 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**4**)*. Yield: 186 mg (0.75 mmol, 54%), yellow oil. R_f = 0.38 [diethyl ether/pentane = 1:3 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.57 (d, 3 H, J = 0.8 Hz), 7.31 (d, 1 H, J = 1.0 Hz). *2-Bromomethyl-3-chlorotetrahydrofuran (**2i**)*. Yield (determined versus *p*-bromobenzaldehyde as internal NMR-standard): 101 mg (506 µmol, 37%, *cis*/*trans* = 47:53), yellow oil. R_f = 0.38 [diethyl ether/pentane = 1:3 (*v*/*v*)]. *trans*-**2i**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.19 (ddt, 1 H, J_d = 13.4, 6.5 Hz, J_t = 4.3 Hz), 2.41–2.55 (m, 1 H), 3.42–3.50 (m, 2 H), 4.02–4.11 (m, 2 H), 4.16–4.22 (m, 1 H), 4.28 (dt, 1 H, J_d = 7.0 Hz, J_t = 4.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.5, 36.1, 58.5, 67.4, 85.6. Retention time (t_r) = 11.56 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 200/198 (1/0.9), 123 (5), 107/105 (34/100), 78/76 (9/29), 53 (7). HRMS (EI$^+$) *m*/*z* 201.9422/199.9418/197.9447 [M$^+$]; calculated mass for $C_5H_8OClBr^+$: 201.9397/199.9418/197.9447. *cis*-**2i**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.30–2.36 (m, 1 H), 2.41–2.55 (m, 1 H), 3.51–3.54 (m, 2 H), 4.02–4.11 (m, 1 H), 4.16–4.22 (m, 2 H), 4.60–4.62 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.2, 36.8, 60.8, 67.0, 82.0. t_r = 12.10 minutes: MS (EI) *m*/*z* 200/198 (1/0.9), 123 (3), 107/105 (33/100), 78/76 (5/14), 53 (6). HRMS (EI$^+$) *m*/*z* 199.9432/197.9457 [M$^+$]; calculated mass for $C_5H_8OClBr^+$: 199.9418/197.9447.

4.3.6 Conversion of 3-(3-trifluoroacetamidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1j). Reactants: MTTOR **1j** (418 mg, 1.28 mmol), bromotrichloromethane (2.03 g, 1.01 mL, 10.2 mmol), and AIBN (53.0 mg, 0.32 mmol) in benzene (7.1 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:2 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**4**)*. Yield: 228 mg (0.92 mmol, 72%), yellow oil. R_f = 0.55 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$,

400 MHz) δ 2.57 (d, 3 H, J = 1.0 Hz), 7.31 (q, 1 H, J = 1.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.3, 96.9, 122.5, 153.3, 155.8.[52] *rel*-(2*S*,3*S*)-*2-Bromomethyl-3-trifluoroacetamido-tetrahydrofuran trans-(**2j**)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 52.4 mg (190 µmol, 15%)] and *3-Bromo-4-trifluoroacetamidotetrahydropyran (**3j**)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 38.6 mg (140 µmol, 11%, *isomer 1*:*isomer 2* = 24:76)], yellow oil. R_f = 0.17 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *rel*-(2*S*,3*S*)-*2-Bromomethyl-3-trifluoroacetamidotetrahydrofuran trans*-(**2j**). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.95–2.01 (m, 1 H), 2.41–2.50 (m, 1 H), 3.46–3.55 (m, 2 H), 3.96–4.04 (m, 2 H), 4.07–4.12 (m, 1 H), 4.40–4.47 (m, 1 H), 6.48 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.3, 32.9, 54.2, 67.3, 82.7, 115.5 (q, $^1J_{C,F}$ = 285 Hz), 157.2 (q, $^2J_{C,F}$ = 37.2 Hz). Retention time (t_r) = 14.39 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 196 (12), 195 (10), 182 (14), 164 (10), 152 (7), 138 (5), 126 (9), 84 (29), 83 (100), 69 (41), 57 (16). HRMS (EI^+) *m*/*z* 196.0580 [M^+–Br]; calculated mass for $C_7H_9NO_2F_3^+$: 196.0585; *m*/*z* 182.0429 [M^+–CH_2Br]; calculated mass for $C_6H_7NO_2F_3^+$: 182.0429. *3-Bromo-4-trifluoroacetamidotetrahydropyran (**3j**)*: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.73–1.84 (m, 1 H), 2.20–2.25 (m, 1 H), 3.54–3.59 (m, 2 H), 3.84–3.92 (m, 1 H), 4.07–4.12 (m, 1 H), 4.15–4.23 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3/27.8, 48.0/48.7, 53.2/54.0, 66.66/66.75, 115.5 (q, $^1J_{C,F}$ = 285 Hz), 157.2 (q, $^2J_{C,F}$ = 37.2 Hz). *Isomer 1*: t_r = 13.80 minutes: MS (EI) *m*/*z* 277/275 (1/1), 196 (47), 178 (8), 152 (21), 139 (34), 138 (39), 126 (11), 114 (13), 108/106 (15/15), 83 (100), 69 (79), 53 (36). HRMS (EI^+) *m*/*z* 276.9739/274.9751 [M^+]; calculated mass for $C_7H_9NO_2BrF_3^+$: 276.9748/274.9769; *m*/*z* 196.0593 [M^+–Br]; calculated mass for $C_7H_9NO_2F_3^+$: 196.0585. *Isomer 2*: t_r = 13.91 minutes: MS (EI) *m*/*z* 277/275 (1/1), 196 (46), 178 (4), 152 (24), 139 (33), 138 (32), 126 (11), 114 (12), 108/106 (16/16), 83 (100), 69 (72), 53 (33). HRMS (EI^+) *m*/*z* 276.9733/274.9750 [M^+]; calculated mass for $C_7H_9NO_2BrF_3^+$: 276.9748/274.9769; *m*/*z* 196.0590 [M^+–Br]; calculated mass for $C_7H_9NO_2F_3^+$: 196.0585. *2-Bromomethyl-3-trifluoroacetamidotetrahydrofuran (**2j**)*. Yield (determined versus pentachlorobenzene as internal NMR-standard): 228 mg (563 µmol, 44%, *cis*/*trans* = 48:52), yellow oil. R_f = 0.10 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *cis*-**2j**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.94–2.07 (m, 1 H), 2.38–2.48 (m, 1 H), 3.35–3.39 (m, 1 H), 3.42–3.46 (m, 1 H), 3.86–3.90 (m, 1 H), 4.05–4.15 (m, 2 H), 4.71–4.78 (m, 1 H), 6.70 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 32.9, 51.9, 66.3, 79.3, 115.6 (q, $^1J_{C,F}$ = 285 Hz), 157.1 (q, $^2J_{C,F}$ = 37.2 Hz). t_r = 14.05 minutes: MS (EI) *m*/*z* 196 (6), 195 (6), 182 (4), 164 (4), 152 (6), 138 (4), 126 (4), 84 (24), 83 (100), 69 (35), 57 (15). HRMS (EI^+) *m*/*z* 276.9770/274.9773 [M^+]; calculated mass for $C_7H_9NO_2BrF_3^+$: 276.9748/274.9769. *trans*-**2j**: NMR data agreed with values from an

authentic sample. *3-trifluoroacetamidopent-4-en-1-ol*. Yield (determined versus pentachlorobenzene as internal NMR-standard): 29.4 mg (149 µmol, 12%), yellow oil. R_f = 0.10 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.70–1.79 (m, 1 H), 1.94–2.06 (m, 1 H), 3.80–3.84 (m, 2 H), 4.66–4.71 (m, 1 H), 5.21–5.27 (m, 2 H), 5.81 (ddd, 1 H, J = 17.2, 10.5, 5.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.0, 50.6, 59.2, 116.6, 135.1, 115.6 (q, $^1J_{C,F}$ = 285 Hz), 157.1 (q, $^2J_{C,F}$ = 37.2 Hz). t_r = 11.52 minutes: MS (EI) *m*/*z* 178 (2), 153 (21), 152 (100), 140 (11), 132 (11), 128 (8), 110 (22), 98 (12), 82 (26), 69 (64), 54 (33).

4.3.7 Conversion of 3-(3-benzenesulfonamidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1k). Reactants: MTTOR **1k** (356 mg, 0.96 mmol), bromotrichloromethane (1.52 g, 0.76 mL, 7.68 mmol), and AIBN (39.0 mg, 0.24 mmol) in benzene (5.2 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 10:1 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (4)*. Yield: 159 mg (0.63 mmol, 66%), orange oil. R_f = 0.71 [diethyl ether/pentane = 10:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (d, 3 H, *J* = 0.8 Hz), 7.31 (d, 1 H, *J* = 0.9 Hz).[52] *3-Bromo-4-benzenesulfonamidotetrahydropyran (**3k**)*. Yield (determined versus *p*-bromobenzaldehyde as internal NMR-standard): 23.8 mg (74.2 µmol, 8%, *isomer 1*:*isomer 2* = 44:56), yellow oil. R_f = 0.40 [diethyl ether/pentane = 10:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.52−1.56 (m, 1 H), 1.67−1.77 (m, 1 H), 2.01 (dtd, 1 H, J_d = 13.4, 4.5 Hz, J_t = 11.1 Hz), 2.24 (ddt, 1 H, J_d = 13.8, 4.6 Hz, J_t = 2.2 Hz), 3.27−3.35 (m, 1 H), 3.38−3.51 (m, 4 H), 3.69 (dd, 1 H, *J* = 13.1, 1.8 Hz), 3.74 (dt, 1 H, J_d = 4.6 Hz, J_t = 10.2 Hz), 3.89−4.01 (m, 3 H), 4.06−4.10 (m, 2 H), 5.06 (d, 1 H, *J* = 8.9 Hz), 5.13 (d, 1H, *J* = 6.0 Hz), 7.50−7.55 (m, 4 H), 7.57−7.63 (m, 2 H), 7.89−7.92 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.4, 35.5, 49.7, 52.2, 55.3, 57.3, 66.6, 66.7, 71.1, 71.9, 126.8, 127.3, 129.0, 129.3, 132.9, 133.0, 139.9, 140.9. *Isomer 1*: Retention time (t_r) = 24.84 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 321/319 (2), 240 (2), 196 (6), 180 (12), 158 (8), 141 (31), 98 (53), 77 (100), 70 (46), 51 (32). HRMS (EI^+) *m*/*z* 320.9837/318.9870 [M^+]; calculated mass for $C_{11}H_{14}NO_3SBr^+$: 320.9857/318.9878; *m*/*z* 240.0686 [M^+−Br]; calculated mass for $C_{11}H_{14}NO_3S^+$: 240.0694. *Isomer 2*: t_r = 24.96 minutes: MS (EI) *m*/*z* 321/319 (2), 240 (3), 196 (7), 180 (15), 141 (39), 98 (8), 77 (100), 51 (23). HRMS (EI^+) *m*/*z* 320.9862/318.9886 [M^+]; calculated mass for $C_{11}H_{14}NO_3SBr^+$: 320.9857/318.9878; *m*/*z* 240.0700 [M^+−Br]; calculated mass for $C_{11}H_{14}NO_3S^+$: 240.0694. *2-Bromomethyl-3-benzenesulfon-*

*amidotetrahydrofuran (**2k**)*. Yield (determined versus *p*-bromobenzaldehyde as internal NMR-standard): 200 mg (626 µmol, 65%, *cis*/*trans* = 39:61), yellow oil. R_f = 0.33 [diethyl ether/pentane = 10:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.75−1.85 (m, 2 H), 2.05−2.20 (m, 2 H), 3.32−3.48 (m, 4 H), 3.68−3.79 (m, 2 H), 3.81−3.85 (m, 1 H), 3.88−3.91 (m, 1 H), 3.93−4.07 (m, 4 H), 4.92 (d, 1 H, J = 9.2 Hz), 4.96 (d, 1 H, J = 7.3 Hz), 7.52−7.57 (m, 4 H), 7.60−7.64 (m, 2 H), 7.89−7.92 (m, 4 H). *cis*-**2k**: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.6, 33.3, 55.3, 66.0, 79.8, 127.0, 129.32, 133.0, 140.2. t_r = 25.01 minutes: MS (EI) *m*/*z* 240 (8), 207 (4), 196 (2), 170 (6), 141 (11), 98 (8), 83 (43), 77 (73), 70 (100), 51 (19). HRMS (EI$^+$) *m*/*z* 320.9846/318.9860 [M^+]; calculated mass for $C_{11}H_{14}NO_3SBr^+$: 320.9857/318.9878; *m*/*z* 240.0691 [M^+−Br]; calculated mass for $C_{11}H_{14}NO_3S^+$: 240.0694; *m*/*z* 226.0536 [M^+−CH_2Br]; calculated mass for $C_{10}H_{12}NO_3S^+$: 226.0538. *trans*-**2k**: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.9, 33.27, 56.7, 67.2, 82.9, 127.1, 129.34, 133.1, 139.9. t_r = 25.16 minutes: MS (EI) *m*/*z* 240 (33), 210 (8), 196 (4), 170 (4), 158 (3), 141 (28), 125 (6), 98 (6), 83 (100), 77 (92), 70 (7), 51 (21). HRMS (EI$^+$) *m*/*z* 320.9851/318.9857 [M^+]; calculated mass for $C_{11}H_{14}NO_3SBr^+$: 320.9857/318.9878; *m*/*z* 240.0688 [M^+−Br]; calculated mass for $C_{11}H_{14}NO_3S^+$: 240.0694; *m*/*z* 226.0537 [M^+−CH_2Br]; calculated mass for $C_{10}H_{12}NO_3S^+$: 226.0538; from a 53:47-mixture of *cis*/*trans*-isomers **2k**: Anal. Calcd. for $C_{11}H_{14}NO_3SBr$ (320.20): C, 41.26; H, 4.41; N, 4.37; S, 10.01. Found: C, 41.14; H, 4.50; N, 4.34; S, 10.15. *3-benzenesulfonamidopent-4-en-1-ol*. Yield (determined versus *p*-bromobenzaldeyde as internal NMR-standard): 24.7 mg (102 µmol, 11%), yellow oil. R_f = 0.15 [diethyl ether/pentane = 10:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.55−1.63 (m, 1 H), 1.74−1.82 (m, 1 H), 3.65 (dt, 1 H, J_d = 11.2 Hz, J_t = 4.9 Hz), 3.83 (ddd, 1 H, J = 11.3, 9.1, 3.8 Hz), 3.94−4.01 (m, 1 H), 4.90−4.97 (m, 2 H), 5.51−5.59 (m, 2 H), 7.46−7.57 (m, 3 H), 7.89−7.87 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.2, 53.7, 58.8, 115.8, 127.0, 129.0, 132.6, 137.1, 140.6. HRMS (EI$^+$) *m*/*z* 240.0676 [M^+−H]; calculated mass for $C_{11}H_{14}NO_3S^+$: 240.0694.

4.3.8 Conversion of 3-(3-benzamidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1l). Reactants: MTTOR **1l** (348 mg, 1.04 mmol), bromotrichloromethane (1.65 g, 0.82 mL, 8.32 mmol), and AIBN (43.0 mg, 0.26 mmol) in benzene (5.7 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether. *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**4**)*. Yield: 229 mg (0.92 mmol, 89%), orange oil. R_f = 0.71 (diethyl ether). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.57 (d, 3 H, J = 1.0 Hz), 7.31 (d, 1 H, J = 1.0 Hz).[52] *rel-(2S,3S)-2-Bromomethyl-3-benzamidotetrahydrofuran trans-(**2l**)*. Yield

(determined versus *p*-bromobenzaldeyde as internal NMR-standard): 65.2 mg (229 µmol, 22%), yellow oil. R_f = 0.37 (diethyl ether). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.99 (ddt, 1 H, J_d = 12.9, 7.4 Hz, J_t = 5.3 Hz), 2.43−2.52 (m, 1 H), 3.60−3.61 (m, 2 H), 3.98−4.06 (m, 2 H), 4.07−4.13 (m, 1 H), 4.54−4.60 (m, 1 H), 6.25 (d, 1 H, J = 6.3 Hz), 7.43−7.47 (m, 2 H), 7.51−7.55 (m, 1 H), 7.74−7.77 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.2, 33.9, 54.3, 67.4, 84.0, 126.9, 128.7, 131.9, 133.8, 167.4. Retention time (t_r) = 24.02 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 204 (14), 160 (1), 122 (2), 105 (100), 83 (40), 77 (45), 51 (12). HRMS (EI$^+$) *m*/*z* 204.1018 [M^+−Br]; calculated mass for $C_{12}H_{14}NO_2^+$: 204.1025; *m*/*z* 190.0865 [M^+−CH_2Br]; calculated mass for $C_{11}H_{12}NO_2^+$: 190.0868. *2-Bromomethyl-3-benzamidotetrahydrofuran* ***(2l)***. Yield (determined versus *p*-bromobenzaldeyde as internal NMR-standard): 99.5 mg (0.35 mmol, 34%, *cis*/*trans* = 52:48), yellow oil. *trans*-**2l**: R_f = 0.37 (diethyl ether). NMR data agreed with values from an authentic sample. *cis*-**2l**: R_f = 0.31 (diethyl ether). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.95−2.07 (m, 1 H), 2.41−2.52 (m, 1 H), 3.40−3.44 (m, 1 H), 3.59−3.63 (m, 1 H), 3.86−3.92 (m, 1 H), 4.14−4.18 (m, 1 H), 4.22 (td, 1 H, J_t = 5.8 Hz, J_d = 4.5 Hz), 4.91−4.98 (m, 1 H), 6.38 (d, 1 H, J = 8.3 Hz), 7.43−7.48 (m, 2 H), 7.51−7.55 (m, 1 H), 7.75−7.79 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3, 33.5, 51.8, 66.4, 79.5, 126.9, 128.7, 131.9, 133.8, 167.2. *2-Phenyl-(cis-tetrahydrofurano[4.5b])-5,6-dihydro-4H-1,3-oxazin*: t_r = 19.89 minutes: MS (EI) *m*/*z* 203 (10), 175 (1), 160 (1), 112 (3), 105 (100), 77 (36), 51 (8). HRMS (EI$^+$) *m*/*z* 203.0965 [M^+]; calculated mass for $C_{12}H_{13}NO_2^+$: 203.0946. *rel-(2R,3S)-2-Bromomethyl-3-benzamidotetrahydrofuran cis-****(2l)*** [Yield (determined versus *p*-bromobenzaldeyde as internal NMR-standard): 16 mg (56.6 µmol, 5%)] and *3-Bromo-4-benzamidotetrahydropyran* ***(3l)*** [Yield (determined versus *p*-bromobenzaldeyde as internal NMR-standard): 20 mg (70.4 µmol, 7%)], yellow oil. R_f = 0.27 (diethyl ether). *cis*-**2l**: R_f = 0.31 (diethyl ether). NMR data agreed with values from an authentic sample. **3l**: R_f = 0.25 (diethyl ether). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.71−1.76 (m, 1 H), 2.06−2.16 (m, 1 H), 3.54−3.61 (m, 1 H), 3.83−3.91 (m, 1 H), 4.05−4.21 (m, 2 H), 4.29−4.36 (m, 1 H), 4.52−4.54 (m, 1 H), 6.51 (d, 1 H, J = 8.5 Hz), 7.39−7.46 (m, 2 H), 7.49−7.54 (m, 1 H), 7.74−7.78 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 48.2, 56.0, 67.1, 71.6, 126.9, 128.7, 131.8, 133.8, 166.6. t_r = 23.68 minutes: MS (EI) *m*/*z* 285/283 (1), 204 (25), 160 (5), 147 (2), 122 (12), 105 (100), 77 (38), 51 (9). HRMS (EI$^+$) *m*/*z* 285.0165/283.0181 [M^+]; calculated mass for $C_{12}H_{14}NO_2Br^+$: 285.0187/283.0208; *m*/*z* 204.1027 [M^+−Br]; calculated mass for $C_{12}H_{14}NO_2^+$: 204.1025.

4.3.9 Conversion of 3-(2-phthalimidopent-4-en-1-oxy)-4-methylthiazole-2(3*H*)-thione (1m). Reactants: MTTOR **1m** (200 mg, 0.55 mmol), bromotrichloromethane (872 mg, 0.43 mL, 4.40 mmol), and AIBN (23.0 mg, 0.14 mmol) in benzene (3 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 2:1 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (**4**)*. Yield: 123 mg (0.49 mmol, 90%), yellow oil. R_f = 0.65 [diethyl ether/pentane = 2:1 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.58 (d, 3 H, J = 0.8 Hz), 7.31 (d, 1 H, J = 0.8 Hz).52 *rel*-(*2S*,*3S*)-*2-Bromomethyl-3-phthalimidotetrahydrofuran trans-(**2m**)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 19.3 mg (62.7 µmol, 11%)] and *3-Bromo-4-phthalimidotetrahydropyran (**3m**)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 19.7 mg (63.7 µmol, 12%)], yellow oil. R_f = 0.46 [diethyl ether/pentane = 2:1 (*v*/*v*)]. *trans*-**2m**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.28−2.37 (m, 1 H), 2.45−2.53 (m, 1 H), 3.44−3.60 (m, 2 H), 4.09−4.15 (m, 1 H), 4.25−4.32 (m, 1 H), 4.36−4.43 (m, 1 H), 4.69 (dt, 1 H, J_d = 10.2 Hz, J_t = 6.7 Hz), 7.72−7.75 (m, 2 H), 7.84−7.87 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.1, 33.2, 53.3, 68.2, 78.7, 123.4, 131.6, 134.2, 176.8. Retention time (t_r) = 24.01 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 266 (0.7), 230 (59), 216 (6), 186 (19), 160 (16), 149 (21), 130 (37), 104 (34), 83 (100), 76 (40). HRMS (EI$^+$) *m*/*z* 310.9979/308.9995 [M^+]; calculated mass for $C_{13}H_{12}NO_3Br^+$: 310.9980/309.0001; *m*/*z* 230.0813 [M^+−Br]; calculated mass for $C_{13}H_{12}NO_3^+$: 230.0817; *m*/*z* 216.0675 [M^+−CH_2Br]; calculated mass for $C_{12}H_{10}NO_3^+$: 216.0661. **3m**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.85−1.90 (m, 1 H), 2.57−2.68 (m, 1 H), 3.44−3.60 (m, 2 H), 4.09−4.15 (m, 1 H), 4.25−4.32 (m, 1 H), 4.36−4.43 (m, 1 H), 4.87 (td, 1 H, J_t = 11.0 Hz, J_d = 4.9 Hz), 7.72−7.75 (m, 2 H), 7.84−7.87 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.5, 46.0, 54.7, 67.4, 72.7, 123.5, 131.5, 134.2, 167.7. t_r = 23.55 minutes: MS (EI) *m*/*z* 311/309 (0.7), 266 (0.7), 230 (100), 186 (21), 173 (30), 148 (27), 130 (36), 104 (30), 83 (26), 76 (39). HRMS (EI$^+$) *m*/*z* 310.9961/309.0044 [M^+]; calculated mass for $C_{13}H_{12}NO_3Br^+$: 310.9980/309.0001; *m*/*z* 230.0816 [M^+−Br]; calculated mass for $C_{13}H_{12}NO_3^+$: 230.0817. *2-Bromomethyl-3-phthalimidotetrahydrofuran (**2m**)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 70 mg (225 µmol, 41%, *cis*/*trans* = 7:93)] and *3-bromo-4-phthalimidotetrahydropyran (**3m**)* [Yield (determined versus pentachlorobenzene as internal NMR-standard): 7.6 mg (24.5 µmol, 4%)], yellow oil. R_f = 0.45 [diethyl ether/pentane = 2:1 (*v*/*v*)]. *trans*-**2m**: NMR data agreed with values from an authentic sample. *cis*-**2m**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.28−2.38 (m, 1 H), 2.45−2.53 (m, 1 H), 3.28−3.31 (m, 1 H), 3.36−3.39 (m, 1 H), 3.89 (td, 1 H, J_t = 8.3 Hz, J_d = 7.1 Hz), 4.25−4.32 (m, 1 H), 4.38−4.43 (m, 1 H),

5.01−5.05 (m, 1 H), 7.72−7.76 (m, 2 H), 7.83−7.88 (m, 2 H). *Assignable shifts*: ^{13}C NMR ($CDCl_3$, 150 MHz) δ 52.1, 67.2, 80.3, 123.4, 131.7, 134.3, 167.8. t_r = 23.93 minutes: MS (EI) *m*/*z* 230 (37), 216 (4), 186 (17), 160 (11), 148 (10), 130 (26), 104 (23), 83 (100), 76 (26). HRMS (EI$^+$) *m*/*z* 230.0808 [M^+−Br]; calculated mass for $C_{13}H_{12}NO_3^+$: 230.0817; *m*/*z* 216.0671 [M^+−CH_2Br]; calculated mass for $C_{12}H_{10}NO_3^+$: 216.0661. **3m**: NMR data agreed with values from an authentic sample.

4.3.10 Conversion of 3-[3-(Benzoylthio)pent-4-en-1-oxy]-4-methylthiazole-2(3*H*)-thione (1n). Reactants: MTTOR **1n** (202 mg, 0.57 mmol), bromotrichloromethane (912 mg, 0.45 mL, 4.60 mmol), and AIBN (23.0 mg, 0.14 mmol) in benzene (3.1 mL) according to procedure 4.3.1. Reaction time: 2 hours. Eluent used for chromatographic purification: diethyl ether/pentane = 1:2 (*v*/*v*). *4-Methyl-2-(trichloromethylsulfanyl)thiazole (4)*. Yield: 99.4 mg (0.40 mmol, 70%), yellow oil. R_f = 0.45 [diethyl ether/pentane = 1:2 (*v*/*v*)]. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.57 (d, 3 H, *J* = 0.6 Hz), 7.31 (d, 1 H, *J* = 0.8 Hz).[52] *2-Bromomethyl-3-(benzoylthio)tetrahydrofuran (**2n**)*. Yield (determined versus *p*-bromobenzaldeyde as internal NMR-standard): 124.8 mg (0.41 mmol, 72%, *cis*/*trans* = 25:75), yellow oil. R_f = 0.45 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *cis*-**2n**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.12−2.20 (m, 1 H), 2.54−2.64 (m, 1 H), 3.44−3.52 (m, 2 H), 3.92−4.00 (m, 1 H), 4.05−4.15 (m, 1 H), 4.41−4.46 (m, 2 H), 7.44−7.49 (m, 2 H), 7.58−7.62 (m, 1 H), 7.93−7.98 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.4, 33.8, 44.9, 67.0, 80.1, 127.33, 128.7, 133.79, 136.45, 190.7. Retention time (t_r) = 24.11 minutes (for GC/MS conditions see Supplementary data): MS (EI) *m*/*z* 302 (0.5), 221 (1), 207 (1), 162 (0.5), 116 (0.5), 105 (100), 77 (27), 51 (8). HRMS (EI$^+$) *m*/*z* 301.9793/299.9810 [M^+]; calculated mass for $C_{12}H_{13}O_2SBr^+$: 301.9799/299.9820; *m*/*z* 207.0463 [M^+−CH_2Br]; calculated mass for $C_{11}H_{11}O_2S^+$: 207.0480. *trans*-**2n**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.02−2.09 (m, 1 H), 2.55−2.64 (m, 1 H), 3.58−3.68 (m, 2 H), 3.92−4.00 (m, 1 H), 4.05−4.15 (m, 3 H), 7.44−7.49 (m, 2 H), 7.58−7.62 (m, 1 H), 7.93−7.98 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.4, 34.5, 44.2, 68.1, 83.7, 127.25, 128.7, 133.76, 136.42, 191.1. t_r = 23.94 minutes: MS (EI) *m*/*z* 221 (1), 207 (1), 162 (6), 121 (1), 105 (100), 77 (30), 51 (8). HRMS (EI$^+$) *m*/*z* 221.0629 [M^+−Br]; calculated mass for $C_{12}H_{13}O_2S^+$: 221.0636; *m*/*z* 207.0478 [M^+−CH_2Br]; calculated mass for $C_{11}H_{11}O_2S^+$: 207.0480.

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5.7 Anhang

Supporting Information for

Controlling Stereoselectivity in 4-Pentenoxyl Radical Cyclization by the Allylic Substituent

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Contents

1 General Remarks

1.1 Numbering of compounds

Compounds in the *Electronic Supplementary Information* are numbered according to the systematic used in the accompanying article.

1.2 References

Electronic Supplementary Information and accompanying article have separate lists of references.

1.3 Molecular graphics

Ball-and stick models displaying energy-minimized structures of 4-pentenoxyl radicals (**I**), 3-substituted tetrahydrofuran-2-ylmethyl radicals *cis*/*trans*-**II**, butenes (**IV**), cyclohexanes (**V**), and transition structures *TS1/2*-**II** were generated by the HyperChem 4.5-software supplemented by the ChemPlus-add-on (Version 1.6),[1] from Gaussian03-outputs,[2] which were converted by Open-Babel[3] into HyperChem input files.

Carbon in the graphics is depicted in gray, oxygen in red, nitrogen in blue, sulfur in yellow, chlorine in emerald green, flurorine in light green, and hydrogen in white.

2 Instrumentation and Solvent Purification

2.1 Nuclear magnetic resonance spectroscopy

Proton- and carbon-13 nuclear magnetic reonance (NMR)-spectra were recorded with FT-NMR DPX 200, DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale. The resonances of residual $CHCl_3$ and of the carbon atom of $CDCl_3$ (δ_H 7.26, δ_C 77.0) were used as internal standards. NMR shift values of isomuscarine bromides in solutions of D_2O were referenced versus 1,4-dioxane as internal standard (δ_H 3.17, δ_C 67.1).

2.2 Electron impact mass spectrometry

Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*).

2.3 High resolution mass spectrometry

Mass spectroscopy (EI, 70 eV), GCT Premier Micromass (*Waters*).

2.4 Combustion analysis

Combustion analysis was performed with a vario Micro cube CHNS (*Elementar Analysentechnik/Hanau*).

2.7 Melting points

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*) and are not corrected.

3 Reagents, Solvents, and Chromatography

3.1 Solvents

Petroleum ether refers to the fraction of hydrocarbons boiling between 40–60 °C and was purchased, like all other solvents, in analytical-grade quality and was used as received.

3.2 Thin layer chromatography

Reaction progress was monitored via thin layer chromatography (tlc) on Polygram sheets coated with silica gel (60 F_{254}, *Merck*). Compounds on developed tlc-sheets were detected with the aid of a UV-VIS indicator commercially disposed on the sheets, showing colored or darker spots by illuminating developed sheets with a lamp emitting 254 nm light. Alternatively, developed tlc-sheets were stained by Ekkert´s reagent and subsequently heated, leading to colored spots for alcohols and carbonyl compounds.

3.3 Column chromatography

Compounds from syntheses were purified by flash chromatography on silica gel (40–63 μm) as stationary phase.

3.4 Gas chromatography coupled to mass spectrometry

GC/MS Analysis was performed with a HP 6890 Series (*Hewlett Packard*) system and mass detector with a HP-5MS column (*Agilent*, 30 m × 0.25 mm, 0.25 μm). Temperature program: 40 °C (3 min), 10 °C min^{-1} → 280 °C, 280 °C (10 min)

4 Synthesis of 3-Fluoropent-4-enyl *p*-toluenesulfonate (6)

Under atmosphere of nitrogen, dry dichloromethane (10 mL) was cooled to –78 °C. Then diethylaminosulfur trifluoride (0.52 mL, 3.91 mmol) was added to the stirring solvent. After adding a solution of 3-hydroxypent-4-enyl *p*-toluenesulfonate (**5**) (1.03 g, 4.02 mmol) in dry dichloromethane (10 mL) in a dropwise manner over 10 minutes, the reaction mixture was stirred for 15 minutes at –78 °C. The reaction was treated with an aqueous saturated solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was washed with dichloromethane (2 × 5 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure (80 mbar, 40 °C). The residue was purified by column chromatography [diethyl ether/pentane: = 1:2 (*v*/*v*)]. *3-Fluoropent-4-enyl p-toluenesulfonate (**6**)* [Yield: 743 mg (2.88 mmol, 72%)] and *5-fluoropent-3-enyl p-toluenesulfonate iso-(**6**)* [Yield: 175 mg (680 µmol, 17%)], yellow liquid. R_f = 0.57 [diethyl ether/pentane = 1:2 (*v*/*v*)]. *3-Fluoropent-4-enyl p-toluenesulfonate (**6**)*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95–2.08 (m, 2 H), 2.46 (s, 3 H), 4.11–4.25 (m, 2 H), 4.89–5.08 (m, 1 H), 5.22–5.27 (m, 1 H), 5.28–5.35 (m, 1 H), 5.82 (dddd, 1 H, J = 17.2, 14.3, 10.8, 6.0 Hz), 7.36 (d, 2 H, J = 8.0 Hz), 7.81 (d, 2 H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 34.5 (d, $^2J_{C,F}$= 22.7 Hz), 66.0 (d, $^3J_{C,F}$ = 18.3 Hz), 89.5 (d, $^1J_{C,F}$= 168.7 Hz), 118.0 (d, $^3J_{C,F}$ = 11.7 Hz), 127.9, 129.9, 132.7, 135.1 (d, $^2J_{C,F}$ = 19.8 Hz), 144.94. ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ –182.70. Retention time (t_r)= 20.67 min: MS (EI) *m/z* (%) 173 (14), 155 (29), 91 (100), 88 (86), 65 (43). IR (NaCl) ν_{max} / cm^{-1} 2962, 1598, 1495, 1360, 1176, 1097, 971, 816, 763, 664. HRMS (EI$^+$) *m/z* 258.0709 [M$^+$]; calculated mass for $C_{12}H_{15}FO_3S^+$: 258.0726. *5-Fluoropent-3-enyl p-toluenesulfonate iso-(**6**)*: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40–2.45 (m, 2 H), 2.45 (s, 3 H), 4.07 (t, 2 H, J = 6.5 Hz), 4.76 (dd, 2 H, J = 47.4, 5.0 Hz), 5.66–5.72 (m, 2 H), 7.50 (d, 2 H, J = 7.8 Hz), 7.61 (d, 2 H, J = 7.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.6, 69.0 (d, $^3J_{C,F}$= 3.7 Hz), 82.8 (d, $^1J_{C;F}$ = 162.1 Hz), 128.16 (d, $^2J_{C,F}$ = 16.9 Hz), 129.8, 132.7, 144.8. ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ –211.53. t_r= 21.57 min: MS (EI) *m/z* 173 (10), 155 (52), 91 (100), 88 (64), 65 (38). IR (NaCl) ν_{max} / cm^{-1} 2962, 1598, 1495, 1360, 1176, 1097, 971, 816, 763, 664. HRMS (EI$^+$) *m/z* 238.0681 [M$^+$–HF]; calculated mass for $C_{12}H_{14}O_3S^+$: 238.0664. From a mixture of (**6**) and *iso*-(**6**): Anal. Calcd. for $C_{12}H_{15}FO_3S$ (258.31): C, 58.80; H, 5.85; S, 12.41; found: C, 55.04; H, 5.97; N, 12.28; S, 12.56.

5 Homolytic Bromocyclization – General Method

Bromotrichloromethane (10 equiv.) and azobisisobutyronitrile (AIBN) (0.25 equiv) were added to a solution of 3-alkenoxythiazole-2(3*H*)-thione **1** (1 equiv, c_0 = 83 mM) in perdeuterobenzene. The solution was heated to reflux for 2 hours. The yields of 4-methyl-2-(trichloromethylsulfanyl)thiazole (**4**), tetrahydrofuran **2** and tetrahydropyran **3** were determined via proton-NMR using pentachlorobenzene or bromobenzaldehyde as internal standard.

6 NMR Spectra

6.1 Bromocyclization products of 1d

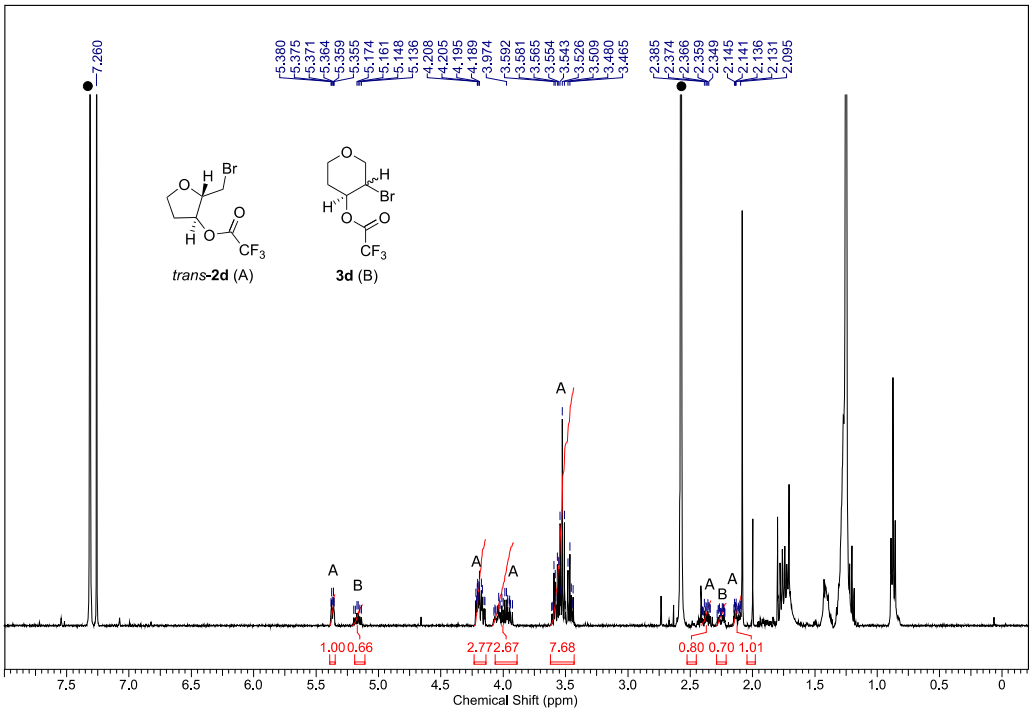

Figure S6.1. ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-trifluoroacetyloxytetrahydrofuran *trans*-(**2d**) and 3-bromo-4-trifluoroacetyloxy-tetrahydropyran (**3d**, *isomer 1*). Labeling (●) refer to 4-methyl-2-(trichloromethylsulfanyl)thiazole (**4**).

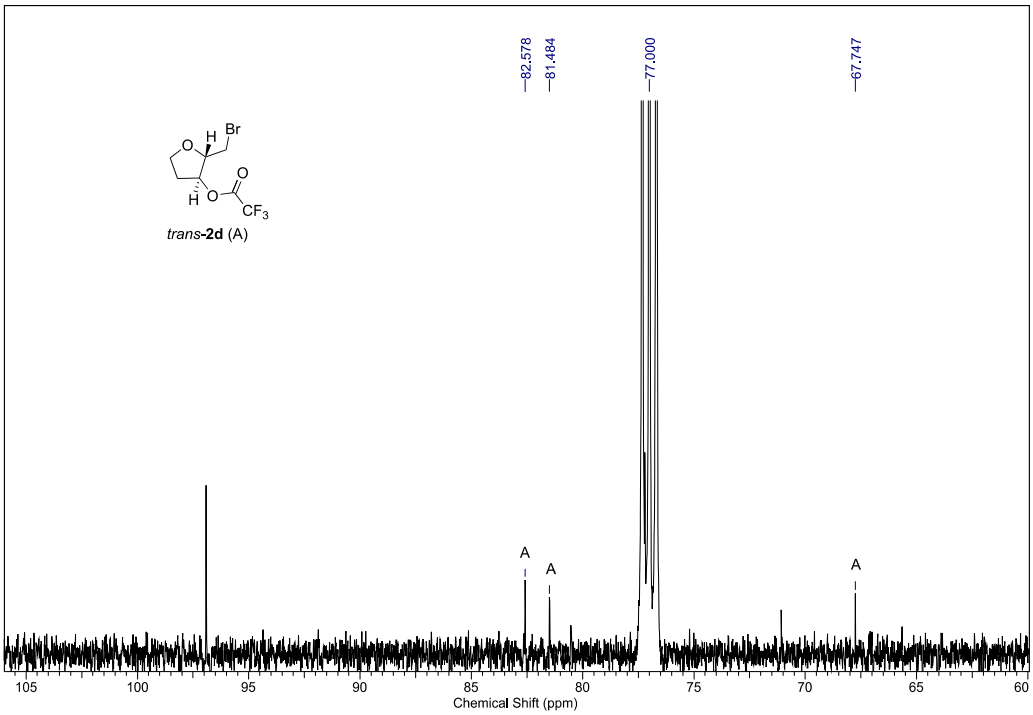

Figure S6.2. Excpert of ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-trifluoroacetyloxytetrahydrofuran *trans*-(**2d**).

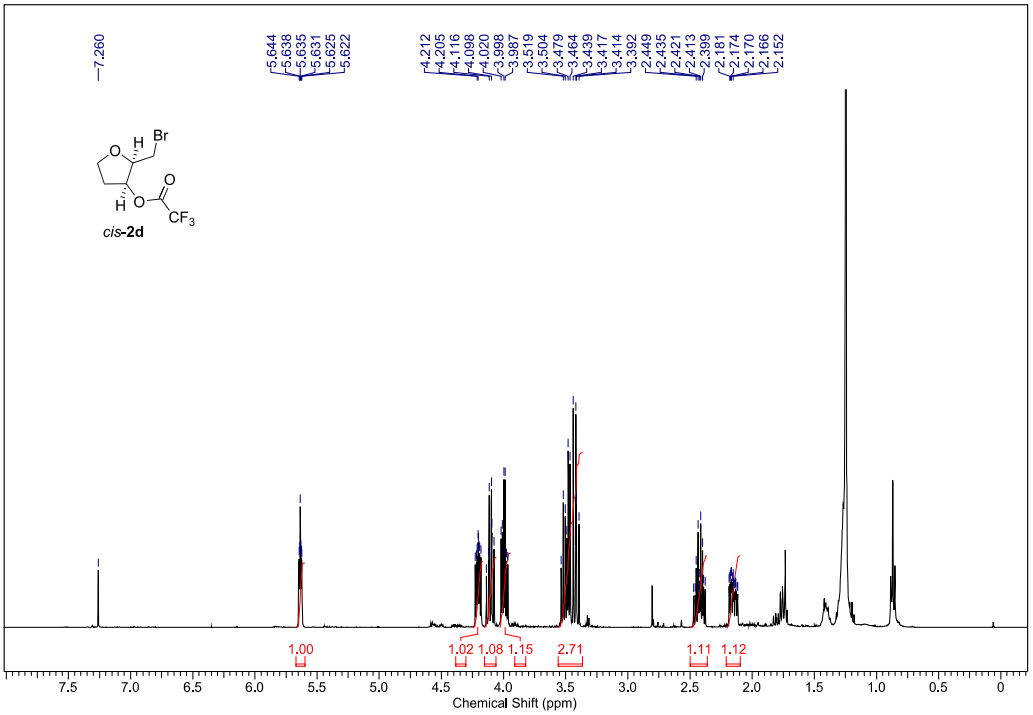

Figure S6.3. ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of *rel*-(2*R*,3*S*)-2-bromomethyl-3-trifluoroacetyloxytetrahydrofuran *cis*-(**2d**).

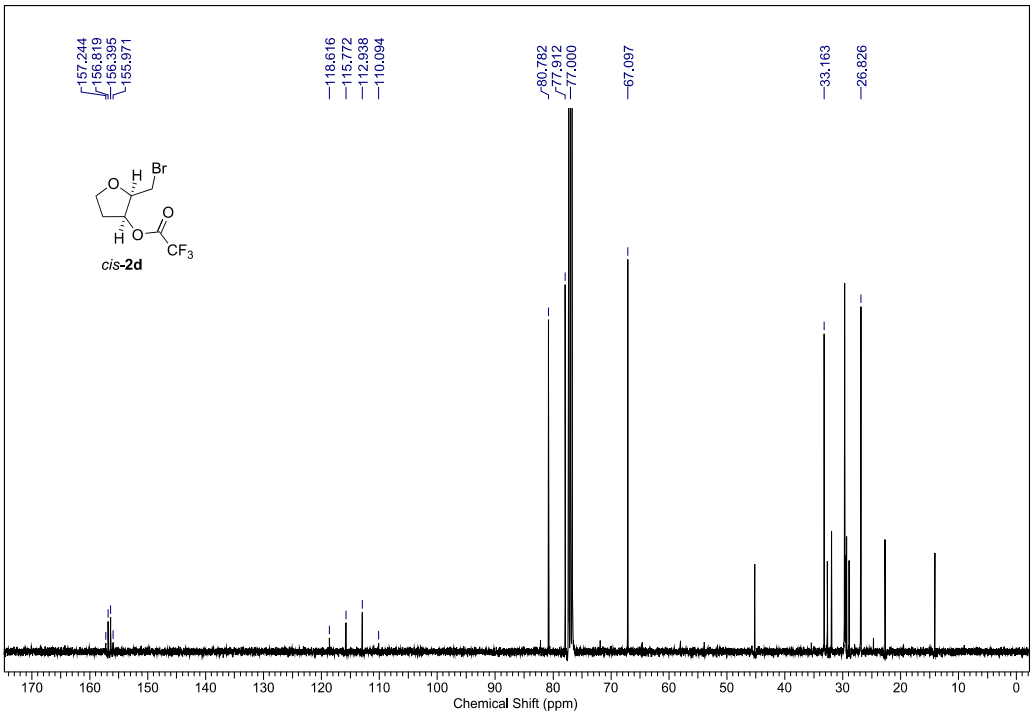

Figure S6.4. ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of *rel*-(2*R*,3*S*)-2-bromomethyl-3-trifluoroacetyloxytetrahydrofuran *cis*-(**2d**).

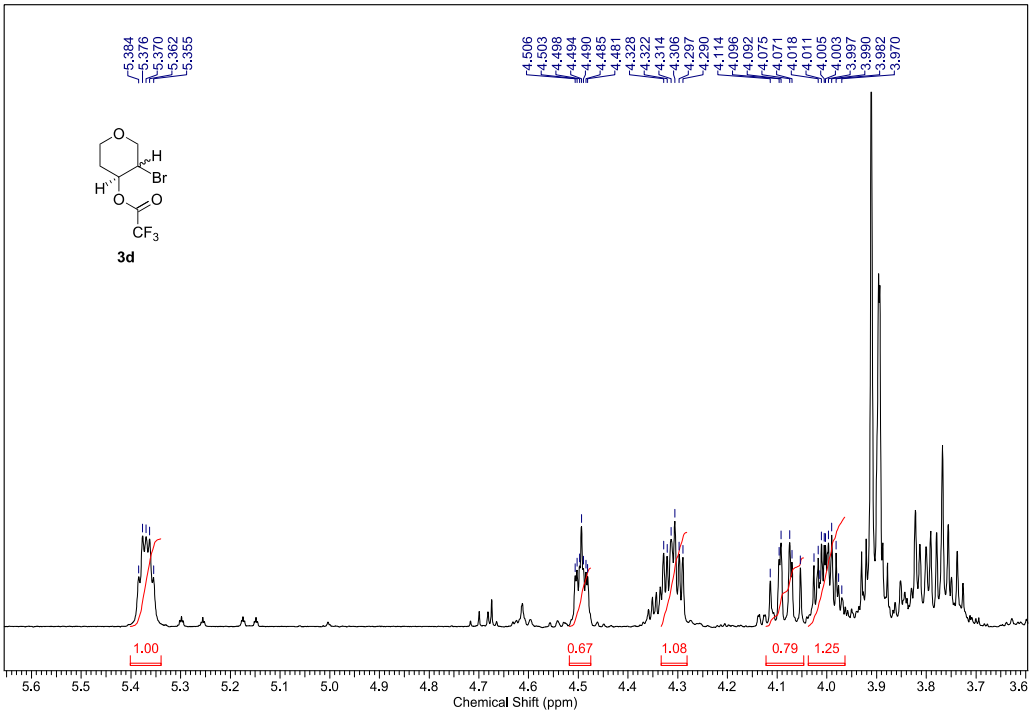

Figure S6.5. Expert of ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 3-bromo-4-trifluoroacetyloxytetrahydropyran (**3d**, *isomer 2*).

6.2 Bromocyclization products of 3-methoxypentenyl thiohydroxamate 1g

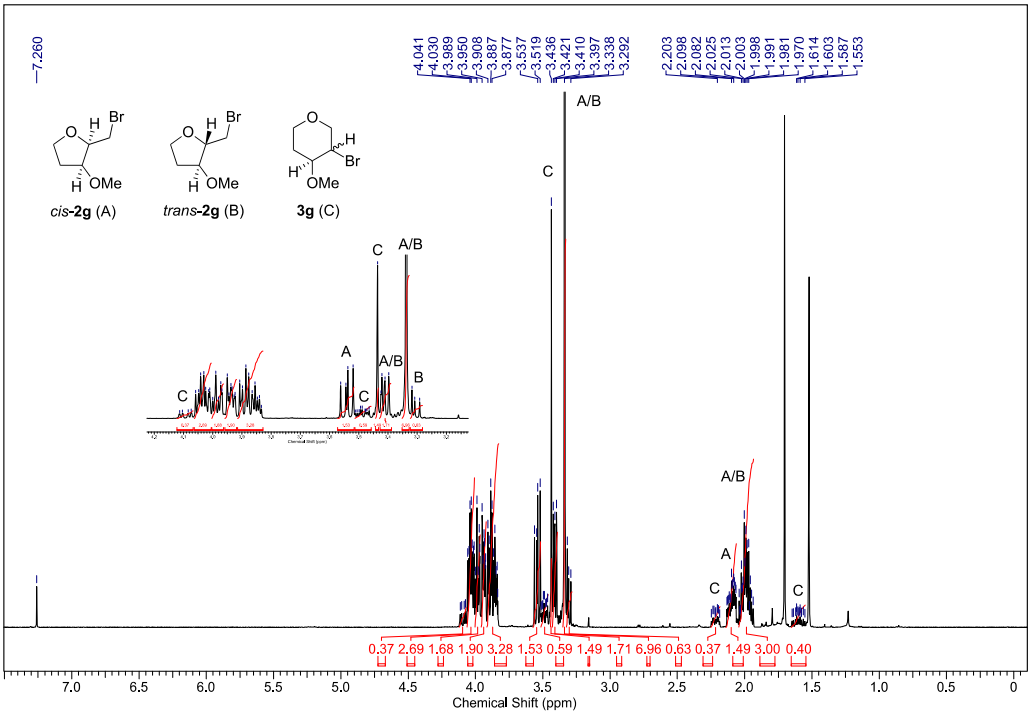

Figure S6.6. ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 2-bromomethyl-3-methoxytetrahydrofuran (**2g**) (71/29-mixture of *cis*/*trans*-isomers) and 3-bromo-4-methoxytetrahydropyran (**3g**, *isomer 1*).

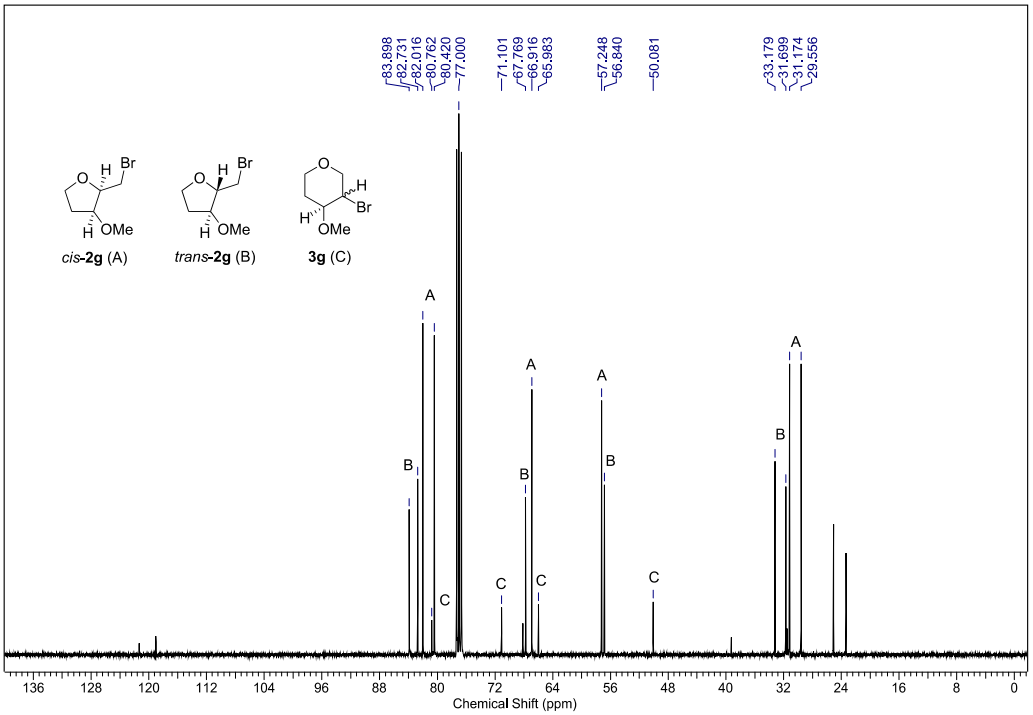

Figure S6.7. ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of 2-bromomethyl-3-methoxytetrahydrofuran (**2g**) (71/29-mixture of *cis*/*trans*-isomers) and 3-bromo-4-methoxytetrahydropyran (**3g**, *isomer 1*).

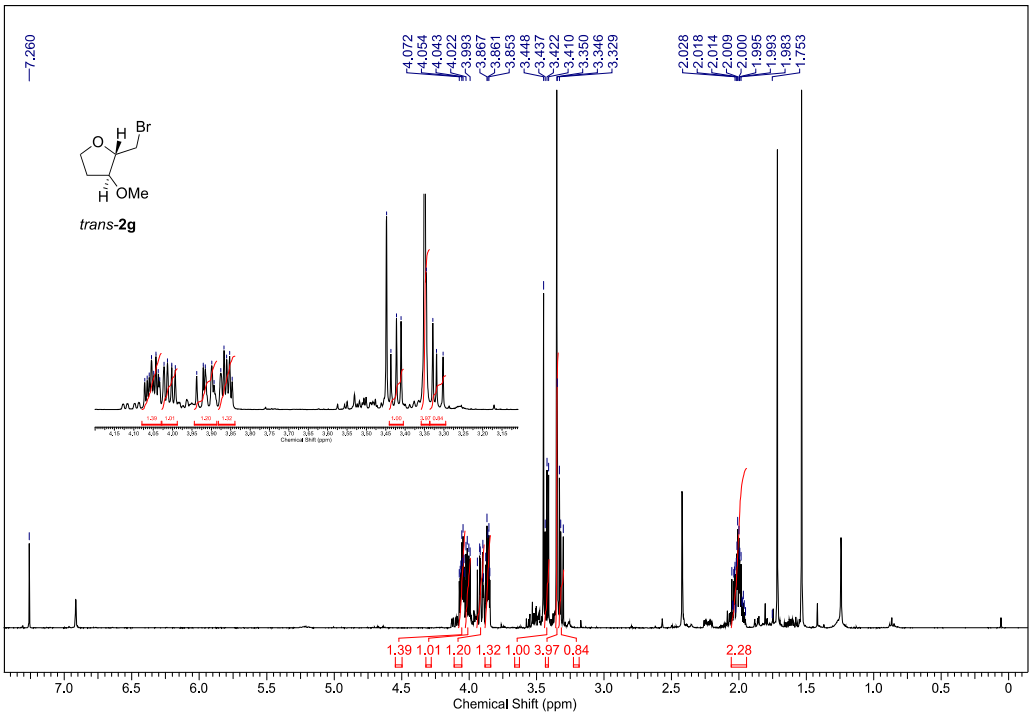

Figure S6.8. ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-methoxytetrahydrofuran *trans*-(**2g**).

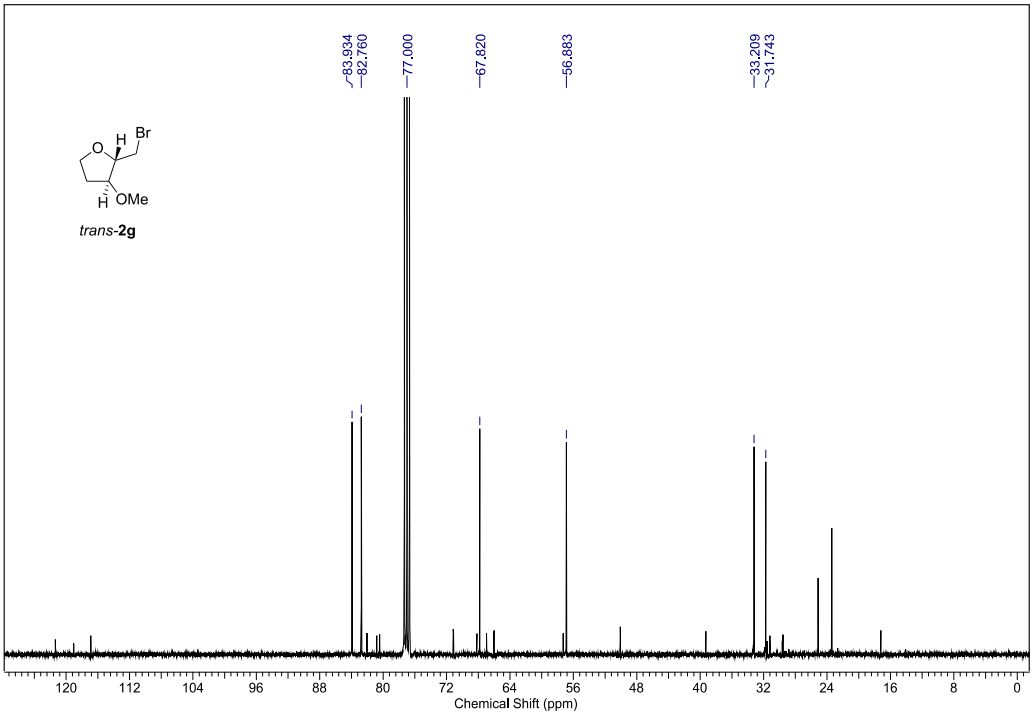

Figure S6.9. ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-methoxytetrahydrofuran *trans*-(**2g**).

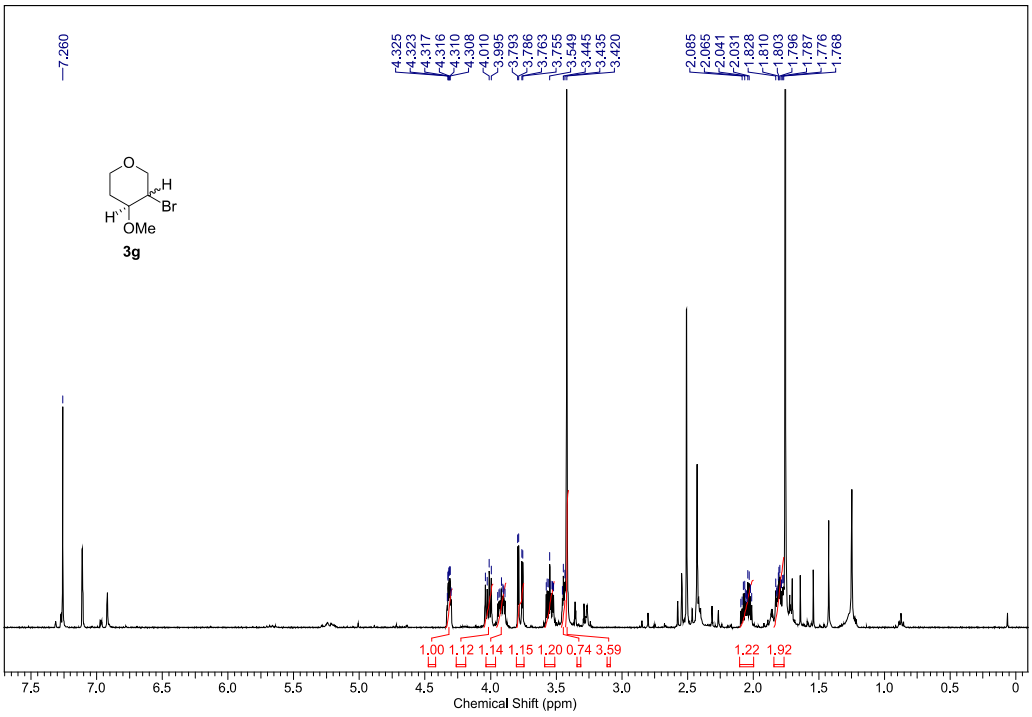

Figure S6.10. ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 3-bromo-4-methoxytetrahydropyran (**3g**, *isomer 2*).

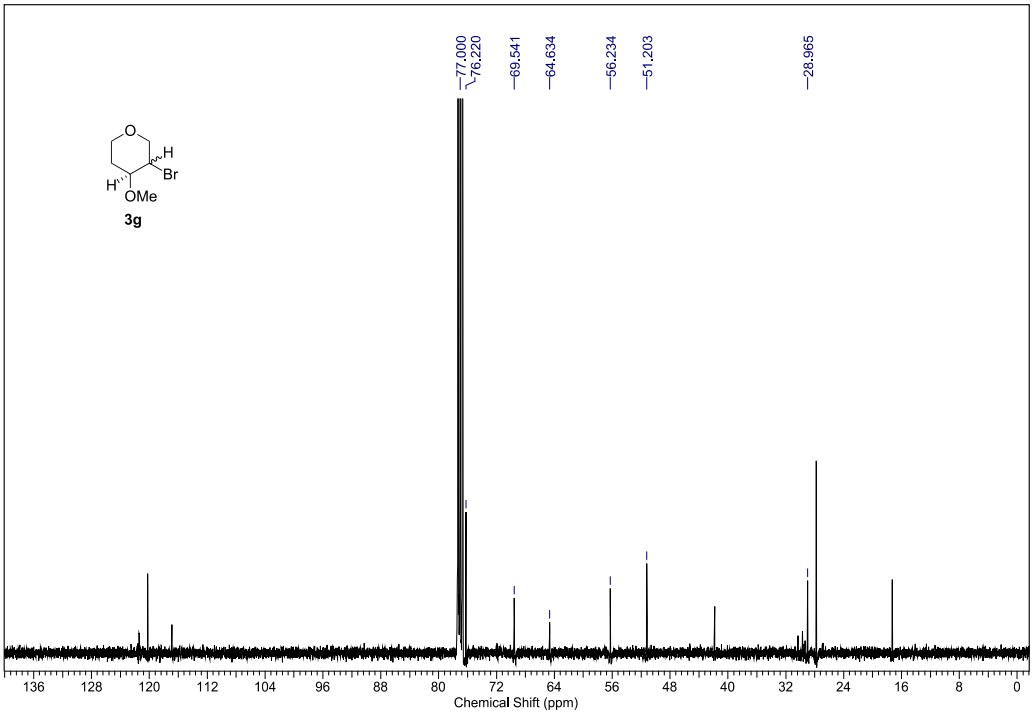

Figure S6.11. ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of 3-bromo-4-methoxytetrahydropyran (**3g**, *isomer 2*).

6.3 Bromocyclization products of 3-fluoropentenyl thiohydroxamate 1h

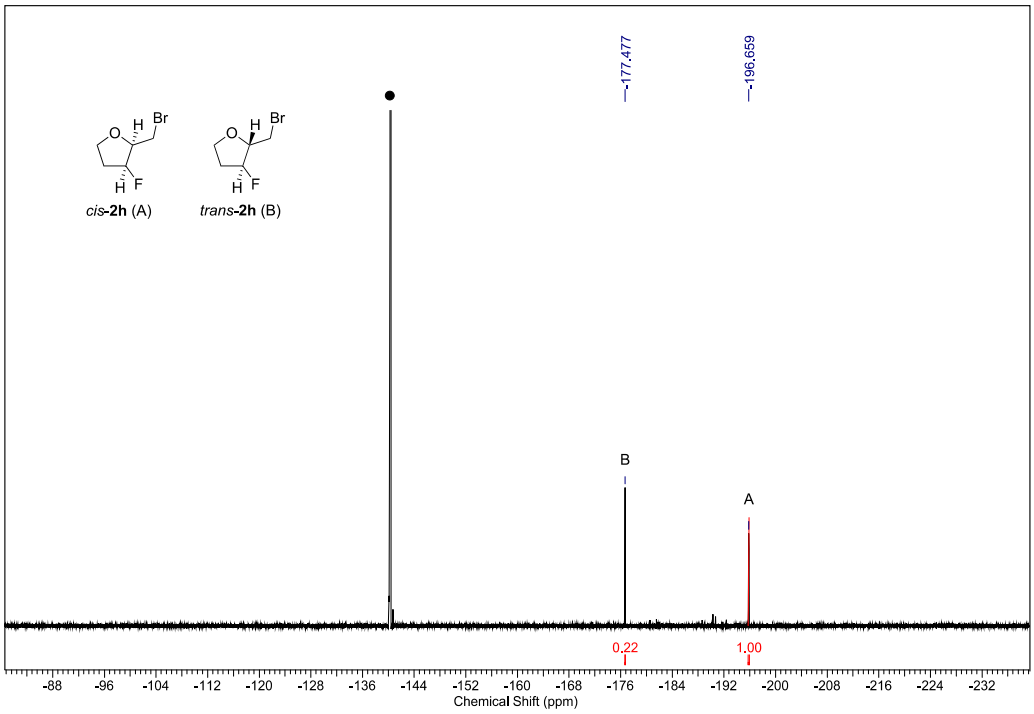

Figure S6.12 ^{19}F-NMR-spectrum ($CDCl_3$, 376.5 MHz) of 2-bromomethyl-3-fluorotetrahydrofurn (**2h**) (18/82-mixture of *cis*/*trans*-isomers). Labeling (●) refer to 2-fluorophenol as internal standard.

6.4 Bromocyclization products of 3-chloropentenyl thiohydroxamate 1i

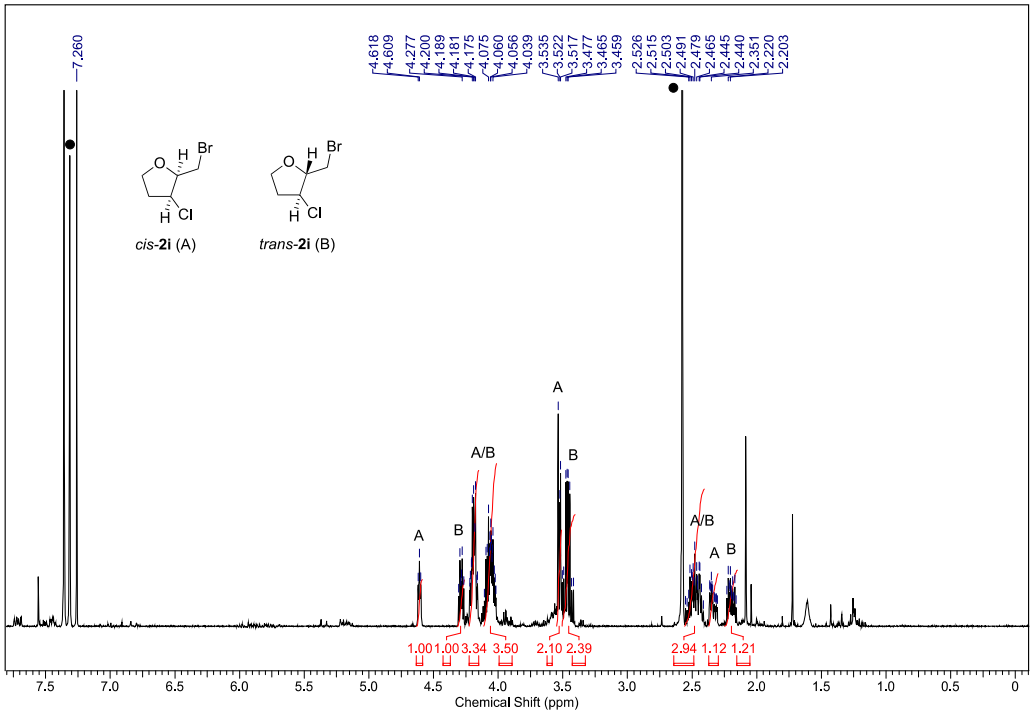

Figure S6.13 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 2-bromomethyl-3-chlorotetrahydrofuran (**2i**) (47/53-mixture of *cis*/*trans*-isomers). Labeling (●) refer to 4-methyl-2-(trichloromethylsulfanyl)thiazole (**4**).

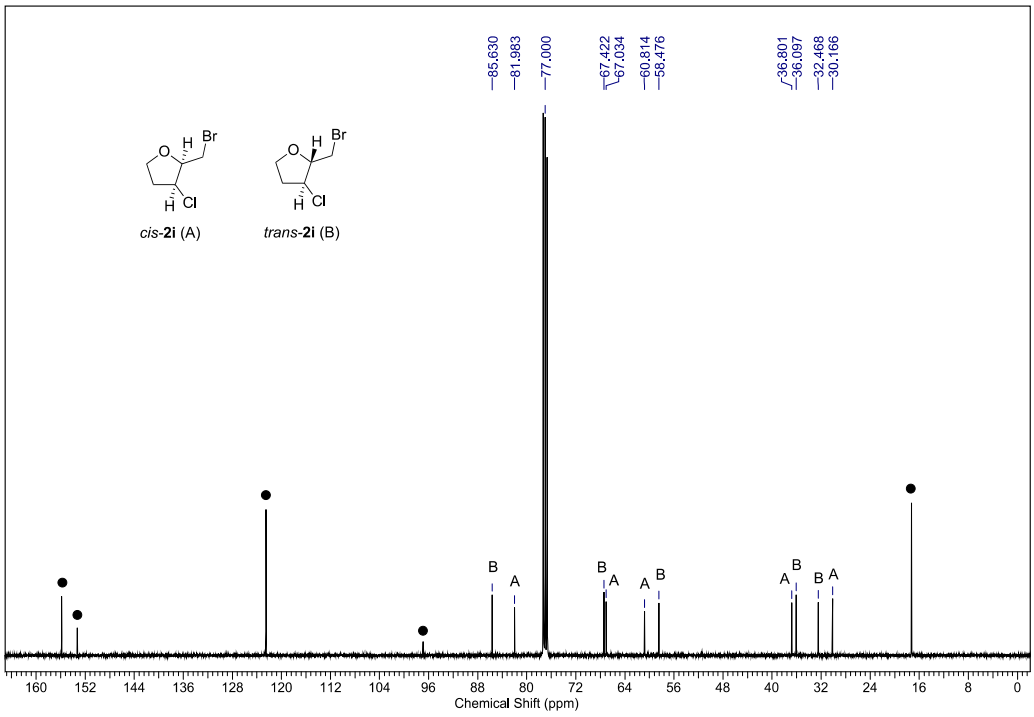

Figure S6.14 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of 2-bromomethyl-3-chlorotetrahydrofuran (**2i**) (47/53-mixture of *cis*/*trans*-isomers). Labeling (●) refer to 4-methyl-2-(trichloromethylsulfanyl)thiazole (**4**).

6.5 Bromocyclization products of 3-trifluoroacetamidopentenyl thiohydroxamate 1j

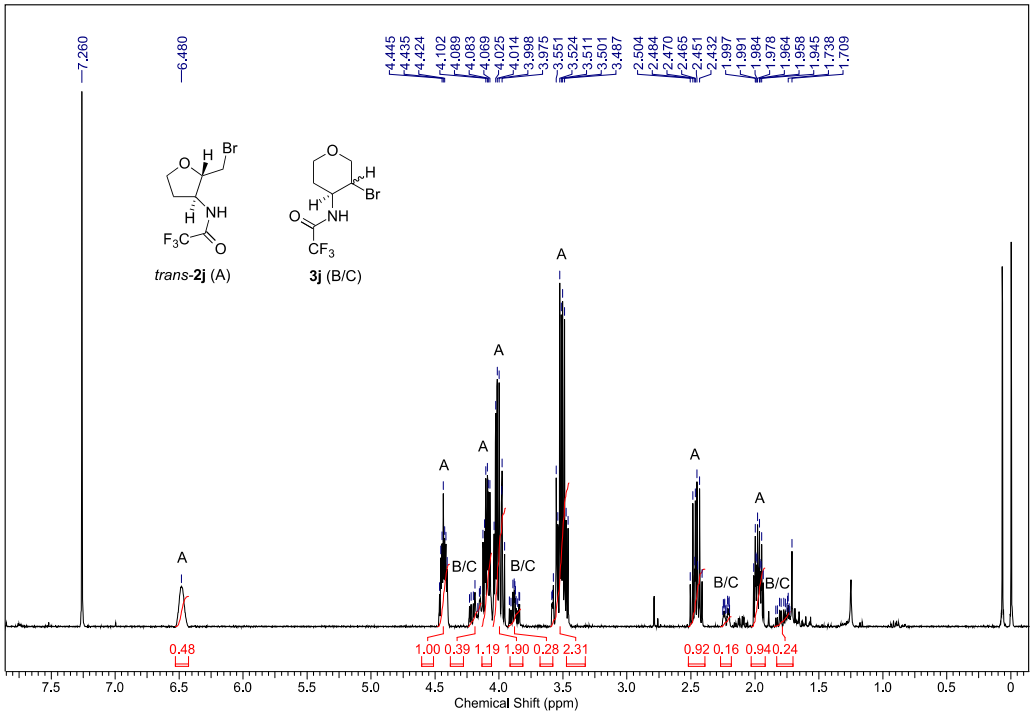

Figure S6.15 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-fluoroacetamidetetrahydrofuran *trans*-(**2j**) and 3-bromo-4-fluoroacetamidetetrahydro-pyran (**3j**) (24/76-mixture of *isomer 1*/*isomer 2*).

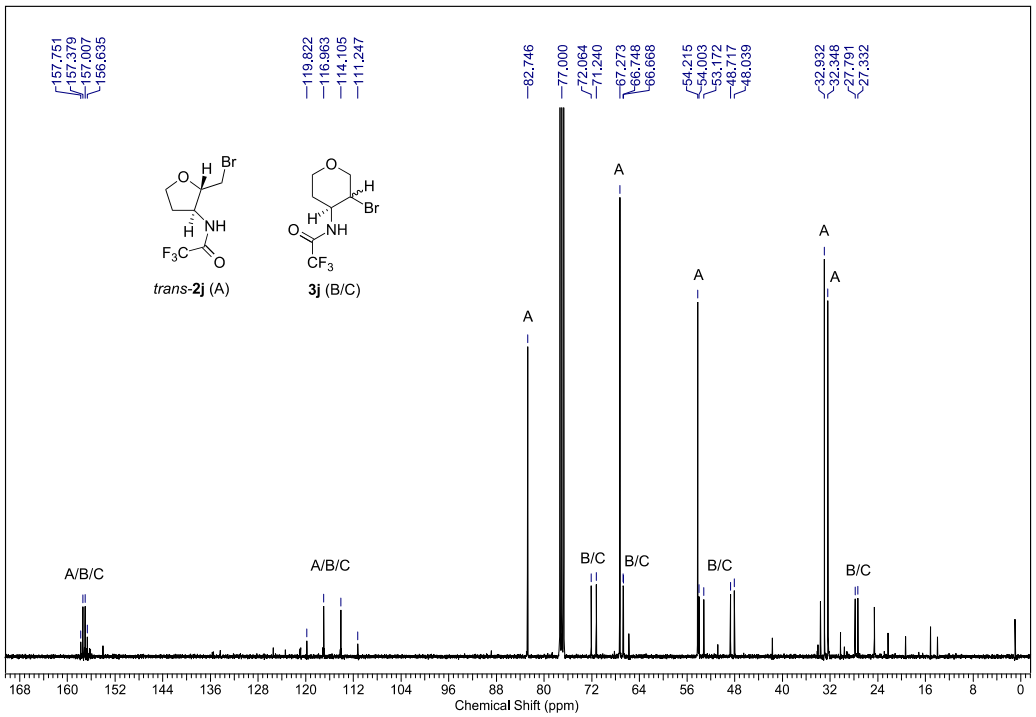

Figure S6.16 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-fluoroacetamidetetrahydrofuran *trans*-(**2j**) and 3-bromo-4-fluoroacetamidetetrahydropyran (**3j**) (24/76-mixture of *isomer 1*/*isomer 2*).

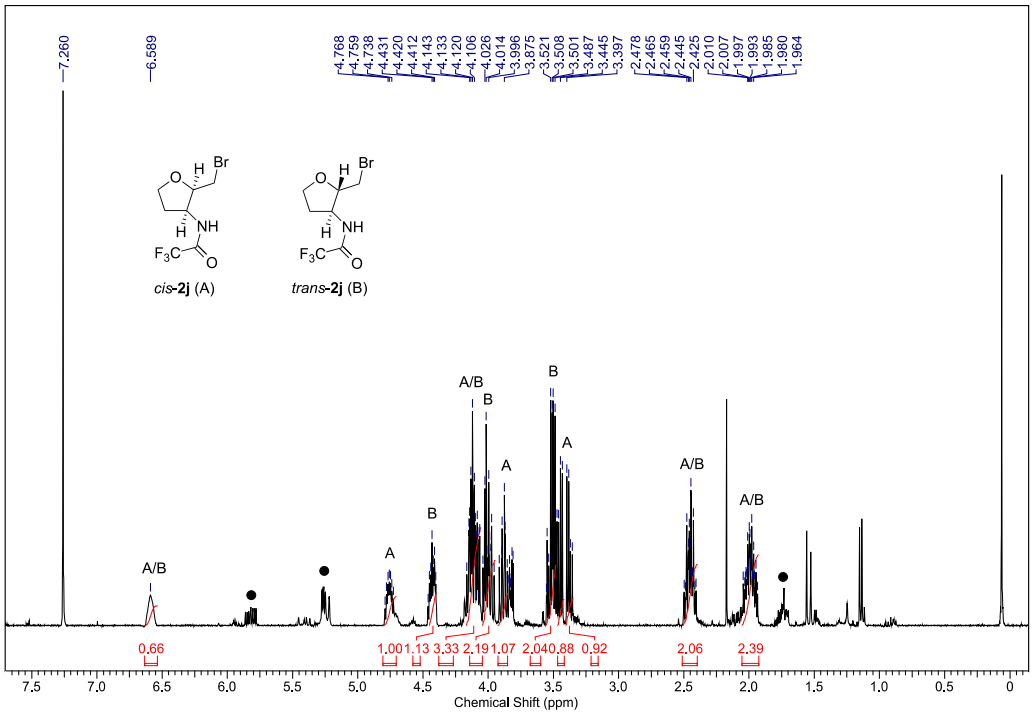

Figure S6.17 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 2-bromomethyl-3-trifluoroacetamidotetrahydrofuran (**2j**) (48/52-mixture of *cis*/*trans*-isomers).

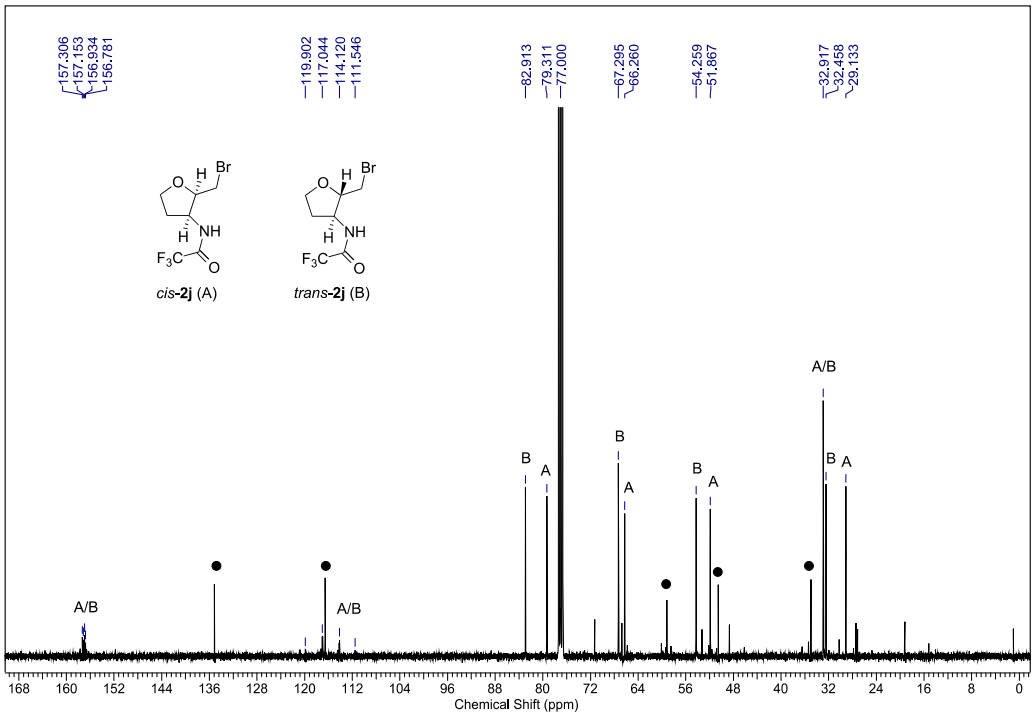

Figure S6.18 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of 2-bromomethyl-3-trifluoroacetamidotetrahydrofuran (**2j**) (48/52-mixture of *cis*/*trans*-isomers).

6.6 Bromocyclization products of 3-benzenesulfonamidopentenyl thiohydroxamate 1k

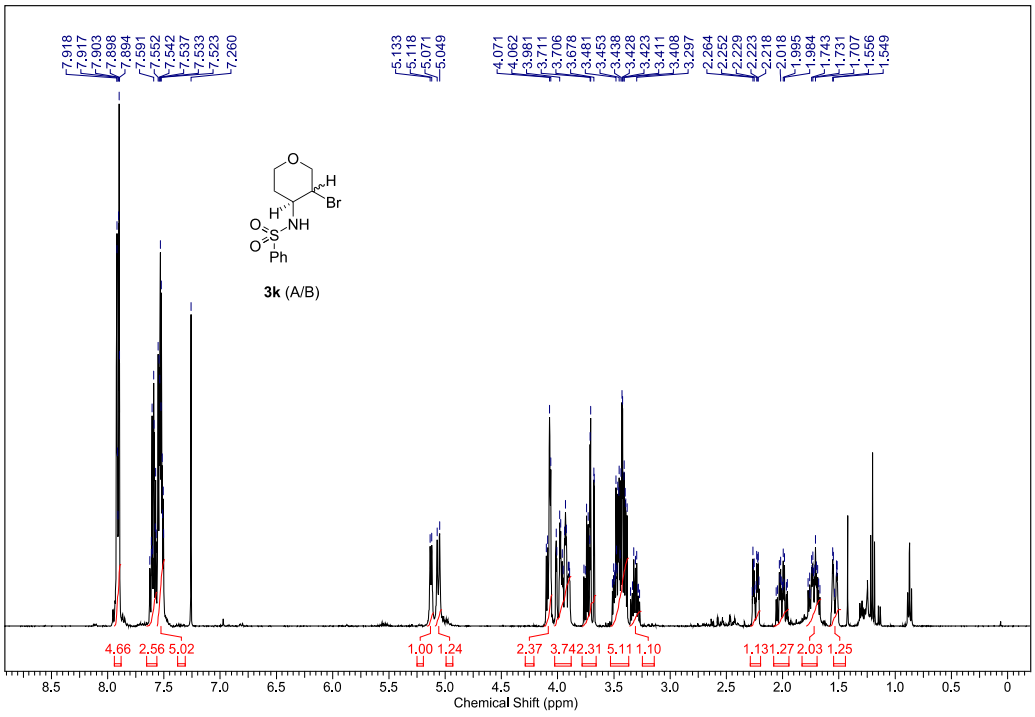

Figure S6.19 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 3-bromo-4-benzenesulfonamidotetrahydropyran (**3k**) (44/56-mixture of *isomer 1*/*isomer 2*).

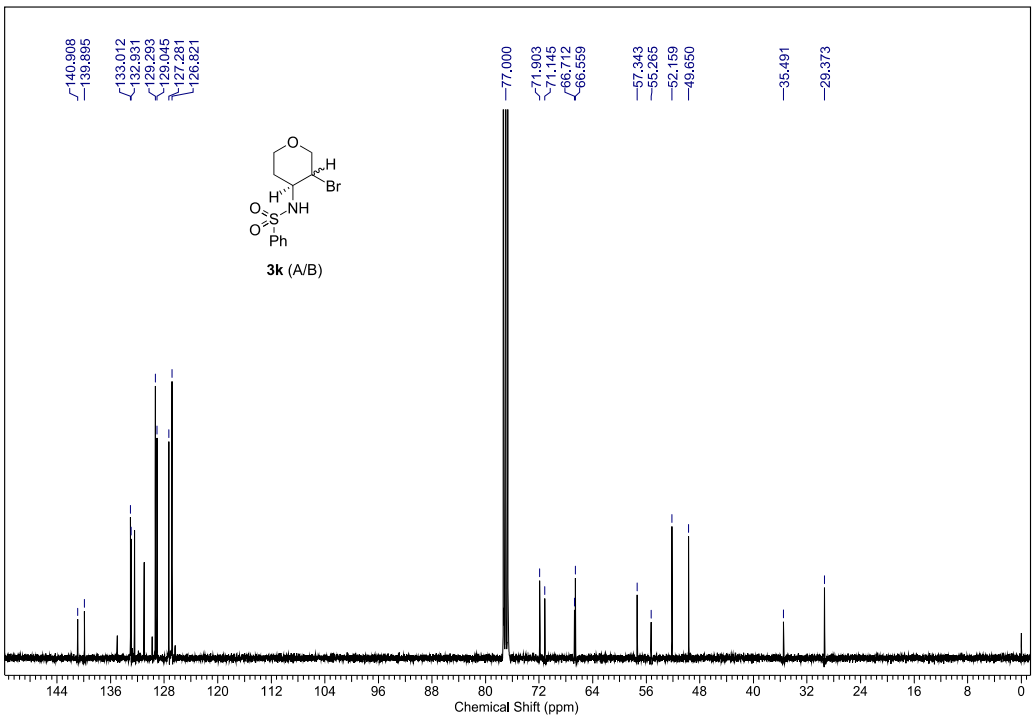

Figure S6.20 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of 3-bromo-4-benzenesulfonamidetetrahydropyran (**3k**) (44/56-mixture of *isomer 1*/*isomer 2*).

6.7 Bromocyclization products of 3-benzamidopentenyl thiohydroxamate 1l

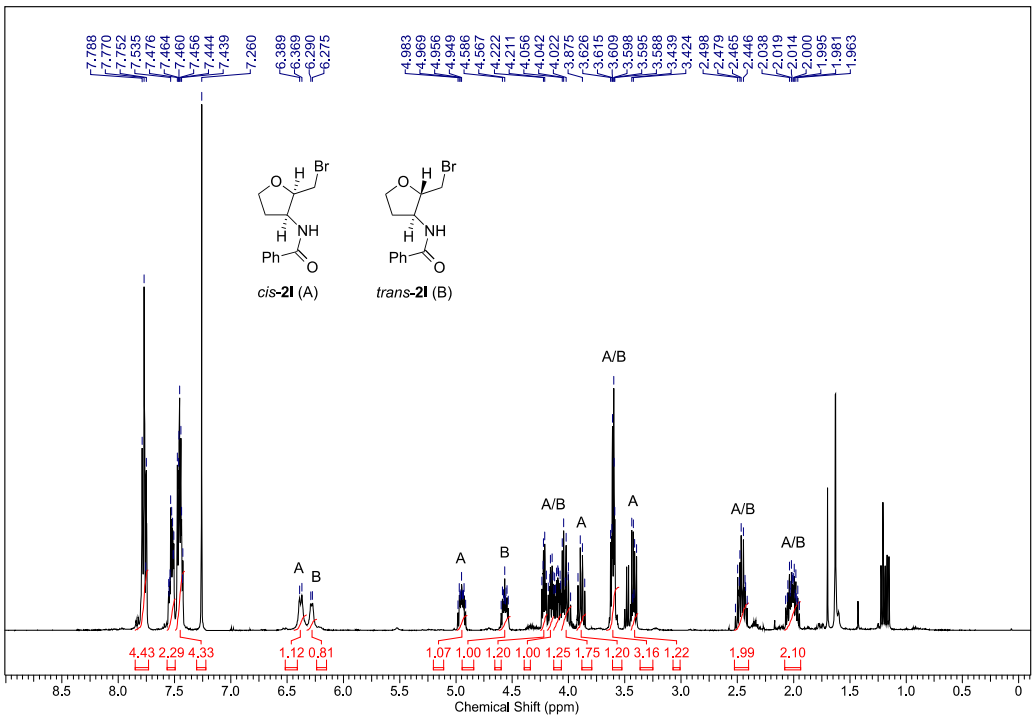

Figure S6.21 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 2-bromomethyl-3-benzamidotetrahydrofuran (**2l**) (52/48-mixture of *cis*/*trans*-isomers).

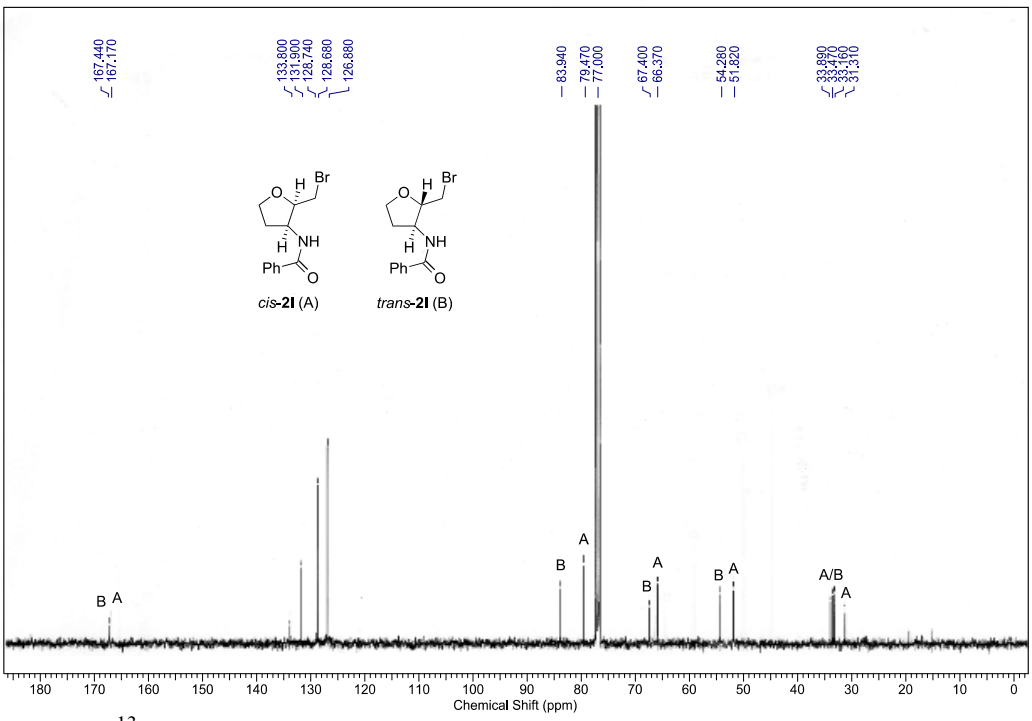

Figure S6.22 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of 2-bromomethyl-3-benzamidotetrahydrofuran (**2l**) (52/48-mixture of *cis*/*trans*-isomers).

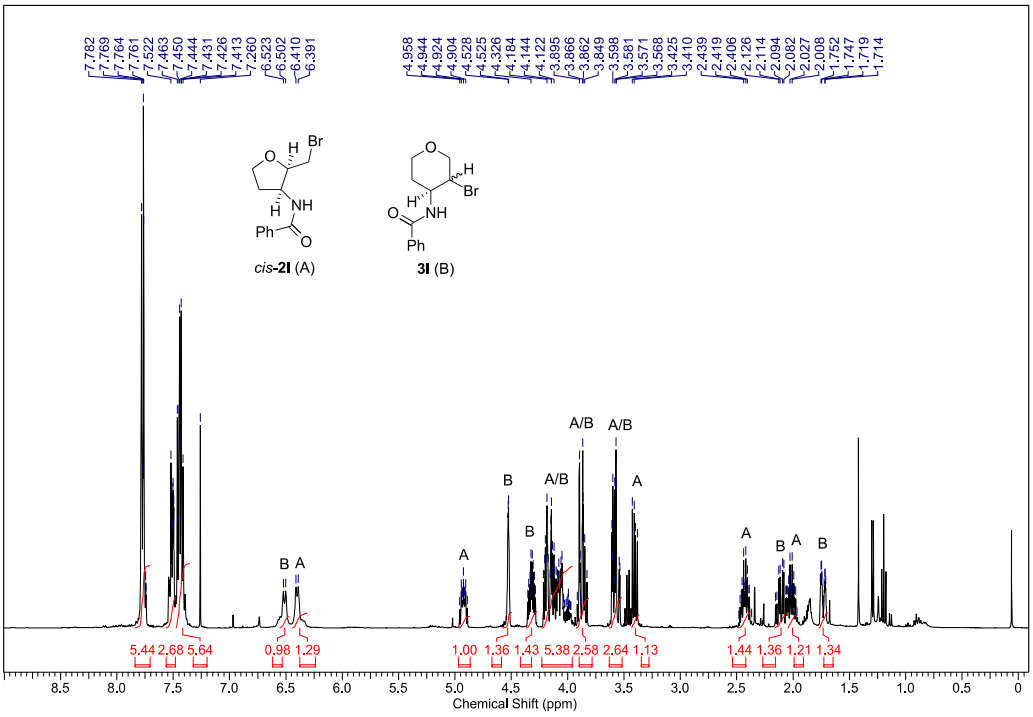

Figure S6.23 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of *rel*-(2*R*,3*S*)-2-bromomethyl-3-benzamidetetrahydrofuran *cis*-(**2l**) and 3-bromo-4-benzamidetetrahydropyran (**3l**).

