Novel Coupling Reactions

For Complex Polycyclic Ethers

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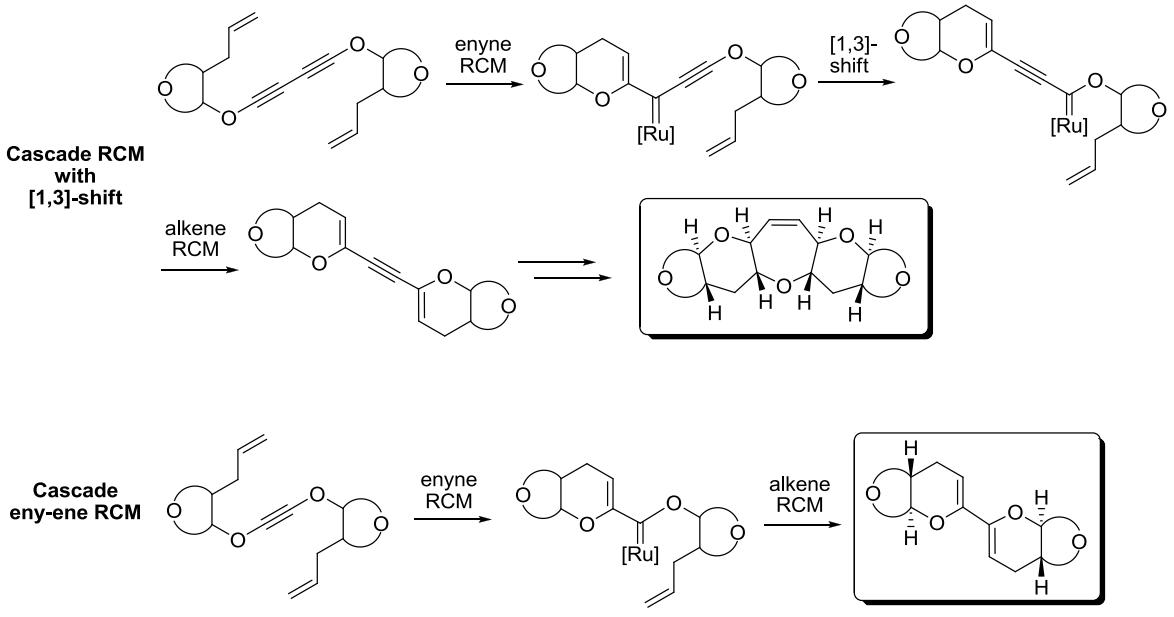
Abstract

Trans-fused polycyclic ether marine natural products are some of the most complex and formidable targets to have been isolated from marine sources. Several iterative and convergent strategies have been reported to build six- and seven-membered cyclic ethers, the two most common units in these natural products.

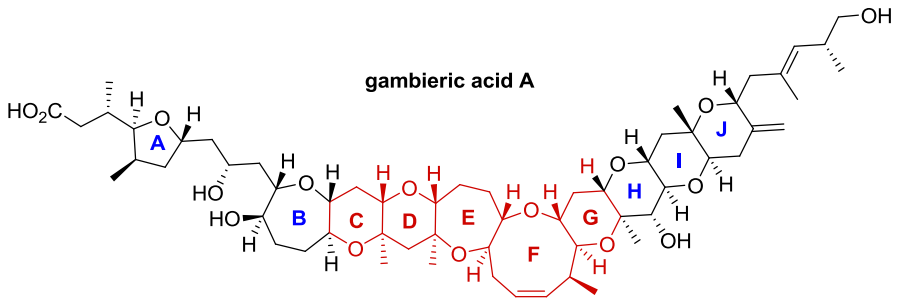
This thesis details the development of two distinctive novel methodologies for the convergent synthesis of complex subunits present in marine polycyclic ethers such as tamulamide, prymnesin, gambierol, maitotoxin and gambieric acid.

The first chapter serves as an introduction to such complex natural products. A literature review of the advances made within the Clark group, as well as in other laboratories, towards the iterative and convergent synthesis of polycyclic ethers is also included, with particular emphasis on the formation of oxepanes. This is followed by a review of olefin metathesis and its application to natural product synthesis.

The second chapter is focused on the development of cascade RCM reactions, where two different approaches are proposed. The first route involves a ruthenium-catalysed enyne RCM reaction, followed by a metallotropic [1,3]-shift and a final alkene RCM. The second route incorporates an enyne RCM reaction followed by direct alkene metathesis. These methodologies provide access to common bicyclic and tricyclic polyether skeletons such as those present in tamulamide, prymnesin, gambierol and maitotoxin, respectively.



Previous work in the group has focused on the synthesis of fragments A-D and G-J of gambieric acid. The second project, presented in Chapter 3, is directed towards the development of methodology for the coupling of these two major fragments, where the key step is the formation of rings E and F. For this, a model C-G ring fragment is employed.



Several synthetic approaches for the construction of the two subunits required for the crucial coupling step, the C-D ring fragment and G ring fragment, are described. Following this, efforts to generate an advanced intermediate containing the oxapane E ring are also detailed. Finally, various options for completion of this route, as well as improved alternative routes are discussed.

Author's Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently submitted, in candidature for any other degree. I further declare that the work presented in this manuscript is the result of my own investigations. Where the work of other investigators has been used, this has been acknowledged in the appropriate manner.

Paloma Engel García

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I have also had the pleasure to meet some fantastic people along the way, who have made this an unforgettable experience, namely: Fred, Alex, Anna, Flavien, Ralph, Thomas, Arnau, Filo, Michael and of course Chao, as well as other past and present members of the Clark group.

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Most of all, I would like to thank my "cielo" (Malcolm), because he has stood by me every step of the way and gave me confidence when I most needed it. Thank you for your endless patience and his support.

Por último, me gustaría darle las gracias a mi familia. Me siento afortunada de tener unos padres tan fantásticos, que me apoyan en todo y que, gracias a sus esfuerzos y sacrificios, me han proporcionado estas oportunidades que ellos nunca tuvieron. A ellos se lo debo todo.

Finally, I would like to thank you, the reader, who surely deserves a special mention.

Abbreviations

^{13}C-NMR	Carbon nuclear magnetic resonance
^{1}H-NMR	Proton nuclear magnetic resonance
9-BBN	9-Borabicyclo[3.3.1]nonane
Å	Ångstrom
Ac	Acetyl
acac	Acetylacetonate
AIBN	2,2'-Azobis(2-methylpropionitrile)
aq	Aqueous
Ar	Aromatic
ax	Axial
Bn	Benzyl
br	broad
Bu	Butyl
^{t}Bu	*tert*-Butyl
n-BuLi	*n*-Butyl lithium
cat.	Catalyst
Cbz	Carboxybenzyl
CDI	1,1'-Carbonyldiimidazole
CM	Cross-metathesis
CMPI	2-Chloro-1-methylpyridinium iodide
Cp	Cyclopentadienyl
CSA	Camphorsulphonic acid
Cy	Cyclohexyl

d	doublet
DBU	1,8-Diazabicycloundec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	Dichloromethane
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-(Dimethylamino)pyridine
DMDO	Dimethyldioxirane
DMF	*N*,*N'*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	Dimethylsulfide
DMSO	dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
h	Hour(s)
HMDS	Hexamethyldisilazane
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectrometry
LDA	Lithium di-*iso*-propylamide
LiHMDS	Lithium bis(trimethylsilyl)amide

M	Molar
*m*CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Mes	1,3,5-Trimethylbenzyl
min	Minute(s)
ML_n	Metal and associated ligands
Ms	Methansulfonyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMM	*N*-methylmorphiline
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
°C	Degrees centigrade
p	*para*
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
^{i}Pr	*iso*-Propyl
PTSA	*para*-Toluenesulfonic acid
quant.	Quantitative
RCAM	Ring-closing alkyne metathesis

RCEM	Ring-closing enyne metathesis
RCM	Ring closing metathesis
ROM	Ring-opening metathesis
ROMP	Ring-opening metathesis polymerisation
recryst.	Recrystallisation
rt	Room temperature
SET	Single electron transfer
SM	Starting material
S_N	Nucleophilic substitution
TBAF	Tetra-*n*-butylammonium fluoride
TBAHS	Tetra-*n*-butylammonium hydrogen sulphate
TBAI	Tetra-*n*-butylammonium iodide
TBDMS or TBS	*tert*-Butyldimethylsilyl chloride
TBDPS	*tert*-butyldiphenylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Thx	Thexyl
TIPS	Tri-*iso*-propylsilyl
TLC	Thin layer liquid chromatography
TMEDA	*N,N,N',N'* -Tetramethylethylenediamine
TMS	Trimethylsilyl
TPAP	Tetra-*n*-propylammoniumperruthenate
Ts	*para*-Toluenesulfonyl

Contents

Chapter 1
Introduction

1. Marine Polycyclic Ethers

Over the last few decades, a huge variety of natural products have been isolated from marine sources. Amongst the most complex and challenging of these are a range of compounds containing polycyclic ether motifs. Despite their structural similarities, polycyclic ethers show a wide range of biological activities including neurotoxicity, cardiovascular and respiratory activity, as well as antifungal activities. These compounds are produced by dinoflagellates, marine unicellular microorganisms, the accumulation of which has been identified as the cause of widespread seafood poisoning (ciguatera), as well as the "red tide" phenomenon.[1]

1.1. Red Tides and Ciguatera

"Red tides" are natural phenomena occurring periodically along the Gulf of Mexico, the north east coast of the United States, French Polynesia and the Caribbean Sea. They are formed by dense blooms of toxic, unicellular marine microorganisms called dinoflagellates, such as *Karenia breve* (formerly known as *Gymnodinium breve*)[2] and *Gymnodinium mikimotoi*.[3] These blooms have received considerable attention from the scientific community due to their environmental toxicity and devastating consequences for the fishing and tourist industries. In recent years, the toxins released during these blooms have been identified as the primary cause of massive fish kills, mollusc contamination, and human food intoxication. Furthermore, exposure to seawater aerosols, found in shore mists near red tides, have been linked to respiratory distress, including coughing and bronchoconstrictions resulting in shortness of breath, in both normal individuals and those with respiratory diseases.[4,1]

Numerous attempts have been made since 1968 to isolate the pure toxins from cultured cells in order to obtain a wider understanding of the red tide phenomenon. It was not until 1981 that the first polycyclic ether toxin, brevetoxin B, was isolated and characterised in crystal form by Nakanishi and co-workers (Figure 1).[5]

Other related compounds such as the gambieric acids,[6,7] gambierol,[8] the ciguatoxins,[9] and maitotoxin[10,11] have since been isolated from various strains of another dinoflagellate called *Gambiediscus toxicus* and linked to ciguatera (Figure 1).[4]

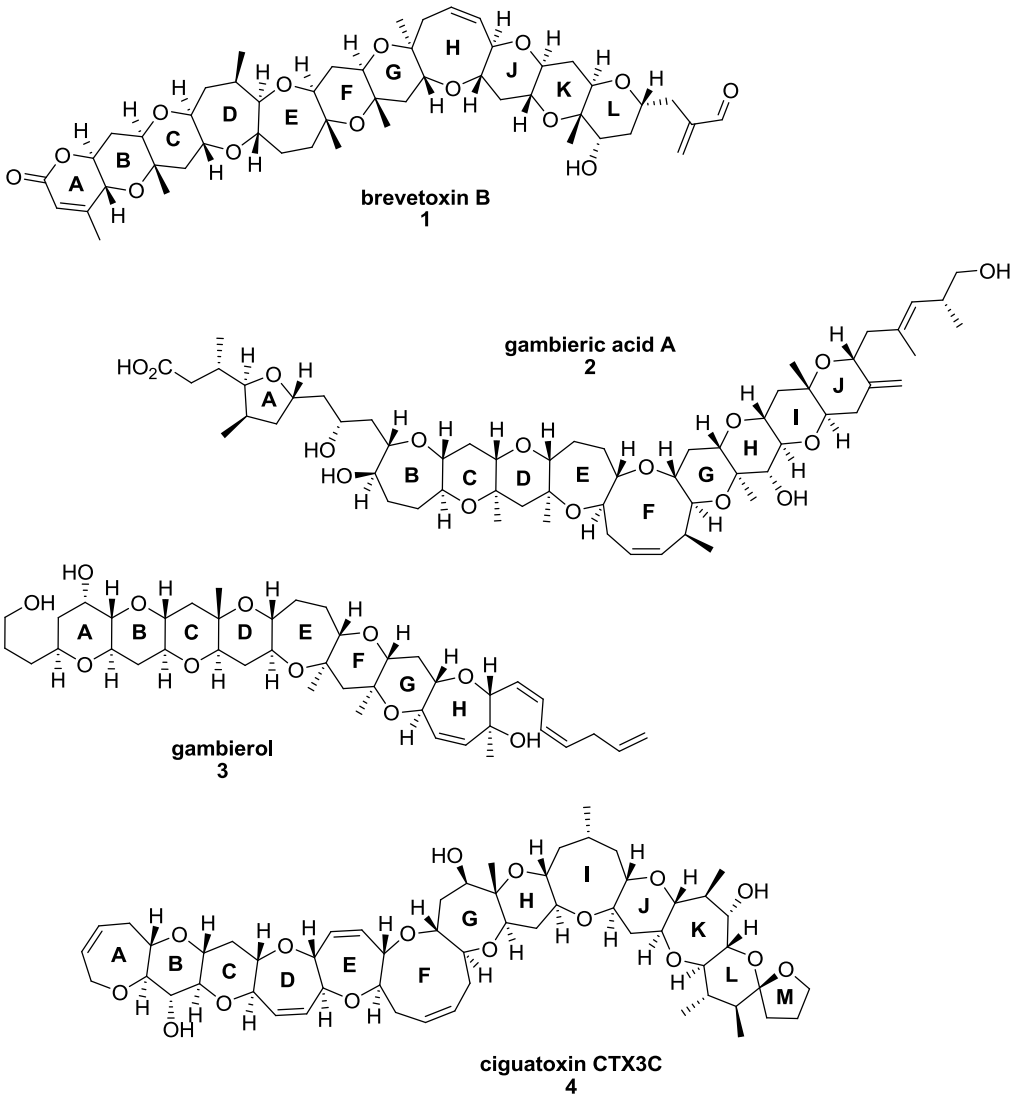


Figure 1. Structure of representative polycyclic ethers

1.2. General Structural Features

The main structural feature of this class of natural product is the extensive presence of the *trans*-fused polyether ring systems, consisting of five- to nine-membered rings, where the oxygen in the ether ring is alternatively placed on the northern and southern section of the ring. This structural motif locks the carbon chain into a long, semi-rigid ladder-like framework. The stereochemical configuration of the centres adjacent to the oxygen atoms of the ether bridge strictly alternate between *R* and *S* configuration, giving rise to the general structure depicted in Figure 2.

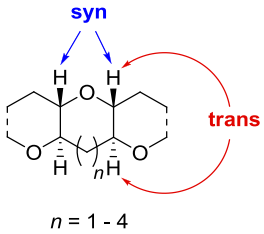


Figure 2. General depiction of *trans*-fused polyether ring systems

These intriguing and challenging structures have served as an inspiration for the development of new methodologies in organic synthesis, because highly efficient synthetic strategies, requiring excellent material throughput and a minimum number of synthetic transformations, are critical.

1.3. Strategies for the Synthesis of Polycyclic Ethers

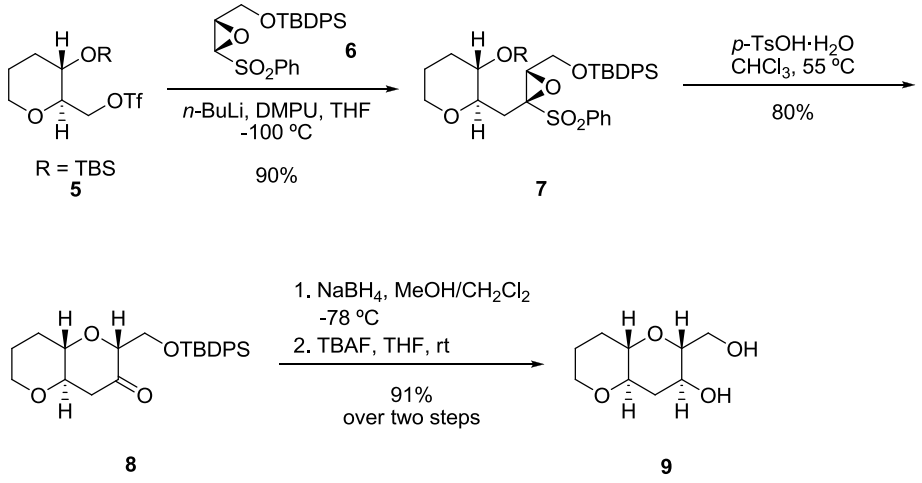
Two general approaches can be envisaged towards the preparation of polycyclic ether compounds: a convergent and an iterative strategy. The most common of these is a convergent approach, in which small cyclic ether subunits are coupled together to form larger fragments. On the other hand, an iterative strategy, designed to take advantage of the repetitive features in the target structure, typically involves a series of steps culminating in a ring closure that yields a suitable precursor for the repetition of the same steps. In both cases, an ideal approach tolerates variations in ring size and substitution pattern.

This section will focus on key strategies, both convergent and iterative, that have been applied extensively in the synthesis of polycyclic ether subunits.

1.3.1. Cation/Anion Intermediates

1.3.1.1. Epoxide Ring Opening Strategies

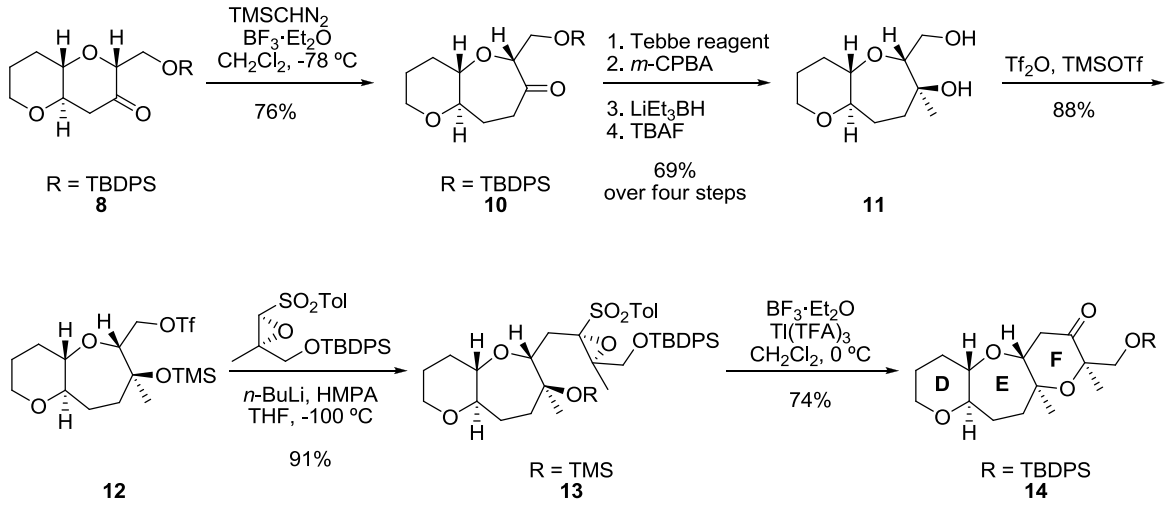
Mori *et al*. have developed a novel iterative strategy for the construction of polypyran domains based on a biosynthetic model, where cyclisation is considered to be the key step (Scheme 1).[12] The nucleophilic substitution of triflate **5** by a sulfone stabilised oxiranyl anion, formed by deprotonation of **6**, created the desired carbon backbone and installed the oxygenation required for the formation of the next ether ring (Scheme 1). Subsequent treatment of **7** with acid induced the desired 6-endo epoxide opening to close the ring, affording ketone **8**. Stereoselective reduction and subsequent deprotection of **8** provided diol **9** in an excellent yield. Furthermore, this method has also been applied to systems bearing axial methyl groups.[13]



Scheme 1. Iterative polypyran synthesis via 6-*endo*-cyclization of epoxysulfones

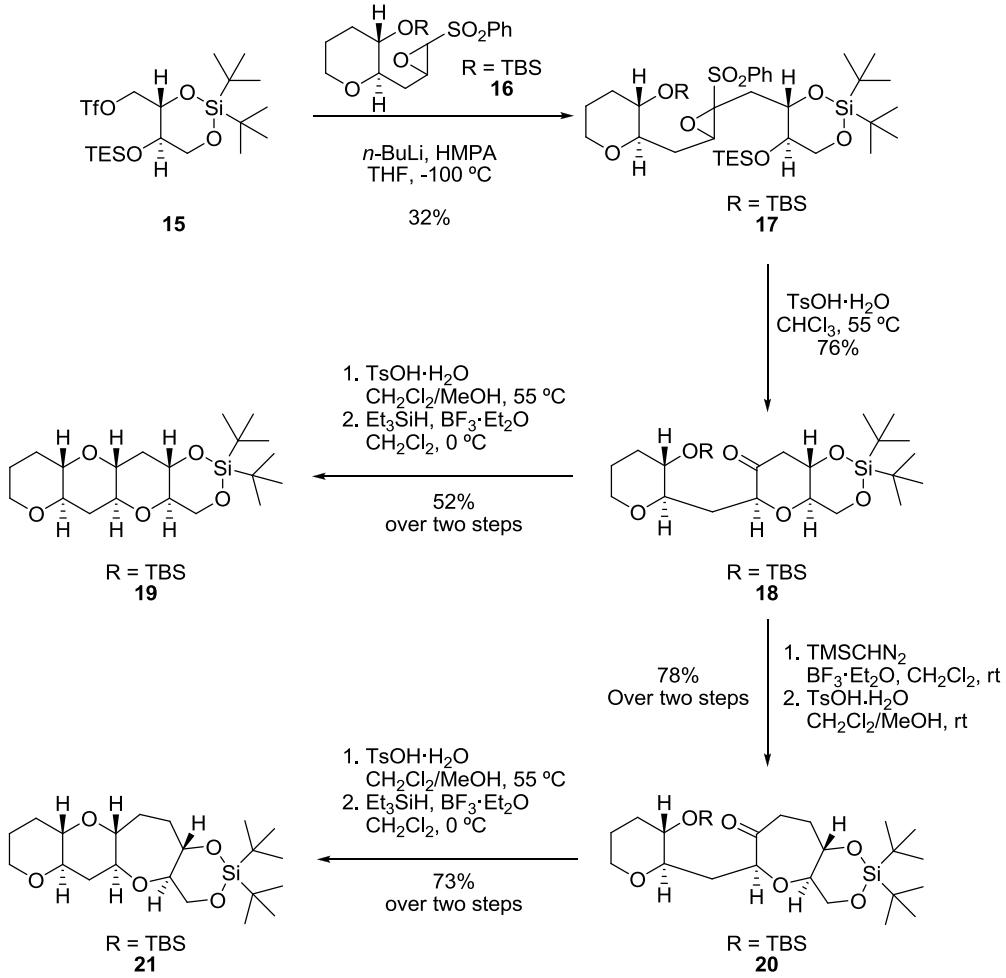
Further exemplifying the flexibility of this approach, Mori *et al*. applied this methodology towards the successful construction of the DEF ring system of yessotoxin **14**, containing a seven-membered ether ring (Scheme 2).[13] The direct formation of oxepanes was circumvented by employing ring-expansion methodology[14] involving the treatment of **8** with trimethylsilyl diazomethane, under Lewis acid catalysis, leading to oxepane **10**. Direct organo-metallic methylation of ketone **10** proved unsuccessful and therefore a four-step protocol was employed to afford the desired α-isomer **11** in an overall yield of 69%. Subsequent one-pot triflation of the primary alcohol and silylation of the tertiary alcohol provided **12**, which was coupled with the oxiranyl anion, generated from a methyl-substituted epoxy sulfone, to furnish the cyclisation precursor

13. Finally, construction of the desired DEF ring fragment **14** was achieved *via* a Lewis-acid promoted 6-*endo*-cyclisation.



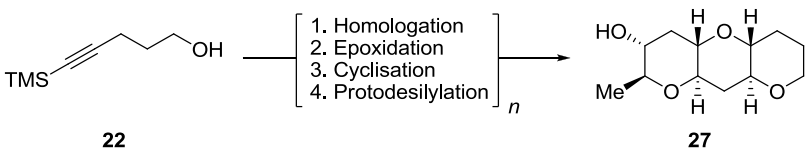
Scheme 2. Synthesis of the DEF ring system of Yessotoxin

Following the successful development of this strategy, Mori and co-workers applied this approach to several other targets allowing the formal total synthesis of hemibrevetoxin B[15] and the ABCD fragment of gambierol[16] to be completed. More recently, this methodology has been adapted as part of a convergent strategy to allow the coupling of two different polycyclic ether subunits.[17] The sequence involved the nucleophilic substitution of triflate **15** with an oxiranyl anion formed from **16**, followed by a 6-*endo*-cyclisation to obtain **18**. At this point, the synthetic pathway diverged to allow for the formation of a six- or seven-membered ring. The six-membered ring was formed by a two-step reductive etherification reaction to afford tricyclic ether **19**, whilst ring expansion of **18** led to the seven-membered ketone **20**. A final two-step etherification reaction led to the formation on tricyclic ether **21** containing an oxepane (Scheme 3).



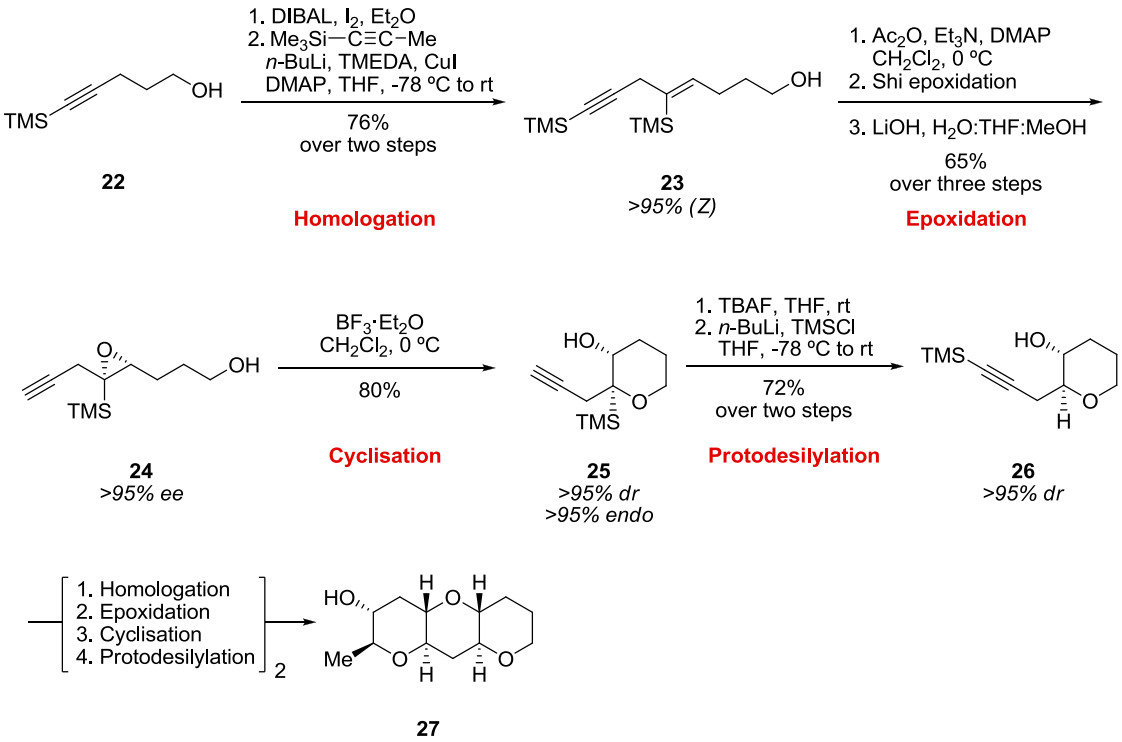
Scheme 3. Convergent strategy using oxiranyl anions

In 2003, Jamison *et al*. reported a strategy emulating the three fundamental proposed[4] processes in the *trans*-fused polycyclic ether biosynthesis: Firstly, polyene synthesis *via* iterative chain homologation; secondly, asymmetric epoxidation; and thirdly, a series of *endo*-selective epoxide-opening events.[18] Incorporation of a trimethylsilyl (TMS) group enabled an efficient and selective emulation of all three proposed biogenetic processes, leading to the rapid and iterative synthesis of a ladder polyether subunit (Scheme 4).



Scheme 4. TMS-based homologation-epoxidation-cyclisation strategy

The synthesis of tricyclic subunit **27** commenced with alcohol **22** (Scheme 5). Following the highly selective hydroalumination-iodination of **22**, direct propargylation proceeded in high yield to afford enyne **23**. From this point, an enantioselective Shi epoxidation[19] of trisubstituted alkene **23** (>95% *ee*) and subsequent deprotection provided epoxide **24**. Lewis acid-promoted hydroxyepoxide cyclisation completed the construction of the first tetrahydropyran ring, **25**. Finally, protodesilylation (TBAF) of **25** cleanly removed the ring TMS group, with retention of configuration to give alcohol **26** (>95% *dr*). The degree of reagent control in subsequent epoxidation reactions was a key factor in the assembly of the tetrahydropyran triad **27** by reiteration of these same four procedures.



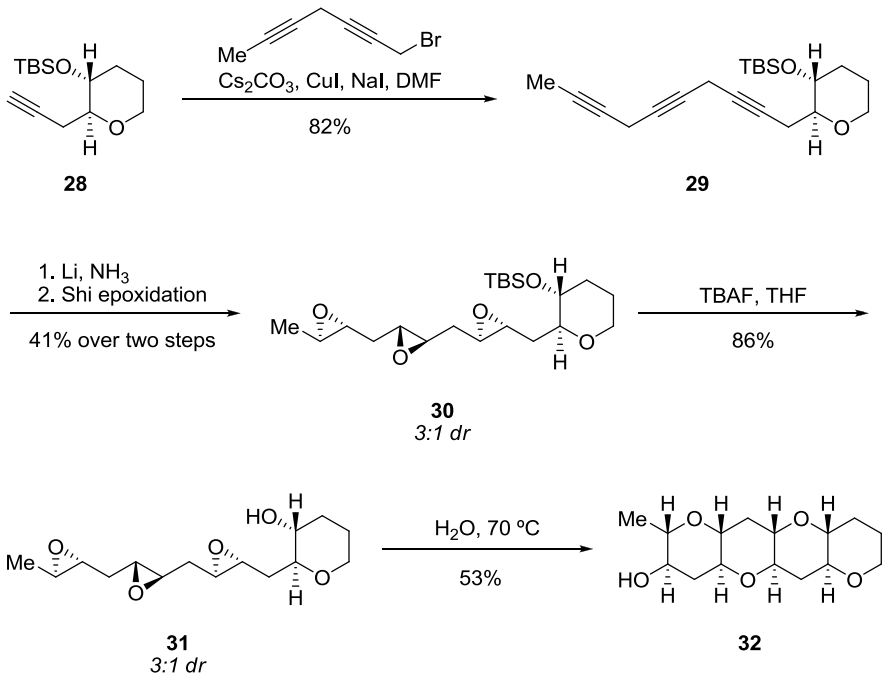
Scheme 5. TMS-Based Homologation-Epoxidation-Cyclisation Strategy for Ladder THP Synthesis

Similar methodology has since been applied to cascade epoxide-opening protocols, using the TMS group as a traceless directing group.[20] However, incorporation of angular methyl groups and the synthesis of larger ring systems have not been reported.

1.3.1.2. Cascade-Epoxide Ring Opening Strategies

The biomimetic aspect of cascade epoxide ring opening sequences has attracted much attention over the years and several elegant syntheses have been reported by Murai,[21] McDonald[22,23] and Jamison.[20] The latter recently reported probably the most innovative process, which involves epoxide-opening cascades promoted by water.[24]

Investigations into the pH dependence of THP-to-THF selectivity led to the conclusion that neutral water acted as an optimal promoter for the required ring-opening selectivity, once a single templating THP had been appended to a chain of epoxides. From these results, a high-yielding route to naturally occurring *trans*-fused systems was developed (Scheme 6). The synthesis of the epoxide chain involved a three-step protocol, commencing by the alkylation of alkyne **28** to form triyne **29**. Reduction of the triple bonds to the corresponding *E*-alkenes, under Birch conditions (Li/NH_3), provided the unstable skipped triene intermediate, which immediately underwent Shi epoxidation[25] to afford polyepoxide **30** (3:1 ratio of diastereomers). It was proposed that the moderate stereoselectivity of the epoxidation reaction was due to the proximity of the protected hydroxyl group to the adjacent internal alkene, whereas more remote alkenes did not suffer from this mismatched double diastereoselection. After TBS deprotection, polyepoxide **31** was heated in water for 72 hours affording the THP tetrad **32**, representative of structural scafolds found in numerous ladder polyethers.

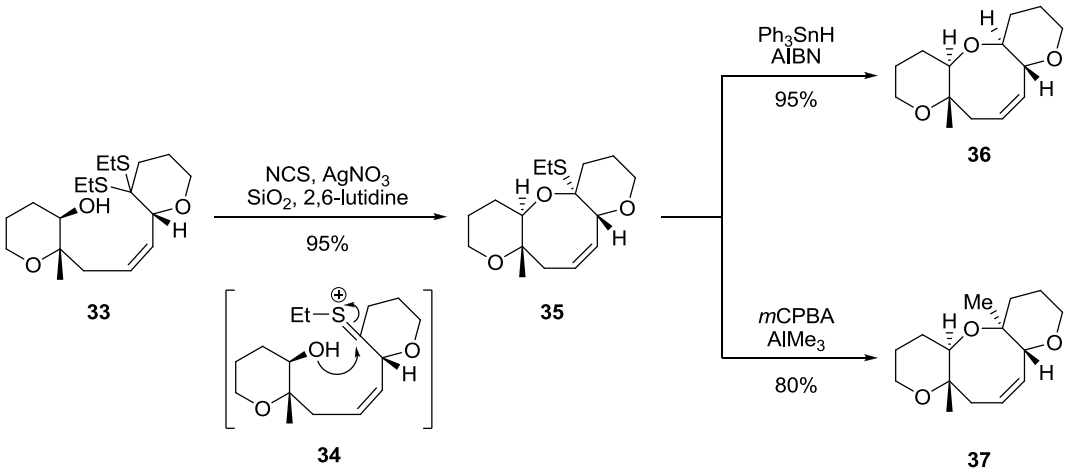


Scheme 6. H_2O promoted epoxide-opening cascade

It should be noted that these THP-selective, epoxide-opening cascade reactions were far higher-yielding than those relying upon covalently attached directing groups, that had been described previously. It is due to this increased synthetic efficiency that a straightforward route for the rapid assembly of ladder polycyclic ethers can be pursued, enabling investigations directed towards understanding the mode of action of these natural products.

1.3.1.3. Hydroxy Ketone-Type Cyclisation

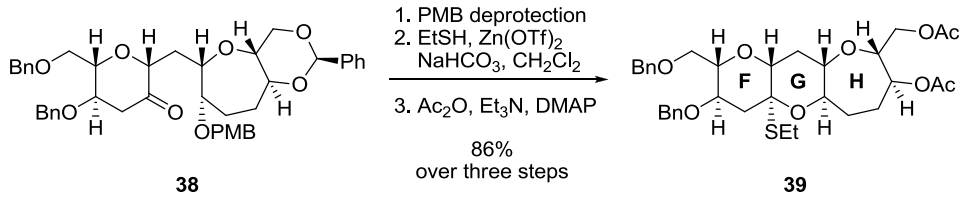
A synthetic strategy that has proved particularly useful in the construction of eight-membered cyclic ethers involves the use of cyclic O,S-acetal intermediates (Scheme 7). First reported by Nicolaou *et al*. in 1986, this method involved the exposure of hydroxy dithioketal **33** to NCS in the presence of $AgNO_3$, SiO_2 and 2,6-lutidine to afford O,S-acetal **35**, presumably through the thionium intermediate **34**. It was from compound **35** that structural diversity could be introduced. Initial investigation showed that the radical reaction of **35** with Ph_3SnH led to oxocene **36** stereoselectively. Alternatively, a separate protocol involving *m*CPBA oxidation to give the corresponding sulfoxide or sulfone, followed by *in situ* addition of $AlMe_3$, furnished the methylated oxocene **37**. This methodology was then employed to couple polycyclic ether subunits during the synthesis of the F-J ring fragment of brevetoxin A.[26]



Scheme 7. Hydroxy dithioketal cyclisation method involving O,S-acetal

Sasaki and co-workers used a zinc-promoted procedure to generate the same kind of cyclic thioacetal in a pyran system (Scheme 8).[27] After PMB removal, treatment of ketone **38** with EtSH and $Zn(OTf)_2$ followed by acetylation afforded O,S-acetal **39** in

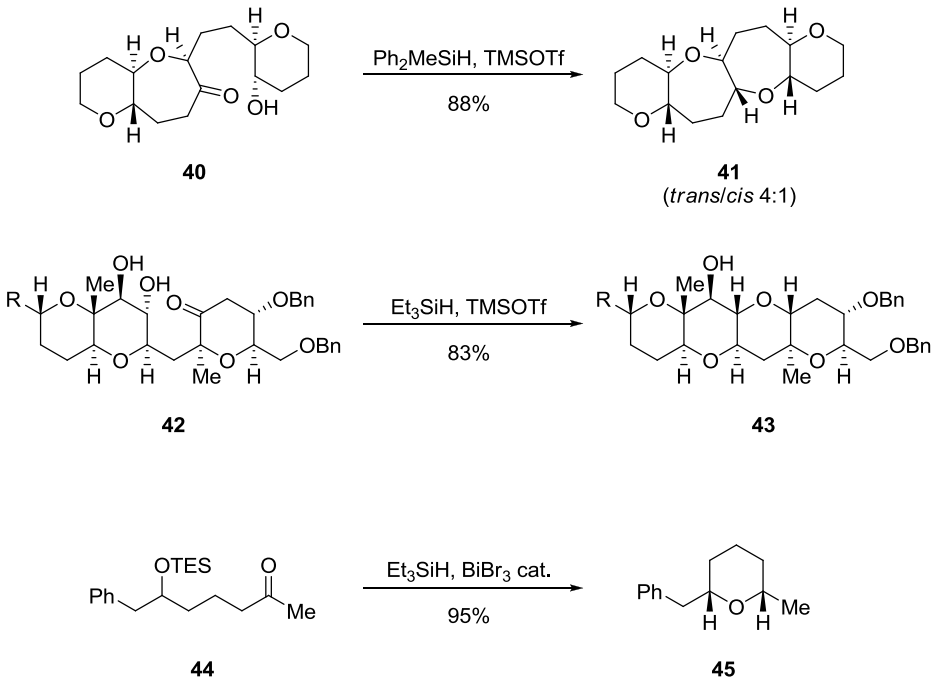
excellent overall yield. This methodology was successfully applied in the synthesis of the FGH ring system of gambierol.



38 **39**

Scheme 8. Synthesis of the FGH ring system of gambierol

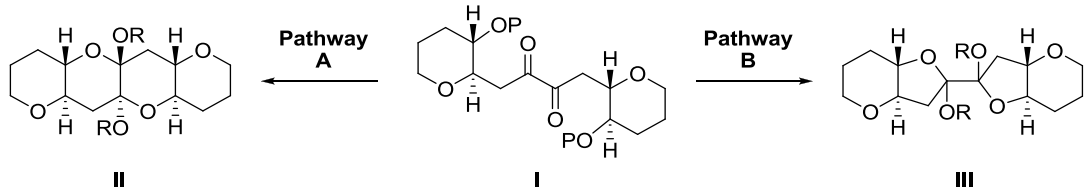
Inspired by the work of Olah and co-workers,[28] Nicolaou reported a direct method for the formation of cyclic ethers from hydroxy ketones (Scheme 9). This method relied on the reductive cyclisation of hydroxy ketone **40** with Ph_2MeSiH in the presence of a Lewis acid, resulting in the formation of dioxepane structure **41**. Whilst the stereoselectivity observed with oxepane systems **41** was relatively poor (*trans*/*cis* 4:1), the construction of pyran systems usually proceeded with complete stereocontrol, as demonstrated several years later by Sasaki *et al*. with the improved transformation of hydroxy ketone **42** into cyclic ether **43**, using Et_3SiH and TMSOTf.[29] The Evans group extended this methodology by employing silyl derivatives of hydroxy ketones, such as **44**, for the preparation of the corresponding tetrahydropyran **45**. Treatment of **44** with Et_3SiH in the presence of $BiBr_3$ afforded the cyclic ether **45** with complete diastereocontrol.[30]



40 **41** **42** **43** **44** **45**

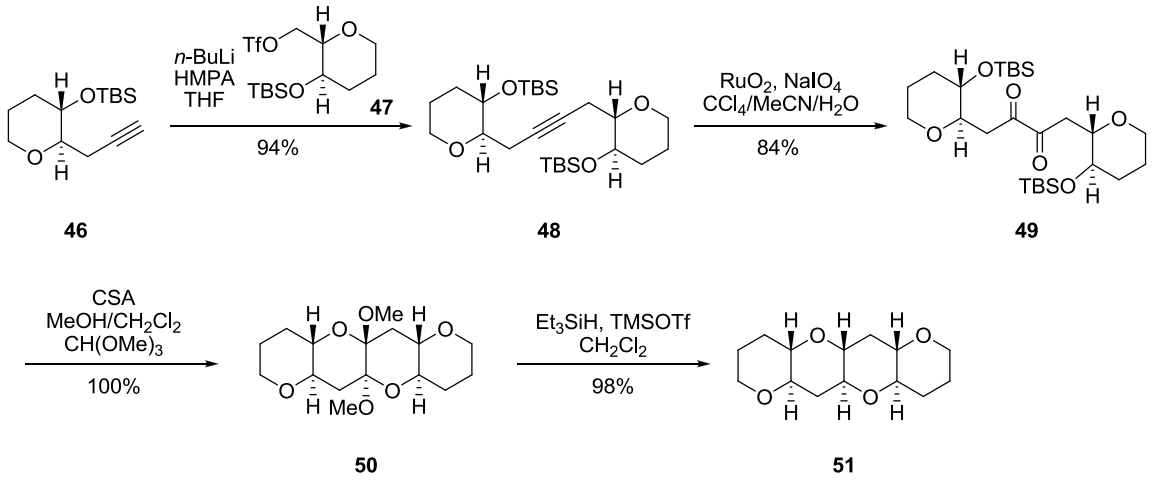
Scheme 9. Hydroxy ketone reductive cyclysation methodology for cyclic ether formation

Hydroxyketone methodology has been used extensively in numerous other convergent syntheses. In 2000, the groups of Nakata[31] and Fujiwara and Murai[32] reported simultaneously, but independently, a four-step convergent synthesis for the construction of a *trans*-fused tetracyclic six-membered ring system, starting from a monocyclic ether acetylene and a triflate segment. The proposed sequence involved: firstly, coupling of the two monocyclic segments; secondly, oxidative formation of an α-diketone; thirdly, construction of *trans*-fused tetracyclic diacetals; and finally, reductive etherification of the diacetal. Critical to the success of this strategy was the outcome of the double diacetalisation, from which two different sized ring systems could be obtained: the desired six-membered diacetal **II** as a result of Pathway A or, on the other hand, the five-membered diacetal **III** *via* Pathway B (Scheme 10). However, thermodynamic studies of **II** (R=Me) and **III** (R=Me), showed that the heat of formation of **II** was 6.0 Kcal/mol lower in energy than that of **III**, suggesting the desired Pathway A would predominate.[33]



Scheme 10. Possible Diacetalisation outcomes

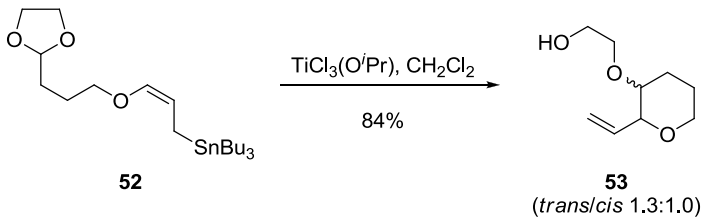
The sequence began with the coupling reaction of the lithium acetylide formed from **46** with triflate **47** in the presence of HMPA, to afford symmetrical alkyne **48** (Scheme 11). Oxidation of the alkyne moiety in **48** with *in situ* formed RuO_4, furnished the α-diketone **49** in 84% yield. As predicted, the crucial double acetalisation step proceeded *via* Pathway A. Thus, upon treatment of **49** with CSA and $CH(OMe)_3$ in $MeOH/CH_2Cl_2$, loss of the TBS groups followed by a double acetalisation resulted in the selective formation of the desired tetracyclic diacetal **50**, in a near quantitative yield. To complete the synthesis, the stereoselective reduction of both acetal groups in **50**, with Et_3SiH in the presence of a Lewis acid, provided the desired *trans*-fused tetracyclic six-membered ring system **51** in excellent yield. Further exemplifying the benefits of this approach, Mori *et al*. subsequently reported a similar strategy for the construction of polypyran structures.[34]



Scheme 11. Four-step convergent synthesis of a *trans*-fused tetracyclic six-membered ring system

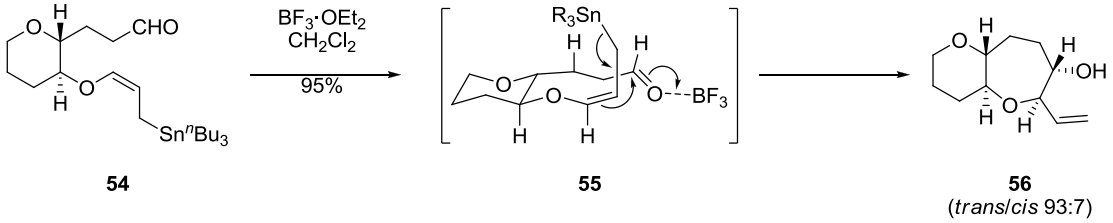
1.3.1.4. Aldehyde Allylation

In 1990, the Yamamoto group reported a new synthesis of the fundamental pyran unit present in all polycyclic ether natural products.[35] This methodology involved a Lewis-acid mediated cyclisation of a trialkylstannyl ether acetal **52** to afford the desired cyclic ether **53** in good yield (Scheme 12). Unfortunately, although the desired ring-closure proved highly effective, the resulting products were obtained with poor diastereoselectivity.



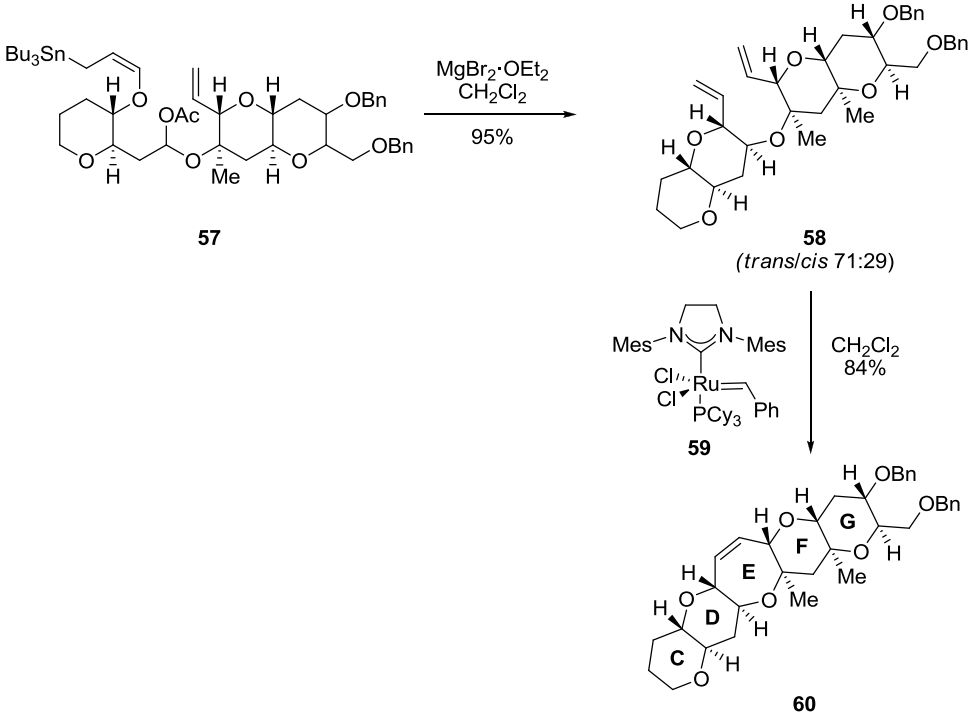
Scheme 12. Early trialkylstannyl ether acetal cyclisation

Dramatic improvements in both yield and stereoselectivity were observed when the acetal functionality was replaced with the corresponding aldehyde (Scheme 13).[36] Thus, activation of aldehyde **54** with $BF_3 \cdot Et_2O$ led to intramolecular allylation and the stereoselective formation of 6,7-bicycle **56** in excellent yield. The high diastereoselectivity was attributed to the proposed transition state **55**, in which the unfavourable interactions between the two axial groups were minimised, leading to the formation of the desired *trans*-system **56**. However, these improvements in stereocontrol were limited to cases in which seven-membered rings were formed.



Scheme 13. Trialkylstannyl ether aldehyde cyclisation

Similarly, methodology involving the intramolecular allylation of α-acetoxy ethers and subsequent ring-closing metathesis (RCM) has also been employed for the convergent synthesis of polycyclic ethers (Scheme 14).[37] Exposure of acetal **57** to $MgBr_2 \cdot OEt_2$ promoted intramolecular allylation, resulting in the formation of pentacyclic ether **58** in excellent yield and moderate stereoselectivity (*trans*/*cis* 71:29). A final ring closing metathesis reaction in the presence of Grubbs' second generation catalyst **59** completed the convergent synthesis of the C-G ring fragment of gambierol **60**.

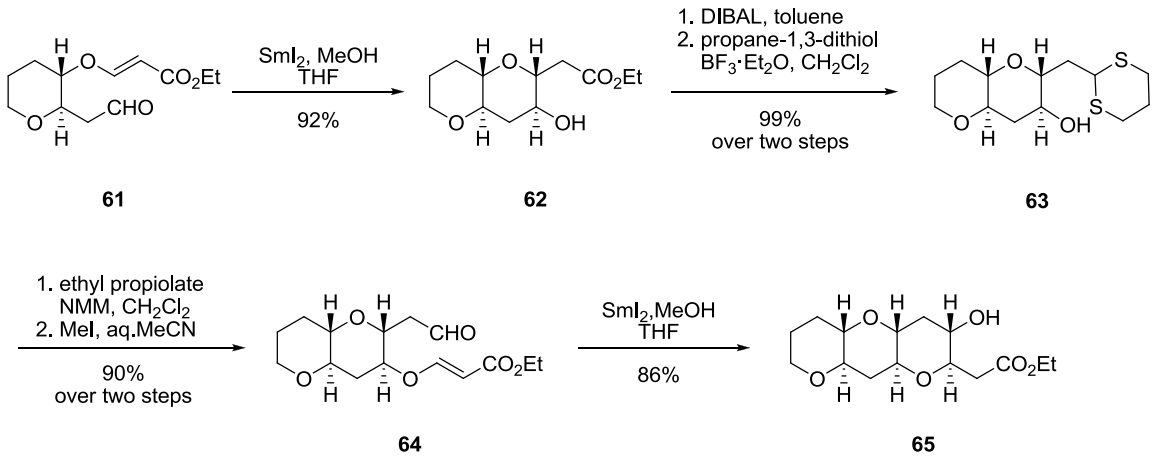


Scheme 14. Synthesis gambierol fragment *via* intramolecular allylation of α-acetoxy ethers and RCM

1.3.2. Radical Intermediates

1.3.2.1. Samarium Induced Reductive Intramolecular Cyclisation

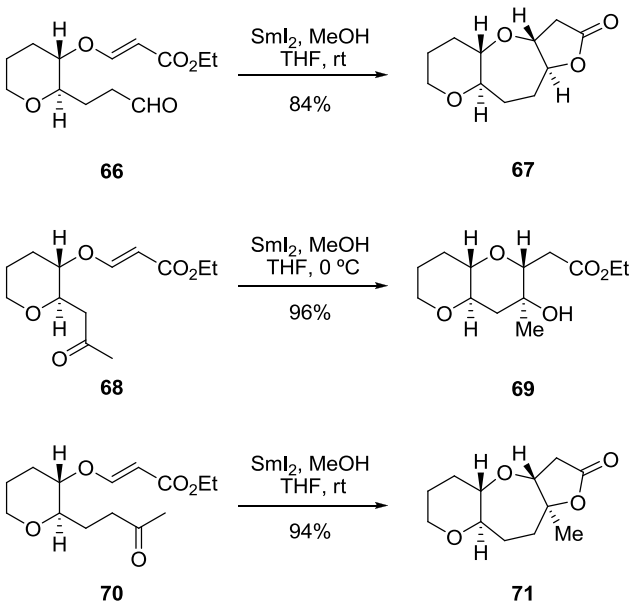
In 1999, Nakata and co-workers disclosed a very efficient approach towards the synthesis of polypyrans based on a stereoselective SmI_2-induced reductive cyclisation (Scheme 15).[38] Treatment of aldehyde **61** with samarium(II) iodide in the presence of MeOH in THF, initiated a radical-mediated reductive cyclisation to afford the 2,3-*trans*-tetrahydropyran **62** stereoselectively. Selective reduction of the ester functionality in **62** with DIBAL furnished the desired aldehyde, which was immediately protected as the corresponding thioacetal, affording **63** in 99% yield over two steps. Thioacetal **63** then underwent a oxa-Michael addition to ethyl propiolate, followed by removal of the thioacetal to afford the cyclisation precursor **64**. The iterative radical protocol was repeated to deliver the tricyclic ether **65** in 86% yield as a single isomer.



Scheme 15. Samarium induced reductive intramolecular cyclisation

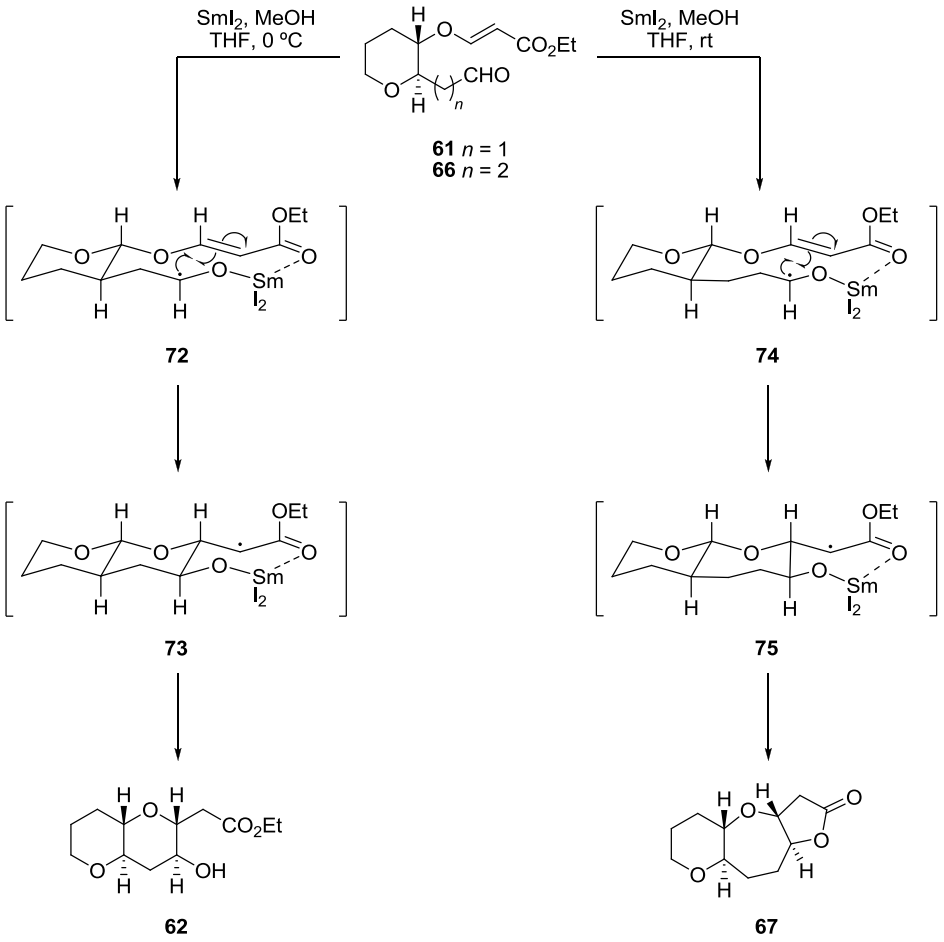
Employing a similar strategy, Nakata *et al.* demonstrated that radical-mediated reductive cyclisation reactions could also be utilised to synthesise oxepanes, allowing the incorporation of angular methyl groups, present in numerous polycyclic ether motifs (Scheme 16).[39,40] Accordingly, treatment of **66** with samarium(II) iodide in the presence of MeOH in THF initiated a reductive cyclisation reaction to afford oxepane **67** as the sole product in 84% yield. Introduction of the axial methyl group, as in compound **69**, proved relatively facile, by exchanging the aldehyde moiety for the corresponding methyl ketone functionality, which provided tetrahydropyran **69** upon exposure to SmI_2 at 0 °C. It should be noted, however, that a slight increase in temperature was required

for the reductive cyclisation of **70**. Thus, the cyclisation performed at room temperature afforded the fused bicyclic ether **71** in 94% yield, as a single product.



Scheme 16. Formation of tetrahydropyrans and oxapanes containing axial methyl groups

The complete stereoselectivity observed in the cyclisations leading to **62** (*n* = 1) and **67** (*n* = 2) was proposed to be the result of chelation control. In this process, an initial SmI_2 promoted single-electron reduction of the aldehyde moieties, followed by chelation of Sm(III) to the ester groups would form the preferred intermediates **72** and **74** respectively.[39,41] The resulting ketyl radicals would undergo a 1,4-addition onto the α,ß-unsaturated carbonyl group to form intermediate radicals **73** and **75**, which ultimately delivered the fused bicyclic (**62**) and tricyclic (**67**) ethers with complete selectivity (Scheme 17).

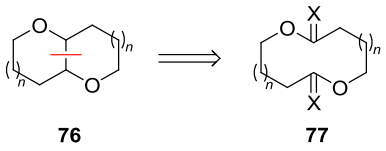


Scheme 17. Mechanism for the stereoselective SmI_2-mediated cyclisation

The introduction of Nakata's methodology represented a significant step forward in the synthesis of polycyclic ethers, allowing the preparation of six- and seven-membered cyclic ether systems in only five steps per iteration and with excellent levels of diastereoselectivity. The clear benefit of this approach is that this methodology also tolerates methyl ketones, as well as aldehydes, allowing incorporation of angular methyl groups in an efficient manner. Following the successful development of this methodology, Nakata and co-workers used this strategy in the synthesis of C'D'E'F' fragments of maitotoxin,[42] the FG ring system found in gambierol[42] and the total synthesis of brevetoxin B.[43]

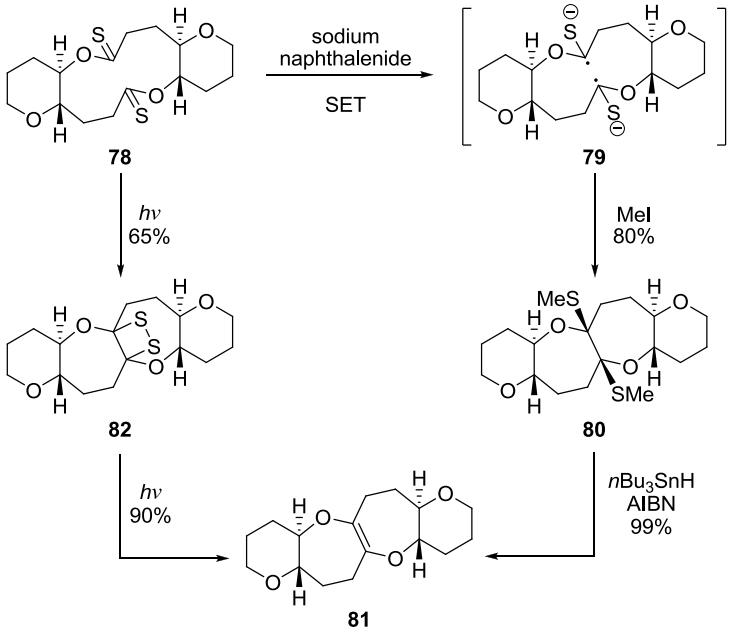
1.3.2.2. Thionolactone Coupling

Nicolaou *et al*. recognised an alternative method for the disconnection of ether polycyclic systems (Scheme 18).[44,45,46,47,48] This involved the disconnection of the central C-C bond in the fused bicyclic ether **76**, suggesting macrocycle **77** as a potential precursor. In the forward synthesis, this would mean that the construction of a single bond in **77** would allow stereoselective access to the *cis*- and *trans*-fused bicyclic ethers **76** as sought.



Scheme 18. Macrocycle bridging strategy for the synthesis of biclyclic ether systems

Initially, this methodology was applied to bis(thionolactone) **78**, synthesised from the corresponding bislactone by treatment with Lawesson's reagent.[49,50] Upon treatment with sodium naphthalenide, precursor **78** underwent two successive single-electron transfers (SET) to afford the diradical intermediate **79**, which was converted to dithioether **80** after quenching with MeI (Scheme 19). Subsequent radical reduction removed both of the methylthio groups to furnish the desired tetracyclic subunit **81**. Alternatively, photoirradiation of bis(thionolactone) **78** led to the formation of the stable[46] 1,2-dithietane **82** and eventually the tetracyclic system **81**.

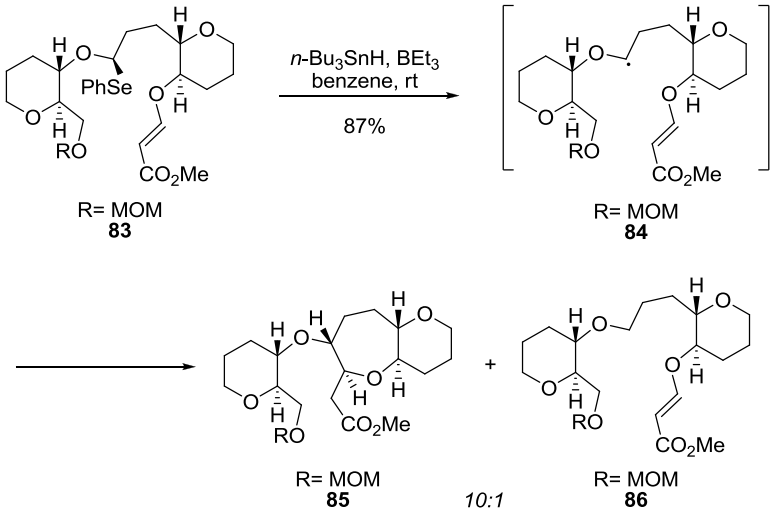


Scheme 19. The bis(thionolactone) bridging method for cyclic ether formation

Following on from the early success, Nicolaou applied this methodology in several synthetic studies concerning the synthesis of the dioxepane region of brevetoxin B.[51,52]

1.3.2.3. Radical Cyclisation of β-Alkoxyacrylates

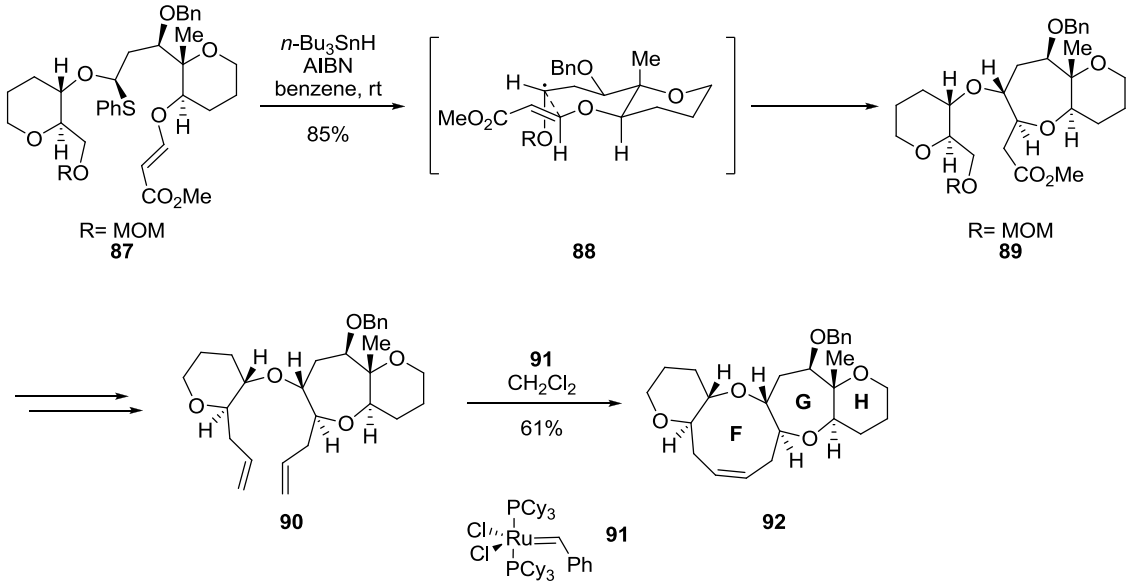
In 1998, Sasaki and co-workers reported a convergent and stereoselective method for the construction of *O*-linked oxepane systems by an intramolecular radical cyclisation from a selenoacetal species (Scheme 20).[53] A comprehensive study of the cyclisation of **83** revealed that the optimal conditions involved treatment of *β*-alkoxyacrylate **83** with *n*-Bu_3SnH in the presence of a sub-stoichiometric amount of triethylborane, at room temperature. The *a*-alkoxyradical intermediate **84** was presumably generated and underwent cyclisation to afford the desired *O*-linked oxepane **85** together with a small amount of reduction product **86**, in a ratio of 10:1 and 87% combined yield.



