DISS. ETH NO. 23251

Towards a Structural Revision of Mytilipin B

A thesis submitted to attain the degree of
DOCTOR OF SCIENCES of ETH ZURICH
(Dr. sc. ETH Zurich)

presented by
MATHIAS JUUL JACOBSEN
MSc, Aarhus University

born on 20.05.1987
citizen of Denmark

accepted on the recommendation of
Prof. Dr. Erick M. Carreira, examiner
Prof. Dr. Karl-Heinz Altmann, co-examiner

2016

Acknowledgments

First, I would like to thank my supervisor Prof. Erick M. Carreira for accepting me in his research group. I am grateful to have had the opportunity to work at ETH. I have definitely learned a lot during my time in his group.

Prof. Karl-Heinz Altmann is greatly acknowledged for accepting to be my co-examiner without hesitation. His comments and corrections are highly valued.

Credit is given to Dr. Matthew Webster, Philipp Sondermann, and Stefan Fischer for their support on this project. It has been a great help.

This manuscript has evolved thanks to a team of proofreaders, consisting of Alberto Kravina, James Hamilton, Christian Ebner, Stefan Fischer, Hannes Zipfel, Matthias Westphal, and Simone Jacobsen. Their comments and corrections have led to substantial improvements.

Working in the Carreira Group has been an exciting experience. I would like to thank past and present members of my lab, Dr. Nicolas Armanino, Dr. Stefan Diethelm, Dr. Lorenz Schneider, Matthias Westphal, Dr. Patrick Brady, Emma Robertson, and Philipp Sondermann. There was never a dull moment in H336 with Problem of the Day, Coopen Sie sessions, Fancy-Pants/Gangsta Fridays, and much, much more. It has been a great learning environment with countless interesting discussions. I would also like to thank the group as a whole for creating an inspiring atmosphere with friendly, helpful, and very knowledgeable individuals.

Frau Anke Kleint is acknowledged for her professional and expedient handling of administrative matters.

Outside of the lab, I have had the pleasure to spend time with awesome people. I would like to thank the skiing crew for some great recreational hours on the slopes (and the following Après-Ski). Thanks to Hannes Zipfel, Matthias Westphal, and Simon Krautwald for hotdogs and stupid-movie nights. Thanks to Dr. Simon Breitler for teaching me the art of the finest Swiss cuisine, Chäsfondue, and to Dr. Nikolas Huwyler for introducing me to the Swiss type of hiking, aka. Horse-Steak-Hike. I acknowledge Dr. Erik Funder for his help in spreading the Danish culture among the Carreira Group members. I greatly appreciate the time spent with Megan, Patrick, and Nolan Brady as well as the seemingly infinite cookie supply.

Special thanks go to Hannes Zipfel and Matthias Westphal for being amazing friends and for providing endless support when needed, especially through the toughest times.

Simone, I cannot express how lucky and thankful I feel to have you by my side. Thank you for your unconditional love, support, and patience as well as always believing in me. I cherish every moment with you and I am looking forward to our exciting future together, I love you!

Thank you Albert for your laughs and hugs – and for keeping me awake at night during the writing process. Without you I would never have gotten this far.

Til sidst vil jeg gerne takke min bror, Andreas, og mine forældre. Tak for, at I altid er der for mig og altid støtter mig.

Publications and Presentations

Publications:

M. Pabst, I. Benešová, S. R. Fagerer, **M. Jacobsen**, K. Eyer, G. Schmidt, R. Steinhoff, J. Krismer, F. Wahl, J. Preisler, R. Zenobi, *J. Proteome Res.* [Online early access].
DOI: 10.1021/acs.jproteome.5b00899
"Differential Isotope Labeling of Glycopeptides for Accurate Determination of Differences in Site-Specific Glycosylation"

M. J. Jacobsen, E. D. Funder, J. R. Cramer, K. V. Gothelf, *Org. Lett.* **2011**, *13*, 3418.
"β-Olefination of 2-Alkynoates Leading to Trisubstituted 1,3-Dienes"

Presentation:

Oral Presentation at Janssen, Pharmaceutical Companies of Johnson&Johnson
April 2015, Schaffhausen, Switzerland

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Abstract

Chlorosulfolipids, an unusual class of polychlorinated natural products, were first detected in the late 1960's by Elovson and Vagelos in extracts from *Ochromonas danica*. In the early 2000's, Ciminiello and Fattorusso isolated mytilipins A, B, and C from the digestive glands of mussels, *Mytilus galloprovincialis,* collected along the Emilia Romagna coastline of Italy (Chart 1). These compounds were suspected to be causative agents for diarrhetic shellfish poisoning. The structures of the mytilipins were assigned based on extensive analyses of NMR spectral data and Mosher ester analysis. The relative configurations were assigned based on *J*-Based Conformational Analysis (JBCA).

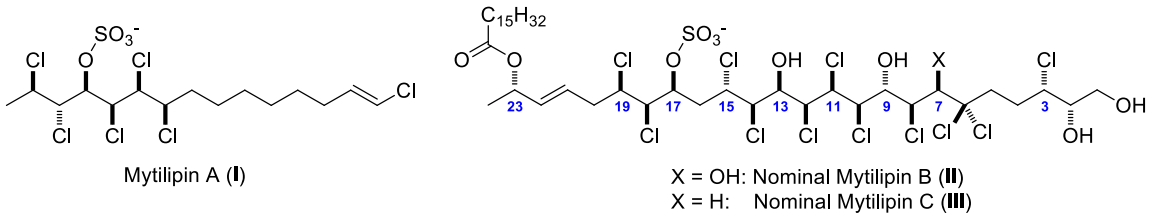


Chart 1 Structure of mytilipin A and proposed structures of mytilipins B and C.

In 2009, Carreira *et al.* disclosed a synthesis of mytilipin A, constituting the first total synthesis of a chlorosulfolipid, and in 2011 they further documented the total synthesis of nominal mytilipin B, the most complex chlorosulfolipid isolated to date. A comparison of NMR spectral data for **II** showed severe mismatches between the isolation report and the data obtained for the synthetic material. Hence, a misassignment of the structure by the isolation group was concluded.

This thesis describes our work on a structural revision of mytilipin B and the synthetic studies towards a confirmation of the structure by total synthesis.

By careful reinvestigation of the isolation data, we observed a key discrepancy in interpretation of a ROESY spectrum which leads to a different conclusion in a JBCA (Chart 2). The isolation group reported the presence of a ROE crosspeak between H_{12} and H_{15}, however, this signal is absent in the reported data. Accordingly, the C_{13}/C_{14} relative configuration should be *anti* as opposed to the reported *syn*-relationship. Ultimately, this leads to a revision of the configuration of five stereogenic centers in the area C_{14}–C_{19} (Chart 2). In addition, it is noted that a correction of the C_{23} configuration might be necessary due to incorrect use of a Mosher ester analysis, however, the (*S*) and (*R*) configuration at C_{23} is equally plausible from our analysis.

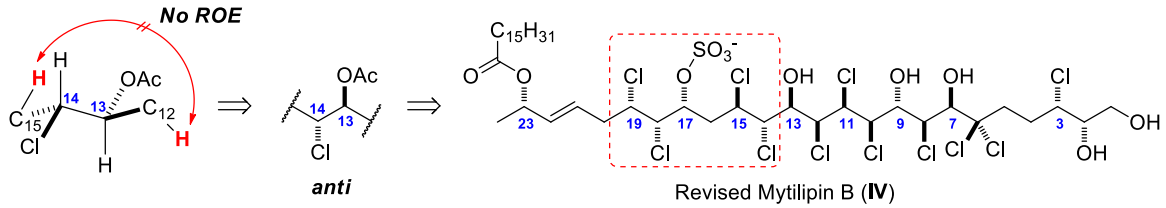
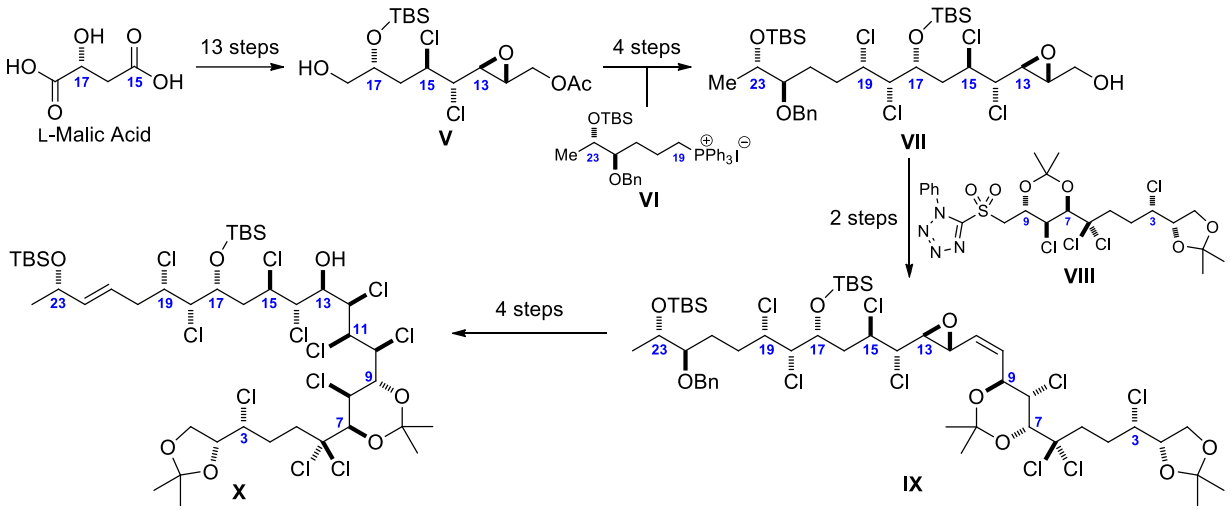


Chart 2 Structural revision of mytilipin B based on an absent ROE crosspeak.

In synthetic studies towards revised mytilipin B (**IV**), synthesis of both fragments **VII** and **VIII** followed by unification in a Julia–Kocienski olefination reaction has been achieved (Scheme 1). Fragment **VIII** was prepared on the basis of known protocols, and the present work describes additional observations, improvements, and attempts at alternative strategies. Fragment **VII** was prepared in 17 steps from L-malic acid *via* primary alcohol **V**. Key transformations to afford **VII** include *trans*-specific dichlorinations, a Sharpless epoxidation, and a highly *cis*-selective Wittig olefination reaction.

From coupling product **IX**, epoxide opening, dichlorination, and deprotection/dehydration allowed for the successful completion of the entire hydrocarbon backbone structure **X** as the most advanced intermediate obtained in this work towards revised mytilipin B (**IV**).



Scheme 1 Synthetic studies towards revised mytilipin B.

Zusammenfassung

Chlorosulfolipide, eine ungewöhnliche Klasse polychlorierter Naturstoffe, wurden erstmals in den späten 1960er Jahren von Elovson und Vagelos aus Extrakten von *Ochromonas danica* isoliert. Anfang des 21. Jahrhunderts isolierten Ciminiello und Fattorusso die Naturstoffe Mytilipin A, B und C aus den Verdauungsdrüsen von Muscheln der Gattung *Mytilus galloprovincialis*, die entlang der Küste von Emilia Romagna in Italien gesammelt wurden (Abbildung 1). Diese Verbindungen wurden verdächtigt Erreger diarrhöischer Schalentiervergiftung zu sein. Die Strukturen der Mytilipine wurden auf Basis von umfangreichen NMR-Daten und Mosher-Ester Analysen zugeordnet. Die relativen Konfigurationen wurden anhand von J-basierter Konformationsanalyse (JBCA) zugeordnet.

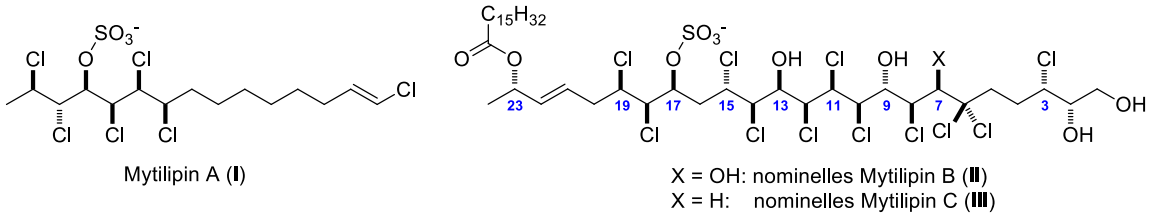


Abbildung 1 Struktur von Mytilipin A und vorgeschlagene Strukturen von Mytilipin B und C.

Im Jahr 2009 veröffentlichten Carreira *et al*. die erste Totalsynthese eines Chlorosulfolipids, Mytilipin A. Eine nachfolgende Arbeit im Jahr 2011 beschrieb die Totalsynthese von nominellem Mytilipin B, des bis dato komplexesten Chlorosulfolipids. Die NMR Daten des Naturstoffs wichen allerdings gravierend von denen des synthetischen Materials (**II**) ab. Dieses Ergebnis legte eine Fehlzuordnung der Struktur durch die Isolationsgruppe nahe.

Diese Dissertation beschreibt unsere Arbeit an einer strukturellen Revision von Mytilipin B sowie synthetische Studien auf dem Weg zu einer experimentellen Bestätigung der Struktur.

Bei der sorgfältigen Überprüfung der Isolationsdaten bemerkten wir eine wesentliche Diskrepanz bei der Interpretation eines ROESY-Spektrums, die in der JBCA-Analyse zu einem anderen Ergebnis führt (Abbildung 2). Die Isolationsgruppe beschrieb ein ROE-Kreuzsignal zwischen H_{12} und H_{15}, welches allerdings in den Originaldaten nicht zu finden ist. Dementsprechend sollte eine relative *anti*-Konfiguration an C_{13}/C_{14} bestehen, statt der beschriebenen *syn*-Konfiguration. Letztendlich führt dies zu einer Revision der Konfiguration von fünf stereogenen Zentren zwischen C_{14} und C_{19} (Abbildung 2). Darüber hinaus ist es möglich, dass die Konfiguration von C_{23} aufgrund der falschen

Anwendung einer Mosher-Ester Analyse korrigiert werden muss. Unserer Analyse nach sind beide Konfigurationen gleichermaßen plausibel.

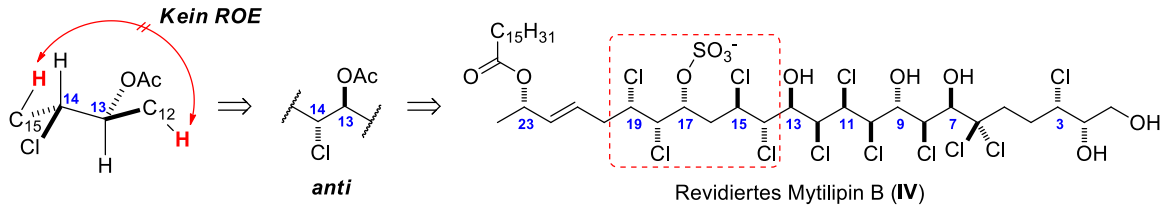
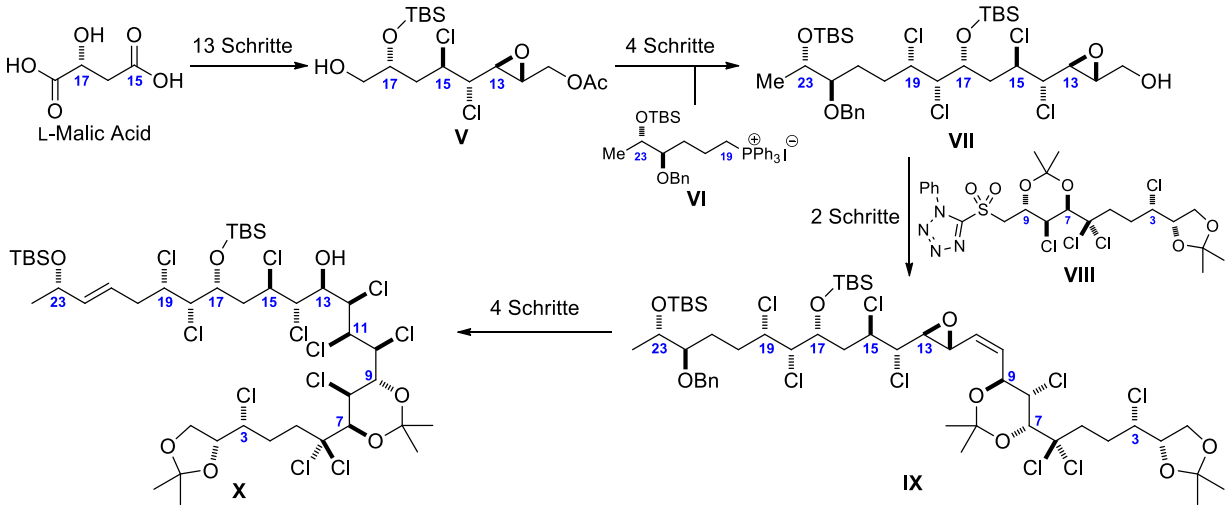


Abbildung 2 Strukturelle Revision von Mytilipin B aufgrund eines nicht vorhandenen ROE-Kreuzsignals.

In synthetischen Studien zur revidierten Struktur von Mytilipin B (**IV**) wurden die beiden Fragmente **VII** und **VIII** erfolgreich dargestellt und mittels einer Julia-Kocienski Olefinierung gekoppelt (Schema 1). Fragment **VIII** wurde auf der Grundlage bekannter Protokolle hergestellt und die vorliegende Arbeit beschreibt zusätzliche Beobachtungen, Verbesserungen und Studien zu alternativen Strategien. Ausgehend von L-Äpfelsäure wurde Fragment **VII** über den primären Alkohol **V** in 17 Schritten hergestellt. Schlüsselschritte auf dem Weg zu **VII** beinhalteten trans-spezifische Dihalogenierungen, eine Sharpless-Epoxidierung sowie eine besonders cis-selektive Wittig Olefinierung.

Von Kopplungsprodukt **IX** führten Epoxidöffnung, Dichlorierung sowie Entschützung/Dehydratisierung zur erfolgreichen Darstellung des gesamten Kohlenstoffgerüsts. Struktur **X** stellt das fortgeschrittenste Intermediat dieser Arbeit auf dem Weg zu strukturell revidiertem Mytilipin B (**IV**) dar.



Schema 1 Synthetische Studien auf dem Weg zu revidiertem Mytilipin B.

Abbreviations, Acronyms, and Symbols

$[\alpha]_D^T$	specific rotation at temperature T at the sodium D line
Å	Ångstrom
$A_{1,3}$	allyl 1,3-interactions
Ac	acetyl
acac	acetylacetonato
AMAA	arylmethoxy acetic acid
anhydr.	anhydrous
aq	aqueous
atm	atmosphere
BINOL	1,1‘-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
bp	boiling point
BPO	bromoperoxidase
bs	broad signal
Bu	butyl
Bz	benzoyl
ºC	degree centrigrade
calcd	calculated
CAM	cerium Ammonium Molybdate stain (Hanessian’s stain)
CAN	ceric ammonium nitrate
cat.	catalytic
CoA	coenzyme A
conc.	concentrated
convn.	conversion
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CPO	chloroperoxidase
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
δ	NMR chemical shift in ppm downfield from a standard
d	doublet, day
Δ	difference
DABCO	1,4-diazabicyclo[2.2.2]octane
DBB	4,4’-di-*tert*-butyl-1,1’-biphenyl
DBU	1,8-diazabicycloundec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DET	diethyl tartrate
DEPT	distortionless enhancement by polarization transfer
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride

DMAP	4-*N*,*N*-dimethylamino pyridine
DMF	*N*,*N*-dimethyl formamide
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E1	unimolecular elimination mechanism
E2	bimolecular elimination mechanism
E	energy
ee	enantiomeric excess
equiv	equivalent
ESI	electron spray ionization
Et	ethyl
ETH	Eidgenössische Technische Hochschule
EtOAc	ethyl acetate
et al.	and others
FAD	flavin adenine dinucleotide
$FADH_2$	reduced form of flavin adenine dinucleotide
g	gram
GLC-MS	gas-liquid chromatography – mass spectrometry
h	hour
HECADE	heteronuclear couplings from aSSCI-domain experiments with e.COSY-type cross peaks
HETLOC	analysis of heteronuclear coupling constants
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMQC	heteronuclear multiple quantum coherence spectroscopy
HMPA	hexamethylphosphoramide
HOHAHA	homonuclear Hartmann-Hahn spectroscopy
HPLC	high performance liquid chromatography
HPO	haloperoxidase
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence spectroscopy
Hz	Hertz
i	*iso*
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocampheyl
IPO	iodoperoxidase
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
JBCA	*J*-Based Conformational Analysis
kcal	kilocalorie
l	liquid, large
L	liter
LC-MS	liquid chromatography / mass spectrometry
LDA	lithium diisopropyl amide
m	multiplet, medium
m	*meta*
µ	micro
M	Molar, molecular ion

mbar	millibar
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
mg	milligram
MHz	Megahertz
min	minute
mL	milliliter
m.p.	melting point
mmol	millimol
MPA	α-methoxymethylphenylacetic acid
Ms	methylsulfonyl
MS	molecular sieves, mass spectrometry
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
n	normal, unbranched alkyl chain
NAD	nicotinamide adenine dinucleotide
NADH	reduced form of nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nd	not determined
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NME	*N*-methylephedrine
NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear *Overhauser* effect
NOESY	nuclear *Overhauser* effect spectroscopy
Ns	nosyl, 2-nitrosulfonyl
ν	vibration frequency in cm^{-1}
o	ortho
[Ox]	oxidation
oct	octyl
p	para
PAPS	3'-phosphoadenosine-5'-phosphosulfate
PG	protecting group
pH	negative logarithm of hydrogen ion concentration
Ph	phenyl
pin	pinacolato
Piv	pivaloyl, trimethylacetate
PMB	4-methoxybenzyl
ppm	parts per million
PPTS	pyridinium 4-toluenesulfonate
Pr	propyl
PS-HMBC	phase-sensitive heteronuclear multiple bond coherence
PTSH	1-phenyl-1*H*-tetrazole-5-thiol
p-TsOH	*para*-toluenesulfonic acid
py	pyridine
q	quartet
quant.	quantitative
rac	racemic

recov.	recovered
Red-Al	sodium *bis*(2-methoxyethoxy)aluminum hydride
R_f	retention factor
ROE	rotating frame *Overhauser* effect
ROESY	rotating frame *Overhauser* effect spectroscopy
r.t.	room temperature
s	second, singlet, small
SAM	*S*-adenosyl-L-methionine
sat.	saturated
S_N1	unimolecular nucleophilic substitution mechanism
S_N2	bimolecular nucleophilic substitution mechanism
t	triplet
t	*tert*
T	temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl (protecting group), *tert*-butylsalicylaldimine (ligand)
TCA	trichloroacetate
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Tf	trifluormethanesulfonyl
TFA	trifluoroacetic acid, trifluoroacetyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	tosyl, 4-methylphenylsulfonyl
X	halogen

1 Introduction

1.1 Halogenated Natural Products

1.1.1 Origins and Significance

In the beginning of the 19th century, the pharmacist's apprentice Friederich Sertürner isolated the pharmacologically active compound morphine from *Papaver somniferum*.[1] Ever since this important discovery, the isolation of complex molecules from natural sources has been an active field of research and the number of isolated and characterized natural products is constantly growing. This is partly due to the continuous search for new biologically active compounds that can serve as lead structures for potential therapeutic agents.[2] Given the abundance of halogens in the environment (Table 1),[3] new halogenated natural products are also frequently isolated.

Table 1 Distributions of halides in the environment (mg/kg).[3]

Halide	Oceans	Sedimentary Rocks	Fungi	Wood pulp	Plants
F^-	1.4	270–740	–	–	–
Cl^-	19,000	10–320	–	70–2100	200–10,000
Br^-	65	1.6–3	100	–	–
I^-	0.05	0.3	–	–	–

With only a dozen of known naturally occurring organohalogens in 1954, the number of halogenated natural products isolated to date has increased to over 5000.[4] Among these, organochlorines and -bromines are the most abundant, whereas organoiodines and -fluorines are less represented.[5] On the contrary, due to (among other reasons) metabolic stability, the distribution is different in medicinal compounds, with fluorine being the most widely introduced halogen in active

[1] G. R. Hamilton, T. F. Baskett, *Can. J. Anaesth.* **2000**, *47*, 367.
[2] J. W.-H. Li, J. C. Vederas, *Science* **2009**, *325*, 161.
[3] L. P. Knauth, *Nature* **1998**, *395*, 554.
[4] Some excellent reviews: a) G. W. Gribble, *Prog. Chem. Org. Nat. Prod.* **1996**, *68*, 1; b) G. W. Gribble, *Prog. Chem. Org. Nat. Prod.* **2010**, *91*, 1; c) G. W. Gribble, *Alkaloids Chem. Biol.* **2012**, *71*, 1.
[5] a) G. W. Gribble, *J. Chem. Educ.* **2004**, *81*, 1441; b) G. W. Gribble, *Am. Sci.* **2004**, *92*, 342.

pharmaceutical ingredients.[6] Figure 1 shows the relative abundance of natural and pharmaceutical organohalogens.

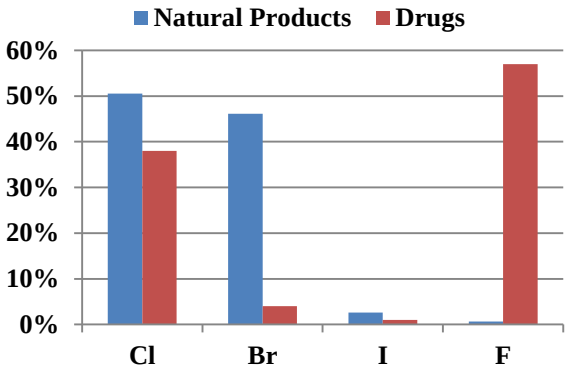


Figure 1 Relative distributions based on halogen. Halogenated natural products isolated as of July 2004,[5] and marketed drugs as of October 2009.[6]

Organohalogens can be found in various different parts of both the oceans, on land, and in the atmosphere. These compounds are produced by a large number of different organisms, i.e. marine and terrestrial plants, bacteria, fungi, insects, marine animals, and mammals. From the literature published from 1998–2005, 15–20% of all newly discovered marine natural products contained halogens.[4] It has been calculated that 25% of naturally occurring organohalogens are alkaloids but the halogenated natural products is a very diverse class of compounds, with members such as simple alkanes, terpenes, steroids, lipids, amino acids, phenols etc. Some examples are shown in Chart 1.

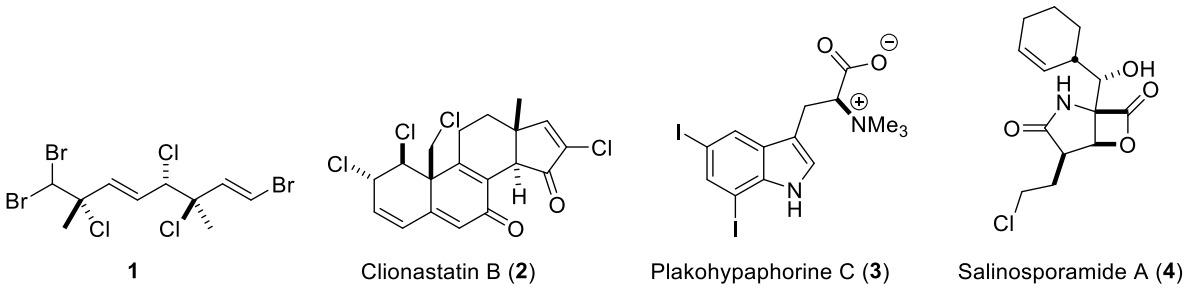


Chart 1 Examples of the diverse range of naturally occurring organohalogens.

One of the first halogenated monoterpenes (**1**) was initially discovered in the digestive glands of the sea hare *Aplysia californica* in 1973 by Faulkner and Stallard[7] and later isolated from the red alga *Plocamium cartilagineum*.[8] As of today, many natural products are identified *via* their biological activity. Hence, as many other natural products, a wide variety of naturally occurring organohalogens have shown interesting therapeutic potential against a diverse range of diseases. For example, the tetrachlorinated steroid clionastatin B (**2**) displays cytotoxic activity against the three tumor cell lines WEHI 164 (murine fibrosarcoma), RAW 264-7 (murine macrophage), and THP-1 (human monocytes),[9] and plakohypaphorine C (**3**), one of the few naturally occurring iodinated indoles

[6] 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*, 1.
[7] D. J. Faulkner, M. O. Stallard, *Tetrahedron Lett.* **1973**, *14*, 1171.
[8] J. S. Mynderse, D. J. Faulkner, *J. Am. Chem. Soc.* **1975**, *96*, 6771.
[9] E. Fatturusso, O. Taglialatela-Scafati, F. Petrucci, G. Bavestrello, B. Calcinnai, C. Cerrano, P. Di Meglio, A. Ianaro, *Org. Lett.* **2004**, *6*, 1633.

isolated to date, has shown potential antihistamine activity.[10] Furthermore, some halogenated natural products have made it to the pharmaceutical market. For example, the primary alkyl chloride salinosporamide A (**4**) is a highly potent and selective proteasome inhibitor.[11]

In several cases, it has been shown that the halogen substitution on the natural product is essential for the biological activity.[12] This has also been recognized in medicinal chemistry where numerous examples show that removal of a halogen from a drug can lead to a dramatic decrease in the activity, or the introduction of a halogen on a natural product skeleton can lead to beneficial effects, such as enhanced activity or increased metabolic stability. Some examples of molecules where the halogen is of great importance for the activity are shown in Chart 2.

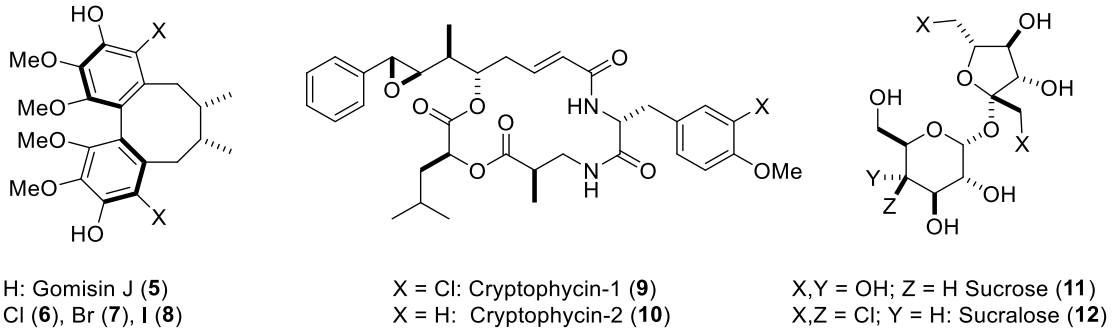


Chart 2 Examples of organic compounds where the halogens have beneficial effects on the activity.

Gomisin J (**5**), a biphenol with anti-HIV activity, has shown enhanced activity when the aryls were functionalized with halogens.[13] The cryptophycins (**9**, **10**) have been tested in a series of cancer cell lines and when comparing the activities of **9** and **10**, the chlorination in this specific example led to up to a 10-fold increase in activity.[14] Furthermore, in the research on food additives, substitution of three hydroxyl-groups on sucrose **11** to give sucralose **12**, the key ingredient in the artificial sweetener Splenda®, has resulted in a significant increase in sweetness.[15] In the latter case it is believed that the observed effect is due to the higher lipophilicity which leads to increased adsorption to target proteins.

By now, halogenated compounds, natural and synthetic, have proven to be important due to their intriguing properties. Hence, it is of continuous interest to identify new sources of halogenated

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[10] F. Borrelli, C. Campagnuolo, R. Capasso, E. Fattorusso, O. Taglialatela-Scafati, *Eur. J. Org. Chem.* **2004**, 3227.
[11] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *8*, 407.
[12] K. Naumann, *J. Prakt. Chem.* **1999**, *341*, 417.
[13] T. Fujihashi, H. Hara, T. Sakata, K. Mori, H. Higuchi, A. Tanaka, H. Kaji, *Antimicrob. Agents Chemother.* **1995**, *39*, 2000.
[14] T. Golakoti, J. Ogino, C. E. Heltzel, T. L. Husebo, C. M. Jensen, L. K. Larsen, G. M. L. Patterson, R. E. Moore, S. L. Mooberry, T. H. Corbett, F. A. Valeriote, *J. Am. Chem. Soc.* **1995**, *117*, 12030.
[15] M. Mathlouthi, A.-M. Seuvre, G. Birch, *Carbohydrate Research* **1986**, *152*, 47.

natural products, and even more so to develop and improve methods for the introduction of halogens into organic molecules.

1.1.2 Enzymatic Halogenations

The mechanisms by which halogens are introduced into organic compounds by biosynthetic pathways have been widely studied and some excellent reviews are available on the subject.[16] In general, one could imagine three different pathways of installation, i.e. by the introduction *via* 1) a halogen anion (X^-), 2) radical pathways involving a halogen radical ($X^{\cdot}$), or 3) a cationic mechanism in which the halogen is formally introduced *via* a hypohalite ion (X^+). Interestingly, although the thermodynamically most stable form of halogens are the anions, in most cases, nature prefers to install Cl, Br, and I *via* oxidative pathways; that is *via* hypohalite ions or halogen radicals. In some instances, however, non-oxidative introduction of a halogen *via* a halide is employed. This is the typical mechanism for enzymatic fluorinations. An accepted explanation for this preference in mechanism is the high oxidation potential of fluorine which makes an oxidative pathway *via* a hypofluorite ion improbable.[16] Table 2 shows an overview of the halogenating enzymes according to their mode of halogen-introduction.

[16] A selection of comprehensive reviews: a) F. H. Vailancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova, C. T. Walsh, *Chem Rev.* **2006**, *106*, 3364; b) C. S. Neumann, D. G. Fujimori, C. T. Walsh, *Chem. Biol.* **2008**, *15*, 99; c) C. Wagner, M. E. Omari, G. M. König, *J. Nat. Prod.* **2009**, *72*, 540; d) A. Butler, M. Sandy, *Nature* **2009**, *460*, 848.

Table 2 Overview of halogenating enzymes.

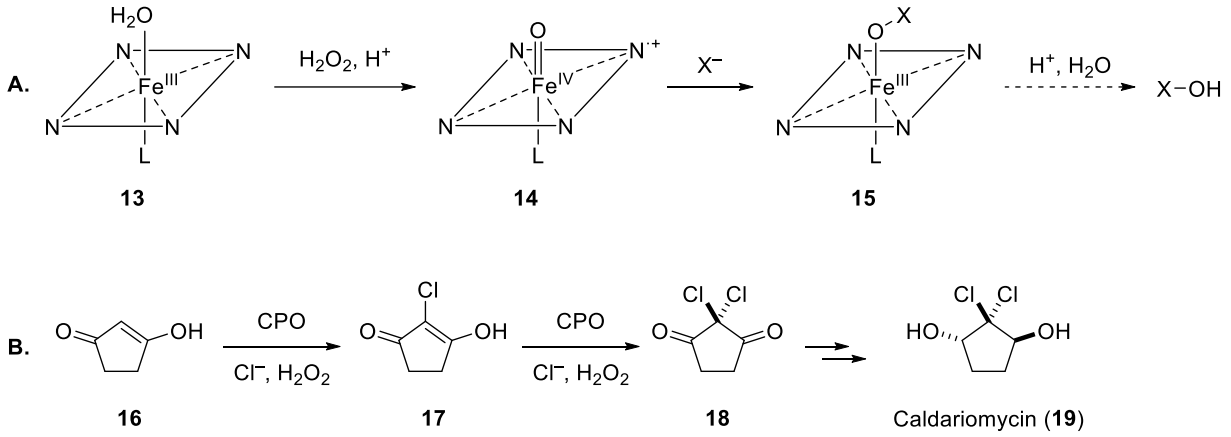
halogenating species	enzyme type	co-factor	co-substrates
X^+	haloperoxidases (HPO)	Heme–Iron *or* Vanadium	H_2O_2, X^-
X^+	O_2-dependent halogenases	$FADH_2$	O_2, X^-
$X^{\bullet}$	O_2-dependent halogenases	Non-heme Iron(II)	O_2, α-ketoglutarate, X^-
X^-	SAM-dependent halogenase	–	SAM, X^-

1.1.2.1 Halogenation *via* X^+

Haloperoxidases (HPOs) catalyze the oxidation of halide ions (Cl^-, Br^-, and I^-) to their corresponding hypohalite equivalents on the expense of hydrogen peroxide as the oxidant. The electrophilic source of halide can then be introduced into organic compounds *via* reaction with nucleophilic moieties, such as electron-rich aromatics and olefins. The haloperoxidases are named according to their oxidation potential. Hence, chloroperoxidases (CPOs) can oxidize chloride, bromide, and iodide whereas bromoperoxidases (BPOs) are only able to oxidize bromide and iodide, and iodoperoxidases (IPOs) will only oxidize iodide.

Within the haloperoxidase class of enzymes, two types of co-factors responsible for the oxidation are found. In 1966, Morris and Hager discovered the first chloroperoxidase, with a heme-dependent iron complex as the operating co-factor, from the fungus *Caldariomyces fumago*.[17] This enzyme showed to be involved in the biosynthesis of caldariomycin (Scheme 1, **19**) and isolation of this enzyme revealed that it is capable of halogenating a range of substrates, such as β-ketoacids and phenols, employing chloride, bromide, or iodide sources in the presence of hydrogen peroxide as an oxidant.[18] Already at this time, it was found that catalytic fluorination is not possible with this enzyme and addition of fluoride only led to inhibition of the enzymatic halogenation reaction.

[17] D. R. Morris, L. P. Hager, *J. Biol. Chem.* **1966**, *241*, 1763.
[18] L. P. Hager, D. R. Morris, F. S. Brown, H. Eberwein, *J. Biol. Chem.* **1966**, *241*, 1769.



Scheme 1 A. Intermediates involved in enzymatic halogenation with a heme–iron co-factor; **B.** Chlorination with a chloroperoxidase (CPO) in the biosynthesis of caldariomycin **20**. Adapted from ref. 16a.

Isolation of this enzyme provided some early insights into how halogenated compounds are biosynthesized and together with later mechanistic studies[19,20] and X-ray analysis of a chloroperoxidase,[21] a deeper understanding of the mechanism of halogenation with haloperoxidases employing a heme–iron co-factor has been formulated (Scheme 1A).

It is believed that the resting porphyrin–iron(III) complex **13** is oxidized to an oxoiron(IV) complex **14** with hydrogen peroxide. Hereafter, attack of a halide anion onto oxygen leads to a hypohalite bound to iron(III), **15**. This complex is then capable of donating an X^+ to an electron-rich acceptor. Given the general lack of substrate specificity for HPOs, it is widely believed that protonation may lead to free hypohalous acids which are then responsible for the halogenations. An example of a chloroperoxidase in action in biosynthesis of caldariomycin (**19**) is shown in Scheme 1B where 1,3-cyclopentadienone (**16**) is chlorinated twice to give **18**.

Further studies on halogenations in marine natural products led to the identification of another type of HPO that contains a vanadium co-factor. Structural studies of a vanadium-dependent CPO from the fungus *Curvularia inaequalis*[22] and of BPOs from the red algae *Coralina officinalis*[23] and the brown algae *Ascophyllum nodosum*[24] provide support to the proposed mechanism of which these HPOs are believed to operate (Scheme 2A).

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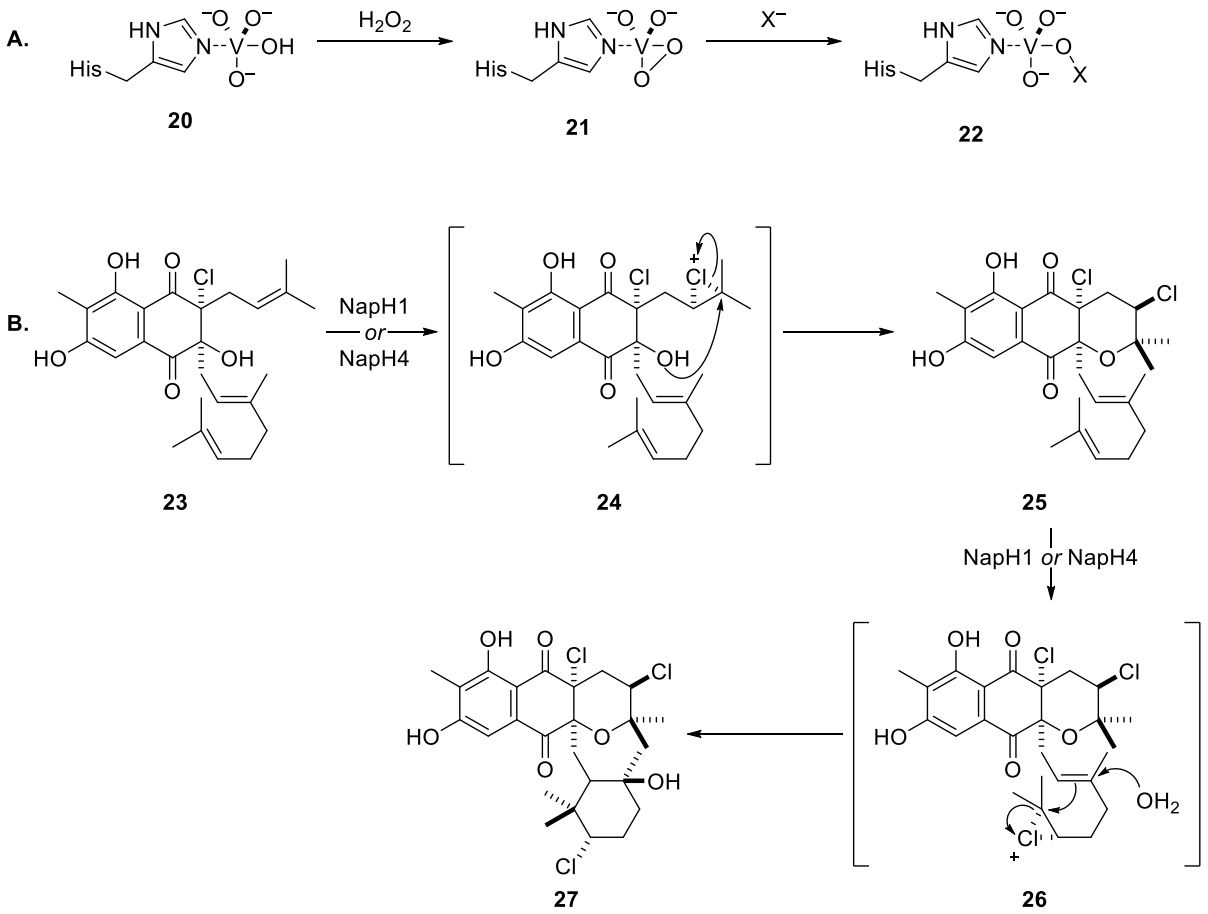
[19] H.-A. Waagenknecht, W. D. Woggon, *Chem. Biol.* **1997**, *4*, 367.
[20] K. L. Stone, R. K. Behan, M. T. Green, *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 16563.
[21] M. Sundaramoorthy, J. Terner, T. L. Poulos, *Structure* **1995**, *3*, 1367.
[22] A. Messerschmidt, R. Wever, *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 392.
[23] M. N. Isupov, A. R. Dalby, A. A. Brindley, Y. Izumi, T. Tanabe, G. N. Murshudov, J. A. Littlechild, *J. Mol. Biol.* **2000**, *299*, 1035.
[24] M. Weyand, H. J. Hecht, M. Kie, M. F. Liaud, H. Vilter, D. Schomburg, *J. Mol. Biol.* **1999**, *293*, 595.



Scheme 2 A. Proposed mechanism for production of hypohalite in a vanadium-dependent HPO; **B.** Biosynthesis of napyradiomycin analogs *via* chloronium-mediated cyclization events catalyzed by the vanadium-dependent CPOs NapH1 or NapH4.

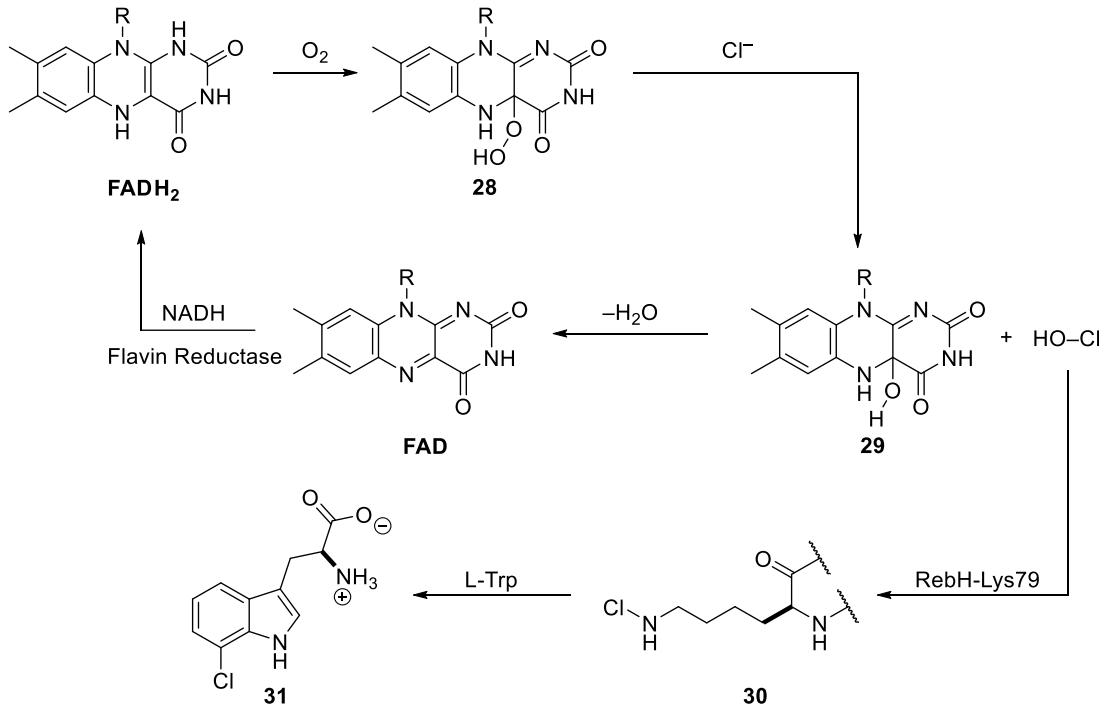
The vanadium co-factor is located in a wide substrate funnel and is bound to the protein *via* coordination to an imidazole nitrogen in a histidine unit. Much like electrophilic halogenation with a heme–iron co-factor, the vanadium is activated with hydrogen peroxide towards an intermediate which can then generate hypohalites from halide ions. Interestingly, in contrast to the heme–iron co-factor, vanadium does not appear to be redox active in this mechanism but does instead maintain oxidation state +V throughout the cycle. Hence, vanadium species **20** binds hydrogen peroxide to give η^2-peroxo-intermediate **21**. Attack of a halide then leads to vanadium-bound hypohalite **22**.

Two vanadium-dependent CPOs were discovered in the biosynthesis of napyradiomycin analogs when Moore and co-workers reported their findings on a study of the napyradiomycin biosynthetic gene cluster (*nap*) from *Streptomyces* sp. CNQ-525 and *Streptomyces aculeolatus* NRRL 18442.[25] It is proposed that two enzymes, NapH1 and NapH4, play key roles in the oxidative cyclizations of the two terpene-derived side chains of dihydroquinone **23** (Scheme 2A). The two vanadium-dependent

[25] J. M. Winther, M. C. Moffit, E. Zazopoulos, J. B. McAlpine, P. C. Dorrestein, B. S. Moore, *J. Biol. Chem.* **2007**, *282*, 16362.

CPOs hereby perform electrophilic chlorinations to give **25** and eventually **27** *via* chloronium-intermediates **24** and **26**, respectively.

The α-chlorine substituent present in dihydroquinone **23** is proposed to be introduced also by means of an electrophilic addition catalyzed by a halogenase. However, this chlorination is most likely catalyzed by a halogenase of another class, namely NapH2, which is an $FADH_2$-dependent halogenase. The first halogenase of this type was discovered in 2000 by van Pée and co-workers[26] and since their seminal work, various other enzymes of this type have been characterized. A series of reports, including the crystal structures of enzymes PrnA[27] and RebH,[28] have supported the proposal of a mechanism for these chlorinating entities, as shown in Scheme 3.



Scheme 3 Mechanism for generation of hypochlorite with $FADH_2$ as the redox co-factor.

It is believed that halogenation proceeds *via* flavin hydroperoxide intermediate **28** generated by oxidation of $FADH_2$ with molecular oxygen. In analogy to the haloperoxidases, hypochlorous acid can now be generated from attack of chloride onto the peroxide. Diffusion of HOCl can then lead to non-selective chlorinations. However, studies on the chlorination of free tryptophan with RebH together with the known reactivity of lysine sidechains with hypochlorous acid[29] suggested that the free hypochlorous acid is trapped by a strategically placed lysine within RebH (Lys79) to give

[26] S. Keller, T. Wage, K. Hohaus, M. Hölzer, E. Eichhorn, K.-H. van Pée, *Angew. Chem. Int. Ed.* **2000**, *39*, 2300.

[27] C. Dong, S. Flecks, S. Unversucht, C. Haupt, K.-H. van Pée, J. H. Naismith, *Science* **2005**, *309*, 2216.

[28] E. Yeh, L. J. Cole, E. W. Barr, J. M. Bollinger, D. P. Ballou, C. T. Walsh, *Biochemistry* **2006**, *45*, 7904.

[29] Z. D. Nightingale, A. H. Lancha Jr, S. K. Handelman, G. G. Dolnikowski, S. C. Busse, E. A. Dratz, J. B. Blumberg, G. J. Handelman, *Free Radical Biol. Med.* **2000**, *29*, 425.

chloramine **30**. This reactive intermediate is then capable of transferring a chloronium ion to tryptophan.

In addition to $FADH_2$, oxygen, and chloride as vital components for chlorinations catalyzed by these enzymes, the cycle is also dependent on an NADH-dependent flavin reductase. [30] Elimination of water from **29** affords FAD which is then turned over by reduction to give $FADH_2$.

1.1.2.2 Halogenation via $X^{\bullet}$

A second type of halogenase which is dependent on molecular oxygen as an oxidant contains a non-heme iron(II) co-factor. Whereas the previously discussed enzymes introduce halogens *via* the generation of hypohalous acids followed by electrophilic addition to nucleophilic sp^2-hybridized carbons, the non-heme iron(II) dependent halogenases are producing C–X bonds of non-activated aliphatic carbon atoms. Therfore, these enzymes are responsible for the biosynthesis of alkyl halides, such as hectochlorin (**32**),[31] barbamide (**33**),[32,33] and armentomycin (**34**)[34] (Chart 3)

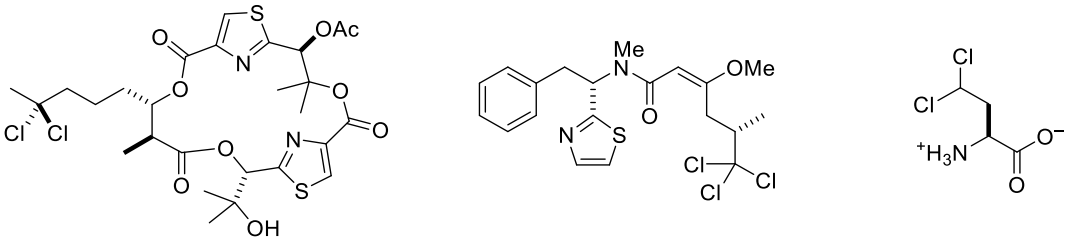


Chart 3 Examples of natural products produced *via* chlorination with a non-heme iron(II) dependent halogenase.

In contrast to other halogenating enzymes working under oxidative conditions, the non-heme iron(II) halogenases are proposed to perform halogenations *via* a radical mechanism (Scheme 4).[35] The histidine bound iron(II)-complex **36** is oxidized with molecular oxygen and after decarboxylation of α-ketoglutarate ligand, reactive iron(IV)-complex **38** is formed.

