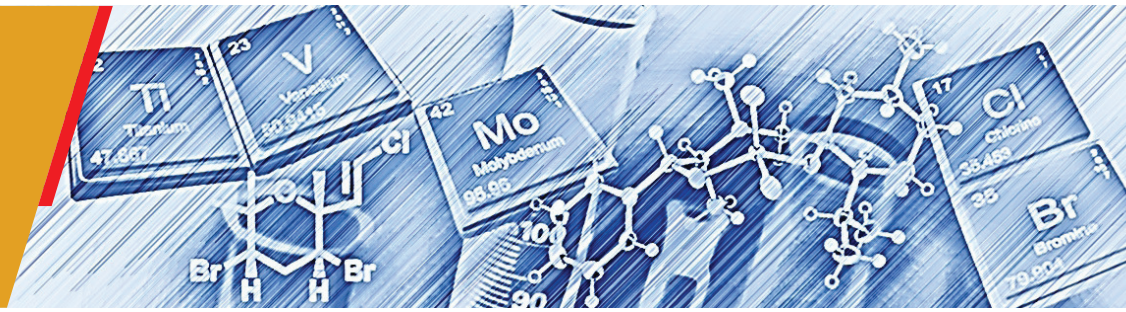
Technische Universität
Kaiserslautern

Fachbereich
Chemie



Über die Entwicklung und Anwendung funktionaler Haloperoxidase-Modelle zur Synthese von Naturstoffderivaten

Oliver Brücher

Dissertation
Fachrichtung Organische Chemie
Dezember 2012

Über die Entwicklung und Anwendung funktionaler Haloperoxidase-Modelle zur Synthese von Naturstoffderivaten

Vom Fachbereich Chemie der Technischen Universität Kaiserslautern
zur Verleihung des akademischen Grades
„Doktor der Naturwissenschaften“
genehmigte Dissertation

D386

vorgelegt von
Oliver Brücher

Betreuer: Prof. Dr.-Ing. Jens Hartung
Kaiserslautern 2012

Für Eva
und
meine Familie

Wenn du etwas machst, wie du es vor zehn Jahren gemacht hast, dann sind die Chancen recht groß, dass du es falsch machst. *Charles Kettering*

Die vorliegende Arbeit wurde in der Zeit von Juli 2007 bis Oktober 2012 im Fachbereich Chemie (Fachrichtung Organische Chemie) der Technischen Universität Kaiserslautern angefertigt.

Mein besonderer Dank gilt Herrn Prof. Dr.-Ing. Jens Hartung für die freundliche Aufnahme in seinen Arbeitskreis, für die Überlassung des interessanten und vielseitigen Themengebiets und das stets mit hilfreichen Anregungen und Diskussionen verbundene Interesse an dieser Arbeit.

Ferner danke ich Herrn Prof. Dr. Stefan Kubik für die Anfertigung des Zweitgutachtens und Herrn Prof. Gereon Niedner-Schatteburg für die bereitwillige Übernahme des Vorsitzes der Prüfungskommission.

Der Deutschen Bundesstiftung Umwelt (DBU) und ihren Mitarbeitern möchte ich für das in mich gesetzte Vertrauen und die finanzielle Unterstützung danken.

Tag der wissenschaftlichen Aussprache: 7. Dezember 2012

Prüfungskommission:
Vorsitzender: Prof. Dr. Gereon Niedner-Schatteburg
Erstgutachter: Prof. Dr.-Ing. Jens Hartung
Zweitgutachter: Prof. Dr. Stefan Kubik

Die Ergebnisse der vorliegenden Dissertation wurden in den folgenden begutachteten Arbeiten vorab veröffentlicht oder eingereicht:

(I) Forschungsartikel (mit Titelseite): **Vanadium(V)-Catalyzed Oxidative Bromination of Acid Labile Alkenols and Alkenes in Alkyl Carbonates.**
Oliver Brücher, Jens Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.

(II) Forschungsartikel: **Controlling 6-*endo*-Selectivity in Oxidation/Bromocyclization Cascades for Synthesis of Aplysiapyranoids and other 2,2,6,6-substituted Tetrahydropyrans.**
Oliver Brücher, Uwe Bergsträßer, Harald Kelm, Jens Hartung, Marco Greb, Ingrid Svoboda, Hartmut Fuess, *Tetrahedron* **2012**, *68*, 6968–6980.

(III) Forschungsartikel: **A Practical Approach to Catalytic and Noncatalytic Oxidative Chlorination of Unsaturated and Saturated Hydrocarbons.**
Oliver Brücher, Jens Hartung, **2012**, *zur Begutachtung eingereicht*.

(IV) Übersichtsartikel: **Bromoperoxidases and Functional Enzyme Mimics as Catalysts for Oxidative Bromination – A Sustainable Synthetic Approach.**
Diana Wischang, Oliver Brücher, Jens Hartung, *Coord. Chem. Rev.* **2011**, *255*, 2204–2217.

Darüber hinaus wurden die Promotionsergebnisse als Posterbeiträge auf folgenden Tagungen präsentiert:

(V) Poster: **Vanadium(V)-catalyzed Oxidative Brominations of Olefins and Alkenols with *tert*-Butyl Hydroperoxide and β-Bromopropionic Acids.**
Oliver Brücher, Jens Hartung, *7th International Vanadium Symposium*, Toyama (Japan), **6.–10. Okt. 2010.**

(VI) Poster: ***In situ*-generated Chlorine as Selective Reagent for Chlorocyclization Reactions of Substituted 4-Pentenols.**
Oliver Brücher, Jens Hartung, *GDCh-Wissenschaftsforum*, Bremen, **4.–7. Sept. 2011**.

Eidesstattliche Erklärung

Hiermit erkläre ich ehrenwörtlich, dass ich die vorliegende Arbeit selbständig 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 24.10.2012

Oliver Brücher

Erläuterungen

Die vorliegende kumulative Dissertation ist in Zusammenfassung, Einleitung (Kapitel 1), Kenntnisstand mit Aufgabenstellung (Kapitel 2), drei unabhängige Ergebnisteile (Kapitel 3–5) und einen Anhang gegliedert. Die zu den jeweiligen Ergebnisteilen gehörenden Forschungsartikel sind den entsprechenden Kapiteln angefügt und besitzen eine eigene Gliederung. Weitere veröffentlichte Inhalte sowie ergänzende experimentelle Daten zu Ergebniskapiteln sind im Anhang der Dissertation aufgeführt. Abbildungen, Schemata und Tabellen sind für das jeweilige Kapitel fortlaufend nummeriert. Strukturformeln sind für die gesamte Arbeit durchgehend nummeriert und stimmen nicht mit der Nummerierung in den zugehörigen Forschungsartikeln überein. Die in Strukturformeln mittels Keilschreibweise angezeigte Stereochemie bezeichnet, sofern nicht explizit anders angegeben, die relative und nicht die absolute Konfiguration. Wenn nicht anders vermerkt, bezieht sich die Angabe der *cis*/*trans*-Verhältnisse betrachteter Tetrahydrofuran- und Tetrahydropyran-Strukturen auf die relative Stellung der Substituenten in 3- und 5-Position. Nummerierung von Atomen und Benennung von Verbindungen entsprechen nicht immer der IUPAC-Empfehlung. Für jedes Kapitel ist ein separates Literaturverzeichnis angegeben.

Verzeichnis verwendeter Abkürzungen

[Kat]	Katalysator
[V-Kat]	Vanadium-abgeleiteter Katalysator
acac	Butan-1,3-dion-Monoanion
aq.	wässrig
CHD	Cyclohexa-1,4-dien
DMC	Dimethylcarbonat
f	partieller Geschwindigkeitsfaktor
kat.	katalytisch
LDA	Lithium-diisopropylamid
LM	Lösungsmittel
Lsg.	Lösung
NBS	*N*-Bromsuccinimid
NHE	Normalwasserstoffelektrode
PC	Propylencarbonat
p-TsOH	*para*-Toluolsulfonsäure
py·HBr	Pyridiniumhydrobromid
py·HCl	Pyridiniumhydrochlorid
TBCD	2,4,4,6-Tetrabromo-2,5-cyclohexadienon
TBHP	*tert*-Butylhydroperoxid
$V_{Br}PO(AnI)$	Vanadat-abhängige Bromoperoxidase I aus *Ascophyllum nodosum*
V_XPO	Vanadat-abhängige Haloperoxidase

Inhaltsverzeichnis

Zusammenfassung

Die vorliegende Arbeit beschäftigt sich mit der Entwicklung funktionaler Modellsysteme von Bromo- und Chloroperoxidasen zur Oxidation von Bromid und Chlorid unter wasserfreien und nachhaltigen Bedingungen. Die neuen Methoden fanden Anwendung in der Synthese halogenierter O-Heterocyclen, welche häufig als Grundstrukturen von Naturstoffen mit ausgeprägten physiologischen Wirkungen auftreten. Die gewonnenen Erkenntnisse lösten vorhandene Probleme mit Reaktivität und Chemoselektivität in oxidativen Bromierungsreaktionen und trugen zu einem besseren Verständnis der beobachteten Regioselektivitäten in Bromcyclisierungen hochsubstituierter 4-Pentenole bei. Aufbauend auf diesen Ergebnissen konnte erstmalig eine analoge Methode zur oxidativen Chlorcyclisierung für die Darstellung β-chlorierter Tetrahydrofurane und Tetrahydropyrane entwickelt werden.

In einem ersten Projekt gelang die Realisierung eines Verfahrens zur oxidativen Bromierung von C,C-Doppelbindungen unter nahezu pH-neutralen und wasserfreien Reaktionsbedingungen, welches sich insbesondere zur Durchführung von Bromcyclisierungen substituierter 4-Pentenole eignete. Dabei konnte das Konzept der *in situ*-Bromidoxidation, neben der Verwendung effektiverer Vanadium-Katalysatoren und organischer Carbonate als Solventien, vor allem durch Einsatz eines neuartigen HBr-Donors auf eine grundlegend neue Basis gestellt werden. Die hierfür entwickelten β-Bromcarbonsäurederivate fragmentieren in Gegenwart katalytischer Mengen an Bromid unter milden Bedingungen und fungieren dabei als Puffersystem, welches eine nahezu pH-neutrale, kontinuierliche Versorgung der Oxidationsreaktion mit HBr-Äquivalenten sicherstellt. Auf diese Weise gelang es, das Verfahren auf die Umsetzung säurelabiler Substrate zu erweitern. Durch Verwendung umweltfreundlicher Alkylcarbonate als Lösungsmittel konnte zudem die Nachhaltigkeit oxidativer Bromierungsreaktionen verbessert und die Aufarbeitung größerer Ansätze vereinfacht werden. Die Methode wurde im folgenden Projekt zur Herstellung bromierter O-heterocyclischer Naturstoffderivate eingesetzt.

Die Resultate der zweiten Projektstudie zur Regioselektivität in Bromcyclisierungen hochsubstituierter 4-Pentenole belegen, dass ein Aryl-Substituent in 5-Position des Alkenols eine Polarisierung der intermediären Bromoniumion-Teilstruktur bewirkt, welche die aufkommenden Ringspannungseffekte kompensieren und den Ringschluss 6-*endo*-selektiv steuern kann. In einer experimentellen Studie wurden hierzu zunächst Bromcyclisierungsreaktionen von 4-Pentenolen unter gezielter Substituentenvariation zur Beobachtung von sterischen und polaren Effekten herangezogen. Diese Selektivitätsstudien hatten den Zweck strukturelle Faktoren heraus-

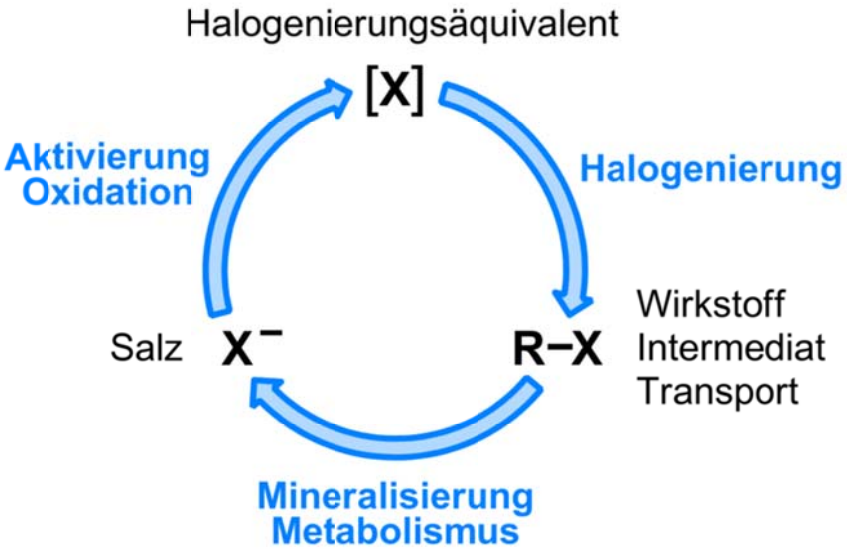
zuarbeiten, mit welchen sich die Regiochemie von Bromcyclisierungen beschreiben lässt und eine selektive Darstellung von Tetrahydropyranen begünstigt werden kann. In Kooperation mit Jens Hartung wurden die experimentellen Untersuchungen durch theoretische Berechnungen der relativen freien Enthalpien eines Satzes Dimethyl-substituierter Tetrahydropyranderivate ergänzt, welche zur Abschätzung der relativen Aktivierungsenergien später Übergangszustände des 6-*endo*-Ringschlusses dienten. Die experimentellen und die theoretischen Resultate zeigten, dass vor allem axiale Substituenten in 2- und 6-Position des entstehenden Tetrahydropyran-gerüstes zu Spannungsenergien führen, welche das System unter verstärkter Bildung des sterisch weniger aufgeladenen Fünfrings zu vermeiden sucht. Vor allem die Bildung 2,2,6,6-substituierter Tetrahydropyranderviate ist dabei energetisch benachteiligt, was bei Synthesen entsprechender Naturstoffderivate zu ungünstigen Selektivitäten führt. Die neuen Erkenntnisse zur Steuerung der Regiochemie durch polare Substituenten konnten im Anschluss bei der Darstellung des Naturstoffs Aplysiapyranoid A und eines 5-Epimers synthetisch genutzt werden.

Im dritten Teil dieser Arbeit gelang erstmals die Realisierung eines Übergangsmetall-katalysierten Verfahrens zur Durchführung oxidativer Chlorcyclisierungen von substituierten 4-Pentenolen unter milden und nachhaltigen Reaktionsbedingungen. Dabei fungieren neuartige Molybdän(VI)- und Titan(IV)-Komplexe als Chloroperoxidase-Modelle für die Generierung elektrophiler Chlorierungsreagenzien aus Pyridiniumhydrochlorid und *tert*-Butylhydroperoxid in einer Lösung von Dimethylcarbonat bei Temperaturen ab 20 °C. Dieses katalytische System wurde ferner durch ein stöchiometrisches Verfahren ergänzt, welches Kaliumchlorid und Kaliumperoxomonosulfat (Oxone©) zur Erzeugung ähnlich reaktiver Chlorierungsäquivalente nutzt. Neben der guten Eignung für Chlorcyclisierungsreaktionen konnten die Methoden ihre Vielseitigkeit auch bei der Chlorierung von Aromaten, Alkanen sowie allylischer Substrate unter Beweis stellen, wobei die gefundenen Produkte und Selektivitäten mit hoher Wahrscheinlichkeit auf das Vorliegen von molekularem Chlor als aktives Chlorierungsmittel hindeuten. In einer ersten synthetischen Anwendung des Verfahrens gelang die Entwicklung einer alternativen Darstellung des Naturstoffs Rosenoxid aus Citronellol in einer Eintopfreaktion.

1 Einleitung

1.1 Bedeutung von Organohalogenverbindungen

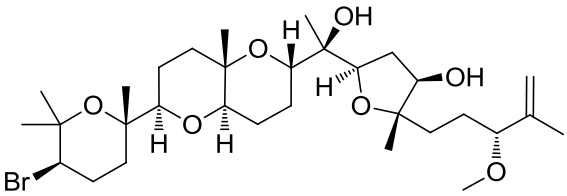
Organohalogenverbindungen zählen zu den wichtigsten Substanzklassen in der organischen Chemie. Obgleich ihr großflächiger Einsatz in den letzten Jahrzehnten aufgrund der Persistenz und der Toxizität einiger Vertreter nicht unumstritten ist, besitzen Organohalogene herausragende Bedeutung als chemische Reagenzien und Intermediate,[1] aber auch als vielfältig einsetzbare aktive Komponenten von Werkstoffen,[2][3] Farbstoffen,[4][5] Flammschutzmitteln,[6][7] Agrochemikalien[4][8] und Pharmazeutika.[9] Vor allem bromierte und chlorierte Derivate stellen dabei den Hauptanteil der bekannten Verbindungen. Wurden diese Stoffe bis vor 50 Jahren noch als fast ausschließlich anthropogenen Ursprungs angesehen, so führten Untersuchungen der chemischen Zusammensetzung verschiedenster Organismen mit modernen Analyse- und Trennverfahren zu der Erkenntnis, dass auch die Natur diese Verbindungen in hohem Maße herstellt und nutzt.[10][11] Bis heute wurden so über 4700 verschiedene, natürlich vorkommende Organohalogenverbindungen identifiziert und jedes Jahr kommen zwischen 100 und 200 Neuentdeckungen hinzu.[12] Da Brom und Chlor aufgrund ihrer hohen Reaktivität in der Natur üblicherweise nicht in elementarer Form vorliegen, müssen die entsprechenden Halogenierungsäquivalente auf Oxidationen von Bromiden und Chloriden zurückgehen. Zusammen mit einer Reihe bekannter Abbaumechanismen ergibt sich damit ein natürlicher Halogenkreislauf zwischen Hydrosphäre, Atmosphäre und Lithosphäre (Schema 1.1).[11][13][14]



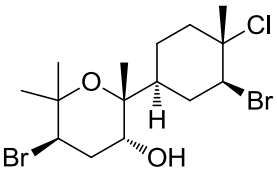
Schema 1.1 Kreislauf natürlicher Halogenidreserven, reaktiver Halogenierungsreagenzien und generierter Organohalogene (X = Cl, Br, I; [X] = HOX, X_2, X_3^-, X·).

Vor dem Hintergrund der großen Halogenidmengen, welche in unseren Ozeanen in gelöster und damit bioverfügbarer Form enthalten sind, ist nachvollziehbar, dass viele der bislang bekannten, halogenierten Verbindungen aus Meereslebewesen stammen. So tragen etwa 15–20 % der in den Jahren 1998 bis 2005 beschriebenen marinen Naturstoffe einen oder mehrere Halogen-Substituenten.[12] Interessanterweise hält sich dabei die Anzahl chlorierter und bromierter Verbindungen in etwa die Waage, obwohl die Chloridkonzentration in den Ozeanen rund 650-mal höher ist als diejenige von Bromiden.[15] Dieser offensichtliche Widerspruch wird jedoch bei Betrachtung des Standardreduktionspotentials (vs. NHE) beider Anionen leicht verständlich, welches für Cl^- mit 1.36 V deutlich höher liegt als für Br^- mit 1.09 V.[16] Dieser Unterschied legt nahe, dass Bromid unter den gegebenen Bedingungen deutlich leichter oxidiert und somit bevorzugt in organische Strukturen eingebaut wird.

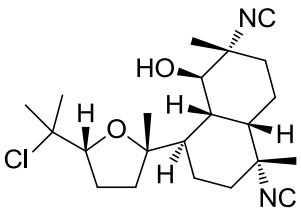
Eine Substanzklasse, welche besonders häufig in halogenierter Form aus marinen Organismen isoliert wird, sind funktionalisierte O-Heterocyclen verschiedener Ringgrößen, wobei hier Strukturmotive mit Tetrahydrofuran- und Tetrahydropyrangerüsten überwiegen.[17] Die zum Teil mehrfach bromierten und/oder chlorierten Verbindungen zeigen häufig ausgeprägte biologische Aktivitäten und sind darum als Wirkstoffe und Leitstrukturen in der pharmakologischen Forschung von großem Interesse. Vor allem der Entwicklung von Therapiemöglichkeiten für die stetig wachsende Anzahl bekannter Krebsarten kommt hier eine herausragende Bedeutung zu. Einige ausgewählte marine Naturstoffe mit halogeniertem O-heterocyclischem Grundgerüst und vielversprechenden cytotoxischen Eigenschaften sind in Abbildung 1.1 dargestellt. Das kürzlich aus *Aplysia dactylomela* isolierte Aplysqualenol A ist strukturell mit Thyrsiferol verwandt und zeigt ebenfalls eine bemerkenswerte cytotoxische Aktivität gegen bestimmte Hirntumor- und Brustkrebszelllinien.[18] Caespitol, welches neben *Laurencia obtusa* auch in mehreren anderen marinen Organismen identifiziert werden konnte, ist wirksam gegen Adenokarzinom- und Epidermoidkarzinomzellen.[19] Als Teil der biologisch sehr aktiven Substanzklasse der Kalihinole, welche aus verschiedenen Meeresschwämmen extrahiert wurden, zeigt Isokalihinol B sowohl antimykotische Eigenschaften als auch eine Aktivität gegen Leukämiezellen.[20] Das gegen Gebärmutterhalskrebszellen wirksame (+)-Aurilol wurde aus dem Seehasen *Dolabella auricularia* isoliert.[21][22]



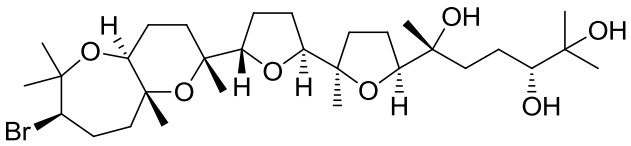
Aplysqualenol A
Aplysia dactylomela



Caespitol
Laurencia obtusa



Isokalihinol B
Acanthella klethra

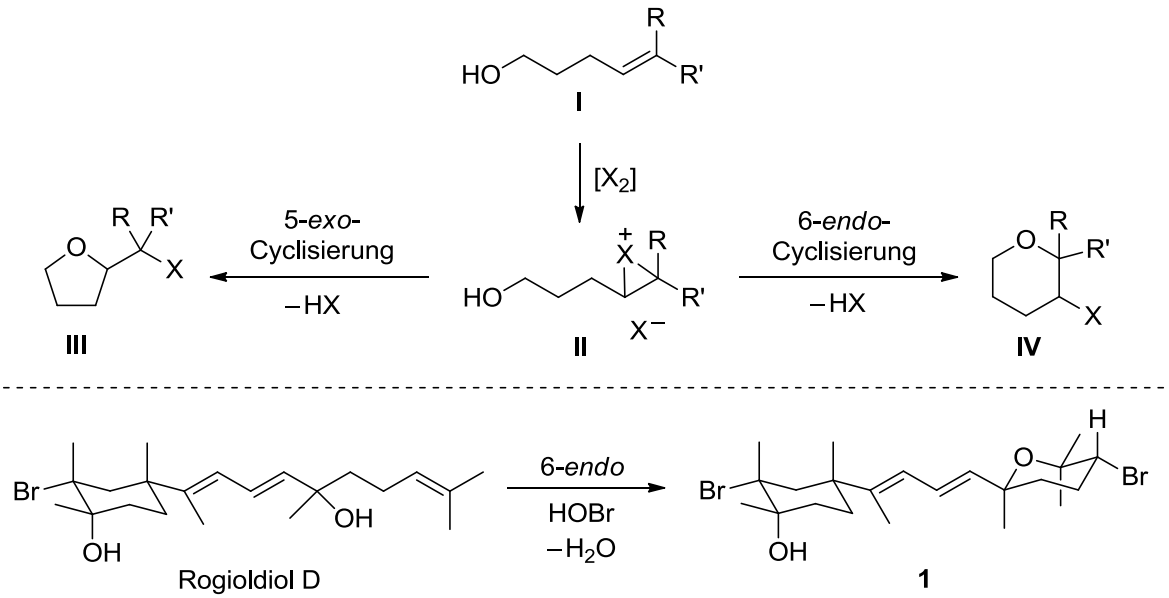


(+)-Aurilol
Dolabella auricularia

Abbildung 1.1 Strukturen ausgewählter mariner Naturstoffe auf Basis β-halogenierter O-Heterocyclen[18–22] mit Fotografien zugehöriger Organismen.[23]

Da die Konzentrationen genannter Naturstoffe in den jeweiligen Organismen äußerst gering und die natürlichen Ressourcen in der Regel begrenzt sind, ist es erforderlich neue Synthesestrategien zu entwickeln, um das pharmakologische Potential dieser Verbindungen und abgeleiteter Derivate weiter erforschen und nutzen zu können. Formal können die gezeigten β-halogenierten Ringetherstrukturen durch Brom- und Chlorcyclisierungsreaktionen eines entsprechenden Alkenolsubstrats **I** nach Durchlaufen einer Haloniumion-Zwischenstufe **II** unter Halogenwasserstoffabspaltung dargestellt werden (Schema 1.2, oben). Ein solcher Mechanismus wird ebenfalls bei der Biosynthese vieler Verbindungen mit β-halogenierter O-heterocyclischer Grundstruktur zugrunde gelegt, wobei die Reihenfolge von Ringbildung und Substituenten- bzw. Seitenkettenmodifikation variabel ist. Belege hierfür liefern umfassende Untersuchungen der Metaboliten entsprechender Organismen, wie beispielsweise die des Seegrases *Laurencia*

microcladia, bei welcher unter anderem der Naturstoff Rogioldiol D zusammen mit dem entsprechenden Tetrahydropyranprodukt **1** einer 6-*endo*-Bromcyclisierung identifiziert werden konnte (Schema 1.2, unten).[24]



Schema 1.2 Mechanismus der Halogencyclisierung zum Aufbau cyclischer β-halogenierter Ether (oben) und postulierte *in vivo*-Derivatisierung von Rogioldiol D in *Laurencia microcladia* (unten).[24] (X = Cl, Br, I; $[X_2]$ = elementares Halogen oder elektrophiles Halogenierungsreagenz)

1.2 Quellen natürlicher Organohalogenverbindungen

Die Suche nach dem Ursprung notwendiger Halogenierungsäquivalente zur Synthese von Organohalogenverbindungen in lebenden Organismen führte zunächst zur Entdeckung der Haloperoxidasen, einer Klasse von Enzymen, welche in der Lage sind Halogenide mit Wasserstoffperoxid zu oxidieren und somit in elektrophile Reagenzien zu überführen.[25][26] Die systematische Benennung dieser Enzyme erfolgt dabei nach demjenigen Halogen mit der höchsten Elektronegativität, dessen Oxidation das Enzym zu katalysieren vermag. So handelt es sich bei der ersten, im Jahre 1959 aus *Caldariomyces fumago* isolierten,[27] Haloperoxidase im Speziellen um eine Chloroperoxidase, welche folglich die Oxidation von Chlorid, Bromid und Iodid zu katalysieren vermag. Dieses Enzym ist an der Biosynthese des chlorierten Antibiotikums Caldariomycin beteiligt und bildet bei Abwesenheit von Chloridionen und unter Zusatz von Bromid auch den analogen Naturstoff in bromierter Form.[28] Haloperoxidasen lassen sich weiterhin nach dem Aufbau ihrer aktiven Zentren in drei Gruppen unterteilen.[29] So trägt

die oben genannte Chloroperoxidase den eisenhaltigen Häm-Komplex als prosthetische Gruppe. Die nicht Häm-abhängigen Haloperoxidasen können wiederum in Vanadat-abhängige Haloperoxidasen (V_XPOs)[30] und in solche ohne metallische Co-Faktoren unterteilt werden. Als erste Vanadat-abhängige Haloperoxidase überhaupt wurde im Jahre 1983 die Bromoperoxidase I aus der Braunalge *Ascophyllum nodosum* [V_{Br}PO(*An*I)] isoliert.[31] Auf Entdeckung und Isolierung des Enzyms folgten zahlreiche Studien, welche unter anderem zur Aufklärung der Enzymstruktur, des Katalysemechanismus sowie der Reaktivität bezüglich unterschiedlicher Reaktionsbedingungen und Substrate führten.[32–36] V_{Br}PO(*An*I) zeichnet sich vor allem durch seine außergewöhnlich hohe Stabilität gegenüber erhöhten Temperaturen und organischen Lösungsmitteln unter turnover-Bedingungen aus. Diese Eigenschaften machen das Enzym interessant für biokatalytische Anwendungen.[37][38]

Die Mitte der 90er Jahre entdeckten Halogenasen katalysieren ebenfalls den Einbau von Halogeniden in organische Moleküle, jedoch unter Verwendung von Disauerstoff als Primäroxidans. Im Gegensatz zu den Haloperoxidasen erfolgt der oxidative Halogenideinbau bei diesen Enzymen überwiegend substratspezifisch und regioselektiv, da die Halogenierung hier über einen Enzym-Substrat-Komplex verläuft, wohingegen bei Haloperoxidasen lediglich die Halogenidoxidation am aktiven Zentrum stattfindet und die eigentliche Halogenierung in einem zweiten Schritt mit räumlichem Abstand zum aktiven Zentrum vollzogen wird.[39] Halogenasen sind demnach leichter spezifischen Halogenierungsreaktionen in Lebewesen zuzuordnen als Haloperoxidasen, für die eine Rolle bei der Biosynthese halogenierter Sekundärmetabolite oftmals nur postuliert werden kann. Des Weiteren konnten in den letzten Jahren weitere Enzyme identifiziert werden, welche in der Lage sind neben ihren Primärfunktionen als Esterasen, Phosphatasen oder Methyltransferasen auch Halogenidoxidationen zu katalysieren.[29][39]

Mit der erstmaligen Entdeckung der Haloperoxidasen wurde zunächst angenommen, dass nur einige, sehr spezialisierte Lebensformen überhaupt in der Lage sind Organohalogen-verbindungen zu generieren. Die rapide steigende Anzahl von Neuentdeckungen halogenierter Moleküle und zugehöriger Enzymkomplexe in unterschiedlichsten Organismen rechtfertigt jedoch mittlerweile die Annahme, dass die Fähigkeit zur oxidativen Aktivierung von Halogeniden in der Natur eher die Regel als eine Ausnahme darstellt.[14] Eine Antwort auf die Frage nach dem evolutionären Nutzen der biologischen Halogenierungsmechanismen liefert möglicherweise ein Blick auf die chemischen Eigenschaften der generierten Verbindungen. Neben ihrer Bedeutung in Zwischenstufen von Biosyntheserouten können Halogen-Substituenten sowohl die physikalischen als auch die physiologischen Wirkungen von organischen Verbindungen entscheidend verändern oder verstärken, weswegen der Einbau von

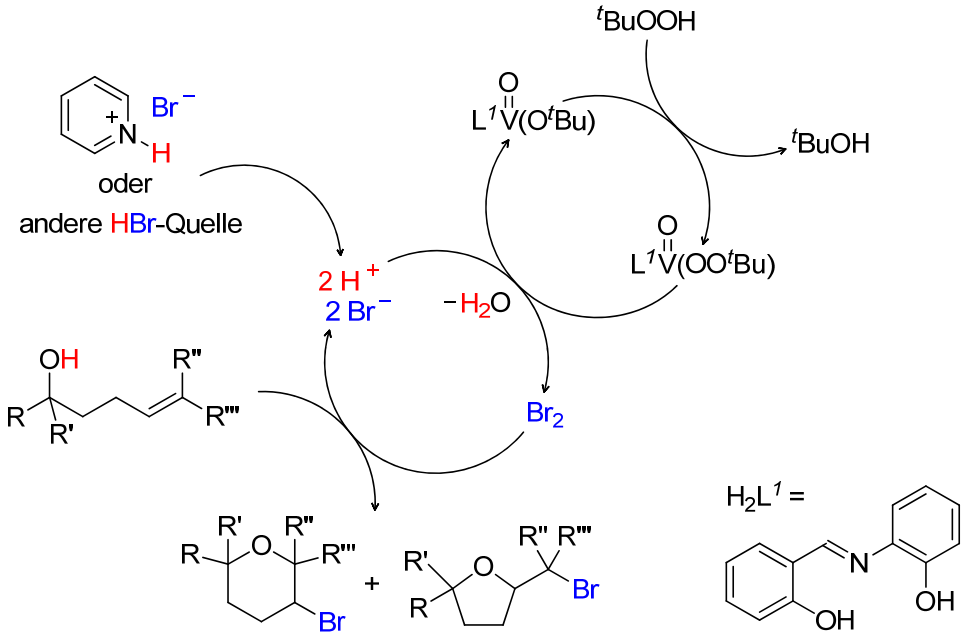
Halogeniden für entsprechende Organismen ein Mittel zur gezielten Modifikation biologischer Aktivitäten ihrer Sekundärmetabolite zu sein scheint.[40] So nutzen sehr viele marine Organismen halogenierte Verbindungen als Abwehrstoffe zur Verteidigung gegen Fressfeinde und Schädlinge oder gegen Bewuchs und Überwucherung durch Mikroorganismen oder konkurrierende Lebensformen.[10][12] Eine weitere vieldiskutierte Funktion von Haloperoxidasen ist der Abbau von oxidativem Stress in Form von Wasserstoffperoxid und die Freisetzung von hypohalogeniger Säure in Stoffwechsel- und Entzündungsprozessen.[41][42]

Neben den anthropogenen und auf natürliche Weise von anderen Organismen produzierten Organohalogenen werden solche Verbindungen in der Umwelt auch auf abiotischem Wege freigesetzt. In Ergänzung zu schon länger bekannten Quellen, wie geothermischen Ereignissen, Vulkanausbrüchen und Waldbränden wurden in jüngster Vergangenheit weitere Mechanismen entdeckt, wonach in feuchten Böden und verrottendem Pflanzenmaterial über Fenton-analoge Reaktionen ebenfalls erhebliche Mengen an Organohalogenverbindungen erzeugt werden.[43]

1.3 Entwicklung funktionaler Haloperoxidase-Modelle

Mit der Aufklärung der Enzymstruktur einiger Haloperoxidasen und zugehöriger Reaktionsmechanismen begann auch die Erforschung vereinfachter Modellsysteme zur synthetischen Anwendung von Halogenidoxidationen im Labormaßstab. Die Oxidation von Halogeniden durch Aktivierung von Wasserstoffperoxid in stark saurer Umgebung ist eine seit langem bekannte Reaktion.[44] Das strukturell einfachste Haloperoxidase-Modell, neben dem Proton, ist das Vanadat-Ion, welches Bromid in wässriger Umgebung mit Hilfe von Wasserstoffperoxid oxidieren kann und in der Bromierung aktivierter Aromaten eingesetzt werden kann.[45] Während der Oxidationsreaktion werden neben Halogenidionen auch Protonen in äquivalenten Mengen verbraucht. Im Gegensatz zu nativen Haloperoxidasen, welche durch den Aufbau ihres aktiven Zentrums in der Lage sind in pH-neutralen Medien zu operieren, ist bei vereinfachten Haloperoxidase-Modellen immer eine Zugabe von Protonenäquivalenten erforderlich. Im Falle des Vanadats führt die damit verbundene pH-Absenkung in Abhängigkeit von der Konzentration auch zur Bildung von Polyoxovanadaten mit der Konsequenz, größere Mengen des Katalysators einsetzen zu müssen. Auch Molybdat- und Wolframat-Ionen zeigen eine ähnliche Reaktivität.[46] Die von Metallaten katalysierten Halogenidoxidationen mit Peroxiden sind zudem aufgrund der schlechten Löslichkeit in organischen Solventien fast ausschließlich für wässrige Systeme untersucht. Für die Halogenierung vieler

Kohlenwasserstoffe sind wässrige Bedingungen jedoch ungeeignet, da die Substrate nicht ausreichend solvatisiert sind oder Halogenierungen in Gegenwart von Wasser zu Nebenprodukten führen, was insbesondere bei Additionsreaktionen an C,C-Doppelbindungen häufig der Fall ist. Zur Lösung der beschriebenen Probleme wurden in der Folge organische Liganden eingesetzt, welche eine Stabilisierung der katalytisch aktiven Vanadium-Einheit, bessere Löslichkeit in organischen Medien und eine mildere Reaktionsführung bewirken sollten. Neben einfachen, kommerziell erhältlichen Verbindungen, beispielsweise $VO(acac)_2$, bewährten sich in der Oxidationskatalyse vor allem Vanadium(V)-Schiffbase-Komplexe mit tridentaten O,N,O-Donor-Liganden (Schema 1.3).[47][48] Im Allgemeinen scheint eine Kombination aus Sauerstoff- und Stickstoff-Donoratomen in Vanadium(V)-Chelatkomplexen sowohl im Hinblick auf Komplexstabilität als auch bezüglich ihrer Fähigkeit zur Aktivierung von Alkylhydroperoxiden von Vorteil zu sein.[49] Mit Hilfe solcher Reaktionssysteme und unter Zugabe von Pyridiniumhydrobromid (py·HBr) als kombinierte Protonen- und Bromidquelle gelang die Kopplung von Bromidoxidation und Bromcyclisierungsreaktion zur Darstellung funktionalisierter cyclischer Ether (Schema 1.3).[50][51]



Schema 1.3 Reaktionsmodell zur Beschreibung Vanadium(V)-Schiffbase-katalysierter Bromidoxidationen mit gekoppelter Bromcyclisierungsreaktion (R = Alkyl, Aryl).[50][51]

Die *in situ*-Halogenerzeugung hat gegenüber der Verwendung von elementarem Chlor bzw. Brom, neben der Verwendung deutlich ungefährlicherer Reagenzien und besserer

Handhabbarkeit, den entscheidenden Vorteil, dass die bei der Ringschlussreaktion anfallenden Halogenwasserstoff-Äquivalente durch erneute Oxidation wieder in den Prozess zurückgeführt werden können und nicht nach Neutralisation mit Basen entsorgt werden müssen. Die katalytische Variante ist damit aus ökologischer und ökonomischer Sicht anderen Halogenierungsreagenzien, wie *N*-Halogensuccinimiden oder Ammoniumtrihalogenid-Salzen, überlegen und gewährleistet zudem eine kontinuierliche Versorgung mit niedrig konzentrierten Halogenierungsäquivalenten, wodurch die Selektivität für Halogencyclisierungen gesteigert wird.

Die vorliegende Studie beschäftigt sich mit der methodischen Weiterentwicklung von Haloperoxidase-Modellsystemen im Hinblick auf die Durchführung von Brom- und Chlorcyclisierungen unter annähernd pH-neutralen Bedingungen sowie mit deren Anwendung in komplexen Naturstoffsynthesen zur Darstellung halogenierter Tetrahydrofurane und Tetrahydropyrane.

1.4 Literatur

[1] Y. Sasson in: *The Chemistry of Functional Groups - Supplement D2*, *The Chemistry of Halides, Pseudo-Halides, and Azides*, Z. Z. Rappoport (Ed.), Wiley, Chinchester, England, **1995**, pp. 535–628.

[2] M. L. Tang, Z. Bao, *Chem. Mater.* **2010**, *23*, 446–455.

[3] P. Metrangolo, G. Resnati, T. Pilati, R. Liantonio, F. Meyer, *J. Polym. Sci., Part A: Polym. Chem.* **2007**, *45*, 1–15.

[4] J. Heitz, *Phytoparasitica* **1997**, *25*, 89–92.

[5] D. C. Neckers, *J. Photochem. Photobiol. A* **1989**, *47*, 1–29.

[6] J. Kaspersma, C. Doumen, S. Munro, A.-M. Prins, *Polym. Degrad. Stab.* **2002**, *77*, 325–331.

[7] J. Green, *J. Fire Sci.* **1996**, *14*, 426–442.

[8] P. Jeschke, *Pest Manag. Sci.* **2010**, *66*, 10–27.

[9] M. Z. Hernandes, S. M. T. Cavalcanti, D. R. M. Moreira, W. F. de Azevedo Junior, A. C. L. Leite, *Curr. Drug Targets* **2010**, *11*, 303–314.

[10] G. W. Gribble, *J. Nat. Prod.* **1992**, *55*, 1353–1395.

[11] G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141–152.

[12] G. W. Gribble in: *Progress in the Chemistry of Organic Natural Products* Vol. 91, *Naturally Occurring Organohalogen Compounds - A Comprehensive Update*, J. Kobayashi (Ed.), Springer, Wien, **2010**, pp. 1–4.

[13] A. A. P. Pszenny, J. Moldanov , W. C. Keene, R. Sander, J. R. Maben, M. Martinez, P. J. Crutzen, D. Perner, R. G. Prinn, *Atmos. Chem. Phys.* **2004**, *4*, 147–168.

[14] G. Öberg, *Appl. Microbiol. Biotechnol.* **2002**, *58*, 565–581.

[15] A. W. Morris, J. P. Riley, *Deep-Sea Res. Oceanogr. Abstr.* **1966**, *13*, 699–705.

[16] D. R. Lide (Ed.), *Handbook of Chemistry and Physics*, 76. Auflage, CRC Press, Boca Raton, Florida, **1995**, p. 8-22.

[17] J. J. Fernandez, M. L. Souto, M. Norte, *Nat. Prod. Rep.* **2000**, *17*, 235–246.

[18] B. Vera, A. D. Rodriguez, E. Aviles, Y. Ishikawa, *Eur. J. Org. Chem.* **2009**, 5327–5336.

[19] C. Lhullier, M. Falkenberg, E. Ioannou, A. Quesada, P. Papazafiri, P. A. Horta, E. P. Schenkel, C. Vagias, V. Roussis, *J. Nat. Prod.* **2010**, *73*, 27–32.

[20] N. Fusetani, K. Yasumuro, H. Kawai, T. Natori, L. Brinen, J. Clardy, *Tetrahedron Lett.* **1990**, *31*, 3599–3602.

[21] Y. Morimoto, Y. Nishikawa, M. Takaishi, *J. Am. Chem. Soc.* **2005**, *127*, 5806–5807.

[22] K. Suenaga, T. Shibata, N. Takada, H. Kigoshi, K. Yamada, *J. Nat. Prod.* **1998**, *61*, 515–518.

[23] Verwendung der Fotografien mit freundlicher Genehmigung von: G. Meinen (*Aplysia dactylomela*, Creative Commons BY-NC-SA 3.0), F.-S. Dijksen (*Laurencia obtusa*, Creative Commons BY-NC-SA 3.0), R. van Soest (*Acanthella klethra*, Creative Commons BY-NC-SA 3.0) und T. Zuberbühler, (*Dollabella auricularia*, Copyright Teresa Zuberbühler).

[24] G. Guella, F. Pietra, *Helv. Chim. Acta* **2000**, *83*, 2946–2952.

[25] M. C. R. Franssen, *Biocatal. Biotransform.* **1994**, *10*, 87–111.

[26] A. Butler, J. V. Walker, *Chem. Rev.* **1993**, *93*, 1937–1944.

[27] P. D. Shaw, L. P. Hager, *J. Am. Chem. Soc.* **1959**, *81*, 6527–6528.

[28] E. L. Patterson, W. W. Andres, L. A. Mitscher, *Appl. Microbiol.* **1967**, *15*, 528–530.

[29] F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova, C. T. Walsh, *Chem. Rev.* **2006**, *106*, 3364–3378.

[30] H. Vilter in: *Metal Ions in Biological Systems* Vol. 31, *Vanadium-Dependent Haloperoxidases*, A. Sigel (Ed.), Dekker, New York, **1995**, pp. 325–362.

[31] H. Vilter, *Phytochemistry* **1984**, *23*, 1387–1390.

[32] H. Vilter, *Meth. Enzymol.* **1994**, *228*, 665–672.

[33] M. Weyand, H. J. Hecht, M. Kiess, M. F. Liaud, H. Vilter, D. Schomburg, *J. Mol. Biol.* **1999**, *293*, 595–611.

[34] J. Hartung, O. Brücher, D. Hach, H. Schulz, H. Vilter, G. Ruick, *Phytochemistry* **2008**, *69*, 2826–2830.

[35] G. Zampella, P. Fantucci, V. L. Pecoraro, L. De Gioia, *Inorg. Chem.* **2006**, *45*, 7133–7143.

[36] A. Butler, J. N. Carter-Franklin, *Nat. Prod. Rep.* **2004**, *21*, 180–188.

[37] J. Hartung, Y. Dumont, M. Greb, D. Hach, F. Kohler, H. Schulz, M. Casny, D. Rehder, H. Vilter, *Pure Appl. Chem.* **2009**, *81*, 1251–1264.

[38] D. Wischang, J. Hartung, *Tetrahedron* **2011**, *67*, 4048–4054.

[39] A. R. K. Ngnigha, K. Muffler, A. Ernyei, K. H. van Pée, R. Ulber, *Chem. Ing. Tech.* **2008**, *80*, 783–794.

[40] K. Naumann, *J. Prakt. Chem.* **1999**, *341*, 417–435.

[41] G. W. Gribble, *Chem. Soc. Rev.* **1999**, *28*, 335–346.

[42] M. J. Davies, *J. Clin. Biochem. Nutr.* **2011**, *48*, 8–19.

[43] F. Keppler, R. Eiden, V. Niedan, J. Pracht, H. F. Scholer, *Nature* **2000**, *403*, 298–301.

[44] O. Maass, P. G. Hiebert, *J. Am. Chem. Soc.* **1924**, *45*, 290–308.

[45] V. Conte, F. Di Furia, S. Moro, *Tetrahedron Lett.* **1994**, *35*, 7429–7432.

[46] G. E. Meister, A. Butler, *Inorg. Chem.* **1994**, *33*, 3269–3275.

[47] H. Mimoun, M. Mignard, P. Brechot, L. Saussine, *J. Am. Chem. Soc.* **1986**, *108*, 3711–3718.

[48] J. Hartung, M. Greb, *J. Organomet. Chem.* **2002**, *661*, 67–84.

[49] D. Rehder, *Coord. Chem. Rev.* **1999**, *182*, 297–322.

[50] M. Greb, J. Hartung, F. Köhler, K. Špehar, R. Kluge, R. Csuk, *Eur. J. Org. Chem.* **2004**, 3799–3812.

[51] T. Gottwald, M. Greb, J. Hartung, *Synlett* **2004**, 65–68.

2 Kenntnisstand und Aufgabenstellung

2.1 Funktionale Bromoperoxidase-Modelle in der organischen Synthese

Die Kopplung von Peroxid-basierter Bromidoxidation und nachfolgender Bromcyclisierungsreaktion wurde erstmals in einem Teilschritt der Totalsynthese des Naturstoffs Aplysiapyranoid A angewendet.[1][2] Die Aplysiapyranoide sind eine Gruppe selten vorkommender, bromierter und chlorierter mariner Naturstoffe mit 2,2,6,6-substituiertem Tetrahydropyrangerüst (Abb. 2.1).[3][4]

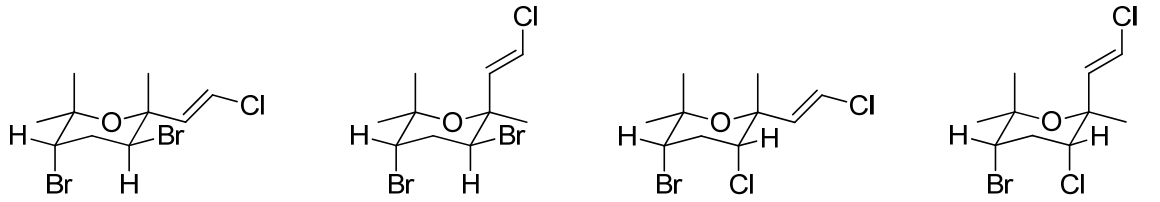
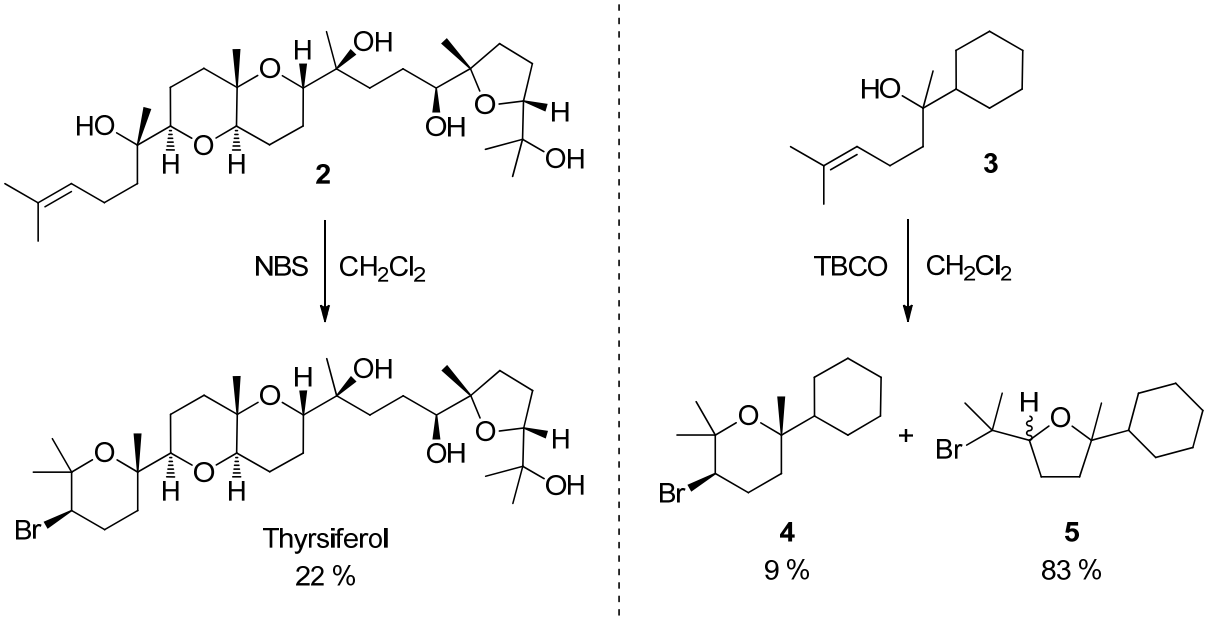


Abbildung 2.1 Strukturen der aus *Aplysia kurodai* isolierten Aplysiapyranoide A–D.[3][4]

Die vier bislang bekannten, als Aplysiapyranoid A–D bezeichneten Vertreter wurden erstmalig 1987 aus dem Verdauungstrakt des Seehasen *Aplysia kurodai* isoliert und zeigten in ersten Testverfahren biologische Aktivitäten gegenüber den Standardkrebszelllinien Vero, MDCK und B_{16} (IC_{50} = 19–96 µg/mL) und humanen Darmkrebszellen (Moser, IC_{50} = 14 µg/mL).[4] Um größere Mengen dieser Substanzen zur Untersuchung von Struktur-Wirkungsbeziehungen zur Verfügung zu stellen, wandten sich synthetisch interessierte Arbeitsgruppen in vergangenen Jahren wiederholt der Aufgabe zu, effektive Syntheserouten für die Aplysiapyranoide zu entwickeln. So befasste sich die Gruppe um Jung als erste mit der Darstellung der Aplysiapyranoide A, C und D.[5–7] Der jeweilige Schlüsselschritt dieser Synthesen bestand in der Bromcyclisierung eines 4-Pentenols, bei dem die in der Tetrahydropyranstruktur enthaltenen Substituenten entweder bereits komplett oder zu großen Teilen eingeführt worden waren. Die Umsetzungen lieferten die gewünschten Naturstoffe in Ausbeuten von 48–58 % zusammen mit je etwa der Hälfte an entsprechenden isomeren Tetrahydrofuranverbindungen. Ein ähnliches Bild zeigt sich bei Darstellungen von Venustatriol- und Thyrsiferol-Derivaten, in denen Cyclisierungen von sterisch aufwendigen Alkenolvorstufen ebenfalls nur zu niedrigen Ausbeuten 2,2,6,6-substituierter Tetrahydropyrane führen, während Fünfringe als Hauptprodukte gebildet werden (Schema 2.1).[8–10]



Schema 2.1 Selektivitäten der Bromcyclisierungsreaktionen zum Aufbau der 2,2,6,6-substituierter Tetrahydropyranstrukturen am Beispiel von Thyrsiferol (links) und einer Modellverbindung **4** (rechts).[9][10]

Der Grund für die beobachteten Selektivitäten scheint somit eine sterische Überladung des entsprechenden Übergangszustands der 6-*endo*-Bromcyclisierung zu sein, auf welche das System durch Ausweichen auf die 5-*exo*-Reaktion antwortet. Im Falle von Aplysiapyranoid A konnte in einer alternativen Synthese von Greb *et al.* die Selektivität einer ähnlichen Bromcyclisierung durch Einfügen eines Phenyl-Substituenten in 5-Position des Alkenols zugunsten des Sechsrings verbessert werden, jedoch blieb die Gesamtausbeute der Reaktion unbefriedigend.[2] Die Bromierungsäquivalente wurden in dieser Synthese durch ein funktionales Modell einer Vanadat-abhängigen Bromoperoxidase *in situ* generiert, wofür sich eine Reagenzmischung aus Pyridiniumhydrobromid und *tert*-Butylhydroperoxid (TBHP), aktiviert durch einen Vanadium(V)-Schiffbase-Komplex, eignete (vgl. Schema 1.3, S. 9). Trotz der Ausnutzung katalytischer Prozesse unter Vermeidung stöchiometrischer Bromierungsreagenzien ist ein genereller Nachteil bei diesem und weiteren Bromoperoxidase-Modellsystemen die unzureichende Nachhaltigkeit der Verfahren, was vor allem durch die Verwendung von Lösungsmitteln wie Acetonitril, Dichlormethan, Chloroform sowie weiterer leichtflüchtiger chlorierter Kohlenwasserstoffe verursacht wird.

Neben mangelnder Nachhaltigkeit und unzureichender Regioselektivität der Bromcyclisierung wurden in dem beschriebenen Verfahren zur *in situ*-Bromidoxidation weitere Schwachstellen identifiziert. So fiel in Kontrollexperimenten eine Untergrundreaktion auf,

welche auch in Abwesenheit des Vanadium(V)-Katalysators zur Freisetzung von Bromierungsäquivalenten führt.[1] Die beobachtete Reaktivität basiert auf Protonen-vermittelter Aktivierung von Peroxiden, welche durch die hohe Acidität des Pyridinium-Wasserstoffs in organischen Medien hervorgerufen wird.[11] Zudem bewirken die sauren Reaktionsbedingungen offenbar weitere Nebenreaktionen, welche die Gesamtausbeute an bromierten O-Heterocyclen schmälern, und scheinen inkompatibel mit einer Reihe funktioneller Gruppen und Schutzgruppen zu sein. Ein ebenfalls kritischer Faktor bei der Reaktionskaskade aus Halogenerzeugung und Halogencyclisierung ist der Wassergehalt der Reaktionsmischung. Zum einen greifen Wassermoleküle in die Ringschlussreaktion ein, indem sie als konkurrierende Nukleophile zur Bildung von Halohydrinen führen und zusätzlich den intramolekularen Angriff des Hydroxylsauerstoffs auf das Halonium-Intermediat durch polare Wechselwirkungen behindern. Zum anderen kann in Gegenwart von Wasser eine Hydrolyse des Vanadium(V)-Komplexes oder des Ligandengerüstes auftreten. Obgleich Kombinationen von *tert*-Butylhydroperoxid und Vanadium-Schiffbase-Komplexen ausgezeichnete Reaktivität und Selektivität zeigen,[12][13] sorgt die inhärente Hydrolyselabilität der Imin-Funktion der Liganden für eine deutliche Einschränkung ihrer Nutzbarkeit in Peroxid-basierten Halogenidoxidationen, bei welchen in jedem Katalyseumlauf zusätzlich ein Wassermolekül erzeugt wird. Durch Liganden mit gesättigten oder aromatischen Stickstoff-Funktionen können prinzipiell Vanadium(V)-Komplexe mit höherer Stabilität in wässrigen Medien erhalten werden.[14] In Oxygenierungsstudien von 4-Pentenolen mit *tert*-Butylhydroperoxid fielen Vanadium(V)-Komplexe mit tridentaten Bishydroxymethyl-Piperidin-Liganden auf, welche sich durch eine mit Schiffbase-Systemen vergleichbare Reaktivität bei hoher Hydrolysestabilität auszeichneten.[15]

2.2 Funktionale Chloroperoxidase-Modellsysteme

Im Gegensatz zur Vielzahl von Untersuchungen über Bromoperoxidase-Modelle sind Chloroperoxidase-Modelle in der Literatur kaum beschrieben. Obwohl dieser Aspekt immer wieder in das Blickfeld der Chemiker rückte, konnte bis heute kein ausgereiftes Verfahren präsentiert werden, welches in der Lage ist, eine Lewis-Säure-aktivierte Chloridoxidation mit Peroxiden durch Verknüpfung mit der Chlorierung organischer Substrate synthetisch nutzbar zu machen. Dies mag zum einen mit dem deutlich höheren Standardreduktionspotential von Chlor gegenüber Brom und zum anderen mit der hohen Reaktivität der erzeugten Chlorierungsreagenzien zusammenhängen. Wie bei der Oxidation von Bromid erübrigt sich auch in Chloridoxidationen bei ausreichend niedrigen pH-Werten, aufgrund Säure-katalysierter Peroxidaktivierung, die Notwendigkeit eines zusätzlichen Katalysators.[16] So kann die

Umsetzung von aktivierten Aromaten mit wässriger Wasserstoffperoxidlösung und einem Überschuss an konzentrierter Salzsäure zwar zur Darstellung von chlorierten Derivaten genutzt werden, jedoch sind die drastischen Reaktionsbedingungen nur für chemisch robuste Substrate verträglich.[17–19] Die wenigen Versuche einer synthetischen Anwendung Übergangsmetall-katalysierter Chloridoxidationen decken ebenfalls lediglich die Umsetzung mit aktivierten Aromaten ab, bei welchen die Reaktionskanäle überschaubar und die Reaktivität leicht beherrschbar bleibt.[20–24] Verfahren zur *in situ*-Oxidation von Chlorid mit anschließender Chlorierung von Alken- oder Alkenoldoppelbindungen unter milder und wasserfreier Reaktionsführung sind folglich kaum vorhanden. Das bedeutet, dass für die Umsetzung solcher Substrate ausschließlich spezielle Chlorierungsreagenzien, wie *N*-Chlorsuccinimid, Tetraethylammoniumtrichlorid und Sulfurylchlorid, verwendet werden oder aber auf elementares Chlor aus Druckgasflaschen zurückgegriffen werden muss. Analog zu den ausgearbeiteten Bromoperoxidase-Modellreaktionen, welche die Synthese β-bromierter Naturstoff-analoger Tetrahydrofuran- und Tetrahydropyranstrukturen ermöglichen, wäre die Entwicklung eines ergänzenden Verfahrens zur Darstellung entsprechender Chlorverbindungen ein lohnenswertes Ziel.

Aus den Vorbemerkungen ergeben sich für die vorliegende Arbeit folgende Aufgabenstellungen:

- Entwicklung effektiver Vanadium(V)-basierter Bromoperoxidase-Modellsysteme für die Synthese bromierter cyclischer Ether aus substituierten 4-Pentenolen unter möglichst milden pH-neutralen Reaktionsbedingungen.
- Herausarbeitung von Parametern zur Steigerung von Ausbeuten und Selektivitäten des 6-*endo*-Ringschlusses in Synthesen bromierter 2,2,6,6-substituierter Tetrahydropyrane am Beispiel der Totalsynthese von Aplysiapyranoid A und verwandter Strukturen.
- Entwicklung eines ersten funktionalen Chloroperoxidase-Modellsystems zur Durchführung von Chlorcyclisierungen substituierter 4-Pentenole.

2.3 Literatur

[1] M. Greb, *Dissertation*, Universität Würzburg, **2004**.

[2] J. Hartung, M. Greb, *Tetrahedron Lett.* **2003**, *44*, 6091–6093.

[3] Y. Inouye, H. Uchida, T. Kusumi, H. Kakisawa, *Chem. Commun.* **1987**, 346–347.

[4] T. Kusumi, H. Uchida, Y. Inouye, M. Ishitsuka, H. Yamamoto, H. Kakisawa, *J. Org. Chem.* **1987**, *52*, 4597–4600.

[5] M. E. Jung, D. C. D'Amico, W. Lew, *Tetrahedron Lett.* **1993**, *34*, 923–926.

[6] M. E. Jung, B. T. Fahr, D. C. D'Amico, *J. Org. Chem.* **1998**, *63*, 2982–2987.

[7] M. E. Jung, W. Lew, *J. Org. Chem.* **1991**, *56*, 1347–1349.

[8] E. J. Corey, D. C. Ha, *Tetrahedron Lett.* **1988**, *29*, 3171–3174.

[9] C. A. Broka, Y. T. Lin, *J. Org. Chem.* **1988**, *53*, 5876–5885.

[10] M. Hashimoto, T. Kan, K. Nozaki, M. Yanagiya, H. Shirahama, T. Matsumoto, *J. Org. Chem.* **1990**, *55*, 5088–5107.

[11] H.-S. Kim, T. D. Chung, H. Kim, *J. Electroanal. Chem.* **2001**, *498*, 209–215.

[12] H. Mimoun, M. Mignard, P. Brechot, L. Saussine, *J. Am. Chem. Soc.* **1986**, *108*, 3711–3718.

[13] M. Greb, J. Hartung, F. Köhler, K. Špehar, R. Kluge, R. Csuk, *Eur. J. Org. Chem.* **2004**, *2004*, 3799–3812.

[14] G. J. Colpas, B. J. Hamstra, J. W. Kampf, V. L. Pecoraro, *J. Am. Chem. Soc.* **1996**, *118*, 3469–3478.

[15] G. Stapf, *Dissertation*, Technische Universität Kaiserslautern, **2010**.

[16] O. Maass, P. G. Hiebert, *J. Am. Chem. Soc.* **1924**, *45*, 290–308.

[17] N. B. Barhate, A. S. Gajare, R. D. Wakharkar, A. V. Bedekar, *Tetrahedron* **1999**, *55*, 11127–11142.

[18] S. Mukhopadhyay, K. H. Chandnani, S. B. Chandalia, *Org. Process Res. Dev.* **1999**, *3*, 196–200.

[19] M. K. Seikel in: *Organic Syntheses*, Collect. Vol. III, Wiley, London, **1963**, p. 262.

[20] M. Mba, M. Pontini, S. Lovat, C. Zonta, G. Bernardinelli, P. E. Kundig, G. Licini, *Inorg. Chem.* **2008**, *47*, 8616–8618.

[21] F. Romano, A. Linden, M. Mba, C. Zonta, G. Licini, *Adv. Synth. Catal.* **2010**, *352*, 2937–2942.

[22] L. J. Yang, Z. Lu, S. S. Stahl, *Chem. Commun.* **2009**, 6460–6462.

[23] K. Yonehara, K. Kamata, K. Yamaguchi, N. Mizuno, *Chem.Commun.* **2011**, *47*, 1692–1694.

[24] T. S. Fedorova, O. L. Kaliya, E. A. Luk'yanets, V. M. Negrimovskii, *Russ. J. Gen. Chem.* **2008**, *78*, 1611–1613.

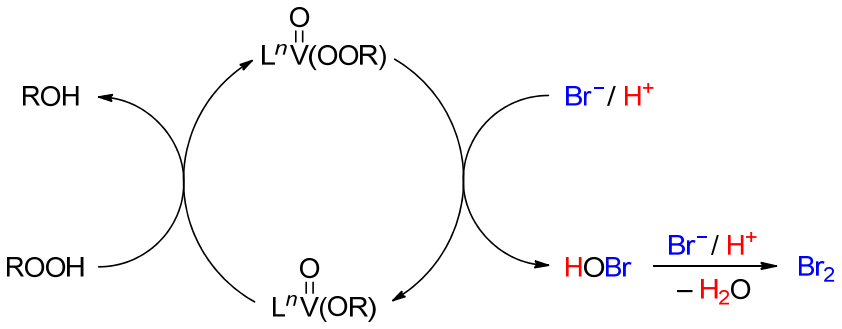
3 Vanadium(V)-katalysierte oxidative Bromierung Säure-labiler Alkenole und Alkene in Alkylcarbonaten

3.1 Zusammenfassung

Die Reagenzkombination aus β-Bromcarbonsäuren, katalytischen Mengen Natriumbromid und *tert*-Butylhydroperoxid, aktiviert durch einen Oxovanadium(V)-Komplex auf Basis eines tridentaten Piperidin-Liganden, ist ein wirkungsvolles System für Bromidoxidationen in Alkylcarbonaten unter annähernd pH-neutralen Bedingungen in Anlehnung an die Chemie Vanadat(V)-abhängiger Bromoperoxidasen. Die eigens dafür konzipierten β-Bromcarbonsäuren dienen als schwach saure Protonen- und Bromidquelle, welche unter Zugabe katalytischer Bromidmengen bei 30 °C in Kohlendioxid, ein Alken sowie in ein formales Äquivalent Bromwasserstoffsäure zerfallen. Die entwickelte Prozedur eignet sich zur Bromierung von C,C-Doppelbindungen und zeigt hohe Kompatibilität mit säurelabilen funktionellen Gruppen. Die Reaktionskaskade aus β-Bromcarbonsäure-Zerfall, Vanadium(V)-katalysierter Bromidoxidation und anschließender Bromierungsreaktion bewährte sich vor allem für den effektiven Aufbau mehrfach funktionalisierter Bromcyclisierungsprodukte aus δ,ε-ungesättigten Alkoholen in Ausbeuten bis zu 82 %. Das Verfahren besitzt dabei das Potential die Darstellung wertvoller und seltener mariner Naturstoffe auf eine sehr viel nachhaltigere Basis zu stellen, als dies bisher möglich war.

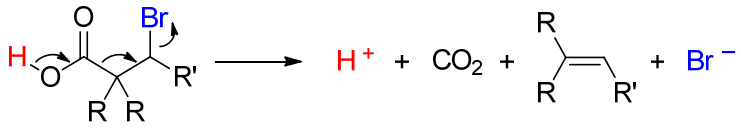
3.2 Wissenschaftlicher Hintergrund, Zielsetzung und Strategie

Vanadat-abhängige Bromoperoxidasen sowie funktionale Bromoperoxidase-Modelle brauchen neben Peroxid- und Bromidäquivalenten auch Protonen, um Bromidoxidationen durchführen zu können.[1–3] Dabei wird pro Katalyseumlauf formal je ein Proton benötigt um hypobromige Säure (HOBr) zu generieren und ein weiteres zur Erzeugung eines Brommoleküls (Schema 3.1).[4]



Schema 3.1 Modell zur Verwendung Vanadat-abhängiger Bromoperoxidasen oder funktionaler Modelle als Katalysatoren in der Bromidoxidation (R = H, *tert*-Butyl, L^n = organischer Ligand oder Enzym-Koordinationssphäre).[4]

Während marine Bromoperoxidasen in der Lage sind Oxidationsreaktionen auch unter den schwach alkalischen Bedingungen des Meerwassers zu katalysieren, konnten Bromoperoxidase-Modellreaktionen in organischen Solventien bisher nur unter Zusatz stöchiometrischer Mengen meist starker Brønsted-Säuren durchgeführt werden.[5] In Verbindung mit Vanadium(V)-Schiffbase-Katalysatoren wurde in früheren Arbeiten Pyridiniumhydrobromid als kombinierte Quelle für Bromidionen und Protonen eingesetzt.[6] Das Reagenz ist günstig verfügbar, in organischen Solventien gut löslich und besitzt mit einem pK_a-Wert von 3.4 (in DMSO)[7] ausreichende Acidität für den Einsatz in Bromidoxidationen. Das Verfahren eignet sich zur Umsetzung substituierter 4-Pentenole in Bromcyclisierungsreaktionen für die Darstellung β-bromierter, naturstoffanaloger Tetrahydrofuran- und Tetrahydropyranstrukturen.[6][8] In Kontrollexperimenten zu diesem Modellsystem konnte jedoch eine Protonen-katalysierte Bromidoxidation als Untergrundreaktion festgestellt werden, welche ohne Kontrolle durch Vanadium(V)-Komplexe für etwa ein Drittel des Gesamtumsatzes verantwortlich war (bei 25 °C).[9] Zur Unterdrückung dieser und weiterer Säure-induzierter Nebenreaktionen bestand somit die Notwendigkeit, das verwendete Pyridiniumhydrobromid durch ein Reagenz zu ersetzen, welches der Bromidoxidation schon im schwach sauren Bereich ausreichend Protonen zur Verfügung stellt. Eine Literaturrecherche zur Verfügbarkeit von HBr-Äquivalenten aus weniger aciden Molekülen als Pyridiniumhydrobromid führte zu einer, erstmals von Fittig *et al.* gegen Ende des 19. Jahrhunderts beschriebenen, Zerfallsreaktion von β-Bromcarbonsäuren, welche unter schwach basischen Bedingungen oder geringer Energiezufuhr neben Kohlendioxid und einem Alken je ein formales Äquivalent HBr liefert (Schema 3.2).[10]



Schema 3.2 Zerfall von β-Bromcarbonsäurederivaten in Kohlendioxid, ein Alken und ein formales Äquivalent Bromwasserstoffsäure (R / R‘ = Alkyl, Aryl).

Die Zerfallsrate dieser β-Bromcarbonsäuren sollte sich unter anderem als Funktion der Bindungsstärke für die Heterolyse von O,H- und C,Br-Bindungen, der Aktivierungsenergie und der Stabilität des resultierenden Alkens beschreiben lassen und somit abhängig von den Substituenten in α- und β-Position sein. Die Hauptaufgabe in der vorliegenden Arbeit bestand darin, zu untersuchen, inwieweit sich Vertreter dieser Verbindungsklasse dazu eignen als schwach saure Puffer zur Versorgung einer Bromoperoxidase-Modellreaktion mit Protonen- und Bromidäquivalenten zu fungieren und ob die Geschwindigkeit und Selektivitäten nachgeschalteter Bromierungsreaktionen synthetisch nutzbar sind. Hierbei sollte der Fokus auf die Bromierung von Alkenen und auf Bromcyclisierungen von 4-Pentenolen gelegt werden. Da als weitere Schwachstelle in dem bislang verwendeten Verfahren die fehlende Hydrolysestabilität des eingesetzten Vanadium(V)-Schiffbase-Katalysators identifiziert werden konnte, war der Einsatz alternativer Vanadium(V)-Verbindungen mit verbesserter Integrität unter Katalysebedingungen ein weiterer Aspekt zur Steigerung der Effizienz des Bromoperoxidase-Modellsystems.

Unter Berücksichtigung der Vorarbeiten zur Bromidoxidation stellten sich für die Entwicklung einer verbesserten Vanadium-katalysierten Methode zur oxidativen Bromierung unter pH-neutralen Bedingungen folgende Aufgaben:

- Identifizierung und Darstellung geeigneter β-Brompropionsäurederivate und Untersuchung ihrer Zerfallsreaktionen zur Versorgung oxidativer Bromierungsreaktionen mit Protonen und Bromidäquivalenten.
- Optimierung der Vanadium(V)-katalysierten oxidativen Bromierung unter Variation von Lösungsmitteln, Katalysatoren und weiteren relevanten Reaktionsparametern.
- Übertragung des neuen Reaktionsprotokolls auf Alkene, säurelabile Substrate und auf Bromcyclisierungen substituierter 4-Pentenole.

3.3 Ergebnisse und Diskussion

3.3.1 Synthese und Eigenschaften von β-Bromcarbonsäuren

Neben kommerziell erhältlicher 3-Brompropionsäure (**6a**) wurden für die Studie zwei Derivate synthetisiert, welche eine gesteigerte Triebkraft zur HBr-Freisetzung aufweisen sollten (Abb. 3.1). So besitzt Brompropionsäure **6b** zwei Methylgruppen in 2-Position, um eine mögliche β-Eliminierung zugunsten der erwünschten δ-Eliminierung zu unterdrücken und zusätzlich die Stabilität des resultierenden Alkens zu erhöhen.[11] Das Zimtsäure-Derivat **6c** wurde ausgewählt, um den positiven mesomeren Effekt der Phenylgruppe auszunutzen, der die geplante Zerfallsreaktion ebenfalls begünstigen sollte.[12] Weiterhin erlaubte die Bildung von Styrol aus **6c** eine kinetische Verfolgung der HBr-Eliminierung mittels gaschromatographischer Analyse der Reaktionsmischung.

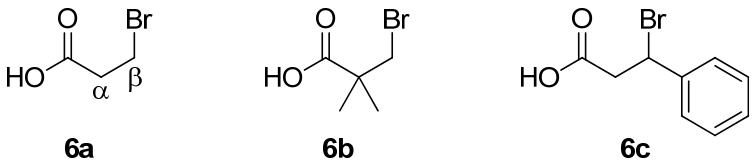


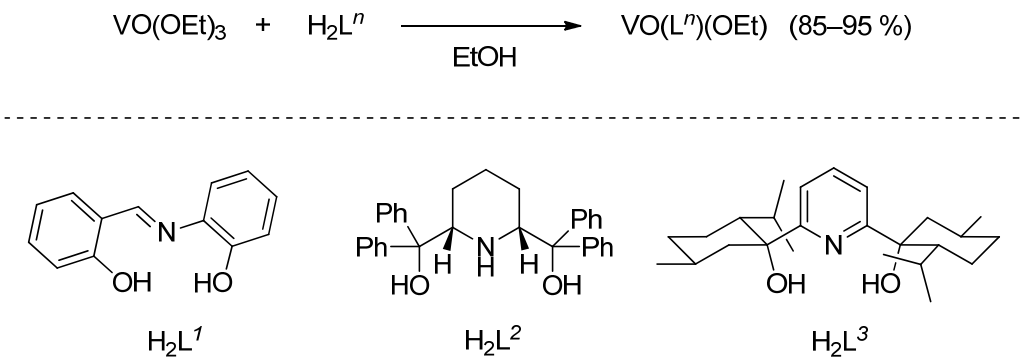
Abbildung 3.1 Strukturformeln untersuchter β-Bromcarbonsäuren (**6a**–**c**).

Erste orientierende Versuche zeigten, dass die Fragmentierungsreaktion der Brompropionsäurederivate **6a**–**c** in Dimethylcarbonat (DMC) bereits bei 30 °C unter Zusatz katalytischer Mengen an Bromid abläuft und die dabei freigesetzten HBr-Äquivalente sich in Gegenwart von *tert*-Butylhydroperoxid und einem Vanadium(V)-Komplex zur oxidativen Bromierung eines Alkensubstrates nutzen lassen. Kinetische Verfolgung der Zerfallsreaktionen unter Katalysebedingungen führten zu relativen Geschwindigkeitsraten, welche entlang der Reihe **6a** (k^{rel} = 1.0) < **6b** (k^{rel} = 1.3) < **6c** (k^{rel} = 1.9) anwachsen.

3.3.2 Methodenentwicklung und Bromierung von Alkenen

Zur Entwicklung und Evaluierung der neuen Bromierungsmethodik diente 4-*tert*-Butylcyclohexen (**7a**) als Reportersubstrat. Das Alken **7a** sowie das daraus resultierende Dibromid **8a** eignen sich für die Ausbeutenbestimmung sowohl in präparativem als auch in analytischem Maßstab. Zudem erlaubt die beobachtete relative Konfiguration des gebildeten Dibromids **8a** Rückschlüsse auf die Natur des vorliegenden Bromierungsreagenzes. Die Reaktion mit 4-*tert*-Butylcyclohexen (**7a**) war am effektivsten unter Verwendung der Dimethyl-

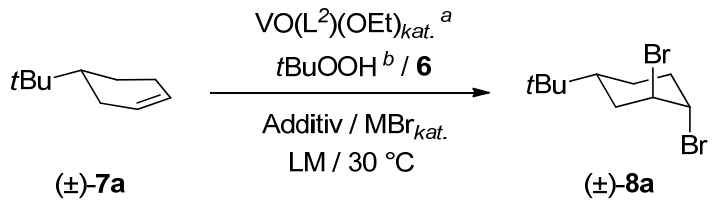
substituierten β-Bromcarbonsäure **6b** in den Lösungsmitteln Propylencarbonat (PC), Dimethylcarbonat und Ethylacetat (Tabelle 3.1, Einträge 1, 3 und 4). Die Abnahme von Geschwindigkeit und Selektivität im Verlauf der Umsetzung und das Auftreten weiterer Oxidationsprodukte deuteten auf radikalische Nebenreaktionen hin, welche durch die Zugabe von Radikalfängern unterdrückt werden sollten. Dabei zeigte sich, dass bei Zugabe unterstöchiometrischer Mengen an Cyclohexa-1,4-dien (CHD) die Ausbeute an Dibromid **8a** um 10 % steigt und sich die Reaktionszeit deutlich verkürzt. Der genaue Grund für diesen positiven Einfluss konnte jedoch im Rahmen dieser Arbeit nicht mehr geklärt werden. Neben dem etablierten Vanadium-Schiffbase-System VO(L^1)(OEt)[13] und den kommerziell erhältlichen Verbindungen $VO(acac)_2$ und $VO(SO_4)\cdot H_2O$ wurden außerdem zwei weitere Vanadium(V)-Komplexe VO(L^2)(OEt)[14] und VO(L^3)(OEt)[15] mit O,N,O-Donormotiv synthetisiert und untersucht (Schema 3.3).



Schema 3.3 Darstellung der Oxovanadium(V)-Komplexe VO($L^{1–3}$)(OEt) durch Metathesereaktion von $VO(OEt)_3$ mit tridentaten Auxiliaren $H_2L^{1–3}$ mit O,N,O-Donormotiv.[13–15]

Eine Variation aller genannten Reaktionsparameter ergab, dass die effektivste Prozedur zur Umsetzung von 4-*tert*-Butylcyclohexen (**7a**) aus Reaktion mit 3-Brom-2,2-dimethylpropionsäure (**6b**), *tert*-Butylhydroperoxid und Vanadium-Katalysator VO(L^2)(OEt) (1 mol%) in Propylencarbonat unter Zusatz katalytischer Mengen an Bromid und Cyclohexa-1,4-dien besteht und 1,2-Dibrom-4-*tert*-butylcyclohexan (**8a**) in einer präparativen Ausbeute von 84 % liefert (Tabelle 3.1, Eintrag 1).

Tabelle 3.1 Vanadium(V)-katalysierte oxidative Bromierung von 4-*tert*-Butylcyclohexen (**7a**) in Gegenwart von 3-Brompropionsäuren **6a**–**c** und *tert*-Butylhydroperoxid.



Eintrag	**6**	LM [c]	Additiv [d]	MBr [e]	**8a** / %
1	**6b**	PC	CHD	NBu_4Br	84
2	**6a**	PC	CHD	NaBr	32
3	**6b**	DMC	CHD	NBu_4Br	74
4	**6b**	EtOAc	CHD	NBu_4Br	83
5	**6b**	PC	CHD	NaBr	82
6	**6b**	PC	–	NaBr	72
7	**6c**	PC	–	NaBr	79

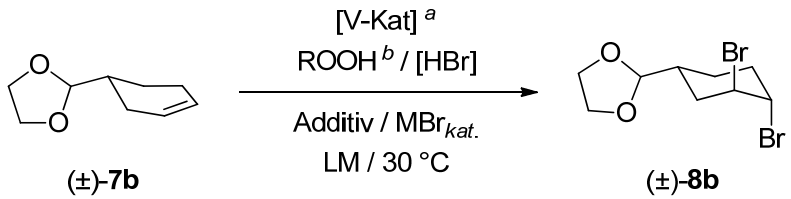
[a] 1 mol%. [b] Wasserfreie 3 M Lsg. in Toluol. [c] PC = Propylencarbonat; DMC = Dimethylcarbonat. [d] CHD = Cyclohexa-1,4-dien; 40 mol%. [e] 10 mol%.

Das erzielte Ergebnis liegt damit im Bereich eigener Kontrollexperimente in Lösungen von Dichlormethan unter Einsatz von molekularem Brom (96 %) oder *N*-Bromsuccinimid (NBS) in Verbindung mit Tetrabutylammoniumbromid (92 %). Der pH-Wert von hydrolysierten Proben des Reaktionsgemisches wurde mittels Universal-Indikatorpapier überprüft und bewegte sich im Bereich von 5–6. Kontrollreaktionen ohne Zugabe einer Vanadium-Verbindung führten zu keiner Bildung von Dibromid **8a** nach einem Zeitraum von 48 h. Mit Ausnahme von $VO(acac)_2$, welches mit einer Ausbeute von 76 % eine günstige, kommerziell erhältliche Alternative zum Oxovanadium(V)-Piperidin-Komplex $VO(L^2)(OEt)$ darstellt, zeigten die Reaktionen mit den übrigen Vanadium-Katalysatoren $VO(L^1)(OEt)$, $VO(L^3)(OEt)$ und $VO(SO_4)\cdot H_2O$ nur Ausbeuten zwischen 42 und 52 %. Die Verwendung des nachhaltigen Lösungsmittels Propylencarbonat lieferte die besten Ausbeuten der Studie und vereinfachte die Isolierung der meist unpolaren, bromierten Produkte. Diese lassen sich dabei durch einfache Extraktion mit Cyclohexan in relativ reiner Form gewinnen, wobei polare Reagenzien und Nebenprodukte in der Propylencarbonat-Phase zurückgehalten werden. Trotz der geringen Katalysatormenge von 1 mol% war die rückständige Propylencarbonat-Lösung noch katalytisch aktiv und konnte nach erneuter Zugabe von β-Bromcarbonsäure **6b**, TBHP und Alkensubstrat **7a** in einer weiteren

Bromierungsreaktion verwendet werden, nach welcher erneut 69 % des gewünschten Produkts **8a** isoliert werden konnten. Zusätzliche Untersuchungen zu der katalytischen Restaktivität und Optimierung der Zweitreaktion in zurückgewonnenen Propylencarbonatmischungen wurden im Rahmen dieser Arbeit aus Zeitgründen nicht durchgeführt.

Die Reaktion mit dem säurelabilen Substrat 3-Dioxolanylcyclohexen (**7b**) lieferte das entsprechende Dibromid **8b** in 80 % Ausbeute (Tabelle 3.2, Eintrag 1). Die Methode mit Pyridiniumhydrobromid lieferte das gleiche Produkt in einer geringeren Ausbeute von 64 %, während in der Kontrollreaktion mit 2 Äquivalenten wässriger HBr und H_2O_2 nur 20 % des Dibromids **8b** isoliert werden konnten (Tabelle 3.2, Einträge 3 und 4).

Tabelle 3.2 Oxidative Bromierung des säurelabilen Substrats 3-Dioxolanylcyclohexen (**7b**).



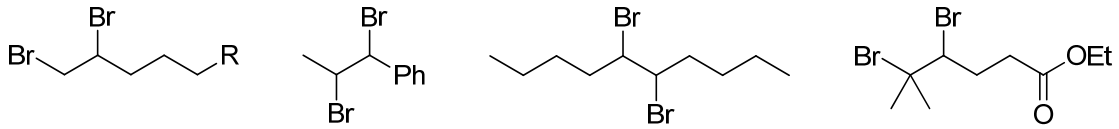
(±)-**7b** (±)-**8b**

Eintrag	[V-Kat] [a]	[HBr]	R [b]	LM [c]	Additiv [d]	MBr [e]	**8b** / %
1	VO(L^2)(OEt)	**6b**	*t*Bu	EtOAc	CHD	NBu_4Br	80
2	VO(L^2)(OEt)	**6b**	*t*Bu	PC	CHD	NaBr	77
3	VO(L^1)(OEt)	py·HBr	*t*Bu	MeCN	–	–	64
4	–	HBr [f]	H	PC	–	–	20

[a] 1 mol%. [b] Wasserfreie 3 M Lsg. in Toluol (R = *t*Bu) oder 30% (*w*/*w*) wässrige Lsg. (R = H). [c] PC = Propylencarbonat. [d] CHD = Cyclohexa-1,4-dien; 40 mol%. [e] 10 mol%. [f] 48% (*w*/*w*) wässrige Lsg.

Diese Ergebnisse veranschaulichen, dass der Einsatz von 3-Bromcarbonsäurederivaten **6a–c** als schwach saure HBr-Donoren zu einer deutlichen Reduktion der Acidität der Reaktionslösung führt, welche sich durch das Ausbleiben von Protonen-vermittelter Bromidoxidation sowie weiterer Säure-induzierter Nebenreaktionen positiv bemerkbar macht.

Bromierungsansätze mit weiteren, terminalen, di- und trisubstituierten Alkensubstraten lieferten die entsprechenden Dibromide **8c–g** in Ausbeuten von 59–73 % als diastereomerenreine Produkte (Abb. 3.2).



8c: 71 % [a] (R = *n*Pr) **8e**: 59 % [a] **8f**: 73 % [a] **8g**: 69 % [b]
8d: 63 % [a] (R = Ph)

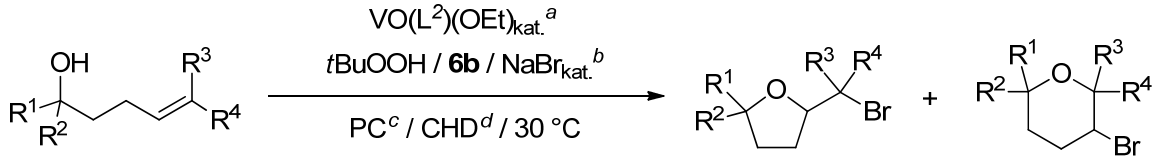
Abbildung 3.2 Produkte der oxidativen Bromierung terminaler, di- und trisubstituierter Alkene in Gegenwart von TBHP, **6b**, VO(L^2)(OEt) (1 mol%), NaBr (10 mol%) und CHD (40 mol%) in PC [a] oder EtOAc [b] bei 30 °C.

Bemerkenswerterweise bewirkt hier der Einsatz von Cyclohexa-1,4-dien nur eine Verbesserung der Bromierung interner Alkene, wohingegen der Effekt bei Bromierungen terminaler Doppelbindungen bislang nicht beobachtet werden konnte. Untersuchungen zur Klärung der Ursache dieses interessanten Verhaltens konnten ebenfalls im Rahmen dieser Arbeit aus Zeitgründen nicht mehr durchgeführt werden.

3.3.3 Bromcyclisierungsreaktionen substituierter 4-Pentenole

Der zuvor formulierte Hauptanwendungszweck der neu entwickelten, pH-neutralen Bromierungsmethodik war die Synthese bromierter Tetrahydrofurane und Tetrahydropyrane mit Bezug zur Naturstoffchemie. Zur Bewertung der Effizienz der Prozedur in diesem Zusammenhang wurden die unterschiedlich substituierten 4-Pentenole **9a–d** den zuvor optimierten Bedingungen der oxidativen Bromierung unterworfen (Tabelle 3.3).

Tabelle 3.3 Ergebnisse der Bromcyclisierung substituierter 4-Pentenol-Substrate **9a–d**.



9 **10** **11**

Eintrag	**9**	R^1	R^2	R^3	R^4	**10** / % (*cis*:*trans*)	**11** / % (*cis*:*trans*)
1	**9a**	H	H	H	Ph	< 5 [e]	71 (<2:98)
2	**9b**	Ph	H	H	CH_3	48 (34:66)	21 (<2:98)
3	**9c**	CH_3	C_2H_3	CH_3	CH_3	37 (62:38)	42 (64:36)
4	**9d**	Ph	H	CH_3	CH_3	14 (41:59)	68 (4:96)

[a] 1 mol%. [b] 10 mol%. [c] PC = Propylencarbonat. [d] CHD = Cyclohexa-1,4-dien; 40 mol%. [e] Spuren.

Die Umsetzungen der Alkenole **9a–d** lieferten, nach chromatographischer Aufreinigung, Bromcyclisierungsprodukte in Gesamtausbeuten von 69–82 % (Tabelle 3.3). Das Ergebnis der Umsetzung von Substrat **9a** erlaubt eine weitergehende Interpretation des Reaktionsverlaufs der Bromcyclisierung. Die Bildung des 2,3-*trans*-konfigurierten Tetrahydropyrans **11a** korrespondiert mit einem zweistufigen Mechanismus unter intermediärer Bildung eines Bromoniumions mit anschließender, regioselektiver und stereospezifischer Öffnung durch Rückseitenangriff des Hydroxylsauerstoffs in der ladungsstabilisierten benzylischen Position. Kontrollexperimente zur Bromcyclisierung unter Verwendung einer wässrigen Lösung von H_2O_2 und HBr (Alkenol **9a**) oder von NBS in Dichlormethan (Alkenol **9c**) lieferten die entsprechenden O-Heterocyclen nur in Gesamtausbeuten von 47 % und 60 %. Zur Überprüfung der Anwendbarkeit der entwickelten Prozedur in größerem Maßstab wurde am Beispiel der Umsetzung von Linalool **9c** der Reaktionsansatz um den Faktor 10 vergrößert. Die Bromierung lieferte die bromierten cyclischen Ether **10c** und **11c** nach Extraktion mit Cyclohexan in befriedigender Reinheit und einer kombinierten Ausbeute von 63 %, wobei das Rohprodukt optional durch Destillation weiter aufgereinigt werden konnte.

3.4 Ausblick

Die vorliegende Studie ist ein erster Schritt zur Anwendung von Bromoperoxidase-Modellreaktionen in organischen Lösungsmitteln unter annähernd neutralen Bedingungen. Da das langwährende Problem zu saurer Reaktionsbedingungen in oxidativen Bromierungsreaktionen durch das entwickelte Konzept mit β-Brompropionsäuren prinzipiell gelöst wurde, steht einer breiteren Anwendung in Synthesen mit säurelabilen Intermediaten und Produkten nichts mehr im Wege. Ergänzende Arbeiten zu diesem Thema könnten Experimente mit alternativen β-Bromcarbonsäurederivaten beinhalten oder auf die Entwicklung ähnlicher Systeme zur HBr-Freisetzung unter neutralen Bedingungen abzielen, welche sich idealerweise zwecks Vermeidung von Abfallprodukten, beispielsweise mit konzentrierter, wässriger HBr, regenerieren und wiederverwenden lassen. Zu diesem Zweck wäre es von Vorteil die entsprechenden Moleküle auf einem Trägermaterial zu fixieren, was ähnlich einem Ionentauscher nach der Reaktion abgetrennt und regeneriert werden könnte. Um die Nachhaltigkeit des Prozesses noch weiter zu erhöhen, wären ebenfalls Experimente bezüglich katalytischer Restaktivität und Wiederverwertung der Propylencarbonat-Mischung nach der Produktabtrennung von Interesse. Hier bestünde auch die Möglichkeit, die Reaktion gekoppelt mit einem Flüssig-Flüssig-Extraktionsverfahren kontinuierlich durchzuführen. Zur Klärung der

Ursache des positiven Effekts von Cyclohexa-1,4-dien sollten mechanistische Untersuchungen durchgeführt werden. Darüber hinaus wäre hier eine weitere Anwendung in Vanadium-katalysierten Oxygenierungsreaktionen zur Steigerung von Selektivität und Geschwindigkeit denkbar. Eine zusätzliche Möglichkeit zur Ausdehnung der Studie wären Untersuchungen zur Durchführung analoger Chloridoxidationen unter Verwendung entsprechender β-Chlorcarbon-säuren. Da jedoch Chloroperoxidase-Modellsysteme im Allgemeinen bislang kaum beschrieben sind, wäre hier zunächst die Entwicklung geeigneter Katalysatoren eine Voraussetzung, um sich anschließend dem Problem der Versorgung mit den notwendigen HCl-Äquivalenten widmen zu können.

3.5 Literatur

[1] A. Butler, J. V. Walker, *Chem. Rev.* **1993**, *93*, 1937–1944.

[2] A. Butler, A. Baldwin in: *Vanadium bromoperoxidase and functional mimics, Structure & Bonding: Metal Sites in Proteins and Models*, Vol. 89, H. Hill, P. Sadler, A. Thomson (Eds.), Springer Berlin-Heidelberg, **1997**, pp. 109–132.

[3] G. J. Colpas, B. J. Hamstra, J. W. Kampf, V. L. Pecoraro, *J. Am. Chem. Soc.* **1996**, *118*, 3469–3478.

[4] G. Zampella, P. Fantucci, V. L. Pecoraro, L. De Gioia, *Inorg. Chem.* **2006**, *45*, 7133–7143.

[5] A. Podgoršek, M. Zupan, J. Iskra, *Angew. Chem. Int. Ed.* **2009**, *48*, 8424–8450.

[6] M. Greb, J. Hartung, F. Köhler, K. Špehar, R. Kluge, R. Csuk, *Eur. J. Org. Chem.* **2004**, 3799–3812.

[7] H.-S. Kim, T. D. Chung, H. Kim, *J. Electroanal. Chem.* **2001**, *498*, 209–215.

[8] J. Hartung, M. Greb, *Tetrahedron Letters* **2003**, *44*, 6091–6093.

[9] M. Greb, *Dissertation*, Universität Würzburg, **2004**.

[10] R. Fittig, F. Binder, *Liebigs Ann.* **1879**, *195*, 56–179.

[11] J. L. Greene, H. J. Hagemeyer, *J. Am. Chem. Soc.* **1955**, *77*, 6065–6066.

[12] R. Anschütz, L. Kinnkutt, *Chem. Ber.* **1878**, *11*, 1221–1222.

[13] H. Mimoun, M. Mignard, P. Brechot, L. Saussine, *J. Am. Chem. Soc.* **1986**, *108*, 3711–3718.

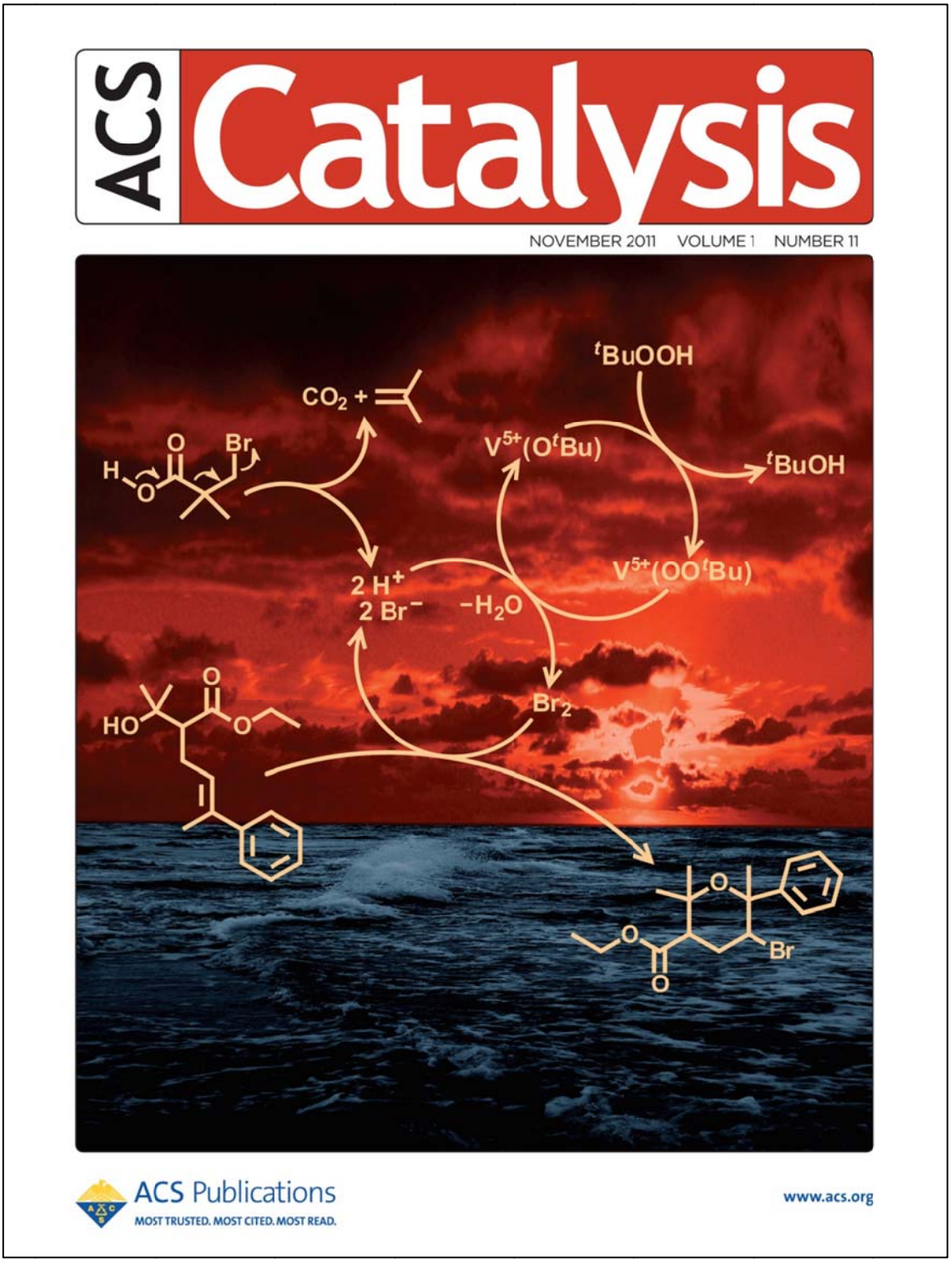
[14] G. Stapf, *Dissertation*, Technische Universität Kaiserslautern, **2010**.

[15] S. Bellemin-Laponnaz, K. S. Coleman, P. Dierkes, J.-P. Masson, J. A. Osborn, *Eur. J. Inorg. Chem.* **2000**, 1645–1649.

3.6 Forschungsartikel (mit Titelgrafik)

Vanadium(V)-Catalyzed Oxidative Bromination of Acid Labile Alkenols and Alkenes in Alkyl Carbonates

Oliver Brücher, Jens Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.



ACS Catalysis

RESEARCH ARTICLE

pubs.acs.org/acscatalysis

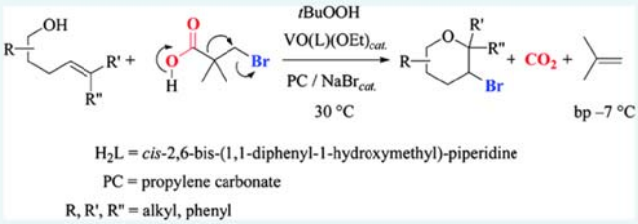
Vanadium(V)-Catalyzed Oxidative Bromination of Acid Labile Alkenols and Alkenes in Alkyl Carbonates

Oliver Brücher and Jens Hartung*

Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

Supporting Information

ABSTRACT: Molecular bromine is formed from bromide and *tert*-butyl hydroperoxide under mild and neutral conditions. The oxidation is catalyzed by vanadium(V)-complexes and requires bromide- and proton- aliquots that are slowly released from a 3-bromopropionic acid-bromide buffer in solutions of alkyl carbonates. In such an environment, bromocyclization of acid labile alkenols occurs without hydrolytically cleaving acetal- or ester-protecting groups. 4-Pentenols having methyl- and/or phenyl-groups attached to the terminal carbon atom of the alkenol double bond undergo 6-*endo*-selective ring closures if subjected to oxidative bromination and provide bromotetrahydropyrans in synthetically useful yields. Application of the new procedure affords a hexasubstituted tetrahydropyran-building block en route to synthesis of the marine natural product aplysiapyranoid A.



KEYWORDS: alkyl carbonate, alkyl hydroperoxide, bromocyclization, bromoperoxidase model, oxidation catalysis, vanadium(V) complex

INTRODUCTION

The growing demand for organobromines we use in our society as intermediates,[1−3] materials,[4,5] flame retardants, emulsifiers,[6] agrochemicals, or pharmaceuticals,[7,8] is covered by hydrocarbon functionalization that mechanistically proceed via nucleophilic substitution, free radical chain reaction, or electrophilic-bromination. The largest proportion of technically produced organobromines thereby originates from reactions between molecular bromine[9−11] and carbon nucleophiles.[12,13]

Molecular bromine is not only a low-cost chemoselective oxidant but also a volatile, toxic, and corrosive chemical. Transport, storage, and application of molecular bromine therefore require safety standards that are met by most protocols based on in situ-generation of bromine from bromide and environmentally benign oxidants, such as dioxygen (O_2), which is economically favored,[14] or a peroxide, which is the more chemoselective route.[12]

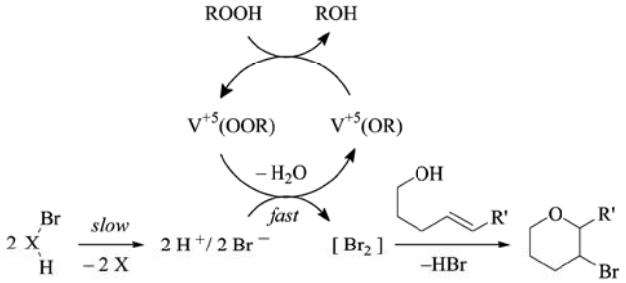
The rates of bromide oxidation by *tert*-butyl hydroperoxide and hydrogen peroxide are surprisingly slow at neutral pH. To accelerate bromide oxidation by hydrogen peroxide, nature uses vanadate(V)-dependent bromoperoxidases, whereas industry uses synthetic Lewis- or Brønsted-acids.[15,16] The strategy to activate peroxides by Brønsted-acids is limited to oxidative transformations of acid-resistant substrates, which, however, are rare in organic chemistry. Bromoperoxidases catalyze the oxidation of bromide under physiological conditions, but require water as solvent.[9,15,16] Water behaves in many organic transformations as a nucleophile and thus changes selectivity to some extend from dibromination or bromocyclization to vicinal bromohydrin formation. To circumvent this problem, hydrogen peroxide-based oxidations are often conducted in biphasic solvent mixtures, where the organic substrate is brominated in the lipophilic layer and a functional bromoperoxidase mimic is added as catalyst.[17] Other approaches for bromocyclization of alkenols start from *tert*-butyl hydroperoxide as oxidant. This reagent dissolves in lipophilic solvents and allows to oxidize substrates in the absence of water.

To effectively mediate oxygen atom transfer to bromide, the alkyl hydroperoxide has to bind rapidly and selectively to a Lewis acid, such as a vanadium(V) complex (Scheme 1).[18,19] The rate of hydroperoxide binding to vanadium(V) compounds thereby gradually increases as the proton concentration rises. Oxidative bromination therefore is performed in most instances in an acidic environment, to obtain reasonable time-yield factors.[9] In strongly acidic aqueous solutions, many functional groups, such as the acetal or the ester group, hydrolyze whereas others, for example nucleophilic carbon−carbon double bonds, add water.[20]

To overcome acid- and water-mediated side reactions in a project dealing with synthesis of brominated marine natural products[21] from acid labile alkenols, we developed a method for in situ-generation of bromine from buffered hydrogen bromide-equivalents and *tert*-butyl hydroperoxide (Scheme 1). In the course of this study we found that 3-bromopropionic acids liberate proton- and bromide-aliquots, which are oxidized by *tert*-butyl hydroperoxide in a vanadium(V)-catalyzed process. The reaction furnishes molecular bromine under mild and neutral conditions, to conduct bromocyclization of acid labile alkenols in alkyl carbonates or ethyl acetate. This new method was used to

Received: July 5, 2011
Revised: September 6, 2011
Published: September 07, 2011

Scheme 1. Concept for Proton- and Bromide- Release from in Situ-Hydrogen Bromide Source (HXBr; section 1), and Mechanistic Proposal for Bromide Oxidation by Hydroperoxides, Catalyzed by a Vanadium Compound, That Is, $V^{+5}(OR)$ (section 2; e.g., R = H; *t*Bu; e.g., R′ = CH_3, Ph)



prepare a hexasubstituted tetrahydropyran-building block required for synthesis of the marine natural product aplysiapyranoid A.

RESULTS AND DISCUSSION

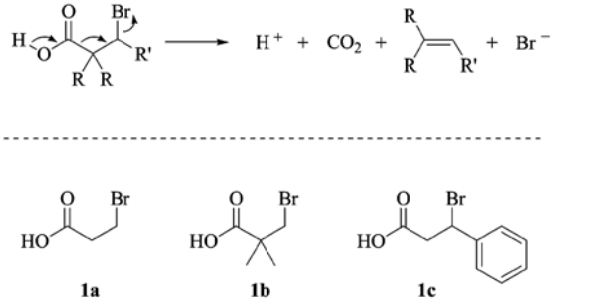
1. Hydrogen Bromide Sources. From a structure−reactivity survey we concluded that 3-bromopropionic acid (**1a**) and substituted derivatives **1b**−c (Scheme 2) quantitatively liberate proton- and bromide-aliquots, if treated at 30 °C with catalytic amounts of bromide in solutions of dimethyl carbonate (DMC), propylene carbonate (PC), or ethyl acetate (EtOAc).[22] For reasons of solubility, we used sodium bromide as catalyst for reactions conducted in propylene carbonate, and tetrabutylammonium bromide for transformations performed in dimethyl carbonate or ethyl acetate. The experimental evidence for bromide and proton liberation from **1a**−**c** comes from the mass balance of dibromides and vicinal bromohydrin ethers, formed after adding *tert*-butyl hydroperoxide and a vanadium catalyst (see sections 2−3).

