Applications of α-Chloroaldehydes toward the Synthesis of Natural Products

by

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Abstract

The stereochemical complexity evident in agrochemicals, pharmaceuticals, and natural products continues to provide motivation for the development of novel synthetic methods. In the last decade, research in the field of asymmetric organocatalysis has provided new tools for the functionalisation of the carbon atoms adjacent to a carbonyl. This thesis describes the use of asymmetric organocatalysis for the α-chlorination of aldehydes and the subsequent use of these compounds as building-blocks for the preparation of a variety of oxygen-containing heterocycles.

With the successful preparation of optically enriched α-chloroaldehydes, these linchpin compounds were elaborated into *trans*-epoxides, substituted-tetrahydrofuranols, and carbohydrate analogues. In particular, this thesis describes the addition of organolithium reagents and lithium enolates to optically pure α-chloroaldehydes to afford 1,2-*anti*-chlorohydrins in a highly diastereoselective manner. Further elaboration of these compounds allowed access to a variety of *trans*-epoxides, in an approach that is flexible and concise. Following the discovery of a novel silver-mediated cyclisation process substituted-tetrahydrofuranols were afforded from the 1,2-*anti*-chlorohydrins and the *trans*-epoxides. It was also realised that chloropolyols undergo regio- and stereoselective cyclisation by simply heating them in water to provide highly functionalised tetrahydrofuranols, including carbohydrate analogues. Together, these methods allowed access to a wide-range of stereochemically diverse oxygen-containing scaffolds.

The methodologies described within this thesis were further applied to the synthesis of an array of biologically active natural products. To demonstrate the utility of

these methods and in order to support field-testing, the synthesis of the *trans*-epoxide-containing insect sex pheromones isolated from *Bupalus piniarius* and *Orgyia postica* was completed. In addition, two marine oxylipids isolated from the alga *Notheia anomala* that exhibit anthelmintic activity were synthesised using a silver-mediated cyclisation of a chlorodiol. The microwave-assisted cyclisation methodology was applied in the total synthesis of (+)-goniothalesdiol, a natural product with potent cytotoxic activity against leukemia cells. Finally, the methods developed within this thesis were applied toward the total synthesis of the haterumalide and biselide families of natural products.

Keywords: natural product, pheromone, total synthesis, methodology, asymmetric synthesis, heterocycles

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°C	Degrees Celsius
δ	Chemical shift in ppm from tetramethylsilane
D	Dextrorotatory
L	Levaorotatory
Δ	Denotes position of olefin
$[\alpha]_D$	Specific rotation at the sodium D line (589 nm) – [deg $dm^{-1}cm^3$ g^{-1}]
ToC	Table of Contents
Ac	Acetyl
AcOH	Acetic acid
Ac_2O	Acetic anhydride
AD	Asymmetric dihydroxylation
AgOTf	Silver trifluoromethanesulfonate
AIBN	Azobis(isobutyronitrile)
aq	Aqueous
B. pinarius	*Bupalus pinarius*
9-BBN	9-Borabicyclo[3.3.1]nonane
BMS	Borane dimethyl sulfide
Bn	Benzyl
Boc	Di-*tert*-butyl dicarbonate
BTSP	bis(trimethylsilyl)peroxide
Bu	Butyl
Bz	Benzoyl
c	Concentration in g/mL; or cyclo
cat.	Catalyst
CSA	Camphor sulfonic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dba	Dibenzylideneacetone
DCC	Dicyclohexyl carbodiimide

DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DET	Diethyltartrate
DHQ	Dihydroquinine
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPT	Diisopropyltartrate
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
DPPBA	diphenylphosphino benzoic acid
d.r.	Diastereomeric ratio
E	Entgegen (trans)
e.e.	Enantiomeric excess
ent	Enantiomeric
equiv.	Equivalents
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOH	Ethanol
EtOAc	Ethyl acetate
FDA	Federal Drug Administration
GC	Gas chromatography
GC-EAD	Gas chromatography - Electro-antennographic detection
h	Hours
HECADE	Heteronuclear couplings from ASSCI-domain experiments
Hex	Hexyl
HMDS	Hexamethyldisilizane

HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
i	*iso*-
IC_{50}	half maximal inhibitory concentration
Ipc_2	Bisisopinocampheyl
JBCA	*J*-Based Configurational Analysis
LD_{50}	Lethal Dose, 50%
LD_{99}	Lethal Dose, 99% (Acute lethal dose)
LDA	Lithium diisopropylamide
lit.	Literature
lut.	Lutidine
M	Molar
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MAPH	methylaluminum bis(2,6-diphenylphenoxide)
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mes	Mesityl
mmol	Millimole(s)
mol	Mole(s)
MOM	Methoxymethyl ether
MPM	4-methoxybenzyl
MPV	Meerwein-Ponndorf-Verley reaction
Ms	Methanesulfonate
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nm	Nanometre
NMO	*N*-Methylmorpholine-*N*-oxide
Nu	Nucleophile
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
NR	No reaction

obs.	Observed
OMe	Methoxy
O. postica	*Orgyia postica*
p	*Para*
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
pH	$-\log_{10}[H^+]$
Ph	Phenyl
PHAL	Phthalazine
PMB	*para*-methoxybenzyl
PNBA	*p*-nitrobenzoic acid
ppm	parts-per-million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
PS	Polymer-supported
Pyr.	Pyridine
Red-Al	Sodium bis(2-methoxyethoxy)aluminumhydride
r.t.	Room temperature
s	Secondary
salen	2,2'-Ethylenebis(nitrilomethylidene)diphenol
SAR	Structure-activity relationship
SCUBA	Self-Contained Underwater Breathing Apparatus
Selectride	tri-*sec*-butyl(hydrido)borate
SOMO	Singly Occupied Molecular Orbital
t	Tertiary
TBAF	Tetra-*n*-Butylammonium fluoride
TBHP	*tert*-Butylhydroperoxide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
temp	Temperature
TES	Triethylsilyl
Tf	Triflate (CF_3SO_2)
TFA	Trifluoroacetate
THF	Tetrahydrofuran

TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
p-Tol	*para*-Tolyl
Ts	Tosyl
TTMS	Tris(trimethylsilyl)silane
Z	Zusammen (cis)

Chapter 1

Introduction

1.1 Synthesis of α-Chloroaldehydes

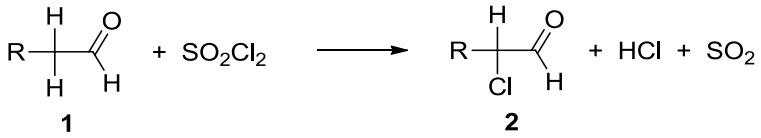
In modern organic chemistry α-halocarbonyl compounds occupy an important niche. These compounds are valuable because their interesting chemical reactivity enables them to undergo a myriad of chemical transformations. The first synthesis of an α-halocarbonyl compound was reported in 1859, with the chlorination of acetone to provide 1,1-dichloroacetone.[1] Since this seminal work, α-halocarbonyl compounds have found increased utility as reactive and versatile electrophiles. Recently, the importance of α-chloroaldehydes has become evident in their ability to serve as linchpins for further stereoselective manipulations and utility in the synthesis of structurally complex agrochemicals, pharmaceuticals, and fine-chemicals. The section will focus on the most common methods used to access α-chloroaldehydes.

Early studies showed that the use of standard halogenation techniques (e.g., haloform reactions) to chlorinate aldehydes leads only to acyl halides, aldol adducts, and/or acids.[2,3] The first successful preparation of an α-chloroaldehyde was reported by Schröder in 1871, who investigated the reaction of chlorine gas with 3-methylbutanal.[4] Building on this result, Guinot and Tabeteau later developed a method for the monochlorination of aliphatic aldehydes using chlorine in 2.5 M HCl.[5] This process was further refined following the discovery that the reaction of aliphatic aldehydes with chlorine in 7-8 M HCl at 10-12 °C generates the corresponding α-chloroaldehydes with

improved yields (40-70%).[6] Further examination revealed that both the concentration and type of acid play key roles in determining the reaction outcome.[2] These formative publications[2-6] provide a foundation for further advances in the α-chlorination of aldehydes.

As an alternative to chlorine gas, the decomposition of sulfuryl chloride into sulfur dioxide and chlorine, which occurs upon standing, has also been exploited for the chlorination of aliphatic aldehydes.[7] This process was first demonstrated by Brown and Ash in the chlorination of butanal,[8,9,10] and the success of these reaction conditions, as summarised in Table 1, has made this method the most common method for the direct conversion of aldehydes (e.g., **1**) into racemic α-chloroaldehydes (e.g., **2**).

Table 1. Chlorination of aldehydes using sulfuryl chloride.

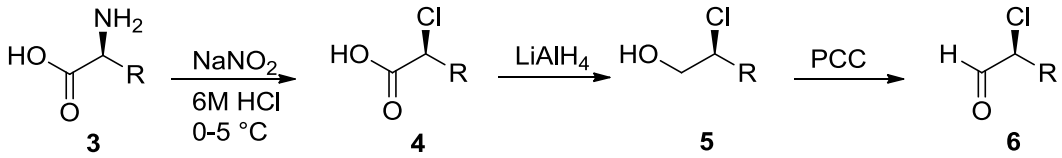


1 **2**

aldehyde	product	yield (%)
butanal	2-chlorobutanal	79[9], 56[11], 56[12], 64[13]
isobutanal	2-chloroisobutanal	60[14], 38[15]
heptanal	2-chloroheptanal	61[11], 78[15]
propanal	2-chloropropanal	66[16]
4-acetoxybutanal	2-chloro-4-acetoxybutanal	98[17]
4-(*t*-butyldimethylsilyloxy)butanal	2-chloro-4-(*t*-butyldimethylsilyloxy)butanal	64[18]
phenylacetaldehyde	2-chlorophenylacetaldehyde	60[19]
4-oxobutyl acetate	2-chloro-4-oxobutyl acetate	73[20]

The majority of early work in the synthesis of nonracemic α-chloroaldehydes relied on the use of chiral-pool starting materials. And, though the first synthesis of enantiopure α-chlorocarbonyl compounds from natural amino acids dates back to 1926,[21] the synthesis of optically enriched α-chloroaldehydes from amino acids was only

recently realised.[22] This practical approach to α-chloroaldehydes was developed by De Kimpe and involves a three-step sequence (Scheme 1) that commences with the diazotisation/nucleophilic substitution reaction of an amino acid (e.g., **3**),[22] which proceeds with retention of configuration due to anchimeric assistance by the amino acid carboxyl group, followed by substitution with a chloride ion.[23] The resultant α-chloroacids (e.g., **4**) are then reduced to the corresponding alcohols (e.g., **5**) with $LiAlH_4$,[24] followed by PCC oxidation[25] to yield the desired α-chloroaldehydes (e.g., **6**) in high yields (44-50% over three-steps) with >80% enantiomeric excess. In addition, the conversion of α-amino-β-hydroxy acids (e.g., threonine) to the corresponding α-chloro-β-hydroxy acids has been reported to proceed with high yields and moderate enantiomeric excess.[23b,26] This method is, however, limited only to the production of α-chloroaldehydes derived from natural amino acids; thus, considerable effort has been devoted to the identification of a more flexible process that can provide access to a large variety of optically enriched α-chloroaldehydes.

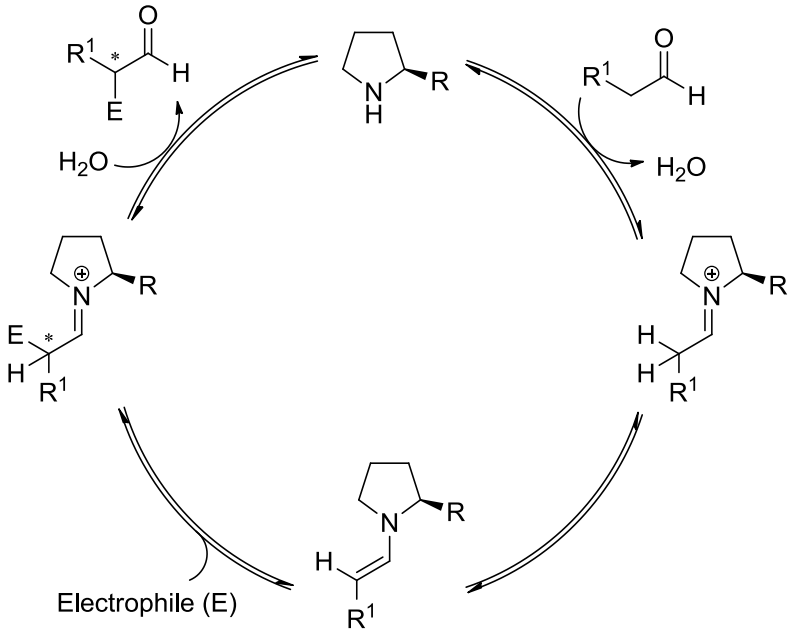


Scheme 1. Synthesis of α-chloroaldehydes from α-amino acids.

Although modern asymmetric synthesis provides a wide selection of C-C, C-O, C-N, and C-H bond-forming reactions to functionalise the α-position of carbonyl compounds, there are a relatively limited number of examples of enantioselective halogenation reactions (i.e., C-X bond-formation). Of the α-chlorocarbonyl compounds, the α-chloroaldehydes are potentially the most valuable as synthons; however, their

instability and hygroscopicity has hindered the development of preparative asymmetric syntheses.[27]

The first catalytic, asymmetric chlorination of carbonyl compounds was described by Tongi,[28] who reported a process that involved chlorination of chiral titanium-centred enolates derived from β-ketoesters, which afforded the corresponding α-chloro-β-ketoesters with good to excellent enantiocontrol (62-90% e.e.). The first examples of catalytic enantioselective α-chlorination of aldehydes used secondary amine catalysis - most commonly termed organocatalysis.[29] This work is the asymmetric extension of research originally conducted by Stork on the α-functionalisation of aldehydes *via* enamine intermediates (Scheme 2).[30] The generally accepted catalytic cycle for the α-functionalisation of aldehydes is described in Scheme 2.

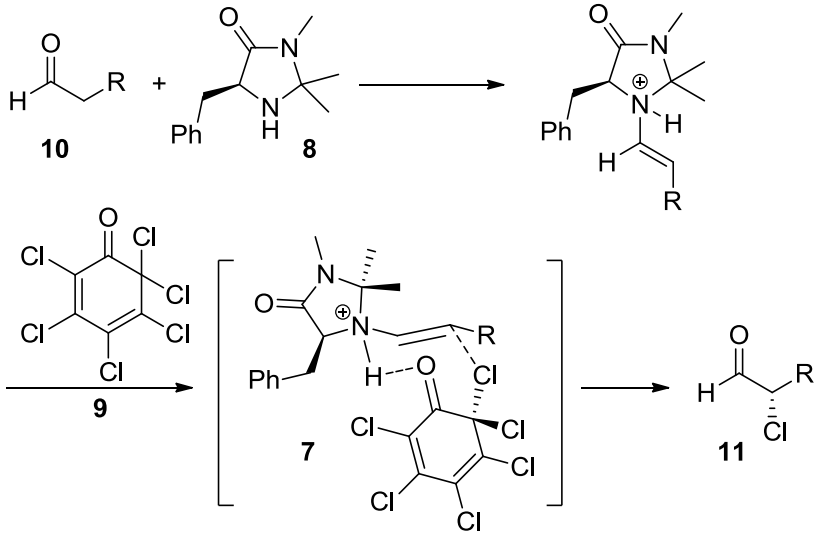


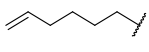
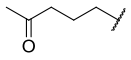
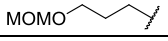
Scheme 2. General catalytic cycle in the α-functionalisation of aldehydes.

One extension of Stork's work was the development of a direct asymmetric α-chlorination of aldehydes by MacMillan in 2004.[31,32] This organocatalytic methodology uses the imidazolidinone catalyst **8** and the Leckta quinone (**9**)[33] as the chlorine source.

The chlorination is proposed to proceed *via* a transition structure that includes a carbonyl-proton hydrogen-bond association with simultaneous chlorine activation (e.g., **7**, Table 2).[32] As a result, chlorine addition occurs predominantly from the less sterically hindered face of the intermediate enamine as shown below. A thorough screen of reaction conditions determined that optimal levels of asymmetric induction is achieved through the combined use of imidazolidinone catalyst **8** and Leckta quinone (**9**). A variety of commercially available aldehydes (e.g., **10**) were chlorinated under these optimised conditions, leading to a range of α-chloroaldehydes (e.g., **11**) in excellent yield and enantiomeric excess (Table 2).

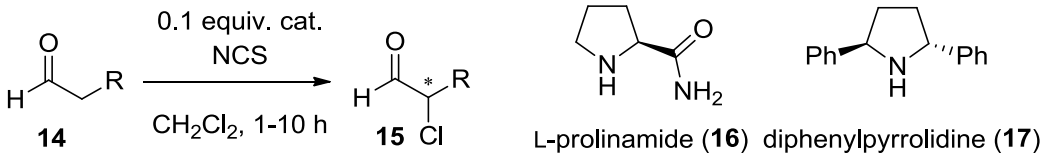
Table 2. Direct asymmetric α-chlorination of aldehydes.



entry	R	yield (%)	e.e. (%)
1	^{n}Hex	71	92
2	^{c}Hex	87	94
3	adamantyl	85	95
4	Bn	92	80
5		76	92
6		78	87
7		94	93

Soon after the aforementioned publication,[31] Jørgensen[34] reported an analogous procedure for the asymmetric α-chlorination of aldehydes that uses proline- and pyrrolidine-based organocatalysts and NCS (**12**) as the electrophilic chlorine source.[34] A catalyst screen indicated that L-proline (**13**) imparts low enantioselectivities (23% e.e.) in the α-chlorination of 3-methylbutanal. However, both L-prolinamide (**16**) and (*2R,5R*)-diphenylpyrrolidine (**17**) were able to impart high levels of stereochemical induction to these reactions (see Table 3). Through the α-chlorination of a variety of aldehydes (e.g., **14** → **15**) with organocatalysts **16** and **17**, Jørgensen determined that the latter organocatalyst afforded greater enantiocontrol (Table 3).

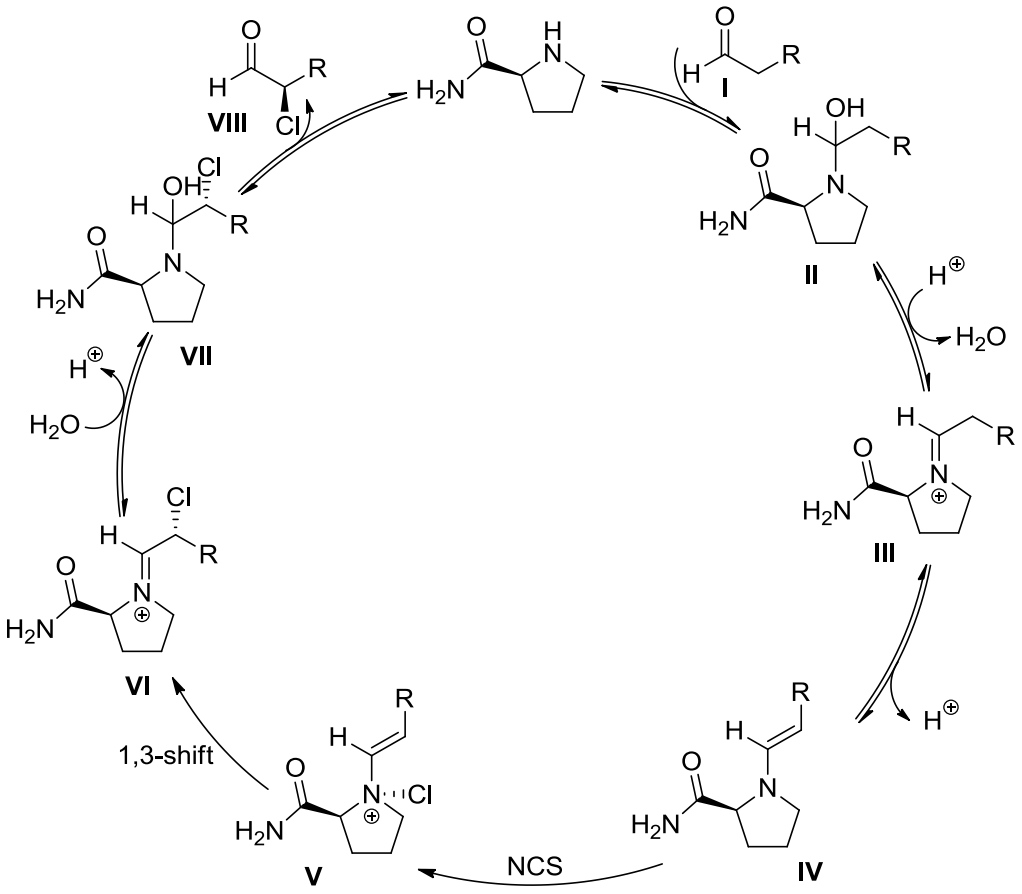
Table 3. Organocatalytic enantioselective α-chlorination of aldehydes.[37]



entry	R	L-prolinamide		diphenylpyrrolidine	
		yield (%)	e.e. (%)	yield (%)	e.e. (%)
1	Me	71	75	-	-
2	Et	87	80	90	97
3	^{i}Pr	95	87	90	94
4	^{t}Bu	93	95	30	94
5	^{n}Hex	95	70	99	95
6	Allyl	90	74	90	95
7	Bn	99	78	82	95
8	$(CH_2)_2OTBS$	92	86	95	81

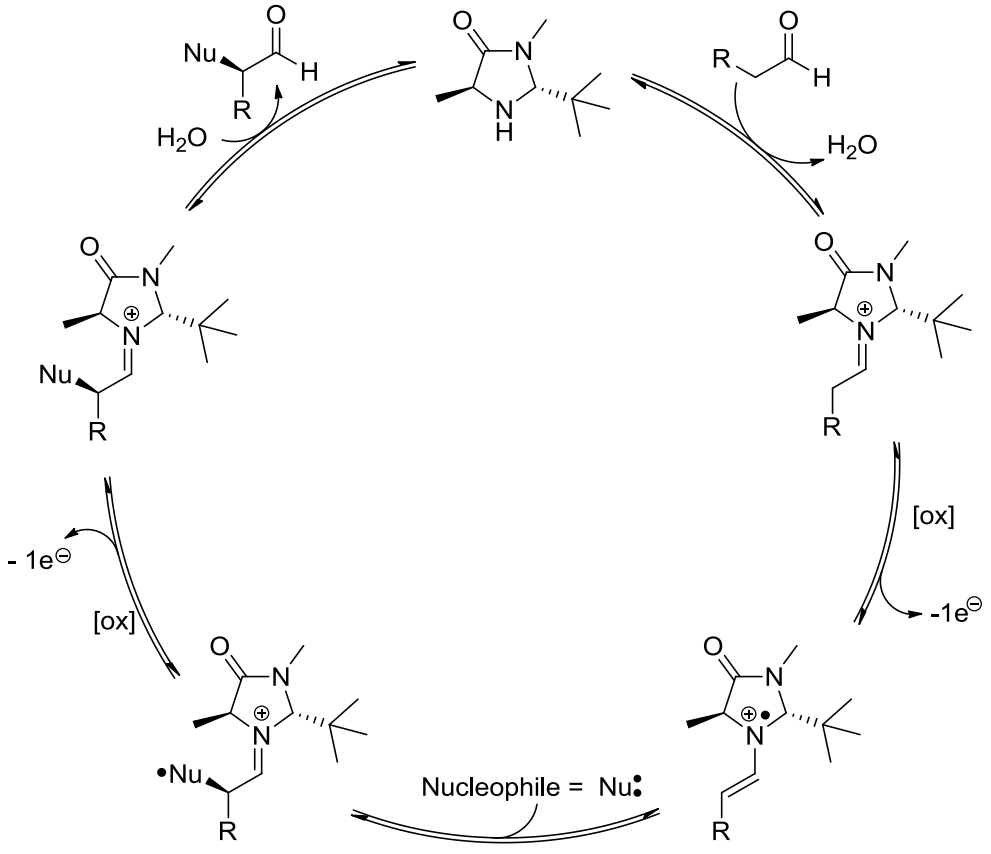
Mechanistic insights into the diphenylpyrrolidine/prolinamide-catalysed α-chlorination of aldehydes suggest that the enantioselectivity does not result from steric shielding of one face of the intermediate enamine by the bulky groups of the catalysts. Rather, the selectivity derives from a kinetically controlled *N*-chlorination (**IV** → **V**) that occurs on the less hindered face of the catalyst-substrate complex **IV**, followed by a 1,3-

sigmatropic shift of the chlorine atom (**V** → **VI**).[35] Next, the iminium ion **VI** is hydrolysed in the rate-determining step of the catalytic cycle, releasing the enantioenriched α-chloroaldehyde **VIII**. This proposed mechanism was supported experimentally by electrospray ionisation mass spectrometry (Scheme 3), which showed the existence of each intermediate.[36] The lower enantioselectivities observed in the proline based catalysts is attributed to the lack of hydrogen-bonding effects in α-halogenation reactions when compared to aldol or Mannich reactions, for which proline imparts significant enantiocontrol.[37]



Scheme 3. **Proposed mechanism of the L-prolinamide-catalysed α-chlorination of aldehydes.**

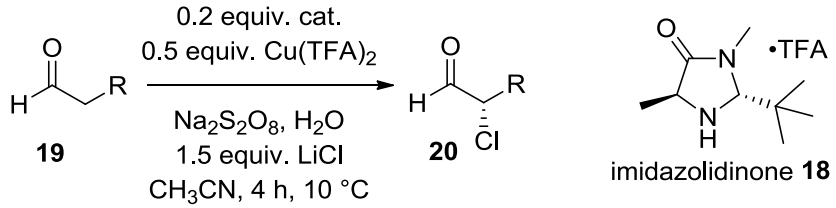
More recently, MacMillan reported an alternative method for the α-chlorination of aldehydes.[38] This new strategy recognises that the organo-SOMO (Singly Occupied Molecular Orbital)[39] activation of aldehydes results in the alteration of the normal electronic properties of an enamine, allowing it to behave as an electrophile. For this purpose, an imidazolidinone catalyst **18** was developed that provides high levels of enantiocontrol in the C-Cl bond-formation and is inert to enamine formation with the α-chloroaldehyde product, thus, minimising racemisation of the product - a significant concern with both previously reported methods. In the proposed reaction mechanism, a one electron oxidant system ($Na_2S_2O_8$ and $Cu(TFA)_2$)[40] reacts with the enamine to generate an enamine radical cation. Rapid chlorination with a SOMO nucleophile, LiCl or NaCl,[41] effectively produces the desired α-chloroaldehyde products (Scheme 4).

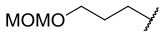
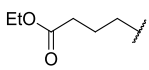
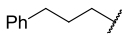
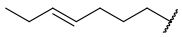
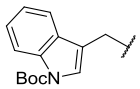
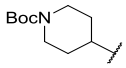


Scheme 4. Proposed catalytic cycle for SOMO-catalysis.

The scope of the SOMO-catalysed α-chlorination of aldehydes (e.g., **19**) was examined and it was observed that a wide range of functional groups on the aldehyde can be tolerated resulting in a high yielding route to enantioenriched α-chloroaldehydes (e.g., **20**, Table 4).

Table 4. Enantioselective α-chlorination of aldehydes under SOMO-catalysis.



entry	R	yield (%)	e.e. (%)
1	^{n}Hex	90	96
2	oct-1-enyl	81	95
3		84	94
4	Bn	89	95
5	^{c}Hex	89	96
6		91	94
7		95	95
8		89	96
9		75	91
10		95	95

1.2 Reactions of α-Chloroaldehydes

As discussed above, advances in organocatalysis have provided several general methods for the production of optically enriched α-chloroaldehydes that are now finding use as chiral building-blocks for complex-molecule synthesis. This section will summarise the common nucleophilic addition reactions involving α-chloroaldehydes that were reported before our contributions in the area.

The first example of an organometallic addition to an α-chloroaldehyde was reported by Cornforth in 1959 and involved the reaction of *n*-BuLi and *n*-BuMgBr with α-chlorobutanal to provide the *anti*-chlorohydrin products.[42] This landmark result was rationalised by what is now referred to as the Cornforth Model, which *"…embraces the assumption that electrostatic [dipole] effects are instrumental in dictating an antiparallel dihedral angle relationship between the carbonyl and the R-Cl substituent."* [43] By employing this model, predictions can be made for the stereochemical outcome of the nucleophilic addition to α-chloroaldehydes (e.g., **21**) as well as other α-polar atom-substituted carbonyl compounds, based on the relative size of the other α-substituents. There are two relevant transition structures (e.g., **22** and **23**, Figure 1), in which the chlorine atom and the carbonyl are in the preferred dipole-minimised orientation. In the transition structure (e.g., **23**), which leads to the favoured 1,2-*anti*-product (e.g., **24**), the nucleophile approaches from the Burgi-Dunitz angle between the chlorine and hydrogen atoms. Conversely, steric interactions between the approaching nucleophile and the R group destabilise transition structure (e.g., (e.g., **22)**, which would lead to the disfavoured 1,2-*syn*-product (e.g., **25**). A recent computational study supports the Cornforth Model for the addition of nucleophiles to α-heteroatom-substituted aldehydes having electronegative substituents (e.g., F, OMe, Cl), and suggests that nucleophilic

additions to aldehydes with less electronegative α-substituents (e.g., NMe_2, SMe, PMe_2) favour the polar Felkin-Ahn[44] transition structure.[43]

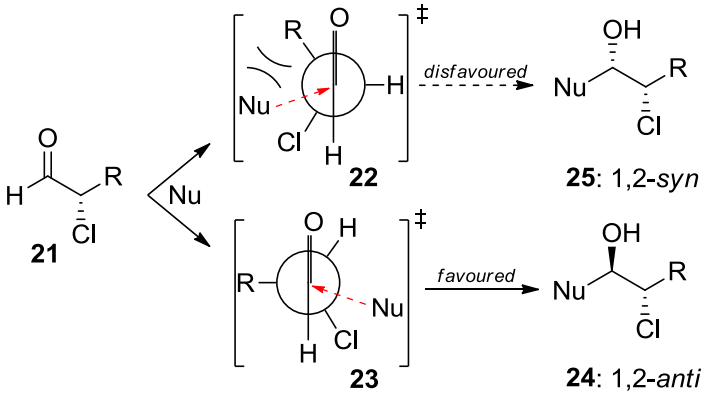
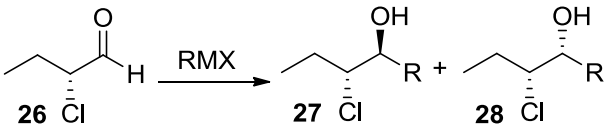


Figure 1. **Rationalisation for the stereochemical outcome of additions to α-chloroaldehydes.**

Despite the widespread adoption of the Cornforth Model, only a few examples of the addition of organometallic reagents to α-chloroaldehydes have been reported and these generally suffer from poor diastereocontrol. In addition, no examples of the preparation of optically enriched chlorohydrins *via* the addition of organometallic reagents to α-chloroaldehydes have been reported.[45] Organometallic additions to racemic α-chloroaldehydes have been reported; for example, the addition of *n*-HexLi to racemic α-chlorobutanal (**26**) afforded the corresponding chlorohydrins (e.g., **27** and **28**) in an 4:1 *anti:syn* ratio (Table 5, entry 1).[45a] Similar diastereoselectivities were observed with the use of *n*-BuTi(O^iPr)$_3$, *n*-BuMgCl, MeMgCl, and MeTi(O*i*-Pr)$_3$ (Table 5, entries 2-5).[45b]

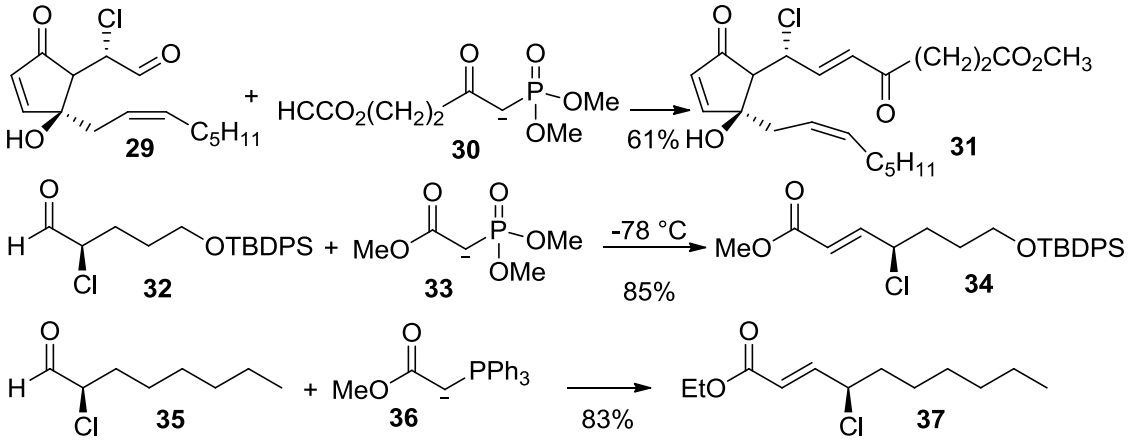
Table 5. Organometallic additions into α-chlorobutanal.



26 **27** **28**

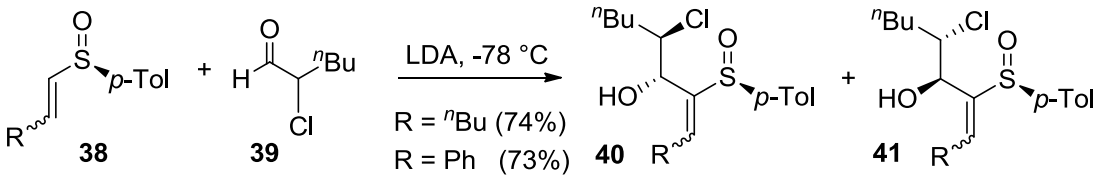
entry	RMX	yield (%)	d.r. (*anti*:*syn*)
1	^{n}HexLi	95	80:20
2	^{n}BuTi(O^{i}Pr)$_3$	80	80:20
3	^{n}BuMgCl	80	77:23
4	MeTi(O^{i}Pr)$_3$	90	85:15
5	MeMgCl	90	88:12

Following the identification of a synthetic route to enantioenriched α-chloroaldehydes, it was shown that these compounds could be converted to optically enriched allyl chlorides *via* olefination reactions. For example, in 1991 Achiwa performed a Horner-Wadsworth-Emmons olefination between α-chloroaldehyde **29** and ylide **30** to furnish the allyl chloride **31**.[46] Similarly, Martín demonstrated that the enantioenriched α-chloroaldehyde **32** undergoes a Horner-Wadsworth-Emmons olefination with **33** to afford the corresponding vinyl chloride **34** (Scheme 5).[47] In addition, Bergman has shown that a Wittig olefination[48] involving the α-chloroaldehyde **35** and Wittig reagent **36** furnished the enantioenriched allylic chloride **37** (Scheme 5).



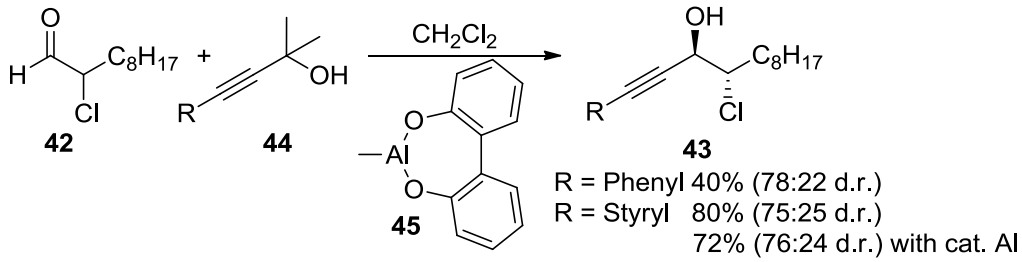
Scheme 5. Olefinations of α-chloroaldehydes.

In 2000, Marino demonstrated that the addition of lithiated enantiopure alkenyl sulfoxide (e.g., **38**) to racemic α-chlorohexanal (**39**) affords a 1:1 mixture of the diastereomeric *anti*-chlorohydrins (92:8 *anti:syn*) (e.g., **40** and **41**, Scheme 6).[49] These chlorohydrin products were then subjected to a base-promoted epoxidation, followed by a sulfoxide-controlled S_N2' displacement reaction between cyanocuprates and the epoxy vinyl sulfoxides (not shown).



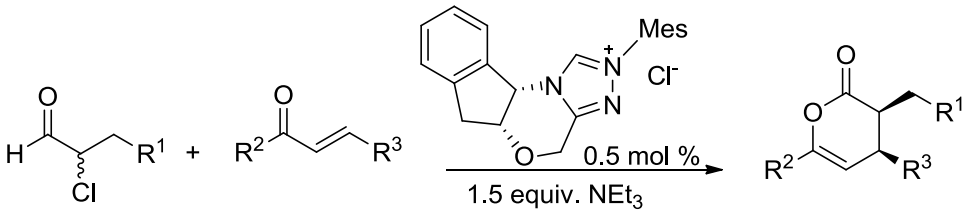
Scheme 6. Addition of lithiated enantiopure alkenyl sulfoxides to racemic α-chlorohexanal.

The work of Meerwein,[50] Ponndorf,[51] and Verley[52] on the reduction of aldehydes and ketones with an alcohol in the presence of aluminum alkoxides[53] inspired Maruoka to exploit this reaction in the transfer of alkynyl groups to various aldehydes (not shown).[54] This included the alkynylation of α-chlorodecanal (e.g., **42** → **43**) with 2,2-disubstituted propargyl alcohols (e.g., **44**), which proceed in good yield (40-80%) and moderate diastereoselectivity (75:25 to 78:22 d.r.) in the presence of stoichiometric amount of the alumunium reagent **45** (Scheme 7). No significant change was observed with catalytic (10 mol%) aluminum alkoxide **45** (72% yield, 76:24 d.r.).



Scheme 7. Alkynylation of α-chlorodecanal.

In 2006, Bode demonstrated the use of α-chloroaldehydes (e.g., **46**) as the dienophile precursors in chiral *N*-heterocyclic carbene-catalysed 1-oxodiene Diels-Alder reactions of a variety of enones (e.g., **47**).[55] This process affords a range of nonracemic, 3,4,6-trisubstituted dihydropyran-2-ones (e.g., **48**) from readily available starting materials (Scheme 8). In addition, Bode determined that the stereochemistry of the α-chloroaldehydes does not affect the stereochemical outcome of this reaction.



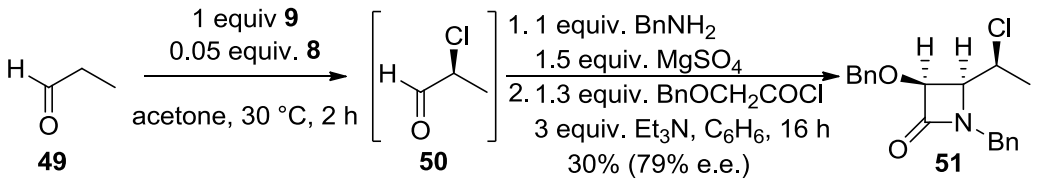
46 **47** **48**

R^1 = Ph, OTBS, ^{n}C$_9$H$_{19}$ 70-98% (3:1 to >20:1 d.r.; 86-99% e.e.)
R^2 = Me, Ph, *p*-Br-C$_6$H$_4$, ^{c}Hex, furyl, CO_2Et
R^3 = *p*-Tol, ^{n}Pr, ^{c}Hex

Scheme 8. Chiral *N*-heterocyclic carbene-catalysed oxodiene Diels-Alder reactions.

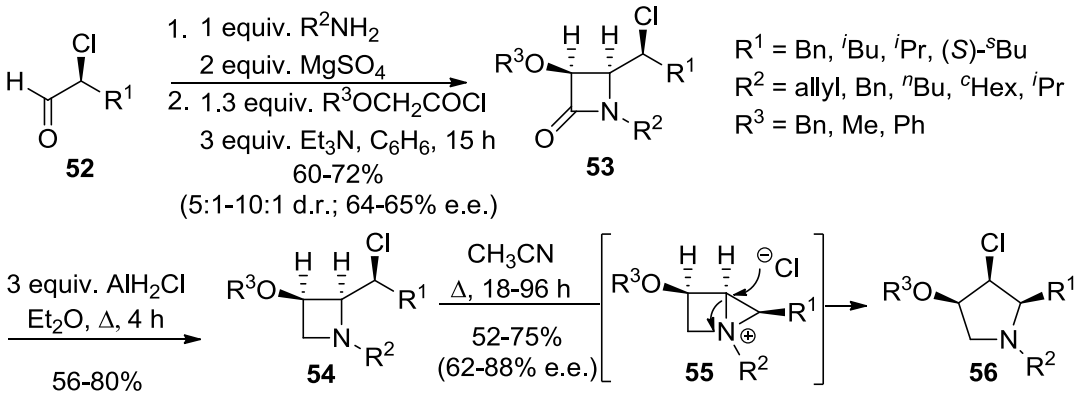
α-Chloroaldehydes have also been exploited in the enantioselective synthesis of β-lactams, which are generally accessed *via* the Staudinger reaction in which a ketene and an imine undergo a [2+2]-cycloaddition.[56] In most cases, chirality is introduced through the use of a chiral imine and an achiral ketene, and the greatest stereoselectivities in the Staudinger reaction are observed when the chiral imines are derived from enantiopure α-substituted aldehydes, primarily α-oxy- and α-aminoaldehydes.[57,58] A computational study performed by Palomo[58] suggested that using α-chloroimines might lead to greater stereoselectivities due to the higher hyperconjugative acceptor ability of halogens compared to oxygen and nitrogen.[59] This prediction was confirmed experimentally by De Kimpe in 2008, when he found that α-chloroimines are powerful directing groups in the stereoselective synthesis of β-lactams, which were produced with excellent diastereocontrol (>10:1 d.r.).[22] Thus, using

MacMillan's asymmetric α-chlorination methodology,[31] (2*S*)-chloropropanal was prepared (**49** → **50**) and subsequently converted *via* the Staudinger reaction to the enantiomerically enriched (79% e.e.) β-lactam **51** in 30% yield (Scheme 9).



Scheme 9. Enantioselective synthesis of a 4-(1-chloroethyl)-β-lactam.

The aforementioned methodology was further elaborated by the same group in the synthesis of β-lactams, azetidines, and pyrrolidines from enantiomerically enriched α-chloroaldehydes.[25] The amino acid-derived α-chloroaldehydes (e.g., **52**) were also subjected to the Staudinger reaction to afford β-lactams (e.g., **53**). Their subsequent conversion into azetidines (e.g., **54**) was accomplished by the reduction of the β-lactams (e.g., **53**) with monochloroalane. Finally, heating the azetidines (e.g., **54**) in acetonitrile led to a rearrangement, *via* an intermediate bicyclic azetidinium ion (e.g., **55**), producing 2-alkyl-3-chloropyrrolidines (e.g., **56**, Scheme 10).



Scheme 10. Enantioselective synthesis of β-lactams, azetidines, and pyrrolidines.

1.3 1,2-Chlorohydrins

The 1,2-chlorohydrin functionality is common to many natural and unnatural products,[60] and is often encountered in biosynthetic pathways (e.g., vinyl chloride-biosynthesis). In nature, introduction of the 1,2-chlorohydrin functionality has been proposed to occur *via* various enzymes, including non-heme iron halogenases that are capable of performing chlorinations on unactivated carbons.[61] From a synthetic standpoint, a number of strategies have been developed for the formation of 1,2-chlorohydrins and their subsequent transformations. This section will summarise the common examples of 1,2-chlorohydrins as well as their preparations and uses that were reported prior to our work in the area.

Many natural and 'unnatural' products contain 1,2-chlorohydrins or are derived from this functionality (Figure 2), including compounds such as rehmaglutin D (**57**), used in traditional Chinese medicines as an antianemic and an antipyretic;[62] and 8-chlorogoniodiol (**58**), which is active against the HepG2 lung cancer-cell line.[63] In recent years, increased focus has been directed toward the chlorosulfolipid class of natural products (e.g., malhamensilipin A (**59**)).[64] These molecules exhibit cytotoxicity toward a variety of cancer-cell lines and are associated with seafood poisonings. A widely used unnatural product, the artificial sweetener sucralose (Splenda) (**60**), also contains the 1,2-chlorohydrin functionality.[65] An example of a vinyl chloride-containing natural product that is produced biogenetically from a 1,2-chlorohydrin is jamaicamide A (**61**).[66] These compounds represent only a small fraction of complex molecules that contain or are derived from 1,2-chlorohydrins (Figure 2).

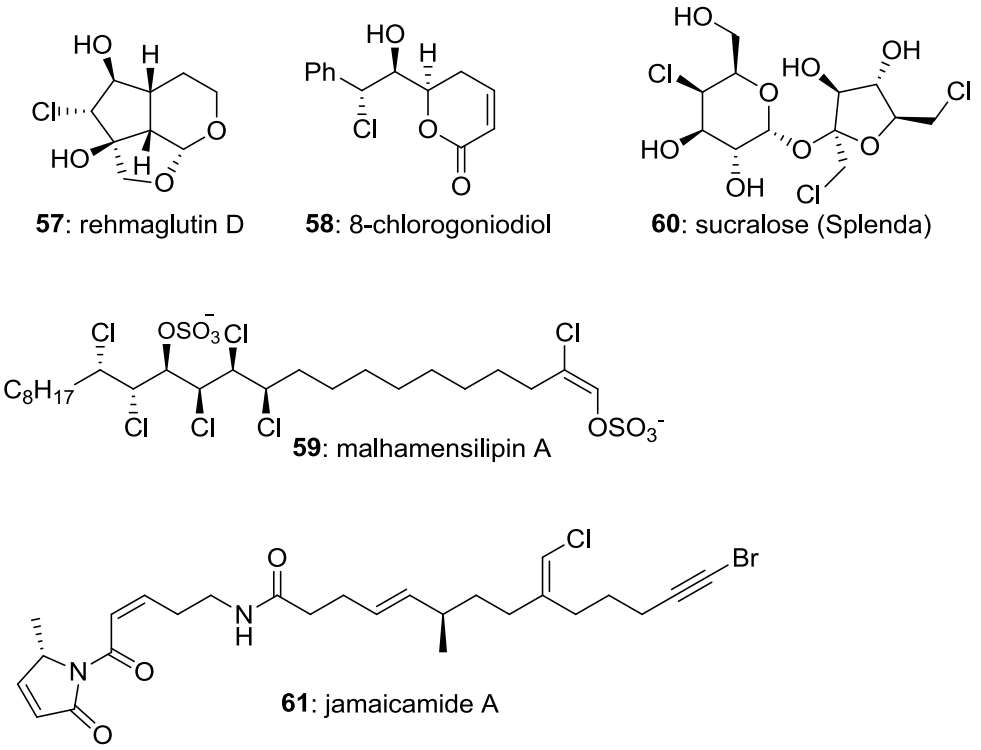


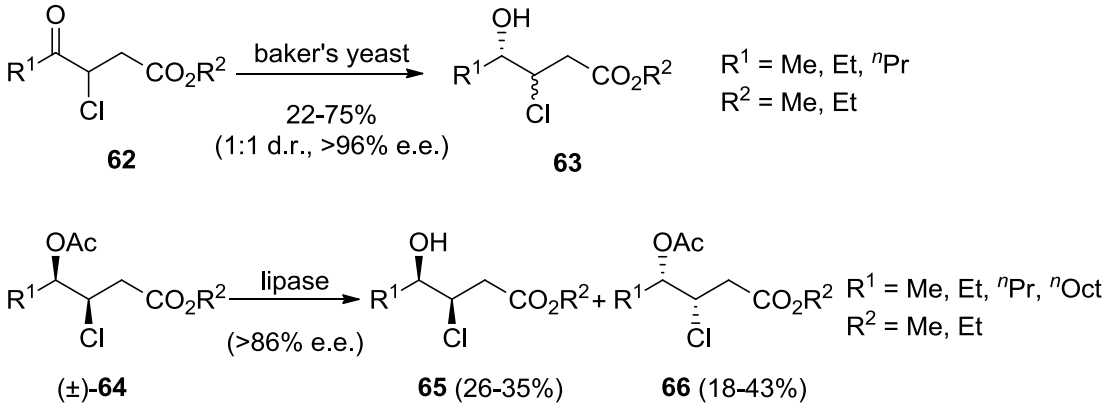
Figure 2. **Representative examples of natural and unnatural products that contain or are derived from 1,2-chlorohydrins.**

The prevalence of 1,2-chlorohydrins in interesting natural and 'unnatural' products, coupled with their potential synthetic utility has led to the development of a variety of methods for their preparation. Even though the straightforward addition of organometallic reagents to α-chloroaldehydes to generate the 1,2-chlorohydrins, albeit in low diastereoselectivity, was presented in Section 1.2, other methods exist that allow access to this functionality. These include epoxide-opening reactions, reduction of α-chloroketones, and chlorohydroxylations of alkenes.

The most common method used for the formation of 1,2-chlorohydrins involves the use of nucleophilic chloride to open epoxides in a stereospecific manner. For example, in 1981 Andrews reported that trimethylsilylchloride can be used in an epoxide-opening reaction catalysed by triphenylphosphine.[67] Since then, phosphaferrocene [68] and phosphazirconocene[69] have been used to catalyse this reaction. In addition, a

variety of Lewis acids accompanied by chlorinating agents (e.g., $Ti(O^iPr)_4/NH_4Cl$,[70] $TiCl_4/LiCl$,[71] Et_2AlCl,[72] $BH_2Cl{\cdot}DMS$,[73] $SiCl_4$,[74] etc.) have been used in the epoxide-opening reactions to afford 1,2-chlorohydrins.[75] The direct preparation of 1,2-chlorohydrins from alkenes, *via* an *in situ* formation of the epoxide, has also been reported. For example, in 1985, Sharpless reported that the chlorohydroxylation reaction of alkenes proceeds with *tert*-butylhydroperoxide (THBP) in the presence of $TiCl_4$.[76] In addition, Shibasaki reported the direct formation of 1,2-chlorohydrins using bis(trimethylsilyl)peroxide (BTSP) with TMSCl and catalytic $SnCl_4$.[77]

A method that is less commonly used to access 1,2-chlorohydrins involves the reduction of α-chloroketones. In 1991, Tsuboi reported the asymmetric reduction of α-chloroketones (e.g., **62** → **63**) with baker's yeast in moderate yields.[78] In addition, racemic chlorohydrins derived from the reduction of α-chloroketones with $NaBH_4$, were acetylated and then treated with lipase 'Amano P' to effect an asymmetric hydrolysis that affords the optically pure 1,2-chlorohydrins (e.g., **64** → **65**) and 1,2-chloroacetates (e.g., **66**).[79]



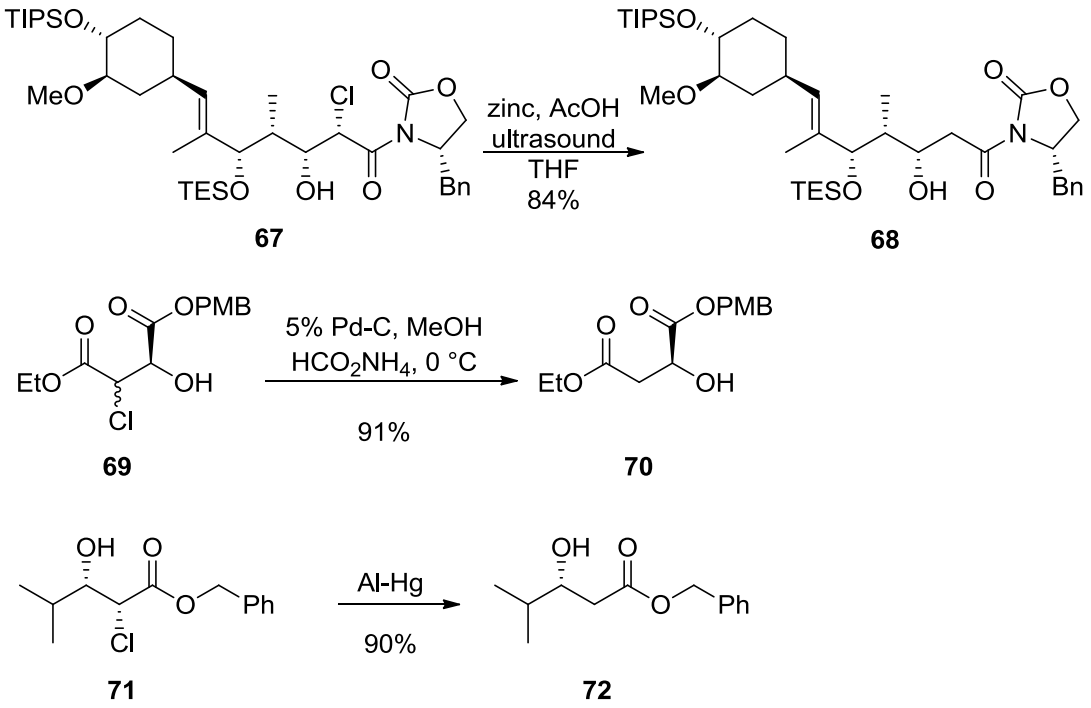
Scheme 11. Asymmetric reduction of chloroketones and the asymmetric hydrolysis of 1,2-chlorohydrins.

In 1996, Oehlschlager demonstrated that 1,2-*cis*-chlorohydrins could be generated through the addition of (*Z*)-(γ-chloroallyl)boranes with aldehydes in high e.e.

and diastereomeric control.[80] The 1,2-*cis*-chlorohydrins were further elaborated to a variety of *cis*-vinyloxiranes.

Though 1,2-chlorohydrins are often the end-product, this functionality can also be further elaborated in a variety of ways (e.g., lactonisations,[81] etherifications,[82] cyclopropanations[83]). Whereas most methods have limited applications, a few common transformations do exist; these include the dechlorination and nucleophilic displacement of the chlorine atom.

The reduction of the chlorine atom of 1,2-chlorohydrins has been reported using a variety of reagents and conditions (Scheme 12). Since 1983, tributylstannane/AIBN has been widely used for these dechlorinations;[84] however, in 1990 Mills reported a tin-free method for the dechlorination of the α-chloro-β-hydroxyamide **67** that uses Zn/AcOH to give the β-hydroxyamide **68** *en route* to the synthesis of the immunosuppressant (-)-FK-506.[85] Shioiri later revealed that the chlorine atom in ester **69** may be reduced by transfer hydrogenation to afford the β-hydroxyester **70** in good yield.[86] Yan has also demonstrated that use of Al-Hg amalgam results in a chemoselective cleavage of the C-Cl bond in the α-chloro-β-hydroxyester **71** to yield the β-hydroxyester **72** in excellent yield.[87]



Scheme 12. Dechlorination reactions of 1,2-chlorohydrins.

1,2-Chlorohydrins have also been shown to undergo direct nucleophilic displacements at the chloromethine centre, and *via* the intermediacy of epoxides. For example, the C-Cl bond of chlorohydrins has been converted to C-N bond using a variety of nucleophiles that include, ammonia,[88] sodium azide,[89] primary amines,[89a,90] and secondary amines.[89a,91] The conversion of the C-Cl bond to C-Br,[92] C-I,[93] and C-F[94] has also been demonstrated to proceed with inversion. Not surprisingly, 1,2-chlorohydrins can also be converted to epoxides.[49,95] Intermolecular C-O bond-forming reaction also includes displacement of the chlorine atom by water,[96] alkoxides,[97] and phenoxides.[98] Conversion of the C-Cl bond to a C-S bond has also been reported.[97c,99]

1.4 Thesis Overview

As the structures of molecules targeted by pharmaceutical and agrochemical sectors continue to increase in complexity, new synthetic methods are constantly sought that rapidly transform readily available starting materials into complex molecules in a stereocontrolled manner. Building on the developments in enantioselective organocatalysis reported over the last decade, the synthetic chemistry community has a number of new tools for asymmetric synthesis as well as easy access to building-blocks that may serve as launching points for the synthesis of biologically active molecules.

The research discussed in this thesis builds upon recent advances in organocatalysis, and more specifically involves exploration of the reactivity and general chemistry of α-chloroaldehydes. These efforts are primarily focused on the use of α-chloroaldehydes as intermediates in the synthesis of natural products. In chronological order, these efforts involved an initial focus on identifying the optimal conditions for the preparation of α-chloroaldehydes using the asymmetric α-chlorination methods described in this Chapter. Nucleophilic additions of a variety of organometallic reagents to α-chloroaldehydes to afford 1,2-chlorohydrins were examined. The results of these studies identified several routes to 1,2-chlorohydrins that proved to be versatile intermediates for the asymmetric synthesis of complex molecular scaffolds prevalent in natural products. Finally, these methods were demonstrated in the total synthesis of several biologically active natural products.

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Chapter 2

A General Method for the Synthesis of Nonracemic *trans*-Epoxides: Concise Syntheses of *trans*-Epoxide-Containing Insect Sex Pheromones

The results discussed in this Chapter have been reported in part, see:. Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083.

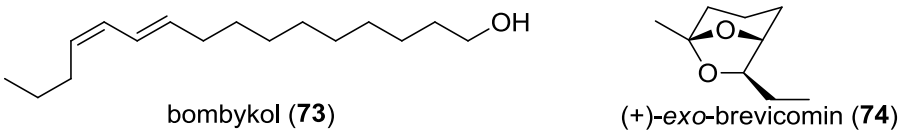
2.1 Introduction to Insect Sex Pheromones

2.1.1 Chemical Ecology and Synthesis

Pheromones (from the Greek *phero* 'to transfer' and *hormon* 'to excite') are unique and highly specific chemicals produced by a given species that affect the behaviour and/or physiology in members of the same species. These chemicals are capable of inducing a variety of social responses (e.g., aggregation, alarm, trail, territorial, attraction).[1] In recent years, the use of insect sex pheromones has increased in the field of pest control, primarily because these molecules can selectively disrupt the reproduction of harmful insects or lure these pests to traps. Owing to increasing concerns regarding toxicity of pesticides toward both humans and the environment, the development of pheromone-based insect control tactics allows for alternative opportunities for ecologically sustainable crop management[2] in the agricultural and

forestry industries. These concerns are exemplified by the fact that the global biopesticides market is estimated at $1 billion, with a recent annual growth rate of 13%.[3]

At the turn of the 20th century Jean-Henri Fabre noted the first indication of pheromones. Specifically, he observed that female emperor moths (*Saturnia pavonia*) attracted males when behind wire-gauze, but not when sealed under glass. Furthermore, he noticed that the females of the giant peacock moth (*Saturnia pyri*) attracted the males of its species from large distances.[4] Fifty years later, Butenandt reported the first publication regarding pheromone chemistry with the structure determination of bombykol (**73**, Figure 3), the sex pheromone of the silkworm moth (*Bombyx mori*).[5] It is important to note that Butenandt and his team spent over 20 years isolating only 12 mg of pure bombykol from 500,000 silkworm moths- highlighting the painstakingly tedious nature of pheromone isolation. However, this amount was sufficient to determine the chemical structure of bombykol (**73**) through a combination of chemical degradation methods and infrared spectroscopy.[5] Shortly thereafter, the first examples of chiral pheromones were reported, which included the structure elucidation of *exo*-brevicomin (**74**, Figure 3), the aggregation pheromone of the western pine beetle (*Dendroctonus brevicomis*).[6] Over the last half century the structure elucidation of over 1600[7] insect sex pheromones has provided a growing arsenal of chemicals for crop protection.



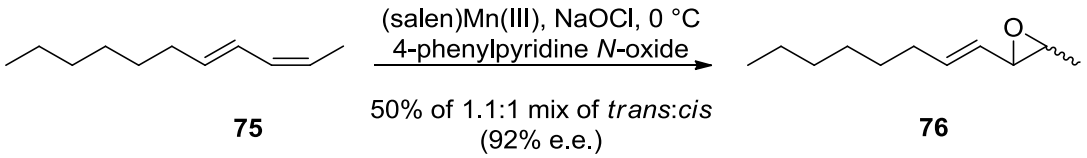
bombykol (**73**) (+)-*exo*-brevicomin (**74**)

Figure 3. Structures of bombykol (73) and *exo*-brevicomin (74).

Owing to the small quantities (i.e., nanograms to micrograms) of material available from natural sources, difficulties are often encountered in the structural assignment and stereochemical analysis of pheromones. As a consequence, the use of

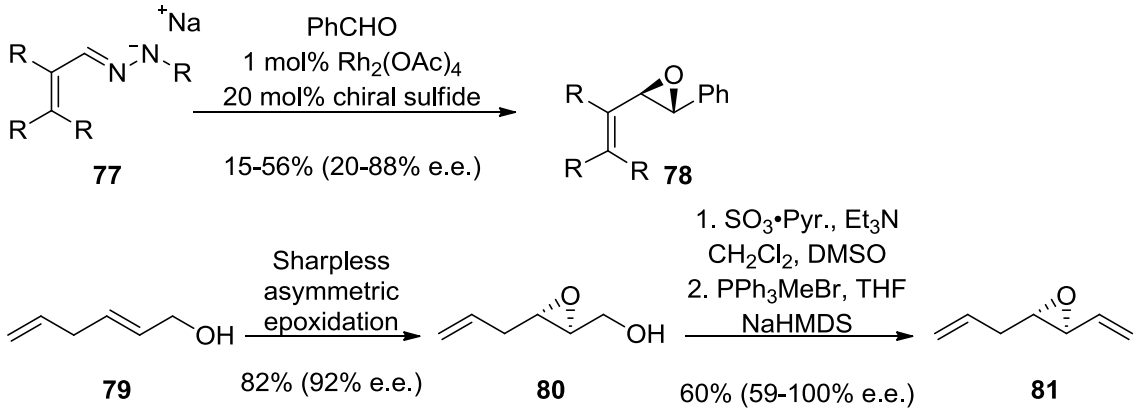
conventional analytical tools (e.g., X-ray crystallography, optical rotation, chemical degradation, etc.) is often ineffective for this purpose. Moreover, comparative methods (e.g., chiral GC, GC-EAD) require enantioselective preparation of synthetic samples of known absolute configuration.[8] Therefore, total synthesis represents the only means to access sufficient supply of these compounds for biological evaluation, field testing, and/or commercialisation purposes.

The structural complexities observed in some pheromones often preclude the development of economically viable syntheses. Aside from being extremely sensitive, insect chemoreception is often highly enantiodiscriminatory,[9] which presents a significant challenge in the development of asymmetric pheromone syntheses. In recent years, however, the enantioselective synthesis of chiral nonracemic pheromones has benefitted from the developments in asymmetric catalysis.[10] In particular, procedures for the asymmetric epoxidation[11] and dihydroxylation[12] of olefins allow access to a variety of epoxide-containing pheromones with high levels of optical purity.[13] Although the asymmetric epoxidation of dienones,[14] α,β,γ,δ-unsaturated amides,[15] esters,[16] and carbinols[17] has been reported, the epoxidation of unfunctionalised dienes[16] is hampered by poor regio- and enantiocontrol.[18] For example, Jacobsen reported that the epoxidation of the unfunctionalised diene **75** results in a 1.1:1 ratio of *trans*:*cis* epoxides **76** (Scheme 13).[16b] Therefore, the asymmetric synthesis of vinyl epoxide-containing pheromones continues to present significant challenges.



Scheme 13. Example of the epoxidation of an unfunctionalised dienes.

Notwithstanding the difficulties mentioned above, several indirect synthetic routes have been reported that provide optically active *trans*-vinyl epoxides. These include, the reaction of tosylhydrazone salts (e.g., **77**) with benzaldehyde using chiral sulfides to afford *trans*-vinyl epoxides (e.g., **78**, Scheme 14).[19] A three-step sequence of reactions involving the Sharpless asymmetric epoxidation of an allylic alcohol **79**, oxidation of the alcohol **80** to an aldehyde, and a Wittig olefination generated the *trans*-vinyl epoxides **81** (Scheme 14).[20] Although these methods deliver vinyl epoxides with good enantiomeric control, they are limited in their scope.



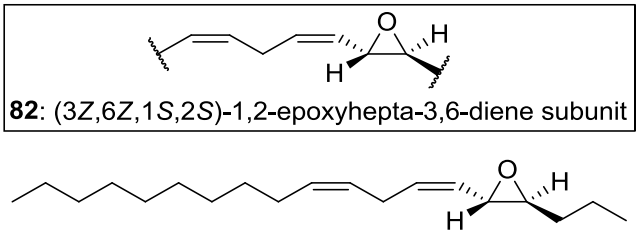
Scheme 14. Routes to optically active vinyl epoxides.

As discussed above, only a limited number of methods for the synthesis of vinyl epoxides have been reported, and most of these methods are not applicable to the synthesis of substituted epoxides (e.g., alkynyl, alkyl, phenyl, etc.). For example, the Shi-epoxidation induces high levels of asymmetry with phenyl substituents (89-99% e.e.),[11c,21,22] the Jacobsen epoxidation of alkyl- and phenyl-substituted alkenes generates mixtures of *cis*- and *trans*-epoxides,[23] and the Sharpless asymmetric epoxidation requires prochiral allylic alcohols. Thus, the development of a general protocol for the asymmetric synthesis of substituted epoxides would be greatly beneficial to the synthetic

chemistry community and potentially prove useful for the synthesis of epoxide-containing insect sex pheromones.

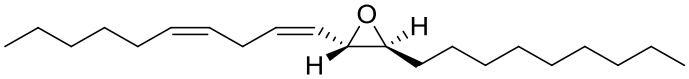
2.1.2 The trans-Epoxide-Containing Insect Sex Pheromones

The first examples of *trans*-epoxide-containing insect sex pheromones were recently reported from the pine looper moth, *Bupalus piniarius,*[24] and the tussock moth, *Orgyia postica*.[25,26] Throughout Europe, the pine looper moth is a serious threat to Scots pine (*Pinus sylvestris*) forests, whereas in Asia the tussock moth is a major concern for fruit producers.[25] Interestingly, the females of these unrelated species of moth rely on structurally similar *trans*-epoxide-containing sex pheromones to attract males. Specifically, both pheromones contain the (3*Z*,6*Z*,1*S*,2*S*)-1,2-epoxyhepta-3,6-diene subunit (i.e., **82**, Figure 4). Based on the importance of these pheromones for crop protection, several syntheses of **83**[24] and **84**[25,27,28,35] have been reported.



82: (3*Z*,6*Z*,1*S*,2*S*)-1,2-epoxyhepta-3,6-diene subunit

83: (6*Z*,9*Z*,4*S*,5*S*)-4,5-epoxynonadeca-6,9-diene



84: (6*Z*,9*Z*,11*S*,12*S*)-11,12-epoxyhenicosa-6,9-diene (posticlure)

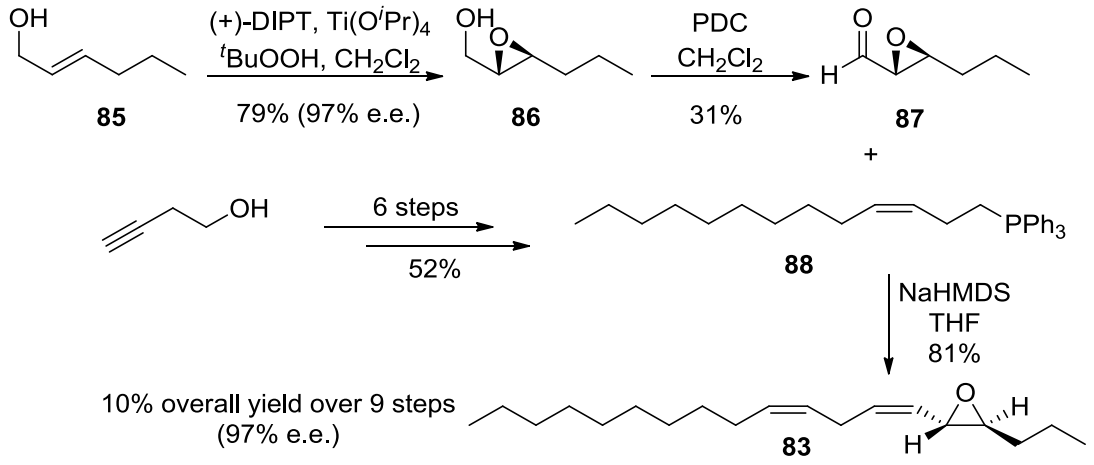
Figure 4. Insect sex pheromones isolated from female *B. piniarius* (83) and *O. postica* (84) and their common subunit (i.e., 82).

The pine looper moth, *Bupalus piniarius*, is an autumn defoliator of Scots pine (*Pinus sylvestris*) trees in Europe.[29] After the initial *B. piniarius* outbreak, a secondary

attack by the pine shoot beetle (*Tomicus piniperda*) further affects mortality of the enfeebled Scots pine forests.[31] Although this pest has been known for at least 200 years in Germany and Poland,[30] in Britain the species attained this status only after large-scale plantings of the Scots pine in the early twentieth century.[31] The associated financial burden of Scots pine defoliation now accounts for major financial losses in the export of timber (e.g., decrease of 5.8-7.5% in timber prices in Britain).[32]

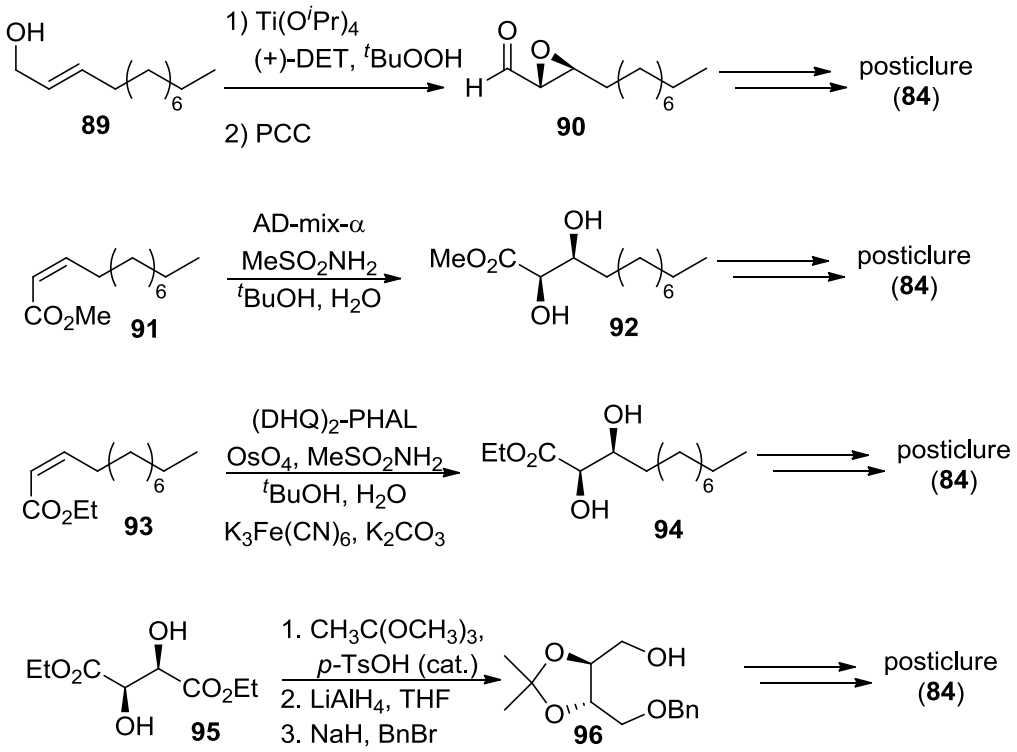
The flightless females of the tussock moth, *Orgyia postica*, cling to the exteriors of their cocoons where they release the sex pheromone **84** to attract the males. After copulation, the eggs are laid.[26] The resulting larvae cause damage to the fruit by attacking the flower stalks, skin, and the pulp, which leads to premature fruit-drop or excessive bruising.[33,34a] The fine bristles that cover the larvae also irritate the skin of fruit-pickers and/or lodges into the fruit itself, rendering it unsuitable for sale.[25,34a] Reports of severe damage to commercial crops (e.g., mango, litchi, durian, poplar, grapes, roses, etc.) across Asia are often associated with *O. postica*.[34]

The unique structural framework of the *B. piniarius* and *O. postica* sex pheromones **83** and **84** presents challenges in defining an efficient chemical synthesis of these compounds. In 1998, Francke reported the only known synthesis of the *B. piniarius* pheromone (**83**).[24] In this approach, a Sharpless asymmetric epoxidation of the allylic alcohol **85** afforded an enantiomerically enriched epoxide **86** (97% e.e.). Subsequent, oxidation to aldehyde **87** and Wittig olefination using the (*Z*)-tridecene triphenylphosphonium ylide **88** afforded the *B. piniarius* pheromone (**83**) in nine-steps (10% overall yield) (Scheme 15).[24]



Scheme 15. Previous synthesis of the *B. piniarius* pheromone (83).

Four syntheses of the *O. postica* pheromone, posticlure (**84**), have been reported.[25,27,28,35] The first synthesis of posticlure (**84**) and its antipode *ent*-**84** employed the Sharpless asymmetric epoxidation of an allylic alcohol (**89** → **90**); however, this reaction proceeded with only moderate asymmetric control (59% e.e.) (Scheme 16).[25] Thus, optically pure synthetic (+)- and (-)-posticlure (**84**) was necessarily obtained by preparative chiral HPLC. Following field testing of each antipode, it was found that only (-)-posticlure (**84**) attracted male *O. postica*, confirming the absolute stereochemistry of the natural pheromone. With this knowledge in hand, two subsequent enantioselective syntheses of (-)-posticlure (**84**) that employed a Sharpless asymmetric dihydroxylation (**91** → **92** and **93** → **94**) *en route* to the natural product were reported (Scheme 16).[27,28] In addition, a chiral-pool synthesis that initiated with the desymmetrisation of diethyl L-tartrate (**95** → **96**) provided enantiomerically pure (-)-posticlure (**84**) in seven-steps (27% overall yield) (Scheme 16).[35]



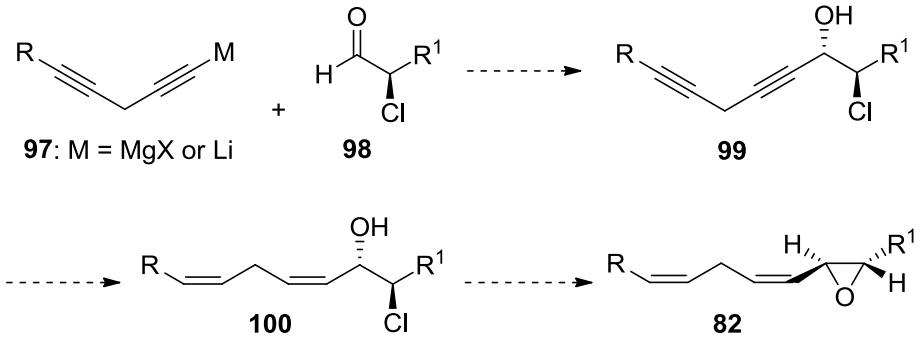
Scheme 16. Key steps in the previous syntheses of (-)-posticlure (84).

Although the synthetic routes discussed above allowed for the confirmation of absolute stereochemistry of the insect sex pheromones **83** and **84**, the overall length of these syntheses (9 and 7-13 overall steps, respectively) may limit their practical application. Bearing this in mind, and in an effort to support the field testing of **83** by the Landesforstanstalt Eberswalde (National Forestry Institute in Eberswalde, Germany), we sought to develop a concise and general method for the synthesis of *trans*-vinyl epoxides, which also affords access to both insect sex pheromones.

2.2 Synthesis of *trans*-Epoxides

2.2.1 Synthetic Plan

Based on complexities encountered in the synthesis of vinyl epoxides, the development of a general asymmetric synthesis of vinyl epoxides, including the *trans*-epoxide-containing pheromones **83** and **84**, would represent an important contribution to the field. With this in mind, we envisioned a straightforward sequence of events to prepare the *trans*-epoxides that involves the addition of organometallic agents to α-chloroaldehydes, followed by conversion of the resulting chlorohydrin into an epoxide. Applications of this methodology to the synthesis of insect sex pheromones **83** and **84** would then involve addition of a diynyl anion (e.g., **97**) to an α-chloroaldehyde (e.g., **98**), followed by Lindlar reduction (**99** → **100**) and epoxide-formation to afford the desired (3*Z*,6*Z*,1*S*,2*S*)-1,2-epoxyhepta-3,6-diene (e.g., **82**, Scheme 17).



Scheme 17. Strategy for the construction of the dienyl epoxide subunit (82).

Our strategy was inspired by independent reports regarding the enantioselective synthesis of α-chloroaldehydes by MacMillan[36] (see page 4) and Jørgensen[37] (see page 6). We envisioned that by using one of these methods, the desired α-chloroaldehydes could be generated with excellent enantiocontrol.

The addition of organometallic reagents to racemic α-chloroaldehydes has been reported to suffer from poor diastereocontrol yielding *anti*- and *syn*-chlorohydrins in ratios ranging from 1:1 to 4:1 (see page 11).[42,38]. We envisioned that changing the nature of the metal, solvent, and other conditions may improve upon these results. In addition, our studies would represent the first examples of organometallic additions to nonracemic α-chloroaldehydes.

Although our ultimate goal was to develop a concise synthesis of the *B. piniarius* and *O. postica* sex pheromones, our initial efforts focused on the development of the general synthetic route toward the *trans*-epoxides. Consequently, we initiated these studies by first exploring the asymmetric α-chlorination reaction of aldehydes and the subsequent addition of organometallic reagents to these substances. It was anticipated that these studies would lay the foundation for rapid synthesis of both insect sex pheromones.

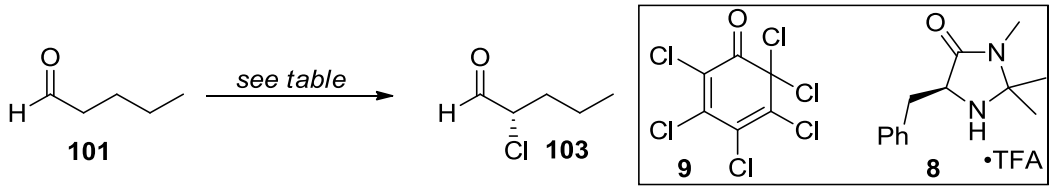
2.2.2 Results

2.2.2.1 Asymmetric α-Chlorination of Aldehydes

The asymmetric α-chlorination of aldehydes was reported independently by MacMillan[36] and Jørgensen[37] in 2008; however, the α-chloroaldehydes reported in these studies were produced in milligram quantities and were seldom isolated from the reaction mixtures due to their expected instability. Cognisant of this, we initially sought to identify a suitable method for the production and storage of gram amounts of enantioenriched α-chloroaldehydes. For this reason, we thoroughly examined the asymmetric α-chlorination of pentanal (**101**) and undecanal (**102**) as summarised in Table 6 and Table 7.

As indicated in Table 6, the α-chlorination of pentanal (**101**) was first examined using the Leckta quinone (**9**) and imidazolidinone catalyst **8**[39], following the standard reaction conditions described by MacMillan.[36] This reaction afforded the α-chloroaldehyde **103** in good yield, but moderate and varying enantiomeric excess (Table 6). In an effort to optimise the reaction conditions it was confirmed that the ideal reaction concentration, solvent, catalyst loading, and temperature for this reaction was congruent with the literature report. Despite this, the most favourable result (Table 6, entry 11) using catalyst **8** resulted in the production of (2*R*)-2-chloropentanal (**103**) in only 58% enantiomeric excess, appreciably lower than reported values (80-92% e.e.). Based on these results and many others (not shown), we postulated that even though the original chlorination proceeded with good levels of enantioselectivity, racemisation occurred during the reaction or in the subsequent purification step. To test these hypotheses, the enantiomeric excess was evaluated over the course of a reaction and a marked deterioration of optical purity was observed over time. Similarly, it was found that longer reaction times resulted in lower enantiomeric excesses (Table 6, entries 9-11). Moreover, subjecting the reaction mixture to column chromatography with Merck silica gel 60 (pH 6.5) also degraded the optical purity of the final product (Table 6, entry 14); whereas, use of Iatrobeads silica (pH 7.1) did not affect the enantiomeric excess (Table 6, entry 15). Additionally, we determined that this procedure was not amenable to scale-up (i.e., >10 mmol) (Table 6, entry 16). Since our original studies, MacMillan has reported an alternative method (see page 8) for the α-chlorination of aldehydes resulting in α-chloroaldehydes with >95% enantiomeric excess, importantly without erosion of optical purity.[40]

Table 6. Asymmetric α-chlorination of using MacMillan's conditions.



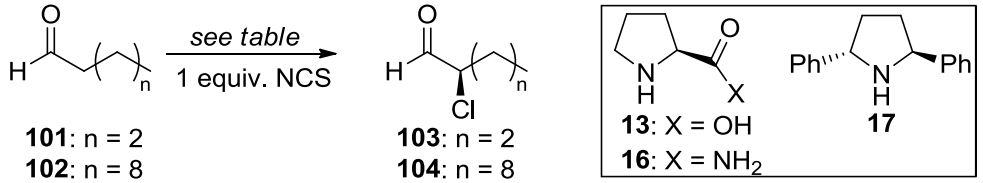
ent	solvent[a]	cat. (mol%)	temp (°C)	time (h)	yield (%)[b]	e.e. (%)[c]
1	acetone	5	22	1	60	13
2	acetone	5	0	4	65	33
3	CH_3Cl	5	-30	6	58	21
4	EtOAc	5	-30	8	61	18
5	MeCN	5	-30	8	76	13
6	acetone	10	0	2	70	31
7	acetone	10	-30	4	55	38
8	acetone	10	-50	8	40	8
9	acetone	5	-30	24	62	18
10	acetone	5	-30	12	75	38
11	acetone	5	-30	6	80	58
12	acetone[d]	5	-30	6	45	38
13	acetone[e]	5	-30	6	70	48
14	acetone	5	-30	6	74[f]	38
15	acetone	5	-30	6	73[g]	56
16	acetone	5	-30	6	55[h]	38

a. 0.5 M; *b.* performed on 1 mmol scale and purified on Iatrobeads silica; *c.* e.e. determined by chiral GC analysis of the corresponding chlorohydrin; *d.* 1.0 M; *e.* 0.2 M; *f.* purified on Merck silica 60; *g.* no silica gel purification; *h.* performed on 10 mmol scale

A screen of catalysts and reaction conditions that were examined based on the α-chlorination method reported by Jørgensen is summarised in Table 7.[37] As indicated, it was found that employing *N*-chlorosuccinimide (**12**) and 10 mol% of the diphenylpyrrolidine catalyst **17**[41], (2*R*)-2-chloropentanal (**103**) was obtained in good yield and optical purity (Table 7, entry 3). Comparatively, the commercially available L-prolinamide (**16**) imparted a significant increase in asymmetric control in providing **103** in 85% enantiomeric excess (Table 7, entry 7). Employing 10 mol% L-proline (**13**) as the

catalyst imparted no enantioselectivity in this reaction, this was consistent with previous studies (Table 7, entry 13).[37] Most importantly, the optimised conditions using catalyst **16** allowed for the scale up (>10 mmol) of (2*R*)-2-chloropentanal (**103**). Following distillation, the product was amenable to short-term storage (up to 4 weeks at 4 °C) without degradation in optical purity (Table 7, entry 8). Analysis of the enantiomeric purity of **103** was performed by chiral gas chromatography on the corresponding chlorohydrin (*via* a sodium borohydride reduction of **103**). Likewise, the asymmetric α-chlorination of undecanal with catalyst **16** provided (2*R*)-2-chloroundecanal (**104**) in good yield and excellent enantiomeric excess (Table 7, entry 14).