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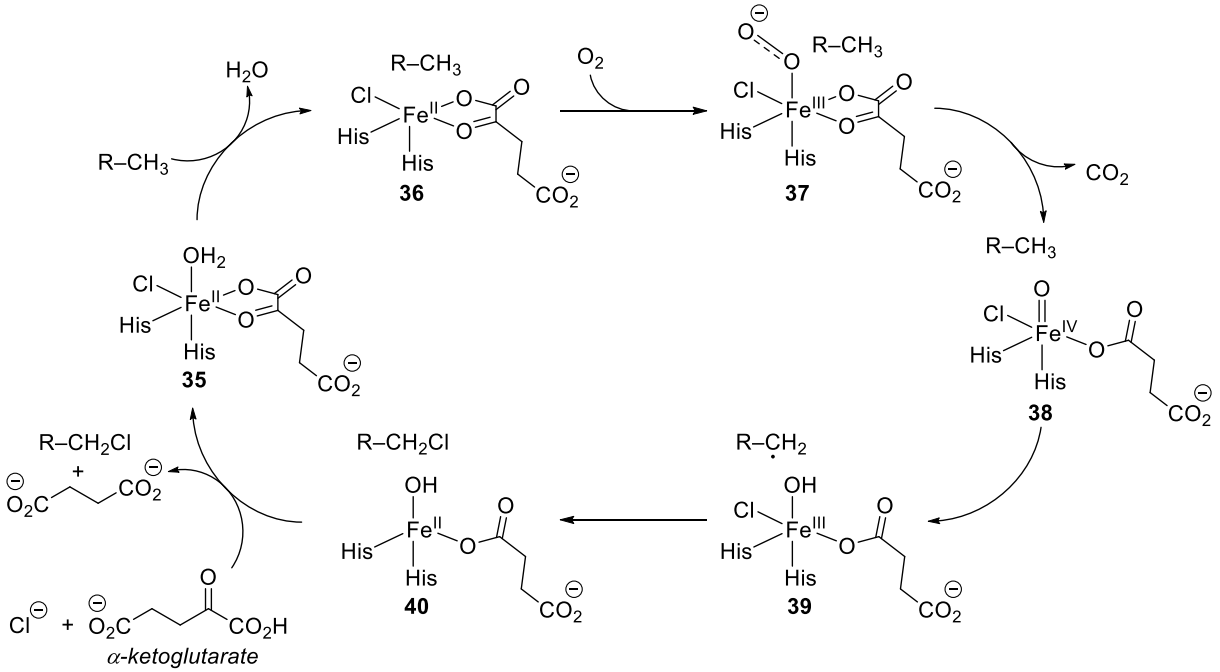
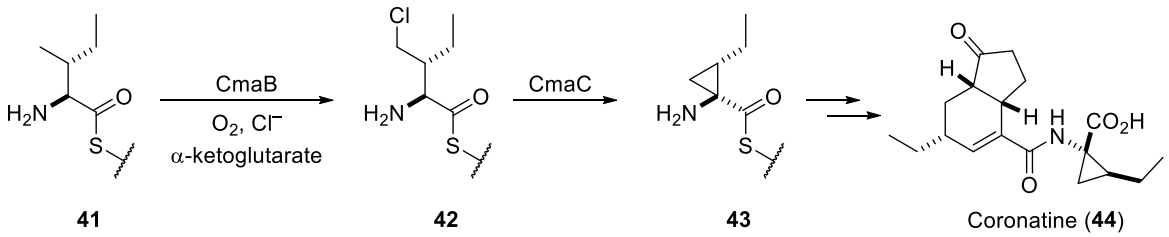
[30] E. Yeh, S. Garneau, C. T. Walsh, *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 3960.
[31] A. V. Ramaswamy, C. M. Sorrels, W. H. Gerwick, *J. Nat. Prod.* **2007**, *70*, 1977.
[32] P. M. Flatt, S. J. O'Connell, K. L. McPhail, G. Zeller, C. L. Willis, D. H. Sherman, W. H. Gerwick, *J. Nat. Prod.* **2006**, *69*, 938.
[33] Z. Chang, P. Flatt, W. H. Gerwick, V.-A. Nguyen, C. L. Willis, D. H. Sherman, *Gene* **2002**, *296*, 235.
[34] M. Ueki, D. P. Galonić, F. H. Vaillancourt, S. Garneau-Tsodikova, E. Yeh, D. A. Vosburg, F. C. Schroeder, H. Osada, C. T. Walsh, *Chem. Biol.* **2006**, *13*, 1183.
[35] M. L. Matthews, C. M. Krest, E. W. Barr, F. H. Vaillancourt, C. T. Walsh, M. T. Green, C. Krebs, J. M. Bollinger, *Biochemistry* **2009**, *48*, 4331.



Scheme 4 Proposed mechanism for radical chlorination with a non-heme iron(II) halogenase.

It is believed that this complex is capable of abstracting a hydrogen atom from an aliphatic substrate. Transfer of a chlorine atom from iron(III)-complex **39** ultimately leads to chlorination of the substrate.

These enzymes are also operating in other biosynthetic sequences of non-halogenated natural products, i.e. in a less obvious role as part of the synthesis of the cyclopropyl moiety of coronatine (**44**). [36] As shown in Scheme 5, enzymatic chlorination of a non-activated methyl-group of a cysteine-bound L-*allo*-Ile allows for nucleophilic displacement to construct the cyclopropyl moiety. Further steps attach this part to the bicyclic structure to give coronatine.



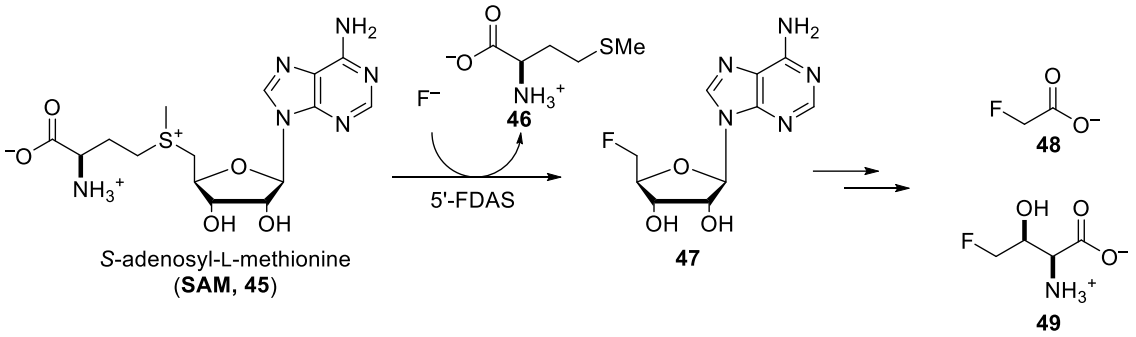
Scheme 5 Proposed biosynthesis of the cyclopropyl moiety of coronatine (**45**).

[36] F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. E. O'Connor, C. T. Walsh, *Nature* **2005**, *436*, 1191.

1.1.2.3 Halogenation via X^-

Up to this point, oxidative halogenation methods *via* hypohalite ions and halogen radicals have been introduced. A final class of enzymes incorporates halogens in natural products *via* their most abundant oxidation state, halide ions.

The first example of this enzyme type to be studied was isolated from *Streptomyces cattleya* in 2002 by O'Hagan and co-workers.[37] The isolated fluorinase was named 5'-fluoro-5'-deoxyadenosine synthase (5'-FDAS) and it was shown that these enzymes rely on *S*-adenosyl-L-methionine (SAM, **45**) as a co-substrate. As depicted in Scheme 6, SAM undergoes nucleophilic substitution on the activated 5'-carbon with, in this example, fluoride to give 5'-fluoro-5'-deoxyadenosine, (**47**). This key intermediate is then further metabolized into a diverse range of fluorinated natural products, such as fluoroacetate (**48**) and 4-fluoro-L-threonine (**49**).



Scheme 6 Biohalogenation with SAM-dependent enzymes, biosynthesis of fluorinated natural products.

Whereas chlorine, bromine, and iodine are most often introduced *via* oxidative methods in biosynthetic sequences, as showcased here, fluorine-containing natural products are produced *via* pathways involving nucleophilic fluorination *via* an S_N2 mechanism by SAM-dependent enzymes. Although S_N2 displacements are fundamental processes in organic chemistry, the fluorinating action of these enzymes is far from trivial. Due to the high degree of hydrogen bonding of fluoride in aqueous media, the nucleophilicity of F^- is dramatically reduced in water. Thus, through structural, thermodynamic, and kinetic studies of the enzyme, it is suggested that fluoride is placed in a hydrophobic pocket of the enzyme where desolvation is achieved by binding of the fluoride to a serine side-chain unit and an N−H of the backbone.[38] In addition, studies of the crystal structure of this enzyme showed that the ribose unit of SAM is bound in a high energy conformation which is believed to weaken the C−S bond and hereby favor substitution.[39]

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[37] D. O'Hagan, C. Schaffrath, S. L. Cobb, J. T. G. Hamilton, C. D. Murphy, *Nature* **2002**, *416*, 279.
[38] X. Zhu, D. A. Robinson, A. R. McEwan, D. O'Hagan, J. H. Naismith, *J. Am. Chem. Soc.* **2007**, *129*, 14597.
[39] C. Dong, F. Huang, H. Deng, C. Schaffrath, J. B. Spencer, D. O'Hagan, J. H. Naismith, *Nature* **2004**, *427*, 561.

1.1.3 Conclusions

In summary, halogenated natural products are produced in a diverse range of biological environments and display a variety of interesting properties. Nature has developed an extensive set of tools for incorporation of halogens into organic scaffolds, where oxidative methods are predominant for chlorine, bromine and iodine.

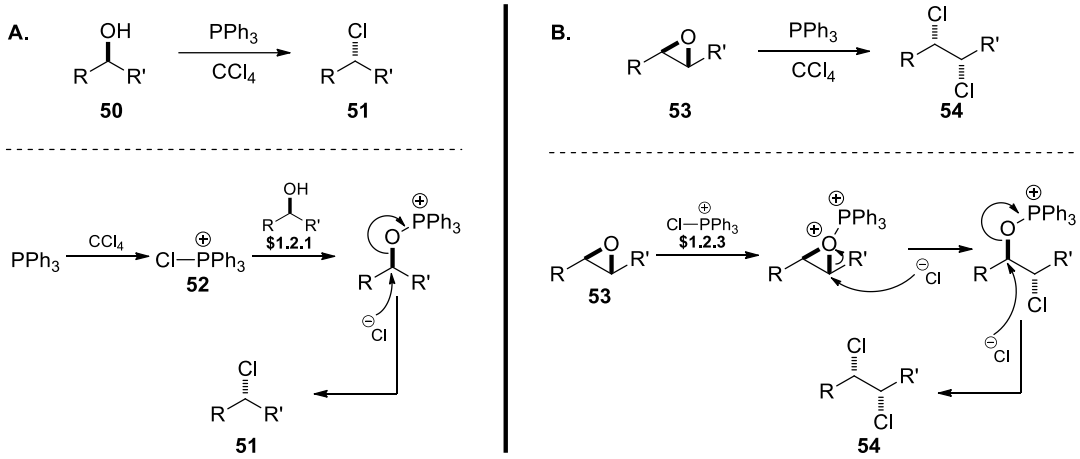
Also in medicinal chemistry, the interesting properties of halogens have been recognized and the use of these as substituents in pharmaceuticals can have beneficial effects towards e.g. higher potency or changes in the pharmacokinetic profile. Therefore, it is of continued interest to further develop methods for incorporation of halogens into organic molecules.

1.2 Chlorination Methods in Stereoselective Synthesis

Given the importance of incorporation of chlorine substituents into organic molecules, several methods have been developed over the years. Nowadays, the introduction of C−Cl bonds can be achieved stereoselectively from a wide range of functionalities, such as alcohols, epoxides, and olefins. In the following chapter, the most important methods will be reviewed.

1.2.1 Nucleophilic Substitutions

Unlike nature's most common approach of introducing chlorine *via* oxidative mechanisms,[16] the oldest synthetic approaches rely on the use of chloride ions as the nucleophilic halogen source. Conversion of alcohol **50** into alkyl chloride **51** in the presence of triphenylphosphine and carbon tetrachloride is known as Appel reaction (Scheme 7A).[40] Activation of the alcohol towards displacement with chloride is achieved by nucleophilic attack of the hydroxyl group onto electrophilic phosphonium intermediate **52**, which is generated from triphenylphosphine and carbon tetrachloride. The subsequent S_N2 substitution with then affords the alkyl chloride with inversion of the configuration and triphenylphosphine oxide as a stoichiometric by-product.



Scheme 7 General reaction scheme and the proposed mechanism for: **A.** Appel reaction, and **B.** conversion of epoxides to 1,2-dichlorides.

[40] For an early review, see: R. Appel, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801.

Over the years, several improvements and alternatives to Appel reaction have appeared in the literature, and the same overall transformation can be accomplished using a wide range of other reagents.[41,42]

The strategy of synthesizing stereochemically enriched alkyl chlorides by stereospecific substitution of optically active alcohols has proven to be a powerful approach, as the alcohol substrates are often easily obtained with high stereoselectivity *via* a variety of different methods, e.g. by asymmetric ketone reductions[43] or asymmetric nucleophilic additions to aldehydes.[44]

Related to the Appel reaction, conversion of epoxides with triphenylphosphine in refluxing carbon tetrachloride to give 1,2-dichlorides was reported around the same time (Scheme 7B).[45] This reaction also utilizes the electrophilic phosphonium intermediate **52** to activate epoxides towards nucleophilic opening with chloride ion. Hereafter, the second displacement takes place, analogous to the Appel reaction, to give 1,2-dichlorides, with inversion of configuration at both stereogenic centers.

Bearing in mind the well-established methods for obtaining enantioenriched epoxides (e.g. by Sharpless,[46] Jacobsen,[47] Shi,[48] and Yamamoto)[49], the stereoselective method of converting oxiranes

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[41] For selected examples on alternative reagents which facilitate this transformation, see: a) phosgene derivatives: C. E. Ayala, A. Villalpando, A. L. Nguyen, G. T. McCandless, R. Kartika, *Org. Lett.* **2012**, *14*, 3676; A. Villalpando, C. E. Ayala, C. B. Watson, R. Kartika, *J. Org. Chem.* **2013**, *78*, 3989; b) oxalyl chloride and catalytic triphenylphosphine oxide: R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis, A. M. Poulton, *J. Org. Chem.* **2011**, *76*, 6749; c) 2,4,6-trichloro[1,3,5]triazine and *N*,*N*-dimethylformamide: L. De Luca, G. Giacomelli, A. Porcheddu, *Org. Lett.* **2002**, *4*, 553; d) Vilsmeier-Haack reagent: M. Benazza, R. Uzan, D. Beaupère, G. Demailly, *Tetrahedron Lett.* **1992**, *33*, 4901; e) a review: R. C. Larock, *Comprehensive Organic Transformations*. 2nd ed.; John Wiley & Sons: 1999; p 689.

[42] Recently, Tristan Lambert reported an interesting variant of this reaction using a dichlorocyclopropene: B. D. Kelly, T. H. Lambert, *J. Am. Chem. Soc.* **2009**, *131*, 13930; C. M. Vanos, T. H. Lambert, *Angew. Chem. Int. Ed.* **2011**, *50*, 12222.

[43] For selected reviews on highly selective asymmetric reductions of ketones, see: a) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986 (oxazaborolidine catalysts); b) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, *92*, 1051 (asymmetric hydrogenation transfer reactions); c) R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed.* **2001**, *40*, 40; d) K. Nakamura, R. Yamanaka, T. Matsuda, T. Harada, *Tetrahedron: Asymmetry* **2003**, *14*, 2659 (biocatalysis).

[44] For selected reviews on asymmetric additions to aldehydes, see: a) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373 (alkyne additions); b) K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833 (organozinc additions); c) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757-824 (organozinc additions); d) J.-i. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109 (Mukiyama aldol reactions); e) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763 (allylation reactions).

[45] N. S. Isaacs, D. Kirkpatrick, *Tetrahedron Lett.* **1972**, *13*, 3869.

[46] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974; Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765.

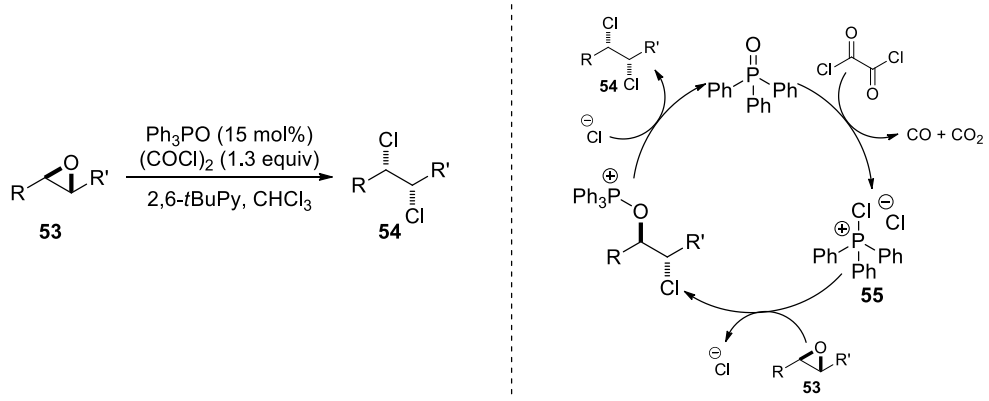
[47] a) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801; b) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.* **1991**, *113*, 7063.

[48] a) Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224; b) H. Tian, X. She, L. Shu, H. Yu, Y. Shi, *J. Am. Chem. Soc.* **2000**, *122*, 11551.

[49] a) W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286; b) C. Wang, H. Yamamoto, *J. Am. Chem. Soc.* **2014**, *136*, 1222 and references herein.

to dichlorides constitutes an intriguing method to the synthetic chemist when challenged with an optically active polychlorinated target.

Although Appel reaction and conversion of epoxides to dichlorides were reported in the literature around the same time, the latter reaction to afford 1,2-dichlorides received much less attention among synthetic chemists, presumably due to low yields. It was not until recent when Tanaka and Yoshimitsu reported a detailed study on this reaction, including improved procedures, that this method gained attention for synthesis of polychlorinated species.[50] It was found that substituting carbon tetrachloride with *N*-chlorosuccinimide (NCS) and triphenylphosphine with chlorodiphenylphosphine resulted in a much faster reaction, and therefore, the reaction proceeded smoothly at room temperature. In 2010, Denton and co-workers reported an interesting modification to facilitate the use of catalytic amounts of triphenylphosphine oxide to generate the electrophilic phosphorus component (Scheme 8). The proposed mechanism suggests that triphenylphosphine oxide is converted into phosphine dichloride **55** by oxalyl chloride, and this species is responsible for the dichlorination.



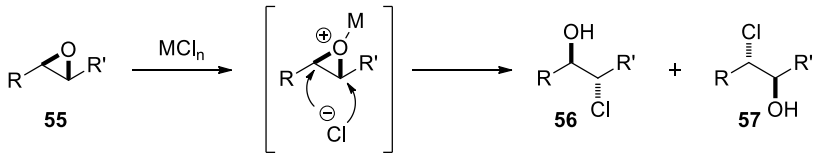
Scheme 8 Modified dichlorination of epoxides using catalytic triphenylphosphine oxide and oxalyl chloride.

Another important reaction class of epoxides in the context of stereoselective alkyl chloride synthesis is the nuecleophilic opening to give 1,2-chlorohydrin products **56** and **57** (Scheme 9). Numerous reactions have been reported over the last decades with a wide range of reagents and conditions to facilitate this transformation.[51] In general, these reactions employ a combination of Lewis acid activation of the epoxide and nucleophilic opening with chloride. To this end, a variety

[50] T. Yoshimitsu, N. Fukumoto, T. Tanaka, *J. Org. Chem.* **2009**, *74*, 696.

[51] For selected examples of epoxide openings with chloride sources, see a) D. Díaz, T. Martín, V. S. Martín, *J. Org. Chem.* **2001**, *66*, 7231 (Ph_3PCl_2); b) N. Daviu, A. Delgado, A. Llebaria, *Synlett* **1999**, *1999*, 1243 (TMSCl); c) G. C. Andrews, T. C. Crawford, L. G. Contillo Jr, *Tetrahedron Lett.* **1981**, *22*, 3803 (TMSCl/PPh_3); d) Y. E. Raifeld, A. A. Nikitenko, B. M. Arshava, *Tetrahedron: Asymmetry* **1991**, *2*, 1083 ($TiCl(OiPr)_3$); e) J. Kagan, B. E. Firth, N. Y. Shih, C. G. Boyajian, *J. Org. Chem.* **1977**, *42*, 343 ($FeCl_3$); f) Z.-X. Guo, A. H. Haines, R. J. K. Taylor, *Synlett* **1993**, *1993*, 607 (Li_2CuCl_4); g) F. Sarabia, A. Sánchez-Ruiz, *J. Org. Chem.* **2005**, *70*, 9514 (LiCl/AcOH); h) F. Sarabia, A. Sánchez-Ruiz, *Tetrahedron Lett.* **2005**, *46*, 1131 ($ZrCl_4$).

of metal chloride salts, such as $ZrCl_4$[51h] that offers both features, can be used, but also combinations of reagents, such as $BF_3{\cdot}OEt_2/Et_4NCl$,[90] successfully afford chlorohydrins. The opening most often takes place with inversion at the carbon undergoing the nucleophilic attack with high stereoselectivity which renders them powerful for the synthesis of enantio- and diastereomerically enriched chlorohydrins.

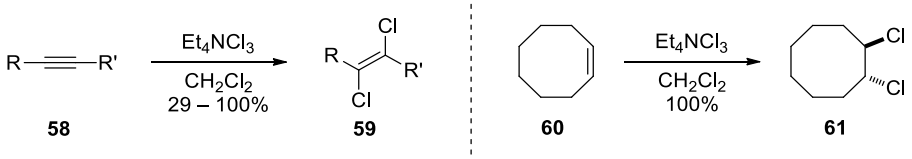


Scheme 9 Epoxide opening with a metal chloride to give 1,2-chlorohydrins.

1.2.2 Dichlorination of Olefins

Olefins can also be precursors for chlorinated entities, and the recognition of this motif as a synthon of alkyl chlorides has led to the development of several diastereo- and enantioselective methods in recent years.

In 1990, Kajigaeshi and co-workers reported the use of benzyltrimethylammonium tribromide ($BnMe_3NBr_3$) for electrophilic bromination of electron-rich aromatics, a reaction which has most commonly been carried out with elemental bromine.[52] Apparently, the reported salt served as a solid source of Br_2. Inspired by this work, Mioskowski and co-workers reported in 1997 the preparation and applications of tetraethylammonium trichloride (Et_4NCl_3) in chlorinations and oxidations of a wide range of molecules.[53] The examples most relevant to our discussion include dichlorination of alkynes **58** to *trans*-1,2-dichloroolefins **59** and cyclooctene (**60**) to *trans*-1,2-dichlorooctane (**61**) as the respective sole products in the presence of Et_4NCl_3 (Scheme 10).

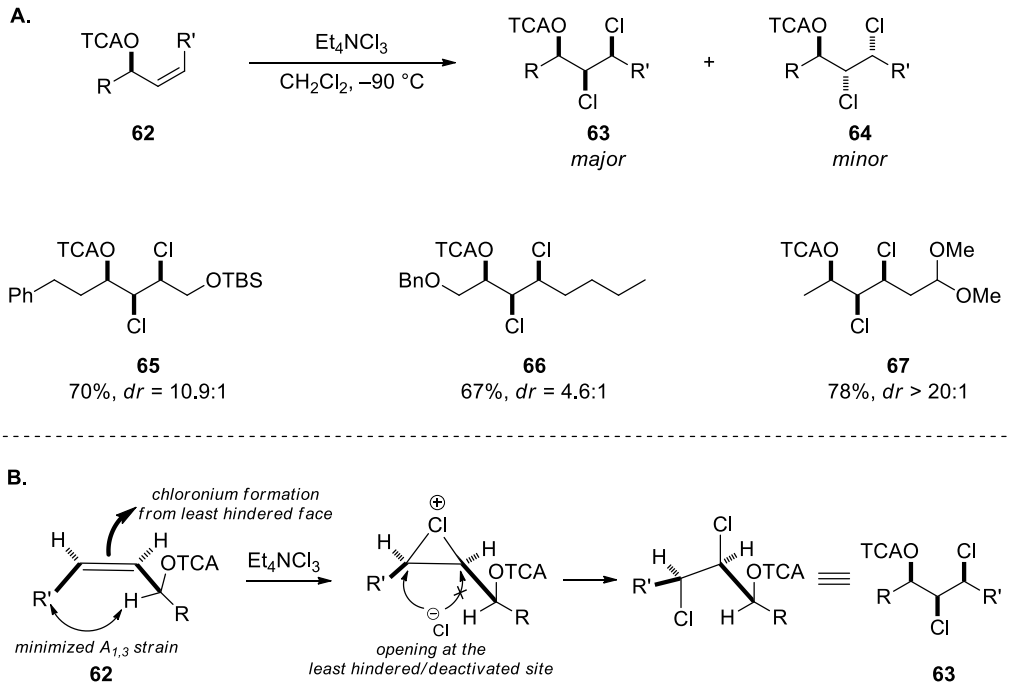


Scheme 10 Examples of dichlorinations with Et_4NCl_3.

[52] S. Kajigaeshi, M. Moriwaki, T. Tanaka, S. Fujisaki, T. Kakinami, T. Okamoto, *J. Chem. Soc., Perkin Trans. 1* **1990**, 897.
[53] T. Schlama, K. Gabriel, V. Gouverneur, C. Mioskowski, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2342.

In addition to the high selectivities and excellent yields, tetraethylammonium trichloride is easily prepared, handled, and stored as a crystalline solid. Consequently, this reagent has become an important addition to the arsenal for dichlorination.

An interesting extension of this work which led to a significant increase in the usage of Mioskowski's reagent in the context of stereoselective synthesis was reported by Vanderwal *et al.* in 2008.[54] Scheme 11 summarizes their detailed study on diastereoselective dichlorination of secondary allylic alcohol derivatives with high selectivity.



Scheme 11 A. Examples of diastereoselective dichlorinations of *cis*-allylic alcohols, and **B.** Rationale for the observed selectivity.

A thorough investigation of protecting groups and reaction conditions revealed that the dichlorination was achieved with the highest selectivity when performing the reaction at –90 °C with the allylic alcohol substrate protected as either the trifluoro- or trichloroacetate (TCA) ester **62**. With other protecting groups, lower selectivities were observed in comparison to the TCA esters. It is noteworthy that the unprotected allylic alcohol did not undergo the reaction with any significant diastereoselectivity, and interestingly, the nature of the substituents R and R` did not seem to have any major effect on the selectivity. In the same study, the authors also showed that using the Marko-

[54] G. M. Shibuya, J. S. Kanady, C. D. Vanderwal, *J. Am. Chem. Soc.* **2008**, *130*, 12514.

Maguire chlorinating conditions ($BnEt_3NCl$, KMnO4, TMSCl)[55] led to similar yields and selectivities.

The major product was determined to be the all-*syn* diastereomer **63**. This outcome can be rationalized by minimization of allylic 1,3-interactions ($A_{1,3}$) which is frequently exploited in diastereoselective reactions of unsaturated acyclic systems.[56] The allylic trichloroacetate **62** is likely to adopt the conformation shown in Scheme 11B in which the $A_{1,3}$-interaction is minimized. The chloronium ion intermediate is thought to be formed from the less hindered face of the olefin and the subsequent opening with chloride at the remote carbon due to steric bulk and deactivation through inductive effect of the trichloroacetate towards substitution leads to the all-*syn* stereotriad **63**.

Synthetic studies towards polychlorinated compounds from both Vanderwal's[57] and Carreira's[58] research groups have provided evidence that the dichlorination of a secondary *cis*-allyl chloride with Mioskowski's reagent indeed results in the corresponding stereochemical outcome, that is the all-*syn* 1,2,3-trichloride as the major product (see section 1.3.4.1 on the total synthesis of mytilipin A).

A few examples of dichlorination of *trans*-1,2-disubstituted olefin have appeared, however, the selectivity dramatically decreases as there is no significant allylic interaction to prefer a specific conformation.[59]

Until recently, most of the reported dichlorination methods gave *trans*-addition dichloride products. The *syn*-dichlorination of olefins constitutes another potentially useful and conceptually distinct approach to access other dichloride diastereomers. A number of seminal publications deemed this transformation feasible, despite the reported low yields and narrow substrate scopes.[60] A breakthrough in this area was achieved in early 2015 by Denmark and co-workers who reported *syn*-dichlorination of alkenes, catalyzed by diphenyl diselenide (Scheme 12).[61]

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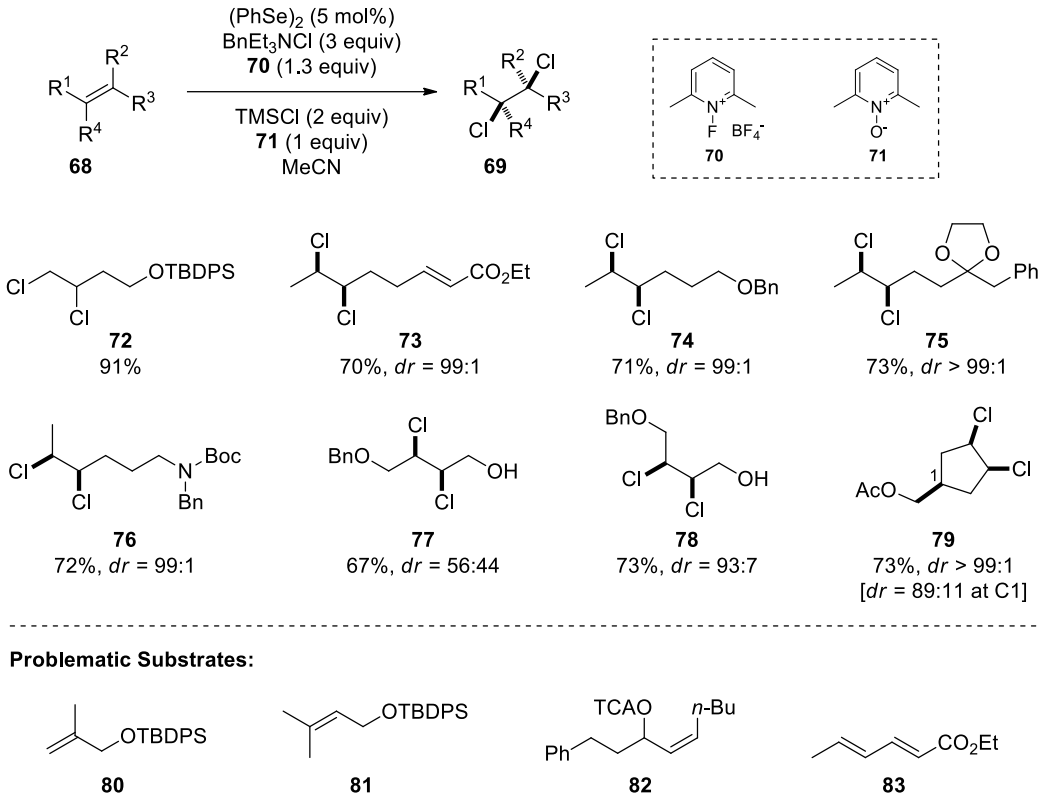
[55] I. E. Markó,P. R. Richardson,M. Bailey,A. R. Maguire,N. Coughlan, *Tetrahedron Lett.* **1997**, *38*, 2339.
[56] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841.
[57] D. K. Bedke, G. M. Shibuya, A. R. Pereira, W. H. Gerwick, C. D. Vanderwal, *J. Am. Chem. Soc.* **2010**, *132*, 2542.
[58] C. Nilewski, R. W. Geisser, E. M. Carreira, *Nature* **2009**, *457*, 573.
[59] J. S. Kanady, J. D. Nguyen, J. W. Ziller, C. D. Vanderwal, *J. Org. Chem.* **2009**, *74*, 2175.
[60] a) S. Uemura, A. Onoe, M. Okano, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 692; b) S. Uemura, A. Onoe, M. Okano, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3121-3124; c) J. San Filippo, A. F. Sowinski, L. J. Romano, *J. Am. Chem. Soc.* **1975**, *97*, 1599; d) W. A. Nugent, *Tetrahedron Lett.* **1978**, *19*, 3427.
[61] A. J. Cresswell, T. C. EeyStanley, S. E. Denmark, *Nature Chem.* **2015**, *7*, 146.



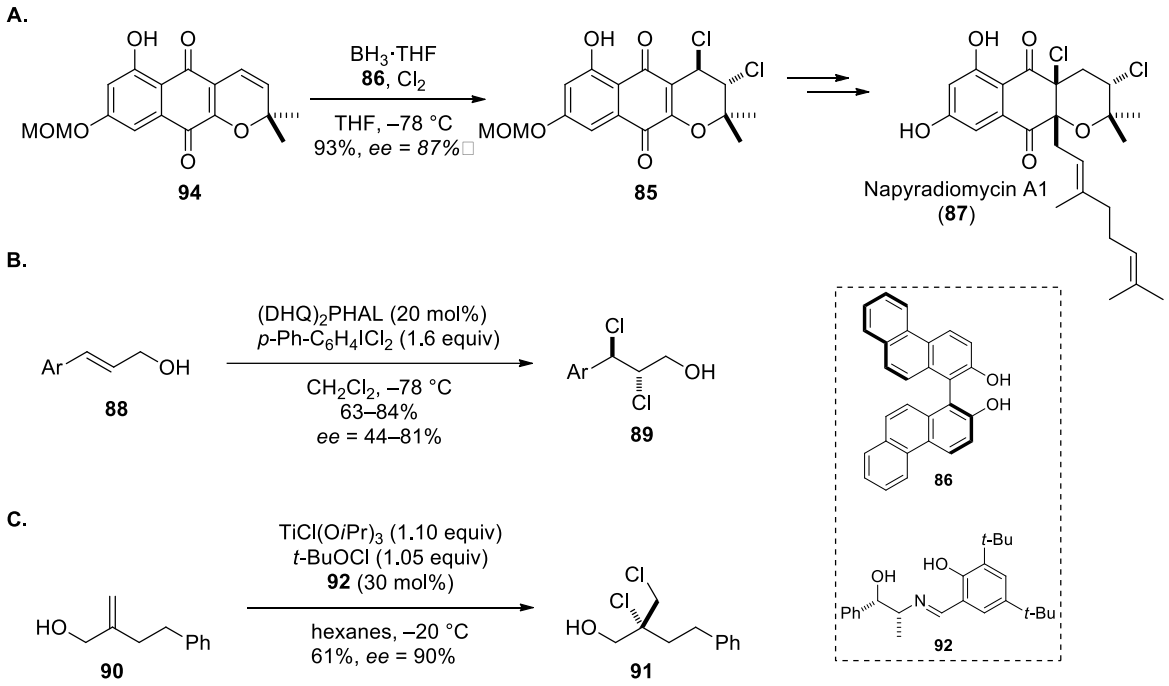
Scheme 12 Diphenyl diselenide-catalyzed *syn*-dichlorination of olefins.

The authors found that their method successfully produced 1,2-dichlorides from a range of terminal and 1,2-disubstituted olefins. A variety of functionalities are tolerated such as silyl- (**72**) and benzylethers (**74**, **77**, and **78**), esters (**73**), acetals (**75**), protected amines (**76**), and unprotected alcohols (**77** and **78**). In general, good yields and high *syn*-selectivities were obtained, however, the described method was unsuccessful in converting 1,1-disubstituted (**80**) and trisubstituted (**81**) olefins into the corresponding dichlorides. Although chlorination to give **79**, from the corresponding cyclopentene, resulted in good diastereoselectivity with respect to C_1, dichlorination of allylic trichloroacetate ester **82** and other branched allylic substrates only led to unsatisfactory product distributions.

Although the aforementioned shortcomings in terms of substrate scope may limit its utility in stereoselctive synthesis of polychlorinated compounds, this precedence of a successful dichlorination with the given reagents provides a platform that can lead to diastereo- and, ultimately, enantioselective extensions of this work.

Only limited developments of enantioselective dichlorinations had been described up until 2009 when Snyder and co-workers reported an asymmetric dichlorination en route to napyradiomycin A1

(Scheme 13A).[62] Utilizing a chiral boron reagent to block one face of olefin **84**, the authors were able to obtain 87% *ee* on this specific transformation, which represented a significant advancement in contrast to earlier reports on enantioselective dichlorinations.[63]



Scheme 13 Examples of enantioselective dichlorinations reported by **A.** Snyder, **B.** Nicolaou, and **C.** Burns.

Following this work, Nicolaou and co-workers reported in 2011 enantioselective dichlorination of allylic alcohols **88** with aryl iododichlorides catalyzed by dimeric cinchona alkaloid derivatives (Scheme 13B).[64] In addition, as a part of the research program directed towards dihalogenation of olefins, Burns *et al.* have reported dichlorination of 1,1-disubstituted allylic alcohol **90** with high enantioselectivity (Scheme 13C).[65] These efforts indicate that enantioselective dichlorination may become an important tool for stereoselective synthesis of more complex halogenated natural products.

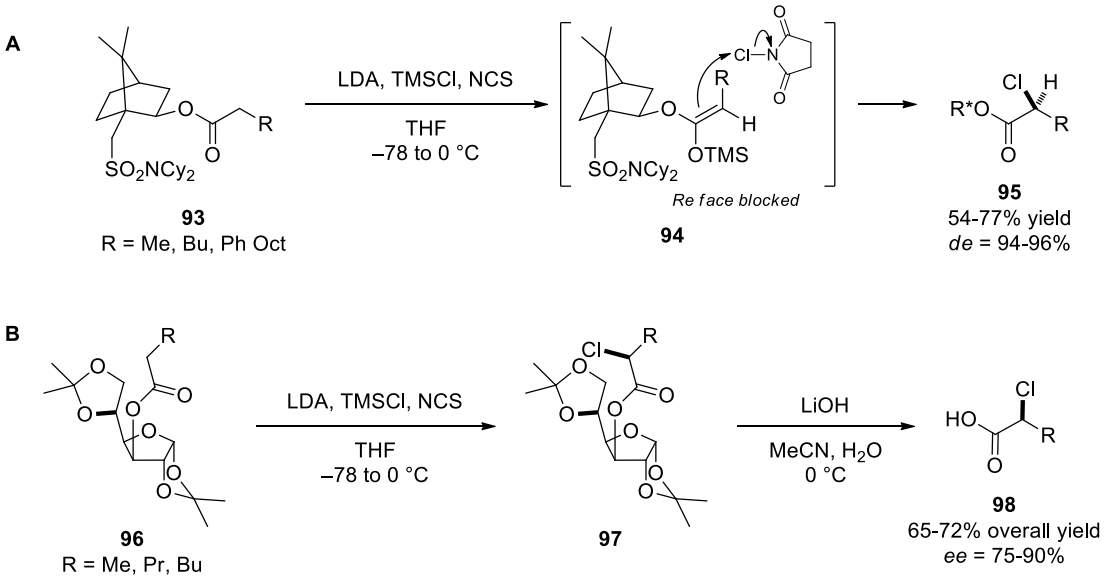
[62] S. A. Snyder, Z.-Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744.
[63] a) S. Juliá, A. Ginebreda, *Tetrahedron Lett.* **1979**, *20*, 2171; b) W. Adam, C. Mock-Knoblauch, C. R. Saha-Möller, M. Herderich, *J. Am. Chem. Soc.* **2000**, *122*, 9685.
[64] K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch, J. S. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 8134.
[65] D. X. Hu, F. J. Seidl, C. Bucher, N. Z. Burns, *J. Am. Chem. Soc.* **2015**, *137*, 3795.

1.2.3 α-Chlorination of Carbonyl Compounds

A vast amount of research has gone into the area of stereoselective α-functionalization of carbonyl compounds, and a countless number of methods and strategies with different merits and limits have been presented in the literature.[66]

Ever since the introduction of chiral auxiliaries, these covalently bound steering wheels have had an enormous impact on stereoselective synthesis by providing substrate-directed *diastereoselectivity*, which after cleavage of the auxiliary, effectively translates into *enantioselectivity*. Conceptually, α-chlorination of chiral auxiliary-based substrates is related to the much more well-documented alkylations and aldol reactions. Hence, similar auxiliaries can be used to impart stereoselectivity. One of the earliest examples was reported by Oppolzer in 1985, using camphor sulfonamide-derived esters **93** (Scheme 14A).[67] Treatment of the ester with LDA and TMSCl resulted in the *trans*-silyl enol ether **94**, which then reacted with NCS from the less congested *Si* face to afford α-chloroesters **95** in good yield and with excellent stereocontrol.

Following a similar strategy, Duhamel and co-workers reported the synthesis of α-chlorocarboxylic acids **98** from protected α-D-glucofuranose derived esters **96** (Scheme 14B).[68]

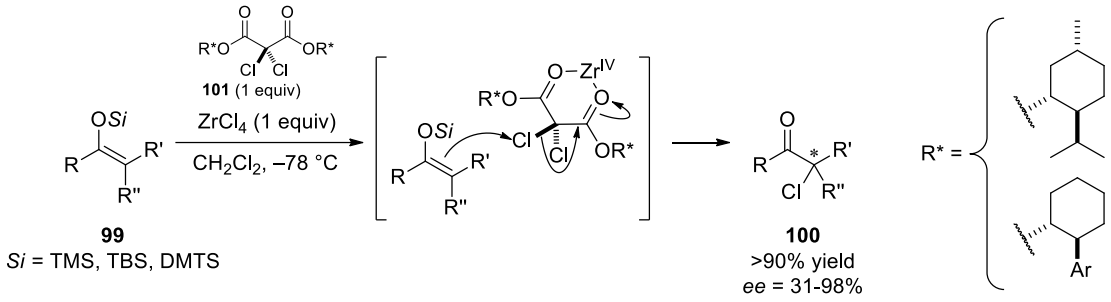


Scheme 14 Examples of diastereoselective α-chlorinations of carbonyl compounds containing a chiral auxiliary.

More recently, enantioselective α-chlorinations have gained substantial attention. In an example of reagent-controlled stereoselectivity from 2004, Yamamoto and co-workers showed that silyl enol

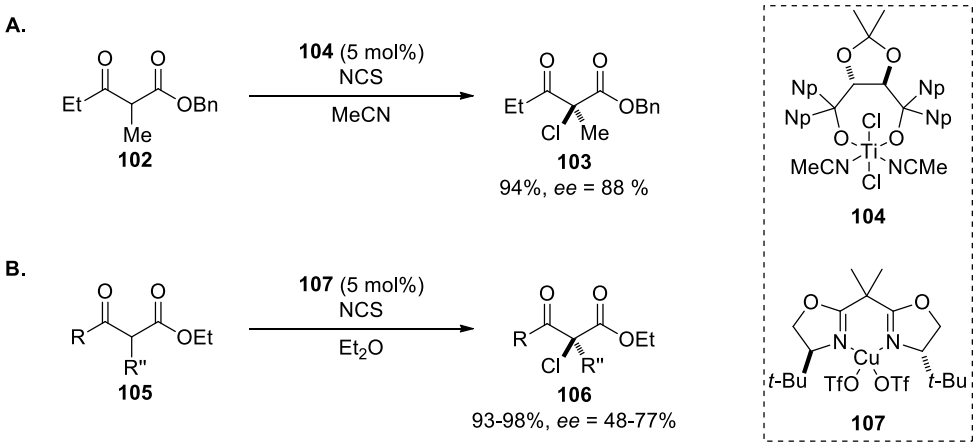
[66] E. M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*. Wiley-VCH: Weinheim, 2009; p 69.
[67] W. Oppolzer, P. Dudfield, *Tetrahedron Lett.* **1985**, *26*, 5036.
[68] L. Duhamel, P. Angibaud, J. R. Desmurs, J. Y. Valnot, *Synlett* **1991**, *1991*, 807.

ethers **99** can be chlorinated in high yields and with excellent enantioselectivities using a combination of Lewis acidic zirconium tetrachloride and chiral α,α-dichloromalonate esters **101** as a chloronium source (Scheme 15).[69] Zirconium(IV) is believed to activate the 1,3-dicarbonyl reagent and, hereby, enhance the electrophilicity of the α chlorine substitutents towards nucleophilic attack from the enol ethers.



Scheme 15 Yamamoto's reagent-controlled enantioselective α-chlorination.

Considerably more interest has recently been placed in catalytic asymmetric chlorination strategies. These methods can roughly be divided into two subcategories: Lewis acid-catalyzed chlorination of 1,3-dicarbonyls and organocatalyzed chlorination to give α-chloro-aldehydes, -ketones, -esters, and -carboxylic acids.



Scheme 16 Asymmetric α-chlorinations enabled by Lewis acid-catalysis.

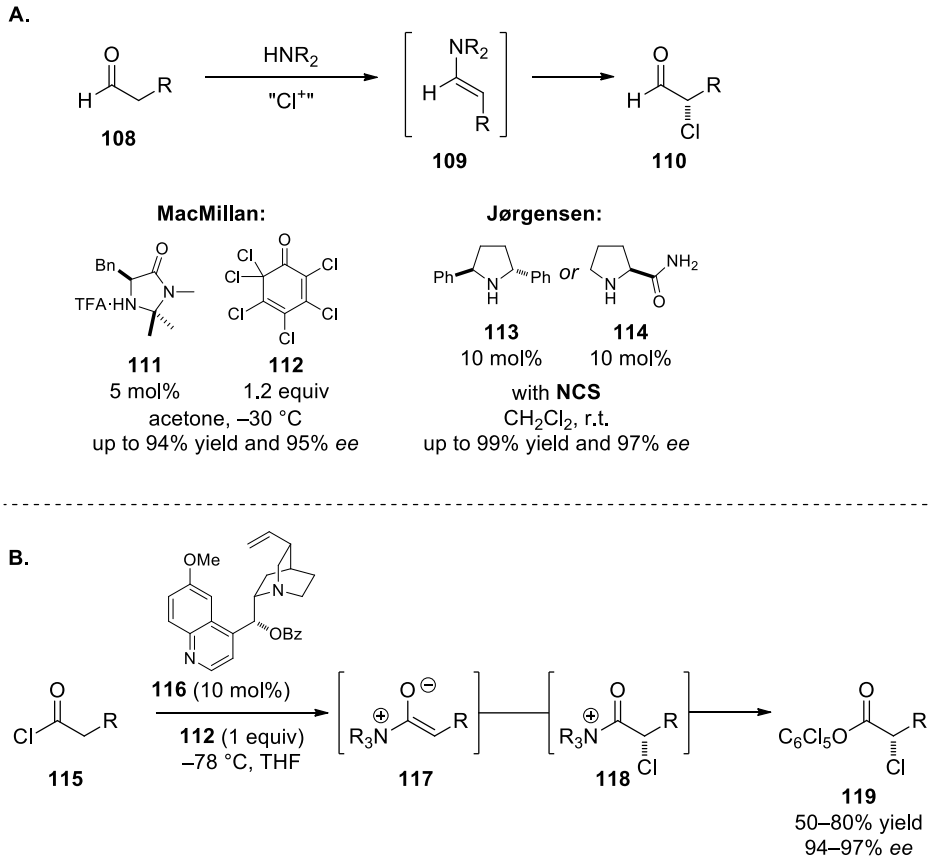
A pioneering work by Togni showed that β-ketoesters, such as **102**, underwent Lewis acid-catalyzed α-chlorination with high yields and good enantioselectivity when employing Ti^{IV}(TADDOL)ato-catalyst **104** (Scheme 16A).[70] Analogously, Jørgensen has later reported the same transformation with Cu^{II}(bisoxozaline)-complexes, such as **107**, with excellent yields and promising

[69] Y. Zhang, K. Shibatomi, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 15038.
[70] L. Hintermann, A. Togni, *Helv. Chim. Acta* **2000**, *83*, 2425.

enantiomeric excesses (Scheme 16B).[71] Following these seminal studies, Jørgensen and co-workers have further reported α-chlorination of β-ketophosphonates using a chiral Zn(II)-catalyst,[72] and Shibata has expanded the scope of 1,3-dicarbonyl compounds to include 3-substituted *N*-Boc-protected oxindoles using a chiral Ni(II)-bisoxazoline catalyst.[73]

Organocatalytic transformations to generate enantioenriched α-chlorocarbonyl compounds can be further divided into three categories, namely reactions catalyzed by secondary amines, tertiary amines, and *N*-heterocyclic carbene (NHC) catalysts (described in the next section).

In 2004, MacMillan[74] and Jørgensen[75] independently reported α-chlorinations of linear aldehydes **108** using secondary amines as catalysts (Scheme 17A).



Scheme 17 Organocatalytic α-chlorinations catalyzed by **A.** secondary amines and **B.** tertiary amines.

The reaction is proposed to proceed *via* condensation of the aldehyde to enamine **109**, which further raises the HOMO and thereby the nucleophilicity at the α-position. Upon treatment with an

[71] M. Marigo, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Eur. J.* **2004**, *10*, 2133.
[72] L. Bernardi, K. A. Jorgensen, *Chem. Commun.* **2005**, 1324.
[73] N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4204.
[74] M. P. Brochu, S. P. Brown, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2004**, *126*, 4108.
[75] N. Halland, A. Braunton, S. Bachmann, M. Marigo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 4790.

electrophilic chlorine source followed by hydrolysis, α-chloroaldehydes **110** are obtained. Employing phenylalanine-derived imidazolidinone organocatalyst **111** in conjunction with hexachloroquinone (**112**) as a chlorinating agent at –30 °C, MacMillan and co-workers were able to achieve good yields and high enantiomeric excesses. Analagously, Jørgensen found that pyrrolidine catalyst **112** or **113** and NCS at room temperature successfully facilitated the title reaction in marginally higher yields and *ee*'s.

An enantioselective approach to α-chloroesters from acyl chlorides catalyzed by tertiary amines was reported in 2001 by Letcka (Scheme 17B).[76] The initially formed ketenes from acyl chlorides **115** are trapped by cinchona alkaloid-derived amine catalyst **116** to give zwitterionic enolates **116** which upon chlorination with hexachloroquinone (**112**) and subsequent acyl transfer of ammonium **118** resulted in α-chloroesters in good yields and excellent *ee*'s.

1.2.4 Indirect Stereoselective Chlorination Methods

A number of strategies to obtain stereoenriched organochlorines without stereoselective formation of C–Cl bonds are present in the literature. These include the stereoselective construction of C–C bonds to carbons bearing a chlorine substituent, stereoselective hydrogenations of alkenyl chlorides, and enantioselective protonation of α-chloroenolates.

In 1984, Lantos, Pridgen, and co-workers published highly diastereoselective aldol reactions of Evans oxazolidinone-derived chloroacetates **120** (Scheme 18A).[77] Similarly, other auxiliaries have been used to facilitate analogous reactions.[78] Additionally, catalytic asymmetric Mukaiyama aldol reactions of chloroenol ethers have proven successful to obtain α-chloro-β-hydroxycarbonyl compounds with high stereoselectivity.[79]

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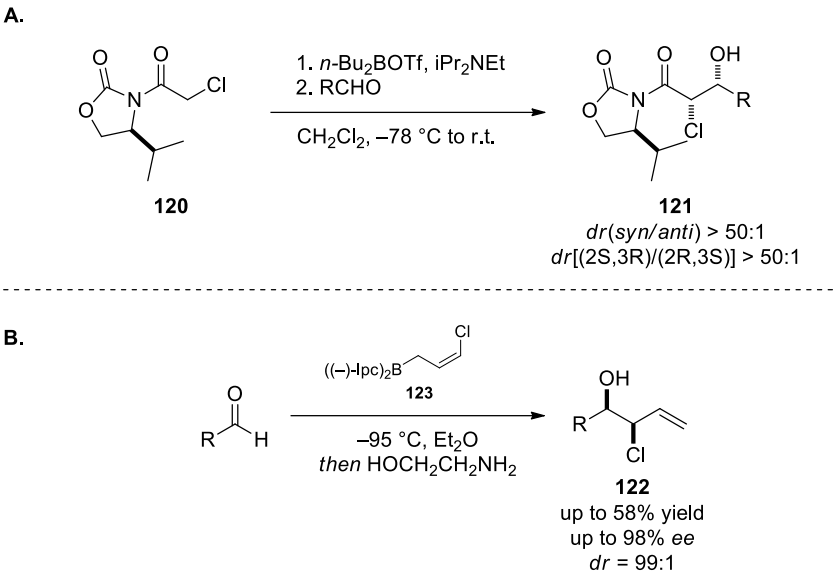
[76] a) H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 1531; b) S. France, H. Wack, A. E. Taggi, A. M. Hafez, T. R. Wagerle, M. H. Shah, C. L. Dusich, T. Lectka, *J. Am. Chem. Soc.* **2004**, *126*, 4245.
[77] a) A. Abdel-Magid, I. Lantos, L. N. Pridgen, *Tetrahedron Lett.* **1984**, *25*, 3273; b) A. Abdel-Magid, L. N. Pridgen, D. S. Eggleston, I. Lantos, *J. Am. Chem. Soc.* **1986**, *108*, 4595.
[78] For an example, see: A. K. Ghosh, J.-H. Kim, *Org. Lett.* **2004**, *6*, 2725.
[79] For an example, see: X.-Y. Xu, Y.-Z. Wang, L.-Z. Gong, *Org. Lett.* **2007**, *9*, 4247.

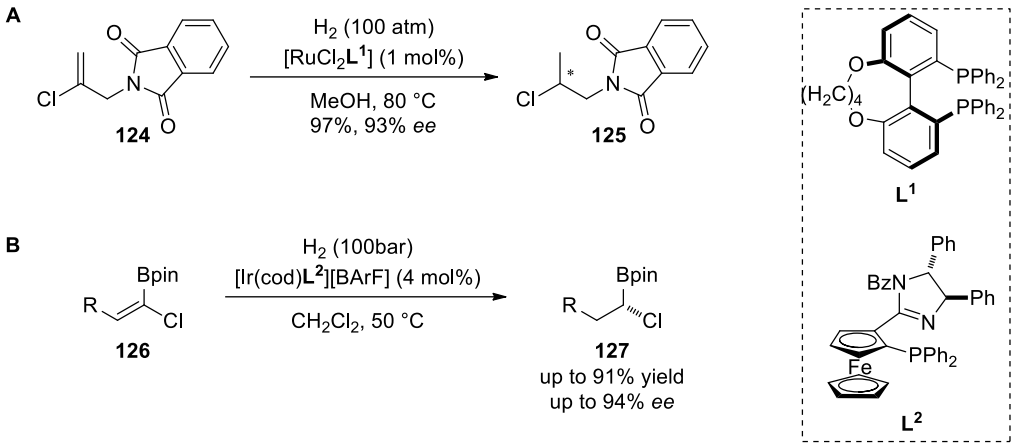


Scheme 18 A. Chloroacetate aldol reaction and **B.** Chloroallylation reaction.