2. Vanadium Compounds. As catalysts to activate peroxides, we used neutral complexes of the general formula O═V(L)-(OEt), having one dibasic tridentate ONO-donor ligand, that is L^{2-}, and one labile ethanolato ligand bound to oxovanadium(V). The auxiliaries H_2L^{1-3} we used to prepare vanadium compounds O═V(L^{1-3})(OEt) from triethyl vanadate (Scheme 3),[23−26] differ in terms of binding affinity toward vanadium(V), thus modifying chemical properties of derived complexes. Piperidine-derived oxovanadium(V) complex VO(L^1)(OEt), for example, is the most reactive catalyst prepared and tested so far in our project on catalytic hydroperoxide-activation, whereas VO(L^2)(OEt) is significantly most stable. The properties of VO(L^3)(OEt) in terms of stability and reactivity are midway between the former two reagents. We also included vanadyl sulfate ($VOSO_4 \cdot 4H_2O$) and oxovanadyl(IV) bis(acetylacetonate) as reagent for peroxide activation into the study, to compare reactivity and selectivity of more readily available vanadium compounds to more specialized catalysts, which we favor for reasons of selectivity (see section 3.1).

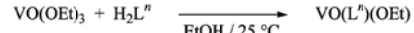
Vanadium complexes VO(L^{1-3})(OEt) are prepared by mixing aliquots of $VO(OEt)_3$ and a chelate ligand H_2L^{1-3} in ethanol at ambient temperature. The complexes separate from solutions of ethanol as pale yellow [VO(L^1)(OEt) and VO(L^3)(OEt)] to brown [VO(L^2)(OEt)] air stable crystalline solids.

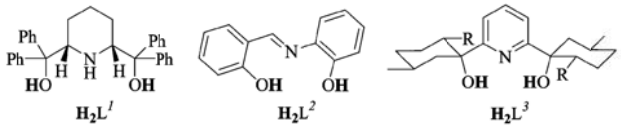
3. Bromofunctionalization of Alkenes. *3.1. Dibromination of Cyclohexenes.* To determine parameters for bromofunctionalization of alkenes in vanadium-catalyzed oxidations, we chose conformationally fixed cycloalkene **2a**,[28−30] and, for testing the significance of acid-mediated hydrolysis of acetal groups in oxidative brominations, protected unsaturated aldehyde **2b** (Tables 1−3). The relative configuration of dibromides formed from the two alkenes allows to model trajectories for π-bond bromination, to identify the underlying mechanism and thus the chemical nature of intermediates involved in brominations. From a systematic variation of reaction conditions, solvents, vanadium compounds, and additives (Tables 1−2), we concluded that the most effective procedure to prepare dibromide **3a** (84%) from the chosen reagents requires treatment of 4-*tert*-butyl cyclohexene (**2a**) with 3-bromo-2,2-dimethylpropionic acid (**1b**), *tert*-butyl hydroperoxide, catalytic amounts of sodium bromide and piperidine-derived vanadium complex VO(L^1)(OEt) in a solution of propylene carbonate containing low concentrations of cyclohexa-1,4-diene (CHD) (Table 1, entry 1).

Scheme 2. Structure Formulas of 3-Bromopropionic Acids 1a−c Relevant for the Study



Scheme 3. Synthesis of Vanadium Compounds VO(L^n)(OEt)[a] from Auxiliaries H_2L^n [b]





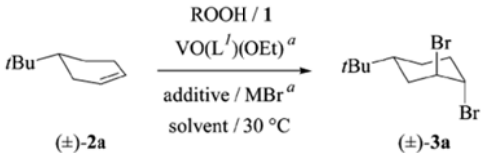
[a] 85% for n = 1, 95% for n = 2, 87% for n = 3. [b] Acidic protons that are removed in the course of complex formation are printed in bold; VO(L^2)(OEt) crystallizes as EtOH adduct[27] from a solution of ethanol; R = $CH(CH_3)_2$.

In the course of method development we noted aspects dealing with (*i*) reactivity of bromopropionic acids **1a**−**c**, (*ii*) reactivity of vanadium catalysts, (*iii*) the effect of terminal oxidants, (*iv*) the effect of cyclohexa-1-4-diene on rate and chemoselectivity of alkene functionalization, (*v*) solvent effects, and (*vi*) product selectivity in alkene functionalization that deserve a comment.

(i) The relative rate of bromopropionic acid fragmentation in dimethyl carbonate increases along the series of compounds **1a** (k^{rel} = 1.0) < **1b** (k^{rel} = 1.3) < **1c** (k^{rel} = 1.9) (Scheme 2, Figure 1; all values for 30 °C). The rates of bromopropionic acid fragmentation correlate with the rates dibromide **3a** forms. The proton concentration in such solutions remains approximately constant during turnover of **1**, as probed via hydrolysis of small reaction

dx.doi.org/10.1021/cs200349c |ACS Catal. 2011, 1, 1448–1454

Table 1. Oxidative Bromination of 4-*tert*-Butyl Cyclohexene (2a) in Vanadium-Catalyzed Reactions

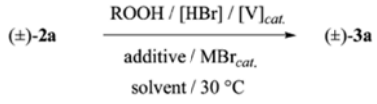


(±)-**2a** (±)-**3a**

entry	1	R[b]	solvent[c]	additive[d]	MBr[e]	3a/%
1	**1b**	*t*Bu	PC	CHD	NBu_4Br	84
2	**1a**	*t*Bu	PC	CHD	NaBr	32
3	**1b**	*t*Bu	DMC	CHD	NBu_4Br	74
4	**1b**	*t*Bu	EtOAc	CHD	NBu_4Br	83
6	**1b**	*t*Bu	PC	none	NaBr	72
7	**1c**	*t*Bu	PC	none	NaBr	79
8	**1b**	H	CH_2Cl_2	none	NBu_4Br	18[f]
9	**1b**	H	PC	none	NBu_4Br	19[g]

[a] 1 mol % of $VO(L^1)(OEt)$. [b] Anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] PC = propylene carbonate, DMC = dimethyl carbonate. [d] CHD = cyclohexa-1,4-diene. [e] 10 mol % of MBr. [f] 42% conversion. [g] 62% conversion; in the absence of $VO(L^1)(OEt)$, 18% of **3a** was obtained

Table 2. Catalyst Variation in Oxidative Bromination of 4-*tert*-Butyl Cyclohexene (2a)



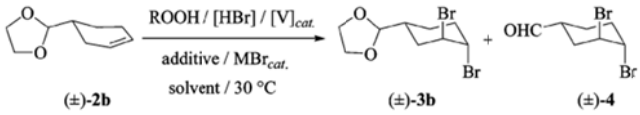
entry	[V][a]	[HBr]	R[b]	solvent[c]	additive[d]	MBr[e]	3a/%
1	$VO(L^1)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	82
1	$VO(L^2)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	44
2	$VO(L^3)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	52
3	$VO(acac)_2$[f]	**1b**	*t*Bu	PC	CHD	NaBr	76
4	$VOSO_4 \cdot 4H_2O$	**1b**	*t*Bu	PC	CHD	NaBr	42
5	none	HBr[g]	H	CH_2Cl_2	none	*h*	84
6	none	HBr[g]	H	DMC	none	*h*	86

[a] 1 mol %. [b] Anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] PC = propylene carbonate. [d] CHD = cyclohexa-1,4-diene. [e] 10 mol %. [f] Hacac = pentane-1,3-dione. [g] 48% (*w*/*w*) aqueous solution. [h] No further bromide added.

volumes in intervals and pH measurement showing values of pH 5–6. In none of the reactions we noticed chemical changes at the acetal group, such as hydrolysis to the free aldehyde, starting from compounds **2b** and **3b**.

Fragmentation of **1** provides ethene (from **1a**), 2-methylpropene (from **1b**), or styrene (from **1c**), which we expected to form dibromides, similar to **2a**. Our experiments showed that 1,2-dibromoethane was not formed in reactions starting from **1a**, whereas small (<10%) amounts of 1,2-dibromo-2-methylpropane formed from **1b**. The latter dibromide was removed by distillation, as the reaction mixtures were concentrated for isolation and purification of target compound **3a**. In reactions starting from bromocinnamate **1c**, styrene (~25%) and (1,2-dibromoethyl)-benzene (~28%) formed as byproduct and thus required

Table 3. Formation of Dibromide 3b from 3-Dioxolanyl Cyclohexene 2b



(±)-**2b** (±)-**3b** (±)-**4**

entry	[V][a]	[HBr]	R[b]	solvent[c]	additive[d]	MBr[e]	3b/%	4/%
1	$VO(L^1)(OEt)$	**1b**	*t*Bu	EtOAc	CHD	NBu_4Br	80	*f*
2	$VO(L^1)(OEt)$	**1b**	*t*Bu	PC	CHD	NaBr	77	*f*
3	none	HBr[f]	H	PC	none	*g*	20	2

[a] 1 mol %. [b] anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] PC = propylene carbonate. [d] CHD = cyclohexa-1,4-diene. [e] 10 mol %. [f] 48% (*w*/*w*) aqueous solution. [g] No further bromide added.

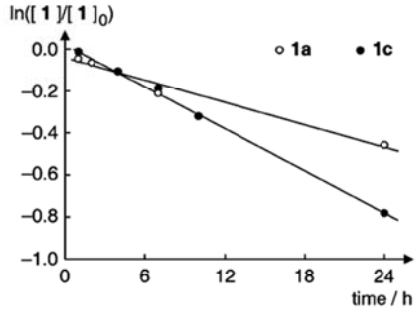


Figure 1. Time dependence of bromopropionic acid-fragmentation in solutions of alkene **2a** (c_0^{2a} = 0.05 M), *tert*-butyl hydroperoxide (c_0 = 0.063 M in toluene) in dimethyl carbonate containing NaOAc (0.02 M), NBu_4Br (0.125 M), and $VO(L^1)(OEt)$ (5×10^{-4} M) (^{1}H NMR, 30 °C, c_0^1 = 0.125 M).

separation by chromatography. We therefore chose 3-bromo-2,2-dimethylpropionic acid (**1b**) as standard hydrogen bromide donor for all succeeding experiments.

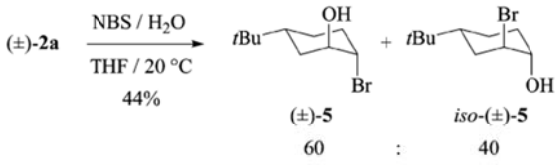
(ii) Reactivity of vanadium catalysts. The reactivity of vanadium compounds to serve as catalyst for bromide oxidation in *tert*-butyl cyclohexene dibromination decreases along the series $VO(L^1)(OEt) > VO(acac)_2 > VO(L^3)(OEt) > VO(L^2)(OEt) > VOSO_4 \cdot 4H_2O$, from 84% to 42% (Table 2). The amount of 1 mol % of catalyst originates from our own specification, to achieve quantitative conversion of alkene **2a** within 24 h. In the absence of vanadium compounds no dibromination of **2a** occurs (48 h reaction time, GC-analysis). From this information we concluded that bromopropionic acids **1a**–**c** are not able to activate *tert*-butyl hydroperoxide for bromide oxidation.

(iii) The effect of terminal oxidants. *tert*-Butyl hydroperoxide was superior to hydrogen peroxide for synthesis of acetal-protected dibromide **3b** (Table 3). Since structures like these are of interest in our natural product project, we restricted ourselves to the use of *tert*-butyl hydroperoxide for the succeeding experiments.

(iv) The effect of cyclohexa-1-4-diene on rate and chemoselectivity of alkene functionalization. A gradual decrease in product selectivity and turnover rates in combination with appearance of new products, such as ~9% of 5-*tert*-butylcyclohex-2-en-1-one **5** after 24 h, caused us to test

dx.doi.org/10.1021/cs200349c |*ACS Catal.* 2011, 1, 1448–1454

Scheme 4. Preparation of Authentic Bromohydrins 5 and *iso*-5 for Tracing Side Product Formation in Oxidative Brominations of 4-*tert*-Butyl Cyclohexene (2a) (See Also Text)



typical H-atom donors to prevent radical-based side reactions to occur. From a series of H-atom donors, that also included ionol and 2,6-di-(*tert*-butyl)phenol, cyclohexa-1,4-diene was the most effective agent to entirely prevent such side reactions of **2a**.[31] About 2−9% of the cyclohexa-1,4-diene thereby were converted into a derived dibromide, which did not complicate target product isolation and purification.

Addition of cyclohexa-1,4-diene not only improved the yield of dibromide, for example from 72% to 84% for **3a**, but also shortened the reaction time to a third (Table 1, entries 2 and 6). The efficiency of dibromide formation in the vanadium-catalyzed reaction thus compares to yields of alkene dibromination by stoichiometric amounts *N*-bromosuccinimide in combination with tetrabutylammonium bromide (92%) or molecular bromine (96%) in solutions of dichloromethane (Supporting Information).

(v) Solvent effects. Dimethyl carbonate (bp. 90 °C), propylene carbonate (bp. 240 °C), and ethyl acetate (bp. 70 °C) are biodegradable non toxic solvents. The use of such Lewis-basic solvents in oxidations catalyzed by Lewis-acidic vanadium complexes is new and poses an interesting alternative to conventional procedures performed, for example, in chlorinated alkanes or acetonitrile. Since propylene carbonate and alkanes are poorly miscible, products **3a**−**b** were on a routine basis extracted from reaction mixtures by cyclohexane. This workup procedure is attractive particular for larger scale applications, because product separation is feasible by extraction and distillation. Propylene carbonate solutions of VO(L^{1})(OEt), which were left from extractions could be charged with further alkene **2a**, bromopropionic acid **1b**, and *tert*-butyl hydroperoxide to provide 69% of dibromide **3a** in a second run.

(vi) Product selectivity in alkene functionalization. To check, whether oxygenation of **2a** or bromohydrin formation from water that forms from *tert*-butyl hydroperoxide and bromide (see Scheme 1) interferes with dibromination of **2a**, we independently prepared 4-*tert*-butyl cyclohexene-1,2-oxide and β-bromohydrins **5** and *iso*-**5** (Scheme 4). None of the two products was detected in the reaction mixtures (GC-MS).

The chemical nature and the configuration of products **3a**−**b** formed in vanadium-catalyzed oxidations point to a bromonium ion pathway, and thus to molecular bromine as key intermediate (Scheme 5). Nucleophilic opening of bromonium ion *anti*-**6** via bromide attack at C4 provides dibromide **3a** having both bromo-substituents attached axially and the *tert*-butyl group equatorially. Formation of the all equatorially substituted stereoisomer of **3a** in this mechanistic picture would occur upon nucleophilic attack of bromide at C3 leading to a boat-like conformer, which is higher

Scheme 5. Stereochemical Model for Synthesis of Trans-Diaxially Substituted Dibromide (±)-3a (for a Description of Ring-Opening of *syn*-6 See Text)

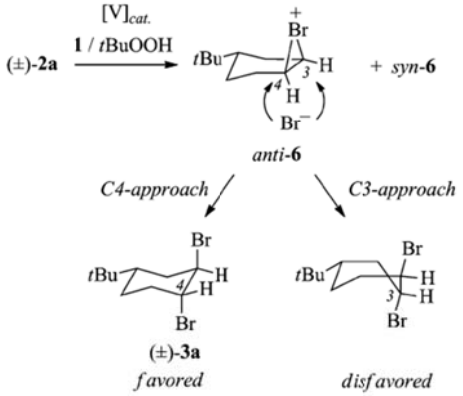
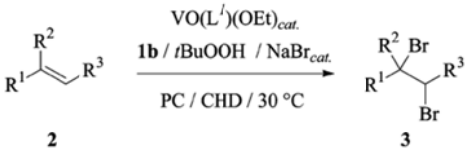


Table 4. Formation of Vicinal Dibromoalkanes via Oxidative Bromination of Terminal and Internal Alkenes[a]



entry	2/3	R^1	R^2	R^3	3/%
1	**c**	C_8H_{17}	H	H	71
2	**d**	$(CH_2)_3Ph$	H	H	63
3	**e**	Ph	H	CH_3	59
4	**f**	C_4H_9	H	C_4H_9	73
5	**g**	CH_3	CH_3	$(CH_2)_2CO_2Et$	69

[a] For reagent abbreviations, concentrations, and equivalents refer to footnotes of Table 1.

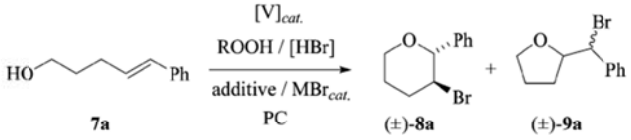
in energy and therefore disfavored.[32,33] For the same reason we propose that bromonium ion opening of *syn*-**6** (not shown in Scheme 5) occurs via attack at C3 to afford the trans-diaxially substituted dibromide **3a**, whereas substitution at C4 would furnish the all equatorially substituted product, which we did not observe.

3.2. Dibromination of Terminal, Di-, and Trisubstituted Alkenes. For a survey on reactivity and chemoselectivity in oxidative alkene bromination (Table 4), we selected substrates **2c**−**g** bearing substituents at the carbon−carbon double bond that reflect patterns occurring in natural products. Under conditions referred to as standard (Table 1, entry 1), alkenes **2c**−**g** gave dibromides **3c**−**g** in yields ranging between 59% [(β-methyl styrene **2e**)] and 73% [(*E*)-5-decene **2f**]. The products were in all instances formed diastereomerically pure. Addition of the cyclohexa-1,4-diene improved the yield of dibromides from internal alkenes (**2e**−**g**) by about 8−12%, but not for bromination of substrates having a terminal double bond (**2c**−**d**).

3.3. Bromocyclization of 4-Pentenols. The results obtained from dibromination of alkenes allowed us to step toward the main objective of this project dealing with development of a catalytic method for oxidative bromocyclization of acid labile alkenols. To explore technical details of this reaction, we chose

dx.doi.org/10.1021/cs200349c |ACS Catal. 2011, 1, 1448–1454

Table 5. Summary of Results from Parameter Variation for Synthesis of Brominated Tetrahydropyran 8a from 5-Phenyl-4-pentenol 7a



entry	[V][a]	[HBr]	R[b]	T/°C	additive[c]	MBr[d]	8a/%	9a/%
1	VO(L^1)(OEt)	**1b**	*t*Bu	30	CHD	NaBr	71	<5
2	VO(L^1)(OEt)	**1b**	H	30	none	NBu_4Br	19[f]	*e*
3	none	HBr[g]	H	20	none	*h*	47	*e*

[a] 1 mol %. [b] Anhydrous 3 M solution in toluene for R = *t*Bu; 30% (*w*/*w*) aqueous solution for R = H. [c] CHD = cyclohexa-1,4-diene. [d] 10 mol %. [e] Not detected. [f] 17% yield in the absence of VOL^1(OEt) under otherwise identical conditions. [g] 48% (*w*/*w*) aqueous solution. [h] No bromide added.

5-phenyl-4-pentenol (**7a**) as substrate. Styrene-type alkenol **7a** bears structural elements relevant for the natural product project. This substrate has a nucleophilic π-bond that is prone to undergo side reactions in the presence of protons and external nucleophiles, such as water. The stereochemical information associated with the π-bond in **7a** furthermore allows to extract mechanistic information of carbon−bromine- and carbon−oxygen-bond formation on the basis of relative configuration of substituents in derived bromocyclization products.

The results from a screening of parameters for bromocyclization showed that phenylpentenol **7a** is most effectively transformed in a solution of propylene carbonate containing bromopropionic acid **1b**, *tert*-butyl hydroperoxide, and 1 mol % of VO(L^1)(OEt). The reaction provides 71% of stereochemically pure 2,3-trans-substituted tetrahydropyran **8a**, besides a minor fraction of bromobenzyltetrahydrofuran **9a** (Table 5, entry 1). Addition of 40 mol % of cyclohexa-1,4-diene improved the yield of product **8a** and shortened the time for quantitative conversion of **7a**. From the yields of **8a** we concluded that *tert*-butyl hydroperoxide is superior to hydrogen peroxide for oxidative bromocyclization of **7a** (Table 5, entry 2). We also checked, whether an aqueous solution of hydrogen peroxide containing hydrogen bromide[34] would provide a simpler alternative for synthesis of tetrahydropyran **8a** compared to the new method, which however was not the case (Table 5, entry 3).

The chemical nature of products formed from oxidative bromination of **7a** is consistent with a two step mechanism proceeding via cyclic bromonium ion formation and opening of this intermediate by backside attack of the hydroxyl oxygen in a S_N2-manner (Scheme 6). Carbon−oxygen bond formation from the proposed intermediate **10** occurs in a late transition state. Since charge effects become important in late transition states, the incoming oxygen nucleophile favors attack of the bromonium ion at the benzylic carbon.[32,33] Stereoelectronic prerequisites associated with the backside attack guide stereospecificity of bromonium ion opening and copies the (*E*)-configuration of substrate **7a** into the 2,3-trans-configuration of product **8a**.

To investigate selectivity in bromocyclization of substrates having terpenol-type π-bonds, we subjected 5-methyl-1-phenyl-4-hexenol **7b** and linalool **7c** to conditions developed in the preceding sections. From these reactions we isolated bromocyclization products **8b**−**c** and **9b**−**c** in combined yields of about

Scheme 6. Mechanistic Model for Synthesis of Cyclic Ethers from 5-Phenyl-4-pentenol (7a) in Oxidative Bromination

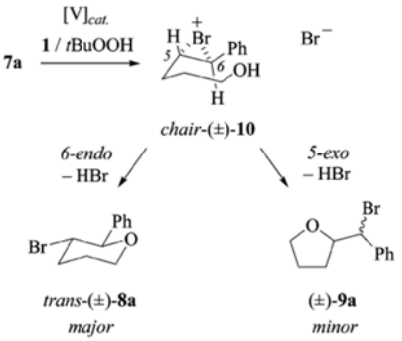
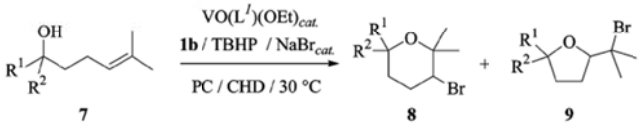
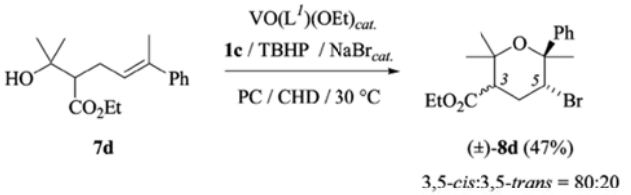


Table 6. Bromocyclization of Alkenols in Vanadium(V)-Catalyzed Oxidations



entry	7−9	R^1	R^2	8/% (*cis*:*trans*)	9/% (*cis*:*trans*)
1	**b**	Ph	H	68 (4:96)	14 (41:59)
2	**c**	CH_3	$CH{=}CH_2$	42 (64:36)	37 (62:38)

Scheme 7. Synthesis of Building Block 8d for the Synthesis of Aplysiapyranoid A[37]



80% (Table 6). We scaled up the process for bromocyclization of linalool **7c** by a factor of 10 and successfully used a simplified work up-procedure via extraction and distillation to obtain pure linalool bromides **8c** and **9c** (Supporting Information). We think that this procedure is quite generally applicable for products having similar polarity to cyclic ethers **8c** and **9c**.

As final step in method development and a first step toward application in synthesis, we chose to prepare the heterocyclic core of the aplysiapyranoids,[35] using the vanadium-catalyzed method. Aplysiapyranoids are functionalized tetrahydropyrans having a total of four substituents attached to carbons 2 and 6, and two additional functional groups at carbons 3 and 5 of the heterocyclic core. The strain imposed by axial positioning of substituents at carbon atoms 2 and 6 generally renders bromocyclization of δ,ε-unsaturated alcohols inefficient for constructing 2,2,6,6-substituted tetrahydropyrans.[36]

We thus subjected tertiary alkenol **7d** to standard conditions using bromocinnamic acid **1c** as hydrogen bromide donor, and isolated 2,2,3,5,6,6,-substituted tetrahydropyran **8d** in 47% yield as only low molecular weight product (Scheme 7). This yield is

higher than the value of 20% obtained for bromocyclization of the O-methyl derivative of **7d** by 2,4,4,6-tetrabromocyclohexa-2,5-dienone and 43% for an oxidative bromination using pyridinium hydrobromide and *tert*-butyl hydroperoxide in acetonitrile.[37] An UV-active spot located at $R_f = 0$ on tlc-sheets using a 50/50-mixture of diethyl ether and pentane as eluent shows that additional products form from substrate **7d**. These products, unfortunately, could not be characterized with our analytical methods.

CONCLUDING REMARKS

The oxidation of bromide by *tert*-butyl hydroperoxide in solutions of alkyl carbonates is an effective and synthetically useful method to prepare vicinal dibromoalkanes from alkenes and products of bromocyclization from alkenols. The fundamentals of this bromination chemistry derive from nature, where vanadate(V)-dependent bromoperoxidases catalyze the oxidation of bromide from ocean water by hydrogen peroxide at ambient temperature and pH 6.

Over the years, substantial effort was spent to mimic the chemistry of the marine bromoperoxidases for conducting organobromine synthesis under approximately neutral conditions.[38,39] The discovery that the combination of bromide and 3-bromopropionic acids act as buffered, slow release hydrogen bromide progenitor in this sense solves a long-standing problem and has the potential to further develop this field of bioinspired organic synthesis.

We are well aware of the fact that other methods for oxidative bromination exist. A number of attractive procedures are based on aerobic oxidation,[14] while others transform bromide by hydrogen peroxide under strongly acidic conditions into bromoelectrophiles, which are suitable for arene bromination or vicinal dibromination of acid stable alkenes.[13] In strongly acidic media, however, peroxides and alkenes are consumed not only by bromination, but also by unspecific acid-induced background reactions.[40] In the new method for oxidative bromination, no background reactivity exists thus explaining efficiency and selectivity for turning over substrates into products. The task to activate *tert*-butyl hydroperoxide is entirely taken over by vanadium(V)-compounds that structurally range from more specialized catalysts, as in our ongoing projects, to commercially available reagents, such as vanadyl(IV)-bis(acetylacetonate).

The vanadium-catalyzed method for oxidative bromination effectively operates in alkyl carbonates and ethyl acetate, which are nontoxic solvents and therefore pose interesting alternatives to aromatic hydrocarbons, acetonitrile, or chlorinated alkanes, which are customarily used as reaction media for peroxide activation by vanadium compounds. In view of the efficiency of this modification we believe that alkyl carbonate solvents will have the potential to provide a stimulus to the field of oxidation catalysis in a broader sense.

EXPERIMENTAL SECTION

1. General Information. For general laboratory practice and instrumentation see ref 10 and the Supporting Information.

2. Oxidative Bromination of 4-*tert*-Butyl Cyclohexene (2a). To a solution of 4-*tert*-butyl cyclohexene (**2a**) (138 mg, 1.0 mmol) in propylene carbonate (20 mL) was added 3-bromo-2,2-dimethylpropionic acid (**1b**) (452 mg, 2.5 mmol), NaBr (10.3 mg, 0.1 mmol), vanadium catalyst VO(L^1)(OEt) (5.6 mg, 0.01 mmol), and *tert*-butyl hydroperoxide (TBHP) (3.5 M in toluene, 455 μL, 1.6 mmol). 1,4-Cyclohexa-1,4-diene (32.1 mg, 0.4 mmol) dissolved in propylene carbonate (3 mL) was added via syringe pump (0.003 mL/min). The reaction mixture was stirred at 30 °C in a water bath for 24 h. The yellowish solution was extracted with cyclohexane (4 × 15 mL), combined organic extracts were washed with H_2O (1 × 20 mL) and sat. aqueous NaCl (1 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2). Quant. conversion (NMR). Yield: 244 mg (82%) *rel*-(1*R*,3*S*,4*S*)-3,4-dibromo-1-*tert*-butyl cyclohexane (**3a**) from 139 mg (1 mmol) of **2a**, colorless oil, R_f 0.77. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.89 (s, 9 H, CH_3), 1.55−1.70 (m, 3 H, 1-H, 6-H), 1.97 (t, J 14.4 Hz, 2 H, 2-H, 5-H), 2.17 (ddd, J 14.6, 11.9, 3.1 Hz, 1 H, 2-H), 2.44 (ddt, J_d 15.3, 12.1, J_t 3.6 Hz,1 H, 5-H), 4.67 (br s, 1 H, 4-H), 4.77 (br s, 1 H, 3-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 21.2 (C6), 27.3 (CH_3), 28.9 (C5), 29.4 (C2), 32.1 (C_q), 41.2 (C1), 53.8 (C4), 54.9 (C3) ppm. Anal. Calc. for $C_{10}H_{18}Br_2$: C, 40.30; H, 6.09; Found: C, 40.54; H, 6.05.

3. 2-[*rel*-(1′*R*,3′*S*,4′*S*)-3′,4′-Dibromocyclohexyl]-1,3-dioxolane (3b). 2-(Cyclohex-3′-enyl)-1,3-dioxolane (**2b**) (155 mg, 1.0 mmol) was converted as described in section 2 for **2a**. Conversion: 96% (NMR). Yield: 251 mg (80%) colorless oil, R_f 0.58. ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.66−1.77 (m, 2 H, 6′-H), 1.95−2.05 (m, 2 H, 2′-H, 5′-H), 2.19 (tq, J_t 11.7, J_q 4.0 Hz, 1 H, -1′-H), 2.28−2.36 (m, 1 H, 2′-H), 2.46 (dddd, J 15.2, 12.2, 4.6, 3.3 Hz, 1 H, 5′-H), 3.82−3.98 (m, 4 H, 3-H, 4-H), 4.61−4.67 (m, 1 H, 4′-H), 4.67−4.74 (m, 2 H, 2-H, 3′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 21.0 (C6′), 27.8 (C2′), 29.1 (C5′), 35.7 (C1′), 52.9 (C3′), 53.1 (C4′), 65.0, 65.0 (C4, C5), 106.3 (C2) ppm. Anal. Calcd. for $C_9H_{14}Br_2O_2$ (314.01): C, 34.42; H, 4.49; Found: C, 34.69; H 4.45.

4. Bromocyclization of (*E*)-5-phenylpent-4-en-1-ol (7a). To a solution of (*E*)-5-phenylpent-4-en-1-ol (**7a**) (162 mg, 1.0 mmol) in propylene carbonate (20 mL) was added 3-bromo-2,2-dimethylpropionic acid (**1b**) (226 mg, 1.25 mmol), NaBr (10.3 mg, 0.1 mmol), vanadium catalyst VO(L^1)(OEt) (5.6 mg, 0.01 mmol), and TBHP (3.5 M in toluene, 455 μL, 1.6 mmol). 1,4-Cyclohexa-1,4-diene (32.1 mg, 0.4 mmol) dissolved in propylene carbonate (3 mL) was added via syringe pump (0.003 mL/min). The reaction mixture was stirred at 30 °C in a water bath for 24 h. The yellowish solution was extracted with cyclohexane (4 × 15 mL), combined organic extracts were washed with H_2O (1 × 20 mL) and sat. aqueous NaCl (1 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2). Quant. conversion (NMR). Yield: 173 mg (71%) of a >95/5-mixture of tetrahydropyran **8a** and tetrahydrofuran **9a**, colorless oil. R_f 0.63. Anal. Calc. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43; Found: C, 54.73; H, 5.30. *rel*-(2*R*,3*S*)-3-Bromo-2-phenyltetrahydropyran (**8a**). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.76 (d, J 13.7 Hz, 1 H, 4-H), 1.88−2.03 (m, 1 H, 4-H), 2.13 (qd, J_q 12.6, J_d 4.1 Hz, 1 H, 3-H), 2.60 (dd, J 9.0, 3.9 Hz, 1 H, 3-H), 3.65 (td, J_t 11.9, J_d 2.0 Hz, 1 H, 5-H), 4.06 (td, J_t 11.0, J_d 4.3 Hz, 1 H, 2-H), 4.14 (dd, J 11.3, 4.7 Hz, 1 H, 5-H), 4.32 (d, J 9.8 Hz, 1 H, 1-H), 7.29−7.43 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 28.3 (C4), 36.2 (C3), 52.3 (C2), 68.7 (C5), 85.5 (C1), 127.5, 128.2, 128.5, 139.5 ppm. 2-(1-Bromo-1-phenylmethyl)-tetrahydrofuran (**9a**). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.90−1.98 (m, 2 H, CH_2), 2.23−2.35 (m, 2 H, CH_2), 3.78−3.98 (m, 2 H, CH_2), 4.43−4.53 (m, 1 H, 2-H), 4.89 (d, J 7.8 Hz, 1 H, CHBr), 7.30−7.48 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C):

dx.doi.org/10.1021/cs200349c |*ACS Catal.* 2011, 1, 1448–1454

$\delta \approx 26.0$ (CH_2), 31.0 (CH_2), 57.3 or 60.4, 69.3, 85.5 (C2), 128.2, 128.4, 128.6, 139.6 ppm.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +49-631-205-2431. Fax: +49-631-205-3921. E-mail: hartung@chemie.uni-kl.de.

Funding Sources

We express out gratitude to the Deutsche Bundesstiftung Umwelt for financial support (Grant 20007/885).

■ DEDICATION

This work is dedicated to Professor Dr. Dr. h.c. Gerhard Bringmann, on the occasion of his 60th birthday, and is part of the Ph.D. thesis of O.B.

■ REFERENCES

(1) De la Mare, P. B. D.; Swedlund, B. E. In *The Chemistry of Functional Groups — The Chemistry of the Carbon-Halogen Bond*; Patai, S., Ed.; Wiley: Chichester, England, 1973; pp 407—548.

(2) Doonan, S. In *The Chemistry of Functional Groups — The Chemistry of the Carbon-Halogen Bond*; Patai, S., Ed.; Wiley: Chichester, England, 1973; pp 865—915.

(3) Sasson, Y. In *The Chemistry of Functional Groups — Supplement D2, The Chemistry of Halides, Pseudo-Halides, and Azides*; Patai, S., Rappoport, Z. Z., Eds.; Wiley: Chichester, England, 1995; pp 535—628.

(4) Kaspersma, J.; Doumena, C.; Munrob, S.; Prinsa, A.-M. *Polym. Degrad. Stab.* **2002**, *77*, 325–331.

(5) Frim, R.; Ukeles, S. D. In *Industrial Minerals & Rocks*, 7th ed.; Kogel, J. E., Trived, N. C., Baker, J. M., Eds.; Society for Mining, Metallurgy, and Exploration: Littleton, CO, 2006; pp 285—294.

(6) Turner, D. L. *J. Food. Sci.* **1972**, *37*, 791–792.

(7) Renner, M. K.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **1998**, *63*, 8346–8534.

(8) Neumann, C. S.; Fujimori, D. G.; Walsh, C. T. *Chem. Biol.* **2008**, *15*, 88–109. Gribble, G. W. *Chemosphere* **2003**, *52*, 289–297.

(9) Wischang, D.; Brücher, O.; Hartung, J. *Coord. Chem. Rev.* **2011**, *255*, 2204–2217.

(10) Wischang, D.; Hartung, J. *Tetrahedron* **2011**, *67*, 4048–4054.

(11) Eissen, M.; Lenoir, D. *Chem.—Eur. J.* **2008**, *14*, 9830–9841.

(12) Podgoršek, A.; Zupan, M.; Iskra, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8424–8450.

(13) Rothenberg, G.; Clark, J. H. *Green Chem.* **2000**, *2*, 248–251.

(14) Kikushima, K.; Moriuchi, T.; Hirao, T. *Tetrahedron* **2010**, *66*, 6906–6911.

(15) Vilter, H. In *Metal Ions in Biological Systems*; Sigel, H., Sigel, A., Eds.; Dekker: New York, 1995; Vol. 31, Chapter 10, pp 325—362.

(16) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944.

(17) Andersson, M.; Conte, V.; Di Furia, F.; Moro, S. *Tetrahedron Lett.* **1995**, *36*, 2675–2678.

(18) Rehder, D. In *Bioinorganic Vanadium Chemistry*; Wiley: Chichester, England, 2008; pp 105—128.

(19) Sheldon, R. A. In *Aspects of Homogeneous Catalysis*; Ugo, R., Ed.; Reidel Publishing: Dordrecht, The Netherlands, 1981; Vol. 4, pp 3—69.

(20) Greene, T. W.; Wuts, P. G. M. In *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(21) Gribble, G. W. *Chemosphere* **2003**, *52*, 289–297.

(22) Schäffner, B.; Schäffner, F.; Verevkin, S. P.; Börner, A. *Chem. Rev.* **2010**, *110*, 4554–4581.

(23) Hartung, J.; Ludwig, A.; Demary, M.; Stapf, G. In *Vanadium the Versatile Metal, ACS-Symposium Series 974*; Kustin, K., Pessoa, J. C., Crans, D. C., Eds.; American Chemical Society: Washington, DC, 2007; Chapter 4, pp 38—50.

(24) Mimoun, H.; Mignard, M.; Brechot, P.; Saussine, L. *J. Am. Chem. Soc.* **1986**, *108*, 3711–3718.

(25) Greb, M.; Hartung, J.; Köhler, F.; Špehar, K.; Kluge, R.; Csuk, R. *Eur. J. Org. Chem.* **2004**, 3799–3813.

(26) Bellemin-Laponnaz, S.; Coleman, K. S.; Dierkes, P.; Masson, J.-P.; Osborn, J. A. *Eur. J. Inorg. Chem.* **2000**, 1645–1649.

(27) Clague, M. J.; Keder, N. L.; Butler, A. *Inorg. Chem.* **1993**, *32*, 4754–4761.

(28) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1967**, 1417–1420.

(29) Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.

(30) Quast, H.; Dietz, T. *Synthesis* **1995**, 1300–1304.

(31) For formation of radical derived products in vanadium-catalyzed allylalcohol epoxidation, see: Sheldon, R. A.; van Doorn, J. A. *J. Catal.* **1973**, *31*, 427–437.

(32) Klumpp, G. W. In *Reaktivität in der Organischen Chemie*; Thieme: Stuttgart, Germany, 1977; Vol. 1, pp 22—25.

(33) March, J. M. In *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992, pp 734—755.

(34) Barhate, B. N.; Gajare, A. S.; Wakharkar, R. D.; Bedakar, A. V. *Tetrahedron* **1999**, *55*, 11127–11142.

(35) Kusumi, T.; Uchida, H.; Inouye, Y.; Ishitsuka, M.; Yamamoto, H.; Kakisawa, H. *J. Org. Chem.* **1987**, *52*, 4597–4600.

(36) Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem.* **1998**, *63*, 2982–2987.

(37) Hartung, J.; Greb, M. *Tetrahedron Lett.* **2003**, *44*, 6091–6093.

(38) Butler, A.; Baldwin, A. H. *Struct. Bonding (Berlin)* **1997**, *89*, 109–132.

(39) Colpas, G. J.; Hamstra, B. J.; Kampf, J. W.; Pecoraro, V. L. *J. Am. Chem. Soc.* **1996**, *118*, 3469–3478.

(40) Hartung, J.; Dumont, Y.; Greb, M.; Hach, D.; Köhler, F.; Schulz, H.; Časný, M.; Rehder, D.; Vilter, H. *Pure Appl. Chem.* **2009**, *81*, 1251–1264.

4 Untersuchungen zur Kontrolle von 6-*endo*-Selektivitäten in oxidativen Bromcyclisierungen zur Darstellung bromierter 2,2,6,6-substituierter Tetrahydropyrane

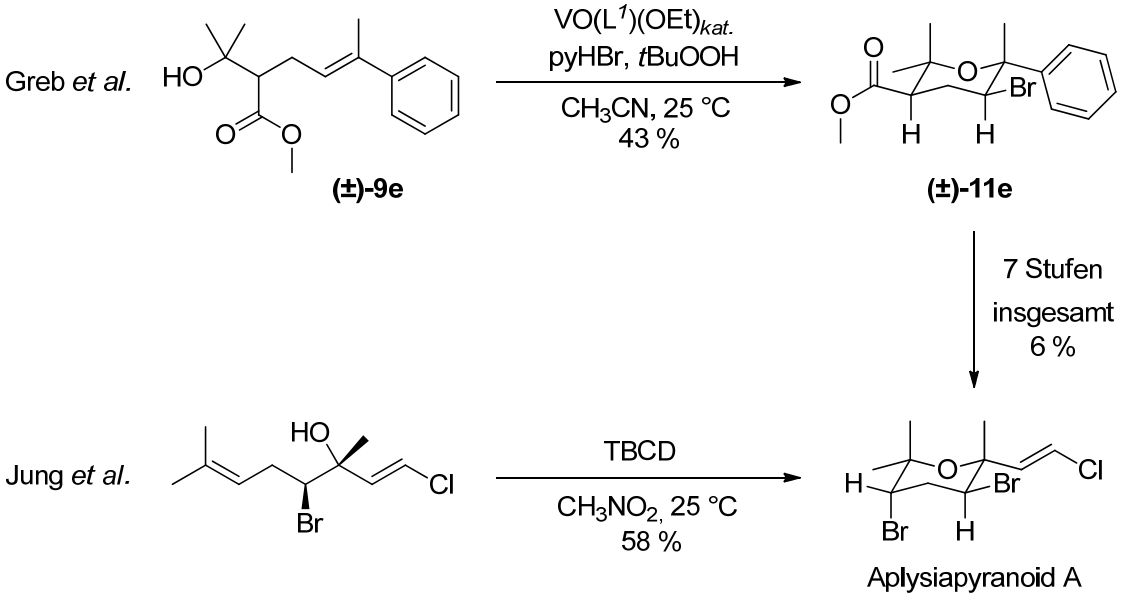
4.1 Zusammenfassung

Naturstoffanaloge 2,2,6,6-substituierte Tetrahydropyrane lassen sich als Hauptprodukte von Bromcyclisierungen δ,ε-ungesättigter Alkohole darstellen, welche in terminaler Position der Alken-Teilstruktur einen aromatischen Substituenten tragen. Durch die Modifikation gelingt es, die aus Wechselwirkung axial-ständiger Methyl-Substituenten im Übergangszustand der Ringschlussreaktion resultierenden Spannungsterme durch polare Effekte zu kompensieren. Fehlt eine dipolare Kompensation, so entstehen isomere Tetrahydrofurane als Hauptprodukte. Die Erkenntnisse dieser Studie fanden Eingang in die Synthese des hochsubstituierten marinen Naturstoffs Aplysiapyranoid A, dessen 2,2,3,5,6,6-substituiertes Tetrahydropyran-Grundgerüst sich durch 6-*endo*-selektive Bromcyclisierung in einer Ausbeute von 73 % darstellen ließ. Zur Erzeugung benötigter Bromäquivalente bewährte sich ein Verfahren, in dem Bromid mit *tert*-Butylhydroperoxid unter katalytischer Aktivierung durch Oxovanadium(V)-Komplexe oxidiert wurde. Die vorgestellte Totalsynthese für Aplysiapyranoide besitzt aufgrund ihrer breiten Variabilität deutliche Vorteile gegenüber anderen Verfahren und könnte somit für Struktur-Wirkungsbeziehungen von weiterführendem Interesse sein.

4.2 Wissenschaftlicher Hintergrund, Zielsetzung und Strategie

Die Tetrahydropyran-Grundstrukturen der Aplysiapyranoide A–D (vgl. Abb. 2.1, S. 14) lassen sich durch Elektrophil-induzierte Cyclisierungen tertiärer Alkohole an terminal zweifach substituierten Doppelbindungen darstellen. Alle existierenden Verfahren zum Aufbau entsprechend hochsubstituierter Verbindungen haben jedoch gemeinsam, dass die Selektivität für den 6-*endo*-Ringschluss und somit die Ausbeuten der Zielmoleküle niedrig sind.[1–6] Im Falle der Synthese von Aplysiapyranoid A nach Jung *et al.* liefert die finale Bromcyclisierung unter Verwendung von 2,4,4,6-Tetrabromo-2,5-cyclohexadienon in Nitromethan den gewünschten Naturstoff in einer Ausbeute von 58 % bei gleichzeitiger Bildung von 30 % des Tetrahydrofuran-Isomers (Schema 4.1, unten).[4] In einer alternativen Synthese des Naturstoffs, welche durch Greb *et al.* entwickelt werden konnte, wurde eine ähnliche Cyclisierungsreaktion durch *in situ*-

Generierung von Bromierungsäquivalenten unter Verwendung des Vanadium(V)-Schiffbasekomplexes VO(L^1)(OEt) mit *tert*-Butylhydroperoxid realisiert (Schema 4.1, oben).[2]



Schema 4.1 Bromcyclisierungsschritte der Totalsynthesen von Aplysiapyranoid A nach Greb (oben) und nach Jung (unten).[2][4]

Bei der Bromcyclisierung des substituierten 4-Pentenols **(±)-9e** gelang, unter Ausnutzung der polaren Effekte eines in 5-Position eingeführten Phenylrestes, zwar eine deutliche Reduktion der Fünfring-Bildung auf 15 %, jedoch blieb die Ausbeute des gewünschten Tetrahydropyrans **(±)-11e** mit 43 % unter den Erwartungen. Trotz der vergleichsweise niedrigen Massenbilanz gelang es nicht, weitere Nebenprodukte der Cyclisierung zu identifizieren, obwohl die Bildung offenkettiger Dibromide und Bromhydrine in analogen Reaktionen bereits beobachtet worden war.[7] Das erhaltene 6-*endo*-Cyclisierungsprodukt wurde im Rahmen der Totalsynthese von Aplysiapyranoid A anschließend durch einen Carboxyl-Brom-Austausch nach Barton-Hunsdiecker und Umwandlung des Phenylrestes in eine Formylgruppe mit abschließendem Einbau der Chlorvinylgruppe durch die Takai-Reaktion in die Zielverbindung überführt (Schema 4.1).[2] Inwieweit sich Spannungsenergien und polare Effekte im Detail auf Selektivitäten der Tetrahydrofuran- und Tetrahydropyran-Bildung in Bromcyclisierungsreaktionen derart hochsubstituierter Systeme auswirken, wurde jedoch im Rahmen der Totalsynthese von Aplysiapyranoid A nicht geklärt. Obgleich der generelle Bedarf zur Darstellung von Naturstoffen mit mehrfach substituierten Tetrahydropyrangerüsten in vergangenen Jahren weiter gestiegen ist, blieb die Frage nach der Systematik, welche dem 6-*endo*-selektiven Ringschluss tertiärer 4-Pentenole zugrunde liegt, weiterhin unbeantwortet.

Aufbauend auf den im letzten Kapitel vorgestellten Fortschritten im Bereich der oxidativen Bromierung[8] sollte die vorliegende Studie das inhärente Problem der Synthese 2,2,6,6-substituierter Tetrahydropyrane durch oxidative Alkenolcyclisierung, insbesondere in Bezug auf die Regioselektivität des Ringschlusses, erneut aufgreifen. Die Untersuchung zielte darauf ab, das Grundstrukturmotiv von 4-Pentenol (±)-**9e**, welches in der Arbeit von Greb *et al.* zur Darstellung des Aplysiapyranoids verwendet wurde,[2] durch Substituentenvariation an geeigneten Positionen abzuwandeln um strukturelle Faktoren und Reaktionsparameter abzuleiten, welche den 6-*endo*-selektiven Ringschluss begünstigen würden. Zur Optimierung der Reaktionskaskade aus Vanadium(V)-katalysierter Bromidoxidation mit *tert*-Butylhydroperoxid und nachfolgender Bromcyclisierungen sollten neben den Originalbedingungen der Aplysiapyranoid-Arbeit, unter Verwendung von Pyridiniumhydrobromid in Acetonitril, auch die neu entwickelte Methode mit β-Bromcarbonsäuren in Alkylcarbonat-Lösungen zum Einsatz kommen.[8][9] Darüber hinaus war von Interesse, inwieweit sich Spannungseffekte an Positionen 2 und 6 von axial zueinander orientierten Substituenten auf die Thermochemie der 5-*exo*- und 6-*endo*-Cyclisierung auswirken würden. Dieser Fragestellung sollte in einer theoretischen Studie in Kooperation mit Jens Hartung durch Untersuchung des Einflusses der relativen Anordnung von Methyl-Substituenten auf die freien Enthalpien von Tetrahydropyrangerüsten nachgegangen werden.

Zur Untersuchung und Optimierung der Selektivitäten für 6-*endo*-Bromcyclisierungen von hochsubstituierten 4-Pentenolen ergaben sich konkret folgende Aufgabenstellungen:

- Ausarbeitung effektiver Synthesen zur Darstellung eines Satzes von 4-Pentenolen mit unterschiedlichen Substituenten an den Positionen 1, 4 und 5.
- Untersuchung des Substituenteneinflusses in Alkenolen auf das 5-*exo*-/6-*endo*-Verhältnis in oxidativen Bromcyclisierungsreaktionen.
- Identifizierung kritischer Reaktionsparameter sowie Nebenprodukte bei der Synthese einer Tetrahydropyran-Vorstufe von Aplysiapyranoid A.
- Diskussion der erhaltenen Daten zur theoretischen Betrachtung von Substituenteneffekten auf die relativen Aktivierungsenergien von 6-*endo*-Bromcyclisierungen und Vergleich mit den Resultaten der experimentellen Selektivitätsstudien.

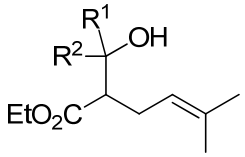
4.3 Ergebnisse und Diskussion

4.3.1 Systematik und Synthese δ,ε-ungesättigter Alkohole

Die für den präparativen Teil der Studie ausgewählten δ,ε-ungesättigten Alkohole können in zwei Gruppen unterteilt werden, welche im Folgenden als Prenyl-Typ und Styryl-Typ bezeichnet werden. Im Fall des Prenyl-Typs (Alkenole **9f–h**) sollte eine strukturelle Analogie zu Terpenen mit vergleichbarem Strukturmotiv hergestellt werden, während bei den Alkenolen des Styryl-Typs (Alkenole **9i–k**) die Bedeutung der aromatisch konjugierten Doppelbindung für die Reaktivität des Moleküls in Bromcyclisierungen herausgestellt werden sollte (Tabelle 4.1).

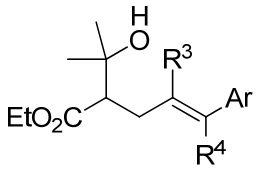
Tabelle 4.1 Substitutionsmuster ausgewählter Alkenolsubstrate **9f–k** für die Bromcyclisierungsstudie.

Prenyl-Typ



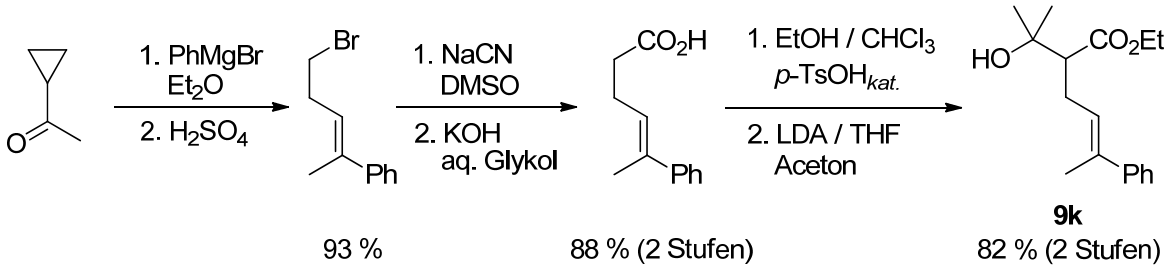
9	R^1	R^2
f	CH_3	CH_3
g	CH_3	H
h	H	H

Styryl-Typ



9	R^3	R^4	Ar
i	CH_3	H	Ph
j	H	CH_3	*p*-$MeOC_6H_4$
k	H	CH_3	Ph

Die Darstellung der racemischen Alkenole **9f–k** folgte einer allgemeinen Route, welche im Rahmen des Projekts ausgearbeitet wurde, und lieferte die gewünschten Zielverbindungen in Gesamtausbeuten von 19–67 %. Die neu entwickelte Synthese des für die Aplysiapyranoid-Darstellung notwendigen Alkenols **9k** löste das Problem der (*E*/*Z*)-Isomerisierung der früheren Methode[7] und lieferte das stereochemisch reine (*E*)-konfigurierte Produkt zudem in einer um 28 % höheren Ausbeute (Schema 4.2).

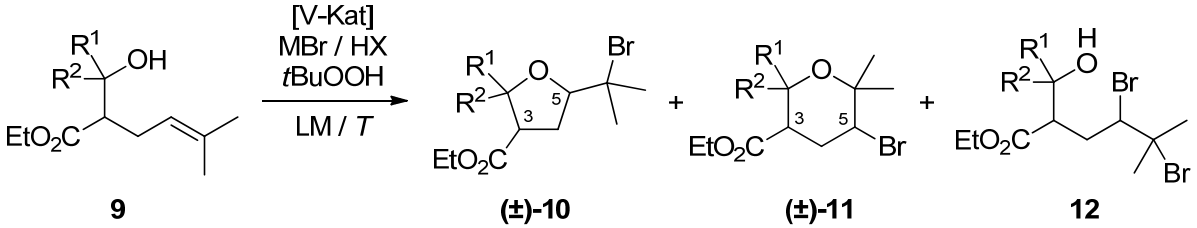


Schema 4.2 Syntheseroute des racemischen, (*E*)-konfigurierten Alkenolsubstrats **9k**.

4.3.2 Selektivitätsstudien und Parametervariation in Bromcyclisierungen

Im Rahmen der Bromcyclisierung des tertiären Prenyl-Typ-Alkenols **9f** wurden die vormals beschriebenen Bedingungen zur *in situ*-Oxidation von Bromid, ausgehend von Pyridiniumhydrobromid, *tert*-Butylhydroperoxid und katalytischer Mengen des Vanadium-Schiffbase-Komplexes VO(L^1)(OEt) in Acetonitril, weiterentwickelt und optimiert. Es zeigte sich, dass die Reaktionen unter Verwendung getrockneter Reagenzien und Lösungsmittel zu deutlich höheren Ausbeuten an isolierbaren Bromierungsprodukten führen (Tabelle 4.2).

Tabelle 4.2 Bromcyclisierung der Prenyl-Typ-Alkenole **9f–h** nach Vanadium(V)-katalysierter Oxidation von Bromid.



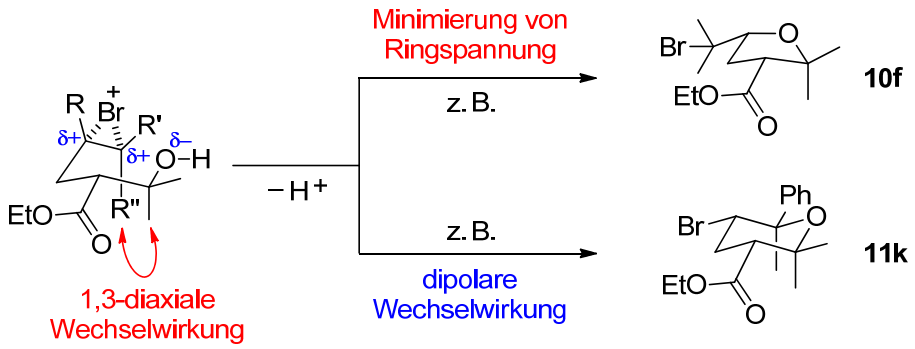
Eintrag	**9**	MBr / HX[a]	[V-Kat][b]	LM[c] / *T* [°C]	(±)-**10** / % (*cis*:*trans*)[d]	(±)-**11** / % (*cis*:*trans*)[d]	**12** / % (*dr*)[e]
1	**f**	py·HBr	–	CH_3CN /25	16 (67:33)	8 (71:29)	5 (58:42)
2	**f**	py·HBr	VO(L^1)(OEt)	CH_3CN/25	50 (69:31)	25 (79:21)	12 (59:41)
3	**f**	py·HBr	VO(L^2)(OEt)	CH_3CN / 25	43 (69:31)	19 (83:17)	27 (60:40)
4	**f**	NaBr / **6c**	VO(L^2)(OEt)	PC / 30	40 (70:30)	17 (83:17)	–[f]
5	**g**	NaBr / **6c**	VO(L^2)(OEt)	PC / 30	15 (–[g])	42 (–[g])	–[f]
6	**h**	NaBr / **6c**	VO(L^2)(OEt)	PC / 30	5 (50:50)	47 (68:32)	–[f]

[a] **6c** = 3-Brom-3-phenylpropionsäure. [b] 5 mol%. [c] LM = Lösungsmittel. [d] 3,5-*cis*:3,5-*trans* (^{1}H NMR). [e] Stereoisomere nicht zugeordnet. [f] Nicht gefunden. [g] Stereoisomere nicht zugeordnet.

Als Nebenprodukt der durchgeführten Bromcyclisierungen konnten dibromierte Alkenolsubstrate identifiziert werden. Die Entstehung des Dibromids **12f** ließ sich jedoch nach Verminderung der Bromidkonzentration durch Erhöhung der Lösungsmittelmenge und langsamer Zugabe des Pyridiniumhydrobromids deutlich zurückdrängen. Diese Variationen führten zu einer Steigerung der Ausbeute an bromierten O-Heterocyclen von 53 % auf 75 % bei gleichzeitiger Absenkung der Dibromidbildung von 25 % auf 12 %. In Verbindung mit den vorgenommenen Parametermodifikationen deutet die verbesserte Massenbilanz von 87 % darauf hin, dass die Minderung des Wassergehaltes eine wesentliche Komponente zur Steigerung von

Reaktivität und Selektivität der Umsetzungen ist. Der Einsatz des Piperidin-abgeleiteten Vanadium(V)-Komplexes VO(L^2)(OEt) brachte keine Verbesserung der Ausbeuten. Die bekannte Säure-katalysierte Untergrundreaktion ohne Vanadium-Katalysator lieferte nach 24 h einen Umsatz von 30 %. Bei Anwendung der neuen Methode mit β-Bromcarbonsäuren erwies sich die Verwendung der Zimtsäure-abgeleiteten 3-Brom-3-phenylpropionsäure (**6c**) als *in situ*-HBr-Donor in Propylencarbonat als vorteilhaft. Die Reaktion mit Alkenol **9f** lieferte in dieser Variante jedoch nur eine kombinierte Tetrahydropyran- und Tetrahydrofuran-Ausbeute von 57 %, wobei Dibromide hier nicht quantifiziert werden konnten, da polare Nebenprodukte bei dieser Methode nach der Extraktion mit Cyclohexan in der Propylencarbonat-Phase zurückbleiben. Kontrollreaktionen des Alkenols mit elementarem Brom oder NBS in Dichlormethan lieferten lediglich 28 % bzw. 37 % an bromierten O-Heterocyclen und waren damit deutlich weniger effektiv als die beiden oxidativen Bromierungsverfahren. Die höchste kombinierte Ausbeute bromierter Tetrahydrofuran- und Tetrahydropyranverbindungen (**10f** und **11f**) konnte durch langsames Zutropfen einer verdünnten Bromlösung zu einer Mischung von Alkenolsubstrat **9f** und Natriumhydrogencarbonat in Acetonitril erzielt werden und betrug hier 91 %.

Bei den Bromcyclisierungen von Alkenolen des Prenyl-Typs (**9f–h**) lässt sich mit sinkendem Substitutionsgrad in 1-Position eine klare Tendenz zur Tetrahydropyranbildung erkennen. Dieser Anstieg der 6-*endo*-Selektivität bei der Cyclisierung von tertiären zu primären Alkenolen kann mit sinkender sterischer Belastung des postulierten sesselartigen Übergangszustands durch Vermeidung 1,3-diaxialer Wechselwirkungen gedeutet werden (Schema 4.3, oben).

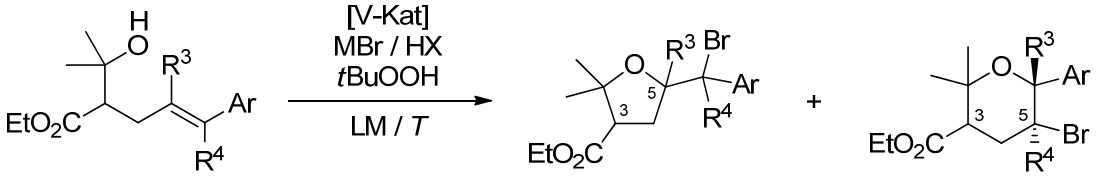


Schema 4.3 Modell zur Erklärung der Regioselektivität der intramolekularen Öffnung von γ-Hydroxypropyl-Bromoniumionen bei überwiegender Steuerung durch sterische (oben) oder polare Effekte (unten). (R = H oder CH_3; R' = H, CH_3 oder Ph; R'' = H oder CH_3).

Bezüglich der Stereoselektivität werden in den Bromcyclisierungen von **9f** und **9h** jeweils die thermodynamisch stabileren 3,5-*cis*-konfigurierten O-Heterocyclen *cis*-**10** und *cis*-**11** erhalten. Dieser Befund deutet auf eine thermodynamische Kontrolle des Reaktionsverlaufs hin, welcher allein durch das Substitutionsmuster des Substrats bestimmt wird. Da die Bromierung von Alkenol **9g** ein Gemisch von acht verschiedenen Isomeren lieferte, welche säulenchromatographisch nicht zu trennen waren, wurde hier lediglich das Verhältnis von Fünfring- zu Sechsring-Isomeren mittels NMR-Analyse bestimmt.

Die oxidativen Bromierungen tertiärer, Styrol-abgeleiteter Alkenole (**9i**–**k**) lieferten in Abhängigkeit der Positionierung einer Methylgruppe in der Alken-Teilstruktur entweder nur stereoisomere Tetrahydrofurane oder Tetrahydropyrane, zeigten jedoch insgesamt niedrigere Ausbeuten als Umsetzungen mit Substraten des Prenyl-Typs (Tabelle 4.3).

Tabelle 4.3 Bromcyclisierung von Styryl-Typ-Alkenolen (**9i**–**k**) nach Vanadium(V)-katalysierter Oxidation von Bromid.



9 **(±)-10** **(±)-11**

Eintrag	**9**	MBr / HX[a]	[V-Kat][b]	LM[c] / *T* [°C]	(±)-**10** / % (*cis*:*trans*)[d]	(±)-**11** / % (*cis*:*trans*)[d]
1	**i**	NaBr / **6c**	VO(L^2)(OEt)	PC / 30	57 (93:7)	–[e]
2	**j**	NaBr / **6c**	VO(L^2)(OEt)	PC / 30	–[e]	47 (53:47)
3	**k**	NaBr / **6c**	VO(L^2)(OEt)	PC / 30	–[e]	47 (77:23)
4	**k**	py·HBr	VO(L^1)(OEt)	CH_3CN / 25	–[e]	73 (76:24)

[a] **6c** = 3-Brom-3-phenylpropionsäure. [b] 5 mol%. [c] LM = Lösungsmittel. [d] 3,5-*cis*:3,5-*trans* (^{1}H NMR); 5,6-*trans*-Konfiguration für **11j** und **11f**. [e] Nicht gefunden (GC).

Die mit Abstand höchste Ausbeute von 73 % des für die Aplysiapyranoid-Synthese benötigten Heterocyclus **11k** konnte ebenfalls mit dem modifizierten Verfahren erzielt werden, in dem Pyridiniumhydrobromid und *tert*-Butylhydroperoxid unter trockenen Bedingungen in Gegenwart katalytischer Mengen des Schiffbase-Komplexes VO(L^1)(OEt) umgesetzt wurden (Tabelle 4.3, Eintrag 4).

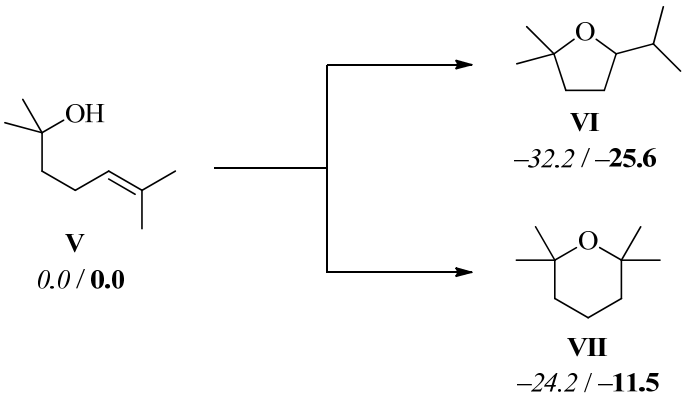
Die erhaltenen Ergebnisse weisen auf molekulares Brom als selektivitätsbestimmendes Reagenz und das Vorliegen eines Bromoniumion-Intermediats hin, welches durch Rückseitenangriff des Hydroxylsauerstoffs geöffnet wird. Demnach wird für diese Substrate ausschließlich das jeweils höher substituierte C-Atom der Aryl-stabilisierten Dreiringzwischenstufe angegriffen. Trotz vergleichbarer sterischer Voraussetzungen wie bei Cyclisierung des Prenyl-Typ-Alkenols **9f** führen die Umsetzungen der terminal Aryl-substituierten Alkenole **9j** und **9k** hier selektiv zu Tetrahydropyran-Produkten. Die Änderung der Selektivität kann dabei auf einen polaren Effekt des aromatischen Substituenten zurückgeführt werden, welcher die positive Ladung des Bromoniumions in benzylischer Position stabilisiert und so den Angriff des Hydroxyl-Sauerstoffs in diese Position dirigiert (Schema 4.3, unten). Die selektive Bildung des Fünfring-Derivates **10i** deutet darauf hin, dass hier der polare Effekt des Phenyl-Substituenten in der sekundären 5-Position nicht ausreicht um einen Angriff auf das tertiäre Zentrum des Bromoniumions zu verhindern.

Ein weiteres wichtiges Indiz für den postulierten Bromoniumion-Mechanismus liefert die relative Stellung von Substituenten in 5- und 6-Position der Tetrahydropyran-Produkte **11j** und **11k**. Die hier beobachtete *trans*-Konfiguration entsteht durch eine *anti*-Addition von Brom und dem intramolekularen Sauerstoff-Nukleophil an die (*E*)-konfigurierte Doppelbindung der eingesetzten Alkenole **9j** und **9k**. Die überwiegende Bildung 3,5-*cis*-konfigurierter O-Heterocyclen, welche auch in den Umsetzungen von Substraten des Prenyl-Typs beobachtet werden konnte, deutet wiederum auf thermodynamische Kontrolle im selektivitätsbestimmenden Reaktionsschritt hin.

Die Ergebnisse der experimentellen Studie zeigen, dass die aus präparativer Sicht interessantesten Selektivitäten für Bromcyclisierungen mit Alkenolen des Styryl-Typs zu erreichen waren, wohingegen Umsetzungen der Alkenole des Prenyl-Typs nur isomere Mischungen substituierter Tetrahydrofurane und Tetrahydropyrane lieferten. Die erhaltenen Resultate lassen somit den Schluss zu, dass polare Effekte in der intermediären Bromoniumion-Teilstruktur und sterische Effekte an den Reaktionszentren die wesentlichen Faktoren zur Beschreibung von Selektivitäten in Bromcyclisierungen substituierter 4-Pentenole sind.

4.3.3 Theoretische Betrachtung von Ringspannungseffekten in Dimethyl-substituierten Tetrahydropyranderivaten

Die in den experimentellen Selektivitätsstudien erhaltenen Daten weisen darauf hin, dass die Tendenz zur Bildung eines Tetrahydropyranprodukts in Bromcyclisierungen mit steigender sterischer Beanspruchung des sesselartigen Übergangszustands sinkt. Zum Vergleich dieser Ergebnisse mit theoretischen Modellstudien, wurden in Kooperation mit Jens Hartung Energieberechnungen unterschiedlich Methyl-substituierter O-Heterocyclen durchgeführt um den Einfluss sterischer Wechselwirkungen auf die Thermochemie zu untersuchen. Die Berechnung der Reaktionsenergien und der freien Reaktionsenthalpien für die Isomerisierung des hochsubstituierten 4-Pentenols **V** in das entsprechende Tetrahydrofuran **VI** und das Tetrahydropyran **VII** weisen auf eine deutliche energetische Bevorzugung der Fünfring-Bildung hin (Schema 4.4).



Schema 4.4 Berechnete Reaktionsenergien (Zahlen in Kursivschrift) und freie Reaktionsenthalpien ($\Delta G_{298.15}$, Zahlen in Fettdruck) für die Isomerisierung des Prenyl-Typ-Alkenols **V** zu Tetrahydrofuran **VI** und Tetrahydropyran **VII** (Methode: B3LYP/6-31+G**; Angaben in kJ mol^{-1}).[14]

Zur genaueren Untersuchung sterischer Substituenteneffekte auf 6-*endo*-Alkenolcyclisierungen wurden die relativen freien Enthalpien eines Satzes von Tetrahydropyranen mit je zwei in unterschiedlichen Positionen und Konfigurationen angeordneten Methyl-Substituenten berechnet und miteinander verglichen. Da Übergangszustände der nukleophilen Öffnung von Bromoniumionen spät auf der Reaktionskoordinate liegen, spiegeln die so ermittelten Spannungsenergien die Aktivierungsbarrieren der Übergangszustände von 6-*endo*-Bromcyclisierungen in relativer Weise wider. Die Auswertung der für den kompletten Satz Dimethyl-substituierter Tetrahydropyrane berechneten freien Enthalpien ergab den niedrigsten $G_{298.15}$-Wert

für das Isomer mit 2,6-*cis*-diäquatorial-positionierten Methylgruppen **VIIIa** (Abb. 4.1, links). Zur besseren Vergleichbarkeit wurden die berechneten $G_{298.15}$-Werte aller Dimethyl-substituierten Tetrahydropyrane in Relation zur freien Enthalpie dieses Isomers **VIIIa** angegeben.

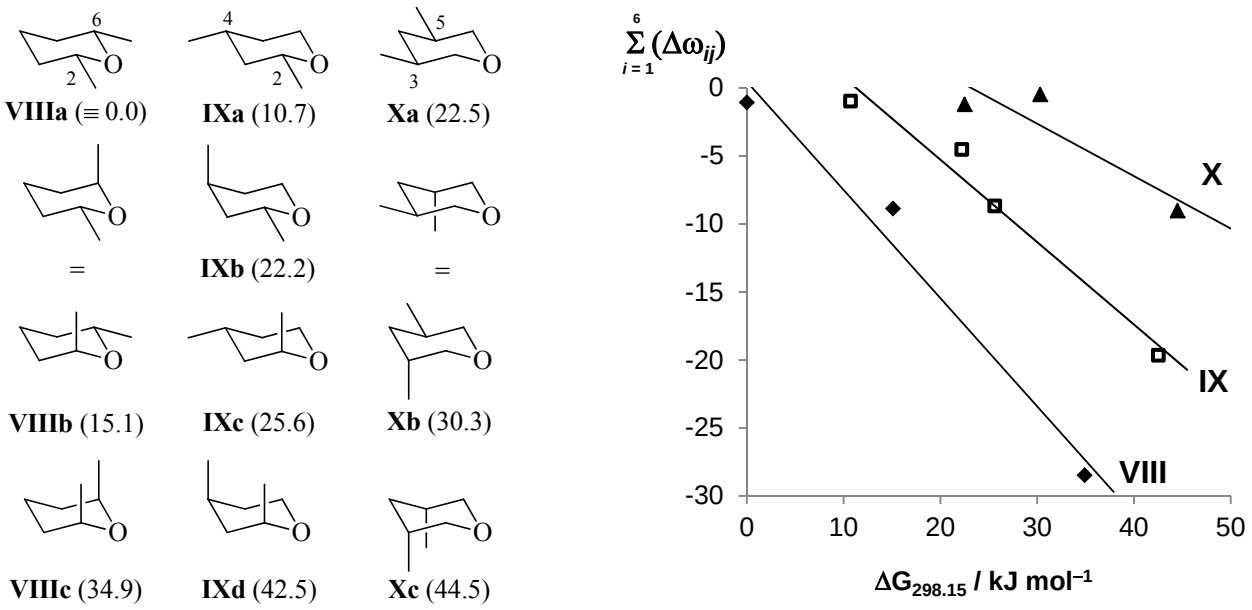


Abbildung 4.1 Auswahl Dimethyl-substituierter Tetrahydropyrane **VIII–X** und berechnete (B3LYP/6-31+G**) relative $G_{298.15}$-Werte in kJ mol^{-1} (links) und Korrelationsdiagramm der Summe von Torsionswinkeländerungen in Dimethyl-substituierten Tetrahydropyranen **VIII–X** gegenüber Tetrahydropyran (thp) [$\Sigma(\Delta\omega_{ij}) = \Sigma(|\omega_{ij}^{thp}|) - \Sigma(|\omega_{ij}^{\boldsymbol{n}}|)$] und relativer, freier Gibbs-Energien (rechts).[10]

Im Vergleich zur 2,6-konfigurierten Verbindung **VIIIa** war die geminale Anordnung der Methylgruppen in 2-Position (nicht gezeigt) in dem gewählten Modell um 19 kJ mol^{-1} ungünstiger. Der allgemeine Trend der freien Enthalpien folgt der relativen Anordnung der beiden Methyl-Substituenten in der Reihe diäquatorial < geminal < äquatorial/axial < diaxial, wobei innerhalb jeder Kategorie die Enthalpien mit sinkendem Abstand der Methyl-Kohlenstoffatome ansteigen. Weiterhin kann ein deutliches Ansteigen der $G_{298.15}$-Werte beobachtet werden, je weiter die Substituenten vom endocyclischen Sauerstoffatom entfernt liegen. Zur Korrelation berechneter geometrischer Parameter mit freien Enthalpien wurde zudem eine Auftragung der Summe der endocyclischen Torsionswinkeländerungen (im Vergleich zu unsubstituiertem Tetrahydropyran) gegen die ermittelten $\Delta G_{298.15}$-Werte durchgeführt, welche für die drei Sätze von Strukturen mit relativer 1,3-Methyl-Substitution in erster Näherung jeweils

lineare Abhängigkeit zeigte (Abb. 4.1, rechts). Aus dem Abszissenabschnitt der Korrelationsgeraden lassen sich relative Spannungsterme entnehmen, die wiederum als eine sterische Grundlast des vorliegenden Substitutionsmusters gedeutet werden können. Diese steigt in der Reihe der Dimethyl-substituierten Tetrahydropyrane mit relativer 1,3-Anordnung, ebenfalls mit wachsendem Abstand zum Ringsauerstoff, entlang der Positionskombinationen 2,6 < 2,4 < 3,5.

Zusammenfassend zeigen die erhaltenen Ergebnisse der Modellstudie, dass vor allem axiale Substituenten in relativer 1,3-Anordnung die Bildung von Tetrahydropyranstrukturen negativ beeinflussen und die Cyclisierung aufgrund auftretender Ringspannungsterme in Richtung Fünfring-Bildung dirigieren. Zur Kompensation der energetischen Benachteiligung derart hochsubstituierter Tetrahydropyrane ist darum eine zusätzliche Triebkraft, beispielsweise in Form von polaren Effekten an der Bromoniumion-Teilstruktur, notwendig um synthetisch verwertbare Selektivitäten in Bromcyclisierungen zu erzielen.

4.4 Ausblick

Die vorliegende Arbeit lieferte wichtige Erkenntnisse über die Abhängigkeit der Selektivität in oxidativen Bromcyclisierungsreaktionen von Anzahl und Stellung der Substituenten eingesetzter 4-Pentenolsubstrate. Die erhaltenen Resultate sind für die Planung zukünftiger Naturstoffsynthesen mit O-heterocyclischen Fünf- oder Sechsring-Strukturen von großem Nutzen und tragen zum tieferen Verständnis der Problematik bei. Ein überraschendes Ergebnis der Studie war die selektive Bildung des Tetrahydrofuranderivats **10i** aus dem Styryl-Typ-Alkenol **9i**, welches durch den intramolekularen Angriff des Hydroxylsauerstoffs am Methyl-substituierten, tertiären Kohlenstoff der Bromoniumion-Zwischenstufe zustande kommt. Unter Berücksichtigung dieses Befunds wären ergänzende Untersuchungen zu den Auswirkungen einer Substituentenvariation in Position 4 des Alkenols auf das 5-*exo*-/6-*endo*-Verhältnis der Cyclisierung ein vielversprechendes Projekt. Durch die Einführung elektronegativer Substituenten, welche sich nachteilig auf eine Öffnung des intermediären Bromoniumions an dieser Stelle auswirken sollte, könnte so beispielsweise die Präferenz für die Bildung von Tetrahydropyranringen weiter gesteigert werden, vorausgesetzt, die Alkenoldoppelbindung ist noch ausreichend reaktiv für die elektrophile Addition von Brom. Eine weitere Variation von Substituenten in 5-Position des Alkenols könnte klären, ob neben untersuchten Aryl-Substituenten auch andere Gruppierungen mit +I- und/oder +M-Effekt [zum Beispiel: $-OSi(CH_3)_3$, $-SCH_3$, $-OCH_3$ oder $-N(CH_3)_3$] zu einer noch stärkeren Steuerung der 6-*endo*-Selektivität befähigt sind, welche beispielsweise die Synthese von Tetrahydropyran-

derivaten aus Alkenolen des Typs **9i** gestatten würden. Zusätzlich wäre hierbei noch interessant zu klären, inwiefern sich ein möglicherweise durch den Substituenten hervorgerufener anomerer Effekt auf die Produktselektivitäten auswirkt. Zur Steuerung von *cis*/*trans*-Selektivitäten in Bromcyclisierungsreaktionen könnten ebenfalls anomere Effekte im Übergangszustand der 6-*endo*-Cyclisierung dienen, welche durch die Einführung geeigneter Substituenten in 1-Position der 4-Pentenole induziert werden könnten. Ein anderes, sehr ambitioniertes Innovationsgebiet ist die Realisierung von stereoselektiven Bromcyclisierungsreaktionen substituierter 4-Pentenole. Da die Bromierung der Doppelbindung selbst nicht durch die zur Bromidoxidation verwendeten Vanadium(V)-Komplexe gesteuert wird, ist der Einsatz von chiralen Metallkatalysatoren auf dieser Stufe nicht zielführend. Eine Möglichkeit in diesem System dennoch Stereoselektivitäten zu induzieren, wäre der Einsatz chiraler Auxiliare im Rahmen einer Organokatalyse. Dieser Ansatz führte bereits in verschiedenen Arbeiten zu enantioselektiven Halolactonisierungsreaktionen substituierter 4-Pentencarbonsäuren zum Erfolg, welche als Grundlage für eine Übertragung des Prinzips auf 4-Pentenolsubstrate dienen könnten.[11–14] Da die Probleme mit mangelnden Selektivitäten und Reaktivitäten bei Bromcyclisierungsreaktionen zur Darstellung 2,2,6,6-substituierter Tetrahydropyranderivate durch die vorgestellten Methoden beherrschbar geworden sind, scheint das Verfahren nun geeignet für eine breitere Anwendung in der Synthese vergleichbarer Naturstoffe zu sein. Die Entwicklung einer ähnlich ausgereiften Prozedur zur katalytischen Chloridoxidation wäre in diesem Zusammenhang ein weiterer Meilenstein, da mit Hilfe eines solchen Verfahrens, aufbauend auf der hier beschriebenen und weiter modifizierten Totalsynthese von Aplysiapyranoid A, die chlorierten Derivate Aplysiapyranoid C und D (vgl. Abb. 2.1, S. 14) in einfacher Weise dargestellt werden könnten.

4.5 Literatur

[1] M. Hashimoto, T. Kan, K. Nozaki, M. Yanagiya, H. Shirahama, T. Matsumoto, *J. Org. Chem.* **1990**, *55*, 5088–5107.

[2] J. Hartung, M. Greb, *Tetrahedron Lett.* **2003**, *44*, 6091–6093.

[3] C. A. Broka, Y. T. Lin, *J. Org. Chem.* **1988**, *53*, 5876–5885.

[4] M. E. Jung, D. C. D'Amico, W. Lew, *Tetrahedron Lett.* **1993**, *34*, 923–926.

[5] M. E. Jung, B. T. Fahr, D. C. D'Amico, *J. Org. Chem.* **1998**, *63*, 2982–2987.

[6] M. E. Jung, W. Lew, *J. Org. Chem.* **1991**, *56*, 1347–1349.

[7] M. Greb, *Dissertation*, Universität Würzburg, **2004**.

[8] O. Brücher, J. Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.

[9] D. Wischang, O. Brücher, J. Hartung, *Coord. Chem. Rev.* **2011**, *255*, 2204–2217.

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

[11] C. K. Tan, L. Zhou, Y. Y. Yeung, *Synlett* **2011**, 1335–1339.

[12] D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300.

[13] W. Zhang, S. Q. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. P. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665.

[14] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem. Int. Ed.* **2010**, *49*, 9174–9177.

4.6 Forschungsartikel

Controlling 6-*endo*-Selectivity in Oxidation/Bromocyclization Cascades for Synthesis of Aplysiapyranoids and other 2,2,6,6-substituted Tetrahydropyrans.

Oliver Brücher, Uwe Bergsträßer, Harald Kelm, Jens Hartung, Marco Greb, Ingrid Svoboda, Hartmut Fuess, *Tetrahedron* **2012**, *68*, 6968–6980.

Tetrahedron 68 (2012) 6968–6980

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Controlling 6-*endo*-selectivity in oxidation/bromocyclization cascades for synthesis of aplysiapyranoids and other 2,2,6,6-substituted tetrahydropyrans

Oliver Brücher [a], Uwe Bergsträßer [a], Harald Kelm [a], Jens Hartung [a,*], Marco Greb [b], Ingrid Svoboda [c], Hartmut Fuess [c]

[a] *Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany*
[b] *Institut für Organische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany*
[c] *Technische Universität Darmstadt, Strukturforschung, FB11 Material- und Geowissenschaften, Petersenstr. 23, D-64287 Darmstadt, Germany*

ARTICLE INFO

Article history:
Received 17 February 2012
Received in revised form 1 May 2012
Accepted 3 May 2012
Available online 11 May 2012

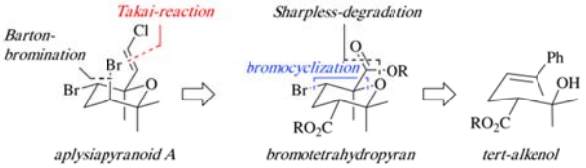
Keywords:
Alkyl hydroperoxide
Bromocyclization
Bromoperoxidase model
Marine natural product
Molecular modeling
Oxidation catalysis
Stereoselective synthesis
Strain
Terpenol
Vanadium(V) complex
X-ray crystallography

ABSTRACT

A cascade, composed of (i) oxovanadium(V)-catalyzed oxidation of bromide by *tert*-butyl hydroperoxide and (ii) stereoselective 6-*endo*-bromocyclization, affords 3-bromo-2-aryl-2,6,6-trimethyltetrahydropyrans from styrene-type tertiary alkenols in synthetically useful yields. (*E*)-Alkenols add the bromo- and the alkoxy substituent anti-selectively across the double bond, indicating a bromonium ion-mechanism for the ring closure. 6-*endo*-control of the alkenol cyclization thereby arises from the polar effect of the aryl substituent. Two methyl substituents bound to the alkene terminus are not similarly able to favor 6-*endo*-cyclization, because strain arising from methyl group repulsion, as the bromonium-activated π-bond and the hydroxyl oxygen approach, directs bromocyclization of tertiary prenyl-type substrates toward tetrahydrofuran formation. A hexasubstituted bromotetrahydropyran prepared from the oxidation/bromocyclization cascade served as starting material for synthesis of racemic aplysiapyranoid A, in a sequence of free radical and polar functional group interconversion.

1. Introduction

Aplysiapyranoids are rare tetrahydropyran-derived natural products, which were isolated from the midgut gland of the sea hare *Aplysia kurodai*.[1,2] The structure of the aplysiapyranoids shows a remarkable accumulation of carbon- and halogen-substituents (cf. Scheme 1).[3] Nothing so far is known about the physiological role of the aplysiapyranoids and little about their medicinal chemical properties.[1]



Scheme 1. Retrosynthetic scheme and named reactions for synthesis of the marine natural product aplysiapyranoid A.

The challenge to prepare larger quantity of the aplysiapyranoids for testing biological properties was taken on by comparatively few groups. All reported strategies thereby relied on 6-*endo*-bromocyclization of appropriately substituted alkenols, for constructing the highly functionalized tetrahydropyran core. Jung and coworkers, for example, prepared accordingly aplysiapyranoid A, and derivatives named C and D, having a chlorine instead of a bromine atom attached next to the chlorovinyl group (for aplysiapyranoid A see Scheme 1).[4–6] The yield of 6-*endo*-bromocyclized products remained in all instances low. We therefore developed an alternative approach, trying to improve the yield of tetrahydropyran formation by increasing dipolar attraction between the reacting entities.[7] None of the strategies, however, satisfactorily provided a solution to the problem of the inherent low 6-*endo*-selectivity in synthesis of 2,2,6,6-substituted tetrahydropyrans from *tert*-alkenols, an objective researchers had pursued from the days of the first venustatriol-synthesis.[8–11]

In a more recent project we had developed an efficient new approach for synthesis of bromotetrahydropyrans from acid labile alkenols via oxidative bromocyclization.[12–14] The convincing chemoselectivity of this method prompted us to address the question

* Corresponding author. Tel.: +49 631 205 2431; fax: +49 631 205 3921; e-mail address: hartung@chemie.uni-kl.de (J. Hartung).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.05.013

of 6-*endo*-control in bromocyclization of tertiary δ,ε-unsaturated alcohols again. We wanted to understand why the strategy to bromocyclize tertiary alkenols bearing two methyl substituents at the terminal alkene carbon (prenyl-type alkenol, vide infra) fails[8,9,15,16] to direct ring closures of tertiary alkenols exclusively toward the 6-*endo*-mode of cyclization, and what functional group would be needed to do so.

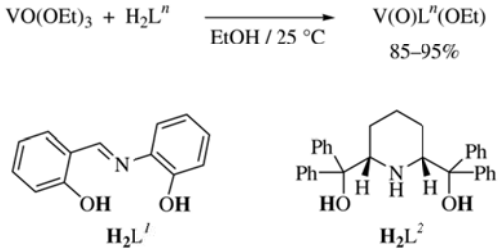
The major finding from the present study shows that an aryl group in combination with a methyl substituent at the terminal alkene carbon (styrene-type alkenol, vide infra) directs bromocyclization of tertiary alkenols almost 6-*endo*-specifically. Two methyl substituents are not able to similarly control regioselectivity, because strain arising from methyl group repulsion, as the reacting entities approach for intramolecular carbon–oxygen bond formation, changes selectivity in tertiary alkenol cyclization toward tetrahydrofuran formation (Section 2.4). A hexasubstituted bromotetrahydropyran prepared from the oxidation/bromocyclization cascade served as starting material for synthesis of racemic aplysiapyranoid A, in a sequence of free radical and polar functional group interconversion (Section 2.5).

2. Results and interpretation

2.1. Vanadium(V)-complexes

In our group, we use catalysis by transition metal complexes to convert alkenols via oxidation/cyclization cascades into bromoethers[12,17–20] (Scheme 2). The preferred oxidant for oxidative bromination in polar aprotic solvents is *tert*-butyl hydroperoxide. *tert*-Butyl hydroperoxide readily dissolves in dialkyl carbonates or acetonitrile and binds at ambient temperature to oxovanadium(V) complexes, for converting the nucleophilic peroxide into a strongly electrophilic reagent that is able to oxidize bromide into molecular bromine.[12] Turnover of bromide and *tert*-butyl hydroperoxide for bromine generation consumes one proton per catalytic cycle. For practical reasons we used pyridinium hydrobromide (pyHBr)[21,22] or β-bromocinnamic acid (BCA)[12,23,24] as combined proton and bromide sources (Scheme 2).[25] β-Bromocinnamic acid decomposes into styrene, carbon dioxide, bromide, and a proton, if treated at 30 °C with a catalytic amount of bromide in propylene carbonate (PC). The rate of BCA-fragmentation under such conditions is close to the rate of bromide oxidation, which prevents reaction mixtures from becoming notably acidic. Pyridinium hydrobromide, on the other hand, considerably acidifies reaction mixtures.[12]

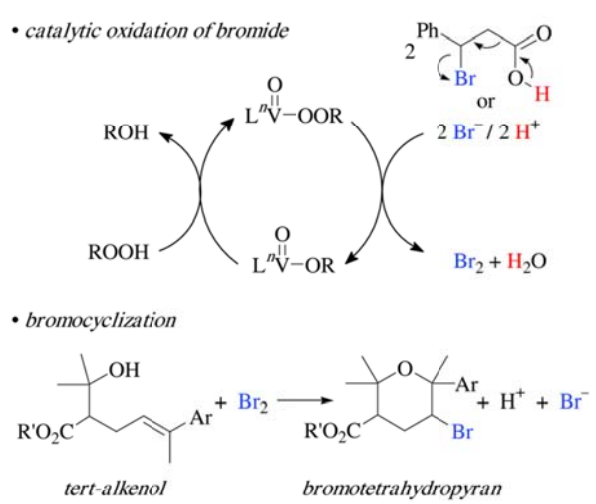
For peroxide activation, we use neutral oxovanadium(V) complexes of the general formula V(O)L(OEt), where L^{2-} denotes a dibasic tridentate auxiliary with two anionic oxygen donor atoms and one neutral nitrogen-donor atom (Scheme 3).[12] From a structure reactivity survey, we selected Schiff-base derived iminodiol[26] H_2L^1 and 2,6-substituted piperidine[27] H_2L^2 as ligands to prepare oxidation catalysts suitable for the present study. Both oxovanadium complexes were prepared by transesterifying triethyl vanadate by diols H_2L^1 or H_2L^2 in a solution of boiling ethanol.[12,22,28] The synthesis affords dark brown Schiff-base complex V(O)L^1(OEt) in 95% yield, and pale yellow piperidine-derived complex V(O)L^2(OEt) in 85% yield. The Schiff-base complex is the thermochemically more stable reagent and the piperidine complex the more reactive and selective catalyst for *tert*-butyl hydroperoxide activation.



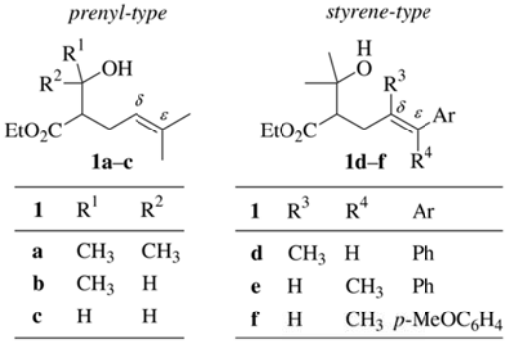
Scheme 3. Synthesis of oxovanadium compounds V(O)L^n(OEt) (95% for n=1, 85% for n=2) from auxiliaries H_2L^1 and H_2L^2 [acidic protons that are substituted by $VO(OEt)^{2+}$ in the course of complex formation are printed in bold; V(O)L^1(OEt) crystallizes as EtOH-adduct from ethanolic solution].[12,28]

2.2. δ,ε-Unsaturated alcohols

To identify factors that control 6-*endo*-selectivity in oxidative bromocyclization of alkenols, we prepared substrates that according to our systematic were subdivided into prenyl-type alkenols (**1a**–**c**), due to structural analogy to the terpenes,[29] and styrene-type alkenols (**1d**–**f**), having the alkenol carbon–carbon double bond substituted by an aryl group (Fig. 1).



Scheme 2. Catalytic cycle for vanadium(V)-catalyzed bromide oxidation by *tert*-butyl hydroperoxide for bromine formation (top; R=^{t}Bu, n=1–2, cf. Scheme 3),[12] and its use in synthesis of bromotetrahydropyrans (bottom; R′=alkyl, Ar=e.g., Ph, *p*-$MeOC_6H_4$).

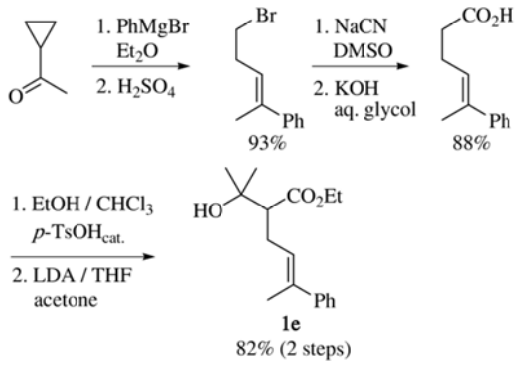


1	R^1	R^2
a	CH_3	CH_3
b	CH_3	H
c	H	H

1	R^3	R^4	Ar
d	CH_3	H	Ph
e	H	CH_3	Ph
f	H	CH_3	*p*-$MeOC_6H_4$

Fig. 1. Indexing of prenyl- and styrene-type δ,ε-unsaturated alcohols to explore systematics of 6-*endo*-selectivity in bromocyclization.

Synthesis of racemic alkenols **1a**–**f** followed a route, that is, exemplified for styrene derivative **1e** in Scheme 4. The procedure solved the inherent problem of (*E*)/(*Z*)-isomerization[7] of alkenols **1e** and **1f**, and affords stereochemically homogeneous products with respect to π-bond configuration. We furthermore observed



Scheme 4. Preparation of styrene-type alkenol **1e** as starting material for synthesis of aplysiapyranoid A (cf. Sections 2.3 and 2.5).

isomerization at the carbon–carbon double bond, if esterification in synthesis of anisole derivative **1f** is performed with ethanol and *p*-toluenesulfonic acid, instead of ethanol in combination with dicyclohexylcarbodiimide.

2.3. Oxidation catalysis

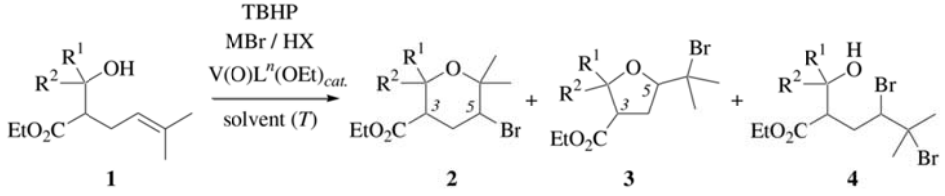
2.3.1. Prenyl-type alkenols. For oxidative bromocyclization of tertiary prenyl-type alkenols by pyridinium hydrobromide and *tert*-butyl hydroperoxide, we modified conditions described[22] for synthesis of cyclic bromoethers from primary and secondary 4-pentenols previously. The modifications relate to exclusion of moisture by drying V(O)L^1(OEt), pyridinium hydrobromide, *tert*-butyl hydroperoxide, and the solvent acetonitrile. We furthermore performed the oxidation/bromocyclization cascade in an atmosphere of dry nitrogen instead of air and lowered the reactant concentration. Finally, we added smaller portions of pyridinium hydrobromide over a longer period of time. These adaptions improved yields of bromoethers **2a** and **3a**, and lowered the fraction of unwanted dibromoalcohol **4a**. The total yield of organobromines increased from 78% to 87% (entry 2, Table 2). In controls we noticed that pyridinium hydrobromide is able to activate *tert*-butyl hydroperoxide for oxidative alkenol bromination, however, at a considerably lower rate than V(O)L^1(OEt) (Table 1, entry 1).[22] A change of vanadium catalyst from Schiff-base complex V(O)L^1(OEt) to piperidine derivative V(O)L^2(OEt) caused the yields of products **2**–**4** to become smaller, but also allowed to use non-toxic propylene carbonate as solvent (Table 1, entries 3–4). In solutions of propylene carbonate, the preferred in situ hydrogen bromide source is a buffer composed of sodium bromide and β-bromocinnamic acid. In such solutions, no bromide oxidation by *tert*-butyl hydroperoxide occurs, unless a Lewis-acid, such as V(O)L^2(OEt), is added.[12] For work-up, products **2a** and **3a**, styrene (~10%), and styrene-derived bromides were extracted from the reaction mixture by cyclohexane, which was followed by chromatographic purification.

As control, to compare efficiency of alkenol bromination from vanadium-catalyzed oxidations to other methods, we treated alkenol **1a** with more traditional reagents, such as *N*-bromosuccinimide or molecular bromine. The highest yields (91%) of bromoethers **2a** and **3a** thereby were obtained by treating alkenol **1a** with a mixture composed of molecular bromine and sodium hydrogen carbonate in acetonitrile. The poorest yields (37–38%) of **2a** and **3a** taken together were gained from reactions between substrate **1a** and either *N*-bromosuccinimide or bromine in dichloromethane (Supplementary data). By taking toxicological aspects into account, we decided to use sodium bromide, β-bromocinnamic acid, and *tert*-butyl hydroperoxide in propylene carbonate as standard combination for supplementing the systematic on regiocontrol in alkenol bromocyclization.

Treatment of secondary prenyl-type alkenol **1b** and primary derivative **1c** under conditions defined as standard in the previous section provided a ratio of tetrahydropyran **2b** and tetrahydrofuran **3b** of 74:26 (entry 5 in Table 1) from secondary substrate **1b**, and a 90/10-mixture of tetrahydropyran **2c** versus tetrahydrofuran **3c** from primary alkenol **1c** (entry 6 in Table 1).

Analysis of the bromocyclization products by GC–MS and NMR showed that eight products are formed from secondary prenyl-type alkenol **1b** and four from **1c**. Structural identification of bromoethers **2c** and **3c** was feasible on the basis of one and two-dimensional NMR-spectroscopy, including NOESY-spectroscopy. Assignment of constitution and configuration of products **2b** and **3c** was complicated by the existence of an additional stereocenter. In the course of data analysis, we found that resonances of methyl protons in

Table 1
Bromocyclization of prenyl-type alkenols **1a**–**c** in vanadium-catalyzed oxidations[a]



Entry	**1**–**4**	MBr/HX	V(O)L^n(OEt)	Solvent[b]/°C	**2**/% (*cis*/*trans*)[c]	**3**/% (*cis*/*trans*)[c]	**4**/% (dr)[d]
1	**a**	pyHBr	None	CH_3CN/25	8 (71:29)	16 (67:33)	5 (58:42)
2	**a**	pyHBr	V(O)L^1(OEt)	CH_3CN/25	25 (79:21)	50 (69:31)	12 (59:41)
3	**a**	pyHBr	V(O)L^2(OEt)	CH_3CN/25	19 (83:17)	43 (69:31)	27 (60:40)
4	**a**	NaBr/BCA[e]	V(O)L^2(OEt)	PC/30	17 (83:17)	40 (70:30)	—[f]
5	**b**	NaBr/BCA[e]	V(O)L^2(OEt)	PC/30	42 (—[g])	15 (—[g])	—[f]
6	**c**	NaBr/BCA[e]	V(O)L^2(OEt)	PC/30	47 (68:32)	5 (50:50)	—[f]

[a] V(O)L^n(OEt) (5 mol %); for structure formulas of ligands H_2L^1 and H_2L^2 refer to Scheme 3; quantitative conversion of **1**, except of entry 1 (70% conversion).
[b] PC=propylene carbonate.
[c] 3,5-*cis*/3,5-*trans* (^{1}H NMR).
[d] Diastereomeric ratio; stereoisomers not further assigned.
[e] BCA=β-bromocinnamic acid.
[f] Not detected.
[g] Stereoisomers not assigned (see text).

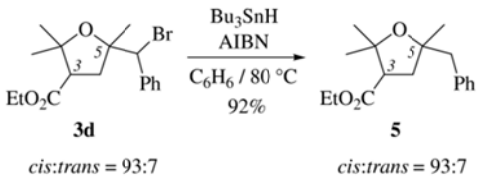
positions 2 and 6 of bromotetrahydropyrans **2a** (1.32–1.43 ppm) and **2c** (1.36–1.39 ppm) are distinctively shifted from those of exocyclic methyl groups in bromotetrahydrofurans **3a** (1.69–1.74 ppm) and **3c** (1.70–1.76 ppm; shift data referring to $CDCl_3$ as solvent). We therefore assigned methyl resonances between 1.68 and 1.77 ppm to the four stereoisomers of bromotetrahydrofuran **3b**. The major bromocyclization product of alkenol **1b**, which was separated by chromatography, shows a characteristic doublet at 1.13 ppm, and two similarly diagnostic singlets at 1.36 and 1.42 ppm for the methyl protons. The protons attached to C4 were sufficiently shift-dispersed in a solution of C_6D_6 to show a baseline-separated quartet (J=13 Hz) at 2.36 ppm for one of the protons and a double doublet for H-5 (J=13 and 4 Hz). From this information we derived that the major product obtained from bromocyclization of secondary alkenol **1b** is a tetrahydropyran, having the bromo-, methyl-, and ethoxycarbonyl substituent positioned equatorially, that is, *rel*-(2*R*,3*R*,5*S*)-5-bromo-3-ethoxycarbonyl-2,6,6-trimethyl-tetrahydropyran *rel*-(2*R*,3*R*,5*S*)-(**2b**).

Regarding stereoselectivity, the oxidation/bromocyclization cascade affords 3,5-*cis*-isomers of bromotetrahydropyrans **2a–c** and bromotetrahydrofurans **3a–c** as major isomers. For both classes of cyclic ethers, the 3,5-*cis*-arrangement of substituents is favored on the basis of strain and thus steric effects. We therefore concluded that stereoselectivity of the alkenol ring closures described above is governed by thermodynamic effects (vide infra).

2.3.2. Styrene-type alkenols. Oxidation/bromocyclization cascades of styrene-type alkenols provide tetrahydrofuran **3d** from β-methylstyrene derivative **1d**, and tetrahydropyrans **2e–f** from α-methyl styrene derivatives **1e–f** (entries 1–4 in Table 2). If judged by efficiency alone, the most convincing result for synthesis of bromotetrahydropyran **2e** (73%), a compound needed in Section 2.5 for synthesis of aplysiapyranoids, was obtained from oxidative bromination of **1e** using pyridinium hydrobromide, *tert*-butyl hydroperoxide, catalytic amounts of Schiff-base complex $V(O)L^1(OEt)$ (entry 4 in Table 2) and the conditions advanced in this study for bromocyclization of **1a**.

associated with the ethoxycarbonyl- and the bromosubstituent compares to the selectivity found in bromocyclization of prenyl-type alkenols, and points to thermodynamic control in the selectivity determining step.

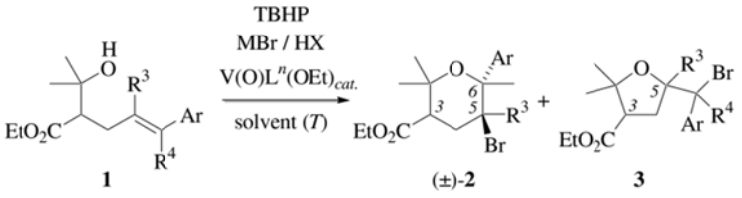
From NMR-spectroscopic analysis of the product obtained from bromocyclization of styrene-type alkenol **1d**, ambiguity remained, whether tetrahydropyran **2d** or tetrahydrofuran **3d** had been formed as 93/7-mixture of stereoisomers. We therefore subjected the latter product to a bromine/hydrogen-exchange using tributylstannane and 10 mol % of azobisisobutyronitrile (AIBN) in boiling benzene (Scheme 5). The reaction afforded product **5** in 92% yield, again, as a 93/7-mixture of stereoisomers. The proton-NMR of **5** shows doublets at 2.94 ppm and 2.91 ppm that are not present in the bromocyclization product, and a singlet at 5.00 ppm ($CDCl_3$) for the latter, that is, not found in the spectrum of **5**. All other resonances experience an upfield shift without changing fine structures, comparing the spectra of the starting alkyl bromide and **5**. From these experimental details we concluded that the product of bromocyclization of β-methylstyrene-type alkenol **1d** is tetrahydrofuran **3d**.



Scheme 5. Bromine/hydrogen exchange for synthesis of tetrahydrofuran **5** from bromocyclization product **3d**.

The major isomer of **3d** crystallizes from a solution of $CDCl_3$ and was investigated by X-ray diffraction to determine relative configuration of stereocenters at C5 and C1′ (Fig. 2). The crystal structure shows relative 5*R*,1′*S*-configuration, which is in line with anti-selective addition of the bromo- and the alkoxy substituent across the (*E*)-double bond in **1d**. Further structural details relevant for discussing strain effects associated with close contacts between

Table 2
Bromocyclization of styrene-type alkenols **1d–f** in vanadium-catalyzed oxidations



Entry	1–3	MBr/HX	$V(O)L^n(OEt)$[a]	Solvent[b]/°C	(±)-**2**/% (*cis*/*trans*)[c]	**3**/% (*cis*/*trans*)[c]
1	**d**	NaBr/BCA[d]	$V(O)L^2(OEt)$	PC/30	—[e]	57 (93:7)
2	**e**	NaBr/BCA[d]	$V(O)L^2(OEt)$	PC/30	47 (77:23)	—[f]
3	**e**	pyHBr	$V(O)L^1(OEt)$	CH_3CN/25	73 (76:24)	—[f]
4	**f**	NaBr/BCA[d]	$V(O)L^2(OEt)$	PC/30	47 (53:47)	—[f]

[a] $V(O)L^n(OEt)$ (5 mol %); for structure formulas of auxiliaries H_2L^1–H_2L^2 refer to Scheme 3.
[b] PC=propylene carbonate.
[c] 3,5-*cis*/3,5-*trans* (^{1}H NMR); 5,6-trans-configuration for **2e** and **2f**.
[d] BCA=β-bromocinnamic acid.
[e] Not detected (NMR).
[f] Not detected (GC).