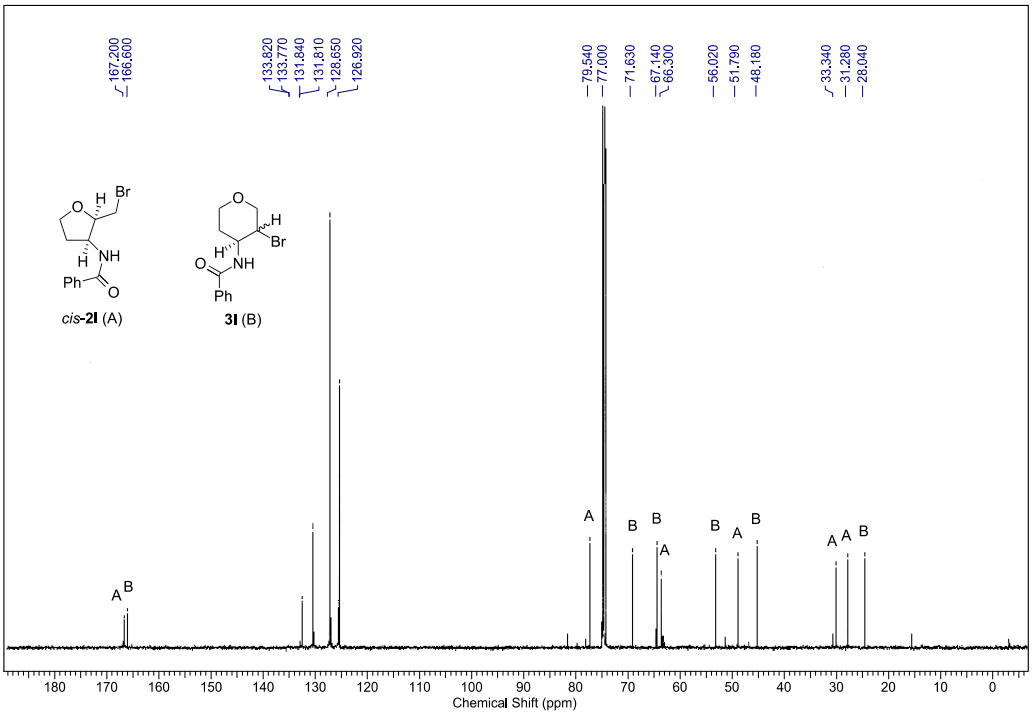

Figure S6.24 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of *rel*-(2*R*,3*S*)-2-bromomethyl-3-benzamidotetrahydrofuran *cis*-(**2l**) and 3-bromo-4-benzamidotetrahydropyran (**3l**).

6.7 Bromocyclization products of 3-(phthalimido-*N*-yl)pentenyl thiohydroxmate 1m

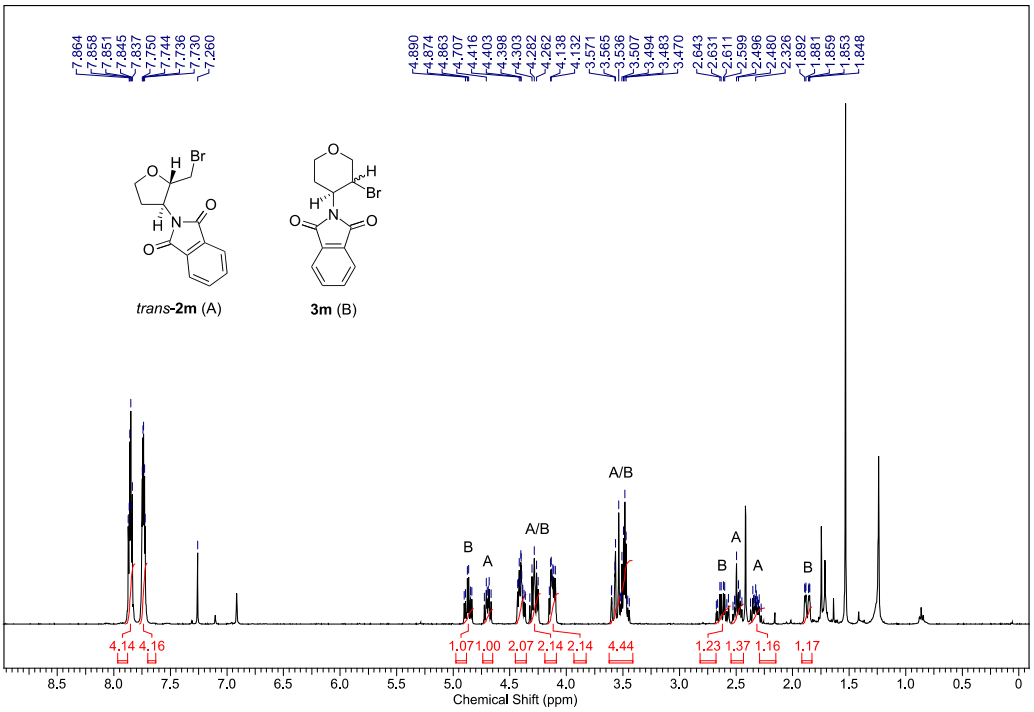

Figure S6.25 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-(*N*-phthalimodyl)tetrahydrofuran *trans*-(**2m**) and 3-bromo-4-(*N*-phthalimidoyl)tetrahydropyran (**3m**).

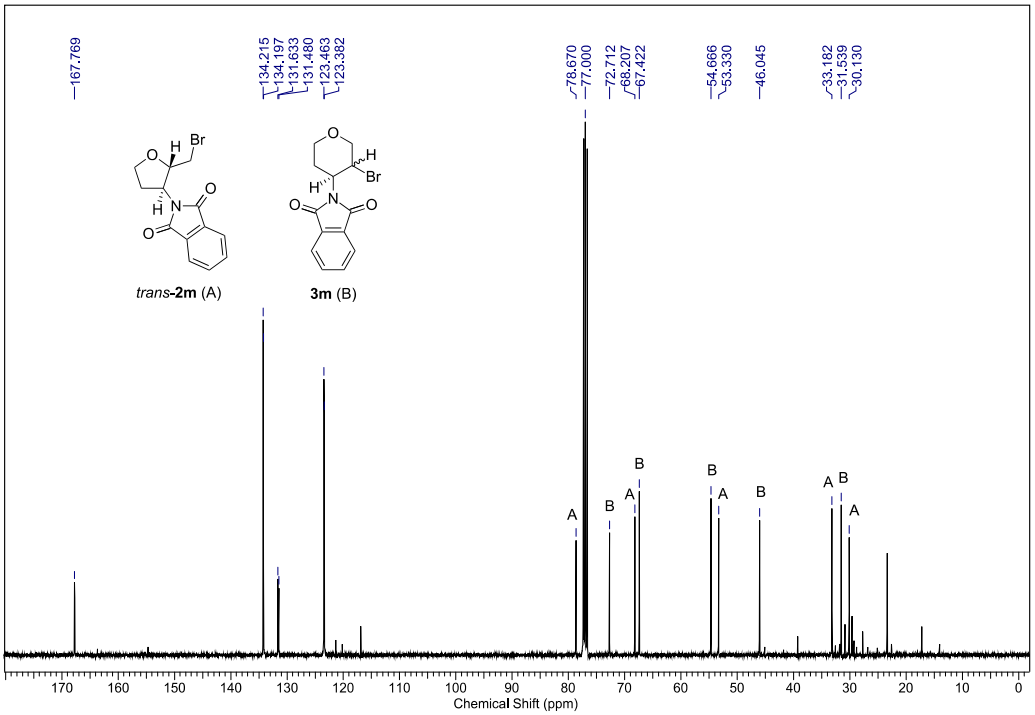

Figure S6.26 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of *rel*-(2*S*,3*S*)-2-bromomethyl-3-(*N*-phthalimodyl)tetrahydrofuran *trans*-(**2m**) and 3-bromo-4-(*N*-phthalimidoyl)tetrahydropyran (**3m**).

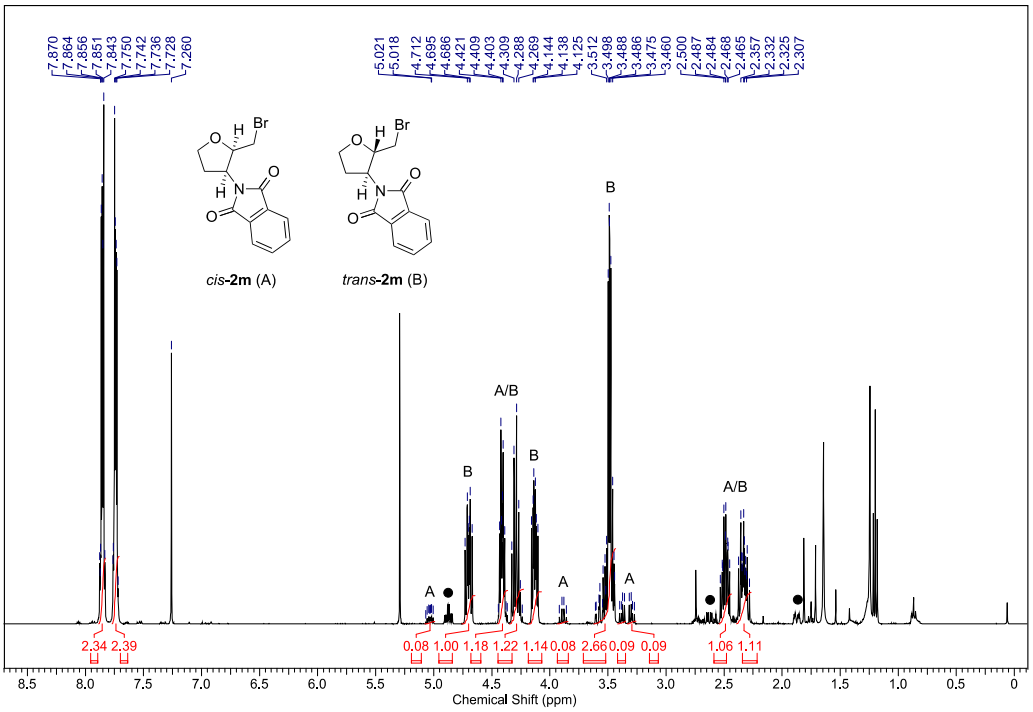

Figure S6.27 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 2-bromomethyl-3-(*N*-phthalimodyl)-tetrahydrofuran (**2m**) (7/93-mixture of *cis*/*trans*-isomers).

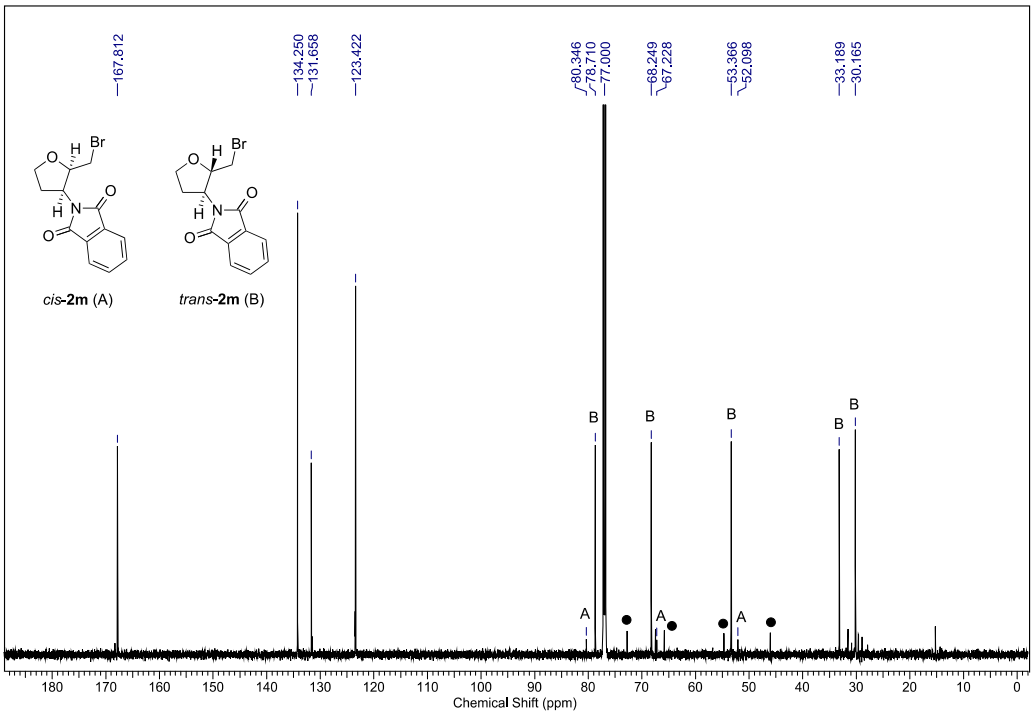

Figure S6.28 ^{13}C-NMR-spectrum ($CDCl_3$, 150 MHz) of 2-bromomethyl-3-(*N*-phthalimodyl)tetrahydrofuran (**2m**) (7/93-mixture of *cis*/*trans*-isomers).

6.8 Bromocyclization products of 3-(benzoylsulfanyl)pentenyl thiohydroxmate 1n

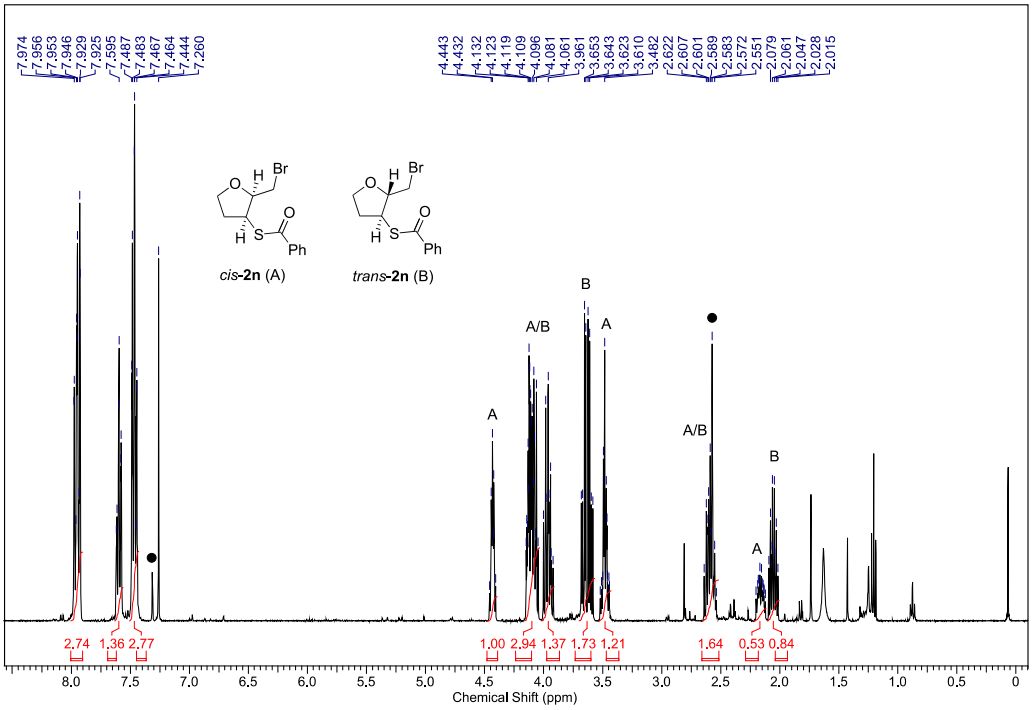

Figure S6.29 ^{1}H-NMR-spectrum ($CDCl_3$, 400 MHz) of 2-bromomethyl-3-(benzoylsulfanyl)tetrahydrofuran (**2n**) (25/75-mixture of *cis*/*trans*-isomers).

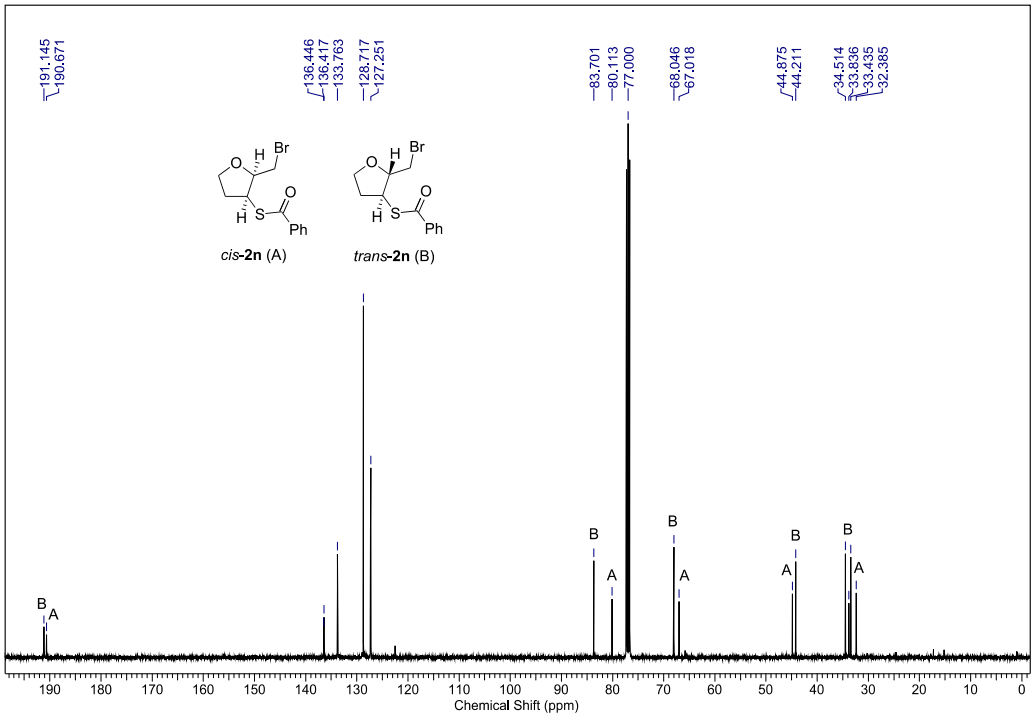

Figure S6.30 ^{13}C-NMR-spectrum ($CDCl_3$, 100 MHz) of 2-bromomethyl-3-benzothiatetetrahydrofuran (**2n**) (25/75-mixture of *cis*/*trans*-isomers).

7 Molecular Modelling

7.1 Electronic structure methods

Structures and energies reported in the associated article were computed with the density functional/Hartree-Fock-hybrid models B3LYP and BHandHLYP in combination with the split valence double-ζ basis sets 6-31+G(d,p) and the triple-ζ basis set B3LYP/6-311++G(d,p) implemented in Gaussian03 (Revision E.01).[2] All energy functions were minimized without adding symmetry constraints or internal coordinates, using the Bernie-algorithm in combination with the tight-option and the ultrafine grid for integration. All structures used for thermochemical calculations pose minima on the associated potential energy, as secured by absence of negative normal modes from calculated vibrational spectra.

The preferred orientation of heteroatom bound hydrogen in alcohols, thiols, and amines, and the methyl radical side chain in (tetrahydrofuran-2-yl)methyl radicals (*cis*/*trans*-**II**) was taken from potential energy scans on the B3LYP/6-31+G**-level of theory of the underlying dihedral angle by the opt=modredundant keyword.

Transition structures were located with the Berny algorithm. Hessian matrices of transition structures had exactly one negative stretching mode. Animations of eigenvector coordinates using Molden[4] were performed to verify that the imaginary mode correlates with the trajectory of C,O bond formation.

Approximate Gibbs free energies ($G°$) were obtained through thermochemical analysis for 298.15 Kelvin and a pressure of 1 atmosphere by unscaled frequency calculation. Gibbs free energies obtained accordingly are corrected for zero-point vibrational energy, temperature, and molecular entropy. Transition structures are maxima on electronic potential energy hypersurfaces, which not necessarily have to be maxima on the free energy surface.

NBO-calculations[5] for characterizing HOMOs of butenes were conducted on the B3LYP/6-31G*-level for B3LYP/6-31+G**-minimized structures.

7.2 Conformational analysis of 4-pentenoxyl radicals

Input coordinates for calculating minimum structures for a 4-pentenoxyl radical on the density functional level of theory were taken from the global minimum of a usage-directed conformational search, conducted with the the MM+-force-field. MM+ is implemented in HyperChem 8.0. Minima from conformational searches were subjected on the density functional level of theory to unconstrained energy minimization-routines, using the default algorithm implemented in Gaussian03.

7.3 4-Pentenoxyl Radicals

7.3.1 3-Hydroxypent-4-enyl-1-oxyl radical (Ia)

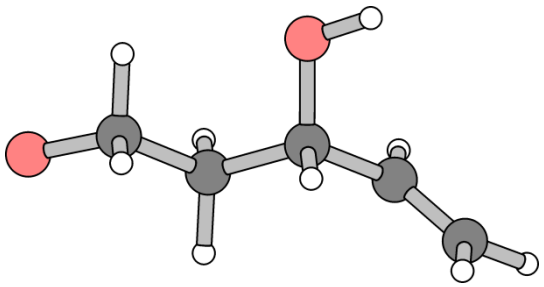

Figure S7.1. Minimum structure for 3-hydroxy-4-pentenoxyl radical **Ia**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.088838	-0.573245	-0.114231
2	6	0	-1.945256	0.020871	0.339422
3	6	0	-0.647311	-0.512765	-0.285197
4	6	0	0.588663	0.242033	0.208636
5	6	0	1.861661	-0.270814	-0.411339
6	6	0	2.895525	-0.754634	0.283181
7	1	0	-2.061572	1.094394	0.072554
8	1	0	-1.909609	0.017945	1.446258
9	1	0	-0.538815	-1.574749	-0.038138
10	1	0	-0.716890	-0.430190	-1.375810
11	8	0	0.377610	1.624961	-0.135246
12	1	0	0.659462	0.144615	1.304253
13	1	0	1.906733	-0.213720	-1.499138
14	1	0	3.795515	-1.113070	-0.207578
15	1	0	2.872763	-0.817130	1.369335
16	1	0	1.162543	2.130031	0.115857

```
Zero-point correction=                          0.132069
(Hartree/Particle)
Thermal correction to Energy=                   0.140353
Thermal correction to Enthalpy=                 0.141297
Thermal correction to Gibbs Free Energy=        0.098481
Sum of electronic and zero-point Energies=           -346.191960
Sum of electronic and thermal Energies=              -346.183676
Sum of electronic and thermal Enthalpies=            -346.182732
Sum of electronic and thermal Free Energies=         -346.225548

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.060197	-0.595100	-0.107169
2	6	0	-1.929620	0.045152	0.326538
3	6	0	-0.644205	-0.497467	-0.280604
4	6	0	0.584299	0.250769	0.208795
5	6	0	1.846623	-0.269206	-0.408228
6	6	0	2.862816	-0.766966	0.280743
7	1	0	-2.069041	1.093165	0.035540
8	1	0	-1.898060	0.046757	1.421085
9	1	0	-0.540557	-1.550062	-0.027275
10	1	0	-0.705611	-0.423830	-1.364280
11	8	0	0.384774	1.615300	-0.130332
12	1	0	0.655481	0.151680	1.295149
13	1	0	1.896024	-0.206823	-1.487144
14	1	0	3.752385	-1.131561	-0.206143
15	1	0	2.835421	-0.834263	1.358126
16	1	0	1.157864	2.119642	0.111486

Zero-point correction= 0.137758
(Hartree/Particle)
Thermal correction to Energy= 0.145817
Thermal correction to Enthalpy= 0.146761
Thermal correction to Gibbs Free Energy= 0.104385
Sum of electronic and zero-point Energies= -345.985707
Sum of electronic and thermal Energies= -345.977649
Sum of electronic and thermal Enthalpies= -345.976705
Sum of electronic and thermal Free Energies= -346.019081

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.054818	-0.584005	-0.121443
2	6	0	-1.926412	0.033723	0.334221
3	6	0	-0.639892	-0.504158	-0.272667
4	6	0	0.583847	0.251161	0.211777
5	6	0	1.847606	-0.259273	-0.406618
6	6	0	2.859597	-0.763421	0.273321
7	1	0	-2.046804	1.088448	0.063344
8	1	0	-1.900099	0.015791	1.428284
9	1	0	-0.531238	-1.555731	-0.022389
10	1	0	-0.705473	-0.428001	-1.354732
11	8	0	0.375123	1.610399	-0.132998
12	1	0	0.657788	0.152528	1.297136
13	1	0	1.897070	-0.179250	-1.483091
14	1	0	3.750189	-1.119151	-0.215731
15	1	0	2.830258	-0.845786	1.348444
16	1	0	1.137392	2.111804	0.134055

Zero-point correction= 0.137375
(Hartree/Particle)
Thermal correction to Energy= 0.145423
Thermal correction to Enthalpy= 0.146368
Thermal correction to Gibbs Free Energy= 0.103997
Sum of electronic and zero-point Energies= -346.051755
Sum of electronic and thermal Energies= -346.043707
Sum of electronic and thermal Enthalpies= -346.042763
Sum of electronic and thermal Free Energies= -346.085133

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7.3.2 3-Methylpent-4-enyl-1-oxyl radical (Ib)

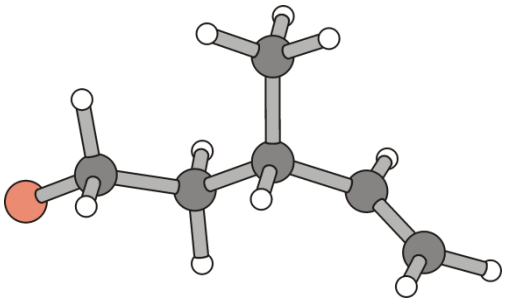

Figure S7.2. Minimum structure for 3-hydroxy-4-pentenoxyl radical **Ib**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.080550	-0.665679	-0.112879
2	6	0	-1.962258	-0.018784	0.343476
3	6	0	-0.653483	-0.430275	-0.346649
4	6	0	0.602665	0.281238	0.209077
5	6	0	1.846400	-0.325886	-0.394015
6	6	0	2.807910	-0.957728	0.285006
7	1	0	-2.187562	1.053479	0.151262
8	1	0	-1.891797	-0.089853	1.446391
9	1	0	-0.536934	-1.513071	-0.222339
10	1	0	-0.748435	-0.243055	-1.424012
11	6	0	0.572739	1.802593	-0.044215
12	1	0	0.639905	0.112183	1.295289
13	1	0	1.941441	-0.223920	-1.477221
14	1	0	3.679198	-1.372441	-0.213561
15	1	0	2.755885	-1.082641	1.364689
16	1	0	1.475492	2.278370	0.351044
17	1	0	0.522421	2.018552	-1.118560
18	1	0	-0.289052	2.280875	0.433964

```
Zero-point correction=                           0.155303
(Hartree/Particle)
Thermal correction to Energy=                    0.163994
Thermal correction to Enthalpy=                  0.164939
Thermal correction to Gibbs Free Energy=         0.121160
Sum of electronic and zero-point Energies=           -310.263009
Sum of electronic and thermal Energies=              -310.254318
Sum of electronic and thermal Enthalpies=            -310.253374
Sum of electronic and thermal Free Energies=         -310.297152

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

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1	8	0	-3.054380	-0.675413	-0.108253
2	6	0	-1.947911	0.006560	0.332736
3	6	0	-0.651081	-0.429696	-0.332809
4	6	0	0.597250	0.277505	0.211343
5	6	0	1.831145	-0.328197	-0.391820
6	6	0	2.789769	-0.946575	0.281856
7	1	0	-2.180081	1.056085	0.112080
8	1	0	-1.887597	-0.055633	1.424467
9	1	0	-0.543067	-1.502498	-0.187580
10	1	0	-0.735091	-0.265078	-1.406670
11	6	0	0.568735	1.786318	-0.048761
12	1	0	0.639473	0.114982	1.289701
13	1	0	1.919806	-0.235910	-1.467852
14	1	0	3.652534	-1.359795	-0.214694
15	1	0	2.743289	-1.061147	1.354512
16	1	0	1.472775	2.257044	0.326539
17	1	0	0.503149	1.993503	-1.115765
18	1	0	-0.277584	2.266265	0.436020

```
Zero-point correction=                          0.161482
(Hartree/Particle)
Thermal correction to Energy=                   0.169936
Thermal correction to Enthalpy=                 0.170881
Thermal correction to Gibbs Free Energy=        0.127597
Sum of electronic and zero-point Energies=           -310.064764
Sum of electronic and thermal Energies=              -310.056310
Sum of electronic and thermal Enthalpies=            -310.055366
Sum of electronic and thermal Free Energies=         -310.098650

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.050007	-0.669572	-0.114034
2	6	0	-1.947193	0.001115	0.338413
3	6	0	-0.651160	-0.426735	-0.332175
4	6	0	0.597333	0.277245	0.210563
5	6	0	1.829776	-0.329675	-0.391048
6	6	0	2.783096	-0.946074	0.280881
7	1	0	-2.173414	1.054568	0.134096
8	1	0	-1.884646	-0.074730	1.428470
9	1	0	-0.541204	-1.499160	-0.194626
10	1	0	-0.740419	-0.255729	-1.403389
11	6	0	0.570860	1.784817	-0.049497
12	1	0	0.638764	0.115280	1.287528
13	1	0	1.917337	-0.237960	-1.465994
14	1	0	3.644939	-1.360782	-0.213471
15	1	0	2.735790	-1.059197	1.352454
16	1	0	1.475896	2.252877	0.323234
17	1	0	0.503233	1.991163	-1.115334
18	1	0	-0.272484	2.266089	0.436485

Zero-point correction= 0.160863
(Hartree/Particle)
Thermal correction to Energy= 0.169326
Thermal correction to Enthalpy= 0.170270
Thermal correction to Gibbs Free Energy= 0.126954
Sum of electronic and zero-point Energies= -310.120491
Sum of electronic and thermal Energies= -310.112028
Sum of electronic and thermal Enthalpies= -310.111084
Sum of electronic and thermal Free Energies= -310.154400

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7.3.3 3-Fluoropent-4-enyl-1-oxyl radical (Ih)

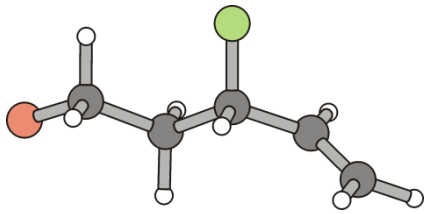

Figure S7.3. Minimum structure of 3-fluoro-4-pentenoxyl radical **Ih**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.076876	-0.585423	-0.119492
2	6	0	-1.940215	0.024302	0.332787
3	6	0	-0.637277	-0.502871	-0.287299
4	6	0	0.596561	0.238469	0.215566
5	6	0	1.876334	-0.224314	-0.410892
6	6	0	2.899174	-0.732217	0.280048
7	1	0	-2.073004	1.096006	0.068136
8	1	0	-1.908885	0.021355	1.439711
9	1	0	-0.528593	-1.566238	-0.043322
10	1	0	-0.698315	-0.421461	-1.378421
11	9	0	0.421261	1.619832	-0.097352
12	1	0	0.666530	0.190145	1.309272
13	1	0	1.928561	-0.134066	-1.495166
14	1	0	3.801982	-1.079428	-0.212992
15	1	0	2.867917	-0.821635	1.363626

```
Zero-point correction=                          0.119749
(Hartree/Particle)
Thermal correction to Energy=                   0.127729
Thermal correction to Enthalpy=                 0.128673
Thermal correction to Gibbs Free Energy=        0.086162
Sum of electronic and zero-point Energies=           -370.224241
Sum of electronic and thermal Energies=              -370.216261
Sum of electronic and thermal Enthalpies=            -370.215317
Sum of electronic and thermal Free Energies=         -370.257828

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.046626	-0.602041	-0.120208
2	6	0	-1.921954	0.040441	0.324993
3	6	0	-0.631277	-0.490631	-0.282436
4	6	0	0.591763	0.249554	0.217364
5	6	0	1.864028	-0.213059	-0.407409
6	6	0	2.865980	-0.745217	0.273902
7	1	0	-2.069455	1.091709	0.049812
8	1	0	-1.897146	0.026256	1.419579
9	1	0	-0.522481	-1.544712	-0.036050
10	1	0	-0.686808	-0.413543	-1.366093
11	9	0	0.418201	1.606889	-0.090591
12	1	0	0.662768	0.195097	1.301762
13	1	0	1.924999	-0.100540	-1.480693
14	1	0	3.760661	-1.090985	-0.216701
15	1	0	2.825419	-0.855475	1.346894

Zero-point correction= 0.124865
(Hartree/Particle)
Thermal correction to Energy= 0.132635
Thermal correction to Enthalpy= 0.133579
Thermal correction to Gibbs Free Energy= 0.091480
Sum of electronic and zero-point Energies= -370.020509
Sum of electronic and thermal Energies= -370.012740
Sum of electronic and thermal Enthalpies= -370.011796
Sum of electronic and thermal Free Energies= -370.053895

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.034970	-0.597308	-0.140006
2	6	0	-1.915767	0.028479	0.326825
3	6	0	-0.619733	-0.503064	-0.266562
4	6	0	0.592167	0.257838	0.224729
5	6	0	1.866729	-0.188436	-0.404249
6	6	0	2.856927	-0.750979	0.259007
7	1	0	-2.042878	1.082960	0.057355
8	1	0	-1.902576	0.009048	1.420855
9	1	0	-0.502894	-1.551938	-0.007724
10	1	0	-0.675540	-0.438635	-1.349901
11	9	0	0.395518	1.603808	-0.084827
12	1	0	0.668483	0.201006	1.307469
13	1	0	1.933151	-0.035469	-1.470979
14	1	0	3.751384	-1.084664	-0.237777
15	1	0	2.809037	-0.901145	1.325696

```
Zero-point correction=                          0.124448
(Hartree/Particle)
Thermal correction to Energy=                   0.132210
Thermal correction to Enthalpy=                 0.133154
Thermal correction to Gibbs Free Energy=        0.091072
Sum of electronic and zero-point Energies=                -370.092337
Sum of electronic and thermal Energies=                   -370.084576
Sum of electronic and thermal Enthalpies=                 -370.083632
Sum of electronic and thermal Free Energies=              -370.125714

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```

7.3.4 3-Chloropent-4-enyl-1-oxyl radical (Ii)

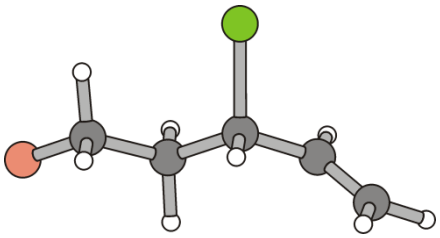

Figure S7.4. Minimum structure of 3-fluoro-4-pentenoxyl radical **Ii**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.195219	-0.720956	-0.129018
2	6	0	-2.034349	-0.187138	0.353980
3	6	0	-0.761623	-0.707838	-0.329312
4	6	0	0.534423	-0.116546	0.225635
5	6	0	1.762153	-0.688761	-0.410040
6	6	0	2.742276	-1.282619	0.275811
7	1	0	-2.134273	0.907294	0.182608
8	1	0	-1.987551	-0.283746	1.456183
9	1	0	-0.709889	-1.794768	-0.186029
10	1	0	-0.828778	-0.525159	-1.407216
11	17	0	0.532233	1.721923	-0.038886
12	1	0	0.581203	-0.227860	1.312148
13	1	0	1.814901	-0.612638	-1.495039
14	1	0	3.604496	-1.710503	-0.226141
15	1	0	2.716408	-1.360251	1.360240

```
Zero-point correction=                          0.118463
(Hartree/Particle)
Thermal correction to Energy=                   0.126711
Thermal correction to Enthalpy=                 0.127655
Thermal correction to Gibbs Free Energy=        0.084133
Sum of electronic and zero-point Energies=           -730.579868
Sum of electronic and thermal Energies=              -730.571620
Sum of electronic and thermal Enthalpies=            -730.570676
Sum of electronic and thermal Free Energies=         -730.614198

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[X(C5H8Cl1O1)]\ NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.169836	-0.732973	-0.126081
2	6	0	-2.020091	-0.159698	0.347493
3	6	0	-0.761084	-0.680713	-0.330228
4	6	0	0.528466	-0.099518	0.224815
5	6	0	1.744089	-0.687188	-0.406215
6	6	0	2.694885	-1.308739	0.273743
7	1	0	-2.144013	0.914639	0.166604
8	1	0	-1.974858	-0.268443	1.436125
9	1	0	-0.712942	-1.759885	-0.192712
10	1	0	-0.823465	-0.494283	-1.399562
11	17	0	0.547829	1.708643	-0.035614
12	1	0	0.571872	-0.220360	1.301751
13	1	0	1.809509	-0.594067	-1.480736
14	1	0	3.546481	-1.742790	-0.223141
15	1	0	2.655422	-1.402829	1.348116

Zero-point correction= 0.123478
(Hartree/Particle)
Thermal correction to Energy= 0.131504
Thermal correction to Enthalpy= 0.132448
Thermal correction to Gibbs Free Energy= 0.089354
Sum of electronic and zero-point Energies= -730.398245
Sum of electronic and thermal Energies= -730.390219
Sum of electronic and thermal Enthalpies= -730.389275
Sum of electronic and thermal Free Energies= -730.432370

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.167011	-0.722500	-0.133191
2	6	0	-2.021021	-0.166188	0.355761
3	6	0	-0.763298	-0.671486	-0.334615
4	6	0	0.526961	-0.101752	0.223267
5	6	0	1.740716	-0.690083	-0.405074
6	6	0	2.680798	-1.318371	0.272948
7	1	0	-2.139061	0.912546	0.204897
8	1	0	-1.973097	-0.302070	1.440549
9	1	0	-0.715223	-1.751999	-0.216953
10	1	0	-0.831034	-0.465964	-1.398645
11	17	0	0.556834	1.709221	-0.034321
12	1	0	0.567516	-0.219103	1.298641
13	1	0	1.808751	-0.590740	-1.477468
14	1	0	3.531557	-1.754225	-0.221119
15	1	0	2.635571	-1.417926	1.345357

```
Zero-point correction=                          0.123016
(Hartree/Particle)
Thermal correction to Energy=                   0.131056
Thermal correction to Enthalpy=                 0.132000
Thermal correction to Gibbs Free Energy=        0.088859
Sum of electronic and zero-point Energies=                -730.473979
Sum of electronic and thermal Energies=                   -730.465939
Sum of electronic and thermal Enthalpies=                 -730.464995
Sum of electronic and thermal Free Energies=              -730.508136

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NImag=0\\@.
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7.3.5 3-Aminopent-4-enyl-1-oxyl radical (Io)

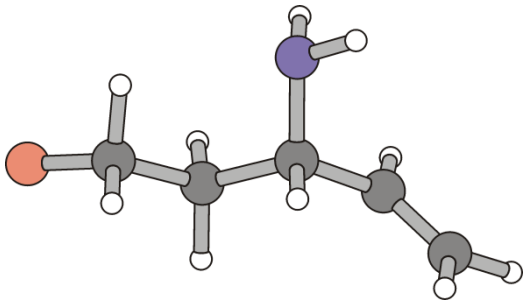

Figure S7.5. Minimum structure of 3-amino-4-pentenoxyl radical **Io**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.092369	-0.531507	-0.156345
2	6	0	-1.935781	-0.071335	0.397093
3	6	0	-0.646915	-0.512012	-0.314546
4	6	0	0.586445	0.247806	0.204036
5	6	0	1.862726	-0.279157	-0.411847
6	6	0	2.889589	-0.791842	0.272574
7	1	0	-2.001981	1.039760	0.326164
8	1	0	-1.897670	-0.271833	1.485461
9	1	0	-0.501357	-1.589000	-0.175702
10	1	0	-0.766580	-0.341089	-1.392882
11	7	0	0.378637	1.691378	-0.023270
12	1	0	0.649789	0.110231	1.292318
13	1	0	1.923642	-0.206828	-1.499964
14	1	0	3.788989	-1.144257	-0.223823
15	1	0	2.862972	-0.880648	1.356848
16	1	0	1.137223	2.234048	0.381345
17	1	0	0.357082	1.901277	-1.019980

```
Zero-point correction=                          0.144855
(Hartree/Particle)
Thermal correction to Energy=                   0.153252
Thermal correction to Enthalpy=                 0.154196
Thermal correction to Gibbs Free Energy=        0.111217
Sum of electronic and zero-point Energies=           -326.312481
Sum of electronic and thermal Energies=              -326.304085
Sum of electronic and thermal Enthalpies=            -326.303141
Sum of electronic and thermal Free Energies=         -326.346119

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[X(C5H10N1O1)]\ NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.065706	-0.580336	-0.140165
2	6	0	-1.926005	-0.030071	0.381220
3	6	0	-0.649307	-0.467305	-0.321605
4	6	0	0.585369	0.262684	0.203439
5	6	0	1.844020	-0.289301	-0.406710
6	6	0	2.841122	-0.834650	0.274425
7	1	0	-2.057974	1.053820	0.273764
8	1	0	-1.878735	-0.210320	1.460041
9	1	0	-0.515600	-1.539126	-0.194894
10	1	0	-0.759017	-0.287091	-1.391357
11	7	0	0.416369	1.697396	-0.016548
12	1	0	0.640848	0.115486	1.282235
13	1	0	1.915972	-0.208680	-1.485083
14	1	0	3.726189	-1.206419	-0.215491
15	1	0	2.803150	-0.931243	1.349325
16	1	0	1.185041	2.215582	0.375620
17	1	0	0.380000	1.910767	-1.001612

```
Zero-point correction=                          0.150852
(Hartree/Particle)
Thermal correction to Energy=                   0.159069
Thermal correction to Enthalpy=                 0.160013
Thermal correction to Gibbs Free Energy=        0.117323
Sum of electronic and zero-point Energies=           -326.108343
Sum of electronic and thermal Energies=              -326.100126
Sum of electronic and thermal Enthalpies=            -326.099182
Sum of electronic and thermal Free Energies=         -326.141872

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NImag=0\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.063090	-0.564146	-0.149654
2	6	0	-1.924850	-0.036449	0.384722
3	6	0	-0.647572	-0.479767	-0.311657
4	6	0	0.583956	0.256444	0.206501
5	6	0	1.844017	-0.284987	-0.405312
6	6	0	2.844233	-0.819581	0.269099
7	1	0	-2.034327	1.049813	0.285175
8	1	0	-1.883976	-0.223733	1.462109
9	1	0	-0.512642	-1.549387	-0.177777
10	1	0	-0.759315	-0.306294	-1.381126
11	7	0	0.405685	1.689797	-0.018484
12	1	0	0.642337	0.111555	1.284159
13	1	0	1.910814	-0.201618	-1.482646
14	1	0	3.731028	-1.181968	-0.222206
15	1	0	2.809637	-0.917675	1.342791
16	1	0	1.182158	2.203014	0.362440
17	1	0	0.380508	1.886918	-1.006423

```
Zero-point correction=                          0.150401
(Hartree/Particle)
Thermal correction to Energy=                   0.158592
Thermal correction to Enthalpy=                 0.159536
Thermal correction to Gibbs Free Energy=        0.116927
Sum of electronic and zero-point Energies=           -326.168067
Sum of electronic and thermal Energies=              -326.159876
Sum of electronic and thermal Enthalpies=            -326.158932
Sum of electronic and thermal Free Energies=         -326.201541

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7.3.6 3-Mercaptopent-4-enyl-1-oxyl radical (Ip)

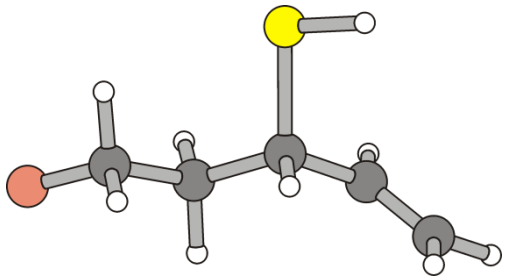

Figure S7.6. Minimum structure of 3-mercapto-4-pentenoxyl radical **Ip**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.219184	-0.674863	-0.125005
2	6	0	-2.041682	-0.210519	0.387800
3	6	0	-0.784002	-0.675158	-0.362785
4	6	0	0.526261	-0.107794	0.210801
5	6	0	1.740024	-0.733193	-0.412013
6	6	0	2.696737	-1.364871	0.275589
7	1	0	-2.132902	0.898033	0.343421
8	1	0	-1.978422	-0.423268	1.473118
9	1	0	-0.732024	-1.768678	-0.304241
10	1	0	-0.881941	-0.416264	-1.423812
11	16	0	0.526628	1.740261	-0.076476
12	1	0	0.546017	-0.268278	1.294705
13	1	0	1.813154	-0.645424	-1.495625
14	1	0	3.553805	-1.808190	-0.222055
15	1	0	2.654476	-1.460669	1.358500
16	1	0	1.661234	1.996685	0.603298

```
Zero-point correction=                          0.126780
(Hartree/Particle)
Thermal correction to Energy=                   0.135671
Thermal correction to Enthalpy=                 0.136615
Thermal correction to Gibbs Free Energy=        0.091915
Sum of electronic and zero-point Energies=           -669.161736
Sum of electronic and thermal Energies=              -669.152845
Sum of electronic and thermal Enthalpies=            -669.151901
Sum of electronic and thermal Free Energies=         -669.196601

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.196348	-0.699474	-0.112755
2	6	0	-2.035252	-0.149721	0.363650
3	6	0	-0.787051	-0.653896	-0.348260
4	6	0	0.519603	-0.097692	0.217348
5	6	0	1.713339	-0.743409	-0.406957
6	6	0	2.653353	-1.384431	0.272731
7	1	0	-2.162984	0.932155	0.235814
8	1	0	-1.976399	-0.303037	1.446280
9	1	0	-0.754274	-1.737406	-0.255407
10	1	0	-0.863881	-0.428357	-1.410189
11	16	0	0.548703	1.724418	-0.071029
12	1	0	0.541768	-0.261418	1.291911
13	1	0	1.783161	-0.660077	-1.482716
14	1	0	3.493978	-1.839841	-0.224062
15	1	0	2.613141	-1.475860	1.347699
16	1	0	1.733079	1.953843	0.498093

Zero-point correction= 0.132166
(Hartree/Particle)
Thermal correction to Energy= 0.140816
Thermal correction to Enthalpy= 0.141760
Thermal correction to Gibbs Free Energy= 0.097555
Sum of electronic and zero-point Energies= -668.973520
Sum of electronic and thermal Energies= -668.964870
Sum of electronic and thermal Enthalpies= -668.963926
Sum of electronic and thermal Free Energies= -669.008131

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-3.192833	-0.692701	-0.115834
2	6	0	-2.036384	-0.150890	0.367074
3	6	0	-0.788635	-0.648561	-0.348714
4	6	0	0.518558	-0.099261	0.216709
5	6	0	1.709824	-0.746685	-0.405987
6	6	0	2.643382	-1.387564	0.271864
7	1	0	-2.159316	0.931920	0.249553
8	1	0	-1.974526	-0.311855	1.447675
9	1	0	-0.757052	-1.731607	-0.264278
10	1	0	-0.868691	-0.415350	-1.407399
11	16	0	0.555064	1.722883	-0.071257
12	1	0	0.538308	-0.259174	1.289898
13	1	0	1.778349	-0.663028	-1.480464
14	1	0	3.482535	-1.845323	-0.222627
15	1	0	2.601850	-1.478252	1.345615
16	1	0	1.739718	1.945921	0.503141

```
Zero-point correction=                          0.131645
(Hartree/Particle)
Thermal correction to Energy=                   0.140313
Thermal correction to Enthalpy=                 0.141257
Thermal correction to Gibbs Free Energy=        0.096986
Sum of electronic and zero-point Energies=                -669.047454
Sum of electronic and thermal Energies=                   -669.038786
Sum of electronic and thermal Enthalpies=                 -669.037842
Sum of electronic and thermal Free Energies=              -669.082112

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NImag=0\\@.
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7.4 Tetrahydrofuran-2-ylmethyl Radicals

7.4.1 *cis*-(3-Hydroxytetrahydrofuran-2-yl)methyl radical *cis*-(IIa)

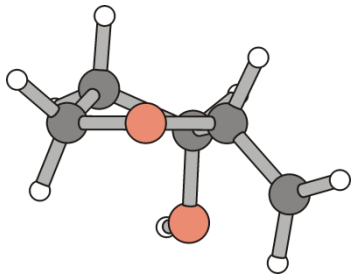

Figure S7.7. Minimum structure of *cis*-(hydroxytetrahydrofuran-2-yl)methyl radical *cis*-**IIa**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.769482	-0.439876	0.516891
2	8	0	-0.037688	-1.425919	-0.207511
3	6	0	-1.321511	-0.872762	-0.525343
4	6	0	-1.507309	0.296820	0.444416
5	6	0	-0.078826	0.850533	0.539382
6	8	0	0.257665	1.648802	-0.598539
7	6	0	2.114483	-0.323169	-0.102015
8	1	0	-2.069296	-1.663176	-0.405964
9	1	0	-1.332791	-0.527188	-1.567930
10	1	0	-1.832296	-0.062716	1.428092
11	1	0	-2.228816	1.044301	0.097199
12	1	0	0.103020	1.414320	1.463721
13	1	0	0.858753	-0.808204	1.548037
14	1	0	-0.286203	2.446464	-0.589326
15	1	0	2.924376	-0.959185	0.237671
16	1	0	2.245525	0.263042	-1.003081

```
Zero-point correction=                          0.134126
(Hartree/Particle)
Thermal correction to Energy=                   0.141780
Thermal correction to Enthalpy=                 0.142725
Thermal correction to Gibbs Free Energy=        0.101728
Sum of electronic and zero-point Energies=           -346.203146
Sum of electronic and thermal Energies=              -346.195491
Sum of electronic and thermal Enthalpies=            -346.194547
Sum of electronic and thermal Free Energies=         -346.235544

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.757693	-0.437995	0.505346
2	8	0	-0.022216	-1.387466	-0.241617
3	6	0	-1.316800	-0.876015	-0.505029
4	6	0	-1.493970	0.289014	0.457945
5	6	0	-0.077481	0.843929	0.529894
6	8	0	0.236688	1.618784	-0.608016
7	6	0	2.114448	-0.308959	-0.075068
8	1	0	-2.039556	-1.672435	-0.353782
9	1	0	-1.374193	-0.541813	-1.539717
10	1	0	-1.801102	-0.065530	1.439815
11	1	0	-2.219262	1.024175	0.119142
12	1	0	0.114918	1.412124	1.438654
13	1	0	0.827971	-0.813134	1.527015
14	1	0	-0.290669	2.412860	-0.608997
15	1	0	2.889383	-0.993482	0.223333
16	1	0	2.273385	0.326853	-0.926927

Zero-point correction= 0.139536
(Hartree/Particle)
Thermal correction to Energy= 0.146967
Thermal correction to Enthalpy= 0.147911
Thermal correction to Gibbs Free Energy= 0.107370
Sum of electronic and zero-point Energies= -345.998968
Sum of electronic and thermal Energies= -345.991537
Sum of electronic and thermal Enthalpies= -345.990593
Sum of electronic and thermal Free Energies= -346.031135

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.761467	-0.431247	0.511673
2	8	0	-0.012902	-1.395800	-0.220131
3	6	0	-1.290996	-0.874597	-0.522410
4	6	0	-1.495741	0.271102	0.454737
5	6	0	-0.087071	0.841226	0.535747
6	8	0	0.218301	1.614930	-0.602857
7	6	0	2.107383	-0.284127	-0.085976
8	1	0	-2.021745	-1.668708	-0.414744
9	1	0	-1.312793	-0.513526	-1.548306
10	1	0	-1.801059	-0.104462	1.427848
11	1	0	-2.227135	1.001448	0.122992
12	1	0	0.095171	1.410047	1.444933
13	1	0	0.848388	-0.800127	1.532625
14	1	0	-0.328271	2.391764	-0.598963
15	1	0	2.883917	-0.980296	0.174191
16	1	0	2.250081	0.376687	-0.919298

```
Zero-point correction=                          0.139250
(Hartree/Particle)
Thermal correction to Energy=                   0.146614
Thermal correction to Enthalpy=                 0.147558
Thermal correction to Gibbs Free Energy=        0.107222
Sum of electronic and zero-point Energies=           -346.064600
Sum of electronic and thermal Energies=              -346.057236
Sum of electronic and thermal Enthalpies=            -346.056292
Sum of electronic and thermal Free Energies=         -346.096627

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7.4.2 *trans*-(3-Hydroxytetrahydrofuran-2-yl)methyl radical *trans*-(IIa)

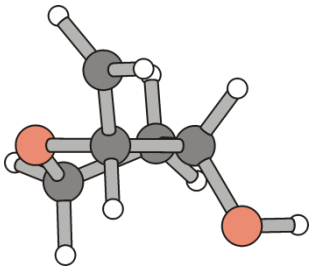

Figure S7.8. Minimum structure of *trans*-(3-hydroxytetrahydrofuran-2-yl)methyl radical *trans*-**IIa**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.867941	-0.169480	-0.319491
2	8	0	-0.664803	1.250397	-0.358488
3	6	0	0.740023	1.494542	-0.281877
4	6	0	1.232703	0.470125	0.742907
5	6	0	0.394181	-0.774275	0.397039
6	8	0	1.031678	-1.637352	-0.550872
7	6	0	-2.174430	-0.465494	0.316166
8	1	0	0.879526	2.536438	0.016308
9	1	0	1.215049	1.335353	-1.261953
10	1	0	0.992055	0.813052	1.755390
11	1	0	2.307387	0.268421	0.688117
12	1	0	0.111462	-1.345341	1.288950
13	1	0	-0.837347	-0.577335	-1.344375
14	1	0	1.746628	-2.114374	-0.109848
15	1	0	-2.621299	-1.447993	0.209955
16	1	0	-2.675674	0.294912	0.903866

```
Zero-point correction=                          0.133825
(Hartree/Particle)
Thermal correction to Energy=                   0.141487
Thermal correction to Enthalpy=                 0.142431
Thermal correction to Gibbs Free Energy=        0.100974
Sum of electronic and zero-point Energies=           -346.205963
Sum of electronic and thermal Energies=              -346.198301
Sum of electronic and thermal Enthalpies=            -346.197357
Sum of electronic and thermal Free Energies=         -346.238814

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.850491	-0.242481	-0.339160
2	8	0	-0.693365	1.162894	-0.453532
3	6	0	0.662272	1.495910	-0.245650
4	6	0	1.115907	0.515301	0.822385
5	6	0	0.417255	-0.768047	0.383996
6	8	0	1.169691	-1.492963	-0.570029
7	6	0	-2.131615	-0.538246	0.341015
8	1	0	0.708060	2.536486	0.055840
9	1	0	1.235045	1.367325	-1.165180
10	1	0	0.741605	0.828448	1.794333
11	1	0	2.194336	0.398205	0.885720
12	1	0	0.159955	-1.412289	1.221396
13	1	0	-0.835013	-0.693832	-1.335276
14	1	0	1.936595	-1.875061	-0.151028
15	1	0	-2.492580	-1.551283	0.394891
16	1	0	-2.738593	0.267937	0.712274

Zero-point correction= 0.139106
(Hartree/Particle)
Thermal correction to Energy= 0.146611
Thermal correction to Enthalpy= 0.147555
Thermal correction to Gibbs Free Energy= 0.106188
Sum of electronic and zero-point Energies= -346.001634
Sum of electronic and thermal Energies= -345.994128
Sum of electronic and thermal Enthalpies= -345.993184
Sum of electronic and thermal Free Energies= -346.034551

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.837347	-0.316605	-0.369653
2	8	0	-0.681351	1.075643	-0.596330
3	6	0	0.606063	1.489635	-0.193197
4	6	0	0.976985	0.530609	0.923073
5	6	0	0.431123	-0.780081	0.374420
6	8	0	1.296261	-1.345397	-0.587769
7	6	0	-2.100769	-0.558199	0.363928
8	1	0	0.545621	2.525789	0.117071
9	1	0	1.309620	1.407607	-1.020085
10	1	0	0.454138	0.797168	1.837385
11	1	0	2.041628	0.487377	1.129766
12	1	0	0.197754	-1.504273	1.150058
13	1	0	-0.843991	-0.840764	-1.327298
14	1	0	2.097778	-1.618076	-0.155838
15	1	0	-2.450501	-1.562655	0.525888
16	1	0	-2.727662	0.273709	0.624421

```
Zero-point correction=                          0.138805
(Hartree/Particle)
Thermal correction to Energy=                   0.146207
Thermal correction to Enthalpy=                 0.147151
Thermal correction to Gibbs Free Energy=        0.106516
Sum of electronic and zero-point Energies=           -346.066957
Sum of electronic and thermal Energies=              -346.059555
Sum of electronic and thermal Enthalpies=            -346.058611
Sum of electronic and thermal Free Energies=         -346.099245

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7.4.3 *cis*-(3-Methyltetrahydrofuran-2-yl)methyl radical *cis*-(IIb)

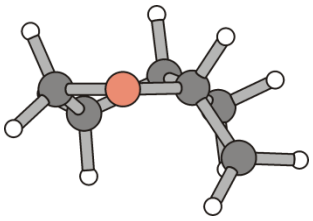

Figure S7.9. Minimum structure of *cis*-(3-methyltetrahydrofuran-2-yl)methyl radical *cis*-**IIb**.

(*i*) B3LYP/6-31+G//B3LYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.032331	0.869961	-0.474882
2	8	0	-1.387737	0.739148	-0.260982
3	6	0	-1.729461	-0.615726	0.071641
4	6	0	-0.422501	-1.279399	0.500802
5	6	0	0.595290	-0.592403	-0.422805
6	6	0	2.059988	-0.734817	-0.012105
7	6	0	0.600508	1.831825	0.509774
8	1	0	-2.156483	-1.115334	-0.811239
9	1	0	-2.493356	-0.588469	0.855094
10	1	0	-0.438528	-2.367661	0.381876
11	1	0	-0.196732	-1.052049	1.550154
12	1	0	0.472265	-1.013298	-1.430559
13	1	0	0.186005	1.268407	-1.491631
14	1	0	1.571804	2.286688	0.341994
15	1	0	0.025370	2.119228	1.382496
16	1	0	2.364833	-1.786836	-0.037280
17	1	0	2.722512	-0.183749	-0.689498
18	1	0	2.227268	-0.356748	1.001902

```
Zero-point correction=                          0.157345
(Hartree/Particle)
Thermal correction to Energy=                   0.165326
Thermal correction to Enthalpy=                 0.166270
Thermal correction to Gibbs Free Energy=        0.124492
Sum of electronic and zero-point Energies=           -310.279294
Sum of electronic and thermal Energies=              -310.271313
Sum of electronic and thermal Enthalpies=            -310.270369
Sum of electronic and thermal Free Energies=         -310.312147

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1=0.\ S2A=0.75001\RMSD=5.721e-09\RMSF=2.777e-07\PG=C01 [X(C6H11O1)]\
NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.001037	0.855753	-0.479266
2	8	0	-1.398379	0.658978	-0.329511
3	6	0	-1.687626	-0.663213	0.100304
4	6	0	-0.357325	-1.266250	0.519671
5	6	0	0.615152	-0.562038	-0.421338
6	6	0	2.078906	-0.643943	-0.028422
7	6	0	0.493062	1.813473	0.545688
8	1	0	-2.129438	-1.219399	-0.727157
9	1	0	-2.416106	-0.613473	0.904506
10	1	0	-0.336821	-2.348120	0.422665
11	1	0	-0.126016	-1.012592	1.552914
12	1	0	0.495919	-0.996884	-1.414384
13	1	0	0.169098	1.281440	-1.472958
14	1	0	1.509653	2.169095	0.520487
15	1	0	-0.207854	2.275984	1.217903
16	1	0	2.424097	-1.674405	-0.061180
17	1	0	2.706075	-0.067342	-0.705345
18	1	0	2.239186	-0.268824	0.978811

Zero-point correction= 0.163269
(Hartree/Particle)
Thermal correction to Energy= 0.171013
Thermal correction to Enthalpy= 0.171958
Thermal correction to Gibbs Free Energy= 0.130640
Sum of electronic and zero-point Energies= -310.082806
Sum of electronic and thermal Energies= -310.075061
Sum of electronic and thermal Enthalpies= -310.074117
Sum of electronic and thermal Free Energies= -310.115434

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.010912	0.853271	-0.480554
2	8	0	-1.406179	0.631932	-0.355261
3	6	0	-1.672680	-0.681938	0.106828
4	6	0	-0.333433	-1.261759	0.528628
5	6	0	0.625237	-0.552248	-0.420713
6	6	0	2.090478	-0.610784	-0.035449
7	6	0	0.450160	1.807625	0.560247
8	1	0	-2.112987	-1.263181	-0.702303
9	1	0	-2.393216	-0.629065	0.916430
10	1	0	-0.298088	-2.342553	0.442092
11	1	0	-0.102130	-0.993916	1.556818
12	1	0	0.504511	-0.992661	-1.409631
13	1	0	0.165571	1.288595	-1.466937
14	1	0	1.461225	2.175732	0.559603
15	1	0	-0.274023	2.268012	1.206385
16	1	0	2.450767	-1.634965	-0.062036
17	1	0	2.704671	-0.030467	-0.719216
18	1	0	2.250038	-0.225987	0.966964

Zero-point correction= 0.162732
(Hartree/Particle)
Thermal correction to Energy= 0.170444
Thermal correction to Enthalpy= 0.171389
Thermal correction to Gibbs Free Energy= 0.130253
Sum of electronic and zero-point Energies= -310.138009
Sum of electronic and thermal Energies= -310.130296
Sum of electronic and thermal Enthalpies= -310.129352
Sum of electronic and thermal Free Energies= -310.170487

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7.4.3 *cis*-(3-Methyltetrahydrofuran-2-yl)methyl radical *cis*-(IIb)

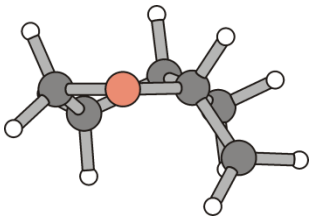

Figure S7.9. Minimum structure of *cis*-(3-methyltetrahydrofuran-2-yl)methyl radical *cis*-**IIb**.

(*i*) B3LYP/6-31+G//B3LYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.032331	0.869961	-0.474882
2	8	0	-1.387737	0.739148	-0.260982
3	6	0	-1.729461	-0.615726	0.071641
4	6	0	-0.422501	-1.279399	0.500802
5	6	0	0.595290	-0.592403	-0.422805
6	6	0	2.059988	-0.734817	-0.012105
7	6	0	0.600508	1.831825	0.509774
8	1	0	-2.156483	-1.115334	-0.811239
9	1	0	-2.493356	-0.588469	0.855094
10	1	0	-0.438528	-2.367661	0.381876
11	1	0	-0.196732	-1.052049	1.550154
12	1	0	0.472265	-1.013298	-1.430559
13	1	0	0.186005	1.268407	-1.491631
14	1	0	1.571804	2.286688	0.341994
15	1	0	0.025370	2.119228	1.382496
16	1	0	2.364833	-1.786836	-0.037280
17	1	0	2.722512	-0.183749	-0.689498
18	1	0	2.227268	-0.356748	1.001902

```
Zero-point correction=                          0.157345
(Hartree/Particle)
Thermal correction to Energy=                   0.165326
Thermal correction to Enthalpy=                 0.166270
Thermal correction to Gibbs Free Energy=        0.124492
Sum of electronic and zero-point Energies=           -310.279294
Sum of electronic and thermal Energies=              -310.271313
Sum of electronic and thermal Enthalpies=            -310.270369
Sum of electronic and thermal Free Energies=         -310.312147

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.001037	0.855753	-0.479266
2	8	0	-1.398379	0.658978	-0.329511
3	6	0	-1.687626	-0.663213	0.100304
4	6	0	-0.357325	-1.266250	0.519671
5	6	0	0.615152	-0.562038	-0.421338
6	6	0	2.078906	-0.643943	-0.028422
7	6	0	0.493062	1.813473	0.545688
8	1	0	-2.129438	-1.219399	-0.727157
9	1	0	-2.416106	-0.613473	0.904506
10	1	0	-0.336821	-2.348120	0.422665
11	1	0	-0.126016	-1.012592	1.552914
12	1	0	0.495919	-0.996884	-1.414384
13	1	0	0.169098	1.281440	-1.472958
14	1	0	1.509653	2.169095	0.520487
15	1	0	-0.207854	2.275984	1.217903
16	1	0	2.424097	-1.674405	-0.061180
17	1	0	2.706075	-0.067342	-0.705345
18	1	0	2.239186	-0.268824	0.978811

Zero-point correction= 0.163269
(Hartree/Particle)
Thermal correction to Energy= 0.171013
Thermal correction to Enthalpy= 0.171958
Thermal correction to Gibbs Free Energy= 0.130640
Sum of electronic and zero-point Energies= -310.082806
Sum of electronic and thermal Energies= -310.075061
Sum of electronic and thermal Enthalpies= -310.074117
Sum of electronic and thermal Free Energies= -310.115434

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NImag=0\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.010912	0.853271	-0.480554
2	8	0	-1.406179	0.631932	-0.355261
3	6	0	-1.672680	-0.681938	0.106828
4	6	0	-0.333433	-1.261759	0.528628
5	6	0	0.625237	-0.552248	-0.420713
6	6	0	2.090478	-0.610784	-0.035449
7	6	0	0.450160	1.807625	0.560247
8	1	0	-2.112987	-1.263181	-0.702303
9	1	0	-2.393216	-0.629065	0.916430
10	1	0	-0.298088	-2.342553	0.442092
11	1	0	-0.102130	-0.993916	1.556818
12	1	0	0.504511	-0.992661	-1.409631
13	1	0	0.165571	1.288595	-1.466937
14	1	0	1.461225	2.175732	0.559603
15	1	0	-0.274023	2.268012	1.206385
16	1	0	2.450767	-1.634965	-0.062036
17	1	0	2.704671	-0.030467	-0.719216
18	1	0	2.250038	-0.225987	0.966964

Zero-point correction= 0.162732
(Hartree/Particle)
Thermal correction to Energy= 0.170444
Thermal correction to Enthalpy= 0.171389
Thermal correction to Gibbs Free Energy= 0.130253
Sum of electronic and zero-point Energies= -310.138009
Sum of electronic and thermal Energies= -310.130296
Sum of electronic and thermal Enthalpies= -310.129352
Sum of electronic and thermal Free Energies= -310.170487

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7.4.4 *trans*-(3-Methyltetrahydrofuran-2-yl)methyl radical *trans*-(IIb)

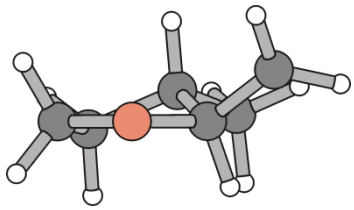

Figure S7.10. Minimum structure of *trans*-(3-methyltetrahydrofuran-2-yl)methyl radical *trans*-**IIb**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.150556	0.809926	0.347400
2	8	0	-1.281606	0.845395	0.199104
3	6	0	-1.790709	-0.468417	-0.093393
4	6	0	-0.595903	-1.425734	-0.011400
5	6	0	0.593278	-0.511458	-0.346056
6	6	0	1.960101	-1.028284	0.097272
7	6	0	0.742375	2.055174	-0.197234
8	1	0	-2.230389	-0.454404	-1.099886
9	1	0	-2.583805	-0.707681	0.624102
10	1	0	-0.688185	-2.275726	-0.695289
11	1	0	-0.483861	-1.822786	1.005644
12	1	0	0.607765	-0.327810	-1.429275
13	1	0	0.397748	0.724208	1.421632
14	1	0	1.664473	2.457629	0.207535
15	1	0	0.272107	2.547478	-1.041666
16	1	0	2.205249	-1.970813	-0.404187
17	1	0	2.752982	-0.310567	-0.139860
18	1	0	1.980568	-1.209936	1.178878

```
Zero-point correction=                          0.157395
(Hartree/Particle)
Thermal correction to Energy=                   0.165394
Thermal correction to Enthalpy=                 0.166338
Thermal correction to Gibbs Free Energy=        0.124689
Sum of electronic and zero-point Energies=           -310.281982
Sum of electronic and thermal Energies=              -310.273982
Sum of electronic and thermal Enthalpies=            -310.273038
Sum of electronic and thermal Free Energies=         -310.314687

Version=AM64L-G03RevE.01\State=2-A\HF=-310.4393766\S2=0.753867\S2-
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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G**// BHandHLYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.155597	0.796018	0.344494
2	8	0	-1.252221	0.857250	0.176502
3	6	0	-1.786905	-0.433487	-0.080444
4	6	0	-0.614600	-1.406413	-0.014400
5	6	0	0.578146	-0.514640	-0.346099
6	6	0	1.927691	-1.048388	0.095291
7	6	0	0.776341	2.029635	-0.183121
8	1	0	-2.246745	-0.424514	-1.067522
9	1	0	-2.560017	-0.651408	0.652201
10	1	0	-0.726004	-2.243541	-0.697819
11	1	0	-0.503665	-1.809530	0.991413
12	1	0	0.594641	-0.330873	-1.420846
13	1	0	0.386563	0.701790	1.412453
14	1	0	1.733139	2.362923	0.179819
15	1	0	0.296126	2.564839	-0.983826
16	1	0	2.157704	-1.987086	-0.402639
17	1	0	2.725571	-0.347592	-0.138336
18	1	0	1.942833	-1.229345	1.168754

```
Zero-point correction=                          0.163194
(Hartree/Particle)
Thermal correction to Energy=                   0.171003
Thermal correction to Enthalpy=                 0.171947
Thermal correction to Gibbs Free Energy=        0.130671
Sum of electronic and zero-point Energies=           -310.085418
Sum of electronic and thermal Energies=              -310.077609
Sum of electronic and thermal Enthalpies=            -310.076665
Sum of electronic and thermal Free Energies=         -310.117941

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NImag=0\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.143233	0.797066	0.347070
2	8	0	-1.265337	0.832879	0.196018
3	6	0	-1.773793	-0.458543	-0.092356
4	6	0	-0.591306	-1.414420	-0.013292
5	6	0	0.586669	-0.505631	-0.344221
6	6	0	1.944331	-1.014739	0.095773
7	6	0	0.735232	2.038297	-0.191455
8	1	0	-2.209036	-0.448025	-1.089653
9	1	0	-2.560262	-0.699426	0.616579
10	1	0	-0.685893	-2.256044	-0.691272
11	1	0	-0.479204	-1.806375	0.995369
12	1	0	0.597821	-0.321639	-1.417656
13	1	0	0.388593	0.708956	1.410990
14	1	0	1.691997	2.387936	0.151536
15	1	0	0.229820	2.561628	-0.982480
16	1	0	2.194061	-1.945530	-0.404853
17	1	0	2.727431	-0.297730	-0.133283
18	1	0	1.961174	-1.198967	1.167463

Zero-point correction= 0.162601
(Hartree/Particle)
Thermal correction to Energy= 0.170395
Thermal correction to Enthalpy= 0.171339
Thermal correction to Gibbs Free Energy= 0.130152
Sum of electronic and zero-point Energies= -310.140362
Sum of electronic and thermal Energies= -310.132567
Sum of electronic and thermal Enthalpies= -310.131623
Sum of electronic and thermal Free Energies= -310.172810

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7.4.5 *cis*-(3-Fluorotetrahydrofuran-2-yl)methyl radical *cis*-(IIh)

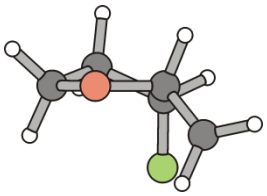

Figure S7.11. Minimum structure of *cis*-(3-fluorotetrahydrofuran-2-yl)methyl radical *cis*-**IIh**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.757223	-0.448347	0.507171
2	8	0	-0.069204	-1.393495	-0.205020
3	6	0	-1.376991	-0.847572	-0.447358
4	6	0	-1.487113	0.390436	0.451449
5	6	0	-0.045056	0.874236	0.500447
6	9	0	0.230470	1.609911	-0.670497
7	6	0	2.116829	-0.389135	-0.082433
8	1	0	-2.119752	-1.617225	-0.215981
9	1	0	-1.465865	-0.578130	-1.507598
10	1	0	-1.810350	0.115284	1.461894
11	1	0	-2.162296	1.158534	0.065594
12	1	0	0.201006	1.523930	1.344400
13	1	0	0.825300	-0.768353	1.560765
14	1	0	2.987187	-0.250689	0.549052
15	1	0	2.234822	-0.402297	-1.159146

```
Zero-point correction=                          0.121811
(Hartree/Particle)
Thermal correction to Energy=                   0.129096
Thermal correction to Enthalpy=                 0.130040
Thermal correction to Gibbs Free Energy=        0.089543
Sum of electronic and zero-point Energies=           -370.238724
Sum of electronic and thermal Energies=              -370.231440
Sum of electronic and thermal Enthalpies=            -370.230496
Sum of electronic and thermal Free Energies=         -370.270992

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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.742263	-0.446953	0.504894
2	8	0	-0.070792	-1.365674	-0.211829
3	6	0	-1.371465	-0.840298	-0.431164
4	6	0	-1.473094	0.399095	0.451066
5	6	0	-0.037999	0.871221	0.487653
6	9	0	0.233401	1.573437	-0.680583
7	6	0	2.104810	-0.395083	-0.066940
8	1	0	-2.102277	-1.602978	-0.180305
9	1	0	-1.480153	-0.585080	-1.483398
10	1	0	-1.791350	0.136261	1.457261
11	1	0	-2.141640	1.159406	0.062025
12	1	0	0.213555	1.524317	1.315810
13	1	0	0.797462	-0.765429	1.550506
14	1	0	2.946409	-0.143929	0.554833
15	1	0	2.236628	-0.486011	-1.129903

Zero-point correction= 0.126675
(Hartree/Particle)
Thermal correction to Energy= 0.133737
Thermal correction to Enthalpy= 0.134681
Thermal correction to Gibbs Free Energy= 0.094690
Sum of electronic and zero-point Energies= -370.037054
Sum of electronic and thermal Energies= -370.029992
Sum of electronic and thermal Enthalpies= -370.029047
Sum of electronic and thermal Free Energies= -370.069038

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(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.740659	-0.446981	0.516166
2	8	0	-0.080698	-1.381668	-0.167805
3	6	0	-1.350156	-0.825042	-0.457074
4	6	0	-1.473297	0.397885	0.440014
5	6	0	-0.040575	0.871246	0.491928
6	9	0	0.238822	1.567001	-0.670421
7	6	0	2.087851	-0.391618	-0.087545
8	1	0	-2.109565	-1.574668	-0.266438
9	1	0	-1.395253	-0.540961	-1.505853
10	1	0	-1.799444	0.115863	1.437000
11	1	0	-2.137587	1.161560	0.054251
12	1	0	0.201921	1.520766	1.324052
13	1	0	0.819345	-0.751418	1.562608
14	1	0	2.931959	-0.067878	0.493867
15	1	0	2.197923	-0.545867	-1.144179

Zero-point correction= 0.126262
(Hartree/Particle)
Thermal correction to Energy= 0.133287
Thermal correction to Enthalpy= 0.134231
Thermal correction to Gibbs Free Energy= 0.094380
Sum of electronic and zero-point Energies= -370.108651
Sum of electronic and thermal Energies= -370.101626
Sum of electronic and thermal Enthalpies= -370.100682
Sum of electronic and thermal Free Energies= -370.140533

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NImag=0\\@.

7.4.6 *trans*-(3-Fluorotetrahydrofuran-2-yl)methyl radical *trans*-(IIh)

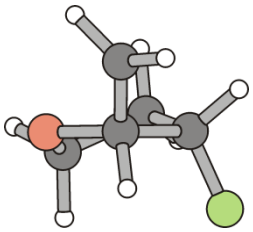

Figure S7.12. Minimum structure of *trans*-(3-fluoroltetrahydrofuran-2-yl)methyl radical *trans*-**IIh**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.877556	-0.192543	-0.350008
2	8	0	-0.578627	1.205169	-0.498828
3	6	0	0.809055	1.423963	-0.222645
4	6	0	1.143492	0.392497	0.857683
5	6	0	0.345804	-0.818124	0.389802
6	9	0	1.117466	-1.551944	-0.541999
7	6	0	-2.180808	-0.352237	0.344793
8	1	0	0.921622	2.462227	0.098459
9	1	0	1.413553	1.261897	-1.126946
10	1	0	0.762911	0.725438	1.829690
11	1	0	2.207417	0.160588	0.952084
12	1	0	0.067665	-1.521831	1.176666
13	1	0	-0.908475	-0.673048	-1.342996
14	1	0	-2.680649	-1.315189	0.352787
15	1	0	-2.652139	0.504724	0.811126

```
Zero-point correction=                          0.121703
(Hartree/Particle)
Thermal correction to Energy=                   0.128926
Thermal correction to Enthalpy=                 0.129870
Thermal correction to Gibbs Free Energy=        0.089379
Sum of electronic and zero-point Energies=                -370.240654
Sum of electronic and thermal Energies=                   -370.233432
Sum of electronic and thermal Enthalpies=                 -370.232487
Sum of electronic and thermal Free Energies=              -370.272979

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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.863757	-0.212160	-0.359935
2	8	0	-0.569743	1.165201	-0.531769
3	6	0	0.781877	1.416937	-0.197803
4	6	0	1.096273	0.394593	0.882813
5	6	0	0.347333	-0.817658	0.375826
6	9	0	1.147040	-1.490084	-0.547792
7	6	0	-2.152852	-0.360579	0.355833
8	1	0	0.857555	2.446796	0.132309
9	1	0	1.422426	1.277296	-1.068984
10	1	0	0.673962	0.710296	1.833696
11	1	0	2.152976	0.188196	1.013580
12	1	0	0.076584	-1.541770	1.134296
13	1	0	-0.911119	-0.700362	-1.337833
14	1	0	-2.599233	-1.334047	0.469528
15	1	0	-2.691808	0.515948	0.667285

Zero-point correction= 0.126554
(Hartree/Particle)
Thermal correction to Energy= 0.133579
Thermal correction to Enthalpy= 0.134523
Thermal correction to Gibbs Free Energy= 0.094397
Sum of electronic and zero-point Energies= -370.038905
Sum of electronic and thermal Energies= -370.031880
Sum of electronic and thermal Enthalpies= -370.030935
Sum of electronic and thermal Free Energies= -370.071062

Version=AM64L-G03RevE.01\State=2-A\HF=-370.1654586\S2=0.755283\S2-1=0.\ S2A=0.750018\RMSD=4.300e-09\RMSF=2.166e-07\PG=C01 [X(C5H8F1O1)]\NImag=0\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.856222	-0.252330	-0.376894
2	8	0	-0.567200	1.116642	-0.603962
3	6	0	0.743427	1.418645	-0.168511
4	6	0	1.023402	0.409745	0.932343
5	6	0	0.359449	-0.823729	0.367332
6	9	0	1.216750	-1.408308	-0.552738
7	6	0	-2.131194	-0.378788	0.366228
8	1	0	0.759296	2.448514	0.165795
9	1	0	1.451934	1.302998	-0.987013
10	1	0	0.525354	0.702519	1.851894
11	1	0	2.075392	0.245927	1.131012
12	1	0	0.103664	-1.584115	1.093201
13	1	0	-0.915671	-0.775951	-1.333746
14	1	0	-2.570630	-1.346939	0.530124
15	1	0	-2.675667	0.507429	0.632080

```
Zero-point correction=                          0.126134
(Hartree/Particle)
Thermal correction to Energy=                   0.133130
Thermal correction to Enthalpy=                 0.134074
Thermal correction to Gibbs Free Energy=        0.094162
Sum of electronic and zero-point Energies=                -370.110064
Sum of electronic and thermal Energies=                   -370.103069
Sum of electronic and thermal Enthalpies=                 -370.102124
Sum of electronic and thermal Free Energies=              -370.142036

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7.4.7 *cis*-(3-Chlortetrahydrofuran-2-yl)methyl radical *cis*-(IIi)

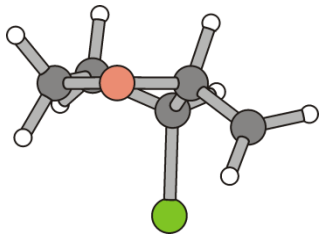

Figure S7.13. Minimum structure of *cis*-(3-chlorotetrahydrofuran-2-yl)methyl radical *cis*-**IIi**.

(*i*) B3LYP/6-31+G//B3LYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.519213	0.989885	0.442576
2	8	0	1.433496	0.548540	-0.571469
3	6	0	1.532510	-0.886831	-0.578165
4	6	0	0.703730	-1.379470	0.617892
5	6	0	-0.325044	-0.263949	0.792667
6	17	0	-1.736542	-0.499143	-0.345895
7	6	0	-0.192888	2.211725	0.001754
8	1	0	2.587809	-1.170275	-0.505689
9	1	0	1.131157	-1.259198	-1.527948
10	1	0	1.319320	-1.424725	1.524635
11	1	0	0.251314	-2.360827	0.461641
12	1	0	-0.763647	-0.205191	1.788642
13	1	0	1.084457	1.215913	1.366892
14	1	0	-0.410563	2.356099	-1.049230
15	1	0	-0.571741	2.917157	0.732668

```
Zero-point correction=                          0.120506
(Hartree/Particle)
Thermal correction to Energy=                   0.128001
Thermal correction to Enthalpy=                 0.128945
Thermal correction to Gibbs Free Energy=        0.087678
Sum of electronic and zero-point Energies=           -730.593183
Sum of electronic and thermal Energies=              -730.585688
Sum of electronic and thermal Enthalpies=            -730.584744
Sum of electronic and thermal Free Energies=         -730.626011

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.486713	0.992337	0.438241
2	8	0	1.385057	0.580478	-0.574185
3	6	0	1.546961	-0.830551	-0.571137
4	6	0	0.738582	-1.347406	0.616860
5	6	0	-0.317497	-0.270694	0.786884
6	17	0	-1.695806	-0.544255	-0.346248
7	6	0	-0.260771	2.191406	0.008755
8	1	0	2.603765	-1.068984	-0.491094
9	1	0	1.170727	-1.223576	-1.512276
10	1	0	1.350228	-1.372580	1.516736
11	1	0	0.321557	-2.335053	0.459987
12	1	0	-0.753928	-0.224632	1.775140
13	1	0	1.051221	1.230539	1.348151
14	1	0	-0.458387	2.347276	-1.036042
15	1	0	-0.700859	2.844959	0.741484

Zero-point correction= 0.125293
(Hartree/Particle)
Thermal correction to Energy= 0.132565
Thermal correction to Enthalpy= 0.133509
Thermal correction to Gibbs Free Energy= 0.092706
Sum of electronic and zero-point Energies= -730.413994
Sum of electronic and thermal Energies= -730.406722
Sum of electronic and thermal Enthalpies= -730.405778
Sum of electronic and thermal Free Energies= -730.446580

Version=AM64L-G03RevE.01\State=2-A\HF=-730.5392866\S2=0.755124\S2-1=0.\ S2A=0.750017\RMSD=3.170e-09\RMSF=5.248e-07\PG=C01 [X(C5H8Cl1O1)]\ NImag=0\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.491914	0.989740	0.438864
2	8	0	1.384074	0.576087	-0.574453
3	6	0	1.535006	-0.833521	-0.574548
4	6	0	0.734725	-1.347328	0.618778
5	6	0	-0.315119	-0.268470	0.791082
6	17	0	-1.693315	-0.538459	-0.346997
7	6	0	-0.254069	2.187763	0.009616
8	1	0	2.588725	-1.082597	-0.503803
9	1	0	1.147528	-1.225629	-1.510012
10	1	0	1.351217	-1.369333	1.513875
11	1	0	0.313742	-2.332304	0.467678
12	1	0	-0.756126	-0.221315	1.774879
13	1	0	1.056929	1.226811	1.347659
14	1	0	-0.426466	2.352445	-1.036720
15	1	0	-0.716535	2.827934	0.738265

Zero-point correction= 0.124832
(Hartree/Particle)
Thermal correction to Energy= 0.132102
Thermal correction to Enthalpy= 0.133046
Thermal correction to Gibbs Free Energy= 0.092275
Sum of electronic and zero-point Energies= -730.488944
Sum of electronic and thermal Energies= -730.481674
Sum of electronic and thermal Enthalpies= -730.480730
Sum of electronic and thermal Free Energies= -730.521502

Version=AM64L-G03RevE.01\State=2-A\HF=-730.6137766\S2=0.755231\S2-1=0.\ S2A=0.750017\RMSD=6.809e-09\RMSF=4.707e-07\PG=C01 [X(C5H8Cl1O1)]\ NImag=0\\@.