Related to the aldol reactions, Oehlschlager and co-workers have shown that allylation reactions with chiral vinylchloride **123** give 1,2-chlorohydrins with high enantio- and diastereoselectivity (Scheme 18B).[80] Another enantioselective chloroallylation was also reported by Cozzi to give *syn*-chlorohydrins.[81]

Although asymmetric hydrogenation of alkenyl chlorides to construct optically active alkylchlorides is a conceptually simple and appealing transformation, it is far from trivial due to the instability of $C(sp^2)$–Cl bonds under standard hydrogenation conditions, effectively leading to hydrodehalogenation as a significant undesired reaction pathway. Despite these challenges, a few examples have been reported. In 2005, Zhang reported hydrogenation of allyl phthalimide **124** in excellent yield and enantioselectivity, employing a ruthenium catalyst with chiral bisphosphine $\mathbf{L^1}$ (Scheme 19A).[82]

[80] S. Hu, S. Jayaraman, A. C. Oehlschlager, *J. Org. Chem.* **1996**, *61*, 7513.
[81] M. Bandini, P. G. Cozzi, P. Melchiorre, S. Morganti, A. Umani-Ronchi, *Org. Lett.* **2001**, *3*, 1153.
[82] C.-J. Wang, X. Sun, X. Zhang, *Angew. Chem. Int. Ed.* **2005**, *44*, 4933.



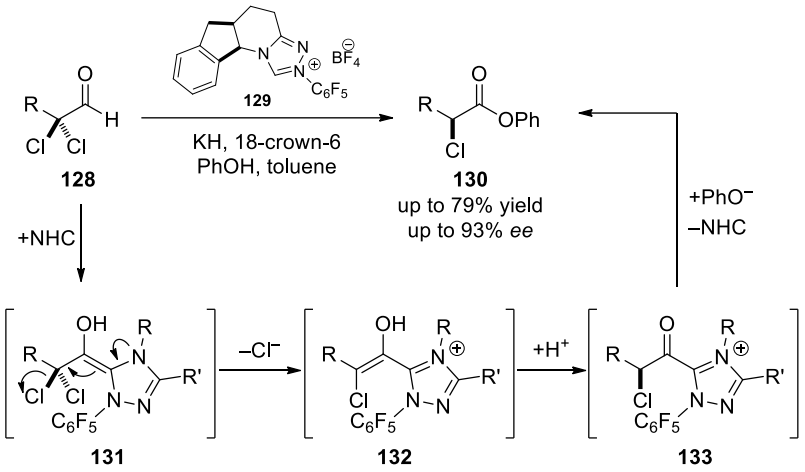
Scheme 19 Asymmetric hydrogenation of alkenyl chlorides.

Furthermore, it has been shown by Časar and co-workers that chiral iridium catalysts perform well in the hydrogenation of chloroalkenyl boronic esters **126** (Scheme 19B).[83] However, high pressure of hydrogen and elevated temperatures are needed in both cases.

Recently, Herzon and co-workers published a non-asymmetric method for selective hydrogenation of a broad range of alkenyl halides relying on a hydrogen atom transfer mechanism.[84] As discussed above, stereoselective hydrogenation of alkenyl chlorides with broad substrate scope remains a challenge to synthetic chemists, even though the presented methods illustrate a moderate progress in the desired direction.

Finally, yet another approach to enantioenriched α-chlorocarbonyls, namely *mono*-chloroesters was reported by Rovis, involving de-chlorination/enantioselective protonation of *di*-chloroaldehydes employing NHC-catalysis (Scheme 20).[85]

[83] a) I. Gazić Smilović, E. Casas-Arcé, S. J. Roseblade, U. Nettekoven, A. Zanotti-Gerosa, M. Kovačevič, Z. Časar, *Angew. Chem. Int. Ed.* **2012**, *51*, 1014; b) S. J. Roseblade, E. Casas-Arcé, U. Nettekoven, I. Gazić Smilović, A. Zanotti-Gerosa, Z. Časar, *Synthesis* **2013**, *45*, 2824.
[84] a) S. M. King, X. Ma, S. B. Herzon, *J. Am. Chem. Soc.* **2014**, *136*, 6884; b) X. Ma, S. B. Herzon, *Chem. Sci.* **2015**, *6*, 6250.
[85] N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406.



Scheme 20 Rovis' NHC-catalyzed enantioselective synthesis of α-chloroester by isomerization of dichloroaldehydes.

In the proposed mechanism of this transformation, elimination of the *gem*-dichloride **131** to give chloroenol **132** sets the stage for a face-selective protonation to give **129**, and the NHC catalyst is released *via* acyl transfer. Later, Rovis has further shown that this reaction can be carried out in a biphasic aqueous media to obtain α-chlorocarboxylic acids also with good yields and high enantioselectivities.[86]

1.2.5 Conclusions

In summary, a wide range of methods to construct chlorinated entities stereoselectively have been developed. A variety of functional groups serve as precursors, such as alcohols, epoxides, olefins, and enolate equivalents. Despite the countless efforts, however, there are still limitations to their applications in stereoselective synthesis and thus, the challenge to stereoselectively construct C−Cl bonds remain a field of research with plenty of room for experimentation.

[86] H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 2860.

1.3 Chlorosulfolipids

The chlorosulfolipids constitute an unusual subclass of halogenated natural products and as many other naturally occurring organochlorines, they display interesting biological activities. Additionally, intriguing biological questions with respect to the role of these compounds in the terrestrial environment emerge. In this chapter, an overview of phytochemical, biological and synthetic research on chlorosulfolipids will be provided.

1.3.1 Discovery, Isolation, and Structural Elucidations

The first chlorosulfolipids were discovered in the late 1960's, when Elovson and Vagelos investigated the fatty acid contents in extracts from *Ochromonas danica*.[87] Following acidic hydrolysis of ether-extractable sulfolipids, the authors found several docosane-diols (C_{22}) with up to six chlorine atoms by GLC-MS analysis of TMS derivatives. Interestingly, a minor fraction of chlorosulfolipids, typically between 10–15% relative abundance, had a tetracosane (C_{24}) core.

Shortly after Elovson and Vagelos' seminal publication on detection of these natural products, Haines and co-workers reported the first structural characterization, including relative and absolute configuration, of one of the less complex chlorosulfolipids from *O. danica* extracts, (*R*13)-chloro-(1,14*R*)-docosanediol disulfate **134** (Chart 4).[88] The relative configuration was established by alkaline treatment of the lipid to give a *cis*-epoxide thus signifying the presence of a 1,2-*syn*-chlorohydrin. The absolute configuration was established by comparison of the optical rotation to known standards.

[87] J. Elovson, P. R. Vagelos, *Proc. Natl. Acad. Sci. USA* **1969**, *62*, 957.
[88] T. H. Haines, M. Pousada, B. Stern, G. L. Mayers, *Biochem. J.* **1969**, *113*, 565.

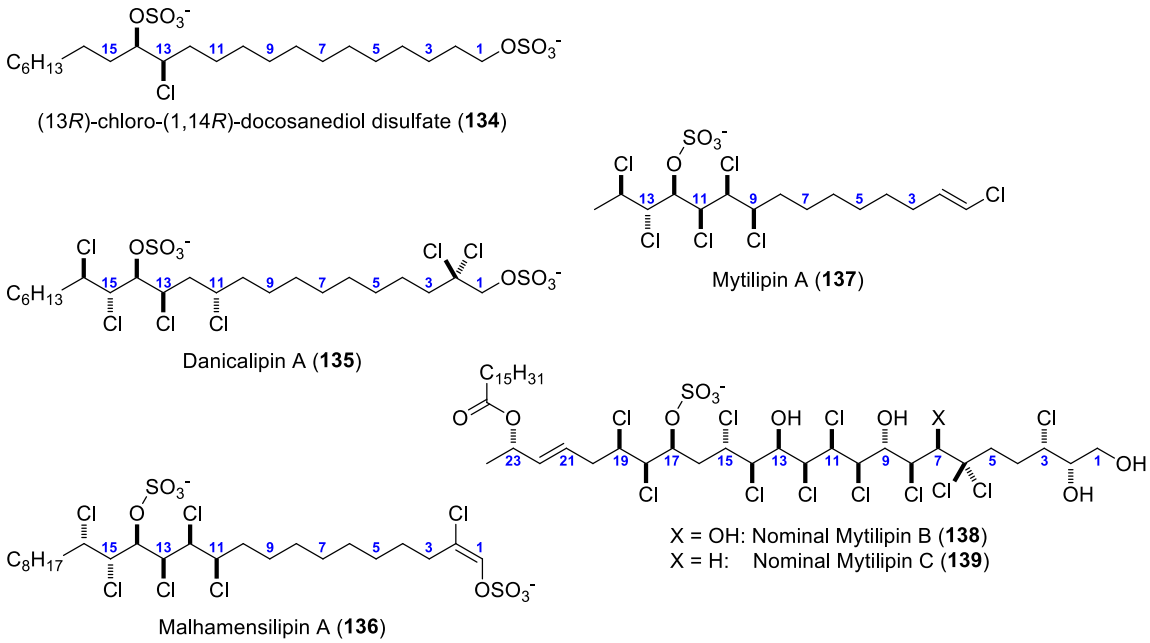


Chart 4 Representative examples of chlorosulfolipids.

Soon after the structural report of **134**, Elovson and Vagelos identified the major component of the chlorosulfolipid mixture from *Ochromonas danica* extracts as hexachlorodocosanediol disulfate **135**.[89] The two-dimensional structure was secured by chemical degradation experiments in conjunction with mass spectrometric analyses; however, due to the dearth of sufficiently sophisticated NMR techniques, the relative configuration of this complex structure remained unsolved. It should take another four decades before the full characterization of danicalipin A (**135**) was disclosed in 2009, when joint research efforts from the groups of Vanderwal and Gerwick in collaboration with Haines resulted in the establishment of the relative configuration.[90] Shortly thereafter, Okino and co-workers reported the absolute configuration using modern NMR techniques in combination with Mosher ester analysis.[91]

The unprecedented polychlorinated lipid structure of these compounds imposes the question of its function within the algae. Elovson and Vagelos estimated that these unusual lipids comprised 3% of the dry cell weight and 15% of the total cellular lipid content of *O. danica*.[87] In addition, a later study established that chlorosulfolipids comprise more than 90 mol% of the total polar lipids in the membrane.[92] This raises some interesting questions concerning the function of these lipids in the membrane. Haines pointed out that normal mono- or bilayer structure with these disulfates is

[89] J. Elovson, P. R. Vagelos, *Biochemistry* **1970**, *9*, 3110.
[90] D. K. Bedke, G. M. Shibuya, A. Pereira, W. H. Gerwick, T. H. Haines, C. D. Vanderwal, *J. Am. Chem. Soc.* **2009**, *131*, 7570.
[91] T. Kawahara, Y. Kumaki, T. Kamada, T. Ishii, T. Okino, *J. Org. Chem.* **2009**, *74*, 6016.
[92] L. L. Chen, M. Pousada, T. H. Haines, *J. Biol. Chem.* **1976**, *251*, 1835.

improbable as one of the sulfate groups would end up in the center of the non-polar membrane. Additionally, a hypothetical membrane structure with all sulfates on the membrane surface would only allow for a short penetration of the hydrocarbon chain into the non-polar membrane. Thus, together with the lack of experimental data for the membrane formation, the biological role of these compounds call for further investigations.

The abundance of chlorosulfolipids is showcased by their detection in several other microalgae, i.e. *Tribonema aequale*,[93] *Botrydium granulatum*, *Monodus subterraneus*, *Elakatothrix viridis*, and *Zygnema* sp.[94] In 1979, Mercer and Davies reported a study on 30 species which showed that although chlorosulfolipids are only present in large quantities in *O. danica* and *O. malhamensis*, these lipids are widely distributed in several algae.[95] In addition, it is noteworthy that chlorosulfolipids were only found in freshwater species and the compounds predominantly belong to the tetracosane (C_{24}) series with tetracosane-1,14-diol disulfate being the parent constituent.

In 1994, Gerwick and co-workers reported the isolation of structurally different chlorosulfolipids from *Poterioochromonas malhamensis*.[96] Interestingly, the major lipid fraction of chlorosulfolipids produced by this organism consisted of tetracosane (C_{24}) lipids, corresponding to the minor fraction of lipids produced by *O. danica*. The lipid component responsible for the major antimicrobial activity of the extracts from *P. malhamensis* was determined to be malhamensilipin A (**136**, Chart 4), a hexachloro-1,14-tetracosanediol disulfate with a unique chlorovinylsulfate moiety. Due to advances in NMR methods, the structure could be determined without resorting to chemical degradation experiments; however, a structural revision to include a second sulfate group on C_{14} was necessary when Gerwick and Vanderwal together reported a detailed structural analysis, including information on relative and absolute configuration, in 2010.[97]

A latest chapter on the isolation of new chlorosulfolipids was composed in the early 2000's when Ciminiello and Fattorusso reported the isolation and full structural characterization of mytilipin A−C (Chart 4, **137–139**) as part of a research program directed towards the identification of seafood toxins.[98,99,100] These compounds were isolated from the digestive glands of *Mytilus galloprovincialis*

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[93] E. I. Mercer, C. L. Davies, *Phytochemistry* **1974**, *13*, 1607.
[94] E. I. Mercer, C. L. Davies, *Phytochemistry* **1975**, *14*, 1545.
[95] E. J. Mercer, C. L. Davies, *Phytochemistry* **1979**, *18*, 457.
[96] J. L. Chen, P. J. Proteau, M. A. Roberts, W. H. Gerwick, D. L. Slate, R. H. Lee, *J. Nat. Prod.* **1994**, *57*, 524.
[97] A. R. Pereira, T. Byrum, G. M. Shibuya, C. D. Vanderwal, W. H. Gerwick, *J. Nat. Prod.* **2010**, *73*, 279.
[98] P. Ciminiello, E. Fattorusso, M. Forino, M. Di Rosa, A. Ianaro, R. Poletti, *J. Org. Chem.* **2001**, *66*, 578.
[99] P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, S. Magno, M. Di Rosa, A. Ianaro, R. Poletti, *J. Am. Chem. Soc.* **2002**, *124*, 13114.
[100] P. Ciminiello, C. Dell'Aversano, E. Fattorusso, M. Forino, S. Magno, P. Di Meglio, A. Ianaro, R. Poletti, *Tetrahedron* **2004**, *60*, 7093.

mussels collected in the northern part of the Adriatic sea. The mytilipins A–C showed moderate cytotoxicity against various cell lines with IC_{50} from 10–20 μg/mL.and in addition, they were suspected to be causative agents for diarrhetic shellfish poisoning.

Several years later, mytilipin A and analogs have also been isolated from the octocoral *Dendronephthya griffin* collected from the Taiwan Strait, suggesting that chlorosulfolpids are widely produced in microalgae and in addition, these organisms most likely serve as dietary sources for higher organisms.[101]

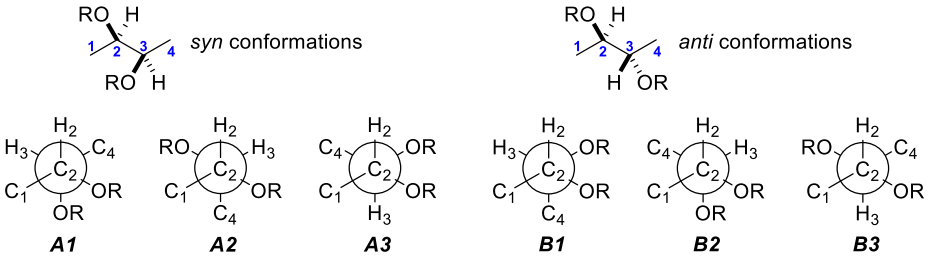
1.3.2 *J*-Based Configurational Analysis

Until the isolation of mytilipin A by Fattorusso and Ciminiello in 2001, only the two-dimensional structures of chlorosulfolipids (Chart 4, **134**–**136**) had been reported.[98] As it is often the case for lipids, none of the isolated chlorosulfolipids were crystalline, thus ruling out the stereochemical characterization by single crystal X-ray diffractometry. Moreover, at the time of most isolations of these compounds, the dearth of suitable spectroscopic methods rendered the determination of relative and absolute configuration difficult. Upon analyzing acyclic molecules, solving the stereochemical structure based solely on ^{3}J(H,H) values is usually an insufficient method. Therefore, an appropriate collection of data from relevant compounds to compare similarities is absolutely necessary to enable a qualified proposal for an unknown structure.[102]

In 1999, Murata *et al*. developed an NMR based method, named *J*-Based Configuration Analysis (JBCA), to determine the relative configuration of polyoxygenated compounds.[103] This method relies on homo- and heteronuclear coupling constants [^{3}J(H,H), ^{2}J(H,C), ^{3}J(H,C)] together with NOE or ROE measurements to form a characteristic set of data correlating to a specific conformation. Hence, the unknown relative configuration between the vicinal stereogenic centers can be established by such an analysis. In Table 3, the six possible staggered conformations of 2,3-dioxygenated butane systems and their specific set of coupling constants are shown.

[101] C.-H. Chao, H.-C. Huang, G.-H. Wang, Z.-H. Wen, W.-H. Wang, I. M. Chen, J.-H. Sheu, *Chem. Pharm. Bull.* **2010**, *58*, 944.
[102] For a good example, see Kishi's universal NMR database for contiguous polyols: S. Higashibayashi, W. Czechtizky, Y. Kobayashi, Y. Kishi, *J. Am. Chem. Soc.* **2003**, *125*, 14379 and references herein.
[103] N. Matsumori, D. Kaneno, M. Murata, H. Nakamura, K. Tachibana, *J. Org. Chem.* **1999**, *64*, 866.

Table 3 Correlation between homo- and heteronuclear coupling constants and conformation of 2,3-dioxygenated butane systems. ^{3}J(H,H): Small = 0–3 Hz, Large = 7–10 Hz; ^{3}J(H,C): Small = 1–3 Hz, Large = 5–7 Hz; ^{2}J(H,C): Small = 0–2 Hz, Large = –4 to –6 Hz.



$^{3}J(H_2,H_3)$	Small	Small	Large	Small	Small	Large
$^{3}J(H_2,C_4)$	Small	Large	Small	Large	Small	Small
$^{3}J(H_3,C_1)$	Small	Large	Small	Small	Large	Small
$^{2}J(H_2,C_3)$	Small	Large	Large	Large	Small	Large
$^{2}J(H_3,C_2)$	Small	Large	Large	Small	Large	Large

Notably, when the system adopts conformation ***A3*** or ***B3***, the coupling constant fingerprints become identical. Hence, when large ^{3}J(H,H) are observed the coupling constant analysis does not entail a definite conclusion on the conformation. When conformation ***A3*** is adopted, an ROE or NOE correlation between neighboring protons is observed, whereas this signal is absent for conformation ***B3*** (Figure 2). It should be mentioned that this method relies on the molecule to obtain a distinct low energy conformation. When two conformations interconvert with a low barrier, conclusions on the stereochemical details might be possible to reach, however, the analysis becomes significantly more complex.

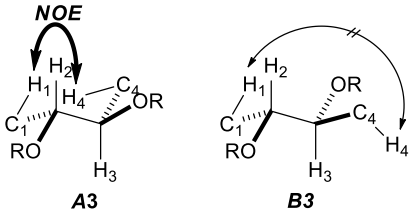


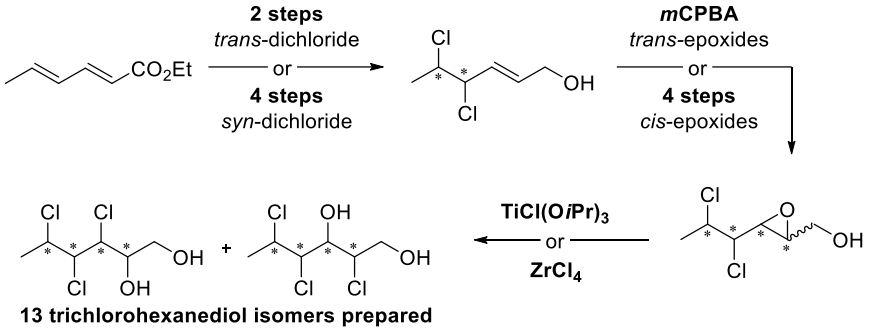
Figure 2 3-dimensional representation of conformations ***A3*** and ***B3***. For ***A3***, an NOE effect can be observed between H_1 and H_4.

In their report on the isolation and structural characterization of mytilipin A, Fattorusso and Ciminiello acknowledged that, although Murata reported the JBCA method for polyoxygenated molecules, it might as well be applicable for the stereochemical elucidation of polychlorinated entities.[98] Thereby they assumed that the reference values for coupling constants in polyhydroxylated compounds would also apply to polychlorinated molecules. The authors established the stereochemical details of mytilipins A–C without further validation.[98,99,100] In addition, Murata's method was further used by Vanderwal, Gerwick and Haines in the determination of the relative configuration of danicalipin A.[90]

Although the structures of mytilipin A and danicalipin A have been unambiguously confirmed by total synthesis, thereby supporting the use of Murata's JBCA method for these entities, the method needed to be calibrated for broader use in structure determination of acyclic polychlorinated molecules. Hence, Carreira and co-workers reported a study on a library of chloro hydroxyl alkanes

in order to obtain reference values for homo- and hetereonuclear coupling constants in dichlorides and chlorohydrins.[104,105,106]

Commencing from ethyl sorbate (**188**) permutations of trichlorohexane-1,2-diols and trichlorohexane-1,3-diols were prepared in a few steps, consisting of dichlorination, *cis*- and *trans*-epoxide syntheses, and epoxide openings (Scheme 21). The serendipitous observation that most of these compounds are crystalline unambiguously confirmed the structural assignment of most of the synthesized compounds.



Scheme 21 General synthetic scheme for the preparation of racemic trichlorohexanediols.

Extracting the relevant homo- and heteronuclear coupling constants and analyzing the values with the information obtained from the corresponding crystal structures, it was concluded that the JBCA method indeed is applicable to vicinal chlorohydrins and dichlorides to determine the relative configuration. Moreover, the homo- and heteronuclear coupling constant ranges were calibrated to fit these types of compounds. A comparison of the values together with the interpretations is shown in Figure 3.

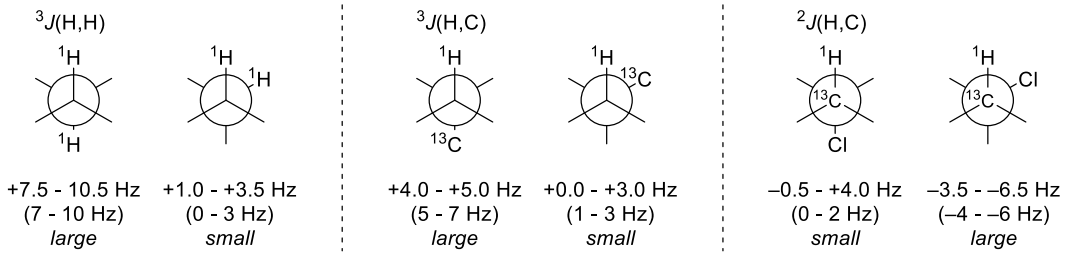


Figure 3 General values for the coupling constants in vicinal dichlorides and chlorohydrins as a function of the dihedral angle. The values in parentheses constitute the values for 1,2-dioxygenated systems.

[104] C. Nilewski, R. W. Geisser, M.-O. Ebert, E. M. Carreira, *J. Am. Chem. Soc.* **2009**, *131*, 15866.
[105] R. W. Geisser, Dissertation ETH No. 19364, ETH Zurich, 2010.
[106] C. Nilewski, Dissertation ETH No. 19549, ETH Zurich, 2011.

Interestingly, the coupling constants were found to be quite similar in value to the dioxygenated systems reported by Murata, however, subtleties showcase the importance of a proper calibration for a specific type of substrate in question.

1.3.3 Biosynthetic Investigations

Following the isolation of chlorosulfolipids in the 1960's and 70's, the question as to how these compounds are produced by the organism promptly received great attention. In their seminal investigations, Elovson and Vagelos noted that the extent to which chloride is introduced into the hydrocarbon backbone varied with the chloride concentration in the growth media.[87] Furthermore, when chloride was substituted with bromide in the medium, the corresponding bromosulfolipids are detected.[107]

Important contributions independently reported by Haines, Elovson, and Mercer in the early 1970's have led to the proposal of a viable biosynthetic pathway for production of chlorosulfolipids from *O. danica* (Scheme 22).[108] Haines and co-workers observed that ^{14}C-labeled acetate as well as the entire carbon chain of other even-numbered ^{14}C-labeled fatty acids were readily incorporated into the chlorosulfolipids.[109] This finding was further corroborated by results from Mercer *et al.*,[110] suggesting that the hydrocarbon backbone is most likely first constructed *via* the normal fatty acid biosynthetic pathways. In addition, Haines and co-workers noted that oleic acid could be incorporated, which led them to hypothesize that the C_{14}-hydroxyl group is introduced *via* hydration to 10-hydroxystearic acid prior to chain elongation. However, briefly hereafter, Elovson demonstrated that 10-hydroxystearic acid is poorly incorporated hereby ruling out the possibility of being an intermediate in the biosynthesis.[111] Furthermore, growing the organism in $H_2{}^{18}O$ only led to ^{18}O incorporation at the primary hydroxyl group, presumably by exchange at the carboxylic acid oxidation state prior to reduction, further supporting the notion that the C_{14}-hydroxyl is not introduced from water. Contrarily, by growing the alga in an $^{18}O_2$-enriched medium, Elovson demonstrated that the C_{14}-hydroxyl is derived from molecular oxygen-mediated oxidation of the saturated fatty acid, **140**.

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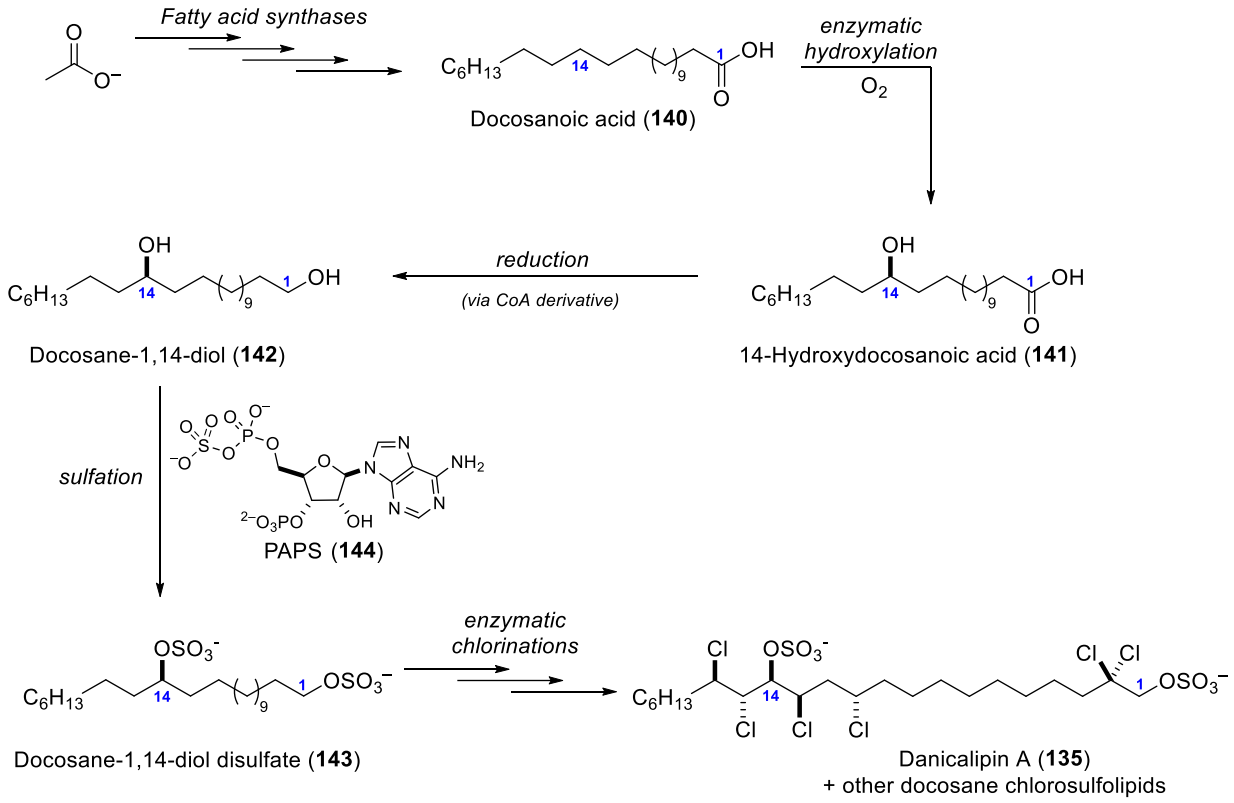
[107] This observation is only mentioned in a review on the early research on chlorosulfolipids: T. H. Haines, *Annu. Rev. Microbiol.* **1973**, *27*, 403.
[108] J. Elovson, *Biochemistry* **1974**, *13*, 3483.
[109] C. L. Mooney, E. M. Mahoney, M. Pousada, T. H. Haines, *Biochemistry* **1972**, *11*, 4839.
[110] G. Thomas, E. I. Mercer, *Phytochemistry* **1974**, *13*, 797.
[111] J. Elovson, *Biochemistry* **1974**, *13*, 2105.



Scheme 22 Proposed biosynthetic pathway to chlorosulfolipids produced by *Ochromonas danica*.

From 1,14-diol **142**, Mercer *et al.* showed that sulfation is most likely carried out with 3′-phosphoadenosine 5′-phosphosulfate (PAPS, **144**) as the sulfating agent.[112] In addition, further experiments by Mercer[110] and Haines[113] demonstrated that disulfate **143** is also readily incorporated to give chlorosulfolipid products, indicating that sulfation takes place prior to the chlorination events. Resubjecting partly chlorinated products resulted in further chlorinations, thereby suggesting that chlorinations occur sequentially and not necessarily in a specific order. Interestingly, it was also shown that the sulfates are not cleaved by the organism which means that chlorinations can take place on the disulfates.

Based on these observations, Elovson[108] proposed the biosynthetic pathway shown in Scheme 22. Last but not least it is noteworthy that the results pointed towards introductions of chlorines on the saturated backbone; hence, most likely *via* radical mechanisms. Keeping the discussion in Chapter 1.1.2 in mind, it can be assumed that chlorinations leading to chlorosulfolipids involve non-heme iron halogenases dependent on α-ketoglutarate.[16]

[112] E. I. Mercer, G. Thomas, J. D. Harrison, *Phytochemistry* **1974**, *13*, 1297.
[113] C. L. Mooney, T. H. Haines, *Biochemistry* **1973**, *12*, 4469.

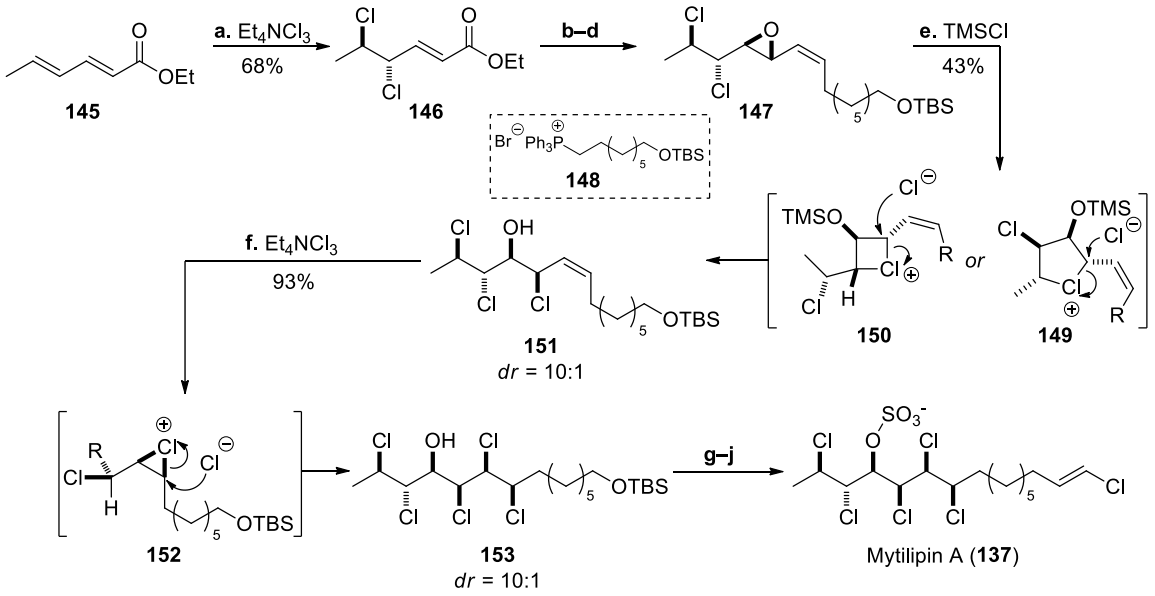
1.3.4 Tactics in Syntheses of Chlorosulfolipids

Little attention had been given from the synthetic community to this family of natural products until 2009, when Carreira and co-workers reported the first synthesis of a chlorosulfolipid.[114] Henceforth, several synthetic chemists showed interest in this field of research and thus, several strategies to access these interesting compounds have appeared in the literature.[115] In the following sections, selected parts of these contributions will be discussed to draw a picture on the different tactics used to facilitate access to members of this class of naturally occurring lipids.

1.3.4.1 Dichlorinations and Epoxide Openings: Syntheses of Mytilipin A

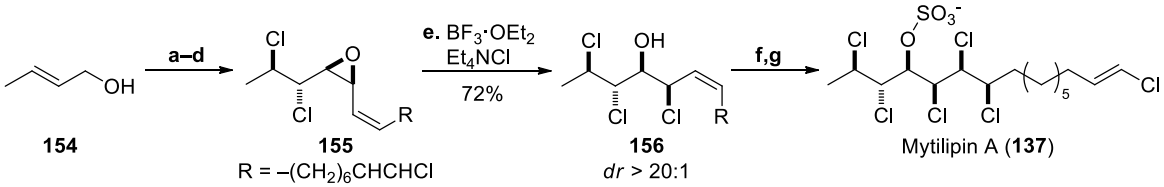
The first chlorosulfolipid targeted for total synthesis was hexachlorosulfolipid **137**, which was later renamed mytilipin A.[98] Scheme 23 summarizes the first synthesis reported by Carreira and co-workers.[114] Starting from ethyl sorbate **145**, the first chlorines were introduced *via* a stereospecific *trans*-dichlorination with Mioskowski's reagent of the most electron-rich γ,δ-olefin to give 1,2-*anti* dichloroester **146**. Following a four-step sequence, including epoxidation and Wittig reaction, key vinyl epoxide **147** was set up for introduction of the third chloride by an epoxide opening. The authors describe the use of trimethylsilyl chloride to afford chlorohydrin **151** with overall retentive opening, presumably *via* anchimmeric assistance from nearby chlorides to provide intermediate chloronium ion **149** or **150**. A second diastereoselective dichlorination completed the stereohexad with good stereoselectivity, and an additional four steps completed the first successful synthesis of mytilipin A.

[114] C. Nilewski, R. W. Geisser, E. M. Carreira, *Nature* **2009**, *457*, 573.
[115] For reviews on the synthetic efforts towards chlorosulfolipids, see: a) D. K. Bedke, C. D. Vanderwal, *Nat. Prod. Rep.* **2011**, *28*, 15; b) C. Nilewski, E. M. Carreira, *Eur. J. Org. Chem.* **2012**, *2012*, 1685; c) W.-J. Chung, C. D. Vanderwal, *Acc. Chem. Res.* **2014**, *47*, 718; d) T. Umezawa, F. Matsuda, *Tetrahedron Lett.* **2014**, *55*, 3003.



Scheme 23 Carreira's synthesis of mytilipin A. Reagents and conditions: a. Et_4NCl_3, CH_2Cl_2, 0 °C, 68%; b. DIBAL-H, PhMe, 0 °C, 72%; c. *m*-CPBA, CH_2Cl_2, 0 °C to r.t., *dr* = 1:1, 95%; d. NMO, TPAP, 4 Å MS, CH_2Cl_2; then **148**, *n*−BuLi, –78 °C to r.t., 34%; e. TMSCl, CH_2Cl_2, EtOAc, 43% (73% brsm); f. Et_4NCl_3, CH_2Cl_2, –78 °C, 93%, *dr* = 10:1; g. CSA, MeOH, 98%; h. $PhI(OAc)_2$, TEMPO, CH_2Cl_2; i. $CrCl_2$, $CHCl_3$, THF, 65 °C, 47% over two steps; j. SO_3·py, THF, 99%.

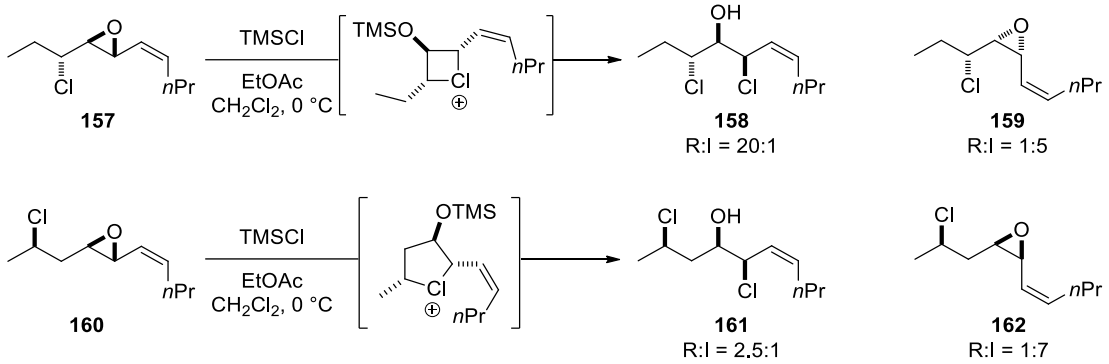
Recently, Vanderwal and co-workers published a second racemic synthesis of mytilipin A.[116] The authors reported the preparation of chloro vinyl epoxide **155** as a key intermediate in four steps (Scheme 24), an intermediate very similar to key vinyl epoxide **147** in Carreira's synthesis (see Scheme 23). Interestingly, Vanderwal found that the properties of the neighboring chlorides to act as participating moieties could be overruled by using a combination of Lewis acid activation and tetraethylammonium chloride as a nucleophilic chloride source to give stereotetrad **156** with inversion in 72% yield. Another salient feature of their synthesis is the use of a *Z*-selective olefin cross-metathesis reaction to access the key vinyl epoxide **155** in only four steps from crotonyl alcohol (**154**).



Scheme 24 Vanderwal's synthesis of mytilipin A. Reagents and conditions: a. Cl_2, Et_4NCl, CH_2Cl_2, 0°C, 89%; b. DMP, CH_2Cl_2, 0 °C; c. allylbromide, LiTMP, Et_2AlCl, THF, –78 °C then NaOH(aq), Et_4NCl, r.t., *dr* = 98:2, 52% over two steps; d. $H_2CCH(CH_2)_6CHCHCl$, Grubbs *Z*-selective metathesis catalyst (CAS no 1352916-84-7), DCE, 35 °C *Z:E* > 20:1, 32%; e. BF_3·OEt_2, Et_4NCl, CH_2Cl_2, –78 °C, 72%; f. Et_4NCl_3, CH_2Cl_2, –78 °C, 86%, *dr* = 97:3; g. SO_3·py, THF, 94%.

[116] W.-j. Chung, J. S. Carlson, D. K. Bedke, C. D. Vanderwal, *Angew. Chem. Int. Ed.* **2013**, *52*, 10052.

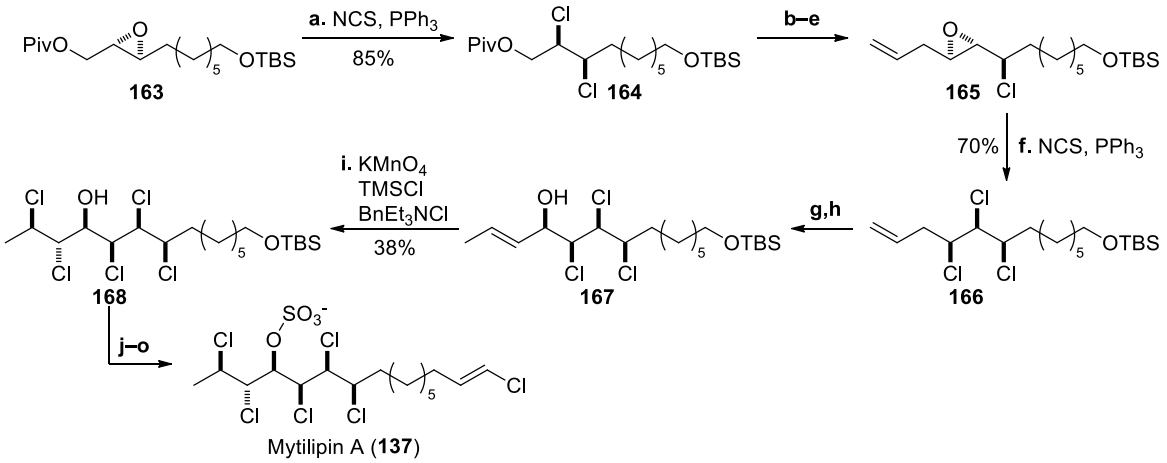
The observation that neighboring chlorides must not be regarded as innocent spectators during the opening of chloro vinyl epoxides (*cf.* Scheme 23, **147**) further complicates the synthetic planning *en route* to chlorosulfolipids. While precedent for the ability of chloride to participate in epoxide openings dates back to 1971, no detailed study of such an anchimeric assistance has been reported.[117] Thus, in order to gain critical insight into the nature of chlorides as participating moieties as well as probing mechanistic understanding, Carreira very recently reported a thoroughly executed study on openings of various chloro vinyl epoxides.[118] Some representative results of this study are shown in Scheme 25. Intriguingly, while opening of **157** proceeds predomninantly with retention, opening of the diastereomer **159** is favored with inversion, thus exemplifying that anchimeric assistance is favored for a *trans*-substituted cyclic chloronium-intermediates. Similar results were obtained for substrate **160** and **162**, albeit with generally lower selectivity towards retention. It is noteworthy, that these results suggest a stronger effect from a four-membered than a five-membered chloronium intermediate.



Scheme 25 Carreira's study on openings of chloro epoxides with trimethylsilyl chloride; R:I = retention:inversion ratio.

A substantially different approach to mytilipin A was reported by Yoshimitsu and co-workers in 2010,[119] building on a series of deoxydichlorinations developed in their own laboratories.[50] Commencing from enantioenriched epoxide **163**, treatment with NCS and triphenylphosphine cleanly delivered the vicinal dichloride **164** with double inversion (Scheme 26). Further steps led to a second epoxide intermediate **165** which under similar conditions could be converted into the all-*syn*-1,2,3-trichloride **166**. Additionally, Yoshimitsu and co-workers demonstrated that *trans*-allylic alcohol **167** underwent dichlorination under Marko-Maguire conditions[55] to give the *trans,trans*−dichlorohydrin system in stereohexad **168**.

[117] P. E. Peterson, J. M. Indelicato, B. R. Bonazza, *Tetrahedron Lett.* **1971**, *12*, 13-16.
[118] A. Shemet, D. Sarlah, E. M. Carreira, *Org. Lett.* **2015**, *17*, 1878.
[119] T. Yoshimitsu, N. Fukumoto, R. Nakatani, N. Kojima, T. Tanaka, *J. Org. Chem.* **2010**, *75*, 5425.



Scheme 26 Yoshimitsu's synthesis of mytilipin A. Reagents and conditions: a. NCS, PPh_3, PhMe, 90 °C, 85%; b. DIBAL, CH_2Cl_2, –78 °C, 95%; c. DMP, $NaHCO_3$, CH_2Cl_2; d. allylTMS, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 to 0 °C, 72%, *dr* = 3.8:1; e. NaH, THF, 0 °C to r.t., 97%; f. NCS, PPh_3, DCE, 90 °C, 70%; g. SeO_2, *t*-BuOOH, salicylic acid, DCE, 80 °C, 49%, *dr* = 3:5; h. 2-butene, Grubbs 2nd gen. catalyst, CH_2Cl_2, 93%; i. $KMnO_4$, $BnEt_3NCl$, TMSCl, CH_2Cl_2, −78 to −10 °C, 38% + 10% of other diastereomer; j. Ac_2O, DMAP, Et_3N, CH_2Cl_2, quant.; k. HF(aq), py, THF, 94%; l. DMP, CH_2Cl_2, 98%; m. $CrCl_2$, $CHCl_3$, THF, 65 °C, 75%; n. DIBAL-H, CH_2Cl_2, –78 °C, 96%; o. $SO_3{\cdot}$py, DMF, 75%.

1.3.4.2 Danicalipin A

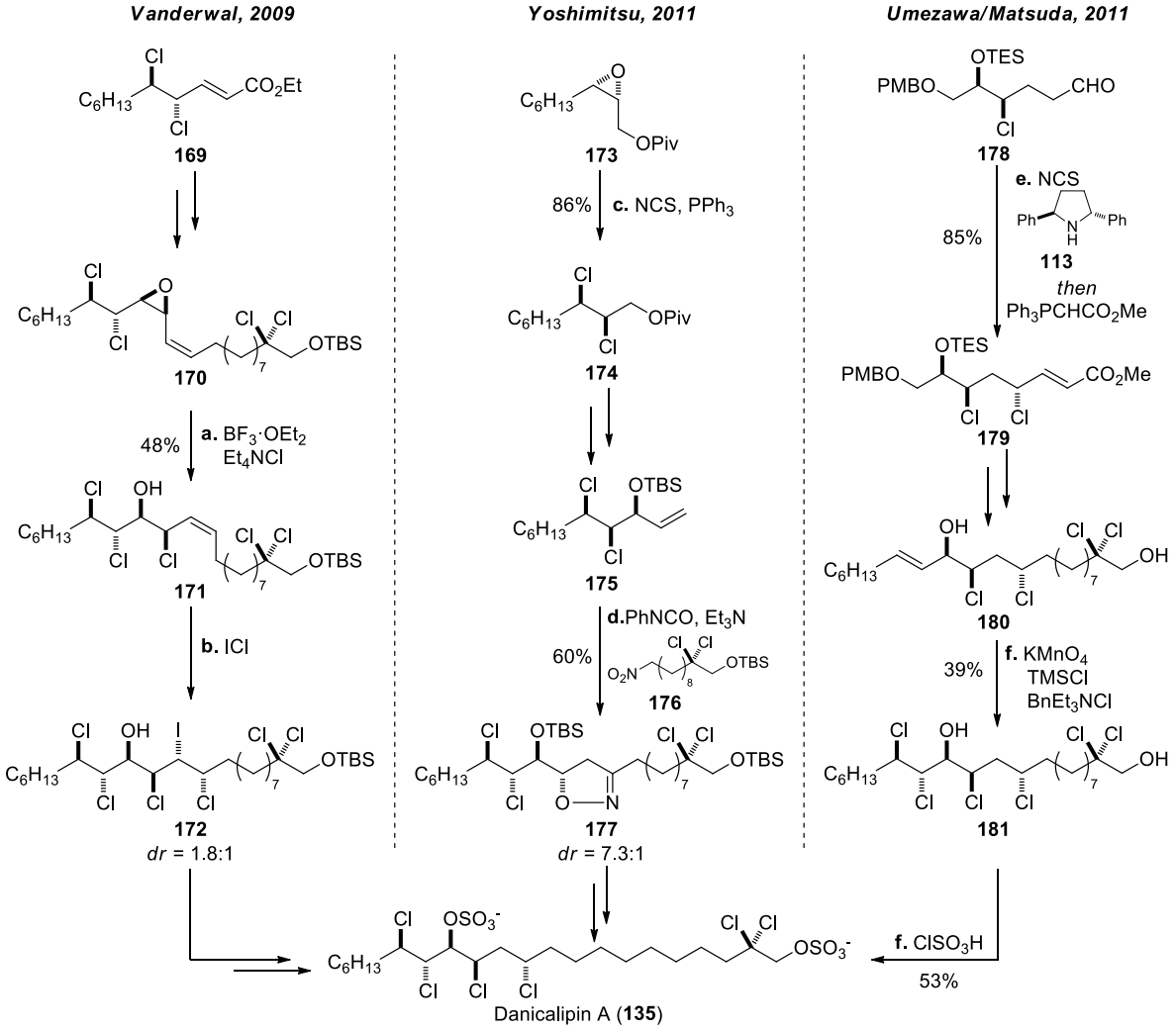
Briefly after Carreira and co-workers reported the first synthesis of a chlorosulfolipid, Vanderwal *et al*. disclosed the first synthesis of danicalipin A.[90] Henceforth, this target gained significant interest from other synthetic chemists, resulting in several other completed syntheses from Umezawa and Matsuda,[120] Yoshimitsu,[121] and very recently also from Carreira.[122] Since many of the strategies used to overcome the challenges of the complex danicalipin A structure resembles the tactics described for mytilipin A (*vide supra*), a brief overview of the various contributions towards danicalipin A are summarized in Scheme 27.

In Vanderwal's synthesis, α,β-unsaturated dichloroester **169**, prepared *via trans*-stereospecific dichlorination of the corresponding ethyl α,β,γ,δ-dienoate, served as precursor for key chloro vinyl epoxide **170** which, upon treatment with borontrifluoride and tetraethylammonium chloride, afforded **171** with inversion. Furthermore, the authors demonstrated that iodochlorination of the resulting allylic chloride with ICl proceeded with complete regiocontrol to give **172**, albeit only with poor diastereoselectivity towards the *trans,syn*- over the all-*syn* product. Interestingly, the stereochemical outcome of this reaction is reversed in comparison to the dichlorinations of allylic chlorides in the

[120] T. Umezawa, M. Shibata, K. Kaneko, T. Okino, F. Matsuda, *Org. Lett.* **2011**, *13*, 904.
[121] T. Yoshimitsu,R. Nakatani,A. Kobayashi,T. Tanaka, *Org. Lett.* **2011**, *13*, 908.
[122] A. M. Bailey, S. Wolfrum, E. M. Carreira, *Angew. Chem. Int. Ed.* [Online early access].
DOI: 10.1002/anie.201509082

mytilipin A syntheses to give all-*syn* products. Although, no comments on these changes in selectivity are given, it might be speculated that the differences in intrinsic properties of intermediate iodonium and chloronium ions play a vital role for the observed selectivities.[123]

In 2010, Vanderwal further disclosed the first synthesis of malhamensilipin A (**136**)[124] following similar strategies to the ones presented for danicalipin A; therefore, this work will not be discussed further.



Scheme 27 Overview of total syntheses of danicalipin A by Vanderwal, Yoshimitsu, and Umezawa and Matusda. Reagents and conditions: a. $BF_3{\cdot}OEt_2$, Et_4NCl, CH_2Cl_2, 48%; b. ICl, CH_2Cl_2, –78 °C, *dr* = 1.8:1; c. NCS, PPh_3, PhMe, 90 °C, 86%; PhNCO, Et_3N, PhMe, 90 °C, 60%, *dr* = 7.3:1; e. **113**, NCS, $BrCH_2CO_2H$, DCE, 0 °C *then* Ph_3PCHCO_2Me, 85%; f. $KMnO_4$, $BnEt_3NCl$, TMSCl, C_8H_{18}, 90 °C, 39%.

In 2011, another two additional syntheses of danicalipin A appeared simultaneously from the Yoshimitsu laboratories and from joint efforts of Umezawa and Matsuda, respectively. Whereas most

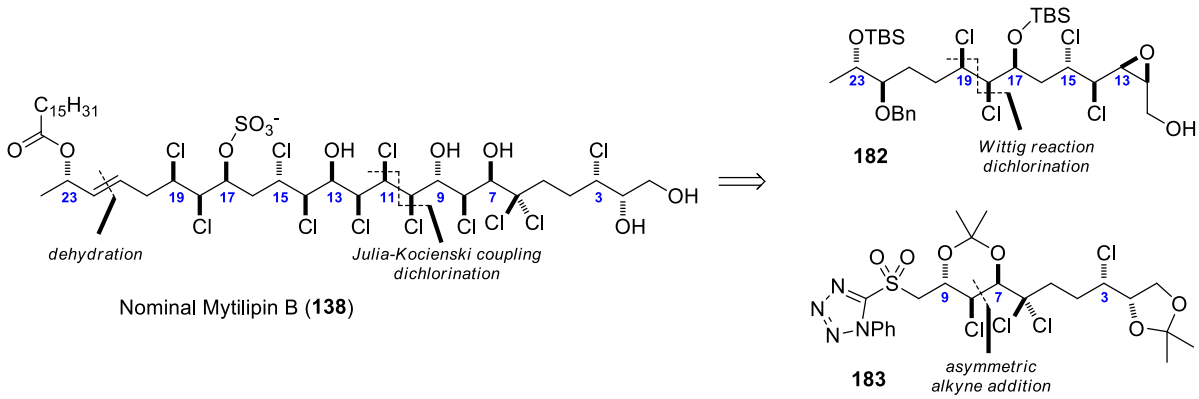
[123] Iodonium ions are known to be configurationlly unstable, however, in a set of experiments, Denmark and co-workers have shown that chloronium ions show absolute configurational stability: S. E. Denmark, M. T. Burk, A. J. Hoover, *J. Am. Chem. Soc.* **2010**, *132*, 1232.
[124] D. K. Bedke, G. M. Shibuya, A. R. Pereira, W. H. Gerwick, C. D. Vanderwal, *J. Am. Chem. Soc.* **2010**, *132*, 2542.

previous strategies to access chlorosulfolipids have relied on joining fragments *via* Wittig reactions, Yoshimitsu showcased the employment of a diastereselective 1,3-dipolar cycloaddition *en route* to danicalipin A.[121] Thus, terminal allylic TBS-ether intermediate **175**, *via* deoxy-dichlorination of epoxide **173**, was reacted with a nitrile oxide, generated *in situ* from nitroalkane **176**, to give dihydroisoxazole **177** with 7.3:1 diastereselectivity (Scheme 27).

