Synthesis of Six- and Seven-Membered Cyclic Ethers by Ring-Closing Metathesis And Synthesis of the A-D Fragment of Gambieric Acid A

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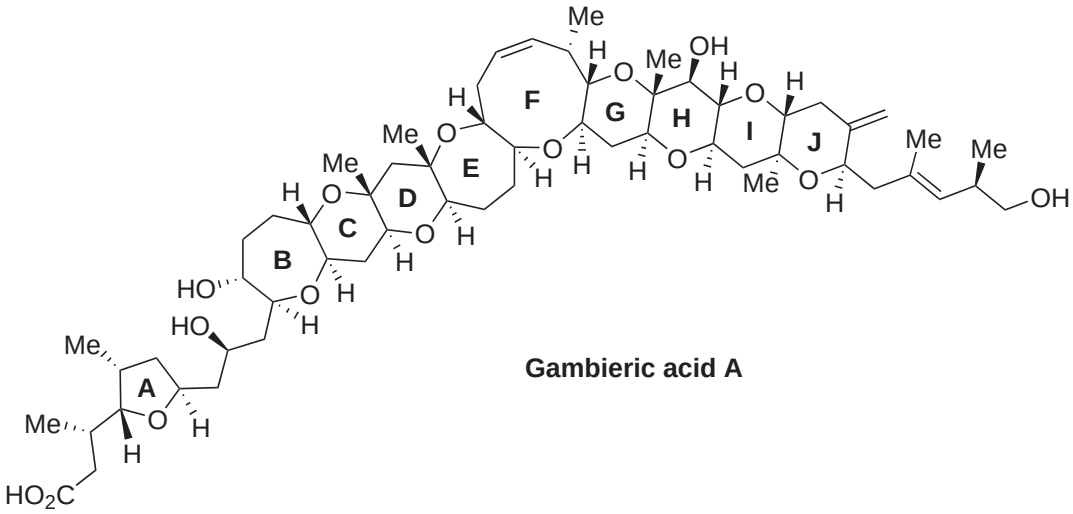
Abstract

Over the past thirty years, numerous fused polycyclic ether natural products have been isolated from small marine organisms. These compounds revealed a variety of interesting biological properties, which has attracted the interest of many synthetic groups. The common structural characteristic of these compounds is an array of *trans*-fused ether rings. Several iterative strategies have been reported to build six- and seven-membered cyclic ethers, which are the two most common units in these natural products.

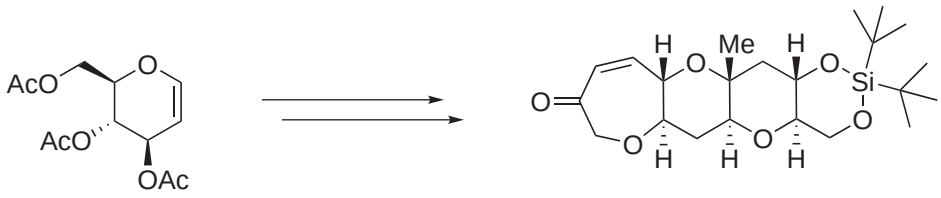
The objective of work described in the first part of this thesis was to develop new synthetic methodology to access these motifs. Each unit must be built in the minimum number of steps and the new methodology must be flexible enough to obtain both six- and seven-membered rings from a common precursor. They key reaction of the strategy will be ring-closing metathesis, as previous work in our group showed that this is a powerful reaction to create cyclic ethers.

The second part of this thesis focus on the total synthesis of one of the marine polyether natural products, gambieric acid A. This compound was isolated in 1992 and has so far eluded total synthesis.

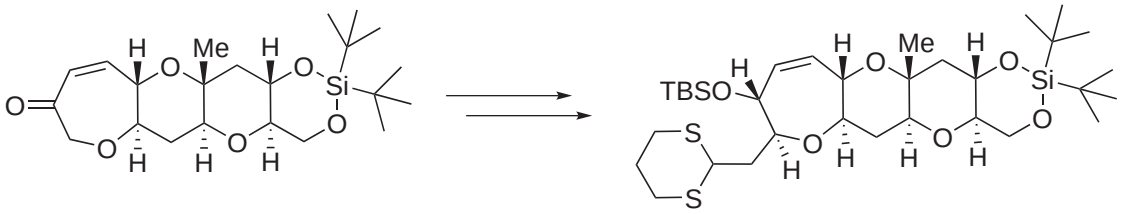


Gambieric acid A

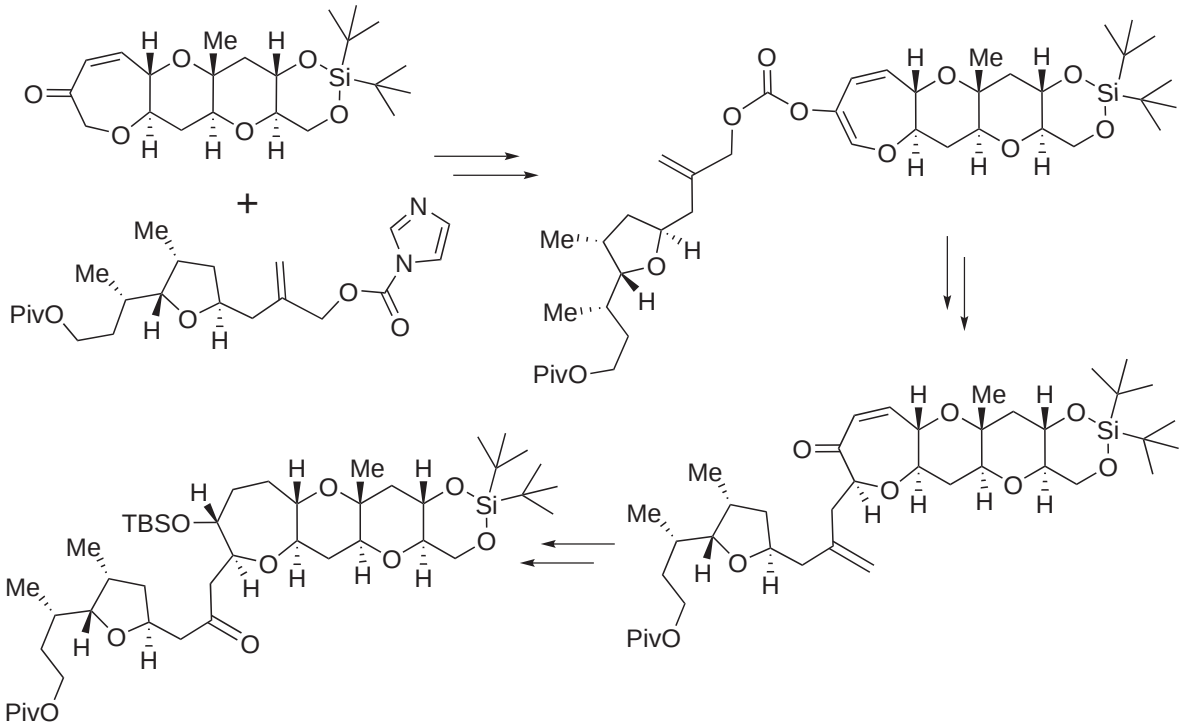
First, the synthesis of the tricyclic B-D core, which has been developed in our group, was optimised and performed on a large scale. The synthetic route relies on the ring-closing metathesis reaction to construct two of the cyclic ethers from a commercially available glucose derivative.



Several strategies for the coupling with the tetrahydrofuran A ring were then investigated. The initial method envisioned for the fragment coupling was a nucleophilic substitution of an alkyl iodide by a lithiated dithiane.



However, this strategy revealed unsuccessful. Instead, a more converging approach using a diastereoselective Tsuji reaction was developed, which allowed the formation of the complete carbon skeleton of the A-D fragment.



Acknowledgements

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Finally, I would like to thank all my friends, especially Cecilia, for their everyday help and support.

Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is concurrently submitted, in candidature for any other degree.

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

Bora Sieng

Prof. J. Stephen Clark

List of Abbreviations

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobis(2-methylpropionitrile)
aq	aqueous
Arom	aromatic
Bn	benzyl
br	broad
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting material
Bu	butyl
CBz/Z	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
CM	cross-metathesis
CSA	camphorsulfonic acid
d	doublet
dba	*E,E*-dibenzylideneacetone
DBU	1,8-diazobicyclo-[5,4,0]-undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
decomp.	decomposition
DET	diethyltartrate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	di-*iso*-propyl azodicarboxylate
DIBAL-H	di-*iso*-butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMEDA	*N,N'*-dimethylethylenediamine
DMF	*N,N*-dimethylformamide
DMM	dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
h	hour(s)
HOBt	1-hydroxybenzotriazole

HRMS	high resolution mass spectrometry
isom.	isomerisation
LDA	lithium di-*iso*-propylamide
LiHMDS	lithium bis(trimethylsilyl)amide
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
Mes	1,3,5-trimethylbenzyl
min	minutes
ML_n	metal and associated ligands
MOM	methoxymethyl
Ms	methanesulfonyl
n	normal
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NOE	nuclear overhauser effect
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
o/n	overnight
PE	petroleum ether (40-60 °C)
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
P	protecting group
Pr	propyl
quant.	quantitative
RCEM	ring-closing enyne metathesis
RCM	ring-closing metathesis
rt	room temperature
t	*tert*
TBAF	tetra-*normal*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
tfacac	trifluoroacetylacetonate
THF	tetrahydrofuran
Thx	thexyl
TIPS	tri-*iso*-propylsilyl

TLC	thin layer chromatography
TMS	trimethylsilyl
TMTU	tetramethylthiourea
TPAP	tetra-*n*-propylammoniumperruthenate
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
Ts	*para*-toluenesulfonyl

Contents

Chapter 1

Introduction

1.1 Polyoxacyclic Natural Products

1.1.1 Red Tides

A red tide, or algal bloom, is a natural phenomenon occurring in coastal waters, where under specific conditions (temperature, salinity and nutrients), microorganisms such as algae, can grow very quickly and results in discolouration of the surface water. Among all the algal species responsible for these blooms, a few of them are toxic. The most important species are members of the dinoflagellate family, especially *Karenia brevis*, which is responsible for the 'Florida red tide', and *Alexandrium fundyense*, which can be found along the Northern East coast of the United States. They usually produce toxins that affect the central nervous system of fish and often result in numerous deaths.[1]

The red tide phenomenon is not very well understood, especially the exact conditions required for it to start. However, high temperatures combined with a lack of wind and rainfall could be at the root of red tides. When nutrients are abundant in the environment, the algae grow by simple cell division, a quick process which allows a single mother cell to generate hundreds of progeny. These tides can be spread over large areas and can have dramatic effects on the local environment. Even non-toxic algae can harm the local ecosystem by depriving it of light, oxygen and nutrients. Humans are barely affected, but some cases of respiratory irritation have been reported by individuals when a strong coastal wind has transported the microorganisms.

When nutrients are rare, the microorganisms are able to switch to sexual reproduction and create dormant cells called cysts that settle to the bottom sediments. These cysts can survive for many years in harsh conditions until suitable conditions reappear.

Although these events are mainly natural, human activities can influence their frequency, especially through agriculture and water pollution, by providing nutrients such

as phosphates and nitrates to algae, thus stimulating the appearance of red tides.

1.1.2 Marine toxins: Brevetoxins, Gambieric Acids and Others

In order to gain a better understanding of red tide events, scientists managed to isolate various metabolites from the algae. Several families of compounds have been identified such as tetrodotoxin, saxitoxin or palytoxin and they all possess very specific and potent pharmacological activities.[2] However, polycyclic ethers are one of the most impressive classes of these metabolites. Brevetoxins A and B were first discovered in the early 80's.[3] Later, similar compounds such as ciguatoxins,[1,4] gambieric acids,[5,6] yessotoxins,[7] maitotoxin[8–10] and the gymnocins[11,12] were identified (Figure 1.1).

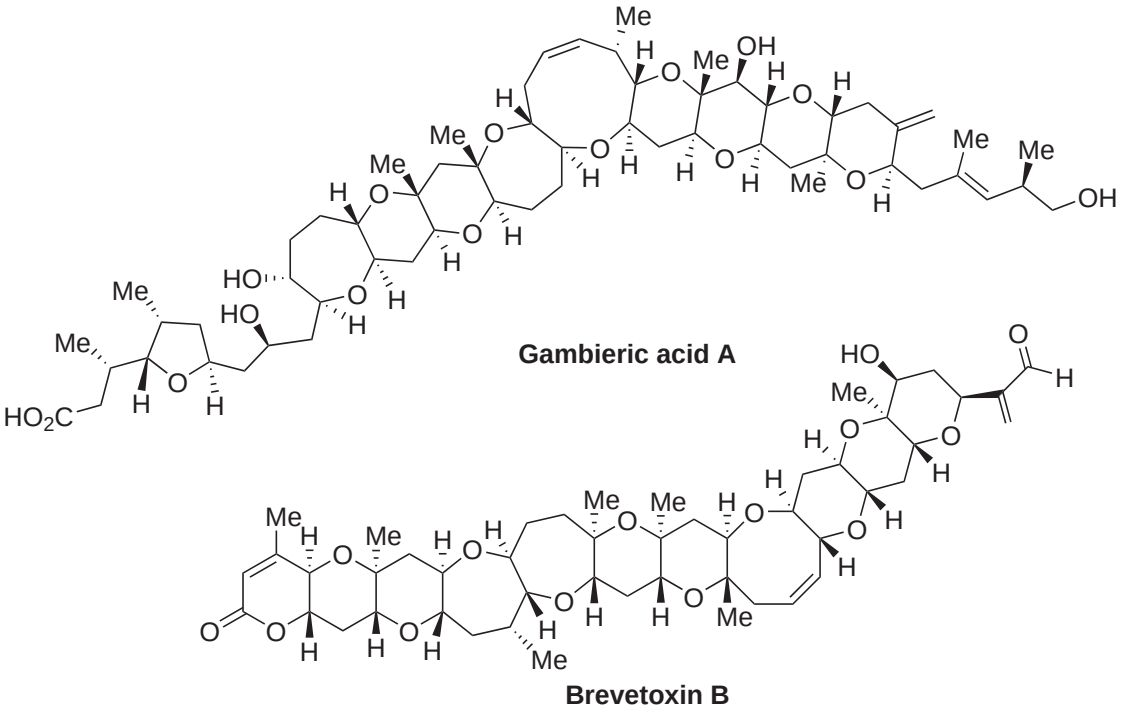
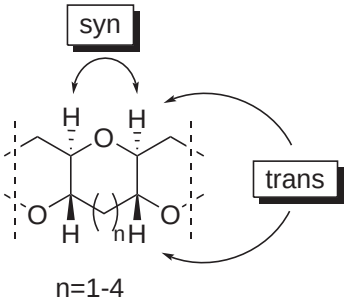


Figure 1.1: Brevetoxin B and Gambieric acid A

All these compounds contain arrays of *trans*-fused cyclic ethers, in which the ring size may vary between five and nine members. The oxygens are placed alternatively on the northern and southern edge of the ring system. The strereochemistry of the carbon atoms adjacent to the oxygen strictly alternates between R and S (Scheme 1.1).



Scheme 1.1: General representation of polycyclic ethers

Finally, it shall be noted that the marine polycyclic ethers usually contain eight- or nine-membered rings in the central regions and six- or seven-membered rings at the periphery.

1.1.3 Toxicology

Although structurally similar, polycyclic ethers display diverse biological activities. For example, brevetoxins are known to be responsible for mass fish deaths during red tides, but recent research has shown that certain fish and seagrass actually accumulate high concentrations of brevetoxins. These species could act as toxin vectors in unusual marine animal mortalities, even in the absence of the toxin-producing algae.[13] Ciguatoxins, on the other hand, are known to be the causative agents of ciguatera poisoning[4] and the yessotoxins have been implicated in outbreaks of diarrhetic shellfish poisoning.[7]

Brevetoxins are highly neurotoxic and the voltage-gated sodium channels of excitable membranes have been identified as their biological target. The molecules can bind to the α-subunit of the sodium channel which results in a conformational change in the channel, stabilising and maintaining its disposition in an open/pre-open state.[14] This prevents the sodium/potassium exchange pump from restoring the resting potential across the membrane, which eventually leads to permanent depolarisation.

Toxicological studies have shown that molecular size is an important factor in the potency of the brevetoxins.[15,16] This accounts for the low toxicity of hemibrevetoxin B, which contains only four rings and has a molecular weight of 490, and the greater toxicity of brevetoxin A (10 rings, MW = 867 g.mol^{-1}) (Figure 1.2). Computational studies have also indicated that the hydrophobicity of polycyclic ethers is an important factor in their bioactivity, the most hydrophobic being the most potent.[16]

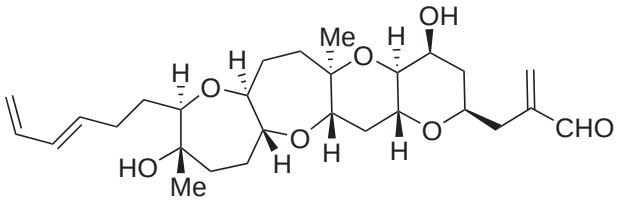
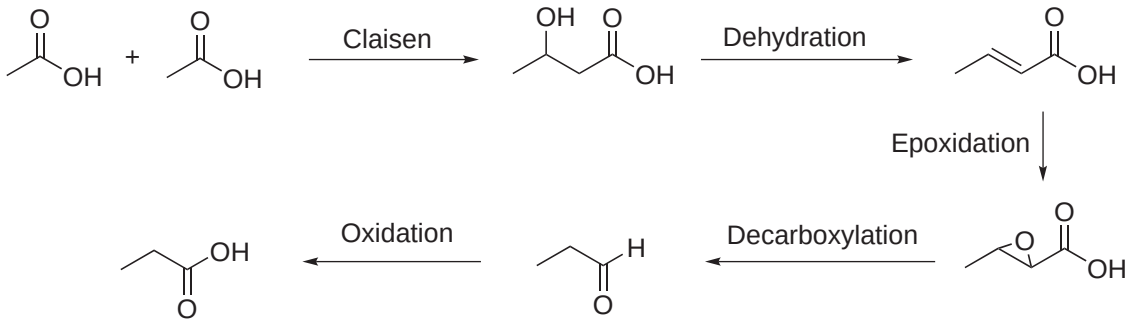


Figure 1.2: Hemibrevetoxin B

1.1.4 Biosynthesis

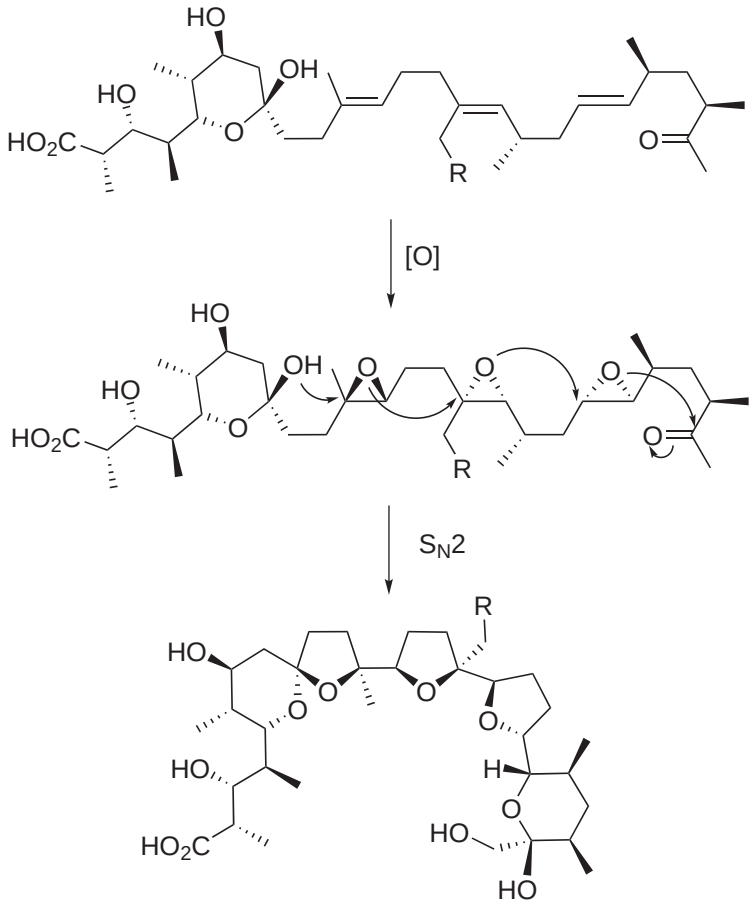
Since these molecules have been discovered, several models have been proposed to explain their biosynthesis. The carbon backbone was initially thought to be built through the standard polyketide pathway, using linear Claisen-type condensations of acetate units.[17–19] However, ^{13}C-labelled studies showed that some carboxyl-derived carbons were missing in the carbon skeleton, and this was explained by a mixed polyketide synthesis. It was thought that the microorganisms could use dicarboxylic acids, generated by the citric acid cycle. The carbon chain would then be produced exactly as in a normal polyketide synthesis but the elongation process might occur *via* a modified fatty acid synthesis. Later, Shimizu proposed another origin of the longer chains present in the skeleton.[20] After a standard Claisen condensation of two acetate units followed by β-elimination, the α,β-unsaturated carboxylic acid could be epoxidised to give the corresponding glycinic acid, which could afford, after decarboxylation, the aldehyde with one less carbon or the corresponding carboxylic acid, if this last step occurs in an oxidative manner (Scheme 1.2).



Scheme 1.2: Formation of propionic acid from acetic acid

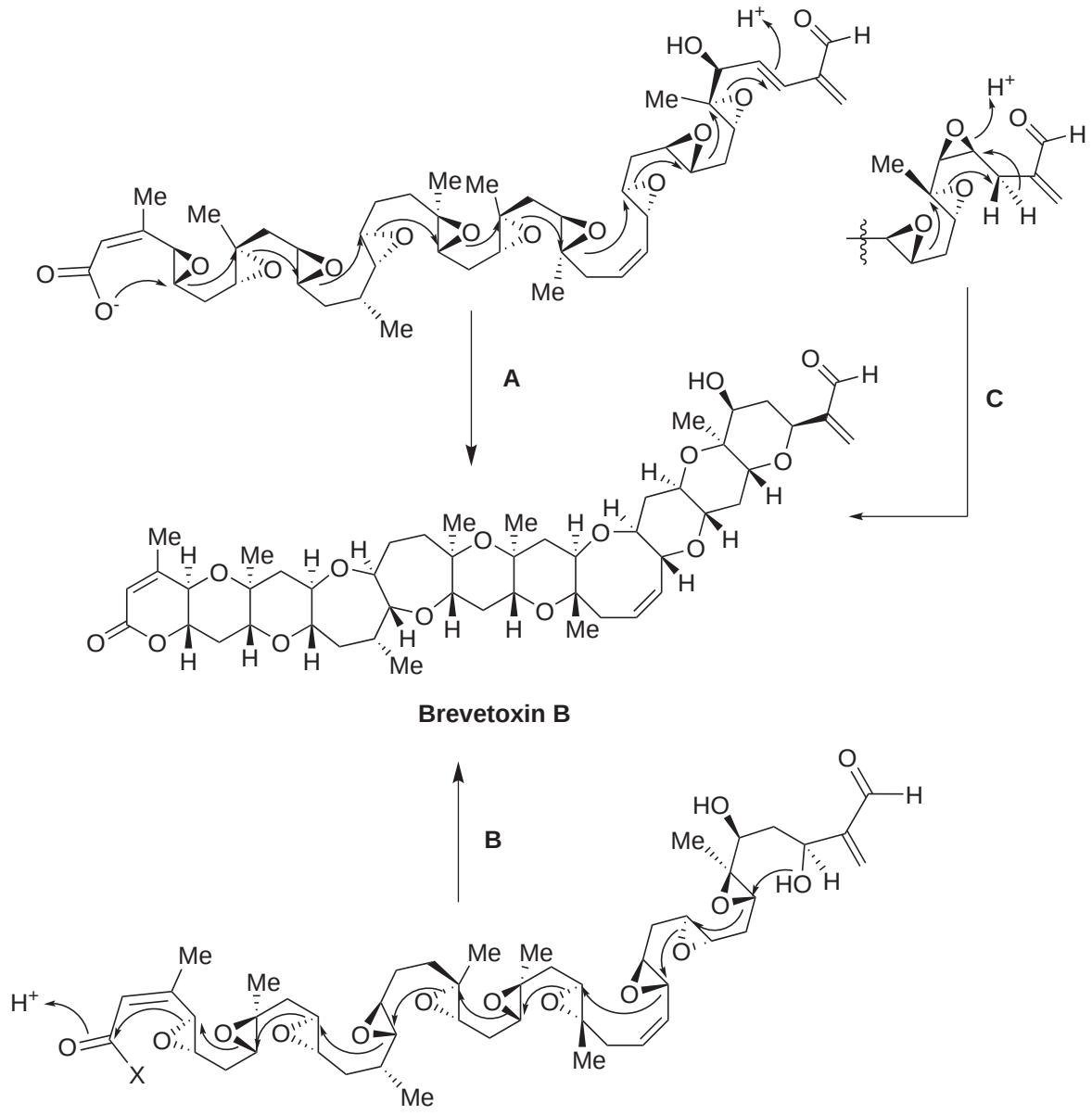
Once the carbon backbone was created, hypotheses regarding the formation of the ether rings were suggested. The first hypotheses were based on a report by Cane, Celmer and Westley, who studied the biosynthesis of monensin, a polyether ionophore antibiotic isolated from *Streptomyces cinnamonensis*.[21,22] They suggested that mon-

ensin could be obtained from a triene intermediate, which would be epoxidised and cyclised in a cascade of S_N2 epoxide opening reactions (Scheme 1.3).



Scheme 1.3: Biosynthesis of monensin by epoxide openings

Nakanishi first proposed that brevetoxin B could be formed by successive ring closure of the poly-epoxide precursor, which would be initiated by the attack of the carboxylate anion of the left terminal acid and the acidic activation of the right terminal alkene (pathway A, Scheme 1.4).[23] An alternative model proposed by Shimizu used the same poly-epoxide precursor but the right terminal double bond was changed into a secondary alcohol. The cyclisation cascade then started with the attack of this alcohol to the closest epoxide and the activation of the left terminal carboxylic acid (pathway B, Scheme 1.4).[24] The propagation was then identical as pathway A, but was occurring in the opposite direction. After the discovery of hemibrevetoxin B, Shimizu proposed a slightly different mechanism, where the starting point of the cyclisation would be the opening of the *cis*-epoxide followed by a hydride ion transfer and consecutive *trans*-epoxide openings (pathway C).[25]

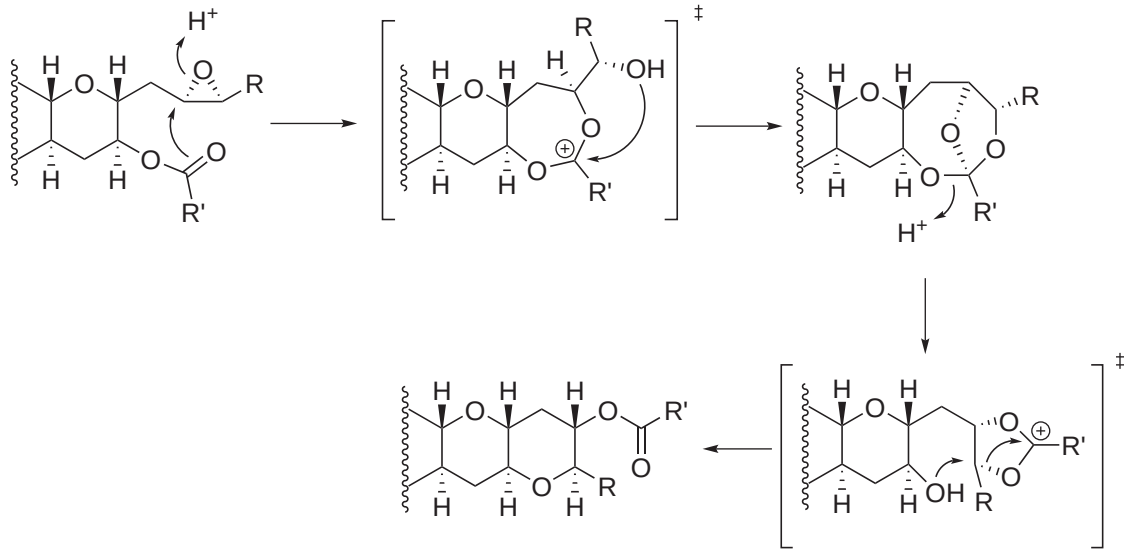


Scheme 1.4: Hypotheses for the biosynthesis of brevetoxin B

Recently, these mechanisms have been questioned by Gallimore and Spencer.[26] The direct application of the Cane-Celmer-Westley model to the brevetoxin family is not fully satisfactory, especially concerning the cyclisation process. In the original monensin model, the three cyclisation reactions occur in a favoured *exo*-tet S_N2 fashion. However, when this is applied to the brevetoxins, the ring-closing operation is a disfavored *endo*-tet manner, violating Baldwin's rules.[27]

At the same time, Giner proposed another model for the cyclisation process, based on the rearrangement of an epoxy-ester obtained from a *cis* alkene.[28] Under acidic conditions, the ester would open the epoxide to form an intermediate cation, which would form a bicyclic orthoester (Scheme 1.5). Subsequent rearrangement would lead

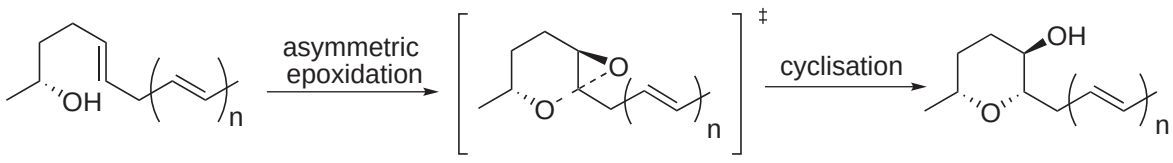
to the cyclic ether.



Scheme 1.5: Epoxy-ester pathway for tetrahydropyrans formation

This model has the advantage that the acyclic precursor requires only *cis*-double bonds, whereas the Nakanishi model requires that there be a mixture of *trans*-alkenes to generate the cyclic ethers in addition to the *cis*-alkenes present in brevetoxin B. However, Giner never managed to obtain the six-membered ring selectively during the cyclisation process, and only obtained a 1:1 mixture of five- and six-membered products.

Finally, the group of Janda proposed a simpler route to the polyether system.[29,30] They managed to direct the *endo* cyclisation of an hydroxy epoxide using a "catalytic antibody" that mimics the *endo*-transition state and modifies the energy balance in favour of the *endo*-cyclisation. A similar biological tool could be a monooxygenase enzyme that epoxidises the double bond and maintains the hydroxy epoxide system in such a manner that the *endo*-pathway would be preferred to the *exo*. Once the product is released, the enzyme can move to the next double bond (Scheme 1.6).



Scheme 1.6: Enzymatic route to polyethers

1.2 Synthesis of Polycyclic Ethers

Because of their highly complex chemical structures and interesting biological properties, the polycyclic ethers have attracted the interest of many synthetic groups. These efforts have culminated in the total synthesis of several members of the marine polyether class, such as brevetoxins A[31] and B,[32–34] ciguatoxin CTX-3C,[35] gambierol,[36–38] gymnocin-A[39,40] and brevenal.[41]

These complex syntheses have been achieved by two different strategies. The most common and, so far, most effective is a convergent approach where small cyclic units are built separately and coupled together to form larger fragments of the natural product. This approach has been applied in all the synthesis mentioned above. The second one is an iterative approach, whereby all the rings are built successively using the same basic reaction. A flexible methodology is required to accomodate the different ring sizes and substitution patterns. The concept is simple and attractive but, so far, it has mainly been successfully applied to the smallest polycyclic ether, hemibrevetoxin B[42–44] or small polycyclic sub-units. Very recently, a total synthesis of gambierol was reported by Mori and co-workers which is the first total synthesis based on an iterative approach.[45]

Detailed reviews of all iterative methodologies for the preparation of polycyclic ethers have been published previously.[46,47] The following section details the major advances made in this field over the past fifteen years.

1.2.1 Recent Progress in the Iterative Synthesis of Polycyclic Ethers

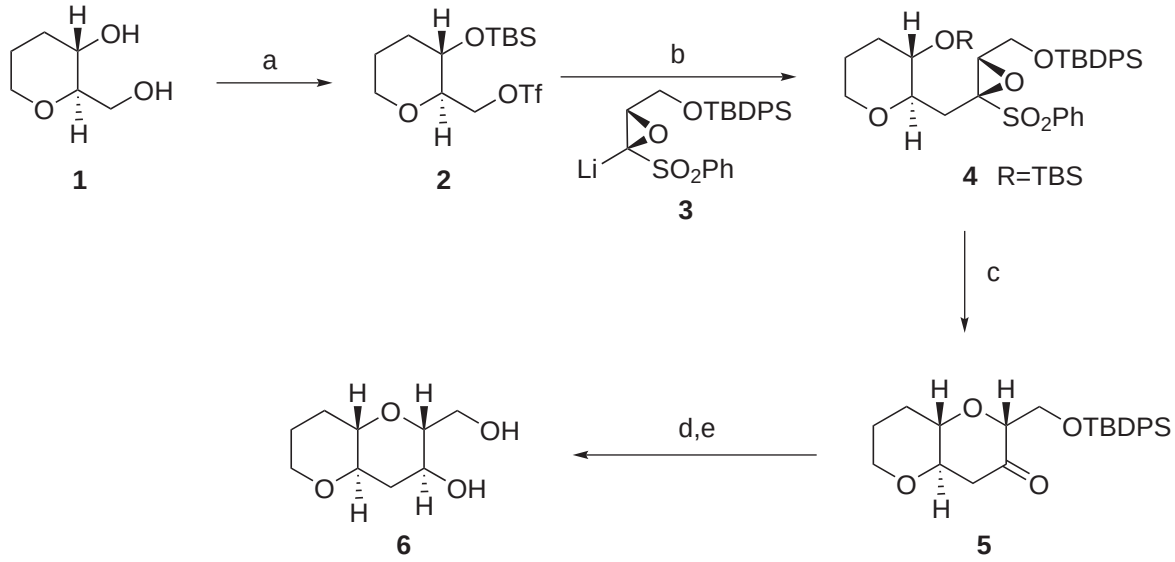
For the iterative synthesis of the marine polyether family of compounds, two main classes of reaction can be defined, depending on a carbon-oxygen or a carbon-carbon bond is formed during the cyclisation process.

C-O Bond Formation

- *6-endo Cyclisation of Epoxysulfones*

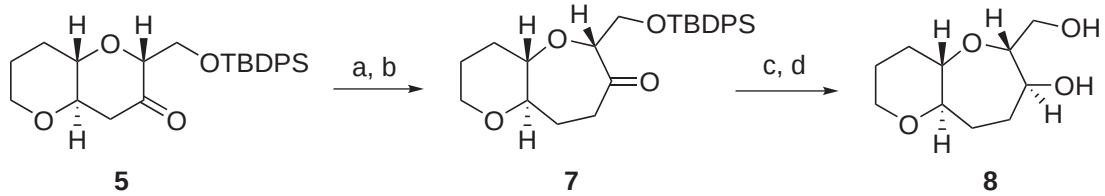
Mori and co-workers have developed an iterative strategy for polycyclic ether synthesis based on an epoxide opening reaction, which is outlined in Scheme 1.7.[48] Diol **1** was converted into triflate **2** in 93% yield. Nucleophilic addition of oxiranyl-lithium **3** to triflate **2** created the carbon backbone **4** and installed the oxygen atom required for the formation of the next ether ring. Subsequent deprotection of secondary hydroxyl group under acidic conditions induced an exclusive 6-*endo*-cyclisation with concomitant elimination of phenylsulfinic acid to give ketone **5** in 80% yield. The electron-withdrawing

nature of the sulfone promotes the cyclisation reaction, which is normally disfavoured according to Baldwin's rule.[27] Stereoselective reduction of ketone with sodium borohydride and deprotection of primary silyl ether gave diol **6** in 91% yield. This method has also been applied to systems bearing axial methyl groups and 1,3-diaxial methyl groups.[49,50]



Scheme 1.7: Conditions: a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C then TBSOTf, −78 °C to 0 °C, 93%; b) DMPU, THF, −100 °C, 90%; c) *p*-TsOH·H_2O, $CHCl_3$, 55 °C, 80%; d) $NaBH_4$, MeOH:CH_2Cl_2, −78 °C; e) TBAF, THF, rt, 91% (2 steps).

The direct formation of oxepanes was circumvented by employing a ring-expansion reaction of tetrahydropyranones.[51] When ketone **5** was treated with trimethylsilyldiazomethane under Lewis acid conditions followed by *in situ* silyl enol ether hydrolysis, oxepane **7** was obtained in 76% yield (Scheme 1.8). Further deprotection and a hydroxy-directed reduction afforded diol **8** in quantitative yield.



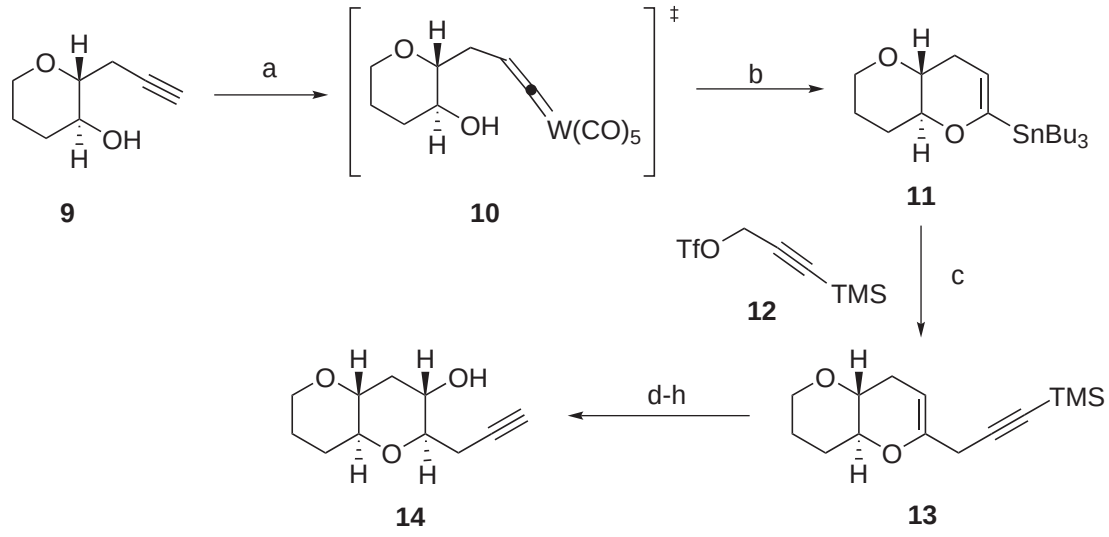
Scheme 1.8: Conditions: a) $TMSCHN_2$, BF_3·Et_2O, CH_2Cl_2, −78 °C; b) PPTS, MeOH, rt, 76% (2 steps); c) TBAF, THF:AcOH, rt; d) $Me_4NBH(OAc)_3$, MeCN, AcOH, −20 °C to rt, 99% (2 steps).

This approach gave access to the simplest six-membered ring in five steps and an overall yield of 61%. This method also allows the installation of angular methyl groups and the access to oxepane rings by a one-carbon ring expansion of tetrahydropyranones.

Mori used this methodology to complete a formal total synthesis of hemibrevetoxin B.[43] More recently, they prepared the ABCDEF core of the yessotoxins,[52] the ABCD fragment of gambierol[53] and finally reported the total synthesis of gambierol using this methodology.[45]

- *6-endo Cyclisation of Tungsten Vinylidene*

McDonald and Bowman have developed an iterative synthesis of polycyclic ethers based on the 6-*endo* cyclisation of a tungsten vinylidene intermediate.[54] Treatment of hydroxy-alkyne **9** with a photo-generated solution of $[W(CO)_5(THF)]$[55] afforded the tungsten vinylidene intermediate **10** (Scheme 1.9). Subsequent stannylation with tributyltin triflate and triethylamine[56] gave the tin-substituted cyclic enol ether **11** in 60% yield. Tin-lithium exchange, followed by addition of copper cyanide formed a high-order cyanocuprate, which displaced triflate **12** to give silyl protected acetylene **13** in 54% yield. Epoxidation and subsequent reduction of the resulting mixed acetal gave an inseparable 3:1 mixture of diastereomers in favour of the desired *trans*-isomer. Deprotection of the alkyne and acetylation of the free hydroxyl group gave the acetate derivative. The diastereoisomers were then separated by flash column chromatography and subsequent removal of the acetate group gave hydroxy-alkene **14** as a single isomer.



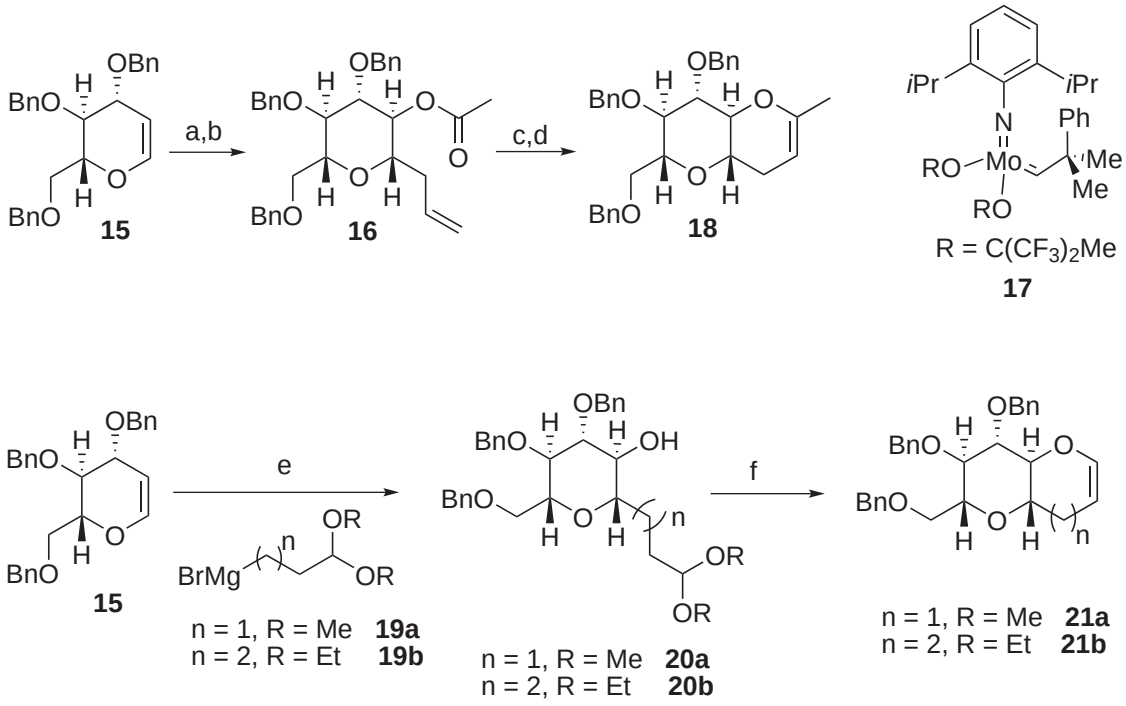
Scheme 1.9: Conditions: a) $W(CO)_6$, THF, hν, rt; b) Bu_3SnOTf, Et_3N, Et_2O, 60%; c) *n*BuLi, CuCN, THF, −78 °C then **12**, −78 °C to 0 °C, 54%; d) *m*CPBA, MeOH, 0 °C; e) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −50 °C to 0 °C; f) TBAF, THF, rt; g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; h) K_2CO_3, MeOH:H_2O, rt, 40% (5 steps).

This method requires seven steps per iteration in an overall yield of 10%. The main problem with this sequence is obviously the poor diastereoselectivity during epoxidation

of the enol ether **13** which means that an additional two-step procedure is required to remove the undesired diastereomer. Incorporation of angular methyl groups and synthesis of larger size rings have not been reported with this methodology.

- *Acid-Mediated Annulation and RCM (C-O and C-C Bond Formation)*

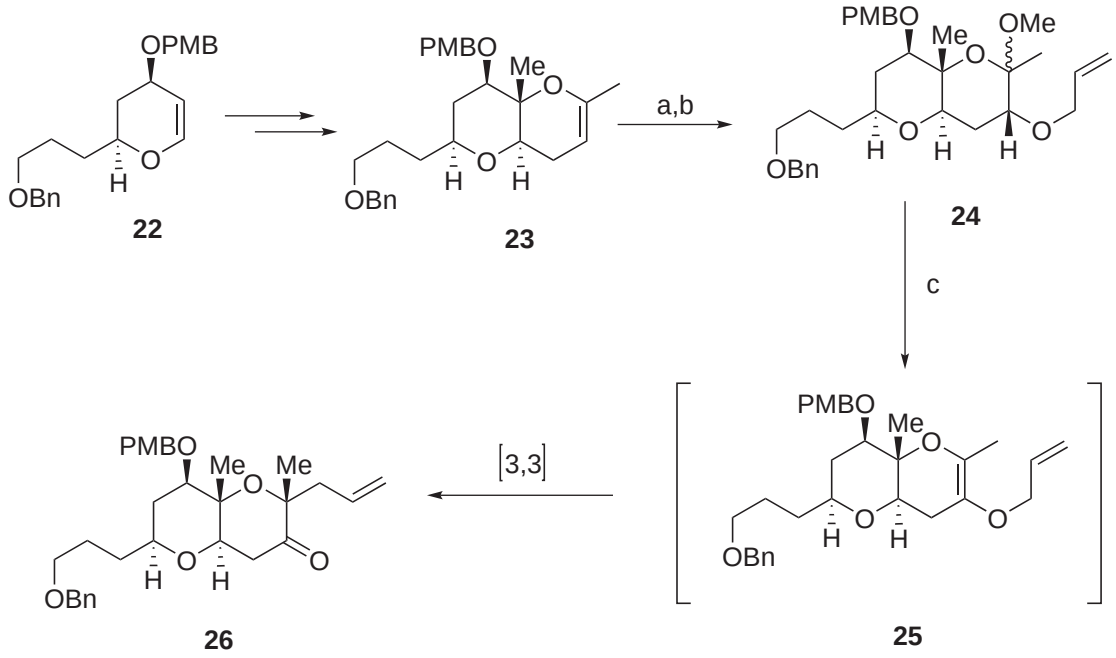
Rainier and co-workers have developed two closely related iterative approaches based on the formation and functionalisation of enol ethers. One method employs a ring-closing metathesis (RCM) reaction[57–59] and the other an acid mediated cyclisation/elimination event to accomplish both ring closure and enol ether formation.[59,60] Starting with glucal **15**, both strategies share a one-pot epoxidation/alkylation protocol, which installs the carbon backbone and the bridgehead stereocentres, to afford **16** and **20a,b** (Scheme 1.10). Takai methylenation[61] of acetate **16** and subsequent RCM with molybdenum catalyst **17** gave the desired methyl substituted cyclic enol ether **18** in 50% overall yield. Use of the corresponding formate ester, to prepare unsubstituted enol ethers, resulted in low yields from the Takai methylenation reaction. Otherwise, heating acetals **20a,b** in the presence of PPTS effected ring closure and elimination to provide cyclic enol ethers **21a,b** in high yield.



Scheme 1.10: Conditions: a) DMDO, CH_2Cl_2 then allylmagnesium bromide, THF, 0 °C; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 77% (2 steps); c) CH_2Br_2, Zn, $TiCl_4$, $PbCl_2$, TMEDA, THF, 65 °C, 65%; d) catalyst **17** (15 mol%), hexanes, 76%; e) DMDO, CH_2Cl_2 then **19a/19b**, CuI, THF, −30 °C to 0 °C, 54% (n=1), 65% (n=2); f) PPTS, pyridine, dichlorobenzene, 140 °C, 91% (n=1), 72% (n=2).

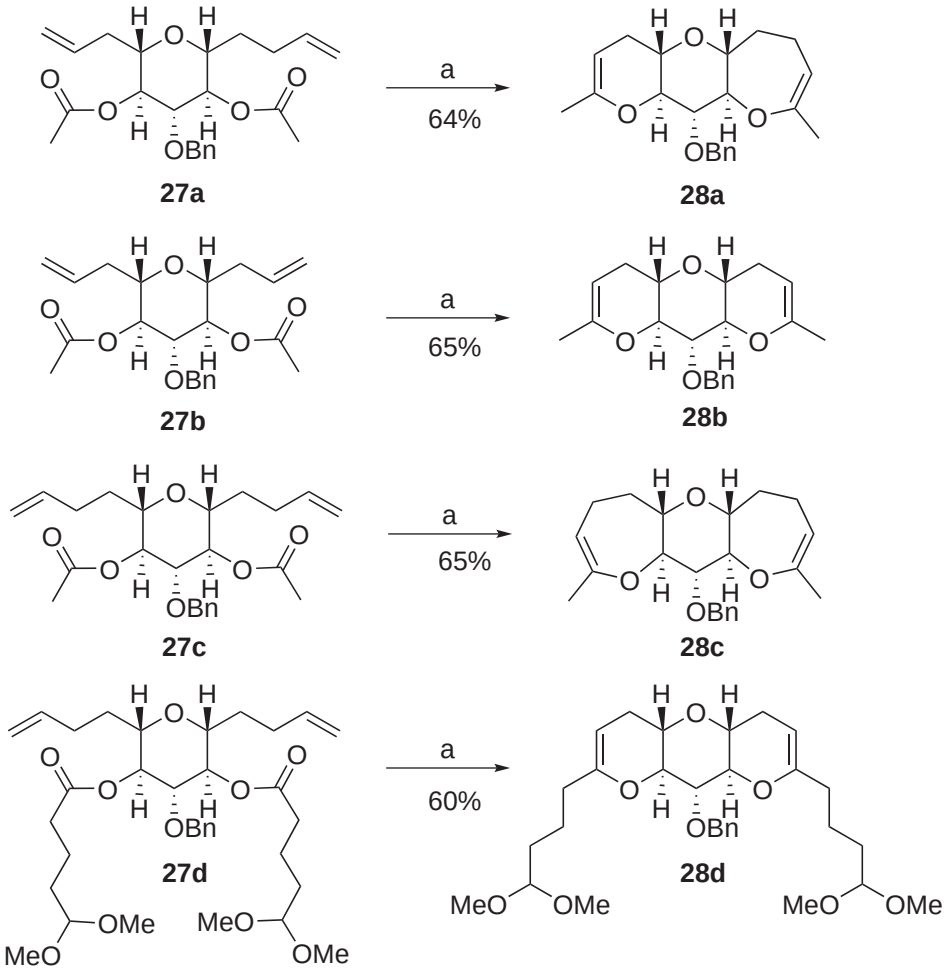
The acid-mediated cyclisation strategy allows the iterative synthesis of both six- and seven-membered ring systems in three steps and in 46% and 47% yield respectively. However, this method does not permit the preparation of substituted cyclic enol ethers. The metathesis approach is slightly longer than the acid cyclisation (five steps) but allows the formation of tri- and tetra-substituted enol ethers.[62]

Rainier and Cox have applied their methodologies to the formal total synthesis of hemibrevetoxin B[44,63] and the synthesis of the ABCD ring system of gambierol.[64] This segment contains the challenging 1,3-diaxial methyl groups. Enol ether **23** was prepared from dihydropyran **22** using the methodology described previously (Scheme 1.11). Epoxidation of **23** and ring-opening with methanol, followed by *O*-allylation furnished acetal **24**. Treatment of **24** with PPTS in pyridine delivered the enol ether intermediate **25** which underwent an *in situ* Claisen rearrangement to deliver ketone **26** with the two methyl groups installed.



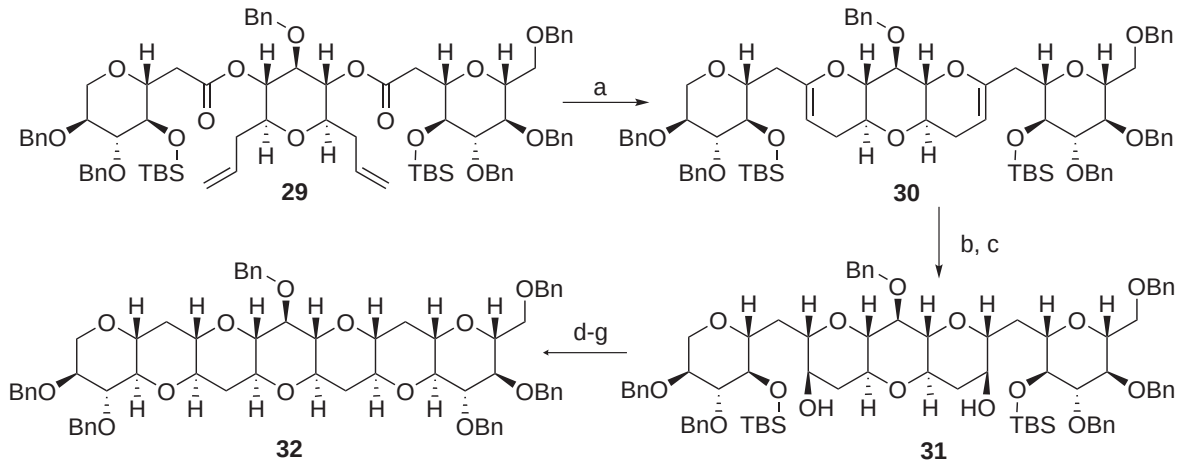
Scheme 1.11: Conditions: a) *m*CPBA, MeOH, −60 °C to rt, 92%; b) NaH, allylbromide, THF, reflux, 78%; c) PPTS, pyridine, 100 °C, 97% (*d.r.* = 8:1).

Recently, Rainier and co-workers reported a two-directional approach based on a modified Takai-Ukimoto protocol.[65] During their synthetic studies towards gambieric acid A, they found that using dibromoethane instead of dibromomethane gave the cyclised adduct as the major product.[66] Applying these conditions to a variety of dienyl diesters **27a-d** gave access to the corresponding tricyclic products **28a-d** in good yields (Scheme 1.12). Six- and seven-membered rings possessing a simple methyl group or a longer side-chain were all formed selectively and no acyclic product was observed.



Scheme 1.12: Conditions: a)$TiCl_4$, TMEDA, Zn dust, $PbCl_2$, CH_3CHBr_2, THF, reflux.

This strategy was also applied to more complex substrate **29** and, after further modifications, the heptacyclic fragment **32** was obtained with complete stereoselectivity (Scheme 1.13).

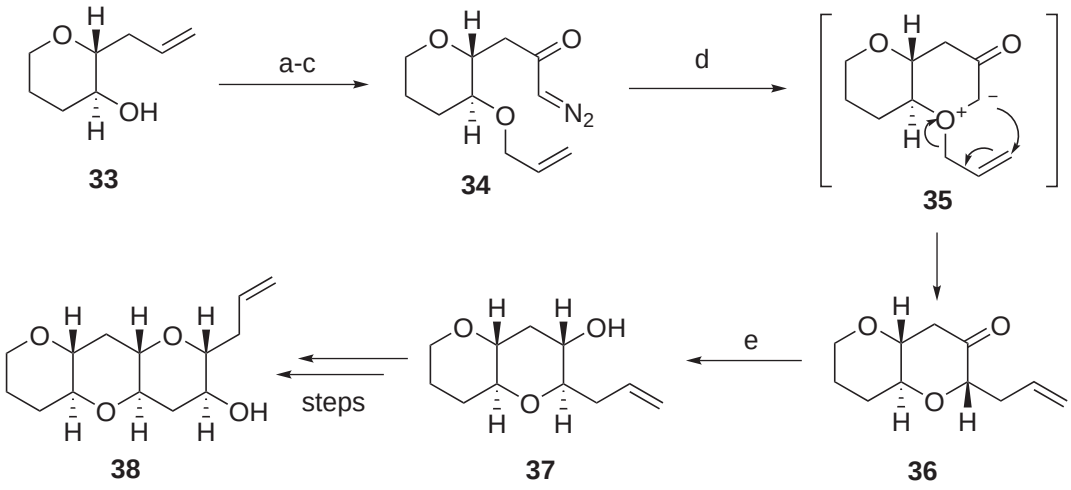


Scheme 1.13: Conditions: a)$TiCl_4$, TMEDA, Zn dust, $PbCl_2$, CH_3CHBr_2, THF, CH_2Cl_2, reflux, 50%; b) DMDO, CH_2Cl_2, −78 °C to 0 °C; c) Dibal-H, CH_2Cl_2, −78 °C, 65% (2 steps); d) TPAP, NMO, 4Å MS, CH_2Cl_2, rt, 92%; e) HF·Py, THF, rt, 91%; f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, reflux; g) Bu_3SnH, AIBN, toluene, reflux, 61% (2 steps).

The methods described above provide rapid and efficient entry to substituted tetrahydropyrans but this *C*-glycoside strategy does suffer from some limitations. Firstly, the anomeric epoxides formed are generally unstable. Secondly, the production of vast quantitites of DMDO is impractical. Finally, the one-pot epoxidation/nucleophilic ring opening sequence frequently leads to mixtures of isomers and is highly substrate dependent.

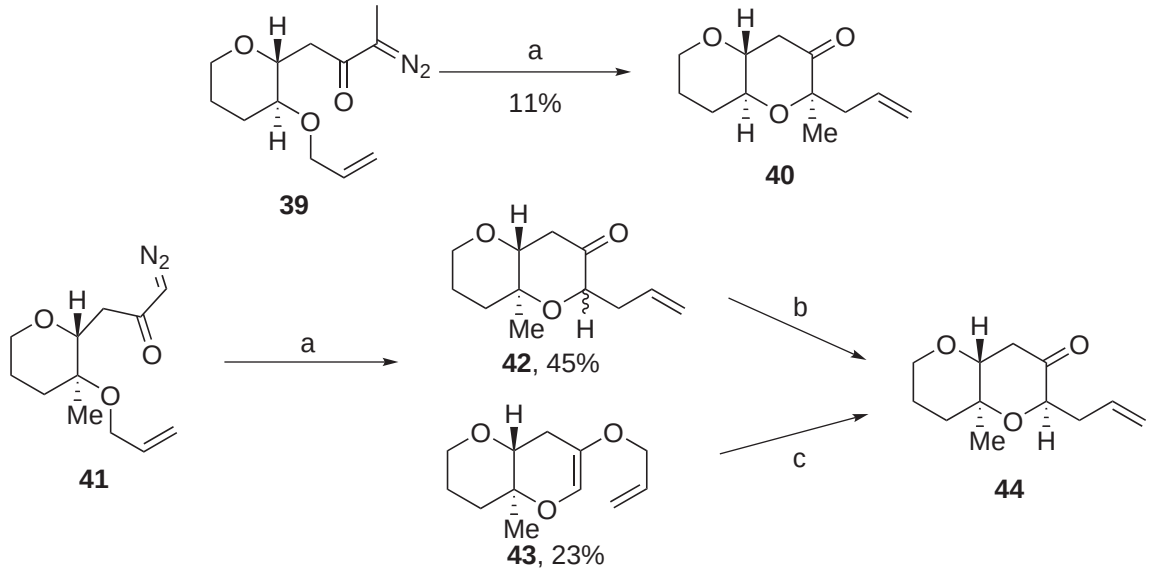
- *Tandem Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement*

Marmsäter and West have described an iterative approach to polyether synthesis based on the [2,3]-shift of cyclic oxonium ylides.[67] This strategy is fundamentally different from the three methods depicted previously. Alcohol **33** was converted into α-diazoketone **34** in three steps (Scheme 1.14). Ozonolysis with oxidative workup followed by *O*-allylation and carbonyl activation/diazomethane acylation gave the cyclisation precursor in 55% yield from alcohol **33**. Treatment of α-diazoketone **34** with a catalytic amount of copper (II) trifluoroacetylacetonate gave bicyclic ketone **36** *via* the intermediate oxonium ylide **35** in 80% yield. Unfortunately, ketone **36** was formed with the undesired configuration at the newly created stereocentre, the allyl chain being in axial position. This compound was therefore epimerised with DBU and reduced in a one-pot procedure to give an 8:1 mixture of alcohol **37** and its epimer in 94% yield. A second iteration was accomplished to afford the tricyclic polyether system **38** in 20% overall yield from alcohol **37**.



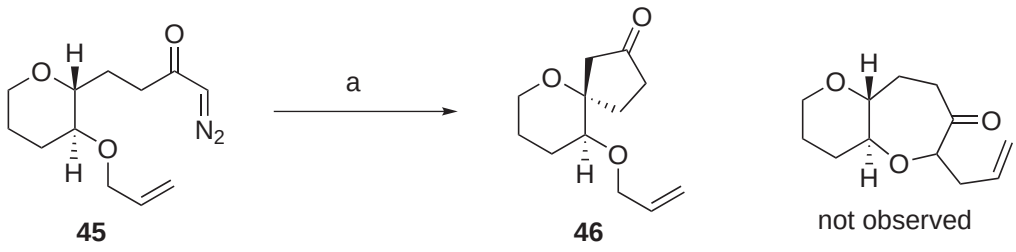
Scheme 1.14: Conditions: a) O_3, CH_2Cl_2:MeOH, −78 °C then H_2O_2, HCO_2H, 85%; b) NaH, allylbromide, THF, reflux, 95%; c) $(COCl)_2$, DMF, CH_2Cl_2, rt then CH_2N_2, Et_2O, −45 °C to rt, 67%; d) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 80%; e) DBU, toluene, reflux then $LiAlH_4$, THF, 0 °C, 95%.

This group also investigated several approaches to introduce an angular methyl group at the bridgehead position.[46,68] Incorporation of the methyl substituent in the diazo ketone **39** furnished the ylide rearrangement product **40** in a disappointingly low yield (Scheme 1.15). However, tertiary allylic ether **41** underwent conversion into ketone **42** in moderate yield. Allyl vinyl ether **43**, arising from an apparent [1,4]-shift was also isolated. Both **42** and **43** could be converted into the desired ketone **44** in 68% yield from **41**.



Scheme 1.15: Conditions: a) $Cu(tfacac)_2$, CH_2Cl_2, reflux; b) DBU, toluene, 80 °C, 99%; c) toluene, reflux, quant.

Finally, formation of seven-membered rings was also investigated, but without any success.[68] When diazo ketone **45** was subjected to copper(II) catalyst, the only isolated product was spirocyclic C-H insertion product **46** (Scheme 1.16).



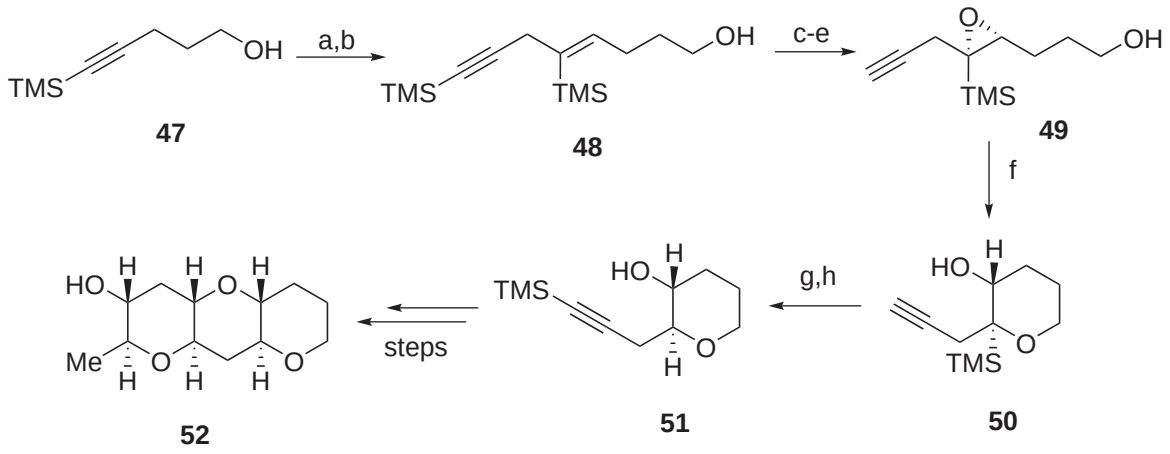
45 **46**

Scheme 1.16: Conditions: a) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 55%.

This method permits the construction of six-membered cyclic ethers in 5 steps and an overall yield of 38%. The incorporation of angular methyl groups has also been accomplished.

- *$SiMe_3$-Based Homologation-Epoxidation-Cyclisation*

Heffron and Jamison have recently reported an iterative approach to the synthesis of laddered polytetrahydropyrans based on a strategy that emulates the three fundamental processes in laddered polyether biosynthesis: chain homologation, stereoselective epoxidation and *endo*-selective, stereospecific hydroxy-epoxide cyclisation.[69] It was found that a TMS group enabled efficient and selective emulation of all three biogenetic processes and was amendable to rapid, iterative synthesis of a polyether sub-unit. After highly selective hydroalumination-iodination of alcohol **47**, direct propargylation gave vinylic silane **48** in high yield (Scheme 1.17). Transient acetate protection of the primary alcohol, followed by highly enantioselective Shi epoxidation[70] (>95% *ee*) and deprotection gave epoxide **49**. Lewis acid promoted hydroxyepoxide cyclisation completed construction of the first tetrahydropyran **50**. Desilylation cleanly removed the TMS group with retention of configuration to give alcohol **51**. Reiteration of these same four steps gave the THP triad **52** in a total of 18 steps and 3% overall yield.



Scheme 1.17: Conditions: a) Dibal-H, I_2, Et_2O; b) 1-(trimethylsilyl)-1-propyne, *n*BuLi, TMEDA, CuI, DMAP, THF, −78 °C to rt, 76% (2 steps); c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C; d) 1,2:4,5-di-*O*-isopropylidene-β-D-erythro-2,3-hexodiulo-2,6-pyranose, Oxone, K_2CO_3, $n Bu_4NHSO_4$, $Na_2B_4O_7 \cdot 10H_2O$ MeCN, DMM; e) LiOH, H_2O, THF, MeOH, 65% (3 steps); f) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C, 80%; g) TBAF, THF, rt; h) *n*BuLi, TMSCl, THF, −78 °C to rt, 72% (2 steps).

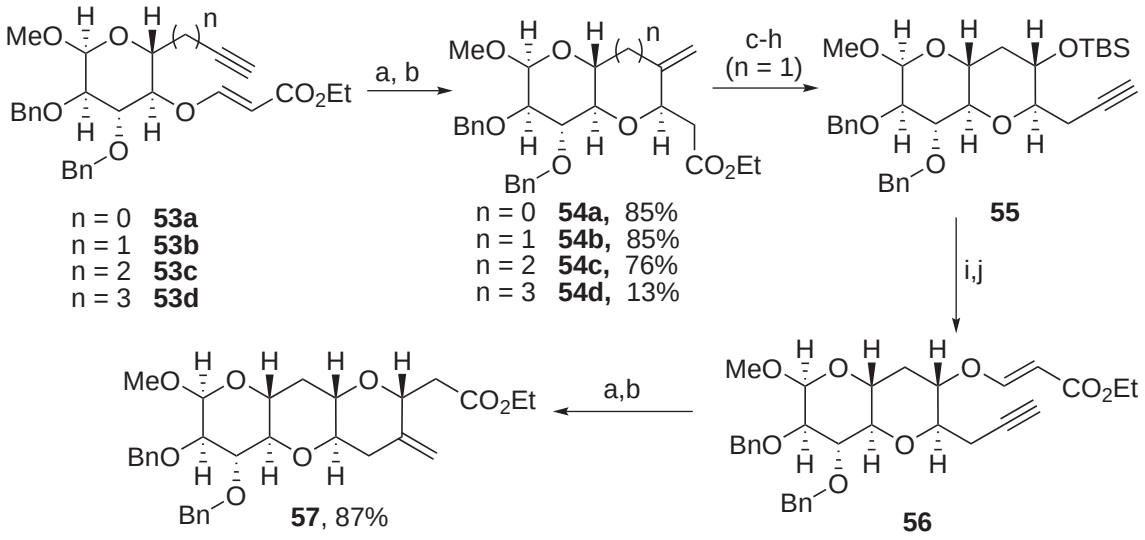
Jamison's methodology permits the rapid construction of unsubstituted fused six-membered ether ring systems. Incorporation of angular methyl groups and synthesis of larger ring systems using this methodology has not been reported.

C-C Bond Formation

- *Radical Cyclisation of β-(Alkynyloxy)acrylates*

Recently, van Boom and co-workers reported the iterative addition of vinyl radicals, derived from alkynes, to vinylogous carbonates to form *trans*-fused polycyclic ethers.[71] This study was based on the early work of Lee and co-workers,[72,73] who described the addition of tributyltin radicals to alkynes to facilitate intramolecular addition of vinyl radicals to β-alkoxy acrylates, which upon acidic destannylation furnished *cis*-2,6-disubstituted tetrahydropyrans. The iterative sequence was initiated by the intramolecular addition of the tributyltin radical to alkynes **53a-d**, affording vinyl radicals that underwent smooth addition to the vinygolous ester to deliver, after acidic destannylation, bicyclic systems **54a-d** in good yields (Scheme 1.18). The cyclisation reactions proceeded uneventfully for the formation of five-, six- and seven-membered rings, but the substrate for the eight-membered ring (n=3) reacted to give mainly hydrostannylation products. The *exo*-cyclic double bond was converted stereoselectively into the *trans*-alcohol by ozonolysis and *in-situ* reduction of the intermediate ozonide with sodium borohydride. Protection of the alcohol as a silyl ether and reduction of the ester, followed by Dess-Martin oxidation gave the intermediate aldehyde. Alkyne **55**

was obtained from the aldehyde using the Corey-Fuchs procedure.[74] Finally, deprotection of the silyl ether gave the free alcohol, which upon reaction with ethyl propiolate gave the bicyclic β-(alkynyloxy)acrylate **56** in high yield. Cyclisation, as previously described, gave the tricyclic ether **57** in 87% yield.

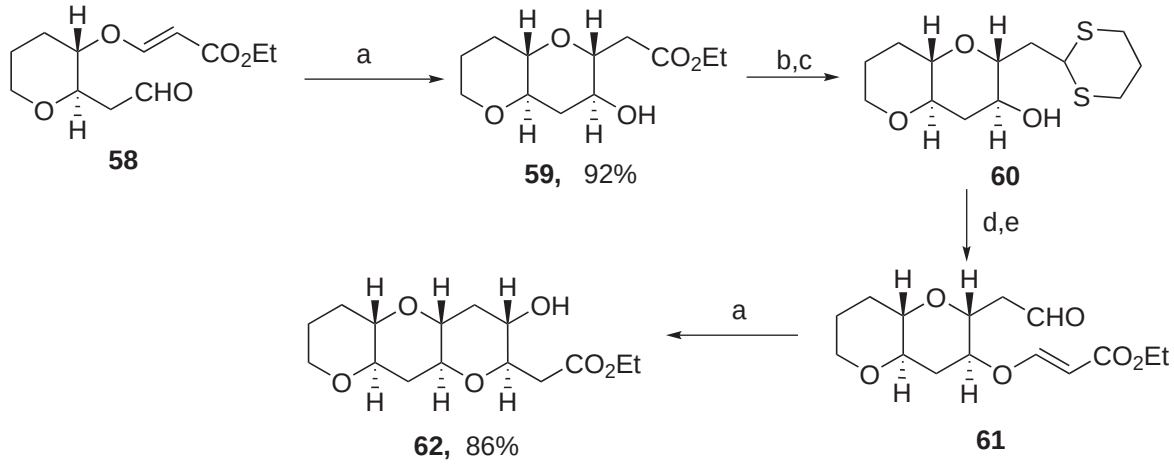


Scheme 1.18: Conditions: a) Bu_3SnH, AIBN cat., toluene, 80 °C; b) TsOH, CH_2Cl_2; c) O_3, $NaBH_4$, MeOH:CH_2Cl_2 (7:1), −70 °C to rt, 92%; d) TBSOTf, iPr$_2$NEt, CH_2Cl_2, 0 °C, 89%; e) $LiAlH_4$, Et_2O, 0 °C, 91%; f) DMP, pyridine, CH_2Cl_2; g) CBr_4, PPh_3, CH_2Cl_2, 86% (2 steps); h) nBuLi, THF, −50 °C, 92%; i) TBAF, THF, 91%; j) ethyl propiolate, NMM, CH_2Cl_2, 99%.

This methodology allows the highly stereoselective preparation of five-, six- and seven-membered cyclic ethers, but each iteration takes ten steps. The incorporation of angular methyl groups has not been reported.

- *Samarium Induced Reductive Cyclisations*

Nakata and co-workers have disclosed a very efficient approach to the synthesis of polycyclic ethers based on a stereoselective samarium iodide-induced reductive cyclisation reaction.[75–77] In this strategy, carbon-carbon bond construction sets both of the bridgehead stereocentres. Aldehyde **58** was treated with samarium (II) iodide to give the bicyclic system **59** as a single isomer in 92% yield (Scheme 1.19). The ester function was selectively reduced to the aldehyde which was then protected as a thioacetal to give **60** in 99% yield over the two steps. Hetero-Michael addition of the alcohol **60** onto ethyl propiolate, followed by removal of the thioacetal with methyl iodide in aqueous acetonitrile gave the cyclisation precursor **61** in 90% yield. The second radical-mediated reductive cyclisation proceeded as before to deliver the tricyclic ether **62** as a single isomer in 86% yield.



Scheme 1.19: Conditions: a) SmI_2, MeOH, THF, 0 °C; b) Dibal-H, toluene, −78 °C; c) propane-1,3-dithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 99% (2 steps); d) ethyl propiolate, NMM, CH_2Cl_2, rt; e) MeI, aq. MeCN, rt, 90% (2 steps).

The complete selectivity observed is the result of chelation of the samarium to the ester function which forms the seven-membered transition state **63** (Figure 1.3). The ketyl radical then attacks the β-alkoxyacrylate to give radical **64**, which is then reduced and protonated.[75–77]

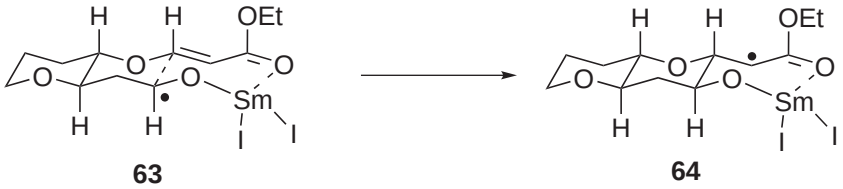
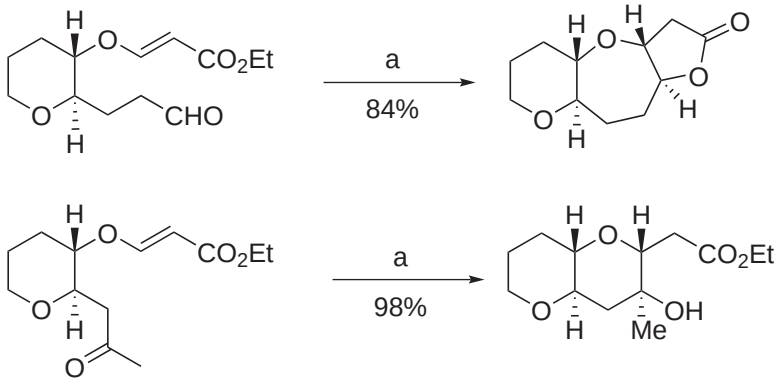


Figure 1.3: Cyclisation model of ketyl radical

The samarium-induced reductive cyclisation reaction was also used to construct oxepanes with excellent diastereoselectivity, but in those cases, the cyclisation event occured with concomitant lactonisation (Scheme 1.20).[75–77] Moreover, cyclisation is not limited to aldehydes, but is also applicable to methyl ketones, thus providing a direct access to ring systems containing angular methyl groups.[78,79]



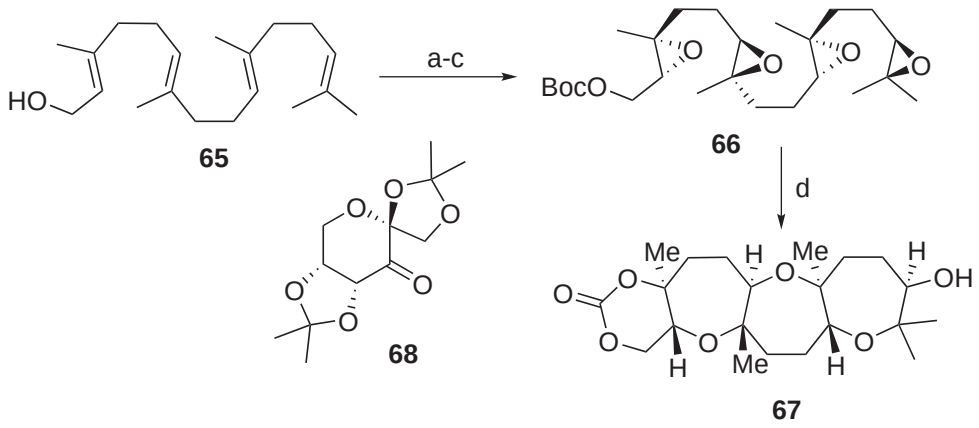
Scheme 1.20: Conditions: a) SmI_2, MeOH, THF, 0 °C.

Nakata's methodology allows the preparation of six- and seven-membered cyclic ether systems in only five steps per iteration and with excellent levels of diastereoselectivity. This approach also allows the incorporation of angular methyl groups. Nakata used this strategy for the synthesis of the C'D'E'F' fragment of maitotoxin,[80] the FG ring system of gambierol[80] and in the total synthesis of brevetoxin B.[33]

1.2.2 Biomimetic Approaches to the Synthesis of Polycyclic Ethers

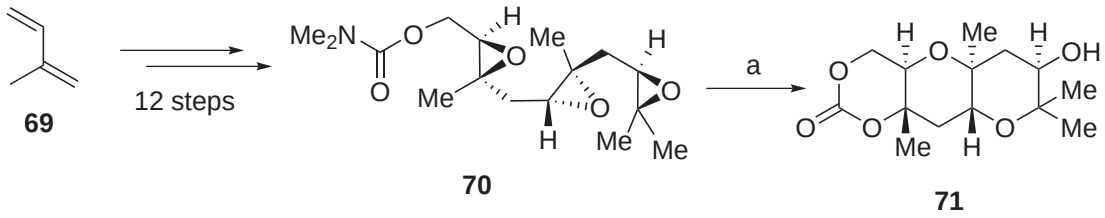
- *Lewis-Acid Promoted Epoxide Openings*

McDonald and co-workers have recently examined the original Shimizu[24] and Nakanishi[23] proposal for biomimetic cascade of *endo*-epoxide openings (Scheme 1.21).[81] Geranylgeraniol **65** was converted into tetraepoxide **66** using a three-step sequence involving Sharpless enantioselective epoxidation[82] of the allylic alcohol, followed by Shi epoxidation[70] of the residual alkenes and protection of the primary alcohol as a *tert*-butyl carbonate. Treatment of tetraepoxide **66** with boron trifluoride etherate at −40 °C furnished tetracyclic ether **67** in 27% yield.



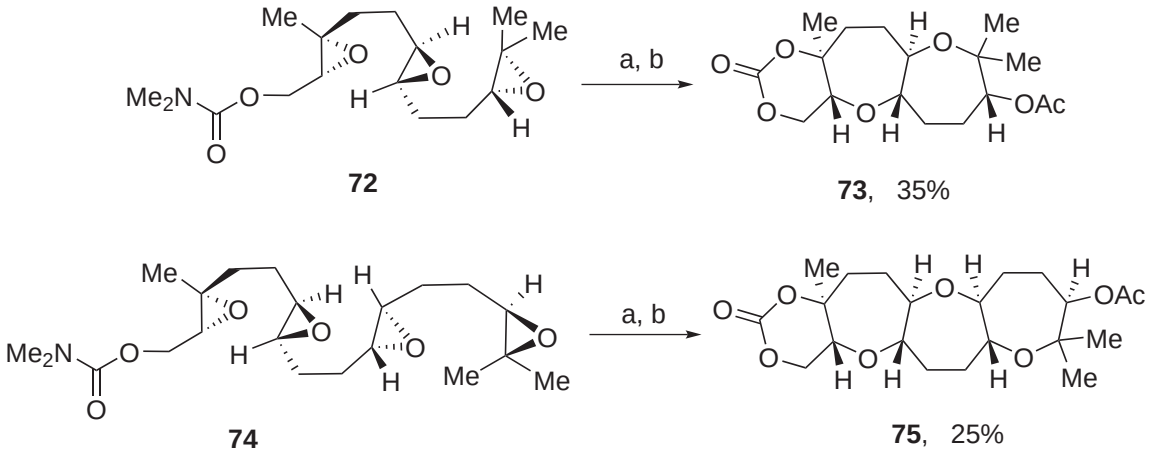
Scheme 1.21: Conditions: a) $Ti(OiPr)_4$ (5 mol%), (-)-DET (6 mol%), TBHP, CH_2Cl_2, −25 °C; b) **68** (60 mol%), Oxone, MeCN, DMM, H_2O, pH = 10.5, 0 °C; c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 30% (3 steps); d) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −40 °C, 27%.

This strategy was also applied to laddered THP synthesis by employing 1,4,7-triepoxides as the cyclisation precusor.[83] Isoprene **69** was converted to triepoxide **70** in a lenghty 12-step sequence (Scheme 1.22). As expected, boron trifluoride etherate promoted oxacyclisation of dimethylcarbamate triepoxide **70** and gave the desired all-fused *trans,trans* tricyclic compound **71** in 31% yield.



Scheme 1.22: Conditions: a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 31%.

Until 2005, McDonald had only studied substrates with internal trisubstituted epoxides. However, alkyl substitution is not found at all ring junctions in the naturally occuring polycyclic ethers. Very recently, they have extended their biomimetic cascade strategy to include substrates with one or more internal disubstituted epoxides.[84] Oxacyclisation of substrates **72** and **74**, bearing one or two internal disubstituted epoxides, resulted in the formation of *trans,syn,trans*-fused polycyclic ethers **73** and **75** in 35% and 25% yield respectively (Scheme 1.23).