7.4.8 *trans*-(3-Chlorotetrahydrofuran-2-yl)methyl radical *tran*-(IIi)

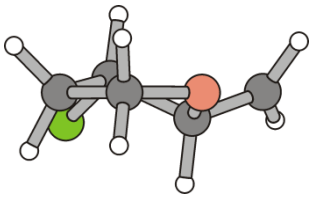

Figure S7.14. Minimum structure of *trans*-(3-chlorotetrahydrofuran-2-yl)methyl radical *trans*-**IIi**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.488933	0.835561	-0.322918
2	8	0	1.816774	0.371462	-0.068125
3	6	0	1.826271	-1.068818	-0.074807
4	6	0	0.359704	-1.531269	0.098779
5	6	0	-0.368713	-0.223085	0.422647
6	17	0	-2.105837	-0.213712	-0.091975
7	6	0	0.346372	2.236018	0.136169
8	1	0	2.474342	-1.388796	0.746111
9	1	0	2.254949	-1.431137	-1.017719
10	1	0	0.236970	-2.278034	0.887100
11	1	0	-0.035318	-1.951919	-0.830169
12	1	0	-0.374812	-0.006064	1.492072
13	1	0	0.248792	0.758203	-1.398803
14	1	0	1.012423	2.618998	0.900980
15	1	0	-0.467712	2.849722	-0.230217

```
Zero-point correction=                          0.120481
(Hartree/Particle)
Thermal correction to Energy=                   0.128218
Thermal correction to Enthalpy=                 0.129162
Thermal correction to Gibbs Free Energy=        0.086463
Sum of electronic and zero-point Energies=           -730.594649
Sum of electronic and thermal Energies=              -730.586912
Sum of electronic and thermal Enthalpies=            -730.585968
Sum of electronic and thermal Free Energies=         -730.628667

Version=AM64L-G03RevE.01\State=2-A\HF=-730.7151299\S2=0.753755\S2-
1=0.\ S2A=0.750009\RMSD=4.126e-09\RMSF=4.371e-07\PG=C01
[X(C5H8Cl1O1)]\ NImag=0\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.475759	0.825832	-0.327006
2	8	0	1.793217	0.373942	-0.096551
3	6	0	1.821512	-1.046821	-0.033518
4	6	0	0.363962	-1.516062	0.069324
5	6	0	-0.365011	-0.227703	0.411580
6	17	0	-2.084356	-0.218640	-0.083571
7	6	0	0.329860	2.218434	0.141806
8	1	0	2.409838	-1.322816	0.836304
9	1	0	2.312106	-1.443786	-0.919341
10	1	0	0.217577	-2.289765	0.815040
11	1	0	0.004847	-1.893219	-0.883291
12	1	0	-0.355997	-0.025848	1.475656
13	1	0	0.228018	0.758780	-1.391898
14	1	0	1.026923	2.610753	0.860968
15	1	0	-0.511497	2.809163	-0.173425

Zero-point correction= 0.125194
(Hartree/Particle)
Thermal correction to Energy= 0.132711
Thermal correction to Enthalpy= 0.133655
Thermal correction to Gibbs Free Energy= 0.091764
Sum of electronic and zero-point Energies= -730.415530
Sum of electronic and thermal Energies= -730.408013
Sum of electronic and thermal Enthalpies= -730.407069
Sum of electronic and thermal Free Energies= -730.448960

Version=AM64L-G03RevE.01\State=2-A\HF=-730.5407242\S2=0.755157\S2-1=0.\ S2A=0.750017\RMSD=5.464e-09\RMSF=1.981e-07\PG=C01 [X(C5H8Cl1O1)]\ NImag=0\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.473841	0.824111	-0.331016
2	8	0	1.792645	0.371766	-0.120120
3	6	0	1.820022	-1.044202	-0.011086
4	6	0	0.363277	-1.513308	0.057453
5	6	0	-0.363063	-0.229556	0.408270
6	17	0	-2.085254	-0.215610	-0.080879
7	6	0	0.334742	2.211437	0.150364
8	1	0	2.373709	-1.295776	0.887411
9	1	0	2.341955	-1.469269	-0.863588
10	1	0	0.202806	-2.299423	0.784730
11	1	0	0.020381	-1.867654	-0.908374
12	1	0	-0.353280	-0.032919	1.471404
13	1	0	0.211685	0.764286	-1.391407
14	1	0	1.048387	2.595867	0.855101
15	1	0	-0.510400	2.805248	-0.143281

```
Zero-point correction=                           0.124701
(Hartree/Particle)
Thermal correction to Energy=                    0.132228
Thermal correction to Enthalpy=                  0.133172
Thermal correction to Gibbs Free Energy=         0.091327
Sum of electronic and zero-point Energies=           -730.490116
Sum of electronic and thermal Energies=              -730.482589
Sum of electronic and thermal Enthalpies=            -730.481645
Sum of electronic and thermal Free Energies=         -730.523490

Version=AM64L-G03RevE.01\State=2-A\HF=-730.6148172\S2=0.755269\S2-
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[X(C5H8Cl1O1)]\ NImag=0\\@.
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7.4.9 *cis*-(3-Aminotetrahydrofuran-2-yl)methyl radical *cis*-(IIo)

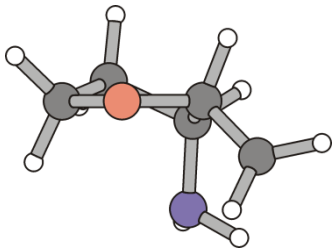

Figure S7.15. Minimum structure of *cis*-(3-aminotetrahydrofuran-2-yl)methyl radical *cis*-**IIo**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.734027	-0.494664	0.492789
2	8	0	-0.078839	-1.393249	-0.283436
3	6	0	-1.390393	-0.839933	-0.481316
4	6	0	-1.494705	0.343919	0.486756
5	6	0	-0.047788	0.856122	0.531762
6	7	0	0.228897	1.665259	-0.657426
7	6	0	2.115058	-0.451796	-0.048617
8	1	0	-2.128586	-1.624512	-0.284219
9	1	0	-1.485666	-0.509813	-1.522417
10	1	0	-1.803312	0.008671	1.483631
11	1	0	-2.201740	1.108356	0.148154
12	1	0	0.173124	1.374927	1.478111
13	1	0	0.769451	-0.865279	1.532247
14	1	0	2.284437	-0.610067	-1.107537
15	1	0	2.962107	-0.289327	0.609772
16	1	0	1.222717	1.860076	-0.745843
17	1	0	-0.261298	2.554257	-0.610667

```
Zero-point correction=                          0.146901
(Hartree/Particle)
Thermal correction to Energy=                   0.154547
Thermal correction to Enthalpy=                 0.155491
Thermal correction to Gibbs Free Energy=        0.114895
Sum of electronic and zero-point Energies=           -326.325604
Sum of electronic and thermal Energies=              -326.317958
Sum of electronic and thermal Enthalpies=            -326.317014
Sum of electronic and thermal Free Energies=         -326.357610

Version=AM64L-G03RevE.01\State=2-A\HF=-326.472505\S2=0.753899\S2-1=0.\
S2A=0.75001\RMSD=8.756e-09\RMSF=3.993e-07\PG=C01 [X(C5H10N1O1)]\
NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.722391	-0.492018	0.488136
2	8	0	-0.072780	-1.363245	-0.299376
3	6	0	-1.380352	-0.838516	-0.469109
4	6	0	-1.481709	0.340542	0.490858
5	6	0	-0.044848	0.847834	0.526645
6	7	0	0.222552	1.641500	-0.659058
7	6	0	2.105612	-0.447866	-0.035923
8	1	0	-2.101206	-1.622951	-0.255511
9	1	0	-1.500733	-0.517502	-1.500645
10	1	0	-1.782951	0.008881	1.482137
11	1	0	-2.186761	1.096637	0.156562
12	1	0	0.180006	1.371313	1.458782
13	1	0	0.746378	-0.870028	1.515575
14	1	0	2.287513	-0.637861	-1.078863
15	1	0	2.932265	-0.230996	0.619143
16	1	0	1.202874	1.845123	-0.758066
17	1	0	-0.279579	2.512994	-0.634341

```
Zero-point correction=                          0.152617
(Hartree/Particle)
Thermal correction to Energy=                   0.160056
Thermal correction to Enthalpy=                 0.161000
Thermal correction to Gibbs Free Energy=        0.120821
Sum of electronic and zero-point Energies=           -326.124215
Sum of electronic and thermal Energies=              -326.116776
Sum of electronic and thermal Enthalpies=            -326.115832
Sum of electronic and thermal Free Energies=         -326.156010

Version=AM64L-G03RevE.01\State=2-A\HF=-326.2768317\S2=0.755318\S2-
1=0.\ S2A=0.750019\RMSD=3.904e-09\RMSF=3.309e-07\PG=C01
[X(C5H10N1O1)]\ NImag=0\\@.
```

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.723858	-0.489214	0.491850
2	8	0	-0.066902	-1.365716	-0.290993
3	6	0	-1.366327	-0.834706	-0.478408
4	6	0	-1.481235	0.329692	0.494692
5	6	0	-0.049303	0.846600	0.530260
6	7	0	0.210158	1.631748	-0.663059
7	6	0	2.101699	-0.432960	-0.040688
8	1	0	-2.094742	-1.617149	-0.291432
9	1	0	-1.468318	-0.492821	-1.503828
10	1	0	-1.774917	-0.017997	1.481317
11	1	0	-2.192355	1.082885	0.171559
12	1	0	0.172899	1.373671	1.459804
13	1	0	0.755582	-0.864734	1.518566
14	1	0	2.273677	-0.625138	-1.083319
15	1	0	2.931085	-0.203502	0.604366
16	1	0	1.187419	1.853437	-0.742564
17	1	0	-0.298367	2.498370	-0.631347

Zero-point correction= 0.152081
(Hartree/Particle)
Thermal correction to Energy= 0.159522
Thermal correction to Enthalpy= 0.160466
Thermal correction to Gibbs Free Energy= 0.120303
Sum of electronic and zero-point Energies= -326.182839
Sum of electronic and thermal Energies= -326.175398
Sum of electronic and thermal Enthalpies= -326.174453
Sum of electronic and thermal Free Energies= -326.214616

Version=AM64L-G03RevE.01\State=2-A\HF=-326.3349199\S2=0.755403\S2-1=0.\ S2A=0.750019\RMSD=5.061e-09\RMSF=4.42**1**7e-07\PG=C01 [X(C5H10N1O1)]\ NImag=0\\@.

7.4.10 *trans*-(3-Aminotetrahydrofuran-2-yl)methyl radical *trans*-(IIo)

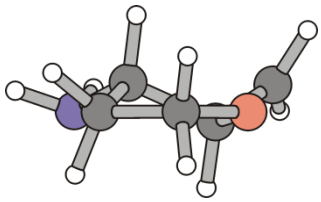

Figure S7.16. Minimum structure of *trans*-(3-aminotetrahydrofuran-2-yl)methyl radical *trans*-**IIo**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.348962	0.738901	-0.342498
2	8	0	1.001570	1.149925	-0.078203
3	6	0	1.847727	-0.009766	0.039021
4	6	0	0.924116	-1.241305	-0.003197
5	6	0	-0.449398	-0.654338	0.341279
6	7	0	-1.557764	-1.444759	-0.187835
7	6	0	-1.293606	1.768480	0.148989
8	1	0	2.392798	0.071059	0.986758
9	1	0	2.578930	-0.011058	-0.778548
10	1	0	1.241932	-2.026521	0.690676
11	1	0	0.877610	-1.671218	-1.010088
12	1	0	-0.512496	-0.485411	1.429408
13	1	0	-0.496603	0.574442	-1.423456
14	1	0	-1.052061	2.337459	1.040607
15	1	0	-2.233825	1.950300	-0.359668
16	1	0	-2.450583	-1.042869	0.088306
17	1	0	-1.533172	-2.394106	0.174909

```
Zero-point correction=                          0.146782
(Hartree/Particle)
Thermal correction to Energy=                   0.154667
Thermal correction to Enthalpy=                 0.155612
Thermal correction to Gibbs Free Energy=        0.114129
Sum of electronic and zero-point Energies=           -326.326894
Sum of electronic and thermal Energies=              -326.319008
Sum of electronic and thermal Enthalpies=            -326.318064
Sum of electronic and thermal Free Energies=         -326.359547

Version=AM64L-G03RevE.01\State=2-A\HF=-326.4736758\S2=0.753861\S2-
1=0.\ S2A=0.75001\RMSD=6.640e-09\RMSF=4.315e-05\PG=C01 [X(C5H10N1O1)]\
NImag=0\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.343788	0.728107	-0.340226
2	8	0	0.984738	1.138701	-0.070847
3	6	0	1.832376	0.002827	0.036037
4	6	0	0.923312	-1.227868	-0.002835
5	6	0	-0.442483	-0.649438	0.338300
6	7	0	-1.539639	-1.437456	-0.181414
7	6	0	-1.293391	1.752103	0.141733
8	1	0	2.378972	0.082563	0.972552
9	1	0	2.552716	0.007467	-0.779115
10	1	0	1.244755	-2.004268	0.686097
11	1	0	0.879473	-1.655674	-1.001712
12	1	0	-0.504313	-0.482340	1.417950
13	1	0	-0.483239	0.565965	-1.413284
14	1	0	-1.041602	2.348161	1.002010
15	1	0	-2.247826	1.887492	-0.336592
16	1	0	-2.428046	-1.048208	0.089050
17	1	0	-1.507480	-2.382967	0.161667

```
Zero-point correction=                          0.152411
(Hartree/Particle)
Thermal correction to Energy=                   0.160102
Thermal correction to Enthalpy=                 0.161046
Thermal correction to Gibbs Free Energy=        0.119981
Sum of electronic and zero-point Energies=           -326.125473
Sum of electronic and thermal Energies=              -326.117781
Sum of electronic and thermal Enthalpies=            -326.116837
Sum of electronic and thermal Free Energies=         -326.157902

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[X(C5H10N1O1)]\ NImag=0\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.332249	0.731016	-0.342045
2	8	0	1.005334	1.119081	-0.096907
3	6	0	1.826863	-0.027903	0.052916
4	6	0	0.901027	-1.241184	-0.007603
5	6	0	-0.453415	-0.643094	0.337283
6	7	0	-1.564012	-1.409903	-0.185655
7	6	0	-1.254332	1.771858	0.152427
8	1	0	2.338659	0.045194	1.008681
9	1	0	2.578212	-0.044236	-0.731760
10	1	0	1.206324	-2.032950	0.668826
11	1	0	0.848391	-1.650219	-1.012376
12	1	0	-0.507815	-0.475186	1.416733
13	1	0	-0.494309	0.566421	-1.410422
14	1	0	-0.965836	2.375144	0.994070
15	1	0	-2.221793	1.911194	-0.294563
16	1	0	-2.437666	-0.984767	0.076334
17	1	0	-1.566117	-2.338077	0.201448

```
Zero-point correction=                          0.151874
(Hartree/Particle)
Thermal correction to Energy=                   0.159540
Thermal correction to Enthalpy=                 0.160485
Thermal correction to Gibbs Free Energy=        0.119534
Sum of electronic and zero-point Energies=           -326.183713
Sum of electronic and thermal Energies=              -326.176047
Sum of electronic and thermal Enthalpies=            -326.175102
Sum of electronic and thermal Free Energies=         -326.216053

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7.4.11 *cis*-(3-Mercaptotetrahydrofuran-2-yl)methyl radical *cis*-(IIp)

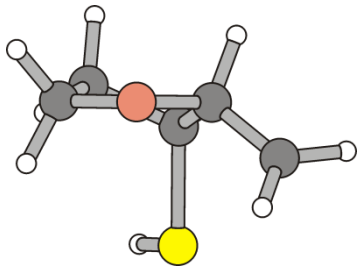

Figure S7.17. Minimum structure of *cis*-(3-mercaptotetrahydrofuran-2-yl)methyl radical *cis*-**IIp**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.550331	0.964433	0.469429
2	8	0	1.493538	0.532677	-0.522786
3	6	0	1.528745	-0.901706	-0.603409
4	6	0	0.697601	-1.412780	0.579948
5	6	0	-0.325079	-0.286792	0.785133
6	16	0	-1.771105	-0.368374	-0.374430
7	6	0	-0.149096	2.190404	0.014338
8	1	0	2.572569	-1.230260	-0.563730
9	1	0	1.095012	-1.211634	-1.561790
10	1	0	1.319469	-1.494367	1.480591
11	1	0	0.244529	-2.390005	0.393051
12	1	0	-0.710166	-0.238390	1.806145
13	1	0	1.097767	1.188356	1.404408
14	1	0	-2.206298	-1.572489	0.052404
15	1	0	-0.659549	2.825063	0.730111
16	1	0	-0.178959	2.434942	-1.040651

```
Zero-point correction=                          0.128817
(Hartree/Particle)
Thermal correction to Energy=                   0.136938
Thermal correction to Enthalpy=                 0.137882
Thermal correction to Gibbs Free Energy=        0.095528
Sum of electronic and zero-point Energies=           -669.174620
Sum of electronic and thermal Energies=              -669.166499
Sum of electronic and thermal Enthalpies=            -669.165554
Sum of electronic and thermal Free Energies=         -669.207908

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.545634	0.956469	0.460688
2	8	0	1.449396	0.527429	-0.540884
3	6	0	1.523789	-0.888807	-0.590748
4	6	0	0.696087	-1.394986	0.586002
5	6	0	-0.324456	-0.278953	0.779681
6	16	0	-1.745812	-0.377923	-0.374281
7	6	0	-0.151871	2.185109	0.024846
8	1	0	2.565317	-1.192085	-0.531161
9	1	0	1.114609	-1.225208	-1.540228
10	1	0	1.310862	-1.468413	1.481835
11	1	0	0.252268	-2.368010	0.403719
12	1	0	-0.708687	-0.226113	1.791776
13	1	0	1.106862	1.171639	1.377818
14	1	0	-2.179447	-1.569262	0.046444
15	1	0	-0.676807	2.791982	0.741731
16	1	0	-0.182248	2.439829	-1.019185

Zero-point correction= 0.133941
(Hartree/Particle)
Thermal correction to Energy= 0.141848
Thermal correction to Enthalpy= 0.142792
Thermal correction to Gibbs Free Energy= 0.100880
Sum of electronic and zero-point Energies= -668.988580
Sum of electronic and thermal Energies= -668.980674
Sum of electronic and thermal Enthalpies= -668.979730
Sum of electronic and thermal Free Energies= -669.021641

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.543100	0.954696	0.461799
2	8	0	1.442768	0.531608	-0.541658
3	6	0	1.521837	-0.881843	-0.590673
4	6	0	0.698915	-1.392655	0.586196
5	6	0	-0.322950	-0.280978	0.781945
6	16	0	-1.739767	-0.379984	-0.377135
7	6	0	-0.161261	2.178568	0.029176
8	1	0	2.562478	-1.184104	-0.532013
9	1	0	1.113074	-1.222572	-1.537282
10	1	0	1.315140	-1.462319	1.479720
11	1	0	0.257410	-2.365013	0.404995
12	1	0	-0.711048	-0.230045	1.790413
13	1	0	1.103954	1.170044	1.378356
14	1	0	-2.171292	-1.575065	0.039101
15	1	0	-0.729183	2.755669	0.735632
16	1	0	-0.124251	2.473556	-1.002172

Zero-point correction= 0.133435
(Hartree/Particle)
Thermal correction to Energy= 0.141359
Thermal correction to Enthalpy= 0.142303
Thermal correction to Gibbs Free Energy= 0.100319
Sum of electronic and zero-point Energies= -669.062180
Sum of electronic and thermal Energies= -669.054256
Sum of electronic and thermal Enthalpies= -669.053312
Sum of electronic and thermal Free Energies= -669.095295

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7.4.12 *trans*-(3-Mercaptotetrahydrofuran-2-yl)methyl radical *trans*-(IIp)

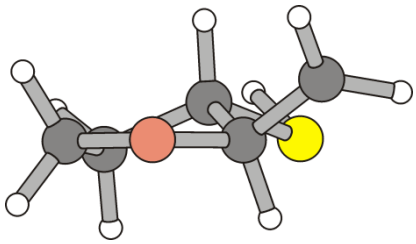

Figure S7.18. Minimum structure of *trans*-(3-mercaptotetrahydrofuran-2-yl)methyl radical *trans*-**IIp**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.491745	0.836397	-0.331102
2	8	0	1.833756	0.335990	-0.216455
3	6	0	1.833760	-1.078954	0.050843
4	6	0	0.365369	-1.528011	0.023245
5	6	0	-0.371066	-0.236312	0.396135
6	16	0	-2.130116	-0.124881	-0.134058
7	6	0	0.417426	2.211091	0.219078
8	1	0	2.294146	-1.242970	1.033555
9	1	0	2.444656	-1.584118	-0.705367
10	1	0	0.159731	-2.350568	0.715019
11	1	0	0.067411	-1.843701	-0.981901
12	1	0	-0.321350	-0.053813	1.474089
13	1	0	0.195001	0.843395	-1.395553
14	1	0	-2.594372	-1.086287	0.689114
15	1	0	1.104113	2.510587	1.002979
16	1	0	-0.360922	2.892394	-0.104561

```
Zero-point correction=                           0.128650
(Hartree/Particle)
Thermal correction to Energy=                    0.137057
Thermal correction to Enthalpy=                  0.138002
Thermal correction to Gibbs Free Energy=         0.094537
Sum of electronic and zero-point Energies=           -669.176503
Sum of electronic and thermal Energies=              -669.168095
Sum of electronic and thermal Enthalpies=            -669.167151
Sum of electronic and thermal Free Energies=         -669.210616

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NImag=0\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.487882	0.824648	-0.330500
2	8	0	1.811336	0.335138	-0.206786
3	6	0	1.822865	-1.062621	0.049169
4	6	0	0.365861	-1.516398	0.025137
5	6	0	-0.369112	-0.234541	0.391611
6	16	0	-2.108233	-0.128709	-0.134023
7	6	0	0.405392	2.197399	0.211951
8	1	0	2.283128	-1.228744	1.021402
9	1	0	2.427900	-1.559186	-0.704583
10	1	0	0.167005	-2.332629	0.713139
11	1	0	0.071063	-1.833147	-0.971619
12	1	0	-0.316966	-0.052153	1.461024
13	1	0	0.199366	0.827820	-1.387815
14	1	0	-2.582309	-1.056913	0.699680
15	1	0	1.134415	2.525934	0.931571
16	1	0	-0.419884	2.836337	-0.048354

Zero-point correction= 0.133695
(Hartree/Particle)
Thermal correction to Energy= 0.141894
Thermal correction to Enthalpy= 0.142839
Thermal correction to Gibbs Free Energy= 0.099834
Sum of electronic and zero-point Energies= -668.990681
Sum of electronic and thermal Energies= -668.982482
Sum of electronic and thermal Enthalpies= -668.981538
Sum of electronic and thermal Free Energies= -669.024543

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.487048	0.823130	-0.334396
2	8	0	1.806698	0.317719	-0.256877
3	6	0	1.812950	-1.061159	0.073240
4	6	0	0.360514	-1.515905	0.031540
5	6	0	-0.372092	-0.232810	0.389807
6	16	0	-2.108087	-0.121238	-0.141709
7	6	0	0.432420	2.184774	0.235428
8	1	0	2.240401	-1.183132	1.066315
9	1	0	2.439946	-1.593210	-0.634584
10	1	0	0.151562	-2.330947	0.715437
11	1	0	0.078325	-1.827596	-0.968990
12	1	0	-0.326353	-0.047550	1.457122
13	1	0	0.173341	0.848332	-1.382694
14	1	0	-2.604716	-0.983782	0.749384
15	1	0	1.194486	2.494086	0.926521
16	1	0	-0.396233	2.833673	0.020135

```
Zero-point correction=                          0.133167
(Hartree/Particle)
Thermal correction to Energy=                   0.141369
Thermal correction to Enthalpy=                 0.142313
Thermal correction to Gibbs Free Energy=        0.099309
Sum of electronic and zero-point Energies=           -669.063847
Sum of electronic and thermal Energies=              -669.055646
Sum of electronic and thermal Enthalpies=            -669.054702
Sum of electronic and thermal Free Energies=         -669.097705

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7.5 Transition Structures for 5-*exo*-4-Pentenoxyl Radical Cyclization

7.5.1 3-Hydroxy-4-pentenoxyl radical-derived transition structures

I. Transition Structure *TS1*$_{cis}$-IIa

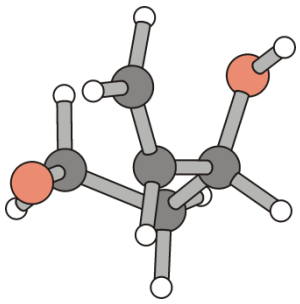

Figure S7.19. Calculated transition *TS1*$_{cis}$-**IIa** structure for 3-hydroxy-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.752950	-1.512854	-0.079987
2	6	0	1.514650	-0.432910	-0.539641
3	6	0	1.281855	0.746870	0.407248
4	6	0	-0.242950	0.886758	0.527669
5	6	0	-0.848688	-0.503097	0.647313
6	6	0	-1.801026	-0.990727	-0.217038
7	1	0	2.568180	-0.758647	-0.515075
8	1	0	1.272969	-0.162267	-1.579086
9	1	0	1.697159	0.506569	1.392262
10	1	0	1.721535	1.687333	0.059127
11	1	0	-0.492964	1.452293	1.438782
12	8	0	-0.692605	1.601753	-0.622772
13	1	0	-0.741032	-0.970241	1.621715
14	1	0	-2.289984	-1.938791	-0.023255
15	1	0	-1.995015	-0.509722	-1.169858
16	1	0	-1.646662	1.740911	-0.555851

```
Zero-point correction=                          0.133209
(Hartree/Particle)
Thermal correction to Energy=                   0.140195
Thermal correction to Enthalpy=                 0.141139
Thermal correction to Gibbs Free Energy=        0.101874
Sum of electronic and zero-point Energies=           -346.181587
Sum of electronic and thermal Energies=              -346.174601
Sum of electronic and thermal Enthalpies=            -346.173657
Sum of electronic and thermal Free Energies=         -346.212922

Version=AM64L-G03RevE.01\State=2-A\HF=-346.314796\S2=0.777912\S2-1=0.\
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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

```
Standard orientation:
---------------------------------------------------------------------
 Center     Atomic     Atomic              Coordinates (Angstroms)
 Number     Number      Type              X           Y           Z
---------------------------------------------------------------------
   1          8             0        0.699084   -1.510551   -0.074752
   2          6             0        1.486390   -0.463245   -0.544001
   3          6             0        1.296568    0.709397    0.400491
   4          6             0       -0.211484    0.883223    0.525570
   5          6             0       -0.837909   -0.489891    0.634739
   6          6             0       -1.821340   -0.930373   -0.212077
   7          1             0        2.517707   -0.822609   -0.534965
   8          1             0        1.231757   -0.187841   -1.568221
   9          1             0        1.709950    0.455623    1.373756
  10          1             0        1.755323    1.630578    0.052624
  11          1             0       -0.449683    1.444683    1.430893
  12          8             0       -0.645465    1.598448   -0.608837
  13          1             0       -0.745566   -0.958449    1.600581
  14          1             0       -2.328034   -1.860724   -0.023968
  15          1             0       -2.013466   -0.435710   -1.148648
  16          1             0       -1.580285    1.776621   -0.541665
---------------------------------------------------------------------

Zero-point correction=                          0.138448
(Hartree/Particle)
Thermal correction to Energy=                   0.145208
Thermal correction to Enthalpy=                 0.146152
Thermal correction to Gibbs Free Energy=        0.107292
Sum of electronic and zero-point Energies=           -345.968405
Sum of electronic and thermal Energies=              -345.961646
Sum of electronic and thermal Enthalpies=            -345.960701
Sum of electronic and thermal Free Energies=         -345.999561

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NImag=1\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.674239	-1.511563	-0.073616
2	6	0	1.469588	-0.477816	-0.548304
3	6	0	1.305948	0.692930	0.401509
4	6	0	-0.198208	0.883024	0.527717
5	6	0	-0.836795	-0.484579	0.636662
6	6	0	-1.825493	-0.900121	-0.212212
7	1	0	2.495002	-0.850212	-0.553485
8	1	0	1.208187	-0.190298	-1.566356
9	1	0	1.718307	0.426713	1.370422
10	1	0	1.774148	1.609002	0.057157
11	1	0	-0.431386	1.445921	1.432237
12	8	0	-0.622971	1.595297	-0.609381
13	1	0	-0.757224	-0.953429	1.601877
14	1	0	-2.352056	-1.819660	-0.033655
15	1	0	-2.002051	-0.393633	-1.143700
16	1	0	-1.553308	1.775099	-0.532755

```
Zero-point correction=                          0.138179
(Hartree/Particle)
Thermal correction to Energy=                   0.144862
Thermal correction to Enthalpy=                 0.145806
Thermal correction to Gibbs Free Energy=        0.107139
Sum of electronic and zero-point Energies=           -346.034953
Sum of electronic and thermal Energies=              -346.028271
Sum of electronic and thermal Enthalpies=            -346.027327
Sum of electronic and thermal Free Energies=         -346.065994

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II. Transition Structure *TS2*$_{cis}$-IIa

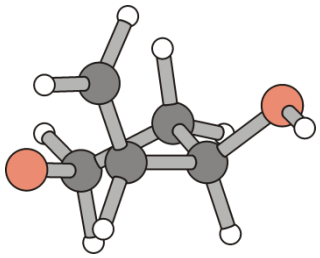

Figure S7.20. Calculated transition *TS2*$_{cis}$-**IIa** structure for 3-hydroxy-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.593057	0.833969	0.109210
2	6	0	-1.784613	-0.548835	-0.028446
3	6	0	-0.459079	-1.188907	-0.450199
4	6	0	0.622798	-0.589996	0.455706
5	6	0	0.412646	0.920716	0.521378
6	6	0	0.836103	1.747208	-0.490097
7	1	0	-2.125490	-0.993713	0.923325
8	1	0	-2.553415	-0.732551	-0.794797
9	1	0	-0.481563	-2.281270	-0.376531
10	1	0	-0.223704	-0.917764	-1.485378
11	1	0	0.521275	-1.005076	1.468882
12	8	0	1.888853	-0.963790	-0.095895
13	1	0	0.183868	1.350883	1.490884
14	1	0	0.743407	2.824570	-0.405744
15	1	0	1.207832	1.343030	-1.426357
16	1	0	2.594290	-0.590653	0.449135

```
Zero-point correction=                          0.132953
(Hartree/Particle)
Thermal correction to Energy=                   0.140231
Thermal correction to Enthalpy=                 0.141176
Thermal correction to Gibbs Free Energy=        0.100798
Sum of electronic and zero-point Energies=           -346.176895
Sum of electronic and thermal Energies=              -346.169617
Sum of electronic and thermal Enthalpies=            -346.168672
Sum of electronic and thermal Free Energies=         -346.209050

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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G**// BHandHLYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.512851	0.913635	0.014458
2	6	0	-1.794897	-0.451475	-0.006374
3	6	0	-0.536021	-1.190966	-0.411466
4	6	0	0.582366	-0.624115	0.450548
5	6	0	0.413473	0.885140	0.517444
6	6	0	0.969838	1.702095	-0.431121
7	1	0	-2.139584	-0.795940	0.973670
8	1	0	-2.594877	-0.619717	-0.728780
9	1	0	-0.624069	-2.267675	-0.292595
10	1	0	-0.297713	-0.977616	-1.450716
11	1	0	0.499260	-1.026692	1.461102
12	8	0	1.805801	-1.026907	-0.125027
13	1	0	0.159242	1.307662	1.474786
14	1	0	0.921510	2.772849	-0.333072
15	1	0	1.390270	1.294703	-1.335162
16	1	0	2.533806	-0.705477	0.401141

```
Zero-point correction=                          0.138065
(Hartree/Particle)
Thermal correction to Energy=                   0.145105
Thermal correction to Enthalpy=                 0.146049
Thermal correction to Gibbs Free Energy=        0.105915
Sum of electronic and zero-point Energies=                -345.963753
Sum of electronic and thermal Energies=                   -345.956713
Sum of electronic and thermal Enthalpies=                 -345.955769
Sum of electronic and thermal Free Energies=              -345.995903

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S2A=0.75082\RMSD=3.289e-09\RMSF=5.724e-07\PG=C01 [X(C5H9O2)]\
NImag=1\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.497389	0.923370	0.006065
2	6	0	-1.794820	-0.434488	-0.007532
3	6	0	-0.545314	-1.189973	-0.405704
4	6	0	0.576090	-0.628435	0.453507
5	6	0	0.408580	0.881126	0.516815
6	6	0	0.986296	1.684206	-0.427171
7	1	0	-2.144286	-0.774008	0.972007
8	1	0	-2.593715	-0.599995	-0.730137
9	1	0	-0.642629	-2.264250	-0.284122
10	1	0	-0.301220	-0.981012	-1.443138
11	1	0	0.491100	-1.028164	1.464317
12	8	0	1.794100	-1.032029	-0.126107
13	1	0	0.156632	1.307871	1.471072
14	1	0	0.947717	2.755032	-0.340439
15	1	0	1.415292	1.263225	-1.319002
16	1	0	2.512430	-0.684038	0.390284

```
Zero-point correction=                          0.137690
(Hartree/Particle)
Thermal correction to Energy=                   0.144688
Thermal correction to Enthalpy=                 0.145632
Thermal correction to Gibbs Free Energy=        0.105608
Sum of electronic and zero-point Energies=           -346.029686
Sum of electronic and thermal Energies=              -346.022688
Sum of electronic and thermal Enthalpies=            -346.021744
Sum of electronic and thermal Free Energies=         -346.061768

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NImag=1\\@.
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III. Transition Structure *TS1*$_{trans}$-IIa

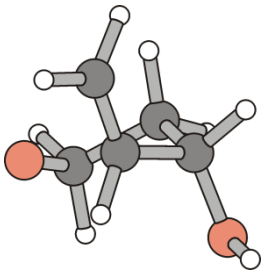

Figure S7.21. Calculated transition *TS1*$_{trans}$-**IIa** structure for 3-hydroxy-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.516444	1.426500	-0.658817
2	6	0	0.777654	1.491584	-0.132611
3	6	0	0.915012	0.412606	0.953853
4	6	0	0.354114	-0.883652	0.358706
5	6	0	-0.952702	-0.559362	-0.344390
6	6	0	-2.136267	-0.424509	0.339484
7	1	0	1.534479	1.321247	-0.914180
8	1	0	0.936153	2.485599	0.315234
9	1	0	1.951981	0.272964	1.276997
10	1	0	0.310176	0.693762	1.822672
11	8	0	1.333896	-1.401924	-0.542871
12	1	0	0.171598	-1.608235	1.166484
13	1	0	-0.970323	-0.714673	-1.419055
14	1	0	-3.067428	-0.240908	-0.184881
15	1	0	-2.164174	-0.398221	1.425493
16	1	0	1.011058	-2.228150	-0.925510

```
Zero-point correction=                           0.132672
(Hartree/Particle)
Thermal correction to Energy=                    0.139952
Thermal correction to Enthalpy=                  0.140896
Thermal correction to Gibbs Free Energy=         0.100663
Sum of electronic and zero-point Energies=           -346.178577
Sum of electronic and thermal Energies=              -346.171297
Sum of electronic and thermal Enthalpies=            -346.170353
Sum of electronic and thermal Free Energies=         -346.210585

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1=0.\ S2A=0.75016\RMSD=2.114e-09\RMSF=8.463e-07\ PG=C01 [X(C5H9O2)]\
NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.485274	1.437315	-0.608372
2	6	0	0.828971	1.443432	-0.148191
3	6	0	0.952860	0.381995	0.933307
4	6	0	0.326724	-0.878684	0.356909
5	6	0	-0.956017	-0.487184	-0.342781
6	6	0	-2.142289	-0.376876	0.333680
7	1	0	1.531493	1.236021	-0.956622
8	1	0	1.039661	2.432916	0.261413
9	1	0	1.982675	0.198605	1.227730
10	1	0	0.386593	0.690745	1.808476
11	8	0	1.258663	-1.442415	-0.541133
12	1	0	0.110185	-1.586088	1.158164
13	1	0	-0.972083	-0.627072	-1.411221
14	1	0	-3.059338	-0.163878	-0.187417
15	1	0	-2.176053	-0.389004	1.411583
16	1	0	0.908266	-2.247541	-0.913612

```
Zero-point correction=                          0.137838
(Hartree/Particle)
Thermal correction to Energy=                   0.144887
Thermal correction to Enthalpy=                 0.145832
Thermal correction to Gibbs Free Energy=        0.105965
Sum of electronic and zero-point Energies=           -345.965324
Sum of electronic and thermal Energies=              -345.958274
Sum of electronic and thermal Enthalpies=            -345.957330
Sum of electronic and thermal Free Energies=         -345.997196

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NImag=1\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.488874	1.373564	-0.678311
2	6	0	0.784096	1.451741	-0.127364
3	6	0	0.894101	0.401284	0.966616
4	6	0	0.345160	-0.877765	0.359695
5	6	0	-0.946179	-0.530516	-0.344292
6	6	0	-2.120731	-0.389683	0.339313
7	1	0	1.549002	1.269706	-0.881967
8	1	0	0.923393	2.448964	0.290494
9	1	0	1.914172	0.258157	1.308362
10	1	0	0.276889	0.689277	1.812231
11	8	0	1.314977	-1.365900	-0.537599
12	1	0	0.154864	-1.611977	1.142218
13	1	0	-0.974550	-0.727104	-1.401910
14	1	0	-3.045991	-0.215922	-0.178988
15	1	0	-2.138809	-0.339298	1.415003
16	1	0	0.993527	-2.163485	-0.941971

```
Zero-point correction=                          0.137533
(Hartree/Particle)
Thermal correction to Energy=                   0.144529
Thermal correction to Enthalpy=                 0.145473
Thermal correction to Gibbs Free Energy=        0.105856
Sum of electronic and zero-point Energies=           -346.031082
Sum of electronic and thermal Energies=              -346.024086
Sum of electronic and thermal Enthalpies=            -346.023142
Sum of electronic and thermal Free Energies=         -346.062759

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NImag=1\\@.
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IV. Transition Structure *TS2*$_{trans}$-IIa

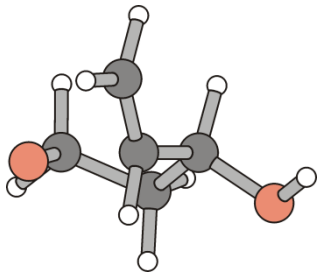

Figure S7.22. Calculated transition *TS2*$_{trans}$-**IIa** structure for 3-hydroxy-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.641065	0.349014	-0.477808
2	6	0	1.566418	-0.840603	0.260742
3	6	0	0.182436	-1.451726	0.053356
4	6	0	-0.803878	-0.307161	0.303426
5	6	0	-0.282126	0.955839	-0.363502
6	6	0	-0.115773	2.131418	0.330291
7	1	0	2.358957	-1.500703	-0.128524
8	1	0	1.776783	-0.676861	1.332049
9	1	0	0.069200	-1.782879	-0.984966
10	1	0	-0.020433	-2.302995	0.712354
11	8	0	-2.077537	-0.689979	-0.221693
12	1	0	-0.883798	-0.126550	1.386637
13	1	0	-0.379987	0.984350	-1.444807
14	1	0	0.138595	3.055607	-0.177565
15	1	0	-0.128955	2.148063	1.416957
16	1	0	-2.721048	0.003086	-0.022011

Zero-point correction= 0.133086
(Hartree/Particle)
Thermal correction to Energy= 0.140175
Thermal correction to Enthalpy= 0.141119
Thermal correction to Gibbs Free Energy= 0.101499
Sum of electronic and zero-point Energies= -346.180955
Sum of electronic and thermal Energies= -346.173866
Sum of electronic and thermal Enthalpies= -346.172921
Sum of electronic and thermal Free Energies= -346.212541

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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.604344	0.383618	-0.475923
2	6	0	1.570757	-0.798737	0.262241
3	6	0	0.215102	-1.441523	0.054154
4	6	0	-0.787608	-0.327213	0.299324
5	6	0	-0.282561	0.935933	-0.361444
6	6	0	-0.172867	2.114650	0.329033
7	1	0	2.379307	-1.425212	-0.119111
8	1	0	1.765382	-0.617702	1.323065
9	1	0	0.113556	-1.773880	-0.976237
10	1	0	0.034923	-2.290139	0.708983
11	8	0	-2.037246	-0.723569	-0.221392
12	1	0	-0.870309	-0.148073	1.373548
13	1	0	-0.382278	0.964392	-1.434184
14	1	0	0.062997	3.036597	-0.174043
15	1	0	-0.204684	2.131934	1.406962
16	1	0	-2.692623	-0.056968	-0.030305

```
Zero-point correction=                          0.138262
(Hartree/Particle)
Thermal correction to Energy=                   0.145132
Thermal correction to Enthalpy=                 0.146076
Thermal correction to Gibbs Free Energy=        0.106862
Sum of electronic and zero-point Energies=           -345.967659
Sum of electronic and thermal Energies=              -345.960789
Sum of electronic and thermal Enthalpies=            -345.959845
Sum of electronic and thermal Free Energies=         -345.999059

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NImag=1\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.598278	0.359020	-0.482811
2	6	0	1.555102	-0.815601	0.260036
3	6	0	0.193231	-1.444237	0.058879
4	6	0	-0.792792	-0.316796	0.301551
5	6	0	-0.264069	0.936579	-0.358509
6	6	0	-0.133980	2.110331	0.331278
7	1	0	2.354173	-1.453317	-0.119391
8	1	0	1.753307	-0.635524	1.319464
9	1	0	0.083995	-1.773067	-0.970521
10	1	0	0.002625	-2.289121	0.713372
11	8	0	-2.044341	-0.690963	-0.223349
12	1	0	-0.871374	-0.134833	1.374937
13	1	0	-0.379885	0.968659	-1.428126
14	1	0	0.109449	3.029372	-0.170820
15	1	0	-0.155647	2.124360	1.408129
16	1	0	-2.673094	-0.002644	-0.037173

```
Zero-point correction=                          0.137869
(Hartree/Particle)
Thermal correction to Energy=                   0.144714
Thermal correction to Enthalpy=                 0.145658
Thermal correction to Gibbs Free Energy=        0.106505
Sum of electronic and zero-point Energies=           -346.033012
Sum of electronic and thermal Energies=              -346.026167
Sum of electronic and thermal Enthalpies=            -346.025223
Sum of electronic and thermal Free Energies=         -346.064376

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NImag=1\\@.
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7.5.2 3-Methyl-4-pentenoxyl radical-derived transition structures

I. Transition Structure *TS1*$_{cis}$-IIb

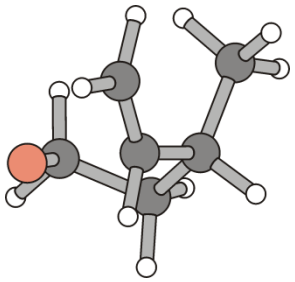

Figure S7.23. Calculated transition *TS1*$_{cis}$-**IIb** structure for 3-methyl-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.891962	-1.439822	-0.218763
2	6	0	1.586944	-0.272483	-0.538756
3	6	0	1.226756	0.803145	0.491555
4	6	0	-0.320659	0.815509	0.573457
5	6	0	-0.770312	-0.633598	0.640025
6	6	0	-1.730470	-1.198720	-0.170888
7	1	0	1.380592	0.071257	-1.567358
8	1	0	2.662231	-0.515455	-0.487218
9	1	0	1.624965	1.792117	0.233072
10	1	0	1.644924	0.513612	1.462660
11	6	0	-0.956522	1.633227	-0.559918
12	1	0	-0.534579	-1.146820	1.567796
13	1	0	-2.095854	-0.702236	-1.063085
14	1	0	-2.074361	-2.212010	0.006660
15	1	0	-0.607604	1.280094	1.527847
16	1	0	-2.047926	1.653353	-0.476802
17	1	0	-0.600004	2.667572	-0.518540
18	1	0	-0.702503	1.234612	-1.547777

```
Zero-point correction=                          0.156882
(Hartree/Particle)
Thermal correction to Energy=                   0.164123
Thermal correction to Enthalpy=                 0.165068
Thermal correction to Gibbs Free Energy=        0.125291
Sum of electronic and zero-point Energies=           -310.254549
Sum of electronic and thermal Energies=              -310.247308
Sum of electronic and thermal Enthalpies=            -310.246364
Sum of electronic and thermal Free Energies=         -310.286141

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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.836482	-1.446121	-0.214140
2	6	0	1.563890	-0.309469	-0.540258
3	6	0	1.242933	0.765526	0.484344
4	6	0	-0.289676	0.815550	0.573503
5	6	0	-0.766858	-0.617640	0.627778
6	6	0	-1.756289	-1.139792	-0.166751
7	1	0	1.352321	0.033618	-1.556536
8	1	0	2.619679	-0.588611	-0.500790
9	1	0	1.663795	1.734944	0.224068
10	1	0	1.657064	0.466506	1.444985
11	6	0	-0.903585	1.644067	-0.549780
12	1	0	-0.549662	-1.135416	1.547651
13	1	0	-2.115672	-0.627269	-1.042098
14	1	0	-2.122208	-2.137451	0.004662
15	1	0	-0.566037	1.278597	1.521481
16	1	0	-1.985464	1.692920	-0.462461
17	1	0	-0.521756	2.660748	-0.509823
18	1	0	-0.666411	1.240929	-1.531036

```
Zero-point correction=                          0.162607
(Hartree/Particle)
Thermal correction to Energy=                   0.169624
Thermal correction to Enthalpy=                 0.170568
Thermal correction to Gibbs Free Energy=        0.131185
Sum of electronic and zero-point Energies=           -310.048842
Sum of electronic and thermal Energies=              -310.041825
Sum of electronic and thermal Enthalpies=            -310.040881
Sum of electronic and thermal Free Energies=         -310.080264

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NImag=1\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.863450	-1.427336	-0.195208
2	6	0	1.557832	-0.282608	-0.547205
3	6	0	1.228447	0.795382	0.469615
4	6	0	-0.303008	0.808517	0.574735
5	6	0	-0.746082	-0.635898	0.626228
6	6	0	-1.717627	-1.174810	-0.174369
7	1	0	1.325948	0.045767	-1.563044
8	1	0	2.619463	-0.535411	-0.520353
9	1	0	1.623216	1.771147	0.198327
10	1	0	1.658705	0.512117	1.426360
11	6	0	-0.945454	1.626612	-0.538485
12	1	0	-0.533207	-1.143122	1.551189
13	1	0	-2.074662	-0.670728	-1.053852
14	1	0	-2.068348	-2.176805	-0.004522
15	1	0	-0.581639	1.259486	1.525888
16	1	0	-2.026633	1.643024	-0.445834
17	1	0	-0.593020	2.652333	-0.492955
18	1	0	-0.702072	1.237709	-1.522655

```
Zero-point correction=                          0.161997
(Hartree/Particle)
Thermal correction to Energy=                   0.168998
Thermal correction to Enthalpy=                 0.169942
Thermal correction to Gibbs Free Energy=        0.130613
Sum of electronic and zero-point Energies=           -310.104223
Sum of electronic and thermal Energies=              -310.097223
Sum of electronic and thermal Enthalpies=            -310.096278
Sum of electronic and thermal Free Energies=         -310.135607

Version=AM64L-G03RevE.01\State=2-A\HF=-310.2662203\S2=0.826238\S2-
1=0.\ S2A=0.750671\RMSD=9.307e-09\RMSF=7.625e-07\PG=C01 [X(C6H11O1)]\
NImag=1\\@.
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II. Transition Structure *TS2*$_{cis}$-IIb

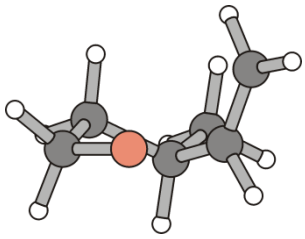

Figure S7.24. Calculated transition *TS2*$_{cis}$-**IIb** structure for 3-methyl-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.752280	0.499518	-0.284231
2	6	0	1.672706	-0.855632	0.056246
3	6	0	0.240463	-1.183985	0.516817
4	6	0	-0.716353	-0.447060	-0.437665
5	6	0	-0.260233	1.000364	-0.506284
6	6	0	-0.321793	1.861950	0.558693
7	1	0	2.390251	-1.092700	0.857582
8	1	0	1.911699	-1.476735	-0.825784
9	1	0	0.093397	-0.822891	1.542238
10	1	0	0.060994	-2.265904	0.517905
11	6	0	-2.194191	-0.603339	-0.036700
12	1	0	-0.089363	1.420953	-1.492508
13	1	0	-0.575233	1.523727	1.559067
14	1	0	-0.033079	2.901837	0.450881
15	1	0	-0.587430	-0.878850	-1.438460
16	1	0	-2.378521	-0.204674	0.966618
17	1	0	-2.853206	-0.074104	-0.732481
18	1	0	-2.481342	-1.660592	-0.037848

```
Zero-point correction=                          0.156680
(Hartree/Particle)
Thermal correction to Energy=                   0.164183
Thermal correction to Enthalpy=                 0.165127
Thermal correction to Gibbs Free Energy=        0.124678
Sum of electronic and zero-point Energies=           -310.253159
Sum of electronic and thermal Energies=              -310.245656
Sum of electronic and thermal Enthalpies=            -310.244712
Sum of electronic and thermal Free Energies=         -310.285161

Version=AM64L-G03RevE.01\State=2-A\HF=-310.4098388\S2=0.77534\S2-1=0.\
S2A=0.75012\RMSD=3.598e-09\RMSF=5.110e-07\PG=C01 [X(C6H11O1)]\
NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.714347	0.520372	-0.280514
2	6	0	1.666728	-0.830152	0.061108
3	6	0	0.255621	-1.180144	0.517470
4	6	0	-0.695637	-0.458399	-0.434743
5	6	0	-0.241041	0.982507	-0.499337
6	6	0	-0.363600	1.847783	0.551942
7	1	0	2.390326	-1.033323	0.852134
8	1	0	1.924417	-1.438528	-0.811055
9	1	0	0.098115	-0.824472	1.534369
10	1	0	0.092868	-2.256282	0.516092
11	6	0	-2.163180	-0.617574	-0.045094
12	1	0	-0.073575	1.402406	-1.477027
13	1	0	-0.633961	1.509703	1.538966
14	1	0	-0.095293	2.884719	0.446117
15	1	0	-0.558608	-0.886560	-1.426921
16	1	0	-2.351854	-0.224062	0.950496
17	1	0	-2.815147	-0.092921	-0.738224
18	1	0	-2.445412	-1.667785	-0.048917

Zero-point correction= 0.162274
(Hartree/Particle)
Thermal correction to Energy= 0.169575
Thermal correction to Enthalpy= 0.170519
Thermal correction to Gibbs Free Energy= 0.130373
Sum of electronic and zero-point Energies= -310.047260
Sum of electronic and thermal Energies= -310.039959
Sum of electronic and thermal Enthalpies= -310.039014
Sum of electronic and thermal Free Energies= -310.079160

Version=AM64L-G03RevE.01\State=2-A\HF=-310.2095334\S2=0.824844\S2-1=0.\ S2A=0.750682\RMSD=4.724e-09\RMSF=1.053e-07\PG=C01 [X(C6H11O1)]\NImag=1\\@.

(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.704722	0.496270	-0.314178
2	6	0	1.653184	-0.839300	0.070410
3	6	0	0.238416	-1.179162	0.522411
4	6	0	-0.700570	-0.449447	-0.432977
5	6	0	-0.227659	0.984530	-0.493115
6	6	0	-0.320254	1.836440	0.567741
7	1	0	2.367023	-1.024755	0.873022
8	1	0	1.916155	-1.473632	-0.780435
9	1	0	0.078950	-0.822204	1.537116
10	1	0	0.066291	-2.252338	0.520947
11	6	0	-2.170642	-0.588474	-0.051819
12	1	0	-0.083093	1.412485	-1.469266
13	1	0	-0.571134	1.488988	1.555065
14	1	0	-0.047435	2.871360	0.467740
15	1	0	-0.562444	-0.877729	-1.423428
16	1	0	-2.358108	-0.191249	0.941276
17	1	0	-2.810567	-0.055371	-0.748007
18	1	0	-2.468270	-1.633243	-0.056521

Zero-point correction= 0.161708
(Hartree/Particle)
Thermal correction to Energy= 0.168998
Thermal correction to Enthalpy= 0.169942
Thermal correction to Gibbs Free Energy= 0.129834
Sum of electronic and zero-point Energies= -310.102784
Sum of electronic and thermal Energies= -310.095495
Sum of electronic and thermal Enthalpies= -310.094550
Sum of electronic and thermal Free Energies= -310.134659

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NImag=1\\@.

III. Transition Structure *TS1*$_{trans}$-IIb

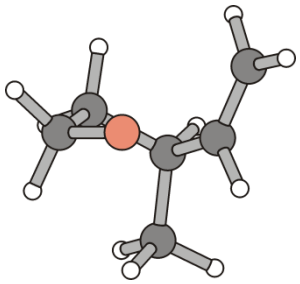

Figure S7.25. Calculated transition *TS1*$_{trans}$-**IIb** structure for 3-methyl-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.833242	1.139307	-0.844578
2	6	0	0.217260	1.676548	-0.098932
3	6	0	0.604329	0.686446	1.019431
4	6	0	0.578079	-0.735382	0.416553
5	6	0	-0.738676	-0.882428	-0.322171
6	6	0	-1.948963	-0.961985	0.317890
7	1	0	-0.080388	2.637156	0.351239
8	1	0	1.092804	1.852279	-0.748433
9	1	0	-0.137412	0.756351	1.822808
10	1	0	1.583803	0.930051	1.449083
11	1	0	0.592994	-1.453894	1.248073
12	1	0	-0.692327	-1.160972	-1.371159
13	1	0	-2.038956	-0.800067	1.388600
14	1	0	-2.867913	-1.110148	-0.238741
15	6	0	1.779843	-1.025707	-0.493728
16	1	0	2.721675	-0.905884	0.052135
17	1	0	1.742168	-2.052222	-0.874506
18	1	0	1.798258	-0.352060	-1.356734

```
Zero-point correction=                          0.156505
(Hartree/Particle)
Thermal correction to Energy=                   0.164012
Thermal correction to Enthalpy=                 0.164957
Thermal correction to Gibbs Free Energy=        0.124409
Sum of electronic and zero-point Energies=           -310.253737
Sum of electronic and thermal Energies=              -310.246230
Sum of electronic and thermal Enthalpies=            -310.245286
Sum of electronic and thermal Free Energies=         -310.285834

Version=AM64L-G03RevE.01\State=2-A\HF=-310.4102423\S2=0.776682\S2-
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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.772442	1.141573	-0.839614
2	6	0	0.290680	1.646933	-0.098741
3	6	0	0.632422	0.660580	1.015205
4	6	0	0.540866	-0.747026	0.417724
5	6	0	-0.772460	-0.818395	-0.324852
6	6	0	-1.977193	-0.881896	0.318382
7	1	0	0.015650	2.613241	0.327590
8	1	0	1.159709	1.791317	-0.746215
9	1	0	-0.097767	0.762841	1.814437
10	1	0	1.615193	0.860586	1.438561
11	1	0	0.519181	-1.467466	1.235054
12	1	0	-0.737012	-1.104912	-1.363270
13	1	0	-2.055747	-0.728488	1.382906
14	1	0	-2.894645	-0.995415	-0.232768
15	6	0	1.718556	-1.084101	-0.490019
16	1	0	2.658694	-1.009914	0.050709
17	1	0	1.634048	-2.098311	-0.872838
18	1	0	1.765006	-0.412628	-1.343440

Zero-point correction= 0.162166
(Hartree/Particle)
Thermal correction to Energy= 0.169469
Thermal correction to Enthalpy= 0.170413
Thermal correction to Gibbs Free Energy= 0.130138
Sum of electronic and zero-point Energies= -310.047772
Sum of electronic and thermal Energies= -310.040470
Sum of electronic and thermal Enthalpies= -310.039525
Sum of electronic and thermal Free Energies= -310.079800

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.710791	1.082117	-0.907676
2	6	0	0.262007	1.639671	-0.089086
3	6	0	0.601186	0.658137	1.032079
4	6	0	0.539476	-0.747119	0.431669
5	6	0	-0.769467	-0.834062	-0.314557
6	6	0	-1.976790	-0.838479	0.318505
7	1	0	-0.088577	2.581527	0.333060
8	1	0	1.158772	1.841752	-0.679459
9	1	0	-0.140537	0.747298	1.820160
10	1	0	1.572414	0.871589	1.471153
11	1	0	0.529217	-1.471813	1.243521
12	1	0	-0.731310	-1.180834	-1.332679
13	1	0	-2.062559	-0.622137	1.369865
14	1	0	-2.889586	-0.971948	-0.233269
15	6	0	1.722068	-1.053118	-0.478282
16	1	0	2.661481	-0.947991	0.056208
17	1	0	1.666562	-2.070065	-0.855831
18	1	0	1.739570	-0.384496	-1.333284

```
Zero-point correction=                          0.161590
(Hartree/Particle)
Thermal correction to Energy=                   0.168885
Thermal correction to Enthalpy=                 0.169829
Thermal correction to Gibbs Free Energy=        0.129613
Sum of electronic and zero-point Energies=           -310.103229
Sum of electronic and thermal Energies=              -310.095934
Sum of electronic and thermal Enthalpies=            -310.094990
Sum of electronic and thermal Free Energies=         -310.135206

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IV. Transition Structure *TS2*$_{trans}$-IIb

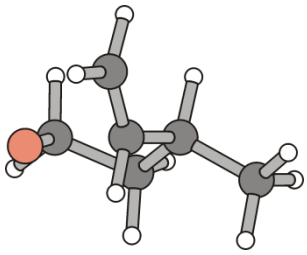

Figure S7.26. Calculated transition *TS2*$_{trans}$-**IIb** structure for 3-methyl-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.719351	0.111952	-0.483388
2	6	0	1.469763	-1.046109	0.257388
3	6	0	0.010310	-1.451915	0.049499
4	6	0	-0.821733	-0.178635	0.313240
5	6	0	-0.124316	0.989832	-0.352605
6	6	0	0.234253	2.130072	0.327442
7	1	0	1.692914	-0.912158	1.331052
8	1	0	2.158194	-1.819486	-0.124208
9	1	0	-0.300043	-2.275454	0.704913
10	1	0	-0.130774	-1.775128	-0.989891
11	1	0	-0.823371	0.007147	1.396621
12	1	0	-0.194109	1.037275	-1.436543
13	1	0	0.223369	2.162305	1.413495
14	1	0	0.630816	2.995585	-0.192676
15	6	0	-2.278797	-0.317254	-0.160120
16	1	0	-2.324418	-0.477619	-1.243779
17	1	0	-2.761389	-1.172579	0.325053
18	1	0	-2.862874	0.578549	0.074003

```
Zero-point correction=                          0.156606
(Hartree/Particle)
Thermal correction to Energy=                   0.163984
Thermal correction to Enthalpy=                 0.164929
Thermal correction to Gibbs Free Energy=        0.124805
Sum of electronic and zero-point Energies=           -310.257726
Sum of electronic and thermal Energies=              -310.250348
Sum of electronic and thermal Enthalpies=            -310.249404
Sum of electronic and thermal Free Energies=         -310.289527

Version=AM64L-G03RevE.01\State=2-A\HF=-310.4143325\S2=0.778196\S2-
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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.686958	0.113462	-0.490033
2	6	0	1.457615	-1.035936	0.256866
3	6	0	0.011720	-1.446611	0.057820
4	6	0	-0.811820	-0.181962	0.313106
5	6	0	-0.105908	0.974582	-0.348971
6	6	0	0.226887	2.117554	0.329200
7	1	0	1.677474	-0.882676	1.317702
8	1	0	2.149623	-1.793833	-0.117991
9	1	0	-0.289776	-2.260262	0.715284
10	1	0	-0.129740	-1.775382	-0.971033
11	1	0	-0.817336	0.006018	1.387468
12	1	0	-0.182547	1.026577	-1.423738
13	1	0	0.203598	2.150939	1.406674
14	1	0	0.621530	2.976575	-0.185787
15	6	0	-2.255334	-0.312068	-0.165236
16	1	0	-2.293601	-0.473193	-1.240834
17	1	0	-2.742962	-1.157164	0.314716
18	1	0	-2.830878	0.581351	0.061101

```
Zero-point correction=                          0.162252
(Hartree/Particle)
Thermal correction to Energy=                   0.169418
Thermal correction to Enthalpy=                 0.170362
Thermal correction to Gibbs Free Energy=        0.130621
Sum of electronic and zero-point Energies=           -310.052015
Sum of electronic and thermal Energies=              -310.044850
Sum of electronic and thermal Enthalpies=            -310.043905
Sum of electronic and thermal Free Energies=         -310.083646

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NImag=1\\@.
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(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.674893	0.103308	-0.496240
2	6	0	1.448153	-1.038920	0.255399
3	6	0	0.002213	-1.447763	0.061989
4	6	0	-0.811487	-0.177465	0.313430
5	6	0	-0.093863	0.971839	-0.348252
6	6	0	0.246499	2.107696	0.332460
7	1	0	1.670116	-0.885538	1.314871
8	1	0	2.135754	-1.800155	-0.117558
9	1	0	-0.302283	-2.257056	0.721161
10	1	0	-0.141413	-1.776701	-0.965171
11	1	0	-0.815978	0.011879	1.386037
12	1	0	-0.181197	1.030390	-1.420373
13	1	0	0.229271	2.134444	1.408840
14	1	0	0.642930	2.966153	-0.179381
15	6	0	-2.253918	-0.293514	-0.166392
16	1	0	-2.291098	-0.459546	-1.240118
17	1	0	-2.752706	-1.128900	0.316289
18	1	0	-2.818118	0.607331	0.053513

Zero-point correction= 0.161626
(Hartree/Particle)
Thermal correction to Energy= 0.168779
Thermal correction to Enthalpy= 0.169724
Thermal correction to Gibbs Free Energy= 0.130027
Sum of electronic and zero-point Energies= -310.107303
Sum of electronic and thermal Energies= -310.100149
Sum of electronic and thermal Enthalpies= -310.099205
Sum of electronic and thermal Free Energies= -310.138902

Version=AM64L-G03RevE.01\State=2-A\HF=-310.2689284\S2=0.826127\S2-1=0.\ S2A=0.750667\RMSD=8.176e-09\RMSF=3.346e-07\PG=C01 [X(C6H11O1)]\NImag=1\\@.

7.5.3 3-Fluoro-4-pentenoxyl radical-derived transition structures

I. Transition Structure *TS1*$_{cis}$-IIh

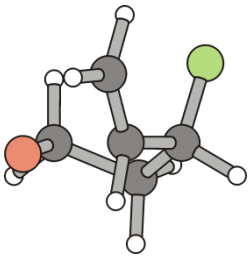

Figure S7.27. Calculated transition *TS1*$_{cis}$-**IIh** structure for 3-fluoro-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.620843	-1.557032	-0.077320
2	6	0	1.481234	-0.549694	-0.522976
3	6	0	1.330506	0.652421	0.415815
4	6	0	-0.173760	0.900112	0.523073
5	6	0	-0.904272	-0.415253	0.643766
6	6	0	-1.911845	-0.790648	-0.211462
7	1	0	2.503958	-0.958971	-0.475038
8	1	0	1.286377	-0.261571	-1.568256
9	1	0	1.712528	0.390891	1.409632
10	1	0	1.845111	1.555535	0.070803
11	1	0	-0.421814	1.554344	1.367431
12	9	0	-0.602433	1.581079	-0.637072
13	1	0	-0.821430	-0.897085	1.612816
14	1	0	-2.480779	-1.694773	-0.026808
15	1	0	-2.099981	-0.243462	-1.127675

```
Zero-point correction=                          0.120992
(Hartree/Particle)
Thermal correction to Energy=                   0.127610
Thermal correction to Enthalpy=                 0.128554
Thermal correction to Gibbs Free Energy=        0.089807
Sum of electronic and zero-point Energies=           -370.215891
Sum of electronic and thermal Energies=              -370.209274
Sum of electronic and thermal Enthalpies=            -370.208330
Sum of electronic and thermal Free Energies=         -370.247077

Version=AM64L-G03RevE.01\State=2-A\HF=-370.3368834\S2=0.778633\S2-
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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.574968	-1.548009	-0.070971
2	6	0	1.452429	-0.570479	-0.526318
3	6	0	1.338244	0.621058	0.409669
4	6	0	-0.148924	0.894789	0.520377
5	6	0	-0.891562	-0.406246	0.631605
6	6	0	-1.921051	-0.735994	-0.207906
7	1	0	2.452933	-1.006479	-0.495036
8	1	0	1.242676	-0.279521	-1.557047
9	1	0	1.718647	0.349246	1.391954
10	1	0	1.866124	1.505593	0.063838
11	1	0	-0.386629	1.542626	1.360458
12	9	0	-0.559525	1.570894	-0.624052
13	1	0	-0.824048	-0.887472	1.592646
14	1	0	-2.504671	-1.622179	-0.030446
15	1	0	-2.103871	-0.174554	-1.106690

Zero-point correction= 0.125687
(Hartree/Particle)
Thermal correction to Energy= 0.132092
Thermal correction to Enthalpy= 0.133036
Thermal correction to Gibbs Free Energy= 0.094679
Sum of electronic and zero-point Energies= -370.005241
Sum of electronic and thermal Energies= -369.998837
Sum of electronic and thermal Enthalpies= -369.997893
Sum of electronic and thermal Free Energies= -370.036250

Version=AM64L-G03RevE.01\State=2-A\HF=-370.1309288\S2=0.826868\S2-1=0.\ S2A=0.750702\RMSD=3.594e-09\RMSF=3.720e-07\PG=C01 [X(C5H8F1O1)]\NImag=1\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.539223	-1.548534	-0.072607
2	6	0	1.430621	-0.589846	-0.529575
3	6	0	1.348569	0.595878	0.415162
4	6	0	-0.132298	0.895835	0.519929
5	6	0	-0.892178	-0.394589	0.633517
6	6	0	-1.926482	-0.696822	-0.206172
7	1	0	2.421635	-1.044779	-0.512976
8	1	0	1.217774	-0.281662	-1.553574
9	1	0	1.721033	0.305923	1.393802
10	1	0	1.893880	1.471079	0.076830
11	1	0	-0.363398	1.546669	1.357960
12	9	0	-0.523535	1.566282	-0.626346
13	1	0	-0.838939	-0.873500	1.594944
14	1	0	-2.532603	-1.567280	-0.034505
15	1	0	-2.090732	-0.127450	-1.101682

Zero-point correction= 0.125304
(Hartree/Particle)
Thermal correction to Energy= 0.131664
Thermal correction to Enthalpy= 0.132609
Thermal correction to Gibbs Free Energy= 0.094380
Sum of electronic and zero-point Energies= -370.077616
Sum of electronic and thermal Energies= -370.071256
Sum of electronic and thermal Enthalpies= -370.070312
Sum of electronic and thermal Free Energies= -370.108540

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II. Transition Structure *TS2*$_{cis}$-IIh

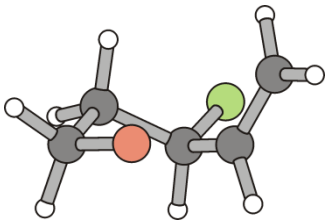

Figure S7.28. Calculated transition *TS2*$_{cis}$-**IIh** structure for 3-fluoro-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.533613	0.912236	0.098659
2	6	0	-1.803604	-0.458170	-0.039662
3	6	0	-0.509583	-1.169088	-0.451028
4	6	0	0.580197	-0.615680	0.466412
5	6	0	0.474722	0.897121	0.527342
6	6	0	0.961287	1.687208	-0.482640
7	1	0	-2.176868	-0.883904	0.908324
8	1	0	-2.574255	-0.599375	-0.812560
9	1	0	-0.587503	-2.258634	-0.376268
10	1	0	-0.251951	-0.907351	-1.483263
11	1	0	0.509988	-1.043006	1.471878
12	9	0	1.843437	-1.002597	-0.033892
13	1	0	0.270010	1.340924	1.494976
14	1	0	0.952266	2.768091	-0.395592
15	1	0	1.318170	1.260406	-1.414282

```
Zero-point correction=                          0.120824
(Hartree/Particle)
Thermal correction to Energy=                   0.127746
Thermal correction to Enthalpy=                 0.128691
Thermal correction to Gibbs Free Energy=        0.088546
Sum of electronic and zero-point Energies=           -370.209614
Sum of electronic and thermal Energies=              -370.202691
Sum of electronic and thermal Enthalpies=            -370.201747
Sum of electronic and thermal Free Energies=         -370.241892

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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.267168	1.146827	-0.238272
2	6	0	-1.839999	-0.091816	0.028221
3	6	0	-0.800162	-1.156949	-0.258642
4	6	0	0.465941	-0.721273	0.465730
5	6	0	0.537601	0.786190	0.527622
6	6	0	1.387789	1.501776	-0.271124
7	1	0	-2.195980	-0.159675	1.061572
8	1	0	-2.702402	-0.200918	-0.631048
9	1	0	-1.116404	-2.154202	0.035151
10	1	0	-0.575729	-1.161955	-1.322074
11	1	0	0.514657	-1.129471	1.471602
12	9	0	1.567257	-1.234105	-0.208808
13	1	0	0.196664	1.231893	1.446855
14	1	0	1.496813	2.563954	-0.137872
15	1	0	1.907391	1.035139	-1.089588

Zero-point correction= 0.125366
(Hartree/Particle)
Thermal correction to Energy= 0.131992
Thermal correction to Enthalpy= 0.132936
Thermal correction to Gibbs Free Energy= 0.093297
Sum of electronic and zero-point Energies= -369.999105
Sum of electronic and thermal Energies= -369.992479
Sum of electronic and thermal Enthalpies= -369.991534
Sum of electronic and thermal Free Energies= -370.031173

Version=AM64L-G03RevE.01\State=2-A\HF=-370.1244704\S2=0.838432\S2-1=0.\ S2A=0.750841\RMSD=3.568e-09\RMSF=2.445e-07\PG=C01 [X(C5H8F1O1)]\NImag=1\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.270057	1.137510	-0.225682
2	6	0	-1.834894	-0.103627	0.025843
3	6	0	-0.787930	-1.156897	-0.268380
4	6	0	0.469190	-0.717099	0.465524
5	6	0	0.524729	0.791330	0.525331
6	6	0	1.372617	1.498578	-0.278906
7	1	0	-2.192324	-0.189140	1.056828
8	1	0	-2.693903	-0.213911	-0.635671
9	1	0	-1.094932	-2.160703	0.007566
10	1	0	-0.554772	-1.141997	-1.328625
11	1	0	0.507408	-1.120492	1.472657
12	9	0	1.573469	-1.218646	-0.197680
13	1	0	0.193621	1.237745	1.445833
14	1	0	1.483938	2.560720	-0.158250
15	1	0	1.887935	1.021799	-1.092231

```
Zero-point correction=                           0.124913
(Hartree/Particle)
Thermal correction to Energy=                    0.131513
Thermal correction to Enthalpy=                  0.132458
Thermal correction to Gibbs Free Energy=         0.092949
Sum of electronic and zero-point Energies=           -370.070769
Sum of electronic and thermal Energies=              -370.064169
Sum of electronic and thermal Enthalpies=            -370.063225
Sum of electronic and thermal Free Energies=         -370.102733

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III. Transition Structure *TS1*$_{trans}$-IIh

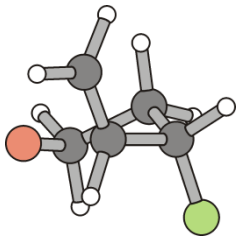

Figure S7.29. Calculated transition *TS1*$_{trans}$-**IIh** structure for 3-fluoro-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.341796	1.453627	-0.658078
2	6	0	0.939543	1.385956	-0.102458
3	6	0	0.952979	0.276046	0.963544
4	6	0	0.250959	-0.928871	0.345487
5	6	0	-1.011278	-0.480861	-0.348315
6	6	0	-2.158981	-0.191544	0.344742
7	1	0	1.693319	1.158073	-0.873014
8	1	0	1.187083	2.349785	0.369145
9	1	0	1.965824	0.017154	1.289783
10	1	0	0.377807	0.598935	1.838964
11	9	0	1.101556	-1.521664	-0.611735
12	1	0	0.047776	-1.705170	1.091840
13	1	0	-1.048869	-0.662803	-1.416966
14	1	0	-3.068848	0.081939	-0.177173
15	1	0	-2.173062	-0.136307	1.429654

```
Zero-point correction=                          0.120592
(Hartree/Particle)
Thermal correction to Energy=                   0.127444
Thermal correction to Enthalpy=                 0.128388
Thermal correction to Gibbs Free Energy=        0.088841
Sum of electronic and zero-point Energies=           -370.212801
Sum of electronic and thermal Energies=              -370.205948
Sum of electronic and thermal Enthalpies=            -370.205004
Sum of electronic and thermal Free Energies=         -370.244551

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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.328097	1.455598	-0.608664
2	6	0	0.968143	1.343044	-0.113964
3	6	0	0.977294	0.251440	0.946844
4	6	0	0.234718	-0.920275	0.340045
5	6	0	-1.002700	-0.420557	-0.350144
6	6	0	-2.158909	-0.174299	0.338440
7	1	0	1.672027	1.092894	-0.909688
8	1	0	1.254400	2.300779	0.323094
9	1	0	1.980595	-0.036708	1.249248
10	1	0	0.432657	0.589271	1.825591
11	9	0	1.049471	-1.528491	-0.609731
12	1	0	0.002316	-1.683410	1.077218
13	1	0	-1.035734	-0.582599	-1.413785
14	1	0	-3.055864	0.117907	-0.178528
15	1	0	-2.182138	-0.162615	1.416417

Zero-point correction= 0.125188
(Hartree/Particle)
Thermal correction to Energy= 0.131836
Thermal correction to Enthalpy= 0.132780
Thermal correction to Gibbs Free Energy= 0.093563
Sum of electronic and zero-point Energies= -370.002025
Sum of electronic and thermal Energies= -369.995378
Sum of electronic and thermal Enthalpies= -369.994434
Sum of electronic and thermal Free Energies= -370.033651

Version=AM64L-G03RevE.01\State=2-A\HF=-370.1272138\S2=0.835866\S2-1=0.\ S2A=0.750825\RMSD=3.833e-09\RMSF=4.372e-07\PG=C01 [X(C5H8F1O1)]\NImag=1\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.337220	1.393318	-0.675095
2	6	0	0.922975	1.355908	-0.092047
3	6	0	0.924301	0.273778	0.978667
4	6	0	0.255312	-0.921636	0.338788
5	6	0	-0.995243	-0.461764	-0.351395
6	6	0	-2.137234	-0.190097	0.344345
7	1	0	1.688010	1.127680	-0.834692
8	1	0	1.138042	2.327108	0.352668
9	1	0	1.923029	0.026054	1.324081
10	1	0	0.330743	0.594167	1.830063
11	9	0	1.108678	-1.457062	-0.609443
12	1	0	0.049694	-1.709931	1.055579
13	1	0	-1.045126	-0.678102	-1.402961
14	1	0	-3.047012	0.062904	-0.167984
15	1	0	-2.138392	-0.119995	1.418845

```
Zero-point correction=                          0.124832
(Hartree/Particle)
Thermal correction to Energy=                   0.131436
Thermal correction to Enthalpy=                 0.132380
Thermal correction to Gibbs Free Energy=        0.093375
Sum of electronic and zero-point Energies=                -370.073722
Sum of electronic and thermal Energies=                   -370.067118
Sum of electronic and thermal Enthalpies=                 -370.066174
Sum of electronic and thermal Free Energies=              -370.105179

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IV. Transition Structure *TS2*$_{trans}$-IIh

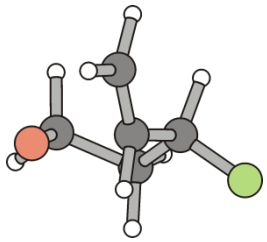

Figure S7.30. Calculated transition *TS2*$_{trans}$-**IIh** structure for 3-fluoro-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.623991	0.255675	-0.518589
2	6	0	1.509968	-0.907300	0.256595
3	6	0	0.093787	-1.456810	0.085608
4	6	0	-0.824152	-0.256212	0.315319
5	6	0	-0.257526	0.978253	-0.353425
6	6	0	0.002747	2.128874	0.350356
7	1	0	2.262159	-1.616522	-0.124677
8	1	0	1.745866	-0.724038	1.319066
9	1	0	-0.047588	-1.803277	-0.943996
10	1	0	-0.141190	-2.281030	0.767604
11	9	0	-2.101535	-0.518716	-0.225761
12	1	0	-0.978676	-0.071570	1.384485
13	1	0	-0.380704	1.023478	-1.430847
14	1	0	0.311116	3.037713	-0.154501
15	1	0	0.001966	2.137458	1.436708

```
Zero-point correction=                          0.120916
(Hartree/Particle)
Thermal correction to Energy=                   0.127653
Thermal correction to Enthalpy=                 0.128598
Thermal correction to Gibbs Free Energy=        0.089401
Sum of electronic and zero-point Energies=           -370.213187
Sum of electronic and thermal Energies=              -370.206450
Sum of electronic and thermal Enthalpies=            -370.205505
Sum of electronic and thermal Free Energies=         -370.244702

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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.587147	0.309331	-0.516078
2	6	0	1.525814	-0.847142	0.259603
3	6	0	0.144183	-1.446508	0.085959
4	6	0	-0.806251	-0.286555	0.310791
5	6	0	-0.271225	0.955201	-0.352239
6	6	0	-0.084371	2.116175	0.348301
7	1	0	2.304818	-1.514945	-0.111721
8	1	0	1.741756	-0.641721	1.311610
9	1	0	0.020159	-1.796286	-0.935975
10	1	0	-0.058898	-2.271869	0.763173
11	9	0	-2.053545	-0.582567	-0.226340
12	1	0	-0.962919	-0.105749	1.371206
13	1	0	-0.395175	0.996816	-1.421312
14	1	0	0.191488	3.028123	-0.151898
15	1	0	-0.105398	2.127050	1.426114

Zero-point correction= 0.125542
(Hartree/Particle)
Thermal correction to Energy= 0.132074
Thermal correction to Enthalpy= 0.133018
Thermal correction to Gibbs Free Energy= 0.094197
Sum of electronic and zero-point Energies= -370.002405
Sum of electronic and thermal Energies= -369.995873
Sum of electronic and thermal Enthalpies= -369.994929
Sum of electronic and thermal Free Energies= -370.033750

Version=AM64L-G03RevE.01\State=2-A\HF=-370.1279469\S2=0.828025\S2-1=0.\ S2A=0.750718\RMSD=5.943e-09\RMSF=2.230e-07\PG=C01 [X(C5H8F1O1)]\NImag=1\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.588774	0.211759	-0.528952
2	6	0	1.467454	-0.927611	0.257985
3	6	0	0.055701	-1.450169	0.094355
4	6	0	-0.826653	-0.237686	0.311806
5	6	0	-0.210275	0.966895	-0.348887
6	6	0	0.058326	2.107300	0.353000
7	1	0	2.205752	-1.641711	-0.106795
8	1	0	1.696246	-0.726687	1.307211
9	1	0	-0.091854	-1.792958	-0.925523
10	1	0	-0.193196	-2.259512	0.773565
11	9	0	-2.079074	-0.457517	-0.229795
12	1	0	-0.971467	-0.044741	1.370802
13	1	0	-0.350908	1.023553	-1.413779
14	1	0	0.385601	3.001795	-0.144982
15	1	0	0.053981	2.111471	1.429726

```
Zero-point correction=                          0.125105
(Hartree/Particle)
Thermal correction to Energy=                   0.131617
Thermal correction to Enthalpy=                 0.132561
Thermal correction to Gibbs Free Energy=        0.093800
Sum of electronic and zero-point Energies=                -370.073592
Sum of electronic and thermal Energies=                   -370.067080
Sum of electronic and thermal Enthalpies=                 -370.066136
Sum of electronic and thermal Free Energies=              -370.104896

Version=AM64L-G03RevE.01\State=2-A\HF=-370.1986967\S2=0.827555\S2-
1=0.\ S2A=0.750678\RMSD=6.601e-09\RMSF=4.925e-07\PG=C01 [X(C5H8F1O1)]\
NImag=1\\@.
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7.5.4 3-Chloro-4-pentenoxyl radical-derived transition structures

I. Transition Structure *TS1*$_{cis}$-IIi

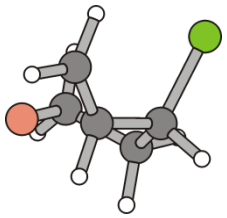

Figure S7.31. Calculated transition *TS1*$_{cis}$-**IIi** structure for 3-chloro-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.904619	0.276102	-0.407461
2	6	0	-1.402010	-1.008551	-0.632431
3	6	0	-0.537983	-1.393673	0.571511
4	6	0	0.411217	-0.208107	0.798417
5	6	0	-0.370324	1.079082	0.649855
6	6	0	-0.040265	2.135347	-0.165058
7	1	0	-2.271110	-1.681702	-0.718619
8	1	0	-0.828965	-1.080059	-1.570457
9	1	0	-1.179023	-1.481088	1.457844
10	1	0	0.009824	-2.332293	0.446660
11	1	0	0.864102	-0.248870	1.792047
12	17	0	1.835730	-0.316240	-0.348324
13	1	0	-1.040291	1.263853	1.485237
14	1	0	-0.607410	3.057837	-0.112315
15	1	0	0.718618	2.044986	-0.932970

```
Zero-point correction=                          0.119635
(Hartree/Particle)
Thermal correction to Energy=                   0.126527
Thermal correction to Enthalpy=                 0.127471
Thermal correction to Gibbs Free Energy=        0.087588
Sum of electronic and zero-point Energies=           -730.569054
Sum of electronic and thermal Energies=              -730.562162
Sum of electronic and thermal Enthalpies=            -730.561218
Sum of electronic and thermal Free Energies=         -730.601101

Version=AM64L-G03RevE.01\State=2-A\HF=-730.6886889\S2=0.779167\S2-
1=0.\ S2A=0.750143\RMSD=9.467e-09\RMSF=6.266e-07\PG=C01
[X(C5H8Cl1O1)]\ NImag=1\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.877008	0.276862	-0.401156
2	6	0	-1.383703	-1.002312	-0.630714
3	6	0	-0.532469	-1.386968	0.566126
4	6	0	0.408480	-0.208979	0.790275
5	6	0	-0.380671	1.064474	0.633021
6	6	0	-0.032777	2.126928	-0.157215
7	1	0	-2.248781	-1.661744	-0.725886
8	1	0	-0.808895	-1.061441	-1.556363
9	1	0	-1.171872	-1.474847	1.442965
10	1	0	0.010116	-2.318419	0.439799
11	1	0	0.852727	-0.240733	1.778317
12	17	0	1.813078	-0.314693	-0.342767
13	1	0	-1.045389	1.247447	1.461855
14	1	0	-0.600266	3.039570	-0.105923
15	1	0	0.732932	2.046196	-0.907439

Zero-point correction= 0.124249
(Hartree/Particle)
Thermal correction to Energy= 0.130918
Thermal correction to Enthalpy= 0.131863
Thermal correction to Gibbs Free Energy= 0.092388
Sum of electronic and zero-point Energies= -730.380509
Sum of electronic and thermal Energies= -730.373840
Sum of electronic and thermal Enthalpies= -730.372896
Sum of electronic and thermal Free Energies= -730.412370

Version=AM64L-G03RevE.01\State=2-A\HF=-730.5047581\S2=0.827896\S2-1=0.\ S2A=0.750715\RMSD=8.236e-09\RMSF=3.468e-07\PG=C01 [X(C5H8Cl1O1)]\ NImag=1\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.877745	0.260973	-0.386134
2	6	0	-1.370767	-1.004797	-0.636377
3	6	0	-0.516013	-1.396023	0.554458
4	6	0	0.406088	-0.207974	0.789573
5	6	0	-0.397284	1.055666	0.631660
6	6	0	-0.060769	2.116056	-0.161499
7	1	0	-2.225848	-1.673730	-0.740694
8	1	0	-0.795738	-1.046574	-1.561674
9	1	0	-1.155591	-1.498982	1.428018
10	1	0	0.038546	-2.317492	0.420596
11	1	0	0.849568	-0.236824	1.775601
12	17	0	1.819278	-0.293624	-0.337786
13	1	0	-1.050731	1.238480	1.467572
14	1	0	-0.631026	3.025251	-0.107776
15	1	0	0.697520	2.036117	-0.917108

```
Zero-point correction=                          0.123785
(Hartree/Particle)
Thermal correction to Energy=                   0.130446
Thermal correction to Enthalpy=                 0.131390
Thermal correction to Gibbs Free Energy=        0.091946
Sum of electronic and zero-point Energies=                -730.455713
Sum of electronic and thermal Energies=                   -730.449052
Sum of electronic and thermal Enthalpies=                 -730.448108
Sum of electronic and thermal Free Energies=              -730.487552

Version=AM64L-G03RevE.01\State=2-A\HF=-730.5794976\S2=0.827768\S2-
1=0.\ S2A=0.75068\RMSD=7.189e-09\RMSF=6.937e-07\PG=C01 [X(C5H8Cl1O1)]\
NImag=1\\@.
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II. Transition Structure *TS2*$_{cis}$-IIi

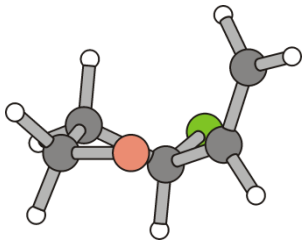

Figure S7.32. Calculated transition *TS2*$_{cis}$-**IIi** structure for 3-chloro-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.125682	0.274770	-0.301312
2	6	0	1.867858	-1.051167	0.084604
3	6	0	0.395285	-1.173722	0.520293
4	6	0	-0.386467	-0.300932	-0.460992
5	6	0	0.230330	1.079297	-0.503176
6	6	0	0.262621	1.918899	0.577933
7	1	0	2.046279	-1.723766	-0.772004
8	1	0	2.529884	-1.349774	0.911009
9	1	0	0.047791	-2.211026	0.506081
10	1	0	0.269726	-0.786357	1.536383
11	1	0	-0.372902	-0.741346	-1.458811
12	17	0	-2.164790	-0.248186	-0.011032
13	1	0	0.453199	1.479206	-1.486402
14	1	0	0.677094	2.916768	0.489338
15	1	0	-0.072871	1.603049	1.560470

```
Zero-point correction=                          0.119629
(Hartree/Particle)
Thermal correction to Energy=                   0.126847
Thermal correction to Enthalpy=                 0.127791
Thermal correction to Gibbs Free Energy=        0.086928
Sum of electronic and zero-point Energies=           -730.565733
Sum of electronic and thermal Energies=              -730.558515
Sum of electronic and thermal Enthalpies=            -730.557571
Sum of electronic and thermal Free Energies=         -730.598434

Version=AM64L-G03RevE.01\State=2-A\HF=-730.6853621\S2=0.776955\S2-
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[X(C5H8Cl1O1)]\ NImag=1\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.092597	0.293650	-0.285512
2	6	0	1.854707	-1.033223	0.083364
3	6	0	0.401279	-1.170741	0.521492
4	6	0	-0.379532	-0.309976	-0.455034
5	6	0	0.246607	1.059283	-0.496975
6	6	0	0.213950	1.917355	0.564315
7	1	0	2.042215	-1.688162	-0.771552
8	1	0	2.526530	-1.317017	0.893572
9	1	0	0.065352	-2.203254	0.507852
10	1	0	0.271787	-0.785081	1.528825
11	1	0	-0.355377	-0.749434	-1.443966
12	17	0	-2.132590	-0.256322	-0.015710
13	1	0	0.477088	1.451507	-1.472134
14	1	0	0.615500	2.911477	0.475361
15	1	0	-0.151904	1.612048	1.530228

```
Zero-point correction=                          0.124086
(Hartree/Particle)
Thermal correction to Energy=                   0.131095
Thermal correction to Enthalpy=                 0.132039
Thermal correction to Gibbs Free Energy=        0.091480
Sum of electronic and zero-point Energies=           -730.377039
Sum of electronic and thermal Energies=              -730.370030
Sum of electronic and thermal Enthalpies=            -730.369086
Sum of electronic and thermal Free Energies=         -730.409645

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1=0.\ S2A=0.750743\RMSD=9.860e-09\RMSF=5.067e-07\PG=C01
[X(C5H8Cl1O1)]\ NImag=1\\@.
```

(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.077353	0.283645	-0.320769
2	6	0	1.849750	-1.028816	0.093209
3	6	0	0.394896	-1.168845	0.525860
4	6	0	-0.378998	-0.308603	-0.452633
5	6	0	0.252177	1.056261	-0.491275
6	6	0	0.241502	1.896560	0.580603
7	1	0	2.045420	-1.708536	-0.738991
8	1	0	2.516498	-1.285099	0.914998
9	1	0	0.059089	-2.199771	0.511400
10	1	0	0.260440	-0.782668	1.530800
11	1	0	-0.358179	-0.747632	-1.439586
12	17	0	-2.134740	-0.244367	-0.019288
13	1	0	0.457341	1.461381	-1.464968
14	1	0	0.639024	2.891311	0.498056
15	1	0	-0.103832	1.576750	1.547748

Zero-point correction= 0.123668
(Hartree/Particle)
Thermal correction to Energy= 0.130675
Thermal correction to Enthalpy= 0.131619
Thermal correction to Gibbs Free Energy= 0.091063
Sum of electronic and zero-point Energies= -730.452351
Sum of electronic and thermal Energies= -730.445344
Sum of electronic and thermal Enthalpies= -730.444400
Sum of electronic and thermal Free Energies= -730.484956

Version=AM64L-G03RevE.01\State=2-A\HF=-730.5760196\S2=0.829007\S2-1=0.\ S2A=0.750688\RMSD=5.228e-09\RMSF=5.431e-07\PG=C01 [X(C5H8Cl1O1)]\ NImag=1\\@.

