Formation of 2,5-*trans*-Tetrahydrofuran-3-one Application Towards the Synthesis of Natural Products

Delphine Rabiller

Ingenieur chimiste ECPM, DEA chimie moleculaire et supramoleculaire

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UNIVERSITY
of
GLASGOW

Abstract

The tetrahydrofuran backbone is one of the most common heterocyclic units found in natural products. Among them structurally complex substituted tetrahydrofuran rings which present a 2,5-*trans* stereochemistry have been of particular interest to many groups as polyether antibiotics and highly biologically active compounds, such as the potent anti cancer Amphidinolide, possess this kind of backbone.

Different methodologies to synthesise this kind of structure have been developped starting in the late 70's. The first efficient methodology was published by Fukuyama in *Tetrahedron Letters* in 1978. It involves the stereospecific epoxidation of bishomoallylic alcohol using $VO(acac)_2$. Treatment of the epoxide with acetic acid led to the desired 2,5-*trans*-tetrahydrofuran in up to 20:1 ratio.

In 1990, Inoki developed an efficient method for the synthesis of *trans*-tetrahydrofurans. Using this methodology, 5-hydroxy-1-alkenes can be converted to the desired cyclisation product *via* oxidative cyclisation with molecular oxygen using cobalt complex as a catalyst. The 5-hydroxy-1-alkene react with the Co complex and the oxygen. The radical complex thus formed could be converted to the cyclised intermediate. The cyclisation occurs in reasonable yields (up to 79 %) and exellent *trans* selectivity (99 %).

More recently Panek published a methodology involving the chelation controlled formation of *trans* tetrahydrofuran. A Lewis acid such as $SnCl_4$ is able to form chelate with a α-benzyloxy group of an aldehyde. This activated intermediate can then undergo the electrophilic substitution. This method led to the *trans* cyclisation product in up to 40:1 ratio.

In order to increase the level of diastereocontrol our group have investigated a methodology based on an intramolecular tandem carbenoid insertion and ylide rearrangement reaction of a diazoketone. This diazoketone undergoes a nucleophilic attack onto an empty d orbital of the transition metal. The transition metal back donates the electrons of one of its d orbital to the carbon to form the metal carbenoid with elimination of nitrogen. Attack of one of the lone pair of the oxygen onto the carbon bonded to the

transition metal led to the formation of the oxonium ylide which undergoes [2,3]-sigmatropic rearrangement. Previous studies made within the group have proved $Cu(acac)_2$ to be the best catalyst for the synthesis of the *trans*-2,5-dialkyl tetrahydrofuran-3-ones. The stereochemistry observed could be explained by the stereochemistry of the substituent R_1. The transition state shows clearly that the *trans*- rearrangement product is favoured.

We have decided to apply this methodology to the synthesis of the (6S, 7S, 9S, 10S)-6,9-epoxynonadec-18-ene-7,10-diol. and the functionalised A-ring fragment of gambieric acid.

Acknowledgements

The work achieved during those three years wouldn't have been possible without the help, support and encouragement of many people.

First of all, I would like to show my gratitutde to my supervisor, Prof. J. Stephen Clark for the opportunity to work in his group on such a challenging project. All his help, advices and support from the initial to the final level, have contributed greatly to the understanding and progress of this project. I am very greatful for leaving the freedom of investigated new synthetic routes. It has been a great source of knowledge for those three years.

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A particular thanks goes to Chris my flatmate, for being here, eating brie with me, and being so funny, you have been such a great moral support. Last but not least, I would like to thank Niall, for his everyday support and patience.

Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently submitted, in candidature for any other degree. Portions of the work described herein have been published elsewhere as listed below.

I also declare that the work presented in this thesis is the result of my own investigations and where the work of other investigators has been used, this has been fully acknowledged in the text.

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Delphine Rabiller

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Prof. J. Stephen Clark

Table of Abbreviations

Ac	Acetyl
acac	acetylacetonate
Ar	aromatic
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
br	broad
brsm	Based on recovered starting material
BTX	brevetoxin
Bu	butyl
Bz	benzoyl
calcd	calculated
cap	caprolactamate
Cat.	catalyst
CSA	Camphorsulfonic acid
CTX	ciguatoxins
d	doublet
DBU	1,8-diaza-bicyclo[5.4.0]undec-7-ene
DCC	dicylcohexylcarbodiimide
DCE	dichloroethane
DEAD	Diethyl azodicarboxylate
DET	Diethyl tartrate
DHP	dihydropyran
DIBAL-H	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess Martin Periodinane
DMPU	*N,N'*-dimethylpropyleneurea
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene

d.r	Diastereomeric ratio
ee	Enantiomeric excess
EPR	Electron paramagnetic resonance
Eq.	Equivalents
Et	Ethyl
Ether	Diethyl ether
H	hour
Hfacac	hexafluoroacetylacetonate
HR-FABMS	High resolution Fast atom bombardment mass spectrometry
HRMS	Highresolution mass spectrometry
IBX	2-iodoxybenzoic acid
Ic_{50}	Median Inhibition Concentration
Ipc	isopinocampheyl
LD_{50}	lethal dose 50%
LDA	lithiumdiisopropylamide
Liq.	Liquid
M	molar
m	multiplet
m-CPBA	m-chloroperbenzoic acid
Me	Methyl
Ms	Methane sulfonyl
MIC	Minimal inhibitory concentration
min	Minutes
ML_n	Metal and associated ligands
MOM	Methoxymethyl
Ms	Methane sulfonyl
MTPA	2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid
NBS	*N*-bromosuccinimide
nOe	Nuclear Overhauser effect
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
petrol	Petroleum ether (40-60°C)
PG – P	Protecting group
pfb	perfluorbutyrate

PGME	phenylglycine methyl ester
Ph	Phenyl
PMB	*p*-methoxybenzyl
PMHS	polymethylhydrosiloxane
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	propyl
q	quartet
RCM	Ring closing metathesis
RT	Room temperature
s	Singlet
SM	Starting material
T	Temperature
t	triplet
TBACl	*tetra*-*n*-butylammonium chloride
TBACN	*tetra*-*n*-butylammonium cyanide
$TBAHSO_4$	*tetra*-*n*-butylammonium hydrogen sulfate
TBAF	*tetra*-*n*-butylammonium fluoride
TBDMS - TBS	*t*-butyldimethyl silyl
TBDPS	*t*-butyldiphenyl silyl
TBHP	*Tert*-butyl hydroperoxide
TEMPO	2,2,6,6-*tetra*-methyl-1-piperidinyloxy
Tf	Trifluoromethane sulfonate
tfacac	Trifluoroacetylacetonate
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylendiamine
TMS	trimethylsilyl
TMSOK	Potassium trimethylsilanolate
tpa	Tris(2-pyridylmethyl)amine
Tr	trityl
X	halogen

Contents

1 Introduction

1.1 Carbenes and carbenoids

1.1.1 Carbene

Definition

Carbenes are neutral species containing a carbon atom with only six valence electrons. Out of these six electrons, four participate to the covalent bonding and two are non-bonding electrons. Carbenes are very reactive species, their existence has been proved by the isolation of a very few stable free carbenes. An example of a free carbene is shown in **Figure 1**, in this case the stability could be explained by electronic and steric effects as well as lone pair donation from the nitrogen.

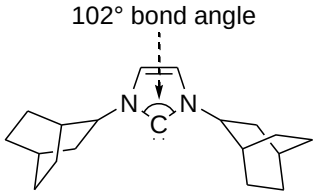


Figure 1: Example of stable carbene

Using spectroscopic analysis, carbenes have been divided into two classes depending on their electronic structure (**Figure 2**). The first class, singlet carbenes, present a bond angle of 100-110°, as determined by spectroscopy (**Figure 2i**). Singlet carbenes possess three orbitals filled with two paired eletrons and one empty orbital. The second class, triplet carbenes, present a bond angle of 130-150° (**Figure 2ii**). They possess a linear geometry with two orbitals filled with paired electrons and two orbitals filled with unpaired electrons. Singlet carbenes can be stabilized by σ-electron withdrawing groups: Π-overlap between the p-orbitals stabilizes the non-bonding orbital, increasing its s character. Triplet carbenes have two unpaired electrons - one in each of a sp^2 and a p orbital - and are paramagnetic. These intermediates can be observed by electron spin resonance spectroscopy (EPR) if they persist long enough. Most carbenes have a non-linear triplet ground state, except for those containing heteroatoms or dihalocarbenes.

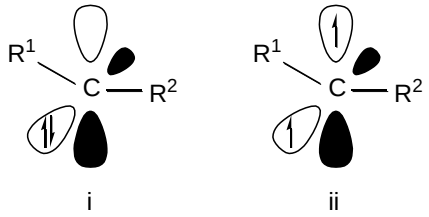
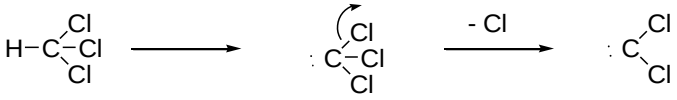


Figure 2: Type of carbenes i) singlet carbene ii) triplet carbene

The nature of the carbene obtained during a chemical reaction depends on both substituents R^1 and R^2 and their method of formation.

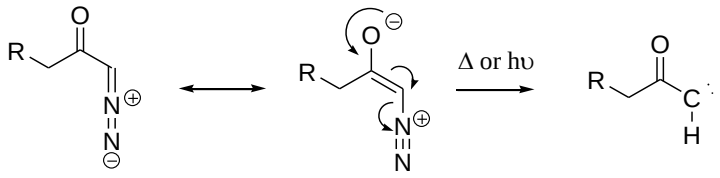
Formation

Carbenes are usually formed by the loss of a stable, small molecule. There are three main reactions for the formation of carbenes; α-elimination, formation from tosylhydrazones and generation from diazo compounds. Carbenes can be formed by α-elimination from trihalomethane, by treatment with a base (hydroxide/alkoxide) followed by loss of a halogen ion (**Scheme 1**). Carbenes can be formed from dihalomethane by deprotonation with stronger bases as LDA and even from primary alkyl chlorides using powerful bases as phenylsodium or $^{t\text{-}}$BuLi/$^{t\text{-}}$BuOK.

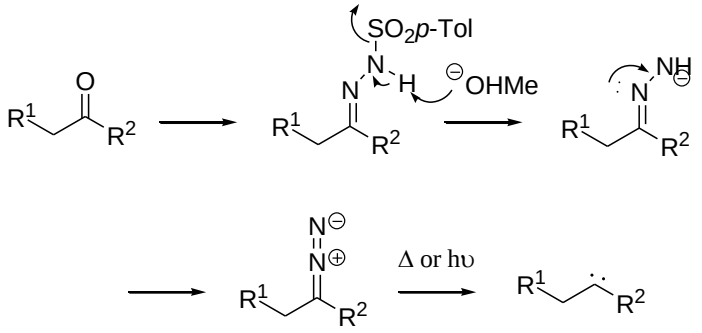


Scheme 1: Carbene formation by α-elimination

Another way to form carbenes is by decomposition of diazocarbonyl compounds using heat or light (**Scheme 2**). The formation of carbenes by diazoalkane decomposition can be performed more safely if the diazoalkane is just an intermediate of the reaction. Useful starting materials for this kind of reaction are tosylhydrazones (**Scheme 3**). In this case the diazoalkane formed is not isolated but is decomposed thermally or photochemicaly to give the carbene.



Scheme 2: Carbene formation by decomposition of diazocarbonyl compounds



Scheme 3: Carbene formation from a tosylhydrazone

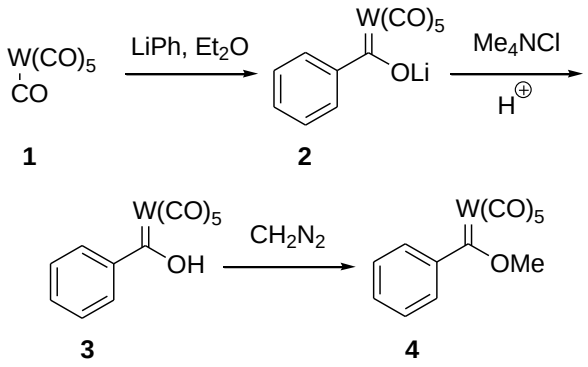
These reactions are very substrate limited due to the high reactivity of carbenes, which means that little functionality is compatible. In order to widen the scope of the reaction, milder conditions have been developed for the formation of carbenes. The use of a transition metal such as copper or rhodium to promote carbene formation *via* diazocarbonyl decomposition is common in modern synthetic chemistry. The carbenes formed this way remain complexed to the transition metal and are called metal carbenoids.

1.1.2 Metal carbenoids

Definition

Carbenoids are reactive intermediates that share characteristics with carbenes. The term carbenoid usually refers to the transition-metal bound carbene formed by metal catalysed decomposition of a diazocompound. In 1964, Fischer reported the first metal-carbene complex: methoxyphenylmethylene tungsten(0). He was followed by Schrock in 1974, who reported the first synthesis of a metal alkylidene complex by α-hydrogen abstraction (**Scheme 4**). [1]

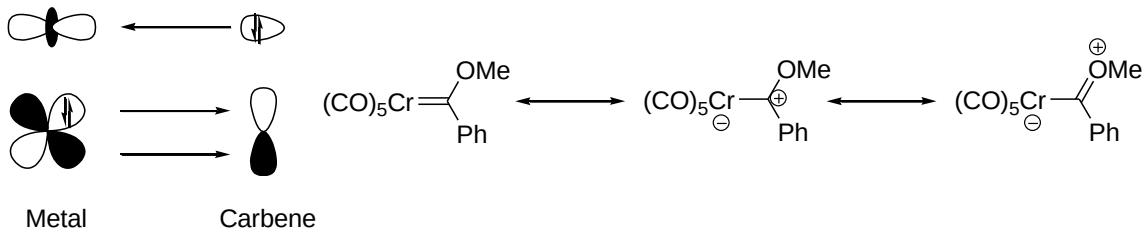
[1] Fischer and Maasboel, *Angew. Chem.* **1964,** 76, (14), 645.; Schrock, *J. Am. Chem. Soc.* **1974,** 96, (21), 6796-7.



Scheme 4: Synthesis of the first recognised metal carbene complex

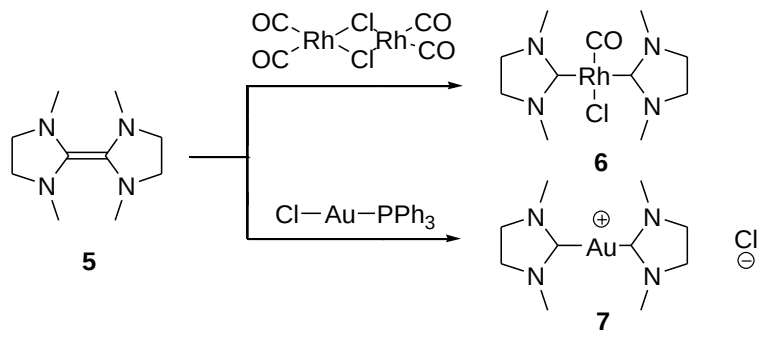
Fischer Carbene

Fischer carbene complexes are heteroatom-containing singlet carbenes. They form a metal-carbon bond by mutual donor-acceptor interactions of two closed shells. The main bonding arises from the carbene-metal σ-donation and simultaneously from the metal-carbene π-back donation (**Scheme 5**).



Scheme 5: Metal-carbene bonding in Fischer carbene complex

One of the most common methods for the synthesis of Fischer carbenes uses enetetramine as a precursor. Enetetramines are eletron-rich alkenes bearing four amino groups. The reaction to form metal-carbenoids is a succession of equilibria relying on the removal by distillation of methanol and diethylamine as a driving force (**Scheme 6**).[2]

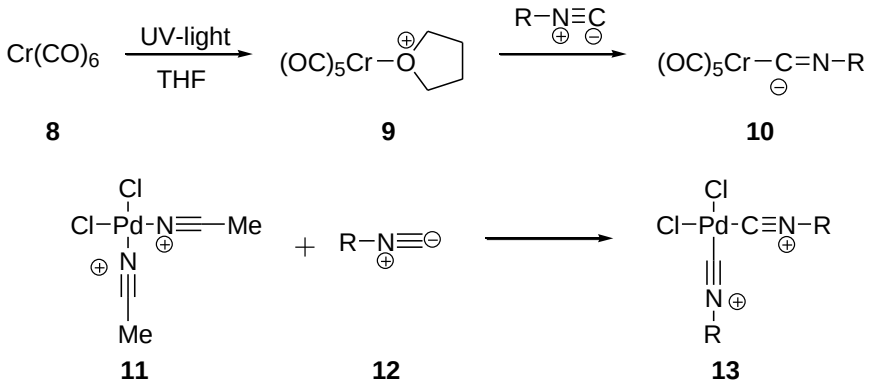


Scheme 6: Carbene-metal complex derived from enetetramines

[2] Winberg, Carnahan, Coffman and Brown, *J. Am. Chem. Soc.* **1965,** 87, (9), 2055-6.

The C=C bond of the enetetramines reacts with electrophilics or protic reagents to give the corresponding aminal. The mechanism of the formation of the metal carbene bond is still to be described, but it is assumed that the C=C bond is not cleaved and the complex is formed by chelation with both amino groups.

Fischer-type metal-carbene complexes can also be formed from isocyanide-metal complexes. Isocyanide compounds are strong bases which can be either polymerised or hydrolysed under acidic conditions, but they can be strongly stabilized by coordination to a metal. Although their use is limited due to their notoriously bad smell, isocyanides can react with metal salts or metal-carbonyl compounds to form the corresponding isocyanide-metal complexes (**Scheme 7**).[3]



Scheme 7: Synthesis of isocyanide-metal complexes

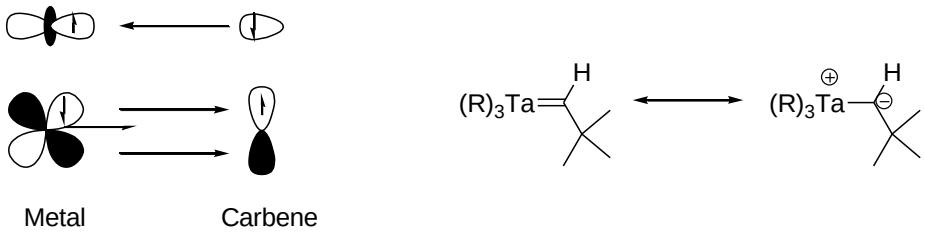
Depending on the Lewis acidity of the metal centre, isocyanide metal complexes can react by nucleophilic attack to yield an aminocarbene-metal complex. Fehlhammer et al. have reported the formation of alkyl-isocyanides in which the nucleophile and the isocyanide were linked prior to the coordination with the metal centre. These ligands, when suitably activated, are also precursor of oxazolinylidenes, triazolidenes, imidazolidenes, by spontaneous cyclisation. Many of the carbenes formed using isocyanide-metal complexes as precursors are difficult to isolate.

These are two of the methods which can be used for the formation of Fischer carbenoid complexes. Many other methods exist such as the use of diazirines and Vilsmeier salts. However, there are other carbenes which are also commonly seen in carbenoid chemistry and present different properties. These carbenoids are called Schrock carbenes.

[3] Hahn, Langenhahn, Meier, Lugger and Fehlhammer, *Chem.--Eur. J.* **2003,** 9, (3), 704-12.

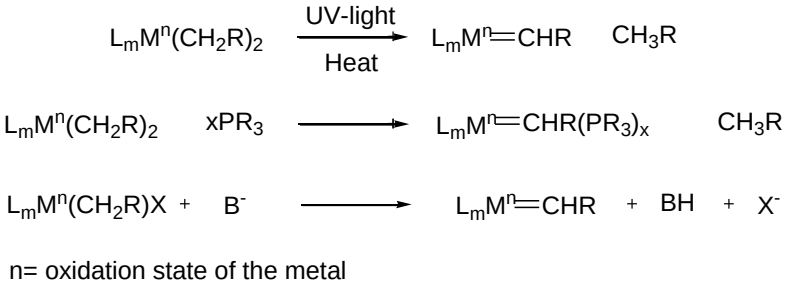
Schrock Carbene Formation

In contrast to Fischer carbenes, Schrock carbene complexes are poorly stabilized. The carbon-metal bond formed in these complexes is covalent. The covalent nature of this bond comes from the coupling of two triplet fragments (**Scheme 8**). The π electrons are nearly equally distributed between the carbon atom and the metal centre and there is effectively a double bond between the metal centre and the carbon atom.



Scheme 8: Metal-carbone bonding in Schrock carbene complexes

Schrock metal-carbenes are accessible through various routes using cyclopropenes, phosphiranes *etc* as precursors. Amongst these routes, two are most frequently used. In the first one, metal alkyl complexes are employed as precursors. These precursors are easily available through reaction of metal halides with alkyl lithium or Grignard reagents. The formation of the carbenoid requires the generation of a thermodynamically and kinetically favoured leaving group (**Scheme 9**).[4] The reaction can be promoted thermally, photochemically, sterically or using a base.

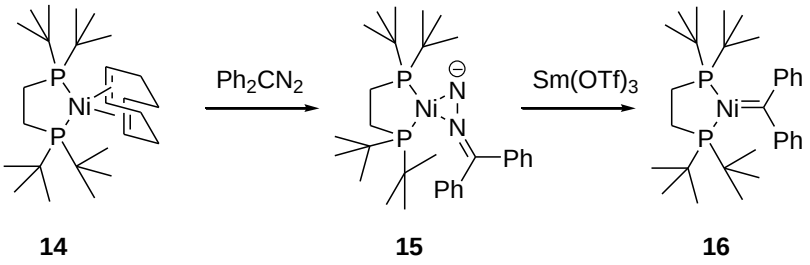


Scheme 9: Formation of alkylidene complexes *via* α-hydrogen elimination

The decomposition of diazo compounds is another popular method for the formation of metal-carbenoids. In 1906, it was found that copper bronze and copper(II) complexes were the best catalysts to promote the decomposition of diazo compounds.

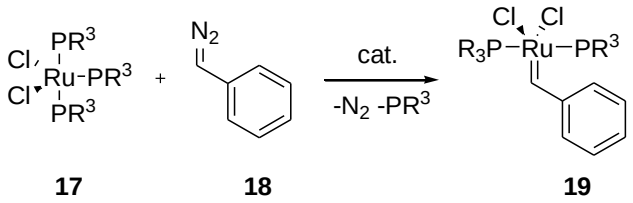
[4] Van Asselt, Burger, Gibson and Bercaw, *J. Am. Chem. Soc.* **1986,** 108, (17), 5347-9, Mindiola Daniel, *Acc Chem Res* **2006,** 39, (11), 813-21.

Increasing interest in this area showed that phosphite, copper(II) acetylacetonate and rhodium(II) carboxylate complexes were usually the best catalysts.[5] The reaction proceeds *via* the formation of a diazo-metal intermediate.[6] Intermediate **15** for example decomposes slowly when heated, but nitrogen elimination occurs more efficiently upon treatment with anhydrous $Sm(OTf)_3$ resulting in the formation of the diphenylcarbene (**Scheme 10**).



Scheme 10: Diazo-decomposition

Most of the carbenes formed by diazo-decomposition are further used as precursors for organic transformations *via* carbene transfer reactions such as cyclopropanation of alkenes or alkynes, cycloaddition to aromatic rings, ylide or ketene formation as well as insertion reactions. They are generally highly reactive species but are sufficiently stabilized by metal binding not to undergo carbene dimerization (**Scheme 11**).



Scheme 11: Synthesis of carbenoids using diazo compounds

Diazoalkanes react also with metal-metal multiple bonds to form metal-diazo intermediates which thermally or photochemically decompose *via* loss of nitrogen to form metal-carbene complexes. The use of transition metals such as rhodium(II) carboxylates showed they were efficient catalysts for the decomposition of diazocarbonyl compounds. The metallocarbenoid product of this reaction is highly reactive and can readily react with an available heteroatom to effect ylide formation.

[5] Nozaki, Moriuti, Yamabe and Noyori, *Tetrahedron Lett.* **1966**, (1), 59-63. Moser, *J. Amer. Chem. Soc.* **1969,** 91, (5), 1141-6, Moser, *J. Amer. Chem. Soc.* **1969,** 91, (5), 1135-40.
[6] Kirmse, *Angew. Chem., Int. Ed.* **2003,** 42, (10), 1088-93.

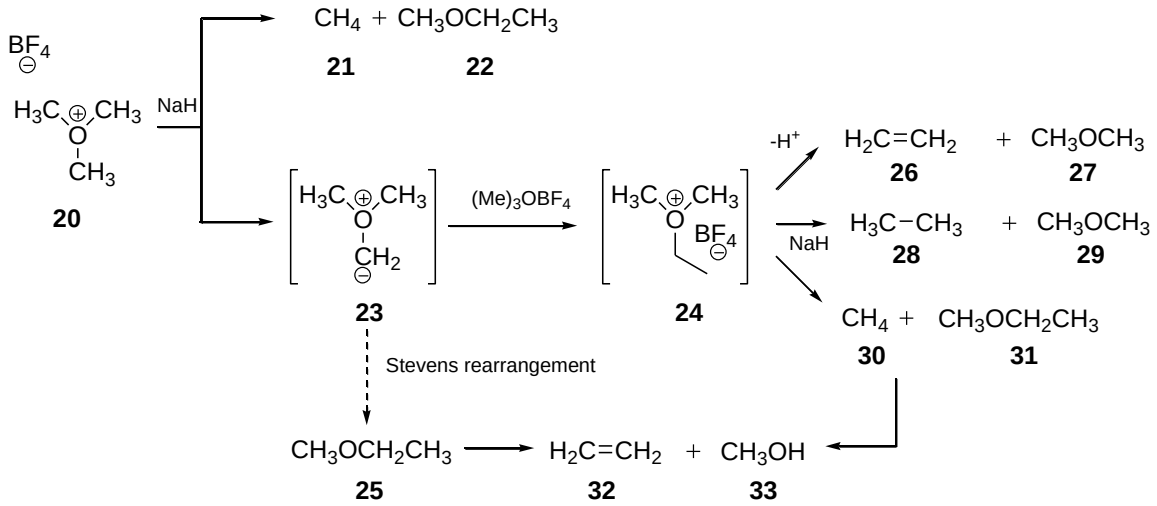
1.1.3 Oxonium ylides

Definition

Ylides are species in which a positively charged heteroatom is connected to a carbon atom possessing an unshared pair of electrons. These highly reactive compounds, which are highly unstable, are widely used as key intermediates in a variety of simple and complex transformations. The intermediacy of oxonium ylides has been shown or invoked in a number of reactions such as deprotonation of oxonium salts in the intermolecular trapping reaction of carbenes and in the production of ethylene from methanol using zeolites. Singlet carbenes can be used as Lewis acids for the formation of ylides by interacting with a pair of non-bonding electrons contributed by a Lewis base. If the Lewis base is an uncharged species, such an acid-base interaction leads to an ylide.

Formation

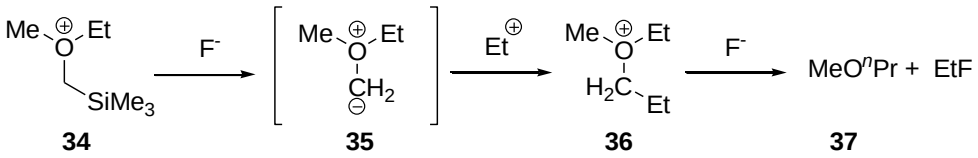
There are several approaches to the generation of oxonium ylides. The first route involves the deprotonation or desilylation of the corresponding oxonium ion. In 1984, Olah *et al.* were amongst the first to investigate the formation of oxonium ylides by the deprotonation of a trimethyloxonium salt with sodium hydride and by desilylation of dialkyl[(trimethylsilyl)methyl]oxonium ions (**Scheme 12**).[7]



Scheme 12: Oxonium formation by deprotonation of trimethyloxonium ion

[7] Olah, Doggweiler and Felberg, *J. Org. Chem.* **1984,** 49, (12), 2112-16.

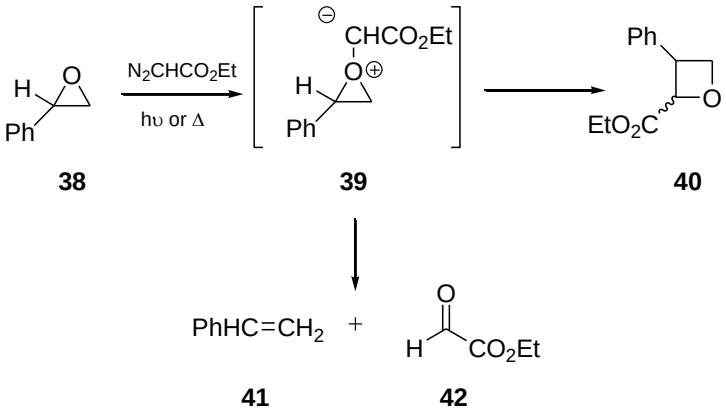
Upon treatment of trimethyloxonium salt **20** with sodium hydride, the deprotonation of the oxonium ion is in competition with the methylation of the hydride. When the trimethyloxonium salt is deprotonated, the resulting methylene(dimethyl) oxonium ylide **23** is methylated by the excess of trimethyloxonium ion to afford the dimethyloxonium ion **24**. In the same paper, Olah described a second approach to oxonium ylide formation which involves the desilylation of dialkyl[(trimethylsilyl)methyl]oxonium ion (**Scheme 13**).



Scheme 13: oxonium formation by desilylation of oxonium ion

This example proved the formation of the final product by oxonium ylide formation and rearrangement. Indeed, whereas the previous formation of ethylene could be explained by either ylide formation or the β-hydride elimination, the formation of MeO-^{n}Pr must be due to the ethylation of the intermediate ylide and subsequent cleavage of the oxonium ion.

Oxonium ylides can also arise from thermally or photochemically generated carbenes. One of the first examples of thermal or photochemical formation of an oxonium ylide was reported by Nozaki in 1965.[8] The oxonium ylide formed by the reaction of carboethoxycarbene with 2-phenyloxirane not only involved deoxygenation but also gave the product resulting from one-carbon ring expansion *via* insertion (**Scheme 14**).

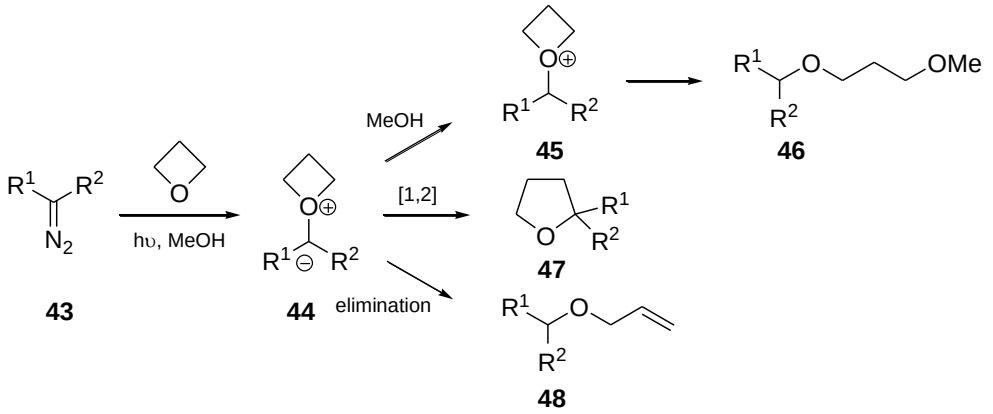


Scheme 14: Oxonium ylide formation by thermal reaction of carbene

In this case, the oxonium ylide is formed by electrophilic attack of the singlet carbene on a lone pair of the oxygen atom of the 2-phenyloxirane **38**. The unstable

[8] Nosaki, Tayaka and Noyari, *Tetrahedron Lett.* **1965**, (30), 2563-7.

intermediate **39** then decomposes to form styrene and ethylglycoxylate or undergoes an isomerization reaction to give a *cis*- *trans*- mixture of the ring-expanded Stevens rearrangement product **40**. Subsequently, Kirmse demonstrated that the reaction of oxetane with a carbene gave the tetrahydrofuran product resulting from a [1,2]-shift (**Table 1**).[9]

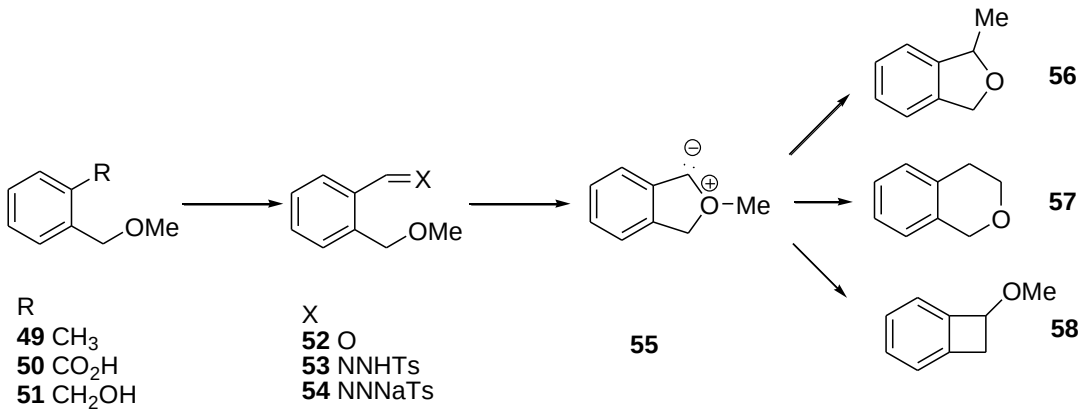


Carbene	Oxetane -> Methanol		Ylide	Carbene
	(**47**+**48**)/**44**	(**47**+**48**+**46**)/**44**	protonation	protonation
:CPh_2	2.4 -> 6	2.4 -> 76	-	++
fluorenylidene	3.7 -> 5.4	3.7 -> 7.8	-	(+)
:CHPh	9.3 -> 4.4	9.3 -> 12	(+)	(+)
:$CHCO_2Et$	4.7 -> 1.0	4.7 -> 3.8	+	-
:$C(CO_2Me)_2$	4.4 -> 0.15	4.4 -> 4.0	+	-

Table 1: Selectivity in the rearrangement of carbenes

A considerable amount of product **46** was observed in some cases. This product arises from the protonation of the oxonium ylide when the reaction is carried out in methanol. The other secondary products obtained came from C-H insertion at positions adjacent to the ether oxygen. In 1989, Krimse reported intramolecular generation of oxonium ylides from functionalised arylcarbenes.[10] The reactive intermediate was generated by thermolysis or photolysis of a diazo compound. Competitive C-H insertion reaction and β-elimination reactions were also observed (**Scheme 15**).

[9] Kirmse, Lelgemann and Friedrich, *Chem. Ber.* **1991,** 124, (8), 1853-63.
[10] Kirmse and Kund, *J. Am. Chem. Soc.* **1989,** 111, (4), 1465-73.



Scheme 15: Intramolecular oxonium ylide formation

conditions	Product distribution %			
	56	**57**	**58**	Other
54, 285ºC, (10^{-3} mmHg)		22.1	63.5	
54, hυ, diglyme	10.2	21.0	52.4	
53, hυ, MeOH	15.7	1.0	2.4	**49** 2.3
53, hυ, EtOH	28.5	1.8	3.1	**49** 2.5
53, hυ, ^{t}BuOH	42.5	4.0	5.8	**49** 0.3

When diglyme was used as a solvent to carry out the reaction, only C-H and C-O insertion products **57** and **58** were observed. However, flash pyrolysis conditions afforded the C-O insertion product with greater selectivity than the photolysis conditions. Changing the solvent from diglyme to methanol led to the formation of **56** predominantly while only trace amounts of the C-H and C-O insertion products were observed. It is interesting that a very small amount of the protonated product was observed when the reaction was carried out in protic solvent.

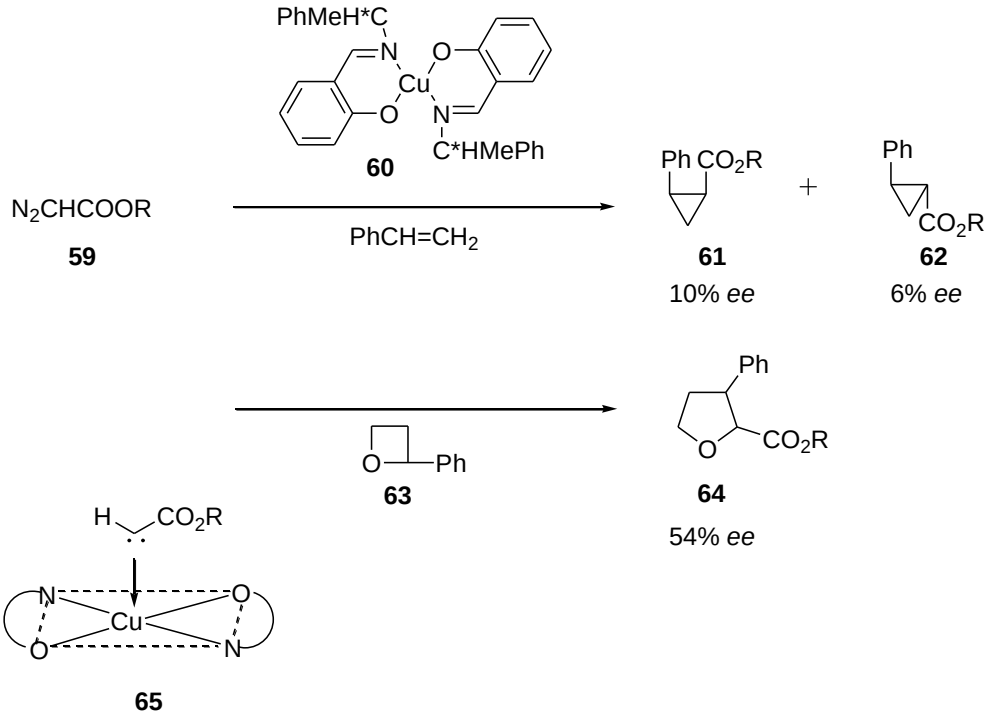
In the same publication Krimse described the influence of the ring size on the rearrangement product isolated. Adding another CH_2 at the position adjacent to the methoxy group gave very a small amount of the four- and seven-membered cyclic-Stevens rearrangement products, the major product being the five-membered cyclic C-H insertion product.

Further investigation of Nozaki's thermal decomposition of diazo compounds has shown the crucial influence of a metal catalyst.[11] Access to novel oxonium ylide intermediates was of major importance when attempting to prepare products with larger ring sizes for organic synthesis. In this report, it was shown that the presence of a copper catalyst during the thermal decomposition of the carbene allowed a considerable increase in the amount of the Stevens ring-expansion product formed. Although some mechanistic investigations are still ongoing, reaction of a diazocarbonyl compound with a metal

[11] Nozaki, Takaya, Moriuti and Noyori, *Tetrahedron* **1968,** 24, (9), 3655-69.

catalyst has been shown to involve an oxonium ylide intermediate. The generation of an oxonium ylide by the catalytic decomposition of a metal carbenoid is now one of the most frequently used processes for oxonium ylide formation.

In 1966, Nozaki reported the decomposition of a diazoalkane in the presence of a copper catalyst.[12] Upon reaction of ethyldiazoacetate with 2-phenyloxetane, he obtained a *cis*/*trans* mixture of the ring-enlarged tetrahydrofuran products (**Scheme 16**).

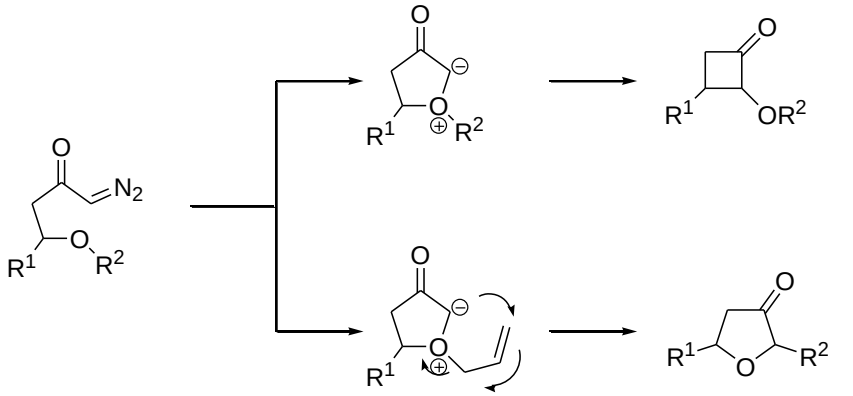


Scheme 16: Catalytic decomposition of diazocarbonyl compound in the presence of styrene or 2-phenyloxetane

In the absence of the catalyst **60**, no reaction was observed between the substrate and the diazocarbonyl compound. It was therefore assumed that a reasonable explanation for the asymmetric reaction is the formation of a reactive complex where the carbene is bonded to the original chelate complex **65**.

The conclusions of Nozaki were validated by a number of other groups a few years later when it was demonstrated that copper or rhodium catalysed reactions of diazoketones often lead to the formation of the Steven's rearrangement product or a [2,3]-sigmatropic shift product. In 1986, Johnson published a paper where the results were in accordance with such a mechanism involving metal carbenoid formation followed by oxonium ylide rearrangement.[13] Upon treatment of a range of diazoketones with rhodium(II) acetate, two main products were observed: the [2,3] product and the [1,2]-shift product (**Table 2**).

[12] Nozaki, Moriuti, Takaya and Noyori, *Tetrahedron Lett.* **1966**, (43), 5239-44.
[13] Roskamp and Johnson, *J. Am. Chem. Soc.* **1986,** 108, (19), 6062-3.



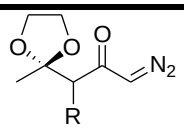
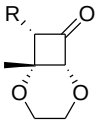
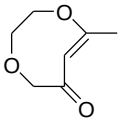
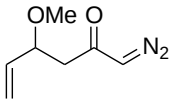
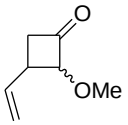
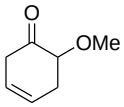
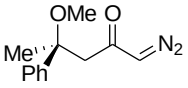
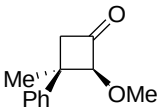
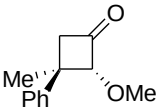
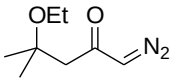
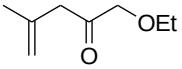
Substrate	Product (yield %)	
 **66**: R = H **67**: R = CH_3	 **68**: 68% **69**: 54%	 **70**: 16%
 **71**	 **72**: 45%	 **73**:10%
 **74**	 **75**: 57%	 **76**: 17%
 **77**	 **78** 70%	

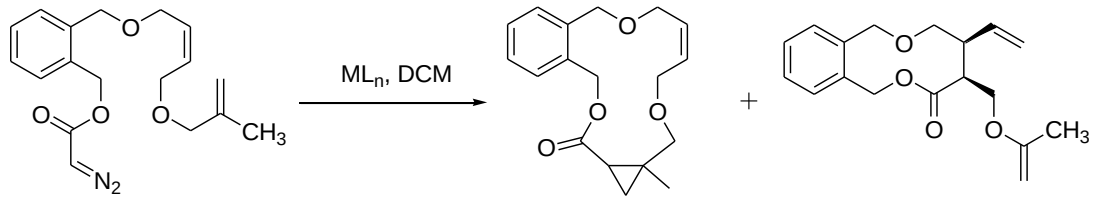
Table 2: Catalytic decomposition of diazoketone

The results above show that the rearrangement of an oxonium ylide resulting from the decomposition of a diazoketone favours the formation of the four-membered ring product arising from a [1,2]-shift. When possible, as shown with substrate **71**, a [2,3]-sigmatropic rearrangement product is formed but as a minor one when a rhodium catalyst is used. All these products result from the rearrangement of an oxonium ylide which supports the conclusion of Nozaki. However, unlike the case for other ylides, such as sulfonium ylides, no stable free oxonium ylide has yet been isolated. The absence of p_π-d_π orbital interactions makes oxonium ylides highly reactive intermediates which can rapidly undergo Stevens rearrangement or a [2,3]-sigmatropic shift.

Rearrangement of metal carbenoids

Cyclopropanation reactions

The metal-catalysed cyclopropanation of alkenes using diazo compounds as a carbene source is one of the most widely used procedures. Doyle is amongst those who have had a particular interest in accessing such cyclopropanes in an asymmetric manner. In 1997, he reported that depending on the catalyst used for the formation of the carbenoid, major amounts of the cyclopropanation product could be isolated.[14] In this paper he showed there is competition between the formation of the cyclopropanation product **80** and of the [2,3]-sigmatropic rearangement product **81** depending on the copper or rhodium catalyst used for decomposition of the diazo compound **79** (**Table 3**).



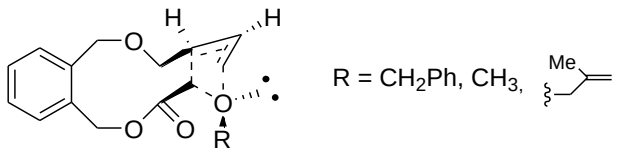
79 **80** **81**

ML_n	Yield %	Cyclopropanation %	[2,3]
$Rh_2(pfb)_4$	68	53	47
$Rh_2(OAc)_4$	71	94	6
$Rh_2(cap)_4$	65	>99	<1
$Cu(MeCN)_4PF_6$	70	84	16

Table 3: Influence of the catayst for the cyclopropanation reaction

As shown in this table, the use of a dirhodium catalyst leads preferentially to the formation of the cyclopropanation product **80** rather than the [2,3]-sigmatropic shift product **81**. The formation of the cyclopropane **80** is highly selective when $Rh_2(cap)_4$ is used. The ylide rearragement reaction is assumed to occur *via* intermediate **82** (**Scheme 17**).

[14] Doyle and Peterson, *Tetrahedron Lett.* **1997,** 38, (30), 5265-68.



82

Scheme 17: Cyclopropanation reaction intermediate

In 2000, Doyle focused his investigation on the stereoselective formation of highly substituted cyclopropanes using the catalytic decomposition of diazo compounds.[15] As a consequence of the broad generality of cyclopropanation reactions, it became crucial to be able to perform the reaction in a stereoselective manner. The goal of this investigation was to be able to understand the influence of ring size on selectivity as a function of catalyst. The results obtained for intramolecular cyclopropanation of allylic ethers showed that there is a large preference for the formation of the *trans*-cyclopropane isomer when a copper or rhodium(II) carboxylate were used as catalyst. On the other hand, the *cis*-isomer was formed preferentially if a rhodium(II) carboxamidate was employed as a catalyst. These results and especially the differences observed in *ee* values are explained by the rotational preferences of the alkene about the carbene.

Although alkene cyclopropanation is a useful reaction, particularly for the formation of macrocycles as described previously, two reactions occurring by metal carbenoid formation followed by oxonium ylide rearrangement have been more widely investigated: [1,2]-Stevens shift and [2,3]-sigmatropic rearrangement.

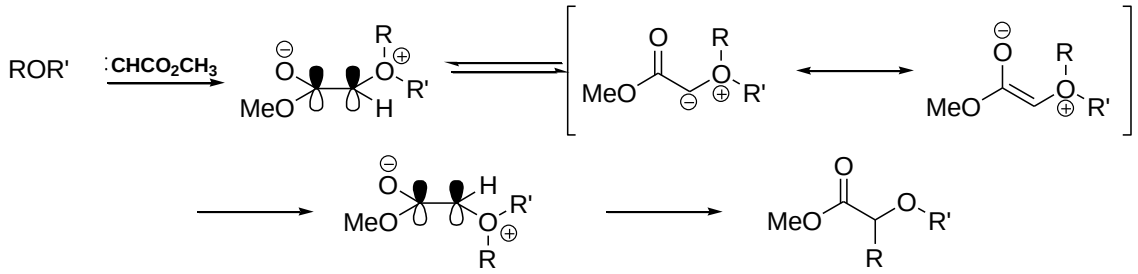
Stevens rearrangement

The reaction of electophilic (methoxycarbonyl)carbene with ethers is characterised by two kinds of reaction:

- insertion into C-O bond
- displacement of one of the alkyl groups

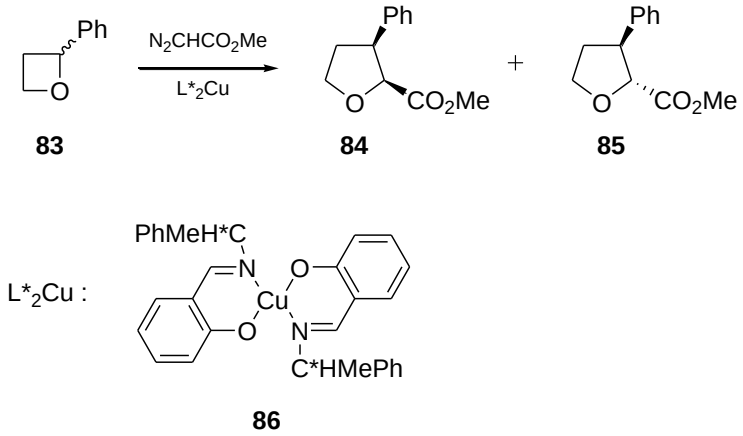
The Stevens rearrangement involves the [1,2]-migration of one of the groups on the oxygen atom. The carbene undergoes nucleophilic attack by the lone pair of a heteroatom to form the oxonium ylide. This can then react by a [1,2]-shift mechanism to form the rearrangement product (**Scheme 18**).

[15] Doyle and Hu, *J. Org. Chem.* **2000,** 65, (26), 8839-47.



Scheme 18: Stevens rearrangement of an oxonium ylide

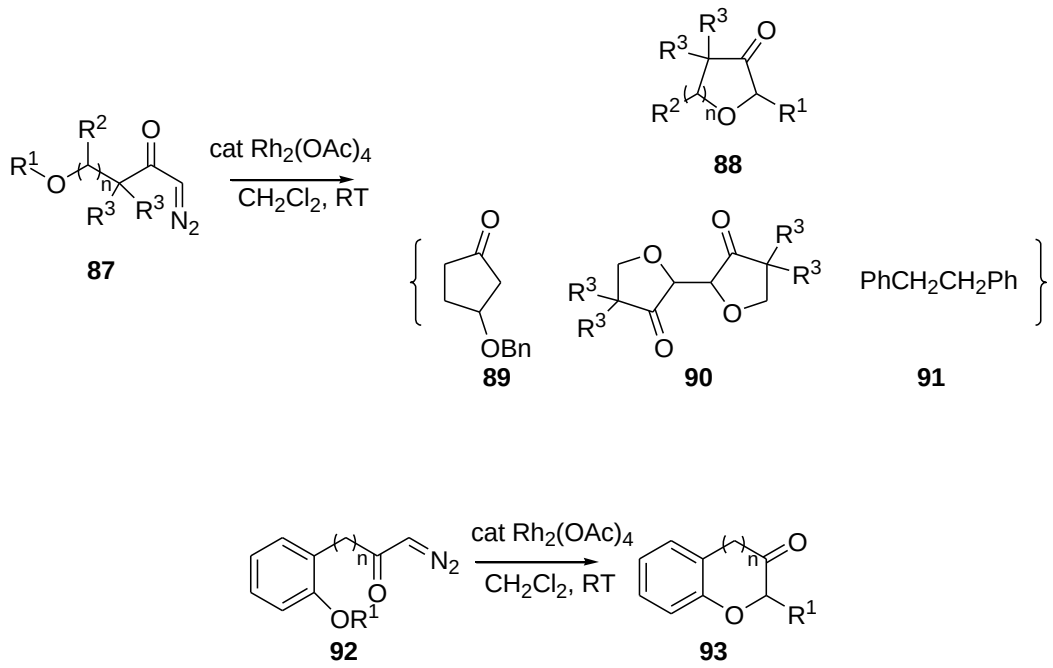
If the rearrangement reaction occurs *via* a concerted mechanism, it is a symmetry-forbidden process according to the *Woodward-Hoffmann* rules. In 1968, Nozaki *et al.* described the preparation of tetrahydrofuran derivatives **84** and **85** from the oxetane **83** by the Stevens rearrangement of oxonium ylides in presence of the chiral copper complex **86** (**Scheme 19**).[16]



Scheme 19: Asymmetric Stevens rearrangement

When the complex used for carbenoid generation wasn't optically active, the diastereomeric products **84** and **85** were obtained as a mixture whereas the use of the chiral copper catalyst led to the formation of optically active 3-phenyltetrahydrofuran-2-carboxylate. This result is consistent with formation of a copper carbenoid intermediate during the reaction. The presence of by-products formed during the reaction arising from cyclopropanation or [2,3]-sigmatropic rearrangement has limited the application of this methodology. In 1992, West reported the results of the application of a rhodium(II) acetate catalysed reaction to form cyclic oxonium ylides.[17] In this report, he demonstrated that the formation of secondary products can be limited under optimum steric and catalytic conditions (**Table 4**).

[16] Nozaki, Takaya, Moriuti and Noyori, *Tetrahedron* **1968,** 24, (9), 3655-69.
[17] Eberlein, West and Tester, *J. Org. Chem.* **1992,** 57, (12), 3479-82.



Entry	Reaction	R^1	R^2	R^3	n	[1,2] (%)	Side product
1	1	Bn	H	H	1	64	**90** (27%), **91** (16%)
2	1	Bn	H	Me	1	65	**90** (17%), **91** (16%)
3	1	Bn	H	H	2	16	**89** (47%)
4	1	Bn	Me	H	1	53	**91** (11%)
5	1	$PhCOCH_2$	H	Me	1	17	-
6	2	Bn	N/A	N/A	0	70	-
7	2	Bn	N/A	N/A	1	67	-

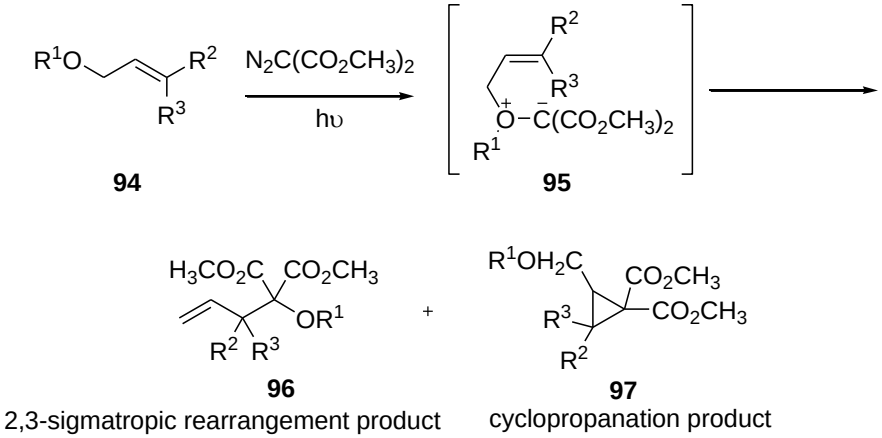
Table 4: Optimisation of the reaction conditions

The results obtained in this table indicate that the C-H insertion reaction is competitive only when the formation of the five-membered ring product *via* C-H insertion is in competition with the formation of a six-membered cyclic oxonium ylide (**Entry 3**). The observation of the formation of the bis(tetrahydrofuran) products is consistent with the accepted mechanism of the Stevens rearrangement where the solvent interacts with a radical-like intermediate. If some of this intermediate escapes from the solvent cage, it can easily dimerise.

The high degree of selectivity as well as the yields obtained following oxonium ylide formation and subsequent Stevens rearrangement, have made this reaction a useful tool in organic synthesis. The high degree of functional group tolerance has proven to be useful for the application of the [1,2]-shift reaction to the total synthesis of natural products.

2,3-Sigmatropic shift

A major reaction of allyl-substituted oxonium ylides is [2,3]-sigmatropic rearrangement. This rearrangement reaction can be defined as a thermal isomerization that occurs through a six-electron, five-membered cyclic transition state. The first example of a [2,3]-sigmatropic rearrangement of an oxonium ylide was reported in 1972.[18] Irradiation of dimethyl diazomalonate and various allylic ethers resulted in the formation of an unexpected product arising from the [2,3]-sigmatropic shift of an oxonium ylide (**Scheme 20**).

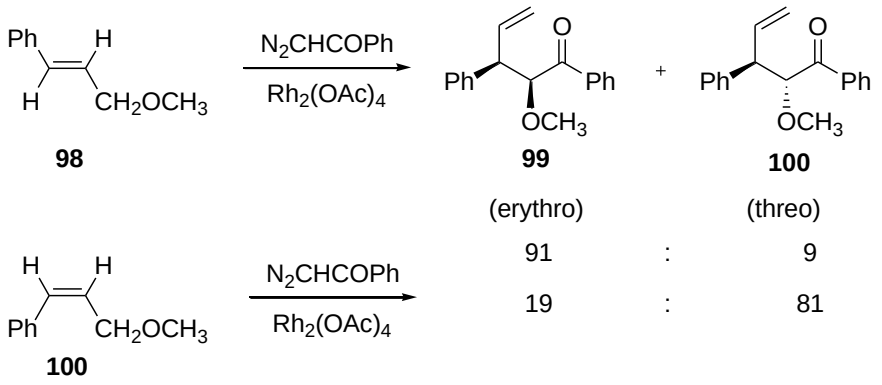


Scheme 20: [2,3]-Sigmatropic rearrangement of an oxonium ylide

It was shown that steric hinderance near the allyl group favours oxonium ylide formation whereas steric bulk around the oxygen atom favours formation of the cyclopropanation product.

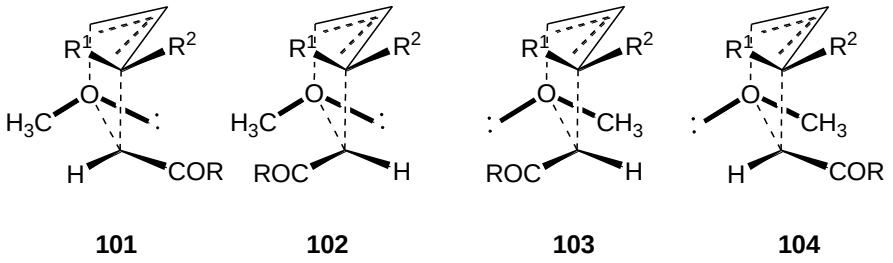
Studies concerning the mechanism of this reaction were performed by Doyle who showed that decomposition of a diazocarbonyl compound catalyzed by rhodium(II) acetate gave an oxonium ylide which would undergo a 2,3-sigmatropic rearrangement with a high degree of stereoselectivity.[19] Examples of the rearrangement of both *cis*- and *trans*-cinnamyl methyl ether showed that the stereochemistry of the 2,3-rearrangement product was dependent on the starting material when the reaction was catalyzed by rhodium(II) acetate (**Scheme 21**).

[18] Ando, Kondo, Nakayama, Ichibori, Kohoda, Yamato, Imai, Nakaido and Migita, *J. Amer. Chem. Soc.* **1972,** 94, (11), 3870-6.
[19] Doyle, Bagheri and Harn, *Tetrahedron Lett.* **1988,** 29, (40), 5119-22.



Scheme 21: Rhodium catalyzed stereoselective [2,3]-sigmatropic rearragement of oxonium ylides derived from cinnamyl methyl ether

The stereochemical outcome of the rearrangement reaction can be explained by analysis of the possible transition states. The transition states **102** and **104** are higher in energy than **101** and **103** (**Scheme 22**). The eclipsing interactions between the methyl group and the COR group are unfavorable, and so rearrangement will occur preferentially *via* the transition state **101** and/or **103**.



Scheme 22: Transition state in [2,3]-sigmatropic rearrangement of cinnamyl methyl ether

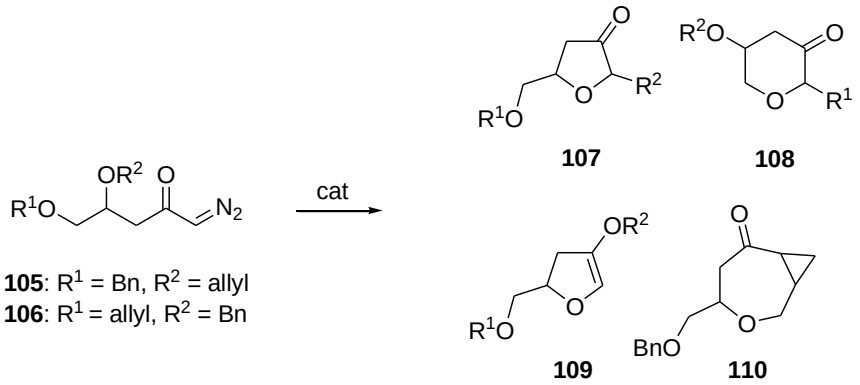
The fact that other rhodium catalysts gave the same stereoselectivity suggests that the rearrangement occurs *via* the free ylide rather than a metal coordinated intermediate in these cases.