Published at the same time, Umezawa and Matsuda demonstrated a strategically different approach, wherein key reactions include an asymmetric α-chlorination of aldehyde **178** using organocatalyst **113**,[75] and a diastereoselective dichlorination of *trans*-allylic alcohol **180** using Marko-Maguire chlorinating conditions.[55]

1.3.4.3 Synthesis of Nominal Mytilipin B

Based on the knowledge gained during their earlier studies *en route* to mytilipin A, Carreira and co-workers reported the total synthesis of the most complex chlorosulfolipid isolated to date, mytilipin B (**138**).[125] The retrosynthetic analysis is outlined in Scheme 28.

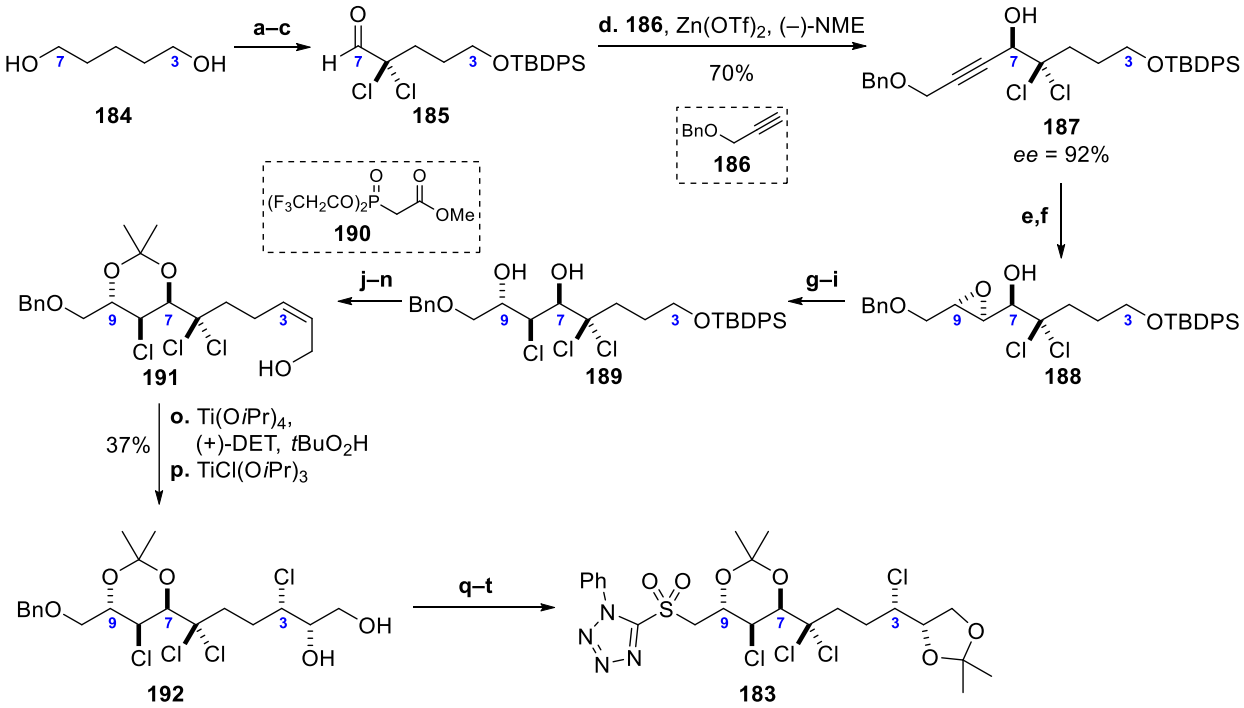


Scheme 28 Retrosynthetic analysis of nominal mytilipin B (**138**).

Introduction of chlorines by means of olefin functionalizations had proven to be efficient strategies to access polychlorides. Hence, the allylic moiety present in **138** called for a late-stage installation, i.e. *via mono*-deprotection and dehydration of a 1,2-diol functionality. Furthermore, retrosynthetic scission *via* Julia–Kocienski olefination between C_{10}–C_{11} would provide two almost equally sized fragments **182** and **183**. The vicinal dichloride at C_{18}/C_{19} in **182** was thought to arise from a dichlorination, rendering this position a good coupling point for two smaller fragments. On sulfone fragment **183**, an asymmetric alkyne addition was believed to set the first stereogenic center at C_7, thus generating a feasible starting point for the construction of the 2-chloro-1,3-diol moiety.

[125] C. Nilewski, N. R. Deprez, T. C. Fessard, D. B. Li, R. W. Geisser, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 7940.

The preparation of C_1–C_{10} sulfone fragment **183** is delineated in Scheme 29. Commencing from pentane-1,5-diol (**184**), the geminal dichloride at C_6 to give aldehyde **185** was installed by dichlorination of the corresponding *t*-butylenamine.[126] An enantioselective addition of zinc-acetylide derivative of **186** afforded propargyl alcohol **187** in 70% yield and 92% *ee*.



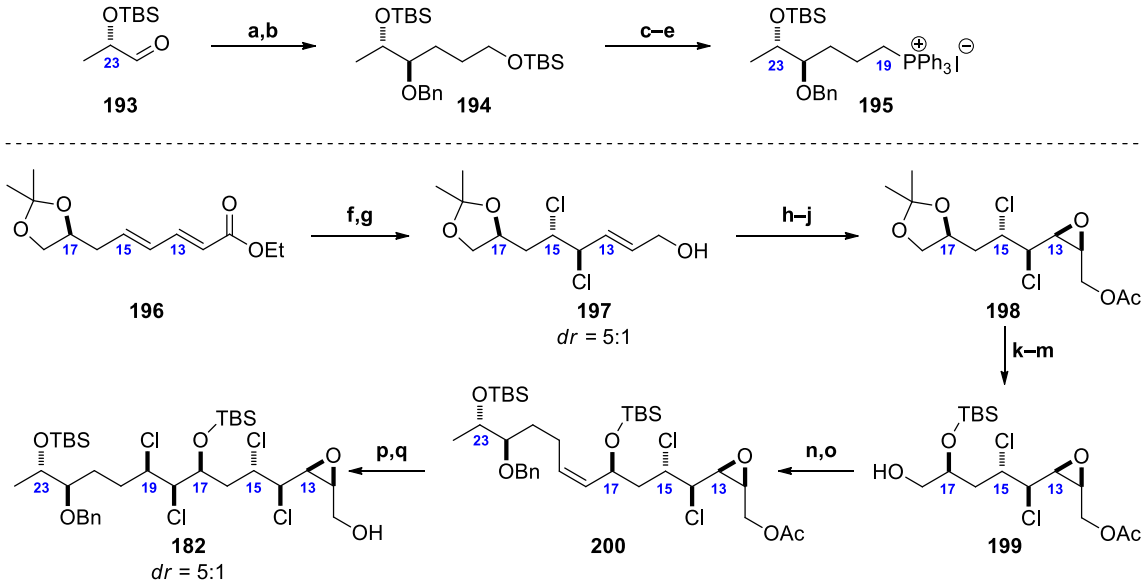
Scheme 29 Synthesis of mytilipin B: C_1–C_{10} sulfone fragment **183**. Reagents and conditions: a. TBDPSCl, imidazole, DMF, 0 °C to r.t., 96%; b. TEMPO, KBr, NaOCl (aq), CH_2Cl_2, 0 °C, 93%; c. *t*-$BuNH_2$, NCS, CCl_4, 0 °C to r.t. *then* HCl (aq), 96%; d. **186**, (–)-*N*-methylephedrine, $Zn(OTf)_2$, Et_3N, PhMe, 70%, *ee* = 92%; e. Red-Al, THF, −78 °C to r.t., 92%; f. $VO(acac)_2$, *t*BuO_2H, CH_2Cl_2, 0 °C to r.t., 62%; g. DMP, CH_2Cl_2, 0 °C to r.t., 95%; h. $ZrCl_4$, CH_2Cl_2, 0 °C to r.t.; i. $NaBH_4$, MeOH, –78 °C, 36% over two steps; j. 2-methoxypropene, PPTS, CH_2Cl_2, 0 °C to r.t., 93%; k. TBAF, AcOH, DMF, 95%; l. DMP, CH_2Cl_2, 0 °C to r.t.; m. **190**, KHMDS, THF, –78 °C, 68% over two steps; n. DIBAL−H, THF, –78 °C, 88%; o. $Ti(OiPr)_4$, *t*-BuO_2H, (+)-DET, CH_2Cl_2, –20 °C, 92% *dr* = 9:1; p. $TiCl(OiPr)_3$, C_6H_6, 40%; q. $CuSO_4$, TsOH, acetone, 83%; r. Pd/C, H_2, EtOAc, 94%; s. 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, PPh_3, THF, 0 °C to r.t., 85%; t. *m*CPBA, 0 °C to 40 °C, 61%.

From **187**, the 2-chloro-1,3-diol **189** could be obtained *via* epoxide opening, however, direct opening of **188** proved unfruitful. Hence, a sequence of oxidation and reduction with regioselective opening of the intermediate ketone in the α-position with $ZrCl_4$ proved necessary to successfully obtain **189**. Having set the stereogenic centers of C_7–C_9 of the fragment, the remaining part of the chain, i.e. C_1–C_2, was introduced *via* a Still-Genari modification of the Horner-Wadworth-Emmons reaction followed by reduction to give *cis*-allylic alcohol **191**. Hereafter, Sharpless epoxidation followed by opening at C_3 with $TiCl(iOPr)_3$ completed the stereochemical array at C_1–C_3 of **192**. A further four

[126] R. Verhe, N. De Kimpe, L. De Buyck, N. Schamp, *Synthesis* **1975**, 455.

steps allowed for the incorporation of the sulfone, hereby finalizing **193** for the Julia–Kocienski reaction.

As shown in Scheme 30, the C_{11}–C_{24} epoxyalcohol was realized commencing from diene **196**. A *trans*-dichlorination of the less electron-poor olefin with a slight preference for the desired stereochemical outcome gave allylic alcohol **197** after reduction, and a dihydroxylation–intramolecular displacement sequence then resulted in the successful construction of *cis*-epoxide **198**.[127]



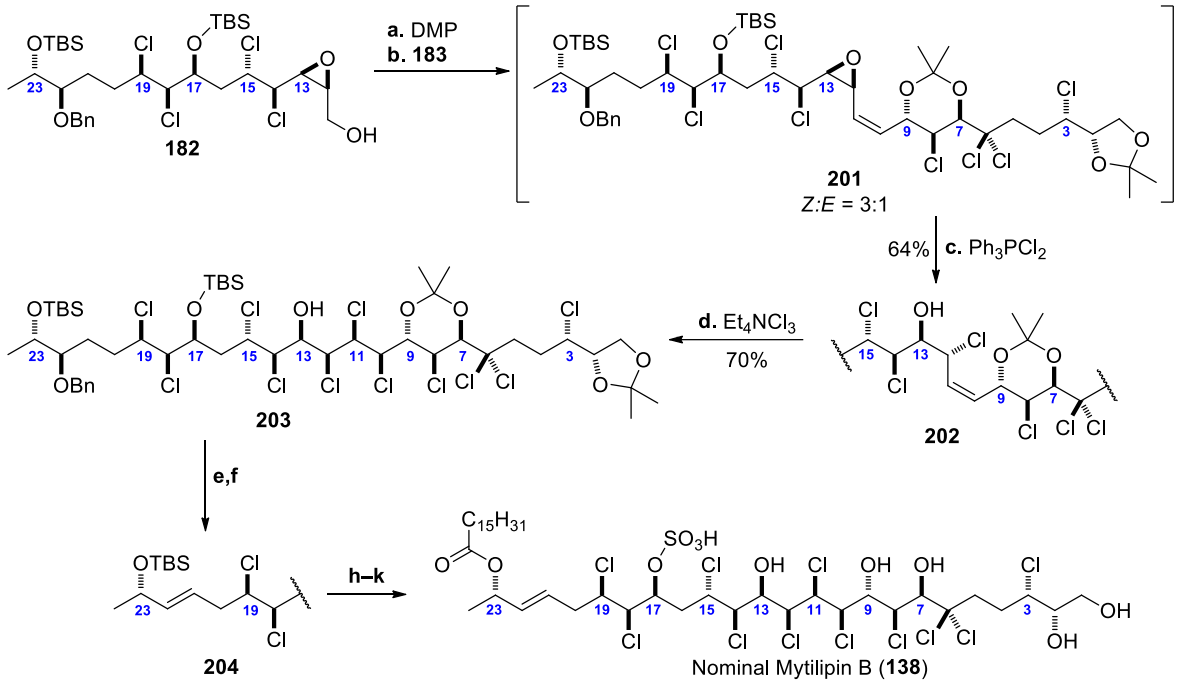
Scheme 30 Synthesis of mytilipin B: C_{11}-C_{24} epoxyalcohol fragment **182**. Reagents and conditions: a. $I(CH_2)_6OTBS$, *t*BuLi, –78 °C; b. BnBr, NaH, TBAI, DMF, 24% over two steps; c. HF·py, py, THF, 0 °C; d. I_2, PPh_3, imidazole, C_6H_6, 0 °C; e. PPh_3, MeCN, reflux, 58% over three steps; f. Et_4NCl_3, CH_2Cl_2, 0 °C, 66%, *dr* = 1.8:1; g. DIBAL-H, PhMe, 0 °C, 43% *dr* = 5:1; h. DMAP , Et_3N, AcCl, CH_2Cl_2, 0 °C, 81%; i. AD-Mix β, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 74%; j. DABCO, Tf_2O, CH_2Cl_2, –78 °C to r.t., 50%; k. CSA, MeOH, 72%; l. 2,6-lutidine, TBSOTf, CH_2Cl_2, –78 to –15 °C, 91%; m. HF·py, py, THF, 0 to 4 °C, 40% (after four cycles 79% overall yield, 86% brsm); n. DMP, 87%; o. **195**, KHMDS, THF,–78 to 0 °C, 55%; p. Et_4NCl_3, CH_2Cl_2, –78 °C, 71% *dr* = 5:1; q. K_2CO_3, MeOH, 0 °C, 98%.

The C_{11}–C_{24} part of the backbone was completed by combining epoxide **199**, after oxidation to the corresponding aldehyde, with phosphonium ylide precursor **195**, prepared in five steps from L-lactate derived aldehyde **193**, in a Wittig reaction. Eventually, the C_{18} and C_{19} stereogenic centers were set by a diastereoselective dichlorination of *cis*-allylic TBS-ether **200** to give the C_{17}–C_{19} all-*syn* product **182** in agreement with the observations by Vanderwal *et al.*[50]

As presented in Scheme 31, with both fragments **182** and **183** in hand, the authors disclosed the endgame. The entire hydrocarbon backbone was united by oxidation of primary alcohol **182** followed a Julia–Kocienski olefination with sulfone **183** under Barbier-type conditions to give **201** as a 3:1 *Z:E* mixture of double-bond isomers. This mixture was most conviently used as such in the

[127] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405.

subsequent epoxide opening with Ph_3PCl_2 affording chlorohydrin **202** with inversion at C_{12} which is in good agreement with the studies on openings of chloro-vinyl-epoxides with similar relative configurations between a *cis*-epoxide and neighboring chlorides.[118]



Scheme 31 Synthesis of mytilipin B: the end-game. Reagents and conditions: a. DMP, CH_2Cl_2, 0 °C to r.t., 95%; b. **183**, PhMe, –78 °C, then NaHMDS, –78 °C to r.t., 67%, *Z:E* =3:1; c. Ph_3PCl_2, CH_2Cl_2, 0 °C, 64%; d. Et_4NCl_3, CH_2Cl_2, 0 to 4 °C, 70%; e. H_2 (1 atm), Pd/C (20 mol%), EtOAc, r.t., 79%; f. Martin sulfurane, C_6H_6, r.t., 50%; g. HF·py, py, MeCN, 0 °C to r.t. to 40 °C, quant.; h. palmitoyl chloride, py, CH_2Cl_2, –78 to –40 °C, 60%; i. SO_3·DMF (excess), $NaSO_4$, DMF/py, 0 °C to r.t. to 45 °C, 60%; j. TFA/H_2O (1:1), 0 °C to r.t.

Completing the synthesis, dichlorination of **202** installed the last two chlorides at C_{10} and C_{11}, and desaturation was accomplished *via* debenzylation/dehydration of **203** to give allyl TBS-ether **204** which was taken through the final four steps, including acylation and sulfation, to successfully provide the proposed structure of mytilipin B (**138**).

At this point, it became evident that there was a severe mismatch in spectral data between the synthesized chlorosulfolipid **138** and the data obtained from the isolation report. Hence, based on these observations, it was concluded that the structure of mytilipin B had been misassigned.

1.4 Summary

Chlorosulfolipids constitute an interesting class of natural products which have attracted much attention from synthetic chemists in recent years. Advances in the field of stereoselective construction of C–Cl bonds have enabled successful total syntheses of several members of this group of unusual lipids. First in line was the synthesis of mytilipin A by Carreira and co-workers in 2009 which identified intriguing features of these systems, displaying unexpected reactivity. Further synthetic studies, among others by Vanderwal and Yoshimitsu, have contributed to the understanding of the properties of such structures. In addition, the advancement of analytical methods has eased the structural elucidation in polychlorinated acyclic compounds.

The developed tactics and strategies have allowed for the total synthesis of mytilipin B, the most complex chlorosulfolipid isolated to date. A comparison of spectral data with the isolation report identified mismatches between the synthesized nominal structure and the natural product, and concludes a misassignment of the structure by the isolation team.

In order to ensure further progress in the field of chlorosulfolipid research, a structural revision of mytilipin B and ultimate confirmation by total synthesis is deemed of high interest to the scientific community.

With this in mind, we decided to re-evaluate the structure of mytilipin B based on the isolation data, and to ultimately proof the correct structure of this natural product by its total synthesis.

2 Revision of Mytilipin B

As described in the previous chapter, the total synthesis of mytilipin B by Carreira *et al.* led to the observation of several severe mismatches in the spectral data of the isolated natural product compared to the material prepared by synthesis. Through detailed structural analyses of synthetic intermediates, the synthesis team felt confident about the assignment of the synthetic material (see Figure 4); hence, the logical conclusion followed: the structure of mytilipin B had been misassigned by Ciminiello and Fattorusso in the isolation report.

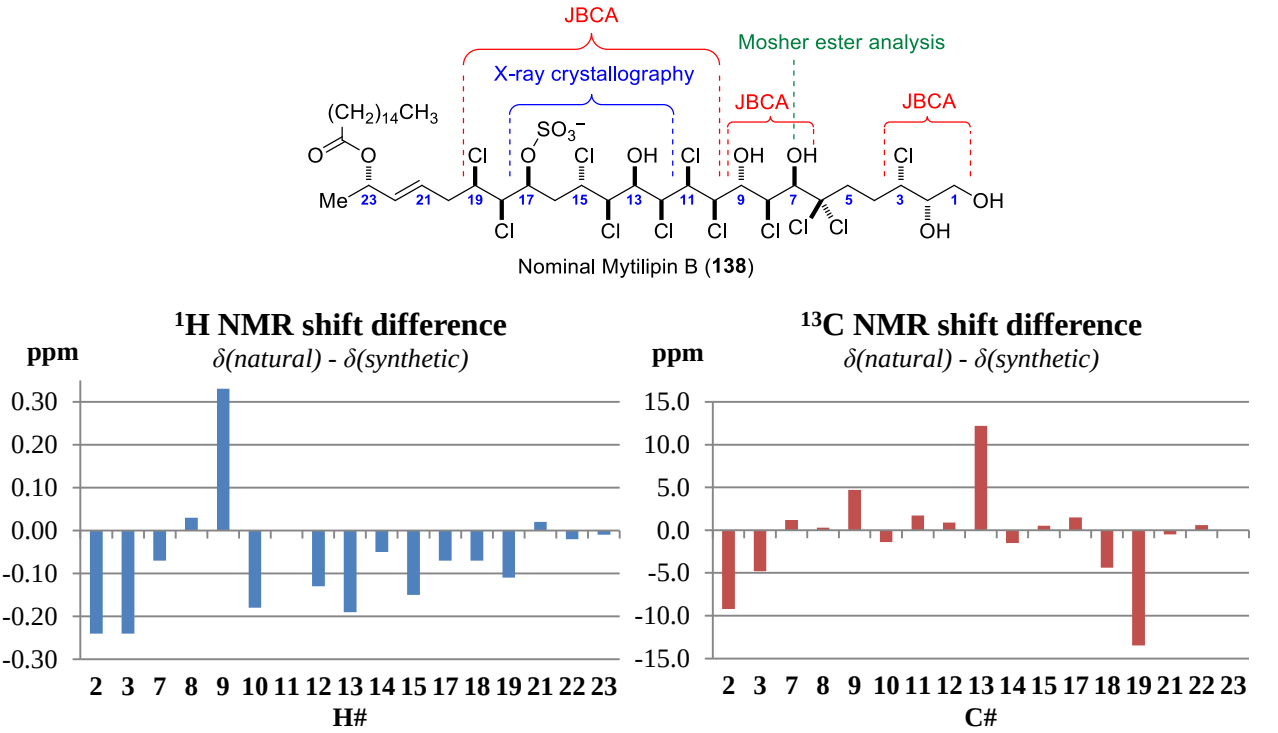


Figure 4 Presentation of structural assignment validations in synthetic **138**, and comparison of ^{1}H and ^{13}C NMR spectral data for synthetic **138** and the natural product.

In the following sections it is described how we re-evaluated the isolation data and came to a plausible structural revision. Unfortunately, it was not possible to obtain raw spectral data nor any sample of the natural product from the isolation group; therefore, the analysis herein is based solely on the published information.

2.1 Re-investigation of Isolation Data

2.1.1 Preliminary Considerations: The Planar Structure

The structure of mytilipin B was established based on extensive analyses of NMR- and IR-spectroscopic as well as mass spectrometric data.[99] As reported by Ciminiello and Fattorusso, the negative ion ESI MS spectrum of the natural product contained a molecular ion cluster at *m/z* 1139, 1141, 1143, 1145, 1147, 1149, 1151 which indicated the presence of eleven chlorides. In addition, an intense fragment ion at *m/z* 255 $[C_{16}H_{31}O_2]^-$ pointed towards the presence of a hexadecanoyl moiety. Furthermore, high resolution mass spectrometric analysis resulted in establishment of the molecular formula as $C_{40}H_{66}O_{11}SCl_{11}$ which includes two unsaturation equivalents (*m/z* calcd 1141.0870, found 1141.0936). This molecular formular was further corroborated by the mass spectrum of the final product reported by Carreira *et al.*[125]

Based on the absorptions at ν_{max} 1240, 1220, and 820 cm^{-1} in the IR spectrum of mytilipin B, a sulfate group was concluded to be present, accounting for the sulfur and four of the eleven oxygens. This was further supported by the intense fragment ions at *m/z* 97 $[HSO_4^-]$ and 80 $[SO_3^-]$ in an acquired MSMS spectrum.

A combined analysis of ^1H, ^{13}C NMR, DEPT, and HMQC spectra revealed information on all remaining functionalities in the natural product. Firstly, 38 carbons showed to be protonated, whereof 36 are sp^3 type (2 methyls, 19 methylenes, and 15 methines), and two carbons are sp^2 methines which indicates the presence of a 1,2-disubstituted olefin. One of the remaining two carbons pointed towards an ester functionality, hereby accounting for another two oxygens. This further explains the two unsaturation equivalents and leaves back 5 oxygens. These could further be assigned to five hydroxyl groups by peracetylation of the natural product to give **205** (Figure 5). Combining this knowledge with information on the number of sp^3 methines indicated the presence of nine chloride-substituted carbons and one *gem*-dichloride moiety.

Significant overlap of signals in the ^1H NMR spectrum of the parent natural product forced the isolation team to resort to derivatives in order to establish the connectivities and thereby the planar structure. It was found, that peracetylated **205** conveniently resulted in NMR spectra with good dispersion of signals. Consequently, the spectral data for **205** were used to establish the gross structure of mytilipin B (Figure 5).

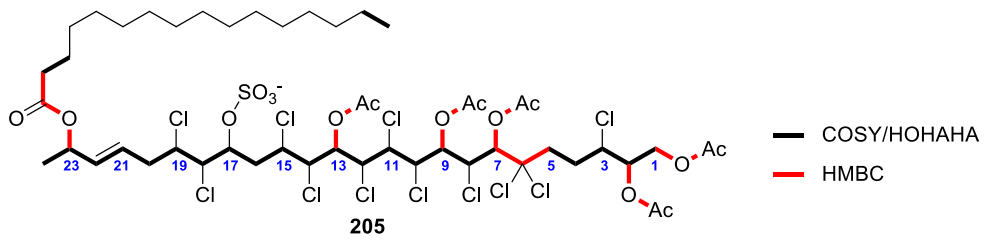


Figure 5 Planar **s**tructure of peracetylated mytilipin B (**205**) with COSY/HOHAHA and HMBC correlations.

By analysis of (^{1}H,^{1}H) COSY and HOHAHA spectra, two spin systems were identified, namely C_1–C_5 and C_7–C_{24}, and furthermore, despite extensive overlap of a number of methylenes, a number of key correlations suggested that the acyl moiety is unbranched. Further investigations of HMBC spectra allowed for the positioning of the five (acetylated) hydroxyl groups at C_1, C_2, C_7, C_9, and C_{15} as well as the palmitoyl ester at C_{23}. The connectivity of the backbone was fully established *via* correlations to the unprotonated C_6. From here on, remaining functionalities were positioned by placing the sulfate at the remaining methine-carbon resonating at lowest field, i.e. C_{17}, followed by distribution of the chlorides over the remaining nine methines, and concluding the gross structure with a *geminal* dichloride at C_6.

Up to this point, a re-investigation of the spectral data and comparison to the above mentioned conclusions, in our hands, did not lead to any major discrepancies concerning the planar structure of mytilipin B. It should be mentioned, however, that a minor point is worth noting; namely the positioning of the sulfate functionality. The authors base this placement solely on the chemical shift of C_{17} compared to the shifts of the remaining chlorine-bearing methine carbons. It is reasonable to assume that the sulfate moiety affects greater deshielding of the adjacent carbon, resulting in a chemical shift further downfield compared to the chlorine-substituted carbons.[128] However, due to the high complexity of the molecule other factors might affect the chemical shifts, such as the folding, making the analysis more complicated. Thus, additional experiments to unambiguously establish the positioning of the sulfate group would have been appropriate. An example of a suitable follow-up experiment would be hydrolysis of the sulfate with subsequent derivatization as was reported by the same research team in the structural elucidation of mytilipin A.[98]

[128] H. Friebolin, *Basic One- and Two-Dimensional NMR Spectroscopy*. 4th ed.; Wiley-VCH: Weinheim, 2005; p 150.

2.1.2 Stereochemical Revisions

After establishing the gross structure, further analyses to obtain stereochemical details were necessary. Firstly, the observation of a large H-H coupling constant $^{3}J(H_{21}, H_{22})$ = 15.3 Hz clearly indicated that the 1,2-disubstituted olefin is displaying a *trans* geometry.

Investigations into the configurations at the fifteen methines proved quite challenging. Taking advantage of the fact that most stereogenic centers are contiguous, Ciminiello and Fattorusso acknowledged the use of Murata's *J*-Based Configuration Analysis (see Chapter 1.3.2) to extract information on the relative configurations (Figure 6). Based on ^{1}H NMR, HETLOC, and PS-HMBC experiments relevant homo- and heteronuclear coupling constants (^{3}J(H,H), ^{3}J(H,C), ^{2}J(H,C)) could be extracted and evaluated. Classification of the values as large/small followed by assessment of the dominant conformations led to establishment of the relative configurations with exception of the relationships between C_7/C_8, C_9/C_{10}, C_{11}/C_{12}, and C_{13}/C_{14}.

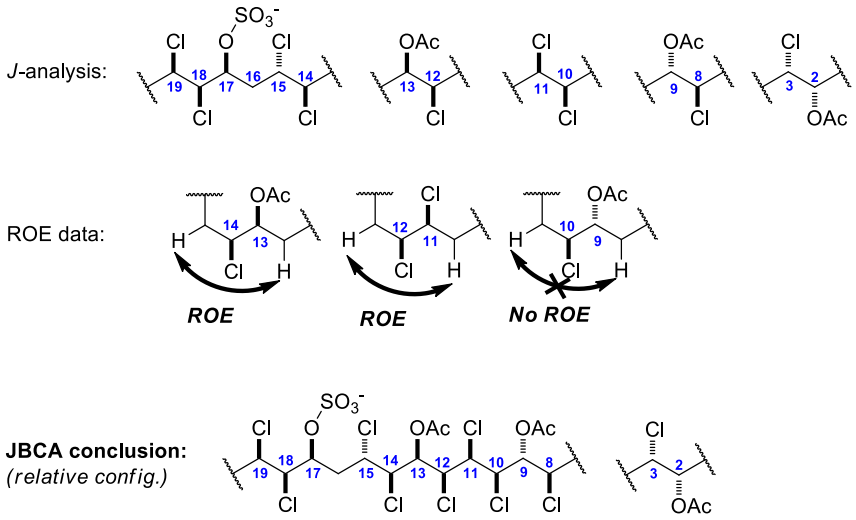


Figure 6 Relative configurations in nominal mytilipin B assigned by the isolation group.

The relative configuration between C_7/C_8 could not be determined by the JBCA method due to the observation of medium sized *J* values. This might be attributed to the adjacent bulky *germinal* dichloride at C_6 which is thought to force the conformation away from perfectly staggered. This leads to unconventional dihedral angles and, as a consequence, inconclusive coupling constants. A second rationale for medium-sized coupling constants might be the rapid interconversion of more conformations, leading to the observation of average-sized values. This option, however, was not commented on in the isolation report. Unfortunately, the authors have not reported further details on the *J* values around C_7/C_8, and thus, this option cannot be considered in a re-evaluation of the spectral data.

In the latter three cases, the dominant conformation could not be established solely based on the coupling constants due to the observation of large ^{3}J(H,H) values. As reported by Murata, in this case two conformations are possible, namely ***A3*** and ***B3***, which may be differentiated by ROE measurements (see chapter 1.3.2). Thus, the authors report the relative configuration C_9/C_{10} to be *anti*, based on the absence of an ROE crosspeak between H_8/H_{11}, and the relationships at C_{11}/C_{12} and C_{13}/C_{14} to be *syn*, based on the presence of crosspeaks between H_{10}/H_{13} and H_{12}/H_{15}, respectively.

With these results in hand, Ciminiello and Fattorusso turned their attention to the investigation of the absolute configuration based on Kakisawa's modified analysis method of Mosher ester derivatives **206**, **207**, and **208** (Figure 7).[129,130]

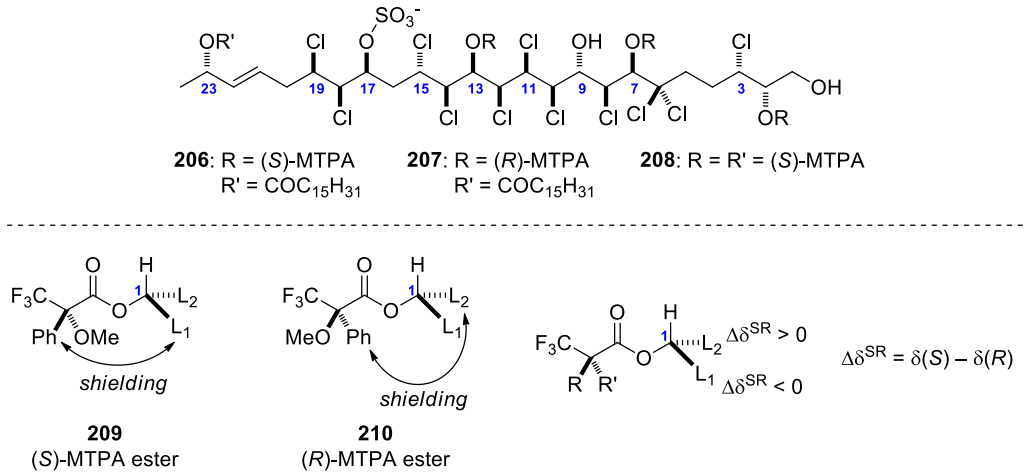


Figure 7 Mosher ester derivatives **206**, **207**, and **208** and simplified model for the establishment of absolute configuration using Mosher ester (MTPA) derivatives.

The method for determination of absolute configuration of methoxytrifluorophenylacetate ester derivatives **209** and **210** (MTPA-esters) of chiral alcohols relies on the assumption that these esters adopt a dominant conformation in which the C_1–H, C=O, and CF_3 groups are situated in the same plane. This leads to anisotropic effects where the phenyl group is shielding the protons in L_1 (for **209**) and L_2 (for **210**) resulting in upfield shifting of the protons in L_1 and L_2, respectively. The net effect then makes possible to establish the spatial position of L_1 and L_2, and thus, the absolute configuration of the derivatized alcohol based on the observed chemical shift differences.

With this method in mind, Ciminiello and Fattorusso measured the chemical shift differences between **206** and **207**, hereby establishing the absolute configurations of hydroxyls at C_2, C_7, and C_{13}. Combining these results with the JBCA analysis, the absolute configuration of the entire fragment C_1–C_{19} was established.

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[129] J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.
[130] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092.

Finally, the absolute configuration of the isolated allylic ester at C_{23} needed to be determined. Once again, the authors relied on Mosher ester analysis to obtain information on this stereogenic center. This time, the natural product was treated with $LiAlH_4$ to liberate the C_{23} hydroxyl group which was then derivatized to give tetra-(*S*)-MTPA ester **208**. Due to the scarce amount of material left at this point, the authors based their analysis only on this one derivative, exploiting the method reported by Riguera *et al.* in 2009.[131] Herein, it was shown how derivatization with one enantiomer of methoxyphenylacetic acid (MPA) to give one MPA-ester derivative can reveal information of the absolute configuration of secondary alcohols alone by NMR temperature experiments.

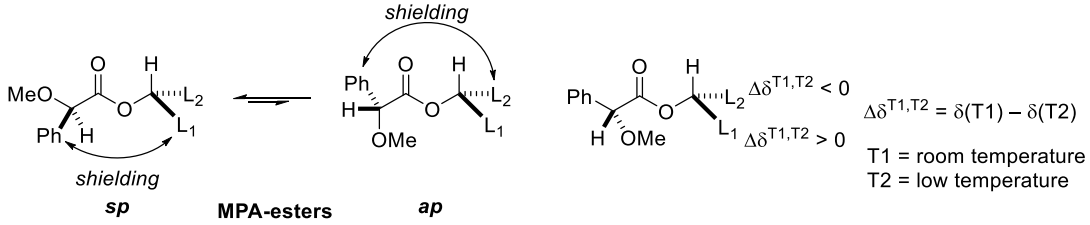


Figure 8 Determination of absolute configuration based on one MPA-ester derivative.

The predominant conformations of MPA-esters, shown in Figure 8, have been calculated to be the ones with αC–OMe being situated *synperiplanar* (***sp***) or *antiperplanar* (***ap***) to the carbonyl group with ***sp*** being the lowest energy conformer.[132,133] The chemical shifts observed for L_1 and L_2 are average values depending on the ratio of population in the two conformations. By lowering the temperature, the relative population in the *sp* conformation is increased which results in a net shielding of L_1 and upfield shifting of protons in this moiety, whereas L_2 becomes effectively less shielded. Hence, subtracting the chemical shifts observed at different temperatures, as before, gives information on the spatial arrangements of L_1 and L_2 and thereby also on the absolute configuration of the derivatized secondary alcohol.

The chemical shifts of MTPA-ester **208** were measured at room temperature and at 243 K followed by analysis of the spectral data to arrive at calculated $\Delta\delta^{T1,T2}$ values which corresponded to the C_{24}-methyl group being L_1 and the olefinic protons being situated in L_2. Thus, the absolute configuration at C_{23} was determined to be *S*. Hereby, the authors disclosed the structure of mytilipin B, accounting for all stereochemical details, as shown in Figure 7.

A re-evaluation of the spectral data for mytilipin B and the conclusions made by Ciminiello and Fattorusso on the relative and absolute configuration led to a number of considerations which called for further investigations. Firstly, several aspects related to the use of Mosher ester derivates in this

[131] S. K. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Am. Chem. Soc.* **1998**, *120*, 877.
[132] J. M. Seco, S. Latypov, E. Quiñoá, R. Riguera, *Tetrahedron Lett.* **1994**, *35*, 2921.
[133] S. K. Latypov, J. M. Seco, E. Quinoa, R. Riguera, *J. Org. Chem.* **1995**, *60*, 504.

context require some comments. Notably, treatment of the natural product with (*R*)- or (*S*)-MTPA-chloride and DMAP in pyridine, resulted in tri-MTPA esters **206** and **207** where the primary hydroxyl at C_1 remains unreacted while the adjacent secondary hydroxyl group gets acylated. This highly unusual reactivity might speak for an intriguing three-dimensional folding of the natural product hampering the reaction of the primary alcohol. The comparison of chemical shifts of the two derivatives resulted in the $\Delta\delta^{SR}$ values shown in Figure 9.

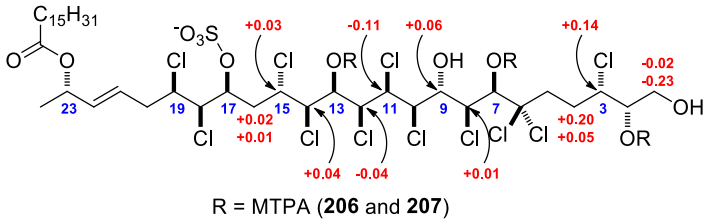


Figure 9 $\Delta\delta^{SR}$ values calculated from proton chemical shifts of **206** and **207**.

The modified Mosher method using MTPA-ester derivatives to establish the absolute configuration of *mono*-alcohols constitutes an important and powerful technique. However, when challenged with the stereochemical assignment of *polyols*, one has to proceed with caution as to exploiting this method. Indeed, many examples with incorrect usage of NMR data for MTPA-esters leading to questionable conclusions have been reported.[134] As the anisotropic effects exerted by the chiral ester derivatives arise from through-space interactions, it is likely, in polyderivatized systems, that the net observed changes are cumulative effects from several of the introduced chemical shift groups.[135]

In general, a set of requirements needs to be fulfilled in order to achieve proper establishment of configuration from derivatized alcohols: 1) the observed $\Delta\delta$ values must be well above the experimental error, 2) all $\Delta\delta$ values must have same sign when arising from protons situated on the same side of the derivatized alcohol, and finally 3) the $\Delta\delta$ must be negative on one side and positive on the other in order to make possible a safe stereochemical assignment. Although mytilipin B contains various hydroxyl sites for potential derivatization, the tri-MTPA esters **206** and **207** obtained by Ciminiello and Fattorusso display good spatial distance between the functionalized sites, i.e. C_2, C_7, and C_{13}. In 2000, Riguera and co-workers studied the *bis*-derivatization of *syn*- and *anti*-(1,2)-, (1,3)-, and (1,4)-diols with arylmethoxy acetic acids (AMAA), such as MPA, to evaluate the combined effects of several anisotropic phenomena.[136] The observations were found to correlate well

[134] J. M. Seco, E. Quiñoá, R. Riguera, *Tetrahedron: Asymmetry* **2000**, *11*, 2781.
[135] For a comprehensive review with a thorough discussion on merits and limitations of various reagents and substrates, see: J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17.
[136] J. M. Seco, M. Martino, E. Quiñoá, R. Riguera, *Org. Lett.* **2000**, *2*, 3261.

to cumulative constructive or destructive anisotropic effects, and hence a successful establishment of the configuration at both hydroxyl-substituted carbons can be achieved simultaneously. In addition, the authors comment that MTPA-esters afford similar results of shielding/deshielding areas, giving rise to similar sign distributions; however, the use of AMAA-esters is preferred over MTPA-esters.

With this in mind, an evaluation of the observed $\Delta\delta^{SR}$ values in Figure 9 made us conclude that the absolute configurations established at C_2, C_7, and C_{13} by Fattorusso and Ciminiello do agree with our independent analysis of the chemical shift data. The sign distributions and values surrounding each of the three derivatized centers are homogeneous which speaks for a safe establishment of configuration. Moreover, the combined anisotropic effects between C_2–C_7, and between C_7–C_{13} should be destructive which is indeed what is observed with no $\Delta\delta$ measured at C_5 and C_{10}.

A second and more rigorous approach to the safe and unambiguous establishment of the absolute configuration of polyols would have been a series of protections/deprotections and *mono*-derivatizations of the polyol in order to assign one configuration at a time; however, in the context of mytilipin B, this may be an improbable task, especially when considering the scarce amount of material isolated (i.e. 6.2 mg).

In an effort to establish the absolute configuration at C_{23}, proton chemical shifts were obtained for MTPA-ester **208** at room temperature and at 243 K. From a comparison of the spectral data, Ciminiello and Fattorusso assigned this stereogenic center to be *S*-configured.[99] Their analysis is based on the assumption that MTPA-esters of secondary alcohols mainly exist as a mixture of two conformations. In analogy to Riguera's work on the determination of absolute configuration based on one MPA-ester derivative,[131] the authors assumed that similar results could be obtained from MTPA-ester **208**. While it has been calculated that MPA-esters exist predominantly as a mixture of the two conformers ***sp*** and ***ap*** shown in Figure 8,[132,133] MTPA-esters are more conformationally flexible, exerting three main conformations, i.e. ***sp1***, ***sp2***, and ***ap1*** as shown in Figure 10, with no notable energy difference.[137] Moreover, it is shown that there is no clear anisotropic effect among lowest energy conformations. Thus, one would expect various degrees of shielding on both sides. This conformational equilibrium is further projected in the relatively small $\Delta\delta$ values usually obtained for MTPA-esters when compared to MPA derivatives. With this in mind it cannot be expected that the relative populations of the individual conformers give rise to a specific preference of shielding/deshielding. These equilibria might result from varying degrees of substrate-dependency arising from steric effects and, to some extent, electronic reasonings. Thus, a clear effect is not

[137] S. K. Latypov, J. M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* **1996**, *61*, 8569.

trivially concluded from theoretical considerations, and hence, it cannot be expected that the outcome of a temperature NMR experiment for an MTPA-ester is analogous to observations for MPA-esters. From these considerations, the use of MTPA-ester **208** as a single derivative to establish the configuration at C_{23} is highly questionable. Given the data presented on the assignment of C_{23}, it cannot be concluded whether the absolute configuration at C_{23} has to be corrected. However, the comparison of spectral data of nominal mytilipin B with the isolation report suggests that this configuration is correctly assigned (Figure 4).

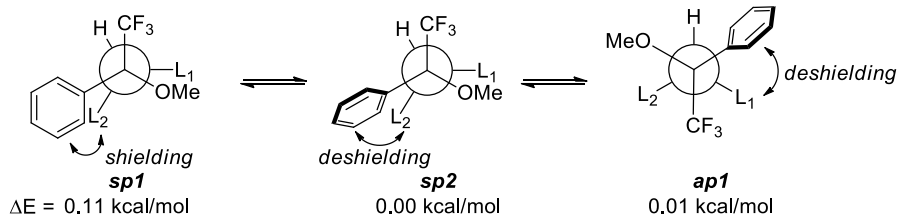
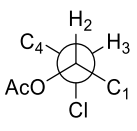
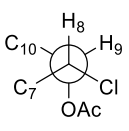
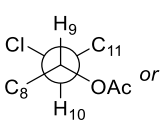
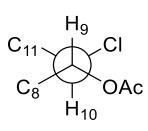
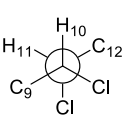


Figure 10 Calculated energy-minimized conformations of (*R*)-MTPA-esters of secondary alcohols with relative energies.

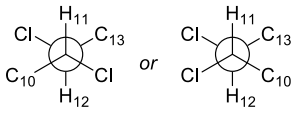
The relative configuration of the C_8–C_{19} part of the hydrocarbon backbone was established using Murata's JBCA method on the peracetylated natural product (**205**). As described, this method was developed for polyoxygenated systems and so, the homo- and heteronuclear coupling constant values were calibrated to fit such systems; this method was only validated and calibrated for chlorinated systems in 2009 when Carreira *et al*. reported the study of trichlorohexanediols. In other words, at the time of Ciminiello and Fattorusso's structural elucidation of mytilipin B (i.e. in 2002) the JBCA method had not yet been confirmed to provide accurate results for chlorinated entities. Therefore, the structural assignment was then based on inappropriate reference values. As described in Chapter 1.3.2, the publication by Carreira and co-workers demonstrates how JBCA may be successfully applied to organochlorines to establish relative configuration in acyclic systems. However, the coupling constant ranges display slightly different values compared to the polyoxygenated systems (Figure 3), and therefore, a re-evaluation of the isolation data should include a conclusion on the relative configuration based on the reference ^2J and ^3J values for dichlorides and chlorohydrins.

A re-investigation of the homo- and heteronuclear *J* values with categorization and ultimate conclusions on relative configuration is shown in Table 4.

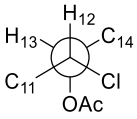
Table 4 Evaluation of ^3J(H,H), ^3J(C,H), and ^2J(C,H) values for **205**; categorizations are given in parentheses: s = small, m = medium, and l = large. The conformational designations refer to the general descriptions in Table 3.

				
A1	***B2***	***B3***	***A3***	***A1***
C_2–C_3	**C_8–C_9**	**C_9–C_{10}**		**C_{10}–C_{11}**

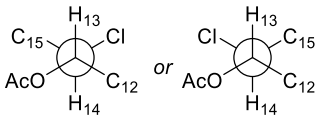
$^3J(H_2,H_3)$	1.8 Hz	(s)	$^3J(H_8,H_9)$	1.8 Hz	(s)	$^3J(H_9,H_{10})$	9.5 Hz	(l)	$^3J(H_{10},H_{11})$	1.6 Hz	(s)
$^3J(H_2,C_4)$	1.3 Hz	(s)	$^3J(H_8,C_{10})$	3.0 H	(s)	$^3J(H_9,C_{11})$	2.7 Hz	(s)	$^3J(H_{10},C_{12})$	0 Hz	(s)
$^3J(H_3,C_1)$	0 Hz	(s)	$^3J(H_9,C_7)$	7.0 Hz	(l)	$^3J(H_{10},C_8)$	2.4 Hz	(s)	$^3J(H_{11},C_9)$	0 Hz	(s)
$^2J(H_2,C_3)$	0 Hz	(s)	$^2J(H_8,C_9)$	-2.1 Hz	(m)	$^2J(H_9,C_{10})$	-4.6 Hz	(l)	$^2J(H_{10},C_{11})$	-2.2 Hz	(m)
$^2J(H_3,C_2)$	-2.3 Hz	(m)	$^2J(H_9,C_8)$	-4.8 Hz	(l)	$^2J(H_{10},C_9)$	-5.4 Hz	(l)	$^2J(H_{11},C_{10})$	0 Hz	(s)



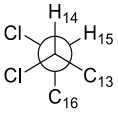
B3 *A3*



A1



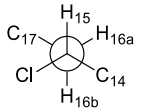
B3 *A3*

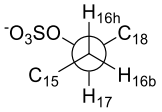


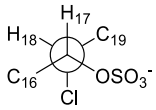
B1

C_{11}–C_{12} **C_{12}–C_{13}** **C_{13}–C_{14}** **C_{14}–C_{15}**

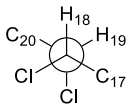
$^3J(H_{11},H_{12})$	8.9 Hz	(l)	$^3J(H_{12},H_{13})$	2.4 Hz	(s)	$^3J(H_{13},H_{14})$	9.7 Hz	(l)	$^3J(H_{14},H_{15})$	2.0 Hz	(s)
$^3J(H_{11},C_{13})$	1.3 Hz	(s)	$^3J(H_{12},C_{14})$	0 Hz	(s)	$^3J(H_{13},C_{15})$	0 Hz	(s)	$^3J(H_{14},C_{16})$	6.1 Hz	(l)
$^3J(H_{12},C_{10})$	2.7 Hz	(s)	$^3J(H_{13},C_{11})$	2.6 Hz	(s)	$^3J(H_{14},C_{12})$	0 Hz	(s)	$^3J(H_{15},C_{13})$	0 Hz	(s)
$^2J(H_{11},C_{12})$	-5.7 Hz	(l)	$^2J(H_{12},C_{13})$	0 Hz	(s)	$^2J(H_{13},C_{14})$	-5.9 Hz	(l)	$^2J(H_{14},C_{15})$	-5.3 Hz	(l)
$^2J(H_{12},C_{11})$	-5.3 Hz	(l)	$^2J(H_{13},C_{12})$	-2.1 Hz	(m)	$^2J(H_{14},C_{13})$	-5.2 Hz	(l)	$^2J(H_{15},C_{14})$	-1.9 Hz	(m)







A1

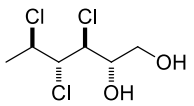


A1

C_{15}–C_{16} **C_{16}–C_{17}** **C_{17}–C_{18}** **C_{18}–C_{19}**

$^3J(H_{15},H_{16a})$	1.1 Hz	(s)	$^3J(H_{16b},H_{17})$	3.3 Hz	(s)	$^3J(H_{17},H_{18})$	1.2 Hz	(s)	$^3J(H_{18},H_{19})$	2.8 Hz	(s)
$^3J(H_{15},H_{16b})$	9.6 Hz	(l)	$^3J(H_{16a},H_{17})$	9.0 Hz	(l)	$^3J(H_{17},C_{19})$	0 Hz	(s)	$^3J(_{18},C_{20})$	0 Hz	(s)
$^3J(H_{15},C_{17})$	0 Hz	(s)	$^3J(H_{16b},C_{18})$	1.9 Hz	(s)	$^3J(H_{18},C_{16})$	1.3 Hz	(s)	$^3J(H_{19},C_{17})$	0 Hz	(s)
$^3J(H_{16b},C_{14})$	1.3 Hz	(s)	$^3J(H_{17},C_{15})$	0 Hz	(s)	$^2J(H_{17},C_{18})$	-2.2 Hz		$^2J(H_{18},C_{19})$	-1.2 Hz	(m)
$^3J(H_{16a},C_{14})$	0 Hz	(s)	$^3J(H_{16a},C_{18})$	0 Hz	(s)	$^2J(H_{18},C_{17})$	0 Hz	(s)	$^2J(H_{19},C_{18})$	-0.8 Hz	(m)
$^2J(H_{16b},C_{15})$	-5.0 Hz	(l)	$^2J(H_{16b},C_{17})$	-2.2 Hz	(m)						
$^2J(H_{16a},C_{15})$	-2.3 Hz	(m)	$^2J(H_{16a},C_{17})$	-4.8 Hz	(l)						

As it became evident during our analysis, a number of the observed heteronuclear ^2J values falls in between the categories ‘small’ and ‘large’, thus designated ‘medium’. Murata presented this as a sign of more than one dominant conformer rapidly interconverting.[103] When this is the case, three or more of the measured coupling constants will display intermediate values. However, in our analysis, the medium values are isolated cases which are scattered over various systems. Thus, the observation of these odd-sized values may not be attributed to equilibria of conformers, rather a slight distortion from the ideal staggered conformations. Hence, our analysis is carried out under the assumption that the medium values can be interpreted as ‘small’.



211

In the context of these observations, it is worth mentioning that Carreira and co-workers reported a rather large variation in *J* values from measurements in different solvents.[104] For example, when the homo- and heteronuclear coupling constants for trichlorohexanediol **211** were measured in $CDCl_3$, CD_3OD, and $(CD_3)_2SO$, the ^2J(H,C) values for the same connectivity were found to span a range of more than 2 Hz in the most extreme case. While the reference *J* values compiled for vicinal dichlorides and chlorohydrins primarily are based on measurements in $CDCl_3$ (with a few exceptions of measurements in acetone−d_6 or THF−d_8), the spectral data from the isolation report are obtained in acetone−d_6. Therefore, it is reasonable to assume that some deviations in the observed coupling constants might arise. With this in mind, we feel confident that the isolated cases of medium-sized ^2J(H,C) values do not result in ambiguous conclusions with respect to the relative configuration at the stereogenic centers in question.

In analogy to the analysis made by Ciminiello and Fattorusso, in our re-examination of the *J* values, we arrived at three cases where the observation of a large ^3J(H,H) values point to either ***A3*** or ***B3*** as the dominant conformation, i.e. C_9/C_{10}, C_{11}/C_{12}, and C_{13}/C_{14}. Hence, the relative configurations cannot be determined based solely on the extracted coupling constants, and therefore, it is necessary to assess ROESY data in addition. Identification of the relevant ROE cross peak sections made possible the establishment of the three relative configurations, as shown in Figure 11. A strong ROE signal between H_{10}/H_{13} clearly indicates that the ***A3*** conformer is dominant along C_{11}/C_{12}. The absence of ROE signals between H_8/H_{11} and H_{12}/H_{15} strongly suggests that the ***B3*** conformation is dominant along C_9/C_{10} and C_{13}/C_{14}, respectively. Interestingly, the relative configuration between C_{13}/C_{14} was assigned to be *syn* by the isolation group, based on the observation of an ROE signal. In our hands, this signal is not observed, as clearly seen in Figure 11, and thus, the relationship between C_{13}/C_{14} has to be reassigned to *anti*. It should be noted that a small artefact is present in one of the two cross peak regions of H_{12}/H_{15}. However, when compared to the intensity of the clear signal between C_{10}/C_{13}, this point can be disregarded as a cross peak.