Table 7. Asymmetric α-chlorination using Jørgensen's method.



ent	ald.	cat. (mol%)	solvent[a]	temp (°C)	time (h)	yield (%)[b]	e.e. (%)[c]
1	**101**	**17** (20)	CH_2Cl_2	0-22	3	**103** (94)	76
2	**101**	**17** (5)	CH_2Cl_2	0-22	3	**103** (80)	65
3	**101**	**17** (10)	CH_2Cl_2	0-22	3	**103** (>97)	77
4	**101**	**17** (10)	DCE	0-22	3	**103** (90)	73
5	**101**	**16** (20)	CH_2Cl_2	0-22	3	**103** (95)	77
6	**101**	**16** (5)	CH_2Cl_2	0-22	3	**103** (78)[d]	76
7	**101**	**16** (10)	CH_2Cl_2	0-22	3	**103** (>97)	85
8	**101**	**16** (10)	CH_2Cl_2	0-22	3	**103** (>97)[e]	85
9	**101**	**16** (10)	DCE	0-22	3	**103** (90)	76
10	**101**	**16** (10)	THF	0-22	3	**103** (76)[d]	68
11	**101**	**16** (10)	CH_2Cl_2	0	18	**103** (10)	-
12	**101**	**16** (10)	CH_2Cl_2	22	3	**103** (65)[d]	40
13	**101**	**13** (10)	CH_2Cl_2	0-22	3	**103** (>97%)	2
14	**102**	**16** (10)	CH_2Cl_2	0-22	3	**104** (91)	89

a. 0.5 M; *b.* performed on 1 mmol scale; *c.*e.e. determined by chiral GC analysis of the corresponding chlorohydrin; *d*. significant amount of dichlorinated product; *e.* performed on 10 mmol scale

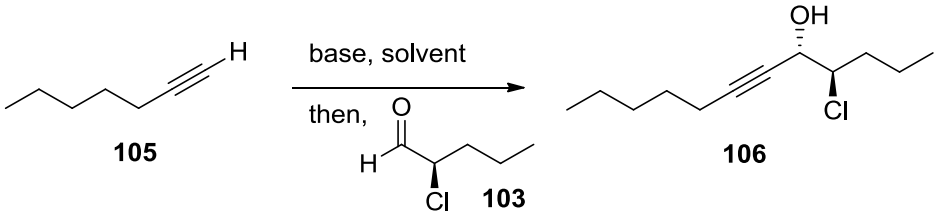
2.2.2.2 Diastereoselective Nucleophilic Additions to α-Chloroaldehydes

With access to sufficient quantities of optically enriched α-chloroaldehydes, using the protocol described above, the diastereoselective addition of organometallic reagents to these optically active electrophiles were then evaluated (Table 8). As predicted by the Cornforth Model (see page 10),[42,43] these reactions were expected to afford predominantly the 1,2-*anti*-chlorohydrin products.

As indicated below, it was found that the addition of the alkynyl Grignard reagent, derived from the reaction of 1-heptyne (**105**) with ethyl magnesium bromide, to α-chloropentanal (**103**) in diethyl ether afforded chlorohydrin **106** in good yield and modest diastereomeric ratio (3:1 *anti*:*syn*), which were in congruence with previous reports[38,42] (Table 8, entries 2 and 3). A brief survey of reaction solvents (THF, hexane) failed to significantly improve upon this result (Table 8, entries 1 and 4). Nevertheless, dramatic improvements in diastereoselectivity were attained through the use of the corresponding alkynyl lithium reagent, derived from the addition *n*-BuLi to 1-heptyne (**105**) in diethyl ether, to **103**, which afforded chlorohydrin **106** as a 9:1 mixture of the *anti*:*syn* diastereomers (Table 8, entry 6). The diastereomeric ratio was further increased to >20:1 after a solvent screen identified THF as the optimal solvent for this reaction (Table 8, entry 7). The marked difference in the diastereochemical outcome of this reaction when repeated in various solvents (e.g., hexanes, diethyl ether, and THF) is most likely the result of changes in the aggregation state of the organolithium reagent in solution.[44] Specifically, electron donor solvents such as THF tend to favour the formation of dimers or monomers of the organolithium reagents, whereas in non-polar solvents such as hexanes, tetramers or hexamers predominate. In addition, these distributions vary with temperature, with lower-order aggregates favoured at lower temperatures.[45] In general, lower-order aggregates are far more reactive than high-order counterparts; for example,

a dimer is $3.2x10^8$ more reactive than a tetramer in the deprotonation of alkynyl protons.[46]

Table 8. Screen of bases and solvents in the nucleophilic addition to α-chloroaldehydes.



105 **103** **106**

entry	base	solvent	temp (°C)	yield (%)	d.r.[a]
1	EtMgBr	Hex	-40	48	1:1
2	EtMgBr	Et_2O	-40	68	3:1
3	EtMgBr	Et_2O	-78	98	3:1
4	EtMgBr	THF	-78	94	4:1
5	^{n}BuLi	Hex	-40	70	4:1
6	^{n}BuLi	Et_2O	-78	85	9:1
7	^{n}BuLi	THF	-78	88	>20:1

a. as determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

The stereochemistry of the chlorohydrin product **106** was confirmed by *J*-Based Configurational Analysis (JBCA) of the $^2J_{C,H}$, $^3J_{C,H}$, and $^3J_{H,H}$ coupling constants using Murata's method.[47] These coupling constants were extracted from ^{1}H homodecoupling and HSQC-HECADE[48] experiments. Because the vicinal homo- and heteronuclear constants ($^3J_{C,H}$ and $^3J_{H,H}$) follow the Karplus curve, they are directly related to the dihedral angle. The geminal carbon-proton coupling constant ($^2J_{C,H}$) provides important information about the spatial relationship between electronegative substituents (e.g., Cl and O) and the adjacent proton.[49] For example, when an electronegative functionality on a carbon is *gauche* to its vicinal proton the $^2J_{C,H}$ value is large, and when the functionality is *anti* the value becomes small. Murata's method of JBCA is summarised in Figure 5,

which shows coupling constants for oxygenated substances and in parentheses are Carreira's modified values[50] for chlorine-bearing compounds.

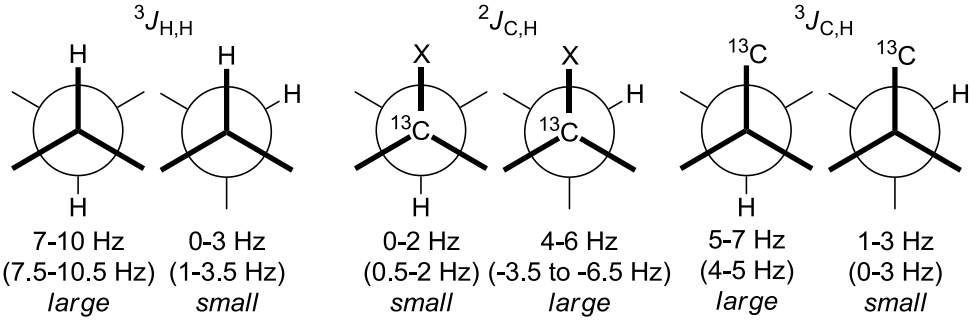
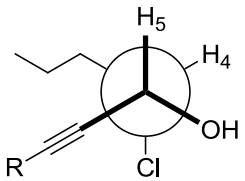


Figure 5. **Murata`s method of *J*-Based Configurational Analysis (JBCA) for X = oxygen bearing substituents (values in parentheses are Carreira's modified value for X = chlorine bearing compounds).**

Our extracted values for the JBCA of chlorohydrin **106** are shown in Table 9. We observed a small $^3J_{H,H}$ which places H4 and H5 in a *gauche* relationship, whereas a small $^3J_{C,H}$ confers a *gauche* relationship between H5 and C3. A medium to large $^2J_{C,H}$ coupling constant between H4 and C5 is consistent with a *gauche* relationship between the oxygen and H_4, and a small $^2J_{C,H}$ for H5-C4 allows assignment of an *anti*-relationship between the chlorine atom and H5. In short, this technique allows for the confident assignment of chlorohydrin **106** as the 1,2-*anti* product.

Table 9. **Stereochemistry conformation of chlorohydrin 106 using JBCA.**

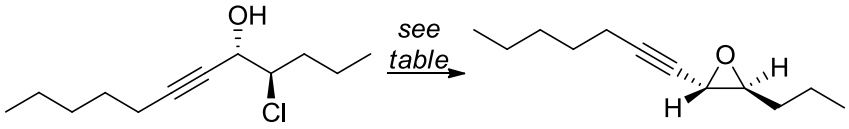


entry	atoms	*J*-value	*J*
1	H_4-H_5	+3 Hz (small)	$^3J_{H,H}$
2	H_4-C_5	-3.5 Hz (med-large)	$^2J_{C,H}$
3	H_5-C_3	+2 Hz (small)	$^3J_{C,H}$
4	H_5-C_4	+2 Hz (small)	$^2J_{C,H}$

2.2.2.3 Epoxidation of the 1,2-*anti*-Chlorohydrin 106

The development of the key transformations mentioned above allowed for investigations into the formation of epoxides from the 1,2-*anti*-chlorohydrin **106**. After evaluating several reaction conditions for the conversion of **106** into the corresponding epoxide (Table 10) it was found that using potassium hydroxide in ethanol permitted clean conversion of the chlorohydrin **106** to the *trans*-epoxide **107** in 93%.

Table 10. Epoxidation of *anti*-chlorohydrin 106.



106 **107**

entry	base	solvent	temp (°C)	time	yield (%)[a]
1	KO^{t}Bu	THF	22	24	35
2	NaOMe	THF	22	24	46
3	KH	THF	-78-22	24	60
4	K_2CO_3	MeOH	-50-22	4	40
5	K_2CO_3	DMF/H_2O	-50-22	4	35[b]
6	Cs_2CO_3	MeOH	-78-22	4	15
7	NaOH	EtOH	-78-22	3	65
8	KOH	EtOH	-78-22	3	84
9	KOH	EtOH	22	1	93

a. isolated yields; *b.* reaction contained unreacted starting material

In an attempt to improve conversion and avoid unnecessary purifications, the unstable crude chlorohydrins were directly subjected to the optimised epoxide-formation conditions. Following this two-step, no purification protocol, the *trans*-epoxide **107** was obtained in 86% overall yield. The *trans*-configuration of the epoxide was confidently assigned by analysis of nOe spectra and coupling constants (Figure 6).

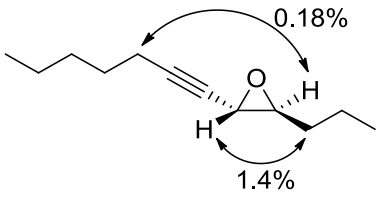


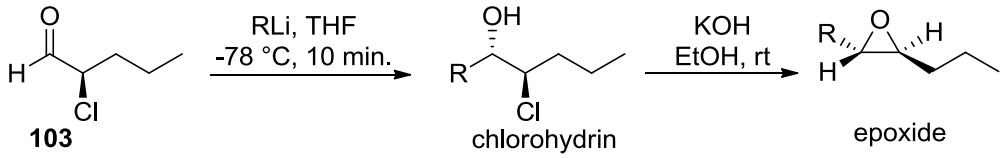
Figure 6. nOe analysis of trans-epoxide 107. Displayed with % enhancements.

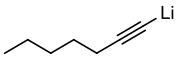
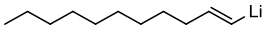
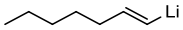
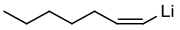
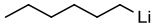
2.2.2.4 Synthesis of *trans*-Epoxides

Having established a synthetic route to the alkynyl-substituted *trans*-epoxide (**107**), the substrate tolerance and scope of this process remained to be explored. Thus investigations were initiated to determine general utility of this asymmetric epoxide synthesis. Specifically, the addition of alkynyl, phenyl, *cis*-alkenyl, *trans*-alkenyl, and alkyl lithium reagents to α-chloroaldehydes were examined.

The requisite organolithium reagents depicted in Table 11 were commercially available (e.g., hexyl lithium), freshly prepared from commercially available reagents (e.g., bromobenzene), or accessible *via* short sequence of reactions (e.g., (*E*)-undec-1-enyl lithium[51] (**108**), (*E*)-hept-1-enyl lithium[52] (**109**), *cis*-hept-1-enyl lithium[53] (**110**)) following known procedures. As indicated in Table 11, the optimised conditions originally developed for addition of alkynyl lithium reagents to α-chloroaldehydes (*vide supra*) were employed in all cases. Each of the freshly prepared organolithium reagents underwent diastereoselective nucleophilic addition to the α-chloropentanal (**103**) to afford the corresponding 1,2-*anti*-chlorohydrins in excellent yield. Subsequent treatment of the crude chlorohydrins under epoxide-forming conditions (KOH, EtOH) then yielded a variety of *trans*-epoxides in excellent yield (Table 11).

Table 11. Synthesis of *trans*-epoxides.



ent	organolithium	chlorohydrin	d.r.[a]	epoxide	yield (%)	d.r.
1		**106**	>20:1	**107**	86	>20:1
2		**111**	17:1	**112**	75	17:1
3		**113**	13:1	**114**	87	>20:1
4		**115**	14:1	**116**	77	>20:1
5		**117**	13:1	**118**	84	14:1
6		**119**	8:1	**120**	79	8:1

a. as determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

The diastereomeric ratios for the *anti*-chlorohydrin products were determined by ^{1}H NMR spectroscopy following analysis of spectra obtained on the crude reaction mixtures. The stereochemical outcome of the 1,2-addition reactions (i.e., the generation of chlorohydrins depicted in Table 11) were confirmed by JBCA (see page 45). In addition, the *trans*-configuration of the resulting epoxides were confidently assigned by nOe analysis and/or analysis of scalar coupling constants with the exception of the *trans*-epoxide **120**, for which the overlapping H4/H5 resonances at δ 2.66 ppm in the ^{1}H NMR spectrum precluded its stereochemical assignment by either method. In this case, the chemical shifts observed in the ^{1}H NMR spectrum were consistent with those reported for the H4/H5 resonances in *trans*-(4*S*,5*S*)-4,5-epoxynonane (δ 2.61-2.70 ppm) and differ significantly from those reported for *cis*-(4*S*,5*R*)-4,5-epoxynonane (δ 2.87-2.96 ppm).[54]

The optical purity of each epoxide was also determined. For example, the enantiomeric excess of both **107** and **116** was determined to be 85% by chiral GC

analysis. Hydrogenation of the alkene function in epoxide **114** provided (4*S*,5*S*)-4,5-epoxydodecane (**121**) with an observed specific rotation ($[\alpha]_D^{25}$ = -24.9). The specific rotation of this sample was consistent with that recorded on a sample of (4*S*,5*S*)-4,5-epoxydodecane (**122**) that was produced from (6*Z*,4*S*,5*S*)-4,5-epoxydodec-6-ene (**116**) (85% e.e. as determined by chiral GC) in the same manner ($[\alpha]_D^{25}$ = -24.7). The enantiomeric excess of **118** was determined following its transformation to (2*S*)-1-phenylpentan-2-ol (**123**) and subsequent measurement of its optical rotation, which was consistent with that reported ($[\alpha]_D^{20}$ = 3.7 (obs.) (c = 1.1, EtOH); lit. 4.2 (c = 1.8, EtOH)).[55] Together, these results indicate that there is no erosion of optical purity during this sequence of reactions.

2.2.2.5 Synthesis of the *B. piniarius* and *O. postica* Sex Pheromones

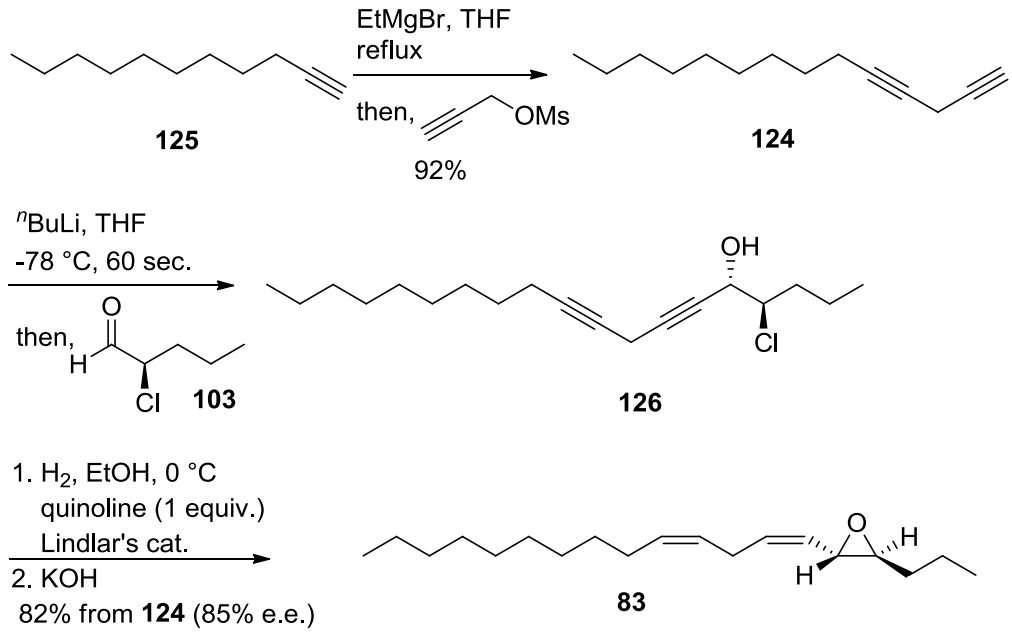
Having developed a general, nonracemic synthesis of *trans*-epoxides that provide ready access to alkynyl-, alkyl-, alkenyl- and phenyl-substituted epoxides; we initiated synthesis of the *trans*-epoxide-containing insect sex pheromones **83** and **84**. As detailed below, we first investigated the synthesis of the *B. piniarius* sex pheromone **83** following the proposed strategy outlined in Scheme 17, then applied the successful process to a total synthesis of (-)-posticlure **84**.

The synthesis of the *B. piniarius* sex pheromone **83** initiated with the preparation of diyne **124**, which was readily available from 1-undecyne (**125**) following deprotonation and alkylation with propargyl mesylate.[56] However, the diyne **124** proved to be unstable with a half-life of only four hours at -22 °C and <30 minutes at room temperature (as determined by ^{1}H NMR spectroscopy). As a result, the diyne **124** was prepared fresh and/or purified by column chromatography immediately prior to its use. Surprisingly, following the standard protocol outlined in Table 11, addition of the lithium anion derived

from **124** to a THF solution of the α-chloroaldehyde **103**, resulted in a complex mixture of products that contained only minor amounts of the diyne chlorohydrin **126** (<10%). After several unsuccessful attempts to improve upon this result, it was determined that treatment of the diyne **124** with *n*-BuLi at -78 °C generated the desired alkynyl lithium intermediate, however, this latter material decomposes after only a short period of time (e.g., roughly 8 minutes) as a result of anion equilibration. Specifically, this equilibration was observed by a D_2O quenching experiment that resulted in deuterium incorporation at the diynyl methylene and the formation of an allene characterised by diagnostic[57] ^{1}H NMR resonances at δ 5.36 (tt, 1H, *J* = 1.2, 6.4 Hz) and 4.95 (dt, 1H, *J* = 2.4, 6.4 Hz). After further experimentation, it was determined that deprotonation of the alkynyl proton in the diyne **124** was complete after only 60 seconds at -78 °C in THF. Based on these findings, addition of *n*-BuLi to the diyne **124**, followed after one minute by the α-chloroaldehyde **103** afforded the desired chlorohydrin **126** in a reproducibly excellent yield (>80%) and diastereomeric ratio (>20:1).

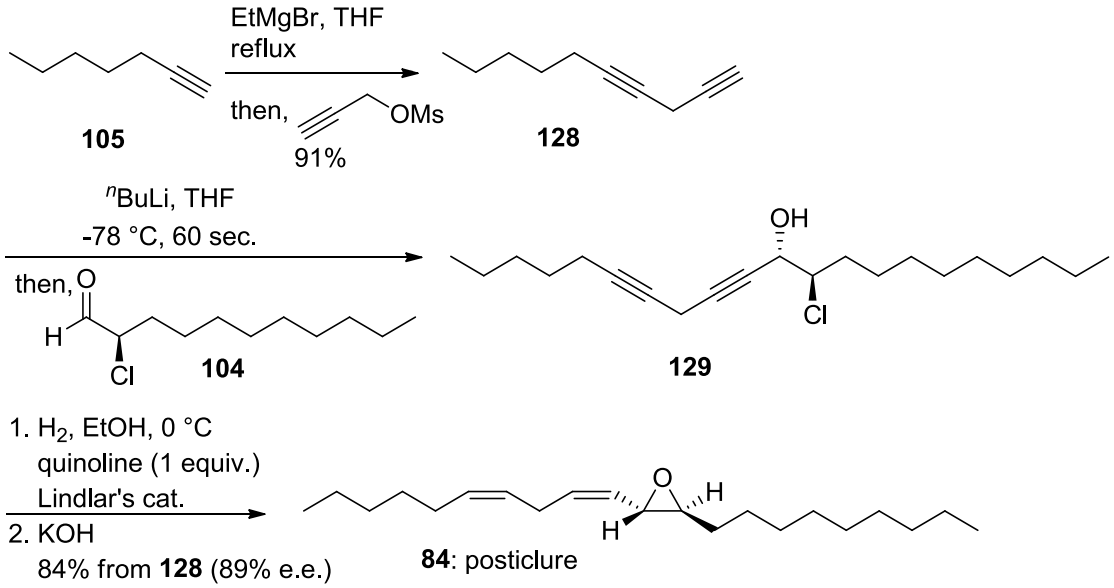
Having established a reliable procedure for generating the diynyl chlorohydrin **126**; we quickly realised that this material could not be stored due to instability. As a result, subsequent transformations planned for the synthesis of the *B. piniarius* sex pheromone (i.e., epoxidation and Lindlar reduction) would necessarily be carried out in rapid succession after isolation of the chlorohydrin **126**. Precedent for the sequence outlined in Scheme 17 was established through our conversion of the alkynyl chlorohydrin **106** sequentially into the corresponding alkynyl epoxide **107** and then to the *cis*-alkenyl epoxide **116** (Lindlar catalyst, quinoline, H_2, EtOH) in excellent yield (94%). However, the unstable diyne chlorohydrin **126** decomposed when treated with base (KOH, EtOH), which prohibited its conversion to the diyne epoxide **127**. Consequently, the proposed order of events (Scheme 17) was reversed and we next explored Lindlar reduction of the diyne chlorohydrin **126**. However, under standard Lindlar reduction

conditions, employing 0.05 equiv. of the Lindlar catalyst and 0.1 equiv. of quinoline in ethanol at room temperature, irreproducible results were obtained. Specifically, we found that use of less than one equivalent of quinoline led to partial hydrogenation of the $\Delta^{9,10}$ alkene function in **126**. Bearing this in mind, the crude chlorohydrin **126** was directly treated with Lindlar catalyst, a stoichiometric amount of quinoline and hydrogenated at 0 °C. The progress of this reaction was monitored by ^{1}H NMR spectroscopy, and upon complete disappearance of the diynyl methylene resonance at δ 3.20 ppm and the enynyl methylene resonance at δ 2.92 ppm, KOH was directly added to effect the epoxide-formation and complete the total synthesis of the *B. piniarius* sex pheromone **83** (Scheme 18). The enantiomeric excess of **83** was determined to be 85% by comparative chiral GC analysis using an authentic sample of **83** obtained from Prof. Gerhard Gries. Likewise, the optical purity was also confirmed by comparison of the optical rotation of the synthetic material ($[\alpha]_D^{25}$ = -11.6 (c = 1.2, $CHCl_3$)) to literature reports (lit. -12.5 (c = 4.1, $CHCl_3$)).[24]



Scheme 18. Total synthesis of the *B. piniarius* insect sex pheromone 83.

As detailed in Scheme 19, synthesis of (-)-posticlure (**84**) was completed using the optimised sequence of reactions described above for the production of the *B. piniarius* sex pheromone **83**. Thus, diyne **128** was prepared in excellent yield from 1-heptyne **105**, following deprotonation with EtMgBr and subsequent addition to propargyl mesylate. The diyne **128** was then treated briefly (60 seconds) with *n*-BuLi and subsequently reacted with α-chloroundecanal (**104**) to afford the diyne chlorohydrin **129** in excellent yield and diastereoselectivity (d.r. >20:1). This latter material was then immediately hydrogenated in the presence of Lindlar catalyst followed by treatment with base to effect epoxide-formation, which led cleanly to the *O. postica* sex pheromone, (-)-posticlure (**84**). The enantiomeric excess of (-)-posticlure (**84**) was determined to be 89%, by comparison of the optical rotation measured on the synthetic material ($[\alpha]_D^{25}$ = -9.6 (c = 1.0, $CHCl_3$)) to a known value (lit. -10.8 (c = 1.08, $CHCl_3$))[27].



Scheme 19. Total synthesis of the *O. postica* insect sex pheromone, posticlure (-)-(84).

2.2.2.6 Conclusion

In conclusion, the work described in this Chapter exploited recent advances in the asymmetric α-chlorination of aldehydes[36,37] through the development of an efficient and general method for the construction of alkynyl-, phenyl-, alkyl-, and alkenyl-substituted *trans*-epoxides. Furthermore, this methodology was applied successfully to the total synthesis of the *trans*-epoxide-containing insect sex pheromones **83** and **84**. Notably, the overall yields for **83** (80%) and (-)-**84** (76%), and the total number of synthetic steps required (four-steps, three-pot) compare very favourably with the reported syntheses of these substances (9-13 total steps).[24-28] Moreover, that the entire process is often completed in one day further highlights the efficiency of the chlorohydrin-based strategy. Importantly, this synthetic process provided sufficient quantities of **83** to initiate a population monitoring study of *B. piniarius* in conjunction with the Landesforstanstalt Eberswalde (National Forestry Institute in Eberswalde, Germany).

2.3 Experimentals

General

All reactions described were performed under an atmosphere of dry argon using oven- or flame-dried glassware unless otherwise specified. THF, Et_2O, CH_2Cl_2 were used directly from an MBraun Solvent Purifier System (MB-SP Series). Commercial anhydrous EtOH (reagent grade) was used without further purification. Cold temperatures were maintained by the use of following reaction baths: 0 °C, ice-water; -30 °C, ethyl acetate-ethanol; -78 °C, acetone-dry ice. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[58] Concentration of solvents was accomplished with a Buchi rotary evaporator using acetone-dry-ice condenser and removal of trace solvents was accomplished with a Welch vacuum pump.

Gas chromatography (GC) analysis was performed on a Hewlett Packard model 6890 gas chromatograph, equipped with a flame ionisation detector and a custom made fused silica column with a 1:1 mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β cyclodextrin and OV-1701.[59]

NMR spectra were recorded using deuterated chloroform ($CDCl_3$) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP cryoprobe (600 MHz) or Varian Inova 500 (500 MHz). Carbon nuclear magnetic

resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP cryoprobe (150 MHz) or Varian Inova 500 (125 MHz).

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 mass spectrometer at 70 eV. High-resolution electron impact (EI) and fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer at 3 kV. Optical rotation was measured on a Perkin Elmer Polarimeter 341 at 589nm.

Preparation of (2*R*)-2-chloropentanal (103)

Procedure A:

To a cold (0 °C), stirred solution of pentanal **101** (170 mg, 2.0 mmol) in CH_2Cl_2 (4 mL), was added L-prolinamide (**16**) (20 mg, 0.2 mmol) and *N*-chlorosuccinimide (**12**) (350 mg, 2.6 mmol). The reaction mixture was stirred for one hour and then allowed to slowly warm to room temperature over the course of three hours at which temperature it was stirred until complete consumption of pentanal **101** (as determined by ^{1}H NMR spectroscopy). After this time, the mixture was diluted with pentanes (10 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice water bath. The resulting oil was dissolved in pentanes (10 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath to give (2*R*)-2-chloropentanal (**103**) (240 mg, >97% yield) as a clear oil.

Procedure B:

To a cold (-30 °C), stirred solution of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (**8**) (11 mg, 0.050 mmol) in acetone (2 mL), was added 2,3,4,5,6,6-hexachloro-2,4-

cyclohexadien-1-one (**9**) (360 mg, 1.2 mmol) and pentanal **101**) (86 mg, 1.0 mmol). The reaction mixture stirred at -30 °C until the aldehyde was consumed (as determined by ^{1}H NMR spectroscopy). After this time the mixture was filtered through Iatrobeads and eluted with Et_2O and concentrated on a rotary evaporator in an ice-water bath to provide (2*R*)-2-chloropentanal (**103**) (97 mg, 80% yield) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.44 (d, 1H, *J* = 2.5 Hz), 4.14 (ddd, 1H, *J* = 2.5, 5.0, 7.5 Hz), 1.90 (m, 1H), 1.77 (m, 1H), 1.47 (m, 2H), 0.91 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.2, 63.6, 33.8, 18.7, 13.2.

IR (neat): 2963, 2936, 2876, 2849, 1735, 1466, 1434, 1382, 1262, 1206, 1055 cm^{-1}

Exact mass calcd. for $C_5H_{10}ClO$: 121.5868; found: 121.5870.

$[\alpha]_D^{25}$: 11.2 (c = 0.8, $CHCl_3$)

The enantiomeric excess of **103** was determined by chiral GC analysis of the primary alcohol derived from the reduction of **103**. Thus, to a solution of (2*R*)-2-chloropentanal (**103**) (12 mg, 0.10 mmol) in MeOH (2 mL) was added $NaBH_4$ (10 mg, 0.25 mmol) and the resulting mixture was stirred at room temperature for one hour. The reaction mixture was then quenched with water (1 mL) and diluted with Et_2O (5 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered, and concentrated to afford (2*R*)-2-chloropentanol. Separation of the enantiomers of 2-chloropentanol was accomplished by chiral GC. Temperature program: 70 °C held for 5 minutes then increased by 20 °C per minute until 150 °C and run for 30 minutes. t_R = 21.0 minutes [(*R*)-enantiomer]; t_R = 21.8 minutes [(*S*)-enantiomer].

Preparation of (2*R*)-2-chloroundecanal (104)

To a cold (0 °C), stirred solution of undecanal **102** (340 mg, 2.0 mmol) in dry CH_2Cl_2 (4 mL), was added L-prolinamide (**16**) (20 mg, 0.2 mmol) and *N*-chlorosuccinimide (**12**) (350 mg, 2.6 mmol). The reaction mixture was stirred for one

hour and then allowed to slowly warm to room temperature over the course of three hours at which temperature it was stirred until complete consumption of undecanal **102** (as determined by ^{1}H NMR spectroscopy). After this time, the mixture was diluted with pentanes (10 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath. The resulting oil was dissolved in pentanes (10 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath to give (2*R*)-2-chloroundecanal (**104**) (400 mg, 97% yield) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.43 (d, 1H, *J* = 2.5 Hz), 4.11 (ddd, 1H, *J* = 2.5, 5.5, 7.5 Hz), 1.94 (m, 1H), 1.77 (m, 1H), 1.38- 1.47 (m, 2H), 1.20-1.30 (m, 12H), 0.91 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.1, 63.8, 31.9, 31.7, 29.3, 29.2, 29.1, 28.8, 25.4, 22.6, 14.0.

IR (neat): 3447, 2964, 2936, 2876, 2839, 1735, 1466, 1382, 1262, 1054 cm^{-1}

Exact mass calcd. for $C_{11}H_{20}ClO$: 203.7322; found: 203.7330.

$[\alpha]_D^{25}$: 14.8 (c = 0.6, EtOH)

Preparation of (4*S*,5*S*)-4-chlorododec-6-yn-5-ol (106)

To a cold (-78 °C), stirred solution of 1-heptyne (**105**) (48 mg, 0.50 mmol) in dry THF (2.5 mL) was added *n*-butyllithium (0.25 mL, 0.50 mmol, 2.0 M in hexanes). After the mixture had stirred for 10 minutes, a solution of (2*R*)-2-chloropentanal (**103**) (66 mg, 0.55 mmol) in THF (0.25 mL) was added and the reaction mixture was stirred for an additional 10 minutes. After this time, the clear solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **106** (>20:1 mixture of diastereomers as

determined by ^{1}H NMR spectroscopy) as a crude oil that was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.51 (m, 1H), 4.03 (ddd, *J* = 10.5, 7.0, 4.5 Hz, 1H), 2.34 (dd, 1H, *J* = 15.0, 10.5 Hz), 2.29-2.16 (m, 2H), 1.83-1.76 (m, 2H), 1.82-1.74 (m, 2H), 1.55-1.48 (m, 2H), 1.42-1.25 (m, 4H), 0.93 (t, 3H, *J* = 7.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz).

Preparation of (4*S*,5*S*)-4,5-epoxydodec-6-yne (107)

To a stirred solution of the crude chlorohydrins **106** (0.50 mmol) in EtOH (2.5 mL) at room temperature was added KOH (84 mg, 1.5 mmol). After the mixture had been stirred for 30 minutes the resulting yellow solution was diluted with pentanes (20 mL) and washed with brine (3 x 10 mL). The aqueous phase was extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (4*S*,5*S*)-4,5-epoxydodec-6-yne (**107**) (75 mg, 86 %) as a light yellow oil.

The enantiomeric excess of **107** was determined to be 85% by chiral GC analysis. Temperature program: temperature set at 100 °C for 30 minutes. t_R = 10.7 minutes [(*S,S*)-enantiomer]; t_R = 11.4 minutes [(*R,R*)-enantiomer].

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.08 (dt, 1H, *J* = 2.0, 1.5 Hz), 3.02 (dt, 1H, *J* = 2.0, 5.0 Hz), 2.19 (dt, 2H, *J* = 1.5, 6.0 Hz), 1.44-1.54 (m, 6H), 1.26-1.38 (m, 4H), 0.96 (t, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 84.9, 77.0, 60.6, 45.9, 34.0, 31.2, 38.3, 23.4, 19.2, 18.9, 14.1, 14.1.

IR (neat): 2959, 2934, 2867, 2238, 1460, 1233, 1154, 898, 862 cm^{-1}

Exact mass calcd. for $C_{12}H_{21}O$: 181.2981; found: 181.2992.

$[\alpha]_D^{25}$: -3 (c = 0.8, $CHCl_3$).

Preparation of (6*E*,4*R*,5*S*)-4-chlorohexadec-6-en-5-ol (111)

To a cold (-78 °C), stirred solution of (*E*)-1-iodoundec-1-ene (**108**) (28 mg, 0.10 mmol) in dry THF (1.0 mL) was added *n*-butyllithium (0.05 mL, 0.1 mmol, 2.0 M in hexanes). After 10 minutes, a solution of (2*R*)-2-chloropentanal (**103**) (13 mg, 0.11 mmol) in THF (0.1 mL) was added and the reaction mixture was stirred for an additional 10 minutes. After this time, the clear solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **111** (17:1 mixture of diastereomers as determined by ^1H NMR spectroscopy) as a crude oil which was used without further purification.

^1H NMR (600 MHz, $CDCl_3$) δ:5.81 (m, 1H), 5.52 (m, 1H), 4.21 (m, 1H), 4.08 (m, 1H), 2.11-2.03 (m, 2H), 1.71-1.62 (m, 6H), 1.45-1.22 (m, 12H), 0.91 (t, 1H, *J* = 7.0 Hz), 0.87 (t, 1H, *J* = 7.0 Hz).

Preparation of (6*E*,4*S*,5*S*)-4,5-epoxyhexadec-6-ene (112)

To a stirred solution of the crude chlorohydrins **111** (0.10 mmol) in EtOH (1.0 mL) at room temperature was added KOH (17 mg, 0.30 mmol). After 30 minutes the resulting yellow solution was diluted with pentanes (20 mL) and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (6*E*,4*S*,5*S*)-4,5-epoxyhexadec-6-ene (**112**) (18 mg, 75 %) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.90 (dt, 1H, *J* = 7.2, 15.6 Hz), 5.15 (dd, 1H, *J* = 8.4, 15.6 Hz), 3.07 (dd, 1H, *J* = 7.8, 8.4 Hz), 2.82 (m, 1H), 2.05 (dt, 2H, *J* = 7.2, 7.0 Hz), 1.53 (m, 6H), 1.37 (m, 2H), 1.26-1.30 (m, 10H), 0.95 (t, 3H, *J* = 7.2 Hz), 0.88 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.8, 127.4, 60.2, 58.8, 34.1, 32.4, 31.9, 29.5, 29.5, 29.3, 29.1, 28.9, 22.7, 19.2, 14.1, 14.0.

IR (neat): 2964, 2926, 2855, 1713, 1455, 1378, 965, 902 cm^{-1}

Exact mass calcd. for $C_{16}H_{30}O$: 238.4084; found: 238.4076.

$[\alpha]_D^{25}$: -7.9 (c = 1.4, $CHCl_3$).

Preparation of (6*E*,4*R*,5*S*)-4-chlorododec-6-en-5-ol (113)

To a cold (-78 °C), stirred solution of (*E*)-1-iodohept-1-ene (**109**) (110 mg, 0.50 mmol) in dry THF (5.0 mL) was added *n*-butyllithium (0.25 mL, 0.50 mmol, 2.0 M in hexanes). After 10 minutes, a solution of (2*R*)-2-chloropentanal (**103**) (66 mg, 0.55 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred for an additional 10 minutes. After this time, the clear solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **113** (13:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy) as a crude oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (m, 1H), 5.53 (ddd, 1H, *J* = 15.4, 7.0, 1.1 Hz), 4.17 (d, 1H, *J* = 15.4 Hz), 4.05 (m, 1H), 2.13-1.98 (m, 2H), 1.75-1.53 (m, 4H), 1.49-1.23 (m, 6H), 0.95 (t, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* = 7.0 Hz).

Preparation of (6*E*,4*S*,5*S*)-4,5-epoxydodec-6-ene (114)

To a stirred solution of the crude chlorohydrins **113** (0.50 mmol) in EtOH (5.0 mL) at room temperature was added potassium hydroxide (85 mg, 1.5 mmol). After 30 minutes the resulting yellow solution was diluted with pentanes (20 mL) and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (6*E*,4*S*,5*S*)-4,5-epoxydodec-6-ene (**114**) (79 mg, 87 %) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.88 (dt, 1H, *J* = 7.0, 15.5 Hz), 5.15 (dd, 1H, *J* = 9.0, 15.5 Hz), 3.04 (m, 1H), 2.80 (m, 1H), 2.04 (dt, 2H, *J* = 7.0, 7.0 Hz), 1.24-1.55 (m, 10H), 0.95 (t, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.6, 127.4, 60.2, 58.8, 34.0, 32.3, 31.3, 28.6, 22.5, 19.2, 14.0, 13.9.

IR (neat): 2950, 2922, 2860, 1710, 1440, 1322, 922 cm^{-1}

Exact mass calcd. for $C_{12}H_{23}O$: 183.3140; found: 183.3152.

$[\alpha]_D^{25}$: -4.5 (c = 0.6, $CHCl_3$).

Determination of optical purity: to a stirred solution of (6*E*,4*S*,5*S*)-4,5-epoxydodec-6-ene (**114**) (5 mg) in EtOH was added Pd/C (0.1 mol%) and the resulting suspension was stirred under an atmosphere of H_2 (balloon) for three hours. After this time, the reaction mixture was filtered through Celite and concentrated and the crude oil was purified by flash chromatography (30:1 hexanes: ethyl acetate) to provide (4*S*,5*S*)-4,5- epoxydodecane (**122**). The observed specific rotation of this material ($[\alpha]_D^{25}$: -24.9) was consistent with that of a sample of (4*S*,5*S*)-4,5-epoxydodecane (**122**) that was produced from (6*Z*,4*S*,5*S*)-4,5-epoxydodec-6-ene (**116**) (85% ee as determined by chiral GC, see below) in the same manner ($[\alpha]_D^{25}$: -24.7).

Preparation of (6*Z*,4*R*,5*S*)-4-chlorododec-6-en-5-ol (115)

To a cold (-78 °C), stirred solution of (*Z*)-1-iodohept-1-ene (**109**) (110 mg, 0.50 mmol) in dry THF (5.0 mL) was added *n*-butyllithium (0.25 mL, 0.50 mmol, 2.0 M in hexanes). After 10 minutes, a solution of (2*R*)-2-chloropentanal (**103**) (66 mg, 0.55 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred for an additional 10 minutes. After this time, the clear solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **115** (14:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy) as a crude oil which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.65 (dt, 1H, *J* = 11.1, 7.5 Hz), 5.50 (m, 1H), 4.55 (dd, 1H, *J* = 8.4, 3.5 Hz), 4.05 (dt, 1H, *J* = 12.6, 4.0 Hz), 2.16-2.02 (m, 2H), 1.80-1.57 (m, 4H), 1.45-1.34 (m, 3H), 1.32-1.26 (m, 3H), 0.92 (t, 3H, *J* = 7.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz).

Preparation of (6*Z*,4*S*,5*S*)-4,5-epoxydodec-6-ene (116)

Procedure A:

To a stirred solution of the crude chlorohydrins **115** (0.50 mmol) in EtOH (5.0 mL) at room temperature was added KOH (85 mg, 1.5 mmol). After 30 minutes the resulting yellow solution was diluted with pentanes (20 mL) and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (6*Z*,4*S*,5*S*)-4,5-epoxyhexadec-6-ene (**116**) (70 mg, 77 %) as a yellow oil.

Procedure B:

To a cold (0 °C), stirred solution of (4*S*,5*S*)-4,5-epoxydodec-6-yne (**19a**) (90 mg, 0.50 mmol) in EtOH (2.5 mL) was added Lindlar's catalyst (5 mg, 0.05 mmol) and quinoline (7 mg, 0.05 mmol) and the resulting suspension was stirred under an atmosphere of H_2 (balloon) for 30 minutes at 0 °C. The reaction mixture was then filtered through Celite and the filtrate was diluted with Et_2O (20 mL) and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with Et_2O (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (6*Z*,4*S*,5*S*)-4,5-epoxydodec-6-ene (**116**) (86 mg, 94 %) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.68 (dt, 1H, *J* = 7.5, 11.0 Hz), 5.03 (ddt, 1H, *J* = 1.5, 9.0, 11.0 Hz), 3.35 (dd, 1H, *J* = 2.5, 9.0 Hz), 2.81 (dt, 1H, *J*= 2.0, 5.0 Hz), 2.20 (m, 2H), 1.54-1.40 (m, 6H), 1.30 (m, 4H), 0.96 (t, 3H, *J*= 7.5 Hz), 0.89 (t, 3H, *J*= 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 136.5, 127.0, 60.0, 54.4, 34.1, 31.3, 29.2, 27.6, 22.5, 19.2, 14.0, 13.9.

IR (neat): 3205, 2960, 2931, 2858, 1636, 1466, 1380, 901 cm^{-1}

Exact mass calcd. for $C_{12}H_{23}O$: 183.3140; found: 183.3152.

$[\alpha]_D^{25}$: -9.7 (c = 1.4, $CHCl_3$).

The enantiomeric excess of the epoxide **116** derived from both procedures A and B was determined by chiral GC analysis to be 85%. Temperature program: temperature held at 70 °C for 50 minutes. t_R = 35.3 minutes [(*S,S*)-enantiomer]; t_R = 36.4 minutes [(*R,R*)-enantiomer].

Preparation of (4*R*,5*S*)-4-chloro-5-phenylpentan-5-ol (117)

To a cold (-78 °C), stirred solution of bromobenzene (79 mg, 0.50 mmol) in dry THF (2.5 mL) under argon was added *n*-butyllithium (0.25 mL, 0.50 mmol, 2.0 M in hexanes). After 10 minutes a solution of (2*R*)-2-chloropentanal (**103**) (66 mg, 0.55 mmol) in THF (0.25 mL) was added and the reaction mixture was stirred for an additional 10 minutes. After this time, the clear solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **117** (13:1 mixture of diastereomers as determined by ^1H NMR spectroscopy) as a crude oil which was used without further purification.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.42-7.29 (m, 5H), 4.90 (m, 1H), 4.19 (m, 1H), 3.08 (d, 1H, *J* = 2.2 Hz), 1.73-1.57 (m, 2H), 1.39-1.29 (m, 2H), 0.90 (m, 3H, *J* = 7.0 Hz).

Preparation of (4*S*,5*S*)-4,5-epoxy-5-phenylpentane (118)

To a stirred solution of the crude chlorohydrins **117** (0.50 mmol) in EtOH (2.5 mL) at room temperature was added KOH (84 mg, 1.5 mmol). After 30 minutes the resulting yellow solution was diluted with pentanes (20 mL) and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (4*S*,5*S*)-4,5-epoxy-5-phenylpentane (**118**) (68 mg, 84 %, d.r.= 14:1) as a light yellow oil.

^1H NMR (500 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 3.61 (d, 1H, *J* = 2.0 Hz), 2.95 (dt, 1H, *J* = 2.0, 5.5 Hz), 1.64-1.70 (m, 2H), 1.52-1.58 (m, 2H), 1.00 (t, 3H, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.1, 128.6, 128.2, 125.7, 63.3, 58.8, 34.6, 19.5, 14.2.

IR (neat): 3080, 3062, 3026, 2961, 2933, 2873, 1605, 1498, 1461, 1380, 1203, 870 cm^{-1}

Exact mass calcd. for $C_{11}H_{14}O$: 162.2278; found: 162.2284.

$[\alpha]_D^{25}$: -31.5 (c = 0.8, $CHCl_3$).

The enantiomeric excess of **118** was determined by transformation to (2*S*)-1-phenylpentan-2-ol (**123**). Thus, a solution of (4*S*,5*S*)-4,5-epoxy-5-phenylpentane (**118**) (16 mg, 0.10 mmol) and $NaBH_4$ (10 mg, 0.25 mmol) in MeOH (2 mL) was stirred at room temperature for one hour. The reaction mixture was then treated with water (1 mL), diluted with Et_2O (5 mL), and the phases were separated. The organic phase was dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (10:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (2*S*)-1-phenylpentan-2-ol (**123**). $[\alpha]_D^{20}$ = 3.7 (obs.) (c = 1.1, EtOH); lit. 4.2 (c = 1.8,EtOH).[55]

Preparation of (4*R*,5*S*)-4-chloroundecan-5-ol (119)

To a cold (-78 °C), stirred solution of *n*-hexyllithium (0.25 mL, 0.50 mmol, 2.0 M in hexanes) in dry THF (2.5 mL) was added a solution of (2*R*)-2-chloropentanal (**103**) (66 mg, 0.55 mmol) in THF (0.25 mL) and the reaction mixture was stirred for 10 minutes. After this time the clear solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **119** (8:1 mixture of diastereomers as determined by ^1H NMR spectroscopy) as a crude oil which was used without further purification.

^1H NMR (500 MHz, $CDCl_3$) δ: 4.02 (m, 1H), 3.74 (dd, 1H, *J* = 9.0, 5.0 Hz), 2.38 (tt, 2H, *J* = 9.0, 4.5 Hz), 1.92 (d, 1H, *J* = 6.0 Hz), 1.75-1.66 (m, 2H), 1.56-1.48 (m, 4H), 1.34-1.27 (m, 6H), 0.95 (t, 3H, *J* = 6.5 Hz), 0.99 (t, 3H, *J* = 7.0 Hz).

Preparation of (4*S*,5*S*)-4,5-epoxyundecane (120)

To a stirred solution of the crude chlorohydrins **119** (0.50 mmol) in EtOH (2.5 mL) at room temperature was added KOH (84 mg, 1.5 mmol). After the mixture had been stirred for 30 minutes the resulting yellow solution was diluted with pentanes (20 mL) and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (4*S*,5*S*)-4,5-epoxyundecane (**120**) (67 mg, 79 %, d.r. = 8:1) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.66 (m, 2H), 1.50 (m, 8H), 1.29 (m, 6H), 0.95 (t, 3H, *J* = 7.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 58.9, 58.8, 34.4, 32.3, 31.9, 29.3, 26.2, 22.7, 19.5, 14.2, 14.1.

IR (neat): 2960, 2928, 2861, 1733, 1465, 1156, 1094, 904 cm^{-1}

Exact mass calcd. for $C_{11}H_{22}O$: 170.2951; found: 170.2962.

$[\alpha]_D^{25}$: -26.5 (c = 0.6, $CHCl_3$).

Preparation of tetradeca-1,4-diyne (124)

A stirred solution of 1-undecyne (**125**) (41 mg, 0.40 mmol) and ethyl magnesium chloride (0.26 mL, 0.52 mmol, 2.0 M solution in Et_2O) in THF (4.0 mL) was heated at reflux for two hours. After this time, the solution was cooled to 0 °C, and copper (I) iodide (8 mg, 0.04 mmol) was added. After an additional 30 minutes at 0 °C, propargyl mesylate (70 mg, 0.52 mmol) was added in one portion and the resulting brown solution was stirred at room temperature for two hours. After this time the reaction mixture was treated with saturated aqueous NH_4Cl (5 mL) and the resulting mixture was diluted with Et_2O (20 mL) and the phases were separated. The organic phase was washed with brine

(3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30 g of silica gel, 60:1 pentanes – diethyl ether) and removal of trace amounts of solvents (vacuum pump) afforded tetradeca-1,4-diyne (**124**) (70 mg, 92 %) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.15 (dt, 2H, *J* = 2.5, 2.4 Hz), 2.15 (tt, 2H, *J* = 2.5, 7.0 Hz), 2.06 (t, 1H, *J* = 2.4 Hz), 1.49 (m, 2H), 1.27-1.37 (m, 12H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 81.4, 79.0, 72.9, 68.3, 31.9, 29.5, 29.3, 29.1, 28.9, 28.7, 22.7, 18.7, 14.1, 9.6.

IR (neat): 3411, 3005, 2925, 2144, 1716, 1420, 1363, 1222, 1093, 902 cm^{-1}

MS (CI, *m/z*): 190.3 (M+H)

Preparation of (6*Z*,9*Z*,4*S*,5*S*)-4,5-epoxynonadeca-6,9-diene (83)

To a cold (-78 °C), stirred solution of tetradeca-1,4-diyne (**124**) (38 mg, 0.20 mmol) and dry THF (2 mL) was added *n*-butyllithium (0.10 mL, 0.20 mmol, 2.0 M in hexanes). After 30 seconds, a solution of (2*R*)-2-chloropentanal (**103**) (29 mg, 0.24 mmol) in THF (0.2 mL) was added and the resulting mixture was stirred for 5 minutes. After this time the light yellow solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **126** (>20:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy) as a crude oil that was used without further purification.

To a cold (0 °C), stirred solution of the crude chlorohydrins **126** (0.20 mmol) in EtOH (2.0 mL) was added Lindlar's catalyst (4 mg, 0.04 mmol) and quinoline (26 mg, 0.20 mmol) and the resulting suspension was stirred under an atmosphere of H_2 (balloon) for two hours at 0 °C. After this time KOH (17 mg, 0.30 mmol) was added and the suspension was stirred for an additional 30 minutes. The reaction mixture was then

filtered through Celite® and the filtrate was diluted with pentanes (20 mL), and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (45:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (6*Z*,9*Z*,4*S*,5*S*)-4,5-epoxynonadeca-6,9-diene (**83**) (46 mg, 82 %) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.66 (dt, 1H, *J* = 7.0, 10.5 Hz), 5.33-5.46 (m, 2H), 5.07 (ddt, 1H, *J* = 1.5, 9.0, 10.5 Hz), 3.37 (dd, 1H, *J* = 2.0, 9.0 Hz), 2.96 (t, 2H, *J* = 7.0 Hz), 2.83 (dt, 1H, *J* = 2.5, 5.5 Hz), 2.06 (dt, 2H, *J* = 7.5, 7.0 Hz), 1.45-1.60 (m, 4H), 1.26-1.37 (m, 14H), 0.97 (t, 3H, *J* = 7.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.4, 131.1, 127.2, 126.7, 60.0, 54.3, 34.1, 31.9, 29.60, 29.59, 29.58, 29.33, 29.32, 27.3, 26.1, 22.7, 19.2, 14.1, 13.9.

IR (neat): 3010, 2958, 2925, 2854, 1717, 1558 cm^{-1}

Exact mass calcd. for $C_{19}H_{33}O$: 277.4704; found: 277.4722.

$[\alpha]_D^{25}$: -11.6 (c = 1.2, $CHCl_3$); lit. -12.5 (c = 4.1, $CHCl_3$).

The enantiomeric excess of (**83**) was determined to be 85% by chiral GC analysis. Temperature program: temperature set at 145 °C for 80 minutes. t_R = 57.1 minutes [(*S,S*)-enantiomer]; t_R = 59.0 minutes [(*R,R*)-enantiomer].

Preparation of deca-1,4-diyne (128)

A stirred solution of 1-heptyne (**105**) (39 mg, 0.40 mmol) and ethyl magnesium chloride (0.26 mL, 0.52 mmol, 2.0 M solution in Et_2O) in dry THF (4 mL) was heated at reflux for two hours. After this time, the solution was cooled to 0 °C, and copper (I) iodide (8 mg, 0.04 mmol) was added. After an additional 30 minutes at 0 °C, propargyl mesylate (70 mg, 0.52 mmol) was added in one portion and the brown solution was stirred at room temperature for two hours. After this time the reaction mixture was

treated with saturated aqueous NH_4Cl (5 mL) and the resulting mixture was diluted with Et_2O (20 mL) and the phases were separated. The organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (30 g of silica gel, 60:1 pentanes: diethyl ether) and removal of trace amounts of solvents (vacuum pump) afforded deca-1,4-diyne (**128**) (49 mg, 91 %) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.14 (dt, 2H, *J* = 2.5, 2.4 Hz), 2.15 (tt, 2H, *J* = 2.5, 7.0 Hz), 2.05 (t, 1H, *J* = 2.4 Hz), 1.49 (tt, 2H, *J* = 7.0, 7.0 Hz), 1.20-1.35 (m, 4H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 81.3, 79.0, 72.9, 68.3, 31.0, 28.3, 22.2, 18.6, 14.0, 9.6.

IR (neat): 3015, 2921, 2854, 2214, 1713, 1467 cm^{-1}

MS (CI, *m/z*): 134.2 (M+H)

Preparation of (6*Z*,9*Z*,11*S*,12*S*)-11,12-epoxyhenicosa-6,9-diene (84)

To a cold (-78 °C), stirred solution of deca-1,4-diyne (**128**) (27 mg, 0.20 mmol) in dry THF (2 mL) was added *n*-butyllithium (0.10 mL, 0.20 mmol, 2.0 M in hexanes). After 30 seconds, a solution of (2*R*)-2-chloroundecanal (**104**) (49 mg, 0.24 mmol) in THF (0.2 mL) was added and the resulting mixture was stirred for 5 minutes. After this time the light yellow solution was treated with saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (20 mL). The phases were separated and the organic phase was washed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the chlorohydrins **129** (>20:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy) as a crude oil that was used without further purification. To a cold (0 °C), stirred solution of the crude chlorohydrins **129** (0.20 mmol) in EtOH (2.0 mL) was added Lindlar's catalyst (4 mg, 0.04 mmol) and quinoline (26 mg, 0.20 mmol) and the resulting suspension was stirred under an atmosphere of H_2 (balloon) for two hours at 0 °C. After this time KOH (17 mg,

0.30 mmol) was added and the suspension was stirred for a further 30 minutes at 0 °C. The reaction mixture was then filtered through Celite® and the filtrate was diluted with pentanes (20 mL) and washed with brine (3 x 10 mL). The combined aqueous phases were extracted with pentanes (3 x 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash column chromatography (45:1 hexanes: ethyl acetate) and removal of trace amounts of solvents (vacuum pump) afforded (6*Z*,9*Z*,11*S*,12*S*)-11,12-epoxyhenicosa-6,9-diene (**84**) (52 mg, 84 %) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.66 (dt, 1H, *J* = 7.0, 10.5 Hz), 5.33-5.47 (m, 2H), 5.06 (ddt, 1H, *J* = 1.5, 9.0, 10.5 Hz), 3.37 (dd, 1H, *J* = 2.0, 9.0 Hz), 2.96 (t, 2H, *J* = 7.0 Hz), 2.82 (dt, 1H, *J* = 2.0, 6.0 Hz), 2.06 (dt, 2H, *J* = 7.5, 7.0 Hz), 1.58 (m, 2H), 1.45 (m, 2H), 1.26-1.38 (m, 18H), 0.89 (t, 3H, *J* = 7.0 Hz), 0.88 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 134.3, 131.1, 127.3, 126.7, 60.2, 54.3, 32.1, 31.9, 31.5, 29.55, 29.52, 29.45, 29.30, 29.24, 27.2, 26.1, 25.9, 22.7, 22.6, 14.11, 14.07.

IR (neat): 3004, 2925, 2855, 1721, 1636 cm^{-1}

Exact mass calcd. for $C_{21}H_{39}O$: 307.5401; found: 307.5421.

$[\alpha]_D^{25}$: -9.6 (c = 1.0, $CHCl_3$); lit. -10.8 (c = 1.08, $CHCl_3$)[27]

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Chapter 3

Development of a Concise and General Enantioselective Approach to 2,5-Disubstituted-3-hydroxytetrahydrofurans

The results discussed in this Chapter have been reported in part, see:. (a) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717. (b) Mowat, J.; Kang, B.; Fonovic, B.; Dudding, T.; Britton, R. *Org. Lett.* **2009**, *11*, 2057.

3.1 Introduction to Biologically Active Marine Natural Products

3.1.1 Marine Natural Products Chemistry

Natural products are chemical compounds produced by organisms for a variety of purposes, often to provide an evolutionary advantage (e.g., defense, reproduction, etc.). Because these compounds may also exhibit pharmacological or biological activity, natural product extracts have been used as therapeutics and/or traditional medicines for thousands of years. Dating back to 400 B.C., Hippocrates' records include reference to pain relief treatments using powder made from the bark of Willow trees (*Salix sp.*).[1] By the mid-1800's, the ability to isolate single chemical entities from crude natural product

extracts permitted the marketing of these compounds as pharmaceuticals, providing a foundation for the modern pharmaceutical industry. This is exemplified by Johann Buchner's isolation of salicin from the bark of the Willow tree, it's constituent salicylic acid was then elaborated to acetylsalicylic acid and marketed under the name Aspirin sold by the German company Bayer.[2] Since 1981, 52% of all new pharmaceuticals approved by the FDA have been natural products or natural product inspired.[3,4,5,6]

Owing to accessibility, terrestrial organisms have traditionally been the predominant source of bioactive natural products such as, plants, microorganisms, vertebrates, invertebrates, fungus, and insects.[7] However, with the advent of SCUBA in the 1960s the marine biosphere became accessible to scientists and provided an additional source of natural products.[8] The ecological and evolutionary pressures that exist within oceanic ecosystems lead to complex interactions between marine organisms that include the production of structurally diverse secondary metabolites, which often play key roles as chemical cues to attract mates or to repel predators.[9] Additionally, in aqueous environments the natural products responsible for communication amongst organisms must be water-soluble chemicals in order to be dispersed. The inherent polarity of these compounds is an important feature that often makes them good lead structures for drug discovery.

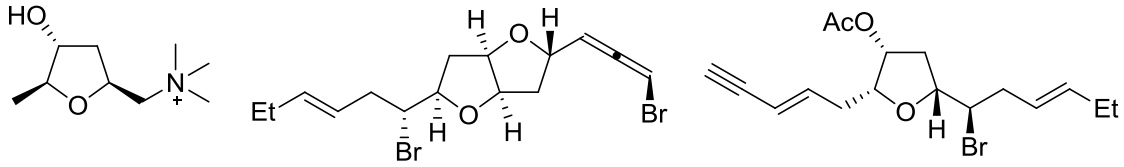
Although marine natural products have demonstrated pharmaceutical potential, the rarity of certain marine organisms and/or the small quantities of compounds available from the natural source make difficult the development of new drugs based on these products. To determine the full therapeutic potential of a natural product, synthetic material is usually required.[10] Thus, the development of concise and flexible syntheses is necessary to obtain a sufficient supply of a pharmacologically interesting compound.

In the last 50 years, over 16,000 structurally unique marine natural products have been reported.[11] *The Dictionary of Marine Natural Products* classifies these compounds

into 10 major structural classes (with some overlap between the categories).[12] These classes include the: aliphatic natural products, carbohydrates, polyketides, polypyrroles, amino acids, terpenoids, steroids, aromatic natural products, alkaloids, and the oxygen heterocycles. Each class is further divided into specific sub-classes of marine natural products. For example, one of the largest classes of marine natural products, the oxygen heterocycles are categorised into the β-lactones, furans, pyrans, and tetrahydrofurans.

3.1.2 2,5-Disubstituted-3-hydroxytetrahydrofuran-Containing Natural Products

Substituted tetrahydrofurans are one of the largest sub-class of oxygen heterocycles found in marine natural products. Among the largest specific group of substituted tetrahydrofuran-containing marine natural products are the 2,5-disubstituted-3-hydroxytetrahydrofurans. Some representative examples of compounds containing this core are depicted in Figure 7. They are found in biologically active molecules such as the acetogenins,[13] lignans,[14] and polyether ionophores.[15] Due to their importance as potential pharmaceuticals, considerable effort has been devoted to their stereoselective syntheses.[16,17d]

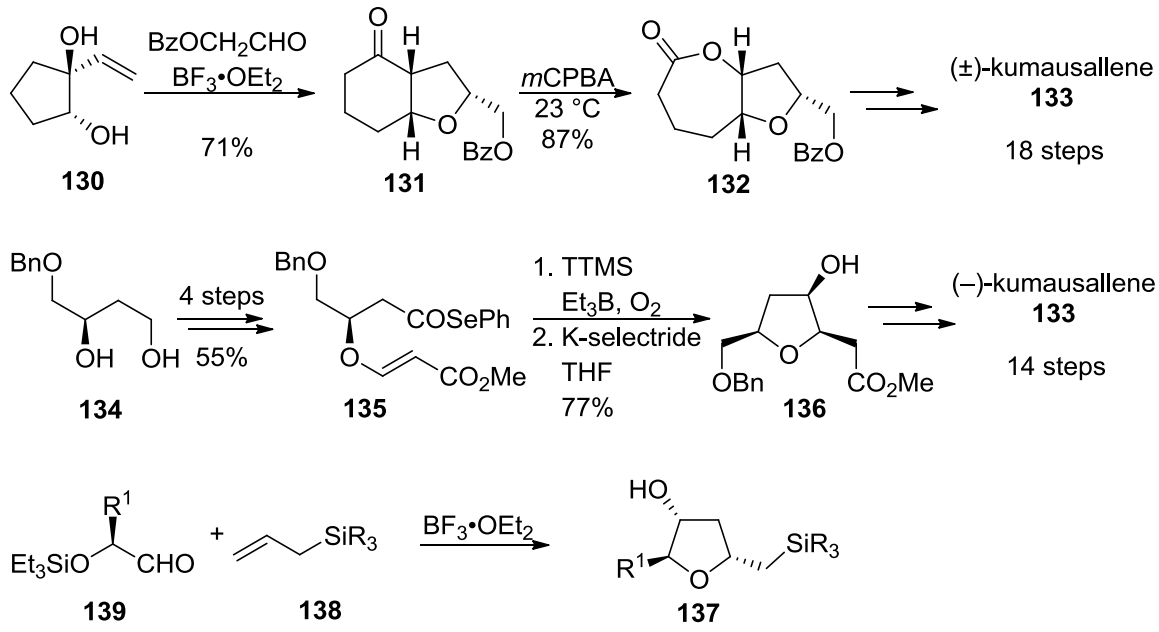


140: (+)-muscarine **133**: kumausallene *trans*-kumausyne

Figure 7. 2,5-Disubstituted-3-hydroxytetrahydrofuran natural products.

The structural and stereochemical complexity inherent in naturally occurring 2,5-disubstituted-3-hydroxytetrahydrofurans makes realising an efficient asymmetric synthesis of these substances significantly challenging. As a result, many synthetic

methods have been developed to construct 2,5-disubstituted-3-hydroxytetrahydrofurans.[17,18] These include a cascade Prins cyclisation-pinacol rearrangement Bäyer-Villiger sequence (**130** → **131** → **132**), used in the synthesis of (±)-kumausallene (*rac*-**133**) (Scheme 20),[19] a marine natural product isolated from the Japanese red algae, *Laurencia niponica*.[2021,22,23] In 1999, Evans reported the synthesis of (-)-kumausallene (**133**) *via* a route that involved conversion of enantiomerically enriched 1,3-butanediol **134**[24] to an acyl selenide **135** in four-steps. After a subsequent acyl radical cyclisation using tris(trimethylsilyl)silane and a reduction, 2,5-disubstituted-3-hydroxytetrahydrofuran **136** was afforded (Scheme 20).[25] The stereoselective synthesis of the silyl-substituted tetrahydrofuran **137** was achieved by a formal [3+2]-cycloaddition of an allyl silane (e.g., **138**) with an α-triethylsiloxy aldehydes (e.g., **139**, Scheme 20).[26] This methodology was further elaborated in the formal synthesis of the fungal natural product, (+)-muscarine (**140**),[27,28,29] a potential therapy for Alzheimer's disease.[30] In addition, many approaches rely on the manipulation of chiral-pool materials, such as (*R*)-malic acid[31] and D-glucose[23d] for controlling the absolute stereochemistry. Although these approaches provide access to specific natural products, they are often limited to the synthesis of a single stereoisomer of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold. To address this limitation, a flexible and divergent method that provides access to all configurational isomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran core would be an extremely useful tool for the synthetic chemistry community.

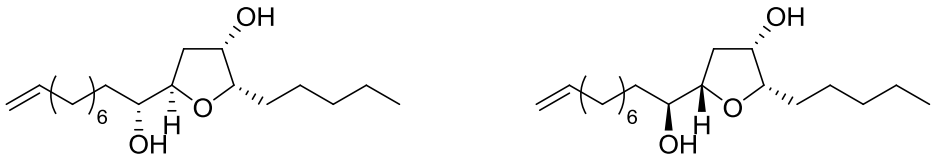


Scheme 20. Synthesis of 2,5-disubstituted-3-hydroxytetrahydrofurans.

3.1.3 Anthelmintic Oxylipids Isolated from the Southern Australian Brown Alga Notheia anomala

Notheia anomala, an epiphyte (a plant that grows on another plant) to *Hormosira banksii* (Neptune's Necklace seaweed), is a marine brown alga found off the coast of southern Australia.[32] In 1980, Warren, Wells, and Blount isolated (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol (**141**) as the major component of an organic extracts of *N. anomala* (4 g isolated from 800 g of freeze-dried alga).[33] Single-crystal X-ray analysis unambiguously confirmed the chemical structure of **141**.[33] More recently, the extraction of 1.3 kg dry weight of *N. anomala* reportedly yielded 6.5 g of **141** along with 5 mg of the C9,C10 bisepimeric oxylipid **142**.[34] Importantly, it was shown that both oxylipids **141** and **142** isolated from *N. anomala* exhibit selective nematocidal activity (i.e., possess anthelmintic activity).[34] For example, the oxylipid **141** exhibited potent anthelmintic activity toward the stomach worms, *Haemonchus contortus* (LD_{50} = 1.8 ppm) and

Trichostrongylus colubriformis (LD_{50} = 9.9 ppm).[34] These activities are comparable to commericially available anthelmintics, such as the benzimidazoles and avermectins.[35] Interestingly, medicinal chemistry efforts indicated that although the relative stereochemistry of the substiuted tetrahydrofuranol does not significantly influence the anthelmintic activity, the terminal alkene functionality proved critical.[34] In fact, oxylipid **142** also exhibits similar levels of anthelmintic activity to oxylipids **141**. Because of growing resistance to commercial anthelmintic drugs the discovery of new nematocidal compounds such as **141** and **142** is an important pursuit.



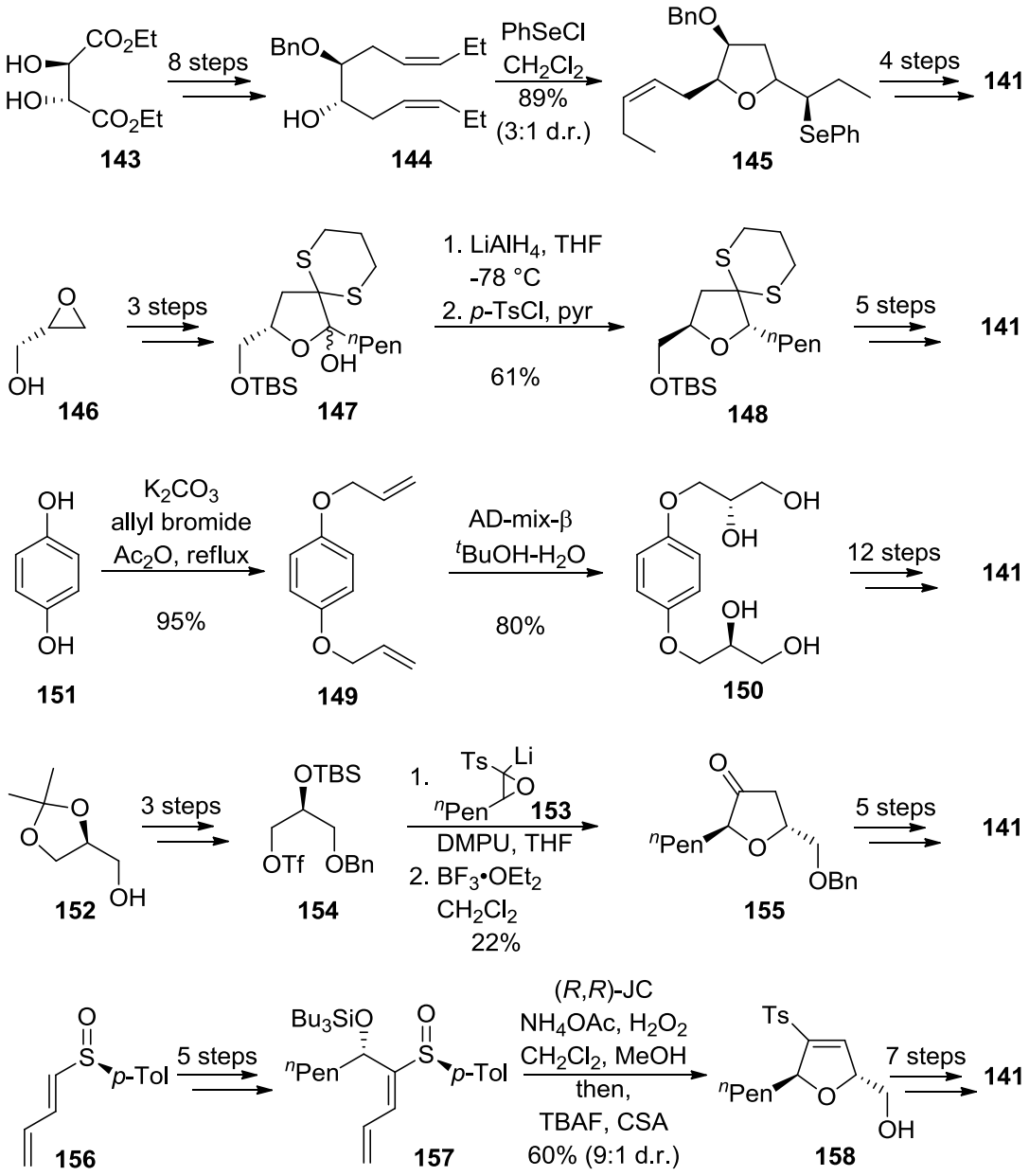
141: *Notheia anomala* oxylipid **142**: *Notheia anomala* oxylipid

Figure 8. The Notheia anomala oxylipid natural products.

Combination of potent nematocidal activity and structural complexity of oxylipids **141** and **142** provides a useful venue to demonstrate new synthetic strategies. For instance, numerous syntheses of the *N. anomala* oxylipds **141** and **142** exist, employing a variety of synthetic tranformations. This includes two racemic syntheses of **141** and **142**,[36,37,38] seven asymmetric syntheses of **141**, and four asymmetric syntheses of **142**.

The seven reported asymmetric syntheses of the oxylipid **141** range in length from 10 to 14-steps. The first of these was reported by Takano, who demonstrated that oxylipid **141** can be obtained in 13-steps (13% overall yield).[39] This strategy employed diethyl L-tartrate (**143**) as the chiral template and involved a selenium-mediated etherification of a hydroxy diene (**144** → **145**) as the key transformation (Scheme 21). Starting with (*S*)-glycidol (**146**), a 10-step synthesis (3% overall yield) of enantiopure **141** was reported that involved a stereocontrolled hydride addition/cyclodehydration

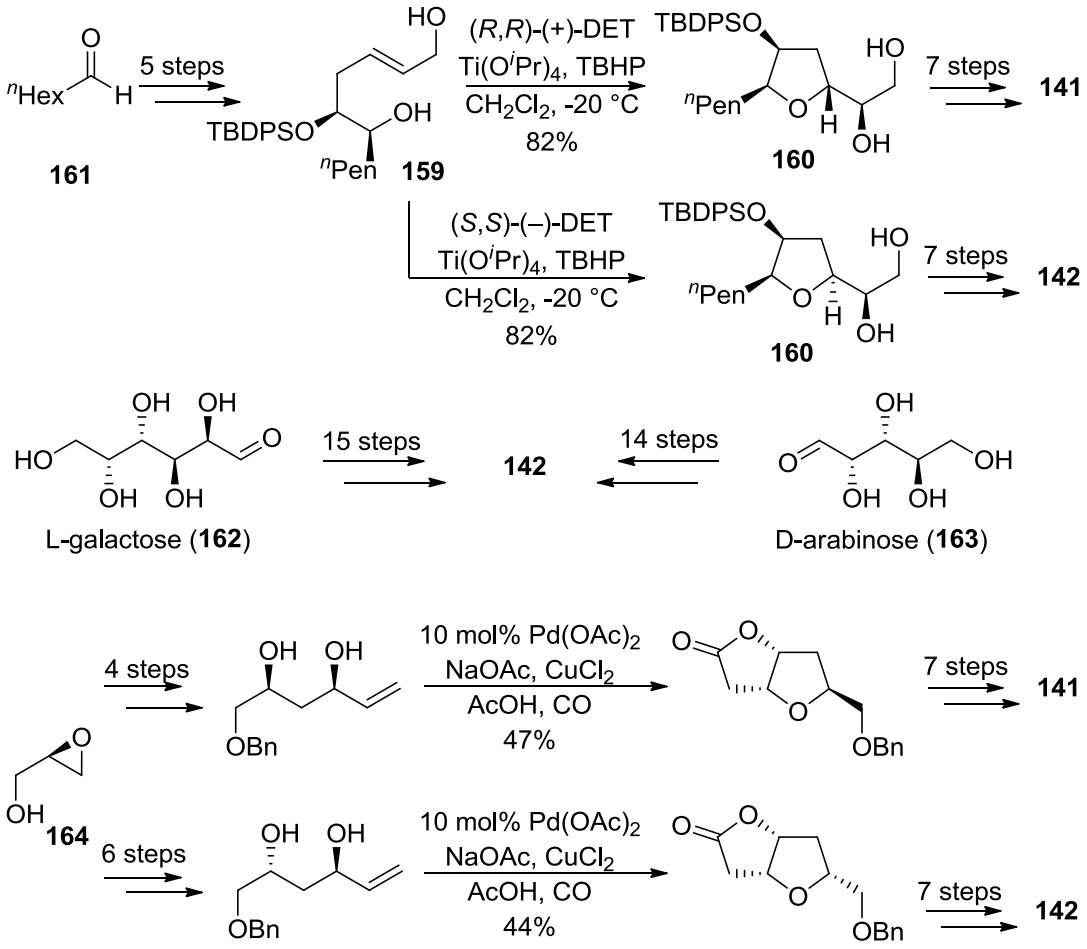
sequence (**147** → **148**) (Scheme 21).[40] A Sharpless asymmetric dihydroxylation of a diallyl ether (**149** → **150**) derived from hydroquinone **151** was also used to access **141** in 14-steps (19% overall yield) (Scheme 21).[41] In 1999, Mori constructed the substituted tetrahydrofuran core of **141** from a commercially available dioxolane **152**. This process involved alkylation of a sulfonyl-stabilised oxiranly anion **153**, followed by a 5-*endo* cyclisation (**154** → **155**), culminating in a 13-step synthesis of oxylipid **141** (6% overall yield) (Scheme 21).[42] More recently, de la Pradilla described a 12-step formal synthesis of **141** starting from a sulfinyl diene **156** (4% overall yield) employing a Katsuki-Jacobsen oxidation-epoxidation[43] of an α-silyloxy sulfinyl diene (**157** → **158**) (Scheme 21).[44]



Scheme 21. Key steps in the previous asymmetric syntheses of 141.

The four asymmetric syntheses of oxylipid **142** use similar chemical transformations as for oxylipid **141**. In 2000, Martin reported the first enantioselective synthesis of oxylipid **142** using a Sharpless asymmetric epoxidation (**159** → **160**).[45] This divergent route gave access to both oxylipid natural products **141** and **142** in 13-steps (17% overall yield) staring from *n*-heptanal (**161**) (Scheme 22). Soon therafter, two

chiral-pool syntheses starting from L-galactose (**162**) and D-arabinose (**163**) provided **142** in 15-steps (2% overall yield),[46,47] and 14-steps (11% overall yield),[48] respectively (Scheme 22). Recently, a divergent synthesis starting from (*S*)-glycidol (**164**) was reported that employs Semmelhack's alkoxypalladation-carbonylation-lactonisation[49] *en route* to the antipodal oxylipids *ent*-**142** in 14-steps (3% overall yield) and *ent*-**141** in 12-steps (3.5% yield) (Scheme 22).[50]



Scheme 22. Key steps in the asymmetric syntheses of 142 and 141.

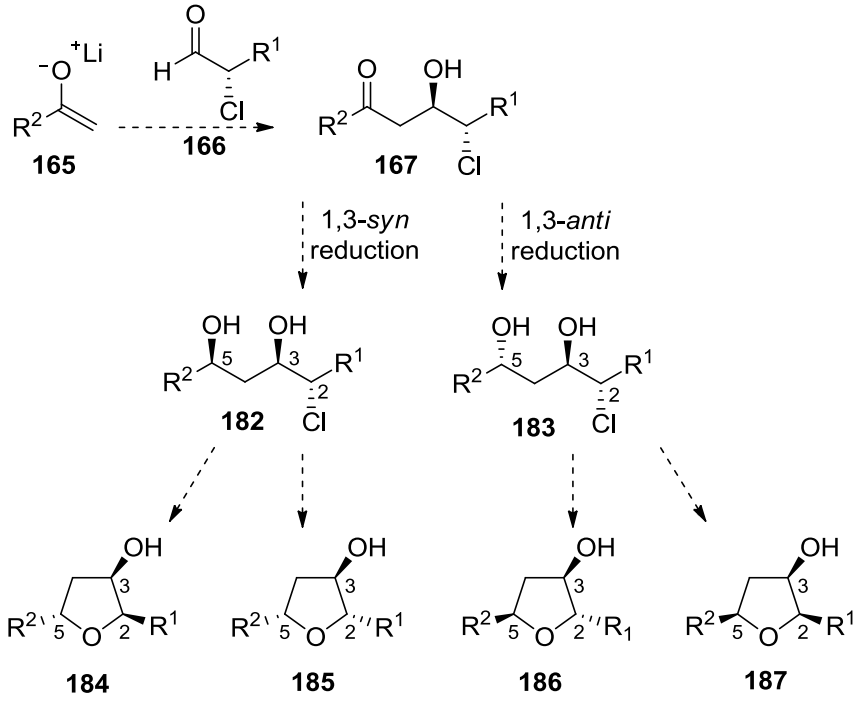
Although many asymmetric syntheses of **141** and **142** have been reported, most provide access to only one of the natural products and are not sufficiently versatile to construct configurational isomers. This singular focus is evident not only in the synthesis

of **141** and **142**, but also in the generation of other 2,5-disubstituted-3-hydroxytetrahydrofurans (see previous section). Consequently, a general strategy that provides access to all configurational isomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold would be useful for both the preparation of **141** and **142**, and other structurally complex natural products.