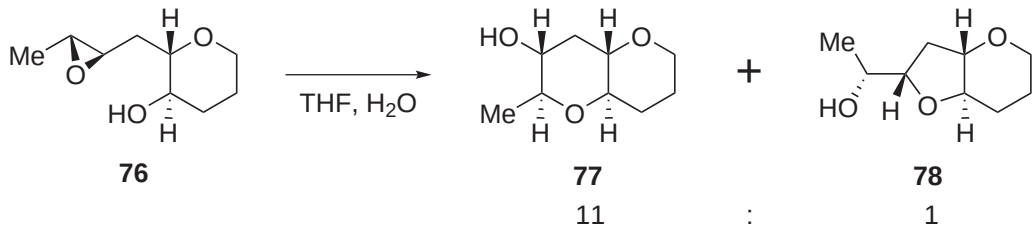
Scheme 1.23: Conditions: a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, -40 °C; b) Ac_2O, pyridine.

The success of McDonald's approach relies on *gem*-dimethyl groups, stabilisation of the positively charge transition state and assistance of the carbonate/carbamate group as the nucleophile terminating the cascade. Overall, despite poor yields, this approach provides a potentially powerful method for the construction of polycyclic ethers.

- *Water Promoted Epoxide Openings*

In 2007, the Nakanishi cascade biosynthesis of brevetoxin B received another strong argument in its favour when Jamison and co-workers described a water-promoted epoxide opening to access *trans*-fused tetrahydropyran rings.[85] They proposed that a substrate already containing a THP would cyclise to give a six-membered ring by decreasing the entropy disadvantage and giving a more stable intermediate. Indeed, *trans*-bicyclo[4.4.0]decane derivatives are typically less strained than their *trans*-bicyclo[4.3.0]nonane counterparts.

Epoxy-alcohol **76** was treated under a variety of conditions and it was found that deionised water in a 1:1 mixture with THF gave the best ratio in favour of the six-membered product **77** (11:1) (Scheme 1.24). Other hydrogen-acceptor additives such as methanol and ethylene glycol also gave good selectivity (8:1 and 9:1 respectively).



Scheme 1.24: Selective 6-endo epoxide opening

The authors suggested a mechanism involving a double hydrogen bond activation of the epoxy-alcohol **76**. Both the nucleophile (hydroxyl group) and the electrophile (epoxide) can be activated by two hydrogen-bonded water molecules, creating a network of hydrogen bonds (Figure 1.4). This model reasonably explains the enhanced regioselectivity in water (relative to other solvents) as well as the marginal effects of temperature on selectivity.

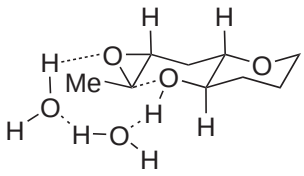
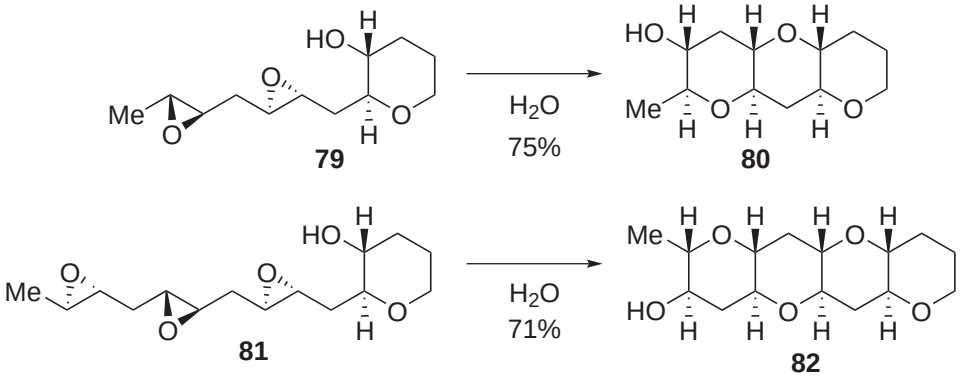


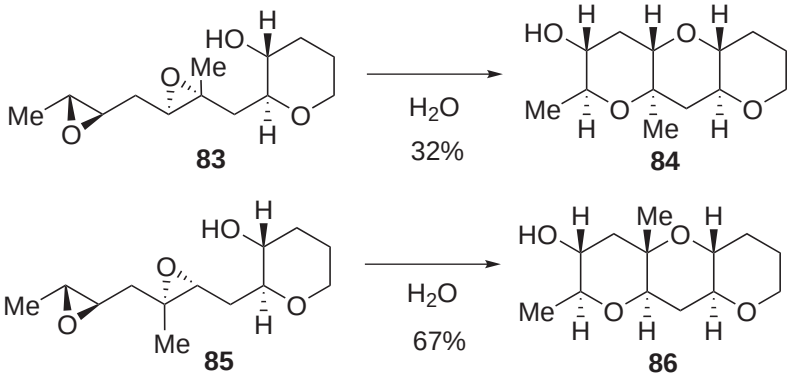
Figure 1.4: Hydrogen-bonding model

These conditions were then applied to cascade sequences to generate more than one tetrahydropyran in a single-pot operation. Bis- and tris-epoxides **79** and **81** were heated in water at 70 °C to give respectively tricyclic and tetracyclic products **80** and **82** in very good yields (Scheme 1.25).



Scheme 1.25: Cascade epoxide openings

Finally, introduction of angular methyl groups was also investigated and it was found that both distal and proximal positions are suitable for this transformation. Bis-epoxides **83** and **85**, containing a methyl group at the distal or proximal position of the nucleophile were stirred in neutral hot water and gave both tricyclic products **84** and **86** in moderate to good yields (Scheme 1.26). While Lewis acids have already been shown to work with distal methyl groups,[83] this was the first example of an *endo*-selective epoxide opening reaction with a proximal methyl group, even though the yield was quite modest.

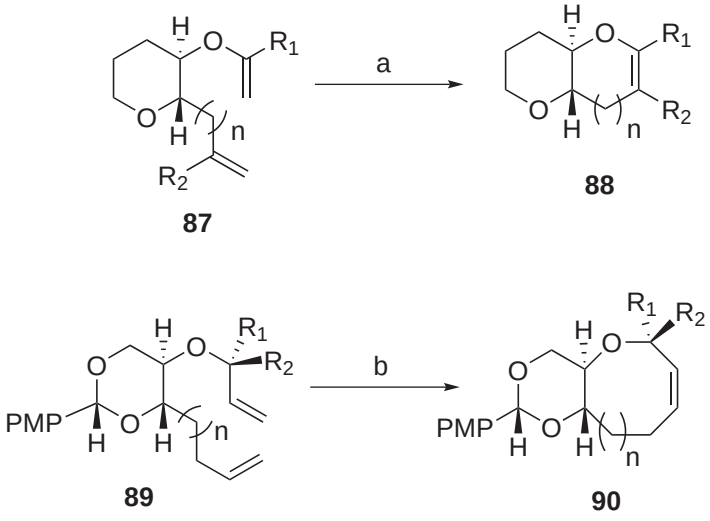


Scheme 1.26: Introduction of methyl angular groups

By finding reaction conditions compatible with a biological media (water at pH=7), Jamison and co-workers got closer to a genuine biosynthetic approach. The cascade reactions proved to be highly efficient and modifications to the substrate, such as introduction of angular methyl groups, did not affect the outcome of the reaction.

1.2.3 Clark Group Strategy Toward Polyether Synthesis

Clark and co-workers have developed several strategies for the preparation of polycyclic ethers using an approach based on the formation of rings by RCM/ring-closing enyne metathesis (RCEM). Three different strategies have been pursued. Firstly, six- and seven-membered cyclic enol ethers **88** were prepared in good yields by RCM of **87** with the Schrock catalyst **17** (Scheme 1.27).[86] Eight- and nine-membered cyclic allylethers **90** were also prepared in good yields.[87]

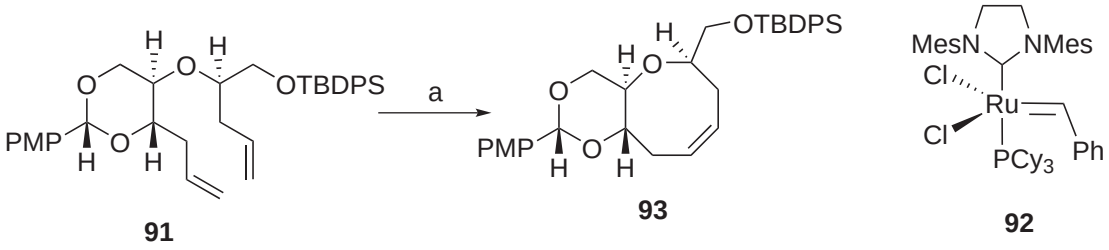


n	R_1	R_2	Yield
1	Et	H	72%
1	H	Me	93%
2	Et	H	42%
2	H	Me	94%

n	R_1	R_2	Yield
1	Et	H	86%
1	H	Me	97%
2	Et	H	14%
2	H	Me	86%

Scheme 1.27: Conditions: a) catalyst **17** (9-14 mol%), pentane, rt; b) catalyst **17** (25 mol%), benzene, 60 °C.

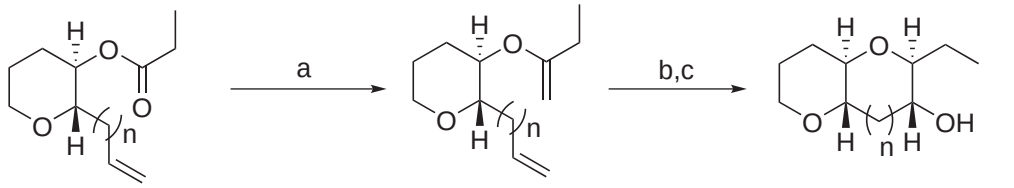
This strategy was used in a stereoselective synthesis of the cyclic core of (+)-laurenyne.[88] RCM of diene **91** with 5 mol% of Grubbs' second generation catalyst **92** gave the eight-membered cyclic ether core **93** in essentially quantitative yield (Scheme 1.28). Clark and co-workers also used this strategy in the synthesis of functionalised polycyclic ether sub-units.[89]



91 **93** **92**

Scheme 1.28: Conditions: a) Grubbs II catalyst **92** (2 mol%), toluene, 80 °C, 99%.

The construction of sub-units of marine polycyclic ethers was also achieved by RCM and hydroboration of enol ethers.[90] Acyclic enol ethers **95a,b** were formed by methylenation of esters **94a,b** using the Takai protocol (Scheme 1.29).[91] Treatment of **95a,b** with molybdenum catalyst **17** furnished the cyclised products, which were subjected to hydroboration to give the functionalised cyclic ethers **96a,b** in moderate yield but with excellent levels of diastereocontrol.



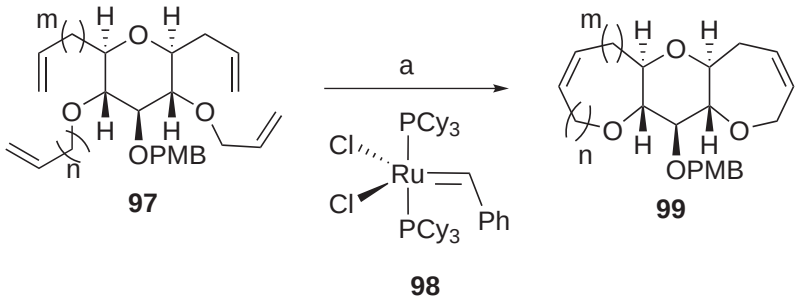
n = 1, **94a**
n = 2, **94b**

n = 1, **95a**, 70%
n = 2, **95b**, 79%

n = 1, **96a**, 61%
n = 2, **96b**, 41%

Scheme 1.29: Conditions: a) $TiCl_4$, TMEDA, CH_2Br_2, Zn, THF, rt; b) catalyst **17** (9-14 mol%), pentane, rt; c) $ThxBH_2$, THF, −20 °C then aq. NaOH, 30% H_2O_2.

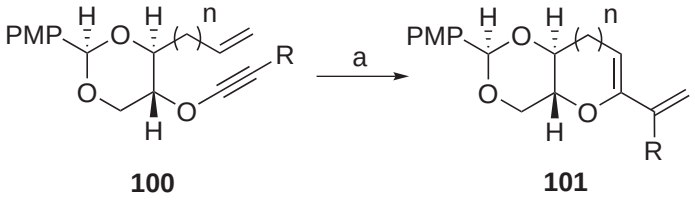
In further work, Clark and Hamelin reported the synthesis of polycyclic ethers by two-directional double RCM.[92] This strategy permitted the construction of polyether fragment **99** possessing a variety of ring sizes in good-to-excellent yields (Scheme 1.30). This strategy has been successfully employed to synthesise the F-J fragment of the gambieric acids.[93]



m	n	Yield
1	1	88%
1	3	65%
2	1	77%
1	0	71%

Scheme 1.30: Conditions: a) Grubbs I catalyst **98** (20-30 mol%), CH_2Cl_2, rt or reflux.

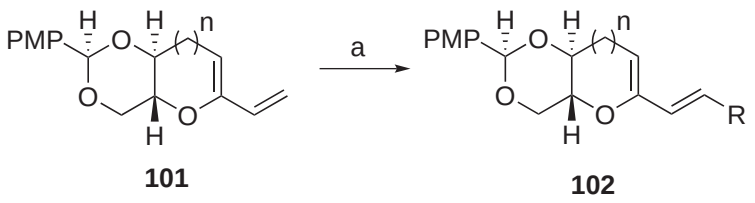
Finally, Clark and co-workers have developed a synthesis of cyclic ethers by catalytic RCEM of alkynyl ethers.[94,95] Six- and seven-membered alkenyl-substituted cyclic enol ethers **101** were prepared from **100** in high yields (Scheme 1.31). It was also shown that the ruthenium catalyst **92** was tolerant of a wide range of alkyne substituents.



n	R	Yield
1	H	90%
1	Me	98%
1	TMS	88%
1	CH_2OAc	72%
2	H	70%
2	Me	72%

Scheme 1.31: Conditions: a) Grubbs II **92** (5 mol%), toluene, 80 °C.

The diene products **101** obtained using this methodology were functionalised by catalytic cross-metathesis (CM) with a large range of alkenes.[96] This permitted the synthesis of highly functionalised six- and seven-membered cyclic ethers **102** bearing a diverse range of side chains in good-to-excellent yields (Scheme 1.32). In addition to allowing rapid chain extension, CM allows selective functionalisation of the side chain without affecting the enol ether, which can be functionalised at a later stage.



n	R	Yield
1	CH_2OAc	87%
1	CH_2TMS	78%
1	CO_2Et	89%
2	CH_2OAc	79%
2	CO_2Et	91%

Scheme 1.32: Conditions: a) Grubbs II catalyst **92** (5 mol%), H_2C=CHR, toluene, 70 °C.

1.2.4 Summary

Over the years, a variety of synthetic methods have been developed to access this interesting class of natural products. These methods all possess advantages and disadvantages in terms of yield, number of steps, selectivity and flexibility. However, the lack of application in total synthesis shows that optimisation studies remain to be done in many cases.

1.3 Olefin Metathesis

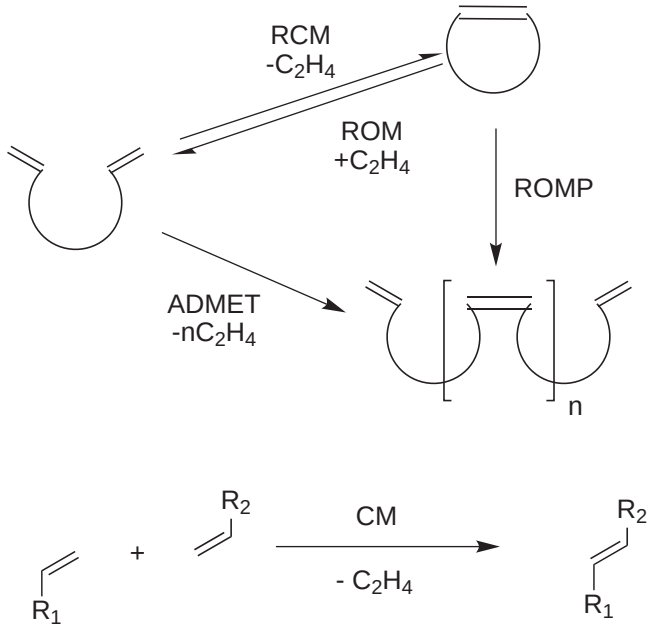
1.3.1 Introduction

The word metathesis is derived from the Greek *metatithenai*, and literally means to transpose: *meta-*, change and *tithenai-*, to place. In chemistry, metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon double bonds are rearranged in the presence of metal carbene complexes.[97]

Olefin metathesis has been known in polymer synthesis since the late 1950's with the discovery by Karl Ziegler that certain transition metals could promote the polymerisation of olefins under mild conditions. By the late 1960's, the Phillips group had developed a commercial process - the triolefin process - and made the scientific community aware of this unique reaction. However, the scope of this reaction was limited to the polymerisation of simple unfunctionalised alkenes.

The discovery that metal alkylidene complexes could promote olefin metathesis, at the beginning of the 1980's, was the first step towards the development of this reaction in organic synthesis. The development of well-defined molybdenum and ruthenium carbene complexes in the 1990's led to a dramatic expansion in the field.[98] Over the past decade, olefin metathesis has emerged as one of the most powerful tools for the formation of carbon-carbon bonds and this was recognised in 2005 through the award of the Nobel prize in Chemistry to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock "for the development of the metathesis method in organic synthesis".

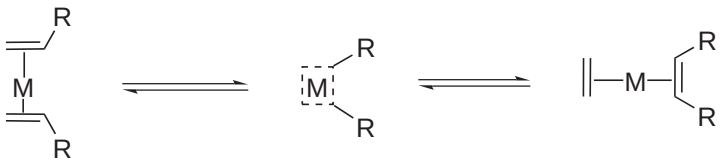
Olefin metathesis can occur between alkenes (diene metathesis) but can also be extended to other π-systems such as between an alkene and an alkyne (enyne metathesis) or two alkynes (diyne metathesis).[99] The reaction can be classified into five closely related reaction types (Scheme 1.33). Firstly, in the case of acyclic dienes, the reaction can be both intramolecular (ring-closing metathesis - RCM) and intermolecular (cross metathesis - CM). In addition, polymerisation may occur (acyclic diene metathesis polymerisation - ADMET) instead of RCM. Strained cyclic alkenes can react by ring-opening metathesis (ROM), which can also be followed by polymerisation (ROMP).



Scheme 1.33: Important types of metathesis reactions.

1.3.2 Mechanism

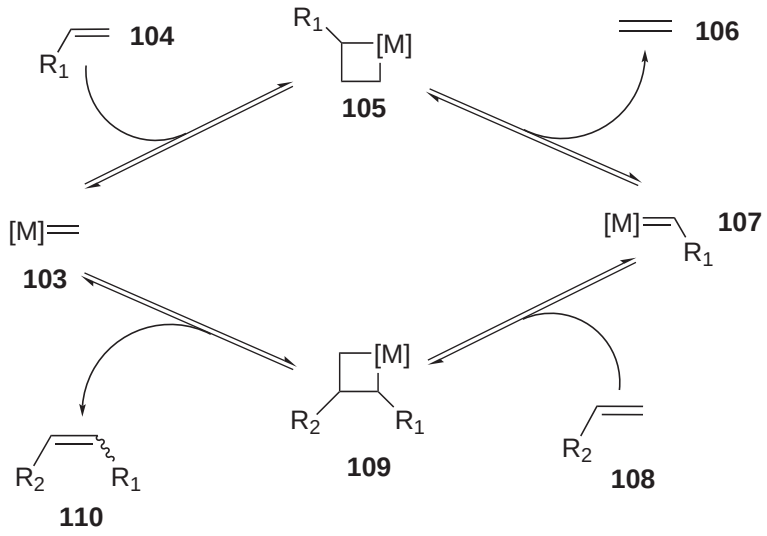
The initially proposed metathesis mechanism involved pair-wise exchange of alkylidenes through a 'quasicyclobutane' mechanism in which two olefins coordinated to the metal and exchanged alkylidene groups through a symmetrical intermediate (Scheme 1.34).[100] With a few assumptions, this mechanism could account for the outcome of most of the basic metathesis transformations.



Scheme 1.34: Quasicyclobutane mechanism of metathesis.

Chauvin proposed a new mechanism to explain a surprising set of observations.[101] He observed that in some cases where a pair-wise mechanism, such as the 'quasicyclobutane' mechanism, predicted only the two olefins resulting from pair-wise exchange of the two ends of the starting olefins, the olefins resulting from cross products were observed very early in the reaction. This led Chauvin to propose that the mechanism for olefin metathesis consisted of a sequence of formal [2+2] cycloadditions/cycloreversions involving alkenes, metal alkylidenes and a metallocyclobutane intermediate (Scheme 1.35). The first step in the catalytic process is a [2+2] cycload-

dition between olefin **104** and the transition metal alkylidene complex **103** to give the first metallocyclobutane **105**. This metallocycle undergoes a [2+2] cycloreversion reaction to liberate ethene **106** and a new metal carbene **107**, which carries the alkylidene substituent R_1. As before, **107** reacts with another alkene **108** to form the second metallocycle **109**. After a further [2+2] cycloreversion, the new disubstituted alkene **110** is liberated and the catalyst **103** is regenerated and can re-enter the catalytic cycle. This mechanism is now widely accepted as the true mechanism of the metathesis reaction.



Scheme 1.35: Chauvin mechanism of metathesis.

Due to the reversible nature of all the steps in the catalytic cycle, it is necessary to displace the equilibrium in favour of the desired product to avoid a mixture of all the possible alkenes. In the case of RCM, the starting diene is transformed into two alkenes and, as such, the reaction is entropically favoured. Furthemore, if one of the alkenes is volatile (ethylene for example), the cycloreversion step becomes irreversible. The substitution pattern of the alkene is also an important factor because it determines the kinetics of the reaction. In general, the more substituted the alkene, the less reactive it is.

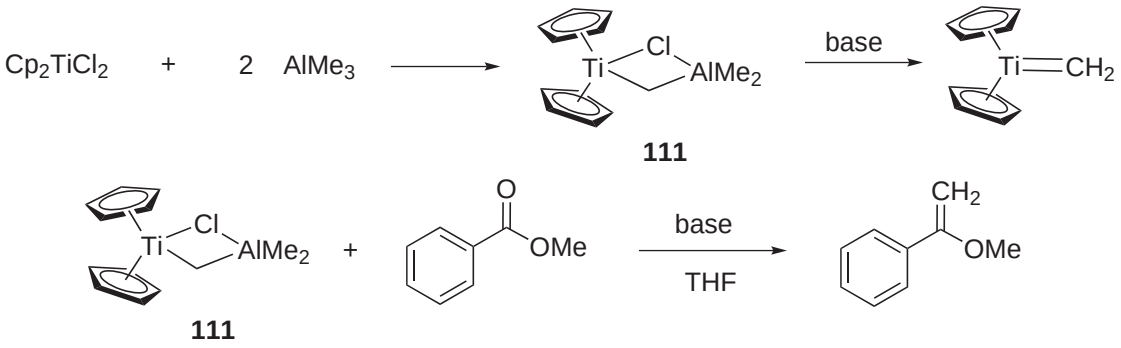
1.3.3 Catalysts

The number of catalyst systems that initiate olefin metathesis is very large. From the mid-1950's to the early 1980's, all olefin metathesis reactions were accomplished with poorly defined, multicomponent homogeneous and heterogeneous catalyst systems.[102] These systems consisted of transition metal salts combined with main group alkylating agents or deposited on solid supports. Some of the classic combinations

include WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 and ReO_7/Al_2O_3, among many others.[103] Although used in many commercial processes, these catalysts require harsh Lewis acidic conditions that are incompatible with most functional groups. They were therefore unsuitable for organic synthesis. Understanding the mechanism of olefin metathesis greatly influenced work on catalyst development in that it provided both a design rationale and a way to begin explaining catalyst activity. Subsequent efforts to synthesise alkylidene and metallacylobutane complexes led to the discovery of the first single component homogenous catalysts for olefin metathesis during the late 1970's and early 1980's.

Titanocene-Based Catalysts

Tebbe demonstrated that a titanium methylene complex would catalyse the non-productive metathesis exchange of the methylenes between two terminal olefins. The reaction of two equivalents of $AlMe_3$ with Cp_2TiCl_2 produces the complex $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$ **111**, commonly known as Tebbe's reagent, and methane (Scheme 1.36).[104] In the presence of a Lewis base, such as pyridine, the reagent is functionally equivalent to "$Cp_2Ti{=}CH_2$".[105]



Scheme 1.36: Synthesis and use of Tebbe's reagent.

Although catalyst **111** is not a particulary active metathesis catalyst, it served as an excellent model system because the complex is reasonably stable and the propagating alkylidene can be observed and studied.[104] These titanium complexes also undergo stoechiometric 'Wittig type' reactions with aldehydes and ketones to give the corresponding methylene derivatives. Most importantly, Evans and Grubbs showed that these complexes convert esters into vinyl ethers, a reaction for which conventional Wittig reagents are not suitable (Scheme 1.36).[106] The mechanism of this reaction is identical to that of the olefin metathesis except that the final step is irreversible.[107]

Tungsten, Molybdenum and Rhenium Catalysts

Schrock has developed a wide variety of well-defined catalysts based on molybdenum, tungsten and rhenium (Figure 1.5).[108] The most important system is the alkoxy-imido-molybdenum complex represented by **17**. One of the major advantage of this system is its high reactivity towards a broad range of substrates with many steric or electronic variations. For example, it has been shown that complex **17** can bring over 1000 equivalents of *cis*-2-pentene to equilibrium in less than one minute at 25 °C. The alkoxides in the [Mo] system can be readily altered to adjust the activity of the complex; when R_1 is a *tert*-butyl, the complex reacts only with strained cyclic olefins, making it an ideal ROMP catalyst.[109]

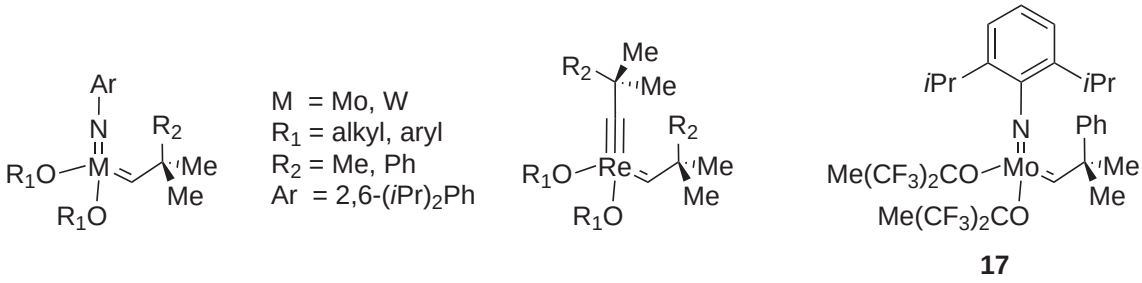


Figure 1.5: Molybdenum, tungsten and rhenium catalysts.

Critical drawbacks of this Mo-based system are, however, its thermal unstability on storage, its moderate to poor functional group tolerance and its high sensitivity to air, moisture or even trace impurities present in solvents.

Ruthenium Catalysts

During the 1990's, Grubbs and co-workers developed a series of well-defined ruthenium alkylidene catalysts that initiate olefin metathesis.[102] The ruthenium carbene complexes have drawn a lot of attention, not only because they exhibit high reactivity in a variety of ROMP, RCM and cross-metathesis processes under mild conditions, but also, because of their remarkable tolerance toward many different organic functional groups.[110] Catalytic activity is not significantly reduced in the presence of air, moisture or minor impurities in solvents. They can be conveniently stored, even under air atmosphere, without decomposition for several weeks or months. Although the ruthenium carbene complexes often exhibit relatively lower propagation rates,[111] especially with sterically bulky substrates, when compared to the Schrock catalyst **17**, their availability and ease of use has made them the catalysts of choice for the metathesis reaction, with all but the most difficult substrates.

The first-generation Grubbs'catalyst **98**[112] possesses two phosphine ligands whereas the second-generation ruthenium complex **92**[113] has one phosphine ligand and one *N*-heterocyclic carbene (NHC) ligand (Figure 1.6). This structural alteration improved the stability and reactivity of the catalyst compared to complex **98**. The other main ruthenium catalyst **112** in wide-spread use was reported by Hoveyda.[114] An *iso*-propyloxy ether group attached to the phenyl carbene unit already connected to the ruthenium replaces the phosphine ligand of **92**. Although many variations of these catalysts have been reported,[115–119] the three described above are commercially available and generally used most frequently.

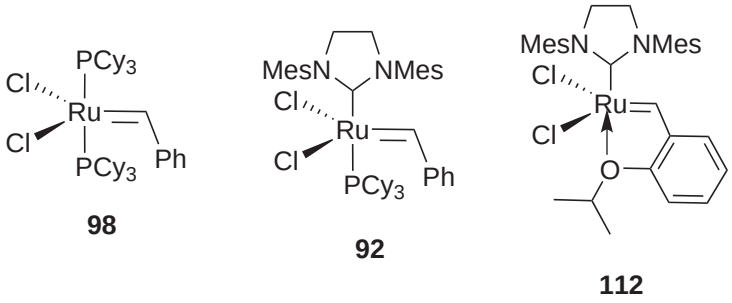
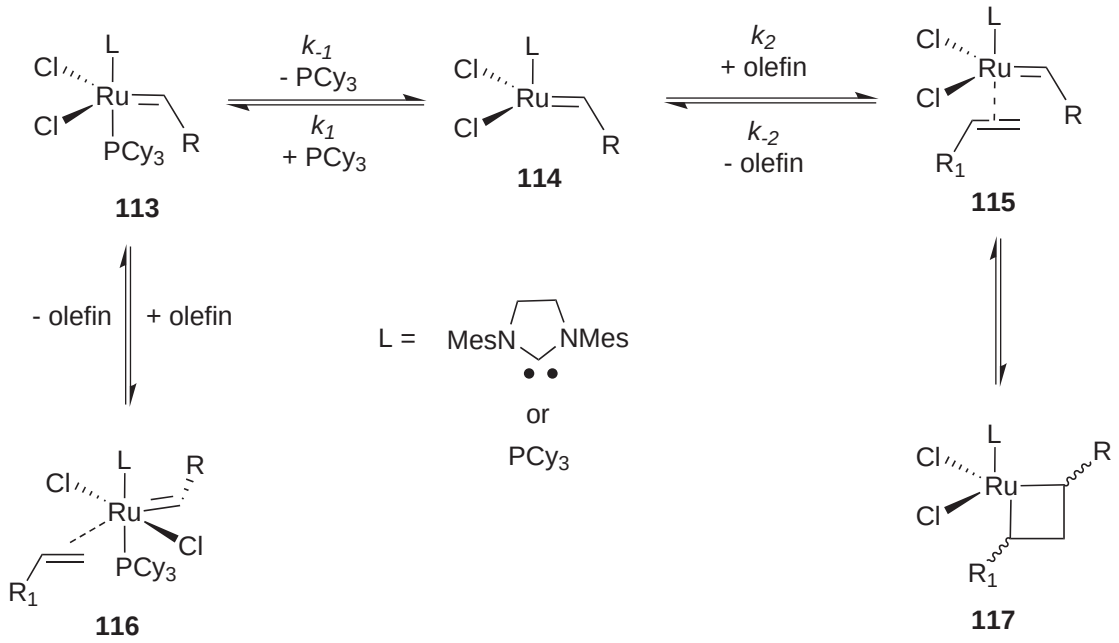


Figure 1.6: Ruthenium catalysts.

In contrast to the Schrock catalyst **17**, the three complexes shown in Figure 1.6 are pre-catalysts; the active species are generated under the reaction conditions. An understanding of the mechanism of the catalyst formation is therefore crucial in order to improve catalyst design.[111,120] Two possible mechanistic pathways have been envisaged (Scheme 1.37). Complex **113** could exchange the phosphine ligand for an olefin *via* the 14-electron complex **114** (dissociative pathway) or by first coordinating the olefin and forming the 18-electron complex **116**. The latest studies by Grubbs and co-workers suggest that **114** is the key intermediate for the olefin metathesis reaction with no evidence for the formation of **116**.

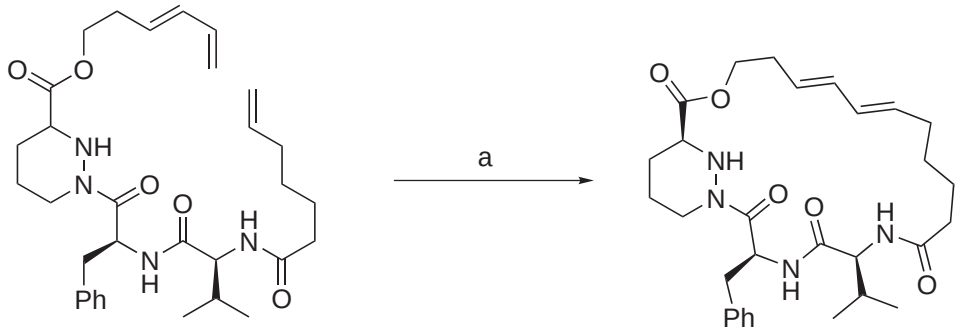


Scheme 1.37: Mechanism of metathesis using ruthenium catalysts.

Other findings by Grubbs also account for the increase of reactivity of the NHC complexes. In the case of the first-generation Grubbs' catalyst **98**, the loss of a phosphine ligand is facile (k_{-1} large) but the re-coordination of the phosphine is much faster than the coordination of the olefin ($k_1/k_2>>1$). Therefore, the active species **114** is formed more frequently but carries out fewer turnovers. Substitution of a phosphine ligand by an NHC ligand will stabilize the metal complex thanks to the strong *sigma*-donor character of the NHC. The dissociation of the phosphine will therefore be slower (k_{-1} small) but the re-binding rate of the phosphine will also decrease. The catalyst will be more stable and once the catalytic species **114** is generated, it can perform a larger number of turnovers.

1.3.4 Ring-Closing Metathesis (RCM)

The most common metathesis reaction used in organic chemistry is ring-closing metathesis (RCM). Various reviews have detailed the use of RCM in the synthesis of small (five-membered rings) to large ring-systems[97,99,121] e.g. the 22-membered core of sanglifehrin, as shown in scheme 1.38.[122]

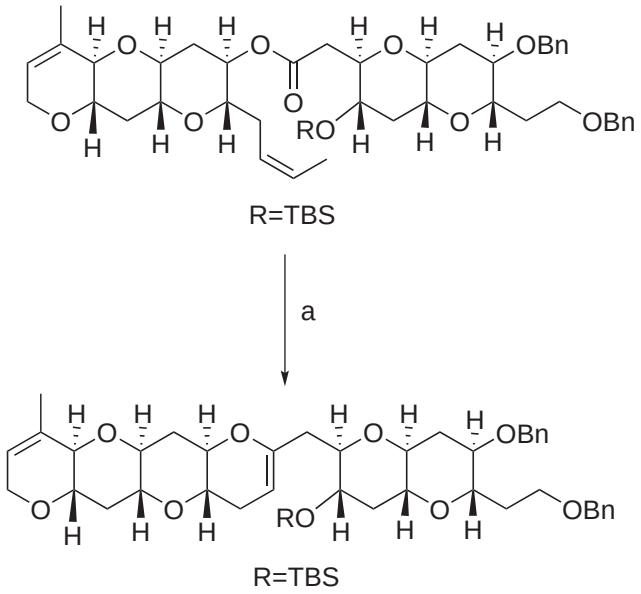


Scheme 1.38: Conditions: a) Grubbs I catalyst **98**, CH_2Cl_2, reflux, 57%.

As my subject is mainly concerned with the preparation of cyclic ethers, the following section will focus on the use of RCM for their synthesis.

Synthesis of Cyclic Ethers by RCM

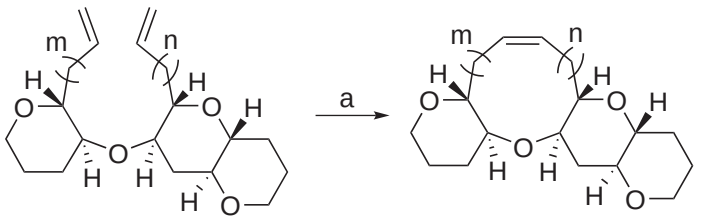
Clark (see chap 1.2.3) and Rainier (see chap 1.2.1) have both used a RCM approach for the synthesis of polycyclic ethers. However, other groups have also prepared cyclic ethers using this strategy. Nicolaou combined methylenation and ring-closing metathesis into a domino process which allowed the transformation of acyclic olefinic ester into cyclic enol ethers.[32] The efficiency of this technique is illustrated by the synthesis of a hexacyclic polyether (Scheme 1.39).[123]



Scheme 1.39: Conditions: a) Tebbe's reagent **111**, reflux, 57%.

Hirama also used the RCM reaction for the synthesis of medium-ring cyclic ethers (Scheme 1.40).[124] He found that the yields for the preparation of seven- to ten-membered

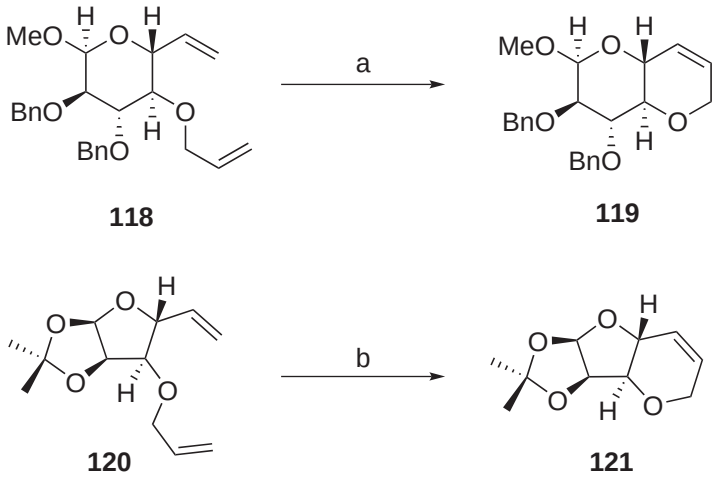
rings were uniformly excellent.



m	n	Solvent	Yield
0	0	benzene	81%
0	1	CH_2Cl_2	94%
1	1	CH_2Cl_2	87%
2	1	CH_2Cl_2	68%

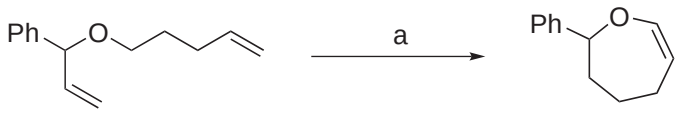
Scheme 1.40: Conditions: a) Grubbs I catalyst **98** (12-21 mol%).

Van Boom and co-workers have disclosed a route to bicyclic ethers based on the RCM of diene carbohydrate derivatives.[125] RCM of dienes **118** and **120** with Grubbs' first-generation catalyst **98** gave the *trans*-fused ethers **119** and **121** in good to excellent yields (Scheme 1.41).



Scheme 1.41: Conditions: a) Grubbs I catalyst **98** (4 mol%), toluene, rt, 93%; b) Grubbs I catalyst **98** (3-5 mol%), CH_2Cl_2, rt, 63%.

More recently, Snapper and co-workers have reported the preparation of cyclic enol ethers through a ruthenium-catalysed RCM-olefin isomerisation sequence.[126] RCM of diene **122** in dichloromethane followed by passage of forming gas (N_2:H_2 = 95:5) through the solution and heating at 70 °C gave the cyclic enol ether **123** in 50% yield (Scheme 1.42). The olefin isomerisation is thought to proceed through several intermediates to provide the less substituted enol ether, although the specific ruthenium catalyst responsible for the isomerisation is still in question.

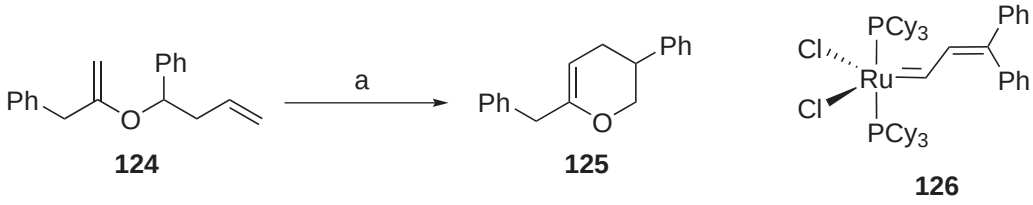


122 **123**

Scheme 1.42: Conditions: a) Grubbs II catalyst **92** (10 mol%), CH_2Cl_2, rt then N_2:H_2 (95:5), 65-70 °C, 50%.

Cyclic Ether Synthesis by RCM of Enol Ethers

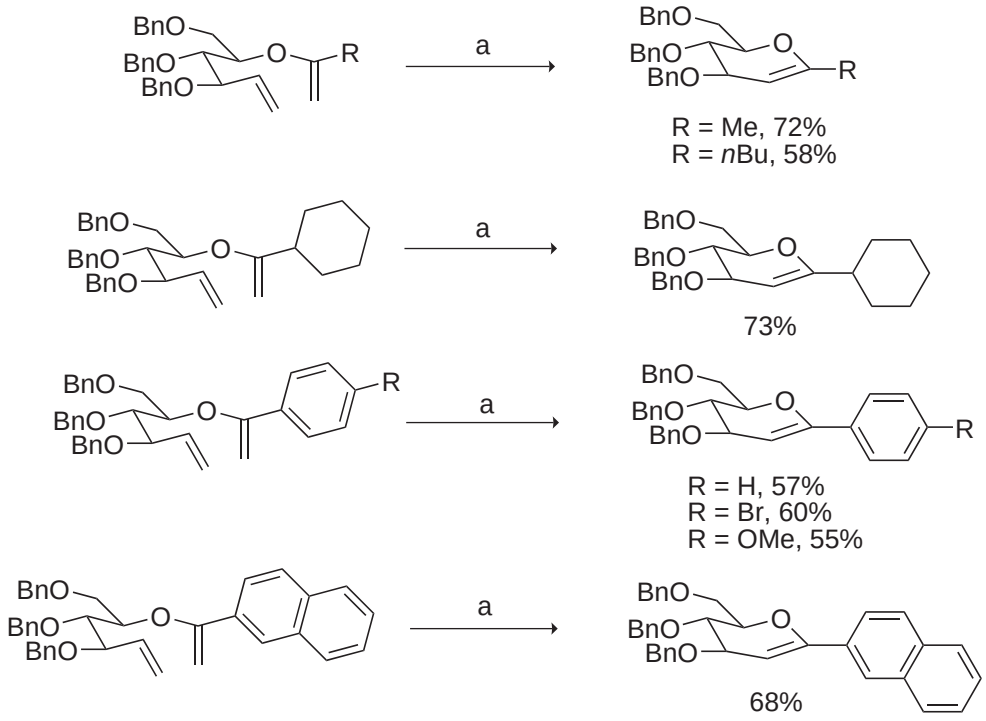
The first report of the RCM of enol ethers appeared from the Grubbs group, who showed that enol ethers were suitable substrates for RCM.[127] Treatment of acyclic enol **124** with Schrock catalyst **17** gave the six-membered cyclic enol ether **125** in 84% yield (Scheme 1.43). Ruthenium catalyst **126** did not catalyse the RCM of acyclic enol ethers but slowly catalysed the dimerisation of starting material.



124 **125** **126**

Scheme 1.43: Conditions: a) Schrock catalyst **19** (13 mol%), *n*-pentane, rt, 84%.

As seen before, the Clark's and Rainier's groups reported soon after that the synthesis of six-membered cyclic enol ethers was possible using Schrock catalyst **17**. Postema and co-workers also reported the use of Schrock catalyst to access *C*1-glycals from the corresponding acyclic dienes.[128,129] A variety of acyclic dienes derived from tri-*O*-benzyl-D-glucal was exposed to the Schrock catalyst and delivered the corresponding cyclic products in average to good yields (Scheme 1.44).



Scheme 1.44: Conditions: a) Schrock catalyst **17** (25-50 mol%), toluene, reflux.

Even though these experiments demonstrated the feasibility of the reaction, the conditions required for the operation - glove box, high catalyst loadings - were not ideal for a routine use in a research laboratory.

The first reports of efficient use of the different Grubbs catalysts for the RCM of enol ethers appeared in 1998 and 2001. First, Sturino and Wong reported the formation of substituted dihydropyrans by RCM reaction of enol ethers using Grubbs' first generation catalyst **98**.[130] Three enol ethers (entries 1, 2 and 3) were treated with Grubbs I catalyst **98** in benzene at reflux and the dihydropyrans were obtained in average to excellent yields (Table 1.1). However, the reaction was very sensitive to the substitution pattern of the substrate: if an alkoxy group was present at the allylic position, the reaction was completely shut down (entries 4, 5 and 6). The addition of a *gem*-dimethyl substituent restored the reactivity, probably due to the Thorpe-Ingold effect (entry 7). 1,1-Disubstituted enol ethers were also unreactive under the same conditions (entry 8).

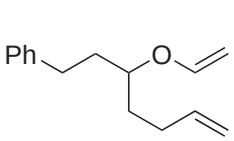
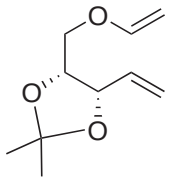
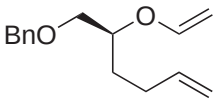
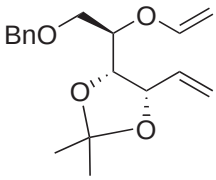
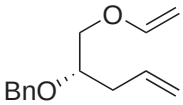
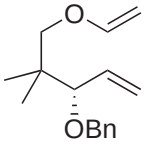
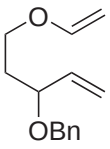
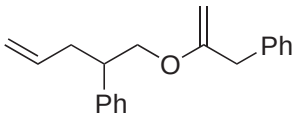
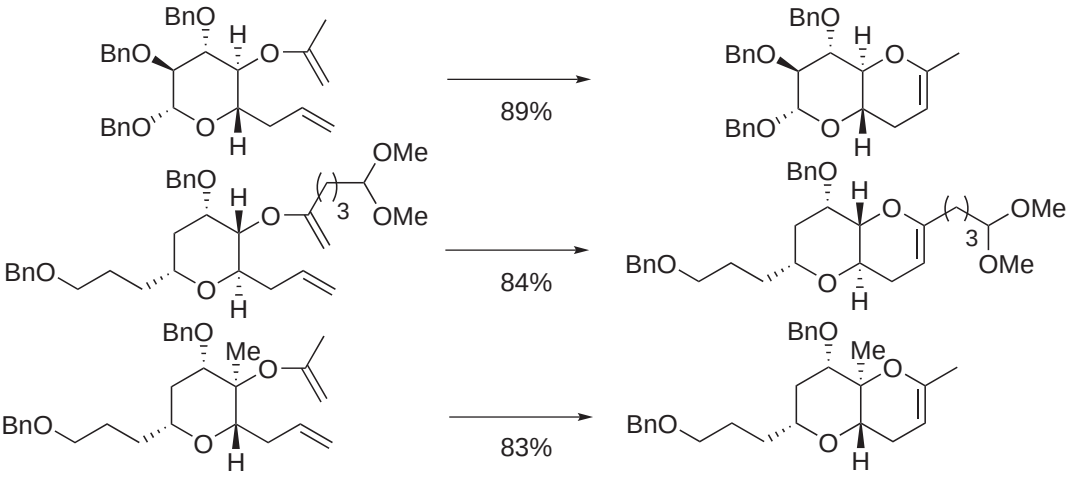
Entry	Substrate	Yield	Entry	Substrate	Yield
1		95%	5		0%
2		69%	6		0%
3		45%	7		45%
4		0%	8		0%

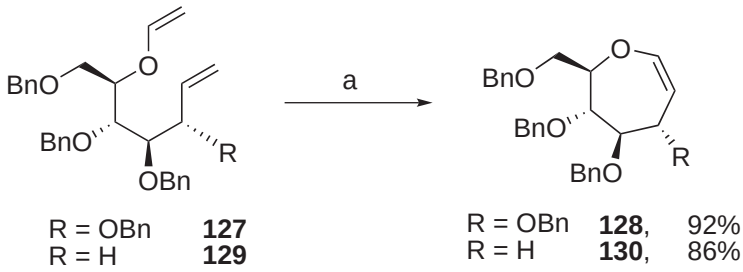
Table 1.1: Conditions: Grubbs I catalyst **98** (20 mol%), benzene, reflux.

Three years later, Rainier and co-workers described the first use of Grubbs' second generation catalyst **92** for the RCM of enol ethers.[58] This time, 1,1-disubstituted enol ethers were tolerated and the catalyst gave the same yields as the Schrock catalyst **17** without the inconvenience of using a glove box (Scheme 1.45).



Scheme 1.45: Conditions: Grubbs II catalyst **92** (20 mol%), benzene, rt.

Seven-membered cyclic enol ethers were also prepared by RCM, but only using the Schrock catalyst **17** (Scheme 1.46).[131] The catalyst loadings were high but the oxepenes **128** and **130** were formed in very good yields. This study also demonstrated the inefficiency of the Grubbs second-generation catalyst **92** to effect the ring-closure.

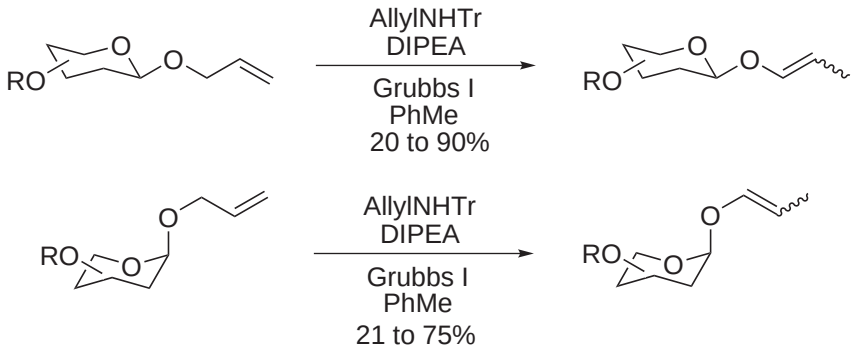


Scheme 1.46: Conditions: a) Schrock catalyst **17** (20 mol%), toluene, 60 °C.

1.3.5 Isomerisation Reactions with Metathesis Catalysts

Since the late 1990's, non-metathesis reactions promoted by ruthenium carbene complexes have been reported such as isomerisation,[132] hydrogenation,[133] radical reaction,[134] silane activation,[135] cycloisomerisation,[136] cyclopropanation,[137] etc.

The isomerisation of carbon-carbon double bonds was first described by Grubbs,[132] and is probably the most studied non-metathetic reaction. Later, Roy and co-workers developed an isomerisation reaction of *O*-allyl glycosides using a combination of first-generation Grubbs' catalyst **98** with *N*-allyltritylamine and *N*,*N*-diisopropylethylamine (Scheme 1.47).[138]



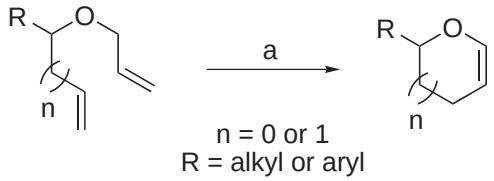
Scheme 1.47: Isomerisation of allylic ethers with Grubbs' first-generation catalyst **98** .

Aly reported the deprotection of allylic amines *via* a ruthenium-catalysed isomerisation followed by hydrolysis of the enamine intermediate.[139] This methodology was later applied by Cossy to allylic or homoallylic ethers and amines.[140]
The isomerisation reaction can also be used in tandem with the metathesis reaction.

Tandem RCM/Isomerisation Reactions

Snapper first described the synthesis of cyclic enol ethers through a RCM/isomerisation sequence (see chap. 1.3.4).

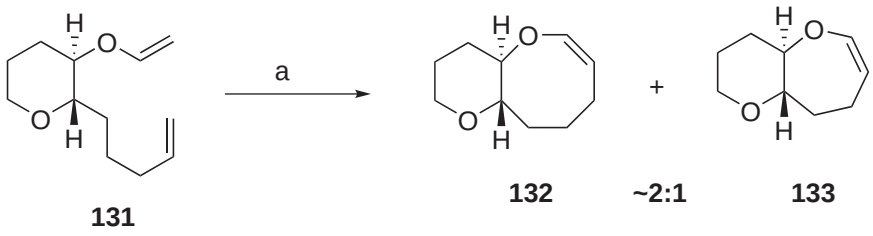
Schmidt introduced the use of additives to promote the isomerisation reaction after completion of the RCM.[141] Hydride sources, such as NaH or $NaBH_4$, were found to be very efficient at providing the less substituted cyclic ethers (Scheme 1.48). He also reported some spectroscopic evidence of the formation of a Ru-H species during the reaction.[142] However, the real nature of the catalyst involved and the mechanism are still open to question.



Scheme 1.48: Conditions: a) Grubbs I catalyst **98** (5 mol%), toluene, rt then NaH or $NaBH_4$ (50 mol%), 110 °C, 64-94%.

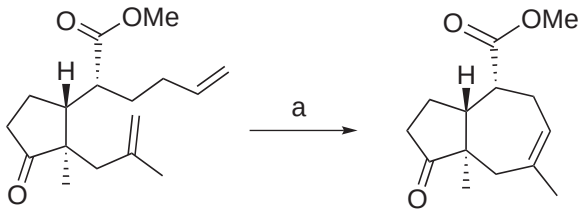
Tandem Isomerisation/RCM Reactions

Clark reported competitive isomerisation occuring during RCM of enol ethers. When diene **131** was subjected to molybdenum catalyst **17**, a 2:1 mixture of eight- and nine-membered cyclic enol ethers (**132** and **133** respectively) was obtained (Scheme 1.49).[86,90]



Scheme 1.49: Conditions: a) Schrock catalyst **17** (33 mol%), 60 °C, 40%.

Micha used a combination of two compatible ruthenium catalysts to realise the two different steps.[143] The first complex $RuCl(CO)H(PPh_3)_3$ isomerised the terminal olefin before the Grubbs II catalyst **92** closed the ring by RCM (Scheme 1.50).



Scheme 1.50: Conditions: a) Grubbs II catalyst **92** (5 mol%), $RuCl(CO)H(PPh_3)_3$ (5 mol%), benzene, reflux, 94%.

1.3.6 Summary

Olefin metathesis has developed into an indispensable tool for advanced organic and polymer synthesis. The application of RCM has revolutionised the logic of retrosynthetic analysis and has become a key reaction in organic synthesis. The continued development of new molybdenum and ruthenium catalysts has resulted in a tremendous expansion in the usefulness of the metathesis reactions.

Although metathesis reactions of dienes will continue to be important, recent developments indicate that metathesis of other π-systems will become more important in the near future. Significant progress is being made towards a deeper understanding of enyne[144] and diyne[145] metathesis. Another area of continued interest is the development of asymmetric metathesis reactions.[146,147]

It can be concluded that metathesis in general, and olefin metathesis in particular, are among the most important advances in preparative chemistry in recent years, although many stimulating discoveries certainly still lie ahead.

1.4 Gambieric Acids

1.4.1 Isolation and Biological Activity

The gambieric acids A-D were first isolated in 1992 by Yasumoto and co-workers from a culture of the marine dinoflagellate *Gambierdiscus toxicus* (GII1 strain).[5,6] These dinoflagellates usually grow on dead corals and were collected near the Gambier Islands in French Polynesia (Figure 1.7).

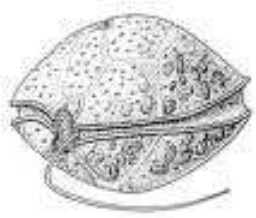


Figure 1.7: *Gambierdiscus toxicus*, magnification x2000.

The gambieric acids exhibit very high antifungal activity against *Aspergillus niger* and several other fungi. They are 2000 times more potent than amphotericin B, which is a natural product currently used as an antifungal drug.[148] They also possess some cytotoxicity but they are much less neurotoxic than other marine polycyclic ether natural products such as the brevetoxins, which means that the gambieric acids have some potential as antifungal drugs. Interestingly, it has also been shown that gambieric acid A inhibits the binding of PbTx-3, a brevetoxin B derivative, to site 5 on the voltage-gated sodium channels of excitable membranes.[149]

However, the biological evaluation is still far from complete. Indeed, the extraction process is very long and low yielding: 5000 L of culture kept at 25 °C for 38 days, followed by numerous extractions and column chromatographies gave only 6 mg of a mixture of the acids. Completing the total synthesis of these compounds would allow further toxicity and activity studies to be conducted and a more complete bioactivity profile to be developed.

1.4.2 Structure

The structures of the gambieric acids were established using extensive 1D and 2D NMR studies.[5] It was found that all of them share a common skeleton made of a nine *trans*-fused six-, seven- and nine-membered cyclic ethers and a side chain containing a trisubstituted THF ring (Figure 1.8). Structural differences lie in the presence of an angular methyl group at the C12 position for gambieric acids B and D and an ester at the end of the other side chain for gambieric acids C and D. The absolute configuration was only established later.[150] The configuration of the alcohol at the C9 position was determined by forming the Mosher's ester with α-methoxy-α-trifluoromethylphenylacetic acid. Analysis of the modification of the chemical shift of the protons around the C9 position suggested a R configuration at this position. The methyl group on the side chain attached to the J ring was assigned R configuration by HPLC analysis of the compound obtained after oxidative cleavage of the trisubstituted double bond and derivatisation of the corresponding carboxylic acid. The absolute configuration of the

A ring was determined by NMR analysis of the phenylglycine methyl ester. The carbons C11 and C12 were then assigned based on NOE analysis and $^{3}J_{H,H}$ values and the configurationof centres in the remainder of the polycyclic core was then deduced.

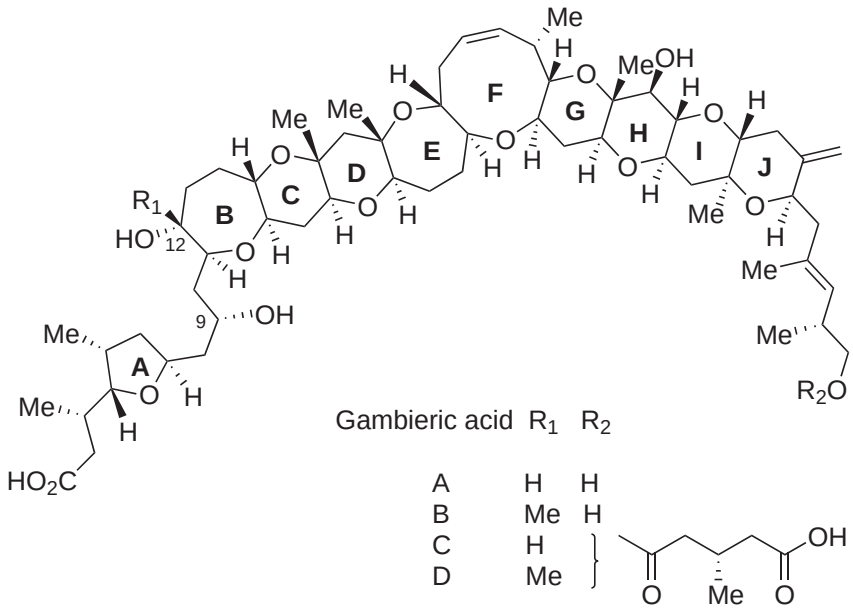


Figure 1.8: Gambieric acids A-D.

Recently, Sasaki and co-workers recently reported the synthesis of the proposed AB fragment of gambieric acid B.[151] The NMR spectrum obtained showed important differences when compared to the spectrum described in the isolation paper and so they suspected that the relative configuration of the polycyclic core to the THF-containing side had been misassigned. To confirm their hypothesis, they prepared the four different diastereomers (**134a** to **134d**) of the AB model system and compared the NMR spectrum of these compounds to those of the natural products (Figure 1.9).

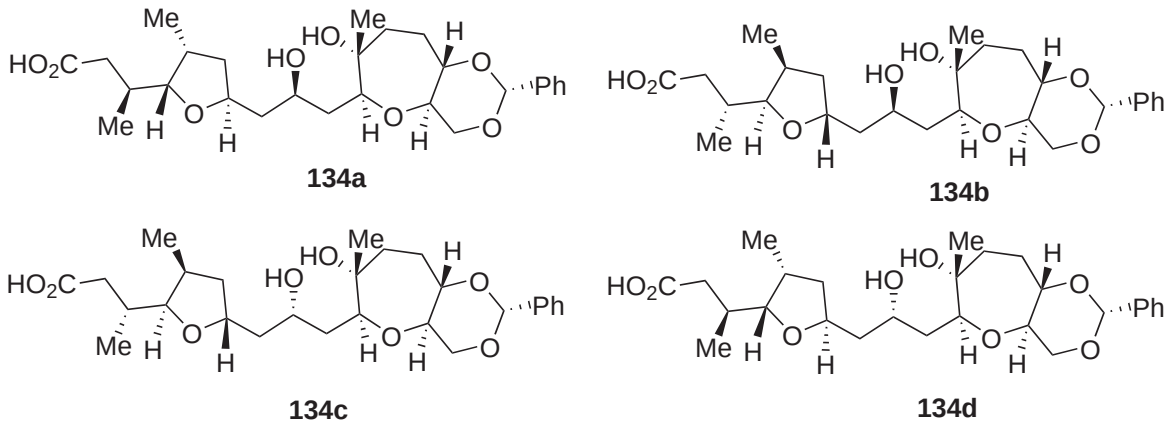


Figure 1.9: Four diastereomers of the AB fragment of gambieric acid B.

They concluded that the data for **134c** matched best with the data for natural products. Since the configuration of the alcohol at C9 has been unambiguously assigned by the Mosher's ester protocol[150] and **134c** possess the opposite configuration, they claimed that the absolute configurations of the stereogenic centres in the polycyclic core (rings B-J) should be reversed (Figure 1.10). Later, they prepared the AB fragment of gambieric acid A and the ABC fragment of gambieric acid B and obtained good correlations between the NMR data for this tricyclic fragment and that of the natural product.[152]

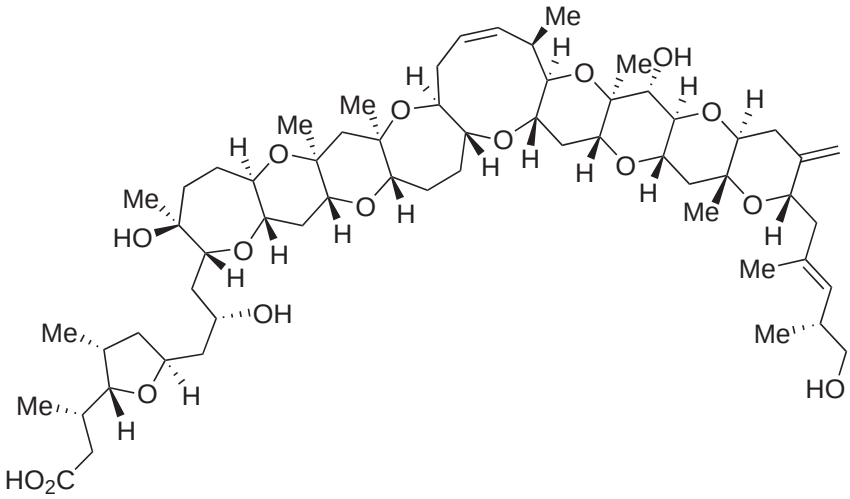


Figure 1.10: Proposed structure of gambieric acid B by Sasaki and co-workers.

1.4.3 Previous Synthetic Studies Towards the Total Synthesis of Gambieric Acids

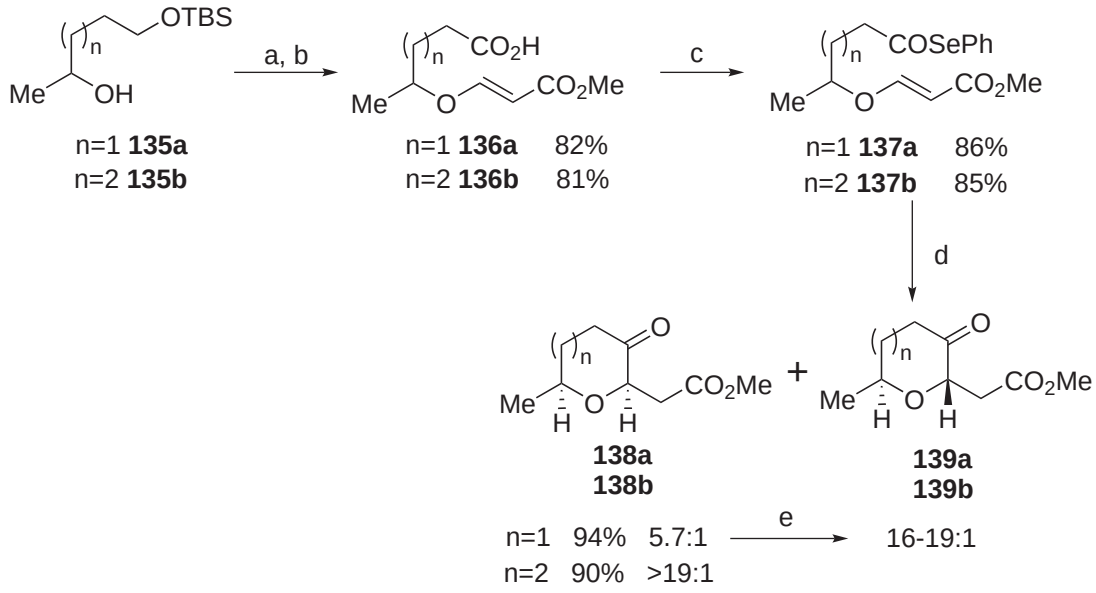
The interesting biological properties of the gambieric acids coupled with their very challenging chemical structures have attracted the interest of many synthetic groups. Although several total syntheses of other polycyclic ether natural products have been described in the literature,[31,33–37] the total synthesis of any gambieric acids has not been published. The following sections provide a brief review of the different synthetic efforts towards fragments of these molecules.

Evans' approach to BC and IJ fragments

Evans and co-workers reported an iterative methodology, using a radical cyclisation of an acyl selenide, to access *trans*-fused ether ring systems containing six- and seven-membered rings.[153] This represents the construction of the BC and IJ fragments of the gambieric acids.

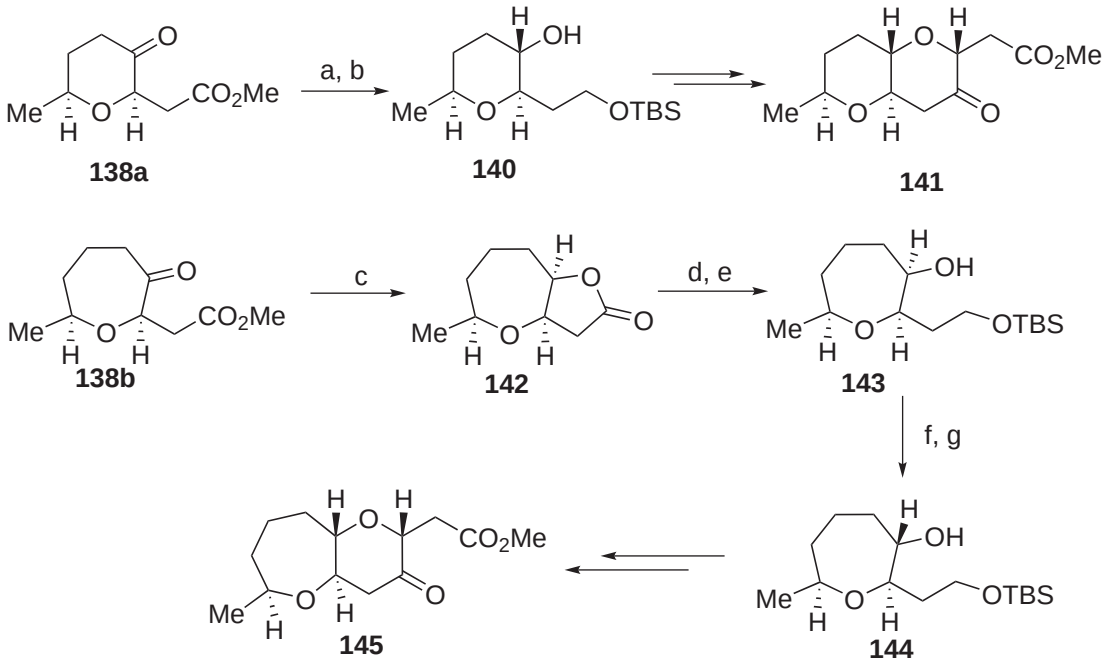
Secondary alcohols **135a,b** were first alkylated with methylpropiolate and the primary

silyl ether was oxidised using Jones conditions to deliver the corresponding carboxylic acids **136a,b** (Scheme 1.51). Using the Crich protocol,[154] triethylamine followed by phenylselenyl chloride and tri-*n*-butylphosphine, acyl selenides **137a,b** were obtained in high yields. Cyclisation occurred upon treatment with tris(trimethylsilyl)silane and triethylborane to deliver the two cyclic ethers **138a,b** and **139a,b**. Surprisingly, the formation of the seven-membered ring **138b** was completely selective towards the formation of the *cis*-product ($dr > 19{:}1$), whereas the tetrahydropyranone **138a** was obtained with a 5.7:1 selectivity and had to be refluxed with a catalytic amount of DBU to deliver the desired isomer **138a** as the sole product.



Scheme 1.51: Conditions: a) methylpropiolate, $(n\text{Bu})_3\text{P}$, CH_2Cl_2, rt; b) Jones' oxidation, acetone, -10 °C to rt; c) Et_3N, CH_2Cl_2, rt then PhSeCl, Bu_3P, THF, rt; d) $(Me_3Si)_3SiH$, Et_3B, benzene, air, rt; e) DBU, toluene, 95%.

The tetrahydropyranone **138a** was then selectively reduced using $LiAlH_4$ and the primary alcohol was protected as a TBS ether to give alcohol **140**, which could then undergo another synthetic sequence to furnish bicyclic compound **141** (Scheme 1.52). Selective reduction of oxepinone **138b** proved to be much more difficult and finally L-selectride was found to give only one alcohol **142** but with the undesired *cis* relative configuration. After reduction of the lactone and protection of the primary alcohol as previously, the stereochemistry of the secondary alcohol was inverted using the Mistunobu protocol to afford alcohol **144**. An iterative sequence was then applied and delivered the bicyclic system **145**.



Scheme 1.52: Conditions: a) $LiAlH_4$, THF, −78 °C to 0 °C, quant.; b) TBSCl, imidazole, CH_2Cl_2, rt, 77%; c) L-selectride, THF, −78 °C, 88%; d) $LiAlH_4$, Et_2O, 0 °C, 89%; e) TBSCl, imidazole, CH_2Cl_2, rt, 90%; f) DEAD, PPh_3, *p*-nitrobenzoic acid, toluene, reflux, 96%; g) KOH, MeOH:H_2O (9:1), rt, 86%.

The increased selectivity for the formation of the second ring, >19:1 for the six-membered substrate and 17:1 for the seven-membered precursor, can be explained by a transition state, in which the pyran and oxepine rings lock the substituents of the newly forming pyran ring in *pseudo*-equatorial environments (Figure 1.11).

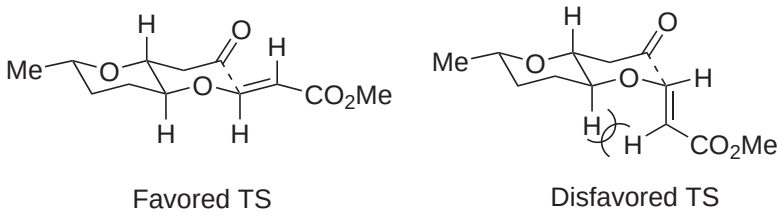
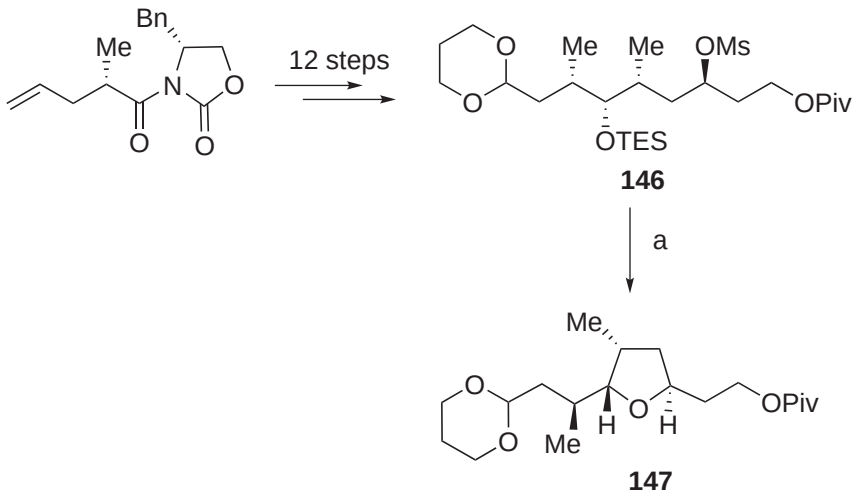


Figure 1.11: Transition states for the second radical cyclisation.

Yamamoto's synthesis of the A and J ring

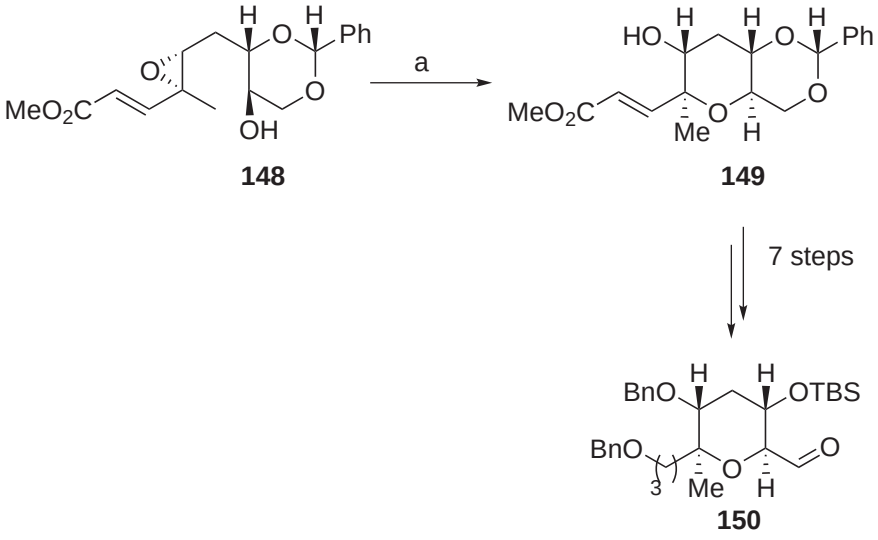
In 2001, Yamamoto and co-workers reported their first synthetic efforts towards the total synthesis of the gambieric acids.[155] They published an approach for the synthesis of the tri-substituted tetrahydrofuran A ring relying on Evans alkylation chemistry and Brown's chiral boron complexes to generate the desired stereocentres (Scheme 1.53). Treatment with TBAF triggered the cyclisation to give tetrahydrofuran **147** in high

yield and with complete stereoselectivity.



Scheme 1.53: Conditions: a) TBAF, THF, rt, 84%.

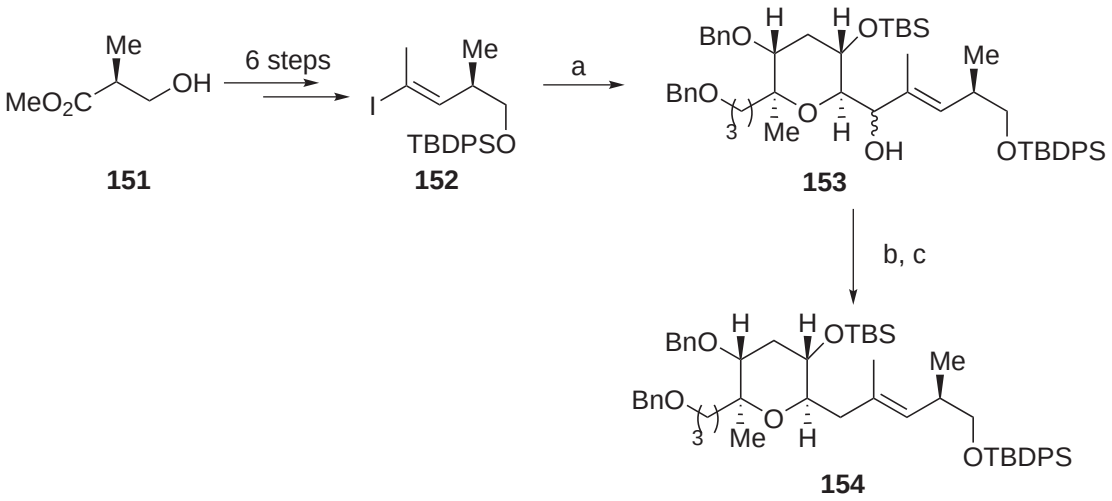
They also disclosed their strategy for the preparation of the terminal tetrahydropyran J ring possessing the side chain present in the natural product.[156] They first prepared the six-membered cyclic ether **149** by an acid-catalysed 6-*endo* cyclisation of hydroxyepoxide **148** (Scheme 1.54). Several functional group manipulations were required to access the desired aldehyde **150**.



Scheme 1.54: Conditions: a) cat. PPTS, CH_2Cl_2, rt, 78%.

The other fragment required for coupling, vinyl iodide **152**, was synthesised in six steps from commercially available (*S*)-Roche ester **151** (Scheme 1.55). Vinyl iodide **152** was then treated with *t*BuLi and the corresponding vinyl lithium reagent was added to the aldehyde **150** to afford the desired alcohol **153** as a mixture of diastereomers.

The hydroxyl group was then removed using the Barton deoxygenation procedure to deliver the J-ring fragment **154** in poor yield.[157]



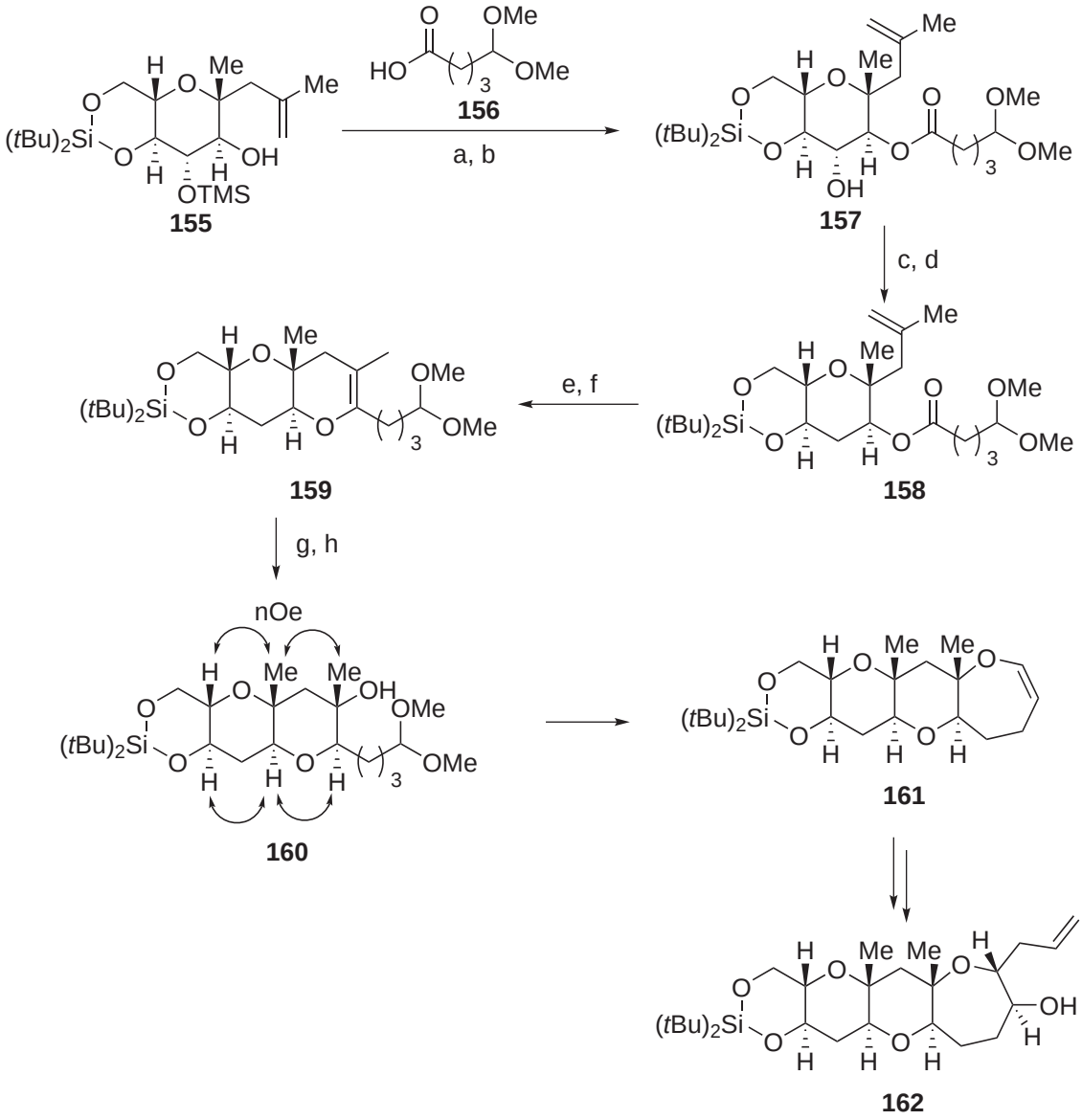
151 **152** **153** **154**

Scheme 1.55: Conditions: a) *t*BuLi, Et_2O then **150**, −78 °C, 76%; b) CS_2, KH, Et_2O, rt then MeI, rt, 98%; c) Bu_3SnH, AIBN, benzene, reflux, 25%.