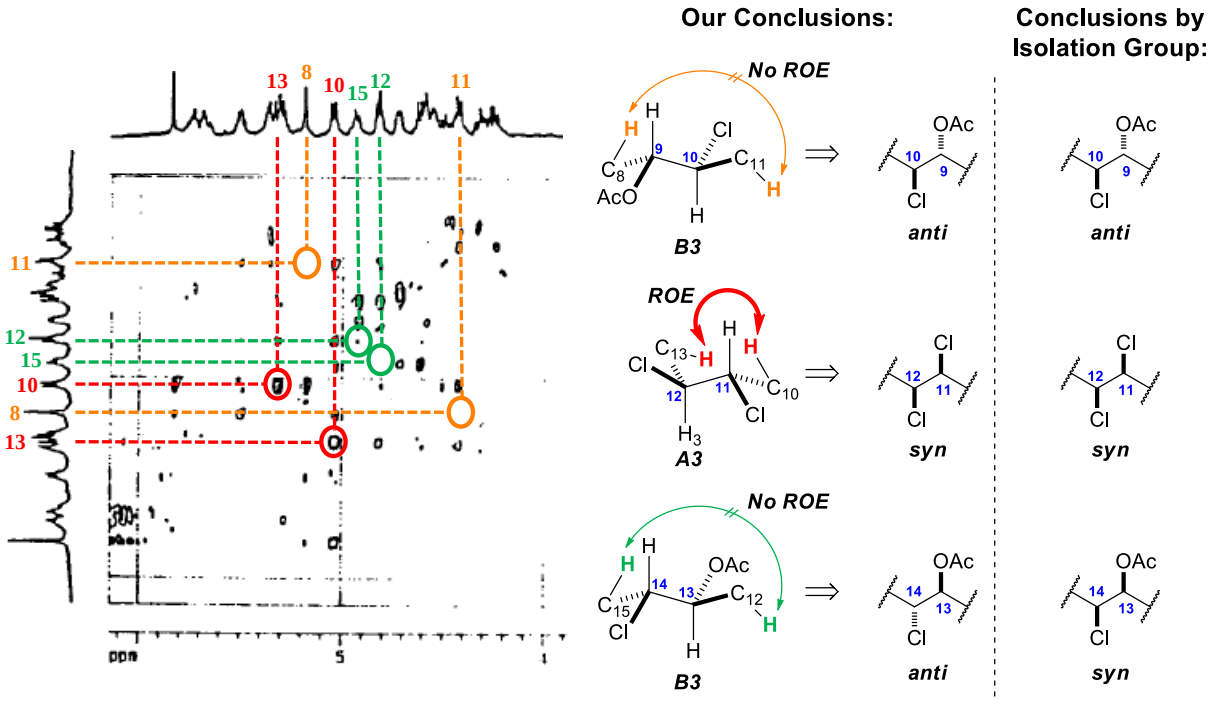


Figure 11 Indication of the presence/absence of relevant cross peaks in the ROESY spectrum of **205** and conclusions thereof. The spectrum is obtained from the supporting information of the isolation report.[99]

Combining the analysis of the extracted data from the ROESY spectrum with the examination of the *J* values, the structure of mytilipin B, with complete stereochemical information, is assigned to be as shown with structure **212** in Figure 12. It should be noted that the absence of the ROE signal not only results in a change of configuration at C_{14}, but effectively results in change of absolute configurations at the five stereogenic centers from C_{14}–C_{19} (Figure 12, highlighted with red frames).

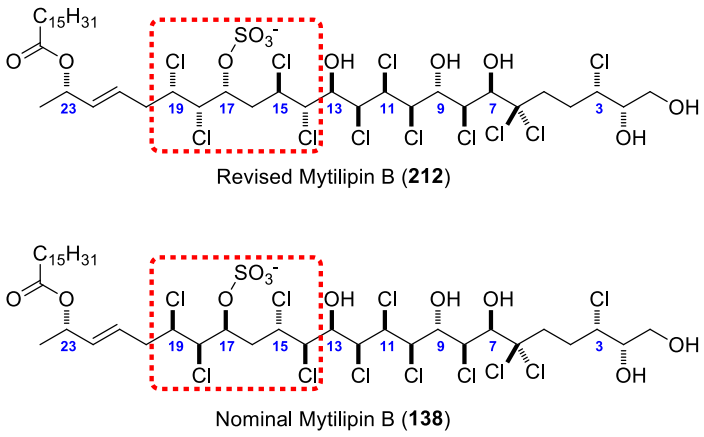


Figure 12 Structure of revised and nominal mytilipin B. The red boxes indicate the stereogenic centers which have been re-assigned.

The eventual re-assignment of five stereogenic centers based on one change in relative configuration arises from the JBCA in Table 4. On the basis of the JBCA, the configurations at C_{14}–C_{19} are ultimately assigned relative to C_{13} which was assigned to have absolute configuration (*R*) by Mosher ester analysis. Thus, correcting the absolute configuration at C_{14} to fulfil the C_{13}/C_{14} *anti*-relationship

effectively results in the correction of the absolute configurations of all five stereogenic centers from C_{14} to C_{19}.

It should be noted that the absolute configuration at C_{23} is intentionally unchanged with respect to the first proposed structure of mytilipin B. From the discussion on the assignment of absolute configuration using a single MTPA-ester derivative **208** (*vide supra*), a correction to (*R*)−configuration at C_{23} is equally plausible to the originally assigned (*S*)-configuration. However, spectral comparison in Figure 4 suggest the assigned (*S*)−configuration at C_{23} be in agreement with the natural product. Hence, at this point it was decided to leave this configuration unchanged.

2.2 Structural Reflections

The JBCA does not only give information on the relative configuration. In fact, the primary observation is the dominant conformation in solution.[103,104] Compiling the Newman projections in Table 4 into a full picture reveals an interesting change in conformation after revsion, as shown in Figure 13. While the nominal structure (A) displays the three hydroxyl groups at C_7, C_9, and C_{13} in the same direction, the C_{17}-sulfate is pointing in the complete opposite direction. This makes the overall structure fairly disordered with the polar groups scattered over the surface. In contrast, the revised structure (B) makes for a conformational change where the sulfate group is spatially positioned on the same side as the three hydroxyl groups in the core part of the hydrocarbon chain. This induces a more clear picture of the order, with a hydrophilic pocket made from the C_7–C_{17} region. In addition, this change results in a more pronounced polar end, giving the surface a closer resemblance to classic lipid structures.

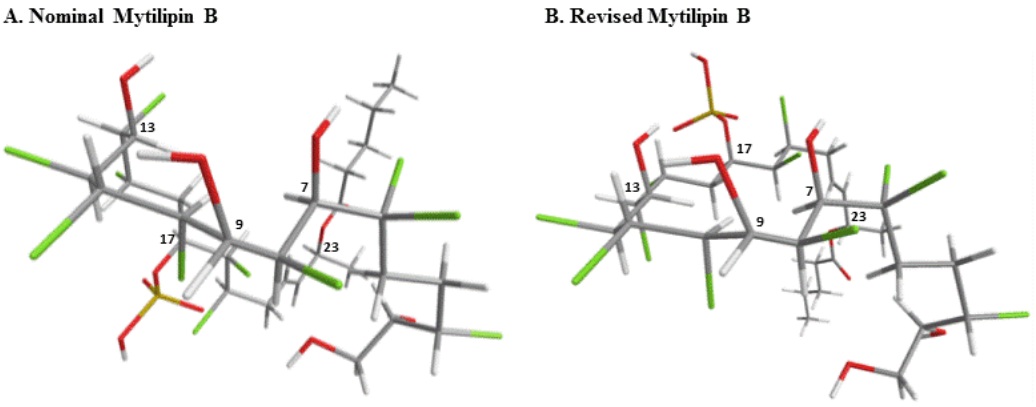


Figure 13 Predominant conformations of nominal (**A**) and revised (**B**) mytilipin B. The palmitoyl side chains have been abbreviated to *n*-pentanoates for clarity.

Not surprisingly, the overall conformation arises from the structure being able to benefit from a high number of *gauche* effects in the vicinal chlorohydrin and dichloride systems.[138] It is noteworthy that in a few cases, i.e. between C_9/C_{10} and C_{13}/C_{14}, an *anti*-relationship between the polar groups is observed (Table 4). It might be speculated that these preferences are attributed to the avoidance of more severe *syn*-pentane like interactions. It should be noted, however, that a *syn*-pentane like interaction between C_{17}-sulfate and C_{19}-chloride is present. At this point, it is unclear why this is preferred.

[138] For a discussion of the stereochemical consequences of the *gauche* effect, see: a) S. Wolfe, *Acc. Chem. Res.* **1972**, *5*, 102; b) L. Phillips, V. Wray, *J. Chem. Soc., Chem. Commun.* **1973**, 90.

When comparing the revised structure to other members of the chlorosulfolipid family, some interesting additional observations were found. In Figure 14, selected members are shown with highlighted similarities.

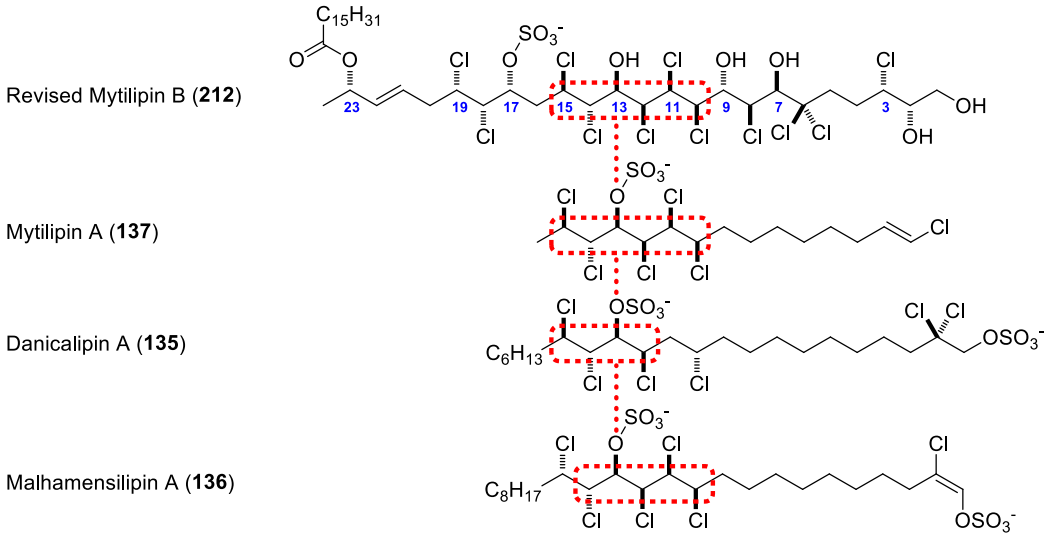


Figure 14 Comparison of structures of selected chlorosulfolipids.

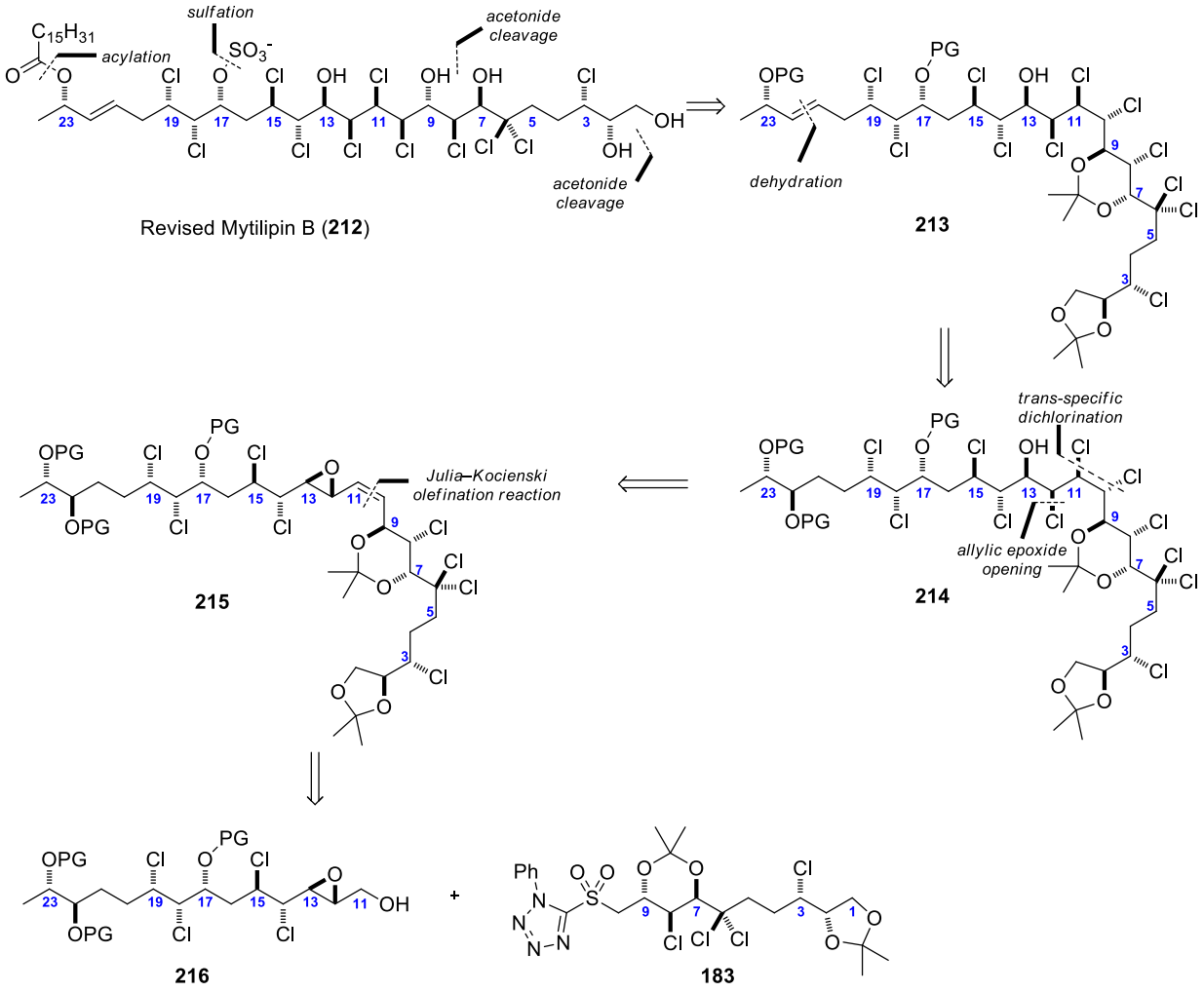
The stereochemical array of six contiguous chiral carbon atoms in mytilipin A (**137**), centered around a sulfate moiety, allows for the natural product to adopt a specific conformation which presumably constitutes a key property to the biological significance. The absolute and relative configurations of mytilipin A have been confirmed by total synthesis. Interestingly, after revising the structure of mytilipin B (**212**), the C_{10}–C_{15} 1,2,4,5,6-pentachloro-3-hydroxyhexyl subunit resembles the stereochemical array present in mytilipin A. Both chlorosulfolipids mytilipin A and B were isolated from the same natural source, the digestive glands of *Mytilus galloprovincialis*. Although, it is unknown which alga is producing these lipids, given the isolation, it is reasonable to assume that they are produced in the same organism *via* very similar biosynthetic mechanisms. This suggests that the stereochemical details logically would resemble one another. In addition, the stereohexad present in mytilipin A cannot be recognized anywhere in the structure of nominal mytilipin B, thus strongly supporting the notion that this particular structural revision indeed leads to the natural diastereomer of mytilipin B.

In addition to mytilipin A, a similar structural feature is also observed in other chlorosulfolipids, such as danicalipin A (**135**) and malhamensilipin A (**136**). Although, the latter naturally occurring chlorosulfolipids were isolated from differenct sources, it is reasonable to think, that the enzymes and overall biosynthetic pathways to produce various members of this product class resemble one another, and thus, the observation of these structural fingerprints in various members strongly supports the structural revision.

With these considerations in mind, we feel confident that the re-investigation of the isolation data in combination with the structural reflections have directed us to a very plausible proposal for a structural revision of mytilipin B. In the following, a description and discussion on the synthetic strategy to overcome the challenges to access revised mytilipin B will be provided.

3 Synthetic Strategy

We envisioned to access mytilipin B *via* union of the almost equally sized fragments **216** and **183**, as this strategy had proven to be successful in the synthesis of nominal mytilipin B (Scheme 32).[125] It is worth noting that the synthesis of nominal mytilipin B relied on a coupling between C_{10} and C_{11}. Since the revised stereogenic centers C_{14}–C_{19} are all placed on the same side of this coupling point it was anticipated that parts of the previous synthesis could be used advantageously in a new strategy.



Scheme 32 Retrosynthetic strategy for revised mytilipin B, Part I.

In a retrosynthetic sense, we thought to liberate the polar groups at a late stage; hence, the natural product could arise from **213** *via* sulfation of the C_{17}–OH and cleavage of various protecting groups. Furthermore, the palmitoyl ester at C_{23} was thought to be introduced in the end-game by acylation of the C_{23} allylic alcohol. At this point, it is worth noting that we opted for selective acylation and

sulfation in the presence of a free C_{13}–OH. We reasoned that this alcohol would not interfere, and high selectivity was assumed, as this alcohol, is believed to be very sterically hindered. This notion is also built on knowledge from the previous synthesis.

Due to the use of olefins as convienient precursors for vicinal dichlorides, the C_{21}/C_{22} *trans*−olefin should be installed late in the synthesis. This was thought to be realized by a selective dehydration from protected 1,2-diol **214**. Furthermore, it is worth noting that in the event of a correction of configuration at C_{23} would be deemed necessary, this could be facilitated late stage, either from **213** or **214**.

To successfully implement the strategy of uniting two fragments, a coupling point needed to be incorporated. Going backwards, a strategic dichlorination at C_{10}/C_{11} would introduce an olefin in **214** which would allow for a handle to perform this unification.

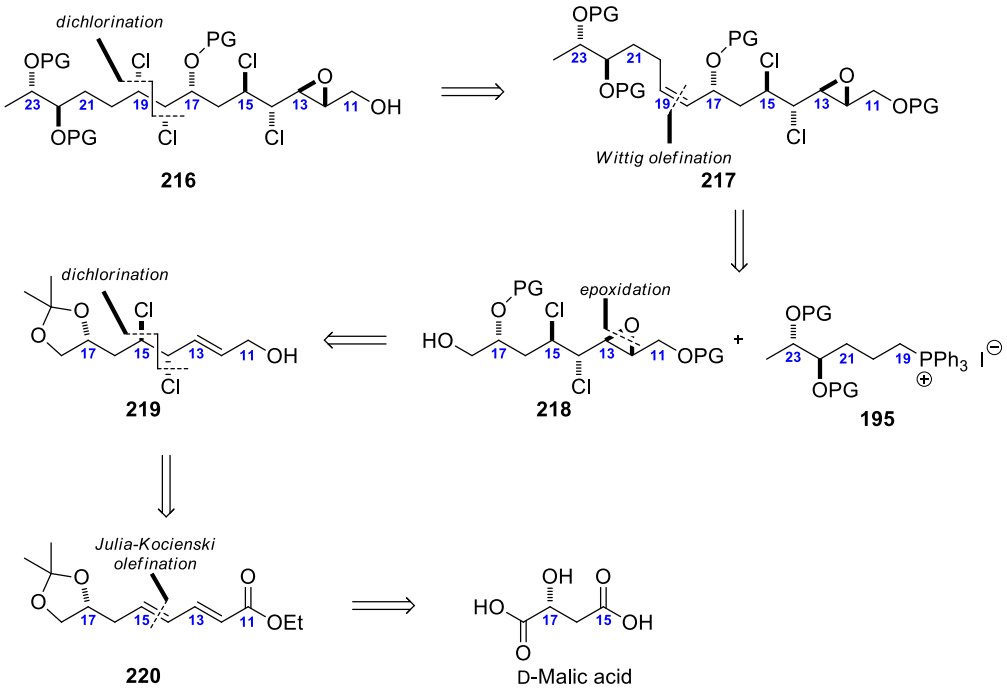
In this context, it should be mentioned that the configurations of the stereogenic centers C_7–C_9 and C_{12}/C_{13} surrounding the double bond display same configurations as in the synthesis of nominal mytilipin B. Therefore, similar selectivity is presumed to be observed in the dichlorination.

In addition, the adjacent chlorohydrin could conveniently be realized from an epoxide opening, thus overall tracing **214** back to **215**. It is noted that the *trans*-epoxide would have to be opened with retention in order to obtain the desired configuration at C_{12}. This strategy was intentionally implemented, considering the opening of a similar allylic epoxide **147** in the synthesis of mytilipin A by Carreira *et al.* (see Chapter 1.3.4.1). Based on this known reactivity, it is expected that a similar result can be obtained in the opening of epoxide **215**.

A *Z*-selective olefination reaction to complete the hydrocarbon backbone would result in the desired compound **215**. In this respect, it was thought that a Julia–Kocienski olefination reaction between the aldehyde arising from oxidation of **216** and sulfone **183** would successfully afford the desired intermediate **215**.

The sulfone **183** was prepared and used in the synthesis of nominal mytilipin B, and thus, the synthesis of this fragment is well documented and it could conveniently be prepared mainly based on the reported protocols. Only minor changes and improvements proved necessary to obtain this intermediate; these will be discussed in the following chapter.

The retrosynthetic analysis of epoxyalcohol **216** is outlined in Scheme 33.



Scheme 33 Retrosynthetic strategy for C_{11}–C_{24} fragment **216**.

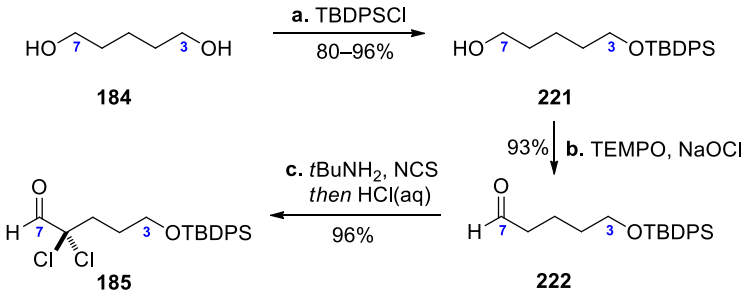
The *syn*,*syn*-stereotriad at C_{17}–C_{19} in **216** could arise from a stereoselective dichlorination of *cis*-allylic TBS-ether **217** in agreement with the report by Vanderwal *et al*.[54] Inspired by the synthesis of nominal mytilipin B, the C_{19}–C_{24} part of the backbone was thought to be introduced by the documented phosphonium ylide precursor **195**.[125] Installation of the *trans*-epoxide in the corresponding aldehyde precursor **218** would conveniently be obtained from the allylic alcohol **219** which then allowed for the use of reagent-controlled epoxidation methods. The enantiomer of allylic alcohol **219** served as an intermediate in the synthesis of nominal mytilipin B, and thus, preparation of this fragment could be realized starting from chiral pool starting material, D-malic acid.

4 Towards Revised Mytilipin B

4.1 Synthesis of C_1–C_{10} Sulfone Fragment

As mentioned in the previous chapter, the C_1–C_{10} sulfone fragment **183** was prepared and used in the synthesis of nominal mytilipin B, **138**.[125] Therefore, its preparation followed the already published route (see Chapter 1.3.4.3),[105] however, some additional observations and a few alternatives are worth mentioning. [139]

The synthesis commenced with the preparation of α,α-dichloroaldehyde **185** in three steps from 1,5-pentanediol according to the previously reported procedures (Scheme 34).[125] The *mono*-TBDPS protection was carried out employing ten-fold excess of pentanediol and using TBDPSCl as the limiting reagent, according to the procedure by Negishi and Gangguo.[140] Although this procedure yields a near quantitative amount of the *mono*-TBDPS ether **221**, the excess pentanediol hampers purification which, especially considering the large scale of the early steps in the synthesis, makes the practical execution of the reaction somewhat tiresome. Hence, it was tested whether the procedure of *mono*-anion formation with sodium hydride[141] would result in similar yields but ease the purification process. Thus, treating 1,5-pentanediol with one equivalent of sodium hydride followed by one equivalent of TBDPSCl resulted in isolation of the *mono*-protected diol in 80% yield. Although the crude product after aqueous work-up was nearly free of impurities, as judged by ^{1}H NMR, the diminished yield did not make it worth resorting to this procedure.



[139] Dr. Matthew Webster and Philipp Sondermann are greatly acknowledged for their support on scale up of this fragment.
[140] G. Zhu, E.-i. Negishi, *Org. Lett.* **2007**, *9*, 2771.
[141] P. G. McDougal, J. G. Rico, Y. I. Oh, B. D. Condon, *J. Org. Chem.* **1986**, *51*, 3388.

Scheme 34 Reagents and conditions: a. TBDPSCl, **184** (10 equiv), imidazole, DMF, 0 °C to r.t., 96% *or* **184**, NaH (1.0 equiv), THF, r.t. *then* TBDPSCl, 80%; b. TEMPO, KBr, NaOCl(aq), CH_2Cl_2, 0 °C, 93%; c. *t*-$BuNH_2$, NCS, CCl_4, 0 °C to r.t. *then* HCl(aq), 96%.

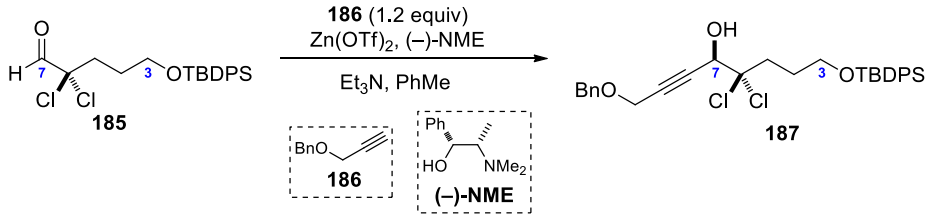
Preparation of α,α-dichloroaldehyde **185** was accomplished by TEMPO-catalyzed oxidation of the primary alcohol **221** to aldehyde **222** followed by dichlorination *via* the *t*-butyl enamine, as reported by Kimpe and co-workers in 1975.[126]

Next, the stage was set for defining the first stereogenic center with an asymmetric alkyne addition to aldehyde **185** (Table 5). Several successful methods to add an alkyne to an aldehyde in an enantioselective fashion have been reported,[142,143] however, R. Geisser found that only the method reported in house by Carreira and co-workers[144] afforded an acceptable yield and enantioselectivity when α,α-dichloroaldehydes were employed.[105]

As reported in the synthesis of nominal mytilipin B, this reaction proceeded well, however, a successful outcome seemed to be highly dependent on several factors. Most notably, the batch of zinc(II) triflate employed (not supplier-dependent) and also the reaction batch size were critical factors. Unfortunately, the success of the reaction was only revealed after addition of the dichloroaldehyde and could not be predicted upon the premixing to form the active Zn-acetylide. Therefore, since the aldehyde could not be re-isolated and purified from the reaction mixture due to instability on silica gel, it proved to be of utmost importance to test the specific batch of zinc(II) triflate on a small scale and then stepwise scale the reaction set-up to the desired size in order to ensure a reproducible outcome.

[142] R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760.
[143] B. M. Trost, A. H. Weiss, A. Jacobi von Wangelin, *J. Am. Chem. Soc.* **2006**, *128*, 8.
[144] D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806.

Table 5 Asymmetric alkyne-addition to α,α-dichloroaldehyde **185**

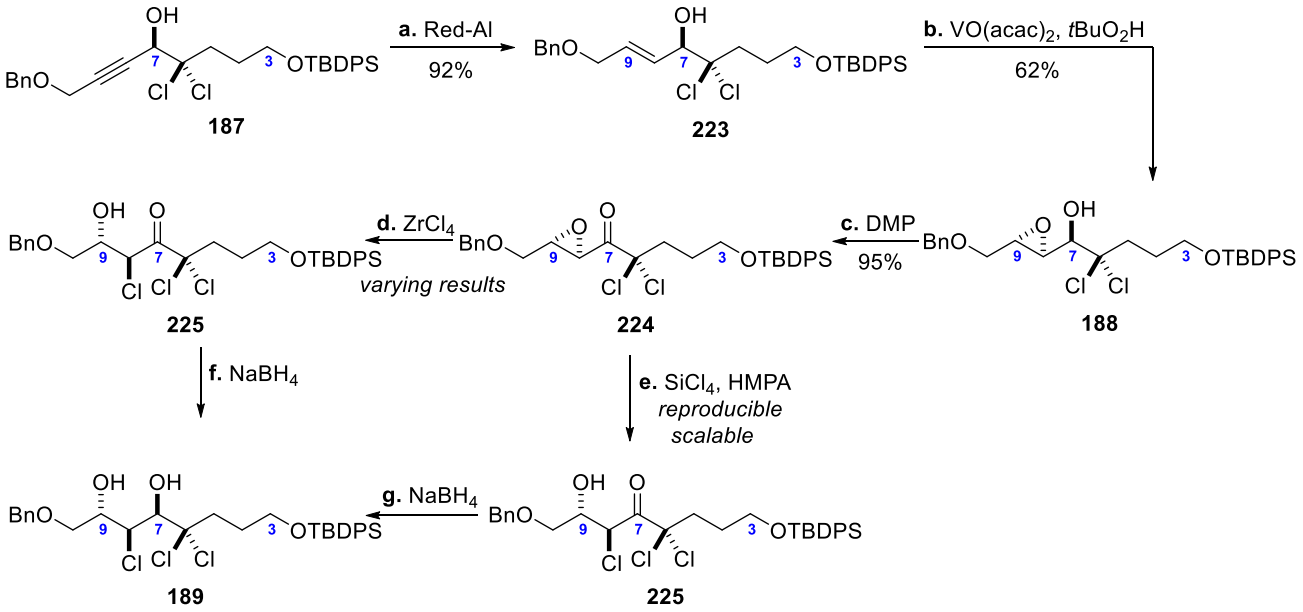


$Zn(OTf)_2$ (equiv)	(–)-NME (equiv)	Et_3N (equiv)	conditions	yield (%)	*ee* (%)
1.1	1.2	1.2	0.3 M in PhMe, r.t.	70%	92%
0.20	0.22	0.50	1 M in PhMe, 60 °C	< 5%	-
0.50	0.55	1.2	1 M in PhMe, 60 °C	< 5%	-

As an extension to the publication of the asymmetric zinc-acetylide addition to aldehydes, Carreira and Anand reported a catalytic version in 2001.[145] In effort to evaluate the critical amount of $Zn(OTf)_2$ and (–)-*N*-methylephedrine to facilitate formation of **187**, the use of catalytic amouns were tested (Table 5). Unfortunately, it was found that only the stoichiometric version afforded the product in acceptable yields whereas the catalytic versions only led to traces of product together with unreacted starting material.

Following the introduction of C_8–C_{10} *via* alkyne addition, the two-step reduction/epoxidation redox sequence to give **188** proceeded uneventfully as described prior to the present work (Scheme 35).[125] Hereafter, oxidation to α,β-epoxyketone **224** allowed for the epoxide-opening with $ZrCl_4$ to give α-chloro-β-hydroxyketone **225**. While opening with $ZrCl_4$ did afford the desired product on a 100 mg reaction scale, the same conditions, however, led to complete decomposition of the starting material when scaled to larger reaction batches.[146] In addition, further investigations revealed that even when conducted on the same scale, the reaction was not always reproducible. Thus, at this point, investments in the development of alternative conditions which would afford reproducible results were deemed highly desirable.

[145] N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687.
[146] The observations on irreproducibility and the experimental work described to develop reliable and scalable conditions to open epoxyketone **224**, affording **225**, was conducted solely by Dr. Matthew Webster.



Scheme 35 Reagents and conditions: a. Red-Al, THF, –78 °C to r.t., 92%; b. $VO(acac)_2$, *t*BuO_2H, CH_2Cl_2, 0 °C to r.t., 62%; c. DMP, CH_2Cl_2, 0 °C to r.t., 95%; d. $ZrCl_4$, CH_2Cl_2, 0 °C to r.t.; e. $SiCl_4$, HMPA, CH_2Cl_2; f. $NaBH_4$, MeOH, –78 °C, 36% from **224**; g. $NaBH_4$, MeOH, –78 °C, 55% from **224**.

In 1998, Denmark and co-workers published a work on epoxide openings with silicon tetrachloride employing phosphoramides as Lewis base catalysts.[147] Based on their work, it was thought that silicon tetrachloride in combination with hexamethylphosphoramide (HMPA) might facilitate the desired opening. In Figure 15, it is shown how HMPA functions as a nucleophilic activator, resulting in a more electrophilic silylating agent.

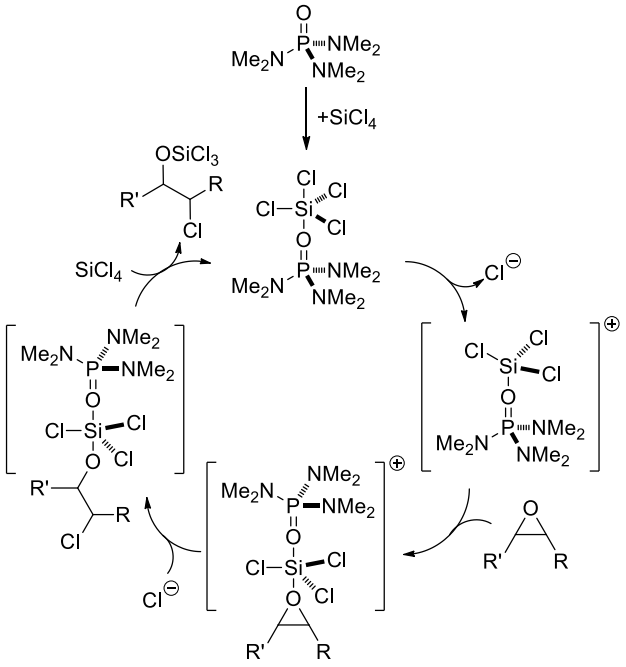


Figure 15 Proposed mechanism for the epoxide opening with HMPA and $SiCl_4$.

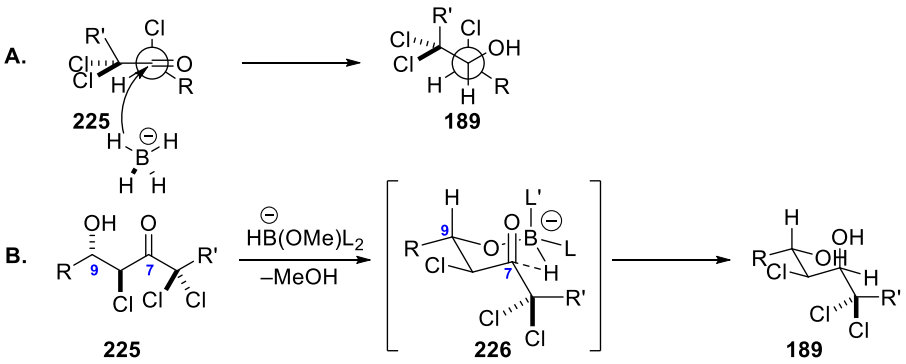
[147] S. E. Denmark, P. A. Barsanti, K.-T. Wong, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 2428.

Thus, after some experimentation, we were pleased to find that treatment of **224** with epoxide-opening conditions employing HMPA as a Lewis base catalyst resulted in the desired product **225** with full reproducibility. Moreover, the procedure has proven robust to scaling.

With a reproducible procedure for the conversion of **224** into **225** developed, the stereochemical triad at C_7–C_9 could be completed *via* reduction with sodium borohydride.

With regard to the practical execution of this reduction, it proved critical for a successful outcome to premix sodium borohydride with methanol and let it stir for fifteen minutes prior to cooling the reaction mixture to cryogenic temperatures. If this was ignored, the reaction did not proceed. This criteria for success is most likely attributed to the rapid formation of methoxy-borohydrides at room temperature which are more soluble in methanol than the parent sodium borohydride.[148] Thus, when the mixture was cooled prematurely, the solubility of the reductants might be too low resulting in sluggish reaction.

Although only a modest yield of *trans*-1,3-diol **189** was obtained, none of the corresponding *cis*-1,3-diol was observed. This high diastereoselectivity is in full agreement with a polar Felkin−Anh transition state model in which the C_8–Cl bond adopts an orthogonal orientation with respect to the C=O bond, and the nucleophilic attack takes place from the less congested *Si* face (Scheme 36A).

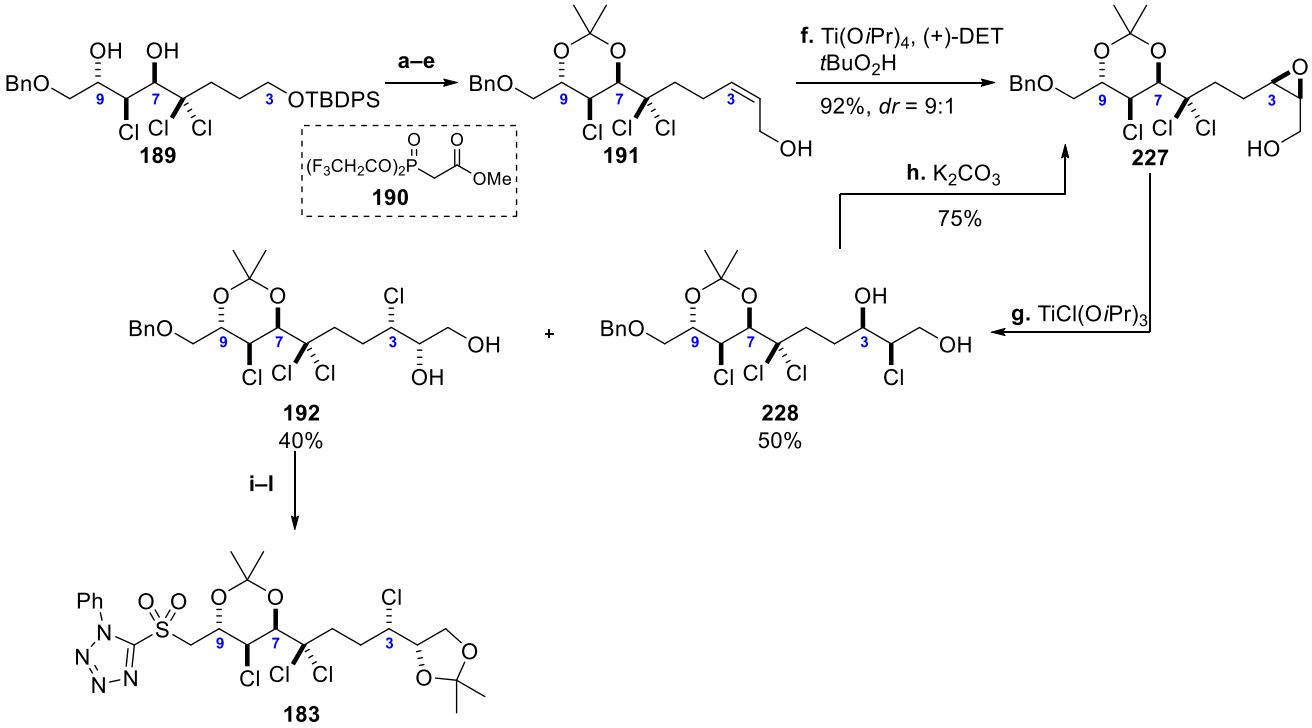


Scheme 36 Rationale for the observed diastereoselectivity in reduction of **225**. **A.** A reasonable polar Felkin-Anh, and **B.** Proposed intramolecular hydride delivery.

In addition, the preformation of methoxy-borohydrides may lead to alkoxy-exchange on boron with the substrate **225** to give **226**, resulting in an intramolecular delivery of a hydride *via* a six-membered transition state, as suggested in the reduction of β-hydroxyketones with $Me_4NBH(OAc)_3$ (Scheme 36B).[149] This notion would further enforce the high diastereoselectivity in a matched case of double diastereodifferentiation.

[148] H. C. Brown, E. J. Mead, B. C. Subba Rao, *J. Am. Chem. Soc.* **1955**, *77*, 6209 and references herein.
[149] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.

The completion of sulfone fragment **183**, according to previously reported procedures, is outlined in Scheme 37. As expected, the opening of epoxide **227** with $TiCl(OiPr)_3$ only resulted in the desired product **192** as the minor component whereas the major product arose from the opening at C_2 (**228**). As reported by R. Geisser, other metal chlorides did not give better yield of the desired product.[105] Attempts at employing $Ti(OiPr)_4$ in combination with secondary and tertiary amine hydrochloride salts (i.e. Et_2NH_2Cl, Et_3NHCl) to furnish the transformation were conducted, however, no better conditions could be identified.[150,151] Fortunately, it was found that treatment of the undesired regioisomer **228** with potassium carbonate in methanol at room temperature resulted in the re-closure of the epoxide to give **227** in 75% yield.

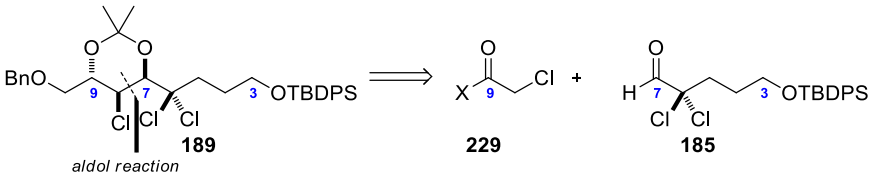


Scheme 37 Reagents and conditions: ; a. 2-methoxypropene, PPTS, CH_2Cl_2, 0 °C to r.t., 93%; b. TBAF, AcOH, DMF, 95%; c. DMP, CH_2Cl_2, 0 °C to r.t.; d. **190**, KHMDS, THF, –78 °C, 68% over two steps; e. DIBAL-H, THF, –78 °C, 88%; f. $Ti(OiPr)_4$, *t*-BuO_2H, (+)-DET, CH_2Cl_2, –20 °C, 92% *dr* = 9:1; g. TiCl(OiPr)3, C_6H_6, 40%; h K_2CO_3, MeOH, 75%; i. $CuSO_4$, TsOH, acetone, 83%; j. Pd/C, H_2, EtOAc, 94%; k. 1-phenyl-1H-tetrazole-5-thiol, DIAD, PPh_3, THF, 0 °C to r.t., 85%; l. *m*CPBA, 0 °C to 40 °C, 61%.

The described strategy to access sulfone **183** relies on asymmetric alkyne-addition followed by several manipulations of the alkyne to achieve the C_7–C_9 2-chloro-1,3-diol substitution pattern (*vide*

[150] $Ti(OiPr)_4/Et_2NH_2Cl$ was successfully employed by Overman to open a *cis*-hydroxymethylene-epoxide preferentially in the 3-position, see: L. E. Overman, A. S. Thompson, *J. Am. Chem. Soc.* **1988**, *110*, 2248.
[151] $Ti(OiPr)_4/Et_3NHCl$ was successfully employed by Jäger to open a *cis*-hydroxymethylene-epoxide preferentially in the 3-position, see: V. Jäger, U. Stahl, W. Hümmer, *Synthesis* **1991**, *1991*, 776.

supra). As an alternative approach, it was recognized that the 1,3-diol system may be assembled *via* construction of the C_7–C_8 bond in an aldol reaction (Scheme 38).

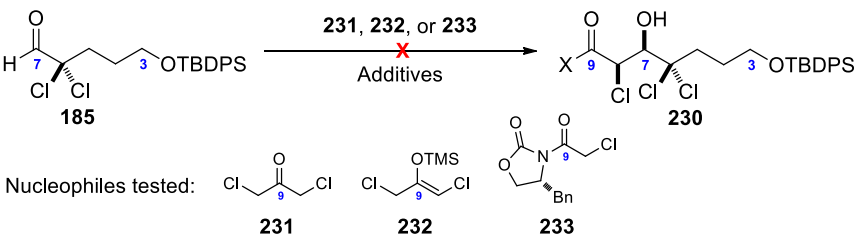


Scheme 38 Alternative retrosynthetic strategy for 1,3-diol **189**.

Thus, protected 1,3-diol **189** could be traced back to aldehyde **185**, already in hand, and an enolate precursor (**229**). At best, the nucleophilic enolate precursor would already contain C_{10} so that extra steps to introduce this carbon could be omitted.

Initially, we decided to test whether 1,3-dichloroacetone (**231**) would undergo an aldol reaction with aldehyde **185** (Scheme 39). If successful, this approach would constitute a significant advancement in terms of targeting the 2-chloro-1,3-diol system. Firstly, all carbons would be in place, and secondly, the primary chloride at C_{10} in the product would allow for direct functionalization to arrive at the sulfone. Although an intriguing approach, the use of 1,3-dichloroacetone as an enol-equivalent in aldol reaction has, to the best of our knowledge, never been documented.

Several attempts to form the boron- (with *n*-Bu_2BOTf , 9-BBN-OTf, or Ipc_2BOTf) and tin enolates (with $Sn(OTf)_2$) and reacting these with the aldehyde were conducted, however, only starting material and none of the desired product was observed. Our attention was then directed towards a Mukaiyama aldol approach employing silyl enol ether **232** as a nucleophile. Treatment of a mixture of **232**[152] and aldehyde **185** with various Lewis acids, including $SnCl_4$, $TiCl_4$, $Sn(OTf)_2$, and $BF_3{\cdot}OEt_2$, also returned with no success, and when the reaction temperatures were increased, only decomposition was observed. This led us to believe that, due to the electron withdrawing α-chlorines, 1,3-dichloroacetone as an enol equivalent in this aldol reaction is lacking sufficient nucleophilicity to undergo addition to aldehyde **185**.



[152] Prepared from 1,3-dichloroacetone according to the following procedure: N. Shimizu, M. Tanaka, Y. Tsuno, *J. Am. Chem. Soc.* **1982**, *104*, 1330.

Scheme 39 Attempted aldol reactions with aldehyde **185**.

After facing these results, we decided to move on to other potential nucleophiles. In this context, the use of a chloro-acetate aldol reaction controlled by Evans oxazolidinone was intriguing.[77] Thus, substrate **233** was prepared and subjected to an aldol reaction with aldehyde **185** under standard Evans aldol conditions (*n*-Bu_2BOTf, DIPEA, CH_2Cl_2). At this point we were pleased to find that the desired aldol-product **230** indeed was observed by crude ^1H NMR of the reaction mixture, albeit only with low conversion (~20%).

Considering the resistance met when following the path of an aldol approach, it was decided to shift focus away from this strategy for the time being and resort to the already developed route to sulfone **183**.

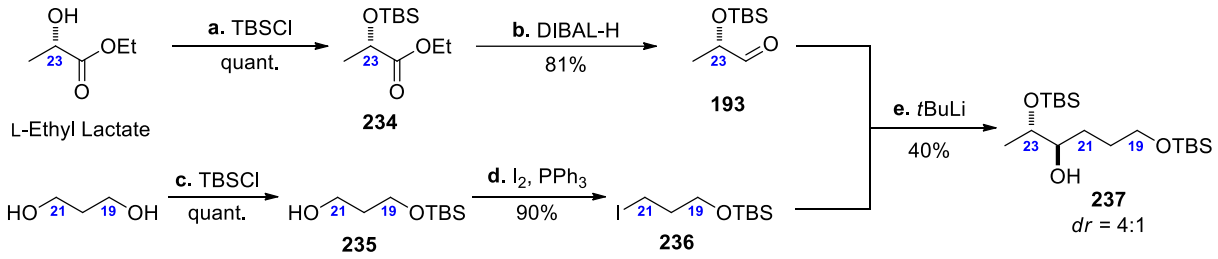
4.2 Synthesis of C_{11}–C_{24} Primary Alcohol Fragment

As presented in Chapter 2.2, fragment **216**, constituting C_{11}–C_{24} of the mytilipin B hydrocarbon backbone, is assembled *via* Wittig reaction. In the following, the syntheses of the Wittig precursors are described, culminating in their union to give the entire C_{11}–C_{24} fragment.

4.2.1 C_{19}–C_{24} Phosphonium Iodide

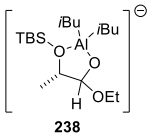
The C_{19}–C_{24} phosphonium iodide was prepared and used in the synthesis of nominal mytilipin B. While these procedures allowed for the preparation of multi-gram quantities of this fragment, additional comments and further optimization studies will be described in the following section.

As outlined in Scheme 40, the synthesis commenced with the preparation of *bis*-TBS-protected triol **237** from L-ethyl lactate and propane-1,3-diol.



Scheme 40 Reagents and conditions: a. TBSCl, imidazole, DMF, 0 °C to r.t., quantitative; b. DIBAL-H, Et_2O, –78 °C, 81%; c. TBSCl, imidazole, DMF, 0 °C to r.t., quantitative; d. I_2, PPh_3, imidazole, benzene, 0 °C *then* MeOH, r.t. *then* silica gel, 90%; e. **236**, *t*BuLi, THF, –78 °C *then* **193**, 40%, *dr* = 4:1.

The preparation of aldehyde **193** proceeded uneventfully *via* TBS-protection followed by DIBAL-H reduction of the ester to directly obtain the desired oxidation state.[153] Interestingly, while excess reducing agent (1.2 equiv) proved necessary to drive the reaction to completion, none of the corresponding alcohol, resulting from over-reduction of **234**, was observed. This may be attributed to the α-oxygentation, facilitating chelation to aluminum in a five-membered tetrahedral intermediate **238** and thus preventing from further reduction by only allowing for collapse into the aldehyde product upon work-up.



238

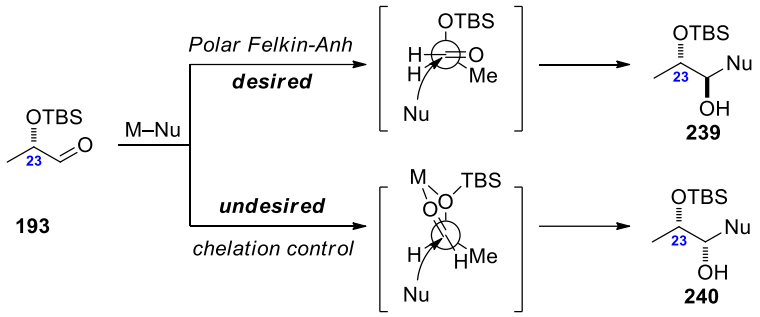
The alkyllithium precursor **236** was prepared from propane-1,3-diol in two steps *via mono*-TBS-protection using ten-fold excess of the diol,[154] followed by Appel reaction with iodine. Using a modified work-up procedure,[155] the excess triphenylphosphine is converted to triphenylphosphine

[153] J. A. Marshall, M. M. Yanik, N. D. Adams, K. C. Ellis, H. R. Chobanian, *Org. Synth.* **2005**, *81*, 157.
[154] C. E. Jakobsche, G. Peris, S. J. Miller, *Angew. Chem. Int. Ed.* **2008**, *47*, 6707.
[155] B.-B. Zeng, Y. Wu, S. Jiang, Q. Yu, Z.-J. Yao, Z.-H. Liu, H.-Y. Li, Y. Li, X.-G. Chen, Y.-L. Wu, *Chem. Eur. J.* **2003**, *9*, 282.

oxide by quenching with methanol and all by-products are removed by simple filtration through silica gel. This ensured the ease of practical execution and rapid production of the alkyl iodide **236**, even on a hectogram scale.

Generation of an alkyllithium reagent from alkyliodide **236** and *tert*-butyllithium followed by slow addition of aldehyde **193** gave the desired secondary alcohol **237** in 40% yield and with 4:1 diastereoselectivity.

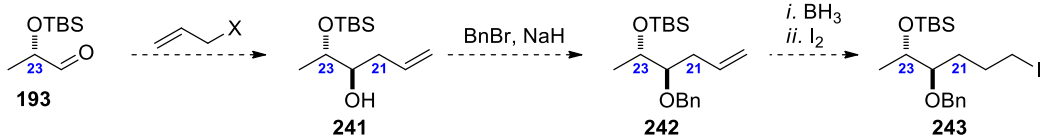
The desired diastereomer arises from addition to the aldehyde in accordance with a polar Felkin-Anh model (Scheme 41). Hence, alignment of the antibonding orbitals $\sigma^*(C_\alpha–OTBS)$ and $\pi^*(C=O)$ in the most reactive conformer to combine to a lower lying LUMO allows for the nucleophilic attack to take place preferentially from the *Re*-face, to give the 1,2-*anti* product **239**.



Scheme 41 Rationale for the stereochemical outcome of addition to aldehyde **193**.

In contrast, the undesired diastereomer, the 1,2-*syn* product **240**, most likely arises from the attack *via* a chelation controlled conformation where the nucleophile approaches from the more accessible *Si*-face. The stereochemical outcome of the addition to an α-oxygenated aldehyde is dependent on a number of factors, such as properties of applied organometals and additives with respect to chelation, protecting group on the α-oxygen, and solvent polarity.[156]

Separation of **237** from the corresponding *syn*-diastereomer proved rather tedious, and combined with the modest yield it was decided to explore potential alternatives. In this context it was thought that an allylation reaction of **193** would serve as an interesting starting point for an alternative route to the intermediate alkyl iodide **243** (Scheme 42).

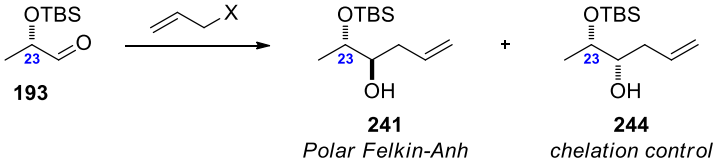


[156] For a comprehensive review, see: A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191.

Scheme 42 Alternative approach to **243**.

If successful, the allylation product **241** could then be taken on in a two-step sequence to intercept the previous route *via* a hydroboration/iodination reaction.[157,158] Thus, we evaluated allylation reactions of aldehyde **193** to introduce the three carbons needed (Table 6).