Stereochemical analysis shows that an (*E*)-configuration in **1e** and **1f** is copied into trans-configuration of substituents at carbons 5 and 6 in tetrahydropyrans **2e** and **2f**. The mechanism that stereochemically explains this selectivity is the anti-addition of bromine and the alkoxy substituent across the (*E*)-double bond, according to a bromonium ion pathway. The cis-configuration carbon substituents in proximal positions to the endocyclic oxygen (Section 2.4) are depicted in Fig. 2 (red rectangle).

2.3.3. On the regioselectivity of oxidation/bromocyclization cascades. The experiments summarized in the previous sections show that bromocyclization of α-styrene-type tertiary alkenols **1e–f**

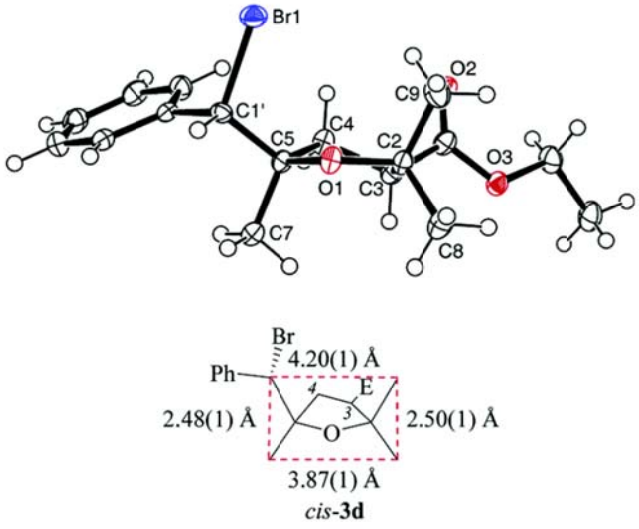
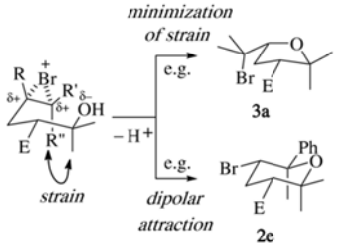


Fig. 2. Ellipsoid graphic (50% probability) of tetrahydrofuran *cis*-**3d** in the solid state showing the $_3T^4$ twist-conformation of the heterocyclic core [150 K; H-atoms are drawn as circles of an arbitrary radius; E=CO_2Et; the (3*R*,5*R*,1′*S*)-isomer of **3d** was arbitrarily selected from the racemate in the unit cell].

afford tetrahydropyrans, prenyl-type alkenols **1a–c** mixtures of tetrahydrofurans and tetrahydropyrans, and β-styrene-type alkenol **1d** a mixture of stereoisomeric tetrahydrofurans. From stereochemical analysis and information gained from previous studies,[12] we reasoned that the selectivity determining reagent for bromocyclization formed from bromide oxidation by *tert*-butyl hydroperoxide is molecular bromine. Bromine adds to a carbon–carbon double bond of an alkene in a kinetically controlled reaction, to furnish a γ-hydroxypropyl bromonium ion (Scheme 6).[30,31] The succeeding step, the anti-selective opening of the bromonium ion by intramolecular attack of the hydroxyl oxygen, is much slower and therefore controlled by thermochemical parameters, such as strain and dipolar attraction.



Scheme 6. Model for explaining regioselectivity in intramolecular γ-hydroxypropyl bromonium ion-opening directed by strain- (top) and charge effects (bottom; E=CO_2Et; R=H or CH_3, R′=H, CH_3, or phenyl; R″=H, CH_3).

The experimental data summarized in this study show that 6-*endo*-regioselectivity in oxidative bromocyclization of prenyl-type alkenols gradually improves, as steric encroachment in proximity to the hydroxyl oxygen becomes smaller. We therefore hypothesized that steric repulsion between methyl groups at the bromonium-activated carbon–carbon double bond and the hydroxyl oxygen disfavor tetrahydropyran formation from **1a**, and supported this interpretation by a modeling study (Section 2.4).

In cyclization of styrene-type alkenols, the higher substituted carbon of the bromonium-activated π-bond is preferentially approached by the incoming oxygen nucleophile. In α-styrene-type alkenols (such as **1e**), the aryl group stabilizes positive charge at the benzylic carbon and favors this position for an incoming nucleophile by dipolar attraction. The attractive component is expected to balance strain imposed by close contacts between substituents in proximity of the hydroxyl oxygen, as the tetrahydropyran ring closes (vide infra and Scheme 6). In β-styrene-type alkenol **1d**, it is the tertiary carbon atom of the bromonium ion, that is, selectively attacked by the approaching oxygen nucleophile, due to dipolar attraction and smaller steric repulsion between methyl groups, as the tetrahydrofuran ring closes.

2.4. On methyl substituent effects in 6-*endo* alkenol ring closures

The selectivity data summarized in the previous section imply that the tetrahydropyran fraction of bromocyclization products gradually decreases, as steric encroachment at oxygen in prenyl-type alkenols rises. We therefore concluded that steric repulsion between methyl substituents in the selectivity determining step changes an inherent 6-*endo*-selectivity of electrophile-induced ring closures of prenyl-type 4-pentenols toward tetrahydrofuran formation. The selectivity determining step, nucleophilic opening of a (tri)substituted hydroxyalkyl bromonium ion by the hydroxyl oxygen, is slow and therefore should occur via a late and therefore product-like transition state. To obtain information on strain imposed by methyl substitution in such late transition states, we computed Gibbs free energies of 2,6- and 2,2-dimethyltetrahydropyrans as models for the proposed intermediates, and compared the data to Gibbs free energies of other 1,3- and geminally substituted tetrahydropyrans (Section 2.4.1). We also computed thermochemistry associated with 6-*endo*- and 5-*exo*-cyclization from a tertiary prenyl-type alkenol (Section 2.4.2), to exemplify the role of strain on selectivity in a thermodynamically controlled ring closure.

2.4.1. Strain in dimethyltetrahydropyrans. For computing a consistent set of relative Gibbs free energies of dimethyltetrahydropyrans **I–VI**, we used Becke's 3 parameter hybrid functional[32,33] in combination with the 6-31+G** basis set.[34–36] The chosen computational method reproduces *A*-values of alkyl substituted tetrahydropyrans within a precision, that is, close to the experimental error.[37,38] The *A*-value reflects the degree of steric interaction between a substituent and the (hetero)cyclic core, the substituent is attached to. The *A*-value therefore is a benchmark for method assessment in conformational analysis.[39]

In the computational study, dimethyltetrahydropyran minimum structures were obtained from gradient searches and verified as such by computing second derivatives of associated wave functions, by diagonalizing underlying Hessian matrices. Minimum structures lacked in negative eigenvalues or imaginary frequencies. Approximate Gibbs free energies ($G_{298.15}$) were computed from thermochemical analysis at 298.15 K, using unscaled frequency calculations, including zero-point vibrational energy corrections, thermal corrections, and entropy.

The lowest in energy isomer from the computed set of compounds (Fig. 3), and from all possible dimethyltetrahydropyrans (Supplementary data), is the stereoisomer of 2,6-dimethyltetrahydropyran **Ia** having both methyl groups attached equatorially. Theory predicts for the other stereoisomers of **I** an increase of $\Delta G_{298.15}$ as the number of axial methyl groups grows (**Ib** and **Ic**), and the distance between methyl carbons becomes smaller (Fig. 4). Both observations are consistent with the fundamentals of conformational analysis.[40] The computed value of +34.9 kJ mol^{-1} for **Ic** is larger than twice the computed *A*-value for the methyl group in 2-methyltetrahydropyran (14.9 kJ mol^{-1} for 298.15 K; experimental:[38] 12.0±0.8 kJ mol^{-1} at 188–173 K) on the same level of theory,

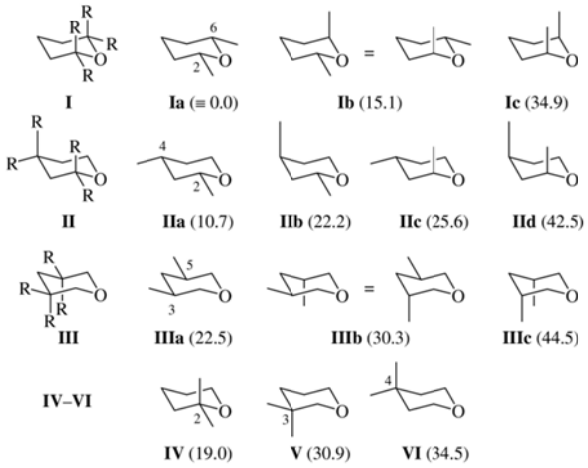


Fig. 3. Structure formulas, indices, and calculated (B3LYP/6-31+G**//B3LYP/6-31+G**) $\Delta G_{298.15}$-values in kJ mol^{-1} (numbers in brackets) of dimethyltetrahydropyrans **I**–**VI**.

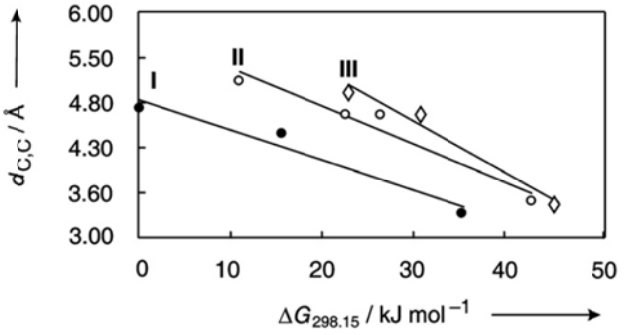


Fig. 4. Correlation between methyl carbon distances ($d_{C,C}$) and calculated $\Delta G_{298.15}$-values (cf. Fig. 3) of **Ia**–**c** [●; $d_{C,C}$=−0.04($G_{298.15}$) Å mol kJ^{-1}+4.84 Å; $R2$=0.978], **IIa**–**d** [○; $d_{C,C}$=−0.05($\Delta G_{298.15}$) Å mol kJ^{-1}+5.75 Å; $R2$=0.978], and **IIIa**–**c** (◇; $d_{C,C}$=−0.08($G_{298.15}$) Å mol kJ^{-1}+6.85 Å; $R2$=0.997).

thus pointing to steric interaction between axial methyl groups at C2 and C6 in *cis*-2,6-dimethyltetrahydropyran **Ic**. In the equilibrium structure, axial methyl carbons of **Ic** are only 3.332 Å apart, which is less than the sum of 3.40 Å for two carbon van der Waals-radii.[41] The carbon–carbon distance of substituents in diaxial isomers of *cis*-2,4- and *cis*-3,5-dimethyltetrahydropyran is slightly larger (3.499 Å for **IId**, and 3.453 Å for **IIIc**) but still expected to induce strain, because the van der Waals radius of a methyl group is by the distance of the carbon–hydrogen bond larger than the corresponding radius of a carbon atom. Since close contacts between methyl groups cause steric repulsion, and the structural response to repulsion is strain, we refer to the computed $\Delta G_{298.15}$-values as strain energy. Strain, particularly in compounds **I**–**III** is evident from a flattening of tetrahydropyran puckering (Fig. 5), and an offset of methyl substituents from idealized axial positions to the periphery (see depictions of the molecules in the Supplementary data).

To quantify the effect of 1,3-dimethyl substitution on puckering, we subtracted the sum of absolute values of the six endocyclic torsion angles $\Sigma(|\omega_{ij}^{n}|)$ for compounds **I**–**III** from the respective value $\Sigma(|\omega_{ij}^{thp}|)$ of the parent heterocycle tetrahydropyran (*thp*) (Fig. 5 and Supplementary data). A plot of the puckering parameter versus computed relative Gibbs free energies is linear for **I**–**III**, showing that the effect of axial methyl substitution on flattening of the heterocyclic core is additive. The effect of substituents in positions 2,6 thereby is smaller than in positions 2,4 and largest in positions 3,5.

Geminal dimethyl substitution also imposes strain on the tetrahydropyran nucleus (see **IV**–**VI**, Fig. 3). If the alkenol used for

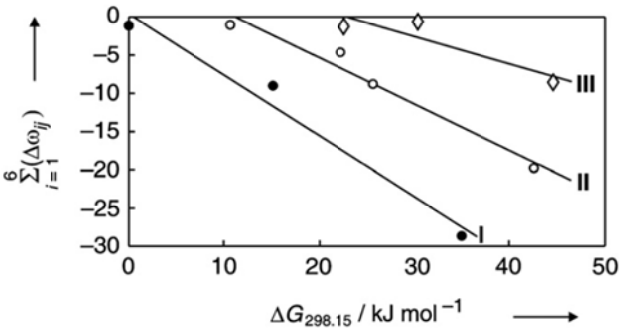


Fig. 5. Correlation of a parameter describing puckering changes in dimethyltetrahydropyrans **Ia**–**c**, referenced toward tetrahydropyran (*thp*) on the basis of endocyclic dihedral angles [$\Sigma(\Delta\omega_{ij})=\Sigma(|\omega_{ij}^{thp}|)-\Sigma(|\omega_{ij}^{I-III}|)$] and $\Delta G_{298.15}$-values (Fig. 3), whereby $\Sigma(|\omega_{ij}^{thp}|)-\Sigma(|\omega_{ij}^{I-III}|)$ denotes summation of absolute values of endocyclic torsion angles between atoms *i* and *j* in tetrahydropyran (*thp*) minus $\Sigma(|\omega_{ij}^{I-III}|)$ for compounds **I**–**III** [for **Ia**–**c** (●): $\Delta\omega_{ij}$=−0.80($\Delta G_{298.15}$) deg mol kJ^{-1}+0.47°; $R2$=0.986; for **IIa**–**c** (○): $\Delta\omega_{ij}$=−0.61($\Delta G_{298.15}$) deg mol kJ^{-1}+6.82°, $R2$=0.983; for for **IIIa**–**c** (◇): $\Delta\omega_{ij}$=0.36($\Delta G_{298.15}$) deg mol kJ^{-1} −8.19°; $R2$=0.904].

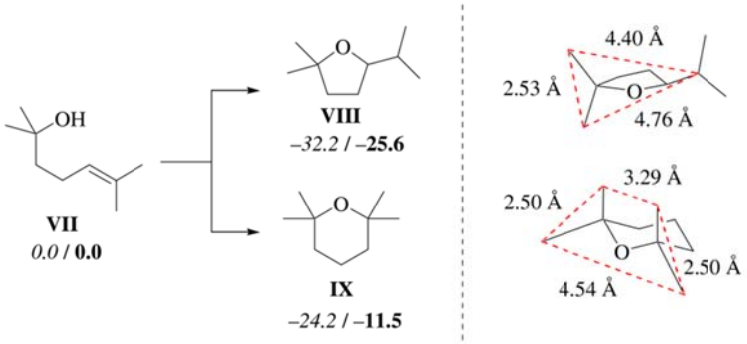
constructing the tetrahydropyran nucleus bears two methyl groups in position 1, backside strain is less relevant for describing regioselectivity as long as no new geminally disubstituted endocyclic carbon atom is formed in the course of the ring closure. If carbons 2 and 6 in tetrahydropyran both bear two methyl substituents, the situation changes, since steric repulsion by the geminal methyl groups at one carbon intensifies repulsive interactions between the two axial substituents at C2 and C6 (cf. Section 2.4.2).[42]

2.4.2. On the thermochemistry of alkenol cyclization. To find out whether methyl substitution has the potential to guide regioselectivity in cyclization of tertiary prenyl type alkenols, we calculated thermochemistry for the isomerization of prenyl-type alkenol **VII** into 2,2-dimethyl-5-isopropyl tetrahydrofuran (**VIII**) and 2,2,6,6-tetramethyltetrahydropyran (**IX**) (Scheme 7).[43] Equilibrium structures of alkenol **VII** and tetrahydrofuran **VIII** (Supplementary data) thereby were obtained from usage directed conformational searches (force field) leading to minima, which served as input for density functional theory calculations. The heterocyclic core of the minimum structure of tetrahydrofuran **VIII** adopts a $_3\mathrm{T}^4$ twist conformation, similar to the heterocyclic core found in the solid state structure of *cis*-**3d**. The isopropyl substituent and one of the methyl groups in this conformation are bound pseudoequatorially, and the second methyl group pseudoaxially. The distances between the secondary isopropyl carbon and the two methyl carbons at C2 are larger than the distances between methyl carbons at positions 2 and 6 in tetrahydropyran **IX**. In a reversible reaction, B3LYP-theory thus favors tetrahydrofuran formation from alkenol **VII**. MP2-theory leads to the same result, although the driving force for tetrahydrofuran formation is less pronounced (Supplementary data).

To sum up, the results from the modeling study show that substituents in axial positions 2 and 6 thermochemically disfavor tetrahydropyran formation from tertiary prenyl-type alkenols on the basis of strain effects, and direct alkenol cyclization toward tetrahydrofuran formation.

2.5. Functional group interconversion for synthesis of aplysiapyranoid A

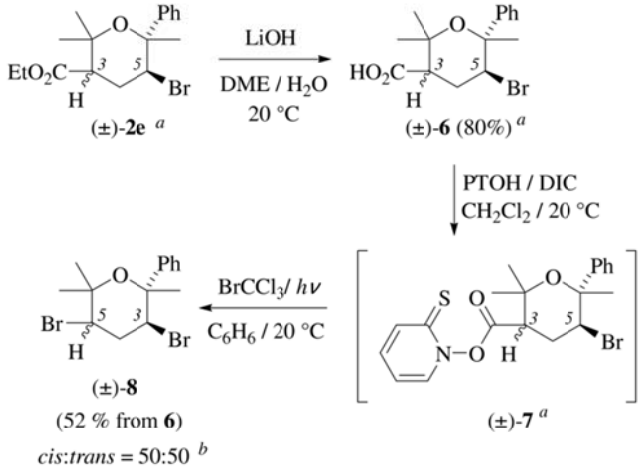
According to the strategy described in the introductory part, we started from ethyl (5-bromo-2,2,6-trimethyl-6-phenyltetrahydropyran)-3-carboxylate (**2e**) to prepare aplysiapyranoid A, and an epimer with inverted configuration at C5 of the heterocyclic core. To achieve this goal, the ethoxycarbonyl group at C5 had to be converted into an axial bromosubstituent for aplysiapyranoid A, and an



Scheme 7. Calculated reaction energies (zero-point vibrational energy-corrected; numbers in italics) and free energy differences (bold arabic figures, ΔG_{298} in kJ mol^{-1}; B3LYP/6-31+G**//B3LYP/6-31+G**) for isomerization of prenyl-type alkenol **VII** into tetrahydrofuran **VIII** and tetrahydropyran **IX** (left; see also the Supplementary data), and distances between carbon atoms of substituents located next to the endocyclic oxygen atom in equilibrium structures of **VIII** and **IX** (right).

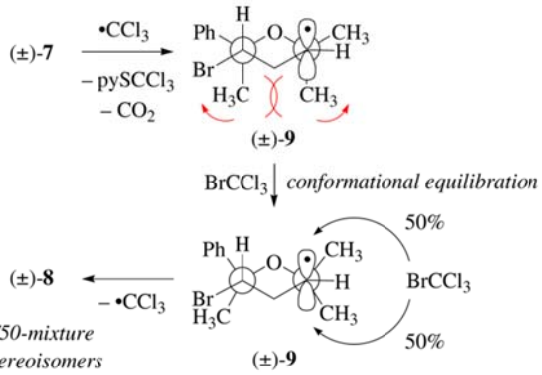
equatorial bromosubstituent for the 5-epimer. The carboxyl-bromine exchange thereby was achieved by the Barton–Hunsdiecker free radical bromination.[44,45] The more challenging part of the synthesis related to transformations in the sterically encroached part of the molecule. In our approach, oxidative degradation afforded a carboxyl from the phenyl group.[46] The carboxyl entity then was transformed in a three step sequence, including a Takai-reaction,[47] into a chlorovinyl group. The synthesis described in the following sections focuses on method development and expands information communicated previously[7] to full detail.

2.5.1. Decarboxylative bromination of 2,2,6,6-substituted tetrahydropyrans. For synthesis of a Barton-type carbon radical precursor, carboxylic acid ester **2e** (76/24-mixture of 3,5-*cis*/3,5-*trans*-stereoisomers) was saponified in aqueous dimethoxyethane (DME) using lithium hydroxide as base, to afford carboxylic acid **6**. For analytical purposes, we recrystallized carboxylic acid **6** from aqueous acetone, which furnished the pure 3,5-*cis*-isomer.[48] For synthetic purposes we directly used 76/24-mixture of stereoisomers to prepare mixed anhydride **7** via condensation of crude acid **6** and *N*-hydroxypyridine-2(1*H*)-thione (PTOH) by diisopropyl carbodiimide (DIC, Scheme 8).[49]



Scheme 8. Synthesis of dibromide **8** from ester **2e**. [a]3,5-*cis*/3,5-*trans*=76:24. [b]Ratio of 3,5-*cis*/3,5-*trans* isomer [PTOH=*N*-hydroxypyridine-2(1*H*)-thione; DIC=diisopropylcarbodiimide; the atom numbering changes in going from **7** to **8** for reasons of functional group hierarchy].

N-Acyloxypyridinethione **7** is a yellow photolabile compound that decomposes, if photoexcited with tungsten light in a solution of benzene and bromotrichloromethane, to afford 3,5-dibromo-substituted tetrahydropyran **8** in 52% yield (from **6**), as 50/50-mixture of cis/trans-isomers (Scheme 8). The new carbon–bromine bond in **8** is formed via homolytic substitution from tetrahydropyranyl radical **9** and bromotrichloromethane. The latter step provides dibromide **8** and a trichloromethyl radical, which adds to the thiocarbonyl group of **7**, leading to carbon dioxide, 2-methylsulfanylpyridine ($pySCCl_3$), and the next carbon radical **9** for propagating the chain reaction. In a stereochemical model, both diastereotopic faces are similarly shielded by vicinal methyl groups at C6, thus explaining the 50/50-stereoselectivity for dibromide formation from reactive intermediate **9** (Scheme 9).



Scheme 9. Mechanistic and stereochemical model for dibromide formation from mixed anhydride **7** ($pySCCl_3$=2-trichloromethylsulfanylpyridine).

The stereoisomers of **8** were separated by chromatography and identified via NMR-spectroscopy. Double doublets for the protons attached to C3 and C5 show cis-diaxial orientation of respective hydrogens in *cis*-**8**. Vicinal coupling constants of 11–12 Hz and 5 Hz point to axial orientation of 3-H and 5-H and thus equatorial arrangement of the bromo- and the ester substituent. The same protons in *trans*-**8** resonate as double doublets composed of 7 Hz- and 5 Hz-couplings, with the 7 Hz-coupling pointing to a conformationally flexible structure, as expected for a 3,5-*trans*-tetrahydropyran. The distances between carbon substituents at C2 and C6 in crystal structures of *cis*-**8** and *trans*-**8** correlate with predictions made from theory in the gas phase (Fig. 6 and Scheme 7). This information allows to estimate the strain imposed by 2,2,6,6-substitution in **8**, leading to a value of about 73 kJ mol^{-1}, based on 35 kJ mol^{-1} for the 2,6-diaxial substitution and 38 kJ mol^{-1} from two geminal substitutions (cf. Figs. 3 and 4). These numbers imply that both isomers of **8** are considerably strained.

2.5.2. Synthesis of aplysiapyranoid A and its 5-epimer. For building the chlorovinyl group of the aplysiapyranoids, we oxidatively

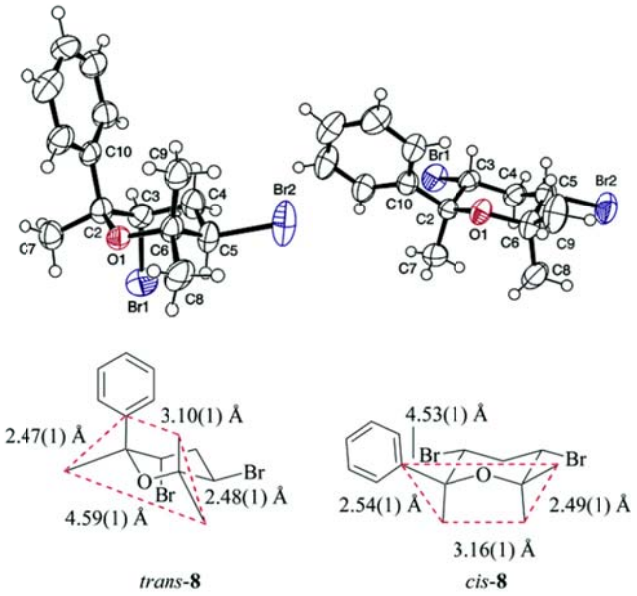
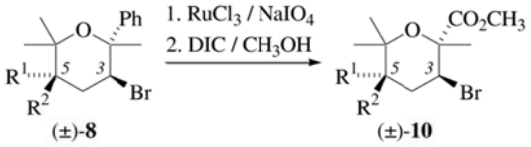


Fig. 6. Ellipsoid graphics (50% probability) of hexasubstituted tetrahydropyrans *cis*-8 and *trans*-8 in the solid state (top; 300 K; H-atoms were drawn as circles of an arbitrary radius), and distances between carbon atoms of substituents attached in positions 2 and 6 (bottom).

degraded the phenyl into a carboxyl group at C2, by adding $RuCl_3$ and $NaIO_4$ to a mixture composed of tetrachloromethane, acetonitrile, water,[46] and one of the dibromides *cis*-**8** and *trans*-**8**. For unknown reasons, the reaction stopped at 80% conversion, regardless of the quantity of $RuCl_3$ and $NaIO_4$ added in attempts to achieve quantitative conversion. Since no other products apart from the desired acid and starting material **8** were detected (TLC), we treated this mixture with methanol and DIC to prepare *O*-methyl carboxylates *cis*-**10** and *trans*-**10** (Table 3). From the work-up, we recovered unspent *cis*-**8** and *trans*-**8**. Alternative methods for esterification, such as the *p*-toluenesulfonic acid-catalyzed reaction with methanol or dimethoxypropane failed to provide methyl ester **10**.

Table 3
Preparation of methyl tetrahydropyranyl 2-carboxylates *cis*-**10** and *trans*-**10**



Entry	(±)-**8**	Conv./%	R^1	R^2	(±)-**10**/% (two steps)
1	*cis*-**8**[a]	80	H	Br	*cis*-**10**[a]: 36
2	*trans*-**8**[a]	80	Br	H	*trans*-**10**[a]: 34

[a] Stereodescriptor refers to relative configuration of substituents at carbons 3 and 5.

The proton-NMR-spectrum of *cis*-**10** shows double doublets at 3.98 and 4.56 ppm (J=12–13 Hz and 5 Hz) being in line with axial positioning of 3-H and 5-H. The same protons have triplet fine structure for 3-H (J=4 Hz) and a double doublet for 5-H (J=13 and 4 Hz), pointing to equatorial arrangement of the former and axial of the latter in $CDCl_3$-solution of *trans*-**10**. Steric crowding in proximity of the endocyclic oxygen in *cis*-**10** and *trans*-**10** is again evident from the crystal structures of the two methyl esters (Fig. 7). The distances between carbon atoms attached to C2 and C6 are close to the values observed for dibromides *cis*-**8** and *trans*-**8**. On the basis of the information available from the modeling study and the structural discussion on dibromides *cis*-**8** and *trans*-**8**, we think that steric crowding is the major reason for the difficulties experienced in chemical transformations of substituents in position 2 of 2,2,6,6-substituted tetrahydropyrans via an addition–elimination sequence.

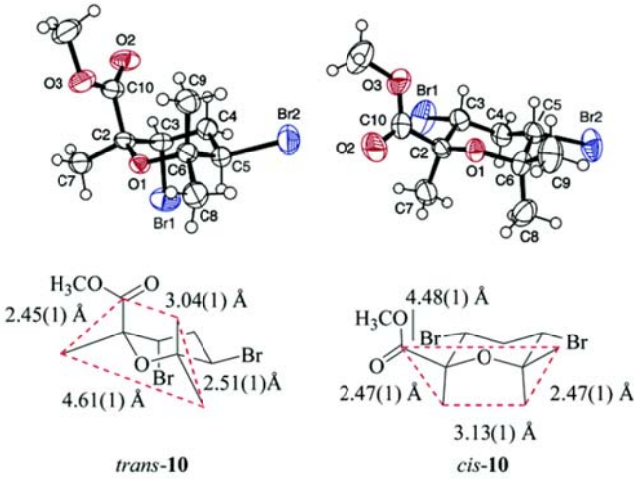
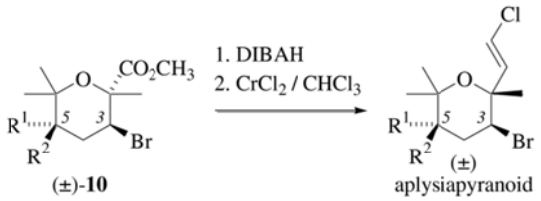


Fig. 7. Ellipsoid graphics (50% probability) of hexasubstituted tetrahydropyrans *cis*-**10** *trans*-**10** in the solid state (top; 300 K; H-atoms were drawn as circles of an arbitrary radius) and distances between carbon atoms of substituents in positions 2 and 6 (bottom).

In the final steps, *O*-methyl carboxylate *trans*-**10** was reduced by DIBAH to furnish the derived aldehyde, which was treated with $CrCl_2$ and $CHCl_3$[47] for building the chlorovinyl group of aplysiapyranoid A (entry 1 in Table 4). The NMR-spectroscopic data of the target molecule are consistent with the values reported for the natural product.[1] By the same reduction-chlorovinylation sequence, we prepared the 5-epimer of the natural product from ester *cis*-**10** (entry 2 in Table 4).

Table 4
Preparation of aplysiapyranoid A and 5-*epi*-A



Entry	**10**	R^1	R^2	Aplysiapyranoid/% (two steps)
1	*trans*-**10**	Br	H	A: 32
2	*cis*-**10**	H	Br	5-*epi*-A: 21

3. Concluding remarks

A proper set of substituents to control 6-*endo* selectivity for synthesis of 2,2,6,6-substituted tetrahydropyrans via alkenol bromocyclization is the combination of an aryl and a methyl group. The aryl group adds a polar component to the ring closure, which is not available from methyl substitution. Methyl substitution moreover induces strain, as the bromonium-activated π-bond and the hydroxyl oxygen of a tertiary prenyl-type alkenol approach for

intramolecular carbon–oxygen bond formation, thus favoring tetrahydrofuran formation from the 5-*exo*-reaction.

The concept used in this study to prepare organobromines from bromide, *tert*-butyl hydroperoxide, and an unsaturated hydrocarbon generally is referred to as oxidative bromination. Oxidative bromination is mechanistically related to bromide oxidation by hydrogen peroxide, catalyzed by marine bromoperoxidases in nature.[50] Vanadium complexes V(O)L^n(OEt) therefore can be regarded as functional bromoperoxidase mimics, and *tert*-butyl hydroperoxide the biomimetic electron acceptor. The results summarized in this work show, that functional bromoperoxidase chemistry has reached a notable degree of maturity. Modern oxidative bromination, for example, uses a buffer composed of sodium bromide and β-bromocinnamic acid to liberate protons and bromide under pH-neutral conditions, and is feasible in solutions of propylene carbonate as nontoxic solvent.

The synthetic potential of oxidative bromination for synthesis of natural products is evident from the third part of the project dealing with synthesis of the marine natural product aplysiapyranoid A. The strategy to interconvert functional groups in a sequence of homolytic and polar reactions, adds a component to synthesis of the aplysiapyranoids which is, not available from other concepts developed so far. The strength of the homolytic substitution in this approach arises from the efficiency of carbon–bromine bond formation at a sterically shielded secondary neopentyl-type carbon at tetrahydropyran. The yields associated with chlorovinyl group formation from the phenyl group, on the other hand, remained below expectation. With the wisdom of hindsight we relate the reluctance of reagents to add to substituents at C2 to strain that additionally builds up as the configuration of the attacked carbon changes from planar to tetrahedral. The increase in steric demand occurs in a severely encroached region of the 2,2,6,6-substituted tetrahydropyran and therefore is expected to require notable activation energy in order to effectively occur.

To continue the project, we consider the aplysiapyranoids C and D[1] as attractive targets. The latter compounds have a chlorosubstituent bound next to the vinyl group and synthesis of the products according to the outlined strategy requires development of an efficient oxidation/chlorocyclization cascade for constructing tetrahydropyran rings. A survey of the literature shows that chlorocyclization is just beginning to evolve.[51,52] To develop a practical method for in situ chlorine generation from transition metal-catalyzed oxidation, therefore is a rewarding objective to pursue.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see Ref. 12 and the Supplementary data.

4.2. Oxovanadium-catalyzed oxidation of bromide

4.2.1. General method. To a solution of vanadium(V)-catalyst V(O)L^n(OEt) (5.7 mg, 0.01 mmol; for structure formula refer to Section 2.2) and NaBr (10.3 mg, 0.10 mmol) in propylene carbonate (10 mL) at 30 °C was added a solution of 3-bromo-3-phenylpropionic acid (286 mg, 1.25 mmol), alkenol **1** (1.00 mmol), and TBHP [4.1 M in toluene, 390 μL, 1.25 mmol] in propylene carbonate (3 mL) via syringe pump (0.005 mL/min). The reaction mixture was stirred at 30 °C for 24 h. The yellowish solution was extracted with cyclohexane (4×20 mL). Combined organic extracts were washed with brine (2×40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2).

*4.2.2. Bromocyclization of ethyl 2-(2′-hydroxyprop-2′-yl)-5-methyl-4-hexenoate (**1a**).* Starting material: 215 mg (1.0 mmol) of ethyl [2-(2′-hydroxyprop-2′-yl)-5-methyl]-4-hexenoate (**1a**). Eluent used for chromatographic purification: petroleum ether/*tert*-butyl methyl ether=10:1 (v/v). *Ethyl rel-(3R,5S)-(5-bromo-2,2,6,6-tetramethyltetrahydropyran)-3-carboxylate cis-(**2a**).* Yield: 42 mg (14%), colorless oil. R_f=0.63 in petroleum ether/*tert*-butyl methyl ether=10:1 (v/v). Anal. Calcd for $C_{12}H_{21}O_3Br$ (293.20): C, 49.16; H, 7.22; found: C, 49.31; H, 7.13. δ_H (600 MHz; $CDCl_3$) 1.26 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.26 (3H, s, CH_3), 1.32 (6H, s, CH_3), 1.43 (3H, s, CH_3), 2.25 (1H, dt, J_d 13.3, J_t 3.8 Hz, 4-H), 2.54 (1H, q, *J* 13.3 Hz, 4-H), 2.63 (1H, dd, *J* 13.3, 3.8 Hz, 3-H), 3.89 (1H, dd, *J* 13.3, 3.8 Hz, 5-H), 4.13 (2H, 2× dq, J_d 10.8, J_q 7.1 Hz, $CO_2CH_2CH_3$). δ_C (150 MHz; $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 23.0 (CH_3), 24.1 (CH_3), 31.0 (CH_3 or C4), 31.1 (CH_3 or C4), 32.0 (CH_3), 54.1 (C3), 56.3 (C5), 60.7 ($CO_2CH_2CH_3$), 73.6 (C2), 75.5 (C6), 171.3 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔5-H, 3-H↔(2-CH_3)$_a$/5-H↔(6-CH_3)$_a$. *Ethyl rel-(3R,5R)-(5-bromo-2,2,6,6-tetramethyltetrahydropyran)-3-carboxylate* (±)-*trans-*(**2a**) *and ethyl* [5-(2′-*bromoprop-2′-yl*)-2,2-*dimethyltetrahydrofuran*]-3-*carboxylate* (**3a**). Yield: 8 mg (3%) *rel-*(3*R*,5*R*)-**2a** in same column fraction with 118 mg (40%), 70/30-mixture of *cis*/*trans*-isomers of **3a**, colorless oil. R_f=0.57 in petroleum ether/*tert*-butyl methyl ether=10:1 (v/v). Anal. Calcd for $C_{12}H_{21}O_3Br$ (293.20): C, 49.16; H, 7.22; found: C, 49.45; H, 7.19. *rel-*(3*R*,5*R*)-**2a** [(±)-*trans-*(**2a**)]. δ_H (600 MHz; $CDCl_3$) 1.22 (3H, s, CH_3), 1.27 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.35 (3H, s, CH_3), 1.42 (6H, s, CH_3), 2.23 (1H, ddd, *J* 15.1, 5.5, 4.2 Hz, 4-H), 2.53–2.61 (1H, m, 4-H), 3.01 (1H, dd, *J* 10.2, 4.1 Hz, 3-H), 4.10–4.22 (2H, m, $CO_2CH_2CH_3$), 4.43 (1H, dd, *J* 5.6, 3.3 Hz, 5-H). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 26.1 (CH_3), 27.8 (CH_3), 29.3 (CH_3 or C4), 29.6 (CH_3 or C4), 31.4 (CH_3), 46.9 (C3), 58.1 (C5), 60.6 ($CO_2CH_2CH_3$), 72.9 (C2 or C6), 73.7 (C2 or C6), 172.9 ($CO_2CH_2CH_3$). *rel-*(3*R*,5*R*)-**3a** [(±)-*cis-*(**3a**)]. δ_H (600 MHz; $CDCl_3$) 1.14 (3H, s, CH_3), 1.27 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.44 (3H, s, CH_3), 1.74 (3H, s, 3H), 1.75 (3H, s, CH_3), 2.16 (1H, ddd, *J* 12.5, 7.0, 5.1 Hz, 4-H), 2.33 (1H, ddd, *J* 12.5, *J* 11.9, 11.0 Hz, 4-H), 2.93 (1H, dd, *J* 11.9, 7.0 Hz, 3-H), 3.97 (1H, dd, *J* 11.0, 5.1 Hz, 5-H), 4.12–4.18 (2H, m, $CO_2CH_2CH_3$). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 25.2 (CH_3), 29.5 (CH_3), 29.3 (CH_3), 31.0 (CH_3), 31.9 (C4), 54.1 (C3), 60.7 ($CO_2CH_2CH_3$), 66.4 (C2′), 82.4 (C2), 85.0 (C5), 171.5 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔5-H. *rel-*(3*R*,5*S*)-**3a** [(±)-*trans-*(**3a**)]. δ_H (600 MHz; $CDCl_3$) 1.12 (3H, s, CH_3), 1.26 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.47 (3H, s, CH_3), 1.69 (3H, s, CH_3), 1.70 (3H, s, CH_3), 2.17 (1H, ddd, *J* 13.7, 9.4, 4.8 Hz, 4-H), 2.57 (1H, ddd, *J* 13.7, 9.4, 8.8 Hz, 4-H), 2.88 (1H, t, *J* 9.4 Hz, 3-H), 3.94 (1H, dd, *J* 8.8, 4.8 Hz, 5-H), 4.12–4.18 (2H, m, $CO_2CH_2CH_3$). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 22.8 (CH_3), 28.2 (CH_3), 29.3 (CH_3), 31.0 (CH_3), 31.7 (C4), 53.1 (C3), 60.6 ($CO_2CH_2CH_3$), 68.9 (C2′), 83.1 (C2), 83.7 (C5), 171.8 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔(2-CH_3)$_a$/5-H↔(2-CH_3)$_b$.

*4.2.3. Bromocyclization of ethyl 2-(1′-hydroxyeth-1′-yl)-5-methyl-4-hexenoate (**1b**).* Starting material: 200 mg (1.0 mmol) of ethyl 2-(1′-hydroxyeth-1′-yl)-5-methyl-4-hexenoate (**1b**). Eluent used for chromatographic purification: CH_2Cl_2. Yield: 156 mg (0.56 mmol/56%) colorless liquid. R_f=0.51–0.35 (CH_2Cl_2) for a 73/27-mixture of **2b**/**3b**, as determined on the basis of ^{1}H NMR-integral ratios of methyl substituents (For analytical data of the mixture of **2b** and **3b**, see the Supplementary data). From this mixture, *rel-*(2*R*,3*R*,5*S*)-5-bromo-3-ethoxycarbonyl-2,6,6-trimethyltetrahydropyran *rel-*(2*R*,3*R*,5*S*)-(**2b**) was separated via chromatography [10/1-diethyl ether/pentane (v/v) as eluent]. Colorless oil, R_f=0.28 for diethyl ether/pentane=10:1. Anal. Calcd for $C_{12}H_{21}O_3Br$ (279.17): C, 47.33; H, 6.86; found: C, 47.34; H, 6.73. δ_H (600 MHz; $CDCl_3$) 1.13 (3H, d, *J* 6.1 Hz, CH_3), 1.26 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.36 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.33–2.38 (3H, m, 3-H, 4-H), 3.86–3.94 (2H, m, 2-H, 5-H), 4.14 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 18.0 (CH_3), 20.2 (CH_3), 29.2 (CH_3), 34.5 (C4), 51.7 (C3), 54.9 (C5), 60.7 ($CO_2CH_2CH_3$), 67.1 (C2), 75.5 (C6), 171.9 ($CO_2CH_2CH_3$).

*4.2.4. Bromocyclization of ethyl 2-hydroxymethyl-5-methyl-4-hexenoate (**1c**).* Starting material: 190 mg (1.0 mmol) of ethyl

2-hydroxymethyl-5-methyl-4-hexenoate (**1c**). Eluent used for chromatographic purification: diethyl ether/pentane 1:5 (v/v). *Ethyl rel-*(3*R*,5*S*)-(5-*bromo*-6,6-*dimethyltetrahydropyran*)-3-*carboxylate* (±)-*cis*-(**2c**). Yield: 98 mg (37%), colorless liquid. R_f=0.36 for diethyl ether/pentane 1:5 (v/v). Anal. Calcd for $C_{10}H_{17}BrO_3$ (265.14): C, 45.30; H, 6.46; found: C, 45.17; H, 6.32. δ_H (600 MHz; $CDCl_3$) 1.25 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.37 (3H, s, CH_3), 1.39 (3H, s, CH_3), 2.26 (1H, q, *J* 13.0 Hz, 4-H), 2.44–2.51 (1H, m, 4-H), 2.76 (1H, tt, *J* 12.1, 4.7 Hz, 3-H), 3.72 (1H, t, *J* 11.8 Hz, 2-H), 3.86–3.94 (2H, m, 2-H, 4-H), 4.13 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$). δ_C (150 MHz; $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 17.2 (CH_3), 28.9 (CH_3), 33.7 (C4), 44.2 (C3), 55.0 (C5), 60.9 ($CO_2CH_2CH_3$), 61.8 (C2), 75.2 (C6), 171.0 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔5-H. *Ethyl rel-*(3*R*,5*R*)-(5-*bromo*-6,6-*dimethyltetrahydropyran*)-3-*carboxylate* (±)-*trans*-(**2c**) *and ethyl* 5-(2′-*bromoprop*-2′-*yl*)-*tetrahydrofuran*]-3-*carboxylate* (**3c**). Yield: 47 mg (18%) of *rel-*(3*R*,5*R*)-**2c** and 16 mg (6%) 50/50-mixture of *cis*/*trans*-isomers of **3c**, colorless oil. R_f=0.29 for diethyl ether/pentane 1:5 (v/v). Anal. Calcd for $C_{10}H_{17}BrO_3$ (265.14): C, 45.30; H, 6.46; found: C, 45.17; H, 6.32. *rel-*(3*R*,5*R*)-**2c** [(±)-*trans*-**2c**]. δ_H (400 MHz; $CDCl_3$) 1.27 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.36 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.26 (1H, ddd, *J* 14.0, 9.3, 4.9 Hz, 4-H), 2.60 (1H, dt, J_d 14.2, J_t 4.8 Hz, 4-H), 2.74–2.82 (1H, m, 3-H), 3.88–3.95 (1H, m, 2-H), 3.99–4.05 (1H, m, 2-H), 4.14–4.22 (2H, m, $CO_2CH_2CH_3$), 4.22–4.28 (1H, m, 5-H). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 22.0 (CH_3), 26.5 (CH_3), 31.9 (C4), 40.7 (C3), 55.3 (C5), 61.0 ($CO_2CH_2CH_3$), 61.8 (C2), 74.7 (C6), 172.5 ($CO_2CH_2CH_3$). *rel-*(3*R*,5*R*)-**3c** [(±)-*cis*-**3c**]: δ_H (400 MHz; $CDCl_3$) 1.27 (3H, t, *J* 6.9 Hz, $CO_2CH_2CH_3$), 1.73 (3H, s, CH_3), 1.76 (3H, s, CH_3), 2.18–2.27 (1H, m, 4-H), 2.29–2.38 (1H, m, 4-H), 3.13–3.23 (1H, m, 3-H), 3.88–3.95 (1H, m, 5-H), 3.98–4.13 (2H, m, 2-H), 4.17 (2H, q, *J* 6.9 Hz, $CO_2CH_2CH_3$). δ_C (100 MHz; $CDCl_3$) 14.0 ($CO_2CH_2CH_3$), 29.4 (CH_3), 30.8 (CH_3), 32.5 (C4), 44.5 (C3), 61.0 ($CO_2CH_2CH_3$), 66.9 (C6), 70.6 (C2), 87.2 (C2′), 172.5 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔5-H. *rel-*(3*R*,5*S*)-**3c** [(±)-*trans*-**3c**]: δ_H (400 MHz; $CDCl_3$) 1.27 (3H, t, *J* 7.3 Hz, $CO_2CH_2CH_3$), 1.70 (3H, s, CH_3), 1.76 (3H, s, CH_3), 2.14 (1H, ddd, *J* 13.1, 9.0, 7.8 Hz, 4-H), 2.38 (1H, ddd, *J* 12.9, 7.6, 4.8 Hz, 4-H), 3.12–3.22 (1H, m, 3-H), 3.87 (1H, t, *J* 7.5 Hz, 5-H), 3.98 (1H, dd, *J* 8.7, 6.0 Hz, 2-H), 4.17 (2H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 4.17–4.23 (1H, m, 2-H). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 30.2 (CH_3), 30.8 (CH_3), 32.30 (C4), 44.3 (C3), 61.0 ($CO_2CH_2CH_3$), 68.2 (C6), 71.1 (C2), 86.4 (C2′), 173.4 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔$(4\text{-H})_a$/5-H↔$(4\text{-H})_b$.

*4.2.5. Bromocyclization of ethyl (E)-2-(2′-hydroxyprop-2′-yl)-4-methyl-5-phenyl-4-pentenoate (**1d**).* Starting material: 307 mg (1.0 mmol) of ethyl (*E*)-2-(2-hydroxyprop-2-yl)-4-methyl-5-phenyl-4-pentenoate (**1d**). Eluent used for chromatographic purification: diethyl ether/pentane=1/5 (v/v). *Ethyl* [5-(1′-*bromo*-1′-*phenylmethyl*)-2,2,5-*trimethyltetrahydrofuran*]-3-*carboxylate* (**3d**). Yield: 204 mg (0.574 mmol/57%), colorless liquid, 93/7-mixture of *cis*/*trans* isomers. R_f=0.34 for diethyl ether/pentane=1/5 (v/v). Anal. Calcd for $C_{17}H_{23}BrO_3$ (355.27): C, 57.47; H, 6.53; found: C, 57.31; H, 6.27. *rel-*(3*R*,5*R*,1′*S*)-**3d** [(±)-*cis*-**3d**]. Colorless solid, mp=65 °C. δ_H (600 MHz; $CDCl_3$) 1.13 (3H, s, CH_3), 1.21–1.26 (3H, m, $CO_2CH_2CH_3$), 1.49 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.43–2.49 (1H, m, 4-H), 2.59–2.72 (2H, m, 3-H, 4-H), 4.06–4.14 (2H, m, $CO_2CH_2CH_3$), 4.85 (1H, s, 1′-H), 7.24–7.33 (3H, m), 7.45–7.52 (2H, m). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 24.8 (CH_3), 28.0 (CH_3), 28.6 (CH_3), 38.6 (C4), 53.8 (C3), 60.7 ($CO_2CH_2CH_3$), 63.0 (C1′), 83.2 (C2), 84.0 (C5), 128.3, 129.7, 129.8, 138.3, 171.1 ($CO_2CH_2CH_3$). X-ray crystallography: $C_{17}H_{23}BrO_3$ (355.26), *T*=150(2) K, λ=0.71073 Å, monoclinic, $P2_1/n$, *a*=14.8542(4) Å, *b*=7.2765(2) Å, *c*=15.6643(4) Å, β=103.562(3)°, *Z*=4, μ=2.505 mm^{-1}, completeness 99.8%, (2θ=60.00°), goodness-of-fit on F^2=0.842, final *R* indices [$I>2\sigma(I)$]: *R*1=0.0293, *wR*2=0.0484. *rel-*(3*R*,5*S*,1′*R*)-**3d** [(±)-*trans*-**3d**]. δ_H (600 MHz; $CDCl_3$) 1.20 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.28 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.43 (3H, s, CH_3), 2.11 (1H, dd, *J* 12.8, 6.9 Hz, 4-H), 2.83 (1H, t, *J* 12.7 Hz, 4-H), 3.06 (1H, dd, *J* 12.5, 6.9 Hz, 3-H), 4.14–4.24 (2H, m, $CO_2CH_2CH_3$), 5.00 (1H, s, 1′-H), 7.25–7.32 (3H, m), 7.43 (2H, d, *J* 7.2 Hz). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 24.4 (CH_3), 25.2 (CH_3), 30.5 (CH_3), 39.0 (C4), 53.5 (C3), 60.7 ($CO_2CH_2CH_3$), 63.4 (C1′), 83.0 (C2), 84.0 (C5), 127.9, 128.1, 129.5, 138.6, 171.2 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔5-CH_3.

*4.2.6. Bromocyclization of ethyl (E)-2-(2′-hydroxyprop-2′-yl)-5-phenyl-4-hexenoate (**1e**).* Starting material: 276 mg (1.0 mmol) of ethyl (*E*)-2-(2′-hydroxyprop-2′-yl)-5-phenyl-4-hexenoate (**1e**). Eluent used for chromatographic purification: ethyl acetate/pentane=1:10 (v/v). *Ethyl* (5-*bromo*-2,2,6-*trimethyl*-6-*phenyltetrahydropyran*)-3-*carboxylate* (**2e**). Yield: 167 mg (47%), colorless oil, 76/24-mixture of *cis*/*trans* isomers. R_f=0.37 for ethyl acetate/pentane=1:10 (v/v). Anal. Calcd for $C_{17}H_{23}BrO_3$ (355.27): C, 57.47; H, 6.53; found: C, 57.37; H, 6.44. *rel-*(3*R*,5*S*,6*R*)-**2e** [(±)-*cis*-**2e**]. δ_H (400 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.41 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.89 (3H, s, CH_3), 2.39 (1H, dt, *J* 13.5, 3.6 Hz, 4-H), 2.71 (1H, q, *J* 13.1 Hz, 4-H), 2.80–2.88 (1H, m, 3-H), 4.04 (1H, dd, *J* 12.8, 3.9 Hz, 5-H), 4.13–4.23 (2H, m, $CO_2CH_2CH_3$), 7.21–7.40 (3H, m), 7.60 (2H, d, *J* 7.8 Hz). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 20.7 (CH_3), 24.7 (CH_3), 31.6 (C4), 32.1 (CH_3), 54.0 (C3), 57.2 (C5), 60.8 ($CO_2CH_2CH_3$), 74.3 (C2), 78.5 (C6), 126.1, 127.5, 127.9, 145.6, 171.1 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔5-H. *rel-*(3*S*,5*S*,6*R*)-**2e** [(±)-*trans*-**2e**]. δ_H (400 MHz; $CDCl_3$) 0.74 (3H, s, CH_3), 1.24 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.50 (3H, s, CH_3), 1.63 (3H, s, CH_3), 2.33 (1H, m, 4-H), 2.59 (1H, ddd, *J* 15.0, 10.7, 3.1 Hz, 4-H), 3.18 (1H, dd, *J* 10.6, 4.1 Hz, 3-H), 4.07–4.23 (2H, m, $CO_2CH_2CH_3$), 5.27 (1H, dd, *J* 5.4, 3.1 Hz, 5-H), 7.21–7.38 (3H, m), 7.51 (2H, d, *J* 7.5 Hz). δ_C (100 MHz; $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 25.6 (CH_3), 30.0 (C4), 31.5 (CH_3), 34.0 (CH_3), 47.2 (C3), 56.8 (C5), 60.6 ($CO_2CH_2CH_3$), 74.5 (C2), 76.4 (C6), 126.3, 127.2, 128.0, 144.8, 172.7 ($CO_2CH_2CH_3$).

*4.2.7. Bromocyclization of ethyl (E)-2-(2′-hydroxyprop-2′-yl)-5-(p-methoxyphenyl)-4-hexenoate (**1f**).* Starting material: 307 mg of 1.0 mmol ethyl (*E*)-2-(2′-hydroxyprop-2′-yl)-5-(*p*-methoxyphenyl)-4-hexenoate (**1f**). Eluent used for chromatographic purification: dichloromethane/pentane=4/1 (v/v). *Ethyl* (5-*bromo*-2,2,6-*trimethyl*-6-(*p*-*methoxyphenyl*)*tetrahydropyran*)-3-*carboxylate* (**2f**). Yield: 182 mg (47%), yellowish liquid, 46/54-mixture of isomers *cis*/*trans*-isomers. R_f=0.18 for dichloromethane/pentane=4/1 (v/v). Anal. Calcd for $C_{18}H_{25}BrO_4$ (385.29): C, 56.11; H, 6.54; found: C, 55.95; H, 6.35. *rel-*(3*R*,5*S*,6*R*)-**2f** [(±)-*cis*-**2f**]. δ_H (600 MHz; $CDCl_3$) 1.29 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.39 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.86 (3H, s, CH_3), 2.38 (1H, dt, J_d 13.8, J_t 3.7 Hz, 4-H), 2.69 (1H, q, *J* 13.1, 4-H), 2.83 (1H, dd, *J* 13.1, 3.3 Hz, 3-H), 3.80 (3H, s, CH_3), 4.03 (1H, dd, *J* 12.9, 4.0 Hz, 5-H), 4.06–4.22 (2H, m, $CO_2CH_2CH_3$), 6.86 (2H, d, *J* 8.7 Hz), 7.51 (2H, d, *J* 8.7 Hz). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 20.7 (CH_3), 24.7 (CH_3), 31.6 (C4), 32.1 (CH_3), 54.1 (C3), 55.2 (CH_3), 57.6 (C5), 60.8 ($CO_2CH_2CH_3$), 74.3 (C2), 78.3 (C6), 113.2, 127.3, 137.9, 158.8, 171.2 ($CO_2CH_2CH_3$). NOESY (cross signals) 3-H↔5-H. *rel-*(3*S*,5*S*,6*R*)-**2f** [(±)-*trans*-**2f**]. δ_H (600 MHz; $CDCl_3$) 0.76 (3H, s, CH_3), 1.24 (3H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.48 (3H, s, CH_3), 1.61 (3H, s, CH_3), 2.32 (1H, ddd, *J* 14.9, 5.6, 4.3 Hz, 4-H), 2.58 (1H, ddd, *J* 14.8, 10.2, 3.1 Hz, 4-H), 3.14 (1H, dd, *J* 10.2, 3.8 Hz, 3-H), 3.80 (3H, s, CH_3), 4.06–4.23 (2H, m, $CO_2CH_2CH_3$), 5.23 (1H, dd, *J* 5.8, 3.2 Hz, 5-H), 6.84 (2H, d, *J* 8.7 Hz), 7.41 (2H, d, *J* 9.0 Hz). δ_C (150 MHz; $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 25.7 (CH_3), 30.1 (C4), 31.4 (CH_3), 33.5 (CH_3), 47.3 (C3), 55.2 (CH_3), 57.0 (C5), 60.6 ($CO_2CH_2CH_3$), 74.3 (C2), 76.2 (C6), 113.1, 127.5, 136.9, 158.6, 172.8 ($CO_2CH_2CH_3$).

4.3. 5-Bromo-2,2,6-trimethyl-6-phenyltetrahydropyran-3-carboxylic acid (±)-(6)

To a solution of ethyl (5-bromo-2,2,6-trimethyl-6-phenyltetrahydropyran)-3-carboxylate (**2e**) [3.00 g, 8.79 mmol, 76/24-mixture of *rel-*(3*R*,5*S*,6*R*)/*rel-*(3*S*,5*S*,6*R*) isomers] in dimethoxyethane (120 mL) was added a solution of LiOH×H_2O (5.94 g, 142 mmol) in H_2O (180 mL). The reaction mixture was stirred for

48–72 h at 20 °C until the starting material was completely consumed (TLC). The solution was acidified (pH 2) with aqueous HCl [37%, (w/w)] and extracted with CH_2Cl_2 (640 mL, 3×500 mL). Combined organic extractions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dried at 20 °C/5×10^{-2} mbar to provide carboxylic acid (±)-(**6**). Yield: 2.67 g (93%), tan solid, 76/24-mixture of *rel*-(3*R*,5*S*,6*R*)/*rel*-(3*S*,5*S*,6*R*) isomers. ν (NaCl) 3463 cm^{-1}, 3046, 2912, 2361, 1689, 1299. Recrystallization of the sample from H_2O/acetone furnishes (±)-*cis*-**6**. Colorless crystals, mp 147–148 °C (dec). *rel*-(3*R*,5*S*,6*R*)-**6** [(±)-*cis*-**6**]. δ_H (250 MHz; $CDCl_3$) 1.46 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.89 (3H, s, CH_3), 2.44 (1H, dt, J_d 13.1, J_t 3.8 Hz, 4-H), 2.70 (1H, q, *J* 13.1 Hz, 4-H), 2.89 (1H, dd, *J* 13.1, 3.8 Hz, 3-H), 4.04 (1H, dd, *J* 13.1, 3.8 Hz, 5-H), 7.26–7.36 (3H, m), 7.59–7.62 (2H, m). δ_C (63 MHz; $CDCl_3$) 20.7 (CH_3), 24.6 (CH_3), 31.4 (C4), 32.0 (CH_3), 53.7 (C3), 56.7 (C5), 74.2 (C2), 78.5 (C6), 125.1, 127.6, 128.0, 145.5, 176.6 (CO_2H). The spectroscopic properties were consistent with those specified above. Anal. Calcd for $C_{15}H_{19}BrO_3$ (327.22): C, 55.06; H, 5.85; found: C, 54.95; H, 5.90. *rel*-(3*S*,5*S*,6*R*)-**6** [(±)-*trans*-**6**]. δ_H (250 MHz; $CDCl_3$) 1.11 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.62 (3H, s, CH_3), 2.29–2.36 (1H, m, 4-H), 2.41–2.48 (1H, m, 4-H), 2.81 (1H, t, *J* 6.3 Hz, 3-H), 4.02 (1H, dd, *J* 7.1, 3.8 Hz, 5-H), 7.26–7.36 (m, 3H), 7.64–7.67 (m, 2H). δ_C (63 MHz; $CDCl_3$) 27.3 (CH_3), 28.2 (CH_3), 28.3 (C4), 28.6 (CH_3), 47.4 (C3), 56.7 (C5), 73.7 (C2), 77.2 (C6), 126.0, 126.9, 127.9, 144.7, 175.8 (CO_2H).

4.4. 3,5-Dibromo-2,6,6-trimethyl-2-phenyltetrahydropyran (±)-(8)

An amber colored flask was charged with a solution of 5-bromo-2,2,6-trimethyl-6-phenyltetrahydropyran-3-carboxylic acid (±)-(**6**) [1.82 g, 5.56 mmol, 76/24-mixture of *rel*-(3*R*,5*S*,6*R*)/*rel*-(3*S*,5*S*,6*R*) isomers] and *N*-hydroxypyridine-2(1*H*)-thione (PTOH, 742 mg, 5.82 mmol) in dry CH_2Cl_2 (30 mL) and treated at 0 °C in a dropwise manner over a period of 30 min with a solution of diisopropyl carbodiimide (DIC, 735 mg, 5.82 mmol) in dry CH_2Cl_2 (25 mL). Stirring was continued for 2 h at 0 °C and 20 h at 20 °C. The solvent was removed under reduced pressure. The residue was taken up in Et_2O. The solids were removed by filtration and successively washed with small portions of Et_2O. Combined filtrate and washings were concentrated under reduced pressure. The remaining yellow oil [2.61 g, composed predominantly (^{1}H HMR) of an 76/24-mixture of (±)-*cis*/(±)-*trans*-**8**; Supplementary data] was dissolved in dry C_6H_6 (45 mL). $BrCCl_3$ (3.96 g, 20.0 mmol) was added and the solution purged with a gentle stream of argon (15 min). The yellow solution was photolyzed under an atmosphere of argon using tungsten light (250 W bulb) until decolorization had occurred (1–5 min). The solution was concentrated under reduced pressure to leave an oil that was purified by chromatography [petroleum ether/Et_2O=10:1 (v/v)]. Yield: 1.05 g [52% from acid (±)-**6**], colorless oil, 50/50-mixture of *rel*-(2*R*,3*S*,5*S*)/*rel*-(2*R*,3*S*,5*R*) isomers. Anal. Calcd for $C_{14}H_{18}Br_2O$ (362.10): C, 46.44; H, 5.01; found: C, 46.89; H 5.08. *rel*-(2*R*,3*S*,5*R*)-**8** [(±)-*cis*-**8**]. Colorless solid, mp 81–82 °C (Et_2O/CH_2Cl_2). R_f=0.62 for petroleum ether/Et_2O=10:1 (v/v). δ_H (600 MHz; $CDCl_3$) 1.46 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.89 (3H, s, CH_3), 2.73 (1H, dt, J_d=13.3, J_t=4.2, 4-H), 2.82 (1H, dt, J_d=13.3, J_t=12.7, 4-H), 4.08 (1H, dd, *J* 12.1, 4.9 Hz, 3-H or 5-H), 4.08 (1H, dd, *J* 11.0, 4.5 Hz, 3-H or 5-H), 7.26–7.30 (m, 1H), 7.33–7.36 (m, 2H), 7.58–7.60 (m, 2H). δ_C (151 MHz; $CDCl_3$) 20.9 (CH_3), 23.9 (CH_3), 30.8 (CH_3), 39.3 (C4), 54.5 (C5), 55.9 (C3), 76.9 (C6), 79.1 (C2), 125.9, 127.7, 128.0, 145.1. X-ray crystallography: $C_{14}H_{18}Br_2O$ (362.10), T=300(2) K, λ=0.71073 Å, triclinic, $P\bar{1}$, a=8.686(1) Å, b=9.311(1) Å, c=10.428(1) Å, α=106.95(1)°, β=110.32(1)°, γ=98.17(1)°, Z=2, μ=5.550 mm^{-1}, completeness 97.8%, (2θ=52.76°), goodness-of-fit on F^2=0.741, final R indices [$I>2\sigma(I)$]: $R1$=0.0329, $wR2$=0.0610. *rel*-(2*R*,3*S*,5*S*)-**8** [(±)-*trans*-**8**]. Colorless oil. R_f=0.73 for petroleum ether/diethyl ether=10:1 (v/v). δ_H (250 MHz; $CDCl_3$) 1.07 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.70 (3H, s, CH_3), 2.72–2.79 (2H, m, 4-H), 4.54 (1H, dd, *J* 7.0, 4.9 Hz, 5-H), 5.03 (1H, dd, *J* 6.7, 4.6 Hz, 3-H), 7.24–7.38 (m, 3H), 7.52–7.57 (m, 2H). δ_C (63 MHz; $CDCl_3$) 27.8 (CH_3), 29.2 (CH_3), 30.5 (CH_3), 38.0 (C4), 56.4 (C5), 56.8 (C3), 76.2 (C6), 77.2 (C2), 126.3, 127.5, 128.0, 144.6. X-ray crystallography: crystals suitable for X-ray diffraction separated from a solution of $CDCl_3$ on standing at 20 °C; $C_{14}H_{18}Br_2O$ (362.10), T=299(2) K, λ=0.71073 Å, monoclinic, $C2/c$, a=24.042(5) Å, b=7.519(1) Å, c=15.951(3) Å, β=93.01(2)°, Z=8, μ=5.613 mm^{-1}, completeness 99.9%, (2θ=51.92°), goodness-of-fit on F^2=0.997, final R indices [$I>2\sigma(I)$]: $R1$=0.0432, $wR2$=0.1074.

4.5. Methyl tetrahydropyrancarboxylates from phenyltetrahydropyrans

4.5.1. General method. Diasterically pure 3,5-dibromo-2,6,6-trimethyl-2-phenyltetrahydropyran (±)-(**7**) (362 mg, 1.0 mmol; Section 4.4) was added to a two-phase system composed of CCl_4 (4 mL), CH_3CN (4 mL) and H_2O (6 mL). $NaIO_4$ (3.41 g, 15.0 mmol) and $RuCl_3\cdot H_2O$ (6 mg, 3 mol %) were added to afford a dark suspension that was well agitated at 20 °C. Additional $NaIO_4$ (213 mg, 1.0 mmol) and $RuCl_3\times H_2O$ (0.5 mg) were added in two portions in 24 h intervals. After a total reaction time of 72 h, CH_2Cl_2 (5 mL), and H_2O (2 mL) were added. The colorless precipitate formed was filtered off using a small pad of cotton. The solids were washed with CH_2Cl_2 (10 mL). Combined filtrate and washings were poured into separation funnel. The organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3×6 mL). The organic phase and combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure to furnish 302 mg of a dark oil that predominantly consisted of the corresponding 3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylic (Supplementary data). This product was dissolved in dry CH_2Cl_2 (2 mL) and MeOH (25.7 mg, 0.80 mmol) and treated in a dropwise manner at 0 °C over a period of 20 min with a solution of diisopropyl carbodiimide (101 mg, 0.80 mmol) in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred for 30 min at 0 °C and 24 h at 20 °C. The solvent was removed under reduced pressure to leave an oil that was purified by chromatography [petroleum ether/*tert*-butyl methyl ether=10:1 (v/v)].

*4.5.2. Methyl rel-(2R,3S,5S)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylate trans-(**10**).* Yield: 117 mg [34% from *rel*-(2*R*,3*S*,5*S*)-3,5-dibromo-2,6,6-trimethyl-2-phenyltetrahydropyran *trans*-(**8**)], colorless solid, mp 103 °C (CH_2Cl_2/Et_2O). R_f=0.44 for petroleum ether/*tert*-butyl methyl ether=10:1 (v/v). δ_H (600 MHz; $CDCl_3$) 1.28 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.55 (1H, dt, J_d 14.9, J_t 3.5 Hz, 4-H), 2.83 (1H, ddd, *J* 14.9, 12.7, 3.5 Hz, 4-H), 3.76 (3H, s, CO_2CH_3), 4.50 (1H, dd, *J* 12.7, 3.5 Hz, 5-H), 4.85 (1H, t, *J* 3.5 Hz, 3-H). δ_C (151 MHz; $CDCl_3$) 20.1 (CH_3), 29.5 (CH_3), 29.6 (CH_3), 38.0 (C4), 52.0 (C3), 52.5 (CO_2CH_3), 56.1 (C5), 76.4 (C2), 77.9 (C6), 173.2 (CO_2CH_3). IR (KBr) ν 3015 cm^{-1}, 3001, 2950, 1740, 1289, 1227, 1108. Anal. Calcd for $C_{10}H_{16}Br_2O_2$ (344.05): C, 34.91; H, 4.69; found: C, 34.94; H, 4.64. X-ray crystallography: $C_{10}H_{16}Br_2O_2$, T=300(2) K, λ=0.71073 Å, monoclinic, $P2_1/c$, a=6.6095(7) Å, b=22.789(2) Å, c=8.6366(8) Å, β=104.145(9)°, Z=4, μ=6.413 mm^{-1}, completeness 99.7%, (2θ=52.76°), goodness-of-fit on F^2=0. 756, final R indices [$I>2\sigma(I)$]: $R1$=0.0283, $wR2$=0.0512.

*4.5.3. Methyl rel-(2R,3S,5R)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylate cis-(**10**).* Yield: 127 mg [36% from *rel*-(2*R*,3*S*,5*R*)-3,5-dibromo-2,6,6-trimethyl-2-phenyltetrahydropyran *cis*-(**8**)], colorless solid, mp 72 °C (CH_2Cl_2/Et_2O). R_f=0.42 from petroleum ether/*tert*-butyl methyl ether=10:1 (v/v). δ_H (250 MHz; $CDCl_3$) 1.35 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.70 (3H, s, CH_3), 2.64 (1H, ddd, *J* 13.4, 12.5 Hz, 12.3 Hz, 4-H), 2.68 (1H, dt, J_d 13.4, J_t 4.6 Hz, 4-H), 3.77 (3H, s, CO_2CH_3), 3.98 (1H, dd, *J* 12.3, 4.6 Hz, 5-H), 4.56 (1H, dd, *J* 12.5, 4.7 Hz, 3-H). δ_C (151 MHz; $CDCl_3$) 19.8 (CH_3), 23.5 (CH_3), 30.1

(CH_3), 37.6 (C4), 47.8 (C3), 53.0 (CO_2CH_3), 53.5 (C5), 77.5 (C6), 80.0 (C2), 170.7 (CO_2CH_3). IR (KBr) ν 3015 cm^{-1}, 3001, 2950, 1740, 1289, 1227, 1108. Anal. Calcd for $C_{10}H_{16}Br_2O_2$ (344.05): C, 34.91; H, 4.69; found: C, 35.32; H, 4.48. X-ray crystallography: $C_{10}H_{16}Br_2O_3$, T=296(2) K, λ=0.71069 Å, monoclinic, $P2_1/c$, a=10.805(2) Å, b=9.008(2) Å, c=13.198(3) Å, β=100.02(2)°, Z=4, μ=6.395 mm^{-1}, completeness 100.0%, (2θ=52.74°), goodness-of-fit on F^2=0. 916, final R indices [$I>2\sigma(I)$]: $R1$=0.0407, $wR2$=0.0912.

4.6. Aplysiapyranoids

4.6.1. General method. A solution of methyl 3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylate (**10**) (91 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −78 °C in an atmosphere of argon. A solution of diisobutylaluminumhydride (DIBAH; 290 μL, 1 M in CH_2Cl_2, 0.29 mmol) was added at that temperature in a dropwise manner. The reaction mixture was stirred at −78 °C for 3 h and then treated with satd. aqueous NH_4Cl (0.5 mL) at −70 °C and subsequently with aqueous HCl [0.5 mL, 4% (w/w)]. The reaction mixture was allowed to warm to 0 °C (ice bath) and then to 20 °C. Dichloromethane (0.5 mL) and H_2O (0.5 mL) were added. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3×1.5 mL). Combined organic layer and extracts were dried ($MgSO_4$) and concentrated under reduced pressure, to furnish 79 mg (0.15 mmol) of crude 3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carbaldehyde (Supplementary data). A solution of this material in dry THF (0.5 mL) was added at 20 °C to a purple slurry obtained from anhydrous $CrCl_2$ (110 mg, 0.90 mmol) and $CHCl_3$ (29 μL, 0.33 mmol) in dry THF (1.5 mL) at 65 °C (oil bath). The reaction mixture was heated under reflux for 5 h. Diethyl ether (7 mL) and H_2O (5 mL) were added at 20 °C and the phases separated. The aqueous phase was extracted with Et_2O (3×4 mL). The combined organic phase and extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave a residue that was purified by chromatography [SiO_2, petroleum ether/diethyl ether=15:1 (v/v)].

4.6.2. Aplysiapyranoid A. From methyl *rel*-(2*R*,3*S*,5*S*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylate *trans*-(**10**) (68 mg, 0.20 mmol), DIBAH (220 μL, 1 M in CH_2Cl_2, 0.22 mmol) in CH_2Cl_2 (1.5 mL) according to the general method provided 46 mg (approximately 0.13 mmol) of crude carbaldehyde that was treated with $CrCl_2$ (93 mg, 0.76 mmol) and $CHCl_3$ (25 μL, 0.28 mmol) in dry THF (2 mL) as described in Section 4.6.1. Yield: 23 mg (33%), yellowish oil. R_f=0.71 for petroleum ether/diethyl ether=15:1 (v/v). δ_H (400 MHz; $CDCl_3$) 1.38 (3H, s, CH_3), 1.43 (6H, s, CH_3), 2.61–2.68 (2H, m, 4-H), 4.39 (1H, dd, J 7.8, 5.0 Hz, 5-H), 4.47 (1H, dd, J 6.2, 4.0 Hz, 3-H), 6.14 (1-H, d, J 13.8 Hz, CH_2=*CHCl*), 6.18 (1H, d, J 13.8 Hz, *CH_2*=CHCl). δ_C (101 MHz; $CDCl_3$) 27.3 (CH_3), 28.7 (CH_3), 29.0 (CH_3), 37.3 (C4), 54.6 (C3 or C5), 55.1 (C3 or C5), 75.8 (C6), 76.0 (C2), 118.4 (CH_2=*CHCl*), 138.4 (*CH_2*=CHCl).

4.6.3. 5-epi-Aplysiapyranoid A. From methyl *rel*-(2*R*,3*S*,5*R*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylate *cis*-(**9**) (91 mg, 0.27 mmol). Yield: 21 mg (22%), yellow oil. R_f=0.80 for petroleum ether/diethyl ether=15:1 (v/v). δ_H (400 MHz; $CDCl_3$) 1.36 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.53 (3H, s, CH_3), 2.59–2.70 (2H, m, 4-H), 3.84–3.91 (2H, m, 3-H, 5-H), 6.09 (1H, d, J 13.1 Hz, CH_2=*CHCl*), 6.29 (1H, d, J 13.1 Hz, *CH_2*=CHCl). δ_C (101 MHz; $CDCl_3$) 22.1 (CH_3), 23.3 (CH_3), 30.4 (CH_3), 38.3 (C4), 52.8 (C3 or C5), 53.9 (C3 or C5), 76.8 (C2), 77.1 (C6), 119.9 (CH_2=*CHCl*), 137.8 (*CH_2*=CHCl). HRMS: [M^+−Cl] calcd 308.9489, found 308.9484.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication [CCDC 859064 (*cis*-**3d**), CCDC 753370 (*cis*-**8**), CCDC 753369 (*trans*-**8**), CCDC 753371 (*cis*-**10**), CCDC 753373 (*trans*-**10**)]. 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).

Acknowledgements

This work is part of Ph.D. Theses of O.B. and M.G., and was supported by the Deutsche Bundesstiftung Umwelt (DBU; grant 20007/885) and the Deutsche Forschungsgemeinschaft (grant Ha1705/8–1).

Supplementary data

Instrumentation, preparation of alkenols **1a**–**e**, additional NMR-spectroscopic information, calculated energies, geometrical parameters, and coordinates of *cis*-**8**, *trans*-**8**, *cis*-**10**, *trans*-**10**, tetrahydropyran (chair conformation), tetrahydropyrans **I**–**VI**, and products associated with isomerization of alkenol **VII** into cyclic ethers **VIII** and **IX** (75 pages). Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.013.

References and notes

1. Kusumi, T.; Uchida, H.; Inouye, Y.; Ishitsuka, M.; Yamamoto, H.; Kakisawa, H. *J. Org. Chem.* **1987**, *52*, 4597–4600.
2. For discription of the biology of the Aplysiomorpha see: Thompson, T. E. *The Biology of the Opistobranch Molluscs*; The Ray Society: London, 1976; Vol. 1, pp 146–161.
3. Inouye, Y.; Uchida, H.; Kusumi, T.; Kakisawa, H. *J. Chem. Soc., Chem. Commun.* **1987**, 346–347.
4. Jung, M. E.; D'Amico, D. C. *Tetrahedron Lett.* **1993**, *34*, 923–926.
5. Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem.* **1998**, *63*, 2982–2987.
6. Jung, M. E.; Lew, W. *J. Org. Chem.* **1991**, *56*, 1347–1349.
7. Hartung, J.; Greb, M. *Tetrahedron Lett.* **2003**, *44*, 6091–6093.
8. Corey, E. J.; Ha, D. C. *Tetrahedron Lett.* **1988**, *29*, 3171–3174.
9. McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593–595.
10. For recent studies on bromocyclization see: (a) Schuch, D.; Fries, P.; Dönges, M.; Menéndez-Pérez, B.; Hartung, J. *J. Am. Chem. Soc.* **2009**, *131*, 12918–12920; (b) Werness, J. B.; Tang, W. *Org. Lett.* **2011**, *13*, 3664–3666; (c) Cui, X. L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653–5658.
11. For a recent review on tetrahydropyran synthesis see: Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053.
12. Brücher, O.; Hartung, J. *ACS Catal.* **2011**, *1*, 1448–1454.
13. Podgoršek, A.; Zupan, M.; Iskra, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8424–8540.
14. For recent examples on enantioselective bromolactonozations, see: (a) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174–9177; (b) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474–15476; (c) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665.
15. González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099–9108.
16. Martín, D. D.; Marcos, I. S.; Basabe, P.; Romero, R. E.; Moro, R. F.; Lumeras, W.; Rodríguez, L.; Urones, J. G. *Synthesis* **2001**, 1013–1022.
17. Wischang, D.; Brücher, O.; Hartung, J. *Coord. Chem. Rev.* **2011**, *255*, 2204–2217.
18. Hartung, J. *Pure Appl. Chem.* **2005**, *77*, 1559–1574.
19. Gottwald, T.; Greb, M.; Hartung, J. *Synlett* **2004**, 65–68.
20. For pioneering studies on bromide oxidation catalyzed by vanadium(V) complexes see: Colpas, G. J.; Hamstra, B. J.; Kampf, J. W.; Pecoraro, V. L. *J. Am. Chem. Soc.* **1996**, *118*, 3469–3478.
21. Barhate, B. N.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127–11142.
22. Greb, M.; Hartung, J.; Köhler, F.; Špehar, K.; Kluge, R.; Csuk, R. *Eur. J. Org. Chem.* **2004**, 3799–3812.
23. Anschütz, R.; Kinnkutt, L. *Chem. Ber.* **1878**, *11*, 1221–1222.
24. Fittig, R.; Binder, F. *Liebigs Ann. Chem.* **1879**, *195*, 56–179.
25. For a survey on methods for oxidative bromination in synthesis see: Rothenberg, G.; Clark, J. H. *Green Chem.* **2000**, *2*, 248–251.
26. Haegele, E. *Chem. Ber.* **1892**, *25*, 2753–2756.
27. Kuczynski, L.; Wilimowski, M.; Baginska, M.; Soloducho, J. *Pol. J. Pharmacol.* **1975**, *27*, 549–553.
28. Clague, M. J.; Keder, N. L.; Butler, A. *Inorg. Chem.* **1993**, *32*, 4754–4761.
29. Breitmaier, E. *Terpene*; Teubner Studienbücher Chemie: Stuttgart, 1999.
30. Nelson, D. J.; Ruibo, L.; Brammer, C. *J. Org. Chem.* **2001**, *66*, 2422–2428.
31. Ruasse, M.-F. *Acc. Chem. Res.* **1990**, *23*, 87–93.
32. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
33. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *B37*, 785–789.
34. Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724–728.
35. Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261.
36. Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974**, *27*, 209–214.
37. Hartung, J.; Kneuer, R.; Rummey, C.; Bringmann, G. *J. Am. Chem. Soc.* **2004**, *126*, 12121–12129.

38. Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, M. *J. Am. Chem. Soc.* **1982**, *104*, 3635–3643.
39. Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562–5578.
40. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; J. Wiley & Sons: New York, NY, 1994, pp 597–615.
41. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.
42. Jung, M. E.; Piizi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.
43. For a discussion on the role of strain in methylcyclohexanes see: (a) Anderson, E. J. *Top. Curr. Chem.* **1974**, *45*, 139–167; (b) Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765–780.
44. Barton, D. H. R.; Ferreira, J. A. *Tetrahedron* **1996**, *52*, 9347–9366.
45. Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413–1432.
46. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
47. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
48. Hartung, J.; Greb, M.; Svoboda, I.; Fuess, H. *Acta Crystallogr.* **2006**, *E62*, o1920–o1922.
49. Greb, M.; Hartung, J. *Synlett* **2004**, 69–72.
50. Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944.
51. Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314.
52. Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300.

5 Entwicklung und Anwendung von Methoden zur oxidativen Chlorcyclisierung substituierter 4-Pentenole

5.1 Zusammenfassung

Mit der vorliegenden Studie konnte gezeigt werden, dass die katalytische Oxidation von Chlorid in wasserfreien, organischen Medien unter milden und nachhaltigen Bedingungen möglich ist. Die erzeugten elektrophilen Chlorierungsäquivalente ließen sich zur Chlorcyclisierung substituierter 4-Pentenole in Ausbeuten von bis zu 80 % nutzen, wobei die erhaltenen Selektivitäten auf einen Chloroniumionen-Mechanismus hinweisen. Die entwickelte Prozedur nutzt Molybdän(VI)- und Titan(IV)-Komplexe zur Aktivierung von *tert*-Butylhydroperoxid in Lösungen von Dimethylcarbonat bei Temperaturen von 20–40 °C. Dabei dient Pyridiniumhydrochlorid (py·HCl) als Quelle für Chloridionen und für Protonen. Die Übergangsmetallkatalysierte Methode zur Chloridoxidation wurde zusätzlich durch ein stöchiometrisches Verfahren ergänzt, welches Kaliumhydrogenperoxomonosulfat als Oxidans und Säurequelle nutzt, um Kaliumchlorid in Dimethylcarbonat zu oxidieren. Die entwickelten Methoden eignen sich ferner zur Chlorierung von Alkanen, aktivierten Aromaten sowie allylischer C,H-Bindungen und fanden Anwendung in einer modifizierten Synthese des Naturstoffs (±)-Rosenoxid aus Citronellol. In allen Umsetzungen beobachtete Selektivitäten deuten gemeinsam auf molekulares Chlor als aktives Chlorierungsreagenz hin.

5.2 Wissenschaftlicher Hintergrund, Zielsetzung und Strategie

Chlorcyclisierungsreaktionen substituierter 4-Pentenole sind in der Literatur weitgehend unbekannt. Die wenigen existierenden Beispiele beschreiben Umsetzungen Methyl-substituierter 4-Pentenolsubstrate mit stöchiometrischen Reagenzien, wie *tert*-Butyl- oder *para*-Nitrobenzolsulfonylhypochlorit, welche die chlorierten O-Heterocyclen meist nur in niedrigen Ausbeuten liefern.[1][2] Für künftige Anwendungen oxidativer Chlorcyclisierungen in der Synthese β-chlorierter O-Heterocyclen sollte in der vorliegenden Arbeit ein Chloroperoxidase-analoges Verfahren zur *in situ*-Generierung elektrophiler Chlorierungsreagenzien entwickelt werden, welches unter milden Bedingungen in wasserfreien Medien operiert. Die derzeit vorhandenen Chloroperoxidase-Modellsysteme zur oxidativen Chlorierung organischer Substrate nutzen Übergangsmetall-Komplexe mit Molybdän-, Eisen- oder Vanadium-Zentren in organisch-wässrigen Medien unter stark sauren Bedingungen und/oder hohen Temperaturen.[3–6] Dabei werden lediglich Chlorierungen elektronenreicher Aromaten beschrieben, wohingegen

Umsetzungen mit anspruchsvolleren Substraten, wie etwa C,C-Doppelbindungen, bis dato weitgehend unberücksichtigt blieben. Aufbauend auf den in Kapitel 3 und 4 vorgestellten Vanadium(V)-katalysierten Verfahren zur oxidativen Bromierung[7][8] sollten daher praktikable Methoden zur Durchführung von oxidativen Chlorcyclisierungen substituierter 4-Pentenole unter ähnlich milden Bedingungen ausgearbeitet werden. Bei der Wahl der Reagenzien und Reaktionsparameter für die möglichst universell einsetzbaren Chloroperoxidase-Modellsysteme sollten die in Bromidoxidationsverfahren gesammelten Erfahrungen berücksichtigt werden. Erkenntnisse einer früheren Studie[9] und orientierende Vorexperimente deuteten jedoch darauf hin, dass die in der oxidativen Bromierung verwendeten Vanadium(V)-Katalysatoren VO(L^{1-3})(OEt) eine Oxidation von Chlorid unter diesen Reaktionsbedingungen nicht mit ausreichender Geschwindigkeit katalysieren können und somit auf alternative Metallzentren zurückgegriffen werden müsste.

Parallel zu der Untersuchung Übergangsmetall-katalysierter Chloridoxidationen sollte ferner eine Methode evaluiert werden, welche das Tripelsalz $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®) und Kaliumchlorid zur Erzeugung elektrophiler Chlorierungsreagenzien nutzt. Das beschriebene Verfahren wurde bereits zur Chlorierung elektronenreicher Aromaten in einer wasserfreien Lösung von Acetonitril eingesetzt,[10] weshalb es sich prinzipiell auch für die Durchführung von Chlorcyclisierungen eignen könnte. Die Resultate oxidativer Chlorierungsexperimente mit ausgewählten Substraten sollten darüber hinaus wichtige Hinweise auf die Natur des selektivitätsbestimmenden Chlorierungsreagenzes liefern.

Aus dem Stand der Forschung zur oxidativen Chlorierung ergaben sich damit für das vorliegende Projekt folgende Aufgaben und Zielsetzungen:

- Entwicklung eines wirkungsvollen Protokolls zur Übergangsmetall-katalysierten oxidativen Chlorcyclisierung von 4-Pentenolen in wasserfreien organischen Medien für die Darstellung β-chlorierter O-Heterocyclen mit Bezug zur Naturstoffchemie.

- Evaluierung und Weiterentwicklung der Chloridoxidation mit Kaliumhydrogen-peroxomonosulfat (Salz-Methode) zur Chlorcyclisierung substituierter 4-Pentenole.

- Untersuchung der Reaktivität generierter Chlorierungsreagenzien bei der Umsetzung von Alkanen, Alkenen und Aromaten zur Ermittlung der Anwendungsbreite der Methode und Identifikation des selektivitätsbestimmenden Chlorierungsreagenzes anhand mechanistischer Untersuchungen.

5.3 Ergebnisse und Diskussion

5.3.1 Methodenevaluierung und Chlorcyclisierung substituierter 4-Pentenole

Für die Ermittlung einer geeigneten Kombination aus Übergangsmetall-Katalysator, Lösungsmittel, Protonenquelle und Chloridquelle zur Verwendung mit *tert*-Butylhydroperoxid als Primäroxidans wurden zahlreiche Vorexperimente mit entsprechenden Reagenzien durchgeführt. Dabei zeigten die kommerziell erhältliche Molybdän(VI)-Verbindung $MoO_2(acac)_2$ sowie drei weitere unabhängig synthetisierte Molybdän-Komplexe $MoO_2(L^{1, 2, 4})$ hohe katalytische Aktivitäten bei Verwendung von Pyridiniumhydrochlorid (py·HCl) und *tert*-Butylhydroperoxid in einer Lösung von Acetonitril. Die Synthese der bekannten Verbindung $MoO_2(L^1)$[11] und der neuen Molybdän(VI)-Komplexe $MoO_2(L^{2, 4})$ wurde in methanolischer Lösung bei Raumtemperatur durchgeführt und lieferte die Koordinationsverbindungen als farblose bis gelbe Feststoffe in Ausbeuten von 68–96 % (Abb. 5.1).

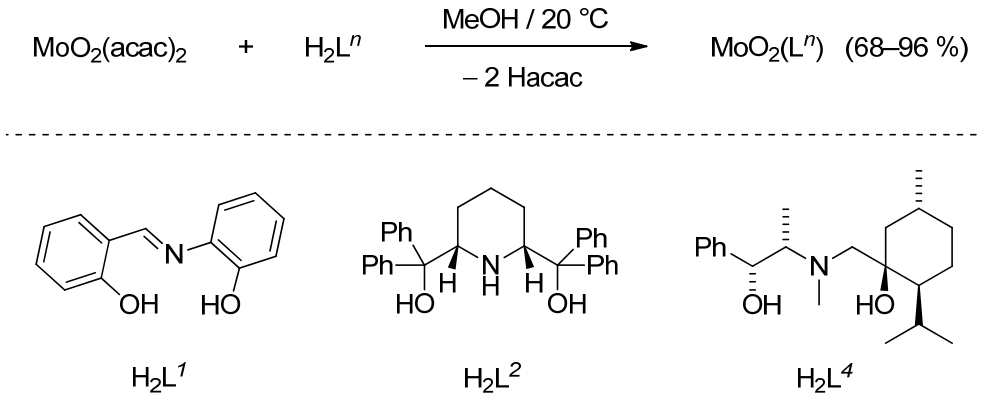


Abbildung 5.1 Synthese der Molybdän(VI)-Komplexe $MoO_2(L^{1, 2, 4})$ und Strukturen verwendeter Liganden $H_2L^{1, 2, 4}$ mit O,N,O-Donormotiv.[12][13]

Weiterhin fiel in den Screenings ein Titan(IV)-Komplex $[TiL^3(OEt)_2]$ auf, welcher die Chloridoxidation schon bei 20 °C mit effektiver Geschwindigkeit katalysierte, während die Reaktionen mit Molybdän(VI)-Verbindungen erwartungsgemäß erst ab 35–40 °C verwertbare Umsatzraten zeigten (Abb. 5.2).

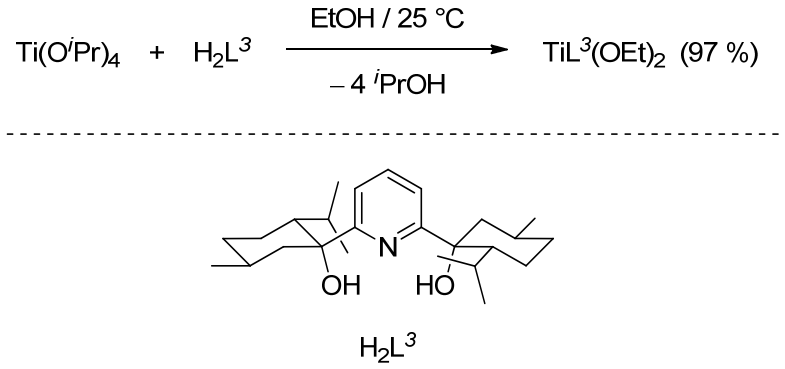
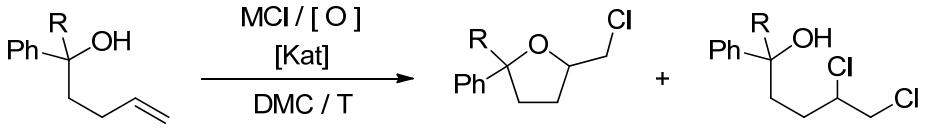


Abbildung 5.2 Synthese des Titan(IV)-Komplexes $TiL^3(OEt)_2$ und Struktur von H_2L^3.[14]

Die in den ersten Experimenten gefundenen Reaktivitäten konnten durch den Einsatz von Dimethylcarbonat als Solvens und durch wasserfreie Reaktionsführung unter Inertgas noch weiter für Chlorcyclisierungen von 4-Pentenolen optimiert werden (Tabelle 5.1). Dabei wurde hier in Abwesenheit des Übergangsmetall-Komplexes, im Gegensatz zu Bromidoxidationen mit Pyridiniumhydrobromid,[9] keine oxidative Halogenierung beobachtet.

Tabelle 5.1 Oxidative Chlorcyclisierung 1-Phenyl-substituierter 4-Pentenole **9l** und **9m**



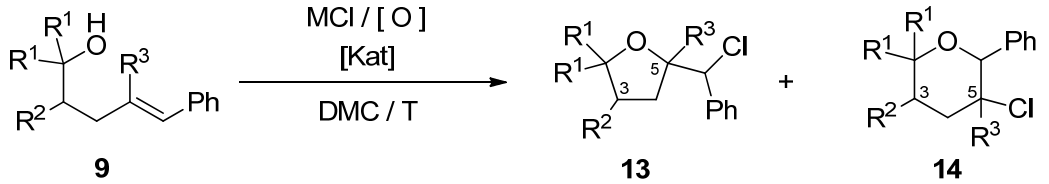
9 **13** **15**

Eintrag	**9**	R	MCl / [O]	[Kat][a]	T / °C	**13** / % (*cis*:*trans*)	**15** / %[b]
1	**l**	H	py·HCl / *t*BuOOH	–	40	–[c]	–[c]
2	**l**	H	py·HCl / *t*BuOOH	$MoO_2(acac)_2$	40	74 (40:60)	13
3	**l**	H	py·HCl / *t*BuOOH	$MoO_2(L^4)$	40	69 (42:58)	15
4	**l**	H	py·HCl / *t*BuOOH	$MoO_2(L^2)$	40	62 (42:58)	29
5	**l**	H	py·HCl / *t*BuOOH	$MoO_2(L^1)$	40	45 (45:55)	18
6	**l**	H	py·HCl / *t*BuOOH	$TiL^3(OEt)_2$	20	62 (41:59)	21
7	**l**	H	KCl / $KHSO_5$[d]	–	30	72 (41:59)	–[c]
8	**m**	CH_3	py·HCl / *t*BuOOH	$MoO_2(L^4)$	40	80 (38:62)	17
9	**m**	CH_3	py·HCl / *t*BuOOH	$TiL^3(OEt)_2$	20	67 (35:65)	19
10	**m**	CH_3	KCl / $KHSO_5$[d]	–	30	78 (41:59)	8

[a] 5 mol%. [b] 50/50-Mischung von Stereoisomeren. [c] Nicht detektiert. [d] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®).

Die Übergangsmetall-katalysierten oxidativen Chlorierungen 1-Phenyl-substituierter 4-Pentenole **9l** und **9m** lieferten die β-chlorierten Tetrahydrofurane **13l** und **13m** als *cis*/*trans*-Gemische in Ausbeuten von 45–80 % zusammen mit 13–19 % der entsprechenden dichlorierten Alkenole **15l** und **15m**. Die Umsetzungen unter Einsatz der alternativen Chloridoxidations-methode mit Kaliumhydrogenperoxomonosulfat (Salz-Methode) zeigten unter Verwendung von Dimethylcarbonat als Solvens ähnliche Ausbeuten von 72 % (für **13l**) und 78 % (für **13m**) wie das katalytische Verfahren. Die Salz-Methode zeichnete sich bei diesen beiden Substraten vor allem dadurch aus, dass die Bildung von unerwünschten acyclischen Dichloriden entweder ganz unterdrückt oder deutlich vermindert wurde, was möglicherweise mit einer geringeren Löslichkeit von KCl gegenüber Pyridiniumhydrochlorid in Dimethylcarbonat zusammenhängen könnte. Bei den Umsetzungen der 5-Phenyl-substituierten Alkenole **9a** und **9i**, welche bereits in Bromcyclisierungsreaktionen als Substrate dienten (vgl. Tabelle 3.3, S. 27 und Tabelle 4.3, S. 45), wurden je nach Methode Gesamtausbeuten von 53–74 % erzielt, wobei keine Dichloride gefunden wurden (Tabelle 5.2).

Tabelle 5.2 Chlorcyclisierung 5-Phenyl-substituierter 4-Pentenole **9a** und **9i**.

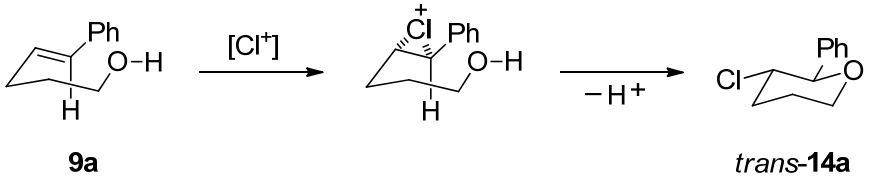


9 **13** **14**

Eintrag	**9**	R^1	R^2	R^3	MCl / [O] / [Kat][a] / *T*	**13** / % (*cis*:*trans*)	**14** / % (*cis*:*trans*)
1	**a**	H	H	H	py·HCl / *t*BuOOH $MoO_2(L^4)$ / 40 °C	–[b]	65 (< 2:98)
2	**a**	H	H	H	py·HCl / *t*BuOOH $TiL^3(OEt)_2$ / 20 °C	–[b]	74 (< 2:98)
3	**a**	H	H	H	KCl / $KHSO_5$[c] –[d] / 30 °C	–[b]	58 (< 2:98)
4	**i**	CH_3	CO_2Et	CH_3	py·HCl / *t*BuOOH $MoO_2(L^4)$ / 40 °C	46 (90:10)	7 (> 98:2)
5	**i**	CH_3	CO_2Et	CH_3	py·HCl / *t*BuOOH $TiL^3(OEt)_2$ / 20 °C	54 (90:10)	5 (> 98:2)
6	**i**	CH_3	CO_2Et	CH_3	KCl / $KHSO_5$[c] –[d] / 30 °C	64 (93:7)	2 (> 98:2)

[a] 5 mol%. [b] Nicht detektiert. [c] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®). [d] Ohne weiteren Katalysatorzusatz.

Anhand der beobachteten Regio- und Stereoselektivitäten des gesamten Satzes an 4-Pentenolen lassen sich Aussagen zum Reaktionsmechanismus der Chlorcyclisierung ableiten. Der intramolekulare Angriff des Hydroxylsauerstoffs verläuft in allen Fällen an der höher substituierten Position der Alkenoldoppelbindung. So führt die Umsetzung von Substraten mit terminaler Doppelbindung (**9l** und **9m**) zu Tetrahydrofuranen und die oxidative Chlorierung der 5-Phenyl-substituierten Substrate **9a** und **9i** selektiv zur Bildung von Tetrahydropyran **14a** und Tetrahydrofuran **13i**. Damit verlaufen die Chlorcyclisierungen analog zu den in Kapitel 4 (vgl. S. 42–46) herausgearbeiteten Faktoren zur Beschreibung von Regioselektivitäten in Alkenolcyclisierungen, was für das Vorliegen eines polaren Mechanismus mit einer Chloroniumion-Zwischenstufe spricht (Schema 5.1).



9a *trans*-**14a**

Schema 5.1 Mechanistisches Modell zur Erklärung von Regio- und Stereoselektivität der Chlorcyclisierung von Alkenol **9a**.

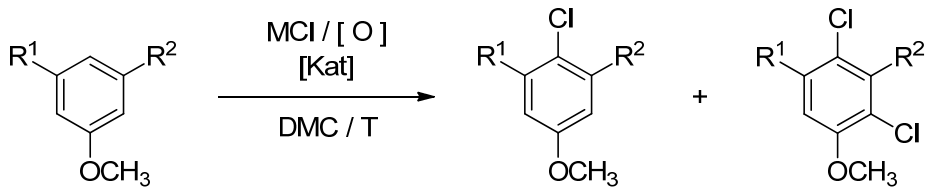
Die selektive Bildung des *trans*-konfigurierten Tetrahydropyrans *trans*-**14a** kommt dabei durch einen S_N2-Typ Rückseitenangriff des Hydroxylsauerstoffs auf die geladene Dreiring-Zwischenstufe zustande, bei dem die (*E*)-Konfiguration des Alkenolsubstrats **9a** in die *trans*-Konfiguration des Cyclisierungsproduktes übertragen wird. Die vorherrschende 3,5-*cis*-Konfiguration des Tetrahydrofuranprodukts **13i** deutet ferner auf thermodynamische Kontrolle des Reaktionsverlaufs hin, da es sich hierbei um das energieärmste Stereoisomer handelt.

Da die Natur des generierten Chlorierungsmittels aus den Experimenten zur Chlorcyclisierung nicht genauer bestimmt werden konnte, wurden hierzu weitere Experimente durchgeführt. Dabei lieferte die Umsetzung von Dimedon mit der Molybdän-katalysierten Variante und der Salzmethode zur oxidativen Chlorierung 2,2-Dichlordimedon in Ausbeuten von 72 bzw. 64 %, was belegt, dass in beiden Verfahren eingesetzte Chloridionen zunächst in elektrophile Reagenzien umgewandelt werden. Als mögliche Chlorierungsmittel wurden dabei hypochlorige Säure (HOCl), molekulares Chlor sowie andere möglicherweise *in situ* generierte Reagenzien wie *tert*-Butylhypochlorit in Betracht gezogen. Zur weiteren Eingrenzung wurden daher Struktur-Reaktivitäts-Studien mit ausgewählten Substraten durchgeführt (vgl. Kap. 5.3.2, 5.3.4 und 5.3.5).

5.3.2 Aromatenchlorierung

Zum Vergleich der neu entwickelten Methoden mit den wenigen bereits literaturbekannten Verfahren zur Chloridoxidation wurden Umsetzungen Methoxy-substituierter Aromaten untersucht. Anisol **16a** lieferte dabei *ortho*- und *para*-Chlormethoxybenzol (**17**) in Ausbeuten von 61 % für die Molybdän-katalysierte und 83 % für die Titan-katalysierte Reaktion (nach 24 h), wobei die Umsätze in beiden Fällen der Stoffmenge an monochlorierten Produkten **17** entsprachen (Tabelle 5.3, Einträge 2 und 3).

Tabelle 5.3 Oxidative Chlorierung Methoxy-substituierter Benzolderivate **16a–c**.



16 **17** **18**

Eintrag	R^1	R^2	**16**	MCl / [O] / [Kat][a] / T	**17** / %	**18** / %
1	H	H	**a**	py·HCl / *t*BuOOH / – / 40 °C	–[b]	–[b]
2	H	H	**a**	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / 40 °C	61 (88:12)[c]	–[b]
3	H	H	**a**	py·HCl / *t*BuOOH / $TiL^4(OEt)_2$ / 20 °C	83 (94:6)[c]	–[b]
4	H	H	**a**	KCl / $KHSO_5$[c] / – / 30 °C	32 (96:4)[c]	–[b]
5	OCH_3	H	**b**	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / 40 °C	79	21
6	OCH_3	H	**b**	py·HCl / *t*BuOOH / $TiL^4(OEt)_2$ / 20 °C	89	11
7	OCH_3	H	**b**	KCl / $KHSO_5$[c] / – / 30 °C	53	–[b]
8	OCH_3	OCH_3	**c**	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / 40 °C	78	21
9	OCH_3	OCH_3	**c**	py·HCl / *t*BuOOH / $TiL^4(OEt)_2$ / 20 °C	82	18
10	OCH_3	OCH_3	**c**	KCl / $KHSO_5$[c] / – / 30 °C	67	11

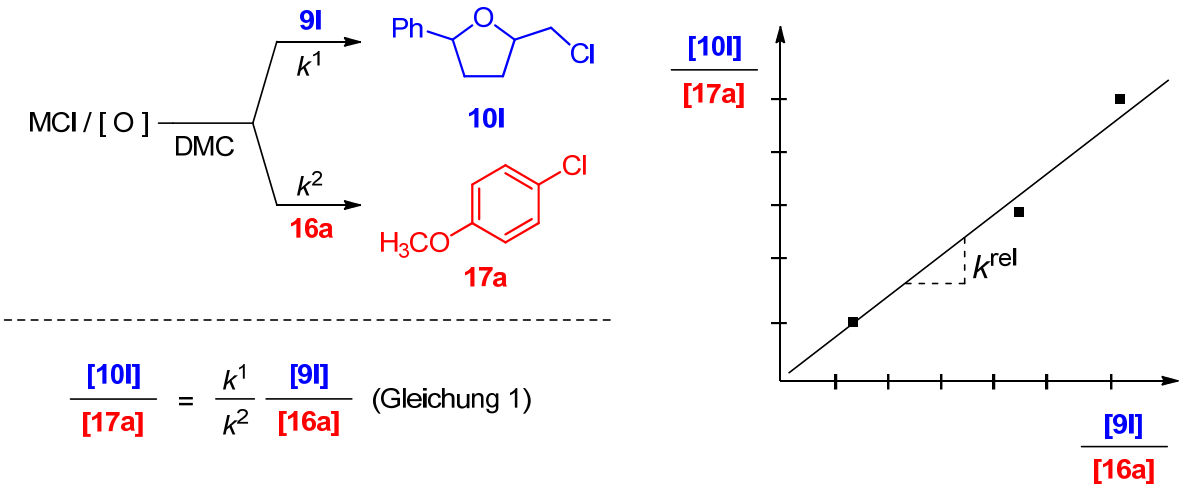
[a] 5 mol%. [b] Nicht detektiert. [c] *para*/*ortho*-Verhältnis. [d] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®).