3.2 Synthesis of the 2,5-Disubstituted-3-hydroxytetrahydrofurans

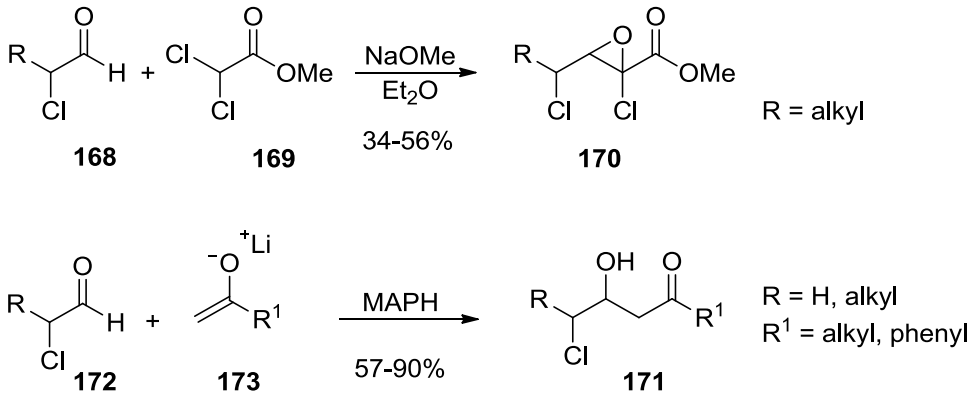
3.2.1 Synthetic Plan

In Chapter 2, a new method involving the nucleophilic addition of organolithium reagents to α-chloroaldehydes was reported to yield optically enriched *trans*-epoxides. As an extension of this methodology, we anticipated that the addition of lithium enolates to α-chloroaldehydes would give rise to aldol adducts (β-ketochlorohydrins) with high diastereocontrol. More importantly, we realised the resultant aldol adducts could offer access to functionalised tetrahydrofurans. Notably, these substances are prevalent in a variety of natural products with varied biological activities.



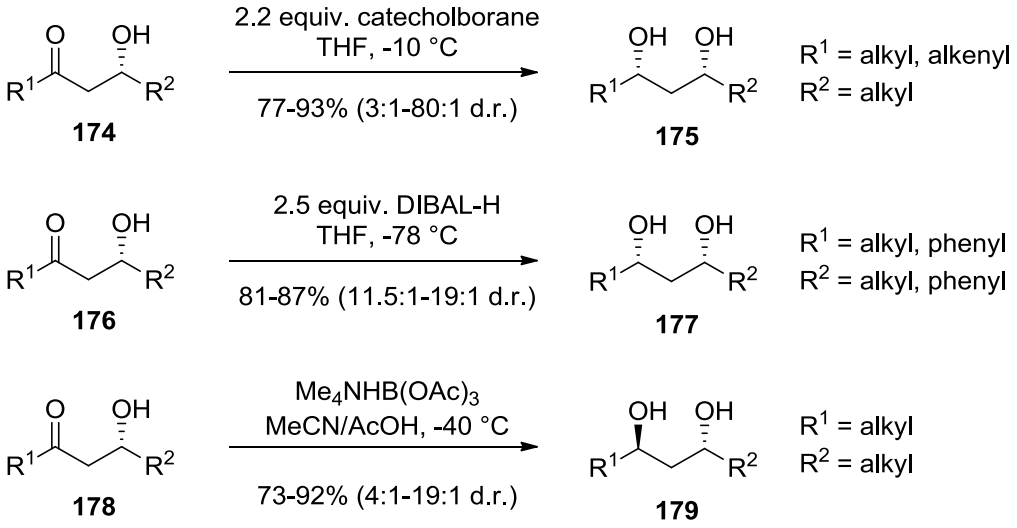
Scheme 23. Proposed synthesis of all configurational isomers of 2,5-disubstituted-3-hydroxytetrahydrofurans from a single chlorohydrin.

As indicated in Scheme 23, the first step in the proposed tetrahydrofuran synthesis would involve addition of an enolate (e.g., **165**) to an α-chloroaldehyde (e.g., **166**) to afford an aldol adduct (e.g., **167**). The enantiomerically pure α-chloroaldehydes (e.g., **166**) required for this work can be accessed using methods described independently by Jørgensen (see page 6) and MacMillan (see page 4).[51,52,53] Although four examples of the addition of enolates to α-chloroaldehydes have been reported, the aldol adducts are generally not isolated.[54] For example, Takeda demonstrated that the condensation of aliphatic α-chloroaldehydes (e.g., **168**) with methyl dichloroacetate (**169**) in the presence of sodium methoxide afforded 2,4-dichloro-2,3-epoxyalkanoates (e.g., **170**, Scheme 24).[54a] In addition, Yamamoto prepared β-ketochlorohydrins (e.g., **171**) from the reaction of α-chloroaldehydes (e.g., **172**) with a variety of lithium enolates (e.g., **173**) in the presence of methylaluminum bis(2,6-diphenylphenoxide) (Scheme 24).[54d] Although, the resulting diastereoselectivites were not reported, it is reasonable to propose that the reaction between the enolate (e.g., **165**) and α-chloroaldehyde (e.g., **166**) would provide the 1,2-*anti*-chlorohydrin (e.g., **167**), as predicted by the Cornforth Model.[55,56] Our work would also represent the first enolate addition to optically pure α-chloroaldehydes.



Scheme 24. Addition of enolates to α-chloroaldehydes.

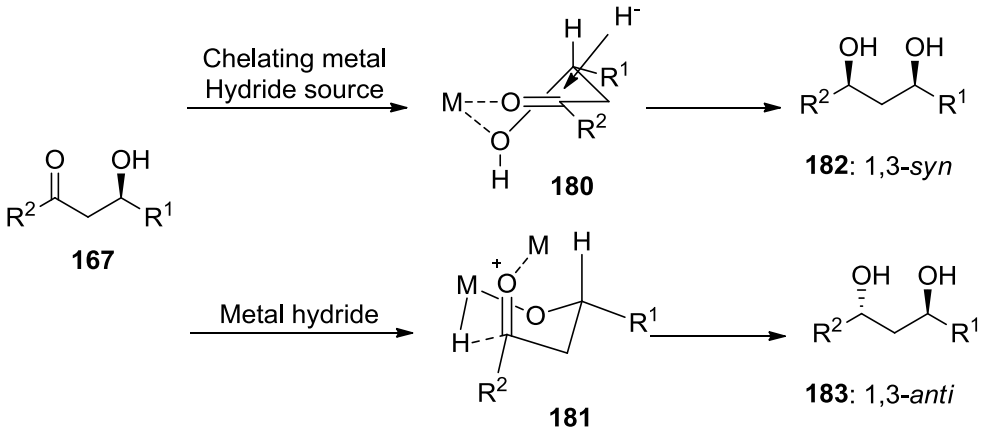
If successful in realising the key diastereoselective aldol coupling, the subsequent step in the proposed synthesis would involve a hydroxyl-directed reduction of the β-ketochlorohydrin (e.g., **167**) (Scheme 23). Significant precedent exists for the stereoselective reduction of acyclic β-hydroxyketones, which provides 1,3-*syn*-[57] or 1,3-*anti*-diols[58]. For example, Evans has reported that treatment of aldol adducts (e.g., **174**) with 2.2 equivalents of catecholborane results in the selective formation of the 1,3-*syn*-diols (e.g., **175**), a reaction that proceeds through a boron-aldolate complex (Scheme 25).[57c] The reduction of β-hydroxyketones (e.g., **176**) with diisobutylaluminum hydride also resulted in formation of 1,3-*syn*-diols (e.g., **177**) with excellent diastereoselectivity (Scheme 25).[59] Alternatively, the stereoselective reduction of aldol adducts (e.g., **178**) with tetramethylammonium triacetoxyborohydride affords 1,3-*anti*-diols (e.g., **179**) in excellent yield (Scheme 25).[58c]



Scheme 25. 1,3-*Syn* and 1,3-*anti* selective reductions of β-hydroxyketones.

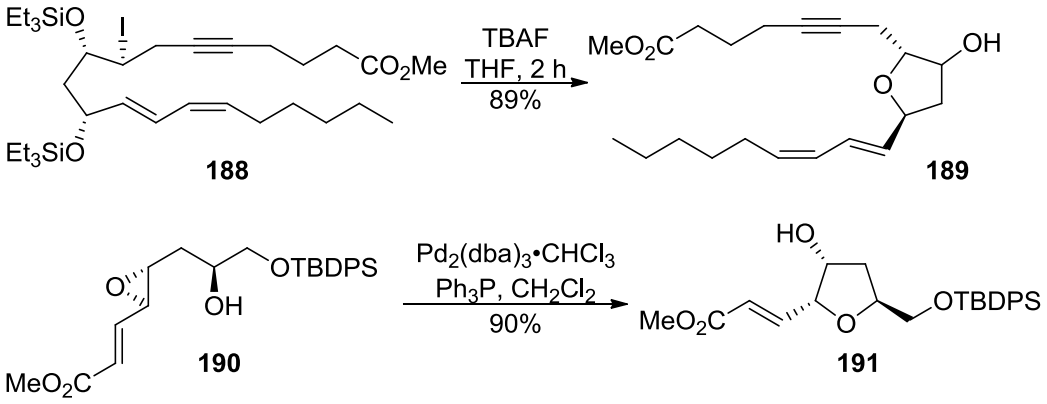
The stereochemical control in the 1,3-hydroxyl-directed reduction of β-hydroxyketones depicted in Scheme 25 results from intermolecular hydride addition to a metal-chelated carbonyl (e.g., **180**) to provide the 1,3-*syn*-diols, or an intramolecular

hydride transfer through a well-defined 6-membered chair-like transition (e.g., **181**) structure, which affords the 1,3-*anti*-diols (Scheme 26). Based on these examples, it was expected that selective reduction of β-ketochlorohydrins (e.g., **167**) would provide access to both the 1,3-*syn*- (e.g., **182**) and 1,3-*anti*-chlorodiols (e.g., **183**, Scheme 23).



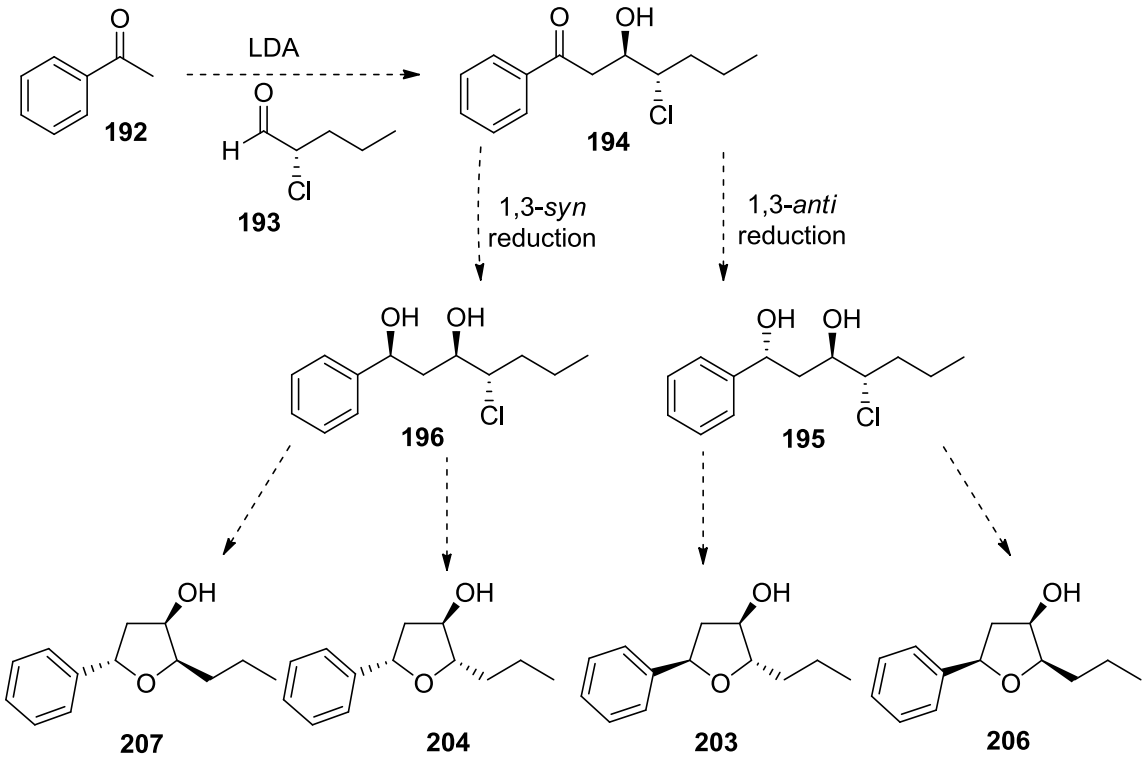
Scheme 26. Transition structures for the hydroxyl-directed reduction of β-hydroxyketones.

Next, we foresaw two cyclisation modes for the chlorodiols (e.g., **182** and **183**) *en route* to all configurational isomers of the substituted tetrahydrofurans (e.g., **184**, **185**, **186**, and **187**) (Scheme 23). To access tetrahydrofurans (e.g., **184** and **186**) from these diols, we visualised a direct S_N2 displacement of the chlorine atom with the distal alcohol function. Even though no precedent exists for this transformation, the direct intramolecular displacement of an iodide with an alkoxide (e.g., **188** → **189**, Scheme 27) has been reported.[60] In addition, to access tetrahydrofurans **185** and **187**, a double inversion at the chloromethine centre would be required. For this we envisioned a sequence involving epoxidation of the chlorodiols followed by a 5-*endo*-tet cyclisation of the resulting epoxyalcohol. A related reaction has been reported by Nishiyama in which the 5-*endo*-tet cyclisation (**190** → **191**) proceeds in the presence of a palladium catalyst (Scheme 27).[61]



Scheme 27. Examples of intramolecular 5-*exo* and 5-*endo* cyclisations.

In summary, our proposed synthetic route (Scheme 28) would provide access to all possible stereoisomers of 2,5-disubstituted-3-hydroxytetrahydrofurans, with the configuration of each stereocentre controlled using the aforementioned protocols. Specifically, the asymmetric α-chlorination would control the stereocentre at C3, position C5 would be established *via* a 1,3-hydroxy-directed reduction of the β-ketochlorohydrin, and the mode of cyclisation would lend control over the C2 stereocentre.



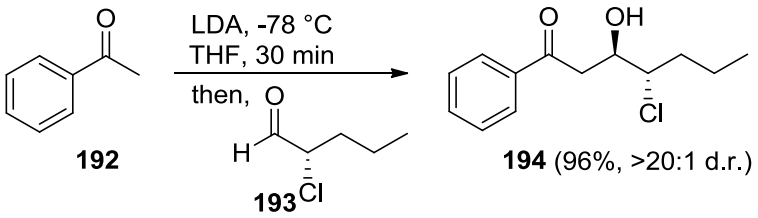
Scheme 28. Proposed route to phenyl-substituted hydroxytetrahydrofurans.

3.2.2 Results

3.2.2.1 Reactions of Lithium Enolates with α-Chloroaldehydes

A key aspect of the methodology developed for the synthesis of nonracemic *trans*-epoxides was the highly diastereoselective addition of organolithium reagents to enantiomerically enriched α-chloroaldehydes.[51-53,62] In an effort to further expand the scope of this methodology, it was discovered that lithium enolates also undergo diastereoselective aldol reactions with α-chloroaldehydes. Specifically, treatment of the lithium enolate derived from acetophenone (**192**) with (2*S*)-2-chloropentanal (**193**) afforded the *anti*-β-ketochlorohydrin **194** with excellent diastereoselectivity (>20:1 *anti*:*syn*) (Scheme 29); thus, representing the first example of a highly diastereoselective aldol reaction involving an enantiomerically enriched α-chloroaldehyde. Moreover, the

successful procurement of aldol adduct **194** was important to the proposed synthesis of substituted tetrahydrofurans described above (Scheme 28).

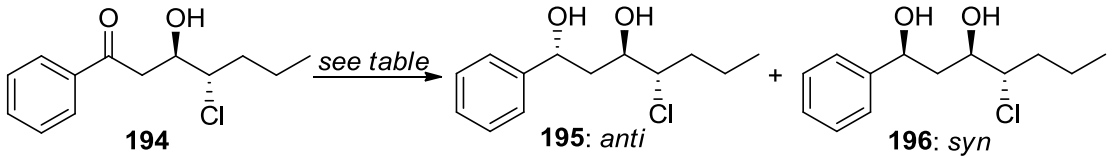


Scheme 29. Preparation of aldol adduct 194.

3.2.2.2 1,3-Hydroxyl-Directed Reductions of β-Ketochlorohydrins

Following the diastereoselective aldol reaction between an α-chloroaldehyde **193** and acetophenone, focus shifted toward exploration of 1,3-*anti*- and 1,3-*syn*-hydroxyl directed reductions of the β-ketochlorohydrin **194**. It was observed that the treatment of **194** with $NaBH_4$ in acetic acid (*in situ* preparation of $NaBH(OAc)_3$) at 0 °C resulted in a 2.3:1 ratio of *anti*:*syn* diastereomers (**195**:**196**) (Table 12, entry 1). However, subjecting **194** to pre-formed $NaBH(OAc)_3$ resulted in a significant increase of diastereocontrol (4:1 d.r.) (Table 12, entry 2). The relative increase in diastereoselectivity between the aforementioned cases may be attributed, in part, to incomplete conversion of $NaBH_4$ in acetic acid to the active reducing agent, $NaBH(OAc)_3$.[63] Changing the counter-ion from sodium to tetramethylammonium is known to increase the solubility of the reducing agent, thus permitting the reduction to be performed at lower temperatures, which generally results in enhanced diastereocontrol.[64,65] In fact, treatment of the aldol adduct **194** with $Me_4NBH(OAc)_3$ at -40 °C resulted in production of the 1,3-*anti*-diol **195** with excellent levels of diastereoselectivity (14:1 *anti*:*syn*) (Table 12, entry 3). It was also established that subjecting **194** to either catecholborane[57c] or DIBAL-H[59] provided the epimeric 1,3-*syn*-diol **196** selectively (Table 12, entries 5-6).

Table 12. 1,3-Hydroxyl-directed reductions of the β-ketochlorohydrin 194.



194 **195**: *anti* **196**: *syn*

entry	reducing agent	solvent	temp (°C)	yield	195:196
1	$NaBH_4$	AcOH/EtOAc	0	95	2.3:1
2	$NaBH(OAc)_3$	AcOH/MeCN	0	80	4:1
3	$Me_4NBH(OAc)_3$	AcOH/MeCN	-40	96	14:1
4	DIBAL-H	THF	0	>97	1:4
5	DIBAL-H	THF	-78	>97	1:11
6	Catecholborane	THF	-10	88	1:20

The relative stereochemistry of the newly formed carbinol stereocentres were confirmed by converting the diols **195** and **196** to their corresponding acetonides **197** and **198**, respectively, and analysis of their ^{13}C NMR spectra using the Rychnovsky method.[66] Typically, the acetonides derived from the 1,3-*syn*-diols exhibit characteristic resonances at δ 19 and 30 ppm in their ^{13}C NMR spectra for the for the methyl groups, and the acetal carbon resonates at δ 98.5 ppm. These characteristic resonances can be rationalised by considering that the acetonide will prefer to adopt a chair-like conformation in which the two methyl groups adopt axial and equatorial orientations. The acetonide **198** derived from the 1,3-*syn*-diol **196**, conformed to this model and displayed diagnostic resonances at δ 19.2, 30.1, and 99.5 ppm for the axial methyl, equatorial methyl, and the acetal carbon, respectively, in its ^{13}C NMR spectra (Figure 9). Conversely, acetonides derived from 1,3-*anti*-diols exist in a equilibration between the axial and equatorial conformations (i.e., equivalent acetonide methyl groups), which results in diagnostic resonances in the ^{13}C NMR spectra at δ 25 ppm for both acetonide methyl groups, and δ 100.5 ppm for the acetal carbon. As depicted in Figure 9, analysis of the ^{13}C NMR, HSQC, and HMBC spectra recorded on **197** allowed assignment of the

resonances at δ 24.6 and 25.0 ppm to the methyl groups, and the resonance at δ 101.2 ppm to the acetal carbon, consistent with those reported for acetonides derived from 1,3-*anti*-diols.

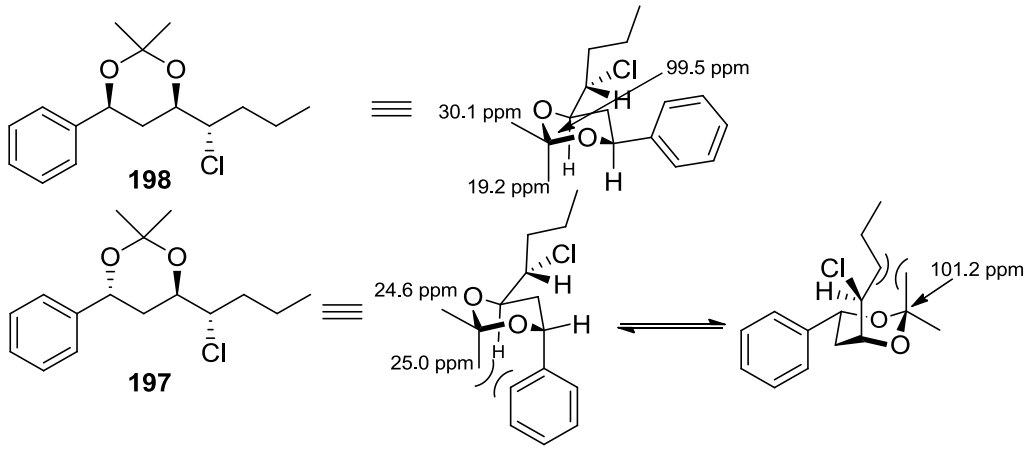


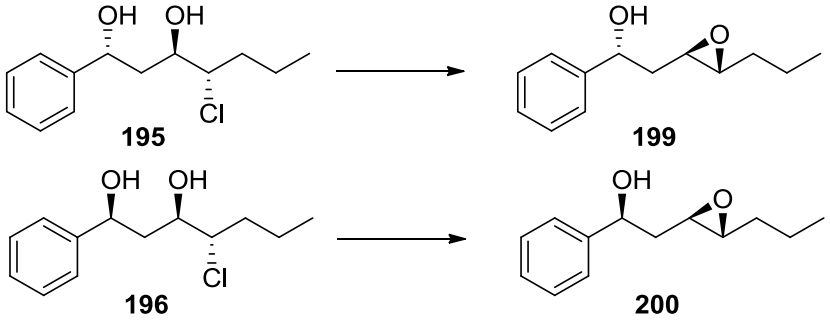
Figure 9. Conformations of the 1,3-*syn*-diol acetonide 198 and the 1,3-*anti*-diol acetonide 197. Characteristic ^{13}C NMR signals are shown.

3.2.2.3 Rearrangement of Epoxyalcohols Derived from Chlorodiols

Following the successful hydroxyl-directed reduction of β-ketochlorohydrin **194** to either the 1,3-*anti*- or 1,3-*syn*-chlorodiols **195** and **196**, the preparation of substituted tetrahydrofurans from these substances *via* a double inversion strategy (i.e., epoxide-formation followed by rearrangement) was investigated (Scheme 28). Thus, a survey of reaction conditions (Table 13) was performed to identify optimal conditions for the conversion of the chlorodiols **195** and **196** into their corresponding epoxyalcohols **199** and **200**. From these experiments, it was determined that the treatment of the chlorodiols **195** and **196** with KOH in ethanol at room temperature effected epoxide-formation in excellent yield (Table 13, entries 7 and 9). The results summarised in Table 13 also indicate that the treatment of chlorodiols **195** and **196** under basic conditions

results only in the formation of the corresponding 3-*exo*-tet (epoxide) products and none of the corresponding 5-*exo*-tet (tetrahydrofuran) products.

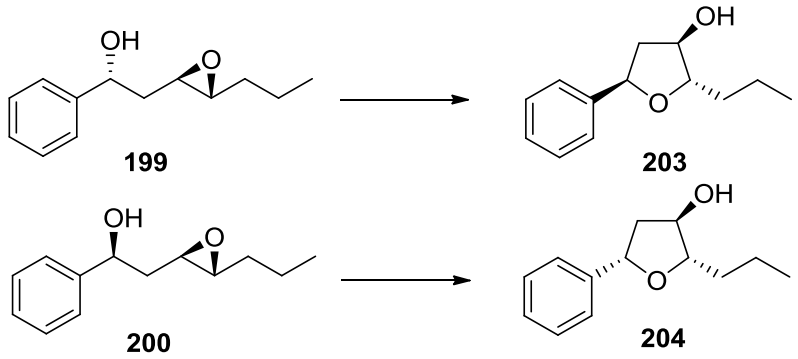
Table 13. Conversion of chlorodiols 195 and 196 to the corresponding epoxyalcohols 199 and 200.



entry	chlorodiol	base	additive/solvent	temp (°C)	time (h)	yield (%)
1	**196**	KH	THF	22	2	42
2	**196**	KH	18-crown-6/THF	22	2	46
3	**196**	KO*t*-Bu	THF	22	1	20
4	**196**	Et_3N	CH_2Cl_2	22-40	6	NR
5	**196**	Pyridine	CH_2Cl_2	22-40	6	NR
6	**196**	KOH	EtOH	50	6	90
7	**196**	KOH	EtOH	22	1.5	>97
8	**196**	KOH	EtOH	0	2	95
9	**195**	KOH	EtOH	22	1.5	97

Based on the high yielding preparation of epoxides **201** and **202**, it was envisioned that the rearrangement of these epoxyalcohols would provide access to the substituted tetrahydrofurans **203** and **204**.[67] After a brief screen of bases, protic acids, and Lewis acids (summarised in Table 14), it was determined that reaction of **199** with catalytic amounts of $BF_3{\cdot}OEt_2$ afforded the 2,5-disubstituted-3-hydroxytetrahydrofuran **203** (Table 14, entry 7). Under similar conditions, epoxyalcohol **200** was converted to the 2,5-disubstituted-3-hydroxytetrahydrofuran **204** in excellent yield (Table 14, entry 9).

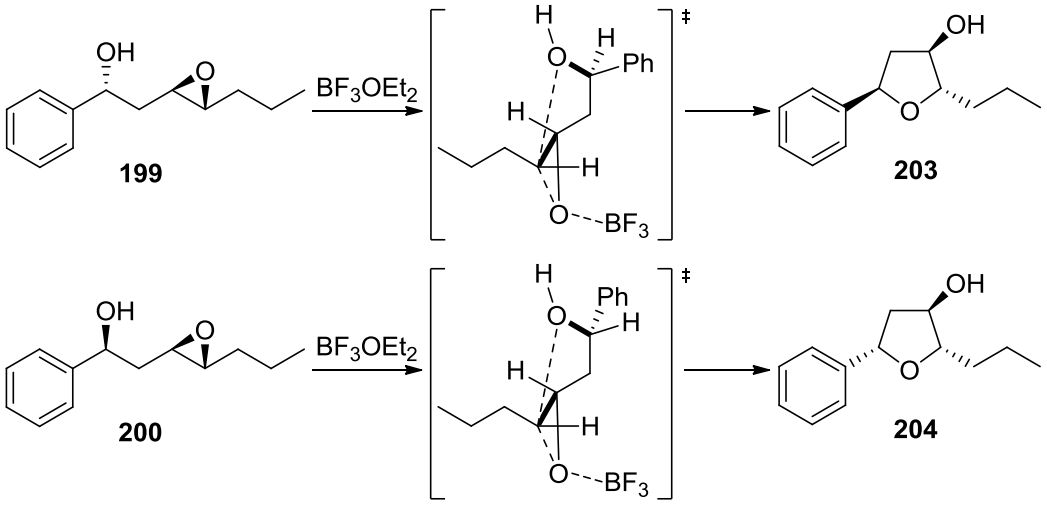
Table 14. Synthesis of tetrahydrofurans 203 and 204 from the epoxyalcohols 199 and 200.



entry	chloroepoxide	reagent	time (h)	temp (°C)	% yield
1	**199**	KOH	3	80	SM and decomp
2	**199**	AcOH	24	22	NR
3	**199**	Et_2AlCl	2	-78	decomp.
4	**199**	$AlCl_3$	2	-78	20[a]
5	**199**	$BF_3{\cdot}OEt_2$	8	-78	10
6	**199**	$BF_3{\cdot}OEt_2$	0.5	40	30
7	**199**	$BF_3{\cdot}OEt_2$	2	22	92
8	**200**	KOH	48	40	NR
9	**200**	$BF_3{\cdot}OEt_2$	2	22	96

a. mixture of the C2 epimers

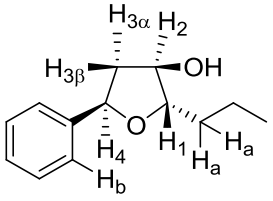
Mechanistically, both substituted tetrahydrofurans **203** and **204** are derived from a direct rearrangement of the epoxide with inversion of configuration.[68] Additionally, the epoxyalcohols **199** and **200** react preferentially to form the five membered tetrahydrofurans as opposed to the more strained four member rings. In both $BF_3{\cdot}OEt_2$-promoted cyclisations (**199** → **203** and **200** → **204**), none of the C2 epimer that would arise from an S_N1-type process or an intermediate halohydrin[69] was detected. However, a 1:1 mixture of the C2 epimeric tetrahydrofurans was observed in the reaction of **199** with $AlCl_3$, which most likely arose from the intermediacy of a discreet cation in this process (Table 14, entry 4).



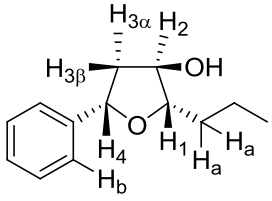
Scheme 30. Transition structures in the cyclisation of the epoxyalcohols under Lewis acid conditions.

The relative stereochemistry for both **203** and **204** was confirmed by nOe analysis as summarised in Table 15.

Table 15. Stereochemical analysis of 203 and 204 by nOe.



203

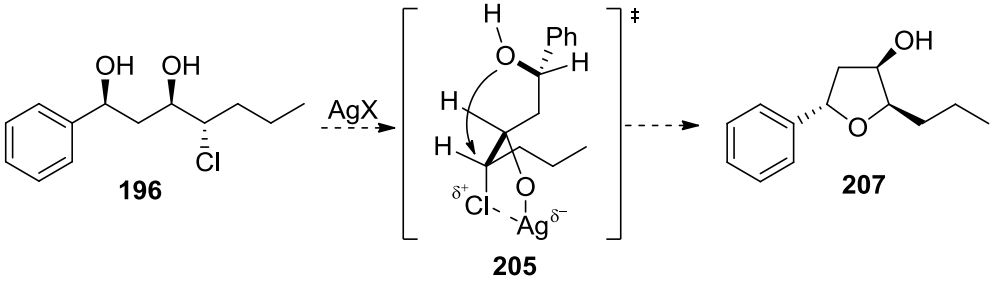


204

nOe correlation	% enhancement	nOe correlation	% enhancement
H4-H2	0.21	H4-H1	0.81
H2-H4	0.15	H1-H4	0.17
H4-Ha	0.34	H2-Hb	0.39
H1-Hb	0.21	H1-H3β	0.05
H1-H3β	0.32	H3β-H1	0.79
H3β-H1	0.53	H3α-Ha	1.49
H3α-Ha	0.83		

3.2.2.4 Direct Cyclisation of the Chlorodiols 195 and 196

Considering that treatment of the chlorodiols **195** and **196** with base, under a variety of reaction conditions, led exclusively to epoxides **199** and **200** and none of the tetrahydrofurans, the direct cyclisation of these chlorodiols to tetrahydrofurans under base-promoted conditions would likely require a selective protection of the alcohol adjacent to the chloromethine. Because a protecting group strategy would detract from the general appeal this methodology, an alternative process was envisioned whereby treatment of the chlorodiols **195** and **196** with a silver salt would lead to a silver alkoxide intermediate in which coordination between the silver and the chlorine would activate the chlorine as a leaving group (i.e., **205**, Scheme 31). Moreover, coordination of this type would also render the molecule incapable of undergoing epoxide-formation. Though no precedent exists for the transformation outlined in Scheme 31, the intramolecular Williamson etherification of primary alkyl bromides has been promoted with silver oxide[70] and with silver triflate/silver oxide.[71,72]

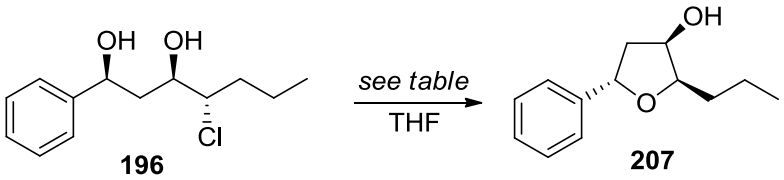


Scheme 31. Proposed silver-promoted cyclisation.

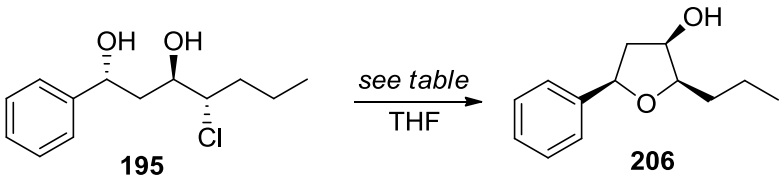
Efforts toward the realisation of this silver-promoted cyclisation are summarised in Table 16. As indicated in entries 1 and 2 (Table 16), it was found that Ag_2O does not promote the cyclisation reaction. Furthermore, treatment of **196** with AgOTf led to complex mixture that contained none of the desired tetrahydrofuran **206**; however, the crude ^{1}H NMR spectrum displayed resonances (e.g., δ 5.73 (dd, *J* = 6.5, 2.5 Hz))

characteristic of a dihydrofuran. It was reasoned that this latter material may form *via* an acid-catalysed dehydration of the desired tetrahydrofuran product, and that the addition of a base may facilitate the desired cyclisation. In an attempt to neutralise the reaction mixture (i.e., triflic acid formation), the affect of various bases on the outcome of the AgOTf-promoted reaction were explored (Table 16, entries 4 and 5). These additives failed to significantly improve upon these results. Because AgOTf can be prepared from the reaction of Ag_2O and triflic acid,[73] the addition of Ag_2O as a triflic acid scavenger (i.e., a mild base) was also investigated. A survey of reaction conditions using 3 equivalents of Ag_2O and 1 equivalent of AgOTf (Table 16, entries 6-9) determined that clean conversion of **196** to **206** results when the reaction was started at 0 °C and gradually warmed to room temperature over the course of 12 hours (Table 16, entries 6-9). Although a system catalytic in both AgOTf and Ag_2O was envisioned, use of sub-stoichiometric amounts of Ag_2O and AgOTf required extended reaction times, which led to decomposition of **196** and/or **206**, and consequently lower isolated yields of the desired product (Table 16, entries 10 and 11). The most favourable conditions for the conversion of **196** into **206** involved the addition of one equivalent of both AgOTf and Ag_2O in THF at 0 °C, followed by the gradual warming of this solution to room temperature over 12 hours (Table 16, entry 13). Similarly, these optimised conditions also effected the cyclisation of chlorodiol **195** to its corresponding 2,5-disubstituted-3-hydroxytetrahydrofuran **207** in good yield (Table 16, entry 14).

Table 16. Silver-promoted cyclisation of the chlorodiol 196 and 195.



196 **207**



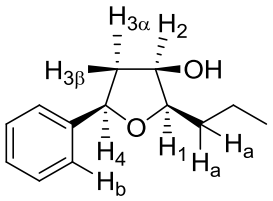
195 **206**

entry	chlorodiol	equiv. AgOTf	additive (equiv.)	time (h)	temp (°C)	yield (%)
1	**196**	0	Ag_2O (1)	36	22	NR
2	**196**	0	Ag_2O (3)	36	22	NR
3	**196**	1	-	12	22	0[a]
4	**196**	1	Pyridine (1)	12	22	10
5	**196**	1	Et_3N (1)	12	22	10[b]
6	**196**	1	Ag_2O (3)	12	22	10
7	**196**	1	Ag_2O (3)	4	-78	0[b]
8	**196**	1	Ag_2O (3)	6	0	0[b]
9	**196**	1	Ag_2O (3)	12	0-22	75
10	**196**	0.2	Ag_2O (0.2)	24	0-22	50
11	**196**	0.5	Ag_2O (0.5)	24	0-22	45
12	**196**	1	Ag_2O (1)	12	22	55
13	**196**	1	Ag_2O (1)	12	0-22	90
14	**195**	1	Ag_2O (1)	12	0-22	83

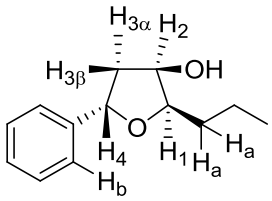
[a] significant conversion to the corresponding dihydrofuran. [b] minimal conversion of **196**.

The relative stereochemistry of both **207** and **206** was confirmed by nOe analysis summarised above (Table 17).

Table 17. Stereochemical analysis of 207 and 206 by nOe.



206

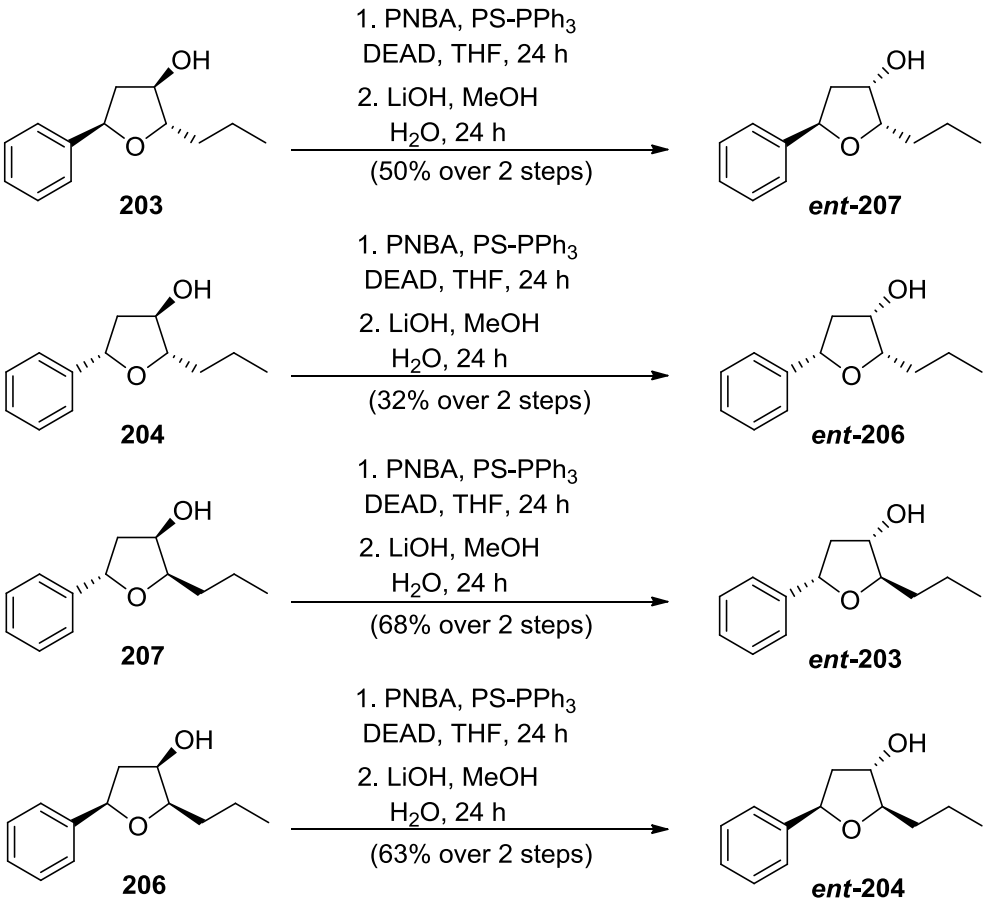


207

nOe correlation	% enhancement	nOe correlation	% enhancement
H4-H2	2.27	H1-H3α	1.69
H2-H4	2.10	H3α-H1	1.25
H4-H1	1.74	H1-Hb	0.77
H1-H4	0.37	H3β-Ha	0.12
H1-H3α	0.92	H2-Hb	0.09
H3α-H1	0.62		

3.2.2.5 Synthesis of the Enantiomeric Series of 2,5-Disubstituted-3-hydroxytetrahydrofurans

The silver-promoted cyclisation and the epoxidation/rearrangement strategies presented above provide rapid and high yielding access to all configurational isomers of the 2,5-disubstitued-3-hydroxytetrahydrofuran scaffold. The antipodal series of tetrahydrofurans may be accessed in an identical manner initiating with an L-prolinamide-catalysed α-chlorination. In addition, these enantiomeric tetrahydrofurans can be accessed through an inversion[74]/hydrolysis sequence on the 2,5-disubstituted-3-hydroxytetrahydrofurans produced above. Thus, it was demonstrated that Mitsunobu inversion carried out on tetrahydrofurans **203** and **204** provide *ent*-**206** and *ent*-**207**, respectively, the antipodes to the silver-promoted cyclisation products. Likewise, Mitsunobu inversion carried out on tetrahydrofuranols **207** and **206** affords *ent*-**204** and *ent*-**203**, respectively, the enantiomers of the tetrahydrofurans derived from the epoxyalcohols **199** and **200**.

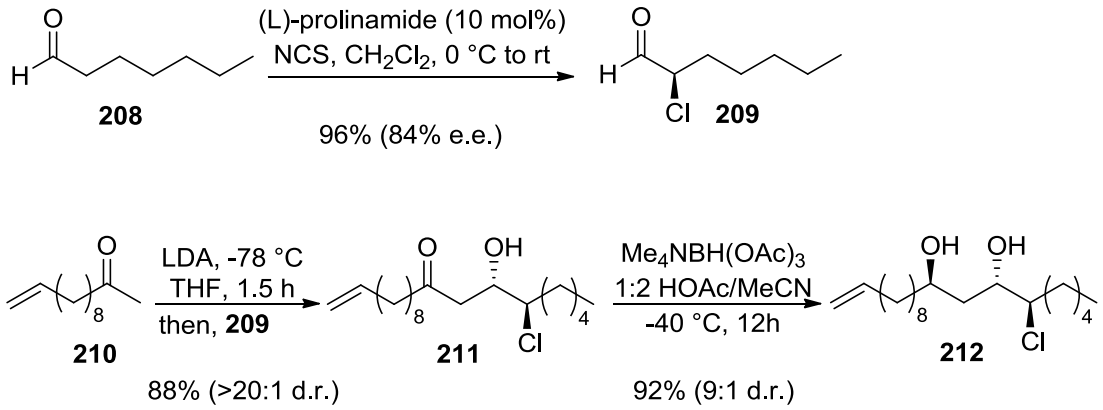


Scheme 32. **Mitsunobu inversion/hydrolysis of 203, 204, 206, and 207 to *ent*-206, *ent*-207, *ent*-203, and *ent*-204.**

3.2.2.6 Synthesis of the 2,5-Dialkyl-3-hydroxytetrahydrofurans

To assess the scope of these new methods for the preparation of 2,5-disubstituted-3-hydroxytetrahydrofurans, the application of this process to the preparation of various tetrahydrofuranols was initiated. Thus, heptanal (**208**) was treated with a catalytic amount of L-prolinamide (**16**) and NCS (**12**) to provide α-chloroheptanal (**209**) in good yield and 84% enantiomeric excess (Scheme 33).[52] Next, addition of the lithium enolate derived from undec-10-en-2-one (**210**) to **209** afforded aldol adduct **211**

with excellent diastereocontrol (>20:1). Finally, stereoselective 1,3-hydroxyl-directed reduction with $Me_4NBH(OAc)_3$ afforded the 1,3-*anti*-diol **212** (Scheme 33).



Scheme 33. Asymmetric synthesis of α-chloroheptanal 209 and the synthesis of the 1,3-anti-diol 212.

As depicted in Figure 10, analysis of the ^{13}C NMR and HSQC spectra derived from acetonide **213** allowed assignment of the resonances at δ 26.4 and 26.3 ppm to the acetonide methyl groups and the resonance at δ 101.9 ppm to the acetal carbon, consistent with those reported for acetonides derived from 1,3-*anti*-diols using the Rychnovsky method.[66]

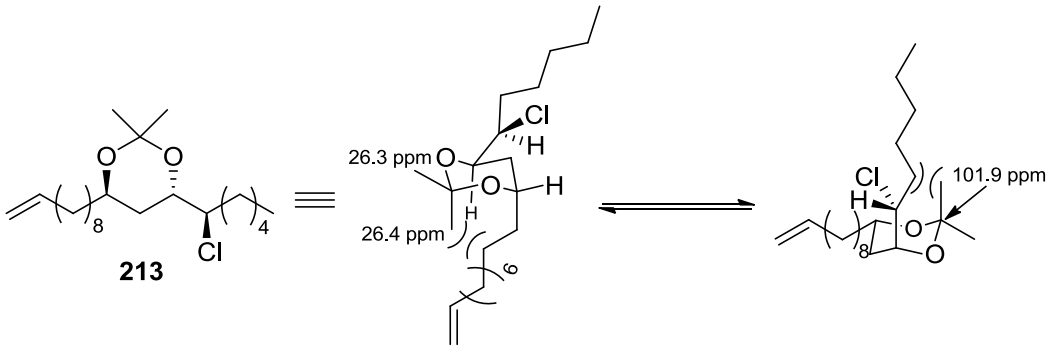
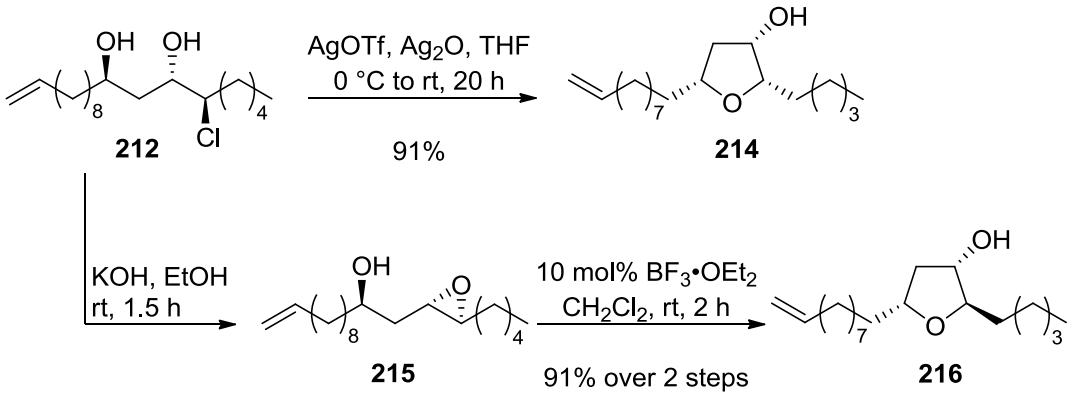


Figure 10. Conformations of the 1,3-*anti*-diol acetonide 213. ^{13}C NMR signals are shown.

Treatment of the 1,3-*anti*-diol **212** with Ag_2O/AgOTf provided the C10-deshydroxy analogue **214** of the *N. anomala* oxylipid **142** (Scheme 34). Alternatively, treatment of

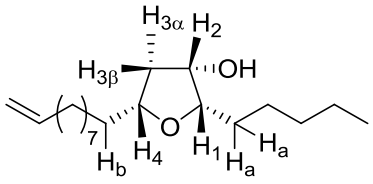
the 1,3-*anti*-diol **212** with KOH in ethanol provided the epoxyalcohol **215**, which was converted to tetrahydrofuran **216** following treatment with catalytic $BF_3{\cdot}OEt_2$ (Scheme 34). These results suggest that the complementary cyclisation strategies are also effective for the synthesis of 2,5-dialkyl-3-hydroxytetrahydrofurans.



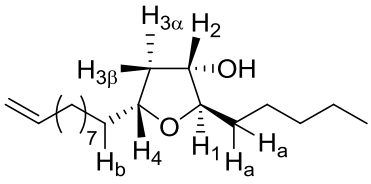
Scheme 34. Synthesis of 2,5-dialkyl-3-hydroxytetrahydrofurans 214 and 216.

The relative stereochemistry of both **214** and **216** was confirmed by nOe analysis as shown in Table 18.

Table 18. Stereochemical analysis of 214 and 216 by nOe analysis.



214

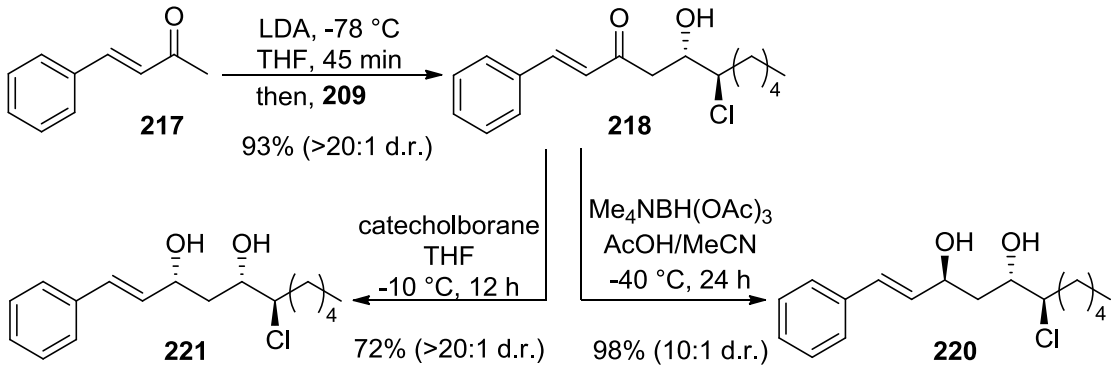


216

nOe correlation	% enhancement	nOe correlation	% enhancement
H2-H4	0.98	H2-H4	1.39
H4-H2	0.29	H4-H2	0.67
H4-H1	1.10	H1-H3α	0.86
H1-H4	0.24	H3β-H1	0.53
H1-H3β	0.71	H3β-Ha	0.13
H3β-H1	0.55		

3.2.2.7 Synthesis of the Alkenyl-Substituted Tetrahydrofurans

Having successfully established a synthesis of all configurational isomers of the phenyl- and alkyl-substituted hydroxytetrahydrofurans the scope of this process was further extended to include alkenyl-substituted hydroxytetrahydrofurans. Notably, these alkenyl-substituted analogues would eventually serve as building-blocks for the synthesis of the *N. anomala* oxylipid natural products **141** and **142**. Thus, α-chloroaldehyde **209** was treated with the lithium enolate derived from (*E*)-4-phenylbut-3-en-2-one **217**, which afforded the β-ketochlorohydrin **218** in excellent yield and diastereomeric ratio (93%, >20:1 d.r.) (Scheme 35). Next, a hydroxyl-directed reduction of **219** provided the 1,3-*anti*-diol **220** with $Me_4NBH(OAc)_3$, and the 1,3-*syn*-diol **221** with catecholborane, both with excellent diastereocontrol (Scheme 35).



Scheme 35. Diastereoselective synthesis of chlorohydrin 218 and hydroxyl-directed reduction to the 1,3-*anti*- 220 and 1,3-*syn*-diols 221.

As depicted in Figure 11, analysis of the ^{13}C NMR spectra and HSQC spectra derived from acetonide **222** allowed assignment of the resonances at δ 25.5 and 24.9 ppm to the acetonide methyl groups, and at δ 101.2 ppm to the acetal carbon, consistent with those reported for the acetonides derived from 1,3-*anti*-diols using the Rychnovsky method.[66] Similarly, the acetonide **223** derived from the 1,3-*syn*-diol **221** also conformed to this model, and displayed diagnostic resonances at δ 20.1, 30.2, and 99.4 ppm for the

axial methyl, equatorial methyl, and the acetal carbon, respectively, in the ^{13}C NMR spectra (Figure 11).

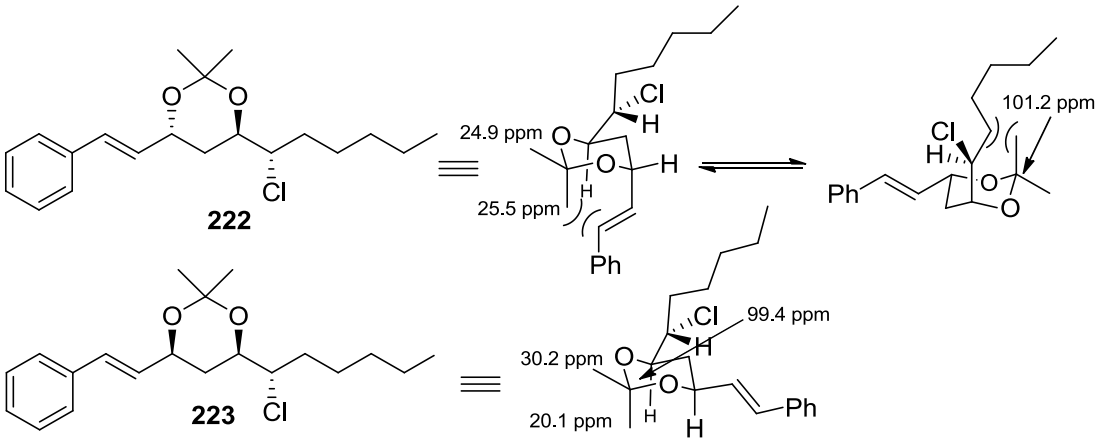
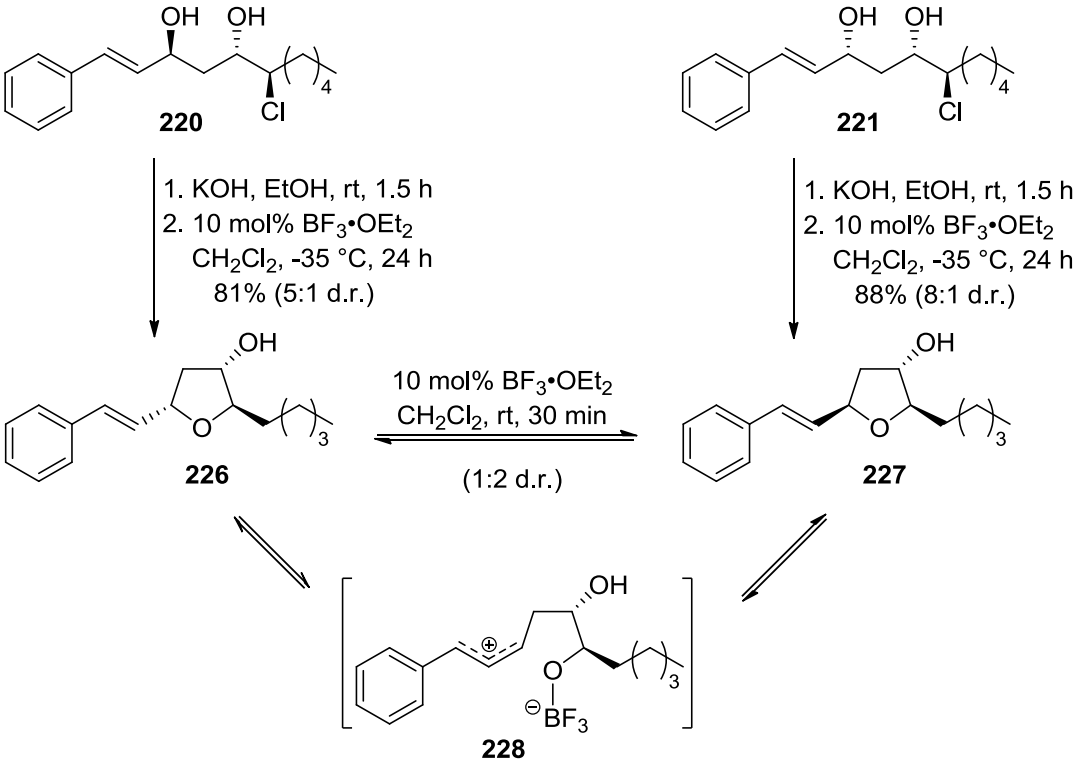


Figure 11. Conformations of the 1,3-*anti*-diol acetonide 222 and the 1,3-*syn*-diol acetonide 223. Characteristic ^{13}C NMR signals are shown.

In an effort to extend the methods described above to the synthesis of tetrahydrofurans *via* double inversion (i.e., epoxide-formation followed by $BF_3{\cdot}OEt_2$-catalysed rearrangement) or direct displacement of chloride (i.e., $AgOTf/Ag_2O$), chlorodiols **220** and **221** were treated with KOH in ethanol to effect their conversion to the corresponding epoxyalcohols **224** and **225**, respectively. These epoxyalcohols were then subjected to a $BF_3{\cdot}OEt_2$-catalysed rearrangement to afford the diastereomeric tetrahydrofurans **226** and **227**. Unexpectedly, reaction of both epoxyalcohols under these conditions led to a mixture of tetrahydrofurans **226** and **227**. When **224** was treated with catalytic $BF_3{\cdot}OEt_2$ at -35 °C, **226** and **227** were produced as a 5:1 mixture. Likewise, epoxyalcohol **225** was converted to **226** and **227** in a 1:8 mixture when treated with $BF_3{\cdot}OEt_2$ at -35 °C. Mr. Jeffrey Mowat, a fellow graduate student in the Britton group, observed that the epoxide-opening did not occur at reaction temperatures below -35 °C, and at elevated temperatures (e.g., room temperature) there was significant degradation in diastereoselectivity. These results suggest that $BF_3{\cdot}OEt_2$ catalyses the

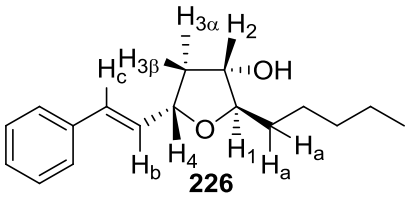
ionisation of styryltetrahydrofurans, leading to a resonance-stabilised cation (e.g., **228**) that can cyclise to form either **226** or **227** (Scheme 36). To verify this hypothesis, purified samples of both **226** and **227** were treated with a catalytic amount of $BF_3{\cdot}OEt_2$ at room temperature which led to an equilibrium mixture of **226** and **227** in a ratio of 1:2.



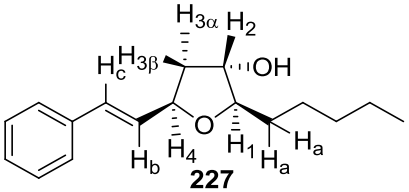
Scheme 36. Synthesis of the alkenyl tetrahydrofurans 226 and 227.

The relative stereochemistry of both **226** and **227** was confirmed by nOe analysis as shown in Table 19.

Table 19. Stereochemical analysis of 226 and 227 by nOe.



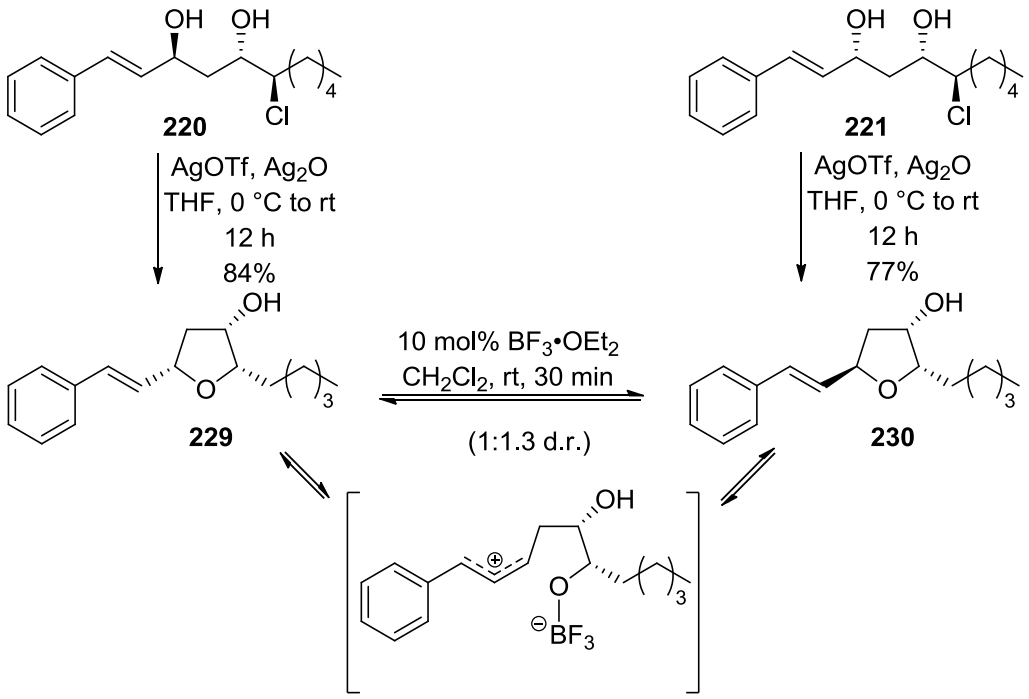
226



227

nOe correlation	% enhancement	nOe correlation	% enhancement
H1-H3α	0.21	H1-H4	0.56
H3α-H1	0.21	H4-H1	0.34
H1-Hb	0.60	H1-H3α	0.11
H1-Hc	0.43	H3α-H1	0.13
H1-OH	0.24	H1-OH	0.36
OH-H1	0.38	H2-Hb	0.05
H2-H4	0.18	H3β-Hc	0.16
H4-H2	0.20	H3α-OH	0.14
H3α-OH	0.17	H4-Ha	0.34
OH-H3α	0.27		

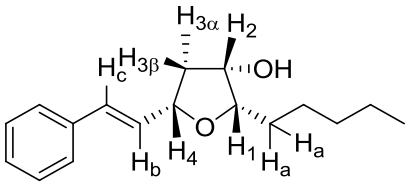
To access the remaining configurational isomers of the alkenyl-substituted hydroxytetrahydrofurans (i.e., **229** and **230**), the silver-promoted cyclisation protocol was employed. Specifically, the 1,3-*anti* and 1,3-*syn*-diols **220** and **221** were separately treated with AgOTf/Ag_2O to afford the corresponding tetrahydrofurans **229** and **230** in excellent yield. Notably, these tetrahydrofurans did not undergo epimerisation under the reaction conditions; however, separate treatment of **229** and **230** with catalytic $BF_3{\cdot}OEt_2$ at room temperature provided a 1:1.3 mixture of these tetrahydrofurans confirming that the equilibration of styrylfunctionalised tetrahydrofurans occurs with $BF_3{\cdot}OEt_2$. This type of equilibration has been reported in literature with aryl substituted tetrahydrofurans in the presence of acids.[75]



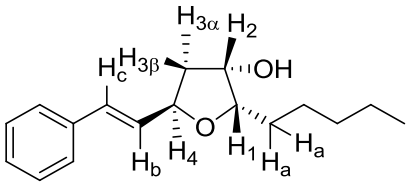
Scheme 37. Synthesis of the alkenyl tetrahydrofurans 229 and 230.

The relative stereochemistry of both **229** and **230** was confirmed by nOe analysis as shown in Table 20.

Table 20. Stereochemical analysis of 229 and 230 by nOe analysis.



229

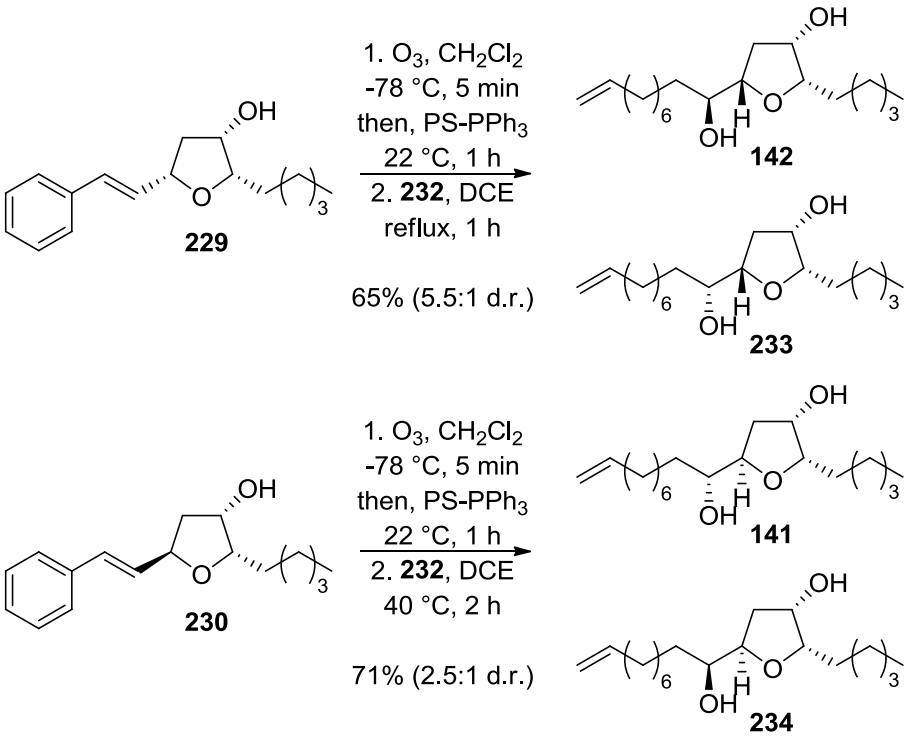


230

nOe correlation	% enhancement	nOe correlation	% enhancement
H1-H4	0.77	H1-Hc	0.22
H4-H1	0.79	H1-H3β	0.54
H1-H3β	0.51	H3β-H1	0.62
H3β-H1	0.55	H3α-OH	0.30
H3α-OH	0.16	H4-OH	0.22
H3α-Ha	0.48		

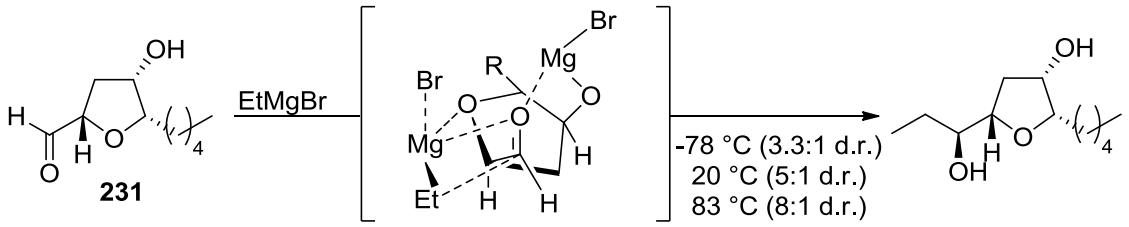
3.2.2.8 Synthesis of the *Notheia anomala Oxylipids.*

Building on the successful development of a concise approach to stereoisomeric 2,5-disubstituted-3-hydroxytetrahydrofurans, a total syntheses of the marine oxylipids **141** and **142** was initiated – this work was completed in collaboration with Mr. Mowat and Mr. Thomas Pinter (co-workers in the Britton laboratory). The synthesis of **142** commenced with an oxidative cleavage of the alkene functionality with ozone, followed by reductive workup with polymer-supported triphenylphosphine, and filtration providing the corresponding aldehyde **231**. Mr. Mowat determined that the oxidative cleavage took approximately five minutes, and that the reductive workup required one hour of shaking on a wrist-action shaker[82] with polymer-supported triphenylphosphine. It was also determined that stirring the reaction mixture resulted in degradation of chemical purity, which complicated the subsequent filtration process. The polymer-supported reagent was used because the crude aldehyde **231** readily decomposed on silica gel. Thus, the by-products from the reaction mixture were readily removed by filtration. The crude aldehyde **231** was then reacted with an excess of 8-nonenylmagnesium bromide (**232**) in DCE at reflux providing **142** as the major component of a separable 5.5:1 mixture containing its C10 epimeric alcohol **233** (Scheme 38). The addition of 8-nonenylmagnesium bromide (**232**) to **231** at lower temperatures required extended reaction times and proceeded with significantly lower diastereoselectivities. Similarly, tetrahydrofuran **230** underwent the same sequence of reactions to afford the other *N. anomala* oxylipid **141** and its C10 epimeric alcohol **234** as a 2.5:1 mixture (Scheme 38).



Scheme 38. Synthesis of marine oxylipid 142 and its C10 epimer 233, and the marine oxylipid 141 and its C10 epimer 234.

During the optimisation of these syntheses, an inverse temperature-dependent diastereoselective Grignard addition reaction was uncovered – this related project was led by Mr. Mowat and has been fully described.[76] The diastereoselectivity of the addition of Grignard reagents to the 3-hydroxytetrahydrofurfural **231** was found to increase with increasing temperatures. This result may be rationalised by a shift in the Schlenk equilibrium as addition of dialkylmagnesium reagents to **231** were found to be non-selective (d.r. = 1:1) (Scheme 39). These results were further supported through a series of DFT calculations performed by Prof. Travis Dudding and Mr. Branden Fonovic at Brock University.



Scheme 39. Addition of ethyl magnesium bromide to tetrahydrofurfural 231.

3.2.2.9 Conclusions

In summary, the development of an efficient route to all configurational isomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold from a single aldol adduct was described within this Chapter. Central to the success of this work was the identification of two cyclisation protocols that selectively afford stereoisomeric tetrahydrofurans from chlorodiols, namely, a chemoselective silver-promoted 5-*exo*-tet cyclisation or epoxide-formation followed by a Lewis acid-catalysed rearrangement. The flexibility and generality of this methodology was demonstrated by expanding the substrate scope to include phenyl-, alkyl- and alkenyl-substituents in the 5-position of the resultant tetrahydrofuranol. These methodologies were successfully applied to the concise total syntheses of the anthelmintic marine oxylipids **141** and **142**, with the assistance of Mr. Mowat and Mr. Pinter. Notably, both oxylipids **142** (37% overall yield) and **141** (26% overall yield) were obtained in six-steps from heptanal, which compares favourably with the reported asymmetric syntheses of these substances.[36-50] Importantly, the functional group tolerance and stereochemical flexibility of this new approach should also provide rapid access to a wide variety of naturally occurring and biologically active 2,5-disubstituted-3-hydroxytetrahydrofuran scaffolds prevalent in natural products.

3.3 Experimentals

General

All reactions described were performed under an atmosphere of dry argon using oven dried glassware unless otherwise specified. THF, Et_2O, CH_2Cl_2 were used directly from an MBraun Solvent Purifier System (MB-SP Series). Commercial anhydrous EtOH (reagent grade) was used without further purification. Cold temperatures were maintained by the use of following reaction baths: 0 °C, ice-water; -78 °C, acetone-dry ice; temperatures between -40 °C to -20 °C were maintained with a Polyscience VLT-60A immersion chiller. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[77] Concentration and removal of trace solvents was done *via* a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Gas chromatography (GC) analysis was performed on a Hewlett Packard model 5890 gas chromatograph, equipped with a flame ionisation detector and a Cyclosil-B chiral column (30 m length, 0.320mm ID, 0.25 μm film).

NMR spectra were recorded using deuterochloroform ($CDCl_3$) as the solvent unless otherwise indicated. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR; CH_3OD: δ 3.31, ^{1}H NMR; δ 49.0). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants, assignment (where possible). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz) or Varian Inova 500 (500 MHz). Carbon nuclear

magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (150 MHz) or Varian Inova 500 (125 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HMBC, HMQC and nOe spectra.

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 mass spectrometer at 70 eV. High resolution fast atom bombardment (HR-FABMS) mass spectra were recorded on a JEOL JMS-AX505HA mass spectrometer at 3 kV.

Optical rotation was measured on a Perkin Elmer Polarimeter 341 at 589nm.

Preparation of (2*S*)-2-chloropentanal (193)

To a cold (0 °C), stirred solution of pentanal (430 mg, 5.0 mmol) in CH_2Cl_2 (20 mL), was added D-prolinamide (58 mg, 0.50 mmol) and *N*-chlorosuccinimide (870 mg, 6.5 mmol). The reaction mixture was stirred for one hour and then allowed to slowly warm to room temperature over the course of three hours at which temperature it was stirred until complete consumption of pentanal (as determined by ^{1}H NMR spectroscopy). After this time, the mixture was diluted with pentane (20 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice water bath. The resultant oil was dissolved in pentane (20 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath to give (2*S*)-2-chloropentanal (**193**) (600 mg, >97% yield, 85% e.e.) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.44 (d, 1H, *J* = 2.5 Hz), 4.14 (ddd, 1H, *J* = 2.5, 5.0, 7.5 Hz), 1.90 (m, 1H), 1.77 (m, 1H), 1.47 (m, 2H), 0.91 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 195.2, 63.6, 33.8, 18.7, 13.2.

IR (neat): 2963, 2936, 2876, 2849, 1735, 1466, 1434, 1382, 1262, 1206, 1055 cm^{-1}

Exact mass calcd for $C_5H_{10}ClO$: 121.5868; found: 121.5870.

$[\alpha]_D^{25}$: -11.4 (c = 0.6, $CHCl_3$).

The enantiomeric excess of (**193**) was determined by chiral GC analysis of the corresponding alcohol. A solution of (**193**) (12 mg, 0.10 mmol) and $NaBH_4$ (10 mg, 0.25 mmol) in MeOH (2 mL) was stirred at room temperature for one hour. The reaction mixture was then treated with water (1 mL) and diluted with diethyl ether (5 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered, and concentrated to afford (2*S*)-2-chloropentanol. (Temperature program: 70 °C held for 5 minutes then increased by 20 °C per minute until 150 °C and run for 30 minutes. Retention time = 21.0 ((*R*)-enantiomer); 21.8 ((*S*)-enantiomer).

Preparation of (3*R*,4*S*)-4-chloro-3-hydroxy-1-phenylheptan-1-one (194)

To a cold (-78 °C) solution of diisopropyl amine (1.1 mL, 8.3 mmol) in THF (80 mL) was added *n*-butyllithium (2.5 M soln. in hexane, 3.2 mL, 7.9 mmol). The resulting solution was stirred at -78 °C for 30 minutes, then warmed to 0 °C and stirred for an additional 15 minutes. After this time, the slightly yellow solution was cooled to -78 °C and acetophenone (**192**) (0.91 mL, 7.8 mmol) was added in one portion. The reaction mixture was stirred for 30 minutes. A solution of (2*S*)-2-chloropentanal (**193**) (1.0 g, 8.3 mmol) in THF (2.0 mL) was then added dropwise over 15 minutes at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (10 ml) was then added, the mixture was diluted with ethyl acetate (20 ml) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 ml) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by

flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (3*R*,4*S*)-4-chloro-3-hydroxy-1-phenylheptan-1-one (**194**) (1.8 g, 96%) as a white solid (m.p. 54-55 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.98 (d, 2H, *J* = 8.4 Hz), 7.61 (tt, 1H, J = 1.3, 7.4 Hz), 7.49 (dt, 2H, J = 1.3, 7.4 Hz), 4.30 (m, 1H), 4.05 (ddd, 1H, *J*= 3.6, 6.6, 9.6 Hz), 3.49 (d, 1H, *J* = 4.8 Hz), 3.42 (dd, 1H, *J* = 2.4, 17.4 Hz), 3.31 (dd, 1H, *J* = 9.0, 17.4 Hz), 1.94 (m, 1H), 1.76-1.63 (m, 2H), 1.47 (m, 1H), 0.97 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 200.4, 136.6, 133.7, 128.7, 128.2, 71.1, 65.8, 41.1, 36.0, 19.6, 13.5.

IR (thin film): 2962, 2954, 2922, 1681, 1597, 1449, 1377, 1021 cm^{-1}

Exact mass calcd for $C_{13}H_{18}ClO_2$: 241.0995 (M-H_2O+H); found: 241.1010 (M-H_2O+H).

$[\alpha]_D^{25}$: -19.6 (c = 2.7, $CHCl_3$).

Preparation of (1*R*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (195)

A solution of tetramethylammonium triacetoxyborohydride (3.5 g, 13 mmol) dissolved in a 1:1.5 mixture of glacial acetic acid: acetonitrile (20 mL) was stirred at room temperature for 30 minutes. This solution was then cooled to -40 °C and a solution of (3*R*,4*S*)-4-chloro-3-hydroxy-1-phenylheptan-1-one (**194**) (400 mg, 1.7 mmol) in acetonitrile (5 mL) was added in one portion and the resulting mixture was stirred for 48 hours. After this time, saturated aqueous sodium tartrate (10 ml) was added, the mixture diluted with ethyl acetate (20 ml) and the phases were separated. The aqueous phase was extracted with ethyl acetate (4 x 15 ml), and the combined organic phases were washed with brine (10 ml), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (1*R*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**195**) (384 mg, 96%, d.r. 14:1) as a white solid (m.p. 94-95 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39-7.27 (m, 5H), 5.10 (dd, 1H, *J* = 3.0, 9.0 Hz), 4.05-4.00 (m, 2H), 2.69 (br s, 1H), 2.02 (ddd, 1H, *J* = 3.0, 8.4, 14.4 Hz), 1.95 (ddd, 1H, *J* = 2.4, 9.0, 14.4 Hz), 1.78-1.58 (m, 3H), 1.39 (m, 1H), 0.93 (t, 3H, *J* = 7.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 144.2, 128.6, 127.6, 125.5, 71.7, 71.3, 67.8, 40.5, 35.3, 19.8, 13.5.

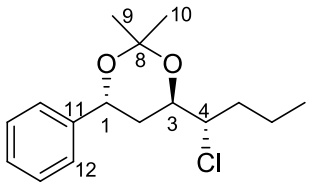
IR (thin film): 3404, 2956, 1281, 1178, 1386, 1054 cm^{-1}

Exact mass calcd for $C_{13}H_{18}ClO$: 225.1046 (M-H_2O+H); found: 225.1047 (M-H_2O+H).

$[\alpha]_D^{25}$: -21.8 (c = 1.2, $CHCl_3$).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by analysis of the ^{1}H and ^{13}C NMR spectra derived from the corresponding acetonide (**197**).

To a solution of the diol (**195**) (10 mg, 0.041 mmol) in dimethoxypropane (3 mL) was added 2 drops of conc. HCl and the reaction mixture was stirred for five hours. After this time the reaction mixture was treated with saturated aqueous sodium bicarbonate (5 mL), diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2, passed through a short plug of silica gel and concentrated to afford the acetonide (**197**).



^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.27 (m, 5H), 4.90 (dd, 1H, *J* = 6.0, 9.6 Hz, H-1), 3.94 (m, 1H, H-3), 3.76 (ddd, 1H, J = 3.0, 7.2, 10.2 Hz, H-4), 2.01 (m, 2H, H-2), 1.67-1.46 (m, 4H), 1.45 (s, 6H, H-9/H-10), 0.94 (t, 3H, *J* = 7.2 Hz, H-7).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.0 (C11), 128.5, 127.7, 126.0, 101.2 (C8), 71.9 (C3), 69.0 (C1), 65.1 (C4), 36.4 (C2), 25.0/24.6 (C9/C10), 19.2, 16.8, 13.6 (C1)

Preparation of (1*S*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (196)

Procedure A:

To a cold (-10 °C) solution of (3*R*,4*S*)-4-chloro-3-hydroxy-1-phenylheptan-1-one (**194**) (65 mg, 0.27 mmol) in THF (3 mL) was added catecholborane (1.00 M soln. in THF, 1.35 mL, 1.35 mmol) and the reaction mixture was stirred at -10 °C for 24 hours. After this time, the solution was treated with methanol (1 mL) and saturated sodium tartrate (1 mL) and stirred for two hours at room temperature. The mixture was then diluted with ether (20 mL), washed with brine (12 x 5 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude brown solid. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (1*S*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**196**) (58 mg, 88%, d.r. 20:1) as a white solid.

Procedure B:

To a cold (-78 °C) solution of (3*R*,4*S*)-4-chloro-3-hydroxy-1-phenylheptan-1-one (**194**) (200 mg, 0.83 mmol) in THF (16 mL) was added diisobutylaluminum hydride (1.00 M soln. in THF, 2.07 mL, 2.07 mmol) and the reaction mixture was stirred for three hours. After this time, an aqueous solution of HCl (1.0 M soln., 5.0 mL) was added, the mixture was diluted with ether (20 mL) and the phases were separated. The aqueous phase was extracted with ether (15 ml), and the combined organic phases were washed with water (3 x 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (1*S*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**196**) (200 mg, >97%, d.r. 11:1) as a white solid (m.p. 93-94 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36-7.28 (m, 5H), 4.91 (dd, 1H, *J* = 4.5, 8.5 Hz), 3.98 (m, 1H), 3.90 (dt, 1H, *J* = 3.9, 9.6 Hz), 3.65 (s, 1H), 3.51 (s, 1H), 2.00-1.91 (m, 2H), 1.76-1.57 (m, 3H), 1.38 (m, 1H), 0.92 (t, 3H, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 143.9, 128.6, 127.8, 125.7, 75.2, 74.8, 67.4, 41.1, 34.9, 19.7, 13.5.

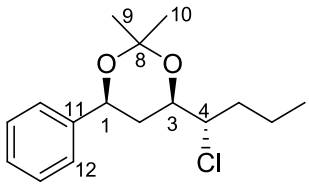
IR (thin film): 3378, 2959, 2391, 2289, 1673, 1560, 1087 cm^{-1}

Exact mass calcd for $C_{13}H_{18}ClO$: 225.1046 (M-H_2O+H); found: 225.1027 (M-H_2O+H).

$[\alpha]_D^{25}$: 17.8 (c = 2.2, $CHCl_3$).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by analysis of the ^{1}H and ^{13}C NMR spectra derived from the corresponding acetonide (**198**).

To a solution of the diol (**196**) (10 mg, 0.041 mmol) in dimethoxypropane (3 mL) was added 2 drops of conc. HCl and the reaction mixture was stirred for five hours then treated with saturated aqueous sodium bicarbonate (5 mL), diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in CH_2Cl_2, passed through a short plug of silica gel and concentrated to afford the acetonide (**198**).



^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39-7.28 (m, 5H), 4.92 (dd, 1H, *J* = 3.0, 12.0 Hz, H-1), 3.99 (m, 1H, H-3), 3.77 (ddd, 1H, J = 3.0, 7.2, 10.2 Hz, H-4), 2.10 (m, 1H, H-2), 1.95 (m, 1H, H-2), 1.69-1.58 (m, 4H), 1.56 (s, 3H, H-9/H-10), 1.51 (s, 3H, H-9/H-10), 0.95 (t, 3H, *J* = 7.2 Hz, H-7).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.1, 128.4, 127.6, 126.1, 99.5 (C8), 72.3 (C3), 71.5 (C1), 65.1 (C4), 36.4 (C2), 30.1 (C9/C10), 19.2 (C9/C10), 19.2, 16.8, 13.6 (C1).