Selectivity of the diazoketone decomposition

West has studied the reaction of substrates containing two ether groups which can react with the carbenoid intramolecularly leading to oxonium ylides intermediates with different ring sizes.[20] The diazoketones were subjected to carbene transfer using rhodium and copper catalysts to investigate whether the formation of a five- or six- membered ring would be favoured under specific catalytic conditions. Bis(benzyl) ethers **105** and **106**

[20] Marmsaeter, Vanecko and West, *Org. Lett.* **2004,** 6, (10), 1657-60.

were treated with a wide range of rhodium and copper based catalysts to observe whether the various rearrangement products could be obtained selectively (**Table 5**).



entry	Substrate	Catalyst/ conditions	Yield **107** (%)	Yield **108** (%)	Other products
1	**105**	$Cu(tfacac)_2$/40ºC	96		
2	**105**	$Cu(hfacac)_2$/40ºC	71		
3	**105**	$Rh_2(OAc)_4$/RT	96		
4	**105**	$Rh_2(tpa)_4$/RT	51		**110** (12%)
5	**105**	$Rh_2(tpa)_4$/40ºC	54		**110** (20%)
6	**106**	$Cu(tfacac)_2$/40ºC	16	67	**109** (12%)
7	**106**	$Cu(hfacac)_2$/40ºC	38	29	**109** (19%)
8	**106**	$Rh_2(OAc)_4$/RT	50	27	
9	**106**	$Rh_2(tpa)_4$/RT	54	22	
10	**106**	$Rh_2(tpa)_4$/40ºC	56	18	

Table 5: Catalyst influence on the ring size of the product

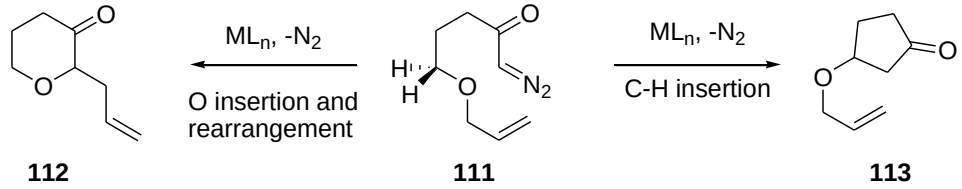
Treatment of **105** with both rhodium and copper catalysts afforded the rearrangement product **107** in good to excellent yield as a mixture of *cis*- and *trans*-diastereomers. This result can be explained by the easier migration of the allyl group *via* a five-membered cyclic ylide to give the [2,3]-shift product. The [1,2]-shift product would involve the six-membered cyclic ylide *via* benzyl migration which is more difficult.

The decomposition reaction of substrate **106** is less selective. Indeed the kinetic reaction would favor the five-membered cyclic ylide intermediate whereas migratory group preferences would give the product derived from the six-membered ylide preferentially. This is shown in **Table 5** (**Entries 6 to 10**) where the catalyst used for the decomposition reaction gives a clear selectivity for the formation of the [1,2]- or [2,3]-shift product.

The need for stereoselectivity during the reaction of carbenoids generated by diazoketone decomposition reaction has resulted in an increasing interest in the

development of a highly selective catalytic process. Recent investigations have shown that the decomposition of a diazoketone can be selective for the rearrangement product formed and can also be stereoselective.[21]

The efficiency of different catalysts as well as the competition between the C-H insertion and 2,3-rearrangement has been studied with regard to the synthesis of 6- to 8-membered cyclic ethers.[22] The rearrangement of precursor **111** was investigated to check the influence of the catalyst on the formation of C-H insertion or 2,3-sigmatropic rearrangement products (**Scheme 23**). Indeed, for the formation of cyclic ethers with ring sizes greater than five, the insertion of a rhodium-carbenoid into a C-H bonds is preferred over reaction with the ether oxygen.



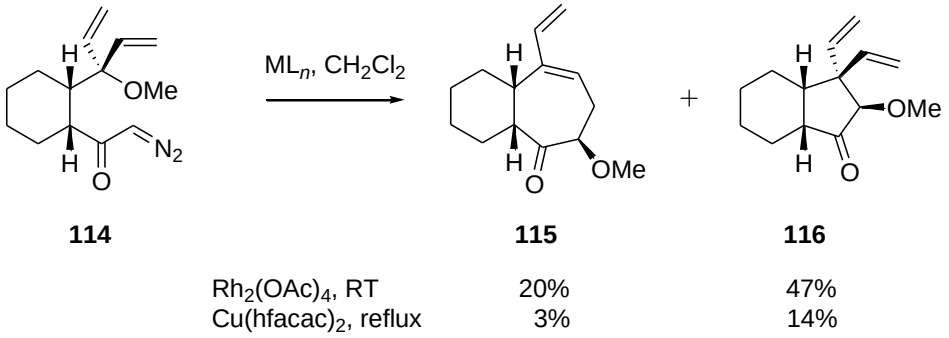
Scheme 23: Competition of C-H insertion and 2,3-rearrangement

The activity of four catalysts under various solvent conditions was investigated. The reaction catalysed by rhodium(II) acetate afforded the tetrahydropyran **112** in modest yield and a significant amount of the C-H insertion product **113** was observed. However, the ratio of the two products was increased in favour of the [2,3]-sigmatropic rearrangement product when the reaction temperature was increased and THF was used as a solvent. In contrast, when a copper catalyst was used, none or a modest amount of the C-H insertion product was obtained. The optimum catalyst was found to be Cu(hfacac)$_2$ and when this complex was used, the desired tetrahydropyran product was obtained in 83% yield with no formation of the C-H insertion product.

In the case of stereoselective rearrangements, it has been demonstrated that both the choice of the catalyst and the relative configuration of the stereogenic centres of the rearrangement precursor are crucial to the stereochemical outcome of the reaction.[23] The formation of secondary products arising from competitive alkene cyclopropanation or Stevens [1,2]-shift of the ylide are also catalyst dependant. The oxonium ylide

[21] Muthusamy, Babu and Gunanathan, *Tetrahedron Lett.* **2002,** 43, (34), 5981-84, Maguire, Buckley, O'Leary and Ferguson, *J. Chem. Soc., Perkin Trans. 1* **1998**, (24), 4077-92.
[22] Clark, Guerot, Wilson and Blake, *Chem. Commun. (Cambridge, U. K.)* **2007**, (40), 4134-36, Clark, Krowiak and Street, *Tetrahedron Lett.* **1993,** 34, (27), 4385-8.
[23] Clark, Guerot, Wilson and Blake, *Chem. Commun. (Cambridge, U. K.)* **2007**, (40), 4134-36, Clark, Walls, Wilson, East and Drysdale, *Eur. J. Org. Chem.* **2006**, (2), 323-27.

rearrangement reaction can also be used to prepare carbocycles in cases where the alkene is tethered to the diazoketone through C rather than O (**Scheme 24**).



114 **115** **116**

$Rh_2(OAc)_4$, RT	20%	47%
$Cu(hfacac)_2$, reflux	3%	14%

Scheme 24: Influence of the catalyst on the products of the rearrangement reaction

In these reactions, the outcome is also heavily catalyst dependant. For example, the rearrangement of the *cis*-cyclohexane substrate **114** yielded two different products: ketone **115** arising from the [2,3]-sigmatropic rearrangement reaction and cyclopentenone **116** product of [1,2]-rearrangement. In this example, the influence of the catalyst is significant. The use of rhodium(II) acetate yielded the [1,2]-rearrangement product as the major product. When copper hexafluoroacetylacetonate was used as a catalyst, the yields of both products dropped dramatically. Further investigations have shown that the relative configuration of the stereogenic centres in the substrate has an important influence on the course of the rearrangement reaction and dictates the relative amount of [1,2] or [2,3] rearrangement products obtained. Furthermore, the choice of the catalyst is also highly substrate dependant.

Application to cyclic ether formation

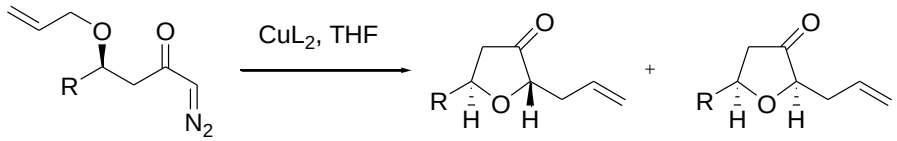
Cyclic ethers are found as sub-units in many biologically active natural products. It has therefore been crucial to develop methodology which can be used to produce cyclic ethers with high yield and more importantly with high stereoselectivity. It has been reported that the formation and rearrangement of oxonium ylides could be used for the stereoselective formation of 5- and 6-membered rings.[24]

The tetrahydrofuran unit is one of the most common heterocyclic units found in natural products. In the recent years, efforts have been focused on the development of efficient and highly selective methods which allow the formation of highly substituted

[24] Clark, *Tetrahedron Lett.* **1992,** 33, (41), 6193-6, Clark and Whitlock, *Tetrahedron Lett.* **1994,** 35, (34), 6381-2.

tetrahydrofurans. Approaches that have been developed include the formation of an epoxide followed by nucleophilic epoxide opening under acidic conditions,[25] and the use of asymmetric condensation reactions.[26] Unfortunately, these methods often deliver poor stereoselectivities and sometimes involve the use of expensive and/or toxic reagents.

Methodology developed by the Clark group involves the catalytic decomposition of a diazoketone to form 2,5-disubstituted tetrahydrofuran-3-one *via* carbenoid and ylide intermediates.[27] Optimisation of the reaction has been realised taking into account the results of previous investigations which showed that copper catalysts are the catalysts of choice to give *trans*-product with a high degree of selectivity (**Table 6**).



117 **118** **119**

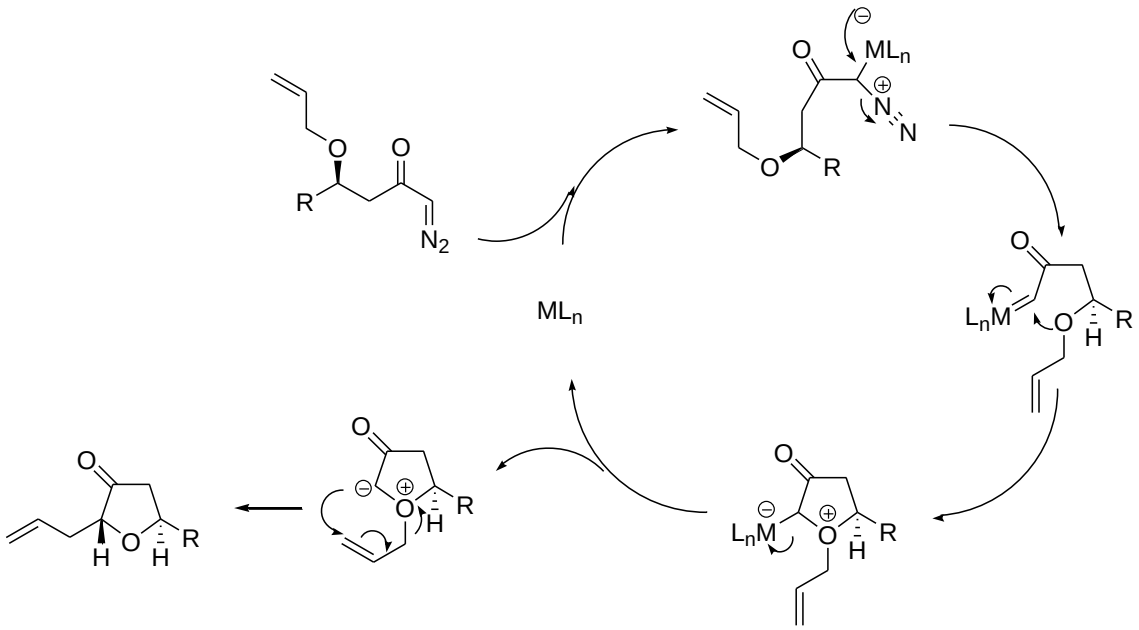
		Cu(acac)$_2$		Cu(hfacac)$_2$	
	R	**Yield (%)**	**Ratio (cis-trans)**	**Yield (%)**	**Ratio (cis-trans)**
a	^{n}Pr	93	98:2	93	65:35
b	^{t}Bu	93	>98:2	90	>98:2
c	Me	92	97:3	91	65:35
d	Ph	82	>98:2	94	73:27
e	$CH_2OTBDPS$	88	>98:2	88	68:32

Table 6: Optimisation of the reaction condition for the formation of 2,5-*trans*-tetrahydrofuran-3-one

The reactions of the diazo-ketones **117** followed by subsequent [2,3]-rearrangement of the oxonium ylides were optimised using Cu(acac)$_2$ as a catalyst in THF, under reflux. The reaction was rapid and the desired rearrangement products **118** were obtained in high yield and with a high degree of stereoselectivity.

The diazoketone undergoes a nucleophilic attack onto an empty d orbital of the transition metal (**Scheme 25**). The transition metal back donates the electrons of one of its d orbitals to the carbon to form the metal carbenoid with elimination of nitrogen. Attack of one of the lone pairs of the ether oxygen onto the carbon bonded to the transition metal leads to the formation of an oxonium ylide intermediate which can then undergo the 2,3-sigmatropic rearrangement.

[25] Fukuyama, Vranesic, Negri and Kishi, *Tetrahedron Lett.* **1978**, (31), 2741-4.
[26] Panek and Beresis, *J. Org. Chem.* **1993,** 58, (4), 809-11.
[27] Clark, *Tetrahedron Lett.* **1992,** 33, (41), 6193-6, Clark, Dossetter and Whittingham, *Tetrahedron Lett.* **1996,** 37, (31), 5605-08, Capon and Barrow, *J Org Chem* **1998,** 63, (1), 75-83, Clark, Fessard and Wilson, *Org Lett* **2004,** 6, (11), 1773-6.



Scheme 25: Mechanism of tandem carbenoid insertion and ylide rearrangement to give substituted tetrahydrofuranones

With these results in hand it was decided to apply this methodology to the synthesis of two marine natural products. The two targets chosen of choice were the (6*S*,7*S*,9*R*,10*R*)6,9-epoxynonadec-18-ene-7,10-diol and the A-ring fragment of gambieric acid.

1.2 (6S,7S,9R,10R)-6,9-epoxynonadec-18-ene-7,10-diol

1.2.1 Origin and biological activity

Isolation

Brown algae are known to be good sources of polyene and polyterpene natural products. These algae have been the subject of particular investigation due to the wide range of chemical compounds they are able to produce. In the late 1970's, Warren *et al.* had a particular interest in the brown alga *Notheia anomala*, a member of the family Notheiaceae, order Chlordaliales. This alga was found growing as a parasite on another brown alga *Hormosira banksii* (**Figure 3**).[28] It is also known as "Neptune's necklace" or "sea grapes" and is mostly found in the mid-tide zone. It can easily be collected off rock platforms along the southern coast of Australia and New Zealand.

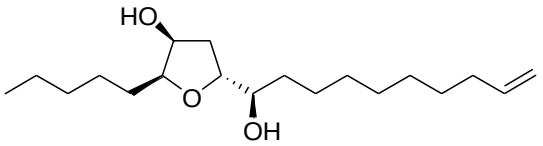
Figure 3: Brown alga Hormosira banksii (left); Southern australian rock platform (right)

The chemistry of brown algae is dominated by the presence of terpenoid metabolites which possess long carbon skeletons and are frequently highly oxygenated. The presence of a secondary metabolite in *Notheia anomala* derived from a possible icosenoic acid precursor led to a more detailed investigation. The analysis of a hexane extraction fraction of the freeze-dried alga revealed a mixture of tetrahydrofurans. Further purification of the extract by column chromatography on silica gel and subsequent analysis of the analytes isolated by NMR spectroscopy and X-ray crystallography afforded the (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol as the major component which crystallised from hexane as colourless needles.

[28] Warren, Wells and Blount, *Australian Journal of Chemistry* **1980,** 33, (4), 891-98.

Structure

The proton NMR spectrum showed a one-proton resonance which could be attributed to a terminal CH_2-CH=CH_2 as well as four CH-O. The spectrum was also consistent with the presence of a linear lipid chain with a terminal methyl group. Functional group manipulation and chemical transformations were used to determine the chemical configuration of the molecule. Using this approach, the molecule was proved to be a mono-unsaturated diol incorporating a single ether bridge. Although the general structure of the molecule could then be written, assignment of the relative stereochemistry of the four stereogenic centres was not possible. This problem was solved using single crystal X-ray analysis to obtain the final structure of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol (**Figure 4**).



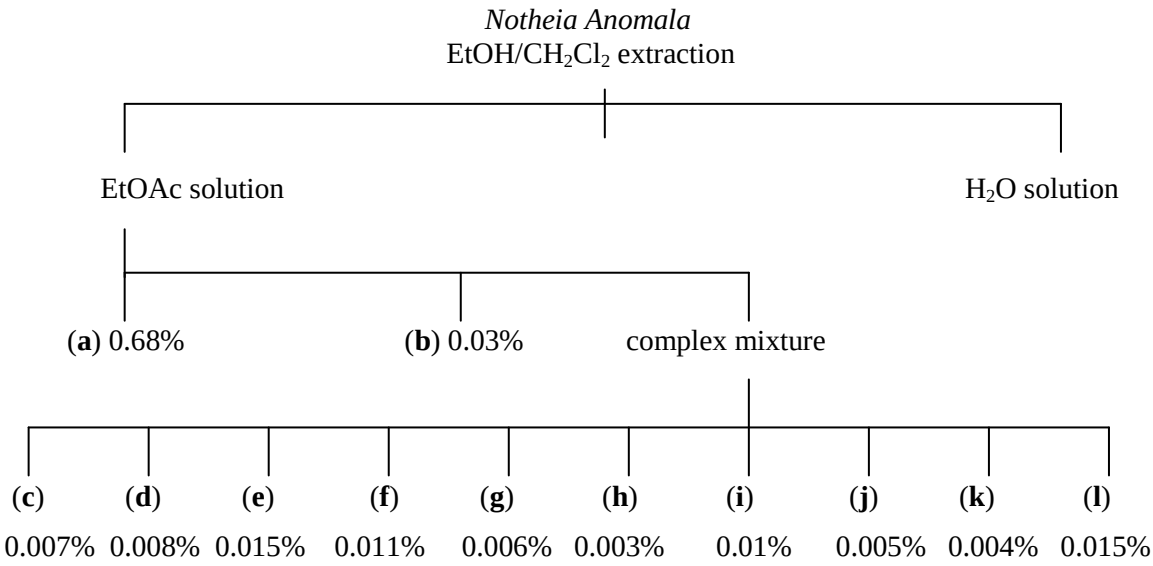
120

Figure 4: (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol

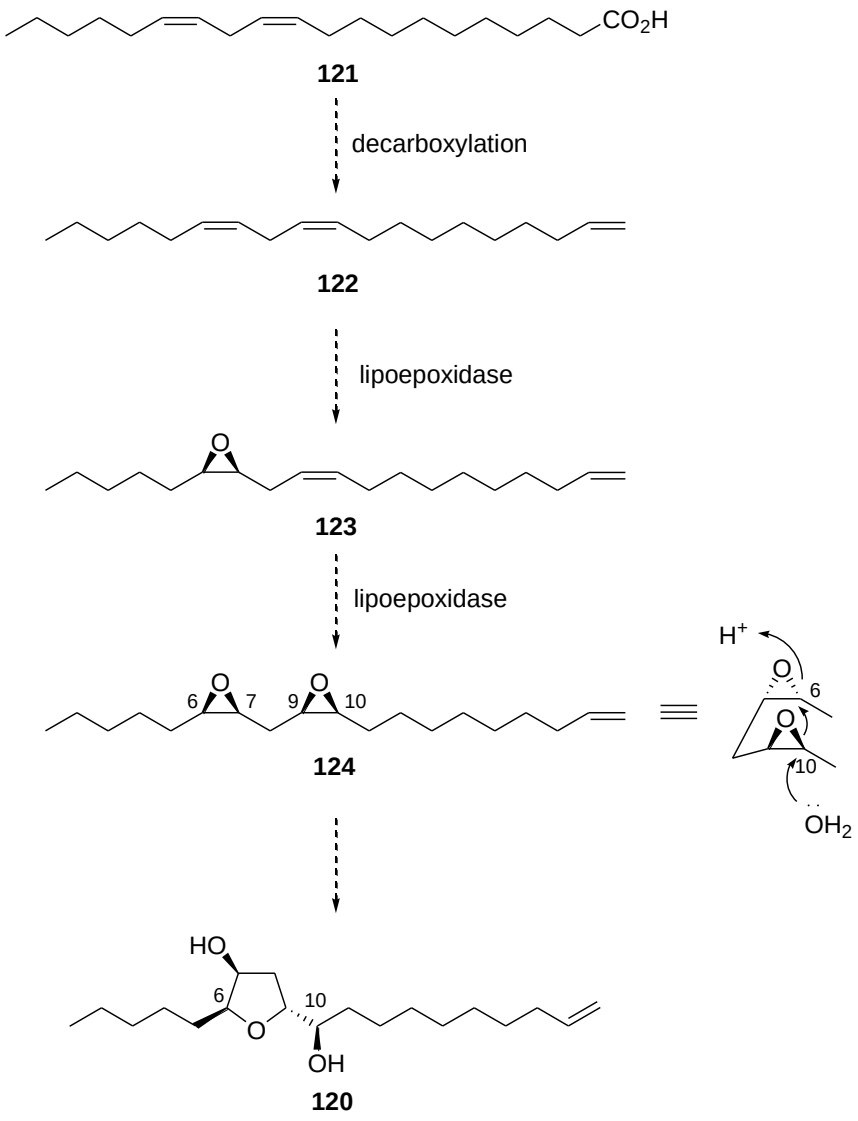
Biological synthesis

Barrow and Cappon have proposed a pathway to account for the biosynthetic origin of this molecule based on the structures of other compounds produced by the alga.[29] The extraction and isolation process allowed the isolation of a total of 19 distinct components possessing different structures.

[29] Barrow and Capon, *Australian Journal of Chemistry* **1990,** 43, (5), 895-911, Capon, Barrow, Rochfort, Jobling, Skene, Lacey, Gill, Friedel and Wadsworth, *Tetrahedron* **1998,** 54, (10), 2227-42.



The major most polar component (**a**) was the known C_{19} lipid **120**. The second most abundant component was (**b**) which was obtained as a colourless oil. A more detailed analytical study showed (**b**) to be a C_{19} linear hydrocarbon incorporating a terminal methyl and vinyl groups and two epoxide functionalities at the C6-7 and C9-10 positions. It is important to say that the two extractions of *Notheia anomala* studied during this investigation yielded different amounts of (**a**) and (**b**) but the combined yield was the same. This could indicate that (**a**) and (**b**) are capable of interconversion. Further analysis of the remaining component isolated during the extraction process led to a potential biosynthetic pathway involving nucleophilic attack on a methylene interrupted bis-epoxide **124** (**Scheme 26**).



Scheme 26: Biosynthetic pathway from methylene interrupted bisepoxide (124) to dihydroxy tetrahydrofuran (120)

Biological activity

The biological activity of the tetrahydrofuran natural products isolated from *Notheia Anomala* was reported for the first time by Capon et al. in the late 90's.[30] Numerous potent biologically active products possess a tetrahydrofuran ring and many can act as anthelmintic drugs which can be used to rid host animals of parasites. The natural tetrahydrofuran **120** was subjected to *in vivo* nematocidal screening, as parasitism from nematodes (unsegemented worms) represents a major source of lost production in the commercial farming industry. The dihydroxytetrahydrofuran was found to exhibit LD_{50} values against two different parasites which are comparable to these of commercially available products. Further investigations on this matter by the same group have led to the

[30] Capon, Barrow, Rochfort, Jobling, Skene, Lacey, Gill, Friedel and Wadsworth, *Tetrahedron* **1998,** 54, (10), 2227-42.

conclusion that compounds of this general structural class exhibit potent and selective nematocidal activity against the free-living stages of the parasitic nematodes Haemonchus contortus and Trichostrongylus colubriformis.

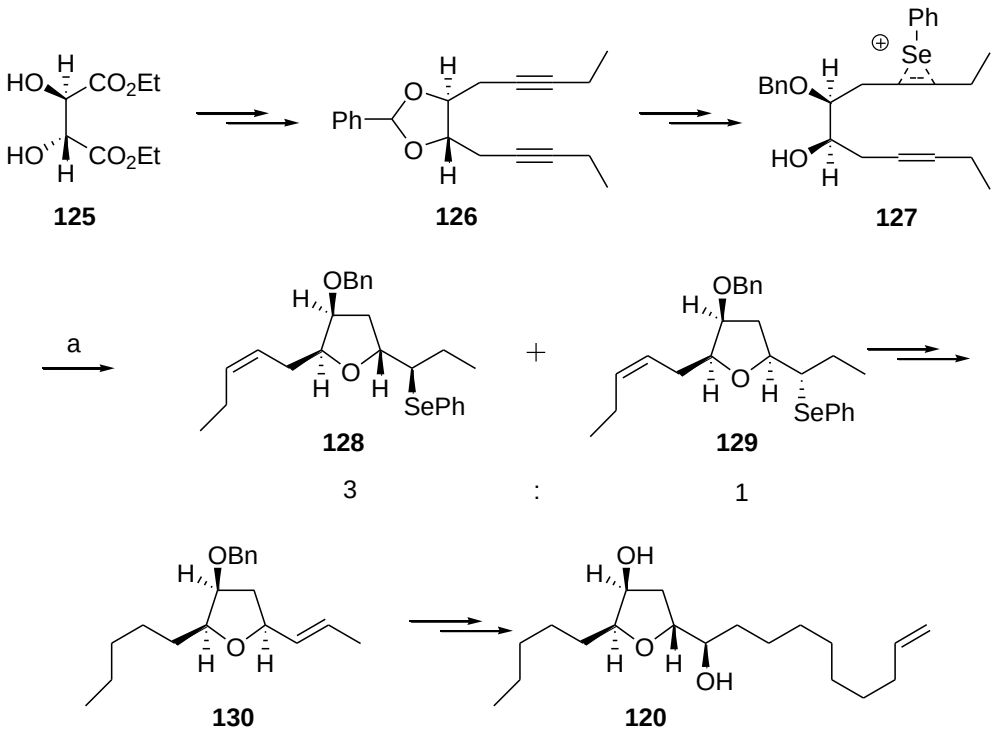
1.2.2 Previous synthesis

The synthesis of natural products possessing oxacyclic systems such as polyether antibiotics and marine products has always been of particular interest in total synthesis. The substituted 2,5-*trans*-tetrahydrofuran system is one of the most common heterocyclic units found in these natural products. The efficient stereocontrolled construction of the highly substituted tetrahydrofuran of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol has always been a challenge and various methods have been explored so far for its construction. In 1984, Willliams achieved the first total synthesis of racemic (6S,7S,9R,10R)-6,9-epoxynonadec-18-ene-7,10-diol using NBS oxidation of a 1,3-dioxalane with participation of a secondary hydroxyl group for the formation of the highly substituted tetrahydrofuran ring.[31]

Takano's total synthesis of the diol

The first stereocontrolled synthesis of the diol was achieved by Takano and co-workers in 1985.[32] Their synthesis relies on the C_2–symmetrical nature of **126** which allowed the formation of the key tetrahydrofuran intermediate possessing three of the required sereogenic centres (**Scheme 27**). The selenoetherification of **127** with phenylselenyl chloride was a simple procedure which delivered the three stereogenic centres with the correct configuration.

[31] Williams, Harigaya, Moore and Dsa, *J. Am. Chem. Soc.* **1984,** 106, (9), 2641-44.
[32] Hatakeyama, Sakurai, Saijo and Takano, *Tetrahedron Lett.* **1985,** 26, (10), 1333-6.



Reactants: a) PhSeCl, DCM, -78 °C

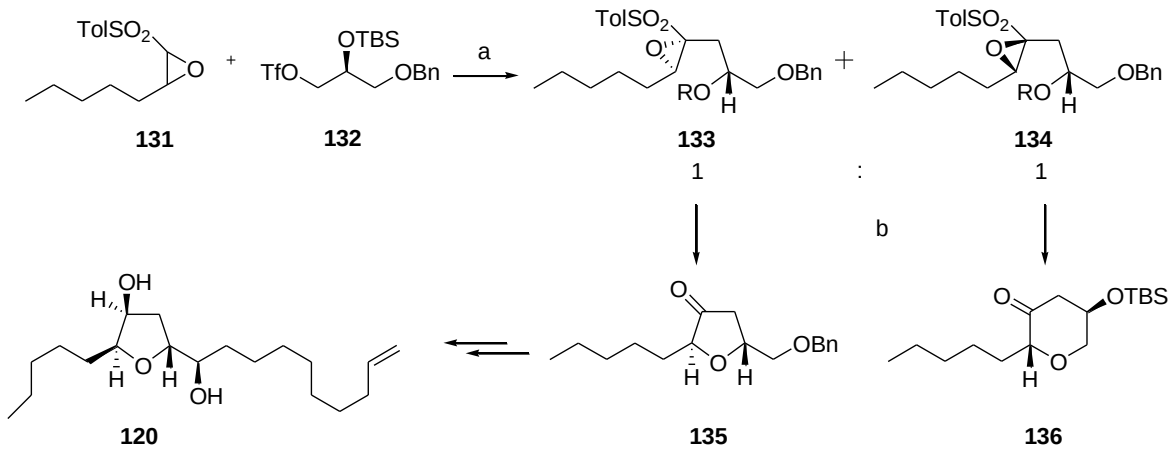
Scheme 27: Takano's approach

Diethyl **L**-tartrate was converted to benzylidene acetal **126** by treatment with an acetylide, in presence of boron trifluoride, followed by protection of the resulting diol with benzaldehyde. Lindlar reduction and treatment with diisobutylaluminium hydride gave benzylic ether **127**. Selenoetherification with phenylselenyl chloride gave an inseparable 3:1 mixture of **128** and **129** which was subjected to diimide reduction. The resulting selenide was converted into the olefin **130**. Dihydroxylation followed by treatment with lead tetraacetate gave a 3:1 mixture of the *trans* and *cis* aldehyde which was treated with an excess of Grignard reagent to give the desired diol **120** in 10 steps and 0.11 % overall yield from **125**.

Mori's approach

Mori *et al*. were the second workers to accomplish the total synthesis of the diol **120** in 1998.[33] The formation of the 2,3,5-trisubstituted tetrahydrofuran ring was performed by alkylation of the sulfonyl-stabilized oxiranyl anion followed by 5-*endo* cyclisation (**Scheme 28**).

[33] Mori, Sawada and Furukawa, *Tetrahedron Lett.* **1999,** 40, (4), 731-34.



Reactants: a) n-BuLi, DMPU, THF, -100 °C, b) $BF_3{\cdot}OEt_2$, DCM, 0 °C

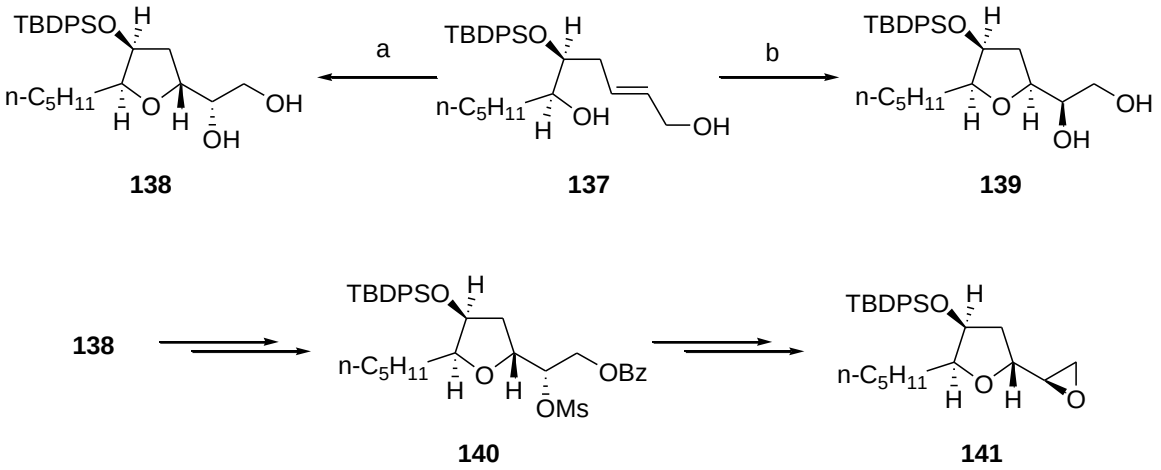
Scheme 28: Mori's approach

By treatment of a mixture of **131** and **132** with *n*-BuLi in THF-DMPU at low temperature, the epoxysulfones **133** and **134** were obtained as a diastereomeric mixture in 82% yield. The mixture was separated by chromatography on silica gel. It is interesting to note that the determination of the stereochemistry of both diastereoisomers was achieved only after treatment of both epoxisulfones with $BF_3{\cdot}OEt_2$ to effect cyclisation. The more polar isomer **133** reacted to give the desired tetrahydrofuran sub-unit **135** whereas the less polar compound, under the same conditions, afforded the tetrahydropyran intermediate **136** as the only product of rearrangement though a six-*endo* pathway. The total synthesis of the diol was achieved in 10 steps (longest linear sequence) and 5.4% overall yield.

Martin's approach

In 2000, Martin published the asymmetric total synthesis of the trisubstituted tetrahydrofuran unit using Sharpless dihydroxylation and Katuki-Sharpless asymmetric epoxidation as tools for the insertion of the stereogenic centres.[34] Functional and protecting group manipulation of the product resulting from the Sharpless dihydroxylation allowed the desired allylic alcohol to be obtained which then underwent the Katsuki-Sharpless asymmetric epoxidation reaction. The highly substituted tetrahydrofuran core of the diol was then easily accessible by epoxide opening (**Scheme 29**).

[34] Garcia, Soler and Martin, *Tetrahedron Lett.* **2000,** 41, (21), 4127-30.



Reactants: a) Ti(OPr-*i*)$_4$, (*R*,*R*)-(+)-DET, TBHP, DCM, -20°C, 2h, 82%, b) Ti(OPr-*i*)$_4$, (*S*,*S*)-(-)-DET, TBHP, DCM, -20°C, 2h, 82%

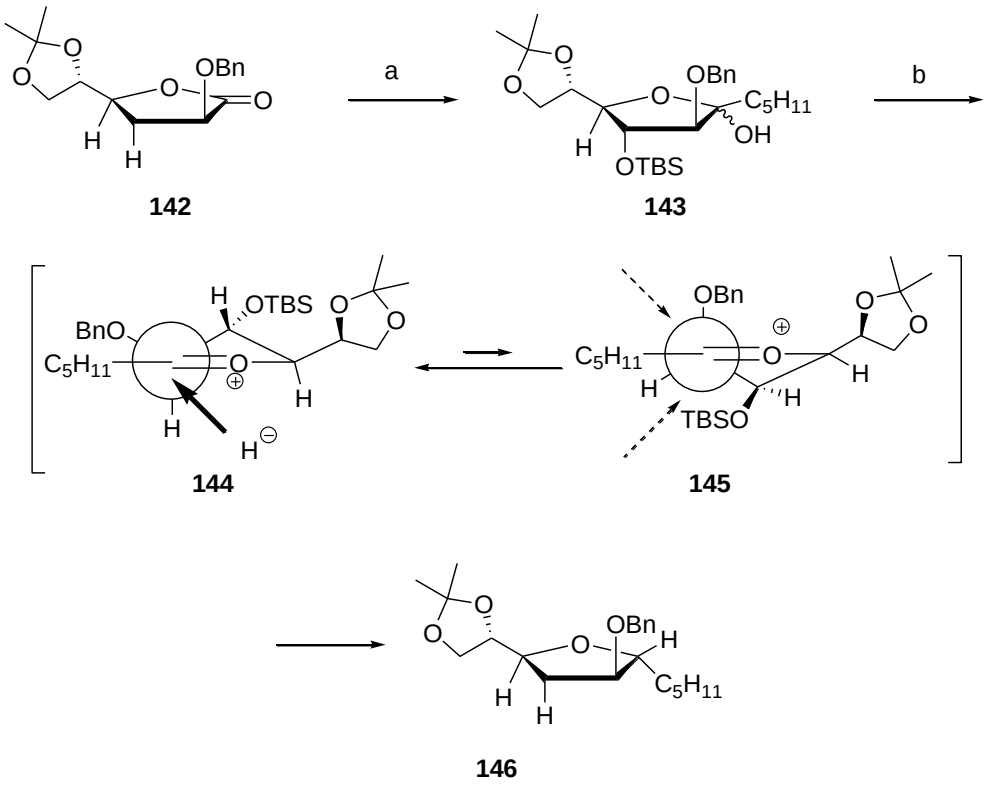
Scheme 29: Martin's approach to the trisubstituted tetrahydrofuran core

The allylic alcohol **137** was obtained in a 5-step sequence from *n*-heptanal. This intermediate was subjected to the asymmetric epoxidation followed by epoxide opening to afford the *trans*-tetrahydrofuran **138** as the sole detected stereoisomer. Use of the enantiomeric chiral ligand provided the *cis*-tetrahydrofuran **139**. Protecting group interconversion on the two free alcohols allowed the formation of the epoxide by intramolecular displacement of the mesylate group with the free hydroxyl group. Epoxide **141** was then subjected to Grignard addition in presence of copper iodide to furnish, after deprotection, the desired diol **120** in 10 steps and 13% overall yield. A few years later Martin *et al* reported the application of this methodology to the synthesis of the other isomers of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol.[35]

Yoda's approach

In 2001, Yoda described a new approach to the total synthesis of the epoxy lipid relying on a stereoselective hydrogenation of a hemiketal derivative and nucleophilic addition of a Grignard reagent in the presence of $CeCl_3$.[36] In order to obtain the desired stereochemistry for the stereogenic centres of the molecule, they decided to use Lewis acid promoted deoxygenation of a hemiketal intermediate (**Scheme 30**).

[35] Garcia, Martin and Martin, *J Org Chem* **2001,** 66, (4), 1420-8.
[36] Yoda, Maruyama and Takabe, *Tetrahedron: Asymmetry* **2001,** 12, (10), 1403-06.



Reactants: a) ($C_5H_{11}MgBr$, $CeCl_3$; b) Et_3SiH, $BF_3{\cdot}OEt_2$,DCM, 36% over 2 steps

Scheme 30: Yoda's key steps to the insertion of the stereogenic centres

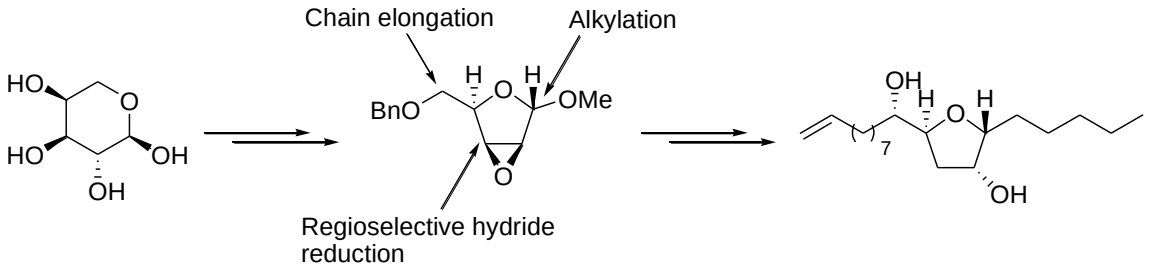
Reaction intermediate **142** is available in two steps from the commercially available and highly functionalised starting material **L**-(+)-galactono-1,4-lactone. Treatment of lactone **142** with pentylmagnesium bromide in presence of $CeCl_3$ provided the hemiketal intermediate **144** and at low temperature this underwent $BF_3{\cdot}OEt_2$ promoted reduction using Et_3SiH. The tetrahydrofuran ring was obtained in 36% yield over these two steps with a rather poor selectivity as **146** was obtained with the corresponding diastereoisomer as a 1:1 mixture. The synthesis was then completed by sequential protecting group interconversion and introduction of the side chain by nucleophilic attack of a Grignard reagent onto an epoxide in presence of copper iodide. The final product was obtained in 7 steps from ***L***-(+)-galactono-1,4-lactone and in a poor 1% overall yield.

Lowary's approach

In the same year as Yoda, Lowary and co-workers reported another total synthesis of the trisubstituted tetrahydrofuran ring. In this investigation they designed four different syntheses for four diasteroisomers of the diol using the epoxide **148** as a common intermediate.[37] The enantiomer of the natural product we are interested in preparing is

[37] Gadikota, Callam and Lowary, *J Org Chem* **2001,** 66, (26), 9046-51.

accessible with the desired stereochemistry using the stereogenic centres of the **D**-Arabinose (**Scheme 31**).



147 **148** **149**

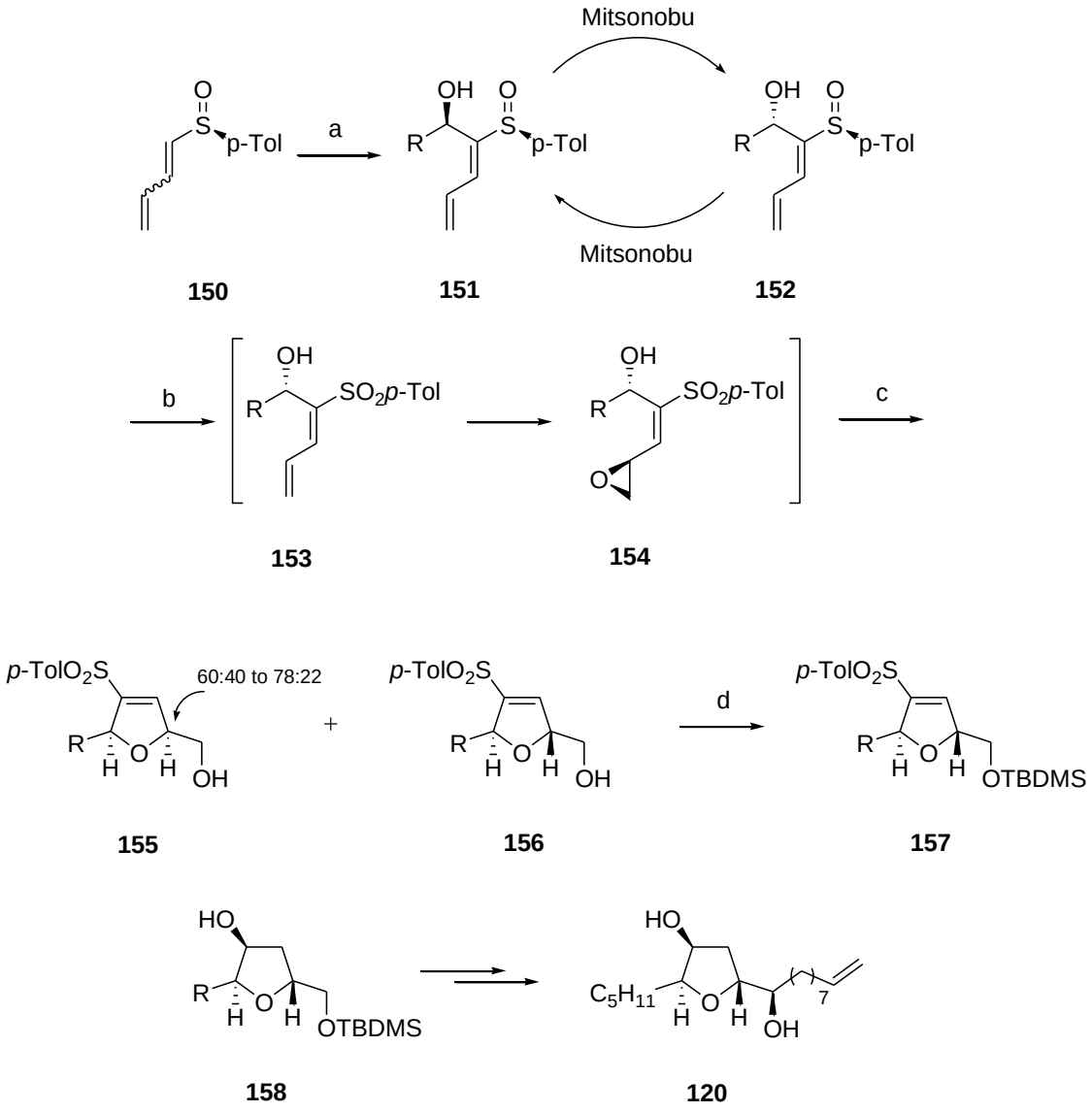
Scheme 31: Stereoselective synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol enantiomer

A screen of a wide range of hydride sources to open the epoxide showed that LAH was the most convenient reagent and afforded the desired product with a high degree of regioselectivity. A trimethylsilyltriflate-catalysed *C*-allylation resulted in allylation at the 2 position in 92% yield but with poor selectivity. Chain elongation at the 5 position was accomplished by deprotection followed by subsequent oxidation and Grignard addition. The enantiomer was obtained in a 9 steps and 19% yield starting from the non-commercially available intermediate **147**.

De la Pradilla's approach

The most recent synthesis is a formal route based on the first synthesis of racemic material conducted by Williams.[38] The approach of de la Pradilla and co-workers relied on the formation of a 2,5-*trans* sulfonyl dihydrofuran by Katsuki-Jacobsen oxidation-epoxidation of an allylic α-silyloxy sulfinyl diene followed by acid promoted cyclisation (**Scheme 32**). This methodology offers a versatile route to highly functionalized sulfinyl and sulfonyl tetrahydrofurans. The presence of this functional group on the tetrahydrofuran is advantageous because it can be easily converted into a wide range of other groups.

[38] de la Pradilla and Castellanos, *Tetrahedron Lett.* **2007,** 48, (37), 6500-04.



Reactants: a) i. LDA, ii. RCHO b) *m*-CPBA; c) CSA.; d) TBDMSCl, DMAP, imidazole, DCM

Scheme 32: De La Pradilla dihydrofuran approach

Epoxidation of **151** was first directly attempted using *m*-CPBA but the low selectivity obtained led to the investigation of a more efficient approach. After screening different oxidation reagents and conditions, it was shown that the Katsuki-Jacobsen epoxidation was the most efficient strategy to obtain the epoxide with the desired stereochemistry without formation of other products. Nucleophilic epoxidation of the 2,5-*trans* diastereomer **156** with KO*t*-Bu gave sulfonyl oxirane as a single isomer. Reductive cleavage of the sulfonyl oxirane and reduction of the resulting ketone was followed by oxidation of the remaining free primary alcohol to give the intermediate precursor **158**, the precursor to Grignard addition reported by Williams in 1984. The addition product was obtained in 15% overall yield and the final natural product **120** was therefore obtained in 8 steps from **151**.

The epoxidation of **153** was further optimised a year later when investigations concerning the reaction conditions for the cyclisation precursor showed that better results could be obtained when the secondary alcohol was protected with a TBS group.[39] The reaction was also applied to more highly substituted dienes in order to afford more substituted and more complex tetrahydrofuran rings.

[39] de la Pradilla, Lwoff and Viso, *Eur. J. Org. Chem.* **2009**, (14), 2312-22.

1.3 Gambieric acids A-D

1.3.1 Ciguatera fish poisoning

History

Ciguatera fish poisoning is the most commonly reported marine toxin disease. This kind of poisoning is known to occur in tropical regions worldwide. There are more than 25,000 reported cases per year but it is believed that this represents only 5% of all cases.[40] The first cases of Ciguatera fish poisoning are thought to have first been discovered in the early 1770s during Quiros, Cook and Morrison's journeys in the south pacific. They recorded episodes of food poisoning aboard ship which were believed to have been caused by ciguatoxic fish.

Ciguatera affects a wide variety of fish in the Pacific (around 400) and has become a significant health and resource utilization problem, limiting local fishing and the economy. The economic problem was such that, in 1968, the South Pacific Commission organised the first international seminar on fish poisoning.[41]

In the late 1960s, it was assumed that the causative agent was accumulated in fish through the food chain. Although its structure wasn't clearly defined at the time, the toxin, called ciguatoxin, was first isolated from moray eels. Focus on the discovery of the organism producing the ciguatoxin (CTX) led 20 years later to the conclusion that the toxin came from a dinoflagellate *Gambierdiscus toxicus* (**Figure 5**).[42]

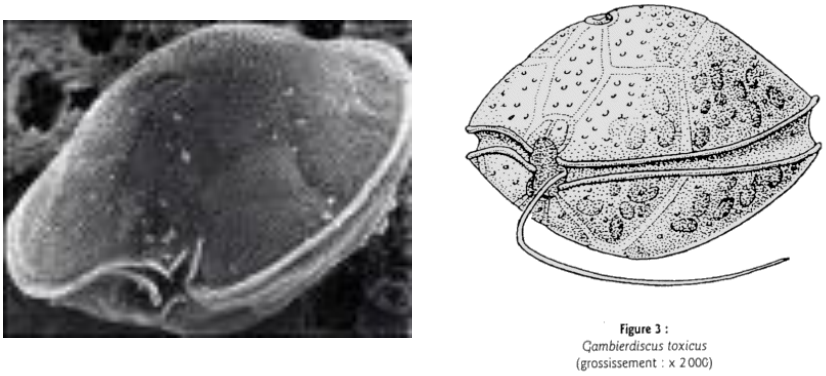


Figure 5: *Gambierdiscus toxicus*[43]

[40] Clark, Williams, Nordt and Manoguerra, *Undersea Hyperb Med* **1999,** 26, (3), 175-84.
[41] Lewis, *South Pacific Bulletin third quarter* **1979**, 8-12.
[42] Yasumoto, *Chem. Rec.* **2001,** 1, (3), 228-42, Bagnis, Chanteau and Yasumoto, *Bull Soc Pathol Exot Filiales* **1977,** 70, (3), 320-4, Bagnis, Chanteau and Yasumoto, *Rev. Int. Oceanogr. Med.* **1977,** 45-46, 29-34.
[43] http://edis.ifas.ufl.edu/pdffiles/IN/IN74200.pdf

Symptoms and transmission

The symptoms of ciguatera primarily involve the nervous system and include tingling of the mouth and limbs, muscle weakness, fatigue, dizziness, fainting, itchy skin and in severe cases inability to breathe. Other symptoms such as diarrhea and nausea are also quite common. The symptoms usually appear between 2 to 30 hours after ingestion of the fish and neurological symptoms can last from several weeks to several months.[44] Most people do recover slowly over time, but in more serious cases it can induce paralysis, coma and for 5% of the cases treated in hospitals, death. Ciguatera symptoms have developed in healthy males and females following sexual intercourse with partners suffering from the poisoning which led to the conclusion that the toxin may be sexually transmitted.[45] Cases of facial rashes observed in the breastfed child of a mother suffering from ciguatera poisoning showed that it is likely that the toxin could also be transferred in breast milk.

Folk science is used widely in areas of the world were the ciguatera fish poisoning is most common. Two different methods are usually believed to be efficient for revealing significant levels of ciguatoxins in fish. The first belief is that if a piece of fish is contaminated with the toxin, flies will not land on it. The second is that the toxin can be detected by feeding a piece of fish to a cat, cats being so sensitive to the ciguatoxins that they will display symptoms very quickly.

The reasons why the ciguatoxin-producing dinoflagellate appears only in certain parts of the Pacific Ocean is still poorly understood. However, it has been clearly determined that the toxin is concentrated in the flesh of small fish which feed on coral reefs.[46] The unicellular microalgae *Gambierdiscus toxicus* is generally found attached to macrophytes that proliferate on dead coral substrates. Events such as cyclons, coral bleaching, marine pollution or seasonal changes are factors which can cause episodic blooms of the dinoflagellate. These blooms provide "new surfaces" for colonisation by microalgae *Gambierdiscus toxicus*. These blooms are called red tides, due to the colour of other dinoflagellates present (**Figure 6**).

[44] Bagnis, Chanteau, Chungue, Hurtel, Yasumoto and Inoue, *Toxicon* **1980,** 18, (2), 199-208, Darius, Ponton, Revel, Cruchet, Ung, Tchou Fouc and Chinain, *Toxicon* **2007,** 50, (5), 612-26, Gatti, Oelher and Legrand, *Toxicon* **2008,** 51, (5), 746-53.
[45] Lange, Lipkin and Yang, **1989**, 193-7.
[46] Lehane and Lewis, *Int J Food Microbiol* **2000,** 61, (2-3), 91-125.

Figure 6: Red algae tide left: Maine coast – photo by Miriam Godfrey, right: New Zealand coast

Prevention and Treatment

It is difficult to avoid ciguatera fish poisoning because the toxin is tasteless and odourless and the contaminated fish doesn't show any particular abnormal behaviour. CTX is heat-stable and therefore cooking or preparation of the fish does not eliminate or destroy toxin in the fish. The risk of eating CTX containing fish is considerably decreased by avoiding small reef fish and species most likely to carry ciguatera. However, there is no reliable method to date which can be used to confirm the presence of the toxin in humans and there is no effective treatment or antidote for ciguatera fish poisoning. There are ways to decrease the severity of the symptoms but the main treatment is supportive care.

The general attention of research groups on the discovery of new treatment methods has resulted in the introduction of medications to reduce symptoms. Medication, such as the use of amitriptyline for paresthesia or fluoxetine to reduce fatigue and paracetamol and nifedipine for headaches, are examples.[47] Supplements such as steroids and vitamins can be used to aid recovery but the effect on the actual toxin is limited. Many traditional herbal medicines and remedies have been reported to treat ciguatera such as extract of *Argusia argentea* leaves or *Davalliea sp.*[48] Mannitol was reported to reverse the symptoms after administration, although the mechanism of action is not clearly understood.[49] However, it is the most effective treatment for people who have ingested the toxin.

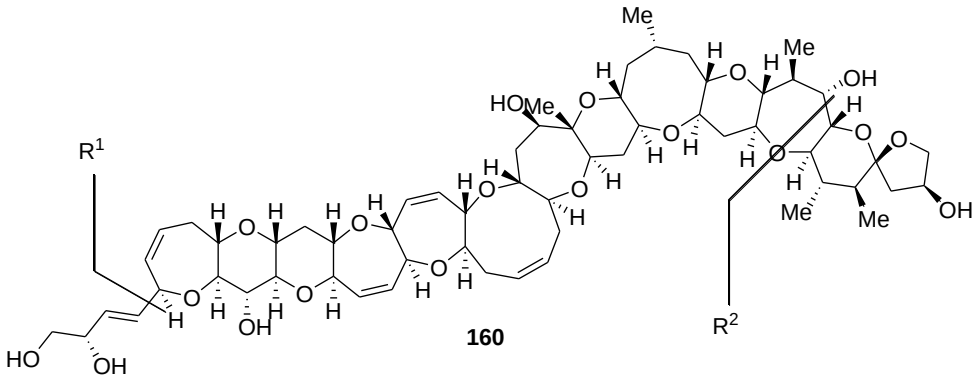
In order to find more efficient methods for the treatment of ciguatera fish poisoning it has been important to investigate the origin of the toxin. The wide variety of signs and symptoms has led researchers to assume that several toxins are involved.

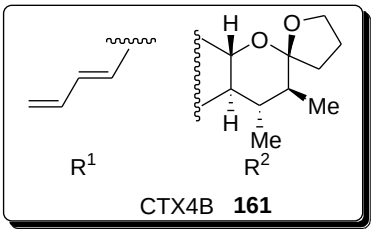
[47] Davis and Villar, *New Engl J. Med* **1986**, 65.
[48] Friedman, Fleming, Fernandez, Bienfang, Schrank, Dickey, Bottein, Backer, Ayyar, Weisman, Watkins, Granade and Reich, *Mar Drugs* **2008,** 6, (3), 456-79.
[49] Clark, Williams, Nordt and Manoguerra, *Undersea Hyperb Med* **1999,** 26, (3), 175-84.

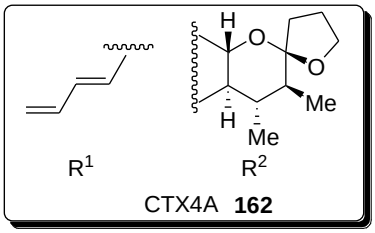
1.3.2 Origin of gambieric acids

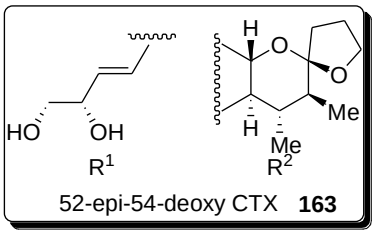
Origin and isolation

The ciguatoxin CTX the main cause of the ciguatera fish poisoning, was isolated in the 1960s. Collecting enough toxic fish to extract sufficient amounts of CTX was a challenge for those attempting to determine its structure. In 1989, Yasumoto and co-workers elucidated the structure of the toxin by isolation of a sample from 4000kg of moray eel.[50] In subsequent studies, five other ciguatoxins were isolated from cultured *Gambierdiscus toxicus* cells (**Figure 7**).









[50] Murata, Legrand, Ishibashi and Yasumoto, *J. Am. Chem. Soc.* **1989,** 111, (24), 8929-31.

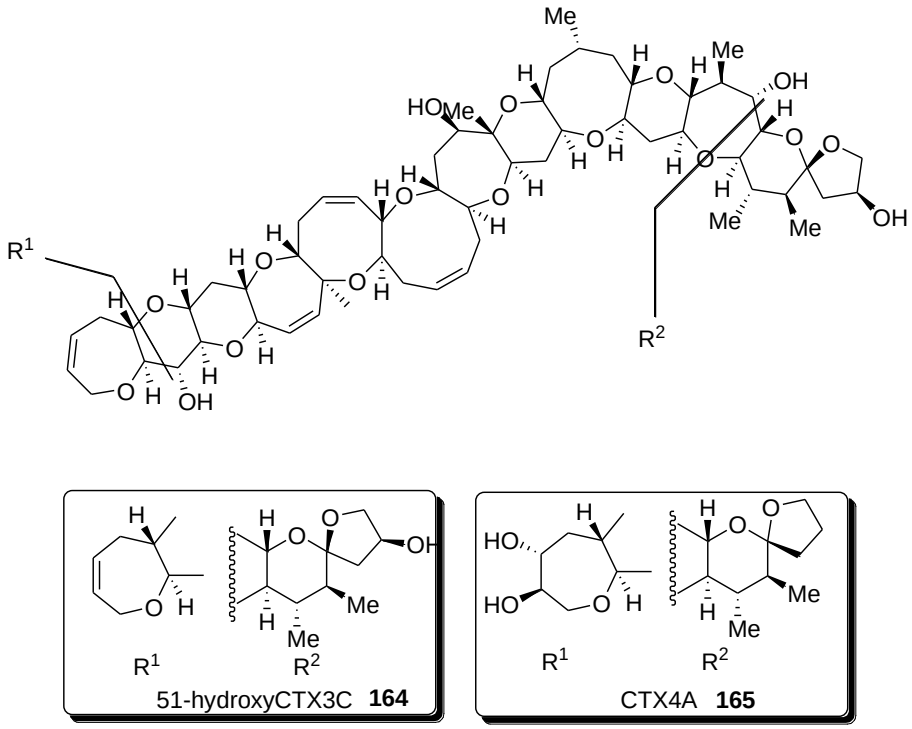


Figure 7: Ciguatoxin configuration

Since 1989, the ciguatoxins have attracted a lot of interest from research groups. To date, dozens of ciguatoxins have been isolated either from toxic fish or from cultured *Gambierdiscus toxicus*, but only a few of them have been fully characterised.

Many *tans*-fused polycyclic ethers produced by unicellular marine algae have been the isolated.[51] Amongst them are brevetoxin-B **166** and A **168**, hemibrevetoxin-B **167**, gambieriol **169** [52] and gambieric acid **170** to **173** (**Figure 8**).[53]

[51] Yasumoto, *Chem. Rec.* **2001,** 1, (3), 228-42, Nagai, Satake and Yasumoto, *J. Appl. Phycol.* **1990,** 2, (4), 305-8, Ciminiello and Fattorusso, *Eur. J. Org. Chem.* **2004**, (12), 2533-51.
[52] Satake, Ishimaru, Legrand and Yasumoto, *Dev. Mar. Biol.* **1993,** 3, (Toxic Phytoplankton Blooms in the Sea), 575-9, Satake, Morohashi, Sasaki and Yasumoto, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1998,** 40th, 133-38.
[53] Nagai, Murata, Torigoe, Satake and Yasumoto, *J. Org. Chem.* **1992,** 57, (20), 5448-53, Nagai, Torigoe, Satake, Murata, Yasumoto and Hirota, *J. Am. Chem. Soc.* **1992,** 114, (3), 1102-3, Morohashi, Satake, Nagai, Oshima and Yasumoto, *Tetrahedron* **2000,** 56, (46), 8995-9001.