III. Transition Structure *TS1*$_{trans}$-IIi

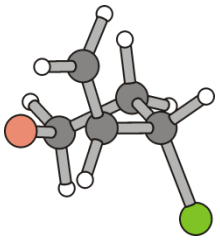

Figure S7.33. Calculated transition *TS1*$_{trans}$-**IIi** structure for 3-chloro-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.481575	0.769651	-0.874483
2	6	0	-0.675652	1.678529	-0.182799
3	6	0	-0.090569	0.970985	1.049879
4	6	0	0.402527	-0.405737	0.592201
5	6	0	-0.642196	-1.032559	-0.305308
6	6	0	-1.759487	-1.627095	0.225008
7	1	0	0.146464	2.042899	-0.819393
8	1	0	-1.283640	2.535952	0.145929
9	1	0	0.702006	1.550846	1.532461
10	1	0	-0.891188	0.805108	1.781166
11	17	0	2.000101	-0.273459	-0.288281
12	1	0	0.616401	-1.046024	1.450518
13	1	0	-0.361945	-1.233937	-1.332310
14	1	0	-2.487209	-2.108738	-0.418346
15	1	0	-1.997752	-1.559249	1.282737

```
Zero-point correction=                          0.119321
(Hartree/Particle)
Thermal correction to Energy=                   0.126470
Thermal correction to Enthalpy=                 0.127414
Thermal correction to Gibbs Free Energy=        0.086587
Sum of electronic and zero-point Energies=           -730.566900
Sum of electronic and thermal Energies=              -730.559752
Sum of electronic and thermal Enthalpies=            -730.558807
Sum of electronic and thermal Free Energies=         -730.599635

Version=AM64L-G03RevE.01\State=2-A\HF=-730.6862215\S2=0.780261\S2-
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[X(C5H8Cl1O1)]\ NImag=1\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.525760	0.749838	-0.806177
2	6	0	-0.667546	1.663963	-0.202976
3	6	0	-0.061218	1.001278	1.023216
4	6	0	0.402993	-0.380343	0.583704
5	6	0	-0.650768	-0.985763	-0.308610
6	6	0	-1.711055	-1.662689	0.231653
7	1	0	0.121231	1.978206	-0.888793
8	1	0	-1.249112	2.539241	0.090619
9	1	0	0.744648	1.580092	1.464249
10	1	0	-0.837706	0.862763	1.773203
11	17	0	1.981517	-0.283243	-0.290628
12	1	0	0.598328	-1.016567	1.437641
13	1	0	-0.386293	-1.154431	-1.337072
14	1	0	-2.434607	-2.143855	-0.402812
15	1	0	-1.910641	-1.647685	1.291131

```
Zero-point correction=                          0.123827
(Hartree/Particle)
Thermal correction to Energy=                   0.130763
Thermal correction to Enthalpy=                 0.131707
Thermal correction to Gibbs Free Energy=        0.091169
Sum of electronic and zero-point Energies=           -730.378453
Sum of electronic and thermal Energies=              -730.371517
Sum of electronic and thermal Enthalpies=            -730.370573
Sum of electronic and thermal Free Energies=         -730.411111

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S2A=0.750842\RMSD=1.778e-09\RMSF=8.272e-07\PG=C01 [X(C5H8Cl1O1)]\
NImag=1\\@.
```

(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.431677	0.763386	-0.870543
2	6	0	-0.626583	1.664977	-0.187401
3	6	0	-0.069334	0.969382	1.044445
4	6	0	0.388988	-0.405786	0.590748
5	6	0	-0.668944	-0.988603	-0.308021
6	6	0	-1.777645	-1.577752	0.228640
7	1	0	0.193490	2.011804	-0.816823
8	1	0	-1.228742	2.522517	0.111870
9	1	0	0.727556	1.528528	1.521987
10	1	0	-0.869317	0.824731	1.766372
11	17	0	1.968408	-0.302640	-0.283456
12	1	0	0.585654	-1.054339	1.432412
13	1	0	-0.384226	-1.218493	-1.317028
14	1	0	-2.505423	-2.052111	-0.403707
15	1	0	-2.007403	-1.498164	1.277544

Zero-point correction= 0.123407
(Hartree/Particle)
Thermal correction to Energy= 0.130333
Thermal correction to Enthalpy= 0.131277
Thermal correction to Gibbs Free Energy= 0.090831
Sum of electronic and zero-point Energies= -730.453720
Sum of electronic and thermal Energies= -730.446794
Sum of electronic and thermal Enthalpies= -730.445850
Sum of electronic and thermal Free Energies= -730.486296

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IV. Transition Structure *TS2*$_{trans}$-IIi

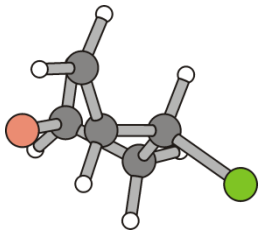

Figure S7.34. Calculated transition *TS2*$_{trans}$-**IIi** structure for 3-chloro-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.027702	-0.017278	-0.523863
2	6	0	1.722301	-1.160691	0.225782
3	6	0	0.225076	-1.445375	0.076883
4	6	0	-0.436670	-0.097837	0.376423
5	6	0	0.295444	1.010684	-0.341797
6	6	0	0.748281	2.124292	0.326756
7	1	0	2.323287	-1.985006	-0.191457
8	1	0	2.005116	-1.053143	1.287230
9	1	0	0.006181	-1.738541	-0.954912
10	1	0	-0.139742	-2.229733	0.748070
11	17	0	-2.201202	-0.100434	-0.112804
12	1	0	-0.445543	0.096096	1.451606
13	1	0	0.169688	1.049427	-1.418631
14	1	0	1.191050	2.956146	-0.209718
15	1	0	0.762184	2.163924	1.412104

```
Zero-point correction=                          0.119640
(Hartree/Particle)
Thermal correction to Energy=                   0.126673
Thermal correction to Enthalpy=                 0.127617
Thermal correction to Gibbs Free Energy=        0.087322
Sum of electronic and zero-point Energies=           -730.570091
Sum of electronic and thermal Energies=              -730.563058
Sum of electronic and thermal Enthalpies=            -730.562114
Sum of electronic and thermal Free Energies=         -730.602409

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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.996023	-0.015746	-0.525520
2	6	0	1.705292	-1.150821	0.226968
3	6	0	0.221991	-1.438639	0.080523
4	6	0	-0.435686	-0.100338	0.373793
5	6	0	0.306440	0.994993	-0.339376
6	6	0	0.733557	2.113686	0.326323
7	1	0	2.310917	-1.962225	-0.180737
8	1	0	1.981771	-1.025172	1.277357
9	1	0	0.005142	-1.733696	-0.942414
10	1	0	-0.136348	-2.215999	0.749506
11	17	0	-2.174419	-0.098610	-0.114072
12	1	0	-0.439831	0.094004	1.440184
13	1	0	0.178267	1.036230	-1.407439
14	1	0	1.173892	2.938797	-0.205748
15	1	0	0.733562	2.157121	1.403293

```
Zero-point correction=                          0.124167
(Hartree/Particle)
Thermal correction to Energy=                   0.130986
Thermal correction to Enthalpy=                 0.131931
Thermal correction to Gibbs Free Energy=        0.092031
Sum of electronic and zero-point Energies=                -730.381662
Sum of electronic and thermal Energies=                   -730.374843
Sum of electronic and thermal Enthalpies=                 -730.373898
Sum of electronic and thermal Free Energies=              -730.413798

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S2A=0.750752\RMSD=3.680e-09\RMSF=5.425e-07\PG=C01 [X(C5H8Cl1O1)]\
NImag=1\\@.
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(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.980521	-0.019402	-0.538287
2	6	0	1.701550	-1.146296	0.223940
3	6	0	0.218997	-1.439505	0.090076
4	6	0	-0.434071	-0.099877	0.377072
5	6	0	0.312466	0.990414	-0.337185
6	6	0	0.746437	2.101369	0.331551
7	1	0	2.304452	-1.959171	-0.181517
8	1	0	1.983746	-1.015372	1.271136
9	1	0	-0.001066	-1.738164	-0.929660
10	1	0	-0.135492	-2.212345	0.764034
11	17	0	-2.172525	-0.091645	-0.116464
12	1	0	-0.445544	0.098272	1.440538
13	1	0	0.169312	1.040163	-1.401315
14	1	0	1.185081	2.927765	-0.197167
15	1	0	0.755998	2.135397	1.407407

```
Zero-point correction=                          0.123705
(Hartree/Particle)
Thermal correction to Energy=                   0.130515
Thermal correction to Enthalpy=                 0.131460
Thermal correction to Gibbs Free Energy=        0.091596
Sum of electronic and zero-point Energies=                -730.456806
Sum of electronic and thermal Energies=                   -730.449996
Sum of electronic and thermal Enthalpies=                 -730.449051
Sum of electronic and thermal Free Energies=              -730.488915

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S2A=0.750715\RMSD=4.093e-09\RMSF=6.163e-07\PG=C01 [X(C5H8Cl1O1)]\
NImag=1\\@.
```

7.5.5 3-Amino-4-pentenoxyl radical-derived transition structures

I. Transition Structure *TS1*$_{cis}$-IIo

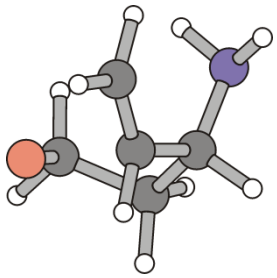

Figure S7.35. Calculated transition *TS1*$_{cis}$-**IIo** structure for 3-amino-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.714492	-1.511617	-0.202875
2	6	0	1.550081	-0.437380	-0.514972
3	6	0	1.296084	0.686572	0.495935
4	6	0	-0.235082	0.876745	0.537823
5	6	0	-0.851082	-0.516581	0.639761
6	6	0	-1.871422	-0.974078	-0.162420
7	1	0	2.587756	-0.803871	-0.436021
8	1	0	1.413374	-0.085103	-1.553597
9	1	0	1.649055	0.360286	1.480521
10	1	0	1.793655	1.626830	0.237554
11	1	0	-0.495968	1.416675	1.457949
12	7	0	-0.669707	1.713426	-0.579457
13	1	0	-0.677473	-1.028732	1.582113
14	1	0	-2.340339	-1.933072	0.028322
15	1	0	-2.168499	-0.447056	-1.063619
16	1	0	-0.451142	1.292952	-1.478597
17	1	0	-1.669876	1.888375	-0.552185

```
Zero-point correction=                          0.145932
(Hartree/Particle)
Thermal correction to Energy=                   0.153068
Thermal correction to Enthalpy=                 0.154012
Thermal correction to Gibbs Free Energy=        0.114454
Sum of electronic and zero-point Energies=           -326.301309
Sum of electronic and thermal Energies=              -326.294173
Sum of electronic and thermal Enthalpies=            -326.293229
Sum of electronic and thermal Free Energies=         -326.332787
Version=AM64L-G03RevE.01\State=2-A\HF=-326.4472412\S2=0.778931\S2-
1=0.\ S2A=0.750145\RMSD=8.769e-09\RMSF=3.045e-07\PG=C01
[X(C5H10N1O1)]\ NImag=1\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.667894	-1.504963	-0.201354
2	6	0	1.527603	-0.460146	-0.516242
3	6	0	1.304665	0.656096	0.490741
4	6	0	-0.209318	0.872272	0.536927
5	6	0	-0.839932	-0.505544	0.627888
6	6	0	-1.883865	-0.924701	-0.155638
7	1	0	2.543940	-0.855024	-0.448836
8	1	0	1.384318	-0.107289	-1.542335
9	1	0	1.653298	0.321764	1.465104
10	1	0	1.817563	1.578165	0.233080
11	1	0	-0.462123	1.409188	1.450214
12	7	0	-0.629882	1.705304	-0.571617
13	1	0	-0.678855	-1.019208	1.561843
14	1	0	-2.364681	-1.869263	0.030708
15	1	0	-2.180257	-0.385643	-1.039477
16	1	0	-0.429488	1.287024	-1.464533
17	1	0	-1.612613	1.914995	-0.535669

```
Zero-point correction=                          0.151506
(Hartree/Particle)
Thermal correction to Energy=                   0.158419
Thermal correction to Enthalpy=                 0.159363
Thermal correction to Gibbs Free Energy=        0.120201
Sum of electronic and zero-point Energies=           -326.090582
Sum of electronic and thermal Energies=              -326.083669
Sum of electronic and thermal Enthalpies=            -326.082725
Sum of electronic and thermal Free Energies=         -326.121887

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1=0.\ S2A=0.750712\RMSD=7.089e-09\RMSF=3.441e-07\PG=C01
[X(C5H10N1O1)]\ NImag=1\\@.
```

(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.676562	-1.497380	-0.184079
2	6	0	1.518370	-0.451221	-0.523770
3	6	0	1.302129	0.670974	0.476403
4	6	0	-0.212440	0.868777	0.540656
5	6	0	-0.827651	-0.516464	0.629239
6	6	0	-1.862311	-0.933852	-0.162629
7	1	0	2.538911	-0.833992	-0.469354
8	1	0	1.358127	-0.107011	-1.549524
9	1	0	1.668549	0.347245	1.446314
10	1	0	1.797961	1.596598	0.204491
11	1	0	-0.462406	1.396977	1.458119
12	7	0	-0.651729	1.700460	-0.562291
13	1	0	-0.676467	-1.025467	1.565644
14	1	0	-2.344517	-1.878113	0.013452
15	1	0	-2.147631	-0.389611	-1.044968
16	1	0	-0.449322	1.274263	-1.450176
17	1	0	-1.642173	1.865640	-0.524719

```
Zero-point correction=                          0.151017
(Hartree/Particle)
Thermal correction to Energy=                   0.157890
Thermal correction to Enthalpy=                 0.158834
Thermal correction to Gibbs Free Energy=        0.119782
Sum of electronic and zero-point Energies=           -326.150059
Sum of electronic and thermal Energies=              -326.143186
Sum of electronic and thermal Enthalpies=            -326.142242
Sum of electronic and thermal Free Energies=         -326.181294

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1=0.\ S2A=0.750675\RMSD=4.963e-09\RMSF=8.405e-07\PG=C01
[X(C5H10N1O1)]\ NImag=1\\@.
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II. Transition Structure *TS2*$_{cis}$-IIo

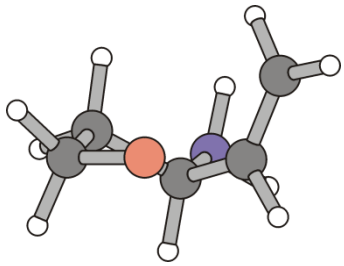

Figure S7.36. Calculated transition *TS2*$_{cis}$-**IIo** structure for 3-amino-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.702375	0.586974	-0.285851
2	6	0	1.698835	-0.772713	0.062092
3	6	0	0.288267	-1.180488	0.514806
4	6	0	-0.705551	-0.495744	-0.434972
5	6	0	-0.327890	0.985436	-0.505359
6	6	0	-0.450212	1.839625	0.558205
7	1	0	1.978922	-1.378704	-0.817564
8	1	0	2.426635	-0.962714	0.865919
9	1	0	0.153694	-2.266720	0.506789
10	1	0	0.115421	-0.829170	1.540497
11	1	0	-0.568829	-0.920898	-1.436099
12	7	0	-2.086780	-0.798399	-0.037565
13	1	0	-0.174325	1.411916	-1.492174
14	1	0	-0.236958	2.897953	0.454580
15	1	0	-0.685604	1.484378	1.557923
16	1	0	-2.290944	-0.420995	0.885056
17	1	0	-2.750253	-0.378743	-0.683792

```
Zero-point correction=                          0.145829
(Hartree/Particle)
Thermal correction to Energy=                   0.153287
Thermal correction to Enthalpy=                 0.154232
Thermal correction to Gibbs Free Energy=        0.113705
Sum of electronic and zero-point Energies=           -326.297544
Sum of electronic and thermal Energies=              -326.290086
Sum of electronic and thermal Enthalpies=            -326.289142
Sum of electronic and thermal Free Energies=         -326.329669

Version=AM64L-G03RevE.01\State=2-A\HF=-326.4433736\S2=0.775873\S2-
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 =C01 [X(C5H10N1O1)]\ NImag=1\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.658905	0.618036	-0.272939
2	6	0	1.696056	-0.737168	0.064747
3	6	0	0.310854	-1.176237	0.513361
4	6	0	-0.680418	-0.510292	-0.432873
5	6	0	-0.310004	0.965014	-0.499415
6	6	0	-0.508206	1.819751	0.547809
7	1	0	1.996141	-1.322571	-0.808950
8	1	0	2.429611	-0.894163	0.856455
9	1	0	0.199560	-2.256734	0.500548
10	1	0	0.126028	-0.834059	1.531174
11	1	0	-0.533381	-0.930705	-1.425370
12	7	0	-2.046496	-0.817799	-0.045075
13	1	0	-0.157877	1.391150	-1.477155
14	1	0	-0.319601	2.874494	0.446337
15	1	0	-0.766685	1.463373	1.532379
16	1	0	-2.259331	-0.456955	0.870601
17	1	0	-2.709929	-0.419930	-0.688756

Zero-point correction= 0.151274
(Hartree/Particle)
Thermal correction to Energy= 0.158522
Thermal correction to Enthalpy= 0.159466
Thermal correction to Gibbs Free Energy= 0.119203
Sum of electronic and zero-point Energies= -326.086805
Sum of electronic and thermal Energies= -326.079558
Sum of electronic and thermal Enthalpies= -326.078613
Sum of electronic and thermal Free Energies= -326.118876

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.651165	0.594101	-0.308275
2	6	0	1.683621	-0.745813	0.075668
3	6	0	0.293753	-1.174691	0.519071
4	6	0	-0.685270	-0.502440	-0.432368
5	6	0	-0.297616	0.967280	-0.494066
6	6	0	-0.466996	1.808490	0.564880
7	1	0	1.991127	-1.358148	-0.775681
8	1	0	2.405877	-0.883983	0.879624
9	1	0	0.172515	-2.252665	0.508145
10	1	0	0.104908	-0.829497	1.533725
11	1	0	-0.533645	-0.923737	-1.422594
12	7	0	-2.057469	-0.792734	-0.052070
13	1	0	-0.170763	1.402577	-1.469738
14	1	0	-0.275539	2.862184	0.472512
15	1	0	-0.703262	1.440980	1.549332
16	1	0	-2.260940	-0.407227	0.854884
17	1	0	-2.702264	-0.371115	-0.698623

```
Zero-point correction=                          0.150813
(Hartree/Particle)
Thermal correction to Energy=                   0.158033
Thermal correction to Enthalpy=                 0.158978
Thermal correction to Gibbs Free Energy=        0.118812
Sum of electronic and zero-point Energies=           -326.145904
Sum of electronic and thermal Energies=              -326.138684
Sum of electronic and thermal Enthalpies=            -326.137740
Sum of electronic and thermal Free Energies=         -326.177905

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III. Transition Structure *TS1*$_{trans}$-IIo

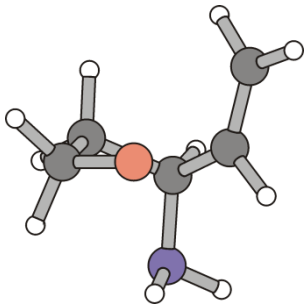

Figure S7.37. Calculated transition *TS1*$_{trans}$-**IIo** structure for 3-amino-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.468483	1.204092	-0.932443
2	6	0	0.550191	1.585465	-0.052583
3	6	0	0.701097	0.518306	1.056478
4	6	0	0.430152	-0.851804	0.412149
5	6	0	-0.903989	-0.749479	-0.316040
6	6	0	-2.099228	-0.506709	0.306296
7	1	0	1.500069	1.656012	-0.611298
8	1	0	0.340801	2.567018	0.399577
9	1	0	1.695450	0.544319	1.512636
10	1	0	-0.041624	0.707901	1.838623
11	7	0	1.554844	-1.248658	-0.439035
12	1	0	0.351920	-1.602208	1.209249
13	1	0	-0.919239	-1.101120	-1.344338
14	1	0	-3.029261	-0.505537	-0.251907
15	1	0	-2.155539	-0.242626	1.358489
16	1	0	1.463746	-2.215784	-0.737492
17	1	0	1.588299	-0.674776	-1.278550

```
Zero-point correction=                          0.145785
(Hartree/Particle)
Thermal correction to Energy=                   0.153196
Thermal correction to Enthalpy=                 0.154141
Thermal correction to Gibbs Free Energy=        0.113690
Sum of electronic and zero-point Energies=           -326.299818
Sum of electronic and thermal Energies=              -326.292407
Sum of electronic and thermal Enthalpies=            -326.291463
Sum of electronic and thermal Free Energies=         -326.331913

Version=AM64L-G03RevE.01\State=2-A\HF=-326.4456031\S2=0.774602\S2-
1=0.\ S2A=0.750118\RMSD=1.432e-09\RMSF=7.047e-07\PG=C01
[X(C5H10N1O1)]\ NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.428847	1.132025	-0.963890
2	6	0	0.531452	1.566864	-0.049755
3	6	0	0.688136	0.521028	1.058392
4	6	0	0.424633	-0.839606	0.421384
5	6	0	-0.895130	-0.723326	-0.314171
6	6	0	-2.086679	-0.480734	0.306587
7	1	0	1.480677	1.682871	-0.579372
8	1	0	0.254673	2.533294	0.372300
9	1	0	1.675422	0.553089	1.509301
10	1	0	-0.047163	0.706538	1.836781
11	7	0	1.539594	-1.225660	-0.424549
12	1	0	0.339991	-1.589450	1.205585
13	1	0	-0.916423	-1.107630	-1.321369
14	1	0	-3.009099	-0.486573	-0.248037
15	1	0	-2.139767	-0.200440	1.346086
16	1	0	1.460938	-2.183392	-0.722421
17	1	0	1.579909	-0.650241	-1.250499

```
Zero-point correction=                          0.151363
(Hartree/Particle)
Thermal correction to Energy=                   0.158541
Thermal correction to Enthalpy=                 0.159485
Thermal correction to Gibbs Free Energy=        0.119463
Sum of electronic and zero-point Energies=           -326.088892
Sum of electronic and thermal Energies=              -326.081714
Sum of electronic and thermal Enthalpies=            -326.080770
Sum of electronic and thermal Free Energies=         -326.120792

Version=AM64L-G03RevE.01\State=2-A\HF=-326.2402551\S2=0.82145\S2-1=0.\
S2A=0.750651\RMSD=3.977e-09\RMSF=4.602e-07\PG=C01 [X(C5H10N1O1)]\
NImag=1\\@.
```

(*iii*) BHandHLYP/6-311G// BHandHLYP/6-311G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.418497	1.041505	-1.019133
2	6	0	0.430079	1.583018	-0.056469
3	6	0	0.659963	0.559455	1.062807
4	6	0	0.457121	-0.817040	0.442036
5	6	0	-0.865251	-0.765416	-0.294114
6	6	0	-2.060449	-0.512281	0.307604
7	1	0	1.381186	1.806448	-0.544285
8	1	0	0.029883	2.511735	0.347511
9	1	0	1.651875	0.640402	1.492619
10	1	0	-0.065726	0.715501	1.854711
11	7	0	1.585729	-1.153069	-0.408688
12	1	0	0.407753	-1.562926	1.231317
13	1	0	-0.876515	-1.211328	-1.274273
14	1	0	-2.979567	-0.574568	-0.246456
15	1	0	-2.122954	-0.170551	1.326404
16	1	0	1.534197	-2.113170	-0.702875
17	1	0	1.558961	-0.588511	-1.241983

```
Zero-point correction=                          0.150919
(Hartree/Particle)
Thermal correction to Energy=                   0.158058
Thermal correction to Enthalpy=                 0.159002
Thermal correction to Gibbs Free Energy=        0.119151
Sum of electronic and zero-point Energies=           -326.148167
Sum of electronic and thermal Energies=              -326.141029
Sum of electronic and thermal Enthalpies=            -326.140085
Sum of electronic and thermal Free Energies=         -326.179935

Version=AM64L-G03RevE.01\State=2-A\HF=-326.2990864\S2=0.81983\S2-1=0.\
S2A=0.750596\RMSD=7.838e-09\RMSF=3.368e-07\PG=C01 [X(C5H10N1O1)]\
NImag=1\\@.
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IV. Transition Structure *TS2*$_{trans}$-IIo

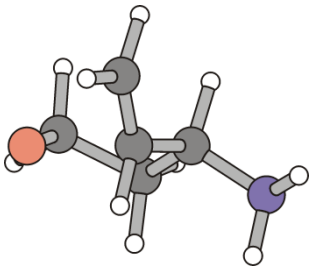

Figure S7.38. Calculated transition *TS2*$_{trans}$-**IIo** structure for 3-amino-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.681204	0.206837	-0.497683
2	6	0	1.508107	-0.957027	0.261910
3	6	0	0.077813	-1.455577	0.070356
4	6	0	-0.826315	-0.234848	0.313645
5	6	0	-0.194415	0.978742	-0.360194
6	6	0	0.087581	2.138392	0.322790
7	1	0	2.243179	-1.688696	-0.113380
8	1	0	1.730672	-0.792387	1.330889
9	1	0	-0.050221	-1.800105	-0.964554
10	1	0	-0.190124	-2.281319	0.738351
11	7	0	-2.201573	-0.516999	-0.109695
12	1	0	-0.858793	-0.039493	1.393708
13	1	0	-0.284797	1.020883	-1.443044
14	1	0	0.413883	3.034933	-0.193668
15	1	0	0.087857	2.161962	1.409360
16	1	0	-2.806993	0.285830	0.038953
17	1	0	-2.239907	-0.755403	-1.098320

```
Zero-point correction=                           0.145867
(Hartree/Particle)
Thermal correction to Energy=                    0.153110
Thermal correction to Enthalpy=                  0.154055
Thermal correction to Gibbs Free Energy=         0.114201
Sum of electronic and zero-point Energies=           -326.302708
Sum of electronic and thermal Energies=              -326.295465
Sum of electronic and thermal Enthalpies=            -326.294521
Sum of electronic and thermal Free Energies=         -326.334375

Version=AM64L-G03RevE.01\State=2-A\HF=-326.4485758\S2=0.778456\S2-
1=0.\ S2A=0.750143\RMSD=5.760e-09\RMSF=5.032e-07\PG=C01
[X(C5H10N1O1)]\ NImag=1\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.649335	0.200919	-0.504069
2	6	0	1.491875	-0.951191	0.262312
3	6	0	0.073655	-1.449186	0.078102
4	6	0	-0.818188	-0.233636	0.311938
5	6	0	-0.172643	0.965108	-0.357390
6	6	0	0.090348	2.123911	0.324544
7	1	0	2.226849	-1.670675	-0.104981
8	1	0	1.709208	-0.767707	1.318457
9	1	0	-0.054372	-1.799106	-0.946113
10	1	0	-0.189836	-2.263421	0.747951
11	7	0	-2.179194	-0.502340	-0.115950
12	1	0	-0.852377	-0.036148	1.382788
13	1	0	-0.268345	1.012618	-1.431043
14	1	0	0.424272	3.010771	-0.186241
15	1	0	0.075475	2.148229	1.402649
16	1	0	-2.782199	0.288462	0.036698
17	1	0	-2.219279	-0.744036	-1.092998

Zero-point correction= 0.151377
(Hartree/Particle)
Thermal correction to Energy= 0.158400
Thermal correction to Enthalpy= 0.159345
Thermal correction to Gibbs Free Energy= 0.119885
Sum of electronic and zero-point Energies= -326.092007
Sum of electronic and thermal Energies= -326.084984
Sum of electronic and thermal Enthalpies= -326.084040
Sum of electronic and thermal Free Energies= -326.123499

Version=AM64L-G03RevE.01\State=2-A\HF=-326.2433841\S2=0.826439\S2-1=0.\ S2A=0.750715\RMSD=5.150e-09\RMSF=2.047e-07\PG=C01 [X(C5H10N1O1)]\ NImag=1\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.637741	0.205288	-0.505540
2	6	0	1.490695	-0.944238	0.260213
3	6	0	0.076431	-1.450937	0.077744
4	6	0	-0.815341	-0.237683	0.313451
5	6	0	-0.168603	0.959827	-0.355461
6	6	0	0.089391	2.117064	0.325845
7	1	0	2.228291	-1.659476	-0.106766
8	1	0	1.706402	-0.762846	1.316140
9	1	0	-0.050545	-1.795465	-0.947194
10	1	0	-0.184887	-2.267109	0.743835
11	7	0	-2.177502	-0.502494	-0.114788
12	1	0	-0.846250	-0.041576	1.383474
13	1	0	-0.276639	1.009960	-1.426481
14	1	0	0.414440	3.006529	-0.183480
15	1	0	0.081555	2.136859	1.402733
16	1	0	-2.763187	0.301488	0.032749
17	1	0	-2.204034	-0.717412	-1.097931

```
Zero-point correction=                          0.150843
(Hartree/Particle)
Thermal correction to Energy=                   0.157844
Thermal correction to Enthalpy=                 0.158788
Thermal correction to Gibbs Free Energy=        0.119396
Sum of electronic and zero-point Energies=           -326.150735
Sum of electronic and thermal Energies=              -326.143735
Sum of electronic and thermal Enthalpies=            -326.142790
Sum of electronic and thermal Free Energies=         -326.182182

Version=AM64L-G03RevE.01\State=2-A\HF=-326.3015783\S2=0.826417\S2-
1=0.\ S2A=0.750679\RMSD=7.687e-09\RMSF=5.226e-07\PG=C01
[X(C5H10N1O1)]\ NImag=1\\@.
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7.5.6 3-Mercapto-4-pentenoxyl radical-derived transition structures

I. Transition Structure *TS1*$_{cis}$-IIp

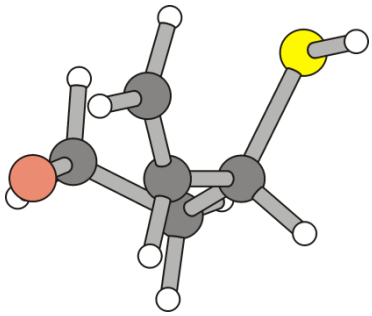

Figure S7.39. Calculated transition *TS1*$_{cis}$-**IIp** structure for 3-mercapto-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.952324	0.219446	-0.368904
2	6	0	-1.398193	-1.036398	-0.626146
3	6	0	-0.497955	-1.407861	0.555407
4	6	0	0.424317	-0.187931	0.787020
5	6	0	-0.416706	1.069859	0.648474
6	6	0	-0.160129	2.121866	-0.199839
7	1	0	-2.239611	-1.744524	-0.712166
8	1	0	-0.843351	-1.064233	-1.578185
9	1	0	-1.122026	-1.540927	1.446614
10	1	0	0.073939	-2.329517	0.401104
11	1	0	0.824867	-0.225198	1.804996
12	16	0	1.871758	-0.329505	-0.364148
13	1	0	-1.068573	1.251265	1.499208
14	1	0	-0.759328	3.024013	-0.145332
15	1	0	0.555532	2.035275	-1.009709
16	1	0	2.541008	0.753156	0.081574

```
Zero-point correction=                          0.128039
(Hartree/Particle)
Thermal correction to Energy=                   0.135564
Thermal correction to Enthalpy=                 0.136508
Thermal correction to Gibbs Free Energy=        0.095492
Sum of electronic and zero-point Energies=           -669.150060
Sum of electronic and thermal Energies=              -669.142534
Sum of electronic and thermal Enthalpies=            -669.141590
Sum of electronic and thermal Free Energies=         -669.182606
Version=AM64L-G03RevE.01\State=2-A\HF=-669.2780986\S2=0.778389\S2-
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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.928695	0.219733	-0.355806
2	6	0	-1.382325	-1.028146	-0.626615
3	6	0	-0.490964	-1.403793	0.543737
4	6	0	0.420149	-0.191273	0.777975
5	6	0	-0.427395	1.052947	0.632719
6	6	0	-0.155037	2.111740	-0.193350
7	1	0	-2.219307	-1.723391	-0.722618
8	1	0	-0.828509	-1.037261	-1.567547
9	1	0	-1.111257	-1.543689	1.426157
10	1	0	0.077172	-2.316323	0.382261
11	1	0	0.811960	-0.222067	1.790111
12	16	0	1.853688	-0.324314	-0.355938
13	1	0	-1.071112	1.233614	1.478850
14	1	0	-0.753795	3.004193	-0.138069
15	1	0	0.563648	2.035200	-0.990167
16	1	0	2.515190	0.752042	0.075687

Zero-point correction= 0.133047
(Hartree/Particle)
Thermal correction to Energy= 0.140318
Thermal correction to Enthalpy= 0.141262
Thermal correction to Gibbs Free Energy= 0.100723
Sum of electronic and zero-point Energies= -668.954754
Sum of electronic and thermal Energies= -668.947483
Sum of electronic and thermal Enthalpies= -668.946539
Sum of electronic and thermal Free Energies= -668.987078

Version=AM64L-G03RevE.01\State=2-A\HF=-669.0878013\S2=0.826127\S2-1=0.\S2A=0.750698\RMSD=4.722e-09\RMSF=4.283e-07\PG=C01 [X(C5H9O1S1)]\NImag=1\\@.

iii) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.929205	0.208827	-0.337143
2	6	0	-1.374010	-1.025452	-0.631654
3	6	0	-0.477479	-1.411469	0.529852
4	6	0	0.418701	-0.192015	0.776095
5	6	0	-0.439292	1.044841	0.631132
6	6	0	-0.175985	2.099254	-0.198787
7	1	0	-2.202683	-1.727274	-0.737195
8	1	0	-0.822038	-1.016679	-1.572508
9	1	0	-1.094928	-1.567342	1.409858
10	1	0	0.099811	-2.314389	0.356849
11	1	0	0.807637	-0.223686	1.786939
12	16	0	1.859034	-0.308329	-0.350364
13	1	0	-1.069736	1.228618	1.484666
14	1	0	-0.773983	2.990452	-0.140867
15	1	0	0.532616	2.018994	-1.002119
16	1	0	2.500788	0.783001	0.077516

```
Zero-point correction=                          0.132521
(Hartree/Particle)
Thermal correction to Energy=                   0.139794
Thermal correction to Enthalpy=                 0.140738
Thermal correction to Gibbs Free Energy=        0.100206
Sum of electronic and zero-point Energies=           -669.028247
Sum of electronic and thermal Energies=              -669.020974
Sum of electronic and thermal Enthalpies=            -669.020030
Sum of electronic and thermal Free Energies=         -669.060562

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S2A=0.750664\RMSD=9.736e-09\RMSF=4.220e-07\PG=C01 [X(C5H9O1S1)]\
NImag=1\\@.
```

II. Transition Structure *TS2*$_{cis}$-IIp

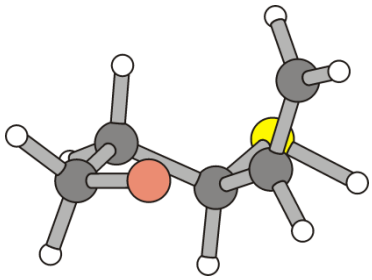

Figure S7.40. Calculated transition *TS2*$_{cis}$-**IIp** structure for 3-mercapto-4-pentenoxyl radical *cis*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.155282	0.281780	-0.260520
2	6	0	1.878025	-1.053992	0.054354
3	6	0	0.405536	-1.184046	0.488813
4	6	0	-0.394714	-0.292526	-0.473357
5	6	0	0.247163	1.078538	-0.496473
6	6	0	0.276764	1.919661	0.585267
7	1	0	2.044084	-1.690514	-0.832696
8	1	0	2.535135	-1.402653	0.866033
9	1	0	0.067697	-2.225431	0.457839
10	1	0	0.289719	-0.819059	1.515246
11	1	0	-0.350373	-0.724199	-1.476589
12	16	0	-2.176624	-0.298706	0.054308
13	1	0	0.500438	1.477548	-1.473666
14	1	0	0.725378	2.903724	0.507682
15	1	0	-0.087820	1.610539	1.559527
16	1	0	-2.617185	0.589285	-0.859762

```
Zero-point correction=                          0.127982
(Hartree/Particle)
Thermal correction to Energy=                   0.135807
Thermal correction to Enthalpy=                 0.136751
Thermal correction to Gibbs Free Energy=        0.094900
Sum of electronic and zero-point Energies=           -669.148733
Sum of electronic and thermal Energies=              -669.140908
Sum of electronic and thermal Enthalpies=            -669.139964
Sum of electronic and thermal Free Energies=         -669.181815

Version=AM64L-G03RevE.01\State=2-A\HF=-669.2767151\S2=0.776947\S2-
1=0.\ S2A=0.750129\RMSD=6.601e-09\RMSF=1.051e-06\PG=C01 [X(C5H9O1S1)]\
NImag=1\\@.
```

(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.120987	0.299235	-0.236105
2	6	0	1.862912	-1.039911	0.050513
3	6	0	0.410380	-1.185404	0.487348
4	6	0	-0.387577	-0.301116	-0.466652
5	6	0	0.268354	1.057583	-0.491172
6	6	0	0.232911	1.923107	0.565902
7	1	0	2.036562	-1.651798	-0.839250
8	1	0	2.532672	-1.378546	0.842076
9	1	0	0.081888	-2.220985	0.452956
10	1	0	0.291904	-0.825738	1.506637
11	1	0	-0.338369	-0.730999	-1.461504
12	16	0	-2.146300	-0.302956	0.051780
13	1	0	0.531904	1.444836	-1.460880
14	1	0	0.672568	2.901924	0.485651
15	1	0	-0.164553	1.629922	1.522992
16	1	0	-2.593558	0.559236	-0.863959

Zero-point correction= 0.132823
(Hartree/Particle)
Thermal correction to Energy= 0.140410
Thermal correction to Enthalpy= 0.141354
Thermal correction to Gibbs Free Energy= 0.099890
Sum of electronic and zero-point Energies= -668.953195
Sum of electronic and thermal Energies= -668.945608
Sum of electronic and thermal Enthalpies= -668.944663
Sum of electronic and thermal Free Energies= -668.986128

Version=AM64L-G03RevE.01\State=2-A\HF=-669.0860179\S2=0.829944\S2-1=0.\ S2A=0.750748\RMSD=7.398e-09\RMSF=5.923e-07\PG=C01 [X(C5H9O1S1)]\NImag=1\\@.

(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.107555	0.289184	-0.271398
2	6	0	1.856366	-1.038205	0.058158
3	6	0	0.403658	-1.181251	0.494416
4	6	0	-0.388221	-0.299031	-0.463127
5	6	0	0.273562	1.055205	-0.485078
6	6	0	0.260594	1.903081	0.582502
7	1	0	2.031983	-1.675646	-0.812073
8	1	0	2.522690	-1.354605	0.860093
9	1	0	0.073135	-2.214749	0.464082
10	1	0	0.283592	-0.817194	1.510475
11	1	0	-0.339268	-0.730992	-1.454943
12	16	0	-2.148366	-0.291290	0.047729
13	1	0	0.511324	1.455641	-1.454274
14	1	0	0.696017	2.882623	0.507032
15	1	0	-0.114023	1.595676	1.542703
16	1	0	-2.587794	0.567611	-0.876799

```
Zero-point correction=                          0.132343
(Hartree/Particle)
Thermal correction to Energy=                   0.139927
Thermal correction to Enthalpy=                 0.140872
Thermal correction to Gibbs Free Energy=        0.099435
Sum of electronic and zero-point Energies=           -669.026800
Sum of electronic and thermal Energies=              -669.019215
Sum of electronic and thermal Enthalpies=            -669.018271
Sum of electronic and thermal Free Energies=         -669.059708

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NImag=1\\@.
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III. Transition Structure *TS1*$_{trans}$-IIp

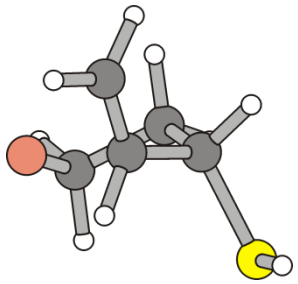

Figure S7.41. Calculated transition *TS1*$_{trans}$-**IIp** structure for 3-mercapto-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.681545	-0.671424	-0.754883
2	6	0	0.825115	-1.642822	-0.233114
3	6	0	0.113571	-1.048810	0.990033
4	6	0	-0.426982	0.337389	0.573312
5	6	0	0.609205	1.018811	-0.302546
6	6	0	1.597336	1.803969	0.244721
7	1	0	0.083887	-1.976625	-0.978111
8	1	0	1.427023	-2.511379	0.080149
9	1	0	-0.676729	-1.701442	1.377673
10	1	0	0.851081	-0.897765	1.786059
11	16	0	-2.062450	0.124218	-0.275208
12	1	0	-0.604845	0.935320	1.471490
13	1	0	0.382032	1.115952	-1.358685
14	1	0	2.308596	2.324097	-0.387609
15	1	0	1.757032	1.850507	1.318585
16	1	0	-2.290716	1.434012	-0.501592

```
Zero-point correction=                          0.127597
(Hartree/Particle)
Thermal correction to Energy=                   0.135449
Thermal correction to Enthalpy=                 0.136393
Thermal correction to Gibbs Free Energy=        0.093917
Sum of electronic and zero-point Energies=           -669.148300
Sum of electronic and thermal Energies=              -669.140448
Sum of electronic and thermal Enthalpies=            -669.139504
Sum of electronic and thermal Free Energies=         -669.181979

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S2A=0.750173\RMSD=4.544e-09\RMSF=5.827e-07\PG=C01 [X(C5H9O1S1)]\
NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.803418	-0.562159	-0.603401
2	6	0	0.922690	-1.588729	-0.285758
3	6	0	0.098735	-1.139518	0.907016
4	6	0	-0.436933	0.259389	0.566148
5	6	0	0.581440	0.979125	-0.289420
6	6	0	1.419938	1.921545	0.249407
7	1	0	0.277034	-1.844196	-1.129345
8	1	0	1.521670	-2.465380	-0.031337
9	1	0	-0.697753	-1.835740	1.159025
10	1	0	0.754450	-1.050791	1.769362
11	16	0	-2.057809	0.085364	-0.273842
12	1	0	-0.603008	0.816181	1.481660
13	1	0	0.393095	1.004135	-1.349488
14	1	0	2.093139	2.481832	-0.376168
15	1	0	1.505839	2.051802	1.316284
16	1	0	-2.262087	1.382740	-0.515678

```
Zero-point correction=                          0.132615
(Hartree/Particle)
Thermal correction to Energy=                   0.140165
Thermal correction to Enthalpy=                 0.141109
Thermal correction to Gibbs Free Energy=        0.099309
Sum of electronic and zero-point Energies=           -668.953196
Sum of electronic and thermal Energies=              -668.945646
Sum of electronic and thermal Enthalpies=            -668.944702
Sum of electronic and thermal Free Energies=         -668.986502

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NImag=1\\@.
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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.655628	0.657634	-0.734239
2	6	0	-0.794944	1.627095	-0.244317
3	6	0	-0.093459	1.056745	0.975327
4	6	0	0.419397	-0.328653	0.570876
5	6	0	-0.627488	-0.981527	-0.302175
6	6	0	-1.596252	-1.774792	0.249889
7	1	0	-0.064211	1.933953	-0.994776
8	1	0	-1.389421	2.497019	0.036980
9	1	0	0.700060	1.698369	1.346889
10	1	0	-0.823278	0.926567	1.768836
11	16	0	2.037540	-0.145806	-0.269705
12	1	0	0.584583	-0.926682	1.457826
13	1	0	-0.394211	-1.097898	-1.344727
14	1	0	-2.301906	-2.295511	-0.371680
15	1	0	-1.747438	-1.814253	1.315418
16	1	0	2.236665	-1.442956	-0.523174

```
Zero-point correction=                          0.131981
(Hartree/Particle)
Thermal correction to Energy=                   0.139584
Thermal correction to Enthalpy=                 0.140529
Thermal correction to Gibbs Free Energy=        0.098526
Sum of electronic and zero-point Energies=           -669.026592
Sum of electronic and thermal Energies=              -669.018988
Sum of electronic and thermal Enthalpies=            -669.018044
Sum of electronic and thermal Free Energies=         -669.060047

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NImag=1\\@.
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IV. Transition Structure *TS2*$_{trans}$-IIp

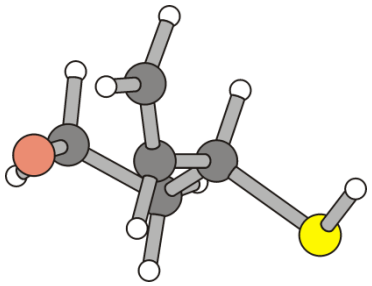

Figure S7.42. Calculated transition *TS2*$_{trans}$-**IIp** structure for 3-mercapto-4-pentenoxyl radical *trans*-cyclization.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.052889	-0.011293	-0.511372
2	6	0	1.739802	-1.151590	0.233910
3	6	0	0.243642	-1.441231	0.079292
4	6	0	-0.437632	-0.093523	0.374678
5	6	0	0.303503	1.005742	-0.348135
6	6	0	0.749696	2.132387	0.306241
7	1	0	2.344368	-1.976808	-0.178045
8	1	0	2.011935	-1.044780	1.298680
9	1	0	0.036385	-1.745432	-0.953224
10	1	0	-0.113775	-2.228517	0.752019
11	16	0	-2.217352	-0.184559	-0.133905
12	1	0	-0.406280	0.094296	1.452882
13	1	0	0.189749	1.031529	-1.427117
14	1	0	1.190226	2.959776	-0.239239
15	1	0	0.766513	2.183215	1.391421
16	1	0	-2.558668	1.059293	0.260157

```
Zero-point correction=                          0.128085
(Hartree/Particle)
Thermal correction to Energy=                   0.135696
Thermal correction to Enthalpy=                 0.136640
Thermal correction to Gibbs Free Energy=        0.095413
Sum of electronic and zero-point Energies=           -669.153916
Sum of electronic and thermal Energies=              -669.146304
Sum of electronic and thermal Enthalpies=            -669.145360
Sum of electronic and thermal Free Energies=         -669.186587

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NImag=1\\@.
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(*ii*) BHandHLYP/6-31+G// BHandHLYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.019379	-0.010494	-0.515890
2	6	0	1.722560	-1.142565	0.234120
3	6	0	0.240066	-1.434957	0.085073
4	6	0	-0.436341	-0.096107	0.372149
5	6	0	0.316279	0.989919	-0.345247
6	6	0	0.740936	2.118771	0.307744
7	1	0	2.330992	-1.954607	-0.169548
8	1	0	1.991033	-1.016833	1.286845
9	1	0	0.033175	-1.743292	-0.937551
10	1	0	-0.110147	-2.213675	0.757675
11	16	0	-2.192921	-0.179546	-0.135265
12	1	0	-0.403470	0.092870	1.441502
13	1	0	0.198570	1.020928	-1.415262
14	1	0	1.182218	2.938531	-0.232133
15	1	0	0.745066	2.171375	1.384636
16	1	0	-2.536723	1.051022	0.252158

Zero-point correction= 0.132986
(Hartree/Particle)
Thermal correction to Energy= 0.140369
Thermal correction to Enthalpy= 0.141313
Thermal correction to Gibbs Free Energy= 0.100508
Sum of electronic and zero-point Energies= -668.958687
Sum of electronic and thermal Energies= -668.951304
Sum of electronic and thermal Enthalpies= -668.950359
Sum of electronic and thermal Free Energies= -668.991165

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(*iii*) BHandHLYP/6-311G**// BHandHLYP/6-311G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.004888	-0.013895	-0.525997
2	6	0	1.718066	-1.138579	0.231898
3	6	0	0.236663	-1.435838	0.092743
4	6	0	-0.435778	-0.095451	0.374245
5	6	0	0.322803	0.985266	-0.343860
6	6	0	0.752835	2.107175	0.311919
7	1	0	2.324229	-1.951988	-0.169163
8	1	0	1.990486	-1.008958	1.282204
9	1	0	0.026834	-1.746915	-0.927071
10	1	0	-0.111021	-2.210423	0.769152
11	16	0	-2.190460	-0.172682	-0.137477
12	1	0	-0.407853	0.095260	1.441344
13	1	0	0.192271	1.024034	-1.410523
14	1	0	1.192624	2.928026	-0.224841
15	1	0	0.764608	2.151703	1.387708
16	1	0	-2.531455	1.057895	0.257133

```
Zero-point correction=                          0.132451
(Hartree/Particle)
Thermal correction to Energy=                   0.139830
Thermal correction to Enthalpy=                 0.140774
Thermal correction to Gibbs Free Energy=        0.099993
Sum of electronic and zero-point Energies=           -669.032152
Sum of electronic and thermal Energies=              -669.024774
Sum of electronic and thermal Enthalpies=            -669.023830
Sum of electronic and thermal Free Energies=         -669.064611

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NImag=1\\@.
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7.6 Conformational Analysis I – Butenes

7.6.1 But-3-en-2-ol (IVa)

I. Anticlinal conformation *ac*-IVa

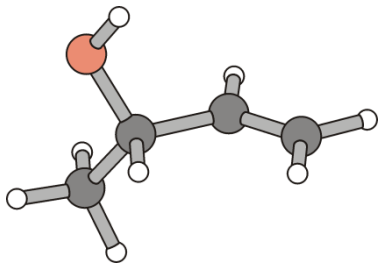

Figure S7.43. Calculated minimum conformation of 2-butenol **IVa**.

(*i*) B3LYP/6-31+G//B3LYP/6-31+G****

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.119525	-0.126979	-0.163944
2	6	0	0.923458	-0.069998	0.429461
3	6	0	-0.388228	0.042865	-0.304059
4	6	0	-1.343787	-1.101722	0.020075
5	1	0	3.039450	-0.204397	0.408264
6	1	0	2.217966	-0.106089	-1.247585
7	1	0	0.848258	-0.088523	1.517418
8	8	0	-1.069767	1.253942	0.072530
9	1	0	-0.191245	0.054627	-1.387521
10	1	0	-2.295535	-0.950907	-0.498200
11	1	0	-0.917011	-2.059033	-0.293960
12	1	0	-1.541289	-1.140525	1.096448
13	1	0	-0.468267	1.998316	-0.064302

```
Zero-point correction=                          0.112951
(Hartree/Particle)
Thermal correction to Energy=                   0.119168
Thermal correction to Enthalpy=                 0.120113
Thermal correction to Gibbs Free Energy=        0.083863
Sum of electronic and zero-point Energies=                -232.348345
Sum of electronic and thermal Energies=                   -232.342127
Sum of electronic and thermal Enthalpies=                 -232.341183
Sum of electronic and thermal Free Energies=              -232.377433

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09\RMSF=1.126e-06\PG=C01[X(C4H8O1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.101967	-0.124877	-0.162463
2	6	0	0.924844	-0.035777	0.424672
3	6	0	-0.391653	0.054175	-0.302884
4	6	0	-1.310869	-1.111846	0.027617
5	1	0	3.014677	-0.189266	0.402806
6	1	0	2.201163	-0.143146	-1.234987
7	1	0	0.856914	-0.014220	1.501436
8	8	0	-1.081850	1.225554	0.070241
9	1	0	-0.201341	0.063590	-1.374582
10	1	0	-2.257290	-0.993699	-0.487656
11	1	0	-0.860867	-2.051677	-0.273142
12	1	0	-1.507513	-1.145109	1.094004
13	1	0	-0.536685	1.979056	-0.111449

```
Temperature=          298.150000 Pressure=                    1.000000
E(ZPE)=                 0.108756 E(Thermal)=                  0.115086
E(QCISD(T))=         -231.723552 E(Empiric)=                 -0.095790
DE(Plus)=              -0.019872 DE(2DF)=                    -0.209671
E(Delta-G3)=           -0.300458 E(G3-Empiric)=              -0.095790
G3(0 K)=             -232.240588 G3 Energy=                -232.234257
G3 Enthalpy=         -232.233313 G3 Free Energy=           -232.269780

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-231.6504418\
QCISD(T)/6-31G(d )=-231.7235522\MP4/6-31G(d)=-231.721369\
MP2/6-31+G(d)=-231.6694474\MP4/6-31+G(d)=-231.7412413\
MP2/6-31G(2df,p)=-231.8481164\MP4/6-31G(2df,p)=-231.93104\
MP2/GTLarge=-232.16758\G3=-232.2405879\ PG=C01 [X(C4H8O1)]\NImag=0\\@.
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II. Synperiplanar conformation *sp*-IVa

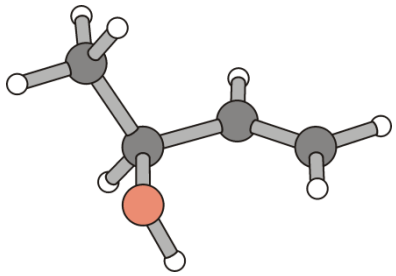

Figure S7.44. Calculated structure for synperiplanar conformation of 2-butenol **IVa**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.956331	-0.100212	-0.266352
2	6	0	-0.861080	-0.643848	0.270711
3	6	0	0.484305	0.029252	0.419266
4	6	0	1.585162	-0.733119	-0.321017
5	1	0	-2.890425	-0.651026	-0.318260
6	1	0	-1.948585	0.897496	-0.696222
7	1	0	-0.907917	-1.654548	0.677907
8	8	0	0.507332	1.365281	-0.083104
9	1	0	0.736603	0.036939	1.494095
10	1	0	2.552502	-0.251275	-0.152906
11	1	0	1.642832	-1.768170	0.030676
12	1	0	1.377800	-0.739415	-1.395428
13	1	0	-0.133801	1.895313	0.409321

```
Zero-point correction=                          0.112880
(Hartree/Particle)
Thermal correction to Energy=                   0.119078
Thermal correction to Enthalpy=                 0.120022
Thermal correction to Gibbs Free Energy=        0.083906
Sum of electronic and zero-point Energies=           -232.346702
Sum of electronic and thermal Energies=              -232.340504
Sum of electronic and thermal Enthalpies=            -232.339560
Sum of electronic and thermal Free Energies=         -232.375676

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RMSF=6.134e-04\ PG=C01[X(C4H8O1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.937089	-0.100554	-0.266129
2	6	0	-0.860171	-0.636178	0.272533
3	6	0	0.483030	0.037854	0.418956
4	6	0	1.574278	-0.729160	-0.317553
5	1	0	-2.864254	-0.642593	-0.318037
6	1	0	-1.928812	0.884035	-0.697292
7	1	0	-0.911813	-1.633389	0.681993
8	8	0	0.496016	1.345452	-0.088998
9	1	0	0.732877	0.053813	1.480453
10	1	0	2.533492	-0.248447	-0.164516
11	1	0	1.637676	-1.752162	0.039117
12	1	0	1.360189	-0.744611	-1.380107
13	1	0	-0.087773	1.887958	0.423524

Temperature=	298.150000	Pressure=	1.000000
E(ZPE)=	0.108840	E(Thermal)=	0.115099
E(QCISD(T))=	-231.723131	E(Empiric)=	-0.095790
DE(Plus)=	-0.018511	DE(2DF)=	-0.210019
E(Delta-G3)=	-0.300848	E(G3-Empiric)=	-0.095790
G3(0 K)=	-232.239459	G3 Energy=	-232.233200
G3 Enthalpy=	-232.232255	G3 Free Energy=	-232.268450

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-231.6498572\
QCISD(T)/6-31G(d)=-231.7231307\MP4/6-31G(d)=-231.7209215\
MP2/6-31+G(d)=-231.6675649\MP4/6-31+G(d)=-231.7394323\
MP2/6-31G(2df,p)=-231.847971\MP4/6-31G(2df,p)=-231.9309403\
MP2/GTLarge=-232.1665263\G3=-232.2394586\PG=C01[X(C4H8O1)]\
NImag=0\\@.

7.6.2 3-Methylbut-1-ene (IVb)

I. Anticlinal conformation *ac*-IVb

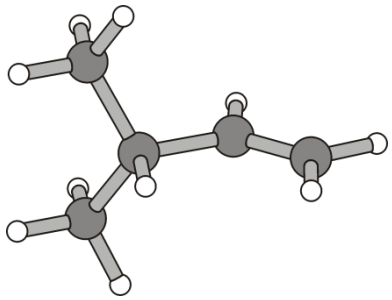

Figure S7.45. Calculated minimum conformation of 3-methylbutene **IVb**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.156216	0.000001	-0.162754
2	6	0	0.951713	0.000001	0.415997
3	6	0	-0.371736	0.000000	-0.308529
4	6	0	-1.179496	-1.268720	0.028022
5	6	0	-1.179494	1.268721	0.028023
6	1	0	-0.166475	0.000001	-1.388075
7	1	0	3.071241	-0.000011	0.422729
8	1	0	2.267568	0.000000	-1.245254
9	1	0	0.889250	-0.000010	1.506888
10	1	0	-2.137346	-1.273412	-0.504768
11	1	0	-0.629451	-2.174073	-0.248076
12	1	0	-1.395607	-1.321269	1.102421
13	1	0	-2.137343	1.273414	-0.504766
14	1	0	-1.395604	1.321269	1.102422
15	1	0	-0.629447	2.174073	-0.248074

```
Zero-point correction=                          0.136321
(Hartree/Particle)
Thermal correction to Energy=                   0.142867
Thermal correction to Enthalpy=                 0.143811
Thermal correction to Gibbs Free Energy=        0.106895
Sum of electronic and zero-point Energies=           -196.421740
Sum of electronic and thermal Energies=              -196.415195
Sum of electronic and thermal Enthalpies=            -196.414250
Sum of electronic and thermal Free Energies=         -196.451166

Version=AM64L-G03RevE.01\State=1-A\HF=-196.5580612\RMSD=1.914e-09\
RMSF=1.422e-06\PG=C01 [X(C5H10)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.139491	0.000000	-0.162086
2	6	0	0.952849	0.000000	0.412758
3	6	0	-0.371640	0.000000	-0.309266
4	6	0	-1.173203	-1.263657	0.029444
5	6	0	-1.173203	1.263657	0.029444
6	1	0	-0.172625	0.000000	-1.378107
7	1	0	3.047462	0.000000	0.414792
8	1	0	2.251970	0.000000	-1.233321
9	1	0	0.894171	-0.000001	1.491962
10	1	0	-2.121113	-1.275053	-0.500591
11	1	0	-0.623481	-2.158906	-0.241626
12	1	0	-1.388775	-1.314236	1.093673
13	1	0	-2.121113	1.275054	-0.500591
14	1	0	-1.388774	1.314236	1.093673
15	1	0	-0.623480	2.158906	-0.241626

```
Temperature=         298.150000 Pressure=                   1.000000
E(ZPE)=                0.130715 E(Thermal)=                 0.137409
E(QCISD(T))=        -195.873719 E(Empiric)=                -0.095790
DE(Plus)=             -0.011664 DE(2DF)=                   -0.195797
E(Delta-G3)=          -0.280103 E(G3-Empiric)=             -0.095790
G3(0 K)=            -196.326359 G3 Energy=               -196.319665
G3 Enthalpy=        -196.318720 G3 Free Energy=          -196.355915

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-195.7897445\
QCISD(T)/6-31G(d)=-195.873719\MP4/6-31G(d)=-195.8704965\
MP2/6-31+G(d)=-195.8009372\MP4/6-31+G(d)=-195.882161\
MP2/6-31G(2df,p)=-195.9744572\MP4/6-31G(2df,p)=-196.0662935\
MP2/GTLarge=-196.2657533\G3=-196.3263585\PG=C01 [X(C5H10)]\NImag=0\\@.
```

II. Synperiplanar conformation *sp*-IVb

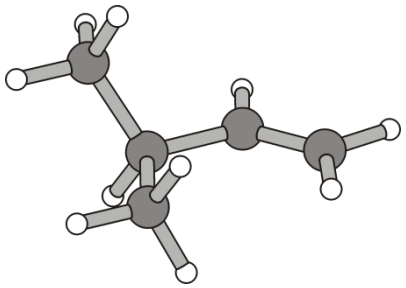

Figure S7.46. Calculated structure for synperiplanar conformation of methylbutene **IVb**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.999405	-0.056501	0.230394
2	6	0	-0.895089	-0.639470	-0.247243
3	6	0	0.473304	-0.017830	-0.417784
4	6	0	0.556635	1.449298	0.019871
5	6	0	1.536313	-0.874090	0.301842
6	1	0	0.704395	-0.061261	-1.494660
7	1	0	-2.932750	-0.606289	0.310478
8	1	0	-2.018268	0.979366	0.556693
9	1	0	-0.957079	-1.685107	-0.554805
10	1	0	1.560796	1.845611	-0.164681
11	1	0	-0.155856	2.076038	-0.526600
12	1	0	0.348756	1.554833	1.091212
13	1	0	2.544118	-0.492849	0.102945
14	1	0	1.375075	-0.860720	1.386040
15	1	0	1.500265	-1.918060	-0.029105

```
Zero-point correction=                          0.136569
(Hartree/Particle)
Thermal correction to Energy=                   0.142992
Thermal correction to Enthalpy=                 0.143936
Thermal correction to Gibbs Free Energy=        0.107394
Sum of electronic and zero-point Energies=           -196.420272
Sum of electronic and thermal Energies=              -196.413850
Sum of electronic and thermal Enthalpies=            -196.412906
Sum of electronic and thermal Free Energies=         -196.449447

Version=AM64L-G03RevE.01\State=1-A\HF=-196.5568416\RMSD=5.584e-09\
RMSF=8.427e-05\PG=C01 [X(C5H10)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.985776	-0.048698	0.230640
2	6	0	-0.901020	-0.628133	-0.246789
3	6	0	0.472041	-0.019323	-0.420792
4	6	0	0.568007	1.440903	0.021548
5	6	0	1.519387	-0.879930	0.301474
6	1	0	0.700116	-0.060504	-1.485929
7	1	0	-2.913105	-0.588384	0.308004
8	1	0	-2.003415	0.973596	0.562858
9	1	0	-0.971899	-1.659520	-0.559313
10	1	0	1.566850	1.824210	-0.161594
11	1	0	-0.131664	2.068915	-0.519776
12	1	0	0.362986	1.544283	1.082947
13	1	0	2.521953	-0.506167	0.116760
14	1	0	1.349177	-0.873433	1.374113
15	1	0	1.483169	-1.911912	-0.034559

Temperature=	298.150000	Pressure=	1.000000
E(ZPE)=	0.130981	E(Thermal)=	0.137555
E(QCISD(T))=	-195.872686	E(Empiric)=	-0.095790
DE(Plus)=	-0.011284	DE(2DF)=	-0.196092
E(Delta-G3)=	-0.280668	E(G3-Empiric)=	-0.095790
G3(0 K)=	-196.325538	G3 Energy=	-196.318964
G3 Enthalpy=	-196.318020	G3 Free Energy=	-196.354849

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-195.788527\
QCISD(T)/6-31G(d)=-195.8726856\MP4/6-31G(d)=-195.8694444\
MP2/6-31+G(d)=-195.7994193\MP4/6-31+G(d)=-195.8807285\
MP2/6-31G(2df,p)=-195.9736347\MP4/6-31G(2df,p)=-196.0655359\
MP2/GTLarge=-196.2651954\G3=-196.3255384\PG=C01 [X(C5H10)]\NImag=0\\@.

7.6.3 3-Fluorobut-1-ene (IVh)

I. Anticlinal conformation *ac*-IVh

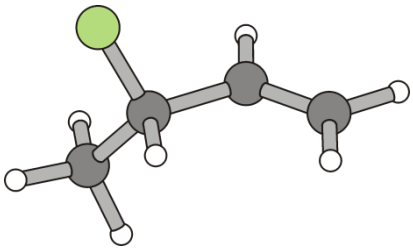

Figure S7.47. Calculated minimum conformation of 3-fluorobutene **IVb**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.116132	-0.127619	-0.166230
2	6	0	-0.927185	-0.021716	0.431227
3	6	0	0.376943	0.046512	-0.305892
4	9	0	1.014825	1.271363	0.043061
5	6	0	1.338286	-1.081973	0.035344
6	1	0	0.201544	0.098465	-1.386576
7	1	0	-3.036921	-0.197852	0.404952
8	1	0	-2.209442	-0.149737	-1.249802
9	1	0	-0.853691	0.008416	1.518034
10	1	0	2.292265	-0.933915	-0.479238
11	1	0	1.524618	-1.115458	1.113544
12	1	0	0.916727	-2.043406	-0.275164

```
Zero-point correction=                          0.100689
(Hartree/Particle)
Thermal correction to Energy=                   0.106576
Thermal correction to Enthalpy=                 0.107520
Thermal correction to Gibbs Free Energy=        0.071661
Sum of electronic and zero-point Energies=           -256.381744
Sum of electronic and thermal Energies=              -256.375857
Sum of electronic and thermal Enthalpies=            -256.374912
Sum of electronic and thermal Free Energies=         -256.410772

Version=AM64L-G03RevE.01\State=1-A\HF=-256.4824325\RMSD=8.304e-09\
RMSF=1.472e-06\PG=C01 [X(C4H7F1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.095784	0.133627	-0.160359
2	6	0	0.927675	-0.052521	0.418786
3	6	0	-0.383953	-0.062792	-0.309149
4	9	0	-1.051084	-1.226512	0.018740
5	6	0	-1.282756	1.102027	0.063132
6	1	0	-0.217142	-0.085449	-1.378813
7	1	0	3.009329	0.160922	0.405776
8	1	0	2.188022	0.266378	-1.225054
9	1	0	0.862216	-0.192670	1.485835
10	1	0	-2.237998	1.010713	-0.441647
11	1	0	-1.461710	1.114811	1.132983
12	1	0	-0.823459	2.041859	-0.222201

```
Temperature=         298.150000 Pressure=                    1.000000
E(ZPE)=                0.096943 E(Thermal)=                 0.102930
E(QCISD(T))=        -255.710393 E(Empiric)=                -0.095790
DE(Plus)=             -0.023971 DE(2DF)=                    -0.209413
E(Delta-G3)=          -0.318295 E(G3-Empiric)=              -0.095790
G3(0 K)=            -256.260918 G3 Energy=                -256.254931
G3 Enthalpy=        -256.253987 G3 Free Energy=           -256.290040

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-255.6407116\
QCISD(T)/6-31G(d)=-255.7103926\MP4/6-31G(d)=-255.7093864\
MP2/6-31+G(d)=-255.6635846\MP4/6-31+G(d)=-255.733357\
MP2/6-31G(2df,p)=-255.8376522\MP4/6-31G(2df,p)=-255.9187997\
MP2/GTLarge=-256.1788201\G3=-256.2609182\PG=C01
[X(C4H7F1)]\NImag=0\\@.
```

II. Synperiplanar conformation *sp*-IVh

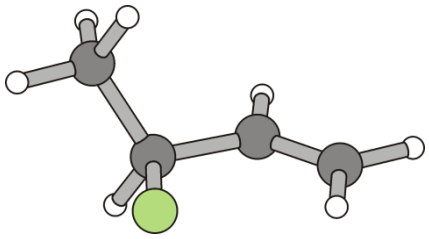

Figure S7.48. Calculated structure for synperiplanar conformation of fluorobutene **IVh**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.949939	-0.078943	-0.251352
2	6	0	0.856117	-0.654515	0.250816
3	6	0	-0.477318	0.016719	0.425682
4	9	0	-0.405193	1.354321	-0.021402
5	6	0	-1.607514	-0.674745	-0.327858
6	1	0	-0.722362	0.076435	1.495568
7	1	0	2.878925	-0.632203	-0.347746
8	1	0	1.943995	0.955851	-0.578023
9	1	0	0.882668	-1.693469	0.579347
10	1	0	-2.550807	-0.146166	-0.163866
11	1	0	-1.391180	-0.694676	-1.400019
12	1	0	-1.721840	-1.705755	0.023628

```
Zero-point correction=                          0.100711
(Hartree/Particle)
Thermal correction to Energy=                   0.106547
Thermal correction to Enthalpy=                 0.107491
Thermal correction to Gibbs Free Energy=        0.071852
Sum of electronic and zero-point Energies=                -256.381152
Sum of electronic and thermal Energies=                   -256.375317
Sum of electronic and thermal Enthalpies=                 -256.374373
Sum of electronic and thermal Free Energies=              -256.410012

Version=AM64L-G03RevE.01\State=1-A\HF=-256.4818638\ RMSD=4.073e-
09\RMSF=1.059e-04\PG=C01 [X(C4H7F1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.928959	-0.077114	-0.252976
2	6	0	0.855053	-0.645639	0.253745
3	6	0	-0.475107	0.029845	0.427022
4	9	0	-0.401552	1.327285	-0.022136
5	6	0	-1.594545	-0.667546	-0.326583
6	1	0	-0.719209	0.080955	1.483214
7	1	0	2.852148	-0.619325	-0.350322
8	1	0	1.922921	0.943655	-0.585973
9	1	0	0.887502	-1.671016	0.586289
10	1	0	-2.530145	-0.140983	-0.176635
11	1	0	-1.371851	-0.688209	-1.387215
12	1	0	-1.713558	-1.687911	0.022607

```
Temperature=         298.150000 Pressure=                   1.000000
E(ZPE)=                0.097069 E(Thermal)=                 0.102981
E(QCISD(T))=        -255.711469 E(Empiric)=                -0.095790
DE(Plus)=             -0.022452 DE(2DF)=                   -0.209605
E(Delta-G3)=          -0.318307 E(G3-Empiric)=             -0.095790
G3(0 K)=            -256.260554 G3 Energy=               -256.254642
G3 Enthalpy=        -256.253698 G3 Free Energy=          -256.289444

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-255.6416904\
QCISD(T)/6-31G(d)=-255.7114693\MP4/6-31G(d)=-255.7104669\
MP2/6-31+G(d)=-255.6631024\MP4/6-31+G(d)=-255.7329194\
MP2/6-31G(2df,p)=-255.8388827\MP4/6-31G(2df,p)=-255.9200717\
MP2/GTLarge=-256.1786012\G3=-256.2605537\PG=C01
[X(C4H7F1)]\NImag=0\\@.
```

7.6.4 3-Chlorobut-1-ene (IVi)

I. Anticlinal conformation *ac*-IVi

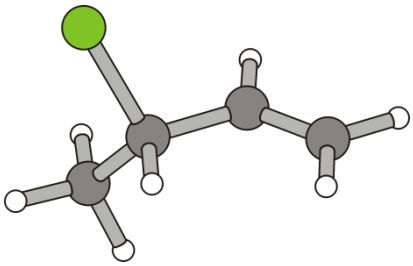

Figure S7.49. Calculated minimum conformation of 3-chlorobutene **IVi**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.338586	-0.498925	-0.156789
2	6	0	1.207690	-0.096002	0.428767
3	6	0	-0.007200	0.347992	-0.324089
4	17	0	-1.389465	-0.837483	0.023171
5	6	0	-0.469092	1.755396	0.038654
6	1	0	0.157207	0.257240	-1.399869
7	1	0	3.207564	-0.786482	0.427101
8	1	0	2.432604	-0.556519	-1.238766
9	1	0	1.133190	-0.057093	1.514866
10	1	0	-1.374939	2.024120	-0.510882
11	1	0	-0.676498	1.835012	1.110016
12	1	0	0.321869	2.470157	-0.215629

```
Zero-point correction=                          0.099492
(Hartree/Particle)
Thermal correction to Energy=                   0.105619
Thermal correction to Enthalpy=                 0.106564
Thermal correction to Gibbs Free Energy=        0.069607
Sum of electronic and zero-point Energies=           -616.737691
Sum of electronic and thermal Energies=              -616.731564
Sum of electronic and thermal Enthalpies=            -616.730620
Sum of electronic and thermal Free Energies=         -616.767576

Version=AM64L-G03RevE.01\State=1-A\HF=-616.8371831\RMSD=7.536e-09\
RMSF=2.474e-07\PG=C01 [X(C4H7Cl1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.326984	-0.488291	-0.157056
2	6	0	1.199082	-0.134872	0.424833
3	6	0	-0.015837	0.326446	-0.322338
4	17	0	-1.395131	-0.809971	0.018317
5	6	0	-0.437517	1.741386	0.049079
6	1	0	0.148342	0.248093	-1.385909
7	1	0	3.184935	-0.786105	0.418025
8	1	0	2.438528	-0.497494	-1.227721
9	1	0	1.112204	-0.144387	1.498691
10	1	0	-1.327279	2.035186	-0.493793
11	1	0	-0.641610	1.818103	1.110696
12	1	0	0.365836	2.428101	-0.198474

Temperature=	298.150000	Pressure=	1.000000
E(ZPE)=	0.095669	E(Thermal)=	0.101899
E(QCISD(T))=	-615.733935	E(Empiric)=	-0.095790
DE(Plus)=	-0.012173	DE(2DF)=	-0.207448
E(Delta-G3)=	-0.567257	E(G3-Empiric)=	-0.095790
G3(0 K)=	-616.520934	G3 Energy=	-616.514704
G3 Enthalpy=	-616.513760	G3 Free Energy=	-616.550926

```
Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-615.6547809\
QCISD(T)/6-31G(d)=-615.7339351\MP4/6-31G(d)=-615.7315753\
MP2/6-31+G(d)=-615.6663813\MP4/6-31+G(d)=-615.7437483\
MP2/6-31G(2df,p)=-615.8458695\MP4/6-31G(2df,p)=-615.9390233\
MP2/GTLarge=-616.4247266\G3=-
616.5209336\PG=C01[X(C4H7Cl1)]\NImag=0\\@.
```

II. Synperiplanar conformation *sp*-IVi

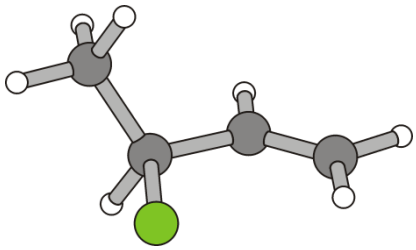

Figure S7.50. Calculated structure for synperiplanar conformation of chlorobutene **IVi**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.069140	-0.482770	-0.231796
2	6	0	-1.291321	0.498734	0.226140
3	6	0	0.199603	0.493078	0.436855
4	17	0	0.971311	-1.104405	-0.017747
5	6	0	0.899047	1.622743	-0.321201
6	1	0	0.408747	0.587923	1.507550
7	1	0	-3.139878	-0.336102	-0.333802
8	1	0	-1.666629	-1.449498	-0.515548
9	1	0	-1.744211	1.452788	0.501763
10	1	0	1.970346	1.632232	-0.105732
11	1	0	0.755231	1.511115	-1.399406
12	1	0	0.474962	2.585720	-0.013110

```
Zero-point correction=                          0.099474
(Hartree/Particle)
Thermal correction to Energy=                   0.105537
Thermal correction to Enthalpy=                 0.106481
Thermal correction to Gibbs Free Energy=        0.069687
Sum of electronic and zero-point Energies=           -616.735206
Sum of electronic and thermal Energies=              -616.729143
Sum of electronic and thermal Enthalpies=            -616.728199
Sum of electronic and thermal Free Energies=         -616.764992

Version=AM64L-G03RevE.01\State=1-A\HF=-616.8346795\RMSD=7.048e-10\
RMSF=6.753e-05\PG=C01 [X(C4H7Cl1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.058609	-0.478366	-0.231877
2	6	0	-1.288496	0.485262	0.226904
3	6	0	0.202452	0.479204	0.438286
4	17	0	0.971151	-1.089314	-0.018805
5	6	0	0.887761	1.611805	-0.320118
6	1	0	0.405836	0.578993	1.495744
7	1	0	-3.118677	-0.327739	-0.328378
8	1	0	-1.673945	-1.436414	-0.525120
9	1	0	-1.736501	1.425912	0.509370
10	1	0	1.950773	1.625396	-0.114948
11	1	0	0.738112	1.501712	-1.387151
12	1	0	0.466187	2.563049	-0.009011

```
Temperature=         298.150000 Pressure=                  1.000000
E(ZPE)=                0.095711 E(Thermal)=                0.101890
E(QCISD(T))=        -615.731946 E(Empiric)=               -0.095790
DE(Plus)=             -0.011845 DE(2DF)=                  -0.207751
E(Delta-G3)=          -0.567965 E(G3-Empiric)=            -0.095790
G3(0 K)=            -616.519587 G3 Energy=              -616.513407
G3 Enthalpy=        -616.512463 G3 Free Energy=         -616.549501

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-615.6526628\
QCISD(T)/6-31G(d)=-615.7319462\MP4/6-31G(d)=-615.7296077\
MP2/6-31+G(d)=-615.6640562\MP4/6-31+G(d)=-615.7414528\
MP2/6-31G(2df,p)=-615.8441878\MP4/6-31G(2df,p)=-615.937359\
MP2/GTLarge=-616.4235458\G3=-
616.5195867\PG=C01[X(C4H7Cl1)]\NImag=0\\@.
```

7.6.5 But-3-en-2-amine (IVo)

I. Anticline conformation *ac*-IVo

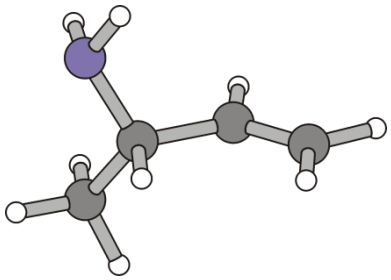

Figure S7.51. Calculated minimum conformation of buten-2-amine **IVo**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.139240	-0.079565	-0.148836
2	6	0	-0.933158	-0.056542	0.427366
3	6	0	0.383850	0.027026	-0.312029
4	6	0	1.288712	-1.167625	0.011763
5	7	0	1.125066	1.272728	-0.034884
6	1	0	0.172488	0.021295	-1.389440
7	1	0	-3.053787	-0.122015	0.435772
8	1	0	-2.251381	-0.059592	-1.231200
9	1	0	-0.857971	-0.077409	1.517319
10	1	0	0.531149	2.084209	-0.187539
11	1	0	1.429582	1.301900	0.936608
12	1	0	2.233196	-1.082671	-0.534008
13	1	0	1.516659	-1.204105	1.085061
14	1	0	0.803620	-2.110471	-0.257968

```
Zero-point correction=                          0.125642
(Hartree/Particle)
Thermal correction to Energy=                   0.132040
Thermal correction to Enthalpy=                 0.132984
Thermal correction to Gibbs Free Energy=        0.096425
Sum of electronic and zero-point Energies=           -212.468187
Sum of electronic and thermal Energies=              -212.461788
Sum of electronic and thermal Enthalpies=            -212.460844
Sum of electronic and thermal Free Energies=         -212.497403

Version=AM64L-G03RevE.01\State=1-A\HF=-212.5938282\RMSD=1.931e-09\
RMSF=8.430e-07\PG=C01 [X(C4H9N1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.121706	-0.075664	-0.149393
2	6	0	-0.934510	-0.033166	0.423049
3	6	0	0.385457	0.032045	-0.311013
4	6	0	1.263368	-1.174333	0.017909
5	7	0	1.138998	1.252286	-0.033562
6	1	0	0.181524	0.025641	-1.377089
7	1	0	-3.029378	-0.113687	0.426647
8	1	0	-2.234115	-0.077625	-1.220769
9	1	0	-0.867960	-0.032693	1.502246
10	1	0	0.578711	2.059955	-0.229647
11	1	0	1.387434	1.300341	0.937407
12	1	0	2.199764	-1.111776	-0.524154
13	1	0	1.491378	-1.208609	1.080955
14	1	0	0.763998	-2.100845	-0.243970

```
Temperature=         298.150000 Pressure=                    1.000000
E(ZPE)=                0.120860 E(Thermal)=                 0.127377
E(QCISD(T))=        -211.886119 E(Empiric)=                -0.095790
DE(Plus)=             -0.017151 DE(2DF)=                    -0.201452
E(Delta-G3)=          -0.288318 E(G3-Empiric)=              -0.095790
G3(0 K)=            -212.367970 G3 Energy=               -212.361453
G3 Enthalpy=        -212.360509 G3 Free Energy=          -212.397311

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-211.8069943\
QCISD(T)/6-31G(d)=-211.886119\MP4/6-31G(d)=-211.8832806\
MP2/6-31+G(d)=-211.8236275\MP4/6-31+G(d)=-211.900432\
MP2/6-31G(2df,p)=-211.9974167\MP4/6-31G(2df,p)=-212.0847322\
MP2/GTLarge=-212.3023682\G3=-212.3679704\PG=C01
[X(C4H9N1)]\NImag=0\\@.
```

II. Synperiplanar conformation *sp*-IVo

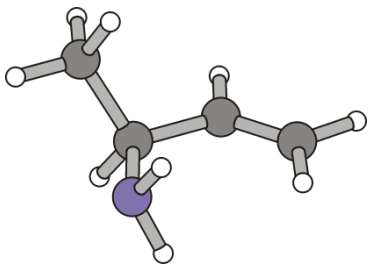

Figure S7.52. Calculated structure for synperiplanar conformation of butenamine **IVo**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.982053	-0.098674	-0.240472
2	6	0	0.868370	-0.653188	0.246432
3	6	0	-0.482762	0.020243	0.418172
4	6	0	-1.577354	-0.784462	-0.302754
5	7	0	-0.572578	1.422048	0.007230
6	1	0	-0.716565	-0.003355	1.493585
7	1	0	2.904824	-0.664931	-0.323103
8	1	0	2.014533	0.935046	-0.575835
9	1	0	0.900965	-1.694745	0.571180
10	1	0	0.098864	1.999587	0.505954
11	1	0	-0.386571	1.522409	-0.988223
12	1	0	-2.559054	-0.348303	-0.098877
13	1	0	-1.410884	-0.773787	-1.386750
14	1	0	-1.579902	-1.829766	0.023187

```
Zero-point correction=                          0.125791
(Hartree/Particle)
Thermal correction to Energy=                   0.132081
Thermal correction to Enthalpy=                 0.133025
Thermal correction to Gibbs Free Energy=        0.096776
Sum of electronic and zero-point Energies=           -212.466968
Sum of electronic and thermal Energies=              -212.460679
Sum of electronic and thermal Enthalpies=            -212.459735
Sum of electronic and thermal Free Energies=         -212.495984

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RMSF=1.969e-04\PG=C01 [X(C4H9N1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.963853	-0.101983	-0.239610
2	6	0	0.866279	-0.647708	0.246727
3	6	0	-0.482868	0.022614	0.419914
4	6	0	-1.570763	-0.776345	-0.302053
5	7	0	-0.563537	1.411569	0.003195
6	1	0	-0.714991	0.003241	1.482528
7	1	0	2.877801	-0.662622	-0.321888
8	1	0	2.001261	0.918982	-0.576537
9	1	0	0.902135	-1.677369	0.570168
10	1	0	0.095635	1.975911	0.503818
11	1	0	-0.350714	1.501558	-0.972509
12	1	0	-2.541914	-0.335047	-0.113159
13	1	0	-1.396636	-0.775499	-1.374726
14	1	0	-1.586824	-1.809615	0.030072

```
Temperature=         298.150000 Pressure=                   1.000000
E(ZPE)=                0.121073 E(Thermal)=                 0.127462
E(QCISD(T))=        -211.885851 E(Empiric)=                -0.095790
DE(Plus)=             -0.016348 DE(2DF)=                   -0.201562
E(Delta-G3)=          -0.288860 E(G3-Empiric)=             -0.095790
G3(0 K)=            -212.367338 G3 Energy=               -212.360948
G3 Enthalpy=        -212.360004 G3 Free Energy=          -212.396430

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-211.8066607\
QCISD(T)/6-31G(d)=-211.8858509\MP4/6-31G(d)=-211.8830123\
MP2/6-31+G(d)=-211.8225316\MP4/6-31+G(d)=-211.8993603\
MP2/6-31G(2df,p)=-211.9972627\MP4/6-31G(2df,p)=-212.0845739\
MP2/GTLarge=-212.301994\G3=-212.3673379\PG=C01 [X(C4H9N1)]\NImag=0\\@.
```

7.6.6 But-3-ene-2-thiol (IVp)

I. Anticline conformation *ac*-IVp

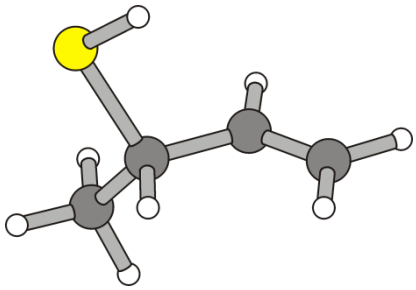

Figure S7.53. Calculated minimum conformation of butene-2-thiol **IVp**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.346090	-0.509429	-0.143559
2	6	0	-1.215071	-0.081233	0.426995
3	6	0	0.006443	0.347097	-0.331088
4	6	0	0.449383	1.772975	0.022740
5	1	0	-3.206377	-0.802451	0.450677
6	1	0	-2.448926	-0.580348	-1.224333
7	1	0	-1.138490	-0.028006	1.513105
8	16	0	1.445101	-0.782004	0.047189
9	1	0	-0.184107	0.282353	-1.406852
10	1	0	1.350205	2.054894	-0.531270
11	1	0	-0.347241	2.479727	-0.230581
12	1	0	0.660831	1.865336	1.093372
13	1	0	0.824495	-1.935897	-0.269674

```
Zero-point correction=                          0.107993
(Hartree/Particle)
Thermal correction to Energy=                   0.114690
Thermal correction to Enthalpy=                 0.115634
Thermal correction to Gibbs Free Energy=        0.077770
Sum of electronic and zero-point Energies=           -555.319821
Sum of electronic and thermal Energies=              -555.313123
Sum of electronic and thermal Enthalpies=            -555.312179
Sum of electronic and thermal Free Energies=         -555.350043

Version=AM64L-G03RevE.01\State=1-A\HF=-555.4278132\RMSD=4.569e-09\
RMSF=2.717e-07\PG=C01 [X(C4H8S1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.329656	-0.511418	-0.144585
2	6	0	-1.212017	-0.104243	0.424605
3	6	0	0.013824	0.330696	-0.327646
4	6	0	0.420648	1.763959	0.024291
5	1	0	-3.183588	-0.804357	0.439456
6	1	0	-2.436727	-0.568414	-1.214641
7	1	0	-1.137094	-0.066264	1.499567
8	16	0	1.446456	-0.759988	0.047778
9	1	0	-0.175031	0.268999	-1.391459
10	1	0	1.305250	2.064869	-0.525804
11	1	0	-0.386838	2.443035	-0.226736
12	1	0	0.629207	1.861417	1.084488
13	1	0	0.884729	-1.913436	-0.289311

```
Temperature=          298.150000 Pressure=                    1.000000
E(ZPE)=                 0.103917 E(Thermal)=                  0.110742
E(QCISD(T))=         -554.335601 E(Empiric)=                 -0.095790
DE(Plus)=              -0.012933 DE(2DF)=                    -0.210426
E(Delta-G3)=           -0.557087 E(G3-Empiric)=              -0.095790
G3(0 K)=             -555.107920 G3 Energy=                -555.101095
G3 Enthalpy=         -555.100151 G3 Free Energy=           -555.138292

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-554.2515062\
QCISD(T)/6-31G(d)=-554.3356011\MP4/6-31G(d)=-554.3326295\
MP2/6-31+G(d)=-554.263889\MP4/6-31+G(d)=-554.3455621\
MP2/6-31G(2df,p)=-554.447453\MP4/6-31G(2df,p)=-554.5430559\
MP2/GTLarge=-555.0169225\G3=-555.10792\PG=C01 [X(C4H8S1)]\NImag=0\\@.
```

II. Synperiplanar conformation *sp*-IVp

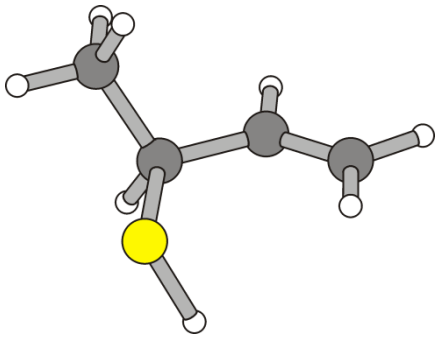

Figure S7.54. Calculated structure for synperiplanar conformation of butenethiol **IVp**.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.052375	-0.604751	-0.263238
2	6	0	1.339543	0.404525	0.241497
3	6	0	-0.154656	0.491824	0.445262
4	6	0	-0.746053	1.701059	-0.300866
5	1	0	3.132319	-0.532354	-0.349376
6	1	0	1.585326	-1.517368	-0.620278
7	1	0	1.865668	1.301552	0.575468
8	16	0	-1.122288	-0.999710	-0.074756
9	1	0	-0.344967	0.631263	1.516639
10	1	0	-1.807821	1.825556	-0.069252
11	1	0	-0.220983	2.615487	-0.004248
12	1	0	-0.633352	1.583961	-1.383453
13	1	0	-0.566841	-1.868670	0.794670

```
Zero-point correction=                          0.107880
(Hartree/Particle)
Thermal correction to Energy=                   0.114551
Thermal correction to Enthalpy=                 0.115495
Thermal correction to Gibbs Free Energy=        0.077697
Sum of electronic and zero-point Energies=           -555.316235
Sum of electronic and thermal Energies=              -555.309563
Sum of electronic and thermal Enthalpies=            -555.308619
Sum of electronic and thermal Free Energies=         -555.346417

Version=AM64L-G03RevE.01\State=1-A\HF=-555.4241143\RMSD=4.928e-09\
RMSF=3.270e-04\PG=C01 [X(C4H8S1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.041729	-0.604767	-0.261164
2	6	0	1.336682	0.388113	0.241213
3	6	0	-0.157172	0.480435	0.444755
4	6	0	-0.729021	1.694741	-0.298471
5	1	0	3.111622	-0.530427	-0.339612
6	1	0	1.592827	-1.510505	-0.623719
7	1	0	1.858890	1.270699	0.580751
8	16	0	-1.123049	-0.984021	-0.075983
9	1	0	-0.341319	0.620423	1.504272
10	1	0	-1.782343	1.824986	-0.079322
11	1	0	-0.205728	2.595292	0.006267
12	1	0	-0.608014	1.582460	-1.370260
13	1	0	-0.610469	-1.859720	0.779347

```
Temperature=          298.150000 Pressure=                   1.000000
E(ZPE)=                 0.103900 E(Thermal)=                 0.110690
E(QCISD(T))=         -554.332658 E(Empiric)=                -0.095790
DE(Plus)=              -0.012161 DE(2DF)=                   -0.210706
E(Delta-G3)=           -0.558143 E(G3-Empiric)=             -0.095790
G3(0 K)=             -555.105558 G3 Energy=               -555.098768
G3 Enthalpy=         -555.097824 G3 Free Energy=          -555.135869

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-554.2483175\
QCISD(T)/6-31G(d)=-554.3326582\MP4/6-31G(d)=-554.3296965\
MP2/6-31+G(d)=-554.2600458\MP4/6-31+G(d)=-554.3418576\
MP2/6-31G(2df,p)=-554.444672\MP4/6-31G(2df,p)=-554.5404024\
MP2/GTLarge=-555.0145432\G3=-555.1055578\PG=C01
[X(C4H8S1)]\NImag=0\\@.
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7.7 Conformational Analysis II – Cyclohexane Chairs

7.7.1 Cyclohexanol

I. Equatorial substituent

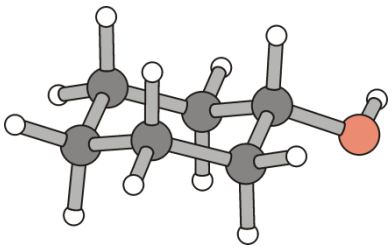

Figure S7.55. Calculated minimum structure of the equatorial cyclohexanol conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.034910	-0.014111	0.320344
2	6	0	0.319353	-1.270570	-0.173885
3	6	0	-1.168336	-1.259346	0.215149
4	6	0	-1.873466	0.014788	-0.277645
5	6	0	-1.147575	1.279748	0.208132
6	6	0	0.339784	1.256452	-0.185139
7	1	0	1.017220	-0.011748	1.424129
8	8	0	2.393959	-0.097603	-0.128198
9	1	0	0.823796	-2.155981	0.229220
10	1	0	0.422582	-1.314123	-1.266767
11	1	0	-1.260529	-1.322866	1.309259
12	1	0	-1.664327	-2.149982	-0.188587
13	1	0	-2.917495	0.025205	0.058781
14	1	0	-1.897694	0.012517	-1.376945
15	1	0	-1.234677	1.349499	1.302246
16	1	0	-1.627735	2.177794	-0.198563
17	1	0	0.851919	2.145292	0.209927
18	1	0	0.440167	1.289145	-1.278760
19	1	0	2.867089	0.694307	0.159901

```
Zero-point correction=                          0.174269
(Hartree/Particle)
Thermal correction to Energy=                   0.181174
Thermal correction to Enthalpy=                 0.182118
Thermal correction to Gibbs Free Energy=        0.143880
Sum of electronic and zero-point Energies=           -310.950118
Sum of electronic and thermal Energies=              -310.943213
Sum of electronic and thermal Enthalpies=            -310.942268
Sum of electronic and thermal Free Energies=         -310.980507

Version=AM64L-G03RevE.01\State=1-A\HF=-311.1243869\RMSD=6.233e-09\
RMSF=9.458e-07\PG=C01 [X(C6H12O1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.035780	-0.015950	0.317884
2	6	0	0.318136	-1.265694	-0.173897
3	6	0	-1.162977	-1.252854	0.216311
4	6	0	-1.863169	0.017070	-0.277036
5	6	0	-1.137526	1.275343	0.208922
6	6	0	0.342638	1.249363	-0.185320
7	1	0	1.019194	-0.013219	1.409128
8	8	0	2.366666	-0.093640	-0.131215
9	1	0	0.816165	-2.143065	0.226177
10	1	0	0.418748	-1.310446	-1.255788
11	1	0	-1.253264	-1.314334	1.299806
12	1	0	-1.656793	-2.133472	-0.183946
13	1	0	-2.896952	0.029186	0.057122
14	1	0	-1.886562	0.014662	-1.365388
15	1	0	-1.223027	1.343666	1.292379
16	1	0	-1.612716	2.164720	-0.194552
17	1	0	0.851237	2.129456	0.205446
18	1	0	0.441494	1.282745	-1.267931
19	1	0	2.851859	0.655559	0.186092

```
Temperature=          298.150000 Pressure=                    1.000000
E(ZPE)=                 0.167479 E(Thermal)=                  0.174595
E(QCISD(T))=         -310.123168 E(Empiric)=                 -0.134106
DE(Plus)=              -0.020260 DE(2DF)=                    -0.290680
E(Delta-G3)=           -0.411681 E(G3-Empiric)=              -0.134106
G3(0 K)=             -310.812416 G3 Energy=                -310.805300
G3 Enthalpy=         -310.804355 G3 Free Energy=           -310.842935

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-310.0220311\
QCISD(T)/6-31G(d)=-310.1231676\MP4/6-31G(d)=-310.1210222\
MP2/6-31+G(d)=-310.0407221\MP4/6-31+G(d)=-310.1412825\
MP2/6-31G(2df,p)=-310.2963193\MP4/6-31G(2df,p)=-310.4117018\
MP2/GTLarge=-310.7266913\G3=-
310.8124155\PG=C01[X(C6H12O1)]\NImag=0\\@.
```

II. Axial substituent

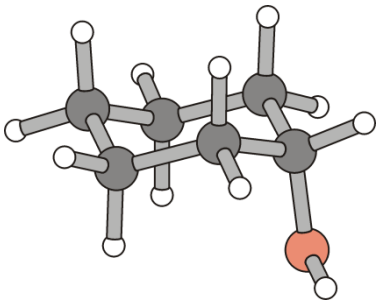

Figure S7.56. Calculated minimum structure of the axial cyclohexanol conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.337318	1.256288	0.605369
2	6	0	-1.161734	-0.029911	0.428097
3	6	0	-0.291263	-1.280395	0.591395
4	6	0	0.953855	-1.250268	-0.310051
5	6	0	1.773075	0.032264	-0.093065
6	6	0	0.907436	1.286332	-0.296437
7	8	0	-1.751649	-0.104318	-0.882121
8	1	0	-1.964456	-0.051560	1.181692
9	1	0	-0.902067	-2.165502	0.380781
10	1	0	0.016285	-1.343486	1.644529
11	1	0	0.637902	-1.307790	-1.358755
12	1	0	1.572191	-2.135032	-0.114747
13	1	0	2.633721	0.052991	-0.772962
14	1	0	2.181741	0.035330	0.928908
15	1	0	0.592543	1.340179	-1.346316
16	1	0	1.491138	2.192583	-0.093290
17	1	0	-0.974489	2.131968	0.415739
18	1	0	-0.032298	1.322364	1.659769
19	1	0	-2.303320	0.676634	-1.020223

```
Zero-point correction=                           0.174342
(Hartree/Particle)
Thermal correction to Energy=                    0.181230
Thermal correction to Enthalpy=                  0.182175
Thermal correction to Gibbs Free Energy=         0.143988
Sum of electronic and zero-point Energies=           -310.948613
Sum of electronic and thermal Energies=              -310.941724
Sum of electronic and thermal Enthalpies=            -310.940780
Sum of electronic and thermal Free Energies=         -310.978967

Version=AM64L-G03RevE.01\State=1-A\HF=-311.1229546\RMSD=2.820e-09\
RMSF=5.217e-06\ZeroPoint=0.1743418\PG=C01 [X(C6H12O1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.349814	1.244871	0.610392
2	6	0	-1.161427	-0.038104	0.414192
3	6	0	-0.288969	-1.277187	0.590766
4	6	0	0.952392	-1.241522	-0.305777
5	6	0	1.759647	0.042236	-0.090733
6	6	0	0.888517	1.286083	-0.289830
7	8	0	-1.711360	-0.103579	-0.883802
8	1	0	-1.967394	-0.066111	1.146141
9	1	0	-0.886158	-2.158151	0.379162
10	1	0	0.014336	-1.336821	1.634351
11	1	0	0.643515	-1.305829	-1.344386
12	1	0	1.572352	-2.111274	-0.105508
13	1	0	2.608168	0.069077	-0.768956
14	1	0	2.168761	0.047412	0.919069
15	1	0	0.575214	1.342640	-1.328284
16	1	0	1.462980	2.185246	-0.083974
17	1	0	-0.984101	2.110128	0.422740
18	1	0	-0.047961	1.307077	1.654307
19	1	0	-2.270908	0.646976	-1.028306

```
Temperature=          298.150000 Pressure=                    1.000000
E(ZPE)=                 0.167694 E(Thermal)=                  0.174747
E(QCISD(T))=         -310.123554 E(Empiric)=                 -0.134106
DE(Plus)=              -0.019135 DE(2DF)=                    -0.290884
E(Delta-G3)=           -0.411535 E(G3-Empiric)=              -0.134106
G3(0 K)=             -310.811521 G3 Energy=                -310.804467
G3 Enthalpy=         -310.803523 G3 Free Energy=           -310.841937

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-310.0225149\
QCISD(T)/6-31G(d)=-310.1235538\MP4/6-31G(d)=-310.1214287\
MP2/6-31+G(d)=-310.040056\MP4/6-31+G(d)=-310.1405641\
MP2/6-31G(2df,p)=-310.2969919\MP4/6-31G(2df,p)=-310.4123128\
MP2/GTLarge=-310.7260677\G3=-
310.8115206\PG=C01[X(C6H12O1)]\NImag=0\\@.
```

7.7.2 Methylcyclohexane

I. Equatorial substituent

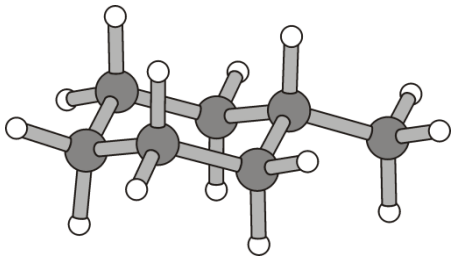

Figure S7.57. Calculated minimum structure of the equatorial methylcyclohexane conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.020758	0.000000	-0.328684
2	6	0	-0.294025	-1.264463	0.168200
3	6	0	1.196044	-1.268971	-0.209570
4	6	0	1.907749	0.000000	0.285329
5	6	0	1.196044	1.268971	-0.209570
6	6	0	-0.294024	1.264463	0.168200
7	1	0	-0.969324	0.000000	-1.429729
8	6	0	-2.500384	0.000000	0.074459
9	1	0	-0.788738	-2.159309	-0.232078
10	1	0	-0.390547	-1.320111	1.263674
11	1	0	1.290874	-1.332197	-1.303652
12	1	0	1.685616	-2.162956	0.196677
13	1	0	2.955627	0.000000	-0.040029
14	1	0	1.921869	0.000000	1.385300
15	1	0	1.290874	1.332197	-1.303652
16	1	0	1.685616	2.162956	0.196677
17	1	0	-0.788738	2.159309	-0.232078
18	1	0	-0.390546	1.320111	1.263674
19	1	0	-2.608792	-0.000001	1.166570
20	1	0	-3.018835	0.885841	-0.310770
21	1	0	-3.018835	-0.885840	-0.310772

```
Zero-point correction=                          0.197708
(Hartree/Particle)
Thermal correction to Energy=                   0.204865
Thermal correction to Enthalpy=                 0.205809
Thermal correction to Gibbs Free Energy=        0.167115
Sum of electronic and zero-point Energies=           -275.023613
Sum of electronic and thermal Energies=              -275.016457
Sum of electronic and thermal Enthalpies=            -275.015512
Sum of electronic and thermal Free Energies=         -275.054206

Version=AM64L-G03RevE.01\State=1-A\HF=-275.2213214\RMSD=2.656e-09\
RMSF=6.486e-07\PG=C01 [X(C7H14)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.015020	0.000000	-0.329507
2	6	0	0.293309	1.259623	0.168475
3	6	0	-1.190706	1.263378	-0.209988
4	6	0	-1.898885	0.000000	0.286114
5	6	0	-1.190707	-1.263377	-0.209988
6	6	0	0.293308	-1.259623	0.168475
7	1	0	0.966170	0.000000	-1.418996
8	6	0	2.489408	0.000000	0.075248
9	1	0	0.780721	2.145879	-0.230762
10	1	0	0.387582	1.316806	1.252763
11	1	0	-1.285002	1.325535	-1.293094
12	1	0	-1.675439	2.148204	0.194009
13	1	0	-2.936586	0.000000	-0.036791
14	1	0	-1.911898	0.000000	1.375091
15	1	0	-1.285002	-1.325535	-1.293094
16	1	0	-1.675440	-2.148203	0.194009
17	1	0	0.780720	-2.145879	-0.230762
18	1	0	0.387581	-1.316807	1.252763
19	1	0	2.596619	0.000000	1.157034
20	1	0	3.002744	-0.877478	-0.307573
21	1	0	3.002744	0.877478	-0.307573

Temperature=	298.150000	Pressure=	1.000000
E(ZPE)=	0.189567	E(Thermal)=	0.196979
E(QCISD(T))=	-274.273770	E(Empiric)=	-0.134106
DE(Plus)=	-0.012001	DE(2DF)=	-0.276641
E(Delta-G3)=	-0.391193	E(G3-Empiric)=	-0.134106
G3(0 K)=	-274.898144	G3 Energy=	-274.890732
G3 Enthalpy=	-274.889788	G3 Free Energy=	-274.928919

Version=AM64L-G03RevE.01\State=1-A'\MP2/6-31G(d)=-274.1617576\
QCISD(T)/6-31G(d)=-274.2737698\MP4/6-31G(d)=-274.2705983\
MP2/6-31+G(d)=-274.1725565\MP4/6-31+G(d)=-274.2825997\
MP2/6-31G(2df,p)=-274.4228992\MP4/6-31G(2df,p)=-274.5472393\
MP2/GTLarge=-274.824891\G3=-274.8981444\PG=CS[SG(C3H4),X(C4H10)]\
NImag=0\\@.

II. Axial substituent

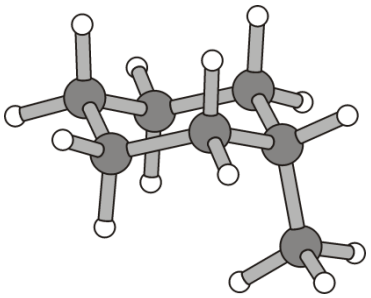

Figure S7.58. Calculated minimum structure of the axial methylcyclohexane conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.129739	0.000000	0.493564
2	6	0	0.252607	1.266051	0.629001
3	6	0	-0.953891	1.269938	-0.325936
4	6	0	-1.804390	0.000000	-0.160125
5	6	0	-0.953891	-1.269938	-0.325936
6	6	0	0.252607	-1.266051	0.629001
7	6	0	1.966865	0.000000	-0.797765
8	1	0	1.840456	0.000000	1.332230
9	1	0	0.865542	2.162919	0.469581
10	1	0	-0.119856	1.324540	1.662050
11	1	0	-0.607916	1.341677	-1.366284
12	1	0	-1.566114	2.162412	-0.145258
13	1	0	-2.634012	0.000000	-0.878247
14	1	0	-2.258682	0.000000	0.842073
15	1	0	-0.607916	-1.341677	-1.366284
16	1	0	-1.566113	-2.162413	-0.145258
17	1	0	0.865542	-2.162919	0.469581
18	1	0	-0.119856	-1.324540	1.662050
19	1	0	2.612133	0.885125	-0.843400
20	1	0	2.612133	-0.885125	-0.843400
21	1	0	1.346785	0.000000	-1.700250