Preparation of (1*R*,3*R*,4*R*)-3,4-epoxy-1-phenylheptan-1-ol (199)

To a solution of (1*R*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**195**) (50 mg, 0.21 mmol) in ethanol (7.5 mL) was added potassium hydroxide (18 mg, 0.32 mmol) and the reaction mixture was stirred for 1.five hours. The resultant yellow solution was then diluted with pentane (20 mL) and brine (20 mL), and the phases were separated. The aqueous phase was extracted with pentane (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes:ethyl acetate) afforded (1*R*,3*R*,4*R*)-3,4-epoxy-1-phenylheptan-1-ol (**199**) (39 mg, 99%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.35-7.24 (m, 5H), 4.88 (d, 1H, *J* = 9.0 Hz), 2.91 (m, 1H), 2.85 (br s, 1H), 2.78 (m, 1H), 2.08 (m, 1H), 1.79 (m, 1H), 1.49-1.38 (m, 4H), 0.95 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 144.1, 128.4, 127.4, 125.5, 71.7, 58.7, 56.2, 40.9, 33.9, 19.2, 13.9.

IR (neat): 3389, 2959, 2872, 1603, 1493, 1454, 1197, 1050 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1364 (M+H).

$[\alpha]_D^{25}$: -5.2 (c = 2.0, $CHCl_3$).

Preparation of (1*S*,3*R*,4*R*)-3,4-epoxy-1-phenylheptan-1-ol (200)

To a solution of (1*S*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**196**) (200 mg, 0.82 mmol) in ethanol (25 mL) was added potassium hydroxide (72 mg, 1.2 mmol) and the reaction mixture was stirred for five hours. The resulting yellow solution was then diluted

with pentane (50 mL) and brine (20 mL), and the phases were separated. The aqueous phase was extracted with pentane (3 x 20 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes:ethyl acetate) afforded (1*S*,3*R*,4*R*)-3,4-epoxy-1-phenylheptan-1-ol (**200**) (160 mg, 99%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.27 (m, 5H), 4.91 (t, 1H, *J* = 7.2 Hz), 2.75 (ddd, 1H, *J* = 2.4, 4.2, 7.2 Hz), 2.67 (ddd, 1H, *J* = 2.4, 5.4, 7.2 Hz), 2.61 (s, 1H), 2.02 (dt, 1H, J = 5.4, 13.8 Hz), 1.90 (m, 1H), 1.47-1.35 (m, 4H), 0.93 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.8, 128.5, 127.7, 125.8, 72.8, 58.5, 56.5, 41.4, 33.8, 19.2, 13.9.

IR (neat): 3378, 2959, 2917, 2875, 2391, 2289, 1560 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1402 (M+H).

$[\alpha]_D^{25}$: -8.1 (c = 2.2, $CHCl_3$).

Preparation of (2*S*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (203)

To a solution of (1*R*,3*R*,4*R*)-3,4-epoxy-1-phenylheptan-1-ol (**199**) (50 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added boron trifluoride etherate (0.10 M soln. in CH_2Cl_2, 0.24 mL, 0.024 mmol). The reaction mixture was stirred for two hours and then treated with water (1 mL), diluted with CH_2Cl_2 (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were washed with brine (4 x 10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (2*S*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**203**) (46 mg, 92%) as a light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39 (d, 2H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.8 Hz), 7.26 (t, 1H, J = 7.2 Hz), 5.05 (t, 1H, *J* = 7.2 Hz), 4.15 (dd, 1H, *J* = 5.4, 10.2 Hz), 3.99 (m, 1H), 2.66 (dt, 1H, *J* = 7.2, 12.6 Hz), 1.96 (ddd, 1H, *J* = 5.4, 7.2, 12.6 Hz), 1.83 (br s, 1H), 1.59-1.41 (m, 4H), 0.98 (t, 3H, *J* = 7.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.3, 128.4, 127.3, 125.6, 85.6, 78.3, 76.8, 43.4, 35.3, 19.1, 14.1.

IR (neat): 3419, 3029, 2958, 2870, 1604, 1493, 1455, 1329, 1011 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1396 (M+H).

$[\alpha]_D^{25}$: -8.3 (c = 0.8, $CHCl_3$).

Preparation of (2*R*,3*S*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (*ent*-203)

To a cold (0 °C) stirred solution of (2*S*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**206**) (52 mg, 0.25 mmol) in THF (2 mL) was added *p*-nitrobenzoic acid (170 mg, 1.00 mmol) and triphenylphosphine (260 mg, 1.0 mmol). While maintaining the temperature below 10 °C, diethyl azodicarboxylate (0.16 mL, 1.0 mmol) was added dropwise. The reaction mixture was allowed to stir for 24 hours at room temperature and was then warmed to 40 °C for three hours. The resulting solution was diluted with diethyl ether (5 mL), washed with sodium bicarbonate (10 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL), and the combined organic layers washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the *p*-nitrobenzoate ester of **206** (67 mg, 75%) that required no further purification.

To the *p*-nitrobenzoate ester of **206** (6 mg, 0.02 mmol) dissolved in 1:1 methanol:water (1.0 mL) was added lithium hydroxide (0.5 mg, 0.02 mmol) and the mixture was stirred at room temperature for 24 hours. The resulting solution was then diluted with ether (10 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL), and the combined organic phases were washed with

brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (2*R*,3*S*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (*ent*-**203**) (3 mg, 90%) as a light yellow oil.

$[\alpha]_D^{25}$: 8.8 (c = 2.0, $CHCl_3$).

Preparation of (2*S*,3*R*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (204)

To a stirred solution of (1*S*,3*R*,4*R*)-3,4-epoxy-1-phenylheptan-1-ol (**196**) (210 mg, 1.0 mmol) in CH_2Cl_2 (25 mL) was added boron trifluoride etherate (0.10 M soln. in CH_2Cl_2, 1.0 mL, 0.10 mmol). The reaction mixture was stirred for two hours and then treated with water (5 mL), diluted with CH_2Cl_2 (50 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL), and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (2*S*,3*R*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**204**) (200 mg, >97%) as a light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.36-7.25 (m, 5H), 5.12 (dd, 1H, *J* = 5.4, 10.2 Hz), 4.17 (d, 1H, *J* = 2.4 Hz)), 3.91 (ddd, 1H, *J* = 2.4, 5.4, 7.8 Hz), 2.21 (tdd, 1H, *J* = 1.8, 5.4, 14.4 Hz), 1.97 (m, 1H), 1.67-1.46 (m, 4H), 0.99 (t, 3H, *J* = 7.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.1, 128.3, 127.4, 125.9, 87.1, 79.5, 76.8, 44.0, 36.5, 19.1, 14.1.

IR (neat): 3419, 3053, 2959, 2860, 1455, 1265, 1089 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1372 (M+H).

$[\alpha]_D^{25}$: 4.0 (c = 2.2, $CHCl_3$).

Preparation of (2*R*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (207)

To a cold (0 °C), stirred solution of (1*R*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**195**) (85 mg, 0.35 mmol) in THF (10 mL) was added silver trifluoromethanesulfonate (110 mg, 0.35 mmol) and silver oxide (96 mg, 0.35 mmol) and the reaction mixture was allowed to slowly warm to room temperature over 20 hours. The resulting suspension was then filtered through Celite and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (2*R*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**207**) (60 mg, 83%) as a light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40 (d, 2H, *J* = 7.8 Hz), 7.34 (t, 2H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 7.2 Hz), 4.87 (dd, 1H, *J* = 6.0 Hz, 8.4 Hz), 4.27 (m, 1H), 3.76 (ddd, 1H, *J* = 9.6, 7.2, 9.6 Hz), 2.70 (ddd, 1H, *J* = 6.0, 8.4, 13.8 Hz), 1.92 (ddd, 1H, *J* = 1.8, 6.0, 13.8 Hz), 1.79 (m, 1H), 1.72 (m, 1H), 1.60-1.44 (m, 3H), 1.00 (t, 3H, *J* = 7.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.0, 128.4, 127.3, 125.9, 83.6, 78.7, 73.1, 44.2, 30.9, 19.6, 14.3.

IR (neat): 3418, 3063, 2957, 2871, 1493, 1455, 1330, 1089 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1376 (M+H).

$[\alpha]_D^{25}$: -3.7 (c = 0.5, $CHCl_3$).

Preparation of (2*S*,3*S*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (*ent*-207)

To a cold (0 °C) stirred solution of (2*S*,3*R*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**204**) (5 mg, 0.3 mmol) in THF (1 mL) was added *p*-nitrobenzoic acid (16 mg, 0.10 mmol) and triphenylphosphine (25 mg, 0.10 mmol). While maintaining the temperature below 10 °C, diethyl azodicarboxylate (0.02 mL, 0.10 mmol) was added dropwise. The reaction mixture was allowed to stir for nine hours at room temperature and was then warmed to 40 °C for one hour. The resulting solution was diluted with diethyl ether (5

mL), washed with sodium bicarbonate (10 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL), and the combined organic layers washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide the crude *p*-nitrobenzoate ester of **204** that required no further purification.

To the *p*-nitrobenzoate ester of **204** (3 mg, 0.01 mmol) dissolved in 1:1 methanol:water (0.5 mL) was added lithium hydroxide (0.3 mg, 0.01 mmol) and the mixture was stirred at room temperature for 10 hours. The resulting solution was then diluted with ether (10 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (2*S*,3*S*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (*ent*-**207**) (2 mg, 32% over two-steps) as a light yellow oil.

$[\alpha]_D^{25}$: -3.5 (c = 0.2, $CHCl_3$).

Preparation of (2*R*,3*R*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (206)

To a cold (0 °C), stirred solution of (1*S*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**196**) (180 mg, 0.72 mmol) in THF (40 mL) was added silver trifluoromethanesulfonate (190 mg, 0.72 mmol) and silver oxide (170 mg, 0.72 mmol) and the reaction mixture was allowed to slowly warm to room temperature over 12 hours. The resulting suspension was then filtered through Celite and concentrated to provide crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (2*R*,3*R*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**206**) (135 mg, 90%) as a light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34-7.23 (m, 5H), 5.26 (dd, 1H, *J* = 6.6, 9.6 Hz), 4.36 (d, 1H, *J* = 1.8 Hz), 4.06 (ddd, 1H, *J* = 3.0, 7.2, 9.6 Hz), 2.45 (dd, 1H, 6.6, 7.2 Hz), 2.08

(ddd, 1H, J = 4.2, 9.6, 13.8 Hz), 1.75 (m, 1H), 1.64 (m, 2H), 1.56 (m, 2H), 1.47 (m, 1H), 1.69-1.45 (m, 4H), 1.01 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.8, 128.4, 127.2, 125.3, 83.1, 78.2, 73.7, 44.7, 31.3, 19.7, 14.3.

IR (neat): 3423, 3063, 2957, 2871, 1455, 1330, 1089 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1364 (M+H).

$[\alpha]_D^{25}$: 23.3 (c = 2.5, $CHCl_3$).

Preparation of (2*S*,3*S*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (*ent*-206)

To a cold (0 °C), stirred solution of (2*S*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**203**) (50 mg, 0.24 mmol) in THF (2 mL) was added *p*-nitrobenzoic acid (170 mg, 1.0 mmol) and polymer supported triphenylphosphine (3.0 mmol/g, 330 mg, 1.0 mmol). While maintaining the temperature below 10 °C, diethyl azodicarboxylate (0.16 mL, 1.0 mmol) was added dropwise. The reaction mixture was allowed to stir for 24 hours at room temperature and was then warmed to 40 °C for three hours. The resulting solution was diluted with diethyl ether (5 mL), washed with sodium bicarbonate (10 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to yield the *p*-nitrobenzoate ester of **203**, which was used without further purification. To the *p*-nitrobenzoate ester dissolved in 1:1 methanol:water (40 mL) was added lithium hydroxide (5 mg, 0.2 mmol) and the resulting mixture was stirred at room temperature for 24 hours. The resulting solution was then diluted with ether (50 mL) and the phases were separated. The aqueous phase was extracted with ether (3 x 25 mL), and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to provide crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded

(2*S*,3*S*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (*ent*-**206**) (25 mg, 50% over two-steps) as a light yellow oil.

$[\alpha]_D^{25}$: -24.1 (c = 2.0, $CHCl_3$).

Preparation of (2*R*)-2-chloroheptanal (209)

To a cold (0 °C), stirred solution of heptanal (11.4 g, 100 mmol) in CH_2Cl_2 (200 mL), was added L-prolinamide (**16**) (1.10 g, 10.0 mmol) and *N*-chlorosuccinimide (**12**) (13.4 g, 100 mmol). The reaction mixture was stirred for one hour and then allowed to slowly warm to room temperature over the course of three hours at which temperature it was stirred until complete consumption of heptanal (as determined by ^{1}H NMR spectroscopy). After this time, the mixture was diluted with pentane (200 mL), cooled to -78 °C, filtered through a fritted funnel, and concentrated on a rotary evaporator. The resulting oil was distilled under vacuum (1 mm Hg) at 40 °C to give (2*R*)-2-chloroheptanal (**209**) (14.2 g, 96% yield, 84% enantiomeric excess) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.49 (d, 1H, *J* = 2.4 Hz), 4.16 (ddd, 1H, *J* = 2.4, 5.4, 8.2 Hz), 1.97 (m, 1H), 1.82 (m, 1H), 1.57-1.41(m, 2H), 1.32 (m, 4H), 0.90 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 195.6, 64.2, 32.2, 31.3, 25.4, 22.6, 14.1.

IR (neat): 2961, 2935, 2874, 1708, 1466, 1380, 1149, 1096 cm^{-1}

Exact mass calcd for $C_7H_{14}ClO$: 149.0733 (M+H); found: 149.0670 (M+H).

$[\alpha]_D^{25}$: 23.4 (c = 1.51, $CHCl_3$)

The enantiomeric excess of **209** was determined by chiral GC analysis of the corresponding epoxide.

A solution of (2*R*)-2-chloroheptanal (**209**) (150 mg, 1.0 mmol) and $NaBH_4$ (76 mg, 2.0 mmol) in MeOH (15 mL) was stirred at room temperature for one hour. The reaction mixture was treated with water (5 mL) and diluted with diethyl ether (15 mL) and the phases were separated. The organic phase was dried ($MgSO_4$), filtered, and

concentrated to afford the corresponding alcohol. To the alcohol (25 mg, 0.18 mmol) in ethanol (3 mL) was added potassium hydroxide (15 mg, 0.26 mmol) and the reaction mixture was stirred for one hour. The resulting yellow solution was then diluted with pentane (10 mL) and washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to afford (2*S*)-1,2-epoxyheptane. (Temperature program: 30 °C held for 35 minutes then increased by 5 °C per minute to 80 °C and run for 10 minutes. Retention time = 32.0 ((*R*)-enantiomer); 32.5 ((*S*)-enantiomer).

$[\alpha]_D^{25}$: -9.2 (c = 1.0, $CHCl_3$) (lit.[78] $[\alpha]_D^{25}$: -9.46 (c = 0.43, $CHCl_3$)).

Preparation of (6*R*,7*S*)-6-chloro-7-hydroxynonadec-18-en-9-one (211)

To a cold (-78 °C), stirred solution of diisopropyl amine (0.51 mL, 3.6 mmol) in THF (15 mL) was added *n*-butyllithium (2.25 M soln. in hexane, 1.60 mL, 3.60 mmol), and the mixture was allowed to stir for 30 minutes at -78 °C, followed by 15 minutes at 0 °C. The reaction mixture was then cooled (-78 °C) and dodec-11-en-2-one[79] (**210**) (550 mg, 3.00 mmol) was added in one portion. After an additional 90 minutes, a solution of (2*R*)-2-chloroheptanal (**209**) (540 mg, 3.60 mmol) in THF (0.5 mL) was then added dropwise over 15 minutes at -78 °C and the reaction mixture was stirred for 30 minutes. After this time the reaction mixture was treated with saturated aqueous NH_4Cl (5 ml), diluted with ethyl acetate (20 ml) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 ml), and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded (6*R*,7*S*)-6-chloro-7-hydroxynonadec-18-en-9-one (**211**) (874 mg, 88%) as a white solid (m.p. 30 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.80 (tdd, 1H, *J* = 6.5, 10.5, 17.5 Hz), 4.98 (dd, 1H, *J* = 1.5, 17.5 Hz), 4.92 (dd, 1H, *J* = 1.5, 10.5 Hz), 4.09 (m, 1H), 3.90 (ddd, 1H, *J* = 3.0, 6.0,

9.5 Hz), 3.31 (d, 1H, *J* = 5.5 Hz), 2.81 (dd, 1H, *J* = 3.0, 9.5 Hz), 2.74 (dd, 1H, *J* = 8.5, 9.5 Hz), 2.45 (t, 2H, *J* = 7.5 Hz), 1.99 (dd, 2H, *J* = 7.0, 15.0 Hz), 1.88 (m, 1H), 1.67-1.57 (m, 4H), 1.46-1.23 (m, 15H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 212.0, 139.1, 114.1, 70.9, 66.0, 44.8, 43.8, 33.81, 33.77, 31.2, 29.29, 29.26, 29.1, 29.0, 28.9, 26.0, 23.5, 22.5, 14.0.

IR (thin film): 3416, 2921, 2852, 1698, 1087 cm^{-1}

Exact mass calcd for $C_{19}H_{36}ClO_2$: 331.2404 (M+H); found: 331.2402 (M+H).

$[\alpha]_D^{25}$: 7.8 (c = 0.7, $CHCl_3$).

Preparation of (6*R*,7*S*,9*R*)-6-chlorononadec-18-en-7,9-diol (212)

A solution of tetramethylammonium triacetoxyborohydride (2.55 g, 9.68 mmol) dissolved in a 1:2 mixture of glacial acetic acid:acetonitrile (33 mL) was stirred at room temperature for 30 minutes, then cooled to -40 °C. A solution of (6*R*,7*S*)-6-chloro-7-hydroxynonadec-18-en-9-one (**211**) (400 mg, 1.21 mmol) in acetonitrile (5 mL) was then added in one portion and the reaction mixture was stirred for 12 hours at -40 °C. After this time, saturated aqueous sodium tartrate (5 ml) was added, the mixture was diluted with ether (25 ml) and the phases were separated. The aqueous phase was extracted with ether (3 x 15 ml), and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 1:1 pentane:diethyl ether) afforded (6*R*,7*S*,9*R*)-6-chlorononadec-18-en-7,9-diol (**212**) (374 mg, 92%, d.r. 9:1) as a white solid (m.p. 46 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.6, 10.2, 17.4 Hz), 4.98 (dd, 1H, *J* = 1.8, 17.4 Hz), 4.92 (dd, 1H, *J* = 1.8, 10.2 Hz), 4.02-3.94 (m, 3H), 2.03 (dd, 2H, *J* = 7.8, 14.4 Hz), 1.88-1.78 (m, 2H), 1.71-1.56 (m, 4H), 1.55-1.45 (m, 2H), 1.42-1.26 (m, 15H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.2, 114.1, 71.9, 69.2, 68.2, 38.3, 37.7, 33.8, 33.3, 31.3, 29.55, 29.51, 29.4, 29.1, 28.9, 26.3, 25.7, 22.5, 14.0.

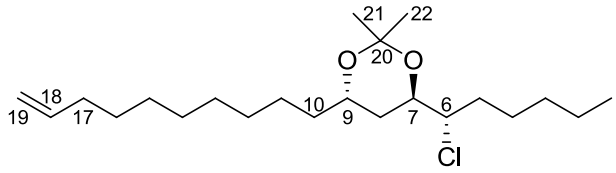
IR (thin film): 3279, 2919, 2849, 1699, 1088 cm^{-1}

Exact mass calcd for $C_{19}H_{38}ClO_2$: 333.2560 (M+H); found: 333.2542 (M+H).

$[\alpha]_D^{25}$: 6.8 (c = 1.5, $CHCl_3$).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by analysis of the ^{1}H and ^{13}C NMR spectra derived from the corresponding acetonide **213**.

To a solution of the diol (**212**) (10 mg, 0.025 mmol) in dimethoxypropane (3 mL) and acetone (3 mL) was added *p*-toluenesulfonic acid (1 mg, 0.006 mmol) and the reaction mixture was stirred for five hours. After this time the reaction mixture was treated with saturated aqueous sodium bicarbonate (5 mL), diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2, passed through a short plug of silica gel and concentrated to afford the acetonide **213**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.6, 10.2, 17.4 Hz, H-18), 4.98 (dd, 1H, *J* = 1.8, 17.4 Hz, H-19), 4.92 (dd, 1H, *J* = 1.8, 10.2 Hz, H-19), 3.85-4.02 (m, 2H, H-9/H-7), 3.55 (m, 1H, H-6), 2.30 (m, 2H, H-17), 1.88-2.07 (m, 2H, H-8), 1.67-1.36 (m, 22H), 1.32 (s, 6H, H-21/H-22), 0.92 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.1 (C18), 114.1 (C19), 101.9 (C20), 72.1 (C7), 71.3 (C9), 68.7 (C6), 33.53, 33.51, 33.4, 33.0, 31.3, 31.2, 30.9, 30.7, 27.2, 27.0, 26.4/26.3 (C21/C22), 23.1, 22.5, 14.0.

Preparation of (2*S*,3*S*,5*R*)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (214)

To a cold (-78 °C), stirred solution of (6*R*,7*S*,9*R*)-6-chlorononadec-18-en-7,9-diol (**212**) (33 mg, 0.10 mmol) in THF (5 mL) was added silver trifluoromethanesulfonate (26 mg, 0.10 mmol) and silver oxide (23 mg, 0.10 mmol) and the reaction mixture was allowed to slowly warm to room temperature over 20 hours. The resulting suspension was then filtered through Celite and concentrated to provide crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:2 pentane:diethyl ether) afforded (2*S*,3*S*,5*R*)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (**214**) (28 mg, 91%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.6, 10.2, 17.4 Hz), 4.98 (dd, 1H, *J* = 1.8, 17.4 Hz), 4.92 (dd, 1H, *J* = 1.8, 10.2 Hz), 4.15 (m, 1H), 3.75 (m, 1H), 3.49 (dt, 1H, *J* = 3.6, 7.2 Hz), 2.37 (ddd, 1H, J = 6.6, 7.8, 14.4 Hz), 2.03 (m, 1H), 1.72-1.59 (m, 3H), 1.53-1.49 (m, 2H), 1.47-1.28 (m, 18H), 0.89 (t, 3H, *J* = 6.6 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.2, 114.1, 83.1, 77.6, 72.9, 41.8, 36.8, 33.8, 32.0, 29.6, 29.5, 29.4, 29.1, 28.9, 28.6, 26.2, 26.0, 22.6, 14.0.

IR (neat): 3316, 2920, 2882, 2875, 1612, 1499, 1491, 1281, 1080 cm^{-1}

Exact mass calcd for $C_{19}H_{37}O_2$: 297.2794 (M+H); found: 297.2795 (M+H).

$[\alpha]_D^{25}$: 5.5 (c = 2.7, $CHCl_3$).

Preparation of (6*S*,7*S*,9*R*)-6,7-epoxynonadec-18-en-9-ol (215)

To a stirred solution of (6*R*,7*S*,9*R*)-6-chlorononadec-18-en-7,9-diol (**212**) (100 mg, 0.30 mmol) in ethanol (6 mL) was added potassium hydroxide (25 mg, 0.45 mmol) and the reaction mixture was allowed to stir for 1.five hours. The resulting yellow solution was then diluted with (15 mL) and brine (10 mL). The aqueous phase was extracted with pentane (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide colourless oil. Purification of the crude product by flash chromatography (silica gel, 2:1 pentane:diethyl ether) afforded (6*S*,7*S*,9*R*)-6,7-epoxynonadec-18-en-9-ol (**215**) (80 mg, 99%)[80] as a white foam.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.6, 10.2, 17.4 Hz), 4.98 (dd, 1H, *J* = 1.8, 17.4 Hz), 4.92 (dd, 1H, *J* = 1.8, 10.2 Hz), 3.78 (m, 1H), 2.89 (ddd, 1H, *J* = 2.4, 4.2, 6.6 Hz), 2.81 (dt, 1H, *J* = 2.4, 5.4 Hz), 2.11 (br s, 1H), 2.03 (dd, 2H, *J* = 6.6, 14.4 Hz), 1.80 (ddd, 1H, *J* = 4.2, 8.4, 14.4 Hz), 1.62 (ddd, 1H, J = 3.0, 6.0, 14.4 Hz), 1.55-1.25 (m, 22H), 0.89 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.2, 114.1, 69.4, 58.5, 56.6, 38.5, 37.6, 33.8, 32.0, 31.6, 29.6, 29.5, 29.4, 29.1, 28.9, 25.62, 25.55, 22.6, 14.0.

IR (thin film): 3409, 2924, 2852, 1456 cm^{-1}

Exact mass calcd for $C_{19}H_{37}O_2$: 297.2794 (M+H); found: 297.2797 (M+H).

$[\alpha]_D^{25}$: -12.2 (c = 2.5, $CHCl_3$).

Preparation of (2*R*,3*S*,5*R*)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (216)

To a solution of (6*S*,7*S*,9*R*)-6,7-epoxynonadec-18-en-9-ol (**215**) (30 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added boron trifluoride etherate (0.10 M soln. in CH_2Cl_2, 0.10 mL, 0.010 mmol) and the reaction mixture was allowed to stir for two hours and then treated with water (5 mL). The resulting solution was diluted with CH_2Cl_2 (10 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10

mL), and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:2 pentane:diethyl ether) afforded (2*R*,3*S*,5*R*)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (**216**) (27 mg, 91%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.6, 10.2, 17.4 Hz), 4.98 (dd, 1H, *J* = 1.8, 17.4 Hz), 4.92 (dd, 1H, *J* = 1.8, 10.2 Hz), 4.04 (dd, 1H, *J* = 5.4, 10.8), 3.95 (dt, 1H, *J* = 7.2, 13.2 Hz), 3.74 (m, 1H), 2.34 (dt, 1H, *J* = 7.2, 12.6 Hz), 2.03 (dd, 2H, *J* = 6.6, 14.4 Hz), 1.75 (br s, 1H), 1.54 (m, 1H), 1.67 (m, 1H), 1.55 (dd, 1H, J = 5.4, 7.2, 12.6 Hz), 1.51-1.42 (m, 4H), 1.40-1.25 (m, 18H), 0.88 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.2, 114.1, 84.8, 77.0, 76.7, 40.8, 36.6, 33.8, 33.0, 31.9, 29.6, 29.5, 29.4, 29.1, 28.9, 26.1, 25.6, 22.6, 14.0.

IR (neat): 3388, 2920, 2912, 2875, 1456, 1388, 1092 cm^{-1}

Exact mass calcd for $C_{19}H_{37}O_2$: 297.2794 (M+H); found: 297.2786 (M+H).

$[\alpha]_D^{25}$: 13.2 (c = 3.0, $CHCl_3$).

Preparation of (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (218)

To a cold (-78 °C), stirred solution of diisopropyl amine (2.70 ml, 19.5 mmol) in THF (100 mL) was added *n*-butyllithium (7.50 mL 19.5 mmol, 2.60 M soln. in hexane). This solution was stirred for 45 minutes at -78 °C, warmed to 0 °C for 15 minutes and then cooled to -78 °C. To this solution was added *trans*-4-phenyl-3-buten-2-one (**217**) (2.20 g, 15.0 mmol) in THF (5 mL), the solution was stirred for 45 minutes at -78 °C, warmed to -40 °C for 15 minutes and then cooled to -78 °C. After this time (2*R*)-2-chloroheptanal (**209**) (2.67 g, 18.0 mmol) in THF (10 mL) was added dropwise over 12 minutes and the reaction mixture was stirred for one hour at -78 °C then treated with saturated aqueous NH_4Cl (15 mL) and allowed to warm to room temperature. The resulting mixture was diluted with diethyl ether (100 mL) and the phases were separated.

The aqueous phase was extracted with diethyl ether (3 x 25 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give the crude chlorohydrin. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes: ethyl acetate) afforded (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (**218**) (3.90 g, 93%) as a white solid (m.p. = 51-53 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.61 (d, 1H, *J* = 16.1 Hz), 7.57 (m, 2H), 7.41 (m, 3H), 6.76 (d, 1H, *J* = 16.1 Hz), 4.21 (m, 1H), 3.98 (ddd, 1H, *J* = 3.1, 6.2, 9.4 Hz), 3.52 (d, 1H, *J* = 4.8 Hz), 3.12 (dd, 1H, *J* = 2.8, 17.4 Hz), 3.03 (dd, 1H, *J* = 8.5, 17.4 Hz) 1.95 (m, 1H), 1.70 (m, 1H), 1.63 (m, 1H), 1.42 (m, 1H), 1.33 (m, 4H), 0.90 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 200.5, 144.3, 134.3, 131.1, 129.3, 128.7, 126.4, 71.4, 66.3, 43.0, 34.1, 31.5, 26.2, 22.7, 14.2.

IR (thin film): 3424, 2950, 2923, 2860, 1659, 1449, 1380, 1177, 1073 cm^{-1}

Exact mass calcd. for $C_{17}H_{24}ClO_2$: 295.1465 (M+H); found: 295.1468 (M+H).

$[\alpha]_D^{25}$: -11.1 (c= 1.51, $CHCl_3$).

Preparation of (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (220)

A solution of tetramethylammonium triacetoxyborohydride (714 mg, 2.70 mmol) dissolved in a 1:1.5 mixture of glacial acetic acid: acetonitrile (25 mL) was stirred at room temperature for 30 minutes and then cooled to -40 °C, (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (**218**) (100 mg, 0.34 mmol) was added as a solution in acetonitrile (5 mL) and the resulting mixture was stirred for 24 hours at -40 °C. After this time, saturated aqueous sodium tartrate (10 ml) was slowly added and the reaction mixture was diluted with ethyl acetate (20 ml) and washed with brine (10 ml). The aqueous phases were extracted with ethyl acetate (4 x 15 ml), the combined organic phases were dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl

acetate) afforded (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**220**) (98 mg, 98%, 10:1 d.r.) as a white solid (m.p. = 88-90 °C).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.39 (d, 2H, *J* = 7.5Hz), 7.33 (t, 2H, *J* = 7.4 Hz), 7.25 (t,1H, *J* = 7.3 Hz), 6.65 (d, 1H, *J* = 15.9 Hz), 6.28 (dd, 1H, *J* = 6.1, 15.9 Hz), 4.69 (m, 1H), 4.09 (dddd, 1H, *J* = 2.3, 4.6, 6.5, 9.1 Hz), 4.02 (m, 1H), 2.75 (dd, 1H, *J* = 1.4, 6.5 Hz), 2.33 (m, 1H), 1.97 (m, 1H), 1.85-1.79 (m, 2H), 1.73-1.58 (m, 2H), 1.43-1.24 (m, 5H), 0.90 (t, 3H, *J* = 7.0 Hz).

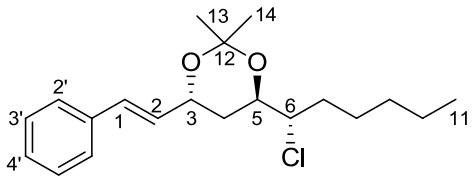
^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.7, 131.8, 130.5, 128.9, 128.0, 126.7, 72.0, 70.3, 68.4, 38.7, 33.4, 31.5, 26.5, 22.7, 14.2.

IR (thin film): 3406, 2955, 2927, 1646, 1049, 967 cm^{-1}

Exact mass calcd. for $C_{17}H_{26}ClO_2$: 297.1621 (M+H); found: 297.1614 (M+H).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by analysis of the ^{1}H and ^{13}C NMR spectra derived from the corresponding acetonide **222**.

To a stirred solution of the diol (**220**) (10 mg, 0.034 mmol) in dimethoxypropane (3 mL) at room temperature was added 2 drops of conc. HCl. After four hours, the reaction mixture was treated with saturated aqueous sodium bicarbonate (5 mL), diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2 and passed through a short plug of silica gel to afford the acetonide **222**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.6 Hz, H-2'), 7.31 (t, 2H, *J* = 7.4 Hz, H-3'), 7.23 (tt, 1H, *J* = 1.1, 7.4 Hz, H-4'), 6.58 (d, 1H, *J* = 15.8 Hz, H-1), 6.23 (dd, 1H, *J* = 6.2, 15.8 Hz, H-2), 4.52 (m, 1H, H-3), 3.95 (td, 1H, *J* = 6.5, 8.7 Hz, H-5), 3.89 (m, 1H, Hz, H-6), 2.01 (m, 2H, H-7), 1.89 (m, 1H, H-4), 1.63 (m, 1H, H-4), 1.44 (s, 3H, H-13), 1.43 (s, 3H, H-14), 1.36 – 1.24 (m, 6H), 0.91 (t, 3H, *J* = 7.1 Hz, H-11).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.8 (C1'), 130.9 (C1), 129.6 (C2), 128.7 (C3'), 127.9 (C4'), 126.7 (C2'), 101.2 (C12), 69.6 (C5), 68.1 (C3), 65.8 (C6), 35.4 (C7), 34.1 (C4), 31.6, 25.9, 25.5 (C13), 24.9 (C14), 22.8, 14.2 (C11).

Preparation of (1*E*,3*R*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (221)

To a cold (-40 °C), stirred solution of (1*E*,5*S*,6*R*)-6-chloro-5-hydroxy-1-phenylundec-1-en-3-one (**218**) (200 mg, 0.68 mmol) in dry THF (5.5 mL) was added catecholborane (3.4 mL, 3.4 mmol, 1.0 M solution in THF). The reaction mixture was stirred for 24 hours then treated with saturated aqueous sodium tartrate (2 mL) and MeOH (2 mL) and allowed to stir at room temperature for an additional two hours. The mixture was then diluted with diethyl ether (10 mL) and the phases were separated. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Excess catechol was removed by flash column chromatography (silica gel, 2:1:0.3 hexanes:CH_2Cl_2:MeOH) to provide the crude diol. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*E*,3*R*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**221**) (145 mg, 72%, >20:1 d.r.) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.4 Hz), 7.32 (t, 2H, *J* = 7.4 Hz), 7.25 (t, 1H, *J* = 7.4 Hz), 6.63 (d, 1H, *J* = 16 Hz), 6.23 (dd, 1H, *J* = 6.7, 16 Hz), 4.58 (m, 1H), 4.01 (m, 1H), 3.93 (td, 1H, *J* = 3.5, 10.0), 3.36 (br. s, 1H), 2.97 (br. s, 1H), 1.92 (ddd, 1H, *J* =

2.3, 3.8, 14.5 Hz), 1.87-1.78 (m, 2H), 1.70 (m, 1H), 1.61 (m, 1H), 1.39 (m, 1H), 1.35-1.25 (m, 4H), 0.90 (t, 3H, *J* = 7.0 Hz).

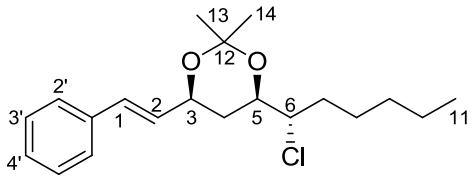
^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.6, 131.5, 130.8, 128.8, 128.1, 126.7, 75.1, 73.3, 68.1, 39.3, 33.2, 31.5, 26.5, 22.7, 14.2.

IR (thin film): 3385, 2955, 2859, 1493, 1449, 967 cm^{-1}

Exact mass calcd. for $C_{17}H_{26}ClO_2$: 297.1621 (M+H); found: 297.1640 (M+H).

The relative stereochemistry of the newly formed carbinol stereocentre was determined by analysis of the ^{1}H and ^{13}C NMR spectra derived from the corresponding acetonide **223**.

To a solution of the diol (**221**) (10 mg, 0.034 mmol) in dimethoxypropane (3 mL) was added 2 drops of conc. HCl at and the reaction mixture allowed to stir for four hours. After this time the reaction mixture was treated with saturated aqueous sodium bicarbonate (5 mL), diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 5 mL), washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in CH_2Cl_2, passed through a short plug of silica gel and concentrated to afford the corresponding acetonide **223**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.2 Hz, H-2'), 7.30 (t, 2H, *J* = 7.4 Hz, H-3'), 7.23 (tt, 1H, *J* = 1.2, 7.4 Hz, H-4'), 6.62 (d, 1H, *J* = 15.9 Hz, H-1), 6.19 (dd, 1H, *J* = 6.3, 15.8 Hz, H-2), 4.54 (dddd, 1H, *J* = 1.1, 2.5, 6.3, 11.5 Hz, H-3), 3.92 (ddd, 1H, *J* = 2.3, 7.3, 11.3 Hz, H-5), 3.75 (m, 1H, H-6), 1.99 (td, 1H, *J* = 2.5, 12.9, H-7), 1.96 (m, 1H,

H-4), 1.66 – 1.56 (m, 2H, H-4/H-8), 1.51 (s, 3H, H-13), 1.47 (s, 3H, H-14), 1.45–1.37 (m, 2H, H-7/H-8), 1.36 – 1.26 (m, 4H), 0.91 (t, 3H, *J* = 7.1 Hz, H-11).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.8 (C1'), 131.1 (C1), 129.8 (C2), 128.7 (C3'), 127.9 (C4'), 126.8 (C2'), 99.4 (C12), 72.0 (C5), 70.3 (C3), 65.7 (C6), 34.5 (C7), 33.7 (C4), 31.6, 30.2 (C13), 25.8, 22.7, 20.1 (C14), 14.2 (C11).

Preparation of (1*E*,3*S*,5*S*,6*S*)-5,6-epoxy-1-phenylundec-1-en-3-ol (224)

To a solution of (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**220**) (80 mg, 0.27 mmol) in ethanol (5.0 mL) was added potassium hydroxide (23 mg, 0.41 mmol) and the reaction mixture was stirred for 1.five hours. The resulting yellow solution was then diluted with pentane (20 mL), washed with brine (10 mL) and the phases were separated. The combined aqueous phases were extracted with pentane (3 x 10 mL), and the organic phases were combined, dried ($MgSO_4$), filtered, and concentrated to provide crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*E*,3*S*,5*S*,6*S*)-5,6-epoxy-1-phenylundec-1-en-3-ol (**224**) (66 mg, 94%)[81] as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.3Hz), 7.31 (t, 2H, *J* = 7.4 Hz), 7.24 (tt, 1H, *J* = 1.9, 7.2 Hz), 6.63 (d, 1H, *J* = 15.9 Hz), 6.26 (dd, 1H, *J* = 6.2, 15.9 Hz), 4.52 (m, 1H), 2.93 (ddd, 1H, *J* = 2.4, 4.1, 6.6 Hz), 2.82 (dt, 1H, *J* = 2.3, 5.6 Hz), 2.40 (br. s, 1H), 1.99 (ddd, 1H, *J* = 4.2, 8.3, 14.4 Hz), 1.76 (ddd, 1H, *J* = 3.9, 6.7, 14.4 Hz), 1.55 (m, 2H), 1.49-1.28 (m, 6H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.8, 131.8, 130.4, 128.8, 127.9, 126.7, 70.6, 58.9, 56.3, 39.2, 32.2, 31.8, 25.8, 22.8, 14.2.

IR (neat): 3417, 3059, 3027, 2956, 2928, 2857, 1600, 1579, 1494, 1465, 1292 cm^{-1}

Exact mass calcd. for $C_{17}H_{25}O_2$: 261.1855 (M+H); found: 261.1897 (M+H).

$[\alpha]_D^{25}$: -17.3 (c = 0.41, $CHCl_3$).

Preparation of (1*E*,3*R*,5*S*,6*S*)-5,6-epoxy-1-phenylundec-1-en-3-ol (225)

To a solution of (1*E*,3*R*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**221**) (100 mg, 0.34 mmol) in ethanol (10 mL) was added potassium hydroxide (29 mg, 0.51 mmol) and the reaction mixture was stirred for five hours. The resulting yellow solution was then diluted with pentane (20 mL) and washed with brine (10 mL). The combined aqueous phases were extracted with pentane (3 x 10 mL), the organic phases were combined, dried (MgSO4), filtered, and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (1*E*,3*R*,5*S*,6*S*)-5,6-epoxy-1-phenylundec-1-en-3-ol (**225**) (85 mg, 96 %) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39 (d, 2H, *J* = 7.3Hz), 7.32 (t, 2H, *J* = 7.4 Hz), 7.25 (tt, 1H, *J* = 1.2, 7.4 Hz), 6.64 (d, 1H, *J* = 15.8 Hz), 6.25 (dd, 1H, *J* = 6.7, 15.8 Hz), 4.55 (m, 1H), 2.87 (ddd, 1H, *J* = 2.3, 4.3, 6.7 Hz), 2.75 (dt, 1H, *J* = 2.3, 5.6 Hz), 2.19 (dd, 1H, *J* = 1.0, 3.0 Hz), 1.98 (ddd, 1H, *J* = 4.3, 5.3, 14.2 Hz), 1.75 (m, 1H), 1.53 (m, 2H), 1.48-1.27 (m, 6H), 0.88 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.7, 131.5, 131.0, 128.8, 128.0, 126.7, 71.7, 58.9, 56.6, 39.8, 32.1, 31.8, 25.9, 22.8, 14.2.

IR (neat) 3415, 3060, 3026, 2929, 2858, 1599, 1578, 1493, 1466, 1450, 1378, 1119 cm^{-1}

Exact mass calcd. for $C_{17}H_{25}O_2$: 261.1855 (M+H); found: 261.1857 (M+H).

$[\alpha]_D^{25}$: -9.5 (c = 1.1, $CHCl_3$).

Preparation of (2*R*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (226)

To a cold (-35 °C), stirred solution of (1*E*,3*S*,5*S*,6*S*)-5,6-epoxy-1-phenylundec-1-en-3-ol (**224**) (45 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) was added boron trifluoride etherate (0.17 mL, 0.017 mmol, 0.10 M solution in CH_2Cl_2). After the reaction mixture had stirred for 24 hours at -35 °C it was treated with water (5 mL). The resulting mixture was diluted

with diethyl ether (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give the crude tetrahydrofurans **226** and **227** (5:1 d.r. as determined by ^{1}H NMR spectroscopy). Purification of the crude mixture by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (2*R*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**226**) (33 mg, 73%) as a white solid (m.p. = 46-48 °C) along with the C5 epimer **227** (6 mg, 13%).

Data for **226**:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.4 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.23 (t, 1H, *J* = 7.4 Hz), 6.59 (d, 1H, *J* = 15.8 Hz), 6.33 (dd, 1H, *J* = 6.7, 15.8 Hz), 4.66 (m, 1H), 4.13 (m, 1H), 3.92 (m, 1H), 2.48 (ddd, 1H, *J* = 6.6, 7.4, 13.1 Hz), 1.86 (ddd, 1H, *J* = 4.8, 6.1, 13.1), 1.73 (d, 1H, *J* = 6.1 Hz)), 1.54-1.48 (m, 3H), 1.42-1.30 (m, 6H), 0.90 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.9, 130.8, 130.6, 128.7, 127.8, 126.7, 82.9, 77.8, 73.5, 42.6, 32.3, 29.3, 26.3, 22.8, 14.3.

IR (thin film): 3409, 3060, 2954, 2929, 2858, 1650, 1600, 1493, 1449, 1376, 1260 cm^{-1}

Exact mass calcd. for $C_{17}H_{24}O_2$: 260.1776 (M+H); found: 260.1739 (M+H).

$[\alpha]_D^{25}$: -10.1 (c= 0.8, $CHCl_3$).

Preparation of (2*R*,3S,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (227)

To a cold (-35 °C), stirred solution of (1*E*,3*R*,5*S*,6*S*)-5,6-epoxy-1-phenylundec-1-en-3-ol (**225**) (60 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) was added boron trifluoride etherate (0.23 mL, 0.023 mmol, 0.10 M solution in CH_2Cl_2). After the reaction mixture had stirred for 24 hours at -35 °C it was treated with water (5 mL) and the resulting mixture was diluted with diethyl ether (10 mL) and the phases were separated. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic phases were

washed with brine, dried ($MgSO_4$), and concentrated to give the crude tetrahydrofurans **227** and **226** (8:1 d.r. as determined by ^{1}H NMR spectroscopy). Purification of the crude mixture by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (2*R*,3*S*,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**227**) (49 mg, 82%) as a white solid (m.p. = 48-50 °C) along with the C5 epimer **226** (6 mg, 10%).

Data for **227**:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.4 Hz), 7.31 (t, 2H, *J* = 7.5 Hz), 7.23 (t, 1H, *J* = 7.4 Hz), 6.62 (d, 1H, *J* = 15.8 Hz), 6.18 (dd, 1H, *J* = 7.1, 15.8 Hz), 4.70 (m, 1H), 4.14 (m, 1H), 3.79 (dt, 1H, *J* = 2.9, 6.9 Hz), 2.05 (ddd, 1H, *J* = 2.0, 5.7, 13.2 Hz), 1.93 (m, 1H), 1.76 (d, 1H, *J* = 3.8), 1.55 (m, 2H), 1.48 (m, 1H), 1.40 (m, 1H), 1.36-1.30 (m, 4H), 0.90 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.9, 131.7, 130.0, 128.7, 127.9, 126.8, 87.4, 78.9, 76.9, 42.1, 34.7, 32.1, 25.9, 22.8, 14.3.

IR (thin film): 3402, 3027, 2929, 2585, 1655, 1594, 1494, 1465, 1450, 1173, 1070 cm^{-1}

Exact mass calcd. for $C_{17}H_{24}O_2$: 260.1776 (M+H); found: 260.1777 (M+H).

$[\alpha]_D^{25}$: 17.4 (c = 1.4, $CHCl_3$).

Interconversion of (2*R*,3*S*,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (227) and (226)

A stirred solution of (2*R*,3*S*,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**227**) (10 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was added boron trifluoride etherate (0.04 mL, 0.004 mmol, 0.1 M solution in CH_2Cl_2). After the reaction mixture had stirred for one hour at room temperature it was treated with water (1 mL). The resulting mixture was diluted with diethyl ether (5 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give the crude tetrahydrofurans **226** and **227** (1:2 d.r. as determined by ^{1}H NMR spectroscopy). Purification of the crude

mixture by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded **226** ($[\alpha]_D^{25}$: -12.0 (c= 0.6, $CHCl_3$)) along with the C5 epimer **227** ($[\alpha]_D^{25}$: 18.8 (c= 0.3, $CHCl_3$)).

Interconversion of (2*R*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (226) and (227)

To a stirred solution of (2*R*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**226**) (25 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was added boron trifluoride etherate (0.1 mL, 0.01 mmol, 0.1 M solution in CH_2Cl_2). After the reaction mixture had stirred for one hour at room temperature it was treated with water (5 mL). The resulting mixture was diluted with diethyl ether (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to give the crude tetrahydrofurans **226** and **227** (1:2 d.r. as determined by ^{1}H NMR spectroscopy). Purification of the crude mixture by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded **226** ($[\alpha]_D^{25}$: -13.6 (c= 0.4, $CHCl_3$)) along with the C5 epimer **227** ($[\alpha]_D^{25}$: 19.6 (c= 2.0, $CHCl_3$)).

Preparation of (2*S*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (229)

To a cold (0 °C), stirred solution of (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**220**) (200 mg, 0.68 mmol) in THF (15 mL) was added silver oxide (274 mg, 1.36 mmol) and silver trifluoromethanesulfonate (349 mg, 1.36 mmol). The resulting mixture was allowed to slowly warm to room temperature and stir for an additional 24 hours. After this time the reaction mixture was filtered through Celite, diluted with diethyl ether (35 mL) and washed with saturated aqueous sodium bicarbonate (3 x 15 mL). The combined aqueous phases were extracted with diethyl ether (3 x 15 mL), and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Purification of the crude product by flash

chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (2*S*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**229**) (148 mg, 84%) as a white solid (m.p. = 63-65 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.2 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.23 (tt, 1H, *J* = 1.1, 7.2 Hz), 6.61 (d, 1H, *J* = 15.9 Hz), 6.31 (dd, 1H, *J* = 6.9, 15.9 Hz), 4.49 (m, 1H), 4.24 (m, 1H), 3.68 (dt, 1H, *J* = 2.3, 6.7 Hz), 2.52 (ddd, 1H, *J* = 5.9, 8.7, 14.2 Hz), 1.84 (ddd, 1H, *J* = 1.6, 5.6, 14.2), 1.77-1.65 (m, 2H), 1.57 (d, 1H, *J* = 7.4 Hz), 1.49 (m, 1H), 1.42 (m, 1H), 1.35 (m, 4H), 0.90 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.5, 131.0, 130.8, 128.5, 127.6, 126.6, 83.7, 78.0, 73.2, 42.3, 32.0, 28.8, 26.0, 22.6, 14.0.

IR (thin film): 3425, 2953, 2925, 2857, 1644, 1493, 1467, 1449, 1342, 1156, 1087 cm^{-1}

Exact mass calcd. for $C_{17}H_{24}O_2$: 260.1776 (M + H); found: 260.1788 (M + H).

$[\alpha]_D^{25}$ = -11.8 (c: 8.0, $CHCl_3$).

Preparation of (2*S*,3*S*,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (230)

To a cold (0 °C), stirred solution of (1*E*,3*R*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**221**) (59 mg, 0.20 mmol) in THF (3.6 mL) was added silver oxide (46 mg, 0.20 mmol) and silver trifluoromethanesulfonate (51 mg, 0.20 mmol). The resulting mixture was allowed to slowly warm to room temperature and stirred for an additional 48 hours. After this time the reaction mixture was filtered through Celite, diluted with diethyl ether (25 mL) and washed with saturated aqueous sodium bicarbonate (3 x 15 mL). The combined aqueous phases were extracted with diethyl ether (3 x 15 mL), and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to provide crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes:ethyl acetate) afforded (2*S*,3*S*,5*R*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**230**) (40 mg, 77%) as a white solid (m.p. = 53-56 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.3 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.23 (tt, 1H, *J* = 1.2, 7.3 Hz), 6.58 (d, 1H, *J* = 15.8 Hz), 6.20 (dd, 1H, *J* = 7.1, 15.8 Hz), 4.83 (m, 1H), 4.31 (m, 1H), 3.92 (dt, 1H, *J* = 2.9, 6.9 Hz), 2.24 (ddd, 1H, *J* = 0.7, 6.4, 13.4 Hz), 1.98 (ddd, 1H, *J* = 4.5, 9.3, 13.4), 1.69 (m, 2H), 1.61 (m, 1H), 1.49 (m, 1H), 1.39 (m, 1H), 1.35 (m, 4H), 0.91 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.9, 130.8, 130.6, 128.7, 127.8, 126.7, 82.9, 77.8, 73.5, 42.6, 32.3, 29.3, 26.3, 22.8, 14.3.

IR (thin film): 3366, 2948, 2929, 2852, 1641, 1493, 1273, 1173, 1072 cm^{-1}

Exact mass calcd. for $C_{17}H_{24}O_2$: 260.1776 (M + H); found: 260.1761 (M + H).

$[\alpha]_D^{25}$: 21.0 (c = 1.0, $CHCl_3$).

Preparation of (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-en-7,10-diol (142) and (6*S*,7*S*,9*S*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (233)

Into a cold (-78 °C), stirred solution of (2*S*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**229**) (50 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was bubbled ozone until the solution turned pale blue (~ 5 min). After this time, the reaction mixture was purged with nitrogen gas for 5 minutes to remove excess ozone. The reaction mixture was then treated with polymer supported triphenylphosphine (641 mg, 1.90 mmol, 3.00 mmol/g) and shaken for one hour.[82] After this time, the mixture was filtered and the mother liquor was concentrated under high vacuum (1 mm Hg) for 30 minutes to give the crude aldehyde **231**, which was used without further purification.

To a stirred solution of the aldehyde **231** in dichloroethane (3.5 mL) at 83 °C was added 8-noneyl magnesium bromide[83] (**232**) (4.8 mL, 1.9 mmol, 0.40 M solution in Et_2O) and the resulting mixture was maintained at this temperature for one hour. The reaction mixture was then treated with water (10 mL), cooled to room temperature, diluted with diethyl ether (10 mL) and the phases were separated. The aqueous phase was

extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried (MgSO4), filtered, and concentrated to give the crude dihydroxytetrahydrofurans **142** and its C10 epimer **233** (5.5:1 d.r. as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded a mixture of **142** and **233** (39 mg, 65% over two-steps). Purification by flash chromatography (silica gel, 6:1 hexanes:ethyl acetate) afforded (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (**142**) as a white solid (m.p. = 32-35 °C).

Data for **142**:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.80 (tdd, 1H, *J* = 6.7, 10.2, 17.0 Hz), 4.99 (dd, 1H, *J* = 1.8, 17.0 Hz), 4.93 (dd, 1H, *J* = 1.8, 10.2 Hz), 4.03 (dd, 1H, *J* = 2.6, 5.3 Hz), 3.96 (td, 1H, *J* = 2.3, 9.9 Hz), 3.62 (dt, 1H, *J* = 2.6, 6.9 Hz), 3.47 (ddd, 1H, *J* = 2.2, 4.8, 7.3 Hz), 2.38 (ddd, 1H, *J* = 5.5, 10.0, 14.3), 2.03 (dd, 2H, *J* = 6.9, 14.2), 1.84 (dd, 1H, *J* = 3.4, 14.2 Hz), 1.66-1.52 (m, 3H), 1.49-1.21 (m, 19H), 0.88 (t, 3H, *J* = 6.9 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.2, 114.1, 84.3, 79.0, 73.9, 71.5, 38.7, 34.4, 33.8, 32.0, 29.5, 29.4, 29.0, 28.9, 28.7, 26.0, 25.9, 22.6, 14.0.

IR (thin film): 3387, 3077, 2927, 2855, 1641, 1465, 1377, 1289, 1184, 1129, 1090 cm^{-1}

Exact mass calcd. for $C_{19}H_{37}O_3$: 313.2743 (M + H); found: 313.2745 (M + H)

$[\alpha]_D^{25}$= +20.0 (c: 0.5, $CHCl_3$) (lit.[48] $[\alpha]_D$= +24.3 (c: 0.3, $CHCl_3$)).

Preparation of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (141) and (6*S*,7*S*,9*R*,10*S*)-6,9-epoxynonadec-18-en-7,10-diol (234)

Ozone was bubbled into a cold (-78 °C), stirred solution of (2*S*,3*S*,5*R*)-2-pentyl-5-styryltetrahydrofuran-3-ol (**230**) (70 mg, 0.27 mmol) in CH_2Cl_2 (7 mL) until the solution turned pale blue (~ 5 min). After this time, the reaction mixture was purged with nitrogen gas for 5 minutes to remove excess ozone. The reaction mixture was then treated with

polymer supported triphenylphosphine (900 mg, 27 mmol, 3.0 mmol/g) and shaken for one hour.[82] After this time, the mixture was filtered and the mother liquor was concentrated under high vacuum (1 mm Hg) for 30 minutes to give the crude aldehyde, which was used without further purification.

To a stirred solution of the aldehyde in dichloroethane (5 mL) at 40 °C was added 8-noneyl magnesium bromide (**232**)[83] (7.0 mL, 27 mmol, 0.40 M solution in Et_2O) and the resulting mixture was maintained at this temperature for two hours. The reaction mixture was then treated with water (10 mL), diluted with diethyl ether (10 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to give the crude dihydroxytetrahydrofurans **141** and its C10 epimer **234** (2.5:1 d.r. as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes:ethyl acetate) afforded (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-en-7,10-diol (**141**) (42 mg, 50% over two-steps) as a white solid (m.p. = 51-54 °C) and the C10 epimer **234** (18 mg, 21% over two-steps) as a white solid (m.p.= 71-73 °C).

Spectral data for **141**:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.7, 10.2, 16.9 Hz), 4.99 (ddd, 1H, *J* = 1.9, 3.4, 16.9 Hz), 4.93 (dd, 1H, *J* = 1.9, 10.2 Hz), 4.25 (m, 1H), 4.02 (dt, 1H, *J* = 6.6, 9.0 Hz), 3.75 (dt, 1H, *J* = 2.7, 7.0 Hz), 3.38 (m, 1H), 2.31 (br. s, 1H), 2.05-2.00 (m, 3H), 1.88 (ddd, 1H, *J* = 4.6, 9.1, 13.5 Hz), 1.67-1.62 (m, 1H), 1.49-1.25 (m, 20H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.4, 114.4, 82.7, 80.4, 74.3, 73.7, 38.1, 34.0, 33.4, 32.2, 29.9, 29.6, 29.3, 29.1, 29.0, 26.2, 25.8, 22.8, 14.3.

IR (thin film): 3431, 2927, 2855, 1641, 1459, 1090 cm^{-1}

Exact mass calcd. for $C_{19}H_{37}O_3$: 313.2743 (M + H); found: 313.2746 (M + H).

$[\alpha]_D^{25}$: 13.8 (c= 0.9, $CHCl_3$) (lit.[33] $[\alpha]_D^{20}$: 15.0 (c= 1.0, $CHCl_3$)).

Spectral data for **234**:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.80 (tdd, 1H, *J* = 6.7, 10.2, 16.9 Hz), 4.98 (ddd, 1H, *J* = 1.7, 3.4, 17.1 Hz), 4.92 (dd, 1H, *J* = 1.7, 10.2 Hz), 4.28 (m, 1H), 4.16 (ddd, 1H, *J* = 3.3, 5.9, 9.7 Hz), 3.84 (m, 2H), 2.11 (ddd, 1H, *J* = 4.5, 10.3, 13.3), 2.05-1.99 (m, 3H), 1.85 (dd, 1H, *J* = 6.1, 13.3 Hz), 1.65-1.20 (m, 21H), 0.89 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.4, 114.4, 83.8, 80.2, 73.5, 72.3, 34.4, 34.0, 32.5, 32.2, 29.8, 29.6, 29.4, 29.3, 29.1, 26.2, 26.1, 22.8, 14.2.

IR (thin film): 3415, 2925, 2853, 1635, 1467, 1091 cm^{-1}

Exact mass calcd. for $C_{19}H_{37}O_3$: 313.2743 (M + H); found: 313.2725 (M + H).

$[\alpha]_D^{25}$: 14.5 (c= 1.1, $CHCl_3$) (lit.[41] $[\alpha]_D$: 15.0 (c= 0.46, $CHCl_3$)).

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[80] Yield calculated from the reaction of the major diastereomer **212** (9:1 d.r.)

[81] Yield calculated from the reaction of the major diastereomer **220** (10:1 d.r.)

[82] Shaken on a Burnell Wrist Action Shaker Model 75 at low speed.

[83] Wide variations in yield for this process were observed following different protocols for the formation of 8-nonenyl magnesium bromide. Ideally, 8-nonenyl magnesium bromide was prepared by the following procedure: To flame dried magnesium turnings (230 mg, 9.5 mmol) was added a solution of 1-bromo-8-nonene (390 mg, 1.9 mmol) in degassed ether (4.8 mL). The mixture was stirred for 30 minutes at room temperature after which time it was heated to reflux for an additional 2.5 hours.

Chapter 4

Regioselective and Stereoselective Cyclisations of Chloropolyols in Water: Rapid Synthesis of Hydroxytetrahydrofurans

4.1 Introduction to the *Goniothalamus* Natural Products

The results discussed in this Chapter have been reported in part, see: Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716.

4.1.1 Natural Products from the Annonaceae Family and the Genus Goniothalamus

Angiosperms (flowering plants) are one of the richest sources of biologically active natural products.[1] Even though a large number of flowering plant families exist, only a small fraction of these have been extensively examined for biologically active components.[1] One family of angiosperms that has been widely investigated is Annonaceae (the custard apple family), which consists of 135 genera[2] of trees, shrubs, and lianans found primarily in the tropics and sub-tropics.[2] For example, chemicals isolated from Annonaceae include the diterpenoid **235**, which possesses leishmanicidal activity;[3] and suberosol (**236**), which exhibits anti-HIV replication activity.[4] In addition,

two natural products produced by members of this family are being clinically evaluated as therapeutics in the treatment of breast cancer (i.e., (+)-bullatacin (**237**)),[5] and Parkinson's disease (i.e., **238**).[6] Furthermore, many other Annonaceae natural products have attracted considerable interest owing to their therapeutic potential toward a variety of other diseases.[7]

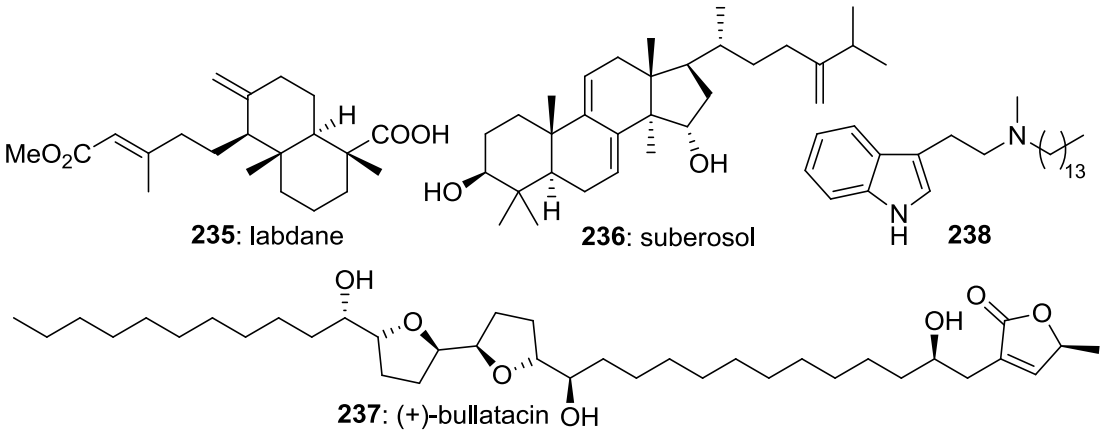


Figure 12. Representative examples of pharmacologically active Annonaceae natural products.

Goniothalamus is the largest genera of the Annonaceae family and consists of 160 species of which only 22 have been comprehensively examined for medicinal natural products.[8] Interestingly, extracts from several of these species have been used as traditional medicines in Asia, primarily for typhoid fever,[9] inflammation,[10] rheumatism,[11] and scabies.[12,13] These effects have been attributed to specific natural products (e.g., acetogenins, styryllactones) isolated from *Goniothalamus*.[14]

The styryllactones are found primarily in the genus *Goniothalamus* and were first isolated in 1972 by Jewers and Blunden who reported the isolation of (+)-goniothalamin (**239**), a biologically active constituent found in the bark of *Goniothalamus andersonii*.[15] Since then, plant extracts from *Goniothalamus* have resulted in the isolation of more than 30 styryllactones (Figure 13). These include, (+)-altholactone (**240**) and (+)-

goniothalesdiol (**241**) isolated from *Goniothalamus borneensis*;[16] (+)-goniopypyrone (**242**), (+)-goniodiol (**243**), (+)-goniofufurone (**244**), and (-)-goniofupyrone (**245**) isolated from *Goniothalamus cardiopetalus.*[17] In terms of styryllactone biosynthesis, all natural products are derived from the shikimic acid pathway through the conversion of phenylalanine to cinnamic acid. Incorporation of two additional acetate-malonate units then affords the simplest styryllactone, goniothalamin (**239**). Biosynthesis of the remaining styryllactones then occurs through various oxidations and cyclisations of **239**.[18]

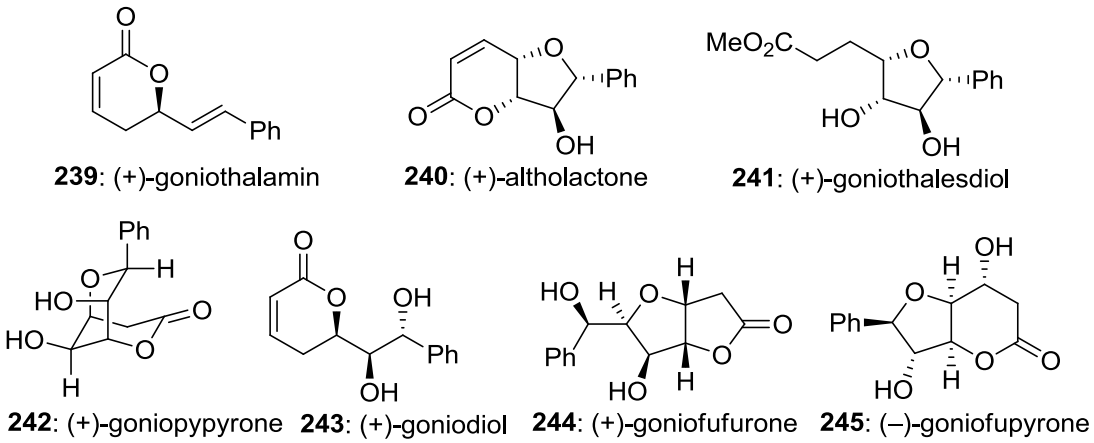


Figure 13. Representative examples of the *Goniothalamus* styryllactones.

The *Goniothalamus* styryllactones exhibit potent biological activities such as pesticidal, teratogenicity, embryotoxicity, and cytotoxicity (Table 21). The cytotoxic activity of these compounds has been attributed to the activation of enzymes responsible for apoptosis *via* the loss of the mitochondrial transmembrane.[19]

Table 21. Antitumour activity of the *Goniothalamus* styryllactones.

entry	styrllactone	cell line	Dose
1	(+)-goniothalamin (**239**)	HepG2 – human liver carcinoma	8.83 μM[20]
2	(+)-goniothalamin (**239**)	HepG2R - human liver carcinoma	8 μM[20]
3	(+)-goniothalamin (**239**)	P388 – murine leukemia	0.75 μg/mL[16]
4	(+)-goniothalamin (**239**)	WEH1164 – murine fibrosarcoma	1.7 μg/mL[16]
5	(+)-altholactone (**240**)	HepG2 – human liver carcinoma	0.7 μM[20]
6	(+)-altholactone (**240**)	HepG2R - human liver carcinoma	6.17 μM[20]
7	(+)-goniothalesdiol (**241**)	P388 – murine leukemia	30 μg/mL[16]
8	(+)-goniopypyrone (**242**)	P388 – murine leukemia	5.33 μM[21]
9	(+)-goniodiol (**243**)	HepG2 – human liver carcinoma	10 μM[20]
10	(+)-goniodiol (**243**)	HepG2R - human liver carcinoma	8.33 μM[20]
11	(+)-goniofufurone (**244**)	K562 – human leukemia	0.41 μM[22]
12	(+)-goniofufurone (**244**)	HeLa – human cervix carcinoma	8.32 μM[22]
13	(+)-goniofupyrone (**245**)	HT-29 – human colon adenocarcinoma	38 μg/mL[22]

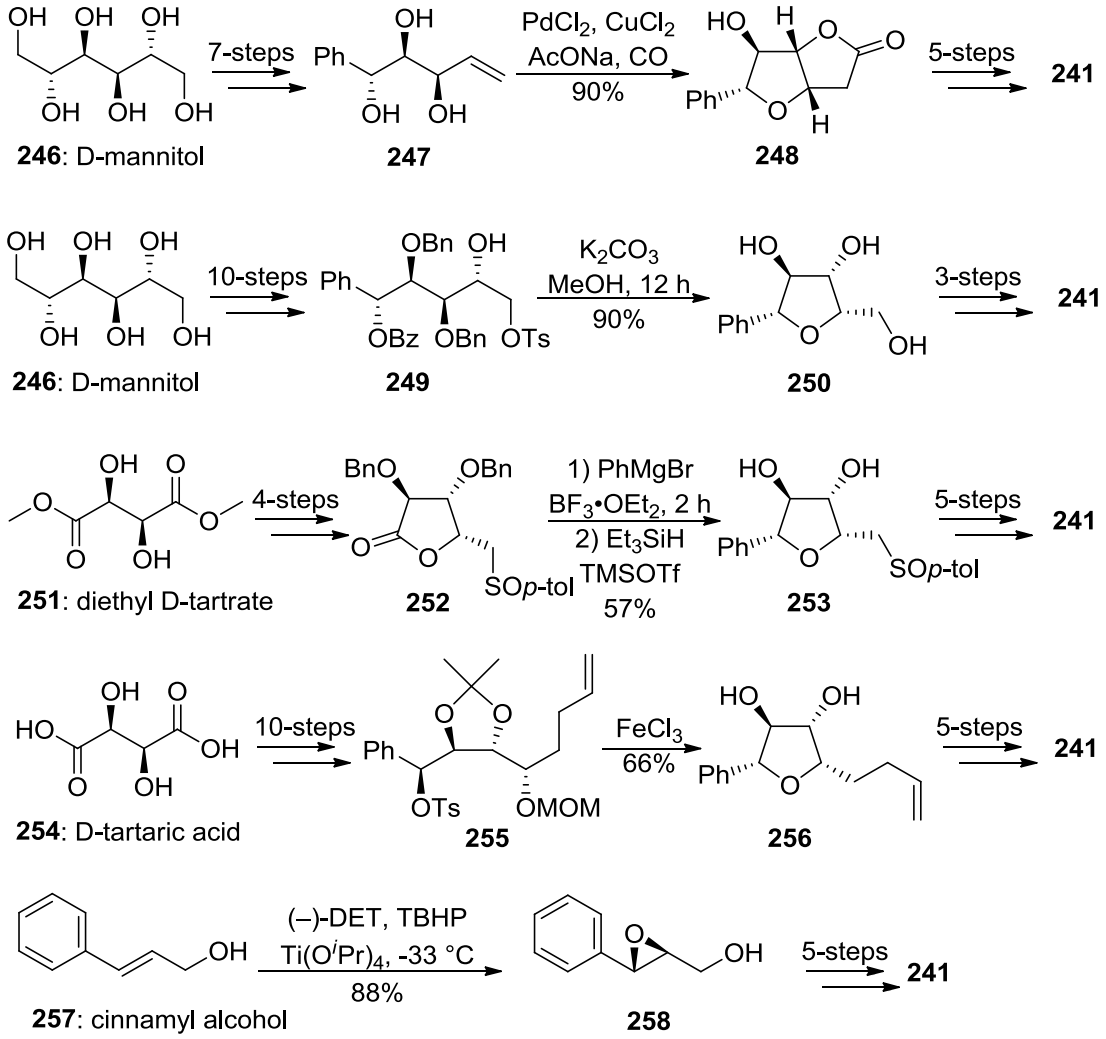
Owing to their potent pharmacological activities, the *Goniothalamus* styryllactones have been the focus of many synthetic efforts. Because these compounds often contain heavily oxygenated and stereochemically rich ring systems, a route to their synthesis often involves the use of carbohydrate starting materials. For example, D-glucose has been used in the synthesis of (+)-goniothalamin (**239**),[23] (+)-altholactone (**240**),[24] (+)-goniofufurone (**244**).[25] Similarly, L-arabinose,[26] D-mannose,[27] and other chiral building-blocks (e.g., (*S*)-glycidol, diethyl tartrate, mandelic acid) have also been employed in the synthesis of the styryllactones. Because of the fixed stereochemical arrangement of the starting materials, these syntheses are often limited in scope and are not amenable to the production of configurationally diverse analogues. Although asymmetric syntheses are relatively more flexible in this regard, they often require lengthy routes and suffer from lower enantiomeric excesses. For example, the Sharpless asymmetric dihydroxylation has been employed in the synthesis of: (+)-goniopypyrone

(**242**) and its C8 epimer;[28] (+)-goniodiol (**243**) and its C7 epimer;[29] (+)-isoaltholactone, and its C2 and C3 epimers.[30]

4.1.2 Natural Products Containing the 2,5-Disubstituted-3,4-hydroxytetrahydrofuran Core

The *Goniothalamus* styryllactones that contain a 2,5-disubstituted-3,4-hydroxytetrahydrofuran core (e.g., **240**, **241**, **244**, **245**) have also been synthesised *via* similar routes to those described above. For example, (+)-goniothalesdiol (**241**) has been synthesised from a wide range of commercially available compounds on six occasions (Scheme 40). For example, starting with carbohydrate building-blocks such as D-mannitol (**246**), a 13-step synthesis to **241** was reported that employs a palladium(II)-catalysed oxycarbonylation as the key transformation (**247** → **248**).[31] Similarly, a 14-step synthesis that afforded (+)-goniothalesdiol (**241**) from D-mannitol (**246**) involved a debenzoylation with concomitant epoxide-formation and an *in situ* 5-*exo* epoxide-opening sequence (**249** → **250**).[32] Other chiral-pool chemicals used for the synthesis of **241** include dimethyl D-tartrate (**251**), which was processed to the natural product *via* a stereoselective Et_3SiH/TMSOTf-promoted reductive cyclisation/deoxygenation reaction (**252** → **253**) as the key transformation in a 11-step synthesis;[33] and D-tartaric acid (**254**), which was converted to **241** in 16-steps and relied on a stereoselective $FeCl_3$-mediated tetrahydrofuran formation (**255** → **256**).[34] Additionally, an asymmetric synthesis of **241** was reported that employed a Sharpless epoxidation of a cinnamyl alcohol (**257** → **258**) *en route* to the natural product in 12-steps.[35] Despite the number of contributions in this area, these strategies do not provide the stereochemical flexibility needed to generate configurational isomers of the 2,5-disubstituted-3,4-hydroxytetrahydrofuran core for medicinal chemistry purposes. In addition, all of these syntheses require >11-steps to access the natural product, which presents challenges to develop libraries of related

compounds for SAR studies.[36] Although *Goniothalamus* is the largest source of the 2,5-disubstituted-3,4-hydroxytetrahydrofuran-containing natural products, these compounds are also found in many other organisms.[37,38,39,40] Similar to the *Goniothalamus* natural products, most compounds with this core exhibit an array of potent biologically activities.[41,42]



Scheme 40. Previous syntheses of (+)-goniothalesdiol 241.

Owing to the aforementioned issues regarding the development of concise and flexible syntheses of these bioactive molecules there is a need for new processes that are both stereochemically flexible and concise in providing dihydroxytetrahydrofurans.

This Chapter will summarise the development of a short synthetic route to these highly functionalised tetrahydrofuranols. Furthermore, these new methods were applied to the synthesis of (+)-goniothalesdiol (**241**), a representative compound with the 2,5-disubstituted-3,4-dihydroxytetrahydrofuran core, and toward the synthesis of other carbohydrate analogues.

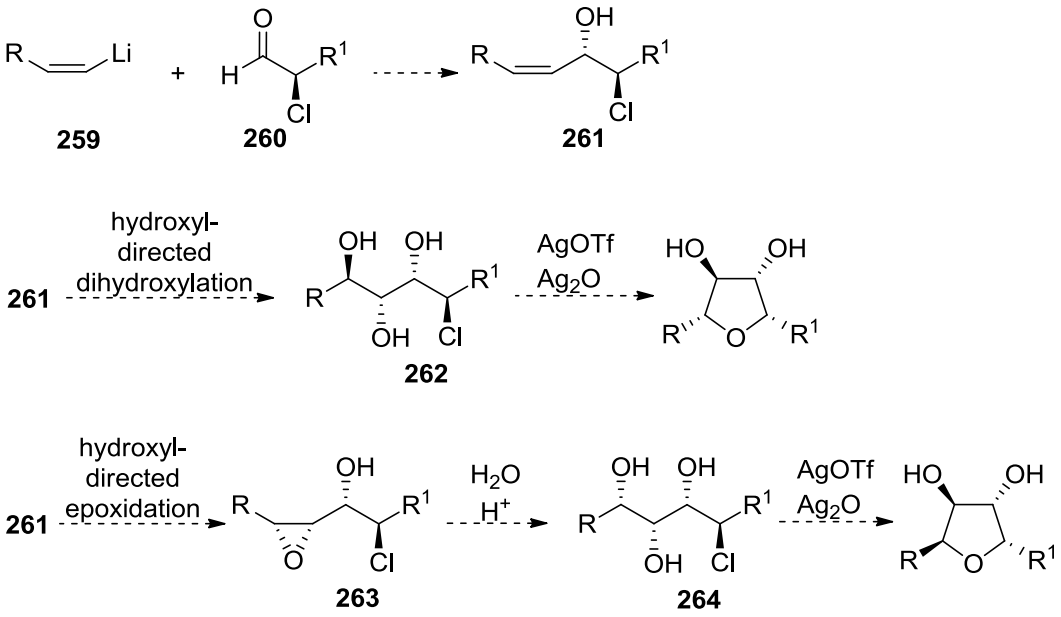
4.2 Synthesis of the 2,5-Disubstituted-3,4-dihydroxytetrahydrofurans

4.2.1 Synthetic Plan

In Chapters 2 and 3, new methods that involved the nucleophilic addition of organolithium reagents or lithium enolates to α-chloroaldehydes afforded optically enriched *trans*-epoxides and 2,5-disubstituted-3-hydroxytetrahydrofurans, respectively, were presented. As an extension of this work, it was envisioned that the chlorohydrins derived from the addition of alkenyl lithium reagents to α-chloroaldehydes may be dihydroxylated to afford chloropolyols. More importantly, it was recognised that the cyclisation of these chloropolyols could afford access the 2,5-disubstituted-3,4-dihydroxytetrahydrofurans. This would offer a flexible and efficient route to the biologically potent natural products discussed above.

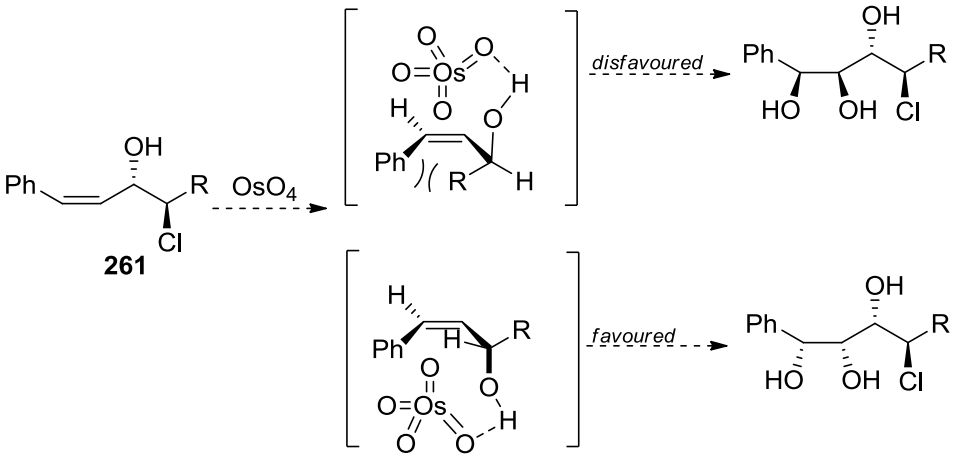
In our original work employing methods reported independently by MacMillan[36] (see page 4) and Jørgensen[37] (see page 6), the asymmetric α-chlorination of aldehydes produced α-chloroaldehydes with enantiomeric excesses between 85-89%. However, during the course of this work, MacMillan reported a novel organo-SOMO approach to the organocatalytic α-chlorination of aldehydes (see page 8).[43] We envisioned that this process would afford better enantiocontrol in the α-chlorination reaction.

As indicated below (Scheme 41), the first step in the proposed tetrahydrofuran synthesis would employ the optimised conditions described in Chapter 2, which involve the addition of an alkenyl lithium reagent (e.g., **259**) to an enantioenriched α-chloroaldehyde (e.g., **260**) to afford the alkenyl chlorohydrin (e.g., **261**).



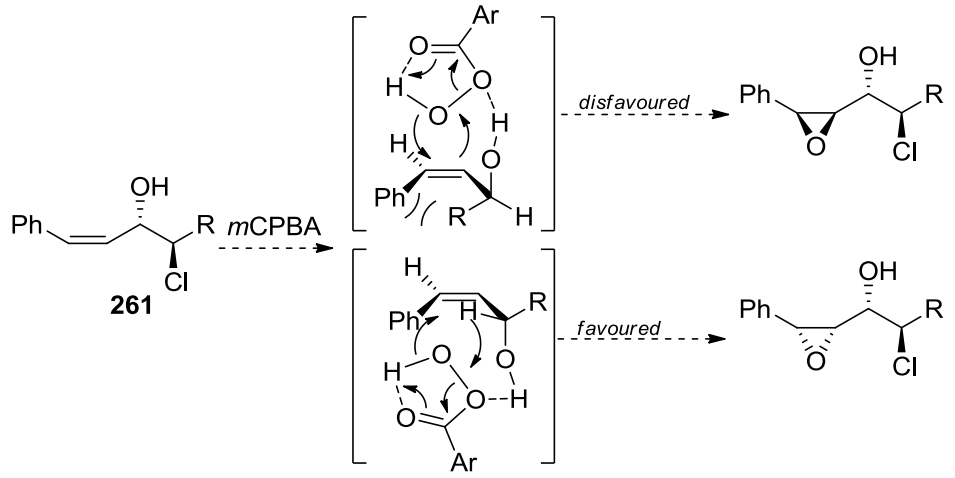
Scheme 41. Proposed synthetic route to 2,5-disubstituted-3,4-dihydroxytetrahydrofurans.

With the alkenyl chlorohydrin (e.g., **261**) in hand, a hydroxyl-directed dihydroxylation should then afford a chlorotriol (e.g., **262**). In this regard, early reports by Criegee on the dihydroxylation of alkenes involved the use of stoichiomeric amounts of the OsO_4, which resulted in good chemo- and regioselectivites.[44] However, due to the high toxicity associated with osmium,[45] the UpJohn company developed a procedure employing catalytic OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) as the stoichiometric co-oxidant, which has since enjoyed widespread use.[46] Following this procedure, two possible transition structures exist in which the favoured hydroxyl-directed dihydroxylation pathway can be distinguished by the relative $A^{1,3}$ strain as depicted below (Scheme 42).[47]



Scheme 42. Proposed transition structures in the hydroxyl-directed dihydroxylation.

As an alternative to dihydroxylation of **261**, a hydroxyl-directed epoxidation would yield an epoxy chlorohydrin (e.g., **263**), which could undergo a ring opening reaction to afford the chlorotriol (e.g., **264**). The stereodiscrimination of the epoxidation arises from the minimisation of the allylic $A^{1,3}$ strain as depicted in Scheme 43.[48] It was expected that the epoxide-opening reaction would occur at the benzylic position under acidic conditions.