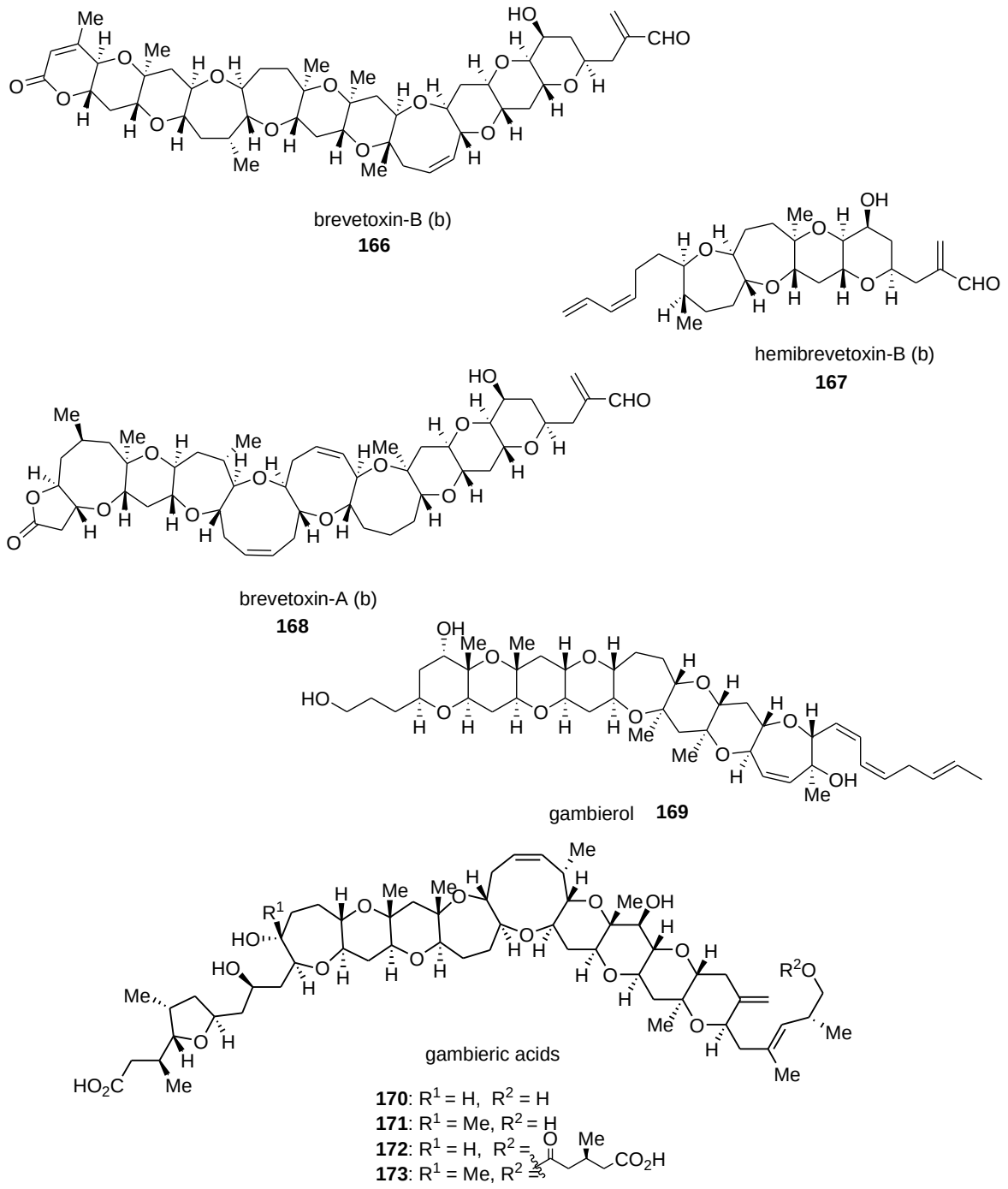


Figure 8: Structures of *trans*-fused polycyclic ethers

An intriguing finding is that these fused polyether natural products all possess seven-, eight- or nine-membered ring(s) in the middle of the molecule. Gambieric acid A, for example, possesses 10 cyclic ethers, 9 of those being *trans*-fused with sizes going from five-membered to a nine-membered. The main problem encountered with such molecules is the limited amount of material available to carry out biological studies. Indeed, in the case of the gambieric acids, 5000 litres of media kept at 25 ºC for 38 days were necessary to obtain 0.6 mg of gambieric acid A, 0.15 mg of gambieric acid B as well as 5.8 mg of a

mixture of gambieric acids C and D.[54] Although biological studies have been limited because of their scarcity, these ladder shaped polyethers have shown interesting biological properties.

Biological activity

Pharmacological studies have revealed that CTXs activate voltage-sensitive sodium channels in nerve membranes at nM to pM concentrations. The target receptor on the voltage gated channel was only identified for brevetoxins and ciguatoxins because of the greater availability of these compounds. They exert their activities by association with a specific binding site on the voltage gated channel of excitable membranes known as site 5 (**Figure 9**).[55]

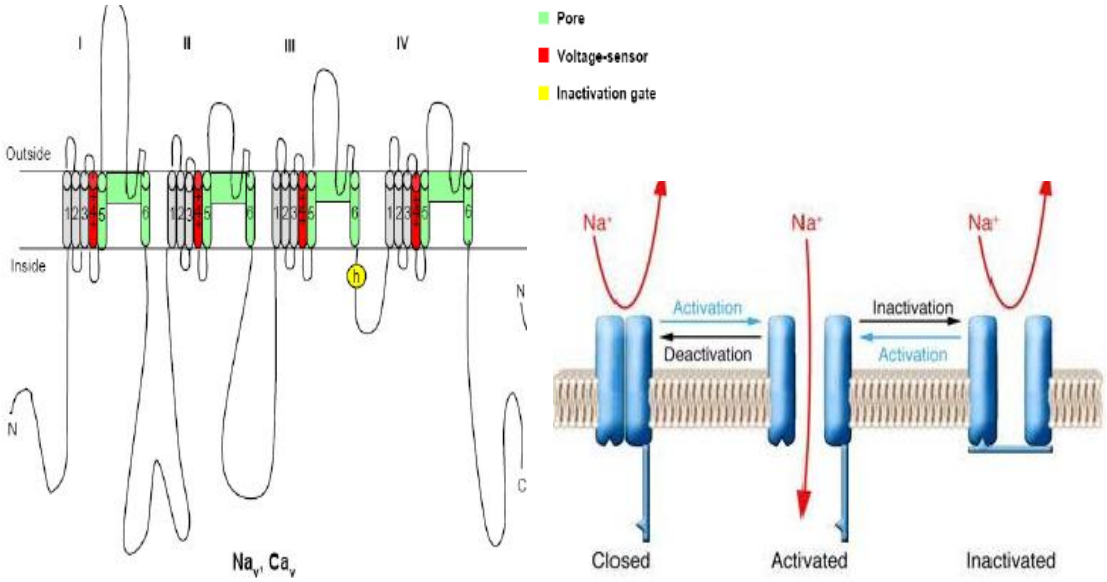


Figure 9: Voltage gated channel [56]

The effects of the interaction of marine polyethers with site 5 include repetitive neuronal firing, shifting of the voltage dependence, and blocking of the channel inactivation process. The difference in activities of the polycyclic ethers was explained in 2003 when Yasumoto compared the influence of the size of the marine toxins on the binding to the site 5 (**Table 7**).

[54] Nagai, Murata, Torigoe, Satake and Yasumoto, *J. Org. Chem.* **1992,** 57, (20), 5448-53, Nagai, Torigoe, Satake, Murata, Yasumoto and Hirota, *J. Am. Chem. Soc.* **1992,** 114, (3), 1102-3.
[55] Inoue, Hirama, Satake, Sugiyama and Yasumoto, *Toxicon* **2003,** 41, (4), 469-74.
[56] Wang, *Mar. Drugs* **2008,** 6, (2), 349-71, Arias, *Mar. Drugs* **2006,** 4, (3), 37-69.

Polyether	K_i (μM)	$\Delta G_{binding}$ (kcal/mol)	Number of fused rings	Accessible surface area ($Å^2$)
CTX	1.5×10^{-4}	12.3	13	1401
CTX3C	0.81×10^{-4}	12.6	13	1380
PbTx-3	0.81×10^{-3}	11.1	11	1140
Gambieric acid A	0.11	8.7	9	1049
Gambierol	1.4	7.3	8	911

Ki = dissociation constant

Table 7: Influence of the number of fused rings to the binding to site 5

PbTx-3 was used as a control and the activities of the polyethers were assessed by the competitive displacement of [^{3}H]PbTx-3 from binding sites in rat brain synaptosomes. Since the activities of brevetoxins and ciguatoxins are known to be insensitive to their side chain structure, it was assumed that the side chain didn't play a crucial role in the binding at site 5. The $\Delta G_{binding}$ was plotted against the number of fused rings of the polycyclic ether. It was found that there is a linear relationship between them. These results show that there is a strong correlation between the number of fused rings and the binding affinity.

Interestingly, the ladder-shaped polycyclic ethers exhibit a broad spectrum of biological activities. For example the brevetoxins (LD_{50} > 200 μgkg^{-1}in mice) and ciguatoxins (LD_{50} = 0.25 μgkg^{-1} in mice) are potent neurotoxins while gambieric acid is not a mamalian toxin but acts as a potent antifungal agent. Both gambieric acids A and B possess potent activity against filamantous fungi such as *Aspergillus Niger* and *Aspergillus fumigatus*.[57] Using the paper disk method to evaluate the antifungal potency of the gambieric acids, it was found that the gambieric acids are 50 to 2,000 times more efficient than amphotericin B in the experimental conditions. The antifungal activity of gambieric acid A was also compared to that of gambieric acid B for different types of microorganism (**Table 8**).

[57] Nagai, Mikami, Yazawa, Gonoi and Yasumoto, *J Antibiot (Tokyo)* **1993,** 46, (3), 520-2.

Microorganism	MIC and sub-MIC value (μg.mL^{-1})		
	GA-A	GA-B	AMPH
Aspergillus fumigatus No. 184	0.39 (0.025)	0.78 (0.05)	3.13
A. niger IFM 40606	0.20 (0.025)	0.2 (0.025)	3.13
A. oryzae IFM 40607	3.13 (>0.01)	6.25 (0.025)	6.25
Epidermophyton floccosum IFM 40770	3.13 (>0.01)	1.56 (>0.01)	3.13
Paecilomyces variotii IFM 30539	0.78 (0.01)	0.78 (0.05)	3.13
Penicillium chrysogenum Q176	1.56 (0.1)	1.56 (0.05)	6.25
P. citrium IAM 7003	3.13 (>0.01)	3.13 (>0.01)	≥12.5
Trichophyton mentagrophytes IFM 45110	0.78 (>0.01)	0.78 (>0.01)	1.56

Table 8: Antifungal activity of gambieric acid A and B

The results obtained in this table show that there is a 60 to 1000 fold difference in the activity of gambieric acids compared to the MIC of amphotericin B. More precise results were obtained using a paper disc assay. Interestingly, these results showed that, although the structures of gambieric acid A and gambieric acid B differ only in the presence of an additional methyl group in the latter, gambieric acid A was slightly more active than gambieric acid B. It was also shown that the antifungal activity of gambieric acids was potentiated by iron salts (e.g. $FeCl_3$ or $FeSO_4$). In the same publication, the cytotoxicity of gambieric acids was tested. Aliquots of serially diluted solutions of gambieric acids in methanol were added to wells containing 100 μL of a culture containing approximatly 5,000 cells. After incubation and the addition of isotopes of ^{3}H-thymidine, ^{14}C-leucine and ^{3}H-uridine, the ratio of isotopes was calculated. IC_{50} values for gambieric acid A were found to be 490, 480 and 120 ng/mL and the cytotoxicity of gambieric acid B was slightly higher.

Structure

In order to investigate the biological properties of these compounds further, it has become necessary to access gambieric acid chemically. The limited quantities of the molecule that are available made it a real challenge to determine the structure; it was only in 1992 that structures of gambieric acids A to D were first reported.[58] After an exhaustive extraction process from a culture of *Gambierdiscus toxicus* followed by purification, gambieric acid A was obtained as a white amorphous solid. HR-FABMS was used to establish the molecular formula of the compound as $C_{59}H_{92}O_{16}$. The IR spectrum (KBr) showed a band at 1735 cm^{-1} which is characteristic of a carboxylic acid group and another at 3500 cm^{-1} which is typical of hydroxyl groups.

[58] Nagai, Murata, Torigoe, Satake and Yasumoto, *J. Org. Chem.* **1992,** 57, (20), 5448-53, Nagai, Torigoe, Satake, Murata, Yasumoto and Hirota, *J. Am. Chem. Soc.* **1992,** 114, (3), 1102-3.

The complete absolute configuration of gambieric acid was reported in 2000 by Yasumoto (**Figure 11**).[59] Most of the stereochemical assignments were made using two-dimensional NMR spectroscopy. Prior to NMR analysis, the anisotropic reagents, 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) and phenylglycine methyl ester (PGME), were introduced at the C9-OH and at position C1 respectively and a chiral fluorescent reagent as used for the assignment at C48. The framework of the molecule comprises of *trans/cis* fused cyclic ethers with ring sizes going from 5 to 9.

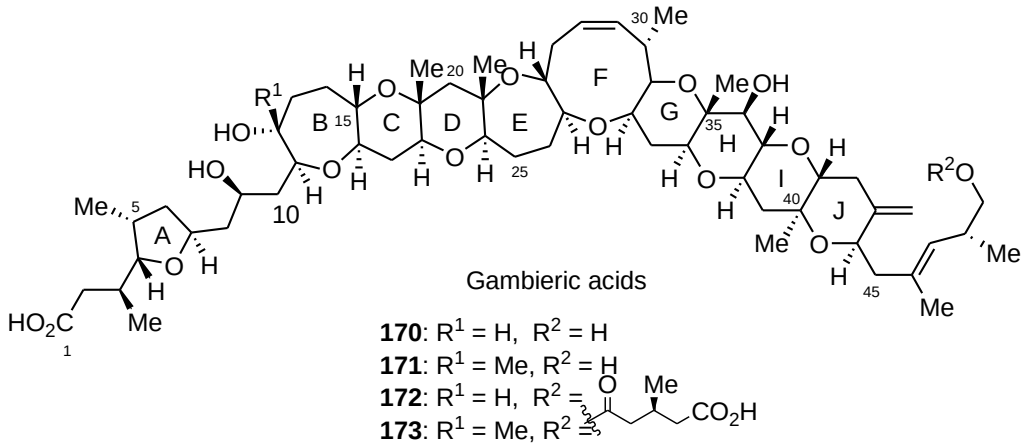
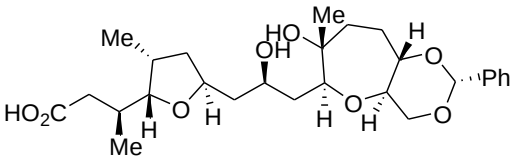


Figure 11: Absolute configuration of gambieric acids

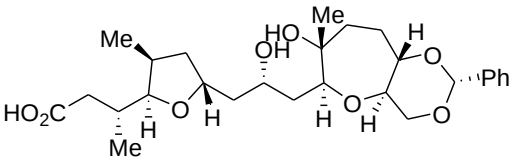
Although reports concerning the stereochemistry of gambieric acids were published in 1992, the sterochemistry of the molecule is still under investigation. Recent work from Sasaki concerning the synthesis of gambieric acid show inconsistencies with the original stereochemistry reported.[60] They reported the synthesis of the A/B ring fragment of gambieric acid B and when comparing the ^{1}H and ^{13}C chemical shifts for the C1-C13 portion of their synthetic intermediate with those of the corresponding moiety of gambieric acid B, they observed significant deviations. The synthesis of three possible diastereomers of the assumed structure and the comparison of their NMR chemical shifts led them to the conclusion that all the stereocentres around the A ring fragment were inverted (**Figure 12**).

[59] Yasumoto, *Chem. Rec.* **2001,** 1, (3), 228-42.
[60] Fuwa, Goto and Sasaki, *Org Lett* **2008,** 10, (11), 2211-4.



172

Yasumoto's structure 1992



173

Sasaki's structure 2008

Figure 12: Comparison of A-ring potential structures

Biosynthesis of polycyclic ethers

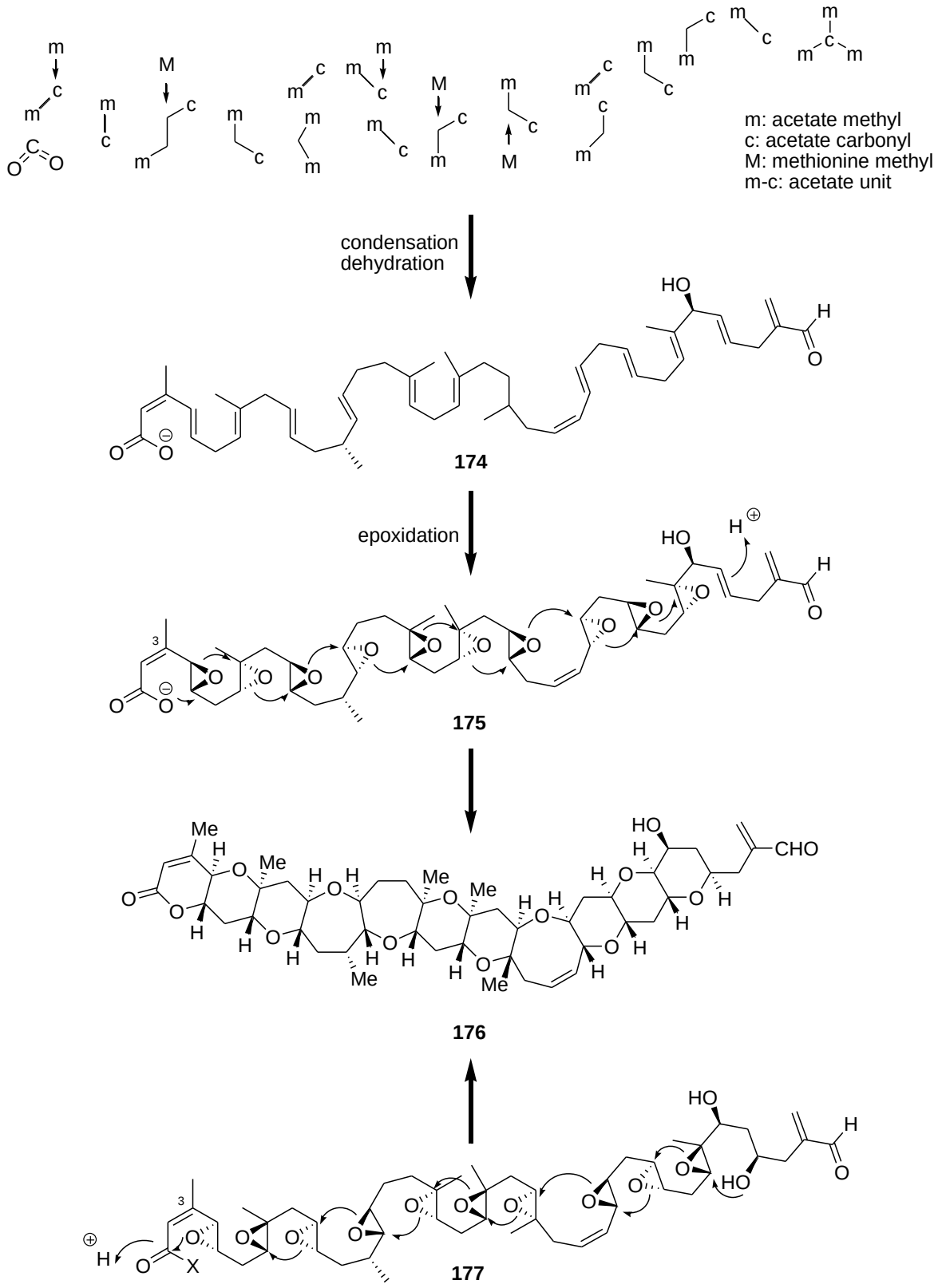
The first schematic pathway for the biosynthesis of polycyclic ethers was described by Nakanishi in 1989.[61] When ^{13}C labelled precursors were fed to the alga, incorporation results indicated that a cyclisation cascade occurs by an epoxide-opening cascade, but it doesn't explain the origin of the oxygen atoms. The reaction pathway was assumed to involve condensation of acetate units to form a polyene, followed by epoxidation and subsequent cyclisation *via* epoxide opening (**Scheme 33**).[62]

Our understanding of the mechanism became clearer when the biomimetic regio- and stereoselective oxacyclization of a substrate containing an internal disubstituted epoxide were achieved.[63] These mechanistic studies showed that the driving force of the reaction was the ring strain. The crucial importance of the substituent in C-3 position of the 7-membered ring was also observed.

One limitation of this biosynthetic pathway is that the cascade of epoxide-opening reactions is kinetically disfavoured in organic solvent. However in 2007, Jamieson reported that the selectivity of the terminal ring cyclisation event was pH dependant.[64] Indeed, he observed that selectivity for formation of the desired THP product increased as the pH approached neutral. Confirming his assumptions, he showed that when using deionised water to carry out the reaction, the ratio of THP product compared to THF product increased to >11:1.

In a review published in 2008, Gallimore described an enzymatic mechanism for epoxide formation as well as the cyclisation reaction, whereas previous reports had involved only Lewis acid catalysed epoxide opening reactions.[65]

[61] Lee, Qin, Nakanishi and Zagorski, *J. Am. Chem. Soc.* **1989,** 111, (16), 6234-41.
[62] Giner, *J Org Chem* **2005,** 70, (2), 721-4.
[63] McDonald, Bravo, Wang, Wei, Toganoh, Rodriguez, Do, Neiwert and Hardcastle, *J Org Chem* **2002,** 67, (8), 2515-23, Valentine and McDonald, *Synlett* **2006**, (12), 1816-28.
[64] Vilotijevic and Jamison, *Science* **2007,** 317, (5842), 1189-92.
[65] Gallimore Andrew, *Nat Prod Rep* **2009,** 26, (2), 266-80.



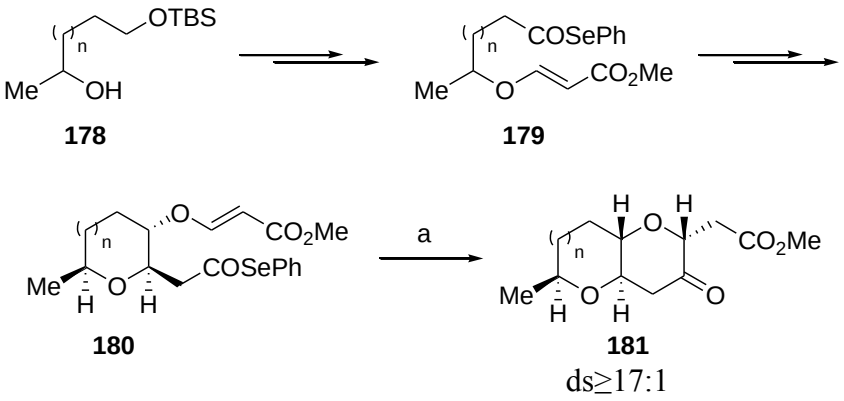
Scheme 33 : Biosynthetic and mechanistic pathway for the formation of brevetoxins B

1.3.3 Previous synthetic studies concerning the gambieric acids

The fascinating structures and stereochemical challenges of the gambieric acids as well as their potential biological properties make these molecules attractive targets for total synthesis. Although no report of the total synthesis has been published to date, these compounds have been the focus of attention for many research groups and several fragments of the molecule have already been synthesised.

Evan's approach

In 1996, Evans and co-workers reported an iterative approach to the synthesis of polycyclic ethers *via* acyl radical cyclisations (**Scheme 34**).[66] This strategy can be applied for the synthesis of the BC- and IJ-segments of the gambieric acids (respectively left and right hand).



Reagents: a) $(TMS)_3SiH$, Et_3B, RT, air, 91-99 %

Scheme 34: Evans iterative strategy to access polycyclic ethers

The precursor for the cyclisation reaction **179** was prepared by short sequence involving treatment of secondary alcohol **178** with methylpropiolate followed by Jones oxidation. The carboxylic acid obtained was converted into the corresponding acyl selenide using Crich's protocol. The cyclisation then occurred by treatment of the selenide with tris(trimethyl)silane and triethylborane at room temperature in presence of air. The six-membered ring was obtained in a 5.7:1 ratio whereas the seven-membered ring was obtained in a ≥ 19:1 ratio. In the case of the 6-membered ring product, the equilibrium could be displaced in the favour of the desired *cis*-compound by treatment with a catalytic amount of DBU in refluxing benzene.

[66] Evans, Roseman and Garber, *J. Org. Chem.* **1996,** 61, (15), 4880-81.

Reduction of the keto esters using appropriate reaction conditions followed by protection of the primary alcohol left the secondary alcohol free to be converted into the corresponding acyl selenide. Treatment of these intermediates using the same conditions as for the first cyclisation reaction furnished the bicyclic ethers in excellent yield and with excellent diastereoselectivity. The improved selectivity for this second cyclisation reaction in comparison to the first one is explained by a transition state where the pyran and oxepane rings lock the substitutents in a pseudo-equatorial environment (**Figure 13**).

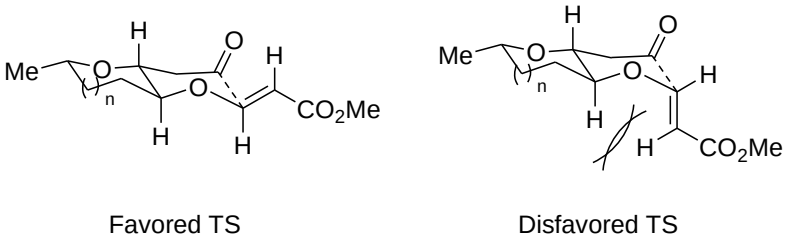
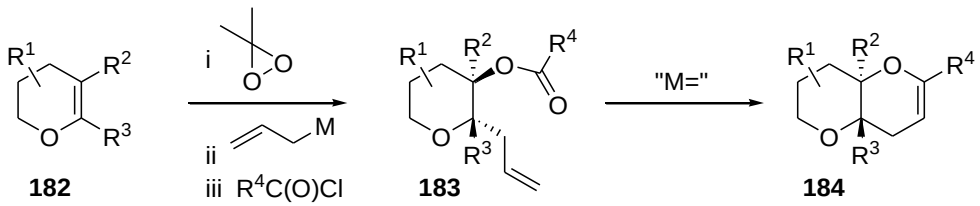


Figure 13: Transition state for the formation of the second ether ring

Rainier's aproach

In 1998, Rainier and co-workers reported a new approach to the formation of polycyclic ethers involving a five-step iterative approach for the formation of the fused ether ring system.[67] The strategy for pyran formation mainly relies on a stereoselective epoxidation followed by nucleophilic epoxide opening and a subsequent annulation reaction (**Scheme 35**).

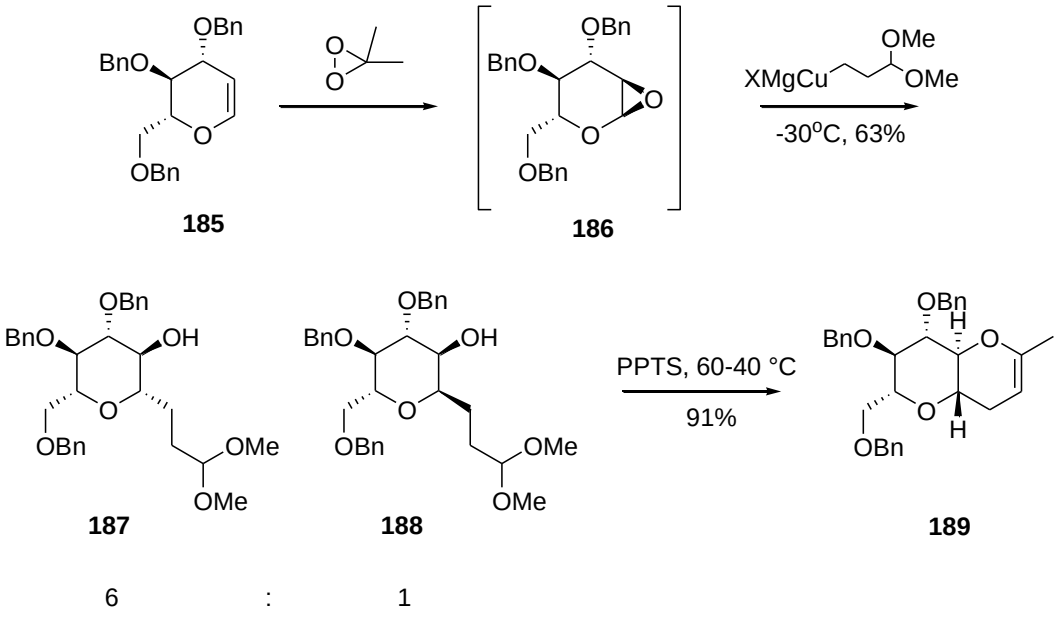


Scheme 35: Rainier's approach to fused ether system formation

Although this synthetic strategy showed promising results, the sequence had some limitations regarding the epoxidation and coupling sequence as well as the annulation reaction. The stereochemical outcome and the yield of formation of **183** were shown to be undesirable and moderate. The formation of intermediate **184** could be achieved but only using a stoichiometric amount of the catalyst.

[67] Rainier and Allwein, *Tetrahedron Lett.* **1998,** 39, (52), 9601-04.

The synthetic strategy above was later optimised. The moderate yield and the lack of selectivity observed for the formation of **183** could be overcome using an appropriate cuprate for the coupling reaction (**Scheme 36**). The mixed acetal was then subjected to the cyclisation and elimination sequence. The desired bicyclic enol ether was isolated in excellent 91% yield using this procedure. Using this approach cyclisation and elimination could be accomplished in a single step.



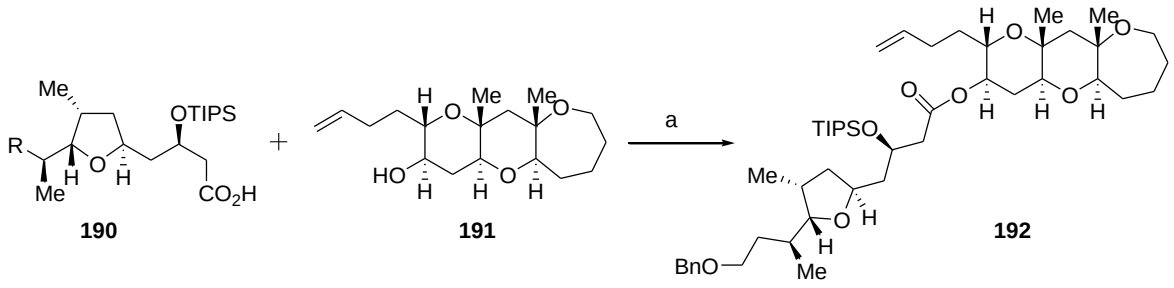
Scheme 36: cyclic ether formation

The bicyclic system produced using the sequence in **Scheme 36** can then undergo additional iteration to introduce another fused ring. Unfortunately, epoxidation using the same conditions as previously resulted in poor yields, but the problem was solved by using the same reaction conditions at higher temperature. In the same publication, Rainier, demonstrated that this approach can also be used to construct larger rings such as 7-membered ring cyclic ethers.

With this methodology in hand, Rainier reported the synthesis of an A-E gambieric acid subunit.[68] The fragment would be formed by the coupling of an appropriately substituted A-ring and C-E sub-units followed by the pairing of the resulting pentacycle with an appropriately trisubstituted tricyclic H-J precursor. In this report, the A-ring was formed in an 8-step sequence from an intermediate available in six steps from the Myers pseudoephedrine auxiliary. A succession of oxidation alkylation and protecting group manipulations then gave the highly substituted A-ring fragment with the desired

[68] Roberts and Rainier, *Org Lett* **2007,** 9, (11), 2227-30.

stereochemistry. With both A-ring and C-E fragment in hand, only the coupling remained to be done (**Scheme 37**).



Reagents: 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, 69%

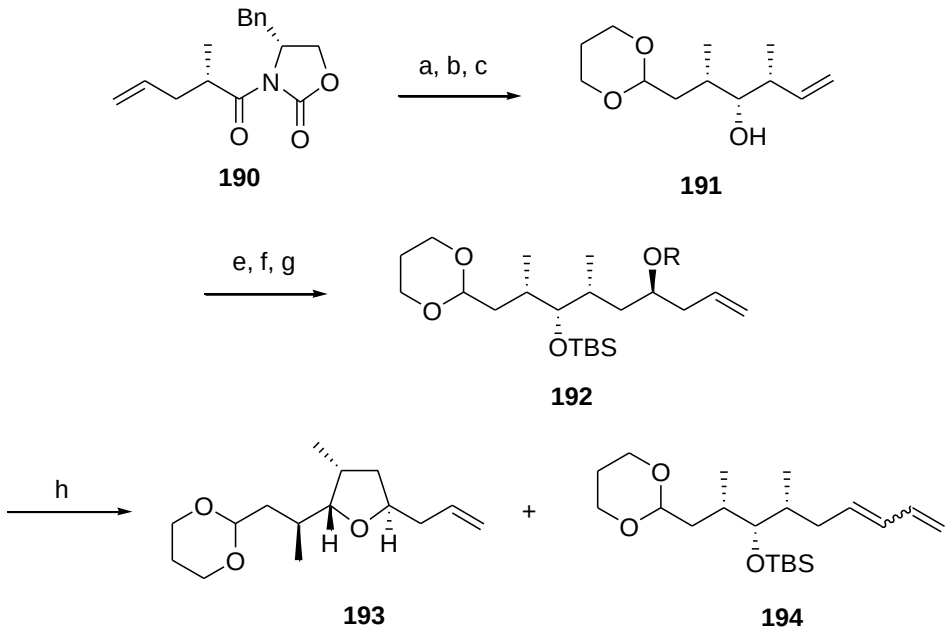
Scheme 37: Coupling of the A-to the C-E ring fragment

The coupling between the fragments was performed using the Yamaguchi protocol. It gave the desired ester with an unoptimised 69% yield. Functional group manipulation followed by ring closing metathesis and the use of an *in situ* prepared titanium ethylidene reagent led to the formation of the B-ring as a mixture of products in < 50% yield.

Yamamoto's approach

In 2001, Yamamoto reported the synthesis of the A and J-segments of the gambieric acids.[69] The strategy employed by Yamamoto for the synthesis of the A-ring fragment of the gambieric acids with the desired stereoselectivity is based on an Evans asymmetric alkylation, Brown asymmetric crotyl-boration and allyl-boration sequence, and an intramolecular S_N2 reaction (**Scheme 38**).

[69] Kadota, Oguro and Yamamoto, *Tetrahedron Lett.* **2001,** 42, (21), 3645-47, Kadota, Takamura and Yamamoto, *Tetrahedron Lett.* **2001,** 42, (21), 3649-51.

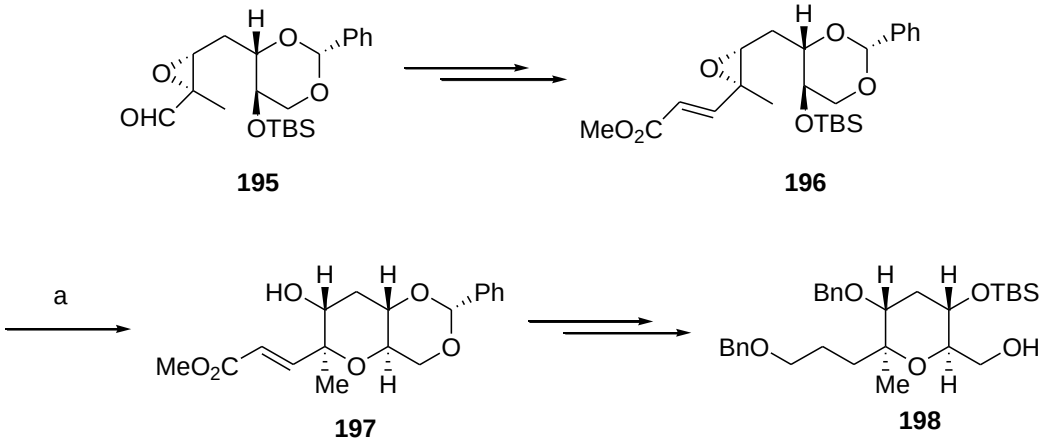


Reagents: a) (i) O_3, MeOH, -78 °C to RT; (ii) 1,3-propanediol, *p*-TsOH, benzene reflux; b) $LiBH_4$, H_2O, ether, 0 °C to RT; c) (i) $(COCl)_2$, DMSO, DCM, Et_3N, -78 °C, (ii) Ipc_2B-(*Z*)-crotyl, THF, -78 °C, H_2O_2, NaOH, 65 °C; d)TBSCl, 2,6-lutidine, DCM 0 °C; e) 9-BBN, THF, RT, H_2O_2, NaOH; f) (i) DMP, $NaHCO_3$, DCM, RT, (ii) Ipc_2B-allyl, ether, -78 °C, H_2O_2, NaOH; g) MsCl, Et_3N, DCM, 0 °C to RT; h) TBAF, THF, RT.

Scheme 38: Yamamoto's strategy to access the A-ring fragment of the gambieric acid

The first step of the synthesis was the introduction of the first stereocentre by Evans stereoselective alkylation and was followed by protection of the resulting aldehyde as a cyclic acetal. The chiral auxiliary was then removed and the resulting primary alcohol was oxidised to give the corresponding aldehyde. The homoallylic alcohol **191** was obtained by treatment of the aldehyde with (*Z*)-crotylborane derived from (+)-pinene. Protection of the secondary alcohol and hydroboration of the terminal alkene gave the desired primary alcohol, which was then oxidised to give the corresponding aldehyde. A Brown asymmetric allylboration reaction led to the formation of the secondary alcohol **192** (R = H). This alcohol could undergo cyclisation by converting the free secondary alcohol into a mesylate and removing the TBS-ether under basic conditions. This sequence allowed the formation of the A-ring fragment in 8 steps from the imide **190** in 40% overall yield.

In the same journal, Yamamoto published the synthesis of the other terminal segment (J-ring) of the gambieric acids. This approach relies on the formation of a highly substituted tetrahydropyran by stereoselective 6-*endo*-cyclisation of a hydroxyepoxide prepared from deoxy-D-ribose. This tetrahydropyran could then undergo coupling with an alkenyl iodide to introduce the terminal side chain (**Scheme 39**).

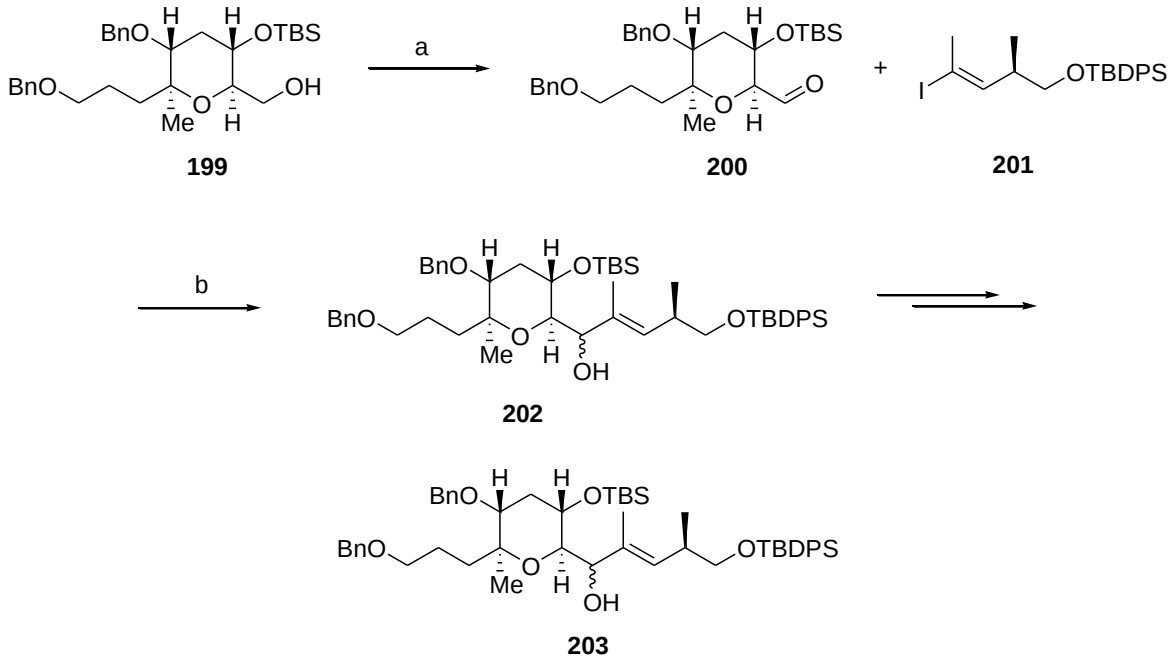


Reagents: a) cat PPTS, DCM, RT

Scheme 39: Tetrahydropyran formation

The tetrahydropyran ring was formed in a few steps from aldehyde **195**. Wittig reaction followed by deprotection of the secondary alcohol gave the cyclisation precursor. A 6-*endo* cyclisation reaction occurred upon treatment of the epoxide with PPTS and resulted in the formation of **197** exclusively. Functional group interconversion and protecting group manipulation gave the desired tetrahydropyran ring **198** in 9 steps and 42% overall yield.

In parallel to the synthesis of the 6-membered ring, the side chain was synthesised in 6 steps by a sequence involving a regio and stereoselective hydrostannation. Optimisation of the coupling between the two fragments was investigated and the best results were obtained by treatment of the fragments with *t*-BuLi (**Scheme 40**).



Reagents: a) $(COCl)_2$, DMSO, DCM, -78 °C, Et_3N ; b) *t*-BuLi, ether, -78 °C

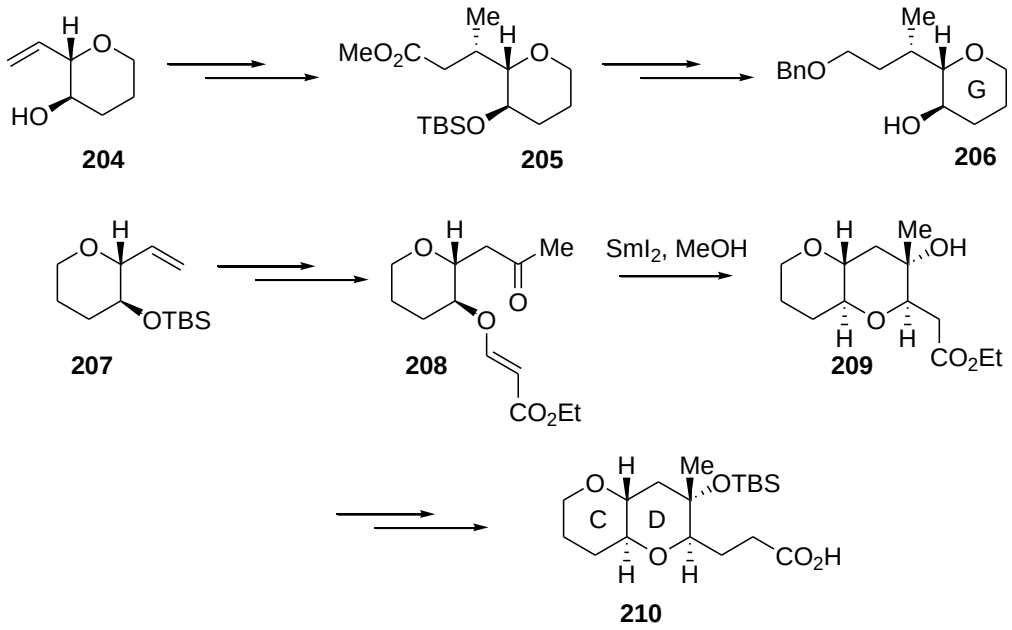
Scheme 40: Coupling of the J-ring tetrahydropyran fragment with the alkenyliodide

Oxidation of the primary alcohol **199** under Swern conditions afforded the aldehyde **200** which could undergo coupling with alkenyliodide to install the side chain. The coupling product was obtained as a mixture of diastereoisomers. The synthesis of the J-fragment was completed by sequential treatment with CS_2/KH, and MeI followed by free radical deoxygenation of the resulting xanthate.

Sasaki 's approach

After completing the total synthesis of gambierol in 2002, Sasaki focused his efforts on the total synthesis of gambieric acid. In 2005, he reported the total synthesis of the C-G fragment of the molecule.[70] The strategy employed for the formation of this fragment involve an intramolecular radical cyclisation to form the seven-membered G-ring and ring closing metathesis for the formation of the nine-membered F-ring. The synthetic sequence started with the formation of the CD-ring system and G-ring individually (**Scheme 41**).

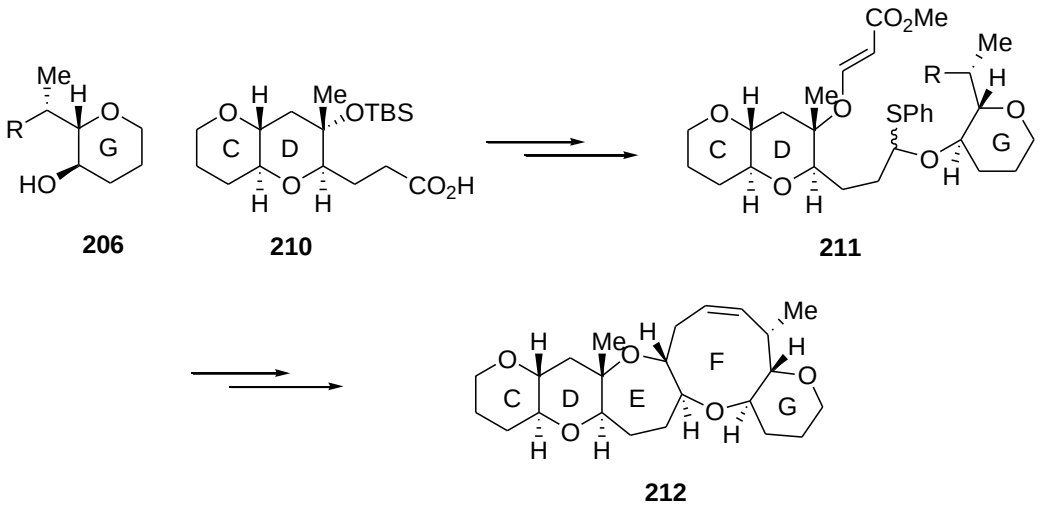
[70] Sato and Sasaki, *Org Lett* **2005,** 7, (12), 2441-4.



Scheme 41: Synthesis of the CD- and G- ring of gambieric acid

Alcohol **204** was first protected as a silyl ether and the alkene was cleaved using osmium tetroxide to allow the formation of the desired ketone which could then undergo Wittig reaction. Cuprate mediated 1,4-addition gave the formation of intermediate **205** as a sole product. Protecting group interconversion led to the formation of the G-ring **206** in 65% overall yield from alcohol **204**.

The synthesis of the CD-fragment started with protected alcohol **207**. Introduction of the methyl ketone was achieved by regioselective hydroboration of the double bond. The primary hydroxyl group was then oxidised to the corresponding aldehyde under Swern conditions which then underwent Grignard addition. The secondary alcohol was then oxidised to form the desired methyl ketone. The TBS-ether was then removed and the primary alcohol treated with ethyl propionated to give the cyclisation precursor **208**. The reductive cyclisation was achieved using SmI_2 in methanol to give bicyclic product **209**. Functional group manipulation led to the formation of the desired CD-fragment in 47% overall yield from **207**. The coupling of the CD- and G-rings was then achieved through esterification followed by the formation of the E-ring as a lactone (**Scheme 42**).

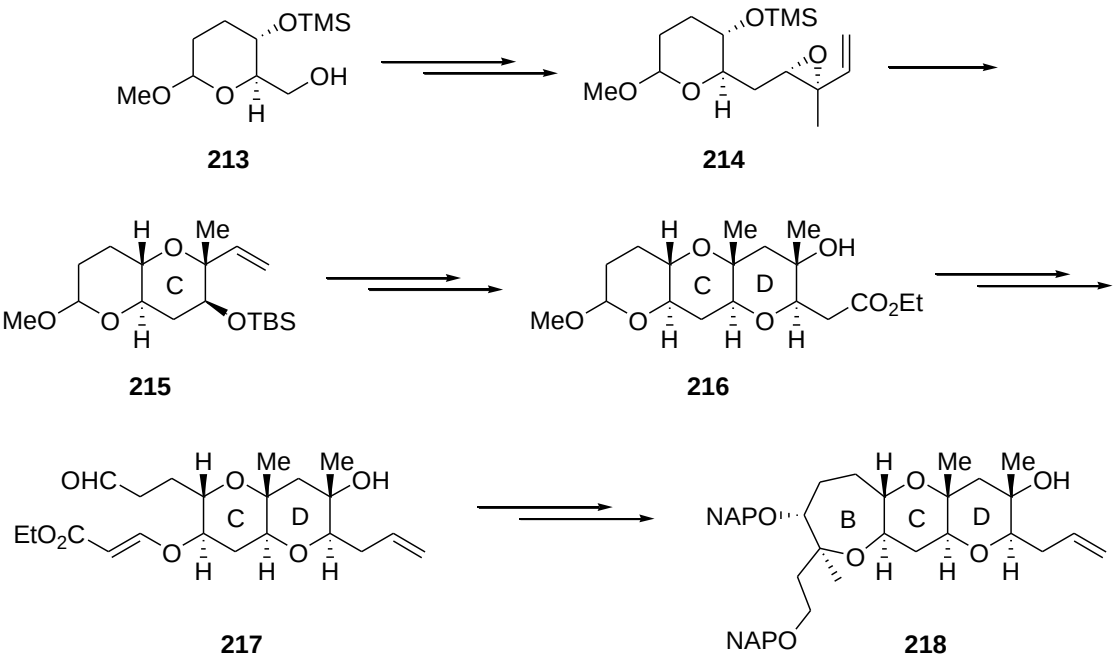


Scheme 42: Sasaki's approach to the C-G ring fragment

The coupling of the two fragments was accomplished by Yamaguchi esterification and led to the coupled product in high yield. Functional group interconversion and stereoselective allylation provided the mixed thioacetal **211,** the precursor for the radical cyclisation, in modest yield. Unfortunately, attempted cyclisation of the compound **211** resulted in the formation of a complex mixture of products. Another route was then chosen involving formation of the E-ring using Yamaguchi lactonisation followed by stereoselective allylation with allytrimethylsilane in presence of BF_3•OEt_2 and subsequent construction of the nine-membered ring by ring closing metathesis using Grubbs second generation catalyst.

This work was followed two years later by the publication of the synthesis of the B-J fragment of gambieric acid.[71] The synthesis of the nonacyclic fragment was achieved by coupling of the B-D and G-J subunits using methodology developed and optimised previously for the C-G fragment. The BCD-ring fragment was available in a 32-step sequence from readily available trisubstituted tetrahydropyran **213** (**Scheme 43**).

[71] Sato and Sasaki, *Angew Chem Int Ed Engl* **2007,** 46, (14), 2518-22, Sato and Sasaki, *Tetrahedron* **2007,** 63, (26), 5977-6003.

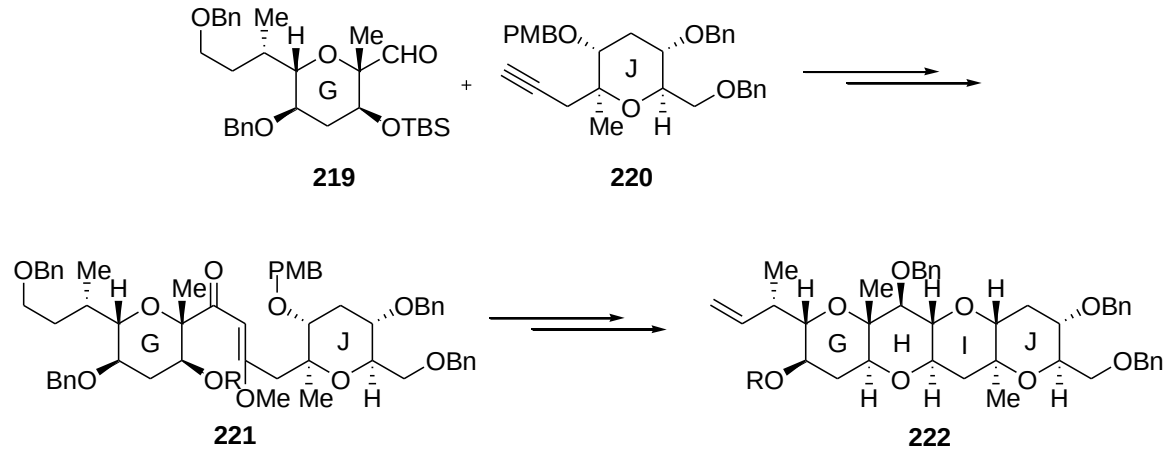


Scheme 43: Sasaki's approach to the B-D-fragment

Treatment of the epoxide **214**, formed using a Sharpless asymmetric epoxidation reaction, with PPTS afforded the desired 6-*endo* cyclisation product **215**. Formation of the D ring was achieved using the procedure described previously and the B-ring was then constructed as a single isomer by reductive cyclisation with SmI_2. The stereostructure of this first sub-unit was confirmed by observing NOEs in the ^1H NMR spectrum.

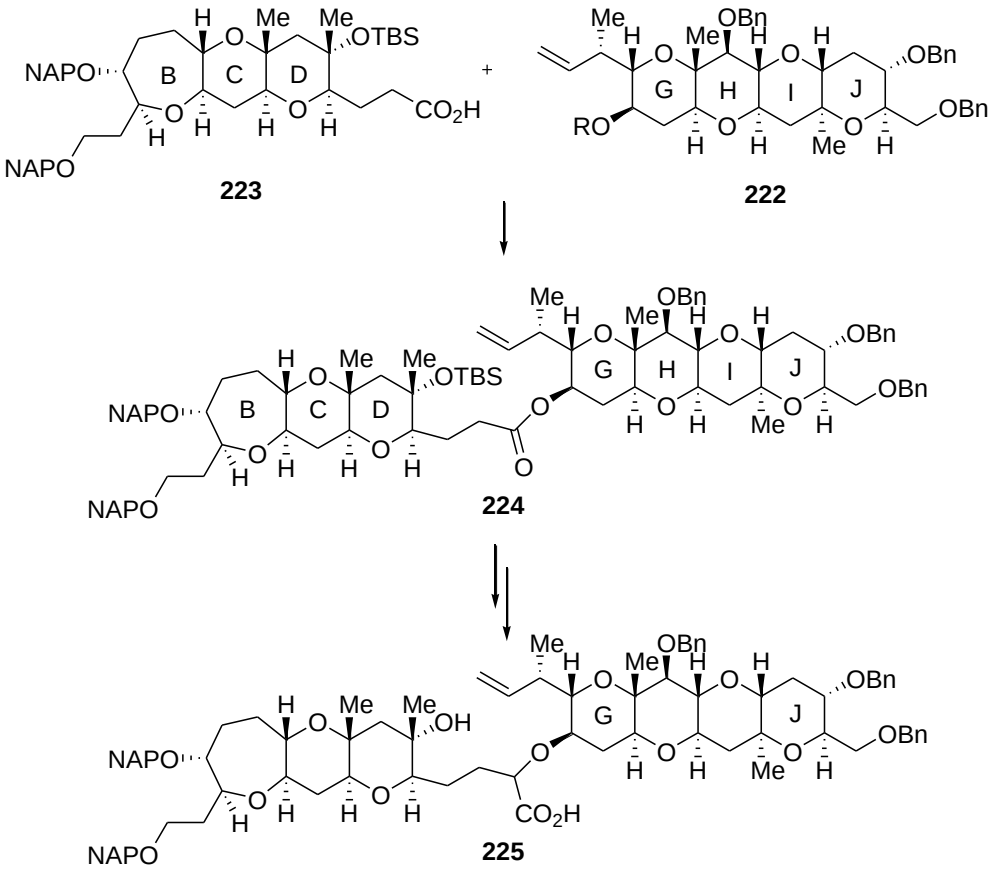
The GHIJ-ring fragment was formed by connection of the G and J rings followed by formation of the H and I rings as reported by the Nakata research group (**Scheme 44)**.[72] Reaction between alkyne **220** and aldehyde **219** provided the coupled product in good yield. The H-ring was formed by an intramolecular hetero-Michael reaction upon treatment of **221** with PPTS. Subsequent functional group interconvertion gave a dihydroxyketone which, after treatment with triethylsilane and TMSOTf, gave the desired tetracyclic ether **222**.

[72] Suzuki and Nakata, *Org Lett* **2002,** 4, (16), 2739-41.

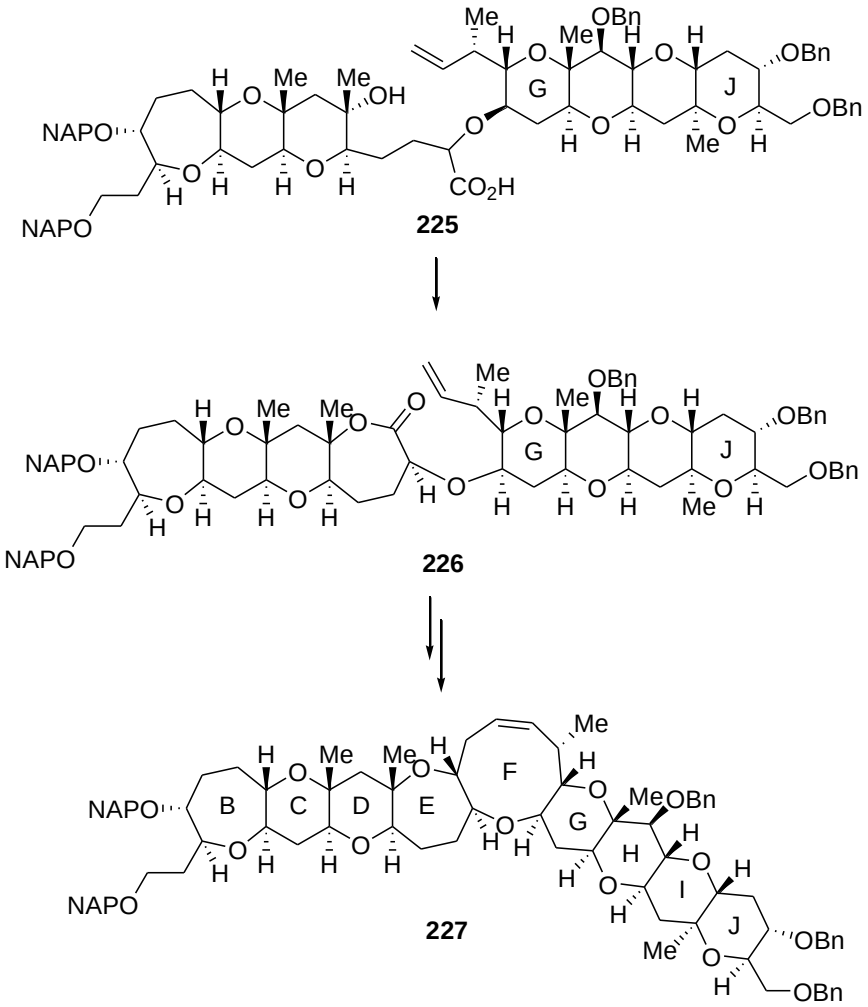


Scheme 44: Sasaki's approach to the G-J fragment of gambieric acid

The completion of the synthesis of the BJ-ring fragment of gambieric acid was achieved by union of BCD- and GHIJ- ring fragment through esterification (**Scheme 45**).[73] The formation of both E and F ring uses the optimised methodology Sasaki had developed previously in the synthesis of the C-G fragment.



[73] Sato and Sasaki, *Tetrahedron* **2007,** 63, (26), 5977-6003.

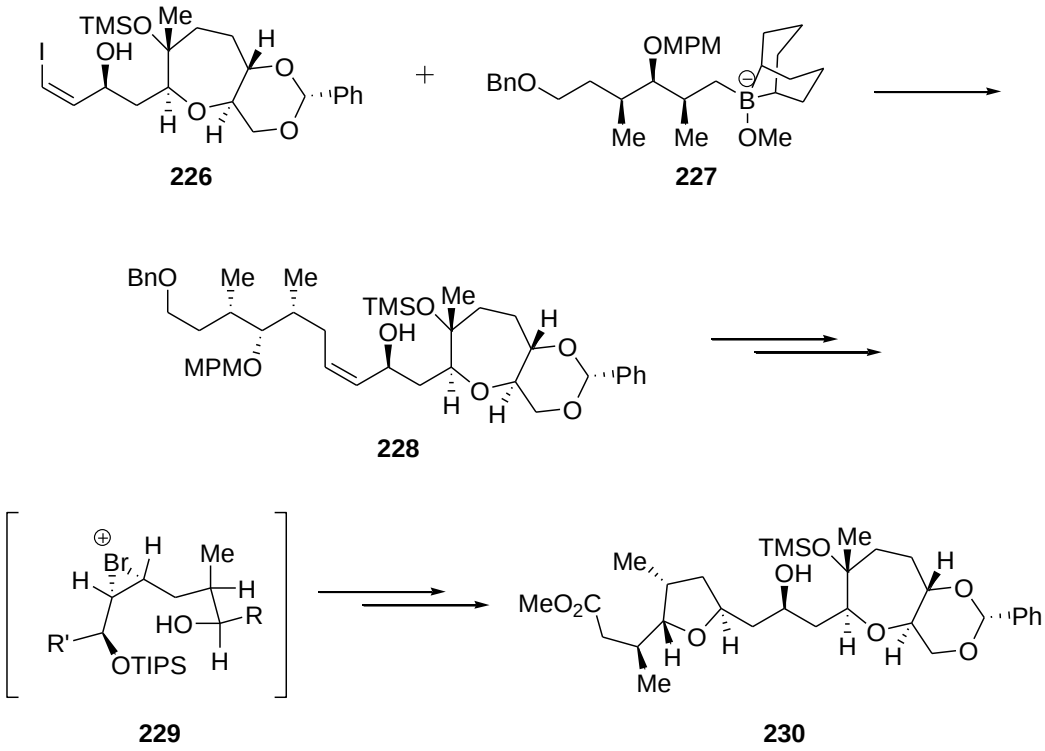


Scheme 45: Completion of the synthesis of the B-J fragment of gambieric acid

The coupling of both fragments **222** and **223** was achieved employing a Yamaguchi esterification and led to the formation of **224** in 92% yield. Functional group interconversion afforded the carboxylic acid **225** as a 1:1 mixture of diastereomers. Yamaguchi cyclisation led to the formation of a separable mixture of seven-membered E-ring **226**. The 9-membered F-ring was formed in a few steps using RCM methodology. The B-J-fragment was obtained in 45 steps (longest linear sequence) and 3.2% overall yield from the coupling reaction between **222** and **223**.