Rainier's Approach to the A-E subunit

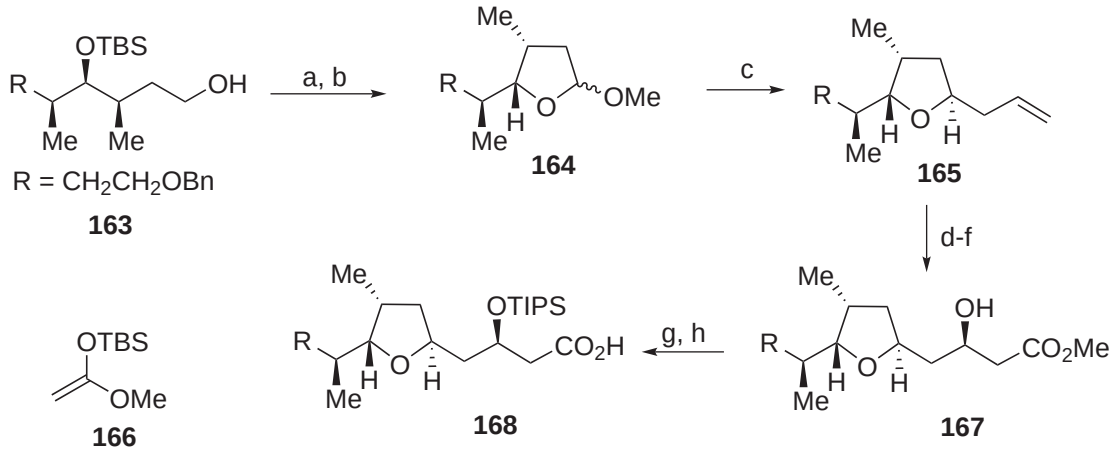
As discussed before (see p. 17), Rainier and co-workers have developed several strategies for the synthesis of polycyclic ether units. In 2007, they reported a synthesis of the A-E fragment of gambieric acid A using their methodology.[66]

Their synthesis started from alcohol **155**, which was obtained from D-glucose in 11 steps. Esterification with carboxylic acid **156** followed by a three-step deoxygenation procedure gave the required precursor **157** (Scheme 1.56). Methylenation of the ester using Takai-Utimoto conditions gave the corresponding enol ether, which was treated with the Grubbs second generation catalyst **92** to give bicyclic compound **159** in good yield.[61] Epoxidation of the enol ether followed by reductive opening with Dibal-H gave alcohol **160**, the configuration of which was confirmed by NOE studies. Cyclisation under acidic conditions gave the system containing the seven-membered E ring in high yield. Subsequent DMDO epoxidation of the enol ether **161** followed by treatment with allylmagnesium chloride introduced the last side chain. Further steps were required to set the exact configuration of both centres and obtain the desired alcohol **162** as a single diastereoisomer. This fragment corresponds to the C-E subunit of gambieric acid A.



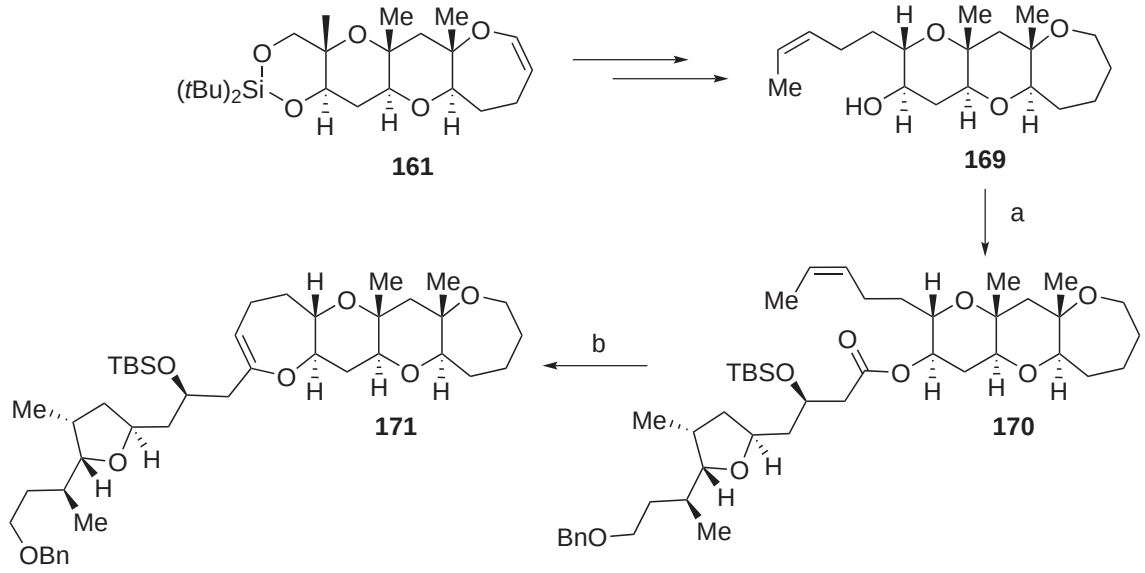
Scheme 1.56: Conditions: a) **156**, DCC, DMAP, CH_2Cl_2, rt, 92%; b) CSA, MeOH, rt, 91%; c) CS_2, NaH, MeI, rt; d) Bu_3SnH, AIBN, toluene, 110 °C, 72% (2 steps); e) $TiCl_4$, Zn, $PbCl_2$, CH_2Br_2, TMEDA, THF, reflux; f) Grubbs II, benzene, reflux, 80% (2 steps); g) DMDO, CH_2Cl_2, rt; h) Dibal-H, CH_2Cl_2, −78 °C, 95% (2 steps); i) PPTS, Pyr., PhCl, 135 °C, 80%.

Next, they prepared the A-ring as a single diastereomer using a $BF_3{\cdot}Et_2O$ catalysed addition of trimethylallylsilane onto lactol **164** (Scheme 1.57). Oxidative cleavage of the terminal alkene **165** followed by a Mukaiyama aldol-type reaction with **166** gave hydroxy ester with **167** in very good yield. Protection of secondary alcohol and ester hydrolysis gave carboxylic acid **168**.



Scheme 1.57: Conditions: a) TPAP, NMO, CH_2Cl_2, rt; b) HCl, MeOH, rt, 75% (2 steps), α:β=4.5:1; c) allylTMS, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, quant. (dr > 95:5); d) OsO_4, NMO, THF, tBuOH, H_2O, rt, 98%; e) $Pb(OAc)_4$, benzene, rt, quant.; f) **166**, Me_2AlCl, toluene, −78 °C, 86% (dr = 5.1:1); g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 83%; h) LiOH, THF, H_2O, rt, 93%.

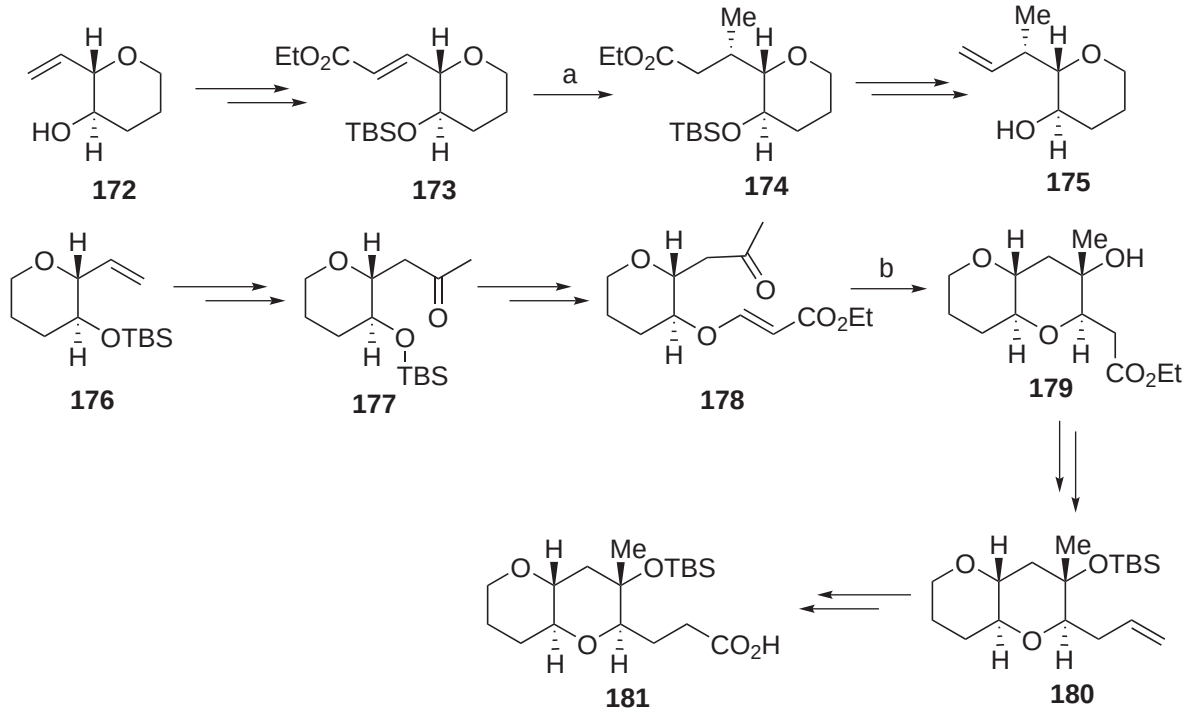
The alcohol partner **169** was a model of the C-E fragment prepared in eight steps from intermediate **161** (Scheme 1.58). Esterification was realised using Yamaguchi conditions and delivered ester **170** quantitatively.[158] Treatment under Takai-Utimoto conditions using dibromoethane instead of dibromethane gave directly the cyclised product with **171** in reasonable yield.



Scheme 1.58: Conditions: a) **168**, Et_3N, 2,4,6-trichlorobenzoyl chloride, DMAP, THF, 40 °C, quant.; b) $TiCl_4$, TMEDA, Zn dust, $PbCl_2$, CH_3CHBr_2, THF, CH_2Cl_2, reflux, 50%.

Sasaki's Approach

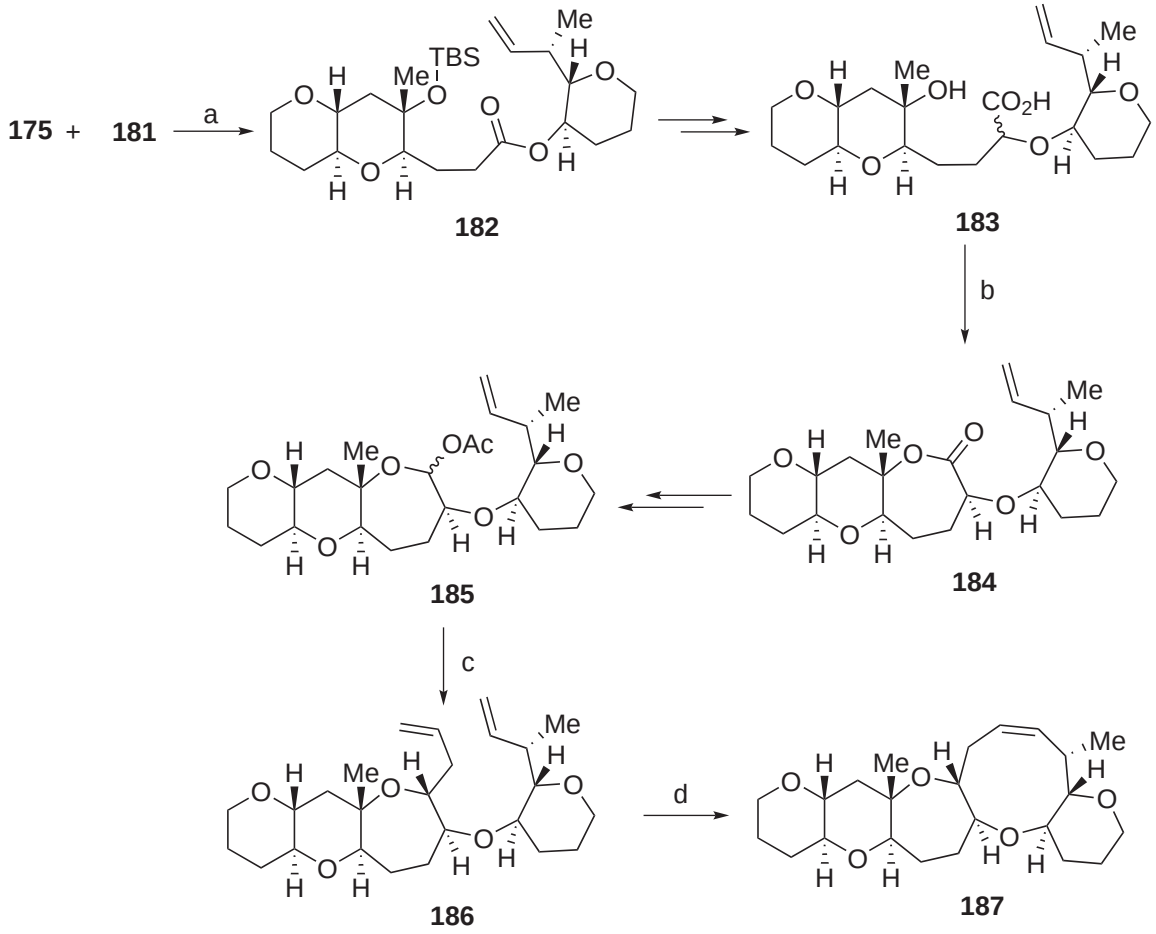
The Sasaki group reported their first synthetic efforts towards the total synthesis of gambieric acids in 2005 with the synthesis of the central C-G fragment.[159] They started the synthesis with the preparation of the six-membered G ring **173** from known alcohol **172** (Scheme 1.59).[160] Protection of secondary alcohol as a silyl ether followed by oxidative cleavage and Wittig reaction gave unsaturated ester **173**. Stereoselective 1,4-addition with methylmagnesium bromide in the presence of *iso*propylsalicylaldimine copper(II) complex gave **174** as a single diastereoisomer. Reduction of the ester, dehydration and TBAF treatment gave terminal alkene **175**. The synthesis of the CD system started from another known alkene **176**,[161] which was transformed in four steps to the corresponding methyl ketone **177**. The secondary alcohol was converted into the enol ether **178** and samarium-induced reductive cyclisation of keto-ester **178** created the two additional stereocentres in a completely selective fashion. Reduction of the ester followed by Wittig methylenation gave alkene **180**, hydroboration and two oxidation reactions completed the homologation sequence and delivered the desired carboxylic acid **181**.



Scheme 1.59: Preparation of G and CD fragments. Conditions: a) *iso*-propylsalicylaldimine copper, MeMgBr, TMSCl, THF, −45 °C, 92%; b) SmI_2, THF, MeOH, 0 °C, 99%.

Intermolecular esterification was conducted under Yamaguchi conditions to deliver ester **182** (Scheme 1.60).[158] The ester was then partially reduced to the mixed acetal,

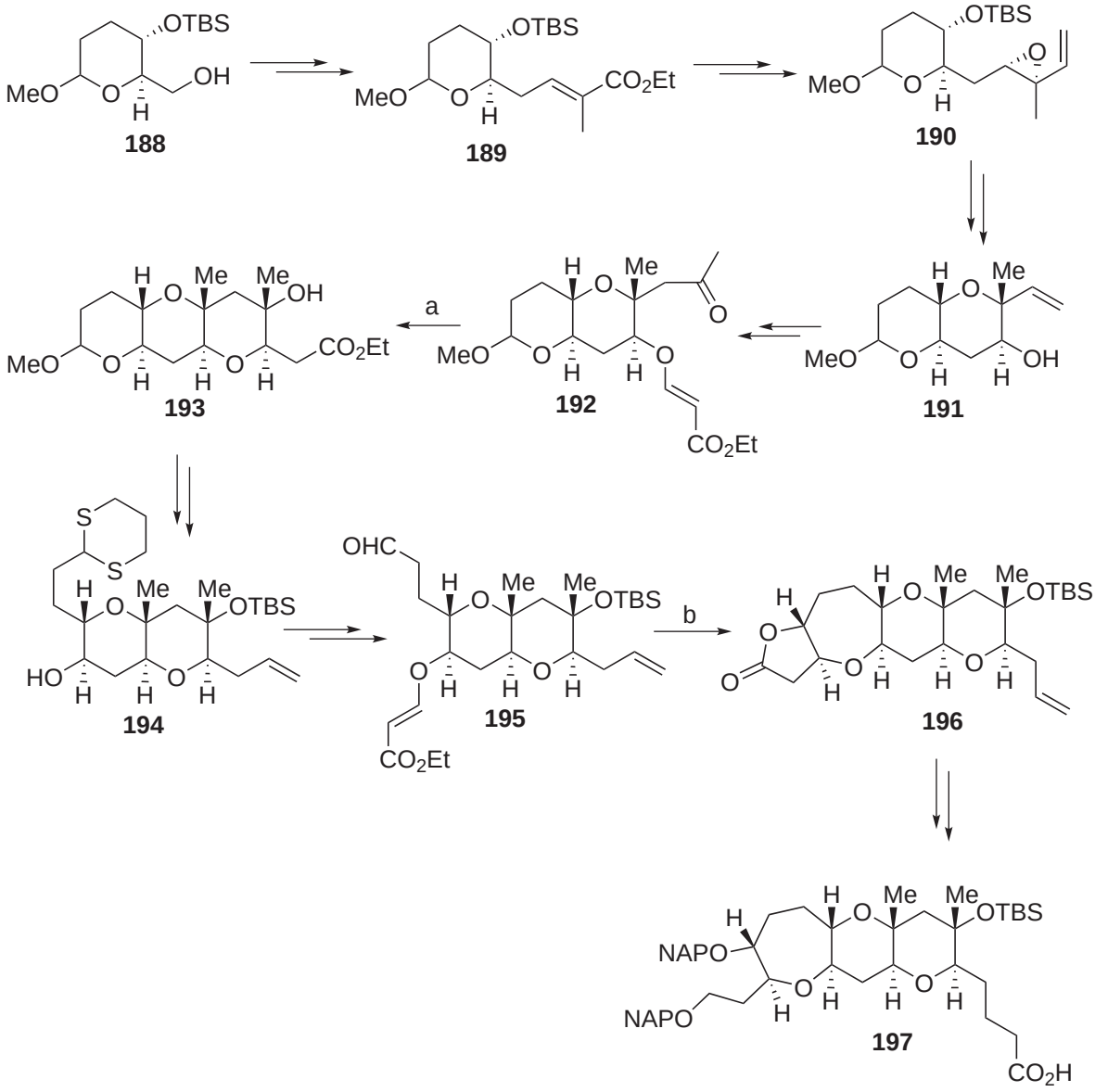
which was treated with TMSCN and TMSOTf to obtain carboxylic acid **183** after TBS deprotection and hydrolysis of the nitrile group. Another Yamaguchi reaction gave lactone **184** as a separable 1:1 mixture of diasteromers. Further partial ester reduction followed by acetate formation gave mixed acetal **185**, which was treated with allyltrimethylsilane under Lewis acid conditions to furnish diene **186**. Final RCM with Grubbs' second generation catalyst delivered the pentacyclic C-G fragment **187** in excellent yield.



Scheme 1.60: Completion of the C-G fragment. Conditions: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 40 °C, 93%; b) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux, 38%; c) allylTMS, $BF_3{\cdot}Et_2O$, CH_3CN, −40 °C to 0 °C, 67%; d) Grubbs II catalyst **92**, CH_2Cl_2, reflux, 98%.

Once the strategy for the synthesis of the two biggest rings had been established on a small fragment, the synthesis of the whole nonacyclic core was reported.[162] The B-D fragment was prepared in 32 steps from known alcohol **188** (Scheme 1.61). Successive Wittig reactions gave unsaturated ester **189** which was reduced and engaged in an enantioselective Sharpless epoxidation reaction. Further oxidation of primary alcohol and Wittig methylenation gave alkene **190**. Deprotection and acid-catalysed epoxide opening formed the C ring and the resulting alcohol **191** was then submitted to a

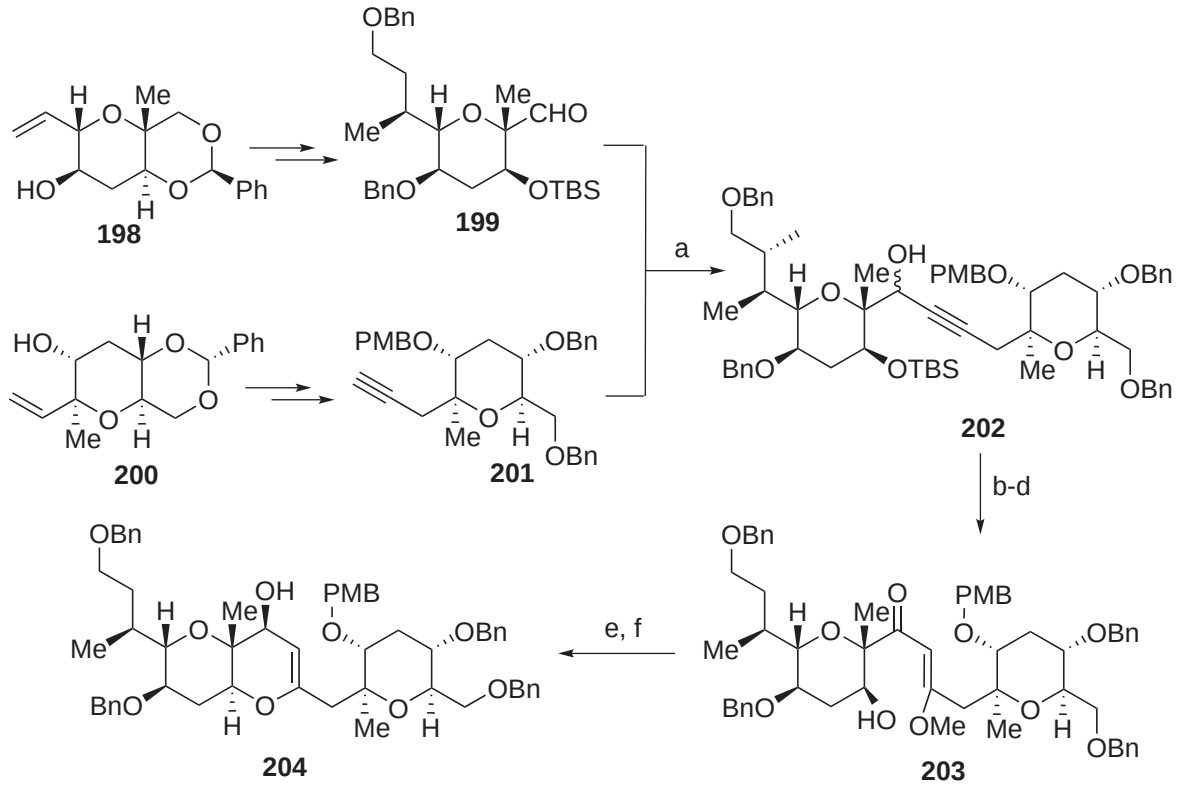
reaction sequence developed earlier to afford intermediate **192**. Samarium-mediated cyclisation gave the D ring. Transformation of the ester to the corresponding alkene and treatment of the mixed acetal with 1,3-propanedithiol gave dithiane **194**. Another samarium-mediated cyclisation reaction of precursor **195** delivered lactone **196** with the seven-membered B ring installed. Another five steps of oxidation/reduction/protection were necessary to access the desired carboxylic acid **197**.



Scheme 1.61: Synthesis of the B-D fragment. Conditions: a) SmI_2, MeOH, THF, 0 °C to rt, 81%; b) SmI_2, MeOH, THF, rt, 89%.

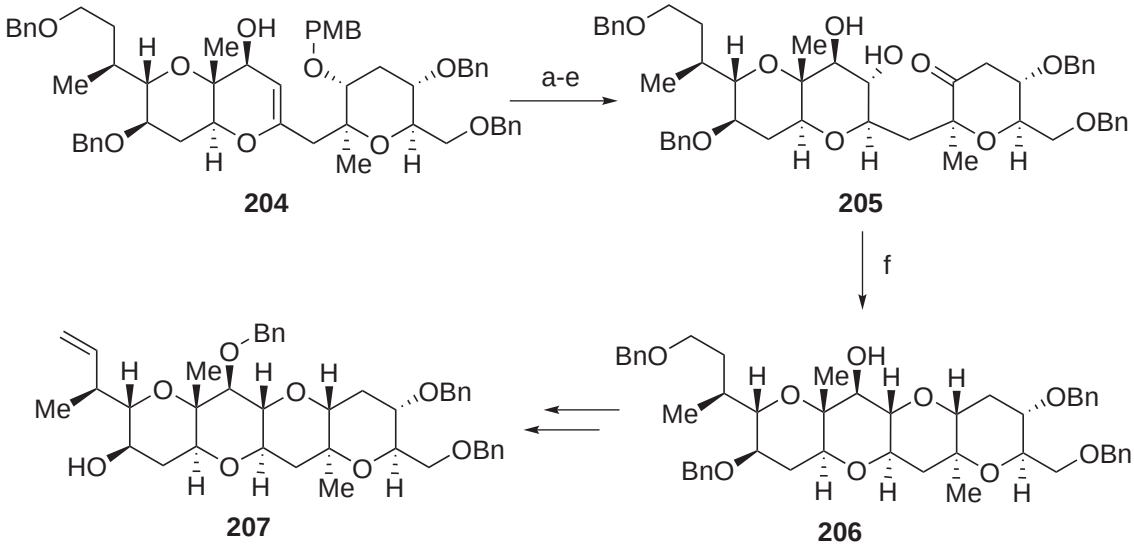
The G-J fragment was prepared using methodology previously reported by Nakata and co-workers.[163] Aldehyde **199** was obtained in ten steps from known alcohol **198** and alkyne **201** was prepared in six steps from known alcohol **200** (Scheme 1.62). Alkyne **201** was deprotonated with *t*BuLi and reacted with aldehyde **199** to give alcohol

202. Oxidation of the alcohol followed by treatment with sodium methoxide gave methoxyenone **203** after TBS cleavage. Acid-catalysed hetero-Michael addition gave dihydropyranone which was reduced selectively with Dibal-H to give alcohol **204**.



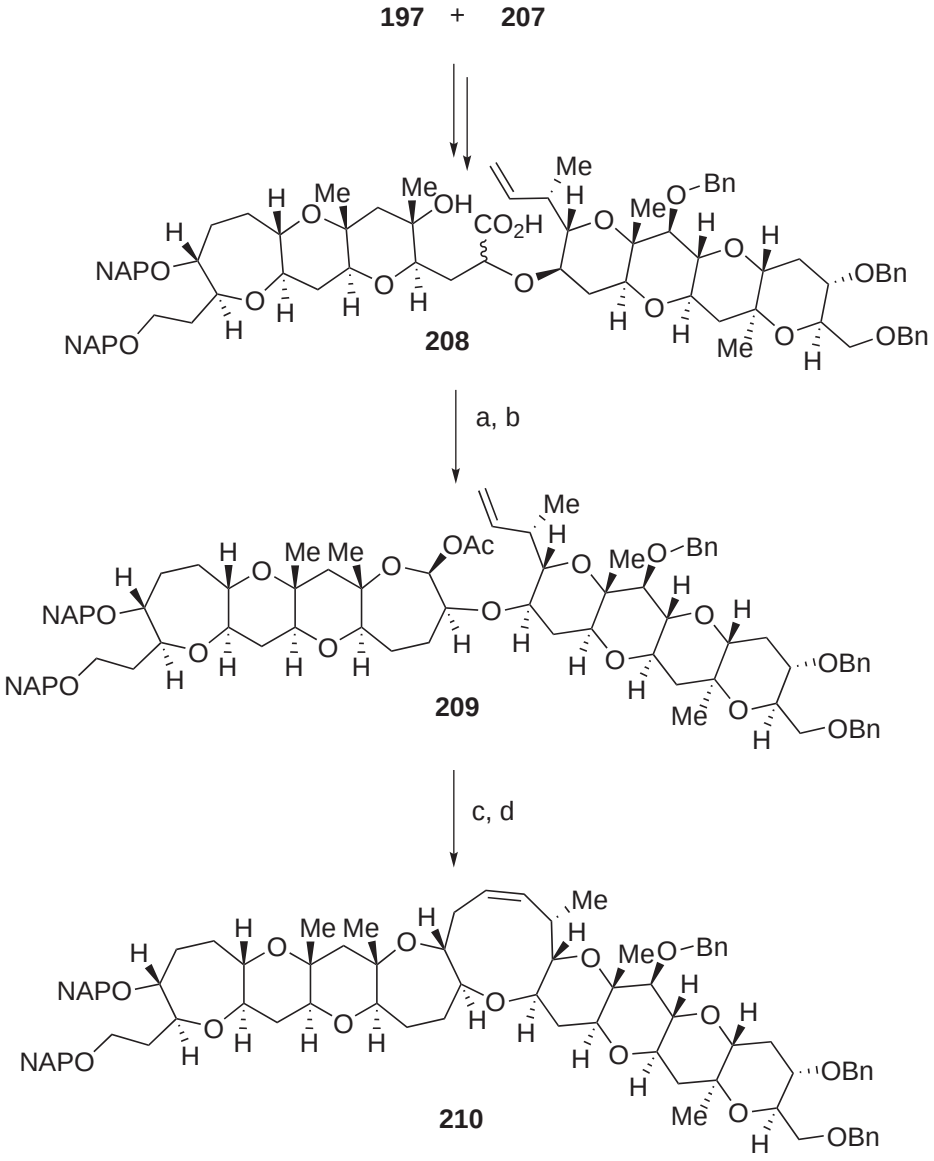
Scheme 1.62: Synthesis of the G-J fragment. Conditions: a) *t*BuLi, THF, HMPA, −78 °C, 95%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 93%; c)NaOMe, MeOH, THF, rt, 98%; d) HF·pyridine, pyridine, THF, 0 °C to rt, 91%; e) PPTS, toluene, 100 °C, 87%; f) DIBAL-H, toluene, −78 °C, 93%; .

Hydroboration of the enol ether moiety followed by a couple of functional group transformations gave hydroxyketone **205** and the I ring was constructed by treatment of this substrate with Et_3SiH and TMSOTf (Scheme 1.63). Protecting group interconversions gave the tetracyclic compound **206** which was converted to the corresponding terminal alkene using selenium chemistry. Final protecting group manipulations gave desired alcohol **207**.



Scheme 1.63: Completion of the G-J fragment. Conditions: a) BH_3·THF, THF, then NaOH aq., H_2O_2, THF, 0 °C to rt, 91%; b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 99%; c) DDQ, CH_2Cl_2, pH 7 buffer, 0 °C; d) TPAP, NMO, 4Å MS, CH_2Cl_2, 0 °C to rt; e) TBAF, AcOH, THF, rt, 81% (3 steps); f) TMSOTf, Et_3SiH, MeCN, −10 °C, 83%.

The nonacyclic core was then completed following the strategy developed earlier. After a Yamaguchi esterification, carboxylic acid **208** was obtained rapidly (Scheme 1.64). Lactone formation followed by partial reduction and acetate formation gave mixed acetal **209**. AllylTMS addition and final RCM delivered the fully functionalised B-J fragment **210** of the gambieric acids. This represents to date the biggest fragment of the gambieric acids ever assembled.

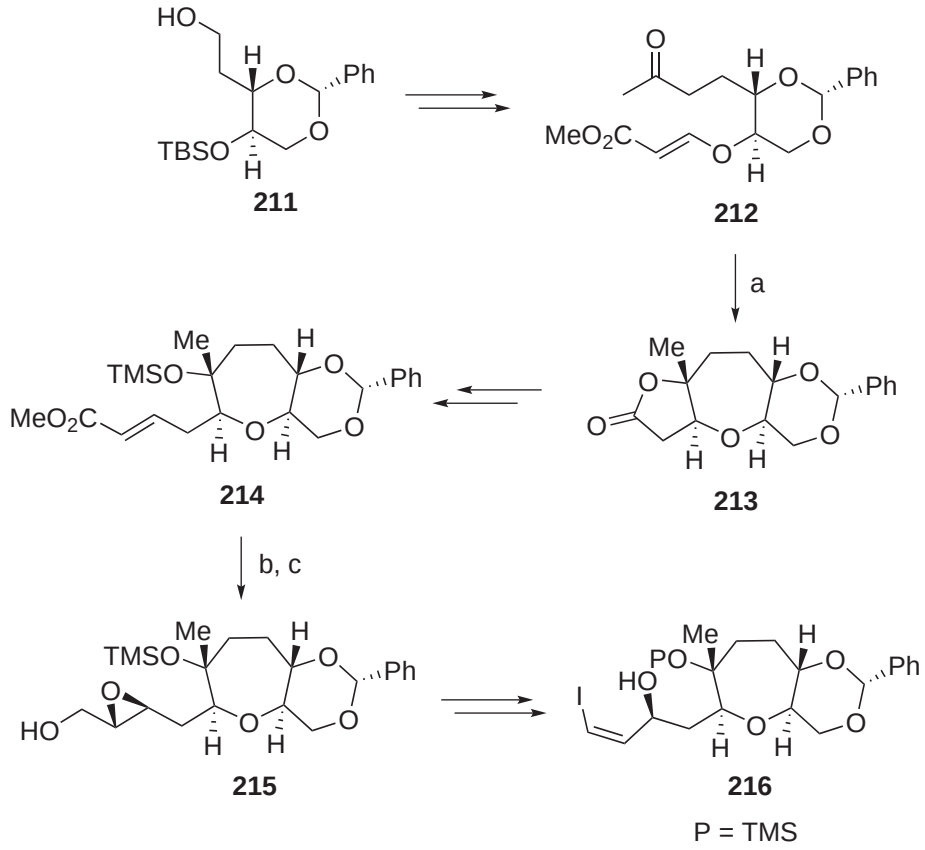


Scheme 1.64: Completion of the B-J fragment. Conditions: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, toluene, DMAP, reflux, 37% (2 steps); b) DIBAL-H, CH_2Cl_2, −78 °C then Ac_2O, DMAP, pyridine, CH_2Cl_2, −78 °C to 0 °C, 68%; c) allylTMS, $BF_3{\cdot}Et_2O$, 4Å MS, MeCN, −40 °C to −30 °C, 58%; d) Grubbs II catalyst **92**, CH_2Cl_2, 40 °C, 67%.

As mentioned before (see chap 1.4.2), this group also reported a synthesis of the A-B fragment.[151,152,164] They planned to prepare the B ring using samarium chemistry then attach the required side chain with a Suzuki-Miyaura cross-coupling reaction before forming the A ring.

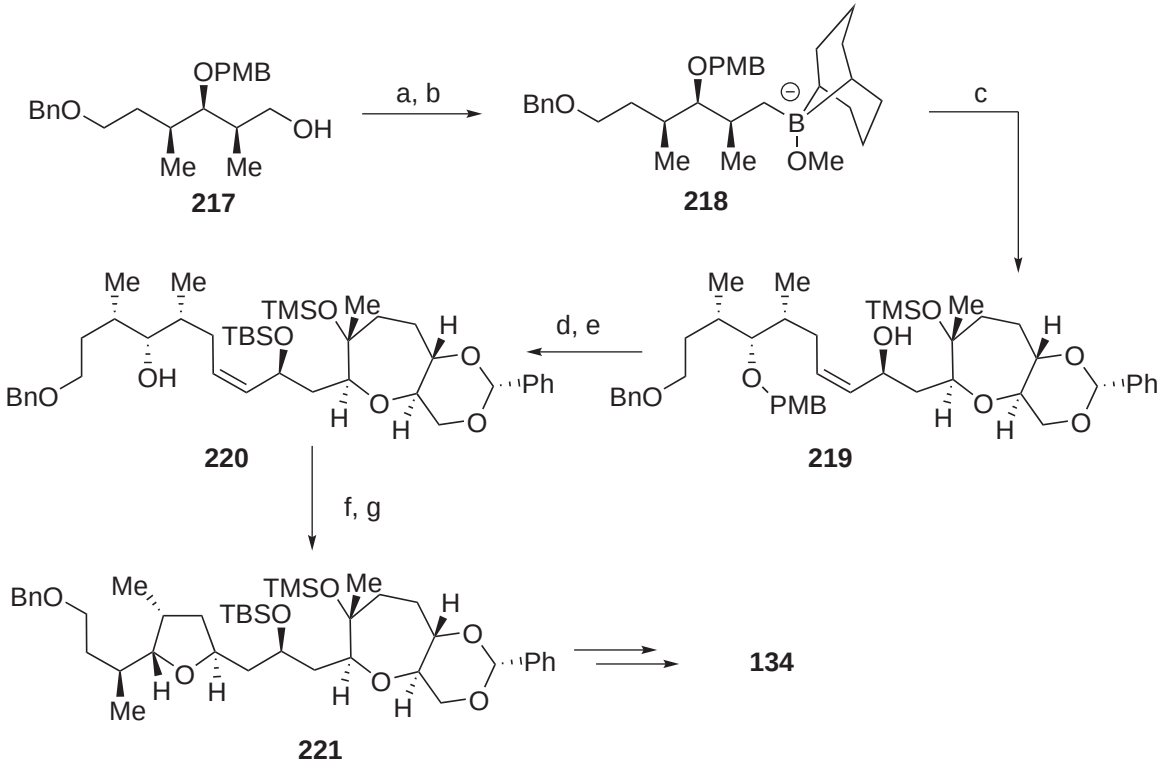
Desired cyclisation precursor **212** was obtained in five steps from known alcohol **211** (Scheme 1.65). Samarium-induced cyclisation delivered the bicyclic lactone **213** with complete stereoselectivity. Reduction to the corresponding lactol followed by Wittig olefination and alcohol protection gave α,β-unsaturated ester **214**. Another reduction gave the allylic alcohol which was subjected to a Sharpless epoxidation reaction. Epoxy-

alcohol **215** was then converted to the corresponding propargylic alcohol according to the Takano protocol and two steps were then necessary to access *Z*-vinyl iodide **216**.[165]



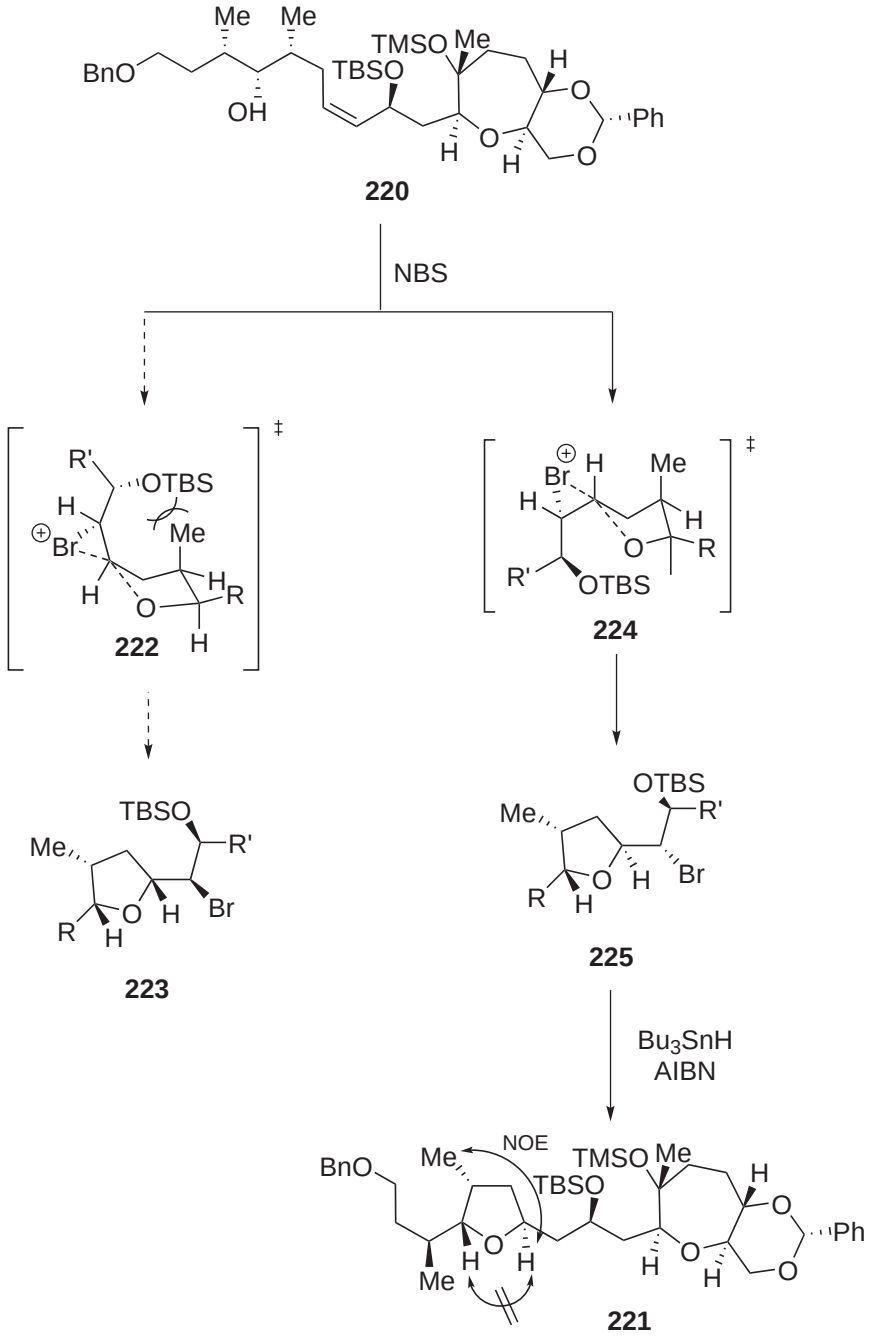
Scheme 1.65: Synthesis of the B ring. Conditions: a) SmI_2, MeOH, THF, rt, 74%; b) DIBAL-H, CH_2Cl_2, −78 °C, quant.; c) (+)-DET, Ti(O*i*Pr)$_4$, *t*BuOOH, 4Å MS, CH_2Cl_2, −20 °C; 83%.

The coupling partner **218** was generated from alcohol **217** in two steps and engaged in a Suzuki-Miyaura cross-coupling to deliver alcohol **219** (Scheme 1.66). Protecting group manipulation gave alcohol **220** which cyclised upon treatment with NBS to give tetrahydrofuran **221** after removal of the bromide under radical conditions. Oxidation of the primary alcohol to the carboxylic acid followed by complete deprotection delivered the carboxylic acid **134**, the spectroscopic data for which were compared with the natural product.



Scheme 1.66: Synthesis of the A-B fragment. Conditions: a) I_2, PPh_3, imidazole, THF, rt, 96%; b) *t*BuLi, *B*-MeO-9-BBN, Et_2O, −78 °C; c) **216**, $PdCl_2(dppf)\cdot CH_2Cl_2$, Ph_3As, Cs_2CO_3, DMF, 50 °C, 75% (2 steps); d) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; e) DDQ, THF, pH 7 buffer, rt, 80% (2 steps); f) NBS, CH_3CN, rt; g) Bu_3SnH, AIBN, toluene, 110 °C, 69% (2 steps).

The stereochemical outcome of the cyclisation step could be explained by the following model (Scheme 1.67). If the bromination had occurred in a *syn*-fashion relative to the adjacent OTBS group, the transition state **222** required for the cyclisation reaction would reveal an important steric interaction between the OTBS group and the methyl group at the C5-position. However, if the bromination occurred at the opposite face, the new transition state **224** would not have this interaction, making it lower in energy and therefore the favored reaction pathway. The relative configuration of the three substituents was confirmed by NOESY studies on tetrahydrofuran **221** after debromination.



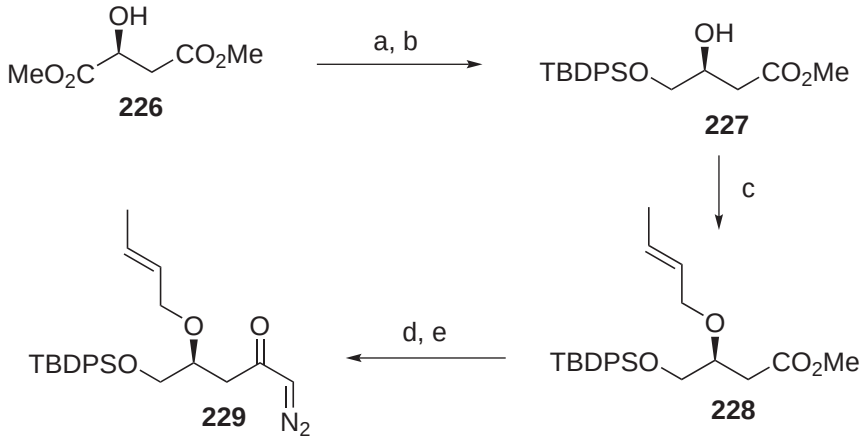
Scheme 1.67: Explanation of the stereoselectivity for the formation of tetrahydrofuran **221**.

Very recently, Sasaki and co-workers reported the synthesis of the G-J fragment possessing the revised absolute configuration.[166]

Clark's Approach

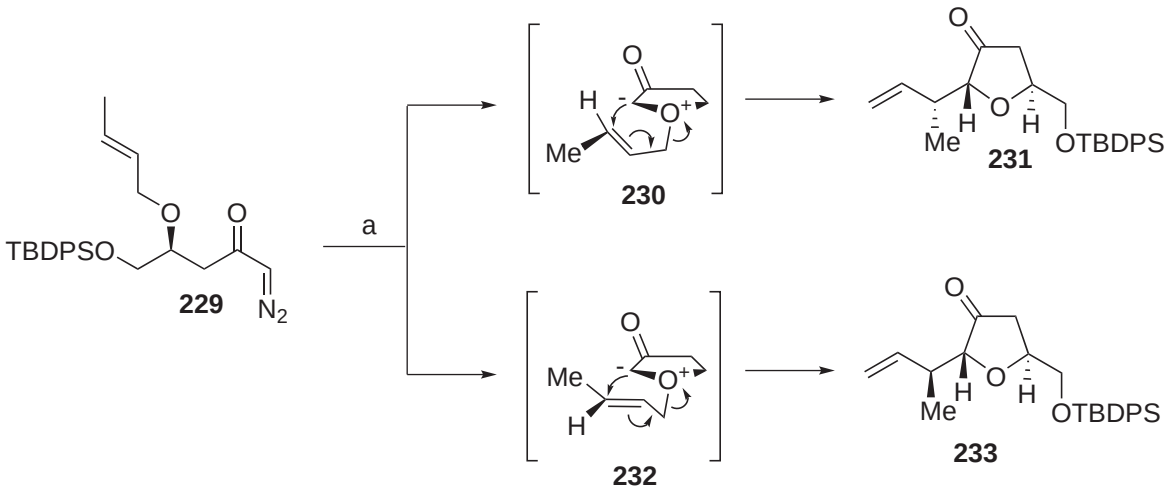
In 2004, Clark reported the stereoselective synthesis of the A-ring fragment of gambieric acid A.[167] The synthesis started from L-dimethylmalate **226** which underwent a regioselective reduction of one of the ester to give intermediate **227** after silyl protection (Scheme 1.68). Formation of the *E*-crotyl ether was achieved using trichloroacetimidate

228 under acidic conditions. Hydrolysis under basic conditions gave the corresponding carboxylic acid which was converted into an acid chloride followed by treatment with an excess of diazomethane to deliver the key diazoketone **229**.



Scheme 1.68: Preparation of diazoketone **229**. Conditions: a) $NaBH_4$, $BH_3{\cdot}SMe_2$, THF, rt, 92%; b) *t*$BuPh_2SiCl$, imidazole, DMF, 89%; c) *E*-crotyl 2,2,2-trichloroacetimidate, CF_3SO_3H, CH_2Cl_2, rt, 60%; d) Me_3SiOK, Et_2O, rt, 86%; e) $(COCl)_2$, DMF, CH_2Cl_2, rt, then CH_2N_2, Et_2O, 0 °C to rt, 74%.

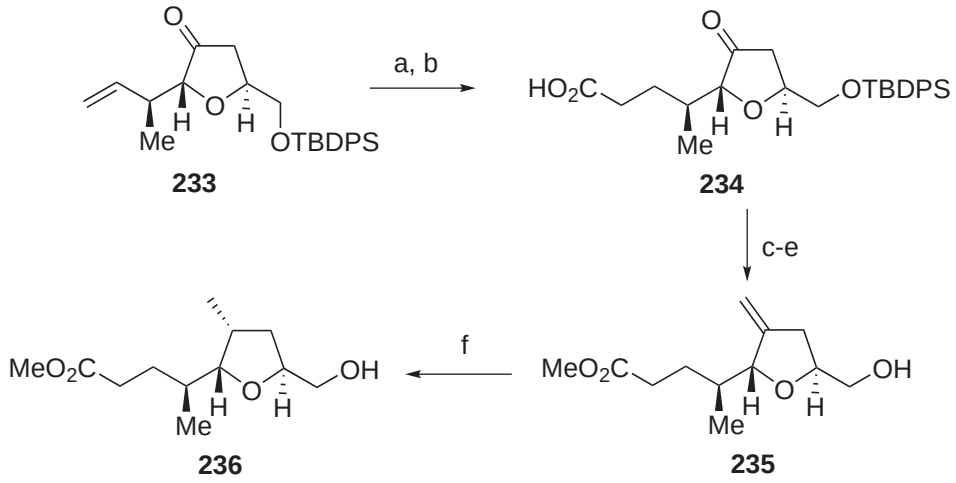
When treated with copper acetylacetonate, the [2,3]-sigmatropic rearrangement could proceed *via* an *exo*-transition state **230** to give tetrahydrofuranone **231** with the methyl group possessing the undesired configuration, or an *endo*-transition state **232** that would deliver the desired compound **233** (Scheme 1.69). The *endo*-character of the mechanism was established on the *Z*-crotyl isomer and the desired tetrahydrofuranone **233** was obtained in high yield and with excellent selectivity (>92:8).



Scheme 1.69: Synthesis of the A fragment. Conditions: a) $Cu(acac)_2$, THF, reflux, 88% (dr > 92:8).

Non-selective hydroboration gave a diol which was fully oxidised to keto-acid **234**

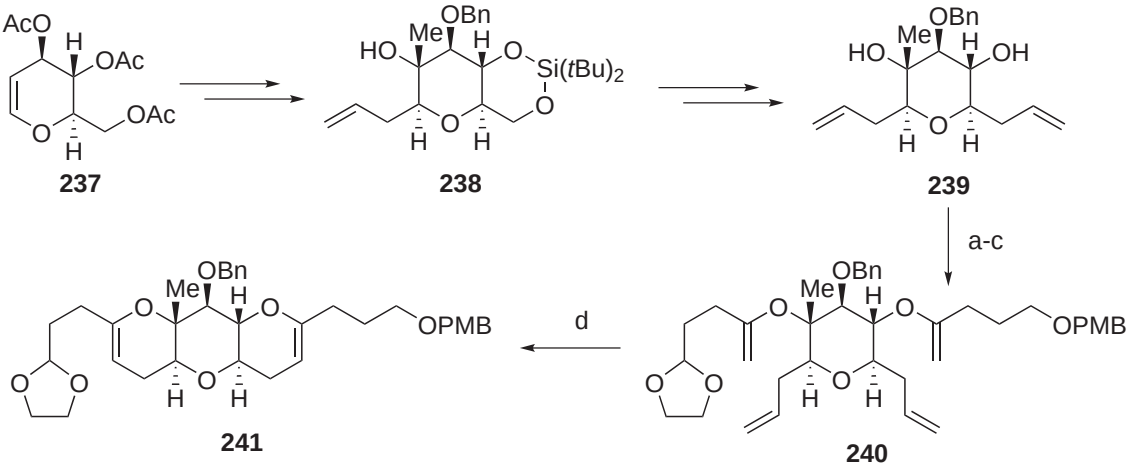
(Scheme 1.70). After esterification of the carboxylic acid, sequential chemoselective methylenation of the ketone using Nysted reagent and TBAF deprotection delivered primary alcohol **235**. The remaining stereocentre was installed using a hydroxy-directed hydrogenation with Wilkinson's catalyst and afforded the A fragment **236** in excellent yield.



Scheme 1.70: Synthesis of the A fragment. Conditions: a) $(c\text{-}C_6H_{11})_2BH$, THF, 0 °C to rt, then H_2O_2, pH 7 buffer, 86%; b) PDC, DMF, rt, 74%; c) CH_2N_2, Et_2O, 0 °C, 99%; d) $Zn(CH_2ZnBr)_2{\cdot}THF$, $TiCl_4$, THF, 0 °C to rt, 67%; e) TBAF, THF, rt, 99%; f) H_2, $(PPh_3)_3RhCl$, PhMe, rt, 95%.

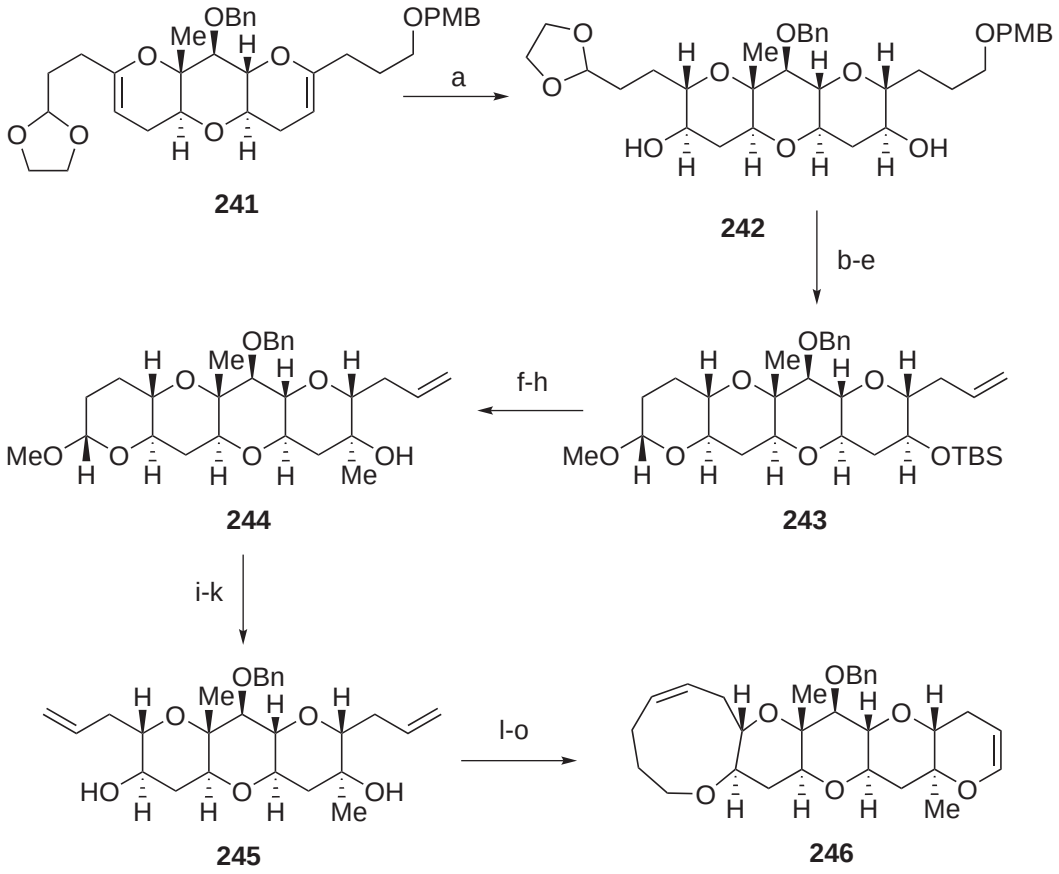
A year later, Clark reported a synthetic strategy for the construction of the F-J fragment of the gambieric acids.[93] The developed approach involved a two-directional strategy based on the ring-closing metathesis reaction to form all the cyclic ethers. As discussed before (see chap. 1.2.3), the Clark group had already shown that RCM reaction is a powerful tool for the construction of cyclic enol ethers and can accommodate a variety of ring-sizes and functional groups.

The synthesis started from tri-*O*-acetyl-D-glucal **237**, which was quickly functionalised to give alcohol **238** (Scheme 1.71). The side chain on the left side was introduced in four steps to give diol **239**. Double alkynyl ether formation followed by sequential carbocupration reactions gave tetraene **240**, which was then exposed to Grubbs II catalyst **92** to afford tricyclic compound **241**.



Scheme 1.71: Synthetic studies torwards the tricyclic G-I fragment. Conditions: a) KH, Cl_2CCHCl, THF, 0 °C then *n*BuLi, Et_2O, −78 °C to −40 °C, 88%; b) PMBO-$(CH_2)_3$MgBr, CuBr, LiBr, THF, −95 °C to −78 °C, 85%; c) $(OCH_2CH_2O)CH(CH_2)_2$MgBr, CuCN, LiCl, THF, −78 °C, 84%; d) Grubbs II catalyst **92** (10 mol%), PhMe, 70 °C, 89%.

The synthesis continued with a stereoselective double hydroboration reaction that transformed both enol ethers into the desired *trans*-diol **242** (Scheme 1.72). Acetal formation followed by TBS protection of the secondary alcohol and Grieco dehydration the primary alcohol gave tetracyclic compound **243**. The TBS group was then removed and the alcohol was oxidised to the corresponding ketone which was treated with methylmagnesium iodide to introduce the second angular methyl group and deliver the tertiary alcohol **244**. The acetal was then opened and reduced to the primary alcohol which was eliminated using again selenium chemistry to deliver diol **245**. Sequential alkylation of both hydroxyl groups gave the second RCM precursor. Grubbs II catalyst **92** was again the catalyst of choice for the double ring closure and treatment of the tetraene afforded the nine- and six-membered rings in high yield thus completing the F-J fragment **246**.



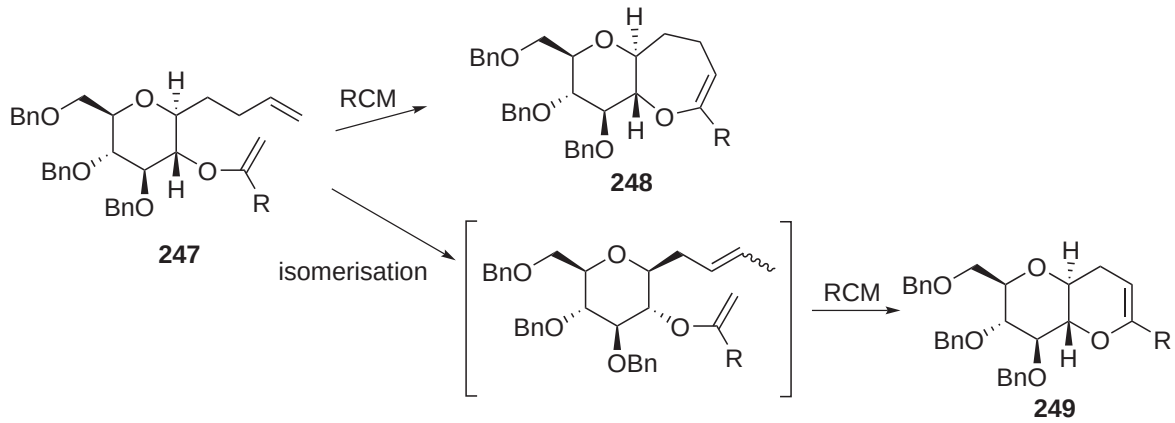
Scheme 1.72: Completion of the G-J fragment. Conditions: a) thexyl borane, THF, 0 °C to rt then $NaBO_3 \cdot 4H_2O$, buffer pH=7, 62%; b) TsOH, MeOH, rt, 71%; c) *t*$BuMe_2SiCl$, DMAP, Et_3N, CH_2Cl_2, rt; d) CAN, MeCN, H_2O, rt, 56%, (2 steps); e) *o*-$O_2NC_6H_4SeCN$, (nBu)$_3$P, THF, rt then H_2O_2, $NaHCO_3$ aq., 40 °C; f) TBAF, THF, rt, 83% (2 steps); g) Dess-Martin periodinane, CH_2Cl_2, 0 °C; h) MeMgI, PhMe, −78 °C, 83% (2 steps); i) HCl aq., THF, 60 °C; j) $NaBH_4$, MeOH, 0 °C, 84% (2 steps); k) *o*-$O_2NC_6H_4SeCN$, (nBu)$_3$P, THF, rt then H_2O_2, $NaHCO_3$ aq., 40 °C, 96%; l) $CH_2CH(CH_2)_3Br$, (nBu)$_4$NI, THF, DMF, reflux, 66% (81% brsm); m) KH, Cl_2CCHCl, THF, 0 °C then nBuLi, Et_2O, −78 °C to −40 °C; n) H_2, Lindlar catalyst, quinoline, EtOAc, rt, 49% (2 steps); o) Grubbs II catalyst **92** (10 mol%), PhMe, 80 °C, 60%.

Chapter 2

Synthesis of Six- and Seven-Membered Cyclic Ethers by Ring-Closing Metathesis

2.1 Introduction

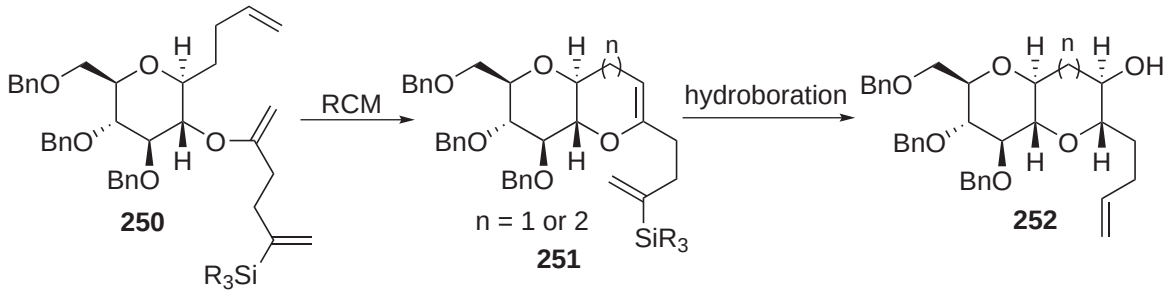
Six- and seven-membered rings are the most common units founds in natural polycyclic ethers. The aim of this work is to develop a new methodology to prepare these structural motifs from a single precursor using ring-closing metathesis. Indeed, metathesis catalysts, such as Grubbs' second-generation catalyst, are known to be able to isomerise alkenes under specific conditions (see chap. 1.3). Thus, starting from diene **247**, it should be possible to obtain by a simple RCM the seven-membered product **248** and by a tandem isomerisation-RCM reaction the six-membered product **249** (Scheme 2.2).



Scheme 2.2: Synthesis of six- and seven-membered cyclic ethers from a single precursor

Furthermore, in order to minimise the number of steps required to create each ring,

the side chain attached to the enol ether was chosen carefully. In order to obtain a terminal alkene after the hydroboration reaction, which is necessary to convert the enol ether **251** into the secondary alcohol, a vinyl silane was chosen. Indeed, hydroboration of such functionality would be followed by Peterson elimination to give the desired terminal alkene (Scheme 2.3). The alcohol **252** would then be ready for submission to another synthetic sequence to create the next ether ring.

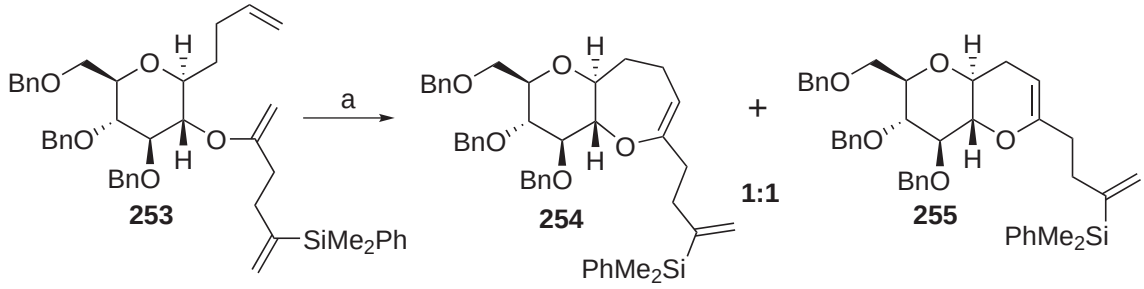


Scheme 2.3: Iterative synthesis of polycyclic ethers

After preliminary studies done in the group, the dimethylphenylsilyl group was chosen.[168]

Preliminary results

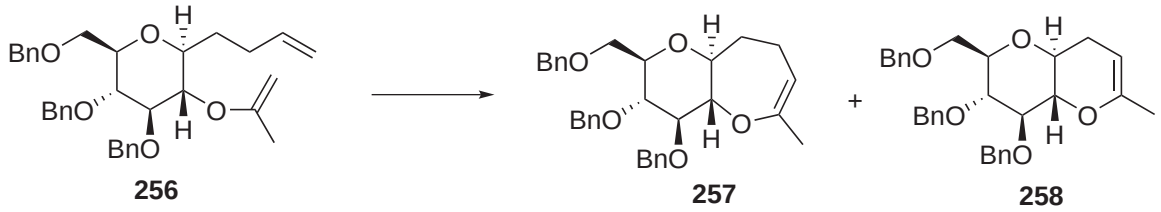
When diene **253** was submitted to standard RCM conditions, a mixture of two cyclic products was obtained in a 1:1 ratio and 78% yield. The first RCM product is the seven-membered cycle **254**, and the second is the six-membered enol ether **255** resulting from a tandem isomerization-RCM (Scheme 2.4).[168]



Scheme 2.4: Conditions: catalyst **92** (10 mol%), benzene, reflux, 78%.

A model system **256**, with a simple methyl group as side chain, was then studied and it was found that the addition of 20 mol% of 1,4-benzoquinone could prevent the isomerization, leading to the selective formation the seven-membered ring **257** in good yield.[169] Furthermore, when the reaction was carried out in a solution saturated with ethylene, the six-membered ring **258** could be produced with high selectivity

(Scheme 2.5).



Grubbs II (10 mol%) 1,4-benzoquinone (20 mol%) toluene, reflux	71 %	95	:	5
Grubbs II (40 mol%) ethylene benzene, reflux	69 %	5	:	95

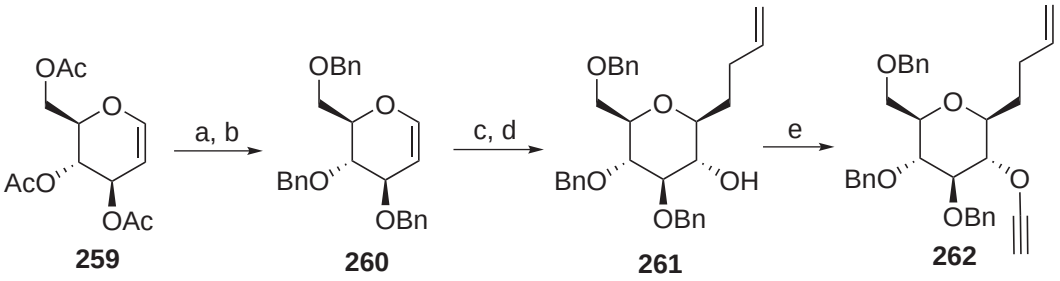
Scheme 2.5: Model studies

The first part of my project consisted in the application of these conditions to the desired triene **253**.

2.2 Results and Discussion

2.2.1 Synthesis of Triene 253

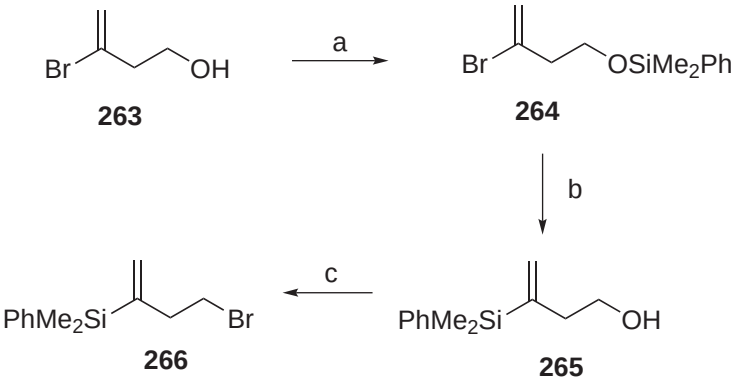
The first objective was the preparation of triene **253**, necessary to test the different RCM conditions. Tri-*O*-benzyl-D-glucal **260** was prepared in excellent yield in two steps from commercially available tri-*O*-acetoxy-D-glucal **259**. It was then epoxidised in a completely stereoselective manner using *in situ* generated DMDO in quantitative yield.[170] This epoxidation method is much more convenient than the original procedure where a highly diluted solution of DMDO in acetone had to be prepared.[171] Only three equivalents of Oxone were used, whereas a yield of about 5% is reported for the distillation process. This procedure is considerably cheaper, leads to much less oxidative Oxone waste and is much more practical to carry out on a large scale. The epoxide was then opened by freshly prepared butenylmagnesium bromide to provide alcohol **261** in 50% yield. The free hydroxyl group was converted into the alkynylether **262** using the Greene protocol in 69% yield (Scheme 2.6).[172] In order to avoid formation of impurities that could affect the subsequent carbocupration reaction, the last sequence was performed in two steps (KH, trichloroethylene then *n*BuLi), the overall yield being the same.



259 **260** **261** **262**

Scheme 2.6: Preparation of alkynyl ether **262**. Conditions: a) NaOMe, MeOH, rt; b) NaH, BnBr, THF, DMF, rt, 96% (2 steps); c) Oxone, acetone, CH_2Cl_2, $NaHCO_{3\ aq.}$, 0 °C to rt; d) 3-butenylmagnesium bromide, THF, −20 °C, 50% (2 steps); e) KH, trichloroethylene, then *n*BuLi, Et_2O, −78 °C to −45 °C, 69%.

The bromide needed for the carbocupration reaction was prepared in three steps. Commercially available 3-bromo-3-buten-1-ol **263** was first protected as a silyl ether in 87% yield using standard conditions (Scheme 2.7). The protected alcohol **264** was then treated with *t*BuLi in THF to furnish the vinyl lithium which underwent a *retro*-Brook rearrangement to provide vinyl silane **265** in 76% yield. The primary alcohol was finally converted to the desired bromide **266** in 95% yield.



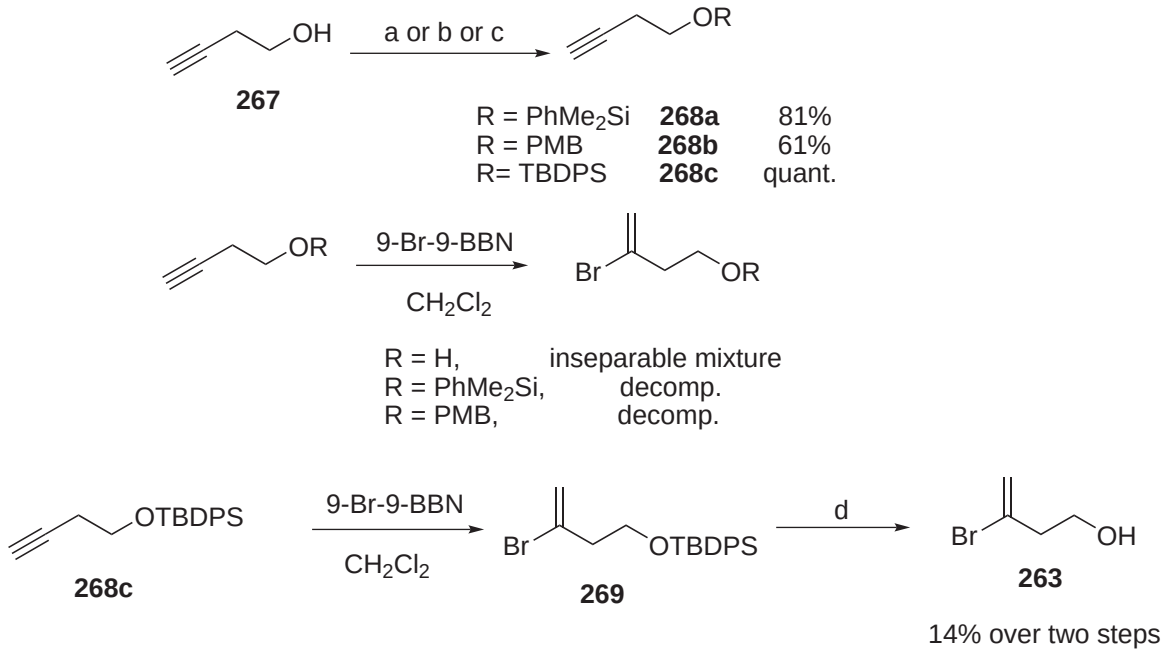
263 **264** **266** **265**

Scheme 2.7: Preparation of bromide **266**. Conditions: $PhMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2, rt, 87%; b) *t*BuLi, THF, −78 °C to −45 °C, 76%; c) PPh_3, CBr_4, CH_2Cl_2, rt, 95%.

Preparation of alcohol 263

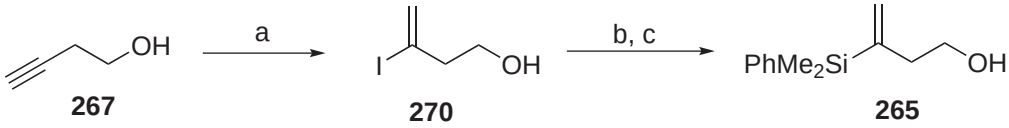
Due to the cost of the starting alcohol **263**, alternative preparative routes were explored. The addition of 9-Br-9-BBN to 4-butyn-1-ol **267**, or its protected version, appeared to be the most promising route to prepare **263**.[173] The bromination reaction was first tested on the free alcohol. NMR indicated that the required vinyl bromide had formed but it was not possible to separate this from the 9-BBN-related by-products (Scheme 2.8).

Various protecting groups were then tested in order to modify the polarity of the bromide product. First, the dimethylphenylsilyl group, required for the next step, was introduced using same conditions as above, but this was found to be unstable under the bromination reaction conditions. The alcohol was also protected as a PMB ether in good yield, but once again, the protecting group was cleaved when exposed to 9-Br-9-BBN. Finally, the very robust *tert*-butyldiphenylsilyl group (TBDPS) was chosen as this group has already been used in bromination reactions.[174] 3-Butyn-1-ol was protected as the silyl ether in quantitative yield, then submitted to the action of 9-Br-9-BBN. The desired vinyl bromide **269** was obtained as a mixture with *tert*-butyldiphenylsilanol. The mixture was then directly treated with TBAF to give the bromoalcohol **263**, but in only 14% yield over two steps.



Scheme 2.8: Preparation of alcohol **263**. Conditions: a) $PhMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2, rt; b) NaH, $n Bu_4NI$, PMBCl, THF, rt; c) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt; d) TBAF, THF, rt, 14% (2 steps).

As an alternative to the preparation of the vinyl bromide, the synthesis of the corresponding vinyl iodide was explored. The synthesis of 3-iodo-3-buten-1-ol **270** had already been reported by Shioiri and co-workers and the application of their conditions gave the desired product in 51 % yield (Scheme 2.9).[175] It was not possible to obtain completely pure product by column chromatography, but it was possible to carry out the next two steps (silylation and *retro*-Brook rearrangement) and obtain the desired vinyl silane **265** in 61% over the two steps.

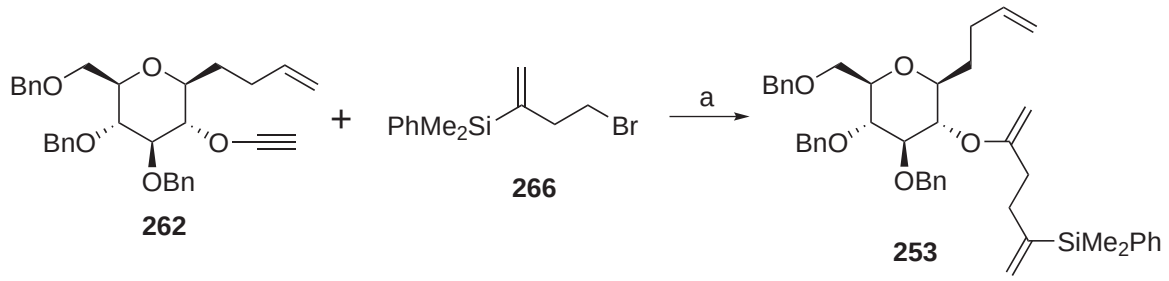


267 270 265

Scheme 2.9: Alternative route to alcohol **265**. Conditions: a) TMSCl, NaI, MeCN, H_2O, rt, 51%. b) $PhMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2, rt; c) *t*BuLi, THF, −78 °C to −45 °C, 61% (2 steps).

Carbocupration

With the two coupling partners in hand, the carbocupration reaction was tested using conditions previoulsy developed in the group. The Grignard reagent prepared from bromide **266** was first added to a solution of CuBr and LiBr in THF at very low temperature (−90 °C) to form the lower-order cuprate, and alkyne **262** was then added. The desired triene **253** was obtained in 61% yield after column chromatography under basic conditions (Et_3N 1% v/v) (Scheme 2.10).

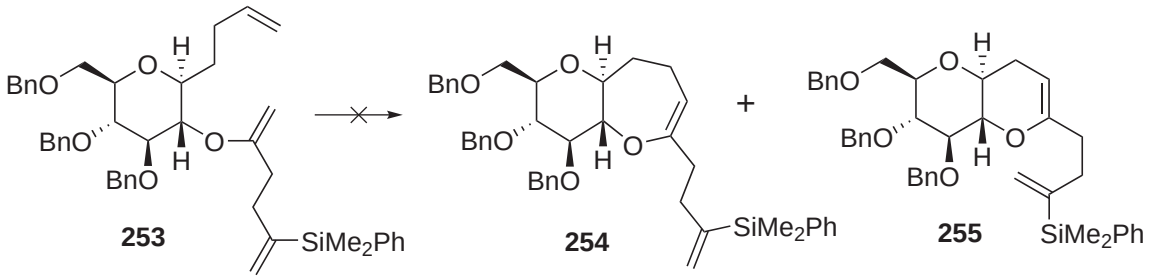


262 266 253

Scheme 2.10: Conditions: a) CuBr, LiBr, Mg, THF, −90 °C then alkyne **262**, −90 °C to −78 °C, 61%.

2.2.2 Tandem Isomerisation-RCM Reaction

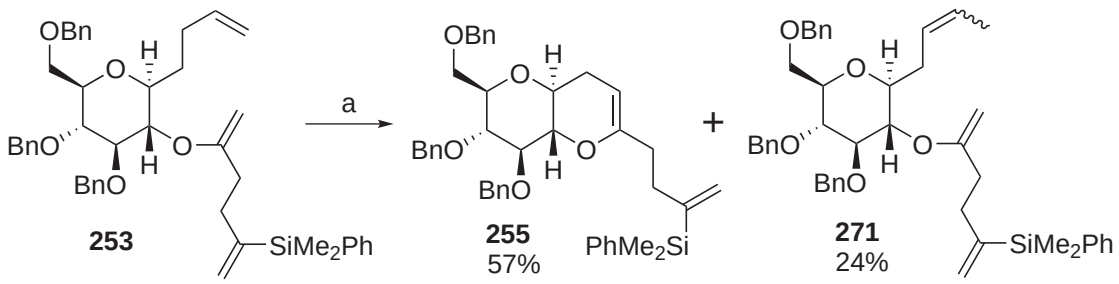
Firstly, conditions previously developed on the model system were investigated, but were much less successful on the more complex system (Table 2.1). Saturating the reaction mixture reaction with ethylene gas gave little selectivity for six-membered ring formation (entry 2). Using another small alkene, such as styrene, had the same effect on the selectivity (entry 3). However, using the conditions described by Wicha and co-workers:[143] cooperative use of $RuCl(CO)H(PPh_3)_3$ and Grubbs' second-generation catalyst **92**, led to the exclusive formation of the 6-membered cyclic enol ether in reasonable yield (entry 4). It is interesting to note that only the mono-substituted terminal alkene is isomerised by the ruthenium-hydride catalyst and the two 1,1-disubtituted double bonds were left untouched.



Entry	Additive	Yield	Ratio **254**:**255**
1	none[a]	50%	50:50
2	ethylene[b]	25%	25:75
3	styrene (40 mol%)[b]	86%	33:67
4	$RuCl(CO)H(PPh_3)_3$ (5 mol%)[a]	57%	>1:99

Table 2.1: Ring-closing metathesis of triene **253**. Conditions a) Grubbs II catalyst **92** (40 mol%), additive, benzene, reflux; b) Grubbs II catalyst **92** (10 mol%), additive, benzene, reflux.

According to the original publication,[143] two protocols can be followed in this reaction. In the first case, both catalysts were added at the beginning of the reaction and the RCM did not start before one of the alkene had isomerised. On the other hand, the isomerisation catalyst was added alone, and the reaction mixture was heated for 10 min before the Grubbs II catalyst was added. In our case, because it was known that the starting triene was reactive towards the Grubbs catalyst, the two-step protocol was chosen: first the triene **253** and the ruthenium hydride catalyst (1 mol%) were heated at reflux at average concentration (0.05 M) to ensure a quick isomerisation. After 10 min, the progress of the reaction was checked by NMR and the Grubbs II catalyst (10 mol%) was added with some solvent to reach typical RCM concentrations (0.005 M). As a safer alternative to benzene, the reaction was also carried out in toluene and only the six-membered product was obtained with the same yield as before (Scheme 2.11). Along the desired product, some of the isomerised product **271** was also isolated, even when an additional amount of Grubbs II catalyst (10 mol%) was added.



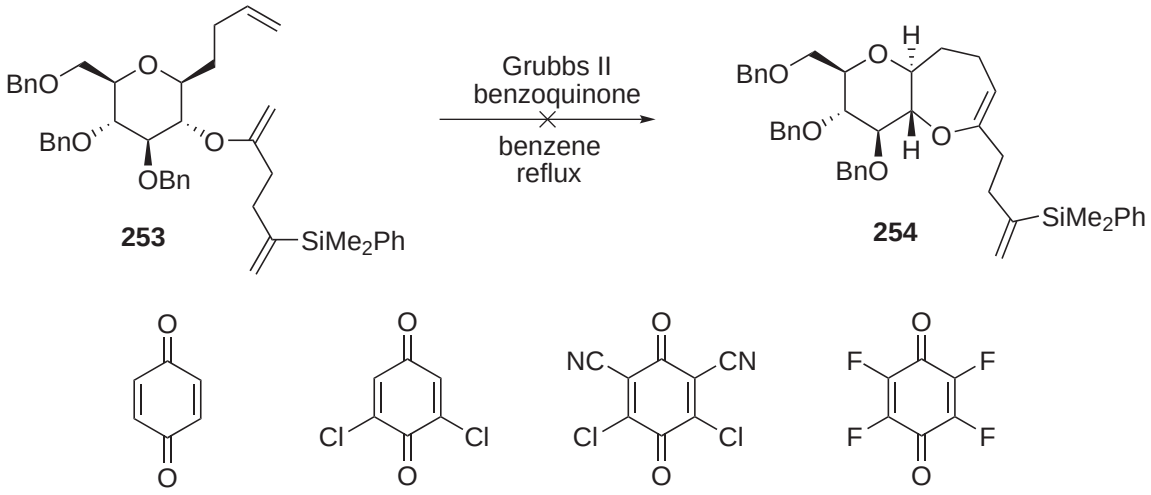
Scheme 2.11: Conditions: a) $RuCl(CO)H(PPh_3)_3$ (5 mol%), then Grubbs II catalyst **92**, toluene, 90 °C.