Table 6 Additions to aldehyde **193**[a]



Entry	Nucleophile	Additives	Conditions	*dr*(241:244)[b]	Comments
1[c]		$BF_3{\cdot}OEt_2$	CH_2Cl_2, –78 °C	1 : 1	–
2		$BF_3{\cdot}OEt_2$	THF, –78 °C	–	No reaction
3		–	Et_2O, –78 °C	1 : 1	–
4		–	THF, –78 °C	2 : 1	40% isolated yield
5[d]		Li, DBB[e]	Et_2O, –78 °C	–	No reaction
6[d]		Li, DBB[e]	THF, –78 °C	2 : 1	–

[a] All reactions were conducted with 200 mg of aldehyde **193** (1.08 mmol) and 1.35 mmol of nucleophile in 10 mL of solvent. Full conversion of the aldehyde was observed in all reactions unless otherwise noted. The products were not isolated unless otherwise noted.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Both premixing of aldehyde and nucleophile as well as aldehyde and additive resulted in the same outcome.
[d] LiDBB was preformed in the solvent before addition of nucleophile to form the R-Li reagent.
[e] DBB = 4,4'-di-*tert*-butyl-1,1'-biphenyl.

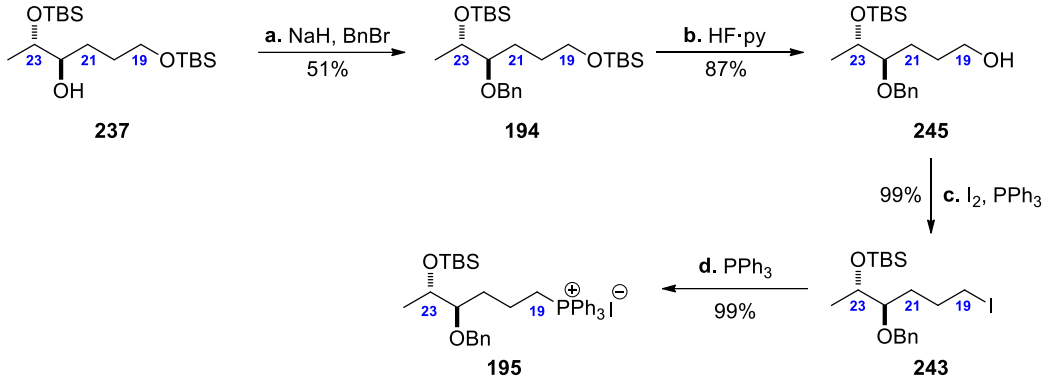
Subjecting aldehyde **193** to allyl trimethylsilane and boron trifluoride resulted in full consumption of the starting material, however, only equimolar amounts of the two diastereomers were obtained in CH_2Cl_2 as the solvent, whereas THF completely shut down the reaction (entries 1 and 2). Turning our attention to allylmagnesium bromide as the nucleophile, we were able to increase the diastereomeric ratio to 2:1 in favor of the desired product (entry 4), albeit only in poor yield. Moreover the diastereomers proved difficult to separate. Final attempts at allylations of aldehyde **193** were conducted with allyllithium as the nucleophile, however, once again we were only able to obtain a diastereomeric ratio of 2:1.

Alternatively, the use of allylating reactions exerting reagent control over the stereochemical outcome were considered.[159] These reagents usually require additional efforts for preparation and

[157] H. C. Brown, M. W. Rathke, M. M. Rogic, *J. Am. Chem. Soc.* **1968**, *90*, 5038.
[158] N. R. De Lue, H. C. Brown, *Synthesis* **1976**, *1976*, 114.
[159] For representative examples, see: a) Roush's tartrate-derived allylboronates: W. R. Roush, A. E. Walts, L. K. Hoong, *J. Am. Chem. Soc.* **1985**, *107*, 8186; b) Hoffmann's camphor-derived allylboronates: T. Herold, R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 768; c) Brown's diisopinocampheyl boranes: H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1983**, *105*, 2092.

thus it would not be advantageous to apply at this stage. Therefore, at this point, it was deemed unfruitful to invest further efforts in optimization of this strategy.

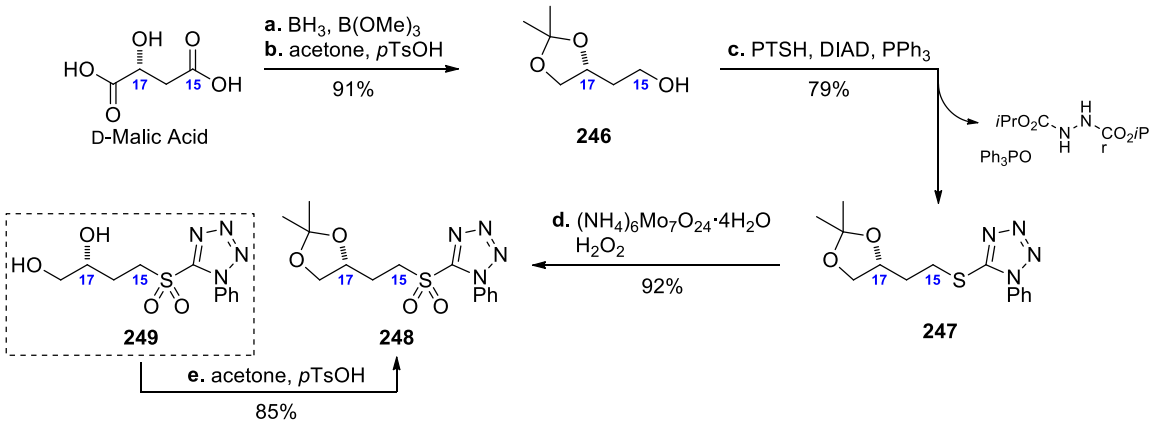
Completion of phosphonium iodide **195** is outlined in Scheme 43, according to previously described procedures.[125] Protecting group manipulations gave primary alcohol **243** which upon iodination and nucleophilic substitution with PPh_3 afforded the Wittig reagent.



Scheme 43 Reagents and conditions: a. BnBr, NaH, TBAI, DMF, 51%; c. HF·py, py, THF, 0 °C, 87%; d. I_2, PPh_3, imidazole, C_6H_6, 0 °C, 99%; e. PPh_3, MeCN, reflux, 99%.

4.2.2 The C_{11}–C_{18} Primary Alcohol Fragment

The synthesis of C_{11}–C_{18} commenced from chiral pool starting material, D-malic acid, constituting the C_{15}–C_{18} part of the chlorosulfolipid hydrocarbon backbone (Scheme 44). With slight modification of known procedures,[160] malic acid was converted to acetonide-protected triol **246** *via* reduction with borane followed by treatment with *para*-toluenesulfonic acid in acetone to selectively form the five-membered acetal under thermodynamic conditions.



[160] S. Hanessian, A. Ugolini, D. Dubé, A. Glamyan, *Can. J. Chem.* **1984**, *62*, 2146.

Scheme 44 Reagents and conditions: a. $BH_3 \cdot SMe_2$, $B(OMe)_3$, THF, 0 °C to r.t.; b. *p*TsOH·H_2O, $CuSO_4$, acetone, 91% over two steps; c. 1-phenyl-1H-tetrazole-5-thiol, DIAD, PPh_3, CH_2Cl_2, 0 °C to r.t., 79%; d. $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, H_2O_2, EtOH, 0 °C to r.t., 92%; e. *p*TsOH·H_2O, $CuSO_4$, acetone, 85%.

For scale-up considerations, it was noted that primary alcohol **246** was most conveniently prepared without purification of the intermediate 1,2,4-butanetriol. Simply quenching the reduction with methanol followed by several cycles of azeotropic removal of most boron-residues with methanol afforded sufficiently pure material for acetalization. Furthermore **246** was purified by distillation which allowed for the preparation of up to 100 grams (~1 mol) of product in one batch.

While subsitution of the primary alcohol with 1-phenyl-1H-tetrazole-5-thiol (PTSH) under Mitsunobu conditions proceeded smoothly to give **247** in 79% yield,[161] scaling up this reaction resulted in problems with respect to the quantity of by-products produced and their influence on the purification procedure. Unfortunately, the subsequent oxidation-step proceeded with poor conversion with impure starting material, and therefore sulfide **247** had to be purified by column chromatography**.** Thus, when conducted on a large scale, the vast amount of triphenylphosphine oxide and diisopropyl hydrazine-1,2-dicarboxylate produced hampered the purification. Moreover, it was found that the hydrazine by-product was difficult to remove by chromatography which deemed alternative purification steps even more critical.

Fortunately, it was found that the physical properties of the product allowed for quantitative removal of triphenylphosphine oxide by precipitation from diethyl ether, whereas the hydrazine by-product could be precipitated from toluene through two cycles.

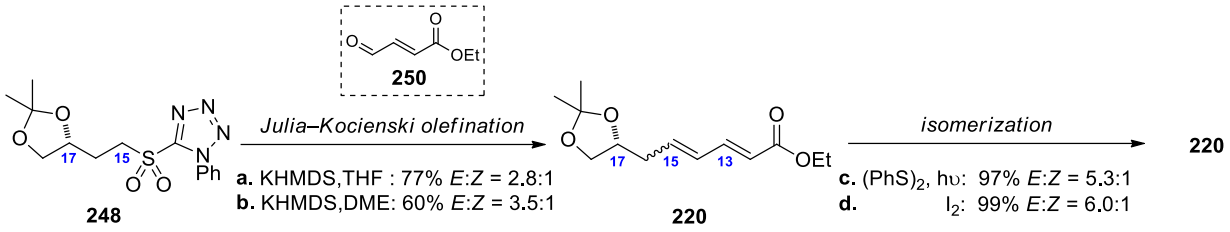
The Julia–Kocienski precursor, sulfone **248**, was completed by a molybdate-mediated oxidation. The success of this oxidation proved very dependent on the batch of ammonium heptamolybdate, as various batches resulted in a more acidic reaction medium which ultimately led to partial deprotection of the acetal to give **249**. In addition, the reaction quench and work-up showed to be critical for the product distribution with reductive and buffered conditions (aqueous $NaHCO_3/Na_2S_2O_3$) being the method of choice.

Fortunately, in cases of extensive hydrolysis of the acetal, the 1,2-diol side-product **249** could be re-protected to give **248** in 85% yield.

The Julia–Kocienski olefination and subsequent double-bond isomerization to give diene **220** is shown in Scheme 45. In accordance with the procedure reported in the synthesis of nominal mytilipin B, under Barbier-type conditions,[162] a solution of sulfone **248** and aldehyde **250** was treated with

[161] Following a protocol by Paquette and Chang, see: L. A. Paquette, S.-K. Chang, *Org. Lett.* **2005**, *7*, 3111.
[162] Barbier-type conditions refer to the addition to the aldehyde of an *in situ* generated organometallic, along the lines of the Barbier reaction, see: a) P. Barbier, *C. R. Acad. Sci.* **1899**, 110; b) C. Blomberg, F. A. Hartog, *Synthesis* **1977**, *1977*, 18.

KHMDS in tetrahydrofuran to give the desired diene in 77% as a mixture of *E*/*Z*-isomers at the C_{14}–C_{15} double bond in a ratio of 2.8 to 1.



Scheme 45 Julia–Kocienski olefination and subsequent double-bond isomerization. Reagents and conditions: a. **250**, KHMDS, THF, –78 °C to r.t. 77% *E*:*Z* = 2.8:1; b. **250**, KHMDS, DME, –55 °C to r.t., 60% *E*:*Z* = 3.5:1; c. $(PhS)_2$ (10 mol%), white light (150 W), benzene, 97%, *E*:*Z* = 5.3:1; d. I_2 (5 mol%), CH_2Cl_2, 99%, *E*:*Z* = 6.0:1.

It was shown by Carreira and co-workers that the resulting *E*/*Z*-ratio could be successfully increased in the favor of the desired *E*-isomer by subjecting the mixture to strong visible light in the presence of diphenyl disulfide. While the initial *E*/*Z*-ratio from the Julia–Kocienski olefination is inconsequential due to the subsequent isomerization, it would, however, be advantageous to increase this ratio in order to skip the subsequent isomerization step.

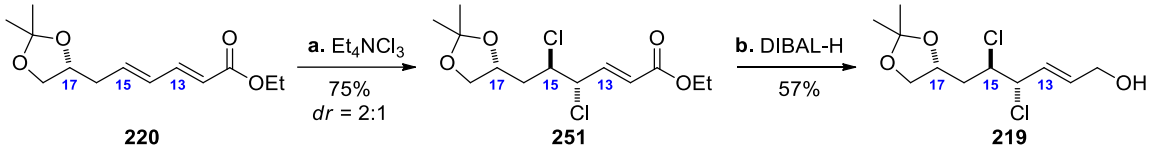
In 1998, Kocienski and co-workers reported that the *E*/*Z*-ratio in olefinations with phenyl-tetrazole sulfones is highly dependent on the choice of solvent and base.[163] Thus, in agreement to those findings we tested the combination which was reported to give the highest *E*/*Z*-ratio, namely KHMDS as the base and DME as the solvent, and indeed the product was obtained with a slight increase in the *E*/*Z*-ratio, albeit in only 60% yield.

With this knowledge in hand, we decided to test alternatives to the subsequent isomerization. Treatment of the diene mixture with catalytic amounts of iodine in dichloromethane resulted in a slightly higher *E*/*Z*-ratio in excellent yield. While this result is not a significant improvement compared to the previously utilized procedure with $(PhS)_2$ the practical execution was found to be advantageous. The latter reaction was performed simply by stirring a solution of diene **220** and iodine with the light turned on in the fume hood, whereas the previous procedure called for the use of a 150W lamp which led to variations in the *E*/*Z*-ratio depending on the reaction scale. In addition, reductive aqueous work-up afforded the pure product without further purification needed.

In accordance to the synthesis of the enantiomeric compound,[125] introduction of the first chlorides in this fragment was facilitated by a *trans*-stereospecific dichlorination of the more electron-rich γ,δ-double bond in **220**. Using Mioskowski's reagent, afforded compound **249** as an inseparable mixture for diastereomers with respect to the existing stereogenic center at C_{17} (Scheme 46). Hereafter

[163] P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, 26.

followed a reduction of the ethyl ester with DIBAL-H to give allylic alcohol **219**, thus setting the stage for epoxidation. The obtained mixture of diastereomers was carried on as such and could most conveniently be separated on the stage of epoxide **252**.

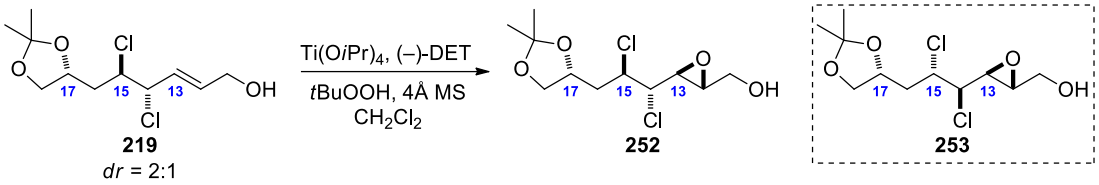


Scheme 46 Reagents and conditions: a. Et_4NCl_3, CH_2Cl_2, 0 °C. 75%, *dr* = 2:1; b. DIBAL-H, PhMe, 0 °C, 57%.

Epoxidation of allylic alcohol **219** was tested under standard Sharpless, as summarized in Table 7. First, epoxidation with stoichiometric amounts of Ti(O*i*Pr)$_4$ was conducted (entry 1).[164] Premixing of Ti(O*i*Pr)$_4$ and (–)-DET in CH_2Cl_2 at –20 °C allowed for the formation of the catalytic complex upon aging. Further addition of *tert*-butyl hydroperoxide and a second aging period followed by addition of allylic alcohol **219** afforded the desired epoxide in 41% yield. Further exploration on this specific set of conditions revealed that the order of addition did not make a difference (entry 2). In addition, the diastereomeric epoxide **253** could be isolated in 20% yield.

[164] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.

Table 7 Epoxidation of **219**[a]



entry	equiv Ti(O*i*Pr)$_4$/(–)-DET	conditions	conversion	yield (252)
1	1.2/1.4	–20 °C, 14h	>95%	41%
2[b]	1.2/1.4	–20 °C, 14h	>95%	41%
3	0.1/0.12	–20 °C, 24h	60%	20%
4	0.1/0.12	–10 °C, 24h	>95%	0%
5	0.2/0.3	–20 °C, 18h	50%	–[c]
6	0.2/0.3	–20 °C, 5 d	>95%	0%

[a] Unless otherwise noted, Ti(O*i*Pr)$_4$ and (–)-DET was premixed and aged for 30 min, then addition of *t*BuOOH and aged for another 30 min before addition of **219**.
[b] Ti(O*i*Pr)$_4$ and (–)-DET was premixed and aged for 30 min, then addition of **219** and aged for another 30 min before addition of *t*BuOOH.
[c]Isolated yield was not determined.

Catalytic versions of the Sharpless epoxidation were also tested with 10-20 mol% of Ti(O*i*Pr)$_4$,[165] however, low conversions and consequently also lower isolated yields were observed (entry 3 and 5). Furthermore, when the reactions were pushed to full conversion, none of the desired product could be observed, which might be attributed to side reactions of the product, such as epoxide opening with isopropoxide, over prolonged reaction times and elevated temperatures.

In accordance with the general model for Sharpless epoxidations, the epoxide-configuration of **252** was tentatively assigned as shown in Figure 16, where (–)-DET directs epoxidation from the *Si*-face.[164]

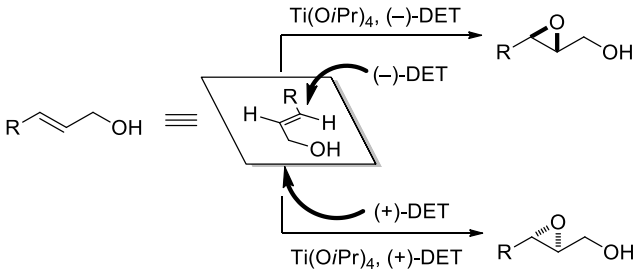
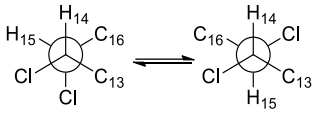


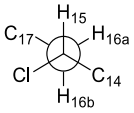
Figure 16 Model for the stereochemical outcome of Sharpless asymmetric epoxidation.

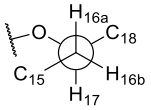
[165] Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765.

In order to confirm the relative configuration of epoxide **252**, a *J*-based configurational analysis was conducted based on ^{1}H NMR and HSQC-HECADE spectral data. The extracted homo- and heteronuclear coupling constants, ^{3}J(H,H), ^{2}J(H,C), and ^{3}J(H,C) are shown in Table 8.

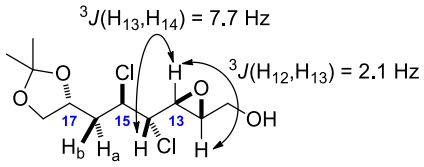
Table 8 Relevant coupling constants for **252**, accompanied by analysis.







C_{14}–C_{15}			C_{15}–C_{16}			C_{16}–C_{17}		
$^{3}J(H_{14},H_{15})$	4.3 Hz	(m)	$^{3}J(H_{15},H_{16a})$	2.5 Hz	(s)	$^{3}J(H_{16b},H_{17})$	3.1 Hz	(s)
$^{3}J(H_{14},C_{16})$	2.7 Hz	(s)	$^{3}J(H_{15},H_{16b})$	11.1 Hz	(l)	$^{3}J(H_{16a},H_{17})$	9.2 Hz	(l)
$^{3}J(H_{15},C_{13})$	3.7 Hz	(m)	$^{3}J(H_{15},C_{17})$	3.0 Hz	(s)	$^{3}J(H_{16b},C_{18})$	1.7 Hz	(s)
$^{2}J(H_{14},C_{15})$	-1.8 Hz	(m)	$^{3}J(H_{16b},C_{14})$	2.0 Hz	(s)	$^{3}J(H_{16a},C_{18})$	3.3 Hz	(s)
$^{2}J(H_{15},C_{14})$	-4.2 Hz	(l)	$^{3}J(H_{16a},C_{14})$	2.1 Hz	(s)	$^{3}J(H_{17},C_{15})$	2.9 Hz	(m)
			$^{2}J(H_{16b},C_{15})$	-7.5 Hz	(l)	$^{2}J(H_{16b},C_{17})$	-0.7 Hz	(s)
			$^{2}J(H_{16a},C_{15})$	0.5 Hz	(s)	$^{2}J(H_{16a},C_{17})$	-6.8 Hz	(l)



252

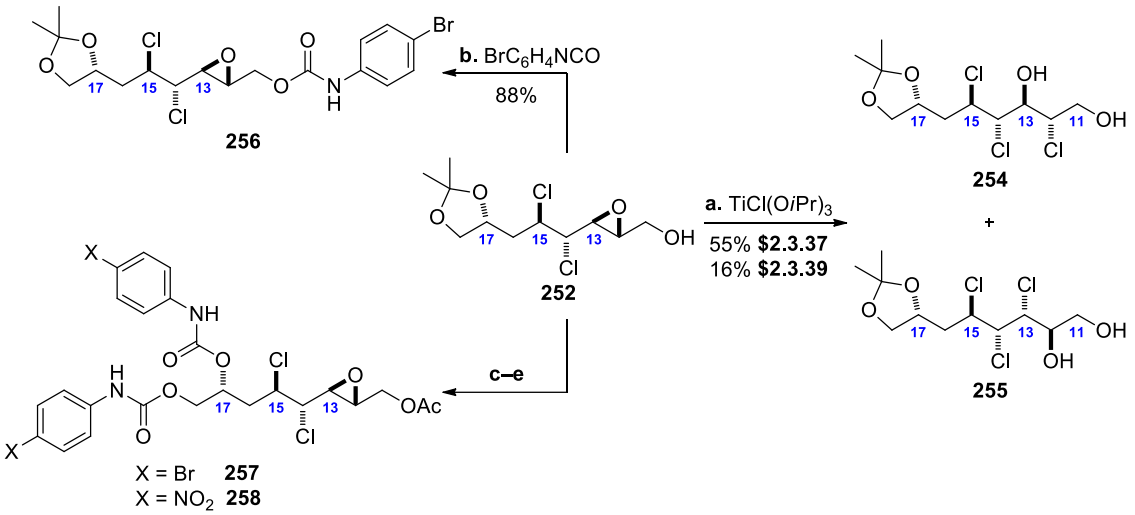
As expected, both relative configurations between C_{14}/C_{15} and C_{15}/C_{17} were concluded to be *anti*, based on the extracted coupling constants. Since the absolute configuration at C_{17} is known to be (*R*) (from D-malic acid), the overall absolute configuration is derived thereof. Interestingly, equilibrium of two conformations around C_{14}/C_{15} is observed. While complicating the analysis slightly, however, the observed coupling constants allow for unambiguous assignment of the relative configuration.[103]

The coupling constant $^{3}J(H_{12},H_{13})$ is observed to be 2.1 Hz. In good agreement with the Karplus relationship, that is the effect of the dihedral angle on ^{3}J(H,H)-values,[166] the coupling constants in 1,2-disubstituted epoxides have been established to usually display values of ~2 Hz for *trans*-epoxides, whereas the ^{3}J(H,H) of *cis*-epoxides exert values in the range of 4 Hz.[167] Hence, the observation of 2.1 Hz confirms the assignment of the 1,2-disubstituted epoxide as *trans*.

In an effort to obtain full proof for the configuration of epoxide **252**, several compounds were prepared in hope of obtaining suitable crystals for X-ray crystallography (Scheme 47). Due to the

[166] M. Karplus, *J. Am. Chem. Soc.* **1963**, *85*, 2870.
[167] J.-M. Lehn, J.-J. Riehl, *Mol. Phys.* **1964**, *8*, 33.

knowledge that a range of trichlorohexanediols are crystalline,[104] it was hoped that opening of the epoxide with a chloride source would afford a crystalline compound. Therefore, **252** was reacted with TiCl(O*i*Pr)$_3$ in benzene to give a separable mixture of 1,3-diol **254** as the major component (55%) and a minor amount of 1,2-diol **255** (16%), however, both as viscous oils.

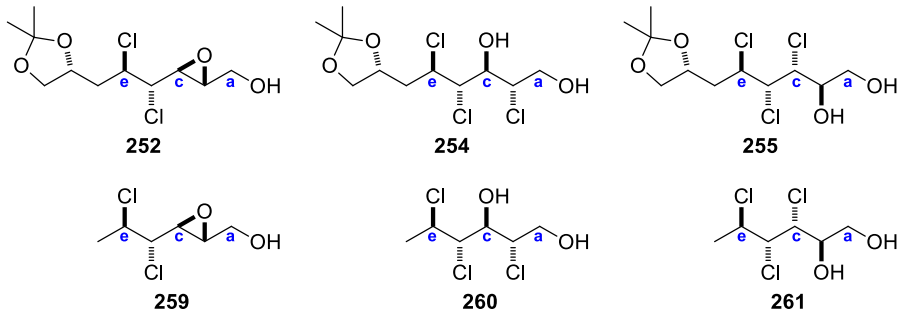


Scheme 47 Representative compounds prepared in attempts to obtain suitable crystals for X-Ray crystallography. Reagents and conditions: a. TiCl(O*i*Pr)$_3$, benzene, 55% of **254**, 16% of **255**; b. *p*-bromophenyl isocyanate, Et_3N, CH_2Cl_2, 88%; c. AcCl, DMAP , Et_3N, CH_2Cl_2, 0 °C, 79%; d. CSA, MeOH, 80%; e. *p*-bromophenyl isocyanate or *p*-nitrophenyl isocyanate, Et_3N, CH_2Cl_2, 62% (X=Br), 70% (X=NO_2).

Unfortunately, despite further extensive experimentations, including the preparations of carbamates **256**, **257**, and **258,** no intermediates exhibiting crystalline properties could be identified.

To further evaluate the stereochemical assignment of **252**, the ^{1}H NMR spectral data of **252**, **254**, and **255** were compared to known compounds **259**, **260**, and **261**, respectively (Table 9).[104]

Table 9 Comparison of ^{1}H NMR spectral data[a]

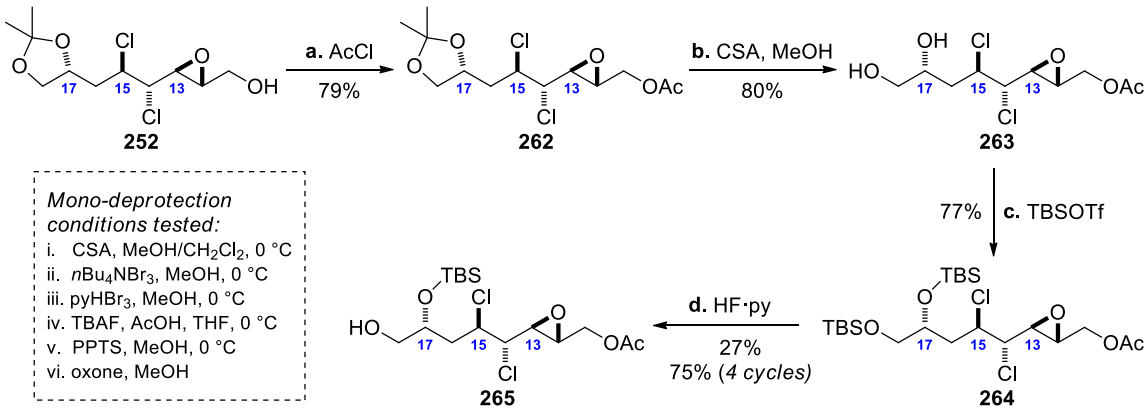


δ, ppm (*J*, Hz)	H_a	H_b	H_c	H_d	H_e
252	3.97(12.9, 2.4) 3.71(12.9, 4.0)	3.15(4.0, 2.3)	3.40(7.7, 2.1)	3.79(7.7, 4.3)	4.46(11.1, 4.3, 2.4)
259	3.98(12.9, 2.4) 3.73 (nd)	3.15(4.0, 2.2)	3.35(7.7, 2.2)	3.73 (nd)	4.33(4.8, 6.7(q))
254	4.05-3.95(nd) 4.11-4.06(nd)	4.44(8.6, 4.3)	4.21-4.13(nd)	4.42(8.1, 3.3)	4.78(10.5, 3.2, 2.4)
260	4.05-3.98(nd) 4.17-4.08(nd)	4.48(8.3, 4.3)	4.17-4.08(nd)	4.33(8.1, 3.8)	4.71(3.8, 6.6(q))
255	4.01-3.89(nd)	4.01-3.89(nd)	4.69(9.1, 1.7)	4.54(10.5, 1.7)	4.38(10.9,1.8)
261	3.81-3.64(nd)	3.81-3.64(nd)	4.63(9.1, 1.5)	4.59(10.3, 1.5)	4.27(10.3,6.5(q))

[a]Chemical shifts are reported in ppm, coupling constants in Hz. Unless otherwise noted, the coupling constants refer to doublets.

As demonstrated, the spectral data, i.e. chemical shifts and ^{3}J(H,H)-values, resembles closely the data obtained for known epoxide **259** and also chlorohydrins **260** and **261**. In particular, the comparison of data for H_c in **252** and **259**, a key signal, are nearly identical, thus further supporting the structural assignment.

With epoxide **252** in hand, the final steps towards C_{11}–C_{18} primary alcohol **265** were conducted as outlined in Scheme 48.



Scheme 48 Reagents and conditions: a. AcCl, DMAP , Et_3N, CH_2Cl_2, 0 °C, 79%; b. CSA, MeOH, 80%; c. TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °, 77%; m. HF·py, py, THF, 0 °C, 27% (after four cycles 75% overall yield, 85% brsm).

Protection of the primary alcohol as the acetate (with acetyl chloride) to give **262** followed by acetal deprotection, with camphorsulfonic acid in methanol, to liberate the terminal 1,2-diol in **263** proceeded smoothly in 79% and 80% yields, respectively.

To successfully obtain the free primary alcohol **265**, a protection of the secondary alcohol was needed. Thus, a double protection followed by *mono*-deprotection was envisioned, however, this proved more challenging than expected. Double TBS-protection was accomplished by treatment of diol **263** with TBSOTf at –78 °C. At this point, it proved of utmost importance to add the very electrophilic silylating agent very carefully, cooling down the reagent by letting it run down the inside wall of the flask. Failure to do so resulted in significant amounts of decomposition products, presumably due to the ability of reactive trialkylsilyl triflates to activate epoxides and esters towards side-reactions.[168]

Successful *mono*-deprotection of *bis*-TBS ether **264** to liberate the primary alcohol **265** was accomplished by the use of HF-pyridine, however, it proved crucial to stop the reaction long before full conversion of the starting material. The reaction time had to be limitied, in general to ca. 4 hours, in order to prevent double-deprotection to give **263**. In other words, one subjection of **264** to the deprotection conditions afforded only 27% of the desired product, and three resubjections were necessary to ensure a good overall yield for this transformation.

A literature survey reveals numerous examples showing that highly selective deprotection of a primary TBS-ether in the presence of a secondary TBS-protected alcohol can be obtained.[169] Therefore, experimentation to identify an alternative approach was conducted, however, with no success. In most cases (i.e. conditions i, iii, iv, v, see Scheme 48), very slow and unselective reaction progress was observed to give a mixture of starting material and diol **263**, whereas in cases of no reaction at first the conditions led to decomposition when temperatures were increased (i.e. with conditions ii, iv).

With both primary alcohol **265** and phosphonium iodide **195** in hand, the stage was set for the coupling and subsequent completion of the C_{11}–C_{24} fragment.

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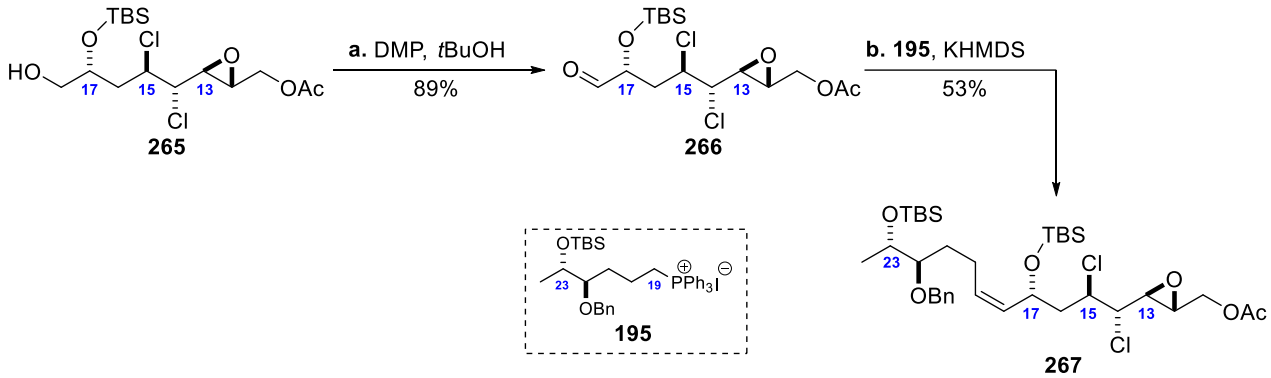
[168] For an example of substrate reatrrangements in epoxides triggered by TBSOTf, see: M. E. Jung, A. van den Heuvel, A. G. Leach, K. N. Houk, *Org. Lett.* **2003**, *5*, 3375.

[169] For representative examples, see: a) D. Crich, F. Hermann, *Tetrahedron Lett.* **1993**, *34*, 3385 (NH_4F); b) A. Kawai, O. Hara, Y. Hamada, T. Shioiri, *Tetrahedron Lett.* **1988**, *29*, 6331 (AcOH, THF); c) J. A. Marshall, K. C. Ellis, *Org. Lett.* **2003**, *5*, 1729 (PPTS, EtOH); d) G. Sabitha, M. Syamala, *Org. Lett.* **1999**, *1*, 1701 (oxone, H_2O/MeOH); e) R. Gopinath, S. J. Haque, B. K. Patel, *J. Org. Chem.* **2002**, *67*, 5842 ($n$$Bu_4NBr_3$); f) N. Tsukada, T. Shimada, Y. S. Gyoung, N. Asao, Y. Yamamoto, *J. Org. Chem.* **1995**, *60*, 143 (NBS, DMSO); g) G. Bartoli, M. Bosco, E. Marcantoni, L. Sambri, E. Torregiani, *Synlett* **1998**, *1998*, 209 ($CeCl_3 \cdot 7H_2O$, NaI).

4.2.3 Coupling and Final Steps

Our efforts to complete the C_{11}–C_{24} fragment **274** called for the use of two key reactions, namely the union of fragments C_{19}–C_{24} (**265**) and C_{11}–C_{18} (**195**) in a Wittig olefination reaction, and subsequent installation of the final chlorides at C_{18}–C_{19} *via* olefin dichlorination.

Due to concerns *vis-a-vis* the potential configurational instability of α-oxygentated aldehyde **266** over prolonged periods of storage, primary alcohol **265** was oxidized just prior to use in the subsequent Wittig olefination reaction with phosphonium salt **195** (Scheme 49).



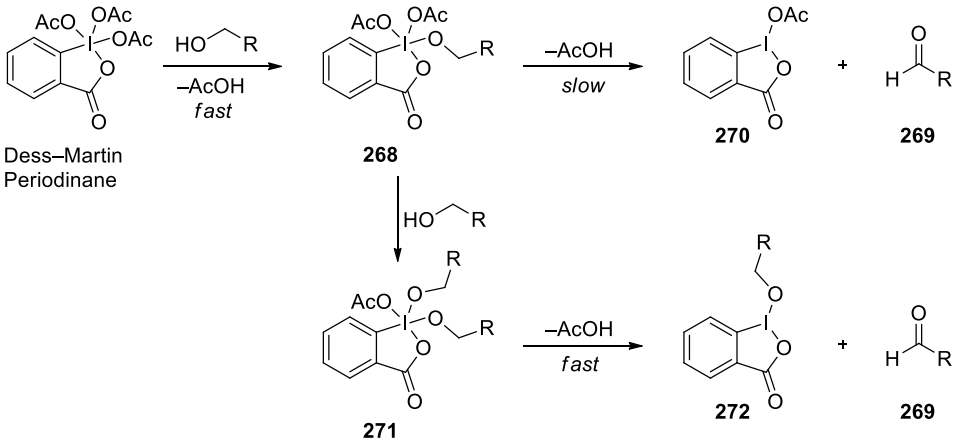
Scheme 49 Reagents and conditions: a. DMP, *t*-BuOH, CH_2Cl_2, 89%; **195** (1.2 equiv), KHMDS (1.2 equiv), THF, 0 °C *then* **266**, –78 °C to 0 °C, 53%.

The oxidation was investigated by use of Dess–Martin periodinane.[170] Initial experimentation of stirring a mixture of alcohol **265** and the oxidant in CH_2Cl_2 led to very slow conversion of the starting material; however, when one equivalent of *t*-butanol was added, the reaction went to completion within minutes and allowed for the isolation of the desired aldehyde **266** in 89% yield.

The observation that DMP oxidation rates can be dramatically accelerated by the presence of water or tertiary alcohol additives is a known phenomenon.[170,171] Supported by ^{1}H NMR spectroscopic analysis and kinetic data, it is suggested that displacement of an acetate by one equivalent of alcohol on the periodinane reagent rapidly forms *mono*alkoxyiodinane **268** which undergoes slow collapse to afford the aldehyde product **269** together with acetoxyiodinane **270** (Scheme 50). However, displacement of another acetate with a second equivalent of alcohol results in a very unstable bisalkoxy intermediate **271** which rapidly breaks down to the desired product **269** and alkoxyiodinane **272**. Hence, when excess DMP is used without additives, initial rapid formation of product is often observed whereafter the reaction slows down as more and more alcohol is consumed. Therefore, by addition of *t*-butanol as a non-oxidizable "second equivalent" of alcohol,

[170] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155; D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.
[171] S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549.

an unstable intermediate in analogy to **279** is obtained, thus facilitating fast reaction and overcoming the rate problem.

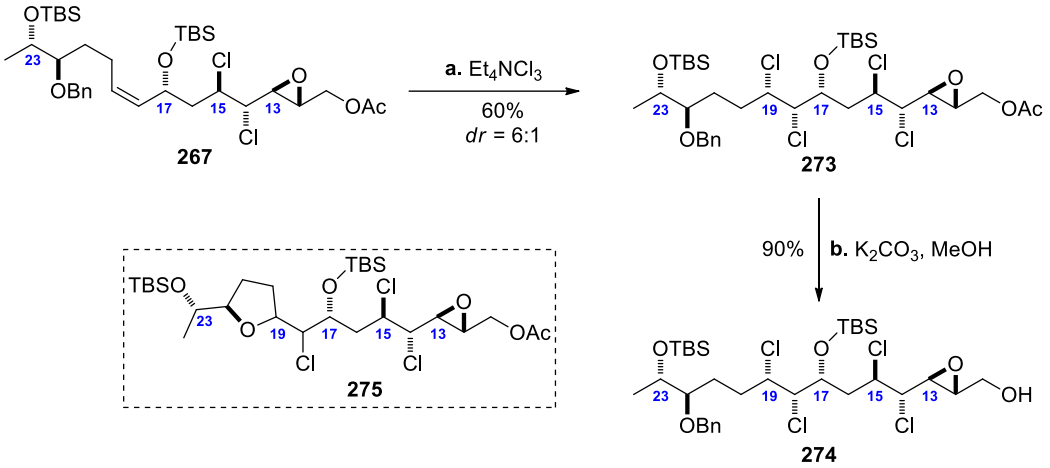


Scheme 50 Acceleration of oxidations with Dess–Martin Periodinane

Immediately following oxidation, aldehyde **266** was taken on to the subsequent Wittig reaction. Consequently, phosphonium iodide **195** was reacted with KHMDS in THF to *in situ* pre-form the corresponding phosphonium ylide, which upon addition of the aldehyde resulted in C_{18}–C_{19} *cis*-olefin **267** in 53% yield. It is worth noting, that the ^{1}H NMR signals of both olefinic protons were overlapping when measured in deuterated chloroform; however, the configuration of the double bond was unambiguously determined by the observation of a ^3J(H,H) value of 11 Hz in deuterated benzene.

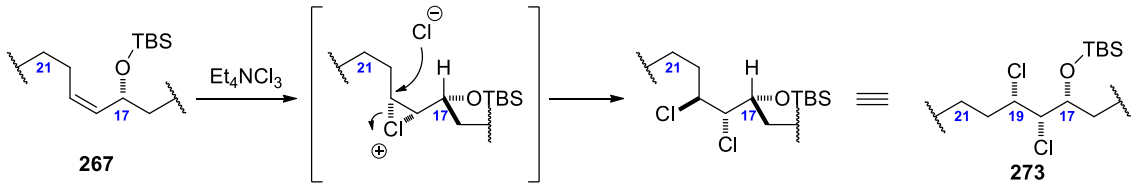
Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed the production of traces of several other olefinic protons, however, no products related to these signals could be isolated and further characterized. It is assumed that these olefins most likely are produced by elimination of HCl from either starting aldehyde **266** or product **267**. Attempts to eliminate these by-products and increase the reaction yield by longer reaction times at cryogenic temperatures were tried; however, this only resulted in poor conversion of the starting material. Similarly, the use of near-stoichiometric amounts of base and phosphonium iodide **195** (i.e. 1–1.1 equivalents) did not improve the reaction outcome.

Final introduction of the last two chlorides in this fragment was accomplished by means of dichlorination of *cis*-olefin **267**. Hence, upon treatment with Mioskowski's reagent (Et_4NCl_3) in dichloromethane at –78 °C, the desired tetrachloride **273** was obtained in 60% yield as an inseparable 6:1 mixture of diastereomers (Scheme 51). Significant amounts of an unavoidable by-product (10–20%), eventually assigned as tetrahydrofuran **275**, were formed during the reaction. This by-product is presumably formed *via* internal opening of the intermediate chloronium ion with the benzyl-ether oxygen at C_{23} followed by debenzylation.



Scheme 51 Completion of C_{11}–C_{24} fragment **274**. Reagents and conditions: a. Et_4NCl_3, CH_2Cl_2, –78 °C, 60%, *dr* = 6:1; b. K_2CO_3, MeOH, 0 °C, 90%.

Based on Vanderwal's report on dichlorination of *cis*-allylic alcohol derivatives to give the all-*syn* product predominantly, the stereochemical outcome of the reaction of **267** with Miskowski's reagent to give **273** was tentatively assigned accordingly (Scheme 52).[54] This assignment was further supported by findings in the synthesis of nominal mytilipin B (dichlorination of **200**, see Chapter 1.3.4.3).[125]



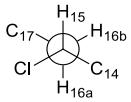
Scheme 52 Rationale for the stereochemical outcome of the dichlorination, in agreement with Vanderwal *et al.*[54]

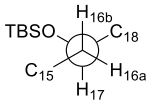
Ultimately, deprotection of the primary acetate **273** (Scheme 51) completed the preparation of C_{11}–C_{24} fragment **274**, thus setting the stage for the olefination reaction to unite the entire hydrocarbon backbone of mytilipin B.

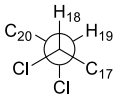
4.2.4 Structural Assignment

In order to validate the structure of **273**, analysis of the relative configuration was conducted using JBCA. Homo- and heteronuclear coupling constant values were extracted from ^{1}H NMR and HSQC-HECADE spectra and evaluated in accordance with the discussion in Chapter 1.3.2. The results of this analysis are shown in Table 10.

Table 10 *J*-Based Configurational Analysis of **273**

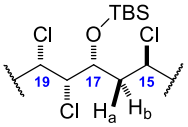






C_{15}-C_{16}			**C_{16}-C_{17}**			**C_{17}-C_{18}**			**C_{18}-C_{19}**		
$^3J(H_{15},H_{16a})$	11.5 Hz	(l)	$^3J(H_{16b},H_{17})$	10.3 Hz	(l)	$^3J(H_{17},H_{18})$	5.7 Hz	(m)	$^3J(H_{18},H_{19})$	2.3 Hz	(s)
$^3J(H_{15},H_{16b})$	2.0 Hz	(s)	$^3J(H_{16a},H_{17})$	1.8 Hz	(s)	$^3J(H_{17},C_{19})$	3.5 Hz	(m)	$^3J(H_{18},C_{20})$	2.2 Hz	(s)
$^3J(H_{15},C_{17})$	2.5 Hz	(s)	$^3J(H_{16b},C_{18})$	2.4 Hz	(s)	$^3J(H_{18},C_{16})$	3.6 Hz	(m)	$^3J(H_{19},C_{17})$	nd	-
$^3J(H_{16b},C_{14})$	1.3 Hz	(s)	$^3J(H_{16a},C_{18})$	0.8 Hz	(s)	$^2J(H_{17},C_{18})$	-3.6 Hz	(l)	$^2J(H_{18},C_{19})$	1.3 Hz	(s)
$^3J(H_{16a},C_{14})$	1.4 Hz	(s)	$^3J(H_{17},C_{15})$	nd	-	$^2J(H_{18},C_{17})$	-4.9 Hz	(l)	$^2J(H_{19},C_{18})$	1.5 Hz	(s)
$^2J(H_{16b},C_{15})$	0.9 Hz	(s)	$^2J(H_{16b},C_{17})$	-6.9 Hz	(l)						
$^2J(H_{16a},C_{15})$	-7.7 Hz	(l)	$^2J(H_{16a},C_{17})$	-0.6 Hz	(s)						

Conclusion:



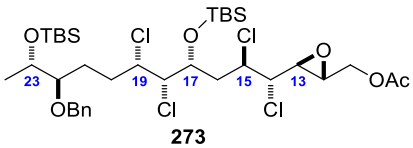
273

Despite the missing $^3J(H_{19},C_{17})$ value, the relative configuration of C_{18}/C_{19} could be assigned to be *syn* with the conformation predominantly existing as ***A1***. This assignment is possible, as no other conformation would lead to the specific pattern of "small" *J* values (see Table 3, Chapter 1.3.2).[103] In addition, the conformation along C_{17}/C_{18} is established to exist in equilibrium between ***A2*** and ***A3***. Again, the couplig constant pattern is specific for exactly the equilibrium between those two conformations, thus supporting a *syn* relative configuration at C_{17}/C_{18}.

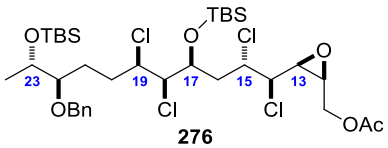
At the stage of α-oxygenated aldehyde **266**, the C_{17} stereogenic center might have been prone to epimerization *via* an equilibrium enol form of the aldehyde. Hence, in order to confirm that no change in configuration at C_{17} had taken place during the later steps, the JBCA was extended from C_{17} to C_{15}. Assignment of the diastereotopic protons, H_a and H_b, at C_{16} allowed for correlations to C_{15} and C_{17}, respectively, from which the confirmation of an *anti*-relationship between the C_{15} chloride and the C_{17} silyl-ether followed directly.

To further support the structural assignment, Table 11 shows a comparison of ^{1}H NMR and HSCQ-HECADE data for C_{17}–C_{19} of **273** and **276**, a synthetic intermediate in the synthesis of nominal mytilipin B with same relative configuration and protecting group on C_{17}-oxygen (i.e. TBS).

Table 11 Comparison of chemical shifts and coupling constants of **273** and **276**



273



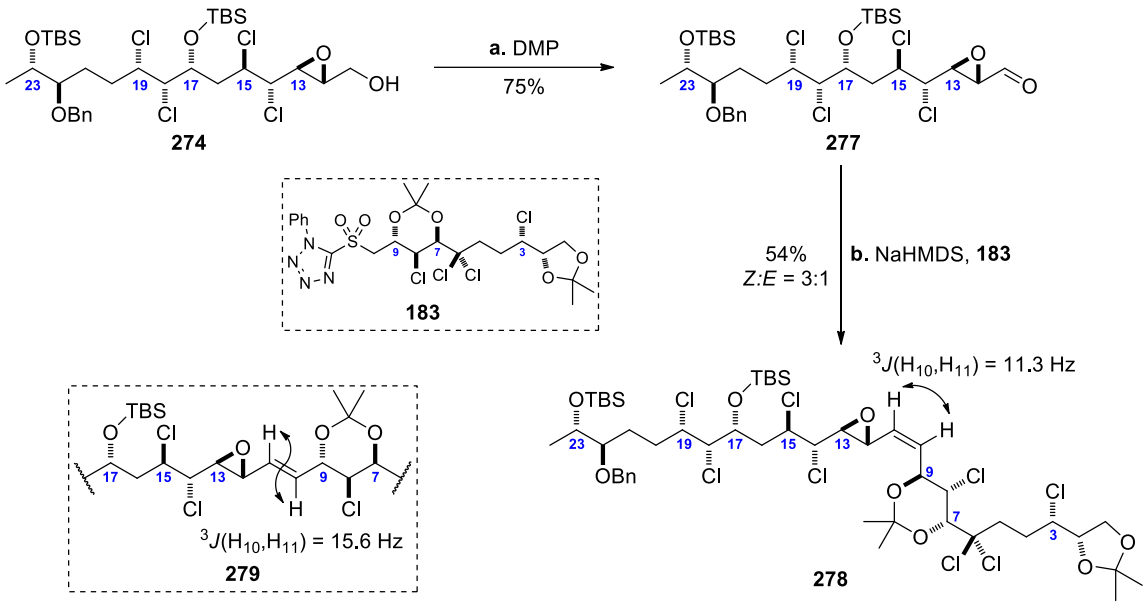
276

	δ(H17)	**δ(H18)**	**^3J(H$_{17}$,H$_{18}$)**	**^3J(H$_{17}$,C$_{19}$)**	**^3J(H$_{18}$,C$_{16}$)**	**^2J(H$_{17}$,C$_{18}$)**	**^2J(H$_{18}$,C$_{17}$)**
273	4.24 ppm	3.93 ppm	5.7 Hz	3.5 Hz	3.6 Hz	-3.6 Hz	-4.9 Hz
276	4.22 ppm	3.93 ppm	5.8 Hz	nd	3.7 Hz	-3.9 Hz	-5.0 Hz
		δ(H19)	**^3J(H$_{18}$,H$_{19}$)**	**^3J(H$_{18}$,C$_{20}$)**	**^3J(H$_{19}$,C$_{17}$)**	**^2J(H$_{18}$,C$_{19}$)**	**^2J(H$_{19}$,C$_{18}$)**
273		4.22 ppm	2.3 Hz	2.2 Hz	nd	1.3 Hz	1.5 Hz
276		4.26 ppm	2.1 Hz	2.2 Hz	nd	<2 Hz	1.6 Hz

As demonstrated by the comparison, the extracted values for the specific C_{17}–C_{19} systems are almost identical, thus further supporting that the relative configuration of this 1,2-dichloro-3-TBS-ether stereotriad is all-*syn*.

4.3 Completion of C_1–C_{24} and Further Investigations

With both sulfone **183** and primary alcohol **274** successfully prepared, the stage was set for completion of the entire C_{24} hydrocarbon backbone. Scheme 53 shows how this was achieved by means of Julia–Kocienski olefination reaction.



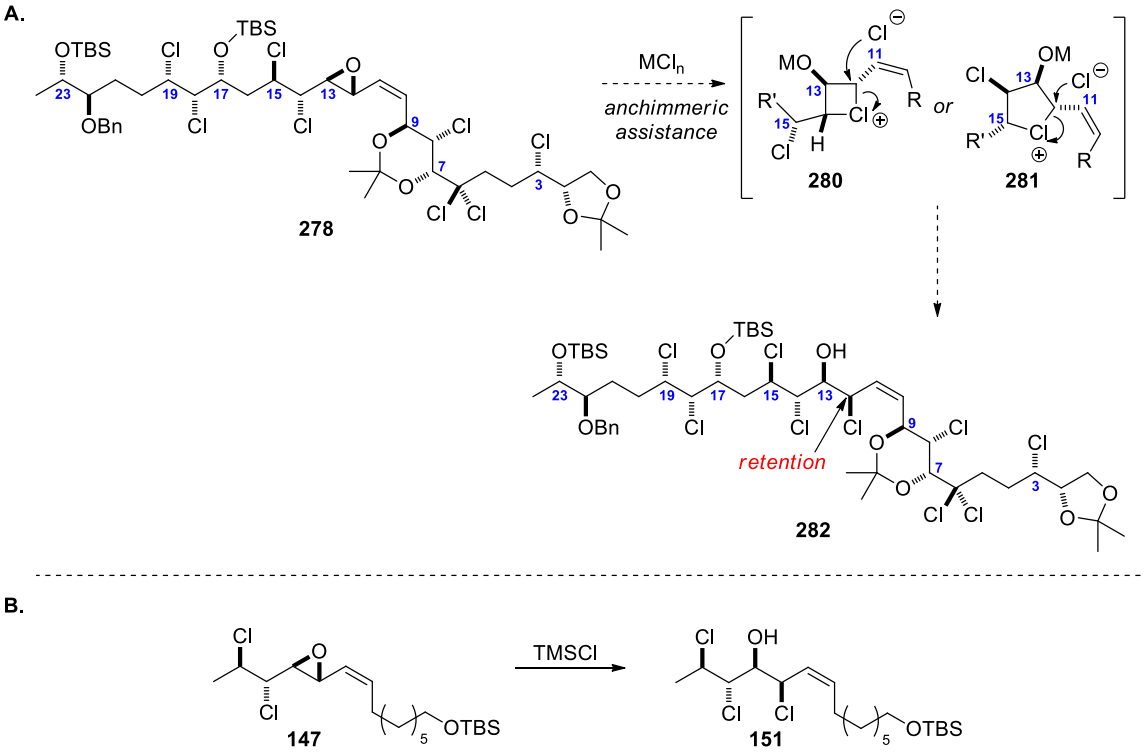
Scheme 53 Reagents and conditions: a. DMP, CH_2Cl_2, 75%; b. **183**, NaHMDS, PhMe, –78 °C to r.t., 54% (of isolated **278**), *Z*:*E* = 3:1 (judged by ^{1}H NMR of the crude reaction mixture).