In 2008 Sasaki published the results of his investigation concerning the stereocontrolled synthesis of the A-B fragment of gambieric acid.[74] The route employed for this synthesis involved a diastereoselective bromoetherification in which stereoselective cyclisation led to the formation of the desired tetrahydrofuran ring (**Scheme 46**). The cyclisation precursor was prepared from *B*-alkyl Suzuki-Miyaura coupling of an alkylborate and a vinylic iodide.

[74] Fuwa, Goto and Sasaki, *Org Lett* **2008,** 10, (11), 2211-4, Fuwa, Suzuki, Sato and Sasaki, *Heterocycles* **2007,** 72, 139-44.



Scheme 46: Sasaki approach to the A-B ring fragment ofgambieric acid

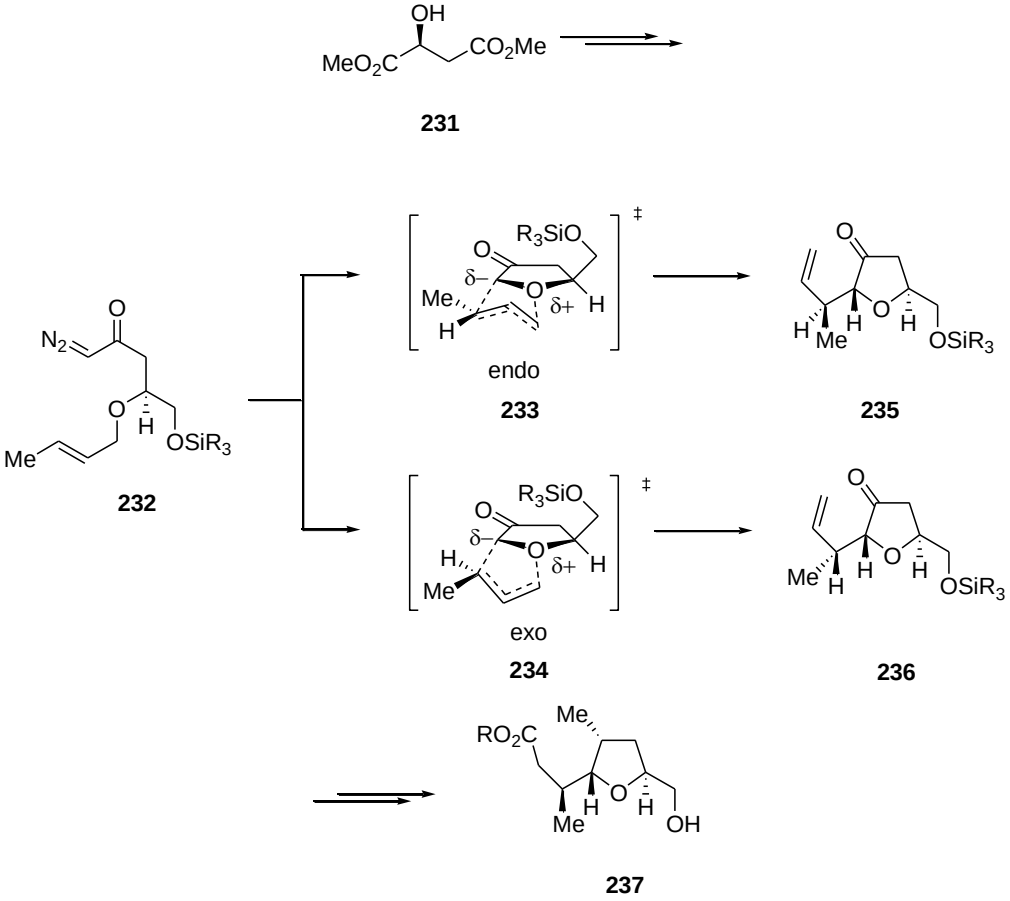
Vinylic iodide **226** was synthesised in 13 steps from readily available (2*R*,4*S*,5*R*)-4-(3-hydroxypropyl)-2-phenyl-1,3-dioxan-5-ol. Protecting group interconversion followed by reductive cyclisation upon treatment with SmI_2 resulted in the formation of the seven-membered ring in high yield. The side chain was introduced subsequently using a Wittig reaction followed by Sharpless epoxidation. Conversion to the corresponding propargylic alcohol was made using Takano protocol. The coupling of alkylborane **227** and iodide **226** was realised in presence of a $[PdCl_2(dppf)]/Ph_3As$ and cesium carbonate, and provided the desired *cis*-olefin. Protecting group manipulations on the hydroxyl groups followed by treatment with NBS in acetonitrile resulted in a diastereoselective bromoetherification to provide a bromide which was immediately reduced under radical conditions to furnish the desired tricyclic compound. The stereochemistry of the molecule around the tetrahydrofuran ring was proven by ^1H NMR spectroscopy (NOESY experiment).

Clark's approach

In 2004, Clark reported the stereoselective synthesis of the A-ring fragment of gambieric acid.[75] The key tetrahydrofuran ring intermediate was formed in a highly selectively manner by intramolecular generation of an oxonium ylide from a crotyl ether

[75] Clark, Fessard and Wilson, *Org. Lett.* **2004,** 6, (11), 1773-76.

and a copper carbenoid followed by subsequent [2,3]-sigmatropic rearrangement. The diazoketone precursor for this rearrangement reaction could be synthesised in a few steps from commercially available malic acid (**Scheme 47**).



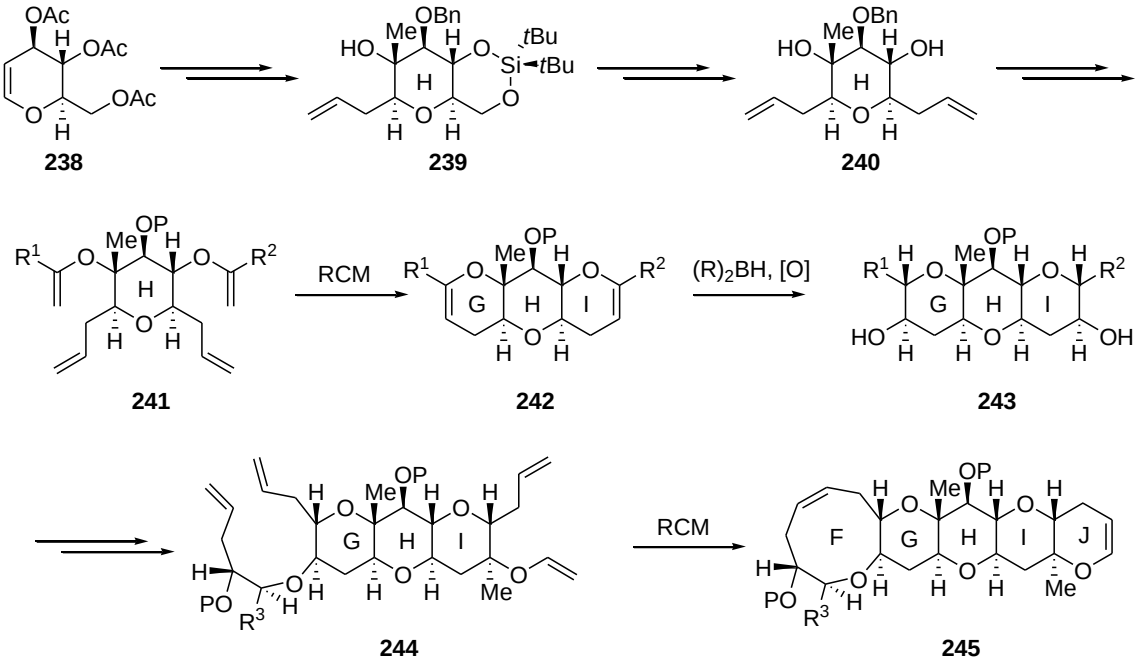
Scheme 47: Clark's synthesis of A-ring fragment of gambieric acid

The conversion of L-malic acid into the corresponding L-dimethylmalate was performed quantitatively by treatment with acidic methanol. One of the ester groups was reduced regioselectively and the resulting primary alcohol was selectively protected as a silyl ether. The secondary alcohol was converted into the desired *trans*-crotyl ether and the methyl ester converted into the corresponding carboxylic acid. Conversion of this carboxylic acid into the acid chloride and treatment with diazomethane gave the diazoketone **232** in a 6 steps sequence and 31% overall yield.

The key reaction of this route was the generation of the copper carbenoid precursor to the cyclisation and rearrangement reaction. Oxonium ylide formation and rearrangement resulted in the formation of both C-O and C-C bonds. Investigation of the mechanism of the reaction showed that the reaction proceeded *via* an endo transition state. Treatment of the diazoketone **232** with copper acetylacetonate afforded the desired cyclisation product

in 88% yield and excellent diastereoselectivity (>92:8). Completion of the synthesis was achieved by regioselective hydroboration followed by oxidation to obtain the keto acid. The carboxylic acid was then converted into the methyl ester and the ketone was converted into the methylene group by reaction with Nysted reagent and titanium(IV) chloride. The final product was obtained by deprotection of the primary alcohol followed by hydrogenation of the double bond to obtain the methyl group with the desired stereochemistry.

A year later, Clark reported a synthetic strategy for the synthesis of the F-J fragment of gambieric acid.[76] The methodology developed to access this fragment relies on the two-directional synthesis by iterative double simultaneous ring closure. The two-directional double-RCM reaction can be used twice in the synthetic route to access the desired fragment (**Scheme 48**).



Scheme 48: Clark's two-directional ring closing metathesis strategy to access F-J fragment of the gambieric acids

It has been demonstrated that RCM was a methodology that would allow access to a variety of ring sizes. This reaction can also tolerate a wide range of functional groups. The precursor for the two-directional ring closing metathesis reaction is accessible in 10 steps from commercially available tri-*O*-acetyl-D-glucal. Protecting group interconversion followed by epoxidation of the double bond allowed the insertion of the first side chain

[76] Clark, Kimber, Robertson, McErlean and Wilson, *Angew. Chem., Int. Ed.* **2005,** 44, (38), 6157-62, Clark, *Chem. Commun. (Cambridge, U. K.)* **2006**, (34), 3571-81.

using allylmagnesium chloride on the H ring. Swern oxidation followed by treatment of the resulting ketone with methyllithium at low temperature afforded the tertiary alcohol **239** with the desired stereochemistry. The side chains on the other side were introduced by protecting group manipulation followed by the displacement of a triflate group on the primary alcohol with a cyanocuprate generated from vinyllithium. The secondary and tertiary alcohol of diol **240** were then converted into the corresponding ethers using a one pot alkynylation procedure.

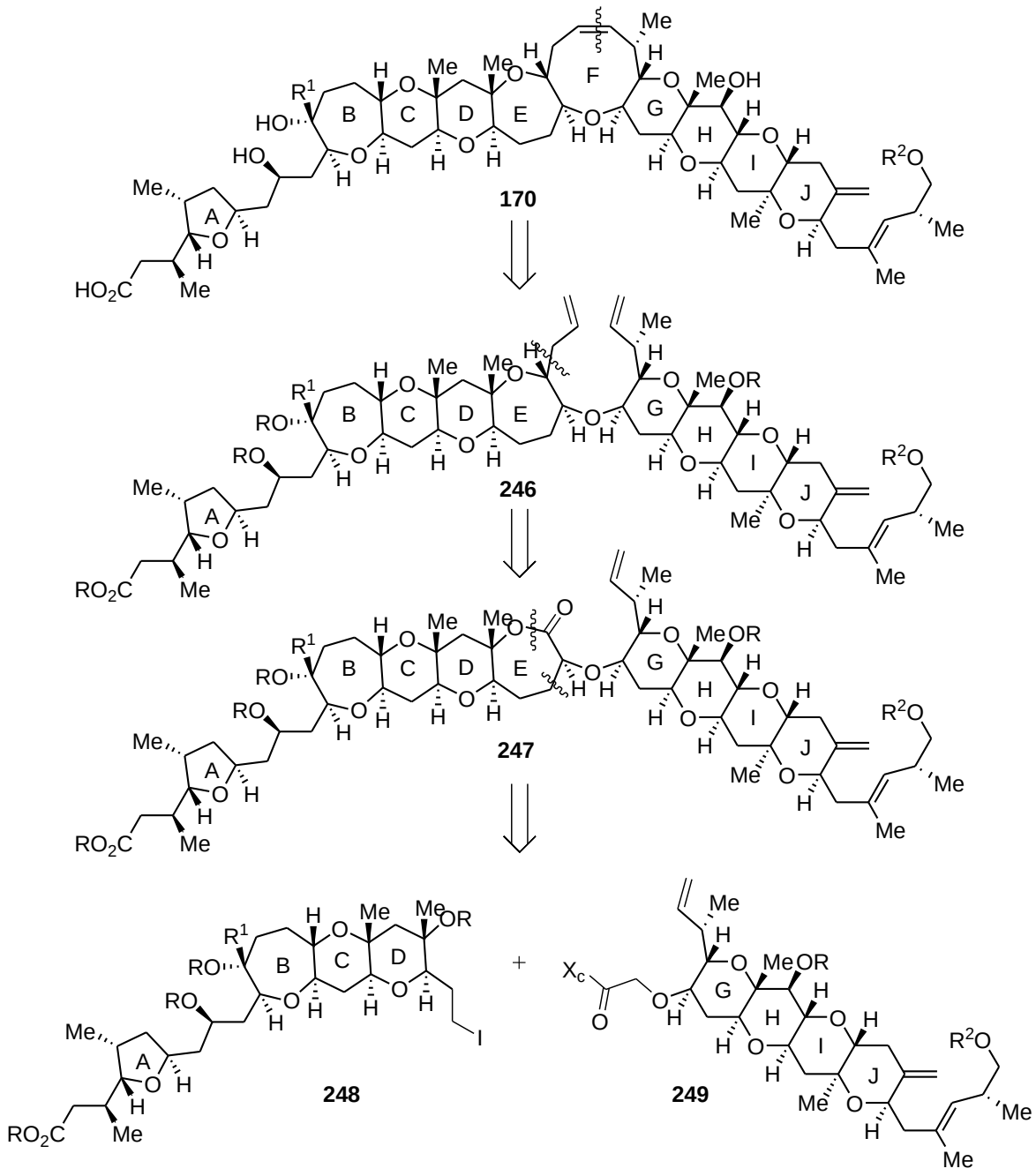
The precursor for the first double RCM reaction was obtained by sequential carbocupration reactions and treatment of the bis enol ether **241** thus obtained with Grubbs' second generation catalyst gave the tricyclic ether product **242**. The secondary alcohols in **243** were introduced by double hydroboration of the metathesis product using an excess of thexylborane. Protecting group manipulation allowed the differentiation of the two secondary hydroxyl groups. A 10-step sequence was used to introduce the alkenes on the side chain to obtain the precursor for the second double RCM reaction. The final double RCM was achieved using the same ruthenium catalyst and gave required 9- and 6-membered cyclic ethers. The polycyclic ether was therefore obtained in a total of 28 steps and 0.5% overall yield.

2 Results and Discussion

2.1 Towards the synthesis of the A-ring fragment of gambieric acid

2.1.1 Retrosynthetic analysis

The strategic approach adopted by our group for the synthesis of gambieric acid is based on the use of a convergent double ring closing metathesis (RCM) reaction as well as oxonium ylide formation and rearrangement (**Scheme 49**).



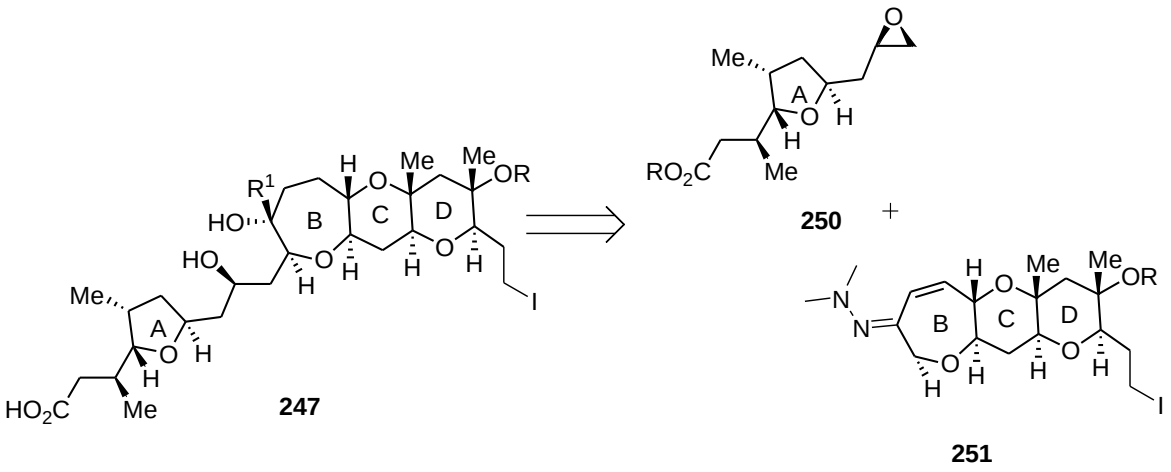
Scheme 49: Retrosynthetic analysis of gambieric acid

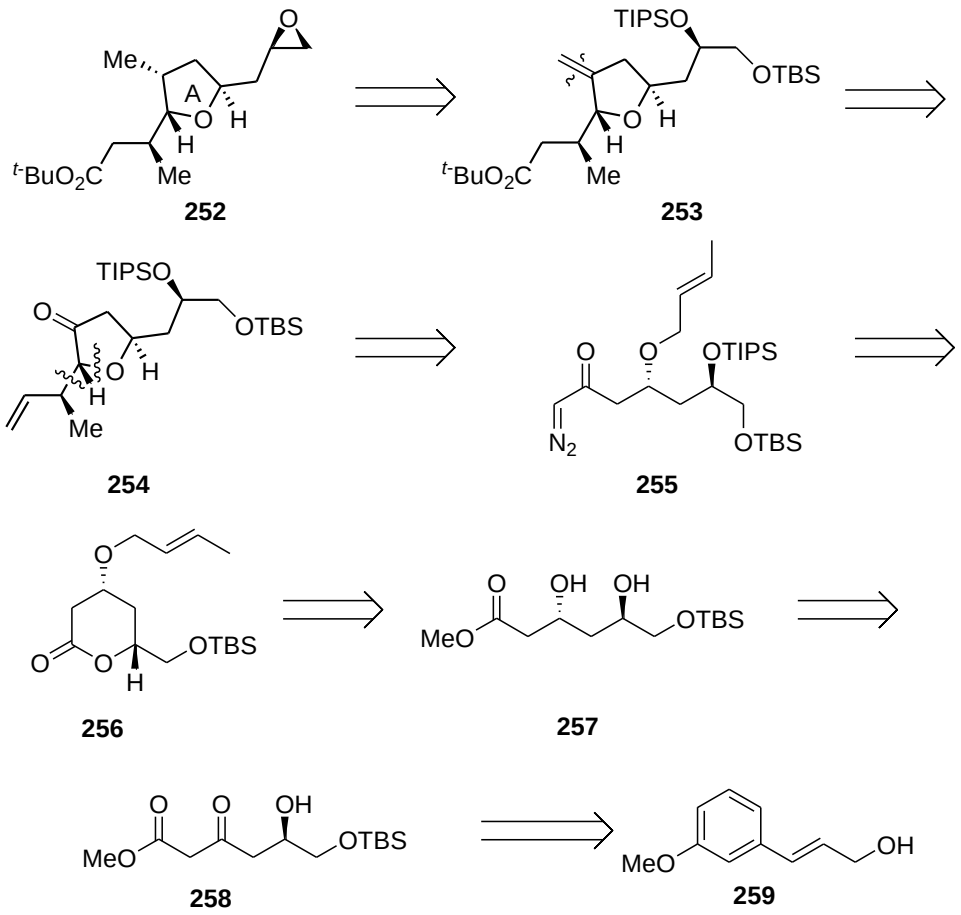
Retro-RCM of **170** would give diene **246**, the precursor for formation of the nine-membered F-ring. Disconnection of the allylic side chain on the E-ring reveals the lactone **247**. The seven-membered ring is then disconnected to give iodide **248** and Evan's auxiliary fragment **249**, which are approximately equivalent in size, by retro-lactonisation/alkylation.

2.1.2 Epoxide approach

Retrosynthetic analysis

The iodide **248** could then be disconnected to reveal both A and B-D fragments of gambieric acid by retro-epoxide opening (**Scheme 50**). The first approach investigated was the disconnection to the A-ring fragment, functionalised as an epoxide, and a B-D ring fragment, functionalised as a hydrazone. The choice of fragments bearing those functional groups is to allow the formation of the secondary alcohol with the desired stereochemistry when coupling both fragments together.



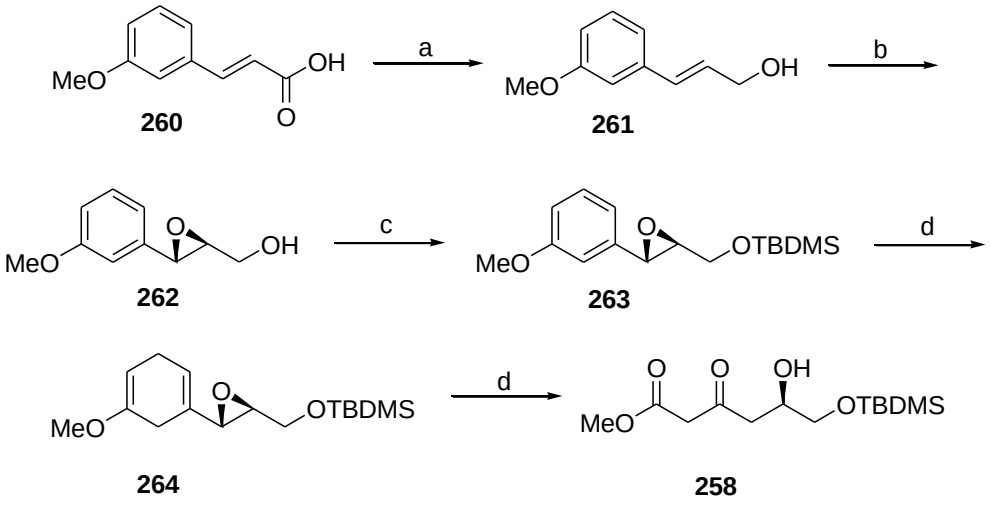


Scheme 50: Retrosynthetic analysis of the A-ring fragment of gambieric acid

Intermediate **252** could be formed by stereoselective hydrogenation and the epoxide would be introduced by protecting group interconversion followed by elimination reaction. Disconnection of the methylene group and retro reduction of the *tert*-butyl ester and retro hydroboration revealed the terminal alkene **254**. This alkene would in turn be the product of the 2,3-sigmatropic rearrangement reaction of an oxonium ylide obtained from catalytic decomposition of diazoketone **255**. Rearrangement precursor **255** could be obtained by ring opening of δ-lactone **256** followed by conversion of the methyl ester into the diazoketone. Ring opening and crotyl ether formation would reveal the diol **257** which would in turn be derived from keto ester **258** *via* stereoselective ketone reduction. Retro Birch reduction and ozonolysis would reveal commercially available *m*-methoxycinnamic alcohol **259**.

Synthesis

The sequence adopted for the first steps of the synthesis follows that described by Evans for the synthesis of amphotericin B and involved a diastereoselective anti reduction of a hydroxy keto ester to introduce the desired stereoselectivity in **257**.[77] The method relies on an enantioselective Sharpless epoxidation and the use of a meta-substituted anisyl ring as masked β-keto ester synthon.[78] The *m*-methoxycinnamic acid was chosen as a starting material for this synthesis. The first step involved reduction of the carboxylic acid to the corresponding primary alcohol. (**Scheme 51**)



Reagents: a) BH_3·THF, THF, -5 °C, 73%; b) $Ti(O^{i}Pr)_4$, L-DIPT, $^{t}BuO_2H$, DCM, -20 °C, 37%; c) TBDMSCl, imidazole, DMAP, RT, quant. d) Li, liq. NH_3, -78 °C to –30 °C; (e) O_3, DMS, Sudan(III) red, 10 min

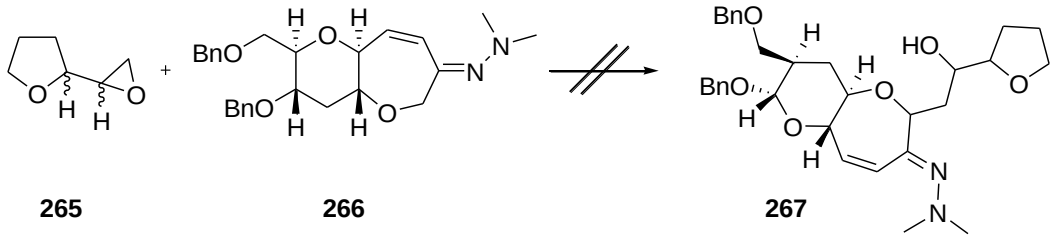
Scheme 51: Synthesis of keto-ester 257

The conditions for reduction of the carboxylic acid to the primary alcohol were investigated and optimised. The first conditions investigated involved the use of BH_3·THF as a hydride source. The desired product was obtained in a moderate 51% yield. Other hydride sources were then investigated to optimise the yield of product.[79] The use of $LiAlH_4$ led to consumption of all the starting material but unfortunately led to the reduction of the double bond as well as the reduction of the carboxylic acid. The reaction conditions for reduction using borane·THF complex as a hydride source were optimised; when the

[77] Evans, Gauchet-Prunet, Carreira and Charette, *J. Org. Chem.* **1991,** 56, (2), 741-50, Evans, Kozlowski, Murry, Burgey, Campos, Connell and Staples, *J. Am. Chem. Soc.* **1999,** 121, (4), 669-85.
[78] Prasad, Chen, Repic and Hardtmann, *Tetrahedron: Asymmetry* **1990,** 1, (5), 307-10.
[79] Kende and Fludzinski, *Org. Synth.* **1986,** 64, 104-7, Richey and Moses, *J. Org. Chem.* **1983,** 48, (22), 4013-17.

reaction was carried out at -5 °C the reduction yielded 73% of the desired product. The next step involved enantioselective epoxidation of the alkene **261** using the conditions described by Evans for the Sharpless asymmetric epoxidation of cinnamyl alcohol.[80] Unfortunately the desired product was obtained only 37% yield.

The resulting primary alcohol **262** was subsequently protected as a hindered silyl ether. TBDMS protection was carried out at room temperature and the desired product was obtained in 72% yield. In order to obtain the desired keto ester, two steps remained: the Birch reduction and ozonolysis. Birch reduction was achieved using a large excess of lithium in presence of liquid ammonia at –35 °C for 45 min. The desired product was obtained in 87% yield but as an inseparable mixture of products. This mixture was nevertheless submitted to the next step without any further purification. Ozonolysis was achieved using Sudan (III) red as an indicator; the reaction mixture turned from red to yellow when both alkenes were successfully oxidised.



265 **266** **267**

Entry	**265**	**266**	^{t}BuLi	Solvent	Lewis Acid
1	1 eq	1 eq	2 eq	THF	None
2	1 eq	1 eq	1.5 eq	Et_2O	TMSOTf
3	1 eq	1 eq	2 eq	Et_2O	TMSOTf
4	1 eq	1 eq	2 eq	THF	$ZnCl_2$
5	1 eq	1 eq	1.5 eq	THF	$BF_3{\cdot}Et_2O$

Table 9: Optimisation of the coupling conditions; Dr D. Grainger, unpublished results

Work was done in parallel to this synthesis by Dr. D. Grainger on a model system to optimise the coupling conditions between an epoxide and a hydrazone (**Table 9**). Reaction conditions were varied in order to investigate their influence on the outcome of the reaction and on the yields obtained. Factors such as temperature and number of equivalents of starting material, although not shown, were investigated. More crucial

[80] Gao, Klunder, Hanson, Masamune, Ko and Sharpless, *J. Am. Chem. Soc.* **1987,** 109, (19), 5765-80.

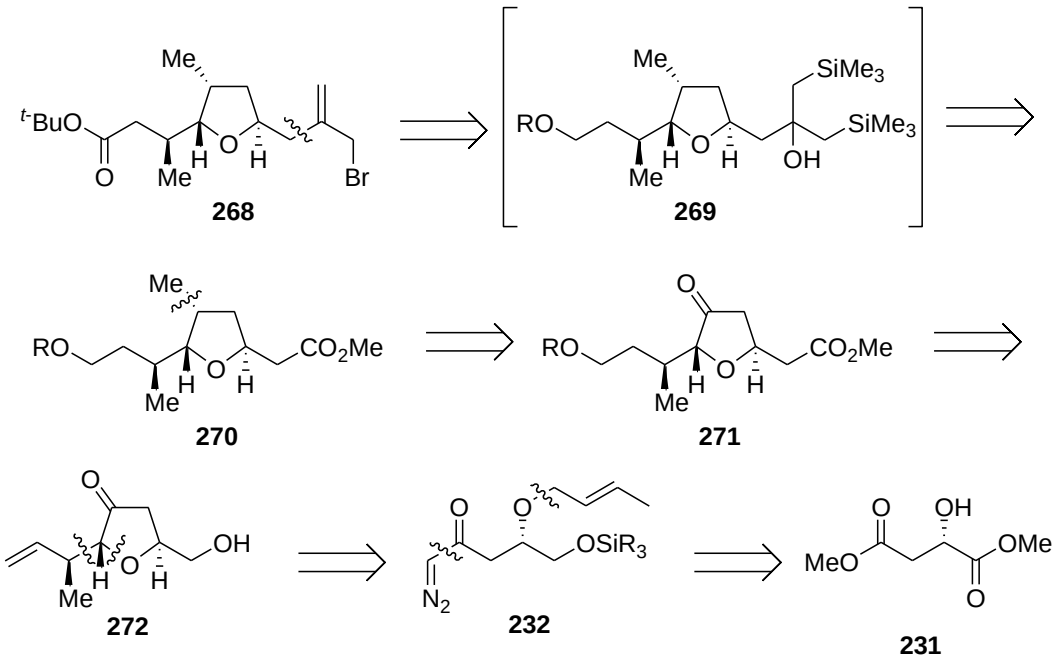
factors such as solvent conditions and Lewis acid activation were also studied. Unfortunately, although many reaction conditions were explored, none of them gave formation of the desired coupling product.

In light of these unsatisfactory results, the strategy towards the synthesis of the A-ring fragment of gambieric acid was changed. The approach now investigated involved the formation of the coupling product by reaction of the B-D hydrazone fragment with an A-ring fragment functionalised with an allylic bromide.

2.1.3 Allyl bromide approach

Retrosynthetic analysis

The retrosynthetic approach for the functionalisation of the A-ring fragment as an allyl bromide is similar to that published in 2004.[81] This route relies on the same methodology as the route involving an epoxide in which an oxonium ylide formation and stereoselective rearrangement is used to construct the tetrahydrofuran (**Scheme 51**).



Scheme 52: Retrosynthetic analysis for the allyl bromide route

Retro Grignard addition and Peterson elimination of the allyl bromide side chain reveals the methyl ester **270**. Disconnection of the methyl group at the 3-position of the tetrahydrofuran gives the corresponding ketone **271**. The protected hydroxyl functionality on intermediate **271** could be obtained by hydroboration of alkene **272**. Tetrahydrofuran

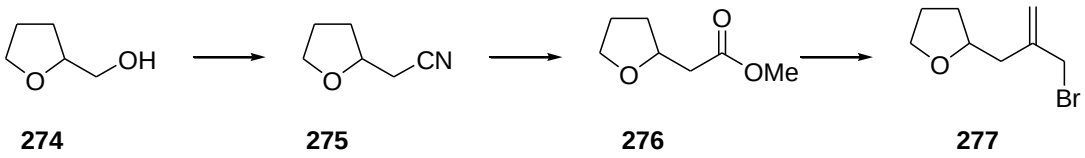
[81] Clark, Fessard and Wilson, *Org Lett* **2004,** 6, (11), 1773-6.

272 would be the [2,3]-sigmatropic rearrangement product of the corresponding diazoketone **232** which can be disconnected to give L-dimethylmalate **231**.

Model study

In order to establish that it is possible to couple the B-D fragment hydrazone and the A-ring fragment bearing an allylic bromide, a model study was conducted. This model study would also allow optimisation of the final steps involving introduction of the side chain at the 5-position.

The first step of the synthesis of this model system starts with commercially available tetrahydrofurfuryl alcohol **274**. The synthetic route investigated relies on the addition of the desired carbon atom by conversion of the hydroxyl group into a nitrile group followed by conversion of the nitrile into the methyl ester precursor of the allylic bromide (**Scheme 53**).



274 **275** **276** **277**

Scheme 53: Synthetic route towards the formation of the allyl bromide model system

The first step involved conversion of the tetrahydrofurfuryl alcohol into the corresponding nitrile **275**. First attempts were made to form the nitrile group using a one-step process. In 1981, Trahanovsky reported a one-pot procedure for the direct conversion of alcohols into nitriles using sodium cyanide, trimethylsilylchloride and a catalytic amount of sodium iodide.[82] Unfortunately, satisfactory results were not obtained using this procedure (**Table 10, Entry 1**).

The strategy which was then adopted was to use a two step process by first activating the hydroxyl group as a tosyl group. Tosylate formation was achieved quantitatively and the primary alcohol was now converted into a better leaving group. The activated tetrahydrofurfuryl alcohol was then treated with NaCN or KCN using standard substitution conditions. (**Table 10, Entries 3 to 8**)

[82] Trahanovsky and Swenson, *J. Org. Chem.* **1981,** 46, (14), 2984-5.

Entry	Starting material	Cyanide source	T (°C)	Solvent	Yield
1	**274**	KCN (2eq), NaI, Me_3SiCl	60°C	Acetonitrile	-
2	**274**	KCN (2eq), NaI, Me_3SiCl	80°C	Acetonitrile	11%
3	Tosylated **274**	KCN (2.8 eq)	40°C	EtOH	-
4	Tosylated **274**	KCN (2.8 eq)	50°C	EtOH	-
5	Tosylated **274**	KCN (2.8 eq)	80°C	EtOH	Decomposition
6	Tosylated **274**	TBACN (1.2 eq)	0°C	Acetonitrile	-
8	Tosylated **274**	NaCN (5eq)	RT	EtOH	-
9	Tosylated **274**	NaCN (5eq)	40°C	EtOH	7%
10	Tosylated **274**	NaCN (5eq)	80°C	EtOH	Decomposition
11	Tosylated **274**	NaCN (5eq)	RT	Acetonitrile	-
12[a]	Tosylated **274**	NaCN (5eq)	50°C	Acetonitrile	10%
13	Tosylated **274**	NaCN (5eq)	80°C	Acetonitrile	Decomposition
14	Tosylated **274**	NaCN (5eq)	40°C	DMF	-
15[a]	Tosylated **274**	NaCN (5eq)	60°C	DMF	42%
16	**274**	NaCN (5eq), Mitsonobu conditions	RT	THF	31%
17	**274**	NaCN (5eq), Mitsonobu conditions polymer bounded PPh_3	RT	THF	67%

[a] Reactions were carried out with both mesylated and tosylated alcohol

Table 10: Reaction conditions for the formation of the nitrile

The first results obtained using cyanide displacement under standard reaction conditions gave none of the desired product. A wide range of solvents and temperatures was then screened. Treatment of the tosylate of tetrahydrofurfuryl alcohol with potassium cyanide did not result in formation of the nitrile. By changing the cyanide source to sodium cyanide, trace amounts of the desired product could be isolated when the reaction was performed in ethanol at 40 °C (**Table 10, Entry 9**). These results also showed that increasing the reaction temperature above 40 °C led to the decomposition of the starting material. Optimisation of the reaction conditions using sodium cyanide revealed that the

best results are obtained when the reaction is carried out in DMF at 42 °C (**Table 10, Entry 15**).

An approach involving the treatment of the protected alcohol under Mitsonobu condition was also explored (**Table 10, Entry 16**).[83] The procedure is also less time consuming as it allows the direct one-pot conversion of a primary alcohol into the corresponding nitrile. Unfortunately, purification problems linked to the use of triphenylphosphine gave a poor isolated yield of the nitrile. The problem could be cricumvented by using polymer bounded triphenylphosphine and the desired product was then isolated in an acceptable 67% yield (**Table 10, Entry 17**).

With the nitrile **275** now in hand the next step involved formation of the methyl ester **276** precursor for the formation of the allylic bromide **277**. The first approach investigated was a single step procedure. A few examples reported in the literature had shown that formation of methyl ester from nitrile could be accomplished by treatment of the nitrile with HCl saturated methanol.[84] Nitrile **275** was dissolved in methanol and the resulting solution cooled down to 0 °C. HCl gas, formed by slow addition of sulfuric acid to ammonium chloride was bubbled through the reaction mixture. Unfortunately, these reaction conditions led to the decomposition of the starting material. The same result was obtained using aqueous and concentrated HCl.

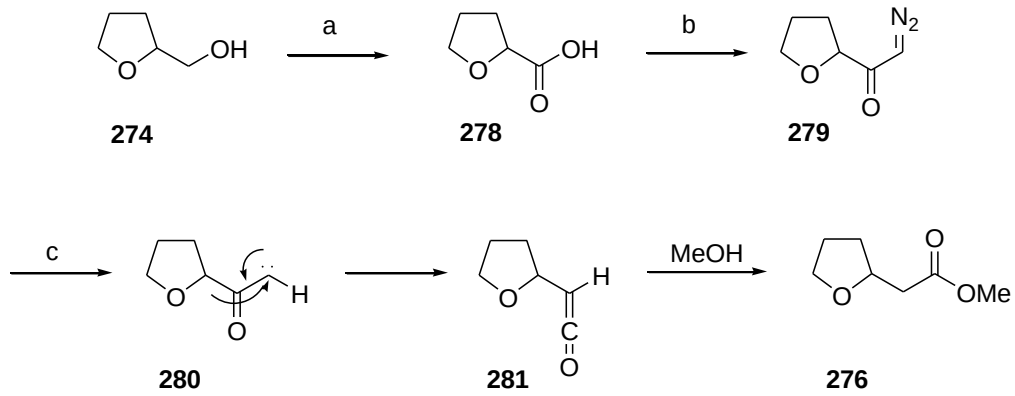
The methyl ester **276** was therefore synthesised in a two-step process. Upon treatment of the nitrile **275** with sodium hydroxide 1M in dioxane at 60 °C the corresponding carboxylic acid could be isolated in 50% yield. The carboxylic acid was then converted quantitatively into the methyl ester **276** upon treatment with methanol under acidic conditions.

Considering that the synthetic route used to access this model system is also going to be the one employed for the synthesis of the A-ring fragment, it was decided that the yields obtained were not satisfactory enough for this approach to be used.

The key reaction to access the desired model allyl bromide **277** is the addition of a carbon atom onto the side chain at the 5 position of the tetrahydrofuran ring. By converting the primary alcohol to the corresponding methyl ester a homologation reaction could then

[83] Lerner, Masjost, Ruf, Gramlich, Jakob-Roetne, Zurcher, Borroni and Diederich, *Org. Biomol. Chem.* **2003,** 1, (1), 42-49.
[84] Cryle, Matovic and De Voss, *Org. Lett.* **2003,** 5, (18), 3341-44, Guzman-Duran, Guzman, Pannell and Lloyd, *Synth. Commun.* **2003,** 33, (19), 3271-83.

be performed to access the same methyl ester with an additional carbon atom. There are some examples where methyl esters have been used as a safe alternative for the Arndt-Eistert reaction.[85] This reaction would therefore be a useful alternative to access the target methyl ester **276** required for the formation of the allyl bromide **277** (**Scheme 54**).



Reagent: a) PDC, DMF, RT, 16 h, 71%; b) i. $(COCl)_2$, DCM, RT, 16 h; ii. CH_2N_2, Et_2O, 0 °C to RT, 16 h, 88%; c) Ag benzoate 10%, Et_3N, MeOH, RT, 3 h, 99%

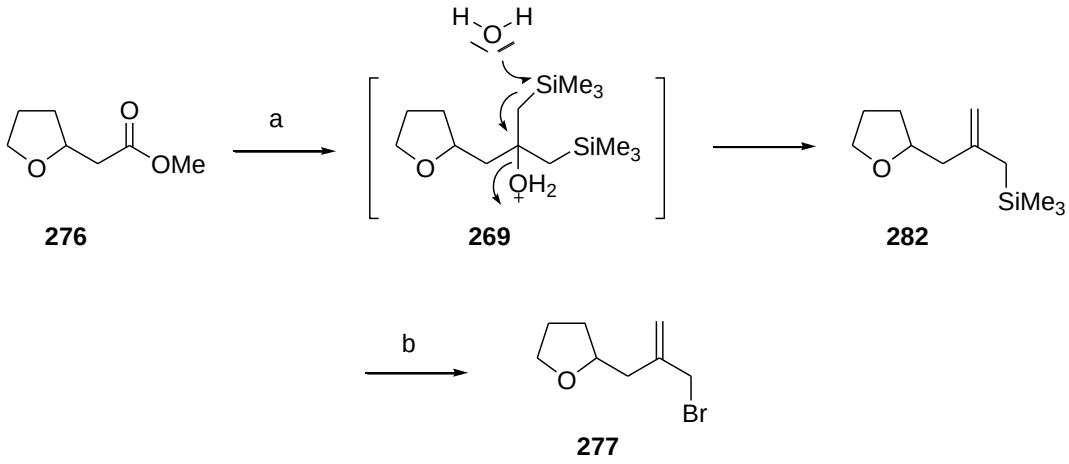
Scheme 54: Mechanism of the homologation reaction

Treatment of tetrahydrofurfuryl alcohol **274** with PDC yielded the desired carboxylic acid **278** in a 71% yield. The carboxylic acid was then converted into the diazoketone **279** required for the homologation reaction. Treatment of the carboxylic acid **278** with oxalyl chloride afforded the acid chloride which was treated, without purification, with diazomethane to afford the desired diazoketone **279** in 88% yield over two steps. The diazoketone **279** underwent Wolf rearrangement upon treatment with a catalytic amount of silver benzoate. The reaction proceeded smoothly and the desired methyl ester **276** product was isolated in 99% yield.

The final step of the synthesis of the model system for the A-ring fragment of gambieric acid is the conversion of the methyl ester **276** into the allylic bromide **277**. The methodology used for this step involves the double addition of (trimethylsilyl)methyl magnesium bromide to the methyl ester followed by *in situ* Peterson elimination. Formation of an allylic silane was reported by addition of allyl silane to a methyl ester

[85] Katritzky, Zhang, Hussein, Fang and Steel, *J Org Chem* **2001,** 66, (16), 5606-12, Kowalski and Reddy, *J. Org. Chem.* **1992,** 57, (26), 7194-208, Podlech and Seebach, *Angew. Chem., Int. Ed. Engl.* **1995,** 34, (4), 471-2.

using $CeCl_3$ to activate the Grignard reagent.[86] The sequence had already been optimised within the group for the addition of the silane reagent to the methyl ester. The formation of the allylic bromide was then achieved by addition of a halogen source.[87]



276 **269** **282** **277**

Reagents: a) $CeCl_3$, $TMSCH_2MgCl$, THF, -78 °C then NH_4Cl, silica gel, DCM 0 °C, 87%; b) pyrrolidone hydrotribromide pyridine THF, -10 °C, 83%

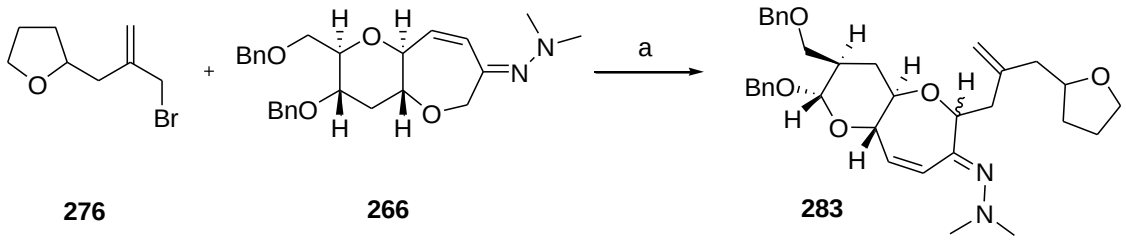
Scheme 55: Completion of the model synthesis

The methyl ester **276** was treated with trimethylsilylmethyl magnesium chloride (**Scheme 55**). Double addition of the Grignard reagent to the methyl ester followed by Peterson elimination led to the formation of the allylic silane **282** in only 37% yield. The yield of the desired allylic silane could be improve significantly to 87% by adding $CeCl_3$ to the reaction and forming the Grignard reagent *in situ*. In this case, the organic magnesium chloride is converted into the more reactive trimethylsilylmethylcerium reagent which then undergoes double addition to the ester. The level of purity and dryness of the cerium reagent proved to be crucial for the efficiency of the synthesis. The process during which $CeCl_3 \bullet 7H_2O$ is dried has to be carefully monitored especially at the beginning to avoid decomposition of this reagent.

The successful synthesis of the allylic silane **282** meant that the last step of the synthesis of the model system could be achieved by treatment with pyrrolidone hydrotribromide, as a halogen source. The desired product **277** was isolated in 83% yield from this reaction. Although the yield of the reaction could be optimised, the product was used directly in the next step.

[86] Clark, Dossetter, Blake, Li and Whittingham, *Chem. Commun. (Cambridge)* **1999**, (8), 749-50, Lee, Channon, Cregg, Porter, Roden and Yeoh, *Tetrahedron* **1989,** 45, (18), 5877-86, Mickelson, Koviach and Forsyth, *J. Org. Chem.* **1996,** 61, (26), 9617-20, Narayanan and Bunnelle, *Tetrahedron Lett.* **1987,** 28, (50), 6261-4, Nishigaichi, Tamura, Ueda, Iwamoto and Takuwa, *Tetrahedron Lett.* **2008,** 49, (13), 2124-27.
[87] Awang and Wolfe, *Can. J. Chem.* **1969,** 47, (4), 706-9.

The final step of this model study involved coupling of the model allylic bromide **277** to the model hydrazone **266** prepared by Dr. J Conroy from a glucose derivative using a route involving RCM for formation of the 7-membered ring. Standard conditions were applied for this coupling reaction (**Scheme 56**).



276 **266** **283**

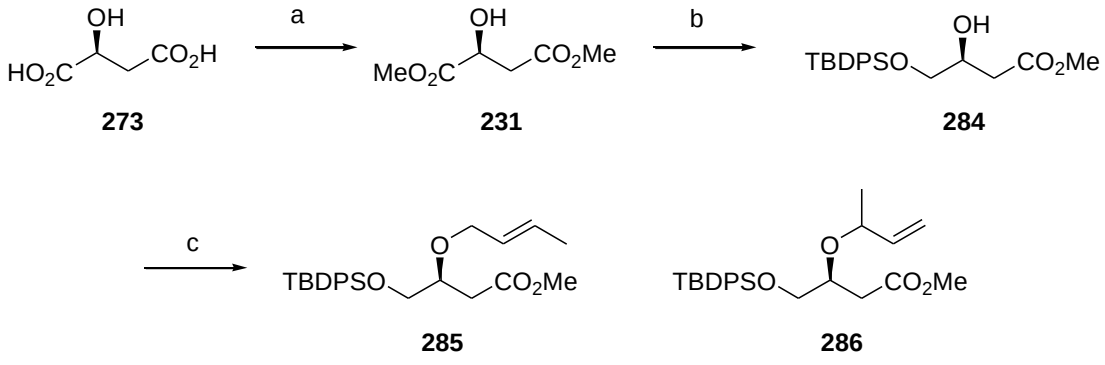
Reagents: a) ^{t}BuLi, THF, -78 °C, 2 h, 66%

Scheme 56: Coupling reaction

The hydrazone **266** was deprotonated at α-position adjacent to the oxygen atom of the 7-membered ring upon treatment with ^{t}BuLi at –78 °C. Subsequent addition of the allylic bromide afforded the substitution product **283** in 66% yield. With these results in hand, the synthesis of the A-ring fragment containing an allylic bromide was commenced.

Synthesis

The synthesis of the A-ring fragment starts as previously reported.[88] Malic acid was converted into the corresponding bis-methyl ester by treatment with thionyl chloride in methanol (**Scheme 57**).



273 **231** **284** **285** **286**

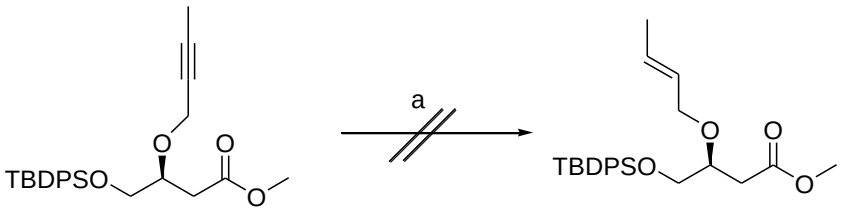
Reagents: a) $SOCl_2$, MeOH, 3 h, RT, quant. ; b) i. $BH_3{\cdot}SMe_2$, $NaBH_4$, THF, 1 h, 0 °C to RT; ii. TPDPSCl, imidazole, DMAP, DMF, 2 h, RT, 93% c) *E*-$Cl_3C(NH)COCH_2CHCHMe$, CF_3SO_3H, cyclohexane, RT, 16 h, 51%

Scheme 57 : Synthesis of the crotyl ether

[88] Clark, Fessard and Wilson, *Org Lett* **2004,** 6, (11), 1773-6.

Regioselective reduction of dimethylmalate has already been reported.[89] The mechanism of the reduction of **231** occurs by intramolecular hydride delivery and led to the formation of an inseparable mixture of diols in a 40:1 ratio (estimated after the subsequent protection step). By completing the reaction between –10 °C and 0 °C, only the desired diol was isolated without any formation of the other regioisomeric diol. The desired product was isolated in excellent yield by selective protection of the resulting primary alcohol as a silyl ether. Formation of the crotyl ether proceeds by treatment of a secondary alcohol **284** with crotyl trichloroacetimidate.[90] The product was isolated in a poor yield and with poor selectivity (6:1 in favor of the desired product). The reaction has further drawbacks because a mixture of S_N2 and S_N2' products was obtained and these compounds were hardly separable by column chromatography even when the silica gel was treated with silver nitrate.[91]

A number of different methods were investigated to optimise the crotyl ether formation and to make purification of the product easier. The geometry of an *E* alkene is usually favoured sterically which make its formation easier than corresponding *Z* alkene. Previous studies have already been performed by Dr. T Fessard to optimise the yield of the *E* alkene. The first approach involved selective reduction of an alkyne to give the *trans* alkene using a metal-catalysed hydrosilylation reaction and subsequent desilylation procedure as described by Trost and co-workers (**Scheme 58**).[92]



287 **285**

Reagents: a) Et_3SiH, $[Cp^*Ru(MeCN)_3]PF_6$, DCM

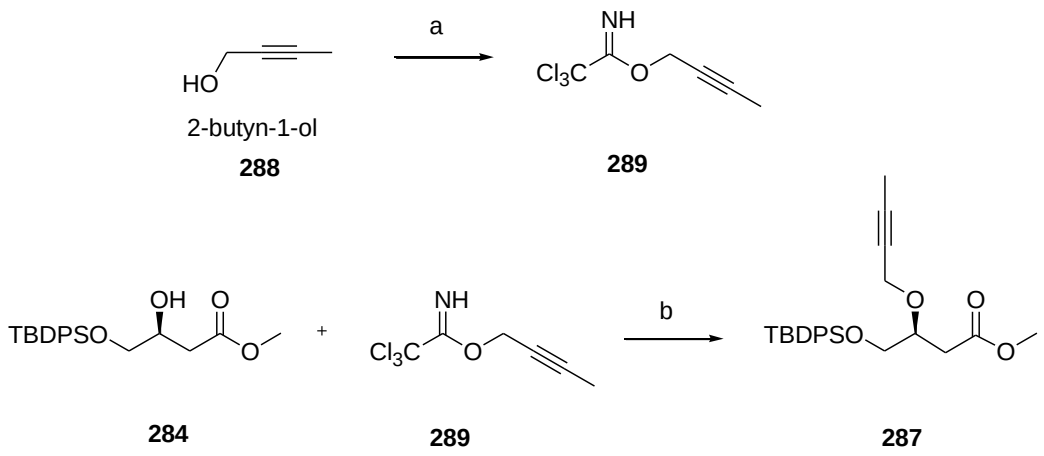
Scheme 58: Trost catalytic formation of *E*-alkene

Unfortunately in this case the reaction gave an inseparable mixture of products. The Suzuki coupling approach to the synthesis of the desired product was also studied.

[89] Saito, Hasegawa, Inaba, Nishida, Fujii, Nomizu and Moriwake, *Chemistry Letters* **1984**, (8), 1389-92, Saito, Ishikawa, Kuroda, Koga and Moriwake, *Tetrahedron* **1992,** 48, (20), 4067-86.
[90] Wessel, Iversen and Bundle, *Journal of the Chemical Society-Perkin Transactions 1* **1985**, (11), 2247-50, Patil, *Tetrahedron Letters* **1996,** 37, (9), 1481-84, Dimitriadis and Massywestropp, *Australian Journal of Chemistry* **1984,** 37, (3), 619-27.
[91] Williams and Mander, *Tetrahedron* **2001,** 57, (3), 425-47.
[92] Oshima, Suzuki and Morooka, *Chem. Lett.* **1984**, (7), 1161-4, Trost Barry, Ball Zachary and Joge, *J Am Chem Soc* **2002,** 124, (27), 7922-3.

Unfortunately the yield and rate of formation of the desired borane were poor and slow respectively. All attempts to optimise this reaction failed and so the original approach using trichloroacetimidate chemistry was used.

Because a low yielding step so early in the synthetic route to a natural product is a major drawback, other approaches to the formation of the crotyl ether were investigated. The first approach investigated was to form the 2-butynyl ether and then reduce the alkyne to give the *E*-alkene. Following the same pattern as for the formation of the crotyl ether, the desired trichloroacetimidate was synthesised (**Scheme 59**).



Reagent: a) CCl_3CN, $TBAHSO_4$, aq KOH 50%, DCM, RT, 97%; b) CF_3SO_3H, cyclohexane, 94%

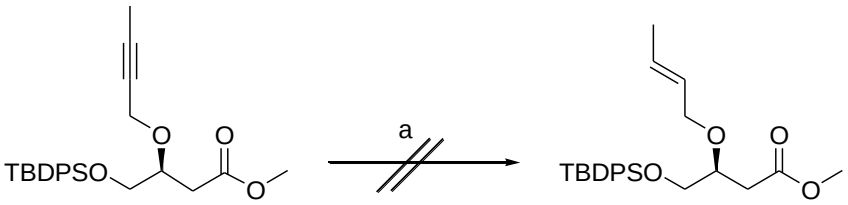
Scheme 59: Synthesis of 2-butyn ether

Formation of the trichloroacetimidate reagent proceeded smoothly by the reaction of 2-butyn-1-ol with trichloroacetonitrile under basic conditions. The trichloroacetimidate **289** was used in the next step for the formation of the alkynyl ether **287** without purification. The reaction between the secondary alcohol and the trichloroacetimidate reagent proceeded under acid catalysis and inert atmosphere to form the desired 2-butynyl ether in 94% yield.

A few methods were then investigated to reduce the triple bond to give the *E*-alkene. One of the most commonly used reactions for doing this is the Birch reduction.[93] Treatment of alkyne **287** with liquid ammonia and lithium at –78 °C was expected to provide the desired *E*-alkene (**Scheme 60**). Unfortunately, none of the desired product **285** was isolated and so the reaction conditions were modified in order to favour formation of the alkene. Addition of ^{t}BuOH was performed at the end of the reaction to allow the free

[93] Clennan, L'Esperance and Lewis, *J. Org. Chem.* **1986,** 51, (9), 1440-6.

radical to react for longer. However, these conditions only led to decomposition of the starting material

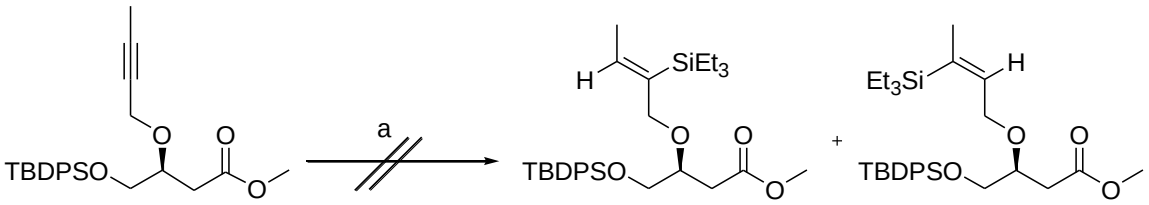


287 **285**

Reagent: a) NH_3, Li, ^{t}BuOH, 30 min, -78°C

Scheme 60: Birch reduction of the triple bond

There are numerous publications which describe the formation of an *E*-alkene from an alkyne by *trans*-hydrostannation[94], hydrosilylation[95] or hydrogermylation,[96] and subsequent cleavage of the carbon-tin or carbon- silicon bond. In this case, for toxicity reasons formation of the *E*-alkene from the substituted ether by Lewis acid assisted *trans*-addition of triethylsilane to the triple bond was attempted (**Scheme 61**). The silyl group could then be removed using copper iodide as described by Takeda and Hosomi.[97]



287

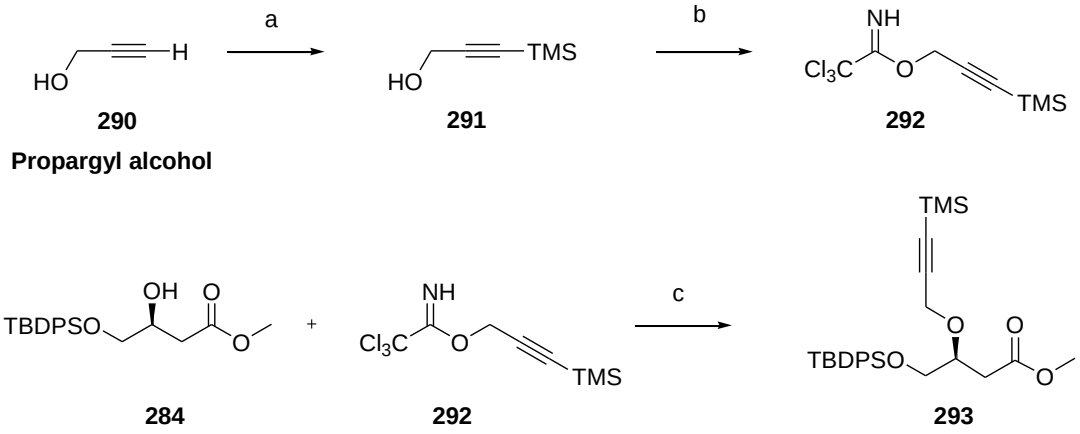
Reagents : a) Et_3SiH, $AlCl_3$, Et_3N, toluene, 3 days

Scheme 61: Lewis acid catalysed *trans*-hydrosilylation

Silylation was performed by reaction of the alkyne **287** with triethylsilane and $AlCl_3$. The mixture was left to react for three days, but only starting material was isolated at the end of the reaction. Many attempts were made to form the desired *trans*-addition product by changing reaction temperature and number of equivalents of the reagents but all these modifications were unsuccesful.

[94] Asao, Liu, Sudoh and Yamamoto, *J. Org. Chem.* **1996,** 61, (14), 4568-71.
[95] Trost Barry, Ball Zachary and Joge, *J Am Chem Soc* **2002,** 124, (27), 7922-3, Sudo, Asao, Gevorgyan and Yamamoto, *J. Org. Chem.* **1999,** 64, (7), 2494-99, Asao, Sudo and Yamamoto, *J. Org. Chem.* **1996,** 61, (22), 7654-55.
[96] Schwier and Gevorgyan, *Org. Lett.* **2005,** 7, (23), 5191-94.
[97] Ito, Sensui, Arimoto, Miura and Hosomi, *Chem. Lett.* **1997**, (7), 639-40, Taguchi, Ghoroku, Tadaki, Tsubouchi and Takeda, *Org. Lett.* **2001,** 3, (23), 3811-14.

In order to establish that the poor reactivity of the 2-butynyl ether does not come from the presence of the methyl group on the triple bond, the same studies were performed on the terminal alkyne. In this case, the desired alkene would be obtained by regioselective addition of triethylsilane or tributyltin hydride. The methyl group would then be introduced by replacement of the terminal silicon, or tin group. The formation of the trichloroacetimidate using propargyl alcohol led to formation of the desired product in low yield. The propargyl alcohol was therefore converted to the TMS-protected alkyne under standard reaction conditions using BuLi and TMSCl (**Scheme 62**).