Die erfolgreiche Umsetzung des Substrats **16a** deutet darauf hin, dass hypochlorige Säure als selektivitätsbestimmendes Chlorierungsreagenz hier keine zentrale Rolle spielt, da HOCl unter neutralen Bedingungen nicht in der Lage ist Methoxybenzol (**16a**) am aromatischen Kern zu chlorieren.[15][16] Die Übergangsmetall-katalysierten oxidativen Chlorierungen von 1,3-Dimethoxybenzol (**16b**) und 1,3,5-Trimethoxybenzol (**16c**) lieferten die einfach chlorierten Verbindungen **17b** und **17c** in nahezu quantitativer Ausbeute, zusammen mit den entsprechend zweifach chlorierten Produkten. (Tabelle 5.3, Einträge 5, 6, 8 und 9). Demgegenüber verliefen

die Chlorierungen mit der Salzmethode für alle aromatischen Substrate mit deutlich verminderter Effizienz. Das elektronenreiche System 1,3,5-Trimethoxybenzol (**16c**) wurde bereits in anderen Arbeiten zur Bewertung von oxidativen Chlorierungen herangezogen und zeigte hier Ausbeuten von 20–93 % in Umsetzungen mit Molybdän(VI)-, Kupfer(II)- oder Vanadium(V)-katalysierten Chloridoxidationen.[5][6][17] Die beschriebenen Methoden benötigen dabei entweder erhöhte Temperaturen (≥ 60 °C), starke Säuren und/oder große Reagenzüberschüsse um die Chloridoxidation mit brauchbarer Geschwindigkeit ablaufen zu lassen. Die neu entwickelten Molybdän- und Titan-katalysierten Verfahren erreichen demnach in dieser Reaktion bessere Ausbeuten bei milderen Temperaturen und verwenden zudem weniger Chlorid- und Protonenäquivalente.

5.3.3 Konkurrenzstudien von Chlorcyclisierung versus Aromatenchlorierung

In Ergänzung zu Untersuchungen von Chlorcyclisierung und Aromatenchlorierung bestand darüber hinaus das Interesse, die relative Reaktivität der beiden Reaktionspfade zu bestimmen, um den Verlauf der Chlorcyclisierungsreaktionen von Alkenolen mit elektronenreichen aromatischen Substituenten besser vorhersagen zu können (vgl. Kap. 4.3.2). Als Testsystem wurde die oxidative Chlorierung von 1-Phenyl-4-pentenol (**9l**) in Gegenwart von Methoxybenzol (**16a**), 1,3-Dimethoxybenzol (**16b**) oder 1,3,5-Trimethoxybenzol (**16c**) gewählt, wobei das ausgearbeitete Verfahren zur Übergangsmetall-katalysierten Chloridoxidation mit den Komplexen $MoO_2(acac)_2$, $MoO_2(L^4)$ und $TiL^3(OEt)_2$ zur Anwendung kommen sollte. Die Substrate wurden dabei in 10-fachem Überschuss zur theoretisch vorhandenen Menge generierter Chlorierungsreagenzien eingesetzt um sicherzustellen, dass die Konkurrenzreaktionen unter Bedingungen pseudo-erster Ordnung verliefen. Die Reaktion des Alkenols **9l** in Gegenwart von 1,3-Dimethoxybenzol (**16b**) oder 1,3,5-Trimethoxybenzol (**16c**) führte, auch bei Anwendung eines 10- oder 50-fachen Überschusses an Alkenolsubstrat zu einer kompletten Umsetzung aktivierter Aromaten, jedoch zu keiner Bildung des chlorierten Tetrahydrofurans **10l**. Die Verwendung von Anisol **16a** bewirkte eine Inversion der Chemoselektivität, so dass bei äquimolarem Einsatz von Alkenol und Aromat lediglich die Chlorcyclisierungsprodukte gefunden wurden. Durch Erhöhung der Anisolkonzentration auf das 10-, 50- und 100-fache gelang es jedoch, analytisch aussagekräftige Mengen beider Chlorierungsprodukte zu erhalten. Die Produktverhältnisse wurden nach Gleichung 1 mit denjenigen eingesetzter Substrate linear korreliert und die relative Geschwindigkeitskonstante $k^{rel} = k^1 / k^2$ des Konkurrenzsystems aus der Geradensteigung abgeleitet (Schema 5.2).



Schema 5.2 Konkurrenzstudie zur Bestimmung relativer Reaktivitäten der Chlorcyclisierung von Alkenol **9l** und der Chlorierung von Anisol **16a**.

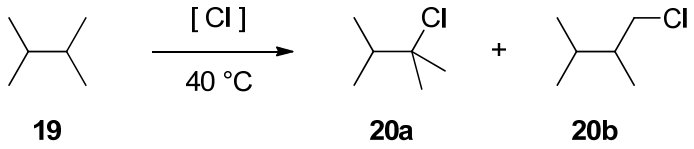
Die für die verschiedenen Katalysatoren resultierenden Werte für k^{rel} variierten in einem Bereich zwischen 500 und 600, was belegt, dass die Tendenz zur Chlorierung eines schwach aktivierten Aromaten in Gegenwart eines 4-Pentenol-Substrates äußerst gering ist und somit nicht mit der Chlorcyclisierung interagieren sollte.

5.3.4 Radikalische Alkanchlorierung

Die radikalische Chlorierung von 2,3-Dimethylbutan (**19**) ist ein häufig durchgeführtes Experiment zur Bewertung der chemischen Natur eines Chlorierungsreagenzes anhand der entstehenden Produktverteilung.[18–21] Bei der Reaktion werden aliphatische Wasserstoffatome in homolytischer Substitution gegen Chloratome ausgetauscht, wobei tertiäre Wasserstoff-Kohlenstoff-Bindungen reaktiver als primäre sind. Unter Einbezug der statistisch verfügbaren Reaktionspositionen leitet sich aus dem Verhältnis der gebildeten Produkte **20a** und **20b** der partielle Geschwindigkeitsfaktor der homolytischen Substitution $f = f^{tert} / f^{prim}$ ab, welcher sowohl von der Temperatur als auch vom Lösungsmittel abhängig ist.[22] Da die untersuchten Molybdän-Komplexe $MoO_2(L^{1,2,4})$ und der Titan-Komplex $TiL^3(OEt)_2$ in 2,3-Dimethylbutan (**19**) kaum löslich waren, wurde dem Reaktionsgemisch Dimethylcarbonat oder Acetonitril zugesetzt. Die Bestrahlung einer homogenen Lösung aus Pyridiniumhydrochlorid, *tert*-Butylhydroperoxid und dem Ephedrin-abgeleiteten Molybdän-Komplex $MoO_2(L^4)$ in 2,3-Dimethylbutan (**19**) und Dimethylcarbonat mit einer Wolfram-Lampe bei einer Temperatur von 40 °C lieferte 2-Chlor-2,3-dimethylbutan (**20a**) und 2-Chlormethyl-3-methylbutan (**20b**) in einer Gesamtausbeute von 52% (Tabelle 5.4, Eintrag 1). Aus dem experimentell bestimmten

Isomerenverhältnis von 27:73 ergab sich ein partieller Geschwindigkeitsfaktor von $f = 2.2$, was bedeutet, dass die Substitution für tertiäre C,H-Bindungen in 2,3-Dimethylbutan (**19**) unter den gewählten Bedingungen 2.2-mal rascher erfolgte als für primäre. Bei einem Wechsel des Lösungsmittels von Dimethylcarbonat zu Acetonitril, unter ansonsten unveränderten Reaktionsbedingungen, betrug der Faktor $f = 2.8$ (Tabelle 5.4, Eintrag 2). Das Salzverfahren lieferte für die Reaktion in Dimethylcarbonat einen ähnlichen Wert von $f = 2.3$ (Tabelle 5.4, Eintrag 4). Die genannten Reaktionen liefen ebenfalls unter dem Ausschluss von Licht ab, wobei zwar die gefundenen Gesamtausbeuten von **20a** und **20b** geringfügig variierten, jedoch die Isomerenverhältnisse und damit die relativen Reaktivitäten praktisch unverändert blieben (Tabelle 5.4, Eintrag 3 und 4).

Tabelle 5.4 Selektivitäten der radikalischen Chlorierung von 2,3-Dimethylbutan (**19**).



19 **20a** **20b**

Eintrag	[Cl]	**20** / % [a]	**20a** / **20b**	f^{tert-}/f^{prim} [b]
1	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / DMC / $h\nu$	52 (26)	27 / 73	2.2
2	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / CH_3CN / $h\nu$	77 (39)	31 / 69	2.8
3	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / DMC	72 (36)	32 / 68	2.7
4	KCl / $KHSO_5$ [c] / DMC	69 (34)	28 / 72	2.3

[a] Ausbeute bzgl. **19** (Ausbeute bzgl. Chlorid). [b] Partielle Geschwindigkeitsfaktoren für die Chlorierung von tertiären gegenüber primären C,H-Bindungen in **19**. [c] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®).

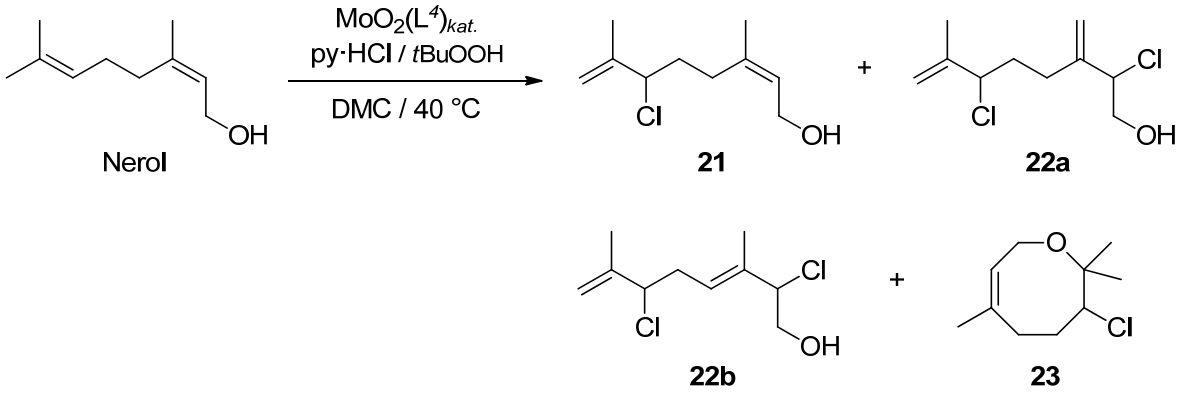
Die gemessenen Werte für die partiellen Geschwindigkeitsfaktoren sind vergleichbar mit dem Referenzwert für die Chlorierung von 2,3-Dimethylbutan mit molekularem Chlor unter Bedingungen einer Radikalkettenreaktion, welcher in flüssiger Phase bei 40 °C ohne Zusatz weiterer Lösungsmittel 3.9 beträgt.[20] Als denkbare Alternative zu molekularem Chlor könnte in einer vorgelagerten Reaktion aus *tert*-Butanol und dem primär generierten Chlorierungsmittel *tert*-Butylhypochlorit gebildet werden, welches jedoch mit einem Selektivitätsfaktor von $f = 44$ (für 40 °C) einen deutlich höheren Referenzwert als die hier beobachteten Reaktionen aufweist.[23] Da hypochlorige Säure als primäres Chlorierungsreagenz bereits in Kapitel 5.3.2 ausgeschlossen werden konnte und die ermittelten Werte von f für beide Verfahren im Bereich des Referenzwerts für homolytisch erzeugte Chlorradikale liegen, sind die in bisherigen

Umsetzungen beobachteten Selektivitäten mit hoher Wahrscheinlichkeit auf molekulares Chlor zurückzuführen.

5.3.5 Allylische Chlorierung ungesättigter Naturstoffe

Neben 1,2-Additionen über einen Chloroniumionen-Mechanismus reagieren vor allem Alkyl-substituierte C,C-Doppelbindungen mit Chlorierungsmitteln unter Wasserstoff-Chlor-Austausch in Allylstellung.[24–26] Diese Reaktion ist besonders interessant, da sie Parallelen mit der bekannten Schenck-En-Reaktion aufweist. Im Verlauf dieser konzertierten Reaktion greift ein Singulett-Sauerstoff-Molekül das Kohlenstoffatom einer C,C-Doppelbindung an, wobei gleichzeitig ein allylischer Wasserstoff abstrahiert wird und es zu einer 1,2-Verschiebung der Doppelbindung unter Ausbildung eines Allylhydroperoxids kommt.[27–29] Zur Untersuchung dieser Reaktivität wurden die ungesättigten Naturstoffe Nerol und Citronellol als Substrate ausgewählt und in einer Molybdän-katalysierten oxidativen Chlorierung mit $MoO_2(L^4)$ umgesetzt. Die Chlorierung von Nerol lieferte in der Hauptreaktion die Produkte einer einfachen (**21**) und einer zweifachen (**22a/b**) allylischen Chlorierung (Tabelle 5.5).[30] Des Weiteren konnte nach säulenchromatographischer Aufarbeitung auch das Produkt **23** einer 8-*endo*-trig Chlorcyclisierung identifiziert werden, welches bereits als Bromderivat nach einer biomimetischen Bromierungsreaktion von Nerol durch Butler *et al.* isoliert werden konnte.[31] Ähnliche β-halogenierte Oxocin-Strukturen sind auch in verschiedenen marinen Naturstoffen zu finden.[32][33] In einem Folgeexperiment gelang es die Ausbeute dieses Tetrahydro-*2H*-oxocin-Derivats **23** durch langsame Zugabe von Pyridiniumhydrochlorid und *tert*-Butylhydroperoxid von 1 % auf 16 % zu steigern (Tabelle 5.5, Eintrag 2).

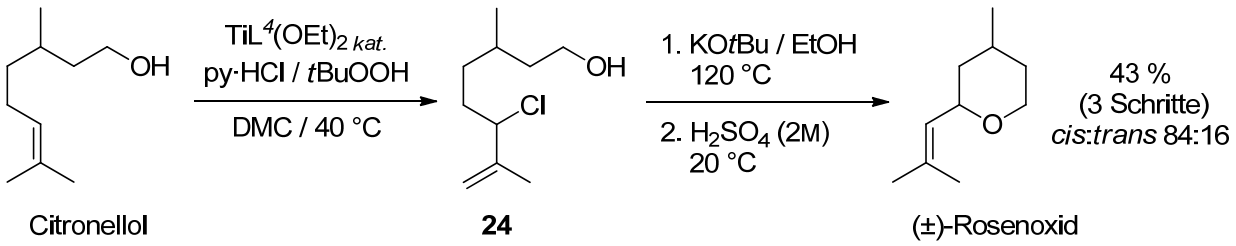
Tabelle 5.5 Produkte der oxidativen Chlorierung von Nerol.[30]



Eintrag	Methode	**21** / %	**22** / % (**22a** / **22b**)	**23** / %
1	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / 40 °C	66	21 (78:22)	1
2	py·HCl / *t*BuOOH / $MoO_2(L^4)$ / 40 °C [a]	50	4 (>98:2)	16

[a] Langsame Zugabe einer Lösung von py·HCl und *t*BuOOH in MeCN.

Die Chlorierung von Citronellol mit $TiL^4(OEt)2$ als Katalysator lieferte ebenfalls das Produkt einer allylischen Monosubstitution in einer Ausbeute von 70 %.[34] Die Verbindung **24** ist das Zwischenprodukt einer literaturbekannten Synthese von (±)-Rosenoxid, in welcher der Naturstoff nach HCl-Eliminierung und anschließender Säure-katalysierter Cyclisierung erhalten wird (Schema 5.3).[35] In Anlehnung an diese Darstellung wurde die nach der oxidativen Chlorierung gewonnene Reaktionsmischung konzentriert, mit einer Lösung von Kalium-*tert*-butanolat in Ethanol erhitzt und nach Abkühlung und Zugabe von 2M H_2SO_4 gerührt. Auf diese Weise konnte (±)-Rosenoxid in einer Eintopfsynthese mit einem *cis*/*trans*-Verhältnis von 84:16 in einer Gesamtausbeute von 43 % erhalten werden.



Schema 5.3 Eintopfsynthese von (±)-Rosenoxid aus Citronellol durch eine Sequenz aus allylischer Chlorierung, HCl-Eliminierung und Säure-katalysierter Umlagerung.

5.4 Ausblick

In der vorliegenden Arbeit konnten Verfahren präsentiert werden, in welchen sich *in situ* dargestellte Chlorierungsäquivalente zur Chlorcyclisierung substituierter 4-Pentenole sowie zur Chlorierung aktivierter Aromaten, Alkane und weiterer Alkensubstrate nutzen ließen. Die hohe Praktikabilität der neu entwickelten Methoden hat das Potential, Anwendungsbereiche für die Synthese von Organochlorverbindungen zu erschließen, die bislang der Chemie von molekularem Chlor oder anderer gefährlicher Chlorierungsreagenzien vorbehalten waren. Eine erste synthetische Anwendung für oxidative Chlorcyclisierungen nach dem neuen Verfahren wären Synthesen von Naturstoffen oder Naturstoffderivaten mit β-chloriertem Tetrahydrofuran- oder Tetrahydropyrangerüst, beispielsweise Aplysiapyranoid C und D.[36] Ähnlich wie bei den vorangegangenen Arbeiten zur Realisierung von Bromidoxidationen unter annähernd neutralen Bedingungen,[7] wäre auch hier der Einsatz einer alternativen, weniger sauren Protonenquelle erstrebenswert, jedoch deuten die Resultate dieser Studie darauf hin, dass zur Durchführung von Chloridoxidationen generell ein niedrigerer pH-Wert nötig ist als für Bromidoxidationen. Großes Innovationspotential lässt sich darüber hinaus auf der Stufe der verwendeten Übergangsmetall-Katalysatoren vermuten, wo beispielsweise die Entwicklung alternativer Titan(IV)-Katalysatoren mit erhöhter Hydrolysestabilität und Reaktivität eine Möglichkeit zur Steigerung der Effizienz des Verfahrens wäre. Zur Realisierung von stereoselektiven Chlorcyclisierungsreaktionen wäre der Einsatz chiraler Organokatalysatoren ein denkbarer Ansatz für zukünftige Forschungsvorhaben. Neben einigen Arbeiten zur enantioselektiven Halolactonisierung ungesättigter Carbonsäuren[37-40] konnte dieses Konzept in jüngster Zeit auch in enantioselektiven Halogencyclisierungen von 4-Pentenolen erfolgreich angewendet werden,[41][42] wobei die benötigten Halogenierungsäquivalente bei diesen Verfahren nicht *in situ* generiert wurden. Die Ergebnisse im Bereich der allylischen Chlorierung bieten weitere Anknüpfungspunkte für mechanistische Arbeiten, beispielsweise stereochemische Studien an chiralen Alkensubstraten, zur Überprüfung von Analogien zur Schenck-En-Reaktion.[24–26]

5.5 Literatur

[1] M. Yoshida, H. Mochizuki, T. Suzuki, N. Kamigata, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3704–3706.

[2] Z. Bugarcic, J. N. Milovanovic, S. Konstantinovic, G. Ponticelli, M. Mihailovic, *J. Serb. Chem. Soc.* **1995**, *60*, 741–744.

[3] M. Mba, M. Pontini, S. Lovat, C. Zonta, G. Bernardinelli, P. E. Kündig, G. Licini, *Inorg. Chem.* **2008**, *47*, 8616–8618.

[4] T. Fedorova, O. Kaliya, E. Luk'yanets, V. Negrimovskii, *Russ. J. Gen. Chem.* **2008**, *78*, 1611–1613.

[5] K. Yonehara, K. Kamata, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2011**, *47*, 1692–1694.

[6] F. Romano, A. Linden, M. Mba, C. Zonta, G. Licini, *Adv. Synth. Catal.* **2010**, *352*, 2937–2942.

[7] O. Brücher, J. Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.

[8] M. Greb, J. Hartung, F. Köhler, K. Špehar, R. Kluge, R. Csuk, *Eur. J. Org. Chem.* **2004**, 3799–3812.

[9] M. Greb, *Dissertation*, Universität Würzburg, **2004**.

[10] N. Narender, P. Srinivasu, S. J. Kulkarni, K. V. Raghavan, *Synth. Commun.* **2002**, *32*, 279–286.

[11] O. A. Rajan, A. Chakravorty, *Inorg. Chem.* **1981**, *20*, 660–664.

[12] E. Haegele, *Chem. Ber.* **1892**, *25*, 2753–2756.

[13] L. Kuczynski, M. Wilimowski, M. Baginska, J. Soloducho, *Pol. J. Pharmacol. Pharm.* **1975**, *27*, 549–553.

[14] S. Bellemin-Laponnaz, K. S. Coleman, P. Dierkes, J. P. Masson, J. A. Osborn, *Eur. J. Inorg. Chem.* **2000**, 1645–1649.

[15] C. G. Swain, D. R. Crist, *J. Am. Chem. Soc.* **1972**, *94*, 3195–3200.

[16] F. G. Soper, G. F. Smith, *J. Chem. Soc.* **1926**, 1582–1591.

[17] L. Yang, Z. Lu, S. S. Stahl, *Chem. Commun.* **2009**, 6460–6462.

[18] K. D. Raner, J. Lusztyk, K. U. Ingold, *J. Org. Chem.* **1988**, *53*, 5220–5225.

[19] G. A. Russell, *J. Am. Chem. Soc.* **1957**, *79*, 2977–2978.

[20] G. A. Russell, *J. Am. Chem. Soc.* **1958**, *80*, 4987–4996.

[21] K. U. Ingold, J. Lusztyk, K. D. Raner, *Acc. Chem. Res.* **1990**, *23*, 219–225.

[22] H. B. Hass, E. T. McBee, P. Weber, *Ind. Eng. Chem.* **1936**, *28*, 333–339.

[23] C. Walling, B. B. Jacknow, *J. Am. Chem. Soc.* **1960**, *82*, 6108–6112.

[24] J. Burger, W. Engs, H. P. A. Groll, G. Hearne, *Ind. Eng. Chem.* **1939**, *31*, 1413–1419.

[25] M. L. Poutsma, *J. Am. Chem. Soc.* **1965**, *87*, 2161–2171.

[26] M. L. Poutsma, *J. Am. Chem. Soc.* **1965**, *87*, 4285–4293.

[27] G. O. Schenck, K. Ziegler, *Naturwissenschaften* **1944**, *32*, 157.

[28] G. O. Schenck, *Naturwissenschaften* **1948**, *35*, 28–29.

[29] M. Prein, W. Adam, *Angew. Chem. Int. Ed.* **1996**, *35*, 477–494.

[30] L. Novák, L. Poppe, C. Szántay, É. Szabó, *Synthesis* **1985**, *1985*, 939–941.

[31] A. Butler, J. N. Carter-Franklin, *Nat. Prod. Rep.* **2004**, *21*, 180–188.

[32] T. Irie, M. Suzuki, T. Masamune, *Tetrahedron* **1968**, *24*, 4193–4205.

[33] M. Norte, J. J. Fernandez, F. Cataldo, A. G. Gonzalez, *Phytochemistry* **1989**, *28*, 647–649.

[34] M. Bulliard, G. Balme, N. Monteiro, J. Gore, *Bull. Soc. Chim. Fr.* **1991**, 222–231.

[35] S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, J. Wolinsky, *Tetrahedron Lett.* **1980**, *21*, 441–444.

[36] T. Kusumi, H. Uchida, Y. Inouye, M. Ishitsuka, H. Yamamoto, H. Kakisawa, *J. Org. Chem.* **1987**, *52*, 4597–4600.

[37] K. Murai, T. Matsushita, A. Nakamura, S. Fukushima, M. Shimura, H. Fujioka, *Angew. Chem. Int. Ed.* **2010**, *49*, 9174–9177.

[38] C. K. Tan, L. Zhou, Y. Y. Yeung, *Synlett* **2011**, 1335–1339.

[39] D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298–3300.

[40] W. Zhang, S. Q. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. P. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664–3665.

[41] S. E. Denmark, M. T. Burk, *Org. Lett.* **2012**, *14*, 256–259.

[42] D. Huang, H. Wang, F. Xue, H. Guan, L. Li, X. Peng, Y. Shi, *Org. Lett*. **2011**, *13*, 6350–6353.

5.6 Forschungsartikel

A Practical Approach to Catalytic and Non-Catalytic Oxidative Chlorocyclization of Alkenols

Oliver Brücher, Jens Hartung, **2012**, *zur Begutachtung eingereicht*.

A Practical Approach to Catalytic and Non-Catalytic Oxidative Chlorocyclization of Alkenols

Oliver Brücher and Jens Hartung*

Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

* Corresponding author. Tel.: +49-631-205-2431, Fax: +49-631-205-3921, e-mail: hartung@chemie.uni-kl.de

Abstract: Chloro-functionalized tetrahydropyrans and tetrahydrofurans were prepared from dihomoallylic alcohols in a cascade composed of chloride oxidation by *tert*-butyl hydroperoxide, or potassium monoperoxysulfate, and electrophilic chlorocyclization. In the ring closure, stereochemical information associated with the alkenol π-bond of styrene-type substrates copies with chloronium ion-type selectivity into relative configuration of substituents of chlorinated tetrahydropyrans (6-*endo*-cyclization) or tetrahydrofurans (5-*exo*-cyclization). Prenyl-type alkenols furnish allylic chlorides with ene-type regioselectivity, as exemplified by synthesis of the fragrance component rose oxide from citronellol. Chloride oxidation by potassium monoperoxysulfate occurs instantaneously by dissolving oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) and potassium chloride at 30 °C in dimethyl carbonate. *tert*-Butyl hydroperoxide has to be activated by newly developed titanium(IV)- or molybdenum(VI) inner complexes, prepared from dibasic tridentate ONO-chelate ligands, for attaining chloride oxidation in the temperature range between 20 to 40 °C.

Keywords: Alkyl carbonate; Allylic chlorination; Arene chlorination, C,H-activation; Chlorine; Chlorocyclization; Chloroperoxidase mimic; Competition kinetics; Fragrance; Oxidation catalysis; Molybdenum(VI); Stereoselective synthesis; Titanium(VI).

Introduction

Chlorinated hydrocarbons share a number of attractive chemical and physical properties, arising from characteristics of the carbon-chlorine bond, such as strength and dipole moment and orbital effects associated with three non-bonding electron-pairs.[1] Organochlorines with strong and polarizable bonds are used in large quantity, for example, as solvents and cooling liquids.[2][3][4] Neighbor group effects and the dipolar character of the carbon-chlorine bond open in aliphatic chlorinated hydrocarbons, pathways for selective carbon skeleton rearrangement and functional group interconversion, which are both at the heart of organic synthesis.[5] The electron withdrawing ability of chlorine lowers the ionization potential of aryl substituents[6] thus reducing rate of oxidative derivatization, for example, by cytochromes in arene metabolism. Non-bonding electron pairs at chlorine affect *in vivo* mobility of chlorinated hydrocarbons, by raising lipophilicity and the propensity for binding to acidic sites. Both effects contribute to strength and biological response of receptor binding by chlorinated hydrocarbons.[7] The changes imposed on molecular properties of hydrocarbons by substituting chlorine for hydrogen, many instances are not attainable by any other functional groups, which provides strong arguments for nature, but also for industry, to use organochlorines in many fields of applications, in seemingly unlimited quantity and structural diversity.[8][9]

Standard approaches in synthesis of organochlorines are substitution and addition, proceeding via nucleophilic, homolytic, and electrophilic mechanisms. Chloride is a poor nucleophile[10] but in polar aprotic solvents a strong base.[11] Nucleophilic displacement therefore requires specialized leaving groups for achieving useful selectivity in carbon-chlorine bond formation.[12] The driving force for organochlorine synthesis by free radical reactions generally is higher, but methods for homolytic chlorination in fine chemical synthesis so far are limited in scope.[8][13] Pathways for synthetically more demanding chlorinations often proceed via electrophilic mechanisms, starting from predominantly *N*-chloro compounds or molecular chlorine (Figure 1).[14–16]

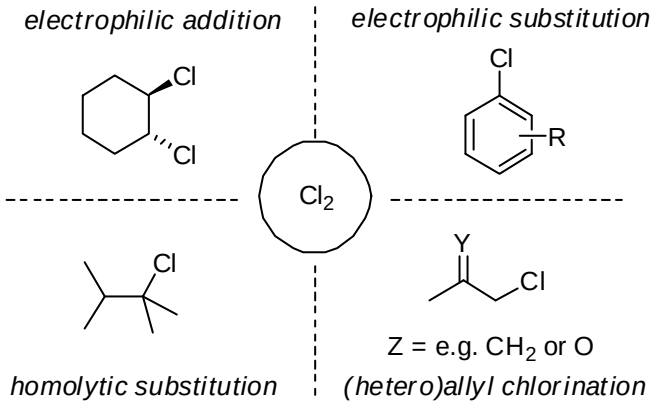
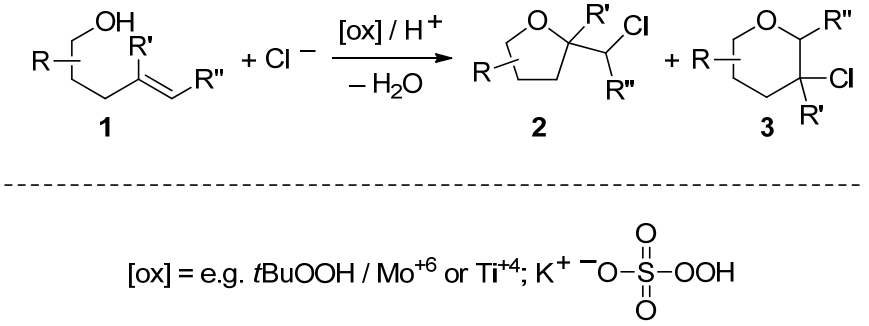


Figure 1. Synopsis of mechanisms and products of hydrocarbon functionalization by chlorine.

Chlorine is a highly reactive chemical,[1] which is technically produced by electrolysis of brines.[17] In fine chemical synthesis, dioxygen, hydrogen peroxide, peracids, and persalts are standard oxidants for *in situ*-converting from aqueous solutions, or two phase systems composed of a brine and an inert lipophilic organic solvent into chloroelectrophiles (Scheme 1).[18] The rate of chloride oxidation by peroxides strongly depends on proton concentration and to become insignificantly slow in pH neutral solutions.[19] For chloride oxidation by hydrogen peroxide in living cells, nature has developed enzymes, the chloroperoxidases.[20][21] Organic synthesis by chloroperoxidases, however, generally furnishes rather complex product patterns from alkenes, because water not only serves as solvent but also acts as nucleophile.[22][23] Probably the most selective substitute for hydrogen peroxide for oxidative transformations in non-aqueous solutions is *tert*-butyl hydroperoxide (TBHP). Like other peroxides, TBHP is a nucleophile and has to be activated by an acidic catalyst, for transferring an oxygen atom to a nucleophilic acceptor, such as chloride.[24][25]

In a project dealing with synthesis of chlorinated natural products,[26][27] we encountered the challenge to prepare chloro-functionalized cyclic ethers from acid-labile dihomoallylic alcohols (4-pentenols, e.g. **1**). Since no method for this transform-step existed in the chemical literature,[28] we explored oxidative alkenol chlorocyclization and report in this article the two most attractive approaches (Scheme 1). The first approach uses transition metal catalysis by a titanium(IV) or a molybdenum(VI) catalysts for selective chloride oxidation by *tert*-butyl hydroperoxide in the temperature range between 20 to 40 °C. In the second approach, chlorocyclization is brought about by dissolving the alkenol, potassium monoperoxysulfate and potassium chloride in dimethyl carbonate at 30 °C. This solvent not only is an environmentally attractive aspect of the reaction but also improves rates and selectivity for chlorocyclization compared to reactions performed in acetonitrile, chloroform, or toluene. The stereochemical

information from the alkenol π-bond of styrene-type substrates copies in chlorocyclizations via chloronium ion-type selectivity into relative configuration of substituents of chlorinated tetrahydropyrans (6-*endo*-cyclization) or tetrahydrofurans (5-*exo*-cyclization). Prenyl-type alkenols furnish allylic chlorides with ene-type regioselectivity, as exemplified by synthesis of the fragrance component rose oxide from citronellol



Scheme 1. Concept for oxidative chlorocyclization of substituted dihomoallylic alcohols (e.g. **1**; R = hydrogen, alkyl, ester; R' = hydrogen, methyl; R'' = hydrogen, phenyl).

Results and Discussion

1 Basic considerations

Chloride oxidation by *tert*-butyl hydroperoxide (TBHP) furnishes *tert*-butanol and hypochlorous acid.[18][19] The oxygen atom transferred to chloride accounts for 18%-weight percent of TBHP. In polar solutions containing acid and chloride, hypochlorous acid undergoes transformations to furnish secondary products, such as chlorine dioxide, molecular chlorine, and trichloride.[29]

The reaction between chloride and peroxides, such as TBHP, is exothermic but kinetically hindered and limited in proton concentration (Scheme 1).[30] From a set of Brønsted-acids we selected pyridinium hydrochloride[31] as combined proton- and chloride source, to overcome kinetic limitation in acid equivalents (see section 3).[32]

Since the pyridinium hydrogen ion only supplies a proton without activating TBHP for peroxidative chloride oxidation in the temperature range between 20 and 40 °C, we screened Lewis-acidic transition metal compounds, having formally d^0-electron count at the metal, for achieving peroxide activation as close as possible to room temperature. Compounds showing the desired reactivity/selectivity-profile were found in the series of *cis*-dioxomolybdenum(VI)

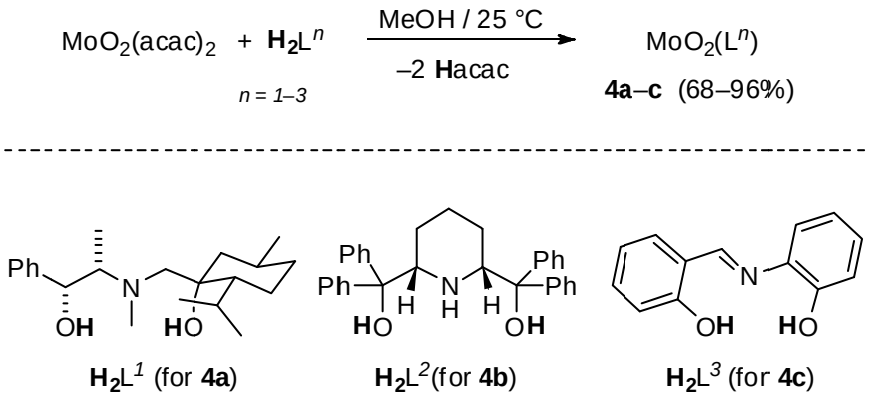
compounds, composed of the general formula MoO_2L (e.g. **4a**–**c**, vide infra). The abbreviation L^{2-} thereby stands for amino- and iminodiol-derived ligands, binding via two negatively charged oxygen donor atoms and one nitrogen atom to molybdenum. We also screened for reactivity of L^{2-}-derived complexes in the titanium series and found that a complex of the general formula $Ti(OR)_2L$ (cf. compound **5**) activates TBHP for chloride oxidation even at room temperature (see section 2).

As non-transition metal-catalyzed alternative for oxidative chlorination, we explored the chemistry of persalts in combination with solid acids, for example clays or hydrogensalts of di- and tribasic acids. By this approach, we found that the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, which is commercialized as oxone® is a sufficiently strong proton source and oxidant to achieve chloride oxidation in anhydrous solutions of dimethyl carbonate (section 3).[33] Protons and peroxidic oxygens consumed in the course of chloride oxidation account for 5.5 weight% per aliquot of the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

2 Preparation of transition metal compounds

Molybdenum complexes of the general formula $MoO_2(L^n)$ (**4a**–**c**) were prepared by metathesis between *cis*-dioxomolybdenum(VI)-bis[acetylacetonato(–1)] $[MoO_2(acac)_2]$ and ephedrine-derived aminodiol H_2L^1 (68% of **4a**), piperidine derivative[34] H_2L^2 (96% of **4b**), and iminodiol[35] H_2L^3 (88% of **4c**), in solutions of methanol (Scheme 2). The complexes precipitated directly from reaction mixtures as colorless solids (**4a** and **4b**) or orange crystals (**4c**)[36], and were characterized by NMR- and IR-spectroscopy, in combination with combustion analysis.

cis-Dioxomolybdenum(VI)-binding of aminodiols H_2L^1 and H_2L^2 shifts resonances of carbons bound to donor oxygens downfield by $\Delta\delta$ = 12–16, and those to nitrogen by $\Delta\delta$ = 2–6 for **4a** and **4b**. Resonances of hydrogens from the nitrogen-bound methylene group in ephedrine-derived complex **4a** experience an upfield-shift by –0.39 ppm, whereas the methine proton of the ephedrine fragment in α-position to nitrogen of **4a**, and also of the aminoalcohol subunit of piperidine-derivative **4b**, are downfield-shifted by molybdenum(VI) binding of ligands H_2L^{1-2}. This shift dispersion possibly arises from magnetic anisotropic due to π-bonding of the oxo ligands, or *d*-orbital population by backbonding from chelate donor atoms.



Scheme 2. Formation of *cis*-dioxomolybdenum complexes [hydrogens substituted by the MoO_2^{2+}-fragment in the course of complex formation are printed in bold; **H**acac = pentane-1,3-dione (acetylacetone)].

From X-ray diffraction analysis performed at –123 °C, we received information on the solid state structure of ephedrine-derived complex **4a**, particularly the spatial arrangement of the chelate ligand with respect to the oxo groups. The data show, that the chelate binds meridionally to the *cis*-dioxomolybdenum fragment, directing the amino nitrogen into *trans*-position of the equatorial oxo ligand. The *trans*-position of the apical oxo ligand remains vacant and is possibly the site where *tert*-butyl hydroperoxide coordinates as part of the activation process. The four oxygens and the nitrogen bound to molybdenum(VI) in **4a** neither form a regular trigonal bipyramid, nor a square pyramid. In a structural model based on a gradual geometric transition between the two bodies, the coordination sphere in **4a** is a hybride composed by 61% square pyramidal character and 39% of trigonal bipyramidal, as expressed by the structural parameter $\tau = 0.61$.[37]

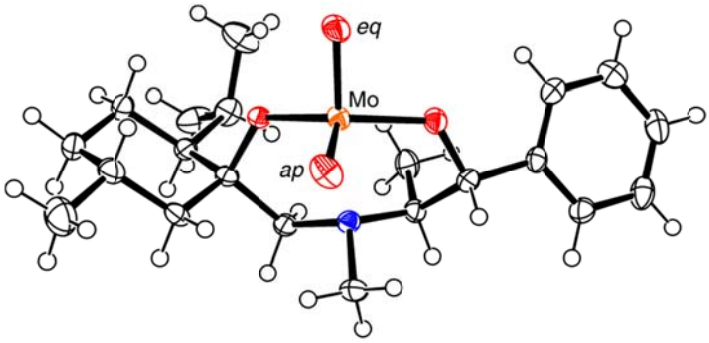
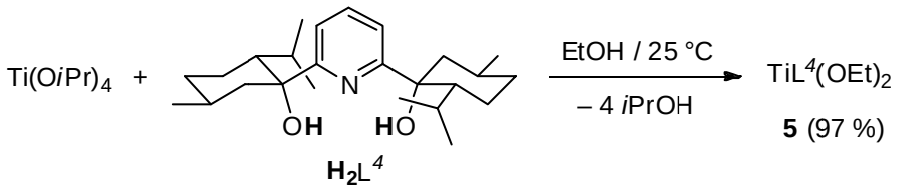


Figure 2. Ellipsoid graphic (50 % probability) of ephedrine-derived molybdenum complex **4a** in the solid state (150 K; molybdenum is depicted in orange, oxygens in red, nitrogen in blue, and carbons in black; hydrogens are drawn as circles of an arbitrary radius;

ap = apical; *eq* = equatorial).

Titanium(IV) complex **5** was prepared from aliquots of Ti(O*i*Pr)$_4$ and pyridine-derived diol[38] H_2L^4 in a solution of dry EtOH. The major fraction of titanium compound **5** crystallizes directly, whereas a second crop of colorless, block-shaped crystals separates as the concentrated filtrate is allowed to rest at –28 °C. Combustion analytical data for both precipitates agree with the constitution formula $TiL^4(OEt)_2$ (**5**). One of the block-shaped crystals was analyzed by X-ray diffraction, showing pentacoordinated titanium(IV), being surrounded by four oxygen donor atoms and one pyridine nitrogen in a sphere that closure resembles a trigonal bipyramid than a square pyramid, as evident from structural parameter[37] $\tau = 0.31$.



Scheme 2. Preparation of 2,6-bis(neomenthyl)pyridine-derived titanium(IV) complex **5**.

Carbon-13 resonances recorded for **5** in perdeuteromethanol show a downfield-shift by 18.6 ppm for oxygen-bound carbons and by 12.6 ppm for nitrogen-bound carbons, referenced versus shifts of the free ligand H_2L^4 in deuterochloroform. The resonances of ethanolato carbons agreed with values reported for ethanol dissolved in a solution of deuterochloroform.

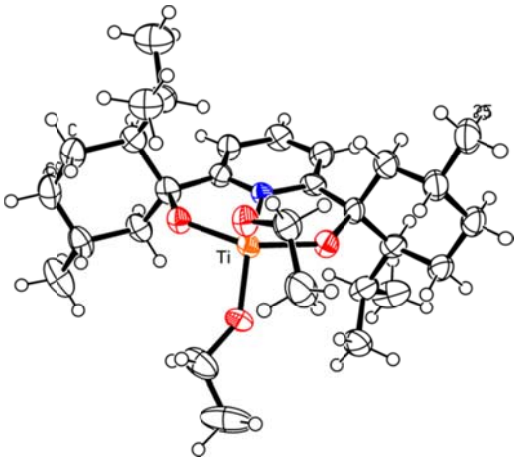


Figure 3. Ellipsoid graphic (50 % probability) of $TiL^4(OEt)_2$ (**5**) in the solid state (150 K; titanium is depicted in orange, oxygens in red, nitrogen in blue, and carbons in black; hydrogens are drawn as circles of an arbitrary radius).

3. Oxidative Chlorination of 4-Pentenols

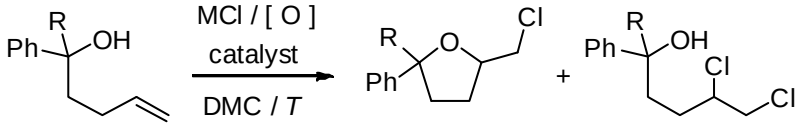
From systematic parameter variation, we found that 1-phenyl-4-penten-1-ol (**1a**) is quantitatively consumed, if stirred for twenty-four hours in a solution of dimethyl carbonate, containing pyridinium hydrochloride, TBHP, and one of the transition metal catalysts $MoO_2(acac)_2$, **4a**–**c**, or **5**. From such solutions we isolated 5-chloromethyl-2-phenyltetrahydrofuran (**2a**) as 40/60 *cis*/*trans*-mixture of stereoisomers as major product and dichloride **6a** as minor component, supplementing the mass balance for organochlorine formation to 63–91% (Table 1, entries 2–6). The yields of product **2a** gradually decreased along the series of applied catalysts $MoO_2(acac)_2$ (74% of **1a**) > $MoO_2(L^1)$ (69%) > $MoO_2(L^2)$ (62%) ≈ $TiL^4(OEt)_2$ (62%) > $MoO_2(L^3)$ (45%).

We used catalyst/substrate-ratios of $5 \cdot 10^{-2}$ for oxidative chlorinations, which enabled to quantitatively turn over the alkenol within twenty-four hours at the lowest possible reaction temperature. Smaller catalyst/substrate-ratios retarded alkenol conversion, similarly to a change of the solvent from dimethyl carbonate to acetonitrile, chloroform, or toluene, or the presence of moisture. The measures taken to keep water concentration as low as necessary for attaining a reasonable reactivity/selectivity profile, refer to drying of the solvent and the reagents, and replacing laboratory atmosphere (30–80% relative humidity) by dry nitrogen.

In controls, no chlorocyclization occurred, if substrate **1a** was treated with py·HCl and TBHP in the absence of metal compounds **4**–**5** (Table 1, entry 1), or in the presence of 10 mol% of oxovanadium(V)-catalysts prepared from auxiliaries H_2L^2 or H_2L^3 (Supplementary Data). Furthermore we found that *N*-chlorosuccinimide[39] is not able to convert alkenol **1a** in a solution of dichloromethane into chloromethyltetrahydrofuran **2a**.

Oxidative chlorocyclization of 2-phenyl-5-hexen-2-ol (**1b**), a tertiary derivative of alkenol **1a**, provided 80% of chlorinated trisubstituted tetrahydrofuran **2b** as 38/62-mixture of *cis*/*trans*-isomers and 17% of vicinal dichloride **6b** at 40 °C (Table 1, entry 9). The titanium-catalyzed reaction provided similar yields at 20 °C (Table 1, entries 8–10). From the results obtained in this part of the study, we decided to use molybdenum complex **4a** and titanium reagent **5** as standard catalysts for the succeeding oxidations.

Table 1. Products of oxidative chlorination of phenyl-pentenols **1a** and **1b**.



1a–b **2a–b** **6a–b**

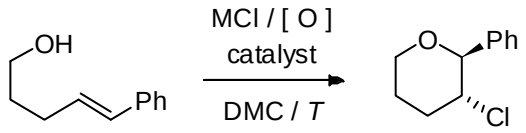
entry	R	**1, 2, 6**	MCl / [O]	catalyst	*T* / °C	**2** / % (*cis*:*trans*)	**6** / % [a]
1	H	**a**	py·HCl / *t*BuOOH	–	40	– [b]	– [b]
2	H	**a**	py·HCl / *t*BuOOH	$MoO_2(acac)_2$	40	74 (40:60)	13
3	H	**a**	py·HCl / *t*BuOOH	**4a**	40	69 (42:58)	15
4	H	**a**	py·HCl / *t*BuOOH	**4b**	40	62 (42:58)	29
5	H	**a**	py·HCl / *t*BuOOH	**4c**	40	45 (45:55)	18
6	H	**a**	py·HCl / *t*BuOOH	**5**	20	62 (41:59)	21
7	H	**a**	KCl / $KHSO_5$ [c]	–	30	72 (41:59)	– [b]
8	CH_3	**b**	py·HCl / *t*BuOOH	$MoO_2(acac)_2$	40	72 (35:65)	– [d]
9	CH_3	**b**	py·HCl / *t*BuOOH	**4a**	40	80 (38:62)	17
10	CH_3	**b**	py·HCl / *t*BuOOH	**5**	20	67 (35:65)	19
11	CH_3	**b**	KCl / $KHSO_5$ [c]	–	30	78 (41:59)	8

[a] 50/50-mixture of stereoisomers. [b] Not detected. [c] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone®). [d] Not determined.

In the second approach to oxidative chlorination, which we refer to as *salt-method*, substrate conversion starts instantaneously by dissolving the alkenol and aliquots of potassium chloride and oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) at 30 °C in dimethyl carbonate. By considering the steps outlined above for keeping moisture level in the reaction mixtures low, we prepared accordingly 2-(chloromethyl)tetrahydrofurans **2a** and **2b** in yields between 72–78% (Table 1, entries 7 and 10), vicinal dichloride **6b** (8%) but surprisingly no **6a**.

As pilot study for a future project on synthesis of aplysiapyranoids C and D from styrene-type alkenols,[27][40] we explored oxidative chlorocyclization of (*E*)-phenylpentenols **1c** and **1d** using catalytic methods for chloride oxidation and the salt-method (Tables 3 and 4).

Table 2. Oxidative chlorocyclization of (*E*)-5-phenylpent-4-en-1-ol (**1c**).



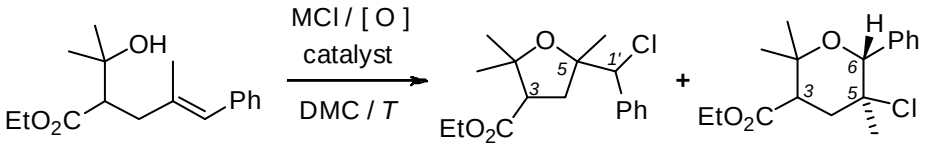
1c **3c**

cis:*trans* < 2:98

entry	MCl / [O]	catalyst	*T* / °C	**3c** / %
1	py·HCl / *t*BuOOH	**4a**	40	65
2	py·HCl / *t*BuOOH	**5**	20	74
3	KCl / $KHSO_5$ [a]	–	30	58

[a] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone®)

Table 3. Synthesis of cyclic β-chlorohydrinethers from styrene-type alkenol **1d**.



1d **2d** (±)-**3d**

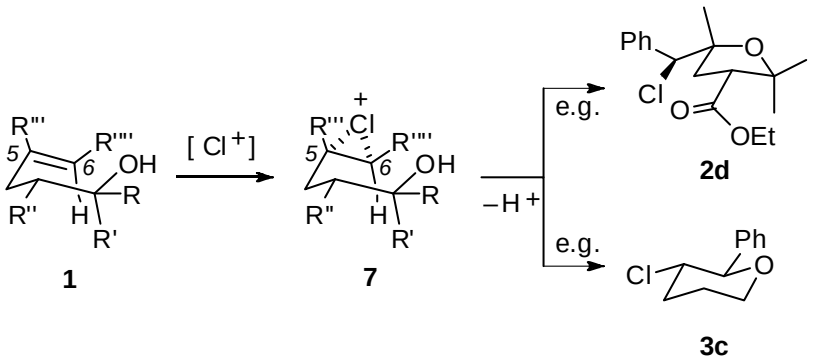
entry	MCl / [O]	catalyst	*T* / °C	**2d** / % (*cis*:*trans*) [a]	**3d** / % (*cis*:*trans*) [a]
1	py·HCl / *t*BuOOH	**4a**	40	46 (90:10)	7 (>98:2)
2	py·HCl / *t*BuOOH	**5**	20	54 (90:10)	5 (>98:2)
3	KCl / $KHSO_5$ [c]	–	30	64 (93:7)	2 (>98:2)

[a] Refers to configuration of substituents in pos. 3 and 5. [b] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone®).

Oxidations starting from (*E*)-5-phenylpent-4-en-1-ol (**1c**) provided the *trans*-isomer of 2-phenyl-3-chlorotetrahydropyran (**3c**) as exclusive product in yields between 58–74% (Table 2), whereas β-methylstyrene-type alkenol **1d** afforded a mixture of chlorocyclized products **2d** and **3d**, being in favor for the 3,5-*cis*-isomer of tetrahydrofuran **2d**. We assigned *rel*-(3*R*,5*R*,1'*S*)-configuration to the major isomer of tetrahydrofuran **2d**, in extension to proton- and carbon-13 NMR-shift values, and fine structure of resonances of the bromoderivative, which is characterized by X-ray diffraction data.[40]

Regio- and stereoselectivity of products obtained from oxidative chlorination point to a polar reaction for the alkenol ring closure, proceeding via *anti*-specific addition of electrophilic

chlorine and nucleophilic oxygen across the (*E*)-double bond in **1c** and **1d**. The mechanism that explains this selectivity is the chloronium ion pathway,[41] starting from a lowest in energy and thus most significantly populated conformer of alkenol **1** in solution (Scheme 3). Ring opening of the proposed intermediate, γ-(hydroxypropyl)chloronium ion **7**, is expected to proceed in a S_N2-reaction and thus stereospecific manner, to copy stereochemical information of the attacked carbon-carbon double bond into relative configuration of substituents in tetrahydropyran **3** or tetrahydrofuran **2** (Scheme 3). Since conformational preferences of the alkenol chain and substituents attached to the flexible part of the molecule are the only stereoinductors, chloronium ion-based ring closures provide products of conformational and thus thermochemical control.[40]



Scheme 3. Model for explaining regio- and stereoselectivity in oxidative 4-pentenol chlorocyclization (R = H, CH_3 or Ph; R' and R''' = H or CH_3; R'' = H or CO_2Et; R'''' = H or Ph).

Regioselectivity of the alkenol ring closure in oxidative chlorinations is guided by substituents attached to positively changed carbons of the proposed chloronium ion **7**. Based on structural analogy between chloronium ions and activated epoxides, the preferred site of attack by the hydroxyl oxygen is the higher substituted carbon. If both carbons of the chloronium ion bear the same number of substituents, the oxygen nucleophile adds to the carbon bearing the more pronounced cation stabilizing group(s) (Scheme 3).

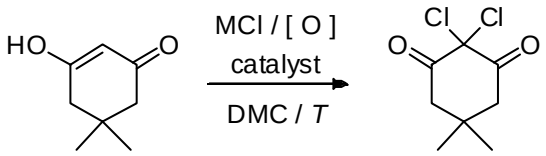
4 Selectivity in oxidative chlorination of aliphatic and aromatic hydrocarbons

The chemical nature of the chlorination reagent attacking the 4-pentenol in the selectivity-determining step did not become apparent from structure-reactivity studies alone. To distinguish whether hypochlorous acid, chlorine, or possibly other reagents formed *in situ*, such as *tert*-butyl hypochlorite from *tert*-butanol and chlorine,[42][43] determine selectivity in oxidative alkenol chlorocyclization, we subjected diagnostic standards to benchmark reactions for electrophilic substitution (section 4.1), homolytic displacement (section 4.2), and allylic chlorination (section 4.3).

4.1 Electrophilic chlorination of activated π-bonds

The dimedone test. Chlorination of dimedone **8** or 2-chlorodimedone is an assay in biochemistry for tracing chloroelectrophiles generated from hydrogen peroxide and chloride in chloroperoxidase-catalyzed oxidations [monochlorodimedone (MCD)-assay].[20] To verify that alkenol cyclization in oxidative chlorination is initiated by attack of a chloroelectrophile, we subjected 1,3-diketone **8** to the methods described in the preceding section. All procedures thereby furnished dichlorodimedone **9**, with the yields ranging from useful (72%) for the molybdenum-catalyzed reaction to poor for the titanium-catalyzed oxidation (Table 4, entries 1–3). The origin of unsatisfactory performance of the titanium-method possibly relates to a side reaction, as judged from a colorless precipitate of unknown composition, which forms in this reaction but did not appear in the other processes. From the results of the dimedone-assay we concluded that TBHP and potassium monoperoxysulfate convert chloride into an electrophilic reagent.

Table 4. Oxidative chlorination of dimedone **8**.



8 **9**

entry	MCl / [O]	catalyst	*T* / °C	**9** / %
1	py·HCl / *t*BuOOH	**4a**	40	72
2	py·HCl / *t*BuOOH	**5**	20	11
3	KCl / $KHSO_5$ [a]	–	30	61

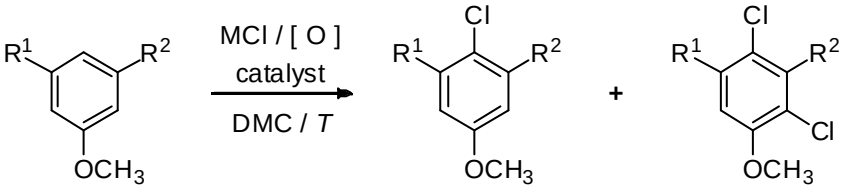
[a] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone®).

Methoxyarene chlorination. Anisole **10a** furnishes chloroanisole **11a**, with the yield gradually increasing from the salt method (33%), via molybdenum-catalyzed oxidation (83%) to the titanium-catalyzed reaction (86%). The *para*/*ortho*-selectivity for electrophilic aromatic chlorination increased from 88:12 for the molybdenum-catalyzed reaction to 96:4 for the titanium-catalyzed method and the salt method, possibly relating to a temperature effect (Table 5, entries 1–3).

1,3-Dimethoxybenzene (**10b**) and 1,3,5-trimethoxybenzene (**10c**) undergo rapid transformations, to afford chloroarenes **11b–c** along with minor fractions of dichloroarenes **12b**–

c, if subjected to catalytic and non-catalytic versions of oxidative chlorination (Table 5, entries 5–10). The yields of organochlorines were quantitative for titanium-catalyzed oxidations, 99% for molybdenum-catalyzed reactions, and 53–78% for the salt method. Unspent arenes **10a–c** were quantified via GC-MS analysis, showing in summary quantitative mass balance for all examples.

Table 5. Oxidative chlorination of methoxy-substituted benzenes.



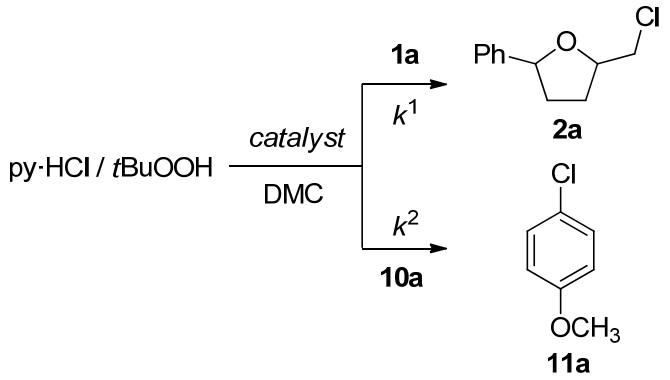
10 **11** **12**

entry	R^1	R^2	**10–12**	MCl / [O]	catalyst	T / °C	**11** / %	**12** / %
1	H	H	**a**	py·HCl / *t*BuOOH	–	40	– [a]	– [a]
2	H	H	**a**	py·HCl / *t*BuOOH	**4a**	40	63 (88:12)[b]	– [a]
3	H	H	**a**	py·HCl / *t*BuOOH	**5**	20	86 (94:6)[b]	– [a]
4	H	H	**a**	KCl / $KHSO_5$ [c]	–	30	33 (96:4)[b]	– [a]
5	OCH_3	H	**b**	py·HCl / *t*BuOOH	**4a**	40	79	21
6	OCH_3	H	**b**	py·HCl / *t*BuOOH	**5**	20	89	11
7	OCH_3	H	**b**	KCl / $KHSO_5$ [b]	–	30	53	– [a]
8	OCH_3	OCH_3	**c**	py·HCl / *t*BuOOH	**4a**	40	78	21
9	OCH_3	OCH_3	**c**	py·HCl / *t*BuOOH	**5**	20	82	18
10	OCH_3	OCH_3	**c**	KCl / $KHSO_5$ [b]	–	30	67	11

[a] Not detected. [b] *para*/*ortho*-ratio. [c] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone®).

Regioselectivity of oxidative anisole chlorination is similar to *para*/*ortho*-ratios reported for synthesis of **11a** from anisole **10a** and molecular chlorine[44] and other methods for *in situ*-oxidative chlorination. Reference reactions from the literature, catalyzed by Brønsted-acids,[24] or vanadium(V)- or molybdenum(VI)-compounds at ambient temperature, generally provide lower yields of organochlorines **11** and **12**[45] than the new methods. The more effective methods for anisole chlorination from the literature require elevated temperatures and therefore are performed in, for example, boiling methanol,[46] a mixture of hot acetic acid and ethylene chloride (60 °C),[47] or hot acetic acid (100 °C).[48] Hypochlorous acid under neutral conditions is not able to chlorinate anisole **10a**.[42]

Competition kinetics. With the knowledge about performance of the new methods for oxidative chlorination, we addressed the competition kinetics for determining relative rates of alkenol chlorocyclization versus arene chlorination. The underlying model considers irreversible carbon-chlorine- and carbon-oxygen bond formation for chlorocyclization (k^1) and for carbon-chlorine bond for chloroanisole formation (k^2) (Scheme 4, eq. 1).[41]



$$\frac{[\mathbf{2a}]}{[\mathbf{11a}]} = \frac{k^1}{k^2}\frac{[\mathbf{1a}]}{[\mathbf{10a}]} \qquad \text{(eq. 1)}$$

Scheme 4. Competition experiments for determining relative reactivity in chlorination of 1-phenyl-4-penten-1-ol (**1a**) and anisole **10a** (cf. Table 6).

In the general experimental set-up for competition kinetics under pseudo-first order conditions, oxidative chlorination of mixtures composed of phenylpentenol **1a** and anisole **10a** under pseudo-first order conditions provided mixtures of 2-(chloromethyl)tetrahydrofuran **2a** and chloroarene **11a** containing less than 5% of dichloride **6a**. The product ratio **2a**/**11a** linearly decreases as the excess of anisole **10a** is raised from 10 via 50 to 100 equivalents. From the slope of a linear correlation derived from product ratios **2a**/**11a** and associated substrate ratios **1a**/**10a**, we derived according to equation 1 relative rate constants $k^{rel} = k^1/k^2$.

Table 6. Relative reactivity (k^{rel}) for chlorocyclization of **1a** versus anisole chlorination in dimethyl carbonate.

entry	MCl / [O]	catalyst	T / °C	$k^{rel} = k^1/k^2$
1	py·HCl / *t*BuOOH	$MoO_2(acac)_2$	40	600±10
2	py·HCl / *t*BuOOH	**4a**	40	540±8
3	py·HCl / *t*BuOOH	**5**	40	510±7
4	py·HCl / *t*BuOOH	**5**	20	590±9

The kinetic data show that the rate of phenylpentenol chlorocyclization at 40 °C is by a factor 540 and 600 faster than anisole chlorination in molybdenum-catalyzed oxidations (Table 6, entries 1–2) and by a factor 510 for the titanium-catalyzed reaction (Table 6, entries 3 and 4). The reactivity split for chlorocyclization versus arene chlorination in the titanium-catalyzed oxidation at 20 °C increases marginally to 590. By taking a representative experimental error of typically ± 10% into account, the values for k^{rel} from the two reaction series and the two temperatures are very similar, if not identical. Attempts to measure k^{rel} from competition experiments between 1,3-dimethoxybenzene **10b** or 1,3,5-trimethoxy derivative **10c** and alkenol **1a** exclusively provided chloroarenes **11b** and **11c** (Supplementary Data).

In an irreversible reaction between a chloroelectrophile and a nucleophile, such as anisole **10a** or propene serving as model for the π-bond in phenylpentenol **1a**, the ionization potential of the unsaturated hydrocarbon should be relevant for explaining relative reactivity. The ionization potential of anisole (8.21 eV) is smaller than the value for propene (9.73 eV).[49][50] Still, alkenol **1a** reacts by a factor of 510–600 faster than the aromatic π-system in **10a**. This split in reactivity is expected to express the rate effect of the additional activation energy needed for overcoming aromatic stabilization for σ-complex formation from **10a**, compared to chloronium ion formation from **1a**. In synthesis, values of k^{rel} = 510–600 imply that oxidative chlorination of methoxyphenyl-substituted 4-pentenols selectively occurs at the alkene entity, but at the aryl nucleus for dimethoxy- or trimethoxyphenyl-substituted derivatives.

To sum up, the results of oxidative methoxyarene chlorination and the competition experiments show that the chloroelectrophile involved in carbon-chlorine bond formation is considerably more electrophilic than hypochlorous acid and comes close in chemical reactivity to molecular chlorine.

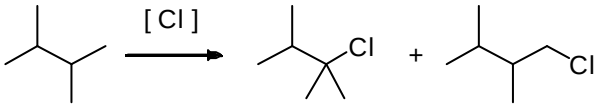
4.2 Chlorination of aliphatic carbon-hydrogen bonds

Molecular chlorine reacts with *tert*-butanol, the product left from TBHP-mediated chloride oxidation to furnish tert-butyl hypochlorite.[51] We therefore investigated oxidative 2,3-dimethylbutane chlorination to find out whether selectivity in hydrocarbon chlorination by the oxidative methods comes closer to molecular chlorine, or possibly *tert*-butyl hypochlorite for the catalyzed reactions.

The reagent to distinguish the chemical nature of a chlorination reagent in alkane chlorination is 2,3-dimethylbutane (**13**). Chlorination of alkane **13** preferentially occurs at the tertiary carbon-hydrogen bond. The analytical expression to quantify selectivity in alkane chlorination is the partial rate factor *f*, referring to normalized reactivity of a secondary (not present in **13**) and tertiary versus a primary carbon-hydrogen bond.[13][51] For 2,3-dimethylbutane chlorination, the partial rate factor *f* is 3.9 for chlorine and 44 for *tert*-butyl hypochlorite (both reactions at 40 °C).[13][51][53–55] Since molybdenum complexes **4a**–**c**, $MoO_2(acac)_2$, and titanium catalyst **5** are not soluble in 2,3-dimethylbutane (**13**), we performed alkane chlorination in solutions of acetonitrile and dimethyl carbonate. This experimental set-up has the potential to provide triphosgene as by-product.[56] We therefore took appropriate safety considerations into account.

Oxidative chlorination of 2,3-dimethylbutane (**13**) by the molybdenum-catalyzed reaction (Table 7, entries 1–3) and the salt method (Table 7, entry 4) provided mixtures of 2-chloro-2,3-dimethylbutane (**14a**) and 1-chloro-2,3-dimethylbutane (**14b**) in yields between 52 and 77%. From the product ratios and statistics for carbon-chlorine bond formation at the primary and tertiary carbons (vide supra), we calculated partial rate factors of $f = 2.7$ for the reaction in dimethyl carbonate in the dark, 2.2 for the photoreaction in dimethyl carbonate (Table 7, entries 1–2), 2.8 for the photoreaction in acetonitrile, and 2.3 for the salt method (Table 7, entries 3–4). All partial rate factors are far off from the value reported for 2,3-dimethylbutane chlorination by *tert*-butyl hypochlorite, but close to the value reported for molecular chlorine in the neat hydrocarbon *and* in polar solvents.[54] As guideline for synthesis, we therefore reasoned that reactivity and selectivity in carbon-chlorine bond formation by the new methods for oxidative chlorination compares to molecular chlorine.

Table 7. Selectivity in oxidative 2,3-dimethylbutane-chlorination.



13 **14a** **14b**

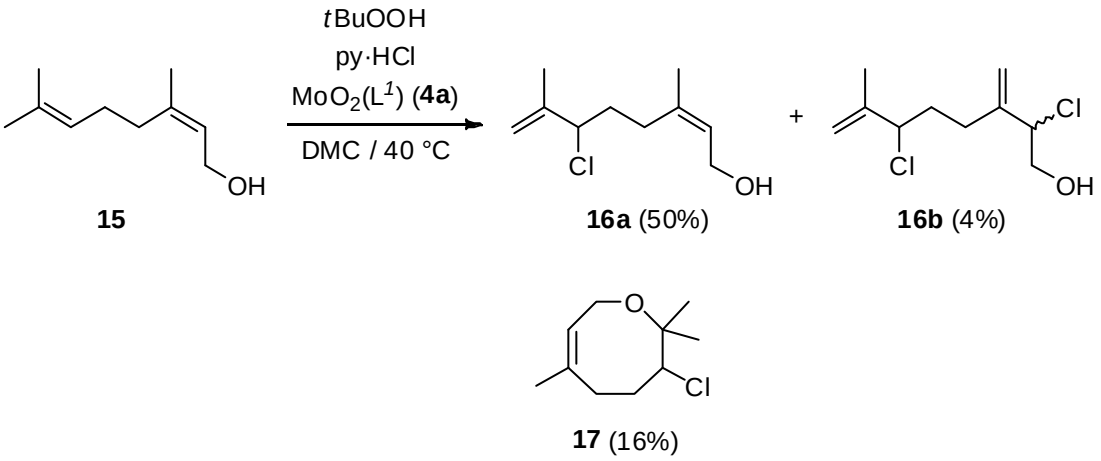
entry	[Cl]	**14** / % [a]	**14a** / **14b**	f [b]
1	py·HCl / *t*BuOOH / **4a** / DMC	72 (36)	32 / 68	2.7
2	py·HCl / *t*BuOOH / **4a** / DMC/ $h\nu$	52 (26)	27 / 73	2.2
3	py·HCl / *t*BuOOH / **4a** / CH_3CN / $h\nu$	77 (39)	31 / 69	2.8
4	KCl / $KHSO_5$ [c] / DMC	69 (34)	28 / 72	2.3

[a] Yields referenced versus consumption of 2,3-dimethylbutane (**13**); numbers in brackets refer to yields referenced versus chloride consumption. [b] Partial rate factors f for chlorination of tertiary versus primary C,H-bonds in **13** (see text and the Supporting Information).[c] $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (oxone®).

4.3 Allylic chlorination

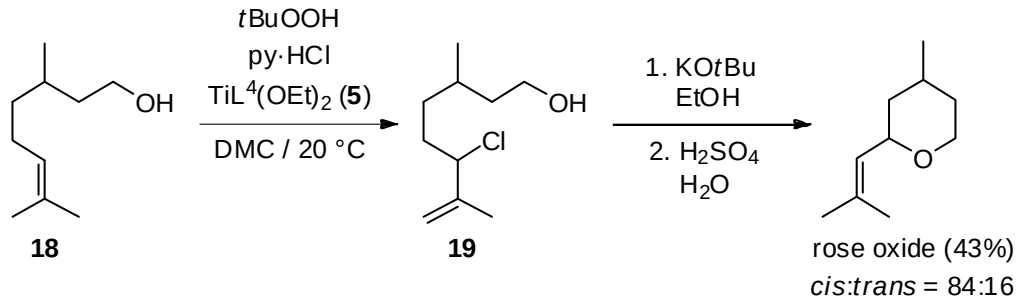
In a final test on reactivity of the new oxidative methods for hydrocarbon chlorination, we treated nerol **15** with TBHP, pyridinium hydrochloride and 5 mol% of ephedrine-derived molybdenum complex **4a** (Scheme 5). From the oxidative conversion of nerol **15**, we isolated allylic chlorides **16a** and **16b** (66%) as major products and the product of 8-*endo*-chlorocyclization, chlorooxocine **17** (1%), as minor component. If pyridinium hydrochloride is added in small portions within 16 hours, the yield of oxocine **17** increases to 16% and the fraction of allylic chlorides **16a** and **16b** drops to 54%.

The experiments showed that prenyl-type alkenol **15** is selectively chlorinated at the sterically least encroached alkene carbon with a simultaneous shift of the double bond toward the end of the hydrocarbon chain. This ene-type selectivity correlates with findings from other chlorination reactions of prenyl-type substrates.[15] From this information we concluded that the scope to oxidative chlorination for alkenol functionalization extends beyond chlorocyclization.



Scheme 5. Products of oxidative nerol chlorination.

The propensity to furnish products of allylic chlorination from prenyl-type alkenols challenged us to prepare the fragrance component rose oxide in a three step sequence starting from citronellol **18** (Scheme 6). Pyridinium hydrochloride for this purpose was added as single batch under standard conditions of a titanium-catalyzed oxidation. Oxidative conversion of alkenol **18** thereby provided allylic chloride **19**, which was heated with potassium *tert*-butoxide in a solution of ethanol for hydrogen chloride-elimination, to leave a diene, which cyclizes upon treatment with dilute aqueous sulfuric acid for concluding the rose oxide-synthesis by the tetrahydropyran ring closure.[57]



Scheme 6. Synthesis of rose oxide from citronellol **18**.

Concluding remarks

With the aim to provide a practical solution to alkenol chlorocyclization, a transform-step of obvious and in our opinion notable synthetic utility, we introduced approaches for oxidative chlorination in general based on catalytic and non-catalytic oxidation in an unusual solvent for oxidations – dimethyl carbonate. From the two approaches, we personally favor the catalytic version since the by-product *tert*-butanol is neither harmful nor difficult to separate from other products. From larger scale batches, the tertiary alcohol can be collected and used as resource for

a succeeding process. The alternative method, based on mixing of potassium chloride and potassium monoperoxysulfate, on the other hand, has the potential to become the method of choice for those who wish to start right away without the need to prepare a transition metal catalyst for peroxide activation.

As guideline for synthesis, we recommend to consider the chlorination reagent involved in carbon carbon-chlorine bond formation as molecular chlorine. This guideline applies for chlorocyclization to explaining stereo- and regioselectivity of alkenol ring closure, regio-selectivity in alkane- and arene chlorination, and ene-type regioselectivity for allylic chlorination of prenyl-type substrates.

Further attractive features of the new chlorination chemistry relate to the solvent and the reaction temperature. Dimethyl carbonate has attracted attention for many applications because it is a biodegradable non-toxic solvent. Still, we were surprised to see how well titanium(IV)- and molybdenum(VI) catalysts retained their ability to activate *tert*-butyl hydroperoxide for chloride oxidation in dimethyl carbonate, being a Lewis-basic solvent, at temperatures of 20–40 °C.

With the information, how to chlorocyclize acid labile alkenols, particularly the styrene-type substrates, we have the ability to continue our project on synthesis of halogenated, sterically encroached, tetrahydropyran-derived secondary metabolites, such as the aplysiapyranoids, [27][40] kalihinenes,[58] or kalihinols.[59] However, we expect other researchers to become attracted by the ease and efficiency for liberating chlorine-like reagent equivalents from readily available and safe-to-handle chemicals, for pursuing other attractive targets in chlorine chemistry.

Experimental

1. General

For synthesis of starting materials, purity and drying of reagents, spectroscopic data, and instrumentation, see the Supporting Information.

2. Transition metal-catalyzed oxidative chlorination of 1-phenylpent-4-en-1-ol (1a)

To a solution of alkenol **1a** (81 mg, 0.5 mmol) in dimethyl carbonate (20 mL) in an atmosphere of argon (99.9%) was added at room temperature pyridinium hydrochloride (87 mg, 0.75 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 180 µL, 0.75 mmol), and $MoO_2(L^1)$ (**4a**) (11.5 mg, 0.025 mmol, 5 mol%). The reaction was stirred for 24 h at 40 °C in the dark (flask wrapped with aluminum foil). The solvent was distilled off under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2, CH_2Cl_2). *5-(1'-Chloromethyl)-2-phenyl-*

tetrahydrofuran (**2a**). Yield: 68.1 mg (0.346 mmol, 69 %) colorless liquid, 42/58-mixture of *cis*/*trans* isomers. R_f = 0.54 [CH_2Cl_2]. Anal. calcd. for $C_{11}H_{13}ClO$ (196.67): C, 67.18; H, 6.66; Found: C, 66.87; H, 6.57. *4,5-Dichloro-1-phenylpentan-1-ol* (**6a**). Yield: 17.7 mg (0.076 mmol, 15 %) colorless oil, 50/50-mixture of *like*/*unlike* isomers. R_f = 0.29 [CH_2Cl_2]. Anal. calcd. for $C_{11}H_{14}C_{l2}O$ (233.13): C, 56.67; H, 6.05; Found: C, 56.98; H, 6.03.

3. Oxidative chlorination of ethyl (*E*)-2-(2-hydroxypropy-2-yl)-4-methyl-5-phenyl-4-pentenoate (1d) with potassium chloride and oxone®

To a solution of alkenol **1d** (138.2 mg, 0.5 mmol) in dimethyl carbonate (10 mL) in an atmosphere of argon (99.9%) was added at room temperature KCl (56 mg, 0.75 mmol), and oxone® (307 mg, 0.5 mmol). The reaction mixture was stirred for 24 h in the dark (flask wrapped with aluminum foil) at a temperature of 30 °C. The solvent was distilled off under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2, CH_2Cl_2). *Ethyl {5-[1'-chloro(phenyl)methyl]-2,2,5-trimethyltetrahydrofuran}-3-carboxylate* (**2d**). Yield: 99.7 mg (0.321 mmol, 64 %) colorless oil, 93/7-mixture of *cis*/*trans* isomers, R_f = 0.52 [CH_2Cl_2]. Anal. calcd. for $C_{17}H_{23}ClO_3$ (310.82): C, 65.69; H, 7.46; Found: C, 65.75; H, 7.40. *Ethyl rel-(3R,5S,6R)-(5-chloro-2,2,5-trimethyl-6-phenyltetrahydropyran)-3-carboxylate* (±)-*cis*-(**3d**). Yield: 3.1 mg (0.010 mmol, 2 %) colorless oil. R_f = 0.63.

CCDC-896274 (for **5**) and CCDC-896275 (for **4a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements. This work was supported by the Deutsche Bundesstiftung Umwelt (DBU grant 20007/885) and is part of the Ph.D. thesis of O.B. We express our gratitude to Dr. Uwe Bergsträßer and Dr. Harald Kelm for performing the x-ray diffraction experiments and for their help in structure determination.

References

[1] G. H. Wagnière, in *The Chemistry of the Carbon-Halogen Bond*, (Ed.: S. Patai), Wiley, London, **1973**, pp. 1–47.

[2] K. G. Drouillard, G. T. Tomy, D. C. G. Muir, K. J. Friesen, *Environ. Toxicol. Chem.* **1998**, *17*, 1252–1260.

[3] (a) D. Henschler, *Angew. Chem.* **1994**, *106*, 1997–2012. (b) G. T. Tomy, A. T. Fisk, J. B. Westmore, D. C. G. Muir in *Reviews of Environmental Contamination and Toxicology*, *Vol. 158*, (Eds.: G. W. Ware, H. N. Nigg, D. R. Doerge), Springer, Heidelberg, **1998**, pp. 53–128.

[4] P. Metrangolo, F. Meyer, T. Pilati, G. Resnati, G. Tarraneo, *Angew. Chem.* **2008**, *120*, 6202–6220.

[5] (a) G. Modena, G. Scorrano, *Directing, Activating and Deactivating Effects*, in *The Chemistry of Functional Groups*, Wiley, London, **1973**, pp. 301–406. (b) C. Rappe, *Rearrangement Involving Halides*, in *The Chemistry of Functional Groups*, Wiley, London, **1973**, pp. 1071–1114.

[6] H. W. Gibson, *Can. J. Chem.* **1973**, *51*, 3065–3070.

[7] (a) K. Naumann, *J. Prakt. Chem.* **1999**, *341*, 417–435. (b) C. S. Neumann, D. G. Fujimori, C. T. Walsh, *Chem. Biol*. **2008**, *15*, 99–109.

[8] K. Ballschmiter, *Chemosphere* **2003**, *52*, 313–324.

[9] G. W. Gribble, *Naturally Occuring Organohalogen Compounds – A Comprehensive Update*, in *Progress in the Chemistry of Organic Natural Products*, *Vol. 91* (Eds.: A. D. Kinghorn, H. Falk, J. Kobayashi), Springer, Wien, **2010**.

[10] M. S. Puar, *J. Chem. Educ.* **1970**, *47*, 473–474.

[11] R. G. Pearson, *The HSAB Principle*, in *Chemical Hardness*, Wiley-VCH, Weinheim, **1997**, pp. 1–27.

[12] E. Schaumann, *Introduction*, in *Science of Syntheses*, *Vol. 35* (Ed.: E. Schaumann), Thieme, Stuttgart, **2006**, pp. 1–13.

[13] J. Hartung, *Synthesis by Substitution of Hydrogen*, in *Science of Syntheses*, *Vol. 35* (Ed.: E. Schaumann), Thieme, Stuttgart, **2006**, pp. 10–46.

[14] J. Iskra, S. Stavber, M. Zupan, *Chem. Commun.* **2003**, 2496–2497.

[15] (a) M. L. Poutsma, *J. Am. Chem. Soc.* **1965**, *87*, 2171–2162. (b) E. W. Meijer, R. M. Kellogg, H. Wynberg, *J. Org. Chem.* **1982**, *47*, 2005–2009. (c) H. Bienaymé, J.-E. Ancel, P. Meilland, J.-P. Simonato, *Tetrahedron Lett.* **2000**, *41*, 3339–3343.

[16] M. S. Newman, M. D. Farbman, H. Hipsher, *Org. Synth.* **1955**, *Coll. Vol. 3*, 188–190

[17] T. F. Florkiewicz, B. Lüke, P. Schmittinger in *Chlorine – Principles and Industrial Practice*, (Ed.: P. Schmittinger), Wiley-VCH, Weinheim, **2000**, pp. 19–107.

[18] C.W. Jones in *Application of Hydrogen Peroxide and Derivatives*, RSC Clean Technology Monographs, (Ed.: J. H. Clark), Royal Chemical Society, Cambridge, **1999**, pp. 156–162.

[19] W. M. Weigert, W. Merk, H. Offermanns, G. Prescher, G. Schreyer, O. Weiberg in *Wasserstoffperoxid und seine Derivate*, (Ed.: W. Weigert), Hüthig, Heidelberg, **1978**, pp. 73–110.

[20] D. R. Morris, L. P. Hager, *J. Biol. Chem.* **1966**, *241*, 1763–1768.

[21] F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova, C. T. Walsh, *Chem. Rev.* **2006**, *106*, 3364–3378.

[22] H.-A. Wagenknecht, C. Claude, W.-D. Woggon, *Helv. Chim. Acta* **1998**, *81*, 1506–1520.

[23] (a) M. Mba, M. Pontini, S. Lovat, C. Zonta, G. Bernardinelli, P. E. Kündig, G. Licini, *Inorg. Chem.* **2008**, *47*, 8616–8618. (b) F. Romano, A. Linden, M. Mba, C. Zonta, G. Licini, *Adv. Synth. Catal.* **2010**, *352*, 2937–2942.

[24] N. B. Barhate, A. S. Gajare, R. D. Wakharkar, A. V. Bedekar, *Tetrahedron* **1999**, *55*, 11127–11142.

[25] (a) N. A. Milas, S. A. Harris, *J. Am. Chem. Soc.* **1938**, *60*, 2434–2436. (b) K. B. Sharpless, T. R. Verhoeven, *Aldrichim. Acta* **1979**, *12*, 63–74. (c) J. G. Hill, B. E. Rossiter, K. B. Sharpless, *J. Org. Chem.* **1983**, *48*, 3607–3608.

[26] O. Brücher, J. Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.

[27] For cyclic β-chlorohydrin ether-derived natural products see: (a) Aplysiapyranoids: T. Kusumi, H. Uchida, Y. Inouye, M. Ishitsuka, H. Yamamoto, H. Kakisawa, *J. Org. Chem.* **1987**, *52*, 4597–4600. (b) Plocamiods: J. Darias, J. Rovirosa, A. San Martin, A.-R. Díaz, E. Dorta, M. Cueto, *J. Nat. Prod.* **2001**, *64*, 1383–1387. (c) Kalihinols: H. Miyaoka, M. Shimomura, H. Kimura, Y. Yamada, H.-S. Kim, W. Yusuke, *Tetrahedron* **1998**, *54*, 13467–13474.

[28] For chlorolactonization by *N*-chloro-compounds see: D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc*. **2010**, *132*, 3298–3300. For polyene chlorocyclization mediated by chloro diethylsulfonium hexachloroantimonate, see: S. Snyder, D. S. Treitler, A. P. Bucks, *J. Am. Chem. Soc*. **2010**, *132*, 14303–14314.

[29] A. F. Hollemann, N. Wiberg in *Lehrbuch der Anorganischen Chemie*, *101st ed.*, Walter de Gruyter: Berlin, **1995**, pp. 471–473.

[30] R. A. Sheldon in *Aspects of Homogeneous Catalysis*, *Vol. 4* (Ed.: R. Ugo), Reidel Publishing, Dordrecht, **1981**, pp. 3–69.

[31] R. Royer, P. Demerseman, *Bull. Chem. Soc. Fr.* **1968**, 2633–2648.

[32] O. Maass, P.G. Hiebert, *J. Am. Chem. Soc*. **1924**, *46*, 290–308.

[33] For recent application of oxone® for oxidative chlorination of arenes in water and in acetonitrile, see: (a) B. V. Tamhankar, U. V. Desai, R. B. Mane, P. P. Wadgaonkar, A. V. Bedekar, *Synth. Commun.* **2001**, *31*, 2021–2027. (b) N. Narender, P. Srinivasu, S. J. Kulkarni, K.V. Radhavan, *Synth. Commun.* **2002**, *32*, 279–286.

[34] L. Kuczynski, M. Wilimowski, M. Baginska, J. Soloducho, *Pol. J. Pharmacol. Pharm*. **1975**, *27*, 549–553.

[35] (a) E. Haegele, *Chem. Ber.* **1892**, *25*, 2753–2756. (b) J. J. Fernández, A. Fernández, D. Vázquez-García, M. López-Torres, A. Suárez, N. Gómez-Blanco, J. M. Vila, *Eur. J. Inorg. Chem.* **2007**, 5408–5418.

[36] (a) O. A. Rajan, A. Chakravorty, *Inorg. Chem.* **1981**, *20*, 660–664. (b) D. Agustin, C. Bibal, B. Neveux, J.-C. Daran, R. Poli, *Z. Anorg. Allg. Chem.* **2009**, *635*, 2120–2125.

[37] A. W. Addison, T. N. Rao, J. Reedijk, van Rijn, G. C. Verschoor, *J. Chem. Soc*., *Dalton Trans*. **1984**, 1349–1356.

[38] S. Bellemin-Laponnaz, K. S. Coleman, P. Dierkes, J. P. Masson, J. A. Osborn, *Eur. J. Inorg. Chem.* **2000**, 1645–1649.

[39] M. Greb,. *Dissertation*, Univ. Würzburg, Germany, **2004**, pp. 75–76.

[40] O. Brücher, U. Bergsträßer, H. Kelm, J. Hartung, M. Greb, I. Svoboda, H. Fuess, *Tetrahedron* **2012**, *68*, 6968–6980.

[41] K. A. V'yunov, A. I. Ginak, *Russ. Chem. Rev*. **1981**, *50*, 151–163.

[42] (a) F. G. Soper, G. F. Smith, *J. Chem. Soc.* **1926**, 1582–1591. (b) C. G. Swain, D. R. Crist, *J. Am. Chem. Soc.* **1972**, *94*, 3195–3200.

[43] T. Schlama, K. Gabriel, V. Gouverneru, C. Mioskowski, *Angew. Chem. Int. Ed*. **1997**, *36*, 2342–2433.

[44] W. D. Watson, *J. Org. Chem.* **1982**, *47*, 5270–5276.

[45] M. Mba, M. Pontini, S. Lovat, C. Zonta, G. Bernardinelli, P. E. Kündig, G. Licini, *Inorg. Chem.* **2008**, *47*, 8616–8618.

[46] H. Lübbecke, P. Boldt, *Tetrahedron* **1978**, *34*, 1577–1579.

[47] K. Yonehara, K. Kamata, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2011**, *47*, 1692–1694.

[48] L. Yang, Z. Lu, S. S. Stahl, *Chem. Commun.* **2009**, 6460–6462.

[49] C. G. Eisenhardt, A. S. Gemechu, H. Baumgärtel, R. Chelli, G. Cardini, S. Califano, *Phys. Chem. Chem. Phys*. **2001**, *3*, 5358–5368.

[50] D. A. Becker, H. Okabe, J. R. McNesby, *J. Phys. Chem*. **1965**, *69*, 538–542.

[51] C. Walling, B.B. Jacknow, *J. Am. Chem. Soc.* **1960**, *82*, 6108–6112.

[52] H. B. Hass, E. T. McBee, Weber, P. *Ind. Eng. Chem.* **1936**, *28*, 333–339.

[53] M. S. Kharasch, H. C. Brown, *J. Am. Chem. Soc.* **1939**, *61*, 2142–2150.

[54] G. A. Russell, *J. Am. Chem. Soc.* **1958**, *80*, 4987–4996.

[55] K. U. Ingold, J. Lusztyk, K. D. Raner, *Acc. Chem. Res.* **1990**, *23*, 219–225.

[56] H. Eckert, B. Forster, *Angew. Chem. Int. Ed.* **1987**, *26*, 894–895.

[57] (a) S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, J. Wolinsky, *Tetrahedron Lett.* **1980**, *21*, 441–444. (b) T. Yamamoto, H. Matsuda, Y. Utsumi, T. Hagiwara, T. Kanisawa, *Tetrahedron Lett.* **2002**, *43*, 9077–9080.

[58] T. Okino, E. Yoshimura, H. Hirota, N. Fusetani, *Tetrahedron Lett.* **1995**, *36*, 8637–8640.

[59] N. Fusetani, K. Yasumuro, H. Kawai, T. Natori, L. Brinen *Tetrahedron Lett.* **1990**, *31*, 3599–3602.

Anhang

Anhang A

Supporting Information for: Vanadium(V)-Catalyzed Oxidative Bromination of Acid Labile Alkenes and Alkenols in Alkyl Carbonates

Oliver Brücher and Jens Hartung

Fachbereich Chemie, Technische Universität Kaiserslautern,
Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

Contents

A1 General remark

The compound numbering in the Supporting Information is consistent with that of the accompanying publication.

A2 Instrumentation and reagents

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*).

^{1}H-, ^{13}C- and ^{51}V-NMR spectra were recorded with FT-NMR AC 250, DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale (coupling constants J are given in Hz). The resonances of residual protons and of the carbon nuclei of $CDCl_3$ (δ_H 7.26, δ_C 77.0) and CD_3OD (δ_H 3.31, δ_C 46.15) were used as internal standards. Chemical shifts of vanadium nuclei were referenced to an external standard of $VOCl_3$ [90% (*v*/*v*)] in C_6D_6 ($\delta_V \equiv 0$).

IR spectra were recorded from pelletized samples in KBr with a FT-IR 1000 spectrometer (*Perkin Elmer*).

UV/Vis spectra were recorded in 1 cm-quartz cuvettes with a Cary 100 spectrometer (*Varian*) at 25 °C using analytical grade solvents. Molar extinction coefficients (lg ε) are reported in $m^2 \times mol^{-1}$.

Combustion analyses were performed with an Elemental Analyser 2400 CHN (*Perkin Elmer*).

Reaction progress was monitored via thin layer chromatography (tlc) on aluminum sheets coated with silica gel (60 F_{254}, *Machery-Nagel*). Compounds were detected on developed tlc sheets via UV light absorption (254 nm) or the use of Ekkert's reagent, prepared from anisaldehyde (1 mL) in EtOH (100 mL), acetic acid (10 ml), and conc. H_2SO_4 (8 mL).

(*E*)-Cinnamic acid (98%), 2-methylpropanal (99%), $VO(OEt)_3$ (95%), cyclohexa-1,4-diene (97%), NBS (99%), 3-bromopropionic acid (**1a**) (97%), bromobenzene (99%), montmorillonite K-10, ethylene glycol (95%), 4-*tert*-butylcyclohexanol (99%), propylene carbonate (99.5%) [*Acros*], β-methylstyrene (**2e**) (99%), 1-decene (**2c**) (94%), cyclohex-3-enecarbaldehyde (97%), cyclopropyl methyl ketone (98%), (*E*)-5-decene (**2f**) (99%) [*Aldrich*], dimethyl carbonate (99%), NaBr (99%), SiO_2 for column chromatography (230–400 mesh) [*Merck*], NBu_4Br (98%) and (3*R*)-linalool (**7c**) (97%) [*Fluka*], EtOAc (99%) and cyclohexane (99%) [*J.T. Baker*] were commercially available and used as received. Solvents not named above were purified according to standard procedures.[1]

(*E*)-5-Phenylpent-4-en-1-ol (**7a**),[2] 5-methyl-1-phenylhex-4-en-1-ol (**7b**),[3] ethyl 5-methylhex-4-eneoate (**2g**),[4] 1-phenylpent-4-ene (**2d**),[5] 4-*tert*-butylcyclohexene oxide,[6] dimethyl piperidine-2,6-dicarboxylate,[7] and {6-[(2-oxidophenyl)iminomethyl]-phenolato}(ethanolato)oxidovanadium(V) [VO(L^2)(OEt)][8] were prepared according to published procedures. *tert*-Butyl hydroperoxide (TBHP) in toluene was prepared according to Sharpless *et al.* and its concentration determined as described.[9]

A3 3-Bromopropionic acids

A3.1 3-Bromo-2,2-dimethylpropionic acid (1b)

A3.1.1 3-Hydroxy-2,2-dimethylpropionic acid.[10]

2-Methylpropanal (36.1 g, 500 mmol) was dissolved in aq. formaldehyde [37% (*w*/*w*), 40.6 g, 500 mmol] and treated with K_2CO_3 (69.0 g, 500 mmol) at 0 °C (ice bath) at such a rate that the temperature of reaction remained below 20 °C. The solution was stirred for 1 h at 0 °C. The ice-bath was removed, H_2O (75 mL) was added to the reaction mixture and stirring was continued for further 90 min. The phases of this mixture were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (3 × 75 mL). The organic phase and the organic washings were combined, dried ($MgSO_4$), and concentrated under reduced pressure (350 mbar / 40 °C) to leave a colorless oil (51.1 g). This residue, which consisted predominantly of 3-hydroxy-2,2-dimethylpropanal, was dissolved in of H_2O (800 mL). To this solution, K_2CO_3 (42.0 g, 30.3 mmol) was added at 25 °C and, over a period of 2 hours, portions of $KMnO_4$ (59.3 g, 375 mmol), while beeing continously stirred. Stirring of the reaction mixture was continued for 16 hours at 25 °C. The solids were afterwards removed by filtration and the pH of the filtrate adjusted to 12 with NaOH-pellets. The basic solution was washed with *tert*-butyl methyl ether (2 × 100 mL) and acidified with concentrated aqueous HCl (50 mL). The acidic solution was extracted with *tert*-butyl methyl ether (4 × 100 mL). The organic washings were combined, dried ($MgSO_4$), and concentrated under reduced pressure (350 mbar / 40 °C) to leave 3-hydroxy-2,2-dimethylpropionic acid (24.5 g, 207 mmol, 41 % from 2-methylpropanal) as a colorless crystalline solid; δ_H (600 MHz; $CDCl_3$) 1.24 (6 H, s, CH_3), 3.60 (2 H, s, 3-H). δ_C (150 MHz; $CDCl_3$) 21.9 (CH_3), 44.0 (C2), 69.3 (C3), 183.2 (C1).

A3.1.2 3-Bromo-2,2-dimethylpropionic acid (1b).[11]

Title compound **1b** was prepared according to Greene *et al.* from 3-hydroxy-2,2-dimethylpropionic acid (30.0 g, 254 mmol).[11] Yield: 36.8 g (80 %). δ_H (600 MHz; $CDCl_3$) 1.36

(6 H, s, CH_3), 3.52 (2 H, s, 3-H). δ_C (150 MHz; $CDCl_3$) 24.0 (CH_3), 40.5 (C3), 43.9 (C2), 181.1 (C1).

A3.2 3-Bromo-3-phenylpropionic acid (1c).[12][13]

To a solution of HBr [30%, (*w*/*w*)] in acetic acid (50 mL) was added (*E*)-cinnamic acid (8.45 g, 57.0 mmol). The mixture was heated to 45–50 °C for 8 h and then kept at 25 °C for 16 h while continously stirred. The formed colorless precipitate was filtered off, washed with ice-water (4 × 50 mL), and dried (25 °C, 0.1 mbar). Yield: 11.3 g (49.3 mmol, 87 %) colorless solid; $C_9H_9BrO_2$ (229.07). δ_H (600 MHz; $CDCl_3$) 3.28 (1 H, dd, *J* 16.8, 6.1 Hz, 2-H), 3.40 (1 H, dd, *J* 16.8, 9.1 Hz, 2-H), 5.38 (1 H, dd, *J* 8.9, 6.1 Hz, 3-H), 7.29–7.33 (1 H, m), 7.33–7.39 (2 H, m), 7.39–7.46 (2 H, m). δ_C (150 MHz; $CDCl_3$) 44.4 (C2), 47.0 (C3), 127.1, 128.9, 128.9, 140.5, 175.1 (C1).

A4 Alkenes and alkenols

A4.1 4-*tert*-Butylcyclohexene (2a)[14–16]

The compound **2a** was prepared from 4-*tert*-butylcyclohexanol (15.6 g, 100 mmol). Yield: 4.01 g, (29 %), colorless liquid. δ_H (600 MHz; $CDCl_3$) 0.86 (9 H, s, CH_3), 1.11–1.19 (1 H, m, 5-H), 1.25–1.31 (1 H, m, 4-H), 1.74–1.83 (2 H, m, 3-H, 5-H), 1.97–2.05 (2 H, m, 3-H, 6-H), 2.06–2.13 (1 H, m, 6-H), 5.63–5.72 (2 H, m, 1-H, 2-H). δ_C (150 MHz; $CDCl_3$) 23.9 (C5), 26.7, 26.8 (C3, C6), 27.2 (CH_3), 32.3 (C_q), 44.1 (C4), 126.9, 127.4 (C1, C2). Anal. calcd. for $C_{10}H_{18}$ (138.25): C, 86.88; H, 13.12; Found: C, 86.90; H, 12.80.

A4.2 2-(Cyclohex-3'-enyl)-1,3-dioxolane (2b)[17]

A slurry of cyclohex-3-ene carbaldehyde (2.75 g, 25 mmol), ethylene glycol (1.87 g, 30 mmol) and montmorillonite K-10 (1.5 g) in cyclohexane (75 mL) was heated under reflux with a Dean-Stark apparatus for 5 h. The reaction mixture was allowed to cool (25 °C). Solids were filtered off. The filtrate was concentrated under reduced pressure (180 mbar, 40 °C) and the residue purified by distillation (bp 59 °C / 0.8 mbar). Yield: 2.17 g (14.1 mmol, 56 %) colorless liquid, $C_9H_{14}O_2$ (154.21). δ_H (600 MHz; $CDCl_3$) 1.34–1.43 (1 H, m, 6'-H), 1.79–1.87 (2 H, m, 1'-H, 6'-H), 1.88–1.96 (1 H, m, 2'-H), 2.01–2.15 (3 H, m, 2'-H, 5'-H), 3.83–3.98 (4 H, m, 4-H, 5-H), 4.70 (1 H, d, *J* 5.3 Hz, 2-H), 5.64–5.70 (2 H, m, 3'-H, 4'-H). δ_C (150 MHz; $CDCl_3$) 23.4 (C6'), 24.6 (C5'), 26.0 (C2'), 37.7 (C1'), 64.9, 65.0 (C4, C5), 107.2 (C1), 125.8, 127.0 (C3', C4').

A4.3 Ethyl (*E*)-2-(2-hydroxypropy-2-yl)-5-phenyl-4-hexenoate (7d)

A4.3.1 (*E*)-1-Bromo-4-phenylpent-3-ene[18][19]

To a solution of phenyl magnesium bromide in Et_2O (75 mL), prepared from magnesium turnings (2.43 g, 100 mmol) and bromobenzene (16.0 g, 102 mmol), was added cyclopropyl methyl ketone (8.20 g, 97 mmol) in diethyl ether (30 mL) within 35 min under cooling in a water bath (25 °C). The mixture was stirred for 1 hour at 25 °C and cooled in an ice bath. At 0 °C, a mixture of conc. H_2SO_4 (15 mL) and H_2O (30 mL) was added at such a rate that the temperature of the reaction mixture did not exceed 10 °C. After being stirred for 30 min at 25 °C, the organic phase was separated and the aqueous phase extracted with *tert*-butyl methyl ether (3 × 40 mL). Combined organic washings were dried ($MgSO_4$) and concentrated under reduced pressure to leave 20.3 g (93 %) of a yellowish liquid. δ_H (600 MHz; $CDCl_3$) 2.07 (3 H, s, CH_3), 2.80 (2 H, q, *J* 7.3 Hz, 2-H), 3.47 (2 H, t, *J* 7.2 Hz, 1-H), 5.77 (1 H, td, J_t 7.2, J_d 1.2 Hz, 3-H), 7.24–7.28 (1 H, m), 7.31–7.35 (2 H, m), 7.39–7.42 (2 H, m). δ_C (150 MHz; $CDCl_3$) 16.1 (CH_3), 32.2 (C2), 32.3 (C1), 124.4 (C3), 125.7, 127.0, 128.2, 137.8 (C4), 143.3.

A4.3.2 (*E*)-5-Phenyl-hex-4-enenitrile[20]

A mixture of (*E*)-1-bromo-4-phenylpent-3-ene (18.0 g, 80 mmol) and sodium cyanide (5.87 g, 120 mmol) in dimethyl sulfoxide (50 mL) was stirred at 100 °C for 18 h. After cooling to 25 °C, the reaction mixture was poured into ice water (150 mL) and extracted with *tert*-butyl methyl ether (4 × 50 mL). The organic washings were combined and dried ($MgSO_4$). The resulting clear solution was concentrated under reduced pressure, to leave 13.44 g (98 %) of a yellow liquid. δ_H (400 MHz; $CDCl_3$) 2.08 (3 H, s, CH_3), 2.44–2.51 (2 H, m, 2-H), 2.58 (2 H, q, *J* 7.1 Hz, 3-H), 5.73 (1 H, td, J_t 7.2, J_d 1.0 Hz, 4-H), 7.23–7.29 (1 H, m), 7.30–7.36 (2 H, m), 7.36–7.40 (2 H, m). δ_C (100 MHz; $CDCl_3$) 16.1 (CH_3), 17.4 (C2), 24.8 (C3), 119.3 (CN), 123.3 (C4), 125.8, 127.2, 128.3, 138.6 (C5), 143.0.

A4.3.3 (*E*)-5-Phenyl-hex-4-enoic acid[21]

To a solution of (*E*)-5-phenyl-hex-4-enenitrile (12.5 g, 73 mmol) in ethyleneglycol (80 mL) and H_2O (13 mL) was added powdered potassium hydroxide (23.0 g, 410 mmol) and the mixture stirred at 100 °C for 10 h. After cooling to 25 °C, the reaction mixture was poured onto crushed ice (100 mL), the pH adjusted to 1–2 with conc. aq. HCl (ca. 30 mL) and extracted with *tert*-butyl methyl ether (3 × 70 mL). The organic washings were dried ($MgSO_4$) and concentrated under reduced pressure to leave a brown residue, which was recrystallized from *tert*-butyl methyl ether/pentane to afford 12.3 g (89 %) of a brownish solid. δ_H (400 MHz; d_6-DMSO) 1.98 (3 H, s,

CH_3), 2.31–2.43 (4 H, m, 2-H, 3-H), 5.71–5.78 (1 H, m, 4-H), 7.18–7.24 (1 H, m), 7.27–7.33 (2 H, m), 7.34–7.49 (2 H, m), 12.12 (1 H, br. s., OH). δ_C (100 MHz; d_6-DMSO) 15.9 (CH_3), 24.0 (C3), 33.9 (C2), 55.3 (CH_3), 113.5, 124.0 (C4), 126.7, 135.8, 136.0 (C5), 158.6, 179.0 (C1).

A4.3.4 (*E*)-Ethyl-5-phenyl-hex-4-enoate[22]

A mixture of (*E*)-5-phenyl-hex-4-enoic acid (6.71 g, 35 mmol), ethanol (15 mL), and *p*-toluenesulfonic acid-monohydrate (190 mg, 1 mmol) in chloroform (135 mL) was heated under reflux with a Dean-Stark-trap for 26 h. The organic phase was washed with 5% (*w*/*w*) aq. $NaHCO_3$ (3 × 40 mL). The combined aqueous washings were extracted with CH_2Cl_2 (2 × 40 mL). The organic washings were combined, dried ($MgSO_4$), and concentrated under reduced pressure to leave 7.45 g (98 %) of a brown liquid. δ_H (400 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.2 Hz, $CO_2CH_2\mathit{CH_3}$), 2.06 (3 H, s, CH_3), 2.41–2.49 (2 H, m, 2-H), 2.50–2.59 (2 H, m, 3-H), 4.15 (2 H, q, *J* 7.3 Hz, $CO_2\mathit{CH_2}CH_3$), 5.70–5.77 (1 H, m, 4-H), 7.20–7.25 (1 H, m), 7.28–7.34 (2 H, m), 7.34–7.39 (2 H, m). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2\mathit{CH_3}$), 15.8 (CH_3), 24.4 (C3), 34.2 (C2), 60.3 ($CO_2\mathit{CH_2}CH_3$), 125.7 (C4), 126.1, 126.7, 128.1, 136.2 (C5), 143.7, 173.1 ($\mathit{CO_2}CH_2CH_3$).

A4.3.5 Ethyl (*E*)-2-(2-hydroxypropy-2-yl)-5-phenyl-4-hexenoate (7d)[23]

Under an atmosphere of nitrogen, a solution of (*E*)-ethyl-5-phenyl-hex-4-enoate (3.60 g, 16.5 mmol) in dry tetrahydrofuran (15 mL) was added to a solution of lithium diisopropyl amide (9.20 mL, 18.4 mmol, 2 M in tetrahydrofuran/hexane/ethylbenzene) in dry tetrahydrofuran (10 mL) at –78 °C (20 min). After stirring for 1 hour at –78 °C, a solution of acetone (1.10 g, 19.0 mmol) in dry tetrahydrofuran (5 mL) was added (10 min), and the reaction mixture stirred at –78 °C for further 2 h. After warming to 0 °C, the mixture was hydrolyzed with water (30 mL) and sat. aq. NH_4Cl (50 mL). The pH of this mixture was adjusted to 5–6 with conc. aq. HCl. Extraction of the resulting mixture with diethyl ether (3 × 60 mL), and concentration of the combined organic washings under reduced pressure afforded an orange oil, which was purified by column chromatography [SiO_2, EtOAc/pentane 1/4 (v/v)], to leave 3.85 g (84%) of a yellowish oil. R_f 0.27. δ_H (600 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7.2 Hz, $CO_2CH_2\mathit{CH_3}$), 1.29 (6 H, 2 × s, CH_3), 2.04 (3 H, s, CH_3), 2.48–2.56 (2 H, m, 3-H, 4-H), 2.72 (1 H, ddd, *J* 15.3, 12.2, 8.5 Hz, 4-H), 3.01 (1 H, s, OH), 4.15 (2 H, q, *J* 7.2 Hz, $CO_2\mathit{CH_2}CH_3$), 5.65–5.72 (1 H, m, 5-H), 7.20–7.25 (1 H, m), 7.27–7.35 (4 H, m). δ_C (150 MHz; $CDCl_3$) 14.3 ($CO_2CH_2\mathit{CH_3}$), 15.9 (CH_3), 26.7 (CH_3), 27.0 (C4), 29.2 (CH_3), 55.5 (C3), 60.6 ($CO_2\mathit{CH_2}CH_3$), 71.0 (C2), 124.9 (C5), 125.7, 126.7, 128.2, 136.8 (C6), 143.7, 175.8 ($\mathit{CO_2}CH_2CH_3$). Anal. calcd. for $C_{17}H_{24}O_3$ (276.37): C, 73.88; H, 8.75; Found: C, 73.72; H, 8.76.