2.2.3 Attempted Selective Formation of the Seven-Membered Ring

Following the identification of reaction conditions that would give the six-membered product exclusively from triene **253**, focus moved towards the selective synthesis of the seven-membered cyclic ether **254**. Several methods were envisioned to favour the formation of the seven-membered product and limit the isomerisation of the starting material.

Use of additives during RCM reaction

Grubbs and co-workers have reported that the addition of a benzoquinone can suppress the isomerisation reaction catalysed by Grubbs catalysts.[176] They suggested that the benzoquinone could reoxidise the decomposed form of ruthenium catalyst responsible for the isomerisation process. However, addition of several substituted benzoquinones to our catalytic system led only to decomposition of the starting material or isomerisation of the mono-substituted double bond.

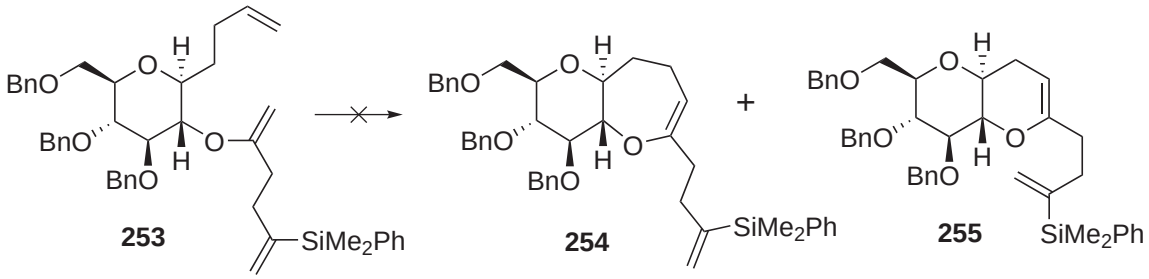


Scheme 2.12: Range of benzoquinones used.

Prunet and co-workers have shown that addition of a weak ligand for ruthenium, such as triphenylphosphine oxide, can also prevent formation of isomerised products.[177] But no such effect was observed when this protocol was used on the model substrate (Table 2.13, entry 1). Meyer reported that formation of bimetallic complexes between the ruthenium catalyst and other transition metals such as tin or iron reduces the decomposition rate of Grubbs catalyst and gives only the expected product of the reaction.[178] However, these additives are also strong Lewis acid and when added to the reaction, led to the cleavage of the enol ether moiety (entry 2). Brönsted acids have also been shown to prevent the underisable isomerisation occuring during the RCM reaction.

Even though the precise mechanism by which the isomerisation reaction occurs is not known, it is believed that a ruthenium hydride complex is responsible. Therefore, it was envisioned that adding an hydride scavanger would sequester any hydride present in the reaction mixture, and thus prevent isomerisation caused by the Grubbs catalyst.

Carboxylic acids[176] as well as phosphoric acids[179] have been proven as efficient isomerisation suppressors for some substrates, but when applied to this system, no improvement was observed and the reaction led to an inseparable mixture of several products (entries 3 and 4). 4-Nitrophenol, a milder Bronsted acid (pKa = 7.15), was also tested but was not able to suppress the isomerisation reaction (entry 5).



Scheme 2.13: Conditions: Grubbs II catalyst **92**, additive ($Ph_3P(O)$, $SnCl_2$, acetic acid, phenylphosphoric acid or 4-nitrophenol), benzene, reflux.

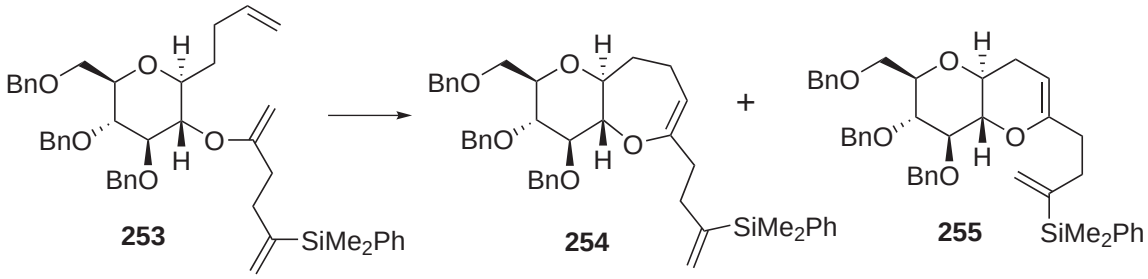
Modifications to the reaction conditions

Adding various additives always led to decomposition of the starting material, so a different approach was required. Changing the reaction conditions (solvent, catalyst, temperature) was the next approach.

First, a range of solvents was tested with Grubbs second generation catalyst. Refluxing DCM did not provide a high enough temperature to activate the catalyst, whereas refluxing in DCE gave some cyclised product, but in poor yield (22 %) and with incorrect selectivity (4:1 for the six-membered ring) (Table 2.2, entries 1 and 2). Recently, fluorinated aromatic solvents have been shown to increase the activity of metathesis catalysts in difficult reactions.[180] In our case, when using perfluorobenzene or perfluorotoluene, only isomerised product was observed (entries 3 and 4). Activation of the catalyst by microwave irradiation was also attempted, but no improvement was observed and only isomerised product was obtained.

Screening various metathesis catalysts was also performed. Grubbs-Hoveyda second generation catalyst gave only isomerised product.[114] A modified version of the Grubbs-Hoveyda catalyst - the Grela-Grubbs catalyst **272** - was also tested in different solvents.[118] In refluxing dichloromethane, no reaction was observed and in refluxing

benzene, complete isomerisation of the mono-substituted alkene was accomplished in 2 h.



Entry	Solvent	Catalyst	Yield	Ratio **254**:**255**
1	DCM	Grubbs II	decomp.	-
2	DCE	Grubbs II	22%	1:4
3	C_6F_6	Grubbs II	decomp.	-
4	C_7F_8	Grubbs II	decomp.	-
5	benzene with microwave irradiation (100 °C for 23 min)	Grubbs II	decomp.	-
6	benzene	Grubbs-Hoveyda II	decomp.	-
7	DCM	Grela-Grubbs II	isom.	-
8	benzene	Grela-Grubbs II	isom.	-

Grela-Grubbs II :

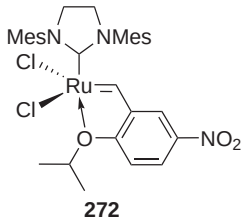


Table 2.2: Modification of the solvent and catalyst

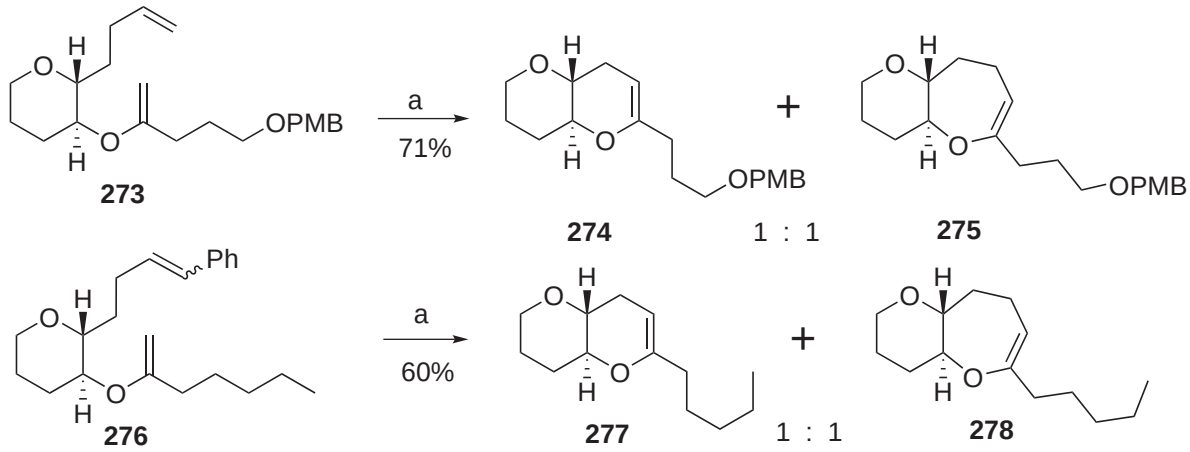
During the past decade, hundreds of metathesis catalysts have been developed, each possessing specific applications.[181] We chose to limit ourselves to catalysts that are easily accessible, in order to be able to scale up the reactions if they were to be used for the total synthesis of polycyclic ethers.

Modifications of the substrate

- *Modification of the terminal alkene*

For all the reactions carried out so far, it seems that the mono-substituted double bond is too reactive towards isomerisation. One possible way to force the reaction towards formation of the seven-membered product was to modify the alkene to decrease its reactivity towards isomerisation, whilst maintaining its metathesis activity. It was envisioned that attaching one or two substituents to the end of the double bond, creating a di- or tri-substituted alkene, would make this alkene far less prone to isomerise.

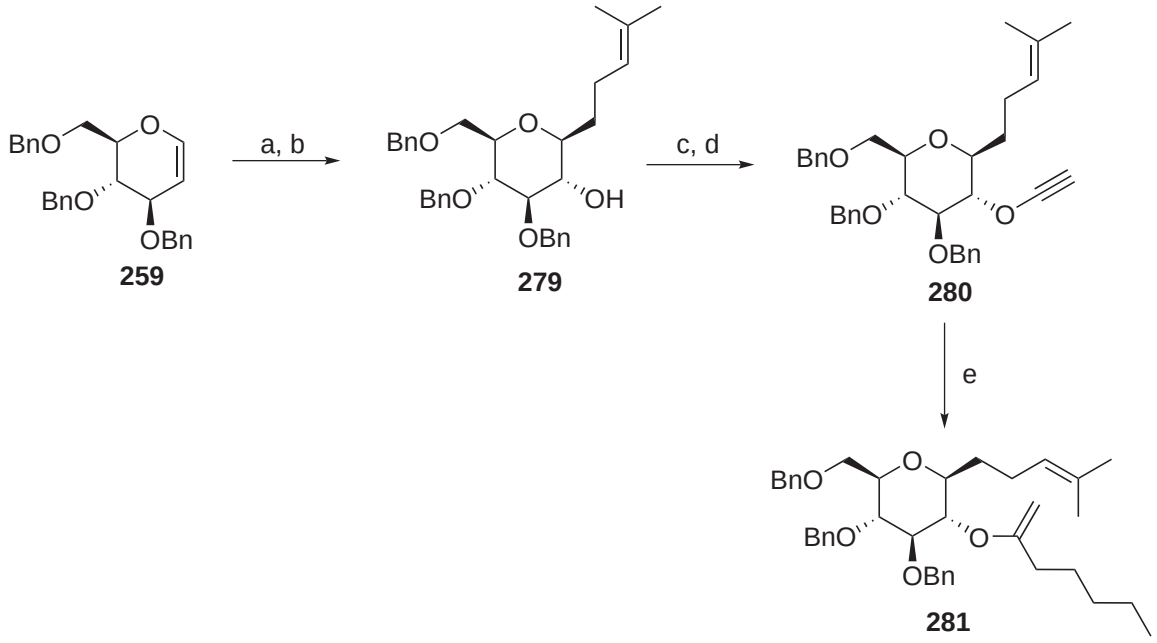
However, this had already been attempted previously in our group: when diene **273** was treated with Grubbs II catalyst, a mixture of six- and seven-membered products **274** and **275** was obtained in 71% yield (Scheme 2.14). It was then decided to attach a phenyl group to the terminus of the double bond. This was supposed to stabilise the alkene in two ways: first, making the alkene di-substituted should decrease or eliminate the energy gained when a mono-substituted alkene was turned into a di-substituted one, and second, conjugation between the alkene and the aromatic ring should make potential isomerisation even more unfavourable. Nevertheless, when the di-substituted substrate **276** was treated with Grubbs II catalyst, the same ratio of products was observed.[182]



Scheme 2.14: Initial modification of terminal alkene. Conditions: a) Grubbs II, benzene, reflux.

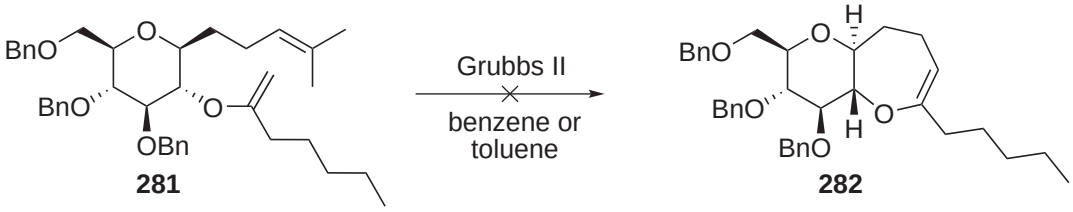
For the target system, it was decided to position two methyl groups at the terminus of the double bond to give a tri-substituted double bond which should be more stable than the potential isomerised product. The introduction of the *gem*-dimethyl group could be achieved by cross-metathesis of alcohol **261** and 2-methyl-2-butene.[183,184] However, it is also possible to prepare 5-bromo-2-methyl-2-pentene[185] and with this in hand, the sequence previously used for preparation of the enol ether **253** was repeated.

Epoxidation of tri-*O*-benzyl-D-glucal followed by addition of the Grignard reagent generated from 5-bromo-2-methyl-2-pentene afforded alcohol **279** directly and in modest yield (Scheme 2.15). The secondary alcohol was transformed into the corresponding alkynyl ether **280** using the two-step protocol. Finally, alkyne carbocupration was performed using a much simpler side-chain than before in order to facilitate the reaction. The diene **281** was obtained in poor yield, but enough material was produced to realise a couple of RCM reactions.



Scheme 2.15: Preparation of modified substrate. Conditions: a) Oxone, acetone, CH_2Cl_2, $NaHCO_3$ $_{aq}$, 0 °C to rt; b) (4-methylpent-3-enyl)magnesium bromide, THF, −20 °C, 25% (2 steps); c) KH, trichloroethylene, Et_2O, rt; d) *n*BuLi, Et_2O, −78 °C to −45 °C, 70% (2 steps); e) CuBr, LiBr, pentylmagnesium bromide, THF, −90 °C to −78 °C, 25%

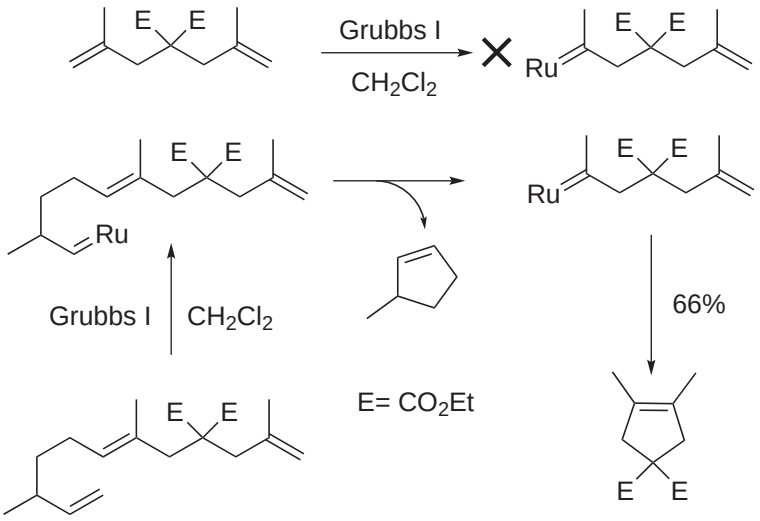
Diene **281** was then treated with Grubbs II catalyst in both refluxing benzene and hot toluene (80 °C), but the substrate was completely unreactive towards those metathesis conditions (Scheme 2.16). The tri-susbtituted alkene was probably too hindered for the metathesis reaction to initiate.



Scheme 2.16: RCM reactions of diene **281**

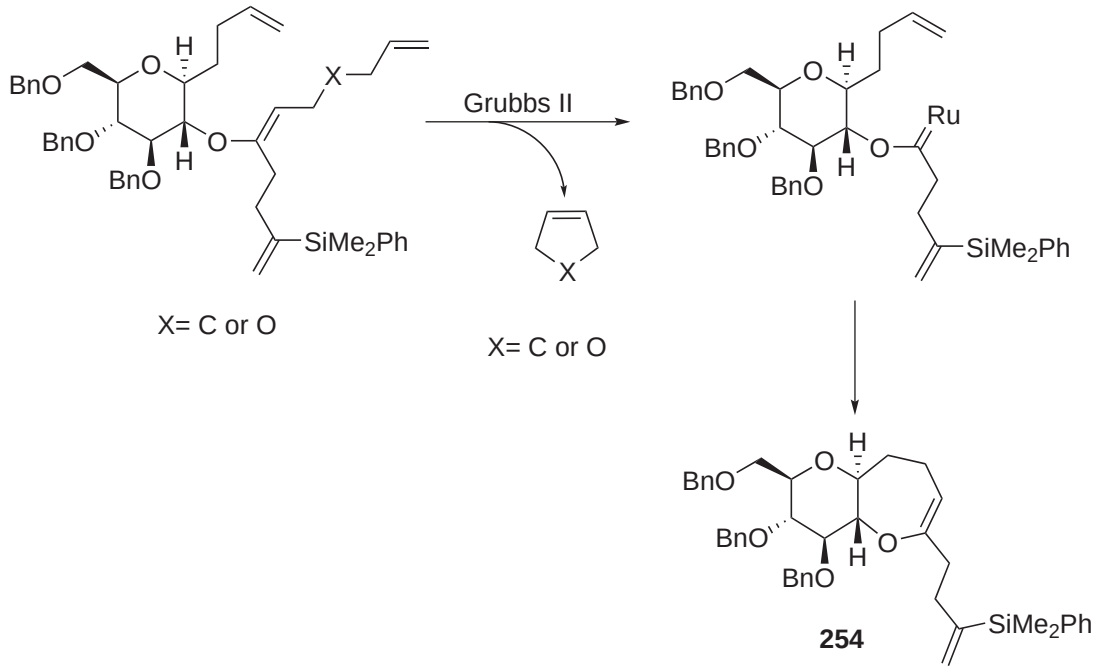
- *Relay metathesis strategy*

The last approach envisioned for this project was based on a relay metathesis process. The relay RCM concept was introduced by Hoye and co-workers in the early part of this decade.[186–189] This process involves the design of substrates that allow one to dictate the sequence of metathesis events by guiding the metal atom through the individual steps of the RCM cascade. This approach is particularly useful for substrates that do not react well under standard RCM conditions. The initial substrate is modified to introduce a small chain that will react quickly with the ruthenium catalyst, which will carry on the first RCM, that will liberate a small molecule, usually cyclopentene or dihydrofuran, to generate a new alkylidene ruthenium which will then react to form the desired product (Scheme 2.17).



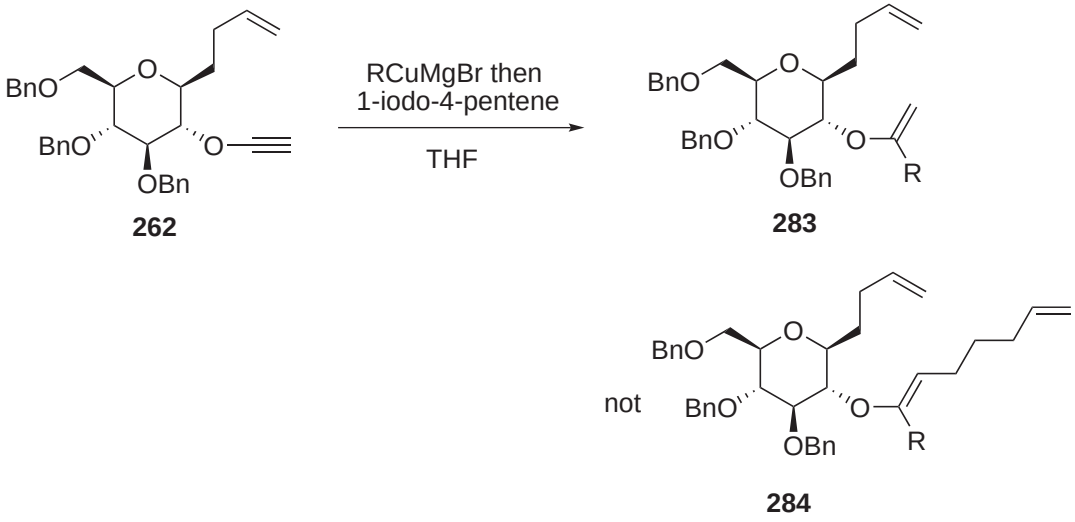
Scheme 2.17: An example of relay RCM

It was thought that in the case of triene **253**, the ruthenium catalyst reacted with the terminal alkene first, but then could not realise the ring-closure step. The relay-RCM strategy would be used to modify the order of these events by first generating the ruthenium carbene at the enol ether moiety. The resulting alkylidene would then react quickly with the terminal alkene to generate the seven-membered product (Scheme 2.18).



Scheme 2.18: Relay RCM strategy

Kleijn and Vermeer reported the formation of tri-substituted enol ethers by sequential 1,2 addition of an alkyl copper followed by quenching the vinyl copper intermediate with various electrophiles, such as iodine and allyl bromide.[190] To obtain the desired relay RCM substrate, 1-iodo- or 1-bromo-4-pentene was the electrophile of choice. But despite the use of various temperatures, reaction times and additives (HMPA), the trisubstituted enol ether was never obtained (Scheme 2.19). Only the 1,1-di-substituted product was observed, resulting from the 1,2 addition followed by quenching of the vinyl cuprate intermediate.



Scheme 2.19: Attempts to generate polyene **284**.

2.3 Summary and Outlook

In summary, selective formation of the six-membered product has been accomplished using a combination of two ruthenium catalysts: first, the ruthenium hydride catalyst $RuCl(CO)H(PPh_3)$ carried out a single isomerisation of the terminal mono-substituted double bond, then the Grubbs II catalyst cyclised the intermediate triene to give the six-membered cyclic enol ether as the sole product.

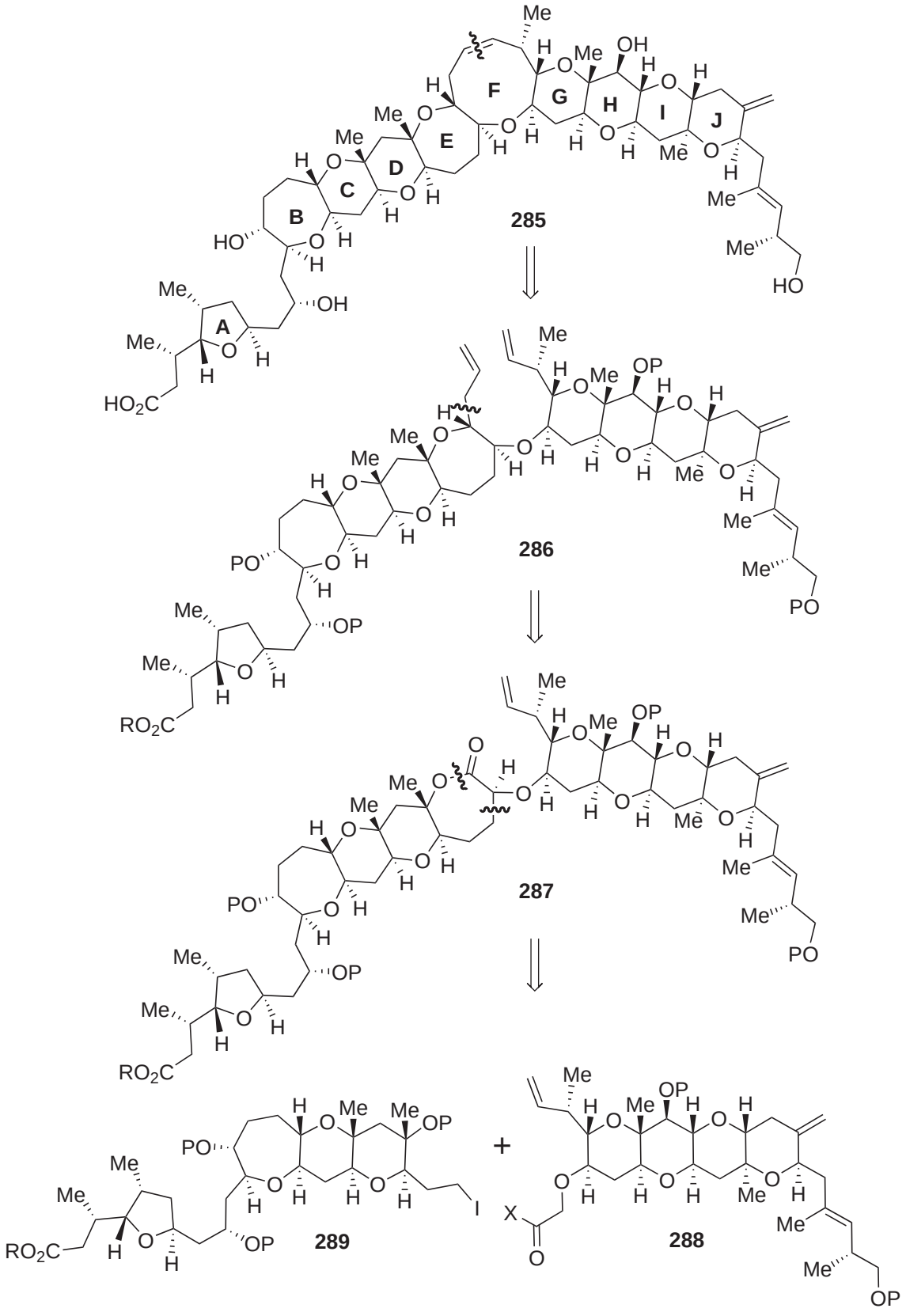
Despite investigating several strategies, the selective formation of the seven-membered ring has not been achieved. The terminal alkene is very prone to isomerisation and no method has been found to avoid the Grubbs catalyst decomposing and isomerising the alkene. The relay RCM approach is attractive, but the formation of the desired substrate requires further investigation.

Chapter 3

Synthesis of the A-D Fragment of Gambieric Acid A

3.1 Introduction

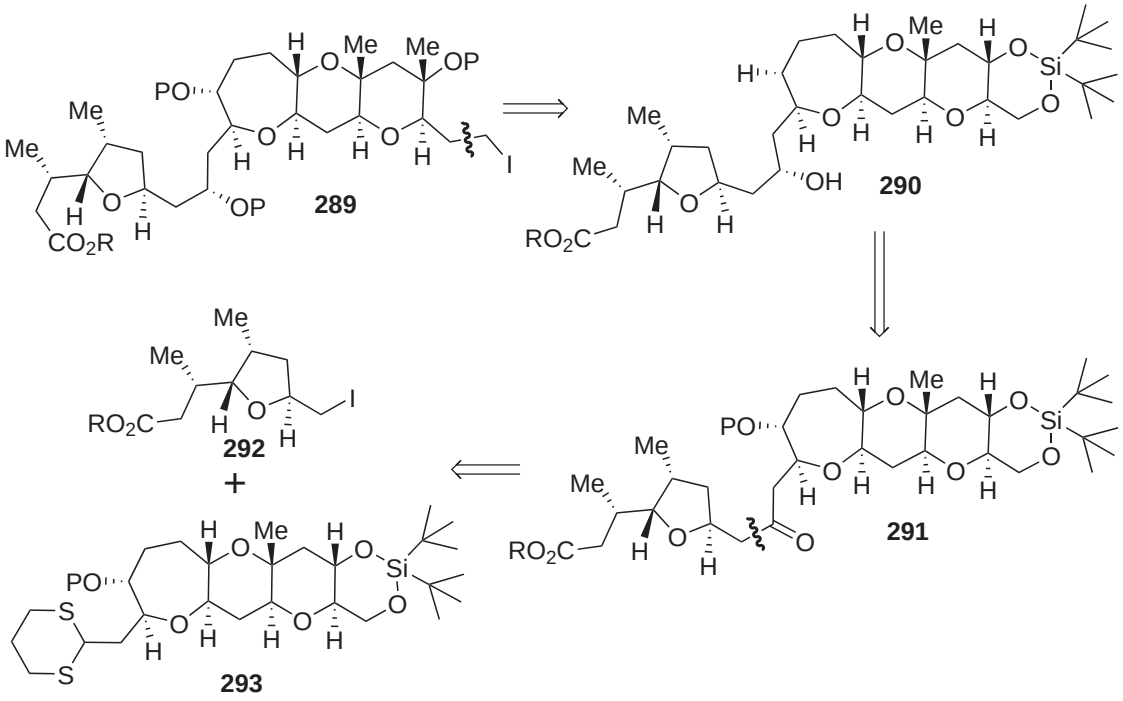
The retrosynthetic strategy for the total synthesis of gambieric acid A **285** developed in our laboratory is presented in Scheme 3.2. The nine-membered ring F would be formed by RCM of diene **286**. The second allyl side chain required for the metathesis step would be introduced from lactone **287** following Sasaki's procedure.[159] Finally, lactone **287** would be obtained by alkylation of carboxylic acid derivative **288** and iodide **289**.



Scheme 3.2: Retrosynthesis of gambieric acid A

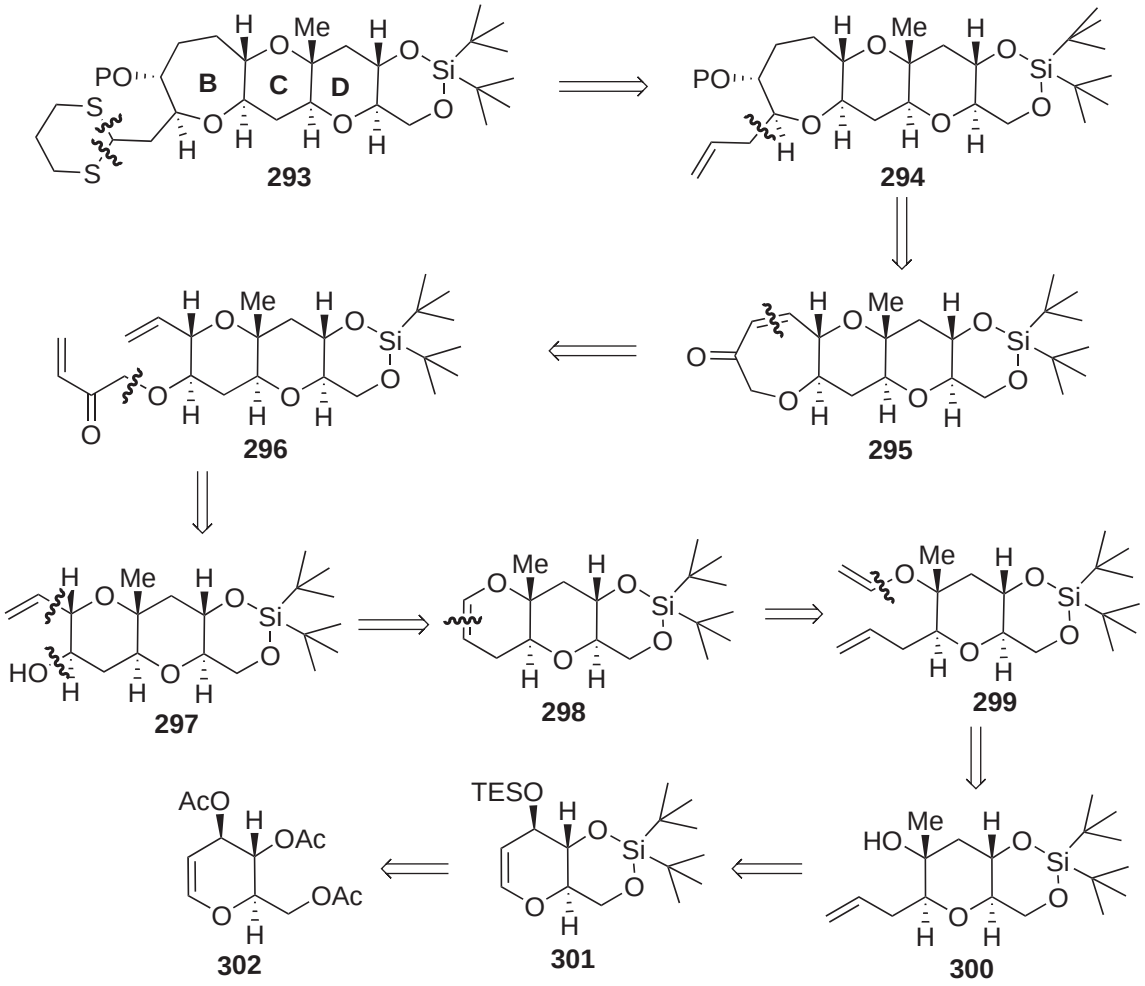
Iodide **289**, which represents the A-D fragment of gambieric acid A, would be accessed from diol **290** (Scheme 3.3). The key secondary alcohol would be derived from

the corresponding ketone **291**. Coupling between iodide **292** and dithiane **293** would give the complete skeleton of the A-D fragment. The advantage of this strategy is that by making the two different enantiomers of the A ring, all four potential diastereomers of the A-D fragment would be accessible and available for spectroscopic comparison with the natural product.



Scheme 3.3: Retrosynthetic approach of the A-D fragment of gambieric acid A

Finally, the retrosynthesis of the B-D fragment is described in Scheme 3.4. Dithiane **293** would be obtained from terminal alkene **294** after oxidative cleavage and dithiane formation. The alkyl side chain would be introduced by alkylation of enone **295** *via* an intermediate hydrazone. Retro-RCM gave diene **296**, which can be obtained by nucleophilic substitution from alcohol **297**. Alcohol **297** can result from opening on an epoxide derived from enol ether **298**. The C ring can be formed by RCM of the vinyl ether **299**. Epoxidation and epoxide opening of glucal **301** would give the required alcohol **300**. The starting material of this synthesis would be tri-*O*-acetyl-D-glucal **302**, a derivative of D-glucose, which is commercially available and reasonably priced.



Scheme 3.4: Retrosynthetic analysis of B-D fragment.

Previous work in our group had realised the synthesis of the tricyclic enone **295** in 22 steps.[182] However, some of the steps were quite low-yielding especially towards the end of the synthesis. The goals of this project were to prepare this enone, optimise the problematic steps and investigate the coupling strategy with the A-ring fragment.

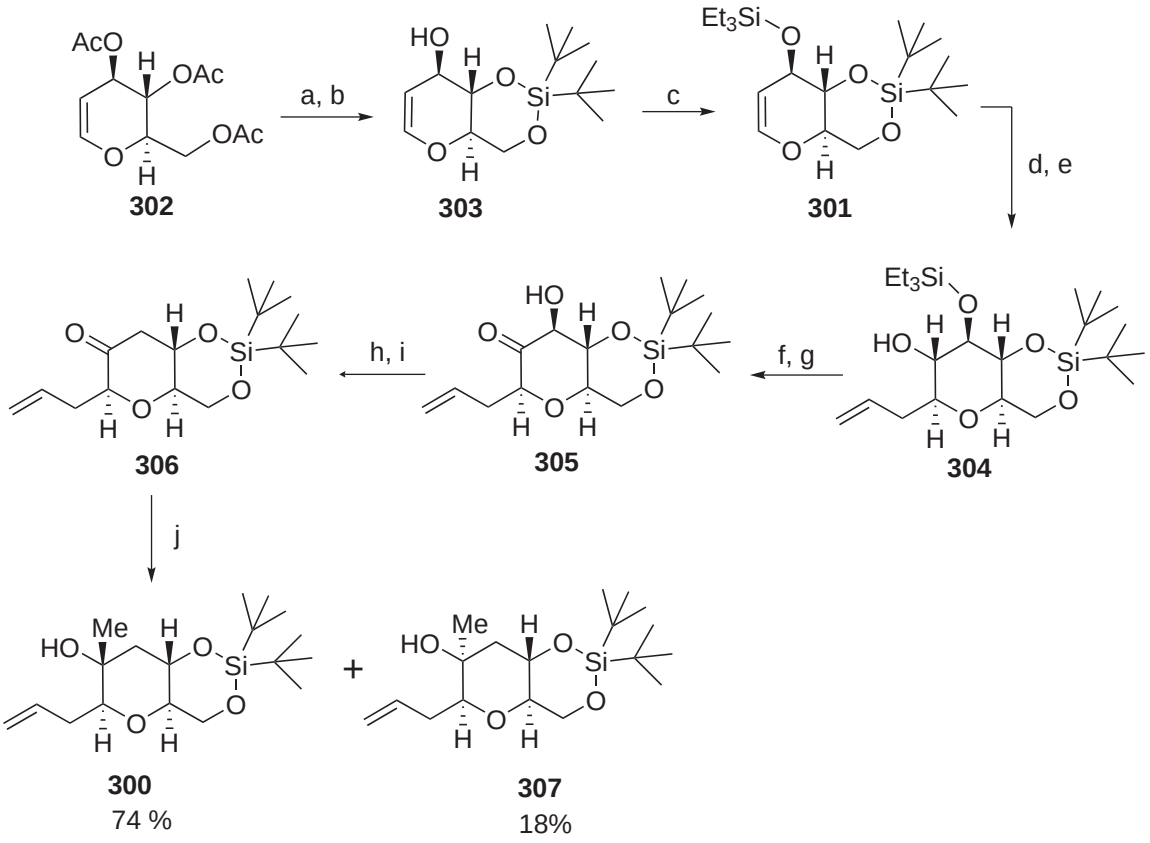
3.2 Results and Discussion

3.2.1 Synthesis of Functionalised D Ring

Initial strategy

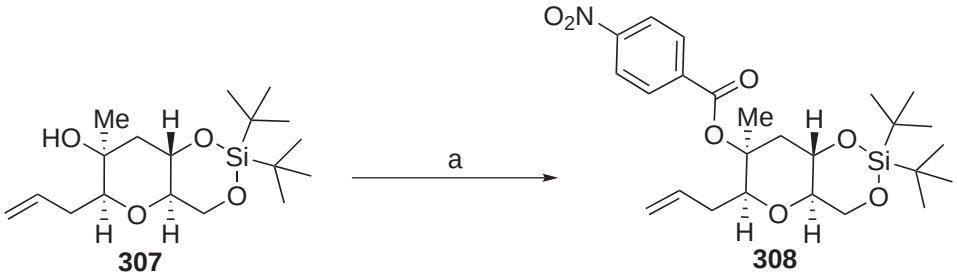
The synthesis started with commercially available tri-*O*-acetoxy-D-glucal **302**. Complete deacetylation using sodium methoxide followed by protection of the 1,2-diol with a di-*tert*-butylsilyl group gave alcohol **303** (Scheme 3.5). The third hydroxyl group was then protected as a triethylsilyl ether in very good overall yield. The enol ether **301** was then epoxidised stereoselectively using *in situ* generated DMDO and subsequent

addition of allylmagnesium chloride opened the epoxide at the anomeric position to deliver the alcohol **304**.[170] Using Swern conditions, the alcohol was oxidised to the corresponding ketone and the triethylsilyl ether was removed under oxidative conditions (DDQ) to yield alcohol **305**.[191] The hydroxyl group was then removed in a two-step sequence: substitution by iodine using standard conditions then radical-mediated reduction promoted by tri-*n*-butyltinhydride. This sequence afforded ketone **306** in a reasonable overall yield (47% over two steps). Nucleophilic addition of methylmagnesium iodide to ketone **306** gave both possible isomers in a 4:1 ratio in favour of the desired isomer **300**.



Scheme 3.5: Preparation of alcohol **300**. Conditions: a) MeONa, MeOH, rt; b) $(t\text{Bu})_2\text{Si(OTf)}_2$, DMF, 0 °C; c) TESCl, imidazole, DMF, rt, 86% (3 steps); d) Oxone, acetone, $NaHCO_3$, CH_2Cl_2, H_2O, 0 °C to rt; e) allylmagnesium chloride, THF, 0 °C, 81% (2 steps); f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 87%; g) DDQ, THF, H_2O, rt, 84%; h) PPh_3, I_2, imidazole, THF, rt; i) Bu_3SnH, AIBN, toluene, reflux, 47% (2 steps); j) MeMgI, toluene, −78 °C.

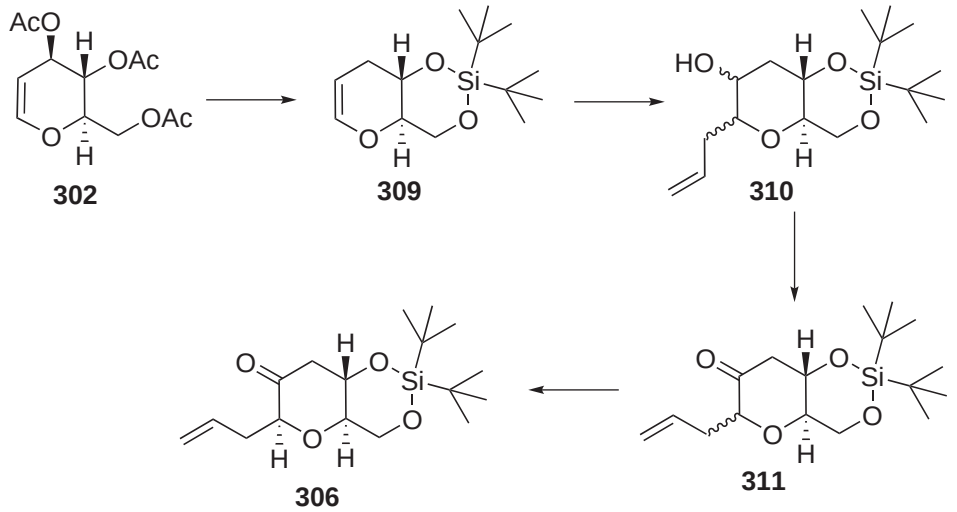
Assignment of the exact configuration of the newly created tertiary alcohol was originally accomplished by obtaining a crystal structure of the *para*-nitrobenzoic ester of the undesired isomer **307**.[182] Ester **308** was prepared by deprotonation of the alcohol with *n*-butyllithium followed by addition of *para*-nitrobenzoyl chloride, affording the desired product in a modest 40% yield (Scheme 3.6).



Scheme 3.6: Formation of ester **308**. Conditions: a) *n*BuLi, *p*NO_2-benzoyl chloride, THF, rt, 40%.

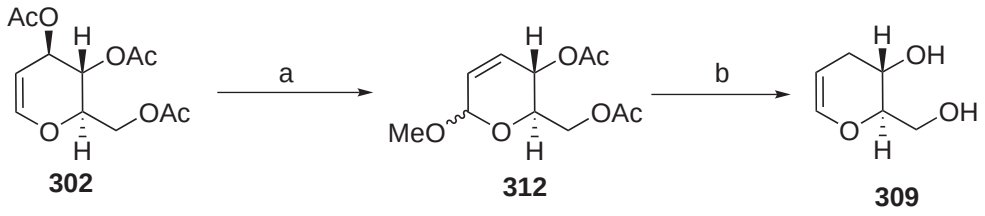
Revised route to ketone 306

The main problem with this first strategy to obtain ketone **306** was the three-step sequence (TES deprotection, iodide formation and abstraction) necessary to remove the hydroxyl group that is present in the starting material but not in the natural product. The yield over the last two steps was moderate at best and involved the use of large amount of highly toxic tin reagent. Furthermore, from a practical point of view, it was quite difficult to process large quantities of material. Due to reduction in molecular weight during these three steps and the average yields, the mass of compound was reduced to a quarter within three steps. Consequently, another strategy was envisioned where the hydroxyl group would be removed at the beginning of the synthesis to avoid the problems encountered above. The starting glucal **302** would be transformed into a similar enol ether **309** without the additional hydroxyl group. Then the same sequence as earlier (epoxidation, allylmagnesium chloride and Swern oxidation) would be applied to give ketone **311**. It was anticipated that the epoxidation would not be selective, but epimerisation after the Swern oxidation would give only the desired isomer **306**.



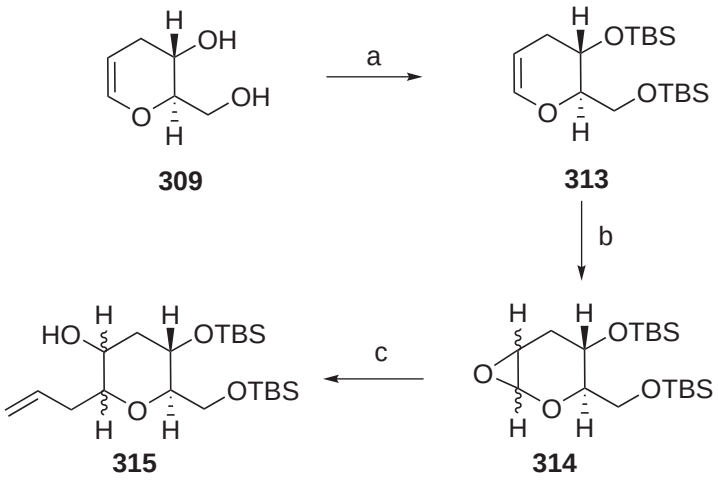
Scheme 3.7: Revised synthetic approach towards ketone **306**.

Diol **309** was prepared in two steps according to a literature procedure.[192] The tri-*O*-acetyl-D-glucal **302** was treated with methanol in the presence of boron trifluoride diethyl etherate to afford the mixed acetal **312** in high yield. Acetal **312** was then treated with lithium aluminium hydride, which displaced the allylic methoxy group and simultaneously deprotected the two acetate groups, to deliver diol **309** in excellent yield (Scheme 3.8).



Scheme 3.8: Preparation of diol **309**. Conditions: a) $BF_3{\cdot}Et_2O$, MeOH, CH_2Cl_2, rt, 88%; b) $LiAlH_4$, dioxane, reflux, 93%.

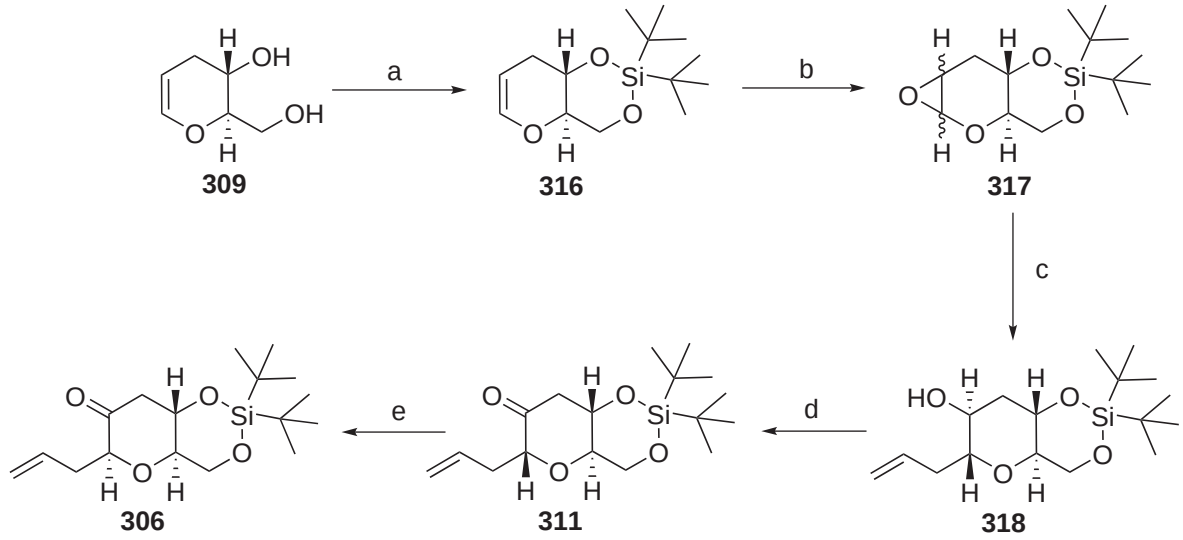
Two different protecting groups were then used. First, two TBDMS groups were installed in 64% yield (Scheme 3.9). The cyclic enol ether **313** was epoxidised using *in situ* generated DMDO and a 7:3 mixture of the epoxides **314** was obtained. The mixture was directly treated with allylmagnesium chloride and only one product **315** was isolated in very poor yield (9%). As the yield was so low, the configuration of the two stereocentres was not investigated.



Scheme 3.9: Conditions: a) TBSCl, imidazole, DMF, rt, 64%; b) Oxone, acetone, $NaHCO_{3\ aq}$, CH_2Cl_2, 0 °C to rt, quant; c) allylmagnesium chloride, THF, 0 °C, 9%.

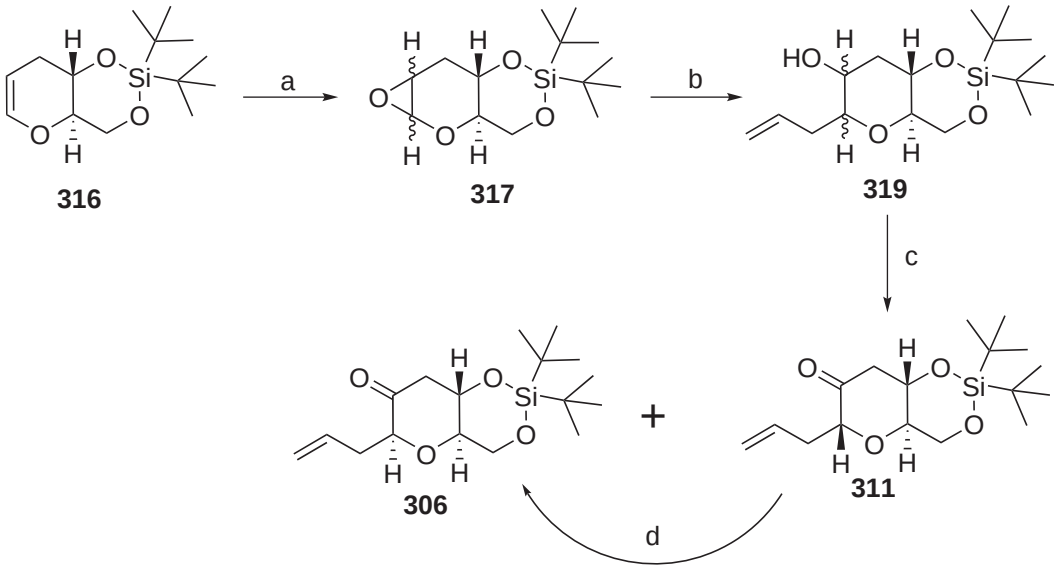
Diol **309** was also protected as the di-*tert*-butylsiloxane using the same conditions as described previously (Scheme 3.10). It was also possible to use di-*tert*-butyldichlorosilane, which is less expensive than the bis-triflate, in presence of silver (I) nitrate. The

dichlorosilane itself is not very reactive, so adding the silver complex creates the bis-nitrate silane which is much more reactive. The enol ether **316** was then epoxidised under the usual conditions to deliver a 55:45 mixture of both epoxides **317**. Treatment with allylmagnesium chloride gave a mixture of several diastereomers, from which one alcohol **318** was isolated after column chromatography in 32% yield. After Swern oxidation, the ketone **311** was confirmed as having the undesired configuration, so an isomerisation step was necessary to yield the desired diastereomer. Refluxing the ketone **311** in toluene with one drop of DBU for five hours led to significant decomposition of the starting material. Switching from DBU to proton sponge gave no reaction at all. Finally, using a sub-stoechiometric amount of DBU in toluene at room temperature gave the desired ketone **306** in 61% yield.



Scheme 3.10: Synthetic efforts towards ketone **306**. Conditions: a) $(t\text{Bu})_2\text{SiOTf}_2$, DMF, rt, 73% or $(t\text{Bu})_2\text{SiCl}_2$, $AgNO_3$, DMF, 0 °C, 67%; b) Oxone, acetone, $NaHCO_{3\ aq}$, CH_2Cl_2, 0 °C to rt, quant; c) allylmagnesium chloride, THF, 0 °C, 32%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 84%; e) DBU, toluene, rt, 61%.

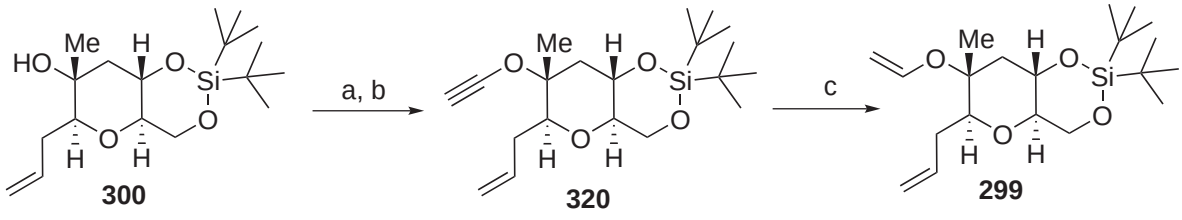
It was then decided to carry out the Swern oxidation directly on the crude mixture obtained from the Grignard step. A 7:3 mixture of ketone **306** and **311** was obtained in favour of the undesired diastereomer in an excellent 71% yield over three steps (Scheme 3.11). The two diastereomers were separated by column chromatography, and the undesired isomer **311** was then treated with DBU to obtain the isomer with the correct configuration.



Scheme 3.11: Optimised route for the synthesis of ketone **306**. Conditions: a) Oxone, acetone, $NaHCO_{3\ aq}$, CH_2Cl_2, 0 °C to rt; b) allylmagnesium chloride, THF, 0 °C; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 71% (3 steps), (**306**-**311**; 3:7); d) DBU, toluene, rt, 61%.

3.2.2 Formation of the C Ring

The introduction of the enol ether moiety required for the RCM was investigated. The first route used a three-step sequence to functionalise the alcohol: formation of the dichloroenol ether, then treatment with *n*BuLi to obtain the alkyne **320** and partial hydrogenation with Lindlar's catalyst to reduce it to the alkene **299** (Scheme 3.12). The hydrogenation reaction had to be monitored carefully by NMR spectroscopy to avoid any over-hydrogenation of the allyl side chain.

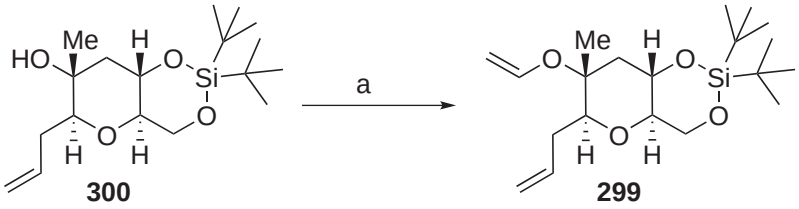


Scheme 3.12: Enol ether formation. Conditions: a) KH, Cl_2CCHCl, THF, rt; b) *n*BuLi, Et_2O, −78 °C to −45 °C, 90% (2 steps); c) Lindlar's catalyst, quinoline, EtOAc, H_2, rt, 96%.

Even though this route worked very well (yields over 90% for each step), it was time-consuming and so shorter alternatives were explored.

A one-step protocol developed by Bosch and Schlaf, using a vinyl ether transfer catalysed by palladium bis(trifluoroacetate) in the presence of 4,7-diphenyl-1,10-phenanthroline (DPP) was investigated.[193] The authors reported some excellent results on

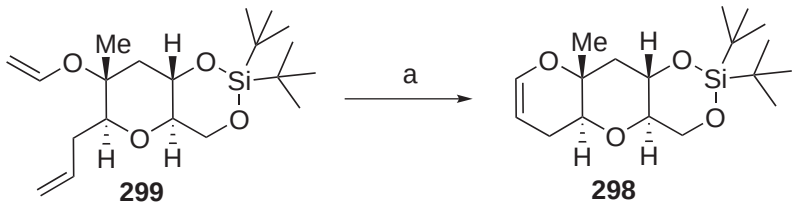
primary and secondary alcohols, and good yields on tertiary alcohols. Since this reaction is a thermodynamic equilibrium, a large excess of butylvinyl ether has to be employed to drive the conversion of the starting material. Despite using butylvinyl ether as the solvent in the reaction, the best yield obtained was 45%, along with 46% of recovered starting material (Scheme 3.13). There were also some reproductibility issues, as the yield would drop to 20% sometimes. Even though the starting material was always recovered from this vinylation procedure, it was not considered to be a viable alternative to the original route.



300 299

Scheme 3.13: Palladium-catalysed vinyl ether transfer. Conditions: a) $Pd(CF_3CO_2)$, DPP, butylvinyl ether, reflux, 45% (84% BRSM).

Diene **299** was then treated with Grubbs' second generation catalyst **92** to deliver the cyclic enol ether **298** in excellent yield (Scheme 3.14).



299 298

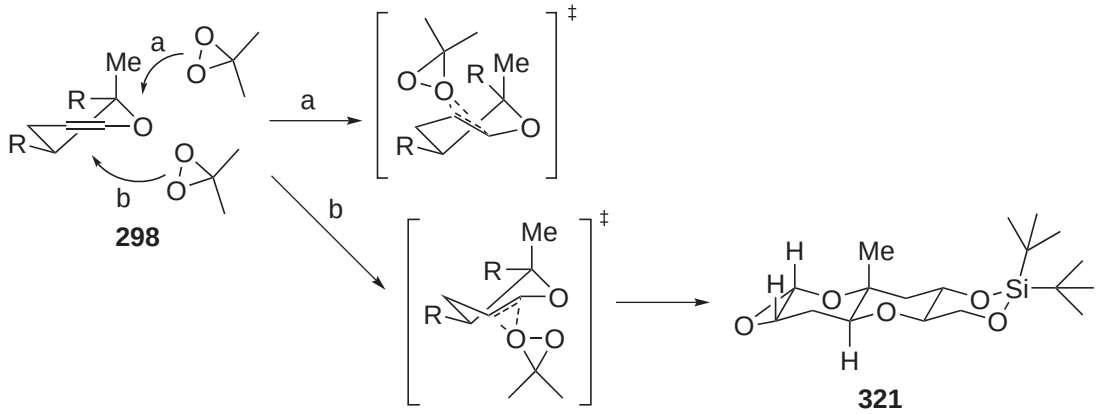
Scheme 3.14: Formation of C-D system. Conditions: Grubbs II catalyst **92**, toluene, 80 °C, 95%.

3.2.3 Formation of Tricyclic Enone

Functionalisation of enol ether 298

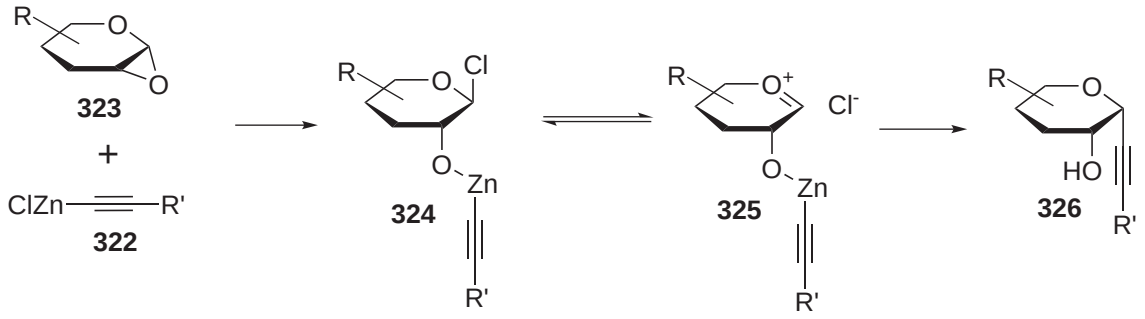
The next steps involved the epoxidation of the enol ether moiety followed by nucleophilic attack to introduce the two-carbon unit necessary for the second RCM step. Epoxidation was realised using DMDO, either using the *in situ* protocol or by preparing a DMDO solution in acetone. In this case, it was found that preparing the DMDO solution then adding it onto the enol ether was preferable. Indeed, the epoxide generated seemed to be rather unstable, so shorter reaction times and cleaner reactions were preferable. However, the DMDO solution had to be used as soon as the distillation was finished and could not be kept in the freezer overnight.

Based on the crude NMR, it was clear that the epoxidation was highly stereoselective ($d.r$>9:1). It was postulated that the attack of the oxidising agent from the upper face of the enol ether would lead to a unstable boat-like transition state (pathway a), whereas an approach from the lower face of the double bond (pathway b) would give a much more stable chair-like transition state (Scheme 3.15).



Scheme 3.15: Epoxidation of enol ether **321**. Conditions: DMDO, CH_2Cl_2, 0 °C, quant.

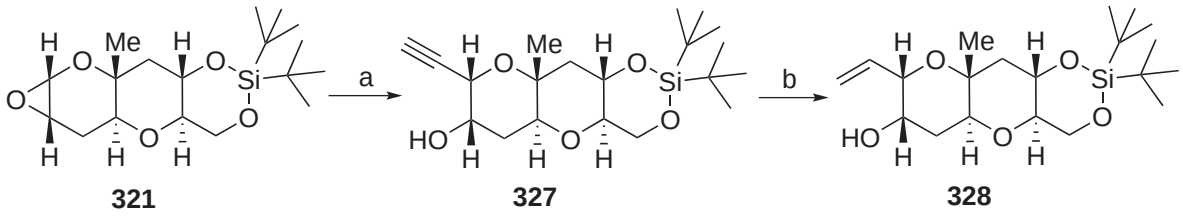
As a consequence of the stereoselective outcome of the epoxidation reaction, standard S_N2 nucleophilic attack onto the epoxide would introduce the carbon chain with the wrong configuration at the ring junction. The initial protocol chosen to introduce the two-carbon unit was based on a report by van Boom and co-workers.[194] They described the addition of various alkyne nucleophiles onto 1,2-anhydrosugar derivatives mediated by $ZnCl_2$ and obtained exclusively the *cis*-product. They proposed a mechanism where an alkynylzinc **322** would activate an epoxide **323**, which would then be opened by a chlorine anion to give intermediate **324** (Scheme 3.16). This would be in equilibrium with the oxonium cation **325** and intramolecular delivery would give the α-product **326**.



Scheme 3.16: Zinc-mediated *syn*-addition onto epoxides.

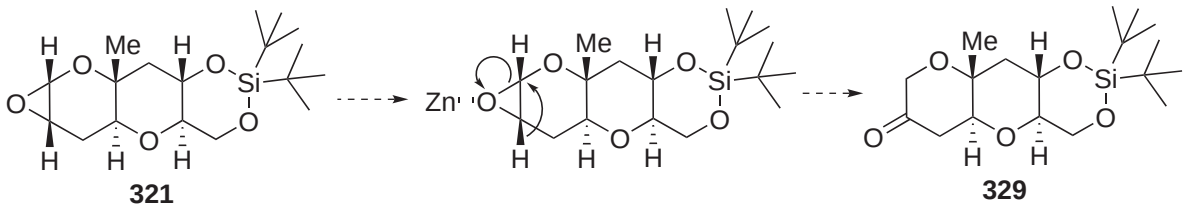
These conditions described above were applied to epoxide **321** using sodium acetylide

as the nucleophile. After some reaction optimisation, the desired secondary alcohol **327** was obtained in 55% yield (Scheme 3.17). The alkyne was then partially hydrogenated using Lindlar catalyst, to deliver alkene **328**.



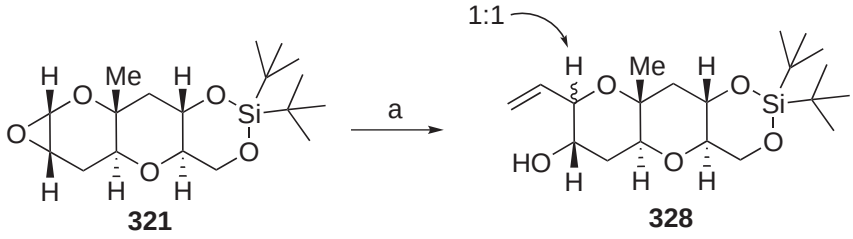
Scheme 3.17: Synthesis of alcohol **328**. Conditions: a) $ZnCl_2$, NaCCH, Et_2O, CH_2Cl_2, 0 °C to rt, 55%; b) Lindlar's catalyst, quinoline, EtOAc, H_2, rt, 84%.

It turned out that the reaction was very sensitive to the reaction conditions employed and it was particurlarly important to warm the solution of epoxide and alkynylzinc very slowly to room temperature, otherwise formation of a by-product was observed. It is believed that this by-product was ketone **329**, resulting from a 1,2-hydride shift as previously observed by Rainier in related reactions (Scheme 3.18).[195]



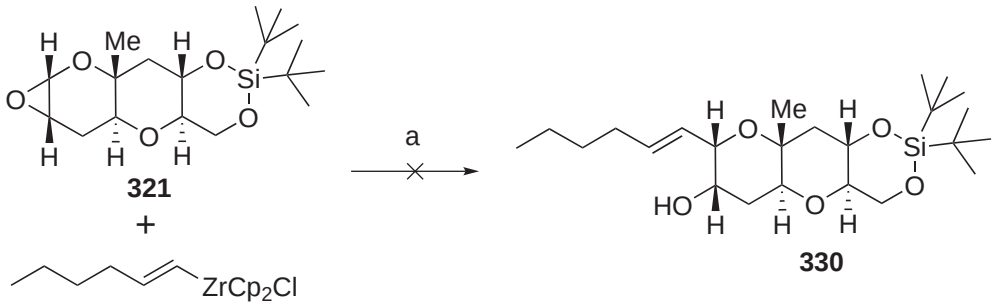
Scheme 3.18: Byproduct formation.

Although the yield of alcohol **328** was acceptable, other possible methods for introduction of the desired side-chain were considered. The direct zinc-catalysed addition of a vinyl Grignard reagent onto a glycal epoxide had been reported to give good yields by Wei and co-workers.[196] However, when applied to our system, the product was obtained in just 27% yield as a 1:1 mixture of α and β isomers (Scheme 3.19).



Scheme 3.19: Conditions: a) $ZnCl_2$, vinylmagnesium bromide, THF, 0 °C to rt, 27%.

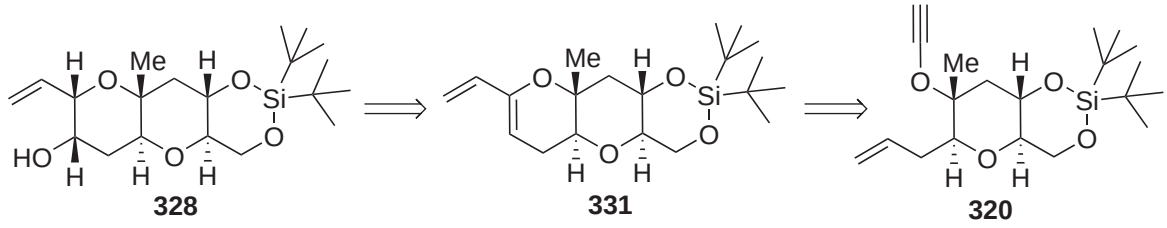
Wipf and co-workers have reported the *syn*-addition of vinylzirconocenes onto glycal epoxides.[197] For our system, the simple 1-hexyne was chosen as the reagent. Although an extra four-carbon chain would be introduced, it would be lost during the RCM step. Upon submission of the epoxide to the literature procedure, none of the required product was isolated (Scheme 3.20).



Scheme 3.20: Conditions: a) $AgClO_4$/Celite, CH_2Cl_2, 0 °C to rt .

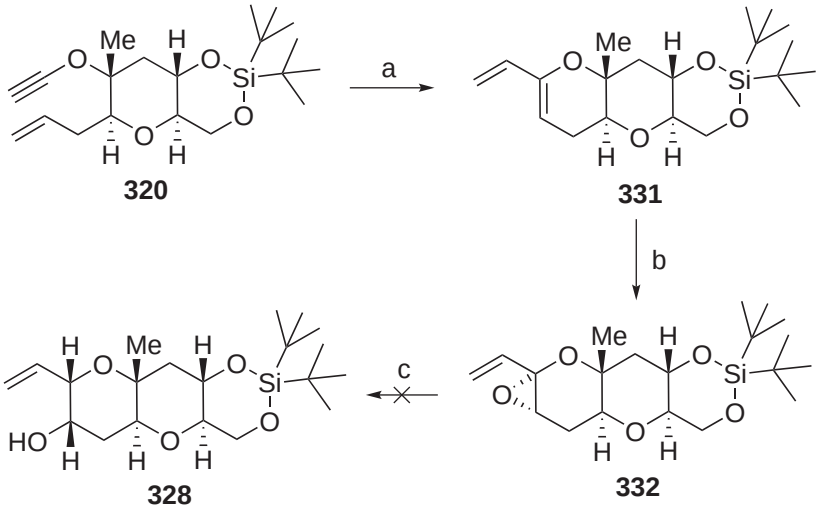
Enyne RCM strategy

Another strategy to obtain alcohol **328**, involving an enyne metathesis reaction, was explored. It was envisaged that alcohol **328** would be obtained from diene **331** by a sequence of chemoselective epoxidation and reductive opening (Scheme 3.21). Diene **331** would be formed by ring-closing metathesis of enyne **320**.



Scheme 3.21: Enyne RCM approach towards alcohol **328**

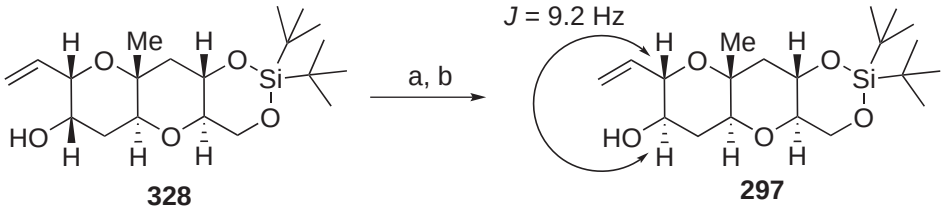
The previously synthesised alkynyl ether **320** was treated with Grubbs II catalyst in toluene under an atmosphere of ethylene to deliver diene **331** in excellent yield. Treatment of diene **331** with DMDO solution gave the crude epoxide **332**, which was treated with a variety of reductive agents (Super-Hydride, Et_3SiH, $NaBH_3CN$). Unfortunately, all of these reagents led to the decomposition of the starting material. Even though this type of reaction has been described several times in the literature, the allylic character of the reactive site might be problematic in this case.



Scheme 3.22: Synthetic efforts towards alcohol **328**. Conditions: a) Grubbs II, toluene, ethylene, 80 °C, 90%; b) DMDO, CH_2Cl_2, 0 °C, quant; c) Super-Hydride or Et_3SiH or $NaBH_3CN$.

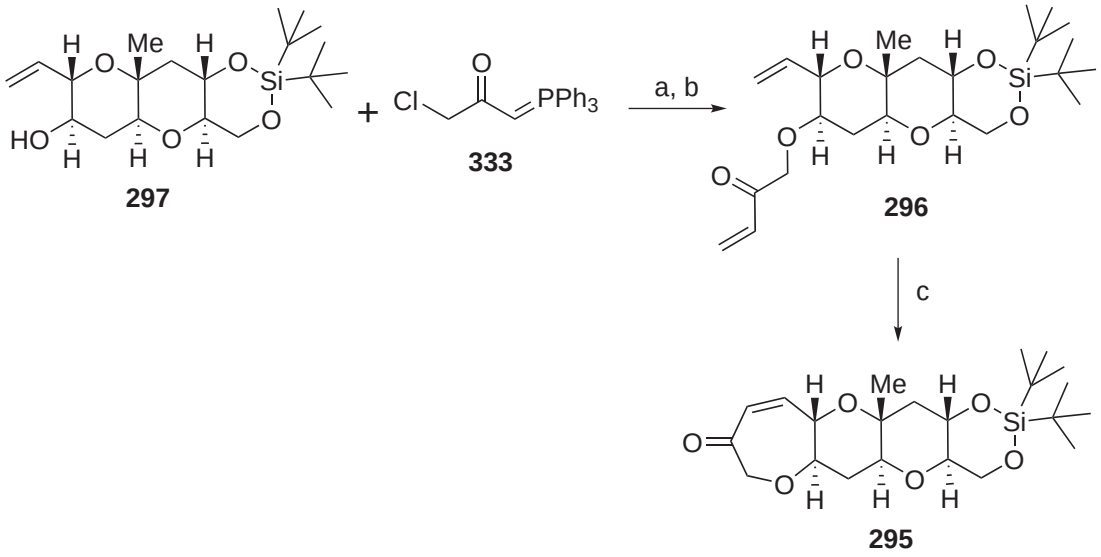
Enone metathesis

The synthesis continued from alcohol **328** (Scheme 3.23). The configuration of the secondary alcohol was corrected using a two-step sequence: oxidation to give the ketone using Dess-Martin periodinane[198] and subsequent sodium borohydride reduction delivered the desired alcohol **297** in excellent yield over two steps. The *trans*-configuration was confirmed by analysis of the coupling constants (^3J = 9.2 Hz).



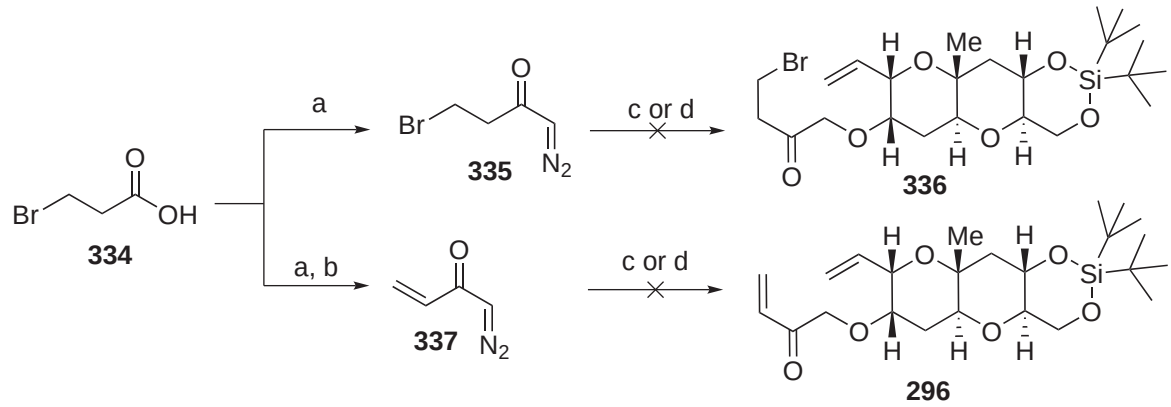
Scheme 3.23: Progress towards the B ring. Conditions: a) DMP, CH_2Cl_2, rt; b) $NaBH_4$, MeOH, CH_2Cl_2, 90% (2 steps).

The enone side-chain required for the construction of the seven-membered B ring was introduced using a procedure developed by Cossy and co-workers.[199] Alcohol **297** was first alkylated with chlorophosphorane **333**,[200] then treated with an aqueous solution of formaldehyde to deliver bicyclic enone **296** (Scheme 3.24). Exposure of the diene to Grubbs II catalyst in refluxing dichloromethane afforded the tricyclic B-D system **295** in 84%.



Scheme 3.24: Formation of tricyclic enone **295**. Conditions: a) phosphorane **333**, NaH, $(n\text{Bu})_4\text{NI}$, THF, reflux; b) CH_2O_{aq}, Et_2O, buffer pH=7, rt, 63%; c) Grubbs II catalyst **92**, CH_2Cl_2, reflux, 84%.

A shorter alternative for the introduction of the enone moiety required for the RCM step was investigated. Minehan and co-workers reported the formation of α-alkoxy ketones by alkylation of alcohols with α-diazoketones mediated by $In(OTf)_3$. Two different diazoketones **335** and **337** were prepared from 3-bromopropanoic acid **334** according to literature procedures (Scheme 3.25).[201] These diazoketones were then reacted in the presence of alcohol **297** and $In(OTf)_3$ or $RuCl_2(PPh_3)_3$.[202] None of the desired alkylated products **336** and **296** were isolated for these reactions.



Scheme 3.25: Conditions: a) $(COCl)_2$, PhH, 38 °C, then CH_2N_2, Et_2O, 0 °C to rt, 18%; b) DBN polymer-bound, hydroquinone, 0 °C; c) alcohol **297**, $In(OTf)_3$, toluene, rt; d) alcohol **297**, $RuCl_2(PPh_3)_3$, benzene, rt.

Enone **295** was a white solid, which could be recrystallised from EtOAc and gave crystals suitable for X-ray crystallography. The X-ray structure confirmed the exact

configuration of all the stereocentres created during the synthesis (Figure 3.2).

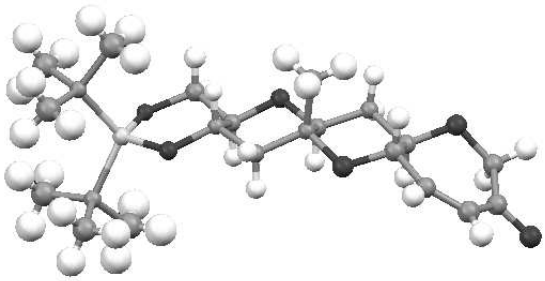
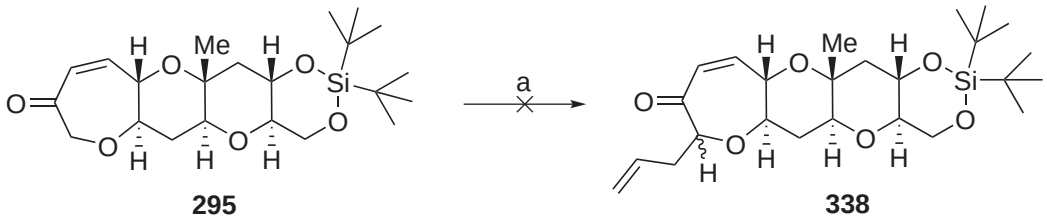


Figure 3.2: X-ray structure of enone **295**

3.2.4 Functionalisation of B-D System

Alkylation of enone 295

Direct alkylation of 3-oxo-α,β-unsaturated ketones is not very common but has been reported once by Cossy and co-workers with methyl iodide as an electrophile.[203] However, direct application of their conditions (LDA, allyl bromide, HMPA) led to decomposition of the starting material (Scheme 3.26) and so alternative strategies were investigated.

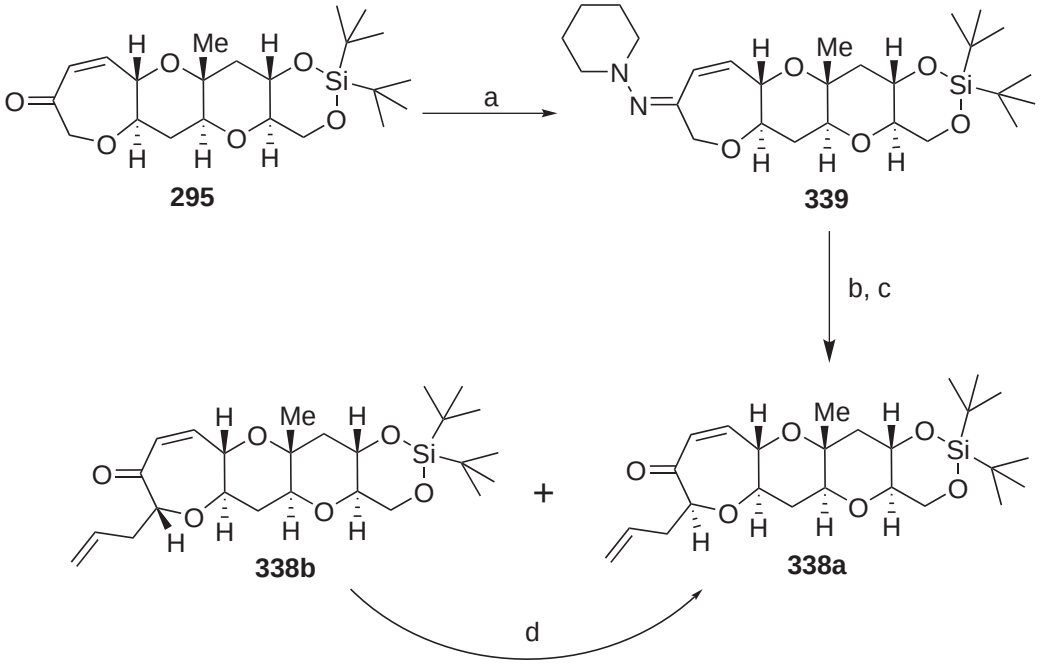


Scheme 3.26: Attempt of direct alkylation of enone **295**. Conditions: LDA, allyl bromide, HMPA, THF, −78 °C.

- *Hydrazone pathway*

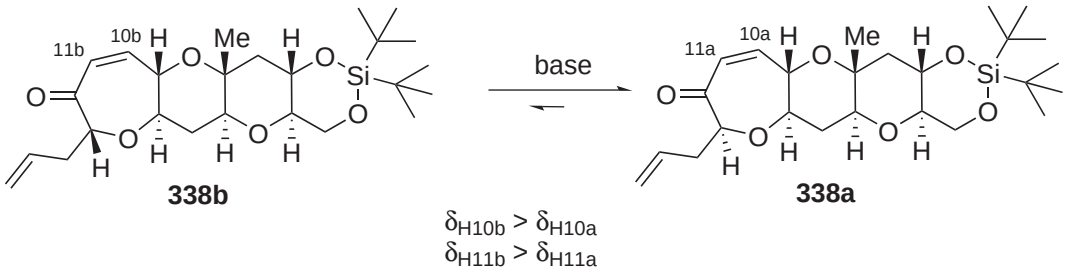
The first strategy for the introduction of the required allyl side chain onto the seven-membered ring that was explored relied on formation and alkylation of a hydrazone. This strategy had already been used in our group with great success.[204,205] Transforming the unsaturated ketone moiety into the corresponding hydrazone reduces the risk of 1,4-addition of the base during the deprotonation step. First, enone **295** was heated in toluene with an excess of 1-aminopiperidine using a Dean-Stark apparatus (Scheme 3.27). The resulting hydrazone **339** was then treated with *t*-butyllithium at low temperature, followed by an addition of excess allyl bromide. The crude product was reacted with copper(II) chloride in aqueous THF to cleave the hydrazone and afford the alkylated enone **338** in low yield (19% over 2 steps). The enone was isolated

as a 5:1 mixture in favour of the undesired isomer and so the epimerisation of the newly created centre was investigated. It was discovered that DBU was suitable for this reaction and gave an 8:1 mixture favouring the desired *cis*-product.



Scheme 3.27: Hydrazone pathway. Conditions: a) 1-aminopiperidine, toluene, 100 °C; b) *t*BuLi, allylbromide, THF, −100 °C to −78 °C; c) $CuCl_2$, THF, H_2O, 19% (*dr* = 1:5) (3 steps); d) DBU, CH_2Cl_2, rt, 68% (*dr* = 8:1).