Scheme 20. Radical cyclisation strategy for the formation of O-linked oxepanes from a selenoacetals

This radical cyclisation strategy, in combination with a ring-closing metathesis reaction, was successfully applied to the assembly of a highly funtionalised system leading to the convergent synthesis of the FGH ring fragment of ciguatoxin **92** (Scheme 21).[54] In this case, the radical intermediate **88** required for the intramolecular cyclisation was generated from monothioacetal **87**, by treatment with *n*-Bu_3SnH in the presence of sub-stoichiometric amounts of triethylborane. The cyclised product **89**, bearing the desired *trans*-stereochemistry, then underwent several transformations to install the required

allylic side-chains in **90**. A final ring-closing metathesis reaction of **90** in the presence of Grubbs' first generation catalyst **91** furnished the complete FGH ring system of ciguatoxin (**92**), in a highly convergent manner.

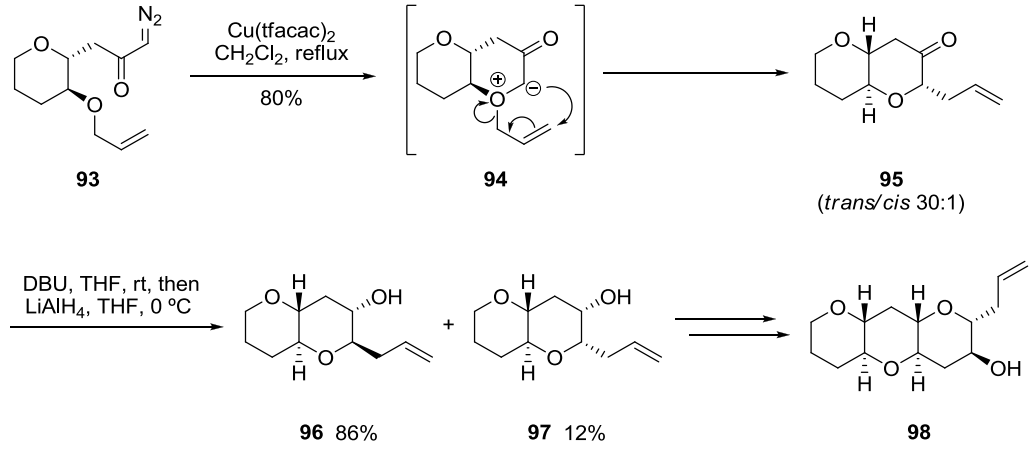


Scheme 21. Covergent synthesis of the FGH ring system of ciguatoxin by radical cyclisation/RCM strategy

1.3.3. Carbene Intermediates

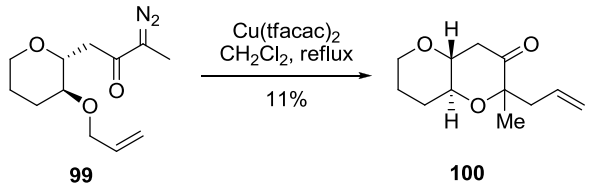
1.3.3.1. Tandem Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement

Marmsäter and West reported an iterative approach to polyether construction based on the [2,3]-sigmatropic rearrangement of cyclic oxonium ylides (Scheme 22).[55] The described protocol involved the treatment of diazoketone **93** with catalytic amounts of copper(II) trifluoroacetylacetonate to furnish the bicyclic ether **95** *via* the intermediate oxonium ylide **94** in 80% yield (*trans*/*cis*, 30:1). Unfortunately, ketone **95** possessed the undesired configuration at the newly formed centre, with the allyl chain axially disposed. Despite the initial setback, investigations quickly identified a one-pot procedure to isomerise and reduce ketone **95**, to produce an 8:1 mixture of **96** and its epimer **97**, in 86% and 12% yield respectively. An additional iteration was accomplished from alcohol **96** to afford the tricyclic product **98** in 20% overall yield.



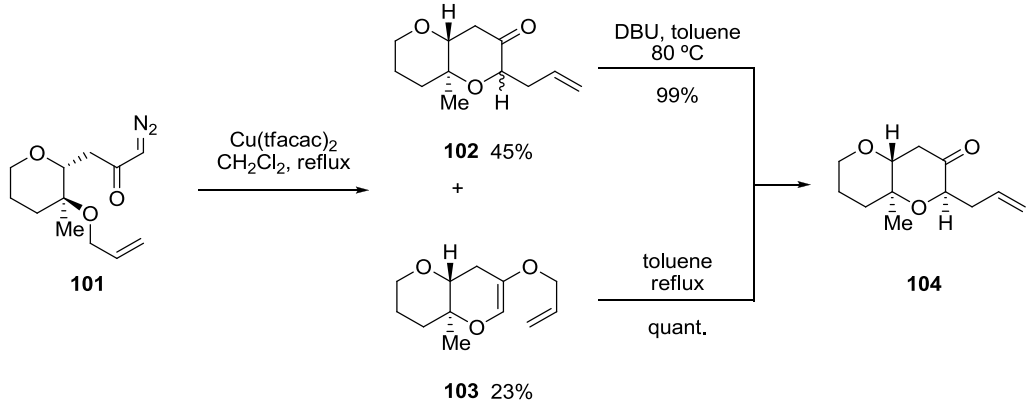
Scheme 22. Iterative polypyran synthesis *via* tandem oxonium ylide formation/[2,3]-rearrangement

An important challenge when assembling polypyran arrays is the introduction of angular methyl groups at bridgehead positions. With this aim in mind, Marmsäter and West attempted to develop several strategies using the oxonium ylide rearrangement methodology. An initial approach involved the incorporation of the methyl substituent in the diazoketone, as in compound **99**. Unfortunately, the copper-catalysed reaction of this substrate furnished the ylide rearrangement product **100** in a disappointing yield (Scheme 23).[56]



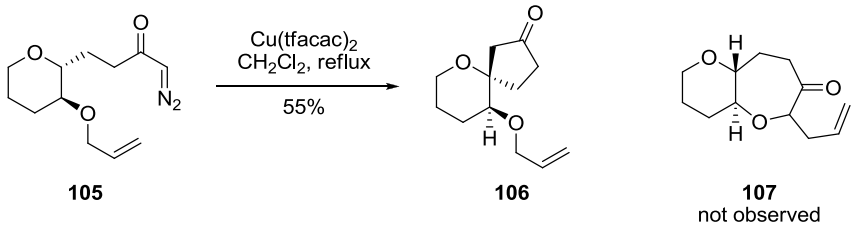
Scheme 23. Incorporation of the methyl substituent through the diazoketone substituent

In a second strategy, the desired quaternary centre was formed prior to the oxonium ylide rearrangement reaction, where tertiary allyl ether **101** was converted to ketone **102** in moderate yields (Scheme 24).[57] Interestingly, the allyl vinyl ether side-product **103**, arising from an apparent [1,4]-shift, was also isolated. Both **102** and **103** were converted into ketone **104** under separate conditions, in very high yields.



Scheme 24. Installation of axial methyl groups through the pyran subunit

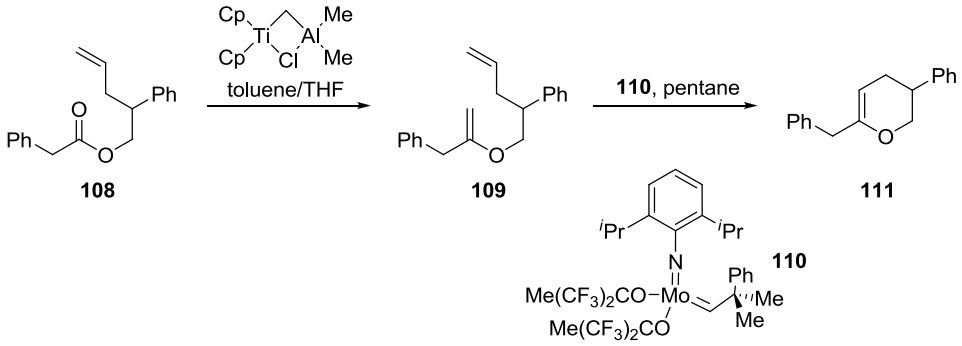
With a procedure to synthesise six-membered rings in place, Marmsäter and West then focused on expanding the scope to encompass the formation of medium-sized heterocycles. Accordingly, diazoketone **105** was subjected to the ylide rearrangement conditions (Scheme 25).[57] Unfortunately, only the spirocyclic C-H insertion product **106** was isolated and the desired oxepane **107** was not observed.



Scheme 25. Attempts to form medium size ether rings through oxonium ylide rearrangement

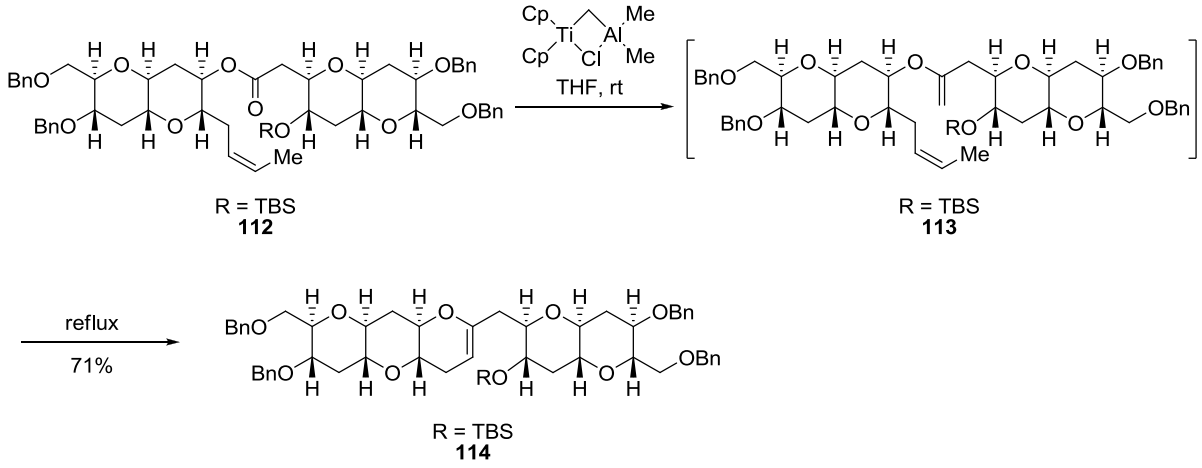
1.3.3.2. Methylenation/Metathesis Strategies

Early pioneering work by Grubbs and co-workers revealed the potential of the ring closing metathesis reaction as a viable option for the synthesis of cyclic enol ethers (Scheme 26).[58,59,60] Dihydropyran **111** was prepared in good yield over two steps from a simple olefinic ester **108**. Exposure of acyclic ester **108** to Tebbe[61,62] reagent furnished olefinic enol ether **109**, which subsequently underwent a ring closing metathesis reaction in the presence of molybdenum complex **110** to afford only the desired cyclic enol ether **111**.



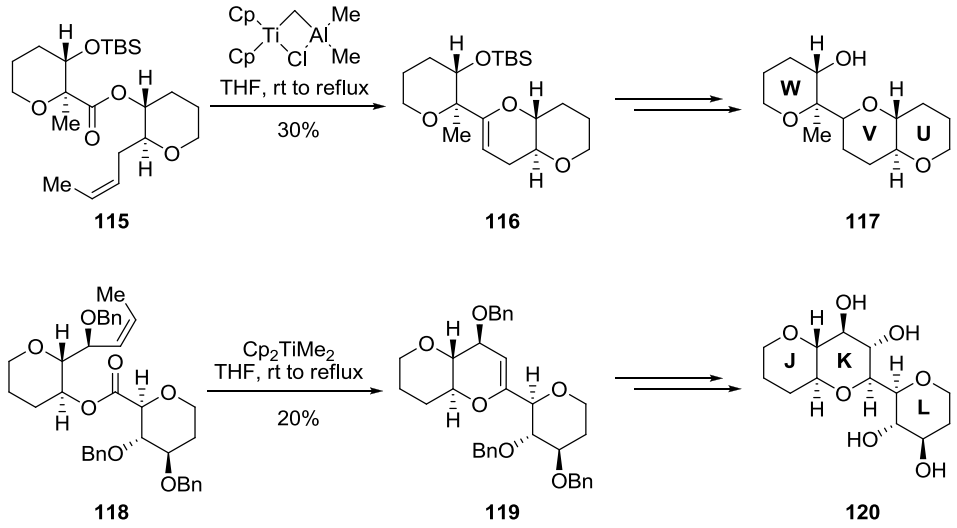
Scheme 26. Grubbs' synthesis of cyclic enol ethers *via* methylenation and metathesis strategy

Inspired by this work, the Nicolaou group developed a new strategy for the generation of cyclic enol ethers directly from olefinic esters, using the Tebbe[61,62] or Petasis reagents.[63,64] This methodology was later applied to the convergent synthesis of complex polycyclic ethers (Scheme 27) as well as several maitotoxin fragments (Scheme 28).[64,65] Polycyclic system **114** was obtained in a one-pot procedure from the complex ester **112**, *via* enol ether intermediate **113**, in very good yield (Scheme 27).



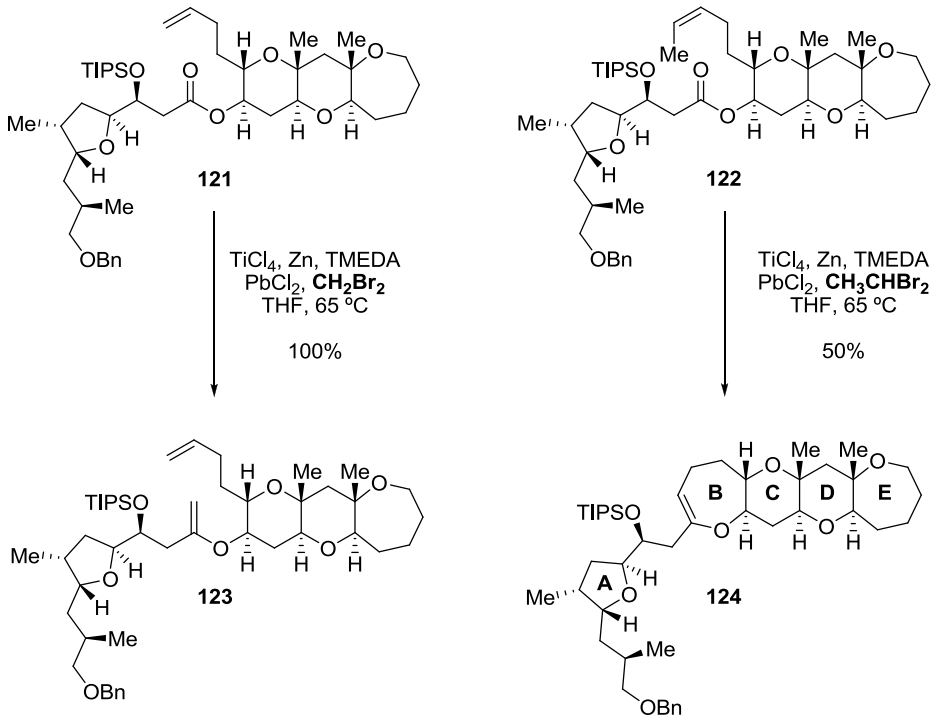
Scheme 27. Convergent synthesis of polycyclic ethers *via* a one-pot methylenation/metathesis procedure

Despite these encouraging results, lower yields were consistently obtained when applying this strategy in the synthesis of the UVW and JKL bridging ring subunits of maitotoxin (**117** and **120**, Scheme 28). Exposure of bicyclic ester **115** to excess Tebbe reagent led to the formation of cyclic enol ether **116** in a modest 36% yield. Several additional transformations were required to obtain the desired UVW ring system **117**. Similarly, treatment of ester **118** with Petasis reagent furnished cyclic enol ether **119** (20% yield), which underwent several additional transformations to complete the targeted JKL ring framework **120**.



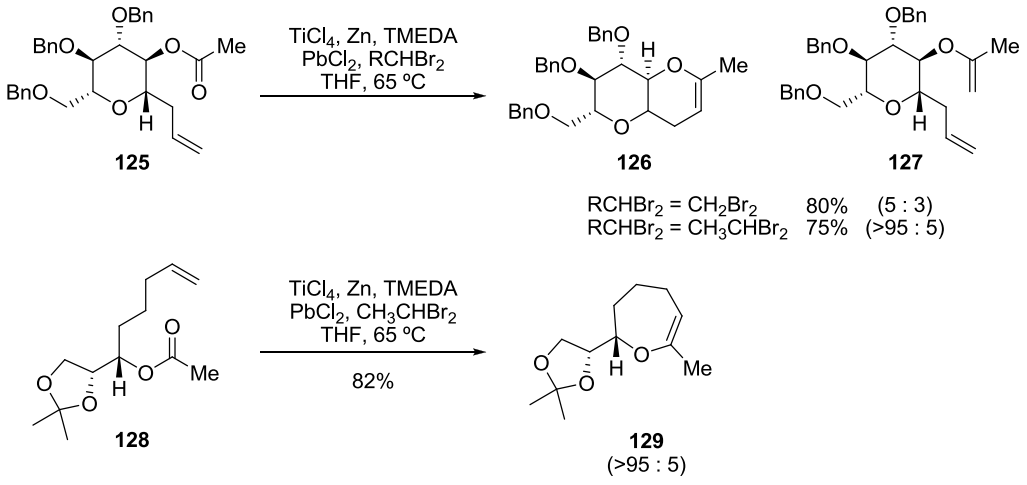
Scheme 28. Convergent synthesis of UVW and JKL ring fragment of maitotoxin

Over a number of years, the Rainier group has investigated the conversion of olefin-esters into cyclic enol ethers *via* a two-step methylenation and metathesis process.[66,67,68,69] However, in 2005 they reported a detailed study of a one-step process, involving the use of the Takai-Utimoto titanium alkylidene.[70] This reagent was prepared *in situ* and provided the necessary increase in reactivity relative to Petasis reagent, as well as the diminished Lewis acidity relative to the Tebbe reagent, critical to the generation of highly substituted targets. During an investigation towards the A-E ring fragment of gambieric acid A, an important observation was noted: the product distribution (acyclic vs cyclic enol ether) from the reaction of the reduced titanium alkylidene reagent was dependent upon the alkylidene reagent used (Scheme 29).[71] The titanium methylidene reagent resulting from the use of dibromomethane as the alkylidene source, furnished only acyclic enol ether **123** from ester **121**, whereas reaction of the precursor **122** with the corresponding ethylidene reagent, generated from dibromoethane, afforded only cyclic enol ether **124**.



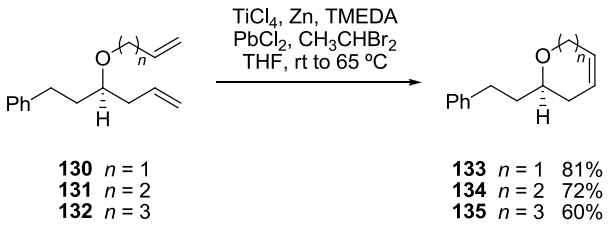
Scheme 29. Initial observations in product distribution using Takai-Utimoto reagent

These observations prompted further investigations, starting with simple olefinic esters (Scheme 30).[72] Reaction of **125** with the corresponding titanium methylidene reagent afforded a mixture of cyclic and acyclic products (**126** and **127** respectively). However, when **125** was subjected to the titanium ethylidene reagent, cyclic enol ether **126** was the only identifiable product. In addition, more challenging substrates lacking a preformed cyclic template were also examined. In this case, the acyclic ester **128** underwent cyclisation successfully to afford oxepane **129** in 82% yield.



Scheme 30. Reaction scope of the olefinic-ester cyclisation employing a titanium ethylidene reagent

In addition, the titanium ethylene reagent was also tested in a series of ring closing metathesis reactions (Scheme 31). Results showed that dienes **130**, **131** and **132** underwent cyclisation in the presence of the titanium ethylidene reagent to furnish the corresponding six-, seven- and eight membered cyclic enol ethers (**133**, **134** and **135** respectively) in good to excellent yield.



130 *n* = 1
131 *n* = 2
132 *n* = 3

133 *n* = 1 81%
134 *n* = 2 72%
135 *n* = 3 60%

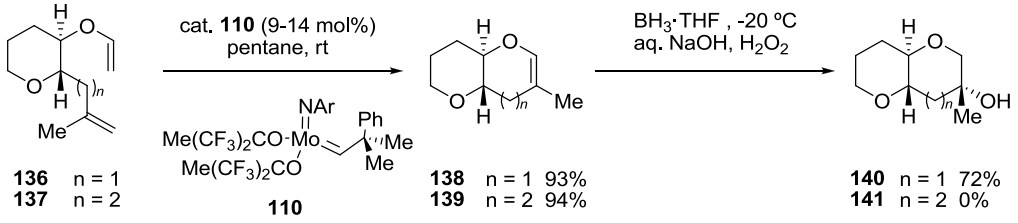
Scheme 31. Reduced titanium-mediated diene ring-closing metathesis

To date, this methodology has been employed extensively in the construction of a number of polycyclic ether natural products, including gambierol,[73] adriatoxin fragments[74] and, more recently, to the total synthesis of brevenal.[75]

1.3.3.3. Clark Group Strategies

Over a number of years, the Clark group has developed several strategies towards the preparation of polycyclic ethers based on the formation of rings by RCM (ring closing metathesis) and RCEM (ring closing enyne metathesis).

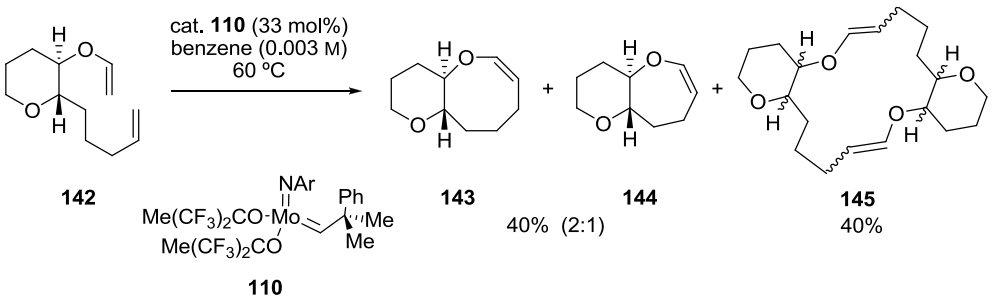
The first approach for the rapid iterative preparation of fused cyclic ethers involved sequential RCM followed by hydroboration of the resulting cyclic enol ether.[76,77] Preliminary studies of the enol ether RCM reaction demonstrated that this reaction was indeed viable for the preparation of fused systems possessing six- and seven-membered rings (**138** and **139**), by treatment of the corresponding precursors **136** and **137** with Schrock's catalyst **110** (Scheme 32).



Scheme 32. Formation of fused cyclic ethers by RCM and hydroboration sequence

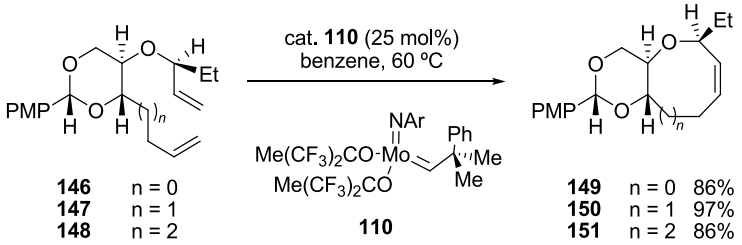
Subsequent conversion of cyclic enol ethers **138** and **139** to the required alcohols **140** and **141** was attempted by hydroboration in the presence of borane-tetrahydrofuran complex. In the case of substrate **140**, poor ratios of diastereomers were observed (n=1, 68:32 mixture of diastereomers with **140** predominating). In addition, the intermediate organoborane, generated from the cyclic enol ether **139**, proved to be highly unstable and underwent decomposition.

Construction of eight-membered cyclic ethers by means of enol ether RCM also proved somewhat problematic (Scheme 33).[76] Treatment of vinyl ether **142** with molybdenum complex **110** under high dilution conditions afforded an inseparable mixture of eight- and seven-membered cyclic enol ethers (**143** and **144**), as well as cyclo-dimer **145**.



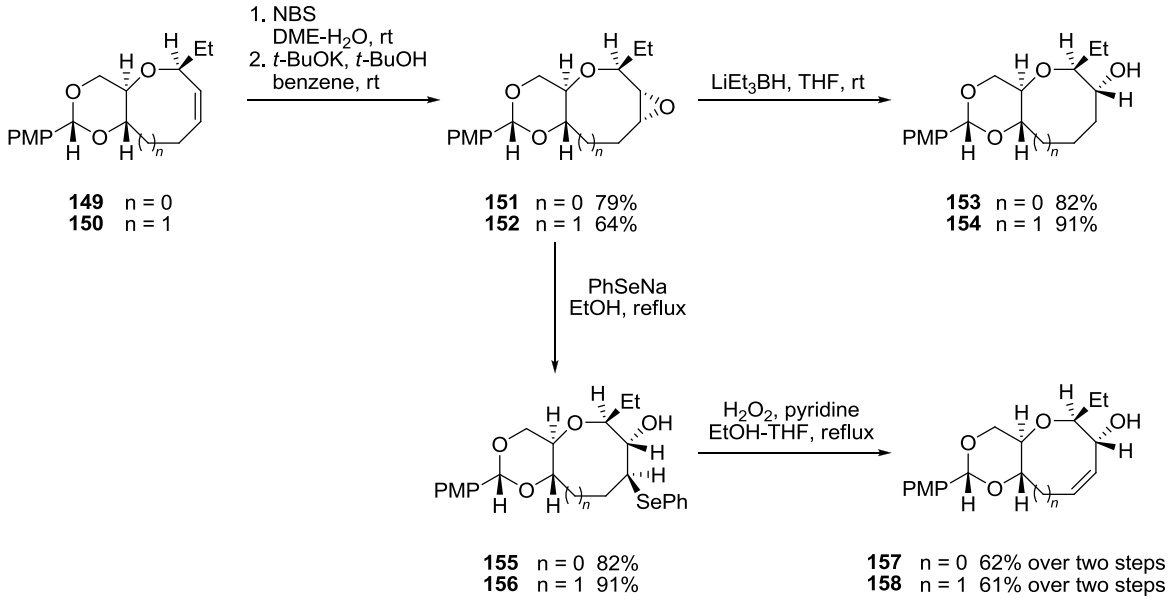
Scheme 33. Formation of eight-membered cyclic ethers by enol ether RCM

To alleviate these obvious difficulties, an alternative sequence for the synthesis of medium-ring cyclic ethers was devised involving RCM of allylic ethers, as opposed to enol ethers (Scheme 34).[77,78] Exposure of allylic ethers **146**, **147** and **148** to molybdenum catalyst **110** afforded the corresponding seven-, eight- and nine-membered cyclic ethers (**149**, **150** and **151** respectively) in excellent yields.



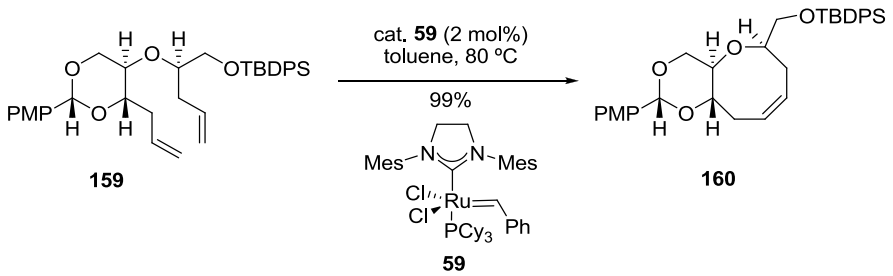
Scheme 34. Ring closing metathesis reaction of allylic ethers

Further elaboration of the cyclic ethers **149** and **150** led to the fully funtionalised saturated and unsaturated seven- and eight-membered cyclic ethers found in the brevetoxins and ciguatoxins (Scheme 35). In addition to the revised protocol, epoxidation and subsequent selective epoxide ring-opening were identified as suitable alternatives to the hydroboration procedure described previously, that would allow access to the desired hydroxylated cyclic ethers. Thus, epoxidation of allylic ethers **149** and **150** proceeded in good yield and with high levels of stereocontrol, favouring the required diastereoisomer. Epoxides **151** and **152** were then converted into the corresponding saturated alcohols **153** and **154** in excellent yield by regioselective reduction with Super Hydride (lithium triethylborohydride). In the case of epoxide **151** (n=0), a small amount (7%) of the regioisomeric alcohol was also observed, whereas ring opening of epoxide **152** (n=1) was entirely regioselective. Additionally, unsaturated cyclic ethers **157** and **158** were obtained in reasonable yield by regioselective opening of epoxides **151** and **152** with sodium phenylselenide affording selenides **155** and **156**. Subsequent oxidation and thermal elimination revealed allylic alcohol **157** (n=0) predominantly and homologue **158** (n=1) exclusively.



Scheme 35. Functionalisation of eight-membered ring cyclic allylic ethers

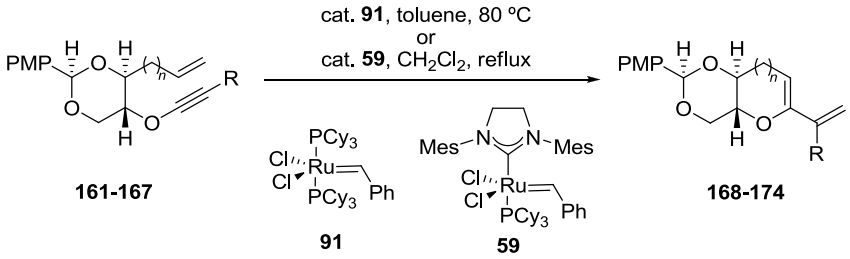
With highly effective methodology for the synthesis of functionalised polycyclic ether subunits in place, the Clark group successfully utilised the allylic ether RCM strategy in the stereoselective synthesis of the cyclic core of (+)-laurenyne (Scheme 36).[79] Diene **159** underwent RCM with 2 mol% of ruthenium catalyst **59** affording the eight-membered cyclic ether core **160** in an excellent 99% yield.



Scheme 36. Synthesis of (+)-laurenyne cyclic core

Another approach developed by Clark and co-workers, involved ring-closing enyne metathesis (RCEM) of alkynyl ethers **161-167** by treatment of each substrate with Grubbs' first or second generation catalyst (Table 1).[80,81] This led to the formation of alkenyl-substituted cyclic enol ethers **168-174**. The highest yields were obtained upon cyclisation of akynyl ethers **161** and **163** to afford six-membered cyclic enol ethers **168** and **170**. Although terminal alkynyl ether **161** underwent RCEM efficiently, a higher yield was obtained upon cyclisation of non-terminal alkyne **163**. The RCEM reactions to

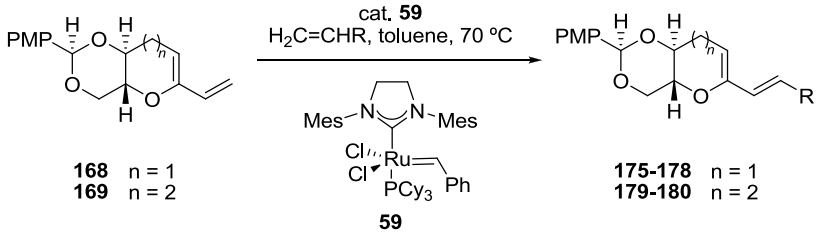
form seven-membered cyclic enol ethers **169** and **171** proved slightly less successful than those to produce dihydropyrans **168** and **170**. Notably, yields for all these enyne RCM reactions were greatly improved when carried out in the presence of Grubbs' second generation catalyst **59** as opposed to Grubbs' first generation catalyst **91**.



Entry	Substrate	n	R	Product	Yield (%; 91)	Yield (%; 59)
1	**161**	1	H	**168**	65	90
2	**162**	2	H	**169**	33	70
3	**163**	1	Me	**170**	77	98
4	**164**	2	Me	**171**	27	72
5	**165**	1	$SiMe_3$	**172**	20	88
6	**166**	1	CH_2OAc	**173**	54	72
7	**167**	1	$CH_2OTBDPS$	**174**	61	91

Table 1. Synthesis of cyclic polyether *via* RCEM

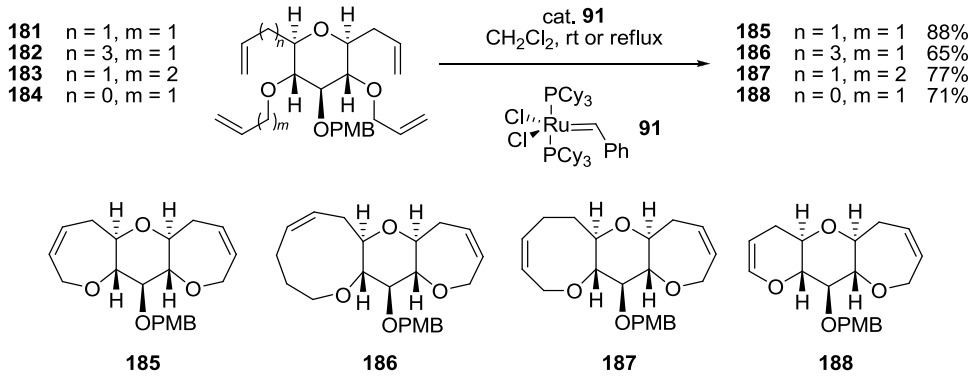
The alkenyl substituted products **168** and **169**, obtained using this methodology, were further functionalised by cross metathesis (CM) in the presence of ruthenium complex **59** (Table 2).[82] Couplings of diene **168** with allyl acetate, allyl trimethylsilane and the electron-deficient alkenes methyl vinyl ketone and ethyl acrylate delivered the corresponding products **175-178** in excellent yields. Cross-metathesis reactions of the seven-membered ring ether **169** with allyl acetate and ethyl acrylate were also successful affording the corresponding products **179** and **180** in excellent yield. This allowed the synthesis of highly functionalised six- and seven-membered cyclic ethers bearing a diverse range of side chains in good to excellent yield.



Entry	Substrate	n	R	Product	Yield (%)
1	**168**	1	CH_2OAc	**177**	87
2	**168**	1	CH_2SiMe_3	**176**	78
3	**168**	1	CH_2OEt	**177**	89
4	**168**	1	COMe	**178**	79
5	**169**	2	CH_2OAc	**179**	79
6	**169**	2	CH_2OEt	**180**	91

Table 2. Funtionalisation by Cross Metathesis

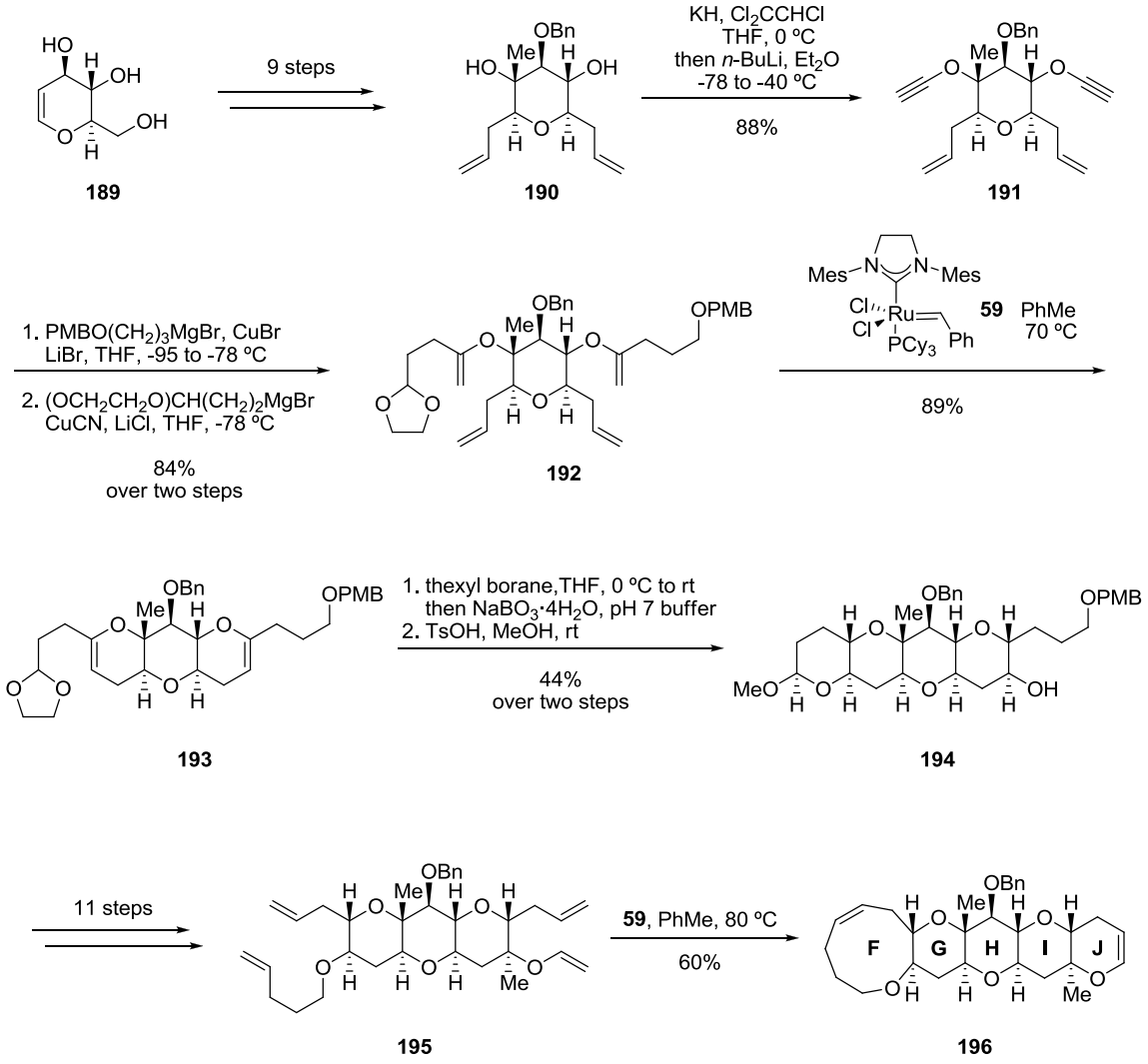
Finally, Clark and Hamelin reported the synthesis of polycyclic ethers by two-directional double RCM.[83] This strategy permitted the construction of tricyclic polyether fragments **185-188**, bearing a variety of ring sizes, from single ring precursors **181-184** in one step (Scheme 37). During these studies, the effectiveness of the molybdenum catalyst **110** was investigated, but in every case the yields were significantly lower than with the ruthenium catalyst **91**, where products were obtained in good to excellent yield.



Scheme 37. Two-directional RCM reaction

This methodology was successfully applied to the synthesis of the F-J fragment of gambieric acids (Scheme 38).[84] The synthesis commenced with D-glucal **189** which was

converted into the fully functionalised H-ring fragment **190** in nine steps. Diol **190** was then converted into bis(alkynylether) **191** by employing a modification of Green's procedure, in the first two-directional reaction.[85] Subsequent selective carbocupration[86] allowed the installation of the two different side chains regioselectively and delivered bis(enol ether) **192** in excellent yield. The second two-directional reaction that followed involved a double RCM of the tetraene **192** to deliver the tricyclic bis(enol ether) **193** in excellent yield. Double hydroboration[87,88] of the metathesis product **193**, with a mild oxidative work-up of the intermediate organoborane under buffered conditions, afforded the required diol. Subsequent acid catalysed cyclisation resulted in the differentiation of the two secondary alcohols and permitted a selective protection of the G-ring hydroxyl group in **194**. Introduction and modification of the side-chains over eleven steps, provided the required tetraene system **195** for the second double two-directional RCM reaction. Treatment of compound **195** with Grubbs' second generation catalyst **59** afforded the complete gambieric acid F-J fragment **196**, demonstrating the validity of an iterative two-directional strategy involving RCM for the construction of complex fused polycyclic ether fragments.



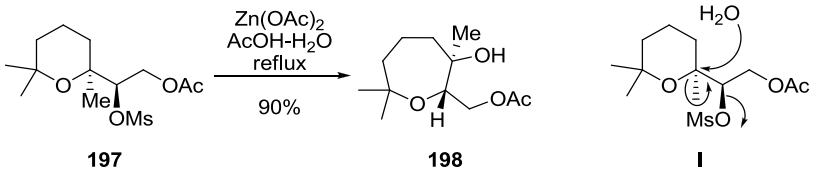
Scheme 38. Iterative two-directional synthesis of the complete gambieric acid F-J fragment

This strategy was also employed in the synthesis of the core of hemibrevetoxin B,[89] as well as the A-E fragment of ciguatoxin CTX3C.[90]

1.3.4. Ring Expansion for the Synthesis of Oxepanes

Oxepanes are frequently encountered in polycyclic ether natural products. These seven-membered cyclic ethers appear *trans*-fused to other cyclic ethers ranging from six to nine members. Several methodologies initially developed for the synthesis of six-membered cyclic ethers have also been successfully applied to the formation of seven-membered ether rings (Section 1.3). However, other methodologies, including ring expansion strategies have also been employed.

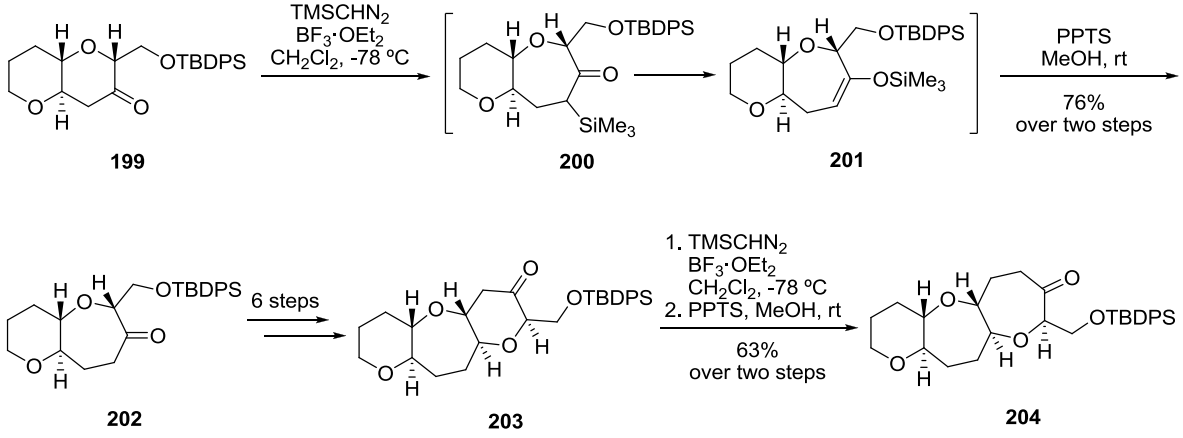
In 1996, Nakata and co-workers examined the rearrangement of a six-membered ether ring containing a mesylate leaving group on the side chain, to form the corresponding oxepane (Scheme 39).[91] Treatment of α,α,α',α'-tetrasubstituted ether **197** with $Zn(OAc)_2$ in AcOH-H_2O at reflux afforded seven-membered cyclic ether **198** in 90% yield. This rearrangement reaction proceeded with complete stereoselectivity, suggesting that a concerted mechanism is involved (**I**).



197 **198** **I**

Scheme 39. Ring expansion through mesylate displacement

Mori *et al.* employed ring expansion methodology in the construction of a 6,7,7-fused polyether system.[14] This involved the direct Lewis-acid promoted insertion of a methylene unit from trimethylsilyldiazomethane through an equatorial attack on the ketone functionality (Scheme 40).[92] The presence of the trimethylsilyl group initially governed the predominant formation of the sterically less crowded α-trimethylsilyl ketone **200** after migration of the substituted carbon. A rapid rearrangement to the silyl enol ether **201** and subsequent acid hydrolysis afforded ketone **202** in good yield. Six additional steps were required for the construction of the adjacent pyran ring in **203**. The tricyclic ether **203** was then treated with trimethylsilyldiazomethane in the presence of boron trifluoride etherate, under previously described conditions, to afford the desired 6,7,7-ring system **204** in good yield.



199 **200** **201**

202 **203** **204**

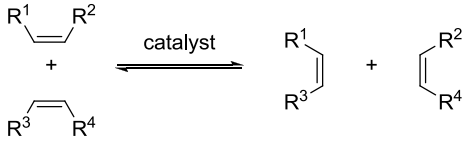
Scheme 40. Synthesis of 6,7,7-*trans* fused bicyclic ether subunit *via* ring expansion

This approach was successfully applied to the formal total synthesis of hemibrevetoxin B,[15] the A-D fragment of gambierol[16] and the D-F ring system of yessotoxin.[13]

2. Olefin Metathesis

2.1 Introduction

The word metathesis is derived from the Greek *meta* (change) and *thesis* (position). In chemistry, olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of a metal carbene complex (Scheme 41).[93]

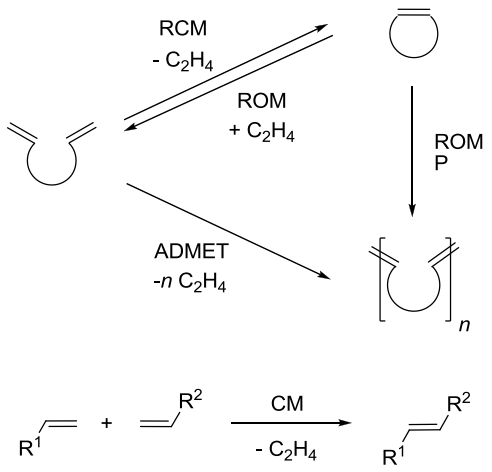


Scheme 41. Principle of olefin metathesis

Catalytic metathesis was discovered in the 1950s by Karl Ziegler, following the observations concerning the polymerisation of ethylene.[94,95] By the late 1960s, the Phillips group had developed a commercial triolefin process, the results of which drew the attention of the scientific community towards the potential of this novel reaction.[96] Unfortunately, early transition metal catalysts were intolerant of various functional groups and were limited to polymerisation reactions of simple substrates.

The discovery that metal alkylidene complexes could act as single-component catalysts for olefin metathesis was the first step towards the development of this reaction in organic synthesis. With the advent of efficient catalysts, such as Schrock's and Grubbs' catalysts and their derivatives, this reaction has emerged as a powerful tool for the formation of C-C bonds in chemistry.[97,98]

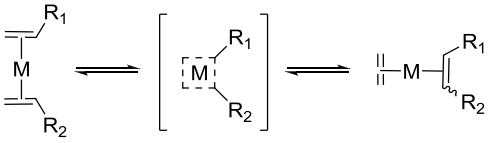
There are several closely related types of reactions in which olefin metathesis can be utilised: ring-closing metathesis (RCM), ring-opening metathesis (ROM), ring-opening metathesis polymerisation (ROMP), acyclic diene metathesis polymerisation (ADMET) and cross metathesis (CM) (Scheme 42).



Scheme 42. Important types of metathesis reactions

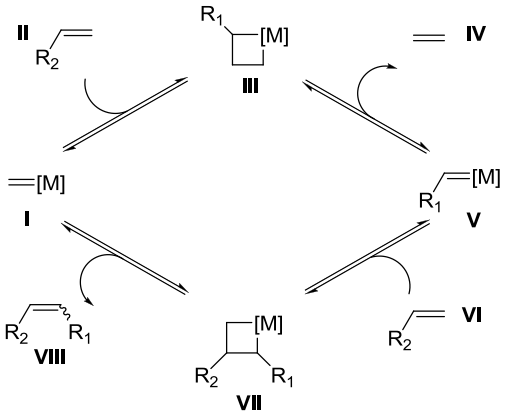
2.2. Olefin Metathesis Mechanism

The initially proposed mechanism proceeded through a "quasicyclobutane" process in which two olefins coordinated to the metal and exchanged alkylidene groups through a symmetrical intermediate (Scheme 43).[99] This mechanism, with a few exceptions, could account for most of the basic metathesis transformations.



Scheme 43. Proposed quasicyclobutane mechanism of metathesis

At the present time, the generally accepted mechanism is the Chauvin mechanism which consists of a sequence of [2+2] cycloaddition and cycloreversion reactions involving alkenes, metal carbenes and metallacyclobutane intermediates (Scheme 44).[100]



Scheme 44. Chauvin's mechanism for alkene metathesis

The first step in the catalytic process involves a [2+2] cycloaddition between olefin **II** and the transition metal alkylidene complex **I**, to obtain the first metallacyclobutane **III**. This metallacycle then undergoes a cycloreversion reaction to liberate ethene **IV** and a new metal carbene **V**, which carries the alkylidene substituent R^1. As before, **V** reacts with another alkene **VI** to generate the second metallacycle **VII**. After a further cycloreversion, the new disubstituted alkene **VIII** is formed and the catalyst **I** is regenerated and can re-enter the catalytic cycle.

Due to the reversibility of all the steps in the catalytic cycle, it is necessary to use appropriate conditions to displace the equilibrium in favour of the desired product to avoid mixtures of all the possible alkenes.[97,98] In the case of RCM of a diene, the forward reaction is entropically favoured since the initial substrate is transformed into two alkenes. Furthermore, if one of the alkenes is volatile, the cycloreversion step becomes irreversible and the desired cycloalkene will accumulate in the reaction mixture. Another important factor in RCM is the substitution pattern of the alkene, as it determines the kinetics of the reaction. In general, increased substitution in the alkene, leads to decreased reactivity.

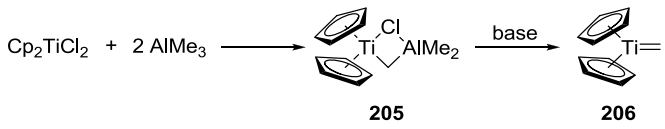
2.3. Catalysts

There are an extensive number of catalyst systems that can initiate an olefin metathesis reaction and most of the early work was based on the use of ill-defined multicomponent homogeneous and heterogeneous catalyst complexes.[93] Some of the most commonly used systems included WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2, and Re_2O_7/Al_2O_3, which consist of transition metal salts combined with main group alkylating agents, or solid supports. The utility of these catalysts was limited, since the harsh conditions and strong Lewis acids required are incompatible with most functional groups.

However, the elucidation of the mechanism by Chauvin greatly influenced work on catalyst development, since it provided the basis for the development of an understanding of catalytic activity. Subsequent efforts, during the late 1970s and early 1980s, to synthesise alkylidene and metallacyclobutane complexes led to the discovery of the first single-component homogeneous catalysts for olefin metathesis.

2.3.1. Titanium-Based Catalysts

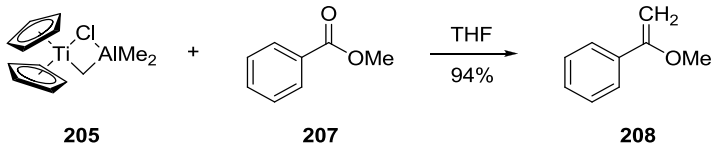
Tebbe and co-workers demonstrated that a titanium methylene complex could catalyse the metathesis exchange of methylenes between two terminal olefins.[61,101] Reaction of Cp_2TiCl_2 with two equivalents of $AlMe_3$ affords complex $Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2$ (**205**), commonly known as the Tebbe Reagent (Scheme 45). In the presence of a Lewis base, such as pyridine, the reagent is functionally equivalent to $Cp_2Ti{=}CH_2$ (**206**).[102]



Scheme 45. Formation of Tebbe reagent

Although this titanium complex was not very active, its stability allowed for the propagation of methylidene to be observed and studied, therefore serving as an excellent model system. Furthermore, Evans and Grubbs showed that a stoichiometric amount of this complex **205** could be employed for the conversion of an ester such as

207 into the corresponding vinyl ether **208**, in 'Wittig type' reactions where conventional Wittig reagents are unsuitable (Scheme 46).[62]



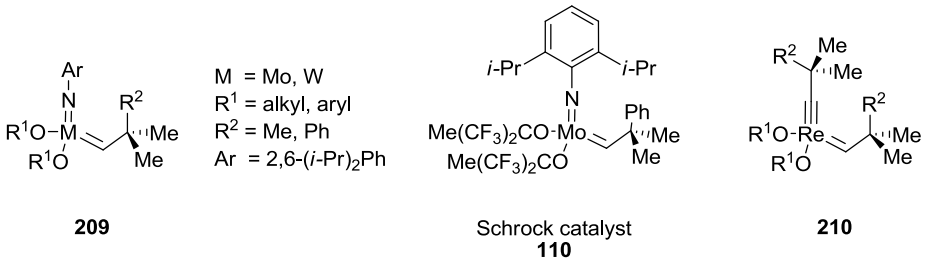
205 **207** **208**

Scheme 46. 'Wittig type' reaction for the conversion of esters to vinyl ethers.

2.3.2. Tungsten, Molybdenum and Rhenium Catalysts

The breakthrough came in the early 1980s when Schrock and co-workers prepared a variety of well-defined, single-component homogeneous catalysts based on tungsten, molybdenum and rhenium (Figure 3).[103,104]

Molybdenum catalyst system **110**, also referred to as Schrock's catalyst, is of particular importance due to its high reactivity with a wide range of alkene substrates, under mild conditions. The reactivity of this system can be readily altered by changing the nature of the ligands. For example, when R^1 represents a *t*-butyl group, the complex reacts only with strained cyclic olefins, making it an ideal catalyst for ROMP reactions.[105]



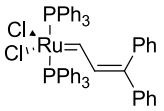
209 Schrock catalyst **110** **210**

Figure 3. Molybdenum, tungsten and rhenium catalysts.

However, some of the main drawbacks concerning this Mo-based catalyst are the extreme sensitivity to air, moisture and impurities. Moreover, its moderate to poor functional group tolerance limits the substrate scope.

2.3.3. Ruthenium Catalyst

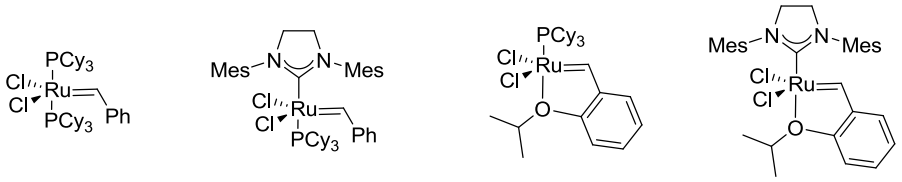
During the 1990s, Grubbs and co-workers synthesised and isolated ruthenium vinylcarbene complex **211** (Figure 4), which allowed the development of well defined, low oxidation, late transition state metal complexes that catalyse olefin metathesis.[106] In addition to the activity of **211** in the metathesis of strained cyclic,[106,107] and exocyclic olefins,[108] the remarkable functional group tolerance and stability towards air, acids and even water, made this class of catalyst particularly attractive for practical applications.



211

Figure 4. Ruthenium vinylcarbene catalyst

Further development led to the so-called first generation Grubbs' catalyst **91**,[109] which contains two phosphine ligands. Although this catalytic system showed high levels of reactivity, the Grubbs' second generation catalyst **59**,[110] where one of the phosphine ligands is replaced by a *N*-heterocyclic carbene (NHC) ligand, displayed increased reactivity and stability (Figure 5). The other widely used and commercially available ruthenium complexes **212** and **213** were reported by Hoveyda,[111] where the lateral isopropyl ether group on the phenylcarbene unit stabilises the complexes in their resting state, but readily opens to provide a coordination site in the presence of the substrate.

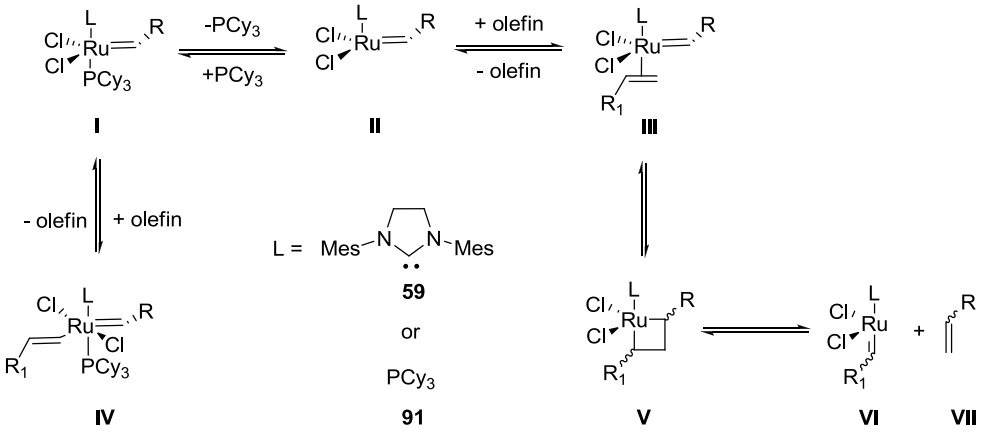


Grubbs **I** **91** | Grubbs **II** **59** | Hoveyda-Grubbs **I** **212** | Hoveyda-Grubbs **II** **213**

Figure 5. Ruthenium catalysts

In contrast with the previously shown Schrock catalyst **110**, the four ruthenium catalysts presented (Figure 5) are all pre-catalysts, meaning that the active species are generated under the reaction conditions. Detailed mechanistic studies performed by Grubbs *et al.* allowed the rationalisation of the effect of the phosphines on the catalytic

activity of these complexes.[112] Two possible pathways were proposed, the first of which involved the dissociation of the phosphine ligand from metal complex **I** to form complex **II** or the second proposed associative pathway, in which both phosphines would remain bound to the Ru-centre resulting in complex **IV** (Scheme 47).



Scheme 47. Proposed mechanism for Grubbs-type catalyst

Looking more closely at the mechanism, complex **I** could exchange a phosphine ligand for an olefin through either the 14-electron complex **II** (dissociative pathway) or by first coordinating the olefin to form complex **IV** (associative pathway). The latest mechanistic studies by Grubbs *et al*. show no evidence for the formation of the later complex.[112] These studies also offer an explanation for the increased reactivity of the NHC complexes. Concerning the first generation Grubbs catalysts **91**, the loss of a phosphine ligand from **I** to form **II** is relatively facile, but the re-coordination of the phosphine ligand is much faster than that of the olefin. Therefore the active species **II** is formed more readily but carries out fewer turnovers. For the NHC complexes, both the dissociation and re-association of the phosphine are slow processes, therefore the catalytic species **II** can undergo a larger number of turnovers. The increased stability of the active complex **II**, provided by the NHC ligand, also encourages a longer lifetime.[113]

Although the activities of the ruthenium alkylidene complexes are usually lower than that of Schrock's molybdenum alkylidene **110**, their tolerance toward an array of functional groups and the ease of handling due to a reasonable stability towards oxygen, water, and minor impurities in the solvents, render them exceedingly practical tools and explain their popularity as pre-catalysts in the organic and polymer chemistry.

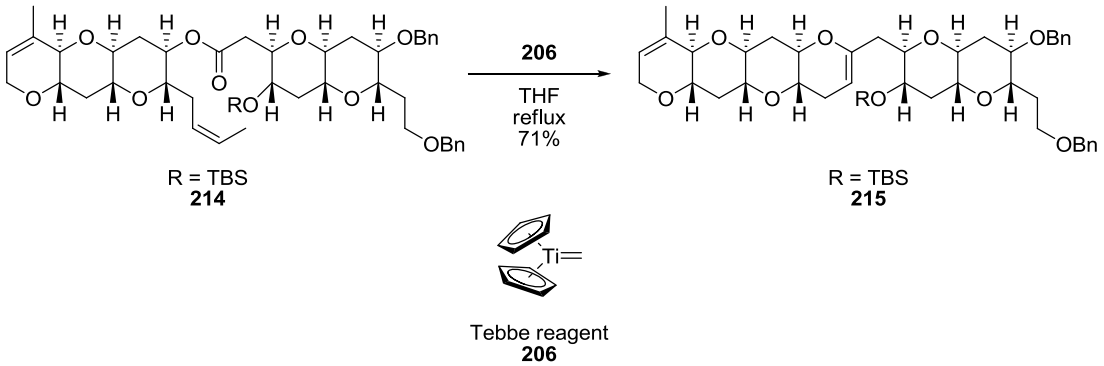
2.4. Ring-Closing Metathesis

New catalysts tolerate a wide spectrum of functionalities, which has allowed metathesis to evolve into an important tool for organic synthesis. One of the most common metathesis reactions is ring closing metathesis (RCM) and various reviews have detailed the use of this reaction in the formation of small to large ring systems.[93,98,114]

This section will focus mainly on the synthesis of cyclic enol ethers using RCM.

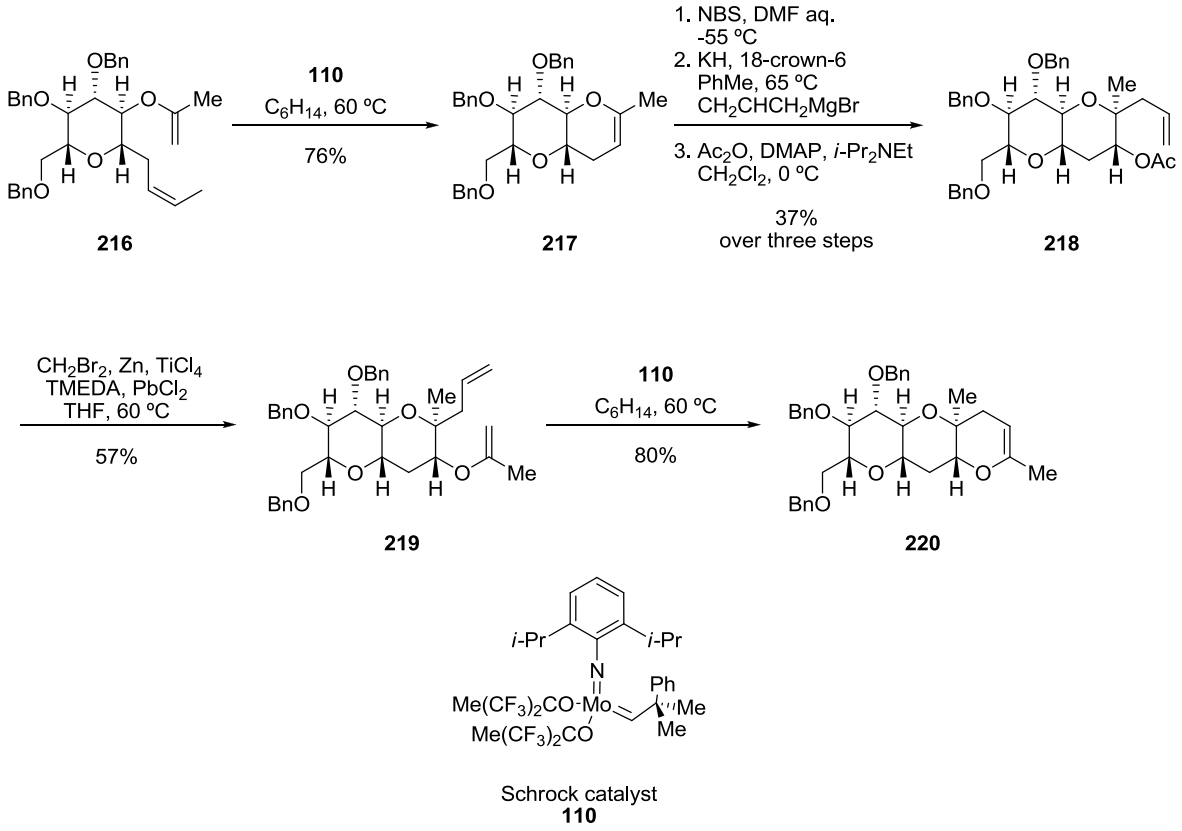
2.4.1. RCM of Enol Ethers

RCM has been used by several research groups (including the Clark group) as a key reaction for the preparation of cyclic ethers. Nicolaou reported the preparation of six-membered cyclic enol ethers by a methylenation and subsequent RCM in a domino process using Tebbe reagent **206** in the synthesis of a maitotoxin fragment (Scheme 48, see also Section 1.3.3.2).[64]



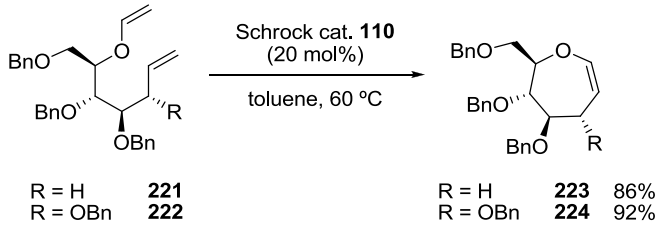
Scheme 48. Synthesis of hexacyclic polyether *via* RCM

Rainier and co-workers have also reported several influential examples in this field.[66,68,69] They demonstrated that an enol ether **216** would undergo RCM to afford bicyclic enol ether **217**, using Schrock catalyst **110** (Scheme 49). Functionalisation of the enol ether **217** was achieved through a minor modification of Spilling's epoxidation conditions and subsequent opening of this epoxide at the anomeric position using allylmagnesium bromide to yield the corresponding alcohol, which was acetylated to afford compound **218**. Methylenation of **218** provided enol ether **219**, which was converted to cyclic enol ether **220** *via* a RCM reaction. It was therefore demonstrated that it was possible to use the reaction sequence for the iterative construction of *trans*-fused polycyclic ethers.