```
Zero-point correction=                          0.197954
(Hartree/Particle)
Thermal correction to Energy=                   0.205075
Thermal correction to Enthalpy=                 0.206019
Thermal correction to Gibbs Free Energy=        0.167428
Sum of electronic and zero-point Energies=           -275.019637
Sum of electronic and thermal Energies=              -275.012517
Sum of electronic and thermal Enthalpies=            -275.011572
Sum of electronic and thermal Free Energies=         -275.050164
Version=AM64L-G03RevE.01\State=1-A\HF=-275.2175914\RMSD=8.126e-09\
RMSF=2.556e-06\PG=C01 [X(C7H14)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.124165	0.000000	0.491742
2	6	0	0.251592	1.260889	0.624812
3	6	0	-0.951233	1.264855	-0.325731
4	6	0	-1.798094	0.000000	-0.157707
5	6	0	-0.951233	-1.264855	-0.325731
6	6	0	0.251592	-1.260889	0.624812
7	6	0	1.962937	0.000000	-0.792356
8	1	0	1.826385	0.000000	1.323015
9	1	0	0.857847	2.149085	0.464335
10	1	0	-0.116753	1.321015	1.647715
11	1	0	-0.612271	1.338296	-1.356569
12	1	0	-1.558306	2.147251	-0.141329
13	1	0	-2.619132	0.000000	-0.869785
14	1	0	-2.247280	0.000000	0.834519
15	1	0	-0.612272	-1.338296	-1.356569
16	1	0	-1.558307	-2.147251	-0.141329
17	1	0	0.857847	-2.149085	0.464335
18	1	0	-0.116753	-1.321015	1.647715
19	1	0	2.603085	0.876758	-0.832475
20	1	0	2.603084	-0.876758	-0.832475
21	1	0	1.354469	0.000000	-1.690144

```
Temperature=         298.150000 Pressure=                    1.000000
E(ZPE)=                0.189863 E(Thermal)=                 0.197219
E(QCISD(T))=        -274.270724 E(Empiric)=                -0.134106
DE(Plus)=             -0.011505 DE(2DF)=                    -0.277047
E(Delta-G3)=          -0.391656 E(G3-Empiric)=              -0.134106
G3(0 K)=            -274.895174 G3 Energy=                -274.887819
G3 Enthalpy=        -274.886874 G3 Free Energy=           -274.925854

Version=AM64L-G03RevE.01\State=1-A'\MP2/6-31G(d)=-274.1587322\
QCISD(T)/6-31G(d)=-274.2707237\MP4/6-31G(d)=-274.2675746\
MP2/6-31+G(d)=-274.1690631\MP4/6-31+G(d)=-274.2790796\
MP2/6-31G(2df,p)=-274.4202556\MP4/6-31G(2df,p)=-274.5446216\
MP2/GTLarge=-274.822242\G3=-274.8951742\PG=CS [SG(C3H4),X(C4H10)]\
NImag=0\\@.
```

7.7.3 Fluorocyclohexane

I. Equatorial substituent

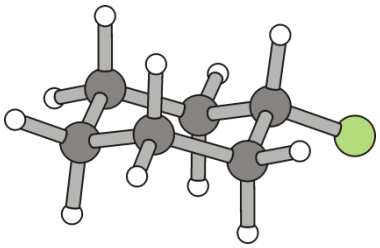

Figure S7.59. Calculated minimum structure of the equatorial fluorocyclohexane conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.026872	0.000000	0.328170
2	6	0	-0.346134	1.266357	-0.175150
3	6	0	1.145044	1.270044	0.210266
4	6	0	1.857642	0.000000	-0.282841
5	6	0	1.145044	-1.270044	0.210266
6	6	0	-0.346134	-1.266357	-0.175150
7	1	0	-1.068168	0.000000	1.425879
8	9	0	-2.378016	0.000000	-0.102437
9	1	0	-0.858747	2.146501	0.228787
10	1	0	-0.450747	1.302511	-1.267752
11	1	0	1.239554	1.337340	1.303758
12	1	0	1.629240	2.165048	-0.197099
13	1	0	2.902794	0.000000	0.049375
14	1	0	1.877383	0.000000	-1.382075
15	1	0	1.239554	-1.337340	1.303758
16	1	0	1.629240	-2.165048	-0.197099
17	1	0	-0.858747	-2.146501	0.228787
18	1	0	-0.450747	-1.302511	-1.267752

```
Zero-point correction=                          0.162339
(Hartree/Particle)
Thermal correction to Energy=                   0.168824
Thermal correction to Enthalpy=                 0.169768
Thermal correction to Gibbs Free Energy=        0.132145
Sum of electronic and zero-point Energies=           -334.985433
Sum of electronic and thermal Energies=              -334.978947
Sum of electronic and thermal Enthalpies=            -334.978003
Sum of electronic and thermal Free Energies=         -335.015627
Version=AM64L-G03RevE.01\State=1-A\HF=-335.1477716\RMSD=5.364e-09\
RMSF=8.112e-07\PG=C01 [X(C6H11F1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.032491	0.000000	0.327563
2	6	0	0.348276	-1.259878	-0.173195
3	6	0	-1.135540	-1.264948	0.210517
4	6	0	-1.845075	0.000000	-0.283629
5	6	0	-1.135540	1.264948	0.210517
6	6	0	0.348276	1.259878	-0.173195
7	1	0	1.063814	0.000000	1.412518
8	9	0	2.341465	0.000000	-0.104377
9	1	0	0.856464	-2.131821	0.226616
10	1	0	0.454016	-1.296700	-1.254785
11	1	0	-1.229858	-1.330253	1.293335
12	1	0	-1.616318	-2.150189	-0.194072
13	1	0	-2.880311	0.000000	0.045182
14	1	0	-1.862609	0.000000	-1.371960
15	1	0	-1.229858	1.330253	1.293335
16	1	0	-1.616318	2.150189	-0.194072
17	1	0	0.856464	2.131821	0.226616
18	1	0	0.454016	1.296700	-1.254785

```
Temperature=         298.150000 Pressure=                  1.000000
E(ZPE)=                0.155958 E(Thermal)=                0.162641
E(QCISD(T))=        -334.112250 E(Empiric)=               -0.134106
DE(Plus)=             -0.024063 DE(2DF)=                  -0.290482
E(Delta-G3)=          -0.429552 E(G3-Empiric)=            -0.134106
G3(0 K)=            -334.834495 G3 Energy=              -334.827813
G3 Enthalpy=        -334.826868 G3 Free Energy=         -334.864804

Version=AM64L-G03RevE.01\State=1-A'\MP2/6-31G(d)=-334.0146762\
QCISD(T)/6-31G(d)=-334.1122502\MP4/6-31G(d)=-334.1113702\
MP2/6-31+G(d)=-334.0369572\MP4/6-31+G(d)=-334.1354327\
MP2/6-31G(2df,p)=-334.2882811\MP4/6-31G(2df,p)=-334.4018524\
MP2/GTLarge=-334.7401145\G3=-334.8344949\PG=CS [SG(C2H3F1),X(C4H8)]\
NImag=0\\@.
```

II. Axial substituent

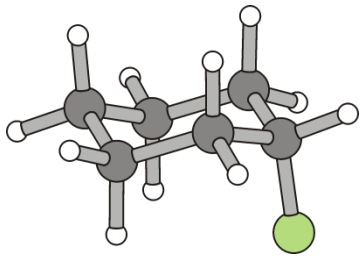

Figure S7.60. Calculated minimum structure of the axial fluorocyclohexane conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.167401	0.000000	0.412315
2	6	0	0.343582	1.273716	0.580255
3	6	0	-0.924362	1.268586	-0.289795
4	6	0	-1.760928	0.000000	-0.057123
5	6	0	-0.924361	-1.268586	-0.289795
6	6	0	0.343582	-1.273716	0.580255
7	9	0	1.723109	0.000000	-0.900096
8	1	0	2.029332	0.000000	1.089532
9	1	0	0.974396	2.140078	0.351287
10	1	0	0.067037	1.351599	1.641518
11	1	0	-0.634264	1.324182	-1.346565
12	1	0	-1.519509	2.164969	-0.078515
13	1	0	-2.638159	0.000000	-0.715334
14	1	0	-2.143960	0.000000	0.974545
15	1	0	-0.634264	-1.324182	-1.346565
16	1	0	-1.519509	-2.164969	-0.078515
17	1	0	0.974397	-2.140077	0.351287
18	1	0	0.067037	-1.351599	1.641518

```
Zero-point correction=                           0.162323
(Hartree/Particle)
Thermal correction to Energy=                    0.168804
Thermal correction to Enthalpy=                  0.169748
Thermal correction to Gibbs Free Energy=         0.132142
Sum of electronic and zero-point Energies=          -334.984952
Sum of electronic and thermal Energies=             -334.978471
Sum of electronic and thermal Enthalpies=           -334.977527
Sum of electronic and thermal Free Energies=        -335.015133

Version=AM64L-G03RevE.01\State=1-A\HF=-335.1472748\RMSD=2.822e-09\
RMSF=2.233e-06\PG=C01 [X(C6H11F1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.172931	0.000000	0.388065
2	6	0	-0.353862	-1.265595	0.586823
3	6	0	0.908590	-1.264559	-0.280729
4	6	0	1.742443	0.000000	-0.052203
5	6	0	0.908590	1.264559	-0.280729
6	6	0	-0.353862	1.265595	0.586823
7	9	0	-1.654816	0.000000	-0.910090
8	1	0	-2.041527	0.000000	1.035775
9	1	0	-0.973910	-2.127222	0.360137
10	1	0	-0.082178	-1.333851	1.638300
11	1	0	0.619435	-1.322965	-1.325990
12	1	0	1.500171	-2.150194	-0.067695
13	1	0	2.607045	0.000000	-0.709841
14	1	0	2.126979	0.000000	0.967063
15	1	0	0.619435	1.322965	-1.325990
16	1	0	1.500170	2.150194	-0.067695
17	1	0	-0.973910	2.127222	0.360137
18	1	0	-0.082178	1.333851	1.638300

```
Temperature=         298.150000 Pressure=                   1.000000
E(ZPE)=                0.156099 E(Thermal)=                 0.162745
E(QCISD(T))=        -334.113339 E(Empiric)=                -0.134106
DE(Plus)=             -0.023036 DE(2DF)=                    -0.290378
E(Delta-G3)=          -0.429473 E(G3-Empiric)=              -0.134106
G3(0 K)=            -334.834232 G3 Energy=                -334.827586
G3 Enthalpy=        -334.826642 G3 Free Energy=           -334.864475

Version=AM64L-G03RevE.01\State=1-A'\MP2/6-31G(d)=-334.0157944\
QCISD(T)/6-31G(d)=-334.1133386\MP4/6-31G(d)=-334.1124655\
MP2/6-31+G(d)=-334.0370256\MP4/6-31+G(d)=-334.1355014\
MP2/6-31G(2df,p)=-334.2892257\MP4/6-31G(2df,p)=-334.4028433\
MP2/GTLarge=-334.7399297\G3=-334.8342325\PG=CS [SG(C2H3F1),X(C4H8)]\
NImag=0\\@.
```

7.7.4 Chlorocyclohexane

I. Equatorial substituent

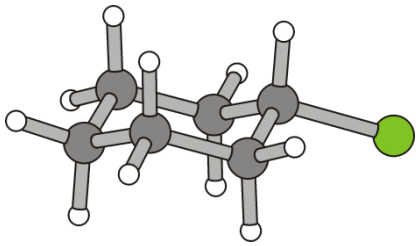

Figure S7.61. Calculated minimum structure of the equatorial chlorocyclohexane conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.609437	0.000000	0.373539
2	6	0	0.059282	1.269220	-0.152256
3	6	0	1.559902	1.268066	0.198479
4	6	0	2.260537	0.000000	-0.313446
5	6	0	1.559902	-1.268066	0.198479
6	6	0	0.059282	-1.269220	-0.152256
7	1	0	-0.608065	0.000000	1.467881
8	17	0	-2.394667	0.000000	-0.067270
9	1	0	-0.435578	2.152904	0.263813
10	1	0	-0.067989	1.310870	-1.241721
11	1	0	1.679449	1.334977	1.289419
12	1	0	2.031594	2.164673	-0.220657
13	1	0	3.313886	0.000000	-0.008414
14	1	0	2.251756	0.000000	-1.412813
15	1	0	1.679449	-1.334977	1.289419
16	1	0	2.031594	-2.164673	-0.220657
17	1	0	-0.435578	-2.152904	0.263813
18	1	0	-0.067989	-1.310870	-1.241721

```
Zero-point correction=                          0.161074
(Hartree/Particle)
Thermal correction to Energy=                   0.167886
Thermal correction to Enthalpy=                 0.168830
Thermal correction to Gibbs Free Energy=        0.129980
Sum of electronic and zero-point Energies=           -695.341217
Sum of electronic and thermal Energies=              -695.334405
Sum of electronic and thermal Enthalpies=            -695.333461
Sum of electronic and thermal Free Energies=         -695.372311
Version=AM64L-G03RevE.01\State=1-A\HF=-695.5022911\RMSD=4.728e-09\
RMSF=1.076e-06\PG=C01 [X(C6H11Cl1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.502935	0.511344	0.000000
2	6	0	0.163535	-0.018198	1.264819
3	6	0	0.163535	-1.552048	1.263277
4	6	0	0.821469	-2.113835	0.000000
5	6	0	0.163535	-1.552048	-1.263277
6	6	0	0.163535	-0.018198	-1.264819
7	1	0	-1.552665	0.252068	0.000000
8	17	0	-0.483769	2.322733	0.000000
9	1	0	-0.350934	0.362987	2.139800
10	1	0	1.184230	0.351465	1.306373
11	1	0	-0.861022	-1.914053	1.328825
12	1	0	0.676306	-1.913501	2.149501
13	1	0	0.764636	-3.198419	0.000000
14	1	0	1.878902	-1.855997	0.000000
15	1	0	-0.861022	-1.914053	-1.328825
16	1	0	0.676306	-1.913501	-2.149501
17	1	0	-0.350934	0.362987	-2.139800
18	1	0	1.184230	0.351465	-1.306373

Temperature=	298.150000	Pressure=	1.000000
E(ZPE)=	0.154639	E(Thermal)=	0.161660
E(QCISD(T))=	-694.135978	E(Empiric)=	-0.134106
DE(Plus)=	-0.012837	DE(2DF)=	-0.288063
E(Delta-G3)=	-0.678229	E(G3-Empiric)=	-0.134106
G3(0 K)=	-695.094575	G3 Energy=	-695.087553
G3 Enthalpy=	-695.086609	G3 Free Energy=	-695.125810

Version=AM64L-G03RevE.01\State=1-A'\MP2/6-31G(d)=-694.0290569\
QCISD(T)/6-31G(d)=-694.1359784\MP4/6-31G(d)=-694.1337428\
MP2/6-31+G(d)=-694.0406453\MP4/6-31+G(d)=-694.1465796\
MP2/6-31G(2df,p)=-694.2963082\MP4/6-31G(2df,p)=-694.4218055\
MP2/GTLarge=-694.9861259\G3=-695.0945747\PG=CS [SG(C2H3Cl1),X(C4H8)]\
NImag=0\\@.

II. Axial substituent

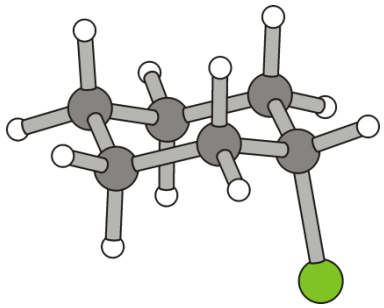

Figure S7.62. Calculated minimum structure of the axial chlorocyclohexane conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.695187	0.000000	0.826931
2	6	0	0.154845	-1.271886	0.764168
3	6	0	1.153550	-1.270292	-0.403479
4	6	0	2.019689	0.000000	-0.402530
5	6	0	1.153550	1.270292	-0.403479
6	6	0	0.154845	1.271886	0.764168
7	17	0	-1.934435	0.000000	-0.548013
8	1	0	-1.320040	0.000000	1.722223
9	1	0	-0.493671	-2.153090	0.727586
10	1	0	0.707315	-1.322927	1.714825
11	1	0	0.602434	-1.337893	-1.349662
12	1	0	1.785846	-2.164002	-0.342607
13	1	0	2.689903	0.000000	-1.270477
14	1	0	2.663937	0.000000	0.489518
15	1	0	0.602434	1.337893	-1.349662
16	1	0	1.785846	2.164002	-0.342607
17	1	0	-0.493671	2.153090	0.727585
18	1	0	0.707315	1.322927	1.714825

```
Zero-point correction=                          0.161106
(Hartree/Particle)
Thermal correction to Energy=                   0.167848
Thermal correction to Enthalpy=                 0.168793
Thermal correction to Gibbs Free Energy=        0.130119
Sum of electronic and zero-point Energies=           -695.339614
Sum of electronic and thermal Energies=              -695.332872
Sum of electronic and thermal Enthalpies=            -695.331928
Sum of electronic and thermal Free Energies=         -695.370601

Version=AM64L-G03RevE.01\State=1-A\HF=-695.5007203\RMSD=1.846e-09\
RMSF=5.328e-07\PG=C01 [X(C6H11Cl1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.703129	0.000000	0.811417
2	6	0	-0.148258	1.266882	0.757462
3	6	0	-1.150127	1.264928	-0.400093
4	6	0	-2.013690	0.000001	-0.390493
5	6	0	-1.150129	-1.264927	-0.400093
6	6	0	-0.148260	-1.266883	0.757462
7	17	0	1.919893	0.000000	-0.544201
8	1	0	1.314498	-0.000001	1.700803
9	1	0	0.492364	2.140116	0.714450
10	1	0	-0.690020	1.316898	1.701156
11	1	0	-0.615495	1.334278	-1.342602
12	1	0	-1.777699	2.148632	-0.330691
13	1	0	-2.682981	0.000001	-1.245832
14	1	0	-2.643974	0.000001	0.497855
15	1	0	-0.615497	-1.334278	-1.342602
16	1	0	-1.777702	-2.148630	-0.330691
17	1	0	0.492362	-2.140116	0.714449
18	1	0	-0.690021	-1.316899	1.701156

```
Temperature=         298.150000 Pressure=                  1.000000
E(ZPE)=                0.154741 E(Thermal)=                0.161679
E(QCISD(T))=        -694.134812 E(Empiric)=               -0.134106
DE(Plus)=             -0.012385 DE(2DF)=                  -0.288762
E(Delta-G3)=          -0.678845 E(G3-Empiric)=            -0.134106
G3(0 K)=            -695.094169 G3 Energy=              -695.087232
G3 Enthalpy=        -695.086287 G3 Free Energy=         -695.125271

Version=AM64L-G03RevE.01\State=1-A'\MP2/6-31G(d)=-694.0279213\
QCISD(T)/6-31G(d)=-694.1348115\MP4/6-31G(d)=-694.1325567\
MP2/6-31+G(d)=-694.0390898\MP4/6-31+G(d)=-694.144942\
MP2/6-31G(2df,p)=-694.2959066\MP4/6-31G(2df,p)=-694.4213188\
MP2/GTLarge=-694.9859204\G3=-695.0941694\PG=CS [SG(C2H3Cl1),X(C4H8)]\
NImag=0\\@.
```

7.7.5 Cyclohexanamine

I. Equatorial substituent

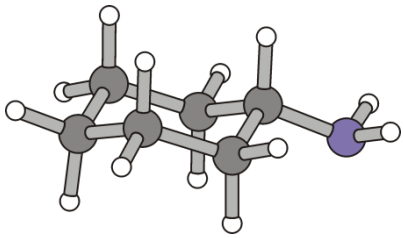

Figure S7.63. Calculated minimum structure of the equatorial cyclohexanamine conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.030179	-0.000001	0.314802
2	6	0	0.311670	-1.261866	-0.184971
3	6	0	-1.172881	-1.269589	0.213256
4	6	0	-1.891243	0.000001	-0.271633
5	6	0	-1.172880	1.269589	0.213257
6	6	0	0.311672	1.261866	-0.184970
7	1	0	0.973617	-0.000001	1.420520
8	7	0	2.419503	-0.000001	-0.164936
9	1	0	0.814417	-2.156250	0.208486
10	1	0	0.409292	-1.299944	-1.278585
11	1	0	-1.257784	-1.337222	1.307742
12	1	0	-1.663762	-2.163050	-0.191408
13	1	0	-2.934009	0.000001	0.069417
14	1	0	-1.920399	0.000001	-1.370899
15	1	0	-1.257783	1.337222	1.307742
16	1	0	-1.663761	2.163051	-0.191407
17	1	0	0.814419	2.156249	0.208488
18	1	0	0.409294	1.299944	-1.278584
19	1	0	2.920417	-0.818907	0.172306
20	1	0	2.920412	0.818914	0.172292

```
Zero-point correction=                          0.187036
(Hartree/Particle)
Thermal correction to Energy=                   0.194055
Thermal correction to Enthalpy=                 0.195000
Thermal correction to Gibbs Free Energy=        0.156590
Sum of electronic and zero-point Energies=           -291.070056
Sum of electronic and thermal Energies=              -291.063036
Sum of electronic and thermal Enthalpies=            -291.062092
Sum of electronic and thermal Free Energies=         -291.100501

Version=AM64L-G03RevE.01\State=1-A\HF=-291.2570918\RMSD=3.883e-09\
RMSF=1.706e-06\PG=C01 [X(C6H13N1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.027879	0.000000	0.314566
2	6	0	0.311755	-1.255831	-0.184771
3	6	0	-1.166811	-1.263886	0.213705
4	6	0	-1.882345	0.000000	-0.271865
5	6	0	-1.166810	1.263886	0.213705
6	6	0	0.311755	1.255830	-0.184770
7	1	0	0.977669	-0.000001	1.408423
8	7	0	2.403129	-0.000001	-0.165832
9	1	0	0.807823	-2.142324	0.205819
10	1	0	0.406985	-1.294678	-1.267168
11	1	0	-1.250596	-1.330287	1.297424
12	1	0	-1.653279	-2.148297	-0.188138
13	1	0	-2.914955	0.000001	0.066754
14	1	0	-1.910563	0.000001	-1.360172
15	1	0	-1.250595	1.330287	1.297424
16	1	0	-1.653278	2.148298	-0.188138
17	1	0	0.807824	2.142323	0.205821
18	1	0	0.406986	1.294678	-1.267167
19	1	0	2.895770	-0.804699	0.173269
20	1	0	2.895767	0.804704	0.173257

```
Temperature=          298.150000 Pressure=                    1.000000
E(ZPE)=                 0.179721 E(Thermal)=                  0.186955
E(QCISD(T))=         -290.285902 E(Empiric)=                 -0.134106
DE(Plus)=              -0.018261 DE(2DF)=                    -0.282306
E(Delta-G3)=           -0.399288 E(G3-Empiric)=              -0.134106
G3(0 K)=             -290.940141 G3 Energy=                -290.932908
G3 Enthalpy=         -290.931963 G3 Free Energy=           -290.970724

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-290.1789047\
QCISD(T)/6-31G(d)=-290.2859016\MP4/6-31G(d)=-290.2830734\
MP2/6-31+G(d)=-290.1959468\MP4/6-31+G(d)=-290.3013341\
MP2/6-31G(2df,p)=-290.4457786\MP4/6-31G(2df,p)=-290.5653799\
MP2/GTLarge=-290.8621083\G3=-290.940141\PG=C01
[X(C6H13N1)]\NImag=0\\@.
```

II. Axial substituent

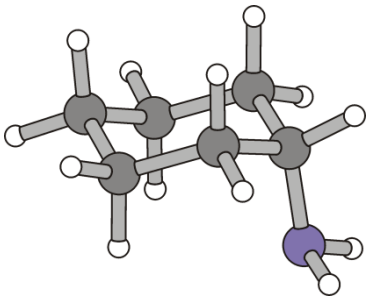

Figure S7.64. Calculated minimum structure of the axial cyclohexanamine conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.282239	-1.266619	0.609552
2	6	0	1.147128	0.000001	0.460276
3	6	0	0.282238	1.266622	0.609549
4	6	0	-0.942389	1.268164	-0.319957
5	6	0	-1.789463	-0.000001	-0.127898
6	6	0	-0.942388	-1.268164	-0.319954
7	7	0	1.796041	0.000000	-0.863039
8	1	0	1.889510	0.000003	1.278028
9	1	0	0.900728	2.157113	0.430221
10	1	0	-0.051541	1.329439	1.654868
11	1	0	-0.605435	1.322272	-1.361956
12	1	0	-1.548218	2.163298	-0.130724
13	1	0	-2.635676	-0.000001	-0.826251
14	1	0	-2.220327	0.000000	0.885138
15	1	0	-0.605436	-1.322275	-1.361954
16	1	0	-1.548214	-2.163301	-0.130719
17	1	0	0.900729	-2.157111	0.430227
18	1	0	-0.051541	-1.329432	1.654870
19	1	0	2.389457	-0.818493	-0.974950
20	1	0	2.389488	0.818473	-0.974936

```
Zero-point correction=                          0.187181
(Hartree/Particle)
Thermal correction to Energy=                   0.194171
Thermal correction to Enthalpy=                 0.195115
Thermal correction to Gibbs Free Energy=        0.156798
Sum of electronic and zero-point Energies=           -291.067824
Sum of electronic and thermal Energies=              -291.060833
Sum of electronic and thermal Enthalpies=            -291.059889
Sum of electronic and thermal Free Energies=         -291.098206

Version=AM64L-G03RevE.01\State=1-A\HF=-291.2550042\RMSD=5.133e-09\
RMSF=1.650e-06\PG=C01 [X(C6H13N1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.284196	-1.259466	0.611878
2	6	0	1.144214	0.000000	0.453099
3	6	0	0.284195	1.259467	0.611877
4	6	0	-0.934039	1.263808	-0.316274
5	6	0	-1.778057	0.000000	-0.129133
6	6	0	-0.934038	-1.263809	-0.316274
7	7	0	1.771330	0.000000	-0.865336
8	1	0	1.890492	0.000000	1.251133
9	1	0	0.894776	2.142989	0.435524
10	1	0	-0.048339	1.318729	1.646656
11	1	0	-0.601289	1.325091	-1.347253
12	1	0	-1.536455	2.147769	-0.122399
13	1	0	-2.611003	-0.000001	-0.827207
14	1	0	-2.211096	0.000000	0.870841
15	1	0	-0.601288	-1.325091	-1.347252
16	1	0	-1.536453	-2.147770	-0.122399
17	1	0	0.894777	-2.142988	0.435525
18	1	0	-0.048338	-1.318727	1.646656
19	1	0	2.358036	-0.805120	-0.976756
20	1	0	2.358039	0.805118	-0.976754

```
Temperature=         298.150000 Pressure=                  1.000000
E(ZPE)=                0.179957 E(Thermal)=                0.187126
E(QCISD(T))=        -290.285516 E(Empiric)=               -0.134106
DE(Plus)=             -0.017046 DE(2DF)=                  -0.282497
E(Delta-G3)=          -0.399307 E(G3-Empiric)=            -0.134106
G3(0 K)=            -290.938514 G3 Energy=              -290.931346
G3 Enthalpy=        -290.930402 G3 Free Energy=         -290.968984

Version=AM64L-G03RevE.01\State=1-A'\MP2/6-31G(d)=-290.1786662\
QCISD(T)/6-31G(d)=-290.2855161\MP4/6-31G(d)=-290.2827273\
MP2/6-31+G(d)=-290.1944551\MP4/6-31+G(d)=-290.2997729\
MP2/6-31G(2df,p)=-290.4457283\MP4/6-31G(2df,p)=-290.5652243\
MP2/GTLarge=-290.8608241\G3=-290.9385143\PG=CS [SG(C2H3N1),X(C4H10)]\
NImag=0\\@.
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7.7.6 Cyclohexanethiol

I. Equatorial substituent

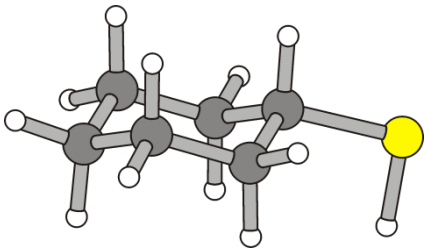


Figure S7.65. Calculated minimum structure of the equatorial cyclohexanethiol conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.077177	1.270192	0.153233
2	6	0	-0.620054	-0.000001	-0.358144
3	6	0	0.077181	-1.270189	0.153238
4	6	0	1.575676	-1.268003	-0.200997
5	6	0	2.278237	-0.000002	0.307750
6	6	0	1.575674	1.268005	-0.200992
7	16	0	-2.439498	0.000000	-0.014017
8	1	0	-0.590366	-0.000004	-1.456256
9	1	0	-0.416859	-2.156726	-0.258167
10	1	0	-0.038070	-1.322702	1.245725
11	1	0	1.688688	-1.332155	-1.293030
12	1	0	2.053680	-2.164013	0.213486
13	1	0	3.331045	0.000002	0.000106
14	1	0	2.273464	-0.000004	1.407558
15	1	0	1.688701	1.332165	-1.293024
16	1	0	2.053684	2.164008	0.213500
17	1	0	-0.416860	2.156726	-0.258179
18	1	0	-0.038079	1.322716	1.245721
19	1	0	-2.340400	-0.000010	1.332310

```
Zero-point correction=                          0.169248
(Hartree/Particle)
Thermal correction to Energy=                   0.176686
Thermal correction to Enthalpy=                 0.177630
Thermal correction to Gibbs Free Energy=        0.137700
Sum of electronic and zero-point Energies=           -633.921809
Sum of electronic and thermal Energies=              -633.914371
Sum of electronic and thermal Enthalpies=            -633.913427
Sum of electronic and thermal Free Energies=         -633.953358

Version=AM64L-G03RevE.01\State=1-A\HF=-634.0910575\RMSD=8.483e-09\
RMSF=8.369e-07\PG=C01 [X(C6H12S1)]\NImag=0\\@.
```

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.074198	-1.265705	0.153583
2	6	0	0.621449	0.000001	-0.358436
3	6	0	-0.074198	1.265708	0.153582
4	6	0	-1.565657	1.262500	-0.201185
5	6	0	-2.264752	-0.000002	0.308720
6	6	0	-1.565655	-1.262500	-0.201189
7	16	0	2.419169	0.000001	-0.013176
8	1	0	0.584465	0.000000	-1.444078
9	1	0	0.411815	2.143497	-0.257661
10	1	0	0.038899	1.320546	1.234912
11	1	0	-1.677640	1.324687	-1.282390
12	1	0	-2.040056	2.148916	0.210332
13	1	0	-3.307276	-0.000004	0.003389
14	1	0	-2.258784	-0.000004	1.397522
15	1	0	-1.677633	-1.324684	-1.282394
16	1	0	-2.040052	-2.148920	0.210325
17	1	0	0.411817	-2.143495	-0.257657
18	1	0	0.038895	-1.320540	1.234913
19	1	0	2.346911	-0.000019	1.313161

```
Temperature=          298.150000 Pressure=                    1.000000
E(ZPE)=                 0.162623 E(Thermal)=                  0.170281
E(QCISD(T))=         -632.736147 E(Empiric)=                 -0.134106
DE(Plus)=              -0.013502 DE(2DF)=                    -0.290825
E(Delta-G3)=           -0.668062 E(G3-Empiric)=              -0.134106
G3(0 K)=             -633.680019 G3 Energy=                -633.672361
G3 Enthalpy=         -633.671417 G3 Free Energy=           -633.711726