The absolute configuration at the new stereocentre was initially assigned based on previous results obtained in our group concerning this type of compound.[204,205] It has been noted that the chemical shifts of the alkene protons of the *trans*-product **338b** are always higher than the chemical shifts of the *cis*-product **338a** (Scheme 3.28). This was consistent with the epimerisation step where the *cis*-product **338a** is expected to be the thermodynamic product.

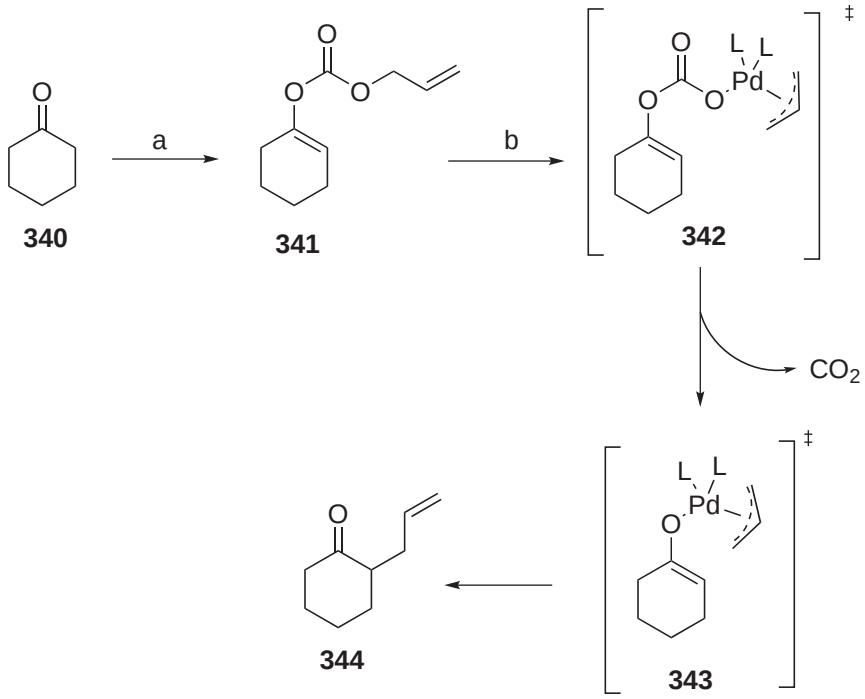


Scheme 3.28: NMR characteristics of epimers **338a** and **338b**.

- *Tsuji allylation*

Clearly, this sequence of hydrazone formation and alkylation was not efficient enough to pursue the synthesis. Consequently, a second approach was investigated, using the Tsuji allylation reaction.

In 1983, Tsuji and co-workers reported the α-allylation of ketone *via* a decarboxylative palladium-catalysed rearrangement (Scheme 3.29).[206] Cyclohexanone **340** was first deprotonated and treated with allylchloroformate to furnish the allyl enol carbonate **341**. When the carbonate was reacted with a source of Pd^0, the palladium inserted into the C-O bond to generate a π-allyl palladium complex **342**, which was followed by decarboxylation to give intermediate **343**. Nucleophilic attack of the enolate onto the electrophilic π-allyl complex delivered the alkylated product **344**.

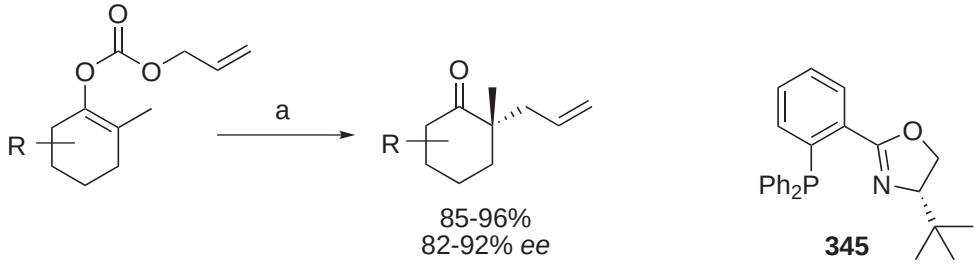


Scheme 3.29: Mechanism of the decarboxylative Tsuji rearrangement. Conditions: a) *t*BuOK, allylchloroformate, DMF, rt; b) $Pd_2dba_3{\cdot}CHCl_3$, PPh_3, DME, rt, 91%.

This reaction has several advantages: it is very regioselective and alkylation will only occur where the ketone has been originally deprotonated. There is no isomerisation of the enolate, even though the reaction is conducted at room temperature. Only one alkylation will occur per reaction. This reaction requires $Pd_2(dba)_3$, which is fairly stable and widely available. Finally, it is a very powerful reaction for the construction of quaternary centers.

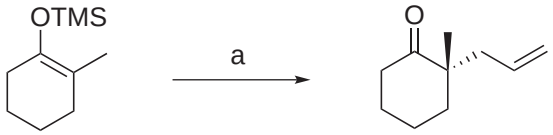
However, its use in organic chemistry has been limited until two groups recently reinvestigated this reaction and developed enantioselective versions. Stoltz and co-workers

reported the first enantioselective Tsuji allylation reaction,[207] using the phosphinooxazoline ligand (*S*)-*t*Bu-PHOX **345**, a P/N ligand previously used in other enantioselective palladium-catalysed reactions.[208–210] They reported the formation of quaternary stereogenic centers with excellent stereocontrol (*ee* = 82-92%) and very high yields (85-96%) (Scheme 3.30).



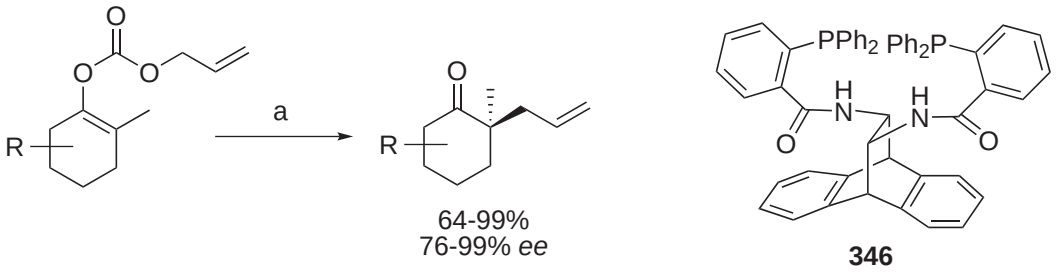
Scheme 3.30: Tsuji enantioselective version by Stoltz and co-workers. Conditions: a) Pd_2dba_3, ligand **345**, THF, rt.

They also investigated the use of TMS enol ethers as starting materials and obtained the desired alkylated ketones in high yield and enantioselectivity. The allyl side chain was introduced from diallylcarbonate and tetrabutylammonium difluorotriphenylsilicate (TBAT) was used as an initiator to generate a reactive enolate (Scheme 3.31). The TMS enol ethers are usually easier to prepare than corresponding enol allyl carbonate, so this represented a useful alternative.



Scheme 3.31: Allylation of TMS enol ethers. Conditions: a) diallylcarbonate, TBAT, $Pd_2(dba)_3$, ligand **345**, THF, rt, 95%, 87 % *ee*.

A few months later, Trost and co-workers reported another enantioselective version of the Tsuji allylation reaction.[211] The reaction conditions were very similar to Stoltz's except that Trost used the C_2-symmetrical bis-phosphine **346**, a ligand he had developed previously for his palladium-catalysed allylic alkylation reactions (Scheme 3.32).[212]

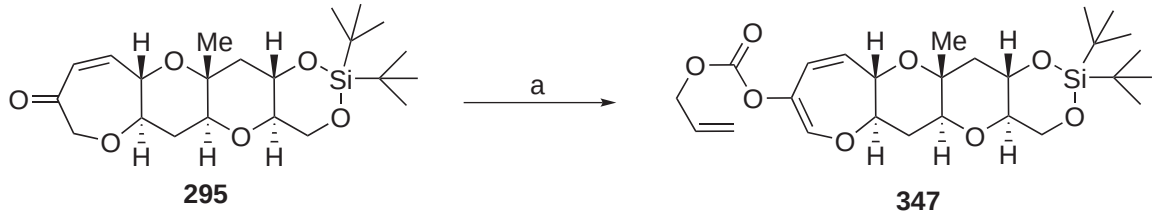


Scheme 3.32: Enantioselective Tsuji reaction developed by Trost and co-workers. Conditions: a) $Pd_2(dba)_3$, ligand **346**, toluene, rt.

Even though there were few examples of application of this method to α,β-unsaturated ketones or seven-membered rings, this methodology appeared to be a potentially efficient method for the introduction of the desired side-chain.

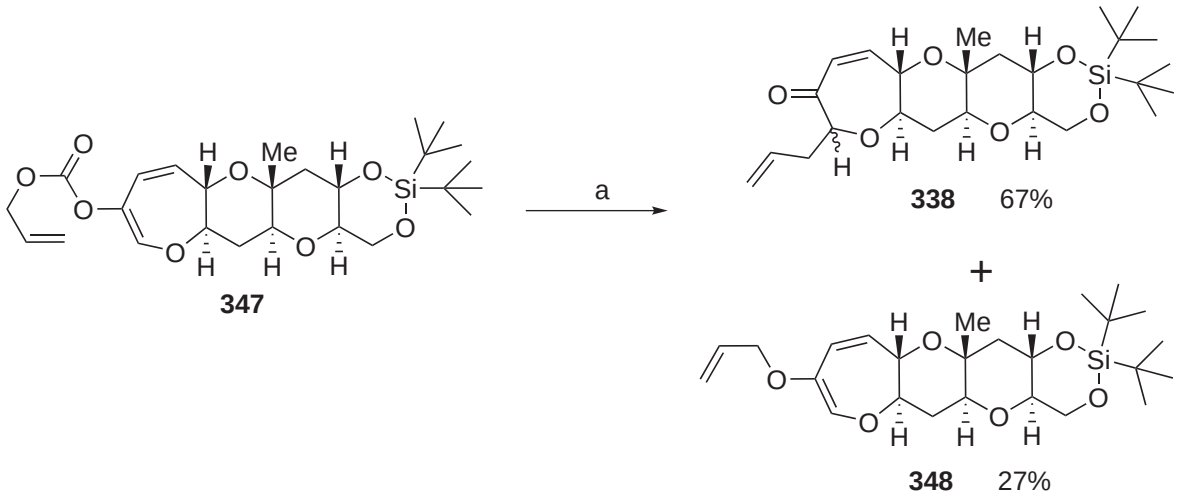
First, formation of the allyl enol carbonate was investigated (Scheme 3.33). The original conditions developed by Trost involved the use of NaHMDS to deprotonate the ketone and TMEDA to favour the *O*-alkylation against the *C*-alkylation. After 15 to 30 min at −78 °C, allylchloroformate was added and the reaction was complete within 15 min. Where Trost and Stoltz reported very high yields using these reaction conditions (> 80%), the average yield obtained was 55% along with 20% of starting material. Although the products are supposedly fairly stable on silica gel, it was found that the isolated yield was variable even though the analysis of the crude mixture by TLC was consistent. This problem was solved by drying the silica gel overnight in an oven to remove traces of water.

Some optimisation studies were performed to improve the yield of this reaction and it was found that Barbier-type conditions, in which the enone **295** and allylchloroformate were cooled down to −78 °C and then the base was added, were better and increased the yield of the required enol allyl carbonate **347** to 80%. It was also found that TMEDA was not necessary for our substrate. Because of the presence of the oxygen atom at the β-position and the alkene which is conjugated with the enolate, the *O*-enolate form is probably more reactive than the *C*-enolate and so no additive is required to achieve complete *O*-allylation.



Scheme 3.33: Formation of allyl enol carbonate **347**. Conditions: a) allylchloroformate, NaHMDS, THF, −78 °C, 80%, 95% BRSM.

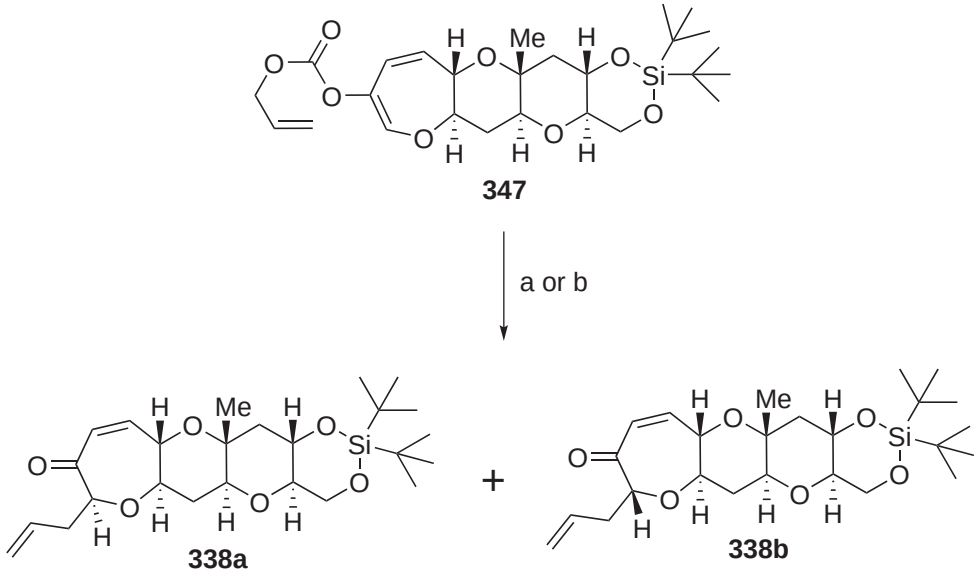
Following identification of optimised reaction conditions to form the carbonate **347**, the palladium-catalysed rearrangement reaction was explored. The reaction was performed initially without a chiral ligand: $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3 in toluene. After 3 h at room temperature, the desired alkylated enone **338** was isolated in 67% as a 3:2 mixture in favour of the required isomer (Scheme 3.34). Low stereoselectivity of the reaction can be explained by the planar configuration of the diene **347**, which offers little conformational preference for the attack at either face. An important by-product **348** was also isolated in 27% yield and was assigned as the allyl enol ether resulting from the *O*-alkylation product.



Scheme 3.34: Tsuji rearrangement reaction of carbonate **346** with a non-chiral ligand. Conditions: a) $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, toluene, rt.

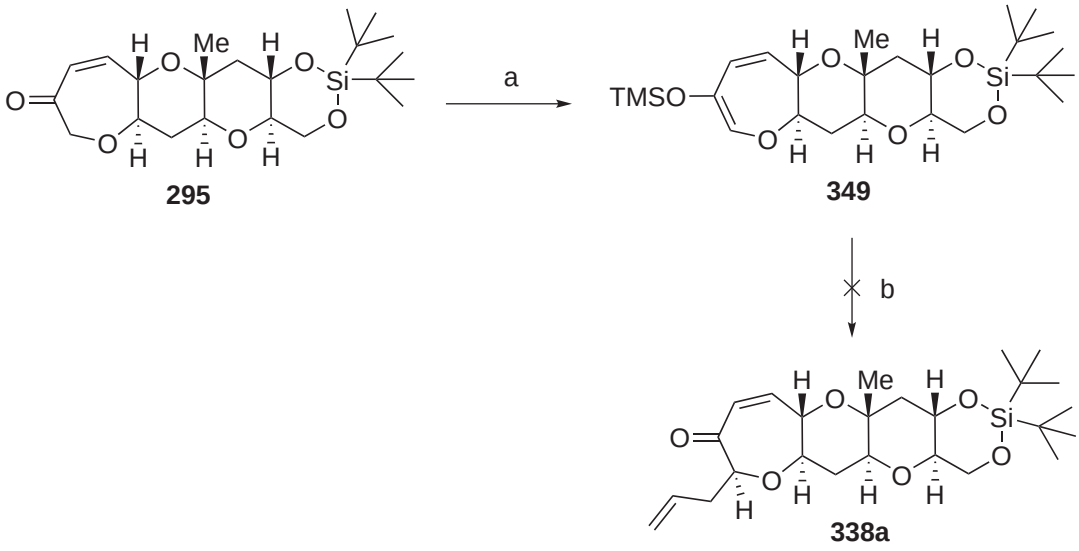
Although it was known that the mixture of products could be epimerised to give the desired isomer exclusively, chiral ligands were probed in order to obtain a single diastereomer from the rearrangement reaction. Based on the original studies, it appeared that the chiral ligand should possess *S*-configuration in order to deliver the desired *cis* isomer **338a**. Both the Trost and Stoltz ligand systems were tested. Initially, the Trost bis-phosphine ligand **346** was screened in oxygenated solvents (dioxane, DME),

but the substrate **347** was completely unreactive under these conditions. Switching to toluene gave the rearranged product in 81% 6.1:1 ratio in favour of the desired isomer **338a** and none of the *O*-alkylated product as observed (Scheme 3.35). Alternatively, the carbonate **347** was treated with the conditions developed by Stoltz and co-workers: $Pd_2(dba)_3$ and the phosphino-oxazoline ligand **345**. NMR analysis of the crude product indicated an excellent diastereomeric ratio (95:5) and after column chromatography, only the desired isomer **338a** was obtained in 87% yield. However, free dibenzylideneacetone from the original palladium complex eluted at the same R_f as the product and it was impossible to separate it from the product, so it was decided to carry onto the next step with this mixture.



Scheme 3.35: Stereoselective Tsuji rearrangement of carbonate **347**. Conditions: a) $Pd_2(dba)_3$, ligand **346**, toluene, rt, 81% (**338a-338b** = 6.1:1); b) $Pd_2(dba)_3$, ligand **345**, toluene, rt, 87% (pure **338a**).

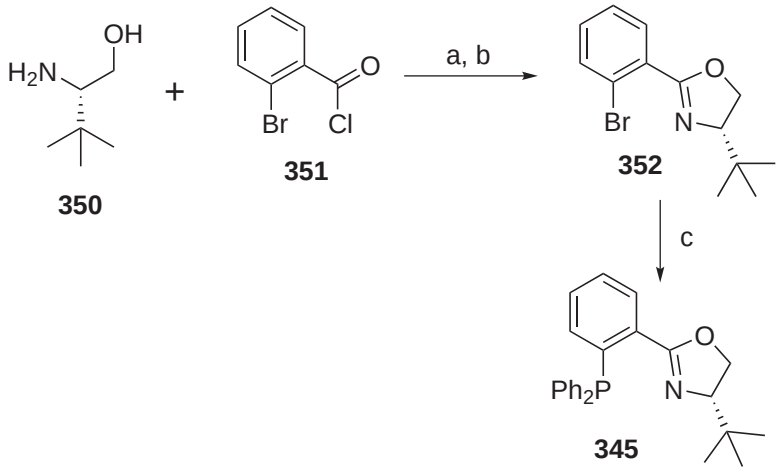
Rearrangement *via* the TMS enol ether was also investigated. Treatment of enone **295** with TMSOTf and triethylamine gave the desired TMS enol ether **349** in excellent yield (Scheme 3.36). However, application of the literature reaction conditions failed to deliver any of the desired alkylated product **338a**, but led to the cleavage of the TMS enol ether and recovery the enone **295**.



Scheme 3.36: Conditions: a) TMSOTf, Et_3N, THF, rt, 94%; b) $Pd_2(dba)_3$, ligand **345**, diallylcarbonate, TBAT, THF, rt.

- *Preparation of chiral ligand **345***

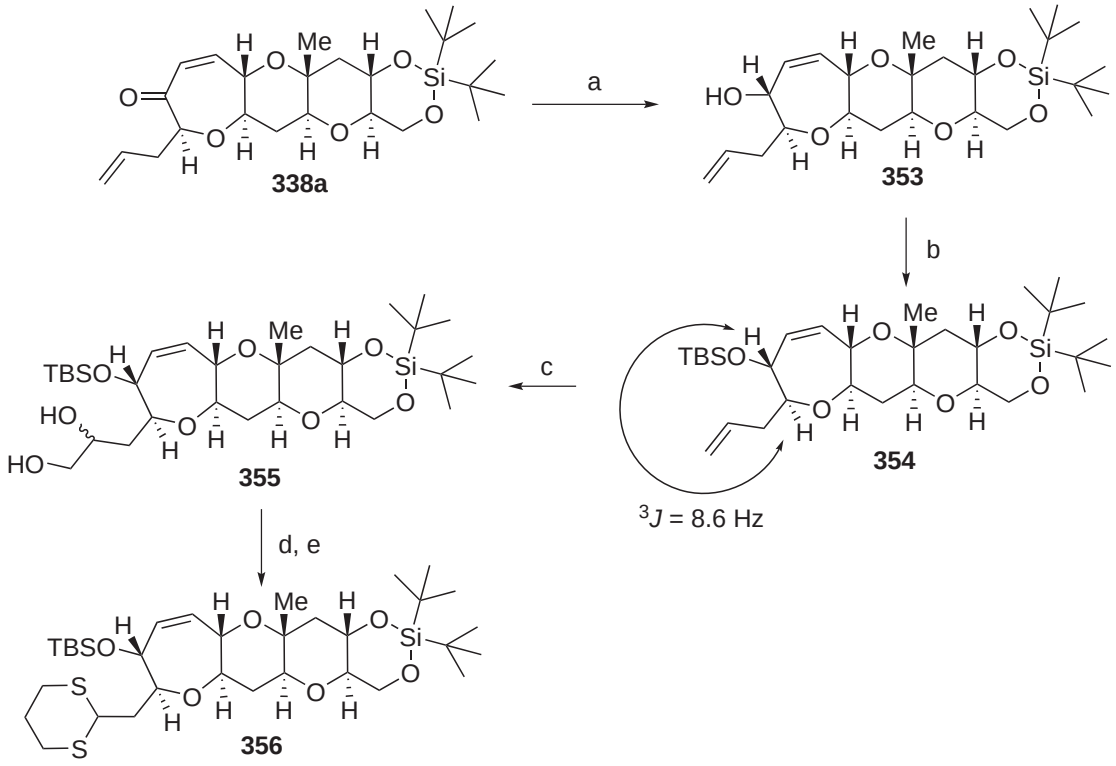
The (*S*)-*t*Bu-PHOX ligand **345** appeared as the best ligand for this reaction. Even though the ligand is commercially available, this reaction would be expensive if it were to be repeated on larger scale. Stoltz and co-workers reported a short and practical preparation of this ligand. The synthesis starts with the chiral pool material, the (*S*)-*tert*-leucinol **350**, which is coupled with 2-bromobenzoyl chloride **351** to give the corresponding amide (Scheme 3.37). Formation of the primary tosylate followed by cyclisation gave the oxazoline ring **352**. Finally, copper-mediated arylation of diphenylphosphine gave the desired chiral ligand **345**.



Scheme 3.37: Conditions: a) Na_2CO_3, CH_2Cl_2, H_2O, rt, 94%; b) TsCl, Et_3N, CH_2Cl_2, rt, then H_2O, 75%; c) CuI, DMEDA, Ph_2PH, $CsCO_3$, toluene, 110 °C, 62%.

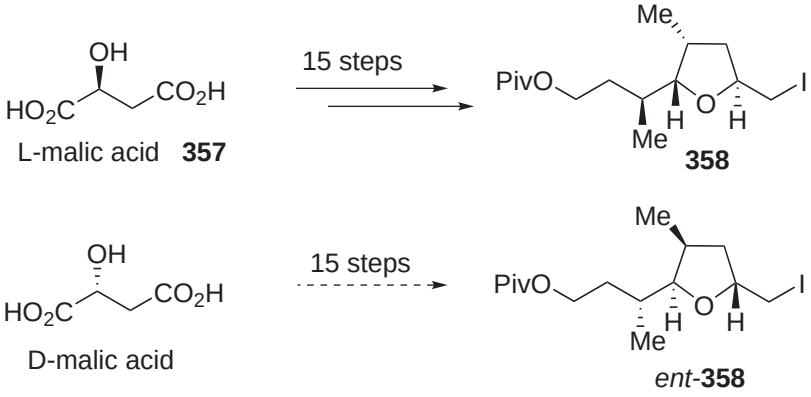
Completion of B-D fragment

With the side chain in place, only a few steps involving functional group manipulation were required to complete the synthesis of the B-D fragment. First, the enone was reduced under Luche conditions to deliver alcohol **353** as a single diastereomer (Scheme 3.38). The exact configuration of the new stereogenic center could not be verified by NMR analysis (coupling constant or NOE studies) at this stage, but based on numerous literature precedents, it was consistent with the required *R*-configuration.[205,213,214] The secondary alcohol was then protected as the TBS ether **354** in high yield. At this stage, analysis of the coupling constants at the newly created stereocenter revealed a *trans*-configuration ($^3J = 8.6$ Hz). Chemoselective dihydroxylation of the terminal double bond was then carried out using OsO_4 and NMO. To avoid the disubstituted endocyclic alkene reacting, only 1.05 equivalent of NMO was used and the reaction was not pushed to completion. The desired diol **355** was obtained in reasonable yield (54%) and most of the rest of the starting material was recovered. The diol was subsequently cleaved under oxidative conditions and the resulting aldehyde was immediately treated with 1,3-propanedithiol and $BF_3{\cdot}Et_2O$ to deliver the dithiane **356**. The latter reaction was carried out at low temperature −30 °C to avoid any cleavage of the TBS ether.[215] The dithiane **356** represents the complete B-D fragment of gambieric acid A.



Scheme 3.38: Completion of the B-D fragment. Conditions: a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, rt, 95%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 82%; c) OsO_4, NMO, THF, H_2O, rt, 54%, 78% BRSM; d) $NaIO_4$, THF, H_2O, rt; e) 1,3-propanedithiol, $BF_3 \cdot Et_2O$, CH_2Cl_2, −30 °C, 53% (2 steps).

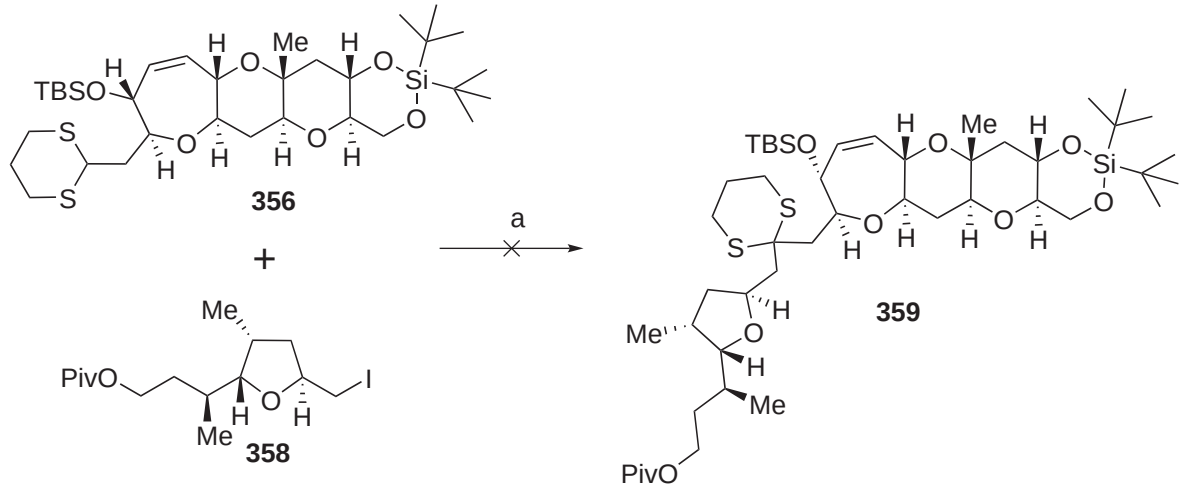
The A ring fragment had been previously prepared within the group (see 1.4.3).[167,216] The synthesis used (L)-malic acid **357** as the starting material and the desired iodide **358** was obtained in 15 steps (Scheme 3.39). The advantage of the synthesis was that both isomers of malic acid are commercially available, so both enantiomers of iodide **358** would be accessible.



Scheme 3.39: Preparation of iodide **358** by Dr S. Chaudhury.

The coupling reaction of the dithiane **356** and the iodide **358** was then tested. The

dithiane **356** was cooled down to −78 °C in THF, before *t*-butyllithium was added. Unfortunately, no colour change was observed and it is known that dithiane anions are usually brown. HMPA and iodide **358** were added to the reaction mixture anyway, but none of the coupled product **359** was obtained after two hours (Scheme 3.40).

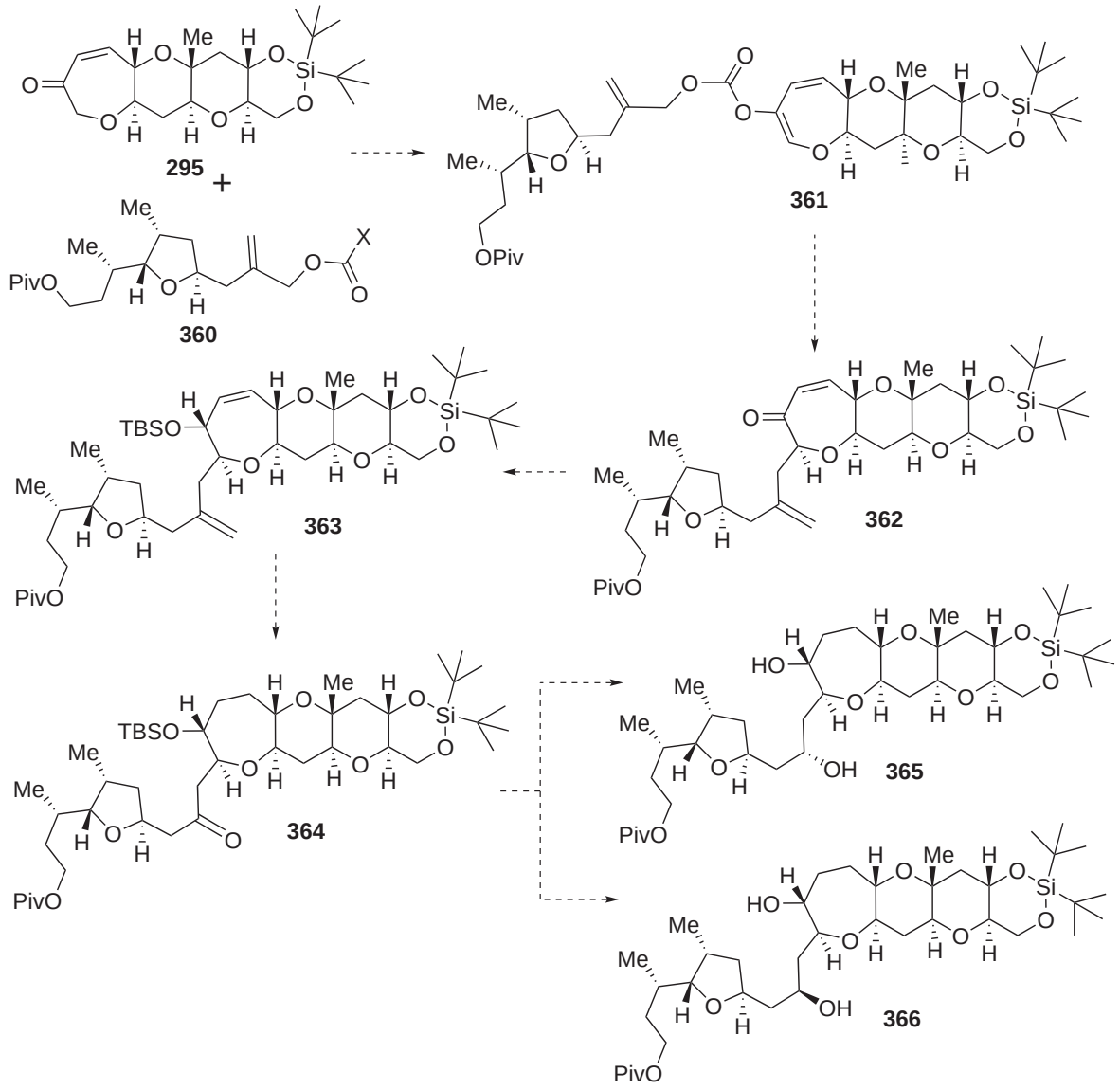


Scheme 3.40: Coupling reaction between dithiane **356** and iodide **358**. Conditions: a) *t*BuLi, HMPA, THF, −78 °C.

3.2.5 Revised Approach to the A-D Fragment

The new strategy

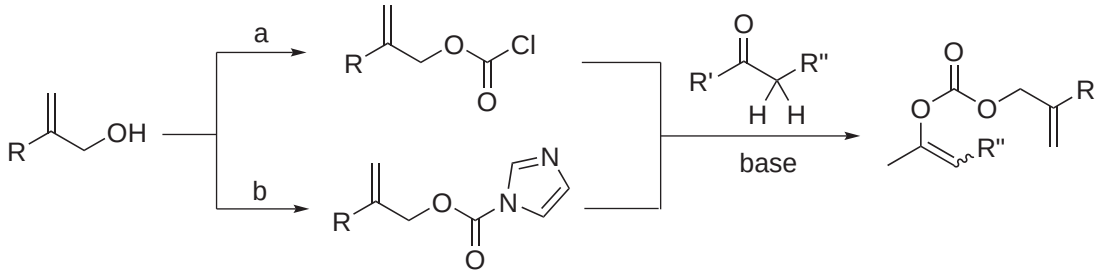
The failure of the coupling reaction led to the design of a new strategy for the coupling of both units. The development of the previous strategy showed that the Tsuji reaction is a very powerful tool to create the stereocentre on the seven-membered B ring while introducing a side chain. This time, it was imagined that the Tsuji reaction would be used to introduce the whole A ring fragment in one step instead of a simple allyl unit (Scheme 3.41). Carbonate **361** should rearrange in presence of Pd^0 to deliver the enone **362**. This intermediate would possess the complete carbon skeleton of the A-D fragment and the corresponding protected alcohol **363** would be obtained in two steps. Selective dihydroxylation followed by oxidative cleavage and hydrogenation would then give the ketone **364**. At this point, the first possibility would be to deprotect the secondary alcohol and then perform hydroxy-directed reduction of the ketone to obtain alcohol **365**. It would also be possible to perform the reduction first to obtain the other diastereomer in high selectivity and then deprotect the alcohol to give the other diastereomer **366**.



Scheme 3.41: Second-generation synthesis of the A-D fragment.

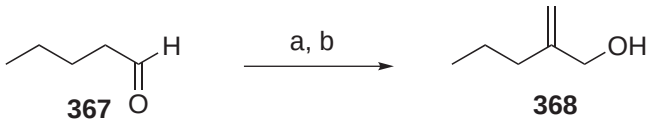
Model studies

The formation of carbonate **361** is the first challenging step of this new synthetic sequence. There is a limited number of ways in the literature to generate enol carbonates from functionalised allylic alcohols. To start with, the alcohol must be transformed into an activated carbonate which will later react with an enolate anion. The first option is to treat the allylic alcohol with trisphosgene and pyridine to generate the chlorocarbonate (Scheme 3.42).[217] The other possibility is to react the allylic alcohol with CDI to form an allyl 1*H*-imidazole-1-carboxylate .[218]



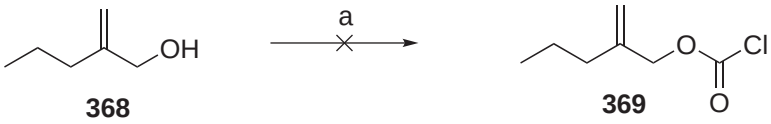
Scheme 3.42: Various options to generate carbonate **361**.

These sets of conditions were first explored using a model system. The model allylic alcohol was prepared in two steps from valeraldehyde **367**. First, a Mannich reaction was used to introduce the exocyclic alkene[219] and subsequent Luche reduction delivered allylic alcohol **368** in excellent yield (Scheme 3.43).



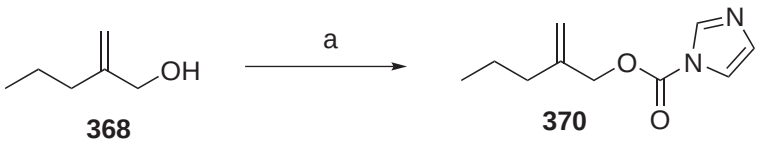
Scheme 3.43: Synthesis of alcohol **368**. Conditions: a) $Me_2NH{\cdot}HCl$, CH_2O_{aq}, 70 °C; b) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, rt, 89% (2 steps).

The formation of the corresponding chlorocarbonate was then attempted following the literature conditions, but the expected product was not obtained (Scheme 3.44). Considering the high toxicity of triphosgene, this route was not pursued further.



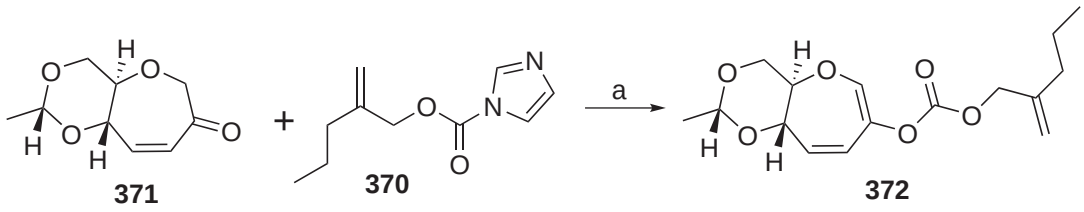
Scheme 3.44: Conditions: a) Triphosgene, pyridine, toluene, 0 °C.

The other method required much milder reagents. When treated with an excess of CDI, alcohol **368** afforded the allyl 1*H*-imidazole-1-carboxylate **370** in good yield (Scheme 3.45). The success of the reaction meant it could be utilised for the required coupling sequence.



Scheme 3.45: Formation of carboxylate **370**. Conditions: a) CDI, THF, rt, 88%.

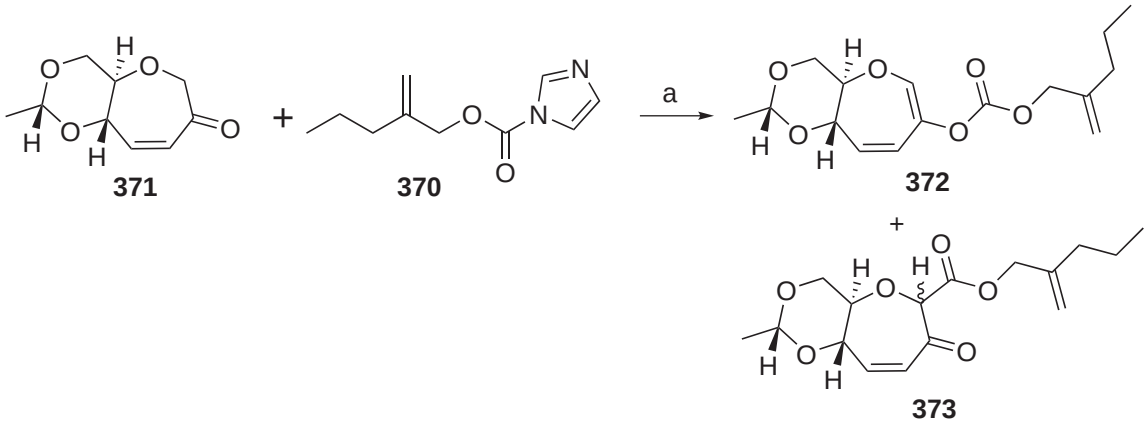
With the carboxylate in hand, the formation of the enol allyl carbonate was explored. A model enone system was also employed for the purposes of preliminary studies. Enone **371** had already been described in the literature by our group and has been prepared in large amounts by another member of the group.[204] The original conditions described by Trost and co-workers were applied to the model system: ketone **371** was first deprotonated with NaHMDS, then a solution of carboxylate **370** and $BF_3{\cdot}Et_2O$ in THF was added to the reaction mixture (Scheme 3.46).[218] The desired carbonate **372** was obtained initially in a modest 30% yield.



Scheme 3.46: First attempt to synthesise the carbonate **372**. Conditions: a) $BF_3{\cdot}Et_2O$, NaHMDS, THF, −78 °C, 30%.

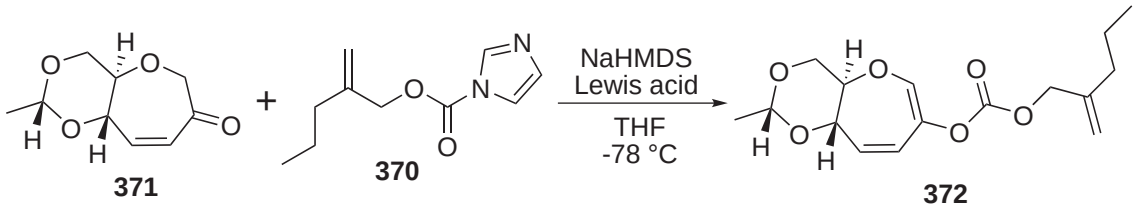
Optimisation studies were performed in order to increase the yield. It was found that minor changes in the reaction protocol had an important effect on the yield. Pre-mixing the enone **371** and the carboxylate **370** together in THF at −78 °C before adding the NaHMDS and the $BF_3{\cdot}Et_2O$ gave an improved 55% yield. It was also possible to pre-mix the carboxylate **370** and $BF_3{\cdot}Et_2O$ for 1 h in THF before adding it onto the enolate solution; again a 55% yield was obtained.

The nature of the Lewis acid was also investigated. During alkylation reactions, it is known that the enolate will react with a soft electrophile to give a *C*-acylated product, whereas hard electrophiles will give an *O*-acylated product. According to Trost and co-workers, a Lewis acid is required to coordinate the imidazole ring and increase its electrophilic character, hence turning the 1*H*-imidazole-1-carboxylate into an hard electrophile. The reaction was first tested in the absence of a Lewis acid, and, as expected, a mixture of *C*- and *O*-acylation products was obtained in very poor yield (Scheme 3.47).



Scheme 3.47: Conditions: a) NaHMDS, THF, −78 °C, 11%.

Addition of various Lewis acids to the reaction was then explored. Because of the presence of various functional groups capable of binding a Lewis acid (*e.g.* carbonyl, ethers), a Lewis acid possessing a high affinity of nitrogen atoms was required. Kobayashi and co-workers recently screened a variety of metal chlorides on aldehydes and aldimines and classified them depending on their selectivity.[220] Several of these azaphilic Lewis acids were then tested on our model system. $Sc(OTf)_3$, $FeCl_3$ and $CuCl_2$ gave very low yield (Table 3.1). In the presence of $InCl_3$, carbonate **372** was isolated in 22% yield. The results of this study were disappointing and so it was decided to continue using $BF_3{\cdot}Et_2O$ as the Lewis acid.

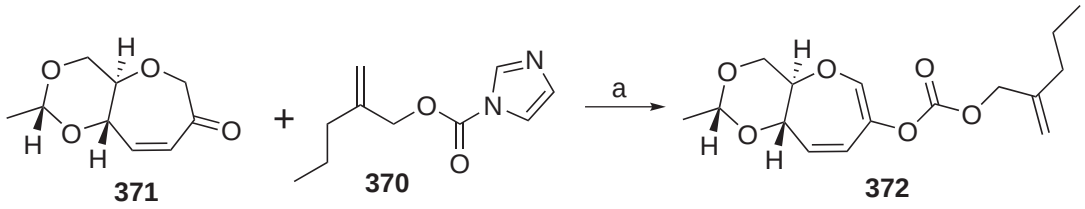


Entry	Lewis acid	Yield	Entry	Lewis acid	Yield
1	$Sc(OTf)_3$	0%	3	$CuCl_2$	6%
2	$FeCl_3$	3%	4	$InCl_3$	22%

Table 3.1: Screening of Lewis acids for the preparation of carbonate **372**.

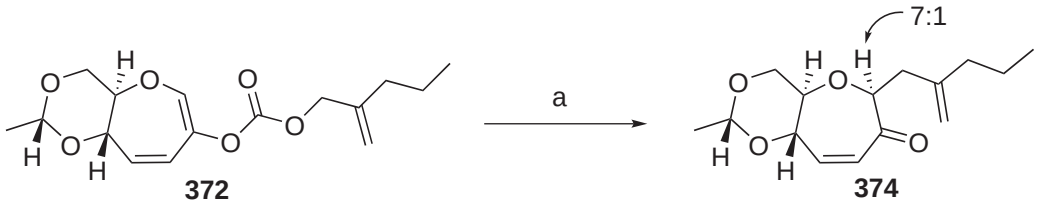
The second reaction parameter to be probed was the nature of the base used to deprotonate the enone. For alkylation reactions, it is known that large counter-cations favour the *O*-alkylation, so KHMDS was the logical choice. The potassium enolate of enone **371** had been shown to be highly reactive and unstable. Therefore, the two previous sets of conditions developed for NaHMDS were combined: the carboxylate

370 was pre-mixed with $BF_3{\cdot}Et_2O$ for 1 h, then cooled down to −78 °C. The enone **371** in THF was then added and finally the KHMDS was introduced in the reaction mixture. This procedure allowed the isolation of carbonate **372** in an isolated yield of 69% (Scheme 3.48). The purification of carbonate **372** had to be done using dry silica gel to avoid any decomposition.



Scheme 3.48: Conditions: a) $BF_3{\cdot}Et_2O$, KHMDS, THF, −78 °C, 69%.

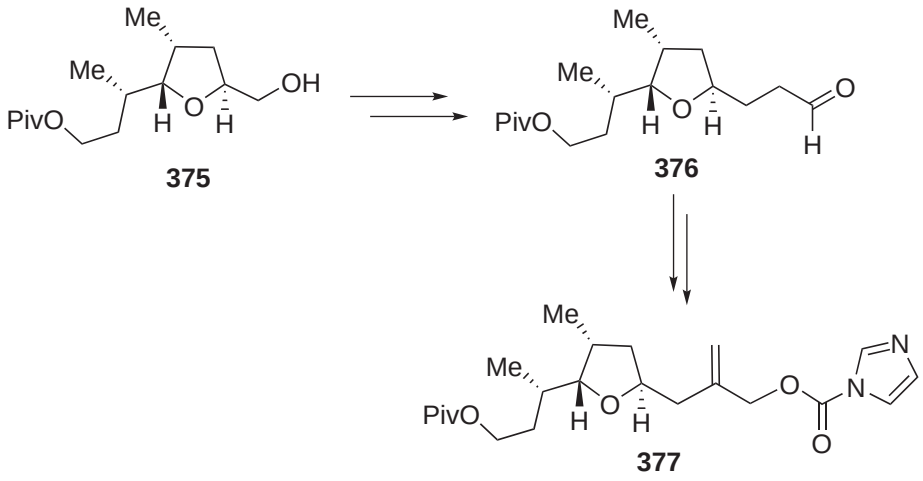
The carbonate **372** was then submitted to the standard conditions used for palladium-catalysed rearrangement. However, on this occasion there was no reaction and the starting material was recovered. The $Pd_2(dba)_3$ was changed for another source of Pd^0: $Pd(PPh_3)_4$. There were some concerns about potential loss of selectivity because $Pd(PPh_3)_4$ is itself capable of promoting the rearrangement reaction. However, considering that the chiral ligand is bidentate, and therefore better ligand than PPh_3, it was envisioned that by pre-mixing the catalyst and an excess of ligand for a prolonged period of time, this problem should be avoided. Using this new palladium catalyst, the rearrangement reaction proceeded very well, and after 2 h at room temperature, the desired alkylated enone **374** was isolated in 69% yield as a 7:1 mixture favouring the desired diastereomer (Scheme 3.49).



Scheme 3.49: Palladium-catalysed rearrangement of carbonate **372**. Conditions: a) $Pd(PPh_3)_4$, ligand **345**, THF, rt, 69%.

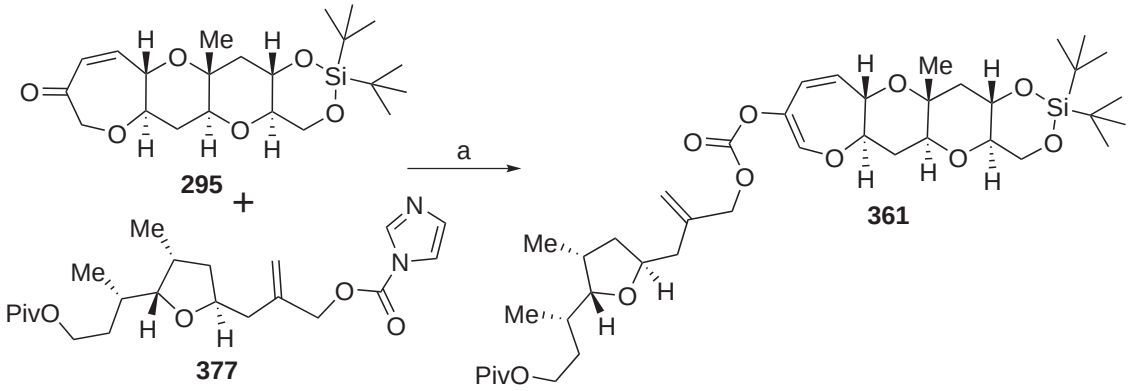
Towards the synthesis of the A-D fragment

The optimised conditions for the key coupling steps were then applied to the target system. Carboxylate **377** was prepared following a similar strategy as for compound **371** by a member of our group (Scheme 3.50).



Scheme 3.50: Preparation of coupling partner **377** by Dr S. Chaudhury.

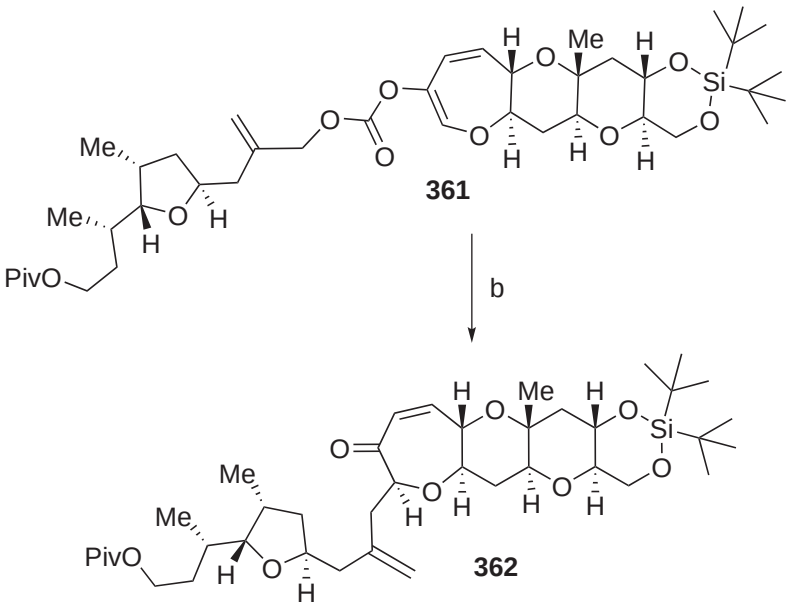
The formation of the carbonate **361** was then carried out. Despite using the optimum conditions for either NaHMDS or KHMDS, the best yield achieved was only 31% (Scheme 3.51). Significant amounts of both starting materials were recovered, meaning that enone **295** and carboxylate **377** did not decompose but failed to react. It is possible that the amount of $BF_3{\cdot}Et_2O$ should be increased because of the presence of many more chelating groups than in the model system. At this point, it was not possible to separate the product **361** from the strating material enone **295** by column chromatography and so it was decided to perform the next step using this mixture because the enone **295** should be unreactive towards the reaction conditions.



Scheme 3.51: Conditions: a) $BF_3{\cdot}Et_2O$, KHMDS, THF, −78 °C, 31%.

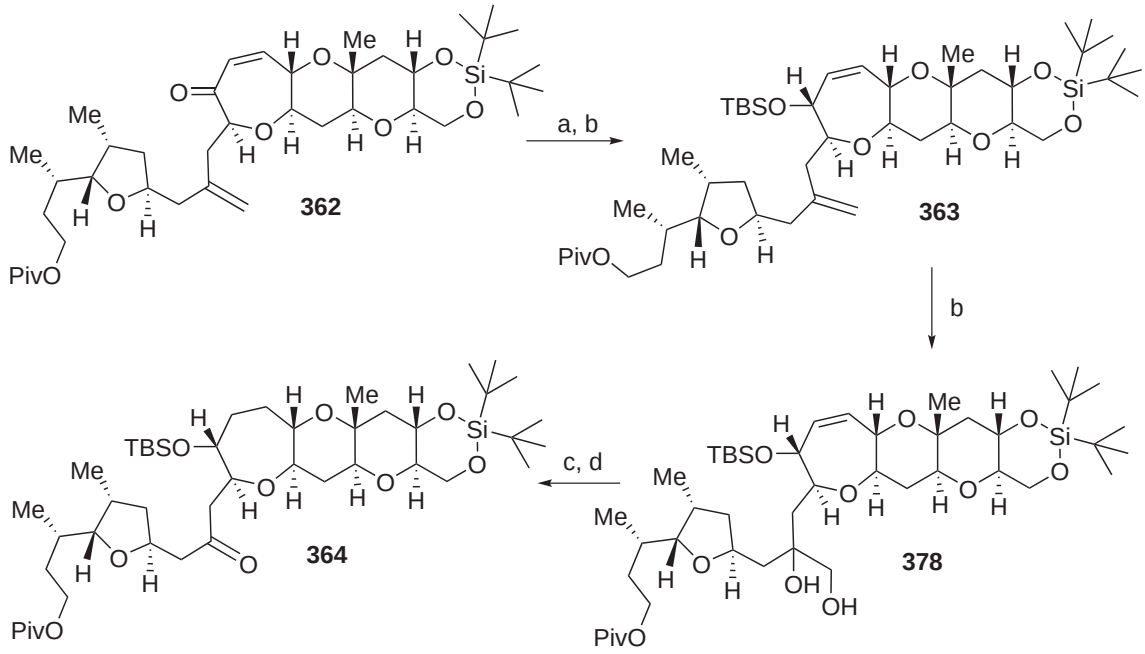
The carbonate **361** was then treated with $Pd(PPh_3)_4$ and the chiral phosphinooxazoline **345** (Scheme 3.52). NMR analysis of the crude mixture revealed a complete diastereoselectivity (> 95:5). The desired enone **362** was isolated in 57% yield. Some non-alkylated enone **295** was also isolated, half of it came from the starting mixture but the other half came from the rearrangement reaction: once the π-allyl enolate palladium

is formed, the enolate can be quenched by a proton to return the non-alkylated enone **295** back.



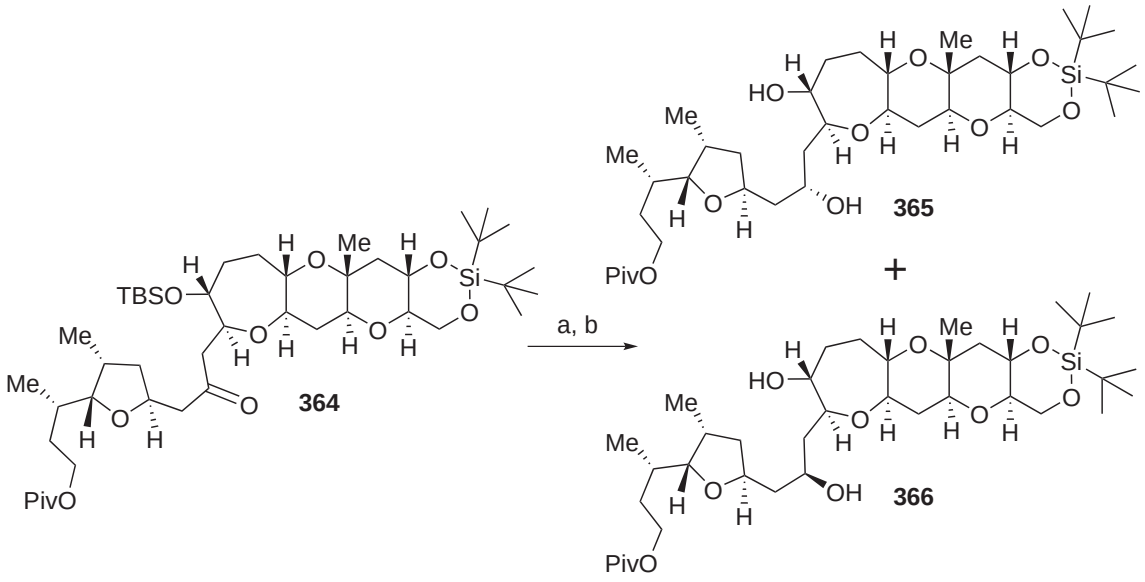
Scheme 3.52: Conditions: a) $Pd(PPh_3)_4$, ligand **345**, THF, rt, 57%.

With the whole carbon skeleton of the A-D fragment in hand, the synthesis was continued. First, a Luche reduction gave the corresponding allylic alcohol (Scheme 3.53). The configuration of the stereocentre was assigned based on previous observations (see chap. 3.2.4). Tha alcohol was protected as the TBS ether **363** under the same conditions as before. Chemoselective dihydroxylation of the 1,1-disubstituted alkene was then performed using the conditions employed previously because it was known that the 1,2-disubstituted endocyclic alkene would not be reactive under these conditions. Conversion only reached 50%, but extended reaction times or additional NMO could further increase the consumption of starting material. The diol **378** was then treated with Pd/C under H_2 atmosphere to hydrogenate the alkene, and the diol was cleaved with sodium periodate to deliver ketone **364**.



Scheme 3.53: Conditions: a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, rt, 98%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 85%; c) OsO_4, NMO, THF, H_2O, rt, 49%; d) Pd/C, EtOH, H_2, rt; e) $NaIO_4$, EtOH, H_2O, rt, 55% (2 steps).

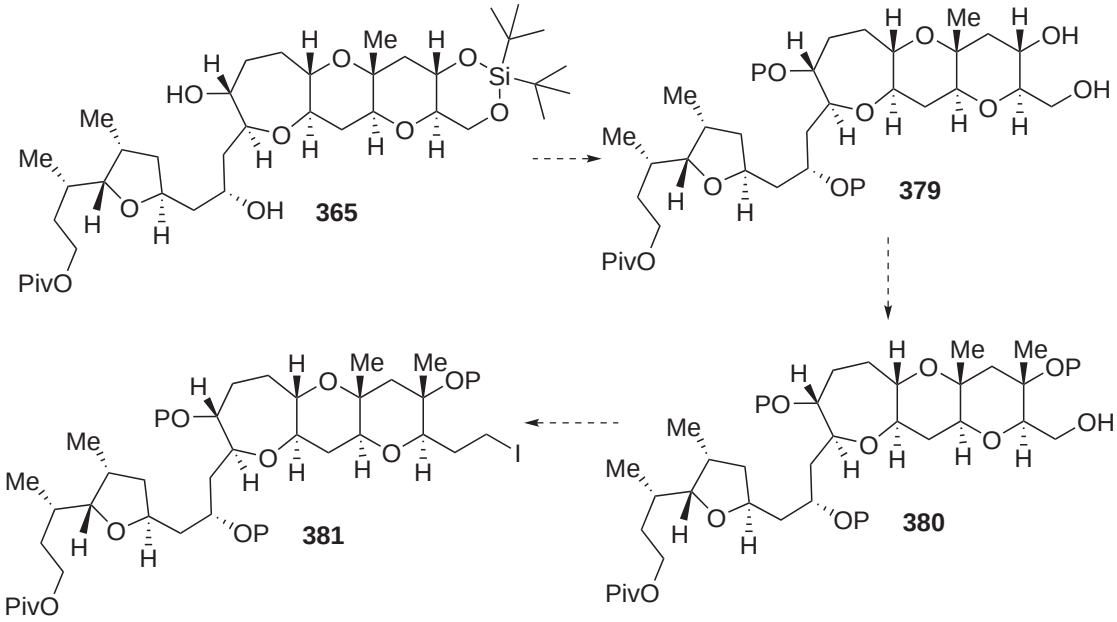
The final steps of the synthesis consisted in the reduction of the ketone to the secondary alcohol and the removal of the TBS ether in the presence of the bis-*t*Bu-silyl ether. It was decided to reduce the ketone **364** with sodium borohydride to obtain the two possible diastereomers and compare their spectroscopic data to that of Sasaki's products.[152] The reduction was quantitative, although it was not possible to determine the ratio of the two diastereomers (Scheme 3.54). For the selective deprotection step, a procedure by Mori and co-workers was used.[221] Wet TsOH failed to remove the TBS ether, but another sulfonic acid, (+)-CSA, in a mixture of MeOH and CH_2Cl_2 was found to be efficient for this reaction. After the reaction, it was possible to observe two distinct spots on TLC: due to intramolecular hydrogen bonds, the two diols **365** and **366** have quite different polarities. Unfortunately, it was not possible to isolate enough material to obtain satisfactory NMR spectra.



Scheme 3.54: Final steps of the A-D fragment synthesis. Conditions: a) $NaBH_4$, MeOH, CH_2Cl_2, rt; b) (+)-CSA, MeOH, CH_2Cl_2, rt.

3.3 Future Work

The synthesis needs to be repeated on larger scale to obtain significant amounts of alcohols **365** and **366**. After comparison with the original spectroscopic data and with Sasaki's work, it should be possible to determine the absolute configuration of the natural product. Once this is done, some work remains to be done on the eastern part of the fragment to prepare it for coupling with the G-J system, especially the introduction the second angular methyl group (**379**→**380**), which could be done following Sasaki's procedure (Scheme 3.55).[222] After one-carbon homologation of alcohol **380** and iodination, the iodide **381** should be ready for coupling with the G-J unit.



Scheme 3.55: Future work.

Chapter 4

Experimental Part

4.1 General conditions

NMR spectra were recorded on a Bruker 400 MHz Spectrospin spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz). Chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent using ($\delta = 7.26$) as internal standard, and for ^{13}C NMR spectra, the chemical shifts are reported relative to the central resonance of $CDCl_3$ ($\delta = 77.16$). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or a combination of these, which refers to the spin-spin coupling pattern observed. DEPT 135 and two-dimensional (COSY, HSQC) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

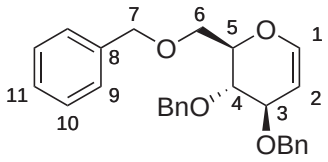
IR spectra were recorded using a JASCO FT/IR 4100 using NaCl plates or a Shimadzu FTIR-8400 without any preparation. High resolution mass spectra were recorded under EI, CI and FAB conditions by the analytical services at the University of Glasgow. Elemental analyses were carried out using an Exeter Analytical Elemental Analyser EA 440. Melting points were recorded with an Electrothermal IA 9100 apparatus. Optical rotations were determined on solutions of samples and irradiating with the sodium D line ($\lambda = 589$ nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}.

Column chromatography was performed under pressure using silica gel (Fluorochem LC60A, 35−70 μ) as solid support and HPLC-grade solvents as eluent. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 covered aluminium plates F254. TLC plates were developed under UV-light and/or with a $KMnO_4$-solution (3 g of $KMnO_4$, 20 g K_2CO_3, 5 mL 5% NaOH(aq) and 300 mL H_2O) or acidic ethanolic anisaldehyde solution (formed by dissolving 15 g of anisaldehyde in 250 mL ethanol and 2.5 mL conc. sulfuric acid). Liquid reagents were distilled prior

to use if necessary. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Reactions involving air-sensitive agents and dry solvents were performed in glassware that had been flame dried prior to use and were carried out under an argon atmosphere.

4.2 Experimental details

(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran : 260



$\mathbf{C_{27}H_{28}O_4}$
Molecular weight: 416.5 g.mol^{-1}

To a solution of tri-*O*-acetyl-α-D-glucal (10.0 g, 36.8 mmol) in MeOH (40 mL) was added sodium methoxide (104 mg, 1.80 mmol). The reaction mixture was stirred at rt for 45 min and concentrated under reduced pressure to afford the crude triol (5.50 g, 36.8 mmol, quant.) which was used without further purification.

To a suspension of degreased NaH (5.88 g, 147 mmol) in THF (140 mL) was added a solution of crude triol (5.50 g, 36.8 mmol) in DMF (40 mL). The solution was stirred for 30 min at rt, then cooled to 0 °C and BnBr (15.4 mL, 129 mmol) was added. The solution was allowed to warm to rt and stirred for 2 h. The reaction was quenched by the addition of MeOH (5 mL) and H_2O (50 mL). The aqueous phase was extracted with Et_2O (2 × 150 mL) and the combined organic phases were washed with brine (2 × 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 100:1→85:15) to give the protected triol **260** (14.8 g, 35.5 mmol, 96%) as a white solid.

R_f = 0.45 (PE-Et_2O; 1:1)

m.p. = 56−57 °C, lit.[223] **m.p.** = 56−57 °C

$[\alpha]_D$ (23.5 °C, $CHCl_3$) = −1.8 (c = 1.04), lit.[223] $[\alpha]_D$ (21 °C, $CHCl_3$) = −2.9 (c = 1.2)

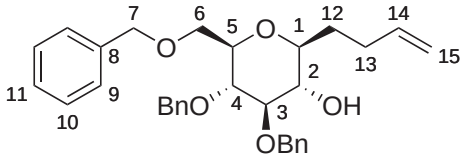
IR : ν_{max} 3063, 3030, 2866, 1647, 1497, 1453, 1238 cm^{-1}.

^{1}**H NMR** : δ 7.34−7.22 (15H, m, CH-C Arom), 6.43 (1H, dd, J = 6.1, 0.8 Hz, CH-C1), 4.88 (1H, dd, J = 6.1, 2.6 Hz, CH-C2), 4.84 (1H, d, J = 7.2 Hz, CH_2-C7a), 4.64 (2H, d, J = 7.2 Hz, CH_2-C7b and CH_2-C7'a), 4.57 (3H, m, CH_2-C7'b and CH_2-C7"), 4.21 (1H, ddd, J = 6.2, 2.6, 0.8 Hz, CH-C3), 4.06 (1H, ddd, J = 8.6, 4.9, 2.9 Hz, CH-C5), 3.86 (1H, dd, J = 8.6, 6.2 Hz, CH-C4), 3.81 (1H, dd, J 10.7, 4.9 Hz, CH_2-C6a), 3.76 (1H, dd, J = 10.7, 2.9 Hz, CH_2-C6b).

^{13}C NMR : δ 144.8 (CH-C1), 138.4 (C-C8), 138.2 (C-C8'), 138.0 (C-C8"), 128.5 (2 CH Arom), 128.4 (2 CH Arom), 128.4 (3 CH Arom), 128.0 (2 CH Arom), 127.9 (2 CH Arom), 127.8 (2 CH Arom), 127.7 (2 CH Arom), 100.0 (CH-C2), 76.8 (CH-C5), 75.8 (CH-C3), 74.4 (CH-C4), 73.8 (CH_2-C7), 73.6 (CH_2-C7'), 70.5 (CH_2-C7"), 68.6 (CH_2-C6).

MS (EI) : *m/z (Int)* 253 (100), 163 (80), 91 (100).

(2*S*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-enyl) tetrahydro-2H-pyran-3-ol : 261



$C_{31}H_{36}O_5$

Molecular weight: 488.6 g.mol^{-1}

To a vigorously stirred biphasic solution of tri-*O*-benzyl-D-glucal **260** (2.6 g, 6.2 mmol) in CH_2Cl_2 (20 mL), acetone (2 mL) and a saturated aqueous solution of $NaHCO_3$ (50 mL) at 0 °C, was added a solution of Oxone (11 g, 18 mmol) in H_2O (35 mL). The mixture was stirred vigorously at 0 °C for 30 min and then at rt for an additional 2 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to the crude afford epoxide (2.7 g, quant.) as a white solid.

To a solution of epoxide (2.7 g, 6.2 mmol) in THF (53 mL), cooled to −20 °C, was added a solution of butenylmagnesiumbromide (25 mL, 12 mmol) in THF. The solution was stirred for 2 h at −20 °C. The solution of butenylmagnesiumbromide (12 mL) was added and the solution was stirred for another 1 h at −20 °C. The reaction was quenched with a saturated aqueous solution of NH_4Cl (12 mL) and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 3:1) to give the alcohol **261** (1.0 g, 2.1 mmol, 34%) as a colourless oil.

R_f = 0.44 (PE-Et_2O; 1:2)

$[\alpha]_D$ (23.8 °C, $CHCl_3$) = +25.4 (c = 0.99)

IR : ν_{max} 3477, 2932, 2867, 1496, 1454, 1324, 1206, 1075 cm^{-1}.

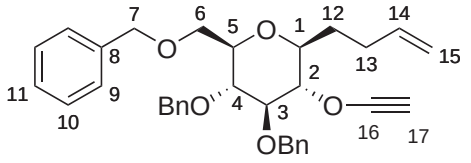
^{1}H NMR : δ 7.30−7.14 (15H, m, CH Arom), 5.83 (1H, dddd, J = 17.0, 10.2, 6.6, 6.6 Hz, CH-C14), 5.03 (1H, dddd, J = 17.0, 1.6, 1.6, 1.6 Hz, CH_2-C15a), 4.95 (1H, dd, J = 10.2, 1.6 Hz, CH_2-C15b), 4.68 (1H, d, J = 11.8 Hz, CH_2-C7a), 4.63 (1H,

d, J = 11.4 Hz, CH_2-C7'a), 4.57 (1H, d, J = 11.8 Hz, CH_2-C7b), 4.57 (1H, d, J = 12.1 Hz, CH_2-C7"a), 4.56 (1H, d, J = 11.4 Hz, CH_2-C7'b), 4.51 (1H, d, J = 12.1 Hz, CH_2-C7"b), 3.98 (1H, ddd, J = 5.0, 5.0, 5.0 Hz, CH-C5), 3.89 (1H, ddd, J = 9.6, 4.0, 4.0 Hz, CH-C1), 3.82−3.78 (1H, m, CH-C4), 3.75−3.69 (2H, m, CH-C3 and CH_2-C6a), 3.66−3.62 (2H, m, CH-C2 and CH_2-C6b), 2.82 (1H, d, J = 7.9 Hz, OH), 2.31−2.23 (1H, m, CH_2-C13a), 2.21−2.11 (1H, m, CH_2-C13b), 1.90−1.80 (1H, m, CH_2-C12a), 1.76−1.68 (1H, m, CH_2-C12b).

^{13}C NMR : δ 138.3 (CH-C14), 138.2 (C-C8), 138.1 (C-C8'), 137.5 (C-C8") 128.6 (2 CH Arom), 128.5 (3 CH Arom), 128.4 (2 CH Arom), 127.9 (3 CH Arom), 127.8 (3 CH Arom), 127.6 (2 CH Arom), 114.8 (CH_2-C15), 78.1 (CH), 75.2 (CH), 73.5 (CH_2-C7), 73.3 (CH_2-C7'), 73.2 (CH), 73.0 (CH_2-C7"), 71.1 (CH), 69.7 (CH), 68.2 (CH_2-C6), 29.7 (CH_2-C13), 27.4 (CH_2-C12).

MS (EI) : *m/z (Int)* 489 (79), 293 (12), 257 (10), 209 (9), 154 (100), 107 (45). HRMS ($C_{31}H_{36}O_5^+$) : calculated : 489.2641; obtained : 489.2640, (Δ = 0.2 ppm).

(2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-6-(but-3-enyl)-5-ethynyloxytetrahydro-2H-pyran : 262



$C_{33}H_{36}O_5$
Molecular weight: 512.6 g.mol^{-1}

To a suspension of KH (0.27 g, 2.0 mmol) in Et_2O (3.5 mL) was added a solution of alcohol **261** (0.40 g, 0.82 mmol) in Et_2O (2.9 mL). The reaction mixture was stirred for 10 min at rt, then cooled to 0 °C. After the addition of a solution of trichloroethylene (89 μL, 1.0 mmol) in Et_2O (1 mL), the reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was cooled to −78 °C and a solution of *n*-butyllithium (1.7 mL, 2.7 mmol) in pentane was added dropwise. The reaction mixture was stirred 30 min at −78 °C, allowed to warm to −45 °C and stirred for another 45 min. The reaction was quenched with MeOH (1 mL) and a satured aqueous solution of NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 10:1, 1% Et_3N) to give the alkynylether **262** (0.29 g, 0.57 mmol, 69%) as a colourless oil.

R_f = 0.59 (PE-Et_2O; 1:1)

$[\alpha]_D$ (22.4 °C, $CHCl_3$) = +21.2 (c = 1.05)

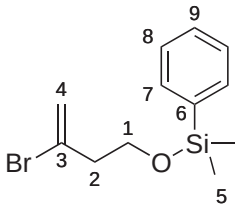
IR : ν_{max} 3321, 2931, 2856, 2150, 1497, 1453, 1356, 1095, 914, 735 cm^{-1}.

^{1}H NMR : δ 7.40−7.24 (15H, m, CH Arom), 5.84 (1H, dddd, J = 17.0, 10.3, 6.6, 6.6 Hz, CH-C14), 5.07 (1H, dddd, J = 17.0, 1.5, 1.5, 1.5 Hz, CH_2-C15a), 5.00 (1H, dd, J = 10.3, 1.5 Hz, CH_2-C15b), 4.89 (1H, d, J = 10.8 Hz, CH_2-C7a), 4.79 (1H, d, J = 10.8 Hz, CH_2-C7'a), 4.72 (1H, d, J = 10.8 Hz, CH_2-C7b), 4.60 (1H, d, J = 12.0 Hz, CH_2-C7"a), 4.48 (1H, d, J = 12.0 Hz, CH_2-C7"b), 4.47 (1H, d, J = 10.8 Hz, CH_2-C7'b), 4.32−4.28 (2H, m, CH-C1 and CH-C5), 3.84 (1H, t, J = 8.4 Hz, CH), 3.70−3.58 (4H, m, CH and CH_2-C6), 2.28−2.20 (1H, m, CH_2-C13a), 2.19−2.06 (1H, m, CH_2-C13b), 1.84−1.66 (2H, m, CH_2-C12), 1.59 (1H, s, CH-C17).

^{13}C NMR : δ 138.2 (C-C8), 138.1 (C-C8'), 138.1 (C-C8"), 137.7 (CH-C14), 128.8 (2 CH Arom), 128.7 (3 CH Arom), 128.6 (2 CH Arom), 128.1 (3 CH Arom), 128.0 (3 CH Arom), 127.8 (2 CH Arom), 115.6 (CH_2-C15), 90.0 (C-C16), 87.8 (CH-C1 or C5), 80.7 (CH), 77.7 (CH), 75.5 (CH_2-C7), 75.3 (CH_2-C7'), 73.7 (CH_2-C7"), 72.3 (CH-C5 or C1), 71.6 (CH), 68.9 (CH_2-C6), 29.3 (CH_2-C13), 27.3 (CH-C17), 24.3 (CH_2-C12).

MS (CI) : *m/z (Int)* 513 (32), 471 (47), 363 (95), 255 (54), 147 (100), 107 (100), 91 (83). HRMS ($C_{33}H_{37}O_5^+$) : calculated : 513.2641; obtained : 513.2634, (Δ = 1.4 ppm).

(3-Bromobut-3-enyloxy)dimethylphenylsilane : 264



$C_{12}H_{17}BrOSi$

Molecular weight: 285.3 $g.mol^{-1}$

To a solution of 3-bromo-3-buten-1-ol **263** (1.0 g, 6.6 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C was added DMAP (80 mg, 0.66 mmol), Et_3N (2.7 mL, 20 mmol) and chlorodimethylphenylsilane (1.2 mL, 6.9 mmol). The mixture was stirred at rt overnight. The reaction was quenched by the addition of H_2O (10 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 99:1) to give the silylether **264** (1.6 g, 5.8 mmol, 87%) as a colourless oil.

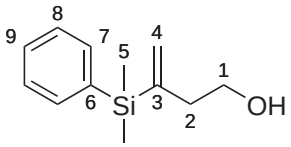
R_f = 0.72 (PE-Et_2O; 1:1)

IR : ν_{max} 2956, 1631, 1428, 1253, 1098 cm^{-1}.

^{1}H NMR : δ 7.52−7.48 (2H, m, CH Arom), 7.34−7.28 (3H, m, CH Arom), 5.54 (1H, dt, J = 1.6, 1.0 Hz, CH_2-C4a), 5.38 (1H, d, J = 1.6 Hz, CH_2-C4b), 3.71 (2H, t, J = 6.4 Hz, CH_2-C1), 2.55 (2H, td, J = 6.4, 1.0 Hz, CH_2-C2), 0.32 (6H, s, CH_3-C5).

^{13}C NMR : δ 139.4 (C), 135.3 (CH Arom), 132.4 (C), 131.5 (CH Arom), 129.7 (CH Arom), 120.4 (CH_2-C4), 62.6 (CH_2-C1), 46.3 (CH_2-C2), 0.0 (CH_3-C5).
MS (CI) : *m/z (Int)* 287 (77), 285 (77), 271 (10), 269 (10), 209 (18), 207 (18), 165 (100), 135 (15), 130 (9). HRMS ($C_{12}H_{18}BrOSi^+$) : calculated : 285.0310; obtained : 285.0313, (Δ = 1.1 ppm).

3-(Dimethylphenylsilyl)but-3-en-1-ol : 265



$C_{12}H_{18}OSi$
Molecular weight: 206.4 g.mol^{-1}

From vinyl bromide **264**: To a solution of vinylbromide **264** (2.0 g, 7.0 mmol) in THF (9 mL) cooled to −78 °C was added a solution of *t*-butyllithium (8.8 mL, 14 mmol) in pentane (1.6 M). The solution was stirred for 30 min at −78 °C, then was allowed to warm to −45 °C and was stirred for another hour at this temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (10 mL). The organic phase was washed with brine (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 2:1) to give the alcohol **265** (1.1 g, 5.3 mmol, 76%) as a colourless oil.

From 3-butyn-1-ol: To a solution of NaI (4.3 g, 29 mmol) in MeCN (20 mL) was added TMSCl (3.6 mL, 29 mmol) and H_2O (260 μL, 14 mmol). The reaction mixture was stirred for 10 min and a solution of 3-butyn-1-ol (1.0 g, 14 mmol) in MeCN (5 mL) was added. After 1 h at rt, H_2O (15 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 5:1→3:1) to give the vinyl iodide **270** (1.4 g, 7.1 mmol, 51%) as a brown oil, which was used directly into the next step.

To a solution of vinyl iodide **270** (450 mg, 2.3 mmol), DMAP (28 mg, 0.23 mmol) and Et_3N (0.94 mL, 6.8 mmol) in CH_2Cl_2 (7 mL) cooled to 0 °C was added chlorodimethylphenylsilane (380 μL, 2.3 mmol) dropwise. The reaction was stirred at rt overnight and the reaction mixture was concentrated under reduced pressure. The residue was filtered on a small plug of silica gel (PE-Et_2O; 99:1) to give the corresponding silylether (0.76 g, 2.3 mmol), as a colourless oil, which was used directly into the next step.

To a solution of vinyliodide (0.76 g, 2.3 mmol) in THF (12 mL) cooled to −78 °C

was added a solution of *t*-butyllithium (2.8 mL, 4.5 mmol) in hexane. The solution was stirred for 30 min at −78 °C, then allowed to warm to −45 °C and stirred for another 1 h at this temperature. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (3 × 20 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 5:1;→3:1) to give the alcohol **265** (280 mg, 1.4 mmol, 61% over 2 steps) as a colourless oil.

R_f = 0.31 (PE-Et_2O; 1:1)

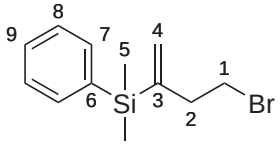
IR : ν_{max} 3336, 2955, 1427, 1249, 1111, 1046 cm^{-1}.

^{1}**H NMR** : δ 7.54−7.50 (2H, m, CH Arom), 7.39−7.35 (3H, m, CH Arom), 5.79 (1H, dt, J = 2.8, 1.4 Hz, CH_2-C4a), 5.57 (1H, dt, J = 2.8, 0.7 Hz, CH_2-C4b), 3.56 (2H, t, J = 6.6 Hz, CH_2-C1), 2.41 (2H, tdd, J = 6.6, 1.4, 0.7 Hz, CH_2-C2), 1.39 (1H, br s, OH), 0.41 (6H, s, CH_3-C5).

^{13}**C NMR** : δ 146.8 (C-C3), 137.8 (C-C6), 133.8 (CH Arom), 129.2 (CH-C9), 128.9 (CH_2-C4), 127.9 (CH Arom), 61.4 (CH_2-C1), 39.3 (CH_2-C2), -3.0 (CH_3-C5).

MS (EI) : *m/z (Int)* 191 (22), 152 (6), 137 (100), 135 (63), 84 (42), 75 (32). HRMS ($C_{11}H_{15}OSi^+$) : calculated : 191.0892; obtained : 191.0896, (Δ = 2.1 ppm).

(4-Bromobut-1-en-2-yl)dimethylphenylsilane : 266



$C_{12}H_{17}BrSi$

Molecular weight: 269.3 $g.mol^{-1}$

To a solution of alcohol **265** (0.87 g, 4.2 mmol) and CBr_4 (2.1 g, 6.3 mmol) in CH_2Cl_2 (42 mL) cooled to 0 °C was added triphenylphosphine (3.3 g, 13 mmol). The solution was stirred for 1 h at rt. Silica gel was added directly to the reaction mixture and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 250:1) to give the bromide **266** (1.1 g, 4.0 mmol, 95%) as a colourless oil.

R_f = 0.71 (PE-Et_2O; 1:1)

IR : ν_{max} 2957, 1428, 1250, 1112 cm^{-1}.

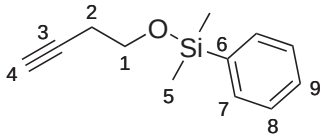
^{1}**H NMR** : δ 7.53−7.48 (2H, m, CH Arom), 7.39−7.35 (3H, m, CH Arom), 5.77 (1H, dt, J = 2.3, 1.3 Hz, CH_2-C4a), 5.55 (1H, dt, J = 2.3, 1.3 Hz, CH_2-C4b), 3.31 (2H, t, J = 8.0 Hz, CH_2-C1), 2.66 (2H, tdd, J = 8.0, 1.3, 1.3 Hz, CH_2-C2), 0.40 (6H, s,

CH_3-C5).

^{13}**C NMR** : δ 147.4 (C-C3), 137.4 (C-C6), 133.9 (CH Arom), 129.3 (CH-C9), 128.5 (CH_2-C4), 127.9 (CH Arom), 39.2 (CH_2-C2), 31.8 (CH_2-C1), -3.1 (CH_3-C5).

MS (EI) : *m/z (Int)* 255 (11), 253 (11), 201 (18), 199 (18), 135 (35), 84 (100), 77 (31), 49 (80).