Scheme 49. Rainier's iterative polycyclic ether synthesis

As well as for the construction of functionalised pyrans, RCM methodologies have been employed extensively to access oxepanes. Seven-membered cyclic enol ethers **223** and **224** were also prepared by RCM using Schrock catalyst **110** (Scheme 50).[115]

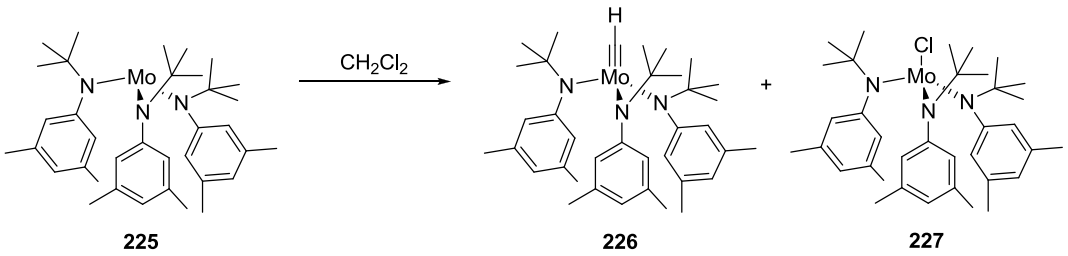


Scheme 50. Synthesis of seven-membered cyclic enol ether *via* RCM

2.4.2. Alkyne Metathesis

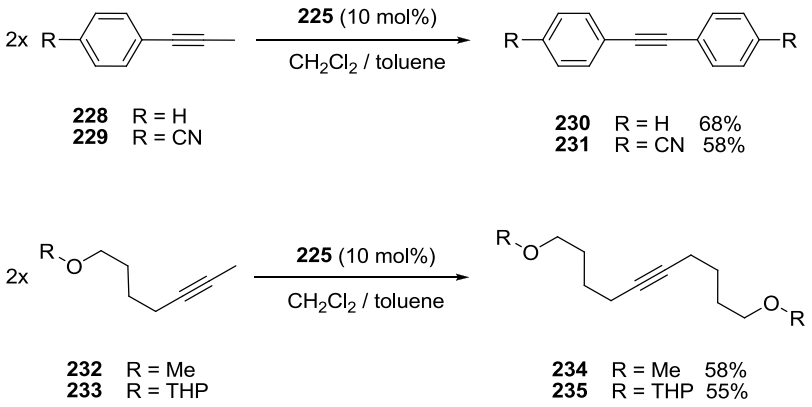
Despite the great impact of alkene metathesis on organic synthesis, alkyne metathesis has attracted considerably less attention. Examples of this reaction were first described by Mortreux and co-workers using ill-defined molybdenum catalysts in conjunction with a number of phenol additives. High temperatures were required and the nature of the alkylidyne species is still unknown.[116] In 1984, Schrock developed a well-defined tungsten based catalyst (t-BuO)$_3$W≡ C−CMe$_3$, which tolerated polar functionalities such as esters and ethers. However, this catalyst was incompatible with soft donor groups such as thioethers or basic amines.[117]

In 1999, Fürstner investigated the reactivity of molybdenum amido complexes of the general type Mo[N(t-Bu)(Ar)]$_3$ **225** (Scheme 51).[118]



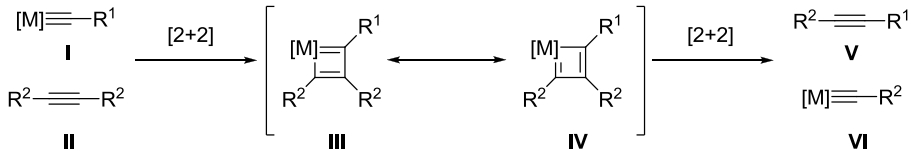
Scheme 51. Fürstner's molybdenum amido catalysist

Originally, Cummins *et al.* discovered that these complexes activate the triple bond of molecular nitrogen in a stoichiometric fashion. It was found that although **225** itself did not effect any metathesis event, upon treatment with CH_2Cl_2, the resulting mixture efficiently catalysed metathetic coupling of different aromatic (**228** and **229**) and aliphatic (**232** and **233**) alkynes (Scheme 52). It has been demonstrated that halide transfer from the solvent to the molybdenum centre plays a decisive role in the formation of the active catalyst, where the actual catalyst species is Cl-Mo-complex **227** as opposed to the methylidyne carbine system **226** (Scheme 51).[119] The **225**/CH_2Cl_2 combination proved to have a high catalytic activity towards both ring closing alkyne metathesis (RCAM) and alkyne cross-metathesis (ACM) reactions, and displayed a high tolerance towards a wide range of functionalities including alcohols, amines and thiols.



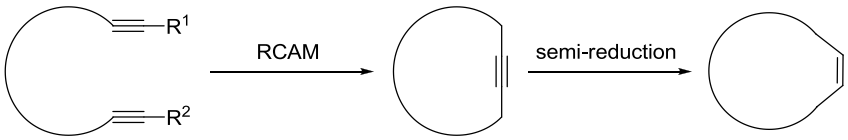
Scheme 52. Mo-complex catalysed metathesis of aliphatic and aromatic alkynes

The generally accepted mechanism is the Chauvin mechanism (Scheme 53), which initially involves the reaction of alkylidyne metal complex **I** with alkyne **II** *via* a [2+2] cycloaddition to form a metallocyclobutadiene **III**. At this stage, a double bond rearrangement to **IV** takes place, followed by a final [2+2] cycloreversion to give the new alkyne **V**.[120]



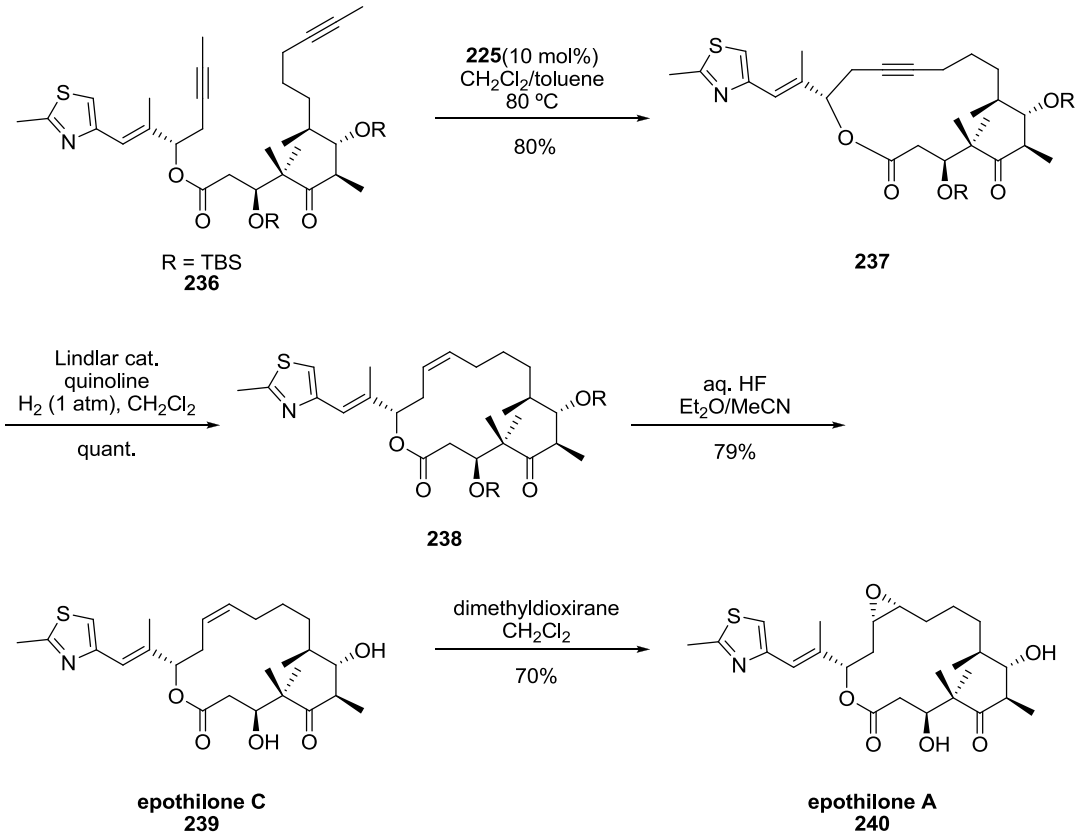
Scheme 53. Chauvin's mechanism for alkyne metathesis

Evolving from the interest in RCM for macrocycle formation, Fürstner *et al*. investigated the potential for alkyne metathesis to accomplish the ring closure of acyclic diynes to afford cyclic alkynes.[121] In these studies they realised that the combination of RCAM and Lindlar hydrogenation constituted a stereoselective route to (*Z*)-configured cycloalkenes (Scheme 54).[122]



Scheme 54. Stereoselective synthesis of macrocyclic (*Z*)-alkenes by RCAM and Lindlar hydrogenation

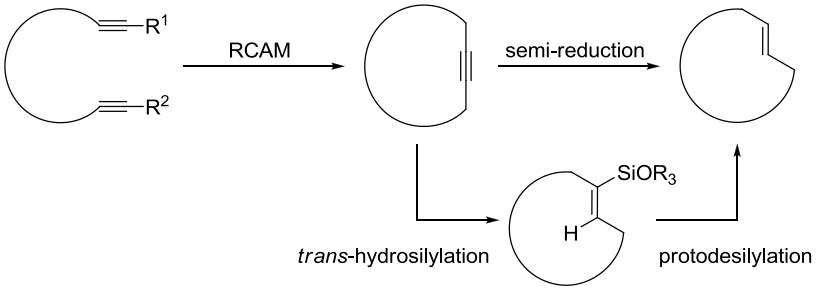
This reaction has been used in numerous occasions in organic synthesis and was the key step in the stereoselective synthesis of epothilone C (Scheme 55).[123,124] Diyne **236** was converted into the 16-membered cycloalkyne **237** on exposure to catalytic amounts of the molybdenum amido complex **225** in toluene–CH_2Cl_2. It is worth noting that the rigorous chemoselectivity of the catalyst was confirmed, which reacted smoothly with alkynes leaving pre-existing alkene moieties unaffected. Lindlar reduction of cycloalkyne **237** resulted in (*Z*)-alkene **238** and a subsequent cleavage of the silyl ether groups delivered epothilone C (compound **239**). Because the selective epoxidation of **239** had already been described by various groups,[125,126] this approach also constituted a formal total synthesis of epothilone A (compound **240**).



Scheme 55. Key steps in the synthesis of epothilone A and C

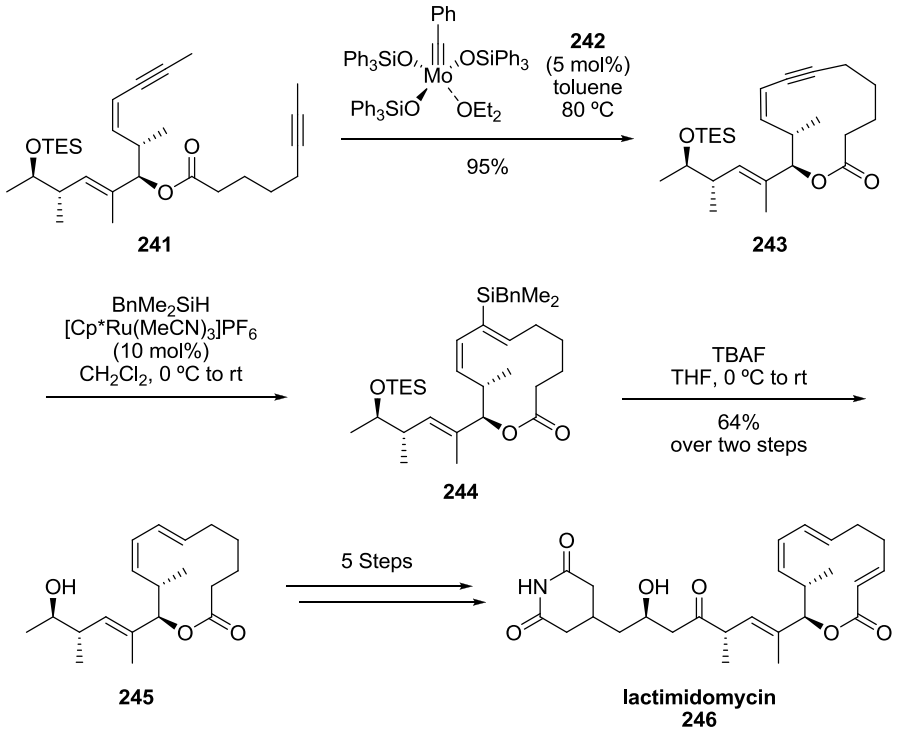
It was therefore established that the sequence of RCAM followed by Lindlar hydrogenation was a convenient, reliable and stereoselective route to (*Z*)-cycloalkenes of various ring sizes. On the other hand, the stereoselective formation of *E*-alkenes by catalytic hydrogenation is inherently difficult. Fürstner and co-workers explored the metathesis/semi-reduction sequence further to provide a complementary method for the conversion of alkynes into the corresponding (*E*)-alkenes (Scheme 56).[127,128] The semi-reduction process, inspired by work from Trost and co-workers,[129,130] is an efficient

two-step catalytic protocol, in which the alkyne first undergoes a *trans*-selective hydrosilylation, followed by a protodesilylation of the resulting alkenylsilane with stoichiometric amounts of a suitable fluoride source.



Scheme 56. Outline of stereoselective synthesis of macrocyclic (*E*)-alkenes by RCAM/semi-reduction

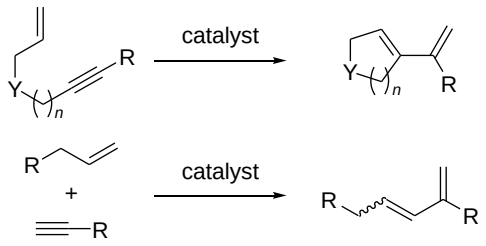
This methodology was then employed in the synthesis of several natural products,[131] including more recently that of lactimidomycin, a potent translation and cell migration inhibitor (Scheme 57).[132] Diyne **241** was exposed to the newly designed Mo-complex **242**[133] and reacted cleanly under high dilution conditions to afford the desired 12-membered enyne **243** as the sole product. A modified hydrosilylation protocol was then implemented, with $BnMe_2SiH$ in the presence of $[Cp^*Ru(MeCN)_3]PF_6$ as the catalytic complex.[130] The hydrosilylation to form compound **244** was clean and regioselective, and the desilylation that followed proved effortless with commercial TBAF as the fluoride source, affording the *E*,*Z*-configured 1,3-diene **245** in 64% yield over two steps. Five additional transformations were necessary for the installation of the enolate moiety and the required side-chains, therefore completing the synthesis of lactimidomycin **246**.



Scheme 57. Key steps in the synthesis of lactimidomysin

2.4.3. Enyne Metathesis

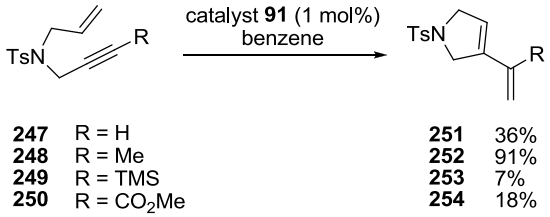
Enyne metathesis is a bond reorganization reaction between alkynes and alkenes to produce 1,3-dienes (Scheme 58).[134] Although this transformation bears similarities to olefin metathesis, enyne metathesis has been less studied. In this section, only enyne metathesis catalysed by ruthenium carbene complexes will be discussed.



Scheme 58. Principle of enyne metathesis

Enyne metathesis with metal carbenes was first reported by Katz in 1985 in a study involving several tungsten Fischer carbene complexes.[135] In 1994 Kinoshita and Mori

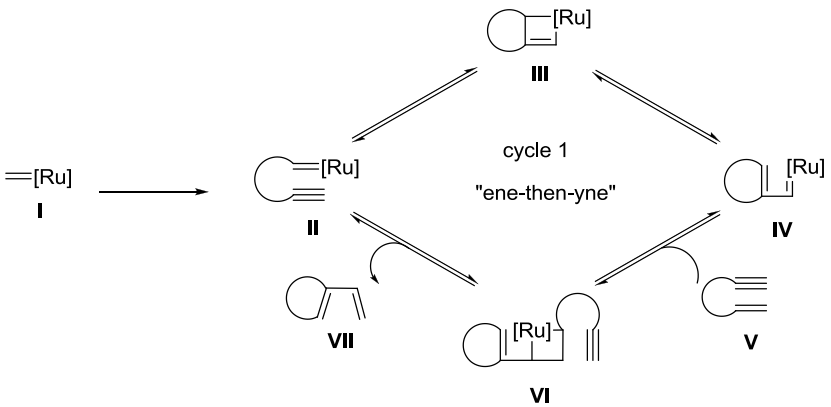
reported the first enyne metathesis reaction with a ruthenium carbene complex (**91**) (Scheme 59).[136]



Scheme 59. First example of an enyne metathesis reaction with a ruthenium carbene complex

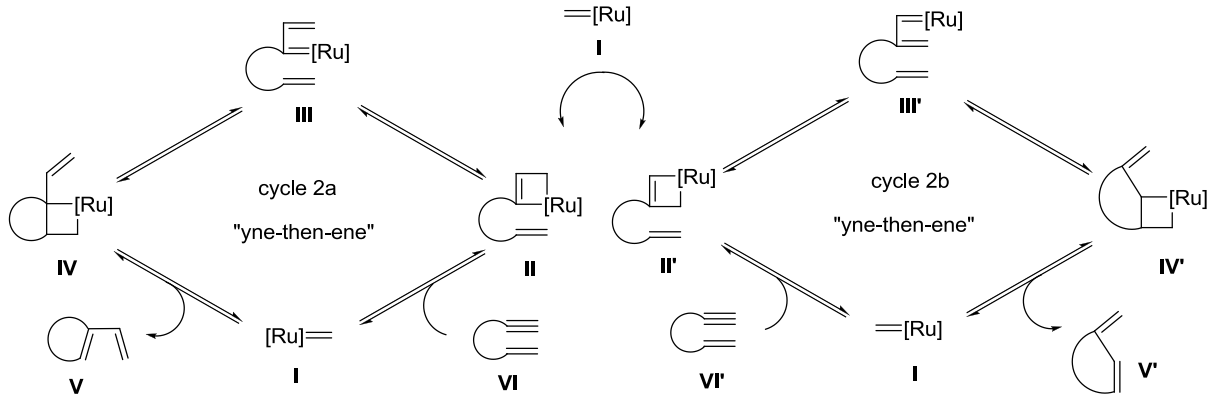
The yields were highly dependant on the nature of the acetylenic substituent. Terminal alkynes such as **247**, or those bearing silane or ester groups (e.g. **249** and **250**) afforded the corresponding products in lower yields. However, alkyl substituted systems such as **248** proceed more efficiently.

In comparison to the diene metathesis reaction mechanism, the enyne metathesis mechanism is poorly understood. Mechanistic analyses are complicated by several aspects. Most of all, two possible complexation sites (alkene or alkyne) exist for the ruthenium alkylidene, leading to different reaction pathways. The active catalyst is methylene complex **I** (Scheme 60). If the initial reaction occurs with the alkene part of the enyne forming complex **II**, a series of [2+2] cycloadditions and retrocycloadditions can be envisioned leading to the 1,3-diene product **VII** (cycle 1).



Scheme 60. The "ene-then-yne" (cycle 1) mechanism for enyne RCM

On the other hand, if the initial reaction occurs with the alkyne moiety two possible ruthenacyclobutene regioisomers **II** and **II'** can be formed (Scheme 61). By a similar series of [2+2] cycloadditions these will then transfer into two different 1,3-dienes (cycle 2a, diene **V** and 2b diene **V'**).



Scheme 61. The "yne-then-ene" (cycle 2a and 2b) mechanisms for enyne RCM

It seems likely that cycle 1 and 2 are both involved in the metathesis of enynes. However, NMR studies indicate that "ene-then-yne" (cycle 1) is the main pathway when the alkene is monosubstituted. Both reports observe initial reaction between the ruthenium carbene catalyst and the alkene.[137] A more detailed mechanistic understanding of the enyne metathesis reaction, however, must await further studies.

2.4.4. Cascade Metathesis

Metathesis is well established as a valuable tool in organic chemistry and is a unique technique for the construction of complex structures in a rapid and effective way. Since all metathesis transformations (except diyne metathesis) can be promoted by the same carbene catalyst, it is possible to combine them in a sequential way to enable a metathesis cascade in one-pot.

A domino reaction had been defined as "a process involving two or more bond-forming transformations which take place under the same reaction conditions, without additional reagents and catalysts, and in which the subsequent reaction result as a consequence of the functionality formed in the previous step."[138] These domino

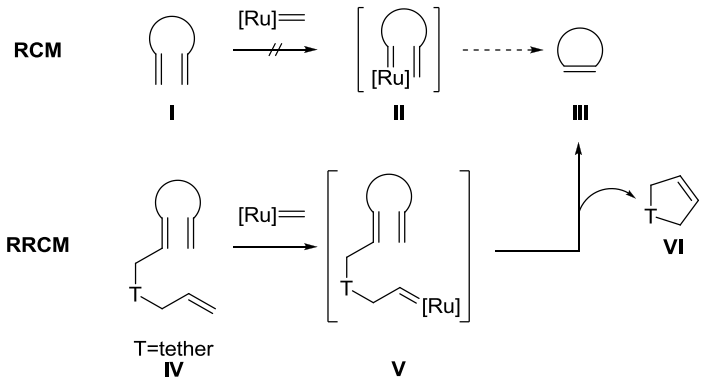
processes, also called tandem reactions, provide tremendous increase in molecular complexity by the use of a single catalyst in one pot.

In this section, a selection of synthetic approaches with ruthenium-catalysed domino reactions will be discussed, with particular focus on those connecting ring-closing metathesis cross-metathesis (RCM-CM) with [1,3]-metallotropic shifts, as well as ene-yne-ene RCM-RCM.

2.4.4.1. Ene-Ene and Ene-Yne-Ene RCM-CM Sequence

There are numerous combinations of metathesis reactions used in domino metathesis transformations and two frequently used in natural product syntheses are ene-ene RCM-CM and ene-yne-ene RCM-CM reactions.

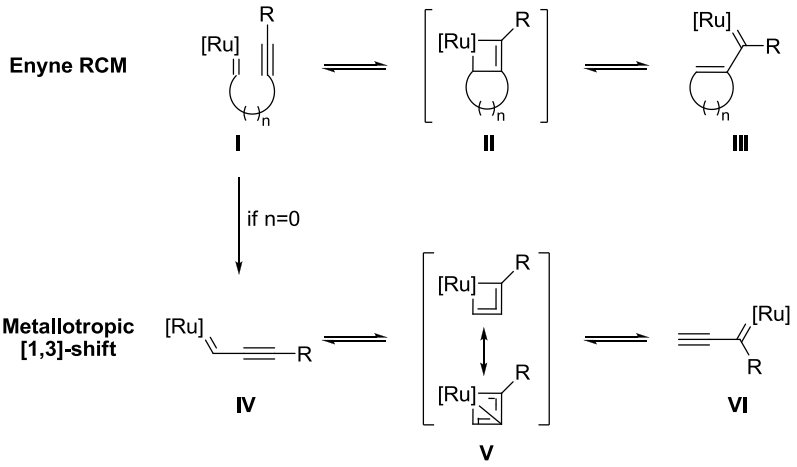
Ene-ene RCM-CM can be considered as an example of relay ring-closing metathesis (RRCM).[139] This methodology is used in RCM of sterically hindered olefins **I**, unreactive to standard metathesis conditions, due to difficulty initiating the catalytic process (Scheme 62). The relay approach incorporates a temporary tether **IV**, containing a sterically accessible olefin, where the catalytic cycle is initiated. The purpose of this strategy is the formation of a kinetically favourable five-membered ring **VI** with concomitant delivery of a ruthenium carbene onto the originally less accessible position to facilitate the subsequent metathesis reactions.



Scheme 62. Generic RCM versus RRCM processes

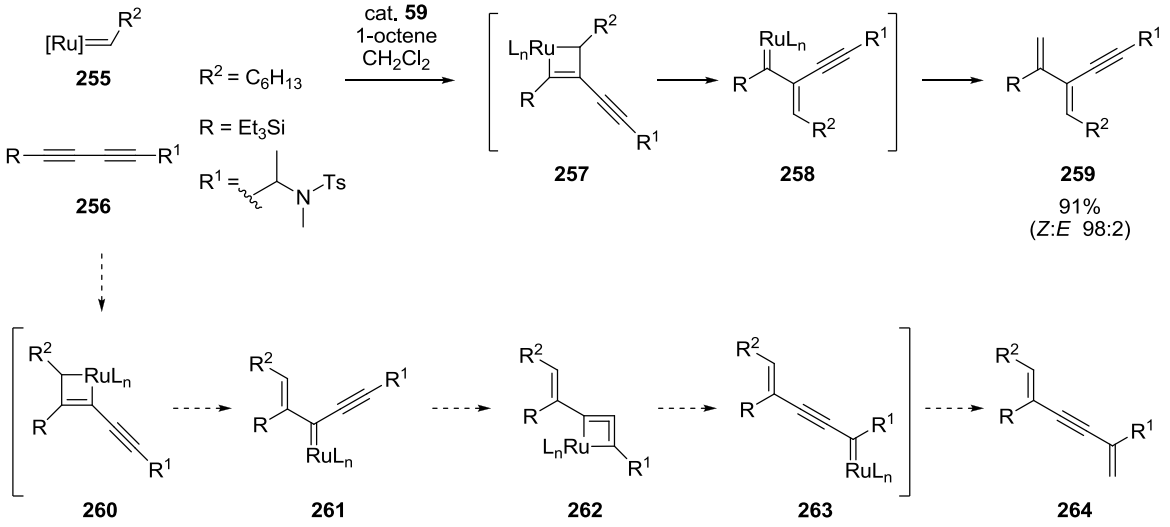
In 2005, Lee and Kim reported an innovative tandem methodology combining metathesis reactions and metallotropy for the constructions of enediynes and oligoenynes.[140,141] Due

to the conceptual similarity between the enyne RCM and the metallotropic [1,3]-shift of a transient ruthenium carbine complex, it was surmised that these two bond reorganisation processes share a close mechanistic relationship and could be incorporated into a joint synthetic design (Scheme 63). From a mechanistic standpoint, the metallotropic shift can be considered a special case of enyne RCM with no tether (n = 0) between the ene and the yne counterparts.



Scheme 63. Mechanistic connection between enyne RCM and [1,3]-metallotropic shift

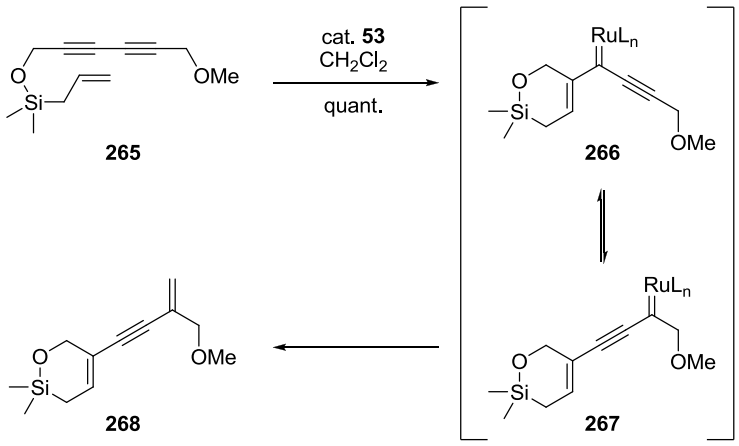
Firstly, the behaviour of 1,3-diynes in the presence of Ru-complex **59** and octene was examined (Scheme 64).[141] Two possible regioisomers **259** and **264** could be envisioned as a result of the reaction between 1,3-diyne **256** and ruthenium alkylidene **255**. Intermediate **260** would undergo a metallotropic [1,3]-shift to generate a new alkylidene **263** and eventually provide a 1,5-diene-3-yne **264** as a final product. However, a 2-alkynyl-1,3-diene **259** was obtained from the cross-metathesis reaction as the only observable product, a consequence of the formation of regioisomeric alkylidene intermediate **257**.



Scheme 64. Cross metathesis of 1,3-diynes without metallotropic shift

These results clearly indicate the role of the alkyne as a directing group to control regioselectivity, favouring the formation of intermediate **257**. Thus, reversing the regioselectivity to form an intermediate such as **260** might induce the [1,3]-shift.

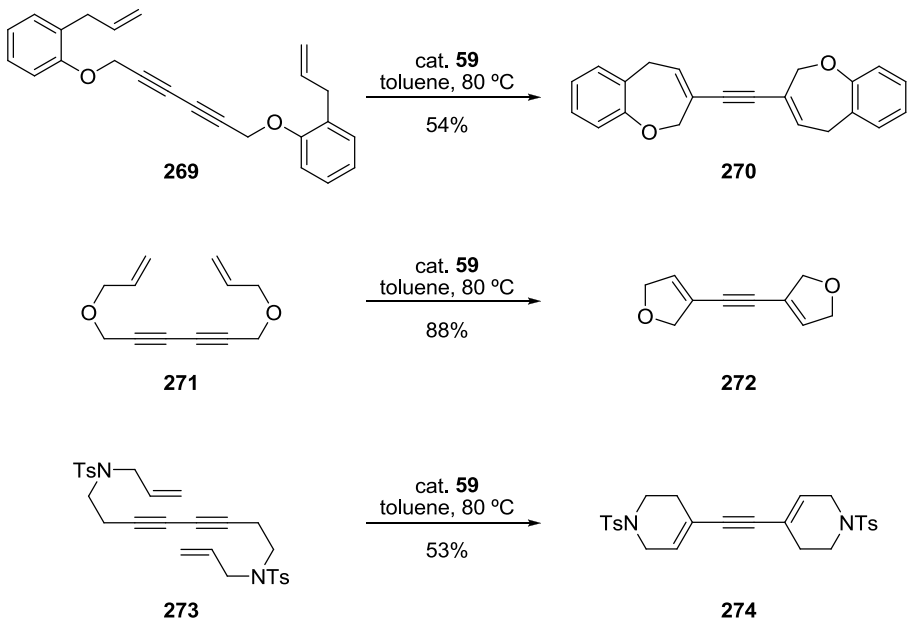
This was achieved by tethering an alkene to a diyne making the formation of intermediates intramolecular. Treatment of enediyne **265** with Grubbs' 2nd generation catalyst **59** afforded a single regioisomer **268** in quantitative yield, further suggesting that the transient carbene **266** underwent a [1,3]-migration to form Ru-complex **267** (Scheme 65).



Scheme 65. RCM of 1,3-diynes with an alkene tether

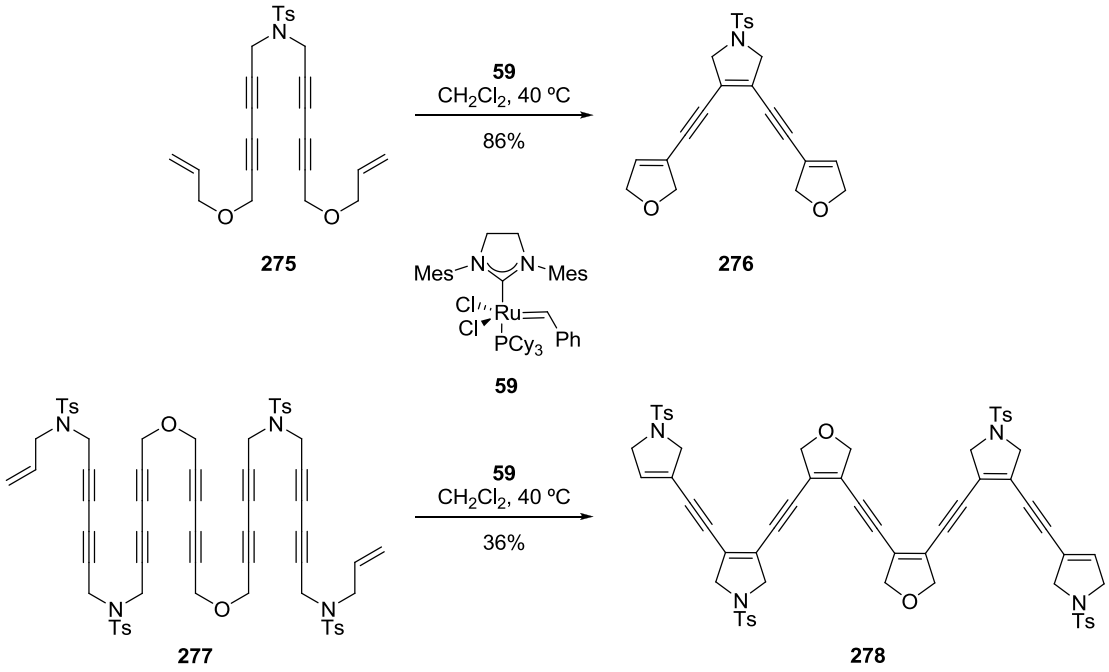
To further expand the scope of the RCM-metallotropic [1,3]-shift sequence, Lee and Kim investigated the synthesis of complex oligomers. These studies were based on work performed by van Otterlo and co-workers, who explored the synthesis of dienynes from

alkenes and diynes using ruthenium-mediated RCM (Scheme 66).[142] Enyne RCM reaction of **269**, **271** and **273** provided products **270**, **272** and **274** respectively. It is reasonable to assume that these products were formed *via* mechanistic steps involving a RCM-metallotropic [1,3]-shift, although this was not explicitly proposed by the authors.



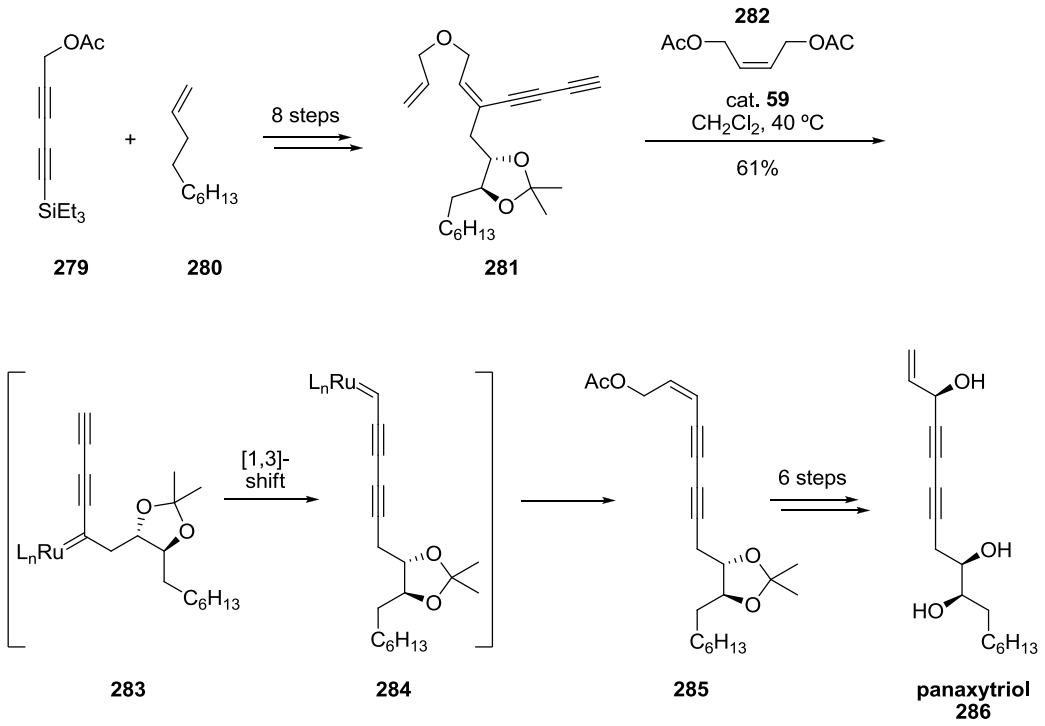
Scheme 66. Van Otterlo's synthesis of bicyclic 1,5-diene-3-ynes

Lee and Kim then designed substrates that could undergo a repetitive RCM-metallotropic [1,3]-shift process, leading to the formation of complex oligoenynes (Scheme 67).[140] This sequence resulted in a highly effective sequential bond-forming process, affording products such as **276** and **278** from the corresponding homologues **275** and **277**, in reasonable yield.



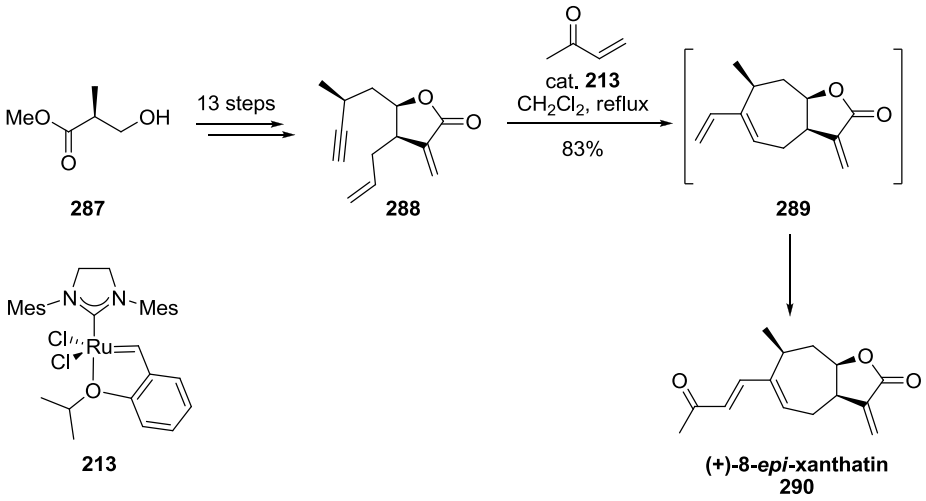
Scheme 67. Oligoenynes generated by RCM-metallotropic [1,3]-shift sequence

This cascade methodology was applied to the synthesis of several[143] natural products including that of panaxytriol **286**, a component of Red Ginseng (Scheme 68).[144] Diyne **281** was synthesised from compounds **279** and **280** in eight steps. Treatment of **281** with Ru-complex **59** generated a propagating carbine **283** and two consecutive metallotropic [1,3]-shifts then formed a new ruthenium species **284**, which underwent a final CM reaction with alkene **282** to complete the catalytic cycle. The desired product **285** was obtained in 61% yield as a mixture of isomers (E/Z, 1:5). Six additional steps delivered the target natural product panaxytriol **286**.



Scheme 68. Synthesis of panaxytriol

Ene-yne-ene RCM-CM is another cascade metathesis combination used extensively. The alkyne moiety has the ability to form a conjugate ruthenium carbene as a result of the reaction with an olefin, which ultimately can react with a second double bond to form a substituted 1,3-diene.[134,145] The synthetic application of this process was exemplified by Martin *et al.*, who employed a tandem process involving an enyne RCM coupled to an intermolecular CM as the key step in the synthesis of (+)-8-*epi*-xanthatin (Scheme 69).[146] The RCM precursor **288** was obtained from commercially available enantiomerically pure **287** in thirteen steps. Enyne **288** was treated with vinyl ketone in the presence of Hoveyda-Grubbs 2nd generation catalyst **213** to afford the desired target **290** in 83% yield. The challenge in this transformation consisted in the final CM reaction with an electron-poor olefin. The phosphine-free ruthenium catalyst **213** was employed in this step because previous reports had shown it to be a superior catalyst in RCM/CM reactions[147] and CM reactions involving electron-deficient olefins.[148]

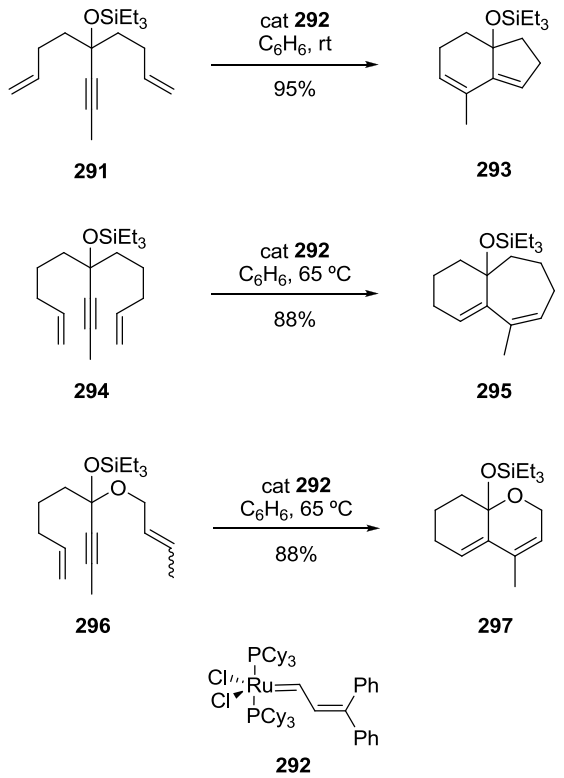


Scheme 69. Synthesis of (+)-8-*epi*-xanthatin through a RCM-CM cascade

2.4.4.2. Ene-Yne-Ene RCM-RCM Sequence

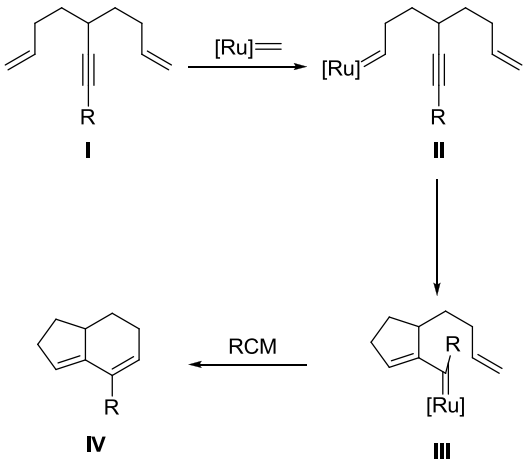
When an initial ring-closing enyne metathesis reaction sets up a second ring-closing metathesis reaction, the sequence can be regarded as a tandem or cascade metathesis process.

The first example of tandem enyne metathesis was reported by Grubbs *et al*. in 1994.[149] In this process, various dienynes (**291**, **294** and **296**) were subjected to ring-closure in the presence of ruthenium complex **292** to yield the corresponding bicyclic systems **293**, **295** and **297** (Scheme 70).



Scheme 70. Ruthenium catalysed double RCM of cyclic dienes

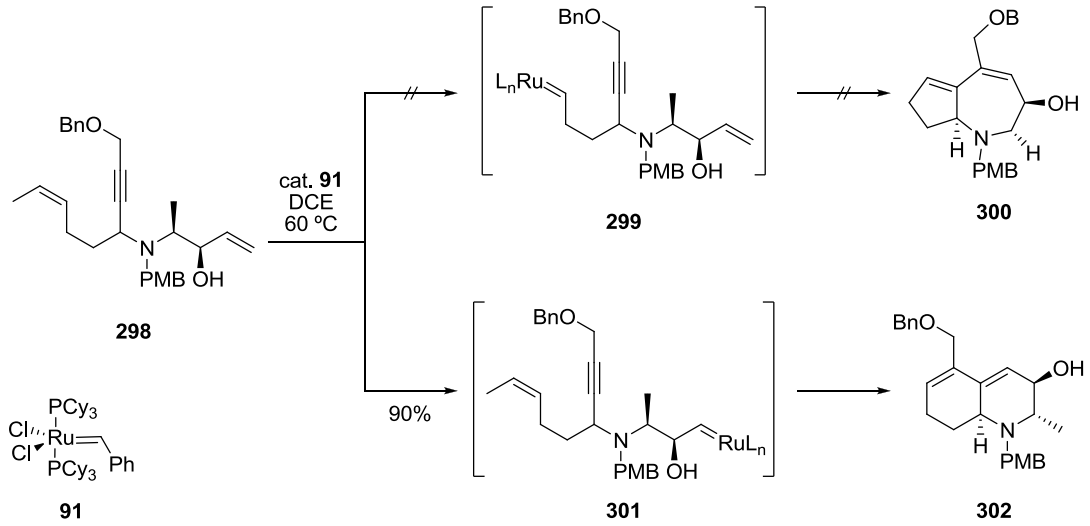
It was presumed that the reaction mechanism would involve an initial alkene metathesis of **I**, followed by ring closing metathesis of **II** onto the hindered internal alkyne (Scheme 71). The resulting vinyl carbene **III** would undergo a second RCM to form the bicyclic system **IV**.



Scheme 71. Presumed mechanism for ene-yne-ene RCM-RCM cascade

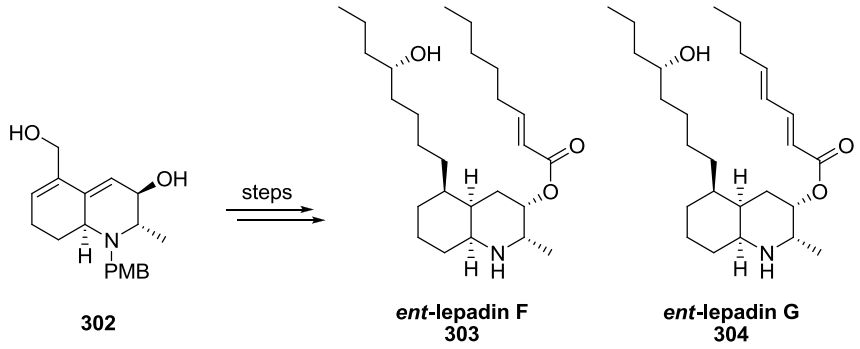
Although this methodology has since then been widely employed for the synthesis of natural products,[134] two specific examples are presented herein.

In 2008, Blechert and co-workers reported the total synthesis of decahydroquinilone-alkaloids *ent*-lepadin F and G (Scheme 72).[150] As the key step, the decahydroquiniline skeleton was synthesised utilising a tandem ene-yne-ene RCM reaction of an acyclic precursor. The success of this strategy relied upon the selectivity of these two steps, which was achieved through a well-directed hydroxyl protection strategy. Subjecting the substrate **298** to RCM conditions could lead to two different pathways: metathesis could be initiated on the disubstituted alkenyl moiety to produce ruthenium carbene **299**, leading to bicyclic compound **300**; or alternatively, metathesis could be initiated at the terminal double bond to produce ruthenium carbene intermediate **301**, which would then react with the alkyne moiety to furnish the desired bicyclic amine **302**.



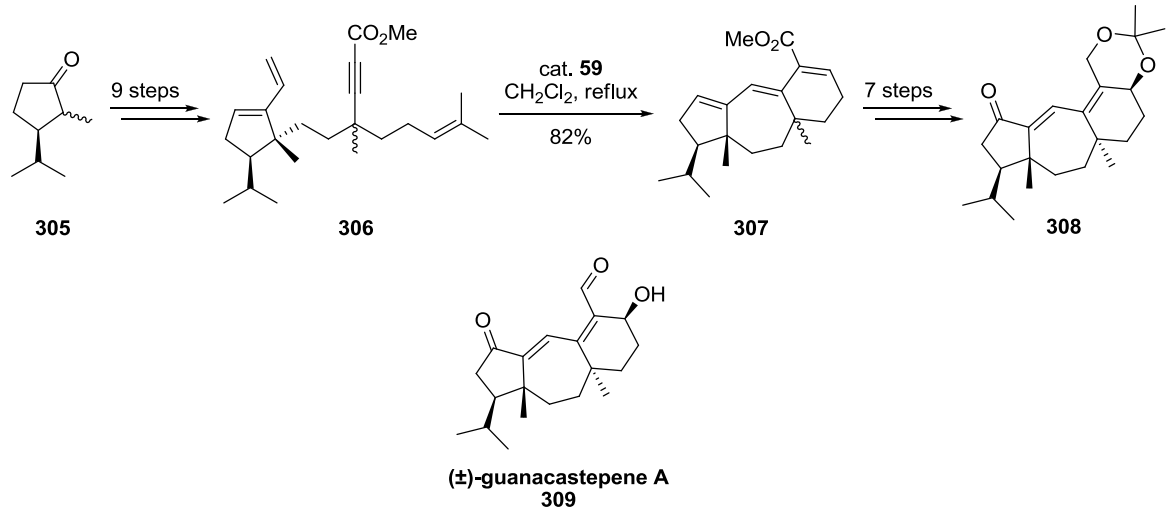
Scheme 72. Possible cascade RCM pathways for the synthesis of lepadin G and F

By exposing **298** to Grubbs 1st generation catalyst **91**, only the desired bicyclic product **302** was obtained in 90% yield (Scheme 72). Selectivity in the metathesis cascade was achieved by a coordinative effect of the unprotected allylic alcohol, which favoured the initiation of the cascade metathesis on the proximal olefin (**301**); together with the use of a disubstituted alkene as the final cross-metathesis partner, a common strategy for the selective catalytic cycle initiation at the monosubstituted alkene.[151,152] Further elaboration of compound **302** led to the formation of *ent*-lepadin F **303** and *ent*-lepadin G **304** (Scheme 73).



Scheme 73. *ent*-lepadin F and *ent*-lepadin G

Hanna and Boyer employed a tandem ene-yne-ene RCM-RCM reaction for the synthesis of the tricyclic core of guanacastepene A.[153] These studies were then employed in the formal synthesis of (±)-guanacastepene A **309** (Scheme 74).[154] The synthesis began with 3-isopropyl-2-methylcyclopentenone **305**, which was transformed into the RCM precursor **306** in nine steps. Compound **306** underwent the key tandem ene-yne-ene RCM reaction to furnish tricyclic product **307** in 82% yield, by exposure to Grubbs 2nd generation catalyst **59**. Triene **307** was converted efficiently into the desired tricyclic formal target **308** in a further seven steps.



Scheme 74. Formal synthesis of guanacastapene A

2.5. Summary

Olefin metathesis has evolved into an indispensable tool for advanced organic and polymer synthesis, especially through the application of RCM reactions. Moreover, the logic of retrosynthetic planning is strongly affected by this transformation which can be used in a strategic manner for the design of unprecedentedly short and efficient synthetic routes. The development of new ruthenium catalysts has permitted advances in this field. Significant progress has been made towards a deeper understanding of enyne metathesis[134] and asymmetric metathesis reactions.[122]

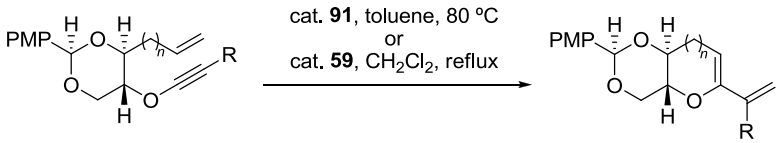
It can be concluded that metathesis reactions, and particularly olefin metathesis reactions, are among the most important advances in preparative chemistry in recent years. It seems fair to predict that the future holds considerable promise for more discoveries and applications.

Chapter 2
Cascade Metathesis Reactions

1. Introduction

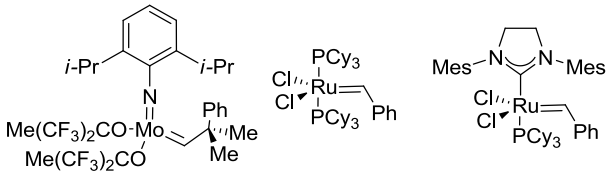
It has been demonstrated that RCM reactions offer an efficient synthetic approach to cyclic enol ethers (Chapter 1). Furthermore, the synthetic pathways towards these structures have been successfully applied to the synthesis of cyclic ether subunits in marine toxins. In the course of these studies, the use of both enyne metathesis in conjunction with metallotropic shifts and alkene metathesis for the formation functionalised cyclic enol ethers will be explored.

Previous studies in the Clark group have shown how ring-closing enyne metathesis can be used to prepare alkenyl-substituted six- and seven-membered cyclic enol ethers in good to excellent yields (Table 3).[80]



310-313 **314-317**

Entry	Substrate	n	R	Product	Yield (%; 91)	Yield (%; 59)
1	**310**	1	H	**314**	65	90
2	**311**	2	H	**315**	33	70
3	**312**	1	Me	**316**	77	98
4	**313**	2	Me	**317**	27	72



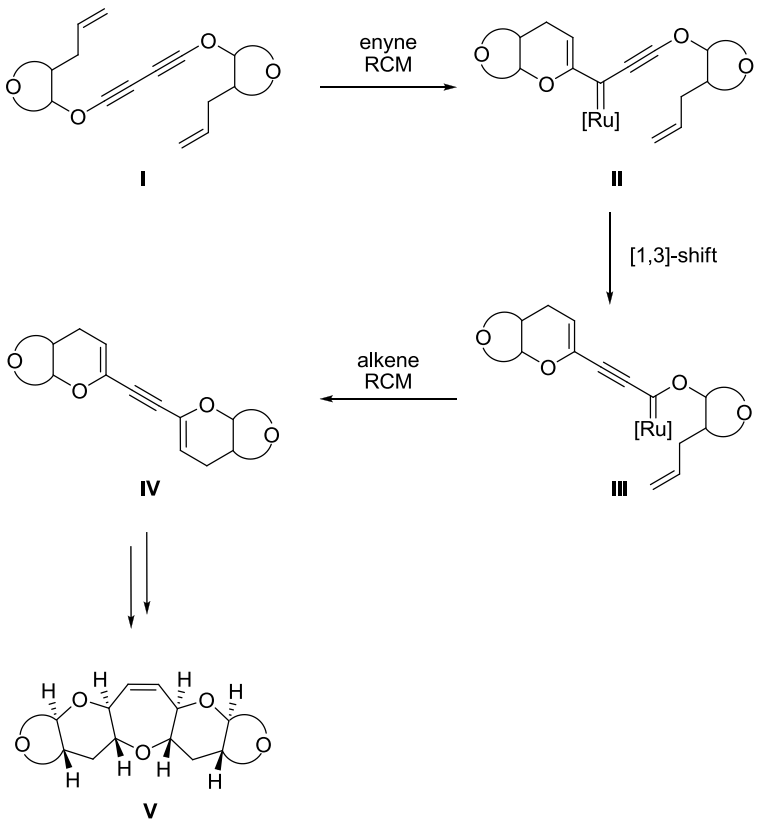
110 **91** **59**

Table 3. Enyne ring-closing metathesis studies

Several important findings emerged from the results of these studies. Firstly, the molybdenum catalyst **110** is not a suitable pre-catalyst in the context of enyne RCM (Table 3).[81] Secondly, terminal alkynyl ethers are also good substrates for the ruthenium catalysed enyne RCM reactions (Table 3, entries 1 and 2). Finally, the formation of seven-membered cyclic ethers is significantly more difficult to achieve, delivering lower yields than the corresponding reactions to form six-membered cyclic ethers (Table 3, entries 2 and 4).

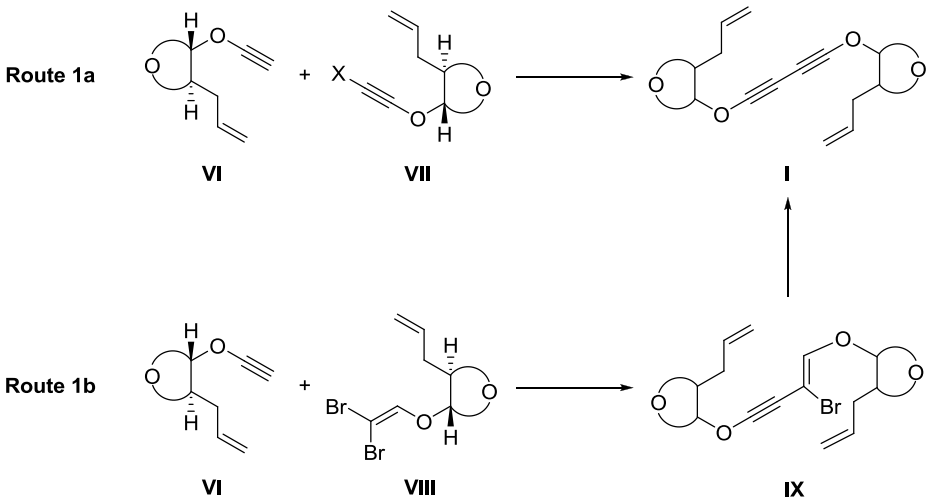
Previously, studies within the Clark group have illustrated that both alkene and enyne RCM reactions can be applied within a complex setting to form cyclic enol ethers that comprise polycyclic ether natural product subunits. In an attempt to create a more convergent, and elegant, route towards the synthesis of such ring structures, the following studies are focused towards the combination of alkene and enyne RCM, in a one-pot process. With respect to this proposal, two different approaches have been explored.

The first transformation involves a one-pot procedure with an initial enyne RCM reaction from precursor **I** to close the first ether ring, leading to intermediate **II** (Scheme 75). This is followed by a metallotropic [1,3]-shift to give intermediate **III**, which then undergoes a final alkene RCM to close the second ether ring in product **IV**. Further manipulation of **IV** would eventually lead to tricyclic system **V**.



Scheme 75. Cascade enyne RCM with [1,3]-metallotropic shift

Two different pathways were envisioned for the formation of RCM precursor **I** (Scheme 76). Firstly, coupling of alkynyl ether **VI**, with the halogenated counterpart **VII** would lead directly to the desired di-akynyl product **I** (Route 1a). Secondly, the coupling of alkynyl ether **VI** with a dibromoolefin species **VIII** would lead to coupled product **IX**, which would then be transformed into the desired RCM precursor **I** (Route 1b).



Scheme 76. Outline of two possible routes towards di-alkynyl ether RCM precursor

This tricyclic core structure **V** is present in numerous polycyclic ether natural compounds such as gambierol,[8] tamulamide[155] and maitotoxin[156,157,158] (Figure 4).

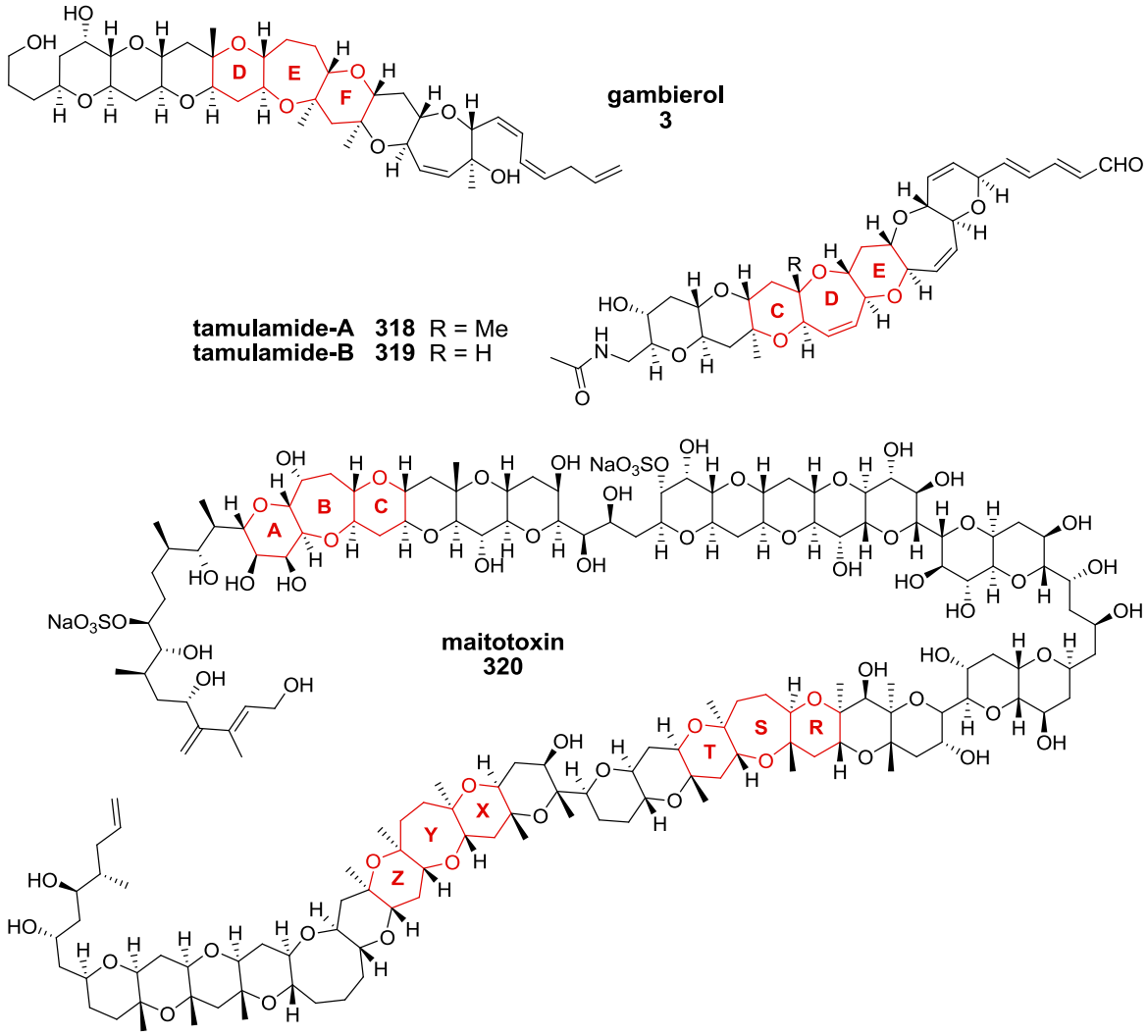
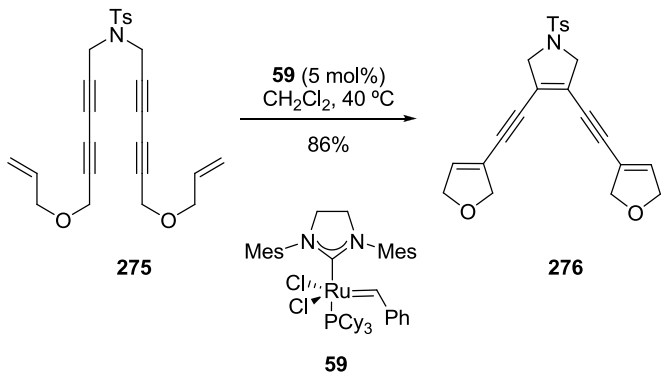


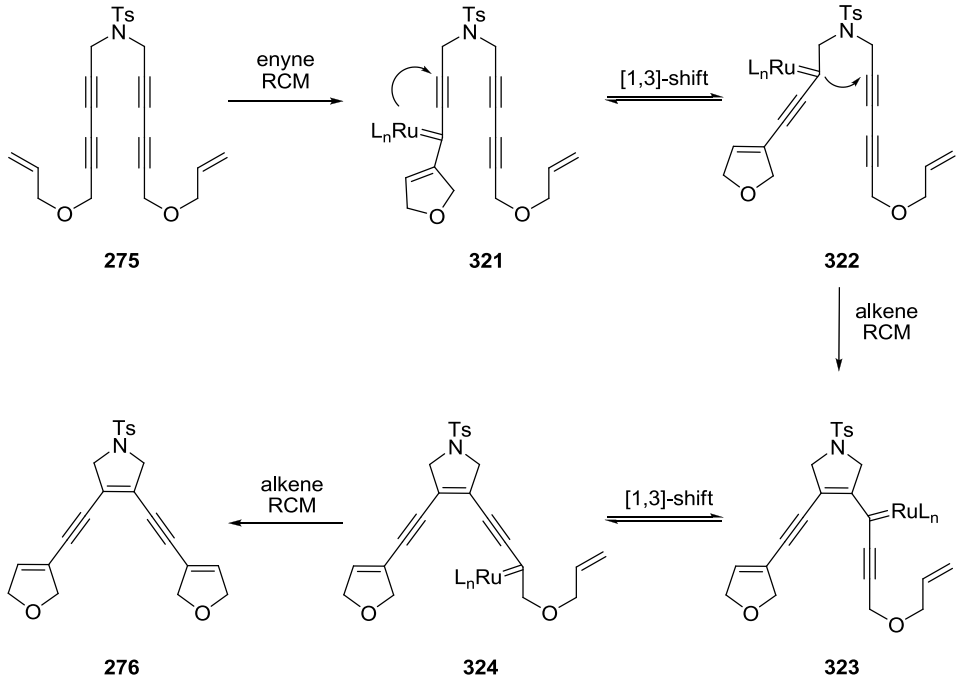
Figure 4. Tricyclic cores in gambierol, tamulamide and maitotoxin

This methodology was based on the work of Lee and Kim.[140,141] As shown in Scheme 77, the metallotropic [1,3]-shift of a transient ruthenium carbene complex in combination with enyne RCM was used to access remarkably complex networks such as **276**.