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-632.6240201\
QCISD(T)/6-31G(d)=-632.7361473\MP4/6-31G(d)=-632.7332835\
MP2/6-31+G(d)=-632.6362478\MP4/6-31+G(d)=-632.7467853\
MP2/6-31G(2df,p)=-632.8959494\MP4/6-31G(2df,p)=-633.0241082\
MP2/GTLarge=-633.5762394\G3=-633.680019\PG=C01
[X(C6H12S1)]\NImag=0\\@.
```

II. Axial substituent

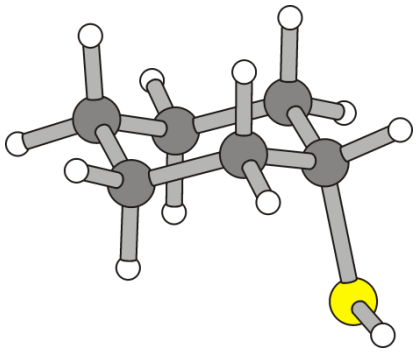


Figure S7.66. Calculated minimum structure of the axial cyclohexanethiol conformer.

(*i*) B3LYP/6-31+G**//B3LYP/6-31+G**

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.692867	0.017029	0.818183
2	6	0	0.180491	-1.251697	0.784704
3	6	0	1.176472	-1.269539	-0.387203
4	6	0	2.039472	0.002477	-0.409458
5	6	0	1.169889	1.270024	-0.428647
6	6	0	0.174848	1.286390	0.742079
7	16	0	-1.950834	-0.091417	-0.557263
8	1	0	-1.269548	0.022985	1.748051
9	1	0	-0.453294	-2.145731	0.771567
10	1	0	0.742447	-1.279940	1.729479
11	1	0	0.630808	-1.355905	-1.335749
12	1	0	1.812106	-2.160112	-0.310843
13	1	0	2.708801	-0.009843	-1.278254
14	1	0	2.684592	0.017309	0.481925
15	1	0	0.616288	1.317528	-1.374577
16	1	0	1.801315	2.165753	-0.384881
17	1	0	-0.460293	2.179122	0.696752
18	1	0	0.734068	1.352005	1.688364
19	1	0	-2.623777	1.031399	-0.233572

Zero-point correction= 0.169352
(Hartree/Particle)
Thermal correction to Energy= 0.176785
Thermal correction to Enthalpy= 0.177729
Thermal correction to Gibbs Free Energy= 0.137799
Sum of electronic and zero-point Energies= -633.918491
Sum of electronic and thermal Energies= -633.911058
Sum of electronic and thermal Enthalpies= -633.910114
Sum of electronic and thermal Free Energies= -633.950044

Version=AM64L-G03RevE.01\State=1-A\HF=-634.0878434\RMSD=8.736e-09\
RMSF=8.181e-07\PG=C01 [X(C6H12S1)]\NImag=0\\@.

(*ii*) G3

Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.697929	0.012686	0.802070
2	6	0	0.177924	-1.249191	0.773089
3	6	0	1.178757	-1.262220	-0.387198
4	6	0	2.037317	0.005665	-0.396384
5	6	0	1.168648	1.266482	-0.422647
6	6	0	0.167182	1.278932	0.735377
7	16	0	-1.943772	-0.089227	-0.550305
8	1	0	-1.260677	0.016750	1.726826
9	1	0	-0.446959	-2.136098	0.750476
10	1	0	0.727594	-1.279010	1.711999
11	1	0	0.649747	-1.348486	-1.332389
12	1	0	1.810518	-2.142126	-0.304238
13	1	0	2.707100	-0.003574	-1.251561
14	1	0	2.667209	0.019472	0.492185
15	1	0	0.634876	1.319078	-1.366610
16	1	0	1.794243	2.152955	-0.365617
17	1	0	-0.463007	2.161749	0.682592
18	1	0	0.712793	1.345670	1.676196
19	1	0	-2.624468	1.007123	-0.240818

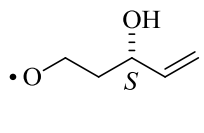
Temperature=	298.150000	Pressure=	1.000000
E(ZPE)=	0.162800	E(Thermal)=	0.170422
E(QCISD(T))=	-632.733483	E(Empiric)=	-0.134106
DE(Plus)=	-0.012855	DE(2DF)=	-0.291713
E(Delta-G3)=	-0.668868	E(G3-Empiric)=	-0.134106
G3(0 K)=	-633.678224	G3 Energy=	-633.670602
G3 Enthalpy=	-633.669657	G3 Free Energy=	-633.709884

Version=AM64L-G03RevE.01\State=1-A\MP2/6-31G(d)=-632.6215419\
QCISD(T)/6-31G(d)=-632.7334828\MP4/6-31G(d)=-632.7306166\
MP2/6-31+G(d)=-632.6331561\MP4/6-31+G(d)=-632.7434713\
MP2/6-31G(2df,p)=-632.8943104\MP4/6-31G(2df,p)=-633.0223294\
MP2/GTLarge=-633.5747923\G3=-
633.6782239\PG=C01[X(C6H12S1)]\NImag=0\\@.

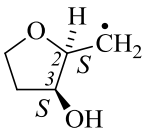
8 Thermochemistry, Structure Data, and Marcus-Analysis

8.1 3-Hydroxy-4-pentenoxyl Radical Cyclization

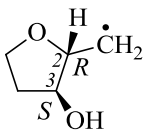
Table S8.1. Energies of pentenoxyl radical **Ia** and 5-*exo* cyclized products *cis*/*trans*-**IIa**



Ia



cis-**IIa**



trans-**IIa**

I/**II** / method [a]	$\langle S^2 \rangle$ [b]	E + ZPVE / a.u. [c]	$G°$ / a.u. [d]
Ia / B3/6-31+G**	0.7537	–346.191960	–346.225548
Ia / BH/6-31+G**	0.7552	–345.985707	–346.019081
Ia / BH/6-311G**	0.7547	–346.051755	–346.085133
cis-**IIa** / B3/6-31+G**	0.7538	–346.203146	–346.235544
cis-**IIa** / BH/6-31+G**	0.7549	–345.998968	–346.031135
cis-**IIa** / BH/6-311G**	0.7551	–346.064600	–346.096627
trans-**IIa** / B3/6-31+G**	0.7539	–346.205963	–346.238814
trans-**IIa** / BH/6-31+G**	0.7553	–346.001634	–346.034551
trans-**IIa** / BH/6-311G**	0.7554	–346.066957	–346.099245

[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Expectation value of spin operator $\hat{S}$. [c] Zero-point vibrational energy-corrected energy at 0 K in atom units. [d] Gibbs free energy for standard conditions (298.15 K, 1 atm) in atom units.

Table S8.2. Reaction energies and Gibbs free energy differences for 5-*exo*-cyclization of 3-hydroxy-4-pentenoxy radical **Ia**

method [a]	ΔE / kJ mol^{-1} [b]	$\Delta G°$ / kJ mol^{-1} [c]	ΔE / kJ mol^{-1} [a]	$\Delta G°$ / kJ mol^{-1} [c]
	Ia→*cis*-**IIa**	**Ia** → *cis*-**IIa**	**Ia**→*trans*-**IIa**	**Ia** → *trans*-**IIa**
B3/6-31+G**	–29.4	–26.2	–36.8	–34.8
BH/6-31+G**	–34.8	–31.6	–41.8	–40.6
BH/6-311G**	–33.7	–30.2	–39.9	–37.1

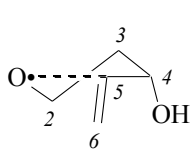
[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Zero-point vibrational energy-corrected reaction energy for 0 K. [c] Gibbs free energy difference for standard conditions; for applied corrections, see section 7.1.

Table S8.3. Energies of relevant transition structures considered for calculating selectivity in 3-hydroxy-4-entenoxyl radical 5-*exo*-cyclization

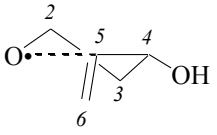
TS / method [a]	$\langle S^2 \rangle$ [b]	*E* + ZPVE / a.u. [c]	*G*° / a.u. [d]
$TS1_{cis}$-**IIa** / B3/6-31+G**	0.7779	–346.181587	–346.212922
$TS1_{cis}$-**IIa** / BH/6-31+G**	0.8256	–345.968405	–345.999561
$TS1_{cis}$-**IIa** / BH/6-311G**	0.8255	–346.034953	–346.065994
$TS2_{cis}$-**IIa** / B3/6-31+G**	0.7807	–346.176895	–346.209050
$TS2_{cis}$-**IIa** / BH/6-31+G**	0.8363	–345.963753	–345.995903
$TS2_{cis}$-**IIa** / BH/6-311G**	0.8367	–346.029686	–346.061768
$TS1_{trans}$-**IIa** / B3/6-31+G**	0.7815	–346.178577	–346.210585
$TS1_{trans}$-**IIa** / BH/6-31+G**	0.8376	–345.965324	–345.997196
$TS1_{trans}$-**IIa** / BH/6-311G**	0.8353	–346.031082	–346.062759
$TS2_{trans}$-**IIa** / B3/6-31+G**	0.7788	–346.180955	–346.212541
$TS2_{trans}$ -**IIa** / BH/6-31+G**	0.8275	–345.967659	–345.999059
$TS2_{trans}$ -**IIa** / BH/6-311G**	0.8272	–346.033012	–346.064376

[a–d] See footnotes for Table S8.1.

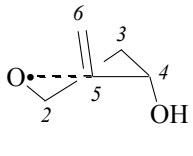
Table S8.4. Imaginary mode of vibration, conformation, and selected geometric parameters of relevant transition structures considered for calculating selectivity in 3-hydroxy-4-pentenoxyl radical 5-*exo*-cyclization



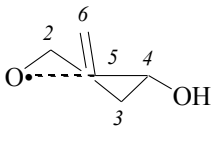
TS1$_{cis}$-**IIa**



TS2$_{cis}$-**IIa**



TS1$_{trans}$-**IIa**



TS2$_{trans}$-**IIa**

TS / method [a]	*i* / cm^{-1}	conf. [b]	O,C2 / Å	O,C5,C6 / deg [c]	H5,C5,C4C6 / deg [c]	O,C4,C5C6 / deg [c]
TS1$_{cis}$-**IIa** / B3	–404	$_2T^3$	2.028	98.3	–160.7	–4.0
TS1$_{cis}$-**IIa** / BH	–557	$_2T^3$	1.977	99.8	–158.3	–6.0
TS1$_{cis}$-**IIa** / BH(T)	–581	$_2T^3$	1.960	100.0	–157.6	–6.6
TS2$_{cis}$-**IIa** / B3	–382	$^2T_3$	2.049	100.3	–162.9	39.2
TS2$_{cis}$-**IIa** / BH	–550	$^2T_3$	1.991	102.1	–159.1	31.5
TS2$_{cis}$-**IIa** / BH(T)	–580	$^2T_3$	1.974	102.5	–158.0	30.2
TS1$_{trans}$-**IIa** / B3	–395	$_2T^3$	2.057	99.4	–163.2	160.8
TS1$_{trans}$-**IIa** / BH	–555	$_2T^3$	1.999	101.1	–159.9	156.3
TS1$_{trans}$-**IIa** / BH(T)	–569	$_2T^3$	1.987	100.6	–159.9	162.0
TS2$_{trans}$-**IIa** / B3	–411	$^2T_3$	2.020	99.8	–159.4	114.5
TS2$_{trans}$-**IIa** / BH	–565	$^2T_3$	1.969	101.2	–157.2	112.7
TS2$_{trans}$-**IIa** / BH(T)	–589	$^2T_3$	1.954	101.3	–156.2	112.9

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] conf. = conformation; T = twist. [c] deg = degrees; sings refer to structures depicted in section 7.5.1.

Table S8.5. Relative Gibbs free activation energies (ΔG°) relative transition structure population (N_i/N_0), and percentage of product formation p_i from a reaction path from equations 1–3 in the associated article

TS / method [a]	ΔG° / kJ mol^{-1}	N_i/N_0	p_i / %
$TS1_{cis}$-**IIa** / B3	≡ 0.00	1.0000	56.53
$TS2_{cis}$-**IIa** / B3	+10.17	0.0165	0.93
$TS1_{trans}$-**IIa** / B3	+6.13	0.0843	4.77
$TS2_{trans}$-**IIa** / B3	+1.00	0.6680	37.77
$TS1_{cis}$-**IIa** / BH3	≡ 0.00	1.0000	59.19
$TS2_{cis}$-**IIa** / BH3	+9.60	0.0208	1.23
$TS1_{trans}$-**IIa** / BH3	+6.21	0.0817	4.83
$TS2_{trans}$-**IIa** / BH3	+1.32	0.5871	34.75
$TS1_{cis}$-**IIa** / BH3(T)	≡ 0.00	1.0000	81.70
$TS2_{cis}$-**IIa** / BH3(T)	+11.10	0.0114	0.93
$TS1_{trans}$-**IIa** / BH3(T)	+8.49	0.0326	2.66
$TS2_{trans}$-**IIa** / BH3(T)	+4.25	0.1801	14.71

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

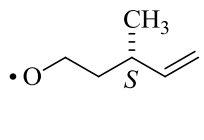
Table S8.6. Approximate location of transition structures for 3-hydroxy-4-pentenoxy cyclization on reaction coordinates, and splitting of energy barrier ($E^{\ddagger}$) into strain-derived intrinsic term $E_S^{\ddagger}$ and thermodynamic term $E_{TD}^{\ddagger}$ from bond braking and forming according to equations 4–6 in the associated article

TS / method [a]	$x^{\ddagger}$	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIa** / B3	0.36	+27.2	40.6	–13.4
TS2$_{cis}$-**IIa** / B3	0.41	+39.6	53.3	–13.7
TS1$_{trans}$-**IIa** / B3	0.37	+35.1	51.9	–16.8
TS2$_{trans}$-**IIa** / B3	0.34	+28.9	45.4	–16.5
TS1$_{cis}$-**IIa** / BH3	0.4	+45.4	61.6	–16.2
TS2$_{cis}$-**IIa** / BH3	0.4	+57.6	74.0	–16.4
TS1$_{trans}$-**IIa** / BH3	0.4	+53.5	72.9	–19.4
TS2$_{trans}$-**IIa** / BH3	0.4	+47.4	66.7	–19.3
TS1$_{cis}$-**IIa** / BH3(T)	0.4	+44.1	59.8	–15.7
TS2$_{cis}$-**IIa** / BH3(T)	0.4	+57.9	73.8	–15.9
TS1$_{trans}$-**IIa** / BH3(T)	0.4	+54.3	72.6	–18.3
TS2$_{trans}$-**IIa** / BH3(T)	0.4	+49.2	67.7	–18.5

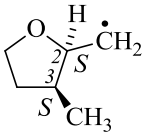
[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

8.2 3-Methyl-4-pentenoxyl Radical Cyclization

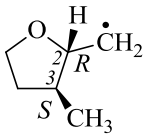
Table S8.7. Energies of pentenoxyl radical **Ib** and 5-*exo* cyclized products *cis*/*trans*-**IIb**



Ib



cis-**IIb**



trans-**IIb**

I/**II** / method [a]	$\langle S^2 \rangle$ [b]	*E* + ZPVE / a.u. [c]	*G*° / a.u. [d]
Ib / B3/6-31+G**	0.7537	–310.263009	–310.297152
Ib / BH/6-31+G**	0.7551	–310.064764	–310.098650
Ib / BH/6-311G**	0.7545	–310.120491	–310.154400
cis-**IIb** / B3/6-31+G**	0.7539	–310.279294	–310.312147
cis-**IIb** / BH/6-31+G**	0.7553	–310.082806	–310.115434
cis-**IIb** / BH/6-311G**	0.7553	–310.138009	–310.170487
trans-**IIb** / B3/6-31+G**	0.7539	–310.281982	–310.314687
trans-**IIb** / BH/6-31+G**	0.7553	–310.085418	–310.117941
trans-**IIb** / BH/6-311G**	0.7554	–310.140362	–310.172810

[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Expectation value of spin operator $\hat{S}$. [c] Zero-point vibrational energy-corrected energy at 0 K in atom units. [d] Gibbs free energy for standard conditions (298.15 K, 1 atm) in atom units.

Table S8.8. Reaction energies and Gibbs free energy differences for 5-*exo*-cyclization of 3-methyl-4-pentenoxyl radical **Ib**

method [a]	ΔE / kJ mol^{-1} [b]	$\Delta G°$ / kJ mol^{-1} [c]	ΔE / kJ mol^{-1} [a]	$\Delta G°$ / kJ mol^{-1} [c]
	Ib→*cis*-**IIb**	**Ib**→*cis*-**IIb**	**Ib**→*trans*-**IIb**	**Ib**→*trans*-**IIb**
B3/6-31+G**	–42.7	–39.4	–49.8	–46.0
BH/6-31+G**	–47.4	–44.1	–54.2	–50.6
BH/6-311G**	–46.0	–42.2	–52.2	–48.3

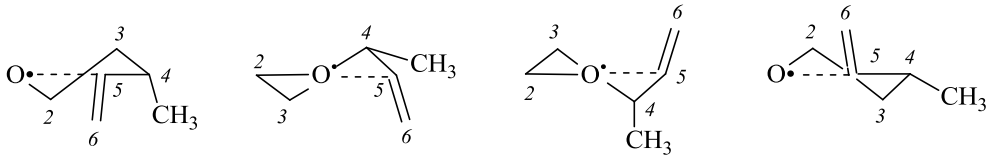
[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Zero-point vibrational energy-corrected reaction energy for 0 K. [c] Gibbs free energy difference for standard conditions; for applied corrections, see section 7.1.

Table S8.9. Energies of relevant transition structures considered for calculating selectivity in 3-methyl-4-entenoxyl radical 5-*exo*-cyclization

TS / method [a]	$\langle S^2 \rangle$ [b]	*E* + ZPVE / a.u. [c]	*G*° / a.u. [d]
$TS1_{cis}$-**IIb** / B3/6-31+G**	0.7789	–310.254549	–310.286141
$TS1_{cis}$-**IIb** / BH/6-31+G**	0.8264	–310.048842	–310.080264
$TS1_{cis}$-**IIb** / BH/6-311G**	0.8262	–310.104223	–310.135607
$TS2_{cis}$-**IIb** / B3/6-31+G**	0.7753	–310.253159	–310.285161
$TS2_{cis}$-**IIb** / BH/6-31+G**	0.8248	–310.047260	–310.079160
$TS2_{cis}$-**IIb** / BH/6-311G**	0.8234	–310.102784	–310.134659
$TS1_{trans}$-**IIb** / B3/6-31+G**	0.7767	–310.253737	–310.285834
$TS1_{trans}$-**IIb** / BH/6-31+G**	0.8269	–310.047772	–310.079800
$TS1_{trans}$-**IIb** / BH/6-311G**	0.8241	–310.103229	–310.135206
$TS2_{trans}$-**IIb** / B3/6-31+G**	0.7782	–310.257726	–310.289527
$TS2_{trans}$-**IIb** / BH/6-31+G**	0.8260	–310.052015	–310.083646
$TS2_{trans}$-**IIb** / BH/6-311G**	0.8261	–310.107303	–310.138902

[a–d] See footnotes for Table S8.7.

Table S8.10. Imaginary mode of vibration, conformation, and selected geometric parameters of relevant transition structures considered for calculating selectivity in 3-methyl-4-pentenoxyl radical 5-*exo*-cyclization



TS1$_{cis}$-**IIb** *TS2*$_{cis}$-**IIb** *TS1*$_{trans}$-**IIb** *TS2*$_{trans}$-**IIb**

TS / method [a]	*i* / cm^{-1}	conf. [b]	O,C2 / Å	O,C5,C6 / deg [c]	H5,C5,C4C6 / deg [c]	C,C4,C5C6 / deg [c]
TS1$_{cis}$-**IIb** / B3	–391	$_2$T^3	2.037	99.1	–161.0	–4.0
TS1$_{cis}$-**IIb** / BH	–537	$_2$T^3	1.991	100.2	–159.0	–5.8
TS1$_{cis}$-**IIb** / BH(T)	–564	$_2$T^3	1.973	100.2	–158.2	–4.9
TS2$_{cis}$-**IIb** / B3	–313	$_3$T^4	2.086	96.4	–166.1	58.6
TS2$_{cis}$-**IIb** / BH	–485	$_3$T^4	2.021	98.5	–162.8	55.7
TS2$_{cis}$-**IIb** / BH(T)	–511	$_3$T^4	2.001	98.5	–162.1	57.2
TS1$_{trans}$-**IIb** / B3	–323	^{3}T$_4$	2.090	97.6	–165.8	165.5
TS1$_{trans}$-**IIb** / BH	–493	^{3}T$_4$	2.026	99.5	–162.6	163.7
TS1$_{trans}$-**IIb** / BH(T)	–513	^{3}T$_4$	2.007	99.6	–162.4	168.1
TS2$_{trans}$-**IIb** / B3	–374	^{2}T$_3$	2.046	98.8	–161.2	110.5
TS2$_{trans}$-**IIb** / BH	–526	^{2}T$_3$	1.994	100.2	–158.9	109.2
TS2$_{trans}$-**IIb** / BH(T)	–553	^{2}T$_3$	1.976	100.3	–158.1	109.2

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] conf. = conformation; T = twist. [c] deg = degrees; sings refer to structures depicted in section 7.5.2.

Table S8.11. Relative Gibbs free activation energies ($\Delta G°$) relative transition structure population (N_i/N_0), and percentage of product formation p_i from a reaction path from equations 1–3 in the associated article

TS / method [a]	ΔG° / kJ mol^{-1}	N_i/N_0	p_i / %
$TS1_{cis}$-**IIb** / B3	+8.89	0.0277	2.62
$TS2_{cis}$-**IIb** / B3	+11.46	0.0098	0.93
$TS1_{trans}$-**IIb** / B3	+9.70	0.0200	1.89
$TS2_{trans}$-**IIb** / B3	≡ 0.00	1.0000	94.56
$TS1_{cis}$-**IIb** / BH3	+8.88	0.0278	2.64
$TS2_{cis}$-**IIb** / BH3	+11.78	0.0086	0.81
$TS1_{trans}$-**IIb** / BH3	+10.10	0.0170	1.61
$TS2_{trans}$-**IIb** / BH3	≡ 0.00	1.0000	94.93
$TS1_{cis}$-**IIb** / BH3(T)	+8.65	0.0305	2.87
$TS2_{cis}$-**IIb** / BH3(T)	+11.14	0.0112	1.05
$TS1_{trans}$-**IIb** / BH3(T)	+9.70	0.0200	1.88
$TS2_{trans}$-**IIb** / BH3(T)	≡ 0.00	1.0000	94.19

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

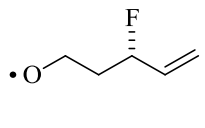
Table S8.12. Approximate location of transition structures for 3-methyl-4-pentenoxy cyclization on reaction coordinates, and splitting of energy barrier ($E^{\ddagger}$) into strain-derived intrinsic term $E_S^{\ddagger}$ and thermodynamic term $E_{TD}^{\ddagger}$ from bond braking and forming according to equations 4–6 in the associated article

TS / method [a]	$x^{\ddagger}$	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIb** / B3	0.3	22.2	40.8	–18.6
TS2$_{cis}$-**IIb** / B3	0.3	25.9	44.7	–18.8
TS1$_{trans}$-**IIb** / B3	0.2	24.3	45.9	–21.5
TS2$_{trans}$-**IIb** / B3	0.1	13.9	34.3	–20.4
TS1$_{cis}$-**IIb** / BH3	0.4	41.8	63.3	–21.5
TS2$_{cis}$-**IIb** / BH3	0.4	46.0	67.6	–21.6
TS1$_{trans}$-**IIb** / BH3	0.3	44.6	69.0	–24.4
TS2$_{trans}$-**IIb** / BH3	0.3	33.5	57.4	–23.9
TS1$_{cis}$-**IIb** / BH3(T)	0.4	42.7	63.6	–20.9
TS2$_{cis}$-**IIb** / BH3(T)	0.4	46.5	67.5	–21.0
TS1$_{trans}$-**IIb** / BH3(T)	0.4	45.3	68.9	–23.6
TS2$_{trans}$-**IIb** / BH3(T)	0.3	34.6	57.8	–23.2

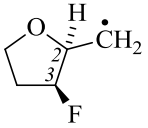
[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

8.3 3-Fluoro-4-pentenoxyl Radical Cyclization

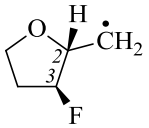
Table S8.13. Energies of pentenoxyl radical **Ih** and 5-*exo* cyclized products *cis*/*trans*-**IIh**



Ih



cis-**IIh**



trans-**IIh**

I/II / method [a]	$\langle S^2 \rangle$ [b]	E + ZPVE / a.u. [c]	$G°$ / a.u. [d]
Ih / B3/6-31+G**	0.7537	–370.224241	–370.257828
Ih / BH/6-31+G**	0.7551	–370.020509	–370.053895
Ih / BH/6-311G**	0.7545	–370.092337	–370.125714
cis-**IIh** / B3/6-31+G**	0.7539	–370.238724	–370.270992
cis-**IIh** / BH/6-31+G**	0.7553	–370.037054	–370.069038
cis-**IIh** / BH/6-311G**	0.7553	–370.108651	–370.140533
trans-**IIh** / B3/6-31+G**	0.7539	–370.240654	–370.272979
trans-**IIh** / BH/6-31+G**	0.7553	–370.038905	–370.071062
trans-**IIh** / BH/6-311G**	0.7554	–370.110064	–370.142036

[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Expectation value of spin operator $\hat{S}$. [c] Zero-point vibrational energy-corrected energy at 0 K in atom units. [d] Gibbs free energy for standard conditions (298.15 K, 1 atm) in atom units.

Table S8.14. Reaction energies and Gibbs free energy differences for 5-*exo*-cyclization of 3-fluoro-4-pentenoxyl radical **Ih**

method [a]	ΔE / kJ mol^{-1} [b]	$\Delta G°$ / kJ mol^{-1} [c]	ΔE / kJ mol^{-1} [a]	$\Delta G°$ / kJ mol^{-1} [c]
	Ih→*cis*-**IIh**	**Ih**→*cis*-**IIh**	**Ih**→*trans*-**IIh**	**Ih**→*trans*-**IIh**
B3/6-31+G**	–38.0	–34.6	–43.1	–39.8
BH/6-31+G**	–43.4	–39.8	–48.3	–45.1
BH/6-311G**	–42.8	–38.9	–46.5	–42.9

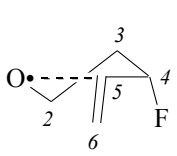
[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Zero-point vibrational energy-corrected reaction energy for 0 K. [c] Gibbs free energy difference for standard conditions; for applied corrections, see section 7.1.

Table S8.15. Energies of relevant transition structures considered for calculating selectivity in 3-fluoro-4-entenoxyl radical 5-*exo*-cyclization

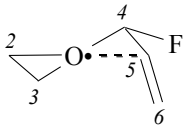
TS / method [a]	$\langle S^2 \rangle$ [b]	*E* + ZPVE / a.u. [c]	*G*° / a.u. [d]
$TS1_{cis}$-**IIh** / B3/6-31+G**	0.7786	–370.215891	–370.247077
$TS1_{cis}$-**IIh** / BH/6-31+G**	0.8269	–370.005241	–370.036250
$TS1_{cis}$-**IIh** / BH/6-311G**	0.8269	–370.077616	–370.108540
$TS2_{cis}$-**IIh** / B3/6-31+G**	0.7809	–370.209614	–370.241892
$TS2_{cis}$-**IIh** / BH/6-31+G**	0.8384	–369.999105	–370.031173
$TS2_{cis}$-**IIh** / BH/6-311G**	0.8390	–370.070769	–370.102733
$TS1_{trans}$-**IIh** / B3/6-31+G**	0.7803	–370.212801	–370.244551
$TS1_{trans}$-**IIh** / BH/6-31+G**	0.8359	–370.002025	–370.033651
$TS1_{trans}$-**IIh** / BH/6-311G**	0.8332	–370.073722	–370.105179
$TS2_{trans}$-**IIh** / B3/6-31+G**	0.7788	–370.213187	–370.244702
$TS2_{trans}$-**IIh** / BH/6-31+G**	0.8280	–370.002405	–370.033750
$TS2_{trans}$-**IIh** / BH/6-311G**	0.8276	–370.073592	–370.104896

[a–d] See footnotes for Table S8.13.

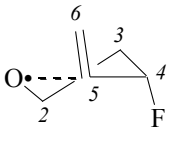
Table S8.16. Imaginary mode of vibration, conformation, and selected geometric parameters of relevant transition structures considered for calculating selectivity in 3-fluoro-4-pentenoxyl radical 5-*exo*-cyclization



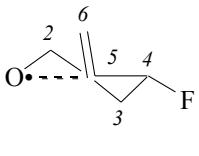
TS1-cis-**IIh**



TS2-cis-**IIh**



TS1-trans-**IIh**



TS2-trans-**IIh**

TS / method [a]	*i* / cm^{-1}	conf. [b]	O,C2 / Å	O,C5,C6 / deg [c]	H5,C5,C4C6 / deg [c]	F,C4,C5C6 / deg [c]
TS1$_{cis}$-**IIh** / B3	–394	$_2T^3$	2.037	100.1	–160.9	–5.2
TS1$_{cis}$-**IIh** / BH	–543	$_2T^3$	1.987	101.5	–158.5	–7.3
TS1$_{cis}$-**IIh** / BH(T)	–569	$_2T^3$	1.970	101.5	–157.8	–8.2
TS2$_{cis}$-**IIh** / B3	–370	$_3T^4$	2.054	100.9	–162.9	41.2
TS2$_{cis}$-**IIh** / BH	–550	$^2T_3$	1.993	104.1	–157.4	15.3
TS2$_{cis}$-**IIh** / BH(T)	–579	$^2T_3$	1.976	104.4	–156.4	15.5
TS1$_{trans}$-**IIh** / B3	–374	$_2T^3$	2.070	98.6	–163.7	162.7
TS1$_{trans}$-**IIh** / BH	–535	$_2T^3$	2.010	100.4	–160.3	158.6
TS1$_{trans}$-**IIh** / BH(T)	–552	$_2T^3$	1.995	100.0	–160.0	164.0
TS2$_{trans}$-**IIh** / B3	–409	$^2T_3$	2.022	99.5	–160.3	116.1
TS2$_{trans}$-**IIh** / BH	–557	$^2T_3$	1.974	101.0	–158.0	114.3
TS2$_{trans}$-**IIh** / BH(T)	–580	$^2T_3$	1.959	100.9	–157.2	115.1

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] conf. = conformation; T = twist. [c] deg = degrees; sings refer to structures depicted in section 7.5.3.

Table S8.17. Relative Gibbs free activation energies ($\Delta G°$) relative transition structure population (N_i/N_0), and percentage of product formation p_i from a reaction path from equations 1–3 in the associated article

TS / method [a]	ΔG° / kJ mol^{-1}	N_i/N_0	p_i / %
$TS1_{cis}$-**IIh** / B3	≡ 0.00	1.0000	87.54
$TS2_{cis}$-**IIh** / B3	13.61	0.0041	0.36
$TS1_{trans}$-**IIh** / B3	6.63	0.0689	6.04
$TS2_{trans}$-**IIh** / B3	6.62	0.0692	6.06
$TS1_{cis}$-**IIh** / BH3	≡ 0.00	1.0000	87.77
$TS2_{cis}$-**IIh** / BH3	13.33	0.0046	0.41
$TS1_{trans}$-**IIh** / BH3	6.82	0.0638	5.60
$TS2_{trans}$-**IIh** / BH3	6.56	0.0709	6.22
$TS1_{cis}$-**IIh** / BH3(T)	≡ 0.00	1.0000	95.09
$TS2_{cis}$-**IIh** / BH3(T)	15.25	0.0021	0.20
$TS1_{trans}$-**IIh** / BH3(T)	8.82	0.0285	2.71
$TS2_{trans}$-**IIh** / BH3(T)	9.57	0.0211	2.00

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

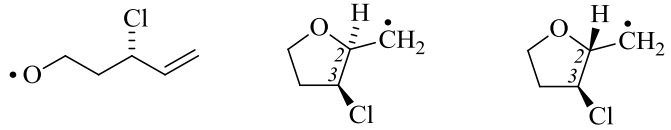
Table S8.18. Approximate location of transition structures for 3-fluoro-4-pentenoxy cyclization on reaction coordinates, and splitting of energy barrier ($E^{\ddagger}$) into strain-derived intrinsic term $E_S^{\ddagger}$ and thermodynamic term $E_{TD}^{\ddagger}$ from bond braking and forming according to equations 4–6 in the associated article

TS / method [a]	x‡	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIh** / B3	0.3	+21.9	38.6	–16.7
TS2$_{cis}$-**IIh** / B3	0.4	+38.4	55.8	–17.4
TS1$_{trans}$-**IIh** / B3	0.3	+30.0	49.2	–19.2
TS2$_{trans}$-**IIh** / B3	0.3	+29.0	48.1	–19.1
TS1$_{cis}$-**IIh** / BH3	0.4	+40.1	59.8	–19.4
TS2$_{cis}$-**IIh** / BH3	0.4	+56.2	76.4	–20.2
TS1$_{trans}$-**IIh** / BH3	0.4	+48.5	70.6	–22.1
TS2$_{trans}$-**IIh** / BH3	0.4	+47.5	69.6	–22.1
TS1$_{cis}$-**IIh** / BH3(T)	0.4	+38.6	58.0	–19.4
TS2$_{cis}$-**IIh** / BH3(T)	0.4	+56.6	76.5	–19.9
TS1$_{trans}$-**IIh** / BH3(T)	0.4	+48.9	70.2	–21.3
TS2$_{trans}$-**IIh** / BH3(T)	0.4	+49.2	70.5	–21.3

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

8.4 3-Chloro-4-pentenoxyl Radical Cyclization

Table S8.19. Energies of pentenoxyl radical **Ii** and 5-*exo* cyclized products *cis*/*trans*-**IIi**



Ii *cis*-**IIi** *trans*-**IIi**

I/II / method [a]	$\langle S^2 \rangle$ [b]	E + ZPVE / a.u. [c]	$G°$ / a.u. [d]
Ii / B3/6-31+G**	0.7537	–730.579868	–730.614198
Ii / BH/6-31+G**	0.7552	–730.398245	–730.432370
Ii / BH/6-311G**	0.7546	–730.473979	–730.508136
cis-**IIi** / B3/6-31+G**	0.7538	–730.593183	–730.626011
cis-**IIi** / BH/6-31+G**	0.7551	–730.413994	–730.446580
cis-**IIi** / BH/6-311G**	0.7552	–730.488944	–730.521502
trans-**IIi** / B3/6-31+G**	0.7538	–730.594649	–730.628667
trans-**IIi** / BH/6-31+G**	0.7552	–730.415530	–730.448960
trans-**IIi** / BH/6-311G**	0.7553	–730.490116	–730.523490

[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Expectation value of spin operator $\hat{S}$. [c] Zero-point vibrational energy-corrected energy at 0 K in atom units. [d] Gibbs free energy for standard conditions (298.15 K, 1 atm) in atom units.

Table S8.20. Reaction energies and Gibbs free energy differences for 5-*exo*-cyclization of 3-chloro-4-pentenoxyl radical **Ii**

method [a]	ΔE / kJ mol^{-1} [b]	$\Delta G°$ / kJ mol^{-1} [c]	ΔE / kJ mol^{-1} [a]	$\Delta G°$ / kJ mol^{-1} [c]
	Ii→*cis*-**IIi**	**Ii**→*cis*-**IIi**	**Ii**→*trans*-**IIi**	**Ii**→*trans*-**IIi**
B3/6-31+G**	–35.0	–31.0	–38.8	–32.9
BH/6-31+G**	–41.3	–37.3	–45.4	–43.6
BH/6-311G**	–39.3	–35.1	–42.4	–40.3

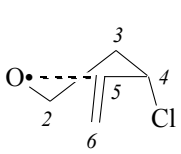
[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Zero-point vibrational energy-corrected reaction energy for 0 K. [c] Gibbs free energy difference for standard conditions; for applied corrections, see section 7.1.

Table S8.21. Energies of relevant transition structures considered for calculating selectivity in 3-chloro-4-entenoxyl radical 5-*exo*-cyclization

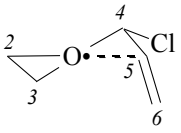
TS / method [a]	$\langle S^2 \rangle$ [b]	*E* + ZPVE / a.u. [c]	*G*° / a.u. [d]
$TS1_{cis}$-**IIi** / B3/6-31+G**	0.7792	–730.569054	–730.601101
$TS1_{cis}$-**IIi** / BH/6-31+G**	0.8279	–730.380509	–730.412370
$TS1_{cis}$-**IIi** / BH/6-311G**	0.8278	–730.455713	–730.487552
$TS2_{cis}$-**IIi** / B3/6-31+G**	0.7770	–730.565733	–730.598434
$TS2_{cis}$-**IIi** / BH/6-31+G**	0.8303	–730.377039	–730.409645
$TS2_{cis}$-**IIi** / BH/6-311G**	0.8290	–730.452351	–730.484956
$TS1_{trans}$-**IIi** / B3/6-31+G**	0.7803	–730.566900	–730.599635
$TS1_{trans}$-**IIi** / BH/6-31+G**	0.8369	–730.378453	–730.411111
$TS1_{trans}$-**IIi** / BH/6-311G**	0.8343	–730.453720	–730.486296
$TS2_{trans}$-**IIi** / B3/6-31+G**	0.7801	–730.570091	–730.602409
$TS2_{trans}$-**IIi** / BH/6-31+G**	0.8302	–730.381662	–730.413798
$TS2_{trans}$-**IIi** / BH/6-311G**	0.8301	–730.456806	–730.488915

[a–d] See footnotes for Table S8.19.

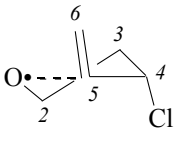
Table S8.22. Imaginary mode of vibration, conformation, and selected geometric parameters of relevant transition structures considered for calculating selectivity in 3-chloro-4-pentenoxyl radical 5-*exo*-cyclization



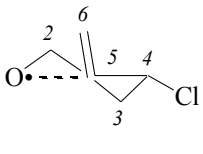
TS1$_{cis}$-**IIi**



TS2$_{cis}$-**IIi**



TS1$_{trans}$-**IIi**



TS2$_{trans}$-**IIi**

TS / method [a]	*i* / cm^{-1}	conf. [b]	O,C2 / Å	O,C5,C6 / deg [c]	H5,C5,C4C6 / deg [c]	Cl,C4,C5C6 / deg [c]
TS1$_{cis}$-**IIi** / B3	–408	$_2T^3$	2.028	100.2	–160.1	–4.8
TS1$_{cis}$-**IIi** / BH	–555	$_2T^3$	1.982	101.5	–157.8	–7.1
TS1$_{cis}$-**IIi** / BH(T)	–582	$_2T^3$	1.964	101.5	–157.1	–6.6
TS2$_{cis}$-**IIi** / B3	–326	$_3T^4$	2.069	98.0	–166.5	59.5
TS2$_{cis}$-**IIi** / BH	–492	$_3T^4$	2.010	100.3	–163.1	55.8
TS2$_{cis}$-**IIi** / BH(T)	–519	$_3T^4$	1.989	100.3	–162.6	57.2
TS1$_{trans}$-**IIi** / B3	–376	$_2T^3$	2.068	98.8	–163.9	158.8
TS1$_{trans}$-**IIi** / BH	–543	$_2T^3$	2.006	100.8	–160.2	152.7
TS1$_{trans}$-**IIi** / BH(T)	–561	$_2T^3$	1.992	100.3	–160.1	157.6
TS2$_{trans}$-**IIi** / B3	–407	$^2T_3$	2.023	100.0	–160.9	109.7
TS2$_{trans}$-**IIi** / BH	–551	$^2T_3$	1.978	101.3	–158.8	108.2
TS2$_{trans}$-**IIi** / BH(T)	–579	$^2T_3$	1.960	101.5	–158.0	108.7

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] conf. = conformation; T = twist. [c] deg = degrees; sings refer to structures depicted in section 7.5.4.

Table S8.23. Relative Gibbs free activation energies ($\Delta G°$) relative transition structure population (N_i/N_0), and percentage of product formation p_i from a reaction path from equations 1–3 in the associated article

TS / method [a]	ΔG° / kJ mol^{-1}	N_i/N_0	p_i / %
$TS1_{cis}$-**IIi** / B3	3.43	0.2507	19.01
$TS2_{cis}$-**IIi** / B3	10.44	0.0148	1.12
$TS1_{trans}$-**IIi** / B3	7.28	0.0530	4.02
$TS2_{trans}$-**IIi** / B3	≡ 0.00	1.0000	75.84
$TS1_{cis}$-**IIi** / BH3	3.75	0.2203	17.07
$TS2_{cis}$-**IIi** / BH3	10.90	0.0123	0.95
$TS1_{trans}$-**IIi** / BH3	7.05	0.0582	4.51
$TS2_{trans}$-**IIi** / BH3	≡ 0.00	1.0000	77.47
$TS1_{cis}$-**IIi** / BH3(T)	3.58	0.2359	17.96
$TS2_{cis}$-**IIi** / BH3(T)	10.39	0.0151	1.15
$TS1_{trans}$-**IIi** / BH3(T)	6.88	0.0623	4.75
$TS2_{trans}$-**IIi** / BH3(T)	≡ 0.00	1.0000	76.14

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

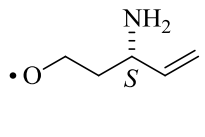
Table S8.24. Approximate location of transition structures for 3-chloro-4-pentenoxy cyclization on reaction coordinates, and splitting of energy barrier ($E^{\ddagger}$) into strain-derived intrinsic term $E_S^{\ddagger}$ and thermodynamic term $E_{TD}^{\ddagger}$ from bond braking and forming according to equations 4–6 in the associated article

TS / method [a]	x‡	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIi** / B3	0.3	28.4	44.2	–15.8
TS2$_{cis}$-**IIi** / B3	0.4	37.1	53.2	–16.1
TS1$_{trans}$-**IIi** / B3	0.4	34.0	51.6	–17.6
TS2$_{trans}$-**IIi** / B3	0.3	25.7	42.9	–17.2
TS1$_{cis}$-**IIi** / BH3	0.4	46.6	65.6	–19.0
TS2$_{cis}$-**IIi** / BH3	0.4	55.7	74.9	–19.2
TS1$_{trans}$-**IIi** / BH3	0.4	52.0	72.9	–20.9
TS2$_{trans}$-**IIi** / BH3	0.4	43.5	64.2	–20.7
TS1$_{cis}$-**IIi** / BH3(T)	0.4	48.0	66.2	–18.2
TS2$_{cis}$-**IIi** / BH3(T)	0.4	56.8	75.2	–18.4
TS1$_{trans}$-**IIi** / BH3(T)	0.4	53.2	72.9	–19.7
TS2$_{trans}$-**IIi** / BH3(T)	0.4	45.1	64.6	–19.5

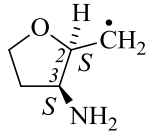
[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

8.5 3-Amino-4-pentenoxyl Radical Cyclization

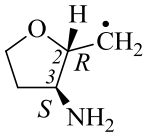
Table S8.25. Energies of pentenoxyl radical **Io** and 5-*exo* cyclized products *cis*/*trans*-**IIo**



Io



cis-**IIo**



trans-**IIo**

I/**II** / method [a]	$\langle S^2 \rangle$ [b]	E + ZPVE / a.u. [c]	$G°$ / a.u. [d]
Io / B3/6-31+G**	0.7539	–326.312481	–326.346119
Io / BH/6-31+G**	0.7554	–326.108343	–326.141872
Io / BH/6-311G**	0.7547	–326.168067	–326.201541
cis-**IIo** / B3/6-31+G**	0.7539	–326.325604	–326.357610
cis-**IIo** / BH/6-31+G**	0.7553	–326.124215	–326.156010
cis-**IIo** / BH/6-311G**	0.7554	–326.182839	–326.214616
trans-**IIo** / B3/6-31+G**	0.7539	–326.326894	–326.359547
trans-**IIo** / BH/6-31+G**	0.7553	–326.125473	–326.157902
trans-**IIo** / BH/6-311G**	0.7554	–326.183713	–326.216053

[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Expectation value of spin operator $\hat{S}$. [c] Zero-point vibrational energy-corrected energy at 0 K in atom units. [d] Gibbs free energy for standard conditions (298.15 K, 1 atm) in atom units.

Table S8.26. Reaction energies and Gibbs free energy differences for 5-*exo*-cyclization of 3-amino-4-pentenoxyl radical **Io**

method [a]	ΔE / kJ mol^{-1} [b]	$\Delta G°$ / kJ mol^{-1} [c]	ΔE / kJ mol^{-1} [a]	$\Delta G°$ / kJ mol^{-1} [c]
	Io→*cis*-**IIo**	**Io**→*cis*-**IIo**	**Io**→*trans*-**IIo**	**Io**→*trans*-**IIo**
B3/6-31+G**	–34.5	–30.2	–37.8	–35.3
BH/6-31+G**	–41.7	–37.1	–45.0	–42.1
BH/6-311G**	–38.8	–34.3	–41.1	–38.1

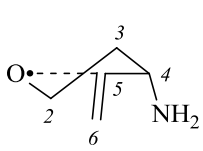
[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Zero-point vibrational energy-corrected reaction energy for 0 K. [c] Gibbs free energy difference for standard conditions; for applied corrections, see section 7.1.

Table S8.27. Energies of relevant transition structures considered for calculating selectivity in 3-amino-4-entenoxyl radical 5-*exo*-cyclization

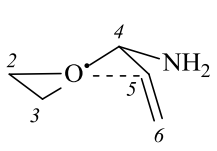
TS / method [a]	$\langle S^2 \rangle$ [b]	*E* + ZPVE / a.u. [c]	*G*° / a.u. [d]
$TS1_{cis}$-**IIo** / B3/6-31+G**	0.7789	–326.301309	–326.332787
$TS1_{cis}$-**IIo** / BH/6-31+G**	0.8266	–326.090582	–326.121887
$TS1_{cis}$-**IIo** / BH/6-311G**	0.8263	–326.150059	–326.181294
$TS2_{cis}$-**IIo** / B3/6-31+G**	0.7759	–326.297544	–326.329669
$TS2_{cis}$-**IIo** / BH/6-31+G**	0.8277	–326.086805	–326.118876
$TS2_{cis}$-**IIo** / BH/6-311G**	0.8260	–326.145904	–326.177905
$TS1_{trans}$-**IIo** / B3/6-31+G**	0.7746	–326.299818	–326.331913
$TS1_{trans}$-**IIo** / BH/6-31+G**	0.8214	–326.088892	–326.120792
$TS1_{trans}$-**IIo** / BH/6-311G**	0.8198	–326.148167	–326.179935
$TS2_{trans}$-**IIo** / B3/6-31+G**	0.7785	–326.302708	–326.334375
$TS2_{trans}$-**IIo** / BH/6-31+G**	0.8264	–326.092007	–326.123499
$TS2_{trans}$-**IIo** / BH/6-311G**	0.8264	–326.150735	–326.182182

[a–d] See footnotes for Table S8.25.

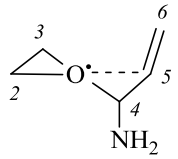
Table S8.28. Imaginary mode of vibration, conformation, and selected geometric parameters of relevant transition structures considered for calculating selectivity in 3-amino-4-pentenoxyl radical 5-*exo*-cyclization



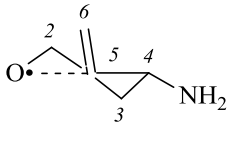
TS1$_{cis}$-**IIo**



TS2$_{cis}$-**IIo**



TS1$_{trans}$-**IIo**



TS2$_{trans}$-**IIo**

TS / method [a]	*i* / cm^{-1}	conf. [b]	O,C2 / Å	O,C5,C6 / deg [c]	H5,C5,C4C6 / deg [c]	N,C4,C5C6 / deg [c]
TS1$_{cis}$-**IIo** / B3	–393	$_2T^3$	2.037	99.6	–160.7	–6.7
TS1$_{cis}$-**IIo** / BH	–541	$_2T^3$	1.990	100.7	–158.6	–8.8
TS1$_{cis}$-**IIo** / BH(T)	–567	$_2T^3$	1.971	100.7	–157.9	–8.1
TS2$_{cis}$-**IIo** / B3	–322	$_3T^4$	2.081	97.2	–165.9	57.1
TS2$_{cis}$-**IIo** / BH	–501	$_3T^4$	2.012	99.4	–162.3	53.6
TS2$_{cis}$-**IIo** / BH(T)	–525	$_3T^4$	1.993	99.5	–161.5	55.1
TS1$_{trans}$-**IIo** / B3	–304	$^3T_4$	2.094	98.6	–166.5	174.2
TS1$_{trans}$-**IIo** / BH	–485	$^3T_4$	2.020	100.6	–163.5	174.4
TS1$_{trans}$-**IIo** / BH(T)	–509	$^3T_4$	1.998	100.9	–163.1	177.9
TS2$_{trans}$-**IIo** / B3	–390	$^2T_3$	2.033	99.5	–159.4	111.0
TS2$_{trans}$-**IIo** / BH	–545	$^2T_3$	1.981	100.8	–157.8	109.9
TS2$_{trans}$-**IIo** / BH(T)	–572	$^2T_3$	1.964	100.9	–156.8	109.6

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] conf. = conformation; T = twist. [c] deg = degrees; sings refer to structures depicted in section 7.5.5.

Table S8.29. Relative Gibbs free activation energies ($\Delta G°$) relative transition structure population (N_i/N_0), and percentage of product formation p_i from a reaction path from equations 1–3 in the associated article

TS / method [a]	ΔG° / kJ mol^{-1}	N_i/N_0	p_i / %
$TS1_{cis}$-**IIo** / B3	+4.17	0.1860	14.69
$TS2_{cis}$-**IIo** / B3	+12.36	0.0066	0.52
$TS1_{trans}$-**IIo** / B3	+6.46	0.0738	5.83
$TS2_{trans}$-**IIo** / B3	≡ 0.00	1.0000	78.97
$TS1_{cis}$-**IIo** / BH3	+4.23	0.1815	14.37
$TS2_{cis}$-**IIo** / BH3	+12.14	0.0075	0.59
$TS1_{trans}$-**IIo** / BH3	+6.46	0.0738	5.85
$TS2_{trans}$-**IIo** / BH3	≡ 0.00	1.0000	79.19
$TS1_{cis}$-**IIo** / BH3(T)	+2.33	0.3907	26.15
$TS2_{cis}$-**IIo** / BH3(T)	+11.23	0.0108	0.72
$TS1_{trans}$-**IIo** / BH3(T)	+5.90	0.0925	6.19
$TS2_{trans}$-**IIo** / BH3(T)	≡ 0.00	1.0000	66.94

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

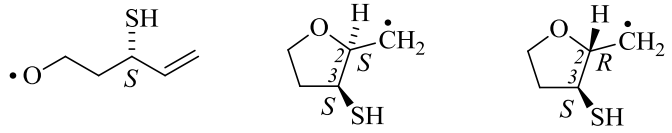
Table S8.30. Approximate location of transition structures for 3-amino-4-pentenoxy cyclization on reaction coordinates, and splitting of energy barrier ($E^{\ddagger}$) into strain-derived intrinsic term $E_S^{\ddagger}$ and thermodynamic term $E_{TD}^{\ddagger}$ from bond braking and forming according to equations 4–6 in the associated article

TS / method [a]	$x^{\ddagger}$	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIo** / B3	0.4	+29.3	44.9	–15.6
TS2$_{cis}$-**IIo** / B3	0.4	+39.2	55.1	–15.9
TS1$_{trans}$-**IIo** / B3	0.4	+33.2	50.3	–17.1
TS2$_{trans}$-**IIo** / B3	0.3	+25.7	42.5	–16.8
TS1$_{cis}$-**IIo** / BH3	0.4	+46.6	65.8	–19.2
TS2$_{cis}$-**IIo** / BH3	0.4	+56.5	75.9	–19.4
TS1$_{trans}$-**IIo** / BH3	0.4	+51.1	71.8	–20.7
TS2$_{trans}$-**IIo** / BH3	0.4	+42.9	63.4	–20.5
TS1$_{cis}$-**IIo** / BH3(T)	0.4	+47.3	65.3	–18.0
TS2$_{cis}$-**IIo** / BH3(T)	0.4	+58.2	76.4	–18.2
TS1$_{trans}$-**IIo** / BH3(T)	0.4	+52.2	71.3	–19.1
TS2$_{trans}$-**IIo** / BH3(T)	0.4	+45.5	64.4	–18.9

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

8.6 3-Mercapto-4-pentenoxyl Radical Cyclization

Table S8.31. Energies of pentenoxyl radical **Ip** and 5-*exo* cyclized products *cis*/*trans*-**IIp**



Ip *cis*-**IIp** *trans*-**IIp**

I/**II** / method [a]	$\langle S^2 \rangle$ [b]	E + ZPVE / a.u. [c]	$G°$ / a.u. [d]
Ip / B3/6-31+G**	0.7538	–669.161736	–669.196601
Ip / BH/6-31+G**	0.7552	–668.973520	–669.008131
Ip / BH/6-311G**	0.7546	–669.047454	–669.082112
cis-**IIp** / B3/6-31+G**	0.7539	–669.174620	–669.207908
cis-**IIp** / BH/6-31+G**	0.7553	–668.988580	–669.021641
cis-**IIp** / BH/6-311G**	0.7554	–669.062180	–669.095295
trans-**IIp** / B3/6-31+G**	0.7538	–669.176503	–669.210616
trans-**IIp**/ BH/6-31+G**	0.7552	–668.990681	–669.024543
trans-**IIp** / BH/6-311G**	0.7553	–669.063847	–669.097705

[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Expectation value of spin operator $\hat{S}$. [c] Zero-point vibrational energy-corrected energy at 0 K in atom units. [d] Gibbs free energy for standard conditions (298.15 K, 1 atm) in atom units.

Table S8.32. Reaction energies and Gibbs free energy differences for 5-*exo*-cyclization of 3-amino-4-pentenoxyl radical **Ip**

method [a]	ΔE / kJ mol^{-1} [b]	$\Delta G°$ / kJ mol^{-1} [c]	ΔE / kJ mol^{-1} [a]	$\Delta G°$ / kJ mol^{-1} [c]
	Ip→*cis*-**IIp**	**Ip**→*cis*-**IIp**	**Ip**→*trans*-**IIp**	**Ip**→*trans*-**IIp**
B3/6-31+G**	–33.8	–29.7	–38.8	–36.8
BH/6-31+G**	–39.5	–35.5	–45.1	–43.1
BH/6-311G**	–8.7	–34.6	–43.0	–40.9

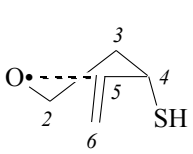
[a] B3/6-31G** = B3LYP/6-31+G**// B3LYP/6-31+G**; BH/6-31G** = BHandHLYP/6-31+G**// BHandHLYP/6-31+G**; BH/6-311G** = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] Zero-point vibrational energy-corrected reaction energy for 0 K. [c] Gibbs free energy difference for standard conditions; for applied corrections, see section 7.1.

Table S8.33. Energies of relevant transition structures considered for calculating selectivity in 3-mercapto-4-entenoxyl radical 5-*exo*-cyclization

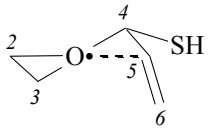
TS / method [a]	$\langle S^2 \rangle$ [b]	*E* + ZPVE / a.u. [c]	*G*° / a.u. [d]
$TS1_{cis}$-**IIp** / B3/6-31+G**	0.7784	–669.150060	–669.182606
$TS1_{cis}$-**IIp** / BH/6-31+G**	0.8261	–668.954754	–668.987078
$TS1_{cis}$-**IIp** / BH/6-311G**	0.8260	–669.028247	–669.060562
$TS2_{cis}$-**IIp** / B3/6-31+G**	0.7769	–669.148733	–669.181815
$TS2_{cis}$-**IIp** / BH/6-31+G**	0.8300	–668.953195	–668.986128
$TS2_{cis}$-**IIp** / BH/6-311G**	0.8288	–669.026800	–669.059708
$TS1_{trans}$-**IIp** / B3/6-31+G**	0.7834	–669.148300	–669.181979
$TS1_{trans}$-**IIp** / BH/6-31+G**	0.8403	–668.953196	–668.986502
$TS1_{trans}$-**IIp** / BH/6-311G**	0.8386	–669.026592	–669.060047
$TS2_{trans}$-**IIp** / B3/6-31+G**	0.7796	–669.153916	–669.186587
$TS2_{trans}$-**IIp** / BH/6-31+G**	0.8285	–668.958687	–668.991165
$TS2_{trans}$-**IIp** / BH/6-311G**	0.8284	–669.032152	–669.064611

[a–d] See footnotes for Table S8.25.

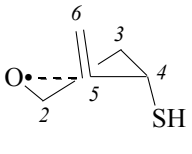
Table S8.34. Imaginary mode of vibration, conformation, and selected geometric parameters of relevant transition structures considered for calculating selectivity in 3-mercapto-4-pentenoxyl radical 5-*exo*-cyclization



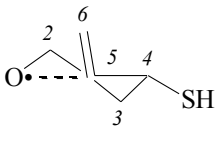
TS1$_{cis}$-**IIp**



TS2$_{cis}$-**IIp**



TS1$_{trans}$-**IIp**



TS2$_{trans}$-**IIp**

TS / method [a]	*i* / cm^{-1}	conf. [b]	O,C2 / Å	O,C5,C6 / deg [c]	H5,C5,C4C6 / deg [c]	S,C4,C5C6 / deg [c]
TS1$_{cis}$-**IIp** / B3	–403	$_2T^3$	2.029	98.8	–160.5	–3.3
TS1$_{cis}$-**IIp** / BH	–552	$_2T^3$	1.981	100.1	–158.3	–5.1
TS1$_{cis}$-**IIp** / BH(T)	–578	$_2T^3$	1.964	100.1	–157.5	–4.4
TS2$_{cis}$-**IIp** / B3	–317	$_3T^4$	2.081	97.2	–166.8	55.5
TS2$_{cis}$-**IIp** / BH	–489	$_3T^4$	2.012	99.4	–163.2	51.4
TS2$_{cis}$-**IIp** / BH(T)	–515	$_3T^4$	1.999	99.4	–162.7	52.9
TS1$_{trans}$-**IIp** / B3	–406	$_2T^3$	2.052	100.5	–162.1	149.5
TS1$_{trans}$-**IIp** / BH	–567	$_2T^3$	1.992	102.6	–158.2	138.0
TS1$_{trans}$-**IIp** / BH(T)	–582	$_2T^3$	1.983	101.5	–157.7	147.6
TS2$_{trans}$-**IIp** / B3	–393	$^2T_3$	2.030	99.7	–160.8	111.1
TS2$_{trans}$-**IIp** / BH	–544	$^2T_3$	1.983	101.0	–158.6	109.8
TS2$_{trans}$-**IIp** / BH(T)	–572	$^2T_3$	1.965	101.1	–157.8	110.1

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**. [b] conf. = conformation; T = twist. [c] deg = degrees; sings refer to structures depicted in section 7.5.6.

Table S8.35. Relative Gibbs free activation energies ($\Delta G°$) relative transition structure population (N_i/N_0), and percentage of product formation p_i from a reaction path from equations 1–3 in the associated article

TS / method [a]	ΔG° / kJ mol^{-1}	N_i/N_0	p_i / %
$TS1_{cis}$-**IIp** / B3	10.45	0.0148	1.42
$TS2_{cis}$-**IIp** / B3	12.53	0.0064	0.61
$TS1_{trans}$-**IIp** / B3	12.09	0.0076	2.02
$TS2_{trans}$-**IIp** / B3	≡ 0.00	1.0000	95.95
$TS1_{cis}$-**IIp** / BH3	10.73	0.0132	1.29
$TS2_{cis}$-**IIp** / BH3	13.22	0.0048	0.47
$TS1_{trans}$-**IIp** / BH3	12.24	0.0072	0.70
$TS2_{trans}$-**IIp** / BH3	≡ 0.00	1.0000	97.54
$TS1_{cis}$-**IIp** / BH3(T)	10.63	0.0137	1.34
$TS2_{cis}$-**IIp** / BH3(T)	12.87	0.0056	0.54
$TS1_{trans}$-**IIp** / BH3(T)	11.98	0.0080	0.78
$TS2_{trans}$-**IIp** / BH3(T)	≡ 0.00	1.0000	97.35

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

Table S8.36. Approximate location of transition structures for 3-mercapto-4-pentenoxy cyclization on reaction coordinates, and splitting of energy barrier ($E^{\ddagger}$) into strain-derived intrinsic term $E_S^{\ddagger}$ and thermodynamic term $E_{TD}^{\ddagger}$ from bond braking and forming according to equations 4–6 in the associated article

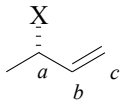
TS / method [a]	$x^{\ddagger}$	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIp** / B3	0.4	30.7	46.0	–15.3
TS2$_{cis}$-**IIp** / B3	0.4	34.1	49.6	–15.5
TS1$_{trans}$-**IIp** / B3	0.4	35.3	53.1	–17.6
TS2$_{trans}$-**IIp** / B3	0.3	20.5	37.4	–16.9
TS1$_{cis}$-**IIp** / BH3	0.4	49.3	67.6	–18.3
TS2$_{cis}$-**IIp** / BH3	0.4	53.4	71.8	–18.4
TS1$_{trans}$-**IIp** / BH3	0.4	53.4	74.2	–20.8
TS2$_{trans}$-**IIp** / BH3	0.4	38.9	59.3	–20.4
TS1$_{cis}$-**IIp** / BH3(T)	0.4	50.4	68.4	–18.0
TS2$_{cis}$-**IIp** / BH3(T)	0.4	54.2	72.3	–18.1
TS1$_{trans}$-**IIp** / BH3(T)	0.4	54.8	74.8	–20.0
TS2$_{trans}$-**IIp** / BH3(T)	0.4	40.2	59.8	–19.6

[a] B3 = B3LYP/6-31+G**// B3LYP/6-31+G**; BH = BHandHLYP/ 6-31+G**// BHandHLYP/6-31+G**; BH(T) = BHandHLYP/6-311G**// BHandHLYP/6-311G**.

9 Polar and Steric Substituent Effects

9.1 HOMO-Energy of Butenes

Table S9.1. Density functional (B3LYP/6-31+G**)-calculated HOMO energies for minimum conformers of butenes

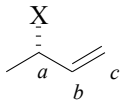


IV

IV	X	X,C_a,C_b,C_c / deg	E^{HOMO} / a.u. [a]	E^{HOMO} / eV [b]
IVa	OH	120.6	–0.27827	–7.57
IVb	CH_3	118.8	–0.26701	–7.27
IVh	F	120.6	–0.28583	–7.80
IVi	Cl	115.5	–0.28557	–7.77
IVi	Cl	115.7	–0.27836	–7.57
IVo	NH_2	116.4	–0.25635	–6.98
IVp	SH	116.9	–0.25311	–6.89
IVq	H	118.9	–0.26659	–7.25

[a] The HOMO in a localized MO-modell is equivalent to the π(C,C)-bond, as concluded from NBO-calculations (B3LYP/6-31+G**// B3LYP/6-31+G**). [b] 1 atom unit (a.u.) in energy = 1 Hartree = 27.2114 eV.

Table S9.2 G3 (MP2/GTLarge/RHF/6-31G*)-calculated HOMO energies for minimum conformers of butenes

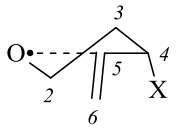


IV

IV	X	X,C_a,C_b,C_c / deg	E^{HOMO} / a.u. [a]	E^{HOMO} / eV [b]
IVa	OH	119.1	–0.37511	–10.21
IVb	CH_3	118.3	–0.35758	–9.72
IVh	F	127.3	–0.38200	–10.39
IVi	Cl	119.1	–0.37656	–10.25
IVo	NH_2	117.7	–0.36126	–9.83
IVp	SH	117.2	–0.35093	–9.55
IVq	H	121.0	–0.35790	–9.74

[a] The HOMO in a localized MO-modell is equivalent to the π(C,C)-bond, as concluded from NBO-calculations (MP2/GTLarge/RHF/6-31G*). For butenethiol **Ip**, the p-type non bonding electron pair at sulfur is the HOMO and the π(C,C)-orbital the HOMO–1. The HOMO–1-energy of butenethiol **Ip** in G3-theory is –0.37547 a.u. (–10.22 eV). [b] 1 atom unit (a.u.) in energy = 1 Hartree = 27.2114 eV.

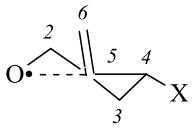
Table 9.3. Compilation of selected structure parameters, imaginary mode of vibration, and activation energies associated with the lowest in energy transition structure for 2,3-*cis*-5-*exo*-cyclization (B3LYP/6-31+G**/B3LYP/6-31+G**)



TS1-cis-**II**

TS1$_{cis}$-**II**	X	X,C3,C4,C5 / deg	O,C5 / Å	*i* / cm^{-1}	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIa**	OH	4.0	2.028	–404	27.2	40.6	–13.4
TS1$_{cis}$-**IIb**	CH_3	4.0	2.037	–391	22.2	40.8	–18.8
TS1$_{cis}$-**IIh**	F	5.2	2.037	–394	21.9	38.6	–16.7
TS1$_{cis}$-**IIi**	Cl	4.8	2.028	–408	28.4	44.2	–15.8
TS1$_{cis}$-**IIo**	NH_2	6.7	2.037	–393	29.3	44.9	–15.6
TS1$_{cis}$-**IIp**	SH	3.3	2.029	–403	30.7	46.0	–15.3
TS1$_{cis}$-**IIq**	H	4.9	2.046	–382	19.8	37.3	–17.5

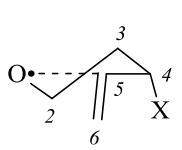
Table 9.4. Compilation of selected structure parameters, imaginary mode of vibration, and activation energies associated with the lowest in energy transition structure for 2,3-*trans*-5-*exo*-cyclization (B3LYP/6-31+G**/B3LYP/6-31+G**)



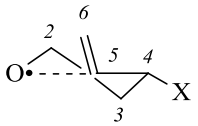
TS2-trans-**II**

TS1$_{cis}$-**II**	X	X,C3,C4,C5 / deg	O,C5 / Å	i / cm^{-1}	$E^{\ddagger}$ / kJ mol^{-1}	$E_S^{\ddagger}$ / kJ mol^{-1}	$E_{TD}^{\ddagger}$ / kJ mol^{-1}
TS1$_{cis}$-**IIa**	OH	114.5	2.020	–411	28.9	45.4	–16.5
TS1$_{cis}$-**IIb**	CH_3	110.0	2.046	–374	13.9	45.9	–21.5
TS1$_{cis}$-**IIh**	F	116.1	2.022	–406	29.0	48.1	–19.1
TS1$_{cis}$-**IIi**	Cl	109.7	2.023	–407	25.7	42.9	–17.2
TS1$_{cis}$-**IIo**	NH_2	111.0	2.033	–390	25.7	42.5	–16.8
TS1$_{cis}$-**IIp**	SH	111.1	2.030	–393	20.5	37.4	–16.9
TS1$_{cis}$-**IIq**	H	112.7	2.046	–382	19.8	37.3	–17.5

Table 9.5. Korrelation relativer freier Aktivierungsenergien mit polaren und sterischen Substituentenparametern (B3LYP/6-31+G**// B3LYP/6-31+G**)



TS1-cis-**II**



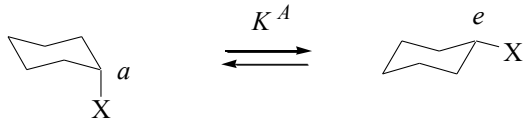
TS2-trans-**II**

TS-**II**	X	$G^{\ddagger}_{cis} - G^{\ddagger}_{trans}$ / kJ mol^{-1} (B3LYP/6-31+G**) [a]	$G^{\ddagger}_{cis} - G^{\ddagger}_{trans}$ / kJ mol^{-1} (BHandHLYP/6-31+G**) [a]	$G^{\ddagger}_{cis} - G^{\ddagger}_{trans}$ / kJ mol^{-1} (BHandHLYP/6-311G**) [a]
TS-**IIa**	OH	–1.00	–1.32	–4.25
TS-**IIb**	CH_3	8.89	8.88	8.65
TS-**IIh**	F	–6.62	–6.56	–9.57
TS-**IIi**	Cl	3.43	3.75	3.58
TS-**IIo**	NH_2	4.17	4.23	2.33
TS-**IIp**	SH	10.45	10.73	10.63

[a] Gibbs free energy difference between lowest transition structure for 2,3-*cis*- and 2,3-*trans*-5-*exo*-cyclization of underlying 4-pentenoxyl radicals **Ia**–**b**, **Ih**–**i**, and **Io**–**p**.

9.2 Winstein-Holness-Parameters for Monosubsituted Cyclohexanes

Table S9.6. Density functional (B3LYP/6-31+G**)-calculated A-Values (Winstein-Holness-parameters) for monosubstituted cyclohexanes



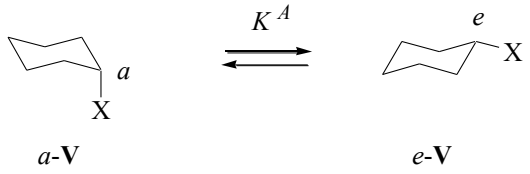
a-**V** *e*-**V**

$$\Delta G = G_e - G_a = -RT \ln K^A = -A$$

V / X	C,X$_a$ / Å	C,X$_e$ / Å	$\Delta G°$ / kJ mol^{-1}	$A_{exp.}$ / kJ mol^{-1} [a]
Va / OH	1.449	1.434	–4.0	4.8 (298)
Vb / CH_3	1.539	1.534	–10.6	7.1 (300)
Vh / F	1.425	1.418	–1.3	0.6 (248)
Vi / Cl	1.851	1.839	–4.5	2.7 (300)
Vo / NH_2	1.476	1.470	–6.0	5.2 (193)
Vp / SH	1.866	1.852	–8.7	5.1 (193)

[a] Experimental data; numbers in brackets refer to valid temperature in Kelvin.[6]

Table S9.7. G3-calculated *A*-Values (Winstein-Holness-parameters) for monosubstituted cyclohexanes



a-**V** *e*-**V**

$$\Delta G = G_e - G_a = -RT \ln K^A = -A$$

V / X	C,X_a / Å	C,X_e / Å	$\Delta G°$ / kJ mol^{-1}	$A_{exp.}$ / kJ mol^{-1} [a]
Va / OH	1.434	1.430	2.6	4.8 (298)
Vb / CH_3	1.528	1.524	8.0	7.1 (300)
Vh / F	1.423	1.401	0.9	0.6 (248)
Vi / Cl	1.805	1.789	1.4	2.7 (300)
Vo / NH_2	1.468	1.465	4.6	5.2 (193)
Vp / SH	1.833	1.824	4.8	5.1 (193)

[a] Experimental data; numbers in brackets refer to valid temperature in Kelvin.[6]

10 References

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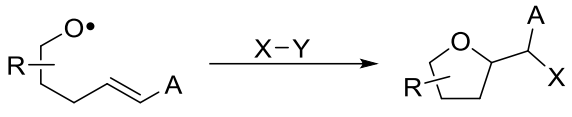
6 Addition an Akzeptor-substituierte C,C-Doppelbindungen

6.1 Zusammenfassung

4-Pentenoxylradikale addieren in einer selektiven 5-*exo*-trig-Reaktion an Cyano- und Ester-substituierte C,C-Doppelbindungen und liefern α-Akzeptor-substituierte Tetrahydrofurane in Ausbeuten von 68−74%. Konkurrenzkinetische Experimente zeigten, dass Alkoxylradikale an Cyano-substituierte Doppelbindungen mit relativen Geschwindigkeitskonstanten addieren vergleichbar mit einer Addition an terminale Alkene. Die Reaktion von O-Radikalen mit Michael-ähnlichen Akzeptor-Systemen resultiert aus einer attraktiven LUMO-SOMO-Wechselwirkung. Diese nucleophile Reaktivität von Alkoxylradikalen wurde zur Darstellung eines N,O-geschützten 5-Phenyltetrahydrofuryl-2-methylglycins genutzt werden. Hierdurch eröffnen sich neue Synthesewege zu Tetrahydrofuran-substituierten Aminosäuren, die bislang ausschließlich über eine ionische Reaktionsführung zugänglich waren.

6.2 Wissenschaftlicher Hintergrund, Zielsetzung und Strategie

In der stereoselektiven Synthesechemie wird die elektrophile Eigenschaft von Alkoxylradikalen genutzt.[1] Die existierenden Richtlinien zur Beschleunigung einer 5-*exo*-trig-Cyclisierung von Pent-4-en-1-oxylradikalen berücksichtigen ausschließlich Donor-Substituenten an der C,C-Doppelbindung.[2,3] Additionen an Michael-ähnliche Akzeptor-Systeme, die aus ionischen Reaktionen bekannt sind, sind für Alkoxylradikale bislang wenig untersucht und würden deren Anwendungsbreite vergrößern. Hierzu gilt zu prüfen, ob ein Sauerstoffradikal in der Lage ist in ausreichend hoher Geschwindigkeit an elektronenarme C,C-Doppelbindungen zu addieren. Die Studie von Guidon *et al.* zeigt erstmals, dass eine Addition von Alkoxylradikalen an endständig Methyl- und Arcylat-substituierte C,C-Doppelbindung möglich ist.[4] Das Reaktionsmodell zur Steuerung der Selektivitäten in 5-*exo*-trig-Cyclisierungen wird auf sterische Effekte zurückgeführt. Durch den Einsatz von Akzeptor-Gruppen wird das bestehende Modell durch einen polaren Effekt erweitert. Um ausschließlich den polaren Effekt von Akzeptor-Substituenten ohne zusätzlichen Einfluss einer aktivierenden Methyl-Gruppe zu analysieren, wurden in der vorliegenden Studie Additionen an C,C-Doppelbindungen mit terminalen Akzeptor-Gruppen untersucht (Schema 6.1).



Schema 6.1 Radikalische Addition an Michael-ähnliche Akzeptor-Systeme zur Untersuchung des polaren Effektes. R = H, Alkyl, Aryl; A = z. B. CN, CO_2CH_3; X–Y = H–$SnBu_3$.

Die Möglichkeit die Reaktivität von Alkoxylradikalen durch polare Substituenteneffekte zu steuern lieferte die Grundlage für ein Projekt mit folgender Aufgabenstellung:

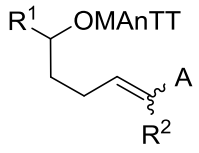
- Untersuchung der intramolekularen Addition von Sauerstoffradikalen an Akzeptor-substituierte C,C-Doppelbindungen.
- Konkurrenzkinetische Studie zur Bestimmung des Akzeptor-Substituenteneinflusses auf die relative Geschwindigkeitskonstante.
- Anwendung der radikalischen C,O-Bindungsknüpfung zur Darstellung von Tetrahydrofuran-substituierten Aminosäuren.

6.3 Ergebnisse und Diskussion

6.3.1 Erzeugung Akzeptor-substituierter Alkenoxylradikale

Zur Untersuchung der nucleophilen Eigenschaft von Alkoxylradikalen wurde die intramolekulare Addition von Pent-4-en-1-oxylradikalen an Cyano- und Ester-substituierte C,C-Doppelbindungen gewählt. Die Synthese der Thiazolthione **1a**–**e** erfolgte ausgehend von den jeweiligen Alkenolen, die zunächst in die entsprechenden Chloride überführt und anschließend mit dem 3-Hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazol-2(3*H*)-thion-Tetraethylammoniumsalz[5] in Ausbeuten zwischen 36–73% substituiert wurden (Tabelle 6.1). Das Thiazolthion **1f** wurde durch die direkte Umsetzung des Alkenols in einer Mitsunobu-Reaktion dargestellt.[6] Eine Phenyl-Gruppe in Position 1 erleichtert aufgrund ihrer UV-Aktivität die spätere Produktanalyse. Um eine Beeinflussung der Cyclisierungsreaktion durch eine Phenyl-Gruppe ausschließen zu können, wird zusätzlich eine Methyl-Gruppe in dieser Position eingeführt.

Tabelle 6.1 Ausbeuten Akzeptor-substituierter *N*-Alkenoxythiazolthione **1a–f**

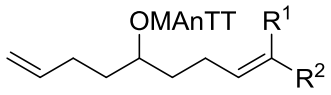


1a–f

Eintrag	**1**	R^1	R^2	A	Ausbeute / %
1	**a**	CH_3	H	CN	36
2	**b**	C_6H_5	H	CN	49
3	**c**	CH_3	H	CO_2CH_3	49
4	**d**	C_6H_5	H	CO_2CH_3	70
5	**e**	C_6H_5	*cyclo*-C_3H_5	CN	73
6	**f**	C_6H_5	NHAc	CO_2CH_3	31

Zur Untersuchung des polaren Substituenteneffektes auf die relative Geschwindigkeit intramolekularer Cyclisierungsreaktionen werden Experimente an konkurrenzkinetischen Dienen **1g–j** durchgeführt. Die Thiazolthione **1g–i** wurden unter Mitsunobu-Bedingungen ausgehend von den jeweiligen Alkenolen in Ausbeuten von 60–67% dargestellt (Tabelle 6.2). Die Synthese der Ester-substituierten Verbindung **1f** verlief über das entsprechende Tosylat, welches dann mit dem 3-Hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazol-2(3*H*)-thion-Tetraethylammoniumsalz in einer Ausbeute von 49% substituiert wurde (Tabelle 6.2).[7]

Tabelle 6.2 Syntheseausbeuten der konkurrenzkinetischen Diene **1g–j**



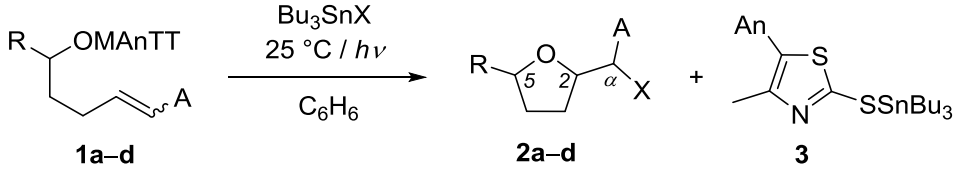
1g–j

Eintrag	**1**	R^1	R^2	Ausbeute / %
1	**g**	CH_3	CH_3	60
2	**h**	H	OCH_3	67
3	**i**	H	CN	63
4	**j**	H	CO_2CH_3	49

6.3.2 Intramolekulare Additionsreaktionen

Die Cyano- und Ester-substituierten Alkenoxylthiazolthione **1a–d** wurden in Gegenwart von Tributylzinnhydrid unter photochemischen Bedingungen (350 nm) zu den Tetrahydrofuran-Derivaten **2a–d** umgesetzt. Die 5-*exo*-Produkte wurden in Ausbeuten von 67–71% mit einem *cis*:*trans*-Verhältnis von 40:60 isoliert (Tabelle 6.3). Das Produkt **3** wurde über ^{1}H-NMR-Spektroskopie aus der Reaktionsmischung quantifiziert, da sich die Verbindung auf Kieselgel zersetzt.[8] Die Additionsreaktionen verliefen selektiv zu den Tetrahydrofuranen, es konnten keine weiteren Produkte identifiziert werden. Durch den Einsatz des Mediators Tributylzinndeuterid konnte gezeigt werden, dass in **2b$_{d1}$** die Deuterierung ausschließlich in α-Position zur Cyano-Gruppe stattfindet (Tabelle 6.3).

Tabelle 6.3 Produktausbeuten bei der reduktiven Umsetzung der Thiazolthione **1a–d**



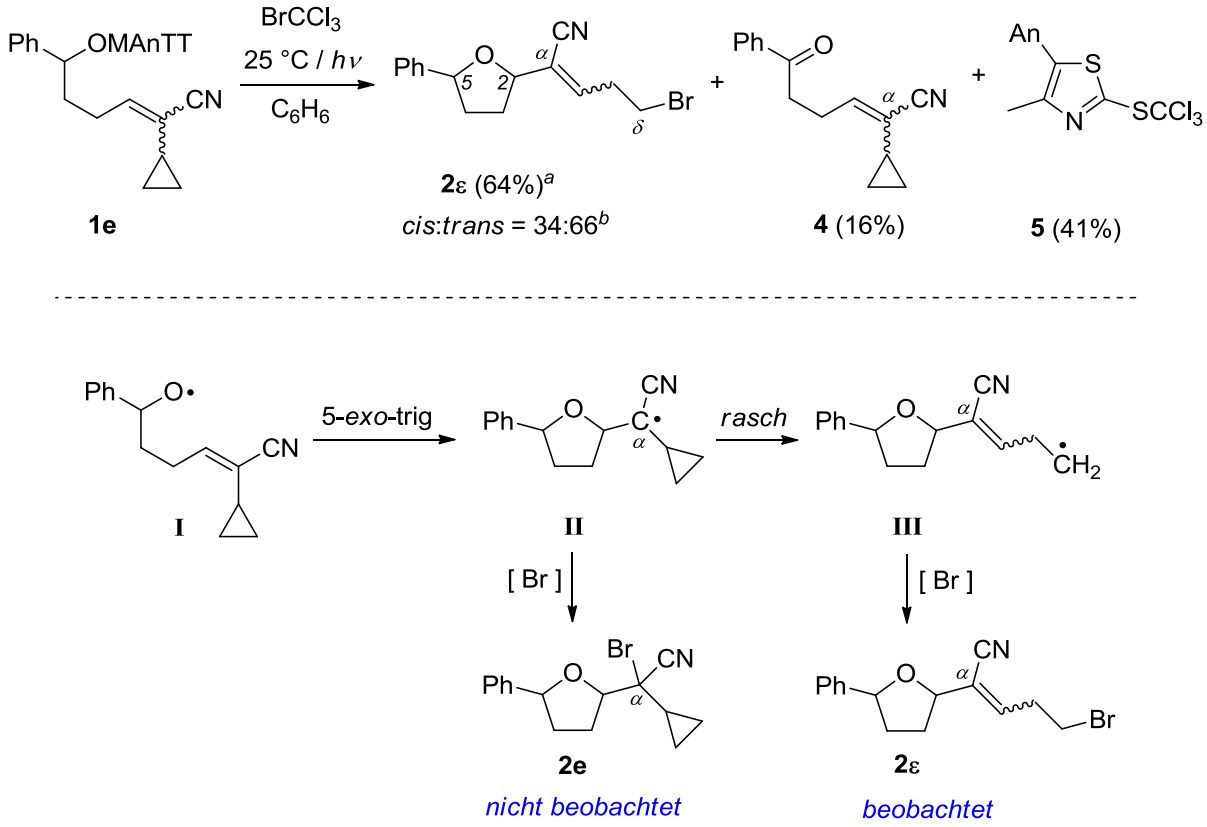
1a–d **2a–d** **3**

Eintrag	**1** / **2**	R	A	X	**2** / % (*cis*:*trans*)[a]	**3** / %[b]
1	**a**	CH_3	CN	H	69 (38:62)	99
2	**b**	C_6H_5	CN	H	67 (44:56)	quant.
3	**b**[c]	C_6H_5	CN	D	74 (46:54)	–[d]
4	**c**	CH_3	CO_2CH_3	H	68 (37:63)	99
5	**d**	C_6H_5	CO_2CH_3	H	71 (41:59)	quant.

[a] Relative Konfiguration bezogen auf C2 und C5; 50:50-Verhältnis der Stereoisomere bezogen auf Cα. [b] Ausbeutenbestimmung über ^{1}H-NMR-Spektroskopie aus der Reaktionsmischung (Pentachlorbenzol als interner Standard). [c] Produktindex: **2b$_{d1}$**. [d] Nicht bestimmt.

Das 2-Cyano-2-cyclopropyl-substiuierte Thiazolthion **1e** lieferte nach photochemischer Umsetzung mit Bromtrichlormethan das Tetrahydrofuran-Derivat **2ε** in einer Ausbeute von 64%. Als weitere Produkte wurden das Keton **4** (16%) und das Produkt **3b** (41%) isoliert (Schema 6.2, oben). Die Öffnung des Cyclopropyl-Rings lässt darauf schließen, dass das bei

der Cyclisierungsreaktion gebildete Intermediat **I** ein Kohlenstoff-Radikal ist, welches eine rasche Ringöffnung induziert.[9] Das Produkt **2e**, welches aus dem direkten Bromabfang des Kohlenstoff-Radikals **I** resultiert, wurde nicht identifiziert (Schema 6.2, unten).

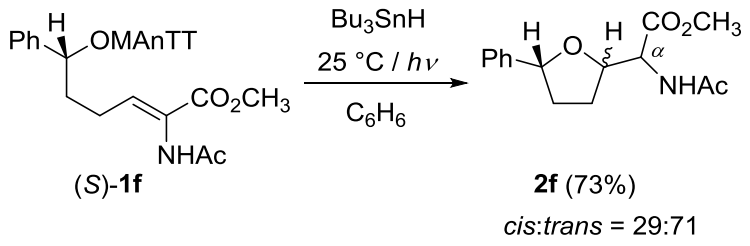


Schema 6.2 Photochemische Umsetzung des Thiazolthions **1e** (oben) und mechanistische Interpretation der Cyclopropyl-Ringöffnung zur Bildung des Tetrahydrofurans **2ε**; [Br] symbolisiert einen homolytischen Bromtransfer von $BrCCl_3$. [a] (*E*)/(*Z*)-Isomere nicht zugeordnet. [b] Relative Konfiguration bezogen auf C2 und C5.

Die durchgeführten Experimente verifizieren, dass intramolekulare Additionsreaktionen an Michael-ähnliche C,C-Doppelbindungen ebenso wie die bereits bekannten Reaktionen an Donor-substituierte Doppelbindungen über einen radikalischen Reaktionsmechanismus verlaufen.[10] Alle Tetrahydrofurane wurden durch die eingesetzten Mediatoren, wie Bu_3SnH, Bu_3SnD oder $BrCCl_3$ funktionalisiert. Die homolytische Substitution dieser Mediatoren durch Kohlenstoffradikale zählt zu deren wichtigsten Eigenschaften.[11] Dies konnte durch die Deuterierung der α-Position in $\mathbf{2b}_{d1}$ gezeigt werden. Ein weiteres Indiz ist die Cyclopropyl-

Ringöffnung zum Tetrahydrofuran **2ε**, welche über ein radikalisches Intermediat verläuft. In allen Cyclisierungsreaktionen wurde das radikalische Produkt **3** beobachtet und vervollständigt die Massenbilanz.

Die homolytische C,O-Bindungsknüpfung an Akzeptor-substituierte C,C-Doppelbindungen ermöglicht die Synthese von Tetrahydrofuran-Aminosäuren über einen radikalischen Reaktionsweg.[12,13] Die Umsetzung des Thiazolthions (*S*)-**1f** mit Bu_3SnH lieferte das Glycin-Derivat **2f** in einer Ausbeute von 73% und ist somit ein Beispiel für die neue Anwendungsmöglichkeit radikalischer Cyclisierungsreaktionen (Schema 6.3).

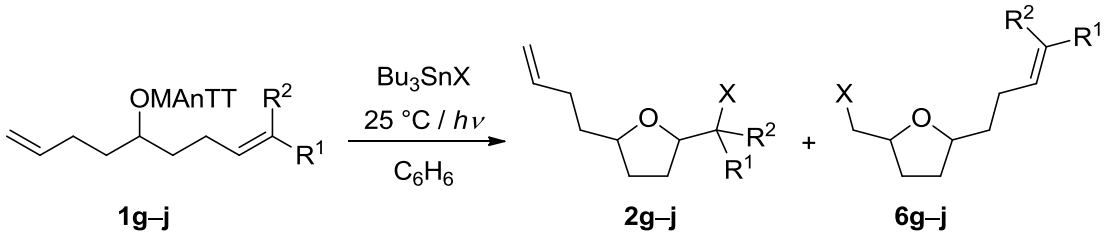


Schema 6.3 Darstellung des N,O-geschützten Glycin-Derivates **2j** (50:50-Verhältnis der Isomere bezogen auf Cα).

6.3.3 Konkurrenzkinetische Untersuchungen

Der Einfluss polarer Substituenten auf die relative Geschwindigkeitskonstante intramolekularer Additionsreaktionen wird anhand der Konkurrenz-Experimente zwischen einer terminalen und einer substituierten Doppelbindung ersichtlich. Die sowohl Donor- als auch Akzeptor-substituierten O-Alkylthiohydroxamate **1g–j** wurden unter identischen Bedingungen in Anwesenheit eines Mediators photochemisch umgesetzt.[14] Im Fall der Methoxy- und Methyl-substituierten Verbindungen **1g–h** wurden ausschließlich die zur Donor-substituierten C,C-Doppelbindung resultierenden Tetrahydrofurane **2g–h** isoliert (Tabelle 6.4). Die Akzeptor-substituierten Vertreter **1i–j** hingegen lieferten ein Gemisch aus beiden Tetrahydrofuranen **2** und **6** (Tabelle 6.4). In allen Cyclisierungen wird das trans-konfigurierte Tetrahydrofuran als Hauptprodukt gebildet.

Tabelle 6.4 Terminale Substituenteneffekte auf die Regioselektivität in 5-*exo*-trig-Cyclisierungsreaktionen

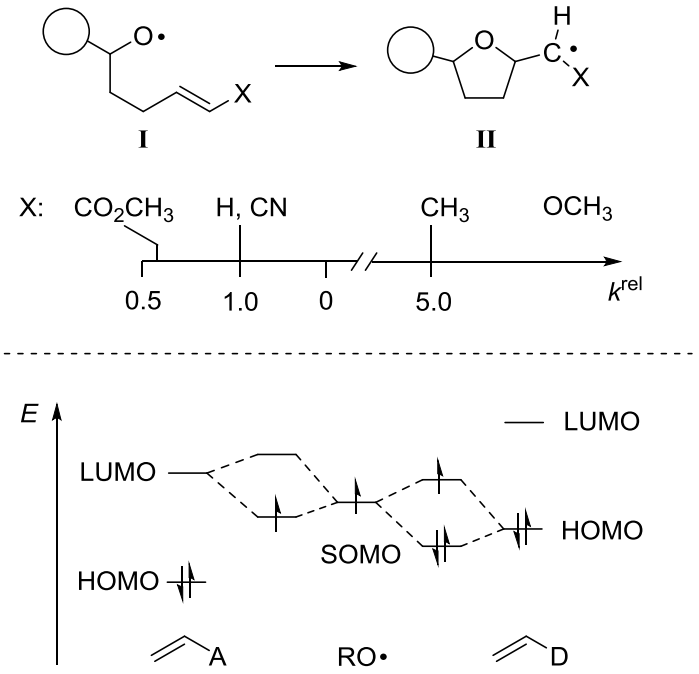


1g–j **2g–j** **6g–j**

Eintrag	**1** / **2** / **6**	R^1	R^2	X	**2** / % (*cis*:*trans*) [a]	**6** / % (*cis*:*trans*) [a]
1	**g**	CH_3	CH_3	H	93 (32:68)	– [b]
2	**h**	OCH_3	H	H	93 (35:65)	– [b]
3	**i**	CN	H	H	46 (38:62)	45 (45:55)
4	**i**[c]	CN	H	D	48 (34:66)	43 (45:55)
5	**j**	CO_2CH_3	H	D	29 (35:65)	55 (39:61)

[a] cis/trans-Verhältnis bezogen auf C2 und C5. [b] Nicht detektiert. [c] Produktindizes: $\mathbf{2i}_{d1}$ und $\mathbf{6i}_{d1}$.

Diese Experimente zeigen, dass die relativen Geschwindigkeitsfaktoren für 5-*exo*-trig-Cyclisierungen entlang der Reihe für terminale Substituenten an C,C-Doppelbindungen von CO_2CH_3 über H und CN bis hin zu OCH_3 steigt (Schema 6.4, oben). Aus früheren Arbeiten ist bekannt, dass eine terminale Methyl-Gruppe die Cyclisierungsreaktion um einen Faktor von 5–7 beschleunigt, für zwei Methyl-Gruppen liegt dieser Faktor bei 12–15.[15] Donor- als auch Akzeptor-Substituenten sind in der Lage die relativen Geschwindigkeitsfaktoren einer Alkoxylradikal-Cyclisierung zu beeinflussen. Im Fall der Donor-Substituenten (R = H, CH_3, OCH_3) zeigt das Sauerstoffradikal elektrophiles Verhalten und addiert an die elektronenreiche π-Bindung. Im Gegensatz dazu besitzt es in Anwesenheit einer Akzeptor-substituierten π-Bindung (R = CN, CO_2CH_3) nucleophile Eigenschaften. Diese Grenzreaktivität zwischen Nucleophilie und Elektrophilie kann anhand der Grenzorbital-Theorie (FMO-Theorie) erklärt werden.[16,17] Das SOMO des Sauerstoffradikals tritt bei einer C,O-Bindungsknüpfung mit dem HOMO oder LUMO der π-Bindung in Wechselwirkung. Donor-Substituenten an C,C-Doppelbindungen führen zu einer Erhöhung der HOMO-Energie, wodurch eine HOMO-SOMO-Wechselwirkung attraktiv wird. Bei Akzeptor-Substituenten wird durch eine Absenkung der HOMO-Energie hingegen die LUMO-SOMO-Wechselwirkung bevorzugt (Schema 6.4, unten).[18–20]



Schema 6.4 Substituenteneffekte auf die relativen Geschwindigkeitsfaktoren in Alkoxylradikal-Cyclisierungen (oben) und FMO-Theorie zur Erklärung der Grenzreaktivität von Sauerstoffradikalen (unten). Kreissymbole = Methyl-, Phenyl- oder 3-Buten-1-yl-Gruppe; A = CN, CO_2CH_3; D = CH_3, OCH_3; R = Alkyl, Aryl. [18–20]

6.4 Ausblick

Die Grenzreaktivität von O-Radikalen erweitert die Anwendungsbreite radikalischer Additionsreaktionen, da von nun an nicht nur deren elektrophile sondern auch nucleophile Eigenschaften in der Synthesechemie genutzt werden können. Durch die Ausweitung des Konzeptes auf weitere Akzeptor-Gruppen, wie Aldehyde, könnte die nucleophile Reaktivität von O-Radikalen zum Aufbau des Tetrahydrofuran-Gerüstes im C-Nukleosid Pyrazofurin[21] eingesetzt werden (Abb. 6.1). In einer Folgereaktion kann die Aldehyd-Gruppe am Tetrahydrofuran-Ring durch die Umsetzung mit einem Amid-Enolat um einen C2-Baustein verlängert werden, woraus anschließend der Pyrazol-Ring aufgebaut werden könnte. C-Nukleoside weisen eine Vielzahl von biologischen Aktivitäten auf und spielen somit in der Synthesechemie eine wichtige Rolle. Die bekannten ionischen Oxa-Michael-Reaktionen sind auf den Abfang der Additionsprodukte mit Protonen beschränkt. Die radikalische Methode ermöglicht eine größere Diversität zur Funktionalisierung der gebildeten C-Radikale. Durch den Abfang mit Alkenen oder Schwefel-Verbindungen können neue Synthesebausteine dargestellt werden.

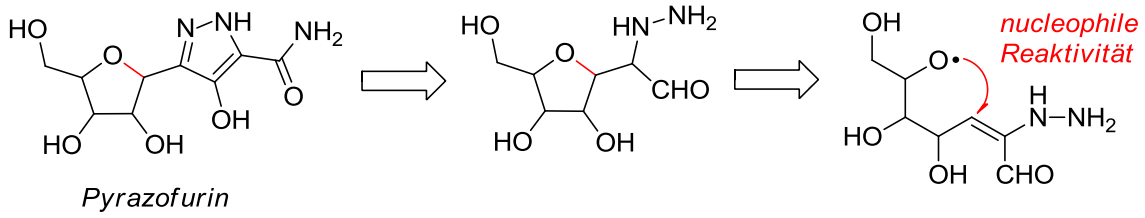


Abbildung 6.1 Selektiver Tetrahydrofuran-Aufbau durch eine radikalische C,O-Bindungsknüpfung als Grundbaustein zur Synthese des C-Nukleosids Pyrazofurin.[21]

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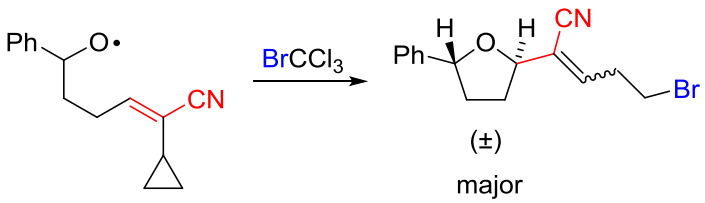
6.6 Forschungsartikel

Alkoxyl radical addition to acceptor-substituted carbon−carbon double bonds

Irina Kempter, Andreas Groß, Jens Hartung, *Tetrahedron* **2012**, *68*, 10378−10390.



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Alkoxyl radical addition to acceptor-substituted carbon–carbon double bonds

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ABSTRACT