Oxidation of primary alcohol **274** with Dess–Martin periodinane facilitated the prearation of α,β-epoxyaldehyde **277** in 75% yield shortly before the olefination event. As judged by TLC analysis, the reaction went to almost full conversion within 10 minutes, however, another hour was needed for the remaining starting material to transform into the desired sensitive aldehyde. Therefore, rate acceleration by addition of one equivalent of *t*BuOH was tested. As a result, full consumption of the starting alcohol was observed almost instantaneously, however, purification of the aldehyde from the by-products arising from DMP proved very challenging. Thus, as an alternative, the oxidation was tested with addition of one equivalent of water,[171] and indeed, the reaction went to completion within 30 min, and the product was cleanly isolated in 75% yield.

With the aldehyde in hand, attention was turned to the investigations of the subsequent olefination reaction. Ideally, we wished for this reaction to afford the *cis*-olefin **278** with high stereoselectivity. Kocienski's systematic study of reaction conditions showed that the *E*/*Z*-ratio of a Julia-Kocienski reaction with phenyl-tetrazolyl sulfones can be influenced by variation of solvent and base, whereas

α-branching in the sulfone or aldehyde has little effect on the stereochemical outcome.[163,172] The *E/Z*-ratio may be increased with the change of base counterion, in the order Li < Na < K, or by increasing solvent polarity, i.e. PhMe < Et_2O < THF < DME. In addition, an earlier report by Charette[173] in conjunction with prior work on the synthesis of nominal mytilipin B by Nilewski[106] suggested the use of NaHMDS in toluene for high *Z*-selectivity.

Accordingly, coupling of sulfone **183** with aldehyde **277** was successfully accomplished under Barbier-type conditions by treatment of the mixture of substrates in toluene with NaHMDS at –78 °C followed by slow warming to room temperature. Using this protocol, the desired *cis*-olefin **278** was obtained as the major product, albeit with modest diastereoselectivity (*E/Z* = 3:1). The minor *trans*-isomer **279** was separately isolated and the identities of the *cis*- and *trans*-products were secured by observation of ^3J(H,H) between the olefinic protons of 11.3 Hz and 15.6 Hz, respectively.



Scheme 54 A. Desired epoxide opening with overall retention at C_{12} *via* double inversion; **B.** epoxide opening in the synthesis of mytilipin A.

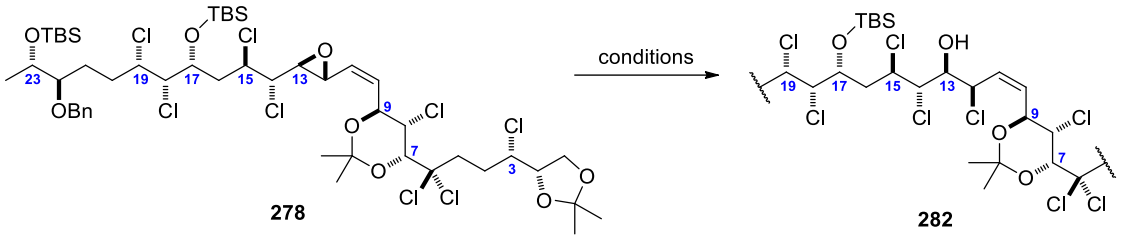
Next synthetic manipulation in line for the introduction of the remaining chlorides in the hydrocarbon backbone was the anticipated opening of vinyl epoxide **278** at the allylic C_{12}-position to give chlorohydrin **282** (Scheme 54A).

[172] For a reviev on the Julia-Kocienski reaction, see: C. Aïssa, *Eur. J. Org. Chem.* **2009**, *2009*, 1831.
[173] A. B. Charette, H. Lebel, *J. Am. Chem. Soc.* **1996**, *118*, 10327.

It is worth noting, that the epoxide will have to be opened with retention in order to obtain the desired configuration at C_{12}. As highlighted during the retrosynthetic considerations in Chapter 2.2, we expected that anchimmeric assistance from neighbouring chloride would facilitate a double inversion sequence *via* cyclic chloronium intermediate **280** or **281**. Keeping in mind the observations during the synthesis of mytilipin A (Scheme 54B)[114] and the resemblance of the stereochemical constitution around the epoxide, it is believed that such an outcome is feasible. In addition, the studies reported by Carreira and co-workers on the opening of chloro vinyl epoxides also support the notion that this specific reaction of **278** would have a preference to undergo retentive opening (see Chapter 1.3.4.1).[118]

Therefore, vinyl epoxide **278** was subjected to a number of conditions to identify a viable protocol. The results are summarized in Table 12.

Table 12 Screening of conditions for opening of epoxide **278**



Entry	Reagents	Conditions[a]	Result
1	TMSCl (10 eq)	EtOAc, sealed tube, 3 d	traces of **282** (<5%)
2	TMSCl (30 eq)	CH_2Cl_2/EtOAc, sealed tube, 5–7 d	73% on 3.5 µmol scale 37–58% on 28 µmol scale
3	TMSCl (30 eq)	CH_2Cl_2/EtOAc, 40 °C	decomposition
4	TMSCl (10 eq), Ph_3P (0.1 eq)	CH_2Cl_2, sealed tube, 14 d	no reaction
5	TMSCl (20 eq), DMAP (0.1 eq)	CH_2Cl_2/EtOAc, sealed tube, 14 d	no reaction
6	$SiCl_4$ (10 eq), HMPA (0.1 eq)	CH_2Cl_2, –78 °C, 14 h	no reaction
7	$SiCl_4$ (10 eq), HMPA (0.1 eq)	CH_2Cl_2, 14 d	no reaction
8	Ph_3PCl_2[b] (3–10 eq)	CH_2Cl_2, 0 °C, 24 h	decomposition

[a] Unless otherwise noted, the reaction was conducted at room temperature.
[b] Freshly prepared from hexachloroethane and triphenylphosphine.[174]

Initial experimentation was inspired by the work from Llebaria *et al*. who nicely demonstrated the clean opening of vinyl epoxides under mild conditions with trimethylsilyl chloride.[51b] Treatment of epoxide **278** with TMSCl in EtOAc did not seem to efficiently furnish the desired transformation and after three days the reaction was stopped (entry 1). Analysis of the crude reaction mixture by ^1H

[174] R. Appel, H. Scholer, *Chem. Ber.* **1977**, *110*, 2382.

NMR spectroscopy, however, did reveal traces of a new product, later assigned to be the desired chlorohydrin **282**. Gratifyingly, it was found that when a 30-fold excess of TMSCl was added as a solution in CH_2Cl_2 the desired product as a single isomer was produced with good conversion (entry 2), although prolonged reaction times were needed. By repetitions of this procedure, it was noted that careful exclusion of moisture is vital for the success of this reaction; otherwise large amounts of a mixture of very polar products are slowly evolving over the course of the long reaction times. While these by-products were not isolated separately, they presumably arise from deprotections of the acetonides and silylethers. In this context, it is worth mentioning that addition of amine bases, such as diisopropylethylamine or 2,6-lutidine, to buffer the reaction mixture did not improve the reaction outcome as it inhibited the formation of product.

Furthermore, the reaction seemed to be rather sensitive to scaling, as indicated by the varying yields, and thus, the bulk of material **282** was produced in parallel reaction batches in contrast to further scale-up.

In efforts to improve the yield and shorten the reaction time, alternative reaction conditions were tested. Firstly, attempts to accelerate the reaction by an increase in temperature to 40 °C led to complete decomposition, demonstrating the narrow window of conditions which may be successful in this transformation. Consequently, attention was then turned to the possibility of exploiting Lewis base catalysis in combination with TMSCl. Phosphines[175,176] and amines[177] have proven to be effective Lewis base promoters, however, in our case, subjecting **278** to TMSCl with additives such as triphenylphosphine and *N*,*N*-dimethylaminopyridine afforded no conversion of the starting material, even after very long reaction times (i.e. 2 weeks, entries 4 and 5). Further attempts at employing Lewis base catalysis were pursued according to the findings by Denmark and co-workers which proved effective in the opening of epoxyketone **224**, as discussed in Chapter 2.3.1.[147] Therefore, in accordance with this procedure, silicon tetrachloride was added to a solution of the epoxide and HMPA in CH_2Cl_2 at –78 °C. However, epoxide **278** proved completely inert to these conditions; even warming the reaction to room temperature and stirring for 24 hours did not affect any reaction (entries 6 and 7).

Eventually, due to the efficiency in the synthesis of nominal mytilipin B,[125] triphenylphosphine dichloride was tested in the opening of **278** (entry 8). In agreement with the original protocol on epoxide openings with this reagent,[51a] Ph_3PCl_2 was added to a solution of the substrate in CH_2Cl_2 but only slow decomposition was observed.

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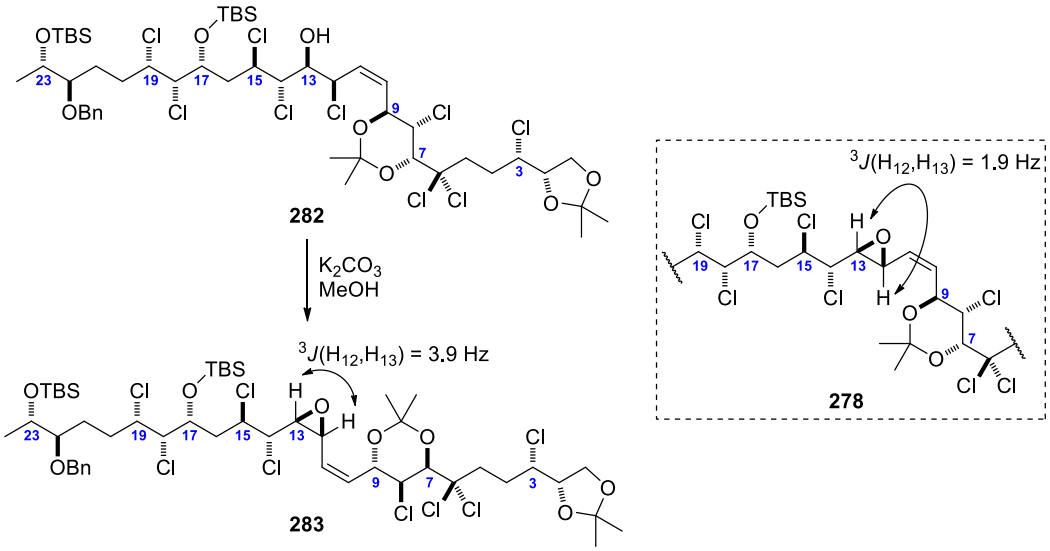
[175] G. C. Andrews, T. C. Crawford, L. G. Contillo Jr, *Tetrahedron Lett.* **1981**, *22*, 3803.
[176] C. E. Garrett, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 4534.
[177] P. Patschinski, C. Zhang, H. Zipse, *J. Org. Chem.* **2014**, *79*, 8348.

Although, retentive epoxide opening was anticipated under the conditions of entry 1/2, validation of this outcome was warranted. Therefore, in order to confirm whether the opening had taken place with inversion or retention, chlorohydrin **282** was treated with potassium carbonate in methanol to give a product slightly more polar than the epoxide opening precursor **278** (Scheme 55). This product was ultimately assigned to be *cis*-epoxide **283**.

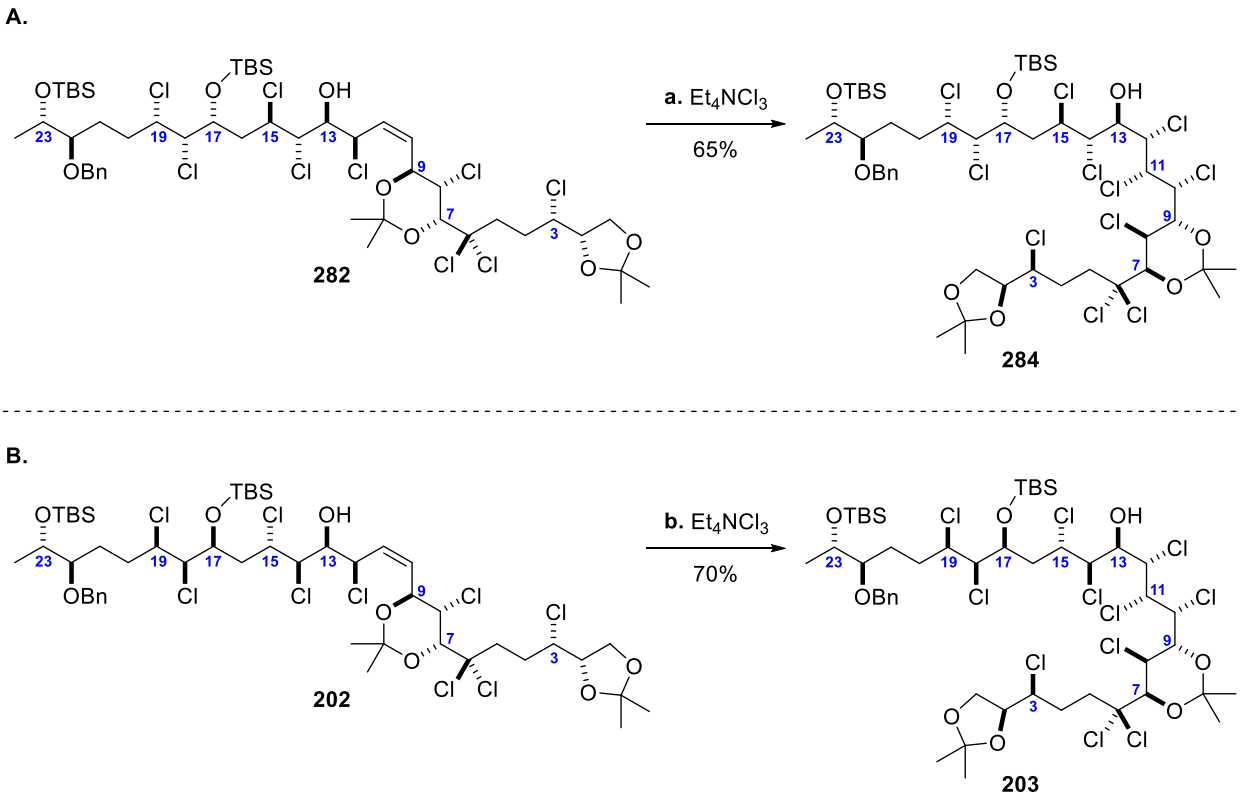


Scheme 55 Intramolecular displacement of **283** to give *cis*-epoxide **283**.

As showcased by the magnitude of coupling constants of oxirane protons H_{12}/H_{13}, the epoxide product from alkaline treatment of chlorohydrin exhibit a $^{3}J(H_{12},H_{13})$-value of 3.9 Hz, whereas the corresponding value for *trans*-epoxide **278** is 1.9 Hz. These values support the assignment of **283** as a *cis*-epoxide in accordance with the reference values reported by Lehn.[167]

It is reasonable to assume that the intramolecular displacement, shown in Scheme 55, proceed with inversion, and thus follows the configuration of C_{12} in **282** and thereby also the conclusion that the epoxide opening proceeded with retention as anticipated.

Introduction of the final two chlorides was achieved *via* dichlorination of allylic chloride **282** to afford undecachloride **284** (Scheme 56A).



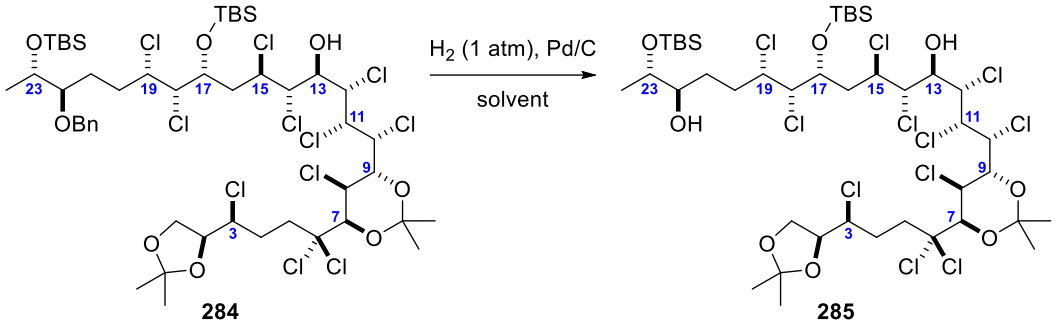
Scheme 56 A. Dichlorination of **282**. Reagents and conditions: a. Et_4NCl_3, CH_2Cl_2, –78 °C to 0 °C to r.t., 65%. **B.** Dichlorination of **202** in the synthesis of nominal mytilipin B.[125] Reagents and conditions: Et_4NCl_3, CH_2Cl_2, 0 °C to 4 °C, 70%.

After some experimentation, it was found that **284** could be obtained in 65% yield when **282** was subjected to Mioskowski's reagent at –78 °C followed by warming to room temperature.

The stereochemical outcome of the dichlorination is assumed to be in agreement with the observations made in the synthesis of nominal mytilipin B where **202** was dichlorinated to give **203** (Scheme 56B). Unfortunately, due to extensive overlap in the NMR spectra of **284**, the configuration could not be confirmed; however, the tentative assignment was deemed reasonable as the surrounding stereogenic centers C_7–C_9 and C_{12}–C_{13} in both substrate have the same configurations, thus any conformational preference resulting in a certain selectivity may be expected to be identical in the two scenarios. Moreover, with the same substitutions surrounding the olefin, any electronic effects would also be alike.

With all eleven chlorines installed, only the dehydration at C_{21}/C_{22} needed to be addressed to complete the structure of the hydrocarbon backbone. In order to achieve such a transformation, the C_{23}-hydroxyl group was deprotected using hydrogenolysis with palladium on charcoal. Table 13 summarizes the experimentations needed to obtain the deprotected product **285**.

Table 13 Hydrogenolysis of benzylether **284**



284 **285**

Entry	Solvent	Comments[a]	Result
1	EtOAc	r.t., 12 h	no reaction
2	EtOAc	H_2 bubbled through the solvent for 1 h stirred at r.t., 12 h	no reaction
3	THF	H_2 bubbled through the solvent for 1 h stirred at r.t., 12 h	traces of product
4	MeOH	H_2 bubbled through the solvent for 1 h stirred at r.t., 12 h	5-10% conversion
5	MeOH:THF (1:1)	H_2 bubbled through the solvent for 1 h stirred at r.t., 30 min	full conversion 66% yield

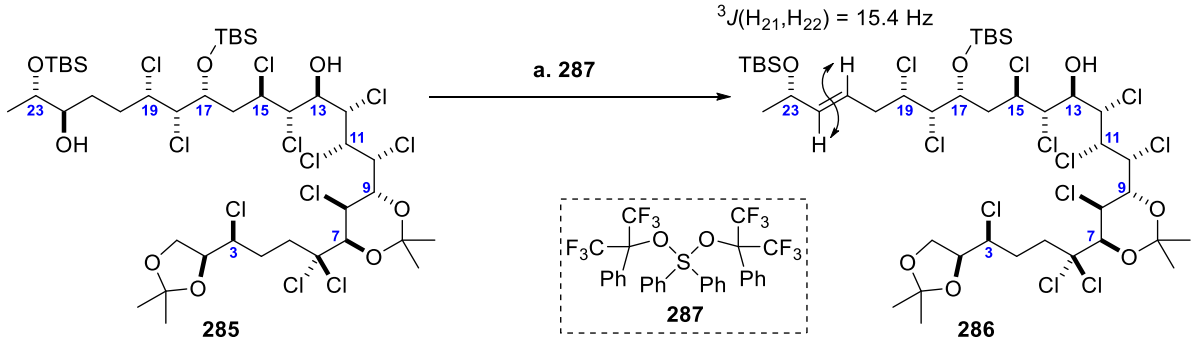
[a] Comments were performed in addition to the following protocol: A suspension of **284** and Pd/C (20 mol%) in solvent (5 mM) under nitrogen atmosphere was evacuated until the solvent started boiling, then the reaction vessel was backfilled with hydrogen. Three cycles of exchange were performed.

Initially, the debenzylation was tested employing standard conditions (Pd/C, H_2, EtOAc, r.t.) but to our disappointment, no reaction was observed and the starting material could be re-isolated when the reaction was stopped after 12 hours. In addition to exchanging the atmosphere in the reation vessel, it was further tested whether continuous bubbling of hydrogen gas through the solution would facilitate reaction progress, however, without success.

Due to concerns regarding potential side-reactions, such as de-chlorinations, elevated temperatures and more reactive catalysts were not investigated at this point. Instead, alternative solvents were tested, as debenzylations are known to be solvent-dependent and, in general, accelerated in more polar solvents.[178] Thus, the desired transformation was tested with THF as the solvent and indeed this led to the first detection of C_{22}-alcohol **285**, albeit only in trace amounts. This prompted the investigation of other solvents. Hydrogenolysis in methanol afforded 5-10% conversion as judged by ^{1}H NMR spectroscopy analysis of the crude reaction mixture. Eventually, it was found that using a 1:1 mixture of methanol and THF resulted in full consumption of the starting material in short time, and this allowed for the isolation of the desired product **285** in 66% yield.

[178] P. G. M. Wuts, T. W. Greene, Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols. In *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc.: 2006; pp 16-366.

Next, attention was turned to dehydration of the freshly liberated C_{22}-alcohol (Scheme 57). Inspired by the previous work on nominal mytilipin B, the dehydration was tested using Martin's Sulfurane (**287**).[179]



Scheme 57 Dehydration of **285**. Reagents and conditions: a. Martin's Sulfurane **287**, benzene, 0 °C, 30-40%.

When conducted on small scale (i.e. 3 mg), treatment of **285** with **287** in benzene at 0 °C resulted in isolation of the desired allyl TBS-ether **286** in 30-40% yield. Observartion of a ^3J value of 15.4 Hz between the alkenyl protons confirmed the configuration be *trans*. In addition, analysis of NMR spectroscopical data revealed that elimination had occurred towards C_{21} installing the double bond the desired C_{21}/C_{22} position. This regioselectivity may be explained by elimination *via* kinetic deprotonation at the more accessible C_{21}-methylene over the C_{23}-methine to give the less substituted olefin, namely the Hofmann product.[180]

A rationale for the stereoselectivity towards the *trans*-configured double bond may be found in a closer look at the mechanism. In their seminal report, Martin and Alhart discovered a strong preference towards *antiperiplanar* arrangement in the elimination from activated secondary alcohols, a characteristic for E2 elimination mechanism.[179] The transition state in such reactions has double bond character and thus, the relative energy of the reacting conformations is expected to correlate to the relative energy of the double bond isomers.[180] Hence, the transition state conformation leading to a *trans*-olefin is expected to be energetically favored over the conformation that leads to the *cis*-olefin.

With the installation of the C_{21}/C_{22} double bond the structure of the hydrocarbon backbone was successfully completed. At this point, a spectral comparison with the isolation report was thought to

[179] a) J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 2339; b) J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 2341; c) J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 4327; d) R. J. Arhart, J. C. Martin, *J. Am. Chem. Soc.* **1972**, *94*, 5003.

[180] For a discussion on regio- and stereoselectivity in elimination reactions, see: E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*. University Science Books: Sausatilo, CA, USA, 2006; p 588–592.

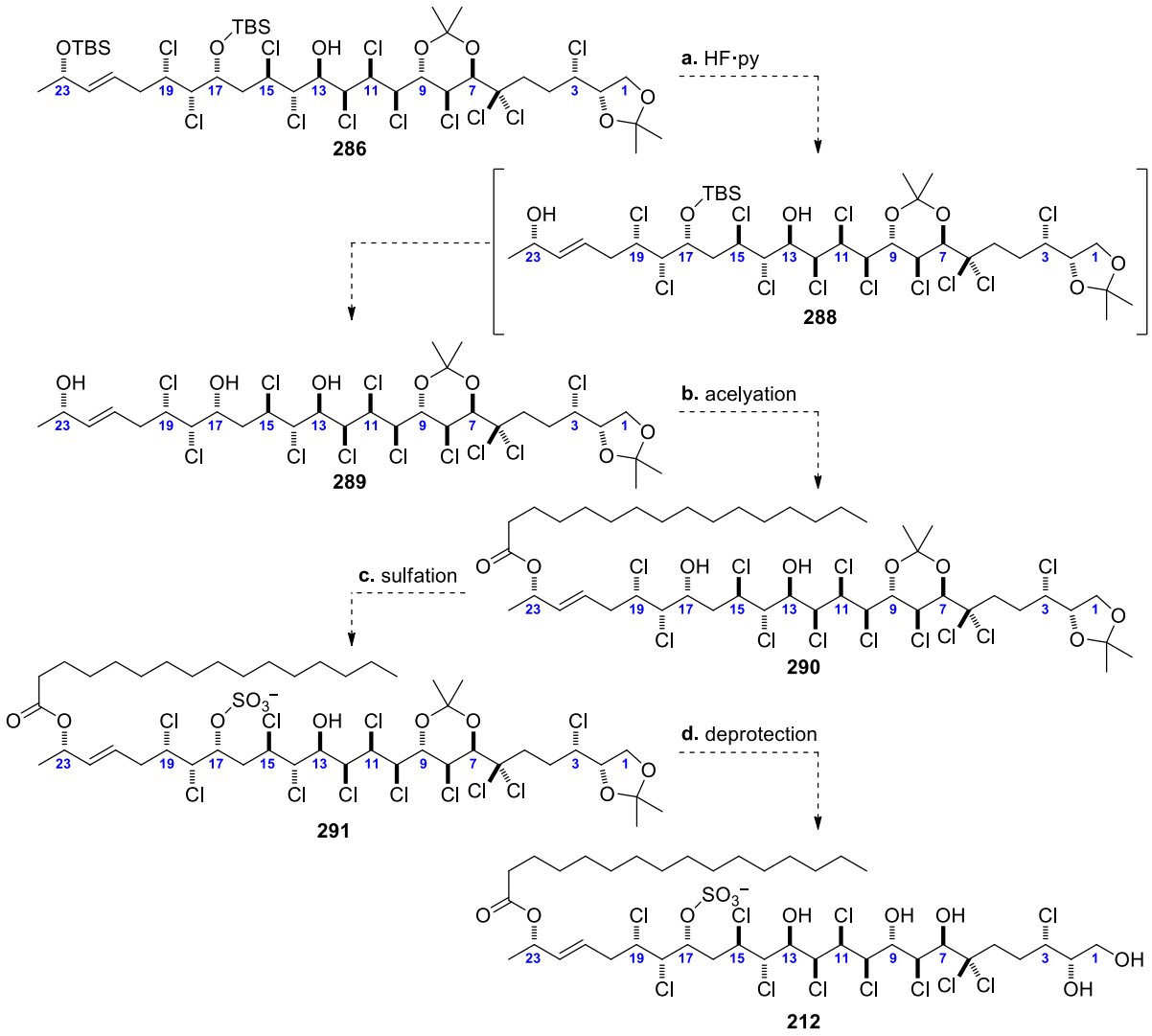
potentially reveal information on the correctness of the structural revision. Nonetheless, the structural differences were apparently too big and no viable conclusions could be made.

Although olefin **286** was detected as the sole product under the dehydration conditions, the reaction outcome turned out to be inconsistent. While repetition of the reaction on slighter larger scale (i.e. 5 mg) once again afforded the desired product, when subjecting the remaining material (in parallel batches) to the same conditions, nearly full decomposition was observed with only re-isolation of traces of starting material. Unfortunately, this outcome forced us to put our progress towards the natural product on hold and focus on bringing forward enough material to investigate the final steps. Despite strong efforts to produce more synthetic material, with the support from fellow doctoral students, Mr. Stefan Fischer and Mr. Philipp Sondermann, we have yet to await arrival at the synthetic frontline, i.e. olefin **286**. Due to time constraints, the practical work on the remaining investigations necessary to successfully complete the synthesis of revised mytilipin B will then be pursued by Mr. Sondermann.[181]

[181] When it was realized that more material was needed, Mr. Sondermann offered his help and has kindly taken on the task of continuing this project, as I was unable to postpone my exit from ETH.

4.4 Future Studies

Once arriving at the stage of allylic TBS-ether **286** with significant quantitites of material, another four steps are anticipated to be needed to complete the synthesis of revised mytilipin B (**212**). The synthetic operations, as outlined in Scheme 58, entail deprotections of the silyl ethers, acylation, sulfation, and finally acetal deprotection.



Scheme 58 Proposed final steps to complete the synthesis of revised mytilipin B (**212**).

Deprotection of the TBS-ethers at C_{17} and C_{23} are assumed to display very different reactivity. In the final steps *en route* to nominal mytilipin B, treatment with HF·pyridine proved effective to liberate the hydroxyl-groups, however, long reaction times and elevated temperatures were needed.[106,125] In preliminary experimentation with the minute amount of **286** obtained, it was observed by TLC analysis that subjecting the *bis*-TBS-ether to HF·pyridine resulted in full conversion to a more polar product, which upon longer reaction time, slowly disappeared with

concomitant appearance of a new and more polar product. These observations suggest inital formation of *mono*-TBS-ether **288** followed by complete deprotection to give **289**. In the event that the configuration at C_{23} would need to be inverted to make the isolated natural product, this observation is potentially useful as **288** represents an interesting substrate for selective inversion under Mitsunobu conditions.[182]

Selective acylation of the allylic alcohol **289** may be achieved using a protocol reported by Yamamoto[183] whereas sulfation to arrive at the penultimate intermediate **291** needs to be conducted under neutral or slightly basic conditions, e.g. with buffered SO_3 complexes,[184] to prevent acetal deprotections which potentially could result in unselective sulfations. Finally, numerous conditions for acetal hydrolysis have been reported,[178] thus allowing for some room for experimentation in case of unforeseen problems towards the end.

[182] As earlier mentioned, it is assumed that the C_{13}-hydroxyl group will be inert to final manipulations due to the surrounding steric bulk.
[183] K. Ishihara, H. Kurihara, H. Yamamoto, *J. Org. Chem.* **1993**, *58*, 3791.
[184] G. R. Heintzelman, W.-K. Fang, S. P. Keen, G. A. Wallace, S. M. Weinreb, *J. Am. Chem. Soc.* **2001**, *123*, 8851.

5 Conclusions and Outlook

With nine chlorinated and six oxygenated stereogenic centers on a C_{24} acyclic hydrocarbon backbone, mytilipin B is the most complex chlorosulfolipid isolated to date. The first total synthesis of this natural product led to the conclusion that the originally proposed structure was misassigned by the isolation group.

In this thesis, it has been described how we have proposed a structural revision based on careful analysis of the spectral data obtained from the isolation report (Chapter 2.1). Key conclusions followed from a *J*-based conformational analysis, an evaluation of the preferred conformation in solution based on homo- and heteronuclear coupling constants. The observation of a missing ROE crosspeak between H_{12} and H_{15}, which was reported to be present by the isolation team, led to a change in the C_{13} configuration. This ultimately resulted in the revision of five stereogenic centers in the revised structure.

Evaluation of common stereochemical arrays in chlorosulfolipids demonstrated that our revision led to a specific pattern which is also found in other chlorosulfolipids (Chapter 2.2). This pattern is not found in the nominal structure. Most notably, the pattern is identical to the configuration of mytilipin A which was isolated from the same source as mytilipin B, hence, providing strong support to our revision.

Synthetic studies on revised mytilipin B was built on a key Julia–Kocienski olefination reaction of two equally complex fragments. The C_1–C_{10} sulfone fragment **183** was previously prepared in the synthesis of nominal mytilipin B, and thus, it was conveniently synthesized following this protocol. Our work on the preparation of this compound led to some additional observations and improved strategies which were described in Chapter 4.1.

The C_{11}–C_{24} fragment, primary alcohol **274**, has been successfully prepared in 17 steps from D-malic acid (Chapter 4.2). Key reactions include *trans*-specific dichlorinations, a Sharpless asymmetric epoxidation, and highly *cis*-selective Wittig olefination with C_{18}–C_{24} phosphonium iodide **195**. By JBCA of key intermediates and comparison to known compounds, the configurations were secured unambiguously.

The phosphonium iodide **195** was prepared in the synthesis of nominal mytilipin B, and herein further observations and improved strategies in the preparation are documented.

Coupling of the two key fragments **183** and **274** *via* Julia–Kocienski olefination reaction was successfully executed to unite the entire hydrocarbon backbone (Chatper 4.3). Conditions for the subsequent key epoxide opening with retention were identified after some experimentation. With a dichlorination, the final two chlorides were introduced and a two-step deprotection/dehydration protocol has afforded C_{21}/C_{22} double bond. Thus, in this work, it has been demonstrated how the backbone structure of revised mytilipin B can be successfully synthesized in 23 steps from commercial material.

The remaining manipulations anticipated to achieve the target structure entail a four step sequence, consisting of silyl ether deprotection, acylation, sulfation, and final acetal hydrolysis (Chapter 4.4). Based on preliminary investigation, it is proposed that the silyl ethers display very different reactivity which, in light of the discussion on the structural revision, may be a useful observation if inversion of the C_{23} allylic alcohol is warranted.

Experimental Section

General Information

Unless otherwise noted, reactions were performed in flame dried glassware under an inert atmosphere of dry N_2. Reaction were monitored by thin layer chromatography (TLC) on Merck silica gel 60 F254 TLC glass plates and products were visualized by staining with Ceric Ammonium Molybdate or $KMnO_4$ stain. Solvent evaporation was performed on a rotary evaporator with a bath temperature of 40 °C. Unless stated otherwise, flash column chromatography was performed on Fluka silica gel (pore size 60Å, 230-400 mesh particle size) at 0.3–0.5 bar over pressure.

For reactions, THF, Et_2O, MeCN, PhMe, and CH_2Cl_2 were dried using an LC Technology Solutions SP-1 solvent purification system under an atmosphere of dry N_2. MeOH was distilled from Mg turnings, pyridine was distilled from KOH, and Et_3N was distilled from CaH_2 under N_2. Mioskowski's reagent, Et_4NCl_3, was prepared according a reported procedure.[53] Unless stated specifically, all other reagents and solvents were purchased from appropriate suppliers and used without further purification.

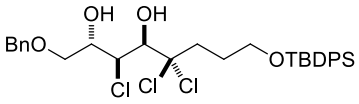
NMR spectra were recorded on Varian Mercury (300 MHz), Bruker DRX (400, 600 MHz), and Bruker Avance (400 MHz) spectrometers at ambient temperature. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard: $CDCl_3$ δ 7.26 (^{1}H NMR) 77.16 (^{13}C NMR); C_6D_6 δ 7.16 (^{1}H NMR) 128.06 (^{13}C NMR); d_6-acetone δ 2.05 (^{1}H NMR) 29.84 (^{13}C NMR); CD_3OD δ 3.31 (^{1}H NMR) 49.0 (^{13}C NMR). Spectral data were processed using MestReNova and data are reported as follows for ^{1}H NMR: chemical shift, multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad signal), coupling constant(s) in Hz, integration. Exact mass data were obtained by high resolution mass spectrometric (HRMS) analyses performed on a Bruker Daltonics maXis ESI-Q-TOF instrument (electrospray ionization measurement, ESI). IR spectra were recorded on a Perkin Elmer Spectrum TWO FT-IR (UATR) instrument. Peaks are reported in cm^{-1} and the intensity is given as strong (s), medium (m), weak (w), or broad (b). Optical rotations were measured on a Jasco DIP-2000 polarimeter in a cell with a 10 cm path length. The measurements are reported as average values of ten measurements and are given with the concentration (in g/100 mL) and solvent in parenthesis.

Experimental Procedures

5-((tert-butyldiphenylsilyl)oxy)pentan-1-ol (221)

To a suspension of NaH (60% in mineral oil; washed with hexane, 3.82g, 95 mmol) in THF (200 mL) was added pentane-1,5-diol (10 mL, 95 mmol) and the mixture was stirred for 1 h. Then, TBDPSCl (24.8 mL, 95 mmol) was added under vigorous stirring, followed by stirring for 1 h. The mixture was poured into diethylether and washed with 10% K_2CO_3 (aq) and brine, followed by drying ($MgSO_4$) and concentration to give the title compound (26 g, 80%) as a colorless oil.
Spectral data were in agreement with previous reports[140] and could be used without further purification.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.57 (m, 4H), 7.53 – 7.32 (m, 6H), 3.73 – 3.56 (m, 4H), 1.66 – 1.49 (m, 4H), 1.49 – 1.31 (m, 2H), 1.05 (s, 9H).

(2*S*,3*S*,4*R*)-1-(benzyloxy)-8-((tert-butyldiphenylsilyl)oxy)-3,5,5-trichlorooctane-2,4-diol (189)



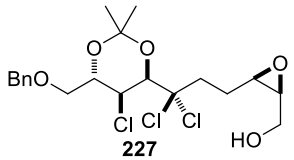
Epoxide opening: To a solution of epoxy ketone **224**[125] (31.7g, 55.5 mmol) in CH_2Cl_2 (555 ml) was added neat $SiCl_4$ (12.7 ml, 18.9 g, 111 mmol). After stirring for 5 minutes, HMPA (1.93 ml, 1.99 g, 11.1 mmol) was added dropwise and the resulting reaction mixture was stirred for three days. The reaction mixture was cooled to 0 °C and 700 ml pre-cooled saturated solution of $NaHCO_3$ (aq) was added to quench excess $SiCl_4$. The reaction mixture was warmed to room remperature and diluted with diethyl ether (500 mL). The mixture was filtered through a plug of celite, and the pad was subsequently washed thrice with diethyl ether. The phases of the filtrate were separated and the organic phase washed with H_2O, 10% $CuSO_4$ (aq), H_2O, and brine. The combined organic phases were re-extracted with 2x300 mL of diethyl ether and the combined organic extracts were then dried with $MgSO_4$, filtered concentrated to yield the crude title compound (33.7 g). Spectroscopic data of the crude material is in agreement with those previously reported[125] and was used without further purification.
Reduction: The reduction was carried out with $NaBH_4$ in MeOH at –78 °C as described in the previous protocol.[125]

$NaBH_4$ (2.51 g, 65.9 mmol) and MeOH (650 mL) were stirred for 15 min prior to cooling to –78 °C. Hereafter, a solution of crude ketone (33.7 g) in MeOH (550 mL) was added slowly and the resulting mixture was stirred for 90 min. The reaction was quenched with brine and warmed to room temperature before the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated. Purification by column chromatography yielded 18.1 g (53%) of the desired 1,3-diol **189** over two steps.

Spectral data were in agreement with those previously reported.[125]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 4H), 7.48 – 7.29 (m, 11H), 4.71 (d, *J* = 8.6 Hz, 1H), 4.66 – 4.56 (m, 2H), 4.55 (d, *J* = 10.4 Hz, 1H), 4.03 – 3.86 (m, 1H), 3.83 – 3.73 (m, 2H), 3.74 (t, *J* = 5.9 Hz, 2H), 2.95 (dd, *J* = 10.3, 1.2 Hz, 1H), 2.79 (dd, *J* = 7.2, 1.2 Hz, 1H), 2.64 – 2.47 (m, 1H), 2.45 – 2.27 (m, 1H), 2.04 – 1.89 (m, 2H), 1.06 (s, 9H).

((2*S*,3*R*)-3-(3-((4*R*,5*S*,6*S*)-6-((benzyloxy)methyl)-5-chloro-2,2-dimethyl-1,3-dioxan-4-yl)-3,3-dichloropropyl)oxiran-2-yl)methanol (227)



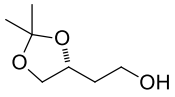
227

Intramolecular displacement of **228**: To a solution of chlorohydrin **228** (1.3 g, 2.7 mmol) in MeOH (54 mL) was added K_2CO_3 (550 mg, 4.0 mmol) and stirred for 4 days. Hereafter, the mixture was diluted with a saturated solution of NH_4Cl (aq) and the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), and concentrated. Purification by column chromatography (50% Et_2O in pentane) afforded epoxide **227** (0.9 g, 75%) as a colorless oil.

Spectral data were in agreement with those previously reported.[125]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.27 (m, 5H), 4.64 – 4.59 (m, 2H), 4.53 – 4.41 (m, 2H), 4.02 (ddd, *J* = 7.5, 4.3, 3.1 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.81 – 3.70 (m, 1H), 3.70 – 3.65 (m, 2H), 3.20 (dt, *J* = 6.8, 4.3 Hz, 1H), 3.15 – 3.05 (m, 1H), 2.85 (ddd, *J* = 14.5, 9.4, 6.6 Hz, 1H), 2.43 (ddd, *J* = 14.5, 9.6, 6.3 Hz, 1H), 2.15 – 2.00 (m, 2H), 1.81 (s, 1H), 1.50 (s, 3H), 1.44 (s, 3H).

(*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (246) [185]



Reduction: To a precooled (0 °C) solution of $BH_3 \cdot SMe_2$ (2 M in THF, 1.6 L, 3.2 mol) was added $B(OMe)_3$ (335 mL, 3.0 mol) followed by very careful addition of a solution of D-malic acid (134 g, 1.0 mol) in THF (0.50 L). After finished addition, the ice bath was removed and the mixture was allowed to warm to room temperature and stirred in total 16 h. The mixture was cooled back to 0 °C and MeOH (200 mL) was slowly added. The volatiles were removed by concentration and hereafter three cycles of evaporation from MeOH (500 mL) were performed to remove $B(OMe)_3$.

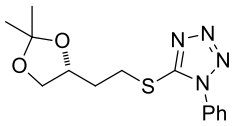
Acetal protection: The crude mixture was dissolved in acetone (2 L) and anhydrous $CuSO_4$ (74 g, 0.75 mol) was added followed by *p*-TsOH (0.86 g, 5 mmol). The mixture was stirred for 5 days, then quenched with K_2CO_3 (21 g, 0.15 mol) and stirred for 15 min. The suspension was filtered through celite and concentrated. Distillation afforded the product (133 g, 91%) as a colorless liquid.

Spectral data were in agreement with those previously reported in the literature.[185]

bp. 95–97 °C at 11 mmHg

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (p, *J* = 6.2 Hz, 1H), 4.08 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.79 (t, *J* = 5.7 Hz, 2H), 3.59 (t, *J* = 7.7 Hz, 1H), 1.90 – 1.75 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H).

(*R*)-5-((2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)thio)-1-phenyl-1H-tetrazole (247)[125]



To a mechanically stirred suspension of 1-phenyl-1H-tetrazole-5-thiol (86.0 g, 483 mol) and PPh_3 (95.0 g, 362 mmol) in CH_2Cl_2 (1.40 L) cooled to 0 °C was added a solution of **246** (35.3 g, 241 mmol) in CH_2Cl_2 (250 mL). A solution of diisopropyl azodicarboxylate (90 mL, 435 mmol) in CH_2Cl_2 (350 mL) was added dropwise over 30 min and the resulting yellow solution was stirred for 1.5 h at 0 °C.

The reaction was quenched with sat. $NaHCO_3$(aq) and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

[185] M. Barth, F. D. Bellamy, P. Renaut, S. Samreth, F. Schuber, *Tetrahedron* **1990**, *46*, 6731.

The crude mixture was dissolved in Et_2O and cooled to –20 °C. After 3 h, the precipitate was removed by filtration and the mother liquor was concentrated under reduced pressure. The crude mixture was then dissolved in PhMe and cooled to 0 °C. After 3 h, the precipitate was removed by filtration and the mother liquor was concentrated under reduced pressure. A second cycle of precipitation from PhMe resulted in further removal of solid impurities.

Purification by column chromatography (2.5% MeCN in PhMe) yielded the title compound (58.3 g, 79%) as a colorless oil.

Spectral data were in agreement with those previously reported for the enantiomeric compound.[125]

TLC: R_f (20% EtOAc in hexane) = 0.18

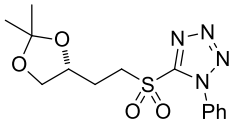
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.48 (m, 5H), 4.25 (dtd, *J* = 8.2, 6.3, 4.1 Hz, 1H), 4.08 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.61 (dd, J = 8.1, 6.6 Hz, 1H), 3.58 – 3.37 (m, 2H), 2.24 – 1.97 (m, 2H), 1.42 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 133.8, 130.3, 130.0, 123.9, 109.4, 74.4, 69.1, 33.6, 29.7, 27.1, 25.7.

HRMS (ESI) exact mass calculated for $C_{14}H_{19}N_4O_2S$ [$(M+H)^+$], 307.1229; found 307.1221.

Optical Rotation: $[\alpha]_D^{25.4} = +8.0$ (*c* = 2.7, $CHCl_3$).

(*R*)-5-((2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)sulfonyl)-1-phenyl-1H-tetrazole (248)[125]



Sulfide **247** (44.3 g, 145 mmol) was dissolved in EtOH (1.45 L) and cooled to 5 °C. Meanwhile, the oxidant solution was prepared by dissolving $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (26.8 g, 21.7 mmol) in 30% H_2O_2 (aq) (112 mL, 1.09 mol).

The oxidant solution was added dropwise to the cold ethanolic solution and the resulting yellow mixture was allowed to warm to r.t. and stirred for 4 h.

The reaction mixture was cooled to 0 °C and quenched by addition of a 1:1 mixture of saturated $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) under vigorous stirring (addition until the mixture turned colorless and gave negative peroxide test). The mixture was extracted with EtOAc three times. The combined organic layers were dried ($NaSO_4$), filtered, and concentrated under reduced pressure.

Purification by column chromatography (50% Et_2O in pentane) afforded **248** (45.0 g, 92%) as a colorless oil which solidified upon standing at r.t.

Reprotection of hydrolyzed product (**249**): The crude mixture was dissolved in dry acetone (0.5−1 M) and anhydrous $CuSO_4$ (1 equiv) was added followed by *p*-TsOH (0.5 mol%) and then stirred for

5 days. K_2CO_3 (0.15 equiv) was added and after 15 min of stirring the suspension was filtered through celite and concentrated. Purification by column chromatography (50% Et_2O in pentane) afforded **248**.

Spectral data were in agreement with those previously reported for the enantiomeric compound.[125]

TLC: R_f (20% EtOAc in hexane) = 0.14

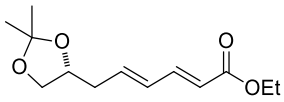
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.51 (m, 5H), 4.25 (dtd, *J* = 8.4, 6.0, 3.7 Hz, 1H), 4.10 (dd, *J* = 8.3, 6.2 Hz, 1H), 3.93 (ddd, *J* = 15.4, 10.3, 5.3 Hz, 1H), 3.81 (ddd, *J* = 14.8, 10.2, 5.7 Hz, 1H), 3.64 (dd, *J* = 8.4, 5.8 Hz, 1H), 2.31 – 2.06 (m, 2H), 1.42 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 133.1, 131.7, 129.9, 125.2, 109.9, 73.5, 68.8, 53.1, 27.0, 27.0, 25.5.

HRMS (ESI) exact mass calculated for $C_{14}H_{19}N_4O_4S$ [$(M+H)^+$], 339.1122; found 339.1122.

Optical Rotation: $[\alpha]_D^{25.4} = -4.7$ (*c* = 1.6, $CHCl_3$).

(2*E*,4*E*)-ethyl 6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)hexa-2,4-dienoate (220)[125]



Olefination: To a solution of **248** (30.4 g, 90.0 mmol) and (*E*)-ethyl 4-oxobut-2-enoate (13.3 mL, 110 mmol) in THF (360 mL) at –78 °C was added a 1.0 M solution of KHMDS in THF (105 mL, 105 mmol). The dark red solution was stirred for 3 h at this temperature and then slowly warmed to r.t. over 1 h. The reaction was quenched with water and extracted with EtOAc three times. The combined organic extracts were washed with sat. $NaHCO_3$(aq), dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The product was obtained (21.6 g, 77%), after purification by column chromatography (10% EtOAc in hexane), as a mixture of *E* and *Z* isomer (*E*/*Z* = 2.8/1).

Z to E Isomerization with Ph_2S_2: To a solution of the diastereomeric mixture (16.5 g, 68.7 mmol) in benzene (250 mL) was added diphenyl disulfide (1.50 g, 6.87 mmol) and the solution was degassed three times, using freeze-pump-thaw. The mixture was subjected to white light (150 W) and stirred at r.t. The reaction progress was monitored by ^{1}H NMR analysis of aliquots. After 12 h the mixture was concentrated under reduced pressure and purified by column chromatography (10% EtOAc in hexane) to give the product (16.0 g, 97%) in a ratio of *E*/*Z* = 5.3:1.

Z to E Isomerization with I_2: To a solution of the diasteremeric mixture (10 g, 41.6 mmol) in CH_2Cl_2 (400 mL) was added I_2 (530 mg, 2.1 mmol) and the mixture was stirred with the light on for 12 h. The mixture was washed three times with a saturated solution of $Na_2S_2O_3$ (aq) followed by washing

with brine. The organic phase was dried over $MgSO_4$ and concentrated to give a diastereomeric mixture (9.9 g, 99%) in a ratio of *E*/*Z* = 6.0:1 which was used as such.

Spectral data were in agreement with those previously reported for the enantiomeric compound.[125]

TLC: R_f (20% EtOAc in hexane) *E*/*Z* = 0.36

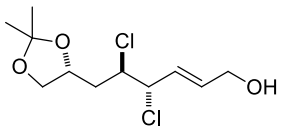
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 15.4, 10.7 Hz, 1H), 6.32 – 6.16 (m, 1H), 6.08 (dt, *J* = 15.1, 7.1 Hz, 1H), 5.81 (d, *J* = 15.4 Hz, 1H), 4.27 – 4.12 (m, 3H), 4.02 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.56 (dd, *J* = 8.1, 6.8 Hz, 1H), 2.52 – 2.30 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 144.4, 138.4, 131.1, 120.6, 109.4, 74.9, 68.9, 60.4, 37.3, 27.0, 25.7, 14.4.

HRMS (ESI) exact mass calculated for $C_{13}H_{21}O_4$ [$(M+H)^+$], 241.1432; found 241.1432.

Optical Rotation: $[\alpha]_D^{23.2} = -1.4$ (*c* = 2.1, $CHCl_3$).

(4*S*,5*R*,*E*)-4,5-dichloro-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)hex-2-en-1-ol (219)[125]



Dichlorination: To a solution of diene **220** (15.7 g, 65.3 mmol, *E*/*Z* = 5.3:1) in CH_2Cl_2 (440 ml) at 0 °C was added solid Et_4NCl_3 (23.2 g) in small portions. After 10 min, the solution had turned colorless again and an additional 15.5 g of Et_4NCl_3 was added. After an additional 10 min, the solution had turned colorless again, and 7.7 g of Et_4NCl_3 was added. The reaction remained yellow after stirring for another 20 min. The reaction mixture was poured into a stirred 1:1 mixture of sat. NaS_2O_3(aq) and sat. Na_2CO_3(aq). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by column chromatography (10% EtOAc in hexane) to give the dichloroester (15.2 g, 75%) as an inseparable mixture of diastereomers (*dr* ~ 2:1) which was used as such.

TLC: R_f (20% EtOAc in hexane) = 0.38

Reduction: To a solution of dihloroesters (15.2 g, 48.9 mmol) in PhMe (490 ml) at 0 °C was added a 1.0 M solution of DIBAL-H in hexane (108 mL, 108 mmol) dropwise, and the mixture was stirred for 25 min. The reaction was quenched with a saturated aqueous solution of Rochelle salt and stirred for 3 h. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (gradient elution with 20 to 50% EtOAc in hexane, 10% increments) yielded the unstable allylic alcohol (7.52 g, 57%) as a mixture of diastereomers (dr ~ 5:1) which was used as such.

Spectral data were in agreement with those previously reported for the enantiomeric compound.[125]

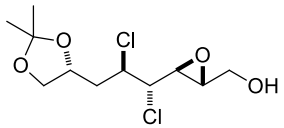
TLC: R_f (20% EtOAc in hexane) = 0.08; R_f (50% EtOAc in hexane) = 0.47

^{1}H NMR (400 MHz, $CDCl_3$ δ 5.97 (dt, *J* = 15.7, 4.9 Hz, 1H), 5.86 (ddt, *J* = 15.3, 8.5, 1.6 Hz, 1H), 4.57 (dd, *J* = 8.3, 5.4 Hz, 1H), 4.35 (dtd, *J* = 9.3, 6.1, 3.2 Hz, 1H), 4.28 (ddd, *J* = 10.7, 5.3, 2.6 Hz, 1H), 4.23 – 4.17 (m, 2H), 4.10 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.59 (dd, *J* = 8.2, 6.1 Hz, 1H), 2.17 (ddd, *J* = 14.3, 9.4, 2.6 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.40 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 127.0, 109.4, 73.0, 69.3, 65.0, 62.6, 62.3, 39.6, 27.2, 25.7.

Optical Rotation: $[\alpha]_D^{24.2} = +6.9$ (*c* = 1.0, $CHCl_3$).

((2*R*,3*S*)-3-((1*S*,2*R*)-1,2-dichloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)oxiran-2-yl)methanol (252)



Powdered 4Å molecular sieves (7 g) were flame dried under high vacuum, and then stirred under high vacuum at 150 °C for 8 h. After allowing the powder to cool to r.t. under nitrogen, CH_2Cl_2 (260 mL) was added and the suspension was cooled to –20 °C. Freshly distilled (–)-D-diethyl tartrate (6.26 mL, 36.4 mmol) was added followed by dropwise addition of freshly distilled $Ti(OiPr)_4$ (9.14 mL, 31.2 mmol). The catalyst was allowed to age for 20 min, whereafter a solution of allylic alcohol **219** (7.00 g, 26.0 mmol) in CH_2Cl_2 (260mL) was added dropwise. After stirring the mixture for 30 min, *t*-BuO_2H (5.5 M in decane, 14.2 mL, 78.0 mmol) was added dropwise and the mixture was stirred for 14 h. Water was added and the biphasic system was allowed to warm to r.t. The mixture was poured into 30 % NaOH(aq) (sat. with NaCl) and stirred for 30 min, then filtered through celite. The aqueous phase was extracted with CH_2Cl_2 three times, and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (30 % EtOAc in hexane) gave the title epoxide (3.05 g, 41%) and **253** (1.47 g, 20%) both as a colorless oils.