A5 Oxidative brominations

A5.1 Dibromoalkanes from alkenes

A5.1.1 General method

To the solution of an alkene (1 mmol) in propylene carbonate (20 mL) was added 3-bromo-2,2-dimethylpropionic acid (**1b**) (452 mg, 2.5 mmol), NaBr (10.3 mg, 0.1 mmol), a vanadium catalyst (0.01 mmol) and TBHP (3.5 m in toluene, 300 µl, 1.05 mmol). Cyclohexa-1,4-diene (32.1 mg, 0.4 mmol) dissolved in propylene carbonate (3 mL) was added via syringe pump (0.003 mL/min). The reaction mixture was stirred at 30 °C in a water bath for the indicated time. The yellowish solution was extracted with cyclohexane (4 × 15 mL), combined organic extracts were washed with water (20 mL), and satd. aq. NaCl (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2).

Brominations of more polar substrates, such as ethyl 5-methylhex-4-enoate (**2g**), were preferentially conducted in ethyl acetate using NBu_4Br instead of NaBr. Product isolation in this case was achieved via removal of the solvent under reduced pressure, which was followed by chromatographic purification of the residue.

A5.1.2 Conversion of 1-decene (2c)

Substrate: 141 mg (1 mmol) **2c**; conversion: 86 % (NMR) after 40 h. *1,2-Dibromodecane* (**3c**).[24] Yield: 207 mg (69 %) colorless oil, R_f 0.91, $C_{10}H_{18}Br_2$ (298.06). δ_H (400 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.8 Hz, CH_3), 1.26 (10 H, br. S, CH_2), 1.34–1.47 (1 H, m, CH_2), 1.50–1.63 (1 H, m, CH_2), 1.78 (1 H, dtd, J_d 14.4, 4.8, J_t 9.7 Hz, CH_2), 2.08–2.19 (1 H, m, CH_2), 3.63 (1 H, t, *J* 9.9 Hz, 10-H), 3.85 (1 H, dd, *J* 10.2, 4.4 Hz, 10-H), 4.13–4.22 (1 H, m, 9-H).

A5.1.3 Conversion of 1-phenylpent-4-ene (2d)

Substrate: 147 mg (1 mmol) **2d**; conversion: 93 % (NMR) after 48 h. *1,2-Dibromo-5-phenylpentane* (**3d**).[25] Yield: 192 mg (63 %) colorless oil, R_f 0.79. δ_H (600 MHz; $CDCl_3$) 1.74–1.81 (1 H, m, 4-H), 1.81–1.88 (1 H, m, 3-H), 1.89–1.98 (1 H, m, 4-H), 2.19 (1 H, dddd, *J* 13.9, 10.4, 5.1, 3.1 Hz, 3-H), 3.62 (1 H, t, *J* 10.0 Hz, 1-H), 2.61–2.74 (2 H, m, 5-H), 3.85 (1 H, dd, *J* 10.2, 4.5 Hz, 1-H), 4.15–4.23 (1 H, m, 2-H), 7.18–7.23 (3 H, m), 7.28–7.32 (2 H, m). δ_C (150 MHz; $CDCl_3$) 28.5 (C4), 35.0 (C5), 35.6 (C3), 36.2 (C1), 52.7 (C2), 126.0, 128.3, 128.4, 141.5; Anal. calcd. for $C_{11}H_{14}Br_2$ (306.04): C, 43.17; H, 4.61; Found: C, 43.31; H, 4.63.

A5.1.4 Conversion of β-methylstyrene (2e)

Substrate: 120 mg (1 mmol) **2e**; conversion: 84 % (NMR) after 24 h. *rel-(1R,2S)-Dibromo-1-phenylpropane* (**3e**).[24] Yield: 156 mg (56 %) colorless oil, R_f 0.76, $C_9H_{10}Br_2$ (277.98). δ_H (400 MHz; $CDCl_3$) 2.05 (3 H, d, *J* 6.5 Hz, CH_3), 4.61 (1 H, dq, J_d 10.2, J_q 6.5 Hz, 2-H), 5.04 (1 H, d, *J* 10.2 Hz, 1-H), 7.28–7.43 (5 H, m).

A5.1.5 Conversion of (*E*)-5-decene (2f)

Substrate: 141 mg (1 mmol) **2f**; conversion: 93 % (NMR) after 24 h. *rel-(5R,6S)-Dibromodecane* (**3f**).[24] Yield: 220 mg (73 %) colorless oil, R_f 0.89, $C_{10}H_{20}Br_2$ (300.07). δ_H (400 MHz; $CDCl_3$) 0.93 (6 H, t, *J* 7.0 Hz, CH_3), 1.23–1.48 (6 H, m, CH_2), 1.53–1.66 (2 H, m, CH_2), 1.88–2.01 (2 H, m, CH_2), 2.04–2.17 (2 H, m, CH_2), 4.12–4.21 (2 H, m, 5-H, 6-H).

A5.1.6 Conversion of ethyl 5-methylhex-4-enoate (2g)

Substrate: 157 mg (1 mmol) **2g**; quant. conversion. (NMR) after 40 h. *Ethyl 4,5-dibromo-5-methylhexanoate* (**3g**). Yield: 218 mg (69 %) colorless oil, R_f 0.74. δ_H (600 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.84 (3 H, s, CH_3), 1.99 (3 H, s, 6-H), 2.07 (1 H, dddd, *J* 14.6, 11.3, 8.3, 4.8 Hz, 3-H), 2.52 (1 H, dt, J_d 16.4, J_t 8.0 Hz, 2-H), 2.67–2.73 (1 H, m, 2-H), 2.76–2.82 (1 H, m, 3-H), 4.16 (2 H, q, *J* 7.1 Hz, $CO_2CH_2CH_3$), 4.25 (1 H, d, *J* 11.2 Hz, 4-H). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$) 28.6 (C6), 31.2 (C3), 33.0 (C2), 35.1 (CH_3), 60.6 ($CO_2CH_2CH_3$), 65.6 (C4), 67.7 (C5), 172.6 (C1). Anal. calcd. for $C_9H_{16}Br_2O_2$ (316.03): C, 34.20; H, 5.10; Found: C, 34.80; H, 5.17.

A5.2 Bromocyclizations

A5.2.1 General method

To the solution of an alkenol (1 mmol) in propylene carbonate (20 mL) was added 3-bromo-2,2-dimethylpropionic acid (**1b**) (226 mg, 1.25 mmol), NaBr (10.3 mg, 0.1 mmol), a vanadium catalyst (0.01 mmol) and TBHP (3.5 m in toluene, 455 µL, 1.6 mmol). 1,4-Cyclohexadiene (32.1 mg, 0.4 mmol) dissolved in propylene carbonate (3 mL) was added via syringe pump (0.003 mL/min). The reaction mixture was stirred at 30 °C in a water bath for 48 h. The yellowish solution was extracted with cyclohexane (4 × 15 mL), combined organic extracts were washed with H_2O (1 × 20 mL) and sat. aqueous NaCl (1 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2).

A5.2.2 Bromocyclization of 5-methyl-1-phenylhex-4-en-1-ol (7b)

From 191 mg (1 mmol) of **7b**. *3-Bromo-2,2-dimethyl-6-phenyltetrahydropyran* (**8b**).[26] Yield: 184 mg (68 %), 4/96-mixture of *cis*/*trans*-isomers, colorless oil. R_f 0.69. $C_{13}H_{17}BrO$ (269.18). *cis*-**8b**. δ_H (400 MHz; $CDCl_3$) 1.43 (3 H, s, CH3), 1.49 (3 H, s, CH3), 1.62–1.69 (1 H, m, 5-H), 2.13–2.21 (2 H, m, 4-H), 4.25 (1 H, t, *J* 3.1 Hz, 3-H), 4.68 (1 H, dd, *J* 11.7, 3.1 Hz, 6-H), 7.31–7.43 (5 H, m). *trans*-**8b**. δ_H (400 MHz; $CDCl_3$) 1.44 (3 H, s, CH3), 1.48 (3 H, s, CH3), 1.61–1.72 (1 H, m, 5-H), 1.81–1.89 (1 H, m, 5-H), 2.23–2.33 (2 H, m, 4-H), 4.02 (1 H, dd, *J* 8.7, 8.4 Hz, 3-H), 4.65 (1 H, dd, *J* 11.7, 2.4 Hz, 6-H), 7.20–7.32 (m, 5 H). *2-(1'-Bromo-1'-methylethyl)-5-phenyltetrahydrofuran* (**9b**).[26] Yield: 38 mg (14 %) 41/59-mixture of *cis*/*trans*-isomers, colorless oil. R_f 0.69. $C_{13}H_{17}BrO$ (269.18). *cis*-**9b**. δ_H (400 MHz; $CDCl_3$) 1.79 (3 H, s, CH3), 1.81 (3 H, s, CH3), 2.05–2.19 (2 H, m, 3-H), 2.21–2.28 (2 H, m, 4-H), 3.93 (1 H, dd, *J* 7.8, 6.2 Hz, 2-H), 4.87 (1 H, dd, *J* 9.4, 5.8 Hz, 5-H), 7.22–7.35 (5 H, m). *trans*-**9b**. δ_H (400 MHz; $CDCl_3$) 1.76 (3 H, s, CH3), 1.82 (3 H, s, CH3), 1.87–1.94 (1 H, m, 3-H), 2.04–2.14 (1 H, m, 4-H), 2.17–2.24 (1 H, m, 3-H), 2.37–2.2.44 (1 H, m, 4-H), 4.10 (1 H, dd, *J* 8.2, 6.6 Hz, 2-H), 5.10 (1 H, dd, *J* 9.0, 5.9 Hz, 5-H), 7.23–7.35 (5 H, m).

A5.2.3 Bromocyclization of (3*R*)-linalool (7c)

From 155 mg (1 mmol) of **7c**. *(5R)-2-(1'-Bromo-1'-methylethyl)-5-methyl-5-vinyltetrahydrofuran* (**9c**). Yield: 87 mg (37 %), 62/38-mixture of *cis*/*trans*-isomers, colorless oil, R_f 0.71, $C_{10}H_{17}BrO$ (233.15). (*2S*,*5R*)-**9c** (*cis*-**9c**). δ_H (600 MHz; $CDCl_3$) 1.30 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 1.75 (3 H, s, CH_3), 1.76–2.30 (4 H, m, CH_2), 4.01 (1 H, t, *J* 6.9 Hz, 2-H), 4.98–5.02 (1 H, m, –HC=CH_2), 5.23 (1 H, dd, *J* 17.3, 1.3 Hz, –HC=CH_2), 5.99 (1 H, dd, *J* 17.3, 10.4 Hz, –*HC*=CH_2) ppm. NOESY (cross peaks) 2-H ↔ 5-CH_3. (*2R*,*5R*)-**9c** (*trans*-**9c**): δ_H (600 MHz; $CDCl_3$) 1.34 (3 H, s, CH_3), 1.72 (3 H, s, CH_3), 1.75 (3 H, s, CH_3), 1.76–2.30 (4 H, m, CH_2), 3.92 (1 H, dd, *J* 7.4, 6.2 Hz, 2-H), 4.93–4.98 (1 H, m, –HC=CH_2), 5.19 (1 H, dd, *J* 17.2, 1.4 Hz, –HC=CH_2), 5.84 (1 H, dd, *J* 17.2, 10.6 Hz, –*HC*=CH_2) ppm. NOESY (cross peaks) 2-H ↔ vinyl-H. *(6R)-3-Bromo-2,2,6-trimethyl-6-vinyltetrahydropyran* (**8c**). Yield: 97 mg (42 %), 64/36-mixture of *cis*/*trans*-isomers, colorless oil, R_f 0.71. $C_{10}H_{17}BrO$ (233.15). (*3R*,*6R*)-**8c** (*cis*-**8c**). δ_H (600 MHz; $CDCl_3$) 1.14 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 1.37 (3 H, s, CH_3), 1.63 (1 H, tdd, *J* 13.7, 3.9, 1.1 Hz, 5-H), 1.76–2.30 (3 H, m, CH_2), 3.94 (1 H, dd, *J* 12.6, 4.1 Hz, 3-H), 4.98–5.02 (2 H, m, –HC=CH_2), 5.97 (1 H, ddd, *J* 17.9, 10.8, 1.1 Hz, –*HC*=CH_2) ppm. NOESY (cross peaks) 3-H ↔ 5-H. (*3S*,*6R*)-**8c** (*trans*-**8c**). δ_H (600 MHz; $CDCl_3$) 1.29 (3 H, s, CH_3), 1.36 (3 H, s, CH_3), 1.39 (3 H, s, CH_3), 1.76–2.30 (4 H, m, CH_2), 4.09 (1 H, dd, *J* 7.5, 3.5 Hz, 3-H), 4.95–5.02 (1 H, m, –HC=CH_2), 5.06 (1 H, d, *J* 17.7 Hz, –HC=CH_2), 5.91 (1 H, dd, *J* 17.7, 11.0 Hz, –

HC=CH_2). Mixture of **8c** *and* **9c**. δ_C (150 MHz; $CDCl_3$) 22.2, 25.5, 26.6, 27.5, 28.5, 28.6, 28.9, 28.9, 29.0, 29.1, 29.2, 29.2, 30.8, 31.2, 31.4, 31.4, 32.0, 35.0, 36.8, 37.5, 58.6, 59.5, 68.4, 68.6, 73.8, 74.2, 74.7, 76.2, 83.9, 84.1, 86.0, 86.1, 110.7, 110.9, 111.5, 111.6, 143.4, 143.8, 145.5, 146.8.

A5.2.4 Bromocyclization of ethyl (*E*)-2-(2-hydroxypropy-2-yl)-5-phenyl-4-hexenoate (7d)

From 276 mg (1 mmol) of **7d** and 344 mg of (1.5 mmol) 3-bromo-3-phenylpropanoic acid (**1c**). *Ethyl (5-bromo-2,2,6-trimethyl-6-phenyltetrahydropyran)-3-carboxylate* (**8d**). Yield: 167 mg (47 %), 76/23-mixture of *cis*/*trans* isomers, colourless oil. R_f = 0.63. Anal. calcd. for $C_{17}H_{23}BrO_3$ (355.27): C, 57.47; H, 6.53; Found: C, 57.37; H, 6.44. *rel*-(3*R*,5*S*,6*R*)-**8d** [(±)-*cis*-**8d**]. δ_H (400 MHz; $CDCl_3$) 1.29 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.41 (3 H, s, CH_3), 1.49 (3 H, s, CH_3), 1.89 (3 H, s, CH_3), 2.39 (1 H, dt, *J* 13.5 Hz, 3.6, 4-H), 2.71 (1 H, q, *J* 13.1 Hz, 4-H), 2.80–2.88 (1 H, m, 3-H), 4.04 (1 H, dd, *J* 12.8, 3.9 Hz, 5-H), 4.13–4.23 (2 H, m, $CO_2CH_2CH_3$), 7.21–7.40 (4 H, m), 7.60 (2 H, d, *J* 7.8 Hz). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 20.7 (CH_3), 24.7 (CH_3), 31.6 (C4), 32.1 (CH_3), 54.0 (C3), 57.2 (C5), 60.8 ($CO_2CH_2CH_3$), 74.3 (C2), 78.5 (C6), 126.1, 127.5, 127.9, 145.6, 171.1 ($CO_2CH_2CH_3$). NOESY (cross peaks) 3-H ↔ 5-H. *rel*-(3*S*,5*S*,6*R*)-**8d** [(±)-*trans*-**8d**]. δ_H (400 MHz; $CDCl_3$) 0.74 (3 H, s, CH_3), 1.24 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.50 (3 H, s, CH_3), 1.63 (3 H, s, CH_3), 2.33 (1 H, m, 4-H), 2.59 (1 H, ddd, *J* 15.0, 10.7, 3.1 Hz, 4-H), 3.18 (1 H, dd, *J* 10.6 Hz, 4.1, 3-H), 4.07–4.23 (2 H, m, $CO_2CH_2CH_3$), 5.27 (1 H, dd, *J* 5.4, 3.1 Hz, 5-H), 7.21–7.38 (3 H, m), 7.51 (2 H, d, *J* 7.5 Hz). δ_C (100 MHz; $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 25.6 (CH_3), 30.0 (C4), 31.5 (CH_3), 34.0 (CH_3), 47.2 (C3), 56.8 (C5), 60.6 ($CO_2CH_2CH_3$), 74.5 (C2), 76.4 (C6), 126.3, 127.2, 128.0, 144.8, 172.7 ($CO_2CH_2CH_3$). NOESY (cross peaks) 3-H ↔ 5-H (missing).

A5.2.5 Larger scale bromocyclization of (3*R*)-linalool (7c)

To a solution of (3*R*)-linalool (**7c**) (10.0 mmol) in propylene carbonate (40 mL) was added 3-bromo-2,2-dimethylpropionic acid (**1b**) (2.26 g, 12.5 mmol), NaBr (26 mg, 0.25 mmol), VO(L^1)(OEt) (0.025 mmol), and TBHP (3.5 M in toluene, 3.00 mL, 10.5 mmol). 1,4-Cyclohexadiene (320 mg, 4.0 mmol) dissolved in propylene carbonate (5 mL) was added via syringe pump (0.003 mL/min). The reaction mixture was stirred at 30 °C in a water bath for 48 h. The yellowish solution was extracted with cyclohexane (4 × 30 mL). The combined organic extracts were washed with H_2O (2 × 60 mL) and sat. aq. NaCl (1 × 60 mL), dried ($MgSO_4$), and concentrated under reduced pressure to leave a colorless oil, which contained the practically pure

products (1.47 g, 6.32 mmol, 63 %). The residue was further purified by distillation (bp 55–57 °C / 0.1 mbar) to give the desired products (4.93 mmol, 49 %) in an analytically pure form.

A6 Controls

A6.1 General remarks

The following paragraphs summarize controls. Additional information on work-up procedures, organobromine purification, and spectroscopic data of products are given in the Experimental part of the associated article and in the sections above.

A6.2 Aqueous hydrogen peroxide as terminal oxidant

A6.2.1 Conversion of 4-*tert*-butyl cyclohexene (2a) with aqueous H_2O_2 / HBr in CH_2Cl_2

Reagents: 4-*tert*-butyl cyclohexene (**2a**) (1 mmol), aq. H_2O_2 [30% (*w*/*w*), 2.5 eq.], aq. HBr [48% (*w*/*w*), 2.5 eq.], CH_2Cl_2 (10 mL). Mixing of the reagents and stirring of the reaction mixture for 24 h at 20 °C, solvent evaporation, and column chromatography yielded 81 % of *rel*-(1*R*,3*S*,4*S*)-3,4-dibromo-1-*tert*-butyl cyclohexane (**3a**).

A6.2.2 Conversion of 4-*tert*-butyl cyclohexene (2a) with aqueous H_2O_2 / HBr in dimethyl carbonate

Reagents: 4-*tert*-butyl cyclohexene (**2a**) (1 mmol), aq. H_2O_2 [30% (*w*/*w*), 2.5 eq.], aq. HBr [48% (*w*/*w*), 2.5 eq.], DMC (10 mL). Mixing of the reagents at 20 °C, stirring of the reaction mixture for 24 h at the same temperature, solvent evaporation and column chromatography yielded 86 % of *rel*-(1*R*,3*S*,4*S*)-3,4-dibromo-1-*tert*-butyl cyclohexane (**3a**).

A6.2.3 Conversion of 2-(cyclohex-3'-enyl)-1,3-dioxolane (2b) with aqueous H_2O_2 / HBr in propylene carbonate

Reagents: 2-(cyclohex-3'-enyl)-1,3-dioxolane (**2b**) (1 mmol), aq. H_2O_2 [30% (*w*/*w*), 2.5 eq.], aq. HBr [48% (*w*/*w*), 2.5 eq., addition via syringe pump within 14 h], PC (20 mL). Mixing of the reagents and stirring of the reaction mixture for 24 h at 20 °C, followed by work-up as described in section A5.2.1 yielded 20 % of 2-[*rel*-(1'*R*,3'*S*,4'*S*)-3',4'-dibromocyclohexyl]-1,3-dioxolane (**3b**) and 2 % of *rel*-(1*R*,3*S*,4*S*)-3,4-dibromo cyclohexyl carbaldehyde (**5**).[17] Colorless oil, R_f 0.71. δ_H (400 MHz; $CDCl_3$) 1.85 (1 H, qd, J_q 12.9, J_d 3.6 Hz, 6-H), 1.91–2.01 (1 H, m, 5-H or 6-H), 2.01–2.10 (1 H, m, 5-H or 6-H), 2.16–2.27 (1 H, m, 2-H), 2.41–2.61 (2 H, m, 2-H, 5-H), 2.78–2.93 (1 H, m, 1-H), 4.60–4.66 (1 H, m, 4-H), 4.69–4.75 (1 H, m, 3-H), 9.68 (1 H, s).

A6.2.4 Conversion of (*E*)-5-phenylpent-4-en-1-ol (7a) with aqueous H_2O_2 / HBr in propylene carbonate

Reagents: (*E*)-5-phenylpent-4-en-1-ol (**7a**) (1 mmol), aq. H_2O_2 [30% (*w*/*w*), 1.25 eq.], aq. HBr [48% (*w*/*w*), 1.25 eq., addition via syringe pump within 14 h], PC (20 mL). Mixing of the reagents and stirring of the reaction mixture for 24 h at 20 °C, followed by work-up as described in section A5.2.1 yielded 47 % of *rel*-(2*R*,3*S*)-3-bromo-2-phenyltetrahydropyran (**8a**).

A6.2.5 Conversion of (*E*)-5-phenylpent-4-en-1-ol (7a) with aqueous H_2O_2 / 3-bromo-2,2 dimethyl-propionic acid (1b) / VO(L^1)(OEt) in propylene carbonate

Reagents: (*E*)-5-phenylpent-4-en-1-ol (**7a**) (1 mmol), aq. H_2O_2 [30% (*w*/*w*), 1.25 eq.], 3-bromo-2,2 dimethylpropionic acid (**1b**) (1.25 eq.), NBu_4Br (0.1 eq.), VO(L^1)(OEt) (0.01 eq.), PC (20 mL). Mixing of the reagents and stirring of the reaction mixture for 24 h at 30 °C, followed by work-up as described in section A5.2.1 yielded 19 % of *rel*-(2*R*,3*S*)-3-bromo-2-phenyltetrahydropyran (**8a**).

A6.2.6 Conversion of (*E*)-5-phenylpent-4-en-1-ol (7a) with H_2O_2 / 3-bromo-2,2 dimethyl-propionic acid (1b) in propylene carbonate

Reagents: (*E*)-5-phenylpent-4-en-1-ol (**7a**) (1 mmol), aq. H_2O_2 [30% (*w*/*w*), 1.25 eq.], 3-bromo-2,2 dimethylpropionic acid (**1b**) (1.25 eq.), NBu_4Br (0.1 eq.), PC (20 mL). Mixing of the reagents and stirring of the reaction mixture for 24 h at 30 °C, followed by work-up as described in section A5.2.1 yielded 17 % of *rel*-(2*R*,3*S*)-3-bromo-2-phenyltetrahydropyran (**8a**).

A6.3 Control experiments with *N*-bromosuccinimide and molecular bromine

A6.3.1 Bromination of (3*R*)-linalool (7c) with *N*-bromosuccinimide

To a solution of NBS (223 mg, 1.25 mmol, recryst. from H_2O) in CH_2Cl_2 (20 mL) at 25 °C was added (3*R*)-linalool (**7c**) (155 mg, 1.0 mmol) and the reaction mixture stirred at the same temperature for 4 h. After concentration under reduced pressure, the oily residue was subjected to column chromatography (SiO_2, CH_2Cl_2). Yield: 78 mg (33 %, *cis*:*trans* = 64:36), R_f 0.71, colorless oil. (6*R*)-3-Bromo-2,2,6-trimethyl-6-vinyltetrahydropyran (**8c**). (5*R*)-2-(1-Bromo-1-methylethyl)-5-methyl-5-vinyltetrahydrofuran (**9c**). Yield: 63 mg (27 %, *cis*:*trans* = 64:36), R_f 0.71, colorless oil. (3*R*)-6,7-Dibromo-3,7-dimethyloct-1-en-3-ol.[27] Yield: 49 mg (16 %, 50/50-mixture of like/unlike-isomers). R_f 0.19. δ_H (600 MHz; $CDCl_3$) 1.32 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 1.35–2.03 (3 H, m, 4-H, 5-H), 1.80 (3 H, s, CH_3), 1.81 (3 H, s, CH_3), 1.96 (3 H, s, CH_3), 1.97 (3 H, s, CH_3), 2.49–2.56 (1 H, m, 5-H), 4.17–4.23 (1 H, m, 6-H), 5.10 (1 H, ddd, *J* 10.8, 7.2, 1.0 Hz, –HC=CH_2), 5.25 (1 H, d, *J* 17.2 Hz, –HC=CH_2), 5.92 (1 H, ddd, *J* 17.3, 14.7, 10.9

Hz, –*HC*=CH_2). δ_C (150 MHz; $CDCl_3$) 27.9 (CH_3), 28.2 (CH_3), 28.2 (CH_3), 28.6 (CH_3), 30.7 (C5), 30.7 (C5), 35.3 (CH_3), 35.3 (CH_3), 40.7 (C4), 40.8 (C4), 67.3 (C6), 67.4 (C6), 68.8 (C7), 68.8 (C7), 72.9 (C3), 73.1 (C3), 112.2 (C2), 112.3 (C2), 144.4 (C1), 144.7 (C1).

A6.3.2 Bromination of 4-*tert*-butyl cyclohexene (2a) with *N*-bromosuccinimide / NBu_4Br in CH_2Cl_2

Reagents: 4-*tert*-butyl cyclohexene (**2a**) (1 mmol), NBS (1.6 eq.), NBu_4Br (1.25 eq.), CH_2Cl_2 (10 mL). Mixing of the reagents at 20 °C, stirring of the reaction mixture for 24 h at the same temperature, solvent evaporation and column chromatography yielded 92 % of *rel*-(1*R*,3*S*,4*S*)-3,4-dibromo-1-*tert*-butyl cyclohexane (**3a**).

A6.3.3 Bromination of 4-*tert*-butyl cyclohexene (2a) with Br_2 in CH_2Cl_2

Reagents: 4-*tert*-butyl cyclohexene (**2a**) (1 mmol), Br_2 (1.25 eq.), CH_2Cl_2 (10 mL). Mixing of the reagents at 20 °C, stirring of the reaction mixture for 24 h at the same temperature, solvent evaporation and column chromatography yielded 96 % of *rel*-(1*R*,3*S*,4*S*)-3,4-dibromo-1-*tert*-butyl cyclohexane (**3a**).

A6.3.4 Hydroxybromination of 4-*tert*-butyl cyclohexene (2a)

A mixture of 4-*tert*-butyl cyclohexene (**2a**) (770 mg, 5.50 mmol) in H_2O (30 mL) was treated with NBS (995 mg, 5.50 mmol) at 25 °C. After stirring for 15 h at the same temperature the mixture was extracted with CH_2Cl_2 (3 × 15 mL). Combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (SiO_2, CH_2Cl_2). Yield: 569 mg (2.42 mmol, 44 %) colorless solid, as mixture of isomers *iso*-6/6 (40:60), R_f 0.31. Anal. calcd. for $C_{10}H_{19}BrO$ (235.16): C, 51.07; H, 8.14; Found: C, 51.12; H, 7.95. *rel*-(1*R*,2*R*,4*R*)-4-*tert*-Butyl-2-bromo cyclohexan-1-ol (*iso*-**6**). δ_H (600 MHz; $CDCl_3$) 0.88 or 0.87 (9 H, s, CH_3), 1.37 (1 H, qd, J_q 13.3, J_d 3.6 Hz, 5-H), 1.54–1.61 (2 H, m, 4-H, 5-H), 1.69–1.75 (1 H, m, 6-H), 1.78 (1 H, br. s, OH), 1.87–1.98 (2 H, m, 3-H), 2.12–2.19 (1 H, m, 6-H), 4.06–4.09 (1 H, m, 1-H), 4.36–4.39 (1 H, m, 2-H). δ_C (150 MHz; $CDCl_3$) 27.3 or 27.4 (CH_3), 27.4 (C6), 29.6 (C3), 32.0 or 32.2 (C_q), 41.2 (C4), 54.8 (C2), 69.6 (C1). *rel*-(1*R*,2*R*,4*S*)-4-*tert*-Butyl-1-bromo cyclohexan-2-ol (**6**). δ_H (600 MHz; $CDCl_3$) 0.88 or 0.87 (9 H, s, CH_3), 1.42 (1 H, tt, *J* 12.5, 3.2 Hz, 4-H), 1.50 (1 H, qd, J_q 12.5, J_d 3.3 Hz, 5-H), 1.54–1.61 (1 H, m, 5-H), 1.69–1.75 (1 H, m, 3-H), 1.78 (1 H, br. s, OH), 1.87–1.98 (2 H, m, 3-H, 6-H), 2.17–2.24 (1 H, m, 6-H), 4.19–4.22 (1 H, m, 2-H), 4.24–4.27 (1 H, m, 1-H). δ_C (150 MHz; $CDCl_3$) 27.3 or 27.4 (CH_3), 27.9 (C3), 28.9 (C6), 32.0 or 32.2 (C_q), 40.5 (C4), 53.6 (C1), 71.1 (C2).

A7 Vanadium catalysts

A7.1 Ligand Synthesis

A7.1.1 *cis*-2,6-Bis-(1-hydroxy-1,1-diphenylmethyl)-piperidine [H_2L^1][28]

To a solution of PhMgBr in anhydrous Et_2O (70 mL) prepared from Mg turnings (3.72 g, 153 mmol) and bromobenzene (24.5 g, 150 mmol) was added dimethyl piperidine-2,6-dicarboxylate (4.60 g, 22 mmol) in anhydrous THF (80 mL) at –10 °C. The brown slurry was allowed to warm to 25 °C and stirred for further 18 h. Sat. aq. NH_4Cl (60 mL) and H_2O (60 mL) were added at 25 °C and the mixture acidified with conc. HCl (10 mL). The formed solids were removed by filtration, washed with H_2O (2 × 20 mL) and suspended in H_2O (80 mL). The pH was adjusted to 7 with aq. NaOH (2m, 1.5 mL) and the mixture extracted with *tert*-butyl methyl ether (3 × 50 mL). Combined extracts were dried ($MgSO_4$), and concentrated under reduced pressure (350 mbar, 40 °C). The remaining solid was recrystallized from acetone. Yield: 1.25 g (2.77 mmol, 13 %) colorless solid, mp 183 °C. δ_H (600 MHz; $CDCl_3$) 1.22–1.39 (5 H, m, 3-H, 4-H, 5-H), 1.77 (1 H, d, *J* 5.9 Hz, 4-H), 3.48 (2 H, br. s., OH), 3.66 (2 H, d, *J* 9.7 Hz, 2-H, 6-H), 7.03–7.08 (2 H, m), 7.11–7.18 (6 H, m), 7.23–7.28 (4 H, m), 7.40–7.47 (8 H, m). δ_C (150 MHz; $CDCl_3$) 23.8 (C4), 24.8 (C3, C5), 62.2 (C2, C6), 78.6 (C_q), 125.4, 125.4, 126.5, 126.8, 128.0, 128.4, 143.8, 145.1; Anal. Calcd. for $C_{31}H_{31}NO_2$ (449.58): C, 82.82; H, 6.95; N, 3.12; Found: C, 82.72; H, 7.04; N, 3.11.

A7.1.2 2,6-Bis-[(1*S*,2*S*,5*R*)-1-hydroxy-2-isopropyl-5-methylcyclohexyl]-pyridine [H_2L^3][29]

The compound was prepared from 2,6-dibromopyridine (5.0 g, 21 mmol) with an overall yield of 31 %.[29] δ_H (600 MHz; $CDCl_3$) 0.67 (6 H, d, *J* 7.0 Hz, CH_3), 0.81 (6 H, d, *J* 6.7 Hz, CH_3), 0.90 (6 H, d, *J* 6.4 Hz, CH_3), 0.99–1.12 (2 H, m), 1.13–1.27 (2 H, m), 1.43–1.60 (4 H, m), 1.60–1.69 (4 H, m), 1.69–1.81 (2 H, m), 1.82–1.97 (4 H, m), 4.08 (2 H, br. s, OH), 7.33 (2 H, d, *J* 7.8 Hz), 7.71 (1 H, t, *J* 7.8 Hz).

A7.2 Vanadium complexes

A7.2.1 {[*cis*-2,6-Bis-(1,1-diphenylmethanolato(–1)]-piperid-2,6-diyl}(ethanolato)oxido-vanadium(V) [$VO(L^1)(OEt)$]

To a solution of H_2L^1 (900 mg, 2.00 mmol) in EtOH (40 mL) was added $VO(OEt)_3$ (404 mg, 2.00 mmol) at 55 °C and the mixture heated to reflux for 1 h. Further stirring at 25 °C for 1 h was followed by cooling to 0 °C for 6 h. The formed yellow solid was removed by filtration, washed with cold EtOH (5 mL) and dried (25 °C, 0.1 mbar). Concentration of the filtrate under

reduced pressure (150 mbar, 40 °C) and cooling to –28 °C resulted in another crop of yellow solid, which was treated as above. Yield: 950 mg (1.70 mmol, 85 %) yellowish solid, mp 192 °C. δ_V (105 MHz; EtOH/$CDCl_3$ 5:1) –592. ν_{max} (KBr) / cm^{-1} 3421, 3056, 3022, 2953, 2927, 2859, 1596 (N–H), 1490, 1447, 1415, 969 (V=O). λ_{max} (EtOH) / nm (lg ε / m^2 mol^{-1}) 249 (1.25), 203 (3.06). Anal. Calcd. for $C_{33}H_{34}NO_4V$ (559.57): C, 70.83; H, 6.12; N, 2.50; Found: C, 70.58; H, 6.29; N, 2.42.

A7.2.2 {2,6-Bis-[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexan-1-olato(–1)]-pyrid-2,6-diyl}-(ethanolato)oxidovanadium(V) [VO(L^3)(OEt)]

To a solution of H_2L^3 (1.06 g, 2.70 mmol) in anhydrous EtOH (27 mL) was added $VO(OEt)_3$ (575 mg, 2.70 mmol) at 25 °C. The mixture was heated under reflux for 1 h and after cooling stored at –28 °C for 16 h. The resulting yellow crystals were filtered, washed with cold EtOH (2 × 10 mL) and dried in vacuo. Concentration of the filtrate under reduced pressure (150 mbar, 40 °C) and cooling to –28 °C resulted in another crop of crystals, which were treated as above. Yield: 1.17 g (2.35 mmol, 87 %) yellow crystalline solid, mp 184 °C. δ_H (600 MHz; CD_3OD) 0.72 (3 H, d, *J* 7.1 Hz, CH_3), 0.78 (3 H, d, *J* 7.1 Hz, CH_3), 0.82 (3 H, d, *J* 6.9 Hz, CH_3), 0.89 (3 H, d, *J* 6.5 Hz, CH_3), 0.97 (3 H, d, *J* 6.7 Hz, CH_3), 1.06–1.21 (3 H, m), 1.10 (3 H, d, *J* 6.9 Hz, CH_3), 1.18 (3 H, t, *J* 7.1 Hz, $OCH_2\mathit{CH_3}$), 1.42 (1 H, t, *J* 12.5 Hz), 1.47–1.55 (1 H, m), 1.57–1.73 (5 H, m), 1.74–1.93 (6 H, m), 2.12 (1 H, dt, J_d 6.8, J_t 3.5 Hz), 2.37–2.44 (1 H, m), 3.61 (2 H, q, *J* 7.1 Hz, $O\mathit{CH_2}CH_3$), 7.45 (2 H, dd, *J* 12.1, 7.7 Hz), 8.11 (1 H, t, *J* 7.7 Hz). δ_C (150 MHz; CD_3OD) 18.5 (CH_3), 19.7 (CH_3), 20.1 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 23.0 (CH_2), 23.4 (CH_2), 24.0 (CH_3), 24.5 (CH_3), 29.7 (CH), 29.8 (CH), 29.8 (CH), 30.1 (CH), 36.2 (CH_2), 36.2 (CH_2), 47.8 (CH_2), 52.0 (CH), 52.2 (CH), 53.9 (CH_2), 58.5 ($O\mathit{CH_2}CH_3$), 100.5 (C_q), 101.3 (C_q), 119.7, 120.0, 144.7, 175.9, 176.7. δ_V (105 MHz; CD_3OD) –511. ν_{max} (KBr) / cm^{-1} 3436, 2947, 2921, 2865, 1600, 1579, 1464, 1294, 1104, 1052, 973, 949, 712, 593, 527. λ_{max} (EtOH) / nm (lg ε / m^2 mol^{-1}) 275 (3.05), 203 (3.36). Anal. Calcd. for $C_{27}H_{44}NO_4V$ (497.58): C, 65.17; H, 8.91; N, 2.81; Found: C, 65.16; H, 9.05; N, 2.75.

Resonances marked in gray correlate with values for uncoordiated EtOH, probably due to ligand exchange with CD_3OD.

A8 ^{13}C-NMR-spectrum of ethyl 4,5-dibromo-5-methylhexanoate (3g)

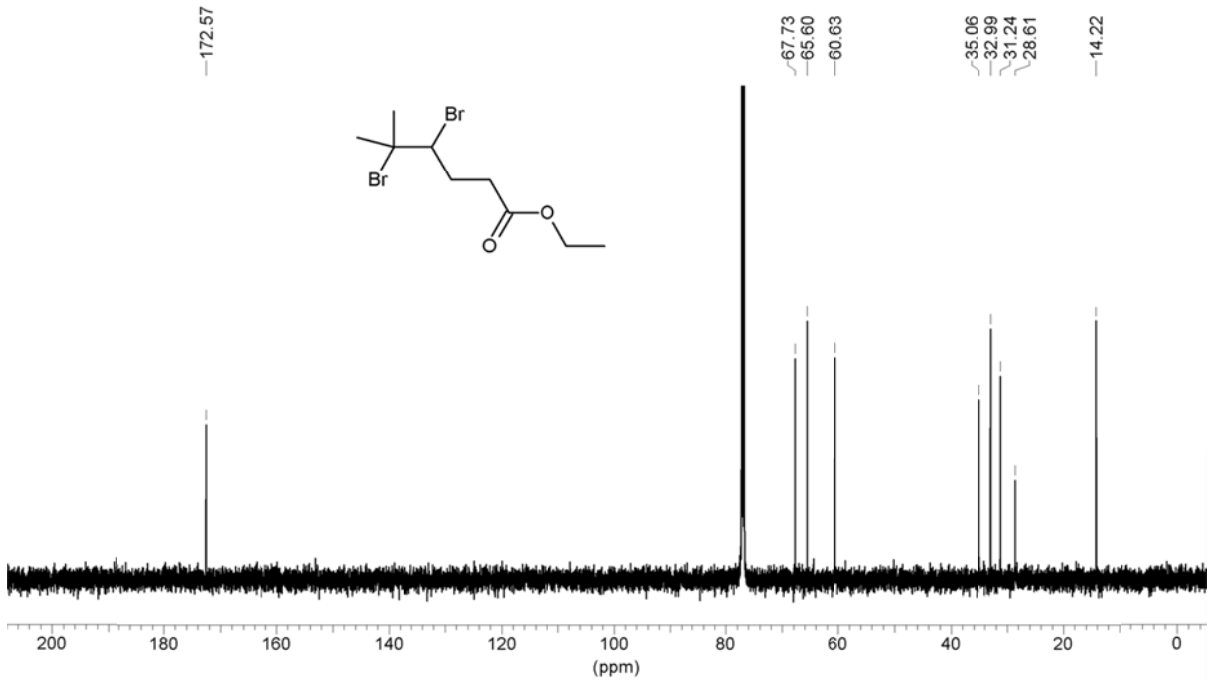


Figure A1. ^{13}C-spectrum of ethyl 4,5-dibromo-5-methylhexanoate (**3g**) in $CDCl_3$ (20 °C).

A9 References

[1] W. L. F. Armarego, D. D. Perrin, *Purification of laboratory chemicals*, Pergamon Press, Oxford, **1996**.

[2] M. Abul Hashem, P. Weyerstahl, *Tetrahedron* **1984**, *40*, 2003–2009.

[3] J. P. Michael, M. M. Nkwelo, *Tetrahedron* **1990**, *46*, 2549–2560.

[4] D. Becker, N. Haddad, *Tetrahedron* **1993**, *49*, 947–964.

[5] N. C. Sih, H. Pines, *J. Org. Chem.* **1965**, *30*, 1462–1466.

[6] J. B. Lambert, G. T. Wang, R. B. Finzel, D. H. Teramura, *J. Am. Chem. Soc.* **1987**, *109*, 7838–7845.

[7] R. Chenevert, M. Dickman, *J. Org. Chem.* **1996**, *61*, 3332–3341.

[8] M. J. Clague, N. L. Keder, A. Butler, *Inorg. Chem.* **1993**, *32*, 4754–4761.

[9] K. B. Sharpless, T. R. Verhoeven, *Aldrichim. Acta* **1979**, *12*, 63–74.

[10] E. Testa, L. Fontanella, G. Cristiani, G. Gallo, *J. Org. Chem.* **1959**, *24*, 1928–1936.

[11] J. L. Greene, H. J. Hagemeyer, *J. Am. Chem. Soc.* **1955**, *77*, 6065–6066.

[12] R. Anschütz, L. Kinnkutt, *Chem. Ber.* **1878**, *11*, 1221–1222.

[13] R. Fittig, F. Binder, *Liebigs Ann.* **1879**, *195*, 56–179.

[14] R. J. Ferrier, N. Prasad, *J. Chem. Soc. C* **1967**, 1417–1420.

[15] T. Okuyama, T. Takino, T. Sueda, M. Ochiai, *J. Am. Chem. Soc.* **1995**, *117*, 3360–3367.

[16] H. Quast, T. Dietz, *Synthesis* **1995**, 1300–1304.

[17] A. K. Kerimov, *Russ. J. Gen. Chem.* **2004**, *74*, 256–260.

[18] W. Biernacki, A. Gdula, *Synthesis* **1979**, 37–38.

[19] R. Bussas, H. Muenster, G. Kresze, *J. Org. Chem.* **1983**, *48*, 2828–2832.

[20] C. H. Oh, T. W. Ahn, R. Reddy V., *Chem. Comm.* **2003**, 2622–2623.

[21] J.-M. Surzur, P. Teissier, *Bull. Soc. Chim. Fr.* **1970**, 653–664.

[22] M. Kitano, N. Ohashi, (Sumitomo Pharma, JP), *Substituted guanidine derivatives and process for producing the same*, US Patent 6,369,110 B1, April 9, **2002**.

[23] J. Hartung, M. Greb, *Tetrahedron Lett.* **2003**, *44*, 6091–6093.

[24] T. S. Butcher, F. Zhou, M. R. Detty, *J. Org. Chem.* **1998**, *63*, 169–176.

[25] R. R. Pavlis, P. S. Skell, *J. Org. Chem.* **1983**, *48*, 1901–1902.

[26] M. Greb, J. Hartung, F. Kohler, K. Spehar, R. Kluge, R. Csuk, *Eur. J. Org. Chem.* **2004**, 3799–3812.

[27] T. Kato, I. Ichinose, *J. Chem. Soc. Perkin Trans. 1* **1980**, 1051–1056.

[28] L. Kuczynski, M. Wilimowski, M. Baginska, J. Soloducho, *Pol. J. Pharmacol. Pharm.* **1975**, *27*, 549–553.

[29] S. Bellemin-Laponnaz, K. S. Coleman, P. Dierkes, J. P. Masson, J. A. Osborn, *Eur. J. Inorg. Chem.* **2000**, 1645–1649.

Anhang B

Supporting Information for: Controlling 6-*endo*-Selectivity in Oxidation/Bromocyclization Cascades for Synthesis of Aplysiapyranoids and other 2,2,6,6-substituted Tetrahydropyrans

Oliver Brücher[a], Uwe Bergsträßer[a], Harald Kelm[a], Jens Hartung[a], Marco Greb[b], Ingrid Svoboda[c], and Hartmut Fuess[c]

[a] *Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany*

[b] *Institut für Organische Chemie, Universität Würzburg, Am Hubland, 97074 Würzburg, Germany*

[c] *Technische Universität Darmstadt, Strukturforschung, FB11 Material- und Geowissenschaften, Petersenstr. 23, D-64287 Darmstadt, Germany*

Contents

B1 General Remarks

(i) The compound numbering in the Supporting Information is consistent with that of the accompanying publication. (ii) ^{1}H- and ^{13}C-NMR signals of all compounds were assigned using appropriate 2D spectra including H,H-COSY, HMQC, HMBC and/or NOESY experiments. (iii) References refer exclusively to the Supplementary Data. (iv) Results from computational chemistry refer to B3LYP/6-31+G**// B3LYP/6-31+G**-calculations (except for section B11).

B2 Instrumentation

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*).

^{1}H and ^{13}C spectra were recorded with FT-NMR DPX 200, DPX 400 and DPX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale. The resonances of residual protons and those of carbons of used deuterated solvents $CDCl_3$ (δ_H 7.26, δ_C 77.0) and d_6-DMSO (δ_H 2.50, δ_C 39.5) were used as internal standards.

HRMS spectra were obtained using a modified Varian Match 7 instrument.

IR spectra were measured either on NaCl plates or from KBr pellets using a Perkin Elmer FT/IR 1600 spectrometer

UV/Vis spectra were recorded in 1-cm quartz cuvettes with a Perkin Elmer UV/Vis 330 and a Varian Cary 100 UV/Vis spectrophotometer at 25 °C using analytical grade solvents. Molar extinction coefficients (lg ε) are reported in $m^2 \times mol^{-1}$.

Reaction progress was monitored via thin layer chromatography (tlc) on aluminium sheets coated with silica gel (60 F_{254}, *Merck*). Compounds were visualized by UV light (254 nm) or the use of Ekkert's reagent.

Combustion analysis was performed with a Carlo Erba 1106 instrument (Universität Würzburg), a Perkin Elmer Elemental Analyzer 2400 CHN, a Perkin Elmer Elemental Analyzer EA 240, or a Elementar Vario Micro Cube instrument (Technische Universität Kaiserslautern).

Petroleum ether refers to the fraction boiling between 40–55 °C. All solvents were purified according to standard procedures.[1] Column chromatography was performed on SiO_2 (0.063–0.2 mm, *Merck*) as stationary phase.

B3 Preparation of β-Bromocinnamic Acid (BCA)

To a solution of HBr [30%, (*w*/*w*)] in acetic acid (50 mL) was added (*E*)-cinnamic acid (8.45 g, 57.0 mmol). The mixture was heated to 45–50 °C for 8 h and then kept at 25 °C for 16 h while continously stirred. The formed colorless precipitate was filtered off, washed with ice-water (4 × 50 mL), and dried (25 °C, 0.1 mbar). Yield: 11.3 g (49.3 mmol, 87 %) colorless solid, mp 136 °C. $C_9H_9BrO_2$ (229.07). δ_H (600 MHz; $CDCl_3$) 3.28 (1 H, dd, *J* 16.8, 6.1 Hz, 2-H), 3.40 (1 H, dd, *J* 16.8, 9.1 Hz, 2-H), 5.38 (1 H, dd, *J* 8.9, 6.1 Hz, 3-H), 7.29 –7.33 (1 H, m), 7.33–7.39 (2 H, m), 7.39–7.46 (2 H, m). δ_C (150 MHz; $CDCl_3$) 44.4 (C2), 47.0 (C3), 127.1, 128.9, 128.9, 140.5 (Ph), 175.1 (C1).[2–4]

B4 Preparation of Alkenol Substrates

B4.1 Ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (1a)

B4.1.1 Diethyl-1-(3'-methylbut-2'-en-1'-yl)-malonate

To a solution of diethyl malonate (30.0 g, 187 mmol) in acetone (250 mL) was added solid K_2CO_3 (28.5 g, 206 mmol) and 1-bromo-3-methylbut-2-ene (27.9 g, 187 mmol). The reaction mixture was heated under reflux for 21 h. After cooling to 25 °C colorless solids were filtered off, the filtrate dried ($MgSO_4$), and concentrated under reduced pressure to leave an oil which was purified by fractional distillation. Yield: 36.4 g (159 mmol, 85%) colorless liquid, bp 80–90 °C / 5 × 10^{-1} mbar. R_f = 0.63 [diethyl ether/petroleum ether 1/10 (*v*/*v*)]. $C_{12}H_{20}O_4$ (324.40). δ_H (250 MHz; $CDCl_3$) 1.23 (6 H, t, *J* 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 1.60 (3 H, s, CH_3), 1.65 (3 H, s, CH_3), 2.56 (2 H, dd, *J* 7.6, 7.4 Hz, 1'-H), 3.30 (1 H, t, *J* 7.6 Hz, 1-H), 4.16 (4 H, q, *J* 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 5.00–5.06 (m, 1 H, 2'-H). δ_C (63 MHz; $CDCl_3$) 14.0 ($CO_2CH_2\mathit{CH_3}$), 17.7 (C1'), 25.7 (CH_3), 27.5 (CH_3), 52.2 (C1), 61.2 ($CO_2\mathit{CH_2}CH_3$), 119.7 (C2'), 134.7 (C3'), 169.2 ($\mathit{CO_2}CH_2CH_3$).[5]

B4.1.2 Ethyl 5-methylhex-4-enoate

To a solution of diethyl-1-(3'-methylbut-2'-en-1'-yl)-malonate (36.0 g, 158 mmol) in DMSO (250 mL) was added H_2O (2.84 g, 157 mmol) and LiCl (20.1 g, 473 mmol). The reaction mixture was heated to 160 °C for 3 h. After cooling to 25 °C the mixture was poured onto crushed ice (300 g), sat. NaCl (200 mL) was added, and the aqueous mixture extracted with diethyl ether (3 × 300 mL). After concentration under reduced pressure, the obtained residue was taken up with diethyl ether (300 mL), washed with H_2O (2 × 100 mL), and the aqueous washings extracted with diethyl ether (2 × 100 mL). Combined organics were dried ($MgSO_4$), concentrated under

reduced pressure, and the residue further dried in vacuo (5×10^{-2} mbar). Yield: 15.7 g (100 mmol, 64%) yellow oil. R_f = 0.81 [diethyl ether/petroleum ether 1/10 (*v*/*v*)]. $C_9H_{16}O_2$ (156.22). δ_H (250 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.60 (3 H, d, *J* 0.9 Hz, CH_3), 1.67 (3 H, s, CH_3), 2.28–2.30 (4 H, m, 2-H, 3-H), 4.11 (2 H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 5.04–5.10 (1 H, m, 4-H). δ_C (63 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 17.6 (C3), 23.6 (CH_3), 25.6 (CH_3), 34.5 (C2), 60.2 ($CO_2CH_2CH_3$), 122.5 (C4), 132.9 (C5), 173.4 ($CO_2CH_2CH_3$).[5][6]

B4.1.3 Ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (1a)

Under an atmosphere of nitrogen, a solution of freshly dried ethyl-5-methylhex-4-enoate (5.00 g, 32.0 mmol) in dry THF (40 mL) was added to a solution of LDA (17.6 mL, 35.2 mmol, 2 M in THF/hexane/ethylbenzene) in dry THF (40 mL) at –78 °C (20 min). After stirring for 1 h at –78 °C, a solution of acetone (2.05 g, 35.2 mmol) in dry THF (5 mL) was added (10 min) and the reaction mixture stirred at –78 °C for further 2 h. After warming to 0 °C, the mixture was hydrolyzed with H_2O (30 mL) and sat. NH_4Cl (50 mL) and pH adjusted to 5–6 with conc. HCl. Extraction with diethyl ether (3 × 100 mL) and concentration of combined organics under reduced pressure afforded an orange oil, which was purified by column chromatography [SiO_2, diethyl ether/petroleum ether 1/10 (*v*/*v*)]. Yield: 5.90 g (28.0 mmol, 86%) yellow oil. R_f = 0.29 [diethyl ether/petroleum ether 1/10 (*v*/*v*)]. Anal. calcd. for $C_{12}H_{22}O_3$ (214.20): C, 67.26; H, 10.35; Found: C, 66.87; H, 10.44. δ_H (400 MHz; $CDCl_3$) 1.24 (6 H, 2 × s, CH_3), 1.25 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.59 (3 H, s, CH_3), 1.66 (3 H, s, CH_3), 2.23–2.33 (1 H, m, 3-H), 2.33–2.42 (1 H, m, 2-H), 2.42–2.55 (1 H, m, 3-H), 2.97 (1 H, br. s, OH), 4.06–4.24 (2 H, m, $CO_2CH_2CH_3$), 5.02–5.08 (1 H, m, 4-H). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 17.6 (C3), 25.7 (CH_3), 26.3 (CH_3), 26.6 (CH_3), 29.2 (CH_3), 55.8 (C2), 60.4 ($CO_2CH_2CH_3$), 70.9 (C2'), 121.2 (C4), 133.6 (C5), 175.8 ($CO_2CH_2CH_3$).

B4.2 (±)-Ethyl 2-(1'-hydroxyeth-1'-yl)-5-methylhex-4-enoate (1b)

B4.2.1 Ethyl 2-acetyl-5-methylhex-4-enoate

To a solution of ethyl acetoacetate (6.50 g, 50 mmol) in acetone (50 mL) was added solid K_2CO_3 (6.90 g, 50 mmol) and 1-bromo-3-methylbut-2-ene (5.96 g, 40 mmol). The reaction mixture was heated under reflux for 24 h. After cooling to 0 °C colorless solids were filtered off and the filtrate concentrated under reduced pressure to leave an oil which was purified by fractional distillation. Yield: 7.48 g (159 mmol, 94 %) colorless liquid, bp 130–131 °C / 28 mbar. $C_{11}H_{18}O_3$ (198.27). δ_H (400 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.3 Hz, $CO_2CH_2CH_3$), 1.62 (3 H, s, CH_3), 1.67 (3

H, s, CH_3), 2.22 (3 H, s, CH_3), 2.53 (2 H, t, *J* 7.1 Hz, 3-H), 3.42 (1 H, t, *J* 7.5 Hz, 2-H), 4.18 (2 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 5.01 (1 H, t, *J* 7.3 Hz, 4-H).[7]

B4.2.2 (±)-Ethyl 2-(1'-hydroxyeth-1'-yl)-5-methylhex-4-enoate (1b)

To a solution of ethyl-2-acetyl-5-methylhex-4-enoate (2.00 g, 10 mmol) in MeOH (15 mL) was added $NaBH_4$ (416 mg, 11 mmol) at 0 °C. After being stirred for 16 h at 25 °C, the reaction mixture was concentrated under reduced pressure. The residue was dispersed in H_2O (15 mL) and 2 M H_2SO_4 (3 mL) and extracted with *tert*-butyl methyl ether (3 × 10 mL). Combined organics were washed with sat. $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure to leave a residue, which was purified by column chromatography [SiO_2, ethyl acetate/pentane 1/4 (*v*/*v*)]. Yield: 1.42 g (7.1 mmol, 71 %) colorless liquid, 55/45-mixture of diastereomers. R_f = 0.27 [ethyl acetate/pentane 1/4 (*v*/*v*)]. Anal. calcd. for $C_{11}H_{20}O_3$ (200.29): C, 65.97; H, 10.07; Found: C, 65.66; H, 9.89. δ_H (400 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6.5 Hz, CH_3), 1.23 (3 H, d, *J* 6.5 Hz, CH_3), 1.26 (6 H, 2 × t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.61 (6 H, 2 × s, CH_3), 1.68 (6 H, 2 × s, CH_3), 2.25–2.51 (7 H, m, 2-H, 3-H, OH), 2.66 (1 H, d, *J* 7.5, OH), 3.85–3.95 (1 H, m, 1'-H), 3.96–4.05 (1 H, m, 1'-H), 4.08–4.23 (4 H, m, $CO_2CH_2CH_3$), 5.03–5.14 (2 H, m, 4-H). δ_C (100 MHz; $CDCl_3$) 14.3 (2 × $CO_2CH_2CH_3$), 17.7 (2 × CH_3), 20.3 (CH_3), 21.6 (CH_3), 25.8 (2 × CH_3), 26.1 and 28.1 (C3), 52.4 and 52.5 (C2), 60.46 (2 × $CO_2CH_2CH_3$), 67.8 and 68.0 (C1'), 120.38 and 121.05 (C4), 133.75 and 134.12 (C5), 174.90 and 175.25 ($CO_2CH_2CH_3$).

B4.3 Ethyl 2-hydroxymethyl-5-methylhex-4-enoate (1c)

Under an atmosphere of nitrogen, a solution of freshly dried ethyl-5-methylhex-4-enoate (1.56 g, 10.0 mmol; for preparation, see section B4.1) in dry THF (20 mL) was added to a solution of LDA (6.5 mL, 13.0 mmol, 2 M in THF/hexane/ethylbenzene) in dry THF (7 mL) at –78 °C (40 min). After stirring for 30 min at –78 °C, a solution of monomeric formaldehyde [freshly prepared from paraformaldehyde (1.50 g, 50 mmol) in dry THF (50 mL) according to Schlosser *et al.*][8] was added (20 min) and the reaction mixture stirred at –78 °C for 1 h. After warming to 0 °C, the mixture was hydrolyzed by addition of sat. NH_4Cl (50 mL) and AcOH (0.50 mL). Phase separation, extraction of the aqueous phase with *tert*-butyl methyl ether (3 × 20 mL) and concentration of combined organics under reduced pressure afforded an orange oil, which was purified by column chromatography [SiO_2, *tert*-butyl methyl ether/pentane 1/2 (*v*/*v*)]. Yield: 640 mg (3.4 mmol, 34%) yellow oil. R_f = 0.23 [*tert*-butyl methyl ether/pentane 1/2 (*v*/*v*)]. Anal. calcd. for $C_{10}H_{18}O_3$ (186.25): C, 64.49; H, 9.74; Found: C, 64.50; H, 9.50. δ_H (400 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.61 (3 H, s, CH_3), 1.69 (3 H, s, CH_3), 2.21 (1 H, t, *J* 6.5

Hz, OH), 2.24–2.41 (2 H, m, 3-H), 2.53–2.63 (1 H, m, 2-H), 3.68–3.82 (2 H, m, CH_2OH), 4.18 (2 H, m, $CO_2CH_2CH_3$), 5.09 (1 H, t, *J* 6.8 Hz, 5-H). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 17.7 (CH_3), 25.8 (CH_3), 27.1 (C3), 47.6 (C2), 60.6 ($CO_2CH_2CH_3$), 62.7 (CH_2OH), 120.4 (C4), 134.3 (C5), 175.1 ($CO_2CH_2CH_3$).

B4.4 Ethyl (*E*)-2-(2'-hydroxypropy-2'-yl)-4-methyl-5-phenylpent-4-enoate (1d)

B4.4.1 (*E*)-1-Chloro-2-methyl-3-phenylprop-2-ene

To an ice-cooled solution of (*E*)-2-methyl-3-phenylprop-2-en-1-ol[9] (14.3 g, 96 mmol) in DMF (80 mL) and CCl_4 (20 mL) was added PPh_3 (60.5 g, 230 mmol) in two portions. The reaction mixture was stirred at 0 °C for 30 min and for 1.5 h at 25 °C. The brown solution was diluted with pentane (100 mL) and filtered. After phase-separation, the polar DMF-phase was extracted with pentane (3 × 60 mL), the combined extractions washed with H_2O (150 mL) and sat. NaCl (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken up in pentane (30 mL), the turbid solution filtered over a pad of silica gel (1 cm), and the colorless filtrate concentrated under reduced pressure. The residue was further dried in vacuo (5×10^{-2} mbar) and sufficiently pure for use in the next step. Yield: 11.8 g (70.5 mmol, 73 %) colorless liquid. An analytical sample was further purified by column chromatography to yield a colorless oil. R_f = 0.22 [pentane]. Anal. calcd. for $C_{10}H_{11}Cl$ (166.05): C, 72.07; H, 6.65; Found: C, 71.86; H, 6.68. δ_H (600 MHz; $CDCl_3$) 1.97 (3 H, d, *J* 1.2 Hz, CH_3), 4.17 (2 H, s, 1-H), 6.57 (1 H, s, 3-H), 7.21–7.27 (3 H, m), 7.30–7.34 (2 H, m). δ_C (150 MHz; $CDCl_3$) 15.9 (CH_3), 52.9 (C1), 127.0, 128.2, 128.9, 129.7 (C3), 134.1 (C2), 136.8.[10]

B4.4.2 Ethyl (*E*)-2-ethoxycarbonyl-4-methyl-5-phenylpent-4-enoate

To a solution of diethyl malonate (13.2 g, 82 mmol) in acetone (90 mL) was added solid K_2CO_3 (11.3 g, 82 mmol) and (*E*)-1-chloro-2-methyl-3-phenylprop-2-ene (11.3 g, 68 mmol). The reaction mixture was heated under reflux for 72 h. After cooling to 0 °C, colorless solids were filtered off, the filtrate dried ($MgSO_4$), and concentrated under reduced pressure to leave the desired product as an yellow oil (22.4 g), which was further dried in vacuo (5×10^{-2} mbar) and used without further purification in the next reaction step. An analytical sample was purified by column chromatography to yield a colorless liquid. R_f = 0.31 [CH_2Cl_2]. Anal. calcd. for $C_{17}H_{22}O_4$ (290.35): C, 70.32; H, 7.64; Found: C, 70.59; H, 7.59. δ_H (600 MHz; $CDCl_3$) 1.26 (6 H, t, *J* 7.0 Hz, 2 × $CO_2CH_2CH_3$), 1.87 (3 H, d, *J* 1.3 Hz, CH_3), 2.78 (2 H, d, *J* 7.9 Hz, 3-H), 3.66 (1 H, t, *J* 7.8 Hz, 2-H), 4.17–4.25 (4 H, m, 2 × $CO_2CH_2CH_3$), 6.33 (1 H, s, 5-H), 7.16–7.23 (3 H, m), 7.27–7.35 (2 H, m). δ_C (150 MHz; $CDCl_3$) 14.1 (2 × $CO_2CH_2CH_3$), 17.4 (CH_3), 39.5 (C3), 50.8 (C2),

61.4 (2 × $CO_2CH_2CH_3$), 126.3, 127.6 (C5), 128.0, 128.8, 134.4 (C4), 137.8, 169.1 (2 × $CO_2CH_2CH_3$).[11]

B4.4.3 Ethyl (*E*)-4-methyl-5-phenylpent-4-enoate

To a solution of the crude (*E*)-ethyl-2-ethoxycarbonyl-4-methyl-5-phenylpent-4-enoate (22.4 g) in DMSO (100 mL) was added H_2O (1 mL) and LiCl (7.50 g, 178 mmol) and the mixture heated under reflux for 5 h. After cooling to 25 °C, the solution was poured onto crushed ice (150 mL), NaCl (50 g) was added, and the aqueous mixture extracted with *tert*-butyl methyl ether (4 × 50 mL). Combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting brown liquid was purified by column chromatography [SiO_2, ethyl acetate/pentane 1/12 (*v*/*v*)]. Yield: 9.40 g (43 mmol, 52 % from (*E*)-1-chloro-2-methyl-3-phenylprop-2-ene) yellow liquid. R_f = 0.36 [ethyl acetate/pentane 1/12 (*v*/*v*)]. Anal. calcd. for $C_{14}H_{18}O_2$ (218.13): C, 77.03; H, 8.31; Found: C, 76.96; H, 8.29. δ_H (600 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.87 (3 H, d, *J* 1.0 Hz, CH_3), 2.47–2.57 (4 H, m, 2-H, 3-H), 4.15 (2 H, q, *J* 7.1 Hz, $CO_2CH_2CH_3$), 6.30 (1 H, s, 5-H), 7.16–7.24 (3 H, m), 7.28–7.35 (2 H, m). δ_C (150 MHz; $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 17.6 (CH_3), 33.2 (C3), 35.6 (C2), 60.4 ($CO_2CH_2CH_3$), 125.6 (C5), 126.1, 128.0, 128.8, 137.1 (C4), 138.2, 173.2 ($CO_2CH_2CH_3$).[12]

B4.4.4 Ethyl (*E*)-2-(2'-hydroxypropy-2'-yl)-4-methyl-5-phenylpent-4-enoate (1d)

Compound was prepared analogously to ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (**1a**) from ethyl (*E*)-4-methyl-5-phenylpent-4-enoate in 72 % yield as a yellow liquid. R_f = 0.41 [*tert*-butyl methyl ether/pentane 1/1 (*v*/*v*)]. Anal. calcd. for $C_{17}H_{24}O_3$ (276.37): C, 73.88; H, 8.75; Found: C, 73.66; H, 8.72. δ_H (400 MHz; $CDCl_3$) 1.21 (3 H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.29 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.88 (3 H, s, CH_3), 2.48 (1 H, dd, *J* 12.6, 2.4 Hz, 3-H), 2.59–2.73 (2 H, m, 2-H, 3-H), 3.02 (1 H, s, OH), 4.13 (2 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 6.30 (1 H, s, 5-H), 7.14–7.23 (3 H, m), 7.27–7.34 (2 H, m). δ_C (100 MHz; $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 17.6 (CH_3), 26.7 (CH_3), 29.3 (CH_3), 38.9 (C3), 54.2 (C2), 60.5 ($CO_2CH_2CH_3$), 71.0 (C2'), 126.1 (C5), 127.1, 128.0, 128.7, 135.8 (C4), 138.1, 175.6 ($CO_2CH_2CH_3$).

B4.5 Ethyl (*E*)-2-(2'-hydroxyprop-2'-yl)-5-phenylhex-4-enoate (1e)

B4.5.1 (*E*)-1-Bromo-4-phenylpent-3-ene

To a solution of PhMgBr in diethyl ether (75 mL), prepared from Mg-turnings (2.43 g, 100 mmol) and bromobenzene (16.0 g, 102 mmol), was added cyclopropylmethylketone (8.20 g, 97 mmol) in diethyl ether (30 mL) within 35 min under cooling in a water bath (25 °C). The mixture was stirred for 1 h at 25 °C and cooled in an ice bath. At 0 °C, a mixture of conc. H_2SO_4 (15

mL) and H_2O (30 mL) was added at a rate that the temperature of the reaction mixture did not exceed 10 °C. After being stirred for 30 min at 25 °C, the organic phase was separated and the aqueous phase extracted with *tert*-butyl methyl ether (3 × 40 mL). Combined organics were dried ($MgSO_4$), concentrated under reduced pressure, and the residue further dried in vacuo (5 × 10^{-2} mbar).[13][14] Yield: 20.3 g (90.2 mmol, 93 %) yellowish liquid. $C_{11}H_{13}Br$ (225.12). δ_H (600 MHz; $CDCl_3$) 2.07 (3 H, s, CH_3), 2.80 (2 H, q, *J* 7.3 Hz, 2-H), 3.47 (2 H, t, *J* 7.2 Hz, 1-H), 5.77 (1 H, td, J_t 7.2, J_d 1.2 Hz, 3-H), 7.24–7.28 (1 H, m), 7.31–7.35 (2 H, m), 7.39–7.42 (2 H, m). δ_C (150 MHz; $CDCl_3$) 16.1 (CH_3), 32.2 (C2), 32.3 (C1), 124.4 (C3), 125.7, 127.0, 128.2, 137.8 (C4), 143.3.[15]

B4.5.2 (*E*)-5-Phenylhex-4-enenitrile

A mixture of (*E*)-1-bromo-4-phenylpent-3-ene (18.0 g, 80 mmol) and NaCN (5.87 g, 120 mmol) in DMSO (50 mL) was stirred at 100 °C for 18 h. After cooling to 25 °C, the reaction mixture was poured into ice water (150 mL) and extracted with *tert*-butyl methyl ether (4 × 50 mL). Combined organics were dried ($MgSO_4$), concentrated under reduced pressure, and the residue further dried in vacuo (5 × 10^{-2} mbar). The compound was used without further purification in the next reaction step. Yield: 13.44 g (78.5 mmol, 98 %) yellow liquid. $C_{12}H_{13}N$ (171.24). δ_H (400 MHz; $CDCl_3$) 2.08 (3 H, s, CH_3), 2.44–2.51 (2 H, m, 2-H), 2.58 (2 H, q, *J* 7.1 Hz, 3-H), 5.73 (1 H, td, J_t 7.2, J_d 1.0 Hz, 4-H), 7.23–7.29 (1 H, m), 7.30–7.36 (2 H, m), 7.36–7.40 (2 H, m). δ_C (100 MHz; $CDCl_3$) 16.1 (CH_3), 17.4 (C2), 24.8 (C3), 119.3 (CN), 123.3 (C4), 125.8, 127.2, 128.3, 138.6 (C5), 143.0.[16]

B4.5.3 (*E*)-5-Phenylhex-4-enoic acid

To a solution of (*E*)-5-phenylhex-4-enenitrile (12.5 g, 73 mmol) in ethyleneglycol (80 mL) and H_2O (13 mL) was added powdered KOH (23.0 g, 410 mmol) and the mixture stirred at 100 °C for 10 h. After cooling to 25 °C, the reaction mixture was poured onto crushed ice (100 mL), the pH adjusted to 1–2 with conc. HCl (ca. 30 mL) and extracted with *tert*-butyl methyl ether (3 × 70 mL). Combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to leave a brown residue which was recrystallized from *tert*-butyl methyl ether / pentane. Yield: 12.3 g (65 mmol, 89 %) tan solid, mp below 25 °C. $C_{12}H_{14}O_2$ (190.24). δ_H (400 MHz; d_6-DMSO) 1.98 (3 H, s, CH_3), 2.31–2.43 (4 H, m, 2-H, 3-H), 5.71–5.78 (1 H, m, 4-H), 7.18–7.24 (1 H, m), 7.27–7.33 (2 H, m), 7.34–7.49 (2 H, m), 12.12 (1 H, br. s., OH). δ_C (100 MHz; d_6-DMSO) 15.9 (CH_3), 24.0 (C3), 33.9 (C2), 55.3 (CH_3), 113.5, 124.0 (C4), 126.7, 135.8, 136.0 (C5), 158.6, 179.0 (CO_2H).[17]

B4.5.4 (*E*)-Ethyl-5-phenylhex-4-enoate

A mixture of (*E*)-5-phenylhex-4-enoic acid (6.71 g, 35 mmol), EtOH (15 mL), and *p*-toluenesulfonic acid-monohydrate (190 mg, 1 mmol) in $CHCl_3$ (135 mL) was heated under reflux with a Dean-Stark trap for 26 h. The organic phase was washed with 5% $NaHCO_3$ (3 × 40 mL) and the combined aqueous washings extracted with CH_2Cl_2 (2 × 40 mL). Combined organics were dried ($MgSO_4$), concentrated under reduced pressure, and the residue further dried in vacuo (5×10^{-2} mbar). The compound was used without further purification in the next reaction step. Yield: 7.45 g (34.3 mmol, 98 %) brown liquid. $C_{14}H_{18}O_2$ (218.29). δ_H (400 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 2.06 (3 H, s, CH_3), 2.41–2.49 (2 H, m, 2-H), 2.50–2.59 (2 H, m, 3-H), 4.15 (2 H, q, *J* 7.3 Hz, $CO_2CH_2CH_3$), 5.70–5.77 (1 H, m, 4-H), 7.20–7.25 (1 H, m), 7.28–7.34 (2 H, m), 7.34–7.39 (2 H, m). δ_C (100 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 15.8 (CH_3), 24.4 (C3), 34.2 (C2), 60.3 ($CO_2CH_2CH_3$), 125.7 (C4), 126.1, 126.7, 128.1, 136.2 (C5), 143.7, 173.1 ($CO_2CH_2CH_3$).[18]

B4.5.5 Ethyl (*E*)-2-(2‘-hydroxyprop-2‘-yl)-5-phenylhex-4-enoate (1e)

Compound was prepared analogously to ethyl 2-(2’-hydroxyprop-2’-yl)-5-methylhex-4-enoate (**1a**) from (*E*)-ethyl-5-phenylhex-4-enoate in 84 % yield as a colorless oil. R_f = 0.27 [ethyl acetate/pentane 1/4 (*v*/*v*)]. Anal. calcd. for $C_{17}H_{24}O_3$ (276.37): C, 73.88; H, 8.75; Found: C, 73.72; H, 8.76. δ_H (600 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.29 (6 H, 2 × s, CH_3), 2.04 (3 H, s, CH_3), 2.48–2.56 (2 H, m, 2-H, 3-H), 2.72 (1 H, ddd, *J* 15.3, 12.2, 8.5 Hz, 3-H), 3.01 (1 H, s, OH), 4.15 (2 H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 5.65–5.72 (1 H, m, 4-H), 7.20–7.25 (1 H, m), 7.27–7.35 (4 H, m). δ_C (150 MHz; $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 15.9 (CH_3), 26.7 (CH_3), 27.0 (C3), 29.2 (CH_3), 55.5 (C2), 60.6 ($CO_2CH_2CH_3$), 71.0 (C2’), 124.9 (C4), 125.7, 126.7, 128.2, 136.8 (C5), 143.7, 175.8 ($CO_2CH_2CH_3$).

B4.6 Ethyl (*E*)-2-(2‘-hydroxyprop-2‘-yl)-5-(*p*-methoxyphenyl)-hex-4-enoate (1f)

B4.6.1 (*E*)-1-Bromo-4-(*p*-methoxyphenyl)-pent-3-ene

Compound was prepared analogously to (*E*)-1-bromo-4-phenylpent-3-ene (see section B4.5) from 1-bromo-4-methoxybenzene in 94 % yield. The compound was used without further purification in the next reaction step. An analytical sample was further purified by column chromatography to yield a colorless liquid. R_f = 0.11 [CH_2Cl_2/pentane 1/6 (*v*/*v*)]. Anal. calcd. for $C_{12}H_{15}BrO$ (255.15): C, 56.49; H, 5.93; Found: C, 56.52; H, 5.90. δ_H (600 MHz; $CDCl_3$) 2.04 (3 H, s, CH_3), 2.78 (2 H, q, *J* 7.3 Hz, 2-H), 3.45 (2 H, t, *J* 7.2 Hz, 1-H), 3.81 (3 H, s, CH_3), 5.69 (1

H, td, J_t 7.2, J_d 1.2 Hz, 4-H), 6.84–6.90 (2 H, m), 7.30–7.37 (2 H, m). δ_C (150 MHz; $CDCl_3$) 16.1 (CH_3), 32.3 (C2), 32.5 (C1), 55.3 (CH_3), 113.5, 122.8 (C3), 126.7, 135.7, 137.0 (C4), 158.7.

B4.6.2 (*E*)-5-(*p*-Methoxyphenyl)-hex-4-enenitrile

Compound was prepared analogously to (*E*)-5-phenylhex-4-enenitrile (see section B4.5) from (*E*)-1-bromo-4-(*p*-methoxyphenyl)-pent-3-ene in 94 % yield after recrystallization from MeOH as a colorless solid, mp 48 °C. Anal. calcd. for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96; Found: C, 77.47; H, 7.33; N, 6.85. δ_H (600 MHz; $CDCl_3$) 2.05 (3 H, s, CH_3), 2.44–2.48 (2 H, m, 2-H), 2.56 (2 H, q, *J* 7.3 Hz, 3-H), 3.81 (3 H, s, CH_3), 5.67 (1 H, td, J_t 7.2, J_d 1.3 Hz, 4-H), 6.84–6.88 (2 H, m), 7.30–7.34 (2 H, m). δ_C (150 MHz; $CDCl_3$) 16.1 (CH_3), 17.5 (C2), 24.7 (C3), 55.3 (CH_3), 113.6, 119.5 (CN), 121.7 (C4), 126.8, 135.4, 137.7 (C5), 158.9.

B4.6.3 (*E*)-5-(*p*-Methoxyphenyl)-hex-4-enoic acid

Compound was prepared analogously to (*E*)-5-phenylhex-4-enoic acid (see section B4.5) from (*E*)-1-bromo-4-(*p*-methoxyphenyl)-pent-3-ene in 81 % yield after recrystallization from EtOH as a colorless solid, mp 85 °C. Anal. calcd. for $C_{13}H_{16}O_3$ (220.26): C, 70.89; H, 7.32; Found: C, 70.84; H, 7.29. δ_H (600 MHz; $CDCl_3$) 2.03 (3 H, s, CH_3), 2.47–2.57 (4 H, m, 2-H, 3-H), 3.81 (3 H, m, CH_3), 5.63–5.70 (1 H, m, 4-H), 6.81–6.89 (2 H, m), 7.27–7.34 (2 H, m). δ_C (150 MHz; $CDCl_3$) 15.9 (CH_3), 24.0 (C3), 33.9 (C2), 55.3 (CH_3), 113.5, 124.0 (C4), 126.7, 135.8, 136.0 (C5), 158.6, 179.0 (CO_2H).[19]

B4.6.4 Ethyl (*E*)-5-(*p*-methoxyphenyl)-hex-4-enoate

A mixture of (*E*)-5-(*p*-methoxyphenyl)-hex-4-enoic acid (2.21 g, 10 mmol), DMAP (122 mg, 1 mmol), and EtOH (1.85 g, 40 mmol) in 10 mL CH_2Cl_2 was cooled to 0 °C. DCC (2.06 g, 10 mmol) was added in one portion and the mixture stirred at 0 °C for 30 min. After being stirred for 20 h at 25 °C, AcOH (300 mg, 5 mmol) was added and the mixture stirred for further 2 h. The reaction mixture was filtered, CH_2Cl_2 evaporated under reduced pressure, the residue taken up in pentane (25 mL) and filtered again. After being washed with 0.5 M HCl (30 mL) and sat. $NaHCO_3$ (30 mL), the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dried in vacuo (5×10^{-2} mbar) and used without further purification in the next step. Yield: 2.16 g (8.70 mmol, 87 %) yellowish liquid. An analytical sample was purified by column chromatography to yield a colorless oil. R_f = 0.42 [diethyl ether/pentane 1/4 (*v*/*v*)]. Anal. calcd. for $C_{15}H_{20}O_3$ (248.32): C, 72.55; H, 8.12; Found: C, 72.41; H, 8.21. δ_H (400 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 2.03 (3 H, s, CH_3), 2.40–2.47 (2 H, m, 2-H), 2.51 (2 H, q, *J* 6.8

Hz, 3-H), 3.80 (3 H, s, CH_3), 4.14 (2 H, q, *J* 7.3 Hz, $CO_2CH_2CH_3$), 5.60–5.70 (1 H, m, 4-H), 6.81–6.87 (2 H, m), 7.27–7.33 (2 H, m). δ_C (100 MHz; $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 15.9 (CH_3), 24.3 (C3), 34.3 (C2), 55.3 (CH_3), 60.3 ($CO_2CH_2CH_3$), 113.5, 124.5 (C4), 126.7, 135.4, 136.2 (C5), 158.6, 173.3 ($CO_2CH_2CH_3$).

B4.6.5 Ethyl (*E*)-2-(2'-hydroxyprop-2'-yl)-5-(*p*-methoxyphenyl)-hex-4-enoate (1f)

Compound was prepared analogously to ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (**1a**) from ethyl (*E*)-5-(*p*-methoxyphenyl)-hex-4-enoate in 76 % yield as a colorless oil. R_f = 0.33 [SiO_2, ethyl acetate/pentane 1/3 (*v*/*v*)]. Anal. calcd. for $C_{18}H_{26}O_4$ (306.40): C, 70.56; H, 8.55; Found: C, 70.52; H, 8.58. δ_H (400 MHz; $CDCl_3$) 1.22 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.29 (6 H, s, 2 × CH_3), 2.00 (3 H, s, CH_3), 2.45–2.57 (2 H, m, 2-H, 3-H), 2.63–2.77 (1 H, m, 3-H), 3.02 (1 H, s, OH), 3.80 (3 H, s, CH_3), 4.14 (2 H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 5.57–5.65 (1 H, m, 4-H), 6.81–6.87 (1 H, m), 7.24–7.29 (2 H, m). δ_C (100 MHz; $CDCl_3$) 14.3 ($CO_2CH_2CH_3$), 15.9 (CH_3), 26.7 (CH_3), 27.0 (C3), 29.2 (CH_3), 55.3 (CH_3), 55.6 (C2), 60.5 ($CO_2CH_2CH_3$), 71.0 (C2'), 113.5, 123.3 (C4), 126.7, 136.1, 136.3 (C5), 158.6, 175.8 ($CO_2CH_2CH_3$).

B5 Bromocyclization Reactions and Controls

B5.1 Bromocyclization of Ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (1a) with py·HBr in MeCN

Under an atmosphere of nitrogen, a mixture of VO(L^1)(EtOH) or VO(L^2)(EtOH) (0.05 mmol) and TBHP [4.1 M in toluene, 0.31 mL, 1.25 mmol] in dry MeCN (50 mL) was heated to reflux and added to a solution of ethyl (*E*)-2-(2'-hydroxyprop-2'-yl)-5-phenylhex-4-enoate (**1a**) (215 mg, 1.0 mmol) and py·HBr (80 mg, 0.5 mmol) in dry MeCN (30 mL). The reaction mixture was stirred at 25 °C for 24 h, during which two further aliquots of py·HBr (80 mg, 0.5 mmol) were added after 5 h and 9 h respectively. The solvents were removed under reduced pressure and the residue subjected to column chromatography (SiO_2, CH_2Cl_2).

Analytical and spectroscopic properties of isolated diastereomeric mixtures of **(±)-2a** and **(±)-3a** were in agreement with those indicated in the Experimental Part. In addition to products of bromocylization, ethyl 4,5-dibromo-2-(2'-hydroxyprop-2'-yl)-5-methylhexanoate [**(±)-4a**] was isolated in yields from 5 to 27 % as yellow oil, 60/40-mixture of diastereomers. R_f = 0.08 [CH_2Cl_2]. Anal. calcd. for $C_{12}H_{22}Br_2O_3$ (374.11): C, 38.53; H, 5.93; Found: C, 38.21; H, 5.78. δ_H (600 MHz; $CDCl_3$) *major isomer*: 1.27 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.33 (3H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.83 (3 H, s, CH_3), 1.97 (3 H, s, CH_3), 2.14 (1 H, ddd, *J* 13.9, 11.4, 1.4 Hz, 3-H),

2.77–2.87 (3 H, m, 2-H, 3-H, OH), 4.10 (1 H, d, *J* 11.2 Hz, 4-H), 4.26 (2 H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$). *minor isomer*: 1.29 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.32 (3 H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.82 (3 H, s, CH_3), 1.99 (3 H, s, CH_3), 2.32 (1 H, ddd, *J* 15.6, 10.4, 7.8 Hz, 3-H), 2.51 (1 H, dd, *J* 7.7, 3.7 Hz, 2-H), 2.66 (1 H, br. s, OH), 3.02 (1 H, ddd, *J* 15.6, 3.7, 1.5 Hz, 3-H), 4.23 (2 H, q, *J* 7.3 Hz, $CO_2CH_2CH_3$), 4.32 (1 H, dd, *J* 10.3, 1.3 Hz, 4-H). δ_C (150 MHz; $CDCl_3$) 14.1 ($CO_2CH_2CH_3$), 14.4 ($CO_2CH_2CH_3$), 26.8 (CH_3), 27.3 (CH_3), 27.6 (CH_3), 28.4 (CH_3), 28.5 (CH_3), 28.9 (CH_3), 34.8 (C3), 35.1 (CH_3), 35.2 (C3), 35.4 (CH_3), 54.2 (C2), 55.4 (C2), 61.0 ($CO_2CH_2CH_3$), 61.1 ($CO_2CH_2CH_3$), 64.5 (C4), 65.2 (C4), 67.5 (C5), 68.8 (C5), 71.1 (C2'), 71.8 (C1'), 174.7 ($CO_2CH_2CH_3$), 175.4 ($CO_2CH_2CH_3$).

B5.2 Bromocyclization of Ethyl (*E*)-2-(2'-hydroxyprop-2'-yl)-5-phenylhex-4-enoate (1e) with py·HBr in MeCN (larger scale method)

Under an atmosphere of nitrogen, a mixture of VO(L^1)(EtOH) (100 mg, 0.25 mmol) and TBHP [4.1 M in toluene, 1.46 mL, 6.0 mmol] in dry MeCN (30 mL) was heated to reflux and added to a solution of ethyl (*E*)-2-(2'-hydroxyprop-2'-yl)-5-phenylhex-4-enoate (**1e**) (1.39 g, 5.0 mmol) in dry MeCN (120 mL). A solution of py·HBr (1.2 g, 7.5 mmol) in dry MeCN (20 mL) was added via syringe pump with a rate of 0.018 mL/min. The reaction mixture was stirred at 25 °C for 48 h. The solvents were removed under reduced pressure and the residue subjected to column chromatography (SiO_2, CH_2CH_2). Yield: 1.30 g (3.66 mmol, 73 %) 76/24-mixture of *cis*/*trans* isomers of **(±)-2e** as a yellowish oil. Analytical and spectroscopic properties of isolated diastereomeric mixture of **(±)-2e** were in agreement with those indicated in the Experimental Part.

B5.3 Control Reactions

B5.3.1 Bromocyclization of Ethyl 2-(2'-hydroxyprop-2'-yl)-5-methyl-4-hexenoate (1a) with Br_2 in CH_2Cl_2

To a solution of ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (215 mg, 1 mmol) (**1a**) in CH_2Cl_2 (10 mL) was added a solution of Br_2 (225 mg, 1.25 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The ice bath was removed and the reaction mixture stirred for 16 h at 25 °C. The mixture was subsequently washed with sat. $Na_2S_2O_3$, H_2O and sat. NaCl (15 mL each), dried ($MgSO_4$) and concentrated under reduced pressure to leave a residue which was purified by column chromatography (SiO_2, CH_2Cl_2). Yields: 45 mg (0.15 mmol, 15%) **(±)-2a** (*cis*/*trans* 38/62), 68 mg (0.23 mmol, 23%) **(±)-3a** (*cis*/*trans* 47/53), and 75 mg (0.20 mmol, 20%) **(±)-4a** (*dr* 57/43).

Analytic and spectroscopic properties of all isolated compounds were in agreement with those indicated in the Experimental Part and section B5.1.

B5.3.2 Bromocyclization of Ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (1a) with Br_2 / $NaHCO_3$ in MeCN

To a mixture of ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (**1a**) (108 mg, 0.5 mmol), NBu_4Br (16 mg, 0.05 mmol) and solid $NaHCO_3$ (120 mg, 1.0 mmol) in MeCN (5 mL) was added a solution of Br_2 (113 mg, 0.625 mmol) in MeCN (5 mL) at 0 °C within 20 min. The reaction mixture was stirred at 0° C for 1 h, the ice-bath was removed and the reaction mixture was stirred for 2 h at 25 °C. The mixture was diluted with CH_2Cl_2 (20 mL), subsequently washed with sat. $Na_2S_2O_3$, H_2O and sat. NaCl (15 mL each), dried ($MgSO_4$) and concentrated under reduced pressure to leave a residue which was purified by column chromatography (SiO_2, CH_2Cl_2). Yields: 38 mg (0.13 mmol, 26%) **(±)-2a** (*cis*/*trans* 82/18), 95 mg (0.32 mmol, 65%) **(±)-3a** (*cis*/*trans* 71/29), and 15 mg (0.04 mmol, 8%) **(±)-4a** (*dr* 54/46). The analytic and spectroscopic properties of all isolated compounds were in agreement with those indicated in the Experimental Part and section B5.1.

B5.3.3 Bromocyclization of Ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (1a) with NBS in CH_2Cl_2

To a solution of NBS (223 mg, 1.25 mmol), which was freshly recrystallized from H_2O and dried, in CH_2Cl_2 (20 mL) was added ethyl 2-(2'-hydroxyprop-2'-yl)-5-methylhex-4-enoate (**1a**) (215 mg, 1 mmol) at 25° C. The reaction mixture was stirred at 25° C for 3 h. The solvent was removed under reduced pressure, the residue treated with pentane (30 mL) and insoluble solids removed by filtration. The filtrate was concentrated under reduced pressure and the residue subjected to column chromatography (SiO_2, CH_2Cl_2). Yields: 40 mg (0.14 mmol, 14%) **(±)-2a** (*cis*/*trans* 47/53) and 84 mg (0.29 mmol, 29%) **(±)-3a** (*cis*/*trans* 56/44). The analytic and spectroscopic properties of all isolated compounds were in agreement with those indicated in the Experimental Part.

B6 Conversion of 3d to Ethyl [5-(1'-phenylmethyl)-2,2,5-trimethyl-tetrahydrofuran]-3-carboxylate (5)

Under an atmosphere of nitrogen, 20 mg (0.12 mmol) AIBN and 295 mg (1.0 mmol) Bu_3SnH were added to a solution of 160 mg (0.45 mmol) of **3d** in degassed, dry benzene (8 mL) at 25 °C. The reaction mixture was heated to 90 °C for 3 h after which TLC indicated complete consumption of the starting material. The mixture was concentrated under reduced pressure and the residue subjected to column chromatography [SiO_2/K_2CO_3 10/1 (*w*/*w*), diethyl ether/pentane 1/10 (*v*/*v*)]. Yield: 115 mg (0.42 mmol, 92 %) colorless solid, 93/7-mixture of *cis*/*trans* isomers, mp 46 °C. R_f = 0.22 [diethyl ether/pentane 1/10 (*v*/*v*)]. Anal. calcd. for $C_{17}H_{24}O_3$ (276.37): C, 73.88; H, 8.75; Found: C, 73.61; H, 8.73. ***rel*-(3*R*,5*R*)-5 [(±)-*cis*-5]** δ_H (600 MHz; $CDCl_3$) 0.93 (3 H, s, CH_3), 1.17 (3 H, s, CH_3), 1.26 (3 H, t, *J* 7.2 Hz, $CO_2CH_2\mathit{CH_3}$), 1.46 (3 H, s, CH_3), 1.84 (1 H, dd, *J* 12.6, 7.0 Hz, 4-H), 2.46 (1 H, t, *J* 12.6 Hz, 4-H), 2.83–2.92 (2 H, m, 1'-H), 3.03 (1 H, dd, *J* 12.6, 7.0 Hz, 3-H), 4.09–4.19 (2 H, m, $CO_2\mathit{CH_2}CH_3$), 7.19–7.31 (5 H, m). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2\mathit{CH_3}$), 25.0 (CH_3), 27.9 (CH_3), 30.4 (CH_3), 38.6 (C4), 48.8 (C1'), 53.3 (C3), 60.5 ($CO_2\mathit{CH_2}CH_3$), 81.8 (C2 or C5), 81.9 (C2 or C5), 126.2, 127.9, 130.7, 137.9, 171.7 ($\mathit{CO_2}CH_2CH_3$). NOESY (cross peaks) 3-H ↔ 5-CH_3, 3-H ↔ 2-$(CH_3)_a$ ↔ 5-CH_3, 5-$\mathit{CH_2}$Ph ↔ 2-$(CH_3)_b$. ***rel*-(3*R*,5*S*)-5 [(±)-*trans*-5]** δ_H (600 MHz; $CDCl_3$) 1.11 (3 H, s, CH_3), 1.24 (3 H, t, *J* 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 1.36 (3 H, s, CH_3), 1.39 (3 H, s, CH_3), 2.18 (1 H, dd, *J* 12.8, 7.4 Hz, 4-H), 2.32 (1 H, t, *J* 12.6 Hz, 4-H), 2.38–2.43 (1 H, m, 3-H), 2.67–2.76 (2 H, m, 1'-H), 4.10–4.18 (2 H, m, $CO_2\mathit{CH_2}CH_3$), 7.19–7.30 (5 H, m). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2\mathit{CH_3}$), 25.1 (CH_3), 29.0 (CH_3), 29.6 (CH_3), 38.6 (C4), 48.4 (C1'), 53.7 (C3), 60.5 ($CO_2\mathit{CH_2}CH_3$), 81.8 (C2 or C5), 82.1 (C2 or C5), 126.4, 127.9, 130.7, 137.9, 171.6 ($\mathit{CO_2}CH_2CH_3$).

B7 Supplementary Spectroscopic Data of Compounds

B7.1 NMR Spectra from Mixture of Isomers of Bromoethers 2b and 3b

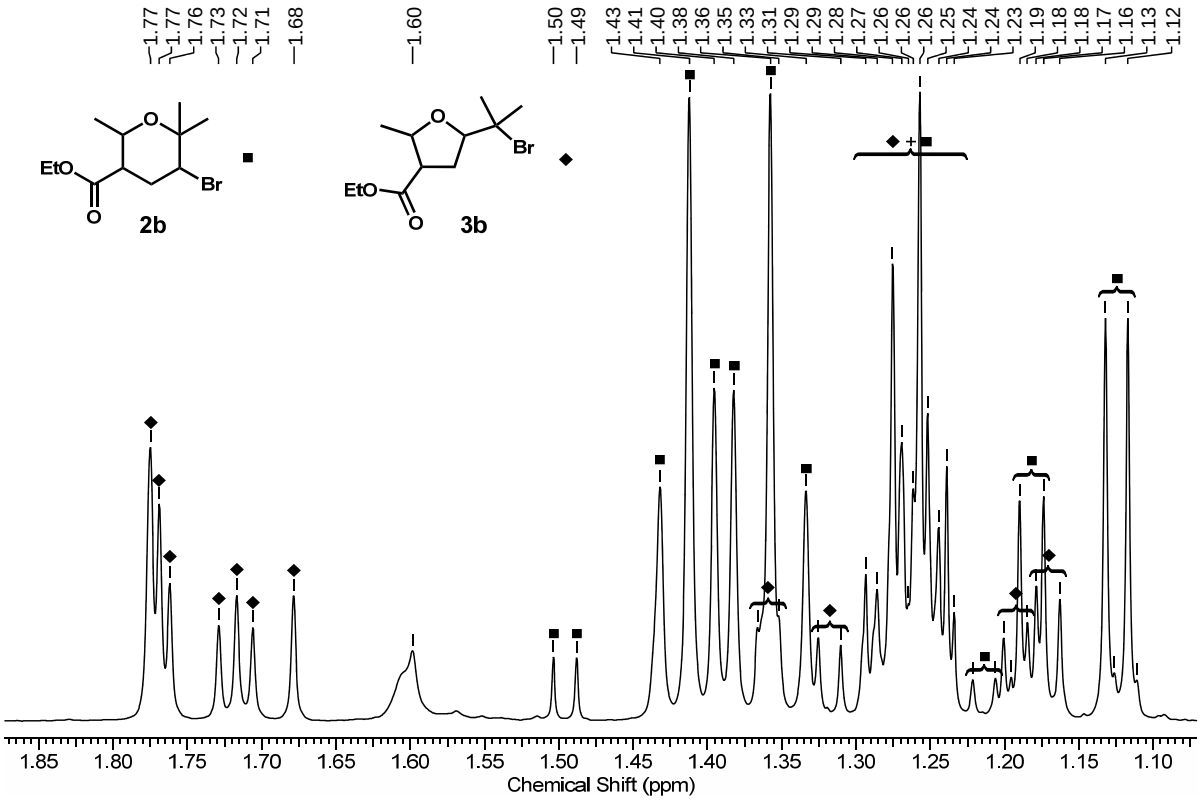


Figure B1. Methyl region of the ^{1}H-NMR spectrum of the mixture of isomers from **2b** and **3b**.

Table B1. Ranges of ^{1}H-NMR methyl resonances of cyclic ethers **2a**/**3a, 2b**/**3b** and **2c**/**3c**.

			δ(THF-CH_3 signals) [ppm]		**δ(THP-CH_3 signals) [ppm]**	
2 / 3	R^1	R^2	2-CH_3	1'-CH_3	2-CH_3	6-CH_3
c	H	H	–	1.70 – 1.76	–	1.36 – 1.39
a	CH_3	CH_3	1.12 – 1.44	1.69 – 1.75	1.22 – 1.32	1.32 – 1.43
b	CH_3	H	1.16 – 1.50	1.68 – 1.77	1.12 – 1.43	

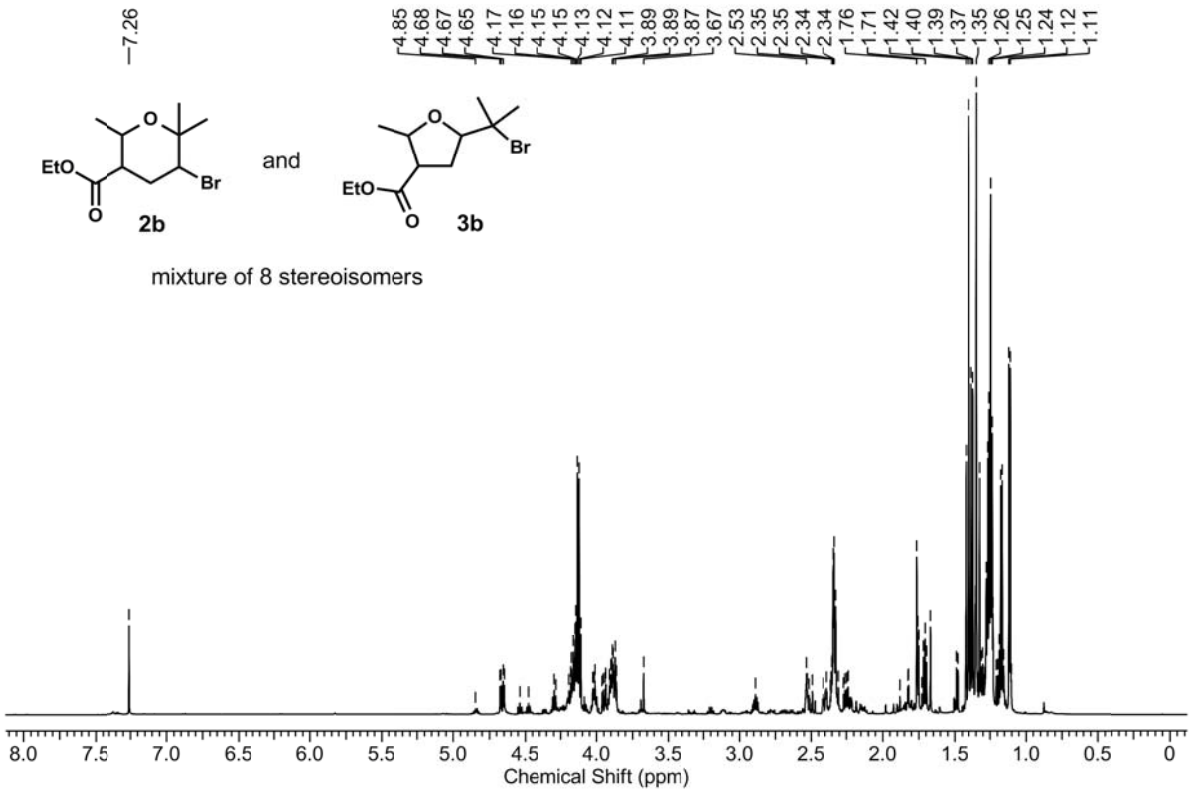


Figure B2. ^{1}H-NMR spectrum of the mixture of isomers of **2b** and **3b**.

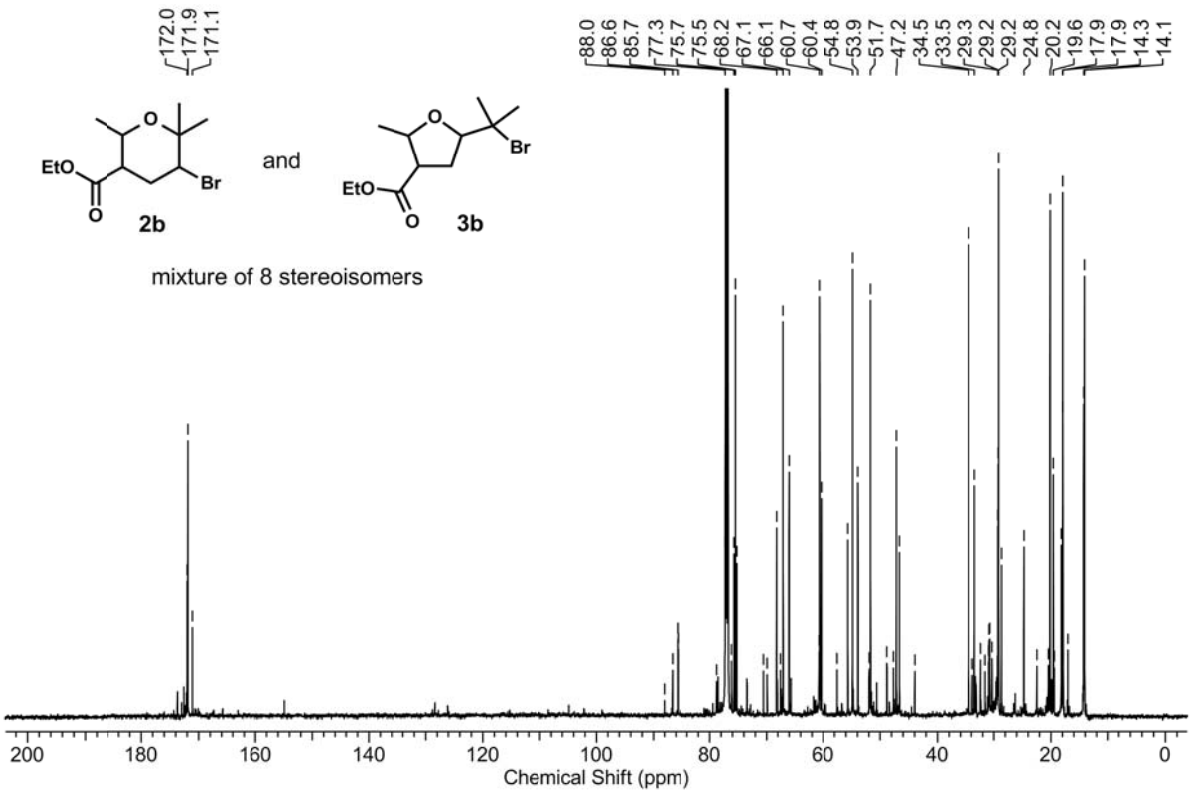


Figure B3. ^{13}C-NMR spectrum of the mixture of isomers of **2b** and **3b**.

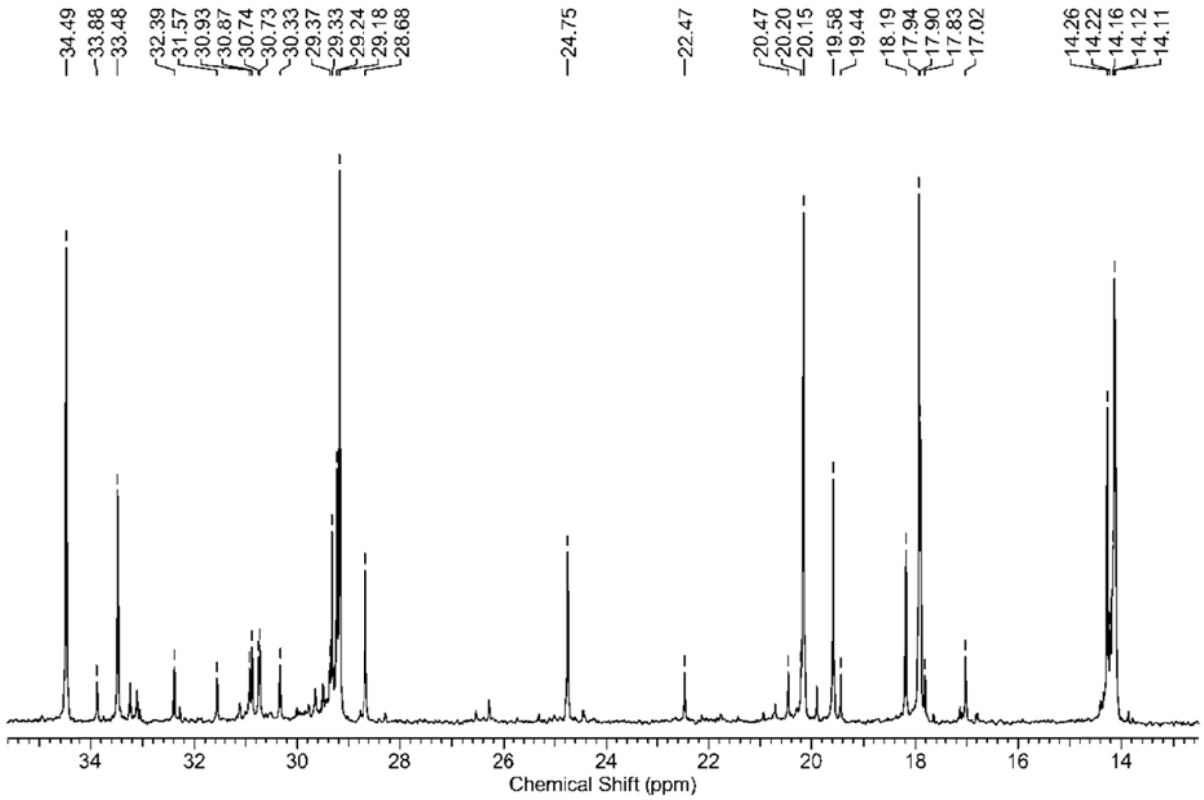


Figure B4. Excerpt from the ^{13}C-NMR spectrum of mixture of isomers of **2b** and **3b**.