(But-3-ynyloxy)dimethyl(phenyl)silane : 268a



$C_{12}H_{16}OSi$

Molecular weight: 204.3 g.mol^{-1}

To a solution of 3-butyn-1-ol (0.40 g, 5.7 mmol) in CH_2Cl_2 (17 mL) cooled to 0 °C was added DMAP (70 mg, 0.57 mmol), Et_3N (2.4 mL, 17 mmol) and chlorodimethylphenylsilane (1.0 mL, 6.0 mmol). The reaction was stirred at rt for 3 days and then quenched with H_2O (10 mL). The organic phase was washed with brine (2 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 99:1) to give the silylether **268a** (0.94 g, 4.6 mmol, 81%) as a colourless oil.

R_f = 0.66 (PE-Et_2O; 1:1)

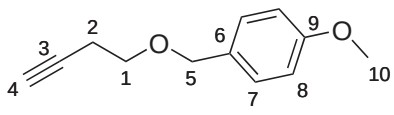
IR : ν_{max} 3296, 2959, 1429, 1253, 1096, 828, 789 cm^{-1}.

^{1}**H NMR** : δ 7.60−7.57 (2H, m, CH Arom), 7.42−7.36 (3H, m, CH Arom), 3.72 (2H, t, J = 7.1 Hz, CH_2-C1), 2.41 (2H, td, J = 7.1, 2.6 Hz, CH_2-C2), 1.96 (1H, t, J = 2.6 Hz, CH-C4), 0.40 (6H, s, CH_3-C5).

^{13}**C NMR** : δ 139.3 (C-C6), 135.3 (CH Arom), 131.6 (CH-C9), 129.7 (CH Arom), 83.2 (C-C3), 71.3 (CH-C4), 63.3 (CH_2-C1), 24.4 (CH_2-C2), 0.0 (CH_3-C5).

MS (CI) : *m/z (Int)* 205 (100), 165 (31), 153 (11), 127 (18). HRMS ($C_{12}H_{17}OSi^+$) : calculated : 205.1049; obtained : 205.1048, (Δ = 0.5 ppm).

1-((But-3-ynyloxy)methyl)-4-methoxybenzene : 268b



$C_{12}H_{14}O_2$

Molecular weight: 190.2 g.mol^{-1}

To a suspension of degreased NaH (0.22 g, 5.6 mmol) and nBu$_4$NI (63 mg, 0.17 mmol) in THF (17 mL) at 0 °C was added 3-butyn-1-ol (0.30 mg, 4.3 mmol). The so-

lution was stirred for 20 min at 0 °C and *p*-methoxybenzylchloride (1.4 mL, 10 mmol) was added. The reaction mixture was stirred for 24 h at rt, then quenched with MeOH (0.5 mL) and diluted with water (40 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 95:5) to give the protected alcohol **268b** (0.51 g, 2.6 mmol, 61%) as a colourless oil.

R_f = 0.63 (PE-Et_2O; 1:1)

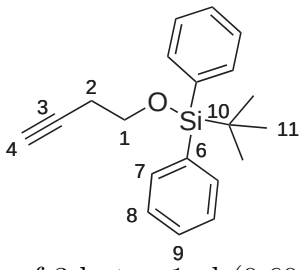
IR : ν_{max} 3292, 2863, 1613, 1512, 1244, 1173, 1093, 1033, 820 cm^{-1}.

^{1}**H NMR** : δ 7.26 (2H, d, J = 8.6 Hz, CH Arom), 6.87 (2H, d, J = 8.6 Hz, CH Arom), 4.49 (2H, s, CH_2-C5), 3.80 (3H, s, CH_3-C10, 3.57 (2H, t, J = 7.0 Hz, CH_2-C1), 2.48 (2H, td, J = 7.0, 2.5 Hz, CH_2-C2), 1.98 (1H, t, J = 2.5 Hz, CH-C4).

^{13}**C NMR** : δ 159.3 (C-C9), 130.1 (C-C6), 129.4 (CH-C7), 113.8 (CH-C8), 81.4 (C-C3), 72.7 (CH_2-C5), 69.3 (CH_3-C10), 67.8 (CH_2-C1), 55.3 (CH-C4), 19.9 (CH_2-C2).

MS (EI) : *m/z (Int)* 190 (38), 159 (43), 135 (71), 121 (100), 77 (40).

(But-3-ynyloxy)(tert-butyl)diphenylsilane : 268c



$C_{20}H_{24}OSi$

Molecular weight: 308.5 $g.mol^{-1}$

To a solution of 3-butyn-1-ol (0.60 mL, 7.9 mmol) and DMAP (90 mg, 0.72 mmol) in CH_2Cl_2 (9 mL) cooled to 0 °C was added Et_3N (1.5 mL, 11 mmol) and chloro-*tert*-butyldiphenylsilane (1.9 mL, 7.3 mmol) dropwise. The reaction was stirred at rt overnight and then filtrated on a small pad of silica gel (PE-Et_2O; 9:1) to give the silyl ether **268c** (2.3 g, 7.3 mmol, quant.) as a colourless oil.

R_f = 0.67 (PE-Et_2O; 1:1)

IR : ν_{max} 3006, 2931, 2858, 1473, 1428, 1105, 823, 700 cm^{-1}.

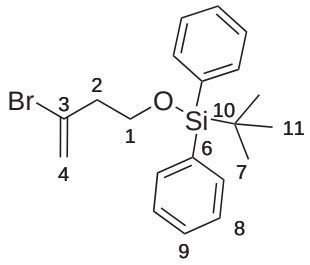
^{1}**H NMR** : δ 7.70−7.67 (4H, m, CH Arom), 7.42−7.36 (6H, m, CH Arom), 3.79 (2H, t, J = 7.1 Hz, CH_2-C1), 2.46 (2H, td, J = 7.1, 2.5 Hz, CH_2-C2), 1.95 (1H, t, J = 2.5 Hz, CH-C4), 1.06 (9H, s, CH_3-C11).

^{13}**C NMR** : δ 135.6 (CH Arom), 133.6 (C-C6), 129.7 (CH-C9), 127.7 (CH Arom), 81.5 (C-C3), 69.4 (CH-C4), 62.3 (CH_2-C1), 26.8 (CH_3-C11), 22.6 (CH_2-C2), 19.2 (C-C10).

MS (FAB) : *m/z (Int)* 309 (29), 251 (100), 221 (100), 197 (65), 159 (53), 136 (83), 106 (53). HRMS ($C_{20}H_{25}OSi^+$) : calculated : 309.1675; obtained : 309.1665, (Δ = 3.2

ppm).

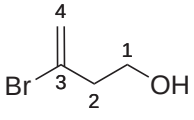
(3-Bromobut-3-enyloxy)(tert-butyl)diphenylsilane : 269



$C_{20}H_{25}BrOSi$
Molecular weight: 389.4 g.mol^{-1}

To a solution of silylether **268c** (1.1 g, 3.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added a freshly prepared solution of 9-Br-9-BBN (5.6 mL, 5.6 mmol) in CH_2Cl_2.[224] The reaction mixture was stirred at rt for 3 days, then cooled to 0 °C and acetic acid (5 mL) was added. The mixture was stirred for 1 h at 0 °C before a saturated aqueous solution of NaOH (10 mL) and a solution of H_2O_2 (30 %wt in water, 5 mL) were added. The reaction mixture was stirred for another 1.5 h at rt. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 9:1) to give a mixture of the vinyl bromide **269** (0.59 g) and TBDPSOH.

3-Bromo-3-buten-1-ol : 263

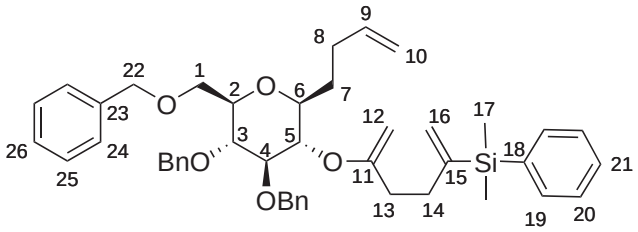


C_4H_7BrO
Molecular weight: 151.0 g.mol^{-1}

To a solution of silylether **269** (0.59 g, 1.5 mmol) in THF at 0 °C was added a solution of TBAF (2.3 mL, 2.3 mmol) in THF (1 M). The reaction mixture was stirred at rt for 30 min and then diluted with H_2O (10 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 1:1) to give the bromo-alcohol **263** (75 mg, 0.5 mmol, 14% over two steps) as an orange oil.
R_f = 0.21 (PE-Et_2O; 1:1)
IR : ν_{max} 3338, 2948, 2885, 1629, 1420, 1204, 1127, 1046, 888 cm^{-1}.
^{1}**H NMR** : δ 5.71 (1H, s, CH_2-C4a), 5.54 (1H, s, CH_2-C4b), 3.82 (2H, br s, CH_2-C1), 2.67 (2H, t, J = 5.8 Hz, CH_2-C2), 1.56 (1H, br s, OH).

^{13}C NMR : δ 130.6 (C-C3), 119.6 (CH_2-C4), 60.2 (CH_2-C1), 44.5 (CH_2-C2).
MS (EI) : *m/z (Int)* 152 (31), 150 (32), 135 (67), 133 (71), 122 (98), 120 (100), 82 (60), 53 (63).

5-[(2*S*,3*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(but-3-enyl)-tetrahydro-2H-pyran-3-yloxy]hexa-1,5-dien-2-yldimethyl(phenyl)silane : 253



$C_{45}H_{54}O_5Si$
Molecular weight: 703.0 g.mol^{-1}

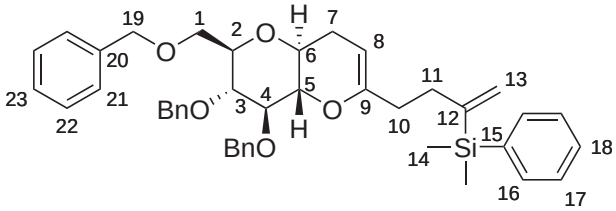
CuBr (0.10 g, 0.71 mmol) and LiBr (62 mg, 0.71 mmol) were dried at 60 °C for 4 h under high vacuum. THF (4.6 mL) was added and the solution cooled to −90 °C. To this was added a solution (0.5 M in THF) of the Grignard reagent prepared from bromide **266** (1.4 mL, 0.71 mmol) and the reaction mixture was stirred for 10 min at −90 °C. Alkyne **263** (0.24 g, 0.47 mmol) in THF (4.7 mL) was then added and the solution was warmed to −78 °C then stirred at this temperature for 45 min. The reaction was quenched by the addition of a solution of NH_4OH (10% in a saturated aqueous solution of NH_4Cl) (3 mL) and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 100:0.5, 1% Et_3N) to give the enol ether **253** (200 mg, 0.29 mmol, 61%) as a colourless oil.
R_f = 0.38 (PE-Et_2O; 4:1)
$[\alpha]_D$ (25.1 °C, $CHCl_3$) = +33.6 (c = 1.51)
IR : ν_{max} 2947, 2864, 1453, 1248, 1098, 816 cm^{-1}.
^{1}H NMR : δ 7.46−7.06 (20H, m, CH Arom), 5.84 (1H, dddd, J = 17.0, 10.3, 6.6, 6.6 Hz, CH-C9), 5.65 (1H, d, J = 2.3 Hz, CH_2-C16a), 5.38 (1H, d, J = 2.3 Hz, CH_2-C16b), 4.98 (1H, dddd, J = 17.0, 1.5, 1.5, 1.5 Hz, CH_2-C10a), 4.92 (1H, dddd, J = 10.3, 1.5, 1.5, 1.5 Hz, CH_2-C10b), 4.75 (2H, d, J = 10.7 Hz, CH_2-C22), 4.63 (1H, d, J = 11.0 Hz, CH_2-C22'a), 4.60 (1H, d, J = 12.1 Hz, CH_2-C22"a), 4.47 (1H, d, J = 12.1 Hz, CH_2-C22"b), 4.40 (1H, d, J = 11.0 Hz, CH_2-C22'b), 4.28−4.19 (2H, m, 2 CH), 4.01 (1H, d, J = 2.2 Hz, CH_2-C12a), 3.87 (1H, d, J = 2.2 Hz, CH_2-C12b), 3.78 (1H, t, J = 8.6 Hz, CH), 3.70−3.54 (4H, m, 2 CH and CH_2-C1), 2.30−2.26 (2H, m, CH_2-C8a), 2.16−2.07 (3H, m, CH_2 and CH_2-C8b), 2.02−1.94 (1H, m, CH_2), 1.78−1.68 (1H, m,

CH_2-C13a), 1.45−1.31 (1H, m, CH_2-C13b), 0.29 (6H, s, CH_3-C17).

^{13}C NMR : δ 161.2 (C-C11), 149.6 (C-C15), 138.8 (C-C23), 138.6 (CH-C9), 138.3 (C-C23'), 138.2 (C-C23"), 138.2 (C-C18), 134.0 (CH Arom), 133.8 (CH Arom), 129.1 (CH Arom), 128.6 (2 CH Arom), 128.5 (2 CH Arom), 128.5 (2 CH Arom), 128.3 (2 CH Arom), 128.1 (2 CH Arom), 128.0 (2 CH Arom), 127.9 (CH Arom), 127.9 (2 CH Arom), 127.8 (CH Arom), 127.7 (CH Arom), 126.0 (CH_2-C16), 114.9 (CH_2-C10), 82.6 (CH_2-C12), 81.7 (CH), 77.9 (CH), 76.8 (CH), 75.4 (CH_2-C22), 75.2 (CH_2-C22'), 73.7 (CH_2-C22"), 72.1 (CH), 71.1 (CH), 69.2 (CH_2-C1), 35.0 (CH_2), 33.7 (CH_2), 33.6 (CH_2), 24.3 (CH_2), -2.9 (CH_3-C17).

MS (FAB) : *m/z (Int)* 725 (16), 363 (14), 271 (9), 181 (100), 136 (99), 93 (95), 92 (95). HRMS ($C_{45}H_{54}O_5SiNa^+$) : calculated : 725.3638; obtained : 725.3637, (Δ = 0.1 ppm).

4-[(4a*S*,6*R*,7*R*,8*S*,8a*S*)-7,8-Bis(benzyloxy)-6-(benzyloxymethyl)-4,4a,6,7,8,8a-hexahydropyrano[3,2-b]pyran-2-yl]but-1-en-2-yldimethyl(phenyl)silane : 255



$C_{42}H_{48}O_5Si$

Molecular weight: 660.9 g.mol^{-1}

To a solution of enol ether **253** (65 mg, 93 μmol) in benzene (2 mL) was added RuCl(CO)H(PPh_3)$_3$ (1.0 mg, 1.0 μmol). The solution was stirred at reflux for 10 min, then benzene (18 mL) and Grubbs second generation catalyst (7.9 mg, 9.0 μmol) were added. The reaction mixture was stirred for 2 h at reflux, then concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 98:2, 1% Et_3N) to give the cyclic enol ether **255** (35 mg, 53 μmol, 57%) as a colourless oil.

R_f = 0.24 (PE-Et_2O; 4:1)

$[\alpha]_D$ (25.8 °C, $CHCl_3$) = +49.1 (c = 1.41)

IR : ν_{max} 2917, 2859, 1681, 1453, 1248, 1065, 815, 775, 731, 695 cm^{-1}.

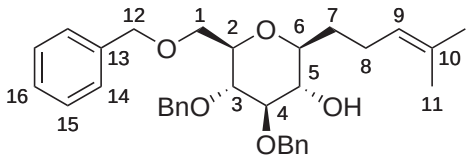
^{1}H NMR : δ 7.40−7.02 (20H, m, CH Arom), 5.60 (1H, s, CH_2-C13a), 5.34 (1H, s, CH_2-C13b), 4.71 (2H, d, J = 12.0 Hz, CH_2-C19a and 19'a), 4.57−4.52 (2H, m, CH_2-C19b and CH_2-C19"a), 4.43 (1H, d, J = 12.0 Hz, CH_2-C19'b), 4.36 (1H, d, J = 10.8 Hz, CH_2-C19"b), 4.28 (1H, br s, CH-C8), 4.25−4.20 (1H, m, CH-C6), 4.07 (1H, dd, J = 8.7, 5.3 Hz, CH-C5), 3.71 (1H, t, J = 8.7 Hz, CH-C4), 3.69 (1H, m, CH), 3.63−3.50

(3H, m, CH and CH_2-C1), 2.33−2.16 (3H, m, CH_2), 2.01−1.94 (3H, m, CH_2), 0.27 (6H, s, CH_3-C14).

^{13}C NMR : δ 151.1 (C-C9), 149.3 (C-C12), 138.4 (C-C20), 138.1 (C-C20'), 138.0 (C-C20"), 137.8 (C-C15), 133.8 (2 CH Arom), 128.9 (3 CH Arom), 128.3 (2 CH Arom), 128.6 (CH Arom), 128.2 (2 CH Arom), 128.0 (3 CH Arom), 127.9 (CH Arom), 127.8 (CH Arom), 127.7 (3 CH Arom), 127.6 (2 CH Arom), 125.9 (CH_2-C13), 91.5 (CH-C8), 79.6 (CH-C4), 77.7 (CH-C2 or C3), 75.1 (CH-C5), 74.9 (CH_2-C19), 74.7 (CH_2-C19'), 73.5 (CH_2-C19"), 72.0 (CH-C3 or C2), 69.1 (CH_2-C1), 67.5 (CH-C6), 33.1 (CH_2-C10 or C11), 33.0 (CH_2-C11 or C10), 20.6 (CH_2-C7), -2.9 (CH_3-C14).

MS (EI) : *m/z (Int)* 660 (11), 569 (10), 269 (26), 181 (19), 135 (87), 91 (100). HRMS ($C_{42}H_{48}O_5Si^+$) : calculated : 660.3271; obtained : 660.3273, (Δ = 0.3 ppm).

(2*S*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(4-methyl pent-3-enyl)tetrahydro-2*H*-pyran-3-ol: 279



$C_{33}H_{40}O_5$

Molecular weight: 516.7 g.mol^{-1}

To a vigorously stirred biphasic solution of tri-*O*-benzyl-D-glucal **260** (1.0 g, 2.4 mmol) in CH_2Cl_2 (10 mL), acetone (1 mL) and a saturated aqueous solution of $NaHCO_3$ (25 mL) at 0 °C, was added a solution of Oxone (4.5 g, 7.2 mmol) in H_2O (20 mL). The mixture was stirred vigorously at 0 °C for 30 min and then at rt for an additional 2 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure to afford epoxide (1.1 g, quant.) as a white solid.

To a solution of epoxide (1.1 g, 2.4 mmol) in THF (24 mL), cooled to −35 °C, was added a solution of (4-methylpent-3-enyl)magnesium bromide (9.6 mL, 4.8 mmol) in THF (0.5 M) and the solution was stirred for 2 h at −30 °C. To the reaction mixture was added a solution of (4-methylpent-3-enyl)magnesium bromide (4.8 mL, 2.4 mmol) in THF (0.5 M) and the mixture was allowed to warm to 0 °C over 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 3:1) to give the alcohol **279** (310 mg, 0.60 mmol, 25%) as a colourless oil.

R_f = 0.43 (PE-Et_2O; 1:1)

$[\alpha]_D$ (24.1 °C, $CHCl_3$) = +22.7 (c = 1.17)

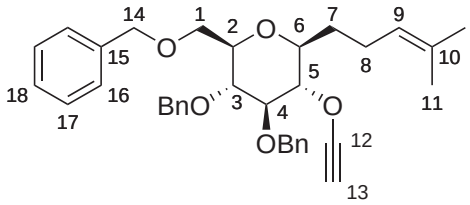
IR : ν_{max} 3445, 2928, 2865, 1453, 1074, 1027, 734, 696 cm^{-1}.

^{1}H NMR : δ 7.37−7.21 (15H, CH Arom), 5.12 (1H, ddd, J = 10.2, 7.2, 2.7 Hz, CH-C9), 4.71 (1H, d, J = 11.6 Hz, CH_2-C12a), 4.65 (1H, d, J = 11.3 Hz, CH_2-C12'a), 4.59 (1H, d, J = 11.6 Hz, CH_2-C12b), 4.59 (1H, d, J = 12.0 Hz, CH_2-C12"a), 4.56 (1H, d, J = 11.3 Hz, CH_2-C12'b), 4.51 (1H, d, J = 12.0 Hz, CH_2-C12"b), 3.95 (1H, ddd, J = 5.6, 5.3, 5.1 Hz, CH-C2), 3.90 (1H, ddd, J = 9.6, 9.6, 4.1 Hz, CH-C6), 3.78 (1H, dd, J = 10.2, 5.3 Hz, CH_2-C1a), 3.74−3.70 (2H, m, CH-C4 and CH_2-C1b), 3.69−3.66 (1H, m, CH-C5), 3.63 (1H, dd, J = 5.6, 5.6 Hz, CH-C3), 2.72 (1H, d, J = 7.2 Hz, OH), 2.17−1.97 (2H, m, CH_2-C8), 1.75−1.67 (1H, m, CH_2-C7a), 1.67 (3H, s, CH_3-C11), 1.63−1.59 (1H, m, CH_2-C7b), 1.60 (3H, s, CH_3-C11').

^{13}C NMR : δ 138.3 (C Arom), 138.2 (C Arom), 137.7 (C Arom), 132.0 (C-C10), 128.7 (2 CH Arom), 128.6 (2 CH Arom), 128.5 (CH Arom), 128.1 (2 CH Arom), 128.1 (3 CH Arom), 127.9 (2 CH Arom), 127.8 (2 CH Arom), 127.8 (CH Arom), 124.1 (CH-C9), 78.8 (CH-C4), 75.8 (CH-C3), 73.8 (CH_2-C12), 73.5 (CH_2-C12'), 73.3 (CH_2-C12"), 73.1 (CH-C2), 71.8 (CH-C6), 70.0 (CH-C5), 68.5 (CH_2-C1), 27.9 (CH_2-C7), 25.9 (CH_3-C11), 24.0 (CH_2-C8), 17.9 (CH_3-C11').

MS (EI): *m/z (Int)* 516 (61), 425 (100), 408 (100), 391 (100), 317 (97), 211 (95), 181 (100), 163 (100), 133 (100). HRMS ($C_{33}H_{40}O_5^+$): calculated: 516.2876; obtained: 516.2874, (Δ = 0.4 ppm).

(2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(ethynyloxy)-6-(4-methylpent-3-enyl)tetrahydro-2*H*-pyran: 280



$C_{35}H_{40}O_5$

Molecular weight: 540.7 $g.mol^{-1}$

To a suspension of KH (0.25 g, 1.9 mmol) in Et_2O (6 mL) was added a solution of alcohol **279** (0.38 g, 0.74 mmol) in Et_2O (5 mL). The reaction mixture was stirred for 10 min at rt, then cooled to 0 °C. Trichloroethylene (80 μL, 0.89 mmol) was added to the solution, which was then warmed to rt and stirred for 3 h. The reaction was quenched with MeOH (1 mL) and H_2O (5 mL), and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography on a small plug of silica gel gave the dichloroenol ether (0.38 g, 0.62

mmol), which was used directly into the next step.

To a solution of dichloroenol ether (0.38 g, 0.62 mmol) in Et_2O (6.2 mL) cooled to −78 °C was added a solution of *n*-butyllithium (0.74 mL, 1.9 mmol) in pentane (2.5 M) dropwise. The reaction was stirred for 30 min at −78 °C, allowed to warm to −45 °C and stirred for another 45 min. The reaction was quenched by addition of MeOH (1 mL) and H_2O (10 mL) then extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 10:1, 1% Et_3N) to give the alkynylether **280** (0.28 g, 0.51 mmol, 70% over 2 steps) as a colourless oil.

R_f = 0.33 (PE-Et_2O; 9:1)

$[\alpha]_D$ (23.6 °C, $CHCl_3$) = +30.0 (c = 1.08)

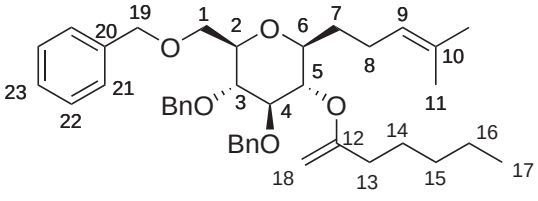
IR : ν_{max} 3317, 2930, 2863, 2150, 1453, 1356, 1093, 1028, 734, 696 cm^{-1}.

^{1}H NMR : δ 7.40−7.28 (13H, m, CH Arom), 7.16−7.13 (2H, m, CH Arom), 5.14 (1H, ddd, J = 9.7, 7.2, 2.5 Hz, CH-C9), 4.90 (1H, d, J = 10.7 Hz, CH_2-C14a), 4.79 (1H, d, J = 10.8 Hz, CH_2-C14'a), 4.72 (1H, d, J = 10.7 Hz, CH_2-C14b), 4.61 (1H, d, J = 12.1 Hz, CH_2-C14"a), 4.50 (1H, d, J = 12.1 Hz, CH_2-C14"b), 4.47 (1H, d, J = 10.8 Hz, CH_2-C14'b), 4.33−4.27 (2H, m, CH-C6 and CH-C5), 3.84 (1H, dd, J = 8.0, 8.0 Hz, CH-C4), 3.71−3.59 (4H, m, CH-C2 and CH-C3 and CH_2-C1), 2.21−2.12 (1H, m, CH_2-C8a), 2.09−2.00 (1H, m, CH_2-C8b), 1.75−1.63 (2H, m, CH_2-C7), 1.69 (3H, s, CH_3-C11), 1.61 (3H, s, CH_3-C11'), 1.59 (1H, s, CH-C13).

^{13}C NMR : δ 138.2 (C-C15), 138.1 (C-C15'), 138.1 (C-C15"), 132.7 (C-C10), 128.6 (2 CH Arom), 128.5 (3 CH Arom), 128.3 (2 CH Arom), 128.1 (3 CH Arom), 128.0 (3 CH Arom), 127.8 (2 CH Arom), 123.3 (CH-C9), 89.0 (C-C12), 87.8 (CH), 80.7 (CH-C4), 77.8 (CH), 75.4 (CH_2-C14), 75.2 (CH_2-C14'), 73.7 (CH_2-C14"), 72.4 (CH), 71.5 (CH), 68.9 (CH_2-C1), 27.0 (CH-C13), 25.9 (CH_3-C11), 25.0 (CH_2-C7), 23.6 (CH_2-C8), 17.8 (CH_3-C11').

MS (EI): *m/z (Int)* 540 (5), 467 (40), 253 (42), 181 (91), 91 (100), 69 (52). HRMS ($C_{35}H_{40}O_5^+$): calculated: 540.2876; obtained: 540.2878, (Δ = 0.4 ppm).

(2*R*,3*R*,4*S*,5*S*,6*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(hept-1-en-2-yloxy)-6-(4-methylpent-3-enyl)tetrahydro-2*H*-pyran: 281



$C_{40}H_{52}O_5$

Molecular weight: 612.8 g.mol^{-1}

CuBr (0.11 g, 0.72 mmol) and LiBr (63 mg, 0.72 mmol) were dried at 60 °C for 4 h under high vacuum. THF (5 mL) was added and the solution cooled to −90 °C. To this was added a solution of the Grignard reagent generated from bromopentane (0.72 mL, 0.72 mmol) in THF (1 M) and the reaction mixture was stirred for 10 min at −90 °C. Alkyne **280** (0.26 g, 0.48 mmol) in THF (5 mL) was then added, the solution was warmed to −78 °C and stirred for 45 min. The reaction was quenched by the addition of a solution of NH_4OH (10% in a saturated solution of NH_4Cl) (4 mL) and the aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 95:5→9:1, 1% Et_3N) to give the enol ether **281** (76 mg, 0.12 mmol, 25%) as a colourless oil.

R_f = 0.55 (PE-Et_2O; 4:1)

$[\alpha]_D$ (23.9 °C, $CHCl_3$) = +47.6 (c = 1.07)

IR : ν_{max} 2929, 2860, 1655, 1453, 1358, 1257, 1095, 1047, 733, 696 cm^{-1}.

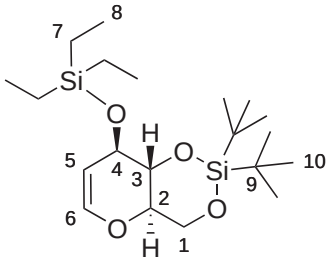
^{1}**H NMR** : δ 7.36−7.25 (13H, m, CH Arom), 7.14−7.11 (2H, m, CH Arom), 5.11 (1H, ddd, J = 9.9, 7.2, 2.7 Hz, CH-C9), 4.86 (1H, d, J = 10.9 Hz, CH_2-C19a), 4.81 (1H, d, J = 10.7 Hz, CH_2-C19'a), 4.71 (1H, d, J = 10.9 Hz, CH_2-C19b), 4.64 (1H, d, J = 12.1 Hz, CH_2-C19"a), 4.51 (1H, d, J = 12.1 Hz, CH_2-C19"b), 4.46 (1H, d, J = 10.7 Hz, CH_2-C19'b), 4.33−4.23 (2H, m, CH-C5 and CH-C6), 4.08 (1H, d, J = 2.1 Hz, CH_2-C18a), 3.96 (1H, d, J = 2.1 Hz, CH_2-C18b), 3.84 (1H, dd, J = 8.6, 8.6 Hz, CH-C4), 3.73−3.61 (4H, m, CH-C2 and CH-C3 and CH_2-C1), 2.19−2.02 (3H, m, CH_2-C8a and CH_2-C13), 2.01−1.91 (1H, m, CH_2-C8b), 1.78−1.68 (1H, m, CH_2-C7a), 1.67 (3H, s, CH_3-C11), 1.60 (3H, s, CH_3-C11'), 1.53−1.46 (3H, m, CH_2-C7b and CH_2-C14), 1.31−1.25 (4H, m, CH_2-C15 and CH_2-C16), 0.90−0.83 (3H, m, CH_3-C17).

^{13}**C NMR** : δ 161.5 (C-C12), 138.9 (C Arom), 138.4 (C Arom), 138.2 (C Arom), 132.3 (C-C10), 128.5 (2 CH Arom), 128.5 (3 CH Arom), 128.1 (2 CH Arom), 128.1 (2 CH Arom), 127.8 (3 CH Arom), 127.8 (2 CH Arom), 127.7 (CH Arom), 123.8 (CH-C9), 82.5 (CH_2-C18), 81.7 (CH-C4), 78.0 (CH), 76.8 (CH-C5), 75.3 (CH_2-C19), 75.2 (CH_2-C19'), 73.7 (CH_2-C19"), 72.0 (CH-C6), 71.2 (CH), 69.2 (CH_2-C1), 35.5 (CH_2-C13), 31.4 (CH_2), 27.1 (CH_2-C14), 25.9 (CH_3-C11), 25.2 (CH_2-C7), 23.9 (CH_2-C8), 22.6 (CH_2), 17.8 (CH_3-C11'), 14.2 (CH_3-C17).

MS (EI): *m/z (Int)* 612 (5), 498 (12), 407 (25), 299 (14), 253 (19), 181 (82), 91 (100).

HRMS ($C_{40}H_{52}O_5^+$): calculated: 612.3815; obtained: 612.3818, (Δ = 0.5 ppm).

(4a*R*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-8-(triethylsilyloxy)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline : 301



$\mathbf{C_{20}H_{40}O_4Si_2}$
Molecular weight: 400.7 g.mol^{-1}

To a solution of tri-*O*-acetyl-D-glucal (10.0 g, 36.8 mmol) in MeOH (40 mL) was added sodium methoxide (104 mg, 1.84 mmol) portionwise. The reaction mixture was sitrred for 45 min before being concentrated under reduced pressure to give the triol (5.40 g, 36.8 mmol, quant.) as a brown oil.

To a solution of triol (5.40 g, 36.8 mmol) in DMF (86 mL) at −40 °C was added di-*tert*-butylsiyl-bis(trifluoromethanesulfonate) (11.0 mL, 40.4 mmol) with a syringe pump over 1 h. The solution was then stirred for 2 h at −40 °C. The reaction was quenched by addition of pyridine (3.8 mL) and diluted with Et_2O (100 mL) and H_2O (100 mL). The aqueous phase was extracted with Et_2O (100 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the alcohol **303** (10.5 g, 36.8 mmol, quant.) as a yellow oil.

To a solution of alcohol **303** (10.5 g, 36.8 mmol) in DMF (100 mL) was added imidazole (6.28 g, 92.4 mmol) and triethylsilylchloride (10.0 mL, 60.0 mmol). The reaction was stirred at rt overnight and diluted with Et_2O (400 mL). The organic phase was washed with H_2O (4 × 400 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE-Et_2O; 99:1→95:5) to give the protected triol **301** (12.7 g, 31.8 mmol, 86% over 3 steps) as a colourless oil.

R_f = 0.72 (PE-Et_2O; 4:1)

$[\alpha]_D$ (22.4 °C, $CHCl_3$) = −42.6 (c = 2.35)

IR : ν_{max} 2957, 2878, 1649, 1473, 1364, 1234, 1162, 1123 cm^{-1}.

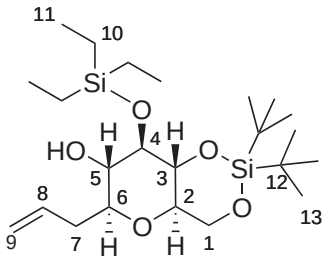
^{1}**H NMR** : δ 6.23 (1H, d, J = 6.0 Hz, CH-C6), 4.61 (1H, dd, J = 6.0, 1.6 Hz, CH-C5), 4.27 (1H, ddd, J = 7.0, 1.6, 1.6 Hz, CH-C4), 4.15 (1H, dd, J = 10.2, 4.9 Hz, CH_2-C1a), 3.98−3.92 (2H, m, CH_2-C1b and CH-C3), 3.81 (1H, ddd, J = 10.2, 10.2, 4.9 Hz, CH-C2), 1.06 (9H, s, CH_3-C10), 1.00 (9H, s, CH_3-C10'), 0.99 (9H, t, J = 7.9 Hz, CH_3-C8), 0.66 (6H, q, J = 7.9 Hz, CH_2-C7).

^{13}**C NMR** : δ 143.0 (CH-C6), 105.2 (CH-C5), 77.3 (CH-C3), 76.7 (CH-C2), 72.9 (CH-

C4), 65.9 (CH_2-C1), 27.5 (CH_3-C10), 27.0 (CH_3-C10'), 22.8 (C-C9), 19.9 (C-C9'), 6.9 (CH_3-C8), 4.9 (CH_2-C7).

MS (CI) : *m/z (Int)* 401 (29), 371 (27), 269 (100), 225 (58), 187 (32), 81 (44). HRMS ($C_{20}H_{41}O_4Si_2^+$) : calculated : 401.2543; obtained : 401.2541, (Δ = 0.5 ppm).

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-2,2-Di-*tert*-butyl-8-(triethylsilyloxy)-6-vinyl-hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol : 304



$C_{23}H_{46}O_5Si_2$

Molecular weight: 458.8 g.mol^{-1}

To a solution of glucal **301** (12.7 g, 31.8 mmol) in a mixture of acetone (30 mL), CH_2Cl_2 (127 mL) and a saturated aqueous solution of $NaHCO_3$ (317 mL) at 0 °C was slowly added a solution of Oxone (58.3 g, 94.8 mmol) in H_2O (228 mL). After 30 min at 0 °C, the solution was stirred for an additional 3 h at rt. The aqueous phase was extracted with CH_2Cl_2 (2 × 150 mL) and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give the epoxide (13.0 g, 31.3 mmol, 98 %) as a colourless oil, which was used directly into the next step.

To a solution of the epoxide (13.0 g, 31.3 mmol) in THF at 0 °C was added a solution of allylmagnesium chloride (31.3 mL, 62.6 mmol) in THF with a syringe pump over 30 min. The reaction mixture was stirred for 2 h at 0 °C and quenched with a saturated aqueous solution of NH_4Cl (150 mL). The aqueous phase was extracted with Et_2O (2 × 150 mL), the combined organic phases were washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE-Et_2O; 98:2→9:1) to give the alcohol **304** (11.7 g, 25.4 mmol, 81%) as a colourless oil.

R_f = 0.55 (PE-Et_2O; 10:1)

$[\alpha]_D$ (23.2 °C, $CHCl_3$) = −19.8 (c = 1.02)

IR : ν_{max} 3601, 2957, 2878, 1643, 1473, 1387, 1165, 1095 cm^{-1}.

^{1}**H NMR** : δ 5.80 (1H, dddd, J = 17.1, 10.2, 7.0, 7.0 Hz, CH-C8), 5.04 (1H, dddd, J = 17.1, 1.4, 1.0, 1.0 Hz, CH_2-C9a), 4.99 (1H, dddd, J = 10.2, 1.4, 1.0, 1.0 Hz, CH_2-C9b), 4.06 (1H, dd, J = 10.1, 5.0 Hz, CH_2-C1a), 3.74 (1H, dd, J = 10.1, 10.1 Hz, CH_2-C1b), 3.57 (1H, dd, J = 8.9, 8.9 Hz, CH-C3), 3.41 (1H, dd, J = 8.9, 8.9 Hz, CH-C4), 3.30−3.24 (2H, m, CH-C2 and CH-C6), 3.17 (1H, ddd, J = 9.4, 8.9, 2.5 Hz,

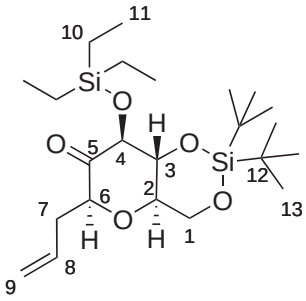
CH-C5), 2.49 (1H, m, CH_2-C7a), 2.18 (1H, dddd, J = 7.3, 7.0, 1.0, 1.0 Hz, CH_2-C7b), 2.14 (1H, d, J = 2.5 Hz, OH), 0.98 (9H, s, CH_3-C13), 0.93 (9H, s, CH_3-C13'), 0.92 (9H, t, J = 7.8 Hz, CH_3-C11), 0.64 (6H, q, J = 7.8 Hz, CH_2-C10).

^{13}C NMR : δ 134.4 (CH-C8), 117.2 (CH_2-C9), 80.0 (CH-C4), 78.6 (CH-C6), 77.5 (CH-C3), 74.9 (CH-C2), 74.5 (CH-C5), 66.5 (CH_2-C1), 36.2 (CH_2-C7), 27.6 (CH_3-C13), 27.0 (CH_3-C13'), 22.8 (C-C12), 20.0 (C-C12'), 7.0 (CH_3-C11), 5.2 (CH_2-C10).

MS (CI) : *m/z (Int)* 459 (100), 429 (8), 327 (9). HRMS ($C_{23}H_{47}O_5Si_2^+$) : calculated : 459.2962; obtained : 459.2959, (Δ = 0.7 ppm).

Elemental analysis: calculated for $C_{23}H_{46}O_5Si_2$: C 60.21, H 10.11; obtained: C 60.10, H 10.28.

(4a*R*,6*S*,8*S*,8a*R*)-6-Allyl-2,2-di-*tert*-butyl-8-(triethylsilyloxy)-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7(6*H*)-one : 366



$C_{23}H_{44}O_5Si_2$

Molecular weight: 456.8 g.mol^{-1}

To a solution of oxalyl chloride (4.31 mL, 47.8 mmol) in CH_2Cl_2 (132 mL) at −78 °C was slowly added a solution of DMSO (6.80 mL, 95.9 mmol) in CH_2Cl_2 (31 mL). The solution was stirred for 30 min at −78 °C before a solution of alcohol **304** (11.6 g, 25.3 mmol) in CH_2Cl_2 (81 mL) was slowly added. The reaction mixture was stirred for 2 h at −78 °C and Et_3N (17.5 mL, 127 mmol) was added. The solution was allowed to warm to rt and diluted with CH_2Cl_2 (300 mL) and H_2O (300 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL) and the combined organic phases were washed with brine (300 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE-Et_2O; 5%) to give the ketone **366** (10.0 g, 22 mmol, 87 %) as a colourless oil.

R_f = 0.78 (PE-Et_2O; 10:1)

$[\alpha]_D$ (22.7 °C, $CHCl_3$) = −52.4 (c = 1.00)

IR : ν_{max} 2936, 2878, 1744, 1180, 1152, 1105 cm^{-1}.

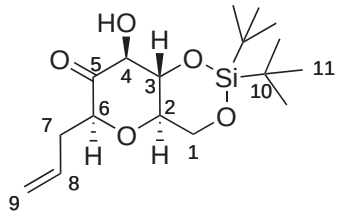
^{1}H NMR : δ 5.75 (1H, dddd, J = 17.1, 10.2, 6.8, 6.8 Hz, CH-C8), 5.04 (1H, dd, J = 17.1, 1.4 Hz, CH_2-C9a), 4.98 (1H, dd, J = 10.2, 1.4 Hz, CH_2-C9b), 4.18 (1H, dd, J = 10.2, 5.0 Hz, CH_2-C1a), 4.07 (1H, d, J = 9.2 Hz, CH-C4), 3.92 (1H, dd, J = 9.2, 9.2 Hz, CH-C3), 3.85−3.78 (2H, m, CH_2-C1b and CH-C6), 3.62 (1H, ddd, J = 9.2, 9.2, 5.0

Hz, CH-C2), 2.58−2.51 (1H, m, CH_2-C7a), 2.26−2.19 (1H, m, CH_2-C7b), 0.98 (9H, s, CH_3-C13), 0.96 (9H, s, CH_3-C13'), 0.93 (9H, t, J = 7.8 Hz, CH_3-C11), 0.61 (6H, q, J = 7.8 Hz, CH_2-C10).

^{13}C NMR : δ 202.3 (C-C5), 133.7 (CH-C8), 117.5 (CH_2-C9), 81.3 (CH-C6), 80.8 (CH-C4), 80.2 (CH-C3), 74.7 (CH-C2), 66.4 (CH_2-C1), 33.1 (CH_2-C7), 27.4 (CH_3-C13), 27.0 (CH_3-C13'), 22.7 (C-C12), 19.9 (C-C12'), 6.8 (CH_3-C11), 4.8 (CH_2-C10).

MS (CI) : *m/z (Int)* 457 (13), 325 (100), 133 (22). HRMS ($C_{23}H_{45}O_5Si_2^+$) : calculated : 457.2806; obtained : 457.2808, (Δ = 0.4 ppm).

(4a*R*,6*S*,8*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butyl-8-hydroxy-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7(6*H*)-one: 305



$C_{17}H_{30}O_5Si$
Molecular weight: 342.5 g.mol^{-1}

To a solution of silyl ether **366** (3.0 g, 6.6 mmol) in a mixture of THF (42 mL) and H_2O (4 mL) was added DDQ (0.15 g, 0.66 mmol). The reaction mixture was stirred for 4 h before being concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE-Et_2O; 3:1) to give the hydroxy-ketone **305** (1.9 g, 5.5 mmol, 84%) as a colourless oil.

R_f = 0.28 (PE-Et_2O; 4:1)

$[\alpha]_D$ (24.1 °C, $CHCl_3$) = −46.5 (c = 1.02)

IR : ν_{max} 3514, 2934, 2859, 1732, 1646, 1475, 1364, 1265, 1144 cm^{-1}.

^{1}H NMR : δ 5.84 (1H, dddd, J = 17.1, 10.2, 6.9, 6.9 Hz, CH-C8), 5.18 (1H, dddd, J = 17.1, 1.5, 1.5, 1.5 Hz, CH_2-C9a), 5.12 (1H, dddd, J = 10.2, 1.5, 1.5, 1.5 Hz, CH_2-C9b), 4.30 (1H, dd, J = 10.2, 5.0 Hz, CH_2-C1a), 4.26 (1H, ddd, J = 9.3, 2.8, 1.0 Hz, CH-C4), 4.02−3.96 (2H, m, CH-C6 and CH-C3), 3.94 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.80 (1H, ddd, J = 10.2, 9.7, 5.0 Hz, CH-C2), 3.55 (1H, d, J = 2.8 Hz, OH), 2.70−2.63 (1H, m, CH_2-C7a), 2.41−2.34 (1H, m, CH_2-C7b), 1.10 (9H, s, CH_3-C11), 1.07 (9H, s, CH_3-C11').

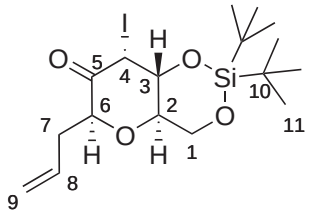
^{13}C NMR : δ 203.0 (C-C5), 133.0 (CH-C8), 118.0 (CH_2-C9), 80.8 (CH-C3 or CH-C6), 80.4 (CH-C6 or CH-C3), 79.7 (CH-C4), 74.3 (CH-C2), 66.1 (CH_2-C1), 32.9 (CH_2-C7), 27.5 (CH_3-C11), 27.0 (CH_3-C11'), 22.7 (C-C10), 20.0 (C-C10').

MS (FAB) : *m/z (Int)* 343 (30), 325 (18), 285 (54), 243 (24), 201 (24), 146 (38), 104 (33), 77 (100), 75 (70). HRMS ($C_{17}H_{31}O_5Si^+$) : calculated : 343.1941; obtained :

343.1945, (Δ = 1.2 ppm).

Elemental analysis: calculated for $C_{17}H_{30}O_5Si$: C 59.61, H 8.83; obtained: C 59.49, H 9.01.

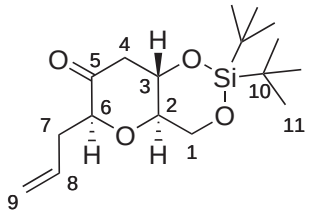
(4a*R*,6*S*,8*R*,8a*R*)-6-Allyl-2,2-di-*tert*-butyl-8-iodo-tetrahydropyrano[3,2-d] dioxasilin-7(6H)-one : 380



$C_{17}H_{29}IO_4Si$
Molecular weight: 452.4 g.mol^{-1}

To a solution of alcohol **305** (1.85 g, 5.40 mmol) in THF (53 mL) was added imidazole (734 mg, 10.8 mmol), PPh_3 (2.12 g, 8.10 mmol) and I_2 (2.19 g, 8.64 mmol). The solution was stirred overnight at rt, then quenched with a saturated aqueous solution of Na_2SO_3 (50 mL). The aqueous phase was extracted with EtOAc (100 mL), the organic phase was washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was filtrated on silica (PE-Et_2O; 4:1) to give the iodide **367** (1.59 g, 3.50 mmol, 65%) as a white solid.

(4a*R*,6*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butyl-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7(6H)-one : 306



$C_{17}H_{30}O_4Si$
Molecular weight: 326.5 g.mol^{-1}

From iodide **367**: To a solution of iodine **367** (1.6 g, 3.5 mmol) in toluene (53 mL) was added tri-*n*-butyltin hydride (2.8 mL, 10 mmol) and AIBN (30 mg, cat.). The reaction was stirred at reflux for 2 h. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (PE-Et_2O; 99:1→9:1) to give the ketone **306** (840 mg, 2.6 mmol, 73%) as a white solid.

From enol ether **316**: To a solution of enol ether **309** (9.30 g, 34.4 mmol) in a mixture of acetone (60 mL), CH_2Cl2 (155 mL) and a saturated aqueous solution of $NaHCO_3$ (330 mL) at 0 °C, was added a solution of Oxone (63.4 g, 103 mmol) in H_2O (250 mL). The mixture was stirred vigorously at 0 °C for 30 min and then at rt for an additional 2 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL). The

organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford the corresponding epoxide (9.80 g, 34.4 mmol, quant) as a white solid, which was used directly into the next step.

To a solution of epoxide (9.80 g, 34.4 mmol) in THF (435 mL) at 0 °C was added a solution of allymagnesium chloride (34.4 mL, 68.8 mmol) in THF (2 M) with a syringe-pump over 30 min. After the addition, the reaction mixture was stirred for another 2 h at 0 °C and a saturated aqueous solution of NH_4Cl (100 mL) was added. The aqueous layer was extracted with Et_2O (2 × 200 mL) and the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the alcohol (11.3 g, 34.4 mmol, quant) as a mixture of 4 possible diastereomers.

To a solution of oxalyl chloride (5.89 mL, 65.4 mmol) in CH_2Cl_2 (175 mL) at −78 °C was slowly added a solution of DMSO (9.29 mL, 131 mmol) in CH_2Cl_2 (44 mL). The solution was stirred for 30 min at −78 °C before a solution of alcohol (11.3 g, 34.4 mmol) in CH_2Cl_2 (106 mL) was slowly added. The reaction mixture was stirred for 2 h at −78 °C and Et_3N (23.8 mL, 172 mmol) was added. The solution was allowed to warm to rt and diluted with CH_2Cl_2 (300 mL) and H_2O (150 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE-Et_2O; 99:1→98:2→95:5) to give the ketone **306** (1.11 g, 3.40 mmol, 10 %) as a white solid. Further elution gave a 9:1 mixture of ketones **311** and **306** (5.16 g, 16.0 mmol, 46%) in favour of the wrong diastereomer.

To a solution of the ketones (5.2 g, 16 mmol) in toluene (160 mL) was added DBU (0.72 mL, 4.8 mmol). The solution was stirred at rt overnight and more DBU (0.36 mL, 2.4 mmol) was added. After another 7 h at rt, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL). The aqueous phase was extracted with EtOAc (2 × 75 mL) and the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE-Et_2O; 99:1→98:2→9:1) to give the ketone **306** (3.2 g, 9.8 mmol, 61 %) as a white solid.

R_f = 0.76 (PE-Et_2O; 1:1)

m.p. = 86−88 °C

$[\alpha]_D$ (24.5 °C, $CHCl_3$) = −24.1 (c = 1.07)

IR : ν_{max} 2934, 2860, 1728, 1643, 1473, 1266, 1115 cm^{-1}.

^{1}**H NMR** : δ 5.73 (1H, dddd, J = 17.1, 10.2, 6.8, 6.8 Hz, CH-C8), 5.04 (1H, dddd, J = 17.1, 1.5, 1.5, 1.5 Hz, CH_2-C9a), 4.99 (1H, dddd, J = 10.2, 1.5, 1.1, 1.1 Hz, CH_2-

C9b), 4.19 (1H, dd, J = 10.3, 5.0 Hz, CH_2-C1a), 4.06 (1H, ddd, J = 11.0, 9.3, 5.7 Hz, CH-C3), 3.83 (1H, dd, J = 10.3, 10.3 Hz, CH_2-C1b), 3.78 (1H, dd, J = 7.7, 4.3 Hz, CH-C6), 3.55 (1H, ddd, J = 10.3, 9.3, 5.0 Hz, CH-C2), 2.95 (1H, dd, J = 15.7, 5.7 Hz, CH_2-C4a), 2.58−2.51 (1H, m, CH_2-C7a), 2.38 (1H, dd, J = 15.7, 11.0 Hz, CH_2-C4b), 2.28−2.19 (1H, m, CH_2-C7b), 0.98 (9H, s, CH_3-C11), 0.94 (9H, s, CH_3-C11').

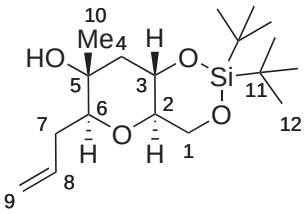
^{13}C NMR : δ 204.7 (C-C5), 133.7 (CH-C8), 117.6 (CH_2-C9), 82.6 (CH-C6), 76.4 (CH-C2), 73.2 (CH-C3), 66.6 (CH_2-C1), 48.3 (CH_2-C4), 33.5 (CH_2-C7), 27.4 (CH_3-C11), 27.0 (CH_3-C11'), 22.6 (C-C10), 19.9 (C-C10').

MS (FAB) : *m/z (Int)* 327 (55), 269 (100), 227 (93), 171 (98), 129 (95), 101 (93).

HRMS ($C_{17}H_{31}O_4Si^+$) : calculated : 327.1992; obtained : 327.1991, (Δ = 0.3 ppm).

Elemental analysis: calculated for $C_{17}H_{30}O_4Si$: C 62.54, H 9.26; obtained: C 62.53, H 9.31.

(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butyl-7-methyl-hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol : 300



$C_{18}H_{34}O_4Si$

Molecular weight: 342.6 g.mol^{-1}

To a solution of ketone **306** (0.80 g, 2.5 mmol) in toluene (245 mL) at −78 °C was added a solution of methylmagnesium iodide (4.0 mL, 12 mmol) in THF. The reaction was stirred at −78 °C for 40 min and quenched by addition of MeOH (5 mL). The solution was diluted with EtOAc (30 mL) and a saturated aqueous solution of NH_4Cl (30 mL) was added. The aqueous phase was extracted with EtOAc (3 × 30 mL), the combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PE-Et_2O; 9:1) to give the tertiary alcohol **300** (0.62 g, 1.8 mmol, 74%) as a colourless oil.

R_f = 0.20 (PE-Et_2O; 5:1)

$[\alpha]_D$ (23.0 °C, $CHCl_3$) = −24.1 (c = 1.07)

IR : ν_{max} 3364, 2934, 2859, 1474, 1094, 826 cm^{-1}.

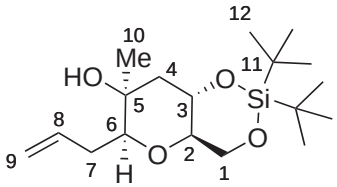
^{1}H NMR : δ 5.90 (1H, dddd, J = 17.2, 10.2, 6.8, 6.8 Hz, CH-C8), 5.12 (1H, dddd, J = 17.2, 1.6, 1.6, 1.6 Hz, CH_2-C9a), 5.06 (1H, dddd, J = 10.2, 1.6, 1.1, 1.1 Hz, CH_2-C9b), 4.14 (1H, dd, J = 10.1, 4.9 Hz, CH_2-C1a), 3.81 (1H, dd, J = 10.1, 10.1 Hz, CH_2-C1b), 3.76 (1H, ddd, J = 11.4, 9.4, 4.6 Hz, CH-C3), 3.29 (1H, ddd, J = 10.1, 9.4, 4.9 Hz,

CH-C2), 3.25 (1H, dd, J = 9.3, 3.6 Hz, CH-C6), 2.45−2.37 (1H, m, CH_2-C7a), 2.22 (1H, dd, J = 11.9, 4.6 Hz, CH_2-C4a), 2.16−2.07 (1H, m, CH_2-C7b), 1.60 (1H, dd, J = 11.9, 11.4 Hz, CH_2-C4b), 1.40 (1H, s, OH), 1.23 (3H, s, CH_3-C10), 1.04 (9H, s, CH_3-C12), 0.98 (9H, s, CH_3-C12').

^{13}C NMR : δ 136.0 (CH-C8), 116.9 (CH_2-C9), 84.3 (CH-C6), 78.5 (CH-C2), 72.5 (CH-C3), 71.4 (C-C5), 67.2 (CH_2-C1), 48.9 (CH_2-C4), 33.6 (CH_2-C7), 27.7 (CH_3-C12), 27.3 (CH_3-C12'), 22.9 (C-C11), 21.9 (CH_3-C10), 20.2 (C-C11').

MS (CI) : *m/z (Int)* 343 (90), 325 (100), 285 (34). HRMS ($C_{18}H_{35}O_4Si^+$) : calculated : 343.2305; obtained : 343.2309, (Δ = 1.2 ppm).

(4*R*,6*S*,7*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butyl-7-methyl-hexahydropyrano[3,2-*d*][1,3,2]di-oxasilin-7-ol: 307



$C_{18}H_{34}O_4Si$
Molecular weight: 342.6 g.mol^{-1}

Further elution (PE-Et_2O; 1:1) gave the other diastereomer **307** (151 mg, 0.44 mmol, 74%) as a colourless oil.

R_f = 0.18 (PE-Et_2O; 9:1)

m.p = 71−73 °C

$[\alpha]_D$ (23.0 °C, $CHCl_3$) = −32.8 (c = 1.01)

IR : ν_{max} 3480, 2932, 2859, 1643, 1474, 1092 cm^{-1}.

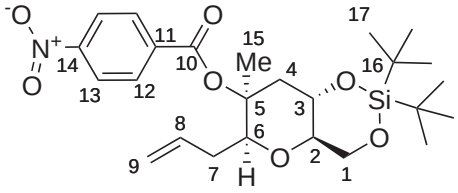
^{1}H NMR : δ 5.89 (1H, dddd, J = 17.0, 10.0, 6.8, 6.8 Hz, CH-C8), 5.09 (1H, d, J = 17.0 Hz, CH_2-C9a), 5.05 (1H, d, J = 10.0 Hz, CH_2-C9b), 4.13 (1H, dd, J = 10.0, 4.9 Hz, CH_2-C1a), 4.01 (1H, ddd, J = 10.2, 10.2, 4.7 Hz, CH-C3), 3.87 (1H, dd, J = 10.2, 10.0 Hz, CH_2-C1b), 3.32−3.25 (2H, m, CH-C2 and CH-C6), 2.37−2.24 (2H, m, CH_2-C7), 2.20 (1H, dd, J = 13.2, 4.7 Hz, CH_2-C4a), 1.89 (1H, br s, OH), 1.50 (1H, dd, J = 13.2, 10.2 Hz, CH_2-C4b), 1.19 (3H, s, CH_3-C10), 1.03 (9H, s, CH_3-C12), 0.98 (9H, s, CH_3-C12').

^{13}C NMR : δ 135.6 (CH-C8), 116.6 (CH_2-C9), 84.0 (CH-C6), 78.3 (CH-C2), 72.1 (C-C5), 71.1 (CH-C3), 66.8 (CH_2-C1), 46.6 (CH_2-C4), 32.9 (CH_2-C7), 27.5 (CH_3-C12), 27.1 (CH_3-C12'), 25.3 (CH_3-C10), 22.6 (C-C11), 20.0 (C-C11').

MS (FAB) : *m/z (Int)* 365 (90), 325 (84), 285 (100), 227 (81), 77 (100). HRMS ($C_{18}H_{34}NaO_4Si^+$) : calculated : 365.2124; found : 365.2121, (Δ = 0.8 ppm).

Elemental Analysis: calculated : C 63.11, H 10.00; found : C 63.18, H 10.20.

(4a*R*,6*S*,7*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butyl-7-methyl-hexahydropyrano[3,2-*d*][1,3,2]di oxasilin-7-yl-4-nitrobenzoate : 308



$C_{25}H_{37}NO_3Si$
Molecular weight: 491.7 g.mol^{-1}

To a solution of alcohol **307** (227 mg, 0.664 mmol) in THF (1.1 mL) at −78 °C was added a solution of *n*-BuLi (0.32 mL, 0.81 mmol) in hexane. The solution was warmed to rt and stirred for 1 h. A solution of *p*-nitrobenzoylchloride (245 mg, 1.32 mmol) in THF (2.6 mL) was added and the reaction mixture was stirred for 4 h at rt. The reaction mixture was diluted with Et_2O (10 mL), washed with an aqueous 1N HCl solution (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL) and brine (5 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 95:5) delivered the ester **308** (130 mg, 0.264 mmol, 40%) as a white solid.

R_f = 0.65 (PE-Et_2O; 2:1)

m.p = 135−136 °C

$[\alpha]_D$ (23.2 °C, $CHCl_3$) = −46.0 (c = 1.01)

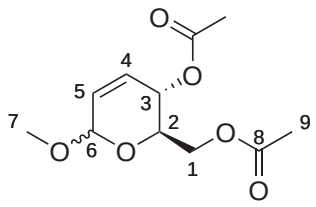
IR : ν_{max} 2929, 2861, 1724, 1531, 1292, 1260, 1098, 847, 827, 720 cm^{-1}.

^{1}**H NMR** : δ 8.30 (2H, d, J = 8.1 Hz, CH-C13), 8.17 (2H, d, J = 8.1 Hz, CH-C12), 5.95 (1H, dddd, J = 16.9, 9.8, 6.8, 6.8 Hz, CH-C8), 5.15 (1H, d, J = 16.9 Hz, CH_2-C9a), 5.10 (1H, d, J = 9.8 Hz, CH_2-C9b), 4.16 (1H, dd, J= 9.8, 4.6 Hz, CH_2-C1a), 3.86 (1H, dd, J = 9.8, 9.8 Hz, CH_2-C1b), 3.86−3.78 (1H, m, CH-C3), 3.40−3.30 (3H, m, CH-C2 and CH-C6 and CH_2-C4a), 2.51−2.41 (2H, m, CH_2-C7), 1.64 (3H, s, CH_3-C15), 1.58−1.53 (1H, m, CH_2-C4b), 0.98 (9H, s, CH_3-C17), 0.94 (9H, s, CH_3-C17').

^{13}**C NMR** : δ 163.6 (C-C10), 150.6 (C-C14), 136.7 (C-C11), 135.2 (CH-C8), 130.6 (CH-C12), 123.7 (CH-C13), 116.9 (CH_2-C9), 84.7 (CH-C6), 83.5 (C-C5), 78.2 (CH-C2), 70.5 (CH-C3), 66.8 (CH_2-C1), 41.1 (CH_2-C4), 31.0 (CH_2-C7), 27.4 (CH_3-C17), 27.1 (CH_3-C17'), 22.7 (C-C16), 22.5 (CH_3-C15), 19.9 (C-C16').

MS (CI) : *m/z (Int)* 492 (8), 462 (17), 325 (47), 97 (48), 71 (100). HRMS ($C_{25}H_{38}NO_7Si^+$) : calculated : 492.2418; found : 492.2405, (Δ = 2.6 ppm).

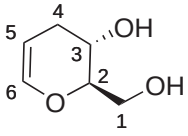
Acetic acid (2*R*,3*S*)-3-acetoxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-ylmethyl ester : 312



$C_{11}H_{16}O_6$
Molecular weight: 244.2 g.mol^{-1}

To a solution of tri-*O*-acetyl-D-glucal (32.0 g, 118 mmol) in CH_2Cl_2 (150 mL) was added methanol (5.20 mL, 128 mmol) and boron trifluoride diethyl etherate (6.40 mL, 52.0 mmol) dropwise. The reaction mixture was stirred for 1h 15min at rt. A saturated aqueous solution of $NaHCO_3$ (200 mL) was added and the reaction mixture was diluted with H_2O (400 mL) and CH_2Cl_2 (400 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 400 mL) and the combined organic phases were washed with brine (400 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The brown oil was filtered through a small plug of silica (PE-Et_2O; 1:1) to give the mixed acetal **312** (25.2 g, 103 mmol, 88%) as a colourless oil, which was used directly to the next step.

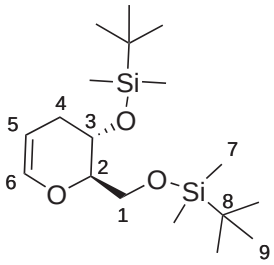
(2*R*,3*S*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-pyran-3-ol : 309



$C_6H_{10}O_3$
Molecular weight: 130.1 g.mol^{-1}

To a solution of the mixed acetal **312** (25.2 g, 103 mmol) in dioxane (690 mL) was added lithium aluminium hydride (8.24 g, 206 mmol) portionwise. The solution was stirred at reflux for 5 h and then cooled to 0 °C. H_2O (8.2 mL) was added slowly, followed by a 6N aqueous solution of NaOH (8.2 mL) and H_2O (24.6 mL). The mixture was then stirred for 45 min at rt, filtered through a Celite plug and concentrated under reduced pressure to afford diol **309** (12.5 g, 96.2 mmol, 93%) as a colourless oil, which was used directly to the next step.

***tert*-Butyl{[(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-3,4-dihydro-2*H*-pyran-2-yl]methoxy}dimethylsilane : 313**



$C_{18}H_{38}O_3Si_2$
Molecular weight: 358.7 g.mol^{-1}

To a solution of diol **309** (0.81 g, 6.3 mmol) in DMF (17.4 mL) were added imidazole (2.1 g, 31 mmol) and *tert*-butyldimethylsilylchloride (3.0 g, 20 mmol). The reaction mixture was stirred for 2 h and Et_2O (50 mL) was added to it. The organic phase was washed with H_2O (5 × 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 99:1) delivered the bis-protected diol **313** (1.4 g, 4.0 mmol, 64%) as a colourless oil.

R_f = 0.75 (PE-Et_2O; 1:1)

$[\alpha]_D$ (22.6 °C, $CHCl_3$) = +75.3 (c = 1.015)

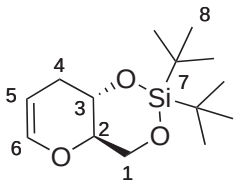
IR : ν_{max} 2928, 2657, 1655, 1474, 1252, 1088 cm^{-1}.

^{1}H NMR : δ 6.32 (1H, d, J = 5.8 Hz, CH-C6), 4.57 (1H, ddd, J = 5.8, 5.6, 2.2 Hz, CH-C5), 3.87−3.80 (2H, m, CH_2-C1a and CH-C3), 3.77 (1H, ddd, J = 11.3, 11.3, 4.8 Hz, CH_2-C1b), 3.49 (1H, ddd, J = 11.3, 4.8, 2.4 Hz, CH-C2), 2.15 (1H, ddd, J = 16.3, 5.6, 5.4 Hz, CH_2-C4a), 1.95 (1H, dddd, J = 16.3, 8.8, 2.5, 2.2 Hz, CH_2-C4b), 0.83 (9H, s, CH_3-C9), 0.82 (9H, s, CH_3-C9'), 0.07 (12H, s, CH_3-C7 and CH_3-C7').

^{13}C NMR : δ 143.2 (CH-C6), 97.5 (CH-C5), 79.8 (CH-C2), 64.3 (CH-C3), 62.6 (CH_2-C1), 30.4 (CH_2-C4), 26.0 (CH_3-C9), 25.7 (CH_3-C9'), 18.5 (C-C8), 18.0 (C-C8'), -4.2 (CH_3-C7a), -4.9 (CH_3-C7a'), -5.10 (CH_3-C7b), -5.3 (CH_3-C7b').

MS (CI) : *m/z (Int)* 359 (34), 97 (28), 86 (75), 82 (75), 69 (100). HRMS ($C_{18}H_{39}O_3Si_2^+$) : calculated : 359.2438; obtained : 359.2440, (Δ = 0.6 ppm).

(4a*R*,8a*S*)-2,2-Di-*tert*-butyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline: 316



$C_{14}H_{26}O_3Si$

Molecular weight: 270.4 $g.mol^{-1}$

Method A: To a solution of diol **309** (5.26 g, 40.5 mmol) in DMF (101 mL) at −45 °C was added di-*tert*-butylsilyl-bis(trifluoromethanesulfonate) (14.4 mL, 44.6 mmol) dropwise. The reaction mixture was stirred at −45 °C for 1 h and pyridine (4.5 mL) was added. The solution was diluted with Et_2O (200 mL). The organic phase was washed with H_2O (5 × 200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 99:1) delivered the bis-protected diol **316** (7.94 g, 29.4 mmol, 73%) as a white solid.

Method B: To a solution of di-*tert*-butyldichlorosilane (22.5 mL, 106 mmol) in DMF (160 mL) at 0 °C was added silver nitrate (35.6 g, 211 mmol). The solution was

stirred for 5 min at 0 °C and a solution of diol **309** (12.5 g, 96.2 mmol) in DMF (81 mL) was added to the reaction mixture. The reaction mixture was stirred at 0 °C for 1h15 and Et_3N (66.4 mL, 480 mmol) was added. The solution was diluted with Et_2O (400 mL). The organic phase was washed with H_2O (4 × 400 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 99:1) delivered the bis-protected diol **315** (18.0 g, 66.7 mmol, 67%) as a white solid.

R_f = 0.75 (PE-Et_2O; 1:1)

m.p = 38−40 °C

IR: ν_{max} 2931, 2859, 1645, 1472, 1238, 1126, 1076 cm^{-1}.

$[\alpha]_D$ (20.4 °C, $CHCl_3$) = +40.1 (c = 1.00)

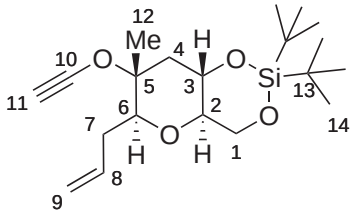
^{1}**H NMR**: δ 6.26 (1H, ddd, J = 5.9, 2.3, 1.4 Hz, CH-C6), 4.69 (1H, ddd, J = 5.9, 5.9, 2.0 Hz, CH-C5), 4.18 (1H, dd, J = 10.3, 4.8 Hz, CH_2-C1a), 4.11 (1H, ddd, J = 9.5, 9.5, 6.0 Hz, CH-C3), 3.92 (1H, dd, J = 10.3, 10.3 Hz, CH_2-C1b), 3.68 (1H, ddd, J = 10.3, 9.5, 4.8 Hz, CH-C2), 2.38 (1H, dddd, J = 16.5, 6.0, 5.9, 1.4 Hz, CH_2-C4a), 2.07 (1H, dddd, J = 16.5, 9.5, 2.3, 2.0 Hz, CH_2-C4b), 1.06 (9H, s, CH_3-C8), 0.99 (9H, s, CH_3-C8').

^{13}**C NMR**: δ 142.6 (CH-C6), 98.9 (CH-C5), 73.9 (CH-C2), 71.4 (CH-C3), 66.4 (CH_2-C1), 30.2 (CH_2-C4), 27.5 (CH_3-C8), 27.0 (CH_3-C8'), 22.7 (C-C7), 19.9 (C-C7').

MS (CI): *m/z (Int)* 271 (100), 213 (13). HRMS ($C_{14}H_{27}O_3Si^+$): calculated: 271.1729; obtained: 271.1733, (Δ = 1.5 ppm).

Elemental analysis: calculated for $C_{14}H_{26}O_3Si$: C 62.18, H 9.69; obtained: C 62.15, H 9.79.

(4a*R*,6*S*,7*R*,8a*S*)-6-allyl-2,2-di-*tert*-butyl-7-(ethynyloxy)-7-methylhexahydropyrano[3,2-*d*][1,3,2]dioxasiline: 320



$C_{20}H_{34}O_4Si$

Molecular weight: 366.6 $g.mol^{-1}$

To a suspension of KH (6.64 g, 49.8 mmol) in THF (70 mL) was added a solution of alcohol **300** (8.50 g, 24.9 mmol) in THF (100 mL). The reaction mixture was stirred for 10 min at rt, then cooled to 0 °C. Trichloroethylene (2.68 mL, 29.9 mmol) was added to the solution, and it was then subsequently warmed to rt and stirred for 3 h. The reaction was quenched with MeOH (10 mL) and H_2O (150 mL), and the aqueous phase

was extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography on a small plug of silica gel gave the dichloroenol ether (10.8 g, 24.7 mmol), which was used directly in the next step.

To a solution of dichloroenol ether (10.8 g, 24.7 mmol) in Et_2O (370 mL) cooled to −78 °C was added dropwise a solution of *n*-butyllithium (29.6 mL, 74.1 mmol) in hexane (2.6M). The reaction was stirred 30 min at −78 °C, allowed to warm to −45 °C and stirred for another 45 min. The reaction was quenched by addition of MeOH (10 mL) and H_2O (150 mL) then extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (PE-Et_2O; 99:1) to give the alkynylether **320** (8.17 g, 22.3 mmol, 90% over 2 steps) as a colourless oil.

R_f = 0.63 (PE-Et_2O; 9:1)

$[\alpha]_D$ (22.6 °C, $CHCl_3$) = −53.0 (c = 1.02)

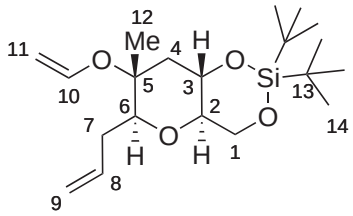
IR : ν_{max} 3329, 2934, 2861, 2141, 1474, 1387, 1113 cm^{-1}.

^{1}H NMR : δ 5.84 (1H, dddd, J = 17.0, 10.2, 6.8, 6.8 Hz, CH-C8), 5.11 (1H, d, J = 17.0 Hz, CH_2-C9a), 5.06 (1H, d, J = 10.2 Hz, CH_2-C9b), 4.14 (1H, dd, J = 10.1, 4.9 Hz, CH_2-C1a), 3.80 (1H, dd, J = 10.1, 10.1 Hz, CH_2-C1b), 3.81−3.74 (1H, m, CH-C3), 3.50 (1H, dd, J = 10.1, 1.7 Hz, CH-C6), 3.30 (1H, ddd, J = 10.1, 10.1, 4.9 Hz, CH-C2), 2.50 (1H, dd, J = 11.8, 4.5 Hz, CH_2-C4a), 2.38 (1H, ddd, J = 14.6, 6.8, 1.7 Hz, CH_2-C7a), 2.11−2.02 (1H, m, CH_2-C7b), 1.94 (1H, dd, J = 11.8, 11.8 Hz, CH_2-C4b), 1.62 (1H, s, CH-C11), 1.40 (3H, s, CH_3-C12), 1.03 (9H, s, CH_3-C14), 0.98 (9H, s, CH_3-C14').

^{13}C NMR : δ 134.8 (CH-C8), 117.0 (CH_2-C9), 85.8 (CH-C11), 84.8 (C-C5), 81.1 (CH-C6), 78.1 (CH-C2), 72.3 (CH-C3), 66.7 (CH_2-C1), 43.7 (CH_2-C4), 33.0 (CH_2-C7), 30.3 (C-C10), 27.4 (CH_3-C14), 27.1 (CH_3-C14'), 22.7 (C-C13), 20.0 (C-C13'), 18.1 (CH_3-C12).

MS (FAB) : *m/z (Int)* 367 (22), 326 (100), 325 (100), 267 (100), 227 (100), 211 (91), 102 (93). HRMS ($C_{20}H_{35}O_4Si^+$) : calculated : 367.2305; obtained : 367.2302, (Δ = 0.8 ppm).

(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butyl-7-methyl-7-(vinyloxy)-hexahydropyrano[3,2-d][1,3,2]dioxasiline : 299



$C_{20}H_{36}O_4Si$
Molecular weight: 368.6 g.mol^{-1}

From alcohol **300**: To a solution of alcohol **300** (0.26 g, 0.76 mmol) in butylvinylether (3.9 mL) was added Et_3N (31 μL, 0.22 mmol), 4,7-diphenyl-1,10-phenanthroline (12.5 mg, 0.038 mmol) and $Pd(CF_3CO_2)_2$ (13 mg, 38 μmol). The reaction was stirred at reflux for 24 h, filtrated on activated carbon and concentrated under reduced pressure. The crude product was purified by flash chromatography (PE-Et_2O; 99:1→1:1) to give the vinyl ether **299** (130 mg, 0.34 mmol, 45%) as a colourless oil and some starting material (120 mg, yield = 84% BRSM).

From alkynyl ether **320**: To a solution of alkyne **320** (8.17 g, 22.3 mmol) in EtOAc (450 mL) was added quinoline (130 μL) and Lindlar catalyst (475 mg, 0.223 mmol). The solution was purged with Ar three times then saturated with H_2 three times. The reaction was stirred for 45 min, then filtered on Celite and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 99:1) delivered the alkene **299** (7.84 g, 21.3 mmol, 96%) as a colourless oil.

R_f = 0.75 (PE-Et_2O; 4:1)

$[\alpha]_D$ (24.1 °C, $CHCl_3$) = −34.0 (c = 0.98)

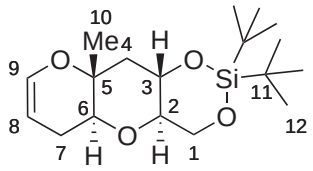
IR : ν_{max} 2934, 2961, 1634, 1474, 1180, 1096 cm^{-1}.

^{1}**H NMR** : δ 6.46 (1H, dd, J = 13.6, 6.2 Hz, CH-C10), 5.87 (1H, dddd, J = 17.0, 10.4, 6.7, 6.7 Hz, CH-C8), 5.10 (1H, dddd, J = 17.0, 1.8, 1.1, 1.1 Hz, CH_2-C9a), 5.04 (1H, dddd, J = 10.4, 1.8, 1.1, 1.1 Hz, CH_2-C9b), 4.48 (1H, dd, J = 13.6, 0.8 Hz, CH_2-C11a), 4.14 (1H, dd, J = 10.2, 4.9 Hz, CH_2-C1a), 4.12 (1H, dd, J = 6.2, 0.8 Hz, CH_2-C11b), 3.81 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.76 (1H, ddd, J = 11.4, 9.3, 4.6 Hz, CH-C3), 3.36 (1H, dd, J = 10.3, 2.2 Hz, CH-C6), 3.29 (1H, ddd, J = 10.2, 9.3, 4.9 Hz, CH-C2), 2.43 (1H, dddt, J = 14.8, 6.7, 2.2, 1.1 Hz, CH_2-C7a), 2.36 (1H, dd,J = 11.9, 4.6 Hz, CH_2-C4a), 2.05−1.97 (1H, m, CH_2-C7b), 1.68 (1H, dd, J = 11.9, 11.4 Hz, CH_2-C4b), 1.27 (3H, s, CH_3-C12), 1.03 (9H, s, CH_3-C14), 0.98 (9H, s, CH_3-C14').

^{13}**C NMR** : δ 114.7 (CH-C10), 135.7 (CH-C8), 116.5 (CH_2-C9), 92.6 (CH_2-C11), 82.6 (CH-C6), 78.2 (CH-C2), 72.2 (CH-C3), 66.7 (CH_2-C1), 65.0 (CH-C5), 44.7 (CH_2-C4), 32.9 (CH_2-C7), 27.5 (CH_3-C14), 27.1 (CH_3-C14'), 22.7 (C-C13), 20.0 (C-C13'), 18.7 (CH_3-C12).

MS (CI) : *m/z (Int)* 369 (18), 325 (60), 85 (52), 71 (70), 69 (100). HRMS ($C_{20}H_{37}O_4Si^+$) : calculated : 369.2461; obtained : 369.2462, (Δ = 0.3 ppm).

(4a*R*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-8a-methyl-4a,5,8a,9,9a,10a-hexahydro-4*H*-1,3,8,10-tetraoxa-2-silaanthracene : 298



$C_{18}H_{32}O_4Si$
Molecular weight: 340.5 g.mol^{-1}

To a solution of diene **299** (120 mg, 0.33 mmol) in toluene (33 mL) was added Grubbs' second generation catalyst **3** (14 mg, 17 μmol). The reaction was stirred for 1 h at reflux and then concentrated under reduced pressure. Purification by flash column chromatography (PE-Et_2O; 99:1, 1% Et_3N) gave the cyclic enol ether **298** (110 mg, 0.31 mmol, 95%) as a white solid.

m.p = 110−112 °C

$[\alpha]_D$ (23.8 °C, $CHCl_3$) = −7.0 (c = 0.96)

IR : ν_{max} 2934, 2857, 1645, 1474, 1240, 1173 cm^{-1}.

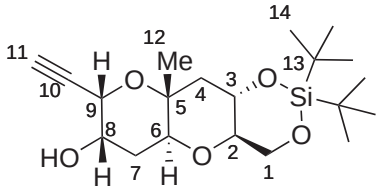
^{1}H NMR : δ 6.08 (1H, ddd, J = 6.1, 2.5, 1.3 Hz, CH-C9), 4.55 (1H, ddd, J = 6.1, 5.8, 1.3 Hz, CH-C8), 4.10 (1H, dd, J = 10.2, 4.9 Hz, CH_2-C1a), 3.83 (1H, ddd, J = 11.4, 9.4, 4.7 Hz, CH-C3), 3.77 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.40 (1H, dd, J = 10.8, 5.8 Hz, CH-C6), 3.33 (1H, ddd, J = 10.2, 9.4, 4.9 Hz, CH-C2), 2.24 (1H, dd, J = 11.7, 4.7 Hz, CH_2-C4a), 2.10 (1H, dddd, J = 16.3, 5.8, 5.8, 1.3 Hz, CH_2-C7a), 1.96−1.78 (1H, m, CH_2-C7b), 1.61 (1H, dd, J = 11.7, 11.4 Hz, CH_2-C4b), 1.48 (3H, s, CH_3-C10), 0.98 (9H, s, CH_3-C12), 0.92 (9H, s, CH_3-C12').

^{13}C NMR : δ 141.0 (CH-C9), 97.8 (CH-C8), 78.7 (CH-C2), 77.2 (CH-C6), 73.8 (C-C5), 72.2 (CH-C3), 67.0 (CH_2-C1),45.5 (CH_2-C4), 27.5 (CH_3-C12), 27.1 (CH_3-C12'), 23.7 (CH_2-C7), 22.7 (C-C11), 20.0 (C-C11'), 16.7 (CH_3-C10).

MS (CI) : *m/z (Int)* 341 (100), 283 (9), 97 (10). HRMS ($C_{18}H_{33}O_4Si^+$) : calculated : 341.2148; obtained : 341.2152, (Δ = 1.2 ppm).

Elemental analysis: calculated for $C_{18}H_{32}O_4Si$: C 63.49, H 9.47; obtained: C 63.27, H 9.48.

(4a*R*,6*S*,7*S*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-7-ethynyl-8a-methyl-octahydro-1,3,8,10-tetraoxa-2-sila-anthracen-6-ol: 327



$C_{20}H_{34}O_5Si$
Molecular weight: 382.6 g.mol^{-1}

To a solution of enol ether **298** (500 mg, 1.48 mmol) in CH_2Cl_2 (6.6 mL) at 0 °C was added a solution of DMDO (21.0 mL, 1.78 mmol) in acetone. After 5 min at 0 °C, the solution was concentrated under reduced pressure, diluted with CH_2Cl_2 (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude epoxide (524 mg, 1.48 mmol, quant.) which was used without further purification.

To a solution of sodium acetylide (1.74 mL, 5.92 mmol) at 0 °C was added a solution of $ZnCl_2$ (790 mg, 5.92 mmol) in Et_2O (12 mL). The reaction mixture was stirred for 15 min at 0 °C, then a solution of epoxide (524 mg, 1.48 mmol) in CH_2Cl_2 (15 mL) was added. The reaction mixture was allowed to warm slowly to 14 °C over 2.5 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 4:1→2:1) delivered the alcohol **327** (310 mg, 0.811 mmol, 55%) as a white solid.

R_f = 0.34 (PE-Et_2O; 1:2)

m.p. = 176−178 °C

$[\alpha]_D$ (22.4 °C, $CHCl_3$) = −22.8 (c = 1.00)

IR : ν_{max} 3486, 3277, 2934, 2861, 1474, 1101 cm^{-1}.