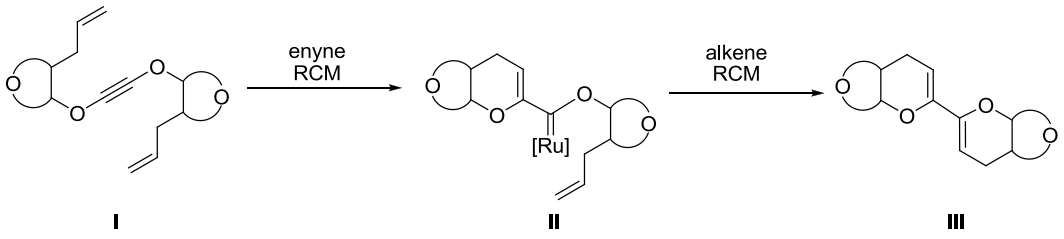
Scheme 77. Enyne metathesis and metallotropic [1,3]-shift

The proposed mechanism for the overall catalytic process involves initiation from one of the terminal alkenes in **275** and relay of the metal carbene to the proximal alkyne (Scheme 78). The newly formed alkyne **321** then undergoes a [1,3]-shift creating a new carbene in **322** which is effectively positioned for a facile RCM to a form the second five-membered ring in **323**. Repetition of this sequence would afford oligoenyne product **276**.



Scheme 78. Mechanism for enyne metathesis and metallotropic [1,3]-shift

The second route that was to be explored involves a one-pot procedure commencing with an enyne RCM reaction from precursor **I** closing the first ether ring in **II**, followed by direct alkene metathesis leading to the bicyclic product **III** (Scheme 79).



Scheme 79. Cascade enyne-ene metathesis

Once an efficient protocol had been established, this methodology would be investigated for the synthesis of marine toxin polycyclic ether subunits, such as the

FGHI and JKLMN fragments of prymnesin-1 and prymnesin-2,[159] as well as several maitotoxin fragments[156,157,158] (Figure 5).

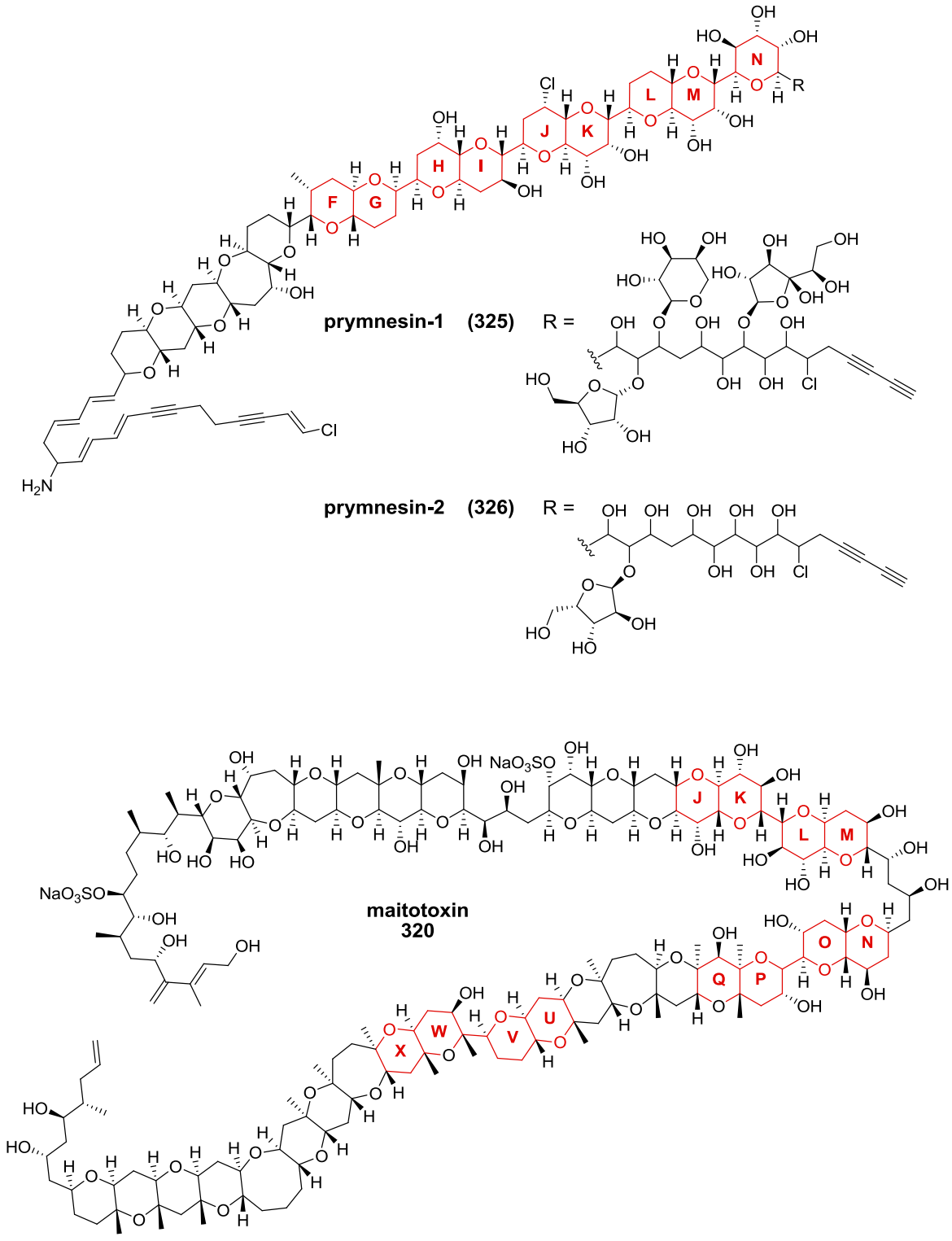
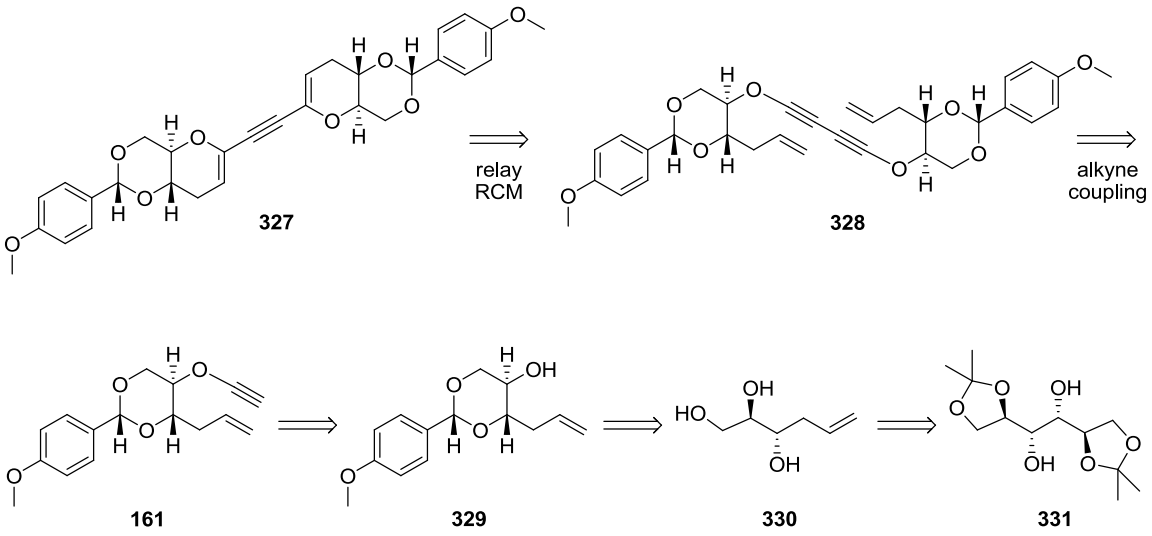


Figure 5. Prymnesin and maitotoxin fragments

2. Cascade Enyne RCM with [1,3]-Metallotropic Shift

2.1. Results and Discussion

Previous work in the Clark group has shown that D-mannitol based models can serve as suitable templates for the construction of polycyclic ether fragments.[80,160,161] These D-mannitol derivatives are composed of cyclic ethers possessing the desired *trans* configuration across the ring, characteristic of polycyclic ether natural products. With this in mind, D-mannitol based tetracycle **327** was chosen as an ideal target. The initial relay RCM reaction for the formation of **327** would require ene-1,3-diyne precursor **328**, which would be prepared from alkyl enol ether **161**. The key building block for the preparation of alkyl enol ether **161** is alcohol **329**, based on the D-mannitol system **331** (Scheme 80).

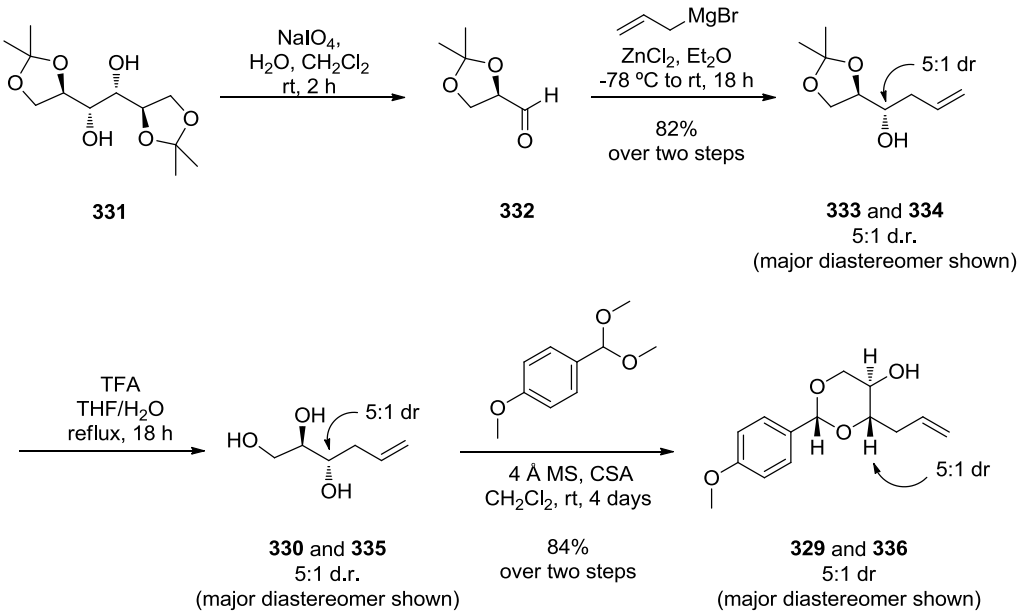


Scheme 80. Retrosynthetic analysis for metathesis and metallotropy route

2.1.1. The Coupling Partners

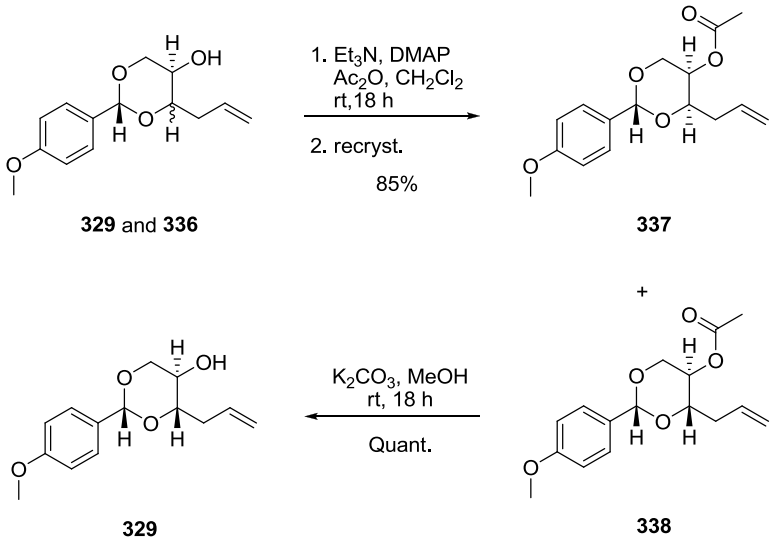
In the forward synthesis, the commercially available bisacetonide **331** was subjected to oxidative cleavage using standard sodium periodate conditions[162] to afford two equivalents of the corresponding aldehyde **332** (Scheme 81). Previous studies performed in the Clark group have shown that reactions of organozinc reagents with aldehyde **332** proceed with good diastereocontrol.[77] As a consequence, a solution of **332** in diethyl

ether was added to a 1 M solution of allylmagnesium bromide in the presence of $ZnCl_2$ to afford diastereomeric alcohols **333** and **334** as a 5:1 mixture (the indicated isomer predominated). At this stage, the diastereoisomers could not be separated efficiently by column chromatography and were used as a mixture in the subsequent step. Acetonides **333** and **334** were converted into the corresponding diastereomeric triols **330** and **335** by acidic deprotection and a subsequent acid-catalysed reprotection using *p*-methoxybenzaldehyde dimethyl acetal, in the presence of CSA and 4 Å molecular sieves, afforded diastereomeric alcohols **329** and **336** as a 5:1 mixture in 84% yield over two steps.



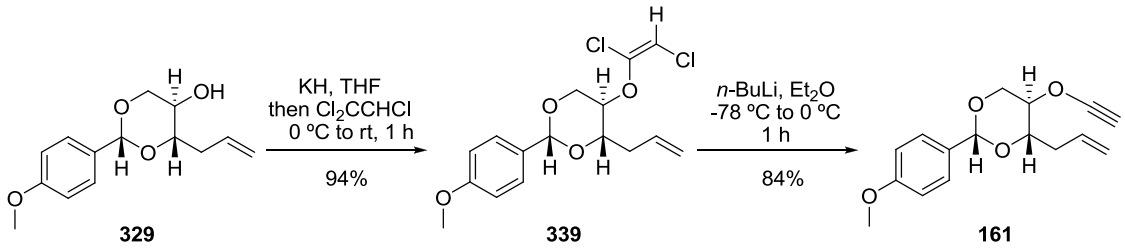
Scheme 81. Synthesis of D-mannitol based model

In a further attempt to separate the two diastereoisomers, alcohols **329** and **336** were converted into the corresponding acetates **337** and **338** and recrystallised to deliver the desired diastereoisomer **338** (Scheme 82). Pleasingly, deprotection of **338** was quantitative and afforded alcohol **329** as a single diastereoisomer.



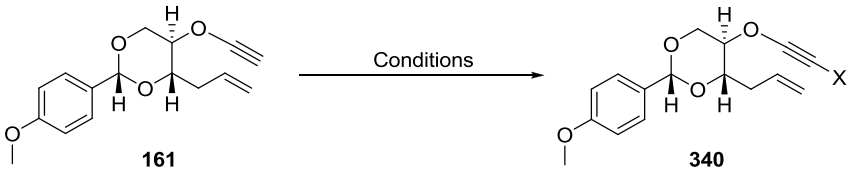
Scheme 82. Acetylation and deprotection for separation of diastereoisomers

With alcohol **329** in hand, the optimised two-step procedure of Green was employed to afford dichloroenol ether **339** in an excellent 94% yield. Treatment of **339** with *n*-BuLi delivered desired alkynyl ether **161** in 84% yield (Scheme 83).



Scheme 83. Synthesis of alternative alkynyl ether model

With alkynyl ether **161** in hand, the preparation of the halogenated coupling partner was attempted under several conditions (Table 4). Initial conditions involved bromination of compound **161** with *N*-bromosuccinimide (NBS) in the presence of $AgNO_3$. However after 18 hours, only unreacted starting material was recovered (Table 4, entry 1). Additionally, a second bromination reaction was performed *via* deprotonation with *n*-BuLi and quenching with bromine, yielding, again, only starting material **161** (Table 4, entry 2). Finally, iodination by deprotonation with *n*-BuLi and quenching with iodine afforded the desired product **340** in 98% yield.[163]

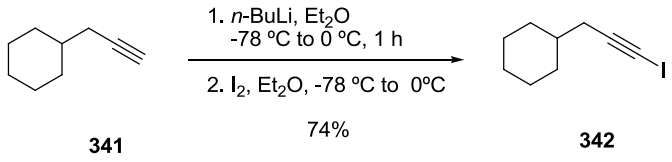


Entry	X	Conditions	Result
1	Br	NBS, $AgNO_3$, acetone, rt, 18 h	SM
2	Br	1) *n*-BuLi, THF, -78 °C to 0 °C, 1 h 2) Br_2, -78 °C to 0 °C	SM
3	I	1) *n*-BuLi, THF, -78 °C to 0 °C, 1 h 2) I_2, -78 °C to 0 °C	98%

Table 4. Halogenation of **161**

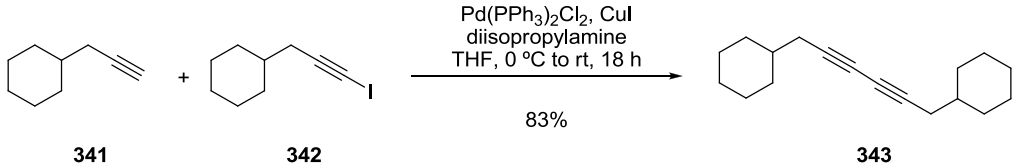
2.1.2. Sonogashira Type Alkyne-Alkyne Couplings

Following the preparation of both the terminal and halogenated alkynyl ether coupling partners, the coupling step could be investigated. The initial strategy involved typical Sonogashira conditions, which were tested by coupling of commercially available 3-cyclohexyl-1-propyne **341**. The halogenated equivalent **342** was obtained by deprotonation with *n*-BuLi and subsequent quenching with iodine affording **342** in 74% yield (Scheme 84).[163]



Scheme 84. Halogenation of 3-cyclohexyl-1-propyne **341**

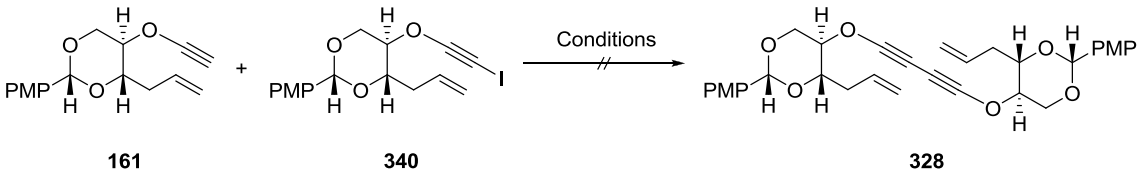
The coupling step between alkyne **341** and iodoalkyne **342** could then proceed, catalysed by $Pd(PPh_3)_2Cl_2$ and CuI in the presence of di-iso-propylamine, affording the desired coupled product **343** in good yield (Scheme 85).



341 **342** **343**

Scheme 85. Typical Sonogashira conditions

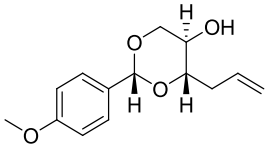
Turning to the specific target, the reaction of both alkynyl ether coupling partners **161** and **340** was attempted using these conditions (Table 5, entry 1). Several other Sonogashira-based palladium/copper mediated procedures,[164] with CuI and a variety of palladium catalysts, $Pd(PPh_3)_2Cl_2$ (Table 5, entries 1 and 2) and $Pd(PPh_3)_4$ (Table 5, entry 3) were attempted. Additionally, Cadiot-Chodkiewicz alkyne-alkyne coupling conditions were also employed, using CuI in conjunction with a number of bases (Table 5, entry 1 to entry 4), as well as CuBr in the presence of pyrrolidine (Table 5, entry 4).



161 **340** **328**

Entry	Catalyst	Base	Solvent	Result [a]
1	CuI or $Pd(PPh_3)_2Cl_2$/CuI	Diisopropylamine	THF	**328** not detected
2	CuI or $Pd(PPh_3)_2Cl_2$/CuI	Et_3N	THF	**328** not detected
3	$Pd(PPh_3)_4$/CuI	Pyridine	DMF	**328** not detected
4	CuI or CuBr	Pyrrolidine	THF	**328** not detected

[a]Following each protocol, traces of alkynyl ether **161** and side product **340** were recovered.

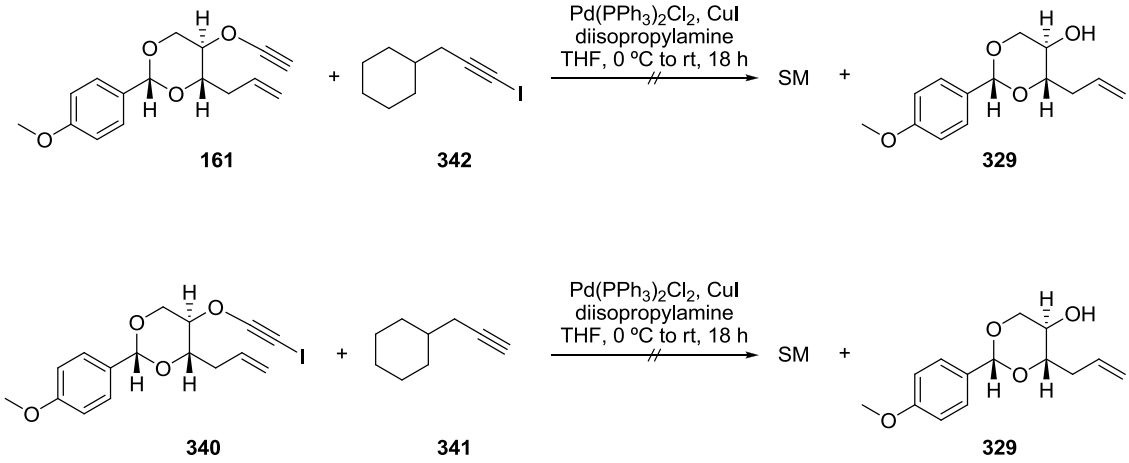


side product
329

Table 5. Conditions for halogenated alkyne with enol alkyne heterocoupling

Disappointingly, each protocol led to the recovery of trace amounts of starting material **161**, as well as decomposition side product **329**. The required product was not obtained using any of the protocols employed.

To further explore the limitations of this reaction and test the suitability of the substrates for coupling, the reaction between each of the alkynyl ether coupling partners **161** and **340** with known alkynes **342** and **341** were studied (Scheme 86). Firstly, alkynyl ether **161** was reacted with iodoalkyne **342** under conditions previously proven suitable in alkyne-alkyne coupling reactions (Scheme 85). Secondly, iodo alkynyl ether **340** was reacted with 3-cyclohexyl-1-propyne **341** under the same conditions. Unfortunately, both reactions were unsuccessful; both starting materials were recovered along with traces of the side product **329**.



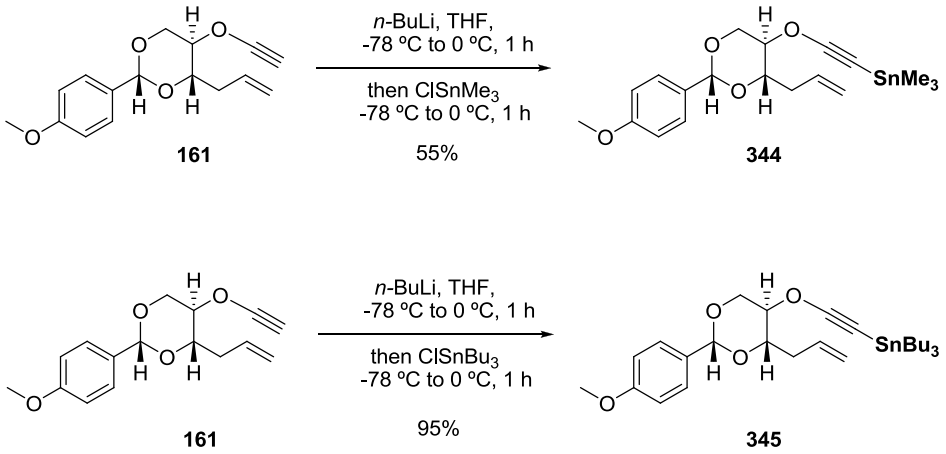
Scheme 86. Exploring the limitations

With respect to this initial strategy, it was evident that alkynyl ethers are more challenging substrates in Sonogashira and Cadiot-Chodkiewicz type couplings than originally anticipated. Therefore an alternative plan was constructed.

2.1.3. Stannane Couplings

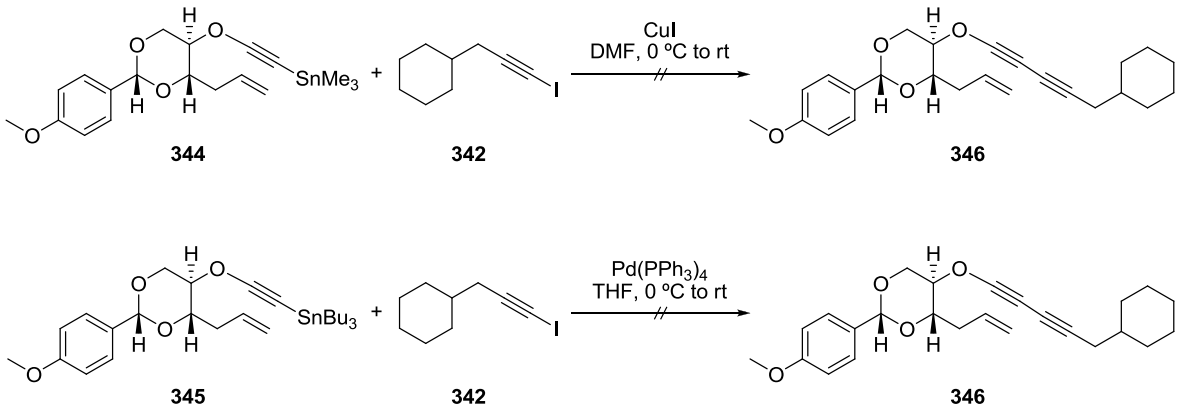
An alternative approach based on Stille cross-coupling, involving a palladium catalysed reaction of organostannanes with aryl, alkynyl or allyl halides was pursued.[165] One of the advantages of this reaction is its tolerance to a wide variety of functional groups, with the main disadvantages being toxicity and the difficulty of removing traces of tin by-products from the reaction mixture.

Firstly, the tin substrate was prepared by treatment of alkyne substrate **161** with *n*-BuLi followed by quenching with trimethyltin chloride, affording **344** in 55% yield (inseparable from tin by-products) (Scheme 87). Upon quenching with tributyltin chloride, the reaction yield improved to 95%, yet still the desired product **345** was contaminated with tin impurities. Any attempts to further purify the stannane products resulted in their decomposition, therefore the mixtures were used directly in the next step.



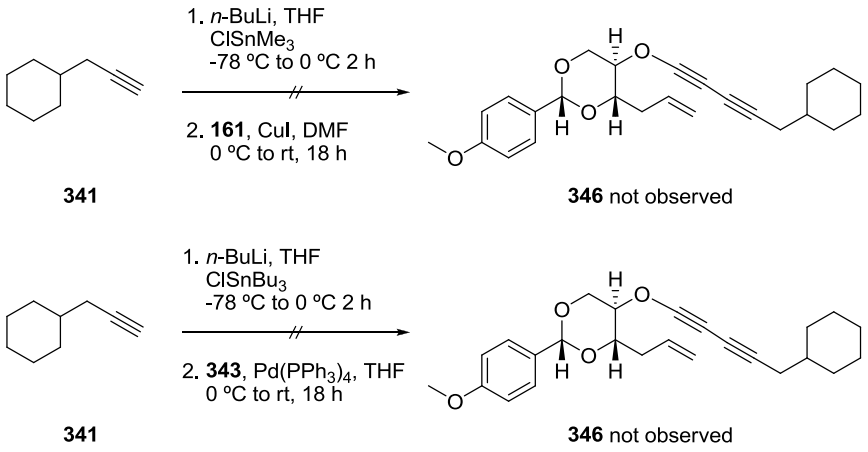
Scheme 87. Stannane preparation

With the required stannane partners **344** and **345** in hand, coupling with the previously prepared iodo alkyne **342** in the presence of CuI or $Pd(PPh_3)_4$ catalysts was attempted (Scheme 88). Frustratingly, only decomposition products were obtained using either protocol.



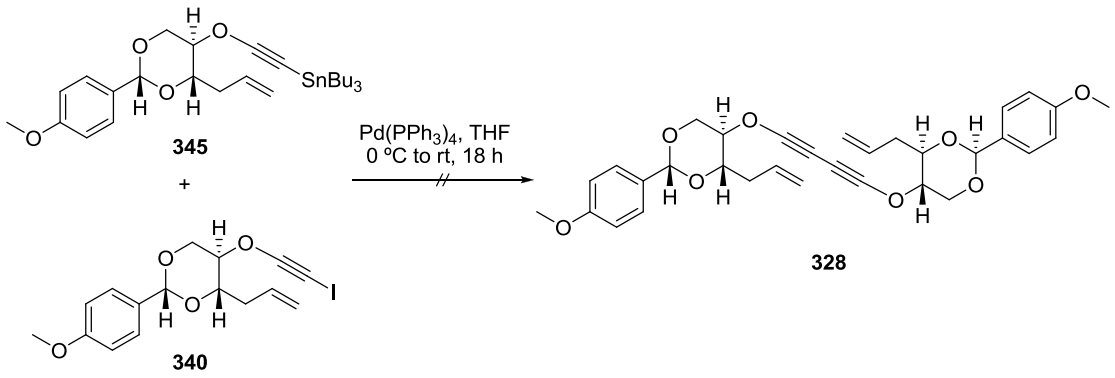
Scheme 88. Stille cross-coupling

In addition to the above experiments, the reverse cross-couplings were also investigated, where the stannane coupling partner was formed from 3-cyclohexyl-1-propyne **341** following conditions described previously (Scheme 89). Both tin substrates could not be purified to remove all tin by-products. Following this, each stannane intermediate was reacted with the corresponding coupling partner; alkynyl ether **161** and iodo alkynyl ether **340**. The CuI catalysed coupling with **161** did not proceed and the starting materials were recovered. On the other hand, reaction with halogenated alkynyl ether **340** in the presence of a Pd(0) catalyst resulted in full decomposition of the starting materials.



Scheme 89. Reverse Stille cross-coupling

Even though the previous results were not wholly positive, the coupling between alkynyl ether stannane **345** and iodo alkynyl ether **340** was attempted, following the conditions already explored (Scheme 90). Unfortunately, this led to total decomposition of the starting materials.



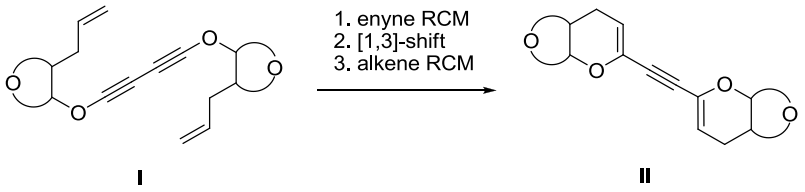
Scheme 90. Stille cross-coupling with alkynyl ether substrates

2.1.6. Summary

Various metal-mediated protocols were investigated in order to obtain a coupled product from an alkynyl ether and a halogenated alkynyl ether. All these attempts were unsuccessful and it became clear that an alternative route was required, which did not involve the direct cross-coupling of alkynyl ethers with halogenated alkynyl ethers.

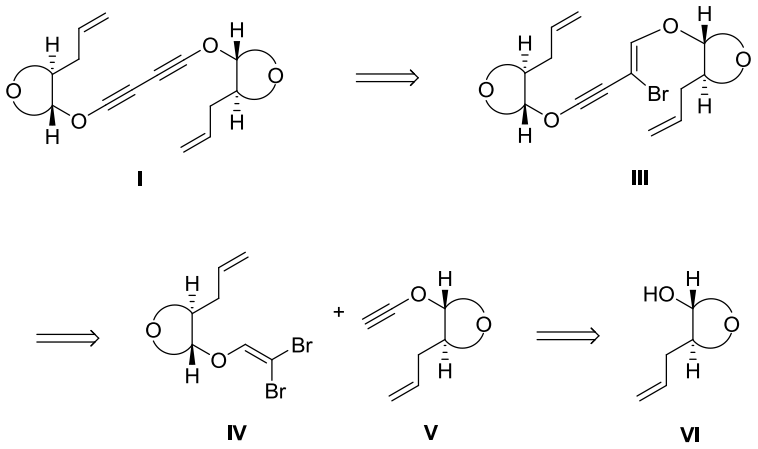
2.2. Alternative Strategy Towards Di-Alkynyl Ether RCM Precursor

In light of the difficulties encountered with the cross-coupling of alkynyl ethers, an alternative route was devised towards the RCM precursor **I** required for this first cascade metathesis reaction. Similar to the methodology described above, this alternative route also involved an enyne RCM reaction, followed by a metallotropic [1,3]-shift and a final alkene RCM starting overall from precursor **I** to obtain target **II** (Scheme 95).



Scheme 95. Key cascade metathesis reaction sequence

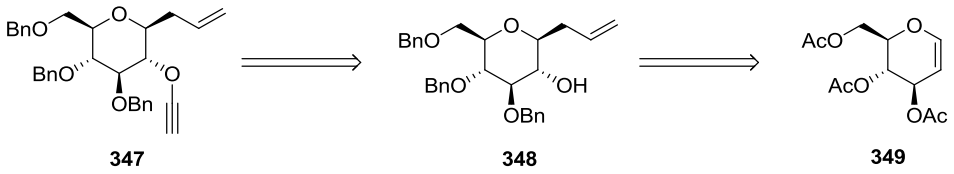
However, the synthetic route followed for the preparation of the RCM precursor **I** varied from that previously reported (Section 2.1). In this case, **I** would be obtained *via* an elimination from **III**, following the coupling of the dibromo species **IV** with alkynyl ether **V**. In turn, both of these compounds would be obtained from the same substrate, alcohol **VI** (Scheme 96). The coupling step would therefore take place prior to the formation of the dialkynyl species.



Scheme 96. Retrosynthesis of alternative strategy

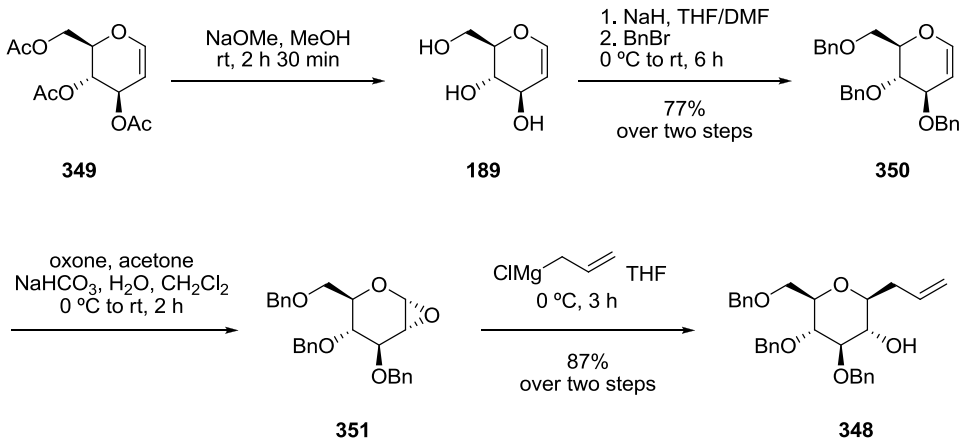
2.2.1. The Coupling Partners

In this strategy, both coupling partners were synthesised from a D-glucal based model. These D-glucal systems are composed of cyclic ethers with the stereochemistry of the centres adjacent to the oxygen atoms of the ether bridge strictly alternating between *R* and *S* configuration, a characteristic feature present in numerous polycyclic ether natural products. Previous and unpublished work in the group has shown that the D-glucal system can serve as a suitable template for the construction of polycyclic ether fragments with higher stability than the D-mannitol derived model.[161,160] The key building block for the preparation of alkynyl ether **347** is alcohol **348**, obtained from the commercially available tri-*O*-benzyl-D-glucal **349** (Scheme 91).



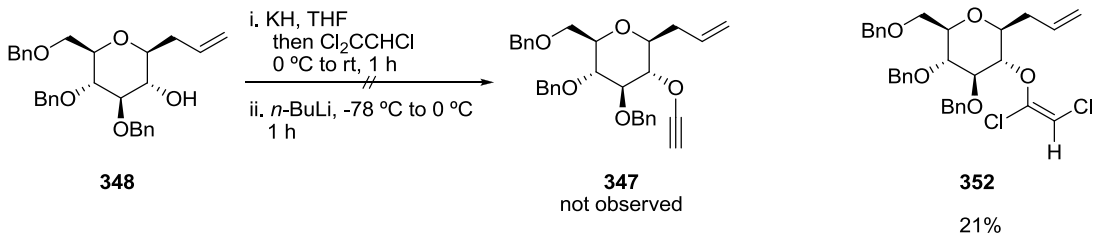
Scheme 91. Retrosynthetic approach for alkynyl ether **359**

In the forward synthesis, tri-*O*-benzyl-D-glucal **350** was prepared in two steps from commercially available tri-*O*-acetyl-D-glucal **349** in good yield (Scheme 92). Diastereoselective epoxidation of **350** using *in situ* generated DMDO[166] provided epoxyglucal **351**, which was opened at the acetal position by allylmagnesium chloride to afford alcohol **348** in 80% yield over two steps as a single diastereoisomer.



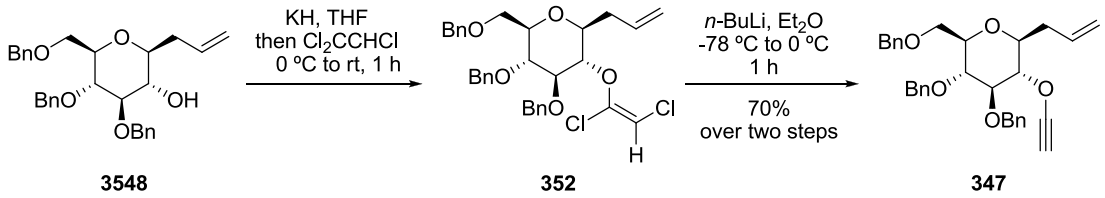
Scheme 92. Synthesis of D-glucal derived alcohol model

A modified version of Greene's method for the synthesis of alkynyl ethers from hindered secondary alcohols was used to synthesise alkynyl ether **347** (Scheme 93).[85] The original method involves deprotonation of the alcohol and reaction of the resulting alkoxide with trichloroethene followed by treatment of the resulting chlorinated enol ether with *n*-butyllithium in a one-pot fashion. However, this one-pot procedure was unsuccessful when employed to convert alcohol **348** into the alkynyl ether **347** and only the intermediate chlorinated enol **352** ether was obtained in 21% yield.



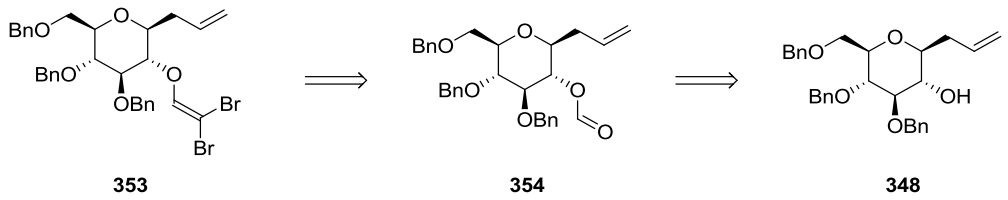
Scheme 93. One-pot synthesis of alkynyl ether **347**

A two-step procedure was then attempted, where after the first step a work-up was performed to afford the crude dichlorinated intermediate **352** (Scheme 94). Further purification led to partial decomposition and so, to avoid further loss of product, the crude dichlorinated compound **352** was treated with *n*-butyllithium at −78 °C to afford alkyl ether **347** in good yield over the two steps.



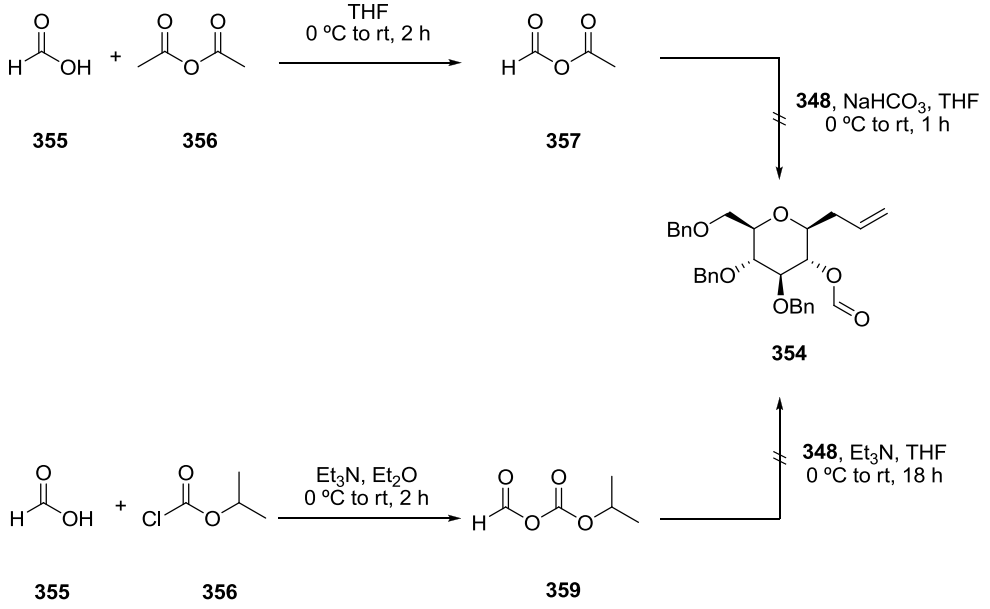
Scheme 94. Two-step synthesis of alkynyl ether **347**

With the alkynyl ether coupling partner **347** in hand, attention turned to the synthesis of the second coupling partner, dibromoolefin **353** (Scheme 98). Compound **353** would be obtained in two steps, *via* formate **354**, from D-glucal derived alcohol **348**.



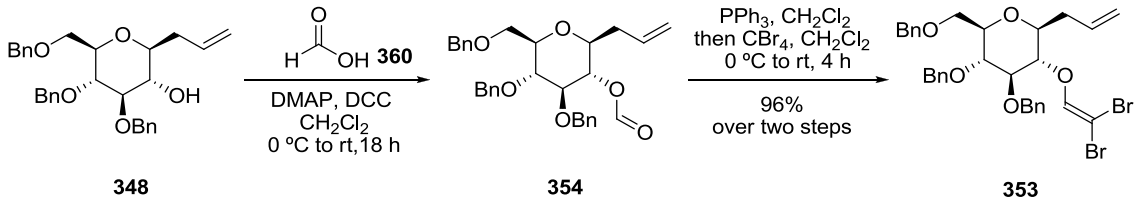
Scheme 98. Retrosynthesis of dibromoolefin coupling partner

Several protocols involving the preparation of mixed anhydrides were attempted in the synthesis of formate **354** (Scheme 99). Initially, formic acid **355** was stirred with acetic anhydride **356** in order to obtain formic acetic anhydride **357** *in situ*, which was then treated with alcohol **348** in the presence of $NaHCO_3$. Unfortunately, this reaction was unsuccessful and only unreacted starting material **348** was recovered. A second procedure involved the *in situ* formation of mixed anhydride **359** from formic acid **355** and isobutylchloroformate **358**. This mixed anhydride was then treated with alcohol **348**, but again only starting materials were recovered.



Scheme 99. Synthesis of formate **354** *via* mixed anhydrides

The final attempt to form the formate ester involved more typical esterification conditions.[167] Compound **348** was treated with anhydrous formic acid **355** in the presence of DCC and DMAP to afford crude formate derivative **354** (Scheme 100). The next step involved the chain extension of formate **354** by one carbon to obtain dibromoolefin **353** and this was accomplished conveniently *via* a modified Corey-Fuchs procedure.[168,169] Compound **354** was stirred with triphenylphosphine in dichloromethane at 0 °C, to which carbon tetrabromide was added, generating the desired dibromoolefin **353** in an excellent overall yield.

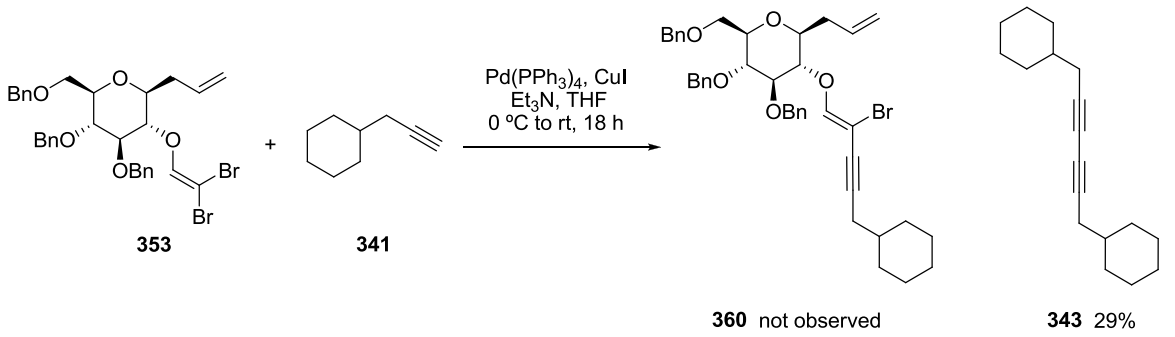


Scheme 100. Synthesis of dibromoolefin **353**

With dibromoolefin **353** in hand, the coupling reaction between alkynyl ether **341** and dibromoolefin **353** could be examined.

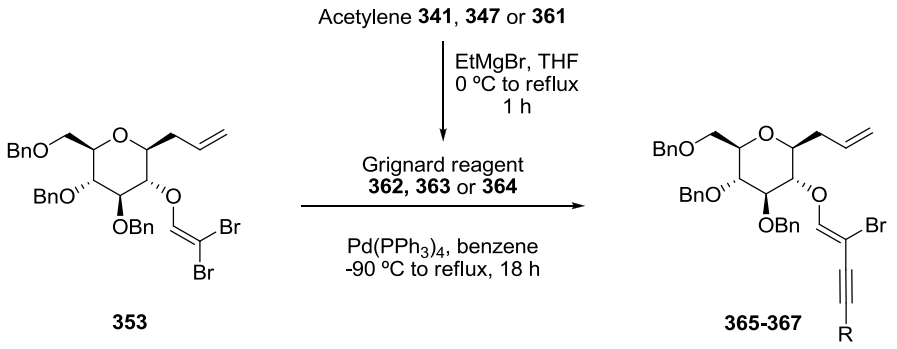
2.2.2. Coupling of Alkynyl Ether 341 and Dibromoolefin 353

Several procedures were explored in order to effect this coupling reaction. To examine the suitability of dibromoolefin **353** in metal catalysed cross-coupling reactions, it was first exposed to commercially available 3-cyclohexyl-1-propyne **341** in the presence of $Pd(PPh_3)_4$ and CuI (Scheme 101). This reaction failed to produce the desired coupled product **360**, and instead yielded 29% of diyne **343** and 82% of recovered starting material **353**.



Scheme 101. $Pd(PPh_3)_4$/CuI catalysed cross-coupling of **358** and 3-cyclohexyl-1-propyne **341**

An alternative cross-coupling procedure based on the Kumada reaction, was then used.[170] A Grignard reagent, formed *in situ* by reaction of 3-cyclohexyl-1-propyne **341** and ethylmagnesium bromide, was exposed to dibromoolefin **353** in the presence of a Pd(0) catalyst, yielding an unknown product (Table 8, entry 1).[171] These results were promising and therefore the conditions employed above were applied to the formation of Grignard reagent **363** and its subsequent coupling to dibromoolefin **353** (Table 8, entry 2). Regrettably, this reaction only led to recovery of the starting materials, suggesting that the formation of Grignard reagent **363** did not take place. These conditions were then applied to the preparation of a less sterically hindered Grignard reagent **364** from commercially available ethoxyacetylene **361**, again leading to the recovery of starting material. In this latter case, it was thought that the volatility of the starting material **361** could be impeding the initial reaction with ethylmagnesium bromide.



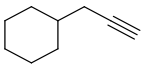
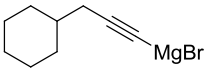
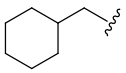
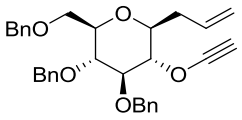
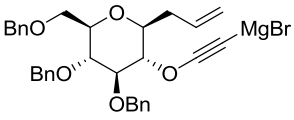
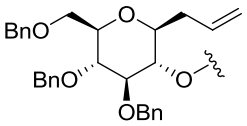
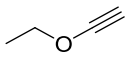
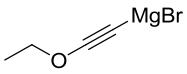
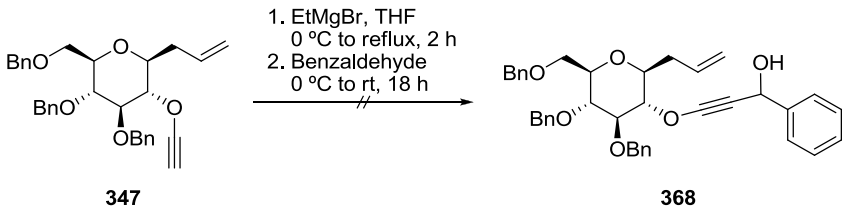
Entry	Acetylene	Grignard Reagent	R	Results
1	 351	 362		SM + unknown product
2	 347	 363		SM
3	 361	 364		SM

Table 8. Kumada type couplings

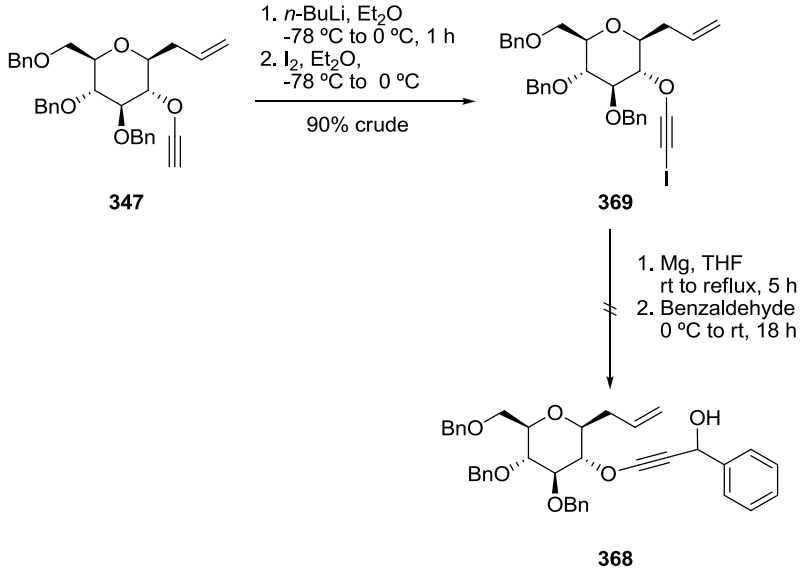
To check whether the Grignard formation was actually taking place, the organomagnesium species was treated with a highly reactive electrophile. Thus, alkynyl ether **347** was deprotonated with ethylmagnesium bromide and then quenched with benzaldehyde (Scheme 102). Only starting material **347** and benzaldehyde were recovered from this reaction, proving that the initial Grignard reagent had not been formed.



Scheme 102. Grignard formation test reaction

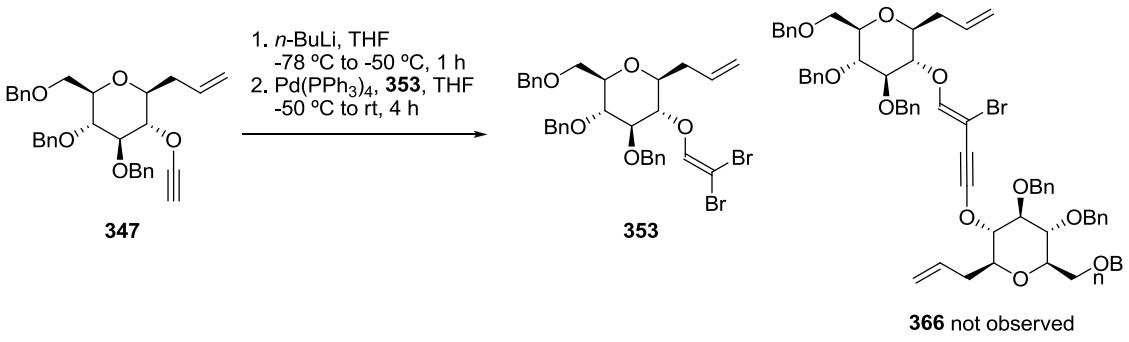
An alternative procedure for the preparation of Grignard species was then employed (Scheme 103). Alkynyl ether **347** was treated with *n*-BuLi and quenched with iodine,

affording iodoalkynyl ether **369** in 90% yield. Attempts to further purify this compound led to decomposition. The protocol then involved the reaction of **369** in the presence of magnesium, forming the Grignard species *in situ*, to which benzaldehyde was added. From observation, the reaction of **369** with magnesium did not initiate and only starting materials **369** and benzaldehyde were recovered.



Scheme 103. Grignard formation from haloalkyne **369** and test reaction

The results described above indicated that the formation of the Grignard species presented the main challenge in the Kumada-type coupling reaction. It was thought that the organomagnesium could be replaced with an organolithium reagent (Scheme 104). Alkynyl ether **347** was treated with *n*-BuLi to form the organolithium species, which was immediately reacted with dibromoolefin **353** in the presence of a Pd(0) catalyst. Disappointingly, this led to the recovery of an inseparable mixture of starting materials **347** and **353**.



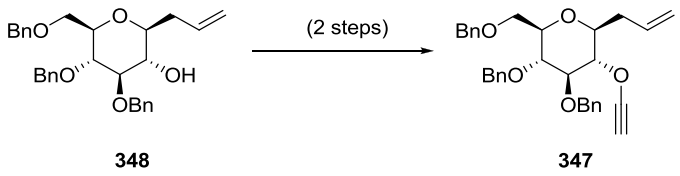
Scheme 104. Organolithium species synthesis and coupling

2.2.3. Summary

In order to complete the synthesis of the RCM precursor, an alternative metal-mediated strategy was explored. Several protocols were investigated, involving an alkynyl metal species and a dibromoolefin. All attempts were unsuccessful which further suggests that alkyl cross-coupling reactions do not translate well to alkynyl ether substrates.

2.3. Homocouplings

The synthesis of the RCM precursor **369** is key to this one-pot cascade enyne RCM with [1,3]-metallotropic shift route. In light of the difficulties encountered in the cross coupling of two different partners for the formation of the RCM precursor **369**, homocoupling procedures were attempted. As such, the study by Pericàs *et al*. on the generation of 1,4-dialkoxy-1,3-butadiynes and their thermal stability was followed.[172] First, the ene-1,3-diyne homocoupling precursor was synthesised from alkynyl ether **347**, prepared in two steps following the procedure based on Greene's work described in Section 2.1.[85]

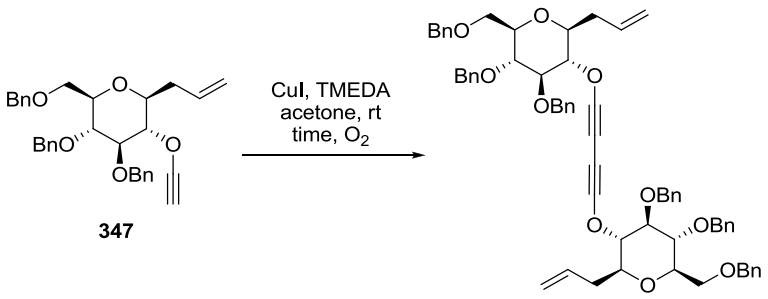


348 **347**

Scheme 97. Synthesis of enol alkyne **347**

With alkynyl ether **347** in hand, focus was shifted towards the homocoupling step. Initially, the dimerisation of **347** was performed following Pericàs' reported conditions with 5 mol% CuI and 0.1 equivalents of TMEDA (Table 6, entry 1).[172] However, as shown by TLC analysis, full conversion of the starting material was not observed. In addition to this, the acidic work-up caused full decomposition of the product. Following these results, the reaction time was extended to 1 hour, but complete consumption of the starting material was still not achieved, and in fact, a higher degree of decomposition was observed (Table 6, entry 2). The work-up was also altered to a less acidic one by using a saturated aqueous solution of NH_4Cl (1 M HCl used in reported conditions). Nevertheless, the crude material decomposed during purification on column chromatography using neutralised silica gel. In an attempt to increase conversion, the amount of catalyst loading was raised to 10 mol%, in addition to doubling the number of

equivalents of TMEDA used (Table 6, entry 3), but disappointingly, this led to decomposition during the reaction. The increase in catalyst loading proved to be ineffective in this reaction, which in the following attempt saw a return to 5 mol% of CuI accompanied by 0.2 equivalents of base (Table 6, entry 4). Again, full conversion was not obtained, but a work-up with a saturated solution of NH_4Cl afforded the dialkynyl ether **369** in a 52% crude yield. Next, the same conditions were employed with a prolonged reaction time of 1 hour 30 minutes to improve conversion, however this had no effect. Drying the compound under vacuum overnight led to its decomposition, which demonstrated further the sensitivity of this product (Table 6, entry 5). In the final attempt (Table 6, entry 6), the catalyst loading was maintained at 5 mol% CuI and the reaction time at 1 hour 30 minutes, although the number of equivalents of base used was again doubled to 0.4 equivalents in an effort to increase conversion. The work-up involved washing the organic layers with a saturated solution of NH_4Cl, drying over $MgSO_4$, and concentrating *in vacuo*. The crude material was then dissolved in diethyl ether and filtered through a short plug of Al_2O_3 which, after *in vacuo* concentration, led to 44% yield of a much cleaner crude product **369**.



347 **369**

Entry	CuI (mol%)	TMEDA	Reaction Time (h)	Yield (%)
1	5	0.1	0.5	Decomposition
2	5	0.1	1	Decomposition
3	10	0.2	1	Decomposition
4	5	0.2	1	52[a]
5	5	0.2	1.5	Decomposition[b]
6	5	0.2	1.5	44[a]

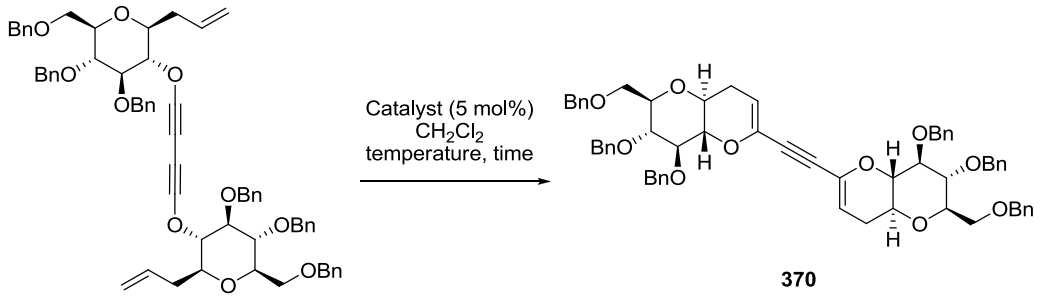
[a]Due to the sensitive nature of product **369**, no further purification was performed.
[b]Overnight vacuum drying.

Table 6. Conditions for the oxidative coupling of alkoxyacetylene **347**

Although the reaction conversion remained less than optimal, a suitable work-up and purification procedure had been established to obtain relatively pure samples of the very sensitive compound **369**.

2.3.1. RCM Cascade Reactions

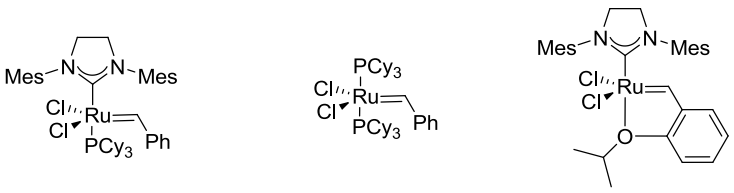
With 1,4-dialkoxy species **369** in hand, attention turned to the ruthenium catalysed RCM cascade reaction. Initially, conditions reported by Lee and Kim were followed, where 1,3-dialkynyl ether **369** was exposed to Grubbs' 2nd generation catalyst (5 mol%), in CH_2Cl_2 (0.02 M) at reflux (Table 7, entry 1).[140] These conditions led to complete decomposition of the starting material. In order to avoid possible cross-metathesis reactions, the concentration was decreased to 0.002 M, but this did not improve the results; complete decomposition of the starting material was observed once again (Table 7, entry 2). These experiments were then repeated at room temperature in an attempt to reduce decomposition (Table 7, entries 3 and 4). However, after 4 hours, only starting material remained and after 18 hours, full decomposition had occurred. Two alternative catalysts were employed under the conditions described above; Grubbs' 1st generation catalyst in CH_2Cl_2 (0.02 M or 0.002 M), at reflux and room temperature (Table 7, entries 5 to 8), as well as Hoveyda-Grubbs 2nd generation catalyst under identical conditions (Table 7, entries 9 to 12). To ensure that the catalyst loading was not the limiting factor, and in an attempt to drive the reaction forward, all of the above experiments were repeated with portion-wise addition of the catalyst every hour (5 mol% each time). However despite all efforts, only discouraging results were obtained.



369 **370**

Entry[a]	Catalyst	Concentration (M)	Temperature (°C)	Time (h)	Results[b]
1	GII	0.02	reflux	4 h	Decomposition
2	GII	0.002	reflux	4 h	Decomposition
3	GII	0.02	rt	4 h to 18 h	SM
4	GII	0.02	rt	4 h to 18 h	SM
5	GI	0.02	reflux	4 h	Decomposition
6	GI	0.002	reflux	4 h	Decomposition
7	GI	0.02	rt	4 h to 18 h	SM
8	GI	0.002	rt	4 h to 18 h	SM
9	HGII	0.02	reflux	4 h	Decomposition
10	HGII	0.002	reflux	4 h	Decomposition
11	HGII	0.02	rt	4 h to 18 h	SM
12	HGII	0.002	rt	4 h to 18 h	SM
13	-	0.02 or 0.002	reflux	4 h	Decomposition

[a]All the above experiments were repeated with portion-wise (5 mol%) addition of the corresponding catalyst every 1h. [b]By TLC analysis.



59 GII **91** GI **213** HGII

Table 7. RCM cascade reaction study

Several patterns emerged from the above study. Firstly, all the reactions carried out at reflux led to decomposition of the starting material **369**, suggesting the 1,3-dialkynyl ether compounds are unstable at higher temperatures. This was proved by the control experiment which involved two samples of compound **369** stirred in CH_2Cl_2 (0.02 M and

0.002 M) at reflux (Table 7, entry 13). Both reactions were monitored by TLC analysis and after 4 hours, the starting material had decomposed fully. Secondly, those reactions carried out at room temperature showed some decomposition, but most of the starting material was recovered, even after an 18 hour period. This suggests that an elevated temperature is required to initiate the sequential metathesis and metallotropy process.

2.3.2. Summary

Various metal-mediated protocols were investigated in order to obtain a coupled product from an alkynyl ether and a halogenated alkynyl ether. All these attempts were unsuccessful and it became clear that an alternative route was required, which did not involve the direct cross-coupling of alkynyl ethers with halogenated alkynyl ethers. To this end, a study was carried out to attain the RCM precursor *via* homocoupling of an alkynyl ether. This proved successful, affording the desired 1,3-dialkynyl ether coupled product.