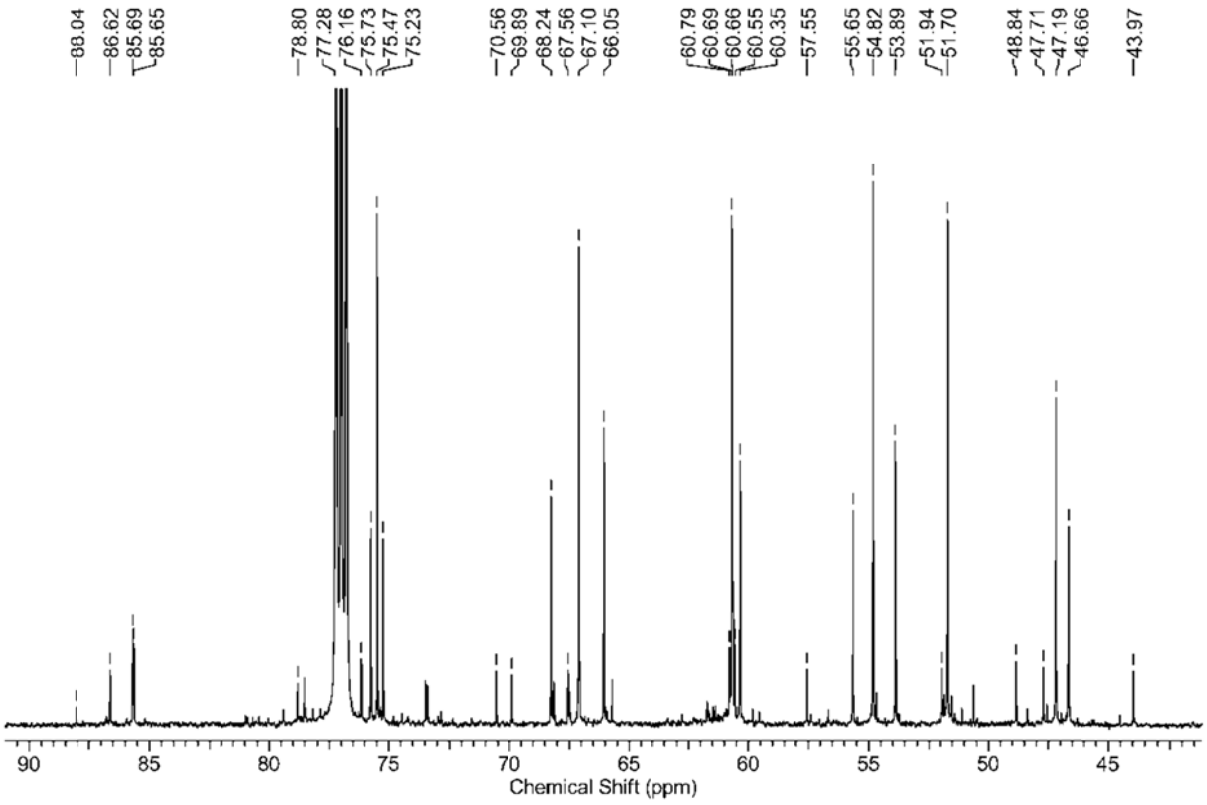


Figure B5. Excerpt from the ^{13}C-NMR spectrum of the mixture of isomers of **2b** and **3b**.

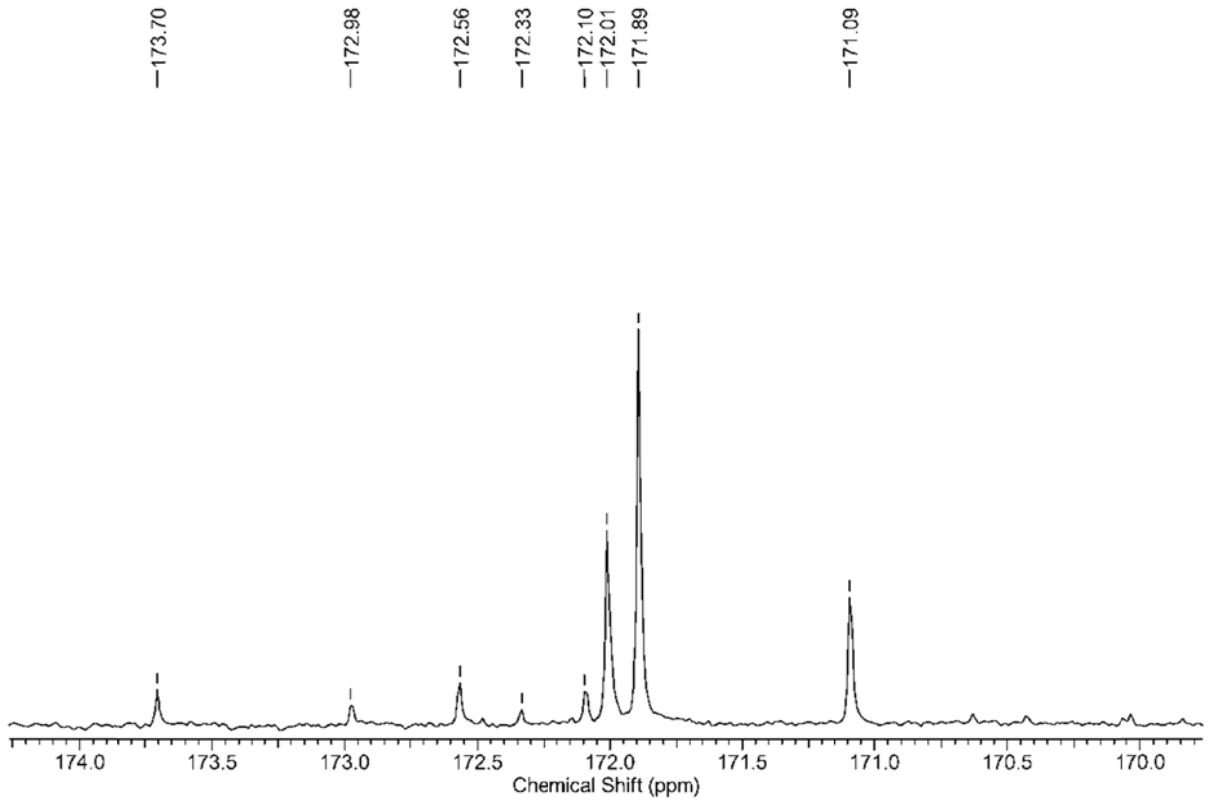


Figure B6. Excerpt from the ^{13}C-NMR spectrum of the mixture of isomers of **2b** and **3b**.

B7.1.1 ^{1}H- and ^{13}C-NMR data for 2b and 3b

For mixture of isomers (only major resonances specified): δ_H (400 MHz; $CDCl_3$) 1.12 (d, *J* 6.0 Hz, CH_3), 1.17 (d, *J* 6.4 Hz, CH_3), 1.18 (d, *J* 6.4 Hz, CH_3), 1.19 (d, *J* 6.2 Hz, CH_3), 1.21 (d, *J* 6.0 Hz, CH_3), 1.23–1.30 (m, $CO_2CH_2CH_3$ and CH_3), 1.32 (d, *J* 6.0 Hz, CH_3), 1.33 (s, CH_3), 1.36 (d, *J* 5.7 Hz, CH_3), 1.36 (s, CH_3), 1.38 (s, CH_3), 1.40 (s, CH_3), 1.41 (s, CH_3), 1.43 (s, CH_3), 1.49 (s, CH_3), 1.50 (s, CH_3), 1.68 (s, CH_3), 1.71 (s, CH_3), 1.72 (s, CH_3), 1.73 (s, CH_3), 1.76 (s, CH_3), 1.77 (3 × s, CH_3), 2.09–2.32 (m), 2.32–2.38 (m), 2.40 (dd, *J* 4.8, 2.0 Hz), 2.43 (dd, *J* 4.8, 2.0 Hz), 2.46–2.51 (m), 2.52–2.58 (m), 2.59–2.74 (m), 2.79 (ddd, *J* 12.4, 10.3, 4.0 Hz), 2.90 (ddd, *J* 11.1, 6.0, 4.8 Hz), 3.12 (ddd, *J* 8.0, 6.2, 3.6 Hz), 3.17–3.25 (m), 3.29 (td, *J* 6.9, 2.6 Hz), 3.34–3.38 (m), 3.67–3.74 (m), 3.85–4.25 (m), 4.25–4.43 (m), 4.49 (t, *J* 6.3 Hz), 4.55 (dd, *J* 8.3, 7.7 Hz), 4.67 (dd, *J* 12.7, 4.7 Hz), 4.80–4.90 (m). δ_C (100 MHz; $CDCl_3$) 14.1, 14.2, 14.3, 17.0, 17.8, 17.9, 18.2, 19.4, 19.6, 20.2, 20.5, 24.8, 28.7, 29.2, 29.3, 29.4, 30.3, 30.7, 30.9, 31.6, 32.4, 33.5, 33.9, 34.5, 44.0, 46.7, 47.2, 47.7, 48.8, 51.7, 51.9, 53.9, 54.8, 55.6, 57.5, 60.4, 60.6, 60.7, 60.8, 66.1, 67.1, 67.6, 68.2, 69.9, 70.6, 75.2, 75.5, 76.2, 77.3, 78.8, 85.7, 86.6, 88.0, 171.1, 171.9, 172.0.

B7.1.2 ^{1}H- and ^{13}C-NMR data of *rel*-(2*S*,3*R*,5*S*)-2b in C_6D_6

δ_H (600 MHz; C_6D_6) 0.89 (3 H, t, *J* 7.0 Hz, $CO_2CH_2\mathit{CH_3}$), 1.14 (3 H, d, *J* 5.9 Hz, CH_3), 1.26 (3 H, s, CH_3), 1.31 (3 H, s, CH_3), 2.11–2.17 (2 H, m, 3-H, 4-H), 2.36 (1 H, q, *J* 13.2 Hz, 4-H), 3.56 (1 H, dd, *J* 12.8, 4.3 Hz, 5-H), 3.86 (2 H, q, *J* 7.2 Hz, $CO_2\mathit{CH_2}CH_3$), 3.93 (1 H, dq, J_d 9.9, J_q 6.0 Hz, 2-H). δ_C (150 MHz; C_6D_6) 14.1 ($CO_2CH_2\mathit{CH_3}$), 17.9 (CH_3), 20.5 (CH_3), 29.4 (CH_3), 35.0 (C4), 52.0 (C3), 55.5 (C5), 60.4 ($CO_2\mathit{CH_2}CH_3$), 67.4 (C2), 75.4 (C6), 171.5 ($\mathit{CO_2}CH_2CH_3$). NOESY (cross signals) 2-H ↔ $(6\text{-}CH_3)_a$, 2-H ↔ $4\text{-}H_a$, $2\text{-}CH_3$ ↔ 3-H, $(6\text{-}CH_3)_a$ ↔ $4\text{-}H_a$, $(6\text{-}CH_3)_b$ ↔ 5-H, 3-H ↔ 5-H.

B7.2 Supplementary Spectroscopic Data of Compounds en Route to Aplysiapyranoids

B7.2.1 ^{13}C-NMR of 5-Bromo-2,2-6-trimethyl-6-phenyltetrahydropyran-3-carboxylic acid (±)-(6)

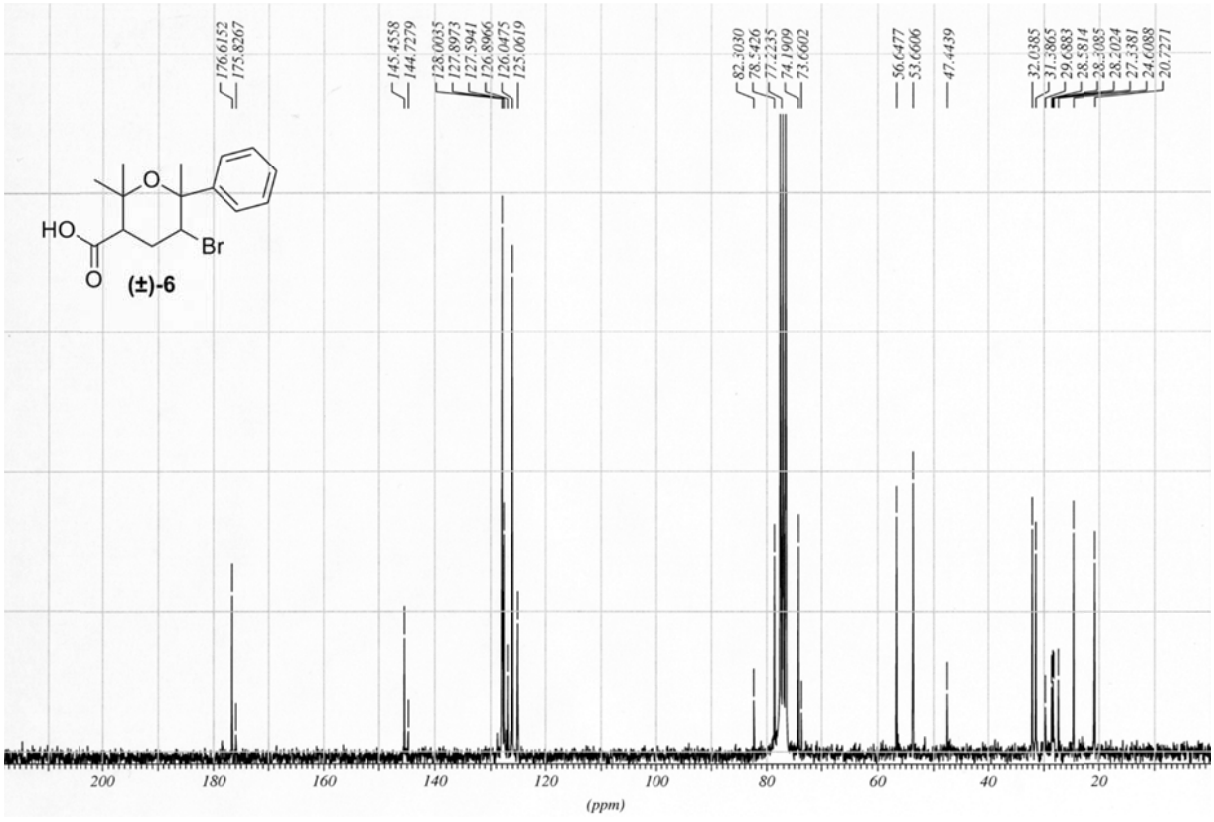


Figure B7. ^{13}C-NMR spectrum of carboxylic acid **6** in $CDCl_3$ (20 °C).

B7.2.2 N-[*rel*-(3*R*,5*S*,6*R*)-5-Bromo-2,2,6-trimethyl-6-phenyltetrahydropyran-3-carbonyloxy]-pyridine-2(1*H*)-thione (±)-*cis*-(7)

δ_H (400 MHz; $CDCl_3$) 1.60 (3 H, s, CH_3), 1.65 (3 H, s, CH_3), 1.92 (3 H, s, CH_3), 2.76–2.86 (2 H, m, 4-H), 3.28 (1 H, dd, *J* 12.2, 7.6 Hz, 3-H), 4.11 (1 H, dd, *J* 12.2, 4.7 Hz, 1 H, 5-H), 6.33 (1 H, dt, J_t 6.8, J_d 1.6 Hz), 7.24–7.39 (m, 5 H), 7.21 (1 H, ddd, *J* 8.5, 6.8, 1.4 Hz), 7.54 (1 H, dd, *J* 6.8, 1.4 Hz), 7.70 (1 H, dd, *J* 8.5, 1.6 Hz). δ_C (63 MHz; $CDCl_3$) 21.0 (CH_3), 24.9 (CH_3), 31.7 (C4), 32.3 (CH_3), 52.1 (C3), 55.9 (C5), 74.1 (C2), 78.7 (C6), 112.7, 125.1, 126.1, 128.0, 133.5, 137.3, 137.5, 145.2, 166.8, 175.7.

Instability and thus appearance of decomposition products of similar intensity to signals of **(±)-*trans*-7** within the time necessary for recording NMR spectra prevented to determine reliable ^{1}H- and ^{13}C-NMR shift values for the minor isomer of pyridinethione **7**.

B7.2.3 *rel*-(2*R*,3*S*,5*S*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylic acid

δ_H (400 MHz; $CDCl_3$) 1.40 (3 H, s, CH_3), 1.45 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 2.52–2.63 (1 H, m, 4-H), 2.73–2.85 (1 H, m, 4-H), 4.50 (1 H, dd, *J* 12.1, 5.7 Hz, 5-H), 4.83 (1 H, t, *J* 3.6 Hz, 3-H). δ_C (63 MHz; $CDCl_3$) 21.1 (CH_3), 29.5 (CH_3), 29.5 (CH_3), 37.9 (C4), 51.8 (C3), 54.7 (C5), 76.5 (C2), 78.4 (C6), 175.4 (CO_2H).

B7.2.4 *rel*-(2*R*,3*S*,5*R*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylic acid

δ_H (400 MHz; $CDCl_3$) 1.41 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 1.75 (3 H, s, CH_3), 2.60–2.73 (2 H, m, 4-H), 3.96 (1 H, dd, *J* 11.8, 4.9 Hz, 5-H), 4.35 (1 H, dd, *J* 11.5, 4.9 Hz, 3-H). δ_C (63 MHz; $CDCl_3$) 19.8 (CH_3), 23.9 (CH_3), 30.1 (CH_3), 37.7 (C4), 46.7 (C3), 52.8 (C5), 78.2 (C6), 79.7 (C2), 173.7 (CO_2H).

B7.2.5 *rel*-(2*R*,3*S*,5*S*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carbaldehyde

δ_H (400 MHz; $CDCl_3$) 1.23 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 1.46 (3 H, s, CH_3), 2.50–2.57 (2 H, m, 4-H), 4.45 (1 H, dd, *J* 10.0, 6.7 Hz, 5-H), 4.72 (1 H, t, *J* 3.3 Hz, 3-H), 9.58 (1 H, s, COH). δ_C (63 MHz; $CDCl_3$) 22.2 (CH_3), 24.5 (CH_3), 29.5 (CH_3), 37.4 (C4), 51.1 (C5), 53.7 (C3), 77.6 (C2), 80.8 (C6), 200.3 (COH).

B7.2.6 *rel*-(2*R*,3*S*,5*R*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carbaldehyde

δ_H (400 MHz; $CDCl_3$) 1.37 (3 H, s, CH_3), 1.49 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 2.60–2.75 (2 H, m, 4-H), 3.90–3.97 (1 H, m, 1 H, 5-H), 4.01–4.08 (1 H, m, 3-H), 9.21 (1 H, s, COH). δ_C (63 MHz; $CDCl_3$) 17.5 (CH_3), 23.1 (CH_3), 29.9 (CH_3), 37.4 (C4), 44.2 (C3), 53.2 (C5), 76.4 (C2), 77.5 (C6), 196.5 (COH).

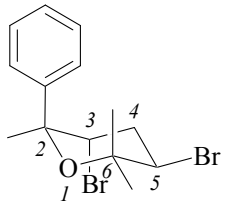
B8 Molecular Modelling – Methods and Assessment

All calculations were carried out with Gaussian03.[20] Structure and energy of dimethyltetrahydropyrans were computed using the density functional/Hartee-Fock hybrid models B3LYP in combination with the split valance double-ζ basis set 6-31+G(d,p). Thermochemical analysis of the alkenol isomerization **VII** → **VIII** and **IX** (section B11) was performed on the B3LYP- and MP2-level of theory using the split valance 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 was used. The absence of imaginary modes of vibration characterized computed structures as minima. Approximate Gibbs free energies ($G_{298.15}$) were obtained by thermochemical analysis for 298.15 K on the basis of unscaled frequency calculation using the thermal correction reported by Gaussian03. Likewise obtained Gibbs free energies take into account zero-point correction, thermal correction, and the entropy term.

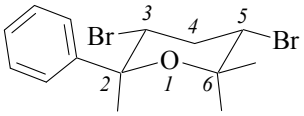
Oxygen atoms in ball-and-stick presentations of computed minima structures are depicted in red, carbons in gray, hydrogens in white, and bromine in blue.

B8.1 Comparison of experimental versus calculated geometrical garameters

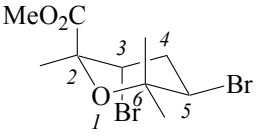
Table B2. Synopsis of experimental (X-ray diffraction; 300±2 K) and calculated (B3LYP/6-31+G**//B3LYP/6-31+G**; 0 K) endocyclic bond lengths d_i.



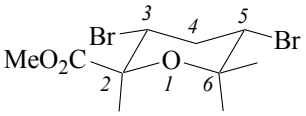
trans-**8**



cis-**8**



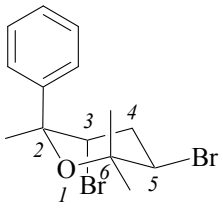
trans-**10**



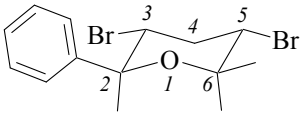
cis-**10**

entry	compound	method	d_1 = 1–2 Å	d_2 = 2–3 Å	d_3 = 3–4 Å	d_4 = 4–5 Å	d_5 = 5–6 Å	d_6 = 6–1 Å
1	*trans*-**8**	X-ray	1.454(4)	1.526(5)	1.513(6)	1.530(6)	1.536(6)	1.460(5)
2		B3LYP	1.441	1.542	1.527	1.521	1.547	1.462
3	*cis*-**8**	X-ray	1.441(3)	1.534(4)	1.519(4)	1.509(4)	1.531(5)	1.462(4)
4		B3LYP	1.454	1.552	1.526	1.524	1.544	1.455
5	*trans*-**10**	X-ray	1.431(3)	1.533(4)	1.513(4)	1.520(4)	1.526(4)	1.458(3)
6		B3LYP	1.425	1.543	1.527	1.522	1.546	1.462
7	*cis*-**10**	X-ray	1.431(6)	1.517(6)	1.500(7)	1.518(7)	1.510(7)	1.451(6)
8		B3LYP	1.448	1.542	1.524	1.527	1.547	1.459

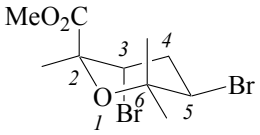
Table B3. Synopsis of experimental (X-ray diffraction; 300±2 K) versus calculated (B3LYP/6-31+G**//B3LYP/6-31+G**; 0 K) endocyclic bond angles ϕ_i.



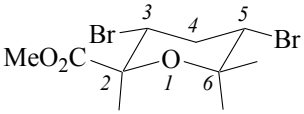
trans-**8**



cis-**8**



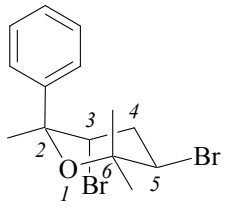
trans-**10**



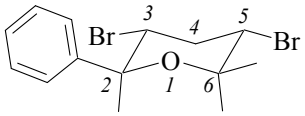
cis-**10**

entry	compound	method	ϕ_1 = 6–1–2	ϕ_2 = 1–2–3	ϕ_3 = 2–3–4	ϕ_4 = 3–4–5	ϕ_5 = 4–5–6	ϕ_6 = 5–6–1
1	*trans*-**8**	X-ray	120.6(3)°	109.4(3)°	112.3(4)°	109.0(4)°	112.0(4)°	106.1(3)°
2		B3LYP	122.9°	109.9°	112.3°	109.8°	113.1°	107.1°
3	*cis*-**8**	X-ray	122.5(2)°	106.7(2)°	113.7(3)°	107.2(3)°	112.9(3)°	106.3(3)°
4		B3LYP	124.3°	106.0°	113.2°	107.7°	113.1°	106.5°
5	*trans*-**10**	X-ray	120.6 (2)°	111.5(2)°	112.0(2)°	109.8(2)°	113.6(2)°	106.6(2)°
6		B3LYP	121.5°	111.5°	111.9°	110.1°	113.4°	106.8°
7	*cis*-**10**	X-ray	121.4(4)°	107.2(4)°	112.0(4)°	106.3(4)°	112.4(4)°	105.2(4)°
8		B3LYP	122.3°	106.7°	112.0°	107.5°	113.6°	106.5°

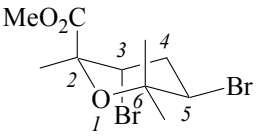
Table B4. Synopsis of experimental (X-ray diffraction; 300±2 K) versus calculated (B3LYP/6-31+G**//B3LYP/6-31+G**; 0 K) endocyclic torsion angles ω_{ij}.



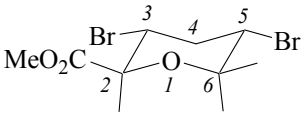
trans-**8**



cis-**8**



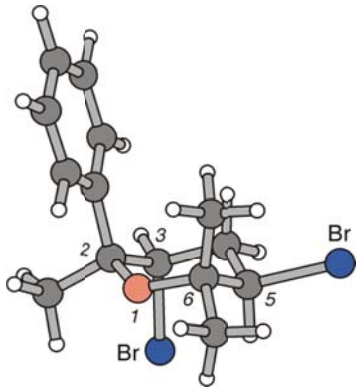
trans-**10**



cis-**10**

entry	compound	method	ω_{23} = 1–2–3–4	ω_{45} = 2–3–4–5	ω_{45} = 3–4–5–6	ω_{56} = 4–5–6–1	ω_{61} = 5–6–1–2	ω_{12} = 6–1–2–3
1	*trans*-**8**	X-ray	–49.8(5)°	55.5(5)°	–59.3(5)°	55.4(5)°	–54.1(5)°	51.9(5)°
2		B3LYP	–48.0°	54.6°	–57.2°	51.8°	–49.4°	48.6°
3	*cis*-**8**	X-ray	51.6(3)°	–58.1(4)°	59.3(4)°	–53.9(4)°	52.6(4)°	–51.3(4)°
4		B3LYP	51.7°	–58.7°	58.5°	–51.7°	51.1°	–51.0°
5	*trans*-**10**	X-ray	47.4(3)°	–51.7(3)°	56.9(3)°	–53.8(3)°	52.2(3)°	–50.4(3)°
6		B3LYP	47.1°	–51.9°	56.4°	–52.4°	51.2°	–49.9°
7	*cis*-**10**	X-ray	54.1(5)°	–60.0(6)°	62.0(6)°	–55.9(6)°	54.3(6)°	–53.7(6)°
8		B3LYP	55.1°	–59.3°	57.6°	–50.8°	51.9°	–54.3°

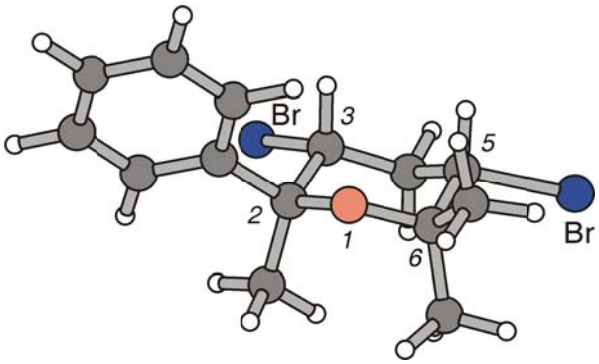
B8.2 *rel*-(2*R*,3*S*,5*S*)-3,5-Dibromo-2,6,6-trimethyl-2-phenyltetrahydropyran *trans*-(8)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.680043	-0.007164	-1.375621
2	6	0	2.245173	0.011845	-0.042638
3	6	0	2.993577	-0.711465	0.901340
4	6	0	4.114543	-1.449625	0.527164
5	6	0	4.523341	-1.479222	-0.809979
6	6	0	3.800375	-0.755589	-1.756811
7	6	0	1.057160	0.860625	0.485372
8	8	0	0.296861	0.154369	1.485294
9	6	0	-0.625672	-0.932797	1.160622
10	6	0	-1.535610	-0.431731	0.014674
11	6	0	-0.756543	0.148838	-1.155709
12	6	0	0.132134	1.291428	-0.670971
13	6	0	1.656275	2.054818	1.247249
14	35	0	-1.065238	2.826458	-0.203062
15	35	0	-2.750770	-1.846274	-0.661673
16	6	0	-1.430225	-1.093274	2.453939
17	6	0	0.114303	-2.238912	0.836743
18	1	0	0.708475	1.715634	-1.489364
19	1	0	-0.121486	-0.623003	-1.605979
20	1	0	-1.439760	0.503129	-1.930334
21	1	0	-2.222762	0.314479	0.410976
22	1	0	2.678166	-0.702914	1.939484
23	1	0	4.669467	-2.002416	1.279993
24	1	0	5.394053	-2.056300	-1.106795
25	1	0	4.106931	-0.761333	-2.798946
26	1	0	2.157668	0.548080	-2.146820
27	1	0	2.359125	1.692557	2.000067
28	1	0	0.867811	2.621578	1.743169
29	1	0	2.195243	2.713555	0.559281
30	1	0	-0.763323	-1.383040	3.270995
31	1	0	-2.198210	-1.862496	2.337323
32	1	0	-1.910500	-0.148082	2.722422
33	1	0	0.845858	-2.441839	1.621893
34	1	0	0.640873	-2.207394	-0.119021
35	1	0	-0.595458	-3.068230	0.802799

Zero-point correction=	0.290755 (Hartree/Particle)	
Thermal correction to Energy=	0.307637	
Thermal correction to Enthalpy=	0.308581	
Thermal correction to Gibbs Free Energy=	0.245840	
Sum of electronic and zero-point Energies=		-5762.778777
Sum of electronic and thermal Energies=		-5762.761895
Sum of electronic and thermal Enthalpies=		-5762.760951
Sum of electronic and thermal Free Energies=		-5762.823692

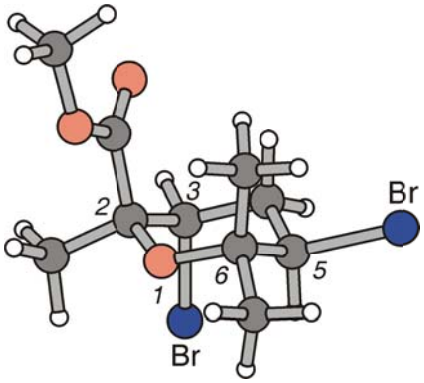
B8.3 *rel*-(2*R*,3*S*,5*R*)-3,5-Dibromo-2,6,6-trimethyl-2-phenyltetrahydropyran *cis*-(8)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.401386	-0.347863	0.747798
2	6	0	2.204469	-0.754312	0.143430
3	6	0	2.278783	-1.643777	-0.940872
4	6	0	3.509615	-2.100528	-1.413179
5	6	0	4.696875	-1.679490	-0.808534
6	6	0	4.636083	-0.800890	0.273316
7	6	0	0.827550	-0.259687	0.622125
8	8	0	-0.041567	-1.408007	0.425273
9	6	0	-1.494971	-1.351189	0.461468
10	6	0	-1.912987	-0.210751	-0.492246
11	6	0	-1.186494	1.100101	-0.213219
12	6	0	0.310439	0.837676	-0.345894
13	6	0	0.843164	0.174368	2.094151
14	35	0	1.300846	2.542035	-0.164450
15	35	0	-3.871729	0.101981	-0.485621
16	6	0	-1.901539	-2.716414	-0.106010
17	6	0	-2.052490	-1.209745	1.889309
18	1	0	0.541642	0.527248	-1.365932
19	1	0	-1.433788	1.484760	0.780140
20	1	0	-1.494496	1.858041	-0.937086
21	1	0	-1.719904	-0.527367	-1.519308
22	1	0	-1.546135	-3.510833	0.556150
23	1	0	-1.455964	-2.869647	-1.093317
24	1	0	-2.988600	-2.789270	-0.192996
25	1	0	-2.051323	-0.182250	2.257601
26	1	0	-1.456413	-1.827840	2.565647
27	1	0	-3.086109	-1.561537	1.920533
28	1	0	1.090395	-0.686678	2.719842
29	1	0	-0.121889	0.569072	2.409173
30	1	0	1.577909	0.960647	2.268485
31	1	0	1.364010	-1.998593	-1.401103
32	1	0	3.539548	-2.791789	-2.250829
33	1	0	5.655942	-2.034525	-1.174444
34	1	0	5.549049	-0.464287	0.756144
35	1	0	3.390284	0.343319	1.581752

Zero-point correction= 0.290510 (Hartree/Particle)
Thermal correction to Energy= 0.307630
Thermal correction to Enthalpy= 0.308574
Thermal correction to Gibbs Free Energy= 0.244262
Sum of electronic and zero-point Energies= -5762.777949
Sum of electronic and thermal Energies= -5762.760829
Sum of electronic and thermal Enthalpies= -5762.759885
Sum of electronic and thermal Free Energies= -5762.824197

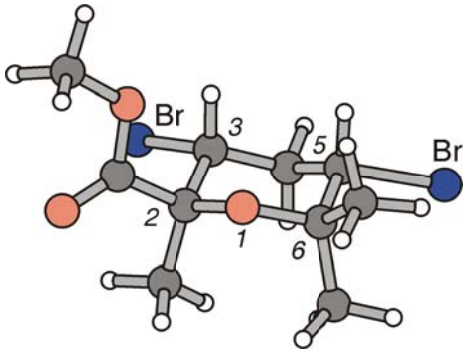
B8.4 Methyl *rel*-(2*R*,3*S*,5*S*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylate *trans*-(10)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.367716	0.025795	0.080257
2	6	0	0.593418	-0.929468	1.017535
3	8	0	-0.698130	-0.300470	1.289585
4	6	0	-1.533210	0.173432	0.236575
5	6	0	-0.749238	1.064440	-0.749988
6	6	0	0.578861	0.430071	-1.157157
7	6	0	0.415997	-2.348381	0.457989
8	6	0	1.246579	-0.985256	2.400243
9	6	0	-2.697305	0.886888	0.941482
10	6	0	-2.176504	-0.978971	-0.593277
11	8	0	-2.715430	-1.918698	0.196408
12	6	0	-3.367298	-3.013926	-0.480013
13	35	0	-0.381989	2.870013	0.009932
14	35	0	3.110691	-0.733764	-0.480958
15	8	0	-2.240043	-1.004946	-1.807837
16	1	0	-1.356753	1.280453	-1.625619
17	1	0	0.362434	-0.442630	-1.782664
18	1	0	1.158437	1.127655	-1.765042
19	1	0	1.653005	0.911619	0.647026
20	1	0	-0.304656	-2.885784	1.078330
21	1	0	1.368582	-2.881463	0.482734
22	1	0	0.066159	-2.360943	-0.577928
23	1	0	0.646917	-1.610852	3.067435
24	1	0	1.306347	0.017889	2.831769
25	1	0	2.253748	-1.403960	2.333363
26	1	0	-3.253813	0.164469	1.540400
27	1	0	-3.368413	1.347766	0.209793
28	1	0	-2.300663	1.664001	1.594889
29	1	0	-3.747684	-3.655762	0.313590
30	1	0	-2.650752	-3.552904	-1.104389
31	1	0	-4.182709	-2.643066	-1.104925

Zero-point correction= 0.252191 (Hartree/Particle)
Thermal correction to Energy= 0.269158
Thermal correction to Enthalpy= 0.270102
Thermal correction to Gibbs Free Energy= 0.207024
Sum of electronic and zero-point Energies= -5759.637434
Sum of electronic and thermal Energies= -5759.620467
Sum of electronic and thermal Enthalpies= -5759.619522
Sum of electronic and thermal Free Energies= -5759.682601

B8.5 Methyl *rel*-(2*R*,3*S*,5*R*)-3,5-dibromo-2,6,6-trimethyltetrahydropyran-2-carboxylate *cis*-(10)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.726150	-1.139335	-0.130679
2	6	0	1.630251	0.031493	-0.510193
3	6	0	1.369986	1.308919	0.322031
4	8	0	-0.066224	1.558719	0.260941
5	6	0	-1.041511	0.542490	0.582690
6	6	0	-0.716191	-0.677987	-0.301954
7	35	0	3.525366	-0.546431	-0.423215
8	6	0	1.957471	2.541094	-0.373231
9	6	0	1.886424	1.234506	1.768155
10	6	0	-1.141901	0.245048	2.082476
11	6	0	-2.367986	1.207595	0.125162
12	8	0	-3.232693	1.593135	0.880426
13	35	0	-1.977037	-2.167077	0.017252
14	8	0	-2.435102	1.325864	-1.211813
15	6	0	-3.617464	1.971777	-1.726147
16	1	0	-0.899686	-0.411450	-1.341406
17	1	0	0.919385	-1.473154	0.892476
18	1	0	0.923753	-1.988234	-0.789460
19	1	0	1.492156	0.274150	-1.565751
20	1	0	1.718174	3.439276	0.202832
21	1	0	1.531821	2.652686	-1.374486
22	1	0	3.043858	2.454052	-0.455108
23	1	0	1.403964	2.018747	2.357114
24	1	0	2.965306	1.403140	1.786800
25	1	0	1.698690	0.271995	2.246803
26	1	0	-1.128468	1.185406	2.635857
27	1	0	-0.324474	-0.387458	2.428690
28	1	0	-2.082452	-0.260654	2.302166
29	1	0	-3.511368	1.947701	-2.810057
30	1	0	-3.669863	3.001201	-1.364297
31	1	0	-4.511507	1.430007	-1.409770

Zero-point correction=	0.252383	(Hartree/Particle)
Thermal correction to Energy=	0.269448	
Thermal correction to Enthalpy=	0.270392	
Thermal correction to Gibbs Free Energy=	0.206723	
Sum of electronic and zero-point Energies=		-5759.633632
Sum of electronic and thermal Energies=		-5759.616567
Sum of electronic and thermal Enthalpies=		-5759.615623
Sum of electronic and thermal Free Energies=		-5759.679293

B9 Calculated Energies and Coordinates of Tetrahydropyrans

Table B5. Calculated (B3LYP/6-31+G**// B3LYP/6-31+G**) energies of tetrahydropyran (thp; chair conformation) and dimethyltetrahydrofurans **I–VI** and **X–XII** (Figure S8)

entry	compound	E / Hartree [a]	E_{rel} [kJ mol^{-1}] [b]	G_{298} / Hartree [a]	ΔG_{298} [kJ mol^{-1}] [b]
1	$C_5H_{10}O$ (thp)	–271.793563	– [b]	–271.676030	– [b]
2	**Ia**	–350.439903	≡ 0.0	–350.270733	≡ 0.0
3	**Ib**	–350.434577	14.0	–350.264974	15.1
4	**Ic**	–350.427421	32.8	–350.257454	34.9
5	**IIa**	–350.436014	10.2	–350.266678	10.7
6	**IIb**	–350.431965	20.8	–350.262295	22.2
7	**IIc**	–350.430698	24.2	–350.260981	25.6
8	**IId**	–350.424631	40.1	–350.254553	42.5
9	**IIIa**	–350.431628	21.7	–350.262172	22.5
10	**IIIb**	–350.428911	28.9	–350.259192	30.3
11	**IIIc**	–350.423747	42.4	–350.253793	44.5
12	**IV**	–350.433228	17.5	–350.263489	19.0
13	**V**	–350.428911	28.9	–350.258977	30.9
14	**VI**	–350.427721	32.0	–350.257605	34.5
15	**Xa**	–350.434026	15.4	–350.264582	16.2
16	**Xb**	–350.431133	23.0	–350.261190	25.1
17	**Xc**	–350.428892	28.9	–350.258742	31.5
18	**Xd**	–350.427498	32.6	–350.257533	34.7
19	**XIa**	–350.435806	10.8	–350.266506	11.1
20	**XIb**	–350.433133	17.8	–350.263550	18.9
21	**XIc**	–350.430594	24.4	–350.260913	25.8
22	**XId**	–350.427710	32.0	–350.257800	34.0
23	**XIIa**	–350.429955	26.1	–350.260327	27.3
24	**XIIa**	–350.425771	37.1	–350.255607	39.7
25	**XIIc**	–350.427176	33.4	–350.257096	35.8
26	**XIId**	–350.425091	38.9	–350.255006	41.3

[a] B3LYP/6-31+G**//B3LYP/6-31+G**; 1 Hartree = 2625.50 kJ mol^{-1}; energie differences (not zero-point energy-corrected) between dimethyletrahydrofurans **I–VI** and **X–XII**. [b] Includes zero-point vibrational energy, thermal correction and an entropy term.

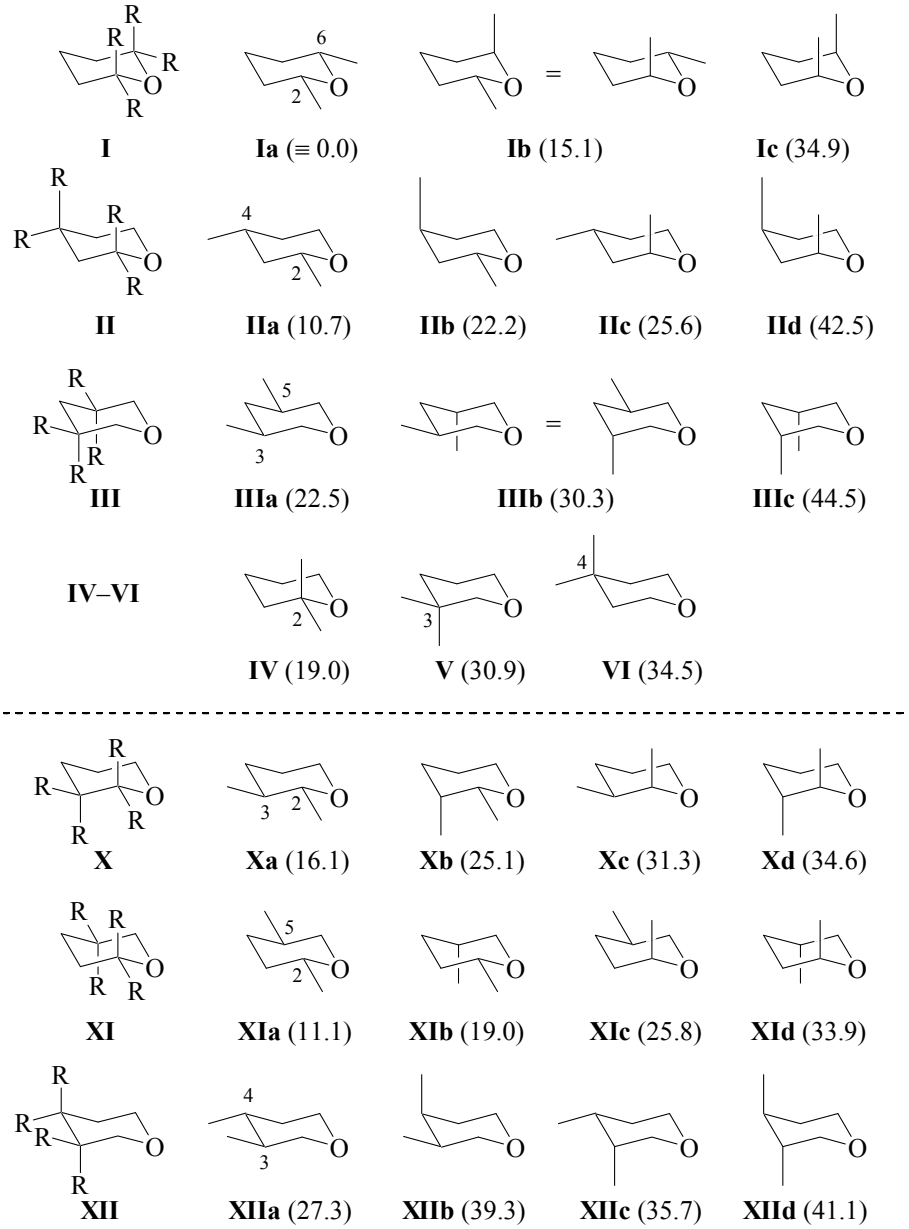
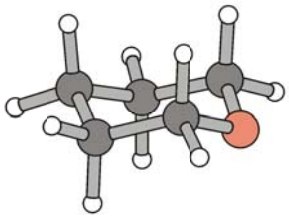


Figure B8. Structure formulae, indices, and calculated (B3LYP/6-31+G**//B3LYP/6-31+G**) $\Delta G_{298.15}$-values in kJ mol^{-1} (numbers in brackets) of dimethyltetrahydrofurans **I**–**VI** and **X**–**XII**.

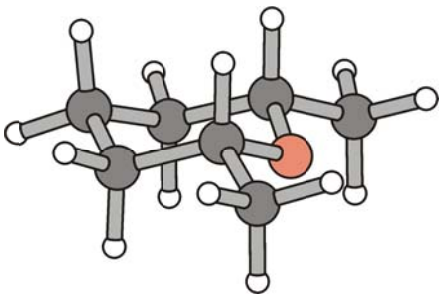
Tetrahydropyran



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.659606	-1.269843	0.000000
2	6	0	-0.020816	-0.797137	1.185102
3	6	0	-0.020816	0.731854	1.260485
4	6	0	0.624448	1.330345	0.000000
5	6	0	-0.020816	0.731854	-1.260485
6	6	0	-0.020816	-0.797137	-1.185102
7	1	0	1.015799	-1.177296	1.218739
8	1	0	-0.571512	-1.241189	2.019254
9	1	0	0.510579	1.054934	2.164789
10	1	0	-1.057766	1.081113	1.349167
11	1	0	1.700343	1.101951	0.000000
12	1	0	0.535197	2.422991	0.000000
13	1	0	0.510579	1.054934	-2.164789
14	1	0	-1.057766	1.081113	-1.349167
15	1	0	1.015799	-1.177296	-1.218739
16	1	0	-0.571512	-1.241189	-2.019254

Zero-point correction=	0.146140	(Hartree/Particle)
Thermal correction to Energy=	0.151614	
Thermal correction to Enthalpy=	0.152558	
Thermal correction to Gibbs Free Energy=	0.117534	
Sum of electronic and zero-point Energies=		-271.647423
Sum of electronic and thermal Energies=		-271.641949
Sum of electronic and thermal Enthalpies=		-271.641005
Sum of electronic and thermal Free Energies=		-271.676030

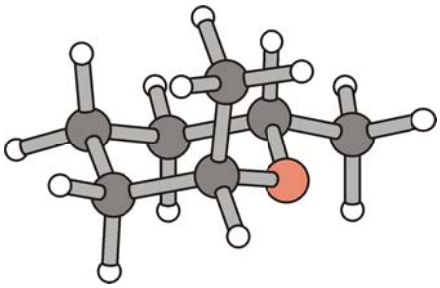
cis-2,6-Dimethyltetrahydropyran (Ia)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.000000	-0.975817	0.096202
2	6	0	1.201951	-0.320590	-0.328882
3	6	0	1.261215	1.108334	0.225954
4	6	0	0.000000	1.897139	-0.155776
5	6	0	-1.261215	1.108334	0.225954
6	6	0	-1.201951	-0.320590	-0.328882
7	1	0	1.191927	-0.268122	-1.433520
8	6	0	2.366286	-1.192437	0.119819
9	1	0	2.161340	1.610662	-0.150473
10	1	0	1.351522	1.052732	1.319481
11	1	0	0.000000	2.079932	-1.240171
12	1	0	0.000000	2.881657	0.326638
13	1	0	-2.161340	1.610662	-0.150473
14	1	0	-1.351522	1.052732	1.319481
15	1	0	-1.191927	-0.268122	-1.433520
16	6	0	-2.366286	-1.192437	0.119819
17	1	0	2.273322	-2.199973	-0.296234
18	1	0	3.317449	-0.763473	-0.213253
19	1	0	2.384015	-1.272619	1.211940
20	1	0	-3.317449	-0.763473	-0.213253
21	1	0	-2.273322	-2.199973	-0.296234
22	1	0	-2.384015	-1.272618	1.211940

Zero-point correction=	0.201385 (Hartree/Particle)
Thermal correction to Energy=	0.209776
Thermal correction to Enthalpy=	0.210720
Thermal correction to Gibbs Free Energy=	0.169170
Sum of electronic and zero-point Energies=	-350.238518
Sum of electronic and thermal Energies=	-350.230127
Sum of electronic and thermal Enthalpies=	-350.229183
Sum of electronic and thermal Free Energies=	-350.270733

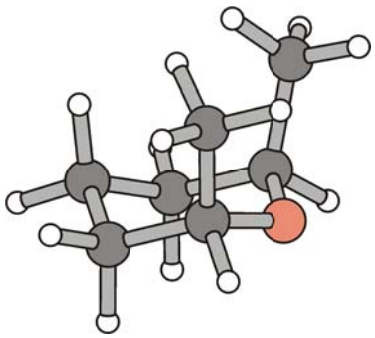
***trans*-2,6-Dimethyltetrahydropyran (Ib)**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.263880	-0.909122	-0.636261
2	6	0	-1.145891	-0.654110	-0.504570
3	6	0	-1.435598	0.854384	-0.601598
4	6	0	-0.566493	1.669264	0.368132
5	6	0	0.912552	1.301133	0.182250
6	6	0	1.117003	-0.215223	0.286556
7	6	0	-1.737663	-1.323353	0.743172
8	1	0	-1.573565	-1.150494	-1.382921
9	1	0	-2.502246	1.036935	-0.421171
10	1	0	-1.222824	1.178095	-1.628486
11	1	0	-0.867112	1.471345	1.405981
12	1	0	-0.720010	2.742030	0.201963
13	1	0	1.537263	1.806165	0.929885
14	1	0	1.256230	1.631986	-0.807766
15	1	0	0.870592	-0.533429	1.313818
16	6	0	2.540606	-0.652407	-0.031214
17	1	0	-1.407200	-0.855330	1.675516
18	1	0	-2.831597	-1.265595	0.714008
19	1	0	-1.451078	-2.379178	0.770976
20	1	0	3.248587	-0.188042	0.663839
21	1	0	2.634566	-1.739389	0.049801
22	1	0	2.810262	-0.360250	-1.051716

Zero-point correction=	0.201726	(Hartree/Particle)
Thermal correction to Energy=	0.210068	
Thermal correction to Enthalpy=	0.211012	
Thermal correction to Gibbs Free Energy=	0.169604	
Sum of electronic and zero-point Energies=		-350.232851
Sum of electronic and thermal Energies=		-350.224510
Sum of electronic and thermal Enthalpies=		-350.223566
Sum of electronic and thermal Free Energies=		-350.264974

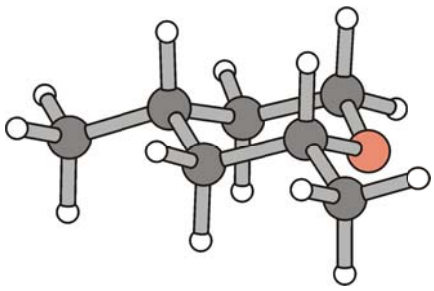
cis-2,6-Dimethyltetrahydropyran (Ic)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.245148	-0.297916	-0.503325
2	8	0	0.000006	-0.676424	-1.118661
3	6	0	-1.245143	-0.297946	-0.503321
4	6	0	-1.251018	1.185938	-0.097647
5	6	0	-0.000016	1.563673	0.706763
6	6	0	1.250990	1.185935	-0.097638
7	6	0	-1.666073	-1.244115	0.630934
8	6	0	1.666104	-1.244074	0.630928
9	1	0	-1.964598	-0.435693	-1.318939
10	1	0	-2.165997	1.404376	0.466519
11	1	0	-1.281794	1.797280	-1.008914
12	1	0	-0.000023	1.053796	1.678773
13	1	0	-0.000027	2.638219	0.923818
14	1	0	2.165967	1.404371	0.466534
15	1	0	1.281763	1.797283	-1.008902
16	1	0	1.964601	-0.435628	-1.318951
17	1	0	-1.097532	-1.088975	1.552073
18	1	0	-2.725869	-1.087471	0.864126
19	1	0	-1.535739	-2.284406	0.318402
20	1	0	1.097562	-1.088948	1.552069
21	1	0	1.535794	-2.284369	0.318397
22	1	0	2.725898	-1.087404	0.864118

Zero-point correction=	0.201985 (Hartree/Particle)
Thermal correction to Energy=	0.210268
Thermal correction to Enthalpy=	0.211212
Thermal correction to Gibbs Free Energy=	0.169967
Sum of electronic and zero-point Energies=	-350.225435
Sum of electronic and thermal Energies=	-350.217153
Sum of electronic and thermal Enthalpies=	-350.216208
Sum of electronic and thermal Free Energies=	-350.257454

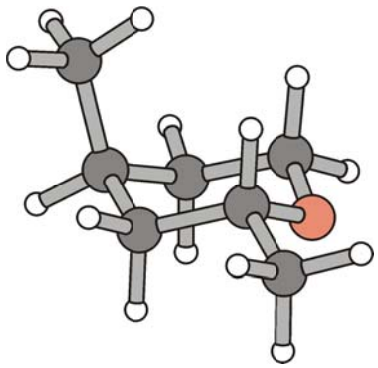
cis-2,4-Dimethyltetrahydropyran (IIa)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.253279	0.992102	-0.261044
2	6	0	1.254745	-0.315381	0.326044
3	6	0	-0.025572	-1.075805	-0.046053
4	6	0	-1.292520	-0.289049	0.335664
5	6	0	-1.190137	1.136147	-0.234760
6	6	0	0.141340	1.783812	0.148921
7	1	0	1.286564	-0.196863	1.425171
8	6	0	2.525783	-1.011512	-0.139234
9	1	0	-0.023985	-2.056479	0.448226
10	1	0	-0.019882	-1.258760	-1.130339
11	1	0	-1.315496	-0.206752	1.434357
12	6	0	-2.572326	-1.003438	-0.111983
13	1	0	-2.019666	1.757692	0.128264
14	1	0	-1.266215	1.099228	-1.330268
15	1	0	0.184655	1.941585	1.241094
16	1	0	0.269837	2.755017	-0.337623
17	1	0	3.407038	-0.427828	0.142753
18	1	0	2.606328	-2.005790	0.312920
19	1	0	2.522524	-1.123585	-1.228639
20	1	0	-2.640352	-2.007187	0.323517
21	1	0	-3.465756	-0.444958	0.190747
22	1	0	-2.599713	-1.110782	-1.203421

Zero-point correction= 0.201546 (Hartree/Particle)
Thermal correction to Energy= 0.209917
Thermal correction to Enthalpy= 0.210862
Thermal correction to Gibbs Free Energy= 0.169335
Sum of electronic and zero-point Energies= -350.234467
Sum of electronic and thermal Energies= -350.226096
Sum of electronic and thermal Enthalpies= -350.225152
Sum of electronic and thermal Free Energies= -350.266678

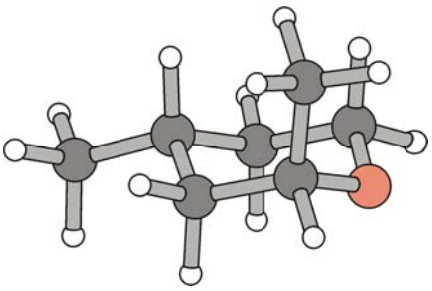
trans-2,4-Dimethyltetrahydropyran (IIb)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.000013	1.159400	-0.091078
2	6	0	-1.135062	-0.254533	-0.291130
3	6	0	-0.184999	-1.020222	0.641076
4	6	0	1.286954	-0.569499	0.500454
5	6	0	1.345146	0.972061	0.579851
6	6	0	0.321779	1.629541	-0.348758
7	1	0	-0.877265	-0.477564	-1.341603
8	6	0	-2.599708	-0.598765	-0.059871
9	1	0	-0.273126	-2.097507	0.448062
10	6	0	1.960141	-1.124587	-0.767152
11	1	0	1.841590	-0.971599	1.358981
12	1	0	2.352243	1.334131	0.333980
13	1	0	1.128311	1.290258	1.607532
14	1	0	0.289626	2.712060	-0.194534
15	1	0	0.576600	1.449595	-1.406694
16	1	0	-3.239446	-0.020298	-0.732927
17	1	0	-2.776855	-1.664501	-0.240012
18	1	0	-2.888050	-0.367217	0.971054
19	1	0	-0.519345	-0.848417	1.673142
20	1	0	1.480735	-0.774442	-1.687333
21	1	0	3.013181	-0.823519	-0.811080
22	1	0	1.926395	-2.220147	-0.776766

Zero-point correction= 0.201813 (Hartree/Particle)
Thermal correction to Energy= 0.210147
Thermal correction to Enthalpy= 0.211091
Thermal correction to Gibbs Free Energy= 0.169670
Sum of electronic and zero-point Energies= -350.230153
Sum of electronic and thermal Energies= -350.221819
Sum of electronic and thermal Enthalpies= -350.220874
Sum of electronic and thermal Free Energies= -350.262295

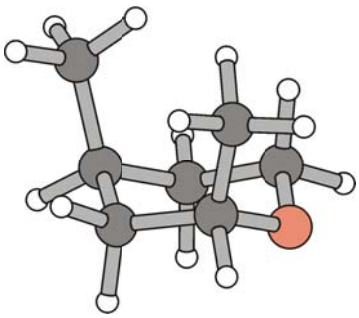
***trans*-2,4-Dimethyltetrahydropyran (IIc)**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.920085	1.272571	0.113559
2	6	0	0.565661	1.606037	0.255899
3	8	0	1.374232	0.839528	-0.636238
4	6	0	1.245421	-0.585866	-0.494405
5	6	0	-0.228377	-1.014098	-0.625062
6	6	0	-1.167492	-0.232644	0.312425
7	6	0	1.935495	-1.100945	0.775697
8	6	0	-2.635778	-0.612971	0.091550
9	1	0	1.798694	-0.976265	-1.355810
10	1	0	-0.313896	-2.093461	-0.443128
11	1	0	-0.545942	-0.838450	-1.661957
12	1	0	-0.909558	-0.481599	1.353048
13	1	0	-1.499119	1.860069	0.838722
14	1	0	-1.258994	1.567684	-0.889403
15	1	0	0.890446	1.452686	1.297672
16	1	0	0.764491	2.650718	-0.000403
17	1	0	1.423588	-0.794801	1.693100
18	1	0	1.967201	-2.196251	0.765003
19	1	0	2.963695	-0.728692	0.817891
20	1	0	-2.798684	-1.684270	0.257699
21	1	0	-3.294904	-0.063272	0.773594
22	1	0	-2.949942	-0.382827	-0.934106

Zero-point correction= 0.201852 (Hartree/Particle)
Thermal correction to Energy= 0.210188
Thermal correction to Enthalpy= 0.211132
Thermal correction to Gibbs Free Energy= 0.169717
Sum of electronic and zero-point Energies= -350.228847
Sum of electronic and thermal Energies= -350.220510
Sum of electronic and thermal Enthalpies= -350.219566
Sum of electronic and thermal Free Energies= -350.260981

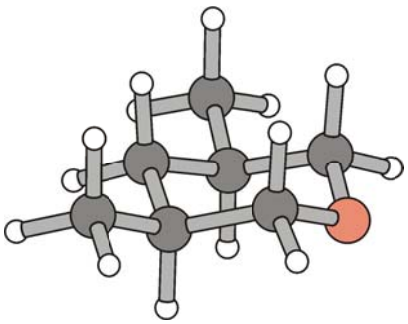
cis-2,4-Dimethyltetrahydropyran (IId)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.223896	1.196844	0.097544
2	6	0	-0.084472	1.513185	-0.627606
3	8	0	-1.221614	1.142841	0.152398
4	6	0	-1.293438	-0.255097	0.483297
5	6	0	0.008688	-0.727438	1.165212
6	6	0	1.322814	-0.298726	0.468013
7	6	0	-1.767350	-1.096682	-0.709453
8	6	0	1.733606	-1.178256	-0.726445
9	1	0	-2.089111	-0.293379	1.236204
10	1	0	-0.020004	-1.817348	1.291496
11	1	0	0.013983	-0.294813	2.173724
12	1	0	2.120838	-0.404919	1.215455
13	1	0	2.075316	1.497717	-0.527256
14	1	0	1.262576	1.802314	1.012137
15	1	0	-0.116957	1.022949	-1.612924
16	1	0	-0.188121	2.589053	-0.796108
17	1	0	-1.062768	-1.096644	-1.544543
18	1	0	-1.913714	-2.137762	-0.400006
19	1	0	-2.724389	-0.709711	-1.073085
20	1	0	1.066509	-1.071093	-1.586680
21	1	0	2.742900	-0.913773	-1.062970
22	1	0	1.743394	-2.238307	-0.448000

Zero-point correction= 0.202137 (Hartree/Particle)
Thermal correction to Energy= 0.210447
Thermal correction to Enthalpy= 0.211391
Thermal correction to Gibbs Free Energy= 0.170077
Sum of electronic and zero-point Energies= -350.222493
Sum of electronic and thermal Energies= -350.214184
Sum of electronic and thermal Enthalpies= -350.213240
Sum of electronic and thermal Free Energies= -350.254553

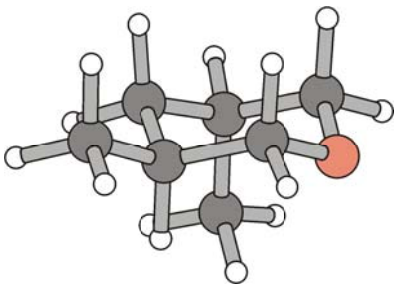
***cis*-3,5-Dimethyltetrahydropyran (IIIa)**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.831920	1.597703	0.000000
2	6	0	-0.801626	0.805370	1.183580
3	6	0	0.463209	-0.058695	1.274863
4	6	0	0.586436	-0.911849	0.000000
5	6	0	0.463209	-0.058695	-1.274863
6	6	0	-0.801626	0.805370	-1.183580
7	1	0	-1.697303	0.158291	1.219498
8	1	0	-0.860104	1.510605	2.018436
9	6	0	0.463209	-0.910970	2.548943
10	1	0	1.320925	0.628577	1.311746
11	1	0	-0.211223	-1.672235	0.000000
12	1	0	1.538487	-1.459369	0.000000
13	6	0	0.463209	-0.910970	-2.548943
14	1	0	1.320925	0.628577	-1.311746
15	1	0	-1.697303	0.158291	-1.219498
16	1	0	-0.860104	1.510605	-2.018436
17	1	0	-0.388219	-1.602836	2.562929
18	1	0	1.377744	-1.510241	2.619533
19	1	0	0.402941	-0.288080	3.449008
20	1	0	-0.388219	-1.602836	-2.562929
21	1	0	0.402941	-0.288080	-3.449008
22	1	0	1.377744	-1.510241	-2.619533

Zero-point correction= 0.201724 (Hartree/Particle)
Thermal correction to Energy= 0.210131
Thermal correction to Enthalpy= 0.211075
Thermal correction to Gibbs Free Energy= 0.169456
Sum of electronic and zero-point Energies= -350.229904
Sum of electronic and thermal Energies= -350.221497
Sum of electronic and thermal Enthalpies= -350.220552
Sum of electronic and thermal Free Energies= -350.262172

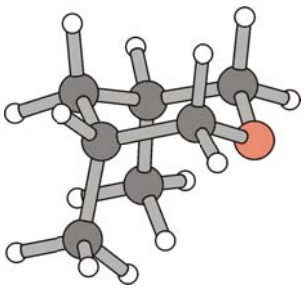
trans-3,5-Dimethyltetrahydropyran (IIIb)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.334294	0.953953	0.568288
2	8	0	-0.481758	1.574986	-0.391583
3	6	0	0.888686	1.242854	-0.185238
4	6	0	1.147550	-0.265138	-0.307126
5	6	0	0.205068	-1.019042	0.650334
6	6	0	-1.268613	-0.580139	0.497338
7	6	0	2.620956	-0.597915	-0.046469
8	6	0	-1.927543	-1.122361	-0.781019
9	1	0	1.207590	1.595508	0.813118
10	1	0	1.451785	1.803886	-0.937648
11	1	0	0.905936	-0.553071	-1.339326
12	1	0	0.529419	-0.820935	1.683232
13	1	0	0.297640	-2.102277	0.497263
14	1	0	-1.831633	-0.967361	1.359021
15	1	0	-1.053358	1.294710	1.580219
16	1	0	-2.343087	1.320058	0.353428
17	1	0	2.917733	-0.313456	0.970878
18	1	0	2.805616	-1.672291	-0.156789
19	1	0	3.281227	-0.072957	-0.746733
20	1	0	-1.851614	-2.214726	-0.828039
21	1	0	-2.991400	-0.860179	-0.811093
22	1	0	-1.462653	-0.710072	-1.681516

Zero-point correction=	0.201917 (Hartree/Particle)
Thermal correction to Energy=	0.210271
Thermal correction to Enthalpy=	0.211215
Thermal correction to Gibbs Free Energy=	0.169718
Sum of electronic and zero-point Energies=	-350.226994
Sum of electronic and thermal Energies=	-350.218640
Sum of electronic and thermal Enthalpies=	-350.217696
Sum of electronic and thermal Free Energies=	-350.259192

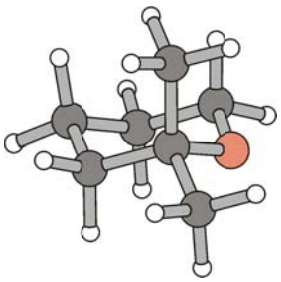
cis-3,5-Dimethyltetrahydropyran (IIIc)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.577305	0.305936	0.000000
2	6	0	0.922539	0.768794	1.179486
3	6	0	-0.504820	0.212021	1.306463
4	6	0	-1.280448	0.514730	0.000000
5	6	0	-0.504820	0.212021	-1.306463
6	6	0	0.922539	0.768794	-1.179486
7	1	0	0.897782	1.872583	1.169694
8	1	0	1.549908	0.450502	2.017998
9	1	0	-0.996892	0.777314	2.111577
10	6	0	-0.504820	-1.267118	1.726562
11	1	0	-1.523894	1.586599	0.000000
12	1	0	-2.240144	-0.017598	0.000000
13	1	0	-0.996892	0.777314	-2.111577
14	6	0	-0.504820	-1.267118	-1.726562
15	1	0	0.897782	1.872583	-1.169694
16	1	0	1.549908	0.450502	-2.017998
17	1	0	-0.102754	-1.375047	2.740838
18	1	0	0.109373	-1.881743	1.063850
19	1	0	-1.520670	-1.678224	1.726233
20	1	0	-1.520670	-1.678224	-1.726233
21	1	0	0.109373	-1.881743	-1.063850
22	1	0	-0.102754	-1.375047	-2.740838

Zero-point correction=	0.202144	(Hartree/Particle)
Thermal correction to Energy=	0.210464	
Thermal correction to Enthalpy=	0.211408	
Thermal correction to Gibbs Free Energy=	0.169954	
Sum of electronic and zero-point Energies=		-350.221603
Sum of electronic and thermal Energies=		-350.213283
Sum of electronic and thermal Enthalpies=		-350.212339
Sum of electronic and thermal Free Energies=		-350.253793

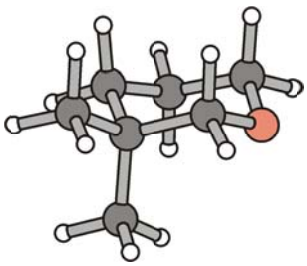
2,2-Dimethyltetrahydropyran (IV)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.168520	-1.293719	0.088555
2	8	0	-0.152115	-1.151122	-0.433717
3	6	0	-0.876810	0.031946	-0.018207
4	6	0	-0.036940	1.291556	-0.332682
5	6	0	1.400766	1.203979	0.203617
6	6	0	2.057313	-0.101443	-0.266305
7	6	0	-1.246656	-0.060124	1.473761
8	6	0	-2.149293	0.011966	-0.867488
9	1	0	-0.546757	2.176983	0.067148
10	1	0	-0.000577	1.408392	-1.423742
11	1	0	1.401199	1.241825	1.301381
12	1	0	1.978437	2.072152	-0.135038
13	1	0	3.047318	-0.232157	0.188937
14	1	0	2.198705	-0.074006	-1.354859
15	1	0	1.138749	-1.432485	1.181251
16	1	0	1.550586	-2.220481	-0.349948
17	1	0	-0.372934	-0.027511	2.130432
18	1	0	-1.899153	0.774020	1.753753
19	1	0	-1.781572	-0.995514	1.666015
20	1	0	-2.736453	-0.886668	-0.653615
21	1	0	-2.768235	0.891035	-0.658065
22	1	0	-1.893792	0.008421	-1.931415

Zero-point correction= 0.201496 (Hartree/Particle)
Thermal correction to Energy= 0.209748
Thermal correction to Enthalpy= 0.210692
Thermal correction to Gibbs Free Energy= 0.169740
Sum of electronic and zero-point Energies= -350.231732
Sum of electronic and thermal Energies= -350.223481
Sum of electronic and thermal Enthalpies= -350.222536
Sum of electronic and thermal Free Energies= -350.263489

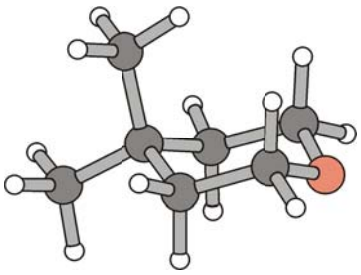
3,3-Dimethyltetrahydropyran (V)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-1.230070	-1.240103	0.224686
2	6	0	0.064651	-1.231654	-0.369757
3	6	0	0.886314	0.026579	-0.012508
4	6	0	0.042719	1.265672	-0.407711
5	6	0	-1.395004	1.196710	0.133216
6	6	0	-2.032041	-0.147983	-0.221392
7	1	0	-0.036478	-1.306222	-1.467144
8	6	0	2.197177	0.010006	-0.816398
9	6	0	1.210019	0.032072	1.494264
10	1	0	0.004059	1.324224	-1.505402
11	1	0	0.541498	2.181231	-0.064230
12	1	0	-1.999732	2.011175	-0.285723
13	1	0	-1.402872	1.320836	1.222506
14	1	0	-3.006314	-0.273657	0.259487
15	1	0	-2.176593	-0.223276	-1.313970
16	1	0	1.849559	-0.819825	1.754164
17	1	0	1.744072	0.948095	1.773566
18	1	0	0.306110	-0.038076	2.104955
19	1	0	0.565137	-2.137865	-0.012686
20	1	0	2.006362	-0.001922	-1.896144
21	1	0	2.799695	0.898498	-0.593898
22	1	0	2.803052	-0.870807	-0.571258

Zero-point correction= 0.201698 (Hartree/Particle)
Thermal correction to Energy= 0.209935
Thermal correction to Enthalpy= 0.210880
Thermal correction to Gibbs Free Energy= 0.169934
Sum of electronic and zero-point Energies= -350.227213
Sum of electronic and thermal Energies= -350.218976
Sum of electronic and thermal Enthalpies= -350.218031
Sum of electronic and thermal Free Energies= -350.258977

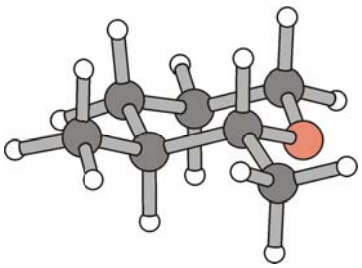
4,4-Dimethyltetrahydropyran (VI)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-2.044254	0.000000	-0.304134
2	6	0	-1.379323	1.181390	0.138803
3	6	0	0.058156	1.251279	-0.383934
4	6	0	0.896838	0.000000	-0.016246
5	6	0	0.058155	-1.251279	-0.383936
6	6	0	-1.379323	-1.181390	0.138802
7	1	0	-1.402729	1.225549	1.240458
8	6	0	1.256422	-0.000001	1.484859
9	6	0	2.203007	0.000001	-0.829928
10	1	0	0.544520	-2.159164	-0.001351
11	1	0	0.017908	-1.343967	-1.477175
12	1	0	-1.971936	-2.019035	-0.239962
13	1	0	-1.402727	-1.225549	1.240458
14	1	0	-1.971936	2.019034	-0.239962
15	1	0	0.544520	2.159163	-0.001346
16	1	0	0.017910	1.343971	-1.477173
17	1	0	0.375671	-0.000001	2.133805
18	1	0	1.851690	-0.885185	1.738350
19	1	0	1.851691	0.885182	1.738351
20	1	0	2.808455	0.885870	-0.602502
21	1	0	2.808455	-0.885869	-0.602505
22	1	0	1.998948	0.000002	-1.906899

Zero-point correction=	0.201801 (Hartree/Particle)
Thermal correction to Energy=	0.209979
Thermal correction to Enthalpy=	0.210923
Thermal correction to Gibbs Free Energy=	0.170116
Sum of electronic and zero-point Energies=	-350.225920
Sum of electronic and thermal Energies=	-350.217742
Sum of electronic and thermal Enthalpies=	-350.216798
Sum of electronic and thermal Free Energies=	-350.257605

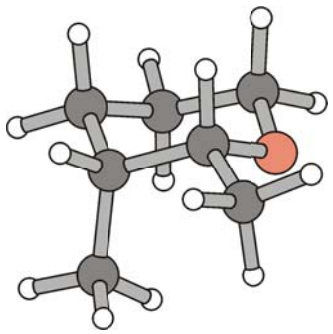
***trans*-2,3-Dimethyltetrahydropyran (Xa)**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.814853	-0.766683	0.290381
2	8	0	0.611305	-1.398586	-0.134663
3	6	0	-0.576512	-0.706604	0.275474
4	6	0	-0.605474	0.725704	-0.302105
5	6	0	0.694324	1.464407	0.074236
6	6	0	1.938206	0.642536	-0.286853
7	6	0	-1.744645	-1.584297	-0.157254
8	6	0	-1.837477	1.520607	0.152462
9	1	0	-0.567460	-0.631337	1.379807
10	1	0	-0.635802	0.623072	-1.397434
11	1	0	0.689580	1.661277	1.157441
12	1	0	0.720530	2.444133	-0.419126
13	1	0	2.849003	1.122541	0.093576
14	1	0	2.037341	0.571894	-1.377723
15	1	0	1.841997	-0.728444	1.393894
16	1	0	2.628758	-1.415721	-0.045909
17	1	0	-1.604882	-2.599566	0.224977
18	1	0	-2.694546	-1.200291	0.224991
19	1	0	-1.801489	-1.635878	-1.250097
20	1	0	-1.897567	1.563783	1.247564
21	1	0	-1.784470	2.551987	-0.214194
22	1	0	-2.771073	1.087220	-0.218501

Zero-point correction=	0.201656 (Hartree/Particle)
Thermal correction to Energy=	0.210023
Thermal correction to Enthalpy=	0.210968
Thermal correction to Gibbs Free Energy=	0.169444
Sum of electronic and zero-point Energies=	-350.232370
Sum of electronic and thermal Energies=	-350.224003
Sum of electronic and thermal Enthalpies=	-350.223059
Sum of electronic and thermal Free Energies=	-350.264582

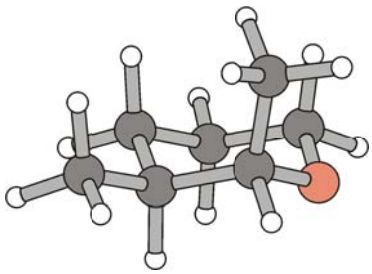
cis-2,3-Dimethyltetrahydropyran (Xb)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.942032	0.035820	-0.212736
2	6	0	1.298116	-1.351545	-0.210676
3	8	0	-0.097519	-1.285361	-0.497002
4	6	0	-0.825868	-0.501399	0.457987
5	6	0	-0.336306	0.966798	0.459581
6	6	0	1.183857	0.971572	0.742493
7	6	0	-2.305367	-0.689564	0.150201
8	6	0	-0.691849	1.730492	-0.826895
9	1	0	-0.620200	-0.914891	1.462735
10	1	0	-0.837033	1.467877	1.300860
11	1	0	1.352986	0.636090	1.775864
12	1	0	1.578189	1.993074	0.676974
13	1	0	2.995322	-0.047423	0.084210
14	1	0	1.927635	0.436526	-1.233370
15	1	0	1.447033	-1.836025	0.770741
16	1	0	1.731770	-2.000190	-0.977462
17	1	0	-2.582233	-1.741457	0.266266
18	1	0	-2.919378	-0.090976	0.832093
19	1	0	-2.533370	-0.391967	-0.877177
20	1	0	-1.773558	1.858488	-0.932995
21	1	0	-0.243658	2.730543	-0.813102
22	1	0	-0.331044	1.210177	-1.719349

Zero-point correction=	0.201963 (Hartree/Particle)
Thermal correction to Energy=	0.210244
Thermal correction to Enthalpy=	0.211188
Thermal correction to Gibbs Free Energy=	0.169943
Sum of electronic and zero-point Energies=	-350.229170
Sum of electronic and thermal Energies=	-350.220889
Sum of electronic and thermal Enthalpies=	-350.219945
Sum of electronic and thermal Free Energies=	-350.261190

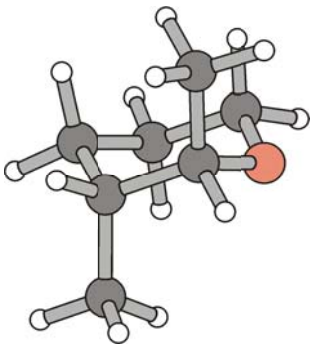
cis-2,3-Dimethyltetrahydropyran (Xc)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.893461	0.234485	0.106840
2	8	0	-1.049390	0.974562	-0.775486
3	6	0	0.353936	0.920053	-0.458508
4	6	0	0.841313	-0.549097	-0.447224
5	6	0	-0.027931	-1.408474	0.489215
6	6	0	-1.515853	-1.246721	0.145501
7	6	0	0.677595	1.732747	0.802776
8	6	0	2.337907	-0.682131	-0.139479
9	1	0	0.823912	1.426785	-1.309775
10	1	0	0.673822	-0.917562	-1.469838
11	1	0	0.146525	-1.116195	1.534738
12	1	0	0.273445	-2.460652	0.409703
13	1	0	-2.148011	-1.769354	0.874813
14	1	0	-1.717207	-1.690739	-0.838130
15	1	0	-1.858677	0.662573	1.121562
16	1	0	-2.907859	0.378028	-0.276709
17	1	0	0.324658	1.257420	1.723166
18	1	0	1.757927	1.879024	0.899088
19	1	0	0.208454	2.718447	0.726616
20	1	0	2.566120	-0.409358	0.896995
21	1	0	2.668864	-1.716182	-0.287654
22	1	0	2.942111	-0.043901	-0.795414

Zero-point correction= 0.202114 (Hartree/Particle)
Thermal correction to Energy= 0.210379
Thermal correction to Enthalpy= 0.211324
Thermal correction to Gibbs Free Energy= 0.170150
Sum of electronic and zero-point Energies= -350.226777
Sum of electronic and thermal Energies= -350.218512
Sum of electronic and thermal Enthalpies= -350.217568
Sum of electronic and thermal Free Energies= -350.258742

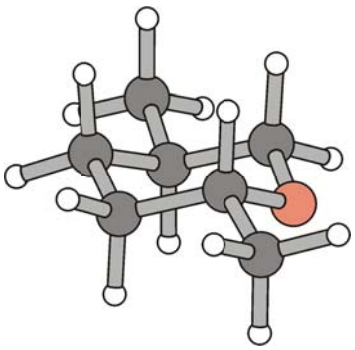
trans-2,3-Dimethyltetrahydropyran (Xd)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.696646	-0.849234	-0.315427
2	8	0	-0.874257	0.339583	-1.107363
3	6	0	-0.711449	1.567585	-0.396348
4	6	0	0.675787	1.675473	0.237609
5	6	0	0.949719	0.447786	1.120619
6	6	0	0.699636	-0.871614	0.354533
7	6	0	1.802951	-1.164280	-0.675961
8	6	0	-1.858508	-1.066522	0.662724
9	1	0	-1.491514	1.671419	0.374934
10	1	0	-0.875369	2.354253	-1.138670
11	1	0	0.739300	2.597892	0.828849
12	1	0	1.428417	1.751299	-0.556240
13	1	0	0.297159	0.489494	2.002988
14	1	0	1.979246	0.466210	1.498734
15	1	0	0.698445	-1.693567	1.084191
16	1	0	-0.736072	-1.651881	-1.061129
17	1	0	2.793102	-1.151997	-0.206015
18	1	0	1.802027	-0.430160	-1.487388
19	1	0	1.660664	-2.152784	-1.127462
20	1	0	-1.865839	-0.345574	1.485884
21	1	0	-1.792251	-2.068060	1.102152
22	1	0	-2.812192	-0.988373	0.131581

```
Zero-point correction=                           0.202037 (Hartree/Particle)
Thermal correction to Energy=                    0.210360
Thermal correction to Enthalpy=                  0.211304
Thermal correction to Gibbs Free Energy=         0.169966
Sum of electronic and zero-point Energies=                -350.225461
Sum of electronic and thermal Energies=                   -350.217138
Sum of electronic and thermal Enthalpies=                 -350.216194
Sum of electronic and thermal Free Energies=              -350.257533
```

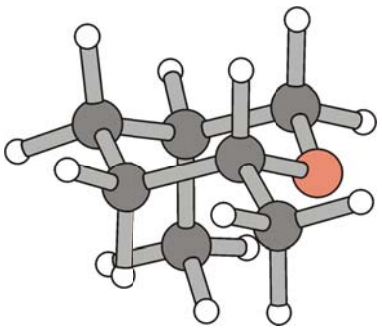
***trans*-2,5-Dimethyltetrahydropyran (XIa)**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.743409	-1.156133	-0.212406
2	6	0	-1.414923	-0.012954	0.333012
3	6	0	-0.748022	1.280600	-0.152368
4	6	0	0.756042	1.278659	0.160614
5	6	0	1.427753	-0.005848	-0.354441
6	6	0	0.633824	-1.220112	0.145442
7	1	0	-1.331004	-0.060033	1.434872
8	6	0	-2.879852	-0.125101	-0.063838
9	1	0	-1.238308	2.143441	0.316056
10	1	0	-0.904810	1.366202	-1.236278
11	1	0	0.902728	1.344810	1.249656
12	1	0	1.240811	2.162236	-0.273401
13	6	0	2.902220	-0.099604	0.052824
14	1	0	1.364343	-0.009067	-1.452474
15	1	0	0.728857	-1.298394	1.244051
16	1	0	1.014027	-2.148496	-0.292446
17	1	0	-3.303901	-1.066377	0.298032
18	1	0	-3.456804	0.703605	0.360344
19	1	0	-2.982781	-0.099000	-1.153863
20	1	0	3.011613	-0.115074	1.144480
21	1	0	3.371551	-1.007796	-0.343058
22	1	0	3.468696	0.759169	-0.324194

Zero-point correction= 0.201547 (Hartree/Particle)
Thermal correction to Energy= 0.209950
Thermal correction to Enthalpy= 0.210894
Thermal correction to Gibbs Free Energy= 0.169301
Sum of electronic and zero-point Energies= -350.234260
Sum of electronic and thermal Energies= -350.225857
Sum of electronic and thermal Enthalpies= -350.224913
Sum of electronic and thermal Free Energies= -350.266506

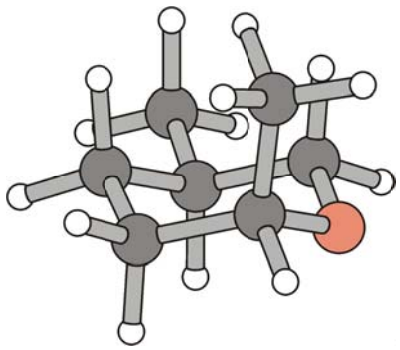
cis-2,5-Dimethyltetrahydropyran (XIb)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.574822	-1.154717	0.037322
2	6	0	1.347096	0.014737	-0.267263
3	6	0	0.560498	1.282378	0.091733
4	6	0	-0.820048	1.286308	-0.586338
5	6	0	-1.585424	-0.031203	-0.333618
6	6	0	-0.657406	-1.207035	-0.678601
7	1	0	1.544290	0.019001	-1.355830
8	6	0	2.666146	-0.112501	0.480673
9	1	0	1.134729	2.167046	-0.211465
10	1	0	0.453357	1.329317	1.182962
11	1	0	-0.682504	1.413274	-1.669635
12	1	0	-1.412765	2.143761	-0.244555
13	1	0	-2.434545	-0.074827	-1.031092
14	6	0	-2.139323	-0.138758	1.095801
15	1	0	-0.450080	-1.213603	-1.762978
16	1	0	-1.114839	-2.165950	-0.414947
17	1	0	3.182544	-1.033261	0.193646
18	1	0	3.318157	0.738281	0.255499
19	1	0	2.491226	-0.140004	1.561480
20	1	0	-2.783865	0.715797	1.331575
21	1	0	-2.736673	-1.050198	1.213870
22	1	0	-1.336839	-0.174449	1.838579

Zero-point correction= 0.201771 (Hartree/Particle)
Thermal correction to Energy= 0.210108
Thermal correction to Enthalpy= 0.211052
Thermal correction to Gibbs Free Energy= 0.169583
Sum of electronic and zero-point Energies= -350.231361
Sum of electronic and thermal Energies= -350.223024
Sum of electronic and thermal Enthalpies= -350.222080
Sum of electronic and thermal Free Energies= -350.263550

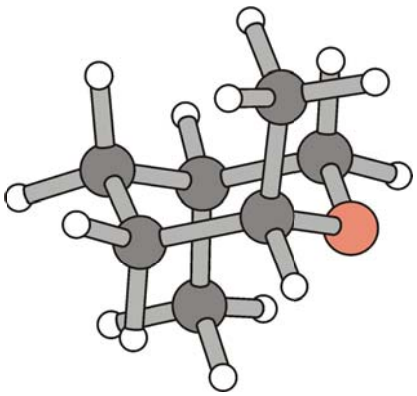
cis-2,5-Dimethyltetrahydropyran (XIc)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.753470	-1.129223	-0.744893
2	6	0	-1.570548	-0.011613	-0.353208
3	6	0	-0.797924	1.307594	-0.531988
4	6	0	0.575910	1.271928	0.156192
5	6	0	1.372526	0.032283	-0.284945
6	6	0	0.506555	-1.217769	-0.081544
7	6	0	-2.169280	-0.199926	1.046760
8	1	0	-2.394232	-0.036625	-1.075275
9	1	0	-1.401769	2.142283	-0.154691
10	1	0	-0.653686	1.476155	-1.606705
11	1	0	0.455539	1.252459	1.249081
12	1	0	1.136760	2.186252	-0.075419
13	6	0	2.712907	-0.096266	0.446503
14	1	0	1.566947	0.119541	-1.364229
15	1	0	0.365407	-1.399876	0.997170
16	1	0	0.992190	-2.103453	-0.503439
17	1	0	-1.420173	-0.140577	1.842203
18	1	0	-2.918118	0.576496	1.239575
19	1	0	-2.661469	-1.175050	1.113531
20	1	0	2.565840	-0.197741	1.529133
21	1	0	3.276066	-0.971730	0.102545
22	1	0	3.337587	0.788262	0.279042

Zero-point correction= 0.201873 (Hartree/Particle)
Thermal correction to Energy= 0.210231
Thermal correction to Enthalpy= 0.211175
Thermal correction to Gibbs Free Energy= 0.169681
Sum of electronic and zero-point Energies= -350.228722
Sum of electronic and thermal Energies= -350.220363
Sum of electronic and thermal Enthalpies= -350.219419
Sum of electronic and thermal Free Energies= -350.260913

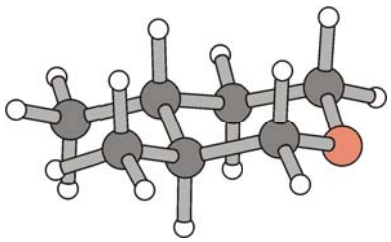
trans-2,5-Dimethyltetrahydropyran (XId)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.467545	-1.151822	-0.626562
2	6	0	-1.320321	0.007909	-0.623561
3	6	0	-0.479257	1.293722	-0.517888
4	6	0	0.519528	1.237521	0.650976
5	6	0	1.363579	-0.055368	0.611742
6	6	0	0.409798	-1.255187	0.495551
7	6	0	-2.432222	-0.097990	0.428485
8	1	0	-1.792230	-0.024128	-1.611884
9	1	0	-1.143849	2.160242	-0.412476
10	1	0	0.065080	1.427450	-1.459831
11	1	0	-0.023663	1.279873	1.604506
12	1	0	1.171947	2.119183	0.628945
13	1	0	1.889093	-0.152990	1.572780
14	6	0	2.418070	-0.050225	-0.506310
15	1	0	-0.169595	-1.363641	1.425912
16	1	0	0.963898	-2.186514	0.340747
17	1	0	-2.059357	-0.015537	1.454060
18	1	0	-3.163623	0.703965	0.278059
19	1	0	-2.950007	-1.057000	0.329192
20	1	0	3.072150	0.825577	-0.425094
21	1	0	3.048918	-0.944666	-0.448174
22	1	0	1.956545	-0.039526	-1.498215

Zero-point correction= 0.202051 (Hartree/Particle)
Thermal correction to Energy= 0.210373
Thermal correction to Enthalpy= 0.211318
Thermal correction to Gibbs Free Energy= 0.169910
Sum of electronic and zero-point Energies= -350.225659
Sum of electronic and thermal Energies= -350.217337
Sum of electronic and thermal Enthalpies= -350.216393
Sum of electronic and thermal Free Energies= -350.257800

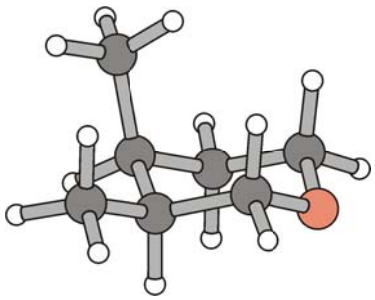
***trans*-3,4-Dimethyltetrahydropyran (XIIa)**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.864707	-0.694797	-0.349782
2	6	0	0.707146	-1.416509	0.054700
3	6	0	-0.605921	-0.700769	-0.302314
4	6	0	-0.603098	0.728519	0.291801
5	6	0	0.712679	1.439481	-0.080810
6	6	0	1.932665	0.588203	0.266603
7	1	0	0.745392	-1.596273	1.144973
8	1	0	0.767628	-2.386694	-0.448054
9	6	0	-1.800224	-1.551972	0.151539
10	1	0	-0.636055	-0.608281	-1.398761
11	1	0	-0.627234	0.624805	1.389673
12	6	0	-1.816879	1.566278	-0.133179
13	1	0	0.779920	2.405838	0.436763
14	1	0	0.721760	1.649419	-1.159249
15	1	0	2.013370	0.466310	1.361396
16	1	0	2.858421	1.047182	-0.092058
17	1	0	-1.839524	-1.626870	1.245661
18	1	0	-2.752045	-1.134162	-0.188308
19	1	0	-1.729668	-2.570265	-0.248547
20	1	0	-2.760304	1.134282	0.214223
21	1	0	-1.749144	2.580795	0.276367
22	1	0	-1.868386	1.652908	-1.225859

Zero-point correction=	0.201860 (Hartree/Particle)
Thermal correction to Energy=	0.210223
Thermal correction to Enthalpy=	0.211167
Thermal correction to Gibbs Free Energy=	0.169627
Sum of electronic and zero-point Energies=	-350.228095
Sum of electronic and thermal Energies=	-350.219732
Sum of electronic and thermal Enthalpies=	-350.218787
Sum of electronic and thermal Free Energies=	-350.260327

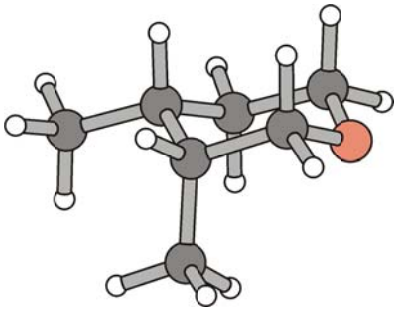
cis-3,4-Dimethyltetrahydropyran (XIIb)



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	1.403073	-1.322372	0.119844
2	6	0	0.017006	-1.381871	0.448641
3	6	0	-0.840739	-0.504050	-0.475120
4	6	0	-0.339664	0.966461	-0.461024
5	6	0	1.184661	0.963904	-0.719276
6	6	0	1.923005	0.002647	0.215196
7	1	0	-0.127657	-1.092237	1.504079
8	1	0	-0.267646	-2.434273	0.351809
9	6	0	-2.333217	-0.661861	-0.158838
10	1	0	-0.671425	-0.879214	-1.494889
11	6	0	-0.708192	1.751473	0.811500
12	1	0	-0.821419	1.481869	-1.304341
13	1	0	1.595846	1.975687	-0.605261
14	1	0	1.377329	0.650959	-1.753410
15	1	0	1.864698	0.346810	1.261412
16	1	0	2.980993	-0.071247	-0.052376
17	1	0	-2.561625	-0.411631	0.883224
18	1	0	-2.941951	-0.011866	-0.797921
19	1	0	-2.660434	-1.693982	-0.328791
20	1	0	-0.310711	1.292569	1.722878
21	1	0	-0.305218	2.769201	0.756387
22	1	0	-1.792527	1.836110	0.931975

Zero-point correction= 0.202183 (Hartree/Particle)
Thermal correction to Energy= 0.210466
Thermal correction to Enthalpy= 0.211410
Thermal correction to Gibbs Free Energy= 0.170164
Sum of electronic and zero-point Energies= -350.223588
Sum of electronic and thermal Energies= -350.215306
Sum of electronic and thermal Enthalpies= -350.214362
Sum of electronic and thermal Free Energies= -350.255607

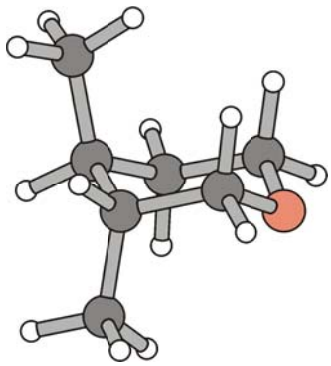
***cis*-3,4-Dimethyltetrahydropyran (XIIc)**



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.488642	-1.223082	0.179479
2	8	0	1.885655	0.145585	0.225597
3	6	0	1.169323	0.939221	-0.718157
4	6	0	-0.344407	0.950495	-0.443303
5	6	0	-0.855679	-0.516411	-0.463011
6	6	0	-0.003370	-1.392022	0.475614
7	6	0	-0.668731	1.726469	0.844163
8	6	0	-2.355996	-0.656309	-0.179222
9	1	0	1.362655	0.558832	-1.736629
10	1	0	1.592837	1.945718	-0.644775
11	1	0	-0.818566	1.479390	-1.284182
12	1	0	-0.682068	-0.883206	-1.487554
13	1	0	-0.280118	-2.448711	0.360901
14	1	0	-0.197083	-1.123902	1.522078
15	1	0	1.724797	-1.638158	-0.816590
16	1	0	2.106990	-1.741576	0.917825
17	1	0	-0.294673	2.753971	0.769578
18	1	0	-1.746649	1.782750	1.023583
19	1	0	-0.198917	1.272300	1.721602
20	1	0	-2.947858	-0.009901	-0.838301
21	1	0	-2.684960	-1.689225	-0.341436
22	1	0	-2.600315	-0.393124	0.855748

Zero-point correction=	0.202111	(Hartree/Particle)
Thermal correction to Energy=	0.210384	
Thermal correction to Enthalpy=	0.211328	
Thermal correction to Gibbs Free Energy=	0.170080	
Sum of electronic and zero-point Energies=		-350.225064
Sum of electronic and thermal Energies=		-350.216792
Sum of electronic and thermal Enthalpies=		-350.215848
Sum of electronic and thermal Free Energies=		-350.257096

trans-3,4-Dimethyltetrahydropyran (XIId)

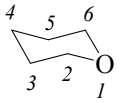


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.803973	1.566483	-0.265702
2	6	0	-0.942057	0.408408	-1.087181
3	6	0	-0.661939	-0.893749	-0.316202
4	6	0	0.745930	-0.837584	0.343035
5	6	0	0.927019	0.503379	1.093189
6	6	0	0.526156	1.703800	0.232228
7	1	0	-0.269223	0.495874	-1.956483
8	1	0	-1.971434	0.425770	-1.458602
9	1	0	-0.658459	-1.708762	-1.055201
10	6	0	-1.775047	-1.187683	0.702721
11	6	0	1.876221	-1.094676	-0.669323
12	1	0	0.794932	-1.644723	1.087016
13	1	0	1.969021	0.616954	1.420277
14	1	0	0.308015	0.507568	1.998135
15	1	0	1.221912	1.833843	-0.613991
16	1	0	0.535662	2.628347	0.816635
17	1	0	-2.742679	-1.299832	0.200220
18	1	0	-1.572288	-2.116522	1.247884
19	1	0	-1.877347	-0.379288	1.432981
20	1	0	1.913852	-0.338131	-1.460306
21	1	0	2.851881	-1.094689	-0.169831
22	1	0	1.750243	-2.069638	-1.153921

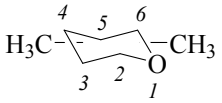
Zero-point correction=	0.202150 (Hartree/Particle)
Thermal correction to Energy=	0.210446
Thermal correction to Enthalpy=	0.211390
Thermal correction to Gibbs Free Energy=	0.170084
Sum of electronic and zero-point Energies=	-350.222941
Sum of electronic and thermal Energies=	-350.214645
Sum of electronic and thermal Enthalpies=	-350.213701
Sum of electronic and thermal Free Energies=	-350.255006

B10 Calculated Bond- and Torsion Angles of Tetrahydropyrans

Table B6. Bond angles ϕ_i in equlibrium structures of tetrahydropyran (thp) and dimethyltetrahydropyrans **I–III** (B3LYP/6-31+G**)



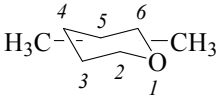
thp



I–III

entry	compound	ϕ_1 = 6–1–2	ϕ_2 = 1–2–3	ϕ_3 = 2–3–4	ϕ_4 = 3–4–5	ϕ_5 = 4–5–6	ϕ_6 = 5–6–1	$\Sigma\phi_i$
1	$C_5H_{10}O$ (thp)	112.31°	111.83°	110.39°	110.15°	110.39°	111.83°	666.91°
2	**Ia**	113.97°	110.54°	110.90°	110.42°	110.90°	110.54°	667.27°
3	**Ib**	115.96°	110.64°	111.94°	109.96°	110.93°	110.79°	670.22°
4	**Ic**	119.76°	111.69°	111.87°	109.22°	111.87°	111.69°	676.10°
5	**IIa**	112.94°	110.60°	111.91°	109.07°	110.93°	111.83°	667.28°
6	**IIb**	112.77°	110.40°	112.86°	108.80°	111.86°	111.62°	668.31°
7	**IIc**	114.83°	110.66°	113.00°	108.65°	110.95°	112.03°	670.12°
8	**IId**	114.68°	110.91°	115.61°	108.78°	111.66°	111.64°	673.28°
9	**IIIa**	112.36°	112.34°	109.20°	111.87°	109.20°	112.34°	667.31°
10	**IIIb**	112.08°	112.31°	109.16°	112.51°	108.64°	112.21°	666.91°
11	**IIIc**	111.58°	112.15°	108.93°	114.98°	108.93°	112.15°	668.72°

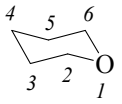
Table B7. Bond angles ϕ_i in equlibrium structures of dimethyltetrahydropyrans **IV**–**VI** and **X**–**XII** (B3LYP/6-31+G**)



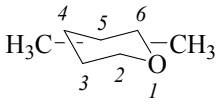
IV–**VI** and **X**–**XII**

entry	compound	ϕ_1 = 6–1–2	ϕ_2 = 1–2–3	ϕ_3 = 2–3–4	ϕ_4 = 3–4–5	ϕ_5 = 4–5–6	ϕ_6 = 5–6–1	$\Sigma\phi_i$
1	**IV**	116.08°	109.59°	113.00°	109.98°	110.09°	112.03°	670.79°
2	**V**	112.09°	113.06°	107.62°	112.54°	110.32°	111.49°	667.11°
3	**VI**	111.86°	111.68°	112.96°	107.60°	112.96°	111.68°	668.74°
4	**Xa**	113.60°	110.85°	109.71°	111.68°	109.86°	111.39°	667.09°
5	**Xb**	112.87°	111.01°	108.31°	111.67°	110.10°	111.61°	665.59°
6	**Xc**	114.87°	110.15°	110.88°	110.61°	110.30°	111.82°	668.63°
7	**Xd**	114.97°	111.17°	110.35°	111.60°	110.09°	111.75°	669.93°
8	**XIa**	113.15°	110.39°	111.10°	111.12°	109,01°	112.51°	667.28°
9	**XIb**	112.87°	110.36°	111.04°	111.75°	108.46°	112.39°	666.89°
10	**XIc**	115.04°	110.43°	112.14°	110.68°	109.05°	112.72°	670.06°
11	**XId**	114.87°	110.44°	112.10°	111.47°	108.44°	112.59°	669.91°
12	**XIIa**	111.87°	113.12°	109.83°	109.56°	111.70°	111.42°	667.50°
13	**XIIa**	112.19°	112.35°	110.82°	108.36°	112.01°	111.52°	667.24°
14	**XIIc**	111.90°	112.34°	108.34°	110.29°	111.01°	111.79°	665.67°
15	**XIId**	111.67°	112.48°	110.27°	110.04°	112.10°	111.40°	667.86°

Table B8. Torsion angles ω_{ij} in equlibrium structures of tetrahydropyran (thp) and dimethyltetrahydropyrans **I–III** (B3LYP/6-31+G**)



thp

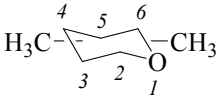


I–III

entry	compound	ω_{23} = 1–2–3–4	ϕ_{34} = 2–3–4–5	ϕ_{45} = 3–4–5–6	ϕ_{56} = 4–5–6–1	ϕ_{61} = 5–6–1–2	ϕ_{12} = 6–1–2–3	$\Sigma\lvert\omega_{ij}\rvert$ [a]
1	$C_5H_{10}O$ (thp)	–55.44°	51.38°	–51.38°	55.44°	–59.87°	59.87°	333.38°
2	**Ia**	–54.71°	51.52°	–51.52°	54.71°	–59.93°	59.93°	332.32°
3	**Ib**	–52.02°	52.05°	–53.02°	54.62°	–57.22°	55.58°	324.51°
4	**Ic**	–50.02°	55.09°	–55.09°	50.01°	–47.35°	47.35°	304.91°
5	**IIa**	–55.11°	51.45°	–51.09°	55.69°	–60.00°	59.08°	332.42°
6	**IIb**	–54.64°	49.35°	–49.01°	55.25°	–60.78°	59.84°	328.87°
7	**IIc**	–52.34°	51.75°	–52.43°	55.71°	–57.55°	54.93°	324.71°
8	**IId**	–47.47°	45.77°	–49.26°	57.25°	–60.07°	53.91°	313.73°
9	**IIIa**	–54.82°	51.13°	–51.13°	54.82°	–60.14°	60.14°	332.18°
10	**IIIb**	–54.39°	50.27°	–50.57°	55.21°	–61.52°	60.95°	332.91°
11	**IIIc**	–53.07°	45.52°	–45.52°	53.07°	–63.89°	63.89°	324.96°

[a] $\Sigma\lvert\omega_{ij}\rvert$ is the sum of absolute torsion angle-values ω_{ij} for endocyclic substituents attached to ring atoms *i* and *j*.