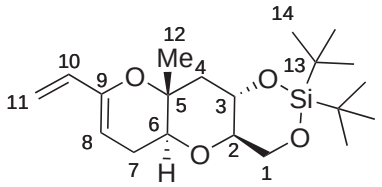
^{1}**H NMR** : δ 4.56 (1H, br s, CH-C9), 4.15 (1H, dd, J = 9.6, 4.9 Hz, CH_2-C1a), 4.00 (1H, br s, CH-C8), 3.96−3.90 (1H, m, CH-C3), 3.80 (1H, dd, J = 10.1, 9.6 Hz, CH_2-C1b), 3.74 (1H, dd, J = 12.5, 3.8 Hz, CH-C6), 3.49−3.43 (1H, m, CH-C2), 2.58 (1H, d, J = 1.9 Hz, CH-C11), 2.32 (1H, br s, OH), 2.24 (1H, dd, J = 11.6, 4.9 Hz, CH_2-C4a), 2.12−2.07 (1H, m, CH_2-C7a), 1.76−1.68 (2H, m, CH_2-C4b and CH_2-C7b), 1.25 (3H, s, CH_3-C12), 1.03 (9H, s, CH_3-C14), 0.98 (9H, s, CH_3-C14').

^{13}**C NMR** : δ 78.5 (CH-C2), 76.2 (C-C10), 74.6 (CH-C11), 74.0 (CH-C6), 73.1 (C-C5), 71.5 (CH-C3), 67.7 (CH-C8), 65.9 (CH_2-C1), 63.6 (CH-C9), 45.0 (CH_2-C4), 29.2 (CH_2-C7), 26.4 (CH_3-C14), 26.1 (CH_3-C14'), 21.6 (C-C13), 18.9 (C-C13'), 13.6 (CH_3-C12).

MS (CI) : *m/z (Int)* 383 (73), 365 (41), 320 (40), 302 (100), 157 (72), 69 (53). HRMS ($C_{20}H_{35}O_5Si^+$) : calculated : 383.2254; found : 383.2252, (Δ = 0.5 ppm).

Elemental analysis: calculated for $C_{20}H_{34}O_5Si$: C 62.79, H 8.96; obtained: C 62.74, H 9.12.

(4a*R*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-8a-methyl-7-vinyl-4a,5,8a,9,9a,10a-hexahydro-4*H*-1,3,8,10-tetraoxa-2-sila-anthracene: 331



$C_{20}H_{34}O_4Si$
Molecular weight: 366.6 g.mol^{-1}

To a stirred solution of Grubbs second generation catalyst (46 mg, 5.0 μmol) in toluene (78 mL) was bubbled ethylene gas for 10 min. A solution of enyne **320** (0.40 g, 1.1 mmol) in toluene (31 mL) was added to the reaction mixture, which was heated at 80 °C for 1.5 h under an atmosphere of ethylene. The reaction mixture was concentrated under reduced pressure and purification by flash column chromatography on silica gel (PE-Et_2O; 99:1) delivered the diene **331** (360 mg, 0.98 mmol, 90%) as a white solid.

R_f = 0.59 (PE-Et_2O; 4:1)

m.p = 110−111 °C

$[\alpha]_D$ (23.4 °C, $CHCl_3$) = −1.95 (c = 1.02)

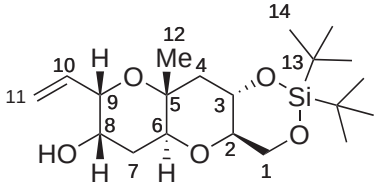
IR : ν_{max} 2934, 2859, 1603, 1472, 1377, 1350, 1101, 1040 cm^{-1}.

^{1}**H NMR** : δ 6.06 (1H, dd, J = 17.1, 10.8 Hz, CH-C10), 5.45 (1H, d, J = 17.1 Hz, CH_2-C11a), 5.01 (1H, d, J = 10.8 Hz, CH_2-C11b), 4.73 (1H, d, J = 5.7 Hz, CH-C8), 4.17 (1H, dd, J = 10.0, 4.8 Hz, CH_2-C1a), 3.92 (1H, ddd, J = 11.4, 11.4, 4.6 Hz, CH-C3), 3.84 (1H, dd, J = 10.2, 10.0 Hz, CH_2-C1b), 3.49 (1H, dd, J = 10.7, 5.9 Hz, CH-C6), 3.40 (1H, ddd, J = 11.4, 10.2, 4.8 Hz, CH-C2), 2.38 (1H, dd, J = 11.9, 4.6 Hz, CH_2-C4a), 2.27 (1H, ddd, J = 17.2, 5.9, 5.7 Hz, CH_2-C7a), 1.99 (1H, dd, J = 17.2, 10.7 Hz, CH_2-C7b), 1.78 (1H, dd, J = 11.9, 11.4 Hz, CH_2-C4b), 1.18 (3H, s, CH_3-C12), 1.05 (9H, s, CH_3-C14), 0.99 (9H, s, CH_3-C14').

^{13}**C NMR** : δ 148.2 (C-C9), 132.2 (CH-C10), 112.8 (CH_2-C11), 99.6 (CH-C8), 78.7 (CH-C2), 77.0 (CH-C6), 73.6 (C-C5), 72.2 (CH-C3), 67.0 (CH_2-C1), 45.6 (CH_2-C4), 27.5 (CH_3-C14), 27.1 (CH_3-C14'), 24.6 (CH_2-C7), 22.7 (C-C13), 20.0 (C-C13'), 16.6 (CH_3-C12).

MS (FAB+) : *m/z (Int)* 367 (56), 309 (100), 271 (20), 227 (35), 122 (49), 77 (68). HRMS ($C_{20}H_{35}O_4Si^+$) : calculated : 367.2305; found : 367.2306, (Δ = 0.3 ppm).

(4a*R*,6*S*,7*S*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-8a-methyl-7-vinyl-octahydro-1,3,8,10-tetraoxa-2-sila-anthracen-6-ol: 328



$C_{20}H_{36}O_5Si$
Molecular weight: 384.6 g.mol^{-1}

To a solution of alkyne **327** (130 mg, 0.35 mmol) in EtOAc (7 mL) was added quinoline (1 drop) and Lindlar catalyst (7.5 mg, 3.5 μmol). The solution was purged with Ar three times then saturated with H_2 three times. The reaction was stirred for 1 h, then filtered on Celite and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 3:1) delivered the alkene **328** (110 mg, 0.29 mmol, 84%) as a white solid.

R_f = 0.45 (PE-Et_2O; 1:2)

m.p. = 159−160 °C

$[\alpha]_D$ (22.9 °C, $CHCl_3$) = −37.6 (c = 0.87)

IR : ν_{max} 3460, 2934, 2861, 1474, 1101, 1051, 826 cm^{-1}.

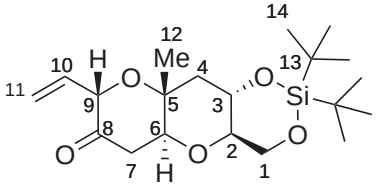
^{1}**H NMR** : δ 5.85 (1H, ddd, J = 17.4, 10.8, 4.4 Hz, CH-C10), 5.46 (1H, ddd, J = 17.4, 1.7, 1.7 Hz, CH_2-C11a), 5.34 (1H, ddd, J = 10.8, 1.7, 1.7 Hz, CH_2-C11b), 4.32 (1H, dddd, J = 4.4, 1.7, 1.7, 1.7 Hz, CH-C9), 4.17 (1H, dd, J = 9.9, 4.9 Hz, CH_2-C1a), 4.00−3.91 (2H, m, CH-C3 and CH-C8), 3.82 (1H, dd, J= 10.1, 9.9 Hz, CH_2-C1b), 3.68 (1H, dd, J = 12.7, 4.1 Hz, CH-C6), 3.46 (1H, ddd, J = 10.1, 10.1, 4.9 Hz, CH-C2), 2.24 (1H, dd, J = 11.7, 4.9 Hz, CH_2-C4a), 2.07 (1H, ddd, J = 13.1, 4.1, 3.6 Hz, CH_2-C7a), 1.81−1.68 (3H, m, CH_2-C4b and CH_2-C7b and OH), 1.26 (3H, s, CH_3-C12), 1.04 (9H, s, CH_3-C14), 0.99 (9H, s, CH_3-C14').

^{13}**C NMR** : δ 134.8 (CH-C10), 117.8 (CH_2-C11), 79.6 (CH-C2), 76.0 (CH-C6), 73.3 (C-C5), 72.6 (CH-C3), 71.9 (CH-C9), 68.6 (CH-C8), 67.1 (CH_2-C1), 46.4 (CH_2-C4), 31.2 (CH_2-C7), 27.5 (CH_3-C14), 27.1 (CH_3-C14'), 22.7 (C-C13), 22.0 (C-C13'), 15.0 (CH_3-C12).

MS (CI) : *m/z (Int)* 385 (84), 367 (19), 89 (100). HRMS ($C_{20}H_{37}O_5Si^+$) : calculated : 385.2410; found : 385.2407, (Δ = 0.8 ppm).

Elemental analysis: calculated for $C_{20}H_{36}O_5Si$: C 62.46, H 9.44; obtained: C 62.50, H 9.63.

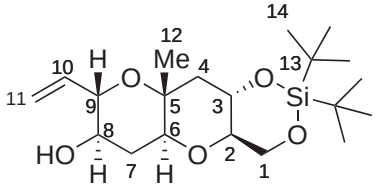
(4a*R*,7*S*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-8a-methyl-7-vinyl-hexahydro-1,3,8,10-tetraoxa-2-sila-anthracen-6-one: 381



$C_{20}H_{34}O_5Si$
Molecular weight: 382.6 g.mol^{-1}

To a solution of alcohol **328** (94 mg, 0.24 mmol) in CH_2Cl_2 (3.7 mL) was added Dess-Martin periodinane (0.14 g, 0.32 mmol). The reaction was stirred for 1.5 h, then quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and the reaction mixture was stirred for 30 min at rt. The aqueous phase was extracted with Et_2O (2 × 7 mL), the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to deliver the ketone **368** (93 mg, 0.24 mmol) which was used without further purification.

(4a*R*,6*R*,7*S*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-8a-methyl-7-vinyl-octahydro-1,3,8,10-tetraoxa-2-sila-anthracen-6-ol: 297



$C_{20}H_{36}O_5Si$
Molecular weight: 384.6 g.mol^{-1}

To a solution of ketone **368** (93 mg, 0.24 mmol) in a mixture of MeOH (3.6 mL) and CH_2Cl_2 (3.6 mL) was added sodium borohydride (9.1 mg, 0.24 mmol). After 10 min, another portion of sodium borohydride (14 mg, 0.24 mmol) was added and the reaction mixture was stirred for another 10 min. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL). The aqueous phase was extracted with Et_2O (3 × 8 mL), the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 2:1 → 1:1) delivered the alcohol **297** (85 mg, 0.22 mmol, 90% (2 steps)) as a white solid.

R_f = 0.45 (PE-Et_2O; 1:2)

m.p. = 135−137 °C

$[\alpha]_D$ (19 °C, $CHCl_3$) = −42.6 (c = 1.05)

IR : ν_{max} 3439, 2934, 2859, 1474, 1103, 1053, 826 cm^{-1}.

^{1}**H NMR** : δ 5.80 (1H, ddd, J = 17.3, 10.1, 7.2 Hz, CH-10), 5.40 (1H, d, J = 17.3

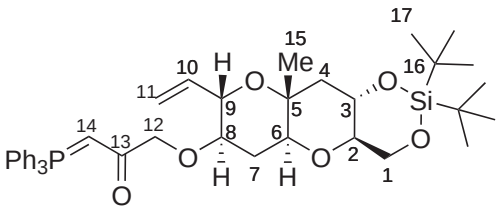
Hz, CH_2-C11a), 5.34 (1H, d, J = 10.1 Hz, CH_2-C11b), 4.17 (1H, dd, J = 10.9, 4.8 Hz, CH_2-C1a), 3.95 (1H, ddd, J = 9.6, 9.6, 4.9 Hz, CH-C3), 3.88−3.84 (1H, dd, J = 9.2, 7.2 Hz, CH-C9), 3.83 (1H, dd, J = 10.9, 10.9 Hz, CH_2-C1b), 3.45−3.36 (2H, m, CH-C2 and CH-C8), 3.25 (1H, dd, J = 12.5, 3.7 Hz, CH-C6), 2.25 (1H, dd, J = 9.6, 4.8 Hz, CH_2-C4a), 2.22−2.16 (1H, m, CH_2-C7a), 1.74 (1H, br s, OH), 1.65−1.52 (2H, m, CH_2-C4b and CH_2-C7b), 1.28 (3H, s, CH_3-C12), 1.04 (9H, s, CH_3-C14), 0.98 (9H, s, CH_3-C14').

^{13}C NMR : δ 136.2 (CH-C10), 119.6 (CH_2-C11), 79.5 (CH-C2), 79.0 (CH-C6), 76.2 (CH-C9), 72.8 (C-C5), 72.5 (CH-C3), 69.9 (CH-C8), 67.1 (CH_2-C1), 46.3 (CH_2-C4), 32.3 (CH_2-C7), 27.5 (CH_3-C14), 27.1 (CH_3-C14'), 22.7 (C-C13), 20.0 (C-C13'), 15.9 (CH_3-C12).

MS (CI) : *m/z (Int)* 385 (100), 367 (26), 327 (8). HRMS ($C_{20}H_{37}O_5Si^+$) : calculated : 383.2410; found : 383.2404, (Δ = 1.6 ppm).

Elemental analysis: calculated for $C_{20}H_{36}O_5Si$: C 62.46, H 9.44; obtained: C 61.96, H 9.37.

1-[(4a*R*,6*R*,7*S*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-8a-methyl-7-vinyl-octahydro-1,3,8,10-tetraoxa-2-sila-anthracen-6-yloxy]-3-(triphenyl-λ^5-phosphanylidene)-propan-2-one: 382

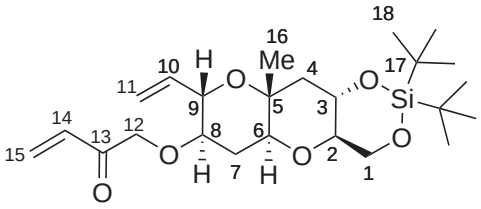


$C_{41}H_{53}O_6PSi$

Molecular weight: 700.9 g.mol^{-1}

To a solution of alcohol **297** (2.05 mg, 5.34 mmol) in THF (113 mL) was added sodium hydride (848 mg, 21.2 mmol). The reaction mixture was stirred for 10 min and TBAI (98 mg, 0.27 mmol) and phosphorane **333** (2.24 g, 6.36 mmol) were added. The reaction mixture was stirred for 3 h at reflux, then cooled to 0 °C and H_2O (20 mL) was added carefully. The aqueous phase was extracted with Et_2O (3 × 40 mL), the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Filtration on silica gel ($CHCl_3$-MeOH; 98:2 → 95:5) gave the phosphorane **382** (3.74 g, 5.34 mmol, quant), which was used directly in the next step.

1-[(4a*R*,6*R*,7*S*,8a*R*,9a*S*,10a*S*)-2,2-Di-*tert*-butyl-8a-methyl-7-vinyl-octahydro-1,3,8,10-tetraoxa-2-sila-anthracen-6-yloxy]-but-3-en-2-one: 296



$C_{24}H_{40}O_6Si$
Molecular weight: 452.7 g.mol^{-1}

To a solution of phosphorane **369** (3.74 g, 5.34 mmol) in Et_2O (45 mL) and pH=7 buffer (23 mL) was added a solution of formaldehyde (4.33 mL, 53.4 mmol) in water (37 %wt). The reaction was stirred for 1.5 h and diluted with H_2O (40 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL), the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 25% → 33%) delivered the enone **296** (1.51 mg, 3.34 mmol, 63% (2 steps)) as a colourless oil.

R_f = 0.64 ($CHCl_3$:MeOH; 9:1)

$[\alpha]_D$ (22.7 °C, $CHCl_3$) = −65.7 (c = 0.85)

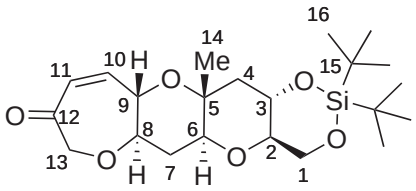
IR : ν_{max} 2934, 2861, 1701, 1474, 1098, 1056, 826 cm^{-1}.

^{1}H NMR : δ 6.53 (1H, dd, J = 17.7, 10.6 Hz, CH-C14), 6.32 (1H, dd, J = 17.7, 1.3 Hz, CH_2-C15a), 5.92 (1H, ddd, J = 17.5, 10.4, 6.3 Hz, CH-C10), 5.82 (1H, dd, J = 10.6, 1.3 Hz, CH_2-C15b), 5.41 (1H, ddd, J = 17.5, 1.8, 1.3 Hz, CH_2-C11a), 5.26 (1H, ddd, J = 10.4, 1.8, 1.0 Hz, CH_2-C11b), 4.31 (1H, d, J = 16.6 Hz, CH_2-C12a), 4.24 (1H, d, J = 16.6 Hz, CH_2-C12b), 4.15 (1H, dd, J = 10.1, 4.8 Hz, CH_2-C1a), 4.02 (1H, dd, J = 9.3, 6.3 Hz, CH-C9), 3.94 (1H, ddd, J = 11.3, 10.3, 4.9 Hz, CH-C3), 3.82 (1H, dd, J = 10.3, 10.1 Hz, CH_2-C1b), 3.39 (1H, ddd, J = 10.3, 10.3, 4.8 Hz, CH-C2), 3.23−3.15 (2H, m, CH-C8 and CH-C6), 2.32−2.23 (2H, m, CH_2-C7a and CH_2-C4a), 1.68−1.53 (2H, m, CH_2-C7b and CH_2-C4b), 1.28 (3H, s, CH_3-C16), 1.04 (9H, s, CH_3-C18), 0.98 (9H, s, CH_3-C18').

^{13}C NMR : δ 196.7 (C-C13), 136.2 (CH-C10), 132.2 (CH-C14), 129.5 (CH_2-C15), 118.1 (CH_2-C11), 79.4 (CH-C2), 79.2 (CH-C8), 78.7 (CH-C6), 73.8 (CH_2-C12), 73.3 (CH-C9), 72.6 (C-C5), 72.4 (CH-C3), 67.0 (CH_2-C1), 46.3 (CH_2-C4), 30.4 (CH_2-C7), 27.5 (CH_3-C18), 27.1 (CH_3-C18'), 22.7 (C-C17), 20.0 (C-C17'), 15.9 (CH_3-C16).

MS (CI) : *m/z (Int)* 453 (58), 413 (18), 367 (30), 81 (54), 69 (100). HRMS ($C_{24}H_{40}O_6Si^+$) : calculated : 453.2672; found : 453.2670, (Δ = 0.4 ppm).

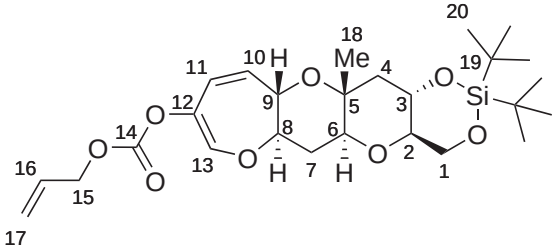
(4a*R*,5a*S*,6a*R*,11a*S*,12a*R*,13a*S*)-2,2-Di-*tert*-butyl-12a-methyl-4a,5a,6,6a,11a,12a,13,13a-octahydro-4H-1,3,5,7,12-pentaoxa-2-sila-cyclohepta[*b*]anthracen-9-one: 295



$C_{22}H_{36}O_6Si$
Molecular weight: 424.6 g.mol^{-1}

To a solution of enone **296** (735 mg, 1.63 mmol) in CH_2Cl_2 (326 mL) was added Grubbs second generation catalyst (69.1 mg, 82.0 μmol) and the reaction mixture was stirred at reflux for 24h. The solution was concentrated under reduced pressure and the crude residue was purified by flash column chromatography on silica gel (PE-Et_2O; 25%) to afford tricyclic enone **295** (584 mg, 1.38 mmol, 84%) as a white solid.
R_f = 0.24 (PE-Et_2O; 4:1)
m.p = 205−207 °C
$[\alpha]_D$ (23.6 °C, $CHCl_3$) = +44.1 (c = 0.96)
IR : ν_{max} 2934, 2859, 1672, 1472, 1101, 1051, 826 cm^{-1}.
^{1}**H NMR** : δ 6.51 (1H, dd, J = 12.8, 2.3 Hz, CH-C10), 6.03 (1H, dd, J = 12.8, 2.6 Hz, CH-C11), 3.37 (1H, d, J = 18.4 Hz, CH_2-C13a), 4.25 (1H, d, J = 18.4 Hz, CH_2-C13b), 4.30 (1H, ddd, J = 9.1, 2.6, 2.3 Hz, CH-C9), 4.17 (1H, dd, J = 10.2, 4.8 Hz, CH_2-C1a), 3.95 (1H, ddd, J = 11.4, 9.3, 5.0 Hz, CH-C3), 3.82 (1H, dd, J = 10.2, 10.1 Hz, CH_2-C1b), 3.46 (1H, ddd, J = 11.1, 9.1, 5.1 Hz, CH-C8), 3.39 (1H, ddd, J = 10.1, 9.3, 4.8 Hz, CH-C2), 3.21 (1H, dd, J = 12.6, 3.8 Hz, CH-C6), 2.26 (1H, dd, J = 11.4, 5.0 Hz, CH_2-C4a), 2.24−2.19 (1H, m, CH_2-C7a), 1.73 (1H, ddd, J = 12.6, 11.8, 11.1 Hz, CH_2-C7b), 1.56 (1H, dd, J = 11.4, 11.4 Hz, CH_2-C4b), 1.30 (3H, s, CH_3-C14), 1.04 (9H, s, CH_3-C16), 0.98 (9H, s, CH_3-C16').
^{13}**C NMR** : δ 201.2 (C-C12), 146.6 (CH-C10), 128.0 (CH-C11), 79.8 (CH-C8), 79.5 (CH-C2), 78.7 (CH-C6), 77.2 (CH_2-C13), 73.3 (C-C5), 73.1 (CH-C9), 72.3 (CH-C3), 67.0 (CH_2-C1), 46.1 (CH_2-C4), 31.5 (CH_2-C7), 27.5 (CH_3-C16), 27.1 (CH_3-C16'), 22.7 (C-C15), 20.0 (C-C15'), 15.4 (CH_3-C14).
MS (CI) : *m/z (Int)* 425 (100), 367 (18), 69 (13). HRMS ($C_{22}H_{37}O_6Si^+$) : calculated : 425.2359; found : 425.2360, (Δ = 0.2 ppm).
Elemental analysis: calculated : C 62.23, H 8.55; found : C 62.36, H 8.74.

Carbonic acid allyl ester (4a*R*,5a*S*,6a*R*,11a*S*,12a*R*,13a*S*)-2,2-di-*tert*-butyl-12a-methyl-4a,5a,6,6a,11a,12a,13,13a-octahydro-4H-1,3,5,7,12-pentaoxa-2-sila-cyclohepta[*b*]anthracen-9-yl ester: 347



$C_{26}H_{40}O_8Si$

Molecular weight: 508.7 g.mol^{-1}

To a solution of enone **295** (0.14 g, 0.32 mmol) in THF (3.2 mL) at −78 °C was added allylchloroformate (51 μL, 0.48 mmol). The mixture was stirred for 2 min at −78 °C and a solution of NaHMDS (0.48 mL, 0.48 mmol) in THF (1 M) was added. The solution was stirred for 30 min at −78 °C. A 5% aqueous solution of KH_2PO_4 (2 mL) was added and the soltuion was diluted with Et_2O (15 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 95:5→9:1→1:1) delivered the enol carbonate **347** (130 mg, 0.26 mmol, 80%) as a white solid, as well as 20 mg of starting material (95% BRSM).

R_f = 0.43 (PE-Et_2O; 4:1)

m.p = 142−144 °C

$[\alpha]_D$ (24.5 °C, $CHCl_3$) = −5.6 (c = 1.00)

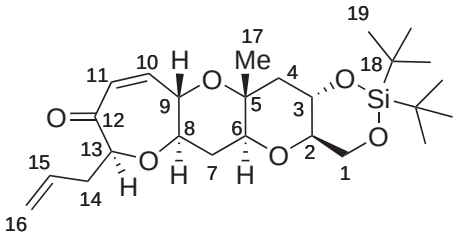
IR : ν_{max} 2934, 2860, 1763, 1474, 1251, 1224, 1103, 1049 cm^{-1}.

^{1}**H NMR** : δ 6.70 (1H, s, CH-C13), 6.00−5.90 (1H, m, CH-C16), 5.78−5.70 (2H, m, CH-C10 and CH_2-C11), 5.39 (1H, dtd, J = 17.2, 1.3, 1.1 Hz, CH_2-C17a), 5.31 (1H, dtd, J = 10.4, 1.3, 1.1 Hz, CH_2-C17b), 4.67 (2H, dt, J = 5.8, 1.3 Hz, CH_2-C15), 4.20−4.15 (2H, m, CH_2-C1a and CH-C9), 3.95 (1H, ddd, J = 11.4, 9.4, 5.1 Hz, CH-C3), 3.83 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.65 (1H, ddd, J = 11.4, 7.5, 5.7 Hz, CH-C8), 3.41 (1H, ddd, J = 10.2, 9.4, 5.1 Hz, CH-C2), 3.24 (1H, dd, J = 12.8, 4.0 Hz, CH-C6), 2.39−2.33 (1H, m, CH_2-C7a), 2.25 (1H, dd, J = 11.8, 5.1 Hz, CH_2-C4a), 1.78 (1H, ddd, J = 12.8, 12.0, 11.4 Hz, CH_2-C7b), 1.57 (1H, dd, J = 11.8, 11.4 Hz, CH_2-C4b), 1.27 (3H, s, CH_3-C18), 1.04 (9H, s, CH_3-C20), 0.98 (9H, s, CH_3-C20').

^{13}**C NMR** : δ 154.6 (C-C14), 141.9 (CH-C13), 133.1 (C-C12), 131.1 (CH-C16), 130.7 (CH), 120.8 (CH), 119.5 (CH_2-C17), 79.4 (CH-C2), 78.2 (CH-C6), 77.0 (CH-C8), 72.4 (CH-C3), 71.9 (C-C5), 70.4 (CH-C9), 69.2 (CH_2-C15), 67.0 (CH_2-C1), 46.0 (CH_2-C4), 31.1 (CH_2-C7), 27.5 (CH_3-C20), 27.1 (CH_3-C20'), 22.7 (C-C19), 20.0 (C-C19'), 15.2 (CH_3-C18).

MS (FAB) : *m/z (Int)* 509 (25), 451 (28), 423 (20), 227 (76), 213 (30), 75 (100). HRMS ($C_{26}H_{41}O_8Si^+$) : calculated : 509.2571; found : 509.2575, (Δ = 0.8 ppm).
Elemental analysis: calculated : C 61.39, H 7.93; found : C 61.61, H 8.05.

(4a*R*,5a*S*,6a*R*,8*S*,11a*S*,12a*R*,13a*S*)-8-Allyl-2,2-di-*tert*-butyl-12a-methyl-4a,5a,6,6a,11a,12a,13,13a-octahydro-4H-1,3,5,7,12-pentaoxa-2-sila-cyclohepta[*b*]-anthracen-9-one: 338a



$C_{25}H_{40}O_6Si$
Molecular weight: 464.7 g.mol^{-1}

From carbonate **347**: To a solution of tris(dibenzylideneacetone)dipalladium (8.2 mg, 9.0 μmol) in THF (2 mL) was added (*S*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline (8.7 mg, 22 μmol). The solution was stirred for 30 min at rt and a solution of enol carbonate **347** (93 mg, 0.18 mmol) in THF (3.4 mL) was added to the reaction mixture, which was stirred for 2 h at rt. The solution was concentrated under reduced pressure and purification by flash column chromatography on silica gel (PE-Et_2O; 95:5→9:1) delivered the ketone **338a** (73 mg, 0.16 mmol, 87%), contaminated with dibenzylideneacetone.

From enone **295**: To a solution of enone **295** (0.14 g, 0.34 mmol) in toluene (3.4 mL) was added 1-aminopiperidine (180 μL, 1.7 mmol). The solution was heated at 100 °C for 20 h with a Dean-Stark apparatus. The solution was concentrated under reduced pressure and the crude was filtered through a small pad of deactivated alumina (PE-Et_2O; 3:1) to give the hydrazone **339** (0.12 g, 0.24 mmol) as a yellow oil, which was used directly in the next step.

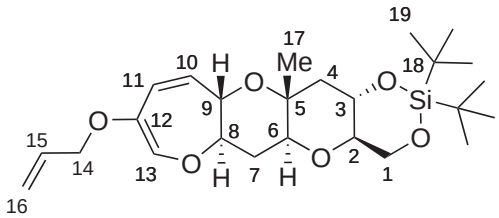
To a solution of hydrazone **339** (0.12 g, 0.24 mmol) in THF (5 mL) at −100 °C was added dropwise a solution of *tert*-butyllithium (0.23 mL, 0.36 mmol) in hexanes (1.6 M). The solution was stirred for 30 min at −78 °C and allyl bromide (62 μL, 0.72 mmol) was added. The solution was stirred for 4 h at −78 °C and a saturated aqueous solution of NH_4Cl (10 mL) was added. The aqueous phase was extracted with Et_2O (3 × 10 mL), the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude alkylated hydrazone (0.13 g, 0.24 mmol) which was used directly in the next step.

To a solution of crude hydrazone (0.13 g, 0.24 mmol) in THF (1 mL) was added a solution of $CuCl_2$ (0.13 g, 0.96 mmol) in H_2O (1 mL). The mixture was stirred vigor-

ously for 1.5 h at rt and a 50% solution of NH_4OH in NH_4Cl (10 mL) was added. The aqueous phase was extracted with Et_2O (3 × 10 mL), the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 4:1→3:1) delivered the enone **338** (31 mg, 66 μmol, 19% over 3 steps) as a mixture (1:5) of diastereoisomers as a colourless oil.

To a solution of a mixture (1:5) of diastereoisomeric enones **338a** and **338b** (26 mg, 56 μmol) in CH_2Cl_2 (8 mL) was added DBU (25 μL, 170 mmol). The reaction was stirred overnight at rt and diluted with EtOAc (10 mL). The organic phases were washed with a saturated aqueous solution of $KHSO_4$ (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 10%) delivered the enone **338a** (18 mg, 38 μmol, 68%) as a mixture of diastereomers (8:1, **338a**:**338b**).

Allyl enol ether: 348



$C_{25}H_{40}O_6Si$
Molecular weight: 464.7 g.mol^{-1}

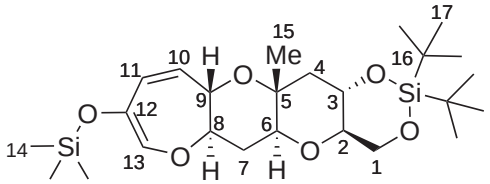
To a solution of tris(dibenzylideneacetone)dipalladium (2.7 mg, 3.0 μmol) in toluene (1.6 mL) was added triphenylphosphine (7.7 mg, 29 μmol). The solution was stirred for 5 min and carbonate **347** (30 mg, 59 μmol) in toluene (2 mL) was added. After 3 h at rt, the reaction mixture was concentrated under reduced pressure and purification by flash column chromatography on silica gel (PE-Et_2O; 95:5→9:1) delivered the ketone **338** (18 mg, 39 μmol, 66%) as a mixture of diastereomers (3:2, **338a**:**338b**) and allyl enol ether **348** (7.2 mg, 16 μmol, 27%) as a colourless oil.
R_f = 0.56 (PE-Et_2O; 4:1)
$[\alpha]_D$ (22.9 °C, $CHCl_3$) = −4.3 (c = 0.36)
IR : ν_{max} 2934, 2859, 1474, 1159, 1102, 1050, 843, 827 cm^{-1}.
^{1}**H NMR** : δ 6.49 (1H, s, CH-C13), 5.93 (1H, ddt, J = 17.2, 10.4, 5.6 Hz, CH-C15), 5.86 (1H, ddd, J = 12.5, 2.6, 1.8 Hz, CH-C10 or C11), 5.68 (1H, dd, J = 12.5, 1.8 Hz, CH-C11 or C10), 5.30 (1H, ddt, J = 17.2, 1.5, 1.5 Hz, CH_2-C16a), 5.22 (1H, ddd, J = 10.4, 1.5, 1.5 Hz, CH_2-C16b), 4.17 (1H, dd, J = 10.0, 4.8 Hz, CH_2-C1a), 4.15−4.12 (3H, m, CH-C9 and CH_2-C14), 3.95 (1H, ddd, J = 11.1, 9.3, 4.8 Hz, CH-C3), 3.83 (1H, dd, J = 10.2, 10.0 Hz, CH_2-C1b), 3.48 (1H, ddd, J = 11.3, 7.7, 5.4 Hz, CH-C8), 3.40

(1H, ddd, J = 10.2, 9.3, 4.8 Hz, CH-C2), 3.23 (1H, dd, J = 12.8, 3.9 Hz, CH-C6), 2.31 (1H, ddd, J = 12.0, 5.4, 3.9 Hz, CH_2-C7a), 2.26 (1H, dd, J = 11.8, 4.8 Hz, CH_2-C4a), 1.75 (1H, ddd, J = 12.8, 12.0, 11.3 Hz, CH_2-C7b), 1.58 (1H, dd, J = 11.8, 11.1 Hz, CH_2-C4b), 1.27 (3H, s, CH_3-C17), 1.04 (9H, s, CH_3-C19), 0.98 (9H, s, CH_3-C19').

^{13}C NMR : δ 140.0 (C-C12), 136.3 (CH-C13), 133.8 (CH-C10), 130.4 (CH-C11), 122.9 (CH-C15), 117.7 (CH_2-C16), 79.5 (CH-C2), 78.7 (CH-C6), 77.1 (CH-C8), 72.5 (CH-C3), 72.1 (C-C5), 72.1 (CH_2-C14), 70.8 (CH-C9), 67.2 (CH_2-C1), 46.3 (CH_2-C4), 31.5 (CH_2-C7), 27.6 (CH_3-C19), 27.2 (CH_3-C19'), 22.8 (C-C18), 20.1 (C-C18'), 15.5 (CH_3-C17).

MS (CI) : *m/z (Int)* 465 (16), 407 (100). HRMS ($C_{25}H_{41}O_6Si^+$) : calculated : 465.2672; found : 465.2675, (Δ = 0.6 ppm).

Trimethylsilyl enol ether: 349



$C_{25}H_{44}O_6Si_2$

Molecular weight: 496.8 g.mol^{-1}

To a solution of enone **295** (52 mg, 0.12 mmol) in THF (2.4 mL) at 0 °C was added triethylamine (100 μL, 0.72 mmol) and TMSOTf (54 μL, 0.36 mmol). The solution was then warmed to rt and stirred for 1h30. A saturated aqueous solution of $NaHCO_3$ (3 mL) was added and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Filtration on a short plug of oven-dried silica gel (PE-Et_2O; 5%) gave the silyl enol ether **349** (55 mg, 0.11 mmol, 94%) as a colourless oil.

R_f = 0.68 (PE-Et_2O; 4:1)

$[\alpha]_D$ (23.5 °C, $CHCl_3$) = −7.2 (c = 1.04)

IR : ν_{max} 2933, 2860, 1474, 1255, 1100, 1050, 842, 826 cm^{-1}.

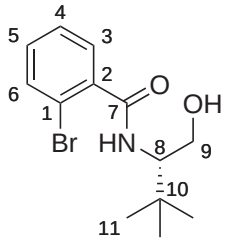
^{1}H NMR : δ 6.43 (1H, s, CH-C13), 5.74 (1H, ddd, J = 12.4, 2.5, 1.6 Hz, CH-C11), 5.60 (1H, dd, J = 12.4, 1.8 Hz, CH-C10), 4.17 (1H, dd, J = 10.1, 4.9 Hz, CH_2-C1a), 4.13 (1H, d, J = 7.6 Hz, CH-C9), 3.95 (1H, ddd, J = 11.2, 9.3, 4.9 Hz, CH-C3), 3.84 (1H, dd, J = 10.2, 10.1 Hz, CH_2-C1b), 3.47 (1H, ddd, J = 11.3, 7.6, 5.5 Hz, CH-C8), 3.40 (1H, dd, J = 10.2, 9.3, 4.9 Hz, CH-C2), 3.24 (1H, dd, J = 12.8, 3.9 Hz, CH-C6), 2.32 (1H, ddd, J = 12.1, 5.5, 3.9 Hz, CH_2-C7a), 2.25 (1H, dd, J = 11.7, 4.9 Hz, CH_2-C4a), 1.75 (1H, ddd, J = 12.8, 12.1, 11.3 Hz, CH_2-C7b), 1.58 (1H, dd, J = 11.7, 11.2 Hz,

CH_2-C4b), 1.27 (3H, s, CH_3-C15), 1.04 (9H, s, CH_3-C17), 0.98 (9H, s, CH_3-C17'), 0.17 (9H, s, CH_3-C14).

^{13}C NMR : δ 137.5 (CH-C13), 134.8 (C-C12), 129.3 (CH-C10), 124.8 (CH-C11), 79.3 (CH-C2), 78.5 (CH-C6), 76.8 (CH-C8), 72.4 (CH-C3), 71.9 (C-C5), 70.6 (CH-C9), 66.9 (CH_2-C1), 46.1 (CH_2-C4), 31.3 (CH_2-C7), 27.4 (CH_3-C17), 27.0 (CH_3-C17'), 22.6 (C-C16), 19.9 (C-C16'), 15.3 (CH_3-C15), -0.1 (CH_3-C14).

MS (CI): *m/z (Int)* 496 (83), 199 (20), 169 (20), 83 (100), 73 (54). HRMS ($C_{25}H_{44}O_6Si_2^+$): calculated: 496.2676; obtained: 496.2672, (Δ = 0.8 ppm).

(*S*)-2-bromo-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide: 383



$C_{13}H_{18}BrNO_2$
Molecular weight: 300.2 g.mol^{-1}

To a solution of (*S*)-*tert*-leucinol (500 mg, 4.27 mmol) in CH_2Cl_2 (14 mL) was added a solution of Na_2CO_3 (1.36 g, 12.8 mmol) in H_2O (10.5 mL) and 2-bromobenzoyl chloride (648 μL, 4.96 mmol). The reaction mixture was stirred overnight at rt. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL) and to the combined organic phases was added a 1 M solution of KOH in MeOH (2 mL). The solution was stirred for 15 min at rt and the pH of the solution was adjusted to 7 by adding a 1 M aqueous solution of HCl. The aqueous phase was then extracted with CH_2Cl_2 (2 × 15 mL), the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-acetone = 3:1→65:35) gave the amide **383** (1.20 g, 4.00 mmol, 94%) as a colourless solid.

R_f = 0.50 (PE-acetone; 1:1)

m.p. = 117−119 °C, lit.[225] **m.p.** = 110−112 °C

$[\alpha]_D$ (22.1 °C, $CHCl_3$) = −3.1 (c = 1.00), lit.[225] $[\alpha]_D$ (21 °C, $CHCl_3$) = −2.2 (c = 1.00)

IR : ν_{max} 3240, 3069, 2961, 1636, 1555, 1468, 1367, 1052, 1020 cm^{-1}.

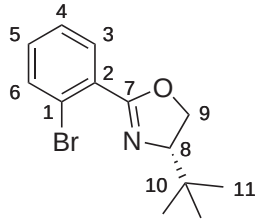
^{1}H NMR : δ 7.59 (1H, dd, J = 8.0, 1.1 Hz, CH Arom), 7.56 (1H, dd, J = 7.6, 1.8 Hz, CH Arom), 7.36 (1H, ddd, J = 8.0, 7.6, 1.1 Hz, CH Arom), 7.31−7.25 (1H, m, CH Arom), 6.17 (1H, br s, NH), 4.07 (1H, ddd, J = 11.0, 7.6, 3.5 Hz, CH-C8), 3.95 (1H, dd, J = 11.4, 3.5 Hz, CH_2-C9a), 3.68 (1H, dd, J = 11.4, 7.6 Hz, CH_2-C9b), 2.39 (1H, br s, OH), 1.04 (9H, s, CH_3-C11).

^{13}C NMR : δ 168.8 (C-C7), 138.0 (C-C2), 133.5 (CH Arom), 131.5 (CH Arom), 129.9 (CH Arom), 127.8 (CH Arom), 119.2 (C-C1), 63.8 (CH-C8), 60.5 (CH_2-C9), 33.9 (C-C10), 272. (CH_3-C11).

MS (CI): *m/z (Int)* 302 (63), 300 (64), 222 (100), 204 (34), 107 (31).

HRMS ($C_{13}H_{19}BrNO_2^+$): calculated: 300.0599; obtained: 300.0596, (Δ = 1.0 ppm).

(*S*)-2-(2-bromophenyl)-4-tert-butyl-4,5-dihydrooxazole: 352



$C_{13}H_{16}BrNO$

Molecular weight: 282.2 g.mol^{-1}

To a solution of amide **383** (1.2 g, 3.9 mmol) in CH_2Cl_2 (29 mL), was added *p*-toluenesulfonyl chloride (0.97 g, 5.1 mmol) and triethylamine (2.7 mL, 19 mmol). The reaction mixture was stirred for 22 h at 55 °C, then H_2O (4 mL) was added and the reaction mixture was stirred for another 2 h at 75 °C. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL), the combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-EtOAc; 97:3→95:5→92:8→9:1) gave the oxazole **352** (0.83 g, 2.9 mmol, 75%) as a white solid.[226]

R_f = 0.54 (PE-acetone; 1:1)

m.p. = 49−50 °C, lit.[227] **m.p.** = 47−48 °C

$[\alpha]_D$ (24.2 °C, $CHCl_3$) = −70.0 (c = 1.00), lit.[228] $[\alpha]_D$ (24.2 °C, $CHCl_3$) = −87.0 (c = 2.6)

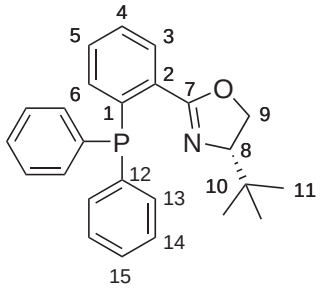
IR : ν_{max} 2959, 2866, 1661, 1588, 1477, 1358, 1273, 1241, 1207, 1096, 1023, 960, 907, 760 cm^{-1}.

^{1}H NMR : δ 7.66 (1H, J = 7.6, 1.9 Hz, CH Arom), 7.63 (1H, dd, J = 8.0, 1.3 Hz, CH Arom), 7.34 (1H, ddd, J = 7.6, 7.5, 1.3 Hz, CH Arom), 7.30−7.25 (1H, m, CH Arom), 4.39 (1H, dd, J = 10.2, 8.1 Hz, CH_2-C9a), 4.26 (1H, dd, J = 8.6, 8.1 Hz, CH_2-C9b), 4.11 (1H, dd, J = 10.2, 8.6 Hz, CH-C8), 1.00 (9H, s, CH_3-C11).

^{13}C NMR : δ 162.8 (C-C7), 133.7 (CH Arom), 131.5 (CH Arom), 131.3 (CH Arom), 130.3 (C-C2), 127.1 (CH Arom), 121.9 (C-C1), 76.7 (CH-C8), 69.0 (CH_2-C9), 34.0 (C-C10), 26.0 (CH_3-C11).

MS (CI): *m/z (Int)* 284 (85), 282 (89), 204 (100). HRMS ($C_{13}H_{16}BrNO^+$): calculated: 282.0494; obtained: 282.0498, (Δ = 1.4 ppm).

(*S*)-4-*tert*-butyl-2-(2-(diphenylphosphino)phenyl)-4,5-dihydrooxazole: 345



$C_{25}H_{26}NOP$

Molecular weight: 387.5 g.mol^{-1}

To a solution of copper iodide (8.3 mg, 44 μmol) in toluene (1.5 mL) was added DMEDA (33 μL, 0.31 mmol) and diphenylphosphine (0.12 mL, 0.66 mmol). The reaction mixture was stirred for 20 min at rt and aryl bromide **352** (0.10 g, 0.35 mmol), cesium carbonate (0.43g, 1.3 mmol) and toluene (1.5 mL) were added. The flask was sealed and the stirring was continued for 6 h at 110 °C. The reaction mixture was filtered, the solid residue washed with CH_2Cl_2 (2 × 2 mL) and the combined organic phases were concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 97:3→95:5→93:7) gave the phosphine **345** (86 mg, 0.22 mmol, 62%) as a white solid.

R_f = 0.21 (PE-Et_2O; 9:1)

m.p. = 109−112 °C, lit.[227] **m.p.** = 113−114 °C

$[\alpha]_D$ (23.7 °C, $CHCl_3$) = −72.4 (c = 0.98), lit.[229] $[\alpha]_D$ (21 °C, $CHCl_3$) = −61.9 (c = 1.76)

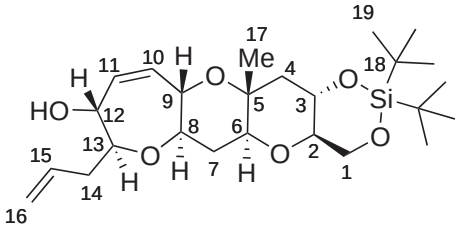
IR : ν_{max} 2959, 1661, 1589, 1477, 1358, 1338, 1096, 1023, 959, 907, 760 cm^{-1}.

^{1}H NMR : δ 7.96−7.92 (1H, m, CH Arom), 7.38−7.22 (12H, m, CH Arom), 6.88−6.85 (1H, m, CH Arom), 4.08 (1H, dd, J = 10.2, 8.4 Hz, CH_2-C9a), 4.01 (1H, dd, J = 8.4, 8.2 Hz, CH_2-C9b), 3.88 (1H, dd, J = 10.2, 8.2 Hz, CH-C8), 0.72 (9H, s, CH_3-C11).

^{13}C NMR : δ 162.8 (C-C7), 138.9 (d, J = 25.7 Hz, C-Arom), 138.6 (C Arom), 138.3 (C Arom), 138.1 (C Arom), 134.5 (d, J = 21.0 Hz, CH Arom), 134.3 (CH Arom), 133.7 (d, J = 20.2 Hz, CH Arom), 130.5 (CH Arom), 130.0 (d, J = 3.1 Hz, CH Arom), 128.6 (d, J = 10.0 Hz, CH Arom), 128.5 (CH Arom), 128.4 (d, J = 5.9 Hz, CH Arom), 128.4 (CH Arom), 128.2 (CH Arom), 76.8 (CH-C8), 68.4 (CH_2-C9), 33.8 (C-C10), 25.9 (CH_3-C11).

MS (EI) : *m/z (Int)* 387 (9), 272 (12), 330 (74), 302 (100). HRMS ($C_{25}H_{26}NOP^+$) : calculated : 387.1752; obtained : 387.1750, (Δ = 0.5 ppm).

(4a*R*,5a*S*,6a*R*,8*S*,9*R*,11a*S*,12a*R*,13a*S*)-8-Allyl-2,2-di-*tert*-butyl-12a-methyl-4a,5a,6,6a,8,9,11a,12a,13,13a-decahydro-4H-1,3,5,7,12-pentaoxa-2-sila-cyclo hepta[*b*]anthracen-9-ol: 353



$C_{25}H_{42}O_6Si$
Molecular weight: 466.7 g.mol^{-1}

To a solution of ketone **338a** (73 mg, 0.16 mmol) in CH_2Cl_2 (1.7 mL) and MeOH (1.7 mL) was added cerium chloride heptahydrate (63 mg, 0.17 mmol). The solution was cooled to −78 °C and sodium borohydride (7.7, mg, 0.20 mmol) was added. After 1 h at −78 °C, H_2O (3 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 9:1→4:1) delivered the alcohol **349** (71 mg, 0.15 mmol, 95%) as a colourless oil.

R_f = 0.12 (PE-Et_2O; 4:1)

$[\alpha]_D$ (26.5 °C, $CHCl_3$) = −11.7 (c = 1.00)

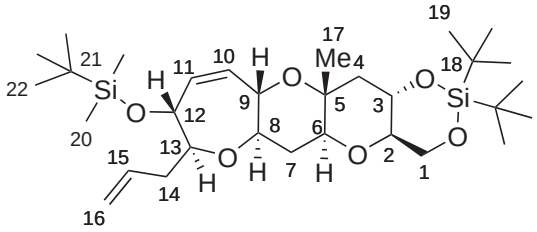
IR : ν_{max} 3464, 2934, 2860, 1474, 1095, 1058, 827, 764 cm^{-1}.

^{1}H NMR : δ 5.93 (1H, dddd, J = 17.2, 10.2, 6.9, 6.9 Hz, CH-C15), 5.67 (1H, ddd, J = 12.9, 1.8, 1.8 Hz, CH-C10), 5.62 (1H, d, J = 12.9 Hz, CH-C11), 5.14−5.10 (1H, m, CH_2-C16a), 5.10−5.05 (1H, m, CH_2-C16b), 4.16−4.13 (3H, m, CH-C9 and CH-C12 and CH_2-C1a), 3.93 (1H, ddd, J = 11.2, 9.4, 4.9 Hz, CH-C3), 3.82 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.40−3.25 (3H, m, CH-C2 and CH-C13 and CH-C8), 3.17 (1H, dd, J = 12.7, 3.8 Hz, CH-C6), 2.59−2.53 (1H, m, CH_2-C14a), 2.29−2.25 (1H, m, CH_2-C14b), 2.22 (1H, dd, J = 11.6, 4.9 Hz, CH_2-C4a), 2.07 (1H, ddd, J = 12.0, 4.5, 3.8 Hz, CH_2-C7a), 1.70 (1H, d, J = 6.0 Hz, OH), 1.62 (1H, ddd, J = 12.7, 12.0, 11.9 Hz, CH_2-C7b), 1.57−1.51 (1H, m, CH_2-C4b), 1.24 (3H, s, CH_3-C17), 1.03 (9H, s, CH_3-C19), 0.98 (9H, s, CH_3-C19').

^{13}C NMR : δ 135.1 (CH-C15), 134.3 (CH-C10 or C11), 132.5 (CH-C11 or C10), 117.2 (CH_2-C16), 84.1 (CH-C13), 80.2 (CH-C8), 79.6 (CH-C2), 79.1 (CH-C6), 73.9 (CH-C12), 72.9 (CH-C9), 72.6 (CH-C3), 72.6 (C-C5), 67.2 (CH_2-C1), 46.4 (CH_2-C4), 37.6 (CH_2-C14), 32.0 (CH_2-C7), 27.6 (CH_3-C19), 27.2 (CH_3-C19'), 22.8 (C-C18), 20.1 (C-C18'), 15.6 (CH_3-C17).

MS (CI) : *m/z (Int)* 467 (96), 449 (100), 409 (28), 327 (12), 107 (15). HRMS ($C_{25}H_{43}O_6Si^+$) : calculated : 467.2829; found : 467.2828, (Δ = 0.2 ppm).

(4a*R*,5a*S*,6a*R*,8*S*,9*R*,11a*S*,12a*R*,13a*S*)-8-Allyl-2,2-di-*tert*-butyl-9-(*tert*-butyl-dimethyl-silanyloxy)-12a-methyl-4a,5a,6,6a,8,9,11a,12a,13,13a-decahydro-4H-1,3,5,7,12-pentaoxa-2-sila-cyclohepta[*b*]anthracene: 354



$\mathbf{C_{31}H_{56}O_6Si_2}$

Molecular weight: 580.9 g.mol^{-1}

To a solution of alcohol **349** (69 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added 2,6-lutidine (110 μL, 0.90 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (100 μL, 0.45 mmol). The solution was stirred for overnight at rt and a saturated aqueous solution of NaH_2CO_3 (5 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 98:2→95:5) delivered the protected alcohol **350** (71 mg, 0.12 mmol, 82%) as a white solid.

R_f = 0.75 (PE-Et_2O; 1:1)

m.p = 64−66 °C

$[\alpha]_D$ (24.2 °C, $CHCl_3$) = −15.8 (c = 0.98)

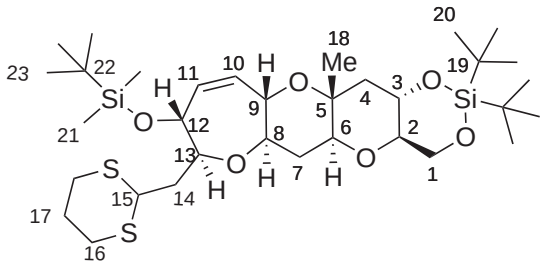
IR : ν_{max} 2931, 2859, 1473, 1252, 1090, 1060, 872, 837, 767 cm^{-1}.

^{1}**H NMR** : δ 5.85 (1H, dddd, J = 17.1, 10.2, 6.8, 6.8 Hz, CH-C15), 5.65 (1H, ddd, J = 12.7, 2.4, 2.4 Hz, CH-C10 or C11), 5.57 (1H, ddd, J = 12.7, 2.1 Hz, CH-C11 or C10), 5.08−5.00 (2H, m, CH_2-C16), 4.18−4.12 (2H, m, CH-C9 and CH_2-C1a), 4.08 (1H, ddd, J = 8.6, 4.1, 2.1 CH-C12), 3.93 (1H, ddd, J = 11.1, 9.3, 4.9 Hz, CH-C3), 3.82 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.40−3.32 (2H, m, CH-C2 and CH-C13), 3.24 (1H, ddd, J = 11.3, 9.3, 5.1 Hz, CH-C8), 3.16 (1H, dd, J = 12.7, 3.9 Hz, CH-C6), 2.53 (1H, dd, J = 14.4, 6.8 Hz, CH_2-C14a), 2.22 (1H, dd, J = 11.7, 4.9 Hz, CH_2-C4a), 2.09−1.97 (2H, m, CH_2-C7a and CH_2-C14b), 1.61 (1H, ddd, J = 12.7, 12.1, 11.3 Hz, CH_2-C7b), 1.58−1.51 (1H, m, CH_2-C4b), 1.24 (3H, s, CH_3-C17), 1.03 (9H, s, CH_3-C19), 0.98 (9H, s, CH_3-C19'), 0.90 (9H, s, CH_3-C22), 0.08 (3H, s, CH_3-C20), 0.06 (3H, s, CH_3-C20').

^{13}**C NMR** : δ 136.5 (CH-C10 or C11), 135.6 (CH-C15), 131.9 (CH-C11 or C10), 116.6 (CH_2-C16), 85.0 (CH-C13), 79.9 (CH-C8), 79.5 (CH-C2), 79.1 (CH-C6), 74.7 (CH-C12), 73.0 (CH-C9), 72.6 (CH-C3), 72.5 (C-C5), 67.2 (CH_2-C1), 46.4 (CH_2-C4), 37.2 (CH_2-C14), 31.9 (CH_2-C7), 27.6 (CH_3-C19), 27.2 (CH_3-C19'), 26.0 (CH_3-C22), 22.8 (C-C18), 20.1 (C-C18'), 18.2 (C-C21), 15.7 (CH_3-C17), -4.2 (CH_3-C20), -4.7 (CH_3-C20').

MS (CI) : *m/z (Int)* 581 (42), 449 (100), 133 (29), 69 (100). HRMS ($C_{31}H_{57}O_6Si_2^+$) : calculated : 581.3694; found : 581.3691, ($\Delta = 0.5$ ppm).
Elemental analysis: calculated : C 64.09, H 9.72; found : C 64.10, H 9.75.

Dithiane: 356



$C_{33}H_{60}O_6S_2Si_2$
Molecular weight: 673.1 g.mol^{-1}

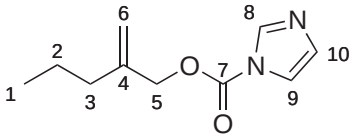
To a solution of diene **350** (0.12 g, 0.21 mmol) in THF (1.8 mL) was added a solution of *N*-methylmorpholin-*N*-oxide (26 mg, 0.22 mmol) in H_2O (0.2 mL) and a solution of osmium tetroxide (92 μL, 14 μmol) in H_2O (4% wt). After stirring overnight at rt, the reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) and stirred for another 15 min at rt. The aqueous phase was extracted with EtOAc (3 × 5 mL), the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography on a short pad of silica gel (PE-Et_2O; 9:1→1:1→pure Et_2O) gave the diol **351** as a 1:1 mixture of diastereoisomers (69 mg, 0.11 mmol, 54%) and 36 mg of starting material (78% BRSM).

To a solution of the diol (69 mg, 0.11 mmol) in THF (0.8 mL) was added a solution of sodium periodate (47 mg, 0.22 mmol) in H_2O (0.3 mL). The solution was stirred for 1.5 h at rt, then diluted with H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic phases were washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure to deliver the crude aldehyde, which was used directly in the next step.

To a solution of crude aldehyde (60 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added 1,3-propanedithiol (20 μL, 0.20 mmol). The solution was cooled to −30 °C and $BF_3{\cdot}Et_2O$ (12 μL, 0.10 mmol) was slowly added. The reaction mixture was stirred for 15 min at −30 °C and a saturated aqueous solution of $NaHCO_3$ (2 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 95:5→9:1) delivered the dithiane **352** (40.4 mg, 60 μmol, 53% over 2 steps) as a colourless oil.
$R_f = 0.58$ (PE-Et_2O; 4:1)
$[\alpha]_D$ (23.5 °C, $CHCl_3$) = +58.6 ($c = 0.27$)
IR : ν_{max} 2932, 2858, 1473, 1253, 1090, 1060, 870, 838, 767 cm^{-1}.

^{1}H NMR : δ 5.64 (1H, ddd, J = 12.8, 2.0, 1.8 Hz, CH-C10 or C11), 5.57 (1H, ddd, J = 12.8, 2.1, 1.8 Hz, CH-C11 or C10), 4.19−4.13 (3H, CH-C9 and CH-C15 and CH_2-C1a), 4.06 (1H, dd, J = 8.6, 1.8 Hz, CH-C12), 3.93 (1H, ddd, J = 11.0, 9.5, 4.9 Hz, CH-C3), 3.83 (1H, dd, J = 10.2, 10.1 Hz, CH_2-C1b), 3.61 (1H, ddd, J = 11.0, 8.6, 2.5 Hz, CH-C13), 3.39 (1H, ddd, J = 10.1, 9.5, 4.7 Hz, CH-C2), 3.30 (1H, ddd, J = 10.9, 9.4, 5.1 Hz, CH-C8), 3.20 (1H, dd, J = 12.6, 3.8 Hz, CH-C6), 2.89−2.70 (4H, m, CH_2-C16), 2.28−2.20 (2H, m, CH_2-C14a and CH_2-C4a), 2.14−2.06 (2H, m, CH_2-C7a and CH_2-C17a), 1.94−1.84 (1H, m, CH_2-C17b), 1.72−1.52 (3H, m, CH_2-C14b and CH_2-C7b and CH_2-C4b), 1.24 (3H, s, CH_3-C18), 1.03 (9H, s, CH_3-C20), 0.97 (9H, s, CH_3-C20'), 0.90 (9H, s, CH_3-C23), 0.07 (3H, s, CH_3-C21), 0.06 (3H, s, CH_3-C21').
^{13}C NMR : δ 136.2 (CH-C10 or C11), 131.9 (CH-C11 or C10), 81.1 (CH-C13), 80.0 (CH-C8), 79.5 (CH-C2), 79.0 (CH-C6), 74.6 (CH-C12), 72.9 (CH-C9), 72.6 (CH-C3), 72.5 (C-C5), 67.2 (CH_2-C1), 46.4 (CH_2-C4), 44.1 (CH-C15), 38.3 (CH_2-C14), 32.0 (CH_2-C7), 30.3 (CH_2-C16), 29.8 (CH_2-C16'), 27.6 (CH_3-C20), 27.2 (CH_3-C20'), 26.3 (CH_2-C17), 26.0 (CH_3-C23), 22.8 (C-C19), 20.1 (C-C19'), 18.1 (C-C22), 15.6 (CH_3-C18), -4.3 (CH_3-C21), -4.6 (CH_3-C21').
MS (FAB) : *m/z (Int)* 695 (6), 615 (9), 557 (24), 228 (83), 123 (93), 78 (100).
Elemental analysis: calculated : C 58.88, H 8.98; found : C 58.71, H 9.04.

2-methylenepentyl 1*H*-imidazole-1-carboxylate: 370



$C_{10}H_{14}N_2O_2$
Molecular weight: 194.2 g.mol^{-1}

To an aqueous solution of formaldehyde (5.7 mL, 70 mmol) was added valeraldehyde (6.2 mL, 58 mmol) and dimethylamine hydrochloride (5.7 g, 70 mmol). The reaction mixture was stirred for 20 h at 70 °C, then diluted with water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated carefully under reduced pressure to deliver the crude unsaturated aldehyde (5.7 g, 58 mmol), which was used directly in the next reaction.

To a solution of crude unsaturated aldehyde (5.7 g, 58 mmol) in MeOH (200 mL) at 0 °C was added $CeCl_3{\cdot}7H_2O$ (22 g, 58 mmol) and $NaBH_4$ (2.7 g, 70 mmol) portionwise. After 30 min at rt, H_2O (200 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and carefully concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 3:1 → 1:1) gave the allylic

alcohol **368** (5.2 g, 5.2 mmol, 89% over 2 steps) which was used directly in the next reaction.

To a solution of allylic alcohol **368** (2.00 g, 20.0 mmol) in THF (100 mL) at 0 °C was added 1,1'-carbonyldiimidazole (4.86 g, 30.0 mmol). After 1 h at 0 °C, the reaction mixture was warmed to rt and stirred for another hour. The solution was concentrated under reduced pressure and purification by flash column chromatography on silica gel (PE-Et_2O; 3:1 → 1:1) delivered the carbamate **370** (3.40 g, 17.5 mmol, 88%) as a colourless oil.

R_f = 0.32 (PE-Et_2O; 1:1)

IR : ν_{max} 2961, 2874, 1759, 1393, 1280, 1237, 1169, 1095 cm^{-1}.

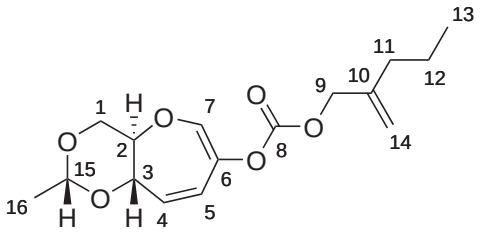
^{1}**H NMR** : δ 8.15 (1H, s, CH-C8), 7.44 (1H, dd, J = 1.4, 1.4 Hz, CH-C9 or CH-C10), 7.08 (1H, s, CH-10 or CH-C9), 5.14 (1H, s, CH_2-C6a), 5.06 (1H, s, CH_2-C6b), 4.84 (2H, s, CH_2-C5), 2.11 (2H, t, J = 7.6 Hz, CH_2-C3), 1.53 (2H, tq, J = 7.6, 7.3 Hz, CH_2-C2), 0.95 (3H, t, J = 7.3 Hz, CH_3-C1).

^{13}**C NMR** : δ 148.5 (C-C7), 142.2 (C-C4), 137.1 (CH-C8), 130.8 (CH-C10), 117.1 (CH-C9), 114.3 (CH_2-C6), 70.5 (CH_2-C5), 35.2 (CH_2-C3), 20.7 (CH_2-C2), 13.7 (CH_3-C1).

MS (FAB): *m/z (Int)* 195 (100), 151 (100), 137 (37), 83 (97), 69 (100), 55 (93), 42 (91).

HRMS ($C_{10}H_{15}O_2N_2^+$): calculated: 195.1134; obtained: 195.1133, (Δ = 0.5 ppm).

(2*R*,4a*R*,9a*S*)-2-methyl-4a,9a-dihydro-4*H*-[1,3]dioxino[5,4-*b*]oxepin-7-yl-2-methylenepentyl carbonate : 372



$C_{16}H_{22}O_6$

Molecular weight: 310.1 $g.mol^{-1}$

Method A: To a solution of carbamate **370** (0.11 g, 0.57 mmol) in THF (1.5 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (70 μL, 0.57 mmol). The solution was stirred for 1 h at rt. Separately, to a solution of enone **371** (76 mg, 0.41 mmol) in THF (2.5 mL) at −78 °C was added NaHMDS (0.29 mL, 0.57 mmol). After 2 min at −78 °C, the solution of carbamate **370** and $BF_3{\cdot}Et_2O$ pre-cooled to −78 °C was added by cannula to the enolate solution at −78 °C and the reaction mixture was stirred for 30 min at −78 °C. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (2 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under

reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 92:8→9:1) gave the carbonate **372** (71 mg, 0.23 mmol, 55%) as a colourless oil.

Method B: To a solution of carbamate **370** (74 mg, 0.38 mmol) in THF (1 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (47 μL, 0.38 mmol). After 1 h at rt, the solution was cooled to −78 °C and a solution of enone **371** (50 mg, 0.27 mmol) in THF (2 mL) was added by cannula into the carbamate solution at −78 °C. The reaction mixture was stirred for 10 min at −78 °C and a solution of KHMDS (0.76 mL, 0.38 mmol) in THF (0.5 M) was added. The reaction mixture was stirred for 30 min at −78 °C. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (2 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (PE-Et_2O; 9:1) gave the carbonate **372** (58 mg, 0.19 mmol, 69%) as a colourless oil.

R_f = 0.68 (PE-Et_2O; 1:1)

$[\alpha]_D$ (23.8 °C, $CHCl_3$) = −6.5 (c = 1.00)

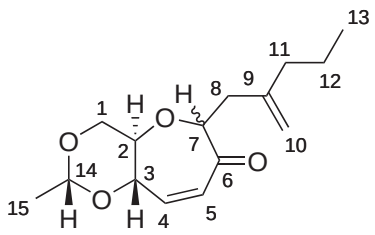
IR : ν_{max} 2961, 2873, 1759, 1406, 1224, 1161, 1132, 1033 cm^{-1}.

^{1}**H NMR** : δ 6.71 (1H, s, CH-C7), 5.83−5.76 (2H, m, CH-C4 and CH-C5), 5.09 (1H, s, CH_2-C14a), 4.99 (1H, s, CH_2-C14b), 4.70 (1H, q, J = 5.0 Hz, CH-C15), 4.61 (2H, s, CH_2-C9), 4.36 (1H, dd, J = 10.2, 4.7 Hz, CH_2-C1a), 4.07 (1H, d, J = 6.7 Hz, CH-C3), 3.57 (1H, ddd, J = 10.4, 6.7, 4.7 Hz, CH-C2), 3.53 (1H, dd, J = 10.4, 10.2 Hz, CH_2-C1b), 2.07 (2H, t, J = 7.6 Hz, CH_2-C11), 1.50 (2H, tq, J = 7.6, 7.3 Hz, CH_2-C12), 1.38 (3H, d, J = 5.0 Hz, CH_3-C16), 0.93 (3H, t, J = 7.3 Hz, CH_3-C13).

^{13}**C NMR** : δ 154.6 (C-C8), 142.9 (C-C6), 142.2 (CH-C7), 133.5 (C-C10), 129.6 (CH), 121.5 (CH), 113.4 (CH_2-C14), 98.5 (CH-15), 77.1 (CH-C3), 71.1 (CH_2-C9), 70.9 (CH-C2), 68.3 (CH_2-C1), 52.2 (CH_2-C11), 20.8 (CH_2-C12), 20.4 (CH_3-C16), 13.9 (CH_3-C13).

MS (FAB): *m/z (Int)* 311 (97), 267 (100), 183 (73). HRMS ($C_{16}H_{23}O_6^+$): calculated: 311.1495; obtained: 311.1497, (Δ = 0.6 ppm).

(2*R*,4a*R*,9a*S*)-2-methyl-6-(2-methylenepentyl)-6,9a-dihydro-4*H*-[1,3]dioxino[5,4-*b*] oxepin-7(4a*H*)-one : 374



$C_{15}H_{22}O_4$

Molecular weight: 266.3 $g.mol^{-1}$

To a solution of $Pd(PPh_3)_4$ (8.4 mg, 7.3 μmol) in THF (1.5 mL) was added (*S*)-*t*Bu-PHOX (4.0 mg, 10 μmol). The reaction mixture was stirred for 30 min at rt. A solution of carbonate **368** (45 mg, 0.15 mmol) in THF (3 mL) was added to the reaction mixture, which was stirred for 2 h at rt. The solution was then concentrated under reduced pressure and purification by flash column chromatography on silica gel (PE-Et_2O; 95:5→9:1) gave the enone **369** (27 mg, 0.10 mmol, 69%), as a mixture (7:1) of isomers favouring that with *cis* configuration, as a colourless oil.

R_f = 0.43 (PE-Et_2O; 4:1)

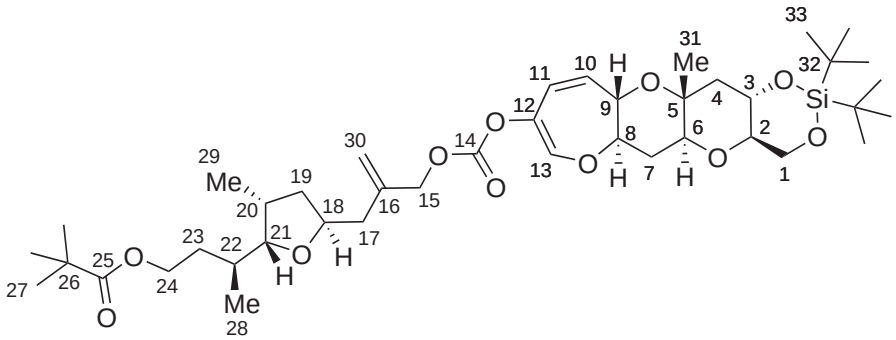
IR : ν_{max} 2959, 29323, 2870, 1665, 1287, 1115, 905 cm^{-1}.

^{1}**H NMR** : δ (major diastereomer) 6.45 (1H, dd, J = 12.7, 2.1 Hz, CH-C4), 6.02 (1H, dd, J = 12.7, 2.6 Hz, CH-C5), 4.80 (1H, s, CH_2-C10a), 4.77 (1H, s, CH_2-C10b), 4.74 (1H, q, J = 5.1 Hz, CH-C14), 4.31 (1H, dd, J = 9.0, 3.5 Hz, CH-C7), 4.19−4.14 (2H, m, CH-C3 and CH_2-C1a), 3.55−3.52 (2H, CH-C2 and CH_2-C1b), 2.57−2.50 (1H, m, CH_2-C8a), 2.31 (1H, dd, J = 15.1, 9.0 Hz, CH_2-C8b), 2.02−1.97 (2H, m, CH_2-C11), 1.48−1.41 (2H, m, CH_2-C12), 1.35 (3H, d, J = 5.1 Hz, CH_3-C15), 0.88 (3H, t, J = 7.3 Hz, CH_3-C13).

^{13}**C NMR** : δ (major diastereomer) 202.7 (C-C6), 144.9 (C-C9), 143.2 (CH-C4), 128.5 (CH-C5), 111.9 (CH_2-C10), 99.4 (CH-C14), 86.4 (CH-C7), 82.0 (CH-C3), 73.8 (CH-C2), 68.4 (CH_2-C1), 39.3 (CH_2-C8), 38.2 (CH_2-C11), 20.6 (CH_2-C12), 20.3 (CH_3-C15), 13.7 (CH_3-C13).

MS (EI): *m/z (Int)* 266 (29), 182 (32), 111 (58), 81 (100). HRMS ($C_{15}H_{22}O_4^+$): calculated: 266.1518; obtained: 266.1520, (Δ = 0.8 ppm).

Carbonate : 361

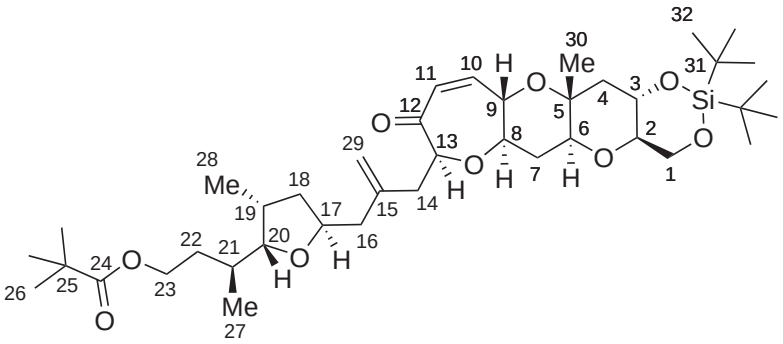


$C_{41}H_{66}O_{11}Si$
Molecular weight: 763.0 $g.mol^{-1}$

To a solution of carbamate **375** (27 mg, 66 μmol) in THF (0.5 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (8.0 μL, 66 μmol). The solution was stirred for 1 h at rt, then cooled to −78 °C. A solution of enone **295** (20 mg, 47 μmol) in THF (0.4 mL) pre-cooled to −78 °C was added by cannula to the first solution. After 10 min at −78 °C, a solution of KHMDS (0.13 mL, 66 μmol) in THF (0.5 M) was added slowly. The re-

action mixture was stirred for 30 min at −78 °C before adding a saturated aqueous solution of NH_4Cl (1 mL) and H_2O (5 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on oven-dried silica gel (PE-Et_2O; 93:7→9:1→85:15) to give the carbonate **361** (11 mg, 14 μmol, 31%), with some starting material enone **295** as a colourless oil. The mixture was directly used in the next step without further purification.

Enone : 362



$C_{40}H_{66}O_9Si$
Molecular weight: 719.0 g.mol^{-1}

A solution of $Pd(PPh_3)_4$ (0.8 mg, 0.7 μmol) and (*S*)-*t*Bu-PHOX (0.4 mg, 1.0 μmol) in THF (0.3 mL) was stirred at rt for 30 min. A solution of carbonate **361** (11 mg, 14 μmol) in THF (0.3 mL) was added to the solution of Pd complex and the reaction mixture was stirred overnight at rt. The reactin mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (PE-Et_2O; 9:1→85:15) to give the single diastereomeric enone **362** (5.6 mg, 7.8 μmol, 57%) as a colourless oil.

R_f = 0.40 (PE-Et_2O; 2:1)

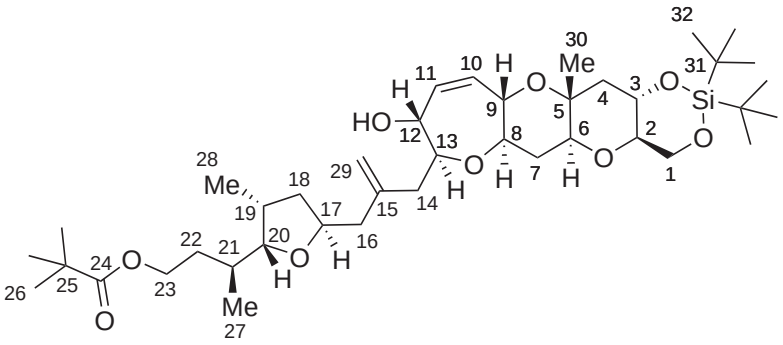
^{1}**H NMR** : δ 6.43 (1H, dd, J = 12.9, 2.3 Hz, CH-C10), 5.98 (1H, dd, J = 12.9, 2.6 Hz, CH-C11), 4.86 (2H, s, CH_2-C29), 4.34 (1H, dd, J = 9.1, 3.2 Hz, CH-C13), 4.26−4.06 (5H, m, CH_2-C1a and CH_2-C23 and CH-C9 and CH-C17), 3.95 (1H, ddd, J = 11.1, 9.6, 4.0 Hz, CH-C3), 3.83 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.47−3.35 (3H, m, CH-C2 and CH-C8 and CH-C20), 3.19 (1H, dd, J = 12.6, 3.7 Hz, CH-C6), 2.63 (1H, dd, J = 15.1, 3.2 Hz, CH_2-C14a), 2.37−2.05 (6H, m, CH_2-C4a and CH_2-C7a and CH_2-C14b and CH_2-C16 and CH-C19), 1.79−1.65 (4H, m, CH_2-C7b and CH_2-C18 and CH-C21), 1.58−1.53 (1H, m, CH_2-C4b), 1.30 (3H, s, CH_3-C30), 1.28−1.22 (2H, m, CH_2-C22), 1.19 (9H, s, CH_3-C26), 1.04 (9H, s, CH_3-C32), 1.04−1.02 (3H, m, CH_3-C27), 0.98 (9H, s, CH_3-C32'), 0.91 (3H, d, J = 7.0 Hz, CH_3-C28).

^{13}**C NMR** : δ 203.2 (C-C12), 178.8 (C-C24), 145.1 (CH-C10), 142.9 (C-C15), 128.3

(CH-C11), 114.4 (CH_2-C29), 86.1 (CH-C13), 85.5 (CH), 79.7 (CH-C2), 79.1 (CH), 79.0 (CH-C6), 75.7 (CH), 73.5 (C-C5), 72.8 (CH), 72.5 (CH-C3), 67.1 (CH_2-C1), 62.2 (CH_2-C23), 46.2 (CH_2-C4), 43.3 (CH_2-C16), 40.7 (CH_2), 39.8 (CH_2-C14), 38.9 (C-C25), 35.1 (CH-C19), 31.9 (CH_2-C22), 31.6 (CH_2-C7), 30.9 (CH_2-C18), 27.6 (CH_3), 27.4 (CH_3), 27.2 (CH_3), 22.8 (C-31), 20.1 (C-31'), 17.0 (CH_3-C27), 15.7 (CH_3-C30), 13.9 (CH_3-C28).

MS (FAB): *m/z (Int)* 719 (37), 391 (55), 241 (34), 149 (78), 95 (74), 57 (100).

Alcohol : 384



$C_{40}H_{68}O_9Si$

Molecular weight: 721.1 g.mol^{-1}

To a solution of enone **362** (5.6 mg, 7.8 μmol) in MeOH (0.2 mL) and CH_2Cl_2 (0.2 mL) was added cerium trichloride heptahydrate (2.9 mg, 7.8 μmol). After 5 min at rt, the reaction mixture was cooled to −78 °C and sodium borohydride (0.4 mg, 9.4 μmol) was added. The reaction mixture was then stirred for another hour at −78 °C and H_2O (0.2 mL) was added. The aqueous layer was extracted with Et_2O (3 × 1 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE-Et_2O; 9:1→4:1→3:2) to give the alcohol **384** (5.5 mg, 7.6 μmol, 98%) as a colourless oil.

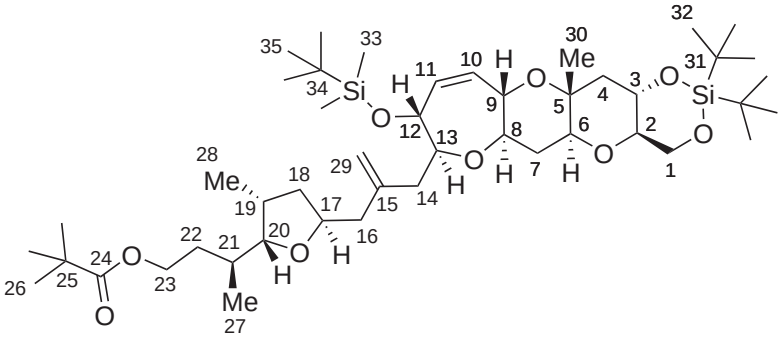
R_f = 0.19 (PE-Et_2O; 1:1)

^{1}H NMR : δ 5.67 (1H, ddd, J = 12.9, 1.9, 1.9 Hz, CH-C10 or C11), 5.61 (1H, d, J = 12.9 Hz, CH-C11 or C10), 4.89 (1H, s, CH_2-C29a), 4.86 (1H, s, CH_2-C29b), 4.23−4.06 (6H, m, CH_2-C1a and CH_2-C23 and CH-C9 and CH-C12 and CH-C17), 3.93 (1H, ddd, J = 11.2, 9.5, 4.8 Hz, CH-C3), 3.81 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.50−3.44 (2H, m, CH-C13 and CH-C20), 3.38 (1H, ddd, J = 10.2, 9.5, 4.8 Hz, CH-C2), 3.27 (1H, ddd, J = 11.1, 9.3, 5.0 Hz, CH-C8), 3.17 (1H, dd, J = 12.7, 4.8 Hz, CH-C6), 2.64 (1H, dd, J = 14.5, 2.9 Hz, CH_2-C14a), 2.36−2.13 (5H, m, CH-C19 and CH_2-C4a and CH_2-C14b and CH_2-C16), 2.07−2.02 (2H, m, CH_2-C7a and OH), 1.81−1.66 (5H, m, CH-C21 and CH_2-C7b and CH_2-C18 and CH_2-C22a), 1.63−1.52 (1H, m, CH_2-C4b), 1.23 (3H, s, CH_3-C30), 1.23−1.21 (1H, m, CH_2-C22b), 1.19 (9H, s, CH_3-C26), 1.03

(9H, s, CH_3-C32), 1.03−1.02 (3H, m, CH_3-C27), 0.97 (9H, s, CH_3-C32'), 0.91 (3H, d, J = 7.0 Hz, CH_3-C28).

^{13}**C NMR** : δ 178.8 (C-C24), 144.3 (C-C15), 134.4 (CH-C10 or C11), 132.3 (CH-C11 or C10), 114.2 (CH_2-C29), 85.6 (CH), 83.7 (CH), 80.4 (CH-C8), 79.5 (CH-C2), 79.1 (CH-C6), 76.2 (CH-C17), 74.2 (CH-C9 or C12), 72.9 (CH-C12 or C9), 72.6 (CH-C3), 72.5 (C-C5), 67.2 (CH_2-C1), 62.2 (CH_2-C23), 46.4 (CH_2-C4), 43.6 (CH_2-C16), 40.8 (CH_2-C18), 40.0 (CH_2-C14), 38.9 (C-C25), 35.1 (CH-C19), 32.0 (CH_2-C22), 31.9 (CH_2-C7), 30.9 (CH-C21), 27.6 (CH_3-C32), 27.4 (CH_3-C26), 27.2 (CH_3-C32'), 22.8 (C-C31), 20.1 (C-C31'), 17.0 (CH_3-C27), 15.7 (CH_3-C30), 13.9 (CH_3-C28).

Diene : 363



$\mathbf{C_{46}H_{82}O_9Si_2}$

Molecular weight: 835.3 g.mol^{-1}

To a solution of alcohol **384** (10 mg, 14 μmol) in CH_2Cl_2 (0.4 mL) at 0 °C was added 2,6-lutidine (10 μL, 84 μmol) and TBSOTf (10 μL, 42 μmol). The reaction mixture was stirred overnight at rt and a saturated aqueous solution of $NaHCO_3$ (0.2 mL) was added. The aqueous layer was extracted with Et_2O (3 × 1 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE-Et_2O; 10%) to give the protected alcohol **363** (10.1 mg, 12 μmol, 85%) as a colourless oil.