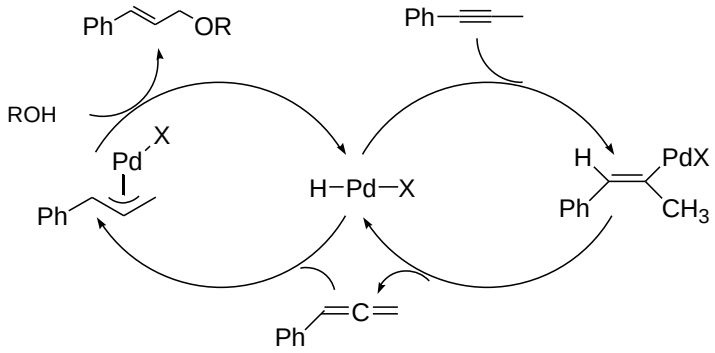
Reagents: a) n-BuLi, TMSCl, THF, 17 h, -78 °C to RT, 97%; (b) CCl_3CN, $TBAHSO_4$, aq KOH 50%, DCM, 17 h, RT, 74%; (c) CF_3SO_3H, cyclohexane, 17 h, 15%

Scheme 62: Formation of the TMS protected propargylic ether

Formation of the TMS protected propargylic alcohol **291** proceeded smoothly in 97% yield. The trichloroacetimidate **292** was then formed by treatment of the alcohol with trichloroacetonitrile and KOH in DCM. The trichloroacetimidate **292** was then engaged in the next step without any futher purification. Both starting materials were dissolved in cyclohexane under inert atmosphere and the mixture was then treated with a catalytic amount of triflic acid. Unfortunately this reaction led to the formation of only trace amounts of the desired product. Increasing the amount of triflic acid led to the decomposition of the secondary alcohol starting material **284**; leaving the reaction for longer did not increase the yield. Due to the poor yields in this route, further work using propargyl alcohol as a starting material was not undertaken.

The failure of this synthesis meant that other approaches for the formation of the desired crotyl ether had to be investigated. In 2001, Yamamoto reported the

palladium/benzoic acid catalyzed hydroalkylation of alkenes. This was followed by a microwave assisted optimisation of the same process three years later.[98] This procedure involved the catalytic hydrocarbonation of an alkyne catalysed by palladium in the presence of benzoic acid. The mechanism of the reaction was assumed to involve activation of the triple bond of 1-phenyl-propyne by *syn*-addition of a palladium hydride intermediate which then would allow the alcohol to attack (**Scheme 63**).



Scheme 63: Mechanism of Yamamoto's catalytic alkyne hydrocarbonation[99]

For the synthesis of the desired *trans*-crotyl ether, the 1-phenyl-1-propyne was replaced with 2-butyne. The first attempt to perform the reaction and to optimise the conditions was made using 1-phenylpropyne as a reagent to conform to the literature reaction. A small quantity of the desired product was obtained heating the reactants for five days at reflux in dioxane. The hindered secondary alcohol could be a reason why a 12% yield was obtained for this reaction.

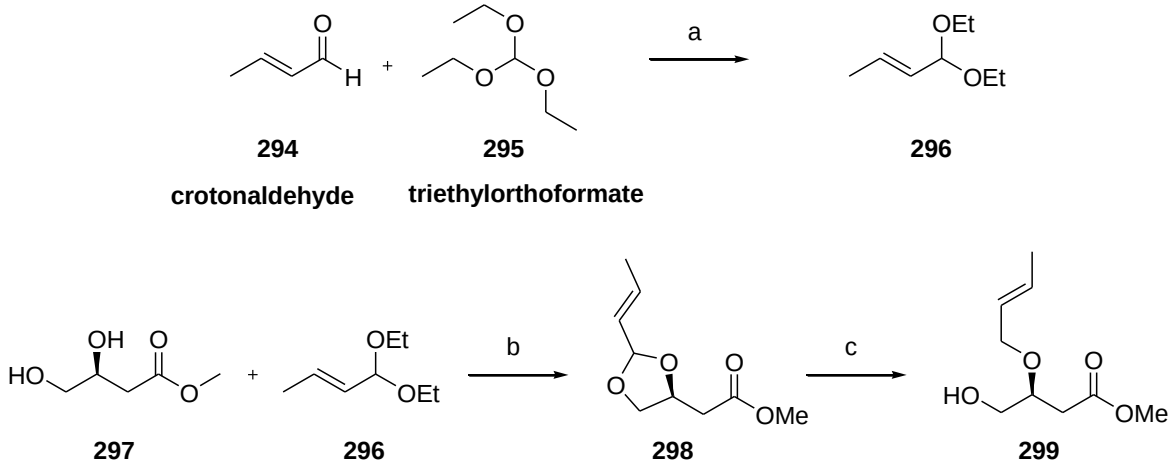
The reaction was then attempted using 2-propyne. A first attempt used standard conditions [($Pd(PPh_3)_4$ 0.1 equiv., benzoic acid 0.1 equiv., 2-butyne 5 equiv., 100 °C] and was performed in a sealed tube because 2-butyne is highly volatile. Unfortunately, only starting material was recovered after five days. Microwave conditions were therefore applied to the reaction using the same number of equivalents of reagents and acetic acid as a catalyst for 30 min at 150 °C and 300 W. TLC showed formation of a new product. The reaction was then attempted at 180°C but on this occasion the sealed tube broke in the microwave before analysis of the product could be performed. For safety reasons, the experiment was not repeated.

Several other approches including formation of the crotyl ether using silver oxide[100] and reduction of triple bond using chromous sulfate in water[101] failed to give satisfactory

[98] Kadota, Lutete, Shibuya and Yamamoto, *Tetrahedron Lett.* **2001,** 42, (35), 6207-10, Patil, Nawaz Khan and Yamamoto, *Tetrahedron Lett.* **2004,** 45, (46), 8497-99.
[99] Kadota, Lutete, Shibuya and Yamamoto, *Tetrahedron Lett.* **2001,** 42, (35), 6207-10.

results for the formation of the desired product. The reactivity of the secondary alcohol was assumed to be poor as the starting material was recovered in all cases.

It was therefore decided to adopt a new approach which does not involve the participation of the protected primary alcohol as a sterically hindered silyl ether. Formation of a cyclic acetal followed by selective acetal opening by hydride attack to reveal the less hindered alcohol is a process frequently used for the selective protection of a secondary hydroxyl group in presence of a primary hydroxyl group.[102] In this case, the transformation requires the formation of a five-membered cyclic acetal bearing an *E*-alkene (**Scheme 64**). This process has the advantage of forming the desired crotyl ether and leaving the free primary alcohol which would permit protection of this hydroxyl group with a less hindered protecting group than TBDPS.



Reagents: a) NH_4Cl, EtOH, RT, 96%; b) PPTS (cat), benzene overnight, RT 72%; c) PMHS, $AlCl_3$, 31%

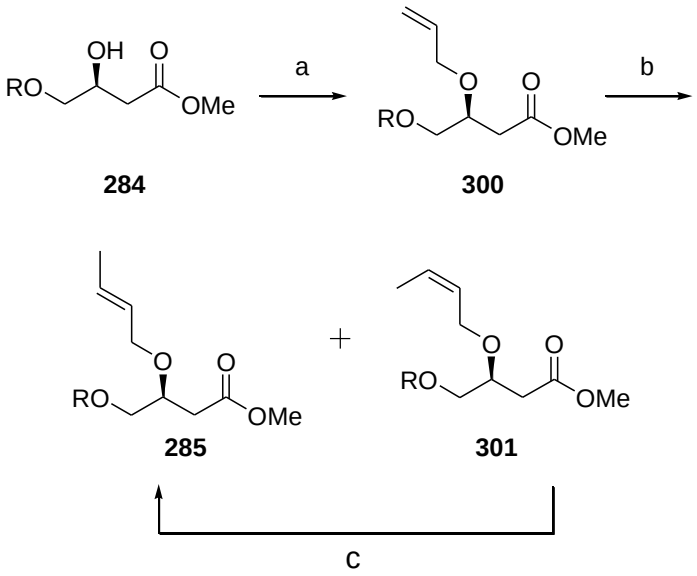
Scheme 64: Crotyl ether formation *via* cyclic acetal formation

The crotonaldehyde **294** was treated with triethylorthoformate **295** in ethanol in presence of ammonium chloride to form diethylacetal **296** in 96% yield. The sensitivity of the product to acid necessitated purification by column chromatography on deactivated alumina. Treatment of the diol **297** with the diethylacetal **296** in the presence of a catalytic amount of acid in benzene gave the desired cyclic acetal **298** in 72% yield. Selective opening of the acetal group was achieved using PMHS and aluminium chloride as an hydride source in 31% yield. Other hydride sources such as $LiAlH_4$ and DIBAL-H were also investigated but none of these reagents gave higher yields of the required product.

[100] Broggini, Molteni and Pilati, *Tetrahedron: Asymmetry* **2000,** 11, (9), 1975-83.
[101] Castro and Stephens, *J. Am. Chem. Soc.* **1964,** 86, (20), 4358-63.
[102] Chandrasekhar, Reddy and Reddy, *Chem. Lett.* **1998**, (12), 1273-74.

Failure to access the desired crotyl ether in satisfactory yield *via* a cyclic acetal necessitated the investigation of a new procedure. One of the most frequently used new processes to access alkenes is cross metathesis. This method could be applied to this synthetic route by accessing the ether intermediate bearing a terminal alkene. This allylic ether could then undergo a cross metathesis reaction with 2-butene to give the desired crotyl ether.

Examples had previously been reported where the cross metathesis was performed using a gaseous reagent.[103] Using cross metathesis methodology it should be possible to form an *E*-alkene by reaction between an allylic ether and 2-butene (**Scheme 65**).



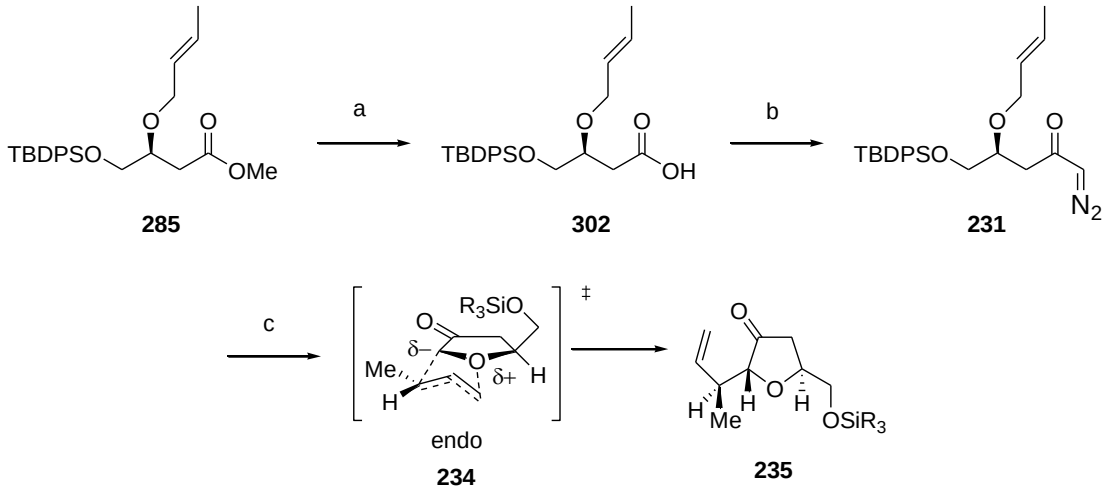
Reagents: a) allyl-trichloroactetimidate, CF_3SO_3H, cyclohexane, 16 h, RT, 93%; b) 2-butene, Grubbs II cat. 7 mol%, toluene, 16 h, 60 °C to 40 °C, 97%; c) $Pd(OAc)_2$, Bu_3SnH, Et_3N, DCM, 4 h, 40 °C, quant.

Scheme 65: Formation of the crotyl ether using cross metathesis

Formation of the trichloroacetimidate proceeded by treatment of allyl alcohol with trichloroacetonitrile under basic conditions. The trichloroacetimidate obtained was used without any further purification in the next step. Reaction between the allyl trichloroacetimidate and secondary alcohol **284** led to formation of the desired allylic ether **300** in 93% yield. The terminal alkene then underwent cross metathesis using 7 mol% of Grubbs second generation catalyst. The reaction led to a 9 to 1 mixture of *E* and *Z* alkene in favour of the desired *E*-alkene when performed on a large scale. The small amount of *Z*-alkene obtained could be converted into the desired *E*-alkene using palladium acetate catalysed conditions reported by Jung.[104]

[103] Giessert and Diver, *J. Org. Chem.* **2005,** 70, (3), 1046-49.
[104] Kim, Dong and Jung, *J. Org. Chem.* **2007,** 72, (14), 5424-26.

The synthetic route was then continued as reported previously by conversion of methyl ester **285** into the corresponding carboxylic acid **302** (**Scheme 66**).[105] Treatment of the methyl ester **285** with TMSOK gave the formation of the corresponding carboxylic acid **302** in 98% yield. Conversion of the carboxylic acid into the acid chloride proceeded over 16 hours and the acid chloride was used in the next step without purification. Treatment of the acid chloride with diazomethane afforded the rearrangement precursor **231** in 98% yield. Carbenoid formation, ylide generation and 2,3-sigmatropic rearrangement then proceeded in high stereoselectivity and good yield by treatment of the diazo ketone **231** with $Cu(acac)_2$.

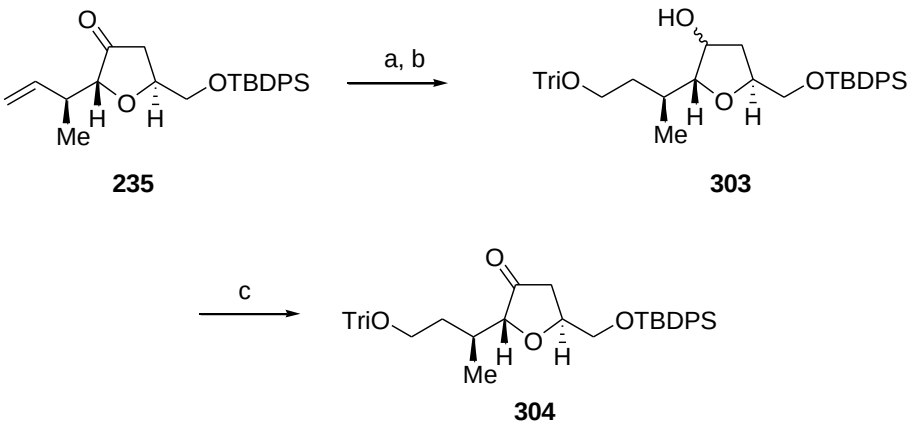


Reagents: a) TMSOK, Et_2O, 0 °C to RT 98%; b) i. $(COCl)_2$, DCM, DMF, RT, 16 h; ii. CH_2N_2, Et_2O, 0 °C, 2 h, 98% ; c) $Cu(acac)_2$, THF, 66 °C, 30 min, 82%

Scheme 66: Formation of the tetrahydrofuran core of the A-ring fragment of gambieric acid

Efforts were then focused on the hydroboration reaction. Hydroboration of the alkene would lead to the formation of two hydroxyl groups; the primary alcohol on what was the double bond and that arising from ketone reduction. The hydroboration reaction was carried out as previously reported (**Scheme 67**). The first step involved the hydroboration of the double bond of intermediate **235**. The crude mixture of secondary alcohols resulting from the reaction was then treated with trityl chloride to selectively protect the primary alcohol. The resulting mixture of products was difficult to separate, and so the crude product was treated with Dess Martin reagent. Unfortunately, none of the desired oxidation product was isolated from this reaction.

[105] Laganis and Chenard, *Tetrahedron Lett.* **1984,** 25, (51), 5831-4.



235 **303** **304**

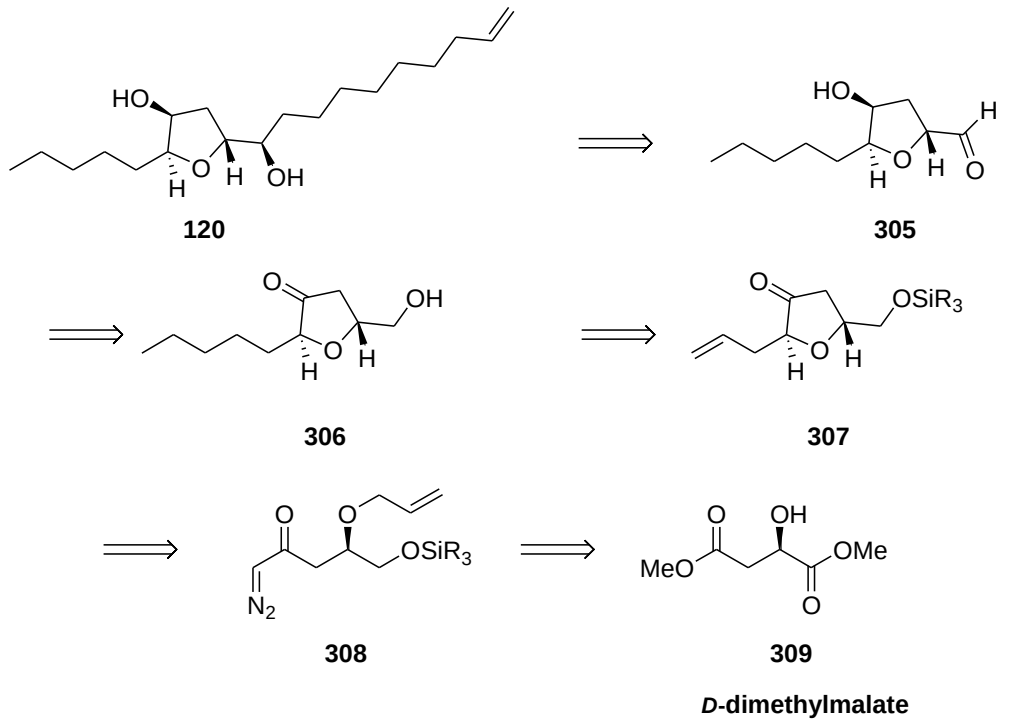
Reagents: a) $BH_3 \cdot SMe_2$, THF, H_2O_2, 6 h, 0 °C; b) $(Ph)_3CCl$, pyridine, 2.5 h, 70 °C;

Scheme 67: Formation of intermediate 304

2.2 Towards the total synthesis of (6S,7S,9R,10R)-6,9-epoxynonadec-18-ene-7,10-diol

2.2.1 Retrosynthetic analysis

The strategy adopted for the synthesis of (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-ene-7,10-diol is similar to that employed for the synthesis of the A-ring fragment of gambieric acid. The 2,5-dialkyl-*trans*-tetrahydrofuran unit of the natural product can be formed using the [2,3]-sigmatropic rearrangement reaction as a key step. The retrosynthetic approach adopted for the synthesis of the natural product relies on the formation of the diazoketone rearrangement precursor **308** (**Scheme 68**).



Scheme 68: Retrosynthetic analysis of the diol natural product

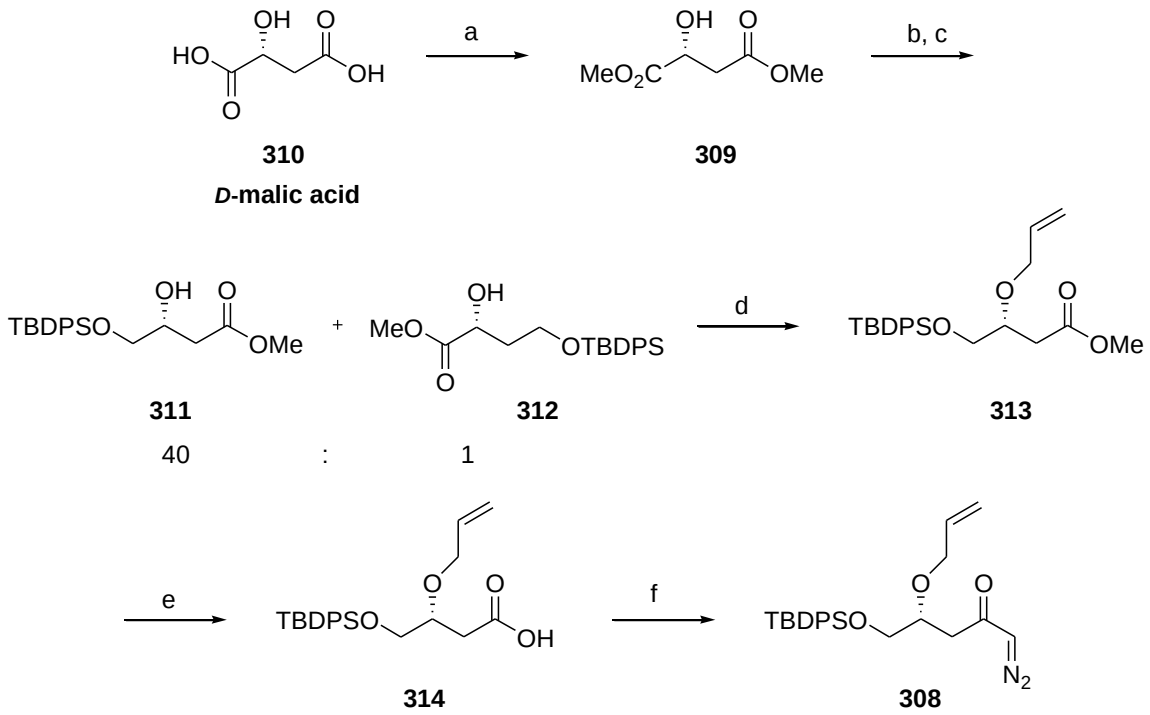
Disconnection of the side chain in 5 position of the tetrahydrofuran reveals the corresponding aldehyde **305** and the associated side chain. Protecting group interconversion allows introduction of a secondary alcohol at the 3-position by stereoselective reduction of the corresponding ketone and introduction of the aldehyde by oxidation of the corresponding primary alcohol **306**. Retro cross-metathesis reveals the terminal alkene precursor for the introduction of the side chain at the 2-position of the

tetrahydrofuran. This terminal alkene **307** is the 2,3-sigmatropic rearrangement product of the key ylide derived from diazoketone **308**. The carbenoid precursor could be synthesised in a few steps from malic acid.

2.2.2 Synthesis

Formation of the substituted tetrahydrofuran ring

To access the key diazoketone precursor required for ylide formation and 2,3-sigmatropic rearrangement, it was decided to follow the same synthetic route as for the synthesis of the A-ring fragment of gambieric acid but using the other enantiomer of malic acid (**Scheme 69**). The two synthetic routes differ in the nature of the secondary ether formed in step four. The difficulties encountered during the synthesis of the crotyl ether as previously discussed were not an issue in this case because an allylic ether was required.



Reagents: a) $SOCl_2$, MeOH, 3 h, RT, quant. ; b) $BH_3.SMe_2$, $NaBH_4$, THF, 0 °C to RT, 3 h c) TBDPSCl, DMAP, imidazole, DMF RT, 1 h 93 % over 2 steps, 40:1 ratio; d) $Cl_3C(NH)COCH_2CHCH_2$, triflic acid, cyclohexane, RT, 16 h, 90 %, e) TMSOK, ether, RT, 16 h, quant. f) i. $(COCl)_2$, DCM, DMF RT, 16 h; ii) CH_2N_2, Et_2O, 0 °C to RT, 3 h 97 % over 2 steps

Scheme 69: Synthesis of the rearrangement precursor 308

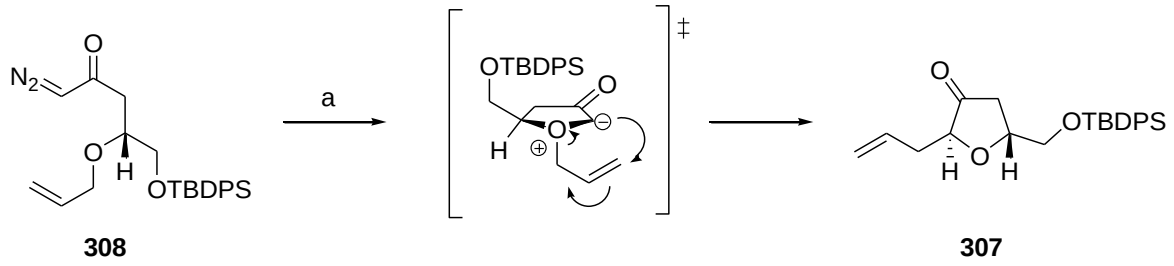
Commercially available **D**-malic acid **310** was used as a starting material for the synthesis. It was first converted into the corresponding di-methyl ester **309** using thionyl

chloride and methanol. [106] Regioselective reduction of the di-ester using borane dimethylsulfide and a catalytic amount of sodium borohydride followed by selective protection of the primary alcohol provided a mixture of alcohols in a 40:1 ratio. By changing the reaction conditions and carrying out the reaction at –10 °C for 5 hours only the desired regioisomer was formed. After protection of the primary alcohol as a TBDPS ether, the desired secondary alcohol was isolated in 93% yield over two steps.

Formation of the allyl trichloroacetimidate was carried out by reaction of allyl alcohol with trichloroacetonitrile under basic conditions using $TBAHSO_4$ as a phase transfer reagent. The resulting trichloroacetimidate was used without further purification in the next step: formation of the allyl ether.[107] Secondary alcohol **311** was treated with the allyl trichloroacetimidate with a catalytic amount of triflic acid. The desired ether was obtained as a single product in 90% yield. Conversion of the methyl ester into the carboxylic acid was achieved quantitatively using TMSOK in diethyl ether at 0 °C.[108] Carboxylic acid **314** was converted into the key intermediate diazoketone in a two-step process. First, conversion of the carboxylic acid into the acid chloride was realised using oxalyl chloride in presence of a catalytic amount of DMF. The crude acid chloride was then treated with an excess of diazomethane in ether at 0 °C and the diazoketone was formed in 1 hour in 97% yield. The diazoketone had to be handled carefully as these compounds are generally unstable to heat and light.

The key rearrangement precursor **307** was immediately used for the formation of the tetrahydrofuran core of the natural product (**Scheme 70**). As previously reported by our group, the conditions used for the formation of 2,5-*trans*-tetrahydrofuran-3-one and optimised for the synthesis of the A-ring fragment of gambieric acid, involve $Cu(acac)_2$ as a catalyst in THF at reflux.[109]

[106] Saito, Hasegawa, Inaba, Nishida, Fujii, Nomizu and Moriwake, *Chemistry Letters* **1984**, (8), 1389-92, Saito, Ishikawa, Kuroda, Koga and Moriwake, *Tetrahedron* **1992,** 48, (20), 4067-86.
[107] Wessel, Iversen and Bundle, *Journal of the Chemical Society-Perkin Transactions 1* **1985**, (11), 2247-50, Patil, *Tetrahedron Letters* **1996,** 37, (9), 1481-84, Dimitriadis and Massywestropp, *Australian Journal of Chemistry* **1984,** 37, (3), 619-27.
[108] Laganis and Chenard, *Tetrahedron Lett.* **1984,** 25, (51), 5831-4.
[109] Clark, Fessard and Wilson, *Org Lett* **2004,** 6, (11), 1773-6.



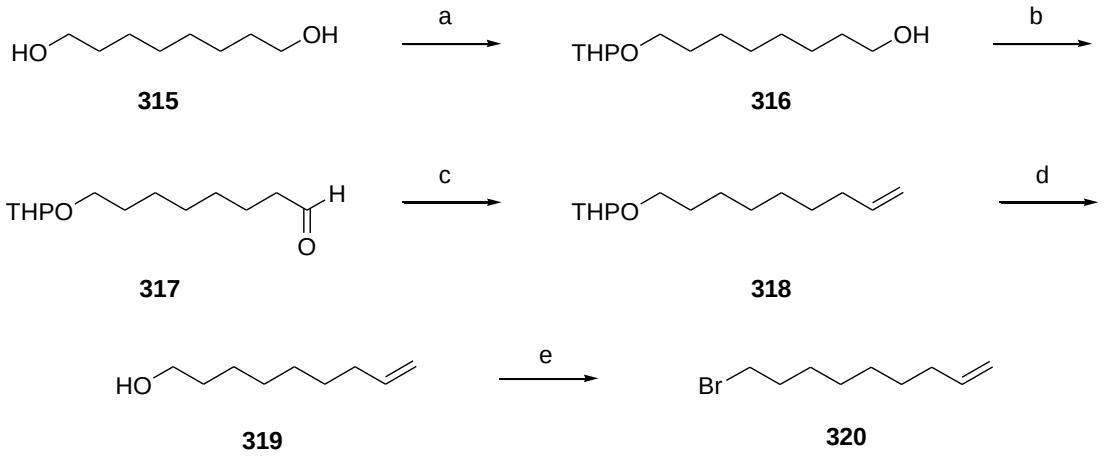
308 **307**

Reagents: a) $Cu(acac)_2$ 10 mol%, THF, 70 °C, 30 min, 92%

Scheme 70: Formation of the key tetrahydrofuran core of the natural product (6*S*,7*S*,9*S*,10*S*)-6,9-epoxynonadec-18-ene-7,10-diol

Diazoketone **308**, dissolved in Et_2O, was added dropwise to a solution of the copper catalyst in THF at reflux. The 2,3-sigmatropic rearrangement product was obtained for this reaction as a single isomer in 92% yield. The *trans* relative stereochemistry of the side chains in 2 and 5 positions of the ring was confirmed by nOe analysis.

The synthetic route adopted relies on a Grignard addition as a last step to introduce the side chain in the 5-position of the tetrahydrofuran ring. Therefore in parallel to the synthesis of the tetrahydrofuran core of the natural product, efforts have been focused on finding optimal conditions for the synthesis of the side chain. Ultimately, the synthesis of the Grignard reagent precursor was achieved in 5 steps from commercially available 1,8-octanediol **315** (**Scheme 71**).



315 **316** **317** **318** **319** **320**

Reagents: a) DHP, *p*-TsOH, DCM, RT, 30 min, 72%; b) oxalyl chloride, DMSO, Et_3N, DCM, -78 °C to RT, 3 hours 98%; c) $Ph_3P(CH_3)Br$, KO^tBu, benzene, 90 °C to RT, 1 hour, 87%; d) *p*-TsOH, MeOH, RT, 16 hours, quant. e) CBr_4, PPh_3, DCM, 0 °C to RT 2 hours, 85%

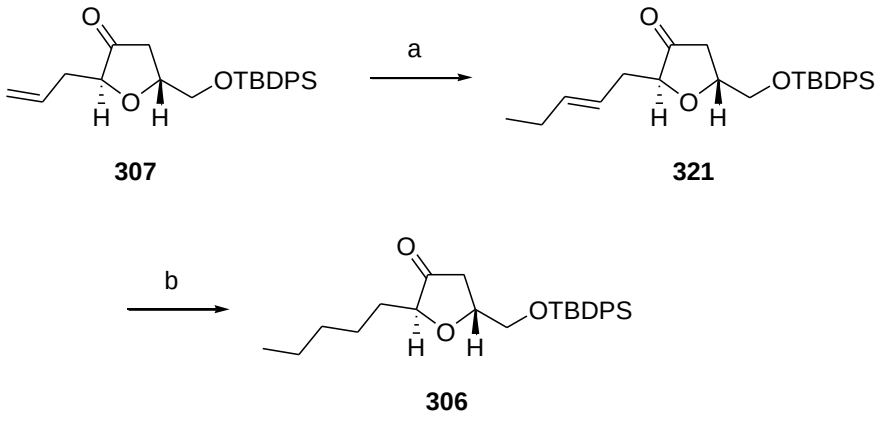
Scheme 71: Synthesis of the Grignard precursor

The first step of this synthesis is the mono-protection of the diol. The reaction was first carried out with DHP and *p*-TsOH using standard conditions. Using this method, the desired mono-protected product **316** was obtained in 72% yield along with the di-protected

product and the starting material. In 2000, Nishiguchi reported optimised conditions for this reaction which allowed the mono-tetrahydropyranylation of symmetrical 1,n-diol using aqueous acid as catalyst.[110] Using the conditions described in this paper-aqueous 5 M $NaHSO_4$, DHP–toluene (5:95)-the formation of by-products was limited and the yield of the desired mono-protected product was increased to 85%.

The remaining free primary hydroxyl group was oxidised to the corresponding aldehyde under standard Swern conditions. The oxidation product **317** was obtained in 98% yield after purification by column chromatography on silica gel. Conversion of the carbonyl group into the terminal alkene was carried out using a Wittig reaction with methyltriphenylphosphonium bromide and potassium *tert*-butoxide. The THP alcohol **318** was then quantitatively deprotected by treatment with a catalytic amount of tosic acid in methanol. The resulting primary alcohol **319** was then converted into the corresponding bromide with carbon tetrabromide and triphenylphosphine. Thus, the side chain precursor required for the Grignard addition reaction was formed in five steps and 52% overall yield.

The synthesis of the tetrahydrofuran core was continued with construction of the side chain at the 2-position of the tetrahydrofuran. The saturated carbon chain was introduced by cross-metathesis of the alkene **307** with 3-hexene (**Scheme 72**).



Reagents: a) *trans*-3-hexene, Grubbs second generation catalyst, toluene, 70 °C, 16 hours 70%; b) H_2, EtOH, Pd/C (10 mol%), RT, 2 hours, quant.

Scheme 72: Introduction of the side chain at the 2-position of the tetrahydrofuran ring

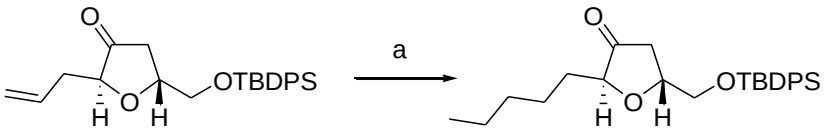
The first approach investigated involved a two-step procedure. The alkene **307** reacted with *trans*-3-hexene using a catalytic amount of Grubbs second generation catalyst (5 mol%) to form the cross metathesis product **321** in 70% yield. The alkene formed during

[110] Nishiguchi, Hayakawa, Hirasaka and Saitoh, *Tetrahedron Lett.* **2000,** 41, (50), 9843-46.

this reaction was then hydrogenated under a hydrogen atmosphere using palladium activated on carbon as a catalyst to obtain the desired saturated side chain.

In 2001, Grubbs reported the formation of a saturated chain using a tandem cross metathesis hydrogenation strategy.[111] The Grubbs second generation catalyst in this case was used for both metathesis reaction and alkene reduction. Using this protocol on the tetrahydrofuran rearrangement product led to incorporation of the side chain in a single step process (**Scheme 73**).

In Grubbs report, the reaction involved the use of H_2 under pressure (>100 psi) at 40 °C. Due to the lack of appropriate high pressure equipment, some investigations regarding the reaction conditions were performed to accomplish the reaction at atmospheric pressure. Parameters such as temperature, solvent conditions and number of equivalents of the catalyst were varied to obtain maximum yield (**Table 11**).



307 **306**

Reagents: a) i. *trans*-3-hexene, Grubbs 2nd generation, toluene, 70 °C, 16 h, 70 %; ii. H_2, ethanol, RT, 2 h, 85%

Scheme 73: Insertion of the side chain using a single step process

Entry	Solvent	Temperature	Reaction time	Eq. of Grubb's catalyst	Results
1	DCM	RT	2h	0.05	-
2	DCM	RT	2h	0.1	-
3	DCM	40 °C	2 weeks	0.1	4 % product isolated
4	DCE	RT	2h	0.05	-
5	DCE	RT	2h	0.1	-
6	DCE	70 °C	16h	0.1	85 %

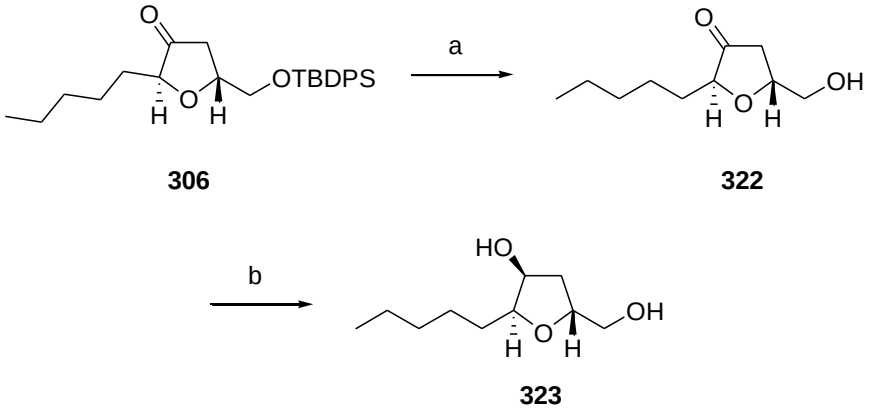
Table 11: Optimisation of the tandem cross-metathesis - hydrogenation reaction

First, the hydrogenation reaction was performed in DCM at room temperature using 5 mol% of Grubbs second generation catalyst (**Table 11, Entry 1**) Unfortunately, only starting material was recovered using these conditions. Increasing the number of equivalents of catalyst did result in formation of the desired product. Trace amounts of the

[111] Louie, Bielawski and Grubbs, *J. Am. Chem. Soc*. **2001,** 123, (45), 11312-13.

cross metathesis product were isolated when the reaction was left at 40 °C for 2 weeks. In order to access higher temperatures, the DCM was changed for DCE. The best yield of 85% was obtained by refluxing the DCE-solution for 16 hours at 70°C and using 10% mol of catalyst. Once the formation of the cross-metathesis product was observed by TLC, and confirmed by NMR of a few microlitres of crude reaction mixture, the alkene was hydrogenated.

Following construction of the side chain at 2 position of the tetrahydrofuran ring, a few steps remained to be completed before construction of the side chain at the 5-position. Efforts were first focussed on the introduction of the secondary alcohol at 3 position of the ring with the desired stereochemistry (**Scheme 74**).



Reagents: a) TBAF, Et_2O, RT, 16 h, 99% ; b) L-selectride, THF, -78 °C, 1 h, 57%

Scheme 74: Formation of the secondary alcohol with the desired stereochemistry

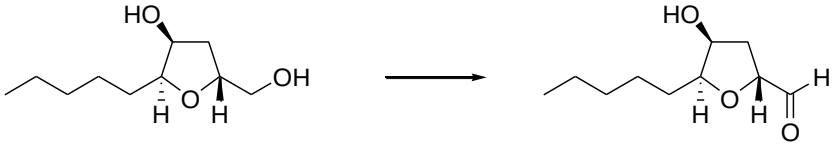
The first approach investigated for the reduction of ketone **306** involved the use of **L**-selectride as a reducing reagent.[112] Using low temperature conditions, the desired diol was obtained in 57% yield and as a 3:1 mixture favouring the desired diastereoisomer. In 1999, Mioskowski reported the use of the free primary hydroxyl group to coordinate to sodium triacetoxy borohydride and deliver the hydride to a pendant ketone to obtain the secondary alcohol with diastereocontrol.[113] In our case, the reducing agent was expected to coordinate to the free primary hydroxyl group and deliver attack of the hydride to the ketone from the bottom face of the tetrahydrofuran ring **322**. Using these conditions, the desired diol was obtained in 98% yield without formation of the other diastereoisomer. With diol **323** in hand, only two steps remained for the completion of the synthesis of the natural product. First, the free primary alcohol needed to be selectively oxidised to the

[112] Brown and Krishnamurthy, *J. Amer. Chem. Soc.* **1972,** 94, (20), 7159-61.
[113] Adams, Poupart and Grenier, *Tetrahedron Lett.* **1989,** 30, (14), 1753-6, Borthwick, Crame, Exall and Weingarten, *Tetrahedron Lett.* **1994,** 35, (41), 7677-80, Ducray, Rousseau and Mioskowski, *J. Org. Chem.* **1999,** 64, (11), 3800-01, Hoveyda, Evans and Fu, *Chem. Rev. (Washington, D. C.)* **1993,** 93, (4), 1307-70.

corresponding aldehyde, and then the addition of the Grignard side chain could be used to install the remainder of the side chain at the 5-position of the tetrahydrofuran.

Selective oxidation of the primary alcohol

In order to complete the synthesis the primary alcohol of intermediate **323** must be selectively oxidised to give the corresponding aldehyde in order to perform the subsequent Grignard addition. Most of the conditions reported in the literature for the selective oxidation of a primary hydroxyl group in presence of a secondary hydroxyl group use TEMPO as an oxidant.[114] The reaction was attempted using several different reaction conditions varying the number of equivalents of TEMPO, and altering the co-oxidant. (**Table 12**).



323 **305**

TEMPO	Additive	Time	Temperature	Result
0.1eq	NCS, NH_4Cl	1h	RT	Starting material
0.3eq	NCS, NH_4Cl	2days	RT	Starting material
0.3eq	NCS, NH_4Cl	1h	40°C	Starting material
0.3eq	NCS, NH_4Cl	2days	40°C	Decomposition
0.1eq	NCS, TBACl	1h	RT	Starting material
0.3eq	NCS, TBACl	2h	RT	Starting material
0.3eq	NCS, TBACl	3days	RT	Starting material
0.2eq	KBr, Bleach	1h	0°C	Starting material
0.2eq	KBr, Bleach	2h	0°C	Starting material
0.2eq	KBr, Bleach	1h	RT	Starting material
0.2eq	KBr, Bleach	2h	RT	Starting material
0.2eq	KBr, Bleach	1week	RT	Starting material
0.1eq	Trichloroisocyanuric ac.	1h	0°C	Starting material
0.1eq	Trichloroisocyanuric ac.	2h	0°C	Starting material
0.1eq	Trichloroisocyanuric ac.	1h	RT	Decomposition

Table 12: Conditions for the selective oxidation of the primary alcohol

The first set of conditions used were those described by Einhorn in which NH_4Cl is used as an additive (**Table 12, Entry 1**).[115] The reaction was first carried out at room temperature but formation of a new compound was not observed by TLC. The temperature of the reaction was therefore increased to 40°C and further 0.5 equivalents of NCS were

[114] Sawayama, Tanaka and Wandless, *J. Org. Chem.* **2004,** 69, (25), 8810-20, De Luca, Giacomelli and Porcheddu, *Org. Lett.* **2001,** 3, (19), 3041-43, Einhorn, Einhorn, Ratajczak and Pierre, *J. Org. Chem.* **1996,** 61, (21), 7452-54.
[115] Einhorn, Einhorn, Ratajczak and Pierre, *J. Org. Chem.* **1996,** 61, (21), 7452-54.

added to the reaction mixture. After 1 hour, TLC analysis showed the formation of two new products and after two days, there was complete consumption of the starting material. Unfortunately, none of the desired product was isolated, and only decomposition products were observed (**Table 12, Entries 5-7**).

The reaction was repeated using TBACl instead of ammonium chloride as an additive. The temperature at which the reaction was carried out was kept below 40°C because decomposition of the starting material was observed when the reaction was attempted above this temperature. The reagents were left to react for up to three days but formation of the desired aldehyde was not observed and only the starting material was recovered. Changing the co-oxidant to a combination of potassium bromide and bleach or trichloroisocyanuric acid at various temperatures led to the same results (**Table 12, Entries 8-13**).

In order to achieve the selective oxidation of the primary hydroxyl group in presence of the secondary one, a new method had to be found. Oxidation methods such as aerobic oxidation of a primary alcohol catalysed by a ruthenium complex and hydroquinone under atmospheric oxygen[116] or copper catalysed oxidation were examined.[117] When the oxidation of the diol using ruthenium catalysis was performed, a new product was isolated. NMR analysis of the isolated intermediate showed that the secondary alcohol had been oxidised in 50% yield and the primary alcohol was unreacted. These results suggested that the primary alcohol might be stabilised by hydrogen bonding either to the oxygen of the tetrahydrofuran or to the secondary alcohol. This hydrogen bonding might stabilise the molecule in a way which makes the primary alcohol unreactive.

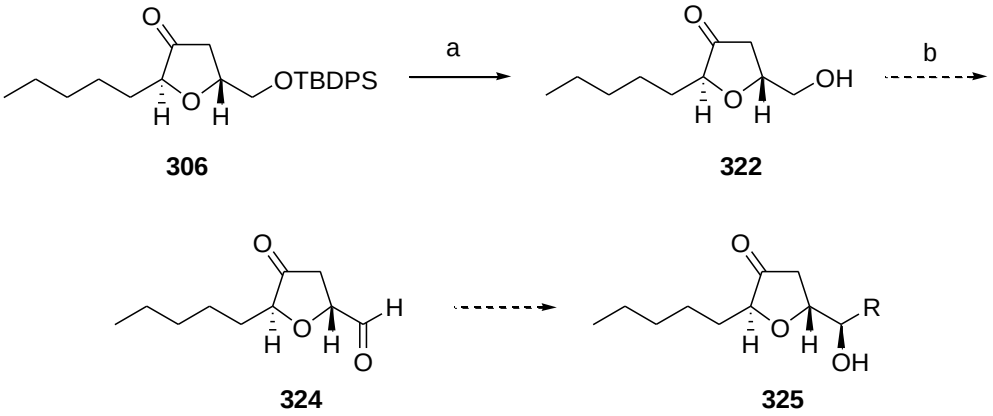
The negative results obtained in all attempts to selectively oxidise the primary alcohol led to a change of strategy. Keeping the same number of steps for the synthetic route, a decision was made to synthesise the di-carbonyl intermediate and perform a selective addition of the Grignard reagent to the aldehyde.

Selective addition of the side chain on the aldehyde

The selective addition of a Grignard reagent to a carbonyl group is a useful tool for synthesis of natural products and has received significant attention from the research

[116] Hanyu, Takezawa, Sakaguchi and Ishii, *Tetrahedron Lett.* **1998,** 39, (31), 5557-60.
[117] Mannam and Sekar, *Tetrahedron Lett.* **2008,** 49, (15), 2457-60.

community. In 1986, Cahiez reported the selective addition of an organomanganese reagent to an aldehyde in the presence of a ketone functionality.[118] Intermediate **322** can be used for this approach because the ketone functionality at the 3-position of the tetrahydrofuran is not reduced. The primary alcohol could first be deprotected and the free primary alcohol can then be oxidised to the corresponding aldehyde. The bromide side chain **320** can then be converted into the organomanganese reagent and can then be selectively added to the aldehyde **324** (**Scheme 75**). Stereoselective reduction of the ketone in the 3-position could be achieved employing the same methodology as previously using $NaBH(OAc)_3$ and with direction from the secondary hydroxyl group produced by introduction of the side chain.



Reagents: a) TBAF, Et_2O, RT, 16 h, 98%; b) oxidation

Scheme 75: Selective addition of the organomanganese to the aldehyde

Intermediate **306** was deprotected using the same conditions as previously and the hydroxy ketone **322** was obtained in 98% yield. Oxidation of the primary alcohol to give corresponding aldehyde was first attempted using Swern conditions. Unfortunately, none of the desired aldehyde was isolated. Standard Dess Martin conditions were also employed, but the free primary hydroxyl group was unreactive. Stronger oxidation conditions such as CrO_3·pyridine, PCC oxidation,[119] and IBX[120] were also used. However, all these reactions led to decomposition of the sarting material. DCC-pyridine[121] combination as well as Oppenauer oxidation[122] were also explored but unfortunately none of the desired aldehyde

[118] Cahiez and Figadere, *Tetrahedron Lett.* **1986,** 27, (37), 4445-8.
[119] Corey and Suggs, *Tetrahedron Lett.* **1975**, (31), 2647-50.
[120] Frigerio and Santagostino, *Tetrahedron Lett.* **1994,** 35, (43), 8019-22.
[121] Hanessian and Lavallee, *Can. J. Chem.* **1981,** 59, (5), 870-7.
[122] Graves, Zeng and Nguyen, *J. Am. Chem. Soc.* **2006,** 128, (39), 12596-97, Ooi, Otsuka, Miura, Ichikawa and Maruoka, *Org. Lett.* **2002,** 4, (16), 2669-72.

product was isolated from these reactions. These reactions were performed at various reaction temperatures, and using various equivalents of oxidant and reaction times but they all resulted in decomposition of the starting material.

The fact that none of the reaction conditions examined were effective for the oxidation of the primary alcohols **322** or **323** provided evidence that the alcohol was particularly unreactive and so the oxidation of a simpler tetrahydrofuran-bearing primary alcohol was investigated. Previous research in this area had shown that simple systems such as tetrahydrofurfuryl alcohol were not very easily oxidised under standard conditions. Indeed, the oxidation of tetrahydrofurfuryl alcohol under standard Swern oxidation conditions gave the corresponding aldehyde in only 42% yield.[123] Only a procedure involving the use of an iridium-aminyl-radical complex catalyst led to the formation of the aldehyde in good yield but lengthy reaction times were required compared to those of the other substrates.[124]

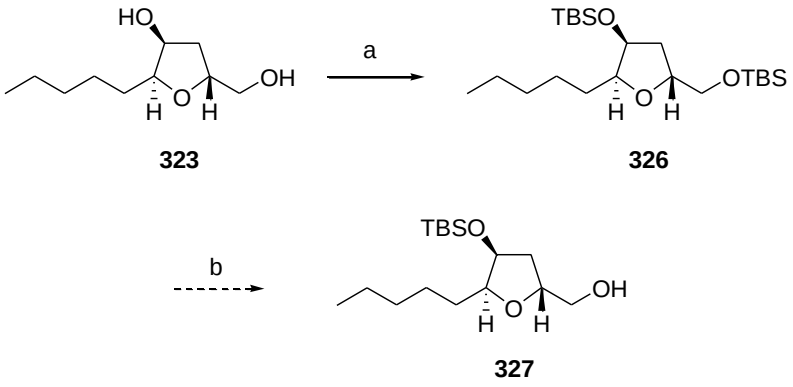
All attempts to oxidise the primary alcohol failed and so the reactivity of this type of primary hydroxy group was questioned. In order to check the reactivity of the primary alcohol, re-protection of the hydroxy group as a silyl ether was attempted. The reaction mixture was left for two days to react but unfortunately only starting material was isolated after purification of the crude mixture. In order to check the presence of the primary hydroxyl group on intermediate **323**, further data analysis was performed. Both high resolution mass spectrometry and NMR data analysis confirmed the formation of the desired intermediate **323**.

If the poor reactivity of the primary hydroxyl group results of a hydrogen bonding, it could arise from two different sources. The first case would involve formation of a hydrogen bond between the proton of the hydroxyl group and the oxygen from the tetrahydrofuran. The second and more likely case would involve formation of a hydrogen bond between that same hydrogen and the oxygen of the carbonyl group. In order to prevent formation of this latter type of hydrogen bonding, it was decided to introduce a protecting group on either the carbonyl or the secondary hydroxyl group on the 3-position of the tetrahydrofuran.

[123] Bianchi, Roda, Riva, Danieli, Zabelinskaja-Mackova and Griengl, *Tetrahedron* **2001,** 57, (11), 2213-20.
[124] Koenigsmann, Donati, Stein, Schoenberg, Harmer, Sreekanth and Gruetzmacher, *Angew. Chem., Int. Ed.* **2007,** 46, (19), 3567-70.

Protection of the ketone

Oxidation of a primary hydroxyl group in presence of a secondary one has always been a synthetic challenge in organic synthesis. Amongst the methods reported, some involve the protection of both hydroxyl groups and subsequent oxidation at the more reactive primary hydroxyl site. The use of the different chemical properties of silyl ethers is one approach that has proved to be highly efficient in some cases.[125] Examples have been reported in which compounds bearing both primary and secondary hydroxyl groups where both functionalities were protected as TBS ethers. Subsequent treatment of the doubly protected compound with HF·pyridine at 0 °C would allow the selective deprotection of the primary hydroxyl group, leaving the secondary hydroxyl group protected as a silyl ether.[126] This methodology was therefore applied to the diol intermediate **323** in our synthetic route (**Scheme 75**).



Reagents: a) TBSOTf, 2,6-lutidine, 0 °C; b) HF·py, THF, 0 °C to RT

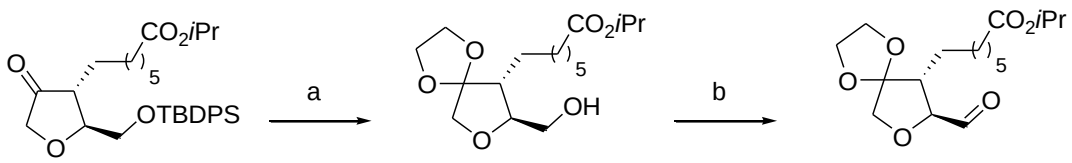
Scheme 76: Selective TBS deprotection strategy

In order to achieve double protection of the diol, the intermediate **323** was treated with TBSOTf and 2,6-lutidine. The reaction was performed under standard conditions, at 0 °C. TLC analysis after one and two hours did not indicate formation of a new product. The reaction was therefore left at room temperature for up to two days. Unfortunately, only starting material was recovered and trace amounts of the protected secondary alcohol could be isolated after purification.

[125] Tolstikov, Miftakhov, Adler, Komissarova, Kuznetsov and Vostrikov, *Synthesis* **1989**, (12), 940-2.
[126] Shin, Fournier, Brueckner, Madiraju, Balachandran, Raccor, Edler, Hamel, Sikorski, Vogt, Day and Curran, *Tetrahedron* **2007,** 63, (35), 8537-62, Ruiz, Murga, Carda and Marco, *J. Org. Chem.* **2005,** 70, (2), 713-16.

It was assumed that the problems with double protection were due to a problem of reactivity of the primary hydroxyl group as encountered during the TBDPS re-protection of the intermediate **322**. The selective TBS deprotection being ineffective, it was decided to investigate another approach for the formation of the desired aldehyde.

Two main groups exist to mask and protect the ketone - the acetal and thioacetal groups. Examples of the protection of a carbonyl in 3-position of a tetrahydrofuran prior to the oxidation of a primary alcohol in the same position as the one of interest, have been reported and patented.[127] To access the aldehyde, the ketone was protected as a dioxolane using the reagent 1,2-bis(trimethylsilyloxy)ethane so as to avoid the use of acidic conditions which could isomerize the stereogenic centre adjacent to the carbonyl group (**Scheme 77**).



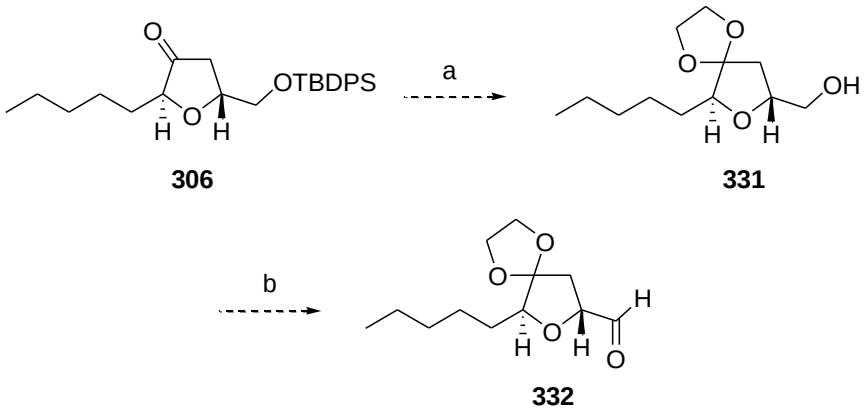
328 **329** **330**

Reagents: a) i. TMSOTf, 1,2-bis(trimethylsilyloxy)ethane, DCM, -78 °C, 18 h; ii. TBAF, THF, RT, 30 min, 90%; b) oxalyl chloride, DMSO, Et_3N, DCM, -78 °C, 60%

Scheme 77: Synthesis of the aldehyde *via* carbonyl protection[128]

The conversion of reported intermediate **328** into the corresponding aldehyde *via* carbonyl protection is very similar to the conversion of the hydroxyketone into the aldehyde **330**, so it was decided to adopt this approach. In the first attempt, the reaction was carried out by protecting the carbonyl as a cyclic acetal and deprotecting the silyl ether in a one-step process as reported in the patent. Unfortunately, this resulted in the formation of a complex mixture of products that was difficult to purify by column chromatography (**Scheme 78**).

[127] Selliah, **1998**, 27 pp.
[128] Selliah, **1998**, 27 pp.



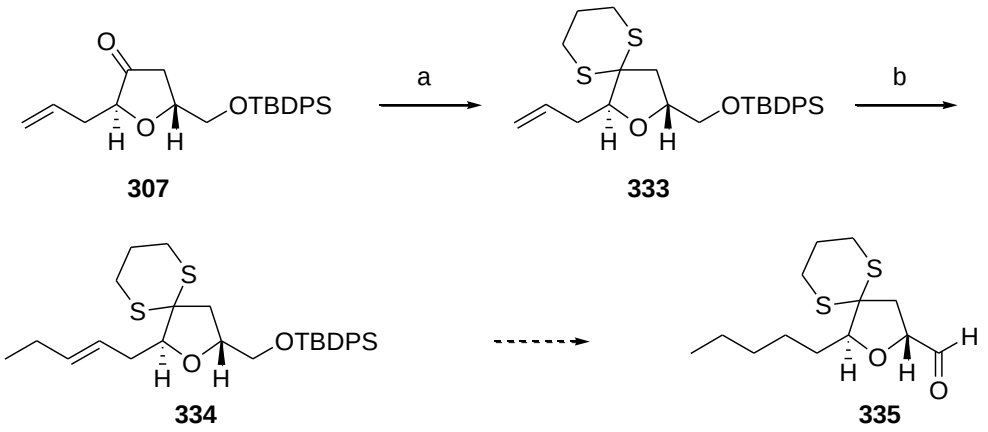
Reagents: a) i. TMSOTf, 1,2-bis(trimethylsilyloxy)ethane, DCM, -78 °C, 18 h; ii. TBAF, THF, RT, 30 min, 51%; b) oxalyl chloride, DMSO, Et_3N, DCM, -78 °C

Scheme 78: Application of the acetal protection strategy to the synthetic route

To avoid the formation of a mixture of products, the alcohol was synthesised in a 2-step manner. First, protection of the ketone as a five-membered cyclic acetal was carried out by treatment of intermediate **306** with TMSOTf and 1,2-bis(trimethylsilyloxy)ethane to give the desired product in 51% yield. Subsequent deprotection of the primary alcohol was achieved quantitatively. With the primary alcohol **331** in hand, the only step remaining was oxidation to give the corresponding aldehyde.

Several oxidation methods to convert intermediate **331** into the desired aldehyde were then explored. Swern oxidation was the first method investigated but unfortunately, this reaction gave only starting material. The number of equivalents of oxalyl chloride, DMSO and Et_3N were doubled, but formation of the desired aldehyde was not observed. It was thought that a higher reaction temperature might be required to oxidise the primary hydroxyl group and so Dess Martin oxidation was also attempted. The reaction mixture was left for one hour without the formation of a new product. Leaving the reaction for up to 16 hours led only to the decomposition of the starting material. This result is probably a consequence of the deprotection of the acetal by the acetic acid evolved during the reaction. Other oxidation procedures were explored such as those using PCC or TEMPO, but none of them gave the desired aldehyde **332**.

In order to prevent the decomposition of the starting material *via* deprotection of the cyclic acetal, it was decided to use a more stable protecting group such as a cyclic thioacetal (**Scheme 79**).



Reagents: a) 1,3-propanedithiol, $BF_3 \cdot OEt_2$, $CHCl_3$, 0 °C to RT, 88%; b) *tran*-3-hexene, Grubbs II, toluene

Scheme 79: Synthesis of the aldehyde *via* cyclic thioacetal

Treatment of intermediate **307** with 1,3-propanedithiol in the presence of $BF_3 \cdot OEt_2$ led to the formation of the desired cyclic thioacetal in excellent yield. Elaboration of the side chain at the 2-position of the tetrahydrofuran was then attempted using the same reaction conditions as previously. Surprisingly, none of the desired cross metathesis product was formed during the reaction, probably due to steric hinderance. Indeed, the introduction of the 6-membered heterocycle at the 3-position made the terminal alkene less accessible to the catalyst for cross metathesis. It is also possible that the ruthenium catalyst complexes to the sulfur atom of the thioacetal. No further work was done on this route and it was decided to adopt an alternative strategy for the completion of the synthesis.

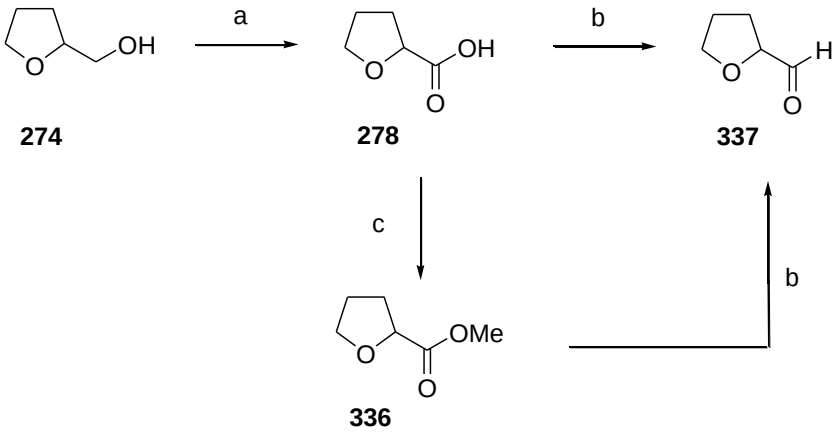
All the approaches described up to this point required oxidation of a primary alcohol to give an aldehyde. This approach was proving to be problematic and so, it was decided to use an alternative approach which would lead to the formation of the same aldehyde.