With the 1,3-dialkynyl ether in hand, the RCM cascade reaction was attempted. Despite an extensive study of this reaction, it was concluded that the 1,3-dialkynyl ether species are too unstable to withstand the conditions required to undergo a cascade metathesis and [1,3]-metallotropic shift sequence.

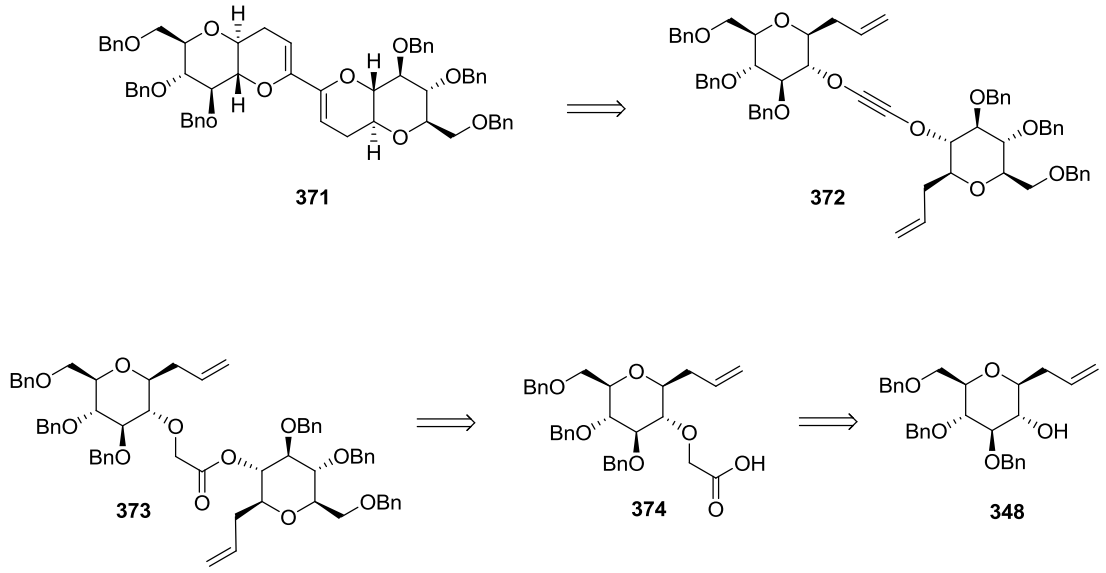
3. Cascade Enyne-Ene Metathesis

3.1. Results and Discussion

This section concerns the development of methodology involving an enyne RCM reaction followed by direct alkene metathesis reaction (Chapter 2, Section 1). Once an efficient protocol had been established, this methodology was to be used in the synthesis of marine toxin polycyclic ether subunits.

The polycyclic ether subunit **371** was chosen as a suitable target following previous experience in the Clark group that has demonstrated how D-glucal derivatives can act as suitable templates for the construction of polycyclic ether fragments. This tetracycle

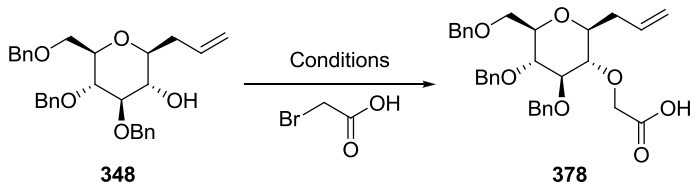
371 also possesses the same basic core as fragments from the natural product targets maitotoxin and prymnesin (Chapter 2, Introduction). Target **375** could be synthesised from alkynyl diether **372**, after a tandem enyne-ene metathesis reaction. An enol triflate elimination[173] from alkoxy ketone **373** would afford alkynyl ether **372**. The elimination precursor **373** would be prepared from D-glucal derived alcohol **348** (Scheme 105), which was synthesised as described previously (Section 2.1.4).



Scheme 105. Retrosynthesis for enyne-ene metathesis strategy

3.1.1. The Coupling Partners

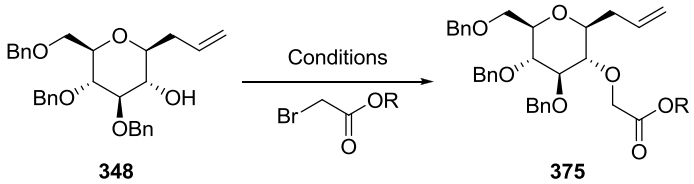
The first step in the synthesis involved the alkylation of alcohol **348** with a bromoacetic acid unit. Initially, the direct addition of the bromoacetic acid functionality was attempted (Table 9).[174] Unfortunately, this reaction proved to be unsuccessful under various conditions and only starting material **348** was recovered in all cases.



Entry	Conditions	Temperature (°C)	Time (h)	Results
1	NaH (3 eq.), THF	0 °C to rt	4	SM
2	NaH (3 eq.), THF	0 °C to reflux	4	SM
3	KH (3 eq.), THF	0 °C to rt	12	SM

Table 9. Alkylation of alcohol **348**

Alkylation to form the corresponding ester was then attempted; several conditions and alkylating substrates were examined (Table 10). Although sodium hydride was used as the base in most reactions, potassium hydride was also employed for the alkylation with ethyl bromoacetate under standard conditions and in the presence of *tetra*-butylammonium iodide (Table 10, entries 6 and 7). This alkylating agent was tested in different solvent media, THF and Et_2O (Table 10, entries 2 and 3), but the reaction did not proceed in either case. Alternative alkylating agents, methyl bromoacetate (Table 10, entry 8) and *tert*-butylbromoacetate (Table 10, entry 10), were employed in THF/DMF mixtures. Unfortunately, most of these conditions resulted in no reaction taking place and the recovery of the starting material. However, the use of phase transfer catalysis conditions (Table 10, entry 11) afforded **375** in 98% yield. This reaction was performed in toluene, in the presence of a saturated aqueous solution of NaOH and tetrabutylammonium hydrogen sulphate.



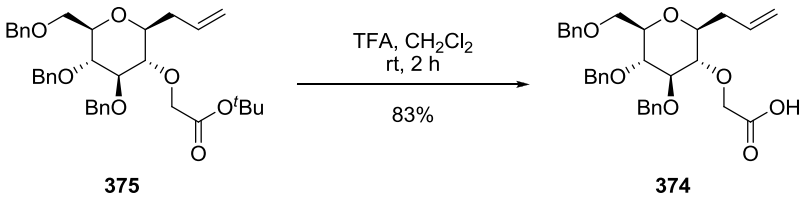
348 **375**

Entry	R	Conditions	Temp. (°C)	Time(h)	Product: Yield (%)
1	Et	NaH, THF	0 °C to rt	3	SM[a]
2	Et	NaH, THF	0 °C to reflux	24	SM[a]
3	Et	NaH, Et_2O	0 °C to reflux	12	SM[a]
4	Et	NaH, TBAI, THF	0 °C to rt	30	SM[a]
5	Et	NaH, TBAI, Et_2O	0 °C to reflux	12	SM[a]
6	Et	KH, Et_2O	0 °C to rt	12	SM[a]
7	Et	KH, TBAI, THF	0 °C to reflux	24	SM[a]
8	Me	NaH, THF/DMF	0 °C to rt	16	SM[a]
9	Me	NaH, TBAI, DMF	0 °C to rt	24	decomposition
10	*t*-Bu	NaH, THF/DMF	0 °C to rt	4	SM[a]
11	*t*-Bu	*n*-Bu_4NHSO_4 NaOH aq/ toluene (1:25)	0 °C to rt	3	**375** : 98%

[a]Starting material (SM) was fully recovered by silica gel chromatography.

Table 10. Alkylating conditions

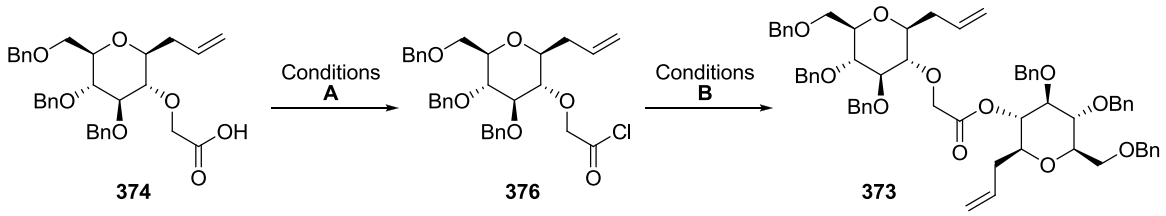
In order to obtain the second coupling partner, ester **375** was treated with TFA to reveal carboxylic acid **374** in 83% yield (Scheme 106).[175]



Scheme 106. Deprotection of carboxylic acid **374**

3.1.2. Esterification Reaction

With both alcohol **348** and carboxylic acid **374** in hand, studies into the esterification step could proceed. Initially, carboxylic acid **374** was to be converted into the corresponding acid chloride and then this would be exposed to compound **348** to afford coupled product **373**. Two different procedures were followed (Table 11). Firstly, carboxylic acid **374** was treated with thionyl chloride in the presence of pyridine, forming acid chloride **376**, which, without further purification, was exposed to alcohol **348** and pyridine (Table 11, entry 1).[176] Only starting material was recovered, indicating that initial formation of the acid chloride did not take place. The second set of conditions involved the reaction of compound **374** with oxalyl chloride in the presence of DMF to obtain acid chloride **376** (Table 11, entry 2). This reaction was followed by coupling with **348** under basic conditions, which resulted in the decomposition of the starting materials.

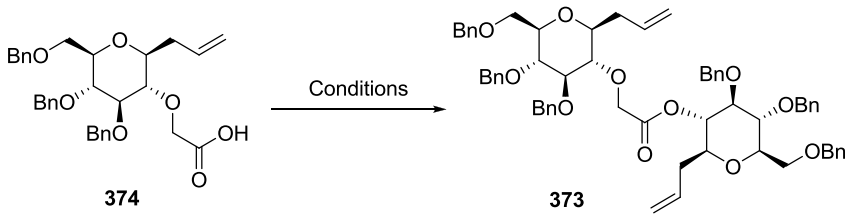


Entry	Conditions A	Conditions B	Results
1	$SOCl_2$, pyridine, CH_2Cl_2, rt, 2 h	**348**, pyridine, CH_2Cl_2, rt, 18 h	**374**[a]
2	$(COCl)_2$, DMF, CH_2Cl_2, rt, 2 h	**348**, Et_3N, CH_2Cl_2, rt, 18 h	Decomposition

[a]Carboxylic acid **374** was fully recovered by silica gel chromatography

Table 11. Acid chloride formation from **374** and coupling with **348**

Alternatively, carboxylic acid **374** underwent several esterification procedures for the direct coupling to alcohol **348**, to afford the ester **373**. The use of 1-chloro-methylpyridinium iodide (CMPI) and DMAP under basic conditions led to no reaction (Table 12, entry 1).[65] The same result was obtained in the presence of 1,1'-carbonyldiimidazole (CDI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile (Table 12, entry 2).[177] On the other hand, Steglich esterification conditions[178] afforded the desired product **373** in 88% yield (Table 12, entry 3). This reaction proceeded with DCC in dichloromethane, activated by the presence of a catalytic amount of DMAP.[179]

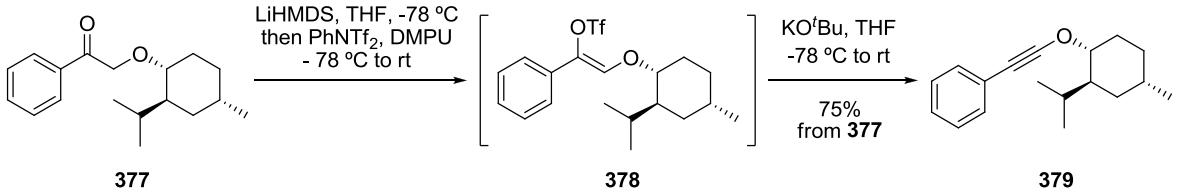


Entry	Conditions	Yield
1	**348**, CMPI, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 4 h	SM
2	**348**, CDI, DBU, MeCN, rt to 60 °C, 4 h	SM
3	**348**, DMAP, DCC, CH_2Cl_2, 0 °C to rt, 4 h	88 %

Table 12. Esterification of **374**

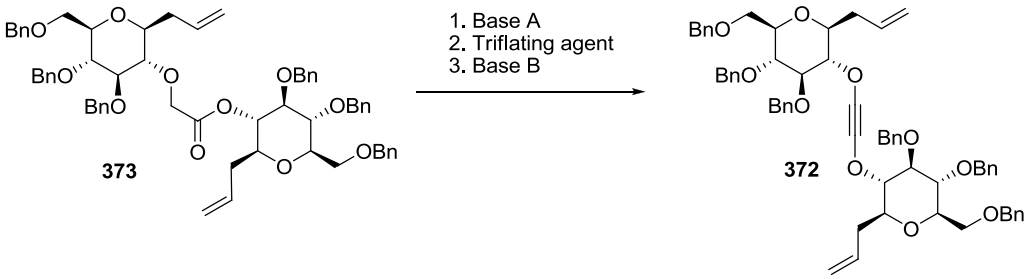
3.1.3. Formation of Alkynyl Diether 372

Transformation of alkoxyketone **373** into alkynyl ether **372** required a two-step procedure involving formation of the enol triflate or phosphate and base-induced elimination (Table 3). This idea followed the work of Minehan and co-workers who showed the transformation of α-alkoxyketone **377** into 1-alkynyl ether **379** through a triflate formation and elimination protocol (Scheme 107).[173]



Scheme 107. Alkynyl ether synthesis through triflate formation and base-induced elimination

Initially, the reaction was carried out following published conditions by treatment of alkoxyketone **373** with LiHMDS at low temperature and trapping of the enolate with $PhNTf_2$ in DMPU/THF (1:2) (Table 13, entry 1). The crude enol triflate was then treated with potassium *tert*-butoxide with the aim of promoting elimination to form alkynyl ether **372**, though only the starting material **373** was recovered. Substitution of LiHMDS with NaHMDS or LDA (Table 13, entries 2 and 3) had no effect on the outcome and again only alkoxyketone **373** was recovered from both reactions. An alternative procedure was then followed where compound **373** was exposed to KH in THF and then quenched with triflic anhydride in order to form the intermediate enol triflate.[180] Poor solubility of the starting material **373** in Et_2O meant the solvent had to be changed to THF. Unfortunately, upon quenching with Tf_2O (two equivalents) at −78 °C, the reaction mixture became a thick and viscous semi-solid, suggesting that polymerisation had occurred (Table 13, entry 4).[181]



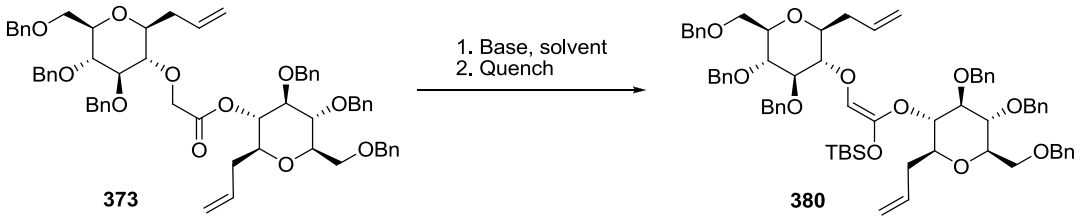
Entry	Base A	Triflating Agent	Base B	Result
1	LiHMDS, THF −78 °C to rt, 1 h	$PhNTf_2$, THF/DMPU −78 °C to rt	KO*t*-Bu, THF −78 °C	SM[a]
2	NaHMDS, THF, −78 °C to rt, 1 h	$PhNTf_2$, THF/DMPU −78 °C to rt	KO*t*-Bu, THF −78 °C	SM[a]
3	LDA, THF, −78 °C to rt, 1 h	$PhNTf_2$, THF/DMPU −78 °C to rt	KO*t*-Bu, THF −78 °C	SM[a]
4	KH, THF 0 °C to rt, 1 h	Tf_2O, −78 °C to rt	-	polymerisation

[a]Starting material (SM) was fully recovered by silica gel chromatography.

Table 13. Direct formation of alkynyl ether **372**

In an attempt to identify the reason for the failure of these procedures, several test reactions were carried out. Problems could arise from each of the three stages of reaction. Firstly, the initial deprotonation of alkoxyketone **373** to form the enolate; secondly, the triflating agent quenching the enolate; and thirdly, the final elimination of the triflic acid leading to product **372**.

In order to find a suitable base for the initial deprotonation of **373**, a variety of bases were explored and *tert*-butyldimethylsilyl chloride (TBSCl) was used as to trap the enolate, since its incorporation would increase the stability of the product and would be detectable by ^{1}H NMR (Table 14). Potassium hydride proved to be unsuitable as a base, no reaction took place and the starting material was recovered (Table 14, entry 1). Even in the presence of 18-crown-6, only 5% of an inseparable mixture of the expected product and impurities was recovered (Table 14, entry 2). In previous reactions, the formation of the enol triflate intermediate with triflic anhydride in THF proved problematic (Table 14, entry 4) and in order avoid this, CH_2Cl_2 was chosen as an alternative solvent (Table 14, entry 3). The preparation of LDA from di-iso-propylamine and *n*-BuLi took place in THF, this was then added to a solution of alkoxyketone **373** in CH_2Cl_2 at −78 °C and the mixture was then allowed to warm to room temperature. This mixture was then quenched with TBSCl in CH_2Cl_2 at 0 °C, resulting in full conversion of the starting material. The instability of product **380** on silica gel led to partial decomposition during purification and a disappointing 45% yield of silyl enolate **380** was obtained. Unfortunately, this reaction was also not reproducible and all future attempts to perform this transformation failed.



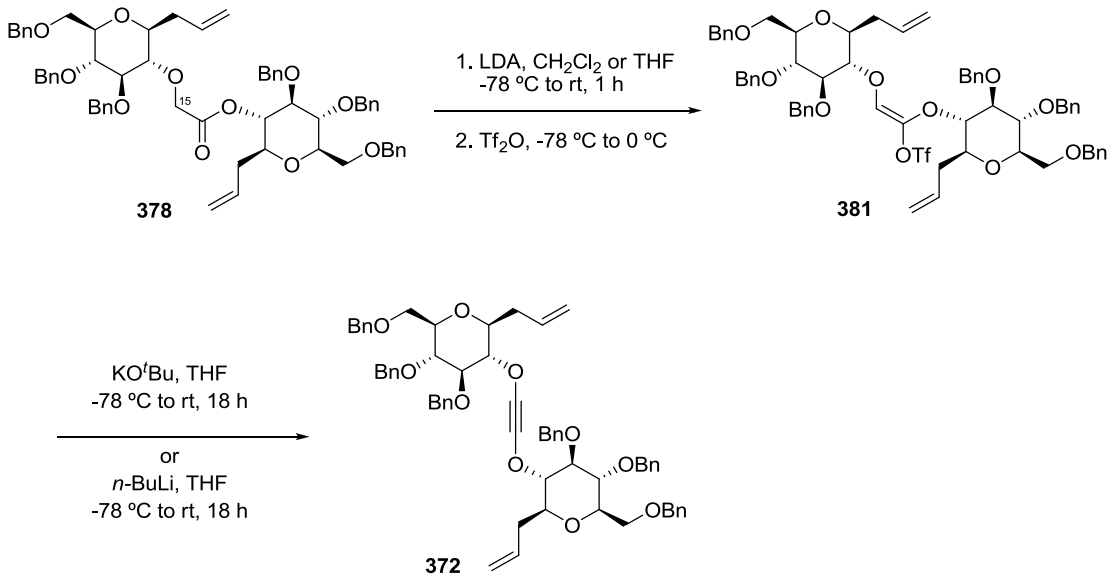
373 **380**

Entry	Base	Solvent	Quench	Yield (%)
1	KH, 0 °C to rt, 1 h	THF	TBSCl in THF, 0 °C to rt, 1 h	SM
2	KH, 18-crown-6, 0 °C to rt, 1 h	THF	TBSCl in THF, 0 °C to rt, 1 h	5% + SM
3	LDA in THF, −78 °C to rt, 1 h	CH_2Cl_2	TBSCl in CH_2Cl_2, 0 °C to rt, 1 h	variable

Table 14. Base tests for enolate formation

Despite the need for further optimisation, the conditions presented above (Table 14, entry 3) were applied to the formation of enol triflate **381** (Scheme 108). Due to possible incompatibility between LDA and CH_2Cl_2, the formation of enol triflate **381** was also attempted in THF, but this time, with very slow dropwise addition of Tf_2O and a reduced number of equivalents (1.1 equivalents). ^{1}H NMR analysis of the crude product **381**, showed the disappearance of the key alkoxyketone protons at 4.24 ppm (2H, d, *J* =

3.6 Hz, CH_2-C15), indicating that the deprotonation and formation of enol triflate **381** had been successful. The presumed enol triflate **381** proved to be highly unstable to light, air and temperature, and was therefore used in the following step without further purification. Base-induced elimination of the triflate was performed under two different sets of reaction conditions. Initially, potassium *tert*-butoxide was chosen as the base, but when this reaction failed, *n*-BuLi was employed instead. Unfortunately, those conditions led to an inseparable mixture of compounds, further showing the instability of triflate **381** and potentially, the product **372** as well.



Scheme 108. Enol triflate formation and elimination

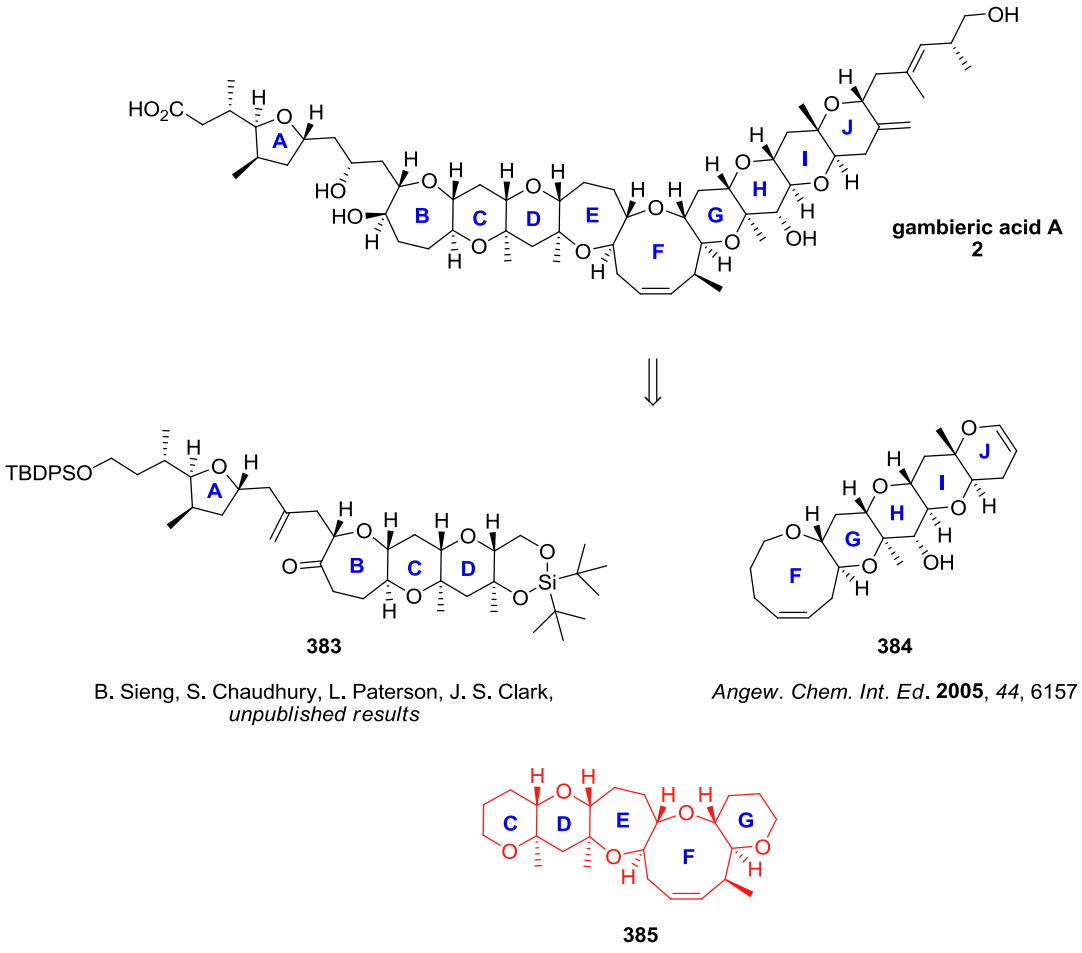
3.2. Summary

This section has demonstrated the efficient formation of carboxylic acid **374** and its successful esterification with alcohol **348** to obtain compound **373** in excellent yield. Nevertheless, numerous difficulties were encountered in the formation of the enol triflate functionality **381**, mainly due to the deactivated nature of the alkoxyketone protons on C-15 (compound **373**), as well as the steric hinderance surrounding them. Further optimisation of this step will be required to allow an in depth study of the subsequent elimination reaction to give alkynyl ether species **372** to take place. However, there are serious concerns over the stability of alkyl diether **372** and its ability to undergo further reactions or even purification.

Chapter 3
The C-G Fragment of Gambieric Acid A

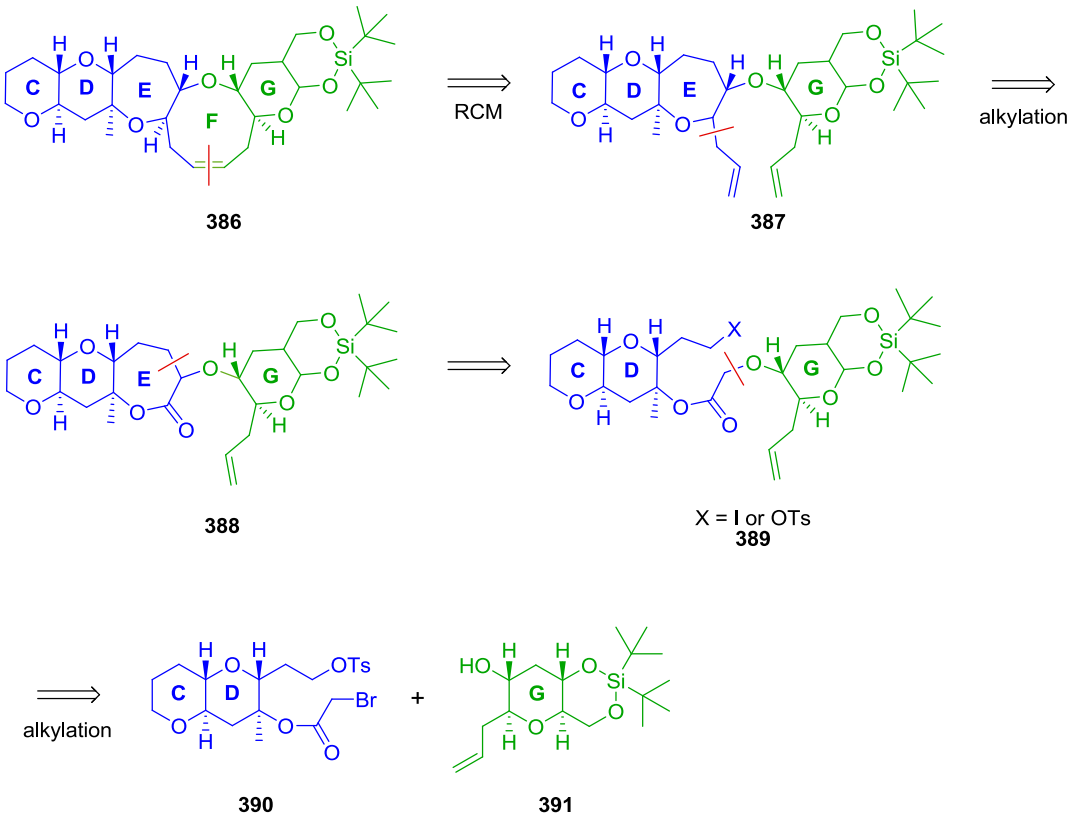
1. Introduction

Previous work in the group has focused on the synthesis of fragments A-D **383** and F-J **384** of gambieric acid A **2** (Section 1).[84] Studies in this second project are directed towards the development of methodology for the coupling of these two major fragments, where the key steps are the formation of rings E and F (Scheme 109). For this, a model for the pentacyclic C-G fragment **385** must be constructed.



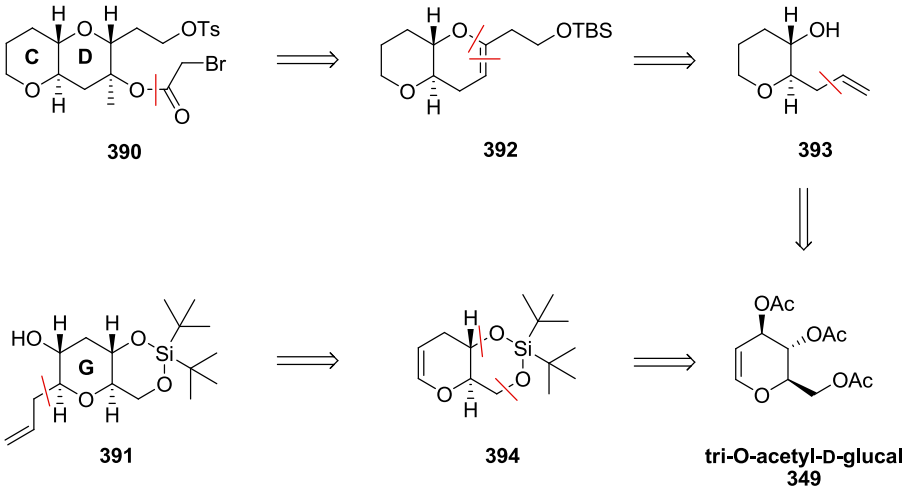
Scheme 109. Project outline

The C-G ring fragment can be represented by the model target **386** (Scheme 110). Scission of the F-ring leads to compound **387** and removal of the side chain by retrosynthetic alkylation reveals the key E-ring formation step. A second ring scission reveals coupled product **389**, which could in turn be obtained by another alkylation from C-D ring fragment **390** and G-ring fragment **391**.



Scheme 110. Retrosynthesis of C-G ring fragment

From C-D ring fragment **390**, removal of the ester substituent followed by functional group interconversion (FGI) leads to bicyclic compound **392** (Scheme 111). Cleavage of the D-ring in **392** then reveals tetrahydropyran **393** and removal of the allyl group along with FGI leads to commercially available tri-*O*-acetyl-D-glucal **349**. From G-ring fragment **391**, removal of the allylic side chain and simplification of the oxygen substituents leads to compound **394** and eventually to tri-*O*-acetyl-D-glucal **349**, the same compound envisaged as a starting material for the synthesis of the C-D ring fragment.

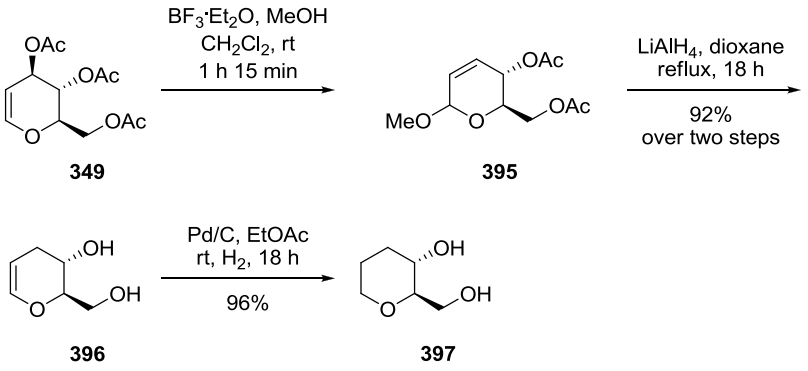


Scheme 111. Retrosynthesis of C-D ring fragment and G-ring fragment

2. Results and Discussion

2.1. The C-D Ring Fragment

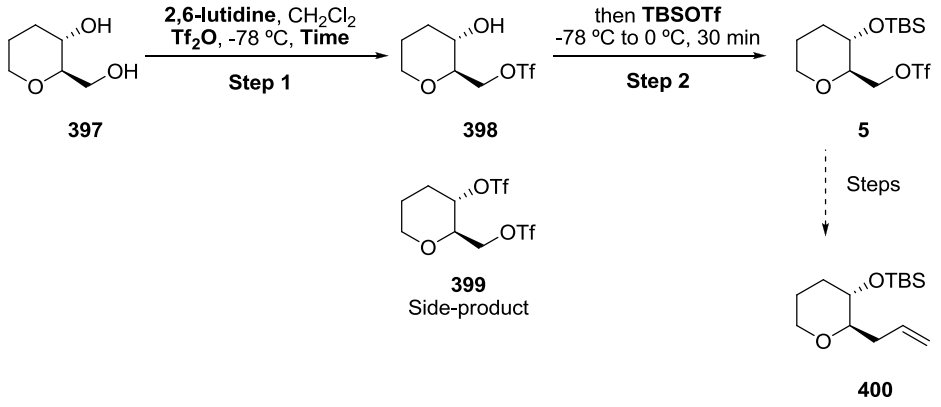
In the forward synthesis, commercially available tri-*O*-acetyl-D-glucal **349** was employed as the starting material, which would eventually represent ring C in fragment **390** (Scheme 112). Tri-*O*-acetyl-D-glucal **349** underwent a Ferrier[182,183] rearrangement by treatment with boron trifluoride diethyl etherate in the presence of methanol to afford the mixed acetal **395**, which was reacted with lithium aluminium hydride in order to reduce the allylic methoxy group and simultaneously remove the two remaining acetate groups, delivering diol **396** in excellent yield. Hydrogenation of the double bond in **396** led to diol **397**, again in excellent yield.



Scheme 112. Synthesis of diol **397**

2.1.1. Triflate as a leaving group

The next task was to find a suitable leaving group to allow the installation of the required side chain in **400**, for the closure of the D-ring. The triflate group was the initial choice. Several conditions were employed in an attempt to install the triflate selectively on the primary alcohol in diol **397** and effect a subsequent silyl protection of the secondary alcohol (Table 15). Initially, conditions described by Mori *et al.* were used involving the addition of triflic anhydride (1.03 equivalents) to a solution of diol **397** and 2,6-lutidine (3 equivalents) at −78 °C and stirring for 30 minutes, before addition of TBSOTf (1.1 equivalents) (Table 15, entry 1).[12] Unfortunately, this resulted in decomposition and the formation of the ditriflate side product **399**. An increase in the amount of base saw a slight stabilisation of product **5**, which was obtained in only 7% yield, but an unacceptable amount of side product was still obtained (Table 15, entry 2). To avoid this, the amount of triflic anhydride was reduced, as well as the reaction time (Table 15, entry 3), which afforded compound **5** in 14% yield and most importantly, no side product **399** was recovered. Despite these improvements, yields were still too low to be useful and so, the number of equivalents of TBSOTf were raised in an attempt to increase the overall yield (Table 15, entry 4). Unfortunately, only 26% of the desired triflate **5** was obtained in this case.



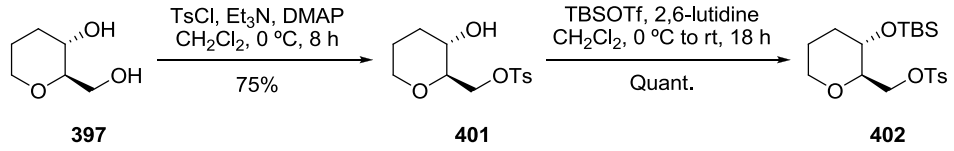
Entry	Step 1			Step 2	Yield (%)	
	2,6-Lutidine (eq.)	Tf_2O (eq.)	Time (min.)	TBSOTf (eq.)	5	399
1	3	1.03	30	1.1	-	20
2	5	1	30	1.1	7	29
3	5	0.9	15	1.1	14	-
4	5	0.9	15	3	26	-

Table 15. Triflate as a leaving group

Due to the numerous problems encountered during the synthesis and manipulation of triflate products **398** and **5**, an alternative leaving group was explored.

2.1.2. Tosyl as a leaving group

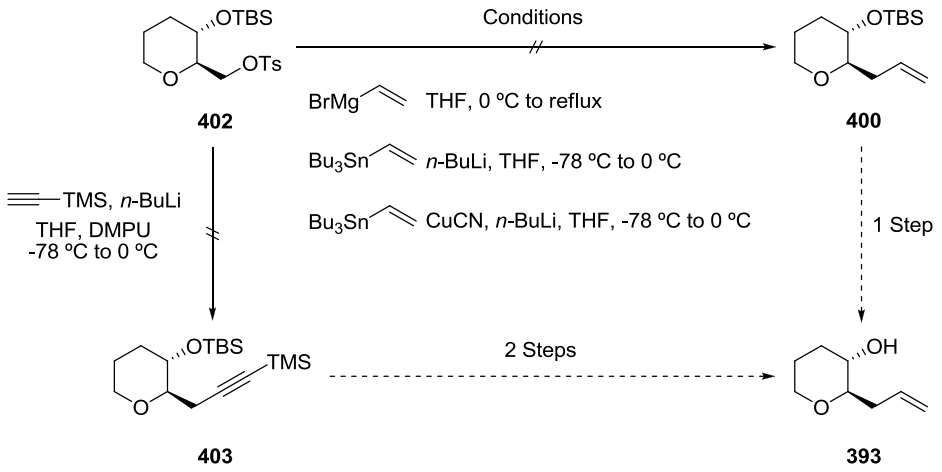
The tosyl functionality was envisioned as a possible alternative leaving group (Scheme 113). The selective tosylation of the primary alcohol in diol **397** was carried out with tosyl chloride in the presence of base and catalytic amounts of DMAP.[184] Pleasingly, the reaction was successful and the resulting tosylated product **401** proved to be relatively stable. Subsequent silyl protection afforded product **402** in quantitative yield.



397 **401** **402**

Scheme 113. Synthesis of tosyl protected alcohol **402**

With tosylate **402** in hand, displacement of the tosyl group was attempted with numerous nucleophiles (Scheme 114). Initially, Grignard, stannane, lithium-stannane and higher-order cuprate reagents were investigated for the direct displacement of the tosyl group to obtain allylic product **400**. However, these reactions all led to full recovery of the starting material. As an alternative, lithium TMS acetylene was also employed as a nucleophile. This would lead to TMS protected acetylene **403** and a further two steps, involving deprotection and hydrogenation, would be required to obtain the desired allylic product **393.** Despite the successful formation of the lithiated side chain in the presence of *n*-BuLi, only the tosylated starting material **402** was recovered from this reaction.

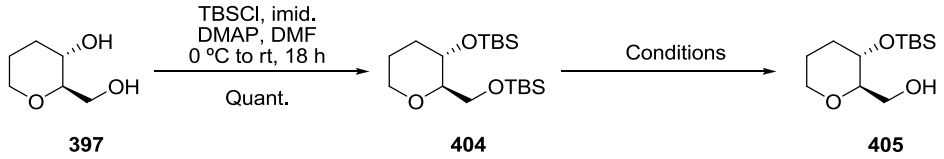


Scheme 114. Side chain addition

The tosyl functionality proved to be an unsuitable leaving group and therefore an alternative route to install the triflate functionality was developed. However, this synthetic route required additional steps.

2.1.3. Alternative Route to triflate 5

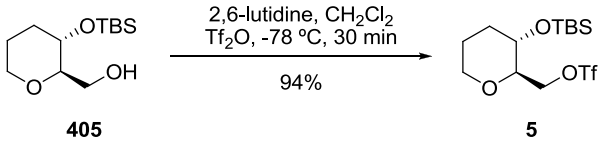
The previously explored route, namely the selective triflation of the primary hydroxyl group prior to the silyl protection of the secondary hydroxyl group, had proven difficult. For this reason, an alternative route was devised where the primary alcohol **405** was prepared from **397** by a two-step procedure involving di-silylation followed by selective monodesilylation, installing the TBS group on the secondary hydroxyl group prior to triflate formation (Table 16). The initial di-silylation of diol **397** with TBSCl in DMF afforded **404** in quantitative yield. Several procedures were attempted for the monodesilylation of **404**. Firstly, deprotection using TBAF led to the recovery of the starting material **397** (Table 16, entry 1). A notable improvement was achieved using acidic conditions described by Nicolaou *et al.* and this reaction afforded mono-silylated product **405** in 53% yield (Table 16, entry 2).[45] However, monodesilylation in the presence of catalytic amounts of camphorsulfonic acid, in a CH_2Cl_2:MeOH mixture proved to be the highest yielding reaction and this afforded the mono-protected alcohol **405** in quantitative yield (Table 16, entry 3).[185]



Entry	Conditions	Yield
1	TBAF (1 M in THF), THF, −78 °C to 0 °C	SM
2	TFA:H_2O:THF (1:1:1), 0 °C	53%
3	CSA, CH_2Cl_2:MeOH (1:1), 0 °C	Quant.

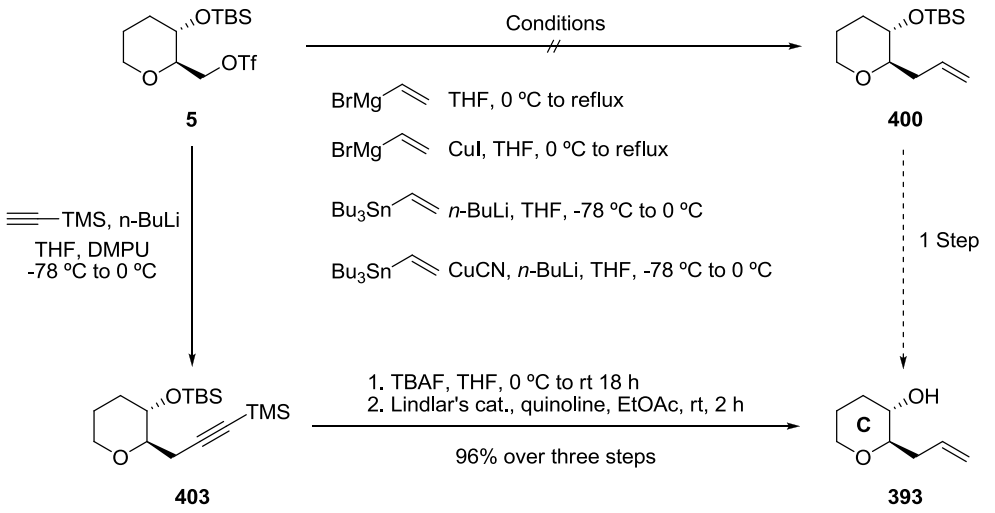
Table 16. Di-silylation and selective monodesilylation of **397**

The activation of the remaining hydroxyl group in **405** was then easily achieved using triflic anhydride under basic conditions to afford triflate **5** in excellent yield (Scheme 115). The instability of compound **5** prevented full characterisation, although the data obtained did agree with that published data for this compound.[12]



Scheme 115. Hydroxyl group activation

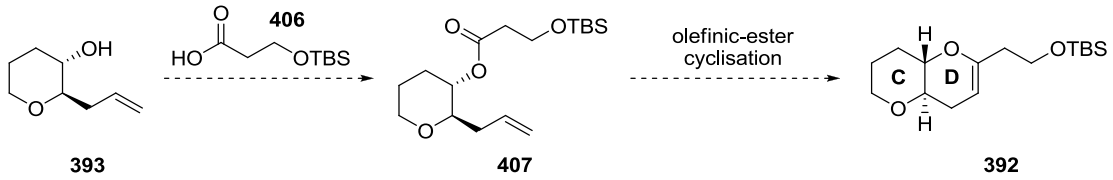
With triflate **5** in hand, focus turned to the displacement step leading to the formation of allylic product **400** (Scheme 116). Again, several Grignard, stannane, lithium-stannane and higher-order cuprate reagents were used for the direct displacement of the triflate functionality to obtain allylic product **400**. However, these reactions all led to complete decomposition of the starting material. Alternatively, reaction of triflate **5** with lithiated TMS acetylene in a THF:DMPU mixture afforded the desired, but highly unstable, product **403**. TBAF deprotection resulted in removal of both silyl groups on compound **403**, which allowed subsequent partial hydrogenation of the terminal alkyne to be performed in the presence of Lindlar catalyst. With careful ^{1}H NMR monitoring of the hydrogenation reaction, the resulting alkene **393** was obtained in excellent yield over three steps.



Scheme 116. Side chain addition

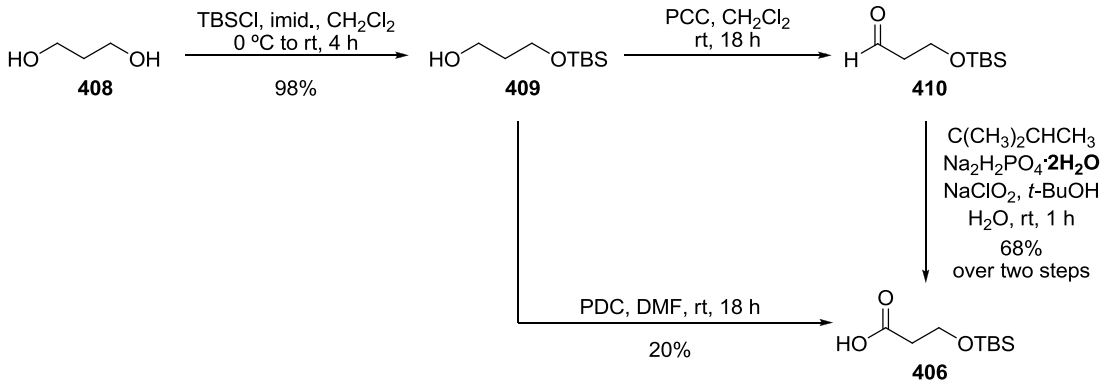
2.1.4. Side-chain formation

The C-ring was now complete and as envisioned, the formation of the D-ring required an initial coupling of **393** with acid **406** followed by an olefinic-ester cyclisation[72] (Scheme 117), therefore the immediate priority was the synthesis of side chain **406**.



Scheme 117. C-D ring fragment synthetic outline

The synthesis of subunit **406** began with propane-1,3-diol **408**, which was monoprotected to give its mono-TBS ether **409** in near quantitative yield (Scheme 118). Oxidation in the presence of PCC in CH_2Cl_2 afforded unstable aldehyde **410**, which underwent Pinnick oxidation with $NaClO_2$ and NaH_2PO_4 to provide acid **406** in acceptable yields.[186] Direct oxidation from alcohol **409** to carboxylic acid **406** was attempted with PDC in DMF; however, after overnight stirring, only 20% yield of the desired compound was obtained.[187] Consequently, the two-step oxidation was selected as the method of choice for the synthesis of side chain **406**.



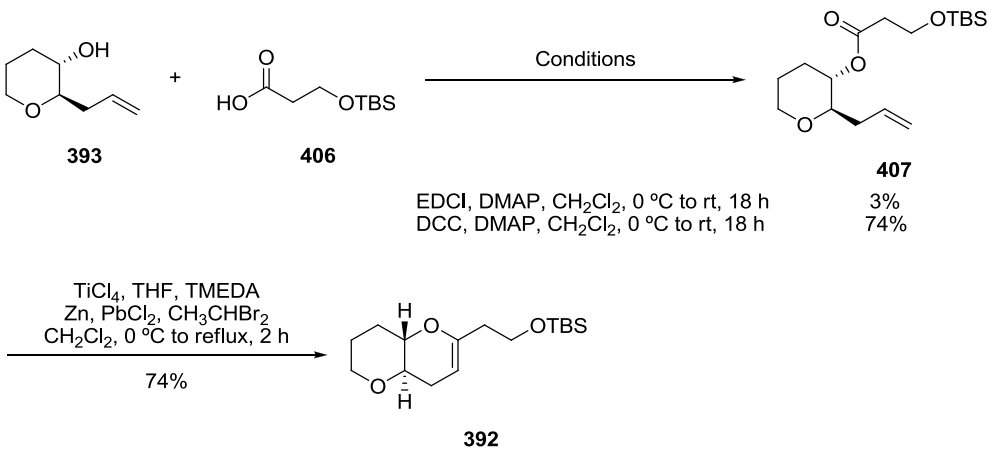
Scheme 118. Synthesis of side chain **406**

2.1.5. Side Chain Coupling and Olefinic-Ester Cyclisation

Following the preparation of alcohol **393** and side chain **406**, the esterification step could take place (Scheme 119). Two different carboxylic acid activating agents were used. Reaction with EDCI afforded the desired esterified product **407** in a very poor 3% yield. When this was replaced by DCC, the yield notably improved to 74%. It is worth noting that an excess amount of DMAP was required to drive these reactions to completion.

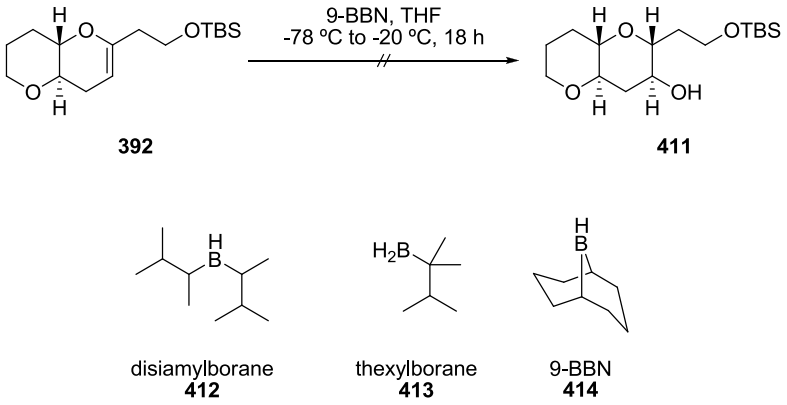
The generation of cyclic enol ethers from the corresponding olefinic esters using the Takai–Utimoto titanium alkylidene was developed by Rainier and co-workers[188] and this methodology has since been employed in several complex polycyclic ether natural product syntheses.[74,75] It is important to note that the product distribution (uncyclised vs cyclised enol ether) observed from the reaction of the reduced titanium alkylidene reagent is dependent upon the alkylidene reagent used. The titanium methylidene reagent that comes from the use of dibromomethane as the alkylidene source gives only uncyclised enol ethers, while the corresponding ethylidene reagent from dibromoethane delivers cyclised enol ethers.

As a result of these observations, 1,1-dibromoethane, in conjunction with titanium tetrachloride, was used in the formation of the corresponding ethylene reagent for the olefinic-ester reaction of **407**, affording only the cyclic product **392** in 74% yield (Scheme 119).



Scheme 119. Side chain coupling and olefinic-ester cyclisation

Concerning the subsequent hydroboration step, it was thought that little diastereocontrol would be obtained using borane itself. However, this difficulty could be overcome by hydroboration with substituted boranes such as disiamylborane **412**, thexylborane **413** or 9-BBN **414** (Scheme 120). The first choice was 9-BBN, since it contains the highest steric bulk and therefore was expected to offer the highest regioselectivity. Regrettably, the subsequent hydroboration with 9-BBN for the formation of the bicyclic C-D ring fragment **411** failed and the remaining starting material decomposed during work-up.



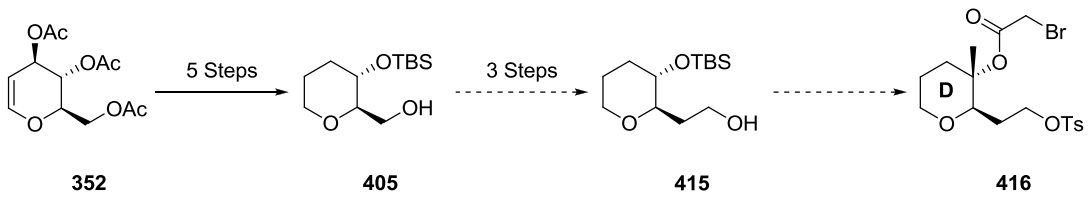
Scheme 120. Hydroboration of **392**

The lack of reaction suggested that 9-BBN was indeed too bulky for this hydroboration and therefore a less sterically hindered reagent was required. As previously mentioned, thexylborane **413** and disiamylborane **412** would be expected to display a higher reactivity than 9-BBN, whilst maintaining a higher selectivity than borane.

Despite these encouraging results and future work ideas, time constraints prevented further work on this aspect of the project.

2.2. The D-Ring Fragment

The main focus of this project was development of methodology for the synthesis of the E-ring of gambieric acids. Therefore, whilst work on the C-D ring fragment was carried out, a route towards a smaller D-ring fragment **416** was pursued (Scheme 121). Commercially available tri-*O*-acetyl-D-glucal **352** was converted into alcohol **405** over five steps, as previously described, and this ring would represent the D-ring in the target fragment **416**. One crucial point in this synthetic route was the three-step homologation sequence, involving an initial oxidation reaction, followed by Wittig olefination and final hydrolysis to elongate the carbon side chain in compound **405** to that of alcohol **415**.

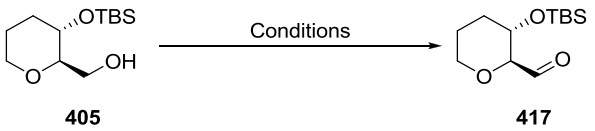


352 **405** **415** **416**

Scheme 121. Synthetic outline for D-ring fragment

2.2.1. Three-Step Homologation

As previously stated, the three-step homologation protocol envisioned consisted of oxidation, followed by a Wittig reaction and hydrolysis. The first step involved the oxidation of alcohol **405** to aldehyde **417** and several conditions were tested for this transformation (Table 17). Oxidation with Dess-Martin periodinane did not proceed and only starting material **405** was recovered (Table 17, entry 1). Results were slightly improved by reaction of alcohol **405** under Swern conditions, affording aldehyde **417** in 40% yield (Table 17, entry 2). However, reaction with SO_3.py following the Parikh-Doering method led to 84% yield of the desired aldehyde **417** (Table 17, entry 3).[184]

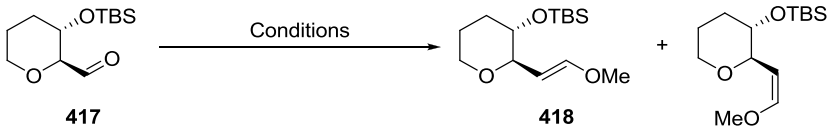


405 417

Entry	Conditions	Yield
1	DMP, CH_2Cl_2, NaHCO3, 0 °C	SM
2	$(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C	40%
3	SO_3.py, Et_3N, DMSO, CH_2Cl_2, 0 °C	84%

Table 17. Oxidation of alcohol **405**

Aldehyde **417** then underwent a Wittig olefination with (methoxymethyl) triphenyl-phosphonium chloride, leading to enol ethers **418** and **419** as a 1:1 mixture (Table 18). Two bases were tested in this reaction: potassium-*tert*-butoxide afforded 34% yield of the desired enol ether (Table 18, entry 1), and NaHMDS delivered an improved yield of 50% (Table 18, entry 2).

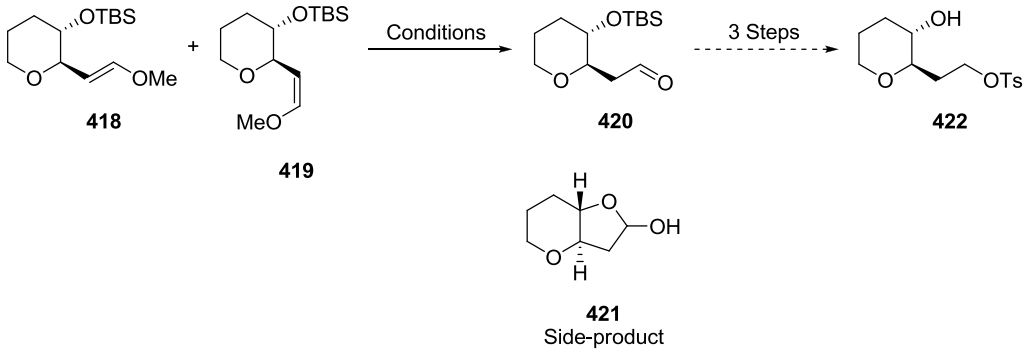


417 418 419

Entry	Conditions	Yield
1	*t*-BuOK, $PPh_3ClCH_2OCH_3$, THF, 0 °C to rt, 18 h	34% (1:1)
2	NaHMDS, $PPh_3ClCH_2OCH_3$, THF, 0 °C to rt, 2 h	50% (1:1)

Table 18. Witting olefination with (methoxymethyl)triphenylphosphonium chloride

Several procedures were followed for the hydrolysis of **418** and **419** leading to aldehyde **420**. Reaction with 2 M HCl afforded a complex mixture of products, in which traces of side-product **421** could be identified, but the data was inconclusive (Table 19, entry 1). Milder conditions delivered worse results, where total decomposition of the starting material was observed (Table 19, entries 2 and 3).[189] Compound **420** and side product **421** would have ultimately been transformed into D-ring fragment **422**. Undoubtedly, an alternative homologation protocol was required.

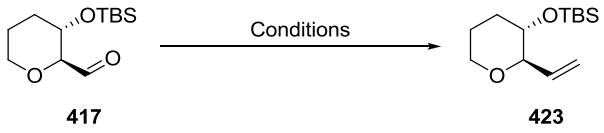


Entry	Conditions	Results
1	2 M HCl, THF, rt, 18 h	Traces of side-product **421**
2	PPTS, dioxane, H_2O, reflux, 1 h	Decomposition
3	PPTS, CH_2Cl_2, rt, 6 h	Decomposition

Table 19. Hydrolysis of **418** and **419**

2.2.2. Alternative Three-Step Homologation and Final Steps

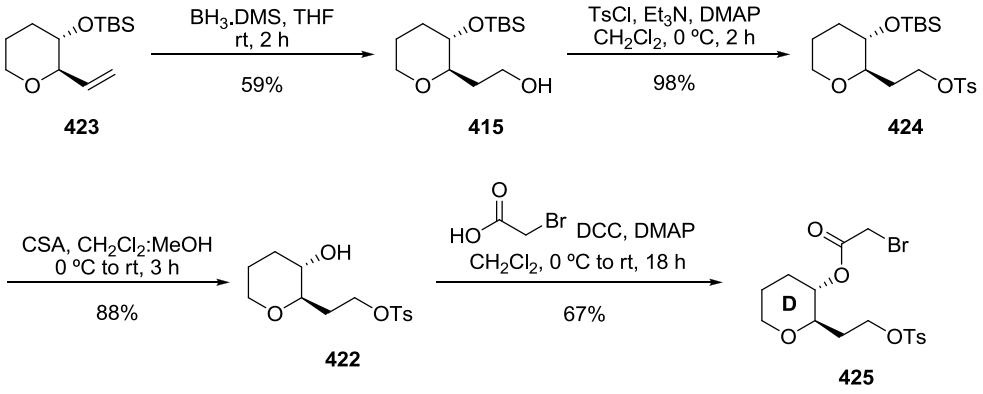
The second homologation approach involved an oxidation of alcohol **405** to form aldehyde **417**, followed by Wittig olefination and a subsequent hydroboration. The oxidation step proceeded as described previously (Section 2.2.1.). Aldehyde **417** underwent a standard olefination reaction with methyltriphenylphosphonium bromide, employing various bases for ylide generation (Table 20). Although NaHMDS proved to be the most suitable base, affording enol ether **423** in 91% yield (Table 20, entry 1), *n*-butyllithium[184] and potassium *tert*-butoxide were also tested with notably poorer results (Table 20, entries 2 and 3).



Entry	Conditions	Yield
1	PPh_3CH_3Br, NaHMDS, THF, 0 °C to rt, 1 h	91%
2	PPh_3CH_3Br, *n*-BuLi, THF, 0 °C to rt, 18 h	22%
3	PPh_3CH_3Br, *t*-BuOK, THF, 0 °C to rt, 18 h	11%

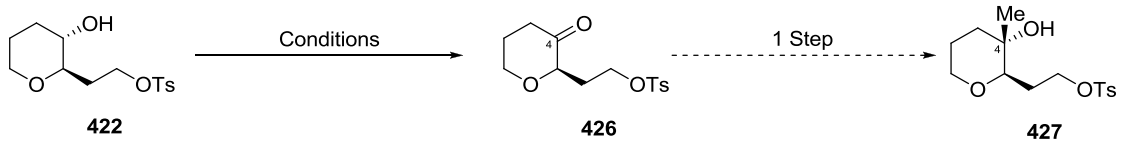
Table 20. Witting olefination

The last step in the homologation process involved hydroboration of alkene **423** in the presence of borane, affording alcohol **415** in moderate yield (Scheme 122). Tosylation of the primary alcohol in **415**, followed by deprotection of the secondary alcohol in **424** led to compound **422** in excellent yield over two steps. The fragment core was then ready for the coupling to the side chain, employing esterification conditions previously optimised (Chapter 2, Section 3.1.2.). This involved treatment of **422** with bromoacetic acid in the presence of DCC and DMAP, resulting in the D-ring fragment **425**.



Scheme 122. Synthesis of the D-ring fragment: the final steps

Although the synthesis of the D-ring fragment core was complete, further work was carried out on the addition of the angular methyl at C4, matching the functionality to the natural product. A two-step protocol was devised involving an oxidation, followed by stereoselective methylation leading to alcohol **427** (Table 21). Several conditions were employed, commencing with an unsuccessful Dess-Martin periodinane oxidation which led to the recovery of starting material **422** (Table 21, entry 1). Chromium-based reagents proved more suitable. Reaction with PCC afforded 36% yield of the desired ketone **426** (Table 21, entry 2) and employing PDC increased the yield to 51% (Table 21, entry 3). Celite® was added to these experiments to facilitate stirring. During these later reactions, full conversion of starting material **422** to the product **426** was observed by TLC analysis, however, the resulting ketone proved to be very unstable and this might account for the loss of product. Unfortunately, ketone **426** underwent decomposition before the methylation step could be explored.



422 **426** **427**

Entry	Conditions	Yield
1	DMP, $NaHCO_3$, CH_2Cl_2, rt, 18 h	SM
2	PCC, CH_2Cl_2, Celite®, rt, 18 h	36%
3	PDC, CH_2Cl_2, Celite®, rt, 18 h	51%

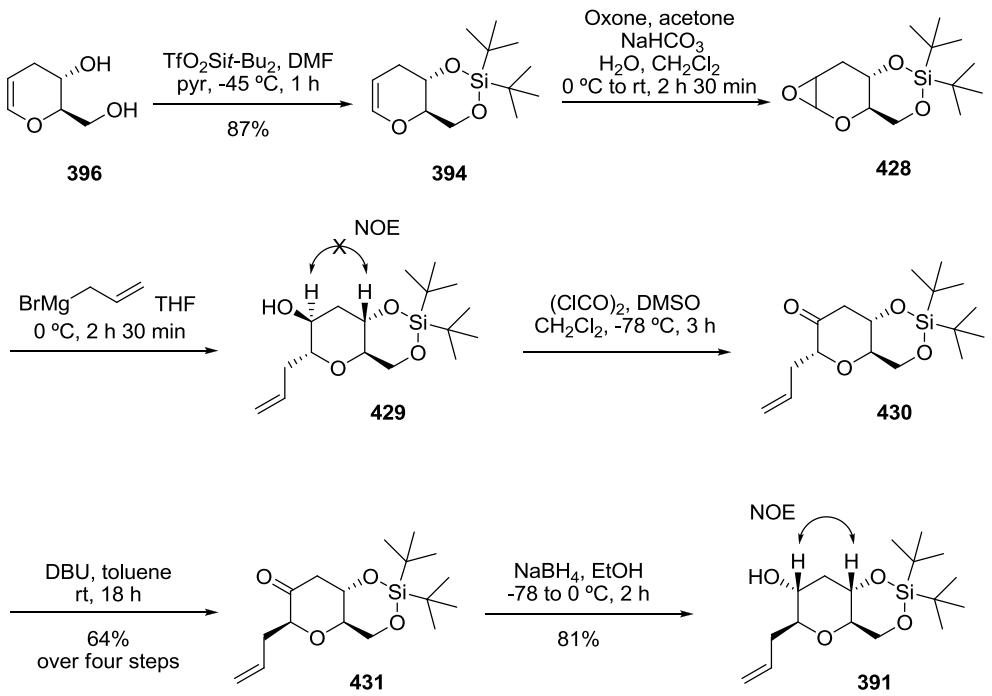
Table 21. Oxidation and methylation steps

Despite the problems encountered with the unstable ketone **426**, the oxidation results were very encouraging and would allow future research to continue. Nevertheless, the successful synthesis of the D-ring fragment core **425** meant that the building of the G-ring fragment was imperative, in order to allow the coupling and E-ring formation steps to be explored.