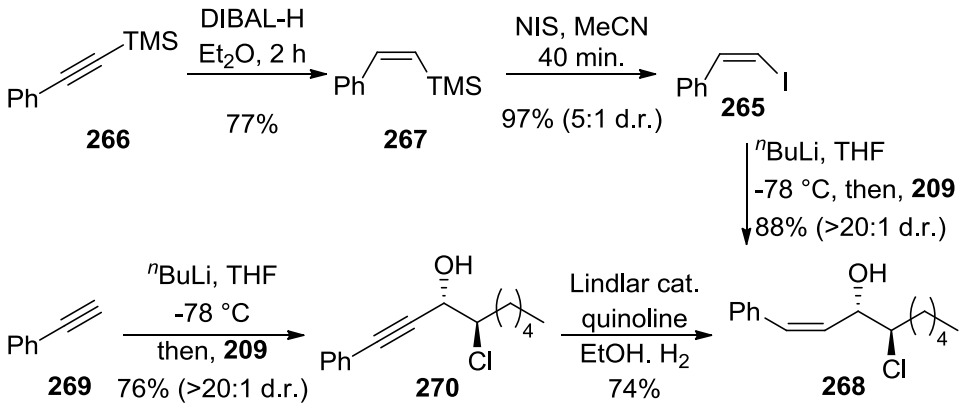
Scheme 43. Proposed transition structures in the hydroxyl-directed epoxidation.

To test the limits of the AgOTf/Ag_2O methodology developed previously, we envisioned that with sufficient modification to this method, the cyclisation of the chlorotriols (e.g., **262** and **264**) could be effected. Thus, this synthetic route (Scheme 41) would provide access to the oxygenated tetrahydrofurans, including the fully functionalised (+)-goniothalesdiol (**241**), a cytotoxic natural product isolated from *G. borneensis*.

4.2.2 Results

4.2.2.1 Preparation of the Alkenyl Chlorohydrin

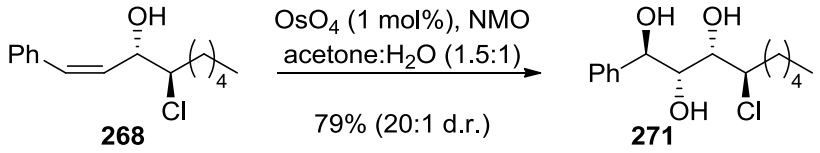
The stereo- and enantioselective preparation of chlorodiols used in Chapter 3 involved aldol coupling of a methyl ketone and an optically active α-chloroaldehyde, followed by hydroxyl-directed reduction of the ketone function. However, to access the chlorotriols required for the synthetic route depicted in Scheme 41, the addition of alkenyl lithium reagents (e.g. **259**) to α-chloroaldehydes (e.g., **260**) was expected to afford alkenyl chlorohydrins (e.g., **261**) that would subsequently undergo dihydroxylation or epoxidation/epoxide-opening. The required, (*Z*)-(2-iodovinyl)benzene (**265**), was prepared from the reduction of trimethylsilyl phenyl acetylene,[49] followed by an iododesilylation (**266** → **267**).[50] The (*Z*)-(2-iodovinyl)benzene (**265**) was then treated sequentially with *n*-BuLi and α-chloroheptanal (**209**) to afford the alkenyl chlorohydrin **268** in excellent yield and diastereomeric excess (Scheme 44). Alternatively, the alkenyl chlorohydrin **268** was also accessible through a sequence of reactions involving the addition of ethynyl benzene (**269**) to α-chloroheptanal (**209**), followed by a Lindlar reduction of alkynyl chlorohydrin **270** (Scheme 44).



Scheme 44. Preparation the alkenyl chlorohydrin 268.

4.2.2.2 Hydroxyl-Directed Dihydroxylation of the Alkenyl Chlorohydrin 268

Following the successful preparation of the alkenyl chlorohydrin **268**, focus shifted to the hydroxyl-directed dihydroxylation. Specifically, subjecting **268** to the UpJohn conditions resulted in preferential formation of chlorotriol **271** (20:1 d.r.) (Scheme 45).



Scheme 45. Hydroxyl-directed dihydroxylation of alkenyl chlorohydrin 268.

As depicted in Figure 14, analysis of the ^{13}C NMR, HSQC, and 1D NOESY spectra recorded on the acetonide **272**, derived from the chlorotriol **271**, allowed assignment of the resonances at δ 24.0 and 24.3 ppm to the acetonide methyl groups and the resonance at δ 102.0 ppm to the acetal carbon, consistent with those reported for acetonides derived from 1,3-*anti*-diols using the Rychnovsky method.[51]

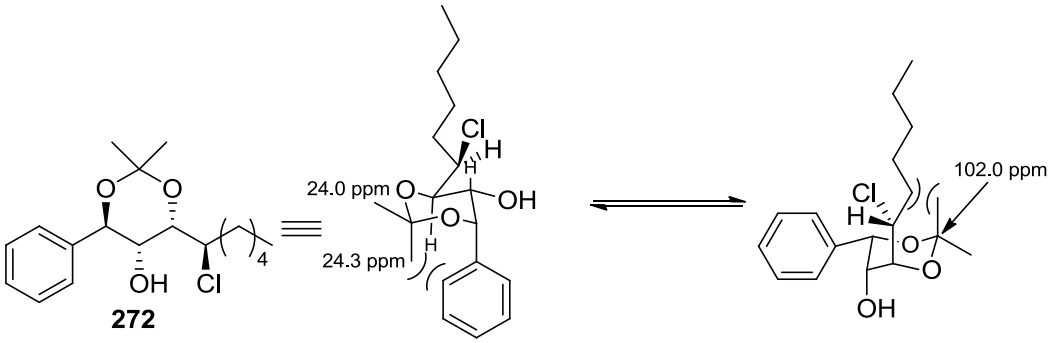
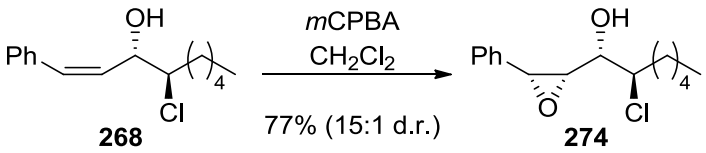


Figure 14. Conformations of the 1,3-*anti*-diol acetonide 272.

4.2.2.3 Hydroxyl-Directed Epoxidation and the Epoxide-Opening Reaction

In an effort to produce the stereoisomeric chlorotriol **273**, a second series of reactions were carried out on the alkenyl chlorohydrin that involved a hydroxyl-directed epoxidation, followed by epoxide-opening with water under acidic conditions. It was found that treatment of **268** with *m*CPBA at room temperature resulted in formation of the epoxy chlorohydrin **274** as the major component of a 15:1 diastereomeric mixture that also contained the *bis*-epimeric *cis*-epoxide **275** (Scheme 46).

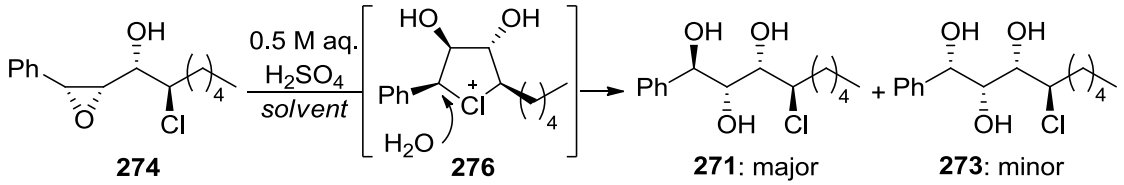


Scheme 46. Hydroxyl-directed epoxidation of the alkenyl chlorohydrin 268.

Preliminary studies into the opening of the epoxide to form the desired chlorotriol **273** indicated that the reaction occurred slowly at room temperature in the presence of aqueous H_2SO_4. After careful analysis it was observed that the spectral data of **271** and its corresponding acetonide **272** derived from the hydroxyl-directed route matched with data obtained from the chlorotriol derived from the epoxide-opening route. Under acid- or

metal-catalysed conditions, epoxides (e.g., **263**) are known to undergo selective attack at the C1 position of the epoxyalcohol with a variety of nucleophiles.[52] It has been reported that when a phenyl group is appended to the epoxide, the ring-opening reaction may proceed *via* an ion-pair resulting in retention of configuration at C1.[53] Furthermore, Olah reported the intermediacy of a tetramethylenechloronium ion in reactions involving the formation carbocations in the presence of a chloromethylene group.[54] If operative in the epoxide-opening of **274**, formation of a chloronium ion (e.g., **276**) and subsequent attack by water would result in retention at C1 (Table 22).[54,55] A survey of co-solvents for the epoxide-opening reactions was performed by Mr. Stanley Chang (Table 22), and it was found that trifluoroethanol was the most effective solvent and offered the greatest diastereoselectivity in the conversion of **274** to the chlorotriols with retention at C1.

Table 22. Solvent screen for the epoxide-opening reaction.



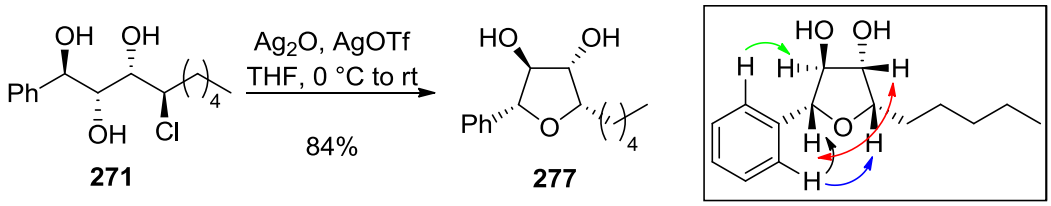
274 **276** **271**: major **273**: minor

entry	solvent	d.r. (271:273)	yield (%)
1	ethanol	2.8:1	46
2	isopropanol	5:1	65
3	*tert*-butanol	5:1	77
4	2,2,2-trifluoroethanol	8:1	79
5	water	3:1	40

4.2.2.4 Synthesis of the 2,5-disubstituted-3,4-dihydroxytetrahydrofurans

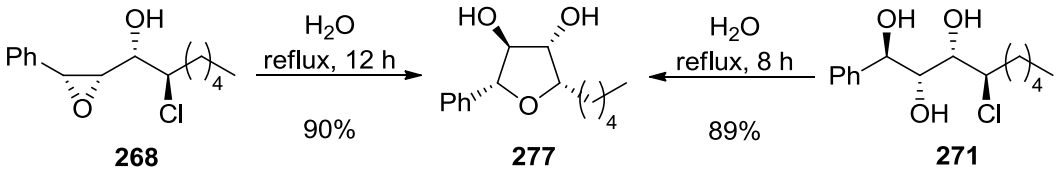
With a concise route to the chlorotriol **271** established, efforts toward the cyclisation of this material were initiated. Specifically, the AgOTf/Ag_2O cyclisation

methodology developed earlier (Chapter 3) was employed to effect the conversion of the chlorotriol **271** into the desired 2,5-disubstituted-3,4-dihydroxytetrahydrofuran **277** in 84% yield. The relative stereochemistry of **277** was confirmed by nOe analysis as shown in Scheme 47. This silver methodology represents a novel and versatile approach to cyclise chlorotriols selectively to substituted tetrahydrofuranols without need for protecting-groups.



Scheme 47. Cyclisation of chlorotriol 271 to the 2,5-disubstituted-3,4-dihydroxytetrahydrofuran 277. Stereochemical analysis by nOe.

Although we had established that the epoxy chlorohydrin **274** undergoes selective epoxide-opening (8:1 d.r.) in trifluoroethanol to afford the chlorotriols **271**:**273**, Mr. Chang also found that the epoxide-opening reaction in water gave rise to a 3:1 ratio of chlorotriols **271**:**273**, along with a 3:1 ratio (<5% yield) of the 2,5-disubstituted-3,4-dihydrotetrahydrofuran **277** and its C2 epimer. This observation prompted a re-examination of the epoxide-opening reaction, whereupon it was eventually discovered that heating the epoxy chlorohydrin **274** in aqueous H_2SO_4 (0.5 M) afforded the 3:1 mixture of the tetrahydrofuran **277** and its C2 epimer in 67% yield. Furthermore, repeating this reaction without acid (i.e., heating in water) provided the tetrahydrofuranol **277** in 90% yield (Scheme 48). Because this cyclisation presumably occurs through the intermediacy of the chlorotriol **271**, a pure sample of this latter material was also heated in water at reflux for eight hours, which resulted in the clean formation of the desired tetrahydrofuran **277** as a single diastereomer in 89% yield (Scheme 48).



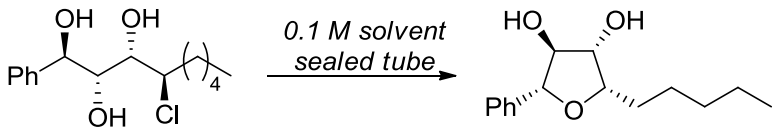
268 **277** **271**

Scheme 48. Cyclisation to tetrahydrofuran 277.

Microwave-assisted organic synthesis was first reported in 1986 when Gedye and Majetich demonstrated the use of microwave heating to accelerate common chemical transformations.[56] As solvents with high dielectric constants absorb microwave radiation and reemit it as heat, microwave-assisted reactions offer specific advantages such as, uniform heating of the reaction, comparatively fast, and minimised vessel wall effects. Thus, microwave-heating generally results in significantly cleaner and quicker reactions. Water has been used as the reaction media in microwave-assisted nucelophilic substitution reactions, and this approach has been recognised as a method for environmentally benign syntheses.[57] An example of microwave-assisted coupling of D-glucuronic acid with alcohols to the corresponding β-D-glucofuranosidurono-6,3-lactones was recently reported by Richel.[58]

In an effort to reduce the time required for the cyclisation (e.g., 12-24 h with AgOTf/Ag_2O, and 8 h traditional heating) of the chlorotriol **271** to the tetrahydrofuranol **277**, this reaction was repeated in a microwave. Table 23 summarises the solvents examined for the cyclisation of **271**. Moderate to excellent yields were observed for most solvents, with complete conversion observed within 10-20 minutes. The cyclisation was also carried out in aqueous pH 7 buffer in nearly identical yield (86% yield) to that obtained in pure water, conditions which may be beneficial for acid-sensitive substrates. The microwave-assisted cyclisation demonstrates an important advancement because it avoids the use of the silver salts and is also much faster than the silver-mediated cyclisation methodology.

Table 23. Microwave-assisted cyclisations of the chlorotriol 271.



271 **277**

entry	solvent	time (min.)	temp (°C)	yield (%)
1	H_2O	10	120	91
2	H_2O	5	180	90
3	DMSO	15	120	82
4	Toluene	30	120	0
5	DMF	10	120	25
6	MeCN	25	120	55
7	MeOH	10	120	90
8	MeCN	25	150	60
9	neat	60	230	0
10	pH 7 buffer	20	120	86

To demonstrate the practical utility of this process, 0.5 g of the chlorotriol **271** was heated for 20 min at 120 °C in 3 mL of water to provide after a simple decantation, 0.39 g (91%) of the tetrahydrofuranol **277**. Figure 15 shows the microwave vial before heating with the chlorotriol **271** completely soluble in solution, and after the heating for 20 minutes at 120 °C the tetrahydrofuranol **277** precipitates from solution. The corresponding ^{1}H NMR spectrum of the crude material after decantation is also shown in Figure 15.

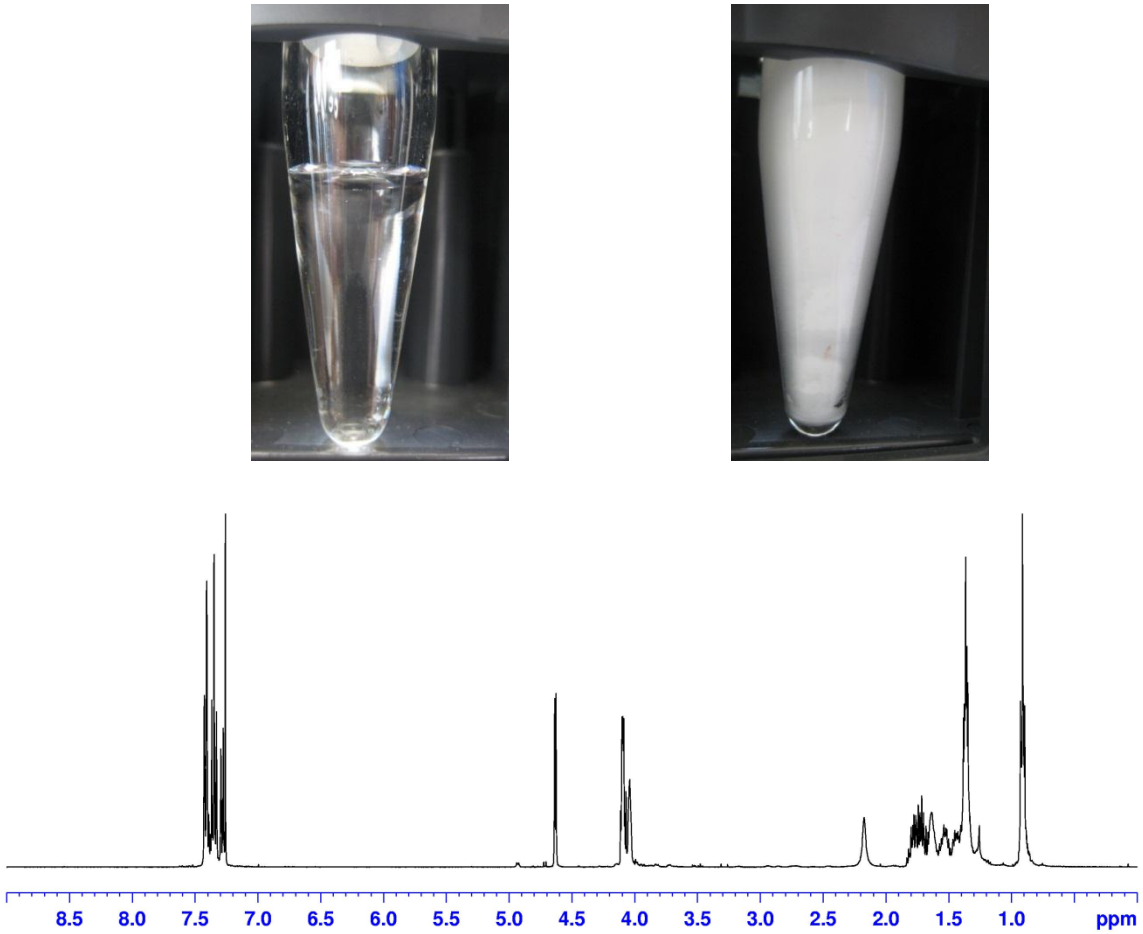


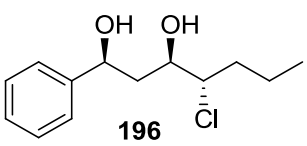
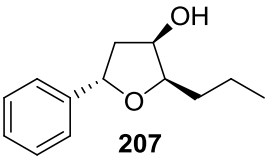
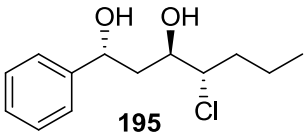
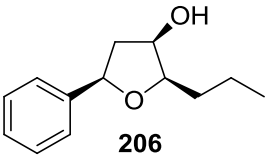
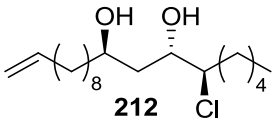
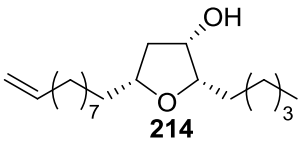
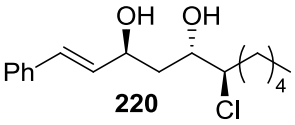
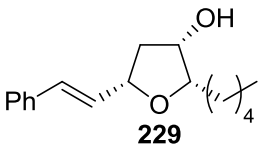
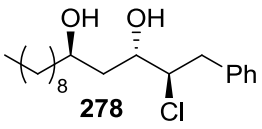
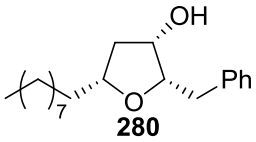
Figure 15. **Before cyclisation of chlorotriol 271 (left), after cyclisation (right) and ^{1}H NMR spectrum of crude tetrahydrofuranol 277.**

4.2.2.5 Microwave-Assisted Synthesis of the 2,5-Disubstituted-3-hydroxytetrahydrofurans

In order to assess the scope of this new tetrahydrofuran synthesis, a number of the chlorotriol precursors for the 2,5-disubstituted-3-hydroxytetrahydrofurans prepared previously using the AgOTf/Ag_2O cyclisation conditions (Chapter 3) were heated in water in a microwave as summarised in Table 24. For example, heating the chlorodiol **196** in a microwave for 20 minutes afforded the tetrahydrofuranol **206** in 93% yield, which compares well with the AgOTf/Ag_2O cyclisation of **196** (90% yield). Similarly, the

chlorodiol **195** also afforded the corresponding tetrahydrofuranol **207** in 82% yield in the microwave, compared to 83% yield with AgOTf/Ag_2O. Tetrahydrofuranol **214**, the deshydroxy analogue of the *N. anomala* oxylipid **142**, was produced in 87% from the chlorodiol **212**, and the tetrahydrofuran **229**, the synthetic precursor to natural product **142** was prepared from the chlorodiol **220** in 88% yield, compared to 84% using the AgOTf/Ag_2O cyclisation protocol. In addition, chlorodiols **278** and **279** were subjected to microwave heating to afford their corresponding 2-benzyl tetrahydrofuranols **280** and **281**, respectively.

Table 24. Cyclisation of chlorodiols to tetrahydrofuranols.

chlorohydrin	product	yield (%) cond. A[a]	yield (%) cond. B[b]
 **196**	 **207**	90	93
 **195**	 **206**	83	82
 **212**	 **214**	91	87
 **220**	 **229**	84	88
 **278**	 **280**	-	81

-	80	

a.1 equiv. AgOTf, 1 equiv. Ag_2O, THF, 0 °C to rt, 12 h; *b.* microwave, H_2O, 120 °C, 20 min.

The relative stereochemistry for each of **195**, **196**, **212**, and **220** was determined previously (Chapter 3). As depicted in Figure 16, analysis of the ^{13}C NMR and HSQC spectra derived from acetonide **282** allowed assignment of the resonances at δ 20.0 and 30.1 ppm to the acetonide methyl groups, and the resonance at δ 99 ppm to the acetal carbon, consistent with those reported for acetonides derived from 1,3-*syn*-diols.[51]

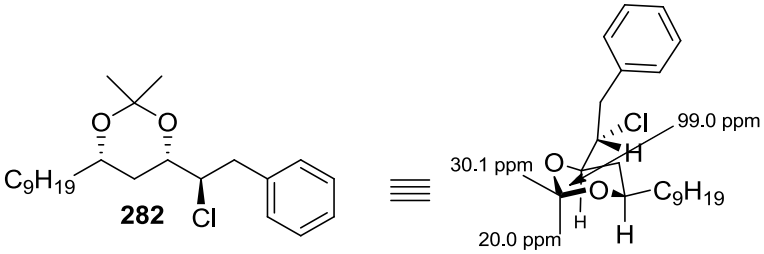


Figure 16. Conformations of the 1,3-*syn*-diol acetonide 282.

The relative stereochemistry of the tetrahydrofuranols **207**, **206**, **214**, and **229** was confirmed by nOe analysis (Chapter 3). The relative stereochemistry of both **280** and **281** was confirmed by nOe analysis as shown in Figure 17.

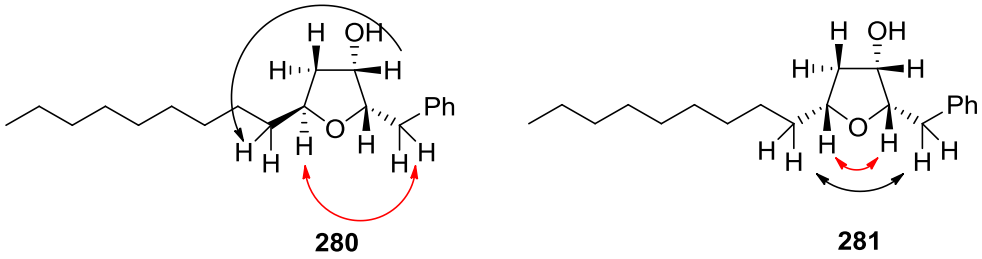


Figure 17. Stereochemical analysis of 280 and 281 by nOe.

4.2.2.6 Microwave-Assisted Cyclisation of Chlorotetrols to Carbohydrate Analogues

Building on the successful development of a microwave-assisted cyclisation of chlorodiols, this strategy was extended to the cyclisation of chlorotetrols, including the preparation of carbohydrate analogues (e.g., ribose analogues). The cyclisation of chlorotetrols is significant in that many bioactive molecules contain a modified ribose moiety, including the liposaccharide **283**, isolated from *Xanthomonas sirensis*;[59] the antiproliferative lactone **284**;[60] and the antibacterial natural product showdomycin (**285**), isolated from *Streptomyces showdoensis*.[61]

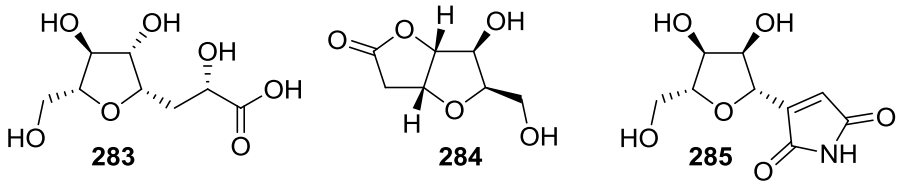
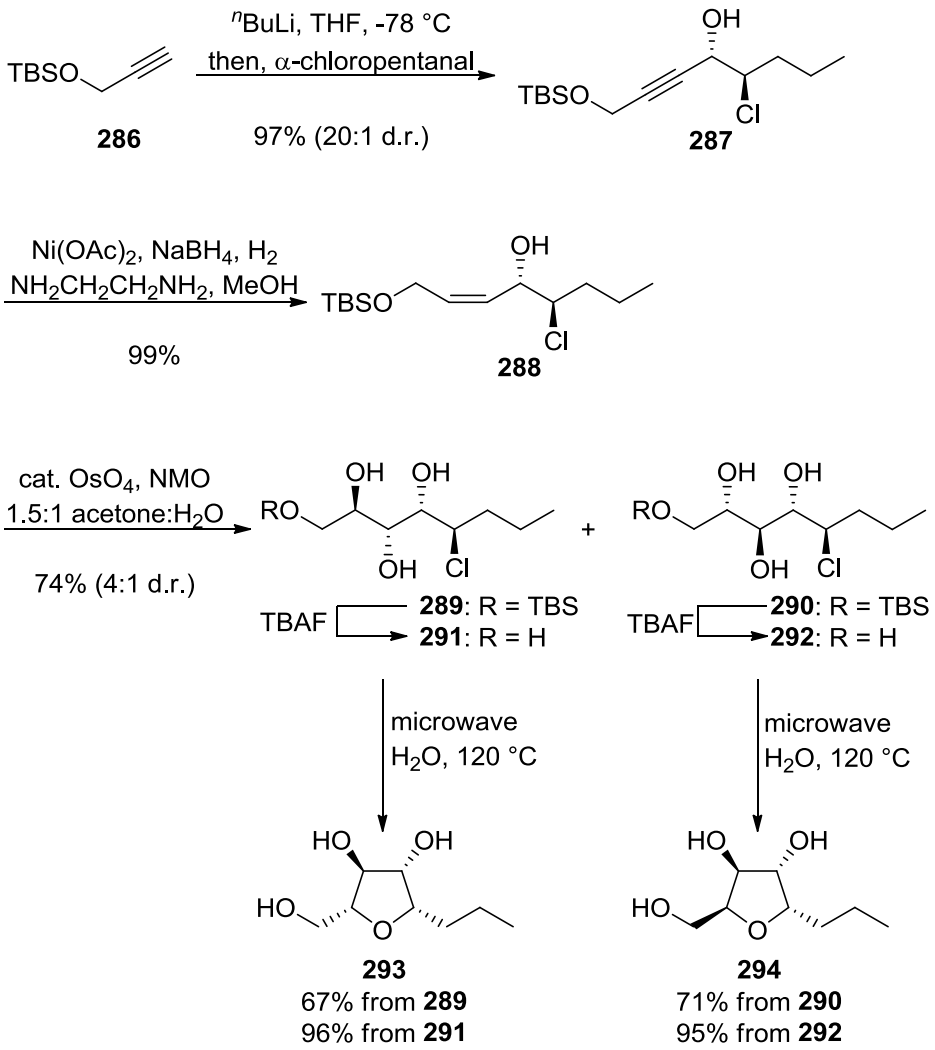


Figure 18. Representative examples of bioactive molecules containing a ribose moiety.

The preparation of chlorotetrols required for this work was initiated with the addition of TBDMS-protected propargyl alcohol **286** to α-chloropentanal (**103**) to afford the alkynyl chlorohydrin **287** with excellent diastereocontrol. Next, a selective reduction of the alkyne functionality in **287** with nickel boride[62] afforded the (*Z*)-alkenyl chlorohydrin **288**. A hydroxyl-directed dihydroxylation of the resulting (*Z*)-alkenyl chlorohydrin produced the monoprotected chlorotetrols **289** and **290** in a 4:1 mixture of diastereomers that were separable by column chromatography. Removal of the silyl protecting group from each of the diastereomers using tetrabutylammonium fluoride gave access to the unprotected chlorotetrols **291** and **292**. These chlorotetrols were then heated following the standard microwave-assisted cyclisation conditions to afford the corresponding carbohydrate analogues **293** and **294** in excellent yields. Interestingly, this method is

highly selective for the formation of the five-membered ring, without the formation of by-products. It was also found that direct cyclisation of the protected chlorotetrols **289** and **290** resulted in the formation of the identical tetrahydrofuranols **293** and **294**, repectively, in improved yields.



Scheme 49. Cyclisation of chlorotetrols to ribose analogues.

The relative stereochemistry of the newly formed carbinol stereocentres was confirmed by converting the chlorotetrol **291** to its corresponding bisacetonide **295**, and analysis using the method reported by Dana and Danechpajouh,[63] whereby stereochemical assignment of the 1,2-diols is based on ^{13}C NMR resonances of the

methyl groups in the corresponding acetonides, which should be within 0.8 ppm of each other for the 1,2-*syn*-diols, and separated by roughly 3 ppm in the 1,2-*anti*-diols. Analysis of the ^{1}H, ^{13}C NMR, 1D NOESY, and HSQC spectra derived from bisacetonide **295** allowed assignment of the resonances at δ 25.4 and 25.5 ppm to the acetonide methyl groups, consistent with those reported for the acetonides derived from 1,2-*syn*-diols using the this method. In addition, the relative stereochemistry of **293** was confirmed by nOe analysis, and the stereochemistry of **294** was determined by conversion to its corresponding acetonide **296**, followed by nOe analysis as shown in Figure 19.

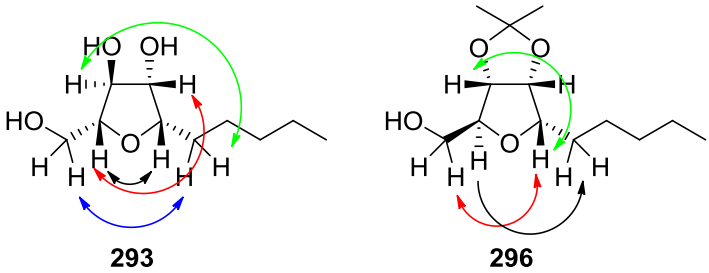
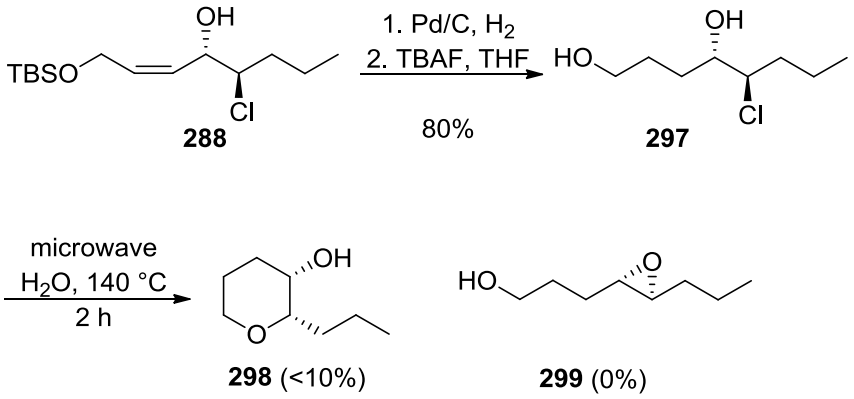


Figure 19. Stereochemical analysis of 293 and 296 by nOe.

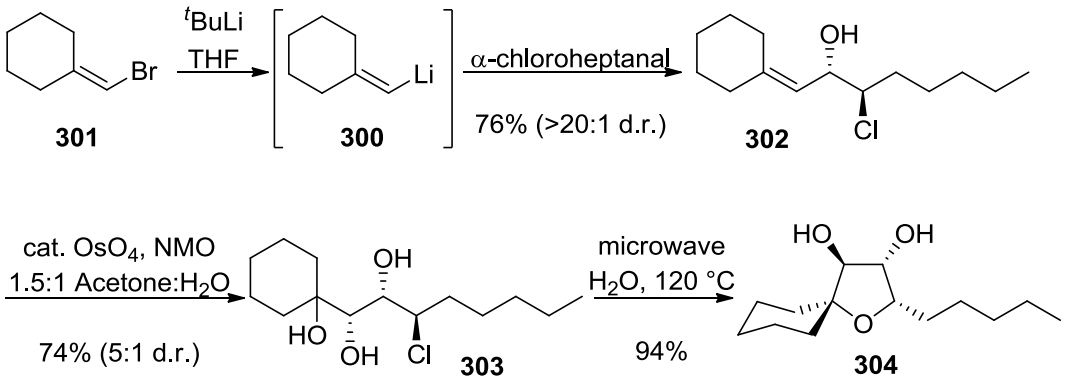
As described above, simply heating the chlorotetrols **291** and **292** (Scheme 49) in water, which could lead to formation of epoxides,[64] oxetanes,[65] tetrahydrofurans,[66] and/or tetrahydropyrans, resulted in selective formation of the corresponding carbohydrate analogues **293** and **294**, respectively. To probe this selectivity further, cyclisation of the chlorodiol **297**, prepared following a sequence of reactions involving reduction of **288** and silyl deprotection, was investigated. As indicated in Scheme 50, under standard reaction conditions, heating of **297** failed to produce appreciable amounts of the tetrahydropyran **298** or epoxide **299**. Thus, the microwave-assisted cyclisation methodology obviates the need for protecting groups on ancillary alcohol functions and is highly selective for the formation of five-membered rings.



Scheme 50. Attempted cyclisation of chlorodiol 297.

4.2.2.7 Microwave-Assisted Cyclisation of a Tertiary Chlorotriol

With the knowledge that the microwave-assisted cyclisation of chloropolyols selectively produces the corresponding tetrahydrofuran (over the corresponding 3, 4, or 6-membered heterocycles), we wished to further probe the scope of this reaction with the attempted cyclisation of a tertiary chlorotriol. Therefore, (cyclohexylidenemethyl)lithium (**300**), prepared from the reaction of bromomethylenecyclohexane (**301**) with *t*-BuLi, was treated with α-chloroheptanal (**209**) to afford the alkenyl chlorohydrin **302** with excellent diastereoselectivity. The resulting alkenyl chlorohydrin **302** was then subjected to the UpJohn dihydroxylation reaction conditions to afford the tertiary chlorotriol **303** as a 5:1 mixture of separable diastereomers. The key microwave-assisted cyclisation of **303** provided the oxaspirotetrahydrofuranol **304** (Scheme 51). This result suggests that the microwave-assisted cyclisation process is sufficiently flexible to include cyclisations of more sterically hindered chloropolyols.



Scheme 51. Synthesis of the oxaspirotetrahydrofuranol 304.

As depicted in Figure 20, analysis of the ^{1}H, ^{13}C NMR, 1D NOESY, and HSQC spectra derived from acetonide **305** allowed assignment of the resonances at δ 27.6 and 28.2 ppm to the acetonide methyl groups, consistent with those reported for the acetonides derived from 1,2-*anti*-diols using the method described by Dana and Danechpajouh.[63]

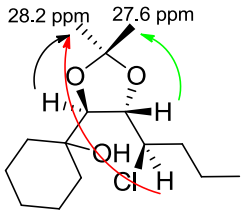
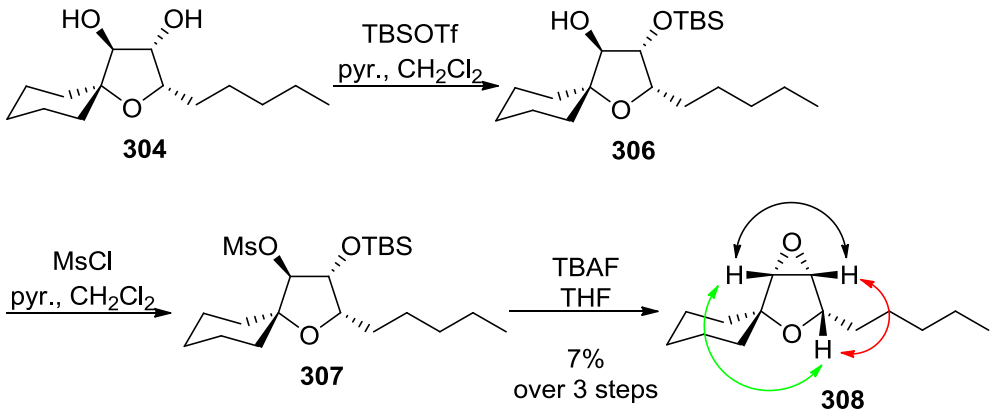


Figure 20. Stereochemical analysis of the bisacetonide 305 by the characteristic ^{13}C NMR and 1D NOESY.

The relative stereochemistry of the oxaspirotetrahydrofuranol **304** could not be accomplished by 1D NOESY analysis due to the overlap of the carbinol signals in the ^{1}H NMR spectra recorded in various solvents. In addition, the ^{1}H NMR resonances of carbinol protons in both mono- and bisacetylated derivatives were also not well resolved. Therefore, the less hindered alcohol of **304** was monosilylated to afford **306**. Next, the remaining free alcohol function was converted to a mesylate. Finally, upon removal of

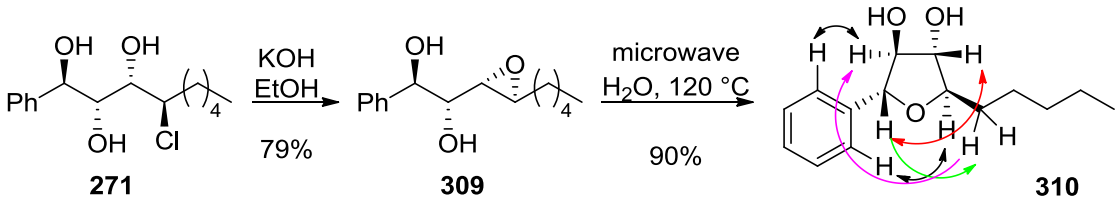
the silyl protecting group, epoxide-formation occurred, providing the dioxaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexane] (**307** → **308**). The relative stereochemistry of **308** was confirmed by nOe analysis as shown in Scheme 52.



Scheme 52. Synthesis of the epoxytetrahydrofuran 308 for the confirmation of relative stereochemistry by nOe analysis.

4.2.2.8 Microwave-Assisted Cyclisation of Epoxydiols

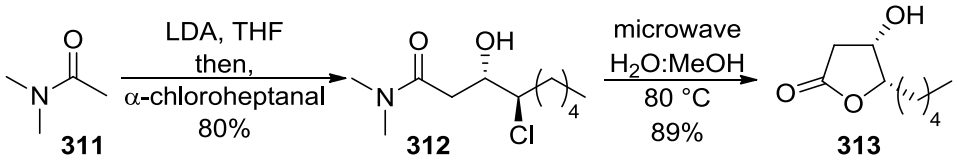
The cyclisation of the chlorotriols described above is limited to the production of 2,3-*syn*-tetrahydrofuranols. Due to this limitation, we were inspired by Jamison's work on 6-*endo*-selective epoxide-opening reactions in aqueous media,[67] to explore the 5-*endo*-epoxide-opening of epoxydiols. These latter substances are readily available from chloropolyols through treatment with base. For example, treatment of the chlorotriol **271** with KOH in EtOH afforded the epoxydiol **309**. Brief microwave-assisted heating of this material in water resulted in smooth conversion to the corresponding tetrahydrofuranol **310** (Scheme 53). The relative stereochemistry of **310** was confirmed by nOe analysis as shown in Scheme 53. Overall, this epoxide-formation/5-*endo*-epoxide-opening sequence results in a stereochemically complementary process to the direct cyclisation highlighted above.



Scheme 53. **Microwave-assisted cyclisation of epoxydiol 309 and its stereochemical analysis by nOe spectroscopy.**

4.2.2.9 Microwave-Assisted Synthesis of 3-Hydroxy-γ-lactone

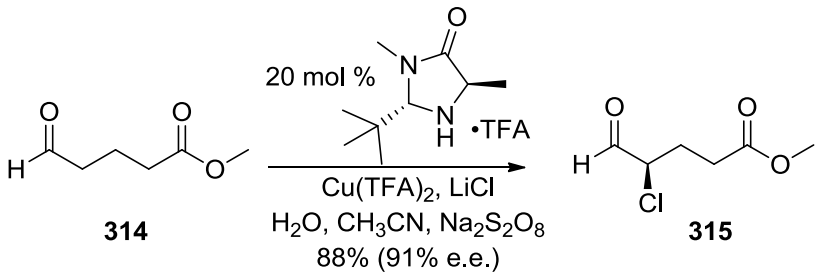
As discussed above, the microwave-assisted cyclisation of chloropolyols effects clean conversion to the corresponding 2,5-disubstituted tetrahydrofurans. As a further demonstration of the utility of this process for the construction of other valuable heterocyclic compounds, this methodology was applied to the synthesis of lactones. For example, *N*,*N*-dimethylacetamide (**311**) was sequentially treated with lithium diisopropylamide, and α-chloroheptanal (**209**), which afforded the aldol adduct **312** with excellent diastereoselectivity. The microwave-assisted cyclisation of **312** was performed in a 1:1 mixture of methanol:water at 80 °C to effect conversion to the 3-hydroxy-γ-lactone **313** in 89% yield. This cyclisation did not require temperature in excess of 100 °C to effect cyclisation. The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported by Takahata and Momose *en route* to the synthesis of cognac lactone.[68]



Scheme 54. **Microwave-assisted synthesis of 3-hydroxy-γ-lactone 313.**

4.2.2.10 Synthesis of (+)-Goniothalesdiol

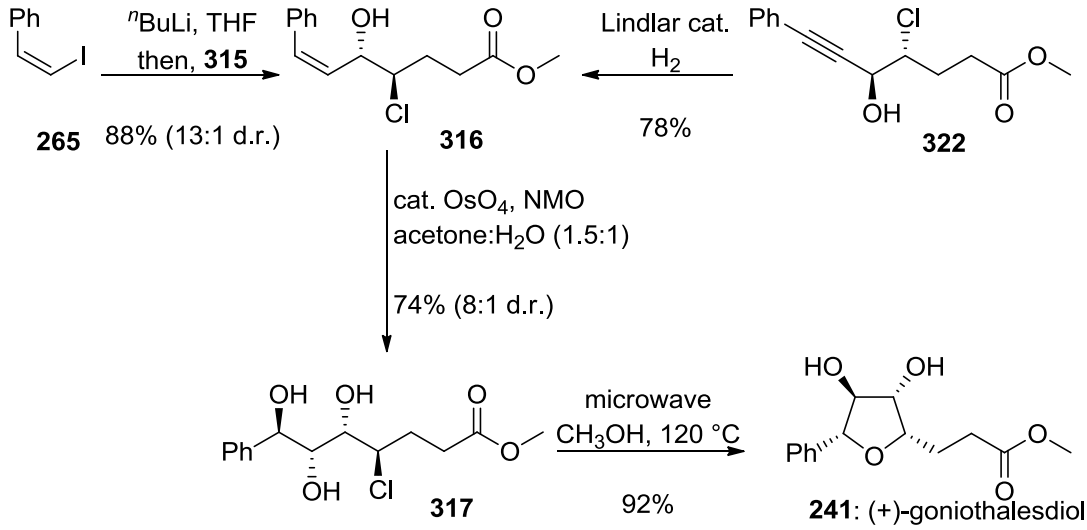
To demonstrate the efficiency of the chloropolyol cyclisation strategy, a short synthesis of (+)-goniothalesdiol (**241**) was undertaken. It was originally intended that the synthesis would initiate with the asymmetric α-chlorination of methyl 5-oxopentanoate (**314**). The prolinamide-catalysed organocatalytic α-chlorination method developed by Jørgensen, and effectively employed in previous natural product syntheses and methodological studies in the Britton research group proved indolent and provided the desired α-chloroaldehyde **315** with low enantioselectivity (40% e.e.) and as a mixutre of both the mono- and dichlorinated products (4:1). This is presumably a result of epimerisation of the α-chloroaldehyde **315** during the extended reaction times required for full conversion. Increasing the cataylst-loading reduced the amount of time required, but led to a 1:1 mixture of the mono- and dichlorinated aldehydes. Similarly, heating the reaction to 30 °C accelerated the reaction; however, these conditions also effected lower enantiocontrol (20% e.e.) and produced a mixture of mono- and dichlorinated products (2:1 mix). As described on page 8, during the course of these studies, a new α-chlorination method was reported by MacMillan. The SOMO-activated aldehyde α-chlorination reaction employs an imidazolidinone catalyst **18**, which was synthesised from L-alanine.[43,39] Fortunately, employing this modified α-chlorination procedure, the desired α-chloroaldehyde **315** was produced in good yield and enantiomeric excess (88% yield, 91% e.e.).



Scheme 55. Synthesis of (*R*)-methyl 4-chloro-5-oxopentanoate 315.

Having successfully accessed the requisite α-chloroaldehyde **315**, we returned to the total synthesis of (+)-goniothalesdiol (**241**). Thus, the sequential treatment of (*Z*)-(2-iodovinyl)benzene (**265**) with *n*-BuLi followed by (*R*)-methyl 4-chloro-5-oxopentanoate **315** afforded the alkenyl chlorohydrin **316** in excellent yield and good diastereomeric excess. Ms. Shannon Decker (summer student in the Britton group) demonstrated that the alkenyl chlorohydrin **316** was also accessible through a Lindlar reduction of the alkynyl chlorohydrin **322**, prepared from ethynyl benzene (**269**) and (*R*)-methyl 4-chloro-5-oxopentanoate **315**. At this stage, the enantiomeric excess of **316** was determined to be 91% using chiral HPLC analysis, consistent with values for the α-chloroaldehyde **315**. Next, the alkenyl chlorohydrin **316** was subjected to the UpJohn dihydroxylation, which afforded access to the chlorotriol **317** as the major component of an 8:1 diastereomeric mixture. Ms. Decker found in preliminary studies that subjecting the chlorotriol **317** to the microwave-assisted cyclisation in water resulted in a low yielding mixture of the corresponding acid **318** and the lactone **319**. It was observed that when the microwave-assisted cyclisation is performed using methanol as the solvent, lactone formation is avoided, and (+)-goniothalesdiol (**241**) is produced in excellent yield. Interestingly, certain resonances in the ^{13}C NMR spectrum of (+)-goniothalesdiol (**241**) recorded in $CDCl_3$ were found to shift slightly and differ from those reported depending on concentration. However, the ^{13}C NMR spectrum of a 0.01 M solution of **241** was identical

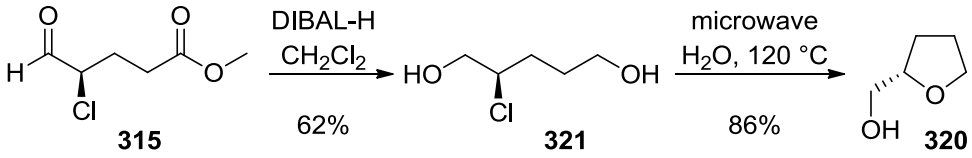
to that reported for both natural and synthetic (+)-goniothalesdiol (**241**). It is noteworthy that this four-step synthesis of (+)-goniothalesdiol (**241**) compares very favourably with those reported in the literature that range in length from 10 to 16 linear steps.[31-35]



Scheme 56. Synthesis of (+)-goniothalesdiol (241).

4.2.2.11 Synthesis of Tetrahydrofurfuryl Alcohol

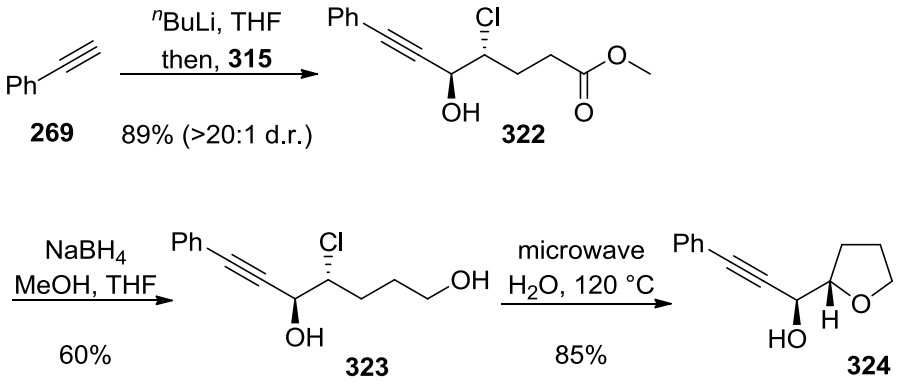
To demonstrate an additional application of (*R*)-methyl 4-chloro-5-oxopentanoate (**315**), the synthesis of tetrahydrofurfuryl alcohol (**320**) was undertaken. To this end, the α-chloroaldehyde **315** was reduced with DIBAL-H to provide the chlorodiol **321**. Following our standard microwave-assisted cyclisation conditions, heating this material in water afforded tetrahydrofurfuryl alcohol (**320**) in 86% yield. The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported by Alvarez-Builla.[69]



Scheme 57. Synthesis of tetrahydrofurfuryl alcohol 320.

4.2.2.12 Synthesis of the Tetrahydrofuran Core Common to the Annonaceous Acetogenins

The synthesis of a substituted hydroxymethyltetrahydrofuran was also carried out from the α-chloroaldehyde **315**. Toward this end, the treatment of ethynyl benzene (**269**) with *n*-BuLi followed by (*R*)-methyl 4-chloro-5-oxopentanoate (**315**) afforded the alkynyl chlorohydrin **322** with excellent diastereocontol. Next, reduction of the ester functionality was accomplished with sodium borohydride in methanol to produce the chlorodiol **323**. A subsequent microwave-assisted cyclisation of this material yielded the acetogenin subunit **324** in 85% yield. The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported by Karakhanov.[70]



Scheme 58. Synthesis of the acetogenins subunit 324.

4.2.2.13 Conclusions

In summary, this Chapter describes the development of a concise and stereochemically flexible approach to functionalised tetrahydrofuranols that involves simply heating readily available chloropolyols in water. This operationally straightforward reaction is both high yielding and regioselective for the formation of tetrahydrofurans. Thus, complicated protecting group strategies can be avoided, as displacement of the chloride by ancillary alcohol functions does not occur at an appreciable rate under these

reaction conditions. The efficiency of this approach to 2,5-disubstituted-3,4-hydroxytetrahydrofurans was also demonstrated in the preparation of carbohydrate analogues, core of acetogenins, and a short (four-step) synthesis of the natural product (+)-goniothalesdiol (**241**).

4.3 Experimental

General

All reactions described were performed under an atmosphere of dry argon using oven dried glassware unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[71] Concentration and removal of trace solvents was done *via* a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) or deuterobenzene (C_6D_6) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR; CH_3OD: δ 3.31, ^{1}H NMR; δ 49.0, ^{13}C NMR; C_6D_6: δ 7.16, ^{1}H NMR; δ 128.1, ^{13}C NMR).

Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants, assignment (where possible). NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz) or Bruker 400 (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of 1H-1H COSY, HMBC, HMQC, TOCSY and 1D NOESY spectra.

High performance liquid chromatography (HPLC) analysis was performed on an Agilent 1200 HPLC, equipped with a variable wavelength UV-Vis detector and Chiracel OD-H chiral column (0.46 cm x 25 cm).

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 GC/MS/MS mass spectrometer. High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS mass spectrometer.

Optical rotation was measured on a Perkin Elmer Polarimeter 341 at 589 nm.

Microwave reactions were performed in either a Biotage Initiator 2.5 or a CEM Discover LabMate at 2.45 GHz. These reactions were not mechanically stirred.

Preparation of (1*Z*,3*S,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (268)**

Method A:

To a cold (-78 °C), stirred solution of (*Z*)-(2-iodovinyl)benzene (**265**)[49,50] (120 mg, 0.50 mmol) in THF (10 mL) was added *n*-butyllithium (2.0 M soln. in hexane, 280 µL, 0.55 mmol). The resultant solution was stirred at -78 °C for 30 minutes. After this time, a solution of α-chloroheptanal (**209**) (82 mg, 0.55 mmol) in THF (1.0 mL) was then added in one portion at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (2 mL) was then added, the mixture was diluted with ethyl acetate (10 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (1*Z*,3*S**,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (**7**) (111 mg, 88%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.37-7.35 (m, 4H), 7.29 (m, 1H), 6.76 (dd, 1H, *J* = 0.9, 11.4 Hz), 5.85 (dd, 1H, *J* = 9.0, 11.4 Hz), 4.63 (dddd, 1H, *J* = 0.9, 4.2, 7.8, 9.0 Hz), 4.11

(m, 1H), 2.22 (d, 1H, *J* = 7.8 Hz), 1.66 (m, 2H), 1.51 (m, 1H), 1.26 (m, 5H), 0.91 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.3, 134.5, 134.2, 129.8, 128.7, 128.5, 128.4, 127.6, 70.1, 68.6, 33.6, 31.2, 26.2, 22.5, 14.0.

IR (neat): 3393, 2955, 2930, 2859 cm^{-1}

Exact mass calcd. for $C_{15}H_{20}Cl$: 235.1254 (M-H_2O); found: 235.1248 (M-H_2O).

Preparation of (1*R,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (271)**

Method A:

To a solution of (1*S**,2*R**)-2-chloro-1-[(2'*S**,3'*R**)-3'-phenyloxiran-2-yl]heptan-1-ol (**274**) (31 mg, 0.12 mmol) in trifluoroethanol (1.0 mL) was added 0.5 M aqueous sulfuric acid (1.0 mL, 0.50 mmol). The resulting solution was stirred for 40 hours. The mixture was then diluted with dichloromethane (10 mL), washed with water (10 mL) and the layers separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude white solid (as a 8:1 diastereomeric mixture). Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**271**) (22 mg, 67%) as a white solid (m.p. 144 °C)

Method B:

To a solution of (1*Z*,3*S**,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (**268**) (500 mg, 2.0 mmol) in acetone (18 mL) and water (12 mL) was added *N*-methylmorpholine *N*-oxide (350 mg, 3.0 mmol) and osmium tetroxide (5 mg, 0.02 mmol). The resulting solution was stirred for 24 hours. After this time, saturated aqueous sodium hydrosulfite (10 mL) was added, the mixture was filtered through a pad of Celite® and the cake washed with acetone (3 x 20 mL). The filtrate was neutralised to pH 7 (phosphate buffer) with

aqueous sulfuric acid, and the acetone was removed by rotary evaporation. The mixture was diluted with ethyl acetate (20 mL) and washed with brine (20 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**271**) (450 mg, 79%) as a white solid (m.p. 144 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40-7.39 (m, 4H), 7.33 (m, 1H), 4.95 (d, 1H, *J* = 5.4 Hz), 4.15 (d, 1H, *J* = 5.4 Hz), 3.95 (ddd, 1H, *J* = 3.0, 7.8, 10.8 Hz), 3.82 (d, 1H, *J* = 7.8 Hz), 2.99 (s, 1H), 2.76 (s, 1H), 2.51 (s, 1H), 1.94 (m, 1H), 1.62-1.52 (m, 2H), 1.34-1.21 (m, 5H), 0.88 (t, 3H, *J* = 6.0 Hz).

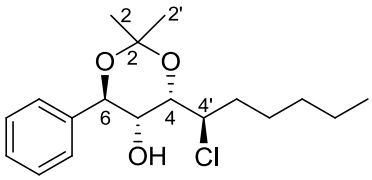
^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.2, 128.9, 128.2, 126.2, 76.1, 72.62, 72.58, 63.1, 33.6, 31.3, 25.7, 22.5, 14.0.

IR (neat): 3549, 3365, 2955, 2926, 2861, 1455 cm^{-1}

Exact mass calcd. for $C_{15}H_{23}ClO_3Na$: 309.1233 (M + Na); found: 309.1231 (M + Na).

The relative stereochemistry of the newly formed carbinol stereocentres were determined by analysis of the ^{1}H and ^{13}C NMR spectra and 1D NOESY spectra recorded on the corresponding acetonide **272** following the method reported by Rychnovsky.[51]

To a solution of (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**271**) (10 mg, 0.035 mmol) in dichloromethane (3 mL) was added 2,2-dimethoxypropane (17 μL, 0.14 mmol) and *p*-toluenesulfonic acid (1 mg, 0.005 mmol). The mixture was allowed to stir for one hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes-ethyl acetate) afforded the corresponding acetonide **272**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48 (d, 2H, *J* = 7.2 Hz), 7.37 (t, 2H, *J* = 7.2 Hz), 7.30 (d, 1H, J = 7.2 Hz), 4.57 (d, 1H, *J* = 7.2 Hz, H-6), 4.19 (ddd, 1H, *J* = 3.2, 5.6, 7.2 Hz, H-5), 4.14 (dt, 1H, *J* = 2.4, 9.6 Hz, H-4'), 3.92 (dd, 1H, *J* = 3.2, 9.6 Hz, H-4), 2.16 (d, 1H, *J* = 5.6 Hz, OH), 2.08 (m, 1H), 1.68 (m, 2H), 1.48 (s, 3H, H-2'), 1.42 (s, 3H, H-2"), 1.38- 1.26 (m, 6H), 0.91 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.5, 128.5, 127.8, 126.3, 102.0 (C2), 75.3 (C6), 74.7 (C5), 73.9 (C4), 59.4 (C4'), 34.0 (C4"), 31.4, 25.2, 24.0 (C2"), 24.3 (C2'), 22.6, 14.0.

Preparation of (1*S,2*R**)-2-chloro-1-[(2'*S**,3'*R**)-3'-phenyloxiran-2-yl]heptan-1-ol (274)**

To a solution of (1*Z*,3*S**,4*R**)-4-chloro-1-phenylnon-1-en-3-ol (**268**) (630 mg, 2.5 mmol) in dichloromethane (20 mL) was added *m*-chloroperoxybenzoic acid (1.7 g, 7.5 mmol). The resulting solution was stirred for three hours. Saturated aqueous sodium thiosulfate (10 mL) was then added; the mixture was diluted with dichloromethane (20 mL) and washed with a saturated aqueous solution of sodium bicarbonate, and the layers separated. The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (1*S**,2*R**)-2-chloro-1-[(2*S**,3*R**)-3-phenyloxiran-2-yl]heptan-1-ol (**274**) (520 mg, 77%, 15:1 diastereomeric mixture) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38-7.30 (m, 5H), 4.27 (d, 1H, *J* = 4.2 Hz), 3.85 (ddd, 1H, *J* = 4.8, 7.2, 7.8 Hz), 3.46 (dd, 1H, *J* = 4.2, 7.8 Hz), 3.27 (m, 1H), 2.41 (d, 1H, *J* = 4.8 Hz), 1.50 (m, 2H), 1.41 (m, 1H), 1.26-1.04 (m, 5H), 0.84 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 134.6, 128.3, 128.1, 126.2, 70.8, 64.9, 60.3, 58.8, 33.7, 31.1, 25.9, 22.3, 13.9.

IR (neat): 3420, 2956, 2930, 2860, 1457 cm^{-1}

Exact mass calcd. for $C_{15}H_{22}ClO_2$: 269.1303 (M+H); found: 269.1291 (M+H).

Preparation of (2*S,3*S**,4*S**,5*R**)-2-pentyl-5-phenyltetrahydrofuran-3,4-diol (277)**

(1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**271**) (500 mg, 1.7 mmol) was placed in a 10 mL vial, deionised water (3 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the water was decanted off and the crude powder dried. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (2*S**,3*S**,4*S**,5*R**)-2-pentyl-5-phenyltetrahydrofuran-3,4-diol (**277**) (390 mg, 91%) as a white solid (m.p. 122 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.41 (d, 2H, *J* = 7.2 Hz), 7.35 (t, 2H, *J* = 7.2 Hz), 7.28 (t, 1H, *J* = 7.2 Hz), 4.62 (d, 1H, *J* = 4.2 Hz), 4.10-4.07 (m, 2H), 4.03 (ddd, 1H, *J* = 1.8, 4.2, 6.6 Hz), 2.21 (d, 1H, *J* = 4.2 Hz), 1.78 (m, 1H), 1.71 (m, 1H), 1.66 (d, 1H, *J* = 6.6 Hz), 1.53 (m, 1H), 1.43 (m, 1H), 1.40-1.32 (m, 4H), 0.91 (t, 3H, *J* = 6.6 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.1, 128.6, 127.8, 126.0, 86.3, 85.4, 81.4, 79.3, 31.9, 28.5, 25.8, 22.5, 14.0.

IR (neat): 3344, 3054, 2917, 2856, 1266 cm^{-1}

Exact mass calcd. for $C_{15}H_{22}O_3$: 251.1642 (M+H); found: 251.1657 (M+H).

Preparation of (2*R*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (207)

The (1*R*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**195**) (25 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*R*,3*R*,5*R*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**207**) (17 mg, 82%) as a light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.40 (d, 2H, *J* = 7.8 Hz), 7.34 (t, 2H, *J* = 7.2 Hz), 7.26 (t, 1H, *J* = 7.2 Hz), 4.87 (dd, 1H, *J* = 6.0 Hz, 8.4 Hz), 4.27 (m, 1H), 3.76 (ddd, 1H, *J* = 9.6, 7.2, 9.6 Hz), 2.70 (ddd, 1H, *J* = 6.0, 8.4, 13.8 Hz), 1.92 (ddd, 1H, *J* = 1.8, 6.0, 13.8 Hz), 1.79 (m, 1H), 1.72 (m, 1H), 1.60-1.44 (m, 3H), 1.00 (t, 3H, *J* = 7.8 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.0, 128.4, 127.3, 125.9, 83.6, 78.7, 73.1, 44.2, 30.9, 19.6, 14.3.

IR (neat): 3418, 3063, 2957, 2871, 1493, 1455, 1330, 1089 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1376 (M+H).

Preparation of (2*R*,3*R*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (206)

The (1*S*,3*R*,4*S*)-4-chloro-1-phenylheptan-1,3-diol (**196**) (25 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl

acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*R*,3*R*,5*S*)-5-phenyl-2-propyltetrahydrofuran-3-ol (**206**) (18 mg, 93%) as a light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.34-7.23 (m, 5H), 5.26 (dd, 1H, *J* = 6.6, 9.6 Hz), 4.36 (d, 1H, *J* = 1.8 Hz), 4.06 (ddd, 1H, *J* = 3.0, 7.2, 9.6 Hz), 2.45 (dd, 1H, 6.6, 7.2 Hz), 2.08 (ddd, 1H, J = 4.2, 9.6, 13.8 Hz), 1.75 (m, 1H), 1.64 (m, 2H), 1.56 (m, 2H), 1.47 (m, 1H), 1.69-1.45 (m, 4H), 1.01 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.8, 128.4, 127.2, 125.3, 83.1, 78.2, 73.7, 44.7, 31.3, 19.7, 14.3.

IR (neat): 3423, 3063, 2957, 2871, 1455, 1330, 1089 cm^{-1}

Exact mass calcd for $C_{13}H_{19}O_2$: 207.1385 (M+H); found: 207.1364 (M+H).

Preparation of (2*S*,3*S*,5*R*)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (214)

The (6*R*,7*S*,9*R*)-6-chlorononadec-18-en-7,9-diol (**212**) (33 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S*,3*S*,5*R*)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (**214**) (27 mg, 87%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.81 (tdd, 1H, *J* = 6.6, 10.2, 17.4 Hz), 4.98 (dd, 1H, *J* = 1.8, 17.4 Hz), 4.92 (dd, 1H, *J* = 1.8, 10.2 Hz), 4.15 (m, 1H), 3.75 (m, 1H), 3.49 (dt, 1H, *J* = 3.6, 7.2 Hz), 2.37 (ddd, 1H, J = 6.6, 7.8, 14.4 Hz), 2.03 (m, 1H), 1.72-1.59 (m, 3H), 1.53-1.49 (m, 2H), 1.47-1.28 (m, 18H), 0.89 (t, 3H, *J* = 6.6 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.2, 114.1, 83.1, 77.6, 72.9, 41.8, 36.8, 33.8, 32.0, 29.6, 29.5, 29.4, 29.1, 28.9, 28.6, 26.2, 26.0, 22.6, 14.0.

IR (neat): 3316, 2920, 2882, 2875, 1612, 1499, 1491, 1281, 1080 cm^{-1}

Exact mass calcd for $C_{19}H_{37}O_2$: 297.2794 (M+H); found: 297.2795 (M+H).

Preparation of (2*S*,3*S*,5*R*)-2-pentyl-5-(dec-9-enyl)tetrahydrofuran-3-ol (229)

The (1*E*,3*S*,5*S*,6*R*)-6-chloro-1-phenylundec-1-en-3,5-diol (**220**) (29 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S*,3*S*,5*S*)-2-pentyl-5-styryl-tetrahydrofuran-3-ol (**229**) (23 mg, 84%) as a white solid (m.p. = 63-65 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, 2H, *J* = 7.2 Hz), 7.30 (t, 2H, *J* = 7.5 Hz), 7.23 (tt, 1H, *J* = 1.1, 7.2 Hz), 6.61 (d, 1H, *J* = 15.9 Hz), 6.31 (dd, 1H, *J* = 6.9, 15.9 Hz), 4.49 (m, 1H), 4.24 (m, 1H), 3.68 (dt, 1H, *J* = 2.3, 6.7 Hz), 2.52 (ddd, 1H, *J* = 5.9, 8.7, 14.2 Hz), 1.84 (ddd, 1H, *J* = 1.6, 5.6, 14.2), 1.77-1.65 (m, 2H), 1.57 (d, 1H, *J* = 7.4 Hz), 1.49 (m, 1H), 1.42 (m, 1H), 1.35 (m, 4H), 0.90 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 136.5, 131.0, 130.8, 128.5, 127.6, 126.6, 83.7, 78.0, 73.2, 42.3, 32.0, 28.8, 26.0, 22.6, 14.0.

IR (thin film): 3425, 2953, 2925, 2857, 1644, 1493, 1467, 1449, 1342, 1156, 1087 cm^{-1}

Exact mass calcd. for $C_{17}H_{24}O_2$: 260.1776 (M+H); found: 260.1788 (M+H).

Preparation of (2*R,3*S**,5*S**)-2-chloro-1-phenyltetradecane-3,5-diol (279) and (2*R**,3*S**,5*R**)-2-chloro-1-phenyltetradecane-3,5-diol (278)**

To a cold (-78 °C), stirred solution of (2*R**,3*S**)-2-chloro-3-hydroxy-1-phenyltetradecan-5-one[72] (170 mg, 0.50 mmol) in THF (10 mL) was added diisobutylaluminum hydride (1.00 M solution in hexanes, 1.25 mL, 1.25 mmol). The resulting solution was stirred at -78 °C for four hours. Aqueous HCl (1 N) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (2*R**,3*S**,5*S**)-2-chloro-1-phenyltetradecane-3,5-diol (**279**) (101 mg, 59%) and its diastereomer (2*R**,3*S**,5*R**)-2-chloro-1-phenyltetradecane-3,5-diol (**278**) (49 mg, 29%) as clear oils.

Data for (**279**):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 4.11 (m, 1H), 4.00 (m, 1H), 3.89 (m, 1H), 3.26 (dd, 1H, *J* = 4.2, 14.4 Hz), 2.99 (dd, 1H, *J* = 9.0, 14.4 Hz), 2.94 (dd, 1H, 9.6, 14.4 Hz), 1.94 (m, 1H), 1.66 (m, 1H), 1.52 (m, 2H), 1.47-1.26 (m, 14H), 0.89 (t, 1H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 137.6, 129.4, 128.4, 126.7, 75.1, 72.7, 67.5, 39.5, 38.6, 38.2, 31.9, 29.54, 29.53, 29.51, 29.3, 25.6, 22.7, 14.1.

IR (neat): 3372, 2954, 2925, 2854, 1454, 1091, 700 cm^{-1}

Exact mass calcd. for $C_{20}H_{34}ClO_2$: 341.2247 (M+H); found: 341.2244 (M+H).

Data for (**278**):

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.36-7.27 (m, 5H), 4.11 (m, 1H), 4.00 (m, 1H), 3.89 (m, 1H), 3.26 (dd, 1H, *J* = 4.2, 14.4 Hz), 2.99 (dd, 1H, *J* = 9.0, 14.4 Hz), 2.94 (dd, 1H, 9.6, 14.4 Hz), 1.94 (m, 1H), 1.66 (m, 1H), 1.52 (m, 2H), 1.47-1.26 (m, 14H), 0.89 (t, 1H, *J* = 7.2 Hz).

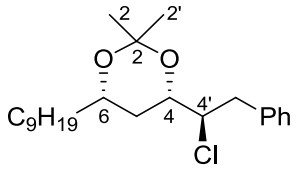
^{13}C NMR (150 MHz, $CDCl_3$) δ: 137.6, 129.4, 128.4, 126.7, 75.1, 72.7, 67.5, 39.5, 38.6, 38.2, 31.9, 29.54, 29.53, 29.51, 29.3, 25.6, 22.7, 14.1.

IR (neat): 3372, 2954, 2925, 2854, 1454, 1091, 700 cm^{-1}

Exact mass calcd. for $C_{20}H_{34}ClO_2$: 341.2247 (M+H); found: 341.2244 (M+H).

The relative stereochemistry of the newly formed carbinol stereocentre in **279** was determined by analysis of the ^{1}H and ^{13}C NMR spectra recorded on the corresponding acetonide **282** following the method reported by Rychnovsky.[51]

To a solution of (2*R**,3*S**,5*S**)-2-chloro-1-phenyltetradecane- 3,5-diol (**279**) (10 mg, 0.03 mmol) in dichloromethane (1 mL) was added 2,2-dimethoxypropane (15 µL, 0.12 mmol) and *p*-toluenesulfonic acid (1 mg, 0.006 mmol). The mixture was allowed to stir for one hour and then concentrated to give crude yellow product. Purification of the crude product by flash chromatography (silica gel, 10:1 hexanes-ethyl acetate) afforded the corresponding acetonide **282**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.32-7.25 (m, 5H), 3.92 (dt, 1H, *J* = 3.6, 7.8Hz, H-4'), 3.80 (m, 1H, H-6), 3.77 (m, 1H, H-4), .32 (dd, 1H, *J* = 3.6, 14.4 Hz, H-4"), 2.94 (dd, 1H, *J* =

7.8, 14.4 Hz, H-4”), 1.90 (dt, 1H, *J* = 2.4, 12.6 Hz, H-5), 1.53 (m, 1H, H-5), 1.44 (s, 3H, H-2’), 1.43 (s, 3H, H-2’), 1.39-1.15 (m, 16H), 0.88 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 129.9, 128.1, 126.8, 99.0, 71.3 (C6), 68.9 (C4), 65.5 (C4’), 39.6 (C4”), 36.4, 34.3 (C5), 31.9, 30.1 (C2’), 29.57, 29.56, 29.53, 29.3, 24.9, 22.7, 20.0 (C2’’), 14.2.

Preparation of (2*S,3*S**,5*S**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (281)**

The (2*R**,3*S**,5*S**)-2-chloro-1-phenyltetradecane-3,5-diol (**279**) (34 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S**,3*S**,5*S**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (**281**) (24 mg, 80%) as a clear oil.

^{1}H NMR (600 MHz, CD_3OD) δ: 7.29 (d, 2H, *J* = 7.2 Hz), 7.25 (t, 2H, *J* = 7.2 Hz), 7.16 (t, 1H, *J* = 7.2 Hz), 4.25 (m, 1H), 4.12 (m, 1H), 4.00 (dt, 1H, *J* = 3.0, 7.2 Hz), 2.95 (dd, 1H, *J* = 6.6, 13.8 Hz), 2.84 (dd, 1H, *J* = 7.2, 13.8 Hz), 2.05 (dd, 1H, *J* = 6.0, 13.2 Hz), 1.71 (ddd, 1H, *J* = 4.8, 9.0, 13.2 Hz), 1.56 (m, 1H), 1.40 (m, 1H), 1.34-1.22 (m, 16H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, CD_3OD) δ: 140.5, 130.3, 129.2, 127.1, 84.7, 78.8, 73.6, 42.6, 37.3, 36.5, 33.1, 30.77, 30.75, 30.7, 30.5, 27.1, 23.7, 14.5.

IR (neat): 3501, 3028, 2925, 2854 cm^{-1}

Exact mass calcd. for $C_{20}H_{33}O_2$: 305.2475 (M+H); found: 305.2477 (M+H).

Preparation of (2*S,3*S**,5*R**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (280)**

The (2*R**,3*S**,5*R**)-2-chloro-1-phenyltetradecane-3,5-diol (**278**) (34 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S**,3*S**,5*R**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (**280**) (24 mg, 81%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.30-7.18 (m, 5H), 7.27-7.24 (m, 3H), 4.10 (m, 1H), 3.83-3.73 (m, 2H), 3.02 (d, 2H, *J* = 6.8Hz), 2.35 (ddd, 1H, *J* = 6.4, 8.2, 14.0 Hz), 1.77-1.63 (m, 1H), 1.55-1.50 (m, 2H, *J* = 9.8, 15.0 Hz), 1.46-1.38 (m, 1H), 1.81 (m, 1H), 1.76 (ddd, 1H, *J* = 2.4, 8.6, 15.0 Hz), 1.53-1.47 (m, 2H), 1.45-1.38 (m, 2H) 1.34-1.26 (m, 14H), 0.88 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 138.6, 129.2, 128.5, 126.3, 83.9, 77.9, 72.4, 41.6, 36.9, 35.1, 31.9, 29.64, 29.57, 29.55, 29.3, 26.2, 22.7, 14.1.

IR (neat): 3450, 2925, 2854, 1092 cm^{-1}

Exact mass calcd. for $C_{20}H_{33}O_2$: 305.2475 (M+H); found: 305.2481 (M+H).

Preparation of (4*S,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-yn-4-ol (287)**

To a cold (-78 °C), stirred solution of *t*-butyldimethyl(prop-2-ynyloxy)silane (**286**)[73] (3.50 g, 20.5 mmol) in THF (100 mL) was added *n*-butyllithium (2.20 M soln. in hexane, 10.3 mL, 22.6 mmol). The resulting solution was stirred at -78 °C for 60 minutes. After this time, a solution of α-chloropentanal (**103**) (3.00 g, 24.6 mmol) in THF (10.0 mL) was

added in one portion at -78 °C and the resulting mixture was stirred for an additional 60 minutes. Saturated aqueous NH_4Cl (10 mL) was then added, the mixture was diluted with diethyl ether (40 mL) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 25 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-yn-4-ol (**287**) (5.78 g, 97%) as a white solid (m.p.79 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.54 (m, 1H), 4.36 (s, 2H), 4.03 (ddd, 1H, *J* = 4.2, 5.4, 7.8 Hz), 2.53 (d, 1H, *J* = 8.4 Hz), 1.80 (m, 2H), 1.61 (m, 1H), 1.42 (m, 1H), 0.94 (t, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), 0.11 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 85.6, 81.3, 66.6, 66.2, 51.6, 35.6, 25.7, 19.7, 18.2, 13.5, -5.1.

IR (neat): 3382, 2971, 2129, 1433 cm^{-1}

Exact mass calcd. for $C_{14}H_{28}ClO_2Si$: 291.1547 (M+H); found: 291.1540 (M+H).

Preparation of (2*Z*,4*S,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-en-4-ol (288)**

To a cold (0 °C), stirred solution of nickel (II) acetate tetrahydrate (230 mg, 0.90 mmol) in methanol (18 mL) was added sodium borohydride (34 mg, 0.90 mmol) and the mixture was stirred for 5 minutes. To the resulting black solution was added ethylenediamine (120 µL, 1.8 mmol) and the mixture was stirred for an additional 5 minutes. After this time the reaction was placed under an atmosphere of H_2 and a solution of (4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-yn-4-ol (**287**) (3.5 g, 12 mmol) in methanol (6 mL) was introduced. This mixture was allowed to stir for three hours at room temperature under an atmosphere of H_2 (balloon). The reaction mixture

was then filtered through Celite® and the filtrate was concentrated. Purification of the crude product by flash column chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (2*Z*,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-en-4-ol (**288**) (3.5 g, 99%) as a white solid (m.p. 75-77 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (m, 1H), 5.61 (m, 1H), 4.52 (m, 1H), 4.30 (ddd, 1H, *J* = 1.6, 6.0, 14.0 Hz), 4.22 (ddd, 1H, *J* = 1.6, 6.0, 14.0 Hz), 3.99 (dt, 1H, *J* = 4.0, 8.0 Hz), 2.74 (d, 1H, *J* = 5.6 Hz), 1.76-1.56 (m, 3H), 1.39 (m, 1H), 0.91 (t, 3H, *J* = 7.2 Hz), 0.89 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.4, 128.9, 70.6, 67.5, 59.9, 35.2, 25.9, 19.7, 18.2, 13.5, -5.32, -5.34.

IR (neat): 3347, 3204, 2955, 2929, 2859, 1504, 1465, 1034 cm^{-1}

Exact mass calcd. for $C_{14}H_{30}ClO_2Si$: 293.1704 (M+H); found: 293.1707 (M+H).

Preparation of (2*R,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (289) and (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (290)**

To a solution of (2*Z*,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooct-2-en-4-ol (**288**) (1.2 mg, 4.1 mmol) in acetone (37 mL) and water (25 mL) was added *N*-methylmorpholine *N*-oxide (720 mg, 6.2 mmol) and osmium tetroxide (10 mg, 0.04 mmol). The resulting solution was stirred for 24 hours. After this time, saturated aqueous sodium hydrosulfite (20 mL) was added, the mixture was filtered through a pad of Celite® and the cake washed with acetone (3 x 20 mL). The filtrate was then neutralised to pH 7 with aqueous sulfuric acid and the acetone was removed by rotary evaporation. The mixture was diluted with ethyl acetate (30 mL) and washed with brine (20 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$),

filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 to 2:1 hexanes-ethyl acetate) afforded (2*R**,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**289**) (793 mg, 59%) as a white solid (m.p. 90-92 °C) and (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**290**) (196 mg, 15%) as a white solid (m.p. 89-90 °C).

Data for (**289**):

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.05-3.99 (m, 2H), 3.85 (t, 1H, *J* = 6.8 Hz), 3.79-3.77 (m, 2H), 3.69 (dd, 1H, *J* = 5.2, 10.0 Hz), 3.36 (d, 1H, *J* = 6.4 Hz), 3.98 (d, 1H, *J* = 6.8 Hz), 2.93 (d, 1H, *J* = 5.2 Hz), 2.02 (m, 1H), 1.71-1.60 (m, 2H), 1.45 (m, 1H), 0.94 (t, 3H, *J* = 7.2 Hz), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 73.1, 71.9, 70.7, 64.1, 62.7, 35.8, 25.8, 19.2, 18.2, 13.5, -5.5.

IR (neat): 3394, 3253, 2957, 2930, 2857, 1464, 1256 cm^{-1}

Exact mass calcd. for $C_{14}H_{32}ClO_4Si$: 327.1753 (M+H); found: 327.1760 (M+H).

Data for (**290**):

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.33 (dt, 1H, *J* = 3.2, 10.4 Hz), 3.92-3.80 (m, 5H), 4.53 (dd, 1H, *J* = 4.2, 8.0 Hz), 3.27 (s, 1H), 3.17 (s, 1H), 2.91 (s, 1H), 1.85 (m, 1H), 1.77 (m, 1H), 1.67 (m, 1H), 1.43 (m, 1H), 0.95 (t, 3H, *J* = 7.2 Hz), 0.91 (s, 9H), 0.11 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 76.9, 73.3, 71.5, 65.8, 64.9, 33.2, 25.8, 19.8, 18.2, 13.5, -5.6.

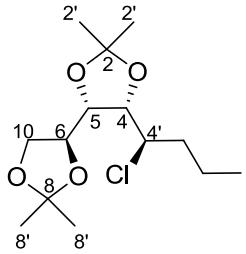
IR (neat): 3401, 3252, 2957, 2930, 2858, 1471, 1464, 1254 cm^{-1}

Exact mass calcd. for $C_{14}H_{32}ClO_4Si$: 327.1753 (M+H); found: 327.1760 (M+H).

The relative stereochemistry of the newly formed carbinol stereocentres in **290** were determined by analysis of the ^{1}H and ^{13}C NMR spectra and 1D NOESY spectra

recorded on the corresponding acetonide **295** following the method reported by Dana and Danechpajouh.[63]

To a solution of (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**290**) (10 mg, 0.03 mmol) in dichloromethane (1 mL) was added 2,2-dimethoxypropane (15 µL, 0.12 mmol) and *p*-toluenesulfonic acid (1 mg, 0.006 mmol). The mixture was allowed to stir for one hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes-ethyl acetate) afforded the corresponding bisacetonide **295**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.28 (dd, 1H, *J* = 5.4, 7.8 Hz, H-4), 4.22 (ddd, 1H, *J* = 5.4, 7.8, 7.8 Hz, H-6), 4.15 (dd, 2H, *J* = 5.4, 7.8 Hz, H-5), 4.11 (ddd, 1H, *J* = 2.4, 7.8, 10.2 Hz, H-4'), 4.09 (dd, 1H, *J* = 5.4, 7.8 Hz, H-10), 3.93 (dd, 1H, *J* = 5.4, 7.8 Hz, H-10), 1.93 (m, 1H, H-4"), 1.74 (m, 1H, H-4"), 1.66 (m, 1H), 1.48 (m, 1H), 1.43 (s, 3H, H-8') 1.42 (s, 3H, H-8'), 1.35 (s, 6H, H-2'), 0.96 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 109.8 (C2), 108.8 (C8), 80.8 (C4), 78.3 (C5), 73.2 (C6), 67.5 (C10), 59.0 (C4'), 36.8, 27.5 (C-8'), 26.6 (C8'), 25.5 (C2'), 25.4 (C2'), 18.8, 13.6.