Alternative approaches to aldehyde formation

Reduction of carboxylic acid or ester

The first approach investigated was the access to aldehyde by hydride reduction of the corresponding carboxylic acid or methyl ester.[129] As already reported for the synthesis of the A-ring fragment of gambieric acid, carboxylic acid **278** could be accessed from tetrahydrofurfuryl alcohol **274** by PDC oxidation (**Scheme 79**).

[129] Belanger and Williams, *Can. J. Chem.* **1983,** 61, (7), 1383-6.



Reagents: a) PDC, DMF, RT, 2 days, 71%; b) DIBAL-H, toluene, Et_2O, -60 °C, 30 min
c) H_2SO_4, MeOH, 65 °C, 3 hours, quant.

Scheme 80: Formation of the aldehyde *via* reduction of carboxylic acid or ester

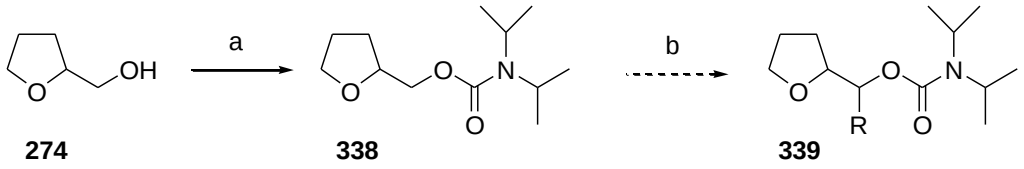
Formation of the carboxylic acid by PDC oxidation was achieved in 71% yield. A first attempt to realise the hydride reduction was performed using DIBAL-H as the hydride source. Unfortunately, this reaction only led to the decomposition of the starting material. Reduction of methyl ester to the corresponding aldehyde being a more reliable transformation, the carboxylic acid was converted into the methyl ester **336** by reaction with methanol under acidic conditions. The desired ester **336** was formed in 98% yield and subsequently engaged in the next step: reduction to the corresponding aldehyde using DIBAL-H as a hydride source.[130] Unfortunately, as for the reduction of the carboxylic acid, the desired product was not isolated. Following these results, another milder approach had to be investigated to allow the formation of the aldehyde.

Addition of the bromide to N,N-diisopropyl carbamate

N,N-diisopropylcarbamates have been widely used in enantioselective homoaldol reactions to give addition products in high yield and with high selectivities.[131] In 1990, Hoppe reported the use of *N,N*-diisopropyl carbamate for the selective silylation, protonation or addition of bromides.[132] Mechanistic studies showed that deprotonation of the diisopropyl carbamate can be performed in an asymmetric manner using a chiral non-racemic diamine. The subsequent addition reaction could therefore be performed

[130] Zakharkin and Khorlina, *Tetrahedron Lett.* **1962**, 619-20.
[131] Becker, Froehlich, Salorinne and Hoppe, *Eur. J. Org. Chem. FIELD Full Journal Title:European Journal of Organic Chemistry* **2007**, (20), 3337-48, Reuber, Froehlich and Hoppe, *Eur. J. Org. Chem.* **2005**, (14), 3017-25.
[132] Hoppe, Carstens and Kraemer, *Angew. Chem.* **1990,** 102, (12), 1455-6 (See also Angew Chem , Int Ed Engl , 990, 29(12), 24-5).

enantioselectively. *N,N*-Diisopropyl carbamate are easily accessible from alcohols by treatment with diisopropylcarbamoyl chloride and sodium hydride (**Scheme 81**).



Reagents: a) diisopropylcarbamoylchloride, NaH, THF, 0 °C, 30 min, 98%; b) sec-BuLi, TMEDA, 9-bromononene

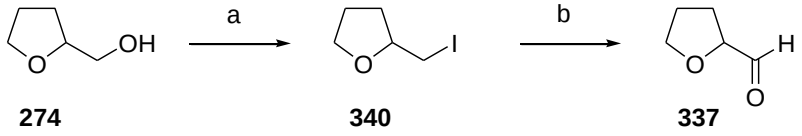
Scheme 81: Formation of the aldehyde *via* diisopropylamide formation

Tetrahydrofurfuryl alcohol **274** was converted into the corresponding *N,N*-diisopropylcarbamate in 98% yield by treatment with diisopropylcarbamoyl chloride and sodium hydride. The deprotonation reaction was then carried out using TMEDA as a diamine. Intermediate **338** was then treated with *sec*-BuLi and TMEDA and 9-bromononene was then added to obtain the addition product. Unfortunately, the reaction only led to decomposition of the starting material. The decomposition of the *N,N*-diisopropylcarbamate **339** undoubtedly results from ring opening of the deprotonated product. Deprotonation in α position of the carbamate is highly likely to result in opening of the tetrahydrofuran ring and the ring-opened product would then be protonated during the work up.

Halide oxidation

Reports have already been published describing the conversion of an iodide into an aldehyde at high temperatures. DMSO is a reagent which has already been reported for the ionisation of the carbon halogen bond.[133] Using this property, DMSO can be used for the oxidation of halides to aldehydes. Oxidation of the halide can then be carried out within the presence of a mild base such as sodium bicarbonate.[134] In 1964, Johnson reported the conversion of an iodide into the corresponding aldehyde by treatment with sodium carbonate at high temperature (**Scheme 82**).[135] The high temperature conditions could be the driving force for the reaction to deliver the desired aldehyde without decomposition of the starting material **340** *via* tetrahydrofuran opening.

[133] Baranac Stojanovic and Markovic, *Tetrahedron Lett.* **2007,** 48, (10), 1695-98.
[134] Kornblum, Jones and Anderson, *J. Am. Chem. Soc.* **1959,** 81, 4113-14.
[135] Johnson and Pelter, *J. Chem. Soc.* **1964**, (Jan.), 520-2, Liu, Du, Dong, Meng, Xiao and Cheng, *Carbohydr. Res.* **2006,** 341, (16), 2653-57.



Reagents: a) PPh_3, imidazole, I_2, THF, RT, 16 hours, 98%; b) $NaHCO_3$, DMSO, 150 °C, 10 min

Scheme 82: Formation of the aldehyde from the corresponding iodide

Conversion of the hydroxyl group into the corresponding iodide was achieved by treatment of tetrahydrofurfuryl alcohol with triphenylphosphine in presence of imidazole and iodine. The desired halide **340** was obtained in excellent yield (98%) after purification. Subsequent conversion of the iodide into the aldehyde **337** was carried out by treatment of intermediate **340** with an excess of DMSO in presence of sodium hydrogen carbonate at high temperature. The mixture was left to react for 10 min at this temperature and then cooled rapidly to room temperature. Unfortunately, the reaction resulted in the formation of a complex mixture of decomposition products.

There are two possible reasons why decomposition of the iodide was observed. Firstly, the tetrahydrofuran could have been sensitive to such high temperatures. Indeed, the intermediate used for the synthesis of the natural product had already been decomposed at lower temperatures. On the other hand, the deprotonation of the molecule on this position could lead to opening of the tetrahydrofuran ring as assumed in the case of addition of the bromide to *N*,*N*-diisopropyl carbamate.

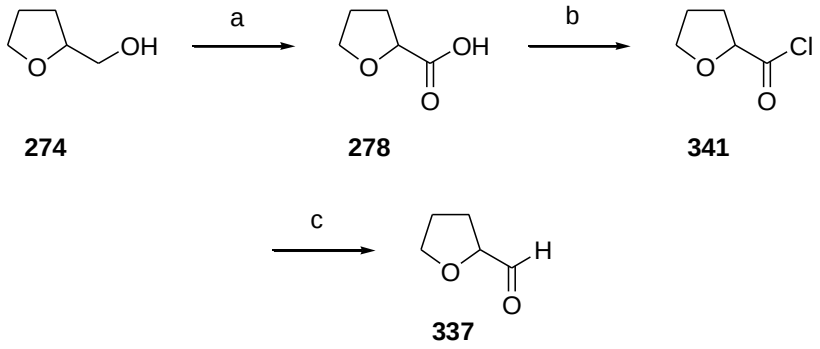
It was decided to adopt another approach to form the desired aldehyde. The procedure known as the Rosenmund reduction of acid chloride is another way of accessing an aldehyde from a carboxylic acid derivative.

Rosenmund reduction of an acid chloride

The Rosemund reduction is a catalytic hydrogenation process which allows the formation of an aldehyde from a carboxylic acid derivative. The reaction is usually catalysed using palladium although it is important not to use untreated palladium.[136] Indeed, untreated catalyst is too reactive and would over-reduce the starting material. To avoid formation of side products, the reaction is usually performed using palladium poisoned with barium sulfate and under anhydrous conditions. As described previously,

[136] Maurer and Hauser, *Helv. Chim. Acta* **1982,** 65, (2), 462-76, Rachlin, Gurien and Wagner, *Org. Syn.* **1971,** 51, 8-11, Tanaka, Mizukami, Niwa, Toba, Tasi and Kunimori, *Appl. Catal.*, **2002,** 229, (1-2), 175-80.

the carboxylic acid **278** can be obtained by oxidation with PDC of tetrahydrofurfuryl alcohol (**Scheme 83**).



Reagents: a) PDC, DMF, RT, 2 days, 71%; b) oxalylchloride, DMF, DCM, RT, 16 hours c) H_2, Pd on barium sulfate, toluene

Scheme 83: Formation of the aldehyde via hydrogenation of acyl chloride

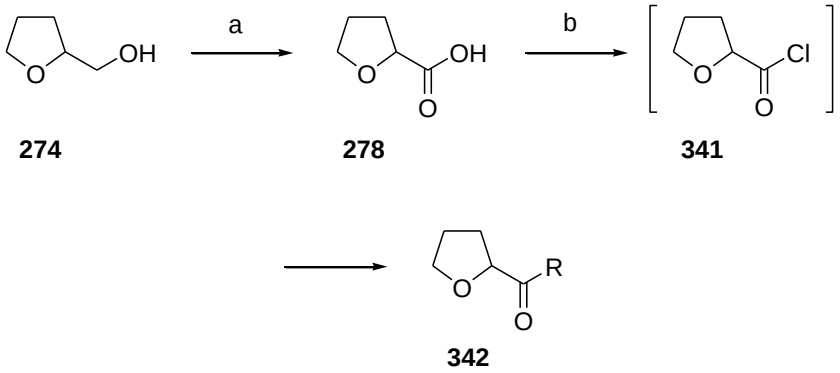
The carboxylic acid **278** was obtained from tetrahydrofurfuryl alcohol in 71% yield. Conversion of the carboxylic acid into the corresponding acyl chloride was achieved upon treatment of the acid with oxalyl chloride with catalytic amount of DMF. The acid chloride was unstable and was so used in the next step without any further purification.

Hydrogenation of the acid chloride in presence of palladium poisoned with barium sulfate was carried out in toluene. The reaction mixture was stirred under a hydrogen atmosphere and under anhydrous conditions at 70 °C for 1 hour. Analysis of the crude reaction mixture was performed after filtration over celite. The NMR spectrum of the crude mixture revealed the presence of traces of the required aldehyde along with a mixture of unidentified products. Due to difficulties in separating the product from various by-products, the reaction was not investigated any further.

Although the Rosenmund reduction did not lead to the formation of the desired product the intermediate acid chloride can be used directly in a Grignard reaction without the formation of the aldehyde.

Grignard addition to an acid chloride

Various reports have demonstrated that efficient addition of a Grignard reagent to an acyl chloride is possible.[137] Substitution of the chlorine atom by the alkyl group of the Grignard reagent would allow the formation of the corresponding ketone which could be reduced stereoselectively to the required secondary alcohol (**Scheme 84**).



Reagents: a) PDC, DMF, RT, 2 days, 71%; b) i. oxalylchloride, DMF, DCM, RT, 16 hours; ii. Grignard reagent, THF, -78 °C, 1h30

Scheme 84: Grignard addition on acid chloride

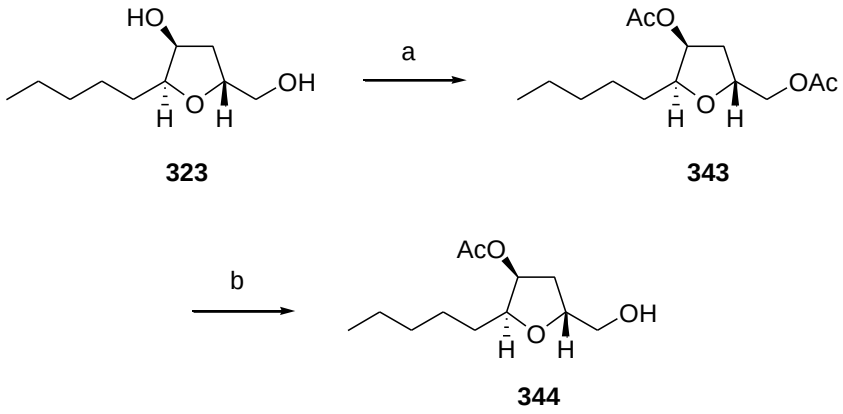
The acid chloride was prepared as described previously by oxidation of the primary alcohol to give the corresponding carboxylic acid **278** using PDC and subsequent treatment of the carboxylic acid with oxalyl chloride and catalytic amount of DMF. The resulting acid chloride was then concentrated and used in the next step without any further purification. Addition of the side chain in the form of a Grignard reagent was attempted in THF at –78 °C. However, this reaction led to the formation of a complex mixture of products. Purification of the resulting oil by column chromatography was attempted but none of the desired product was isolated and the starting material was not recovered.

In the light of the results above, it was decided to investigate further the formation of the aldehyde *via* oxidation of the corresponding primary alcohol. Because all previous attempts to achieve this reaction in a selective manner had failed, it was decided to access the aldehyde after protecting group manipulation.

[137] Figadere, Harmange, Laurens and Cave, *Tetrahedron Lett.* **1991,** 32, (51), 7539-42, Hanessian, Giroux and Buffat, *Org. Lett.* **2005,** 7, (18), 3989-92, Nicolaou, Brenzovich, Bulger and Francis, *Org. Biomol. Chem.* **2006,** 4, (11), 2119-57.

Protecting group manipulation

Selective mono-protection of the diol as a silyl ether was unsuccesful, and so it was decided to perform hydroxyl protection using a more reactive protecting group such as an ester. Selective acetylation of a secondary hydroxyl group in the presence of a primary one has been reported when either aluminium oxide or silca gel was added to the reaction mixture.[138] Unfortunately, the mechanism of this reaction relies on the adsorption of the diol onto SiO_2 in large quantities and the reaction was achieved for physical study purposes. Selective removal of an ester from a primary alcohol in presence of a secondary one has been reported,[139] and so acetylation was performed using an excess of acetic anhydride in order to give a double protection. Subsequent selective cleavage of the primary acetate would then give the free hydroxyl group required. (**Scheme 85**).



Reagents: a) Ac_2O, py., DCM, RT, 16 hours, quant.; b) KOH, EtOH, H_2O, 80 °C, 16 hours, 77%

Scheme 85: Selective deprotection of the primary alcohol

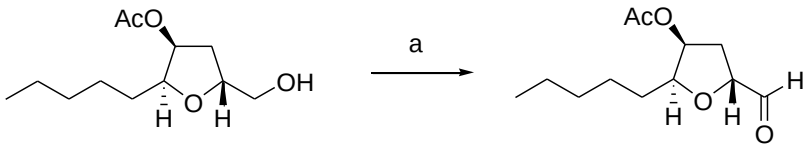
Double acetylation of the diol **323** was achieved by treatment with acetic anhydride and pyridine overnight at room temperature. Fortunately, the diacetate resulting from the protection of both primary and secondary hydroxyl groups was isolated quantitatively as shown by ^{1}H-NMR spectroscopy by the alteration of the chemical shift of the protons in the α-position of the hydroxyl group. The subsequent selective deprotection was performed by treatment of the diacetate **343** with one equivalent of potassium hydroxide in ethanol at

[138] Breton, Kurtz and Kurtz, *Tetrahedron Lett.* **1997,** 38, (22), 3825-28, Ogawa, Ide, Honda and Chihara, *J. Phys. Org. Chem.* **2003,** 16, (6), 355-58.
[139] Jacobson, Beroza and Jones, *J. Am. Chem. Soc.* **1961,** 83, 4819-24, Nicolaou, Hwang, Marron, DeFrees, Couladouros, Abe, Carroll and Snyder, *J. Am. Chem. Soc.* **1990,** 112, (8), 3040-54.

80 °C. The mono-acetylated product was obtained in 77% yield and with this intermediate in hand, the oxidation of the primary alcohol could be investigated further.

Various conditions have been investigated for the oxidation of the primary alcohol to the corresponding aldehyde. For example, Swern oxidation leads to the recovery of the starting material. However, if the low reactivity of the primary alcohol is due to hydrogen bonding with the oxygen of the tetrahydrofuran it might be more effective to perform the reaction at RT rather than – 78 °C. As an alternative to the Swern oxidation, Dess-Martin oxidation at RT was explored.

Under Dess-Martin conditions after 30 min reaction at RT, formation of the desired aldehyde was observed by TLC. The presence of the aldehyde was confirmed by NMR of the crude reaction mixture, but it was only formed in trace amounts. An alternative procedure to the Swern oxidation is the Parikh-Doering oxidation which uses sulfur trioxide-pyridine as an oxidant (**Scheme 86**).[140] The activation of the DMSO by sulfur trioxide-pyridine as well as using reaction conditions close to room temperature make this procedure attractive. The procedure is also attractive because of the ease of the work up.



344 **345**

Reagents: a) SO_3·pyridine, $^{i-}Pr_2NEt$, DMSO, DCM, 0 °C to RT, 3 hours

Scheme 86: Oxidation of the primary alcohol via Parikh-Doering oxidation

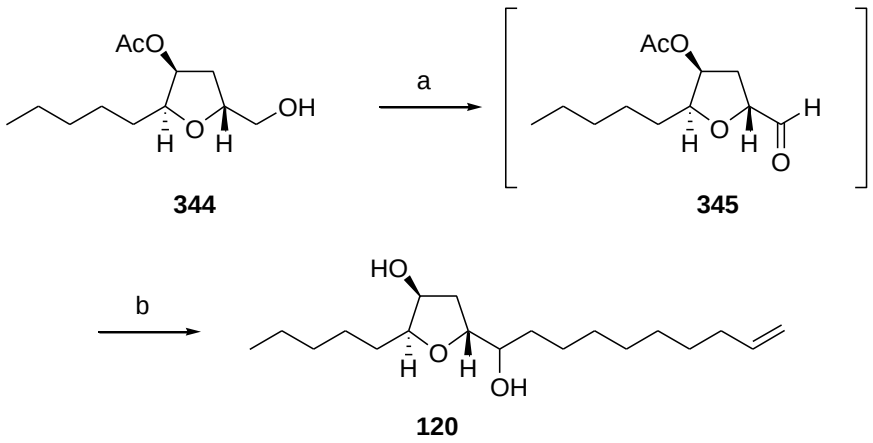
After oxidation for 3 hours at room temperature, the reaction mixture was quenched with sodium thiosulfate; after extraction, the crude reaction mixture was analysed by ^{1}H-NMR. The crude NMR showed a doublet at 9.70 ppm; furthermore, IR analysis showed absorption frequencies at 1726 cm^{-1} characteristic of carbonyl group and at 2875 cm^{-1} characteristic from C-H bond of an aldehyde. Unfortunately, the product was very unstable which limited purification and meant that the Grignard addition had to be performed straight after formation of the aldehyde **345**. The intermediate was confirmed to be the

[140] Evans, Murthy, Roseman and Rheingold, *Angew. Chem., Int. Ed.* **1999,** 38, (21), 3175-77, Parikh and Doering, *J. Am. Chem. Soc.* **1967,** 89, (21), 5505-7.

desired aldehyde by comparison of its ^{1}H-NMR data to that of a similar aldehyde that had already been reported.[141]

Attempts towards the completion of the synthesis

The instability of the aldehyde meant that the Grignard reaction had to be performed immediately after the aldehyde formation and without performing purification of the crude product **345**. The side chain Grignard reagent was synthesised under standard conditions using magnesium turnings and 1,2-dibromoethane as an activating reagent. The procedure was then performed following a synthetic procedure similar to the one described by Williams on the benzoate equivalent of our intermediate.[142] The side chain Grignard reagent was added a crude solution of the aldehyde under inert atmosphere (**Scheme 87**).



Reagents: a) SO_3·pyridine, $^{i}Pr_2NEt$, DMSO,DCM, 0 °C to RT, 3 hours; b) i. **320**, Mg, 1,2-dibromoethane, Et_2O, 40 °C, 2 hours; ii. **345**, THF, -78 °C to 0 °C, 3 hours

Scheme 87: Towards completion of the synthesis of the (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol

The stereochemistry of the final product should match the stereochemistry of the natural product because Grignard addition should occur with chelation control. Indeed, following the assumed mechanism, the magnesium is chelated to both the carbonyl group and the secondary hydroxyl group at the 3-position of the tetrahydrofuran inducing nucleophilic attack on the desired face of the aldehyde. Unfortunately, when the reaction mixture was warmed up from – 78 °C to 0 °C over 3 hours the desired addition product was not obtained. It was assumed that the Grignard reagent was not formed because of the

[141] de la Pradilla and Castellanos, *Tetrahedron Lett.* **2007,** 48, (37), 6500-04.
[142] Williams, Harigaya, Moore and Dsa, *J. Am. Chem. Soc.* **1984,** 106, (9), 2641-44.

small scale of the reaction. In order to address this problem, the magnesium turnings were activated prior to the reaction. The magnesium turnings was activated by prior washing with dilute HCl to remove oxide layer and therefore increase the reactive surface area. Unfortunately, the use of activated magnesium did not improve matters and the Grignard reaction was not successful.

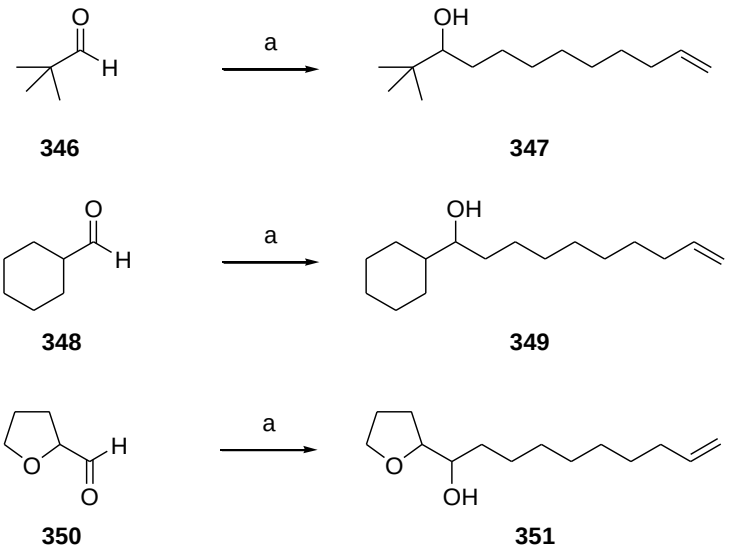
In 1981, Rieke reported several methods for the activation of magnesium depending on the subsequent nature of the Grignard reagent and carbonyl compound.[143] According to this report, the Grignard reagent generated from 1-bromooctane was formed quantitatively when a solution of the bromide was added to a combination of magnesium(II) chloride and potassium at room temperature. When this procedure was used to form the Grignard reagent **320**, formation of the final natural product was not observed. The bromide side chain was recovered but none of the aldehyde starting material.

Due to the limited quantities of aldehyde available for optimisation of the reaction conditions, it was decided to adopt another model system to discover the origin of the problem with the Grignard addition reaction.

Model studies concerning Grignard addition

Investigations were made to discover the origin of the problem encoutered during attempted Grignard addition to the adehyde **345**. Difficulties encoutered during addition of the side chain to the aldehyde could have resulted from the non-formation of the Grignard reagent or from the reagent failing to react with the aldehyde. To rule out the possibility that the problems were resulting from a failure to form the Grignard reagent, model studies were carried out using 9-bromononene and three model aldehydes; isobutyraldehyde, cyclohexanecarboxaldehyde and tetrahydrofuran-2-carboxaldehyde (**Scheme 88**) .

[143] Rieke, Li, Burns and Uhm, *J. Org. Chem.* **1981,** 46, (21), 4323-4.



Regents: a) i. Mg, **320**, iodine, THF, 60 °C to RT, 2 hours; ii. aldehyde, Et_2O, -78 °C to 0 °C, 3 hours

Scheme 88: Addition of the side chain Grignard reagent to model aldehydes

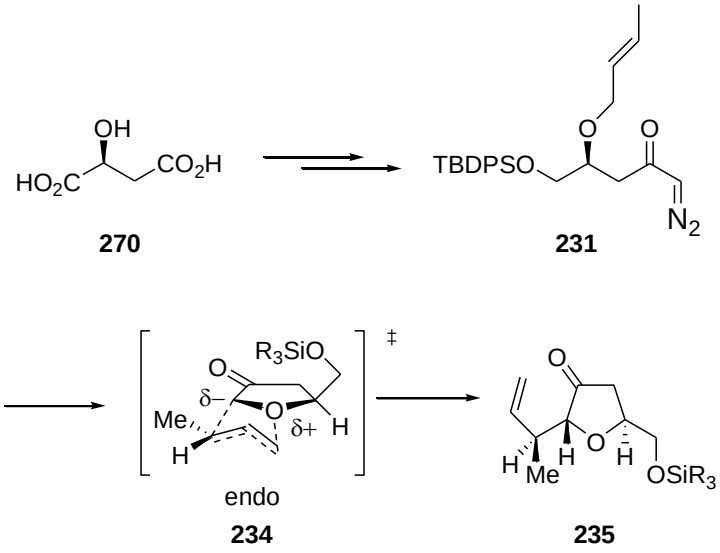
The aldehydes were treated with freshly prepared 9-nonenylmagnesium bromide at –78 °C. Slow addition of the Grignard reagent to a solution of the aldehyde was performed by canula to avoid any decomposition of the reagent. All the desired products were isolated after column chromatography on silica gel. 2,2-Dimethyldodec-11-en-3-ol **347** was isolated in 90% yield from isobutyraldehyde **346**, 1-cyclohexyldec-9-en-1-ol **349** was obtained from cyclohexanecarboxaldehyde **348** in 70% yield and most importantly the synthesis of 1-(tetrahydrofuran-2-yl)dec-9-en-1-ol **351** from tetrahydrofuran-2-carboxaldehyde **350** was accomplished in 68% yield.

These latest results showed that the Grignard reagent was formed successfully without activation other than by using iodine.

2.3 Conclusions and Future work

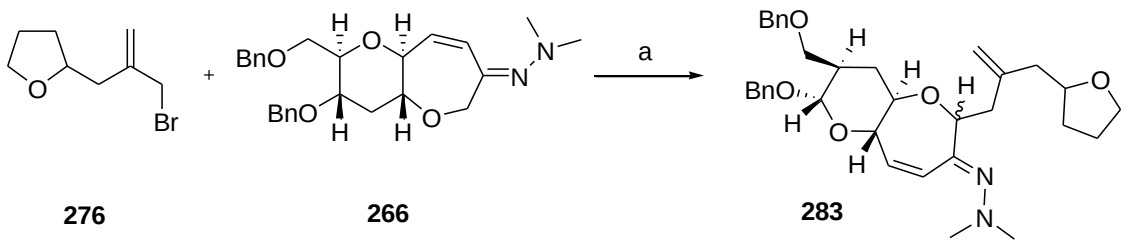
2.3.1 Towards the total synthesis of the A-ring fragment of the gambieric acids

The synthesis of the tetrahydrofuran core of the gambieric acids was succesfully achieved in excellent yield and with high diastereoselectivity using oxonium ylide formation and subsequent [2,3]-sigmatropic rearangement. Introduction of the crotyl ether which was problematic was optimised by applying cross metathesis methodology to a terminal alkene and gave the desired *E*-alkene in excellent yield and high selectivity. The formation of the highly substituted 2,5-*trans*-tetrahydrofuran-3-one intermediate for the synthesis of the A-ring fragment was formed in 9 steps and 49% overall yield (**Scheme 89**).



Scheme 89: Synthesis of the key tetrahydrofuran core of the A-ring fragment of gambieric acid

A model study on the feasability of the coupling reaction between the allylic bromide and a hydrazone was completed successfully. It has been shown that the side chain in 5 position of the tetrahydrofuran ring could be introduced using a five-step synthetic route starting from the deprotected primary alcohol. The conditions used to synthesise the side chain have been optimised. The coupling of the allylic bromide to the model hydrazone has proven to be viable but the yield is modest (**Scheme 90**).



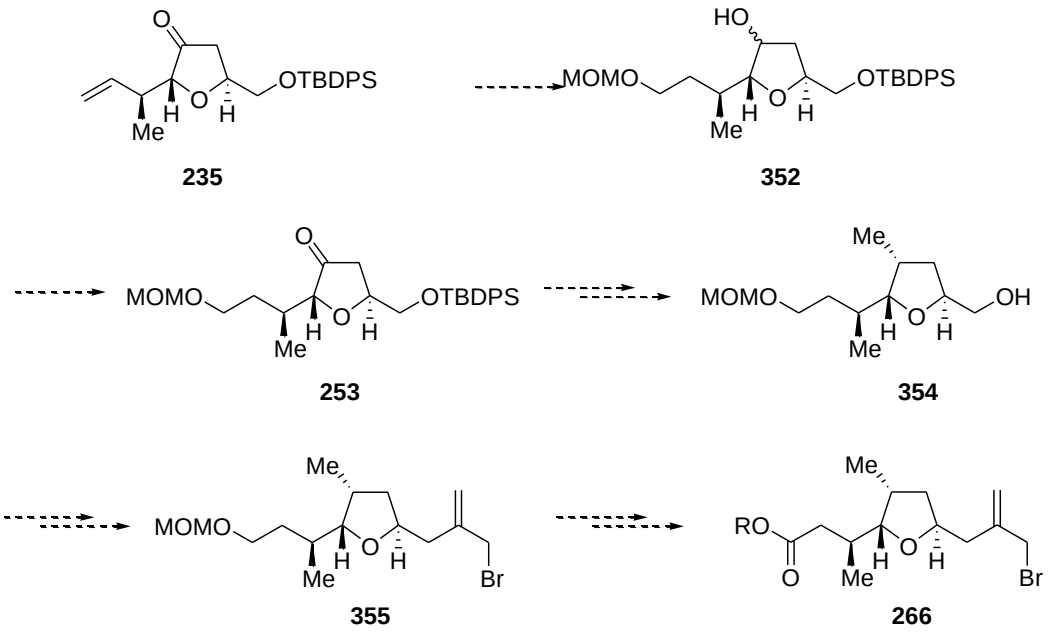
Reagents: a) ^{t}BuLi, THF, -78 °C, 2 h, 66%

Scheme 90: coupling reaction between allyl bromide and hydrazone

Efforts have been made to hydroborate the [2,3]-rearrangement product and its corresponding protected intermediate, but the selective protection of the primary alcohol resulting from the hydroboration and the subsequent oxidation of the secondary alcohol remains to be done. The selective protection of the primary alcohol could be performed using a trityl protecting group. However, the steric effect of such a protecting group could be a problem for the final steps of the synthesis, especially as a TBDPS protecting group is already in place.

A smaller protecting group could be used for the selective protection of the primary alcohol such as methoxymethyl. The selective MOM protection of primary alcohol in presence of a secondary one as already been reported in a natural product synthesis.[144] The completion of the synthesis of the A-ring fragment of gambieric acid could be achieved using a selective MOM protection and subsequent oxidation of the secondary alcohol (**Scheme 91**).

[144] Ihara, Suzuki and Fukumoto, *Heterocycles* **1990,** 30, (1, Spec. Issue), 381-4, Matsuo, Ogawa, Pudhom and Mukaiyama, *Chem. Lett.* **2004,** 33, (2), 124-25, Srikrishna and Beeraiah, *Tetrahedron: Asymmetry* **2008,** 19, (7), 884-90.



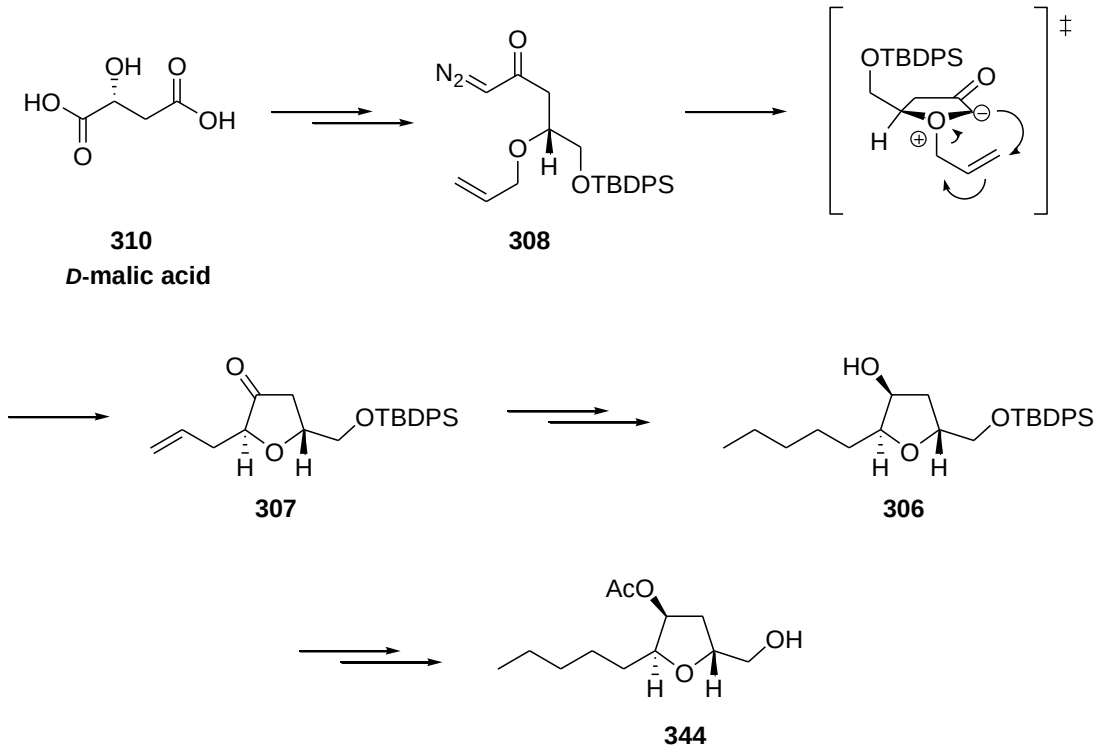
Scheme 91:Towards the completion of the synthesis of the functionalised A-ring fragment of gambieric acid A

The ketone in the 3-position of the ring could then be converted into a methyl group following the methodology previously developed in the group.[145] Deprotection of the primary alcohol at the 5-position of the tetrahydrofuran would give the precursor required for the introduction of the allylic bromide as described previously for the model system. Deprotection of the primary hydroxyl group in the 2-position followed by oxidation would give the desired A-ring fragment of gambieric acid.

[145] Clark, Fessard and Wilson, *Org Lett* **2004,** 6, (11), 1773-6.

2.3.2 Towards the total synthesis of (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol

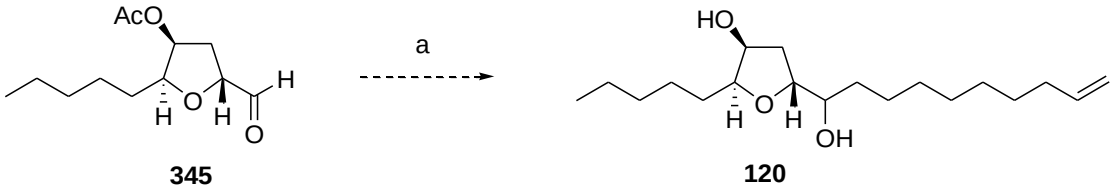
The synthesis of the tetrahydrofuran core was succesfully achieved using oxonium ylide formation and subsequent 2,3-sigmatropic rearangement in excellent yield and diastereoselectivity. The completion of the side chain in the 2-position of the tetrahydrofuran ring was achieved using a tandem cross metathesis – hydrogenation reaction strategy in high yield. The reduction of the ketone in 3 position with the desired stereochemistry was achieved using sodium triacetoxyborohydride. The synthesis towards the formation of the (6*S*,7*S*,9*R*,10*R*)-6,9-epoxynonadec-18-ene-7,10-diol was achieved up to the stage where mono-protected intermediate **344** had been obtained (**Scheme 92**).



Scheme 92: Synthesis of the mono-acetylated intermediate 344

The synthesis of the monoacetylated intermediate was achived using a 13-step synthetic route and with an excellent 39% overall yield. Oxidation of the primary alcohol was achieved using a Parikh-Doering oxidation procedure which allowed formation of the desired aldehyde. However, isolation of this intermediate was problematic because it was very unstable.

Future work will involve completion of the final Grignard addition. Activation of the Grignard reagent could be increased by formation of an organocerium reagent by addition of $CeCl_3$.[146] Other metals can be used as substitutes in Grignard-type addition reaction to the aldehyde **345**. Zinc as been proven to be able to activate alkyl bromides prior to the addition to carbonyl compounds (**Scheme 93**).[147]

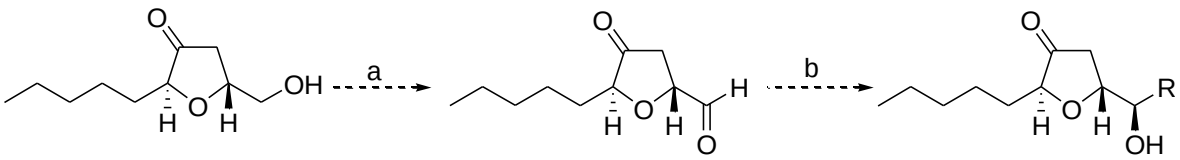


345 **120**

Reagents: a) **320,** Zn, NH_4Cl, H_2O

Scheme 93: Synthesis of the natural product using zinc as an activating reagent

Another approach would involve the oxidation of diol **322** using the Parikh-Doering procedure followed by selective addition of an organomanganese to the aldehyde following the procedure reported by Cahiez (**Scheme 94**).[148]



322 **324** **325**

Reagents: a) SO_3·pyridine, $^{i}Pr_2NEt$, DMSO,DCM, 0 °C to RT, 3 hours; b) RMnCl

Scheme 94: Synthesis of the natural product using organomanganese

[146] Clark, Dossetter, Blake, Li and Whittingham, *Chem. Commun. (Cambridge)* **1999**, (8), 749-50, Lee, Channon, Cregg, Porter, Roden and Yeoh, *Tetrahedron* **1989,** 45, (18), 5877-86, Mickelson, Koviach and Forsyth, *J. Org. Chem.* **1996,** 61, (26), 9617-20, Narayanan and Bunnelle, *Tetrahedron Lett.* **1987,** 28, (50), 6261-4, Nishigaichi, Tamura, Ueda, Iwamoto and Takuwa, *Tetrahedron Lett.* **2008,** 49, (13), 2124-27.
[147] Gurjar, Ravindranadh and Kumar, *Chem. Commun. (Cambridge, U. K.)* **2001**, (10), 917-18, Sharma, Begum, Kumar, Krishna, Prabhakar and Kunwar, *Tetrahedron Lett.* **2005,** 46, (23), 4131-35.
[148] Cahiez and Figadere, *Tetrahedron Lett.* **1986,** 27, (37), 4445-8.

3 Experimental

3.1 General

^{1}H NMR spectra were recorded on a Bruker DRX 500, Brucker AV 400 FT or JEOL EX 270 spectrometer at room temperature. Spectra were recorded in deuterochloroform, using residual chloroform as the internal standard (δ= 7.26 ppm) or in deuterated methanol, using residual methanol as the internal standard (δ= 3.31 ppm). *J* values are given in Hertz. Signals in NMR spectra are described as singlets (s), doublets (d), quartets (q), multiplets (m), broad (b) or combination of these, which refers to the spin-spin coupling pattern observed. Data are reported as follows; chemical shift in ppm, multiplicity, integration, coupling constants and assignments. ^{13}C NMR spectra were recorded on a Bruker DRX 500, Brucker AV 400 FT or JEOL EX 270 spectrometer at room temperature. Spectra were performed in deuterochloroform, using residual chloroform as the internal standard (δ= 77.0 ppm) or in deuterated methanol, using residual methanol as the internal standard (δ= 49.05 ppm). Data are reported as follows; chemical shift in ppm and assignments. Assignments were based on HMQC and HMBC experiments.

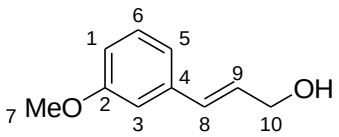
IR spectra were recorded in the range 4000-600 cm^{-1} on a Perkin-Elmer 1600 series FT-IR spectrometer with internal calibration using solution cells and a JASCO FT-IR 4100 using NaCl plates. High resolution mass spectra were recorded under EI, CI, ES and FAB conditions by the analytical services of the University of Nottingham and the University of Glasgow. Optical rotations were determined using a JASCO DIP-370 digital polarimeter or an Autopol ®V automatic polarimeter. $[\alpha]_D$ values were measured at the concentration and temperature shown. Elemental analyses were carried out on an Exeter Analytical Inc. CE-400 elemental analyser or an Exeter Analytical EA-440 elemental analyser.

Air- and moisture-sensitive reactions were performed in oven-dried or flame-dried glassware under an atmosphere of dry argon or nitrogen. Petroleum ether 40-60 °C is described as petroleum ether in the text. Reagents and solvents were either used as supplied or, where necessary, purified by the following procedures. Tetrahydrofuran was distilled from sodium-benzophenone ketyl, dichloromethane was distilled from calcium

hydride. Toluene and Et_2O were dried by filtration through towers of activated alumina, through a 7 micron filter and through a non-metering hand operated valve to Luer-lock connector. Dry benzene, 1,4-dioxane, DMF, DMSO and methanol were purchased and used as supplied. Triethylamine and pyridine were distilled from calcium hydride and were stored under argon over KOH.

Reactions were monitored by TLC performed on Merck Kieselgel 60 F_{254} plates and visualisations were performed using a combination of UV light, ethanolic anisaldehyde, ethanolic phosphomolybdic acid, potassium permanganate or cerium-ammonium-molybdate with heat. Flash column chromatography was performed using Fluorochem LC60A, 35-70 micron silica gel or Acros Organics neutral alumina 50-200 μm. Solutions of diazo compounds were transferred, where necessary, using syringes equipped with a PTFE needle.

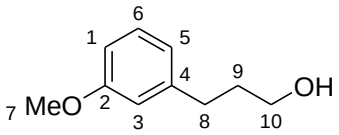
3.2 Selected ^{1}H and ^{13}C NMR spectra



(*E*)-3-(3-Methoxyphenyl)prop-2-en-1-ol (261)

To a solution of *m*-methoxycinnamic acid (3.2 g, 18 mmol) in dry THF (20 mL) at – 5 °C was added dropwise BH_3·THF complex (1 M in THF, 23.3 mL, 23.3 mmol, 1.3 eq). The reaction mixture was then allowed to warm up to room temperature over a period of 3 hours. The colourless solution was quenched with acetic acid in water (1:1, 20 mL). The organic phase was washed with Na_2CO_3 (saturated aq. solution, 20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (DCM-MeOH 99:1) to afford *m*-methoxycinnamic alcohol **261** as a colourless oil (1.0 g, 13.5 mmol, 73 %).

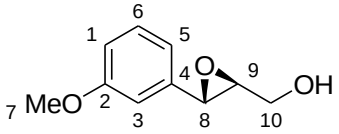
R_f = 0.55 (DCM-MeOH, 95:5); ν_{max} (NaCl) 3233, 2940, 2835, 1655, 1488, 1258, 1155, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 1H, *J* = 8.0, 8.0 Hz, CH-C6), 6.99 (d, 1H, *J* = 8.0 Hz, CH-C1), 6.93 (bs, 1H, CH-C3), 6.81 (dd, 1H, *J* = 8.0, 1.9 Hz, CH-C5), 6.59 (bd, 1H, *J* = 15.9 Hz, CH-C8), 6.37 (dt, 1H, *J* = 15.9, 5.7 Hz, CH-C9), 4.33 (dd, 2H, *J* = 5.7, 1.2 Hz, CH-C10), 3.81 (s, 3H, CH_3-C7), 1.61 (bs, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7 (C-C2), 138.0 (C-C4), 130.9 (CH-C8), 129.5 (CH-C6), 128.8 (CH-C9), 119.1 (CH-C1), 113.2 (CH-C5), 111.7 (CH-C3), 63.6 (CH_2-C10), 55.2 (CH_3-C7);
HRMS (CI/Isobutane) for $C_{10}H_{12}O_2$ ($[M+H]^+$) calculated 164.0837, found 164.0836



3-(3-Methoxyphenyl)-propan-1-ol (356)

To a solution of $LiAlH_4$ (1.6 g, 43 mmol, 1.3 eq) in dry THF (50 mL) at 0 ºC under Ar atmosphere was added *m*-methoxycinnamic acid (6.0 g, 34 mmol) in dry THF (20 mL). The reaction mixture was then stirred for 45 min at 0 ºC. The reaction mixture was then quenched with water (20 mL) and NaOH (10 % aq., 10 mL). The suspension was filtered and the solution was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The residue was purified by column chromatography on silica gel (petroleum ether-EtOAc, 4:1) to give alcohol **356** as a colourless oil, (3.88 g, 23.3 mmol, 69 %).

R_f = 0.32 (petroleum ether, EtOAc, 2:1); ν_{max} (NaCl) 3578, 2938, 2835, 1611, 1151, 1037, 779 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (ddd, 1H, *J* = 7.7, 7.7, 0.6 Hz, CH-C6), 6.80 (bd, 1H, *J* = 7.7 Hz, CH-C1), 6.75 (bs, 1H, CH-C3), 6.74 (dd, 1H, *J* = 7.7, 2.2 Hz, CH-C5), 3.8 (s, 3H, CH_3-C1), 3.68 (t, 2H, *J* = 6.4 Hz, CH_2-C9), 2.69 (m, 2H, CH_2-C8), 1.90 (m, 2H, CH_2-C9), 1.59 (bs, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6 (C-C2), 143.4 (C-C4), 129.3 (CH-C6), 120.8 (CH-C5), 114.1 (CH-C3), 111.0 (CH-C1), 62.2 (CH_2-C10), 55.1 (CH_3-C7), 34.0 (CH_2-C8), 32.1 (CH_2-C9);
HRMS (CI/Isobutane) for $C_{10}H_{14}O_2$ ($[M+H]^+$) calculated 166.0994, found 166.0992

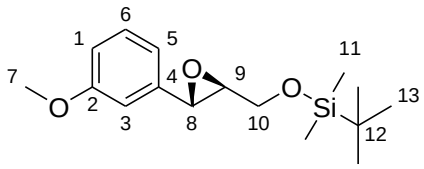


[(2*S*,3*S*)-3-(3-Methoxyphenyl)oxiranyl]methanol (262)

To a solution of **L**-diisopropyltartrate (0.28 mL, 1.3 mmol, 0.1 eq) in dry DCM (100 mL) was added dry molecular sieves (4 Å, 1.1 g). The reaction mixture was cooled down to –30 ºC and treated sequentially with $Ti(O^iPr)_4$ (0.18 mL, 0.60 mmol, 0.05 eq) and *tert*-butyl hydroperoxide (3.2 M in 2,2,4-trimethylpentane, 7.6 mL, 24 mmol, 2 eq). The reaction mixture was then stirred for 1 hour at –30 ºC. Allylic alcohol **261** (2.0 g, 12 mmol) in dry DCM (7 mL) was then added dropwise at –30 ºC. The reaction mixture was then stirred for

7 hours at – 30 ºC. The suspension was quenched at that temperature with an aqueous solution of 30 % sodium hydroxide saturated with sodium chloride (3.5 mL). Ether (100 mL) was added to the reaction mixture and the resulting suspension was then stirred at –10 ºC for 20 min. Celite (7.0 g) and anhydrous $MgSO_4$ (1.0 g) were added to the reaction mixture, and the resulting suspension was stirred at room temperature overnight. The mixture was filtered through a plug of celite and the solution was concentrated *in vacuo* to give a yellow oil. The residue was purified by flash column chromatography on silica gel (Petroleum ether, EtOAc, DCM, 2:1:1) to give epoxide **262** as a colourless oil, (2.0 g, 4.5 mmol, 37 %).

R_f = 0.26 (PE/EtOAc/DCM, 2:1:1); ν_{max} (NaCl) 3202, 2937, 2836, 1605, 1491, 1261, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, 1H, *J* = 7.9 Hz, CH-C6), 6.89 (dt, 1H, *J* = 7.9, 1.5 Hz, CH-C1), 6.85 (ddd, 1H, *J* = 7.9, 2.5, 1.5 Hz, CH-C5), 6.81 (dd, 1H, *J* = 2.5, 1.5 Hz, CH-C3), 4.05 (ddd, 1H, *J* = 12.4, 4.0, 2.0 Hz, CH-C10), 3.92 (d, 1H, *J* = 2.2 Hz, CH-C8), 3.80 (s, 3H, CH_3-C7), 3.80 (ddd, 1H, *J* = 12.4, 7.8, 3.8 Hz, CH-C10), 3.21 (dt, 1H, *J* = 3.8, 2.2 Hz, CH-C9), 1.85 (dd, 1H, *J* = 6.8, 5.7 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8 (C-C2), 138.3 (C-C4), 129.5 (CH-C6), 118.1 (CH-C5), 114.0 (CH-C3), 110.7 (CH-C1), 62.3 (CH-C8), 61.1 (CH-C9), 55.4 (CH_2-C10), 55.2 (CH_3-C7);
$[\alpha]_D$ = −57.5 (c = 1.02 in $CHCl_3$, T = 24.6 ºC), lit. $[\alpha]_{546}$ = − 66.8 (c = 0.820 in CH_2Cl_2);
HRMS (CI/Isobutane) for $C_{10}H_{13}O_3$ ($[M+H]^+$) calculated 180.0786, found 180.0787.

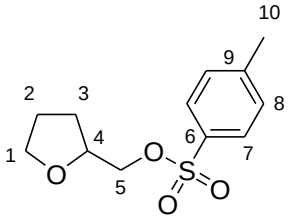


Triisopropyl[(2*S*,3*S*)-3-(3-methoxyphenyl)oxiranylmethoxy]silane (263)

To a solution of epoxy alcohol **262** (0.1 g, 0.5 mmol) in dry DCM (10 mL) was added imidazole (0.08 g, 1.0 mmol, 2 eq) and DMAP (several crystals). The reaction mixture was stirred at room temperature until a colourless solution was obtained. Freshly distilled *tert*-butyldimethylsilyl chloride (0.2 mL, 1.1 mmol, 2.1 eq) was added to the solution at room temperature, and the resulting solution was stirred at room temperature overnight. The solution was then poured into $KHSO_3$ (0.25 M in water, 4 mL). The aqueous layer was extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (10 mL) dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified

by column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to give protected alcohol **263** as a colourless oil (161 mg, 0.55 mmol, quant).

R_f = 0.35 (Petroleum ether, EtOAc, 9:1); ν_{max} (NaCl) 2954, 1736, 1428, 1112, 702 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.25 (t, 1H, *J* = 8.7 Hz, CH-C6), 6.85 (dt, 1H, *J* = 8.7, 1.2 Hz, CH-C1), 6.79 (ddd, 1H, *J* = 8.7, 3.0, 1.2 Hz, CH-C5), 6.77 (dd, 1H, *J* = 3.0, 1.2 Hz. CH-C3), 3.60 (dd, 1H, *J* = 13.4, 3.4 Hz, CH_2-C10), 3.43 (dd, 1H, *J* = 13.4, 4.6 Hz, CH_2-C10), 3.44 (d, 1H, *J* = 2.3 Hz, CH_2-C8), 3.42 (s, 3H, CH_3-C7), 2.66 (ddd, 1H, *J* = 4.6, 3.4, 2.3 Hz, CH-C9), 0.21 (s, 9H, CH_3-C13), −0.67 (s, 3H, CH_3-C11), −0.68 (s, 3H, CH_3-C11'), ^{13}C NMR (64 MHz, $CDCl_3$) δ 159.8 (C-C2), 138.3 (C-C4), 129.5 (CH-C6), 118.2 (CH-C5), 114.1 (CH-C3), 110.5 (CH-C1), 62.2 (CH-C8), 61.1 (CH-C9), 51.4 (CH_2-C10), 55.2 (CH_3-C7), 26.7 (CH_3-C13), 19.1 (C-C12), 12.1 (CH_3-C11);
$[\alpha]_D$ = −40 (c = 1.00 in $CHCl_3$, T = 24.9 ºC), lit.[149] $[\alpha]_{546}$ = −66.8 (c = 0.870 in CH_2Cl_2);
HRMS (CI/Isobutane) for $C_{10}H_{13}O_3$ ($[M+H]^+$) calculated 181.0865, found 181.0867.



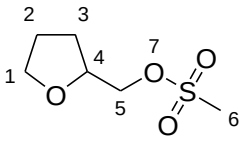
Toluene-4-sulfonic acid (tetrahydro-furan-2-yl)methyl ester (357)[150]

To a solution of tetrahydrofurfuryl alcohol (3.8 mL, 39 mmol) and *p*-toluenesulfonyl chloride (7.5 g, 40 mmol, 1 eq) in ether (50 mL) at –10 °C, was added portionwise, a fine powder of KOH (4.4 g, 78 mmol, 2 eq). The colourless solution turned into a white suspension. The white suspension was stirred between –5 °C and –10 °C for 2 h 30 min. The reaction mixture was then poured onto ice cold water. The aqueous layer was extracted with Et_2O (3 × 10 mL). The etheral extracts were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give **357** as a white solid (10.0 g, 39 mmol, 100 %)

R_f = 0.67 (petroleum ether, EtOAc 1:1); Mp = 49-51 °C; ν_{max} ($CHCl_3$) 3022, 1364, 1210 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* = 8.2 Hz, CH-C7), 7.34 (d, 2H, *J* = 8.2

[149] Evans, Gauchet-Prunet, Carreira and Charette, *J. Org. Chem.* **1991,** 56, (2), 741-50.
[150] Laxmi and Lyengar, *Synthesis* **1996**, (5), 594-96.

Hz, CH-C8), 4.11-4.05 (m, 1H, CH-C4), 4.01 (dd, 1H, *J* = 10.8, 5.1 Hz, CH_2-C5), 3.97 (dd, 1H, *J* = 10.8, 6.2 Hz, CH_2-C5), 3.78 (dt, 1H, *J* = 8.3, 6.6 Hz, CH_2-C1), 3.72 (dt, 1H, *J* = 8.3, 6.7 Hz, CH_2-C1), 2.44 (s, 3H, CH_3-C10), 2.01-1.93 (m, 1H, CH_2-C3), 1.90-1.86 (m, 1H, CH_2-C2), 1.86-1.82 (m, 1H, CH_2-C2), 1.66 (ddt, 1H, *J* = 11.9, 7.8, 6.7, CH_2-C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7 (C-C9), 132.8 (C-C6), 129.7 (CH-C8), 127.9 (CH-C7), 75.8 (CH-C4), 71.4 (CH_2-C5), 68.6 (CH_2-C1), 27.8 (CH_2-C3), 25.5 (CH_2-C2), 21.6 (CH_3-C10);
HRMS (CI) $C_{12}H_{17}O_4S$ ($[M+H]^+$) calculated, 257.0848 found 257.0845.

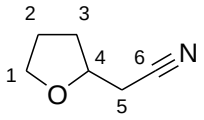


Methanesulfonic acid(tetrahydrofuran-2-yl)methyl ester (358)[151]

To a solution of tetrahydrofurfuryl alcohol (0.25 g, 2.4 mmol) in dry DCM (25 mL) was added freshly distilled Et_3N (1 mL, 7 mmol, 3 eq). The colourless solution was cooled to 0 °C and freshly distilled methanesulfonyl chloride (0.28 mL, 3.6 mmol, 1.5 eq) was added. The resulting solution was stirred at 0 °C for 1 hour. The reaction mixture was then diluted with EtOAc (20 mL). The organic phase was washed with H_2O (20 mL) and a saturated aqueous solution of NaCl (20 mL), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 2:1) to give mesylated alcohol **358** as a light yellow oil (426 mg, 2.36 mmol, 96 %).

R_f = 0.34 (petroleum ether-ethyl acetate, 1:1); ν_{max} (NaCl) 2956, 1349, 1172, 955 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (td, 1H, *J* = 6.3, 4.4, CH-C4), 4.20-4.14 (m, 2H, CH_2-C5), 3.89 (dt, 1H, *J* = 8.2, 6.7 Hz, CH_2-C1), 3.81 (dt, 1H, *J* = 8.2, 6.7 Hz, CH_2-C1), 3.06 (s, 3H, CH_3-C6), 2.06-1.99 (m, 1H, CH_2-C3), 1.97-1.89 (m, 2H, CH_2-C2), 1.72-1.64 (m, 1H, CH_2-C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 76.2 (CH-C4), 71.3 (CH_2-C5), 68.6 (CH_2-C1), 37.6 (CH_2-C3), 27.5 (CH_2-C2), 25.6 (CH_3-C6);
HRMS (CI/isobutane) $C_6H_{13}O_4S$ ($[M+H]^+$) calculated, 181.0535 found 181.0527.

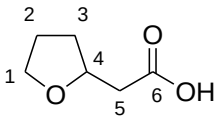
[151] Zief, Fletcher and Kirshen, *J. Am. Chem. Soc.* **1946,** 68, 2743-4.



Tetrahydrofuran-2-ylacetonitrile (275)[152]

To a solution of **357** (5.0 g, 20 mmol) in dry DMF (100 mL) was added sodium cyanide (4.8 g, 98 mmol, 5 eq). The reaction mixture was stirred at 60 °C for 16 h. The dark red suspension was poured onto water (100 mL). The aqueous layer was extracted five times with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 2:1) to afford nitrile **275** as a colourless oil (933 mg, 8.2 mmol, 42 %).

R_f = 0.55 (petroleum ether, EtOAc, 1:1); ν_{max} (NaCl) 2927, 2251, 1658, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16-4.10 (m, 1H, CH-C4), 3.96 (dt, 1H, *J* = 8.0, 6.8 Hz, CH_2-C1), 3.80 (dt, 1H, *J* = 8.0, 6.3 Hz, CH_2-C1), 2.60 (dd, 1H, *J* = 16.9, 5.9 Hz CH_2-C5), 2.55 (dd, 1H, *J* = 16.9, 5.4 Hz CH_2-C5), 2.15 (dddd, 1H, *J* = 12.3, 8.2, 6.8, 5.4 Hz, CH_2-C3) , 2.03-1.97 (m, 2H, CH_2-C2), 1.73 (ddt, 1H, *J* = 12.3, 8.4, 7.1 Hz, CH_2-C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 117.4 (C-C6), 74.0 (CH-C4), 68.7 (CH_2-C1), 30.9 (CH_2-C5), 25.6 (CH_2-C3), 24.0 (CH_2-C2);
HRMS (CI/Isobutane) for $C_6H_{10}NO$ ($[M+H]^+$) calculated 112.0762, found 112.0751.



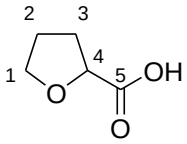
Tetrahydrofuran-2-yl-acetic acid (359)[153]

To a solution of nitrile **275** (0.5 g, 4 mmol) in 1,2-dioxane (15 mL) was added an aqueous solution of NaOH (4 M, 15 mL). The resulting colourless solution was stirred at 60 °C for 16 hours. Aqueous HCl (1M) was added to the reaction mixture at room temperature until pH = 1. The aqueous layer was extracted with ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue

[152] Laxmi and Lyengar, *Synthesis* **1996**, (5), 594-96.
[153] Laxmi and Lyengar, *Synthesis* **1996**, (5), 594-96.

was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 4:6) to give carboxylic acid **359** as a colourless oil (263 mg, 1.9 mmol, 50 %).

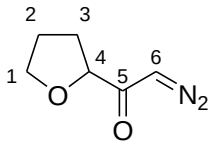
R_f = 0.32 (petroleum ether-EtOAc, 1:1); ν_{max} (NaCl) 2928, 1713, 1228, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (bs, 1H, OH), 3.54-3.47 (m, 1H, CH-C4), 3.13 (dt, 1H, *J* = 8.0, 6.9 Hz, CH_2-C1), 3.01 (dt, 1H, *J* = 8.0, 6.5 Hz, CH_2-C1), 1.86 (dd, 1H, *J* = 15.5, 7.3 Hz, CH_2-C5), 1.74 (dd, 1H, *J* = 15.5, 5.9 Hz, CH_2-C5), 1.40-1.29 (m, 1H, CH_2-C2), 1.19-1.11 (m, 2H, CH_2-C3), 0.81 (dddd, 1H, *J* = 12.1, 6.9, 6.5, 6.5 Hz, CH_2-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7 (C-C6), 75.0 (CH-C4), 68.2 (CH_2-C1), 40.0 (CH_2-C5), 25.5 (CH_2-C3), 22.6 (CH_2-C2);
HRMS (CI/Isobutane) for $C_6H_{11}O_3$ ($[M+H]^+$) calculated 131.0708, found 131.0704.