2.3. The G-Ring Fragment

The G-ring fragment was prepared from the same starting material as the C-D ring fragment. The route followed was presidented within the group up to alcohol **391**, although several steps underwent optimisation. Commercially available tri-*O*-acetyl-D-glucal **352** was employed and would eventually represent ring G in fragment **391** (Scheme 123). Diol **396** (Scheme 112, Section 2.1) was protected with di-*tert*-butylsilyl-bistriflate in DMF; maintaining the temperature below −45 °C proved vital in ensuring a high yield. Original epoxidation methods involved the distillation of DMDO, however epoxidation of enol ether **394** using *in situ* generated DMDO[166] delivered a 1:1 mixture of diastereomeric epoxides **428** with increased yield. Subsequent addition of allylmagnesium bromide afforded a complex mixture of products, of which alcohol **429**, bearing the undesired stereochemistry, was unfortunately the major component. The stereochemistry was verified by NOE correlation between CH-C5 at 1.75 ppm and CH_2-C9 at 2.55 and 2.31 ppm suggesting a synclical relationship (No correlation was observed between CH-C2 and CH-C4). In order to correct the stereochemistry, an efficient three-step procedure was undertaken. The mixture of alcohols was oxidised under Swern conditions and the resulting ketone **430** underwent epimerisation with DBU to afford

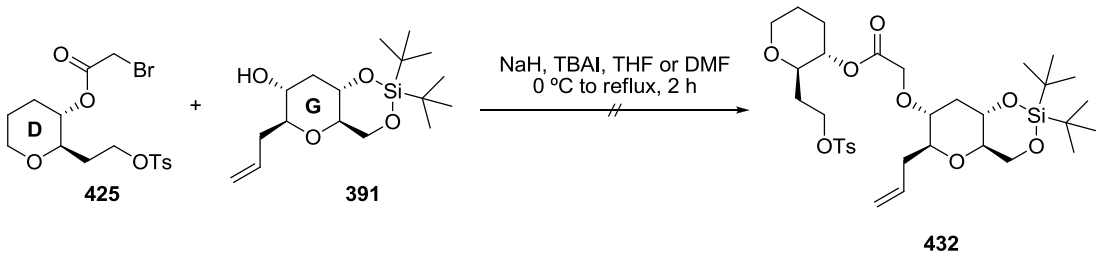
ketone **431**, possessing the desired stereochemistry, in 64% yield over the four steps. A final reduction with sodium borohydride led to the desired alcohol **391**. The stereochemistry of **391** was verified by NOE correlation between CH-C1 at 3.18 ppm and CH-C5 at 3.27 ppm and CH_2-C3ax at 1.49 ppm suggesting a synclical relationship; and careful examination of the ^{1}H-NMR coupling constants revealed a J_3 coupling constant of J = 9.7 between CH-C2 and CH-C1, suggesting a 1,3-*trans*-diaxial relationship.



Scheme 123. Synthesis of G-ring fragment

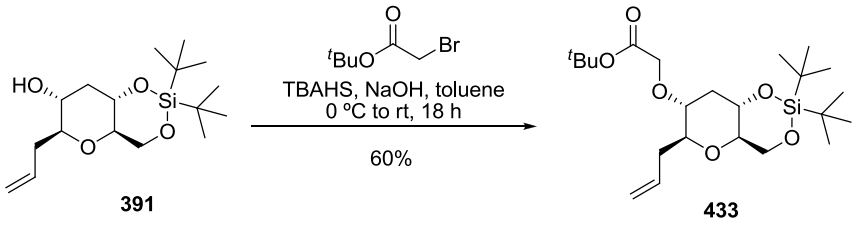
2.4. Coupling of D- and G-Ring Fragments

With D- and G-ring fragments in hand (compound **425** and **391** respectively), attention then turned to the coupling step (Scheme 124). Alcohol **391** underwent an initial deprotonation in the presence of NaH, followed by treatment with **425**, with the aim of promoting the displacement of the halide to afford coupled product **432**. Although it is believed that the deprotonation was successful, unfortunately the displacement reaction failed.



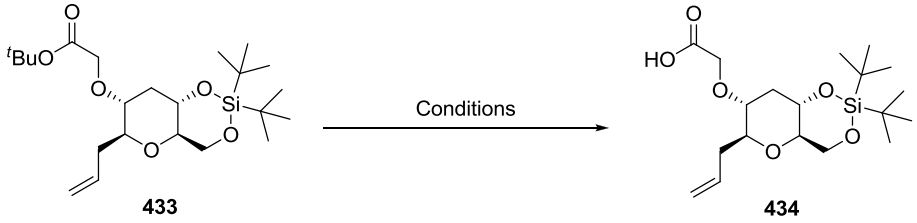
Scheme 123. Coupling step

In order to avoid this problematic step, an alternative coupling sequence was developed, where the linking side-chain *tert*-butyl bromoacetate was added to the G-ring fragment **433** prior to the coupling step (Scheme 124). Alcohol **391** was reacted with *tert*-butyl bromoacetate under phase transfer catalysis conditions, in the presence of a saturated aqueous solution of NaOH and tetrabutylammonium hydrogen sulphate in toluene. The desired product was obtained in 60% yield.



Scheme 124. Side chain addition to G-ring fragment

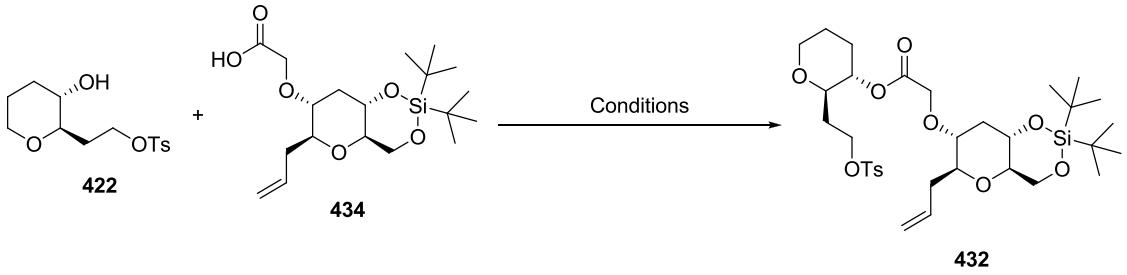
Previous work had shown that the best sequence for the addition of the carboxylic acid side chain onto fragment **433** was under phase transfer catalysis conditions followed by acid promoted removal of the *t*-butyl group. Initially, it was thought that acidic conditions would cleave the siloxy protecting group in compound **433** and therefore several basic and enzymatic procedures were explored, unfortunately, without success (Table 22, entries 1, 2 and 3).[190] Finally, TFA was employed and the *t*-butyl group was indeed removed without affecting the siloxy protecting group, therefore affording carboxylic acid **434** in excellent yield.



Entry	Conditions	Yield
1	NaOMe (1 M in MeOH), THF, rt, 3 h	Decomposition
2	LiOH, THF:H_2O (3:1), rt to reflux, 18 h	SM
3	Pig liver esterase, pH7 buffer, rt, 18h	SM
4	TFA, CH_2Cl_2, rt, 18 h	99%

Table 22. Removal of *t*-Bu group

An appropriate set of D- and G-ring fragments (alcohol **422** and carboxylic acid **434** respectively) had been synthesised successfully and so the focus returned to the coupling step (Table 23). Two carboxylic acid activating agents were attempted; in this case, reaction with EDCI (Table 23, entry 1) afforded slightly higher yields than DCC (Table 23, entry 2). It is worth noting that an excess amount of DMAP was required to drive both these reactions to completion.



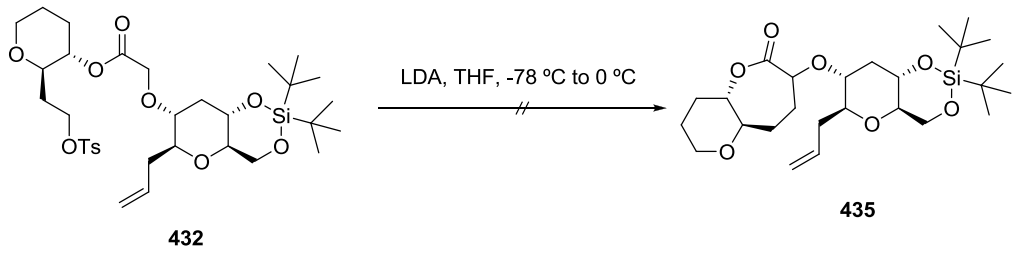
Entry	Conditions	Yield
1	EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 18 h	59%
2	DCC, DMAP, CH_2Cl_2, 0 °C to rt, 18 h	54%

Table 23. Coupling step

Despite the moderate yields obtained in the coupling step, work could now begin in the main task of this project, the formation of the E-ring.

2.5. E-ring Formation

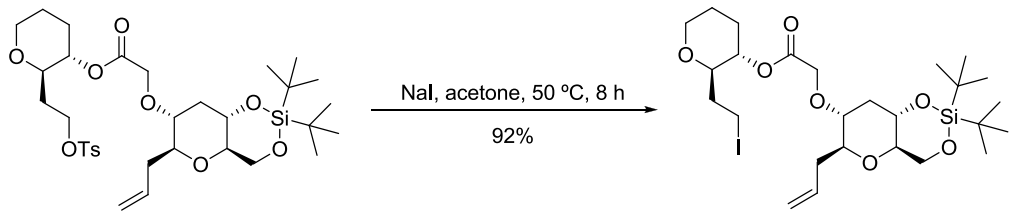
The formation of the E-ring involved an initial deprotonation, followed by displacement of the tosyl functionality (Scheme 126). Previous work had shown that the most suitable base for deprotonation in this kind of deactivated system is LDA. Unfortunately, the tosyl functionality proved to be an unsuitable leaving group and cyclisation to form the E-ring did not occur. However, all starting material **432** was recovered.



432 **435**

Scheme 126. E-ring formation

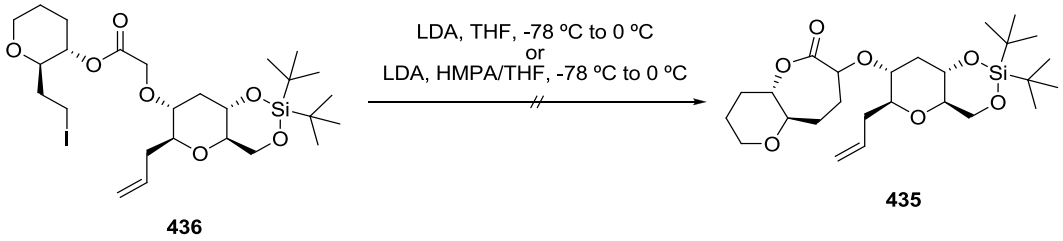
In order to improve the leaving group in **432**, the tosyl functionality was converted into an iodide using NaI, affording compound **436** in excellent yield (Scheme 127).



432 **436**

Scheme 127. Iodination step

With iodide **436** in hand, the E-ring formation step was repeated (Scheme 128). Initially, the same conditions as above (deprotonation with LDA in THF) were applied to allow displacement of the iodide and closure of the E-ring to afford the desired product **435**. Unfortunately, these conditions led to the decomposition of the starting material. In an attempt to increase the strength of the base and accelerate this intramolecular S_N2 reaction, HMPA was used as an additive in conjunction with the previous conditions. Regrettably, this had no effect on the outcome of the reaction and most of the starting material decomposed.

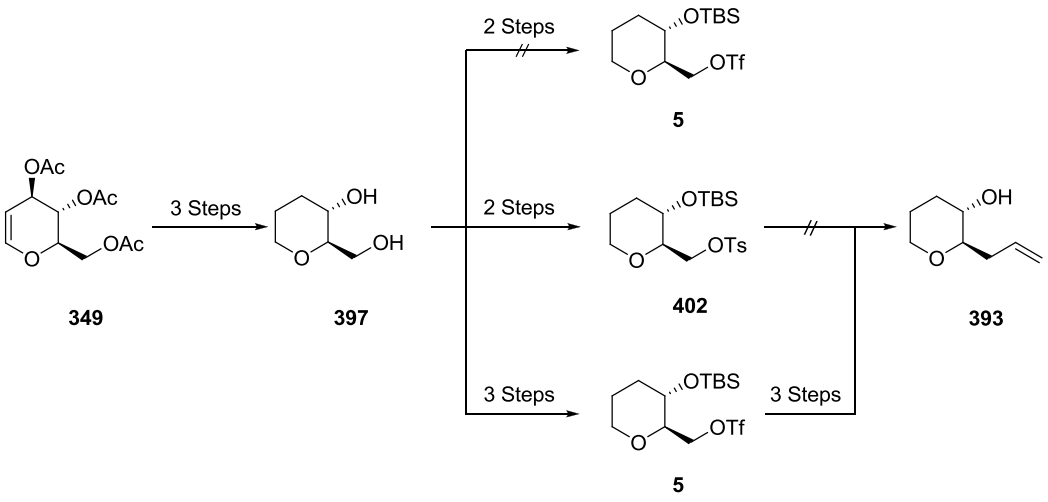


Scheme 128. E-ring formation

For these reasons, alternative leaving groups have to be explored. Unfortunately, due to time constraints this work could not be undertaken, but plans are discussed in detail in Summary and Outlook section that follows.

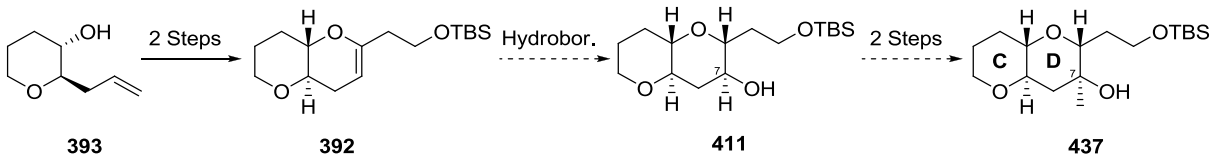
3. Summary and Outlook

The synthesis of the C-D ring fragment commenced with commercially available tri-*O*-acetyl-D-glucal **349** (Scheme 129). The selective two-step protection of alcohol **397** with triflic anhydride and TBSOTf proved problematic and the products were difficult to handle. On the other hand, the selective protection of the primary alcohol with a tosyl functionality was both more efficient as well as selective. Unfortunately, the tosyl group in **402** proved to be an inadequate leaving group in this case. A two step procedure was necessary for the introduction of the triflate functionality, which proved to be an excellent leaving group, allowing the synthesis of the funtionalised C-ring **393** in an additional three steps.



Scheme 129. Synthetic summary to alcohol **393**

From alcohol **393**, two additional steps involving an esterification and an olefinic-ester cyclisation led to bicyclic C-D ring system **392** (Scheme 130). The hydroboration reaction with 9-BBN that followed proved problematic, although alternative borane reagents such as disiamylborane and thexylborane are likely to be more effective. The decrease in steric bulk in these reagent should mean a higher reactivity than observed with 9-BBN, whilst maintaining an increased selectivity over BH_3. A successful hydroboration reaction would afford the C-D ring fragment core **411**. Oxidation and subsequent methylation would introduce the angular methyl at C7, therefore completing the complete C-D ring fragment **437** in preparation for coupling.



393 **392** **411** **437**

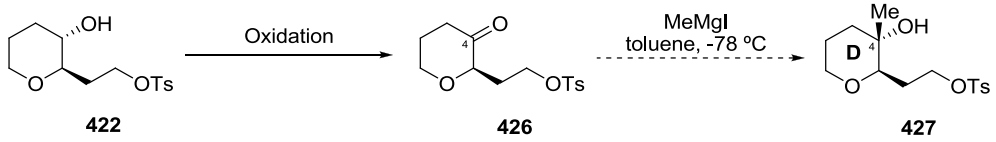
Scheme 130. Last steps towards C-D ring fragment and future work

The simplified D-ring fragment core **422** was synthesised from tri-*O*-acetyl-D-glucal **349** in ten steps (Scheme 131). From this synthesis it is worth highlighting the studies surrounding the three-step homologation sequence from alcohol **405** to alcohol **415**, initially involving oxidation, followed by Wittig reaction with a (methoxymethyl) triphenylphosphonium ylide and final hydrolysis. Unfortunately, the later step failed and an alternative sequence was developed, involving Parikh-Doering oxidation, followed by Wittig olefination with the ylide from methyltriphenylphosphonium bromide and a final hydroboration reaction. Two additional steps afforded the D-ring fragment core **422**.

349 **405** **415** **422**

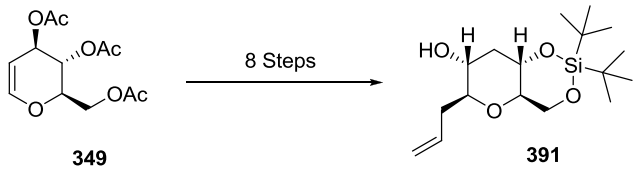
Scheme 131. Synthetic summary to D-ring fragment core **422**

The introduction of the angular methyl in C4 involved sequential oxidation and methyl addition (Scheme 132). Despite the problems encountered due to the unstable nature of ketone **426**, the results of the oxidation reaction were very encouraging and should allow future research to continue. The methyl addition step could be attempted according to conditions previously used in the group.



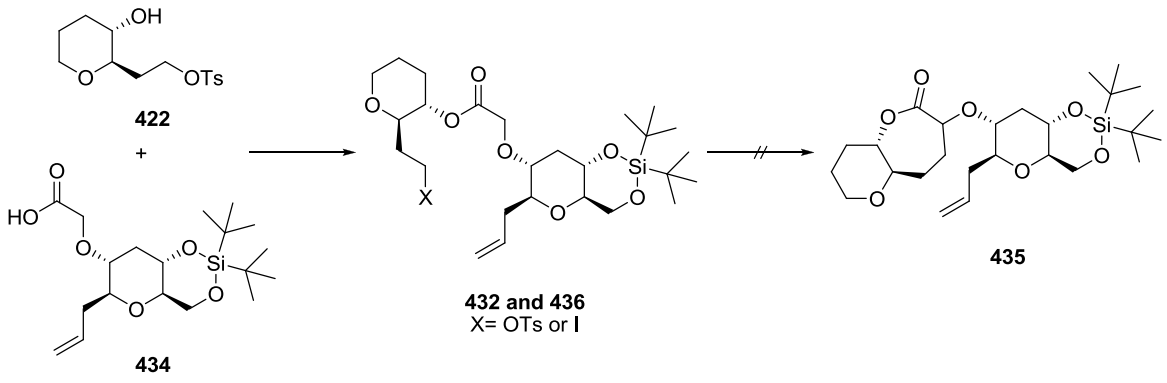
Scheme 132. Last steps towards D-ring fragment and future work

During the synthesis of the G-ring fragment **391**, several issues arose regarding stereocontrol, but these were easily corrected and the complete fragment was obtained from tri-*O*-acetyl-D-glucal **349** in 8 steps (Scheme 133).



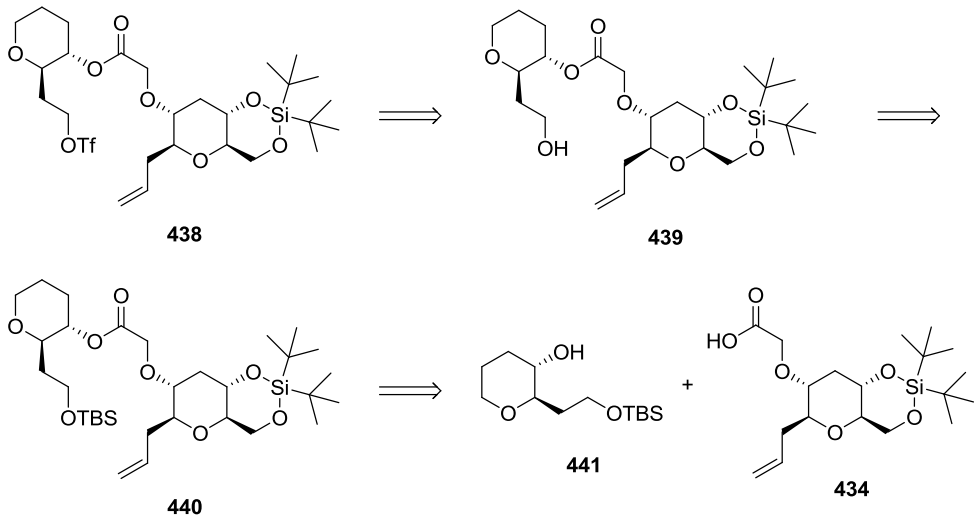
Scheme 133. Synthetic summary to G-ring fragment **391**

The coupling step between the D- and G-ring fragments (**422** and **434** respectively) took place in relatively good yield (Scheme 134). However, the subsequent attempts towards the formation of the E-ring proved fruitless, even though substrates containing a variety of leaving groups were tested.



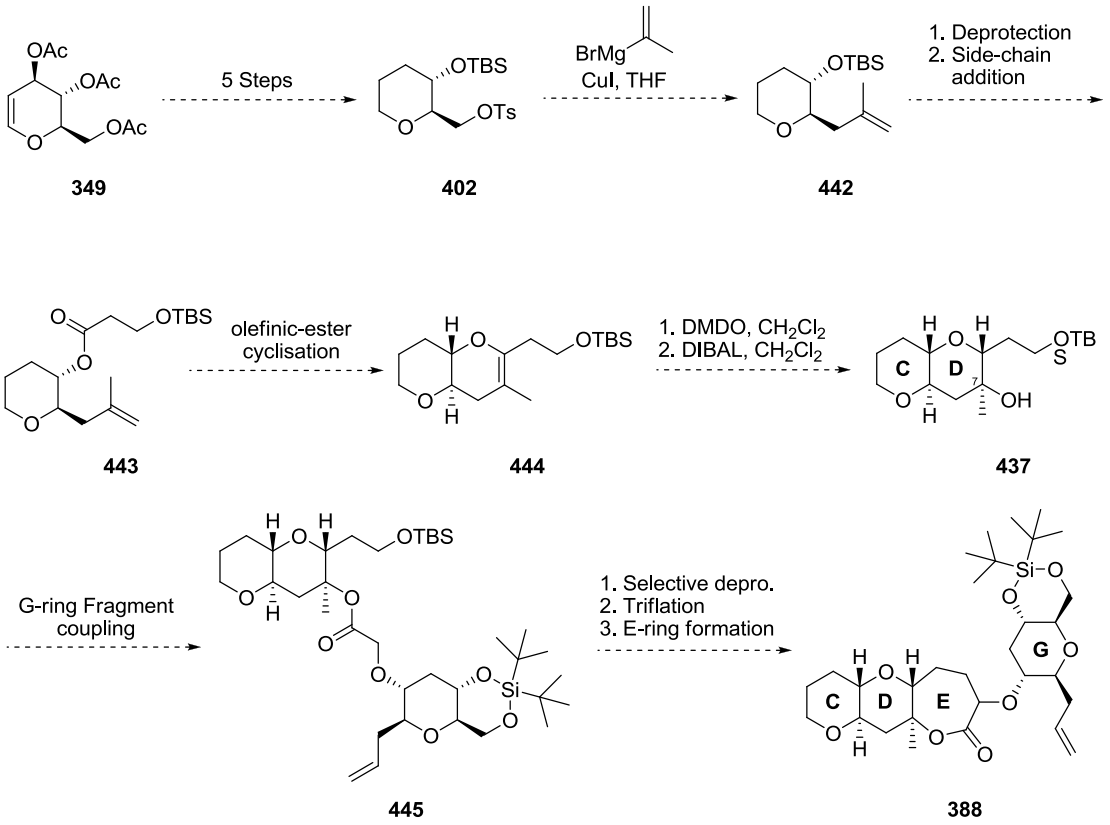
Scheme 134. Fragment coupling and E-ring formation

To allow the introduction of triflate functionality as an alternative leaving group, the synthetic route would have to be altered slightly. Due to the sensitivity of the triflate, addition onto **439** would be required, once the coupling step had taken place, as depicted in the retrosynthetic route below (Scheme 135).



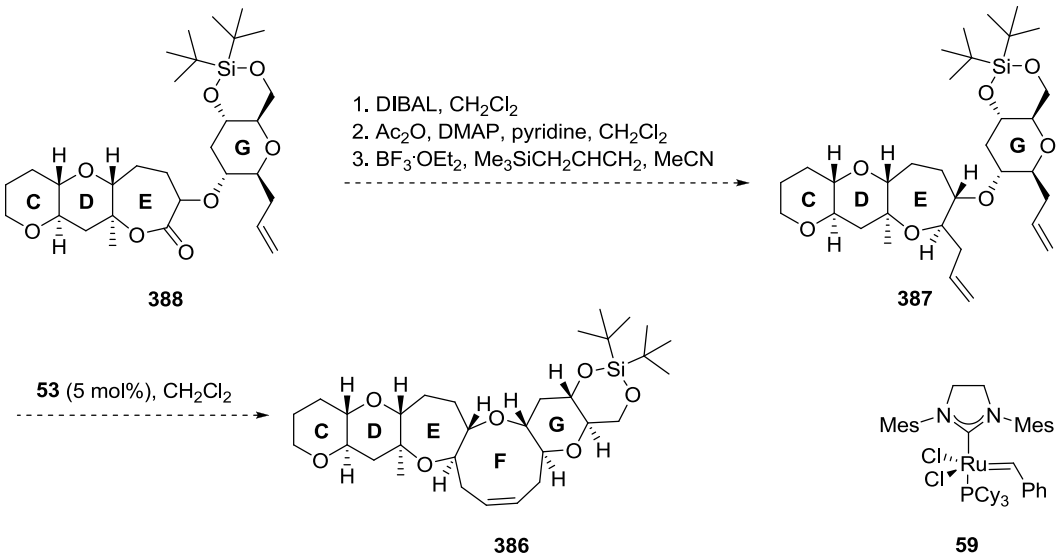
Scheme 135. Introduction of triflate leaving group

The lessons learnt throughout the project allowed the conception of an alternative, more concise and efficient synthetic pathway towards the C-D ring fragment (Scheme 136). Firstly, commencing from tri-*O*-acetyl-D-glucal **349**, the initial five steps towards tosylate **402** would take place as previously described. Secondly, there were concerns about the stereochemical outcome during introduction of the angular methyl at C7 and the route proposed below would avoid this problem by an early methylation through Grignard displacement of the tosyl group in **402**, leading to **442**.[191] Side chain addition would be accomplished in two steps affording **443** and the subsequent olefinic-ester cyclisation would close the D-ring to give the bicyclic enol ether **444**.[188] Epoxidation of enol ether **444** followed by reductive opening with Dibal-H would result in formation of the complete C-D ring fragment **437**. The fragment coupling step would be carried out under previously described conditions affording **445**. Results in this project revealed the possibility of performing selective TBS deprotection in the presence of the siloxane functionality. This would allow the transformation of the deprotected alcohol into a leaving group, in preparation for the E-ring formation studies. This alternative route would reduce the number of steps from 20 to 15, as well as simplifying the methylation step.



Scheme 136. Alternative synthesis for C-G ring fragment

For the completion of the C-G ring model fragment, the synthesis would continue as follows. Reduction of lactone **388** and trapping of the intermediate with acetic anhydride at low temperature would provide a lactol acetate (Scheme 137). Subsequent stereoselective replacement of this acetate with allyl trimethylsilane in the presence of a Lewis acid would lead to allylated product **387**.[192] Finally, diene RCM would lead to the target C-G fragment **386**.



Scheme 137. Final steps towards the C-G ring fragment

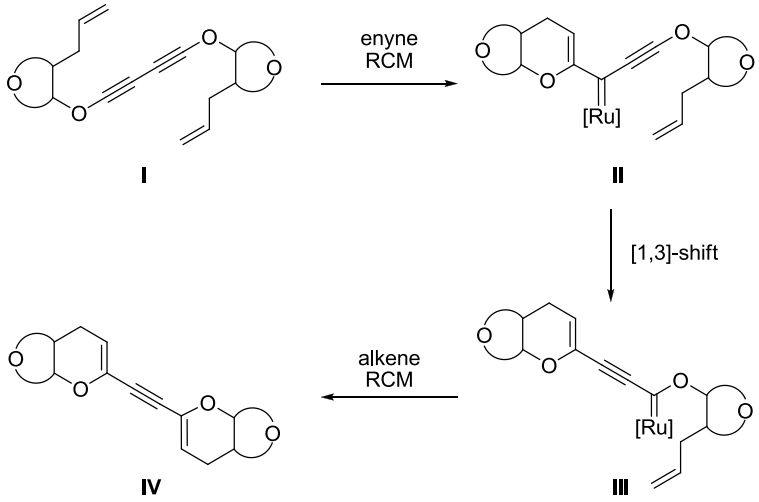
Efficient synthetic routes leading to the coupled product have been described, making future work towards the formation of the E-ring fragment feasible. Nevertheless, the proposed alternative route could be applied directly to the actual gambieric acid target.

Chapter 4
Conclusion

This thesis has detailed the attempts to develop two distinct novel methodologies for the convergent synthesis of complex subunits present in marine polycyclic ethers such as tamulamide, prymnesin, gambierol, maitotoxin and gambieric acid.

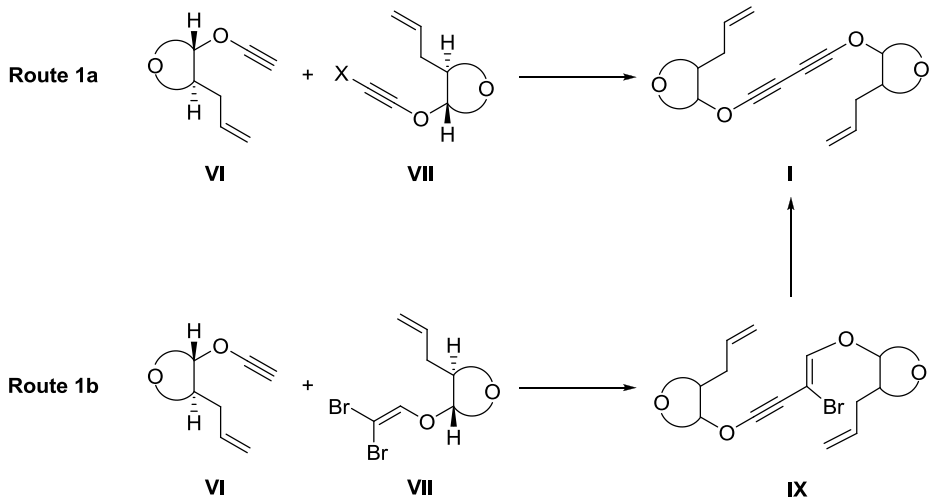
Chapter 2 described the first of these methodologies, involving cascade metathesis reactions. Previous studies within the Clark group have illustrated that both alkene and enyne RCM reactions can be applied to the construction of polycyclic ether natural product subunits. In an attempt to create a more convergent and elegant route towards the synthesis of such ring structures, the following studies focused on the combination of alkene and enyne RCM, in a one-pot process. To this end, two different approaches were investigated.

The first transformation involved a one-pot procedure with an initial enyne RCM reaction from precursor **I**, followed by a metallotropic [1,3]-shift from **II** to give intermediate **III**, which then undergoes a final alkene RCM to close the second ether ring in product **IV** (Scheme 138).



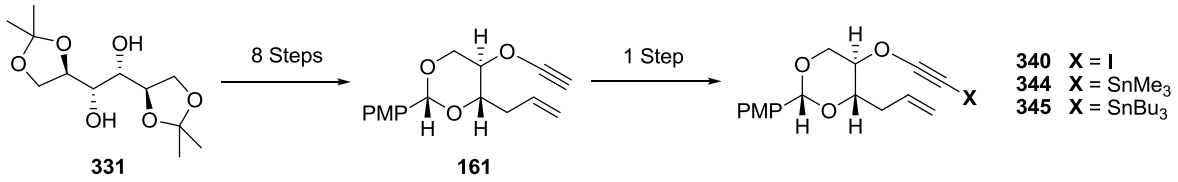
Scheme 138. Cascade enyne RCM with [1,3]-metallotropic shift

The first task involved the formation of RCM precursor **I** for which two different pathways were devised (Scheme 139). Firstly, coupling of alkynyl ether **VI**, with the halogenated counterpart **VII** would lead directly to the desired di-akynyl product **I** (Route 1a). Secondly, the coupling of alkynyl ether **VI** with a dibromoolefin species **VIII** would lead to coupled product **IX**, which would then be transformed into the desired RCM precursor **I** by elimination (Route 1b).



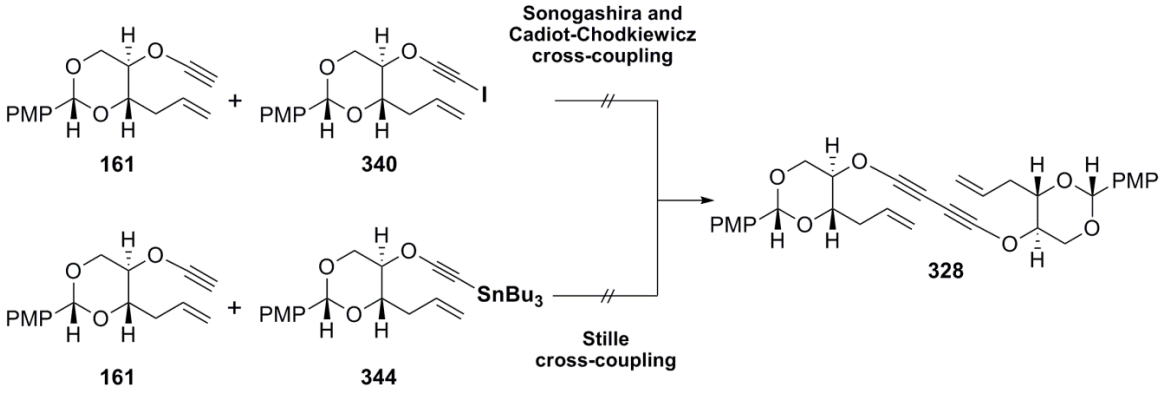
Scheme 139. Outline of two possible routes towards di-alkynyl ether RCM precursor

Initially, the formation of RCM precursor **328** was attempted through several cross-coupling reactions, where the coupling partners were synthesised from commercially available D-mannitol system **331** (Scheme 140). Eight steps were required for the synthesis of terminal alkynyl ether **161**, which was further functionalised to form the halogenated species **340** and stannanes **344** and **345**.



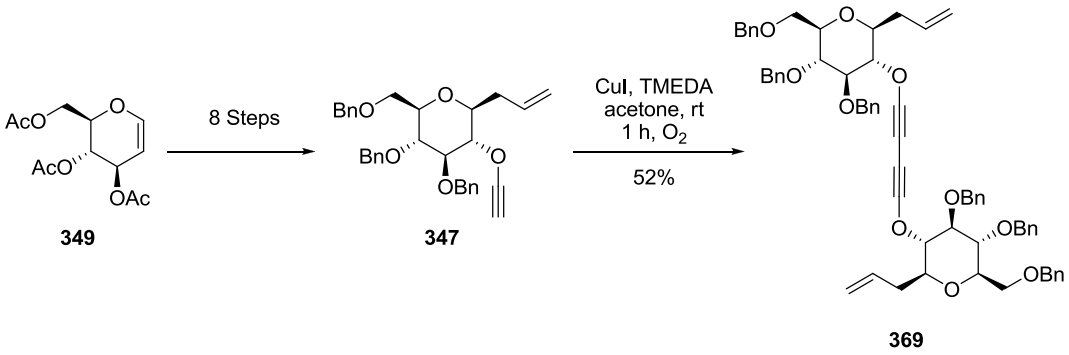
Scheme 140. Summary of the synthesis of D-mannitol based cross-coupling partners

An extensive study of several cross-coupling strategies, involving appropriate combinations of the substrates **161**, **340**, **244** and **345**, were then attempted (Scheme 141). Unfortunately, these alkynyl compounds proved to be sensitive to air, light and temperature and the reactions mainly led to decomposition of the starting materials.



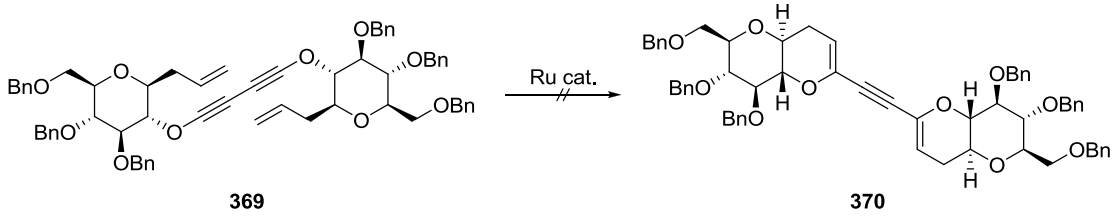
Scheme 142. Summary of D-mannitol based cross-couplings for the formation of RCM precursor **328**

In light of the difficulties encountered in the cross-coupling of two different partners for the formation of RCM precursor **369**, homocoupling procedures were attempted employing a D-glucal based model system (Scheme 143). Alkynyl ether **347** was synthesised from commercially available tri-*O*-acetyl-D-glucal in eight steps. Homocoupling of **347** in the presence of CuI catalyst afforded the RCM precursor **369**, although the conversion of starting material during this reaction remained a problem.



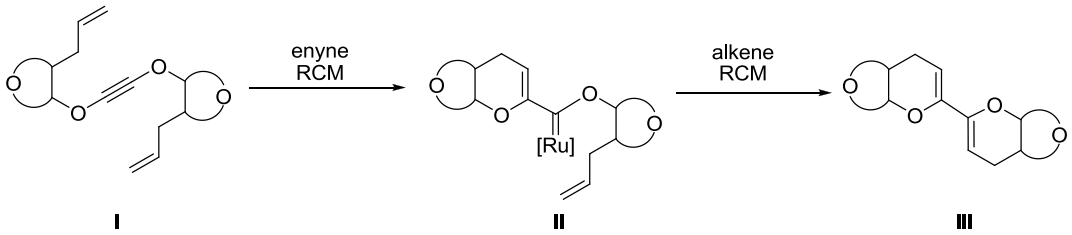
Scheme 143. Summary of RCM precursor **356** by homocoupling of D-glucal based alkynyl ether

With 1,3-dialkynyl ether **369** in hand, attention was turned to the ruthenium-catalysed RCM cascade reaction (Scheme 144). Despite an extensive study of this reaction, it was concluded that 1,3-dialkynyl ether species are too unstable to withstand the conditions required to facilitate a cascade metathesis and [1,3]-metallotropic shift sequence.



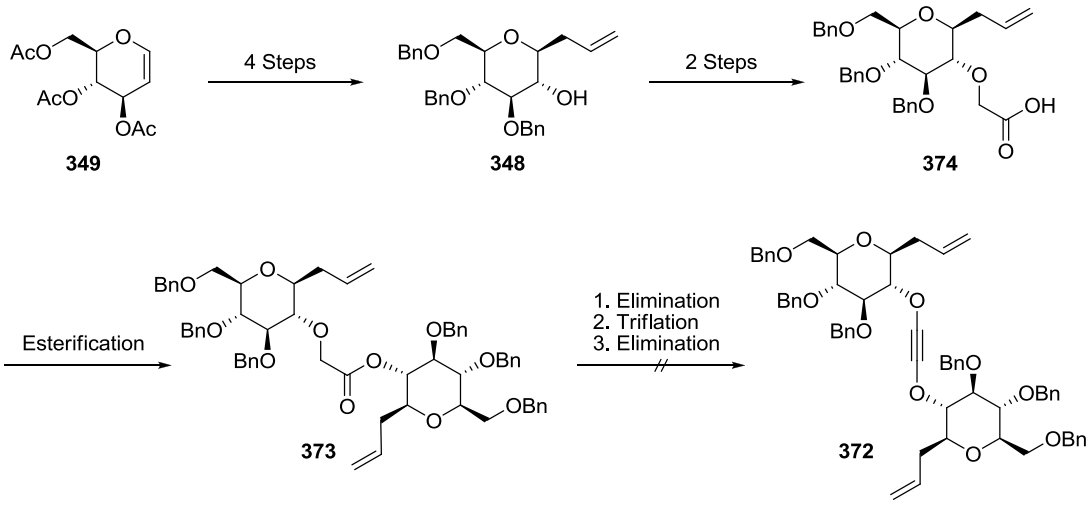
Scheme 144. RCM cascade reaction study involving enyne-RCM, [1,3]-metallotropic shift and ene-RCM

The second route involved a one-pot procedure commencing with an enyne RCM reaction of precursor **I**, followed by direct alkene metathesis of **II** leading to the bicyclic product **III** (Scheme 145).



Scheme 145. Cascade enyne-ene metathesis

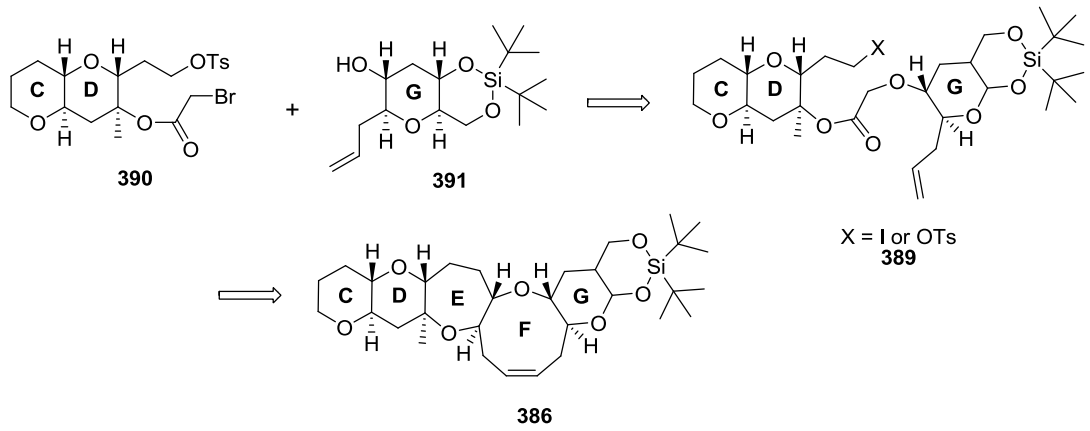
The first task involved the synthesis of the RCM precursor (Scheme 146). Commercially available tri-*O*-acetyl-D-glucal **349** was utilised for the efficient construction of both alcohol **348** and carboxylic acid **374**, which upon esterification afforded compound **373** in excellent yield.



Scheme 146. Summary of the synthesis of D-glucal based RCM precursor

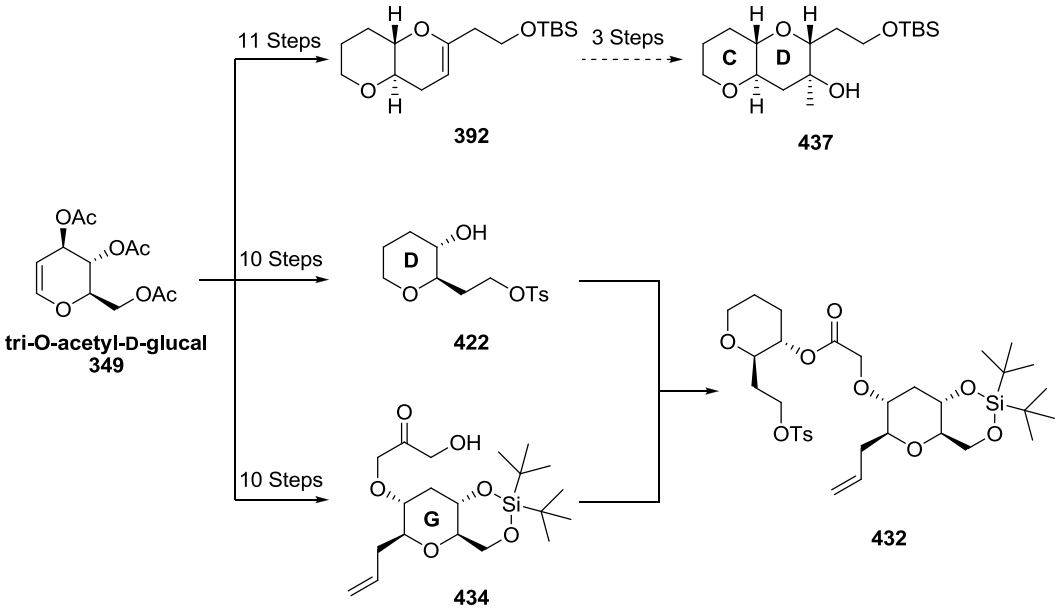
Numerous difficulties were encountered in the formation of the enol triflate functionality, mainly due to the deactivated nature of the alkoxyketone protons in compound **373**, as well as the steric hindrance surrounding them. Further optimisation of this step is required, which would enable an in depth study of the subsequent elimination reaction to give RCM precursor **372** to take place. However, serious concerns remain over the stability of alkyl diether **372** and its ability to undergo further reactions or even purification.

The second project, described in Chapter 3, was directed towards the development of methodology for the coupling of two major fragments of the gambieric acids, where the key steps involved the coupling of the two separate subunits, as well as the formation of the E ring oxepane. For this, a model C-G ring pentacyclic subunit **386** was targeted, constructed from the C-D and G ring fragments, **390** and **391** (Scheme 147).



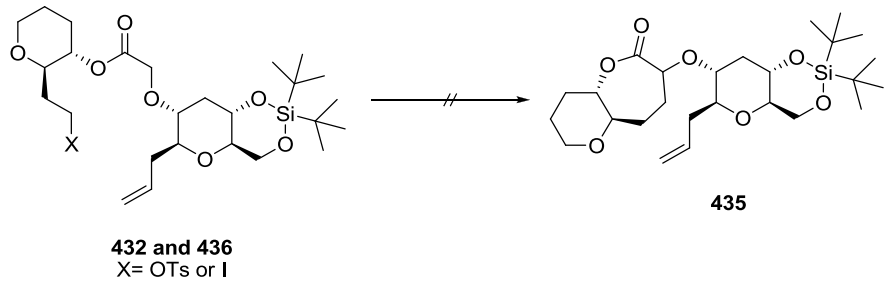
Scheme 147. Gambieric acid project outline

The synthesis of the C-D ring fragment **437** commenced with commercially available tri-*O*-acetyl-D-glucal **349** (Scheme 148). The advanced bicyclic intermediate **392** was obtained from **349** by an eleven-step process, but time constraints prevented the completion of the C-D ring fragment **437**. A simplified D-ring fragment **422** and the G-ring fragment **434** were also synthesised successfully from tri-*O*-acetyl-D-glucal **352** in ten steps each. These fragments were then coupled using an esterification reaction to afford the desired ester **432**.



Scheme 148. Summary of fragment synthesis

Formation of the E-ring was attempted *via* an intramolecular nucleophilic substitution reaction (Scheme 149). Despite several attempts with the tosyl and iodo functionalities, the cyclisations of both **432** and **436** were unsuccessful. Alternative leaving groups were suggested (Chapter 3, Summary and Outlook), though these experiments were not performed.



Scheme 149. E-ring formation

Although this thesis does not present the completed synthesis, the work within has delineated a concise and robust strategy towards the coupling of the two fragments, with optimised and high-yielding transformations. In addition, the lessons learnt throughout this project have also allowed the conception of an alternative, more concise and efficient synthetic pathway towards the C-D ring fragment, contributing to the continuation of this project.

Chapter 5
Experimental Section

General information

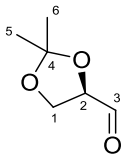
NMR spectra were recorded on a Bruker 400 MHz Spectrospin spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz). Samples were dissolved in deuterochloroform unless otherwise stated. Chemical shifts are quoted in ppm with residual chloroform (δ_H = 7.27 ppm) or methanol (δ_H = 3.35 ppm) as the internal standard for ^{1}H NMR. For ^{13}C spectra, the chemical shifts are reported relative to the central resonance of $CDCl_3$ (δ_H = 77.16). Signals in the NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad (b), or a combination of these which refers to the spin−spin coupling pattern observed. Nomenclature: Compound are named according to IUPAC, whereas structure numbering is strictly for NMR reference only.

Infrared (IR) spectra were recorded employing a Golden Gate™ attachment which used a type IIa diamond as single reflexion element, allowing the IR spectrum of the compound (solid or liquid) to be detected directly (neat) without any sample preparation (Shimadzu FTIR-8400). Specific rotations ($[\alpha]_D$) were measured on an Autopol V Automatic polarimeter.

Column chromatography was performed under pressure using silica gel as solid support, unless otherwise stated, and distilled or HPLC-graded solvent as eluents. Neutralised silica gel refers to silica gel stirred overnight with 2% Et_3N. Reactions were monitored by thin layer chromatography (TLC) on Aldrich silica gel 60 covered alumina plates. The TLC plates were visualised under UV-light and/or developed with anisaldehyde solution (*para*-anisaldehyde (15 g) and H_2SO_4 conc. (2.5 mL) in EtOH (96%, 250 mL)) or using phosphomolybdic acid hydrate solution [phosphomolydic acid anhydrate (5 g) in EtOH (96%) 100 mL].

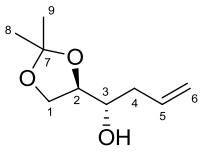
Reagents were purchased from commercial suppliers and all liquid reagents (including DMF solvent) were distilled prior to use. Common solvents (THF, Et_2O, CH_2Cl_2, MeCN and toluene) were dried and purified by a solvent purifier system. Anhydrous MeOH was purchased from commercial suppliers and used without further purification. Reactions involving air-sensitive agents and dry solvents were performed in flame-dried glassware prior to use. These reactions were carried out with the exclusion of air under an argon atmosphere. Reactions involving light sensitive reagents were carried out in the dark (synthesis and manipulation of dichloro- and alkynyl-ether substituted substrates).

(*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (332)[162]



To a stirred solution of bis-acetonide **331** (6.38 g, 24.3 mmol) in dichloromethane (46 mL) and water (2 mL) was added portionwise at 0 °C, $NaIO_4$ (10.4 g, 48.7 mmol). After complete addition, the cooling bath was removed and the mixture was allowed to stir at room temperature for 2 h before $MgSO_4$ was added. The salts were removed by filtration and the solvent was removed carefully *in vacuo* to yield the crude product. The resulting aldehyde **332** was used without further purification; $[a]_D^{26}$ +71.9 (*c* = 1.30 in $CHCl_3$), Lit. $[a]_D^{24}$ +75 (*c* = 1.40 in $CHCl_3$)[193]; ν_{max} 2987, 2936, 2893, 1735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 9.72 (1H, s, CH-C3), 4.39 (1H, ddd, *J* = 7.4, 4.7, 1.8 Hz, CH-C2), 4.18 (1H, dd, *J* = 8.8, 7.4, Hz, CH_2-C1), 4.10 (1H, dd, *J* = 8.8, 4.7, Hz, CH_2-C1), 1.49 (3H, s, CH_3-C6), 1.42 (3H, s, CH_3-C5); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 201.7 (CH-C3), 111.2 (C-C4), 79.8 (CH-C2), 65.5 (CH_2-C1), 26.2 (CH_3-C5), 25.0 (CH_3-C6); HRMS (CI+, isobutane) for $C_6H_{11}O_3$ ($[M+H]^+$) calcd 131.0679, found 131.0704.

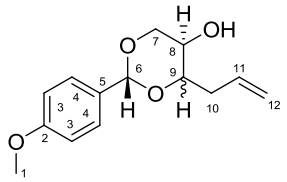
(*S*)-1-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]but-3-en-1-ol (333)[194]



To a stirred solution of dry zinc chloride (13.3 g, 97.4 mmol) in Et_2O (120 mL) was added dropwise at 0 °C allylmagnesium bromide (98 mL of a 1 M solution in Et_2O, 98 mmol) over 20 min. The resulting mixture was sonicated for 30 min at 0 °C and then stirred for 1 h at room temperature. The mixture was cooled to −78 °C and a solution of the crude aldehyde **332** (2.04 g, 15.6 mmol) in Et_2O (45 mL) was added dropwise over 30 min. The solution was stirred and allowed to warm to room temperature overnight, and the reaction was quenched with saturated aqueous NH_4Cl solution (200 mL). The aqueous layer was extracted with Et_2O (3 × 200 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude alcohol as a mixture (5:1) of diastereoisomers. Flash column chromatography (petroleum ether-Et_2O, 7:3 to pure Et_2O) afforded the desired product **333** as a mixture (5:1) of diastereomers (6.90 g, 82% over 2 steps) as a colourless oil. Diagnostic peak for diastereomeric ratio 5.86 ppm (major diastereomer) and 5.75 ppm (for minor diastereomer). A small sample of the

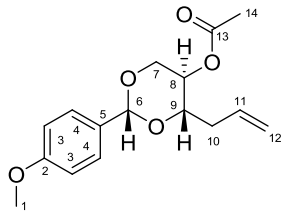
major diastereomer was separated for characterisation purposes. R_f = 0.41; (dichloromethane–methanol, 97:3); $[a]_D^{25}$ +18.1 (*c* = 1.02 in $CHCl_3$),), Lit. $[a]_D^{20}$ +17.9 (*c* = 1.70 in $CHCl_3$)[195]; ν_{max} 3462, 1642, 1456, 1158, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 5.86 (1H, dddd, *J* = 17.2, 10.1, 7.1, 7.1 Hz, CH-C5), 5.18–5.14 (2H, m, CH_2-C6), 4.04–4.00 (2H, m, CH_2-C1), 3.96–3.91 (1H, m, CH-C2), 3.80–3.76 (1H, m, CH-C3), 2.37–2.30 (1H, m, CH_2-C4), 2.24–2.16 (1H, m, CH_2-C4), 1.99 (1H, d, *J* = 3.1 Hz, OH-C3), 1.44 (3H, s, CH_3-C8), 1.37 (3H, s, CH_3-C9); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 134.0 (CH-C5), 118.4 (CH_2-C6), 109.1 (C-C7), 78.1 (CH-C2), 70.4 (CH-C3), 65.2 (CH_2-C1), 37.6 (CH_2-C4), 26.6 (CH_3-C8), 25.3 (CH_3-C9); HRMS (CI+, isobutane) for $C_9H_{17}O_3$ ($[M+H]^+$) calcd 173.1179, found 173.1176.

4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-ol (329 and 336)



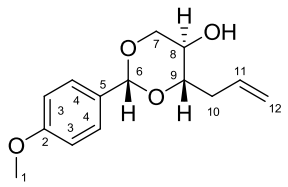
To a stirred solution of alcohols **333** and **334** (5.66 g, 32.8 mmol) in THF at room temperature (120 mL) were added water (14 mL) and TFA (3 mL, 40 mmol). The solution was heated to reflux overnight and then cooled to 0 °C. The mixture was neutralised by addition of solid K_2CO_3 (5.45 g, 39.4 mmol) and filtered. After azeotropic removal of water with toluene (3 × 50 mL), the resulting oil was diluted in ethyl acetate (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the corresponding triols **330** and **335**, which were used without further purification. To a suspension of the resulting triol (4.34 g, 32.8 mmol) in dry dichloromethane (100 mL) were added *p*-methoxybenzaldehyde dimethyl acetal (7 mL, 40 mmol), CSA (1.5 g, 6.6 mmol) and activated 4 Å molecular sieves. The reaction was stirred for 4 days at room temperature. The resulting mixture was filtered through Celite® and the solvent removed *in vacuo*. The resulting oil was dissolved in diethyl ether (300 mL), followed by the addition of Et_3N (25 mL) and water (200 mL). The aqueous phase was extracted with diethyl ether (3 × 200 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether-Et_2O, 1:1) to afford alcohol **329** and **336** as a 5:1 mixture of diastereomers (6.89 g, 84% over two steps) as a colourless solid. R_f = 0.29; (petroleum ether-Et_2O, 1:1). Diagnostic peak for diastereomeric ratio 6.00 ppm (major diastereomer) and 5.92 ppm (for minor diastereomer). For analytical data, refer to compound **329** (*vide infra*).

(2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-yl acetate (338)



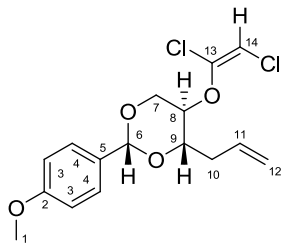
The mixture (5:1) of diastereoisomeric alcohols **329** and **336** (5.37 g, 21.5 mmol) was dissolved in dichloromethane (70 mL). Et_3N (4.5 mL, 32 mmol) and DMAP (100 mg, 1.08 mmol) were added to the solution at room temperature, followed by acetic anhydride (3.1 mL, 32 mmol). The reaction was stirred at room temperature overnight and then quenched with a saturated aqueous solution of $NaHCO_3$ (70 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether-Et_2O-Et_3N, 95:5:1 to 90:10:1) to afford a solid. Crystallisation (petroleum ether-Et_2O, 20:7) afforded the desired acetate **338** (4.00 g, 64%) as a colourless solid. R_f = 0.63; (petroleum ether-Et_2O, 1:1); m.p. 50–51 °C; $[a]_D^{25}$ −45.1 (*c* = 0.97 in $CHCl_3$); ν_{max} 2938, 2859, 1740, 1614, 1517, 1369, 1227, 1086, 1032, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.41 (2H, d, *J* = 8.7 Hz, CH-C3), 6.89 (2H, d, *J* = 8.7 Hz, CH-C4), 5.91 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH-C11), 5.46 (1H, s, CH-C6), 5.14–5.08 (2H, m, CH_2-C12), 4.82 (1H, ddd, *J* = 10.1, 9.8, 5.3 Hz, CH-C8), 4.35 (1H, dd, *J* = 10.5, 5.3 Hz, CH_2-C7), 3.84–3.80 (1H, m, CH-C9), 3.81 (3H, s, CH_3-C1), 3.58 (1H, dd, *J* = 10.5, 10.1 Hz, CH_2-C7), 2.49–2.44 (1H, m, CH_2-C10), 2.40–2.34 (1H, m, CH_2-C10), 2.07 (3H, s, CH_3-C14); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 169.9 (C-C13), 160.2 (C-C2), 133.6 (CH-C11), 130.1 (C-C5), 127.6 (2 × CH-C3), 117.6 (CH_2-C12), 113.8 (2 × CH-C4), 101.2 (CH-C6), 78.7 (CH-C9), 68.1 (CH_2-C7), 66.6 (CH-C8), 55.4 (CH_3-C1), 36.6 (CH_2-C10), 21.0 (CH_3-C14); HRMS (EI+) for $C_{16}H_{20}O_5$ ($[M]^+$) calcd 292.1311, found 292.1314; Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74%; H, 6.90%. Found: C, 65.65%; H, 6.86%.

(2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-ol (329)[69]



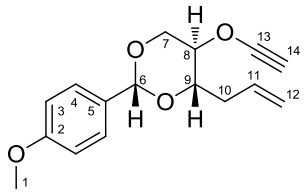
K_2CO_3 (96.5 mg, 0.698 mmol) was added to a solution of acetate **338** (2.04 g, 6.98 mmol) in dry methanol (82 mL) at room temperature. The resulting mixture was stirred overnight at room temperature and the solvent was then evaporated *in vacuo*. The remaining oil was dissolved in Et_2O (100 mL) and a saturated aqueous solution of NH_4Cl (90 mL) was added. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether-Et_2O, 1:1) to afford alcohol **329** (1.75 g, quantitative) as a colourless solid. R_f = 0.19; (petroleum ether-Et_2O, 2:1); m.p. 56−57 °C; $[a]_D^{25}$ −23.2 (*c* = 1.00 in $CHCl_3$),), Lit. $[a]_D^{22}$ −23.5 (*c* = 0.70 in $CHCl_3$)[196]; ν_{max} 3418, 2936, 2859, 1612, 1518, 1250, 1076, 1060, 1020, 964, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (2H, d, *J* = 8.7 Hz, CH-C3), 6.88 (2H, d, *J* = 8.7 Hz, CH-C4), 6.00 (1H, dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, CH-C11), 5.45 (1H, s, CH-C6), 5.20 (1H, ddd, *J* = 17.2, 2.7, 1.5 Hz, CH_2-C12), 5.12 (1H, ddt, *J* = 10.2, 2.7, 1.0 Hz, CH_2-C12), 4.25 (1H, dd, *J* = 10.5, 5.1 Hz, CH_2-C7), 3.80 (3H, s, CH_3-C1), 3.68 (1H, dddd, *J* = 11.7, 10.1, 5.1, 5.0 Hz, CH-C8), 3.63 (1H, ddt, *J* = 11.7, 6.7, 4.4 Hz, CH-C9), 3.57 (1H, dd, *J* = 10.5, 10.1 Hz, CH_2-C7), 2.66−2.59 (1H, m, CH_2-C10), 2.51−2.44 (1H, m, CH_2-C10), 1.70 (1H, d, *J* = 5.0 Hz, OH-C8); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.1 (C-C2), 134.4 (CH-C11), 130.4 (C-C5), 127.5 (2 × CH-C3), 117.7 (CH_2-C12), 113.7 (2 × CH-C4), 101.0 (CH-C6), 81.1 (CH-C9), 71.1 (CH_2-C7), 65.9 (CH-C8), 55.4 (CH_3-C1), 36.9 (CH_2-C10); HRMS (EI+) for $C_{14}H_{18}O_4$ ($[M]^+$) calcd 250.1205, found 250.1204; Anal. calcd for $C_{14}H_{18}O_4$: C, 67.18%; H, 7.25%. Found C, 67.15%; H, 7.29%.

(2*R*,4*S*,5*R*)-4-Allyl-5-[(*E*)-1,2-dichlorovinyloxy]-2-(4-methoxyphenyl)-1,3-dioxane (339)[81]



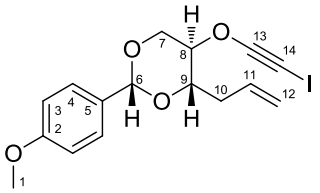
KH (4.79 g of 30% suspension in mineral oil, 35.8 mmol) was washed with petroleum ether (3 × 10 mL) and suspended in THF (30 mL). Alcohol **329** (2.99 g, 11.9 mmol) in THF (60 mL) was then added dropwise at 0 °C and the mixture was stirred at room temperature for 1 h until gas evolution ceased. The mixture was then cooled to 0 °C and Cl_2CCHCl (1.56 mL, 17.9 mmol) was added dropwise. This mixture was stirred at room temperature for 1 h until complete consumption of **329**, as analysed by TLC. The reaction was then quenched by careful addition of MeOH (5 mL) and H_2O (40 mL). The organic phase was separated and the remaining aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether-Et_2O-Et_3N, 95:5:1 to 90:10:1) to afford the desired product **339** as a single isomer (4.03 g, 98% yield), as a colourless solid. R_f = 0.19 (petroleum ether-Et_2O, 4:1); $[\alpha]_D^{25}$ −14.6 (*c* = 0.90 in $CHCl_3$), Lit. $[\alpha]_D^{26}$ −14.9 (*c* = 0.89 in $CHCl_3$)[81]; ν_{max} (neat) 3110, 2928, 2865, 1616, 1589, 995, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.43 (2H, d, *J* = 8.8 Hz CH-C3), 6.91 (2H, d, *J* = 8.8 Hz, CH-C4), 5.99 (1H, dddd, *J* = 17.2 , 10.1, 7.4, 6.6, Hz, CH-C11), 5.60 (1H, s, CH-C14), 5.50 (1H, s, CH-C6), 5.25−5.16 (2H, m, CH_2-C12), 4.41 (1H, dd, *J* = 10.8, 5.2 Hz, CH_2-C7), 4.27 (1H, ddd, *J* = 10.0, 9.3, 5.2 Hz, CH-C8), 3.95 (1H, ddd, *J* = 9.3, 7.2, 3.2 Hz, CH-C9), 3.83−3.78 (1H, m, CH_2-C7), 3.82 (3H, s, CH_3-C1), 2.74−2.69 (1H, m, CH_2-C10), 2.54−2.46 (1H, m, CH_2-C10); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.1 (C-C2), 142.1 (C-C13), 133.3 (CH-C11), 129.8 (C-C5), 127.4 (2 × CH-C3), 118.1 (CH_2-C12), 113.7 (2 × CH-C4), 101.0 (CH-C6), 99.2 (CH-C14), 78.7 (CH-C9), 72.8 (CH-C8), 68.3 (CH_2-C7), 55.3 (CH_3-C1), 35.8 (CH_2-C10); HRMS (EI+) for $C_{16}H_{18}{}^{35}Cl_2O_4$ ($[M]^+$) calcd 344.0582, found 344.0578.