Preparation of (2*R,3*R**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (291)**

To a solution of (2*R**,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**289**) (98 mg, 0.30 mmol) in THF (6 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.33 mL, 0.33 mmol). The resulting solution was stirred for two hours. Saturated aqueous ammonium chloride (2 mL) was then added, the

mixture was diluted with ethyl acetate (20 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 5% methanol in ethyl acetate) afforded (2*R**,3*R**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**291**) (50 mg, 78%) as a white solid (m.p. 162-163 °C).

^{1}H NMR (400 MHz, CD_3OD) δ: 4.02 (dt, 1H, *J* = 2.4, 9.2 Hz), 3.93 (d, 1H, *J* = 7.6 Hz), 3.81 (m, 2H), 3.69-3.60 (m, 2H), 2.01 (m, 1H), 1.66 (m, 2H), 1.49 (m, 1H), 0.96 (t, 3H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 74.1, 72.9, 71.4, 65.2, 63.0, 37.4, 20.3, 14.0.

IR (neat): 3395, 3388, 3210, 2950, 1464, 1254 cm^{-1}

Exact mass calcd. for $C_8H_{18}ClO_4$: 213.0888 (M+H); found: 213.0898 (M+H).

Preparation of (2*S,3*S**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (292)**

To a solution of (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**290**) (100 mg, 0.30 mmol) in THF (5 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.33 mL, 0.33 mmol). The resulting solution was stirred for three hours. Saturated aqueous ammonium chloride (2 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 5% methanol in ethyl acetate) afforded (2*S**,3*S**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**292**) (57 mg, 90%) as a white solid (m.p. 160-162 °C).

^{1}H NMR (400 MHz, CD_3OD) δ: 4.31 (dt, 1H, *J* = 4.4, 6.8 Hz), 4.21 (t, 1H, *J* = 4.4 Hz), 3.88 (dd, 2H, *J* = 6.8, 8.4 Hz), 3.67 (dd, 1H, *J* = 6.8, 8.0 Hz), 3.59 (dd, 1H, *J* = 3.6, 8.0 Hz), 1.63 (m, 2H), 1.42 (m, 2H), 0.96 (t, 3H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 84.9, 73.2, 72.9, 72.2, 70.9, 37.2, 19.6, 14.5.

IR (neat): 3407, 3399, 3300, 2960, 1477, 1199 cm^{-1}

Exact mass calcd. for $C_8H_{17}ClO_4Na$: 235.0708 (M + Na); found: 235.0716 (M + Na).

Preparation of (2*R,3*S**,4*S**,5*S**)-2-(hydroxymethyl)-5-propyltetrahydrofuran-3,4-diol (293)**

Method A:

The (2*R**,3*R**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**289**) (33 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S**,3*S**,5*S**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (**293**) (17 mg, 96%) as a clear oil.

Method B:

The (2*R**,3*R**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**291**) (22 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and

maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S**,3*S**,5*S**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (**293**) (12 mg, 67%) as a clear oil.

^{1}H NMR (600 MHz, CD_3OD) δ: 3.95 (m, 1H), 3.92 (ddd, 1H, *J* = 3.0, 6.6, 10.2 Hz), 3.78 (d, 1H, *J* = 3.0 Hz), 3.72 (m, 1H), 3.67 (dd, 1H, *J* = 4.2, 11.4 Hz), 3.63 (dd, 1H, *J* = 4.8, 11.4 Hz), 1.61 (dt, 2H, *J* = 6.6, 7.2 Hz), 1.42 (m, 2H), 0.96 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 87.3, 82.8, 80.6, 78.8, 63.6, 31.7, 20.5, 14.6.

IR (neat): 3344, 2961, 2931, 2870, 1265, 1092, 1038, 738 cm^{-1}

Exact mass calcd. for $C_8H_{17}O_4$: 177.1121 (M+H); found: 177.1127 (M+H).

Preparation of (2*S,3*R**,4*S**,5*S**)-2-(hydroxymethyl)-5-propyltetrahydrofuran-3,4-diol (294)**

Method A:

The (2*S**,3*S**,4*S**,5*R**)-1-[(*tert*-butyldimethylsilyl)oxy]-5-chlorooctane-2,3,4-triol (**290**) (33 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography

afforded (2*S**,3*S**,5*S**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (**294**) (17 mg, 95%) as a clear oil.

Method B:

The (2*R**,3*R**,4*S**,5*R**)-5-chlorooctane-1,2,3,4-tetrol (**292**) (22 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S**,3*S**,5*S**)-2-benzyl-5-nonyltetrahydrofuran-3-ol (**294**) (13 mg, 71%) as a clear oil.

^{1}H NMR (600 MHz, CD_3OD) δ: 4.12 (dd, 1H, *J* = 4.2, 7.8 Hz), 3.97-3.92 (m, 2H), 3.79 (ddd, 1H, *J* = 3.0, 4.8, 7.8 Hz), 3.75 (dd, 1H, *J* = 3.0, 12.0 Hz), 3.58 (dd, 1H, *J* = 4.8, 12.0 Hz), 1.70-1.57 (m, 2H), 1.48-1.36 (m, 2H), 0.97 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, CD_3OD) δ: 82.8, 82.2, 73.9, 73.7, 63.3, 32.7, 20.1, 14.6.

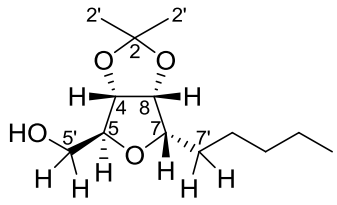
IR (neat): 3380, 2960, 2932, 2873, 1265 cm^{-1}

Exact mass calcd. for $C_8H_{17}O_4$: 177.1121 (M+H); found: 177.1127 (M+H).

The relative configuration of **294** was determined by analysis of the ^{1}H and ^{13}C NMR spectra and 1D NOESY spectra recorded on the corresponding acetonide **296**.

To a solution of (2*S**,3*R**,4*S**,5*S**)-2-(hydroxymethyl)-5-propyltetrahydrofuran-3,4-diol (**294**) (11 mg, 0.06 mmol) in dichloromethane (2 mL) was added 2,2-dimethoxypropane (31 µL, 0.25 mmol) and *p*-toluenesulfonic acid (2.4 mg, 0.012 mmol). The mixture was allowed to stir for one hour and then concentrated to give a crude

yellow product. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded the corresponding acetonide **296**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.62 (dd, 1H, *J* = 3.6, 6.0 Hz, H-8), 4.58 (dd, 1H, *J* = 1.2, 6.0 Hz, H-4), 4.11 (m, 1H, H-5), 3.87 (dt, 1H, *J* = 3.6, 6.6 Hz, H-7), 3.57 (m, 2H, H-5'), 1.92 (m, 1H, OH), 1.69 (m, 2H, H-7'), 1.50 (s, 3H, H-2'), 1.44 (m, 2H), 1.33 (s, 3H, H-2'), 0.96 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 112.5 (C2), 83.9 (C5), 82.4 (C4), 81.7 (C8), 80.6 (C7), 61.7 (C5'), 31.2 (C7'), 26.4 (C2'), 25.2 (C2'), 19.6, 14.4.

Preparation of (2*S,3*R**)-3-chloro-1-cyclohexylideneoctan-2-ol (302)**

To a cold (-78 °C), stirred solution of bromomethylenecyclohexane (**301**) (530 mg, 3.0 mmol) in THF (15 mL) was added *t*-butyllithium (1.8 M solution in pentanes, 3.5 mL, 6.3 mmol). The resulting solution was stirred at -78 °C for 60 minutes. After this time, a solution of (2*R**)-2-chloroheptanal (**209**) (540 mg, 3.6 mmol) in THF (2.0 mL) was added in one portion at -78 °C and the resulting mixture was stirred for an additional 60 minutes. Saturated aqueous NH_4Cl (5 mL) was then added, the mixture was diluted with ethyl acetate (25 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes-ethyl acetate) afforded (2*S**,3*R**)-3-chloro-1-cyclohexylideneoctan-2-ol (**302**) (560 mg, 76%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.25 (d, 1H, *J* = 8.4 Hz), 4.52 (dd, 1H, *J* = 4.0, 8.4 Hz), 4.03 (dt, 1H, *J* = 4.0, 9.2 Hz), 2.21-2.13 (m, 4H), 1.72-1.48 (m, 10H), 1.37-1.27 (m, 4H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 146.0, 119.3, 70.5, 69.0, 37.2, 33.2, 31.3, 29.8, 28.5, 27.9, 26.6, 26.3, 22.5, 14.0.

IR (neat): 3476, 3044, 2980, 1711, 1411 cm^{-1}

Exact mass calcd. for $C_{14}H_{25}ClONa$: 267.1486 (M + Na); found: 267.1487 (M + Na).

Preparation of (1*S,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (303)**

To a solution of (2*S**,3*R**)-3-chloro-1-cyclohexylideneoctan-2-ol (**302**) (350 mg, 1.4 mmol) in acetone (10 mL) and water (8 mL) was added *N*-methylmorpholine *N*-oxide (330 mg, 2.8 mmol) and osmium tetroxide (2.5 mg, 0.010 mmol). The resulting solution was stirred for 24 hours. After this time, saturated aqueous sodium hydrosulfite (5 mL) was then added, the mixture was filtered through a pad of Celite® and the cake was washed with acetone (3 x 15 mL). The filtrate was then neutralised to pH 7 (phosphate buffer) with aqueous sulfuric acid, and the acetone was removed by rotary evaporation. The mixture was diluted with ethyl acetate (10 mL) and washed with brine (10 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude mixture by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (1*S**,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (**303**) (360 mg, 92%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.03 (dt, 1H, *J* = 2.8, 8.8 Hz), 3.91 (d, 1H, *J* = 8.8 Hz), 3.80 (m, 1H), 3.55 (s, 1H), 2.54 (s, 1H), 2.13 (s, 1H), 2.06 (m, 1H), 1.78 (m, 1H), 1.69-1.51 (m, 12H), 1.35-1.26 (m, 4H), 0.90 (t, 3H, *J* = 7.2 Hz).

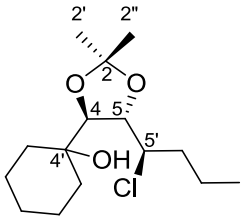
^{13}C NMR (100 MHz, $CDCl_3$) δ: 75.2, 73.5, 72.7, 63.0, 34.9, 33.6, 33.5, 31.4, 25.6, 25.5, 22.6, 21.6, 21.5, 14.0.

IR (neat): 3054, 2987, 2685, 2305, 1422, 1265 cm^{-1}

Exact mass calcd. for $C_{14}H_{27}ClO_3Na$: 301.1541 (M + Na); found: 301.1540 (M + Na).

The relative stereochemistry of the carbinol stereocentres in **303** were determined by analysis of the ^{1}H and ^{13}C NMR spectra from the corresponding acetonide **305** using the method reported by Dana and Danechpajouh.[63]

To a solution of (1*S**,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (**303**) (12 mg, 0.050 mmol) in dichloromethane (2 mL) was added 2,2-dimethoxypropane (21 µL, 0.17 mmol) and *p*-toluenesulfonic acid (1 mg, 0.005 mmol). The mixture was allowed to stir for one hour and then concentrated to give a crude yellow product. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded the corresponding acetonide **305**.



^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.23 (dd, 1H, *J* = 5.4, 7.2 Hz, H-5), 3.94 (ddd, 1H, *J* = 2.4, 2.4, 7.2 Hz, H-5'), 3.90 (d, 1H, *J* = 5.4 Hz, H-4), 1.98 (m, 1H), 1.77-1.69 (m, 2H), 1.77-1.69 (m, 2H), 1.66-1.54 (m, 7H), 1.45 (s, 3H, H-2'), 1.40 (s, 3H, H-2''), 1.36-1.20 (m, 8H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 110.1 (C2), 86.0 (C4), 80.3 (C5), 71.4 (C4'), 63.8 (C5'), 34.7, 33.6, 33.4, 31.2, 28.2 (C2'), 27.6 (C2''), 25.7, 25.6, 22.5, 21.42, 21.40, 14.0.

Preparation of (2*S,3*S**,4*S**)-2-pentyl-1-oxaspiro[4.5]decane-3,4-diol (304)**

The ((1*S**,2*S**,3*R**)-3-chloro-1-(1-hydroxycyclohexyl)octane-1,2-diol (**303**) (28 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*S**,3*S**,4*S**)-2-pentyl-1-oxaspiro[4.5]decane-3,4-diol (**304**) (23 mg, 94%) as a clear oil.

^{1}H NMR (400 MHz, CD_3OD) δ: 3.93 (m, 1H), 3.89 (m, 1H), 3.75 (d, 1H, *J* = 2.4 Hz), 1.69-1.35 (m, 18H), 0.92 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, CD_3OD) δ: 84.2, 83.8, 80.1, 79.5, 38.1, 33.2, 31.5, 30.5, 27.0, 26.8, 24.5, 23.9, 23.7, 14.4.

IR (neat): 3067, 2990, 2805, 2609, 1417 cm^{-1}

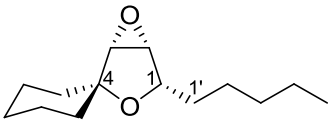
Exact mass calcd. for $C_{14}H_{27}O_3$: 243.1955 (M+H); found: 243.1963 (M+H).

Preparation of (1*R,4*R**,5*R**)-4-pentyl-3,6-dioxaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexane] (308)**

To a solution of (2*S**,3*S**,4*S**)-2-pentyl-1-oxaspiro[4.5]decane-3,4-diol (**304**) (20 mg, 0.080 mmol) in dichloromethane (2 mL) was added pyridine (12 µL, 0.16 mmol) and *t*-butyldimethylsilyl triflate (15 µL, 0.080 mmol). The mixture was allowed to stir for one hour and then concentrated to give a crude yellow product **306**. Purification of the crude product **306** by flash chromatography (silica gel, 7:1 hexanes-ethyl acetate) afforded (2*S**,3*S**,4*S**)-3-(tert-butyldimethylsilyloxy)-2-pentyl-1-oxaspiro[4.5]decan-4-ol (**306**),

which was then treated with methanesulfonyl chloride (12 μL, 0.16 mmol) and pyridine (12 μL, 0.16 mmol) in dichloromethane (2 mL). The mixture was allowed to stir for 10 minutes and concentrated to give a crude yellow product **307**. Purification of the crude product by flash chromatography (silica gel, 8:1 hexanes-ethyl acetate) afforded (2*S**,3*R**,4*S**)-3-(tertbutyldimethylsilyloxy)-2-pentyl-1-oxaspiro[4.5]decan-4-yl methanesulfonate (**307**) which was then treated with tetrabutylammonium fluoride (1.0 M solution in THF, 0.16 μL, 0.16 mmol) in THF (2 mL). The mixture was allowed to stir for 30 minutes and then concentrated to give a crude brown product. Purification of the crude product by flash chromatography (silica gel, 12:1 hexanes-ethyl acetate) afforded (1*R**,4*R**,5*R**)-4-pentyl-3,6-dioxaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexane] (**308**) (1 mg, 7% over three-steps).

Data for epoxide **308**:



^{1}H NMR (600 MHz, C_6D_6) δ: 3.56 (t, 1H, *J* = 6.6 Hz, H-1), 3.12 (d, 1H, *J* = 3.0 Hz, H-5), 3.08 (d, 1H, *J* = 3.0 Hz, H-4), 1.89 (m, 1H), 1.80 (m, 1H, H-1'), 1.70-1.63 (m, 3H), 1.67 (m, 1H), 1.43-1.14 (m, 6H), 1.35 (m, 1H), 1.25-1.20 (m, 5H), 0.85 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, C_6D_6) δ: 75.7 (C1), 60.3 (C4), 57.0 (C5), 32.3, 32.1, 31.8, 31.0 (C1'), 26.0, 25.9, 23.2, 22.82, 22.78, 22.5, 14.1.

Preparation of (1*R,2*R**)-1-((2*S**,3*S**)-3-pentyloxiran-2-yl)-2-phenylethane-1,2-diol (309)**

To a solution of (1*R**,2*R**,3*S**,4*R**)-4-chloro-1-phenylnonane-1,2,3-triol (**271**) (35 mg, 0.12 mmol) in ethanol (0.7 mL) was added potassium hydroxide (0.20 M, 1.2 mL, 0.24 mmol). The resulting solution was stirred for 30 minutes. The mixture was then

diluted with pentane (10 mL), washed with water (10 mL) and the layers separated. The aqueous phase was extracted with pentane (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 7:3 hexanes-ethyl acetate) afforded (1*R**,2*R**)-1-((2*S**,3*S**)-3-pentyloxiran-2-yl)-2-phenylethane-1,2-diol (**309**) (24 mg, 79%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28-7.15 (m, 5H), 4.79 (m, 1H), 3.54 (m, 1H), 3.05 (d, 1H, *J* = 2.8 Hz), 2.87 (m, 1H), 2.80 (dd, 1H, *J* = 2.8, 5.2 Hz), 2.50 (ddd, 1H, *J* = 2.8, 5.2, 7.6 Hz), 1.27-1.19 (m, 2H), 1.16-1.05 (m, 6H), 0.84 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.8, 128.4, 127.8, 126.1, 75.4, 74.7, 57.8, 57.0, 31.5, 31.3, 25.2, 22.5, 13.9.

IR (neat): 3509, 3308, 2997, 2902, 1534, 1437 cm^{-1}

Exact mass calcd. for $C_{15}H_{23}O_3$: 251.1642 (M+H); found: 251.1636 (M+H).

Preparation of (2*R,3*S**,4*S**,5*R**)-2-pentyl-5-phenyltetrahydrofuran-3,4-diol (310)**

The (1*R**,2*R**)-1-((2*S**,3*S**)-3-pentyloxiran-2-yl)-2-phenylethane-1,2-diol (**309**) (25 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (2*R**,3*S**,4*S**,5*R**)-2-pentyl-5-phenyltetrahydrofuran-3,4-diol (**310**) (22.5 mg, 90%) as a clear oil.

^{1}H NMR (600 MHz, C_6D_6) δ: 7.46 (d, 2H, *J* = 7.8 Hz), 7.20 (t, 2H, *J* = 7.8 Hz), 7.11 (t, 1H, *J* = 7.8 Hz), 4.73 (d, 1H, *J* = 7.2 Hz), 3.96 (m, 1H), 3.78 (t, 1H, *J* = 7.2 Hz), 3.71 (t, 1H, *J* = 7.2 Hz), 1.70-1.58 (m, 7H), 1.43 (m, 1H), 1.28 (t, 3H, *J* = 7.2 Hz), 0.55 (s, 1H).

^{13}C NMR (150 MHz, C_6D_6) δ: 142.1, 128.7, 128.3, 126.2, 85.1, 83.1, 82.7, 82.4, 34.3, 32.3, 25.8, 23.0, 14.3.

IR (neat): 3347, 2919, 2856, 1455, 1266, 1008 cm^{-1}

Exact mass calcd. for $C_{15}H_{22}O_3$: 251.1642 (M+H); found: 251.1654 (M+H).

Preparation of (3*S,4*R**)-4-chloro-3-hydroxy-*N*,*N*-dimethylnonanamide (312)**

To a cold (0 °C), stirred solution of diisopropyl amine (617 μL, 4.40 mmol) in THF (20 mL) was added *n*-butyllithium (2.50 M soln. in hexane, 1.80 mL, 4.40 mmol) and the resulting mixture was stirred for 30 minutes. After this time, the slightly yellow solution was cooled to -78 °C and *N*,*N*-dimethylacetamide (**311**) (372 μL, 4.00 mmol) was added in one portion. The reaction mixture was stirred for 30 minutes, a solution of 2-chloroheptanal (**209**) (713 mg, 4.80 mmol) in THF (2.0 mL) was then added in one portion at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (10 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:2 to 1:2 hexanes-ethyl acetate) afforded (3*S**,4*R**)-4-chloro-3-hydroxy-*N*,*N*-dimethylnonanamide (**312**) (760 mg, 80%) as a white solid (m.p. 54-55 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.80 (d, 1H, *J* = 4.4 Hz), 4.00 (m, 1H), 3.93 (m, 1H), 3.03 (s, 3H), 2.97 (s, 3H), 2.76 (dd, 1H, J = 2.8, 16.4 Hz), 2.64 (dd, 1H, *J* = 7.8, 16.4 Hz), 2.02 (m, 1H), 1.71-1.60 (m, 2H), 1.44-1.27 (m, 6H), 0.90 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.4, 71.7, 65.7, 37.2, 35.23, 35.19, 34.2, 31.3, 25.9, 22.5, 14.0.

IR (neat): 3347, 2961, 2874, 2772, 2447, 1771, 1709, 1643, 1467, 1171 cm^{-1}

Exact mass calcd. for $C_{11}H_{23}ClNO_2$: 236.1412 (M+H); found: 236.1404 (M+H).

Preparation of (4*S,5*S**)-4-hydroxy-5-pentyldihydrofuran-2(3*H*)-one (313)**

The (3*S**,4*R**)-4-chloro-3-hydroxy-*N*,*N*-dimethylnonanamide (**312**) (24 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water:methanol (0.5 mL each) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 80 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (4*S**,5*S**)-4-hydroxy-5-pentyldihydrofuran-2(3*H*)-one (**313**) (15 mg, 89%) as a clear oil.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[68]

Preparation of (*R*)-methyl 4-chloro-5-oxopentanoate (315)

To a cold (10 °C), stirred solution of (2*S*,5*R*)-2-*tert*-butyl-3,5,dimethylimidazolidin-4-one trifluoroacetate (100 mg, 0.40 mmol) in acetonitrile (30 mL) was added water (75 µL, 4.1 mmol), lithium chloride (120 mg, 2.80 mmol), copper (II) trifluoroacetate hydrate (270 mg, 0.90 mmol), sodium persulfate (450 mg, 1.8 mmol). The resulting solution was stirred at 10 °C for 5 minutes. After this time, a solution of methyl 5-oxopentanoate (**314**)

(240 mg, 1.8 mmol) in acetonitrile (1.0 mL) was then added in one portion at 10 °C and the resulting mixture was stirred for an additional four hours. Water (10 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (3 x 15 mL), dried ($MgSO_4$), filtered, and concentrated to provide (*R*)-methyl 4-chloro-5-oxopentanoate (**315**) (271 mg, 88%) as clear oil which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.48 (d, 1H, *J* = 1.6 Hz), 4.32 (ddd, 1H, *J* = 1.6, 5.2, 8.0 Hz), 3.65 (s, 3H), 2.51 (m, 2H), 2.34 (m, 1H), 2.05 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.3, 172.4, 62.6, 51.7, 29.5, 26.8.

IR (neat): 2955, 2849, 1732, 1439, 1250, 1174 cm^{-1}

Exact mass calcd. for $C_6H_{10}ClO_3$: 165.0318 (M+H); found: 165.0312 (M+H).

$[\alpha]_D^{25}$: 24.3 (c = 1.0, EtOH)

Preparation of (2*S)-2-chloropentane-1,5-diol (321)**

To a cold (0 °C), stirred solution of methyl (4*S**)-4-chloro-5-oxopentanoate (**315**) (329 mg, 2.00 mmol) in dichloromethane (25 mL) was added diisobutylaluminum hydride (1.00 M solution in dichloromethane, 12.5 mL, 12.5 mmol). The resulting solution was stirred for two hours at 0 °C. To this solution was added aqueous HCl (1.0 M, 2.0 mL) the mixture was diluted with dichloromethane (10 mL) and the layers separated. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a yellow oil. Purification of the crude product by flash chromatography (silica gel, 1:2 to 0:1 hexanes-ethyl acetate) afforded (2*S**)-2-chloropentane-1,5-diol (**321**) (170 mg, 62%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.08 (m, 1H), 3.81 (m, 1H), 3.73-3.67 (m, 3H), 2.05 (dd, 1H, *J* = 5.6, 7.6 Hz), 1.99-1.68 (m, 5H), 1.34 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.0, 64.9, 62.2, 30.6, 29.3.

IR (neat): 3345, 2951, 2879, 1722, 1444, 1057 cm^{-1}

Exact mass calcd. for $C_5H_{12}ClO_2$: 139.0520 (M+H); found: 139.0525 (M+H).

Preparation of (*R*)-(tetrahydrofuran-2-yl)methanol (320)

The (2*R*)-2-chloropentane-1,5-diol (**321**) (56 mg, 0.40 mmol) was placed in a 10 mL vial, deionised water (2 mL each) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (*R*)-(tetrahydrofuran-2-yl)methanol (**320**) (35 mg, 86%) as a clear oil.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[69]

Preparation of methyl (4*R*,5*S*)-4-chloro-5-hydroxy-7-phenylhept-6-ynoate (322)

To a cold (-78 °C), stirred solution of phenylacetylene (204 mg, 2.00 mmol) in THF (10 mL) was added *n*-butyllithium (2.50 M soln. in hexane, 880 µL, 2.20 mmol). The resulting solution was stirred at -78 °C for 30 minutes. After this time, a solution of methyl (4*R*)-4-chloro-5-oxopentanoate (**315**) (395 mg, 2.40 mmol) in THF (1.0 mL) was then added in one portion at -78 °C and the resulting mixture was stirred for an

additional 30 minutes. Saturated aqueous NH_4Cl (5 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 to 2.5:1 hexanes-ethyl acetate) afforded methyl (4*R*,5*S*)-4-chloro-5-hydroxy-7-phenylhept-6-ynoate (**322**) (474 mg, 89%, 15:1 diastereomeric mixture) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.46 (d, 2H, *J* = 7.2 Hz), 7.35-7.29 (m, 3H), 4.77 (dd, 1H, *J* = 3.6, 8.4 Hz), 4.21 (dt, 1H, *J* = 3.6, 10.2 Hz), 3.70 (s, 3H), 2.70-2.52 (m, 3H), 2.34 (m, 1H), 2.15 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.4, 132.4, 128.8, 128.4, 122.3, 87.0, 85.7, 66.8, 52.3, 30.9, 29.0.

IR (neat): 3452, 2953, 2926, 2232, 1737, 1441 cm^{-1}

Exact mass calcd. for $C_{14}H_{16}ClO_3$: 267.0782 (M+H); found: 267.0793 (M+H).

Preparation of (4*R*,5*S*)-4-chloro-7-phenylhept-6-yne-1,5-diol (323)

To a solution of methyl (4*R*,5*S*)-4-chloro-5-hydroxy-7-phenylhept-6-ynoate (**322**) (70 mg, 0.25 mmol) in THF (5 mL) and methanol (1.0 mL) was added sodium borohydride (100 mg, 2.50 mmol). The resulting solution was stirred for 18 hours. Saturated aqueous ammonium chloride (2 mL) was then added, the mixture was diluted with ethyl acetate (10 mL) and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude white solid. Purification of the crude product by flash chromatography (silica gel, 2:3 hexanes-ethyl acetate) afforded (4*R*,5*S*)-4-chloro-7-phenylhept-6-yne-1,5-diol (**323**) (35 mg, 60%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.45 (m, 2H), 7.34-7.30 (m, 3H), 4.76 (dd, 1H, *J* = 4.0, 7.6 Hz), 4.16 (dt, 1H, *J* = 4.0, 9.6 Hz), 3.72 (t, 2H, *J* = 6.0 Hz), 2.82 (d, 1H, *J* = 7.6 Hz), 2.09 (m, 1H), 1.93 (m, 2H), 1.73 (m, 1H).

^{13}C NMR (100 MHz, CD_3OD) δ: 131.9, 128.8, 128.4, 122.0, 86.9, 85.6, 66.7, 62.2, 30.1, 29.5.

IR (neat): 3503, 3433, 3329, 2955, 2857, 2201, 1401 cm^{-1}

Exact mass calcd. for $C_{13}H_{15}O_2Na$: 261.0653 (M + Na); found: 261.0661 (M + Na).

Preparation of (*S*)-3-phenyl-1-((*S*)-tetrahydrofuran-2-yl)prop-2-yn-1-ol (324)

The (4*R*,5*S*)-4-chloro-7-phenylhept-6-yne-1,5-diol (**323**) (24 mg, 0.10 mmol) was placed in a 10 mL vial, deionised water (1 mL each) was added and the vial was sealed in a CEM Discover LabMate. The reaction mixture was then heated to 120 °C in a microwave (MW) (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) washed with brine (5 mL), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (*S*)-3-phenyl-1-((*S*)-tetrahydrofuran-2-yl)prop-2-yn-1-ol (**324**) (17 mg, 85%) as a clear oil.

The ^{1}H and ^{13}C NMR spectra recorded on this material were identical to that reported in the literature.[70]

Preparation of methyl (4*R*,5*S*,6*Z*)-4-chloro-5-hydroxy-7-phenylhept-6-enoate (316)

To a cold (-78 °C), stirred solution of iodostyrene (50 mg, 0.22 mmol) in THF (5 mL) was added *n*-butyllithium (2.1 M soln. in hexane, 110 µL, 0.24 mmol). The resulting solution was stirred at -78 °C for 30 minutes. After this time, a solution of methyl (4*R*)-4-

chloro-5-oxopentanoate (**315**) (40 mg, 0.24 mmol) in THF (0.5 mL) was added in one portion at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (1 mL) was then added, the mixture was diluted with ethyl acetate (10 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded methyl (4*R*,5*S*,6*Z*)-4-chloro-5-hydroxy-7-phenylhept-6-enoate (**316**) (51 mg, 88%, 13:1 diastereomeric mixture) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.27 (m, 5H), 6.77 (d, 1H, *J* = 11.4 Hz), 5.83 (dd, 1H, *J* = 9.2, 11.4 Hz), 4.64 (m, 1H), 4.14 (m, 1H), 3.66 (s, 3H), 2.56 (m, 1H), 2.47 (m, 1H), 2.32 (d, 1H, *J* = 6.8 Hz), 2.10 (m, 1H), 1.98 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 136.1, 134.8, 128.7, 128.5, 128.3, 127.7, 70.2, 66.8, 51.7, 30.7, 28.5.

IR (neat): 3536, 3080, 3007, 2965, 2920, 2884, 1723, 1441, 1093 cm^{-1}

Exact mass calcd. for $C_{14}H_{18}ClO_3$: 269.0944 (M+H); found: 269.0963 (M+H).

$[\alpha]_D^{25}$: -16.4 (c = 0.7, EtOH)

The enantiomeric excess of (**316**) was determined to be 91% by chiral HPLC analysis. Injection volume: 10 µL (5 mg/mL solution); Solvent: 95:5 Hexane:Methanol; Flow rate: 1 mL/min; Wavelength: 254 nm; Retention time = 20.3 min (4*S*, 5*R* isomer), 25.4 min (4*R*, 5*S* isomer).

Preparation of methyl (4*R*,5*S*,6*R*,7*R*)-4-chloro-5,6,7-trihydroxy-7-phenylheptanoate (317)

To a solution of methyl (4*R*,5*S*,6*Z*)-4-chloro-5-hydroxy-7-phenylhept-6-enoate (**316**) (269 mg, 1.00 mmol) in acetone (5 mL) and water (3 mL) was added *N*-methylmorpholine *N*-oxide (176 mg, 1.50 mmol) and osmium tetroxide (2 mg, 0.01 mmol). The resulting solution was stirred for three hours. After this time, saturated aqueous sodium hydrosulfite (5 mL) was added, the mixture was filtered through a pad of Celite® and the cake washed with acetone (3 x 15 mL). The filtrate was then neutralised to pH 7 (phosphate buffer) with aqueous sulfuric acid, and the acetone was removed by rotary evaporation. The mixture was diluted with ethyl acetate (10 mL) and washed with brine (10 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the 8:1 diastereomeric mixture by flash chromatography (silica gel, 1:2 hexanes-ethyl acetate) afforded methyl (4*R*,5*S*,6*R*,7*R*)-4-chloro-5,6,7-trihydroxy-7-phenylheptanoate (**317**) (222 mg, 74%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.3-7.29 (m, 5H), 4.9 (dd, 1H, *J* = 4.8, 4.8 Hz), 4.13 (dd, 1H, *J* = 6.0, 6.0 Hz), 4.07 (dt, 1H, *J* = 3.0, 7.8 Hz), 3.75-3.70 (m, 2H), 3.64 (s, 3H), 3.34 (d, 1H, *J* = 4.2 Hz), 2.80 (m, 1H), 2.58 (m, 1H), 2.46 (m, 1H), 2.35 (m, 1H), 1.96 (m, 1H), 1.82 (s, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.3, 140.6, 128.6, 127.9, 126.1, 76.0, 72.7, 72.5, 60.6, 51.8, 30.0, 28.5.

IR (neat): 3535, 3409, 2928, 1729, 1609, 1414, 1087 cm^{-1}

Exact mass calcd. for $C_{14}H_{20}ClO_5$: 303.0994 (M+H); found: 303.0992 (M+H).

$[\alpha]_D^{25}$: 11.1 (c = 0.7, EtOH)

Preparation of (+)-goniothalesdiol (241)

To a 10 mL microwave vial with (4*R*,5*S*,6*R*,7*R*)-4-chloro-5,6,7-trihydroxy-7-phenylheptanoate (**317**) (50 mg, 0.16 mmol) was added methanol (1.6 mL) and the vial was sealed in a CEM Discover LabMate microwave. The reaction mixture was then heated to 120 °C (monitored by a vertically focused IR temp. sensor) and maintained at this temperature for 60 minutes. After this time, the mixture was diluted with ethyl acetate (5 mL) and washed with brine (5 mL), and the layers separated. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude product. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes-ethyl acetate) afforded (+)-goniothalesdiol (**241**) (39 mg, 92%) as a clear oil.

Data for a 50 mg/mL solution:

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.42 (d, 2H, *J* = 7.2 Hz), 7.35 (t, 2H, *J* = 7.2 Hz), 7.29 (d, 1H, *J* = 7.2 Hz), 4.61 (d, 1H, *J* = 4.8 Hz), 4.03-4.12 (m, 3H), 3.70 (s, 3H), 2.63 (m, 1H), 2.55-2.47 (m, 2H), 2.28 (d, 1H, *J* = 4.0 Hz), 2.18-2.03 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.8, 140.0, 128.6, 127.8, 126.2, 85.6, 85.0, 80.3, 78.9, 51.9, 30.6, 24.0.

Data for a 10 mg/mL solution:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, 2H, *J* = 7.2 Hz), 7.34 (t, 2H, *J* = 7.2 Hz), 7.26 (d, 1H, *J* = 7.2 Hz), 4.59 (d, 1H, *J* = 4.8 Hz), 4.02-4.10 (m, 3H), 3.68 (s, 3H), 2.62 (m, 1H), 2.54-2.44 (m, 2H), 2.28 (d, 1H, *J* = 4.0 Hz), 2.18-2.00 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 140.0, 128.7, 127.9, 126.2, 86.2, 85.3, 80.7, 78.9, 51.9, 30.6, 23.8.

IR (neat): 3449, 2954, 2952, 2929, 1736, 1449, 1417 cm^{-1}

Exact mass calcd. for $C_{14}H_{19}O_5$: 267.1227 (M+H); found: 267.1227 (M+H).

$[\alpha]_D^{25}$: +7.2 (c = 0.2, EtOH); lit.[36] $[\alpha]_D^{25}$: +7.5 (c = 0.23, EtOH)

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Chapter 5

Studies Toward the Total Synthesis of Haterumalide and Biselide Natural Products

The results discussed in this Chapter have been reported in part, see: Halperin, S.; Kang, B.; Britton, R. *Synthesis.* **2011**, *12*, 1946.

5.1 Introduction to the Haterumalide and Biselide Family of Natural Products

5.1.1 Isolation and Structure of the Haterumalide and Biselide Natural Products

The haterumalide family of natural products was first isolated in 1999 from the Okinawan ascidian *Lissoclinum sp.*[1] and the Okinawan sponge *Ircinia sp.*[2] A standard extraction process afforded five members of the haterumalide family, namely haterumalide NA (**325**), B (**326**), NB (**327**), NC (**328**), ND (**329**), and NE (**330**). In the same year, Strobel reported the isolation of haterumalide NA (**325**) from a strain of a bacterium, *Serratia marcencens*, growing as an epiphyte on an aquatic plant in Venezuela.[3] Subsequently, a similar soil bacterium, *Serratia plymuthica*, from Sweden was shown to produce haterumalides NA (**325**), B (**326**), NE (**330**) and X (**331**),[4,5] and *Serratia liquefaciens* from New Zealand was reported to produce haterumalide NA (**325**).[6] The multiple isolations of this family of natural products from various sources suggest that these compounds are not metabolites of the sea sponge/ascidian, but

rather a metabolite of bacterium that lives synergistically within these organisms. A synergistic relation is further suggested by the potent activity of haterumalide NA (**325**) toward phytopathogenic oomycetes (i.e., water moulds).[4,5]

The most studied member of this family of natural products is haterumalide NA (**325**), which consists of a 2,5-disubstituted-3-hydroxytetrahydrofuran, a *trans*-bridged 14-membered lactone, a *Z*-chloroolefin, and contains 5-stereogenic centres. The original structural assignment of haterumalide NA (**325**) by Takada[2] was proven incorrect after a total synthesis by Kigoshi revised the structure by inverting the stereochemistry at C3, C11, and C13.[7] The other members of this family only differ through functionalisation of the various alcohol/acid groups (Figure 21). For example, haterumalide NA (**325**) is the free carboxylic acid, haterumalide NB (**327**) and haterumalide B (**326**) are the *n*-butyl and 3-methylbut-3-en-2-one esters, respectively. Haterumalide NE (**330**) lacks the acetate group at C3; and NC (**328**) and ND (**329**) are oxidised at C9, the former with an *n*-butyl ester and the latter with a carboxylic acid.

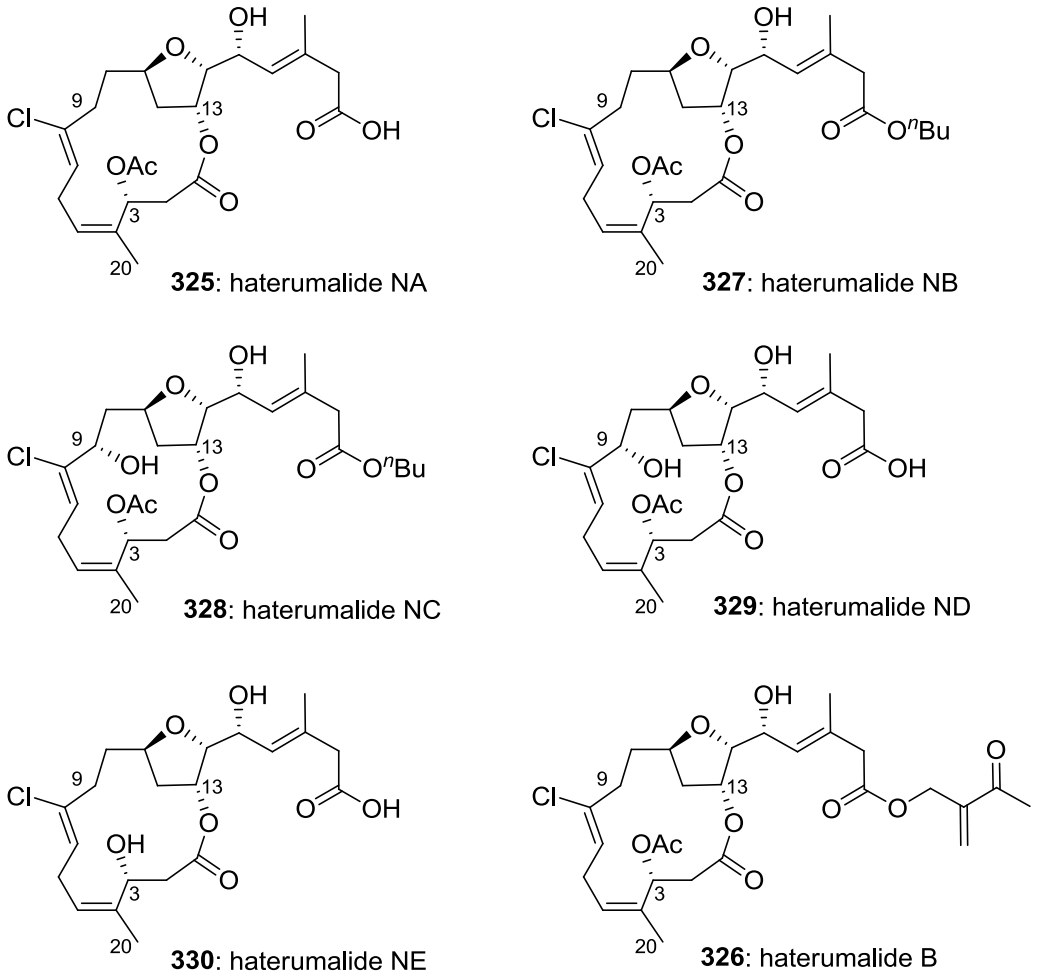


Figure 21. Structures of the haterumalides family of natural products.

In 2004, biselides A (**332**) and B (**333**) were isolated from an Okinawan ascidian *Didemnidae sp.*[8] The following year, three other natural products from this family, biselides C (**334**), D (**335**), and E (**336**), were isolated from the same ascidian.[9] These five compounds are structurally similar to the haterumalide natural products, with biselides A-C (**332**, **333**, **334**) possessing additional oxidation at C20 and biselide E (**336**) representing the linear variant of these natural products. Based on the structural similarities between the biselides and haterumalides, it is probable that the biselide

family of natural products are also metabolites of microorganisms living in a synergistic relationship with the ascidians.

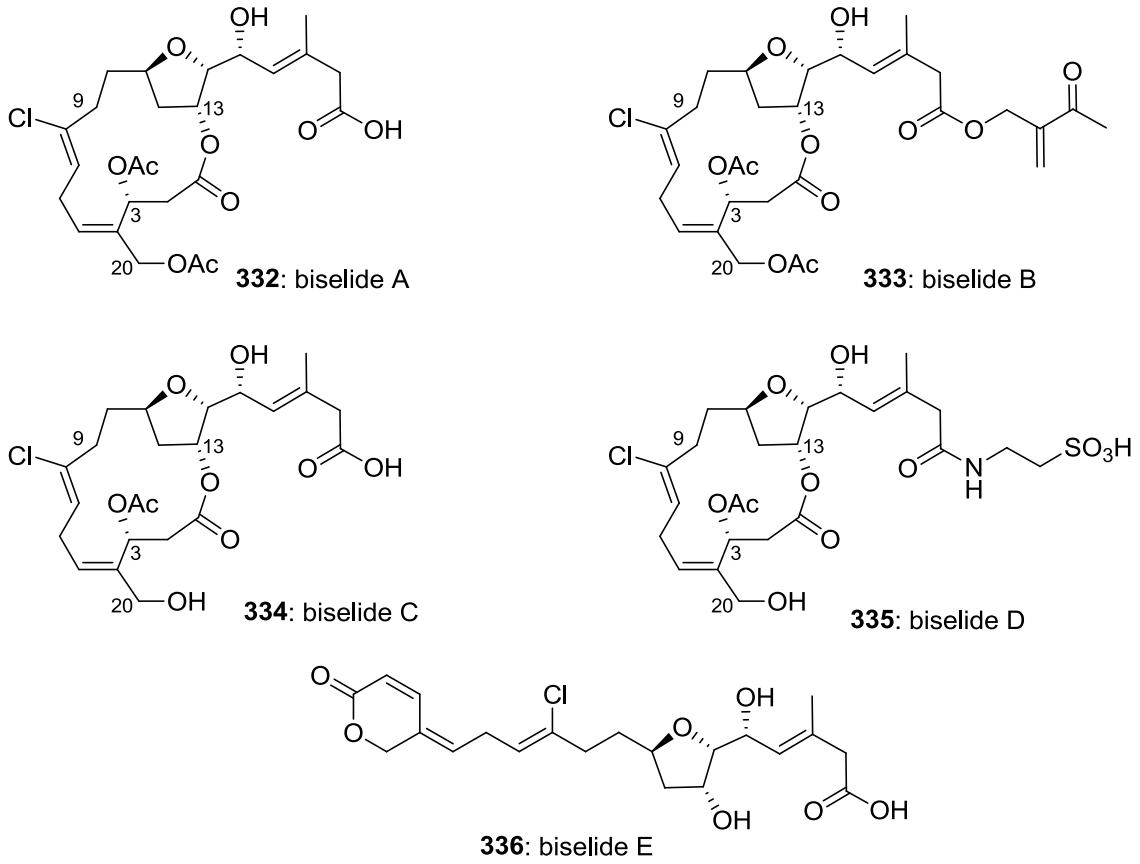


Figure 22. Structures of the biselide family of natural products.

5.1.2 Biological Activity of the Haterumalide and Biselide Natural Products

Limited biological analyses have been performed on the haterumalide and biselide families of natural products. However, even with the limited information these families have been shown to display: moderate activity against cancer-cell lines, significant anti-oomycete activity, and potential for the management of hypertriglyceridemia.

Haterumalide NA (**325**), its methyl ester (**337**), and biselides A (**332**) and C (**334**) have been tested against a variety of cancer-cell lines. Preliminary studies on the cytotoxicity of haterumalide NA (**325**) revealed activity against the breast cancer-cells lines BT-20 (IC_{50} of 0.2 μg/mL) and MCF-7 (IC_{50} of 0.42 μg/mL), and P388 leukemia cells (IC_{50} of 0.32 μg/mL).[2,3] However, toxicity against a normal mammary cell line (IC_{50} of 0.6 μg/mL) suggested that this compound is not a viable pharmaceutical lead due to its narrow therapeutic window.[3] In addition the acute toxicity (LD_{99}) of haterumalide NA (**325**) was reported to be 0.24 g/kg in mice. In 2005, Kigoshi tested haterumalide NA methyl ester (**337**), biselide A (**332**), and biselide C (**334**) against several cancer-cell lines (Table 25),[9] and when compared to commercial chemotherapeutics, cisplatin and Adriamycin, they were shown to exhibit similar cytotoxic activities.

Table 25. Cytotoxicity of biselide A (332), C (334), and haterumalide NA methyl ester (337) with IC_{50} values (μM).

cell line	biselide A (332)	biselide C (334)	haterumalide NA methyl ester (337)	cisplatin	Adriamycin
MB-231 *breast*	3.72	25.5	0.406	4.83	0.186
HOP18 *lung*	9.35	82.7	0.739	4.08	0.159
NCI-H460 *lung*	3.53	18.0	0.135	0.600	0.00823
A498 *renal*	1.79	16.3	0.335	4.01	0.166
PC-3 *prostate*	2.07	18.2	0.539	4.01	0.357
DLD-1 *colon*	0.513	17.1	0.141	2.11	0.190
HCT116 *colon*	3.01	18.0	0.292	2.23	0.0629
P388 *leukemia*	3.72	21.2	0.408	0.0754	0.0252
ADR *leukemia*	7.78	34.6	0.621	0.271	5.79
Mean toxicity	3.94	27.9	0.402	2.47	0.772

Although haterumalide NA methyl ester (**337**) displayed strong mean cytotoxicity against a variety of cancer-cell lines, it was also toxic toward brine shrimp (LD_{50} of 0.6 μg/mL).[9] Whereas, the biselides A (**332**) and C (**334**) are only slightly less cytotoxic than

337, they do not exhibit general toxicity toward brine shrimp at concentrations as high as 50 μg/mL.[9] These results suggest that the biselides may selectively target cancer-cells; however, insufficient supply of these compounds has limited further biological assessment. Thus, a flexible and concise synthetic route is needed to access these compounds and their analogues for medicinal chemistry purposes.

In addition to cytotoxic activity toward cancer-cell lines, the haterumalides are also known to be active against fungal plant pathogens. These pathogens affect both aquatic and moisture rich terrestrial plants and organisms. Concerns about fungicidal resistant diseases have garnered great interest from the agrochemicals industry, especially considering the emergence of resistance to the current commercial antifungal treatments (e.g., metalaxyl).[10] Haterumalides NA (**325**), B (**326**), NE (**330**), and pyrrolnitrin (a known antifungal agent) were examined for the Minimum Inhibitory Concentration (MIC) required to inhibit spore germination in a screen of fungal strains (Table 26). Of note, haterumalide NA (**325**) exhibits antifungal activity against *Sclerotinia sclerotiorum*, a serious threat to economically important crops such as soybeans, carrots, sunflowers, and oil seed rape. Because only one antifungal treatment exists for *S. sclerotiorum*, other antifungals are continuously sought in case the existing treatment develops resistance.[11]

Table 26. MIC (μg/mL) of haterumalides NA, B, NE, and pyrrolnitrin needed to inhibit spore germination.

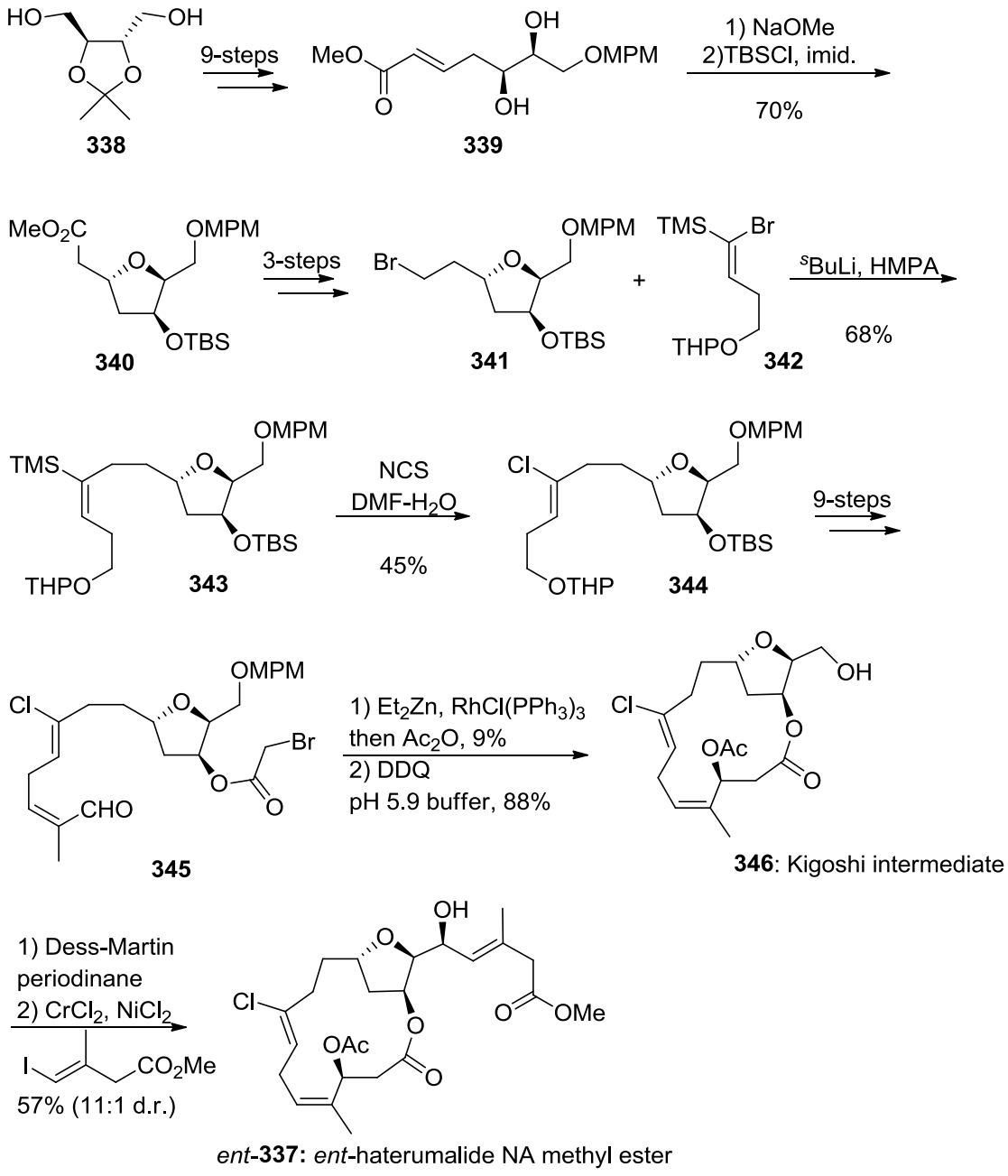
fungus	haterumalide NA (325)	haterumalide B (326)	haterumalide NE (330)	pyrrolnitrin
A. fumigatus	5	13	15	3
A. euteiches	3	1	10	5
F. culmorum	2	1	5	0.06
F. oxysporum	0.8	0.8	25	20
H. annosum	35	20	>50	50
M. canis	15	40	>75	1
P. ultimum	0.4	1	8	>50
S. sclerotiorum	0.8	3	3	10

In a search for hyperlipidemic agents from microbial products, a group at the Fujisawa Pharmaceutical Co. identified compound FR177391 to be structurally consistent with haterumalide NA (**325**).[6] In addition, microbial oxidation of **325** resulted in oxidation at C20 (i.e., biselide C (**334**)).[6] Results showed that both **325** and **334** exhibit a dose-dependent increase in high density lipoprotein (HDL) cholesterol levels and a decrease in triglyceride (TG) levels.[6] These preliminary results suggest that these compounds could potentially be useful in the treatment of hypertriglyceridemia. The molecular target was identified as the protein phosphatase 2A (PP2A), which is responsible for dephosphorylating hormone-sensitive lipase – an enzyme that hydrolyses triglycerides to free fatty acids from fats. PP2A is also responsible for oncogenic signaling cascades.[6]

5.1.3 Previous Syntheses of Haterumalides

5.1.3.1 The Kigoshi Synthesis of *ent*-Haterumalide NA Methyl Ester

The first total synthesis of a member of the haterumalide family of natural products was reported by Kigoshi in 2003, who completed an enantioselective synthesis of *ent*-haterumalide NA methyl ester (**337**, Scheme 59).[7] The completion of this synthesis resulted in the revision of the previously reported absolute stereochemical assignment at C3, C11, C13, and C14. This asymmetric synthesis relied on a chiral-pool starting material ((+)-2,3-*O*-isopropylidene-L-threitol (**338**)), which was elaborated in nine-steps to diol **339**. A key Michael-addition/cyclisation and silyl protection afforded the tetrahydrofuran **340** - securing the required stereochemistry at C11, C13, and C14. Next, the side chain of tetrahydrofuran **340** was converted into the primary bromide **341**, then coupled to vinylsilane **342** to provide alkenyl silane **343**. Using the Tamao protocol,[12] the alkenyl silane **343** was directly converted to the corresponding vinyl chloride **344**, and subsequently transformed to the desired aldehyde **345**. This latter material was subjected to a screen of macrocyclisation reaction conditions and it was found that a Honda-modified Reformatsky reaction,[13] followed by the addition of Ac_2O and deprotection of the MPM group afforded the desired cyclisation product, known as the Kigoshi intermediate **346**, albeit in low yield (9%). Oxidation of the alcohol function in **346**, and a Nozaki-Hiyama-Kishi coupling[14] with vinyl iodide **347** produced *ent*-haterumalide NA methyl ester (**337**). The overall synthesis of *ent*-**337** was achieved in 32-steps (0.2% overall yield) from commercially available starting materials.

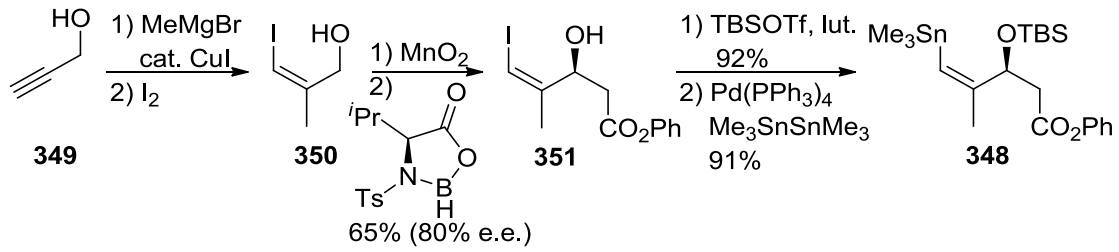


Scheme 59. Total synthesis of *ent*-haterumalide NA methyl ester (337).

5.1.3.2 The Snider Synthesis of *ent*-Haterumalide NA Methyl Ester

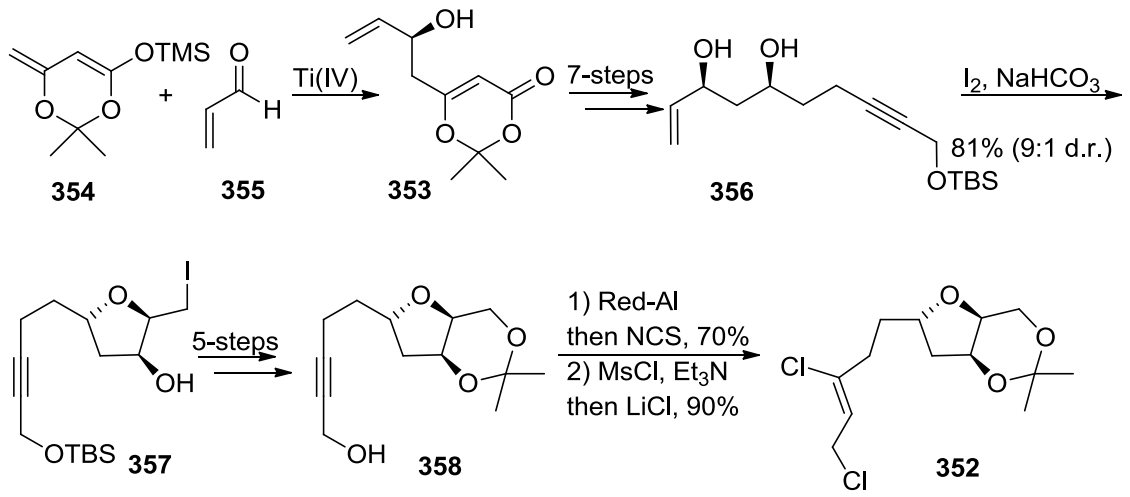
After Kigoshi's synthesis of the *ent*-haterumalide NA methyl ester (**337**) was reported, Snider described a second total synthesis of this molecule.[15] This route began

with preparation of the optically active vinylstannane **348** (Scheme 60). Specifically, propargyl alcohol (**349**) was subjected to a Cu-catalysed methylmagnesation, followed by iodinolysis to afford allylic alcohol **350**.[16] After oxidation of the allylic alcohol **350**, an asymmetric aldol reaction using Kiyooka's oxaborolidinone provided the β-hydroxy phenyl ester **351**.[17] Protection of the alcohol function as the silyl ether and cross-coupling of the vinyl iodide **350** with hexamethylditin furnished the vinylstannane **348**.



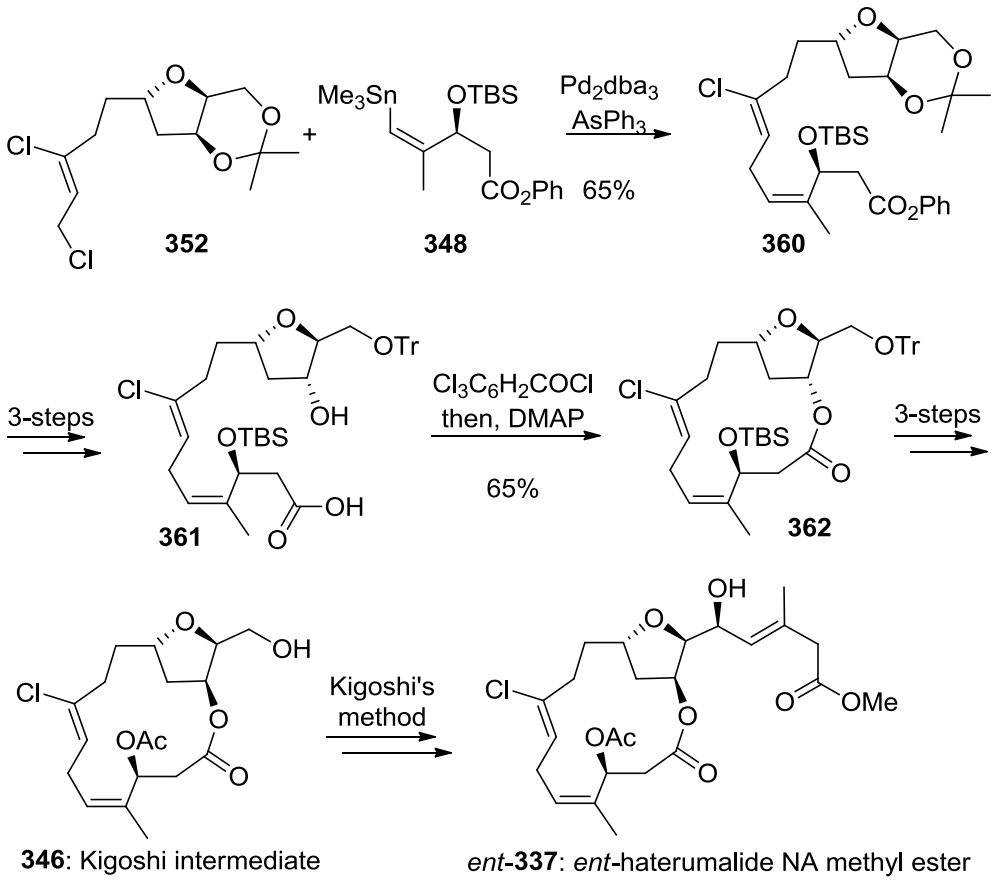
Scheme 60. Synthesis of vinylstannane 348.

The tetrahydrofuran subunit **352** was synthesised as outlined in Scheme 61. First, the allylic alcohol **353** was prepared using a Carreira asymmetric aldol reaction between the OTMS dienolate **354** and acrolein (**355**).[18] The allylic alcohol **353** was then converted in seven-steps to the diol **356**, which underwent an intramolecular iodoetherification to afford the iodomethyltetrahydrofuran **357**. Following a sequence of functional group manipulations that afforded the tetrahydrofuran **358**, this material was subjected sequentially to a regioselective hydroalumination using Red-Al, followed by treatment with NCS, and finally reacted with MsCl and LiCl to give the dichloride **352**.



Scheme 61. Synthesis of tetrahydrofuran subunit 359.

As depicted in Scheme 62, a Stille coupling between **352** and **348** afforded the desired skipped diene **360**,[19] and it was subsequently converted to the seco acid **361**. A Yamaguchi macrolactonisation afforded macrocycle **362**,[20] and following several functional group interconversions the Kigoshi intermediate **346** was produced. This latter intermediate was elaborated to the natural product following the procedure previously reported by Kigoshi.[7] Overall, the Snider route gave access to *ent*-haterumalide NA methyl ester (**337**) in 28-steps (0.7% overall yield).

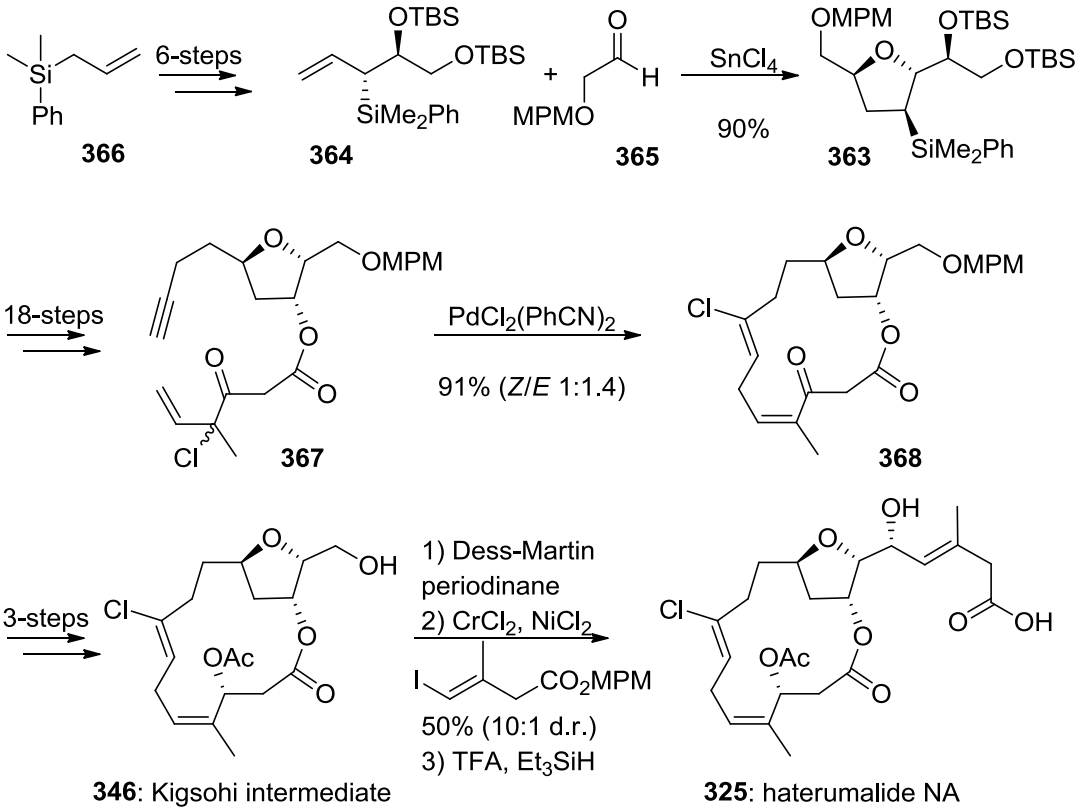


Scheme 62. Synthesis of *ent*-haterumalide NA methyl ester (337) by Snider.

5.1.3.3 The Hoye Synthesis of Haterumalide NA

The first total synthesis of the correct enantiomer of haterumalide NA (**325**) was reported by Hoye in 2005 (Scheme 63).[21] This strategy employed a method described by Roush for the synthesis of the desired tetrahydrofuran subunit **363**,[22] using a [3+2] annulation of an allylsilane **364** and an α-hydroxyaldehyde **365**. The allylsilane **364** was prepared in six-steps from silane **366** using (+)-$(Ipc)_2$BOMe to impart asymmetry in a crotylboration reaction.[23] Next, ene-yne **367** was accessed from **363** in 18-steps, and then subjected to a macrocyclisation using the Kaneda chloroallylation[24] reaction to yield the desired macrocycle **368**, albeit with poor stereocontrol at the $\Delta^{7,8}$ alkene (*Z*/*E*

1:1.4).This material was converted to the Kigoshi intermediate **346** in three-steps. A Nozaki-Hiyama-Kishi coupling of **346** with vinyl iodide **369**, followed by a MPM ester cleavage afforded haterumalide NA (**325**). In summary, the Hoye synthesis provided access to the natural product in 32-steps (0.2% overall yield).

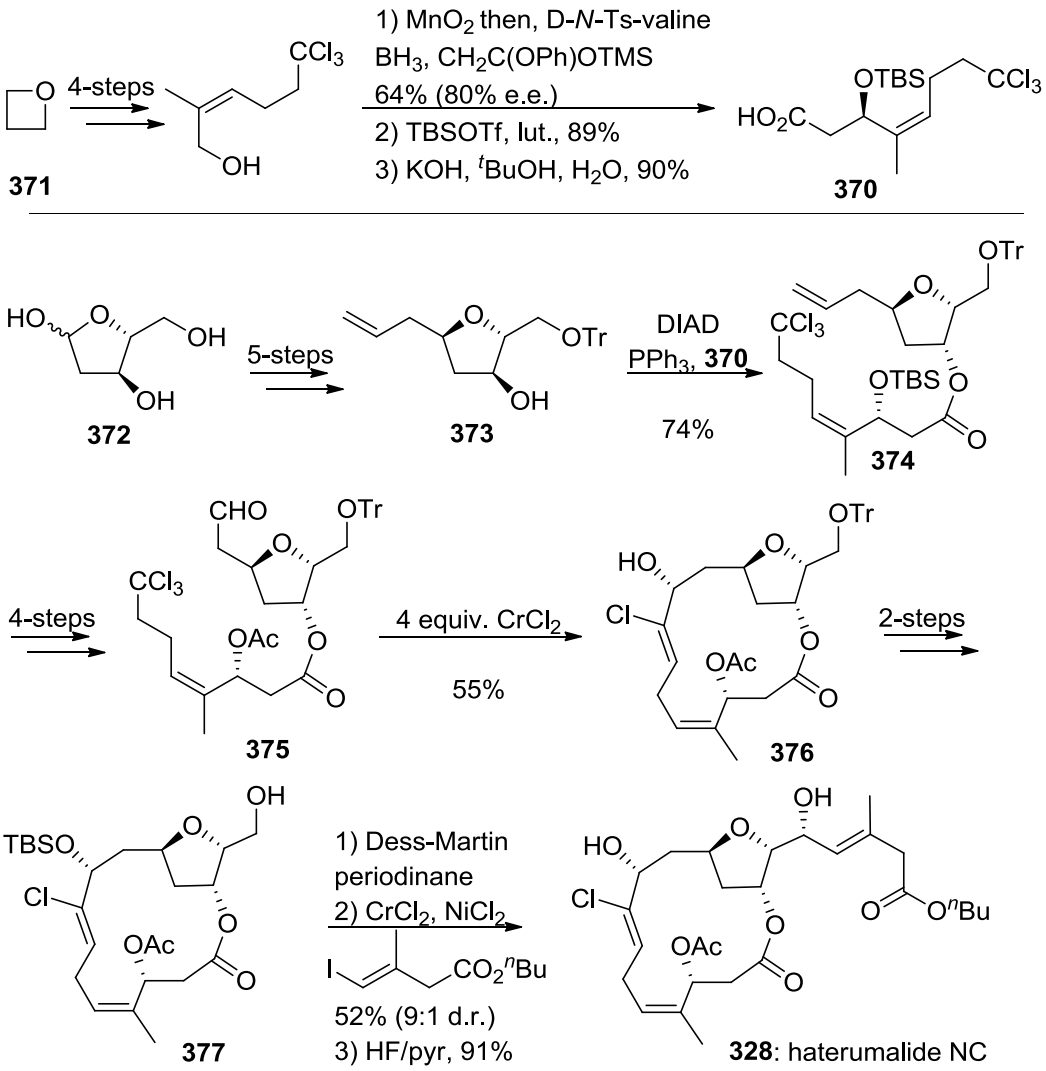


Scheme 63. Synthesis of haterumalide NA (325) by Hoye.

5.1.3.4 The Borhan Synthesis of Haterumalide NC

In 2008, Borhan reported the first total synthesis of haterumalide NC (**328**), and a formal synthesis of haterumalide NA methyl ester (**337**). This strategy was inspired by methods reported by Falck and Mioskowski on the chemistry of chlorovinylidene chromium carbenoids.[25] The required 1,1,1-trichloroalkane substrate **370** was prepared from oxetane **371**, and involved a key asymmetric Mukaiyama aldol reaction.[26] The

coupling partner for the Falck-Mioskowski reaction[25] was accessed from 2-deoxy-D-ribose **372**, which was converted to tetrahydrofuranol **373** in five-steps. A Mitsunobu esterification between tetrahydrofuranol **373** and the carboxylic acid **370** yielded the ester **374**, whereby inversion at C13 established the correct stereochemistry. After several functional group interconversions and oxidative cleavage of an alkene function, intermediate **375** was obtained. This latter material then underwent a chromium carbenoid-mediated macrocyclisation to afford macrocycle **376** in 55% yield, which was subsequently elaborated to the C9 OTBS analogue **377** of the Kigoshi intermediate. A Nozaki-Hiyama-Kishi coupling with vinyl iodide **378**, followed by a desilylation afforded haterumalide NC (**328**). In addition, macrocycle **376** was subjected to a Barton-McCombie deoxygenation[27] to afford the C9 deoxy intermediate **362** also reported in the Snider synthesis[15] (*vide supra*), thus completing a formal synthesis of haterumalide NA methyl ester (**337**). In summary, haterumalide NC (**328**) was accessed in 18-steps (6% overall yield) using the Falck-Mioskowski reaction[25] as a novel macrocyclisation.

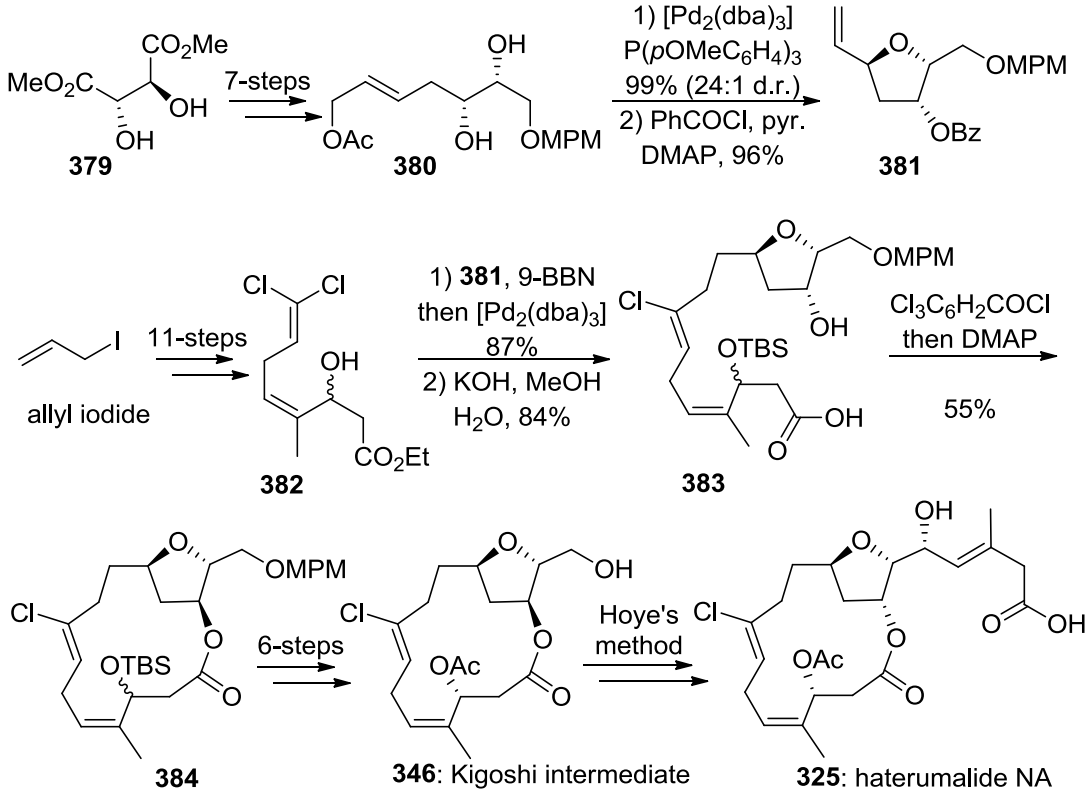


Scheme 64. Synthesis of haterumalide NC (328) by Borhan.

5.1.3.5 The Roulland Synthesis of Haterumalide NA

In 2008, Roulland reported that the C8-C9 bond of haterumalide NA (**325**) could be constructed using a Suzuki-Miyaura coupling.[28] Specifically, dimethyl D-tartrate (**379**), the sole source of chirality in this synthesis, was first converted in seven-steps to acetate **380**. This latter material was then subjected to a palladium-catalysed etherification to afford the tetrahydrofuranol **381**, the coupling partner for the key Suzuki-Miyaura

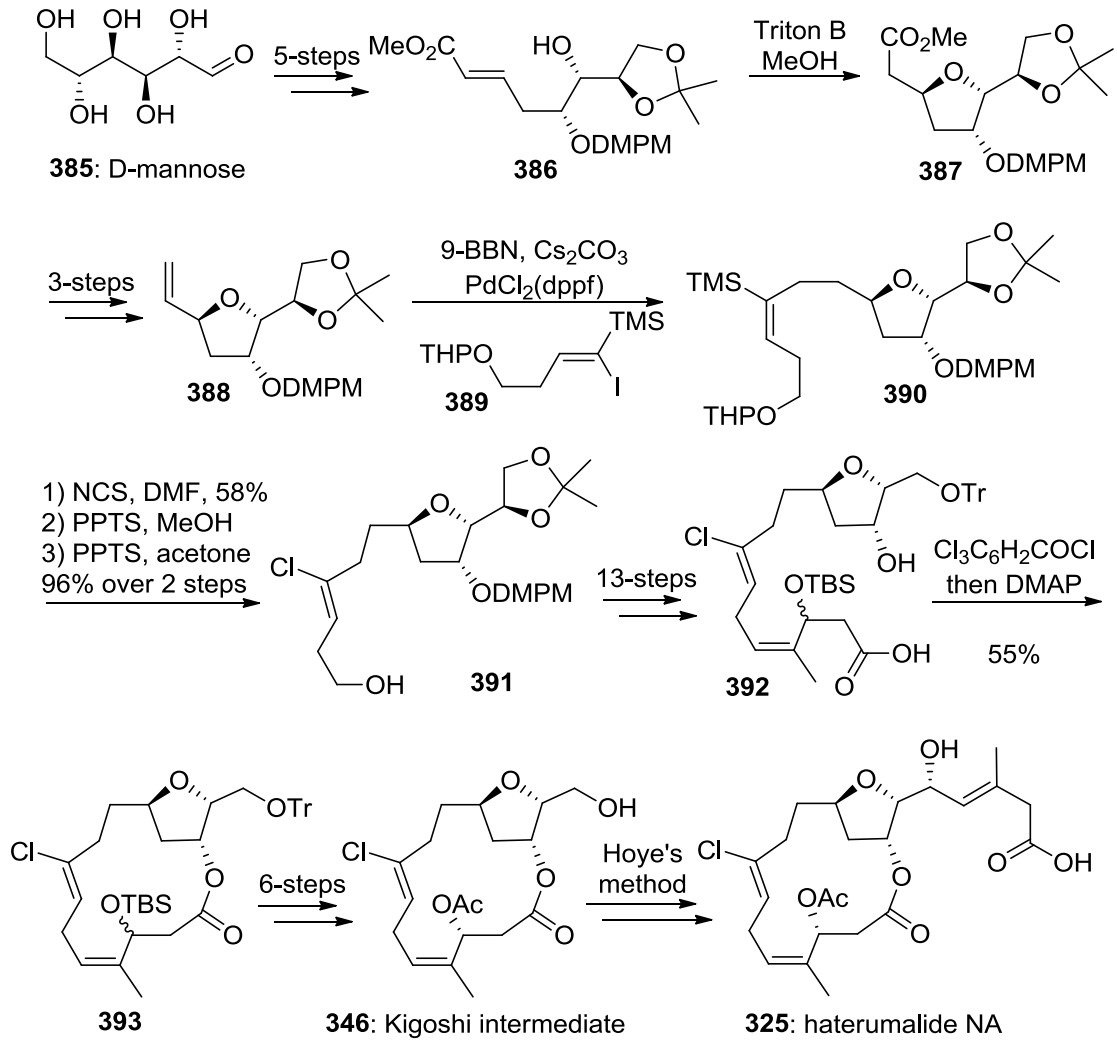
reaction,[29] with excellent diastereoselectivity (24:1 d.r.). The required 1,1-dichloroalkene **382**, was accessed from allyl iodide in ten-steps.[30] With both coupling partners in hand, the Suzuki-Miyaura reaction was carried out using 9-BBN and catalytic $[Pd_2(dba)_3]$,[31] followed by hydrolysis to provide the seco acid **383**. Macrolactonisation was effected under Yamaguchi esterification[20] conditions to produce macrolactone **384**, which was converted to the Kigoshi intermediate **346**. The synthesis was completed using the sequence developed by Hoye,[21] resulting in a 22-step (4% overall yield) route to haterumalide NA (**325**).



Scheme 65. Synthesis of haterumalide NA (325) by Roulland.

5.1.3.6 The Second Generation Kigoshi Synthesis

In a second generation synthesis of the haterumalides, Kigoshi also identified the C8-C9 bond as a retrosynthetic disconnection and planned a route to the macrolactone using a Suzuki-Miyaura coupling[32] as the key step.[33] This second generation synthesis started with the conversion of D-mannose (**385**) to the α,β-unsaturated ester **386**. An intramolecular oxy-Michael cyclisation employing Triton B in methanol then gave tetrahydrofuran **387** as a single diastereomer.[34] The tetrahydrofuran **387** was subsequently converted to alkene **388**, and subjected to the Suzuki-Miyaura reaction with iodoalkene[7] **389** using 9-BBN and $PdCl_2$(dppf) to obtain adduct **390** in quantitative yield. The chloroolefin **391** was stereoselectivily constructed from this latter material using the procedure reported by Tamao.[12] Next, **391** was advanced to the seco acid **392** in 13-steps, followed by a Yamaguchi lactonisation[20] to yield macrolactone **393**. Finally this material was transformed into the Kigoshi intermediate (**346**), and following Hoye's endgame strategy,[21] haterumalide NA (**325**) was obtained (33-steps, 1.2% overall yield).