Alkoxyl radicals add 5-*exo*-*trig* selectively to cyano- and methoxycarbonyl-substituted carbon–carbon double bonds, to afford α-acceptor-α-tetrahydrofuryl-2-methyl radicals. Trapping of cyclized radicals by Bu_3SnD furnishes products of site-specific deuterium-labeling in α-position to the acceptor group. In intramolecular competition experiments, alkoxyl radicals add similarly fast to a cyano-substituted double bond than to a terminal alkene, but by a factor >25 faster to an enol ether. The nucleophilic component of alkoxyl radical reactivity opens an interesting new access to tetrahydrofuryl amino acids via C,O-cyclization, as shown by synthesis of a *N,O*-protected 5-phenyltetrahydrofuryl-2-methyl glycine.

1. Introduction

The oxygen nucleus attracts an unpaired valence electron in alkoxyl radicals stronger than the carbon nucleus in alkyl radicals. Oxygen radicals therefore attack higher in energy σ- and π-bonds with a reactivity/selectivity profile that is characteristic for many electrophiles.[1,2] Since oxygen forms strong bonds to hydrogen and carbon, the odd electron in alkoxyl radicals gives rise to chemical reactivity that is by orders of magnitude higher than carbon radical reactivity. Typical examples for reactions that take profit from unique alkoxyl radical reactivity are found in metabolic pathways,[3] and in oxidative hydrocarbon degradation, which clear the atmosphere from volatile organic compounds.[4,5]

In spite of enormous reactivity, alkoxyl radicals generally react selectively, following guidelines that allow to apply the intermediates in organic synthesis.[1] A method that has received growing attention for stereoselective synthesis within the past decade is the alkoxyl radical addition to carbon–carbon double bonds.[6–8] The current mechanistic picture shows that alkoxyl radicals add to constitutionally dissymmetric π-bonds with selectivity that often complements additions of alcohols or alkoxides to oxidatively activated alkenes. Additions of oxygen radicals that are too slow to compete with other radical consuming processes, such as β-fragmentation[9–11] or homolytic substitution,[12] generally are accelerated by substituting the carbon double bond with typical donor groups, such as methyl, phenyl, or silyloxy.[13–16] A drawback for pursuing new reactions in alkoxyl radical chemistry in synthesis, however, is the inherent electrophilicity, restricting selectivity control by the polar effect so far exclusively to donor substituents.

The scope of alkoxyl radical chemistry extends, if the intermediates add to Michael-type acceptors. In a communication on alkenoxyl radical generation from *O*-phenylsulfenates for studying stereochemical aspects of 4-pentenoxyl radical cyclization,[17] α-methacrylate-type double bonds were used as *O*-radical acceptors, however, without addressing the role of the polar effect.[18] In view of the potential arising from a nucleophilic component in alkoxyl radical reactivity, we decided to explore in a systematic manner addition to acrylate- and acrylonitrile-type π-bonds, lacking in an activating α-methyl group (Fig. 1). The major results from the study show that 4-pentenoxyl radicals add to the cyano-substituted carbon–carbon double in a rate that compares to the rate of addition to a terminal double bond. The fastest reaction in the series of competition experiments, however, is addition to an enol ether π-bond. From this dichotomic behavior we concluded that alkoxyl radicals are both, electrophiles and nucleophiles, depending on substitution at the π-bond. We used the nucleophilic component of

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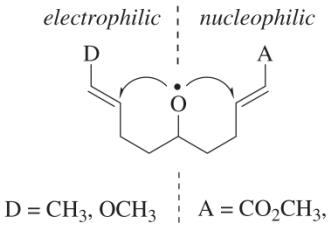


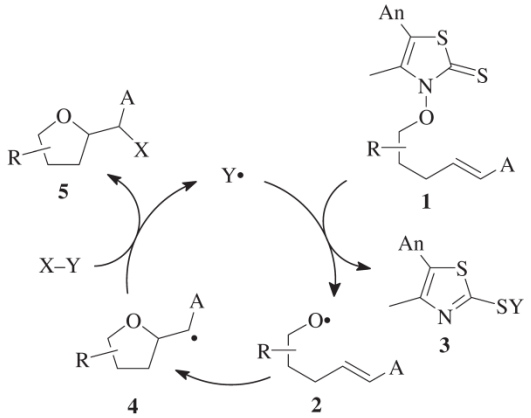
Fig. 1. Structure, substituent effects, and proposed chemical reactivity of alkoxyl radicals used in this study to explore the polar effect in additions to carbon–carbon double bonds.

alkoxyl radical reactivity to develop a new route to synthesis of a *N*,*O*-protected tetrahydrofuryl-2-methyl amino acid via C,O-cyclization.

2. Results and interpretation

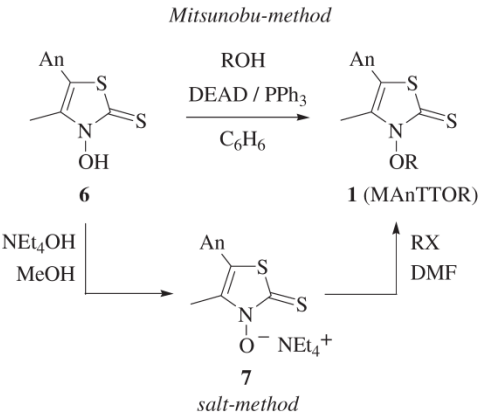
2.1. Alkoxyl radical generation and synthesis of radical precursors

We applied *O*-alkenyl thiohydroxamates of the type **1** in this study as alkoxyl radical progenitors. The compounds add electrophilic radicals Y• at the thione sulfur, which causes the nitrogen–oxygen bond to homolytically break. Radicals used for inducing alkoxyl radical liberation from **1** generally originate from an initiator, such as α,α-azobisisobutyronitrile (AIBN), or from a mediator X–Y in a propagating step of a chain reaction (Scheme 1). Typical mediators X–Y used in this chemistry are tributylstannane, the deuterium derivative Bu_3SnD for isotope labeling, and bromotrichloromethane. An alternative approach to oxygen radical generation from **1** is photochemistry. Excitation of electronic transitions in the molecule, by shining light into the broad electronic band at ~335 nm, selectively induces homolysis of the nitrogen–oxygen bond. The reaction between chain propagating radical Y• and *O*-alkenyl thiohydroxamate **1** thus provides alkenoxyl radical **2** and substituted thiazole **3**.[5,19] For synthesis of tetrahydrofurans (e.g. **5**), bimolecular trapping of alkenoxyl radical **2** by the mediator X–Y must be slower than the cyclization **2**→**4**.[20–23] Trapping of carbon radical **4** by the mediator provides target product **5** and supplies the chain with propagating radical Y•.[5]



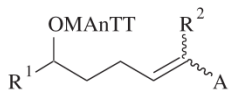
Scheme 1. Steps for alkoxyl radical generation in a chain reaction between *N*-alkoxythiazole-2(3*H*)-thione **1** (R=e.g. CH_3 or Ph; A=e.g. CN, CO_2CH_3; An=*p*-anisyl, i.e. *p*-methoxyphenyl) and a mediator X–Y (Bu_3SnH, Bu_3SnD, or $BrCCl_3$).

For synthesis of alkenyl thiohydroxamates **1a**–**j**, cyclic thiohydroxamic acid **6** was esterified by alkenols using the Mitsunobu-method, or a procedure that we refer to as the *salt-method* (Scheme 2, Supplementary data, and Experimental). Selectivity in the salt-method follows Pearson's principle of hard soft acids and bases. O-Alkylation at the hard oxygen instead of soft sulfur is attainable with a hard carbon electrophile, reacting with a thiohydroxamate anion experiencing no contact from a hard, strongly polarizing cation. This approach is put into practice by converting acid **6** into tetraethylammonium salt **7**, which subsequently is treated in a strongly polar aprotic solvent, such as dimethyl formamide, with an alkenyl chloride (for **1a**–**e**) or a tosylate (for **1i**) (Table 1). In the Mitsunobu-method, the electrophile is generated in situ from an alkenol and the combination of diethyl azodicarboxylate (DEAD) and triphenylphosphine in a solution of benzene, to furnish *O*-alkenyl thiohydroxamates **1f**–**h** and **1j** in yields between 31 and 67% (Fig. 2). After chromatographic purification, the target compounds were received as colorless (**1g**–**i**) to yellow (**1a**–**e**, **1j**) compounds, which are stable for months if stored in a refrigerator. *O*-Alkenyl thiohydroxamates of the type **1** show characteristic electronic spectra having a broad band located at λ=332–338 nm (lg ε ~3.00–3.28 $m^2\ mol^{-1}$, in EtOH for **1a**–**c**, and $CHCl_3$ for **1d**), which allows to photoexcite the molecules for homolytically breaking the nitrogen–oxygen bond (vide supra).



Scheme 2. Methods for synthesis of alkoxyl radical precursors of the type **1** [for yields, see Table 1 and Fig. 2; X=Cl, OTs; R=alkenyl; all reactions were performed at 20–25 °C].

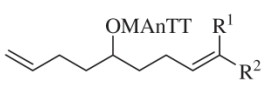
Table 1
Yields of ester- and cyano-substituted *N*-alkenoxythiazolethiones **1a**–**e** prepared from alkenyl chlorides via the salt-method[a]



1a–e

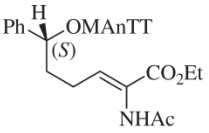
Entry	1	R^1	R^2	A	Yield/%	(*E*)/(*Z*)
1	**a**	CH_3	H	CN	36	77:23
2	**b**	C_6H_5	H	CN	49	76:24
3	**c**	CH_3	H	CO_2CH_3	49	>98:2
4	**d**	C_6H_5	H	CO_2CH_3	70	>98:2
5	**e**	C_6H_5	*cyclo*-C_3H_5	CN	73	62:38

[a] (RX=RCl, cf. Scheme 2; MAnTT=5-(4-methoxyphenyl)-4-methyl-2-thiooxo-2,3-dihydrothiazol-3-yl).



1f–i

1	R^1	R^2	yield / %	(*E*):(*Z*)
f	CH_3	CH_3	60	–
g	H	OCH_3	67	80:20
h	H	CN	63	72:28
i	H	CO_2Et	49	>98:2



(*S*)-**1j** (31%)
(*E*):(*Z*) >98:2

Fig. 2. Structure formulas, indexing of compounds, and yields of *N*-alkenoxythiazolethiones **1f**–**j** (Mitsunobu-method for **1f**–**h** and **1j**, and salt-method for **1i** from the alkenyl tosylate).

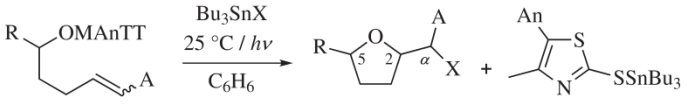
2.2. Alkoxyl radical addition to acceptor-substituted carbon–carbon double bonds

In the standard approach to tetrahydrofuran synthesis we photolyzed cyano-substituted alkenoxythiazolethiones **1a**–**b** and ester derivatives **1c**–**d** with near UV-light (350 nm) in solutions of benzene containing 3.7 equiv of tributylstannane (c^0=185 mM). From the solutions, we isolated 2,5-disubstituted tetrahydrofurans **5a**–**d**, as mixtures of cis/trans-stereoisomers in yields between 67 and 71% (Table 2, entries 1–2 and 4–5). The trans-stereoisomer of heterocycles **5a**–**d**, in all instances, is the major product, as derived from stereochemical analysis by proton NMR, carbon-13 NMR, and NOESY-spectroscopy. For supplementing the mass balance and supporting the mechanistic interpretation, we quantified in all instances tributylstannylsulfanylthiazole **3a**. This compound forms in 99% to quantitative yield, but decomposes upon contact with silica gel used for separating tetrahydrofurans **5a**–**d**, particularly from residual organotin compounds. Since we had fully characterized stannylated thiazole **3a** in a previous study, we restricted ourselves at this point to identifying heterocycle **3a** by proton NMR-spectroscopy.[5] A supplementary photoreaction performed with Bu_3SnD as mediator, provides tetrahydrofuran **5b**$_{d1}$ in 74%, bearing the deuterium label exclusively in α-position to the cyano group (Table 2, entry 3).

From a boiling solution of *O*-alkenyl thiohydroxamate **1d** in benzene, containing 0.5 M concentration of bromotrichloromethane and minor amounts of azobisisobutyronitrile (AIBN) to initiate the reaction, we isolated 62% of α-thiazylsulfanyl ester **8d** in a cis/trans-ratio of 43:57, 21% of α-bromoester **9d** as 44/56-mixture of cis/trans-isomers, and 30% of trichloromethylsulfanylthiazole **3b** (Scheme 3). From this result we concluded that regio- and stereoselectivity of intramolecular carbon–oxygen bond formation are independent possibly from β-carbon–carbon fragmentation of alkoxyl radicals or *O*-alkenyl thiohydroxamates **1a**–**d**. Authentic references of the assumed products were available from the synthetic part of the study. None of the assumed products, however, had formed in sufficient amounts for being detected, under conditions applied to prepare **5a**–**d**.

In controls to investigate whether tetrahydrofuran **5b** possibly had formed from an alkoxide-mediated cyclization, we treated 1-phenyl-6-hydroxyhex-2-enenitrile, the underlying alcohol of **1b**, with tributylstannane in benzene. Also, we stirred 50/50-mixtures of this alcohol and the derived ketone in a solution containing tributylstannane for 90 min in the dark, and in a photoreactor shining 350 nm-light into the sample. From the controls, we exclusively recovered the starting materials. The only chemical change we noticed was a photoisomerization at the double bond of 6-phenyl-6-hydroxyhex-2-enenitrile from (*E*)/(*Z*)=87:13 to 51:49.

Table 2
Products of reductive 3-alkenoxythiazole-2(3*H*)-thione (MAnTTOR) conversion

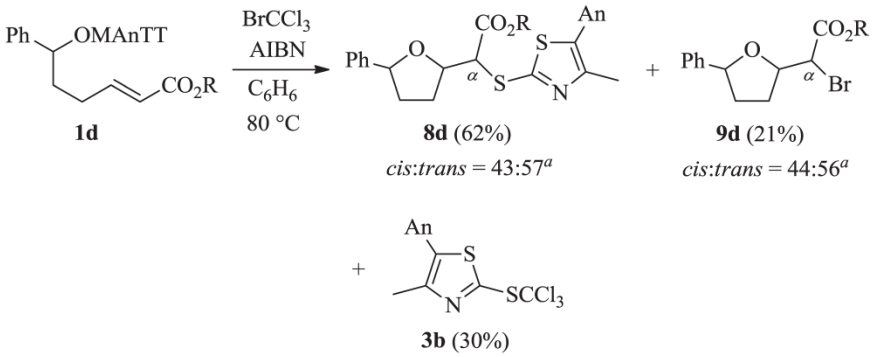


1 **5** **3a**

Entry	**1**/**5**	R	A	X	**5**/% (*cis*/*trans*)[a]	**3a**/%[b]
1	**a**[b]	CH_3	CN	H	69 (38:62)	99
2	**b**	C_6H_5	CN	H	67 (44:56)	quant.
3	**b**[c]	C_6H_5	CN	D	74 (46:54)	—[d]
4	**c**[c]	CH_3	CO_2CH_3	H	68 (37:63)	99
5	**d**[d]	C_6H_5	CO_2CH_3	H	71 (41:59)	quant.

[a] Relative tetrahydrofuran configuration at C2 and C5; 50/50-ratio of stereoisomers with respect to C_2.
[b] From reaction mixtures via ^{1}H NMR-spectroscopy (pentachlorobenzene as internal standard).
[c] Compound indexing for **5**: **b**$_{d1}$.
[d] Not determined.

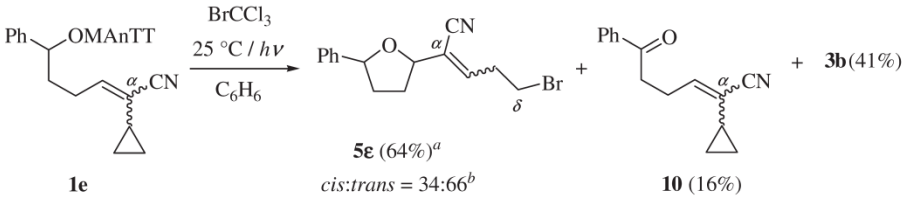
In routine analysis of product mixtures obtained from reactions between tributylstannane and *O*-alkenyl thiohydroxamates **1a**–**d**, we searched via GC–MS and NMR-spectroscopy for additional products that could have been formed, for example, alcohols from alkoxyl radical reduction by tributylstannane, aldehydes or ketones from the chemical nature of the mediator, as predicted on the basis of the general mechanistic scheme for *O*-alkenyoxythiazolethione conversion under conditions that favor homolytic reactions (Scheme 1). The preference for thioether- over alkyl bromide formation in this experiment arises from the low affinity of the



Scheme 3. Selectivity of product formation from ester-substituted thiazolethione **1d** and $BrCCl_3$ (R=CH_3). [a] Relative configuration at C2 and C5; 50/50-ratio of stereoisomers at C_α.

intermediate electrophilic α-alkoxycarbonyl alkyl radical, for abstracting a bromine atom from bromotrichloromethane.[24–26]

From a photolyzed solution of benzene containing bromotrichloromethane and 2-cyano-2-cyclopropyl-substituted thiazolethione **1e**, we isolated 64% of α-substituted pentenonitrile **5ε**, 16% of ketone **10**, and 41% of trichloromethylsulfanylthiazole **3b** (Scheme 4). The appearance of ketone **10** in this experiment surprised us, although ketone formation from secondary benzylic *N*-alkenoxythiazolethiones is not an entirely new reaction. Benzylic *N*-alkenoxythiazolethiones tend to dissociate into a thiolactam and a carbonyl compound in a non-radical reaction, if stored, heated, or photolyzed.[27]



Scheme 4. Formation of α-(phenyltetrahydrofuryl)-δ-bromopentenonitrile **5ε** from 2-cyclopropyl-2-cyano-substituted thiazolethione **1e** [62:38-mixture of (*E*)/(*Z*)-isomers]. [a] (*E*)/(*Z*)-Isomers not assigned. [b] Relative tetrahydrofuran configuration at C2 and C5.

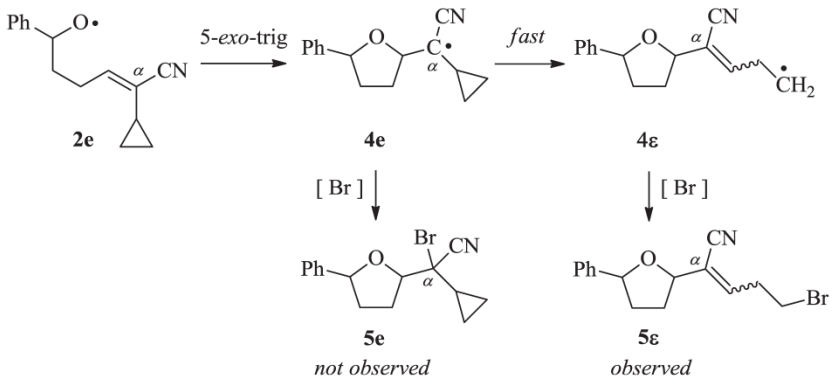
Regarding the general mechanism, we think for the following four reasons that synthesis of side chain acceptor-substituted tetrahydrofurans from *N*-alkenoxythiazolethiones **1a**–**e** having Michael-type carbon–carbon double bonds, follows the general alkoxyl radical pathway (Scheme 1):

(i) The concluding step of the tetrahydrofuran synthesis is hydrogen atom transfer from Bu_3SnH to a reactive intermediate, deuterium-labeling by Bu_3SnD, or bromination by $BrCCl_3$. The three reagents have in common to favor homolytic substitution by carbon radicals to reactions with cations or anions.[28] The position of site specific labeling, deuteration for synthesis of tetrahydrofuran **5b$_{d1}$** and bromination for synthesis of α-bromoester **9d**, correlates with the proposed position of a carbon radical in the intermediate (Schemes 1 and 5).

(ii) The fact that α-cyano-α-cyclopropyl-substituted *N*-alkenoxythiazolethione **1e** furnishes exclusively (δ-bromo-α-cyanobutenyl)tetrahydrofuran **5ε**, and not (α-bromo-α-cyclopropyltetrahydrofuryl)acetonitrile **5e**, shows that the underlying intermediate is able to induce rapid cyclopropyl ring opening (Scheme 5). From the site of bromine labeling, we also knew that the ring opening occurs in a β-fragmentation pathway, to furnish, in extension to arguments provided in the previous paragraph, a carbon radical that is trapped by bromotrichloromethane. The mechanism that combines adequate reactivity with selectivity to explain formation of (δ-bromo-α-cyanobutenyl)tetrahydrofuran **5ε** under such conditions is the cyclopropylmethyl to butenyl radical ring opening,[29] which in turn points to an alkoxyl radical addition mechanism to the cyano-substituted double bond in **2e**.

(iii) Stereoselectivity for tetrahydrofuran formation from **1a**–**e** leaves a fingerprint-type 60/40-selectivity in favor of the 2,5-trans-stereoisomer. This value is close to the 65/35-cis/trans-selectivity for 5-*exo*-*trig*-cyclization of the (*E*)-1-phenyl-4-penten-1-yl radical.[30] Alkoxide-based cyclization of 6-hydroxy-6-phenyl-2-pentenenitrile, catalyzed by potassium *tert*-butoxide in a solution of ethanol, furnishes a mixture of stereoisomers for tetrahydrofuran **5b**, which is by 52/48 slightly in favor for the cis-isomer.

(iv) The yields of thiazole- and alkoxyl radical-derived products **3** and **5** are in many experiments similar, as predicted from an underlying chain mechanism. In instances of diverging mass balances, we find explanations from the literature that are consistent with homolytic reactions starting from **1a**–**d**. For example, 2-trichloromethylsulfanyl thiazole **3b** is a photolabile compound, which gradually decomposes as substrate conversion in a photochemical experiment progresses, thus explaining the low yield of this product.[5] In other instances (cf. Scheme 4), additional thiazole-derived products appeared. We had described the existence of such products in a previous study dealing with alkoxyl radical generation from *tert*-*O*-alkyl thiohydroxamates. Since the new thiazole derivatives now and then remained unidentified we could not use this information for improving the thiazole mass balance.[7]



Scheme 5. Mechanistic interpretation of (cyanobutenyl)tetrahydrofuran formation from cyano-substituted cyclopropylmethyl radical **2e** ([Br] symbolizes a homolytically transferable bromine atom, for example, from $BrCCl_3$).

2.3. Reactivity in intramolecular additions

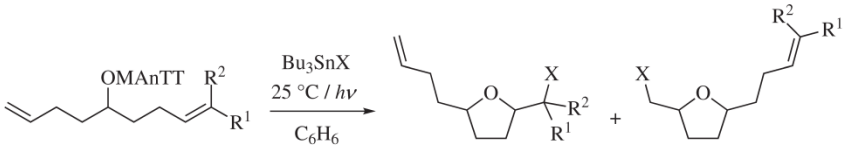
The affinity for alkoxyl radicals to add to Michael-type carbon–carbon double caused us to address the question on alkoxyl radical polarity in additions by a competition kinetic study. In our approach, we used *N*-dienoxythiazolethiones **1f**–**i** for determining the polar effect of substituents on relative rates in cyclizations.

In the general experimental set-up, solutions of *O*-alkylthiohydroxamates **1f**–**i** ($c^0_{\mathbf{1f–i}}$=55 mM) containing tributylstannane (c^0=205 mM; Table 3, entries 1–3) or Bu_3SnD (Table 3, entries 4–5) were photolyzed with 350 nm-light until the starting material is entirely consumed.[31] Methoxy- and dimethyl-substituted thiazolethiones **1f**–**g** provided exclusively products **5f** and **5g** from addition to the donor-substituted double bond (GC, NMR). Acceptor-substituted thiazolethiones **1h**–**i** furnished 52/48- (for R^1=CN, R^2=H) and 42/58-mixtures (for R^1=CO_2CH_3, R^2=H) of products **5** versus **11** (GC, NMR; 3 independent runs). All cyclizations afforded the *trans*-tetrahydrofuran as major stereoisomer (Table 3).

Alkoxyl radical 5-*exo*-trig cyclization to terminal- and donor-substituted double bonds, unlike the oxygen radical β-fragmentation,[32,33] proceed irreversibly,[34] and terminal substitution by a polar substituent is not expected to change this situation.[35] In this mechanistic interpretation, the ratio of products **5** and **11** directly reflects relative reactivity of the two double bonds for accepting the alkoxyl radical. For the discussion on relative reactivity by comparing results from competition experiments performed under identical conditions, we propose to use the term *relative rate factor* instead of relative rate constant. A relative rate constant is the result of a reaction series performed by parameter variation, providing from numeric analysis the desired kinetic information.

Relative rate factors for alkoxyl radical 5-*exo*-cyclization increase along the series of alkene-substituents R from OCH_3 (from **1g**) and methyl (from **1f**) via H (from **1h** and **1i**) and CN (from **1h**) to CO_2CH_3 (from **1i**; Scheme 6). The fastest (R=OCH_3) and the slowest (R=CO_2CH_3) reaction differ by an approximated factor of 35. This value considers a rate factor of 25 for addition to the enol ether

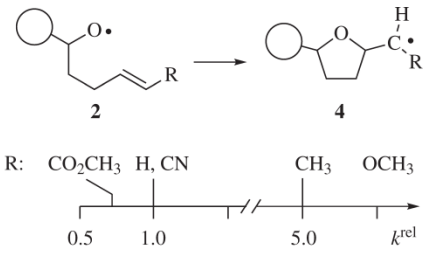
Table 3
Effect of terminal substituents on regioselectivity in 5-*exo*-trig alkenoxyl radical cyclization



1f–i **5f–i** **11f–i**

Entry	**1**/**5**/**11**	R^1	R^2	X[a]	**5**/% (*cis*/*trans*)[b]	**11**/% (*cis*/*trans*)[b]
1	**f**	CH_3	CH_3	H	93 (32:68)	—[c]
2	**g**	OCH_3[d]	H	H	93 (35:65)	—[c]
3	**h**	CN[e]	H	H	46 (38:62)	45 (45:55)[f]
4	**h**[g]	CN[e]	H	D	48 (34:66)	43 (45:55)[h]
5	**i**	CO_2CH_3[i]	H	D	29 (35:65)	55 (39:61)[i]

[a] Bu_3SnH for X=H, Bu_3SnD for X=D.
[b] cis/trans-Ratios determined via GC, stereochemical assignment via NOESY.
[c] Not detected (^{1}H NMR).
[d] (*E*)/(*Z*)=80:20.
[e] (*E*)/(*Z*)=72:28.
[f] (*E*)/(*Z*)=46:54.
[g] Compound indexing for **5** and **11**: $\mathbf{h}_{d1}$.
[h] (*E*)/(*Z*)=53:47.
[i] (*E*)/(*Z*) >98:2.



Scheme 6. Summary of substituent effects on relative rate factors in alkenoxyl radical cyclization (the open circle symbolizes a phenyl, methyl or a 3-buten-1-yl group).

group in **1g**, based on selectivity for formation of **5g** of larger than 96/4, according results from proton NMR-spectroscopy. From previous work we knew that one methyl group increases the rate of 5-*exo*-trig alkenoxyl radical cyclization by a factor of 5–7, and two methyl groups by a factor of 12–15.[30,36] We therefore assigned the methoxy group a larger activating effect than the methyl group (Scheme 6).

A gradual increase in relative rate factor in going from substituents R=H via CH_3 to OCH_3 points to an electrophilic behavior of the radical oxygen.[37] The progression of the rate factor as R changes from methoxycarbonyl via hydrogen to cyano points to an accelerating contribution of the cyano group, although the effect is small. Since the cyano is the strongest acceptor in the series of investigated substituents, known to activate a conjugated carbon–carbon double bond for addition of nucleophiles to the β-carbon in a reaction known as Micheal-addition, we attribute the driving force of alkoxyl addition to acrylonitrile-type double bonds to nucleophilic behavior of the O-radical.

The underlying theory to explain reactivity and selectivity in alkoxyl radical additions is frontier molecular orbital theory, because the reactions are fast and exothermic and therefore proceed via transition states located early on a reaction coordinate.[6,38] According to FMO-theory, the major bonding contribution, as the radical approaches the π-bond of the alkene, arises from interactions between the singly occupied molecular orbital (SOMO) and either the highest occupied molecular orbital (HOMO) or the lowest unoccupied molecular orbital (LUMO). As the alkene is substituted by donor groups, such as methoxy or methyl, orbital energies rise and the HOMO–SOMO-interaction becomes more prominent (Fig. 3, right; D=OCH_3, CH_3).[6,38] Acceptor groups, such as a cyano- or an ester-group, lower orbital energies of the alkene, causing attractive LUMO–SOMO interactions to become more significant (Fig. 3, left; A=CN, CO_2CH_3). Electrophilic radicals (e.g. •CCl_3) have low and nucleophilic radicals [e.g. •$C(CH_3)_3$] high SOMO-energies. Radicals that interact by their SOMO to a similar extent with the LUMO and the HOMO of an alkene are on the borderline between nucleophilic and electrophilic. The responsivity of substituent effects on rates in alkoxyl radical additions shows this typical dichotomic behavior of borderline cases, being an electrophile if the alkene bears a donor group, or a nucleophile if the attacked π-bond is substituted by a cyano- or an ester-group (Fig. 3).[39–41]

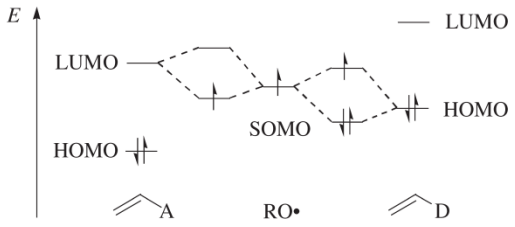
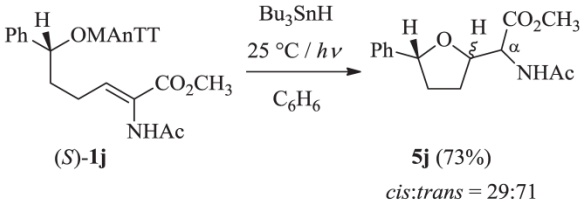


Fig. 3. FMO-correlation diagram for explaining borderline reactivity of alkoxyl radicals in additions to substituted alkenes, on the basis of stabilizing interactions in transition states (A=CN, CO_2CH_3; D=CH_3, OCH_3).

2.4. Application in synthesis

The propensity of alkoxyl radicals for adding to acceptor-substituted double bonds opens new perspectives for synthesis, since substrates now become accessible for homolytic carbon–oxygen bond formation that so far were not attainable by this approach. Tetrahydrofurylamino acids have not yet been prepared via C,O-cyclization. Some tetrahydrofuryl amino acids, such as the furanomycin derivatives, show antibiotic activity.[42] We therefore considered synthesis of a *N*,*O*-protected tetrahydrofuryl glycine an attractive target for documenting the scope of our findings.

We put our strategy into practice by photolyzing *N*-alkenoxythiazolethione (*S*)-**1j** and tributylstannane in a solution of benzene at room temperature. From the reaction mixture, we isolated *N*,*O*-protected α-(5-phenyltetrahydrofuran-2-yl)methyl glycine **5j** in a yield of 73%, thus proofing the proposed concept (Scheme 7).



Scheme 7. Synthesis of *N*,*O*-protected 2-(5-phenyltetrahydrofuran-2-yl)methyl glycine **5j** from *N*-alkenoxythiazolethione (*S*)-**1j** and Bu_3SnH (50/50-mixtures of isomers at C_α).

3. Concluding remarks

The affinity for adding to cyano- and ester-substituted double bonds in rates that compare to reactivity of terminal alkenes, adds a new component to synthesis with oxygen radicals. From the kinetic information provided in this work it seems that further accepting groups, for example halogens, nitro, or arylsulfonyl, will sufficiently activate alkenes to construct carbon–oxygen bonds via an alkoxyl radical mechanism. The argument, to consider in future syntheses radical and not ionic reactions for addition of oxygen compounds to Michael-type acceptors, possibly arises from stereoselectivity of the ring closure, and diversity of methods available for functionalizing carbon radicals. Alkoxide-based additions to Michael-type acceptors have the disadvantage of being reversible and often difficult to terminate with other reagents than the proton.

Nucleophilic properties of alkoxyl radicals could have been predicted from the day, additions were explained by frontier molecular orbital (FMO)-theory, based on kinetic[36] and theoretical data.[6] In FMO-theory nucleophilicity of an alkoxyl radical is a logical consequence of the LUMO-energy of an accepting entity, for example a π^*-type orbital predominantly located at an alkene subunit, falling below the SOMO energy of the unpaired electron.

We have not yet performed experiments to explore whether borderline reactivity extends to other alkoxyl radical elementary reactions, such as homolytic substitution, rearrangements, or β-fragmentation. Bond formation and bond breaking in all such processes is explicable by FMO-theory. According to FMO-theory, orbital energies of reactants are controlled by substituents in a systematic and predictable manner. We therefore expect borderline reactivity to be a general phenomenon in alkoxyl radical

chemistry. Since alkoxyl radicals play an important role in combustion processes, atmospheric chemistry, biochemistry, and synthesis, we think that the findings summarized in this article have the potential to double the scope of alkoxyl radical chemistry.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see Ref. 7 and the Supplementary data.

4.2. 3-Alkoxythiazole-2(3*H*)-thiones 1a–e from alkenyl chlorides

4.2.1. General procedure. An alkenol was dissolved in CCl_4 and treated with PPh_3. The reaction mixture was stirred at 80 °C for 2–4 h. The precipitate was filtered off by suction and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (SiO_2) to afford an alkenyl chloride, which was added to a solution of 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt[43] in dry DMF. The resulting mixture was stirred at 22 °C for 6–13 days in the dark. The solution was treated at 22 °C with Et_2O or CH_2Cl_2 and H_2O. The aqueous layer was extracted with Et_2O or CH_2Cl_2 and the combined layers were dried ($MgSO_4$). The solvent was removed under reduced pressure to leave a crude product, which was purified by chromatography (SiO_2).

*4.2.2. 3-(1′-Cyanohex-1′-en-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1a**).* 6-*Chlorohept-2-enenitrile*: According to 4.2.1 from 6-hydroxyhept-2-enenitrile (1.06 g, 8.47 mmol), PPh_3 (2.89 g, 11.01 mmol) and CCl_4 (10 mL). Reaction time: 3 h. Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). Yield: 879 mg [6.12 mmol, 72%, (*E*)/(*Z*)=83:17], yellow oil, R_f 0.63 [SiO_2, pentane/Et_2O=1:1 (v/v)]. (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.53 (d, 3H, *J* 6.4, 7-H), 1.78–1.89 (m, 2H, CH_2), 2.35–2.41 (m, 1H, CH_2), 2.45–2.51 (m, 1H, CH_2), 3.96–4.05 (m, 1H, 6-H), 5.37–5.41 (m, 1H, 2-H), 6.70 (dt, 1H, J_d 16.2, J_t 7.0, 3-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.3 (C7), 30.4 (CH_2), 37.8 (CH_2), 57.2 (C6), 100.8 (C2), 117.2 (CN), 154.1 (C3). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.53 (d, 3H, *J* 6.4, 7-H), 1.78–1.89 (m, 2H, CH_2), 2.55–2.67 (m, 2H, CH_2), 3.96–4.05 (m, 1H, 6-H), 5.37–5.41 (m, 1H, 2-H), 6.49 (dt, 1H, J_d 10.9, J_t 7.6, 3-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.2 (C7), 29.1 (CH_2), 38.4 (CH_2), 57.2 (C6), 100.5 (C2), 115.7 (CN), 153.3 (C3). 3-(1′-*Cyanohex*-1′-*en*-5′-*oxy*)-5-(*p*-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1a**): According to 4.2.1 from 6-chlorohept-2-enenitrile (879 mg, 6.12 mmol), 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (2.34 g, 6.12 mmol) and DMF (12 mL). Reaction time: 13 days. The reaction mixture was treated with Et_2O (50 mL) and H_2O (50 mL). The layers were separated and the organic layer was kept. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). Eluent used for chromatography: pentane/Et_2O=1:2 (v/v). Yield: 798 mg [2.21 mmol, 36%, (*E*)/(*Z*)=77:23], yellow oil, R_f 0.30 [SiO_2, pentane/Et_2O=1:2 (v/v)]. UV (MeOH) λ_{max} (lg ε/m^2 mol^{-1})=335 nm (3.25). (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.31 (d, 3H, *J* 6.2, 6′-H), 1.79–1.84 (m, 1H, CH_2), 1.86–1.96 (m, 1H, CH_2), 2.28 (s, 3H, 4-CH_3), 2.58–2.62 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 5.42–5.45 (m, 1H, 1′-H), 5.46–5.52 (m, 1H, 5′-H), 6.79–6.84 (m, 1H, 2′-H), 6.95 (d, 2H, *J* 8.8, Ar–H), 7.24 (d, 2H, *J* 8.5, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.7 (4-CH_3), 18.7 (C6′), 29.2 (CH_2), 33.2 (CH_2), 55.4 (OCH_3), 80.2 (C5′), 100.5 (C1′), 114.5 (Ar–C), 117.4 (CN), 119.5 (C5), 122.5 (Ar–C), 129.8 (Ar–C), 133.2 (C4), 154.8 (C2′), 159.9 (Ar–C), 179.1 (C2). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.34 (d, 3H, *J* 6.5, 6′-H), 1.86–1.96 (m, 1H, CH_2), 1.98–2.04 (m, 1H, CH_2), 2.29 (s, 3H, 4-CH_3), 2.66–2.77 (m, 2H, CH_2), 3.83 (s, 3H, OCH_3), 5.37 (d, 1H, *J* 10.9, 1′-H), 5.46–5.52 (m, 1H, 5′-H), 6.70–6.74 (m, 1H, 2′-H), 6.95 (d, 2H, *J* 8.8, Ar–H), 7.24 (d, 2H, *J* 8.5, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.7 (4-CH_3), 18.4 (C6′), 27.6 (CH_2), 33.3 (CH_2), 55.4 (OCH_3), 80.3 (C5′), 100.1 (C1′), 114.5 (Ar–C), 115.9 (CN), 119.5 (C5), 122.5 (Ar–C), 129.8 (Ar–C), 133.3 (C4), 154.2 (C2′), 159.9 (Ar–C), 179.1 (C2).

*4.2.3. 3-(1′-Cyano-5′-phenylpent-1′-en-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1b**).* 6-*Chloro*-6-*phenylhex*-2-*enenitrile*: According to 4.2.1 from 6-hydroxy-6-phenylhex-2-enenitrile (1.00 g, 5.34 mmol), PPh_3 (1.82 g, 6.94 mmol) and CCl_4 (6 mL). Reaction time: 4 h. Eluent used for chromatography: pentane/Et_2O=2:1 (v/v). Yield: 896 mg [4.36 mmol, 82%, (*E*)/(*Z*)=88:12], colorless oil, R_f 0.52 [SiO_2, pentane/Et_2O=2:1 (v/v)]. (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10–2.48 (m, 4H, CH_2), 4.80–4.84 (m, 1H, 6-H), 5.36 (d, 1H, *J* 16.2, 2-H), 6.68 (dt, 1H, J_d 16.2, J_t 6.8, 3-H), 7.31–7.37 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.7 (CH_2), 37.6 (CH_2), 62.2 (C6), 101.0 (C2), 117.1 (CN), 126.8, 128.6, 128.8, 140.7 (Ph–C), 153.6 (C3). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10–2.48 (m, 4H, CH_2), 4.80–4.84 (m, 1H, 6-H), 5.42 (d, 1H, *J* 16.5, 2-H), 6.82 (dt, 1H, J_d 16.2, J_t 6.4, 3-H), 7.31–7.37 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.7 (CH_2), 36.0 (CH_2), 62.2 (C6), 100.7 (C2), 117.3 (CN), 126.8, 128.6, 128.8, 140.7 (Ph–C), 153.3 (C3). 3-(1′-*Cyano*-5′-*phenylpent*-1′-*en*-5′-*oxy*)-5-(*p*-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1b**): According to 4.2.1 from 6-chloro-6-phenylhex-2-enenitrile (519 mg, 2.52 mmol), 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (1.20 g, 3.14 mmol) and DMF (6 mL). Reaction time: 10 days. The reaction mixture was treated with Et_2O (15 mL) and H_2O (20 mL). The layers were separated and the organic layer was kept. The aqueous layer was extracted with Et_2O (4×50 mL). Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). Yield: 519 mg [1.23 mmol, 49%, (*E*)/(*Z*)=76:24], pale yellow solid, R_f 0.26 [SiO_2, pentane/Et_2O=1:1 (v/v)]. UV (MeOH) λ_{max} (lg ε/m^2 mol^{-1})=336 nm (3.28). Anal. calcd. for $C_{23}H_{22}N_2O_2S_2$ (422.56): C, 65.38; H, 5.25; N, 6.93; S, 15.17; found: C, 65.27; H, 5.12; N, 6.69; S, 15.04. (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.50 (s, 3H, 4-CH_3), 2.15–2.20 (m, 1H, CH_2), 2.54–2.70 (m, 3H, CH_2), 3.79 (s, 3H, OCH_3), 5.44 (d, 1H, *J* 16.4, 1′-H), 6.19 (t, 1H, *J* 6.7, 5′-H), 6.79–6.84 (m, 1H, 2′-H), 6.86 (d, 2H, *J* 8.7, Ar–H), 6.99 (d, 2H, *J* 8.7, Ar–H), 7.35–7.45 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.1 (4-CH_3), 29.8 (CH_2), 30.4 (CH_2), 55.4 (OCH_3), 84.9 (C5′), 100.7 (C1′), 114.4 (Ar–C), 117.4 (CN), 118.5 (C5), 122.5 (Ar–C), 128.9, 129.0, 129.8, 130.2 (Ph–C and Ar–C), 133.7 (C4), 136.2 (Ph–C), 154.5 (C2′), 159.8 (Ar–C), 178.5 (C2). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.52 (s, 3H, 4-CH_3), 2.15–2.20 (m, 1H, CH_2), 2.54–2.70 (m, 3H, CH_2), 3.79 (s, 3H, OCH_3), 5.36 (d, 1H, *J* 10.7, 1′-H), 6.19 (t, 1H, *J* 6.7, 5′-H), 6.79–6.84 (m, 1H, 2′-H), 6.86 (d, 2H, *J* 8.7, Ar–H), 6.99 (d, 2H, *J* 8.7, Ar–H), 7.35–7.45 (5H, m, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.1 (4-CH_3), 29.8 (CH_2), 30.4 (CH_2), 55.4 (OCH_3), 84.9 (C5′), 100.7 (C1′), 114.4 (Ar–C), 117.4 (CN), 118.5 (C5), 122.5 (Ar–C), 128.9, 129.0, 129.8, 130.2 (Ph–C and Ar–C), 133.7 (C4), 136.2 (Ph–C), 154.5 (C2′), 159.8 (Ar–C), 178.5 (C2).

*4.2.4. 3-[1′-(Methoxycarbonyl)hex-1′-en-5′-oxy]-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1c**). Methyl* 6-*chlorohept*-2-*enoate*: According to 4.2.1 from methyl 6-hydroxyhept-2-enoate (1.11 g, 6.95 mmol), PPh_3 (2.37 g, 9.03 mmol) and CCl_4 (8 mL). Reaction time: 3 h. Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). Yield: 731 mg (4.14 mmol, 60%), pale yellow oil, R_f 0.58 [SiO_2, pentane/Et_2O=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52 (d, 3H, *J* 6.6, 7-H), 1.79–1.90 (m, 2H, CH_2), 2.25–2.55 (m, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.92–4.09 (m, 1H, 6-H), 5.87 (d, 1H, *J* 15.6, 2-H), 6.94 (dt, 1H, J_d 15.6, J_t 7.0, 3-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 25.3 (C7), 29.2 (CH_2), 38.3 (CH_2), 51.5 (OCH_3), 57.5 (C6), 12.8 (C2), 147.6 (C3), 166.9 (C=O). 3-[1′-(*Methoxycarbonyl*)*hex*-1′-*en*-5′-*oxy*]-5-(*p*-*methoxyphenyl*)-4-*methylthiazole*-2(3*H*)-*thione* (**1c**): According to 4.2.1 from methyl 6-chlorohept-2-enoate (731 mg, 4.14 mmol), 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (1.58 g, 4.14 mmol) and DMF (8.5 mL).

Reaction time: 6 days. The reaction mixture was treated with CH_2Cl_2 (40 mL) and H_2O (40 mL). The layers were separated and the organic layer was kept. The aqueous layer was extracted with CH_2Cl_2 (3×40 mL). Eluent used for chromatography: pentane/EtOAc=1:1 (v/v). Yield: 452 mg (1.15 mmol, 49%), pale yellow oil, R_f 0.62 [SiO_2, pentane/EtOAc=1:1 (v/v)]. UV (MeOH) λ_{max} (lg ε/m^2 mol^{-1})= 332 nm (3.00). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (d, 3H, J 6.3, 6′-H), 1.72–2.02 (m, 1H, CH_2), 2.28 (s, 3H, 4-CH_3), 2.45–2.56 (m, 2H CH_2), 3.72 (s, 3H, $COOCH_3$), 3.83 (s, 3H, OCH_3), 5.39–5.55 (m, 1H, 5′-H), 5.89 (d, 1H, J 15.7, 1′-H), 6.94 (d, 2H, J 8.7, Ar–H), 6.94–7.09 (m, 1H, 2′-H), 7.24 (d, 2H, J 7.6, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.7 (4-CH_3), 18.4 (C6′), 28.0 (CH_2), 33.3 (CH_2), 51.4 (OCH_3), 55.4 (OCH_3), 80.7 (C5′), 114.5 (Ar–C), 119.4 (C5), 121.4 (C1′), 122.5 (Ar–C), 129.8 (Ar–C), 133.3 (C4), 148.1 (C2′), 159.9 (Ar–C), 166.9 (C=O), 179.1 (C2).

*4.2.5. 3-(1′-Methoxycarbonyl-5′-phenylpent-1′-en-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1d**). Methyl 6-chloro-6-phenylhex-2-enoate*: According to 4.2.1 from methyl 6-hydroxy-6-phenylhex-2-enoate (2.91 g, 13.21 mmol), PPh_3 (4.50 g, 17.17 mmol) and CCl_4 (15 mL). Reaction time: 3 h. Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). Yield: 2.53 g [10.60 mmol, 80%, (*E*)/(*Z*)=91:9], pale yellow oil, R_f 0.92 [SiO_2, pentane/Et_2O=1:1 (v/v)]. UV ($CHCl_3$) λ_{max} (lg ε/m^2 mol^{-1})=338 nm (3.17), 240 nm (3.12). (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.14–2.42 (m, 4H, CH_2), 3.73 (s, 3H, OCH_3), 4.83–4.85 (m, 1H, 6-H), 5.86 (d, 1H, J 15.5, 2-H), 6.94 (dt, 1H, J_d 15.7, J_t 6.8, 3-H), 7.30–7.33 (m, 1H, Ph–H), 7.35–7.37 (m, 4H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.5 (CH_2), 38.0 (CH_2), 51.5 (OCH_3), 62.5 (C6), 122.0 (C2), 126.8, 128.4, 128.7, 141.1 (Ph–C), 147.1 (C3), 166.8 (C=O). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.14–2.42 (m, 4H, CH_2), 3.74 (s, 3H, OCH_3), 4.83–4.85 (m, 1H, 6-H), 5.91 (d, 1H, J 15.8, 2-H), 7.05 (dt, 1H, J_d 15.7, J_t 6.5, 3-H), 7.30–7.33 (m, 1H, Ph–H), 7.35–7.37 (m, 4H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.5 (CH_2), 35.2 (CH_2), 51.5 (OCH_3), 62.5 (C6), 121.8 (C2), 126.8, 128.4, 128.7, 141.1 (Ph–C), 146.8 (C3), 166.8 (C=O). 3-(1′-*Methoxycarbonyl-5′-phenylpent-1′-en-5′-oxy*)-5-(*p-methoxyphenyl*)-4-*methylthiazole-2*(3*H*)-*thione* (**1d**): According to 4.2.1 from methyl 6-chloro-6-phenylhex-2-enoate (2.53 g, 10.60 mmol), 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (4.06 g, 10.60 mmol) and DMF (21 mL). Reaction time: 10 days. The reaction mixture was treated with CH_2Cl_2 (100 mL) and H_2O (100 mL). The layers were separated and the organic layer was kept. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The product was crystallized from Et_2O/pentane. Yield: 3.38 g (7.42 mmol, 70%), pale yellow solid, R_f 0.42 [SiO_2, pentane/Et_2O=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.53 (s, 3H, 4-CH_3), 2.17–2.23 (m, 1H, CH_2), 2.40–2.46 (m, 1H, CH_2), 2.51–2.63 (m, 2H, CH_2), 3.73 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 5.89 (d, 1H, J 15.6, 1′-H), 6.21 (t, 1H, J 7.0, 5′-H), 6.86 (d, 2H, J 8.7, Ar–H), 7.00 (d, 2H, J 8.7, Ar–H), 7.01–7.05 (m, 1H, 2′-H), 7.36–7.39 (m, 4H, Ph–H), 7.40–7.43 (m, 1H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.1 (4-CH_3), 28.5 (CH_2), 30.5 (CH_2), 51.5 ($COOCH_3$), 55.3 (OCH_3), 85.3 (C5′), 114.3 (Ar–C), 118.3 (C5), 121.5 (C1′), 122.6 (Ar–C), 128.8, 129.0, 129.7, 129.9, 133.7 (Ph–C and Ar–C), 136.4 (C4), 147.9 (C2′), 159.7 (Ar–C), 166.9 (C=O), 178.5 (C2). Anal. calcd. for $C_{24}H_{25}NO_4S_2$ (455.59): C, 63.27; H, 5.53; N, 3.07; S, 14.07; found: C, 63.20; H, 5.55; N, 3.12; S, 13.94.

*4.2.6. 3-(1′-Cyano-1′-cyclopropyl-5′-phenylpent-1′-en-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1e**). 2-Cyclopropyl-6-chloro-6-phenylhex-2-enenitrile*: According to 4.2.1 from 2-cyclopropyl-6-hydroxy-6-phenylhex-2-enenitrile (2.48 g, 10.91 mmol), PPh_3 (3.72 g, 14.18 mmol) and CCl_4 (12 mL). Reaction time: 2 h. Eluent used for chromatography: pentane/Et_2O=1:3 (v/v). Yield: 2.26 g [9.20 mmol, 84%, (*E*)/(*Z*)=63:37], yellow oil, R_f 0.53 [SiO_2, pentane/Et_2O=1:3 (v/v)]. (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65–0.69 (m, 1H, cyclopropyl), 0.72–0.80 (m, 2H, cyclopropyl), 0.85–0.89 (m, 1H, cyclopropyl), 1.22–1.23 (m, 1H, cyclopropyl), 2.11–2.32 (m, 2H, CH_2), 2.38–2.55 (m, 2H, CH_2), 4.83–4.86 (m, 1H, 6-H), 6.17 (t, 1H, J 7.7, 3-H), 7.31–7.38 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 5.9, 6.4, 14.1 (cyclopropyl), 29.1 (CH_2), 38.8 (CH_2), 62.5 (C6), 115.5 (CN), 118.8 (C2), 126.8, 128.5, 128.8, 141.0 (Ph–C), 143.1 (C3). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65–0.69 (m, 1H, cyclopropyl), 0.72–0.80 (m, 2H, cyclopropyl), 0.85–0.89 (m, 1H, cyclopropyl), 1.48–1.56 (m, 1H, cyclopropyl), 2.11–2.32 (m, 2H, CH_2), 2.38–2.55 (m, 2H, CH_2), 4.83–4.86 (m, 1H, 6-H), 6.28 (t, 1H, J 7.7, 3-H), 7.31–7.38 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 5.9, 6.4, 9.4 (cyclopropyl), 26.0 (CH_2), 38.4 (CH_2), 62.5 (C6), 117.5 (CN), 119.3 (C2), 126.9, 128.6, 128.7, 140.9 (Ph–C), 144.4 (C3). 3-(1′-*Cyano-1′-cyclopropyl-5′-phenylpent-1′-en-5′-oxy*)-5-(*p-methoxyphenyl*)-4-*methylthiazole-2*(3*H*)-*thione* (**1e**): According to 4.2.1 from 2-cyclopropyl-6-chloro-6-phenylhex-2-enenitrile (623 mg, 2.53 mmol), 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (968 mg, 2.53 mmol) and DMF (5 mL). Reaction time: 7 days. The reaction mixture was treated with Et_2O (20 mL) and H_2O (25 mL). The layers were separated and the organic layer was kept. The aqueous layer was extracted with Et_2O (3×25 mL). Eluent used for chromatography: pentane/Et_2O=1:2 (v/v). Yield: 858 mg [1.85 mmol, 73%, (*E*)/(*Z*)=62:38], yellow oil, R_f 0.41 [SiO_2, pentane/Et_2O=1:2 (v/v)]. (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.66–0.69 (m, 1H, cyclopropyl), 0.74–0.88 (m, 3H, cyclopropyl), 1.24–1.27 (m, 1H, cyclopropyl), 1.52 (s, 3H, 4-CH_3), 2.17–2.25 (m, 1H, CH_2), 2.52–2.65 (m, 3H, CH_2), 3.79 (s, 3H, OCH_3), 6.18–6.24 (m, 1H, 5′-H), 6.38–6.46 (m, 1H, 2′-H), 6.86 (d, 2H, J 8.5, Ar–H), 7.00 (d, 2H, J 8.8, Ar–H), 7.38–7.42 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.9, 6.3 (cyclopropyl), 12.1 (4-CH_3), 14.1 (cyclopropyl), 27.6 (CH_2), 31.1 (CH_2), 55.3 (OCH_3), 85.1 (C5′), 114.4 (Ar–C), 118.3 (CN), 118.4 (C5), 122.6 (C1′), 128.8, 129.1, 129.7, 130.0, 133.7 (Ph–C and Ar–C), 136.1 (C4), 144.0 (C2′), 159.7 (Ar–C), 178.5 (C2). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.66–0.69 (m, 1H, cyclopropyl), 0.74–0.88 (m, 3H, cyclopropyl), 1.24–1.27 (m, 1H, cyclopropyl), 1.53 (s, 3H, 4-CH_3), 2.17–2.25 (m, 1H, CH_2), 2.52–2.65 (m, 3H, CH_2), 3.79 (s, 3H, OCH_3), 6.18–6.24 (m, 1H, 5′-H), 6.38–6.46 (m, 1H, 2′-H), 6.86 (d, 2H, J 8.5, Ar–H), 7.00 (d, 2H, J 8.8, Ar–H), 7.38–7.42 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.9, 6.3, 9.4 (cyclopropyl), 12.1 (4-CH_3), 25.1 (CH_2), 31.1 (CH_2), 55.3 (OCH_3), 85.3 (C5′), 114.4 (Ar–C), 115.7 (CN), 118.7 (C5), 122.5 (C1′), 128.8, 129.0, 129.7, 130.1, 133.7 (Ph–C and Ar–C), 136.4 (C4), 145.3 (C2′), 159.7 (Ar–C), 178.5 (C2).

4.3. 3-Alkoxythiazole-2(3*H*)-thiones 1f–h and 1j from alcohols

4.3.1. General procedure. In an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$), a solution of PPh_3 (3.0 equiv), 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1.5 equiv) and a dienol (1 equiv) in dry benzene (10 mL/mmol) was treated at 0 °C in a dropwise manner with diethyl azodicarboxylate (3.0 equiv). The solution was stirred for 48 h in the dark at 22 °C. The reaction mixture was treated with a 2 M aqueous solution of NaOH (20 mL/mmol). The layers were separated and the organic layer was kept. The aqueous layer was extracted with Et_2O (2×20 mL/mmol) and CH_2Cl_2 (2×20 mL/mmol). Combined organic solutions were washed with H_2O (20 mL/mmol) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by chromatography (SiO_2).

*4.3.2. 3-(9′-Methyldeca-1′,8′-dien-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1f**).* According to 4.3.1 from 9-methyldeca-1,8-dien-5-ol (500 mg, 2.97 mmol) and 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1.13 g, 4.46 mmol). Eluent used for chromatography: pentane/Et_2O=4:1 (v/v). Yield: 718 mg (1.78 mmol, 60%), pale yellow oil, R_f 0.50 [SiO_2, pentane/Et_2O=4:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 3H, CH_3), 1.69 (s,

3H, CH_3), 1.69–1.86 (m, 4H, CH_2), 2.07–2.32 (m, 4H, CH_2), 2.28 (s, 3H, 4-CH_3), 3.83 (s, 3H, OCH_3), 4.98–5.13 (m, 3H, 1′-H and 8′-H), 5.31–5.37 (m, 1H, 5′-H), 5.80–5.90 (m, 1H, 2′-H), 6.93–6.96 (m, 2H, Ar–H), 7.23–7.26 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9 (4-CH_3), 17.9 (CH_3), 23.9 (CH_2), 25.8 (CH_3), 29.4 (CH_2), 31.6 (CH_2), 32.3 (CH_2), 55.6 (OCH_3), 84.7 (C5′), 114.7 (Ar–C), 115.2 (C1′), 119.3 (C5), 123.0 (Ar–C), 123.5 (C8′), 130.0, 131.7, 132.6 (C9′), 138.0 (C2′), 160.1 (Ar–C), 179.4 (C2).

*4.3.3. 3-(1′-Methoxynona-1′,8′-dien-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1g**).* According to 4.3.1 from 1-methoxynona-1,8-dien-5-ol [580 mg, 3.40 mmol, (*E*)/(*Z*)=72:28] and 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (1.29 g, 5.10 mmol). Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). The product was crystallized from pentane/Et_2O. Yield: 921 mg [2.28 mmol, 67%, (*E*)/(*Z*)=80:20], colorless solid, R_f 0.35 [SiO_2, pentane/Et_2O=1:1 (v/v)]. Anal. calcd. for $C_{21}H_{27}NO_3S_2$ (405.58): C, 62.19; H, 6.71; N, 3.45; found: C, 62.13; H, 6.86; N, 3.44. (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.69–1.82 (m, 4H, CH_2), 2.05–2.27 (m, 4H, CH_2), 2.28 (s, 3H, 4-CH_3), 3.51 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.72–4.77 (m, 1H, 2′-H), 4.98–5.01 (m, 1H, 9′-H), 5.04–5.07 (m, 1H, 9′-H), 5.32–5.39 (m, 1H, 5′-H), 5.80–5.88 (m, 1H, 8′-H), 6.34 (d, 1H, *J* 12.6, 1′-H), 6.93–6.96 (m, 2H, Ar–H), 7.23–7.25 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.9 (4-CH_3), 23.6 (CH_2), 29.3 (CH_2), 31.4 (CH_2), 33.5 (CH_2), 55.5 (OCH_3), 56.1 (1′-OCH_3), 84.2 (C5′), 101.9 (C2′), 115.3 (C9′), 114.6 (Ar–C), 119.4, 122.8, 130.0, 133.6, 137.8 (C8′), 147.8 (C1′), 160.0 (Ar–C), 179.2 (C2). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.69–1.82 (m, 4H, CH_2), 2.05–2.27 (m, 4H, CH_2), 2.28 (s, 3H, 4-CH_3), 3.57 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.33–4.37 (m, 1H, 2′-H), 4.98–5.01 (m, 1H, 9′-H), 5.04–5.07 (m, 1H, 9′-H), 5.32–5.39 (m, 1H, 5′-H), 5.80–5.88 (m, 1H, 8′-H), 5.89–5.90 (m, 1H, 1′-H), 6.93–6.96 (m, 2H, Ar–H), 7.23–7.25 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.9 (4-CH_3), 19.6 (CH_2), 29.3 (CH_2), 31.3 (CH_2), 32.0 (CH_2), 55.5 (OCH_3), 56.7 (1′-OCH_3), 84.7 (C5′), 105.3 (C2′), 115.1 (C9′), 114.6 (Ar–C), 119.3, 122.9, 130.0, 133.8, 138.0 (C8′), 147.0 (C1′), 160.0 (Ar–C), 179.2 (C2).

*4.3.4. 3-(1′-Cyanonona-1′,8′-dien-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1h**).* According to 4.3.1 from 6-hydroxydeca-2,9-dienenitrile [1.01 g, 6.09 mmol, (*E*)/(*Z*)=71:29] and 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (2.31 g, 9.14 mmol). Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). The product was crystallized from pentane/Et_2O. Yield: 1.53 g [3.82 mmol, 63%, (*E*)/(*Z*)=72:28], colorless solid, R_f 0.43 [SiO_2, pentane/Et_2O=1:1 (v/v)]. Anal. calcd. for $C_{21}H_{24}N_2O_2S_2$ (400.56): C, 62.97; H, 6.04; N, 6.99; found: C, 62.81; H, 6.08; N, 6.89. (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57–1.87 (m, 4H, CH_2), 2.05–2.09 (m, 2H, CH_2), 2.27 (s, 3H, 4-CH_3), 2.58–2.79 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.99–5.01 (m, 2H, 9′-H), 5.36–5.45 (m, 2H, 1′-H and 5′-H), 5.74–5.84 (m, 1H, 8′-H), 6.76–6.83 (m, 1H, 2′-H), 6.93–6.97 (m, 2H, Ar–H), 7.23–7.26 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.8 (4-CH_3), 29.1 (CH_2), 29.2 (CH_2), 30.5 (CH_2), 31.4 (CH_2), 55.4 (OCH_3), 83.4 (C5′), 100.6 (C1′), 114.5 (Ar–C), 115.8 (C9′), 117.3 (CN), 119.6, 122.4, 129.9 (Ar–C), 133.2, 136.9 (C8′), 154.9 (C2′), 159.6 (Ar–C), 179.2 (C2). (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57–1.87 (m, 4H, CH_2), 2.05–2.09 (m, 2H, CH_2), 2.27 (s, 3H, 4-CH_3), 2.58–2.79 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.99–5.01 (m, 2H, 9′-H), 5.36–5.45 (m, 2H, 1′-H and 5′-H), 5.74–5.84 (m, 1H, 8′-H), 6.65–6.74 (m, 1H, 2′-H), 6.93–6.97 (m, 2H, Ar–H), 7.23–7.26 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.8 (4-CH_3), 27.3 (CH_2), 29.3 (CH_2), 30.7 (CH_2), 31.1 (CH_2), 55.4 (OCH_3), 83.4 (C5′), 100.2 (C1′), 114.5 (Ar–C), 115.8 (C9′), 117.3 (CN), 119.6, 122.4, 129.9 (Ar–C), 133.2, 137.0 (C8′), 154.2 (C2′), 159.6 (Ar–C), 179.2 (C2).

*4.3.5. 3-(1′-Methoxycarbonyl-1′-acetylamino-5′-phenylpent-1′-en-5′-oxy)-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1j**).* In an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$), methyl (6*S*)-2-(acetylamino)-6-hydroxy-6-phenylhex-2-enoate (496 mg, 1.79 mmol), diethylphosphinoethane (713 mg, 1.79 mmol) and 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (681 mg, 2.69 mmol) were dissolved in dry benzene (10 mL). Diethyl azodicarboxylate (655 mg, 3.76 mmol) was added to this solution at 0 °C in a dropwise manner. The resulting mixture was stirred for 18.5 h in the dark at 22 °C. The solution was treated with 2 M aqueous NaOH (20 mL) and CH_2Cl_2 (20 mL). The layers were separated and the organic layer was kept. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL). Combined organic layers were washed with brine (2×20 mL) and concentrated under reduced pressure. The residue was purified by chromatography [SiO_2, pentane/EtOAc=1:3 (v/v)]. Yield: 291 mg (0.55 mmol, 31%), pale yellow solid, R_f 0.33 [SiO_2, pentane/EtOAc=1:3 (v/v)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (s, 3H, CH_3), 2.09 (s, 3H, 4-CH_3), 2.22–2.30 (m, 1H, CH_2), 2.42–2.53 (m, 2H, CH_2), 2.59–2.66 (m, 1H, CH_2), 3.78 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3), 6.24 (t, 1H, *J* 7.0, 5′-H), 6.75 (t, 1H, *J* 7.4, 2′-H), 6.86 (d, 2H, *J* 8.6, Ar–H), 6.98 (d, 2H, *J* 8.6, Ar–H), 7.20 (br s, 1H, NH), 7.34–7.39 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.2 (4-CH_3), 23.3 (CH_3), 25.2 (CH_2), 30.4 (CH_2), 52.4 ($COOCH_3$), 55.4 (OCH_3), 85.2 (C5′), 114.4 (Ar–C), 118.6 (C5), 122.5 (C1′), 126.1, 128.7, 129.2, 129.3, 130.0, 133.9 (Ph–C and Ar–C), 136.2 (C4), 137.3 (C2′), 159.3 (Ar–C), 165.0 (C=O), 168.9 (C=O), 178.3 (C2).

4.4. 3-Alkoxythiazole-2(3*H*)-thione 1i from alkenyl tosylates

*4.4.1. 3-[1′-(Methoxycarbonyl)nona-1′,8′-dien-5′-oxy]-5-(p-methoxyphenyl)-4-methylthiazole-2(3H)-thione (**1i**).* A solution of 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione tetraethylammonium salt (4.00 mmol) in dry DMF was treated in an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$) with (*E*)-1-(methoxycarbonyl)nona-1,8-dien-5-yl *p*-toluene sulfonate (1.41 g, 4.00 mmol) and stirred for 3 days in the dark at 22 °C. The reaction mixture was treated with H_2O (50 mL) and Et_2O (30 mL). The layers were separated and the organic layer was kept. The aqueous layer was extracted with Et_2O (2×30 mL). Combined organic layers were washed with a 2 M aqueous solution of NaOH (2×20 mL) and with brine (20 mL). The organic solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography [SiO_2, pentane/Et_2O=1:1 (v/v)] and then crystallized from pentane/Et_2O. Yield: 844 mg (1.95 mmol, 49%), colorless solid, R_f 0.24 [SiO_2, pentane/Et_2O=1:1 (v/v)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.73–1.93 (m, 4H, CH_2), 2.16–2.33 (m, 5H, 4-CH_3 and CH_2), 2.47–2.50 (m, 2H, CH_2), 3.73 (s, 3H, $COOCH_3$), 3.84 (s, 3H, OCH_3), 5.00–5.07 (m, 2H, 9′-H), 5.38–5.40 (m, 1H, 5′-H), 5.78–5.89 (m, 2H, 1′-H and 8′-H), 6.94–7.02 (m, 3H, 2′-H and Ar–H), 7.24–7.25 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.8 (4-CH_3), 27.9 (CH_2), 29.3 (CH_2), 30.7 (CH_2), 31.3 (CH_2), 51.5 ($COOCH_3$), 55.4 (OCH_3), 83.8 (C5′), 114.6, 115.6 (C9′), 119.3, 121.5 (C1′), 122.6, 129.9, 133.3, 137.3 (C8′), 148.2 (C2′), 156.0 (Ar–C), 167.0 (C=O), 179.2 (C2). Anal. calcd. for $C_{22}H_{27}NO_4S_2$ (433.58): C, 60.94; H, 6.28; N, 3.23; found: C, 60.52; H, 6.14; N 3.60.

4.5. Conversion of 3-alkoxythiazolethiones 1a–e and 1j with Bu_3SnH or Bu_3SnD

4.5.1. General procedure. To a solution of 3-alkoxylthiazole-2(3*H*)-thione **1** (1 equiv, c^0=50 mM) in deaerated benzene was added Bu_3SnH or Bu_3SnD (3.7 equiv, c^0=185 mM). The solution was photolyzed for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by chromatography (SiO_2).

*4.5.2. Conversion of **1a** with Bu_3SnH.* According to 4.5.1 from 3-(1′-cyanohex-1′-en-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-

2(3*H*)-thione (**1a**) (252 mg, 0.70 mmol) and Bu_3SnH (754 mg, 0.69 mL, 2.59 mmol) in benzene (14 mL). Eluent used for chromatography: CH_2Cl_2. (5-*Methyltetrahydrofuran-2-yl*)*acetonitrile* (**5a**): Yield: 61 mg (0.48 mmol, 69%, *cis*/*trans*=38:62), pale yellow oil, R_f 0.20 (SiO_2, CH_2Cl_2). HRMS: calcd. for $C_7H_{10}NO$ [M^+−H]: 124.0762; found: 124.0780. cis-isomer: MS (EI, 70 eV) *m/z* 124 (2), 110 (27), 85 (100), 82 (42), 80 (7), 67 (22), 57 (22), 55 (40). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.26 (d, 3H, *J* 6.2, CH_3), 1.51–1.62 (m, 1H, CH_2), 1.75–1.82 (m, 1H, CH_2), 2.00–2.05 (m, 1H, CH_2), 2.10–2.16 (m, 1H, CH_2), 2.51–2.61 (m, 2H, CH_2CN), 4.00–4.05 (m, 1H, 2-H), 4.09–4.13 (m, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.0 (CH_3), 24.6 (*C*H_2CN), 30.8 (CH_2), 32.6 (CH_2), 74.0 (C5), 76.6 (C2), 117.5 (CN). trans-isomer: MS (EI, 70 eV) *m/z* 124 (3), 110 (25), 85 (100), 82 (49), 80 (10), 67 (28), 57 (28), 55 (49). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.22 (d, 3H, *J* 6.1, CH_3), 1.51–1.62 (m, 1H, CH_2), 1.75–1.82 (m, 1H, CH_2), 2.10–2.16 (m, 1H, CH_2), 2.19–2.24 (m, 2H, CH_2), 2.51–2.61 (m, 2H, CH_2CN), 4.20–4.28 (m, 2H, 2-H and 5-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.9 (CH_3), 24.3 (*C*H_2CN), 31.7 (CH_2), 33.6 (CH_2), 73.6 (C5), 76.1 (C2), 117.6 (CN).

4.5.3. Conversion of ***1b*** *with* Bu_3SnH. According to 4.5.1 from 3-(1′-cyano-5′-phenylpent-1′-en-5′-oxy)-5-(*p*-methoxylphenyl)-4-methylthiazole-2(3*H*)-thione (**1b**) (212 mg, 0.50 mmol) and Bu_3SnH (538 mg, 0.49 mL, 1.85 mmol) in benzene (10 mL). Eluent used for chromatography: CH_2Cl_2. (5-*Phenyltetrahydrofuran-2-yl*)*acetonitrile* (**5b**): Yield: 63 mg (0.34 mmol, 67%, *cis*/*trans*=44:56), pale yellow oil, R_f 0.30 (SiO_2, CH_2Cl_2). HRMS: calcd. for $C_{12}H_{13}NO$ (M^+): 187.0997; found: 187.0989. cis-isomer: MS (EI, 70 eV) *m/z* 186 (36), 147 (9), 144 (42), 129 (9), 120 (32), 117 (27), 115 (16), 105 (100), 91 (36), 77 (42), 51 (21). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.92–2.00 (m, 2H, CH_2), 2.25–2.38 (m, 2H, CH_2), 2.63–2.76 (m, 2H, CH_2CN), 4.30–4.34 (m, 1H, 2-H), 4.92 (t, 1H, *J* 7.3, 5-H), 7.27–7.39 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.4 (*C*H_2CN), 30.9 (CH_2), 34.0 (CH_2), 74.2 (C5), 81.5 (C2), 117.4 (CN), 125.8, 127.6, 128.4, 141.5 (Ph–C). trans-isomer: MS (EI, 70 eV) *m/z* 186 (35), 147 (8), 144 (41), 129 (11), 120 (32), 117 (27), 115 (17), 105 (100), 91 (36), 77 (39), 51 (21). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.92–2.00 (m, 2H, CH_2), 2.25–2.38 (m, 1H, CH_2), 2.45–2.49 (m, 1H, CH_2), 2.63–2.76 (m, 2H, CH_2CN), 4.46–4.50 (m, 1H, 2-H), 5.15 (t, 1H, *J* 7.2, 5-H), 7.27–7.39 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.4 (*C*H_2CN), 31.7 (CH_2), 35.0 (CH_2), 74.6 (C5), 82.0 (C2), 117.4 (CN), 125.5, 127.5, 128.4, 142.2 (Ph–C).

4.5.4. Conversion of ***1b*** *with* Bu_3SnD. According to 4.5.1 from 3-(1′-cyano-5′-phenylpent-1′-en-5′-oxy)-5-(*p*-methoxylphenyl)-4-methylthiazole-2(3*H*)-thione (**1b**) (211 mg, 0.50 mmol) and Bu_3SnD (540 mg, 0.49 mL, 1.85 mmol) in benzene (10 mL). Eluent used for chromatography: CH_2Cl_2. (5-*Phenyltetrahydrofuran-2-yl*)-*2-d*$_1$-*acetonitrile* (**5b$_{d1}$**): Yield: 69 mg (0.37 mmol, 74%, *cis*/*trans*=46:54), pale yellow oil, R_f 0.41 (SiO_2, CH_2Cl_2). cis-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.92–1.99 (m, 2H, CH_2), 2.25–2.38 (m, 2H, CH_2), 2.63–2.73 (m, 1H, CHCN), 4.30–4.33 (m, 1H, 2-H), 4.91 (t, 1H, *J* 7.3, 5-H), 7.27–7.39 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.13 (t, $^1J_{C,D}$ 20.34, *C*HDCN), 30.8 (CH_2), 34.0 (CH_2), 74.2 (C5′), 82.0 (C2′), 117.4 (CN), 125.8, 127.6, 128.4, 141.6 (Ph–C). trans-isomer: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.92–1.99 (m, 2H, CH_2), 2.25–2.38 (m, 1H, CH_2), 2.44–2.50 (m, 1H, CH_2), 2.63–2.73 (m, 1H, CHCN), 4.46–4.50 (m, 1H, 2-H), 5.14 (t, 1H, *J* 7.2, 5-H), 7.27–7.39 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.13 (t, $^1J_{C,D}$ 20.34, *C*HDCN), 31.7 (CH_2), 35.0 (CH_2), 74.5 (C5′), 81.4 (C2′), 117.4 (CN), 125.4, 127.5, 128.4, 142.2 (Ph–C).

4.5.5. Conversion of ***1c*** *with* Bu_3SnH. According to 4.5.1 from 3-[(1′-(methoxycarbonyl)hex-1′-en-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1c**) (249 mg, 0.63 mmol) and Bu_3SnH (678 mg, 0.62 mL, 2.33 mmol) in benzene (12.5 mL). Eluent used for chromatography: pentane/Et_2O=2:1 (v/v). *Methyl* (5-*methyltetrahydrofuran-2-yl*)*acetate* (**5c**): Yield: 68 mg (0.43 mmol, 68%, *cis*/*trans*=37:63), pale yellow oil, R_f 0.43 [SiO_2, pentane/Et_2O=2:1 (v/v)]. cis-isomer: MS (EI, 70 eV) *m/z* 157 (1), 143 (9), 127 (4), 116 (63), 111 (15), 85 (89), 83 (30), 67 (22), 59 (37), 55 (100). HRMS: calcd. for $C_8H_{14}O_3$ [M^+]: 158.0943; Found: 158.0950. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19–1.23 (m, 3H, 5-CH_3), 1.42–1.53 (m, 1H, CH_2), 1.55–1.64 (m, 1H, CH_2), 1.94–2.08 (m, 2H, CH_2), 2.41–2.50 (m, 1H, CH_2COOCH$_3$), 2.57–2.66 (m, 1H, CH_2COOCH$_3$), 3.68 (s, 3H, OCH_3), 3.93–4.01 (m, 1H, 2-H), 4.19–4.26 (m, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4 (5-CH_3), 31.2 (CH_2), 32.6 (CH_2), 41.0 (*C*H_2COOCH$_3$), 51.6 (OCH_3), 75.3 (C5), 75.7 (C2). trans-isomer: MS (EI, 70 eV) *m/z* 157 (2), 143 (6), 127 (6), 116 (56), 111 (14), 101 (14), 85 (82), 83 (30), 67 (23), 59 (41), 55 (100). HRMS: calcd. for $C_8H_{14}O_3$ [M^+]: 158.0943; Found: 158.0947. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19–1.23 (m, 3H, 5-CH_3), 1.42–1.53 (m, 1H, CH_2), 1.55–1.64 (m, 1H, CH_2), 1.94–2.08 (m, 1H, CH_2), 2.10–2.19 (m, 1H, CH_2), 2.41–2.50 (m, 1H, CH_2COOCH$_3$), 2.57–2.66 (m, 1H, CH_2COOCH$_3$), 3.86 (s, 3H, OCH_3), 4.07–4.15 (m, 1H, 2-H), 4.37–4.44 (m, 1H, 5-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2 (5-CH_3), 32.1 (CH_2), 33.6 (CH_2), 40.8 (*C*H_2COOCH$_3$), 51.6 (OCH_3), 74.8 (C5), 75.0 (C2).

4.5.6. Conversion of ***1d*** *with* Bu_3SnH. According to 4.5.1 from 3-(1′-methoxycarbonyl-5′-phenylpent-1′-en-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1d**) (319 mg, 0.70 mmol) and Bu_3SnH (754 mg, 0.69 mL, 2.59 mmol) in benzene (14 mL). Eluent used for chromatography: pentane/Et_2O=2:1 (v/v). *Methyl* (5-*phenyltetrahydrofuran-2-yl*)*acetate* (**5d**): Yield: 111 mg (0.50 mmol, 71%, *cis*/*trans*=41:59), colorless oil, R_f 0.24 [SiO_2, pentane/Et_2O=2:1 (v/v)]. HRMS: calcd. for $C_{13}H_{16}O_3$ [M^+]: 220.1099; found: 220.1105. cis-isomer: MS (EI, 70 eV) *m/z* 220 (M^+, 7), 219 (5), 147 (28), 129 (12), 120 (100), 117 (26), 105 (46), 91 (37), 77 (28), 55 (22). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71–1.80 (m, 1H, CH_2), 1.82–1.94 (m, 1H, CH_2), 2.16–2.43 (m, 2H, CH_2), 2.53–2.64 (m, 1H, CH_2COOCH$_3$), 2.71–2.82 (m, 1H, CH_2COOCH$_3$), 3.71 (s, 3H, OCH_3), 4.43–4.50 (m, 1H, 2-H), 4.91 (t, 1H, *J* 7.1, 5-H), 7.23–7.27 (m, 1H, Ph–H), 7.32–7.33 (m, 4H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.2 (CH_2), 34.3 (CH_2), 40.8 (*C*H_2COOCH$_3$), 51.7 (OCH_3), 75.8 (C5), 81.2 (C2), 125.7, 127.2, 128.3, 142.8 (Ph–C), 171.6 (C=O). trans-isomer: MS (EI, 70 eV) *m/z* 220 (M^+, 6), 219 (3), 147 (24), 129 (12), 120 (100), 117 (22), 105 (43), 91 (32), 77 (22), 55 (16). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.71–1.80 (m, 1H, CH_2), 1.82–1.94 (m, 1H, CH_2), 2.16–2.43 (m, 2H, CH_2), 2.53–2.64 (m, 1H, CH_2COOCH$_3$), 2.71–2.82 (m, 1H, CH_2COOCH$_3$), 3.72 (s, 3H, OCH_3), 4.60–4.66 (m, 1H, 2-H), 5.04 (t, 1H, *J* 7.1, 5-H), 7.23–7.27 (m, 1H, Ph–H), 7.32–7.33 (m, 4H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 32.1 (CH_2), 35.1 (CH_2), 40.7 (*C*H_2COOCH$_3$), 51.7 (OCH_3), 75.9 (C5), 80.5 (C2), 125.5, 127.1, 128.3, 143.3 (Ph–C), 171.7 (C=O).

4.5.7. Conversion of ***1j*** *with* Bu_3SnH. According to 4.5.1 from 3-(1′-methoxycarbonyl-1′-acetylamino-5′-phenylpent-1′-en-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1j**) (179 mg, 0.35 mmol) and Bu_3SnH (378 mg, 0.34 mL, 1.30 mmol) in benzene (7 mL). Eluent used for chromatography: pentane/EtOAc=1:3 (v/v). *rel*-(2*R*,6*R*)-*Methyl N-acetylamino*-(5-*phenyltetrahydrofuran-2-yl*) *acetate rel*-(2*R*,6*R*)-(**5j**): Yield: 18 mg (65.0 μmol, 19%, *cis*/*trans*=32:68), pale yellow oil, R_f 0.45 [SiO_2, pentane/EtOAc=1:3 (v/v)]. *rel*-(2*R*,5*S*,6*R*)-(**5j**) (cis-isomer): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76–1.87 (m, 2H, CH_2), 1.91 (s, 3H, CH_3), 2.06–2.08 (m, 1H, CH_2), 2.25–2.31 (m, 1H, CH_2), 3.72 (s, 3H, OCH_3), 4.50 (td, 1H, J_t 7.1, J_d 2.6, 2-H), 4.75 (dd, 1H, *J* 9.0, 2.6, 6-H), 4.83 (t, 1H, *J* 7.0, 5-H), 6.08 (d, 1H, *J* 8.8, NH), 7.16–7.32 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (CH_3), 28.2 (CH_2), 33.5 (CH_2), 52.6 (OCH_3), 54.7 (C6), 79.2 (C5), 81.0 (C2), 125.6, 127.6, 128.5, 141.9 (Ph–C), 170.4 (C=O), 171.0 (C=O). *rel*-(2*R*,5*R*,6*R*)-(**5j**) (trans-isomer): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76–1.87 (m, 2H, CH_2), 2.05 (s, 3H, CH_3), 2.06–2.08 (m, 1H, CH_2), 2.25–2.31 (m, 1H, CH_2), 3.73 (s, 3H, OCH_3), 4.62 (td, 1H, J_t 7.3, J_d 2.5, 2-H), 4.71 (dd, 1H, *J* 8.8, 2.7, 6-H), 4.95 (t, 1H, *J* 7.0, 5-H), 6.31 (d, 1H, *J* 8.7, NH), 7.16–7.32 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (CH_3), 29.0 (CH_2), 35.1 (CH_2), 52.6 (OCH_3), 54.8 (C6), 79.4 (C5), 81.8