(2*R*,4*S*,5*R*)-4-Allyl-5-ethynyloxy-2-(4-methoxyphenyl)-1,3-dioxane (161)[81]



A solution of dichloroenol ether **339** (700 mg, 2.04 mmol) in dry Et_2O (9 mL) was added dropwise at −78 °C to a solution of *n*-BuLi (2.44 mL of a 2.5 M solution in hexane, 6.10 mmol) in dry Et_2O (9 mL) over a period of 5 min. The mixture was stirred at −78 °C for 30 min then warmed to 0 °C and stirred at this temperature for a further 1 h. The reaction was then quenched with water (20 mL) and the mixture was extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O- Et_3N, 95:5:2 to 80:20:2) to afford alkynyl ether **161** (472 mg, 84% yield) as a yellow oil. R_f 0.54 (petroleum ether-Et_2O, 4:1); $[a]_D^{22}$ −20.3 (*c* = 1.13 in $CHCl_3$), Lit. $[a]_D^{25}$ −21.7 (*c* = 1.40 in $CHCl_3$)[81]; ν_{max} (neat) 3322, 2866, 2155, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (2H, d, *J* = 8.8 Hz, CH-C3), 6.90 (2H, d, *J* = 8.8 Hz, CH-C4), 5.96 (1H, dddd, *J* = 17.1, 10.2, 7.2, 6.7 Hz, CH-C11), 5.46 (1H, s, CH-C6), 5.23−5.16 (2H, m, CH_2-C12), 4.55 (1H, dd, *J* = 10.8, 5.3 Hz, CH_2-C7), 4.07 (1H, ddd, *J* = 10.2, 9.5, 5.3, Hz, CH-C8), 3.88−3.80 (1H, m, CH-C9), 3.82 (1H, dd, *J* = 10.8, 10.2 Hz CH_2-C7), 3.82 (3H, s, CH_3-C1), 2.75−2.68 (1H, m, CH_2-C10), 2.53−2.45 (1H, m, CH_2-C10), 1.62 (1H, s, CH-C14); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 160.2 (C-C2), 133.0 (C-C11), 129.6 (C-C5), 127.5 (2 × CH-C3) 118.4 (CH_2-C12), 113.8 (2 × CH-C4), 101.1 (CH-C6), 88.6 (C-C13), 78.2 (CH-C8), 78.1 (CH-C9), 67.6 (CH_2-C7), 55.4 (CH_3-C1), 35.9 (CH_2-C10), 27.8 (C-C14); HRMS (CI+, isobutane) for $C_{16}H_{19}O_4$ ($[M+H]^+$) calcd 275.1279, found 275.1278.

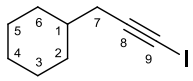
(2*R*,4*S*,5*R*)-4-Allyl-5-(iodoethynyloxy)-2-(4-methoxyphenyl)-1,3-dioxane (340)



A solution of alkynyl ether **161** (449 mg, 1.64 mmol) in THF (6.5 mL) was added dropwise to a solution of *n*-BuLi (0.72 mL of a 2.5 M solution in hexane, 1.80 mmol) in dry THF (6.5 mL) at −78 °C over a period of 5 min, and the resulting mixture was stirred

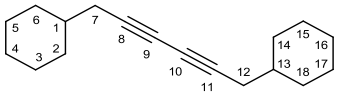
at this temperature for 30 min and then for a further 30 min at 0 °C. The solution was then cooled to −78 °C and a solution of I_2 (419 mg, 1.65 mmol) in THF (2 mL) was added dropwise until the yellow-brown colour persisted. The reaction was quenched with H_2O (5 mL) and the mixture was warmed to room temperature. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with a saturated solution of $Na_2S_2O_3$ (2 × 15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product **340** (640 mg, 98% crude yield) was used in the next step without further purification. R_f 0.56 (petroleum ether-Et_2O, 10:1); ν_{max} (neat) 2866, 2212, 1776, 1688, 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (2H, d, *J* = 8.8 Hz, CH-C3), 6.90 (2H, d, *J* = 8.8 Hz, CH-C4), 5.96 (1H, dddd, *J* = 17.1, 10.2, 7.2, 6.7 Hz, CH-C11), 5.46 (1H, s, CH-C6), 5.23−5.16 (2H, m, CH_2-C12), 4.55 (1H, dd, *J* = 10.8, 5.3 Hz, CH_2-C7), 4.07 (1H, ddd, *J* = 10.2, 9.5, 5.3, Hz, CH-C8), 3.88−3.80 (1H, m, CH-C9), 3.82 (1H, dd, *J* = 10.8, 10.2 Hz CH_2-C7), 3.82 (3H, s, CH_3-C1), 2.75−2.68 (1H, m, CH_2-C10), 2.53−2.45 (1H, m, CH_2-C10); HRMS (EI+) for $C_{16}H_{17}IO_4$ ($[M]^+$) calcd 400.0172, found 400.0174.

(3-Iodo-2-propyn-1-yl)-cyclohexane (342)



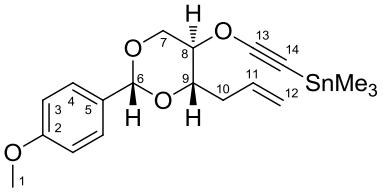
A solution of *n*-BuLi (1.21 mL of a 2.5 M solution in hexane, 3.04 mmol) was added dropwise to a solution of commercially available 3-cyclohexyl-1-propyne **341** (338 mg, 2.77 mmol) in dry Et_2O (5 mL) at −78 °C and the mixture was stirred at 0 °C for 1.5 h. A solution of I_2 (707 mg, 2.79 mmol) in dry THF (4 mL) was slowly added at −78 °C until a dark orange/brown colour persisted. The mixture was allowed to warm to room temperature and the reaction was quenched by the addition of petroleum ether (10 mL) and water (20 mL). The phases were separated and the aqueous phase was extracted with petroleum ether (2 × 20 mL). The combined organic extracts were washed with a saturated solution of $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give compound **342** (618.3 mg, 90% crude yield) as a yellow oil. The resulting product was employed in the next step without further purification. R_f 0.75 (petroleum ether-Et_2O, 3:1); ν_{max} (neat) 2919, 2850, 1447, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.28−2.22 (2H, d, *J* = 6.7 Hz, CH_2-C7), 1.85−1.60 (5H, m, 5 × CH equatorial), 1.54−1.40 (1H, m, CH-C1), 1.32−0.90 (5H, m, 5 × CH axial); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 83.5 (C-C9), 68.9 (CH_2-C7), 37.3 (CH-C1), 35.5 (CH_2-C2 and CH_2-C6), 26.5 (CH_2-C4), 26.2 (CH_2-C3 and CH_2-C5). C8 not found; HRMS (EI+) for $C_9H_{13}I$ ($[M]^+$) calcd 248.0066, found 248.0062.

1,6-dicyclohexylhexa-2,4-diyne (343)[197]



Diisopropylamine (0.75 mL, 5.3 mmol) was added to a solution of 3-cyclohexyl-1-propyne **341** (0.509 mL, 3.52 mmol), iodo alkyne **342** (727 mg, 2.93 mmol), $Pd(PPh_3)_2Cl_2$ (36.4 mg, 0.088 mmol) and CuI (16.7 mg, 0.088 mmol) in THF (25 mL) at room temperature and the resulting mixture was stirred overnight. The reaction was then quenched with a mixture of water and saturated aqueous solution of NH_4Cl (1:1, 10 mL). The organic phase was then separated and washed with brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether) to afford the desired product **343** (710 mg, 83% yield) as a yellow oil. R_f 0.81 (petroleum ether-Et_2O, 9:1); ν_{max} (neat) 2923, 2850, 1711, 1449, 1216, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.15 (4H, d, J = 6.6 Hz, CH_2-C7 and CH_2-C12), 1.85–1.59 (10H, m, 10 × CH), 1.56–1.42 (2H, m, CH-C1 and CH-C13), 1.36–0.75 (10H, m, 10 × CH); HRMS (CI+, isobutane) for $C_{18}H_{27}$ ($[M+H]^+$): 242.2113, found 242.2096.

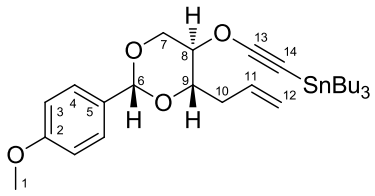
{[(2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-yloxy]ethynyl} trimethylstannane (344)[69]



A solution of alkynyl ether **161** (458 mg, 1.64 mmol) in dry Et_2O (6.0 mL) was added dropwise to a solution of *n*-BuLi (0.676 mL of a 2.5 M solution in hexane, 1.69 mmol) in dry Et_2O (2.0 mL) at −78 °C and the resulting mixture was stirred at 0 °C for 1 h. After cooling the solution to −78 °C, trimethyltin chloride (1.67 mL of a 1 M solution in Et_2O, 1.67 mmol) was added dropwise. The mixture was allowed to warm to 0 °C and the reaction was quenched with H_2O (6 mL). The organic phase was separated and washed with brine (2 × 8 mL), dried over $MgSO_4$ and concentrated *in vacuo* to deliver stannane **343** (508 mg, 55% crude yield). This product was utilised in the next step without further purification. R_f 0.54 (petroleum ether-Et_2O, 4:1). Note: product **344** was contaminated with tin residues, therefore full analytical data could not be obtained.

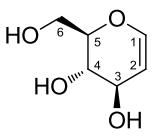
Diagnostic features include: ν_{max} (neat) disappearance of 3322 cm^{-1} stretch (terminal alkynyl ether C−H stretch); ^1H NMR (400 MHz, $CDCl_3$) δ_H Disappearance of 1.62 (1H, s, CH-C14 terminal alkynyl ether proton peak).

{[(2*R*,4*S*,5*R*)-4-Allyl-2-(4-methoxyphenyl)-1,3-dioxan-5-yloxy]ethynyl}tributyl-stannane (345)



A solution of alkynyl ether **161** (372 mg, 1.36 mmol) in dry THF (3.0 mL) was added dropwise to a solution of *n*-BuLi (0.60 mL of a 2.5 M solution in hexane, 1.5 mmol) in dry THF (2.0 mL) at −78 °C and the resulting mixture was stirred at 0 °C for 1 h. After cooling the solution to −78 °C, tributyltin chloride (0.33 mL, 1.22 mmol) was added dropwise. The mixture was then allowed to warm to 0 °C and the reaction was quenched with H_2O (5 mL). The organic phase was separated and washed with brine (2 × 6 mL), dried over $MgSO_4$ and concentrated *in vacuo* to deliver stannane **345** (727.2 mg, 95% crude yield). This product was utilised in the next step with no further purification. R_f 0.54 (petroleum ether-Et_2O, 4:1); ν_{max} 2956, 2924, 2871, 2854, 2156 cm^{-1}; Note: product **345** was contaminated with tin residues, therefore full analytical data could not be obtained. Diagnostic features include: ν_{max} (neat) disappearance of 3322 cm^{-1} stretch (terminal alkynyl ether C−H stretch); ^1H NMR (400 MHz, $CDCl_3$) δ_H Disappearance of 1.62 (1H, s, CH-C14 terminal alkynyl ether proton peak).

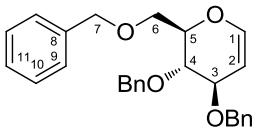
(2*R*,3*S*,4*R*)-2-Hydroxymethyl-3,4-dihydro-*2H*-pyran-3,4-diol (D-glucal) (189)[83]



NaOMe (150 mg, 2.76 mmol) was added to a solution of commercially available tri-*O*-acetyl-D-glucal **349** (15.0 g, 55.1 mmol) in methanol (100 ml) at room temperature and

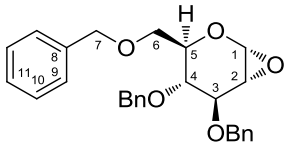
then stirred for 2.5 h. The solvent was evaporated *in vacuo*. The crude product was directly used in the next step.

(2*R*,3*S*,4*R*)-3,4-Bis-benzyloxy-2-benzyloxymethyl-3,4-dihydro-*2H*-pyran (350)[198]



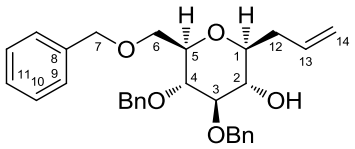
D-Glucal **189** (8.05 g, 55.1 mmol) was slowly added dropwise at 0 °C to a suspension of NaH (60% in mineral oil, 8.82 g, 229 mmol) in a mixture of THF (240 mL) and DMF (60 mL), over a period of 15 min. The mixture was stirred at 0 °C for 30 min, followed by a dropwise addition of benzyl bromide (23.0 mL, 192 mmol) over a period of 15 min. The mixture was then stirred at 0 °C for 2 h and a further 3 h at room temperature. The reaction mixture was then cooled to 0 °C and the reaction was quenched by slow addition of MeOH (60 mL) and H_2O (160 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with a saturated aqueous solution of NH_4Cl (80 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 95:5 to 80:20) to obtain **350** (17.6 g, 77% yield over two steps) as a colourless powder. R_f 0.45 (petroleum ether-Et_2O, 1:1); $[a]_D^{21}$ −2.9 (*c* = 1.20 in $CHCl_3$), Lit. $[a]_D^{22}$ −2.7 (*c* = 1.89 in $CHCl_3$)[199]; ν_{max} (neat) 3063, 3030, 2866, 1647, 1497, 1453, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 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 benz), 4.64 (2H, d, *J* = 7.4 Hz, CH_2 benz), 4.69−4.59 (3H, m, CH_2 benz), 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-C6), 3.76 (1H, dd, *J* = 10.7, 2.9 Hz CH_2-C6); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.8 (CH-C1),138.4 (C-C arom), 138.2 (C-C arom), 138.0 (C-C arom), 128.5 (3 × CH arom), 128.4 (3 × CH arom), 128.0 (3 × CH arom), 127.9 (3 × CH arom), 127.7 (3 × 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); HRMS (EI) for $C_{27}H_{27}O_4$ ($[M]^+$) calcd 416.1988, found 416.1980.

(1*S*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-3-(benzyloxymethyl)-2,7-dioxabicyclo[4.1.0] heptane (351)[166]



A solution of 3,4-bis-benzyloxy-2-benzyloxymethyl-3,4-dihydro-2*H*-pyran **350** (6.00 g, 14.4 mmol) in a mixture of acetone (25 mL), CH_2Cl_2 (63 mL) and saturated aqueous solution of $NaHCO_3$ (150 mL) was stirred vigorously at 0 °C. A suspension of oxone (26.6 g, 43.2 mmol) in H_2O (86 mL) was added dropwise over a period of 20 min and the resulting mixture was stirred for 35 min at 0 °C and a further 75 min at room temperature. Once the reaction was complete as observed by TLC analysis, the organic phase was separated and the remaining aqueous phase was extracted with CH_2Cl_2 (3 × 120 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was directly used in the next step.

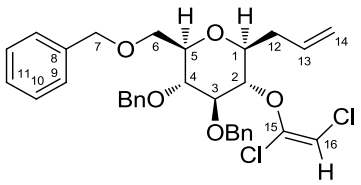
(1*S*,3*R*,4*S*,6*R*)-2-Allyl-4,5-bis-benzyloxy-6-benzyloxymethyl-tetrahydro-pyran-3-ol (348)[69, 200, 201]



Allylmagnesium chloride (14.4 mL of a 2.0 M in THF, 28.8 mmol) was added dropwise at 0 °C to a solution of (1*S*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-3-(benzyloxymethyl)-2,7-dioxabicyclo[4.1.0]heptane **348** (6.23 g, 14.4 mmol) in THF (40 mL) and the mixture was stirred at this temperature for 3 h. Once the reaction had reached completion as indicated by TLC analysis, a saturated aqueous solution of NH_4Cl (120 mL) was added. The organic phase was separated and the remaining aqueous phase was extracted with Et_2O (3 × 120 mL). The combined organic extracts were washed with brine (80 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 95:5 to 80:20) to obtain **348** (5.94 g, 87% yield) as a colourless powder. R_f 0.62 (petroleum ether-Et_2O, 1:1); $[a]_D^{20}$ +10.8 (*c* = 1.28 in $CHCl_3$), Lit. $[a]_D^{25}$ +11.4 (*c* = 0.50 in $CHCl_3$)[202]; ν_{max} (neat) 3610, 2956, 1460, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.31−7.19 (15H, m, CH-C arom), 5.91 (1H, dddd, *J* = 17.1, 14.5, 10.1, 7.2 Hz CH-C13), 5.15 (1H, dd, *J* = 17.1, 1.9 Hz, CH_2-C14), 5.14 (1H, d, *J* = 10.1 Hz, CH_2- C14), 4.80 (1H, d, *J* = 11.5 Hz, CH_2 benz), 4.76 (1H,

d, *J* = 10.8 Hz, CH_2 benz), 4.62 (1H, d, *J* = 11.5 Hz, CH_2 benz), 4.59 (1H, d, *J* = 12.0 Hz, CH_2 benz), 4.56 (1H, d, *J* = 10.8 Hz, CH_2 benz), 4.55 (1H, d, *J* = 12.0 Hz, CH_2 benz), 3.88–3.80 (2H, m, CH_2-C6), 3.72 (1H, t, *J* = 9.5 Hz, CH-C5), 3.58 (1H, t, *J* = 9.5 Hz, CH-C4), 3.57–3.51 (1H, m, CH-C3), 3.47 (1H, t, *J* = 9.0 Hz, CH-C2), 3.39 (1H, dt, *J* = 8.2, 3.2 Hz, CH-C1), 2.59–2.53 (1H, m, CH_2-C12), 2.31 (1H, dt, *J* = 14.8, 7.2 Hz, CH_2-C12), 2.06 (1H, d, *J* = 2.7 Hz, OH) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.6 (C-C arom), 138.3 (C-C arom), 138.1 (C-C arom), 134.7 (CH-C13), 128.7 (2 × CH arom), 128.5 (2 × CH arom), 128.4 (2 × CH arom), 128.1 (3 × CH arom), 128.0 (2 × CH arom), 127.9 (CH arom), 127.8 (2 × CH arom), 127.6 (CH arom), 117.1 (CH_2-C14), 86.8 (CH-C4), 79.2 (CH-C3), 78.8 (CH-C1), 78.5 (CH-C5), 75.2 (CH_2-C7), 74.08 (CH_2-C7), 73.5 (CH_2-C7 and CH-C2), 36.2 (CH_2-C12); HRMS (CI+, isobutane) calcd. for $C_{30}H_{35}O_5$ ($[M+H]^+$) 475.2485, found 475.2483.

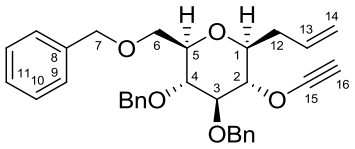
(1*S*,3*R*,4*S*,6*R*)-2-Allyl-4,5-bis-benzyloxy-6-benzyloxymethyl-3-(1,2-dichloro-vinyloxy) tetrahydro-pyran (352)



KH (929 mg of a 30% suspension in mineral oil, 6.95 mmol) was washed with petroleum ether (3 × 8 mL) and suspended in Et_2O (15 mL). 2-Allyl-4,5-bis-benzyloxy-6-benzyloxymethyl-tetrahydropyran-3-ol **348** (1.32 g, 2.79 mmol) in Et_2O (8 mL) was then added dropwise at 0 °C and stirred at room temperature for 15 min until gas evolution had ceased. The reaction mixture was cooled to 0 °C and Cl_2CCHCl (0.26 mL, 3.42 mmol) in Et_2O (6 mL) was added dropwise. This mixture was stirred at room temperature for 30 min until completion. The reaction was then quenched by the addition of MeOH (7 mL) and H_2O (2 × 20 mL). The organic phase was separated and the remaining aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was filtered through a short plug of silica gel (petroleum ether-Et_2O, 95:5 to 80:20). The filtrate was concentrated *in vacuo* and used directly in the next step. R_f 0.78 (petroleum ether-Et_2O 4:1); $[a]_D^{27}$ +38.9 (*c* = 1.18 in $CHCl_3$); ν_{max} (neat) 3063, 3030, 2866, 1624, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.22 (13H, m, CH-C arom), 7.19–7.14 (2H, m, CH-C arom), 5.92 (1H, ddt, *J* = 17.6, 10.2, 7.2 Hz CH-C13), 5.38 (1H, s, CH-C16), 5.15 (1H, dd, *J* = 17.6, 2.2 Hz, CH_2-C14), 5.14 (1H, dd, *J* = 10.1 Hz, 2.2 CH_2-C14), 4.82 (2H, s, CH_2 benz), 4.76 (1H, d, *J* = 10.9 Hz, CH_2 benz), 4.62 (1H, d, *J* = 12.3 Hz, CH_2 benz), 4.56 (1H, d, *J* = 10.9 Hz, CH_2 benz), 4.56 (1H, d, *J* = 12.3 Hz, CH_2 benz),

4.30 (1H, dd, *J* = 9.7, 9.0 Hz, CH-C2), 3.77 (1H, t, *J* = 9.0 Hz), 3.76–3.68 (2H, m, CH_2-C6), 3.65 (1H, dd, *J* = 9.6, 9.0 Hz, CH-C4), 3.54 (1H, ddd, *J* = 9.7, 7.2, 3.2 Hz, CH-C1), 3.46 (1H, ddd, *J* = 9.6, 4.0, 2.4 Hz, CH-C5), 2.60–2.52 (1H, m, CH_2-C12), 2.31 (1H, dt, *J* = 19.2, 5.9 Hz, CH_2-C12). HRMS (CI+, isobutane) calcd. for $C_{32}H_{35}O_5\ Cl_2$ ($[M+H]^+$) 569.1862, found 569.1865.

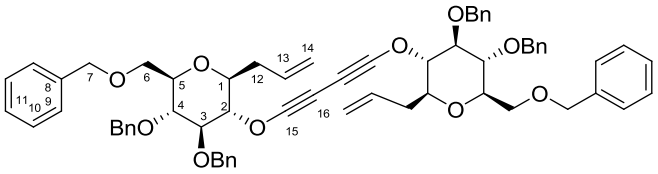
(2*S*,3*S*,4*S*,5*R*,6*R*)-2-allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-(ethynyloxy)tetrahydro-*2H*-pyran (347)



n-BuLi (3.83 mL of a 2.5 M solution in hexane, 9.57 mmol) was added dropwise to a solution of (1*S*,3*R*,4*S*,6*R*)-2-allyl-4,5-bis-benzyloxy-6-benzyloxymethyl-3-(1,2-dichloro-vinyloxy) tetrahydropyran **352** (1.59 g, 2.79 mmol) in Et_2O (30 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min then warmed to −40 °C and stirred at this temperature for a further 1 h. The reaction was then quenched by the addition of water (20 mL) and extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O-Et_3N, 95:5:2) to afford alkynyl ether **347** (1.11 g, 70% yield over two steps) as a colourless oil. R_f 0.63 (petroleum ether-Et_2O 4:1); $[\alpha]_D^{26}$ +18.9 (*c* = 1.36 in $CHCl_3$); ν_{max} (neat) 3318, 2951, 2928, 2857, 2153, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.48–7.23 (13H, m, CH-C arom), 7.22–7.12 (2H, m, CH-C arom), 5.92 (1H, ddt, *J* = 17.2, 10.2, 7.2 Hz, CH-C13), 5.21 (1H, dd, *J* = 17.2, 1.7 Hz, CH_2-C14), 5.14 (1H, dd, *J* = 10.2, 1.7 Hz, CH_2-C14), 4.97 (1H, d, *J* = 10.6 Hz, CH_2 benz), 4.81 (1H, d, *J* = 10.8 Hz, CH_2 benz), 4.80 (1H, d, *J* = 10.6 Hz, CH_2 benz), 4.60 (1H, d, *J* = 12.2 Hz, CH_2 benz), 4.55 (1H, d, *J* = 10.8 Hz, CH_2 benz), 4.54 (1H, d, *J* = 12.2 Hz, CH_2 benz), 3.91 (1H, t, *J* = 8.7 Hz, CH-C5), 3.85 (1H, t, *J* = 9.7 Hz, CH-C3), 3.74–3.66 (2H, m, CH_2-C6), 3.66–3.58 (1H, m, CH-C4), 3.54 (1H, ddd, *J* = 9.7, 7.2, 3.3 Hz, CH-C1), 3.41 (1H, ddd, *J* = 9.7, 4.3, 2.0 Hz, CH-C2), 2.71–2.61 (1H, m, CH_2-C12), 2.40 (1H, dt, *J* = 14.7, 7.2 Hz, CH_2-C12), 1.63 (1H, s, CH-C16); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.3 (C-C arom), 138.3 (C-C arom), 138.1 (C-C arom), 133.4 (CH-C13), 128.6 (2 × CH-C arom), 128.5 (2 × CH-C arom), 128.5 (2 × CH-C arom), 128.4 (2 × CH-C arom), 128.1 (3 × CH-C arom), 128.0 (CH-C arom), 127.8 (2 × CH-C arom), 127.8 (CH-C arom), 118.3 (CH_2-C14), 89.1 (C-C15), 88.1 (CH-C5), 83.3 (CH), 79.1 (CH), 78.2 (CH), 76.5 (CH), 75.5 (CH_2 benz), 75.3 (CH_2 benz), 73.6 (CH_2 benz), 68.8

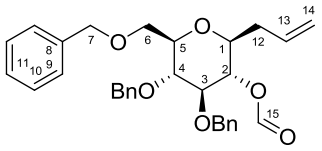
(CH_2-C6), 35.7 (CH_2-C12), 28.3 (CH-C16); HRMS (CI+, isobutane) calcd. for $C_{32}H_{35}O_5$ ($[M+H]^+$) 499.2484, found 499.2473.

1,4-Bis((2*S*,3*S*,4*S*,5*R*,6*R*)-2-allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl) tetrahydro-2*H*-pyran-3-yloxy)buta-1,3-diyne (369)



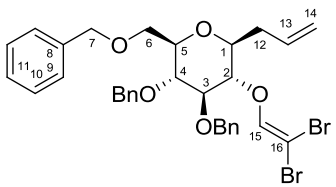
A solution of alkynyl ether **347** (593 mg, 1.188 mmol) in acetone (2 mL) was added to a mixture of TMEDA (36.1 µL, 0.241 mmol) and CuI (5.73 mg, 0.030 mmol) in acetone (1 mL) at room temperature, under an argon atmosphere. The reaction atmosphere was then changed to O_2 and the mixture was stirred for 1.5 h. The solvent was removed *in vacuo* and the residue dissolved in diethyl ether (4 mL) and filtered through a short pad of Al_2O_3, eluting with more Et_2O. The filtrate was concentrated *in vacuo* to afford crude diyne **369** (261 mg, 44% crude yield). To note: due to the sensitive nature of product **369**, full analytical data could not be obtained. R_f 0.36 (petroleum ether-Et_2O, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 (2H, d, *J* = 7.2 Hz, CH-C arom), 7.34–7.23 (24H, m, CH-C arom), 7.17 (4H, dd, *J* = 7.2, 2.1 Hz, CH-C arom), 5.90 (ddt, *J* = 17.1, 10.3, 7.2 Hz, CH-C13), 5.21 (2H, dd, *J* = 17.1, 1.4 Hz, CH_2-C14), 5.14 (2H, dd, *J* = 10.3, 1.4 Hz, CH_2-C14), 4.94 (2H, d, *J* = 10.7 Hz, CH_2 benz), 4.81 (2H, d, *J* = 10.7 Hz, CH_2 benz), 4.80 (2H, d, *J* = 10.6 Hz, CH_2 benz), 4.60 (2H, d, *J* = 12.2 Hz, CH_2 benz), 4.55 (2H, d, *J* = 10.6 Hz, CH_2 benz), 4.53 (2H, d, *J* = 12.2 Hz, CH_2 benz), 3.96–3.80 (3H, m, CH-C1 to CH-C6), 3.73–3.58 (7H, m, CH-C1 to CH-C6), 3.56–3.49 (2H, m, CH-C1 to CH-C6), 3.41 (2H, ddd, *J* = 9.8, 4.0, 1.8 Hz, CH-C1 to CH-C6), 2.71–2.58 (2H, m, CH_2-C12), 2.39 (2H, dt, *J* = 14.7, 7.2 Hz, CH_2-C12). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{13} 138.3 (C-C arom and CH-C arom), 138.2 (C-C arom and CH-C arom), 138.1 (C-C arom and CH-C arom), 133.2 (CH-C13), 128.6−127.7 (12 × CH arom), 118.5 (CH_2-C14), 88.7 (CH), 83.2 (CH), 82.0 (CH), 79.1 (CH), 78.3 (CH), 76.4 (CH), 75.6 (CH_2-C7), 75.3 (CH_2-C7), 73.6 (CH_2-C7), 73.6 (C-C16), 68.8 (CH_2-C6), 35.7 (CH_2-C12), 27.9 (C-C15).

(2*S*,3*S*,4*S*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-3-yl formate (354)



Dry formic acid (80.0 µL, 2.11 mmol), was added dropwise to a solution of alcohol **348** (500 mg, 1.06 mmol), DCC (501 mg, 2.43 mmol) and DMAP (129 mg, 1.06 mmol) in CH_2Cl_2 (7 mL) at 0 °C and the resulting mixture stirred overnight at room temperature. This mixture was then filtered, and the filtrate washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford crude formate **354**. Due to the sensitive nature of this compound, the crude product was taken directly onto the next step with no further purification. R_f 0.67 (petroleum ether-Et_2O, 2:1); ν_{max} (neat) 3083, 2915, 2860, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (1H, s, CH-C15), 7.40–7.16 (15H, m, CH-C arom), 5.94–5.77 (1H, m, CH-C13), 5.09 (1H, bdd, *J* = 6.7, 1.5 Hz, CH_2-C14), 5.06 (1H, d, *J* = 1.5 Hz, CH_2- C14), 4.83 (1H, d, *J* = 11.1 Hz, CH_2 benz), 4.79 (1H, d, *J* = 10.8 Hz, CH_2 benz), 4.65 (1H, d, *J* = 11.1 Hz, CH_2 benz), 4.59 (1H, d, *J* = 13.0 Hz, CH_2 benz), (1H, d, *J* = 10.8 Hz, CH_2 benz), 4.61 (1H, d, *J* = 13.0 Hz, CH_2 benz), 3.75 (1H, d, *J* = 2.1 Hz, CH_2-C6), 3.72 (1H, d, *J* = 2.1 Hz, CH_2-C6), 4.70 (1H, d, *J* = 4.3 Hz, CH), 3.69–3.63 (2H, m, 2 × CH), 3.51–3.36 (2H, m, 2 × CH), 2.40–2.30 (1H, m, CH_2-C12), 2.28 (1H, dt, *J* = 14.3, 7.0 Hz, CH_2-C12); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{13} 160.5 (CH-C15), 138.3 (C-C arom), 138.1 (C-C arom), 138.0 (C-C arom), 133.7 (CH-C13), 128.6 (2 × CH arom), 128.6 (2 × CH arom), 128.5 (2 × CH arom), 128.2 (2 × CH arom), 128.1 (2 × CH arom), 128.0 (CH arom), 128.0 (CH arom), 127.9 (2 × CH arom), 127.8 (CH arom), 117.8 (CH_2-C14), 84.3 (CH), 79.3 (CH), 78.5 (CH), 77.1 (CH), 75.5 (CH_2-C7), 75.2 (CH_2-C7), 73.6 (CH_2-C7), 68.8 (CH_2-C6), 36.0 (CH_2-C12).

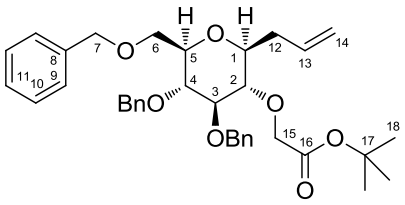
(2*S*,3*S*,4*S*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-(2,2-dibromovinyloxy) tetrahydro-2*H*-pyran (353)



CBr_4 (1.05 g, 3.17 mmol), in CH_2Cl_2 (3 mL), was added dropwise to a solution of the formate **354** (530 mg, 1.06 mmol) and PPh_3 (1.66 g, 6.33 mmol) in CH_2Cl_2 (5 mL) at 0 °C. This mixture was then stirred at 0 °C for 15 min and a further 4 h at room

temperature. Once the reaction reached completion, the reaction mixture was poured into petroleum ether (30 mL) and applied directly to a short plug of neutralised silica gel. The crude product was so purified by flash column chromatography (petroleum ether-Et_2O, 95:5 to 85:15) to afford dibromo-olefin **353** (0.669 g, 96% yield over two steps) as a colourless solid. R_f 0.60 (petroleum ether-Et_2O, 4:1); $[a]_D^{26}$ 32.1 (*c* = 1.26 in $CHCl_3$); ν_{max} (neat) 3063, 3032, 2909, 2862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.24 (13H, m, CH-C arom), 7.20 (2H, dd, *J* = 7.3, 1.9 Hz, CH-C arom), 6.97 (1H, s, CH-C15), 5.89 (1H, dddd, *J* = 16.7, 10.4, 7.5, 6.1 Hz, CH-C13), 5.14 (1H, d, *J* = 7.5 Hz, CH_2-C14), 5.11 (1H, s, CH_2-C14), 4.83 (1H, d, *J* = 11.0 Hz, CH_2 benz), 4.80 (1H, d, *J* = 11.0 Hz, CH_2 benz), 4.70 (1H, d, *J* = 10.4 Hz, CH_2 benz), 4.61 (1H, d, *J* = 12.2 Hz, CH_2 benz), 4.58 (1H, d, *J* = 10.4 Hz, CH_2 benz), 4.54 (1H, d, *J* = 12.2 Hz, CH_2 benz), 3.74–3.63 (3H, m, CH-C1 to CH-C6), 3.58 (2H, td, *J* = 9.3, 1.8 Hz, CH-C1 to CH-C6), 3.50–3.46 (1H, m, CH-C1 to CH-C6), 3.43 (1H, ddd, *J* = 9.7, 4.0, 1.9 Hz, CH-C1 to CH-C6), 2.60–2.50 (1H, m, CH_2-C12), 2.31 (1H, dt, *J* = 14.6, 7.5 Hz, CH_2-C12). ^{13}C NMR (100 MHz, $CDCl_3$) δ_{13} 148.8 (CH-C15), 138.3 (C-C arom), 138.1 (C-C arom), 137.8 (C-C arom), 133.7 (CH-C13), 128.8 (2 × CH arom), 128.6 (2 × CH arom), 128.6 (2 × CH arom), 128.5 (2 × CH arom), 128.1 (CH arom), 128.0 (3 × CH arom), 127.9 (2 × CH arom), 127.8 (CH arom), 118.2 (CH_2-C14), 85.6 (CH), 84.5 (CH), 79.2 (CH), 78.3 (CH), 77.2 (CH), 76.0 (CH_2-C7), 75.2 (CH_2-C7), 73.6 (CH_2-C7), 70.8 (C-C16), 68.3 (CH_2-C6), 35.7 (CH_2-C12); HRMS (FAB/NOBA) calcd for $C_{32}H_{35}O_5Br_2$ ($[M+H]^+$) 657.0852, found 659.0828 for $C_{32}H_{35}O_5{}^{79}Br^{81}Br$.

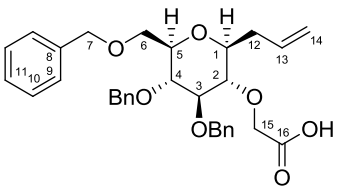
(1*S*,3*R*,4*S*,6*R*)-(2-Allyl-4,5-bis-benzyloxy-6-benzyloxymethyl-tetrahydro-2*H*-pyran-3-yloxy) -acetic acid *tert*-butyl ester (375)



To a solution of alcohol **348** (2.00 g, 4.21 mmol) in toluene (10 mL) at 0 °C was added tetrabutylammonium hydrogensulfate (286 mg, 0.842 mmol) followed by a saturated aqueous solution of NaOH (8.4 mL). The mixture was stirred at 0 °C for 5 min and *tert*-butyl bromoacetate was added. The reaction mixture was stirred at room temperature for 2.5 h. The solvent was evaporated *in vacuo* and water was added (2 mL). The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 95:5 to 80:20) to

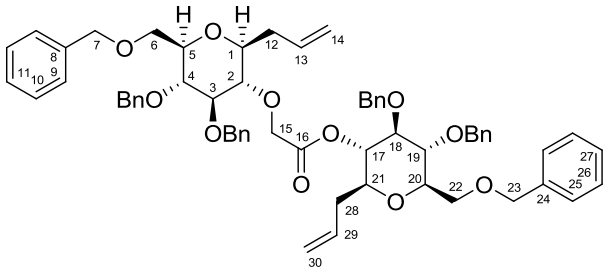
deliver **375** (2.43 g, 98% yield) as a colourless oil. R_f 0.62 (petroleum ether-Et_2O, 1:1); $[a]_D^{27}$ −1.4 (*c* = 1.40 in $CHCl_3$); ν_{max} (neat) 2905, 2861, 1751, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.44–7.07 (15H, m, CH-C arom), 5.95 (1H, dddd, *J* = 17.2, 10.1, 7.4, 6.7 Hz, CH-C13), 5.12 (1H, dd, *J* = 17.2, 1.9 Hz, CH_2- C14), 5.08 (1H, dd, *J* = 10.1, 1.9 Hz, CH_2- C14), 4.90 (1H, d, *J* = 10.9 Hz, CH_2-benz), 4.85 (1H, d, *J* = 10.9 Hz, CH_2-benz), 4.79 (1H, d, *J* = 10.6 Hz, CH_2-benz), 4.62 (1H, d, *J* = 12.4 Hz, CH_2-benz), 4.57 (1H, d, *J* = 10.6 Hz, CH_2-benz), 4.56 (1H, d, *J* = 12.4 Hz, CH_2-benz), 4.30 (1H, d, *J* = 15.6 Hz, CH_2-C15), 4.17 (1H, d, *J* = 15.6 Hz, CH_2-C15), 3.75–3.63 (3H, m, CH_2-C6 and CH-C5), 3.56 (1H, t, *J* = 9.4 Hz, CH-C2), 3.44–3.35 (2H, m, CH-C1 and CH-C3), 3.17 (1H, t, *J* = 9.2 Hz, CH-C4), 2.76–2.62 (1H, m, CH_2-C12), 2.37 (1H, dt, *J* = 14.8, 7.4 Hz, CH_2-C12), 1.44 (9H, s, CH_3-C18). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.1 (C-C16), 138.6 (C-C arom and CH-C arom), 138.4 (C-C arom and CH-C arom), 138.2 (C-C arom and CH-C arom), 134.9 (CH-C13), 128.5-127.6 128.4–127.4 (12 × CH arom), 117.1 (CH_2-C14), 87.1 (CH-C5), 82.4 (CH-C4), 81.5 (C-C17), 79.1 (CH-C1), 78.7 (CH-C2), 78.4 (CH-C3), 75.4 (CH_2 benz), 75.0 (CH_2 benz), 73.5 (CH_2 benz), 70.9 (CH_2-C15), 69.0 (CH_2-C6), 36.2 (CH_2-C12), 30.4 (3 × CH_3-C18); HRMS (CI+, isobutane) calcd for $C_{36}H_{45}O_7$ ($[M]^+$) 589.3087, found 589.3065.

2-[(2*S*,3*S*,4*R*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-3-yloxy]acetic acid (374)



Tert-butyl ester **375** (1.65 g, 2.80 mmol) was dissolved in a solution of TFA (4.2 mL, 56.0 mmol) in CH_2Cl_2 (4.16 mL). The mixture was stirred for 1 h, co-evaporated with toluene (3 × 10 mL) and concentrated *in vacuo*. The resulting residue was dissolved in Et_2O (10 mL) and basified using a saturated aqueous solution of $NaCO_3$. The organic phase was then separated and the aqueous phase was acidified with a 10% aqueous HCl solution and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford crude product **374** (1.51 g, quantitative yield) as a colourless oil. R_f 0.052 (petroleum ether-Et_2O, 2:1); Note: due to the sensitive nature of product **374**, full analytical data could not be obtained. Diagnostic features include: Crude ^1H NMR (400 MHz, $CDCl_3$) δ_H disappearance of 1.44 (9H, s, CH_3-C18), indicating the loss of *t*Bu functionality. LRMS (FAB/NOBA) calcd for $C_{32}H_{36}O_7$ ($[M+H]^+$) 532.6, found 532.8.

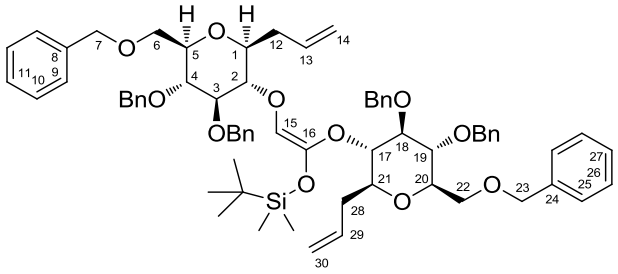
(2*S*,3*S*,4*S*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-3-yl 2-[(2*S*,3*S*,*4R*,5*R*,6*R*)-2-allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl) tetrahydro-2*H*-pyran-3-yloxy]acetate (373)



DCC (339 mg, 1.64 mmol) was added to a solution of alcohol **348** (519 mg, 1.10 mmol), carboxylic acid **374** (700 mg, 1.31 mmol), and DMAP (53.6 mg, 0.438 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was stirred at room temperature overnight, then filtered *in vacuo*. The filtrate was washed with H_2O (6 mL) and brine (6 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on neutralised silica gel (petroleum ether-Et_2O, 95:5 to 50:50) to afford ester product **373** (0.952 g, 88% yield) as a colourless solid. R_f 0.5 (petroleum ether-Et_2O, 1:1); ^{1}H NMR (400 Hz, $CDCl_3$) δ_H 7.36–7.09 (30H, m, CH-C arom), 5.99–5.76 (2H, m, CH-C13 and CH-C29), 5.09 (2H, d, *J* = 16.0 Hz, CH_2-C14 and CH_2-C30), 5.04 (2H, d, 8.6 Hz, CH_2-C14 and CH_2-C30), 4.97 (1H, t, *J* = 9.1 Hz, CH-C1 to CH_2-C6 and CH-C17 to CH_2-C22), 4.86 (1H, d, *J* = 11.3 Hz, CH_2 benz), 4.74 (1H, d, *J* = 10.7 Hz, CH_2 benz), 4.73 (2H, d, *J* = 11.0 Hz, CH_2 benz), 4.69 (1H, d, *J* = 11.8 Hz, CH_2 benz), 4.62 (1H, d, *J* = 12.3 Hz, CH_2 benz), 4.61 (1H, d, *J* = 12.3 Hz, CH_2 benz), 4.59–4.50 (5H, m, CH_2 benz), 4.26 (1H, d, *J* = 16.0 Hz, CH_2-C15), 4.21 (1H, d, *J* = 16.0 Hz, CH_2-C15) 3.78–3.51 (8H, m, CH-C1 to CH_2-C6 and CH-C17 to CH_2-C22), 3.46–3.29 (4H, m, CH-C1 to CH_2-C6 and CH-C17 to CH_2-C22), 3.18 (1H, t, *J* = 9.1 Hz, CH-C1 to CH_2-C6 and CH-C17 to CH_2-C22), 2.77–2.61 (1H, m, CH_2-C12), 2.35 (1H, dt, *J* = 14.7, 7.4 Hz, CH_2-C12), 2.26 (2H, t, *J* = 6.2 Hz CH_2-C28); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.0 (C-C16), 138.5 (2 × C-C arom), 138.4 (2 × C-C arom), 138.4 (2 × C-C arom), 138.3 (2 × C-C arom), 138.1 (2 × C-C arom), 138.1 (2 × C-C arom), 135.0 (CH-C13 and CH-C29), 133.9 (CH-C13 and CH-C29), 128.5 (CH arom), 128.5 (CH arom), 128.5 (CH arom), 128.1 (CH arom), 128.0 (CH arom), 127.9 (CH arom), 127.9 (CH arom), 127.9 (CH arom), 127.8 (CH arom), 127.8 (CH arom), 127.7 (CH arom), 127.7 (CH arom), 127.5 (CH arom), 117.4 (CH_2-C14 and CH_2-C30), 117.1 (CH_2-C14 and CH_2-C30), 87.2 (CH-C1 to CH-C5), 84.3 (CH-C1 to CH-C5), 82.4 (CH-C1 to CH-C5), 79.4 (CH-C1 to CH-C5), 79.1 (CH-C1 to CH-C5), 78.8 (CH-C1 to CH-C5), 78.5 (CH-C1 to CH-C5), 78.4 (CH-C1 to CH-C5), 77.3 (CH-C1 to CH-C5), 75.3 (CH_2-benz), 75.1 (CH_2-benz), 75.0 (CH_2-benz), 74.3 (CH-C1 to CH-C5), 73.6 (CH_2-benz), 70.1(CH_2-C15), 69.0 (CH_2-C6 and CH_2-

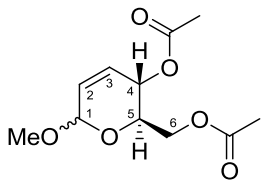
C22), 36.4 (CH_2-C12), 36.2 (CH_2-C28); HRMS (FAB/NOBA/NaI) calcd 1011.4659 for $C_{62}H_{68}O_{11}Na$ ($[M+Na]^+$), found 1011.4662.

{(*E*)-1,2-Bis[(2*S*,3*S*,4*S*,5*R*,6*R*)-2-allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)tetra hydro-*2H*-pyran-3-yloxy]vinyloxy}(*tert*-butyl) dimethylsilane (380)



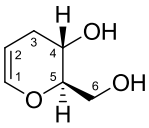
n-BuLi (0.25 mL of a 2.5 M solution in hexanes, 0.62 mmol) was added to a solution of diisopropylamine (80 µL, 0.61 mmol) in THF (2 mL) at −78 °C and the mixture was allowed to warm to room temperature over 1 h. This solution was then added dropwise to a solution of **373** (150 mg, 0.152 mmol) in CH_2Cl_2 (2 mL) at −78 °C and stirred at 0 °C for 1 h. The reaction was quenched with H_2O (4 mL) and the mixture was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on neutralised silica gel (petroleum ether-Et_2O, 95:5 to 50:50) to afford the desired product **380** (74.9 mg, 45% yield) as a yellow oil. To note: Rapid decomposition of this compound upon isolation, prevented any further analysis. R_f 0.71 (petroleum ether−Et_2O, 1:1); ^1H NMR (400 Hz, $CDCl_3$) δ_H 7.34−6.98 (30H, m, CH-C arom), 5.94 (2H, m, CH-C13 and CH-C29), 5.12 (4H, m, CH_2-C14 and CH_2-C30), 5.02−4.48 (13H, CH_2 benz and CH-C15), 3.66 (7H, m, CH-C1 to CH_2-C6 and CH-C17 to CH_2-C22), 3.42 (5H, m, CH-C1 to CH_2-C6 and CH-C17 to CH_2-C22), 3.21 (2H, m, CH-C1 to CH_2-C6 and CH-C17 to CH_2-C22), 2.60 (2H, m, CH_2-C12 and CH_2-C28), 2.29 (1H, m, CH_2-C12 and CH_2-C28), 2.26 (2H, m, CH_2-C12 and CH_2-C28), 0.18 (3H, s, CH_3-*t*Bu), 0.08 (6H, s, CH_3-*t*Bu), 0.02 (3H, s, CH_3-Me), 0.01 (3H, s, CH_3-Me).

[(2*R*,3*S*)-3-Acetoxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl]methyl acetate (395)[203]



To a solution of tri-*O*-acetyl-D-glucal **349** (25.0 g, 91.8 mmol) in CH_2Cl_2 (115 mL) was added dropwise methanol (4.09 mL, 101 mmol) and boron trifluoride diethyl etherate (5.00 mL, 40.4 mmol). The reaction mixture was stirred for 75 min at room temperature. A saturated aqueous solution of $NaHCO_3$ (150 mL) was added and the reaction mixture was diluted with H_2O (300 mL) and CH_2Cl_2 (300 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 300 mL) and the combined organic phases were washed with brine (400 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The brown oil was filtered through a small plug of silica (petroleum ether-EtOAc, 1:1) followed by concentration of the filtrate *in vacuo*, affording mixed acetal **395** as a colourless oil, which was used directly in the next step.

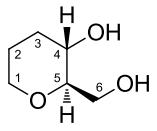
(2*R*,3*S*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-pyran-3-ol (396)[183]



A suspension of $LiAlH_4$ (6.96 g, 183.7 mmol) in dioxane (400 mL) was heated to reflux and a solution of mixed acetal **395** in dioxane (200 mL) was added dropwise over a period of 20 min. The resulting mixture was stirred overnight, then cooled to 0 °C and carefully diluted with Et_2O (270 mL). The reaction was then quenched by dropwise addition of with H_2O (7 mL), followed by a solution of NaOH (6 M, 7 mL) and further H_2O (14 mL). The reaction mixture was allowed to warm to room temperature, followed by addition of $MgSO_4$ (10.0 g) and stirring for 30 min. The resulting mixture was filtered through a Celite® pad and the filtrate was concentrated *in vacuo* to afford diol **396** (11.0 g, 92% yield over two steps) as a colourless oil. R_f 0.50 (EtOAc); $[\alpha]_D^{26}$ +80.4 (*c* = 1.1, in $CHCl_3$); ν_{max} (neat) 3345, 2923, 2883, 2852, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.35–6.30 (1H, m, CH-C1), 4.68 (1H, ddd, *J* = 6.3, 5.1, 2.6 Hz, CH-C2), 3.99 (1H, tt, *J* = 8.5, 5.6 Hz, CH-C4), 3.92–3.87 (2H, m, CH_2-C6), 3.69 (1H, dt, *J* = 8.5, 4.2 Hz, CH-C5), 2.35 (1H, ddd, *J* = 12.5, 5.6, 1.6 Hz, CH_2-C3), 2.35 (1H, d, *J* = 5.6 Hz, OH), 2.11 (1H, t, *J* = 6.3 Hz, OH), 2.11–2.03 (1H, m, CH_2-C3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 142.90 (CH-C1),

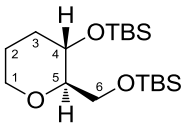
98.38 (CH-C2), 78.64 (CH-C5), 64.82 (CH-C4), 62.56 (CH_2-C6), 29.35 (CH_2-C3); HRMS (EI+) for $C_6H_{10}O_3$ ($[M+H]^+$): 130.0630, found 130.0633.

(2*R*,3*S*)-2-(Hydroxymethyl)tetrahydro-2*H*-pyran-3-ol (397)[45]



Pd/C (5%, 4.89 g) was added to a solution of diol **396** (11.0 g, 84.6 mmol) in EtOAc (400 mL) at room temperature. The resulting suspension was placed under a H_2 atmosphere and stirred overnight. Once the reaction reached completion, the mixture was filtered through Celite®, washed with EtOAc (5 × 100 mL) and the filtrate was concentrated *in vacuo* affording diol **397** (10.7 g, 96% yield) as a colourless oil. R_f 0.21 (EtOAc); $[a]_D^{23}$ +28.7 (*c* = 1.8, in $CHCl_3$), Lit. $[a]_D^{20}$ +33.3 (*c* = 5.20, in CH_2Cl_2)[45]; ν_{max} (neat) 3345, 2935, 2859 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 3.95–3.88 (1H, m, CH_2-C1), 3.80 (2H, qd, *J* = 11.6, 4.4 Hz, CH_2-C6), 3.55 (1H, ddd, *J* = 10.9, 9.2, 4.7 Hz, CH-C4), 3.38–3.33 (1H, m, CH_2-C1), 3.12 (1H, dt, *J* = 9.2, 4.4 Hz, CH-C5), 2.84 (2H, bs, OH), 2.11 (1H, ddd, *J* = 12.3, 4.7, 1.4 Hz, CH_2-C3), 1.67 (2H, qd, *J* = 8.1, 3.9 Hz, CH_2-C2), 1.43 (1H, ddd, *J* = 12.3, 10.9, 8.1 Hz, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{13} 81.9 (CH-C5), 67.8 (CH_2-C1), 67.4 (CH-C4), 63.3 (CH_2-C6), 32.6 (CH_2-C3), 25.5 (CH_2-C2); HRMS (CI+, isobutane) for $C_6H_{13}O_3$ ($[M+H]^+$): 132.0865, found 133.0863.

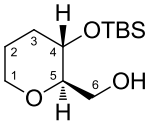
***Tert*-butyl(2*R*,3*S*)-2-[(*tert*-butyldimethylsilyloxymethyl)tetrahydro-2H-pyran-3-yloxy]dimethylsilane (404)[45]**



TBSCl (7.19 g, 47.1 mmol), was added to a solution of diol **397** (2.07 g, 15.7 mmol), imidazole (4.28 g, 62.3 mmol) and DMAP (384 mg, 3.14 mmol) in DMF (52 mL) at 0 °C. The resulting mixture was stirred at room temperature overnight. The reaction was cooled to 0 °C and quenched with H_2O (50 mL). The product was then extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 95:5 to 90:10) to afford

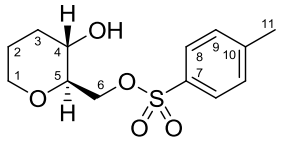
the desired product **404** (5.67 g, quantitative yield) as a colourless oil. R_f 0.95 (petroleum ether-EtOAc, 1:1); $[a]_D^{26}$ +43.6 (*c* = 1.0, in $CHCl_3$), Lit. $[a]_D^{20}$ +36.4 (*c* = 6.70, in CH_2Cl_2)[45]; ν_{max} (neat) 2954, 2929, 2886, 2857 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 3.88 (1H, dd, *J* = 11.2, 1.9 Hz, CH_2-C6), 3.93–3.85 (1H, m, CH_2-C1), 3.66 (1H, dd, *J* = 11.2, 6.1 Hz, CH_2-C6), 3.49–3.40 (1H, m, CH-C4), 3.36–3.27 (1H, m, CH_2-C1), 3.08 (1H, ddd, *J* = 8.6, 6.1, 1.9 Hz, CH-C5), 1.99 (1H, dtd, *J* = 11.6, 4.8, 3.1 Hz, CH_2-C3), 1.66–1.56 (2H, m, CH_2-C2), 1.42 (1H, tdd, *J* = 11.6, 7.3, 5.4 Hz, CH_2-C3), 0.89 (9H, s, CH_3-*t*Bu), 0.87 (9H, s, CH_3-*t*Bu), 0.07 (3H, s, CH_3-Me), 0.06 (3H, s, CH_3-Me), 0.05 (6H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{13} 83.8 (CH-C5), 67.6 (CH_2-C1), 67.4 (CH-C4), 64.0 (CH_2-C6), 33.6 (CH_2-C3), 26.2 (3 × CH_3-*t*Bu), 25.9 (3 × CH_3-*t*Bu), 25.6 (CH_2-C2), 18.7 (C-*t*Bu), 18.1 (C-*t*Bu), –4.0 (CH_3-Me), –4.7 (CH_3-Me), –4.8 (CH_3-Me), –5.0 (CH_3-Me); HRMS (CI+, isobutane) for $C_{18}H_{41}O_3Si_2$ ($[M+H]^+$): 361.2594, found 361.2595.

((2*R*,3*S*)-3-((*Tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-yl)methanol (405)[45]



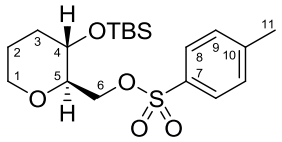
Camphorsulfonic acid (82.8 mg, 0.356 mmol) was added to a solution of **404** (428 mg, 1.19 mmol) in a mixture of CH_2Cl_2 (6.5 mL) and MeOH (6.5 mL) at 0 °C and the resulting mixture was stirred for 2.5 h at this temperature. The reaction was then quenched with Et_3N (0.4 mL, 0.6 mmol) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 95:5 to 70:30) to afford the desired product **405** (293 mg, quantitative yield) as a thick colourless oil. R_f 0.42 (petroleum ether-EtOAc, 2:1); $[a]_D^{27}$ +52.4 (*c* = 1.00, in $CHCl_3$), Lit. $[a]_D^{21}$ +50.3 (*c* = 1.01, in $CHCl_3$)[204]; ν_{max} (neat) 3489, 2930, 2886, 2857 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 3.91 (1H, ddt, *J* = 11.2, 3.8, 1.8 Hz, CH_2-C1), 3.83 (1H, ddd, *J* = 11.4, 6.2, 2.2 Hz, CH_2-C6), 3.61 (1H, dt, *J* = 11.4, 6.2 Hz, CH_2-C6), 3.48 (1H, ddd, *J* = 10.6, 9.0, 4.7 Hz, CH-C4), 3.37 (1H, ddd, *J* = 11.2, 7.9, 4.9 Hz, CH_2-C1), 3.14 (1H, ddd, *J* = 9.0, 6.2, 2.2 Hz, CH-C5), 2.05–2.01 (1H, m, CH_2-C3), 2.00 (1H, t, *J* = 6.2 Hz, OH), 1.65 (2H, tdd, *J* = 11.7, 7.9, 3.8 Hz, CH_2-C2), 1.50–1.40 (1H, m, CH_2-C3), 0.87 (9H, s, CH_3-*t*Bu), 0.06 (6H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_{13} 82.7 (CH-C5), 68.2 (CH-C4), 67.8 (CH_2-C6), 63.3 (CH_2-C1), 33.5 (CH_2-C3), 25.9 (3 × CH_3-*t*Bu), 25.7 (CH_2-C2), 18.1 (C-*t*Bu), −3.9 (CH_3-Me), −4.7 (CH_3-Me); HRMS (CI+, isobutane) for $C_{12}H_{27}O_3Si$ ($[M+H]^+$): 247.1730, found 247.1732.

[(2*R*,3*S*)-3-hydroxytetrahydro-2*H*-pyran-2-yl]methyl 4-methylbenzenesulfonate (401)[184,205]



p-Toluenesulfonyl chloride (433 mg, 2.27 mmol) was added to a solution of **397** (300 mg, 2.27 mmol), Et_3N (0.48 mL, 3.4 mmol) and DMAP (27.7 mg, 0.227 mmol) in CH_2Cl_2 (23 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 8 h and then quenched with H_2O (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 50:50) to afford the desired product **401** (486 mg, 75% yield) as a yellowish oil. R_f 0.26 (EtOAc); $[a]_D^{26}$ +25.4 (*c* = 1.00, $CHCl_3$), Lit. $[a]_D^{25}$ +8.5 (*c* = 2.62, $CHCl_3$)[206]; ν_{max} (neat) 3464, 2930, 2855, 1597 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.81 (2H, d, *J* = 8.4 Hz, CH-C8), 7.34 (2H, d, *J* = 8.2 Hz, CH-C9), 4.36 (1H, dd, *J* = 11.1, 4.4 Hz, CH_2-C6), 4.19 (1H, dd, *J* = 11.1, 2.0 Hz, CH_2-C6), 3.89 (1H, ddt, *J* = 11.4, 4.0, 2.0 Hz, CH_2-C1), 3.63–3.53 (1H, m, CH-C4), 3.34–3.26 (1H, m, CH_2-C1), 3.21 (1H, ddd, *J* = 9.3, 4.4, 2.0 Hz, CH-C5), 2.45 (3H, s, CH_3-C11), 2.18–2.09 (1H, m, CH_2-C3), 1.66 (2H, qd, *J* = 5.9, 3.3 Hz, CH_2-C2), 1.48–1.36 (1H, m, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 145.1 (C-C7), 133.0 (C-C10), 130.0 (2 × CH-C9), 128.1 (2 × CH-C8), 80.3 (CH-C5), 69.8 (CH_2-C6), 68.1 (CH_2-C1), 65.9 (CH-C4), 32.5 (CH_2-C3), 25.4 (CH_2-C2), 21.8 (CH_3-C11); HRMS (CI+, isobutane) for $C_{13}H_{19}O_5S$ ($[M+H]^+$): 287.0953, found 287.0950.

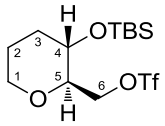
[(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl]methyl 4-methylbenze-nesulfonate (402)[207]



TBSOTf (0.78 mL, 3.4 mmol), was added to a solution of alcohol **401** (486 mg, 1.70 mmol) and 2,6-lutidine (0.59 mL, 5.1 mmol) in CH_2Cl_2 (16 mL) at 0 °C. The resulting mixture was stirred for 1 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL). The product was then extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude

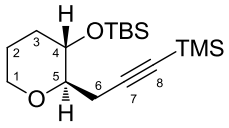
product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 70:30) to afford the desired product **402** (682 mg, quantitative yield) as a colourless oil. R_f 0.83 (petroleum ether-Et_2O, 2:1); $[\alpha]_D^{26}$ +25.4 (*c* = 1.9, $CHCl_3$); ν_{max} (neat) 2955, 2928, 2855, 1746, 1599 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.3 Hz, CH-C8), 7.32 (2H, d, *J* = 8.0 Hz, CH-C9), 4.22 (1H, dd, *J* = 10.2, 2.0 Hz, CH_2-C6), 4.07 (1H, dd, *J* = 10.2, 6.1 Hz, CH_2-C6), 3.87–3.80 (1H, m, CH_2-C1), 3.41 (1H, ddd, *J* = 9.8, 9.3, 4.4 Hz, CH-C4), 3.30–3.19 (2H, m, CH_2-C1 and CH-C5), 2.43 (3H, s, CH_3-C11), 2.01 (1H, ddd, *J* = 12.5, 7.5, 4.4 Hz, CH_2-C3), 1.59 (2H, dt, *J* = 9.8, 4.4 Hz, CH_2-C2), 1.39 (1H, dtd, *J* = 12.5, 9.8, 4.4 Hz, CH_2-C3), 0.81 (9H, s, CH_3-*t*Bu), 0.03 (3H, s, CH_3-Me), 0.01 (3H, s, CH_3-Me); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.69 (C-C7), 133.2 (C-C10), 129.8 (2 × CH-C9), 128.2 (2 × CH-C8), 80.3 (CH-C5), 70.3 (CH_2-C6), 67.8 (CH_2-C1), 67.1 (CH-C4), 33.4 (CH_2-C3), 25.8 (3 × CH_3-*t*Bu), 25.2 (CH_2-C2), 21.8 (CH_3-C11), 17.9 (C-*t*Bu), –3.8 (CH_3-Me), –4.9 (CH_3-Me); HRMS (CI+, isobutane) for $C_{19}H_{33}O_5SiS$ ($[M+H]^+$): 401.1818, found 401.1810.

{(2*R*,3*S*)-3-[(*Tert*-butyldimethylsilyl)oxy]tetrahydro-2*H*-pyran-2-yl}methyltrifluoro methanesulfonate (5)[12]



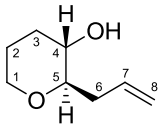
Triflic anhydride (0.58 mL, 3.5 mmol), was added to a solution of alcohol **405** (426 mg, 1.73 mmol) and 2,6-lutidine (0.60 mL, 5.2 mmol) in CH_2Cl_2 (3.5 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 30 min the reaction was then quenched with H_2O (2 mL). The product was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with a saturated solution of Cu_2SO_4 (2 × 5 mL), H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was filtered through a small plug of silica (petroleum ether-EtOAc, 95:5) to afford the unstable product **5** (613 mg, 94% yield) as a yellow oil. R_f 0.70 (petroleum ether−EtOAc, 4:1); ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.72 (1H, dd, *J* = 10.4, 1.8 Hz, CH_2-C6), 4.55 (1H, dd, *J* = 10.4, 5.6 Hz, CH_2-C6), 3.41−3.35 (1H, m, CH_2-C1), 3.49 (1H, ddd, *J* = 10.3, 9.2, 4.8 Hz, CH-C4), 3.36 (1H, ddd, *J* = 11.1, 9.5, 2.8 Hz, CH_2-C1), 3.40−3.31 (1H, m, CH-C5), 2.13−2.04 (1H, m, CH_2-C3), 1.72−1.63 (2H, m, CH_2-C2), 1.46 (1H, dtd, *J* = 17.0, 10.3, 4.8 Hz, CH_2-C3), 0.88 (9H, s, CH_3-*t*Bu), 0.08 (3H, s, CH_3-Me), 0.07 (3H, s, CH_3-Me); ^{19}F NMR (400 MHz, $CDCl_3$) δ_F −74.60 (CF_3).