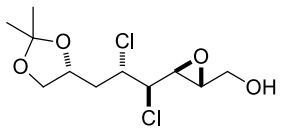
TLC: R_f (50% EtOAc in hexane) = 0.48

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.46 (ddd, *J* = 11.1, 4.3, 2.4 Hz, 1H), 4.39 (dtd, *J* = 9.2, 6.0, 3.0 Hz, 1H), 4.12 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.97 (dd, *J* = 12.9, 2.4 Hz, 1H), 3.79 (dd, *J* = 7.7, 4.3 Hz, 1H), 3.71 (dd, *J* = 12.9, 4.0 Hz, 1H), 3.62 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.40 (dd, *J* = 7.7, 2.1 Hz, 1H), 3.15 (dt, *J* = 4.0, 2.3 Hz, 1H), 2.16 (ddd, *J* = 14.4, 9.5, 2.4 Hz, 1H), 2.00 (ddd, *J* = 14.3, 11.1, 3.0 Hz, 1H), 1.65 (br s, 1H), 1.41 (d, *J* = 0.8 Hz, 3H), 1.37 – 1.34 (m, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 109.5, 72.8, 69.3, 64.1, 61.4, 60.7, 57.8, 54.7, 39.5, 27.3, 25.7.

HRMS (ESI) exact mass calculated for $C_{11}H_{18}Cl_2NaO_4$ [$(M+Na)^+$], 307.0478; found 307.0478.

IR: ν 3460(b), 2987(m), 2936(m), 2877(m), 1744(m), 1381(s), 1224(s), 1156(m), 1059(s), 833(s).
Optical Rotation: $[\alpha]_D^{24.4} = +28$ (c = 1.1, $CHCl_3$).



Data for 253:

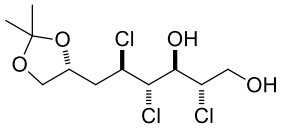
TLC: R_f (50% EtOAc in hexane) = 0.33

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 – 4.38 (m, 1H), 4.16 – 4.07 (m, 2H), 4.00 – 3.89 (m, 2H), 3.77 – 3.69 (m, 1H), 3.62 (dd, *J* = 8.2, 6.7 Hz, 1H), 3.34 – 3.23 (m, 2H), 2.34 (dt, *J* = 14.7, 6.8 Hz, 1H), 2.26 – 2.13 (m, 1H), 1.96 – 1.86 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.6, 72.6, 69.1, 64.4, 61.0, 60.4, 59.5, 57.1, 38.5, 26.9, 25.8.

HRMS (ESI) exact mass calculated for $C_{11}H_{18}Cl_2NaO_4$ [$(M+Na)^+$], 307.0478; found 307.0480.

(2*S*,3*S*,4*S*,5*R*)-2,4,5-trichloro-6-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)hexane-1,3-diol (254)



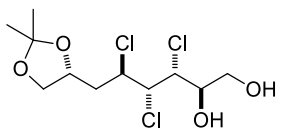
To a solution of **252** (0.055 g, 0.193 mmol) in benzene (2 mL) was added TiCl(O*i*-Pr)$_3$ (0.069 ml, 0.29 mmol) and the mixture was stirred for 4 h. Hereafter, the reaction was quenched with a saturated solution of Rochelle salt and stirred overnight. The aqueous phase was extracted three times with EtOAc, whereafter the combined organic phases were dried ($MgSO_4$) and concentrated.
Column chromatography (20–50% EtOAc in hexane) afforded **254** (34 mg, 55%) and **255** (10 mg, 16%) both as colorless oils.

TLC: R_f (50% EtOAc in hexane) = 0.35

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (ddd, *J* = 10.5, 3.2, 2.4 Hz, 1H), 4.44 (td, *J* = 8.6, 4.3, 1H), 4.42 (td, *J* = 8.1, 3.3, 1H), 4.37 (dp, *J* = 9.2, 3.0 Hz, 1H), 4.19 – 4.15 (m, 1H), 4.12 (dd, *J* = 8.3, 6.1 Hz, 1H), 4.09 – 3.95 (m, 2H), 3.62 (dd, *J* = 8.3, 5.9 Hz, 1H), 3.53 (d, *J* = 6.0 Hz, 1H), 2.50 (s, 1H), 2.18 (ddd, *J* = 14.5, 9.4, 2.5 Hz, 1H), 1.98 (ddd, *J* = 14.5, 10.5, 3.2 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 75.7, 73.2, 69.4, 66.8, 63.7, 62.0, 59.1, 38.0, 27.2, 25.7.

HRMS (ESI) exact mass calculated for $C_{11}H_{19}Cl_3NaO_4$ [$(M+Na)^+$], 343.0241; found 341.0243.



Data for 255:

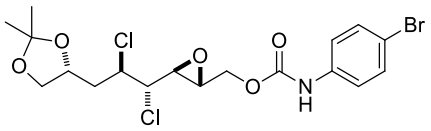
TLC: R_f (50% EtOAc in hexane) = 0.30

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, *J* = 9.1, 1.7 Hz, 1H), 4.54 (dd, *J* = 10.5, 1.7 Hz, 1H), 4.44 (ddd, *J* = 9.2, 6.3, 3.4 Hz, 1H), 4.38 (td, *J* = 10.9, 1.8 Hz, 1H), 4.14 (dd, *J* = 8.2, 6.0 Hz, 1H), 4.02 – 3.90 (m, 3H), 3.66 (dd, *J* = 8.2, 5.7 Hz, 1H), 2.76 (s, 1H), 2.68 (ddd, *J* = 14.3, 9.3, 2.0 Hz, 1H), 1.75 (ddd, *J* = 14.4, 11.1, 3.3 Hz, 1H), 1.63 (s, 1H) 1.44 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 72.9, 72.4, 69.4, 64.6, 63.1, 60.0, 59.5, 40.4, 27.3, 25.8.

HRMS (ESI) exact mass calculated for $C_{11}H_{19}Cl_3NaO_4$ [$(M+Na)^+$], 343.0241; found 341.0244.

((2*R*,3*S*)-3-((1*S*,2*R*)-1,2-dichloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)oxiran-2-yl)methyl (4-bromophenyl)carbamate (256)



To a solution of **252** (47 mg, 0.17 mmol) and Et_3N (50 µL, 0.33 mmol) in CH_2Cl_2 (1.6 mL) was added *p*-bromophenyl isocyanate (39 mg, 0.20 mmol) and the mixture was stirred for 1h. The organic phase was washed twice with water, dried ($MgSO_4$), and concentrated. Purification by preparative TLC (eluent 50% EtOAc in hexane) gave the title compound (72 mg, 88%) as a viscuous oil.

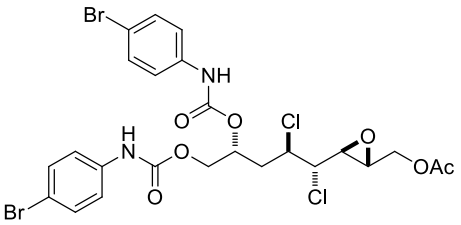
TLC: R_f (50% EtOAc in hexane) = 0.56

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.90 (s, 1H), 4.51 – 4.37 (m, 3H), 4.18 (dd, *J* = 12.3, 5.7 Hz, 1H), 4.13 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.85 (dd, *J* = 7.1, 4.2 Hz, 1H), 3.63 (dd, *J* = 8.3, 5.6 Hz, 1H), 3.32 (dd, *J* = 7.1, 2.0 Hz, 1H), 3.28 (ddd, *J* = 5.7, 3.7, 2.0 Hz, 1H), 2.15 (ddd, *J* = 14.4, 9.6, 2.5 Hz, 1H), 1.99 (ddd, *J* = 14.3, 11.1, 3.1 Hz, 1H), 1.42 (d, *J* = 0.8 Hz, 3H), 1.36 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 136.7, 132.2, 132.1, 120.4, 109.6, 72.7, 69.2, 64.3, 63.6, 61.1, 55.7, 54.5, 39.5, 27.3, 25.7.

HRMS (ESI) exact mass calculated for $C_{18}H_{23}BrCl_2NO_5$ [$(M+H)^+$], 482.0131; found 482.0135.

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*)-4,5-bis(((4-bromophenyl)carbamoyl)oxy)-1,2-dichloropentyl)oxiran-2-yl)methyl acetate (257)



To a solution of **263** (43 mg, 0.15 mmol) and Et_3N (0.08 mL, 0.6 mmol) in CH_2Cl_2 (0.75 mL) was added *p*-bromophenyl isocyanate (90 mg, 0.45 mmol) and the mixture was stirred for overnight. The organic phase was washed twice with water, dried ($MgSO_4$), and concentrated. Purification by preparative TLC (40% EtOAc in hexane) gave the title compound (63 mg, 62%) as a viscuous oil.

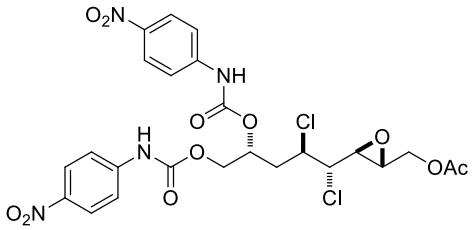
TLC: R_f (50% EtOAc in hexane) = 0.80

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 8H), 6.79 (s, 1H), 6.75 (s, 1H), 5.40 (ddt, *J* = 10.1, 5.9, 3.1 Hz, 1H), 4.44 (ddd, *J* = 12.5, 10.3, 3.5 Hz, 1H), 4.33 (ddd, *J* = 11.1, 4.3, 2.2 Hz, 1H), 4.26 (dd, *J* = 12.0, 5.5 Hz, 1H), 4.04 (dd, *J* = 12.5, 5.8 Hz, 1H), 3.78 (dd, *J* = 7.5, 4.2 Hz, 1H), 3.76 – 3.72 (m, 1H), 3.31 (dd, *J* = 7.5, 2.0 Hz, 1H), 3.25 (ddd, *J* = 5.5, 3.4, 1.9 Hz, 1H), 2.33 (ddd, *J* = 15.0, 10.2, 2.2 Hz, 1H), 2.15 (ddd, *J* = 15.2, 11.2, 2.6 Hz, 1H), 2.11 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 136.6, 136.5, 132.3, 132.3, 132.1, 132.1, 130.4, 121.6, 77.2, 69.9, 65.9, 63.4, 63.1, 59.5, 55.5, 55.0, 36.1, 25.6, 20.7.

HRMS (ESI) exact mass calculated for $C_{24}H_{25}Br_2Cl_2N_2O_7$ $[(M+H)^+]$, 680.9400; found 680.9403.

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*)-1,2-dichloro-4,5-bis(((4-nitrophenyl)carbamoyl)oxy)pentyl)oxiran-2-yl)methyl acetate (258)



To a solution of **263** (50 mg, 0.17 mmol) and Et_3N (0.1 mL, 0.7 mmol) in CH_2Cl_2 (0.87 mL) was added *p*-nitrophenyl isocyanate (86 mg, 0.52 mmol) and the mixture was stirred for overnight. The organic phase was washed twice with water, dried ($MgSO_4$), and concentrated. Purification by preparative TLC (40% EtOAc in hexane) gave the title compound (75 mg, 70%) as a viscuous oil.

TLC: R_f (50% EtOAc in hexane) = 0.76

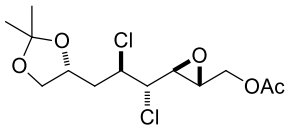
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.09 (m, 4H), 7.67 – 7.50 (m, 4H), 5.45 (ddd, *J* = 8.4, 4.1, 1.8 Hz, 1H), 4.54 (dd, *J* = 12.0, 3.5 Hz, 1H), 4.42 (dd, *J* = 12.5, 3.4 Hz, 1H), 4.35 (ddd, *J* = 11.2, 4.2,

2.2 Hz, 1H), 4.29 (dd, *J* = 12.0, 5.5 Hz, 1H), 4.04 (dd, *J* = 12.5, 5.8 Hz, 1H), 3.80 (dd, *J* = 7.5, 4.1 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.32 (dd, *J* = 7.5, 2.0 Hz, 1H), 2.37 (ddd, *J* = 15.1, 10.2, 2.2 Hz, 1H), 2.19 (ddd, *J* = 15.1, 11.2, 2.7 Hz, 1H), 2.11 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 152.4, 152.1, 143.8, 143.7, 143.4, 143.3, 125.3, 118.1, 70.5, 68.1, 66.3, 63.5, 63.3, 59.5, 55.7, 55.2, 36.0, 25.7, 20.9.

HRMS (ESI) exact mass calculated for $C_{24}H_{25}Cl_2N_4O_{11}$ [$(M+H)^+$], 615.0891; found 615.0889.

((2*R*,3*S*)-3-((1*S*,2*R*)-1,2-dichloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propyl)oxiran-2-yl)methyl acetate (262)



To a solution of **252** (3.13 g, 11.0 mmol) in CH_2Cl_2 (110 mL) cooled to 0 °C was added, in the following order, Et_3N (7.65 mL, 54.9 mmol), DMAP (134 mg, 1.10 mmol), and AcCl (1.56 mL, 22.0 mmol). After stirring for 15 min, the reaction was quenched with sat. NH_4Cl(aq), the phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and concentrated. Column chromatography (20% EtOAc in hexane) yielded the acetate (2.83 g, 79%) as a colorless oil.

TLC: R_f (50% EtOAc in hexane) = 0.74

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 – 4.34 (m, 3H), 4.12 (dd, *J* = 8.2, 6.1 Hz, 1H), 4.00 (dd, *J* = 12.5, 5.9 Hz, 1H), 3.75 (dd, *J* = 7.7, 4.3 Hz, 1H), 3.61 (dd, *J* = 8.2, 6.0 Hz, 1H), 3.30 (dd, *J* = 7.7, 2.0 Hz, 1H), 3.21 (ddd, *J* = 5.9, 3.2, 2.0 Hz, 1H), 2.06 (s, 3H), 2.00 (ddd, *J* = 14.3, 11.0, 3.1 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H).

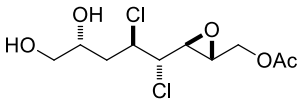
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 109.5, 72.7, 69.3, 63.7, 63.4, 61.4, 55.5, 54.8, 39.6, 27.3, 25.7, 20.8.

HRMS (ESI) exact mass calculated for $C_{13}H_{21}Cl_2O_5$ [$(M+H)^+$], 327.0761; found 327.0760.

IR: ν 2987(m), 2939(m), 2879(w), 1745(s), 1454(w), 1381(m), 1227(s), 1039(m), 833(w).

Optical Rotation: $[\alpha]_D^{24.5} = +29$ (*c* = 1.0, $CHCl_3$).

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*)-1,2-dichloro-4,5-dihydroxypentyl)oxiran-2-yl)methyl acetate (263)



To a solution of acetal **262** (2.83 g, 8.65 mmol) in MeOH (170 mL) was added (–)-camphorsulfonic acid (201 mg, 0.865 mmol) and the reaction was stirred for 3.5 h. Hereafter, the mixture was diluted with EtOAc and sat. $NaHCO_3$(aq). The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography (gradient elution with 50 to 90% EtOAc in hexane, then EtOAc) gave diol **263** (1.98 g, 80%) as a colorless oil.

TLC: R_f (50% EtOAc in hexane) = 0.16

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (ddd, *J* = 10.9, 4.1, 2.6 Hz, 1H), 4.40 (dd, *J* = 12.5, 3.2 Hz, 1H), 4.05 – 3.96 (m, 1H), 4.00 (dd, *J* = 12.5, 5.9 Hz, 1H), 3.79 (dd, *J* = 7.7, 3.8 Hz, 1H), 3.71 – 3.65 (m, 1H), 3.48 (dd, *J* = 11.2, 6.8 Hz, 1H), 3.32 (dd, *J* = 7.7, 2.0 Hz, 1H), 3.29 – 3.15 (m, 3H), 2.09 (s, 3H), 2.00 (ddd, *J* = 14.7, 10.3, 2.6 Hz, 1H), 1.92 – 1.82 (m, 1H).

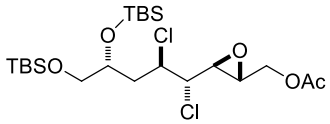
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 68.8, 66.8, 63.8, 63.4, 61.3, 55.5, 55.0, 37.9, 20.8.

HRMS (ESI) exact mass calculated for $C_{10}H_{16}Cl_2NaO_5$ [$(M+Na)^+$], 309.0267; found 309.0267.

IR: ν 3396(b), 2931(w), 1740(s), 1369(w), 1235(s), 1039(m).

Optical Rotation: $[\alpha]_D^{24.7} = +19$ (*c* = 2.6, $CHCl_3$).

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*)-4,5-bis((tert-butyldimethylsilyl)oxy)-1,2-dichloropentyl)oxiran-2-yl)methyl acetate (264)



A solution of **263** (2.18 g, 7.58 mmol) in CH_2Cl_2 (76 mL) was cooled to –78 °C and 2,6-lutidine (4.06 mL, 34.9 mmol) was added followed by drop wise addition of TBSOTf (4.00 mL, 17.4 mmol). After stirring the reaction for 40 min, sat. $NaHCO_3$(aq) was added, the phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography (gradient elution with 5 to 10% Et_2O in pentane) afforded the *bis*-TBS-ether **264** (3.00 g, 77%) as a colorless liquid.

TLC: R_f (50% EtOAc in hexane) = 0.84; R_f (20% EtOAc in hexane) = 0.63

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 – 4.36 (m, 2H), 4.00 (dd, J = 12.4, 5.9 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.76 (dd, J = 7.6, 4.0 Hz, 1H), 3.60 (dd, J = 10.1, 5.0 Hz, 1H), 3.42 (dd, J = 10.1, 6.6 Hz, 1H),

3.28 (dd, J = 7.6, 2.0 Hz, 1H), 3.20 (ddd, J = 5.9, 3.3, 2.0 Hz, 1H), 2.14 – 2.05 (m, 4H), 1.90 (ddd, J = 14.4, 10.0, 2.2 Hz, 1H), 0.89 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.05 (s, 6H).

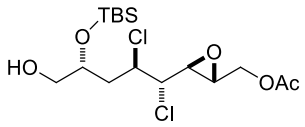
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 70.0, 67.5, 64.4, 63.5, 61.2, 55.6, 54.8, 39.7, 26.1, 26.0, 20.8, 18.5, 18.2, -3.9, -4.7, -5.2, -5.2.

HRMS (ESI) exact mass calculated for $C_{22}H_{45}Cl_2O_5Si_2$ [$(M+H)^+$], 515.2177; found 515.2175.

IR: ν 2955(m), 2930(m), 2858(m), 1748(s), 1478(m), 1363(m), 1227(m), 1115(m), 1087(m), 1005(w), 833(s).

Optical Rotation: $[\alpha]_D^{24.8} = +32$ (*c* = 5.0, $CHCl_3$).

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*)-4-((tert-butyldimethylsilyl)oxy)-1,2-dichloro-5-hydroxypentyl)-oxiran-2-yl)methyl acetate (265)



To a solution of **265** (2.77 g, 5.37 mmol) in THF (53 mL) at 0 °C was dropwise added a solution of HF-pyridine (2.88 mL, 22.4 mmol) and pyridine (5.76 mL, 71.2 mmol) in THF (14.2 mL). The mixture was stirred for 5 h, then diluted with EtOAc and quenched carefully with sat. $NaHCO_3$(aq). The aqueous phase was extracted with EtOAc twice, and the combined organics were dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (5 to 20 to 50% EtOAc in hexane) gave 585 mg of **265** and 2.12 g of reisolated starting material **264**. Resubjecting the starting material to the conditions above through another three cycles (4 cycles in total) resulted in a total of 1.62 g (75%) of **265** and 210 mg (8%) of **264**.

TLC: R_f (20% EtOAc in hexane) = 0.19

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (dd, *J* = 12.4, 3.3 Hz, 1H), 4.36 (ddd, *J* = 11.4, 3.9, 2.1 Hz, 1H), 4.07 (dddd, *J* = 10.0, 4.2, 3.3, 2.2 Hz, 1H), 4.01 (dd, *J* = 12.5, 5.9 Hz, 1H), 3.74 (dd, *J* = 7.8, 3.9 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.51 (ddd, *J* = 10.7, 7.3, 3.3 Hz, 1H), 3.29 (dd, *J* = 7.8, 2.0 Hz, 1H), 3.21 (ddd, *J* = 5.9, 3.3, 2.0 Hz, 1H), 2.21 (ddd, *J* = 14.5, 10.2, 2.1 Hz, 1H), 2.10 (s, 3H), 1.92 (ddd, *J* = 14.5, 11.4, 2.2 Hz, 1H), 1.79 – 1.72 (m, 1H), 0.91 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H).

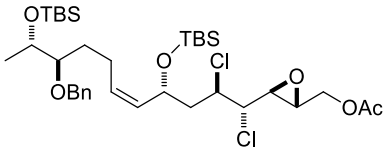
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 69.6, 66.8, 64.3, 63.5, 61.4, 55.6, 55.0, 38.9, 26.0, 20.8, 18.2, -4.2, -4.6.

HRMS (ESI) exact mass calculated for $C_{16}H_{34}Cl_2NO_5Si$ [$(M+NH_4)^+$], 418.1578; found 418.1578.

IR: ν 3474(b), 2954(m), 2930(m), 2858(w), 1745(s), 1472(w), 1388(w), 1230(s), 1039(m), 837(s).

Optical Rotation: $[\alpha]_D^{25.0} = +24$ (*c* = 1.4, $CHCl_3$).

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*,9*R*,10*S*,*Z*)-9-(benzyloxy)-4,10-bis((tert-butyldimethylsilyl)oxy)-1,2-dichloroundec-5-en-1-yl)oxiran-2-yl)methyl acetate (267)



Oxidation: To a solution of primary alcohol **265** (5.52 g, 13.8 mmol) and *t*BuOH (1.3 mL, 14 mmol) in CH_2Cl_2 (140 mL) was added Dess–Martin Periodinane (8.75 g, 20.6 mmol) and the reaction was stirred for 15 min. A 1:1 mixture of sat. $NaHCO_3$(aq) and sat. $Na_2S_2O_3$(aq) was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed first with a 1:1 mixture of sat. $NaHCO_3$(aq) and sat. $Na_2S_2O_3$(aq), then with brine, and the organics were then dried (Na_2SO_4), filtered, and concentrated. Purification by chromatography on a short plug of silica (20% EtOAc in hexane) afforded the aldehyde **266** (3.72 g, 89%) which was used directly in the next step.

Olefination: Aldehyde **266** (3.60 g, 9.01 mmol) and triphenylphosphonium iodide **195**[125] (7.51 g, 10.6 mmol) were azeotropically dried by concentration under reduced pressure from a solution in benzene three times. The flasks were then evacuated and backfilled with nitrogen. The phosphonium iodide was dissolved in THF (60 mL) and cooled to 0 °C. A freshly prepared 0.5 M solution of KHMDS (20.7 mL, 10.4 mmol) was added dropwise and the mixture was stirred for 30 min before it was cooled to –78 °C. Hereafter, a solution of the aldehyde in THF (46 mL) was added dropwise and the resulting mixture was stirred for 30 min, then warmed to 0 °C and stirred for another 30 min. The reaction was diluted with Et_2O and quenched with phosphate buffer (pH 7). The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated, and the product was purified by column chromatography (5 to 10% EtOAc in hexane) to give **267** (3.38 g, 53%) as a colorless oil.

TLC: R_f (20% EtOAc in hexane) = 0.56

^{1}H NMR (400 MHz, C_6D_6) δ 7.49 – 7.36 (m, 3H), 7.27 (t, *J* = 7.6 Hz, 2H), 5.49 (dd, *J* = 10.8, 8.5 Hz, 1H), 5.38 (dt, *J* = 11.0, 7.2 Hz, 1H), 5.03 (td, *J* = 9.2, 3.5 Hz, 1H), 4.74 – 4.64 (m, 2H), 4.48 (d, *J* = 11.6 Hz, 1H), 3.99 (dd, *J* = 12.4, 3.3 Hz, 1H), 3.87 (qd, *J* = 6.3, 3.8 Hz, 1H), 3.58 (dd, *J* = 12.4, 6.1 Hz, 1H), 3.35 (dd, *J* = 7.9, 3.4 Hz, 1H), 3.23 (dt, *J* = 8.3, 3.5 Hz, 1H), 3.05 (dd, *J* = 7.9, 1.9 Hz, 1H), 2.70 (ddd, *J* = 6.0, 3.3, 1.8 Hz, 1H), 2.53 – 2.36 (m, 1H), 2.24 – 2.08 (m, 1H), 2.04 (ddd, *J* = 11.6, 7.6, 2.9 Hz, 2H), 1.75 (dddd, *J* = 13.4, 9.9, 8.2, 5.0 Hz, 1H), 1.63 – 1.48 (m, 1H), 1.57 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.24 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H).

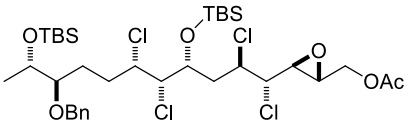
^{13}C NMR (100 MHz, C_6D_6) δ 169.6, 139.6, 133.6, 130.5, 128.6, 128.0, 127.7, 83.7, 72.9, 70.7, 66.0, 64.7, 63.5, 61.9, 55.4, 55.0, 43.5, 30.9, 26.2, 26.1, 24.6, 20.1, 19.8, 18.4, 18.3, -3.8, -4.3, -4.5, -4.7.

HRMS (ESI) exact mass calculated for $C_{35}H_{61}Cl_2O_6Si_2$ [$(M+H)^+$], 703.3378; found 703.3378.

IR: ν 2954(m), 2929(m), 2857(m), 1748(s), 1472(w), 1363(w), 1227(s), 1080(s), 833(s).

Optical Rotation: $[\alpha]_D^{23.4} = +31$ (*c* = 1.6, $CHCl_3$).

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*,5*S*,6*S*,9*R*,10*S*)-9-(benzyloxy)-4,10-bis((tert-butyldimethylsilyl)oxy)-1,2,5,6-tetrachloroundecyl)oxiran-2-yl)methyl acetate (273)



To a solution of **267** (2.96 g, 4.20 mmol) in CH_2Cl_2 (63 mL) cooled to -78 °C was added a solution of Et_4NCl_3 (4.0 g) in CH_2Cl_2 (21 mL) dropwise (the solution was cooled by letting it run down the wall), and the resulting solution was stirred for 45 min. The reaction was quenched with a 1:1 mixture of sat. $NaHCO_3$(aq) and sat. $Na_2S_2O_3$(aq) and allowed to warm to r.t. The aqueous phase was extracted three times with CH_2Cl_2 and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (5-10% EtOAc in hexane) gave tetrahydrofuran **275** (0.5 g) and tetrachloride **273** (1.96 g, 60%) as a colorless oil together with inseparable diastereomer (*dr* = 6:1).

Data for 273

TLC: R_f (20% EtOAc in hexane) = 0.54

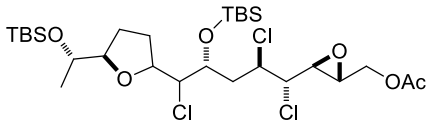
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.40 (dd, *J* = 12.4, 3.3 Hz, 1H), 4.28 (ddd, *J* = 11.4, 4.3, 1.9 Hz, 1H), 4.26 – 4.20 (m, 2H), 4.00 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.93 (dd, *J* = 5.7, 2.3 Hz, 1H), 3.86 (dd, *J* = 6.2, 4.0 Hz, 1H), 3.70 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.31 – 3.24 (m, 1H), 3.27 (dd, *J* = 7.6, 1.9 Hz, 1H), 3.20 (ddd, *J* = 6.0, 3.3, 1.9 Hz, 1H), 2.27 (ddd, *J* = 14.4, 11.5, 1.8 Hz, 1H), 2.15 (ddd, *J* = 14.4, 10.3, 2.0 Hz, 1H), 2.10 (s, 3H), 2.03 – 1.95 (m, 1H), 1.90 (dddd, *J* = 14.1, 11.4, 9.7, 4.5 Hz, 1H), 1.82 (dddd, *J* = 14.3, 11.3, 4.5, 3.1 Hz, 1H), 1.51 (dddd, *J* = 13.7, 11.4, 8.7, 4.8 Hz, 1H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.90 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 139.0, 128.5, 127.9, 127.7, 83.8, 73.0, 72.5, 70.9, 67.8, 64.0, 63.5, 61.3, 61.2, 55.6, 54.8, 37.9, 34.2, 28.6, 26.1, 26.0, 20.8, 19.5, 18.3, 18.2, -3.8, -4.3, -4.3, -4.6.

HRMS (ESI) exact mass calculated for $C_{35}H_{61}Cl_4O_6Si_2$ [$(M+H)^+$], 773.2755; found 773.2747.

IR: ν 2930(m), 2857(m), 1747(s), 1472(m), 1364(m), 1228(s), 1097(s), 835(s).

Optical Rotation: $[\alpha]_D^{23.7} = +27$ (*c* = 1.6, $CHCl_3$).



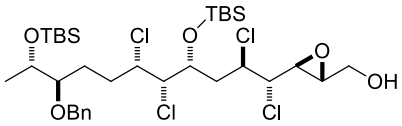
Data for 275:

TLC: R_f (20% EtOAc in hexane) = 0.56

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 – 4.64 (m, 1H), 4.59 – 4.47 (m, 1H), 4.41 (ddd, *J* = 12.4, 4.8, 3.2 Hz, 1H), 4.24 – 4.15 (m, 1H), 4.00 (ddd, *J* = 12.4, 6.1, 2.3 Hz, 1H), 3.92 – 3.79 (m, 2H), 3.77 (dd, *J* = 7.9, 4.0 Hz, 1H), 3.73 – 3.68 (m, 1H), 3.67 – 3.55 (m, 1H), 3.30 – 3.24 (m, 1H), 3.21 (ddd, *J* = 5.5, 3.3, 1.9 Hz, 1H), 2.33 – 2.14 (m, 1H), 2.10 (s, 3H), 2.05 – 1.72 (m, 4H), 1.18 (d, *J* = 5.9 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H).

HRMS (ESI) exact mass calculated for $C_{28}H_{54}Cl_3O_6Si_2$ [$(M+H)^+$], 647.2519; found 647.2523.

((2*R*,3*S*)-3-((1*S*,2*R*,4*R*,5*S*,6*S*,9*R*,10*S*)-9-(benzyloxy)-4,10-bis((tert-butyldimethylsilyl)oxy)-1,2,5,6-tetrachloroundecyl)oxiran-2-yl)methanol (274)



Acetate **273** (2.12 g, 2.74 mmol) was dissolved in MeOH (27 mL) and cooled to 0 °C, then K_2CO_3 (1.13 g, 8.21 mmol) was added and the reaction was stirred for 20 min. The mixture was diluted with sat. NH_4Cl(aq), extracted with EtOAc three times, and the combined organics were dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (10-20% EtOAc in hexane) gave **274** (1.80 g, 90%) as a colorless oil together with inseparable diastereomer (dr ~ 6:1).

TLC: R_f (20% EtOAc in hexane) = 0.33

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 4H), 7.31 – 7.27 (m, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 4.30 (ddd, *J* = 11.2, 4.4, 2.2 Hz, 1H), 4.28 – 4.19 (m, 2H), 4.02 – 3.91 (m, 2H), 3.91 – 3.82 (m, 1H), 3.78 – 3.66 (m, 2H), 3.36 (ddd, *J* = 10.9, 7.7, 2.1 Hz, 1H), 3.32 – 3.24 (m, 1H), 3.16 – 3.09 (m, 1H), 2.34 – 2.24 (m, 1H), 2.17 (ddd, *J* = 14.5, 10.1, 2.2 Hz, 1H), 2.09 – 1.75 (m, 3H), 1.51 (dddd, *J* = 13.5, 11.4, 9.1, 4.8 Hz, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.07 (br s, 6H).

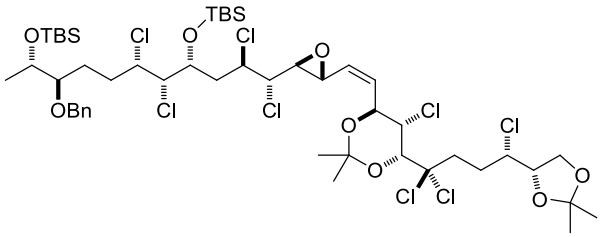
^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.5, 128.0, 127.7, 83.9, 73.1, 72.5, 71.0, 67.8, 64.3, 61.5, 61.1, 60.6, 57.9, 54.8, 37.7, 34.2, 28.7, 26.1, 26.0, 19.5, 18.3, 18.2, -3.8, -4.2, -4.3, -4.5.

HRMS (ESI) exact mass calculated for $C_{33}H_{59}Cl_4O_5Si_2$ [$(M+H)^+$], 731.2650; found 731.2654.

IR: ν 3407(b), 2954(m), 2930(m), 2857(m), 1472(m), 1254(s), 1088(s), 834(s).

Optical Rotation: $[\alpha]_D^{23.9} = +29$ (*c* = 2.7, $CHCl_3$).

(5*R*,6*S*,7*S*,10*R*,11*S*)-10-(benzyloxy)-6,7-dichloro-5-((2*R*,3*S*)-2,3-dichloro-3-((2*S*,3*R*)-3-((*Z*)-2-((4*S*,5*S*,6*R*)-5-chloro-2,2-dimethyl-6-((*S*)-1,1,4-trichloro-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxan-4-yl)vinyl)oxiran-2-yl)propyl)-2,2,3,3,11,13,13,14,14-nonamethyl-4,12-dioxa-3,13-disilapentadecane (278)



Oxidation: To a solution of alcohol **274** (650 mg, 0.887 mmol) in CH_2Cl_2 (8 mL) was added water (16 μL, 0.89 mmol) Dess–Martin Periodinane (564 g, 1.33 mmol) and the mixture was stirred for 30 min. The reaction was then quenched with a 1:1 mixture of sat. $NaHCO_3$(aq) and sat. $Na_2S_2O_3$(aq) and stirred until two clear phases were obtained. The aqueous phase was extracted twice with CH_2Cl_2 and hereafter the combined organic phases were washed with a 1:1 mixture of sat. $NaHCO_3$(aq) and sat. $Na_2S_2O_3$(aq), brine, then dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (20% EtOAc in hexane) on a short pad afforded the aldehyde **277** (484 mg, 75%) which was used directly in the next step.

TLC: R_f (20% EtOAc in hexane) = 0.45

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (d, *J* = 6.0 Hz, 1H), 7.44 – 7.30 (m, 5H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.35 – 4.16 (m, 3H), 3.95 (ddd, *J* = 5.7, 4.1, 2.1 Hz, 1H), 3.87 (dt, *J* = 6.2, 3.2 Hz, 1H), 3.76 – 3.69 (m, 2H), 3.69 – 3.61 (m, 2H), 3.37 (dd, *J* = 5.9, 1.6 Hz, 1H), 3.34 – 3.22 (m, 1H), 2.36 – 2.15 (m, 2H), 2.04 – 1.79 (m, 2H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H).

Olefination: Aldehyde **277** (484 mg, 0.662 mmol) and sulfone **183**[125] (360 g, 0.569 mmol) were azeotropically dried together by concentrating from benzene three times. The flask was evacuated and backfilled with nitrogen. The starting materials were dissolved in toluene (60 mL) and the solution was cooled to –78 °C. A freshly prepared solution of NaHMDS in PhMe (1.0 M, 0.63 ml, 0.63 mmol) was added drop wise and the mixture was stirred for 3.5 h, and hereafter allowed to warm to r.t. over night. Sat. $NaHCO_3$(aq) was added and after separating the phases, the aqueous phase was extracted with Et_2O three times. The combined organic phases were washed with brine, dried

($MgSO_4$), filtered, and concentrated. Repeated column chromatography (8% Et_2O in pentane) gave the title compound **278** (347 mg, 54%) with a minor amount of inseparable aldehyde **277**.[186]

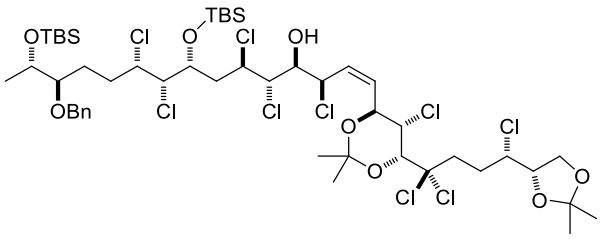
TLC: R_f (20% EtOAc in hexane) = 0.53

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 4H), 7.21 – 7.13 (m, 1H), 5.78 (ddd, *J* = 11.3, 8.1, 1.0 Hz, 1H), 5.34 (ddd, *J* = 11.3, 8.6, 1.1 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.83 – 4.69 (m, 1H), 4.59 (d, *J* = 4.1 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.38 – 4.28 (m, 2H), 4.28 – 4.19 (m, 3H), 4.12 (dd, *J* = 8.7, 6.6 Hz, 1H), 4.00 – 3.90 (m, 3H), 3.86 (dd, *J* = 6.3, 4.1 Hz, 1H), 3.77 (ddd, *J* = 8.6, 1.9, 0.9 Hz, 1H), 3.71 (dd, *J* = 7.9, 4.3 Hz, 1H), 3.30 – 3.23 (m, 2H), 2.71 (m, 2H), 2.44 – 2.24 (m, 4H), 2.24 – 2.09 (m, 2H), 2.05 – 1.77 (m, 2H), 1.54 (s, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.90 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 132.0, 130.2, 129.2, 128.5, 127.9, 110.4, 103.9, 92.1, 83.8, 78.5, 77.0, 73.1, 73.0, 72.5, 70.9, 67.7, 66.3, 64.4, 62.1, 61.7, 61.3, 61.3, 59.1, 54.3, 39.9, 37.8, 34.2, 29.1, 28.6, 26.4, 26.1, 26.0, 25.3, 24.2, 23.7, 19.5, 18.3, 18.2, -3.8, -4.2, -4.3, -4.5.

HRMS (ESI) exact mass calculated for $C_{49}H_{84}Cl_8NO_8Si_2$ [$(M+NH_4)^+$], 1150.3238; found 1150.3236.

(3*R*,4*S*,5*S*,6*R*,8*R*,9*S*,10*S*,13*R*,14*S*,*Z*)-13-(benzyloxy)-8,14-bis((tert-butyldimethylsilyl)oxy)-3,5,6,9,10-pentachloro-1-((4*S*,5*S*,6*R*)-5-chloro-2,2-dimethyl-6-((*S*)-1,1,4-trichloro-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxan-4-yl)pentadec-1-en-4-ol (282)



Epoxide **278** (245 mg, 0.215 mmol) was dried by azeotropic concentration from benzene three times and then dissolved in EtOAc (7.2 mL). The solution was divided in 5 portions and to each portion was added a freshly prepared solution of TMSCl in CH_2Cl_2 (2.0 M, total amount of 3.23 mL, 6.46 mmol). The resulting mixtures were stirred for 5 days and then quenched with sat. $NaHCO_3$(aq). The combined aqueous phases were extracted with EtOAc three times, and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (15% Et_2O in pentane, then EtOAc) gave chlorohydrin **282** (93 mg, 37%) as a colorless oil and a complex mixture of TBS- and acetal-deprotected by-products (80 mg).

[186] Repeated column chromatography with various elution systems to remove the aldehyde proved unsuccessful. Attempts to remove the aldehyde by reduction ($NaBH_4$, MeOH) followed by further purification resulted in complete decomposition.

TLC: R_f (20% EtOAc in hexane) = 0.47

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 5.99 (dddd, *J* = 11.3, 10.0, 4.4, 1.2 Hz, 1H), 5.71 – 5.62 (m, 2H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.71 – 4.63 (m, 2H), 4.61 – 4.56 (m, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.37 – 4.28 (m, 2H), 4.29 – 4.20 (m, 2H), 4.11 (ddd, *J* = 8.6, 6.7, 1.2 Hz, 1H), 3.94 (ddt, *J* = 8.7, 3.8, 2.0 Hz, 3H), 3.90 – 3.81 (m, 2H), 3.33 – 3.21 (m, 1H), 2.75 – 2.63 (m, 2H), 2.45 – 2.29 (m, 2H), 2.21 – 2.09 (m, 1H), 2.07 – 1.72 (m, 4H), 1.55 (s, 3H), 1.51 – 1.48 (m, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

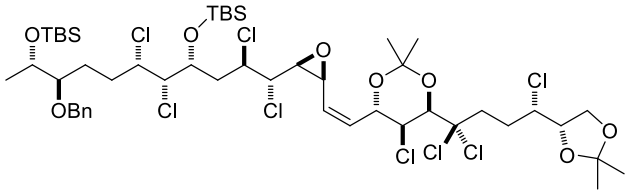
^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 130.5, 129.0, 128.5, 128.0, 127.7, 110.4, 104.1, 91.9, 83.8, 78.5, 76.9, 74.3, 73.1, 73.1, 72.5, 70.9, 67.5, 66.6, 66.3, 62.0, 61.4, 61.1, 59.5, 59.4, 40.0, 36.0, 34.3, 29.1, 28.6, 26.4, 26.1, 26.0, 25.3, 24.2, 23.6, 19.5, 18.3, 18.2, -3.9, -4.2, -4.3, -4.5.

HRMS (ESI) exact mass calculated for $C_{49}H_{85}Cl_9NO_8Si_2$ [$(M+NH_4)^+$], 1186.3005; found 1186.3010.

IR: ν 3567(b), 2931(m), 2858(m), 1472(m), 1382(s), 1257(s), 1222(s), 1094(s), 837(s).

Determination of the stereochemical outcome of epoxide opening:

To a solution of chlorohydrin **282** (2 mg, 1.7 μmol) in MeOH (0.1 mL) was added K_2CO_3 (1.2 mg, 8.5 μmol) and stirred for 1 h. Hereafter, the mixture was diluted with CH_2Cl_2 and washed three times with water, dried ($MgSO_4$), and concentrated. Purification by column chromatography (10% Et_2O in pentane) afforded *cis*-olefin **283** as a colorless oil.

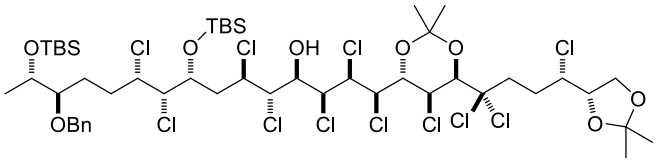


TLC: R_f (20% EtOAc in hexane) = 0.49

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.94 – 5.85 (m, 1H), 5.61 (dd, *J* = 11.0, 5.3 Hz, 1H), 4.92 – 4.70 (m, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 4.67 – 4.57 (m, 1H), 4.57 – 4.46 (m, 1H), 4.42 – 4.20 (m, 5H), 4.14 (dd, *J* = 8.6, 6.7 Hz, 1H), 4.04 – 3.92 (m, 3H), 3.92 – 3.85 (m, 1H), 3.77 (dd, *J* = 9.1, 3.9 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.36 – 3.25 (m, 2H), 2.78 – 2.65 (m, 2H), 2.46 – 2.29 (m, 4H), 2.26 – 2.10 (m, 2H), 2.10 – 1.80 (m, 2H), 1.57 (s, 3H), 1.51 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H), 1.20 (d, *J* = 6.1 Hz, 3H), 0.93 (s, 9H), 0.92 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H).

HRMS (ESI) exact mass calculated for $C_{49}H_{84}Cl_8NO_8Si_2$ [$(M+NH_4)^+$], 1150.3238; found 1150.3235.

(1*R*,2*R*,3*S*,4*R*,5*S*,6*R*,8*R*,9*S*,10*S*,13*R*,14*S*)-13-(benzyloxy)-8,14-bis((tert-butyldimethylsilyl)oxy)-1,2,3,5,6,9,10-heptachloro-1-((4*R*,5*S*,6*R*)-5-chloro-2,2-dimethyl-6-((*S*)-1,1,4-trichloro-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxan-4-yl)pentadecan-4-ol (284)



A solution of allyl chloride **282** (92 mg, 0.078 mmol) in CH_2Cl_2 (1.8 mL) was divided in two portions and cooled to –78 °C. To each flask was added a solution of Et_4NCl_3 (46 mg) in CH_2Cl_2 (0.45 mL) and the mixtures were stirred for 1.5 h, then warmed to 0 °C and stirred for 1.5 h, and finally warmed r.t. and stirred for 30 min before quenching with a 1:1 mixture of sat. $NaHCO_3$(aq) and sat. $Na_2S_2O_3$(aq). The combined aqueous phases were extracted three times with CH_2Cl_2 and the combined organics were then dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography (10% Et_2O in pentane) afforded undecachloride **284** (63 mg, 65%) as a colorless oil.

TLC: R_f (20% EtOAc in hexane) = 0.52

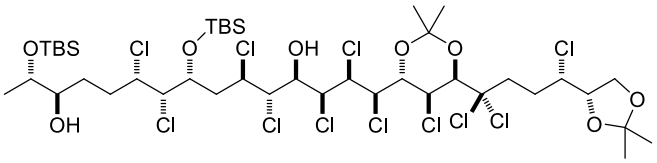
^{1}H NMR (600 MHz, acetone-d_6) δ 7.47 – 7.31 (m, 4H), 7.31 – 7.24 (m, 1H), 5.19 (dd, *J* = 12.8, 11.2 Hz, 1H), 4.98 – 4.83 (m, 2H), 4.83 – 4.68 (m, 5H), 4.65 – 4.51 (m, 5H), 4.42 – 4.34 (m, 2H), 4.35 – 4.25 (m, 2H), 4.19 – 4.09 (m, 3H), 4.08 – 3.96 (m, 1H), 3.91 (dd, *J* = 8.5, 6.0 Hz, 1H), 3.35 (dd, *J* = 8.5, 3.4 Hz, 1H), 2.75 – 2.70 (m, 2H), 2.58 – 2.42 (m, 1H), 2.41 – 2.30 (m, 1H), 2.24 – 2.08 (m, 3H), 2.03 – 1.66 (m, 1H), 1.54 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.93 (s, 9H), 0.92 (s, 9H), 0.22 (s, 3H), 0.22 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (150 MHz, acetone-d_6) δ 140.2, 129.0, 128.5, 128.1, 110.4, 104.6, 93.5, 84.3, 79.5, 79.0, 77.6, 73.9, 73.1, 71.7, 71.1, 69.7, 68.8, 68.7, 67.6, 66.9, 65.5, 63.1, 63.1, 61.4, 61.1, 59.7, 41.2, 37.3, 34.8, 30.5, 26.6, 26.5, 26.3, 25.6, 25.4, 23.5, 19.9, 19.0, 18.6, -3.6, -4.0, -4.3, -4.4.

HRMS (ESI) exact mass calculated for $C_{49}H_{85}Cl_{11}NO_8Si_2$ [$(M+NH_4)^+$], 1256.2382; found 1256.2369.

Optical Rotation: $[\alpha]_D^{23.3} = +19$ (*c* = 0.94, $CHCl_3$).

(2*S*,3*R*,6*S*,7*S*,8*R*,10*R*,11*S*,12*R*,13*S*,14*R*,15*R*)-2,8-bis((tert-butyldimethylsilyl)oxy)-6,7,10,11,13,14,15-heptachloro-15-((4*R*,5*S*,6*R*)-5-chloro-2,2-dimethyl-6-((*S*)-1,1,4-trichloro-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxan-4-yl)pentadecane-3,12-diol (285)



To a solution of **284** (66 mg, 0.053 mmol) in a mixture of MeOH and THF (1:1, 10.6 mL) was added Pd/C (10% Pd, 14 mg, 0.013 mmol), and the suspension was evacuated and backfilled with nitrogen three times, then evacuated and backfilled with hydrogen three times. Hydrogen was then bubbled through the vigorously stirred suspension for 1 h and hereafter then mixture was stirred for another 30 min. After evacuation and backfilling with nitrogen three times, the crude reaction mixture was filtered through celite and concentrated. Column chromatography (10% EtOAc in hexane) afforded the desired diol (40 mg, 66%) as a colorless foam.

TLC: R_f (20% EtOAc in hexane) = 0.40

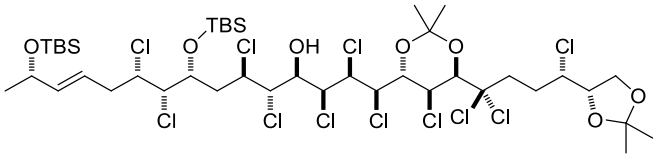
^{1}H NMR (600 MHz, acetone-d_6) δ 5.20 (dd, J = 13.0, 10.8 Hz, 1H), 4.95 – 4.84 (m, 2H), 4.83 – 4.68 (m, 4H), 4.67 – 4.56 (m, 4H), 4.55 – 4.42 (m, 1H), 4.42 – 4.35 (m, 1H), 4.35 – 4.27 (m, 2H), 4.24 – 4.11 (m, 3H), 3.91 (dd, J = 8.5, 6.0 Hz, 1H), 3.83 – 3.68 (m, 1H), 3.58 – 3.49 (m, 1H), 3.44 – 3.33 (m, 1H), 2.79 – 2.68 (m, 2H), 2.60 – 2.42 (m, 1H), 2.42 – 2.29 (m, 1H), 2.26 – 2.11 (m, 3H), 2.01 – 1.70 (m, 1H), 1.54 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.14 (d, J = 6.2 Hz, 3H), 0.94 (s, 9H), 0.91 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (150 MHz, acetone-d_6) δ 110.4, 104.7, 93.6, 79.5, 79.0, 77.6, 76.3, 75.4, 73.9, 73.0, 71.7, 70.4, 69.8, 68.8, 67.7, 66.9, 65.6, 63.1, 61.5, 61.1, 59.7, 41.2, 37.4, 35.3, 30.6, 26.6, 26.5, 26.3, 25.7, 25.4, 23.5, 19.5, 19.0, 18.6, -3.6, -4.0, -4.1, -4.4.

HRMS (ESI) exact mass calculated for $C_{42}H_{79}Cl_{11}NO_8Si_2$ $[(M+NH_4)^+]$, 1166.1913; found 1166.1925.

Optical Rotation: $[\alpha]_D^{22.9} = +11$ (c = 0.30, $CHCl_3$).

(1*R*,2*R*,3*S*,4*R*,5*S*,6*R*,8*R*,9*S*,10*S*,14*S*,*E*)-8,14-bis((tert-butyldimethylsilyl)oxy)-1,2,3,5,6,9,10-heptachloro-1-((4*R*,5*S*,6*R*)-5-chloro-2,2-dimethyl-6-((*S*)-1,1,4-trichloro-4-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)butyl)-1,3-dioxan-4-yl)pentadec-12-en-4-ol (286)



Secondary alcohol **285** (3 mg, 2.60 µmol) was dried twice by concentrating a solution in benzene. The starting material was then dissolved in benzene (0.50 mL) (freshly distilled from K/benzophenone), and a solution of Martin's Sulfurane (0.2 M, 40 µL, 8.0 µmol) in benzene was added. The mixture was stirred for 2.5 h, TLC showed poor conversion. A second portion of Martin's Sulfurane (0.2 M, 40µL, 8.0 µmol) was added and the mixture was stirred for another 24 h. The reaction mixture was diluted with diethyl ether and quenched with a saturated solution of $NaHCO_3$ (aq). The organics were extracted three times with diethyl ether, then dried over $MgSO_4$ and concentrated.

Purification by column chromatography (10% Et_2O in pentane, then 10% EtOAc in hexane) afforded the title compound (1 mg, 34%) as a colorless oil.[187]

TLC: R_f (20% EtOAc in hexane) = 0.77

^{1}H NMR (600 MHz, acetone-d_6) δ 5.70 (dd, *J* = 15.4, 4.6 Hz, 1H), 5.65 (dtd, *J* = 15.4, 6.4, 1.1 Hz, 1H), 5.43 – 5.38 (m, 1H), 4.89 – 4.85 (m, 1H), 4.87 – 4.84 (m, 1H), 4.83 – 4.78 (m, 1H), 4.76 – 4.70 (m, 5H), 4.69 – 4.64 (m, 1H), 4.63 – 4.58 (m, 1H), 4.44 (ddd, *J* = 8.3, 6.1, 2.2 Hz, 1H), 4.38 – 4.27 (m, 5H), 4.23 – 4.16 (m, 2H), 4.16 – 4.11 (m, 5H), 4.10 – 4.06 (m, 1H), 3.98 (dd, *J* = 5.7, 3.1 Hz, 1H), 3.92 (dd, *J* = 8.5, 6.0 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.19 (d, *J* = 6.3 Hz, 1H), 0.94 (s, 9H), 0.90 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (150 MHz, acetone-d_6) δ 140.2, 124.1, 110.4, 104.6, 93.6, 79.6, 79.0, 77.6, 73.8, 71.6, 71.6, 69.5, 68.9, 68.8, 66.9, 65.6, 65.6, 63.2, 61.2, 59.7, 59.6, 41.3, 40.6, 37.4, 30.6, 26.6, 26.5, 26.3, 25.7, 25.4, 24.9, 23.5, 19.0, 18.8, -3.6, -4.0, -4.3, -4.5.

HRMS (ESI) exact mass calculated for $C_{42}H_{77}Cl_{11}NO_7Si_2$ [$(M+NH_4)^+$], 1148.1807; found 1148.1804.

[187] Due to instability on Fluka Ca-enriched silica gel of a similar intermediate in the synthesis of nominal mytilipin B,[125] SilicaFlash ultrapure silica gel by Silicycle, Quebec, Canada was used in this purification.