Table B9. Bond angles in equlibrium structures of dimethyltetrahydropyrans **IV–VI** and **X–XII** (B3LYP/6-31+G**)



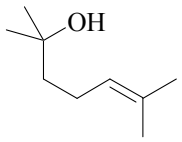
IV–VI and **X–XII**

entry	compound	ω_{23} = 1–2–3–4	ϕ_{34} = 2–3–4–5	ϕ_{45} = 3–4–5–6	ϕ_{56} = 4–5–6–1	ϕ_{61} = 5–6–1–2	ϕ_{12} = 6–1–2–3	$\Sigma\lvert\omega_{ij}\rvert$ [a]
1	**I**	–51.02°	52.07°	–52.63°	55.14°	–57.73°	54.27°	321.86°
2	**II**	–55.08°	49.77°	–50.58°	54.35°	–60.49°	62.06°	332.34°
3	**III**	–55.33°	48.50°	–48.50°	55.33°	–59.98°	59.98°	327.62°
4	**IVa**	–53.99°	51.16°	–51.56°	55.09°	–60.82°	60.13°	332.75°
5	**IVb**	–56.56°	52.41°	–51.49°	53.98°	–60.26°	61.90°	336.60°
6	**IVc**	–53.80°	52.52°	–52.14°	54.24°	–58.56°	57.70°	328.96°
7	**IVd**	–52.03°	50.98°	–51.89°	54.40°	–58.64°	57.19°	523.13°
8	**VIa**	–54.52°	51.81°	–50.87°	55.05°	–60.74°	59.31°	332.30°
9	**VIb**	–54.14°	51.01°	–50.35°	55.41°	–62.07°	60.12°	333.10°
10	**VIc**	–51.93°	52.25°	–52.24°	55.00°	–58.25°	55.26°	324.94°
11	**VId**	–51.22°	51.23°	–51.67°	55.37°	–59.67°	55.96°	325.12°
12	**IXa**	–55.19°	49.84°	–51.12°	55.77°	–59.50°	60.19°	331.61°
13	**IXa**	–55.79°	50.62°	–51.21°	55.86°	–59.25°	59.81°	332.51°
14	**IXc**	–57.53°	51.96°	–51.34°	54.38°	–59.40°	62.00°	336.61°
15	**IXd**	–55.37°	48.16°	–48.56°	54.65°	–60.79°	61.98°	329.51°

[a] $\Sigma\lvert\omega_{ij}\rvert$ is the sum of absolute torsion angle-values ω_{ij} for endocyclic substituents attached to ring atoms *i* and *j*.

B11 Calculated Energies and Coordinates of Compounds Associated with the 2,6-Dimethylhept-5-en-2-ol-Isomerization

B11.1 2,6-Dimethylhept-5-en-2-ol (VII)



VII

B11.1.1 B3LYP/6-31+G**// B3LYP/6-31+G**-coordinates and –energies

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.199096	-0.548273	1.150178
2	6	0	2.244747	-0.016663	0.069508
3	8	0	2.623414	-0.564061	-1.212849
4	6	0	0.791796	-0.423454	0.409326
5	6	0	-0.283475	0.030680	-0.597635
6	6	0	-1.616259	-0.619438	-0.333157
7	6	0	-2.784211	-0.043617	0.002704
8	6	0	-2.996166	1.440720	0.184662
9	6	0	2.407017	1.497839	-0.088074
10	6	0	-4.024349	-0.879377	0.223772
11	1	0	4.235367	-0.313025	0.888249
12	1	0	2.978096	-0.105232	2.127450
13	1	0	3.108477	-1.637238	1.251570
14	1	0	0.761962	-1.520730	0.490552
15	1	0	0.539590	-0.042886	1.407888
16	1	0	-0.370320	1.120607	-0.581153
17	1	0	0.057121	-0.238331	-1.606480
18	1	0	-1.612140	-1.707562	-0.427665
19	1	0	-4.826367	-0.584733	-0.466720
20	1	0	-3.828378	-1.946044	0.080400
21	1	0	-4.419584	-0.738215	1.238990
22	1	0	-3.746474	1.813283	-0.525738
23	1	0	-3.387216	1.652860	1.188738
24	1	0	-2.086417	2.028381	0.048150
25	1	0	1.816544	1.867576	-0.930187
26	1	0	2.086785	2.018265	0.820631
27	1	0	3.455802	1.744201	-0.279395
28	1	0	2.620666	-1.529203	-1.150197

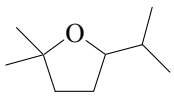
Zero-point correction= 0.253287 (Hartree/Particle)
Thermal correction to Energy= 0.266488
Thermal correction to Enthalpy= 0.267432
Thermal correction to Gibbs Free Energy= 0.213673
Sum of electronic and zero-point Energies= -428.803423
Sum of electronic and thermal Energies= -428.790222
Sum of electronic and thermal Enthalpies= -428.789278
Sum of electronic and thermal Free Energies= -428.843037

B11.1.2 MP2/6-31+G**// MP2/6-31+G**-coordinates and –energies

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.026291	-0.148461	1.349635
2	6	0	2.170310	-0.004542	0.097152
3	6	0	0.704877	-0.302382	0.427969
4	6	0	-0.267903	-0.174049	-0.747277
5	6	0	-1.618041	-0.723166	-0.393921
6	6	0	-2.704369	-0.027829	-0.002201
7	6	0	-3.988840	-0.728601	0.343701
8	6	0	-2.753440	1.468873	0.127426
9	6	0	2.353750	1.370090	-0.521809
10	8	0	2.641041	-0.923048	-0.912658
11	1	0	4.075832	0.000861	1.100510
12	1	0	2.735737	0.582007	2.104761
13	1	0	2.908909	-1.144025	1.781635
14	1	0	0.650827	-1.322013	0.826364
15	1	0	0.380661	0.358084	1.237897
16	1	0	-0.345462	0.868654	-1.051717
17	1	0	0.139101	-0.721489	-1.599485
18	1	0	-1.706296	-1.806347	-0.428307
19	1	0	-4.802879	-0.379637	-0.294905
20	1	0	-3.899486	-1.807155	0.226465
21	1	0	-4.280478	-0.517046	1.374434
22	1	0	-3.509797	1.884721	-0.541316
23	1	0	-3.041370	1.747917	1.142912
24	1	0	-1.802914	1.945638	-0.095548
25	1	0	1.849649	1.426062	-1.483666
26	1	0	1.950800	2.140455	0.135796
27	1	0	3.413369	1.563007	-0.681425
28	1	0	2.619664	-1.814901	-0.537181

Zero-point correction=	0.259677 (Hartree/Particle)	
Thermal correction to Energy=	0.272780	
Thermal correction to Enthalpy=	0.273724	
Thermal correction to Gibbs Free Energy=	0.219695	
Sum of electronic and zero-point Energies=		-427.459697
Sum of electronic and thermal Energies=		-427.446593
Sum of electronic and thermal Enthalpies=		-427.445649
Sum of electronic and thermal Free Energies=		-427.499679

B11.2 2,2-Dimethyl-5-(prop-2-yl)-tetrahydrofuran (VIII)



VIII

B11.2.1 B3LYP/6-31+G**// B3LYP/6-31+G**-coordinates and –energies

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.370803	-0.743428	0.026225
2	6	0	-1.685728	-0.124776	0.010852
3	6	0	-1.421730	1.369472	-0.314781
4	6	0	0.063795	1.560793	0.018785
5	6	0	0.650876	0.193363	-0.351910
6	6	0	-2.293557	-0.316886	1.405429
7	6	0	-2.536691	-0.818540	-1.057481
8	6	0	1.970364	-0.192934	0.327230
9	6	0	2.384743	-1.626457	-0.037614
10	6	0	3.084024	0.806985	-0.023670
11	1	0	-2.081106	2.035130	0.250662
12	1	0	-1.595090	1.560494	-1.380449
13	1	0	0.206930	1.747670	1.090671
14	1	0	0.520776	2.387056	-0.533325
15	1	0	0.795404	0.143285	-1.447675
16	1	0	-1.708988	0.216992	2.161688
17	1	0	-3.324647	0.053371	1.437269
18	1	0	-2.298436	-1.379180	1.669157
19	1	0	-2.667076	-1.878432	-0.816420
20	1	0	-3.528326	-0.355980	-1.126848
21	1	0	-2.054297	-0.747644	-2.037726
22	1	0	1.790779	-0.152034	1.411498
23	1	0	3.303456	-1.909918	0.488441
24	1	0	1.600710	-2.341211	0.224216
25	1	0	2.577602	-1.713823	-1.114831
26	1	0	4.026550	0.513475	0.450915
27	1	0	3.257732	0.838812	-1.107004
28	1	0	2.847876	1.823237	0.308925

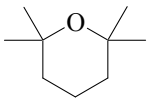
```
Zero-point correction=                          0.256132 (Hartree/Particle)
Thermal correction to Energy=                   0.267777
Thermal correction to Enthalpy=                 0.268721
Thermal correction to Gibbs Free Energy=        0.219152
Sum of electronic and zero-point Energies=                -428.815570
Sum of electronic and thermal Energies=                   -428.803925
Sum of electronic and thermal Enthalpies=                 -428.802981
Sum of electronic and thermal Free Energies=              -428.852550
```

B11.2.2 MP2/6-31+G**// MP2/6-31+G**-coordinates and –energies

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	-0.365703	-0.751308	0.053933
2	6	0	-1.675853	-0.121188	0.009932
3	6	0	-1.403856	1.344569	-0.367798
4	6	0	0.061374	1.542798	0.006897
5	6	0	0.649198	0.185167	-0.350198
6	6	0	-2.272767	-0.254547	1.402216
7	6	0	-2.516901	-0.848343	-1.025454
8	6	0	1.953012	-0.189240	0.332461
9	6	0	2.365434	-1.611256	-0.033697
10	6	0	3.052377	0.808185	-0.023797
11	1	0	-2.082859	2.028120	0.142264
12	1	0	-1.531113	1.484753	-1.443478
13	1	0	0.175916	1.716080	1.079625
14	1	0	0.530736	2.366775	-0.529113
15	1	0	0.787306	0.119327	-1.442223
16	1	0	-1.675467	0.299112	2.125837
17	1	0	-3.294767	0.126268	1.422427
18	1	0	-2.282904	-1.302960	1.697125
19	1	0	-2.654509	-1.889214	-0.735512
20	1	0	-3.497588	-0.379614	-1.121697
21	1	0	-2.019431	-0.820412	-1.994180
22	1	0	1.763283	-0.144743	1.410025
23	1	0	3.284579	-1.889021	0.482949
24	1	0	1.586828	-2.322471	0.231971
25	1	0	2.547901	-1.687503	-1.107663
26	1	0	3.996398	0.512003	0.432930
27	1	0	3.202865	0.842127	-1.104714
28	1	0	2.816350	1.814970	0.318587

```
Zero-point correction=                          0.263074 (Hartree/Particle)
Thermal correction to Energy=                   0.274437
Thermal correction to Enthalpy=                 0.275381
Thermal correction to Gibbs Free Energy=        0.226393
Sum of electronic and zero-point Energies=                -427.480445
Sum of electronic and thermal Energies=                   -427.469082
Sum of electronic and thermal Enthalpies=                 -427.468138
Sum of electronic and thermal Free Energies=              -427.517126
```

B11.3 2,2,6,6-Tetramethyltetrahydropyran (IX)



IX

B11.3.1 B3LYP/6-31+G**// B3LYP/6-31+G**-coordinates and –energies

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.000000	-0.877028	-0.352374
2	6	0	-1.268077	-0.250209	-0.041428
3	6	0	-1.251504	1.240979	-0.436435
4	6	0	0.000000	1.968647	0.067078
5	6	0	1.251504	1.240979	-0.436435
6	6	0	1.268077	-0.250209	-0.041428
7	6	0	1.646108	-0.441674	1.441338
8	6	0	2.270278	-1.018687	-0.911402
9	6	0	-1.646108	-0.441674	1.441338
10	6	0	-2.270278	-1.018687	-0.911402
11	1	0	-2.163111	1.721765	-0.060838
12	1	0	-1.281194	1.310300	-1.532030
13	1	0	0.000000	2.024449	1.163056
14	1	0	0.000000	3.004929	-0.291015
15	1	0	2.163111	1.721765	-0.060838
16	1	0	1.281194	1.310300	-1.532030
17	1	0	1.056666	0.182666	2.116192
18	1	0	1.502391	-1.487433	1.729201
19	1	0	2.700688	-0.185490	1.593134
20	1	0	3.280063	-0.612112	-0.788558
21	1	0	2.284845	-2.076789	-0.631287
22	1	0	1.988317	-0.947884	-1.966007
23	1	0	-1.056666	0.182665	2.116192
24	1	0	-2.700688	-0.185490	1.593134
25	1	0	-1.502391	-1.487433	1.729201
26	1	0	-2.284845	-2.076789	-0.631287
27	1	0	-3.280063	-0.612112	-0.788557
28	1	0	-1.988317	-0.947884	-1.966007

Zero-point correction=	0.256694 (Hartree/Particle)
Thermal correction to Energy=	0.267764
Thermal correction to Enthalpy=	0.268709
Thermal correction to Gibbs Free Energy=	0.221945
Sum of electronic and zero-point Energies=	-428.812730
Sum of electronic and thermal Energies=	-428.801660
Sum of electronic and thermal Enthalpies=	-428.800716
Sum of electronic and thermal Free Energies=	-428.847479

B11.3.2 MP2/6-31+G**// MP2/6-31+G**-coordinates and –energies

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	0.000000	-0.880064	-0.374197
2	6	0	-1.258173	-0.246051	-0.041992
3	6	0	-1.240310	1.228724	-0.442735
4	6	0	0.000000	1.951441	0.068289
5	6	0	1.240310	1.228724	-0.442734
6	6	0	1.258173	-0.246051	-0.041992
7	6	0	1.613021	-0.428994	1.434384
8	6	0	2.261317	-1.013494	-0.889559
9	6	0	-1.613021	-0.428994	1.434384
10	6	0	-2.261317	-1.013495	-0.889559
11	1	0	-2.153554	1.705732	-0.078008
12	1	0	-1.255243	1.287666	-1.534811
13	1	0	0.000000	1.995546	1.159592
14	1	0	0.000000	2.985572	-0.281198
15	1	0	2.153554	1.705732	-0.078007
16	1	0	1.255243	1.287666	-1.534810
17	1	0	1.034821	0.212590	2.093348
18	1	0	1.443707	-1.465709	1.722021
19	1	0	2.667480	-0.194132	1.585203
20	1	0	3.261868	-0.599405	-0.760894
21	1	0	2.274248	-2.062184	-0.595056
22	1	0	1.981956	-0.950293	-1.939669
23	1	0	-1.034821	0.212590	2.093348
24	1	0	-2.667480	-0.194131	1.585203
25	1	0	-1.443707	-1.465709	1.722021
26	1	0	-2.274248	-2.062184	-0.595055
27	1	0	-3.261868	-0.599405	-0.760894
28	1	0	-1.981956	-0.950293	-1.939669

```
Zero-point correction=                          0.263635 (Hartree/Particle)
Thermal correction to Energy=                   0.274415
Thermal correction to Enthalpy=                 0.275359
Thermal correction to Gibbs Free Energy=        0.229181
Sum of electronic and zero-point Energies=                -427.481688
Sum of electronic and thermal Energies=                   -427.470907
Sum of electronic and thermal Enthalpies=                 -427.469963
Sum of electronic and thermal Free Energies=              -427.516141
```

B12 References

[1] W. L. F. Armarego, D. D. Perrin, *Purification of laboratory chemicals*, Pergamon Press, Oxford, **1996**.

[2] R. Anschütz, L. Kinnkutt, *Chem. Ber.* **1878**, *11*, 1221–1222.

[3] R. Fittig, F. Binder, *Liebigs Ann.* **1879**, *195*, 56–179.

[4] O. Brücher, J. Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.

[5] B. Flachsbarth, M. Fritzsche, P. J. Weldon, S. Schulz, *Chemistry & Biodiversity* **2009**, *6*, 1–37.

[6] M. H. Sherlock, J. J. Kaminski, W. C. Tom, J. F. Lee, S. C. Wong, W. Kreutner, R. W. Bryant, A. T. McPhail, *J. Med. Chem.* **1988**, *31*, 2108–2121.

[7] M. Peña-López, M. M. Martínez, L. A. Sarandeses, J. Pérez Sestelo, *J. Org. Chem.* **2010**, *75*, 5337–5339.

[8] M. Schlosser, T. Jenny, Y. Guggisberg, *Synlett* **1990**, *11*, 704.

[9] L. Hülskämper, P. Weyerstahl, *Chem. Ber.* **1981**, *114*, 746–756.

[10] M. Movassaghi, G. Piizzi, D. S. Siegel, G. Piersanti, *Angew. Chem.* **2006**, *118*, 5991–5995.

[11] G. Frenking, L. Hülskämper, P. Weyerstahl, *Chem. Ber.* **1982**, *115*, 2826–2835.

[12] J.-F. Zhao, T.-P. Loh, *Angew. Chem. Int. Ed.* **2009**, *48*, 7232–7235.

[13] W. Biernacki, A. Gdula, *Synthesis* **1979**, *1979*, 37–38.

[14] H. C. Brown, E. N. Peters, M. Ravindranathan, *J. Am. Chem. Soc.* **1977**, *99*, 505–509.

[15] R. Bussas, H. Muenster, G. Kresze, *J. Org. Chem.* **1983**, *48*, 2828–2832.

[16] C. H. Oh, T. W. Ahn, R. Reddy V., *Chem. Commun.* **2003**, 2622–2623.

[17] L. B. Din, O. Meth-Cohn, N. D. A. Walshe, *J. Chem. Soc., Perkin Trans. 1* **1991**, 781–786.

[18] M. Kitano, N. Ohashi, (Sumitomo Pharma, JP), *Substituted guanidine derivatives and process for producing the same*, US Patent 6,369,110 B1, April 9, **2002**

[19] W. H. Puterbaugh, *J. Org. Chem.* **1962**, *27*, 4010–4015.

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

Anhang C

Supporting Information for: A Practical Approach to Catalytic and Non-Catalytic Oxidative Chlorination of Alkenols

Oliver Brücher and Jens Hartung*

Fachbereich Chemie, Technische Universität Kaiserslautern,
Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

Contents

C1 General Remarks

(i) The compound numbering in the Supporting Information is consistent with the accompanying publication. (ii) References refer exclusively to the Supporting Information.

C2 Instrumentation and Reagents

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*).

^{1}H- and ^{13}C-NMR spectra were recorded with FT-NMR instruments Avance 400 or Avance 600 (*Bruker*). Chemical shifts refer to the δ-scale (coupling constants J are given in Hz). The resonances of carbon nuclei and residual protons of $CDCl_3$ (δ_H 7.26, δ_C 77.0), DMSO-d_6 (δ_H 2.50, δ_C 39.5), and CD_3OD (δ_H 3.31, δ_C 49.0) served as internal standards.

GC-MS-analyses were performed with HP 6890 Series-instrument (*Hewlett Packard*) equipped with a ZB5 column (*Phenomenex*, 30 m × 0.25 mm, 0.25 μm) using helium carrier gas (1 mL min^{-1}, 59.7 kPa). Temperature program: 40 °C (3 min), linear temperature gradient (10 °C min^{-1}) to 280 °C, final temperature 280 °C (10 min).

Mass spectra (EI, 70 eV) were recorded with a mass selective detector HP 5972 (*Hewlett Packard*). HRMS spectra were obtained with a GCT Premier instrument (*Waters*).

IR spectra were recorded from pelletized samples in KBr with a FT-IR 1000 spectrometer (*Perkin Elmer*).

UV/Vis spectra were recorded on a Cary 100 spectrometer (*Varian*) at 25 °C in 1 cm-quartz cuvettes using analytical grade solvents. Molar extinction coefficients are reported in lg (ε / m^2 × mol^{-1}).

Combustion analyses were performed with an Elemental Analyzer 2400 CHN (*Perkin Elmer*) or a Vario Micro Cube (*Elementar*).

Reaction progress was monitored via thin layer chromatography (tlc) on aluminium sheets, coated with silica gel (60 F_{254}, *Machery-Nagel*). Developed tlc-sheets were analyzed with UVlight (254 nm) or by staining with Ekkert′s reagent.

All reactions and manipulations under inert gas were carried out via standard Schlenk techniques using high purity N_2 (99.999%), which was further dried by passing through a column filled with anhydrous $CaCl_2$ and P_2O_5.

Dimethyl carbonate (DMC) was dried over molecular sieves (3 Å) and stored under nitrogen. All other solvents were purified according to standard procedures.[1]

A 4.1 M solution of *tert*-butyl hydroperoxide (TBHP) in toluene was prepared according to Sharpless *et al.* and the concentration determined as described.[2] Pyridiniumhydrochloride (py·HCl) was prepared from pyridine and 12 M HCl in 90 % yield and purified by recrystallization from acetone / MeOH [9:1, (*v*/*v*)]. Oxone® was purchased from *Aldrich* and used as received. 1-Phenylpent-4-en-1-ol (**1a**),[3][4] 2-phenylhex-5-en-2-ol (**1b**),[4][5] 5-phenylpent-4-en-1-ol (**1c**),[6] and ethyl (*E*)-2-(2-hydroxypropy-2-yl)-4-methyl-5-phenylpent-4-enoate (**1d**)[7] were synthesized according to published procedures.

C3 Syntheses of Auxiliaries H_2L^n

C3.1 (1*R*,2*S*,5*R*,1′*R*,2′*S*)-1-{[(1′-Hydroxy-1′-phenylpropan-2′-yl)(methyl)amino]-methyl}-5-methyl-2-(prop-2′′-yl)cyclohexanol (H_2L^1)

C3.1.1 (1*S*,4*S*,7*R*)-4-Isopropyl-7-methyl-1-oxaspiro[2.5]octane

The title compound was prepared from (2*S*,5*R*)-menthone (6.17 g, 40 mmol) according to a reported procedure in a yield of 86 %.[8] δ_H (400 MHz; $CDCl_3$) 0.79 (3 H, d, *J* 6.7 Hz, CH_3), 0.90 (3 H, d, *J* 6.7 Hz, CH_3), 0.91 (3 H, d, *J* 6.5 Hz, CH_3), 0.97–1.09 (1 H, m), 1.30–1.50 (4 H, m), 1.53–1.63 (1 H, m), 1.68–1.75 (1 H, m), 1.78–1.90 (2 H, m), 2.47 (1 H, d, *J* 4.4 Hz, 1-H), 2.91 (1 H, d, *J* 4.4 Hz, 1-H). $[\alpha]_D^{20}$ +6.5 (*c* 1, CH_2Cl_2).

C3.1.2 (1*R*,2*S*,5*R*,1′*R*,2′*S*)-1-{[(1′-Hydroxy-1′-phenylpropan-2′-yl)(methyl)amino]-methyl}-5-methyl-2-(prop-2′′-yl)cyclohexanol (H_2L^1)

A pressure Schlenk tube, charged with (1*R*,2*S*)-ephedrine (3.7 g, 22.4 mmol), (1*S*,4*S*,7*R*)-4-isopropyl-7-methyl-1-oxaspiro[2.5]octane (4.0 g, 23.8 mmol) and LiBr (200 mg, 2.3 mmol) was heated in an oil bath for 72 h to 80 °C. The mixture was allowed to cool to room temperature and purified by Kugelrohr distillation. Yield: 6.1 g (18.3 mmol, 86 %) colorless resin, bp 190–210 °C / 0.1 mbar. δ_H (600 MHz; $CDCl_3$) 0.67 (1 H, t, *J* 12.7 Hz, $CH_2^{menthyl}$), 0.76 (1 H, qd, J_q 12.2, J_d 3.8 Hz, $CH_2^{menthyl}$), 0.80 (3 H, d, *J* 6.6 Hz, CH_3), 0.86 (3 H, d, *J* 3.5 Hz, CH_3), 0.88 (3 H, d, *J* 3.7 Hz, CH_3), 0.89–0.92 (1 H, m, $CH^{menthyl}$), 1.03 (3 H, d, *J* 6.6 Hz, CH_3), 1.37–1.58 (4 H, m, $CH^{menthyl}$, $CH_2^{menthyl}$), 1.64–1.72 (1 H, m, $CH_2^{menthyl}$), 2.05 (1 H, quint, *J* 6.8 Hz, $CH(CH_3)_2$), 2.09 (1 H, d, *J* 14.3 Hz, CH_2-menthyl), 2.30 (1 H, br. s., OH), 2.40 (3 H, s, CH_3), 2.79 (1 H, quin, *J* 6.4 Hz, 2-H), 2.95 (1 H, d, *J* 14.0 Hz, CH_2-menthyl), 2.99 (1 H, br. s., OH), 4.79 (1 H, d, *J* 5.0 Hz, 1-H), 7.23–7.27 (1 H, m), 7.31–7.37 (4 H, m). δ_C (150 MHz; $CDCl_3$) 8.4 (CH_3), 18.2 (CH_3), 21.0 ($CH_2^{menthyl}$), 22.4 (CH_3), 23.7 (CH_3), 25.8 ($CH(CH_3)_2$), 27.7 ($CH^{menthyl}$), 35.1 ($CH_2^{menthyl}$), 42.1 (CH_3), 47.7 ($CH_2^{menthyl}$), 47.8 ($CH^{menthyl}$), 62.4 (CH_2-menthyl), 66.4 (C2), 74.5 (C1), 76.6

($C_q^{menthyl}$), 126.1, 127.2, 128.1, 143.3. ν_{max} (KBr) / cm^{-1} 3430, 2952, 2867, 1452, 1368, 1046, 1025, 758, 702, 555; λ_{max} (EtOH) / nm (lg ε / m^2 mol^{-1}) 206 (7.88). $[\alpha]_D^{20}$ –37 (*c* 1, CH_2Cl_2). Anal. calcd. for $C_{21}H_{35}NO_2$ (333.51): C, 75.63; H, 10.58; N, 4.20, Found: C, 75.65; H, 10.57; N, 4.21.

C3.2 *cis*-2,6-Bis-(1′-hydroxy-1′,1′-diphenylmethyl)-piperidine (H_2L^2)

Aminodiol $\mathbf{H_2L^2}$ was prepared in a total yield of 13 % from dimethyl piperidine-2,6-dicarboxylate (4.60 g, 22 mmol) in 3 steps according to a documented procedure.[9][10] δ_H (600 MHz; $CDCl_3$) 1.22–1.39 (5 H, m, 3-H, 4-H, 5-H), 1.77 (1 H, d, *J* 5.9 Hz, 4-H), 3.48 (2 H, br. s., OH), 3.66 (2 H, d, *J* 9.7 Hz, 2-H, 6-H), 7.03–7.08 (2 H, m), 7.11–7.18 (6 H, m), 7.23–7.28 (4 H, m), 7.40–7.47 (8 H, m).

C3.3 2-(Salicylidene)aminophenol (H_2L^3)

Iminodiol $\mathbf{H_2L^3}$ was prepared from 2-aminophenol (7.42 g, 68 mmol) and salicyl aldehyde (8.30 g, 68 mmol) according to a published procedure in a yield of 92 %.[11–13] δ_H (600 MHz; DMSO-d_6) 6.88 (1 H, t, *J* 7.5 Hz), 6.92–6.99 (3 H, m), 7.13 (1 H, t, *J* 7.7 Hz), 7.34–7.41 (2 H, m), 7.61 (1 H, d, *J* 7.7. Hz), 8.96 (1 H, s, *CH*=N), 9.78 (1 H, s, OH), 13.83 (1 H, s, OH).

C3.4 (1′*S*,2′*S*,5′*R*)-2,6-Bis-(1′-hydroxy-2′-isopropyl-5′-methylcyclohexyl)-pyridine (H_2L^4)

Aminodiol $\mathbf{H_2L^4}$ was prepared from 2,6-dibromopyridine (5.0 g, 21 mmol) according to a reported procedure with an overall yield of 31 %.[14] δ_H (600 MHz; $CDCl_3$) 0.67 (6 H, d, *J* 7.0 Hz, CH_3), 0.81 (6 H, d, *J* 6.7 Hz, CH_3), 0.90 (6 H, d, *J* 6.4 Hz, CH_3), 0.99–1.12 (2 H, m, $CH_2^{menthyl}$), 1.13–1.27 (2 H, m, $CH^{menthyl}$), 1.43–1.60 (4 H, m, $CH_2^{menthyl}$), 1.60–1.69 (4 H, m, $CH_2^{menthyl}$), 1.69–1.81 (2 H, m, $CH^{menthyl}$), 1.82–1.97 (4 H, m, $CH_2^{menthyl}$, $CH(CH_3)_2$), 4.08 (2 H, br. s, OH), 7.33 (2 H, d, *J* 7.8 Hz), 7.71 (1 H, t, *J* 7.8 Hz). $[\alpha]_D^{20}$ –16.5 (*c* 1, CH_2Cl).

C4 Syntheses of Transition Metal Compounds

C4.1 Syntheses of molybdenum(VI)-complexes 4b–d

To a suspension of $MoO_2(acac)_2$ (1 equiv.) in MeOH (10 mL/mmol) was added a solution of ligand $\mathbf{H_2L^{1–3}}$ (1 equiv.) in MeOH (5 mL/mmol) at 25 °C. The reaction mixture was stirred for 18 h at 25 °C. The solids were filtered off, washed with cold MeOH, and dried under reduced

pressure (1×10^{-2} mbar). On concentration of the filtrate and cooling to –28 °C another crop of colorless crystals was obtained.

(1*R*,2*S*,5*R*,1′*R*,2′*S*)-[1-{[(1′-Hydroxo-1′-phenylpropan-2′-yl)(methyl)amino]methyl}-5-methyl-2-(prop-2′′-yl)cyclohexan-1-olato(–2)]-*cis*-(dioxo)molybdenum(VI) (4a).

Yield: 2.83 g (6.2 mmol, 68 %) colorless solid, mp 212 °C (dec.). δ_H (400 MHz; $CDCl_3$) 0.83–0.92 (1 H, m, $CH_2^{menthyl}$), 0.86 (3 H, d, *J* 6.7 Hz, CH_3), 0.89 (3 H, d, *J* 7.0 Hz, CH_3), 0.89 (3 H, d, *J* 6.3 Hz, CH_3), 0.96 (3 H, d, *J* 7.0 Hz, CH_3), 1.06 (1 H, t, *J* 12.6 Hz, $CH_2^{menthyl}$), 1.23 (1 H, dd, *J* 12.0, 2.9 Hz, $CH^{menthyl}$), 1.49–1.62 (2 H, m, $CH_2^{menthyl}$), 1.62–1.79 (2 H, m, $CH^{menthyl}$, $CH_2^{menthyl}$), 1.97 (1 H, m, ($CH(CH_3)_2$), 2.54 (1 H, d, *J* 13.5 Hz, CH_2-menthyl), 2.76 (1 H, d, *J* 13.2 Hz, $CH_2^{menthyl}$), 3.24–3.31 (1 H, m, 2-H), 3.30 (3 H, s, CH_3), 3.71 (1 H, d, *J* 13.8 Hz, CH_2-menthyl), 6.09 (1 H, d, *J* 3.2 Hz, 1-H), 7.21–7.39 (5 H, m). δ_C (100 MHz; $CDCl_3$) 12.0 (CH_3), 18.3 (CH_3), 21.5 (CH_3), 22.2 ($CH_2^{menthyl}$), 23.6 (CH_3), 26.5 ($CH(CH_3)_2$), 28.0 ($CH^{menthyl}$), 34.7 ($CH_2^{menthyl}$), 46.1 ($CH_2^{menthyl}$), 48.5 ($CH^{menthyl}$), 50.8 (CH_3), 62.9 (CH_2-menthyl), 72.3 (C2), 86.9 (C1), 92.3 ($C_q^{menthyl}$), 125.3, 127.5, 128.4, 140.0. ν_{max} (KBr) / cm^{-1} 3436, 2958, 2925, 2870, 1451, 1092, 1011, 932; λ_{max} (EtOH) / nm (lg ε / m^2 mol^{-1}) 205 (3.23), 236 (sh, 2.75). $[\alpha]_D^{20}$ –24 (*c* 1, CH_2Cl_2). Anal. calcd. for $C_{21}H_{33}MoNO_4$ (459.46): C, 54.90; H, 7.24; N, 3.05, Found: C, 54.91; H, 7.27; N, 2.99. X-ray crystallography: $C_{21}H_{33}MoNO_4$ (459.46), T = 150 K, λ = 0.71073 Å, monoclinic, $P2_1$, a = 9.6034(2) Å, b = 12.2982(3) Å, c = 10.1290(3) Å, β = 116.265(3) °, Z = 2, μ = 0.636 mm^{-1}, completeness 99.2 %, (2 θ = 32.41°), goodness-of-fit on F^2 = 0.923, final R indices [I>2 $\sigma(I)$]: $R1$ = 0.0263, $wR2$ = 0.0460.

{*cis*-2,6-Bis-[1′,1′-diphenylmethanolato(–1)]-piperidine-2,6-diyl}-*cis*-dioxo-molybdenum (VI) (4b)

Yield: 276 mg (0.48 mmol, 96 %) colorless solid, mp 220 °C (dec.). δ_H (600 MHz; $CDCl_3$) 1.35 (1 H, d, *J* 13.5 Hz, 4-H), 1.43–1.59 (4 H, m, 3-H, 5-H), 1.88 (1 H, dt, J_d 13.7, J_t 3.3 Hz, 4-H), 4.35–4.42 (3 H, m, 2-H, 6-H, NH), 7.11–7.14 (2 H, m), 7.15–7.19 (2 H, m), 7.20–7.26 (8 H, m), 7.35 (4 H, d, *J* 7.7 Hz), 7.41 (4 H, d, *J* 7.5 Hz). δ_C (150 MHz; $CDCl_3$) 21.5 (C4), 24.7 (C3, C5), 65.7 (C2, C6), 94.2 (C_q), 125.1, 125.4, 127.2, 128.1, 128.3, 129.1, 141.5, 142.5. ν_{max} (KBr) / cm^{-1} 3436, 3196, 1449, 1210, 1061, 993, 946, 904, 698; λ_{max} (EtOH) / nm (lg ε / m^2 mol^{-1}) 203 (3.72), 256 (sh, 2.66), 302 (2.43). Anal. calcd. for $C_{31}H_{29}MoNO_4$ (575.52): C, 64.70; H, 5.08; N, 2.43, Found: C, 64.34; H, 4.88; N, 2.42.

[2-(2′-Oxidobenzylidenamino)phenolato(–2)](methanol)-*cis*-(dioxo)molybdenum(VI) (4c)

Yield: 861 mg (2.62 mmol, 88 %) orange solid, mp 120 °C (dec.). δ_H (400 MHz; DMSO-d_6) 3.16 (3 H, d, *J* 5.3 Hz, *CH*$_3$OH), 4.12 (1 H, q, *J* 5.3 Hz, CH$_3$*OH*), 6.85 (1 H, d, *J* 8.0 Hz), 6.90–6.98 (2 H, m), 7.07 (1 H, t, *J* 7.3 Hz), 7.23 (1 H, t, *J* 7.2 Hz), 7.50–7.57 (1 H, m), 7.77 (1 H, dd, *J* 7.7, 1.3 Hz), 7.82 (1 H, d, *J* 7.4 Hz), 9.28 (1 H, s, *CH*=N). δ_C (150 MHz; DMSO-d_6) 48.6 (*CH*$_3$OH), 116.4, 117.3, 118.9, 120.3, 120.9, 122.0 (C$_q$), 130.1, 135.1, 135.5, 135.6 (C$_q$), 156.7 (*CH*=N), 160.1 (C$_q$), 161.1 (C$_q$). ν_{max} (KBr) / cm^{-1} 3235, 2363, 1610, 1584, 1552, 1473, 1392, 1289, 1246, 931, 912, 849, 749; λ_{max} (EtOH) / nm (lg ε / m^2 mol^{-1}) 203 (3.49), 218 (3.50), 239 (sh, 3.30), 306 (3.26), 345 (sh, 2.90), 4.17 (2.66).

C4.2 Synthesis of (1′*S*,2′*S*,5′*R*)-{2,6-bis-[2′-isopropyl-5′-methylcyclohexan-1′-olato(–1)]-pyridine-2,6-diyl}bis(ethanolato)-titanium(IV) (5)

To a solution of ligand **H$_2$L^4** (460 mg, 1.17 mmol) in dry EtOH (6 mL) was added Ti(O^{i}Pr)$_4$ (370 mg, 1.25 mmol) at 25 °C under an inert gas atmosphere. The reaction mixture was stirred for 24 h at 25 °C after which the colorless solids were filtered off, washed with cold EtOH (2 × 5 mL), and dried under reduced pressure (1 × 10^{-2} mbar). On concentration of the filtrate and cooling to –28 °C another crop of colorless crystals was obtained. Yield: 597 mg (1.14 mmol, 97 %) colorless solid, mp 183 °C; δ_H (600 MHz; MeOH-d_4) 0.67 (6 H, d, *J* 7.1 Hz, CH$_3$), 0.89 (12 H, d, *J* 6.7 Hz, CH$_3$), 1.07 (2 H, dd, *J* 12.3, 4.0 Hz, CH$_2^{menthyl}$), 1.18 (6 H, t, *J* 7.1 Hz, OCH$_2$*CH*$_3$), 1.24 (1 H, td, J_t 6.9, J_d 2.4 Hz, *CH*(CH$_3$)$_2$), 1.49–1.55 (1 H, m, CH$_2^{menthyl}$), 1.59–1.64 (4 H, m, CH$_2^{menthyl}$), 1.66–1.74 (4 H, m, CH^{menthyl}, CH$_2^{menthyl}$), 1.79–1.86 (2 H, m, CH$_2^{menthyl}$), 1.94–2.05 (2 H, m, CH^{menthyl}), 3.61 (4 H, q, *J* 7.1 Hz, O*CH*$_2$CH$_3$), 7.46 (2 H, d, *J* 7.7 Hz), 8.05 (1 H, t, *J* 7.8 Hz). δ_C (150 MHz; MeOH-d_4) 18.5 (OCH$_2$*CH*$_3$), 19.6 (CH$_3$), 22.8 (CH$_3$), 23.5 (CH$_2^{menthyl}$), 24.4 (CH$_3$), 29.7 (*CH*(CH$_3$)$_2$), 29.8 (CH^{menthyl}), 36.3 (CH$_2^{menthyl}$), 51.7 (CH^{menthyl}), 53.1 (CH$_2^{menthyl}$), 58.5 (O*CH*$_2$CH$_3$), 96.6 (C$_q^{menthyl}$), 119.4, 143.6, 176.3. ν_{max} (KBr) / cm^{-1} 3433, 2948, 2921, 2863, 1598, 1578, 1465, 1102, 1060, 709; λ_{max} (EtOH) / nm (lg ε / m^2 mol^{-1}) 203 (3.40), 278 (2.84). $[\alpha]_D^{20}$ –23 (*c* 1, EtOH). Anal. calcd. for C$_{29}$H$_{49}$NO$_4$Ti (523.57): C, 66.53; H, 9.43; N, 2.68, Found: C, 66.53.; H, 9.41; N, 2.63. X-ray crystallography: C$_{29}$H$_{49}$NO$_4$Ti (523.59), *T* = 150 K, λ = 1.54184 Å, monoclinic, P2$_1$, *a* = 8.2646(2) Å, *b* = 16.5627(2) Å, *c* = 11.3757(2) Å, β = 106.958(2) °, *Z* = 2, μ = 2.676 mm^{-1}, completeness 97.9 %, (2 θ = 62.670°), goodness-of-fit on F^2 = 1.080, final *R* indices [$I>2\sigma(I)$]: *R*1 = 0.0463, *wR*2 = 0.1167.

C5 Chlorocyclization of Alkenols

C5.1 General procedure for transition metal-catalyzed oxidative chlorination of 4-penten-1-ols 1a–d

To a solution of alkenol **1a–d** (0.5 mmol) in DMC (20 mL) under an atmosphere of nitrogen was added dry py·HCl (87 mg, 0.75 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 180 µL, 0.75 mmol), and a transition metal catalyst **4** or **5** (0.025 mmol, 5 mol%) at 20 °C. The reaction mixture was stirred for 24 h in the dark (flask wrapped in aluminium foil) at 20 °C [for titanium(IV)-catalyst **5**] or 40 °C [for molybdenum(VI)-catalysts]. Colorless to yellow reaction mixtures were concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2).

C5.2 General procedure for solid acid-catalyzed oxidative chlorination of 4-penten-1-ols 1a–d

To a solution of an alkenol **1a–d** (0.5 mmol) in dry DMC (10 mL) under an atmosphere of nitrogen was added KCl (56 mg, 0.75 mmol), and oxone® (307 mg, 0.5 mmol) at 30 °C. The reaction was stirred for 24 h in the dark at 30 °C and reaction progress monitored via tlc and glc. The mixture was concentrated under reduced pressure and the oily residue purified by column chromatography (SiO_2).

C5.3 Experimental data of chlorocyclization products

C5.3.1 Oxidative chlorination of 1-phenyl-4-penten-1-ol (1a)

5-(1′-Chloromethyl)-2-phenyl-tetrahydrofuran (2a). Colorless liquid, 42/58-mixture of *cis*/*trans* isomers, R_f = 0.54 [CH_2Cl_2]. Anal. calcd. for $C_{11}H_{13}ClO$ (196.67): C, 67.18; H, 6.66; Found: C, 66.87; H, 6.57. ***cis*-2a**. δ_H (400 MHz; $CDCl_3$) 1.83–2.04 (2 H, m, 3-H, 4-H), 2.12–2.26 (1 H, m, 3-H), 2.27–2.36 (1 H, m, 4-H), 3.56–3.72 (2 H, m, 1′-H), 4.29–4.38 (1 H, m, 5-H), 4.90–4.98 (1 H, m, 2-H), 7.21–7.43 (5 H, m). δ_C (100 MHz; $CDCl_3$) 29.5 (C3), 34.2 (C4), 47.0 (C1′), 78.8 (C5), 81.9 (C2), 125.8, 127.5, 128.3, 142.2. NOESY (cross peaks) 2-H ↔ 5-H. ***trans*-2a**. δ_H (400 MHz; $CDCl_3$) 1.82–2.03 (2 H, m, 3-H, 4-H), 2.13–2.26 (1 H, m, 3-H), 2.35–2.46 (1 H, m, 4-H), 3.56–3.73 (2 H, m, 1′-H), 4.44–4.53 (1 H, m, 5-H), 5.08 (1 H, t, *J* 6.7 Hz, 2-H), 7.21–7.43 (5 H, m). δ_C (100 MHz; $CDCl_3$) 30.0 (C3), 35.0 (C4), 47.2 (C1′), 78.9 (C5), 81.5 (C2), 125.6, 127.4, 128.3, 142.6. NOESY (cross peaks) 5-H ↔ Ph-H. **4,5-Dichloro-1-phenylpentan-1-ol (6a)**. Colorless oil, mixture of *like*/*unlike* isomers (50:50), R_f = 0.29 [CH_2Cl_2]. Anal. calcd. for $C_{11}H_{14}Cl_2O$ (233.13): C, 56.67; H, 6.05; Found: C, 56.98; H, 6.03. δ_H (600 MHz; $CDCl_3$)

1.65–1.77 (1 H, m, 3-H), 1.81–2.10 (8 H, m, 2-H, 3-H, OH), 2.16–2.26 (1 H, m, 3-H), 3.59–3.68 (2 H, m, 5-H), 3.75 (2 H, dd, *J* 11.3, 5.1 Hz, 5-H), 4.02–4.13 (2 H, m, 4-H), 4.67–4.77 (2 H, m, 1-H), 7.28–7.32 (2 H, m), 7.32–7.40 (8 H, m). δ_C (150 MHz; $CDCl_3$) 31.2 and 31.7 (C3), 34.9 and 35.2 (C2), 48.1 (C5), 60.8 and 61.2 (C4), 73.6 and 74.1 (C1), 125.7, 125.8, 127.8, 127.9, 128.6, 128.7, 144.1, 144.2.

C5.3.2 Oxidative chlorination of 2-phenyl-5-hexen-2-ol (1b)

5-(1′-Chloromethyl)-2-methyl-2-phenyltetrahydrofuran (2b). Colorless liquid, 62/38-mixture of *cis*/*trans* isomers, R_f = 0.92 [CH_2Cl_2]. Anal. calcd. for $C_{12}H_{15}ClO$ (210.70): C, 68.40; H, 7.18; Found: C, 68.39; H, 7.19. ***cis*-2b**. δ_H (600 MHz; $CDCl_3$) 1.52 (3 H, s, CH_3), 1.75 (1 H, dq, J_d 12.2, J_q 7.3 Hz, 4-H), 2.10–2.16 (1 H, m, 3-H), 2.21 (1 H, td, J_t 12.5, J_d 6.7 Hz, 4-H), 2.25–2.30 (1 H, m, 3-H), 3.44 (1 H, dd, *J* 10.8, 6.7 Hz, 1′-H), 3.63 (1 H, dd, *J* 10.8, 5.4 Hz, 1′-H), 4.40 (1 H, quint, *J* 6.3 Hz, 5-H), 7.20–7.25 (1 H, m), 7.29–7.35 (2 H, m), 7.44 (2 H, dd, *J* 8.4, 1.0 Hz). δ_C (100 MHz; $CDCl_3$) 29.7 (C4), 29.7 (CH_3), 39.1 (C3), 47.0 (C1′), 78.8 (C5), 85.5 (C2), 124.6, 126.5, 128.2, 148.1. NOESY (cross peaks) 2-CH_3 ↔ 5-H. ***trans*-2b**. δ_H (600 MHz; $CDCl_3$) 1.56 (3 H, s, CH_3), 1.88–1.96 (2 H, m, 4-H), 2.06–2.11 (1 H, m, 3-H), 2.24–2.30 (1 H, m, 3-H), 3.59 (1 H, dd, *J* 11.0, 5.9 Hz, 1′-H), 3.66 (1 H, dd, *J* 11.0, 4.6 Hz, 1′-H), 4.29 (1 H, dt, J_d 11.7, J_t 6.0 Hz, 5-H), 7.20–7.25 (1 H, m), 7.29–7.35 (2 H, m), 7.37–7.41 (2 H, m). δ_C (100 MHz; $CDCl_3$) 29.1 (C4), 30.3 (CH_3), 38.8 (C3), 47.2 (C1′), 78.0 (C5), 85.8 (C2), 124.5, 126.5, 128.1, 147.5. NOESY (cross peaks) 5-H ↔ Ph-H. **5,6-dichloro-2-phenylhexan-2-ol (6b)**. Colorless oil, 50/50-mixture of *like*/*unlike* isomers, R_f = 0.48 [CH_2Cl_2]. δ_H (400 MHz; $CDCl_3$) 1.47–1.57 (1 H, m, 4-H), 1.60 (6 H, s, CH_3), 1.70 (2 H, br. s., OH), 1.73–1.96 (4 H, m, 3-H, 4-H), 1.98–2.08 (2 H, m, 3-H, 4-H), 2.10–2.20 (1 H, m, 4-H), 3.53–3.64 (2 H, m, 6-H), 3.61–3.96 (2 H, m, 6-H), 3.92–3.99 (1 H, m, 5-H), 3.99–4.07 (1 H, m, 5-H), 7.23–7.29 (2 H, m), 7.32–7.39 (4 H, m), 7.40–7.47 (4 H, m). δ_C (100 MHz; $CDCl_3$) 29.79 and 29.83 (C4), 30.4 (CH_3), 31.0 (CH_3), 40.1 (C3), 48.0 (C6), 61.4 and 61.5 (C5), 74.1 and 74.3 (C2), 124.6, 124.7, 126.79, 126.84, 128.3, 146.9, 147.3.

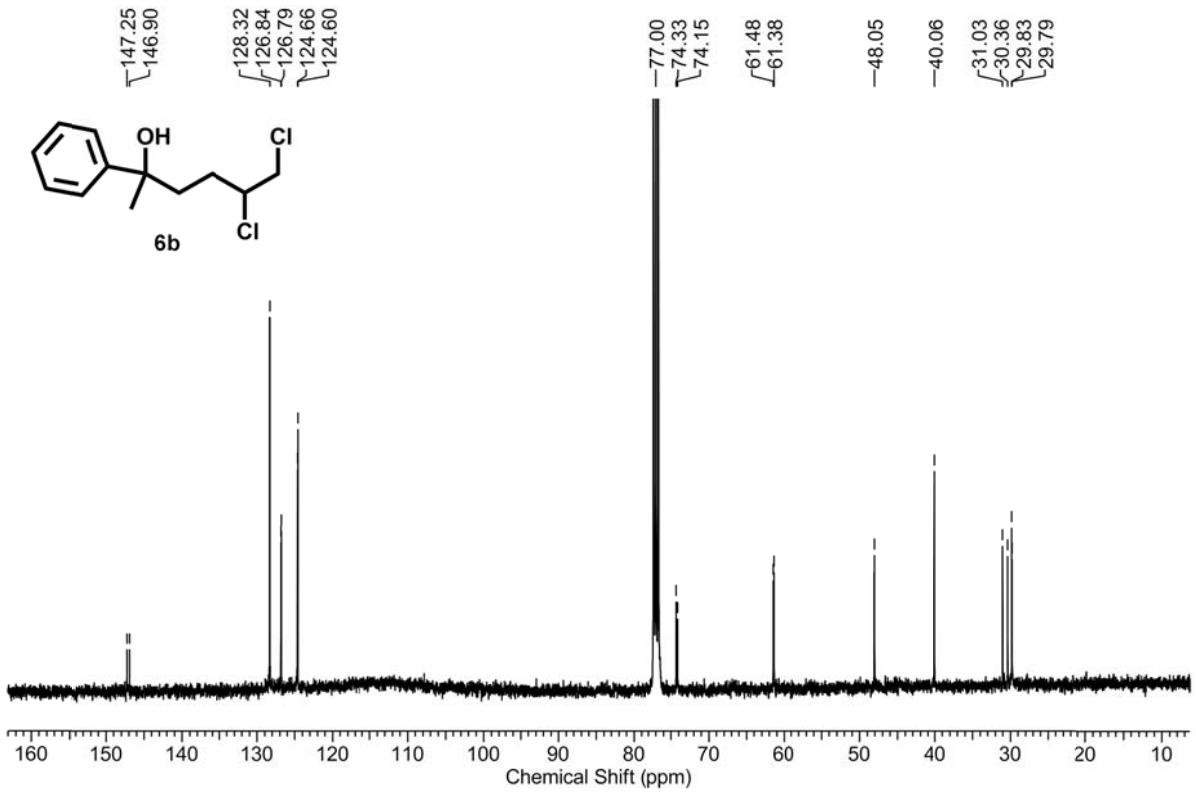


Figure C1. ^{13}C-NMR spectrum of the *like*/*unlike* mixture of 5,6-dichloro-2-phenylhexan-2-ol (**6b**).

C5.3.3 Oxidative chlorination of 5-phenyl-4-penten-1-ol (1c)

***trans*-5-Chloro-6-phenyltetrahydropyran (3c)**. Colorless oil, R_f = 0.68 [CH_2Cl_2]. δ_H (600 MHz; $CDCl_3$) 1.76–1.84 (1 H, m, 3-H), 1.88–1.99 (2 H, m, 3-H, 4-H), 2.44–2.52 (1 H, m, 4-H), 3.58–3.64 (1 H, m, 2-H), 3.91 (1 H, td, J_t 10.0, J_d 4.5 Hz, 5-H), 4.08–4.13 (1 H, m, 2-H), 4.20 (1 H, d, J 9.7 Hz, 6-H), 7.31–7.43 (4 H, m). δ_C (150 MHz; $CDCl_3$) 27.2 (C3), 35.2 (C4), 59.6 (C5), 68.5 (C2), 85.5 (C6), 127.5, 128.2, 128.5, 139.1. NOESY (cross peaks) 5-H ↔ Ph-H. Anal. calcd. for $C_{11}H_{13}ClO$ (196.67): C, 67.18; H, 6.66; Found: C, 67.07; H, 6.37.

C5.3.4 Oxidative chlorination of ethyl (*E*)-2-(2-hydroxypropy-2-yl)-4-methyl-5-phenyl-4-pentenoate (1d)

Ethyl *rel*-(3*R*,5*S*,6*R*)-(5-chloro-2,2,5-trimethyl-6-phenyltetrahydropyran)-3-carboxylate (±)-*cis*-(3d). Colorless oil, R_f = 0.63 [CH_2Cl_2]. Anal. calcd. for $C_{17}H_{23}ClO_3$ (310.82): C, 65.69; H, 7.46; Found: C, 65.46; H, 7.40. δ_H (600 MHz; $CDCl_3$) 1.29 (3 H, t, J 7.0 Hz, $CO_2CH_2CH_3$), 1.35 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 2.28 (1 H, dd, J 13.3, 3.5 Hz, 4-H), 2.69 (1 H, t, J 13.3 Hz, 4-H), 2.83 (1 H, dd, J 13.6, 3.3 Hz, 3-H), 4.08–4.26 (2 H, m, $CO_2CH_2CH_3$), 4.82 (1 H, s, 6-H), 7.21–7.39 (3 H, m), 7.41–7.53 (2 H, m). δ_C (150 MHz; $CDCl_3$) 14.2 (CH_3), 19.0

(CH_3), 22.6 (CH_3), 29.9 (CH_3), 41.1 (C4), 50.1 (C3), 60.8 ($CO_2CH_2CH_3$), 68.0 (C5), 74.4 (C2), 78.8 (C6), 127.4, 127.9, 128.5, 137.2, 171.5 ($CO_2CH_2CH_3$). NOESY (cross peaks) 3-H ↔ 5-CH_3.. **Ethyl {5-[1′-chloro(phenyl)methyl]-2,2,5-trimethyl-tetrahydrofuran}-3-carboxylate (2d)**. Colorless oil, 90/10-mixture of *cis*/*trans* isomers, R_f = 0.52 [CH_2Cl_2]. Anal. calcd. for $C_{17}H_{23}ClO_3$ (310.82): C, 65.69; H, 7.46; Found: C, 65.75; H, 7.40. ***rel*-(3*R*,5*R*,1′*S*)-2d [(±)-*cis*-2d]**. δ_H (600 MHz; $CDCl_3$) 1.15 (3 H, s, CH_3), 1.19 (3 H, s, CH_3), 1.28 (3 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), 1.44 (3 H, s, CH_3), 2.07 (1 H, dd, *J* 12.9, 7.0 Hz, 4-H), 2.82 (1 H, t, *J* 12.7 Hz, 4-H), 3.05 (1 H, dd, *J* 12.3, 6.8 Hz, 3-H), 4.10 –4.25 (2 H, m, $CO_2CH_2CH_3$), 4.91 (1 H, s, 1′-H), 7.25–7.35 (3 H, m), 7.37–7.45 (2 H, m). δ_C (150 MHz; $CDCl_3$) 14.2 ($CO_2CH_2CH_3$), 23.9 (CH_3), 25.1 (CH_3), 30.4 (CH_3), 38.2 (C4), 53.3 (C3), 60.7 ($CO_2CH_2CH_3$), 70.1 (C1′), 83.0 (C2), 84.1 (C5), 127.8, 128.1, 128.9, 138.2, 171.3 ($CO_2CH_2CH_3$). NOESY (cross peaks) 3-H ↔ 5-CH_3. ***rel*-(3*R*,5*S*,1′*R*)-2d [(±)-*trans*-2d]**. δ_H (600 MHz; $CDCl_3$) 1.13 (3 H, s, CH_3), 1.25 (3 H, t, *J* 7.1 Hz, $CO_2CH_2CH_3$), 1.42 (3 H, s, CH_3), 1.49 (3 H, s, CH_3), 2.37–2.45 (1 H, m, 4-H), 2.55–2.63 (1 H, m, 4-H), 2.64–2.70 (1 H, m, 3-H), 4.06–4.15 (2 H, m, $CO_2CH_2CH_3$), 4.75 (1 H, s, 1′-H), 7.27–7.50 (5 H, m). δ_C (150 MHz; $CDCl_3$) 14.2 (CH_3), 24.8 (CH_3), 26.6 (CH_3), 28.7 (CH_3), 38.1 (C4), 53.6 (C3), 60.7 ($CO_2CH_2CH_3$), 69.5 (C1′), 83.2 (C2), 84.2 (C5), 128.3, 129.1, 129.2, 137.8, 171.2 ($CO_2CH_2CH_3$). NOESY (cross peaks) 3-H ↔ 1′-H.

C5.4 Treatment of 1-phenylpent-4-en-1-ol (1a) with *N*-chlorosuccinimide

To a solution of alkenol **1a** (81 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added *N*-chlorosuccinimide (100 mg, 0.75 mmol) and the reaction was mixture stirred at 20 °C. Repeated filtration and GC/MS-analysis of small samples of the reaction mixture displayed neither signals of 5-(chloromethyl)-2-phenyl-tetrahydrofuran (**2a**) nor of 4,5-dichloro-1-phenylpentan-1-ol (**6a**) within 4 d.

C5.5 Treatment of 1-phenylpent-4-en-1-ol (1a) with TBHP and VO(L^1)(OEt)

To a solution of alkenol **1a** (325 mg, 2.0 mmol) in MeCN (20 mL) was added dry py·HCl (346 mg, 3.0 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 1.36 mL, 3.0 mmol), and VO(L^1)(OEt)[15] (0.04 mmol, 2 mol%) at 20 °C. The reaction mixture was stirred for 24 h at 50 °C and for further 4 d at 20 °C. The mixture was concentrated under reduced pressure. The oily residue was purified by column chromatography (SiO_2, Et_2O/pentane 1/10 → 1/1).

Isolated fractions contained the recovered alkenol **1a**[4] (84 mg, 26 %) and 1-phenyl-4-penten-1-one[16] (87 mg, 27 %), along with two unknown minor side products (16 mg and 24 mg). Neither products of chlorocyclization (e.g. **2a**) nor dichlorination (**6a**) were detected (NMR, GC/MS).

C6 Oxidative Chlorination of 5,5-Dimethylcyclohexane-1,3-dione (8)

C6.1 Transition metal-catalyzed oxidative chlorination of 5,5-Dimethylcyclohexane-1,3-dione (8)

To a solution of 5,5-Dimethylcyclohexane-1,3-dione (**8**) (0.5 mmol) in dry DMC (10 mL) under an atmosphere of nitrogen was added dry py·HCl (173 mg, 1.5 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 360 µL, 1.5 mmol), and transition metal catalyst (**4a** or **5**) (0.025 mmol, 5 mol%) at 20 °C. The reaction mixture was stirred in the dark (flask wrapped in aluminium foil) for 24 h at 20 °C (for catalyst **5**) or 40 °C (for catalyst **4a**). The mixture was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2, CH_2Cl_2).

C6.2 Oxidative chlorination of 5,5-Dimethylcyclohexane-1,3-dione (8) via the salt-method

To a solution of 5,5-Dimethylcyclohexane-1,3-dione (**8**) (0.5 mmol) in dry DMC (10 mL) under an inert gas atmosphere was added KCl (112 mg, 1.5 mmol), and oxone® (615 mg, 1.0 mmol) at 30 °C. The reaction was stirred for 20 h in the dark (flask wrapped in aluminium foil) at 30 °C. The mixture was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2, CH_2Cl_2).

Experimental data for 2,2-dichloro-5,5-dimethyl-1,3-cyclohexanedione (9)[17][18] Colorless solid, R_f = 0.64 [CH_2Cl_2]. δ_H (400 MHz; $CDCl_3$) 1.04 (6 H, s, 2 × CH_3), 2.95 (4 H, s, 4-H, 6-H). δ_C (100 MHz; $CDCl_3$) 28.0 (2 × CH_3), 30.4 (C5), 48.9 (C4 and C6), 85.1 (C2), 192.1 (C1 and C3).

C7 Arene Chlorination

C7.1 General procedure for transition metal-catalyzed oxidative chlorination of arenes 10a–c

To a solution of an arene **10a–c** (0.5 mmol) in dry DMC (10 mL) under an atmosphere of nitrogen was added dry py·HCl (87 mg, 0.75 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 180 µL, 0.75 mmol), and a transition metal catalyst (**4a** or **5**) (0.025 mmol, 5 mol%) at 20 °C. The reaction was stirred for 24 h in the dark (flask wrapped in aluminium foil) at 20 °C (for

catalyst **5**) or 40 °C (for catalyst **4a**). The mixture was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2, CH_2Cl_2).

C7.2 General procedure for oxidative chlorination of arenes 9a–c via the salt-method

To a solution of an arene **10a–c** (0.5 mmol) in dry DMC (10 mL) under an inert gas atmosphere was added KCl (56 mg, 0.75 mmol), and oxone® (307 mg, 0.5 mmol) at 20 °C. The reaction was stirred for 24 h in the dark (flask wrapped in aluminium foil) at 30 °C. The mixture was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2, CH_2Cl_2).

C7.3 Experimental data of reaction products

C7.3.1 Oxidative chlorination of anisole (10a)[19][20]

Colorless oil, mixture of isomers. **2-Chloro-1-methoxybenzene (*ortho*-11a)**. δ_H (400 MHz; $CDCl_3$) 3.91 (3 H, s, CH_3), 6.89–6.94 (2 H, m), 7.22–7.24 (1 H, m), 7.34–7.40 (1 H, m). **4-Chloro-1-methoxybenzene (*para*-11a)** δ_H (400 MHz; $CDCl_3$) 3.79 (3 H, s, CH_3), 6.80–6.86 (2 H, m), 7.21–7.26 (2 H, m).

C7.3.2 Oxidative chlorination of 1,3-dimethoxybenzene (10b)[20][21]

Colorless solid, mixture of isomers. **4-Chloro-1,3-dimethoxybenzene (11b)**. δ_H (400 MHz; $CDCl_3$) 3.70 (3 H, s, CH_3), 3.78 (3 H, s, CH_3), 6.34 (1 H, dd, *J* 8.8, 2.7 Hz), 6.41 (7 H, d, *J* 2.5 Hz), 7.15 (7 H, d, *J* 8.6 Hz). δ_C (100 MHz; $CDCl_3$) 55.6 (CH_3), 56.0 (CH_3), 100.0, 105.1, 114.1, 130.1, 155.6, 159.4. **4,6-Dichloro-1,3-dimethoxybenzene (12b)**. δ_H (400 MHz; $CDCl_3$) 3.82 (6 H, s, 2 × CH_3), 6.44 (1 H, s), 7.17 (1 H, s). δ_C (100 MHz; $CDCl_3$) 56.5 (2 × CH_3), 97.7, 114.0, 130.5, 154.5.

C7.3.3 Oxidative chlorination of 1,3,5-trimethoxybenzene (10c)[20][21]

Colorless solid, mixture of isomers. **2-Chloro-1,3,5-trimethoxybenzene (11c).** δ_H (400 MHz; $CDCl_3$) 3.81 (3 H, s, CH_3), 3.88 (6 H, s, CH_3), 6.18 (2 H, s). δ_C (100 MHz; $CDCl_3$) 55.5 (CH_3), 56.3 (CH_3), 91.5, 102.6, 156.5, 159.4. **2,4-Dichloro-1,3,5-trimethoxybenzene (12c).** δ_H (400 MHz; $CDCl_3$) 3.89 (3 H, s, CH_3), 3.91 (6 H, s, CH_3), 6.37 (1 H, s). δ_C (100 MHz; $CDCl_3$) 56.5 (CH_3), 60.6 (CH_3), 93.2, 109.7, 153.9, 154.8.

C8 Competition Kinetic Experiments

C8.1 General procedure for transition metal-catalyzed oxidative chlorocyclization of 1-phenyl-4-penten-1-ol (1a) versus oxidative chlorination of anisole 10a

A solution of 1-phenyl-4-penten-1-ol (**1a**) (0.1 mmol), dry py·HCl (0.02 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 0.02 mmol), and a transition metal catalyst (0.005 mmol, 5 mol%) in a mixture of dry DMC (0.5 mL) and MeCN (0.5 mL) was added to a solution of anisole **10a** (1, 5, or 10 mmol) in dry DMC (5 mL) under an atmosphere of nitrogen at 20 °C. The reaction mixture was stirred for 24 h in the dark (flask wrapped in aluminium foil) at the indicated temperature (see Table 6 of the associated article), after which the yields of chlorination products were quantified by GC-MS using authentic samples of **2a** and **11a** as references and *n*-decane as internal standard.

C9 Oxidative Chlorination of 2,3-Dimethylbutane (13)

C9.1 Preparation of 2-chloro-2,3-dimethylbutane (14a) and 1-chloro-2,3-dimethylbutane (14b)[22]

Chlorodimethylbutanes **14a** and **14b** were prepared from 2,3-dimethylbutane (**13**) (6.6 g, 77 mmol) and SO_2Cl_2 according to Russel *et al.*. The reaction mixture was purified by distillation to furnish a colorless liquid (36 %, 39/61-mixture of **14a** and **14b**). bp 117–119 °C.[23]

2-Chloro-2,3-dimethylbutane (14a). δ_H (600 MHz; $CDCl_3$) 1.02 (6 H, d, *J* 6.7 Hz, 2 × CH_3), 1.54 (6 H, s, 2 × CH_3), 1.86–1.93 (1 H, sept, *J* 6.7 Hz, 3-H). δ_C (150 MHz; $CDCl_3$) 18.3 (CH_3), 30.2 (CH_3), 40.4 (C3), 75.6 (C2). **1-Chloro-2,3-dimethylbutane (14b)**. δ_H (600 MHz; $CDCl_3$) 0.86 (3 H, d, *J* 6.9 Hz, CH_3), 0.92 (3 H, d, *J* 6.9 Hz, CH_3), 0.96 (3 H, d, *J* 6.7 Hz, CH_3), 1.61–1.68 (1 H, m, 2-H), 1.74–1.81 (1 H, m, 3-H), 3.43 (1 H, dd, *J* 10.8, 6.9 Hz, 1-H), 3.53 (1 H, dd, *J* 10.6, 5.2 Hz, 1-H). δ_C (150 MHz; $CDCl_3$) 14.0 (CH_3), 18.1 (CH_3), 20.4 (CH_3), 29.8 (C3), 41.4 (C2), 49.9 (C1).

C9.2 Transition metal-catalyzed oxidative chlorination of 2,3-dimethylbutane (13)

To a solution of 2,3-dimethylbutane (**13**) (173 mg, 2 mmol) in dry, deaerated DMC or MeCN (5 mL) was added py·HCl (46 mg, 0.40 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 100 µL, 0.40 mmol), and catalyst **4a** (9 mg, 0.02 mmol) at 40 °C under an atmosphere of nitrogen. The reaction mixture was irradiated with a 150 W tungsten light bulb or stirred for 24 h in the

dark (flask wrapped in aluminium foil) at 40 °C and filtrated through a small pad of SiO_2. The filtrate was analyzed by quantitative GC-MS using *n*-decane as internal standard.

C9.3 Solid acid-catalyzed oxidative chlorination of 2,3-dimethylbutane (13) via the salt-method

To a solution of 2,3-dimethylbutane (**13**) (173 mg, 2 mmol) in dry, deaerated DMC or MeCN (5 mL) was added KCl (30 mg, 0.40 mmol), and oxone® (246 mg, 0.40 mmol) at 40 °C under an atmosphere of nitrogen. The reaction mixture was irradiated with a 150 W light bulb or stirred for 24 h in the dark (flask wrapped in aluminium foil) at 40 °C and filtrated through a small pad of SiO_2. The filtrate was analyzed by quantitative GC-MS using *n*-decane as internal standard.

C10 Allylic Chlorination

C10.1 Molybdenum-catalyzed oxidative chlorination of nerol (15) (single batch addition of py·HCl)

To a solution of nerol **15** (77.0 mg, 0.5 mmol) in dry DMC (20 mL) was added dry py·HCl (87 mg, 0.75 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 180 µL, 0.75 mmol), and catalyst **4a** (11.5 mg, 0.025 mmol, 5 mol%) at 20 °C. The reaction was stirred for 24 h in the dark (flask wrapped in aluminium foil) at 40 °C. The mixture was concentrated under reduced pressure and the oily residue purified by column chromatography (SiO_2, CH_2Cl_2). **(6*Z*)-3-Chloro-2,2,6-trimethyl-3,4,5,8-tetrahydro-*2H*-oxocine (17)**.[24] Yield: 1.1 mg (0.006 mmol, 1 %) colorless oil, R_f = 0.71. δ_H (400 MHz; $CDCl_3$) 1.32 (3 H, s, CH_3), 1.37 (3 H, s, CH_3), 1.66–1.71 (1 H, m, 4-H), 1.72 (3 H, br. q, *J* 1.9 Hz, CH_3), 1.97–2.10 (2 H, m, 5-H), 3.32–3.41 (1 H, m, 4-H), 4.18–4.23 (3 H, m, 3-H, 8-H), 5.20 (1 H, br. s., 7-H). δ_C (100 MHz; $CDCl_3$) 21.6 (CH_3), 24.6 (CH_3), 26.1 (CH_3), 29.7 (C4), 33.3 (C5), 63.2 (C3 or C8), 63.3 (C3 or C8), 79.8 (C2), 124.0 (C7), 132.8 (C6). HRMS (EI): Calc. for: $C_{10}H_{17}OCl^{35}$ 188.0968, Found: 188.0963; Calc. for: $C_{10}H_{17}OCl^{37}$ 190.0938 Found: 190.0951.

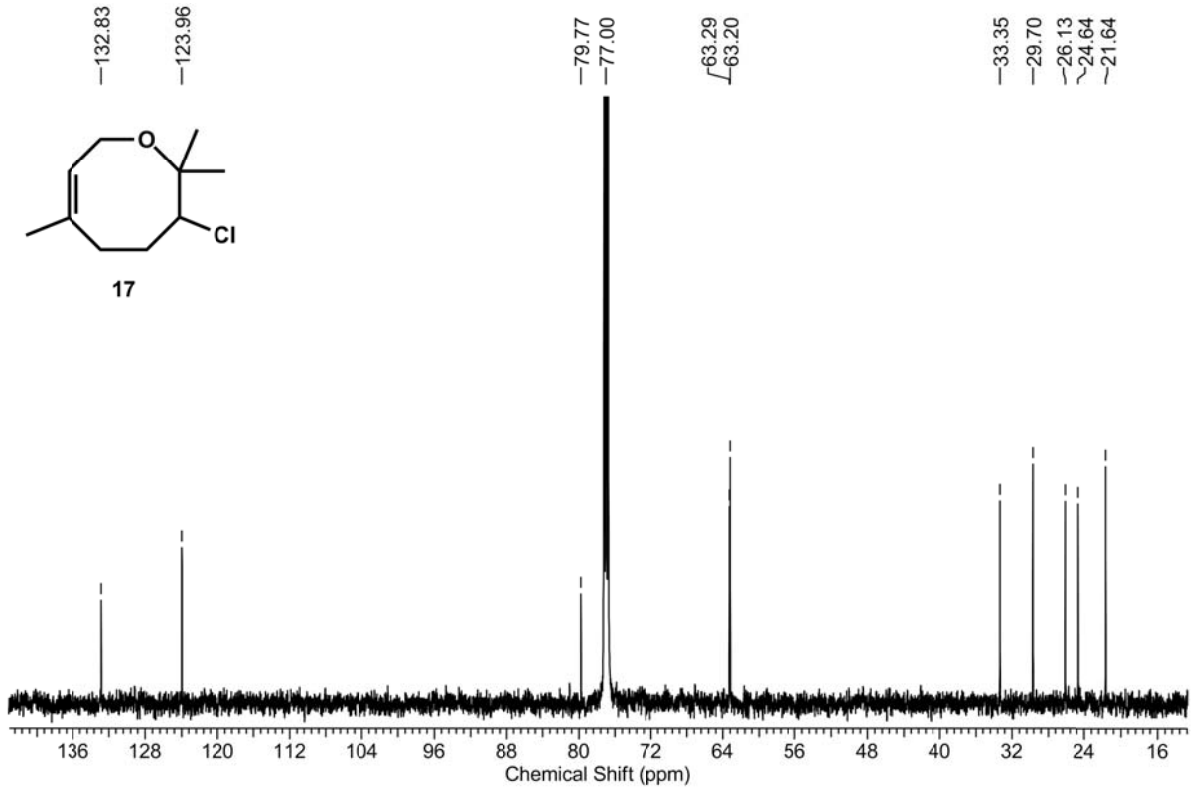


Figure C2. ^{13}C-NMR spectrum of (6*Z*)-3-chloro-2,2,6-trimethyl-3,4,5,8-tetrahydro-*2H*-oxocine (**17**).

2,6-Dichloro-7-methyl-3-methyleneoct-7-en-1-ol (16b)[25] and **(*E*)-2,6-chloro-3,7-dimethyl-octa-3,7-dien-1-ol (16c)**. Yield: 23.7 mg (0.106 mmol, 21 %) colorless oil, 78/22-mixture of isomers, R_f = 0.39. Anal. calcd. for $C_{10}H_{16}Cl_2O$ (223.14): C, 53.83; H, 7.23; Found: C, 53.93; H, 7.16. **2,6-Dichloro-7-methyl-3-methyleneoct-7-en-1-ol (16b)**. δ_H (400 MHz; $CDCl_3$) 1.82 (3 H, s, CH_3), 1.93–2.16 (4 H, m, 4-H, 5-H, OH), 2.21–2.26 (1 H, m, 4-H), 3.72–3.78 (1 H, m, 1-H), 3.79–3.86 (1 H, m, 1-H), 4.37–4.42 (1 H, m, 6-H), 4.43–4.50 (1 H, m, 2-H), 4.92–4.94 (1 H, m, 8-H), 5.04 (1 H, s, 8-H), 5.10 (1 H, s, methylene), 5.27 (1 H, s, methylene). **(*E*)-2,6-Chloro-3,7-dimethylocta-3,7-dien-1-ol (16c)**. δ_H (400 MHz; $CDCl_3$) 1.74 (3 H, s, CH_3), 1.82 (3 H, s, CH_3), 1.84–1.90 (1 H, m, OH), 2.52–2.62 (1 H, m, 5-H), 2.63–2.72 (1 H, m, 5-H), 3.79–3.87 (2 H, m, 1-H), 4.37–4.43 (1 H, m, 6-H), 4.43–4.50 (1 H, m, 2-H), 4.93 (1 H, s, 8-**H**), 5.02 (1 H, s, 8-H), 5.52–5.60 (1 H, d, *J* 7.0, 4-H). δ_C (100 MHz; $CDCl_3$) [mixture of stereo- and regioisomers] 12.2, 12.5, 17.05, 17.07, 17.3, 17.4, 29.2, 29.30, 30.3, 34.2, 34.6, 34.8, 34.97, 35.04, 63.8, 65.1, 65.2, 65.41, 65.48, 65.53, 65.9, 66.0, 66.1, 66.2, 68.8, 68.9, 114.5, 114.6, 114.8, 115.4, 125.5, 126.7, 126.9, 134.4, 134.50, 135.7, 143.7, 143.8, 143.96, 144.03, 144.17, 144.22 (only major resonances specified). HRMS (EI): Calc. for: $C_{10}H_{16}O^{35}Cl_2$ 222.0578, Found: 222.0568; Calc. for: $C_{10}H_{16}O^{35}Cl^{37}Cl$ 224.0549, Found: 224.0556; Calc. for: $C_{10}H_{16}O^{37}Cl_2$ 226.0519, Found: 226.0551.

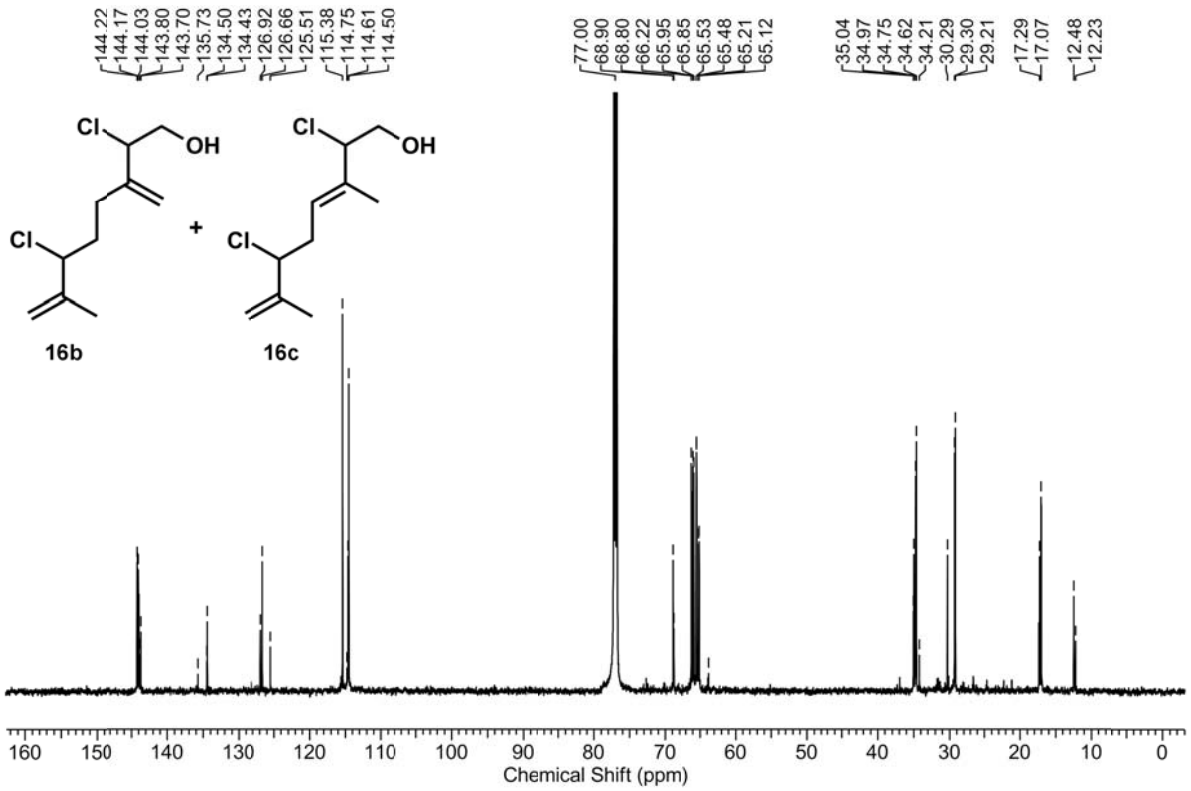


Figure C3. ^{13}C-NMR spectrum of the isomeric mixture of 2,6-dichloro-7-methyl-3-methyleneoct-7-en-1-ol (**16b**) and (*E*)-2,6-chloro-3,7-dimethylocta-3,7-dien-1-ol (**16c**).

(*Z*)-6-Chloro-3,7-dimethylocta-2,7-dien-1-ol (16a).[26][27] Yield: 62.3 mg (0.33 mmol, 66 %) colorless liquid, R_f = 0.27. δ_H (400 MHz; $CDCl_3$) 1.44 (1 H, br. s., OH), 1.74 (3 H, s, CH_3), 1.81 (3 H, s, CH_3), 1.83–1.99 (2 H, m, 5-H), 2.11–2.23 (2 H, m, 4-H), 4.07–4.20 (2 H, m, 1-H), 4.31 (1 H, dd, *J* 8.2, 6.1 Hz, 6-H), 4.89–4.93 (1 H, m, 8-H), 5.02 (1 H, s, 8-H), 5.48 (1 H, t, *J* 7.1 Hz, 2-H). δ_C (100 MHz; $CDCl_3$) 17.1 (CH_3), 23.2 (CH_3), 29.0 (C4), 34.8 (C5), 58.9 (C1), 66.2 (C6), 114.3 (C8), 125.5 (C2), 138.1 (C3), 144.3 (C7). Anal. calcd. for $C_{10}H_{17}ClO$ (188.69): C, 63.65; H, 9.08; Found: C, 64.02; H, 9.09.

C10.2 Molybdenum-catalyzed oxidative chlorination of nerol (15) (slow addition of py·HCl)

To a solution of nerol **15** (77 mg, 0.5 mmol) and $MoO_2(L^1)$ (11.5 mg, 0.025 mmol, 5 mol%) in dry DMC (20 mL) was added a solution of py·HCl (87 mg, 0.75 mmol) and *tert*-butyl hydroperoxide (4.1 M in toluene, 180 µL, 0.75 mmol) in dry MeCN (4 mL) via syringe pump (0.004 mL/min) at 40 °C. The reaction mixture was stirred in the dark (flask wrapped in aluminium foil) at 40 °C for 24 h. After concentration under reduced pressure the oily residue was purified by column chromatography (SiO_2, CH_2Cl_2). **(6*Z*)-3-chloro-2,2,6-trimethyl-3,4,5,8-**

tetrahydro-*2H*-oxocine (17).[24] Yield: 15.1 mg (0.08 mmol, 16 %) colorless oil. **2,6-Dichloro-7-methyl-3-methyleneoct-7-en-1-ol (16b)**.[25] Yield: 3.8 mg (0.02 mmol, 4 %) colorless oil. **(*Z*)-6-Chloro-3,7-dimethylocta-2,7-dien-1-ol (16a)**.[26][27] Yield: 47 mg (0.25 mmol, 50 %) colorless liquid. Analytical and spectroscopic data of all compounds are consistent with that specified in section C10.1.

C10.3 Molybdenum-catalyzed oxidative chlorination of citronellol (18)

Oxidative chlorination of citronellol **18** (78 mg, 0.5 mmol) as described in section C10.1 furnished 67.5 mg (0.354 mmol, 71 %) 6-chloro-3,7-dimethylocta-7-en-1-ol (**19**)[28] as a 50/50-mixture of *like*/*unlike* isomers. R_f = 0.15 [CH_2Cl_2]. δ_H (400 MHz; $CDCl_3$) 0.92 (3 H, dd, *J* 6.6, 1.2, CH_3), 1.26–1.50 (3 H, m, 2-H, 4-H), 1.54–1.65 (3 H, m, 2-H, 3-H, OH), 1.74–1.92 (2 H, m, 5-H), 1.80 (3 H, d, *J* 0.8, CH_3), 3.61–3.75 (2 H, m, 1-H), 4.35 (1 H, t, *J* 7.4, 6-H), 4.86–4.91 (1 H, m, 8-H), 5.00 (1 H, s, 8-H). δ_C (100 MHz; $CDCl_3$) 16.8 and 17.0 (CH_3), 19.5 (CH_3), 29.1 and 29.2 (C3), 33.9 and 34.0 (C4), 34.1 (C5), 39.7 (C2), 60.9 (C1), 67.1 (C6), 114.1 and 114.2 (C8), 144.4 and 144.5 (C7).

C10.4 Synthesis of (±)-rose oxide

To a solution of citronellol **18** (780 mg, 5 mmol) in DMC (25 mL) was added py·HCl (925 mg, 8 mmol), *tert*-butyl hydroperoxide (4.1 M in toluene, 1.95 mL, 8 mmol), $TiL^4(OEt)_2$ (131 mg, 0.25 mmol, 5 mol%) at 20 °C. The reaction mixture was stirred in the dark (flask wrapped in aluminium foil) at 20 °C for 24 h and concentrated under reduced pressure. The oily residue was dissolved in dry EtOH (20 mL). KO^{t}Bu (1.12 g, 10 mmol) was added, and the mixture heated in a pressure Schlenk tube to 150 °C for 2.5 h. After cooling to 20 °C the suspension was poured into aq. HCl (2 M, 30 mL) and stirred for 1 h at 20 °C. The aqueous mixture was extracted with Et_2O (3 × 30 mL) and the combined extracts were subsequently washed with aq. NaOH (2 M, 3 × 30 mL), H_2O (30 mL), and aq. sat. NaCl (30 mL). After drying ($MgSO_4$), the solution was concentrated under reduced pressure to leave an oil, which was purified by column chromatography (SiO_2, CH_2Cl_2). Yield: 329 mg (2.14 mmol, 43 % for 3 steps) colorless liquid, 84/16-mixture of *cis*/*trans*-isomers.[27][29] ***cis*-2-(2′-methyl-1′-propenyl)-4-methyl-tetrahydropyran (*cis*-rose oxide)**. δ_H (400 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6.4 Hz, CH_3), 0.96–1.08 (1 H, m, 3-H), 1.14–1.28 (1 H, m, 5-H), 1.47–1.58 (2 H, m, 3-H, 5-H), 1.58–1.66 (1 H, m, 4-H), 1.68 (3 H, d, *J* 1.2 Hz, CH_3), 1.71 (3 H, d, *J* 1.2 Hz, CH_3), 3.46 (1 H, td, J_t 11.9, J_d 2.1 Hz, 6-H), 3.92–4.02 (2 H, m, 2-H, 6-H), 5.15 (1 H, dt, J_d 8.1, J_t 1.3 Hz, 1′-H). δ_C (100 MHz; $CDCl_3$) 18.3 (CH_3), 22.3 (CH_3), 25.7 (CH_3), 30.3 (C4), 34.4 (C5), 40.8 (C3), 67.9 (C6), 74.6 (C2), 126.4 (C1′), 135.1

(C2′). ***trans*-2-(2′-methyl-1′-propenyl)-4-methyl-tetrahydropyran (*trans*-rose oxide)**. δ_H (400 MHz; $CDCl_3$) 1.06 (3 H, d, *J* 6.1 Hz, CH_3), 1.23–1.29 (1 H, m, 3-H), 1.47–2.05 (4 H, m, 3-H, 4-H, 5-H), 1.68 (3 H, s, CH_3), 1.71 (3 H, s, CH_3), 3.64–3.77 (1 H, m, 6-H), 4.36 (1 H, td, J_t 8.1, J_d 3.3 Hz, 2-H), 5.26–5.31 (1 H, m, 1′-H). δ_C (100 MHz; $CDCl_3$) 18.3 (CH_3), 19.2 (CH_3), 24.9 (CH_3), 25.8 (C4), 32.5 (C5), 38.2 (C3), 62.2 (C6), 69.1 (C2), 125.4 (C1′), 135.5 (C2′).

C11 References

[1] W. L. F. Armarego, D. D. Perrin, *Purification of laboratory chemicals*, Pergamon Press, Oxford, **1996**.

[2] K. B. Sharpless, T. R. Verhoeven, *Aldrichim. Acta* **1979**, *12*, 63–74.

[3] V. H. Rawal, S. P. Singh, C. Dufour, C. Michoud, *J. Org. Chem.* **1993**, *58*, 7718–7727.

[4] A. C. Dupont, V. H. Audia, P. P. Waid, J. P. Carter, *Synth. Commun.* **1990**, *20*, 1011–1021.

[5] Y.-S. Hon, Y.-W. Liu, C.-H. Hsieh, *Tetrahedron* **2004**, *60*, 4837–4860.

[6] M. A. Hashem, P. Weyerstahl, *Tetrahedron* **1984**, *40*, 2003–2009.

[7] O. Brücher, U. Bergsträßer, H. Kelm, J. Hartung, M. Greb, I. Svoboda, H. Fuess, *Tetrahedron* **2012**, *68*, 6968–6980.

[8] J. Duran, D. Oliver, A. Polo, J. Real, J. Benet-Buchholz, X. Fontrodona, *Tetrahedron: Asymmetry* **2003**, *14*, 2529–2538.

[9] L. Kuczynski, M. Wilimowski, M. Baginska, J. Soloducho, *Pol. J. Pharmacol. Pharm.* **1975**, *27*, 549–553.

[10] O. Brücher, J. Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.

[11] E. Haegele, *Chem. Ber.* **1892**, *25*, 2753–2756.

[12] J. J. Fernández, A. Fernández, D. Vázquez-García, M. López-Torres, A. Suárez, N. Gómez-Blanco, J. M. Vila, *Eur. J. Inorg.Chem.* **2007**, *2007*, 5408–5418.

[13] D. K. Zheglova, V. Gindin, A. I. Koltsov, *J. Chem. Res., Synop.* **1995**, 32–33.

[14] S. Bellemin-Laponnaz, K. S. Coleman, P. Dierkes, J. P. Masson, J. A. Osborn, *Eur. J. Inorg. Chem.* **2000**, 1645–1649.

[15] M. J. Clague, N. L. Keder, A. Butler, *Inorg. Chem.* **1993**, *32*, 4754–4761.

[16] W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard, F. D. Toste, *Angew. Chem. Int. Ed.* **2010**, *49*, 5519–5522.

[17] C. D. Gabbutt, J. D. Hepworth, B. M. Heron, *Tetrahedron* **1994**, *50*, 5245–5254.

[18] L. P. Hager, D. R. Morris, F. S. Brown, H. Eberwein, *J. Biol. Chem.* **1966**, *241*, 1769–1777.

[19] B. S. Moon, H. Y. Choi, H. Y. Koh, D. Y. Chi, *Bull. Korean Chem. Soc.* **2011**, *32*, 472–476.

[20] M. Hirano, S. Yakabe, H. Monobe, T. Morimoto, *Can. J. Chem.* **1997**, *75*, 1905–1912.

[21] L. Yang, Z. Lu, S. S. Stahl, *Chem. Commun.* **2009**, 6460–6462.

[22] M. S. Kharasch, H. C. Brown, *J. Am. Chem. Soc.* **1939**, *61*, 2142–2150.

[23] G. A. Russell, *J. Am. Chem. Soc.* **1958**, *80*, 5002–5003.

[24] A. Butler, J. N. Carter-Franklin, *Nat. Prod. Rep.* **2004**, *21*, 180–188.

[25] B. V. Lyalin, A. V. Lozanova, V. A. Petrosyan, A. M. Moiseenkov, *Russ. Chem. Bull.* **1989**, *38*, 309–313.

[26] L. Novák, L. Poppe, C. Szántay, É. Szabó, *Synthesis* **1985**, *1985*, 939–941.

[27] S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver, J. Wolinsky, *Tetrahedron Lett.* **1980**, *21*, 441–444.

[28] M. Bulliard, G. Balme, N. Monteiro, J. Gore, *Bull. Soc. Chim. Fr.* **1991**, 222–231.

[29] L. Coulombel, M. Weïwer, E. Duñach, *Eur. J. Org. Chem.* **2009**, *2009*, 5788–5795.

Anhang D

Übersichtsartikel

Bromoperoxidases and Functional Enzyme Mimics as Catalysts for Oxidative Bromination – A Sustainable Synthetic Approach.

Diana Wischang, Oliver Brücher, Jens Hartung, *Coord. Chem. Rev.* **2011**, *255*, 2204–2217.

Coordination Chemistry Reviews 255 (2011) 2204–2217

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Bromoperoxidases and functional enzyme mimics as catalysts for oxidative bromination—A sustainable synthetic approach

Diana Wischang, Oliver Brücher, Jens Hartung*

Fachbereich Chemie, Organische Chemie, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern, Germany

Contents

ARTICLE INFO

Article history:
Received 1 December 2010
Accepted 4 April 2011
Available online 12 April 2011

Dedicated to Prof. Dr. Bernd Giese on the occasion of his 70th birthday.

Keywords:
Bromoperoxidase
Bromocyclization
Brown alga
Pyrrole
Oxidation catalysis
Vanadium

ABSTRACT

The discovery of enzymes that utilize hydrogen peroxide to oxidize bromide under physiological conditions provided a strong stimulus to the field of oxidative bromination. A synthetically useful enzyme, to catalyze the oxidation of bromide, for bromofunctionalization of donor-substituted arenes in solutions of hydrogen peroxide and sodium bromide, is a vanadate(V)-dependent bromoperoxidase from the brown alga *Ascophyllum nodosum*. This enzyme operates in homogeneous solutions of buffered aqueous *tert*-butanol (pH 6.2), or, to simplify repetitive use, in a two-phase system after immobilization onto magnetic beads. Synthesis of cyclic bromohydrin ethers (tetrahydrofurans and tetrahydropyrans) and vicinal dibromides from unsaturated hydrocarbons, on the other hand, occurs more effectively in polar aprotic solvents. Under such conditions the more lipophilic *tert*-butyl hydroperoxide serves as oxidant, which is activated by oxovanadium(V) complexes (functional bromoperoxidase mimics). Protons and bromide ions, which are consumed for in situ generation of bromine, are supplied in organic solution by fragmentation of 3-bromopropionic acids. The structure-reactivity data obtained from oxidations catalyzed by bromoperoxidases and functional enzyme mimics pose a valuable guideline for predicting selectivity in biomimetic synthesis of organobromines from terpenes, acetogenins, and pyrrole alkaloids.

Abbreviations: BPO, bromoperoxidase; CHD, cyclohexa-1,4-diene; DTAB, dodecyl trimethyl ammonium bromide; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; MES, morpholine-4-ethanesulfonic acid; M-PVA, magnetic polyvinyl alcohol-coated beads, either epoxide (E) or amino-functionalized (N), 01 and 12 refer to particle sizes; ^{118}NBS, *N*-bromosuccinimide; NHE, normal hydrogen electrode; TBHP, *tert*-butyl hydroperoxide; V_{Br}PO, vanadate(V)-dependent bromoperoxidase; V_{Br}PO(*An*I), vanadate(V)-dependent bromoperoxidase from *Ascophyllum nodosum*, isoenzyme I, PDB access code 1QI9.

* Corresponding author. Tel.: +49 631 205 2431; fax: +49 631 205 3921.
E-mail address: hartung@chemie.uni-kl.de (J. Hartung).

0010-8545/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ccr.2011.04.003

1. Introduction

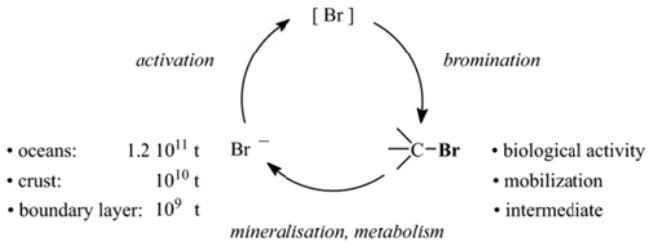
> ...A myriad of simple haloalkanes have been isolated from marine algae...It seems likely that the "smell of the ocean" is due to this potpourri of volatile halocarbons.... [1]

Organobromines have always come along with human civilization and will continue to do so [2,3]. Bromoalkanes are formed in enormous quantity and diversity from photochemical reactions in the marine boundary layer [4,5], geothermal events [6], and metabolic pathways (Scheme 1) [7–9]. Industrial production of organobromines started in the middle of the 19th century [10], that is, with some offset from the time that Carl Löwig (1825) [11,12] and Antoine-Jérôme Balard (1826) discovered bromine as a new chemical element [13,14].

The use of organobromines in life and society is a tribute to the unique properties of the carbon–bromine bond. A bromosubstituent is able to raise lipophilicity of an organic molecule, which improves properties of a substance to serve as emulsifier, insecticide, or biologically active compound [15,16]. Aryl-bound bromosubstituents lower the rate of oxidative arene metabolism, which is important to increase the in vivo stability of pharmaceuticals. Conjugation between an aromatic π-system and a pair of non bonding electrons at bromine shifts electronic excitation energies of chromophors and thus induces auxochromic effects. In other arenes, the carbon bromine bond is a key structural element to achieve flame retarding properties of a material (vide infra) [17–20]. The aliphatic carbon–bromine bond, on the other hand, combines in a unique manner stability and chemical reactivity. This bond can be selectively broken in heterolytic or homolytic reactions, to serve as progenitor of carbocations, carbanions, or free carbon radicals [10,21]. The propensity to undergo chemical transformations is the reason for the use of bromoalkanes as rodenticides [22], fire extinguishants [23], and gasoline additives [10]. Surprisingly little is known about the biological role of naturally occurring organobromines [3], but it seems reasonable to assume that producing organisms have similar interests in these substances as man.

The common bromine source for synthesis of organobromines is bromide. Bromide-containing minerals, such as bromocarnallite ($MgBr_2{\cdot}KBr{\cdot}6H_2O$), bromosylvinite [K(Cl,Br)], and silver halide ores {bromoargyrite (AgBr), embolite [Ag(Cl,Br)], capgaronnite [HgS·Ag(Cl,Br)]} unfortunately are rare in the earth's crust [10]. Seemingly unlimited quantities of bromide, however, are dissolved in the oceans (65 mg L^{-1} to 6.5 g L^{-1}), which therefore serve as industrial bromide resource to produce electrophilic bromination agents [10].

In synthesis, carbon–bromine bonds are formed from radical reactions, nucleophilic substitutions, and electrophilic additions [2,24]. The majority of organobromines, however, originates from electrophilic additions, which requires an a priori oxidation of bromide [25,26]. To oxidize bromide on a technical scale, manufacturers in the early days used manganese dioxide–sulfuric acid blends, whereas chlorine (Steaming-Out Process) or air–chlorine mixtures in combination with sulfuric acid (Blowing-Out Process) are standard procedures today. The annual production of bromine has continuously increased over the past decades and has reached a global volume of more than 563,000 ton world wide in 2004 [10].



Scheme 1. Sources and sinks of organobromine compounds in the planetary bromine cycle {[Br] = Br^+_{solv}, Br•, BrO_n•, BrX_n^- (n = 1, 2, ...; X = e.g. Cl, Br), BrY (Y = Br, OH)}.

Molecular bromine is a favorable agent for synthesis, but it is corrosive and toxic. Transport, storage, and handling of bromine therefore require strict safety standards [10]. For synthesis of 1 ton of the flame retardant tetrabromobisphenol A (Scheme 2), 1.18 ton of bromine are needed. To produce this amount of bromine, bromide from about 134 m^3 of Dead Sea brine [ρ_{20} = 1.2334 g L^{-1}, 0.055 molar in bromide] [27,28] has to be crystallized as alkali salt and subsequently oxidized. Production of 1 ton of tetrabromobisphenol A also provides 165 m^3(0.6 ton), of hydrogen bromide as by-product. The hydrogen bromide must be separated in a recovery unit and disposed of, or oxidatively recycled. Hydrogen bromide, which is either supplied from a waste stream or an alkali bromide–mineral acid mixture, is oxidized on a technical basis with hydrogen peroxide at elevated temperature, to in situ-produce bromine. This method is the chemical basis for a procedure called the *on-site bromination* and is used to industrially prepare bromoarenes [29]. Low world market prices of bromine (1.39 $ per kilogram in 2006 in the United States) [30], high energy costs, and limited fields of application, however, preclude a wider spread use of the on-site bromination concept at the moment.

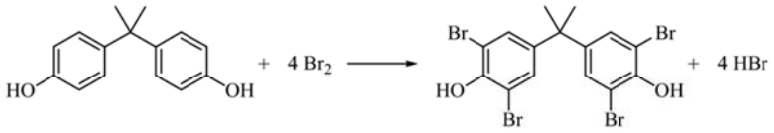
The lessons learned from nature show that the chemical elements are turned over in cycles, and sustainable production of organobromines therefore has to somehow follow the planetary bromine cycle (Scheme 1) [31]. The planetary bromine cycle starts from bromide. By looking at the structures of brominated secondary metabolites it is obvious that in biochemistry, as in organic synthesis, electrophilic hydrocarbon bromination dominates. To perform electrophilic bromination in nature requires the existence of effective pathways for bromide oxidation under physiological conditions. The quest for the origin of naturally produced organohalogens [32–34], led, among others, to the discovery of the marine bromoperoxidases [7,35–37], which utilize hydrogen peroxide to oxidize bromide dissolved in ocean water [38–40].

In the decades that followed the discovery of the bromoperoxidases, oxidative bromination has expanded into a dynamic area of research [25]. In this article, we therefore summarize the most recent developments in bromoperoxidase chemistry, and transformations using functional mimics for sustainable synthesis of organobromines [41,42]. To give the reader a better understanding of vanadate(V)-catalyzed oxidation for synthesis of naturally occurring organobromines, we included aspects of peroxide chemistry of vanadium(V), and peroxide-mediated oxidation of bromide. For bromide oxidation catalyzed by rhenium- [43], molybdenum- [44], tungsten- [39,45], and cobalt complexes [46], as well as organobromine formation via free radical reactions [47,48] or nucleophilic substitutions [49], the reader is referred to specialized articles, reviews, and book chapters [50,51]. The same should be done for aspects dealing with the systematics of brominated secondary metabolites [52–54].

2. General aspects

2.1. Peroxide-mediated oxidation of bromide

Standard reagents to oxidize bromide in bromoperoxidase chemistry are hydrogen peroxide and *tert*-butyl hydroperoxide (TBHP) [55]. For both compounds the mass fraction of transferable and therefore *active* oxygen is significant (47% for hydrogen peroxide and 17.8% for *tert*-butyl hydroperoxide), and by-products that are left from the oxygen atom transfer (water and *tert*-butanol) pose no concern for waste disposal. Hydrogen peroxide is administered



Scheme 2. Stoichiometry for synthesis of tetrabromobisphenol A [10,18].

as aqueous 30–50% solution, crystalline urea hydrogen peroxide (UHP) inclusion compound, or as hydrolyzable persalt (percarbonate, perborate or persulfate) [56]. *tert*-Butyl hydroperoxide is commercially available as 5.5 molar solution in nonane, 80% solution in di-*tert*-butylperoxide and water, and a reasonably priced 70% aqueous solution. The aqueous solution may be used to prepare an anhydrous ~3 molar solution of *tert*-butyl hydroperoxide in toluene [57], which is suited for most applications in oxidation catalysis.

Oxidation potentials show that hydrogen peroxide and *tert*-butyl hydroperoxide are able to oxidize bromide in aqueous or in polar aprotic solvents to furnish bromine (Table 1). At neutral pH, the two peroxides, however, are surprisingly inert toward bromide and have to be activated by a Brønsted- or a Lewis-acid [58–60]. The activated peroxide converts bromide into hypobromite (BrO^-), which exists in neutral aqueous solution predominantly as undissociated hypobromous acid ($pK_a = 8.7$) [61] (Scheme 3) [58].

2.2. Reactivity of oxovanadium(V) compounds toward nucleophiles and hydrogen peroxide

Vanadate(V) exists in neutral aqueous solution as a mixture of monovanadate (HVO_4^{2-} and $H_2VO_4^-$), divanadate, and tetravanadate. The equilibrium in a concentration range of 1–10 mM of vanadate(V) is in favor of the monomer [70]. Monovanadate reacts in pH-neutral to weakly acidic solution with alcohols [71,72], diols [73], and phenols [74], to furnish esters of orthovanadic acid, that is H_3VO_4 ($pK_a^1 = 3.5$, $pK_a^2 = 7.8$, $pK_a^3 = 12.5$) [75]. If treated with carboxylic acids [76], peptides [77,78], phosphate [79,80], or arsenate [79], monovanadate forms mixed anhydrides. Condensation of monovanadate and hydroxycarboxylic acid [81–83], provides mixed anhydride esters and water. Hydrogen peroxide (pK_a 11.6) and monovanadate ($H_2VO_4^-$) form oxoperoxovanadate(V) (Eq. (4); Scheme 4) [84]. The observed rate constant of this condensation in strongly acidic solution is $k^5 = 5 \times 10^3\ M^{-1}\ s^{-1}$ ($I = 3$ M, 25 °C; Eq. (5)) [85]. From acid and hydrogen peroxide dependence it was concluded that k^5 consists of three terms. One of the terms is directly proportional to proton concentration, the second indirectly, and the third independent from the acid strength. From pressure dependence of these rate constants in the pH-range of 0–1.5 activation parameters for oxoperoxovanadate(V) formation (Eq. (5)) of $\Delta H^{\ddagger} = 21\ kJ\ mol^{-1}$, $\Delta S^{\ddagger} = -69\ J\ mol^{-1}\ K^{-1}$ and $\Delta V^{\ddagger} = 15\ cm^3\ mol^{-1}$ were determined [85]. The equilibrium constant for oxoperoxovanadate(V)-formation in the range between pH 6.7 ($K^4 = 3 \times 10^3\ M^{-1}$; ~20 °C; $I = 1.0$ M) [86] and pH 1 ($K^5 = 3.7 \times 10^4\ M^{-1}$; 25 °C; $I = 0.3$–1.0 M) [87] is only moderately dependent on acid concentration [88].

Table 1
Oxidation potentials of elementary reactions associated with oxidative bromination

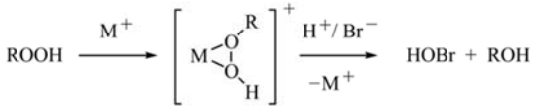
$Br^- \rightleftharpoons \frac{1}{2} Br_2 + e^-$ E^0_1 (eq. 1)

$Br^- + H_2O \rightleftharpoons HOBr + H^+ + 2e^-$ E^0_2 (eq. 2)

$ROOH + 2H^+ + 2e^- \rightleftharpoons ROH + H_2O$ E^0_3 (eq. 3)

Solvent	Eq.	E^0/V[a]
H_2O	(1)	$E^0_1 = 1.09$ [62,63]
CH_3CN	(1)	$E^0_1 = 0.86$ [64]
H_2O[b]	(2)	$E^0_2 = 1.33$ [65]
H_2O[c]	(3) (R = H)	$E^0_3 = 1.35$ [66]
CH_3OH/C_6H_6	(3) (R = *t*Bu)	$E^0_3 = 1.20$ [67]

[a] Versus NHE.
[b] pH 0; 0.76 V at pH 14.
[c] pH 7; 1.76 V at pH 0 and 0.87 V at pH 14 [66].



Scheme 3. Proposed mechanism for peroxide activation and bromide oxidation (R = H or *t*Bu; M = e.g. H or V^V) [42,68,69].