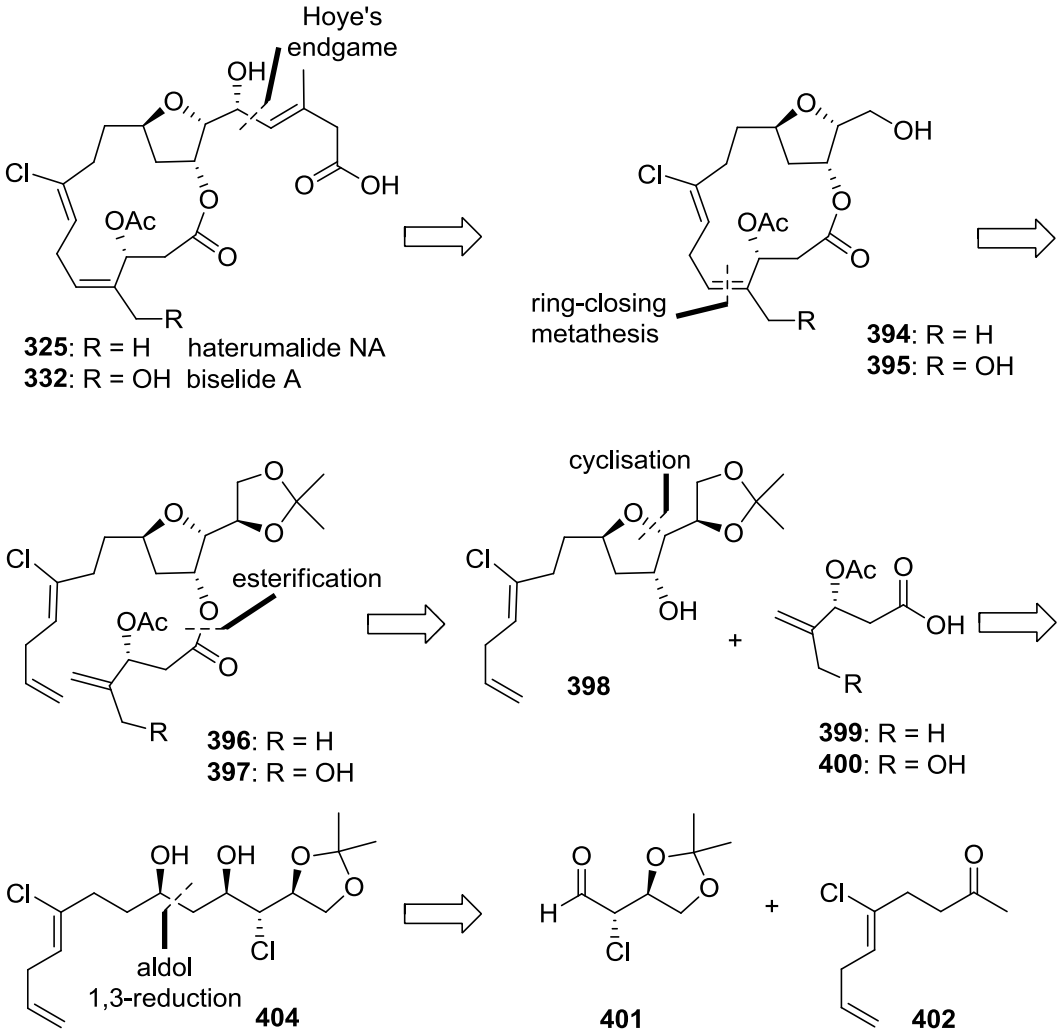


Scheme 66. Synthesis of haterumalide NA (325) by Kigoshi.

5.2 Toward the Synthesis of the Haterumalide and Biselide Natural Products

5.2.1 Synthetic Plan: Ring-Closing Metathesis Strategy

Six previous syntheses of the haterumalides have been reported that employ a variety of strategies to construct the 2,5-disubstituted-3-hydroxytetrahydrofuran core, the (*Z*)-chloroolefin, and the macrocyclic ring. It was our contention that haterumalide NA (**325**) and the related natural product, biselide A (**332**), could be accessed efficiently using methods developed for the construction of tetrahydrofurans discussed in Chapters 3 and 4. Bearing this in mind, a retrosynthetic strategy for the synthesis of these natural products is depicted in Scheme 67. It was envisioned that Hoye's endgame strategy[21] could be used to install the carboxylic acid portion of the natural products in the final-steps of the synthesis; consequently, the proposed synthesis would converge with previous syntheses at the Kigoshi intermediate (e.g., **394** and **395**). As depicted below, the Kigoshi intermediate (e.g., **394** and **395**) could be accessed through a ring-closing metathesis reaction carried out on the corresponding triene (e.g., **396** and **397**). This latter material could itself be derived from an esterification reaction between the tetrahydrofuranol **398** and carboxylic acid (e.g., **399** and **400**). The tetrahydrofuranol **398** could be prepared through the use of methodologies described in Chapters 3 and 4, which would require an aldol reaction between an optically enriched α-chloroaldehyde (e.g., **401**) and the ketone (**402**), followed by hydroxyl-directed reduction of the β-ketochlorohydrin **403** (not shown), and cyclisation of the resulting chlorodiol (e.g., **404**). The α-chloroaldehyde and ketone subunits could be procured by a variety of methods, and the preparation of these compounds were the initial focus of this work.



Scheme 67. Retrosynthetic strategy toward the synthesis of haterumalide NA (325) and biselide A (332).

In the previous Chapters, the asymmetric α-chlorination was performed on aldehydes void of chirality at the β-position. However, for this work, it was envisioned that a chiral β-functionalised aldehyde would allow for the preparation of an optically pure chloroaldehyde. In 2004, MacMillan examined the ability of an organocatalyst to override the substrate control, and found that the α-chlorination of chiral β-functionalised aldehydes is under catalyst control.[50] Thus, the desired α-chloroaldehyde **401** could be generated from the parent aldehyde using an asymmetric α-chlorination reaction.

It was envisioned that the ketone **402** required for the aldol reaction depicted in Scheme 67, could be accessed using the Kaneda chloroallylation reaction.[24,35] This transformation was first reported in 1979 by Kaneda and involved the reaction of substituted alkynes **405** and alkyl halides with palladium complexes to give (*Z*)-chlorodienes.[24] The mechanism depicted in Figure 23 has been proposed for this process in which insertion of palladium **406** occurs in a *cis* manner and then the allyl halide (**407**) inserts into the palladium-vinyl bond **408** → **409**. Finally, **410** undergoes a β-elimination to give the (*Z*)-chlorodiene **411**.

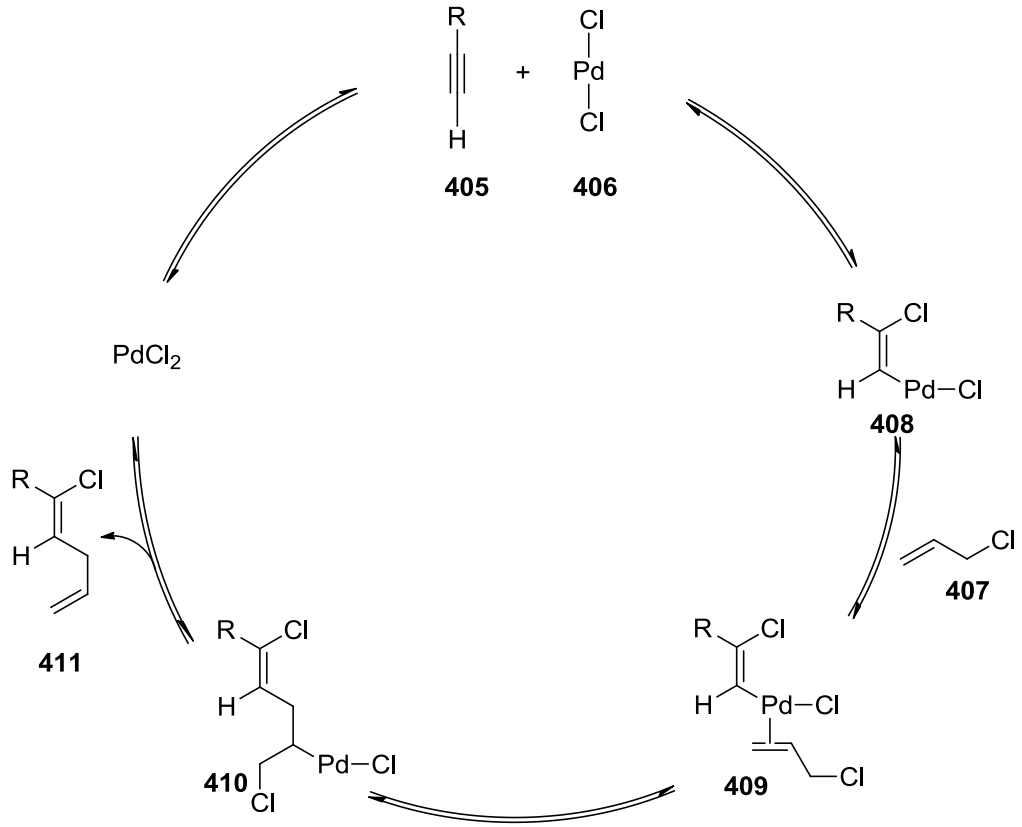
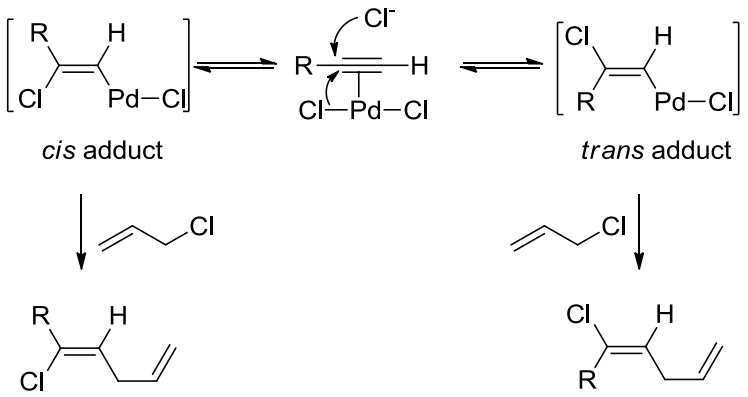


Figure 23. Proposed mechanism for the Kaneda alkyne chloropalladation.

Bäckvall probed this reaction in detail and found that the concentration of chloride in solution influences the amount of *Z*- and *E*-isomers produced.[35] A lower concentration of chloride leads preferentially to the *Z*-chlorodiene, whereas a higher

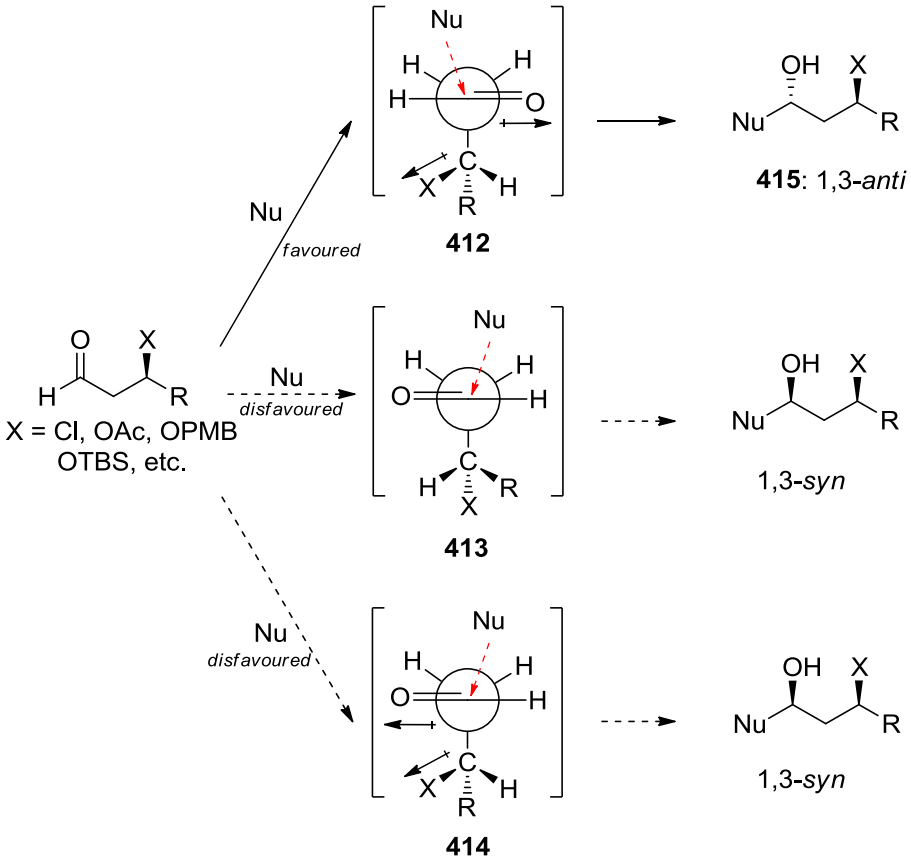
concentration of chloride results in an external addition of the chloride ion leading to the *E*-chlorodiene (Scheme 68). Bäckvall suggested that although the *cis* and *trans* chloropalladation adducts are in equilibrium with the π-acetylenic complex, the trapping reaction is much quicker, especially with excess allyl halide. Thus, a careful choice of catalyst, chloride concentration and amount of allyl halide should result in the construction of the desired ketone **402**.



Scheme 68. Synthesis of *Z*- and *E*-chlorodienes.

With successful preparation of the both fragments (e.g., **401** and **402**) it was expected that these substances could be coupled effectively through a diastereoselective aldol reaction. In previous work (Chapter 2-4), in the addition of nucleophiles (e.g., organolithium reagents, lithium enolates) to α-chloroaldehydes the stereochemical outcome of the reaction was controlled by 1,2-induction, as rationalised by the Cornforth Model[36] (Chapter 2). However, in the case of an aldehyde bearing a stereogenic centre (i.e., 1,3-stereoinduction) in the β-position the influence of this second stereocentre must be considered. To predict the outcome of such reactions, a similar model is invoked that takes both steric and electronics into consideration.[37] As depicted in Scheme 69, it has been proposed that such nucleophilic additions proceed *via* a transition structure (e.g., **412**) in which there is complementary minimisation of

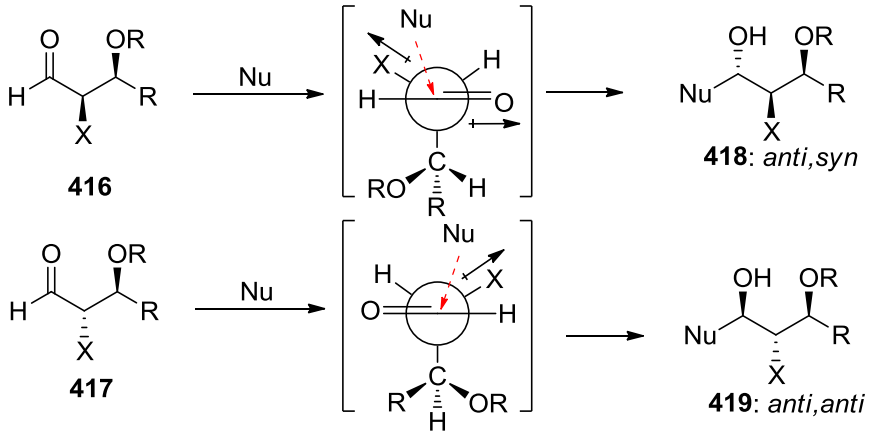
interacting dipoles and non-bonding steric interactions. In contrast, transition structure **413** introduces a destablising gauche interaction (R ↔ C=O), which is amplified for larger R groups. Similarly, transition structure **414** is disfavoured due to electrostatic repulsion of the associated dipoles. Thus, it follows that the 1,3-*anti*-isomer **415** would be produced as the major product.



Scheme 69. Model for 1,3-asymmetric induction.

For the purpose of our work, which would involve the use of an α-chloro-β-alkoxy aldehyde, the task of defining the stereochemical outcome is difficult, as no related examples have been reported. However, the addition of nucleophiles to α-alkyl-β-alkoxy aldehydes has been thoroughly studied by Evans, who proposed a merged 1,2- and 1,3-asymmetric induction model.[38] Although, this does not directly translate to α-chloro-β-

alkoxy aldehydes, this study revealed that there will be a matched combination where the α- and β-stereocentres mutually reinforce the formation of a particular product, and a mismatched combination that results in a mixture of stereoisomers. In 2006, Evans[39] investigated the addition of nucleophiles into α,β-bisalkoxy aldehydes and hypothesised that the *syn*-aldehyde diastereomer should mutually reinforce the stereochemical outcome of the reaction whereas the *anti*-aldehyde diastereomer should be non-reinforcing. This model predicts high levels of diastereomeric control for the *syn*-aldehyde, and low levels for the *anti*-aldehyde. However, after considerable experimentation Evans found that the addition of lithium enolates to the *syn*-α,β-bisalkoxyaldehydes (e.g., **416**) afforded only modest levels of diastereoselectivity, whereas the *anti*-α,β-bisalkoxyaldehydes (e.g., **417**) proceeds with excellent control. These observations allowed for the development of a model for merged 1,2- and 1,3-asymmetric induction, where the Cornforth Model (i.e., the 1,2-asymmetric induction) plays a predominant role. The favoured transition structures are shown in Scheme 70, leading to the *anti*,*syn* **418** and *anti*,*anti* **419** products.



Scheme 70. Model for merged 1,2- and 1,3-asymmetric induction.

After a successful aldol coupling between the ketone **402** and the α-chloroaldehyde **401**, the resultant aldol adduct **403** would undergo a hydroxyl-directed

1,3-*syn* reduction. This affords the *syn*-chlorodiol **404**, which would then undergo conversion to the corresponding tetrahydrofuran using methodologies developed in Chapters 3 and 4. At this stage, esterification with carboxylic acid (e.g., **399** and **400**) would yield the tetrahydrofuran ester (e.g., **396** and **397**). A ring-closing metathesis is required to generate the desired macrocycle, which would then be elaborated to the Kigoshi intermediate (e.g., **394** and **395**). The ring-closing metathesis reaction has inspired the synthesis of many macrocycle-containing natural products.[40] For example, Hoveyda reported the macrocyclisation of a 14-membered ring in the total synthesis of the antifungal agent Sch 38516.[41] In particular, epothilone C was the early testing-ground for macrocyclic ring-closing metathesis, with syntheses reported by Nicolaou,[42] Danishevsky,[43] and Schinzer[44]. These studies addressed issues regarding *E*/*Z* selectivity, and the compatibility of functional groups. They found that even subtle modifications on the backbone drastically affect the ring-closing metathesis reaction, such that a general model can not be attained for this transformation.

Although the ring-closing metathesis is one of the most widely used reactions for the construction of macrocyclic natural products, there are also a significant amount of limitations that have been reported. The general catalytic cycle is described in Figure 24. The first step is reaction of the catalyst with one of the alkenes **420,** typically the most accessible olefin, to form alkylidene **421** after release of styrene from the catalyst. The second step involves a [2+2] cycloaddition with a second alkene to afford metallacyclobutane **422**, followed by a retro-[2+2] cycloaddition to form the macrocyclic alkene **423** and regenerate the catalyst. Limitations arise when one or both of the alkenes are sterically hindered at the vinylic or the allylic position, or are electronically deactivated.

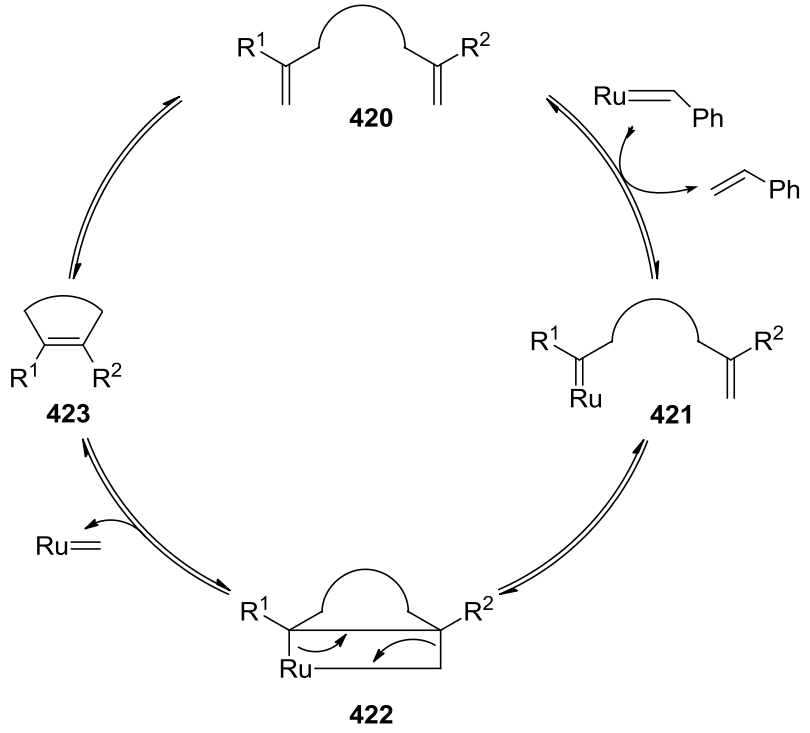


Figure 24. Catalytic cycle for a ring-closing metathesis.

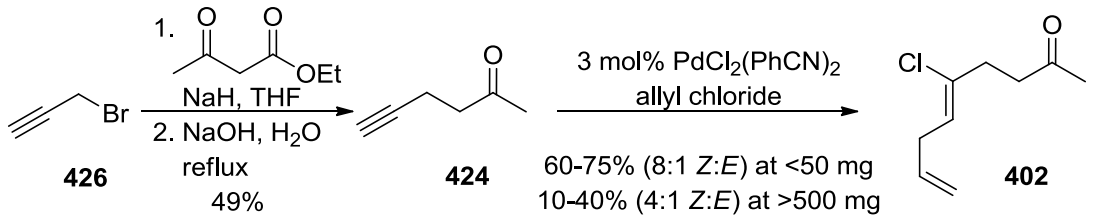
After successful preparation of the Kigoshi intermediate (e.g., **394** and **395**), the endgame strategy described by Hoye[21] would be employed. This proposed synthesis would represent a significant improvement (five-steps from commercially available materials) over previously reported methods (11-17-steps) for the preparation of the tetrahydrofuran core. Furthermore, the chloroolefin would be installed at an early stage using Kaneda chloroallylation conditions- an eloquent method for the synthesis of vinyl chlorides. Lastly, a novel ring-closing metathesis would be used for the construction of the macrocyclic ring. If successful, this route would provide access to the Kigoshi intermediate in nine-steps and allow necessary flexibility required to generate a library of analogues for SAR purposes. In addition, the lengthy routes used in previous syntheses allowed only ~11 mg of the haterumalides to be produced. It is expected that our

proposed synthesis would permit the production of gram quantities of the natural products and their analogues.

5.2.2 Results

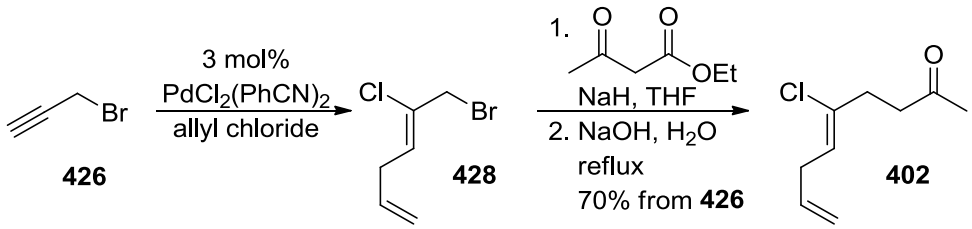
5.2.2.1 Synthesis of Ketone 402

A key aspect of our proposed synthesis of haterumalide NA (**325**) and biselide A (**332**) involved gaining rapid access to the tetrahydrofuranol core, which would include a diastereoselective aldol reaction and the formation of the requisite vinyl chloride functionality. Toward this end, the alkynyl ketone **424** was prepared by alkylation of ethyl acetoacetate (**425**) with propargyl bromide (**426**), followed by hydrolysis and decarboxylation, which were carried out in a one-pot process.[45] Next, various reaction conditions (e.g., temperature, catalyst, catalyst loading, solvent) were screened for the chloroallylation and it was found that the best results were obtained when the reaction was carried out in THF at room temperature with slow addition of the palladium catalyst and the alkynyl ketone **424** to a solution containing excess allyl chloride (**427**).[24,35] It was found that the optimal palladium catalyst for this transformation was bis(benzonitrile)palladium(II) chloride used in a 3 mol% catalyst loading. Although, on smaller scale (<50 mg) the yield and stereoselectivity for this reaction were consistent (60-75%, 8:1 *Z*:*E*), on larger scale (e.g., >500 mg) this reaction afforded the ketone **402** in yields ranging from 10-40% (4:1 *Z*:*E*) with significant formation of undesired by-products. A further survey of conditions (e.g., concentration, catalyst loading, temperature) failed to identify the source of inconsistency between scale and yield.



Scheme 71. Synthesis of ketone 402 *via* the alkynyl ketone 424.

To circumvent the difficulties in converting useful quantities of ketone **424** into chloroalkene **402**, an alternative sequence of reactions was employed. It was found that the optimised conditions discussed above facilitated the palladium-catalysed chloroallylation reaction of propargyl bromide (**426**) and provided access to multi-gram quantities of the allyl bromide **428**.[24,35] Alkylation of ethylacetoacetate (**425**) with the allyl bromide **428**, followed by a decarboxylation afforded ketone **402**.

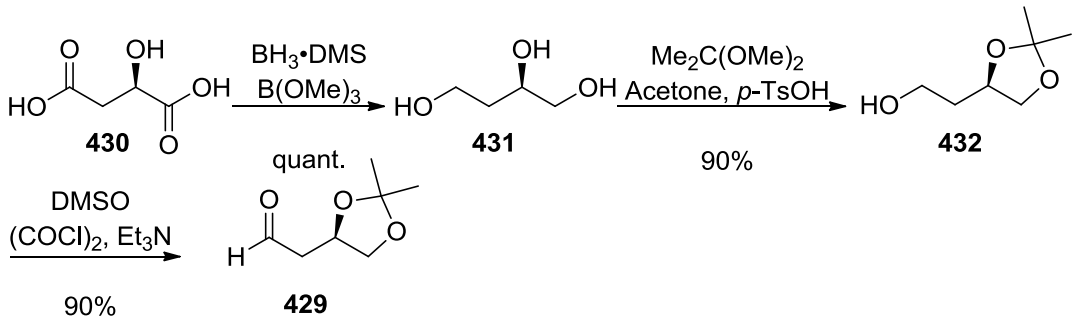


Scheme 72. Synthesis of ketone 402 *via* the allyl bromide 428.

5.2.2.2 Synthesis of α-Chloroaldehyde 401

The enantioselective synthesis of the targeted natural products, haterumalide NA (**325**) and biselide A (**332**), required the asymmetric preparation of α-chloroaldehyde **401** as a source of chirality. Bearing this in mind, significant efforts were directed to the development of a method that would produce a sufficient amount of **401**. The parent aldehyde **429** for the α-chlorination reaction was accessed from D-malic acid (**430**), through an efficient three-step sequence. Specifically, D-malic acid (**430**) was subjected

to a borane-dimethyl sulfide reduction[46] to give (*R*)-butane-1,2,4-triol (**431**) in quantitative yield. The crude triol **431** was then converted directly to an 11:1 mixture of 5-membered-ring acetonide **432** and the corresponding 6-membered-ring acetonide (not shown).[47] A subsequent Swern oxidation[48] of acetonide **432** afforded the corresponding aldehyde **429** in 90% yield.

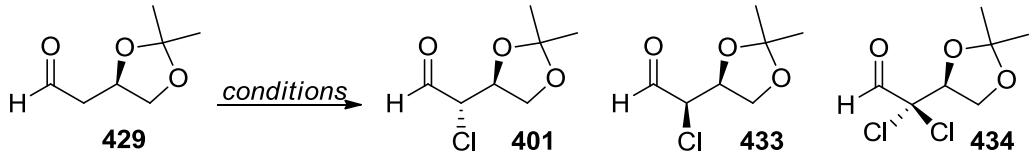


Scheme 73. Preparation of the aldehyde 429.

With the aldehyde **429** in hand, the key α-chlorination reaction was investigated. As three possible products could arise from this reaction (i.e., 2,3-*anti*-chloroaldehyde **401**, 2,3-*syn*-chloroaldehyde **433**, dichloroaldehyde **434**), it was envisioned that the stereochemical outcome of the α-chlorination could be controlled by the choice of catalyst. The stereochemistry of these chloroaldehydes was tentatively assigned as depicted and confirmed later (*vide infra*). As indicated in Table 27, when DL-proline was used an equal mixture of all three products were produced, indicating that the catalyst may override inherent substrate bias in the chlorination reaction. Similarly L-proline, which reportedly imparts only minimal (e.e. <10%) asymmetric control in α-chlorination reactions, produced an equal mixture of aldehydes **401** and **433**, which were characterised by resonances (doublets) at δ 9.51 and 9.56 ppm, respectively, in the ^{1}H NMR specta recorded on crude reaction mixtures. Using D-prolinamide as the catalyst and NCS as the chlorinating agent, it was found that α-chloroaldehyde **401** was the

major product, and L-prolinamide afforded the α-chloroaldehyde **433** with similar stereocontrol. It is notable that in these chlorination reactions, the desired product was accompanied by significant amounts of the dichloroaldehyde **434** (characterised by a resonance at δ 9.30 ppm in the ^{1}H NMR spectrum). Based on studies reported by Jørgensen that highlight the critical role played by water in organocatalytic reactions,[49] the addition of water to these chlorination reactions was investigated. As summarised in Table 27, it was found that the addition of two equivalents of water resulted in less dichlorination and greater stereocontrol. Even though the optimised conditions afforded the α-chloroaldehydes **401** and **433** in yields of 90% on small scale (e.g., 10-50 mg), on larger scales (e.g., >250 mg) polymerisation predominated. In addition, MacMillian's imidazolidinone[50] catalyst (**8**) afforded primarily the dichloroaldehyde **434**. At the time of this study MacMillan's SOMO α-chlorination process had not yet been reported.[51]

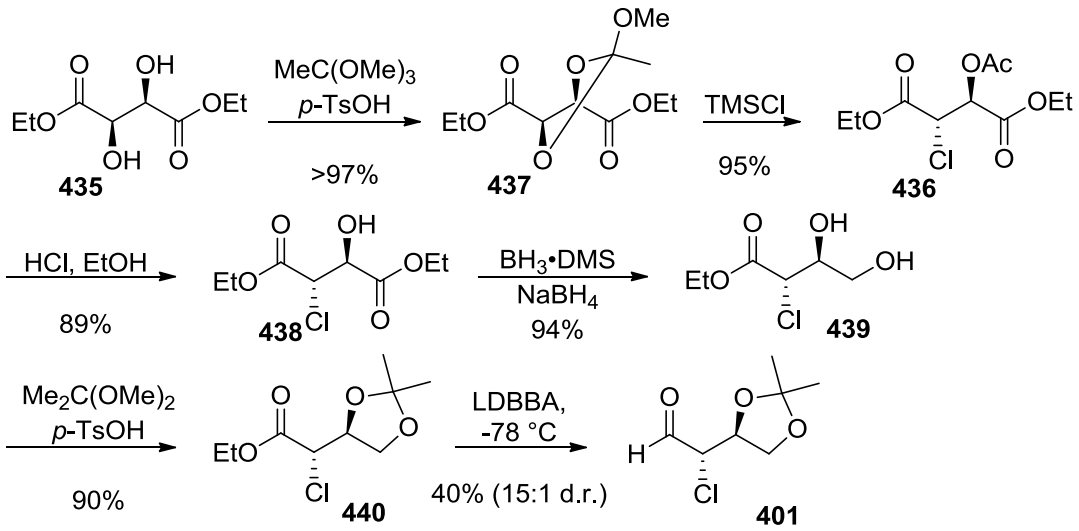
Table 27. α-Chlorination of Aldehyde 429.



catalyst	Time (h)	Cl agent (equiv.)	additive	401: 433: 434 [c]
DL-proline	92	NCS (1)	-	25:25:25
L-proline	92	NCS (1)	-	25:20:20
D-prolinamide	24	NCS (1.1)	-	50:10:25
D-prolinamide	30	NCS (1)	-	50:20:30
L-prolinamide	24	NCS (1.1)	-	40:30:20
L-prolinamide	36	NCS (1)	-	40:20:10
D-prolinamide[a]	48	NCS (1)	H_2O	70:10:10
D-prolinamide[a]	48	NCS (1.5)	H_2O	90:5:5
D-prolinamide[b]	64	NCS (1.5)	H_2O	20:5:5
Imidazolidinone (**8**)	12	Leckta quinone (1)	-	5:5:40

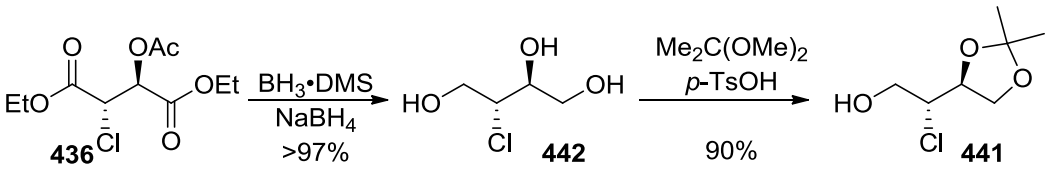
a.10-50 mg scale. b. >250 mg. significant polymerisation. c. determined by ^{1}H NMR on crude material.

To gain access to useful quantities of the 2,3-*anti*-chloroaldehyde **401**, an alternative route was developed initiating with (+)-diethyl tartrate (**435**). A method developed by Sharpless was employed to access the chloroester **436**,[52] this process involved treatment of diethyl tartrate **435** with trimethyl orthoacetate in the presence of TMSCl, however, the only isolated product from this reaction was a mono-TMS protected diethyl tartrate. Thus, a step-wise approach to the chloroacetate **436** was used in which the ortho ester **437** was isolated, followed by treatment with TMSCl. Hydrolysis using ethanol in HCl then provided the chlorohydrin **438**, which was subsequently treated with borane-dimethyl sulfide to give the chlorodiol **439**.[53] This latter material was treated with dimethoxypropane and *p*-TsOH to yield the 5-membered-ring acetonide **440**. Several attempts to partially reduce the ester **440** directly to the aldehyde using DIBAL-H failed to produce the desired α-chloroaldehyde **401**; however, using LDBBA[54] as a reducing agent resulted in **401** in 40% yield (15:1 d.r.), which was isolated as a mixture containing 10% of the corresponding alcohol **441**. Notably, the stereochemistry of **401** derived from the α-chlorination route was confirmed by this approach.



Scheme 74. Synthesis of α-chloroaldehyde 401 from (+)-diethyltartrate (435).

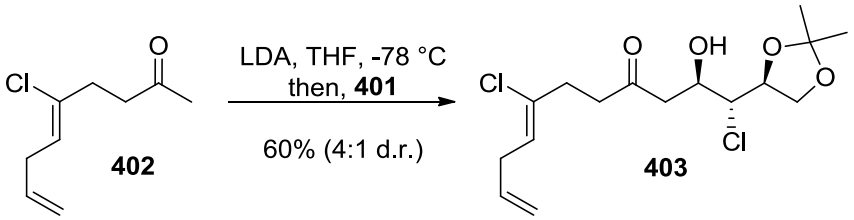
As an alternative strategy, oxidation of the alcohol **441**, which would also offer access to the desired α-chloroaldehyde **401**, was investigated. Thus, a global reduction of chloroacetate **436** with excess borane-dimethyl sulfide afforded chlorotriol **442**, and subsequent treatment with dimethoxypropane and *p*-TsOH yielded **441**. Unfortunately, attempted oxidation of **441** with a variety of oxidation agents (e.g., Swern,[48] Tempo/BAIB,[55] DMP,[56] PCC[57]) resulted in epimerisation of the C-Cl bond and/or significant decomposition, rendering this alternative route unsuitable.



Scheme 75. Attempted synthesis of α-chloroaldehyde 401 starting from chloroacetate 436.

5.2.2.3 Synthesis of Aldol Adduct 403

With a successful route to the ketone **402** and the α-chloroaldehyde **401** established, the subsequent aldol reaction was examined. Specifically, treatment of the ketone with freshly prepared lithium diisopropylamide, followed by slow addition of the α-chloroaldehyde **401** afforded the desired aldol adduct **403** in 60% yield (4:1 d.r.), as determined by ^{1}H NMR spectroscopy. Because only small amounts of the α-chloroaldehyde **401** could be obtained by the methods described above, this route was not amenable to scale-up. As such, we initiated an investigation into the use of an alternative chloroaldehyde that would provide access to useful quantities of the tetrahydrofuranols required for the synthesis of haterumalide NA (**325**) and biselide A (**332**).



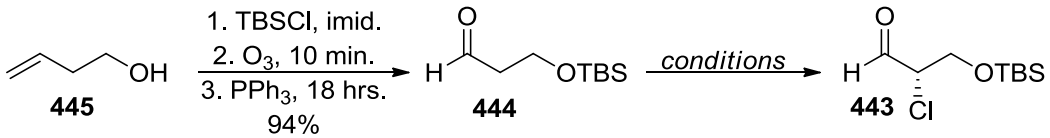
Scheme 76. Synthesis of aldol adduct 403.

5.2.2.4 Synthesis of α-Chloro-β-hydroxyaldehyde 443

Due to difficulties encountered in the preparation of α-chloroaldehyde **401**, the structurally austere α-chloroaldehyde **443** was targeted. It was expected that this latter material would undergo an aldol reaction with the ketone **402** to afford an aldol adduct that may also be elaborated to the desired tetrahydrofuran. Thus, the synthesis of α-chloroaldehyde **443** initiated with the construction of the parent aldehyde **444** from but-3-en-1-ol (**445**). This sequence of reactions involved a silyl protection of the free alcohol function, followed by ozonolysis and a reductive work-up to afford the desired aldehyde **444** in good yield.[58] Using L-proline as the catalyst for the α-chlorination reaction resulted in clean formation of the α-chloroaldehyde **443** in 95% yield, albiet with low enantiocontrol (20% e.e.). The reaction of aldehyde **444** with D-prolinamide required lengthy reaction times; as a result, product formation was accompanied by polymerisation and low isolated yields, typically between 30-40% (80% e.e.). Following these setbacks, the second generation α-chlorination method reported by MacMillan that uses SOMO-activation of aldehydes with the imidazolidinone catalyst **18** was explored (see page 8).[43,39] As summarised in Table 28, after a thorough screen of reaction conditions, it was found that although this method imparts high enantiocontrol in the α-chlorination reaction (94% e.e.), the yield of the desired product was consistently low. This result was primiarly due to a competing elimination reaction that generates acrolein

(the source of the polymeric material), which was characterised by resonances at δ 9.59, 6.52, 6.37, and 6.35 ppm in the ^{1}H NMR spectra recorded on crude reaction mixtures. Attempts to reduce the formation of acrolein by buffering the reaction mixture had no positive affect on the outcome of the reaction, and the addition of various amounts of water; or changing the scale of the reaction, catalyst loading, or temperature also failed to improve the yield of the desired chloroaldehyde **443**. In addition, α-chlorination reactions carried out on the corresponding triisopropyl silyl and benzyl protected aldehydes resulted in the formation of the α-chloroaldehydes **446** (30% yield) and **447** (40% yield) in modest yield accompanied by significant amounts of acrolein. Based on the challenges encountered in the preparation of optically pure **443**, it was determined that the most prudent course of action would be to progress racemic chloroaldehyde **443**, which could be generated in excellent yield *via* proline catalysts to the synthesis of the desired tetrahydrofuranol. Thus, our concerns regarding the preparation of optically pure α-chloroaldehyde **443** would be addressed following the successful incorporation of this intermediate into a synthesis of the tetrahydrofuranols.

Table 28. α-Chlorination of aldehyde 444.



Catalyst	scale (mmol)	temp. (°C)	time (h)	e.e. (%)	yield	side pdt.
L-proline[a]	1	22	1	-	50	dichlorination
L-proline[a]	1	0	4	15	90	-
L-proline[a]	10	0	5	20	95	-
D-prolinamide[a]	1	22	18	80	40	~70% purity
D-prolinamide[a]	1	0	48	-	-	no rxn
D-prolinamide[a]	10	22	18	80	30	polymerisation
15% imidazolidinone (**18**)[b]	0.2	0	4	-	30	acrolein

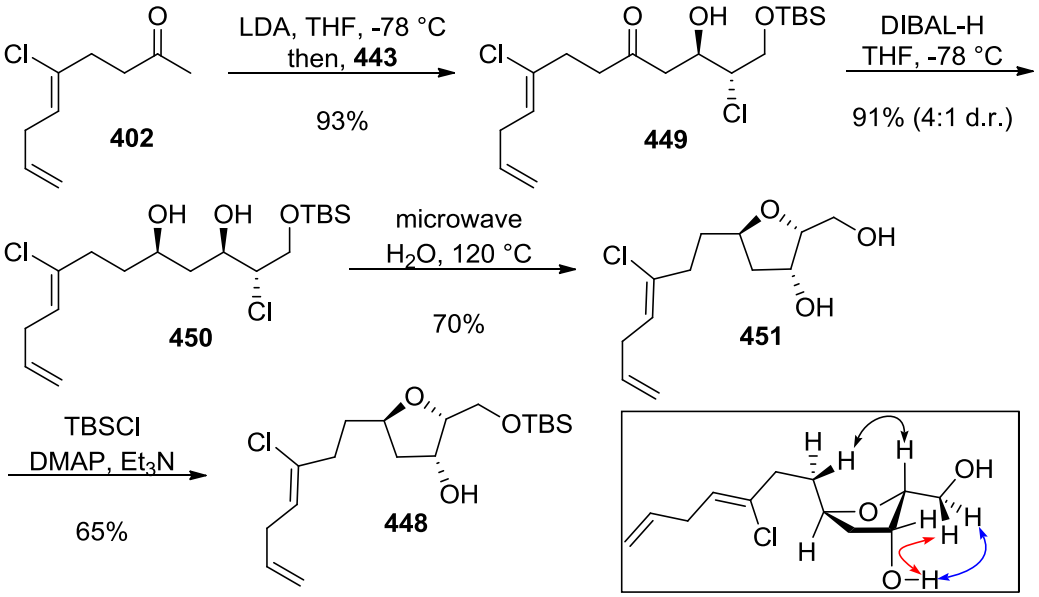
15% imidazolidinone (**18**)[b]	0.2[c]	0	4	-	30	acrolein
15% imidazolidinone (**18**)[b]	0.2[d]	0	4	-	30	acrolein
15% imidazolidinone (**18**)[b]	0.2[e]	0	4	-	30	acrolein
15% imidazolidinone (**18**)[b]	0.2	22	4	-	30	acrolein
50% imidazolidinone (**18**)[b]	0.2	0	4	92	30	acrolein
5% imidazolidinone (**18**)[b]	0.2	0	4	-	10	acrolein
15% imidazolidinone (**18**)[b]	10	22	16	94	35	acrolein
15% imidazolidinone (**18**)[b]	10	10	16	90	40	acrolein
10% imidazolidinone (**18**)[b]	10	10	72	-	-	acrolein
20% imidazolidinone (**18**)[b]	10	10	16	90	30	acrolein
15% imidazolidinone (**18**)[b]	10	30	8	-	-	acrolein

a. 10 mol% cat. loading, 1 equiv. NCS b. 1.5 equiv. LiCl, 0.5 equiv. $Cu(TFA)_2$, 1 equiv. $Na_2S_2O_8$, 2.1 equiv. H_2O c.without H_2O. d. with 2,6-Di-tert-butyl-4-methylpyridine e. with pH 8 buffer

5.2.2.5 Synthesis of the Tetrahydrofuran 448

With a suitable method developed for the synthesis of racemic α-chloroaldehyde **443**, an investigation into the synthesis of the tetrahydrofuran core **448** was initiated. To start, the ketone **402** was treated with lithium diisopropylamide, followed by a slow addition of α-chloroaldehyde **443**, which resulted in the production of the aldol adduct **449** as the major component of a separable 6:1 mixture of *anti*:*syn* diastereomers. Nevertheless, a 1,3-hydroxyl-directed reduction of the purified aldol adduct **449** employing DIBAL-H afforded an inseparable 4:1 mixture of the chlorodiol **450** and the corresponding 1,3-*anti*-diol diastereomer in 91% yield. This mixture of diols was then heated in water in a microwave reactor, which resulted in the removal of the TBS group and concomitant cyclisation to afford the tetrahydrofuran **451**. In an attempt to effect the desired cyclisation without deprotection, the reaction was repeated in both pH 7 (phosphate) buffer and with the addition of 2,6-di-*tert*-butyl-4-methylpyridine, but in both reactions complete removal of the silyl protecting group was observed. When the reaction was closely monitored by NMR spectroscopy, it was observed that deprotection

occurs within four minutes at 100 °C, whereas the desired cyclisation begins shortly thereafter and is complete by 20 minutes. These results suggest that the removal of the TBS group may help solubilise the chlorohydrin, and once in solution the cyclisation occurs. Even though the unwanted deprotection could not be avoided, the product of the cyclisation could be selectively reprotected at the primary alcohol position to afford the desired tetrahydrofuranol **448**. The relative stereochemistry of **451** was confirmed by nOe analysis as shown in Scheme 77.

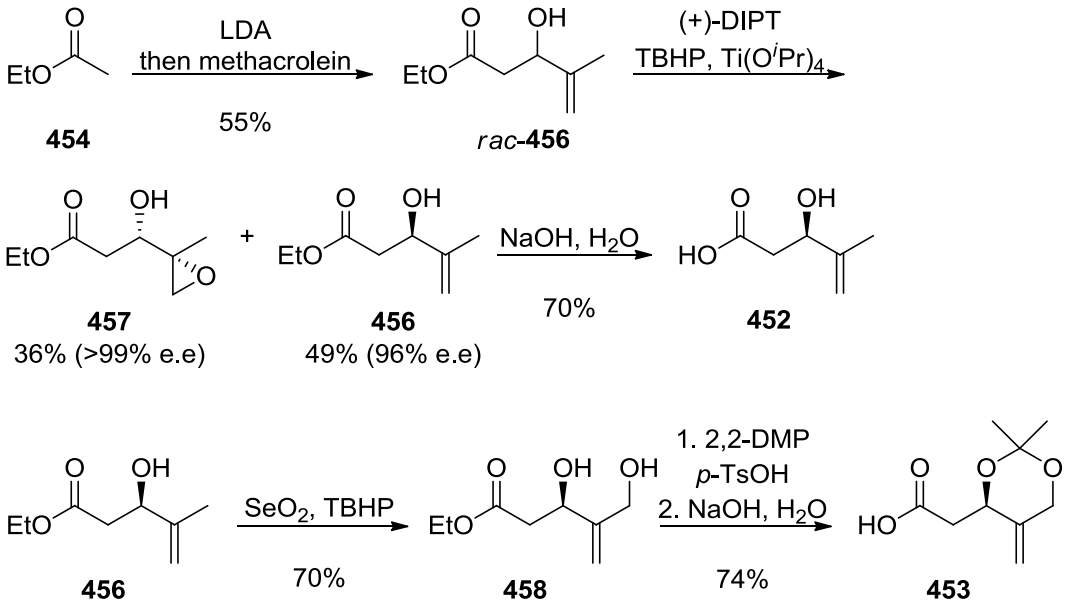


Scheme 77. Synthesis of the tetrahydrofuranol 448 and its stereochemical analysis by nOe.

5.2.2.6 Synthesis of the Carboxylic Acids 452 and 453

With a successful route to the tetrahydrofuranol **448** established, the preparation of the carboxylic acid fragments **452** and **453** required for the total synthesis of haterumalide NA (**325**) and biselide A (**332**), respectively, was initiated. As depicted in Scheme 78, these efforts began with the addition of the lithium enolate derived from ethyl acetate (**454**) to methacrolein (**455**), which afforded the aldol adduct *rac*-**456** in

good yield. Next, a Sharpless asymmetric kinetic resolution[59] was performed on this material to afford the optically enriched epoxide **457** and the unreacted (*R*)-enantiomer of the β-hydroxy ester **456**, which was recovered in 96% enantiomeric excess (determined by chiral GC analysis).[59] Hydrolysis of the ester function in the latter material with aqueous NaOH afforded the carboxylic acid **452** that was required for the synthesis of haterumalide NA (**325**). The enantioenriched aldol adduct **456** was also subjected to an allylic oxidation to afford the diol **458**,[60] which was then converted into the corresponding acetonide prior to hydrolysis of the ester functionality to afford the carboxylic acid **453** required for the proposed synthesis of biselide A (**332**).

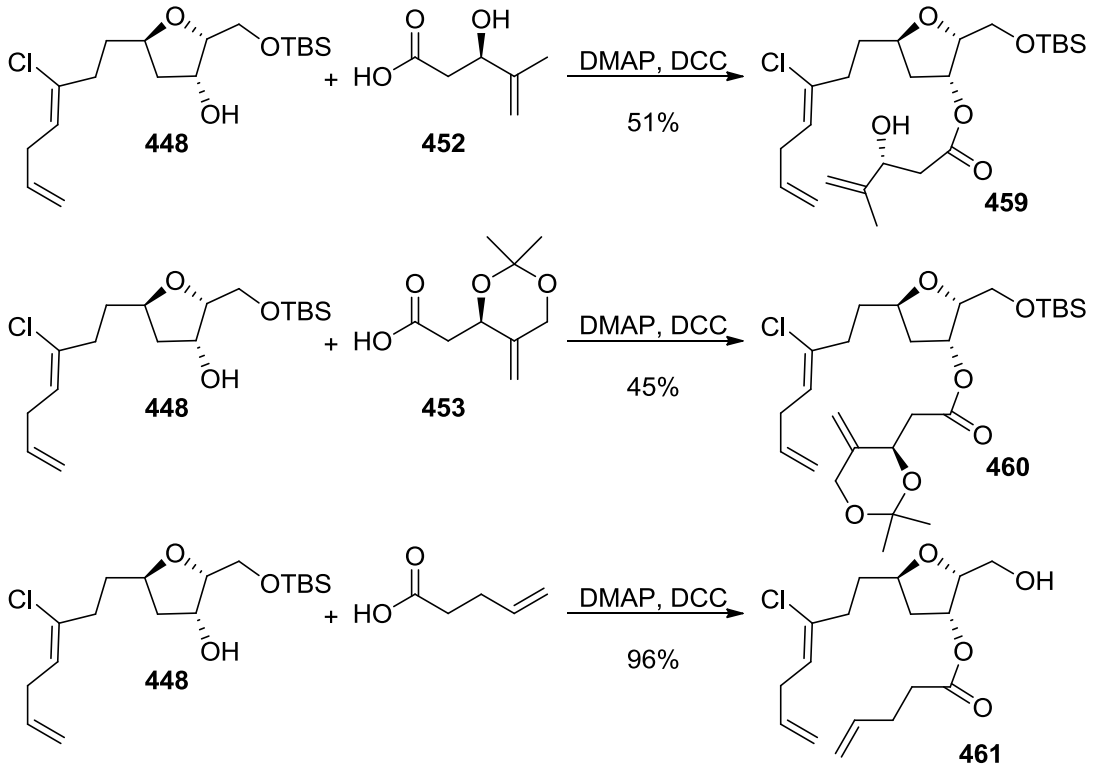


Scheme 78. Synthesis of carboxylic acids 452 and 453.

5.2.2.7 Ring-Closing Metathesis

With the successful procurement of both the tetrahydrofuranol **448** and the carboxylic acids **452** and **453**, several strategies were explored to form the C4/C5 alkene. In anticipation of the proposed ring closing metathesis, the esters **459** and **460**

required for the intramolecular ring-closing route were prepared. As detailed in Scheme 79, these substances were prepared through the *N*,*N'*-dicyclohexylcarbodiimide (DCC)-promoted coupling of each of the carboxylic acids **452** and **453**, respectively. As part of a model study, pent-4-enoic acid was also coupled with the tetrahydrofuranol **448** under identical conditions to afford ester **461**.



Scheme 79. Synthesis of esters 459, 460, and 461.

The ring-closing metathesis of esters **459**, **460**, and **461** was then examined in an attempt to construct the corresponding macrocycles **462**, **463**, and **464**. As summarised in Table 29, neither of the esters **459** or **460** engaged in a reaction with the first generation Grubbs catalyst,[61] even at elevated temperatures (e.g., 60 °C, 120 °C). When the second generation Grubbs catalyst,[61] the Grubbs-Hoveyda II catalyst,[62] and Schrock catalyst[63] were employed the starting materials were completely consumed, however, no macrocycle was observed in the ^{1}H NMR spectra recorded on the crude

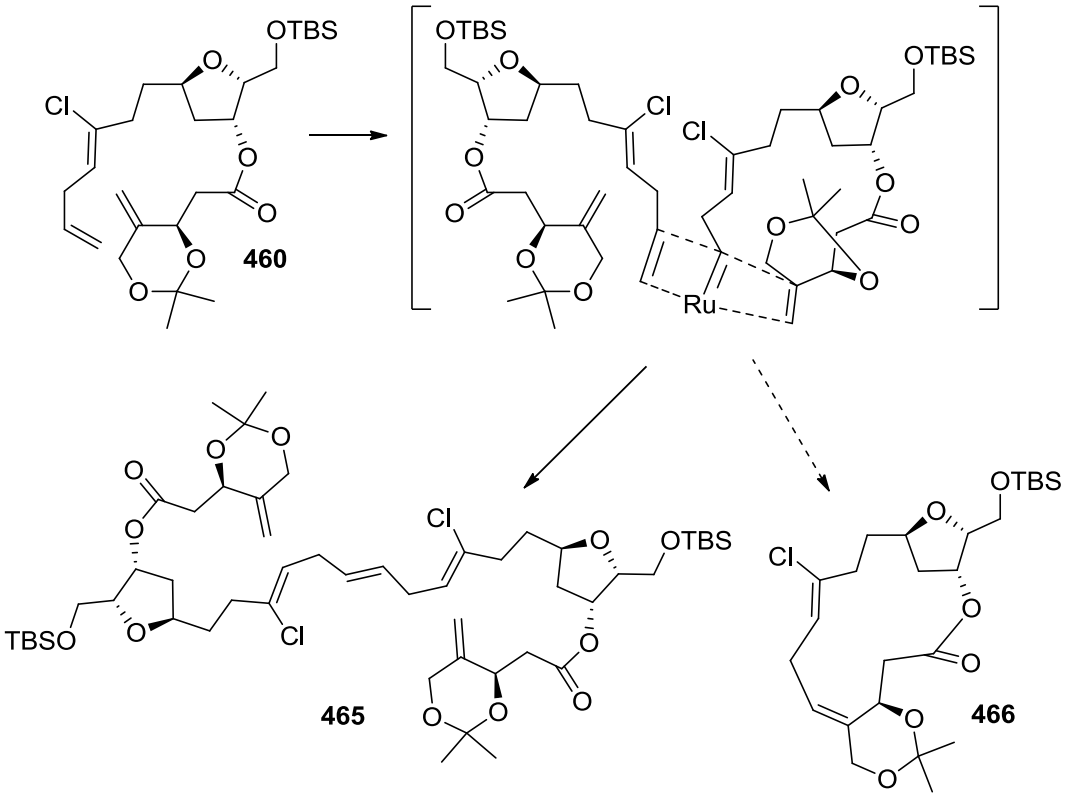
reaction mixtures. Instead, a product consistent with dimerisation of the starting alkene was detected as the major product. The apparent dimerisation product **465** derived from **460** gave a complex ^{1}H NMR spectra in which the resonances at δ 5.81 and 5.12-4.98 ppm, diagnostic of the terminal alkene in compound **460**, were noticeably absent. In addition, an upfield shift of the resonances at δ 5.53 to 5.49 ppm corresponding to the proton on the trisubstituted olefin; and an upfield shift in the dienyl methylene resonances at δ 2.92 to 2.86 ppm was observed. The remainder of the ^{1}H NMR spectra was similar to that of the starting material, indicating that the only structural difference between the product and starting material was the loss of the terminal alkene. In addition to the ^{1}H NMR data, hi-resolution (ESI+) mass spectroscopy carried out on this product included a distinct signal at m/z 1029.5111 amu (calculated m/z 1029.5113 amu), which is consistent with the chemical formula $C_{52}H_{87}Cl_2O_{12}Si_2$ corresponding to the dimer + H.

Table 29. Intramolecular ring-closing metathesis of esters 459, 460, and 461.

entry	ester	catalyst	temp. (°C)	results
1	**459**	10% Grubbs I	22-120	no reaction
2	**459**	5% Grubbs II	22	<10% dimer + starting material
3	**460**	10% Grubbs I	22-120	no reaction
4	**460**	5% Grubbs II	22	<30% dimer + starting material
5	**460**	5% Grubbs II	-40-0	<5% dimer + starting material
6	**460**	2.5% Grubbs-Hoveyda	22-40	90% dimer
7	**460**	5% Schrock	22	<30% dimer + starting material
8	**461**	5% Grubbs II	22-120	no reaction
9	**461**	2.5% Grubbs-Hoveyda	22-120	<20% dimer + starting material

The failure of these reactions to afford the desired macrocyclic products (e.g. **466**) is likely the result of a combination of factors that include steric encumbrance from the 1,1-disubstituted olefin that precludes formation of the required metallacycle, and the *trans*-relationship of the two alkene fragments. The former issue was discussed in detail

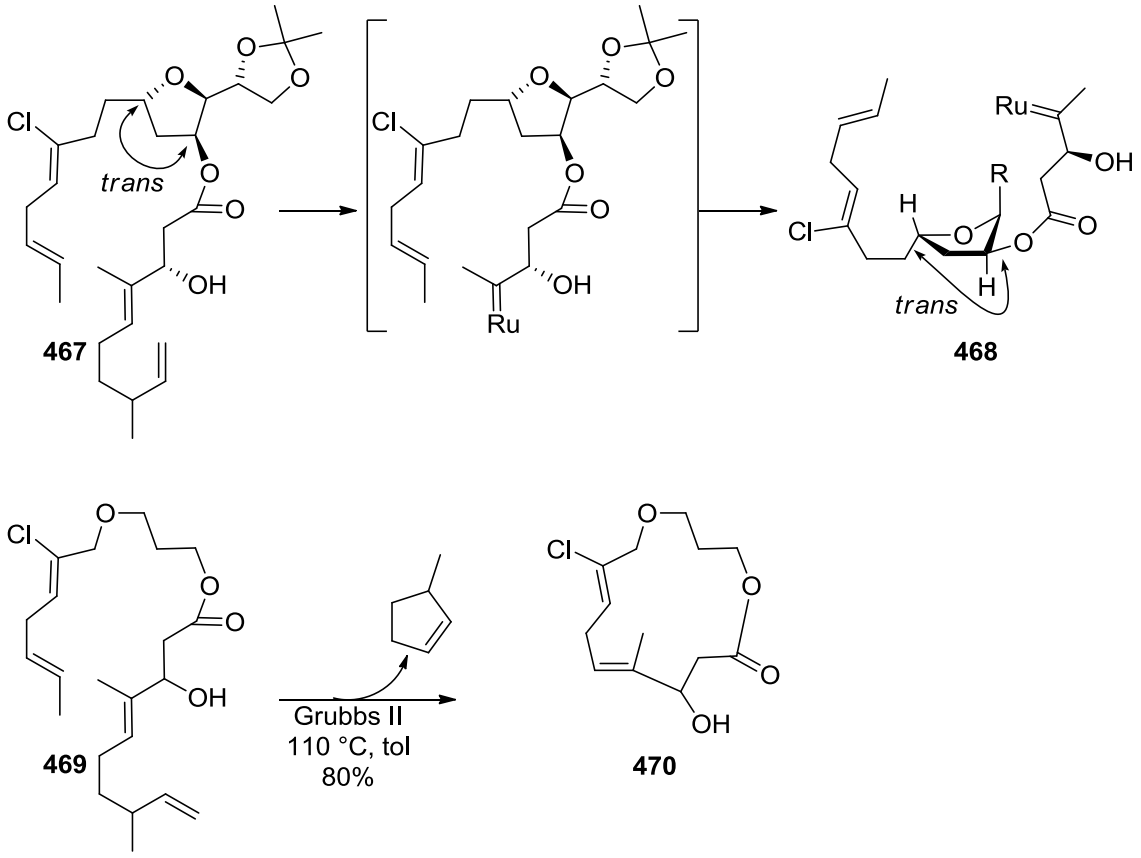
in Zhao's attempt at the synthesis of callipeltoside A using a ring-closing metathesis on a substrate containing a sterically hindered 1,1-disubstituted alkene.[64] Moreover, functional groups in close proximity to the reacting double bonds play an important role in determining the outcome of the macrocyclisation reaction, although these effects are not well understood.[65] Thus, the pathway leading to intermolecular dimerisation is favoured over the intramolecular ring-closing metathesis (Scheme 80).



Scheme 80. Intermolecular dimerisation and intramolecular ring-closing pathways.

To further assess whether the 1,1-disubstituted alkene is responsible for failure of the desired reaction, ester **461** was reacted under the ring-closing metathesis conditions using the Grubbs-Hoveyda II catalyst. Even though the ^{1}H NMR spectrum recorded on the crude reaction products was difficult to analyse, hi-resolution (ESI+) mass spectrum recorded on the crude product included a signal consistent with a

dimeric product at m/z 629.2644 amu (calculated m/z 629.2648 amu). In addition, a signal that may correspond to the trimeric compound at m/z 929.3770 amu (calculated m/z 929.3776 amu) was also observed. These results suggest that although the 1,1-disubstituted olefin may hinder the ring-closing metathesis reaction to a degree, the most important factor impeding this reaction is the *trans*-relationship at the C3/C5 positions on the tetrahydrofuranol, which precludes the two alkene fragments from coming in close proximity required for ring-closing metathesis. In related work, Hoye has demonstrated that the ring-closing metathesis does not proceed due to ring strain associated with the *trans* relationship between the appendages at C3 and C5 on the tetrahydrofuran ring (i.e., **467** → **468**). Hoye was able to provide further evidence for this hypothesis by performing a successful ring-closing metathesis on the acyclic precursor (**469** → **470**), which was void of this additional ring strain.[21]

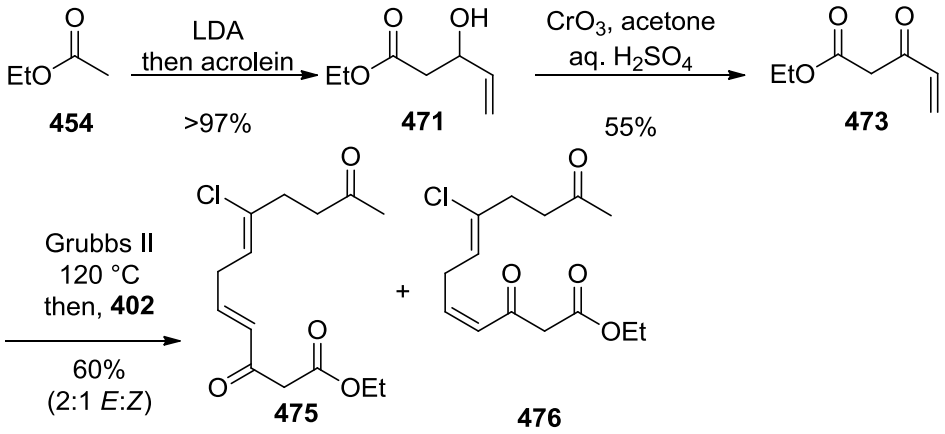


Scheme 81. Hoye's test on the ring strain hypothesis.

5.2.2.8 Intermolecular Alkene Metathesis

After unsuccessful attempts at the ring-closing metathesis, the intermolecular alkene metathesis was studied. It was envisioned that an intermolecular reaction would circumvent the limitations presented in the intramolecular mode (*vide supra*). As a model system, ketone **402** was used instead of the tetrahydrofuran. Unfortunately, the treatment of ester **458** with the Grubbs II or Grubbs-Hoveyda II catalysts, followed by slow addition of the ketone did not provide product. In each case, only dimerisation of the ketone **402** was observed, suggesting that the ruthenium alkylidene of ester **458** did not form. Adding a solution of the Grubbs-Hoveyda II catalyst to a solution of 1 equivalent of the ketone **402** and 10 equivalents of the ester **458** also resulted in the

formation of products derived from dimerisation. Nevertheless, a simpler alkene fragment was produced to further probe this reaction. First, aldol adduct **471** was prepared from the reaction between ethyl acetate (**454**) and acrolein (**472**). This aldol adduct **471** was oxidised to the β-ketoester **473**.[66] The treatment of ester **471** with either the Grubbs II or the Grubbs-Hoveyda II catalysts, followed by addition of the ketone **402** resulted in a complex mixture continaing the alkene **474** as a 1:1 mix of *E:Z* isomers. Interestingly the β-ketoester **473** proceeded to give dimerisation products at 40 °C, but at 120 °C gave rise to a 2:1 mixture of the *E:Z* isomers **475** and **476**, respectively. Attempts at exploiting this result through the introduction of a hydroxymethylene unit (required for the synthesis of biselide A (**332**)) and rearranging the C4 double-bond under Baylis-Hillman conditions using formaldehyde and tributylphosphine or DABCO resulted in decomposition.[67] Based on these results, the ring-closing metathesis approach to the haterumalide or biselide family of natural products was abandoned.



Scheme 82. Intermolecular alkene metathesis.

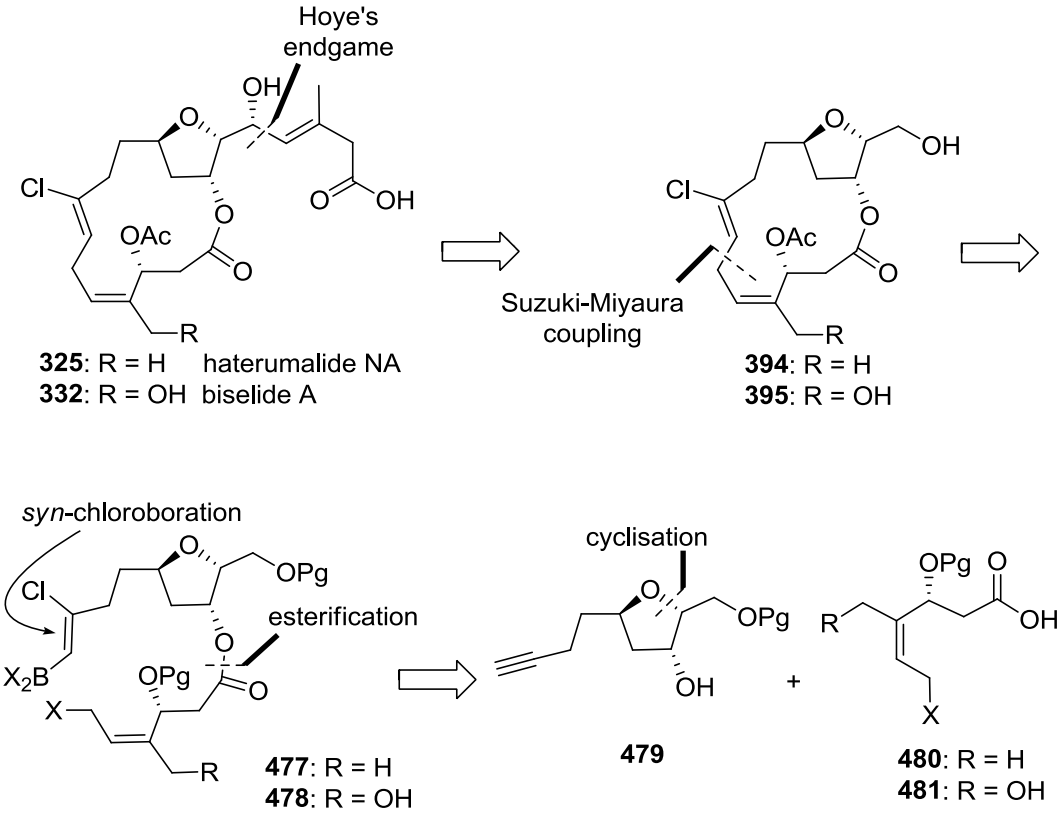
5.2.2.9 Conclusion

After a considerable amount of experimentation, it was determined that limitations to the intramolecular ring-closing metathesis reaction preclude its use as a

part of a viable synthesis of the haterumalide and biselide natural products. Though some success was realised with intermolecular ring-closing metathesis reactions which would circumvent these issues, it was found unsuitable due to lack of stereoisomeric control and inability to introduce the requisite hydroxymethylene at C4.

5.2.3 Synthetic Plan: Suzuki-Miyaura Strategy

An alternative route toward the synthesis of haterumalide NA (**325**) and biselide A (**332**) was also envisioned and is depicted in Scheme 83. The revised synthetic plan would use a Suzuki-Miyaura reaction as the key step (e.g., **477** → **394** or **478** → **395**) in the formation of the macrocyclic ring through the construction of the bond between C6 and C7. For this purpose, the precursor would come from the esterification of tetrahydrofuranol (e.g., **479**) and carboxylic acid (e.g., **480**, **481**). The tetrahydrofuranol (e.g., **479**) itself could be accessed using methodologies developed in Chapter 3 and 4, followed by a *syn*-chloroboration.



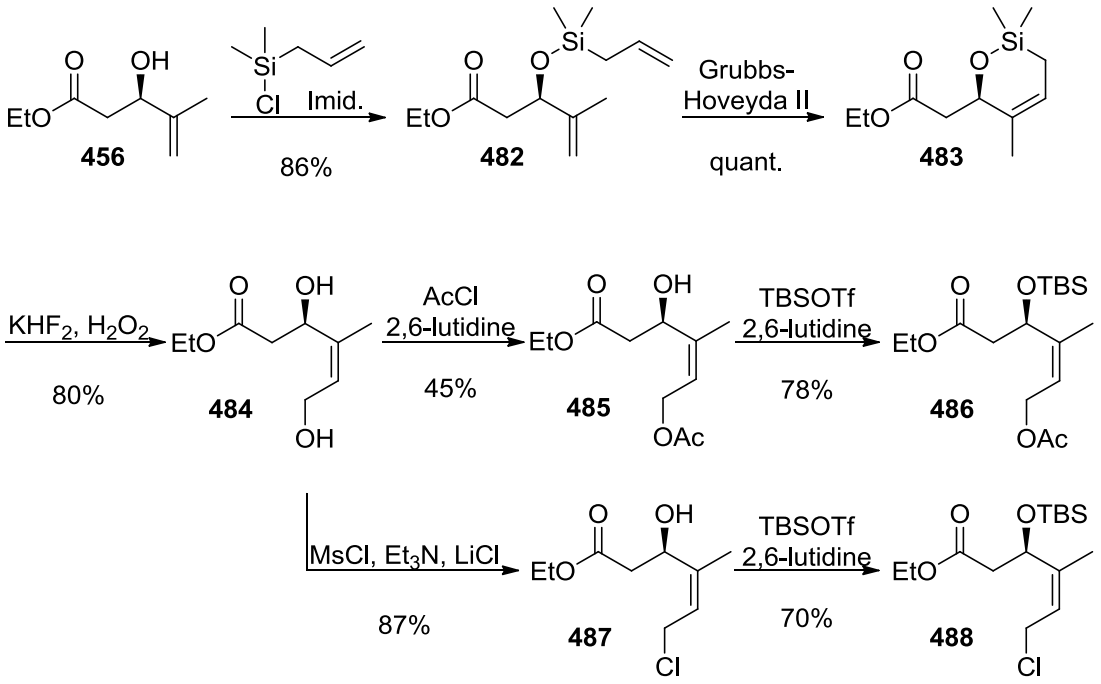
Scheme 83. Retrosynthetic strategy employing a Suzuki-Miyaura coupling.

The strategy depicted in Scheme 83 was inspired by a report by Kabalka that described the successful Suzuki-Miyaura coupling of alkenyltrifluoroborates with allyl acetates using microwave irradiation to afford 1,4-dienes.[68] Although the palladium-coupling of arylboronic acids with allyl halides and allyl acetates has been reported,[69] the reaction of alkenylboron species with allyl halides and allyl acetates had not been studied previously. In addition, Roulland reported the preparation of potassium (*Z*)-2-chloroalk-1-enyl trifluoroborates, and their coupling to alkenyl and phenyl halides.[70] The (*Z*)-2-chloroalk-1-enyl trifluoroborates were accessed from the *syn*-addition of BCl_3 to a C-C triple bond,[71] which proceeds with excellent regioselectivity, followed by treatment with aqueous KHF_2 to afford the desired product.

5.2.4 Results: Suzuki-Miyaura Strategy

5.2.4.1 Synthesis of Esters 485, 486, 487, and 488

Having successfully prepared the optically enriched ester **456**, it was realised that this material could be elaborated into the allyl coupling partner required for the Suzuki-Miyaura reaction. Initial attempts to effect this transformation involved the esterification of carboxylic acid **452** with allyl bromide. However, the subsequent ring-closing metathesis did not proceed, and led to significant amounts of dimerisation. Thus, an alternative strategy was developed in which the ester **456** was converted to the allyl silyl ether **482**, followed by a ring-closing metathesis to afford oxasiline **483**. A ring-closing metathesis reaction carried out on this latter material proceeded smoothy in part due to the β-effect of the silicon. [72,73] The Si-C bond in the oxasiline **483** was then oxidised by the action of hydrogen peroxide in the presence of KHF_2 to afford diol **484** in high yield.[74] This material was then converted to allyl acetate **485** and its corresponding TBS ether **486**, and also to the allyl chloride **487** and its corresponding TBS ether **488**.

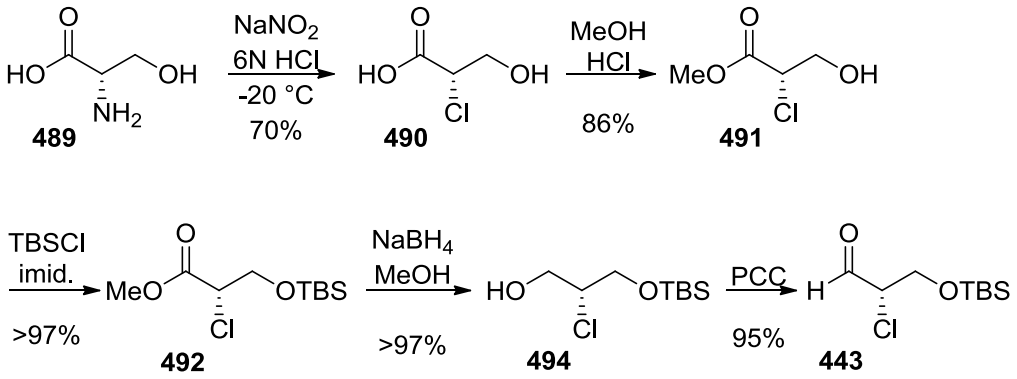


Scheme 84. Synthesis of esters 485, 486, 487, and 488.

5.2.4.2 Synthesis of Enantioenriched α-Chloroaldehyde 443

The asymmetric α-chlorination methodologies reported by Jørgensen and MacMillan were not suitable for the preparation of large quantities of optically enriched α-chloroaldehyde **443**. Thus, an alternative strategy was employed that was inspired by recent reports by De Kimpe[75] (page 3), toward the synthesis of optically enriched α-chloroaldehyde **443**. Specifically, L-(-)-serine (**489**) was dissolved in 6 N HCl, to this a solution of $NaNO_2$ in a minimal amount of water was added over three hours to yield (*S*)-chloroacid **490**. Esterification of **490** with methanol resulted in the methylester **491**, followed by TBS protection of the free alcohol to α-chloroester **492**. Reduction with $LiAlH_4$ resulted in formation of glycidol **493**, as characterised by resonances at δ 3.17, 2.82, and 2.77 ppm in the ^1H NMR spectrum. However, employing $NaBH_4$ in the presence of methanol afforded the desired chlorohydrin **494** in high yield. This latter

material was oxidised with pyridinium chlorochromate (PCC)[76] to afford the desired α-chloroaldehyde **443**. It was determined that when the diazotisation/chlorination reaction is performed at temperatures between 0-5 °C the enantiomeric excess was 60%, but if the reaction is kept between -20 and -15 °C enantiomeric excesses >97% are observed for **443**. The enantiomeric excess was determined by chiral GC analysis. This five-step route was also shown to be amenable to produce multi-gram quantities of material.

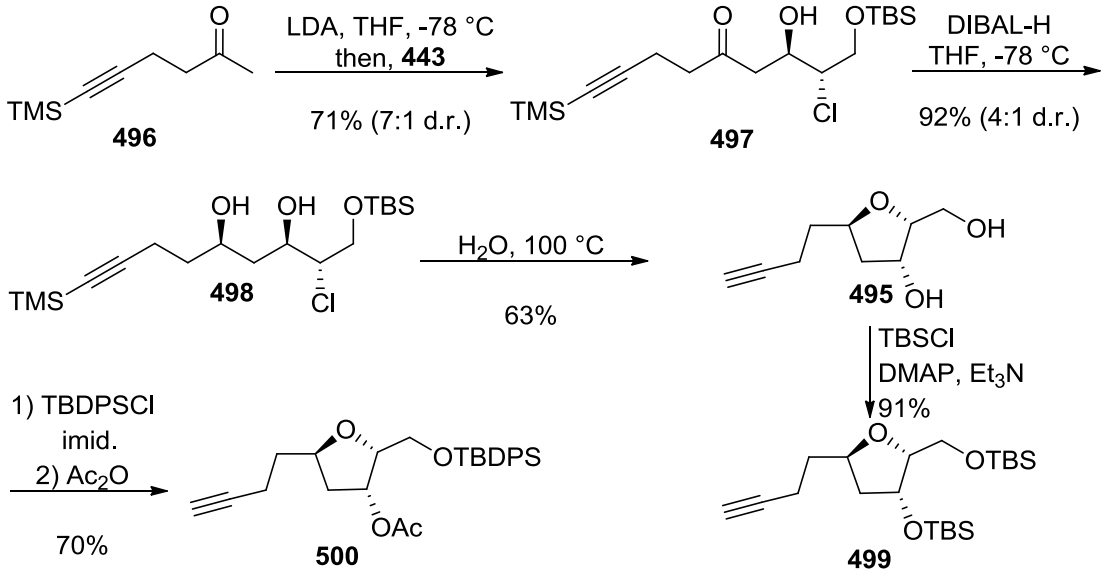


Scheme 85. Synthesis of α-chloroaldehyde 443.

5.2.4.3 Synthesis of Tetrahydrofuran 495

With the successful development of a route to the optically pure α-chloroaldehyde **443**, focus shifted to the synthesis of tetrahydrofuran **495**. Starting with the alkynyl ketone **424**, a TMS protection of the alkynyl function[77] was performed to afford the TMS protected ketone **496**. This latter material was subjected to lithium diisopropylamide, followed by a slow addition of α-chloroaldehyde **443** resulting in the corresponding aldol adduct **497** as an inseparable 7:1 *anti*:*syn* diastereomeric mixture (71% yield). The 1,3-hydroxyl-directed reduction of aldol adduct **497** with DIBAL-H afforded an inseperable 4:1 *syn*:*anti* mixture of chlorodiol **498** and its C5-epimer. This material was then heated in a microwave to afford the tetrahydrofuran **495**, which lacked a silyl protecting group. It was found that conventional heating (e.g., 100 °C, 12 h) of **498**

resulted in similar yields of tetrahydrofurandiol **495**. Both alcohol functions of **495** were protected as the correspoding *tert*-butyldimethylsilyl ethers **499**, and as the *tert*-butyldiphenylsilyl ether/acetate **500**.



Scheme 86. Synthesis of tetrahydrofuran 495.

The relative stereochemistry was confirmed by nOe analysis on tetrahydrofuran **500** as shown in Figure 25.

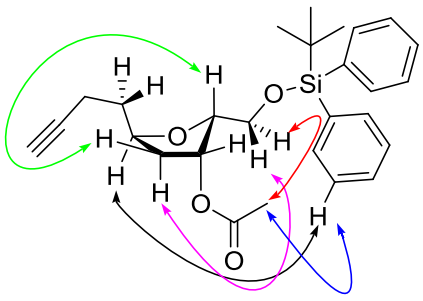
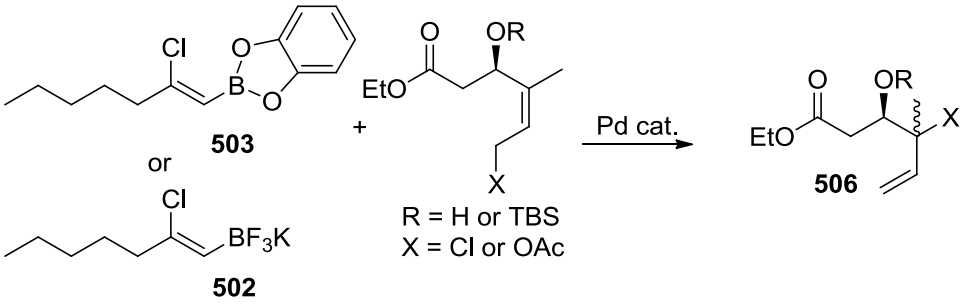


Figure 25. Stereochemical analysis of 500 by nOe.

5.2.4.4 Studies Toward the Suzuki-Miyaura Coupling using a Model System

Before attempting the Suzuki-Miyaura reaction using tetrahydrofuran **495** as the precursor, a model study was performed. For this purpose, hept-1-yne (**501**) was converted to the potassium (*Z*)-2-chlorohept-1-enyl trifluoroborate (**502**) and (*Z*)-2-(2-chlorohept-1-enyl)benzo[*d*][1,3,2]dioxaborole (**503**). Couplings were attempted with a variety of allyl acetates and allyl halides, including neranyl acetate (**504**), allyl acetates **485** and **486**, allyl chlorides **487** and **488**, and allyl bromide (**505**). A thorough screen of reaction conditions was conducted, in which mutliple palladium catalysts (i.e., $PdCl_2(dppf)\cdot CH_2Cl_2$, $Pd(TFA)_2$, $PdCl_2$, $PdCl_2(MeCN)_2$, $Pd(PPh_3)_4$), additives (i.e., PPh3, P(*t*-Bu)$_3$HBF$_4$), and bases (i.e., Hünig's base, NaOH, Cs_2CO_3, K_2CO_3, NaOEt) were examined in a variety of solvents (i.e., *i*-PrOH/H_2O, THF/H_2O, CH_2Cl_2, DMF, toluene). Even though no productive reactions were observed, a small amount of the S_N2' product was observed in the reaction between allyl acetate **486** and the trifluoroborate **502**. The rearranged products result from the quenching of the π-allyl species yielding a diastereomeric mixture of alkenes (e.g., **506**, Scheme 87). This was characterised by the olefinic resonances in the ^{1}H NMR spectra at 5.86 (dd, 1H, *J* = 17.0, 11.0 Hz), 5.34 (d, 1H, *J* = 17.0 Hz), and 5.19 (d, 1H, *J* = 11 Hz) for one diastereomer; and 5.95 (dd, *J* = 17.5, 11.0 Hz), 5.51 (d, 1H, *J* = 17.5 Hz), and 5.42 (d, 1H, *J* = 11.0 Hz) for the other diastereomer. And when allyl acetate **485** was used, a diastereomeric mixture of the epoxides was produced. This suggested that the initial oxidative addition of the allyl species to the palladium catalyst occurs, but the transmetallation of the boron species does not occur.