Tetrahydrofuran-2-carboxylic acid (278)

To a solution of tetrahydrofurfuryl alcohol (0.1 mL, 1 mmol) in dry DMF (10 mL) at room temperature was added PCC (2.2 g, 10 mmol, 10 eq) in one portion and the mixture was stirred at room temperature for 2 days. The reaction mixture was then diluted with H_2O (10 mL) and the aqueous layer extracted with EtOAc (5 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 1:1) to afford carboxylic acid **278** as a colourless oil (82 mg, 0.7 mmol, 71 %).

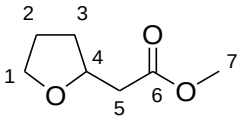
R_f = 0.27 (Petroleum ether-EtOAc, 1:1); ν_{max} (NaCl) 2985, 1739, 1206, 1080, 929 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H, CO_2H-C5), 4.49 (dd, 1H, *J* = 8.4, 5.6 Hz, CH-C4), 4.02 (dd, 1H, *J* = 14.5, 6.9 Hz, CH_2-C1), 3.96 (dd, 1H, *J* = 14.5, 7.3 Hz, CH_2-C1), 2.31 (ddt, 1H, *J* = 13.0, 8.4, 7.9 Hz, CH_2-C3), 2.09 (dtd, 1H, *J* = 13.0, 6.8, 5.6 Hz, CH_2-C3), 1.97-1.90 (m, 2H, CH_2-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8 (CO_2H-C5), 76.2 (CH-C4), 69.6 (CH_2-C1), 30.1 (CH_2-C3), 25.2 (CH_2-C2);
HRMS (CI) for $C_5H_8O_3$ ($[M]^+$) calcd 117.0552, found 117.0555;
Anal. calculated for $C_5H_8O_3$: C, 51.72%; H, 6.94%. Found: C 51.56%, H 7.02%.



2-Diazo-1-(tetrahydrofuran-2-yl)-ethanone (279)

To a solution of carboxylic acid **278** (0.1 g, 0.9 mmol) in dry DCM (5 mL) was added oxalyl chloride (0.08 mL, 1 mmol, 1.2 eq) and dry DMF (1 drop). Reaction mixture was stirred at room temperature for 1 hour. The crude acid chloride was then concentrated. The residue was dissolved in DCM and concentrated (3 × 5 mL). The residue was dissolved in Et_2O (5 mL) and added to a freshly distilled solution of diazomethane (10 eq) in Et_2O at 0 °C. The reaction mixture was stirred for 3 hours at 0 °C. The excess of diazomethane was quenched with AcOH (0.5 mL). The organic layer was washed with $NaHCO_3$ (10 mL), NH_4Cl (10 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 1:1) to give diazoketone **279** as a bright yellow oil (111 mg, 0.79 mmol, 88%).

R_f = 0.54 (Petroleum ether-EtOAc, 1:1); ν_{max} (NaCl) 2875, 2117, 1629, 1363, 932 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1H, CH-C6), 4.34 (dd, 1H, *J* = 8.3, 5.7 Hz, CH-C4), 3.91 (dt, 1H, *J* = 8.4, 6.8 Hz, CH_2-C1), 3.88 (dt, 1H, *J* = 8.4, 6.7 Hz, CH_2-C1), 2.22 (ddt, 1H, *J* = 12.7, 8.2, 7.5 Hz, CH_2-C3), 2.07-1.99 (m, 1H, CH_2-C3), 1.91-1.83 (m, 2H, CH_2-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6 (C-C5), 82.2 (CH-C4), 69.3 (CH_2-C1), 52.2 (CH-C6), 30.3 (CH_2-C3), 25.4 (CH_2-C2);
HRMS (CI) for $C_6H_9O_2N_2$ ($[M+H]^+$) calcd 141.0664, found 141.0661.



Tetrahydro-furan-2-yl acetic acid methyl ester (276)

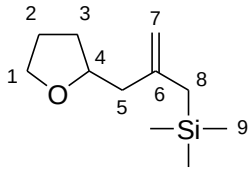
Method A

To a solution of carboxylic acid **359** (286 mg, 2.2 mmol) in MeOH (30 mL) at room temperature was added concentrated sulphuric acid (1 drop). The resulting colourless solution was then stirred at 64 °C for 16 hours. The reaction mixture was then cooled to room temperature and diluted with DCM (20 mL). The organic phase was washed with H_2O (10 mL). The aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether, EtOAc 3:1) to afford methyl ester **276** as a colourless oil (132 mg, 0.9 mmol, 41 %).

Method B

To a solution of diazoketone **279** (1.4 g, 10 mmol) in dry MeOH (140 mL) was added, under argon atmosphere, silver benzoate (0.7 g, 3 mmol, 0.3 eq) along with freshly distilled Et_3N (3.8 mL, 27 mmol, 2.7 eq). The black suspension was stirred at room temperature for 3 hours. The reaction mixture was then filtered through celite and the residue washed with ether (3 × 25 mL). The resulting solution was then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 3:1) to afford methyl ester **276** as a colourless oil (1.43 g, 9.9 mmol, 99 %).

R_f = 0.66 (petroleum ether-EtOAc, 1:1); ν_{max} (NaCl) 2953, 1734, 1437, 1162, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (tt, 1H, *J* = 6.9, 6.9 Hz, CH-C4), 3.87 (dd, 1H, *J* = 14.5, 7.5 Hz, CH_2-C1), 3.75 (dd, 1H, *J* = 14.5, 7.2 Hz, CH_2-C1), 3.69 (s, 3H, CH_3-C7), 2.59 (dd, 1H, *J* = 15.2, 6.9, CH_2-C5), 2.48 (dd, 1H, *J* = 15.2, 6.9 Hz, CH_2-C5), 2.08 (ddd, 1H, *J* = 12.4, 6.9, 6.5 CH_2-C3), 1.94-1.87 (m, 2H, CH_2-C2), 1.54 (dtd, 1H, *J* = 12.4, 8.6, 6.9 Hz, CH_2-C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7 (C-C6), 75.24 (CH-C4), 68.0 (CH_2-C1), 51.6 (CH_3-C7), 40.4 (CH_2-C5), 31.2 (CH_2-C3), 31.2 (CH_2-C2);
HRMS (CI/Isobutane) for $C_7H_{13}O_3$ ($[M+H]^+$) calculated 145.0865, found 145.0869.

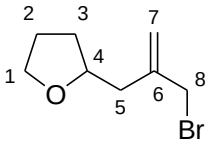


Trimethyl[2-(tetrahydrofuran-2-ylmethyl)allyl]silane (282)

Cerium(III) chloride heptahydrate (11.6 mg, 31.2 mmol, 3 eq) was heated at 120 °C under vacuum for 16 hours. The flask was then cooled to room temperature and flushed with Ar. To the dry cerium(III) chloride was then added dry THF (65 mL). The resulting white suspension was submitted to sonication for 2 hours and stirred vigorously at room temperature under Ar atmosphere for 16 hours. The suspension was then cooled to −78 °C and (trimethylsilyl)methylmagnesium bromide (solution in THF, 31.2 mmol, 3 eq) was added dropwise over a period of 25 min *via* a canula. The cream suspension was stirred at −78 °C for 1 hour. Methyl ester **276** (1.5 g, 10 mmol) in dry THF (5 mL) at was added dropwise over a period of 5 min. The reaction mixture was stirred at −70 °C for 2 hours and left to warm to room temperature under vigorous stirring overnight.

The reaction mixture was then cooled to 0 °C and quenched with HCl (1 M, 100 mL). The aqueous phase was then extracted with DCM (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 15:1) to give allylic silane **282** as a colourless oil (1.60 g, 8.7 mmol, 87 %).

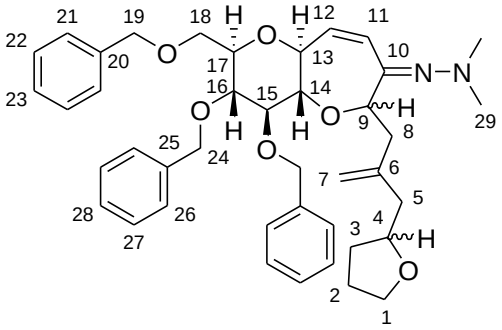
R_f = 0.78 (petroleum ether-EtOAc, 8:2); ν_{max} (NaCl) 2954, 1632, 1419, 1248, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (td, 1H, *J* = 2.2, 1.2 Hz, CH_2-C7), 4.59-4.58 (m, 1H, CH_2-C7), 3.99 (ddt, 1H, *J* = 13.2, 6.6, 6.6 Hz, CH-C4), 3.88 (ddd, 1H, *J* = 7.9, 7.2, 6.2 Hz, CH_2-C1), 3.72 (dt, 1H, *J* = 7.9, 6.5 Hz, CH_2-C1), 2.27 (ddd, 1H, *J* = 14.2, 6.6, 2.2 Hz, CH_2-C5), 2.08 (ddd, 1H, *J* = 14.2, 6.6, 2.2 Hz, CH_2-C5), 2.02-1.94 (m, 1H, CH_2-C3), 1.91-1.84 (m, 2H, CH_2-C2), 1.57 (d, 2H, *J* = 1.2 Hz, CH_2-C8), 1.49 (ddt, 1H, *J* = 11.7, 8.3, 6.6 Hz, CH_2-C3), 0.02 (s, 9H, CH_3-C9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7 (C-C6), 108.9 (CH_2-C7), 77.6 (CH-C4), 67.7 (CH_2-C1), 44.3 (CH_2-C5), 31.3 (CH_2-C3), 26.9 (CH_2-C8), 25.5 (CH_2-C2), -1.3 (CH_3-C9).



2-(2-Bromomethylallyl)tetrahydrofuran (277)

To a solution of allylic silane **282** (30 mg, 0.15 mmol) and freshly distilled pyridine (70 μL, 0.8 mmol, 5.3 eq) in dry THF (7 mL) at −10 °C was added pyrrolidone hydrotribromide (0.1 g, 0.4 mmol, 2.7 eq) under argon. The mixture was stirred for 2 hours and allowed to warm to room temperature over this period. The reaction mixture was then quenched with sodium thiosulfate (aqueous saturated solution, 10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The etheral extracts were combined and washed with water (10 mL), and brine (10 mL) then dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The residue was purified by column chromatography on silica gel (petroleum ether 100 %) to give allylic bromide **277** as a colourless oil (20 mg, 0.1 mmol, 83%).

R_f = 0.46 (petroleum ether–ethyl acetate, 20:1); ν_{max} (NaCl) 2972, 1639, 1061, 842, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (d, 1H, *J* = 1.1 Hz, CH_2-C7), 5.05 (d, 1H, *J* = 1.1 Hz, CH_2-C7), 4.03(d, 2H, *J* = 0.8, CH_2-C8), 4.03-3.98 (m, 1H, CH-C4), 3.90-3.85 (dt, 1H, *J* = 8.4, 8.6 Hz, CH_2-C1), 3.74-3.69 (ddd, 1H, *J* = 8.4, 8.0, 6.4 Hz, CH_2-C1), 2.47-2.42 (ddd, 1H, *J* = 15.2, 5.5, 1.1 Hz, CH_2-C5), 2.42-2.36 (ddd, 1H, *J* = 15.2, 7.9, 1.0 Hz, CH_2-C5), 2.02-1.97 (bddd, 1H, *J* = 11.8, 8.6, 6.4 Hz, CH_2-C2), 1.93-1.89 (ddd, 1H, *J* = 9.7, 5.3, 2.5 Hz, CH_2-C3), 1.88-1.82 (m, 1H, CH_2-C3), 1.56-1.47 (bddd, 1H, *J* = 11.8, 8.6, 8.0 Hz, CH_2-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (C-C6), 116.9 (CH_2-C7), 77.4 (CH-C4), 67.8 (CH_2-C1), 39.3 (CH_2-C8), 37.1 (CH_2-C5), 31.4 (CH_2-C3), 25.4 (CH_2-C2);
HRMS (CI/Isobutane) for $C_8H_{14}OBr$ ($[M+H]^+$) calculated 205.0228, found 205.0214



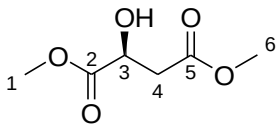
_N'_-[3-benzyloxy-2-benzyloxymethyl-6-[2-(tetrahydrofuran-2-ylmethyl)-allyl]-3,4, 4a,9a-tetrahydro-2_H_-1,5-dioxa-benzocyclohepten-(7Z)-ylidene]-_N,N_-dimethyl-hydrazine (283)

To a solution of dimethylhydrazine **266** (12 mg, 0.03 mmol) in dry THF (4 mL) at –78 °C was added ^{t}BuLi (1.5 M in pentane, 30 µL, 0.045 mmol, 1.5 eq). The resulting colourless solution was stirred for 15 min at –78 °C. Allylic bromide **277** (30 mg, 0.15 mmol, 5 eq) in dry THF (3 mL) under argon atmosphere was then added dropwise to the reaction mixture at –78 °C. The solution was then allowed to warm up to room temperature over a period of 6 hours. The reaction mixture was quenched at 0 °C with water (6 mL). The aqueous layer was extracted with ether (3 × 6 mL). The etheral extracts were combined and washed with water (10 mL), and brine (10 mL) then dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The residue was purified by column chromatography on silica gel (petroleum ether 100 %) to give the coupling product **283** as a colourless oil (11 mg, 0.02 mmol, 66 %, mixture of diastereoisomers).

R_f = 0.20 (petroleum ether–Et_2O, 1:1); Mp = 97-99 °C; ν_{max} (NaCl) 3029, 2860, 1453, 1357, 1099, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 15 H, Ar-H), 6.28 (d, 1H, *J* = 11.7 Hz, CH-C11), 6.05 (ddd, 1H, *J* = 11.7, 9.6, 6.8 Hz, CH-C12), 4.95 (d, 1H, *J* = 10.8 Hz, CH_2-C24), 4.83 (d, 1H, *J* = 10.8 Hz, CH_2-C24), 4.76 (d, 1H, *J* = 10.8 Hz, CH_2-C24), 4.71 (d, 1H, *J* = 14.8 Hz, CH_2-C19), 4.60 (s, 1H, CH-C7), 4.57 (s, 1H, CH-C7), 4.56 (q, 2H, *J* = 12.3 Hz, CH_2-C18), 4.48 (d, 1H, *J* = 10.8 Hz, CH_2-C24), 4.40 (d, 1H, *J* = 14.8 Hz, CH_2-C19), 3.69 (dd, 1H, *J* = 9.6, 1.7 Hz, CH-C13), 3.64-3.59 (m, 1H, CH-C4), 3.63 (bd, 1H, *J* = 8.5 Hz, CH-C9), 3.59 (dd, 1H, *J* = 5.8, 4.9 Hz, CH-C15), 3.53-3.50 (m, 2H, CH_2-C1), 3.47-3.45 (m, 1H, CH-C16), 3.41 (bt, 1H, *J* = 12.3 Hz, CH-C17), 3.26 (dd, 1H, *J* = 4.3, 4.3, CH-C14), 2.60 (s, 6H, CH_3-C29), 2.04-2.03 (m, 2H, CH_2-C8), 1.71-1.62 (m, 2H, CH_2-C5), 1.61-1.56 (m, 4H, CH_2-C2,C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4 (C-C10), 141.5 (C-C6), 138.5 (C-C20), 138.0 (C-C20), 137.9 (C-C20), 130.1 (CH-C12), 128.4 (CH-C21), 128.3 (CH-C21), 128.3 (CH-C21), 128.1 (CH-C22), 127.9 (CH-C22),

127.8 (CH-C22), 127.7 (CH-C23), 127.7 (CH-C23), 127.6 (CH-C23), 124.0 (CH-C11), 115.8 (CH_2-C7), 88.4 (CH-C13), 85.2 (CH-C14), 79.1 (CH-C15), 77.9 (CH-C16), 77.1 (CH-C17), 76.9 (CH-C4), 76.9 (CH-C9), 75.7 (CH_2-C19), 75.0 (CH_2-C24), 73.4 (CH_2-C18), 69.0 (CH_2-C1), 67.9 (CH_2-C8), 47.4 (CH_3-C29), 38.1 (CH_2-C5), 33.4 (CH_2-C3), 20.2 (CH_2-C2);

HRMS (CI/Isobutane) for $C_{41}H_{51}O_6N_2$ ($[M+H]^+$) calculated 667.3747, found 667.3749



Dimethyl(S)-malate (231)[154]

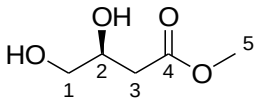
To a solution of **L**-malic acid (25 g, 0.19 mol) in dry MeOH (300 mL) at 0 °C was added dropwise over 1 hour thionyl chloride (30 mL, 0.41 mol, 2.2 eq). The reaction mixture was then allowed to warm at room temperature for 3 hours. The solution was then concentrated. The residue was partitioned between DCM (150 mL) and $NaHCO_3$ (150 mL). The aqueous phase was extracted with DCM (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was then removed *in vacuo*. The residue was purified by column chromatography on silica gel (Petroleum ether-EtOAc, 1:9) to give **L**-dimethyl malate **231** (31 g, quant) as a colourless oil.

R_f = 0.77 (petroleum ether, EtOAc, 1:9); ν_{max} (NaCl) 3019, 2399, 1741, 1215, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, 1H, *J* = 6.1, 4.4 Hz, CH-C3), 3.79 (s, 3H, CH_3-C1), 3.70 (s, 3H, CH_3-C6), 3.26 (bs, 1H, OH), 2.86 (dd, 1H, *J* = 16.5, 4.4 Hz, CH_2-C4), 2.78 (dd, 1H, *J* = 16.5, 6.1 Hz, CH_2-C4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (C-C2), 170.9 (C-C5), 67.1 (CH-C3), 52.8 (CH_3-C1), 51.9 (CH_3-C6), 38.3 (CH_2-C4).

$[\alpha]_D = -4.6$ (c = 1% in $CHCl_3$, T = 24 °C), lit.[155] $[\alpha]_D = -6.8$.

HRMS (CI-isobutane) for $C_6H_{11}O_5$ ($[M+H]^+$) calculated 163.0606, found 163.0602.

[154] Dahlgren, Johansson, Kvarnstrom, Musil, Nilsson and Samuelsson, *Bioorg. Med. Chem.* **2002,** 10, (6), 1829-39.
[155] Clough, *J. Chem. Soc.* **1926**, 1674-6.

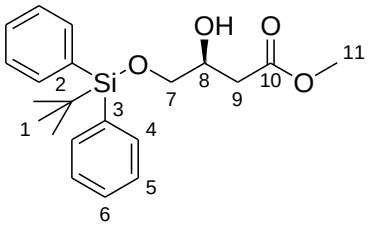


(*S*)-3,4-Dihydroxybutyric acid methyl ester (297)[156]

To a solution of **L**-dimethylmalate **231** (7.01 g, 43.2 mmol) in dry THF (100 mL) at 0 °C was added, dropwise, a solution of boran dimethyl sulfide complex (5.3 mL, 56 mmol, 1.3 eq). The reaction mixture was then stirred 0 °C until no more gas evolution occurred (approximately 1 hour). Sodium borohydride (82 mg, 2.2 mmol, 0.05 eq) was then added in one portion to the solution and the reaction mixture was stirred at 0 °C for 3 hours. Methanol (28 ml) was then added dropwise to quench the reaction. The resulting solution was stirred for 1 hour at room temperature and the solvent was then removed *in vacuo*. The residue was washed with toluene and methanol (1:1, 80 mL) and the solvent removed *in vacuo*. The operation was repeated twice. The residue was then washed with toluene (80 mL) and the solvent removed *in vacuo*. The operation was repeated. The residue was purified by flash column chromatography on silica gel (EtOAc 100%) to give diol **297** (5.21 g, 38.8 mmol, 90 %) as a colourless oil.

R_f = 0.23 (EtOAc 100%); ν_{max} (NaCl) 3404, 2955, 1725, 1440, 1042 cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 4.04 (ddt, 1H, *J* = 8.7, 5.1, 5.1 Hz, CH-C2), 3.35 (s, 3H, CH_3-C5), 3.50 (dd, 1H, *J* = 11.4, 5.1 Hz, CH_2-C1), 3.48 (dd, 1H, *J* = 11.4, 5.1 Hz, CH_2-C1), 2.57 (dd, 1H, *J* = 15.6, 5.1 Hz, CH_2-C3), 2.50 (dd, 1H, *J* = 15.6, 8.7 Hz, CH_2-C3); ^{13}C NMR (125 MHz, MeOD) δ 173.1 (C-C4), 68.6 (CH-C2), 65.9 (CH_2-C1), 52.2 (CH_3-C5), 37.6 (CH_2-C3).
$[\alpha]_D$= −15 (c = 1% in $CHCl_3$, T = 27.3 °C), lit.[157] $[\alpha]_D$ = − 23.2 ;
HRMS (EI+) for $C_5H_9O_3$ ($[M]^+$) calculated 117.0551, found 117.0550;
Anal. calculated for $C_5H_{10}O_4$: C, 44.77 %; H, 7.51 %. Found: C 44.55 %, H 7.50 %.

[156] Clark, Fessard and Wilson, *Org. Lett.* **2004,** 6, (11), 1773-76.
[157] Cooksey, Gunn, Kocienski, Kuhl, Uppal, Christopher and Bell, *Org. Biomol. Chem.* **2004,** 2, (12), 1719-31.



(*S*)-4-(*tert*-Butyldiphenylsilanoxy)-3-hydroxybutyric acid methyl ester (284)[158]

To a solution of diol **297** (1 g, 7 mmol) in dry DMF (12 mL) was added chlorodiphenylmethyl silane (2.1 mL, 8.2 mmol, 1.1 eq). Imidazole (0.6 g, 9 mmol, 1.2 eq) and DMAP (a catalytic amount) were added to the colourless solution in one portion. The reaction mixture was then flushed with argon, stirred at room temperature for 1 hour. EtOAc (20 mL) was added to the reaction mixture. The organic layer was washed with H_2O (10 mL), HCl (2 M, 10 mL) and a saturated solution of $NaHCO_3$ (40 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 9:1) to give silyl ether **284** (2.42 g, 6.9 mmol, 93 %) as a colourless oil.

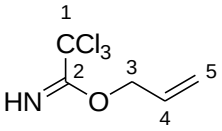
R_f = 0.38 (petroleum ether-EtOAc, 9:1); ν_{max} (NaCl) 2931, 1737, 1428, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H, CH-C4), 7.44-7.37 (m, 6H, CH-C5,C6), 4.17 (dddd, 1H, *J* = 7.4, 5.8, 5.2, 5.2 Hz, CH-C8), 3.69 (s, 3H, CH_3-C11), 3.67 (dd, 1H, *J* = 10.2, 5.2 Hz, CH_2-C7), 3.63 (dd, 1H, *J* = 10.2, 5.8 Hz, CH_2-C7), 2.58 (dd, 1H, *J* = 14.4, 5.2 Hz, CH_2-C9), 2.52 (dd, 1H, *J* = 14.4, 7.4 Hz, CH_2-C9), 1.06 (s, 9H, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C-C10), 135.5 (CH-C4), 132.9 (C-C3), 129.8 (CH-C6), 127.7 (CH-C5), 68.5 (CH-C8), 66.8 (CH_2-C7), 51.7 (CH_3-C11), 37.8 (CH_2-C9), 26.8 (CH_3-C1), 19.2 (C-C2).

$[\alpha]_D = -8$ (c = 1 % in $CHCl_3$ T = 24 °C);

HRMS (ESI) for $C_{21}H_{28}O_4SiNa$ ($[M+Na]^+$) calculated 395.1649, found 395.1641;

Anal. calculated for $C_{21}H_{28}O_4Si$: C, 67.71 %; H, 7.58 %. Found: C 67.66 %, H 7.58 %.

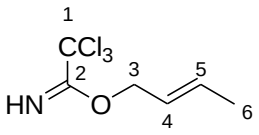
[158] Clark, Fessard and Wilson, *Org. Lett.* **2004,** 6, (11), 1773-76.



2,2,2-Trichloroacetimidic acid allyl ester (360)

To a solution of allyl alcohol (2.35 mL, 34.4 mmol) in KOH (50 % aqueous solution, 40 mL) and DCM (40 mL) was added $TBAHSO_4$ (35 mg, 0.1 mmol, 0.003 eq). The colourless solution was cooled down to 0 °C and stirred at this temperature for 10 min before trichloroacetonitrile (4.1 mL, 40 mmol, 1.2 eq) was added dropwise over a period of 20 min. The resulting yellow solution was stirred at room temperature overnight. The reaction mixture was then extracted with DCM (3 × 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The brown liquid obtained was distilled under reduced pressure to give trichloroacetimidate **360** as a colourless liquid (6.53 g, 32.3 mmol, 94 %).

R_f = 0.78 (petroleum ether-EtOAc, 19:1); bp (°C) = 47-49 °C at 0.3 mmHg; ν_{max} (NaCl) 3344, 2944, 1652, 1310, 994 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1H, NH), 6.02 (ddt, 1H, *J* = 17.2, 10.5, 5.4 Hz, CH-C4), 5.44 (dtd, 1H, *J* = 17.2, 2.6, 1.4 Hz, CH_2-C5), 5.30 (dtd, 1H, *J* = 10.5, 1.6, 1.4 Hz, CH_2-C5), 4.81 (dt, 1H, *J* = 5.4, 1.4 Hz, CH_2-C3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4 (C-C2), 131.4 (CH-C4), 118.4 (CH_2-C5), 91.3 (C-C1), 69.5 (CH_2-C3).

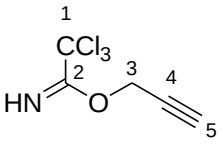


2,2,2-Trichloroacetimidic acid (*E*)-but-2-enyl ester (361)

To a solution of crotyl alcohol (1.2 mL, 14 mmol) in KOH (50 % aqueous solution, 14 mL) and DCM (14 mL) was added $TBAHSO_4$ (0.02 mg, 0.04 mmol, 0.003 eq). The colourless solution was cooled to 0 °C and stirred at this temperature for 10 min before trichloroacetonitrile (1.6 mL, 16 mmol, 1.2 eq) was added dropwise over a period of 10 min. The resulting yellow solution was stirred at room temperature overnight. The reaction mixture was then extracted with DCM (3 × 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The brown liquid

obtained was distilled under reduced pressure to give trichloroacetimidate **361** as a colourless liquid (2.2 g, 10 mmol, 71 %)

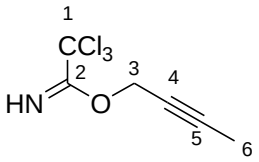
R_f = 0.81 (petroleum ether, EtOAc, 19:1); bp (°C) = 54-57 °C at 0.3 mmHg; ν_{max} (NaCl) 3343, 2941, 1662, 1308, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H, NH), 5.99-5.58 (m, 1H, CH-C4), 5.76-5.66 (m, 1H, CH-C5), 4.63 (ddq, 2H, *J* = 6.6, 2.1, 1.0 Hz, CH_2-C3), 1.38 (ddt, 1H, *J* = 7.2, 2.7, 1.0 Hz, CH_3-C6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 (C-C2), 130.1 (CH-C4), 128.1 (CH_2-C5), 91.3 (C-C1), 63.7 (CH_2-C3), 17.8 (CH_3-C6).



2,2,2-Trichloroacetimidic acid prop-2-ynyl ester (362)

To a solution of propargyl alcohol (3.1 mL, 52 mmol) in KOH (50 % aq. solution, 150 mL) and DCM (150 mL) was added $TBAHSO_4$ (54 mg, 0.16 mmol, 0.003 eq). The colourless solution was cooled to 0 °C and stirred at this temperature for a 10 min, at which point tricholoracetonitrile (6.4 mL, 64 mmol, 1.2 eq) was added dropwise over a period of 10 min. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature overnight. The aqueous phase was extracted with DCM (3 × 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated. The brown oil obtained was purified by distillation to give trichloroacetonitrile **362** as a colourless liquid (1.6 g, 8 mmol, 14 %).

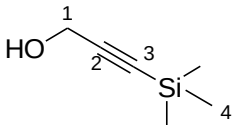
R_f = 0.83 (petroleum ether-EtOAc, 19:1); bp (°C) = 51-54 °C at 0.3 mmHg; ν_{max} (NaCl) 3378, 2854, 1533 1231, 997 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H, NH), 4.89 (d, 2H, *J* = 2.5 Hz, CH_2-C3), 2.54 (t, 1H, *J* = 2.5 Hz, CH-C5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6 (C-C2), 76.8 (C-C1), 75.5 (C-C4), 66.4 (CH_2-C3), 13.6 (CH-C5);
HRMS (CI/Isobutane) for $C_5H_5ONCl_3$ ($[M+H]^+$) calculated 199.9437, found 199.9438.



2,2,2-Trichloroacetimidic acid but-2-ynyl ester (289)

To a solution of 2-butyn-1-ol (1.07 mL, 14.2 mmol) in KOH (50 % aq. solution, 40 mL) and DCM (40 mL) was added $TBAHSO_4$ (15 mg, 0.04 mmol, 0.003 eq). The colourless solution was cooled down to 0 °C and stirred at this temperature for a 10 min, at which point tricholoracetonitrile (1.72 mL, 17.1 mmol, 1.2 eq) was added dropwise over a period of 10 min. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature overnight. The aqueous phase was extracted with DCM (3 × 40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated. The brown oil thus obtained was purified by distillation to give trichloroacetonitrile **289** as a colourless liquid (2.20 g, 10.2 mmol, 72 %).

R_f = 0.78 (petroleum ether-EtOAc, 19:1); bp (°C) = 52-54 °C at 0.3 mmHg; ν_{max} (NaCl) 3341, 2921, 2242, 1666, 1293, 1075, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H, NH), 4.86 (q, 2H, *J* = 2.4 Hz, CH_2-C3), 1.87 (t, 3H, *J* = 2.4 Hz, CH_3-C6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (C-C2), 84.0 (C-C4), 77.2 (C-C1), 72.4 (C-C5), 57.5 (CH_2-C3), 37.3 (CH_3-C6).
HRMS (CI/Isobutane) for $C_6H_7ONCl_3$ ($[M+H]^+$) calculated 213.9593, found 213.9591.

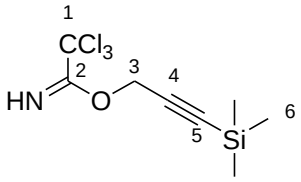


3-Trimethylsilyl-2-propyn-1-ol (291)

To a solution of propargyl alcohol (1.00 mL, 16.9 mmol) in dry THF (70 mL) at –78 °C was added *n*-BuLi (2.4 M in hexane, 21.4 mL, 51.4 mmol, 3 eq), dropwise. The colourless solution was left to stir at –78 °C for 20 min at which point a freshly distilled solution of TMSCl (7.7 mL, 60 mmol, 3.5 eq) was added dropwise. The cooling bath was removed and the reaction mixture was left to warm to room temperature. The colourless solution was then stirred at room temperature for 2 hours. The reaction mixture was quenched with water (50 mL) and HCl (10 % in water, 25 mL). The aqueous phase was extracted with

ether (3 × 50 mL). The etheral extracts were combined, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The brown residue obtained was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 8:2) to give the desired silane **291** (1.5 g, 11.7 mmol, 69 %).

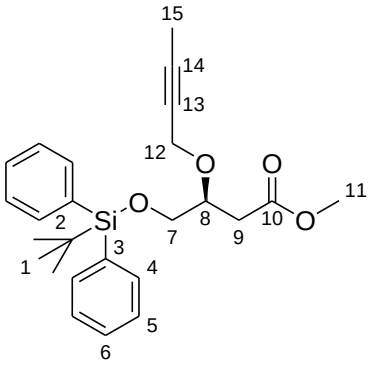
R_f = 0.90 (petroleum ether-EtOAc, 10:1); ν_{max} (NaCl) 2960, 2177, 1410, 983, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (s, 2H, CH_2-C1), 2.73 (bs, 1H, OH), 0.13 (s, 9H, CH_3-C4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9 (C-C2), 90.2 (C-C3), 51.2 (CH_2-C1), -0.3 (CH_3-C4);
HRMS (CI/Isobutane) for $C_6H_{13}OSi$ ($[M+H]^+$) calculated 129.0736, found 129.0729;



2,2,2-Trichloroacetimidic acid 3-trimethylsilyl 2-propynyl ester (292)

To a solution of TMS-protected propargyl alcohol **291** (2.1 g, 16 mmol) in KOH (50 % aq. solution, 50 mL) and DCM (50 mL) was added $TBAHSO_4$ (17 mg, 0.05 mmol, 0.003 eq). The colourless solution was cooled to 0 °C and stirred at this temperature for 10 min, at which point trichloroacetonitrile (2.0 mL, 20 mmol, 1.2 eq) was added dropwise over a period of 10 min. The reaction mixture was then allowed to warm to room temperature and stirred at room temperature overnight. The aqueous phase was extracted with DCM (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting brown oil was purified by distillation to give trichloroacetonitrile **292** as a colourless liquid (3.40 g, 12.5 mmol, 78 %).

R_f = 0.90 (petroleum ether-EtOAc, 20:1); bp (°C) = 57-59 °C at 0.3 mmHg; ν_{max} (NaCl) 2964, 1724, 1640, 1265, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 2H, CH_2-C3), -0.07 (s, 9H, CH_3-C6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7 (C-C2), 102.9 (C-C4), 90.2 (C-C1), 79.2 (C-C5), 59.0 (CH_2-C3), 0.1 (CH_3-C6).

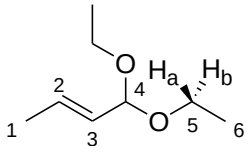


(*S*)-4-(*tert*-Butyldiphenylsilanyloxy)-3-(but-2-ynyloxy)-butyric acid methyl ester (287)

A solution of alcohol **284** (500 mg, 1.34 mmol) and crude trichloroacetimidate **289** (576 mg, 2.68 mmol, 2 eq) in freshly distilled cyclohexane (3 mL) was cooled to 0 °C. The light yellow solution was stirred at this remperature for 10 min and then CF_3SO_3H (11 μL, 0.12 mmol, 0.1 eq) was added. After the appearance of a white suspension, the iced-water bath was removed and the reaction mixture left to warm at room temperature. The white suspension was then stirred overnight. The reaction mixture was filtered, and the white solid washed with cyclohexane (3 × 10 mL). The solution was then concentrated *in vacuo* and the brown residue was then purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 15:1) to afford ether **290** as a colourless oil (535 mg, 1.26 mmol, 94 %).

R_f = 0.72 (petroleum ether-EtOAc, 10:1); ν_{max} (NaCl) 2931, 2857, 1740, 1428, 1112, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H, CH-C4), 7.43-7.36 (m, 6H, CH-C5,C6), 4.17 (dq, 2H, *J* = 4.8, 2.4 Hz, CH_2-C12), 4.04 (dtd, 1H, *J* = 8.1, 5.6, 5.1 Hz, CH-C8), 3.79 (dd, 1H, *J* = 10.6, 5.6 Hz, CH_2-C7), 3.68 (s, 3H, CH_3-C11), 3.62 (dd, 1H, *J* = 10.6, 5.6 Hz, CH_2-C7), 2.70 (dd, 1H, *J* = 15.9, 5.1 Hz, CH_2-C9), 2.57 (dd, 1H, *J* = 15.9, 8.1 Hz, CH_2-C9), 1.79 (t, 3H, *J* = 2.4 Hz, CH_3-C15), 1.05 (s, 9H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9 (C-C10), 135.5 (CH-C4), 135.5 (CH-C4), 133.2 (C-C3), 133.1 (C-C3), 129.6 (CH-C6), 127.6 (CH-C5), 127.6 (CH-C5), 82.1 (C-C13), 75.9 (CH-C8), 75.2 (C-C14), 65.0 (CH_2-C7), 58.3 (CH_2-C12), 51.6 (CH_3-C11), 37.2 (CH_2-C9), 26.7 (CH_3-C2), 19.1(C-C1).

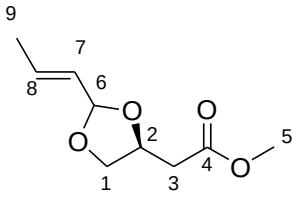
HRMS (CI-isobutane) for $C_{25}H_{33}O_4Si$ ($[M+H]^+$) calculated 425.2148, found 425.2144.



(*E*)-1,1-Diethoxy but-2-ene (296)

To a solution of crotonaldehyde (2.0 g, 29 mmol) in dry EtOH (5 mL) under Ar atmosphere was added ammonium chloride (900 mg, 16.8 mmol, 0.6 eq) and triethylorthoformate (5.3 mL, 31 mmol, 1.05 eq). The resulting colourless solution was stirred at room temperature for 3 hours. The reaction mixture was then diluted with EtOAc (10 mL) and washed with $NaHCO_3$ (saturated aqueous solution, 10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography on deactivated alumina afforded protected aldehyde **296** as a colourless oil (4.0 g, 28 mmol, 96%).

R_f = 0.80 (petroleum ether–ethyl acetate, 9:1); ν_{max} (NaCl) 2976, 2880, 1446, 1372, 1125, 1051, 996, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dqd, 1H, *J* = 15.4, 6.5, 0.8 Hz, CH-C2), 5.51 (ddq, 1H, *J* = 15.4, 5.4, 1.6 Hz, CH-C3), 4.80 (bd, 1H, *J* = 5.4 Hz, CH-C4), 3.64 (q, 1H, *J* = 7.1 Hz, $H_{a/a'}$ or $H_{b/b'}$ CH_2-C5), 3.61 (q, 1H, *J* = 7.1 Hz, $H_{a/a'}$ or $H_{b/b'}$ CH_2-C5), 3.49 (q, 1H, *J* = 7.1 Hz, $H_{a/a'}$ or $H_{b/b'}$ CH_2-C5), 3.46 (q, 1H, *J* = 7.1 Hz, H_a or H_b CH_2-C5), 1.71 (ddd, 3H, *J* = 6.5, 1.6, 0.4 Hz, CH_3-C1), 1.20 (bdd, 6H, *J* = 7.0, 1.1 Hz, CH_3-C6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.7 (CH-C2), 128.7 (CH-C3), 101.8 (CH-C4), 60.9 (CH_2-C5), 17.5 (CH_3-C1), 15.1 (CH_3-C6);

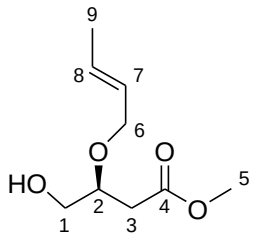


(*S*,*E*)-(2-Propenyl-1,3-dioxolan-4-yl) acetic acid methyl ester (298)

To a solution of diol **297** (500 mg, 3.73 mmol) in dry DCM (25 mL) was added a solution of diethyl acetate **296** (700 mg, 4.85 mmol, 1.3 eq) in dry DCM (5 mL) under argon atmosphere. The reaction mixture was stirred at room temperature for 5 min and PPTS (10 mg, 0.04 mmol, 0.01 eq) was added in one portion. The colourless solution was stirred at 30 ºC overnight. The organic layer was then washed with water (20 mL), $NaHCO_3$

(saturated aqueous solution, 20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on deactivated neutral alumina (Petroleum ether-EtOAc, 15:1) to afford a diastereomeric mixture of both cyclic acetal **298** as a colourless oil (500 mg, 2.68 mmol, 72 %).

R_f = 0.78 (petroleum ether-EtOAc, 7:3); ν_{max} (NaCl) 2955, 1725, 1645, 1440, 1113, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddq, 1H, *J* = 15.6, 6.6, 0.8 Hz, CH-C8), 5.43 (ddq, 1H, *J* = 15.6, 6.7, 3.0 Hz, CH-C7), 5.13 (bd, 1H, *J* = 6.7 Hz, CH-C6), 4.48-4.31 (m, 1H, CH-C2), 3.99 (ddd, 1H, *J* = 8.2, 6.6 Hz, CH_2-C1), 3.63 (s, 3H, CH_3-C5), 3.62 (dd, 1H, *J* = 8.2, 2.8 Hz, CH_2-C1), 2.69 (ddd, 1H, *J* = 16.0, 6.5, 2.5 Hz, CH_2-C3), 2.50 (ddd, 1H, *J* = 16.0, 10.7, 7.0, CH_2-C3), 1.69 (ddd, 3H, *J* = 6.6, 3.0, 1,7, CH_3-C9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7 (C-C4), 134.1 (CH-C8), 127.4 (CH-C7), 104.3 (CH-C6), 72.2 (CH-C2), 69.3 (CH_2-C1), 51.6 (CH_3-C5), 38.5 (CH_2-C3), 17.4 (CH_3-C9);
HRMS (CI/Isobutane) for $C_9H_{15}O_4$ ($[M+H]^+$) calculated 187.0970, found 187.0966.

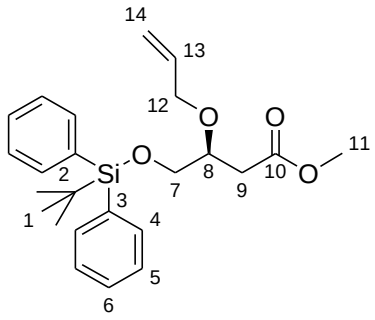


(*S*,*E*)-3-(But-2-enyl)oxy-4-hydroxybutyric acid methyl ester (299)

To a solution of cyclic acetal **298** (50 mg, 0.26 mmol) in dry DCM (2 mL) at 0 ºC was added triethylsilane (0.2 mL, 1 mmol, 5 eq). The reaction mixture was stirred for 5 min at 0 ºC and TFA (0.1 mL, 1 mmol, 5 eq) was added dropwise. The colourless solution was stirred at room temperature for 16 hours. The solution was diluted with EtOAc (5 mL). The organic phase was washed subsequently with $NaHCO_3$ (saturated aqueous solution, 5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 7:3) to afford alcohol **299** as a colourless oil (16 mg, 0.1 mmol, 31 %).

R_f = 0.48 (petroleum ether-EtOAc, 7:3); ν_{max} (NaCl) 3421, 1646, 1264, 1097, 1013, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74-5.69 (m, 1H, CH-C7), 5.59-5.52 (m, 1H, CH-C8), 4.19-4.22 (m, 1H, CH-C2), 3.96-3.94 (m, 2H, CH_2-C6), 3.71 (s, 3H, CH_3-C5), 3.46 (dd, 1H, *J* = 9.6, 4.4 Hz, CH_2-C1), 3.40 (ddd, 1H, *J* = 9.6, 6.2, Hz, CH_2-C1), 2.55-2.53 (m,

2H, CH_2-C3), 1.72 (ddt, 3H, *J* = 6.4, 2.5, 1.1 Hz, CH_2-C9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.5 (C-C4), 127.1 (CH-C7), 126.2 (CH-C8), 77.2 (CH-C2), 72.7 (CH_2-C1), 72.0 (CH_2-C6), 51.8 (CH_3-C5), 38.0 (CH_2-C3), 17.7 (CH_3-C9);
HRMS (CI/Isobutane) for $C_9H_{17}O_4$ ($[M+H]^+$) calculated 189.1127, found 189.1126

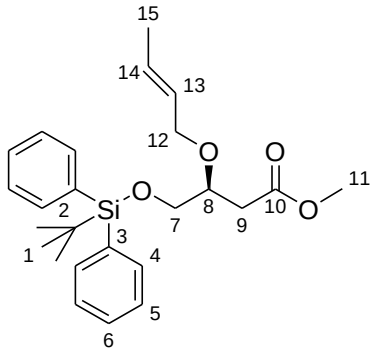


(*S*)-3-Allyloxy-4-(*tert*-butyldiphenylsilanyloxy) butyric acid methyl ester (300)

A solution of protected alcohol **284** (4.0 g, 11 mmol) and crude trichloroacetimidate **360** (4.4 g, 21 mmol, 2 eq) in freshly distilled cyclohexane (20 mL) was cooled to 0 °C. The light yellow solution was stirred at this temperature for 10 min. At this point CF_3SO_3H (50 μL, 0.56 mmol, 0.05 eq) was added. After the appearance of a white suspension, the iced-water bath was removed and the reaction mixture left to warm at room temperature. The white suspension was then left to stir overnight. The reaction mixture was then filtered, and the white solid washed with cyclohexane (3 × 20 mL). The organic extracts were concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether 100% to petroleum ether-Et_2O, 15:1) to afford ether **300** as a colourless oil (4.23 g, 10.3 mmol, 93 %).

R_f = 0.58 (petroleum ether-EtOAc, 9:1); ν_{max} (NaCl) 2931, 2858, 1739, 1112, 1089, 969 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H, CH-C4), 7.43-7.36 (m, 6H, CH-C5,C6), 5.84 (ddt, 1H, *J* = 17.2, 10.4, 5.7 Hz, CH-C13), 5.20 (ddt, 1H, *J* = 17.2, 1.6, 1.3 Hz, CH_2-C14), 5.12 (ddt, 1H, *J* = 10.4, 1.6, 1.3 Hz, CH_2-C14), 4.06 (ddt, 1H, *J* = 12.6, 5.7, 1.3 Hz, CH_2-C12), 3.99 (ddt, 1H, *J* = 12.6, 5.7, 1.3 Hz, CH_2-C12), 3.93 (dtd, 1H, *J* = 8.3, 5.5, 5.0 Hz, CH-C8), 3.72 (dd, 1H, *J* = 10.6, 5.5 Hz, CH_2-C7), 3.67 (s, 3H, CH_3-C11), 3.60 (dd, 1H, *J* = 10.5, 5.5 Hz, CH_2-C7), 2.68 (dd, 1H, *J* = 15.7, 5.0 Hz, CH_2-C9), 2.55 (dd, 1H, *J* = 15.7, 8.3 Hz, CH_2-C9), 1.04 (s, 9H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (C-C10), 135.5 (CH-C5), 135.5 (CH-C5), 134.8 (CH-C13), 133.2 (C-C3), 133.2 (C-C3), 129.7 (CH-C6), 127.6 (CH-C4), 127.6 (CH-C4), 116.8 (CH_2-C14), 76.2 (CH-C8), 71.4 (CH_2-C12), 65.0 (CH_2-C7), 51.6 (CH_3-C11), 37.4 (CH_2-C9), 26.7 (CH_3-C1), 19.1 (C-C2);

HRMS (Ic) for $C_{25}H_{34}O_4SiNa$ ($[M+Na]^+$) calculated 449.2126, found 449.2119.



(*S*,*E*)-3-(But-2-enyl)oxy-4-(*tert*-butyldiphenylsilanyloxy)butyric acid methyl ester (285)

Method A[159]

A solution of protected alcohol **284** (176 mg, 0.5 mmol) and crude trichloroacetimidate **361** (204 mg, 0.9 mmol, 2 eq) in freshly distilled cyclohexane (3 mL) was cooled to 0 °C. The light yellow solution was stirred at this remperature for 10 min and then CF_3SO_3H (2 μL, 0.02 mmol, 0.04 eq) was added. After the appearance of a white suspension, the iced-water bath was removed and the reaction mixture left to warm to room temperature. The white suspension was then left to stir overnight.

The reaction mixture was then filtered, and the white solid washed with cyclohexane (3 × 5 mL). The combined solution and washings were then concentrated *in vacuo* and the colourless oil was found to be a mixture of Sn2 and Sn2' products in a 6:1 ratio favouring the desired ether. This mixture was purified by flash column chromatography (silica gel, petroleum ether 100% to petroleum ether-Et_2O, 15:1) to afford ether **285** as a colourless oil (100 mg, 0.23 mmol, 46 %).

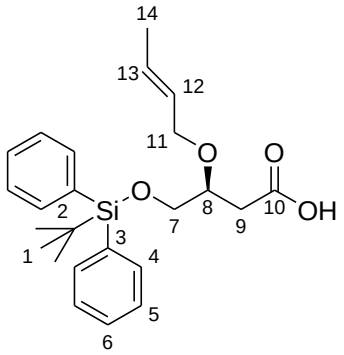
Method B

To a solution of alkene **300** (4.0 g, 9.7 mmol) in dry toluene (70 mL) was added, in one portion, Grubbs' second generation catalyst (300 mg, 0.35 mmol, 0.035 eq). The reaction mixture was flushed with 2-butene. The resulting solution was stirred under an atmosphere of 2-butene at 68 °C overnight. The reaction mixture was concentrated *in vacuo* and the remaining solid was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 15:1) to afford *E*-alkene in a 15:1 ratio **285** as a colourless oil (4.10 g, 9.6 mmol, 97 %)

[159] Clark, Fessard and Wilson, *Org. Lett.* **2004,** 6, (11), 1773-76.

R_f = 0.48 (petroleum ether-EtOAc, 9:1); ν_{max} (NaCl) 2931, 2857, 1739, 1428, 1112, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.67 (m, 4H, CH-C4), 7.40-7.39 (m, 6H, CH-C5,C6), 5.42-5.33 (dtdd, 1H, *J* = 12.6, 6.3, 6.2, 0.8 Hz, CH-C13), 5.24-5.19 (bdd, 1H, *J* = 12.6, 6.2 Hz, CH-C14), 3.99 (dd, 1H, *J* = 11.6, 6.3 Hz, CH_2-C12), 3.94-3.90 (m, 2H, CH_2-C12, CH-C8), 3.72 (dd, 1H, *J* = 10.5, 5.1 Hz, CH_2-C7), 3.68 (s, 3H, CH_3-C11), 3.58 (dd, 1H, *J* = 10.5, 5.9 Hz, CH_2-C7), 2.68 (dd, 1H, *J* = 15.6, 4.6 Hz, CH_2-C9), 2.53 (dd, 1H, *J* = 15.6, 8.3 Hz, CH_2-C9), 1.67 (d, 3H, *J* = 6.2 Hz, CH_2-C15), 1.05 (s, 9H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (C-C10), 135.5 (CH-C4), 135.5 (CH-C13), 133.2 (C-C3), 133.2 (C-C3), 129.6 (CH-C6), 129.4 (CH-C14), 127.6 (CH-C5), 75.8 (CH-C8), 71.1 (CH_2-C12), 65.1 (CH_2-C7), 51.5 (CH_3-C11), 37.4 (CH_2-C9), 26.7 (CH_3-C2), 19.1(C-C1), 17.7 (CH_3-C15).

HRMS (CI/Isobutane) for $C_{24}H_{33}O_4Si$ ($[M+Na]^+$) calculated 413.2148, found 413.2144.



(*S*,*E*)-3-(But-2-enyl)oxy-4-(*tert*-butyldiphenylsilanyloxy) butyric acid (302)[160]

To a solution of ester **285** (6 g, 14 mmol) in dry ether (120 mL) was added TMSOK (9.0 g, 70 mmol, 5 eq) in one portion. The resulting reaction mixture was stirred at room temperature overnight under Ar atmosphere. The reaction mixture was the cooled to 0 ºC and the pH was lowered to 2 by addition of HCl (1 N, ~100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to give the carboxylic acid **302** as a colourless oil (5.64 g, 13.7 mmol, 98%).

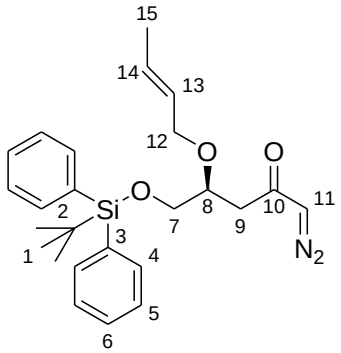
R_f = 0.47 (petroleum ether-EtOAc, 3:1); ν_{max} (NaCl) 3183, 2931, 2858, 1710, 1362, 1112, 968 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.68 (m, 4H, CH-C4), 7.45-7.37 (m, 6H, CH-C5,C6), 5.69-5.47 (m, 2H, CH-C13, CH-C12), 4.02-3.90 (m, 3H, CH_2-C11, CH-C8),

[160] Clark, Fessard and Wilson, *Org. Lett.* **2004,** 6, (11), 1773-76.

3.75 (dd, 1H, *J* = 10.6, 5.1 Hz, CH_2-C7), 3.63 (dd, 1H, *J* = 10.6, 5.5 Hz, CH_2-C7), 2.75 (dd, 1H, *J* = 15.8, 4.7 Hz, CH_2-C9), 2.59 (dd, 1H, *J* = 15.8, 8.1 Hz, CH_2-C9), 1.67 (d, 3H, *J* = 6.3 Hz, CH_3-C14), 1.06 (s, 9H, CH_3-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (C-C10), 135.5 (CH-C13), 135.5 (CH-C5), 133.2 (C-C3), 129.7 (CH-C6), 127.8 (CH-C4), 127.7 (CH-C12), 75.4 (CH-C8), 66.0 (CH_2-C11), 60.4 (CH_2-C7), 37.4 (CH_2-C9), 26.7 (CH_3-C1), 19.1 (C-C2), 17.7 (CH_3-C14);

$[\alpha]^{24}_D = -12.6$ (c = 0.95 in $CHCl_3$, T= 25 °C);

HRMS (Ic) for $C_{24}H_{32}O_4SiNa$ ($[M+Na]^+$) calculated 435.1962, found 435.1976.



(*S*,*E*)-4-(But-2-enyl)oxy-5-(*tert*-butyldiphenylsilanyloxy)-1-diazopentan-2-one (231)[161]

To a solution of acid **302** (5.9 g, 14 mmol) in dry DCM (40 mL) was added oxalyl chloride (1.5 mL, 17 mmol, 1.2 eq) along with dry DMF (3 drops). The mixture was stirred at room temperature overnight under argon atmosphere for 3 hours. The reaction mixture was then concentrated and the residue obtained washed with DCM (3 × 15 mL). The yellow oil obtained was dissolved in ether (10 mL) and added to a freshly distilled solution of diazomethane in ether (10 eq) at 0 °C. The mixture was stirred at 0 °C for 2 hours. The excess diazomethane was quenched with acetic acid (3 mL), and the solution was stirred at room temperature for 1 hour. The organic phase was washed carefully with $NaHCO_3$ (3 × 40 mL) and then dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether-ether, 5:1) to afford **231** as bright yellow oil (6.05 g, 13.8 mmol, 98 %).

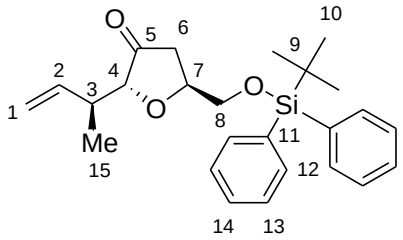
R_f = 0.76 (petroleum ether-EtOAc, 3:1); ν_{max} (NaCl) 2930, 2858, 2108, 1637, 1362, 1111, 998 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H, CH-C4), 7.43-7.37 (m, 6H, CH-C5,C6), 5.68-5.60 (m, 1H, CH-C14), 5.55-5.48 (m, 1H, CH-C13), 5.31 (s, 1H, CH-C11), 4.01-3.89 (m, 3H, CH_2-C12, CH-C8), 3.71 (dd, 1H, *J* = 10.6, 5.0 Hz, CH_2-C7), 3.64-3.60 (dd, 1H, *J* = 10.6, 5.5 Hz, CH_2-C7), 2.61 (dd, 1H, *J* = 14.6, 3.7 Hz, CH_2-C9), 2.51

[161] Clark, Fessard and Wilson, *Org. Lett.* **2004,** 6, (11), 1773-76.

(dd, 1H, J = 14.6, 6.2 Hz, CH_2-C9), 1.68 (dd, 3H, J = 6.3, 1.1 Hz, CH_3-C15), 1.07 (s, 9H, CH_3-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0 (C-C10), 140.2 (CH-C14), 135.6 (CH-C5), 129.7 (C-C3), 129.4 (CH-C6), 127.7 (CH-4), 127.6 (CH-C13), 76.7 (CH-C8), 71.2 (CH_2-C12), 65.3 (CH_2-C7), 55.3 (CH-C11), 43.7 (CH_2-C9), 26.8 (CH_3-C1), 19.2 (C-C2), 17.8 (CH_3-C15);

$[\alpha]_D = -29.3$ (c = 2.84, $CHCl_3$, T = 23 °C);

HRMS (Ic) for $C_{24}H_{32}O_4SiNa$ ($[M+Na]^+$) calculated 435.1962, found 435.1976.



(2*R*,5*S*)-5-(*tert*-Butyldiphenylsilanyloxy)methyl-2-[(*S*)-1-methylprop-2-enyl]dihydro furan-3-one (235)[162]

To a vigorously stirred solution of $Cu(acac)_2$ (30.8 mg, 0.12 mmol, 0.1 eq) in dry THF (15 mL) at 66 ºC was added dropwise *via* a teflon needle, a solution of diazoketone **231** (0.5 g, 1.15 mmol) in dry THF (7 mL). The solution turned from blue to brown. The reaction mixture was stirred at 66 ºC for 30 min. The reaction mixture was then concentrated *in vacuo*, and the residue thus obtained was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 15:1) to afford the rearrangement product **235** as a white solid (387 mg, 0.94 mmol, 82 %).

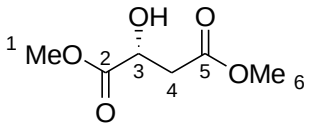
R_f = 0.75 (Petroleum ether-EtOAc, 9:1); Mp = 57-59 ºC; ν_{max} (NaCl) 3053, 2859, 1754, 1112, 1265, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.63 (m, 4H, CH-C12), 7.42-7.38 (m, 6H, CH-C13, C14), 5.90 (ddd, 1H, J = 17.2, 10.4, 6.8 Hz, CH-C2), 5.14 (dt, 1H, J = 17.2, 1.4 Hz, CH_2-C1), 5.12 (dt, 1H, J = 10.4, 1.4 Hz, CH_2-C1), 4.50 (tt, 1H, J = 5.8, 2.9 Hz, CH-C7), 4.17 (d, 1H, J = 3.5 Hz, CH-C4), 3.96 (dd, 1H, J = 11.0, 2.9 Hz, CH_2-C8), 3.64 (dd, 1H, J = 11.0, 2.9 Hz, CH_2-C8), 2.65-2.62 (m, 1H, CH-C3), 2.56-2.53 (m, 2H, CH_2-C6), 1.03 (d, 3H, J = 6.6 Hz, CH_3-C15), 1.03 (s, 9H, CH_3-C10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6 (C-C5), 139.9 (CH-C13), 135.6 (CH-C2), 132.9 (C-C11), 129.9 (CH-C14), 127.9 (CH-C12), 115.1 (CH_2-C1), 83.2 (CH-C4), 75.9 (CH-C7), 67.6 (CH_2-C8), 40.0 (CH-C3), 39.2 (CH_2-C6), 26.8 (CH_3-C10), 19.2 (C-C9), 13.6 (CH_3-C15);

HRMS (ESI) for $C_{25}H_{32}O_3SiNa$ ($[M+Na]^+$) calculated 431.2013, found 431.1997;

[162] Clark, Fessard and Wilson, *Org. Lett.* **2004,** 6, (11), 1773-76.

$[\alpha]_D$ = + 78.0 (c = 2.84, T = 23 °C, $CHCl_3$);

Anal. calculated for $C_{25}H_{32}O_3Si$: C, 73.49 %; H, 7.90 %. Found: C 73.18 %, H 7.97%.



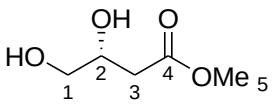
Dimethyl (*R*)-malate (309)[163]

To a solution of **D**-malic acid (25 g, 0.19 mol) in dry MeOH (300 mL) at 0 °C was added dropwise, over 1 hour, thionyl chloride (30 mL, 0.4 mol, 2.2 eq). The reaction mixture was then allowed to warm at room temperature for 3 hours. The solution was then concentrated and the residue was partitioned between DCM (150 mL) and $NaHCO_3$ (150 mL). The aqueous phase was extracted with DCM (3 × 100 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. The solvent was then removed under *vacuo* and the residue was purified by column chromatography on silica gel (Petroleum ether-EtOAc 1:9) to give **D**-dimethyl malate **309** (30.8 g, quant) as a colourless oil.

R_f = 0.77 (petroleum ether-EtOAc, 1:9); ν_{max} (NaCl) 3007, 2956, 1741, 1412, 1276, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (bt, 1H, *J* = 5.1 Hz, CH-C3), 3.81 (s, 3H, CH_3-C1), 3.71 (s, 3H, CH_3-C6), 3.22 (s, 1H, OH), 2.86 (dd, 1H, *J* = 16.5, 5.1 Hz, CH_2-C4), 2.79 (dd, 1H, *J* = 16.5, 5.1 Hz, CH_2-C4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (C-C2), 171.0 (C-C5), 67.2 (CH-C3), 52.8 (CH_3-C1), 52.0 (CH_3-C6), 38.4 (CH_2-C4);

$[\alpha]_D$ = +4.6 (c= 1.05 in $CHCl_3$, T= 24 °C); $[\alpha]^{25}_D$ = +6.2 (neat); lit.[164] $[\alpha]_D$ = +6.4

HRMS (CI-isobutane) for $C_6H_{11}O_5$ ($[M+H]^+$) calculated 163.0606, found 163.0604.