Hydrogen peroxide reacts with monoperoxovanadate(V) to give bisperoxovanadate(V) (Scheme 4). The rate constant at pH 2 (aqueous $HClO_4$) is $k^7 = 3.5 \times 10^3\ M^{-1}\ s^{-1}$ ($I = 3$ M, 25 °C). Activation parameter for this reaction (Eq. (7)) are $\Delta H^{\ddagger} = 40\ kJ\ mol^{-1}$, $\Delta S^{\ddagger} = -42\ J\ mol^{-1}\ K^{-1}$ and $\Delta V^{\ddagger} = 0\ cm^3\ mol^{-1}$ [85]. The equilibrium constant decreases from $K^6 = 2 \times 10^5\ M^{-1}$ (pH 6.7, ~20 °C, $I = 1$ M) [86] to $K^7 = 0.6$ M (pH 1.0, 25 °C, $I = 0.3$) [87], as the solution becomes more acidic.

Even higher concentration and aliquots of hydrogen peroxide provide tris- and tetrakisperoxovanadates from vanadate(V) [89]. The conditions required to prepare tris- and tetrakisperoxo complexes differ from parameters used in oxidation catalysis. Kinetic and thermochemical aspects dealing with tris- and tetrakisperoxovanadate formation therefore are not further considered in this article.

Molecular orbital theory predicts that peroxo coordination between vanadium(V) and oxygen occurs via σ- and π-bonding (Fig. 1). π-Bonding shifts electron density from the pair of non bonding electrons at the peroxide oxygens toward the metal, thus lowering repulsive interactions within the peroxo entity [90]. Transfer of electron density from the ligand to the metal is spectroscopically detectable by a ligand-to-metal-charge-transfer band at 455 nm ($\varepsilon = 278$, in 5×10^{-3} M $HClO_4$), which gives rise to the reddish brown color of oxoperoxovanadate [91]. Bonding of a second peroxo ligand causes the π-bond order to decrease from 1 to 0.5 because p-orbitals from two oxygen atoms now interact with the same vanadium-d-orbital. This model helps to explain the

$H_2VO_4^- + H_2O_2 \rightleftharpoons VO_2(O_2)^- + 2\,H_2O$ K^4 (eq. 4)

$VO_2^+ + H_2O_2 \overset{k^5}{\rightleftharpoons} VO(O_2)^+ + H_2O$ K^5 (eq. 5)

$VO_2(O_2)^- + H_2O_2 \rightleftharpoons VO(O_2)_2^- + H_2O$ K^6 (eq. 6)

$VO(O_2)^+ + H_2O_2 \overset{k^7}{\rightleftharpoons} VO(O_2)_2^- + 2\,H^+$ K^7 (eq. 7)

Scheme 4. Stoichiometry for peroxovanadate (Eqs. 4 and 5) and bisperoxovanadate formation (Eqs. 6 and 7; c_{H_2O} was treated as constant to obtain values and dimensions of K^{4-7} provided in the text) [85–88].

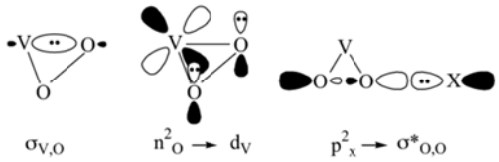


Fig. 1. MO models for peroxo ligand coordination to vanadium via σ- and π-bonding (left and center; n^2_O = pair of non bonding electrons in p-type orbitals at oxygen atoms), and bonding interaction relevant for oxygen atom transfer from peroxovandate(V) to a nucleophile X (X = e.g. Br^-).

hypsochromic shift of the ligand-to-metal-charge-transfer band to λ_{max} = 350 nm (ε = 310) in the pale yellow oxobisperoxovandate(V) ion [91].

Binding to vanadium(V) lowers the energy of the oxygen–oxygen σ^*-orbital of the peroxide, which facilitates oxygenation of a nucleophile (Fig. 1, right) [92,93]. Although molecular orbital theory predicts that the π-bond order between the peroxo oxygen atoms and vanadium in bisperoxovanadates is lower than in monoperoxovanadates, the bisperoxo complex is generally less reactive toward nucleophiles than the monoperoxo form. The origin of this dichotomy is the acid strength of neutral bisperoxovanadate, that is $VO(O_2)_2H$ [pK_a = 0.43] [91]. In neutral solution, the bisperoxo compound exists predominantly as anion and therefore repels an incoming nucleophile. Protonation of a bisperoxovanadate, in turn, enhances bisperoxo complex reactivity, for example, by a factor of 10^4 for sulfoxidation, if referenced toward reactivity of the monoperoxo form [94].

Dipeptides with carboxyl-, hydroxyl-, or amino-functionalized side chains preferentially bind via the deprotonated amide nitrogen to vanadate(V). The carboxylate oxygen is the second best donor in peptides, which, however, binds stronger to vanadate(V) than the N-terminus. No significant affinity seems to exist for vanadate(V)-coordination to the heterocyclic nitrogen atom of *N*-methyl imidazole, glycyl L-histidine, or L-histidyl glycine. Equilibrium constants for peptide binding to vanadate(V) and its peroxo derivatives at pH 6.7 are generally small [95–97].

Physical organic investigations on haloperoxidases [98,99] show that a protein interacts with vanadate(V) in more complex manner than a dipeptide. The constant for monovandate dissociation from the apoenzyme of the bromoperoxidase I from the brown alga *Ascophyllum nodosum* [V_{Br}PO(*An*I), EC 1.11.1.10] is 55 nM. In the crystal (PDB accession code 1QI9), the vanadate(V) co-factor is attached to the distal imidazol nitrogen of the L-histidine486 side chain. This binding site is situated at the bottom of a substrate funnel, which is about 12 Å wide and 8 Å deep. The substrate funnel is located at the end of a four-helix bundle that constitutes an important structural domain of the 120 kDa-homodimer. X-ray diffraction analysis of a hydrogen peroxide-soaked crystal shows that His486 also is the binding site for the monovanadate(V) co-factor in its peroxo form (Fig. 2). In the absence of bromide, the peroxo-loaded-vanadate cofactor shows little to no catalase activity, and seems to bind stronger to the apoenzyme than monovanadate [100,101]. Experimentally, no evidence so far exists that a second hydrogen peroxide molecule enters the monoperoxovanadate coordination sphere of the loaded co-factor [102]. For reasons given above, protein-bound bisperoxovanadate(V) is expected to be a less reactive oxidant for bromide than the monoperoxo form.

Differences in binding affinities of vanadate(V) toward dipeptides and the apoenzyme of V_{Br}PO(*An*I) point to a decisive role of hydrogen bonding between the co-factor, amino acid side chains, and presumably water. On the basis of computational analysis, hydrogen-bonded water molecules at the active site play an essential role for rapid hydrogen peroxide-loading of vanadate, and its activation for bromide oxidation [103]. This water structure would

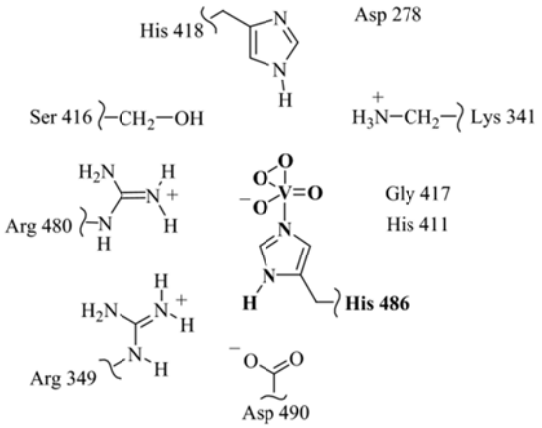


Fig. 2. Proposed structure of the active site in peroxo-loaded V_{Br}PO(*An*I) (adapted from X-ray diffraction data; numbers refer to amino acid sequence of the protein) [98].

collapse, if the apoenzyme was removed from the co-factor, to leave monovandate in homogeneous aqueous solution.

2.3. Alkylperoxy complexes of oxovanadium(V)

Oxovanadium(V) compounds undergo ligand substitution, if treated with alkyl hydroperoxides (Scheme 5) [59]. The equilibrium constant for the reaction between triethyl vanadate and *tert*-butyl hydroperoxide (pK_a 12.3; Scheme 7, Eq. (8)) is $K^8 = 6 \times 10^{-2}$ ($CDCl_3$, −40 °C), and thus significantly smaller than the reference value for monoperoxo complex formation [104]. Substitution of *tert*-butyl peroxy for ethoxy is detectable, for example, via mass spectrometry or vanadium-51 NMR-spectroscopy, but generally not by UV/vis-spectroscopy, because electronic changes associated with the substitution are comparatively small [41,104,108].

Binding to a d^0-transition metal, such as vanadium(V), is a prerequisite for activation and the use of an alkyl hydroperoxide as terminal oxidant in oxidation catalysis [42,60,105,106]. According to molecular orbital theory, coordination between the distal oxygen (O^d) and vanadium occurs via σ- and π-bonding (Fig. 3). In extension to the principles of structural peroxide chemistry, it is expected that VOOR (e.g. R = *t*Bu) preferentially adopts a gauche conformation to minimize lone pair repulsion. In the gauche conformer $n^2_O \rightarrow \sigma^*_{V,O-}$ and $n^2_O \rightarrow \sigma^*_{C,O-}$ interactions reduce Coulomb repulsion within the peroxy entity. The sp^2-type lone pair at the proximal oxygen (O^p), in this model, does not point in a noteworthy manner toward vanadium. A perester-type alkylperoxy binding, which means an end-on coordination, therefore is favored. This interpretation deviates from the crystal structure analysis of oxo[2,6-dipicolinato(−2)](*tert*-butylperoxy)vanadium(V), which so far is the only report in the literature on a solid state structure of an alkylperoxy complex [107]. In the investigated crystal, the *tert*-butyl peroxy ligand is side-on bound. In solution and in the gas phase, however, the end-on mode of binding seems to be the adequate structural model to describe alkyl peroxy binding to vanadium(V) [108].

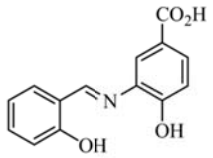
3. Bromoperoxidase catalysis

In the decade that followed the discovery of vanadate(V)-dependent bromoperoxidases (V_{Br}POs), several experiments were performed using enzymes from different organisms, inconsistent enzyme/substrate-ratios, and a variety of buffers to conduct oxidative transformations of nucleophiles. The results showed that bromoamine formation, bromocyclization, indole function-

$VO(OEt)_3 + tBuOOH \rightleftharpoons VO(OEt)_2(OOtBu) + EtOH \quad K_s$ (eq. 8)

$VOL^1(OEt) + tBuOOH \longrightarrow VOL^1(OOtBu) + EtOH$ (eq. 9)

$\delta = -538$ $\delta = -578$

$H_2L^1 =$ 

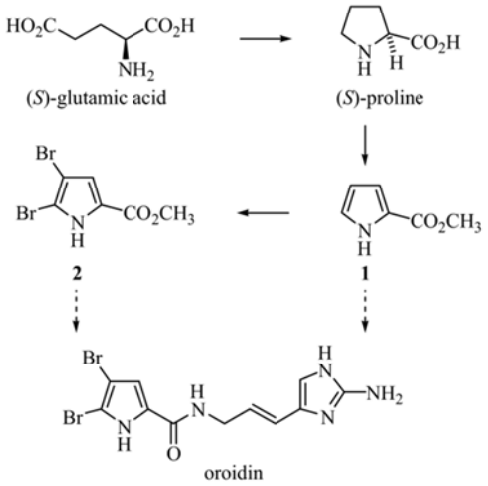
Scheme 5. Oxoperoxyvanadium(V) compound formation from triethyl vanadate (top) [104] and an oxovanadium(V) Schiff-base complex (bottom) [41].

alization, and bromohydrin synthesis are feasible under such conditions [40,109]. None of the reports, however, provided information relevant to organic synthesis, such as yields, mass balances, turnover numbers, catalyst lifetimes in different buffers, or residual activity for repetitive use of bromoperoxidases. Also, no functional group systematic was set up to predict selectivity for natural product transformation via bromoperoxidase-catalyzed oxidation. The aspect of functional group systematic was recently addressed in a study on methyl pyrrole-2-carboxylate bromination (Schemes 6 and 7) [110]. Methyl pyrrole-2-carboxylate (**1**) is a metabolite from the amino acid pathway [111], and gives a diagnostic mixture of bromination products from electrophilic aromatic substitution, to provide insight into reactivity and selectivity of bromoperoxidase chemistry [110,112].

The selected enzyme, that is the $V_{Br}PO(AnI)$, catalyzes oxidation of bromide with hydrogen peroxide in weakly acidic solutions (pH 6.2–6.5) [37]. The turnover rate of this process exceeds the most active nonenzymatic alternatives by four orders of magnitude [39]. The enzyme tolerates organic co-solvents, such as alcohols, 1,4-dioxane, acetonitrile, and temperatures of up to 60 °C, without notably loss of bromoperoxidase activity over time spans that are required to perform synthesis [100,113]. Vanadate-dependent bromoperoxidases from other organisms than *A. nodosum*, for example from fungi or lichens, have been isolated [36,114]. None of these enzymes, however, shows similarly favorable characteristics for application in organic synthesis as $V_{Br}PO(AnI)$ [25,26,115].

3.1. Bromoperoxidase preparations

In the time between January and April, *A. nodosum* exhibits particularly high levels of $V_{Br}PO(AnI)$ [35,116], which makes isolation of the bromoperoxidase attractive during this season. An established freeze–drying, milling, and liquid–liquid partitioning process provides a mixture of isoenzymes, which must



Scheme 6. Proposed biosynthetic relationship between methyl pyrrole-2-carboxylate (**1**), compounds prepared from sustainable bromination, and natural products [110,111].

be separated via hydrophobic interaction and size exclusion chromatography [116]. Preparations of the $V_{Br}PO(AnI)$ obtained from this procedure exhibit peroxidase activity of up to 693 units U_T mg^{-1} in the triiodide test [117] (pH 6.3). In this test iodide is oxidized into triiodide, as expressed with the index in U_T. One unit (1 U) thereby refers to the amount of enzyme necessary for turning over 1 μmol of substrate per minute. The specific activity, on the other hand, refers to the number of units per mg of enzyme, that is, U_T mg^{-1}. The enzymatic activity in the monochlorodimedone assay [34] was up to 172 U_{MCD} mg^{-1} (pH 6.5). In the MCD-assay, the time dependent decrease of the MCD-absorbance at $\lambda_{max} = 290$ nm

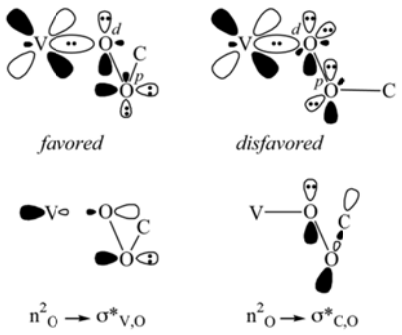
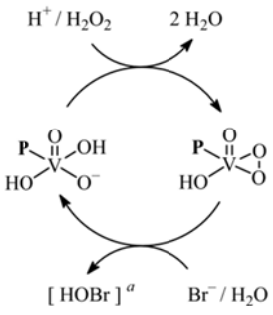
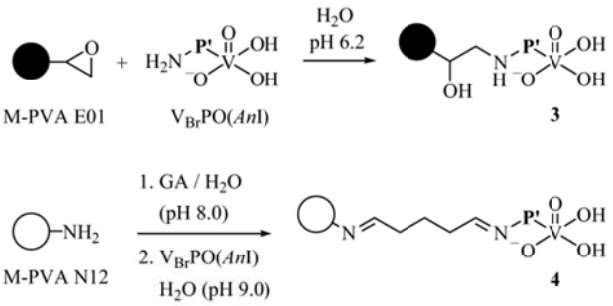


Fig. 3. Molecular orbital model for alkylperoxy binding to vanadium(V) (C refers to a carbon substituent such as *tert*-butyl; n^2_O = p-type lone pair at oxygen).



Scheme 7. Stoichiometry for $V_{Br}PO(AnI)$-catalyzed bromide oxidation (**P** = protein, i.e. apoenzyme; [a]proposed intermediate in an early phase of the reaction; see also Section 5).



Scheme 8. Immobilization of the $V_{Br}PO(AnI)$ on magnetic (M) polyvinyl alcohol (PVA)-coated supports (0.5–1.3 μm polydisperse size distribution for epoxide functionalized beads E01 ○, and 0.7–4.5 μm for amino-functionalized beads ●; GA = glutardialdehyde) [118].

is correlated with the rate of 2-bromo-2-chlorodimedone formation.

The $V_{Br}PO(AnI)$ was immobilized on magnetite particles for collecting the enzyme after substrate turnover from the reaction mixture via magnetic separation with a neodyme/iron bar magnet (Scheme 8, Fig. 4) [118]. The bromoperoxidase retains about 30–40% of its initial activity, upon attachment to the solid phase. Long term measurements show that preparations stored in Tris–HCl buffer (pH 9.0, 4 °C) lose about a third of their bromoperoxidase activity within the first 70 days. For the immobilized $V_{Br}PO(AnI)$, such as preparations **3** and **4**, bromoperoxidase activity beyond this point remains approximately constant [100,118].

3.2. Sustainable bromination in homogeneous and heterogeneous systems

Parameter variation showed that a bromoperoxidase activity of 1.3 U_T is necessary to quantitatively convert 36 μmol of pyrrole **1** into 94% of bromopyrrole **5** within 24 h (Table 2, entry 1). Bromoperoxidase reactivity in homogeneous solution and from immobilized preparations, that is **3** and **4**, are approximately similar (Table 2, entries 2–4). The use of morpholine-4-ethanesulfonic acid (MES)-buffer for synthetic application poses a major improvement, compared to the phosphate buffers used in the early days. For example, the half-life time of bromoperoxidase activity of the enzyme is about 5 h, if stored at 4 °C in phosphate buffer (pH 6.3), which extends to about 9 days in MES-buffer (pH 6.2). On the micromolar scale, the hydrogen peroxide may be added in portions or in a single batch, whereas continuous administration is more effective as the process is scaled-up (vide infra).

An alternative to external administration of the oxidant, is the in situ hydrogen peroxide generation via aerobic oxidation

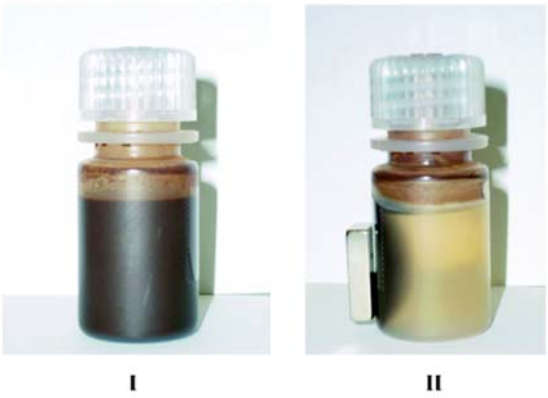
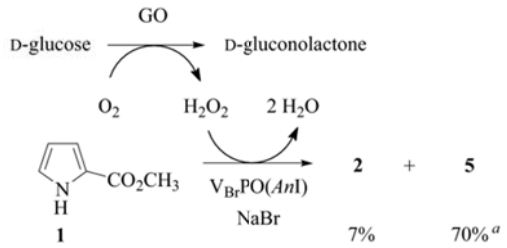


Fig. 4. Illustration of a reaction vessel for $V_{Br}PO(AnI)$-catalyzed oxidation during substrate turnover (**I**) and after magnetic separation of the immobilized enzyme (**II**) (e.g. **3**, **4**) [110].

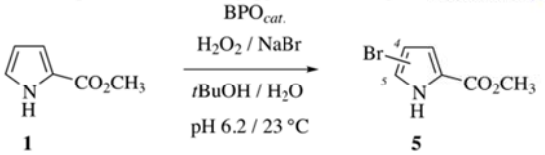


Scheme 9. Combination of two enzymatic processes for pyrrole bromination (GO = D-glucose oxidase; [a] 77/23-mixture of 4/5-isomers of **5**) [118].

of D-glucose, catalyzed by D-glucoseoxidase (GO) [119,120] from *Aspergillus niger* (1.67 U, 147 U mg^{-1}). In order to effectively combine the two enzymatic processes, the pH of the reaction mixture has to be set to 5.8. This value is a compromise between the pH for maximum activity of the $V_{Br}PO(AnI)$ (6.2) and the applied D-glucoseoxidase (5.6). Pyrrole conversion under such conditions is 97%, to furnish 77% of bromopyrroles **2** and **5** (Scheme 9) [118].

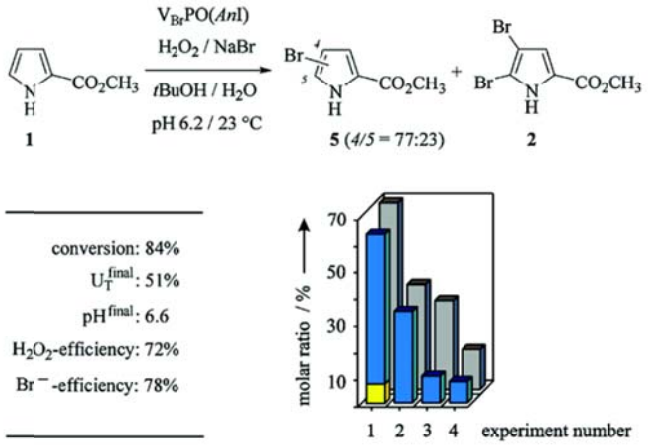
The $V_{Br}PO(AnI)$-activity, that is conserved in oxidative bromination of **1**, may be used for further experiments, leading to a maximum turnover number of 2×10^6 (Scheme 10) [118]. In state-of-the-art oxidation catalysis, it is not only the turnover number of the catalyst that is important but also the efficiency for the use of *all* substrates. To attain maximum efficiency for substrate bromination, sodium bromide (1.3 equivalents), hydrogen peroxide (1.1 equivalents) and MES-buffer must be added continuously to a solution containing 0.75–1.5 mmol of pyrrole **1** and the enzyme at ~20 °C. Regioselectivity of monobromide forma-

Table 2
Reaction parameters for methyl pyrrole-2-carboxylate bromination [118]

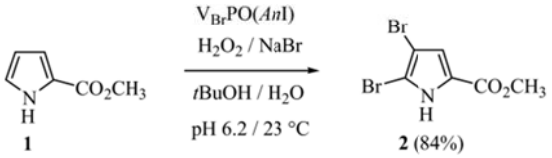


Entry	n_1/μmol	Conv. **1**/%	Time/h	BPO	U_T	U_T^{final} mg^{-1} [a]	**5**/% (4/5)
1	36	Quant.	24	$V_{Br}PO(AnI)$	1.3	117	94 (93/7)
2	36	77	3	$V_{Br}PO(AnI)$	1.3	239	60 (82/18)
3	200	54	3	**3**	6.9	Active	40 (90/10)
4	200	75	3	**4**	6.9	Active	32 (93/8)

[a] Initial enzyme activity 526 U_T^0 mg^{-1} for entries 1–2, 118 ± 12 U_T^0 mg^{-1} for entry 3, and 194 ± 39 U_T^0 mg^{-1} for entry 4; active refers to residual enzyme activity as judged by triiodide tests.



Scheme 10. Efficiency for oxidative methyl pyrrole-2-carboxylate bromination (144 μmol) in sequential reactions [4.96 U_T^0 of V$_{Br}$PO(*An*I); homogeneous MES-buffered solutions; histograms refer to conversion of **1** (gray), and yields of **2** (yellow) and **5** (blue)] [118].



Scheme 11. Synthesis of naturally occurring brominated pyrrole **2** from *A. oroides* [110,121].

tion thereby declines and dibromide **2** is formed as additional product, presumably due to higher reactant concentrations (cf. Scheme 10, experiment 1). The dibromide becomes the major product, if amounts of V$_{Br}$PO(*An*I) (34.6 U_T), sodium bromide, and hydrogen peroxide are doubled. Synthesis of methyl 3,4-dibromopyrrole-2-carboxylate **3a** poses a biomimetic approach to prepare a naturally occuring constituent from the marine sponge *Agelas oroides* (Scheme 11) [121]. The compound shows antiplasmoidal, cytotoxic, and interesting electrophysiologic properties and therefore has attracted attention of medicinal chemists [122,123].

To conserve a higher degree of bromoperoxidase activity for a use in consecutive runs, immobilized V$_{Br}$PO(*An*I) is recommended to be used as oxidation catalyst. For immobilized V$_{Br}$PO(*An*I)-preparation **3**, the maximum number of experiments attainable so far is 15 (Fig. 5). The turnover number under such conditions is 1.1×10^6. Although this number is by a factor of two smaller than for the enzyme in homogeneous solution, the use of immobilized bromoperoxidase is by far the more practical method for

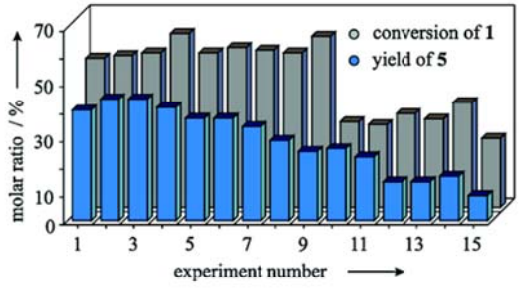


Fig.5. Histograms for presenting conversion (gray) and yields (blue) for consecutive use of V$_{Br}$PO(*An*I)-preparation **3** for oxidative pyrrole bromination (in aqueous *tert*-butanol, pH 6.2, 23 °C) [118].

catalyst recycling. The origin of irreversible bromoperoxidase activity loss in oxidation catalysis is unclear. Attempts to reconstitute bromoperoxidase activity by orthovanadate addition failed.

3.3. Bromination of arenes

Substituted benzenes are models for acetogenins and shikimates, to investigate selectivity of arene bromination in bromoperoxidase-catalyzed oxidation (Table 3). Brominated phenols, for example, were isolated from marine sponges of the genera *Didiscus* or *Dysidea* (Scheme 12, bottom) [124,125].

The substrates chosen for probing reactivity of arene bromination in V$_{Br}$PO(*An*I)-catalyzed oxidations differ in turnover efficiency. The yields of products **7**–**8** under conditions that are limited in hydrogen peroxide (1.0 equivalent) and sodium bromide (1.1 equivalents), decrease along the series of substrates aniline (**6a**) > phenol (**6b**) > *O*-methyl thymol (**6f**) > 2-*tert*-butyl phenol (**6c**) > thymol (**6d**) > anisole (**6e**) (Table 3, entries 1–6) [126]. Evidence for sidechain bromination of, for example, isopropyl-substituted benzenes **6d** and **6f** were not apparent from NMR-spectra of associated reaction mixtures [126]. *tert*-Butylbenzene, chlorobenzene, and methyl benzoate were not brominated under such conditions, even as aliquots of hydrogen peroxide and sodium bromide were increased by a factor of three. Triiodide tests showed that V$_{Br}$PO(*An*I)-activity in all instances is retained. The lack in reactivity therefore is not caused by enzyme inhibition, either by the substrate or the product(s), but points to insufficient reactivity of the applied arenes.

α-Naphthol **9**, a model for naturally occurring hexaketides, is converted in a bromoperoxidase-catalyzed reaction into a 65/35-mixture of 4/2-isomers of bromonaphthol **10** [127,128]. Substrate, reactant, and buffer were added continuously. Enzymatic activity (17.3 U_T for 0.75 mmol of **9**) was lost at a substrate conversion of about 58%. Attempts to brominate 1-methylnaphthalene under standard conditions led to phase separation without affecting enzyme activity. Bromination of 1-methylnaphthalene, however, did not occur under such conditions.

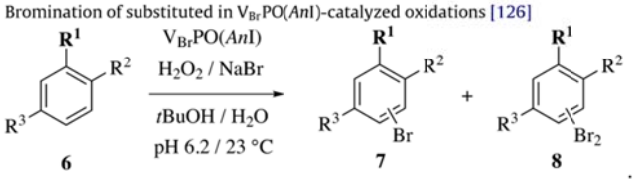
4,6,8-Trimethylazulene (**11**) [129], a compound of similar reactivity in electrophilic aromatic substitution as pyrrole, undergoes 20% conversion (formation of 19% of bromoazulene **12**), if treated with sodium bromide and hydrogen peroxide in aqueous, MES-buffered *tert*-butanol. If the reaction is performed in aqueous acetonitrile containing diethyl ether as additional co-solvent, and dodecyl trimethyl ammonium bromide (DTAB) as phase transfer catalyst, the yield of brominated azulenes **12** and **13** [130] increased to a total value of 71% (Scheme 13, top). The end of substrate conversion correlated with the loss of bromoperoxidase activity. Brominated azulenes are natural products. 1-Bromoguiazulene, for example, is a bluish purple pigment of the deep sea gorgonian *Euplexaura erecta* [131].

To sum up, bromoperoxidase-catalyzed oxidation of bromide in solutions of hydrogen peroxide is the basis for synthesis of bromoarenes from π-nucleophilic aromatics. The method is a sustainable version of the on-site halogenation, and provides insight into selectivity of biomimetic organobromine synthesis.

4. Functional bromoperoxidase mimics

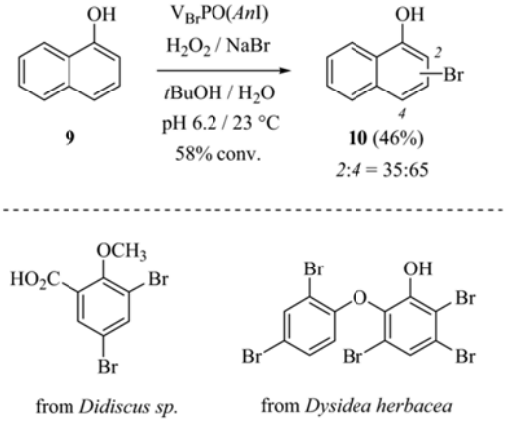
Transition metal complexes, that are able to catalyze the oxidation of bromide, are named functional bromoperoxidase mimics [42,132,133]. The difficulty to use bromoperoxidase mimics in synthesis of complex natural products arises from the fact that one proton is consumed per equivalent of oxidized bromide (Scheme 14). In order to maintain turnover rates for bromide oxidation at a reasonable level, protons must be supplied from an external source. In the first generation of bromoperoxidase mim-

Table 3
Bromination of substituted in $V_{Br}PO(AnI)$-catalyzed oxidations [126]



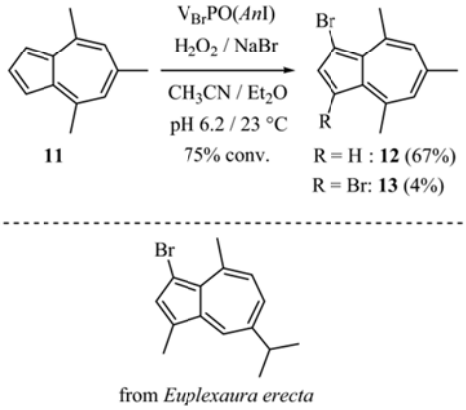
Entry	7	R^1	R^2	R^3	Conv. 6/%[a]	7/% (o/p)[b]	8/% (o,o/o,p)[b]
1	**6a**	NH_2	H	H	93	**7a**: 66 (45/55)	**8a**: 20 (20/80)
2	**6b**	OH	H	H	90[c]	**7b**: 69 (9/91)	**8b**: 1 (<2/98)
3	**6c**	OH	*t*Bu	H	62	**7c**: 33 (30/70)	**8c**: 11 (<2/98)
4	**6d**	OH	*i*Pr	CH_3	46	**7d**: 34 (18/82)	**8d**: 1 (<2/98)
5	**6e**	OCH_3	H	H	22	**7e**: 18 (<2/98)	**8e**: –[e]
6	**6f**	OCH_3	*i*Pr	CH_3	64	**7f**: 53 (<2/98)	**8f**: –[e]

[a] 34.6 U_T for 1.5 mmol of **6**.
[b] Referenced versus R^1; *o* = *ortho*; *p* = *para*.
[c] Additional product: 6% of 2,4,6-tribromophenol.
[e] Not detected.

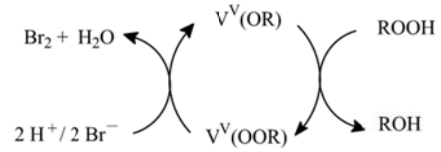


Scheme 12. Bromination of α-naphthol **9** (top) and structure formula of naturally occurring brominated phenol derivatives (bottom; compare also products shown in Table 3) [110,124,125].

ics, this prerequisite was met by running oxidative bromination in strongly acidic aqueous solutions (pH ~ 1) [68,69]. Such conditions, however, are incompatible with the stability of most organic functional groups and therefore precluded a wider spread use of this method in natural product synthesis. A reexamination of published procedures moreover showed that none of the existing methods



Scheme 13. Bromination of 4,6,8-trimethylazulene **11** (top; 8.65 U_T^0 for 0.375 mmol of **11**) and structure formula of a bluish purple pigment of a deep see gorgonian [110,131].



Scheme 14. Reaction cycle for bromide oxidation using a vanadium(V)-based functional bromoperoxidase mimic [V^V(OR); R = e.g. *t*Bu] as catalyst [42].

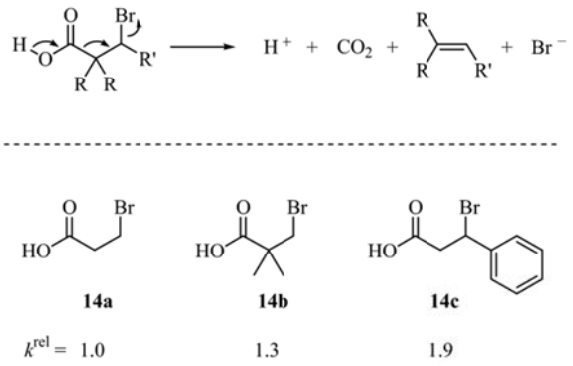
is able to maintain the catalytic cycle for oxidative bromination at neutral pH [26]. Either strong aqueous Brønsted-acids (pH < 2–3) or substantial amounts of vanadium(V) reagents in aqueous solutions were essential to achieve notable substrate conversion for reasons given above. In all instances, the acidity of the reaction mixture drove peroxide activation and thus bromide oxidation. This finding agrees with results from the pioneering study of Maass and Hiebert, who published in 1924 that hydrogen peroxide oxidizes hydrogen bromide in a rapid and exothermic reaction, to give bromine [58]. No external catalyst is needed!

4.1. Masked hydrogen bromide-equivalents

The quest for a proton source that does not notably affect acid strength of an organic solution led to the discovery of the 3-bromopropionic acids, such as **14a–c**, as buffer reagents. The compounds are available from renewable resources or low-priced bulk chemicals, and decompose if treated at ambient temperature with catalytic amounts of bromide in solutions of dimethyl carbonate (DMC), propylene carbonate (PC), or ethyl acetate (EtOAc). Fragmentation of 3-bromopropionic acids furnishes a proton, a bromide ion, carbon dioxide, and an alkene [134]. Relative rates of fragmentation correlate with stability of the resulting alkene (Scheme 15).

If *tert*-butyl hydroperoxide is added to a solution of a 3-bromopropionic acid **14** and a catalytic amount of sodium bromide in, for example, propylene carbonate, no bromide oxidation occurs, as probed by addition of 3-*tert*-butylcyclohexene (**15**) to quench possibly formed bromoelectrophiles. Addition of 1 mol% of Schiff–Base complex $VOL^2(OEt)(EtOH)$ [41,135], aminodiol-derived coordination compound $VOL^3(OEt)$, pyridine analogue $VOL^4(OEt)$ [136], $VO(acac)_2$ (Hacac = pentane-2,5-dione), or $VOSO_4{\cdot}4H_2O$ as low-priced alternative (Fig. 6; Table 4, entries 1–5), induces rapid and stereoselective conversion of cycloalkene **15** into dibromocyclohexane **16** (Table 4).

From parameter and reagent variation it was concluded that piperidine complex $VOL^3(OEt)$ in combination with **14b**, *tert*-butyl



Scheme 15. Relative reactivity of 3-bromopropionic acid-fragmentation [134].

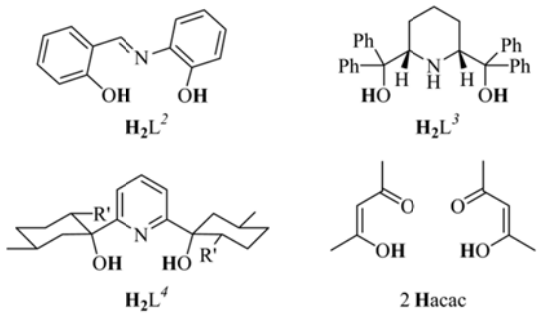


Fig. 6. Structure formulae of auxiliaries used for synthesis of functional bromoperoxidase mimics [cf. Table 4; protons that are released as auxiliaries coordinate to vanadium(V) are printed in bold].

hydroperoxide, and 40 mol% of cyclohexa-1,4-diene (CHD) as co-reductant poses an efficient reagent combination to convert an alkene into a vicinal dibromide. Addition of cyclohexa-1,4-diene accelerates conversion of alkene **15** by a factor of three and improves the yield of dibromide **16** by 12% points to 84%. In the absence of cyclohexa-1,4-diene, additional products appear, such as 3-*tert*-butylcyclohex-5-enone. Isolation of dibromide **16** from propylene carbonate solution is feasible by extraction with cyclohexane and distillation of the hydrocarbon-extract. The cyclohexane extraction leaves a yellow propylene carbonate solution containing the catalyst. To resume oxidative bromination, aliquots of cycloalkene **15**, *tert*-butyl hydroperoxide, and bromopropionic acid **14b**, simply have to be added.

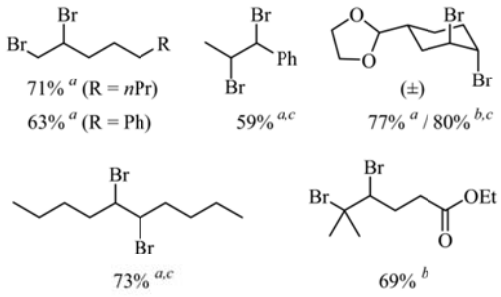


Fig. 7. Products of vicinal dibromination of alkenes from vanadium-catalyzed oxidations (for conditions see text) in propylene carbonate[a] or ethyl acetate[b]; [c]diastereomerically pure [134].

4.2. Dibromination of alkenes

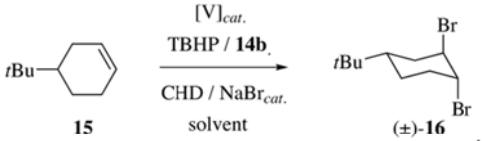
Almost all substitution patterns of alkenes that occur in nature provide dibromides, if treated with the reagent combination of $VOL^3(OEt)$, *tert*-butyl hydroperoxide, and **14b** (Fig. 7). (*E*)- and (*Z*)-configured alkenes are transformed into diastereomerically pure dibromides. pH-measurements of hydrolyzed samples show that no acid accumulates in the course of 3-bromopropionic acid turnover, which allows to brominate acid labile substrates according to this method (Fig. 7). Bromination of polar alkenes provides products that are not quantitatively extractable from solutions of propylene carbonate with cyclohexane. In such instances, ethyl acetate is recommended as solvent for conducting the oxidative bromination [134].

4.3. Bromocyclizations

(*R*)-Linalool (**17a**) provides a 47/53-mixture of brominated tetrahydrofuran **18a** and tetrahydropyran **19a**, if treated with $VOL^3(OEt)$, **14b**, and *tert*-butyl hydroperoxide (Scheme 16, top) [134]. Vicinal bromohydrin ethers **18a** and **19b** are structural related to a number of marine secondary metabolites, such as furoplocamioid A [137] and aplysiapyranoid A [138] (Scheme 16, bottom).

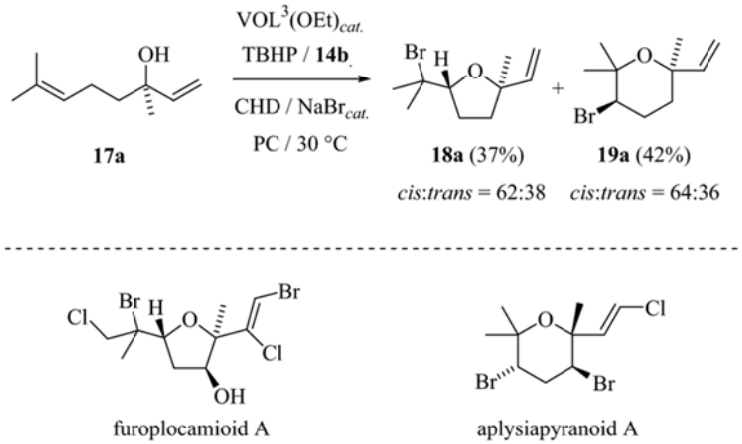
The reagent combination of a 3-bromopropionic acid, *tert*-butyl hydroperoxide and a bromoperoxidase mimic seems to be a quite general system to bromocyclize alkenols, such as **17b–e**, which differ from linalool **17a** in the chemical nature of substituents attached to the π-bond. As the ε-substituent of the alkenol changes from phenyl via methyl to hydrogen, the fraction of 6-endo-cyclized product **19** thereby decreases in a synthetically interesting manner, which is explained below (Table 5, entries 1–5).

Table 4
The use of 2,2-dimethyl-3-bromopropionic acid (**14b**) as in situ hydrogen bromide source in oxidative bromination of cycloalkene **15** (30 °C)[a]



Entry	$[V]_{cat.}$ (mol%)	Additive	MBr	Solvent	(±)-**16**/%
1	$VOL^2(OEt)(EtOH)$	CHD	NaBr	PC	44
2	$VOL^3(OEt)$	CHD	NaBr	PC	**84**
3	$VOL^4(OEt)$	CHD	NaBr	PC	52
4	$VO(acac)_2$	CHD	NaBr	PC	76
5	$VOSO_4 \cdot 4H_2O$	CHD	NaBr	PC	42
6	$VOL^3(OEt)$	None	NaBr	PC	72
7	$VOL^3(OEt)$	CHD	NBu_4Br	DMC	74
8	$VOL^3(OEt)$	CHD	NBu_4Br	EtOAc	83

[a] Conditions: 1.25 equiv. of **14b**, 1.1 equiv. of TBHP, 30 °C, 0.1 equiv. MBr, 1% $[V]_{cat.}$



Scheme 16. Products of linalool bromocyclization (top) and structurally related natural products (bottom) [134,137,138].

The yields in oxidations catalyzed by functional bromoperoxidase mimics compare to results obtained from conventional procedures that, however, applied stoichiometric amounts of *N*-bromosuccinimide or 2,4,4,6-tetrabromocyclohexa-2,5-dienone in acetonitrile, nitromethane, or dichloromethane, to achieve bromocyclization [139–141].

To sum up, alkenes and alkenols afford products of oxidative bromination, if treated at 30 °C with a 3-bromopropionic acid, such as **14a–c**, and *tert*-butyl hydroperoxide in an organic carbonate or ethyl acetate. The reaction is catalytic in vanadium(V) and bromide.

5. Mechanistic considerations

Bromoperoxidase-catalyzed oxidations occur in water and require hydrogen peroxide as oxidant, while oxidations catalyzed by functional mimics, for reasons of selectivity, are preferentially conducted in polar aprotic organic solvents and use *tert*-butyl hydroperoxide as terminal oxidant. Nevertheless, parallels between the methods exist that justify a unified discussion of mechanistic aspects of organic substrate bromination in the following chapters.

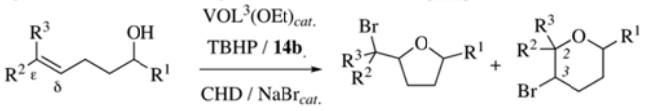
5.1. Equilibria and reactivity in aqueous solution

Hypobromous acid is the primary product of bromoperoxidase-catalyzed oxidation in an aqueous solution of sodium bromide and hydrogen peroxide. Hypobromous acid and bromide react to afford bromine (Eq. (10)), which is transformed by additional bromide to give tribromide as major product (Eq. (11)), and pentabromide (Br_5^-), and bromate (BrO_3^-) as minor products [142–144].

The law of mass action for Eq. (10) transforms on the assumption of infinitesimal substrate concentrations ($I = 0$ M) into $lg(c_{HOBr}/c_{Br_2}) = -7.05 + pH - lg\, c_{Br^-}$. This correlation shows, that the fraction of bromine in an aqueous solution of hypobromous acid increases, as the pH decreases and bromide-concentration rises (Fig. 8).

Selectivity profiles of arene bromination in $V_{Br}PO(AnI)$-catalyzed reactions, and bromine-mediated electrophilic aromatic

Table 5
Synthesis of vicinal bromohydrin ethers from alkenols [134]



Entry	17	R^1	R^2	R^3	CHD	18/% (*cis*:*trans*)	19/% (*cis*:*trans*)
1	**17b**	Ph	H	H	–	**18b**: 51 (29:71)	**19b**: –[a]
2	**17c**	Ph	CH_3	H	CHD	**18c**: 48 (34:66)	**19c**: 21 (>98:2)
3	**17d**	Ph	CH_3	CH_3	CHD	**18d**: 14 (41:59)	**19d**: 68 (96:4)
4	**17e**	H	Ph	H	CHD	**18e**: <5[b]	**19e**: 71(<2:98)[c]

[a] Not detected (^{1}H NMR).
[b] Traces
[c] Refers to relative configuration at C2 and C3.

Table 6
Physical and chemical properties of selected bromination reagents.

Reagent	EA/eV	IP/eV	EN[a]	$BDE_{Br,X}$/kJ mol^{-1}
Br_2	2.51 ± 0.10 [148]	10.52 ± 0.01 [149]	2.96	111.9 ± 0.2 [150]
Br_3^-	–[b]	4.1 [151]	1.97	42–54 [152]
HOBr	1.00 [153]	10.638 ± 0.001 [154]	2.91	202 ± 3 [155]

[a] Electronegativity (EN) of bromination reagents calculated according to Sanderson's principle of group electronegativity [156], using atomic electronegativity values from the Pauling scale [157].
[b] Not available.

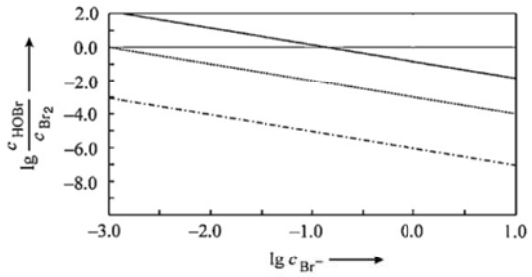


Fig. 8. Double logarithmic plot derived from Eq. (10) for $I = 0$ M at pH 6.2 (– – –), 4.1 (·····), and 1.0 (– · – ·; bottom).

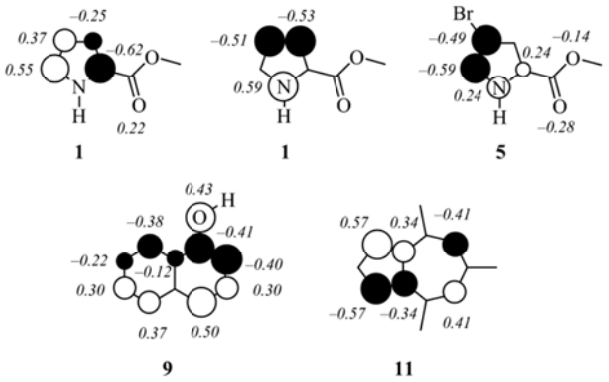


Fig. 10. HOMO coefficients of selected aromatic compounds that undergo electrophilic aromatic substitution in bromoperoxidase-catalyzed oxidations (for **1**: HOMO (top left) and HOMO−1 (top center); coefficients of relative magnitude <0.10 have been omitted for clarity; for theoretical method refer to legend of Fig. 9) [160].

substitutions, are nearly identical [110,130,158]. Molecular bromine is a strong electrophile that rapidly reacts with π-nucleophilic aromatics. Electrophilicity of bromine is reflected by its electron affinity (EA), whereas nucleophilicity of the arene is given by its ionization potential (IP) (Table 6). In frontier molecular orbital (FMO)-theory [159], the electron affinity correlates with the energy of the lowest unoccupied molecular orbital (LUMO) and the ionization potential with the highest occupied molecular orbital (HOMO). For reactions between bromine and nucleophilic arenes, such as phenol (**6b**) (IP = 8.5 eV), anisole (**6e**) (8.4 eV), pyrrole (IP = 8.2 eV), aniline (**6a**) (7.7 eV), and azulene (7.4 eV), favorable $LUMO_{Br_2}$–$HOMO_{arene}$ interactions exist in the transitions states as evident from correlation diagrams [for anisole (**6e**) see Fig. 9]. Selectivity in this model originates from interactions between the electrophile and the site of the largest HOMO-coefficient of the nucleophile (Figs. 9 and 10). If the energy difference between HOMO and HOMO−1 is small, such as for **1** (Fig. 10), two occupied orbitals interact with the electrophile, which makes interpretation of selectivity more difficult.

In terms of reactivity, a limit of IP < 8.8 seems to exist for an arene to undergo electrophilic aromatic substitution in $V_{Br}PO(AnI)$-catalyzed reactions, as concluded from the observation that ethyl benzoate (IP = 9.3 eV), chlorobenzene (9.1 eV), and *tert*-butylbenzene (~8.8 eV) were inert under such conditions. The fact that 1-methylnaphthalene (IP = 8.1 eV for naphthalene) was not brominated, and bromination of 4,6,8-trimethylazulene required a more lipophilic co-solvent in addition to a phase transfer catalyst to notably occur, shows that the role of substrate lipophilicity on reactivity in bromoperoxidase-catalyzed oxidations needs to be addressed in a future study.

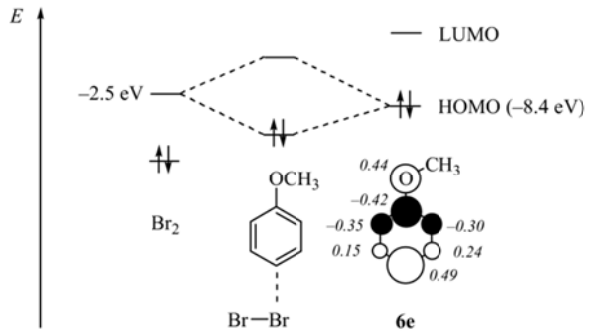


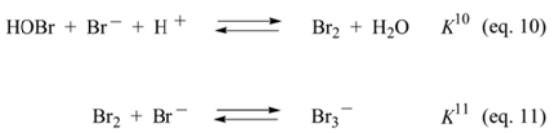
Fig. 9. Correlation diagram displaying most attractive interaction between the LUMO (i.e. σ*) of Br_2 and the HOMO of anisole (**6e**) (HOMO coefficients refer to B3LYP/6-31G-population analysis of B3LYP/6-31 + G**-minimized wavefunction) [159,160].

5.2. Selectivity in polar aprotic solvents

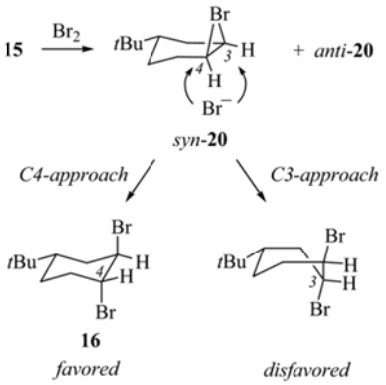
In polar aprotic solvents, stereoselectivity of oxidative alkene bromination, and regioselectivity of carbon–oxygen bond formation in bromocyclization, agrees with reactivity of bromine toward π-bonds (Scheme 17).

The reaction between bromine and an alkene follows a two-step mechanism. Both steps leave stereochemical fingerprints. In the first step, a cyclic bromonium ion is formed from bromine and the alkene in a rapid irreversible reaction. Selectivity in this step is guided by frontier molecular orbital interactions between bromine and the π-bond of the alkene. In the second step, the cyclic bromonium ion opens in a stereospecific S_N2-type reaction with bromide, via a late and therefore product-like transition state. Charge effects and steric repulsion between substituents are more important for opening of cyclic bromonium ions than for their formation. In this mechanistic picture, cycloalkene **15** provides axially dibromosubstituted cyclohexane **16** because nucleophilic attack at C4 furnishes the product directly in a chair conformation (Scheme 18). Attack of bromide at C3 leads to a high in energy, boat-like conformer, before the structure can relax into a chair conformation, having the two bromosubstituents bound equatorially [161].

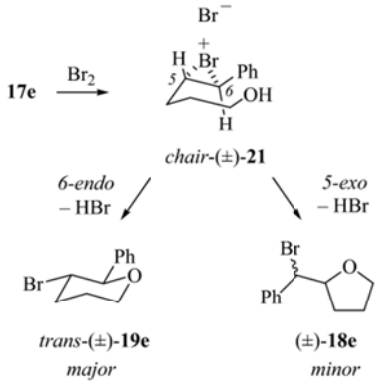
In a similar way, selectivity of carbon–bromine- and carbon–oxygen bond formation in bromocyclization reflects a two-steps mechanism that proceeds via a cyclic bromonium ion and nucleophilic opening of this intermediate by backside attack of the hydroxyl oxygen. Carbon–oxygen bond formation from the bromonium ion proceeds via a late transition state. Polar solvent molecules and substituents attached to the π-bond therefore exhibit a pronounced charge stabilizing effect to guide regioselectivity of carbon–oxygen bond formation (Scheme 19). In this mechanistic picture, bromocyclization of (*E*)-configured alkenol **17e** gives 2,3-trans-disubstituted tetrahydropyran **19e** as major product. The phenyl group is able to stabilize positive charge, which weakens (lengthens) the proximal carbon bromine bond, to guide the incoming oxygen nucleophile toward the benzylic car-



Scheme 17. Equilibria between HOBr, Br_2, and Br_3^- in H_2O [$K^{10} = 1.45 \times 10^8\ M^{-2}$ for H_2O at 20 °C ($I = 0.1$ M, pH 2.6–3.8) [145] or $1.04 \times 10^8\ M^{-2}$ in H_2O at 25 °C (pH 1.5) [146]; $K^{11} = 16.9\ M^{-1}$ in H_2O at 25 °C [147]; $9 \times 10^6\ M^{-1}$ in CH_3CN at 25 °C; $1.5 \times 10^7\ M^{-1}$ in DMC at 25 °C].



Scheme 18. Stereochemical model for explaining selectivity in the synthesis of dibromide **16**.



Scheme 19. Mechanistic model for stereoselective synthesis of tetrahydropyran *trans*-**19e** on the basis of stereoelectronic and polar effects via intermediate bromonium ion chemistry.

bon of the bromonium ion. Regioselectivity of bromocyclizations conducted in organic carbonates favor tetrahydropyran formation more than alternatives using, for example, *N*-bromosuccinimide or 2,4,4,6-tetrabromocyclohexa-2,5-dieneone as bromination reagent in solutions of in dichloromethane or nitromethane [139,141], presumably for reason of such polar effects.

To sum up, thermochemical data imply that tribromide is the major product formed from bromide oxidation with hydrogen peroxide catalyzed by the vanadate(V)-dependent bromoperoxidase from *A. nodosum* and from oxidations using bromoperoxidase mimics in polar aprotic solutions. Tribromide, however, is a nucleophile, as documented by its low group electronegativity of 1.97, compared to bromine (2.96) and hypobromous acid (2.81) (Table 6) [162,163]. Only the electrophilic reagent bromine exhibits adequate reactivity to explain the observed selectivities in oxidative substrate brominations using the enzyme and functional models thereof as catalyst.

6. Concluding remarks

The discovery of the bromoperoxidases completely changed our view on organobromine formation, and challenged scientists to uncover the mechanism of bromide oxidation under physiological conditions. The largest body of mechanistic data so far is available for a vanadate(V)-dependent bromoperoxidase from the brown alga *A. nodosum*. This enzyme combines high affinity toward hydrogen peroxide and sodium bromide with stability toward organic co-solvents. Also, the bromoperoxidase tolerates elevated temperature and significant concentration of organic substrates. To explain these characteristics, we assume that bromide oxidation occurs at the active vandate site at some distance from electrophilic hydrocarbon bromination, which we expect for reasons of reactivity and selectivity to take place in bulk solution. We therefore expect that the bromoperoxidase will find its place as catalyst in synthesis, wherever a sustainable alternative to bromine in water is needed.

The typical reaction medium for the bromoperoxidases is ocean water. Water, however is a nucleophile and therefore able to intercept electrophiles, to change selectivity of, for example, alkenol bromocyclization to vicinal bromohydrin formation. In such instances, water needs to be replaced by a polar aprotic solvent. To achieve bromide oxidation in organic solvents, an alkyl hydroperoxide generally is needed as a more lipophilic oxidant, and peroxide activation is achieved by a functional bromoperoxidase mimic instead of an enzyme. The role of the buffer to deliver protons without changing the acid strength, is taken over in organic solutions by 3-bromopropionic acids (pK_s 4–5). Since the major problems for application of oxidative bromination of acid labile substrates in synthesis were solved in the course of this project, we expect that additional examples that apply this knowledge will be reported in the upcoming years.

By looking at the achievements of bromoperoxidase chemistry, future perspectives, in our opinion, will not only deal with organic synthesis in ocean water, but also with an understanding of the role, the bromoperoxidases play in secondary metabolite synthesis. The structure-reactivity data collected in the past years for vanadate(V)-dependent bromoperoxidases justify the assumption, that electrophilic bromination possibly not always is the final step of a (bio)synthesis [53]. For arenes, a reactivity limit seems to exist, which is guided by the energy of the highest occupied molecular orbital. Methods for crossing this border are not yet discovered. Alkenols furthermore provide racemic vicinal bromohydrins as major components rather than enantiopure products of stereoselective bromocyclization [100]. As the scientific journey to unravel the principles of stereoselective aliphatic carbon–bromine bond formation in natural product chemistry continues, it might be instructive to turn back and see how far chemistry has already come along this way. About three decades ago, the role of organohalogens in science and society was summarized in an excellent textbook as follows.

> Although large numbers of organohalogens are known, very few of them occur naturally. . .. Almost all of the organohalogen compounds in use today are synthetic in origin. Your may wonder why, if nature doesn't choose to make them, man elects to do so. . .. [164]

Nature does these experiments over and over! All it needs is the right hypothesis and the right idea where to look!

Acknowledgements

This work was made possible by funding from the Deutsche Bundesstiftung Umwelt (grants 20008/982 and 20007/885; scholarships for D.W. and O.B.) and NanoKat. The studies are part of Ph.D. theses of D.W. and O.B. We express our gratitude to all the people from our group who contributed to this project. Their names are given in the references. Astrid Hoppe assisted in conducting bromoperoxidase reactions, which we gratefully acknowledge. We are furthermore indebted to Dr. Hans Vilter for numerous helpful discussions and his continuous interest in this work.

References

[1] G.W. Gribble, Acc. Chem. Res. 31 (1998) 141.
[2] K. Ballschmitter, Chemosphere 52 (2003) 313.

[3] G.W. Gribble, Chemosphere 52 (2003) 289.
[4] R. Sander, W.C. Keene, A.A.P. Pszenny, R. Arimoto, G.P. Ayers, E. Baboukas, J.M. Cainey, P.J. Crutzen, R.A. Duce, G. Hönninger, B.J. Huebert, W. Maenhaut, N. Mihalopoulos, V.C. Turekian, R. Van Dingensen, Atmos. Chem. Phys. 3 (2003) 1301.
[5] H. Herrmann, Z. Majdik, B. Ervens, D. Weise, Chemosphere 52 (2003) 485.
[6] R.A. Rasmussen, M.A.K. Khalil, R.W. Dalluge, S.A. Penkett, B. Jones, Science 215 (1982) 655.
[7] S.L. Neidleman, J. Geigert, Biohalogenation, Principles, Basic Roles and Application, Ellis Horwood, Chichester, 1986.
[8] A. Butler, M. Sandy, Nature 460 (2009) 848.
[9] F.H. Vaillancourt, E. Yeh, D.A. Vosburg, S. Garneau-Tsodikova, C.T. Walsh, Chem. Rev. 106 (2006) 3364.
[10] R. Frim, S.D. Ukeles, in: J.E. Kogel, N.C. Trived, J.M. Baker (Eds.), Industrial Minerals & Rocks, 7. ed, Society for Mining, Metallurgy, and Exploration, Littleton, Colorado, 2006, pp. 285–294.
[11] H.H. Landolt, Ber. dtsch. Chem. Ges. 23 (1890) 905.
[12] E.M. Weeks, J. Chem. Educ. 9 (1932) 1915.
[13] A.J. Balard, Ann. Chim. Phys. 32 (1826) 337.
[14] J. Wisniak, Ind. J. Chem. Technol. 9 (2002) 263.
[15] D.L. Turner, J. Food Sci. 37 (1972) 791.
[16] D.A. Laskowski, Rev. Environ. Contam. Toxicol. 174 (2002) 49.
[17] G.H. Wanière, in: S. Patai (Ed.), The Chemistry of Functional Groups – The Chemistry of the Carbon-Halogen Bond, Wiley, Chichester, 1973, pp. 1–47.
[18] J. Green, J. Fire Sci. 14 (1996) 426.
[19] G.W. Gribble, Chem. Soc. Rev. 28 (1999) 335.
[20] P. Friedländer, Ber. dtsch. chem. Ges. 42 (1909) 765.
[21] S. Doonan, in: S. Patai (Ed.), The Chemistry of Functional Groups – The Chemistry of the Carbon-Halogen Bond, Wiley, Chichester, 1973, pp. 865–915.
[22] S.J. Decanio, C.S. Norman, Contemp. Econ. Policy 23 (2005) 376.
[23] J. Kaspersma, C. Doumena, S. Munrob, A.-M. Prinsa, Polym. Degrad. Stab. 77 (2002) 325.
[24] P.B.D. De la Mare, B.E. Swedlund, in: S. Patai (Ed.), The Chemistry of Functional Groups – The Chemistry of the Carbon-Halogen Bond, Wiley, Chichester, 1973, pp. 407–548.
[25] A. Podgoršek, M. Zupan, J. Iskra, Angew. Chem. Int. Ed. 48 (2009) 8424.
[26] G. Rothenberg, J.H. Clark, Green Chem. 2 (2000) 248.
[27] I. Steinhorn, Limnol. Oceanogr. 30 (1985) 451.
[28] I. Gertman, A. Hecht, J. Mar. Sys. 35 (2002) 169.
[29] C.W. Jones, Application of Hydrogen Peroxide and Derivatives, RSC Clean Technology Monographs, Cambridge, 1999, pp. 156–162.
[30] S.M. Jasinski, U.S. Geological Survey Minerals Yearbook – 2006, Bromine, (2007) pp. 14.1–14.6.
[31] J.H. Clark, F.E. Deswarte, in: J.C. Clark, F. Deswarte (Eds.), Introduction to Chemicals from Biomass, Wiley, 2008, pp. 1–20.
[32] H. Raistrick, G. Smith, Biochem. J. 30 (1936) 1315.
[33] M.C.R. Franssen, H.C. van der Plas, Adv. Appl. Microbiol. 37 (1992) 41.
[34] L.P. Hager, D.R. Morris, F.S. Brown, H. Everwein, J. Biol. Chem. 241 (1966) 1769.
[35] H. Vilter, Phytochemistry 23 (1984) 1387.
[36] H. Vilter, in: H. Sigel, A. Sigel (Eds.), Vanadium and its Role in Life, vol. 31, Dekker, New York, 1995, pp. 325–362.
[37] A. Butler, J.V. Walker, Chem. Rev. 93 (1993) 1937.
[38] S.L. Neidleman, J. Geigert, Trends Biotechnol. 1 (1983) 21.
[39] G.E. Meister, A. Butler, Inorg. Chem. 33 (1994) 3269.
[40] A. Butler, J.N. Carter-Franklin, Nat. Prod. Rep. 21 (2004) 180.
[41] M. Greb, J. Hartung, F. Köhler, K. Špehar, R. Kluge, R. Csuk, Eur. J. Org. Chem. (2004) 3799.
[42] J. Hartung, Pure Appl. Chem. 77 (2005) 1559.
[43] J.H. Espenson, O. Pestovsky, P. Huston, S. Staudt, J. Am. Chem. Soc. 116 (1994) 2869.
[44] M.S. Reynolds, S.J. Morandi, J.W. Raebiger, S.P. Melican, S.P.E. Smith, Inorg. Chem. 33 (1994) 4977.
[45] M.S. Reynolds, K.J. Babinski, M.C. Bouteneff, J.L. Brown, R.E. Campbell, M.A. Cowan, M.R. Durwin, T. Foss, P. O'Brien, H.R. Penn, Inorg. Chim. Acta 263 (1997) 225.
[46] D. Schuch, P. Fries, M. Dönges, J. Hartung, J. Am. Chem. Soc. 131 (2009) 12918.
[47] E.S. Huyser, in: S. Patai (Ed.), The Chemistry of Functional Groups – The Chemistry of the Carbon-Halogen Bond, Wiley, Chichester, 1973, pp. 549–607.
[48] J. Hartung, in: E. Schaumann (Ed.), Science of Syntheses, vol. 35, Thieme, Stuttgart, 2006, pp. 287–300.
[49] N. Kreutzkamp, H. Meerwein, R. Stroh, in: E. Müller (Ed.), Houben-Weyl, Methoden der Organischen Chemie, vol. V/4, George Thieme Verlag, Stuttgart, 1960, pp. 679–776.
[50] D. Rehder, Bioinorganic Vanadium Chemistry, Wiley, Chichester, 2008, pp. 105–128.
[51] A. Butler, A.H. Baldwin, Struct. Bond. 89 (1997) 109.
[52] R.M. Moore, Handbook of Enivronmental Chemistry, vol. 3, Part P, Springer, Heidelberg, 2003, pp. 85–101.
[53] J.-M. Kornprobst, Enzyclopedia of Marine Natural Products, vols. 1–3, Wiley–VCH, Weinheim, 2010.
[54] J.W. Blunt, B.R. Copp, W.-P. Hu, M.H.G. Munro, P.T. Northcote, M.R. Prinsep, Nat. Prod. Rep. 26 (2009) 170.
[55] W.H. Richardson, V.F. Hodge, J. Org. Chem. 35 (1970) 4012.
[56] F. Beer, G. Düsing, H. Pistor, in: W. Weigert (Ed.), Wasserstoffperoxid und seine Derivate – Chemie und Anwendung (translates into: hydrogen peroxide and its derivatives – chemistry and application), Hüthig, Heidelberg, 1998, pp. 23–35.
[57] K.B. Sharpless, T.R. Verhoeven, Aldrichim. Acta 12 (1979) 63.
[58] O. Maass, P.G. Hiebert, J. Am. Chem. Soc. 46 (1924) 290.
[59] J. Hartung, M. Greb, J. Organomet. Chem. 661 (2002) 67.
[60] R.A. Sheldon, in: R. Ugo (Ed.), Aspects of Homogeneous Catalysis, vol. 4, Reidel Publishing, Dordrecht, 1981, pp. 3–69.
[61] E.A. Shilov, J. Am. Chem. Soc. 60 (1938) 490.
[62] T. Michalowski, J. Chem. Educ. 71 (1994) 560.
[63] L.G. Lavrenova, T.V. Zegzhda, V.M. Shul'man, Elektrokhimiya 7 (1971) 83.
[64] B. Jakuszewski, S. Taniewska-Osinka, Acta Chim. Soc. Sci. Lodz. 4 (1959) 17.
[65] R. Holze, in: M.D. Lechner (Ed.), Landolt-Börnstein, New Series, IV, Vol. 9A. Physical Chemistry, Electric Properties, Electrode Potentials, Springer, Heidelberg, 2009, p. 41.
[66] T. Sawyer, Oxygen Chemistry, Oxford University Press, New York, N.Y., 1991, p. 25.
[67] C.O. Willits, C. Ricciuti, H.B. Knight, D. Swern, Anal. Chem. 24 (1952) 785.
[68] O. Bortolini, M. Carraro, V. Conte, S. Moro, Eur. J. Inorg. Chem. (2003) 42–46.
[69] G.J. Colpas, B.J. Hamstra, J.W. Kampf, V.L. Pecoraro, J. Am. Chem. Soc. 118 (1996) 3469.
[70] A.S. Tracey, J.S. Jaswal, S.J. Angus-Dunne, Inorg. Chem. 34 (1995) 5680.
[71] A.S. Tracey, B. Galeffi, S. Mahjour, Can. J. Chem. 66 (1988) 2294.
[72] M.J. Gresser, A.S. Tracey, J. Am. Chem. Soc. 107 (1985) 4215.
[73] A.S. Tracey, M.J. Gresser, Inorg. Chem. 27 (1988) 2695.
[74] B. Galeffi, A.S. Tracey, Can. J. Chem. 66 (1988) 2565.
[75] G.R. Willsky, in: D.N. Chasteen (Ed.), Vanadium in Biological Systems, Physiology and Biochemistry, Kluwer, Dordrecht, 1990, p. 4.
[76] A.S. Tracey, H. Li, M.J. Gresser, Inorg. Chem. 29 (1990) 2267.
[77] A.S. Tracey, J.S. Jaswal, F. Nxumalo, S.J. Angus-Dunne, Can. J. Chem. 73 (1995) 489.
[78] J.S. Jaswal, A.S. Tracey, Can. J. Chem. 69 (1991) 1600.
[79] M.J. Gresser, A.S. Tracey, K.M. Parkinson, J. Am. Chem. Soc. 108 (1986) 6229.
[80] A.S. Tracey, M.J. Gresser, B. Galeffi, Inorg. Chem. 27 (1988) 157.
[81] A.S. Tracey, M.J. Gresser, K.M. Parkinson, Inorg. Chem. 26 (1987) 629.
[82] S. Hati, R.J. Batchelor, F.W.B. Einstein, A.S. Tracey, Inorg. Chem. 40 (2001) 6258.
[83] B. Galeffi, A.S. Tracey, Inorg. Chem. 28 (1989) 1726.
[84] A. Butler, M.J. Clague, G.E. Meister, Chem. Rev. 94 (1994) 625.
[85] S. Funahashi, K. Ishihara, M. Inamo, M. Tanaka, Inorg. Chim. Acta 157 (1989) 65.
[86] J.S. Jaswal, A.S. Tracey, Inorg. Chem. 30 (1991) 3718.
[87] F. Secco, Inorg. Chem. 19 (1980) 2722.
[88] M. Orhanović, R.G. Wilkins, J. Am. Chem. Soc. 89 (1967) 278.
[89] T.-J. Won, C.L. Barnes, E.O. Schlemper, R.C. Thompson, Inorg. Chem. 34 (1995) 4499.
[90] J. Hartung, I. Svoboda, in: Z. Rappoport (Ed.), The Chemistry of Functional Groups – The Chemistry of Peroxides, Wiley, Chichester, 2006, pp. 93–144.
[91] V. Conte, F. Di Furia, S. Moro, J. Mol. Catal. 94 (1994) 323.
[92] R.A. Sheldon, in: S. Patai (Ed.), The Chemistry of Functional Groups, Peroxides, Wiley, Chichester, 1983, pp. 162–199.
[93] T. Hirao, Chem. Rev. 97 (1997) 2707.
[94] A.F. Ghiron, R.C. Thompson, Inorg. Chem. 29 (1990) 4457.
[95] A.S. Tracey, J.S. Jaswal, Inorg. Chem. 32 (1993) 4235.
[96] J.S. Jaswal, A.S. Tracey, J. Am. Chem. Soc. 115 (1993) 5600.
[97] A.S. Tracey, J.S. Jaswal, J. Am. Chem. Soc. 114 (1992) 3835.
[98] A. Messerschmidt, R. Wever, Proc. Natl. Acad. Sci. USA 93 (1996) 392.
[99] M. Weyand, H.J. Hecht, M. Kieß, M.F. Liaud, H. Vilter, D. Schomburg, J. Mol. Biol. 293 (1999) 595.
[100] J. Hartung, Y. Dumont, M. Greb, D. Hach, F. Köhler, H. Schulz, M. Časný, D. Rehder, H. Vilter, Pure Appl. Chem. 81 (2009) 1251.
[101] H.S. Soedjak, A. Butler, Biochim. Biophys. Acta 1079 (1991) 1.
[102] D. Rehder, M. Časný, R. Grosse, Magn. Res. Chem. 42 (2004) 745.
[103] D. Geibig, R. Wilcken, M. Bangesh, W. Plass, in: G. Münster, D. Wolf, M. Kremer (Eds.), NIC Series 39, 2008, p. 71.
[104] F. Di Furia, G. Modena, R. Curci, J. Mol. Catal. 14 (1982) 219.
[105] E. Wojaczyńska, J. Wojaczyński, Chem. Rev. 110 (2010) 4303.
[106] F. Baumberger, A. Vasella, Helv. Chim. Acta 66 (1983) 2210.
[107] H. Mimoun, P. Chaumette, M. Mignard, L. Saussine, J. Fischer, R. Weiss, Nouv. J. Chim. 7 (1983) 467.
[108] C. Wikete, P. Wu, G. Zampella, L. De Gioia, G. Licini, D. Rehder, Inorg. Chem. 46 (2007) 196.
[109] V.M. Dembitsky, Tetrahedron 39 (2003) 4701.
[110] D. Wischang, O. Brücher, J. Hartung, Proceedings of the 7th Symposium on the Chemistry and Biological Chemistry of Vanadium, Toyama, Japan, 6th–9th October, 2010.
[111] C.T. Walsh, S. Garneau-Tsodikova, A.R. Howard-Jones, Nat. Prod. Rep. 23 (2006) 517.
[112] C. Schroif-Gregoire, N. Travert, A. Zaparucha, A. Al-Mourabit, Org. Lett. 8 (2006) 2961.
[113] E. de Boer, H. Plat, R. Wever, in: C. Laane, J. Tramper, M.D. Lilly (Eds.), Biocatalysis in Organic Media, Elsevier, Amsterdam, 1987, pp. 317–322.
[114] E.E. Coupe, M.G. Smyth, A. Fosberry, R.M. Hall, J.A. Littlechild, Protein Expr. Purif. 52 (2007) 265.
[115] For guidelines of sustainable synthesis see F.M. Kerton, in: J. Clark, F. Deswarte (Eds.), Introduction to Chemicals from Biomass, Wiley, 2008, Ch. 3, pp. 47–76.

[116] J. Hartung, O. Brücher, D. Hach, H. Schulz, H. Vilter, G. Ruick, Phytochemistry 69 (2008) 2826.
[117] F. Björkstén, Eur. J. Biochem. 5 (1968) 133.
[118] D. Wischang, J. Hartung, T. Hahn, R. Ulber, T. Stumpf, C. Fecher-Trost, Green Chem. 13 (2011) 102.
[119] D. Keilin, E.F. Hartree, Biochem. J. 50 (1952) 331.
[120] M. Hartmann, C. Streb, J. Porous Mater. 13 (2006) 347.
[121] S. Forenza, L. Minale, R. Riccio, E. Fattorusso, J. Chem. Soc. Chem. Commun. (1971) 1129.
[122] G.M. König, A.D. Wright, A. Linden, Planta Med. 64 (1998) 443.
[123] U. Bickmeyer, C. Drechsler, M. Köck, M. Assmann, Toxicon 44 (2004) 45.
[124] N.K. Utkina, S.A. Fedoreyev, S.G. Ilyin, M. Yu, Antipin. Russ. Chem. Bull. 47 (1998) 2292.
[125] B.F. Bowden, L. Towerzey, P.C. Junk, Aust. J. Chem. 53 (2000) 299.
[126] D. Wischang, J. Hartung, manuscript in preparation.
[127] V. Upender, D.J. Pollart, J. Liu, P.D. Hobbs, C. Olsen, W.-R. Chao, B. Bowden, J.L. Crase, D.W. Thomas, A. Pandey, J.A. Lawson, M.I. Dawson, J. Het. Chem. 33 (1996) 1371.
[128] W.J. Militzer, J. Am. Chem. Soc. 60 (1938) 256.
[129] K. Hafner, H. Kaiser, Org. Synth. 44 (1964) 94.
[130] K. Hafner, H. Patzelt, H. Kaiser, Liebigs Ann. Chem. 656 (1962) 24.
[131] M.K.W. Li, P.J. Scheuer, Tetrahedron Lett. 25 (1984) 587.
[132] V. Conte, B. Floris, Inorg. Chim. Acta 363 (2010) 1935.
[133] K. Kikushima, T. Moriuchi, T. Hirao, Tetrahedron 66 (2010) 6906.
[134] O. Brücher, J. Hartung, Proceedings of the 7th Symposium on the Chemistry and Biological Chemistry of Vanadium, Toyama, Japan, 6th–9th October, 2010.
[135] H. Mimoun, M. Mignard, P. Brechot, L. Saussine, J. Am. Chem. Soc. 108 (1986) 3711.
[136] S. Bellemin-Laponnaz, K.S. Coleman, P. Dierkes, J.P. Masson, J.A. Osborn, Eur. J. Inorg. Chem. 7 (2000) 1645.
[137] J. Darias, J. Rovirosa, A. San Martin, A.R. Diaz, E. Dorta, M. Cueto, J. Nat. Prod. 64 (2001) 1383.
[138] T. Kusumi, H. Uchida, Y. Inouye, M. Ishitsuka, H. Yamamoto, H. Kakisawa, J. Org. Chem. 52 (1987) 4597.
[139] J.G. Urones, D. Díez, I.S. Marcos, P. Basabe, A.M. Lithgow, R.F. Moro, N.M. Garrido, R. Escarcena, Tetrahedron 51 (1995) 3691.
[140] J.-C. Harmange, B. Figadère, Tetrahedron: Asymm. 4 (1993) 1711.
[141] T. Gottwald, M. Greb, J. Hartung, Synlett (2004) 65.
[142] G. Jones, S. Baeckström, J. Am. Chem. Soc. 56 (1934) 1517.
[143] H.A. Young, J. Am. Chem. Soc. 72 (1950) 3310.
[144] C.M. Kelley, H.V. Tartar, J. Am. Chem. Soc. 78 (1956) 5752.
[145] M. Eigen, K. Kustin, J. Am. Chem. Soc. 84 (1962) 1355.
[146] J.M. Pink, Can. J. Chem. 48 (1970) 1169.
[147] D.B. Scaife, H.J.V. Tyrrell, J. Chem. Soc. 80 (1958) 386.
[148] T.M. Miller, in: D.R. Lide (Ed.), Handbook of Chemistry and Physics, 78th ed., CRC Press, Boca Raton, 1997, pp. 10–189.
[149] S.G. Lias, in: D.R. Lide (Ed.), Handbook of Chemistry and Physics, 78th ed., CRC Press, Boca Raton, 1997, pp. 10–218.
[150] J.A. Kerr, Chem. Rev. 66 (1966) 465.
[151] G.L. Gutsev, J. Struct. Chem. 30 (1989) 733.
[152] W. Gabes, R. Elst, J. Mol. Struct. 21 (1974) 1.
[153] H. Keller-Rudek, D. Koschel, P. Merlet, U. Ohms-Bredemann, J. Wagner, A. Wietelmann, in: R. Haubold, J.V. Jonanne, H. Keller-Rudek, D. Koschel, P. Merlet, J. Wagner (Eds.), Gmelin Handbook of Inorganic and Organometallic Chemistry, 8th ed., Springer–Verlag, Heidelberg, 1992, Suppl. 2.
[154] B. Ruscic, J. Berkowitz, J. Chem. Phys. 101 (1994) 7795.
[155] M.N. Glukhovtsev, A. Pross, L. Radom, J. Phys. Chem. 100 (1996) 3498.
[156] R.T. Sanderson, J. Chem. Educ. 65 (1988) 112.
[157] S.G. Bratsch, J. Chem. Educ. 62 (1985) 101.
[158] G.A. Olah, Acc. Chem. Res. 4 (1971) 240.
[159] I. Fleming, Grenzorbitale und Reaktionen organischer Verbindungen, VCH, Weinheim, 1979, pp. 56–78.
[160] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J.A. Pople, Gaussian 03, Revision E.01, Gaussian, Inc., Wallingford CT, 2004.
[161] G.W. Klumpp, Reaktivität in der Organischen Chemie, vol. 1, Thieme, Stuttgart, 1977, pp. 22–25.
[162] L. Huai, W. Qingwei, L. Lixin, J. Chem. Educ. 69 (1992) 783.
[163] G.A. Olah, B.G. Balaram Gupta, R. Malhotra, S.C. Narang, J. Org. Chem. 45 (1980) 1638.
[164] J.D. Roberts, M.C. Caserio, in: Basic Principles of Organic Chemistry, 2nd ed., W.A. Benjamin Inc., Menlo Park, 1977, pp. 535–536.

Anhang E

Poster

Vanadium(V)-catalyzed Oxidative Brominations of Olefins and Alkenols with *tert*-Butyl Hydroperoxide and β-Bromopropionic Acids.

Oliver Brücher, Jens Hartung, *7th International Vanadium Symposium*, Toyama (Japan), **2010**.

Vanadium(V)-catalyzed Oxidative Brominations of Olefins and Alkenols with *tert*-Butyl Hydroperoxide and β-Bromopropionic Acids

Oliver Brücher and Jens Hartung*

Department of Organic Chemistry, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern

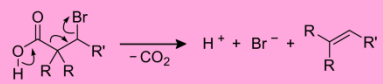
Fax: +49 631 205 3921, Email: hartung@chemie.uni-kl.de

Summary: Vicinal dibromoalkanes and β-brominated tetrahydrofurans / tetrahydropyrans were prepared from olefins and alkenols upon treatment with β-bromocarboxylic acids as *in situ* HBr-sources, *tert*-butyl hydroperoxide (TBHP), catalytic amounts of NaBr, and a suitable vanadium catalyst at 30 °C. Propylene carbonate (PC) served as solvent of choice due to its low vapor pressure, availability from renewable resources, and its excellent effects on rate and selectivity of organobromine compound formation.

Background

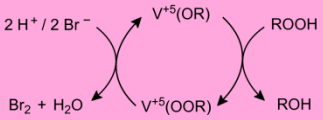
As part of a project on sustainable synthesis of terpene-derived brominated secondary metabolites we were interested to apply bromoperoxidase-like catalysis in environmentally benign solvents as alternative to alkene and alkenol brominations in chlorinated solvents or CH_3CN.[1–4] In order to perform effective oxidative brominations under approximately neutral conditions it was appropriate to replace so far used strongly acidic HBr-sources (*e.g.* pyridinium hydrobromide) preferably with neutral compounds that liberate protons and Br^- at a rate similar to oxidative consumption of the substrates. The strategy was put into practice utilizing β-bromocarboxylic acids (pK_a 4–5) as masked HBr-equivalents.[5] These compounds were available from inexpensive bulk chemicals and decomposed preferentially in propylene carbonate (PC) upon treatment with catalytic amounts of Br^- at 30 °C.

hydrogen bromide generation



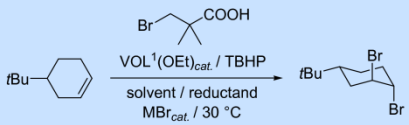
k^{rel}	R	R'
1.0	H	H
2.2	CH_3	H
5.0	H	Ph

bromide oxidation



Results

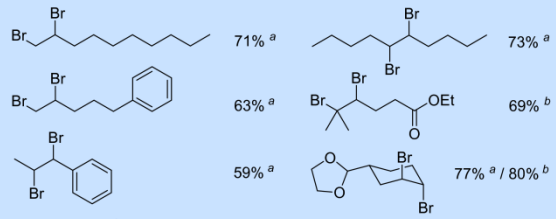
In the presence of 3-bromo-2,2-dimethylpropionic acid, TBHP, and 1 mol % of a suitable vanadium catalyst, 4-*tert*-butylcyclohexene was successfully converted into a diastereomerically pure dibromide. The use of 0.4 equiv. of cyclohexa-1,4-diene (CHD) raised product yields and reduced the required time for quantitative substrate conversion. No bromination was observed in controls lacking the vanadium catalyst.



entry	solvent	reductand	MBr	yield / %
1	PC	CHD	NBu_4Br	84
2	DMC	CHD	NBu_4Br	74
3	AcOEt	CHD	NBu_4Br	83
4	PC	CHD	NaBr	82
5	PC	–	NaBr	72

H_2L^1 = *cis*-2,6-bis-(1,1-diphenyl-1-hydroxymethyl)-piperidine. DMC = dimethyl carbonate.

For exploring the scope of the method, selected examples of widely distributed substitution patterns of olefins in nature and synthesis were chosen as substrates. The alkenes were successfully converted into the corresponding diastereomerically pure dibromides in highly competitive yields.



a Reaction in PC. b Reaction in AcOEt.

After optimization of reaction parameters with 4-*tert*-butylcyclohexene as reporter substrate the developed approach was used to investigate selective bromocyclization reactions of δ,ε-unsaturated alcohols. Formation of tetrahydropyran products was thereby more favored than with other known bromination reagents.[3]

entry	R^1	R^2	R^3	R^4	THF / % (*cis*:*trans*)	THP / % (*cis*:*trans*)
1	Ph	H	H	CH_3	48 (34:66)	21 (>98:2)
2	CH_3	C_2H_3	CH_3	CH_3	37 (62:38)	42 (64:36)
3	Ph	H	CH_3	CH_3	14 (41:59)	68 (96:4)
4	H	H	H	Ph	< 5 a	71 (<2:98) b

a Traces. b Refers to relative configuration at C2 and C3.

Brominated products were isolated by extraction of the PC phase with cyclohexane and further purified by column chromatography or distillation. The remaining PC solution still showed catalytic activity for bromide oxidation and could successfully be reused for a second bromination experiment.

Conclusions

From an ecological point of view the most forward-looking approach for bromo-functionalization of hydrocarbons comprises *in situ* generation of bromine from brines and an oxidant.[1,2] The study clarified that exploitation of bromoperoxidase-like reactivity under mild conditions for conducting bromocyclizations and vicinal dibromide formation using the principles of oxidation catalysis and sustainable chemistry is possible.[5] We furthermore concluded that construction of more complex terpenol-derived building blocks from acid labile precursors is feasible. The beneficial effects of CHD and organic carbonates, in particular of PC, as solvent in peroxide-mediated vanadium-catalyzed oxidations require further attention.

References and further reading:

[1] A. Podgoršek, M. Zupan, J. Iskra, *Angew. Chem. Int. Ed.* **2009**, 48, 8424–8450.
[2] J.Y. Kravitz, V.L. Pecoraro, *Pure Appl. Chem.* **2005**, 55, 1595–1605.
[3] M. Greb, J. Hartung, F. Köhler, K. Špehar, R. Kluge, R. Csuk, *Eur. J. Org. Chem.* **2004**, 3799–3813.
[4] A. Butler, J.V. Walker, *Chem. Rev.* **1993**, 93, 1937–1944.
[5] O. Brücher, J. Hartung, *Chem. Comm.*, *submitted.*

Acknowledgements:

This work was generously supported by the Deutsche Bundesstiftung Umwelt.

Deutsche Bundesstiftung Umwelt

7th International Vanadium Symposium, Oct. 6–9, 2010, Toyama, Japan

Anhang F

Poster

In situ-generated Chlorine as Selective Reagent for Chlorocyclization Reactions of Substituted 4-Pentenols.

Oliver Brücher, Jens Hartung, *GDCh-Wissenschaftsforum*, Bremen, **2011**.

TECHNISCHE UNIVERSITÄT KAISERSLAUTERN

In situ-generated Chlorine as Selective Reagent for Chlorocyclization Reactions of Substituted 4-Pentenols

Oliver Brücher and Jens Hartung*

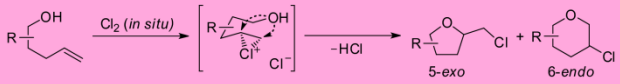
Department of Organic Chemistry, Technische Universität Kaiserslautern, Erwin-Schrödinger-Straße, D-67663 Kaiserslautern

Fax: +49 631 205 3921, Email: hartung@chemie.uni-kl.de

Summary: An efficient procedure for *in situ*-generation of molecular chlorine *via* Mo(VI)- and Ti(IV)-catalyzed oxidation of chloride equivalents with *tert*-butyl hydroperoxide under mild conditions is presented. Oxidation reactions were carried out in anhydrous solutions of eco-friendly dimethyl carbonate. In presence of substituted 4-pentenols, chloride oxidations selectively furnished *β*-chlorinated tetrahydrofurans and -pyrans in synthetically useful yields. The chlorination of other organic substrates like activated arenes, *β*-diketons, and terpenes was also feasible.

Background

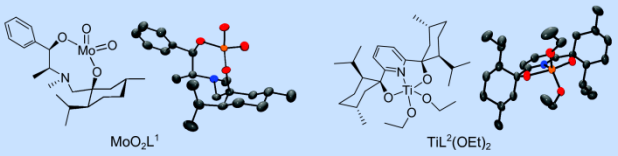
Molecular chlorine is a versatile reagent, but also a toxic and corrosive gas. Storage, transport, and handling, thus, require strict safety standards and prevent a widespread use in chemical industry and laboratory practice. A possibility to circumvent the aforementioned safety risks is the *in situ*-generation of chlorine from chloride equivalents *via* catalytic oxidation with peroxides. This approach is already established for the generation of molecular bromine from bromide salts and works well both under aqueous and anhydrous conditions.[1,2] The reaction, however, requires activation of the peroxide by protons or Lewis-acid transition metal catalysts, to proceed with reasonable rates at mild temperatures. In our efforts to prepare substituted tetrahydrofuran- and tetrahydropyran derivatives from substituted 4-pentenol precursors, we were interested in chlorocyclization reactions of the latter, whereas chlorine equivalents should emerge from oxidation of chloride ions.[3] Since strongly acidic and aqueous conditions decrease the performance of halogen cyclizations, we focused on the activation by transition metal catalysts.



Results

Catalytic Chloride Oxidation

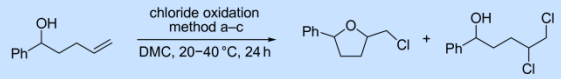
In parameter screenings we found that a Ti(IV)- and a Mo(VI)-complex with *O,N,O*-donor ligands (*see figure below*), which were available from a foregoing project, efficiently catalyzed the oxidation of chloride ions, applied as pyridinium-hydrochloride (py·HCl), with *tert*-butyl hydroperoxide (TBHP) in dimethyl carbonate (DMC) at 20 °C or 40 °C respectively.



It appeared that reactions, especially chlorocyclizations, not only proceeded better under anhydrous conditions, but also became faster and more effective under inert gas. In addition to catalytic approaches, we reinvestigated a previously described chloride oxidation system for arene chlorinations using KCl and Oxone in aqueous MeCN.[4] We were pleased to find that the procedure worked as well in anhydrous DMC and thus, was also applicable for chlorocyclizations.

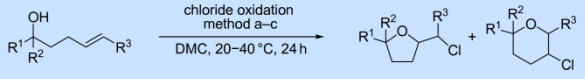
Chlorocyclizations of 4-Pentenols

Optimized procedures for *in situ*-generation of chloro electrophiles were subsequently adopted to chlorocyclization reactions of substituted 4-pentenols. It became apparent that opening of the chloronium intermediate by chloride ion was the major side reaction for the methods using py·HCl, whereas no such reaction was observed in the KCl / Oxone system (*see below*).



oxidation method	yield (*cis*:*trans*)	yield (*like*:*unlike*)
(a) KCl, Oxone, 30 °C	72 % (41:59)	-
(b) *cat.* MoO_2L^1, py·HCl, TBHP, 40 °C	69 % (42:58)	15 % (50:50)
(c) *cat.* $TiL^2(OEt)_2$, py·HCl, TBHP, 20 °C	53 % (41:59)	34 % (50:50)

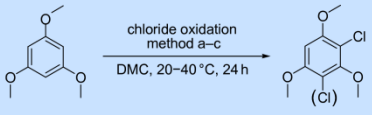
The chlorocyclizations proceeded in good yields for a variety of substituted 4-pentenols and regioselectivity of ring formation followed the same guidelines as found for bromocyclizations.[1,2] Work-up of reaction mixtures was easily performed upon removal of the solvent followed by chromatographic purification of the crude product. Larger scale conversions clearly favor catalytic methods (b) and (c) due to high generation of waste salts in the KCl / Oxone system.



R^1	R^2	R^3	oxidation method	yield (*cis*:*trans*)	yield (*cis*:*trans*)
Ph	CH_3	H	(a) KCl, Oxone, 30 °C	78 % (41:59)	-
			(b) *cat.* MoO_2L^1, py·HCl, TBHP, 40 °C	80 % (38:62)	-
			(c) *cat.* $TiL^2(OEt)_2$, py·HCl, TBHP, 20 °C	67 % (38:62)	-
H	H	Ph	(a) KCl, Oxone, 30 °C	-	58 % (<2:98)
			(b) *cat.* MoO_2L^1, py·HCl, TBHP, 40 °C	-	65 % (<2:98)
			(c) *cat.* $TiL^2(OEt)_2$, py·HCl, TBHP, 20 °C	-	74 % (<2:98)

Arene Chlorinations

To expand the scope of the reaction, developed methods were further applied to chlorinations of activated arenes. In the row of methoxybenzene, 1,3-dimethoxybenzene, and 1,3,5-trimethoxybenzene only the disubstituted and trisubstituted derivatives showed quantitative conversion after 24 h, whereas anisole exhibited only minor reactivity. The reaction with 1,3,5-trimethoxybenzene, moreover, indicated that chloride utilization in the catalytic methods exceeded 80 % (*see below*).



oxidation method	yield (*mono*-Cl:*di*-Cl)
(a)	78 % (86:16)
(b)	99 % (79:21)
(c)	99 % (82:18)

oxidation methods: (a) KCl, Oxone, 30 °C; (b) *cat.* MoO_2L^1, py·HCl, TBHP, 40 °C; (c) *cat.* $TiL^2(OEt)_2$, py·HCl, TBHP, 20 °C.

Mechanistic Considerations

From an analysis of reaction products and mass balances, the generated chloro electrophile was assumed to be molecular chlorine rather than *tert*-butyl hypochlorite. Further support for this assumption was provided by chlorination reactions of 2,3-dimethylbutane under radical conditions, with an excess of alkane substrate and irradiation with UV-light. Quantitative determination of the *mono*-chlorinated reaction products showed a *tertiary* / *primary* ratio of ~13, which is closer to tabulated values for molecular chlorine (~4.2) than for *tert*-butyl hypochlorite (~44) in neat reaction mixtures.[5]

Conclusions

The study showed that *in situ*-generation of electrophilic chlorination equivalents *via* catalytic oxidation of chloride ions with *tert*-butyl hydroperoxide under mild and anhydrous conditions is feasible. Slow release of the chlorinating species in presence of substituted 4-pentenols selectively initiated chlorocyclization reactions, which are largely unexplored to date, and furnished *β*-chlorinated tetrahydrofurans and -pyrans in synthetically useful yields. Chlorination of activated arenes proceeded in very high yields and indicated a chloride utilization of more than 80 %. The chemical nature of the generated chlorination reagent most likely is molecular chlorine as derived from mechanistic investigations on fingerprint-regioselectivities in radical alkane chlorinations.

References and further reading:

[1] D. Wischang, O. Brücher, J. Hartung, *Coord. Chem. Rev.* **2011**, *255*, 2204–2212.
[2] O. Brücher, J. Hartung, *ACS Catal.*, *accepted*.
[3] O. Brücher, J. Hartung, *manuscript in preparation*.
[4] N. Narender, P. Srinivasu, S.J. Kulkarni, K.V. Raghavan, *Synth. Commun.* **2002**, *32*, 279–286.
[5] M.L. Poutsma, In *Methods in Free Radical Chemistry*, E.S. Huyser, Ed., Marcel Dekker: NY, (**1969**), *Vol.1*, p 79.

Acknowledgements:

This work was generously supported by the Deutsche Bundesstiftung Umwelt.

DBU Deutsche Bundesstiftung Umwelt

Curriculum Vitae

Oliver Brücher (Diplom-Chemiker)
geboren in Birkenfeld / Nahe

PROMOTION

07/2007 – 10/2012	Anfertigung der Doktorarbeit in organischer Synthesechemie und Übergangsmetall-vermittelter Oxidationskatalyse Promotion mit der Gesamtnote: „mit Auszeichnung“ (0.0) Arbeitsgruppe von Prof. Dr.-Ing. Jens Hartung, Technische Universität Kaiserslautern Titel der Dissertation: „*Über die Entwicklung und Anwendung funktionaler Haloperoxidase-Modelle zur Synthese von Naturstoff-derivaten*“

STUDIUM

10/2001 – 09/2006	Studium der Chemie mit Schwerpunkt Organische Chemie Diplom mit der Gesamtnote: „sehr gut” (1.2) Arbeitsgruppe von Prof. Dr.-Ing. Jens Hartung, Technische Universität Kaiserslautern Titel der Diplomarbeit: „*Beiträge zur stereoselektiven Synthese 2,2,6,6-substituierter Tetrahydropyrane*“

AUSLANDSSTUDIUM

04/2005 – 07/2005	Forschungspraktikum in supramolekularer Chemie Arbeitsgruppe von Prof. Dr. Leroy Cronin, University of Glasgow

WEHRDIENST

07/2000 – 04/2001	Grundwehrdienst in Dillingen/Donau, Kusel und Idar-Oberstein

SCHULAUSBILDUNG

08/1991 – 06/2000	Gymnasium Birkenfeld Abitur mit der Gesamtnote: „sehr gut” (1.3)

AUSZEICHNUNGEN

10/2010	Reisestipendium des Deutschen Akademischen Austauschdienstes zu einer Fachtagung in Toyama/Japan
07/2007 – 06/2010	Doktoranden-Stipendium der Deutschen Bundesstiftung Umwelt
06/2000	Buchpreis des Fonds der Chemischen Industrie

PUBLIKATIONEN

[1] Full Paper: **Inorganic Crown Ether: the Host–Guest Chemistry of a High Nuclearity 'Celtic-ring' Isopolyoxotungstate $[H_{12}W_{36}O_{120}]^{12-}$.** D.-L. Long, O. Brücher, C. Streb, L. Cronin, *Dalton Trans.* **2006**, 2852–2860.

[2] Full Paper: **Hybrid Host–Guest Complexes: Directing the Supramolecular Structure through Secondary Host–Guest Interactions.** C. Streb, T. McGlone, O. Brücher, D.-L. Long, L. Cronin, *Chem. Eur. J.* **2008**, *14*, 8861–8868.

[3] Full Paper: **Bromoperoxidase Activity and Vanadium Level of the Brown Alga *Ascophyllum nodosum*.** J. Hartung, O. Brücher, D. Hach, H. Schulz, H. Vilter, G. Ruick, Phytochemistry **2008**, *69*, 2826–2830.

[4] Poster: **Bromoperoxidases (*Ascophyllum nodosum*) as Sustainable Environmental Oxidative Catalysts.** O. Brücher, D. Hach, H. Schulz, J. Hartung, *NanoKat-Tagung*, Kaiserslautern, **2009**.

[5] Poster: **Vanadium(V)-catalyzed Oxidative Brominations of Olefins and Alkenols with *tert*-Butyl Hydroperoxide and *β*-Bromopropionic Acids.** O. Brücher, J. Hartung, *7th International Vanadium Symposium*, Toyama (Japan), **2010**.

[6] Review: **Bromoperoxidases and Functional Enzyme Mimics as Catalysts for Oxidative Bromination – a Sustainable Synthetic Approach.** D. Wischang, O. Brücher, J. Hartung, *Coord. Chem. Rev.* **2011**, *255*, 2204–2217.

[7] Full Paper (Cover Article): **Vanadium(V)-Catalyzed Oxidative Bromination of Acid Labile Alkenols and Alkenes in Alkyl Carbonates.** O. Brücher, J. Hartung, *ACS Catal.* **2011**, *1*, 1448–1454.

[8] Structure Report: ***tert*-Butyl 1-hydroxypiperidine-2-carboxylate.** O. Brücher, U. Bergsträsser, H. Kelm, J. Hartung, *Acta Cryst.* **2011**, E67, o2061.

[9] Poster: ***In situ*-generated Chlorine as Selective Reagent for Chlorocyclization Reactions of Substituted 4-Pentenols.** O. Brücher, J. Hartung, *GDCh-Wissenschaftsforum*, Bremen, **2011**.

[10] Full Paper: **Controlling 6-*endo*-Selectivity in Oxidation/Bromocyclization Cascades for Synthesis of Aplysiapyranoids and other 2,2,6,6-substituted Tetrahydropyrans.** O. Brücher, U. Bergsträßer, H. Kelm, J. Hartung, M. Greb, I. Svoboda, H. Fuess, *Tetrahedron* **2012**, *68*, 6968–6980.

[11] Full Paper: **A Practical Approach to Catalytic and Noncatalytic Oxidative Chlorination of Unsaturated and Saturated Hydrocarbons.** O. Brücher, J. Hartung, **2012**, *submitted for peer review*.

Danksagungen

Ich möchte mich zunächst bei Herrn Professor Hartung für die freundliche Aufnahme in seinen Arbeitskreis und seine Unterstützung bedanken. Weiterhin bedanke ich mich für die vielen hilfreichen Anregungen und Diskussionen, aber auch für die mir gewährten Freiheiten bei der Bearbeitung meines Forschungsthemas.

Mein Dank gilt hier auch allen Mitgliedern des AK Hartung für das fantastische Arbeitsklima im Labor und für die Ablenkung bei zahlreichen gemeinsamen Freizeitaktivitäten. Besonders bedanken möchte ich mich bei meinen ehemaligen Kommilitonen und Mitbewohnern Domi und Georg. Ich freue mich darauf, nun endlich auch gemeinsam mit Euch an die vielen schönen Momente des Studiums und der Promotionszeit zurückblicken zu können. Der „alten“ Riege des AK Hartung vertreten durch Andreas, Arne, Babsi, Heiko, Mario, Nina und Thommy danke ich für den besonderen und bis heute fortbestehenden Zusammenhalt. Der neueren Doktorandengeneration bestehend aus Diana, Christine, Irina, Patrick, Matthias, Alex, Madlen und Melanie möchte ich vor allem Dank dafür aussprechen, dass Ihr die alte Riege so würdig vertreten habt. Auch die vielen Tage an denen mich meine Chemie nicht sonderlich zu begeistern vermochte, konnten durch die von Euch erzeugte Laboratmosphäre noch gerettet werden. Ich kann wirklich von Glück reden mich gleich zwei so fabelhaften Generationen zugehörig zu fühlen und hoffe wir bleiben weiter in Kontakt. Ein großes Dankeschön geht dabei auch an “Uns Uwe“, für seine vielen hilfreichen Ideen zur Lösung von Problemen verschiedenster Art. Weiterhin bedanken möchte ich mich bei meinen Forschungspraktikanten Michaela und Matthias, sowie bei allen aktuellen und ehemaligen Diplomanden des AK Hartung (Britta, Janina, Alex, Benny und Swen) für die gute Zusammenarbeit.

Ich danke den Mitarbeitern der Abteilung Analytik (Frau Biehl, Birgit, Jana und Ruth) für die Vermessung von HRMS-, GC-MS- und CHN-Proben und vor allem der Dame am Magnetresonanzspektrometer Christiane für die Aufnahme unzähliger NMR-Spektren. Mein besonderer Dank geht an Harry für das Anfertigen von Kristallstrukturanalysen und für die Rolle als mein Tandempartner im interkulturellen Austausch zwischen organischer und anorganischer Chemie. Den Chemikalienbrüdern Luki, Frank und Jürgen danke ich für die Versorgung mit hochreinen Ausgangsmaterialien auch außerhalb der Lageröffnungszeiten und für die alljährliche Verkostung von Feuerzangenbowle mit Schuss. Dank gilt auch den Sekretärinnen der organischen Chemie Edith und Susanne für die Bewältigung des Papierkrams und der Verwaltungsaufgaben.

Für die finanzielle Unterstützung, aber vor allem für die Förderung und die gute Betreuung, danke ich der Deutschen Bundesstiftung Umwelt und den Mitarbeitern des Stipendienprogramms. Ein besonderer Dank geht dabei an Herrn Dr. Maximilian Hempel für die mir unvergesslichen Stipendiatenseminare und seinen persönlichen Einsatz.

Ich danke meiner Familie und meinen Freunden, die mich in schwierigen Zeiten besonders unterstützt haben. Allen voran meinen Eltern – die schnell wussten, wann sie besser nicht nach dem Verlauf meiner Experimente fragen sollten, mich aber Ihr Vertrauen stets spüren ließen – möchte ich von ganzem Herzen danken, dass sie mir während der Promotion mit vielen Kleinigkeiten den Rücken frei gehalten haben. Meinem Kumpel Tom danke ich für die Therapiesitzungen beim donnerstäglichen ICQ-Stammtisch.

Das größte Dankeschön geht an meine Eva, ohne deren Liebe und Beistand ich diese Arbeit hätte nicht zu Ende bringen können. Danke für Dein Verständnis und dass Du mich davor bewahrt hast, mit den Folgen einer falschen Entscheidung leben zu müssen.