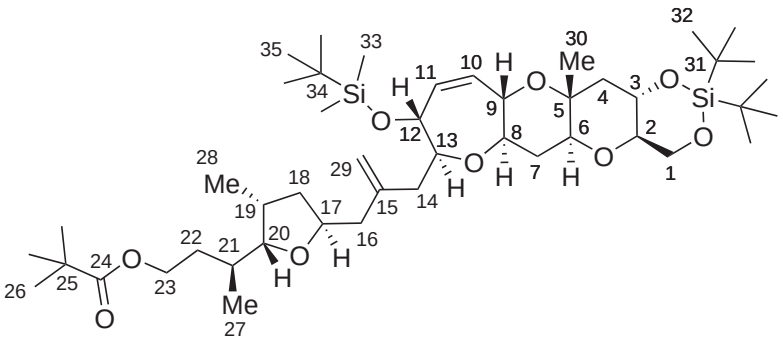
R_f = 0.26 (PE-Et_2O; 9:1)

^{1}**H NMR** : δ 5.65 (1H, d, J = 12.8 Hz, CH-C10 or C11), 5.56 (1H, d, J = 12.8 Hz, CH-C11 or C10), 4.81 (1H, s, CH_2-C29a), 4.79 (1H, s, CH_2-C29b), 4.23−4.05 (6H, m, CH-C9 and CH-C12 and CH-C17 and CH_2-C1a and CH_2-C23), 3.96−3.89 (1H, m, CH-C3), 3.81 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.50 (1H, dd, J = 9.1, 9.1 Hz, CH-C13), 3.45 (1H, dd, J = 9.6, 4.0 Hz, CH-C20), 3.37 (1H, ddd, J = 10.2, 9.6, 4.7 Hz, CH-C2), 3.26−3.20 (1H, m, CH-C8), 3.16 (1H, dd, J = 12.5, 3.5 Hz, CH-C6), 2.58 (1H, d, J = 14.4 Hz, CH_2-C14a), 2.34 (1H, dd, J = 13.8, 6.7 Hz, CH_2-C16a), 2.27−2.17 (2H, m, CH-C19 and CH_2-C4a), 2.08 (1H, dd, J = 13.8, 6.7 Hz, CH_2-C16b), 2.05−1.99 (1H, m, CH_2-C7a), 1.93 (1H, dd, J = 14.4, 9.1 Hz, CH_2-C14b), 1.78−1.64 (4H, CH-C21 and CH_2-C18 and CH_2-C22b), 1.61−1.51 (2H, m, CH_2-C4b and CH_2-C7b), 1.29−1.24

(1H, m, CH_2-C22b), 1.23 (3H, s, CH_3-C30), 1.19 (9H, s, CH_3-C26), 1.04−1.02 (3H, m, CH_3-C27), 1.03 (9H, s, CH_3-C32), 0.97 (9H, s, CH_3-C32'), 0.90−0.85 (3H, s, CH_3-C28), 0.89 (9H, s, CH_3-C35), 0.06 (3H, s, CH_3-C33), 0.05 (3H, s, CH_3-C33').

^{13}**C NMR** : δ 178.8 (C-C24), 144.3 (C-C15), 136.6 (CH-C10 or CH-C11), 131.8 (CH-C11 or CH-C10), 113.4 (CH_2-C29), 85.5 (CH-C20), 84.0 (CH-C13), 80.0 (CH-C8), 79.5 (CH-C2), 79.1 (CH-C6), 75.4 (CH-C17), 74.7 (CH-C12), 73.0 (CH-C9), 72.6 (CH-C3), 72.5 (C-C5), 67.2 (CH_2-C1), 62.2 (CH_2-C23), 46.4 (CH_2-C4), 43.5 (CH_2-C16), 40.7 (CH_2-C18), 39.4 (CH_2-C14), 38.9 (C-C25), 35.2 (CH-C19), 32.0 (CH_2-C7 or CH_2-C22), 31.9 (CH_2-C22 or CH_2-C7), 31.0 (CH-C21), 27.6 (CH_3-C32), 27.4 (CH_3-C26), 27.2 (CH_3-C32'), 26.0 (CH_3-C35), 22.8 (C-C31), 20.1 (C-C31'), 18.1 (C-C34), 17.0 (CH_3-C27), 15.7 (CH_3-C30), 13.9 (CH_3-C28), -4.3 (CH_3-C33), -4.7 (CH_3-C33').

Ketone : 364



$C_{45}H_{82}O_{10}Si_2$

Molecular weight: 839.3 g.mol^{-1}

To a solution of diene **363** (10 mg, 12 μmol) in THF (0.1 mL) was added a solution of NMO (1.5 mg, 13 μmol) in H_2O (10 μL) and a solution of OsO_4 (3.8 μL, 0.6 μmol) in H_2O (4% wt). After 3 h at rt, a solution of OsO_4 (3.8 μL, 0.6 μmol) in H_2O (4% wt) was added and the reaction mixture was stirred for another 2 h. A saturated aqueous solution of $Na_2S_2O_3$ (2 drops) was added and the aqueous layer was extracted with EtOAc (3 × 1 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE-Et_2O; 4:1→1:2) to give the diol **376** (5.1 mg, 5.9 μmol, 49%) as a colourless oil as a mixture of diastereomers along with starting material (2.3 mg, 2.8 μmol).

To a solution of diol **376** (5.1 mg, 5.9 μmol) in EtOH (0.5 mL) was added Pd/C (0.6 mg, 0.6 μmol). The reaction mixture was stirred under an H_2 atmosphere for 5 h, and filtrated on Celite to give the corresponding saturated diol (4.5 mg, 5.2 μmol), which was used directly in the next step.

To a solution of diol (4.5 mg, 5.2 μmol) in EtOH (0.2 mL) was added a solution of $NaIO_4$ (2.2 mg, 10 μmol) in H_2O (0.2 mL). The reaction mixture was stirred overnight

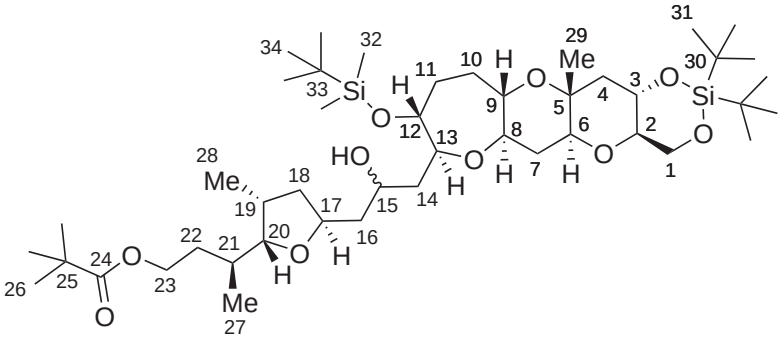
at rt. A saturated aqueous solution of $Na_2S_2O_3$ (2 drops) was added and the aqueous layer was extracted with EtOAc (3 × 1 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (PE-Et_2O; 20%) to give the ketone **364** (2.7 mg, 3.2 μmol, 55% over 2 steps) as a colourless oil.

R_f = 0.76 (PE-Et_2O; 1:3)

^{1}H NMR : δ 4.48−4.41 (1H, m, CH-C17), 4.18−4.03 (3H, CH_2-C1a and CH_2-C23), 3.95−3.88 (2H, m, CH-C3 and CH-C13), 3.81 (1H, dd, J = 10.2, 10.2 Hz, CH_2-C1b), 3.76−3.73 (1H, m, CH-C12), 3.44 (1H, dd, J = 9.7, 4.1 Hz, CH-C20), 3.40−3.33 (3H, m, CH-C2 and CH-C8 and CH-C9), 3.13 (1H, dd, J = 9.6, 3.8 Hz, CH-C6), 2.75 (1H, dd, J = 15.6, 6.8 Hz, CH_2-C16a), 2.60 (1H, dd, J = 15.8, 9.2 Hz, CH_2-C14a), 2.53−2.45 (2H, m, CH_2-C14b and CH_2-C16b), 2.29−2.21 (1H, m, CH-C19), 2.21−2.17 (1H, m, CH_2-C4a), 2.02−1.97 (1H, m, CH_2-C7a), 1.92−1.83 (1H, m, CH_2-C18a), 1.76−1.64 (3H, m, CH-C21 and CH_2-C18b and CH_2-C22a), 1.57−1.48 (2H, m, CH_2-C4b and CH_2-C7b), 1.33−1.17 (4H, m, CH_2-C10 and CH_2-C11 and CH_2-C22b), 1.25 (3H, CH_3-C29), 1.19 (9H, CH_3-C26), 1.04−1.01 (3H, m, CH_3-C27), 1.03 (9H, CH_3-C31), 0.98 (9H, CH_3-C31'), 0.92−0.86 (3H, CH_3-C28), 0.89 (9H, CH_3-C34), 0.05 (3H, CH_3-C32), 0.04 (3H, CH_3-C32').

^{13}C NMR : δ 207.2 (C-C15), 178.8 (C-C24), 85.8 (CH-C20), 82.7 (CH-C13), 80.5 (CH-C2), 79.6 (CH-C8), 79.5 (CH-C6), 74.3 (CH-C12), 74.0 (CH-C9), 72.8 (CH-C17), 72.6 (CH-C3), 72.5 (C-C5), 67.2 (CH_2-C1), 62.1 (CH_2-C23), 50.5 (CH_2-C16), 48.2 (CH_2-C14), 46.5 (CH_2-C4), 40.9 (CH_2-C18), 38.9 (C-C25), 35.2 (CH-C19), 32.0 (CH_2-C7 or CH_2-C22), 31.8 (CH_2-C22 or CH_2-C7), 31.1 (CH-C21), 29.9 (CH_2-C10 or CH_2-C11), 27.6 (CH_3-C31), 27.4 (CH_3-C26), 27.3 (CH_3-C31'), 26.0 (CH_3-C34), 22.8 (C-C30), 22.7 (CH_2-C11 or CH_2-C10), 20.1 (C-C30'), 18.1 (C-C33), 16.9 (CH_3-C27), 16.2 (CH_3-C29), 14.3 (CH_3-C28), -4.3 (CH_3-C32), -4.6 (CH_3-C32').

Alcohols : 365 and 366



$C_{39}H_{70}O_{10}Si$

Molecular weight: 726.5 g.mol^{-1}

To a solution of ketone **364** (2.7 mg, 3.2 μmol) in MeOH (0.2 mL) and CH_2Cl_2 (0.2

mL) was added sodium borohydride (0.2 mg, 6.4 μmol). After 1 h at rt, H_2O (0.2 mL) was added and the aqueous layer was extracted with Et_2O (3 $\times$ 1 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude alcohol (2.7 mg, 3.2 μmol), which was used directly in the next step.

To a solution of alcohol (2.7 mg, 3.2 μmol) in MeOH (0.3 mL) and CH_2Cl_2 (0.15 mL) was added (+)-CSA (1.5 mg, 6.4 μmol). The reaction mixture was stirred overnight at rt and more (+)-CSA (1.5 mg, 6.4 μmol) was added. After another 7 h at rt, triethylamine (0.1 mL) and H_2O (0.2 mL) were added. The aqueous layer was extracted with Et_2O (3 $\times$ 1 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The two products were clearly visible on TLC, but not enough material was obtained from flash chromatography on silica gel (PE-EtOAc: 9:1$\rightarrow$3:1$\rightarrow$1:1)

R_f = 0.50 and 0.57 (EtOAc)

Bibliography

[1] Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929–8931.

[2] Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909.

[3] Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773–6775.

[4] Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380–4386.

[5] Nagai, H.; Torigoe, K.; Satake, M.; Murata, M.; Yasumoto, T.; Hirota, H. *J. Am. Chem. Soc.* **1992**, *114*, 1102–1103.

[6] Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448–5453.

[7] Michio, M.; Masanori, K.; Jong, S. L.; Takeshi, Y. *Tetrahedron Lett.* **1987**, *28*, 5869–5872.

[8] Murata, M.; Naoki, H.; Iwashita, T.; Matsunaga, S.; Sasaki, M.; Yokoyama, A.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 2060–2062.

[9] Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293–314.

[10] Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem.* **1988**, *104*, 184–187.

[11] Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett.* **2002**, *43*, 5829–5832.

[12] Satake, M.; Tanaka, Y.; Ishikura, Y.; Oshima, Y.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **2005**, *46*, 3537–3540.

[13] Flewelling, L. J. et al. *Nature* **2005**, *435*, 755–756.

[14] Trainer, V. L.; Baden, D. G.; Catterall, W. A. *J. Bio. Chem.* **1994**, *269*, 19904–19909.

[15] Rein, K. S.; Baden, D. G.; Gawley, R. E. *J. Org. Chem.* **1994**, *59*, 2101–2106.

[16] Rein, K. S.; Lynn, B.; Gawley, R. E.; Baden, D. G. *J. Org. Chem.* **1994**, *59*, 2107–2113.

[17] Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855–7856.

[18] Lee, M. S.; Qin, G.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234–6241.

[19] Chou, H. N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184–2185.

[20] Shimizu, Y. *Curr. Opin. Microbiol.* **2003**, *6*, 236–243.

[21] Cane, D. E.; Liang, T. C.; Hasler, H. *J. Am. Chem. Soc.* **1982**, *104*, 7274–7281.

[22] Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594–3600.

[23] Nakanishi, K. *Toxicon* **1985**, *23*, 473–479.

[24] Shimizu, Y. *Natural Toxins*; Oxford:Oxford Press, 1986; pp 115–125.

[25] Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476–6477.

[26] Gallimore, A. R.; Spencer, J. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4406–4413.

[27] Baldwin, J. E. *J. Chem. Soc., Chem. Comm.* **1976**, 734–736.

[28] Giner, J.-L. *J. Org. Chem.* **2005**, *70*, 721–724.

[29] Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490–493.

[30] Gouverneur, V. E.; Houk, K. N.; de Pascual-Teresa, B.; Beno, B.; Janda, K. D.; Lerner, R. A. *Science* **1993**, *262*, 204–208.

[31] Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gartner, P. *Nature* **1998**, *392*, 264–269.

[32] Nicolaou, K. C. *Angew. Chem. Int. Ed.* **1996**, *35*, 589–607.

[33] Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374–14376.

[34] Kadota, I.; Takamura, H.; Nishii, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9246–9250.

[35] Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904–1907.

[36] Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983–14992.

[37] Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46–47.

[38] Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848–849.

[39] Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 14294–14295.

[40] Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326–4335.

[41] Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989–16999.

[42] Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557–4558.

[43] Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200–6209.

[44] Rainier, J.; Allwein, S.; Cox, J. *J. Org. Chem.* **2001**, *66*, 1380–1386.

[45] Furuta, H.; Hasegawa, Y.; Mori, Y. *Org. Lett.* **2009**, *11*, 4382–4385.

[46] Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4346–4353.

[47] Evans, P. A.; Delouvrie, B. *Curr. Op. Drug Discov. Develop.* **2002**, *5*, 986–999.

[48] Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158–8159.

[49] Mori, Y.; Furuta, H.; Takase, T.; Mitsuoka, S.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 8019–8022.

[50] Furuta, H.; Takase, T.; Hayashi, H.; Noyori, R.; Mori, Y. *Tetrahedron* **2003**, *59*, 9767–9777.

[51] Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917–12932.

[52] Mori, Y.; Takase, T.; Noyori, R. *Tetrahedron Lett.* **2003**, *44*, 2319–2322.

[53] Furuta, H.; Hase, M.; Noyori, R.; Mori, Y. *Org. Lett.* **2005**, *7*, 4061–4064.

[54] Bowman, J. L.; McDonald, F. E. *J. Org. Chem.* **1998**, *63*, 3680–3682.

[55] Hoye, T. R.; Suriano, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1154–1156.

[56] McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675–4678.

[57] Rainier, J.; Allwein, S. *J. Org. Chem.* **1998**, *63*, 5310–5311.

[58] Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179–181.

[59] Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58*, 1997–2009.

[60] Rainier, J. D.; Allwein, S. P. *Tetrahedron Lett.* **1998**, *39*, 9601–9604.

[61] Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668–2670.

[62] Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5*, 913–916.

[63] Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* **2000**, *2*, 231–234.

[64] Cox, J.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919–2922.

[65] Zhang, Y.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 237–239.

[66] Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2007**, *9*, 2227–2230.

[67] Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144–5145.

[68] Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027–2040.

[69] Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339–2342.

[70] Warren, J.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675–7677.

[71] Leeuwenburgh, M. A.; Litjens, R. E. J. N.; Codee, J. D. C.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Org. Lett.* **2000**, *2*, 1275–1277.

[72] Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831–4834.

[73] Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C.; Yun, M.; Kim, S. *Tetrahedron Lett.* **1994**, *35*, 129–132.

[74] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

[75] Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099–1101.

[76] Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, *2*, 148–149.

[77] Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853–1864.

[78] Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859–8862.

[79] Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8653–8655.

[80] Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749–2752.

[81] McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917–2919.

[82] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

[83] Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123–2126.

[84] Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586–4587.

[85] Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189–1192.

[86] Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127–130.

[87] Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123–126.

[88] Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 8639–8642.

[89] Clark, J. S.; Hamelin, O.; Hufton, R. *Tetrahedron Lett.* **1998**, *39*, 8321–8324.

[90] Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231–8248.

[91] Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410–4412.

[92] Clark, J. S.; Hamelin, O. *Angew. Chem. Int. Ed.* **2000**, *39*, 372–374.

[93] Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 6157–6162.

[94] Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *Chem. Commun.* **1998**, 2629–2630.

[95] Clark, J. S.; Elustondo, F.; Trevitt, G. P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, *58*, 1973–1982.

[96] Clark, J. S.; Elustondo, F.; Kimber, M. C. *Chem. Commun.* **2004**, 2470–2471.

[97] Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.

[98] Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

[99] Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043.

[100] Calderon, N.; Chen, H. Y.; Scott, K. W. *Tetrahedron Lett.* **1967**, *8*, 3327–3329.

[101] Herisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161–176.

[102] Trnka, T.; Grubbs, R. *Acc. Chem. Res.* **2001**, *34*, 18–29.

[103] Calderon, N.; Ofstead, E. A.; Judy, W. A. *Angew. Chem. Int. Ed.* **1976**, *15*, 401–409.

[104] Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613.

[105] Howard, T. R.; Lee, J. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876–6878.

[106] Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272.

[107] Dötz, K. H. *Angew. Chem. Int. Ed.* **1984**, *23*, 587–608.

[108] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

[109] Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378–8387.

[110] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.

[111] Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897.

[112] Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **1995**, *34*, 2039–2041.

[113] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.

[114] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

[115] Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974–3975.

[116] Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858–9859.

[117] Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503–5511.

[118] Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4038–4040.

[119] Yun, J.; Marinez, E.; Grubbs, R. *Organometallics* **2004**, *23*, 4172–4173.

[120] Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

[121] Maier, M. E. *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077.

[122] Cabrejas, L. M. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2443–2446.

[123] Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565–1566.

[124] Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041–1042.

[125] Leeuwenburgh, M. A.; Kulker, C.; Duynstee, H. I.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron* **1999**, *55*, 8253–8262.

[126] Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391.

[127] Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029–4031.

[128] Calimente, D.; Postema, M. H. D. *J. Org. Chem.* **1999**, *64*, 1770–1771.

[129] Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061–6068.

[130] Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623–9626.

[131] Peczuh, M. W.; Snyder, N. L. *Tetrahedron Lett.* **2003**, *44*, 4057–4061.

[132] Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614.

[133] Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312–11313.

[134] Tallarico, J. A.; Malnick, L. M.; Snapper, M. L. *J. Org. Chem.* **1999**, *64*, 344–345.

[135] Maifeld, S. V.; Miller, R. L.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 6363–6366.

[136] Mukai, C.; Itoh, R. *Tetrahedron Lett.* **2006**, *47*, 3971–3974.

[137] Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52–53.

[138] Hu, Y.-J.; Dominique, R.; Das, S. K.; Roy, R. *Can. J. Chem.* **2000**, *78*, 838–845.

[139] Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781–3784.

[140] Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 1839–1841.

[141] Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687.

[142] Schmidt, B. *J. Mol. Cata. A* **2006**, *254*, 53–57.

[143] Michalak, M.; Wicha, J. *Synlett* **2005**, 2277–2280.

[144] Diver, S.; Giessert, A. *Chem. Rev.* **2004**, *104*, 1317–1382.

[145] Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307–2320.

[146] Cortez, G.; Schrock, R.; Hoveyda, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4534–4538.

[147] Gillingham, D.; Hoveyda, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 3860–3864.

[148] Nagai, H.; Mikami, Y.; Yazawa, K.; Gonoi, T.; Yasumoto, T. *J. Antibiot.* **1993**, *46*, 520–522.

[149] Inoue, M.; Hirama, M.; Satake, M.; Sugiyama, K.; Yasumoto, T. *Toxicon* **2003**, *41*, 469–474.

[150] Morohashi, A.; Satake, M.; Nagai, H.; Oshima, Y.; Yasumoto, T. *Tetrahedron* **2000**, *56*, 8995–9001.

[151] Fuwa, H.; Goto, T.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2211–2214.

[152] Fuwa, H.; Ishigai, K.; Goto, T.; Suzuki, A.; Sasaki, M. *J. Org. Chem.* **2009**, *74*, 4024–4040.

[153] Evans, P. A.; Roseman, J. D.; Garber, L. T. *J. Org. Chem.* **1996**, *61*, 4880–4881.

[154] Batty, D.; Crich, D. *Synthesis* **1990**, 273–275.

[155] Kadota, I.; Oguro, N.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3645–3647.

[156] Kadota, I.; Takamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 3649–3651.

[157] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.

[158] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

[159] Sato, K.; Sasaki, M. *Org. Lett.* **2005**, *7*, 2441–2444.

[160] Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.

[161] Nicolaou, K. C.; Hwang, C. K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040–3054.

[162] Sato, K.; Sasaki, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2518–2522.

[163] Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 2739–2741.

[164] Fuwa, H.; Suzuki, A.; Sato, K.; Sasaki, M. *Heterocycles* **2007**, *72*, 139–144.

[165] Takano, S.; Samizu, K.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1344–1345.

[166] Tsubone, K.; Hashizume, K.; Fuwa, H.; Sasaki, M. *Tetrahedron Lett.* **2011**, *52*, 548–551.

[167] Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773–1776.

[168] Elustundo, F. unpublished results.

[169] Borsch, V. unpublished resulsts.

[170] Cheshev, P.; Marra, A.; Dondoni, A. *Carbo. Res.* **2006**, *341*, 2714–2716.

[171] Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377–2377.

[172] Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919–2922.

[173] Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731–734.

[174] White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006**, *8*, 6039–6042.

[175] Sugiyama, H.; Yokokawa, F.; Shioiri, T. *Org. Lett.* **2000**, *2*, 2149–2152.

[176] Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

[177] Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643-644*, 247–252.

[178] Meyer, W. H.; McConnell, A. E.; Forman, G. S.; Dwyer, C. L.; Kirk, M. M.; Ngidi, E. L.; Blignaut, A.; Saku, D.; Slawin, A. M. Z. *Inorg. Chim. Acta* **2006**, *359*, 2910–2917.

[179] Gemino, N.; Formentin, P.; Steinke, J. H. G.; Vilar, R. *Eur. J. Org. Chem.* **2007**, *2007*, 918–924.

[180] Samojlowicz, C.; Bieniek, M.; Zarecki, A.; Kadyrov, R.; Grela, K. *Chem. Commun.* **2008**, 6282–6284.

[181] Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787.

[182] Stewart, A. unpublished results.

[183] Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 1103–1106.

[184] Bradshaw, B.; Etxebarria-Jard, G.; Bonjoch, J. *J. Am. Chem. Soc.* **2010**, *132*, 5966–5967.

[185] Schwartz, B. D.; Tilly, D. P.; Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2006**, *2006*, 3181–3192.

[186] Hoye, T. R.; Thomas, R.; Zhao, H. *218th ACS National Meeting, (New Orleans, LA)* **1999**, ORGN–620.

[187] Hoye, T. R.; Zhao, H. *218th ACS National Meeting (New Orleans, LA)* **1999**, ORGN–303.

[188] Hoye, T. R.; Wang, J. *226th ACS National Meeting (New York, NY)* **2003**, ORGN–670.

[189] Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.

[190] Kleijn, H.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 5143–5148.

[191] Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D. *Synlett* **1998**, 915–917.

[192] Lesimple, P.; Beau, J.-M.; Jaurand, G.; Sina„, P. *Tetrahedron Lett.* **1986**, *27*, 6201–6204.

[193] Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225–5227.

[194] Leeuwenburgh, M. A.; Timmers, C. M.; van der Marel, G. A.; van Boom, J. H.; Mallet, J.-M.; Sina„, P. G. *Tetrahedron Lett.* **1997**, *38*, 6251–6254.

[195] Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380–1386.

[196] Cheng, G.; Fan, R.; HernÃąndez-Torres, J. M.; Boulineau, F. P.; Wei, A. *Org. Lett.* **2007**, *9*, 4849–4852.

[197] Wipf, P.; Pierce, J. G.; Zhuang, N. *Org. Lett.* **2005**, *7*, 483–485.

[198] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

[199] Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472 – 4490.

[200] Hudson, R. F.; Chopard, P. A. *J. Org. Chem.* **1963**, *28*, 2446–2447.

[201] Rosenquist, N. R.; Chapman, O. L. *J. Org. Chem.* **1976**, *41*, 3326–3327.

[202] Sengupta, S.; Das, D.; Sarma, D. S. *Tetrahedron Lett.* **1996**, *37*, 8815–8818.

[203] Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263–7266.

[204] Clark, J. S.; Grainger, D. M.; Ehkirch, A. A.-C.; Blake, A. J.; Wilson, C. *Org. Lett.* **2007**, *9*, 1033–1036.

[205] Clark, J. S.; Conroy, J.; Blake, A. J. *Org. Lett.* **2007**, *9*, 2091–2094.

[206] Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793–1796.

[207] Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

[208] Loiseleur, O.; Meier, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1996**, *35*, 200–202.

[209] Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602.

[210] Sagasser, I.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 261–264.

[211] Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.

[212] Trost, B. M.; Breit, B.; Peukert, S.; Zambrano, J.; Ziller, J. W. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2386–2388.

[213] Kobayashi, S.; Alizadeh, B. H.; Sasaki, S.-y.; Oguri, H.; Hirama, M. *Org. Lett.* **2004**, *6*, 751–754.

[214] Fujiwara, K.; Takaoka, D.; Kusumi, K.; Kawai, K.; Murai, A. *Synlett* **2001**, *2001*, 691–693.

[215] Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H.-X.; Weyershausen, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3849–3854.

[216] Dr Chaudhury, S. based on literature procedures.

[217] Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2009**, *65*, 5747–5751.

[218] Trost, B. M.; Xu, J. *J. Org. Chem.* **2007**, *72*, 9372–9375.

[219] Ragoussis, V.; Giannikopoulos, A.; Skoka, E.; Grivas, P. *J. Agri. Food Chem.* **2007**, *55*, 5050–5052.

[220] Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *6*, 3491–3494.

[221] Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789–1797.

[222] Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371–8375.

[223] Blackburne, I. D.; Fredericks, P. M.; Guthrie, R. D. *Aust. J. Chem.* **1976**, *29*, 381–391.

[224] Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281–293.

[225] McKeon, S. C.; Müller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2009**, *2009*, 4833–4841.

[226] Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531.

[227] Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181.

[228] Qi-Lin, Z.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467–4478.

[229] Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Rieck, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583.

Appendix A

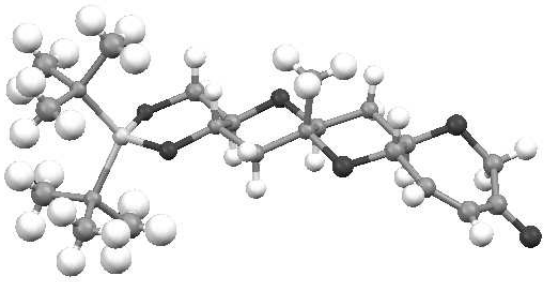


Figure 1: X-ray structure of enone **295**

Empirical formula	C_{44} H_{72} O_{12} Si_2	
Formula weight	849.20	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 6.3950(7) Å	α = 90 °
	b = 46.881(6) Å	β = 111.164(5) °
	c = 8.2621(10) Å	γ = 90 °
Volume	2309.9(5) $Å^3$	
Z	2	
Density (calculated)	1.221 Mg/m^3	
Absorption coefficient	0.135 mm^{-1}	
F(000)	920	
Theta range for data collection	1.74 to 19.98 °	
Index ranges	-6≤h≤6, -44≤k≤44, -7≤l≤7	
Reflections collected	22727	
Independent reflections	4232 [R(int) = 0.0739]	
Completeness to theta = 19.98 °	99.4%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7444 and 0.5826	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4232 / 1 / 233	
Goodness-of-fit on F^2	3.505	
Final R indices [I>2sigma(I)]	R1 = 0.1064, wR2 = 0.1983	
R indices (all data)	R1 = 0.1196, wR2 = 0.2000	
Absolute structure parameter	0.2(4)	
Largest diff. peak and hole	1.153 and -0.527 e.$Å^{-3}$	

Table 1: Table 1: Crystal data and structure refinement

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	-512(5)	5922(1)	-1266(4)	24(1)
O(7)	-1160(11)	5648(2)	-290(9)	23(2)
O(8)	2085(10)	5884(2)	-1090(9)	24(2)
O(9)	4116(11)	5248(2)	1607(10)	24(2)
O(10)	329(12)	4728(2)	2420(10)	29(2)
O(11)	5463(12)	4292(2)	3933(10)	32(2)
O(12)	2978(13)	3612(2)	2424(12)	49(3)
C(23)	2489(18)	5427(3)	420(16)	25(3)
C(24)	524(17)	5479(3)	958(16)	25(3)
C(25)	-520(17)	5199(2)	1255(15)	23(3)
C(26)	1300(18)	5002(3)	2433(16)	29(3)
C(27)	3162(16)	4979(2)	1767(16)	22(3)
C(29)	5001(17)	4778(2)	2768(16)	24(3)
C(30)	3870(17)	4488(3)	2819(16)	24(3)
C(31)	1939(17)	4514(3)	3393(17)	29(3)
C(32)	678(18)	4256(3)	3430(15)	27(3)
C(33)	1176(19)	3978(3)	3227(16)	33(4)
C(34)	3090(20)	3874(3)	2928(17)	37(4)
C(35)	5267(18)	4006(3)	3239(17)	29(3)
C(36)	-2334(16)	5887(3)	-3664(13)	20(3)
C(37)	-701(17)	6265(2)	-126(14)	20(3)
C(38)	-1560(20)	5626(3)	-4280(20)	61(4)
C(39)	-1990(20)	6145(3)	-4683(19)	58(4)
C(40)	270(20)	6515(3)	-828(18)	49(4)
C(41)	-3054(19)	6341(3)	-168(18)	42(4)
C(42)	730(20)	6225(3)	1753(16)	43(4)
C(28)	3624(17)	5689(3)	190(15)	26(3)
C(43)	2077(17)	5125(3)	4335(14)	26(3)
C(44)	-4774(18)	5865(3)	-3902(17)	47(4)
Si(2)	3895(5)	7448(1)	6221(5)	26(1)
O(1)	6230(10)	7492(2)	5913(9)	22(2)
O(2)	2313(11)	7723(2)	5408(10)	27(2)
O(3)	5422(11)	8135(2)	3176(10)	29(2)
O(4)	905(11)	8643(2)	2725(10)	36(2)
O(5)	4119(12)	9092(2)	801(10)	34(2)
O(6)	3234(12)	9767(2)	2545(11)	38(2)

C(1)	6477(18)	7688(3)	4630(16)	31(3)
C(2)	5124(17)	7958(3)	4525(16)	25(3)
C(3)	2628(16)	7895(3)	4075(15)	22(3)
C(4)	1329(17)	8169(2)	3837(15)	26(3)
C(5)	1833(17)	8361(3)	2563(15)	23(3)
C(6)	4329(17)	8401(3)	3082(16)	26(3)
C(7)	4979(17)	8612(3)	1981(16)	26(3)
C(8)	3819(18)	8892(3)	2031(17)	29(3)
C(9)	1348(19)	8858(3)	1622(18)	34(4)
C(10)	692(18)	8253(3)	708(15)	38(4)
C(11)	137(19)	9116(3)	1800(16)	33(3)
C(12)	710(20)	9396(3)	1997(17)	38(4)
C(13)	2807(19)	9513(3)	2026(17)	34(4)
C(14)	4562(18)	9381(3)	1487(17)	33(4)
C(15)	4473(16)	7470(3)	8635(14)	25(3)
C(16)	5680(20)	7206(3)	9617(18)	47(4)
C(17)	6080(20)	7721(3)	9326(19)	53(4)
C(18)	2295(18)	7517(3)	8931(17)	45(4)
C(19)	2543(17)	7107(3)	5135(15)	23(3)
C(20)	1740(20)	7157(3)	3124(17)	49(4)
C(21)	520(20)	7014(3)	5531(18)	48(4)
C(22)	4207(19)	6870(3)	5499(17)	47(4)

Table 3: Bond lengths [Å] and angles [°].

Si(1)-O(8)	1.624(7)	C(35)-H(35A)	0.9700
Si(1)-O(7)	1.648(8)	C(35)-H(35B)	0.9700
Si(1)-C(37)	1.887(12)	C(36)-C(38)	1.479(17)
Si(1)-C(36)	1.909(11)	C(36)-C(44)	1.504(14)
O(7)-C(24)	1.431(13)	C(36)-C(39)	1.536(17)
O(8)-C(28)	1.471(12)	C(37)-C(42)	1.501(15)
O(9)-C(23)	1.416(13)	C(37)-C(41)	1.535(15)
O(9)-C(27)	1.431(13)	C(37)-C(40)	1.536(16)
O(10)-C(26)	1.427(14)	C(38)-H(38A)	0.9600
O(10)-C(31)	1.454(13)	C(38)-H(38B)	0.9600
O(11)-C(30)	1.433(13)	C(38)-H(38C)	0.9600
O(11)-C(35)	1.447(14)	C(39)-H(39A)	0.9600
O(12)-C(34)	1.291(15)	C(39)-H(39B)	0.9600
C(23)-C(28)	1.477(15)	C(39)-H(39C)	0.9600
C(23)-C(24)	1.496(14)	C(40)-H(40A)	0.9600
C(23)-H(23)	0.9800	C(40)-H(40B)	0.9600
C(24)-C(25)	1.535(16)	C(40)-H(40C)	0.9600
C(24)-H(24)	0.9800	C(41)-H(41A)	0.9600
C(25)-C(26)	1.526(16)	C(41)-H(41B)	0.9600
C(25)-H(25A)	0.9700	C(41)-H(41C)	0.9600
C(25)-H(25B)	0.9700	C(42)-H(42A)	0.9600
C(26)-C(27)	1.485(15)	C(42)-H(42B)	0.9600
C(26)-C(43)	1.576(15)	C(42)-H(42C)	0.9600
C(27)-C(29)	1.500(15)	C(28)-H(28A)	0.9700
C(27)-H(27)	0.9800	C(28)-H(28B)	0.9700
C(29)-C(30)	1.546(15)	C(43)-H(43A)	0.9600
C(29)-H(29A)	0.9700	C(43)-H(43B)	0.9600
C(29)-H(29B)	0.9700	C(43)-H(43C)	0.9600
C(30)-C(31)	1.479(14)	C(44)-H(44A)	0.9600
C(30)-H(30)	0.9800	C(44)-H(44B)	0.9600
C(31)-C(32)	1.460(16)	C(44)-H(44C)	0.9600
C(31)-H(31)	0.9800	Si(2)-O(1)	1.616(7)
C(32)-C(33)	1.364(16)	Si(2)-O(2)	1.627(8)
C(32)-H(32)	0.9300	Si(2)-C(19)	1.881(12)
C(33)-C(34)	1.423(16)	Si(2)-C(15)	1.895(12)
C(33)-H(33)	0.9300	O(1)-C(1)	1.452(13)
C(34)-C(35)	1.456(16)	O(2)-C(3)	1.438(13)

O(3)-C(6)	1.418(13)	C(15)-C(16)	1.528(17)
O(3)-C(2)	1.456(13)	C(15)-C(17)	1.532(17)
O(4)-C(9)	1.454(14)	C(16)-H(16A)	0.9600
O(4)-C(5)	1.473(14)	C(16)-H(16B)	0.9600
O(5)-C(8)	1.448(14)	C(16)-H(16C)	0.9600
O(5)-C(14)	1.457(14)	C(17)-H(17A)	0.9600
O(6)-C(13)	1.262(14)	C(17)-H(17B)	0.9600
C(1)-C(2)	1.517(15)	C(17)-H(17C)	0.9600
C(1)-H(1A)	0.9700	C(18)-H(18A)	0.9600
C(1)-H(1B)	0.9700	C(18)-H(18B)	0.9600
C(2)-C(3)	1.531(14)	C(18)-H(18C)	0.9600
C(2)-H(2)	0.9800	C(19)-C(22)	1.495(15)
C(3)-C(4)	1.502(15)	C(19)-C(21)	1.510(15)
C(3)-H(3)	0.9800	C(19)-C(20)	1.569(17)
C(4)-C(5)	1.507(16)	C(20)-H(20A)	0.9600
C(4)-H(4A)	0.9700	C(20)-H(20B)	0.9600
C(4)-H(4B)	0.9700	C(20)-H(20C)	0.9600
C(5)-C(6)	1.507(14)	C(21)-H(21A)	0.9600
C(5)-C(10)	1.527(15)	C(21)-H(21B)	0.9600
C(6)-C(7)	1.500(16)	C(21)-H(21C)	0.9600
C(6)-H(6)	0.9800	C(22)-H(22A)	0.9600
C(7)-C(8)	1.515(17)	C(22)-H(22B)	0.9600
C(7)-H(7A)	0.9700	C(22)-H(22C)	0.9600
C(7)-H(7B)	0.9700		
C(8)-C(9)	1.501(14)	O(8)-Si(1)-O(7)	107.4(4)
C(8)-H(8)	0.9800	O(8)-Si(1)-C(37)	107.3(4)
C(9)-C(11)	1.471(17)	O(7)-Si(1)-C(37)	110.3(4)
C(9)-H(9)	0.9800	O(8)-Si(1)-C(36)	107.7(4)
C(10)-H(10A)	0.9600	O(7)-Si(1)-C(36)	105.8(5)
C(10)-H(10B)	0.9600	C(37)-Si(1)-C(36)	117.8(5)
C(10)-H(10C)	0.9600	C(24)-O(7)-Si(1)	121.8(6)
C(11)-C(12)	1.359(17)	C(28)-O(8)-Si(1)	122.1(7)
C(11)-H(11)	0.9300	C(23)-O(9)-C(27)	110.7(8)
C(12)-C(13)	1.443(16)	C(26)-O(10)-C(31)	113.5(8)
C(12)-H(12)	0.9300	C(30)-O(11)-C(35)	113.6(9)
C(13)-C(14)	1.484(16)	O(9)-C(23)-C(28)	108.0(9)
C(14)-H(14A)	0.9700	O(9)-C(23)-C(24)	112.2(9)
C(14)-H(14B)	0.9700	C(28)-C(23)-C(24)	113.8(10)
C(15)-C(18)	1.515(15)	O(9)-C(23)-H(23)	107.5

C(28)-C(23)-H(23)	107.5	C(32)-C(31)-C(30)	118.1(11)
C(24)-C(23)-H(23)	107.5	O(10)-C(31)-H(31)	106.0
O(7)-C(24)-C(23)	111.8(9)	C(32)-C(31)-H(31)	106.0
O(7)-C(24)-C(25)	109.3(8)	C(30)-C(31)-H(31)	106.0
C(23)-C(24)-C(25)	111.5(10)	C(33)-C(32)-C(31)	129.2(11)
O(7)-C(24)-H(24)	108.0	C(33)-C(32)-H(32)	115.4
C(23)-C(24)-H(24)	108.0	C(31)-C(32)-H(32)	115.4
C(25)-C(24)-H(24)	108.0	C(32)-C(33)-C(34)	127.1(12)
C(26)-C(25)-C(24)	110.0(9)	C(32)-C(33)-H(33)	116.5
C(26)-C(25)-H(25A)	109.7	C(34)-C(33)-H(33)	116.5
C(24)-C(25)-H(25A)	109.7	O(12)-C(34)-C(33)	115.5(11)
C(26)-C(25)-H(25B)	109.7	O(12)-C(34)-C(35)	113.7(10)
C(24)-C(25)-H(25B)	109.7	C(33)-C(34)-C(35)	130.6(13)
H(25A)-C(25)-H(25B)	108.2	O(11)-C(35)-C(34)	113.9(10)
O(10)-C(26)-C(27)	109.5(10)	O(11)-C(35)-H(35A)	108.8
O(10)-C(26)-C(25)	108.0(9)	C(34)-C(35)-H(35A)	108.8
C(27)-C(26)-C(25)	109.8(10)	O(11)-C(35)-H(35B)	108.8
O(10)-C(26)-C(43)	108.4(10)	C(34)-C(35)-H(35B)	108.8
C(27)-C(26)-C(43)	113.0(9)	H(35A)-C(35)-H(35B)	107.7
C(25)-C(26)-C(43)	108.0(10)	C(38)-C(36)-C(44)	111.1(10)
O(9)-C(27)-C(26)	113.2(9)	C(38)-C(36)-C(39)	109.3(10)
O(9)-C(27)-C(29)	109.3(8)	C(44)-C(36)-C(39)	109.1(10)
C(26)-C(27)-C(29)	114.6(10)	C(38)-C(36)-Si(1)	106.1(8)
O(9)-C(27)-H(27)	106.4	C(44)-C(36)-Si(1)	110.9(8)
C(26)-C(27)-H(27)	106.4	C(39)-C(36)-Si(1)	110.3(8)
C(29)-C(27)-H(27)	106.4	C(42)-C(37)-C(41)	106.1(9)
C(27)-C(29)-C(30)	106.5(9)	C(42)-C(37)-C(40)	107.9(10)
C(27)-C(29)-H(29A)	110.4	C(41)-C(37)-C(40)	109.7(10)
C(30)-C(29)-H(29A)	110.4	C(42)-C(37)-Si(1)	106.6(8)
C(27)-C(29)-H(29B)	110.4	C(41)-C(37)-Si(1)	115.2(8)
C(30)-C(29)-H(29B)	110.4	C(40)-C(37)-Si(1)	110.8(8)
H(29A)-C(29)-H(29B)	108.6	C(36)-C(38)-H(38A)	109.5
O(11)-C(30)-C(31)	109.2(9)	C(36)-C(38)-H(38B)	109.5
O(11)-C(30)-C(29)	110.5(8)	H(38A)-C(38)-H(38B)	109.5
C(31)-C(30)-C(29)	113.0(10)	C(36)-C(38)-H(38C)	109.5
O(11)-C(30)-H(30)	108.0	H(38A)-C(38)-H(38C)	109.5
C(31)-C(30)-H(30)	108.0	H(38B)-C(38)-H(38C)	109.5
C(29)-C(30)-H(30)	108.0	C(36)-C(39)-H(39A)	109.5
O(10)-C(31)-C(32)	107.3(8)	C(36)-C(39)-H(39B)	109.5
O(10)-C(31)-C(30)	112.6(10)	H(39A)-C(39)-H(39B)	109.5

C(36)-C(39)-H(39C)	109.5	H(44A)-C(44)-H(44C)	109.5
H(39A)-C(39)-H(39C)	109.5	H(44B)-C(44)-H(44C)	109.5
H(39B)-C(39)-H(39C)	109.5	O(1)-Si(2)-O(2)	107.7(4)
C(37)-C(40)-H(40A)	109.5	O(1)-Si(2)-C(19)	109.1(4)
C(37)-C(40)-H(40B)	109.5	O(2)-Si(2)-C(19)	111.4(5)
H(40A)-C(40)-H(40B)	109.5	O(1)-Si(2)-C(15)	108.6(4)
C(37)-C(40)-H(40C)	109.5	O(2)-Si(2)-C(15)	104.3(5)
H(40A)-C(40)-H(40C)	109.5	C(19)-Si(2)-C(15)	115.5(6)
H(40B)-C(40)-H(40C)	109.5	C(1)-O(1)-Si(2)	123.2(7)
C(37)-C(41)-H(41A)	109.5	C(3)-O(2)-Si(2)	121.6(6)
C(37)-C(41)-H(41B)	109.5	C(6)-O(3)-C(2)	110.2(8)
H(41A)-C(41)-H(41B)	109.5	C(9)-O(4)-C(5)	112.8(8)
C(37)-C(41)-H(41C)	109.5	C(8)-O(5)-C(14)	112.8(9)
H(41A)-C(41)-H(41C)	109.5	O(1)-C(1)-C(2)	110.9(9)
H(41B)-C(41)-H(41C)	109.5	O(1)-C(1)-H(1A)	109.5
C(37)-C(42)-H(42A)	109.5	C(2)-C(1)-H(1A)	109.5
C(37)-C(42)-H(42B)	109.5	O(1)-C(1)-H(1B)	109.5
H(42A)-C(42)-H(42B)	109.5	C(2)-C(1)-H(1B)	109.5
C(37)-C(42)-H(42C)	109.5	H(1A)-C(1)-H(1B)	108.0
H(42A)-C(42)-H(42C)	109.5	O(3)-C(2)-C(1)	106.9(9)
H(42B)-C(42)-H(42C)	109.5	O(3)-C(2)-C(3)	109.6(9)
O(8)-C(28)-C(23)	112.1(9)	C(1)-C(2)-C(3)	112.2(10)
O(8)-C(28)-H(28A)	109.2	O(3)-C(2)-H(2)	109.4
C(23)-C(28)-H(28A)	109.2	C(1)-C(2)-H(2)	109.4
O(8)-C(28)-H(28B)	109.2	C(3)-C(2)-H(2)	109.4
C(23)-C(28)-H(28B)	109.2	O(2)-C(3)-C(4)	111.0(9)
H(28A)-C(28)-H(28B)	107.9	O(2)-C(3)-C(2)	110.1(8)
C(26)-C(43)-H(43A)	109.5	C(4)-C(3)-C(2)	110.4(10)
C(26)-C(43)-H(43B)	109.5	O(2)-C(3)-H(3)	108.4
H(43A)-C(43)-H(43B)	109.5	C(4)-C(3)-H(3)	108.4
C(26)-C(43)-H(43C)	109.5	C(2)-C(3)-H(3)	108.4
H(43A)-C(43)-H(43C)	109.5	C(3)-C(4)-C(5)	110.8(9)
H(43B)-C(43)-H(43C)	109.5	C(3)-C(4)-H(4A)	109.5
C(36)-C(44)-H(44A)	109.5	C(5)-C(4)-H(4A)	109.5
C(36)-C(44)-H(44B)	109.5	C(3)-C(4)-H(4B)	109.5
H(44A)-C(44)-H(44B)	109.5	C(5)-C(4)-H(4B)	109.5
C(36)-C(44)-H(44C)	109.5	H(4A)-C(4)-H(4B)	108.1

O(4)-C(5)-C(4)	106.1(8)	C(11)-C(12)-C(13)	125.1(12)
O(4)-C(5)-C(6)	106.5(9)	C(11)-C(12)-H(12)	117.4
C(4)-C(5)-C(6)	110.3(9)	C(13)-C(12)-H(12)	117.4
O(4)-C(5)-C(10)	109.1(9)	O(6)-C(13)-C(12)	116.7(11)
C(4)-C(5)-C(10)	110.9(10)	O(6)-C(13)-C(14)	113.6(10)
C(6)-C(5)-C(10)	113.6(9)	C(12)-C(13)-C(14)	129.7(13)
O(3)-C(6)-C(7)	111.9(9)	O(5)-C(14)-C(13)	116.2(10)
O(3)-C(6)-C(5)	111.0(9)	O(5)-C(14)-H(14A)	108.2
C(7)-C(6)-C(5)	113.9(9)	C(13)-C(14)-H(14A)	108.2
O(3)-C(6)-H(6)	106.5	O(5)-C(14)-H(14B)	108.2
C(7)-C(6)-H(6)	106.5	C(13)-C(14)-H(14B)	108.2
C(5)-C(6)-H(6)	106.5	H(14A)-C(14)-H(14B)	107.4
C(6)-C(7)-C(8)	108.0(9)	C(18)-C(15)-C(16)	110.5(10)
C(6)-C(7)-H(7A)	110.1	C(18)-C(15)-C(17)	111.0(11)
C(8)-C(7)-H(7A)	110.1	C(16)-C(15)-C(17)	106.5(9)
C(6)-C(7)-H(7B)	110.1	C(18)-C(15)-Si(2)	109.7(7)
C(8)-C(7)-H(7B)	110.1	C(16)-C(15)-Si(2)	112.6(9)
H(7A)-C(7)-H(7B)	108.4	C(17)-C(15)-Si(2)	106.5(8)
O(5)-C(8)-C(9)	107.8(9)	C(15)-C(16)-H(16A)	109.5
O(5)-C(8)-C(7)	110.7(9)	C(15)-C(16)-H(16B)	109.5
C(9)-C(8)-C(7)	112.9(10)	H(16A)-C(16)-H(16B)	109.5
O(5)-C(8)-H(8)	108.4	C(15)-C(16)-H(16C)	109.5
C(9)-C(8)-H(8)	108.4	H(16A)-C(16)-H(16C)	109.5
C(7)-C(8)-H(8)	108.4	H(16B)-C(16)-H(16C)	109.5
O(4)-C(9)-C(11)	106.2(9)	C(15)-C(17)-H(17A)	109.5
O(4)-C(9)-C(8)	111.1(10)	C(15)-C(17)-H(17B)	109.5
C(11)-C(9)-C(8)	116.1(11)	H(17A)-C(17)-H(17B)	109.5
O(4)-C(9)-H(9)	107.7	C(15)-C(17)-H(17C)	109.5
C(11)-C(9)-H(9)	107.7	H(17A)-C(17)-H(17C)	109.5
C(8)-C(9)-H(9)	107.7	H(17B)-C(17)-H(17C)	109.5
C(5)-C(10)-H(10A)	109.5	C(15)-C(18)-H(18A)	109.5
C(5)-C(10)-H(10B)	109.5	C(15)-C(18)-H(18B)	109.5
H(10A)-C(10)-H(10B)	109.5	H(18A)-C(18)-H(18B)	109.5
C(5)-C(10)-H(10C)	109.5	C(15)-C(18)-H(18C)	109.5
H(10A)-C(10)-H(10C)	109.5	H(18A)-C(18)-H(18C)	109.5
H(10B)-C(10)-H(10C)	109.5	H(18B)-C(18)-H(18C)	109.5
C(12)-C(11)-C(9)	132.9(11)	C(22)-C(19)-C(21)	110.1(11)
C(12)-C(11)-H(11)	113.6	C(22)-C(19)-C(20)	105.1(10)
C(9)-C(11)-H(11)	113.6	C(21)-C(19)-C(20)	107.2(9)

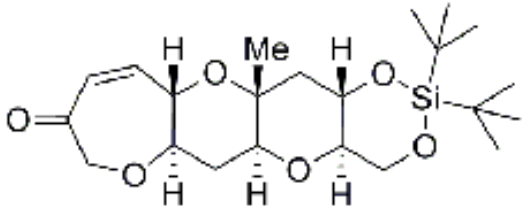
C(22)-C(19)-Si(2)	111.4(8)
C(21)-C(19)-Si(2)	115.1(8)
C(20)-C(19)-Si(2)	107.3(8)
C(19)-C(20)-H(20A)	109.5
C(19)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(19)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(19)-C(21)-H(21A)	109.5
C(19)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
C(19)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(19)-C(22)-H(22A)	109.5
C(19)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(19)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5

Table 4: Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^{2}x10^3).

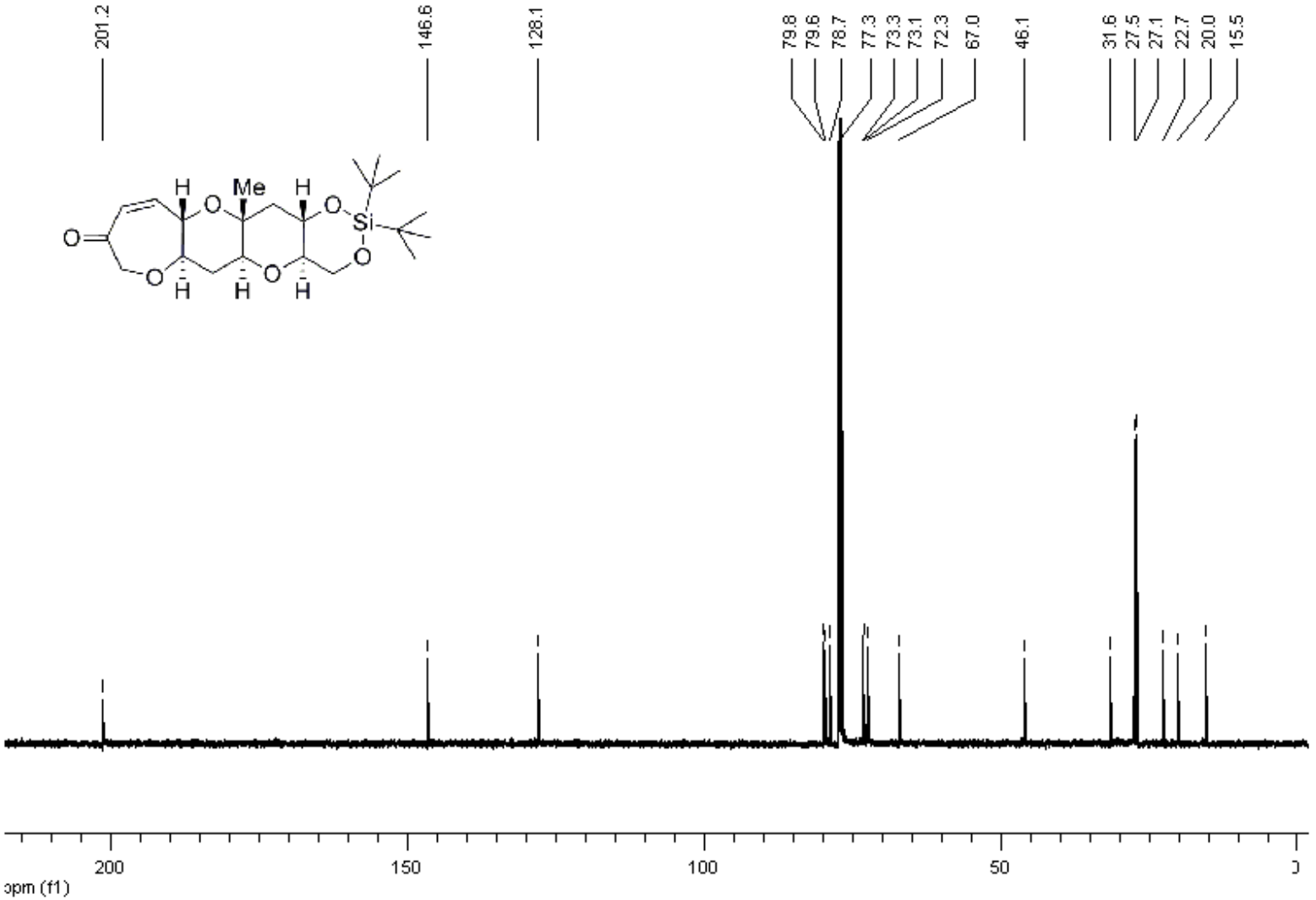
	x	y	z	U(eq)
H(23)	1932	5328	-700	30
H(24)	1058	5585	2057	30
H(25A)	-1617	5238	1786	28
H(25B)	-1282	5105	151	28
H(27)	2507	4901	591	26
H(29A)	5771	4849	3936	28
H(29B)	6082	4758	2201	28
H(30)	3325	4409	1643	29
H(31)	2552	4583	4592	34
H(32)	-654	4285	3620	32
H(33)	149	3843	3291	39
H(35A)	6424	3888	4044	35
H(35B)	5532	4011	2156	35
H(38A)	-2	5645	-4123	91
H(38B)	-2420	5598	-5495	91
H(38C)	-1752	5464	-3638	91
H(39A)	-2488	6315	-4280	88
H(39B)	-2845	6119	-5896	88
H(39C)	-431	6163	-4512	88
H(40A)	1737	6467	-797	74
H(40B)	354	6681	-122	74
H(40C)	-691	6555	-2002	74
H(41A)	-4039	6369	-1348	63
H(41B)	-2981	6513	480	63
H(41C)	-3614	6189	338	63
H(42A)	2233	6181	1854	65
H(42B)	134	6071	2227	65
H(42C)	721	6397	2378	65
H(28A)	4255	5787	1296	31
H(28B)	4848	5639	-186	31
H(43A)	813	5136	4699	39
H(43B)	2695	5312	4358	39
H(43C)	3196	5002	5106	39
H(44A)	-5230	6036	-3479	70
H(44B)	-4996	5704	-3266	70

H(44C)	-5652	5842	-5112	70
H(1A)	5973	7595	3503	37
H(1B)	8047	7736	4936	37
H(2)	5711	8058	5638	30
H(3)	2078	7789	2981	26
H(4A)	1718	8266	4945	31
H(4B)	-263	8127	3417	31
H(6)	4866	8479	4262	31
H(7A)	4522	8543	796	31
H(7B)	6592	8638	2425	31
H(8)	4495	8973	3198	35
H(9)	672	8792	418	40
H(10A)	1058	8377	-78	57
H(10B)	-903	8251	418	57
H(10C)	1202	8063	618	57
H(11)	-1305	9079	1772	40
H(12)	-344	9523	2122	46
H(14A)	4785	9502	610	40
H(14B)	5957	9380	2481	40
H(16A)	7071	7181	9438	70
H(16B)	4753	7041	9196	70
H(16C)	5973	7229	10833	70
H(17A)	7440	7687	9118	79
H(17B)	6414	7742	10551	79
H(17C)	5387	7893	8744	79
H(18A)	1313	7358	8477	67
H(18B)	1593	7688	8351	67
H(18C)	2599	7535	10152	67
H(20A)	678	7311	2801	74
H(20B)	1051	6986	2527	74
H(20C)	3009	7205	2813	74
H(21A)	-528	7169	5309	72
H(21B)	979	6959	6728	72
H(21C)	-181	6855	4807	72
H(22A)	5496	6932	5259	70
H(22B)	3537	6709	4776	70
H(22C)	4658	6815	6697	70

Appendix B


H
Me
H
O
O
Si
O
O
O
O
H
H
H

1.00
0.93
0.98
1.90
0.99
1.00
0.97
1.97
1.04
1.97
0.96
1.03
3.04
8.78
8.95
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00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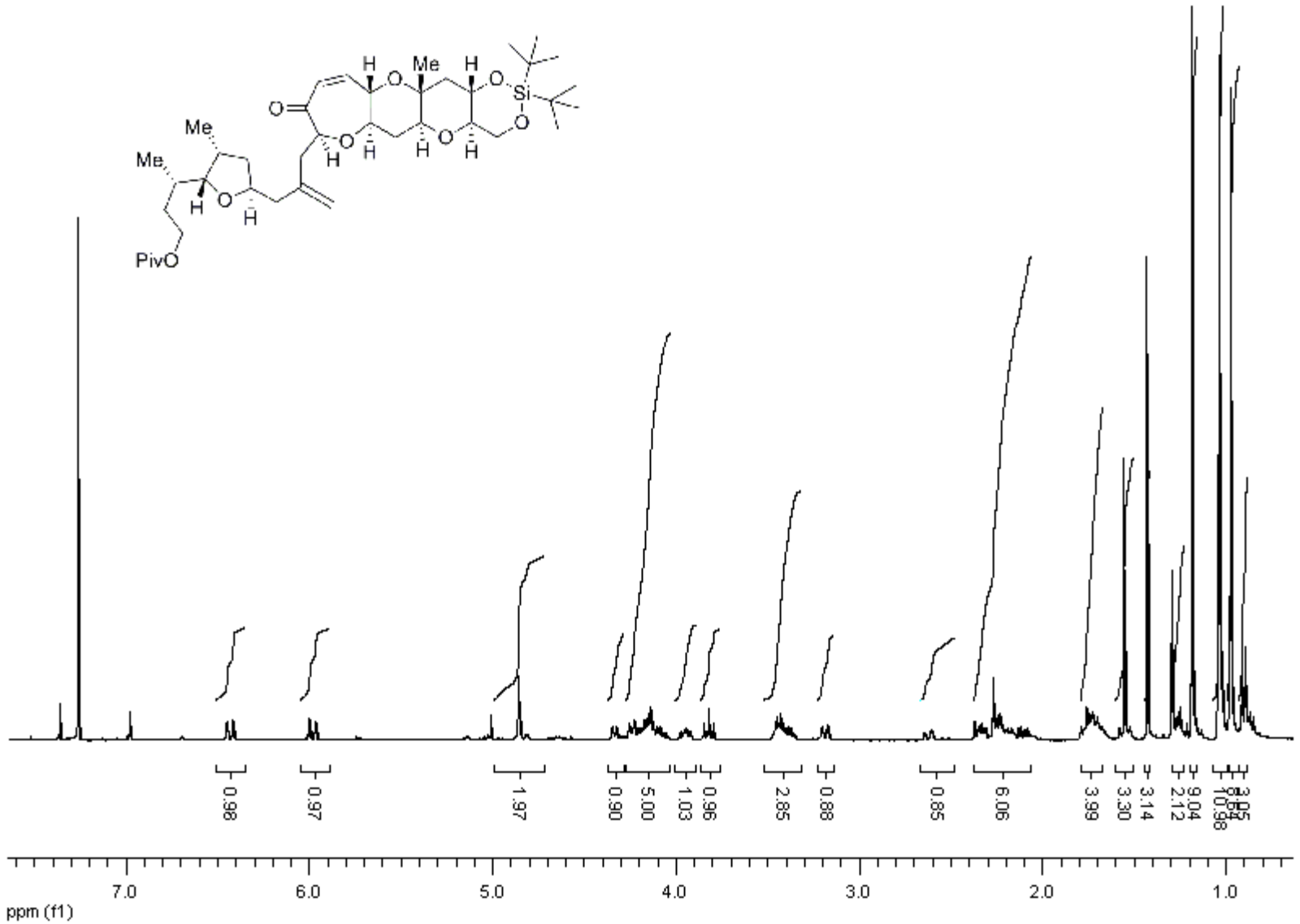
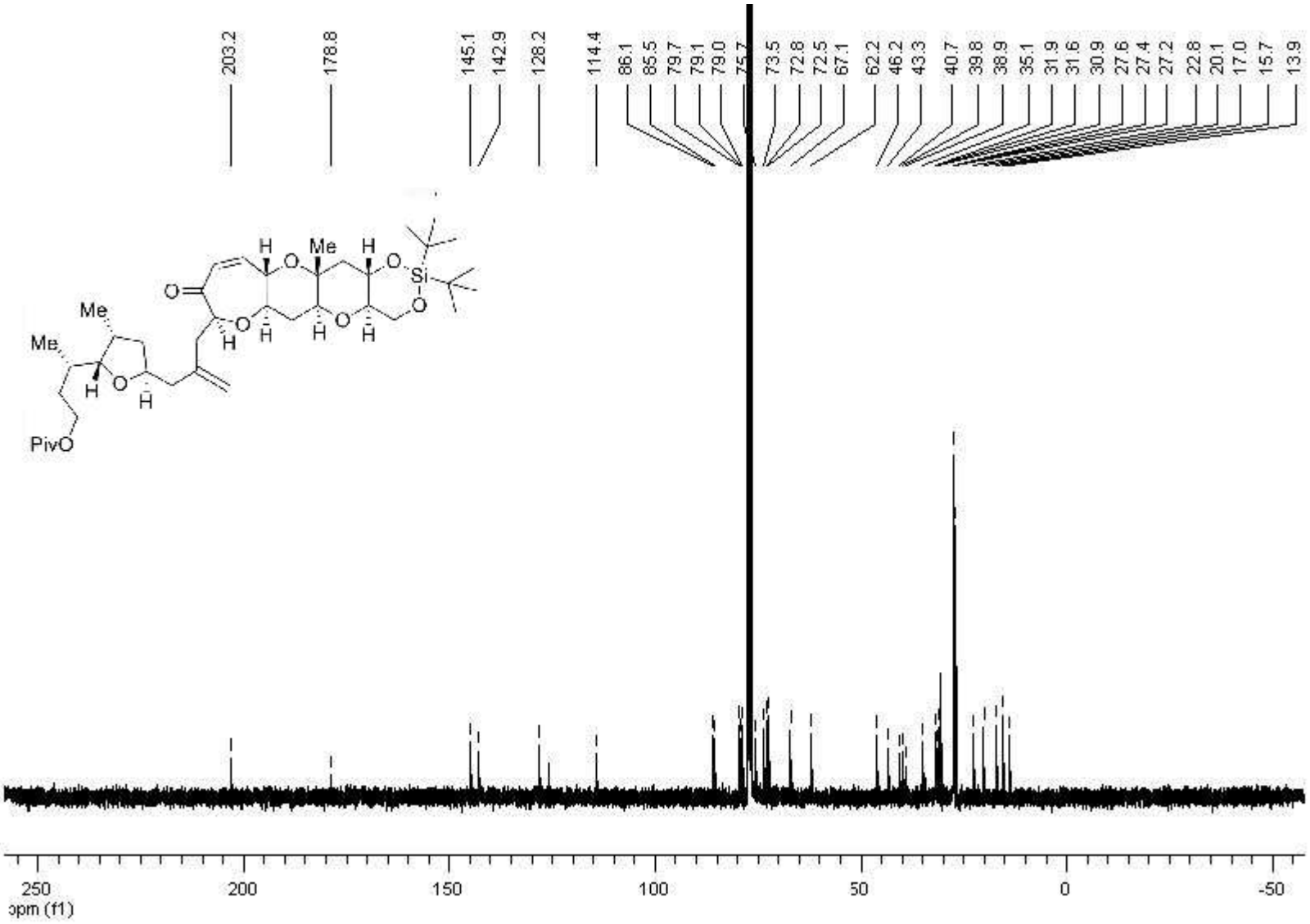
146.6
128.1
79.8
79.6
78.7
77.3
73.3
73.1
72.3
67.0
46.1
31.6
27.5
27.1
22.7
20.0
15.5
H
Me
H
O
O
Si
O
O
O
O
H
H
H
200
150
100
50
ppm (f1)


Me
Me
PivO
H
O
Me
H
O
Si
O
O
H
H
H
H
H
O
O
H
0.98
0.97
1.97
0.90
5.00
1.03
0.96
2.85
0.88
0.85
6.06
3.99
3.30
3.14
2.12
9.04
10.98
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


203.2
178.8
145.1
142.9
128.2
114.4
86.1
85.5
79.7
79.1
79.0
75.7
73.5
72.8
72.5
67.1
62.2
46.2
43.3
40.7
39.8
38.9
35.1
31.9
31.6
30.9
27.6
27.4
27.2
22.8
20.1
17.0
15.7
13.9
Me
Me
Me
H
O
H
O
Si
O
O
H
H
H
H
O
H
PivO
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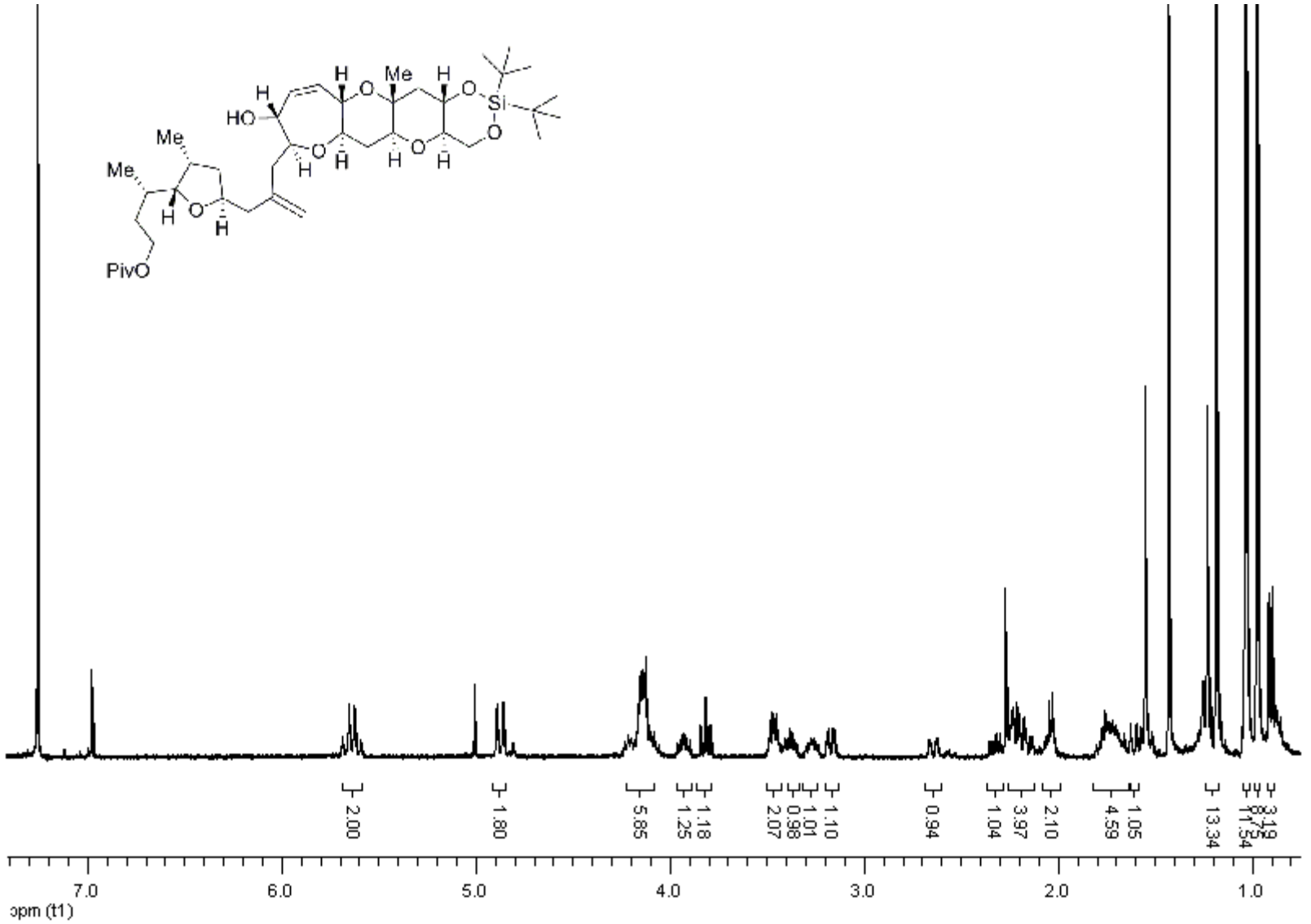
200
150
100
50
0
-50
ppm (f1)


HO
Me
Me
PivO
Si
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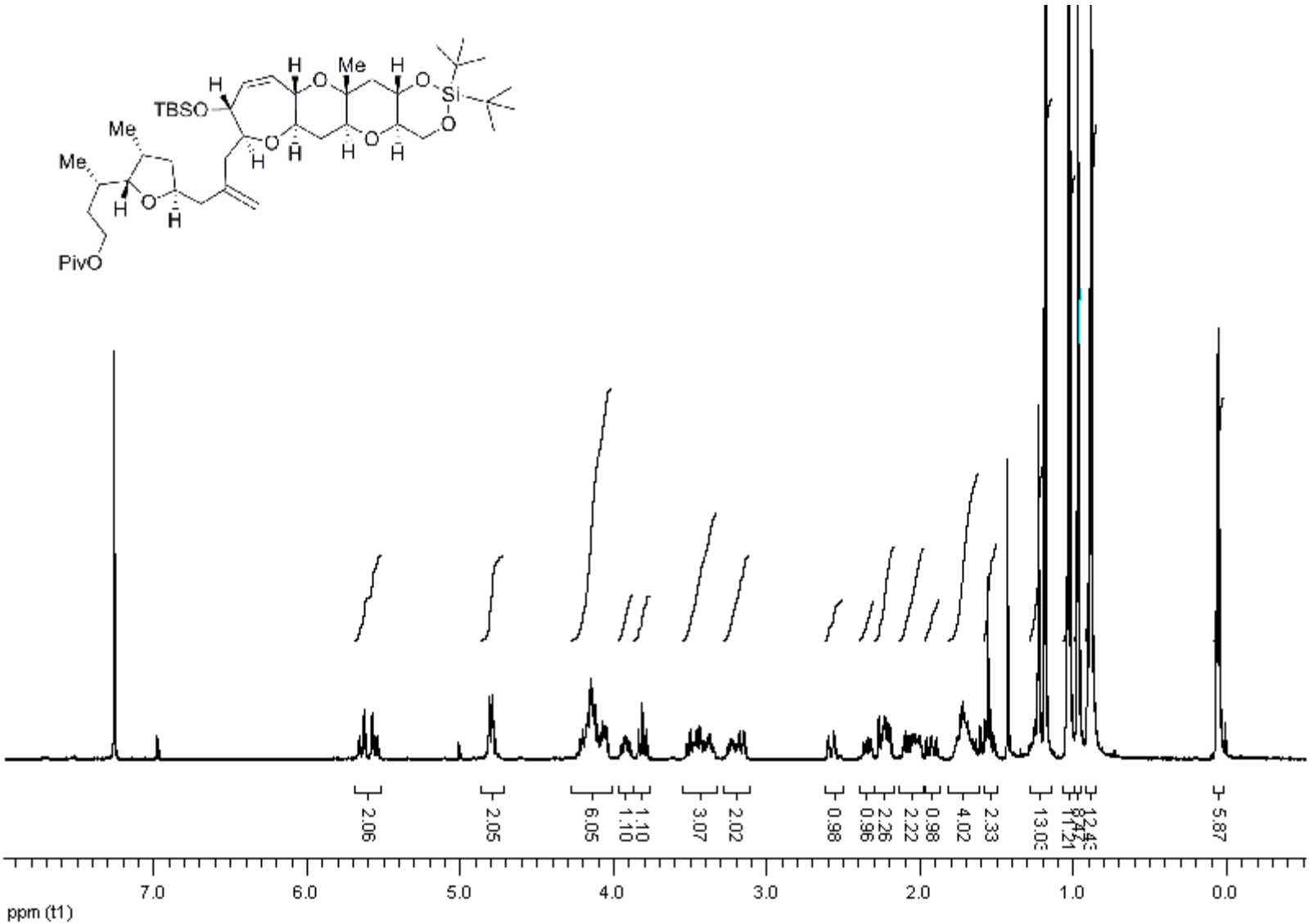
1.18
2.07
0.98
1.01
1.10
0.94
1.04
3.97
2.10
4.59
1.05
13.34
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


TBSO
Me
Me
PivO
Me
H
O
Si
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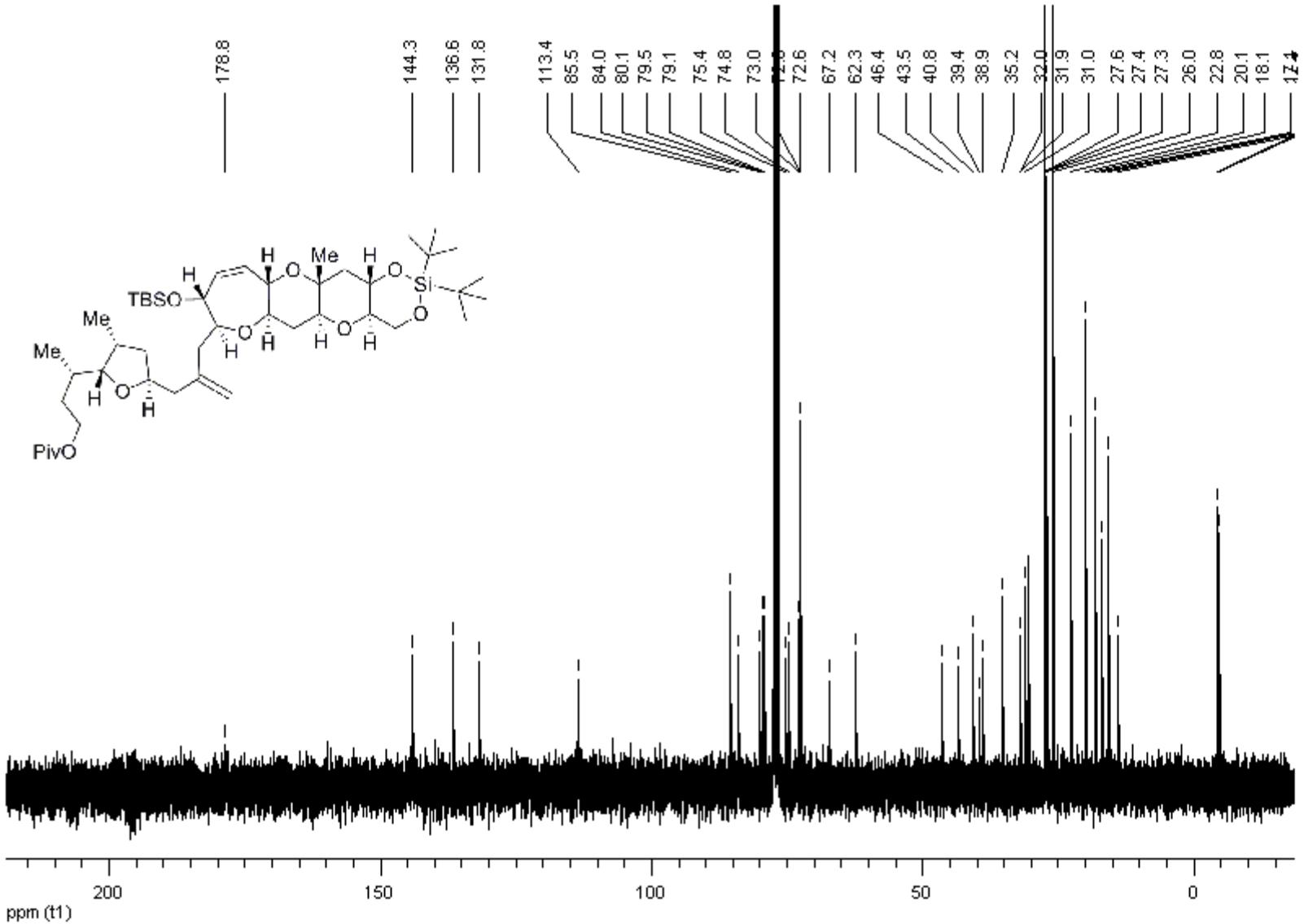
2.05
6.05
1.10
1.10
3.07
2.02
0.98
0.96
2.26
2.22
0.98
4.02
2.33
13.05
5.87
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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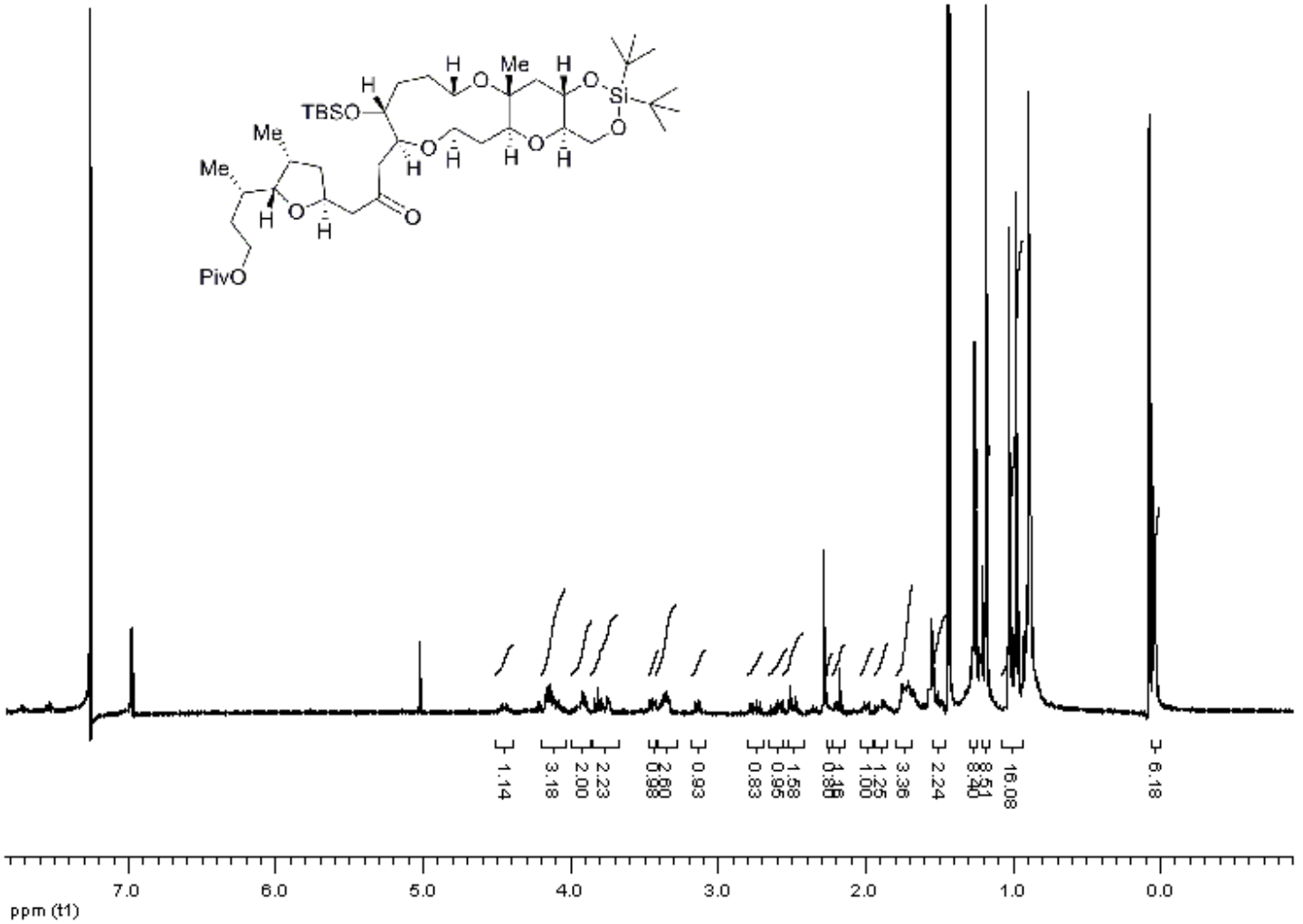
144.3
136.6
131.8
113.4
85.5
84.0
80.1
79.5
79.1
75.4
74.8
73.0
72.6
67.2
62.3
46.4
43.5
40.8
39.4
38.9
35.2
32.0
31.9
31.0
27.6
27.4
27.3
26.0
22.8
20.1
18.1
TBSO
Me
Me
PivO
200
150
100
50
0
ppm (t1)


TBSO
Me
Me
PivO
Me
Si
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2.23
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0.83
1.58
0.95
1.25
1.00
3.36
2.24
16.08
6.18
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)