Scheme 87. Non-productive products generated from the Suzuki-Miyaura coupling.

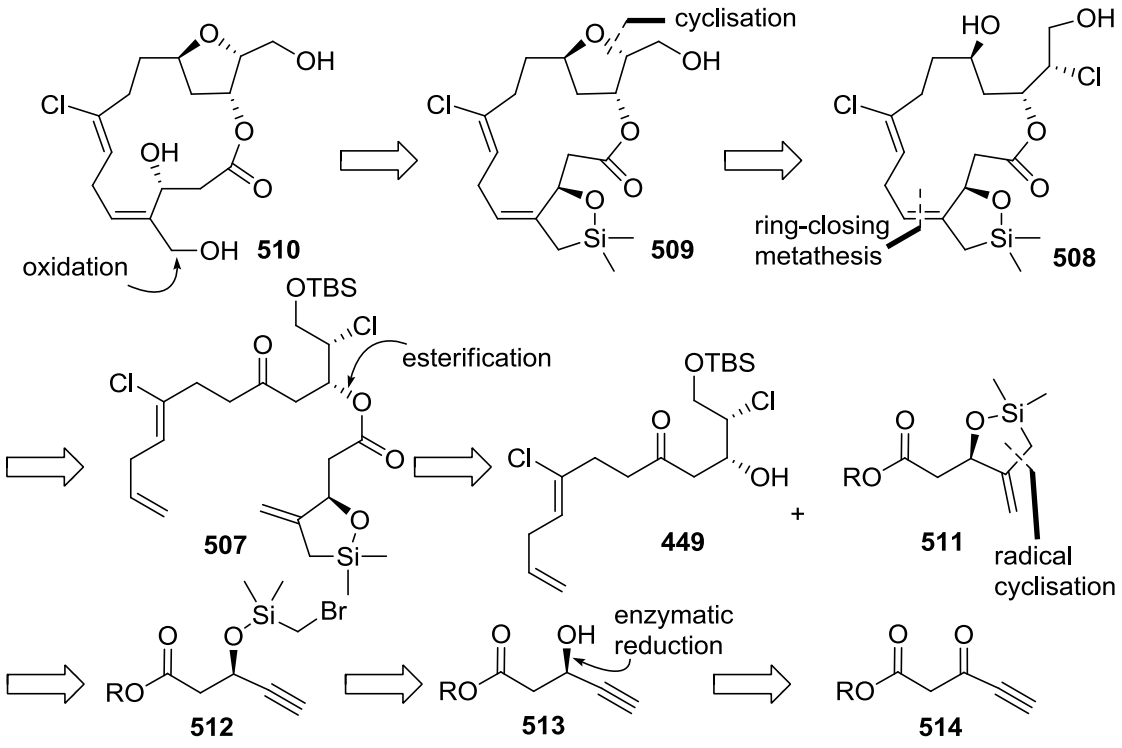
5.2.4.5 Conclusion

Based on the results discussed above, the Suzuki-Miyaura route was deemed non-productive. In addition, we also discovered that the conversion of either tetrahydrofuran **499** or **500** to the chlorotrifluoroborate salt led to significant amounts of decomposition. Thus, an alternative strategy must be sought for the construction of the haterumalide and biselide natural products.

5.2.5 Future Work

With regards to the completion of the synthesis of the haterumalide and biselide family of natural products, a new strategy is required. A successful ring-closing metathesis must overcome the ring strain imparted by the tetrahydrofuran by changing the sequence of events used in the unsuccessful route (Section 5.3.2). Specifically, the ring-closing metathesis reaction performed on an acyclic intermediate (e.g., **507** → **508**) would eliminate issues regarding ring-strain. In addition, issues regarding the lack of reactivity of the 1,1-disubstituted alkene could be overcome by using an allyl silane for the ring-closing metathesis, the electron-rich C-Si bond enhances olefin nucleophilicity

through hyperconjugation.[78] This would be followed by a microwave-assisted cyclisation to form the tetrahydrofuran ring **509**. After a successful ring-closing metathesis/cyclisation the silane would undergo a Tamao-Fleming oxidation[79] to afford the bicyclic core **510**. The acyclic triene **507** would be derived from the esterification reaction of the previously prepared aldol adduct **449** and the oxasilolane **511**. The radical cyclisation developed by Malacria would permit the formation of the oxasilolane **511** from alkyne **512** using tributyltin hydride and AIBN.[80] The enantiopure β-hydroxyester **513** has been previously synthesised from β-ketoesters **514** using an enzyme-mediated reduction.[81]



Scheme 88. Future directions toward the ring-closing metathesis strategy.

5.3 Experimentals

General

All reactions described were performed under an atmosphere of dry argon using oven dried glassware unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60) following the technique described by Still.[82] Concentration and removal of trace solvents was done *via* a Buchi rotary evaporator using acetone-dry-ice condenser and a Welch vacuum pump.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) or deuterobenzene (C_6D_6) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ 7.26, ^{1}H NMR; δ 77.0, ^{13}C NMR; CH_3OD: δ 3.31, ^{1}H NMR; δ 49.0, ^{13}C NMR; C_6D_6: δ 7.16, ^{1}H NMR; δ 128.1, ^{13}C NMR).

Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), number of protons, coupling constants, assignment (where possible). NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz) or Bruker 400 (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of 1H-1H COSY, HMBC, HMQC, TOCSY and 1D NOESY spectra.

High performance liquid chromatography (HPLC) analysis was performed on an Agilent 1200 HPLC, equipped with a variable wavelength UV-Vis detector and Chiracel OD-H chiral column (0.46 cm x 25 cm).

Infrared (IR) spectra were recorded on a MB-series Bomem/Hartman & Braun Fourier transform spectrophotometer with sodium chloride plates. Only selected, characteristic absorption data are provided for each compound.

Chemical ionisation (CI) mass spectra were recorded on a Varian 4000 GC/MS/MS mass spectrometer. High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS mass spectrometer.

Optical rotation was measured on a Perkin Elmer Polarimeter 341 at 589 nm.

Microwave reactions were performed in a CEM Discover LabMate at 2.45 GHz.

Preparation of hex-5-yn-2-one (424)

To sodium hydride (60% in oil, 2.6 g, 0.065 mmol) in THF (60 mL) at -10 °C was slowly added ethyl acetoacetate (**425**) (12.5 mL, 100 mmol). The mixture was allowed to stir for two hours and then propargyl bromide (**426**) (80% in tol., 7.25 mL, 65.0 mmol). The solution changed colour from a light yellow to an opaque orange overnight. At this time, 1 N HCl (10 mL) was added, diluted with diethyl ether (3 x 50 mL) and the layers separated. the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a yellow oil. To this was added aq. 5% NaOH (60 mL), and the solution stirred at reflux for five hours. At this time, the solution was cooled to room temperature, and then concentrated HCl was added until the solution reached pH 4. Solution was extracted with diethyl ether (4 x 50 mL). The combined organic phases were washed with sodium bicarbonate (100 mL), brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to provide crude yellow oil. Purification of the crude product by fractional distillation (25 mmHg, 60 °C) afforded hex-5-yn-2-one (**424**) (3.10 g, 49%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.68 (m, 2H, *J* = 6.2 Hz), 2.42 (td, 2H, *J* = 7.2, 3.0 Hz), 2.16 (s, 3H), 1.94 (t, 1H, *J* = 3.0 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 206.4, 83.0, 68.7, 42.1, 29.9, 12.9.

HRMS: *m*/*z* calcd for C_6H_9O: 97.0653 (M + H); found: 97.0660 (M + H).

Preparation of (*Z*)-5-chloronona-5,8-dien-2-one (402)

Method A:

To a stirred solution of allyl chloride (**427**) (2.0 mL, 25 mmol) in THF (100 mL) at room temperature was added sequentially bis(benzonitrile)palladium(II) chloride (58 mg, 0.15 mmol) and hex-5-yn-2-one (**424**) (480 mg, 5.0 mmol) dropwise over 30 min. The reaction mixture was stirred for 2 h. After this time, the mixture was filtered over Celite, the filtrate was concentrated to provide the (*Z*)-5-chloronona-5,8-dien-2-one (**402**) (248 mg, 28%).

Method B:

To a cold (–10 °C) stirred solution of NaH (0.55 g, 14 mmol) in THF (25 mL) was added ethyl acetoacetate (**425**) (1.80 mL, 13.8 mmol) dropwise over 20 min. After this time, the freshly prepared allyl bromide (**428**) was added in one portion and the reaction mixture was allowed to warm to room temperature and the stirring was continued for 18 h. The resulting mixture was quenched with aq 1 N HCl (5 mL), diluted with Et_2O (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. To this oil was added aq 5% NaOH (10 mL) and the mixture was heated at reflux for 2 h. The mixture was then acidified to pH 4 with concentrated HCl, diluted with Et_2O (20 mL), and the Et_2O layer was washed with sat. aq $NaHCO_3$ (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide a yellow

oil. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes–EtOAc) afforded (*Z*)-5-chlorononа-5,8-dien-2-one (**402**) (1.2 g, 70%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.78 (m, 1 H), 5.56 (t, *J* = 6.4 Hz, 1 H), 5.08-4.99 (m, 2 H), 2.91 (t, *J* = 6.4 Hz, 2 H), 2.71 (m, 2 H), 2.62 (m, 2 H), 2.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.5, 135.0, 134.1, 123.8, 115.4, 41.4, 33.5, 32.7, 30.1.

IR (neat): 3080, 2979, 2920, 2229, 1718, 1432, 1362, 1162 cm^{-1}.

HRMS: *m*/*z* calcd for $C_9H_{13}ClONa$: 195.0553 (M + Na); found: 195.0559 (M + Na).

Preparation of (*Z*)-6-bromo-5-chlorohexa-1,4-diene (428)

To a stirred solution of allyl chloride (**427**) (4.05 mL, 50.0 mmol) in THF (60 mL) at room temperature was added sequentially bis(benzonitrile)palladium(II) chloride (110 mg, 0.30 mmol) and propargyl bromide (**426**) (1.1 g, 10 mmol) dropwise over 30 min. The reaction mixture was stirred for 2 h. After this time, the mixture was filtered over Celite, the filtrate was concentrated to provide the crude (*Z*)-6-bromo-5-chlorohexa-1,4-diene (**428**), which was used directly in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.96 (t, 1H, *J* = 7.0 Hz), 5.79 (ddt, 1H, *J* = 16.5, 10.0, 6.5 Hz), 5.08 (m, 2H), 4.14 (d, 2H, *J* = 0.5 Hz), 3.05-2.91 (m, 2H).

Preparation of (*R*)-butane-1,2,4-triol (431)

To ᴅ-malic acid (**430**) (5.1 g, 0.038 mol) in THF (50 mL) was added trimethylborate (12.5 mL, 120 mmol). The solution was cooled to 0 °C and slowly added BH_3·DMS (2.0 M in THF, 48 mL, 120 mmol). The reaction mixture was stirred for 18 hours. At this time, methanol (25 mL) was slowly added over an hour. The solution was concentrated, methanol (50 mL) added, and concentrated. This was repeated 3 times to afford (*R*)-butane-1,2,4-triol (**431**) (3.95 g, quant.)

^{1}H NMR (500 MHz, D_2O) δ:3.68-3.58 (m, 1H), 3.55 (m, 2H), 3.44 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.33 (dd, 1H, *J* = 7.0, 11.5 Hz), 1.58-1.48 (m, 2H).

^{13}C NMR (125 MHz, D_2O) δ: 69.2, 65.6, 58.5, 34.8.

IR (neat): 3360, 3350, 2938, 2933, 1425, 980 cm^{-1}

$[\alpha]_D^{25}$ 28.3 (*c* 1.0, MeOH).

Preparation of (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (432)

To (*R*)-butane-1,2,4-triol (**431**) (5.30 g, 50.0 mmol) in acetone (150 mL) was added p-toluenesulfonic acid (476 mg, 2.50 mmol). The solution was stirred for 24 hours. At this time triethylamine was added, the solution concentrated to near-dryness. The solution was then filtered through a plug of silica gel to afford (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (**432**) (6.58 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.27 (m, 1 H), 4.09 (m, 1 H), 3.78-3.69 (m, 2 H), 3.60 (m, 1 H), 2.08 (s, 1H), 1.87-1.79 (m, 2 H), 1.42 (s, 3 H), 1.37 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 108.6, 74.0, 69.2, 59.5, 35.6, 26.7, 25.3.

IR (neat): 3418, 2930, 2924, 2361, 1654, 1414, 1240, 1050, 750 cm^{-1}.

$[\alpha]_D^{25}$ 2.6 (*c* 1.0, $CHCl_3$).

Preparation of (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (429)

To a solution of oxalyl chloride (3.50 mL, 40.5 mmol) in CH_2Cl_2 (96 mL) at -78 °C was added DMSO (5.75 mL, 81.0 mmol) in CH_2Cl_2 (24 mL) over 20 minutes. This solution was stirred for 30 minutes at -78 °C, followed by the addition of (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (**432**) (4.0 g, 27 mmol) over 30 minutes. Next, the solution was stirred for 30 minutes at room temperature. Then, H_2O (20 mL) was added, diluted with CH_2Cl_2 (100 mL), and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were washed with

brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by flash chromatography afforded (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (**429**) (3.50 g, 90%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.80 (t, 1H, *J* = 1.2 Hz), 4.53 (quint, 1H, *J* = 6.6 Hz), 4.19 (dd, 1H, *J* = 8.4, 6.0 Hz), 3.58 (dd, 1H, *J* = 8.4, 6.6 Hz), 2.84 (ddd, 1H, *J* = 17.4, 6.6, 1.8 Hz), 2.65 (ddd, 1H, *J* = 17.4, 6.0, 1.2 Hz), 1.41 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 200.0, 109.2, 70.6, 69.1, 47.8, 26.8, 25.4.

IR (neat): 2988, 2935, 2932, 1724, 1382, 1372, 1189 cm^{-1}

$[\alpha]_D^{25}$ -8.9 (*c* 1.2, $CHCl_3$).

HRMS: *m*/*z* calcd for $C_7H_{13}O_3$: 145.0865 (M + H); found: 145.0872 (M + H).

Preparation of (*S*)-2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (401)

Method A:

To a cold (0 °C), stirred solution of (*R*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (**429**) (144 mg, 1.00 mmol) in CH_2Cl_2 (10 mL), was added D-prolinamide (23 mg, 0.20 mmol), H_2O (36 µL, 2.0 mmol), and *N*-chlorosuccinimide (**12**) (200 mg, 1.5 mmol). The reaction mixture was stirred for one hour and then allowed to slowly warm to room temperature over the course of three hours at which temperature it was stirred until complete consumption (48 h) of **429** (as determined by ^{1}H NMR spectroscopy). After this time, the mixture was diluted with pentanes (10 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice water bath. The resulting oil was dissolved in pentanes (10 mL), cooled (-78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath to give (*S*)-2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (**401**) (160 mg, >90% yield) as a clear oil.

Method B:

To a solution of (*S*)-ethyl 2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate (**440**) (150 mg, 0.70 mmol) in THF (15 mL) was added LDBBA (0.50 M in THF, 1.3 mL, 0.70 mmol) over 30 minutes at -78 °C. The solution was allowed to stir three hours at -78 °C, and at this time quenched with aq. 0.5 M HCl (0.5 mL), diluted with Et_2O (20 mL), and the Et_2O layer was washed with sat. aq. $NaHCO_3$ (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide an inseparable 15:1 diastereomeric mixture of (*S*)-2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (**401**) and its C2 epimer, and 10% of the corresponding alcohol (**441**) (60 mg, >90% yield) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.51 (d, *J* = 3.0 Hz, 1H), 4.46 (ddd, 1H, *J* = 8.4, 6.0, 4.2 Hz), 4.18 (dd, 1H, *J* = 9.0, 6.0 Hz), 4.14 (dd, 1H, *J* = 8.4, 3.0 Hz), 4.05 (dd, 1H, *J* = 9.0, 4.2 Hz), 1.46 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 192.4, 111.1, 75.0, 66.9, 62.4, 26.7, 25.1.

$[\alpha]_D^{25}$ -13.1 (*c* 2.0, $CHCl_3$).

Preparation of (4*R*,5*R*)-diethyl 2-methoxy-2-methyl-1,3-dioxolane-4,5-dicarboxylate (437)

To (+)-diethyl tartrate (**435**) (8.24 g, 40.0 mmol) in CH_2Cl_2 (160 mL) was added p-toluenesulfonic acid (380 mg, 2.00 mmol) and trimethyl orthoacetate (7.64 mL, 60.0 mmol). The solution was stirred for 24 hours. At this time the solution concentrated to afford (4*R*,5*R*)-diethyl 2-methoxy-2-methyl-1,3-dioxolane-4,5-dicarboxylate (**437**) (10.65 g, >97%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.97 (d, 1H, *J* = 5.4 Hz), 4.73 (d, 1H, *J* = 5.4 Hz), 4.34-4.18 (m, 4H), 3.32 (s, 3H), 1.67 (s, 3H), 1.32 (t, 3H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.9, 168.8, 124.5, 76.6, 76.2, 61.8, 61.8, 50.4, 21.1, 13.94, 13.91.

IR (neat): 2985, 2948, 1753, 1465, 1222, 1160 cm^{-1}

HRMS: *m*/*z* calcd for $C_{11}H_{19}O_7$: 263.1131 (M + H); found: 263.1142 (M + H).

Preparation of (2*S*,3*S*)-diethyl 2-acetoxy-3-chlorosuccinate (436)

To a solution of (4*R*,5*R*)-diethyl 2-methoxy-2-methyl-1,3-dioxolane-4,5-dicarboxylate (**437**) (10.66 g, 40 mmol) in CH_2Cl_2 was added chlorotrimethylsilane (7.6 mL, 60 mmol). The solution was stirred at reflux for 18 hours, at which time the solution was cooled, then water (50 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude material by fractional distillation (0.5 mmHg, 120 °C) afforded (2*S*,3*S*)-diethyl 2-acetoxy-3-chlorosuccinate (**436**) (10.3 g, 95%), and was carried on to the next step.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.66 (d, 1H, *J* = 3.6 Hz), 4.85 (d, 1H, *J* = 3.6 Hz), 4.34-4.25 (m, 4H), 2.19 (s, 3H), 1.31 (t, 3H, *J* = 6.6 Hz), 1.28 (t, 3H, *J* = 6.6 Hz).

Preparation of (2*S*,3*S*)-diethyl 2-chloro-3-hydroxysuccinate (438)

To a solution of (2*S*,3*S*)-diethyl 2-acetoxy-3-chlorosuccinate (**436**) (500 mg, 1.90 mmol) in ethanol (20 mL) was added HCl (1.0 M in dioxane, 3.8 mL, 3.8 mmol) in one portion. The mixture was allowed to stir at reflux for 18 hours. At this time, the solution was cooled and concentrated to a yellow oil. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes–EtOAc) afforded (2*S*,3*S*)-diethyl 2-chloro-3-hydroxysuccinate (**438**) (380 mg, 89%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.79-4.71 (m, 1H), 4.36-4.22 (m, 2H), 3.48-3.27 (m, 1H), 1.81-1.46 (m, 1H), 1.41-1.24 (m, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.2, 166.2, 72.6, 62.83, 62.78, 59.9, 14.02, 14.00.

HRMS: *m*/*z* calcd for $C_8H_{14}ClO_5$: 225.0530 (M + H); found: 225.0528 (M + H).

Preparation of (*S*)-ethyl 2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate (440)

To a solution of (2*S*,3*S*)-diethyl 2-chloro-3-hydroxysuccinate (**438**) (360 mg, 1.6 mmol) in THF (8 mL) was added over 10 minutes the BH_3·DMS (2.0 M in THF, 0.83 mL, 1.6 mmol). The reaction mixture was stirred at room temperature for 30 minutes. At this time, the solution is cooled to 10 °C, $NaBH_4$ (3 mg, 0.1 mmol) added, and stirred for an additional one hour. Ethanol (3 mL) and *p*-toluenesulfonic acid (one crystal) are then added to the solution and allowed to stir for 30 minutes. At this time, the solution is concentrated, ethanol (50 mL) added, and concentrated. This was repeated 3 times to afford crude (2S,3S)-ethyl 2-chloro-3,4-dihydroxybutanoate (**439**) (292 mg, >97%), which was carried forward without further purification.

To the crude (2S,3S)-ethyl 2-chloro-3,4-dihydroxybutanoate (**439**) (292 mg, 1.60 mmol) was added acetone (10 mL), 2,2-dimethoxypropane (235 µL, 1.90 mmol), and *p*-toluenesulfonic acid (38 mg, 0.20 mmol). The solution was allowed to stir at room temperature for 18 hours. At this time, $MgSO_4$ was added, the solution filtered and then concentrated. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes–EtOAc) afforded (*S*)-ethyl 2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate (**440**) (320 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.48 (ddd, 1H, *J* = 9.0, 6.0, 3.6 Hz), 4.29-4.27 (m, 2H), 4.14 (d, 1H, *J* = 9.0 Hz), 4.13 (dd, 1H *J* = 9.0, 6.0 Hz), 4.07 (dd, 1H, *J* = 9.0, 3.6 Hz), 1.45 (s, 3H), 1.34 (s, 3H), 1.31 (t, 3H, *J* = 6.0 Hz).

IR (neat): 1763, 1757, 1390, 1378, 1250, 1090 cm^{-1}

$[\alpha]_D^{25}$ -6.7 (*c* 1.0, $CHCl_3$).

Preparation of (2*S*,3*R*)-3-chlorobutane-1,2,4-triol (442)

To a solution of (2*S*,3*S*)-diethyl 2-acetoxy-3-chlorosuccinate (**436**) (400 mg, 1.50 mmol) in THF (10 mL) was added over 10 minutes the BH_3·DMS (2.0 M in THF, 3.4 mL, 6.8 mmol). The reaction mixture was stirred at room temperature for 18 hours. At this time, the solution is cooled to 10 °C, $NaBH_4$ (3 mg, 0.1 mmol) added, and stirred for an additional one hour. At this time, the solution is concentrated, methanol (50 mL) added, and concentrated. This was repeated 3 times to afford (2*S*,3*R*)-3-chlorobutane-1,2,4-triol (**442**) (210 mg, >97%).

^{1}H NMR (500 MHz, MeOD) δ: 3.91 (td, 1H, *J* = 6.5, 4.0 Hz), 3.85 (dd, 1H, *J* = 12.0, 4.0 Hz), 3.77-3.67 (m, 3H), 3.60 (dd, 1H, *J* = 12.0, 5.0 Hz).

^{13}C NMR (125 MHz, MeOD) δ: 70.3, 70.0, 63.1, 62.5.

IR (neat): 3440, 3368, 3270, 3211, 2976, 2920, 1080 cm^{-1}

Preparation of (*R*)-2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (441)

To a solution of (2*S*,3*R*)-3-chlorobutane-1,2,4-triol (**442**) (1.25 g, 8.90 mmol) in CH_2Cl_2 was added 2,2-dimethoxypropane (1.1 mL, 9.0 mmol), and *p*-toluenesulfonic acid (95 mg, 0.50 mmol). The solution was allowed to stir at room temperature for 18 hours. At this time, $MgSO_4$ was added, the solution filtered and then concentrated. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes–EtOAc) afforded (*R*)-2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol (**441**).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.24 (ddd, 1H, *J* = 9.0, 6.0, 4.8 Hz), 4.17 (dd, 1H, *J* = 9.0, 6.0 Hz), 4.00 (dd, 1H, *J* = 9.0, 4.8 Hz), 3.97 (m, 1H), 3.91-3.83 (m, 2H), 2.29 (dd, 1H, *J* = 7.2, 6.0 Hz), 1.44 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 110.6, 76.7, 68.0, 64.8, 62.6, 26.8, 25.3.

IR (neat): 3450, 2976, 2940, 1460, 1080 cm^{-1}

$[\alpha]_D^{25}$ -9.7 (*c* 2.0, EtOH).

Preparation of (1*R*,2*R*,7*Z*)-1,7-dichloro-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyundeca-7,10-dien-4-one (403)

To a cold (0 °C), stirred solution of diisopropyl amine (84 µL, 0.60 mmol) in THF (5 mL) was added *n*-butyllithium (2.5 M soln. in hexane, 0.24 mL, 0.60 mmol) and the resulting mixture was stirred for 30 minutes. After this time, the slightly yellow solution was cooled to -78 °C and (*Z*)-5-chloronona-5,8-dien-2-one (**402**) (86 mg, 0.50 mmol) in THF (0.5 mL) was added in one portion. The reaction mixture was stirred for one hour, a solution of (*S*)-2-chloro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (**401**) (107 mg, 0.600 mmol) in THF (0.5 mL) was then added in one portion at -78 °C and the resulting mixture was stirred for an additional one hour. Saturated aqueous NH_4Cl (10 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes-ethyl acetate) afforded (1*R*,2*R*,7*Z*)-1,7-dichloro-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyundeca-7,10-dien-4-one (**403**).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.77 (ddt, 1H, *J* = 13.0, 6.5, 4.5 Hz), 5.57 (t, 1H, *J* = 7.0 Hz,), 5.08-4.97 (m, 2H), 4.44 (m, 1H), 4.24 (m, 1H), 4.18 (dd, 1H, *J* = 9.0, 6.0 Hz), 3.97 (dd, 1H, *J* = 9.0, 5.5 Hz), 3.91 (dd, 1H, *J* = 9.0, 5.5 Hz), 3.47 (d, 1H, *J* = 3.5 Hz), 2.91 (t, 2H, *J* = 6.0 Hz), 2.84-2.80 (m, 2H), 2.77 (td, 2H, *J* = 7.0, 3.5 Hz), 2.63 (t, 2H, *J* = 7.5 Hz), 1.43 (s, 3H), 1.35 (s, 3H).

IR (neat): 3580, 3420, 3011, 2977, 1726, 1618, 1080 cm^{-1}

HRMS: *m*/*z* calcd for $C_{16}H_{25}Cl_2O_4$: 351.1130 (M + H); found: 351.1132 (M + H).

Preparation of 3-[(*tert*-butyldimethylsilyl)oxy]propanal (444)

To a solution of *tert*-butyldimethylsilyl chloride (6.9 g, 46 mmol) in CH_2Cl_2 (100 mL) was added imidazole (3.1 g, 46 mmol). This solution was allowed to 18 hours at room temperature. At this time, H_2O (50 mL) was then added, the mixture was diluted with ethyl acetate (20 mL) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and then concentrated to give a yellow oil.

This crude yellow oil was diluted with CH_2Cl_2 (84 mL), cooled to -78 °C and O_3 was bubbled through the solution for three hours. At this time, triphenylphosphine (22 g, 84 mmol) was added and the solution allowed to stir for 18 hours. The solution was then diluted with pentanes (50 mL), filtered, and concentrated. This was repeated five times to afford a crude yellow oil. Purification of this material under fractional distillation (2 mmHg, 50 °C) afforded 3-[(*tert*-butyldimethylsilyl)oxy]propanal (**444**) (7.5 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.80 (t, 1H, *J* = 2.0 Hz), 3.99 (t, 2H, *J* = 6.0 Hz), 2.60 (td, 2H, *J* = 6.0, 2.0 Hz), 0.88 (s,97H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.2, 57.7, 46.8, 26.2, 18.4, -5.3.

IR (neat): 2958, 2930, 2855, 1728, 1466, 1080, 880 cm^{-1}

HRMS: *m*/*z* calcd for $C_9H_{21}O_2Si$: 189.1311 (M + H); found: 189.1319 (M + H).

Preparation of (2*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-chloropropanal (443)

Method A:

To a cold (0 °C) stirred solution of 3-[(*tert*-butyldimethylsilyl)oxy]propanal (**444**) (1.88 g, 10.0 mmol) in CH_2Cl_2 (20 mL) was added D-proline (115 mg, 1.00 mmol) and *N*-chlorosuccinimide (1.33 g, 10 mmol). The reaction mixture was stirred for 18 h. After this time, the mixture was diluted with pentane (20 mL), cooled (–78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice water bath. The resulting

oil was dissolved in pentane (20 mL), cooled (–78 °C), filtered through a fritted funnel, and concentrated on a rotary evaporator in an ice-water bath to give (2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-chloropropanal (**443**) (1.9 g, 86% yield) as a clear oil.

Method B:

To a suspension of 4 Å molecular sieves (10.8 g) in CH_2Cl_2 (250 mL) was added the pyridinium chlorochromate (10.8 g, 50.0 mmol) and allowed to age for 30 minutes. The suspension was cooled to 0 °C and (2*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-chloropropan-1-ol (**494**) (5.6 g, 25 mmol) in CH_2Cl_2 was added in one portion. This suspension was allowed to stir 3 hour, at which time it was filtered over a pad of Celite, washed with CH_2Cl_2 (250 mL), and concentrated to provide (2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-chloropropanal (**443**) (5.3 g, 95%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (d, 1H, *J* = 2.4 Hz), 4.19 (ddd, 1H, *J* = 2.4, 4.8, 6.0 Hz), 4.05 (m, 2 H), 0.88 (s, 9 H), 0.08 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 195.0, 69.8, 63.3, 35.6, 25.6, -5.6.

IR (neat): 2955, 2930, 2857, 1710, 1632, 1471, 1256 cm^{-1}

HRMS: *m*/*z* calcd for $C_9H_{19}ClO_2Si$: 223.0916 (M + H); found: 223.0910 (M + H).

$[\alpha]_D^{25}$ 12.2 (*c* 1.1, $CHCl_3$).

Preparation of (2*S,3*R**,8*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,8-dichloro-3-hydroxydodeca-8,11-dien-5-one (449)**

To a cold (–78 °C) stirred solution of diisopropyl amine (0.37 mL, 2.7 mmol) in THF (22 mL) was added *n*-BuLi (2.5 M in hexane, 0.97 mL, 2.4 mmol). The resulting solution was stirred at –78 °C for 30 min, then warmed to 0 °C, and stirred for an additional 15 min. After this time, the slightly yellow solution was cooled to –78 °C and (*Z*)-5-chloronona-5,8-dien-2-one (**402**) (0.39 g, 2.2 mmol) was added in one portion. The reaction mixture was then stirred for 30 min. A solution of (*S*)-3-[(*tert*-

butyldimethylsilyl)oxy]-2-chloropropanal (**443**) (0.59 g, 2.7 mmol) in THF (2.0 mL) was then added dropwise over 5 min at –78 °C and the resulting mixture was stirred for an additional 30 min. Sat. aq NH_4Cl (10 mL) was then added, the mixture was diluted with EtOAc (20 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes/EtOAc) afforded (2*S**,3*R**,8*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,8-dichloro-3-hydroxydodeca-8,11-dien-5-one (**449**) (0.80 g, 93%) as a yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.77 (m, 1 H), 5.56 (t, 1H, *J* = 6.6 Hz,), 5.07-5.00 (m, 2 H), 3.97-3.85 (m, 4 H), 2.92-2.60 (m, 6 H), 0.91 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 209.2, 135.3, 135.2, 123.1, 115.3, 75.7, 71.0, 65.9, 39.8, 35.6, 35.4, 32.9, 25.8, 25.7, -5.6.

IR (neat): 3583, 3001, 2957, 2904, 2863, 2275, 1723, 1613, 1464, 1092 cm^{-1}

HRMS: *m*/*z* calcd for $C_{18}H_{32}Cl_2O_3Si$: 395.1596 (M + H); found: 395.1601 (M + H).

Preparation of (2*S,3*R**,5*R**,8*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,8-dichlorododeca-8,11-diene-3,5-diol (450)**

To a cold (–78 °C) solution of **449** (325 mg, 0.82 mmol) in THF (15 mL) was added DIBAL-H (1.0 M in THF, 2.0 mL, 2.0 mmol) and the reaction mixture was stirred for 4 h. After this time, a solution of aq 1 M HCl (5 mL) was added, the mixture was diluted with Et_2O (20 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (15 mL), and the combined organic phases were washed with H_2O (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to provide an oil. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes/EtOAc) afforded an inseparable 4:1 mixture of (2*S**,3*R**,5*R**,8*Z*)-1-[(*tert*-

Butyldimethylsilyl)oxy]-2,8-dichlorododeca-8,11-diene-3,5-diol (**450**) and the C-5 epimer (278 mg, 91%) as a clear oil.

450 (Major Diastereomer)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.78 (m, 1 H), 5.56 (t, 1H, *J* = 6.8 Hz,), 5.10-5.00 (m, 2 H), 4.07-3.82 (m, 5 H), 2.93 (m, 2 H), 2.63-2.40 (m, 4 H), 1.84-1.58 (m, 2 H), 0.91 (s, 9 H), 0.11 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.7, 128.9, 123.3, 115.4, 75.8, 70.7, 66.1, 63.1, 39.7, 35.6, 35.4, 32.5, 25.8, 25.7, -5.1.

IR (neat): 3525, 3003, 2957, 2906, 2862, 2837, 1513, 1248, 1098 cm^{-1}

HRMS: *m*/*z* calcd for $C_{18}H_{34}Cl_2O_3Si$: 419.1552 (M + Na); found: 419.1555 (M + Na).

Preparation of (2*R,3*R**,5*R**)-5-[(3'*Z*)-3'-Chlorohepta-3',6'-dien-1'-yl]-2-(hydroxymethyl) tetrahydrofuran-3-ol (451)**

A 4:1 mixture of (2*S**,3*R**,5*R**,8*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-2,8-dichlorododeca-8,11-diene-3,5-diol (**450**) and the C-5 epimer (100 mg, 0.25 mmol) were placed in a 10 mL vial, deionised H_2O (2 mL) was then added, and the vial was sealed in a CEM Discover LabMate microwave. The reaction mixture was then heated to 120 °C (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 20 min. After this time, the mixture was diluted with EtOAc (10 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes–EtOAc) afforded (2*R**,3*R**,5*R**)-5-[(3'*Z*)-3'-chlorohepta-3',6'-dien-1'-yl]-2-(hydroxymethyl) tetrahydrofuran-3-ol (**451**) (43 mg, 70%) as a clear oil.

^{1}H NMR (400 MHz, CD_3OD) δ: 5.80 (m, 1 H), 5.61 (t, 1H, *J* = 6.8 Hz,), 5.08-4.97 (m, 2 H), 4.38 (m, 1 H), 4.21 (m, 1 H), 3.92 (m, 1H), 3.81-3.67 (m, 2 H), 2.92 (m, 2 H), 2.58-2.32 (m, 3 H), 2.04 (dd,1H, *J* = 6.0, 13.2 Hz), 1.73-1.84 (m, 2 H).

^{13}C NMR (150 MHz, CD_3OD) δ: 136.4, 136.3, 124.3, 115.8, 83.7, 77.9, 73.5, 62.1, 42.5, 37.1, 35.1, 33.7.

IR (neat): 3453, 2952, 2857, 1658, 1639, 1430, 1255, 1087 cm^{-1}

HRMS: *m*/*z* calcd for $C_{12}H_{19}ClO_3$: 247.1101 (M + H); found: 247.1111 (M + H).

Preparation of (2*R,3*R**,5*R**)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-[(*Z*)-3-chlorohepta-3,6-dien-1-yl]tetrahydrofuran-3-ol (448)**

To a solution of (2*R**,3*R**,5*R**)-5-[(3'*Z*)-3'-chlorohepta-3',6'-dien-1'-yl]-2-(hydroxymethyl) tetrahydrofuran-3-ol (**451**) (100 mg, 0.40 mmol) in CH_2Cl_2 (8 mL) was added 4-dimethylaminopyridine (2 mg, 0.02 mmol), triethylamine (68 µL, 0.50 mmol), and *tert*-butyldimethylsilyl chloride (66 mg, 0.44 mmol). This solution was stirred for three hours at which time the solution was cooled, then water (25 mL) was added and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. Purification of the crude product by flash chromatography (silica gel, 4:1 hexanes–EtOAc) afforded (2*R**,3*R**,5*R**)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-[(*Z*)-3-chlorohepta-3,6-dien-1-yl]tetrahydrofuran-3-ol (**448**) (94 mg, 65%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.79 (ddt, 1H, *J* = 16.8, 10.0, 6.4 Hz), 5.52 (m, 1H), 5.09-4.96 (m, 2H), 4.52 (dd, 1H, *J* = 7.7, 3.8 Hz), 4.21 (m, 1H), 3.94 (dt, 2H, *J* = 10.0, 5.6 Hz), 3.56 (d, 1H, *J* = 3.6 Hz), 2.92 (t, 2H, *J* = 6.4 Hz), 2.50-2.35 (m, 3H), 2.08 (m, 1H), 1.88-1.67 (m, 2H), 0.90 (s, 9H), 0.10 (s, 6H).

IR (neat): 3520, 2940, 1412, 1256, 1080, 880 cm^{-1}

Preparation of racemic ethyl 3-hydroxy-4-methylpent-4-enoate (*rac*-456)

To a cold (–78 °C) stirred solution of diisopropyl amine (13.7 mL, 97.5 mmol) in THF (150 mL) was added *n*-BuLi (2.5 M in hexane, 36 mL, 90 mmol). The resulting solution was stirred at –78 °C for 30 min, then warmed to 0 °C, and stirred for an additional 15 min. After this time, the slightly yellow solution was cooled to –78 °C and ethyl acetate (6.6 g, 75 mmol) was added in one portion. The reaction mixture was then stirred for 10 min. A solution of methacrolein (6.2 mL, 75 mmol) in THF (10 mL) was then added dropwise over two minutes at –78 °C and the resulting mixture was stirred for an additional 30 min. Sat. aq NH_4Cl (10 mL) was then added, the mixture was diluted with EtOAc (20 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Purification of the crude product by fractional distillation (2 mmHg, 70 °C) afforded racemic ethyl 3-hydroxy-4-methylpent-4-enoate (*rac*-**456**) (6.1 g, 55%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.04 (s, 1H), 4.89 (s, 1H), 4.47 (dd, 1H, *J* = 8.5, 4.0 Hz), 4.18 (q, 2H, *J* = 7.0 Hz), 2.91 (s, 1H), 2.62-2.50 (m, 2H), 1.76 (s, 3H), 1.28 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.5, 145.7, 111.4, 71.7, 61.0, 40.2, 18.3, 14.4.

IR (neat): 3465, 3211, 2988, 2955, 1734, 1644, 1082 cm^{-1}

HRMS: *m*/*z* calcd for $C_8H_{14}O_3Na$: 181.0841 (M + Na); found: 181.0836 (M + Na).

Preparation of (3*R*)-ethyl 3-hydroxy-4-methylpent-4-enoate (456)

To a suspension containing 4 Å molecular sieves (6 g) and titanium isopropoxide (4.60 mL, 15.6 mmol) in CH_2Cl_2 (150 mL) was added (+)-diisopropyltartrate (4.10 mL, 19.3 mmol) at -20 °C. This suspension was allowed to stir for 20 minutes before addition of the racemic ethyl 3-hydroxy-4-methylpent-4-enoate (*rac*-**456**) (6.1 g, 39 mmol). After

an additional 20 minutes, *tert*-butylhydroperoxide (5.0 M in toluene, 7.7 mL, 39 mmol) was added. This suspension was stirred at -20 °C for 7two hours, and at this time sat. aq. sodium potassium tartrate (150 mL) was added and the mixture was diluted with EtOAc (20 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes–EtOAc) afforded ethyl 3-hydroxy-4-methylpent-4-enoate (**456**) (3.0 g, 49%) as a clear oil.

$[\alpha]_D^{25}$ 27.2 (*c* 1.1, $CHCl_3$).

Preparation of (3*R*)-ethyl 3-hydroxy-4-(hydroxymethyl)pent-4-enoate (458)

To a solution of ethyl 3-hydroxy-4-methylpent-4-enoate (**456**) (3.0 g, 19 mmol) in CH_2Cl_2 was added SeO_2 (1.1 g, 10 mmol) and *tert*-butylhydroperoxide (5.0 M in toluene, 16 mL, 80 mmol). This solution was allowed to stir 24 hours and at this time the solution was filtered over Celite and concentrated. Purification of the crude product by flash chromatography (silica gel, 1:5 hexanes–EtOAc) afforded (3*R*)-ethyl 3-hydroxy-4-(hydroxymethyl)pent-4-enoate (**458**) (2.3 g, 70%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.16 (d, 1H *J* = 7.2 Hz), 4.70 (dt, 1H, *J* = 8.0, 4.0 Hz), 4.26 (dd, 1H, *J* = 13.2, 8.0 Hz), 4.19 (q, 2H, *J* = 7.2 Hz), 3.38 (d, 1H, *J* = 4.0 Hz), 2.68 (dd, 1H, *J* = 6.4, 5.0 Hz), 2.10 (t, 1H, *J* = 6.0 Hz), 1.28 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.60, 148.2, 112.9, 69.9, 64.3, 60.9, 40.4, 14.2.

HRMS: *m*/*z* calcd for $C_8H_{15}O_4$: 175.0970 (M + H); found: 175.0966 (M + H).

Preparation of (*R*)-2-(2,2-dimethyl-5-methylene-1,3-dioxan-4-yl)acetic acid (453)

To a solution of (3*R*)-ethyl 3-hydroxy-4-(hydroxymethyl)pent-4-enoate (**458**) (375 mg, 2.10 mmol) in CH_2Cl_2 (15 mL) was added 2,2-dimethoxypropane (1.1 mL, 9.0 mmol), and *p*-toluenesulfonic acid (19 mg, 0.10 mmol). The solution was allowed to stir at room temperature for 30 hours. At this time, $MgSO_4$ was added, the solution filtered and then concentrated to afford the crude acetonide.

Next, the crude acetonide was treated with NaOH (1.35 mL) in methanol (3 mL). This solution was stirred for three hours and then the mixture was then acidified to pH 5-6 with aq. HCl, diluted with Et_2O (20 mL), and the Et_2O layer was washed with sat. aq $NaHCO_3$ (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide (*R*)-2-(2,2-dimethyl-5-methylene-1,3-dioxan-4-yl)acetic acid (**453**) (254 mg, 74% over two-steps) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.90 (d, 1H, *J* = 1.2 Hz), 4.88-4.76 (m, 2H), 4.40-4.31 (m, 1H), 4.26 (dd, 1H, *J* = 13.6, 1.2 Hz), 2.83 (dd, 1H, *J* = 16.0, 4.4 Hz), 2.65 (dd, 1H, *J* = 16.0, 8.4 Hz), 1.49 (s, 3H), 1.39 (s, 3H).

Preparation of triene (460)

To a solution of (2*R**,3*R**,5*R**)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-[(*Z*)-3-chlorohepta-3,6-dien-1-yl]tetrahydrofuran-3-ol (**448**) (74 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of *N*,*N'*-dicyclohexylcarbodiimide (45 mg, 0.20 mmol), *(R)*-2-(2,2-dimethyl-5-methylene-1,3-dioxan-4-yl)acetic acid (**453**) (33 mg, 0.20 mmol), and DMAP (5 mg, 0.04 mmol). This solution was allowed to stir overnight. At this time the solution was filtered over Celite and concentrated. Purification of the crude product by flash chromatography (silica gel, 5:1 → 1:2 hexanes–EtOAc) afforded (2*R*,3*R*,5*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-((*Z*)-3-chlorohepta-3,6-dien-1-

yl)tetrahydrofuran-3-yl 2-((*R*)-2,2-dimethyl-5-methylene-1,3-dioxan-4-yl)acetate (**460**) (47 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.81 (m, 1H), 5.53 (t, 1H, *J* = 6.4 Hz), 5.44 (d, 1H, *J* = 4.0 Hz), 5.12-4.98 (m, 2H), 4.88 (d, 1H, *J* = 1.6 Hz), 4.83 (s, 1H), 4.78 (s, 1H), 4.33 (d, 1H, *J* = 13.2 Hz), 4.24 (d, 1H, *J* = 13.2 Hz), 4.14 (m, 1H), 4.06 (ddd, 1H, *J* = 9.6, 6.4, 3.6 Hz), 3.74 (m, 2H), 2.92 (t, 2H, *J* = 6.4 Hz), 2.76 (m, 2H), 2.60 (m, 2H), 2.47 (m, 1H), 2.12 (ddd, 1H, *J* = 13.6, 6.0, 1.0 Hz), 1.82-1.74 (m, 2H), 1.48 (s, 3H), 1.47 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.5, 144.7, 136.5, 136.1, 124.4, 115.1, 109.0, 99.9, 80.7, 74.8, 74.7, 67.7, 64.1, 61.4, 39.3, 39.1, 38.1, 36.2, 33.8, 31.2, 25.6, 26.6, -5.4.

Preparation of (2*R*,3*R*,5*R*)-5-((*Z*)-3-chlorohepta-3,6-dien-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl pent-4-enoate (461)

To a solution of (2*R**,3*R**,5*R**)-2-{[(tert-butyldimethylsilyl)oxy]methyl}-5-[(*Z*)-3-chlorohepta-3,6-dien-1-yl]tetrahydrofuran-3-ol (**448**) (26 mg, 0.070 mmol) in CH_2Cl_2 (3 mL) was added dropwise a solution of *N*,*N*′-dicyclohexylcarbodiimide (15 mg, 0.070 mmol), pentenoic acid (7 μL, 0.07 mmol), and DMAP (2 mg, 0.02 mmol). This solution was allowed to stir overnight. At this time the solution was filtered over Celite and concentrated. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes–EtOAc) afforded (2*R*,3*R*,5*R*)-5-((*Z*)-3-chlorohepta-3,6-dien-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-yl pent-4-enoate (**461**) (24 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88-5.69 (m, 2H), 5.53 (t, 1H, *J* = 7.0 Hz), 5.43 (t, 1H, *J* = 4.0 Hz), 5.08-5.01 (m, 4H), 4.33-4.10 (m, 4H), 2.92 (t, 2H, *J* = 6.0 Hz), 2.50-2.36 (m, *7*H), 2.11 (ddd, 1H, *J* = 14.0, 5.6, 1.2 Hz), 1.94-1.72 (m, 2H).

HRMS: *m*/*z* calcd for $C_{17}H_{26}ClO_4$: 329.1520 (M + H); found: 329.1518 (M + H).

Preparation of dimer (465)

To a degassed solution of (2*R*,3*R*,5*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-((*Z*)-3-chlorohepta-3,6-dien-1-yl)tetrahydrofuran-3-yl 2-((*R*)-2,2-dimethyl-5-methylene-1,3-dioxan-4-yl)acetate (**460**) (10 mg, 0.02 mmol) in CH_2Cl_2 (3 mL) was added the ring-closing metathesis catalyst (0.005 mmol). The solution was stirred for two hours. At this time, the solution was directly purified by flash chromatography (silica gel, 4:1 hexanes–EtOAc) afforded (*R*)-(2*R*,2'*R*,3*R*,3'*R*,5*R*,5'*R*)-5,5'-((3*Z*,6*E*,9*Z*)-3,10-dichlorododeca-3,6,9-triene-1,12-diyl)bis(2-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-5,3-diyl) bis(2-((*R*)-2,2-dimethyl-5-methylene-1,3-dioxan-4-yl)acetate) (**465).**

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.49 (t, 2H, *J* = 6.6 Hz), 5.48-5.40 (m, 4H), 4.90-4.89 (m, 2H), 4.83 (s, 2H), 4.78 (s, 2H), 4.33 (d, 2H, *J* = 13.6 Hz), 4.25 (d, 2H, *J* = 13.6 Hz), 4.13 (dd, 2H, *J* = 15.4, 8.0 Hz), 4.09-4.03 (m, 2H), 3.74 (m, 4H), 2.86 (s, 4H), 2.76 (td, 4H, *J* = 15.4, 4.2 Hz), 2.61 (dt, 4H, *J* = 15.8, 8.6 Hz), 2.48 (m, 1H), 2.36 (dd, 2H, *J* = 14.0, 6.6 Hz), 2.12 (dd, 2H *J* = 13.6, 6.0 Hz), 1.89-1.81 (m, 2H), 1.77 (d, 2H, *J* = 4.2 Hz), 1.48 (s, 6H), 1.47 (s, 6H), 0.87 (s, 18H), 0.04 (s, 12H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.3, 144.7, 144.5, 127.3, 123.6, 106.9, 99.8, 81.2, 80.7, 75.4, 67.6, 64.1, 61.3, 39.1, 38.7, 36.2, 34.3, 31.6, 27.2, 25.8, 23.5, -5.3.

HRMS: *m*/*z* calcd for $C_{52}H_{87}Cl_2O_{12}Si_2$: 1029.5113 (M + H); found: 1029.5111 (M + H).

Preparation of ethyl 3-hydroxypent-4-enoate (471)

To a cold (–78 °C) stirred solution of diisopropyl amine (10.9 mL, 78.0 mmol) in THF (120 mL) was added *n*-BuLi (2.50 M in hexane, 28.6 mL, 71.5 mmol). The resulting solution was stirred at –78 °C for 30 min, then warmed to 0 °C, and stirred for an additional 15 min. After this time, the slightly yellow solution was cooled to –78 °C and ethyl acetate (6.4 mL, 65 mmol) was added in one portion. The reaction mixture was then stirred for 10 min. A solution of acrolein (5.3 mL, 75 mmol) in THF (10 mL) was then

added dropwise over two minutes at –78 °C and the resulting mixture was stirred for an additional 30 min. Sat. aq NH_4Cl (10 mL) was then added, the mixture was diluted with EtOAc (20 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. Purification of the crude product by fractional distillation (2 mmHg, 63 °C) afforded ethyl 3-hydroxypent-4-enoate (**471**) (9.6 g, >97%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.89 (m, 1H), 5.32 (d, 1H, *J* = 17.0 Hz), 5.16 (d, 1H, *J* = 10.5 Hz), 4.54 (s, 1H), 4.18 (q, 2H, *J* = 7.0 Hz), 2.95 (s, 1H), 2.59 (dd, 1H, *J* = 16.5, 4.0 Hz), 2.52 (dd, 1H, *J* = 16.5, 8.5 Hz), 1.28 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 138.8, 115.5, 69.9, 60.7, 41.2, 14.1.

IR (neat): 3460, 3005, 2925, 2900, 1732, 1440, 1060 cm^{-1}

Preparation of ethyl 3-oxopent-4-enoate (473)

To chromium oxide (8.0 g, 80 mmol) was added concentrated H_2SO_4 (7 mL), and then diluted with deionised water (58 mL). After stirring this solution for 30 minutes, it was transferred to an addition funnel. Next, to a solution of ethyl 3-hydroxypent-4-enoate (**471**) (9.6 g, 65 mmol) in acetone (133 mL) was over 30 minutes added the contents from the addition funnel. The solution was allowed to stir for four hours, and at this time methanol (7 mL) was added, and allowed to stir for an additional 20 minutes. The mixture was then diluted with Et_2O (100 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. Purification of the crude product by fractional distillation (2 mmHg, 40 °C) afforded ethyl 3-oxopent-4-enoate (**473**) (5.1 g, 55%) as a 1:1 mixture of the keto-enol tautomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.80 (s, 1H, enol), 6.42 (dd, 1H, *J* = 17.5, 10.5 Hz, enol), 6.27 (d, 1H, *J* = 17.5 Hz, keto), 6.11 (s, 1H, enol), 6.10 (d, 1H, *J* = 2.0 Hz, keto), 5.97 (d, 1H, *J* = 10.5 Hz, enol), 5.54 (dd, 1H, *J* = 7.0, 5.0 Hz, keto), 5.07 (s, 1H, enol), 4.23-4.19 (m, 4H, keto and enol), 3.63 (s, 2H, keto), 1.28 (t, 6H, *J* = 7.0 Hz, keto and enol).

IR (neat): 3440, 2980, 1740, 1680, 1650, 1590, 1540, 1430, 1040 cm^{-1}

Preparation of (4*E*,7*Z*)-ethyl 8-chloro-3,11-dioxododeca-4,7-dienoate (475) and (4*Z*,7*Z*)-ethyl 8-chloro-3,11-dioxododeca-4,7-dienoate (476)

To a degassed solution of ethyl 3-oxopent-4-enoate (**473**) (142 mg, 1.00 mmol) and (*Z*)-5-chloronona-5,8-dien-2-one (**402**) (17 mg, 0.10 mmol) in toluene (200 µL) was added the Grubbs-Hovyeda II catalyst (3 mg, 0.005 mmol). The solution was stirred at 120 °C for two hours. At this time, the solution was cooled to room temperature and directly purified by flash chromatography (silica gel, 3:1 hexanes–EtOAc) afforded a 2:1 mixture of (4*E*,7*Z*)-ethyl 8-chloro-3,11-dioxododeca-4,7-dienoate (**475**) and (4*Z*,7*Z*)-ethyl 8-chloro-3,11-dioxododeca-4,7-dienoate (**476**).

(4*E*,7*Z*)-ethyl 8-chloro-3,11-dioxododeca-4,7-dienoate (**475**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.81 (dt, 1H, *J* = 16.0, 6.4 Hz), 6.16 (dt, 1H, *J* = 16.0, 1.6 Hz), 5.57 (t, 1H, *J* = 7.2 Hz), 4.20 (q, 2H, *J* = 7.2), 3.57 (s, 2H), 3.09 (m, 1H) 2.78-2.68 (m, 2H), 2.66-2.57 (m, 2H), 2.17 (s, 3H), 1.20 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.8, 192.0, 167.3, 145.4, 136.5, 130.0, 120.9, 61.4, 47.0, 41.2, 33.4, 31.4, 30.1, 22.3, 14.0.

(4*Z*,7*Z*)-ethyl 8-chloro-3,11-dioxododeca-4,7-dienoate (**476**)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.57 (dt, 1H, *J* = 15.6, 6.6 Hz), 5.81 (m, 1H), 5.57 (t, 1H, *J* = 7.2 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 3.57 (s, 3H), 3.04 (m, *1*H), 2.78-2.68 (m, 2H), 2.66-2.57 (m, 2H), 2.13 (s, 3H), 1.20 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.9, 192.0, 169.0, 145.4, 135.4, 125.2, 122.2, 60.1, 47.0, 41.3, 33.5, 31.5, 30.1, 24.4, 14.3.

Preparation of (*R*)-ethyl 3-((allyldimethylsilyl)oxy)-4-methylpent-4-enoate (482)

To solution of allylchlorodimethylsilane (830 μL, 5.50 mmol) and imidazole (370 mg, 5.50 mmol) in CH_2Cl_2 was added ethyl 3-hydroxy-4-methylpent-4-enoate (**456**) (790 mg, 5.00 mmol). This solution was stirred for three hours at room temperature. At this time, H_2O (10 mL) was added and then diluted with Et_2O (20 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 6:1 hexanes–EtOAc) afforded (*R*)-ethyl 3-((allyldimethylsilyl)oxy)-4-methylpent-4-enoate (**482**) (1.1 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (ddt, 1H, *J* = 17.2, 10.0, 8.0 Hz), 4.96 (m, 1H), 4.87 (m, 1H), 4.85 (dd, 1H, *J* = 2.4, 1.2 Hz), 4.81 (m, 1H), 4.13 (q, 2H, *J* = 7.2 Hz), 2.52 (dd, 1H, *J* = 14.4, 8.8 Hz), 2.44 (dd, 1H, *J* = 14.4, 4.4 Hz), 1.70 (s, 3H), 1.65-1.54 (m, 2H), 1.26 (t, 3H, *J* = 7.2 Hz), 0.09 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 146.3, 134.1, 113.6, 111.6, 73.7, 60.4, 42.3, 24.7, 17.1, 14.2, -2.21, -2.29.

HRMS: *m*/*z* calcd for $C_{13}H_{25}O_3Si$: 257.1573 (M + H); found: 257.1580 (M + H).

Preparation of (*R*)-ethyl 2-(2,2,5-trimethyl-3,6-dihydro-2H-1,2-oxasilin-6-yl)acetate (483)

To a degassed solution of (*R*)-ethyl 3-((allyldimethylsilyl)oxy)-4-methylpent-4-enoate (**482**) (130 mg, 0.50 mmol) in CH_2Cl_2 (10 mL) was added the Grubbs-Hoveyda II catalyst (9 mg, 0.01 mmol). The solution was stirred at reflux for two hours. At this time,

the solution was cooled to room temperature and directly purified by flash chromatography (silica gel, 9:1 hexanes–EtOAc) afforded (*R*)-ethyl 2-(2,2,5-trimethyl-3,6-dihydro-2H-1,2-oxasilin-6-yl)acetate (**483**) (114 mg, >97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.64 (dd, 1H, *J* = 5.5, 3.5 Hz), 4.66 (d, 1H, *J* = 9.5 Hz), 4.30-4.01 (m, 2H), 2.61 (dd, 1H, *J* = 14.5, 3.5 Hz), 2.40 (dd, 1H, *J* = 14.5, 9.5 Hz), 1.65 (d, 3H, *J* = 1.5 Hz), 1.27 (t, 3H, *J* = 7.2 Hz), 0.18 (s, 6H), 0.10 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 136.5, 120.6, 73.4, 60.4, 41.9, 21.6, 14.3, 12.2, 0.59, -0.57.

HRMS: *m*/*z* calcd for $C_{11}H_{21}O_3Si$: 229.1260 (M + H); found: 229.1255 (M + H).

Preparation of (*R*,*Z*)-ethyl 3,6-dihydroxy-4-methylhex-4-enoate (484)

To a solution of (*R*)-ethyl 2-(2,2,5-trimethyl-3,6-dihydro-2H-1,2-oxasilin-6-yl)acetate (**483**) (55 mg, 0.24 mmol) in DMF (5 mL) was added H_2O_2 (80 µL) and KHF_2 (39 mg, 0.50 mmol). This solution was allowed to stir for 18 hours. At this time, 10% aq. sodium thiosulfate (5 mL) was added, diluted with EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 1:1 hexanes–EtOAc) afforded (*R*,*Z*)-ethyl 3,6-dihydroxy-4-methylhex-4-enoate (**484**) (36 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.53 (t, 1H, *J* = 7.0 Hz), 4.96 (dd, 1H, *J* = 8.5, 5.0 Hz), 4.19 (dd, 1H, *J* = 12.5, 8.5 Hz), 4.13 (q, 2H, *J* = 7.0 Hz), 4.06 (dd, 1H, *J* = 12.5, 6.5 Hz), 2.66 (dd, 1H, *J* = 16.0, 8.5 Hz), 2.45 (dd, 1H, *J* = 16.0, 5.0 Hz), 1.24 (t, 3H, *J* = 7.0 Hz).

Preparation of (*R*,*Z*)-ethyl 6-acetoxy-3-hydroxy-4-methylhex-4-enoate (485)

To a solution of (*R*,*Z*)-ethyl 3,6-dihydroxy-4-methylhex-4-enoate (**484**) (75 mg, 0.40 mmol) in acetonitrile (15 mL) was added 2,6-lutidine (230 µL). The solution was cooled to -10 °C, followed by the addition of acetyl chloride (29 µL) in acetonitrile (2 mL) dropwise over one hour. This solution was allowed to stir at -10 °C for two hours. At this time, 5% aq. HCl (1 mL) was added, diluted with EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 2:1 hexanes–EtOAc) afforded (*R*,*Z*)-ethyl 6-acetoxy-3-hydroxy-4-methylhex-4-enoate (**485**) (43 mg, 45%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.41 (t, 1H, *J* = 7.2 Hz), 5.03 (dt, 1H, *J* = 9.2, 3.2 Hz), 4.76 (dd, 1H, *J* = 12.8, 8.0 Hz), 4.55 (dd, 1H, *J* = 12.8, 6.4 Hz), 4.18 (q, 2H, *J* = 7.2 Hz), 3.02 (d, 1H, *J* = 2.8 Hz), 2.67 (dd, 1H, *J* = 16.0, 9.6 Hz), 2.43 (dd, 1H, *J* = 16.0, 4.0 Hz), 2.05 (s, 3H), 1.78 (s, 3H), 1.28 (t, 3H, *J* = 7.3 Hz).

Preparation of (*R*,*Z*)-ethyl 6-acetoxy-3-((tert-butyldimethylsilyl)oxy)-4-methylhex-4-enoate (486)

To a solution of (*R*,*Z*)-ethyl 6-acetoxy-3-hydroxy-4-methylhex-4-enoate (**485**) (43 mg, 0.19 mmol) in CH_2Cl_2 (4 mL) was added the 2,6-lutidine (24 µL). The solution was cooled to 0 °C, followed by the addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (48 µL). The solution was stirred for 18 hours. At this time, H_2O (2 mL) was added, diluted with CH_2Cl_2 (10 mL), layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 4:1 hexanes–

EtOAc) afforded (*R*,*Z*)-ethyl 6-acetoxy-3-((tert-butyldimethylsilyl)oxy)-4-methylhex-4-enoate (**486**) (51 mg, 78%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.35 (t, 1H, *J* = 6.6 Hz), 4.99 (dd, 1H, *J* = 9.0, 4.6 Hz), 4.71 (dd, 1H, *J* = 12.6, 7.8 Hz), 4.59 (dd, 1H, *J* = 12.6, 6.4 Hz), 4.12 (q, 2H, *J* = 7.2 Hz), 2.63 (dd, 1H, *J* = 14.4, 9.0 Hz), 2.36 (dd, 1H, *J* = 14.4, 4.8 Hz), 2.05 (s, 3H), 1.75 (s, 3H), 1.26 (t, 3H, *J* = 7.2 Hz), 0.86 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.91, 170.88, 142.9, 120.2, 67.5, 60.6, 60.1, 42.0, 25.6, 21.0, 18.1, 17.9, 14.2, -5.0, -5.3.

HRMS: *m*/*z* calcd for $C_{17}H_{33}O_5Si$: 345.2097 (M + H); found: 345.2097 (M + H).

Preparation of (*R*,*Z*)-ethyl 6-chloro-3-hydroxy-4-methylhex-4-enoate (487)

To a solution of (*R*,*Z*)-ethyl 3,6-dihydroxy-4-methylhex-4-enoate (**484**) (140 mg, 0.75 mmol) in THF (15 mL) was added methanesulfonyl chloride (75 µL, 1.0 mmol) and triethylamine (135 µL, 1.00 mmol). This mixture was allowed to stir at room temperature for two hours. At this time, lithium chloride (85 mg, 2.0 mmol) was added, and the solution was allowed to stir for an additional 30 minutes. At this time, H_2O (5 mL) was added, diluted with EtOAc (10 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 2:1 hexanes–EtOAc) afforded (*R*,*Z*)-ethyl 6-chloro-3-hydroxy-4-methylhex-4-enoate (**487**) (145 mg, 87%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.58 (m, 1H), 4.97 (dd, 1H, *J* = 9.0, 4.6 Hz), 4.20-4.15 (m, 4H), 2.69 (dd, 1H, *J* = 16.4, 9.0 Hz), 2.50 (dd, 2H, *J* = 16.4, 4.5 Hz), 1.28 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 172.5, 139.4, 127.0, 66.6, 61.0, 58.0, 39.6, 18.4, 14.1.

HRMS: *m*/*z* calcd for $C_9H_{15}ClO_3Na$: 229.0607 (M + Na); found: 229.0599 (M + Na).

IR (neat): 3460, 2955, 2811, 1736, 1281 cm^{-1}

Preparation of (*R*,*Z*)-ethyl 3-((tert-butyldimethylsilyl)oxy)-6-chloro-4-methylhex-4-enoate (488)

To a solution of (*R*,*Z*)-ethyl 6-chloro-3-hydroxy-4-methylhex-4-enoate (**487**) (120 mg, 0.60 mmol) in THF (15 mL) was added the 2,6-lutidine (270 µL). The solution was cooled to -78 °C, followed by the addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (270 µL). The solution was stirred at room temperature for one hours. At this time, H_2O (5 mL) was added, diluted with EtOAc (50 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 30 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. The crude product was purified by flash chromatography (silica gel, 10:1 hexanes–EtOAc) afforded (*R*,*Z*)-ethyl 3-((tert-butyldimethylsilyl)oxy)-6-chloro-4-methylhex-4-enoate (**488**) (130 mg, 70%)

^1H NMR (500 MHz, $CDCl_3$) δ: 5.43 (t, 1H, *J* = 8.0 Hz), 5.02 (dd, 1H, *J* = 9.0, 5.0 Hz), 4.24 (dd, 1H, *J* = 11.5, 9.0 Hz), 4.16-4.01 (m, 3H), 2.64 (dd, 1H, *J* = 14.5, 9.0 Hz), 2.38 (dd, 1H, *J* = 14.5, 5.0 Hz), 1.76 (s, 3H), 1.26 (t, 3H, *J* = 7.0 Hz), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).

HRMS: *m*/*z* calcd for $C_{15}H_{30}ClO_3Si$: 321.1653 (M + H); found: 321.1650 (M + H).

IR (neat): 2968, 2409, 1731, 1240, 861 cm^{-1}

Preparation of (2*S*)-2-chloro-3-hydroxypropanoic acid (490)

To a solution of aq. HCl (6 N, 120 mL) and L-serine (10 g, 95 mmol) at -20 °C was added over three hours (using a syringe pump) a solution of sodium nitrite (7.9 g, 110 mmol) in water (20 mL). This solution was not allowed to reach temperatures above

-15 °C, and was stirred for an additional three hours. At this time, the solution was diluted with Et_2O (100 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to provide (2*S*)-2-chloro-3-hydroxypropanoic acid (**490**) (8.2 g, 70%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s br, 1H), 5.28 (s br, 1H), 4.49 (t, 1H, *J* = 5.2 Hz), 4.06 (d, 2H, *J* = 5.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 64.2, 56.8.

HRMS: *m*/*z* calcd for $C_4H_7ClO_3Na$: 160.9976 (M + Na); found: 160.9978 (M + Na).

Preparation of (2*S*)-methyl 2-chloro-3-hydroxypropanoate (491)

To a solution of (2*S*)-methyl 2-chloro-3-hydroxypropanoate (**491**) (4.0 g, 32 mmol) in methanol (50 mL) was added concentrated HCl (0.2 mL). The solution was allowed to stir for two hours. At this time, the solution was diluted with Et_2O (100 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to provide (2*S*)-methyl 2-chloro-3-hydroxypropanoate (**491**) (3.8 g, 86%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.42 (t, 1H, *J* = 5.6 Hz), 4.03 (dd, 1H, *J* = 12.0, 5.6 Hz), 3.97 (dd, 1H, *J* = 12.0, 5.6 Hz), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 64.2, 56.8, 53.2.

$[\alpha]_D^{25}$ 9.9 (*c* 1.0, MeOH).

HRMS: *m*/*z* calcd for $C_4H_8ClO_3$: 139.0162 (M + H); found: 139.0164 (M + H).

Preparation of (2*S*)-methyl 3-((tert-butyldimethylsilyl)oxy)-2-chloropropanoate (492)

To a solution of *tert*-butyldimethylsilane (4.10 g, 27.4 mmol) in CH_2Cl_2 (60 mL) was added imidazole (4.1 g, 60 mmol), and the solution allowed to stir for 15 minutes. At this time, (2*S*)-methyl 2-chloro-3-hydroxypropanoate (**491**) (3.80 g, 27.4 mmol) was added and the solution allowed to stir for 18 hours. At this time, H_2O (20 mL) was added, diluted with CH_2Cl_2 (100 mL), and layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to provide (2*S*)-methyl 3-((tert-butyldimethylsilyl)oxy)-2-chloropropanoate (**492**) (6.30 g, >97%) as a clear oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.29 (dd, 1H, *J* = 7.5, 6.0 Hz), 4.01 (dd, 1H, *J* = 10.0, 7.5 Hz), 3.92 (dd, 1H, *J* = 10.0, 6.0 Hz), 3.79 (s, 3H), 0.87 (s, 9H), 0.07 (s, 6H).

HRMS: *m*/*z* calcd for $C_{10}H_{21}SiClO_3Na$: 275.0846 (M + Na); found: 275.0857 (M + Na).

Preparation of (2*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-chloropropan-1-ol (494)

At 0 °C, a solution of (2*S*)-methyl 3-((tert-butyldimethylsilyl)oxy)-2-chloropropanoate (**492**) (6.3 g, 25 mmol) in methanol (125 mL) was treated with $NaBH_4$ (2.40 g, 62.5 mmol). The solution was allowed to stir at room temperature for three hours. At this time, H_2O (25 mL) was added, diluted with EtOAc (100 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to provide (2*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-chloropropan-1-ol (**494**) (5.60 g, >97%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.02 (tt, 1H, *J* = 9.6, 5.0 Hz), 3.95-3.74 (m, 4H), 0.90 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 64.9, 64.7, 61.6, 25.7, 18.2, -5.45, -5.52.

HRMS: *m*/*z* calcd for $C_9H_{21}SiClO_2$: 225.1078 (M + H); found: 225.1070 (M + H).

Preparation of 6-(trimethylsilyl)hex-5-yn-2-one (496)

To a cold (–78 °C) stirred solution of diisopropyl amine (12.4 mL, 88.5 mmol) in THF (150 mL) was added *n*-BuLi (2.50 M in hexane, 34.2 mL, 85.2 mmol). The resulting solution was stirred at –78 °C for 30 min, then warmed to 0 °C, and stirred for an additional 15 min. After this time, the slightly yellow solution was cooled to –78 °C and trimethylsilyl chloride (12.0 mL, 93.6 mmol) was added in one portion. The reaction mixture was then stirred for 10 min. A solution of hex-5-yn-2-one (**424**) (3.60 g, 37.4 mmol) in THF (5 mL) was then added and the resulting mixture was stirred for an additional two hours. At this time, this solution was quenched with aq. H_2SO_4 (1.0 M, 170 mL) and allowed to stir for 18 hours. The mixture was then diluted with EtOAc (20 mL), neutralised with aq. $NaHCO_3$ (100 mL) and the phases separated. The aqueous phase was extracted with EtOAc (3 × 100 mL) and the combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to provide 6-(trimethylsilyl)hex-5-yn-2-one (**496**) (5.8, 92%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.65 (dd, 1H, *J* = 8.4, 6.4 Hz), 2.45 (dd, 1H, *J* = 8.4, 6.4 Hz), 2.15 (s, 3H), 0.11 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.6, 105.6, 85.1, 42.5, 29.9, 14.4, 0.0.

IR (neat): 2380, 2176, 2009, 1720, 1601, 860 cm^{-1}

HRMS: *m*/*z* calcd for $C_9H_{16}SiONa$: 191.0863 (M + Na); found: 191.0862 (M + Na).

Preparation of (7*R*,8*S*)-9-((*tert*-butyldimethylsilyl)oxy)-8-chloro-7-hydroxy-1-(trimethylsilyl)non-1-yn-5-one (497)

To a cold (-78 °C) solution of diisopropyl amine (745 µL, 5.30 mmol) in THF (50 mL) was added *n*-butyllithium (2.5 M soln. in hexane, 2.0 mL, 4.9 mmol). The resulting solution was stirred at -78 °C for 30 minutes, then warmed to 0 °C and stirred for an additional 15 minutes. After this time, the slightly yellow solution was cooled to -78 °C

and 6-(trimethylsilyl)hex-5-yn-2-one (**496**) (690 mg, 4.1 mmol) was added in one portion. The reaction mixture was stirred for 30 minutes. A solution of (2*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-chloropropanal (**443**) (1.0 g, 4.5 mmol) in THF (2.0 mL) was then added dropwise over 15 minutes at -78 °C and the resulting mixture was stirred for an additional 30 minutes. Saturated aqueous NH_4Cl (10 ml) was then added, the mixture was diluted with ethyl acetate (20 ml) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 15 ml) and the combined organic phases were washed with brine (15 mL), dried (MgSO4), filtered, and concentrated to provide a crude yellow solid. Purification of the crude product by flash chromatography (silica gel, 9:1 hexanes:ethyl acetate) afforded (7*R*,8*S*)-9-((*tert*-butyldimethylsilyl)oxy)-8-chloro-7-hydroxy-1-(trimethylsilyl)non-1-yn-5-one (**497**) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.34 (dddd, 1H, *J* = 8.8, 7.2, 4.2, 3.0 Hz), 3.96 (dd, 1H, *J* = 10.2, 4.4 Hz), 3.92 (m, 1H), 3.87 (dd, 1H, *J* = 10.2, 6.0 Hz), 3.45 (d, 1H, *J* = 4.2 Hz), 2.88 (dd, 1H, *J* = 16.8, 3.0 Hz), 2.77 (dd, 1H, *J* = 16.8, 8.4 Hz), 2.72 (dd, 2H, *J* = 8.4, 6.4 Hz), 2.50 (dd, 2H, *J* = 8.4, 6.4 Hz), 0.90 (s, 9H), 0.13 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 208.5, 105.3, 85.3, 69.5, 65.0, 63.0, 45.8, 42.5, 25.8, 14.2, 0.0, -5.45, -5.50.

HRMS: *m*/*z* calcd for $C_{18}H_{36}Si_2ClO_3$: 391.1886 (M + H); found: 391.1887 (M + H).

Preparation of (2*S*,3*R*,5*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-chloro-9-(trimethylsilyl)non-8-yne-3,5-diol (498)

To a cold (–78 °C) solution of (7*R*,8*S*)-9-((*tert*-butyldimethylsilyl)oxy)-8-chloro-7-hydroxy-1-(trimethylsilyl)non-1-yn-5-one (**497**) (1.1 g, 2.8 mmol) in THF (28 mL) was added DIBAL-H (1.0 M in THF, 7.0 mL, 7.0 mmol) and the reaction mixture was stirred for one hour. After this time, a solution of aq 1 M HCl (5 mL) was added, the mixture was diluted with EtOAc (20 mL) and the phases were separated. The aqueous phase was

extracted with EtOAc (15 mL), and the combined organic phases were washed with H_2O (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to provide an oil. Purification of the crude product by flash chromatography (silica gel, 6:1 hexanes/EtOAc) afforded (2*S*,3*R*,5*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-chloro-9-(trimethylsilyl)non-8-yne-3,5-diol (**498**) (1.01 g, 92%) as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.17 (m, 1H), 4.09-3.84 (m, 4H), 3.46 (d, 1H, *J* = 2.1 Hz), 2.48-2.31 (m, 2H), 1.99-1.91 (m, 1H), 1.89-1.79 (m, 1H), 1.77-1.63 (m, 2H), 1.24 (d, 1H, *J* = 6.0 Hz), 0.93 (s, 9H), 0.17 (s, 9H), 0.13 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 106.9, 77.3, 75.0, 71.4, 65.6, 39.5, 36.3, 25.8, 18.0, 16.1, 0.1, -5.45, -5.50.

HRMS: *m*/*z* calcd for $C_{18}H_{37}Si_2ClO_3Na$: 415.1867 (M + H); found: 415.1871 (M + H).

Preparation of (2*R*,3*R*,5*R*)-5-(but-3-yn-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (495)

A solution of (2*S*,3*R*,5*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-chloro-9-(trimethylsilyl)non-8-yne-3,5-diol (**498**) (300 mg, 0.75 mmol) in water was heated to 100 °C. This solution was stirred at this temperature for 12 hours. At this time, the mixture was diluted with EtOAc (20 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (5 x 15 mL), and the combined organic phases were dried ($MgSO_4$), and concentrated to provide an oil. This material was carried forward to the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.54 (s, 1H), 4.40 (m, 1H), 3.95 (m, 3H), 3.16 (s, 1H), 2.39-2.26 (m, 3H), 2.14 (dd, 1H, *J* = 14.0, 6.6 Hz), 1.96 (t, 1H, *J* = 2.56 Hz), 1.87-1.68 (m, 3H).

Preparation of (((2*R*,3*R*,5*R*)-5-(but-3-yn-1-yl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (499)

To a solution of *tert*-butyldimethylsilane (300 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) was added imidazole (270 mg, 4.0 mmol), DMAP (5 mg, 0.04 mmol), and the solution allowed to stir for 15 minutes. At this time, (2*R*,3*R*,5*R*)-5-(but-3-yn-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (**495**) (130 mg, 0.75 mmol) was added and the solution allowed to stir for 18 hours. At this time, H_2O (10 mL) was added, diluted with CH_2Cl_2 (20 mL), and layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. Purification of the crude product by flash chromatography (silica gel, 10:1 hexanes/EtOAc) afforded (((2*R*,3*R*,5*R*)-5-(but-3-yn-1-yl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (**499**) (270 mg, 91%) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 4.37 (t, 1H, *J* = 3.3 Hz), 4.25 (m, 1H), 3.86 (td, 1H, *J* = 6.0, 3.3 Hz), 3.77 (dd, 1H, *J* = 10.0, 6.0 Hz), 3.70 (dd, 1H, *J* = 10.0, 6.0 Hz), 2.33 (dddd, 1H, *J* = 17.0, 8.6, 6.0, 2.7 Hz), 2.26 (m, 1H), 1.97 (dd, 1H, *J* = 12.6, 5.5 Hz), 1.93 (t, 1H, *J* = 2.7 Hz), 1.79 (dtd, 1H, *J* = 14.0, 8.0, 6.0 Hz), 1.71 (m, 1H), 1.65 (ddd, 1H, *J* = 12.6, 10.0, 4.2 Hz), 0.89 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 84.2, 83.2, 76.4, 72.6, 68.2, 61.8, 41.8, 34.8, 26.0, 25.7, 15.4, -4.7, -5.1, -5.22, -5.26.

HRMS: *m*/*z* calcd for $C_{21}H_{42}Si_2O_3Na$: 421.2570 (M + Na); found: 421.2563 (M + Na).

Preparation of (2*R*,3*R*,5*R*)-5-(but-3-yn-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-3-yl acetate (500)

To a solution of *tert*-butyldiphenylsilyl chloride (130 µL, 0.50 mmol) and imidazole (68 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added (2*R*,3*R*,5*R*)-5-(but-3-yn-1-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (**495**) (85 mg, 0.50 mmol) in a solution of CH_2Cl_2 (1 mL). The solution was allowed to stir overnight. At this time, H_2O (10 mL) was added, diluted with CH_2Cl_2 (20 mL), and layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated to provide a crude yellow oil. To this crude oil was added CH_2Cl_2 (2 mL), pyridine (1 mL), and acetic anhydride (1 mL). This solution was allowed to stir overnight. At this time, the solution was concentrated and residual solvents removed under vacuum to provide (2*R*,3*R*,5*R*)-5-(but-3-yn-1-yl)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-3-yl acetate (**500**).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.55 (m, 4H), 7.49-7.32 (m, 6H), 5.47 (t, 1H, *J* = 4.0 Hz), 4.23 (m, 1H), 4.14 (td, 1H, *J* = 6.4, 4.0 Hz), 3.97 (m, 1H), 3.82-3.78 (m, *2*H), 2.29 (m, 2H), 2.16 (ddd, 1H, *J* = 13.5, 6.0, 1.2 Hz), 1.96 (s, 3H), 1.94 (t, 1H, *J* = 2.6 Hz), 1.85 (ddd, 1H, *J* = 16.6, 8.5, 3.8 Hz), 1.81-1.67 (m, 2H), 1.03 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.2, 135.6, 135.5, 129.7, 127.7, 83.7, 80.4, 77.2, 74.4, 68.5, 61.8, 39.1, 34.7, 26.7, 21.0, 19.0, 15.3.

HRMS: *m*/*z* calcd for $C_{27}H_{34}SiO_4Na$: 473.2119 (M + Na); found: 473.2117 (M + Na).

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Chapter 6

Conclusion

This thesis demonstrates the development of new methods to construct complex molecular scaffolds that are commonly encountered in natural products. By improving the asymmetric chlorination of aldehydes reported by MacMillan[1] and Jørgensen,[2] gram-quantities of optically pure α-chloroaldehydes were prepared and further elaborated to useful synthons. For example, in Chapter 2 a general method for the synthesis of chiral nonracemic *trans*-epoxides was developed that provides rapid access to alkyl-, alkenyl-, alkynyl-, and phenyl-substituted *trans*-epoxides from aldehydes was presented. Key to this work was the realisation that organolithium reagents add in a highly diastereoselective manner to α-chloroaldehydes. This methodology was then applied in a concise and high yielding syntheses of two *trans*-epoxide-containing insect sex pheromones. In Chapter 3 an efficient route to all configurational isomers of the 2,5-disubstituted-3-hydroxytetrahydrofuran scaffold was described. The success of this work relied on the discovery of both a high yielding and chemoselective, AgOTf-promoted cyclisation of chlorodiols and a stereochemically complementary rearrangement of epoxyalcohols. These methods were then applied to the preparation of two structurally related marine oxylipids. The concise, stereoselective synthesis of functionalised tetrahydrofuranols that involved heating readily available chloropolyols in water was presented in Chapter 4. These reactions are operationally straightforward and chemoselective for the formation of tetrahydrofurans, obviating the need for complicated protecting group strategies. The efficiency of this process was demonstrated in a short asymmetric synthesis of the natural product (+)-goniothalesdiol. Finally, Chapter 5

outlines the attempts to synthesise the haterumalide and biselide family of natural products using methods reported in this thesis. Although attempts at constructing the macrocyclic ring were not successful, studies geared toward the synthesis of these natural products is currently underway in the Britton laboratory that build on the observations documented herein.

These methods have also found additional applications within the Britton group, including the synthesis of a banana volatile by Mr. Mowat,[3] hydroxypyrrolidines and the natural product (+)-preussin by Mr. Jason Draper,[4] and a number of other methodological and target-oriented synthesis projects that have not yet been published. In addition, the methods developed in this thesis have been used by other research groups. For example, these methods have been exploited in multiple syntheses of chlorosulfolipids,[5] as a part of the total synthesis of varitriol,[6] and the preparation of 8- and 9-membered laurencia bromoethers.[7] This work also provided inspiration for the development of a one-pot asymmetric bromination of aldehydes, followed by nucleophilic addition to afford highly enantio- and diastereoselective synthesis of bromohydrins.[8]

The primary focus of this thesis involved development of methods that were subsequently applied to the target-oriented syntheses of natural products. However, many of these methods could also find use in diversity-oriented synthesis in which the population of a given chemical space is maximised from a single building-block and allows for the production of libraries of compounds for drug development.[9] The complexity of molecules that can be produced using the methodologies described within this thesis may well provide new opportunities for the agrochemical, pharmaceutical, and fine-chemical industries.

6.1 References

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