(C2), 125.4, 127.4, 128.4, 142.7 (Ph–C), 170.6 (C=O), 171.1 (C=O). *rel*-(2*R*,6*S*)-*Methyl N-acetylamino*-(5-*phenyltetrahydrofuran*-2-*yl*) *acetate rel*-(2*R*,6*S*)-(**5j**): Yield: 53 mg (0.19 mmol, 54%, *cis*/*trans*=28:72), pale yellow oil, R_f 0.37 [SiO_2, pentane/EtOAc=1:3 (v/v)]. *rel*-(2*R*,5*S*,6*S*)-(**5j**) (cis-isomer): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60–1.70 (m, 1H, CH_2), 1.97 (s, 3H, CH_3), 2.08–2.14 (m, 1H, CH_2), 2.16–2.22 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 4.22–4.26 (m, 1H, 2-H), 4.75–4.78 (m, 2H, 5-H and 6-H), 6.55 (br s, 1H, NH), 7.17–7.28 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (CH_3), 28.3 (CH_2), 34.3 (CH_2), 52.4 (OCH_3), 55.5 (C6), 80.0 (C5), 81.8 (C2), 125.6, 127.5, 128.3, 141.6 (Ph–C), 169.8 (C=O), 170.5 (C=O). *rel*-(2*R*,5*R*,6*S*)-(**5j**) (trans-isomer): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76–1.85 (m, 1H, CH_2), 1.98 (s, 3H, CH_3), 2.08–2.14 (m, 2H, CH_2), 2.24–2.32 (m, 1H, CH_2), 3.72 (s, 3H, OCH_3), 4.38 (td, 1H, J_t 7.1, J_d 4.6, 2-H), 4.70 (dd, 1H, *J* 8.6, 4.6, 6-H), 4.90 (t, 1H, *J* 7.1, 5-H), 6.55 (br s, 1H, NH), 7.17–7.28 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (CH_3), 28.6 (CH_2), 34.5 (CH_2), 52.4 (OCH_3), 55.5 (C6), 80.6 (C5), 81.4 (C2), 125.5, 127.4, 128.3, 142.5 (Ph–C), 169.8 (C=O), 170.8 (C=O).

4.6. Conversion of 3-alkoxythiazolethiones 1d and 1e with $BrCCl_3$

4.6.1. Conversion of ***1d****.* To a solution of 3-(1′-methoxycarbonyl-5′-phenylpent-1′-en-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1d**) (456 mg, 1.00 mmol) in deaerated benzene (12 mL) was added $BrCCl_3$ (1.98 g, 1.00 mL, 10.00 mmol) and AIBN (41 mg, 0.25 mmol). The reaction mixture was stirred for 3 h at 80 °C. The solvent was removed under reduced pressure and the residue was purified by chromatography. R_f 0.49 [SiO_2, pentane/Et_2O=1:1 (v/v)]: *Methyl* 2-*bromo*-2-(5′-*phenyltetrahydrofuran*-2′-*yl*) *acetate* (**9d**)[24] [Yield: 62 mg (0.21 mmol, 21%, *cis*/*trans*=44:56) as a mixture of diastereomers $A_{cis/trans}$ and $B_{cis/trans}$] and 5-(*p*-*methoxyphenyl*)-4-*methyl*-2-(*trichloromethylsulfanyl*)*thiazole* (**3b**) [Yield: 106 mg (0.23 mmol, 30%)], yellow oil. *Methyl* 2-*bromo*-2-(5′-*phenyltetrahydrofuran*-2′-*yl*)*acetate* (**9d**): cis-isomer (diastereomer A and B): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.82–2.09 (m, 2H, CH_2), 2.18–2.47 (m, 2H, CH_2), 3.79 and 3.82 (s, 3H, OCH_3), 4.23 (d, 1H, *J* 8.6, CHBr), 4.47–4.61 (m, 1H, 2′-H), 4.94–5.02 (m, 1H, 5′-H), 7.26–7.36 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.6, 29.8 (CH_2), 34.1, 35.0 (CH_2), 47.3, 48.6 (CHBr), 53.0 (OCH_3), 79.4, 79.5 (C2′), 82.0, 82.7 (C5′), 125.6, 125.7, 128.3 (2C), 129.0, 129.7, 141.79, 141.83 (Ph–C), 168.6, 168.9 (C=O). trans-isomer (diastereomer A and B): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.82–2.09 (m, 2H, CH_2), 2.18–2.47 (m, 2H, CH_2), 3.80 and 3.81 (s, 3H, OCH_3), 4.22 (d, 0.3H, *J* 8.7, A-CHBr), 4.38 (d, 0.7H, *J* 6.9, B-CHBr), 4.64–4.75 (m, 1H, 2′-H), 5.05–5.12 (m, 1H, 5′-H), 7.26–7.36 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 30.0, 30.4 (CH_2), 34.9, 35.3 (CH_2), 47.6, 48.2 (CHBr), 53.0, 53.1 (OCH_3), 79.5, 79.7 (C2′), 81.7, 81.8 (C5′), 125.5, 125.6, 127.4, 127.5, 128.3 (2C), 142.22, 142.23 (Ph–C), 168.7, 169.0 (C=O). 5-(*p*-*methoxyphenyl*)-4-*methyl*-2-(*trichloromethylsulfanyl*)*thiazole* (**3b**): NMR data agreed with published values.[5] R_f 0.33 [SiO_2, pentane/Et_2O=1:1 (v/v)]: Methyl 2-[5″-(*p*-methoxyphenyl)-4″-methyl-2″-(methylsulfanyl)-thiazole]-2-(5′-phenyltetrahydrofuran-2′-yl)acetate (**8d**): Yield: 282 mg (0.62 mmol, 62%, *cis*/*trans*=43:57) as a mixture of diastereomers $A_{cis/trans}$ and $B_{cis/trans}$, yellow oil. cis-isomer (diastereomer A and B): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85–2.00 (m, 1H, CH_2), 2.09–2.33 (m, 3H, CH_2), 2.41 (s, 3H, 4″-CH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.36–4.40 (m, 1H, CHS), 4.63–4.87 (m, 1H, 2′-H), 4.90–5.01 (m, 1H, 5′-H), 6.91–6.91 (m, 2H, Ar–H), 7.26–7.32 (m, 7H, Ph–H and Ar–H). trans-isomer (diastereomer A and B): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.85–2.00 (m, 1H, CH_2), 2.09–2.33 (m, 3H, CH_2), 2.41 (s, 3H, 4″-CH_3), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.36–4.40 and 4.63–4.66 (m, 1H, CHS), 4.63–4.87 (m, 1H, 2′-H), 5.05–5.16 (m, 1H, 5′-H), 6.91–6.91 (m, 2H, Ar–H), 7.26–7.32 (m, 7H, Ph–H and Ar–H). cis- and trans-isomer (diastereomer A and B): ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 15.92, 16.1 (CH_3), 29.36, 29.43, 29.8, 30.0 (CH_2), 34.2, 34.4, 34.6, 34.9 (CH_2), 52.4, 52.5, 52.6 (CHS), 54.55, 54.6, 55.1, 55.2, 55.4, 55.6 (2× OCH_3), 78.5, 78.8, 79.2, 79.3 (C2′), 81.1, 81.5, 81.8, 82.1 (C5′), 113.97, 113.99, 114.2 (Ar–C), 121.2, 121.5, 123.5, 123.6 (C5″), 125.35, 125.4, 125.5, 125.6, 127.08, 127.09, 127.1, 127.2, 127.8, 128.07, 128.1, 128.2, 128.5 (Ph–C), 130.1, 130.3 (Ar–C), 133.02, 133.06, 134.05, 134.1 (Ar–C), 141.6, 142.0, 142.4, 142.6 (Ar–C), 147.1, 147.2, 147.57, 147.6 (C4″), 155.87, 155.89, 157.4, 157.6 (C2″), 159.16, 159.2, 159.8 (Ar–C), 170.1, 170.2 (C=O).

4.6.2. Conversion of ***1e****.* To a solution of 3-(1′-cyano-1′-cyclopropyl-5′-phenylpent-1′-en-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**) (467 mg, 1.01 mmol) in deaerated benzene (20 mL) was added $BrCCl_3$ (2.00 g, 1.00 mL, 10.10 mmol). The solution was photolyzed for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by chromatography. R_f 0.31 [SiO_2, pentane/Et_2O=3:1 (v/v)]: 5-*bromo*-2-(*trans*-5′-*phenyltetrahydrofuran*-2′-*yl*)-*pent*-2-*enenitrile trans*-(**5ε**) [Yield: 43 mg (0.14 mmol, 17% with respect of converted **1e**)], 2-*cyclopropyl*-6-*oxo*-6-*phenylhex*-2-*enenitrile* (**10**) [Yield: 14 mg (0.06 mmol, 7% with respect of converted **1e**)] and 5-(*p*-*methoxyphenyl*)-4-*methyl*-2-(*trichloromethylsulfanyl*)-*thiazole* (**3b**) [Yield: 124 mg (0.35 mmol, 41% with respect of converted **1e**)], yellow oil. 5-*Bromo*-2-(*trans*-5′-*phenyltetrahydrofuran*-2′-*yl*)-*pent*-2-*enenitrile trans*-(**5ε**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91–2.00 (m, 1H, CH_2), 2.06–2.16 (m, 1H, CH_2), 2.33–2.42 (m, 1H, CH_2), 2.43–2.50 (m, 1H, CH_2), 2.96–3.00 (m, 2H, CH_2), 3.47 (t, 2H, *J* 6.5, CH_2Br), 4.78 (t, 1H, *J* 7.0, 2′-H), 5.16–5.19 (m, 1H, 5′-H), 6.54 (t, 1H, *J* 7.2, 3-H), 7.27–7.43 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0, 32.1, 33.7, 34.7 (CH_2), 79.3 (C2′), 81.8 (C5′), 115.7 (CN), 120.1 (C2), 125.5, 127.6, 128.4, 142.1 (Ph–C), 143.5 (C3). 2-*Cyclopropyl*-6-*oxo*-6-*phenylhex*-2-*enenitrile* (**10**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.69–0.90 (m, 4H, cyclopropyl), 1.50–1.57 (m, 1H, cyclopropyl), 2.74–2.80 (m, 2H, CH_2), 3.15 (t, 2H, *J* 6.9, CH_2), 6.37 (t, 1H, *J* 7.6, 3-H), 7.45–7.49 (m, 2H, Ph–H), 7.56–7.60 (m, 1H, Ph–H), 7.95–7.97 (m, 2H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.9, 14.1 (cyclopropyl), 25.7, 37.3 (CH_2), 115.7 (CN), 118.5 (C2), 128.0, 128.7, 133.3, 136.5 (Ph–C), 143.9 (C3), 198.2 (C=O). 5-(*p*-*Methoxyphenyl*)-4-*methyl*-2-(*trichloromethylsulfanyl*)-*thiazole* (**3b**): NMR data agreed with published values.[5] R_f 0.28–0.15 [SiO_2, pentane/Et_2O=3:1 (v/v)]: 5-*bromo*-2-(5′-*phenyltetrahydrofuran*-2′-*yl*)-*pent*-2-*enenitrile* (**5ε**) [Yield: 73 mg (0.24 mmol, 29% with respect of converted **1e**, *cis*/*trans*=18:82) and 2-*cyclopropyl*-6-*oxo*-6-*phenylhex*-2-*enenitrile* (**10**) [Yield: 16 mg (0.13 mmol, 9% with respect of converted **1e**, (*E*)/(*Z*)= 58:42)], yellow oil. 5-*Bromo*-2-(5′-*phenyltetrahydrofuran*-2′-*yl*)-*pent*-2-*enenitrile* (**5ε**): cis-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90–2.00 (m, 1H, CH_2), 2.07–2.16 (m, 1H, CH_2), 2.32–2.41 (m, 1H, CH_2), 2.43–2.52 (m, 1H, CH_2), 2.96–3.01 (m, 2H, CH_2), 3.48 (t, 2H, *J* 6.5, CH_2Br), 4.61 (t, 1H, *J* 6.4, 2′-H), 4.92–4.96 (m, 1H, 5′-H), 6.54 (t, 1H, *J* 7.4, 3-H), 7.27–7.43 (m, 5H, Ph–H). ^{13}C NMR ($CDCl_3$, 100 MHz) 30.0, 31.6, 33.8, 34.7 (CH_2), 79.0 (C2′), 82.3 (C5′), 117.4 (CN), 119.8 (C2), 126.1, 127.8, 128.5, 141.2 (Ph–C), 145.1 (C3). trans-isomer: NMR data agreed with values from an authentic sample. 2-*Cyclopropyl*-6-*oxo*-6-*phenylhex*-2-*enenitrile* (**10**): ^{1}H NMR data agreed with values from an authentic sample. ^{13}C NMR ($CDCl_3$, 100 MHz) 5.8, 6.4, 9.3, 14.1 (cyclopropyl), 22.9, 25.7 (CH_2), 36.9, 37.3 (CH_2), 115.7, 155.8 (CN), 118.5, 118.9 (C2), 127.95, 128.0, 128.68, 128.7, 133.3, 133.4, 136.48, 136.5 (Ph–C), 143.9, 144.3 (C3), 198.1, 198.2 (C=O). R_f 0.13 [SiO_2, pentane/Et_2O=3:1 (v/v)]: 5-*bromo*-2-(*cis*-5′-*phenyltetrahydrofuran*-2′-*yl*)-*pent*-2-*enenitrile* (**5ε**) [Yield: 41 mg (0.13 mmol, 16% with respect of converted **1e**)] and 3-(1′-cyano-1′-cyclopropyl-5′-phenylpent-1′-en-5′-oxy)-5-(4-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**) [Yield: 76 mg (0.16 mmol, 16%)], yellow oil. 5-*Bromo*-2-(*cis*-5′-*phenyltetrahydrofuran*-2′-*yl*)-*pent*-2-*enenitrile cis*-(**5ε**): NMR data agreed with values from an authentic sample. 3-(1′-cyano-1′-cyclopropyl-5′-phenylpent-1′-en-5′-oxy)-5-(4-methoxy-

phenyl)-4-methylthiazole-2(3*H*)-thione (**1e**): NMR data agreed with values from 4.2.6.

4.7. Conversion of 3-alkoxythiazolethiones 1f–i with Bu_3SnH or Bu_3SnD

4.7.1. General procedure. To a solution of 3-alkoxythiazole-2(3*H*)-thione **1** (1 equiv, c^0=55 mM) in deaerated benzene was added Bu_3SnH or Bu_3SnD (3.7 equiv, c^0=205 mM). The solution was photolyzed for 45 min. The solvent was removed under reduced pressure and the residue was purified by chromatography (SiO_2).

*4.7.2. Conversion of **1f** with Bu_3SnH.* According to 4.7.1 from 3-(9′-methyldeca-1′,8′-dien-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1f**) (202 mg, 500 μmol), Bu_3SnH (540 mg, 0.49 mL, 1.85 mmol) and benzene (9 mL). Eluent used for chromatography: pentane/Et_2O=3:1 (v/v). 2-(*But*-3′-*en*-1′-*yl*)-5-(1″-*methylethyl*)-*tetrahydrofuran* (**5f**): Yield: 79 mg (466 μmol, 93%, *cis*/*trans*=32:68), colorless oil, R_f 0.69 [SiO_2, pentane/Et_2O=3:1 (v/v)]. cis-isomer: MS (EI, 70 eV) *m*/*z* 168 (M^+, 0.4), 125 (92), 113 (14), 97 (33), 95 (78), 81 (84), 55 (100). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, 3H, *J* 6.6, CH_3), 0.95 (d, 3H, *J* 6.6, CH_3), 1.42–2.17 (m, 9H, CH and CH_2), 3.48–3.54 (m, 1H, 5-H), 3.78–3.93 (m, 1H, 2-H), 4.92–5.04 (m, 2H, 4′-H), 5.78–5.89 (m, 1H, 3′-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5 (CH_3), 19.5 (CH_3), 28.5 (CH_2), 30.6 (CH_2), 31.3 (CH_2), 33.4 (CH), 35.4 (CH_2), 78.8 (C2), 84.9 (C5), 114.4 (C4′), 138.9 (C3′). trans-isomer: MS (EI, 70 eV) *m*/*z* 168 (M^+, 3), 125 (90), 113 (14), 97 (34), 95 (77), 81 (88), 55 (100). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, 3H, *J* 6.6, CH_3), 0.95 (d, 3H, *J* 6.6, CH_3), 1.42–2.17 (m, 9H, CH and CH_2), 3.58–3.64 (m, 1H, 5-H), 3.78–3.93 (m, 1H, 2-H), 4.92–5.04 (m, 2H, 4′-H), 5.78–5.89 (m, 1H, 3′-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.4 (CH_3), 19.5 (CH_3), 29.6 (CH_2), 30.6 (CH_2), 32.5 (CH_2), 33.4 (CH), 35.3 (CH_2), 78.5 (C2), 84.2 (C5), 114.5 (C4′), 138.8 (C3′).

*4.7.3. Conversion of **1g** with Bu_3SnH.* According to 4.7.1 from 3-(1′-methoxynona-1′,8′-dien-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1g**) (292 mg, 719 μmol), Bu_3SnH (774 mg, 0.70 mL, 2.66 mmol) and benzene (13 mL). Eluent used for chromatography: pentane/Et_2O=2:1 (v/v). 2-(*But*-3′-*en*-1′-*yl*)-5-(*methoxymethyl*)-*tetrahydrofuran* (**5g**): Yield: 114 mg (670 μmol, 93%, *cis*/*trans*=35:65), colorless oil, R_f 0.44 [SiO_2, pentane/Et_2O=2:1 (v/v)]. MS (EI, 70 eV) *m*/*z* 170 (M^+, 0.04), 125 (58), 115 (7), 97 (15), 81 (64), 55 (100). cis-isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46–1.79 (m, 4H, CH_2), 1.89–2.18 (m, 4H, CH_2), 3.37–3.40 (m, 5H, OCH_3 and CH_2OCH_3), 3.82–3.89 (m, 1H, 5-H), 3.92–4.06 (m, 1H, 2-H), 4.92–5.04 (m, 2H, 4′-H), 5.77–5.88 (m, 1H, 3′-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0 (CH_2), 30.3 (CH_2), 30.6 (CH_2), 35.0 (CH_2), 59.2 (OCH_3), 75.8 (CH_2OCH_3), 77.8 (C5), 79.4 (C2), 114.3 (C4′), 138.5 (C3′). trans-isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.46–1.79 (m, 4H, CH_2), 1.89–2.18 (m, 4H, CH_2), 3.37–3.40 (m, 5H, OCH_3 and CH_2OCH_3), 3.92–4.06 (m, 1H, 2-H), 4.12–4.19 (m, 1H, 5-H), 4.92–5.04 (m, 1H, 4′-H), 5.77–5.88 (m, 1H, 3′-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5 (CH_2), 30.2 (CH_2), 31.6 (CH_2), 34.8 (CH_2), 59.2 (OCH_3), 75.6 (CH_2OCH_3), 77.2 (C5), 78.8 (C2), 114.3 (C4′), 138.5 (C3′).

*4.7.4. Conversion of **1h** with Bu_3SnH.* According to 4.7.1 from 3-(1′-cyanonona-1′,8′-dien-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1h**) (181 mg, 499 μmol), Bu_3SnH (540 mg, 0.49 mL, 1.85 mmol) and benzene (9 mL). Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). [5-(*But*-3′-*en*-1′-*yl*)-*tetrahydrofuran*-2-*yl*]*acetonitrile* (**5h**) and 5′-[5-*methyltetrahydrofuran*-2-*yl*]-*pent*-2′-*enenitrile* (**11h**): Yield: 75 mg [453 μmol, 91%, **5h** (*cis*/*trans*=38:62):**11h** (*cis*/*trans*=45:55)=51:49], colorless oil, R_f 0.28 [SiO_2, pentane/Et_2O=1:1 (v/v)]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.24 (m, 3H, CH_3-**11h**), 1.42–1.80 (m, 10H, CH_2), 1.95–2.51 (m, 6H, CH_2), 2.55–2.58 (m, 2H, CH_2CN-**5h**), 3.77–4.15 (m, 3H, 2-H and 5-H), 4.20–4.26 (m, 1H, 2-H and 5-H), 4.94–5.05 (m, 2H, 4′-H-**5h**), 5.29–5.36 (m, 1H, 2′-H-**11h**), 5.76–5.86 (m, 1H, 3′-H-**5h**), 6.50–6.57 [m, 0.46H, 3′-H-(*Z*)-**11h**], 6.71–6.78 [m, 0.54H, 3′-H-(*E*)-**11h**]. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.29 (CH_3-*trans*-**11h**), 21.41 (CH_3-*cis*-**11h**), 24.4 (CH_2CN-*trans*-**5h**), 24.6 (CH_2CN-*cis*-**5h**), 28.78, 28.81, 30.2, 30.3, 30.7, 30.8, 31.2, 31.3, 31.6, 31.8, 32.2, 32.3, 32.8, 33.88, 33.93, 34.03, 34.07, 34.47, 34.52, 34.8, 34.9 (CH_2), 73.7 (C2-*trans*-**5h**), 73.9 (C2-*cis*-**5h**), 74.75, 74.77, 75.5 (2C), 77.5, 77.8, 78.2, 78.4 [C2- and C5-*cis*/*trans*-(*E*)/(*Z*)-**11h**], 79.6 (C5-*trans*-**5h**), 80.0 (C5-*cis*-**5h**), 99.5 [C2′-(*E*)/(*Z*)-**11h**], 99.9 [C2′-(*E*)/(*Z*)-**11h**], 114.8 (C4′-**5h**), 116.0 [CN-(*E*)/(*Z*)-**11h**], 117.6 [CN-(*E*)/(*Z*)-**11h**], 117.64 (CN-**5h**), 138.16 (C3′-*trans*-**5h**), 138.23 (C3′-*cis*-**5h**), 154.8, 155.0, 155.81, 155.83 [C3′-*cis*/*trans*-(*E*)/(*Z*)-**11h**]. ν (NaCl)/cm^{-1} 1087, 1375, 1447, 1641, 1733, 2222, 2251, 2931. *cis*/*trans*-(*E*)/(*Z*)-**11h**: MS (EI, 70 eV) *m*/*z* 165 (M^+, 0.3), 164 (1), 150 (3), 136 (5), 120 (5), 108 (6), 85 (100). *cis*-**5h**: MS (EI, 70 eV) *m*/*z* 165 (M^+, 0.2), 164 (1), 136 (13), 123 (26), 110 (100), 82 (43). *trans*-**5h**: MS (EI, 70 eV) *m*/*z* 165 (M^+, 0.2), 164 (1), 136 (22), 123 (47), 110 (100), 82 (59). *cis*/*trans*-(*E*)/(*Z*)-**11h**: MS (EI, 70 eV) *m*/*z* 165 (M^+, 0.2), 164 (1), 150 (3), 136 (2), 120 (3), 108 (5), 85 (100).

*4.7.5. Conversion of **1h** with Bu_3SnD.* According to 4.7.1 from 3-(1′-cyanonona-1′,8′-dien-5′-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1h**) (111 mg, 277 μmol), Bu_3SnD (297 mg, 0.27 mL, 1.02 mmol) and benzene (5 mL). Eluent used for chromatography: pentane/Et_2O=1:1 (v/v). [5-(*But*-3′-*en*-1′-*yl*)-*tetrahydrofuran*-2-*yl*]-2-d_1-*acetonitrile* (**5h**$_{d1}$) and 5′-[5-*methyl*-d_1-*tetrahydrofuran*-2-*yl*]-*pent*-2′-*enenitrile* (**11h**$_{d1}$): Yield: 42 mg [253 μmol, 91%, **5h**$_{d1}$ (*cis*/*trans*=34:66):**11h**$_{d1}$ (*cis*/*trans*=45:55)=53:47], colorless oil, R_f 0.28 [SiO_2, pentane/Et_2O=1:1 (v/v)]. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19–1.24 (m, 2H, CH_2D-**11h**$_{d1}$), 1.42–1.82 (m, 8H, CH_2), 1.95–2.53 (m, 8H, CH_2), 2.54–2.58 (m, 1H, CHDCN-**5h**$_{d1}$), 3.77–4.15 (m, 3H, 2-H and 5-H), 4.20–4.26 (m, 1H, 2-H or 5-H), 4.94–5.04 (m, 2H, 4′-H-**5h**$_{d1}$), 5.29–5.36 (m, 1H, 2′-H-**11h**$_{d1}$), 5.75–5.87 (m, 1H, 3′-H-**5h**$_{d1}$), 6.50–6.57 [m, 0.47H, 3′-H-(*Z*)-**11h**$_{d1}$], 6.71–6.78 [m, 0.53H, 3′-H-(*E*)-**11h**$_{d1}$]. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.90 (t, $^1J_{C,D}$ 18.96, CH_2D-*trans*-(*E*)/(*Z*)-**11h**$_{d1}$), 20.92 (t, $^1J_{C,D}$ 18.96, CH_2D-*trans*-(*E*)/(*Z*)-**11h**$_{d1}$), 21.02 (t, $^1J_{C,D}$ 18.96, CH_2D-*cis*-**11h**$_{d1}$), 24.18 (t, $^1J_{C,D}$ 21.13, *C*HCDCN-*trans*-**5h**$_{d1}$), 24.39 (t, $^1J_{C,D}$ 21.13, *C*HCDCN-*cis*-**5h**$_{d1}$), 28.79, 28.84, 30.2, 30.3, 30.7, 30.9, 31.3, 31.4, 31.6, 31.9, 32.5, 32.3, 32.9, 33.89, 33.94, 34.1, 34.2, 34.5, 34.6, 34.9, 35.0 (CH_2), 73.7 (C2-*trans*-**5h**$_{d1}$), 74.0 (C2-*cis*-**5h**$_{d1}$), 74.74, 74.76, 75.5 (2C), 77.6, 77.8, 78.3, 78.5 [C2- and C5-*cis*/*trans*-(*E*)/(*Z*)-**11h**$_{d1}$], 79.7 (C5-*trans*-**5h**$_{d1}$), 80.1 (C5-*cis*-**5h**$_{d1}$), 99.6 [C2′-(*E*)/(*Z*)-**11h**$_{d1}$], 100.0 [C2′-(*E*)/(*Z*)-**11h**$_{d1}$], 114.8 (C4′-**5h**$_{d1}$), 116.0 [CN-(*E*)/(*Z*)-**11h**$_{d1}$], 117.48 [CN-(*E*)/(*Z*)-**11h**$_{d1}$], 117.5 (CN-**5h**$_{d1}$), 138.2 (C3′-*trans*-**5h**$_{d1}$), 138.3 (C3′-*cis*-**5h**$_{d1}$), 154.95, 155.0, 155.76, 155.8 [C3′-*cis*/*trans*-(*E*)/(*Z*)-**11h**$_{d1}$]. ν (NaCl)/cm^{-1} 1081, 1368, 1447, 1641, 2222, 2250, 2935. *cis*/*trans*-(*E*)/(*Z*)-**11h**$_{d1}$: MS (EI, 70 eV) *m*/*z* 166 (M^+, 0.4), 165 (1), 164 (0.3), 150 (3), 137 (5), 120 (5), 108 (6), 86 (100). *cis*-**5h**$_{d1}$: MS (EI, 70 eV) *m*/*z* 166 (M^+, 0.3), 165 (1), 137 (12), 124 (26), 111 (100), 83 (53). *trans*-**5h**$_{d1}$: MS (EI, 70 eV) *m*/*z* 166 (M^+, 0.2), 165 (1), 137 (21), 124 (45), 111 (100), 83 (65). *cis*/*trans*-(*E*)/(*Z*)-**11h**$_{d1}$: MS (EI, 70 eV) *m*/*z* 166 (M^+, 0.3), 165 (1), 164 (0.3), 150 (3), 137 (2), 120 (5), 108 (3), 86 (100).

*4.7.6. Conversion of **1i** with Bu_3SnD.* According to 4.7.1 from 3-[1′-(methoxycarbonyl)nona-1′,8′-dien-5′-oxy]-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1i**) (86 mg, 198 μmol), Bu_3SnD (214 mg, 0.19 mL, 733 μmol) and benzene (3.6 mL). Eluent used for chromatography: [SiO_2, pentane/Et_2O=1:1 (v/v)]. *Methyl* [5-(*but*-3′-*en*-1′-*yl*)-*tetrahydrofuran*-2-*yl*)-2-d_1-*acetate* (**5i**): Yield: 11 mg (57 μmol, 29%, *cis*/*trans*=35:65), colorless oil, R_f 0.28 [SiO_2, pentane/Et_2O=1:1 (v/v)]. ν (NaCl)/cm^{-1} 1081, 1272, 1437, 1657, 1726, 2935. MS (EI, 70 eV) *m*/*z* 168 (2), 167 (1), 112 (6), 100 (13), 85 (100). cis-isomer: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.73 (m, 4H, CH_2), 1.92–2.17 (m, 4H, CH_2), 2.41–2.46 (m, 1H, CHD), 3.68 (s, 3H, OCH_3), 3.82–3.88 (m, 1H, 5-H), 4.23 (q, 1H, *J* 6.6, 2-H), 4.92–5.03 (m, 2H, 4′-

H), 5.78–5.86 (m, 1H, 3′-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.3 (CH_2), 31.0 (CH_2), 31.8 (CH_2), 35.3 (CH_2), 40.73 (t, $^1J_{C,D}$ 20.34, CHD), 51.5 (OCH_3), 75.1 (C2), 79.2 (C5), 114.4 (C4′), 138.4 (C3′), 171.7 (C=O). NOESY (cross peaks) 2-H↔5-H. trans-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20–1.73 (m, 4H, CH_2), 1.92–2.17 (m, 4H, CH_2), 2.41–2.46 (m, 1H, CHD), 3.68 (s, 3H, OCH_3), 3.92–4.00 (m, 1H, 5-H), 4.25 (q, 1H, *J* 6.5, 2-H), 4.92–5.03 (m, 2H, 4′-H), 5.78–5.86 (m, 1H, 3′-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.3 (CH_2), 30.8 (CH_2), 31.6 (CH_2), 34.9 (CH_2), 40.45 (t, $^1J_{C,D}$ 20.34, CHD), 51.5 (OCH_3), 74.7 (C2), 78.5 (C5), 114.4 (C4′), 138.4 (C3′), 171.7 (C=O). NOESY (cross peaks) 5-H↔1′-H. *Methyl* 5-[5′-*methyl*-d_1-*tetrahydrofuran*-2′-*yl*]-*pent*-2-*enoate* (**11i**): Yield: 22 mg (108 μmol, 55%, *cis*/*trans*=39:61), colorless oil, R_f 0.22 [SiO_2, pentane/Et_2O=1:1 (v/v)]. ν (NaCl)/cm^{-1} 1081, 1272, 1437, 1657, 1726, 2935. MS (EI, 70 eV) *m*/*z* 170 (8), 157 (14), 144 (88), 125 (30), 117 (52), 112 (89), 55 (100). cis-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17–1.25 (m, 2H, CH_2D), 1.47–1.77 (m, 4H, CH_2), 1.91–2.09 (m, 2H, CH_2), 2.21–2.38 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.77–3.85 (m, 1H, 2′-H), 3.89–4.01 (m, 1H, 5′-H), 5.84 (m, 1H, 3-H), 6.95–7.02 (m, 1H, 4-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.09 (t, $^1J_{C,D}$ 19.43, CH_2D), 28.9 (CH_2), 31.2 (CH_2), 32.8 (CH_2), 34.5 (CH_2), 51.3 (OCH_3), 75.3 (C5), 78.5 (C2), 121.0 (C4′), 149.1 (C3′), 167.1 (C=O). trans-isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.17–1.25 (m, 2H, CH_2D), 1.47–1.77 (m, 4H, CH_2), 1.91–2.09 (m, 2H, CH_2), 2.21–2.38 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.89–4.01 (m, 1H, 2-H), 4.04–4.10 (m, 1H, 5-H), 5.84 (m, 1H, 3′-H), 6.95–7.02 (m, 1H, 4′-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8–21.3 (t, $^1J_{C,D}$ 19.43, CH_2D), 29.0 (CH_2), 32.2 (CH_2), 33.8 (CH_2), 34.4 (CH_2), 51.3 (OCH_3), 74.5 (C5), 77.8 (C2), 121.0 (C4′), 149.1 (C3′), 167.1 (C=O).

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Supplementary data

Instrumentation, reagent specification, preparation of alkenols, carbon-13 NMR-spectra of *N*-alkenoxythiazolethiones and tetrahydrofurans. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.08.083.

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6.7 Anhang

Supplementary Data for

Alkoxyl Radical Addition to Acceptor-Substituted Carbon-Carbon Double Bonds

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Contents

1 General Remarks

(i) The compound numbering in the Supporting information is consistent with that of the accompanying publication. (ii) References refer exclusively to the Supporting Information.

2 Instrumentation

^{1}H, ^{13}C NMR-spectroscopy: FT-NMR DPX 200, DPX 400, and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale (coupling constants J are given in Hz). ^{13}C resonances of $CDCl_3$ (δ_C 77.0) and ^{1}H resonances of residual protons of $CHCl_3$ (δ_H 7.26) were used as internal standards.

Combustion analysis: Elemental Analyzer 2400 CHN (*Perkin Elmer*) and Elementar Vario Micro Cube (*Elementar Analysentechnik/Hanau*).

UV/Vis spectra: Cary 100 Conc spectrometer (*Varian*).

HRMS analysis: Mass spectroscopy (EI, 70 eV), GCT Premier Micromass (*Waters*).

GC/MS analysis: HP 6890 Series (*Hewlett Packard*) GC system and mass detector with a HP-5-MS column (*Agilent*, 30 m × 0.25 mm, 0.25 μm). Temperature program: 40 °C (3 min), 10 °C min^{-1} → 280 °C, 280 °C (10 min).

Reaction progress was monitored via thin layer chromatography (tlc) on aluminum sheets coated with silica gel (60 F_{254}, *Machery-Nagel*). Developed tlc-sheets were subjected to UV-analysis (254 nm) or stained with Ekkert's reagent.

IR spectroscopy: FT-IR 1000 spectrometer, model 16PC (*Perkin Elmer*).

Photochemical reactions were performed in a Southern England Rayonet®-chamber reactor equipped with 12 lights bulbs (λ = 350 nm). The photoreactor was ventilated from the bottom in order to maintain approximately 25 °C inside the cavity. Stirring was achieved with a micro magnetic stirring device.

3 Reagents

1-Phenylpent-4-en-1-ol,[1,2] 1-methylpent-4-en-1-ol,[3,4] 5-phenyltetrahydrofuran-2-ol,[5,6] 5-methyltetrahydrofuran-2-ol,[7] 6-hydroxy-6-phenylhex-2-enoate,[6] methyl 2-(acetylamino)-6-hydroxy-6-phenylhex-2-enoate,[8] (cyanomethyl)triphenylphosphonium bromide,[9] (methoxycarbonylmethyl)triphenylphosphonium bromide,[10] isopropyl-triphenyl-phosphonium bromide,[11] cyclopropylacetonitrile,[12] 3-hydroxy-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione[13] were prepared according to published procedures.

4 Synthesis of Alkenols

4.1 Synthesis of 5-substituted 1-phenylpent-4-en-1-ol

4.1.1 General procedure. In an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$), a solution of 5-methyltetrahydrofuran-2-ol or 5-phenyl-tetrahydrofuran-2-ol in toluene was treated with a triphenyl(alkyliden)phosphoran and stirred for 1.5 h at 60–80 °C. Pentane and Et_2O were added causing a precipitate to separate, which was filtered off by suction. The solvent was removed under reduced pressure and the residue was purified by chromatography (SiO_2).

4.1.2 6-Hydroxyhept-2-enenitrile. According to 4.1.1 from 5-methyltetrahydrofuran-2-ol (2.91 g, 28.46 mmol), (cyanomethyl)triphenylphosphonium ylide (8.58 g, 28.46 mmol) and toluene (75 mL). Reaction temperature: 60 °C. Eluent used for chromatography: pentane/Et_2O = 1:2 (*v*/*v*). Yield: 1.06 g [8.47 mmol, 30%, (*E*):(*Z*) = 85:15], pale yellow oil, R_f 0.21 [SiO_2, Et_2O]. **(*E*)-isomer**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (d, 3 H, *J* 6.2, 7-H), 1.52–1.66 (m, 2 H, CH_2), 1.55 (s, 1 H, OH), 2.19–2.46 (m, 2 H, CH_2), 3.73–3.89 (m, 1 H, 6-H), 5.31–5.40 (m, 1 H, 2-H), 6.75 (dt, 1 H, J_d 16.4, J_t 7.0, 3-H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.8 (C7), 29.6 (CH_2), 36.7 (CH_2), 67.0 (C6), 100.0 (C2), 117.4 (CN), 155.6 (C3). **(*Z*)-isomer**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (d, 3 H, *J* 6.1, 7-H), 1.52–1.66 (m, 2 H, CH_2), 1.55 (s, 1 H, OH), 2.48–2.59 (m, 2 H, CH_2), 3.73–3.89 (m, 1 H, 6-H), 5.31–5.40 (m, 1 H, 2-H), 6.53 (dt, 1 H, J_d 10.9, J_t 7.7, 3-H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.6 (C7), 28.3 (CH_2), 37.3 (CH_2), 67.2 (C6), 99.7 (C2), 117.4 (CN), 154.8 (C3).

4.1.3 6-Hydroxy-6-phenylhex-2-enenitrile. According to 4.1.1 from 5-phenyltetrahydrofuran-2-ol (1.50 g, 9.14 mmol), (cyanomethyl)triphenylphosphonium ylide (3.03 g, 10.05 mmol) and toluene (25 mL). Reaction temperature: 80 °C. Eluent used for chromatography: pentane/Et_2O = 1:1 (*v*/*v*). Yield: 1.10 g [5.87 mmol, 58%, (*E*):(*Z*) = 87:13], pale yellow oil, R_f 0.25 [SiO_2, pentane/Et_2O = 1:1 (*v*/*v*)]. **(*E*)-isomer**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76–1.93 (m, 2 H, CH_2), 2.21–2.37 (m, 2 H, CH_2), 4.63–4.68 (m, 1 H, 6-H), 5.29 (d, 1 H, *J* 16.2, 2-H), 6.69 (dt, 1 H, J_d 16.3, J_t 7.0, 3-H), 7.27–7.37 (m, 5 H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.6 (CH_2), 36.6 (CH_2), 73.4 (C6), 100.0 (C2), 117.4 (CN), 125.7, 127.9, 128.6, 143.9 (Ph-C), 155.4 (C3). **(*Z*)-isomer**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.76–1.93 (m, 2 H, CH_2), 2.44–2.56 (m, 2 H, CH_2), 4.63–4.68 (m, 1 H, 6-H), 5.29 (d, 1 H, *J* 16.2, 2-H), 6.48 (dt, 1 H, J_d 10.9, J_t 7.7, 3-H), 7.27–7.37 (m, 5 H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.4 (CH_2), 37.3 (CH_2), 73.6 (C6), 99.7 (C2), 115.9 (CN), 125.7, 127.9, 128.6, 143.9 (Ph-C), 154.6 (C3).

4.1.3 Methyl 6-hydroxyhept-2-enoate. According to 4.1.1 from 5-methyltetrahydrofuran-2-ol (2.91 g, 28.46 mmol), (methoxycarbonylmethyl)triphenyl-phosphonium ylide (9.52 g, 28.46 mmol) and toluene (75 mL). Reaction temperature: 60 °C. Eluent used for chromatography: pentane/Et_2O = 1:1 (*v*/*v*). Yield: 1.11 g (6.95 mmol, 24%), pale yellow oil, R_f 0.22 [SiO_2, pentane/Et_2O = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, 3 H, *J* 6.2, 7-H), 1.53–1.64 (m, 2 H, CH_2), 1.66 (s, 1 H, OH), 2.23–2.38 (m, 2 H, CH_2), 3.71 (s, 3 H, OCH_3), 3.77–3.86 (m, 1 H, 6-H), 5.79–5.89 (m, 1 H, 2-H), 6.98 (dt, 1 H, J_d 15.6, J_t 6.9, 3-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6 (C7), 28.5 (CH_2), 37.3 (CH_2), 51.3 (OCH_3), 67.2 (C6), 121.2 (C2), 149.0 (C3), 167.0 (C=O).

4.1.4 2-Cyclopropyl-6-hydroxy-6-phenylhex-2-enenitrile. In an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$), n-BuLi (31.2 mL, 49.71 mmol) in dry THF (33 mL) was cooled to –78 °C and a solution of diisopropylamine (5.03 g, 49.71 mmol) in dry THF (24 mL) was added in a dropwise manner. The reaction mixture was stirred for 10 min at –78 °C and then treated with a solution of cyclopropylacetonitrile (1.92 g, 23.67 mmol) in dry THF (24 mL). After stirring for 1.5 h at –78 °C a solution of diethylchlorophosphate (3.42 mL, 23.67 mmol) in dry THF (24 mL) was added in a dropwise manner, the reaction mixture was stirred for 15 min at –78 °C and 15 min at 20 °C. This mixture was cooled to –78 °C, treated with 5-phenyltetrahydrofuran-2-ol (3.89 g, 23.67 mmol) and stirred for 1.5 h

at –78 °C and 45 min at 20 °C. The mixture was treated with EtOAc (70 mL) and washed with a saturated aqueous solution of NH_4Cl (2 × 70 mL). Combined organic layers were washed with brine (70 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to leave a residue, which was purified by chromatography [SiO_2, pentane/Et_2O = 2:1 (*v*/*v*)]. Yield: 2.60 g [11.45 mmol, 48%, (*E*):(*Z*) = 68:32], pale yellow oil, R_f 0.16 [SiO_2, pentane/Et_2O = 2:1 (*v*/*v*)]. **(*E*)-isomer**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.63–0.86 (m, 4 H, cyclopropyl), 1.47–1.54 (m, 1 H, cyclopropyl), 1.78–1.97 (m, 2 H, CH_2), 2.08 (brs, 1 H, OH), 2.35–2.52 (m, 2 H, CH_2), 4.66–4.70 (m, 1 H, 6-H), 6.20 (t, 1 H, *J* 7.6, 3-H), 7.27–7.38 (m, 5 H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.8, 6.2, 14.0 (cyclopropyl), 28.0 (CH_2), 37.7 (CH_2), 73.7 (C6), 115.9 (C2), 117.7 (CN), 125.8, 127.8, 128.5, 144.0 (Ph-C), 144.8 (C3). **(*Z*)-isomer**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.63–0.86 (m, 4 H, cyclopropyl), 1.56–1.60 (m, 1 H, cyclopropyl), 1.78–1.97 (m, 2 H, CH_2), 2.08 (brs, 1 H, OH), 2.35–2.52 (m, 2 H, CH_2), 4.66–4.70 (m, 1 H, 6-H), 6.32 (t, 1 H, *J* 7.6, 3-H), 7.27–7.38 (m, 5 H, Ph-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.8, 6.2, 9.2 (cyclopropyl), 24.8 (CH_2), 37.3 (CH_2), 73.6 (C6), 117.6 (C2), 118.3 (CN), 125.8, 127.9, 128.6, 144.0 (Ph-C), 146.1 (C3).

4.2 Synthesis of dienols

4.2.1 5-(But-1'-en-4'-yl)dihydrofuran-2(3*H*)-one. To a well agitated solution of 4-oxooct-7-enoic acid (5.55 g, 35.50 mmol) in EtOH (70 mL) was added $NaBH_4$ (2.70 g, 71.37 mmol) in portions. The reaction mixture was stirred for 2.5 h at 25 °C and then treated at 25 °C with H_2O (30 mL) and 2 M aqueous HCl (30 mL). The resulting solution was extracted with Et_2O (4 × 20 mL). Combined organic washings were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Yield: 4.49 g (32.0 mmol, 90%), yellow oil, R_f 0.28 [SiO_2, pentane/Et_2O = 1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.60–1.96 (m, 3 H, CH_2), 2.10–2.44 (m, 3 H, CH_2), 2.50–2.58 (m, 2 H, CH_2), 4.44–4.58 (m, 1 H, 5-H), 4.95–5.12 (m, 2 H, 1'-H), 5.71–5.91 (m, 1 H, 2'-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.9 (CH_2), 28.8 (CH_2), 29.4 (CH_2), 34.7 (CH_2), 80.2 (C5), 115.6 (C1'), 137.0 (C2'), 177.2 (C2). MS (EI, 70 eV) *m*/*z* 140 (M^+, 1), 122 (1), 111 (2), 98 (7), 85 (100). Anal. Calcd. for $C_8H_{12}O_3$ (140.18): C, 68.54; H, 8.63; Found: C, 68.72; H 8.64.

4.2.2 5-(But-1'-en-4'-yl)dihydrofuran-2(3*H*)-ol. A solution of 5-(but-1'-en-4'-yl)dihydrofuran-2(3*H*)-one (3.70 g, 26.40 mmol) in dry Et_2O (30 mL) was treated in an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$) at –78 °C with a solution of DIBAL-H (1 M in CH_2Cl_2, 32 mL, 32.00 mmol) in such a rate that the temperature remained below –65 °C. After 15 min at 20 °C H_2O (10 mL) was added. Stirring was continued for 30 min at 20 °C. The precipitate was filtered off and washed with CH_2Cl_2 (25 mL). Combined filtrate and washings were concentrated under reduced pressure to afford 2.23 g of a colorless oil. A soxhlet-extraction of the solid (CH_2Cl_2, 12 h) yielded further 904 mg of 5-(But-1'-en-4'-yl)dihydrofuran-2(3*H*)-ol. Combined yield: 3.22 g (22.60 mmol, 86%) as a mixture of diastereomers A/B = 40:60, colorless oil, R_f 0.41 [SiO_2, pentane/Et_2O = 1:2 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.44–1.55 (m, 1 H), 1.61–1.98 (m, 4 H), 2.01–2.21 (m, 3 H), 4.17–4.23 (m, 0.6 H, 5-H, diastereomer A), 3.97–4.02 (m, 0.4 H, 5-H, diastereomer B), 4.94–5.04 (m, 2 H, 1'-H), 5.46 (d, 0.4 H, *J* 4.6, 2-H, diastereomer A), 5.54–5.55 (dd, 0.6 H, *J* 5.1, 1.7, 2-H, diastereomer B), 5.76–5.85 (m, 1 H, 2'-H). Diastereomer A and B: ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.1 (CH_2), 29.3 (CH_2), 30.2 (CH_2), 30.4 (CH_2), 32.9 (CH_2), 33.8 (CH_2), 34.7 (CH_2), 36.4 (CH_2), 77.8 (C5), 80.3 (C5), 98.1 (C2), 114.6 (C1'), 138.1 (C2').

4.2.3 9-Methyldeca-1,8-dien-5-ol. In an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$), a suspension of isopropyltriphenylphosphonium bromide (3.18 g, 8.25 mmol) in dry THF (50 mL) was cooled to –45 °C. n-BuLi (5.2 mL, 1.6 M in hexane, 8.32 mmol) was added in such a rate that the temperature remained below –40 °C and the mixture was stirred at –45 °C for 45 min. A solution of 5-(but-1'-en-4'-yl)dihydrofuran-2(3*H*)-ol (501 mg, 3.52 mmol) in dry THF (10 mL) was added at –45 °C. The suspension was stirred for 20 h at 20 °C. The mixture was treated with a saturated aqueous solution of NH_4Cl (20 mL) and filtered over celite. The residue was washed with EtOAc (2 × 20 mL). Combined organic solutions were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography [SiO_2, pentane/Et_2O = 4:1 (*v*/*v*)]. The oily product crystallized at –20 °C (12 h). Yield: 385 mg (2.29 mmol, 65%), pale yellow oil, R_f 0.27 [SiO_2, pentane/Et_2O = 4:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.43–1.58 (m, 4 H, CH_2), 1.62 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 2.04–2.21 (m, 4 H, CH_2), 3.61–3.65 (m, 1 H, 5-H), 4.95–4.98 (m, 1 H, 1-H), 5.02–5.06 (m, 1 H, 1-H), 5.11–5.15 (m, 1 H, 8-H), 5.80–5.87 (m, 1 H, 2-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.0 (CH_3), 24.4 (CH_2), 25.7 (CH_3), 30.1 (CH_2), 36.5 (CH_2), 37.4 (CH_2), 71.3 (C5), 114.7 (C9), 124.1 (C2), 132.1 (C1), 138.6 (C8). MS (EI, 70 eV) *m*/*z* 168 (M^+, 2), 150 (3), 135 (14), 111 (21), 95 (72), 82 (64), 55 (100).

4.2.4 1-Methoxynona-1,8-dien-5-ol. In an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$), a suspension of (methoxymethyl)triphenylphosphonium chloride (5.03 g, 14.70 mmol) in dry THF (50 mL) was treated with KO*t*Bu (1.65 g, 14.70 mmol). The mixture was stirred for 30 min at 65 °C. 5-(But-1'-en-4'-yl)dihydrofuran-2(3*H*)-ol (696 mg, 4.89 mmol) was added at 20 °C in a dropwise manner over a period of 5 min. The reaction mixture was stirred for 1.5 h at 65 °C and 14 h at 20 °C. A saturated aqueous solution of NH_4Cl (50 mL) was added and the mixture was stirred for 15 min at 20 °C. The layers were separated and the organic layer was kept. The aqueous layer was extracted with EtOAc (3 × 20 mL). Combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by chromatography [SiO_2, petroleum ether/Et_2O = 1:1 (*v*/*v*)]. Yield: 496 mg [2.91 mmol, 60%, (*E*):(*Z*) = 72:28], colorless oil, R_f 0.31 [SiO_2, pentane/Et_2O = 1:1 (*v*/*v*)]. Anal. Calcd. for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66; Found: C, 70.56; H, 10.53. **(*E*)-Isomer**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45–1.56 (m, 4 H, CH_2), 1.97–2.28 (m, 4 H, CH_2), 3.49 (s, 3 H, OCH_3), 3.60–3.66 (m, 1 H, 5-H), 4.68–4.75 (m, 1 H, 2-H), 4.92–4.97 (m, 1 H, 9-H), 5.00–5.06 (m, 1 H, 9-H), 5.78–5.86 (m, 1 H, 8-H), 6.29–6.32 (m, 1 H, 1-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0 (CH_2), 30.0 (CH_2), 36.6 (CH_2), 38.3 (CH_2), 55.9 (OCH_3), 70.8 (C5), 102.6 (C2), 114.7 (C9), 138.6 (C8), 147.4 (C1). MS (EI, 70 eV) *m*/*z* 170 (M^+, 0.2), 155 (0.4), 138 (18), 123 (7), 115 (9), 109 (12), 97 (41), 71 (100). **(*Z*)-Isomer**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45–1.56 (m, 4 H, CH_2), 1.97–2.28 (m, 4 H, CH_2), 3.58 (s, 3 H, OCH_3), 3.60–3.66 (m, 1 H, 5-H), 4.39–4.44 (m, 1 H, 2-H), 4.92–4.97 (m, 1 H, 9-H), 5.00–5.06 (m, 1 H, 9-H), 5.78–5.88 (m, 1 H, 8-H), 5.90–5.92 (m, 1 H, 1-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.9 (CH_2), 29.7 (CH_2), 36.3 (CH_2), 36.9 (CH_2), 59.5 (OCH_3), 70.4 (C5), 106.1 (C2), 114.4 (C9), 138.8 (C8), 146.7 (C1). MS (EI, 70 eV) *m*/*z* 138 (20), 123 (7), 115 (12), 109 (13), 97 (43), 71 (100).

4.2.5 6-Hydroxydeca-2,9-dienenitrile. To a solution of (cyanomethyl)triphenylphosphonium bromide (2.23 g, 5.83 mmol) in CH_2Cl_2 was added a 1 M aqueous solution of NaOH (10 mL). The mixture was shaken at 20 °C for 1 min. The layers were separated. The organic layer was kept and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). Combined organic solutions were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting colorless solid (1.56 g) was suspended in toluene (25 mL) in an atmosphere of nitrogen (5.0-quality, purged through a tube filled with

$CaCl_2$) and treated with neat 5-(but-1'-en-4'-yl)dihydrofuran-2(3*H*)-ol (491 mg, 3.45 mmol). The reaction mixture was stirred for 4 h at 60 °C and cooled to 20 °C. The precipitate that was formed during cooling to 20 °C was filtered off by suction and washed with toluene (10 mL). Combined filtrates and washings were concentrated under reduced pressure. The residue was purified by chromatography [SiO_2, petroleum ether/Et_2O = 1:2 (*v*/*v*)]. Yield: 514 mg [3.11 mmol, 90%, (*E*):(*Z*) = 81:19], colorless oil, R_f 0.45 [SiO_2, petroleum ether/Et_2O = 1:2 (*v*/*v*)]. ν (NaCl)/cm^{-1} 3449, 2930, 2224, 1764, 1633, 1448. Anal. Calcd. for $C_{10}H_{15}NO$ (165.23): C, 72.69; H, 9.15; N, 8.48; Found: C, 72.20; H, 9.57; N, 8.28. **(*E*)-isomer**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.51–1.62 (m, 4 H, CH_2), 2.10–2.50 (m, 4 H, CH_2), 3.60–3.67 (m, 1 H, 6-H), 4.97–5.00 (m, 1 H, 10-H), 5.04–5.08 (m, 1 H, 10-H), 5.33–5.37 (m, 1 H, 2-H), 5.79–5.86 (m, 1 H, 9-H), 6.72–6.77 (m, 1 H, 3-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.6 (CH_2), 30.0 (CH_2), 35.0 (CH_2), 36.5 (CH_2), 70.6 (C6), 99.9 (C2), 115.2 (C10), 117.4 (CN), 138.1 (C9), 155.7 (C3). MS (EI, 70 eV) *m*/*z* 165 (M^+, 0.1), 132 (13), 110 (22), 85 (39), 81 (100). **(*Z*)-isomer**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.51–1.62 (m, 4 H, CH_2), 2.10–2.50 (m, 4 H, CH_2), 3.60–3.67 (m, 1 H, 6-H), 4.97–5.00 (m, 1 H, 10-H), 5.04–5.08 (m, 1 H, 10-H), 5.33–5.37 (m, 1 H, 2-H), 5.79–5.86 (m, 1 H, 9-H), 6.72–6.77 (m, 1 H, 3-H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.3 (CH_2), 30.0 (CH_2), 35.6 (CH_2), 36.4 (CH_2), 70.4 (C6), 99.7 (C2), 115.1 (C10), 116.0 (CN), 138.2 (C9), 154.9 (C3). MS (EI, 70 eV) *m*/*z* 165 (M^+, 0.1), 146 (21), 132 (15), 110 (25), 85 (17), 81 (100).

4.2.6 Methyl 6-hydroxydeca-2,9-dienoate. To a solution of (methoxycarbonyl-methyl)triphenylphosphonium bromide (6.90 g, 16.60 mmol) in CH_2Cl_2 (100 mL) was added a 1 M aqueous solution of NaOH (10 mL). The mixture was shaken at 20 °C for 1 min. The layers were separated. The organic layer was kept and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). Combined organic solutions were washed with brine (40 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The resulting colorless solid (5.14 g) was suspended in toluene (25 mL) in an atmosphere of nitrogen (5.0-quality, purged through a tube filled with $CaCl_2$) and treated with neat 5-(but-1'-en-4'-yl)dihydrofuran-2(3*H*)-ol (1.09 g, 7.68 mmol). The reaction mixture was stirred for 4 h at 60 °C and cooled to 20 °C. The precipitate that was formed during cooling to 20 °C was filtered off by suction and washed with toluene (30 mL). Combined filtrate and washings were concentrated under reduced pressure. The residue was purified by chromatography [SiO_2, petroleum ether/Et_2O = 1:1 (*v*/*v*)]. **(*Z*)-isomer**: Yield: 50 mg (253 µmol, 3%), colorless oil, R_f 0.34

[SiO_2, petroleum ether/Et_2O = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.52–1.68 (m, 4 H, CH_2), 2.13–2.38 (m, 4 H, CH_2), 3.51–3.73 (m, 4 H, $COOCH_3$ and 6-H), 4.93–5.07 (m, 2 H, 10-H), 5.73–5.93 (m, 2 H, 9-H and 2-H), 6.18–6.32 (m, 1 H, 3-H). MS (EI, 70 eV) *m*/*z* 198 (M^+, 0.1), 183 (0.1), 166 (1), 143 (43), 121 (16), 114 (82), 111 (100), 83 (87). **(*E*)-isomer**: Yield: 1.19 g (6.00 mmol, 78%), colorless oil, R_f 0.25 [SiO_2, petroleum ether/Et_2O = 1:1 (*v*/*v*)]. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53–1.64 (m, 4 H, CH_2), 2.13–2.37 (m, 4 H, CH_2), 3.52–3.72 (m, 4 H, $COOCH_3$ and 6-H), 4.95–5.09 (m, 2 H, 10-H), 5.81–5.88 (m, 2 H, 9-H and 2-H), 6.94–7.02 (m, 1 H, 3-H). MS (EI, 70 eV) *m*/*z* 198 (M^+, 0.1), 183 (1), 166 (3), 143 (41), 121 (33), 114 (53), 111 (98), 83 (100). *v* (NaCl)/cm^{-1} 3440, 2933, 1725, 1657, 1437, 1277, 1207. Anal. Calcd. for $C_{11}H_{18}O_3$ (198.26): C, 66.64; H, 9.15; Found: C, 66.47; H 9.28.

5 ^{13}C NMR-spectra

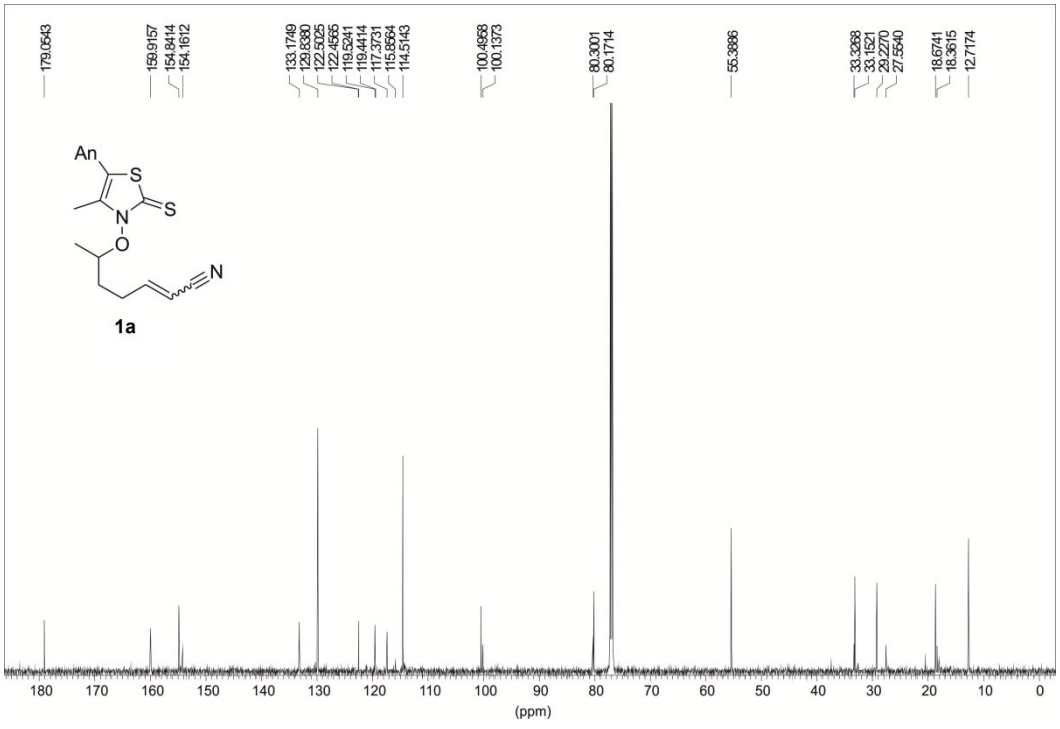

Figure S1: ^{13}C NMR-spectrum (150 MHz, $CDCl_3$) of 3-(1'-cyanohex-1'-en-5'-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1a**) (77:23-mixture of (*E*):(*Z*)-isomers).

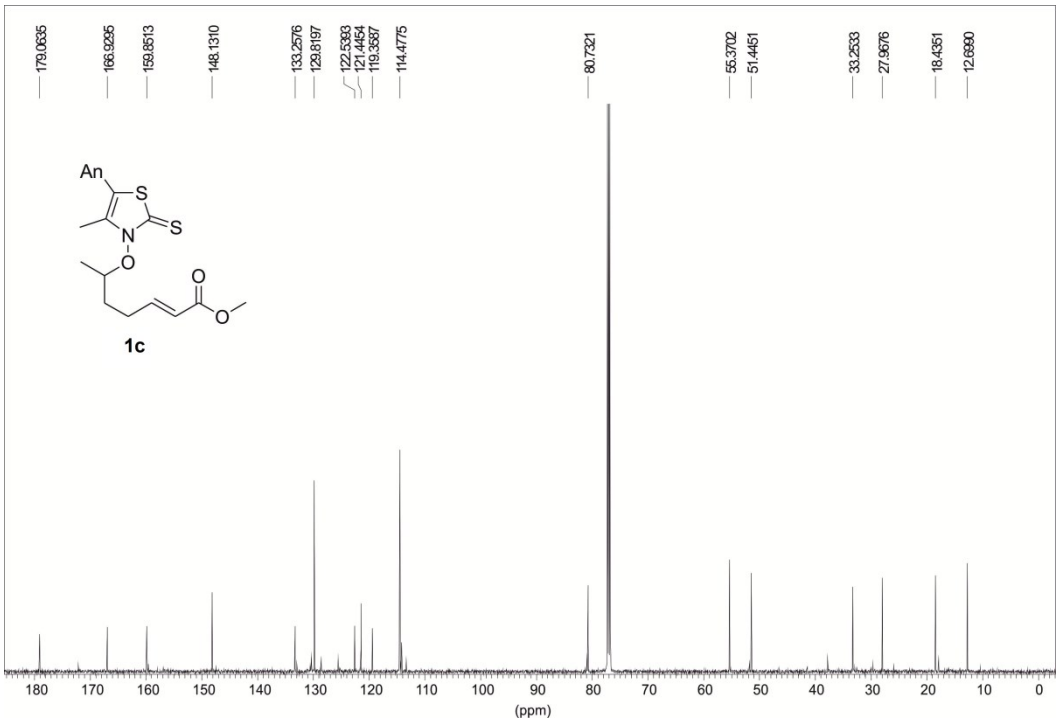

Figure S2: ^{13}C NMR-spectrum (150 MHz, $CDCl_3$) of 3-[1'-(methoxycarbonyl)hex-1'-en-5'-oxy]-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1c**).

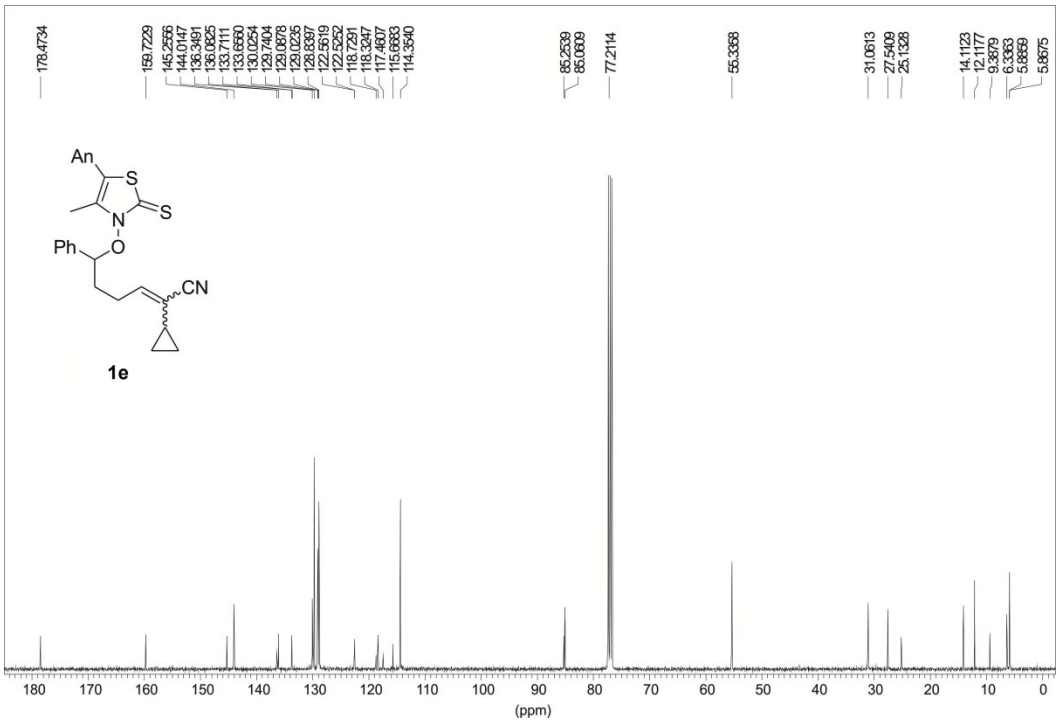

Figure S3: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of 3-(1'-cyano-1'-cyclopropyl-5'-phenylpent-1'-en-5'-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1e**) (62:38-mixture of (*E*):(*Z*)-isomers).

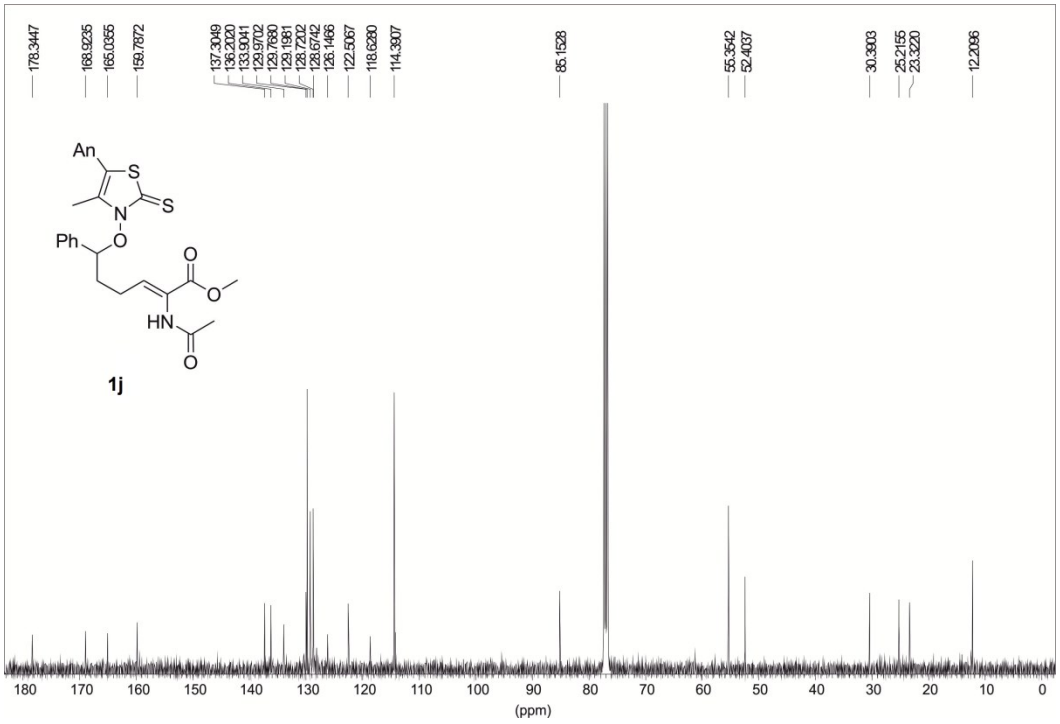

Figure S4: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of 3-(1'-methoxycarbonyl-1'-acetylamino-5'-phenylpent-1'-en-5'-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1j**).

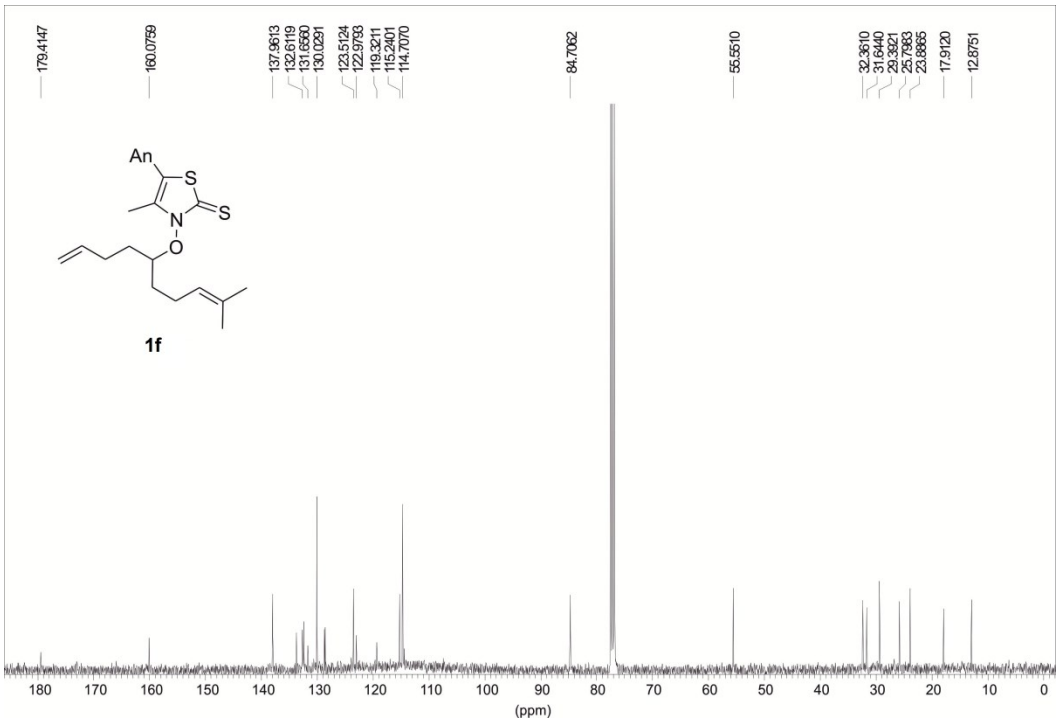

Figure S5: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of 3-(9'-methyldeca-1',8'-dien-5'-oxy)-5-(*p*-methoxyphenyl)-4-methylthiazole-2(3*H*)-thione (**1f**).

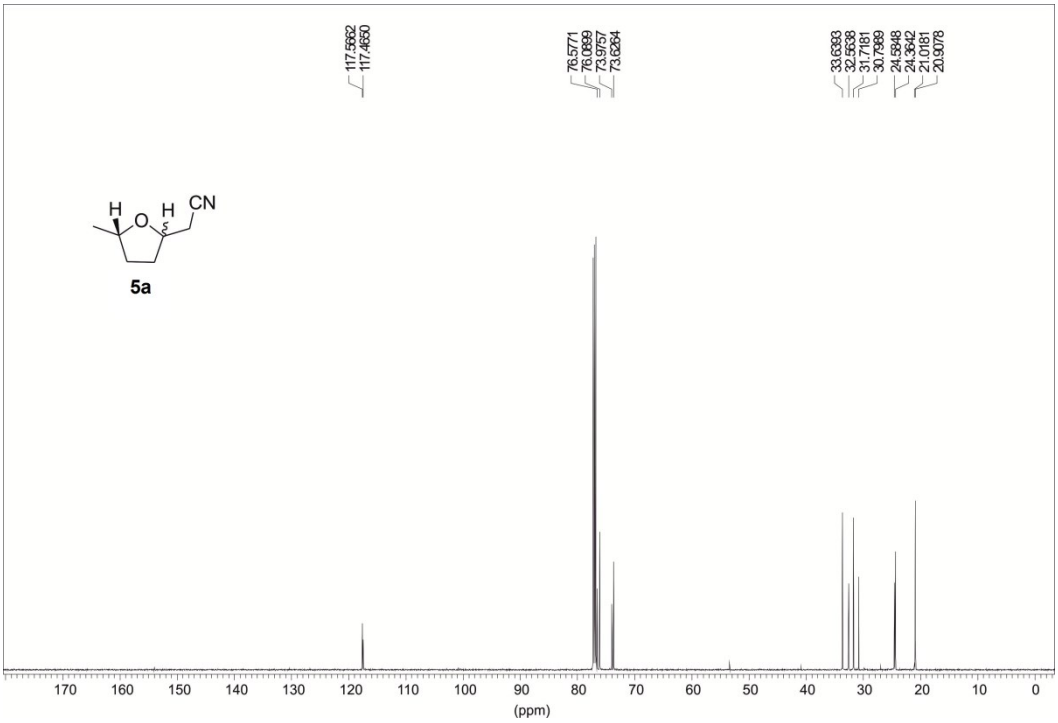

Figure S6: ^{13}C NMR-spectrum (150 MHz, $CDCl_3$) of (5-methyltetrahydrofuran-2-yl)acetonitrile (**5a**) (38:62-mixture of *cis*/*trans*-isomers).

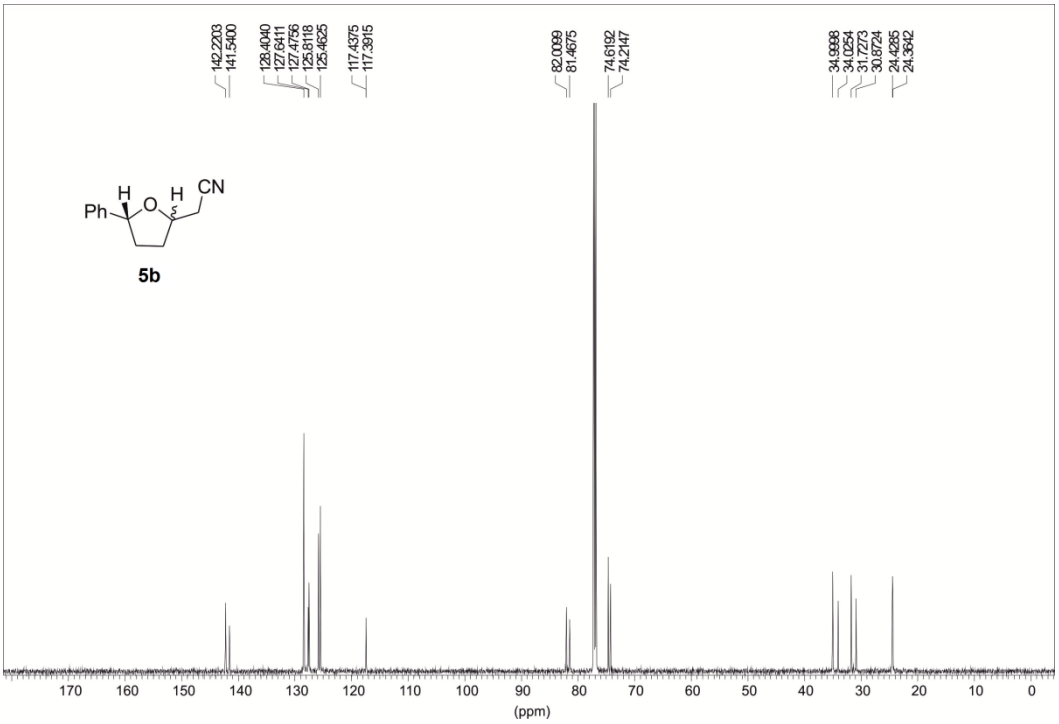

Figure S7: ^{13}C NMR-spectrum (150 MHz, $CDCl_3$) of (5-phenyltetrahydrofuran-2-yl)acetonitrile (**5b**) (44:56-mixture of *cis*/*trans*-isomers).

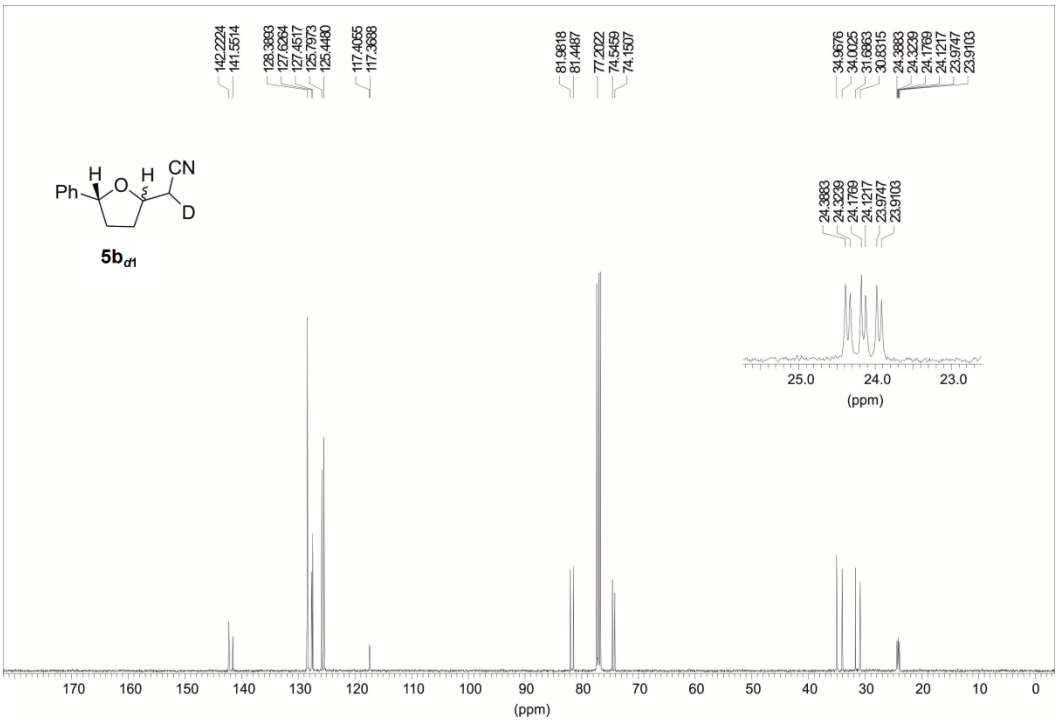

Figure S8: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of (5-phenyltetrahydrofuran-2-yl)-2-d_1-acetonitrile (**5b$_{d1}$**) (46:54-mixture of *cis*/*trans*-isomers).

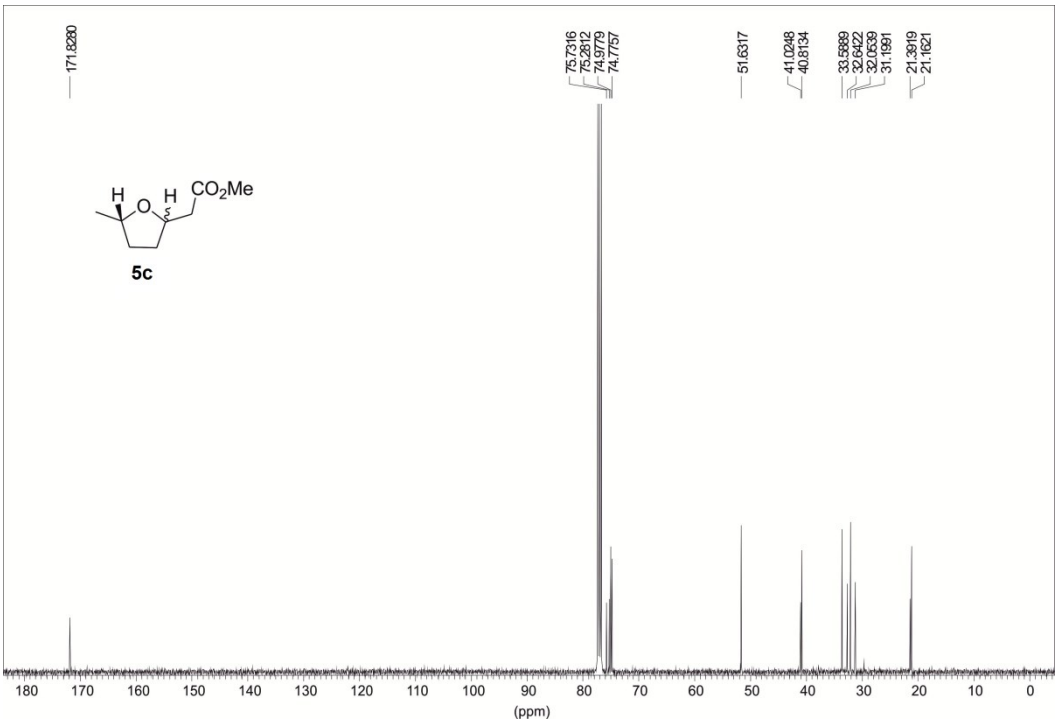

Figure S9: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of methyl (5-methyltetrahydrofuran-2-yl)acetate (**5c**) (37:63-mixture of *cis*/*trans*-isomers).

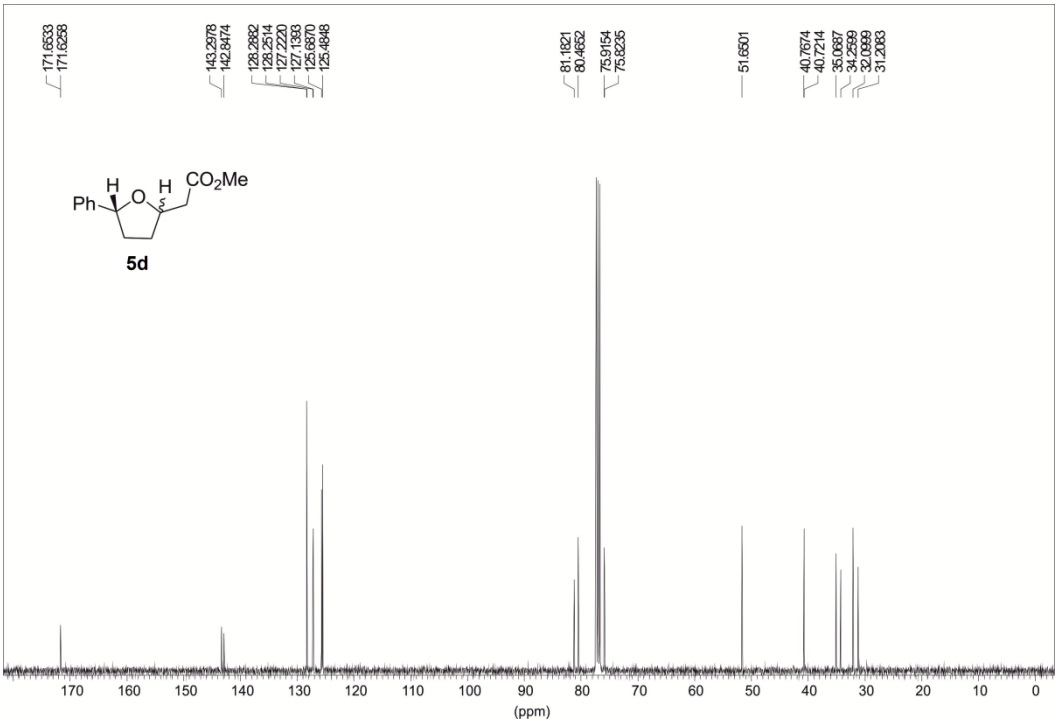

Figure S10: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of methyl (5-phenyltetrahydrofuran-2-yl)acetate (**5d**) (41:59-mixture of *cis*/*trans*-isomers).

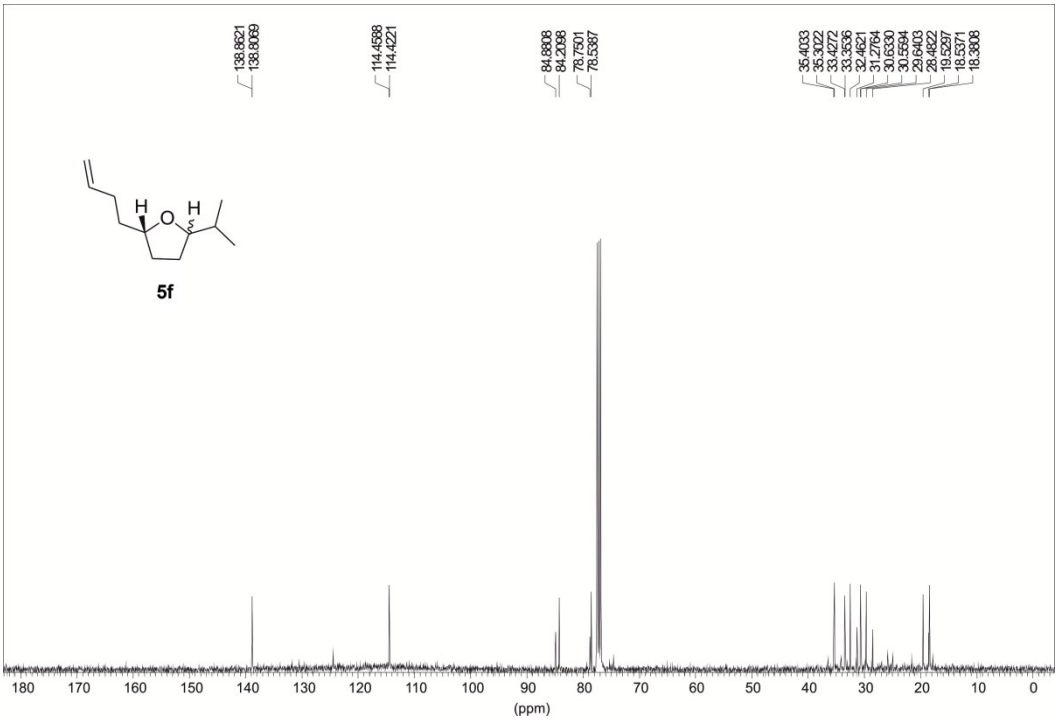

Figure S11: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of 2-(but-3'-en-1'-yl)-5-(1''-methylethyl)tetrahydrofuran (**5f**) (32:68-mixture of *cis*/*trans*-isomers).

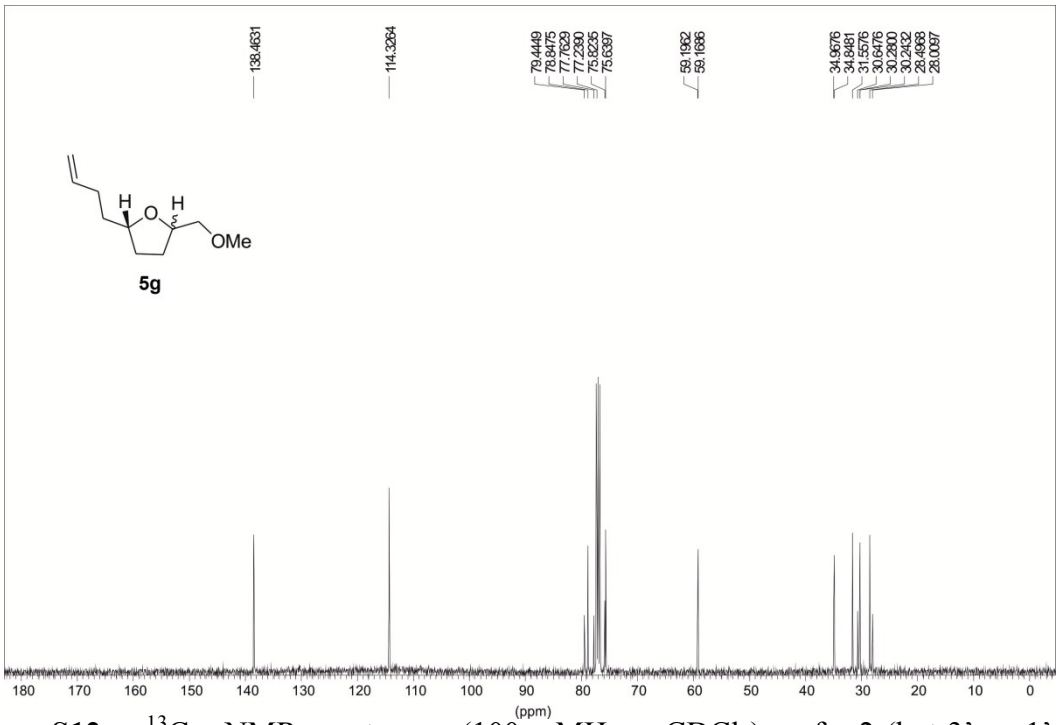

Figure S12: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of 2-(but-3'-en-1'-yl)-5-(methoxymethyl)tetrahydrofuran (**5g**) (35:65-mixture of *cis*/*trans*-isomers).

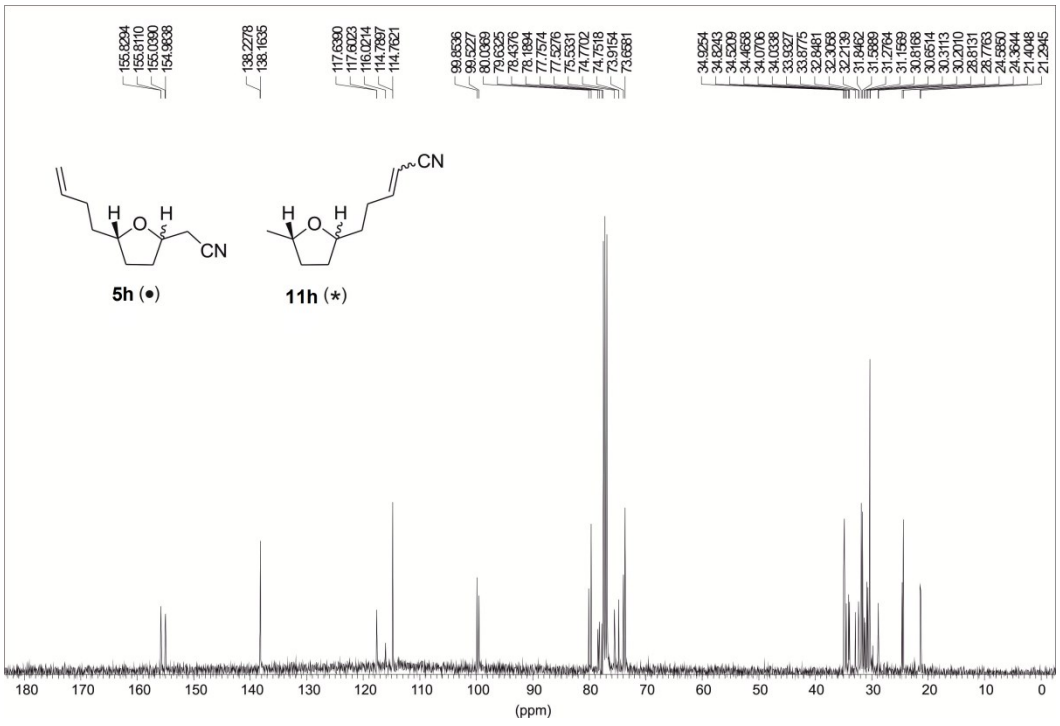

Figure S13: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of [5-(but-3'-en-1'-yl)tetrahydrofuran-2-yl]acetonitrile (**5h**) (38:62-mixture of *cis*/*trans*-isomers) and 5'-[5-methyltetrahydrofuran-2-yl]pent-2'-enenitrile (**11h**) (45:55-mixture of *cis*/*trans*-isomers).

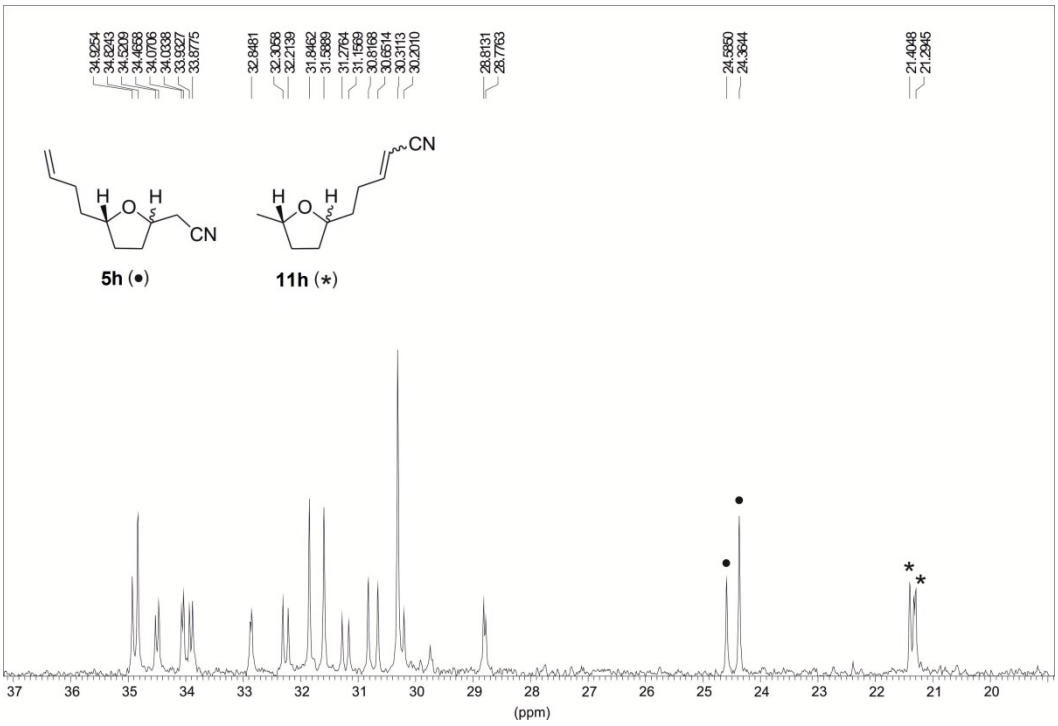

Figure S14: Expert of the ^{13}C NMR-spectrum of [5-(but-3‘-en-1‘-yl)tetrahydrofuran-2-yl]acetonitrile (**5h**) (38:62-mixture of *cis*/*trans*-isomers) and 5‘-[5-methyltetrahydrofuran-2-yl]pent-2‘-enenitrile (**11h**) (45:55-mixture of *cis*/*trans*-isomers) (cf. figure S13).

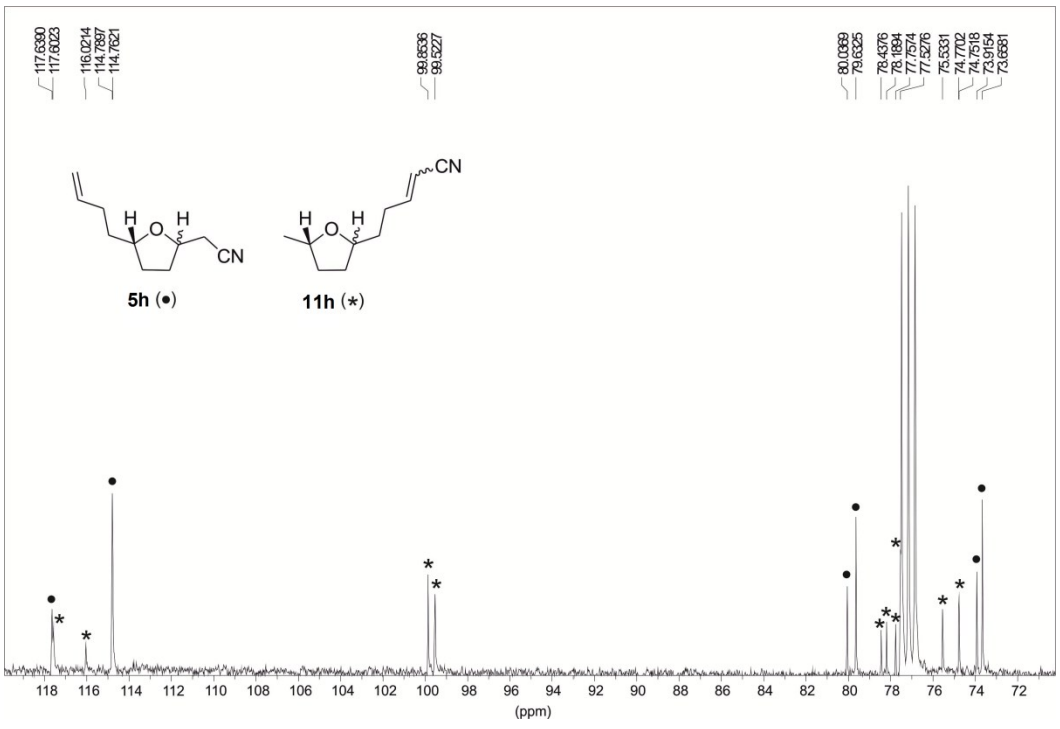

Figure S15: Expert of the ^{13}C NMR-spectrum of [5-(but-3‘-en-1‘-yl)tetrahydrofuran-2-yl]acetonitrile (**5h**) (38:62-mixture of *cis*/*trans*-isomers) and 5‘-[5-methyltetrahydrofuran-2-yl]pent-2‘-enenitrile (**11h**) (45:55-mixture of *cis*/*trans*-isomers) (cf. figure S13).

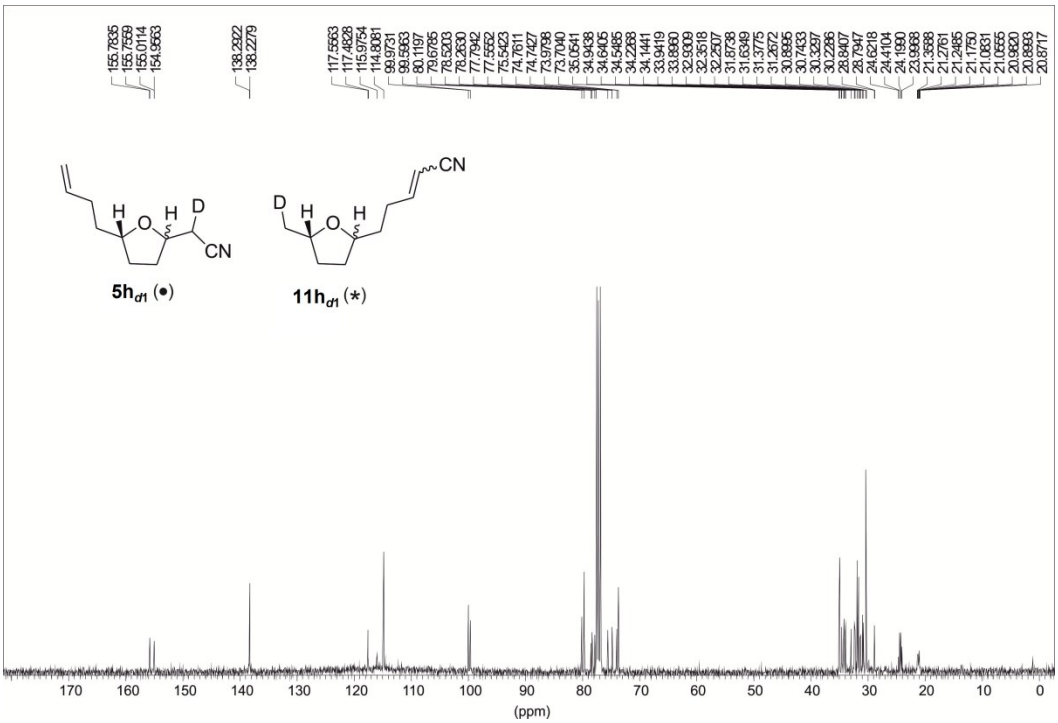

Figure S16: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of [5-(but-3‘-en-1‘-yl)tetrahydrofuran-2-yl]-2-d_1-acetonitrile (**5h$_{d1}$**) (34:66-mixture of *cis*/*trans*-isomers) and 5‘-[5-methyl-d_1-tetrahydrofuran-2-yl]pent-2‘-enenitrile (**11h$_{d1}$**) (45:55-mixture of *cis*/*trans*-isomers).

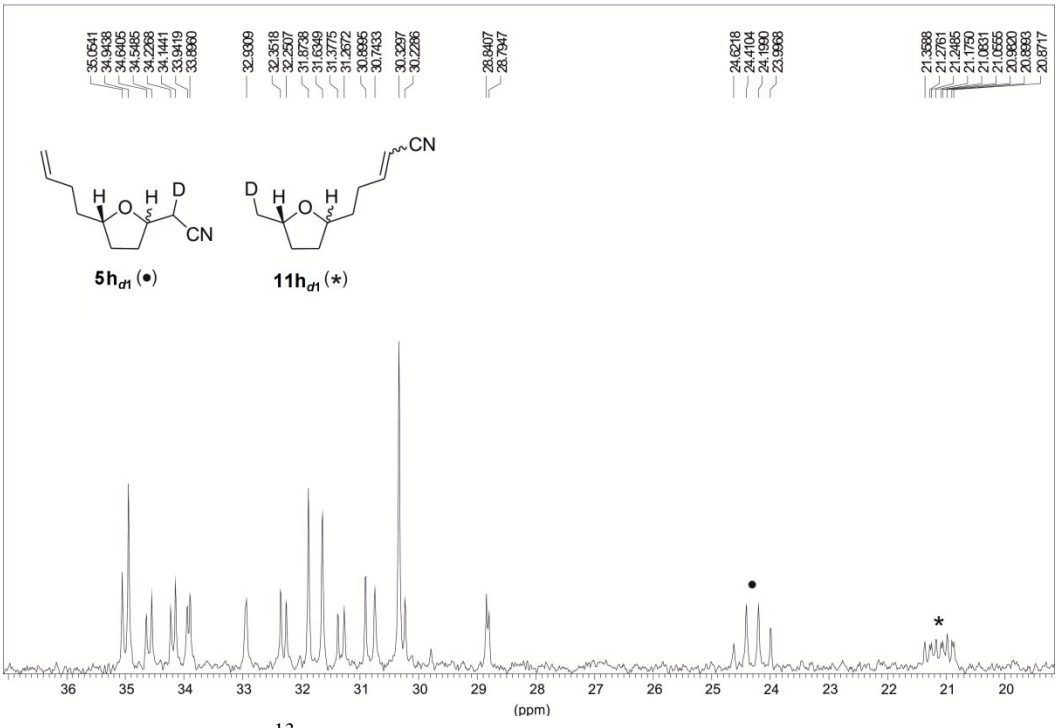

Figure S17: Expert of the ^{13}C NMR-spectrum of [5-(but-3‘-en-1‘-yl)tetrahydrofuran-2-yl]-2-d_1-acetonitrile (**5h$_{d1}$**) (34:66-mixture of *cis*/*trans*-isomers) and 5‘-[5-methyl-d_1-tetrahydrofuran-2-yl]pent-2‘-enenitrile (**11h$_{d1}$**) (45:55-mixture of *cis*/*trans*-isomers) (cf. figure S16).

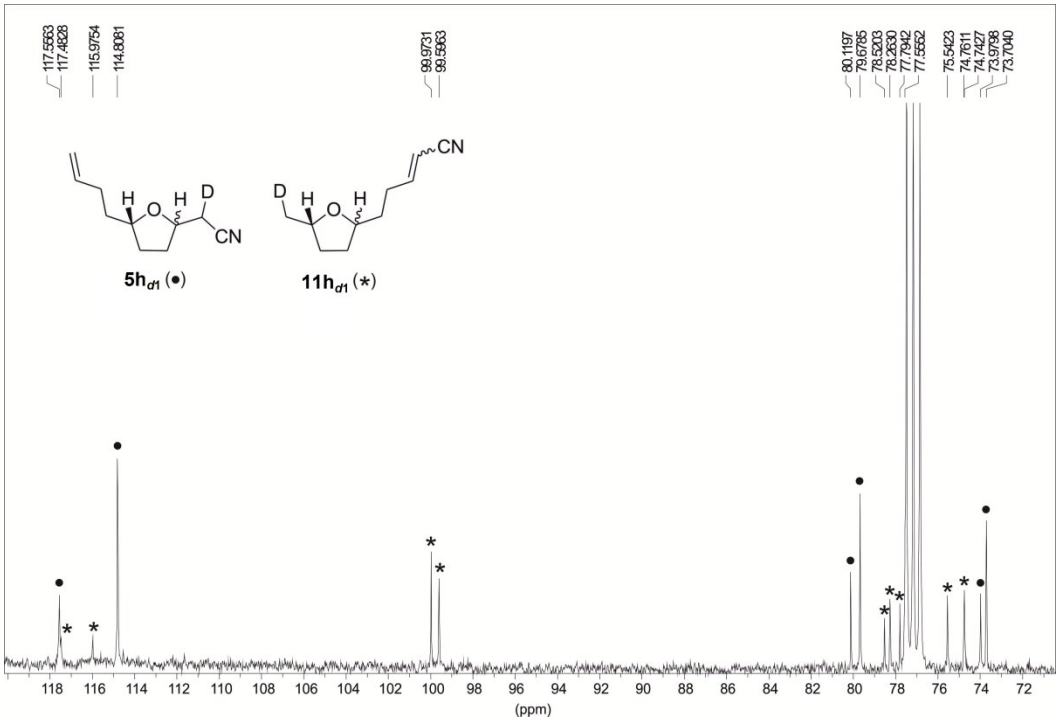

Figure S18: Expert of the ^{13}C NMR-spectrum of [5-(but-3‘-en-1‘-yl)tetrahydrofuran-2-yl]-2-d_1-acetonitrile (**5h$_{d1}$**) (34:66-mixture of *cis*/*trans*-isomers) and 5‘-[5-methyl-d_1-tetrahydrofuran-2-yl]pent-2‘-enenitrile (**11h$_{d1}$**) (45:55-mixture of *cis*/*trans*-isomers) (cf. figure S16).

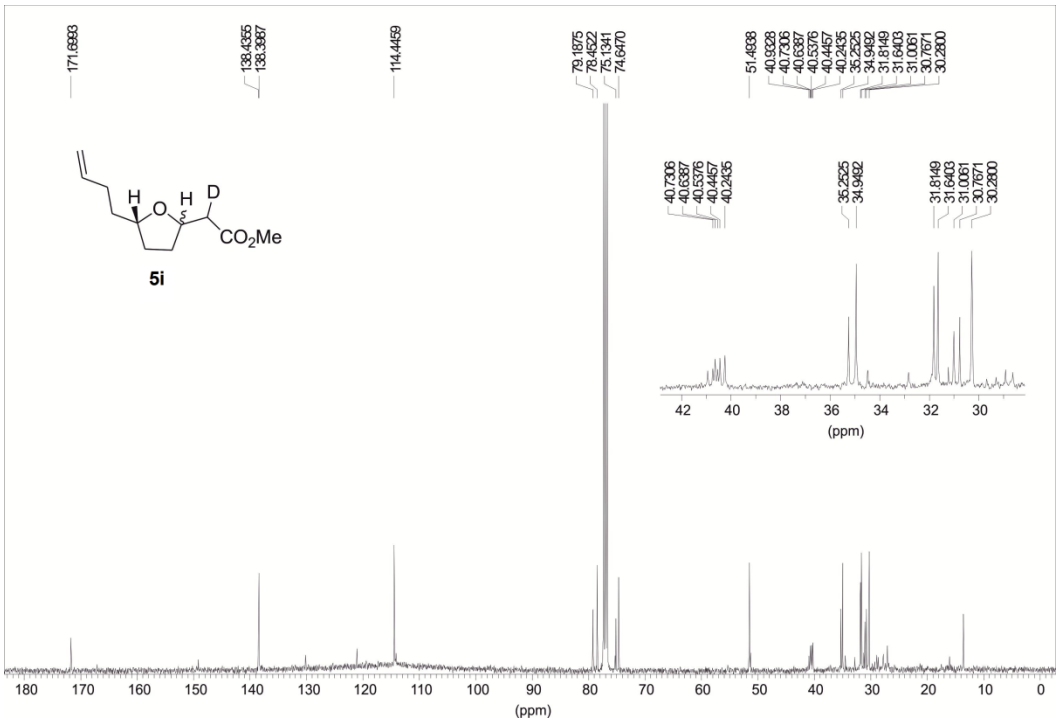

Figure S19: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of methyl [5-(but-3‘-en-1‘-yl)tetrahydrofuran-2-yl)-2-d_1-acetate (**5i**) (35:65-mixture of *cis*/*trans*-isomers).

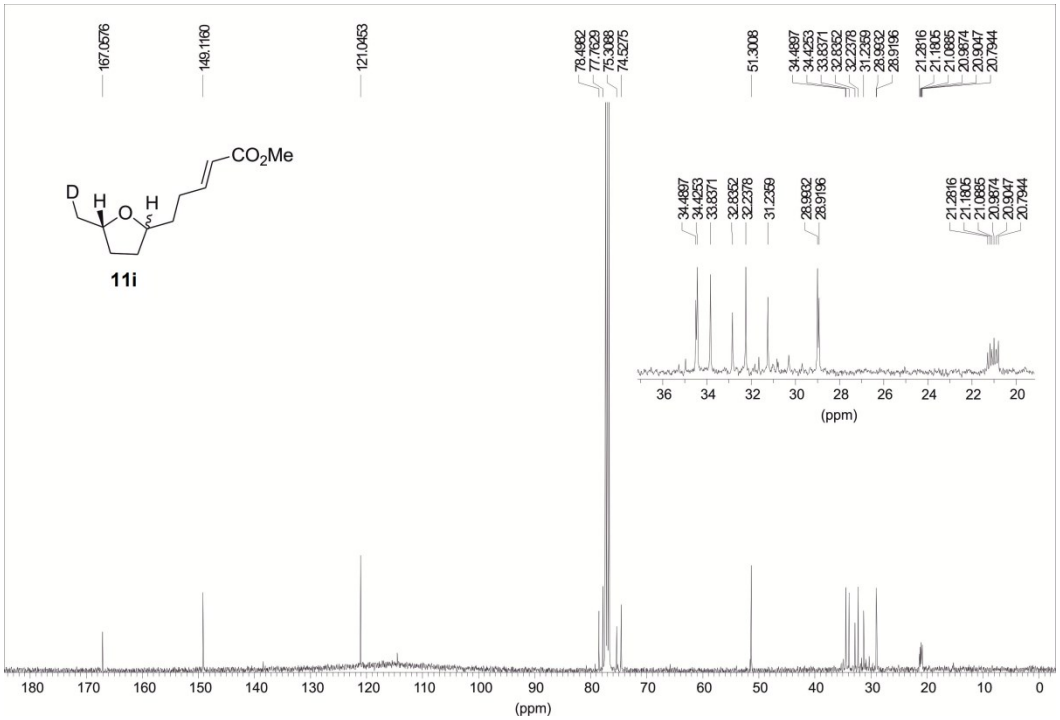

Figure S20: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of methyl 5-[5‘-methyl-d_1-tetrahydrofuran-2‘-yl]pent-2-enoate (**11i**) (39:61-mixture of *cis*/*trans*-isomers).

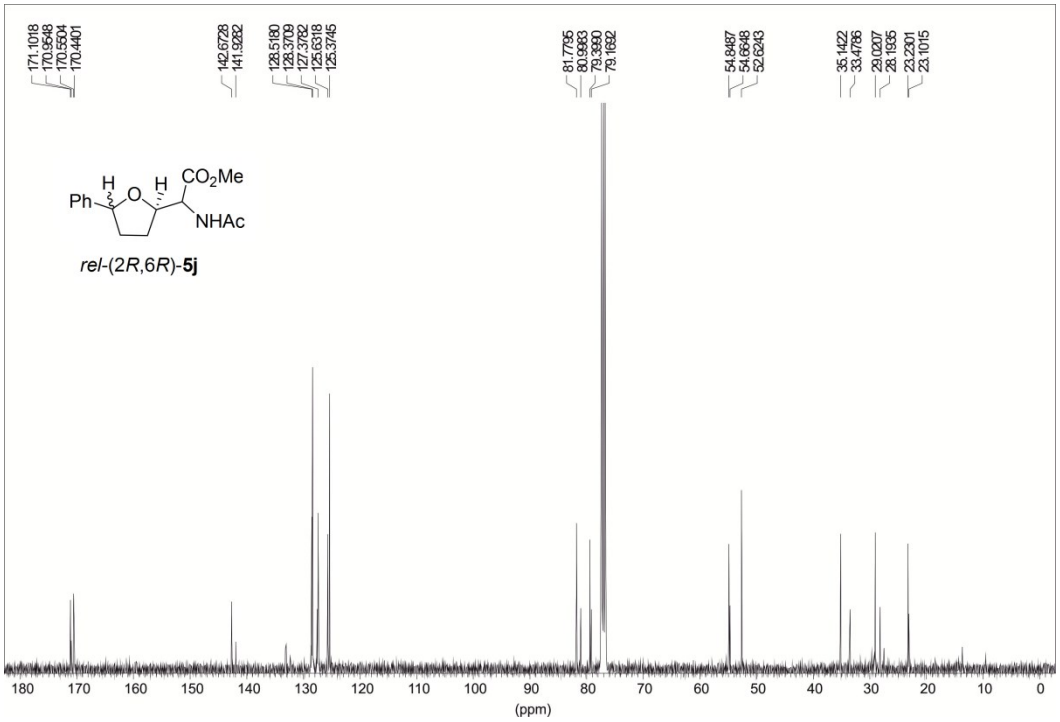

Figure S21: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of *rel*-(2*R*,6*R*)-methyl *N*-acetylamino-(5-phenyltetrahydrofuran-2-yl)acetate *rel*-(2*R*,6*R*)-(**5j**) (32:68-mixture of *cis*/*trans*-isomers).

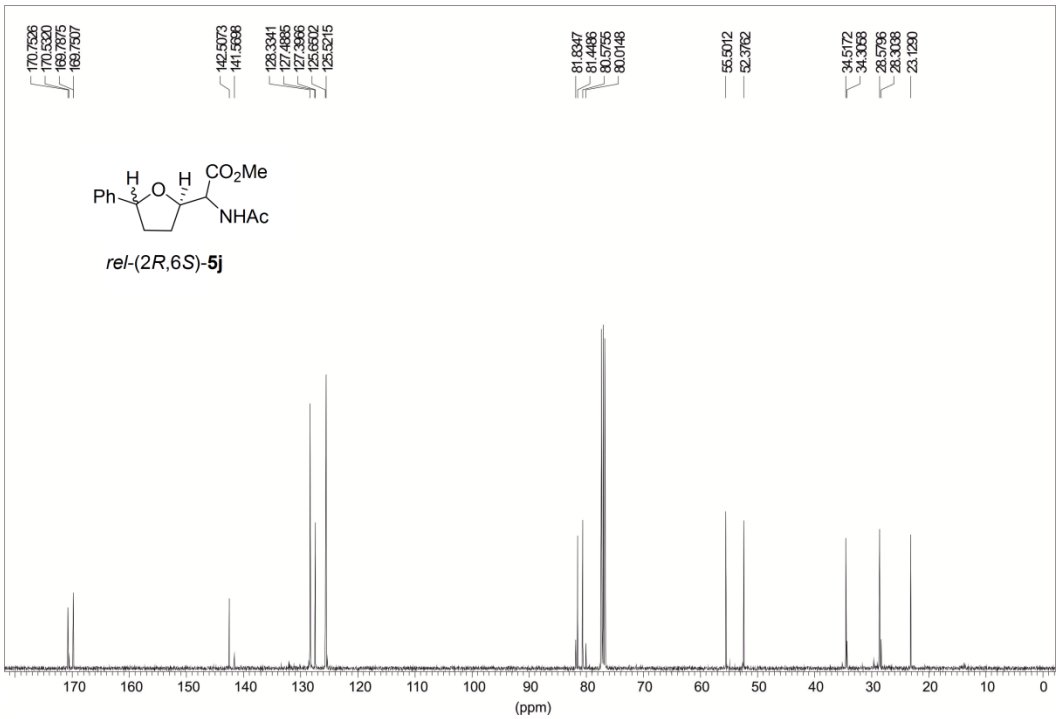

Figure S22: ^{13}C NMR-spectrum (100 MHz, $CDCl_3$) of *rel*-(2*R*,6*S*)-methyl *N*-acetylamino-(5-phenyltetrahydrofuran-2-yl)acetate *rel*-(2*R*,6*S*)-(**5j**) (28:72-mixture of *cis*/*trans*-isomers).

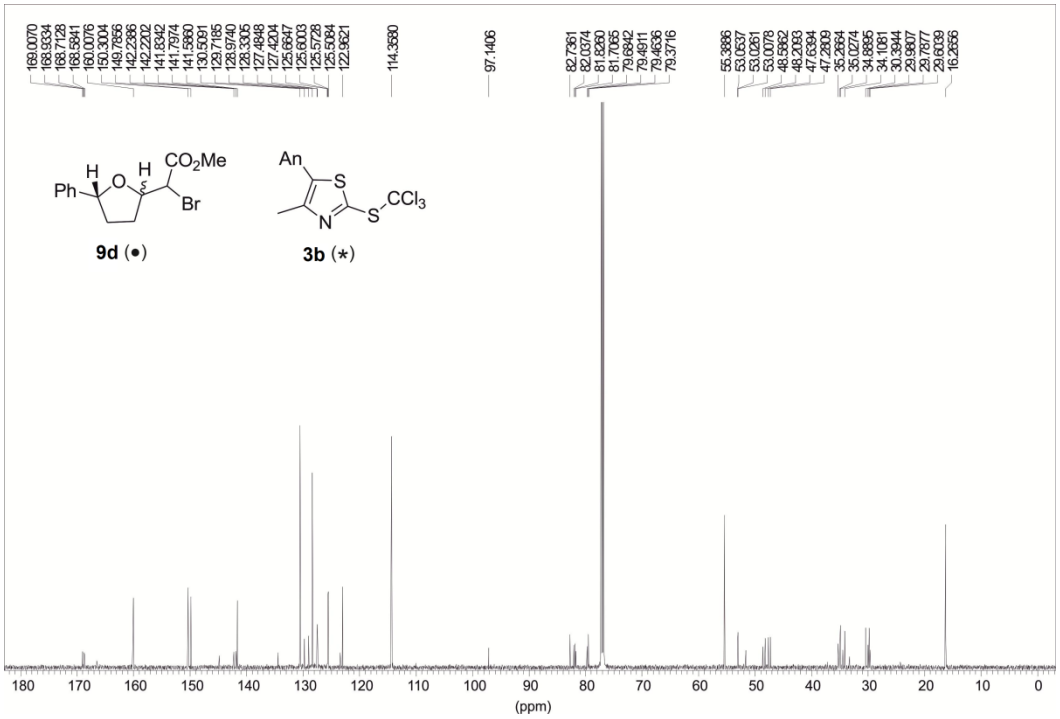

Figure S23: ^{13}C NMR-spectrum (150 MHz, $CDCl_3$) of methyl 2-bromo-2-(5'-phenyltetrahydrofuran-2'-yl)acetate (**9d**) (44:56-mixture of *cis*/*trans*-isomers) and 5-(*p*-methoxyphenyl)-4-methyl-2-(trichloromethylsulfanyl)thiazole (**3b**).

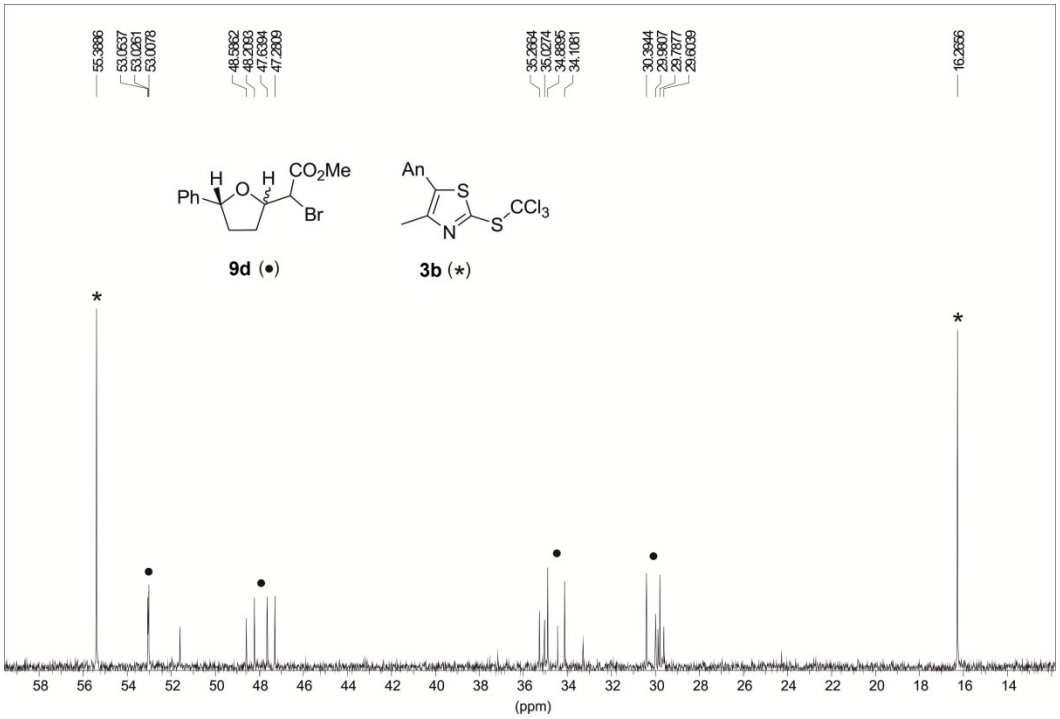

Figure S24: Expert of the ^{13}C NMR-spectrum of methyl 2-bromo-2-(5'-phenyltetrahydrofuran-2'-yl)acetate (**9d**) (44:56-mixture of *cis*/*trans*-isomers) and 5-(*p*-methoxyphenyl)-4-methyl-2-(trichloromethylsulfanyl)thiazole (**3b**) (cf. figure S23.)

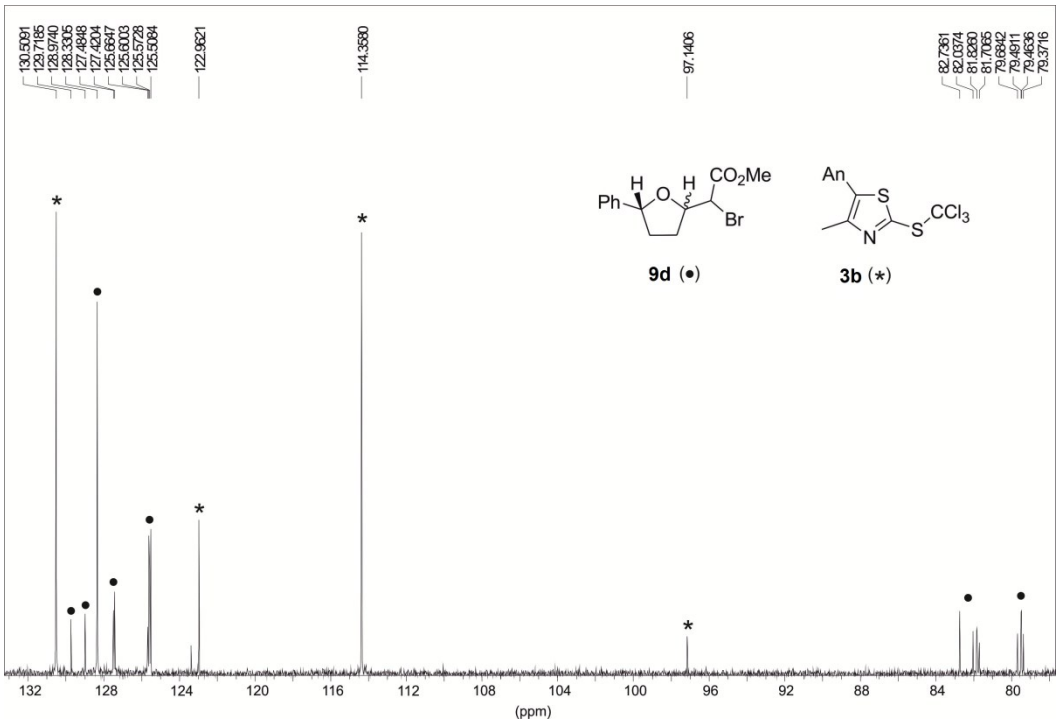

Figure S25: Expert of the ^{13}C NMR-spectrum of methyl 2-bromo-2-(5'-phenyltetrahydrofuran-2'-yl)acetate (**9d**) (44:56-mixture of *cis*/*trans*-isomers) and 5-(*p*-methoxyphenyl)-4-methyl-2-(trichloromethylsulfanyl)thiazole (**3b**) (cf. figure S23.)

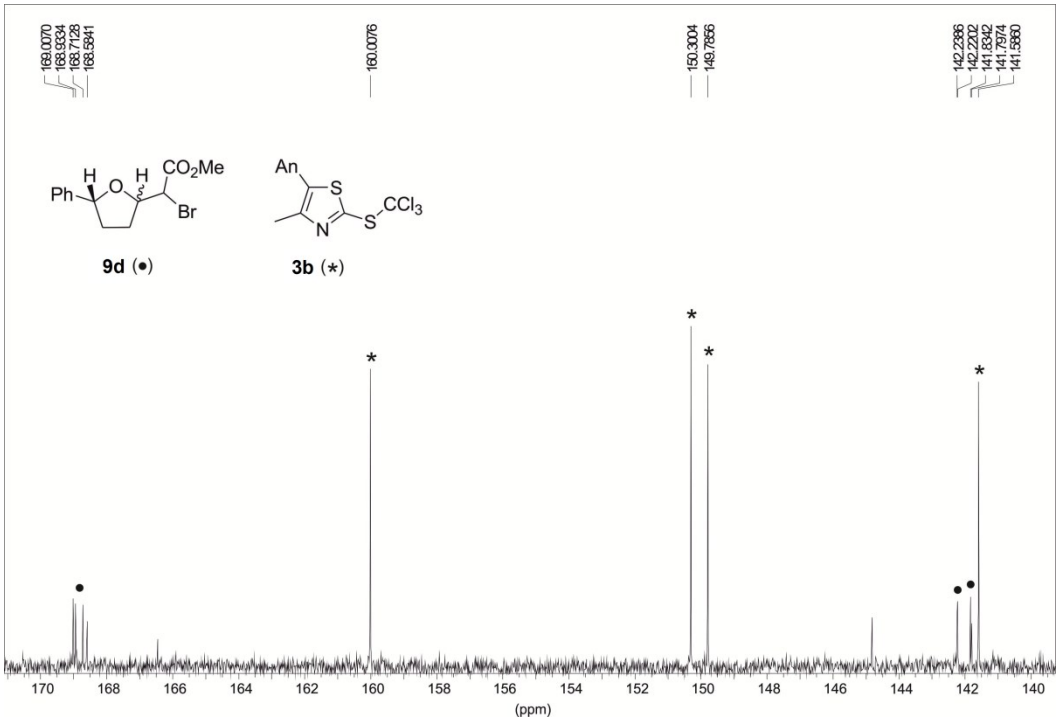

Figure S26: Expert of the ^{13}C NMR-spectrum of methyl 2-bromo-2-(5'-phenyltetrahydrofuran-2'-yl)acetate (**9d**) (44:56-mixture of *cis*/*trans*-isomers) and 5-(*p*-methoxyphenyl)-4-methyl-2-(trichloromethylsulfanyl)thiazole (**3b**) (cf. figure S23).

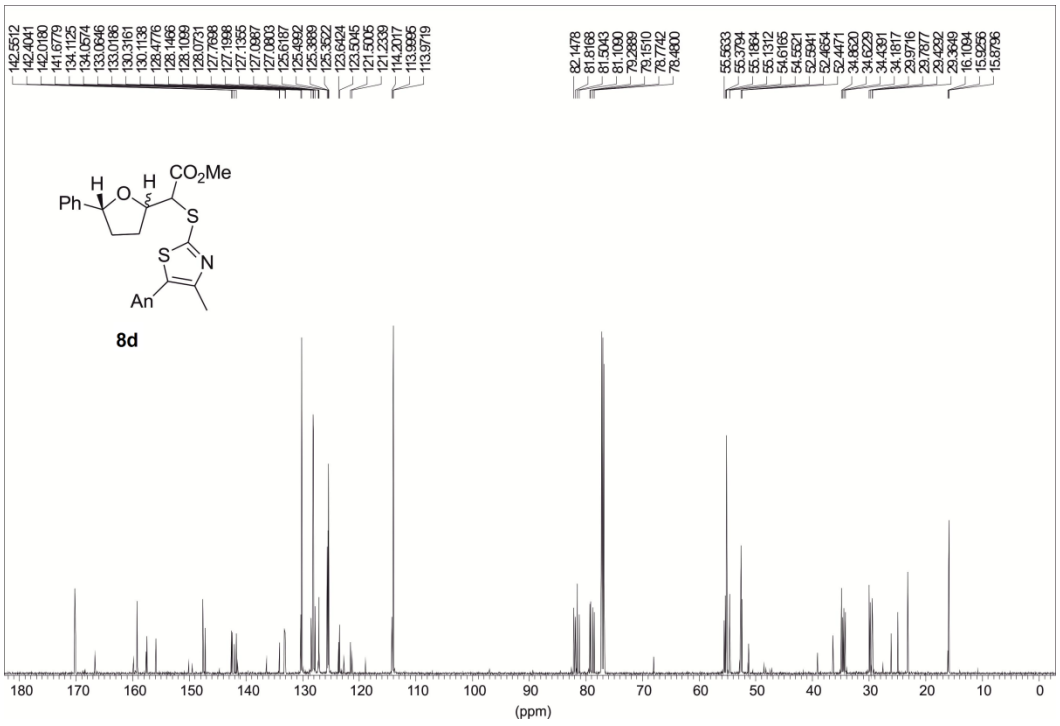

Figure S27: ^{13}C NMR-spectrum (150 MHz, $CDCl_3$) of methyl 2-[5''-(*p*-methoxyphenyl)-4''-methyl-2''-(methylsulfanyl)thiazole]-2-(5'-phenyltetrahydrofuran-2'-yl)acetate (**8d**) (43:57-mixture of *cis*/*trans*-isomers).

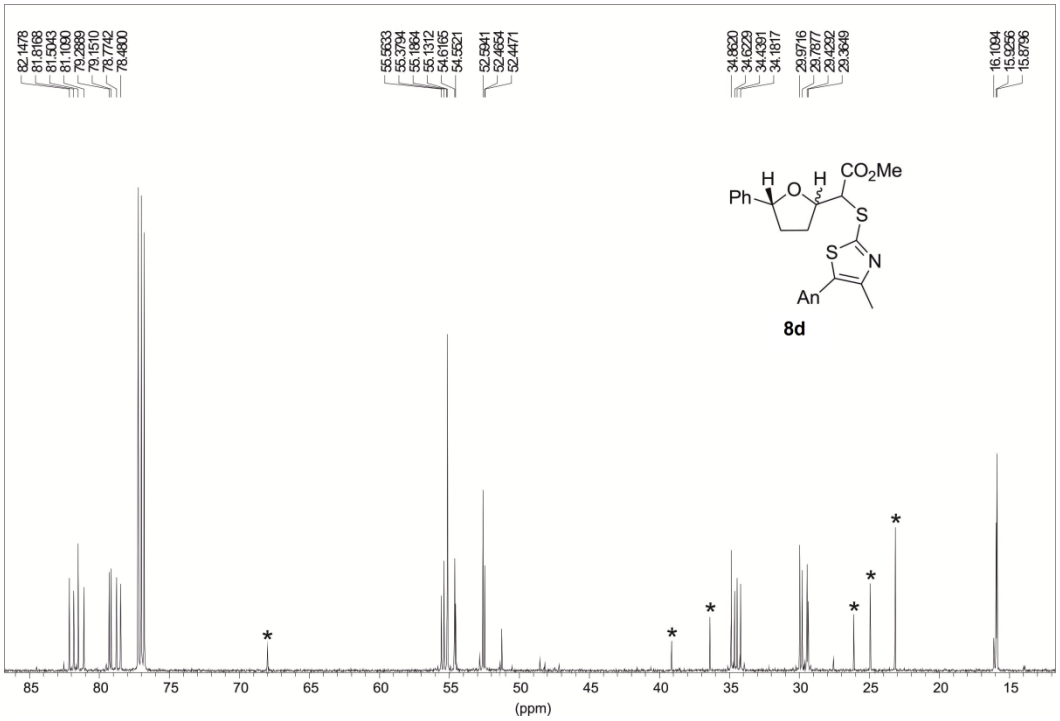

Figure S28: Expert of the ^{13}C NMR-spectrum of methyl 2-[5''-(*p*-methoxyphenyl)-4''-methyl-2''-(methylsulfanyl)thiazole]-2-(5'-phenyltetrahydrofuran-2'-yl)acetate (**8d**) (43:57-mixture of *cis*/*trans*-isomers) (cf. figure S27). Labeling (∗) refer to impurities of unknown identity.

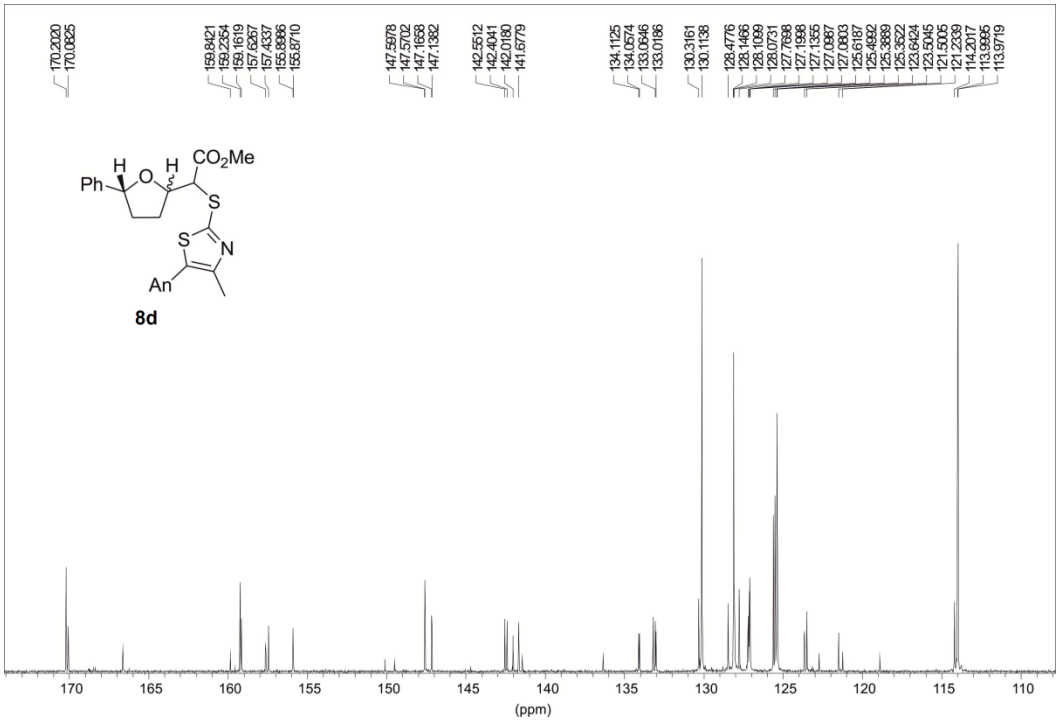

Figure S29: Expert of the ^{13}C NMR-spectrum of methyl 2-[5''-(*p*-methoxyphenyl)-4''-methyl-2''-(methylsulfanyl)thiazole]-2-(5'-phenyltetrahydrofuran-2'-yl)acetate (**8d**) (43:57-mixture of *cis*/*trans*-isomers) (cf. figure S27).

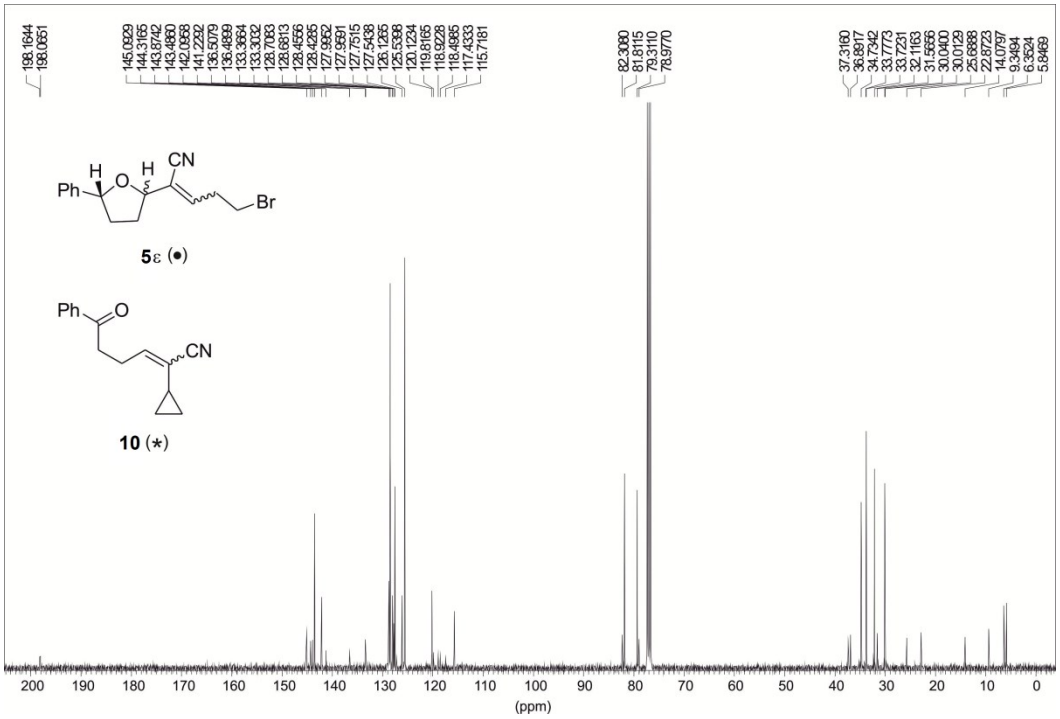

Figure S30: ^{13}C NMR-spectrum (150 MHz, $CDCl_3$) of 5-bromo-2-(5'-phenyltetrahydrofuran-2'-yl)pent-2-enenitrile (**5ε**) (18:82-mixture of *cis*/*trans*-isomers) and 2-cyclopropyl-6-oxo-6-phenylhex-2-enenitrile (**10**) (58:42-mixture of (*E*):(*Z*)-isomers).

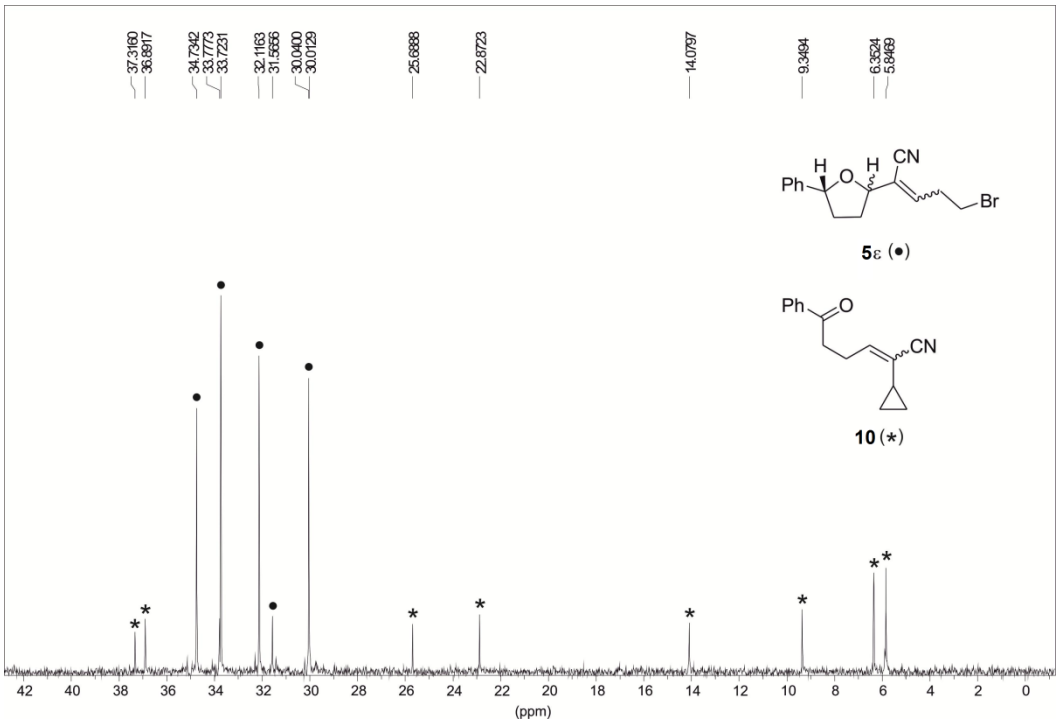

Figure S31: Expert of the ^{13}C NMR-spectrum of 5-bromo-2-(5'-phenyltetrahydrofuran-2'-yl)pent-2-enenitrile (**5ε**) (18:82-mixture of *cis*/*trans*-isomers) and 2-cyclopropyl-6-oxo-6-phenylhex-2-enenitrile (**10**) (58:42-mixture of (*E*):(*Z*)-isomers) (cf. figure S30).

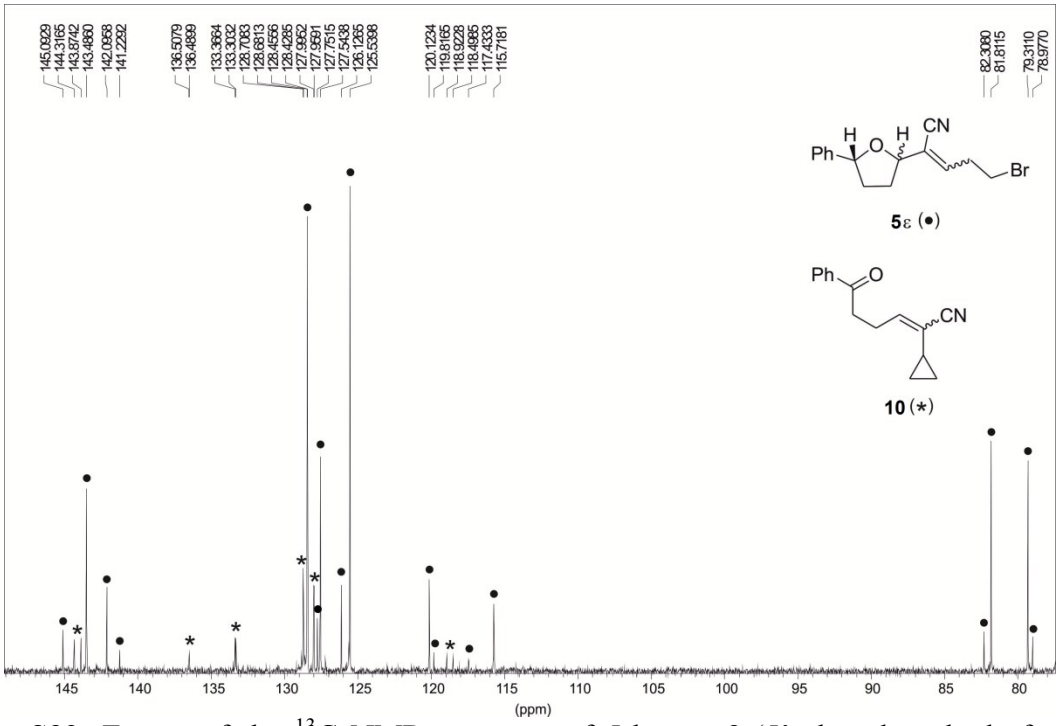

Figure S32: Expert of the ^{13}C NMR-spectrum of 5-bromo-2-(5'-phenyltetrahydrofuran-2'-yl)pent-2-enenitrile (**5ε**) (18:82-mixture of *cis*/*trans*-isomers) and 2-cyclopropyl-6-oxo-6-phenylhex-2-enenitrile (**10**) (58:42-mixture of (*E*):(*Z*)-isomers) (cf. figure S30).

6 References

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[3] *in dependence on*: Hartung, J.; Hiller, M.; Schmidt, P. *Chem. Eur. J.* **1996**, *2*, 1014–1023.

[4] *in dependence on*: (*a*) Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 7718–7727. (*b*) Michael, J. P.; Nkwelo, M. M. *Tetrahedron* **1990**, *46*, 2549–2560.

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7 Anhang

Posterbeitrag A

Solid State Reactivity of 3-(Alkoxy)-4-(*p*-chlorophenyl)-thiazole-2(3*H*)-thiones

Irina Kempter, Uwe Bergsträßer, Jens Hartung, *11th International Symposium on Organic Free Radicals (ISOFR-11)*, Bern (Schweiz), **2012**.

Posterbeitrag B

Synthesis and Structural Characterization of the Isomuscarines

Irina Kempter, Britta Frensch, Jens Hartung, *EuCheMS Conference on Organic Free Radicals (ECOFR 2014)*, Prag (Tschechien), **2014**.

Posterbeitrag C

2,3-*cis*-Stereocontrol in Alkoxyl Radical Cyclization

Irina Kempter, Jens Hartung, *GDCh-Wissenschaftsforum Chemie*, Dresden, **2015**.

TECHNISCHE UNIVERSITÄT KAISERSLAUTERN

Solid State Reactivity of 3-(Alkoxy)-4-(*p*-chlorophenyl)-thiazole-2(3*H*)-thiones

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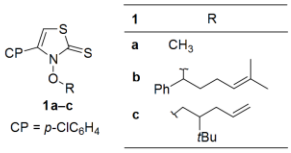
Abstract

Synthetic, spectroscopic, and structural investigations indicated that 3-(alkoxy)-4-(*p*-chlorophenyl)-thiazole-2(3*H*)-thiones (CPTTOR), once developed to serve as alkoxyl radical precursors for long-term storage and use on demand, showed unexpected background reactivities in the solid state. The new products were identified and characterized by NMR spectroscopy as well as X-ray crystallography to elucidate the new reaction pathways. The study revealed that selectivity of decomposition depends on the *O*-alkyl substituent of neat CPTTORs and leads to fragmentation, isomerization, or rearrangement.

Background

3-(Alkoxy)-4-(*p*-chlorophenyl)-thiazole-2(3*H*)-thiones (**1a**–**c**) were developed as reagents for alkoxyl radical generation in absence of strong oxidants and metal ions at neutral pH.[1] Oxygen-centered radicals can be effectively liberated from this type of precursor *via* N,O-bond homolysis upon photochemical excitation, microwave irradiation or heating in presence of an initiator.[2]

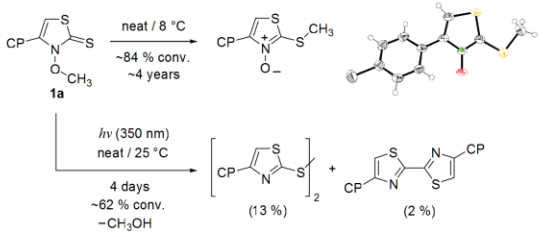


CPTTORs form colorless solids that can be stored and applied on demand. In refrigerated samples of radical precursor **1a–c** new products appeared unexpectedly when stored for prolonged periods of time. The investigation of the products showed that CPTTORs decomposed selectively by isomerization, fragmentation, or rearrangement.

Results

Isomerization

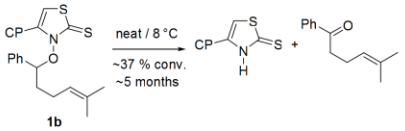
CPTTOMe (**1a**) isomerized selectively *via* methyl transfer from oxygen to sulfur to furnish a heteroaromatic *N*-oxide. The rearrangement product was sythesized in an independent reaction and its structure verified by NMR spectroscopy as well as X-ray diffraction analysis. The enthalpy of the slow isomerization was calculated to be weakly endothermic.[3] Further examples of alkyl migration, for example of primary or secondary substituents, have not been observed so far.



Photoactivation (350 nm, 25 °C) of solid **1a** provided the disulfide in yield of 13 % along with 2 % of the substituted 2,2'-bithiazole, which is a familiar photo-decomposition product of disulfide, without providing evidence for formation of *N*-oxide.

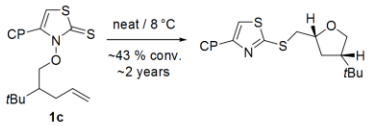
Fragmentation

Radical precursor **1b** underwent fragmentation *via* formal 1,5-H-atom shift into thiolactam and ketone after storage for 5 months at 8 °C. Alternative CPTTOR decomposition products were not observed. Apart from **1b**, none of the thiazolethiones in this study (see above) exhibited similar reactivity.



Rearrangement

Thiazolethione **1c** was developed for predicting stereoselectivity in alkenoxyl radical 5-*exo*-trig cyclization.[4] In a sample of neat **1c**, which was kept for 2 years at 8 °C in the dark, only one stereoisomer (*cis*-tetrahydrofuran) was found. The rearrangement occured in the solid state without being photoactivated or subjected to higher temperatures. Activated solution of **1c** afforded in presence of a radical mediator, such as Bu_3SnH, a mixture of stereoisomeric tetrahydrofurans in a *cis*:*trans*-ratio of 90:10.



Conclusion

The investigations uncovered that at least three modes of CPTTORs decomposition exist, which are distinctively different from homolytic substitutions in radical chain reactions. Two pathways reflected the inherent weakness of the N,O-bond, leading to fragmentation and rearrangement products. The third mode of decomposition furnished a heteroaromatic *N*-oxide *via* methyl translocation from oxygen to sulfur. The discovered background reactivities occured selectively in neat solid CPTTOR samples and the observation suggests that the reason for the noticed specificity resides in crystal lattices. However, none of the reactions provided a potent inhibitor for radical chain reactions.

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ISOFR-11, July 1–5, 2012, Berne, Switzerland

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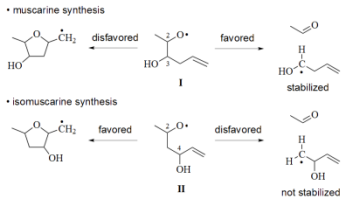
Synthesis and Structural Characterization of the Isomuscarines

Irina Kempter, Britta Frensch and Jens Hartung*

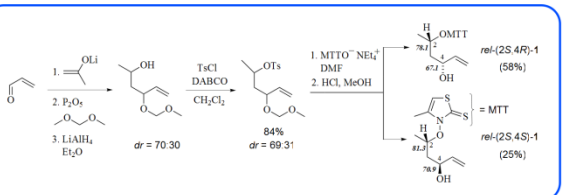
Abstract

From a study on synthesis of *allo*-muscarine via 3-hydroxylhex-5-en-2-oxyl radical cyclization we learned that a hydroxyl group in β-position to the radical oxygen induces rapid β-fragmentation to the aliphatic chain.[1] Driving forces for breaking the β-carbon-carbon bond in alkenoxyl radical **I** are entropy, strength of the newly formed carbon-oxygen double bond, and radical stabilization by an α-hydroxyl substituent. We predicted that a hydroxyl substituent in γ-position to the radical oxygen exerts no similiar rate enhancing for β-carbon-carbon breaking, as in regioisomer **I**. Based on this argument, we predicted alkenoxyl radical **II** to cyclize regio- and stereoselectively providing for the first time access to all diastereomers of the isomuscarines. Isomuscarines are tetrahydrofuran-derived quaternary ammonium cations structurally related to the muscarines[2] by changing position of the endocyclic hydroxyl group.[3] The four diastereomers are trivially named isomuscarine, *allo*-isomuscarine, *epi*-isomuscarine, and *epiallo*-isomuscarine, depending on relative orientation of the hydroxyl group and the trimethylammoniummethyl side chain with respect to the methyl substituent.

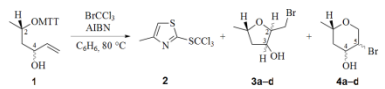


Results

Preparation of 3-(alkenoxy)-4-methylthiazole-2(3*H*)-thiones

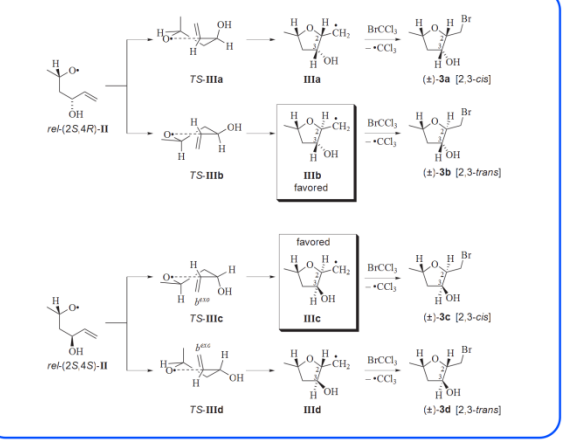


Alkenoxyl radical bromocyclizations

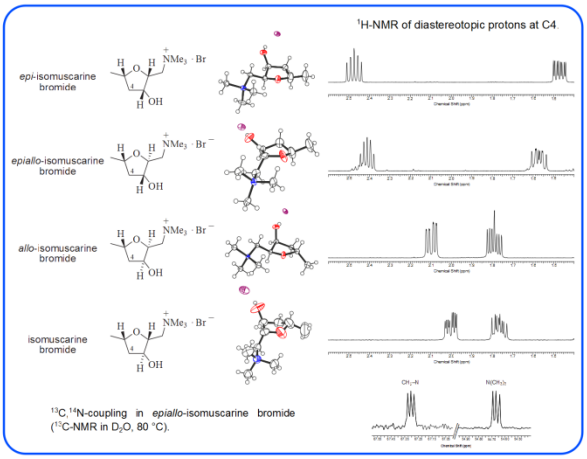


entry	configuration 1	2	**3a–d** (2,3-*cis*:*trans*)	**4a–d** (4,5-*cis*:*trans*)
1	*rel*-(2*S*,4*R*)	96%	62% (37:63 = **3a**:**3b**)	10% (40:60 = **4a**:**4b**)
2	*rel*-(2*S*,4*S*)	84%	67% (72:28 = **3c**:**3d**)	2%

Transition structures of the 5-*exo*-trig-cyclization



Characterization of the isomuscarine bromides



Conclusion

The four diastereomers were prepared as bromide salts starting from 2,4-*like*- and 2,4-*unlike*-configured 3-(4-hydroxyhex-5-en-2-oxy)-4-methylthiazole-2-(3*H*)-thiones. Bromine atom trapping of cyclized radicals furnishes derived bromomethyltetrahydrofurans, which are used as building blocks for preparing isomuscarine bromides.[4] The study showed that the allylic hydroxyl group is able to direct 5-*exo*-cyclization 2,3-cis-selectively, which is entirely new and only observed so far for the 2,4-*like*-configured 4-hydroxyhex-5-en-2-oxyl radical. The *unlike*-configured alkenoxyl radical undergoes a 2,3-trans-selective 5-*exo*-ring closure and the allylic hydroxyl group increases the fraction of 6-*endo*-cyclized product by one order of magnitude compared to the fingerprint-type regioselectivity of 98:2 in 4-pentenoxyl radical cyclizations. We think that the new directing effect of the allylic hydroxyl group is a polar effect exerted by oxygen arises from σ-electron accepting and π-type lone pair-donating contributions.[5]

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2,3-*cis*-Stereocontrol in Alkoxyl Radical Cyclization

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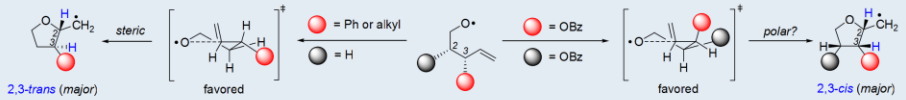
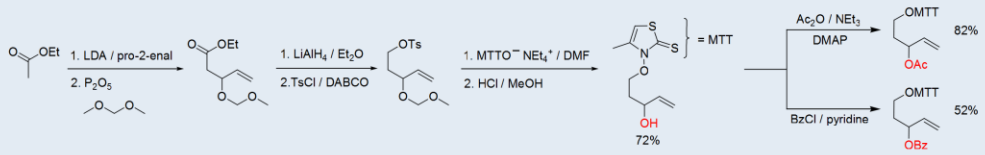
Introduction

Stereoselectivity of 5-*exo*-trig-cyclizations of alkoxyl radicals can be controlled by steric substituent effects. Existing guidelines predict 2,3-*trans*-selective 5-*exo*-ring closure of 3-alkyl- or phenyl-substituted 4-pentenoxyl radicals.[1] The influence of stereoselectivity depends only on the steric demand of substituents. Benzyloxy-substituents in position 2 and 3 of alkoxyl radicals surprisingly direct cyclization 2,3-*cis*-selectively. The origin of the new 2,3-*cis*-stereocontrol possibly arises from a polar effect.[2] This study investigates the influence of acceptor-substituents in position 3 of 2,3-*cis*-stereoselectivity in 5-*exo*-trig-cyclizations and should clarify the existence of a polar effect of oxygen-substituents, like hydroxyl, acetyloxy and benzyloxy. This 2,3-*cis*-directing effect can be utilized for preparing 2,3-*cis*-configured *allo*-isomuscarine bromide[3], a tetrahydrofuran-derived quarternary ammonium cation structurally related to the muscarine.[4,5]

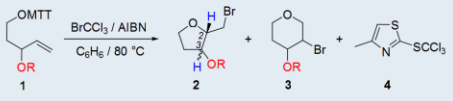


Results

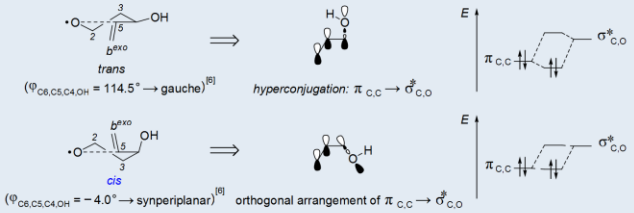
Synthesis of 3-allyl-substituted 3-(alkenoxy)-4-methylthiazole-2(3*H*)-thione



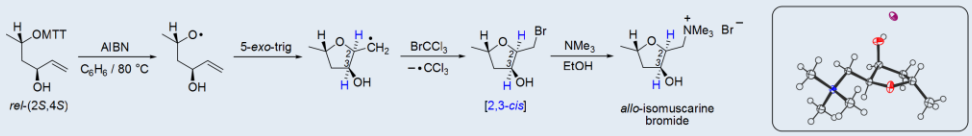
2,3-*cis*-stereocontrol in alkenoxyl radical bromocyclizations



entry	OR	2 (2,3-*cis*:2,3-*trans*)	3	4
1	OH	56% (74:26)	3,5%	84%
2	OAc	71% (68:32)	10,5%	94%
3	OBz	69% (68:32)	12%	75%



Application of 2,3-*cis*-directing effect for preparing 2,3-*cis*-configured *allo*-isomuscarine bromide



Conclusion

Acceptor-substituents in position 3 of 4-pentenoxyl radicals influence the stereoselectivity of 5-*exo*-trig-cyclizations and direct the cyclization 2,3-*cis*-selectively. The effect was observed for oxygen-substituents, like hydroxyl, acetyloxy and benzyloxy. The new 2,3-*cis*-stereocontrol arising from a polar effect causes an advancement of the existing guidelines for radical ring closures. The polar effect is based on $\pi_{C,C} \rightarrow \sigma^*_{C,O}$ hyperconjugation, pointing to lower reactivity of 2,3-*trans*-configured intermediates. In this study the acceptor-substituents are limited to oxygen, but this effect should also exist for other acceptor-groups, like nitrogen or sulfur, which is currently under investigation in our laboratories.[7] The results contribute to the understanding of the 2,3-*cis*-directing effect in alkenoxyl radical cyclizations and extend the application of radical cyclization reactions.

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GDCh-Wissenschaftsforum Chemie, 30.8. – 2.9.2015, Dresden, Germany

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PUBLIKATIONEN

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- *2,3-cis-Cyclization of 4-pentenoxyl radicals.* I. Kempter, C. Schur, K. Huttenlochner, R.-M. Bergsträßer, B. Wolff, T. Kopf, J. Hartung, *Tetrahedron* **2016**, *72*, 7699−7714.

- *Synthesis and Structural Characterization of the Isomuscarines.* I. Kempter, B. Frensch, T. Kopf, R. Kluge, R. Csuk, I. Svoboda, H. Fuess, J. Hartung, *Tetrahedron* **2014**, *70*, 1918−1927.

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- *Lessons of 3-Alkoxy-4-(p-chlorophenyl)-1,3-thiazole-2(3H)-thione Chemistry Learned from Structural Investigations*. J. Hartung, K. Daniel, U. Bergsträßer, I. Kempter, N. Schneiders, S. Danner, P. Schmidt, I. Svoboda, H. Fuess, *Eur. J. Org. Chem.* **2009**, 4135–4142

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