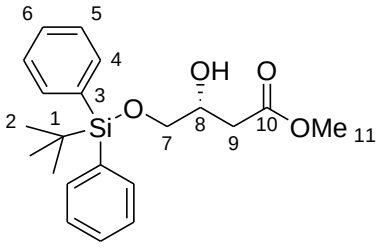
(*R*)-3,4-Dihydroxy butyric acid methyl ester (363)[165]

To a solution of **D**-dimethylmalate **309** (3 g, 0.02 mol) in dry THF (30 mL) at 0 °C was added dropwise a solution of borane dimethyl sulfide complex (1.90 mL, 0.02 mol, 1.02

[163] Dahlgren, Johansson, Kvarnstrom, Musil, Nilsson and Samuelsson, *Bioorg. Med. Chem.* **2002,** 10, (6), 1829-39.
[164] Hungerbuehler, Seebach and Wasmuth, *Helv. Chim. Acta* **1981,** 64, (5), 1467-87.
[165] Fox, Jackson, Lennon and McCague, *J. Org. Chem.* **2005,** 70, (4), 1227-36.

eq). The reaction mixture was then stirred 0 °C until no more gas evolution occurred (approximately 1 hour). Sodium borohydride (30 mg, 0.80 mmol, 0.04 eq) was then added in one portion to the solution and the reaction mixture was stirred at 0 °C for 3 hours. Methanol (10 ml) was then added dropwise to quench the reaction and the resulting solution was then stirred for 1 hour at room temperature. The solvent was then removed under *vacuo*. The residue was washed with toluene and methanol (1:1, 50 mL) and the solvent removed *in vacuo* and the operation was repeated twice. The residue was washed with toluene (30 mL) and the solvent removed *in vacuo*. The operation was repeated. The residue was purified by flash column chromatography on silica gel (EtOAc 100%) to give diol **363** (2.41 g, 17.9 mmol, 90 %) as a colourless oil.

R_f = 0.23 (EtOAc 100%); ν_{max} (NaCl) 3436, 2955, 1736, 1440, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (m, 1H, CH-C2), 3.72 (s, 3H, CH_3-C5), 3.68 (dd, 1H, *J* = 11.4, 3.5 Hz, CH_2-C1), 3.53 (dd, 1H, *J* = 11.4, 6.2 Hz, CH_2-C1), 2.86 (d, 1H, *J* = 2.7 Hz, OH), 2.57 (dd, 1H, *J* = 16.5, 8.5 Hz, CH_2-C3), 2.50 (dd, 1H, *J* = 16.5, 4.1 Hz, CH_2-C3) 1.58 (t, 1H, *J* = 2.6 Hz, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1 (C-C4), 68.6 (CH-C2), 65.9 (CH_2-C1), 52.2 (CH_3-C5), 37.6 (CH_2-C3);
$[\alpha]_D$ = + 9.6 (c = 1% in $CHCl_3$, T = 24 °C), lit.[166] $[\alpha]_D$ = + 13.8;
HRMS (CI-isobutane) for $C_5H_{11}O_4$ ($[M+H]^+$) calculated 135.0657, found 135.0663.



(*R*)-4-(*tert*-Butyldiphenylsilanyloxy)-3-hydroxy butyric acid methyl ester (311)

To a solution of diol **363** (2.2 g, 16 mmol) in dry DMF (40 mL) was added chlorodiphenylmethylsilane (4.7 mL, 18 mmol, 1.1 eq). Imidazole (1.3 g, 20 mmol, 1.2 eq) and DMAP (a catalytic amount) were added to the colourless solution in one portion. The reaction mixture was then flushed with Ar and stirred at room temperature for 1 hour. EtOAc (40 mL) was added to the reaction mixture and the organic layer was washed sequentially with H_2O (40 mL), HCl (2 M, 40 mL) and a saturated solution of $NaHCO_3$ (40 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by

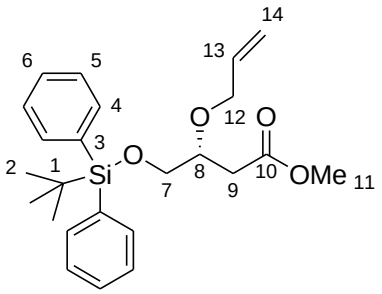
[166] Pospisil and Marko, *Tetrahedron Lett.* **2008,** 49, (9), 1523-26.

flash column chromatography on silica gel (petroleum ether-EtOAc, 9:1) to give silyl ether **311** (5.55 g, 14.9 mmol, 93 %) as a colourless oil.

R_f = 0.38 (petroleum ether, EtOAc, 9:1); ν_{max} (NaCl) 3072, 3050, 2931, 2892, 2857, 1968, 1818, 1737, 1373, 1254, 1051, 1006, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H, CH-C4), 7.44-7.37 (m, 6H, CH-C5,C6), 4.16 (dtdd, 1H, *J* = 7.4, 5.0, 5.0, 5.0 Hz, CH-C8), 3.69 (s, 3H, CH_3-C11), 3.67 (dd, 1H, *J* = 10.3, 5.0 Hz, CH_2-C7), 3.63 (dd, 1H, *J* = 10.3, 5.0 Hz, CH_2-C7), 2.87 (d, 1H, *J* = 5.0 Hz, OH), 2.57 (dd, 1H, *J* = 14.4, 5.0 Hz, CH_2-C9), 2.53 (dd, 1H, *J* = 14.4, 7.5 Hz, CH_2-C9), 1.06 (s, 9H, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4 (C-C10), 135.5 (CH-C4), 132.9 (C-C3), 129.8 (CH-C6), 127.7 (CH-C5), 68.5 (CH-C8), 66.8 (CH_2-C7), 51.7 (CH_3-C11), 37.8 (CH_2-C9), 26.8 (CH_3-C2), 19.2 (C-C1);

$[\alpha]_D$ = + 7.2 (c = 1.05 in $CHCl_3$ T = 24 °C);

HRMS (CI-isobutane) for $C_{21}H_{29}O_4Si$ ($[M+H]^+$) calculated 373.1835, found 373.1840.



(*R*)-3-Allyloxy-4-(*tert*-butyldiphenylsilanyloxy) butyric acid methyl ester (313)

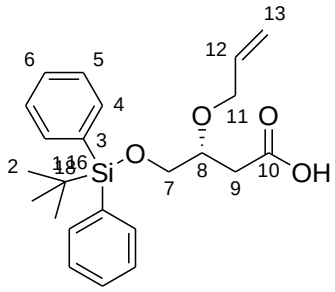
To a solution of alcohol **311** (1 g, 3 mmol) and crude trichloroacetimidate **360** (1.08 g, 5.3 mmol, 1.8 eq) in freshly distilled cyclohexane (10 mL) was added trifluoromethane sulfonic acid (4 µL, 0.04 mmol, 0.01 eq). The reaction mixture was then placed under Ar atmosphere. The resulting white suspension was stirred at room temperature overnight. The reaction mixture was then filtered and the white powder was washed with cyclohexane (3 × 10 mL). The filtrate was then concentrated and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to give allylic ether **313** as a colourless oil (1.13 g, 2.7 mmol, 90 %).

R_f = 0.42 (petroleum ether, EtOAc, 9:1); ν_{max} (NaCl) 3071, 2957, 2932, 2894, 2857, 1740, 1428, 1246, 1112, 1087, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H, CH-C4), 7.41-7.38 (m, 6H, CH-C5, C6), 5.84 (ddt, 1H, *J* = 17.2, 10.4, 5.7 Hz, CH-C13), 5.20

(ddd, 1H, *J* = 17.2, 3.3, 1.4 Hz, CH_2-C14), 5.12 (ddd, 1H, *J* = 10.4, 3.3, 1.4 Hz, CH_2-C14), 4.06 (ddt, 1H, *J* = 12.6, 5.7, 1.4 Hz, CH_2-C12), 3.99 (ddt, 1H, *J* = 12.6, 5.7, 1.4 Hz, CH_2-C12), 3.93 (dtd, 1H, *J* = 8.3, 5.5, 5.0 Hz, CH_2-C8), 3.72 (dd, 1H, *J* = 10.5, 5.5 Hz, CH_2-C7), 3.67 (s, 3H, CH_3-C11), 3.60 (dd, 1H, *J* = 10.5, 5.5 Hz, CH_2-C7), 2.68 (dd, 1H, *J* = 15.6, 5.0 Hz, CH_2-C9), 2.55 (dd, 1H, *J* = 15.6, 8.3 Hz, CH_2-C9), 1.04 (s, 9H, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (C-C10), 135.5 (CH-C4), 135.5 (CH-C4), 134.9 (CH-C13), 133.2 (C-C3), 133.2 (C-C3), 129.7 (CH-C6), 127.6 (CH-C5), 127.6 (CH-C5), 116.8 (CH_2-C14), 76.2 (CH-C8), 71.4 (CH_2-C12), 65.1 (CH_2-C7), 51.6 (CH_3-C11), 37.4 (CH_2-C9), 26.7 (CH_3-C2), 19.1(C-C1);

$[\alpha]_D$ = + 18.4 (c = 0.95, $CHCl_3$, T = 24 °C);

HRMS (CI-isobutane) for $C_{24}H_{33}O_4Si$ ($[M+H]^+$) calculated 413.2148, found 413.2146.



(*R*)-3-Allyloxy-4-(*tert*-butyldiphenylsilanyloxy) butyric acid (314)

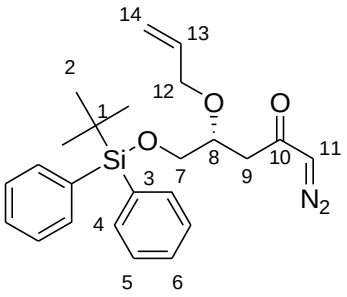
To a solution of ester **313** (125 mg, 0.3 mmol) in dry diethyl ether (5 mL) was added TMSOK (194 mg, 2 mmol, 5 eq) in one portion. The resulting reaction mixture was stirred at room temperature overnight under argon atmosphere. The reaction mixture was the cooled to 0 ºC and the pH was lowered to 2 by addition of HCl (2 N). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue obtained was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 5:1) to give carboxylic acid **314** as a colourless oil (118 mg, 0.3 mmol, quant.).

R_f = 0.27 (petroleum ether, EtOAc, 3:1); ν_{max} (NaCl) 3072, 3050, 3015, 2998, 2958, 2932, 2892, 2857, 2564, 1962, 1891, 1739, 1463, 1109, 1048, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H, CH, C4), 7.42-7.37 (m, 6H, CH-C5, C6), 5.84 (ddt, 1H, *J* = 17.1, 10.4, 5.7 Hz, CH-C12), 5.21 (ddt, 1H, *J* = 17.1, 1.6, 1.6 Hz, CH_2-C13), 5.14 (ddt, 1H, *J* = 10.4, 1.6, 1.4 Hz, CH_2-C13), 4.07 (ddt, 1H, *J* = 12.6, 5.7, 1.6 Hz, CH_2-C11), 4.00 (tdd, 1H, *J* = 12.6, 5.7, 1.4 Hz, CH_2-C11), 3.90 (dddd, 1H, *J* = 7.9, 5.5, 4.8 Hz, CH-C8), 3.73

(dd, 1H, *J* = 10.6, 4.8 Hz, CH_2-C7), 3.63 (dd, 1H, *J* = 10.6, 5.5 Hz, CH_2-C7), 2.74 (dd, 1H, *J* = 16.0, 4.8 Hz, CH_2-C9), 2.62 (dd, 1H, *J* = 16.0, 7.9 Hz, CH_2-C9), 1.05 (s, 9H, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (C-C10), 135.6 (CH-C4), 135.6 (CH-C4), 134.4 (C-C3), 134.3 (CH-C12), 129.8 (CH-C6), 127.7 (CH-C5), 117.38 (CH_2-C13), 75.8 (CH-C8), 71.3 (CH_2-C11), 64.8 (CH_2-C7), 37.2 (CH_2-C9), 26.7 (CH_3-C2), 19.2 (C-C1).

$[\alpha]_D$ = + 17.8 (c = 1.00, $CHCl_3$, T = 25 °C);

HRMS (FAB/NOB) for $C_{23}H_{31}O_4Si$ ($[M+H]^+$) calculated 399.1992, found 399.1993



(*R*)-4-Allyloxy-5-(*tert*-butyldiphenylsilanyloxy)-1-diazo-pentan-2-one (308)

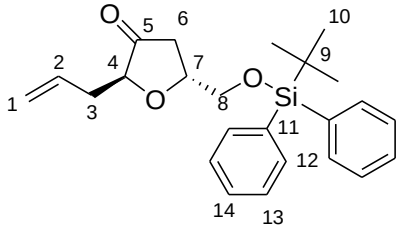
To a solution of acid **314** (2.5 g, 6.3 mmol) in dry DCM (20 mL) was added oxalyl chloride (0.7 mL, 8 mmol, 1.3 eq) along with dry DMF (3 drops). The mixture was stirred at room temperature overnight under Ar atmosphere for 3 hours. The reaction mixture was then concentrated and the residue obtained washed with DCM (3 × 5 mL). The yellow oil obtained was dissolved in Et_2O (3 mL) and added to a freshly distilled solution of diazomethane in ether (10 eq) at 0 °C. The mixture was stirred at 0 °C for 2 hours. The excess diazomethane was quenched with acetic acid (1 mL), and the solution stirred at room temperature for 1 hour. The organic phase was washed carefully with $NaHCO_3$ (3 × 10 mL) and then dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether-ether, 5:1) to afford **308** as bright yellow oil (2.58 g, 6.1 mmol, 97 %).

R_f (Petroleum ether-ether, 3:1) = 0.44; ν_{max} (NaCl) 3072, 2931, 2857, 2104, 1737, 1644, 1472, 1372, 1112, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.65 (m, 4H, CH-C4), 7.43-7.36 (m, 6H, CH-C5, C6), 5.84 (ddt, 1H, *J* = 17.2, 10.4, 5.7 Hz, CH-C13), 5.31 (bs, 1H, CH-C11), 5.21 (dd, 1H, *J* = 17.2, 1.4 Hz, CH_2-C14), 5.12 (tdd, 1H, *J* = 10.4, 1.4 Hz, CH_2-C14), 4.05 (bdd, 1H, *J* = 12.6, 5.7, CH_2-C12), 3.99 (bdd, 1H, *J* = 12.6, 5.7 Hz, CH_2-C12), 3.93 (ddt, 1H, *J* = 8.4, 5.2, 5.2 Hz, CH_2-C8), 3.71 (dd, 1H, *J* = 10.7, 5.2 Hz, CH_2-C7), 3.62 (dd, 1H, *J* = 10.7, 5.2 Hz, CH_2-C7), 2.61 (dd, 1H, *J* = 14.5, 5.2 Hz, CH_2-C9),

2.55 (dd, 1H, *J* = 14.5, 8.4 Hz, CH_2-C9), 1.04 (s, 9H, CH_3-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0 (C-C10), 135.5 (CH-C5), 135.5 (CH-C5), 134.8 (CH-C13), 133.2 (C-C3), 133.1 (C-C3), 129.7 (CH-C6), 127.7 (CH-C4), 127.6 (CH-C4), 116.8 (CH_2-C14), 76.4 (CH-C8), 71.3 (CH_2-C12), 65.2 (CH_2-C7), 43.6 (CH_2-C9), 55.2 (CH-C11), 26.7 (CH_3-C2), 19.1 (C-C1);

$[\alpha]_D$ = + 22.8 (c = 0.95 in $CHCl_3$, T = 24 °C);

HRMS (FAB-NOB) for $C_{24}H_{31}O_3N_2Si$ ($[M+H]^+$) calculated 423.2104, found 423.2107.



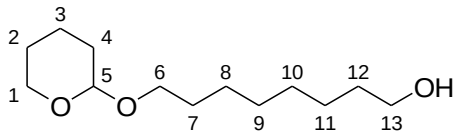
(2*R*,5*S*)-2-Allyl-5-(*tert*-butyldiphenylsilanyl)oxymethyl dihydrofuran-3-one (307)

A solution of diazoketone **308** (3.5 g, 8.3 mmol) in dry THF (20 mL) was added dropwise to a refluxing solution of $Cu(acac)_2$ (0.2 g, 0.8 mmol, 0.1 eq) in dry THF (100 mL). The solution was stirred at reflux for 30 min and then cooled at room temperature. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 15:1) to afford the rearrangement product **307** as a colourless oil (3.0 g, 7.6 mmol, 92 %).

R_f = 0.31 (Petroleum ether-EtOAc, 9:1); ν_{max} (NaCl) 3072, 2956, 2931, 2858, 1758, 1739, 1112, 1047, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H, CH-C12), 7.44-7.36 (m, 6H, CH-C13, C14), 5.83 (dddd, 1H, *J* = 17.2, 10.4, 7.2, 6.8 Hz, CH-C2), 5.19-5.12 (m, 2H, CH_2-C1), 4.49 (tt, 1H, *J* = 6.1, 2.9 Hz, CH-C7), 4.23 (dd, 1H, *J* = 7.2, 4.4 Hz, CH-C4), 3.96 (dd, 1H, *J* = 11.0, 2.9 Hz, CH_2-C8), 3.64 (dd, 1H, *J* = 11.0, 2.9 Hz, CH_2-C8), 2.56 (d, 2H, *J* = 6.2 Hz, CH_2-C6), 2.51 (dddt, 1H, *J* = 14.7, 6.8, 4.4, 1.2 Hz, CH_2-C3), 2.31 (dddt, 1H, *J* = 14.7, 7.2, 7.2, 1.1 Hz, CH_2-C3), 1.02 (s, 9H, CH_3-C10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5 (C-C5), 135.6 (CH-C12), 135.5 (CH-C12), 133.1 (C-C11), 132.8 (C-C11), 129.8 (CH-C13), 129.8 (CH-C14), 127.7 (CH-C2), 118.0 (CH_2-C1), 79.6 (CH-C4), 75.6 (CH-C7), 67.3 (CH_2-C8), 38.3 (CH_2-C6), 36.3 (CH_2-C3), 26.7 (CH_3-C10), 19.1 (C-C9).

$[\alpha]_D$ = −24.3 (c = 1.05, $CHCl_3$, T = 25.0 °C);

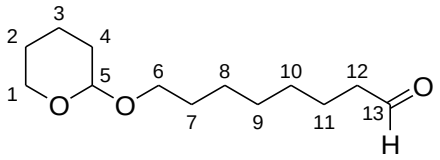
HRMS (CI/Isobutane) for $C_{24}H_{31}O_3Si$ ($[M+H]^+$) calculated 395.2042, found 395.2051.



8-(Tetrahydropyran-2-yloxy)-octan-1-ol (316)

To a solution of 1,8-octanediol (10.0 g, 68.4 mmol) in dry DCM (100 mL) was added portionwise DHP (5.8 mL, 68 mmol, 1 eq). The reaction mixture was stirred for 5 min at room temperature and *p*-TsOH (a catalytic amount) was added. The white suspension was stirred at room temperature until the starting material dissolved and the resulting colourless solution was stirred at room temperature for 30 min. The solution was then washed with $NaHCO_3$ (100 mL) and brine (100 mL) and the organic layer was dried over anhydrous $MgSO_4$. The solvent was then removed under *vacuo* and the residue obtained was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 1:1) to give mono-protected intermediate **316** (11.4 g, 49.4 mmol, 72 %) as a colourless oil.

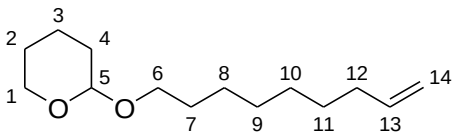
R_f = 0.61 (Petroleum ether-EtOAc, 3:7); ν_{max} (NaCl) 3442, 2933, 2847, 1450, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (s, 1H, CH-C5), 3.88-3.83 (m, 1H, CH_2-C1), 3.72 (dt, 1H, *J* = 8.9, 7.0 Hz, CH_2-C6), 3.63 (t, 2H, *J* = 6.6 Hz, CH_2-C13), 3.50-3.47 (m, 1H, CH_2-C1), 3.37 (dt, 1H, *J* = 8.9, 6.8 Hz, CH_2-C6), 1.85-1.79 (m, 1H, CH_2-C3), 1.73-1.67 (m, 1H, CH_2-C4), 1.58-1.53 (m, 8H, CH_2-C2, C3, C4, C7, C12), 1.45 (s, 1H, OH), 1.33-1.31 (m, 8H, CH_2-C8, C9, C10, C11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8 (CH-C5), 67.6 (CH_2-C6), 63.0 (CH_2-C13), 62.3 (CH_2-C1), 32.7 (CH_2), 30.7 (CH_2-C4), 29.7 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 19.6 (CH_2-C3) ;
HRMS (CI/isobutane) for $C_{13}H_{27}O_3$ ($[M+H]^+$) calculated 231.1960, found 231.1961 ;
Anal. calculated for $C_{14}H_{26}O_2$: C, 67.79%; H, 11.38%. Found: C 67.80%, H 11.48%.



8-(Tetrahydropyran-2-yloxy) octanal (317)

To a solution of oxalyl chloride (4.5 mL, 53 mmol, 1.2 eq) in dry DCM (200 mL) at – 78 °C was added dropwise dry DMSO (6.8 mL, 96 mmol, 2.2 eq). The solution was then stirred at – 78 °C for 10 min until there was no more gas evolution. Alcohol **316** (10.0 g, 43.4 mmol) in dry DCM (50 mL) was then added dropwise and the reaction mixture was then stirred at – 78 °C for 3 hours. Freshly distilled NEt_3 (15.8 mL, 113 mmol, 2.6 eq) was then added to the white suspension at – 78 °C and the reaction mixture was left to warm to room temperature for 2 hours. An aqueous solution of NH_4Cl (300 mL) was added to the reaction mixture and the organic layer was separated and washed with H_2O (200 mL). The aqueous layer was extracted with Et_2O (3 × 200 mL). The etheral fractions were combined and dried over anhydrous $MgSO_4$. The solvent was then removed under *vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 8:1) to give aldehyde **317** (9.7 g, 43 mmol, 98 %) as a colourless oil.

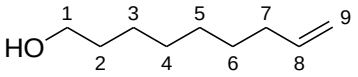
R_f = 0.33 (petroleum ether-EtOAc, 10:1); ν_{max} ($CHCl_3$) 2937, 2785, 1725, 1455, 1121, 869, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H, CH-C13), 4.56 (t, 1H, *J* = 3.4 Hz, CH-C5), 3.88-3.83 (m, 1H, CH_2-C1), 3.72 (dt, 1H, *J* = 9.2, 6.9 Hz, CH_2-C6), 3.51-3.46 (m, 1H, CH_2-C1), 3.37 (dt, 1H, *J* = 9.2, 6.6 Hz, CH_2-C6), 2.42 (td, 2H, *J* = 7.3, 1.3 Hz, CH_2-C12), 1.86-1.78 (m, 1H, CH_2-C4), 1.73-1.68 (m, 1H, CH_2-C11), 1.64-1.51 (m, 8H, CH_2-C2, C3, C4, C7, C11), 1.37-1.33 (m, 6H, CH_2-C8, C9, C10); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8 (CH-C13), 98.8 (CH-C5), 67.5 (CH_2-C6), 62.3 (CH_2-C1), 43.8 (CH_2-C12), 30.7 (CH_2-C11), 29.6 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.0 (CH_2), 25.4 (CH_2), 21.9 (CH_2), 19.7 (CH_2);
HRMS (CI/isobutane) for $C_{13}H_{25}O_3$ ($[M+H]^+$) calculated 229.1804, found 229.1806.



2-(Non-8-enyloxy) tetrahydropyran (318)

To a solution of KO^{t}Bu (13.1 g, 0.117 mol, 3 eq) in dry benzene (600 mL) was added portionwise methyltriphenylphosphonium bromide (41.8 g, 0.117 mol, 3 eq). The yellow suspension was then stirred at 80 °C for 1 hour. The reaction mixture was then cooled to room temperature and aldehyde **317** (8.4 g, 37 mmol) in dry benzene (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 30 min and the yellow suspension was then partitioned between H_2O and Et_2O (400 mL, 1:1). The aqueous layer was extracted with Et_2O (3 × 200 mL). The combined etheral fractions were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 10:1) to give alkene **318** (7.3 g, 32 mmol, 87 %) as a colourless oil.

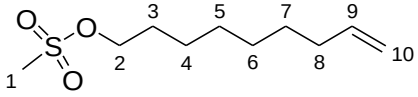
R_f = 0.64 (petroleum ether-EtOAc, 10:1); ν_{max} (NaCl) 3095, 2928, 2855, 1136, 1034, 869, 814 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, 1H, *J* = 16.9, 10.2, 6.8 Hz, CH-C13), 4.99 (ddt, 1H, *J* = 16.9, 2.3, 1.6 Hz, CH_2-C14), 4.92 (ddt, 1H, *J* = 10.2, 2.3, 1.2 Hz, CH_2-C14), 4.57 (dd, 1H, *J* = 4.3, 2.7 Hz, CH-C5), 3.87 (ddd, 1H, *J* = 11.1, 7.4, 3.6 Hz, CH_2-C1), 3.73 (dt, 1H, *J* = 9.6, 6.9 Hz, CH_2-C6), 3.52-3.40 (m, 1H, CH_2-C1), 3.38 (dt, 1H, *J* = 9.6, 6.7 Hz, CH_2-C6), 2.05 (dt, 1H, *J* = 6.8, 1.6 Hz, CH_2-C12), 2.02 (dt, 1H, *J* = 6.8, 1.2 Hz, CH_2-C12), 1.82 (tdd, 1H, *J* = 8.7, 6.2, 2.7 Hz, CH_2-C4), 1.71 (tdd, 1H, *J* = 7.5, 3.6, 2.7 Hz, CH_2-C2), 1.61-1.51 (m, 6H, CH_2), 1.37-1.29 (m, 8H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (CH-C13), 114.1 (CH_2-C14), 98.8 (CH-C5), 67.6 (CH_2-C6), 62.3 (CH_2-C1), 33.7 (CH_2-C12), 30.7 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 26.1 (CH_2), 25.4 (CH_2), 19.6 (CH_2).
HRMS (CI) $C_{14}H_{27}O_2$ $[M+H]^+$ calculated 227.2011 found 227.2012;
Anal. calculated for $C_{14}H_{27}O_2$: C, 74.33%; H, 11.50%. Found: C 74.15%, H 11.62%.



Non-8-en-1-ol (319)

To a solution of alkene **318** (5.2 g, 23 mmol) in MeOH (120 mL) was added *p*-TsOH (a catalytic amount) at room temperature. The colourless solution was then stirred at room temperature for 3 hours. The solvent was then removed *in vacuo* and the residue obtained was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 8:2) to give alcohol **319** (3.2 g, 23 mmol, quant.) as a colourless oil.

R_f = 0.15 (petroleum ether-EtOAc, 10:1); ν_{max} (NaCl) 3335, 3076, 2928, 2856, 1641, 1057, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, 1H, *J* = 16.9, 10.2, 6.7 Hz, CH-C8), 4.98 (ddt, 1H, *J* = 16.9, 2.0, 1.2 Hz, CH_2-C9), 4.92 (ddt, 1H, *J* = 10.2, 2.0, 1.2 Hz, CH_2-C9), 3.64 (t, 2H, *J* = 6.7 Hz, CH_2-C1), 2.04 (ddt, 2H, *J* = 6.7, 6.7, 1.2 Hz, CH_2-C7), 1.57-1.52 (m, 2H, CH_2-C2), 1.47 (bs, 1H, -OH), 1.39-1.20 (m, 8H, CH_2-C3,C4,C5,C6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (CH-C8), 114.1 (CH_2-C9), 63.0 (CH_2-C1), 33.7 (CH_2-C7), 32.7 (CH_2-C2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 25.6 (CH_2).
HRMS (CI/isobutane) for $C_9H_{19}O$ ($[M+H]^+$) calculated 143.1436, found 143.1436.



1-Methanesulfonylnon-8-ene (364)[167]

To a solution of alcohol **319** (4.2 g, 29 mmol) in dry DCM (140 mL) at – 78 °C was added freshly distilled triethylamine (8.3 mL, 67 mmol, 2.3 eq) and freshly distilled methanesulfonyl chloride (3.5 mL, 45 mmol, 1.5 eq). The reaction mixture was warmed slowly to room temperature while stirring and then stirred at room temperature for a further 30 min. The solution was washed with $NaHCO_3$ (aq. saturated solution, 100 mL) and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and The solvent was then removed *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc 20:1) to give protected alcohol **364** (6.5 g, 29 mmol, quant) as a light yellow oil.

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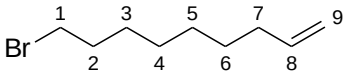
R_f = 0.19 (petroleum ether-EtOAc, 10:1); ν_{max} (NaCl) 3075, 3027, 2929, 1640, 1353, 1174, 974, 822, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, 1H, *J* = 16.9, 10.1, 6.7 Hz, CH-C9), 4.98 (dd, 1H, *J* = 16.9, 0.9 Hz, CH_2-C10), 4.93 (dd, 1H, *J* = 10.1, 0.9 Hz, CH_2-C10), 4.21 (t, 2H, *J* = 6.6 Hz, CH_2-C2), 2.99 (s, 3H, CH_3-C1), 2.03 (dt, 2H, *J* = 6.7, 6.7 Hz, CH_2-C8), 1.77-1.70 (m, 2H, CH_2-C7), 1.40-1.31 (m, 8H, CH_2-C2, C3, C4, C5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9 (CH-C9), 114.2 (CH_2-C10), 70.1 (CH_2-C2), 37.2 (CH_3-C1), 33.6 (CH_2-C8), 29.0 (CH_2-C7), 28.8 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 25.3 (CH_2);



9-Bromomonon-1-ene (320) [168]

Method A

To a solution of alcohol **319** (0.9 g, 6 mmol) in dry DCM (10 mL) was added carbon tetrabromide (2.7 g, 8.2 mmol, 1.4 eq). The reaction mixture was cooled to 0 °C and a solution of triphenylphosphine (2.66 g, 10.1 mmol, 1.7 eq) in dry DCM (10 mL) was added dropwise. The colourless solution was then stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (Petroleum ether-EtOAc, 20:1) to give bromide **320** (1.08 g, 5.3 mmol, 85 %) as a colourless oil.

Method B

The mesylated alcohol **364** (9.7 g, 44 mmol) was dissolved in dry THF (140 mL) and lithium bromide (3.9 g, 44 mmol, 1 eq) was added in one portion under argon atmosphere. The suspension was then stirred at room temperature for 16 hours. The reaction mixture was washed with $NaHCO_3$ (aq. saturated solution, 100 mL) and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined etheral layers were dried over anhydrous $MgSO_4$ and the solvent was then removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 20:1) to give bromide **320** (5.6 g, 27 mmol, 62 %) as a colourless oil.

R_f = 0.78 (petroleum ether-EtOAc, 15:1); ν_{max} (NaCl) 2930, 2856, 908, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, 1H, *J* = 16.9, 10.0, 6.7 Hz, CH-C8), 4.99 (dd, 1H, *J* = 16.9,

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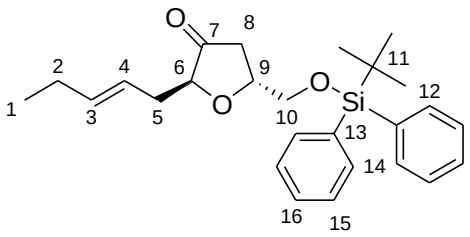
1.2 Hz, CH_2-C9), 4.93 (dd, 1H, *J* = 10.0, 1.2 Hz, CH_2-C9), 3.41 (t, 2H, *J* = 6.8 Hz, CH_2-C1), 2.06 (dt, 2H, *J* = 6.7, 6.7 Hz, CH_2-C7), 1.88-1.81 (m, 2H, CH_2-C2), 1.44-1.33 (m, 4H, CH_2-C3, C6), 1.33-1.30 (m, 4H, CH_2-C4, C5); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0 (CH-C8), 114.2 (CH_2-C9), 34.0 (CH_2-C1), 33.7 (CH_2-C7), 32.7 (CH_2-C2), 28.8 (CH_2), 28.7 (CH_2), 28.5 (CH_2), 28.1 (CH_2);

Anal. calculated for $C_9H_{17}Br$: C, 52.68%; H, 8.29%. Found: C 52.46%, H 8.31%.



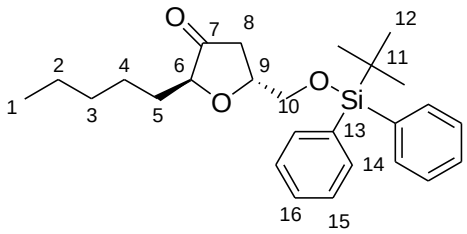
(2*S*,5*R*)- 2-[(*E*)-Pent-2-enyl]-5-(*tert*-butyldiphenylsilanyl)oxymethyl dihydrofuran-3-one (321)

To a solution of alkene **307** (100 mg, 0.25 mmol) in dry toluene (5 mL) was added *trans*-3-hexene (90 μL, 0.72 mmol, 2.9 eq) and Grubbs' second-generation catalyst (11 mg, 5 mol%). The solution was flushed with Ar. The reaction mixture was then stirred at 70 °C for 16 hours under argon atmosphere. The solvent was then removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether-ether, 15:1) to afford **321** as colourless oil (77 mg, 0.18 mmol, quant).

R_f = 0.33 (Petroleum ether-EtOAc, 9:1); ν_{max} (NaCl) 3071, 2958, 2930, 1758, 1428 ,1112, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H, CH-C14), 7.44-7.36 (m, 6H, CH-C15, C16), 5.62-5.61 (m, 1H, CH-C4), 5.45-5.38 (m, 1H, CH-C3), 4.50-4.44 (m, 1H, CH-C9), 4.22-4.13 (m, 1H, CH-C6), 3.95 (dd, 1H, *J* = 11.1, 3.1 Hz, CH_2-C10), 3.64 (dd, 1H, *J* = 11.1, 2.8 Hz, CH_2-C10), 2.57 (dd, 1H, *J* = 15.6, 8.2 Hz, CH_2-C8), 2.54 (dd, 1H, *J* = 15.6, 5.2 Hz, CH_2-C8), 2.46-2.39 (m, 1H, CH_2-C5), 2.30-2.20 (m, 1H, CH_2-C5), 2.15-1.95 (m, 2H, CH_2-C2), 1.02 (s, 9H, CH_3-C12), 1.02-0.86 (m, 3H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8 (C-C7), 135.6 (CH-C14), 135.5 (CH-C14), 132.8 (C-C13), 129.8 (CH-C16), 129.7 (CH-C16), 127.7 (CH-C15), 127.6 (CH-C15), 123.2 (CH-C4), 123.1 (CH-C3), 80.1 (CH-C6), 75.5 (CH-C9), 67.3 (CH_2-C10), 38.5 (CH_2-C8), 38.4 (CH_2-C5), 35.0 (CH_2-C2), 26.7 (CH_3-C12), 19.1 (C-C11), 13.6 (CH_3-C1);

$[\alpha]_D$ = − 26 (c = 1%, $CHCl_3$, T = 25 °C);

HRMS (FAB/NOBA+NaI) for $C_{26}H_{34}O_3Si$ ($[M+Na]^+$) calculated 445.2175, found 445.2180;



(2*R*,5*S*)-5-(*tert*-Butyldiphenylsilanyloxy)methyl-2-pentyl dihydrofuran-3-one (306)

Method A

To a solution of alkene **321** (82 mg, 0.19 mmol) in absolute EtOH (5 mL) was added Pd catalyst (10 % wt/C, 2.3 mg, 0.1 eq). The reaction mixture was stirred under H_2 atmosphere at room temperature for 2 hours. The reaction mixture was filtered through celite and the solvent was then removed *in vacuo*. The residue was then purified by flash column chromatography on silica gel (petroleum ether-ether, 9:1) to afford **306** as colourless oil (83 mg, 0.19 mmol, quant).

Method B

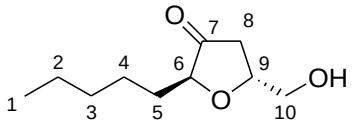
To a solution of rearrangement product **307** (3.5 g, 9.0 mmol) in DCE (70 mL) was added *trans*-3-hexene (2.75 mL, 22.1 mmol, 2.5 eq) and Grubbs second-generation catalyst (750 mg, 0.88 mmol, 0.1 eq). The reaction mixture was stirred under argon atmosphere for 16 hours at 60 °C. The reaction was then stirred under H_2 atmosphere for a further 16 hours at 60 °C. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether-ether, 10:1) to afford **306** as colourless oil (3.21 g, 7.6 mmol, 85 %).

R_f = 0.71 (Petroleum ether-Et_2O, 8:2); ν_{max} (NaCl) 2927, 2857, 1742, 1373, 1041, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68-7.63 (m, 4H, CH-C14), 7.45-7.37 (m, 6H, CH-C15, C16), 4.47 (ddt, 1H, *J* = 5.0, 3.1, 3.1 Hz CH-C9), 4.14 (dd, 1H, *J* = 7.7, 4.3 Hz, CH-C6), 3.95 (dd, 1H, *J* = 11.0, 3.1 Hz, CH_2-C10), 3.66 (dd, 1H, *J* = 11.0, 3.1 Hz, CH_2-C10), 2.60 (dd, 1H, *J* = 16.8, 5.0 Hz, CH_2-C8), 2.55 (dd, 1H, *J* = 16.8, 3.1 Hz, CH_2-C8), 1.73-1.62 (m, 1H, CH_2-C5), 1.57-1.51 (m, 1H, CH_2-C5), 1.33-1.26 (m, 6H, CH_2-C2,C3,C4), 1.03 (s, 9H,

CH_3-C12), 0.93-0.87 (m, 3H, CH_3-C12); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4 (C-C7), 135.6 (CH-C14), 135.5 (CH-C14), 132.8 (C-C13), 129.8 (CH-C16), 129.7 (CH-C16), 127.7 (CH-C15), 127.7 (CH-C15), 80.1 (CH-C6), 75.3 (CH-C9), 67.3 (CH_2-C10), 38.4 (CH_2-C8), 31.9 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 26.7 (CH_3-C12), 26.6 (CH_2), 19.1 (C-C11), 13.6 (CH_3-C1);

$[\alpha]_D$ = − 30.3 (c = 0.92, $CHCl_3$, T = 25 °C);

HRMS (CI/Isobutane) for $C_{26}H_{37}O_3Si$ ($[M+H]^+$) calculated 425.2512, found 425.2510;



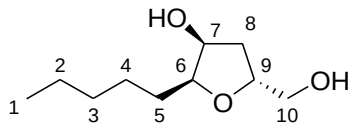
(2*R*,5*S*)-5-hydroxymethyl-2-pentyl dihydro furan-3-one (322)

To a solution of protected alcohol **306** (0.1 g, 0.2 mmol) in dry THF (6 mL) was added TBAF (1 M in THF, 0.47 mL, 0.47 mmol, 2 eq). The resulting solution was stirred at room temperature for 1 hour. The reaction mixture was then quenched with NH_4Cl (saturated aqueous solution, 15 mL). The aqueous layer was extracted with ether (3 × 5 mL) and the combined etheral extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 1:1) to give primary alcohol **322** as a colourless oil (43 mg, 0.23 mmol, 99 %).

R_f = 0.14 (Petroleum ether-EtOAc, 8:2); ν_{max} (NaCl) 3458, 2928, 2857, 1742, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48-4.42 (m, 1H, CH-C9), 4.01 (dd, 1H, *J* = 8.1, 4.5 Hz, CH-C6), 3.86 (dd, 1H, *J* = 11.9, 2.9 Hz, CH_2-C10), 3.65 (dd, 1H, *J* = 11.9, 4.9 Hz, CH_2-C10), 2.52 (bs, 1H, CH_2-C8), 2.50 (bs, 1H, CH_2-C8), 1.45-1.36 (m, 2H, CH_2-C5), 1.31-1.24 (m, 6H, CH_2-C2,C3,C4), 0.89-0.85 (m, 3H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8 (C-C7), 79.9 (CH-C6), 75.3 (CH-C9), 64.2 (CH_2-C10), 37.7 (CH_2-C8), 31.5 (CH_2-C5), 31.0 (CH_2), 24.9 (CH_2), 22.4 (CH_2), 13.9 (CH_3-C1).

$[\alpha]_D$ = − 25.4 (c = 0.98, $CHCl_3$, T = 24.6 ºC);

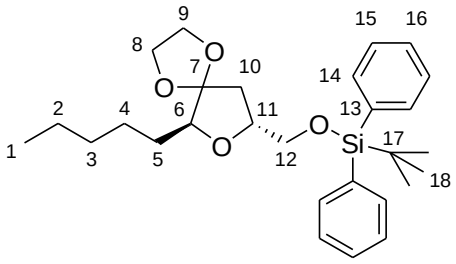
HRMS (CI/Isobutane) for $C_{10}H_{18}O_3$ ($[M+H]^+$) calculated 187.1334, found 187.1335.



(2*R*,3*S*,5*S*)-5-hydroxymethyl-2-pentyltetrahydrofuran-3-ol (323)

To a solution of ketone **322** (0.1 g, 0.5 mmol) in dry THF (4 mL) was added sodium triacetoxyborohydride (0.7 g, 3.2 mmol, 6 eq) and acetic acid (0.3 mL). The resulting white suspension was stirred at room temperature for 1 hour. Sodium potassium tartrate (saturated aq. solution, 6 mL), NH_4Cl (saturated aq. solution, 5 mL) and $NaHCO_3$ (saturated aq solution, 5 mL) were added to the suspension and the resulting colourless solution was then stirred at room temperature for 90 min. The aqueous phase was extracted with ether (3 × 5 mL) and the combined etheral extracts were dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 1:1) to give diol **323** as a colourless oil (100 mg, 0.53 mmol, 98 %).

R_f (Petroleum ether-EtOAc, 1:1) = 0.1; ν_{max} (NaCl) 3424, 1638, 483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (dddd, 1H, *J* = 9.3, 6.4, 6.4, 3.1 Hz, CH-C9), 4.25 (bs, 1H, CH-C7), 3.78 (td, 1H, *J* = 6.9, 2.8 Hz, CH-C6), 3.70 (ddd, 1H, *J* = 11.5, 6.6, 3.1 Hz, CH_2-C10), 3.48 (dt, 1H, *J* = 11.5, 6.4 Hz, CH_2-C10), 2.01 (ddd, 1H, *J* = 13.4, 6.4, 1.0 Hz, CH_2-C8), 1.92 (dd, 1H, *J* = 13.4, 9.3 Hz, CH_2-C8), 1.91 (bs, 1H, OH), 1.67-1.60 (m, 2H, CH_2-C5), 1.40-1.33 (m, 6H, CH_2-C2, C3, C4), 0.92-0.86 (m, 3H, CH_3-C1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.6 (CH-C6), 77.3 (CH-C7), 73.0 (CH-C9), 64.8 (CH_2-C10), 36.9 (CH_2-C8), 31.9 (CH_2-C5), 28.8 (CH_2), 25.9 (CH_2), 22.5 (CH_2), 13.9 (CH_3-C1);
$[\alpha]_D$ = + 26.3 (c = 1.02, $CHCl_3$, T = 24.8 ºC);
HRMS (CI/Isobutane) $C_{10}H_{21}O_3$ $[M+H]^+$ calculated 189.1491 found 189.1494.

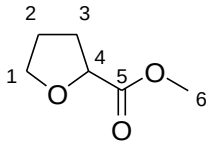


tert-Butyl-{(6*S*,8*R*)-6-pentyl-1,4,7-trioxaspiro[4]non-8-ylmethoxy}-diphenylsilane (365)

To a solution of trimethylsilyltriflate (2 μL, 0.01 mmol, 0.01 eq) in dry DCM (1.5 mL) was added 1,2-bis(trimethylsilyloxy)ethane (0.5 mg, 0.4 mL, 2.3 mmol, 1.3 eq) and ketone **306** (500 mg, 1.17 mmol) in dry DCM (2.5 mL). Reaction mixture was stirred at – 78 °C for 3 hours and left at –20 °C for 16 hours without stirring. Freshly distilled pyridine (1.5 mL) was then added to the reaction mixture at –78 °C and the reaction mixture was allowed to warm to room tempeature while stirring. EtOAc (5 mL) and $NaHCO_3$ (saturated aqueous solution, 5 mL) were added to the white suspension and the aqueous layer was extracted with EtOAc (2 × 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and solvent was removed *in vacuo*. The residue was purified by flash column chromatography on deactivated neutral alumina (petroleum ether-EtOAc, 10:1) to give protected ketone **365** as a colourless oil (280 mg, 0.6 mmol, 51 %).

R_f (Petroleum ether-EtOAc, 9:1) = 0.61; ν_{max} (NaCl) 2959, 2253, 1710, 1363, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H, CH-C14), 7.42-7.35 (m, 6H, CH-C15, C16), 4.21 (tt, 1H, *J* = 7.8, 4.7 Hz, CH-C11), 4.00-3.92 (m, 4H, CH_2-C8,C9), 3.85 (dd, 1H, *J* = 8.7, 3.6 Hz, CH-C6), 3.75 (dd, 1H, *J* = 10.6, 4.7 Hz, CH_2-C12), 3.68 (dd, 1H, *J* = 10.6, 4.7 Hz, CH_2-C12), 2.19 (dd, 1H, *J* = 12.8, 7.8 Hz, CH_2-C10), 2.10 (dd, 1H, *J* = 12.8, 7.8 Hz, CH_2-C10), 1.53-1.46 (m, 2H, CH_2-C5), 1.36-1.25 (m, 6H, CH_2-C2, C3, C4), 1.05 (s, 9H, CH_3-C18), 0.91-0.86 (m, 3H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6 (CH-C14), 135.5 (CH-C14), 133.6 (C-C13), 133.5 (C-C13), 129.5 (CH-C16), 129.5 (CH-C16), 127.6 (CH-C15), 127.5 (CH-C15), 115.4 (C-C7), 81.2 (CH-C6), 76.4 (CH-C11), 66.0 (CH_2-C12), 65.0 (CH_2-C8/9), 64.8 (CH_2-C8/9), 37.8 (CH_2-C10), 28.8 (CH_2), 28.6 (CH_2), 29.1 (CH_2), 26.7 (CH_3-C18), 22.6 (CH_2), 19.2 (C-C17), 14.1 (CH_3-C1);

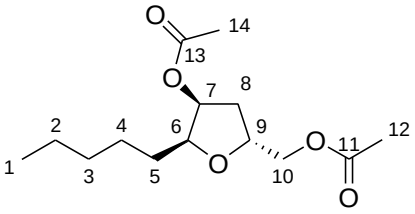
$[\alpha]_D$ = − 18.7 (c = 1.00 in $CHCl_3$, T = 25.0 °C);



Tetrahydrofuran-2-carboxylic acid methyl ester (336)

To a solution of carboxylic acid **278** (1 g, 9 mmol) in MeOH (50 mL) was added H_2SO_4 (1 drop). The reaction mixture was stirred at 65 ºC for 3 hours. The reaction mixture was then diluted with DCM (50 mL) and water (30 mL). The aqueous layer was extracted with DCM (3 × 50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 1:1) to give methyl ester **336** as a colourless oil (1.19 g, 9 mmol, quant).

R_f = 0.65 (petroleum ether-EtOAc, 1:1); ν_{max} (NaCl) 2987, 1729, 1438, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (dd, 1H, *J* = 8.2, 5.5 Hz, CH-C4), 4.01 (dt, 1H, *J* = 7.2, 7.2 Hz, CH-C1), 3.91 (dt, 1H, *J* = 7.2, 7.2 Hz, CH-C1), 3.74 (s, 3H, CH_3-C6), 2.29-2.20 (m, 1H, CH_2-C3), 2.05-1.97 (m, 1H, CH_2-C3), 1.97-1.88 (m, 2H, CH_2-C2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (C-C5), 76.6 (CH-C4), 69.3 (CH_2-C1), 52.0 (CH_3-C6), 30.1 (CH_2-C3), 25.2 (CH_2-C2);
HRMS (CI/Isobutane) for $C_6H_{11}O_3$ ($[M+H]^+$) calculated 131.0708, found 131.0706

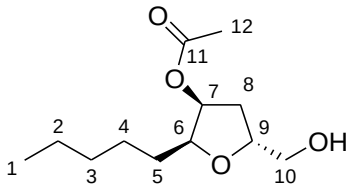


Acetic acid (2*R*,3*S*,5*S*)-5-acetoxymethyl-2-pentyltetrahydrofuran-3-yl ester (343)

To a solution of diol **323** (0.02 g, 0.07 mmol) in dry DCM (3 mL) was added freshly distilled acetic anhydride (20 μL, 0.21 mmol, 3 eq) and freshly distilled pyridine (10 μL). The colourless solution was stirred at room temperature overnight and the reaction mixture was then diluted with DCM (3 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum

ether-EtOAc, 1:1) to give doubly protected alcohol **343** as a colourless oil (0.02 g, 0.07 mmol, quant).

R_f (Petroleum ether-EtOAc, 8:2) = 0.55; ν_{max} (NaCl) 2956, 2857, 1741, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.32-5.31 (m, 1H, CH-C7), 4.42-4.35 (m, 1H, CH-C9), 4.15 (dd, 1H, *J* = 11.7, 3.4 Hz, CH_2-C10), 4.03 (dd, 1H, *J* = 11.7, 6.4 Hz, CH_2-C10), 3.95 (td, 1H, *J* = 7.0, 3.3 Hz, CH-C6), 2.12-2.05 (m, 1H, CH-C8), 2.08 (s, 3H, CH_3-C14), 2.07 (s, 3H, CH_3-C12), 1.97 (ddd, 1H, *J* = 13.9, 9.0 4.9 Hz, CH-C8), 1.58-1.48 (m, 2H, CH_2-C5), 1.34-1.24 (m, 6H, CH_2-C2, C3, C4), 0.90-0.85 (m, 3H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C-C13), 170.4 (C-C11), 81.4 (CH-C6), 74.7 (CH-C9), 74.6 (CH-C7), 66.2 (CH_2-C10), 35.5 (CH_2-C8), 31.8 (CH_2), 28.9 (CH_2-C5), 25.7 (CH_2), 22.4 (CH_2), 20.9 (CH_3-C14), 20.9 (CH_3-C12), 13.9 (CH_3-C1);
$[\alpha]_D$ = +51.2 (c = 1.00 in $CHCl_3$, T = 24.3 °C);
HRMS (CI/Isobutane) $C_{14}H_{25}O_5$ $[M+H]^+$ calculated 273.1702 found 273.1699.



Acetic acid (2*R*,3*S*,5*S*)-5-hydroxymethyl-2-pentyltetrahydrofuran-3-yl ester (344)

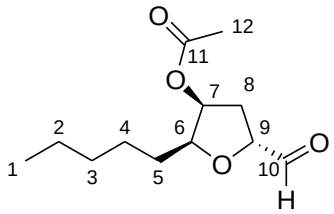
A solution of diacetate **343** (1.0 g, 3.7 mmol) was dissolved in EtOH:H_2O (10 mL, 4:1). To the colourless solution was added KOH (200 mg, 3.6 mmol, 1 eq) in one portion. Reaction mixture was stirred at 90 °C for 3 hours. Reaction mixture was then diluted with H_2O (5 mL). The aqueous layer was extracted with ether (3 × 10 mL). The combined etheral extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (Petroleum ether-EtOAc, 1:1) to give primary alcohol **344** as a colourless oil (660 mg, 2.9 mmol, 77 %).

R_f (Petroleum ether-EtOAc, 8:2) = 0.45; ν_{max} (NaCl) 3433, 3055, 2857, 1639, 1265, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (bt, 1H, *J* = 3.4 Hz, CH-C7), 4.28 (ddd, 1H, *J* = 12.0, 5.5, 3.0 Hz, CH-C9), 3.96-3.91 (m, 1H, CH-C6), 3.72 (dd, 1H, *J* = 11.8, 3.0 Hz, CH_2-C10), 3.50 (dd, 1H, *J* = 11.8, 5.5 Hz, CH_2-C10), 2.08 (s, 3H, CH_3-C12), 2.06-2.01 (m, 2H, CH_2-C8), 1.83 (s, 1H, OH), 1.58-1.51 (m, 2H, CH_2-C5), 1.40-1.25 (m, 6H, CH_2-

C2,C3,C4), 0.91-0.85 (m, 3H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (C-C11), 81.4 (CH-C6), 77.4 (CH-C9), 75.2 (CH-C7), 64.5 (CH_2-C10), 34.5 (CH_2-C8), 31.8 (CH_2), 29.1 (CH_2-C5), 25.8 (CH_2), 22.4 (CH_2), 21.0 (CH_3-C12), 13.9 (CH_3-C1);

$[\alpha]_D$ = +45.6 (c = 1.05 in $CHCl_3$, T = 24.9 °C);

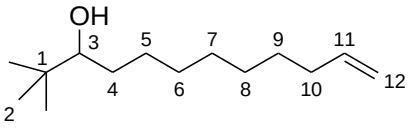
HRMS (CI/Isobutane) $C_{12}H_{23}O_4$ $[(M+H)^+]$ calculated 231.1596 found 231.1599.



Acetic acid (2*R*,3*S*,5*S*)-5-formyl-2-pentyltetrahydrofuran-3-yl ester (345)

To a solution of alcohol **344** (50 mg, 0.21 mmol) in dry DCM (2 mL) at 0 °C under Ar atmosphere, was added dry DMSO (0.15 mL, 2.1 mmol, 10 eq). Dry $^{i}Pr_2EtN$ (0.19 mL, 1.1 mmol, 5 eq) and SO_3·pyridine complex (121 mg, 0.76 mmol, 3.5 eq) were then added to the colourless solution at 0 °C. The reaction mixture was allowed to warm at room temperature and stirred for 3 hours under Ar atmosphere. The reaction mixture was quenched with sodium thiosulfate (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* and the residue was engaged in the next step without any further purification.

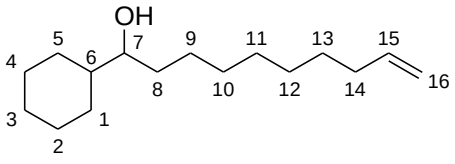
R_f (Petroleum ether–EtOAc, 8:2) = 0.28; ν_{max} (NaCl) 3488, 2980, 2875, 1775, 1726, 1460, 1257, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, 1H, *J* = 1.6 Hz, CH-C10), 5.34-5.32 (m, 1H, CH-C7), 4.47 (td, 1H, *J* = 8.3, 1.3 Hz, CH-C9), 3.93-3.88 (m, 1H, CH-C6), 2.09 (s, 3H, CH_3-C12), 1.55-1.52 (m, 2H, CH_2-C8), 1.45-1.43 (m, 2H, CH_2-C5), 1.32-1.27 (m, 6H, CH_2-C2,C3,C4), 0.91-0.86 (m, 3H, CH_3-C1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7 (CH-C10), 167.8 (C-C11), 90.0 (CH-C9), 80.7 (CH-C7), 77.2 (CH-C6), 34.6 (CH_2-C8), 23.6 (CH_2), 21.8 (CH_2), 21.6 (CH_2), 21.5 (CH_2), 19.1 (CH_3-C12), 14.0 (CH_3-C1);



2,2-Dimethyldodec-11-en-3-ol (347)

To a solution of trimethylacetaldehyde (0.2 mL, 2 mmol) in dry THF (3 mL) at – 78 °C was added dropwise 9-nonenyl-magnesium bromide in dry THF (2 eq). The reaction mixture was left to warm to 0 °C and the reaction mixture was then quenched with EtOH (5 mL). The organic layer was washed with NH_4Cl (saturated aqueous solution, 10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to give alcohol **347** as a colourless oil (311 mg, 1.5 mmol, 83%).

R_f = 0.55 (petroleum ether-EtOAc, 10:1); ν_{max} (NaCl) 3388, 2926, 2855, 1465, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, 1H, *J* = 16.9, 10.2, 6.7 Hz, CH-C11), 4.99 (ddt, 1H, *J* = 16.9, 2.1, 1.6 Hz, CH-C12), 4.93 (ddt, 1H, *J* = 10.2, 2.1, 1.2 Hz, CH-C12), 3.18 (ddd, 1H, *J* = 9.8, 5.3, 1.4 Hz, CH-C3), 2.06 (ddd, 1H, *J* = 6.7, 1.6, 1.2 Hz, CH-C10), 2.02 (ddd, 1H, *J* = 6.7, 1.6, 1.2 Hz, CH-C10), 1.56-1.21 (m, 13H, CH_2-C4, C5, C6, C7, C8, C9, OH), 0.88 (s, 9H, CH_3-C2) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2 (CH-C11), 114.1 (CH_2-C12), 79.9 (CH-C3), 34.9 (C-C1), 33.7 (CH_2-C10), 31.4 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 27.0 (CH_2), 25.6 (CH_3-C2).
Anal. calculated for $C_{14}H_{28}O$: C, 79.24%; H, 13.21%. Found: C 79.08%, H 13.44%.

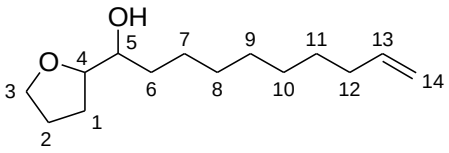


1-Cyclohexyldec-9-en-1-ol (349)

To a solution of cyclohexane carboxaldehyde (0.2 mL, 2 mmol) in dry THF (3 mL) at –78 °C was added dropwise 9-nonenyl-magnesiumbromide in dry THF (2 eq). The reaction mixture was left to warm to 0 °C and the reaction mixture was then quenched with EtOH

(5 mL). The organic layer was washed with NH_4Cl (saturated aqueous solution, 10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to give alcohol **349** as a colourless oil (269 mg, 1.1 mmol, 70%).

R_f = 0.40 (petroleum ether-EtOAc, 10:1); ν_{max} (NaCl) 3365, 2925, 1449, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dtt, 1H, *J* = 17.0, 10.2, 6.7 Hz, CH-C15), 4.99 (ddd, 1H, *J* = 17.0, 2.3, 1.2 Hz, CH_2-C16), 4.93 (ddd, 1H, *J* = 10.2, 2.3, 1.2 Hz, CH_2-C16), 3.34 (bs, 1H, CH-C7), 2.05 (bdd, 1H, *J* = 6.7, 1.2 Hz, CH-C13), 2.02 (bd, 1H, *J* = 6.7 Hz, CH-C13), 1.80 (s, 1H, OH), 1.77-1.73 (m, 2H, CH_2-cyclohexane), 1.67-1.63 (m, 2H, CH_2-cyclohexane), 1.47-1.43 (m, 2H, CH_2-cyclohexane), 1.37-1.27 (m, 12H, CH_2-C8, C9, C10, C11, C12, C13), 1.23-0.98 (m, 5H, CH_2-cyclohexane); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2 (CH-C15), 114.1 (CH_2-C16), 76.2 (CH-C7), 43.5 (CH_2), 34.1 (CH_2), 33.7 (CH-C6), 29.6 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 27.6 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 25.9 (CH_2);
Anal. calculated for $C_{16}H_{30}O$: C, 80.61%; H, 12.68%. Found: C 80.61%, H 12.76%.



1-(Tetrahydrofuran-2-yl)dec-9-en-1-ol (351)

To a solution of tetrahydrofurfuryl alcohol (0.2 g, 0.16 mL, 1.6 mmol) in dry DCM (10 mL) was added dry DMSO (1.0 mL, 14 mmol, 8.6 eq) and dry DIPEA (1.4 mL, 8.2 mmol, 5 eq). The reaction mixture was cooled down to 0 °C and SO_3·pyridine complex (0.9 g, 6 mmol, 3.5 eq) was added in one portion. The reaction mixture was then stirred at room temperature for 3 hours under Ar atmosphere. The suspension was quenched with an aqueous saturated solution of sodium thiosulfate (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the aldegyde **350** which was used in the next step without any further purification.
To a solution of tetrahydrofuran-2-carbaldehyde **350** (163 mg, 1.63 mmol) in dry THF (3 mL) at –78 °C was added dropwise, freshly prepared 9-nonenylmagnesium bromide (3.2

mmol, 2 eq) in dry THF (2.5 mL). The reaction mixture was then left to warm to 0 °C. At this point, EtOH (5 mL) was added to the reaction mixture and the organic phase was washed with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 10:1) to give alcohol **351** as a colourless oil (250 mg, 68 %).

R_f = 0.37 (petroleum ether-EtOAc, 8:2); ν_{max} (NaCl) 3435, 2926, 1462, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddt, 1H, *J* = 16.9, 10.2, 6.7 Hz, CH-C13), 4.99 (bddd, 1H, *J* = 16.9, 3.7, 1.6 Hz, CH_2-C14), 4.92 (dtd, 1H, *J* = 10.2, 2.1, 1.6 Hz, CH_2-C14), 3.89 (dt, 1H, *J* = 8.2, 6.6 Hz, CH_2-C3), 3.81 (dt, 1H, *J* = 8.2, 1.5 Hz, CH_2-C3), 3.81-3.75 (m, 1H, CH-C5), 3.75-3.61 (m, 1H, CH-C4), 2.05-2.00 (m, 2H, CH_2-C12), 1.93-1.86 (m, 2H, CH_2-C2), 1.63-1.47 (m, 2H, CH_2), 1.44-1.25 (m, 12H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (CH-C13), 114.1 (CH_2-C14), 73.9 (CH-C4), 71.8 (CH-C5), 68.5 (CH_2-C3), 33.7 (CH_2-C12), 29.6 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 26.1 (CH_2-C2), 25.9 (CH_2-C1), 25.6 (CH_2-C11), 24.3 (CH_2-C6);
HRMS (CI/Isobutane) $C_{14}H_{27}O_2$ [$(M+H)^+$] calculated 227.2011 found 227.2015.

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