***Tert*-butyldimethyl(2*R*,3*S*)-2-[3-(trimethylsilyl)prop-2-yn-1-yl]tetrahydro-*2H*-pyran-3-yloxysilane (403)[208]**



n-BuLi (2.20 mL of a 2.5 M solution in hexanes, 5.60 mmol) was added to a solution of trimethylsilylacetylene (0.80 mL, 5.6 mmol) in THF (10 mL) at −78 °C and the mixture was stirred at 0 °C for 30 min. A solution of triflate **5** (544 mg, 1.44 mmol) in THF (10 mL) was then added, followed by DMPU (2.1 mL). After 1 h at 0 °C, EtOAc (4 mL) was added and the reaction mixture was allowed to warm to room temperature. The mixture was diluted with Et_2O (10 mL), washed with a saturated aqueous solution of NH_4Cl (6 mL) dried over $MgSO_4$ and concentrated *in vacuo*, affording the unstable protected acetylene **403** as a yellowish oil, which was used directly in the next step. R_f 0.88 (petroleum ether-EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.96–3.89 (1H, m, CH_2-C1), 3.52 (1H, ddd, *J* = 10.7, 8.8, 4.7 Hz, CH-C4), 3.34 (1H, td, *J* = 11.4, 3.1 Hz, CH_2-C1), 3.12 (1H, ddd, *J* = 8.8, 5.6, 3.4 Hz, CH-C5), 2.62 (1H, dd, *J* = 17.1, 3.4 Hz, CH_2-C6), 2.53 (1H, dd, *J* = 17.1, 5.6 Hz, CH_2-C6), 2.06–1.96 (1H, m, CH_2-C3), 1.75–1.60 (2H, m, CH_2-C2), 1.42 (1H, ddt, *J* = 12.7, 10.7, 4.9 Hz, CH_2-C3), 0.88 (9H, s, $SiMe_3$), 0.15 (9H, s, 3 × CH_3-Me), 0.10 (3H, s, CH_3-Me), 0.08 (3H, s, CH_3-Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 103.9 (C-C8), 86.1 (C-C7), 80.5 (CH-C5), 69.7 (CH-C4), 68.1 (CH_2-C1), 33.5 (CH_2-C3), 25.9 (3 × CH_3-*t*Bu), 25.6 (CH_2-C2), 23.7 (CH_2-C6), 18.1 (C-*t*Bu), 0.3 (3 × CH_3-Me), –3.9 (CH_3-Me), –4.6 (CH_3-Me).

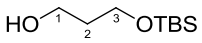
{[(2*R*,3*S*)-2-Allyltetrahydro-2*H*-pyran-3-yl]oxy}(*tert*-butyl)dimethylsilane (393)[55]



The silyl acetylene **403** (470 mg, 1.44 mmol) was dissolved in THF (16 mL), cooled to 0 °C and TBAF (4.9 mL of a 1 M solution in THF, 4.9 mmol) was added. The mixture was stirred for 18 h at room temperature and then cooled to 0 °C, and the reaction was quenched by careful addition of a saturated aqueous solution of NH_4Cl (4 mL). The mixture was diluted with EtOAc (15 mL), washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude terminal acetylene was reacted in the next step without further purification.

To a solution of the terminal acetylene (201 mg, 1.44 mmol) in EtOAc (10 mL) were added Lindlar's catalyst (5% Pd on $CaCO_3$, 11.7 mg), and quinoline (0.03 mL). The reaction vessel was then purged of air and filled with H_2. The mixture was stirred at room temperature for 1.5 h. The H_2 was then purged from the reaction vessel and the reaction mixture was filtered through Celite®. The filter cake was washed with Et_2O (3 × 10 mL) and the filtrate and washings were concentrated *in vacuo*. The resulting crude product was diluted with Et_2O (10 mL) and washed with 1 M aqueous HCl solution (10 mL). The solvent was removed *in vacuo*. The high volatility of this compound prevented complete evaporation of the solvent and therefore minor Et_2O signals were present in the ^{1}H-NMR at 3.47 (q) and 1.20 (t). Despite this, the yield of alcohol **393** was calculated to be 96% over three steps (198 mg). R_f 0.38 (petroleum ether-Et_2O, 3:1); $[\alpha]_D^{26}$ +23.4 (*c* = 1.30 in $CHCl_3$), Lit. $[\alpha]_D^{23}$ +22.6 (*c* = 1.14 in $CHCl_3$)[209]; ν_{max} (neat) 3392, 2934, 2927, 2855, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.93 (1H, ddt, *J* = 17.2, 10.2, 7.2 Hz, CH-C7), 5.14 (1H, ddd, *J* = 17.2, 2.9, 1.3 Hz, CH_2-C8), 5.08 (1H, ddt, *J* = 10.2, 2.9, 1.3 Hz, CH_2-C8), 3.94–3.87 (1H, m, CH_2-C1), 3.34 (1H, ddd, *J* = 14.7, 12.9, 5.7 Hz, CH_2-C1), 3.41–3.28 (1H, m, CH-C4), 3.11 (1H, ddd, *J* = 8.8, 7.2, 3.8 Hz, CH-C5), 2.58 (1H, dddt, *J* = 14.6, 7.2, 3.8, 1.3 Hz, CH_2-C6), 2.29 (1H, dtt, *J* = 14.6, 7.2, 1.3 Hz, CH_2-C6), 2.09 (1H, dqd, *J* = 6.4, 3.6, 1.7 Hz, CH_2-C3), 1.69–1.63 (2H, m, CH_2-C2), 1.44–1.37 (1H, m, CH_2-C3); HRMS (CI+, isobutane) for $C_8H_{15}O_2$ ($[M+H]^+$): 143.1072, found 143.1070.

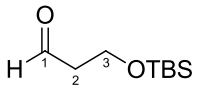
3-((*Tert*-butyldimethylsilyl)oxy)propan-1-ol (409)[210]



TBSCl (3.96 g, 26.3 mmol), was added to a solution of diol **408** (2.00 g, 26.3 mmol) and imidazole (3.76 g, 55.2 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The resulting mixture was stirred at room temperature for 4 h. The mixture was cooled to 0 °C and the reaction was quenched with H_2O (10 mL). The product was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 75:25) to afford the desired product **409** (4.15 g, 83% yield) as a colourless oil. R_f 0.78 (petroleum ether-EtOAc, 1:1); ν_{max} (neat) 3349, 2953, 2930, 2857 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.79 (2H, t, *J* = 5.7 Hz, CH_2-C1), 3.74 (2H, t, *J* = 5.7 Hz, CH_2-C3), 2.85 (1H, s, OH), 1.78–1.70 (2H, m, CH_2-C2), 0.86 (9H, s, CH_3-*t*Bu), 0.04 (6H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 62.6

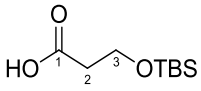
(CH_2-C1), 62.0 (CH_2-C3), 34.5 (CH_2-C2), 26.0 (CH_3-*t*Bu), 18.3 (C-*t*Bu), –5.4 (CH_3-Me); HRMS (CI+, isobutane) for $C_9H_{23}O_2Si$ ($[M+H]^+$): 191.1467, found 191.1469.

3-((*Tert*-butyldimethylsilyl)oxy)propanal (410)[186]



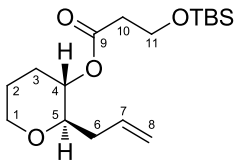
Pyridinum chlorochromate (1.73 g, 8.03 mmol) was added to a solution of alcohol **409** (764 mg, 4.02 mmol) in CH_2Cl_2 (16 mL) at room temperature. The resulting suspension was stirred overnight and then filtered through Celite®, washing with CH_2Cl_2 (3 × 10 mL). The filtrate was carefully concentrated *in vacuo* and the resulting volatile crude product was reacted directly in the subsequent step. R_f 0.76 (petroleum ether-EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.80 (1H, t, *J* = 2.0 Hz, CH-C1), 3.99 (2H, t, *J* = 6.0 Hz, CH_2-C3), 2.60 (2H, td, *J* = 6.0, 2.0 Hz, CH_2-C2), 0.88 (9H, s, CH_3-*t*Bu), 0.06 (6H, s, CH_3-Me).

3-((*Tert*-butyldimethylsilyl)oxy)propanoic acid (406)[186]



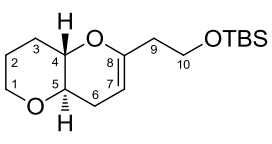
To a solution of aldehyde **409** (4.02 mmol) in *t*-BuOH (20 mL) and 2-methyl-2-butene (2.25 g, 32.1 mmol) was added a solution of $NaClO_2$ (2.18 g, 24.1 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (4.07 g, 24.1 mmol) in water (40 mL) dropwise. After stirring for 1 h, the reaction was partitioned between brine (30 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 75:25) to afford the desired product **406** (559 mg, 68% yield over two steps) as a colourless oil. R_f 0.57 (petroleum ether-EtOAc, 4:1); ν_{max} (neat) 3067, 2955, 2930, 2857, 1715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 11.03 (1H, bs, OH), 3.91 (2H, t, *J* = 6.2 Hz, CH_2-C3), 2.58 (2H, t, *J* = 6.2 Hz, CH_2-C2), 0.89 (9H, s, CH_3-*t*Bu), 0.08 (6H, s, CH_3-Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 176.7 (C-C1), 58.9 (CH_2-C2), 37.7 (CH_2-C3), 25.9 (3 × CH_3-*t*Bu), 18.4 (C-*t*Bu), –5.3 (CH_3-Me); HRMS (CI+, isobutane) for $C_9H_{21}O_3Si$ ($[M+H]^+$): 205.1261, found 205.1264.

(2*R*,3*S*)-2-Allyltetrahydro-2*H*-pyran-3-yl 3-[(*tert*-butyldimethylsilyl)oxy]propanoate (407)



DMAP (145 mg, 1.19 mmol) was added to a solution of alcohol **393** (29.0 mg, 0.203 mmol) and side-chain **406** (107 mg, 0.523 mmol) in CH_2Cl_2 (3.5 mL) at 0 °C. The resulting mixture was stirred at room temperature for 4 h. The mixture was cooled to 0 °C and the reaction was quenched with H_2O (5 mL). The product was then extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 95:5) to afford the desired product **407** (51.9 mg, 74% yield) as a colourless oil. R_f 0.83 (petroleum ether-EtOAc, 4:1); $[\alpha]_D^{25}$ +19.0 (*c* = 1.0 in $CHCl_3$); ν_{max} (neat) 2955, 2930, 2857, 1740, 1470 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 5.85 (1H, ddt, *J* = 17.2, 10.4, 6.9 Hz, CH-C7), 5.07 (1H, dd, *J* = 10.4, 1.8 Hz, CH_2-C8), 5.05−5.03 (1H, m, CH_2-C8), 4.59 (1H, ddd, *J* = 10.8, 10.0, 4.7 Hz, CH-C4), 3.95–3.90 (1H, m, CH_2-C1), 3.89 (2H, t, *J* = 6.3 Hz, CH_2-C10), 3.39–3.31 (1H, m, CH_2-C1), 3.32 (1H, ddd, *J* = 10.8, 6.1, 3.0 Hz, CH-C5), 2.50 (2H, t, *J* = 6.3 Hz, CH_2-C11), 2.42–2.34 (1H, m, CH_2-C6), 2.23–2.13 (2H, m, CH_2-C6 and CH_2-C3), 1.72 (1H, ddt, *J* = 12.7, 11.8, 4.2 Hz, CH_2-C2), 1.69–1.62 (1H, m, CH_2-C2), 1.45 (1H, tdd, *J* = 12.7, 10.0, 4.6 Hz, CH_2-C3), 0.89 (9H, s, CH_3-*t*Bu), 0.06 (6H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.9 (C-C9), 134.7 (CH-C7), 117.0 (CH_2-C8), 79.3 (CH-C5), 71.8 (CH-C4), 67.9 (CH_2-C1), 59.2 (CH_2-C10), 38.5 (CH_2-C11), 36.7 (CH_2-C6), 29.6 (CH_2-C3), 26.02 (3 × CH_3-*t*Bu), 25.36 CH_2-C2), 18.40 (C-*t*Bu), –5.26 (2 × CH_3-Me); HRMS (CI+, isobutane) for $C_{17}H_{33}O_4Si$ ($[M+H]^+$): 329.2148, found 329.2146.

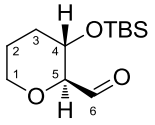
***Tert*-butyl(2-{(4a*R*,8a*S*)-4,4a,6,7,8,8a-hexahydropyrano[3,2-*b*]pyran-2-yl}ethoxy)dimethylsilane (392)**



An oven dried two-necked flask fitted with a condenser was cooled to 0 °C and charged with CH_2Cl_2 (1.8 mL) followed by $TiCl_4$ (0.086 mL, 0.78 mmol). To the resulting solution

was added THF (2.02 mL, 25.0 mmol) dropwise (solution turned yellow). TMEDA (3.74 mL, 25.0 mmol) was then added dropwise (solution turned brown). The ice bath was removed and the mixture was allowed to stir for 20 min. Activated Zn dust (612 mg, 9.36 mmol) and $PbCl_2$ (145 mg, 0.52 mmol) were added (colour changed over a 3 min period from brown, to green, then purple and finally to a dark blue-green). A solution of ester **407** (90.0 mg, 0.260 mmol) and CH_3CHBr_2 (0.380 mL, 4.16 mmol) in CH_2Cl_2 (1.8 mL) was then added at room temperature and the resulting reaction mixture was heated to reflux and stirred for 2 h. The mixture was then cooled to 0 °C and the reaction was quenched dropwise with a saturated aqueous solution of K_2CO_3 (3 mL). After stirring at 0 °C for 30 min, the resulting mixture was filtered through Celite®, washing with petroleum ether-EtOAc (1:1, 3 × 10 mL). The filtrate was concentrated *in vacuo* and the resulting crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 95:5) to afford the desired product **392** (32.9 mg, 74% yield) as a colourless oil. R_f 0.83 (petroleum ether-EtOAc, 1:9); $[a]_D^{23}$ –13.9 (*c* = 1.1 in $CHCl_3$); ν_{max} (neat) 2955, 2950, 2928, 2857, 1678, 1472, 1463 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 4.48 (1H, dd, *J* = 5.2, 1.8 Hz, CH-C7), 3.93 (1H, ddt, *J* = 11.4, 4.3, 1.5 Hz, CH_2-C1), 3.70 (2H, t, *J* = 6.9 Hz, CH_2-C10), 3.48–3.40 (2 × 1H, m, CH_2-C1 and CH-C4), 3.30 (1H, td, *J* = 9.6, 6.8 Hz, CH-C5), 2.25 (1H, dd, *J* = 14.7, 6.8 Hz, CH_2-C6), 2.21 (2H, t, *J* = 6.9 Hz, CH_2-C9), 2.18–2.10 (1H, m, CH_2-C3), 2.00 (1H, ddd, *J* = 14.7, 9.6, 1.8 Hz, CH_2-C6), 1.78 (1H, dt, *J* = 13.0, 4.3 Hz, CH_2-C2), 1.75–1.69 (1H, m, CH_2-C2), 1.52 (1H, tdd, *J* = 13.0, 11.6, 4.8 Hz, CH_2-C3), 0.89 (9H, s, CH_3-*t*Bu), 0.04 (6H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 151.3 (C-C8), 95.0 (CH-C7), 75.2 (CH-C5), 74.8 (CH-C4), 68.0 (CH_2-C1), 61.0 (CH_2-C9), 37.5 (CH_2-C10), 29.4 (CH_2-C3), 27.8 (CH_2-C6), 26.1 (3 × CH_3-*t*Bu), 25.5 (CH_2-C2), 18.5 (C-*t*Bu), –5.13 (2 × CH_3-Me); HRMS (CI+, isobutane) for $C_{16}H_{31}O_3Si$ ($[M+H]^+$): 299.2042, found 299.2039.

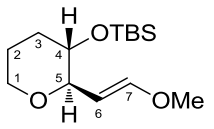
(2*S*,3*S*)-3-[(*Tert*-butyldimethylsilyl)oxy]tetrahydro-2*H*-pyran-2-carbaldehyde (417)[45,207]

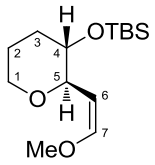


A solution of SO_3·py complex (1.91 g, 12.2 mmol) in DMSO (4.32 mL, 60.9 mmol) was added to a solution of alcohol **405** (1.00 g, 4.06 mmol) and Et_3N (2.80 mL, 20.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring at 0 °C for 3 h, the mixture was diluted with H_2O (10 mL) and allowed to warm to room temperature. The aqueous phase was further

extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and carefully concentrated *in vacuo*. The resulting crude product was quickly filtered through a small plug of silica (petroleum ether-EtOAc, 80:20) to afford the volatile product **417** (8.74 mg, 89% yield) as a yellow oil which was immediately reacted in the next step. R_f 0.48 (petroleum ether-EtOAc, 4:1); ν_{max} (neat) 2953, 2930, 2888, 2857, 1746 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 9.79 (1H, s, CH-C6), 4.03–3.96 (1H, m, CH_2-C1), 3.76–3.68 (2H, m, CH-C4 and CH-C5), 3.43–3.37 (1H, m, CH_2-C1), 2.12–2.05 (1H, m, CH_2-C3), 1.72–1.65 (2H, m, CH_2-C2), 1.58 (1H, ddd, *J* = 8.7, 7.0, 2.8 Hz, CH_2-C3), 0.88 (9H, s, CH_3-*t*Bu), 0.08 (3H, s, CH_3-Me), 0.05 (3H, s, CH_3-Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 199.8 (CH-C6), 85.7 (CH-C5), 68.1 (CH-C4), 67.5 (CH_2-C1), 33.8 (CH_2-C3), 25.8 (3 × CH_3-*t*Bu), 24.6 (CH_2-C2), 18.4 (C-*t*Bu), −3.9 (CH_3-Me), −4.8 (CH_3-Me); LRMS (CI+, isobutane) for $C_{12}H_{25}O_3Si$ ($[M+H]^+$): 245.1, found 245.1.

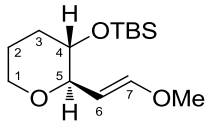
Tert-butyl{(2*R*,3*S*)-2-[(*E*)-2-methoxyvinyl]tetrahydro-2*H*-pyran-3-yloxy} dimethylsilane (418) and _Tert_-butyl{(2*R*,3*S*)-2-[(*Z*)-2-methoxyvinyl] tetrahydro-2*H*-pyran-3-yloxy}dimethylsilane (419)





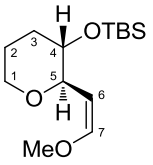
NaHMDS (0.95 mL of a 2 M solution in THF, 1.90 mmol) was added to a solution of (methoxymethyl)triphenylphosphonium chloride (760 mg, 2.22 mmol) in THF (3 mL) at 0 °C. After stirring for 1 h at 0 °C, a solution of **417** (155 mg, 0.633 mmol) in THF (5 mL) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction was then quenched by the addition of saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$ and carefully concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 98:2) to afford the desired products **418** and **419** (86.7 mg, 50% yield as a 1:1 mixture of *E*/*Z* isomers) as a colourless oil. $[\alpha]_D^{23}$ +9.5 (*c* = 1.3 in $CHCl_3$) for the isomeric mixture. Small samples of each *E* and *Z* products were isolated for characterisation purposes.

***Tert*-butyl{(2*R*,3*S*)-2-[(*E*)-2-methoxyvinyl]tetrahydro-2*H*-pyran-3-yloxy]dimethylsilane (418)**



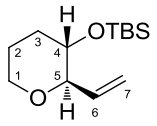
R_f 0.78 (petroleum ether-EtOAc, 4:1); ^{1}H NMR (500 Hz, $CDCl_3$) δ_H 6.54 (1H, d, *J* = 12.7 Hz, CH-C7), 4.74 (1H, dd, *J* = 12.7, 8.5 Hz, CH-C6), 3.92–3.87 (1H, m, CH_2-C1), 3.54 (3H, s, CH_3-OMe), 3.41 (1H, t, *J* = 8.5 Hz, CH-C5), 3.37 (1H, td, *J* = 11.4, 3.3 Hz, CH_2-C1), 3.31 (1H, ddd, *J* = 10.4, 8.5, 4.8 Hz, CH-C4), 2.04 (1H, qdd, *J* = 4.8, 3.6, 1.9 Hz, CH_2-C3), 1.71–1.61 (2H, m, CH_2-C2), 1.50–1.44 (1H, m, CH_2-C3), 0.88 (9H, s, CH_3-*t*Bu), 0.05 (3H, s, CH_3-Me), 0.04 (3H, s, CH_3-Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 151.2 (CH-C7), 102.6 (CH-C6), 81.7 (CH-C5), 71.9 (CH-C4), 67.8 (CH_2-C1), 55.8 (CH_3-OMe), 34.0 (CH_2-C3), 26.0 (CH_3-*t*Bu), 25.9 (CH_2-C2), 18.2 (3 × C-*t*Bu), −4.0 (CH_3-Me), −4.3 (CH_3-Me).

***Tert*-butyl{(2*R*,3*S*)-2-[(*Z*)-2-methoxyvinyl]tetrahydro-2*H*-pyran-3-yloxy}dimethylsilane (419)**



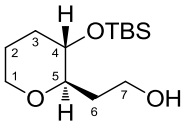
R_f 0.70 (petroleum ether-EtOAc, 4:1); ^{1}H NMR (500 Hz, $CDCl_3$) δ_H 6.06 (1H, d, *J* = 6.4 Hz, CH-C7), 4.35 (1H, dd, *J* = 8.9, 6.4 Hz, CH-C6), 4.02 (1H, t, *J* = 8.9 Hz, CH-C5), 3.88 (1H, ddd, *J* = 7.2, 4.2, 2.6 Hz, CH_2-C1), 3.61 (3H, s, CH_3-OMe), 3.41 (1H, td, *J* = 7.2, 4.5 Hz, CH_2-C1), 3.32 (1H, ddd, *J* = 10.3, 8.9, 4.6 Hz, CH-C4), 2.09–1.98 (1H, m, CH_2-C3), 1.66–1.62 (2H, m, CH_2-C2), 1.52–1.47 (1H, m, CH_2-C3), 0.86 (9H, s, CH_3-*t*Bu), 0.04 (3H, s, CH_3-Me), 0.03 (3H, s, CH_3-Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 151.0 (CH-C7), 106.1 (CH-C6), 76.5 (CH-C5), 71.6 (CH-C4), 67.6 (CH_2-C1), 59.9 (CH_3-OMe), 33.8 (CH_2-C3), 26.0 (3 × CH_3-*t*Bu), 25.8 (CH_2-C2), 18.2 (C-*t*Bu), −4.0 (CH_3-Me), −4.3 (CH_3-Me).

***Tert*-butyldimethyl{[(2*R*,3*S*)-2-vinyltetrahydro-*2H*-pyran-3-yl]oxy}silane (423)[45]**



NaHMDS (12.2 mL of a 1 M solution in THF, 12.2 mmol) was added to a solution of methyltriphenylphosphonium bromide (5.08 g, 14.2 mmol) in THF (17 mL) at 0 °C. After stirring for 1 h at 0 °C, a solution of **417** (880 mg, 3.06 mmol) in THF (34 mL) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (15 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and carefully concentrated *in vacuo*. The resulting volatile crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 98:2) to afford the desired product **423** (791 mg, 91% yield) as a colourless oil. R_f 0.75 (petroleum ether-EtOAc 9:1); $[\alpha]_D^{26}$ +40.5 (*c* = 1.0 in $CHCl_3$); ν_{max} (neat) 2953, 2930, 2857, 1464 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 5.92 (1H, ddd, *J* = 17.3, 10.7, 5.8 Hz, CH-C6), 5.31 (1H, ddd, *J* = 17.3, 1.9, 1.2 Hz, CH-C7), 5.18 (1H, ddd, *J* = 10.7, 1.9, 1.2 Hz, CH-C7), 3.93 (1H, ddt, *J* = 11.3, 4.1, 1.9 Hz, CH_2-C1), 3.50 (1H, ddt, *J* = 8.6, 5.8, 1.2 Hz, CH_2-C5), 3.38 (1H, ddd, *J* = 11.3, 4.6, 3.6 Hz, CH_2-C1), 3.31 (1H, ddd, *J* = 10.5, 8.6, 4.6 Hz, CH-C4), 2.07–1.98 (1H, m, CH_2-C3), 1.72–1.61 (2H, m, CH_2-C2), 1.54–1.44 (1H, m, CH_2-C3), 0.87 (9H, s, CH_3-*t*Bu), 0.04 (3H, s, CH_3-Me), 0.02 (3H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 137.7 (CH-C6), 116.6 (CH_2-C7), 83.4 (CH-C5), 71.5 (CH-C4), 67.7 (CH_2-C1), 33.8 (CH_2-C3), 25.9 (3 × CH_3-*t*Bu), 25.7 (CH_2-C2), 18.2 (C-*t*Bu), −4.0 (CH_3-Me), −4.4 (CH_3-Me); HRMS (CI+, isobutane) for $C_{13}H_{27}O_2Si$ ($[M+H]^+$): 243.1781, found 243.1780.

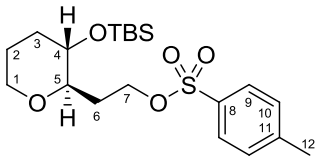
2-[(2*R*,3*S*)-3-(*Tert*-butyldimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl]ethanol (415)[207]



To a solution of alkene **423** (397 mg, 1.64 mmol) in THF (13 mL) at 0 °C was added BH_3·DMS complex (1.64 mL of a 2 M solution in THF, 3.28 mmol) dropwise. After stirring at room temperature for 2 h, the mixture was cooled to 0 °C and the reaction was carefully quenched with H_2O (6 mL), followed by the addition of pH 7 buffer (3 mL) and

$NaBO_3 \cdot 4H_2O$ (1.00 g, 6.52 mmol). The mixture was stirred overnight at room temperature. The aqueous phase was then extracted with EtOAc (5 × 10 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 75:25) to afford the desired product **415** (251 mg, 59% yield) as a colourless oil. R_f 0.37 (petroleum ether-EtOAc, 4:1); $[a]_D^{26}$ +24.5 (*c* = 1.0 in $CHCl_3$), Lit. $[a]_D^{26}$ +50.5 (*c* = 1.05 in $CHCl_3$)[206]; ν_{max} (neat) 3426, 2949, 2930, 2857 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 3.82 (1H, ddt, *J* = 11.1, 3.9, 1.8 Hz, CH_2-C1), 3.72 (2H, dd, *J* = 9.7, 5.0 Hz, CH_2-C7), 3.34–3.23 (1H, m, CH-C4), 3.29 (1H, td, *J* = 11.1, 5.3 Hz, CH_2-C1), 3.19 (1H, td, *J* = 9.1, 2.8 Hz, CH-C5), 2.95 (1H, bs, OH), 2.07–1.91 (2H, m, CH_2-C6 and CH_2-C3), 1.66–1.51 (3H, m, CH_2-C6 and CH_2-C2), 1.37 (1H, dddd, *J* = 15.3, 12.5, 6.0, 5.2 Hz, CH-C3), 0.82 (9H, s, CH_3-*t*Bu), 0.01 (3H, s, CH_3-Me), 0.01 (3H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 83.4 (CH-C5), 71.2 (CH-C4), 67.8 (CH_2-C6), 61.5 (CH_2-C7), 34.4 (CH_2-C6), 33.6 (CH_2-C3), 25.9 (3 × CH_3-*t*Bu), 25.6 (CH_2-C2), 18.0 (C-*t*Bu), −3.9 (CH_3-Me), −4.6 (CH_3-Me); HRMS (CI+, isobutane) for $C_{13}H_{29}O_3Si$ ($[M+H]^+$): 261.1886, found 261.1884.

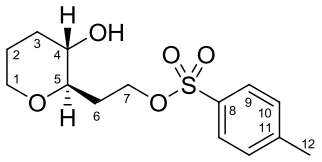
2-[(2*R*,3*S*)-3-(*Tert*-butyldimethylsilyloxy)tetrahydro-2*H*-pyran-2-yl]ethyl 4-methylben-zenesulfonate (424)



p-Tosyl chloride (396 mg, 2.08 mmol) was added to a solution of **415** (180 mg, 0.693 mmol), Et_3N (0.39 mL, 2.8 mmol) and DMAP (84.7 mg, 0.693 mmol) in CH_2Cl_2 (5.7 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h and then the reaction was quenched with H_2O (10 mL). The product was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 80:20) to afford the desired product **424** (281 mg, 98% yield) as a yellowish oil. R_f 0.62 (petroleum ether-EtOAC, 4:1); $[a]_D^{26}$ +52.8 (*c* = 1.0 in $CHCl_3$); ν_{max} (neat) 2937, 2930, 2857, 1599 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.2 Hz, CH-C9), 7.33 (2H, d, *J* = 8.2 Hz, CH-C10), 4.14 (2H, dd, *J* = 8.0, 5.2 Hz, CH_2-C7), 3.72 (1H, ddt, *J* = 7.3, 3.4, 1.7 Hz, CH_2-C1), 3.19 (1H, ddd, *J* = 10.7, 9.3, 4.7 Hz, CH-C4), 3.14 (1H, ddd, *J* = 14.8, 7.3, 4.4 Hz, CH-C1), 3.01 (1H, td, *J* = 9.3, 2.6 Hz, CH-C5), 2.44 (3H, s, CH_3-C12),

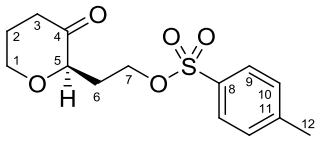
2.24–2.17 (1H, m, CH_2-C6), 1.99–1.93 (1H, m, CH_2-C3), 1.62–1.57 (2H, m, CH_2-C2), 1.54 (1H, ddd, *J* = 10.6, 9.3, 5.2 Hz, CH_2-C6), 1.37 (1H, dtd, *J* = 12.5, 10.7, 7.4 Hz, CH_2-C3), 0.85 (9H, s, CH_3-*t*Bu), 0.03 (3H, s, CH_3-Me), 0.01 (3H, s, CH_3-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.6 (C-C8), 133.4 (C-C11), 129.9 (2 × CH-C10), 128.1 (2 × CH-C9), 78.7 (CH-C5), 71.5 (CH-C4), 67.9 (CH_2-C6), 67.7 (CH_2-C7), 33.6 (CH_2-C3), 31.9 (CH_2-C6), 25.9 (3 × CH_3-*t*Bu), 25.7 (CH_2-C2), 21.7 (CH_3-C12), 18.0 (C-*t*Bu), −3.9 (CH_3-Me), −4.6 (CH_3-Me); HRMS (CI+, isobutane) for $C_{20}H_{35}O_5SiS$ ($[M+H]^+$): 415.1974, found 415.1975.

2-[(2*R*,3*S*)-3-Hydroxytetrahydro-2*H*-pyran-2-yl]ethyl 4-methylbenzenesulfonate (422)



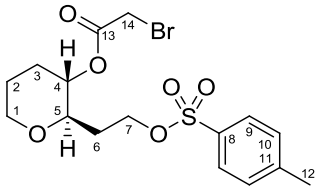
Camphorsulfonic acid (158 mg, 0.678 mmol) was added to a solution of **424** (281 mg, 0.678 mmol) in CH_2Cl_2/MeOH (1.52 mL / 1.52 mL) at 0 °C and the resulting mixture was stirred at room temperature for 3 h. The reaction was then quenched by the addition of Et_3N (0.140 mL, 1.02 mmol) and the mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-Et_2O, 50:50) to afford the desired product **422** (179 mg, 88% yield) as a colourless oil. R_f 0.41 (petroleum ether-EtOAc, 1:1); $[\alpha]_D^{26}$ +24.0 (*c* = 0.8 in $CHCl_3$); ν_{max} (neat) 3430, 2937, 2857, 1599 cm^{-1}; ^{1}H NMR (500 Hz, $CDCl_3$) δ_H 7.80 (2H, d, *J* = 8.4 Hz, CH-C9), 7.34 (2H, dd, *J* = 8.4, 0.6 Hz, CH-C10), 4.19 (2 × 1H, dd, *J* = 7.5, 5.3 Hz, CH_2-C7), 3.77 (1H, ddd, *J* = 11.4, 5.9, 2.7 Hz, CH_2-C1), 3.25 (1H, ddd, *J* = 9.8, 8.6, 4.1 Hz, CH-C4), 3.22–3.15 (1H, m, CH_2-C1), 3.05 (1H, td, *J* = 8.6, 2.9 Hz, CH-C5), 2.44 (3H, s, CH_3-C12), 2.25 (1H, dtd, *J* = 12.4, 7.5, 2.9 Hz, CH_2-C6), 2.13–2.04 (1H, m, CH_2-C3), 1.71 (1H, ddt, *J* = 12.4, 8.6, 5.3 Hz, CH_2-C6), 1.66–1.59 (2H, m, CH_2-C2), 1.52 (1H, s, OH), 1.41–1.29 (1H, m, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 144.7 (C-C8), 133.8 (C-C11), 129.9 (2 × CH-C10), 128.1 (2 × CH-C9), 78.7 (CH-C5), 70.5 (CH-C4), 67.7 (CH_2-C7), 67.6 (CH_2-C1), 33.6 (CH_2-C3), 32.0 (CH_2-C6), 25.8 (CH_2-C2), 21.7 (CH_3-C12); HRMS (CI+, isobutane) for $C_{14}H_{21}O_5S$ ($[M+H]^+$): 301.1110, found 301.1105.

(*R*)-2-(3-oxotetrahydro-2*H*-pyran-2-yl)ethyl 4-methylbenzenesulfonate (426)



Pyridinum dichromate (84.3 mg, 0.224 mmol) was added to a solution of alcohol **422** (33.7 mg, 0.112 mmol) in CH_2Cl_2 (2 mL) at room temperature. The resulting suspension was stirred overnight and then filtered through Celite®, washing with CH_2Cl_2 (3 × 5 mL). The filtrate was carefully concentrated *in vacuo* and the resulting crude product was quickly purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 50:50) to afford the desired unstable ketone **426** (17.0 mg, 51% yield) as a cream coloured oil. R_f 0.41 (EtOAc); $[a]_D^{28}$ +18.3 (*c* = 0.9 in $CHCl_3$); ν_{max} (neat) 2963, 2926, 1736, 1599 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 8.2 Hz, CH-C9), 7.28 (2H, d, *J* = 8.2 Hz, CH-C10), 4.16–4.01 (2H, m, CH_2-C7), 3.91 (1H, dddd, *J* = 11.7, 4.7, 2.8, 1.8 Hz, CH_2-C1), 3.81 (1H, dd, *J* = 8.7, 4.1 Hz, CH-C5), 3.59 (1H, ddd, *J* = 11.7, 10.7, 3.7 Hz, CH_2-C1), 2.48 (1H, dddd, *J* = 15.8, 5.4, 4.0, 1.5 Hz, CH_2-C3), 2.38 (3H, s, CH_3-C12), 2.38–2.30 (1H, m, CH_2-C3), 2.20–2.12 (1H, m, CH_2-C6), 2.05–1.96 (2H, m, CH_2-C2), 1.76 (1H, ddt, *J* = 14.8, 8.7, 5.1 Hz, CH_2-C6); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 207.4 (C-C4), 144.9 (C-C8), 133.2 (C-C11), 130.0 (2 × CH-C10), 128.1 (2 × CH-C9), 78.9 (CH-C5), 66.8 (CH_2-C7), 66.4 (CH_2-C1), 38.0 (CH_2-C3), 30.5 (CH_2-C6), 26.7 (CH_2-C2), 21.8 (CH_3-C12).

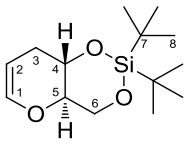
(2*R*,3*S*)-2-[2-(Tosyloxy)ethyl]tetrahydro-2*H*-pyran-3-yl 2-bromoacetate (425)



Bromoacetic acid (65.5 mg, 0.471 mmol), was added to a mixture of alcohol **422** (94.3 mg, 0.314 mmol), DCC (130 mg, 0.628 mmol) and DMAP (15.4 mg, 0.126 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C and the resulting solution was stirred overnight at room temperature. The reaction mixture was then diluted with H_2O (5 mL). The product was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 80:20) to afford the desired product **425** (89.4 mg, 67% yield) as a colourless oil. R_f 0.88 (petroleum ether-EtOAc, 1:1); $[a]_D^{26}$ +251.1 (*c*

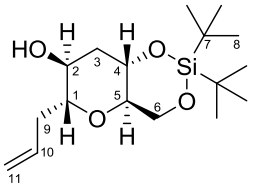
= 0.56 in $CHCl_3$); ν_{max} (neat) 2928, 2855, 1732, 1599, 1454, 1375 cm^{-1}; ^1H NMR (500 Hz, $CDCl_3$) δ_H 7.77 (2H, d, *J* = 8.2 Hz, CH-C9), 7.33 (2H, d, *J* = 8.2 Hz, CH-C10), 4.47 (1H, ddd, *J* = 10.7, 9.5, 4.7 Hz, CH-C4), 4.18 (1H, td, *J* = 9.4, 5.4 Hz, CH_2-C7), 4.11 (1H, ddd, *J* = 14.9, 9.4, 6.6 Hz, CH_2-C7), 3.81–3.77 (1H, m, CH_2-C1), 3.77 (1H, s, CH_2-C14), 3.76 (1H, s, CH_2-C14), 3.31 (1H, td, *J* = 9.5, 2.3 Hz, CH-C5), 3.26–3.17 (1H, m, CH_2-C1), 2.43 (3H, s, CH_3-C12), 2.16 (1H, dtt, *J* = 8.3, 3.8, 1.7 Hz, CH_2-C3), 2.01 (1H, dddd, *J* = 15.3, 9.4, 6.6, 2.3 Hz, CH_2-C6), 1.72–1.59 (3H, m, CH_2-C6 and CH_2-C2), 1.52–1.39 (1H, m, CH_2-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.3 (C-C13), 144.7 (C-C8), 133.8 (C-C11), 129.9 (2 × CH-C10), 128.1 (2 × CH-C9), 74.9 (CH-C5), 73.4 (CH-C4), 67.2 (CH_2-C1), 66.4 (CH_2-C7), 31.2 (CH_2-C6), 28.6 (CH_2-C3), 24.7 (CH_2-C14), 24.6 (CH_2-C2), 21.1 (CH_3-C12); HRMS (CI+, isobutane) for $C_{16}H_{22}O_6S$ ($[M+H]^+$): 421.0320, found 421.0316.

(4a*R*,8a*S*)-2,2-Di-*tert*-butyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasiline (394)



To a solution of diol **396** (1.00 g, 7.69 mmol) in DMF (19 mL) at −45 °C was added di-*tert*-butylsilyl-bis(trifluoromethanesulfonate) (2.50 mL, 7.69 mmol) dropwise, by means of a syringe pump, over a period of 20 min. The reaction mixture was stirred at −45 °C for 30 min and pyridine (0.84 mL) was added. The solution was diluted with Et_2O (20 mL). The organic phase was washed with H_2O (5 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 98:2) to afford the desired product **394** (1.80 g, 87% yield) as a white solid. R_f 0.8 (petroleum ether-EtOAc, 1:1); m.p. 38–40 °C; $[\alpha]_D^{25}$ +37.9 (*c* = 1.1 in $CHCl_3$); ν_{max} (neat) 2933, 2888, 2859, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.26 (1H, dddd, *J* = 5.8, 2.6, 1.5, 0.4 Hz, CH-C1), 4.69 (1H, td, *J* = 5.8, 2.0 Hz, CH-C2), 4.18 (1H, dd, *J* = 10.4, 4.8 Hz, CH_2-C6), 4.11 (1H, td, *J* = 9.5, 5.8 Hz, CH-C4), 3.91 (1H, t, *J* = 10.4 Hz, CH_2-C6), 3.73–3.63 (1H, m, CH-C5), 2.38 (1H, dtd, *J* = 16.5, 5.8, 1.5 Hz, CH_2-C3), 2.13–2.02 (1H, m, CH_2-C3), 1.06 (9H, s, CH_3-*t*Bu), 0.99 (9H, s, CH_3-*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.3 (CH-C1), 99.0 (CH-C2), 74.1 (CH-C5), 71.5 (CH-C4), 66.5 (CH_2-C6), 30.4 (CH_2-C3), 27.6 (3 × CH_3-C8), 27.2 (3 × CH_3-C8), 22.9 (C-C7), 20.0 (C-C7); HRMS (EI+) for $C_{14}H_{27}O_3Si$ ($[M+H]^+$): 271.1730, found 271.1733.

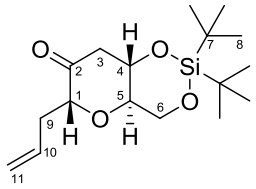
(4a*R*,6*R*,7*S*,8a*S*)-6-Allyl-2,2-Di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (429)



To a solution of enol ether **394** (1.00 g, 3.70 mmol) in a mixture of acetone (6.5 mL), CH_2Cl_2 (17 mL) and a saturated aqueous solution of $NaHCO_3$ (36 mL) at 0 °C, was added a solution of Oxone (5.69 g, 18.5 mmol) in H_2O (27 mL). The mixture was stirred vigorously at 0 °C for 30 min and then at room temperature for an additional 2 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford the corresponding unstable epoxide **428** (1.05 g, quantitative yield, 1:1 mixture of diastereomers) as a white solid, which was reacted directly in the next step. Diagnostic peaks for diastereomeric epoxide mixture: 4.83 ppm (1H, d, *J* = 2.4 Hz, CH-C1) and 4.80 ppm (1H, d, *J* = 1.3 Hz, CH-C1) in a 1:1 ratio.

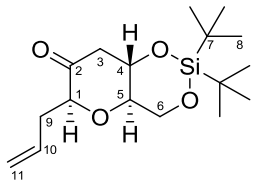
To a solution of epoxide **428** (1.05 g, 3.70 mmol) in THF (70 mL) at 0 °C was added allymagnesium bromide (11.1 mL of a 1 M solution in THF, 11.1 mmol) *via* syringe pump over 30 min. After stirring the mixture at 0 °C for 2 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the undesired diastereomeric alcohol **429** as the major product. The crude product was reacted directly in the next step. R_f 0.59 (petroleum ether-EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.78 (1H, ddt, *J* = 17.4, 10.4, 7.0 Hz, CH-C10), 5.13 (1H, dd, *J* = 17.4, 1.0 Hz, CH_2-C11), 5.12 (1H, dd, *J* = 10.4, 1.0 Hz, CH_2-C11), 4.14 (1H, ddd, *J* = 11.3, 10.0, 5.0 Hz, CH-C4), 4.02 (1H, dd, *J* = 10.0, 4.9 Hz, CH_2-C6), 3.90 (1H, ddd, *J* = 5.9, 2.9, 1.6 Hz, CH-C2), 3.84 (1H, t, *J* = 10.0 Hz, CH_2-C6), 3.81 (1H, dd, *J* = 7.0, 1.6 Hz, CH-C1), 3.54 (1H, td, *J* = 10.0, 4.9 Hz, CH-C5), 2.55 (1H, ddd, *J* = 14.4, 8.3, 7.0 Hz, CH_2-C9), 2.31 (1H, dt, *J* = 14.4, 7.0 Hz, CH_2-C9), 2.26–2.1 (1H, m, CH_2-C3), 1.84 (1H, d, *J* = 6.4 Hz, OH), 1.75 (1H, ddd, *J* = 13.9, 11.3, 2.9 Hz, CH_2-C3), 1.04 (9H, s, CH_3-C8), 0.99 (9H, s, *J* = 2.8 Hz, CH_3-C8).

(4a*R*,6*R*,7*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (430)



To a solution of oxalyl chloride (1.30 mL, 14.8 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added slowly a solution of DMSO (2.00 mL, 29.5 mmol) in CH_2Cl_2 (10 mL). The solution was stirred for 30 min at −78 °C before a solution of alcohol **429** (3.70 mmol) in CH_2Cl_2 (11 mL) was slowly added. The reaction mixture was stirred for 2 h at −78 °C and Et_3N (4.70 mL, 33.3 mmol) was added. The mixture was allowed to warm to room temperature and diluted with CH_2Cl_2 (30 mL) and H_2O (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product, composed mainly of the undesired diastereomeric ketone **430**, was reacted in the next step without further purification. R_f 0.88 (petroleum ether-EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.76 (1H, ddt, *J* = 17.0, 9.8, 7.0 Hz, CH-C10), 5.15 (1H, dd, *J* = 17.0, 1.5 Hz, CH-C11), 5.14 (1H, dd, *J* = 9.8, 1.5 Hz, CH-C11), 4.16 (1H, dt, *J* = 9.7, 4.7 Hz, CH_2-C6), 4.16–4.12 (1H, m, CH-C4), 4.06 (1H, dd, *J* = 9.6, 5.5 Hz, CH-C1), 3.87 (1H, t, *J* = 9.7 Hz, CH_2-C6), 3.76 (1H, td, *J* = 9.7, 4.7 Hz, CH-C5), 2.98 (1H, ddd, *J* = 16.4, 5.6, 0.9 Hz, CH_2-C3), 2.65–2.56 (1H, m, CH_2-C9), 2.48 (1H, dd, *J* = 16.4, 11.1 Hz, CH_2-C3), 2.44–2.37 (1H, m, CH_2-C9), 1.05 (9H, s, CH_3-C8), 1.01 (9H, s, CH_3-C8).

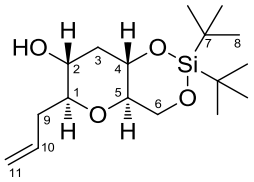
(4a*R*,6*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butyltetrahydropyrano[3,2-*d*][1,3,2]dioxasilin-7(6*H*)-one (431)[211]



To a solution of ketone **430** (3.70 mmol) in toluene (37 mL) was added DBU (0.17 mL, 1.10 mmol). The solution was stirred in the dark, at room temperature, overnight, then more DBU (0.17 mL, 1.1 mmol) was added. After another 8 h at room temperature, the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (2 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The

crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 98:2) to afford the desired ketone **431** (772 mg, 64% yield over 4 steps) as a colourless oil. R_f 0.91 (petroleum ether-EtOAc, 4:1); $[a]_D^{25}$ −18.9 (*c* = 1.0 in $CHCl_3$); ν_{max} (neat) 2969, 2932, 2884, 2861, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 5.80 (1H, ddt, *J* = 17.1, 10.2, 7.2 Hz, CH-C10), 5.11 (1H, dd, *J* = 17.1, 1.5 Hz, CH_2-C11), 5.06 (1H, dd, *J* = 10.2, 1.5 Hz, CH_2-C11), 4.26 (1H, dd, *J* = 10.0, 5.0 Hz, CH_2-C6), 4.13 (1H, ddd, *J* = 11.1, 10.0, 5.7 Hz, CH-C4), 3.90 (1H, t, *J* = 10.0 Hz, CH_2-C6), 3.85 (1H, dd, *J* = 7.2, 4.3 Hz, CH-C1), 3.61 (1H, td, *J* = 10.0, 5.0 Hz, CH-C5), 3.02 (1H, dd, *J* = 15.7, 5.7 Hz, CH_2-C3), 2.65–2.58 (1H, m, CH_2-C9), 2.45 (1H, dd, *J* = 15.7, 11.1 Hz, CH_2-C3), 2.30 (1H, dt, *J* = 14.7, 7.2 Hz, CH_2-C9), 1.05 (9H, s, CH_3-C8), 1.01 (9H, s, CH_3-C8); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 204.8 (C-C2), 133.8 (CH-C10), 117.7 (CH-C11), 82.8 (CH-C1), 76.5 (CH-C5), 73.3 (CH-C4), 66.7 (CH_2-C6), 48.4 (CH_2-C3), 33.6 (CH_2-C9), 27.6 (3 × CH_3-C8), 27.2 (3 × CH_3-C8), 22.8 (C-C7), 20.1 (C-C7); HRMS (CI+, isobutane) for $C_{17}H_{31}O_4Si$ ($[M+H]^+$): 327.1992, found 327.1994.

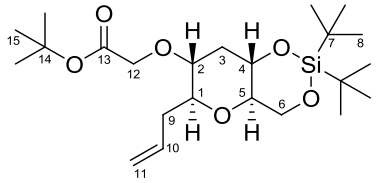
(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (391)[211]



A solution of $NaBH_4$ (41.8mg, 1.11 mmol) in EtOH (10 mL) was added to a solution of ketone **431** (95.0 mg, 0.291 mmol) in EtOH (22 mL) at −78 °C. The mixture was allowed to warm to 0 °C in an ice bath over the course of 2 h. The reaction was then quenched carefully with acetone (22 mL) followed by stirring at room temperature for 15 min and concentration *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 60:40) to afford the desired alcohol **391** (77.5 mg, 81% yield) as colourless oil. R_f 0.17 (petroleum ether-EtOAc, 4:1); $[a]_D^{26}$ +29.3 (*c* = 1.00 in $CHCl_3$),Lit. $[a]_D^{29}$ +27.3 (*c* = 1.00 in $CHCl_3$)[211]; ν_{max} (neat) 3355, 2961, 2933, 2879, 2860, 1473, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 5.90 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, CH-C10), 5.12 (1H, dd, *J* = 17.2, 1.9 Hz, CH_2-C11), 5.07 (1H, dd, *J* = 10.2, 1.9 Hz, CH_2-C11), 4.13 (1H, dd, *J* = 10.2, 5.0 Hz, CH_2-C6), 3.79 (1H, t, *J* = 10.2 Hz, CH_2-C6), 3.78–3.73 (1H, m, CH-C4), 3.50−3.42 (1H, ddt, *J* = 11.7, 9.7, 4.5 Hz CH-C2), 3.27 (1H, ddd, *J* = 10.2, 9.3, 5.0 Hz, CH-C5), 3.18 (1H, ddd, *J* = 9.7, 7.0, 4.0 Hz, CH-C1), 2.54 (1H, dddt, *J* = 14.3, 7.0, 4.0, 1.3 Hz, CH_2-C9), 2.46 (1H, dt, *J* = 11.7, 4.5 Hz,

CH_2-C3), 2.28 (1H, dt, *J* = 14.3, 7.0 Hz, CH_2-C9), 1.49 (1H, dd, *J* = 22.9, 11.7 Hz, CH_2-C3), 1.04 (9H, s, CH_3-C8), 1.00 (9H, s, CH_3-C8); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 134.88 (CH-C10), 117.14 (CH_2-C11), 81.72 (CH-C1), 77.48 (CH-C5), 72.60 (CH-C4), 69.53 (CH-C2), 67.10 (CH_2-C6), 42.19 (CH_2-C3), 36.61 (CH_2-C9), 27.65 (3 × CH_3-C8), 27.28 (3 × CH_3-C8), 22.78 (C-C7), 20.13 (C-C7); HRMS (CI+, isobutane) for $C_{17}H_{33}O_4Si$ ($[M+H]^+$): 329.2149, found 329.2148.

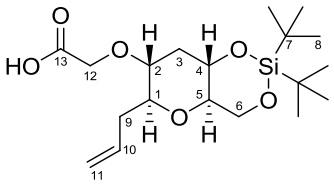
Tert-butyl-2-((4a*R*,6*S*,7*R*,8a*S*)-6-allyl-2,2-di-_tert_-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yloxy)acetate (433)



To a solution of alcohol **391** (220 mg, 0.670 mmol) in toluene (1.6 mL) at 0 °C were added tetrabutylammonium hydrogen sulfate (90.9 mg, 0.268 mmol) and a saturated aqueous solution of NaOH (2.68 mL). The mixture was stirred at 0 °C for 5 min and *tert*-butyl bromoacetate (0.148 mL, 1.01 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and water was added (2 mL). The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 90:10) to obtain **433** (180 mg, 60% yield) as a colourless oil. R_f 0.87 (petroleum ether-EtOAc, 4:1); $[a]_D^{25}$ −48.6 (*c* = 1.3 in $CHCl_3$); ν_{max} (neat) 2967, 2934, 2880, 2861, 1751, 1719, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ_H 5.87 (1H, ddt, *J* = 17.2, 10.2, 7.1 Hz, CH-C10), 5.09 (1H, dd, *J* = 17.2, 1.9 Hz, CH_2-C11), 5.03 (1H, dd, *J* = 10.2, 1.9 Hz, CH_2-C11), 4.11 (1H, dd, *J* = 10.2, 4.9 Hz, CH_2-C6), 4.02 (1H, d, *J* = 16.1 Hz, CH_2-C12), 3.97 (1H, d, *J* = 16.1 Hz, CH_2-C12), 3.77 (1H, t, *J* = 10.2 Hz, CH_2-C6), 3.71 (1H, ddd, *J* = 11.2, 9.2, 4.4 Hz, CH-C4), 3.33–3.24 (2H, m, CH-C1 and CH-C5), 3.21 (1H, ddd, *J* = 10.9, 9.2, 4.4 Hz, CH-C2), 2.68 (1H, ddd, *J* = 14.9, 7.1, 2.9 Hz, CH_2-C9), 2.59 (1H, dt, *J* = 11.8, 4.4 Hz, CH_2-C3), 2.21 (1H, dt, *J* = 14.9, 7.1 Hz, CH_2-C9), 1.48 (9H, s, CH_3-C15), 1.45–1.42 (1H, m, CH_3-C3), 1.02 (9H, s, CH_3-C8), 0.97 (9H, s, CH_3-C8); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 169.5 (C-C13), 135.0 (CH-C10), 116.9 (CH_2-C11), 81.8 (C-C14), 80.3 (CH-C5), 77.2 (CH-C1), 76.9 (CH-C2), 72.5 (CH-C4), 67.0 (CH_2-C6), 66.8 (CH_2-C12), 38.2 (CH_2-C3), 36.2

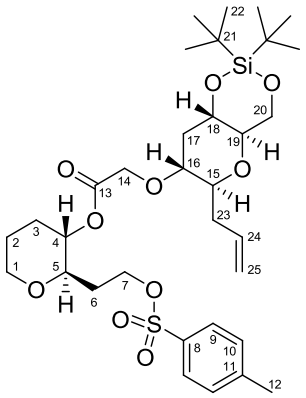
(CH_2-C9), 28.3 (3 × CH_3-C15), 27.6 (3 × CH_3-C8), 27.2 (3 × CH_3-C8), 22.8 (C-C7), 20.1 (C-C7); HRMS (CI+, isobutane) for $C_{23}H_{43}O_6Si$ ([M+H]$^+$): 443.2829, found 443.2822.

2-((4a*R*,6*S*,7*R*,8a*S*)-6-allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yloxy)acetic acid (434)



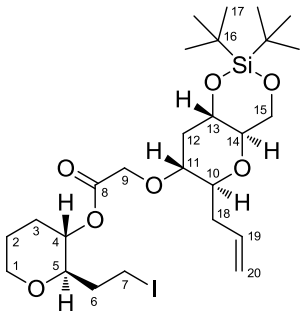
To a solution of ester **433** (178 mg, 0.402 mmol) in CH_2Cl_2 (0.6 mL) was added TFA (0.60 mL, 8.0 mmol) at room temperature. After stirring at room temperature for 1 h, the mixture was co-evaporated with toluene (3 × 5 mL) and the resulting oily product **434** (153 mg, 99% yield) was reacted in the following step without further purification. R_f 0.75 (petroleum ether-EtOAc, 2:1); $[a]_D^{26}$ −31.9 (*c* = 1.2 in $CHCl_3$); ν_{max} (neat) 2933, 2881, 2861, 1737, 1733, 1727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.69 (1H, bs, OH), 5.86 (1H, ddt, *J* = 17.4, 10.3, 6.9 Hz, CH-C10), 5.09 (1H, dd, *J* = 17.4, 1.0 Hz, CH_2-C11), 5.06 (1H, dd, *J* = 10.3, 1.0 Hz, CH_2-C11), 4.22 (1H, d, *J* = 16.9 Hz, CH_2-C12), 4.15 (1H, d, *J* = 16.9 Hz, CH_2-C12), 4.13 (1H, dd, *J* = 10.2, 5.0 Hz, CH_2-C6), 3.78 (1H, t, *J* = 10.2 Hz, CH_2-C6), 3.72 (1H, ddd, *J* = 11.2, 8.5, 3.6 Hz, CH-C4), 3.38–3.22 (3H, m, CH-C5, CH-C1 and CH-C2), 2.67–2.56 (2H, m, CH_2-C9 and CH_2-C3), 2.24 (1H, dt, *J* = 14.7, 6.9 Hz, CH_2-C9), 1.49 (1H, q, *J* = 11.2 Hz, CH_2-C3), 1.03 (9H, s, CH_3-C8), 0.98 (9H, s, CH_3-C8); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 174.8 (C-C13), 134.6 (CH-C10), 117.2 (CH_2-C11), 79.9 (CH-C5), 77.2 (CH-C1), 77.2 (CH-C2), 72.4 (CH-C4), 66.9 (CH_2-C6), 65.8 (CH_2-C12), 38.1 (CH_2-C3), 36.2 (CH_2-C9), 27.6 (3 × CH_3-C8), 27.2 (3 × CH_3-C8), 22.7 (C-C7), 20.1 (C-C7); HRMS (CI+, isobutane) for $C_{19}H_{34}O_6Si$ ([M+H]$^+$): 387.2204, found 387.2207.

(2*R*,3*S*)-2-[2-(Tosyloxy)ethyl]tetrahydro-2*H*-pyran-3-yl 2-{(4a*R*,6*S*,7*R*,8a*S*)-6-allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yloxy}acetate (432)



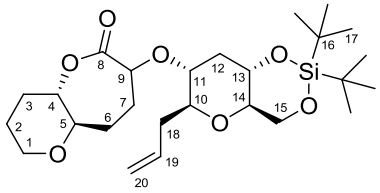
To a solution of alcohol **422** (34.2 mg, 0.114 mmol), carboxylic acid **434** (43.9 mg, 0.114 mmol) and DMAP (47.4 mg, 0.388 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (87.4mg, 0.456 mmol). After stirring overnight at room temperature, H_2O (2 mL) was added, followed by extraction of the aqueous phase with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, 90:10) to obtain the desired coupled product **432** (46.1 mg, 59% yield) as a colourless oil. R_f 0.57 (petroleum ether-EtOAc, 4:1); $[\alpha]_D^{27}$ −11.9 (*c* = 0.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* = 8.2 Hz, CH-C9), 7.34 (2H, d, *J* = 8.2 Hz, CH-C10), 5.87 (1H, ddt, *J* = 17.2, 10.2, 6.3 Hz, CH-C24), 5.09 (1H, dd, *J* = 17.2, 1.6 Hz, CH_2-C25), 5.04 (1H, d, *J* = 10.2 Hz, CH_2-C25), 4.52 (1H, td, *J* = 10.6, 4.9 Hz, CH-C4), 4.15 (1H, dd, *J* = 11.6, 5.0 Hz, CH-C20), 4.13 (1H, d, *J* = 16.4 Hz, CH_2-C14), 4.21–4.05 (2H, m, CH_2-C7), 4.06 (1H, d, *J* = 16.4 Hz, CH_2-C14), 3.78 (1H, t, *J* = 11.6 Hz, CH_2-C20), 3.76 (1H, ddd, *J* = 11.2, 9.3, 4.5 Hz, CH-C18), 3.79–3.75 (1H, m, CH_2-C1), 3.36–3.14 (5H, m, CH-C5, CH-C15, CH-C16, CH-C19 and CH_2-C1), 2.70–2.62 (1H, m, CH_2-C23), 2.59 (1H, dt, *J* = 11.7, 4.5 Hz, CH_2-C17), 2.45 (3H, s, CH_3-C12), 2.24 (1H, dd, *J* = 13.2, 6.3 Hz, CH_2-C23), 2.17 (1H, dd, *J* = 13.0, 4.9 Hz, CH_2-C3), 1.98 (1H, dddd, *J* = 15.3, 9.0, 6.2, 2.4 Hz, CH_2-C6), 1.70–1.64 (2H, m, CH_2-C2), 1.64–1.56 (1H, m, CH_2-C6), 1.53–1.43 (2H, m, CH_2-C17 and CH_2-C3), 1.02 (9H, s, CH_3-C22), 0.98 (9H, s, CH_3-C2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.6 (C-C13), 144.8 (C-C8), 134.9 (CH-C24), 133.6 (C-C11), 129.9 (2 ×CH-C10), 128.1 (2 × CH-C9), 116.9 (CH_2-C25), 80.3 (CH-C5), 77.4 (CH-C19), 77.3 (CH-C16), 75.5 (CH-C15), 72.6 (CH-C18), 72.6 (CH-C4), 67.7 (CH_2-C1), 67.0 (CH_2-C20), 66.9 (CH_2-C7), 66.3 (CH_2-C14), 38.4 (CH_2-C17), 36.2 (CH_2-C23), 32.0 (CH_2-C6), 29.5 (CH_2-C3), 27.6 (3 × CH_3-C22), 27.3 (3 × CH_3-C22), 25.3 (CH_2-C2), 22.8 (C-C21), 21.7 (CH_3-C12), 20.1 (C-C21); HRMS (CI+, isobutane) for $C_{33}H_{53}O_{10}SiS$ ($[M+H]^+$): 669.3129, found 669.3120.

(2*R*,3*S*)-2-(2-Iodoethyl)tetrahydro-2*H*-pyran-3-yl 2-[(4*R*,6*S*,7*R*,8*S*)-6-allyl-2,2-di-*tert*-butylhexahydropyrano[3,2][1,3,2]dioxasilin-7-yloxy]acetate (436)



To a solution of tosylated coupled compound **432** (44.0 mg, 0.0658 mmol) in acetone (3 mL) was added NaI (49.3 mg, 0.329 mmol) and the resulting solution was stirred at reflux in the dark for 8 h. The reaction mixture was then diluted with Et_2O (5 mL) and a 10% aqueous solution of $Na_2S_2O_3$ (5 mL) was added. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting white, oily product **436** (37.9 mg, 92% yield) was reacted in the following step without further purification. R_f 0.77 (petroleum ether-EtOAc, 4:1); ν_{max} (neat) 2932, 2880, 2859, 2363, 1761, 1736, 1474, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.87 (1H, ddt, *J* = 17.2, 10.2, 6.6 Hz, CH-C19), 5.10 (1H, dd, *J* = 17.2, 2.0 Hz, CH_2-C20), 5.05 (1H, dd, *J* = 10.2, 2.0 Hz, CH_2-C20), 4.62 (1H, ddd, *J* = 10.7, 9.4, 4.7 Hz, CH-C4), 4.15 (1H, d, *J* = 16.4 Hz, CH_2-C9), 4.12 (1H, dd, *J* = 10.3, 5.1 Hz, CH_2-C15), 4.08 (1H, d, *J* = 16.4 Hz, CH_2-C9), 3.92 (1H, ddt, *J* = 11.4, 4.0, 1.8 Hz, CH_2-C1), 3.77 (1H, t, *J* = 10.3 Hz, CH_2-C15), 3.72 (1H, ddd, *J* = 11.2, 8.6, 4.2 Hz, CH-C13), 3.43–3.20 (7H, m, CH-C1, CH-C5, CH-C10, CH-C11, CH-C14 and CH_2-C7), 2.66 (1H, dddd, *J* = 13.5, 6.6, 2.9, 1.5 Hz, CH_2-C18), 2.59 (1H, dt, *J* = 11.7, 4.2 Hz, CH_2-C12), 2.22 (1H, dd, *J* = 13.5, 6.6 Hz, CH_2-C18), 2.23–2.15 (1H, m, CH_2-C3), 2.11–2.00 (1H, m, CH_2-C6), 1.87 (1H, dddd, *J* = 14.6, 9.4, 6.6, 4.4 Hz, CH_2-C6), 1.77–1.67 (2H, m, CH_2-C2), 1.57–1.45 (2H, m, CH_2-C12 and CH_2-C3), 1.03 (9H, s, CH_3-C17), 0.97 (9H, s, CH_3-C17); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.6 (C-C8), 134.9 (CH-C19), 117.1 (CH_2-C20), 80.1 (CH-C5), 78.8 (CH-C4), 77.2 (CH-C11), 77.0 (CH-C10), 72.5 (CH-C13), 72.3 (CH-C14), 67.8 (CH_2-C1), 67.0 (CH_2-C15), 66.2 (CH_2-C9), 38.2 (CH_2-C12), 36.2 (CH_2-C18), 36.2 (CH_2-C6), 29.5 (CH_2-C3), 27.6 (3 × CH_3-C17), 27.2 (3 × CH_3-C17), 25.3 (CH_2-C2), 22.8 (C-C16), 20.1 (C-C16), 2.0 (CH_2-C7); HRMS (CI+, isobutane) for $C_{26}H_{46}O_7SiI$ ($[M+H]^+$): 625.2058, found 625.2062.

Methods for the preparation of (4a*S*,9a*R*)-7-((4a*R*,6*S*,7*R*,8a*S*)-6-allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yloxy)hexahydro-*2H*-pyrano[3,2-*b*]oxepin-6(*3H*)-one (435)



Method A

n-BuLi (0.10 mL of a 2.5 M solution in hexanes, 0.27 mmol) was added to a solution of diisopropylamine (37 µL, 0.26 mmol) in THF (1 mL) at −78 °C and the mixture was allowed to warm to room temperature over 1 h. This solution was then added dropwise to a solution of tosylate **432** (44.0 mg, 0.066 mmol) in THF (1 mL) at −78 °C and stirred at 0 °C for 1 h. The reaction was quenched with H_2O (2 mL) and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. This reaction was unsuccessful and led to the full recovery of the starting material **432**.

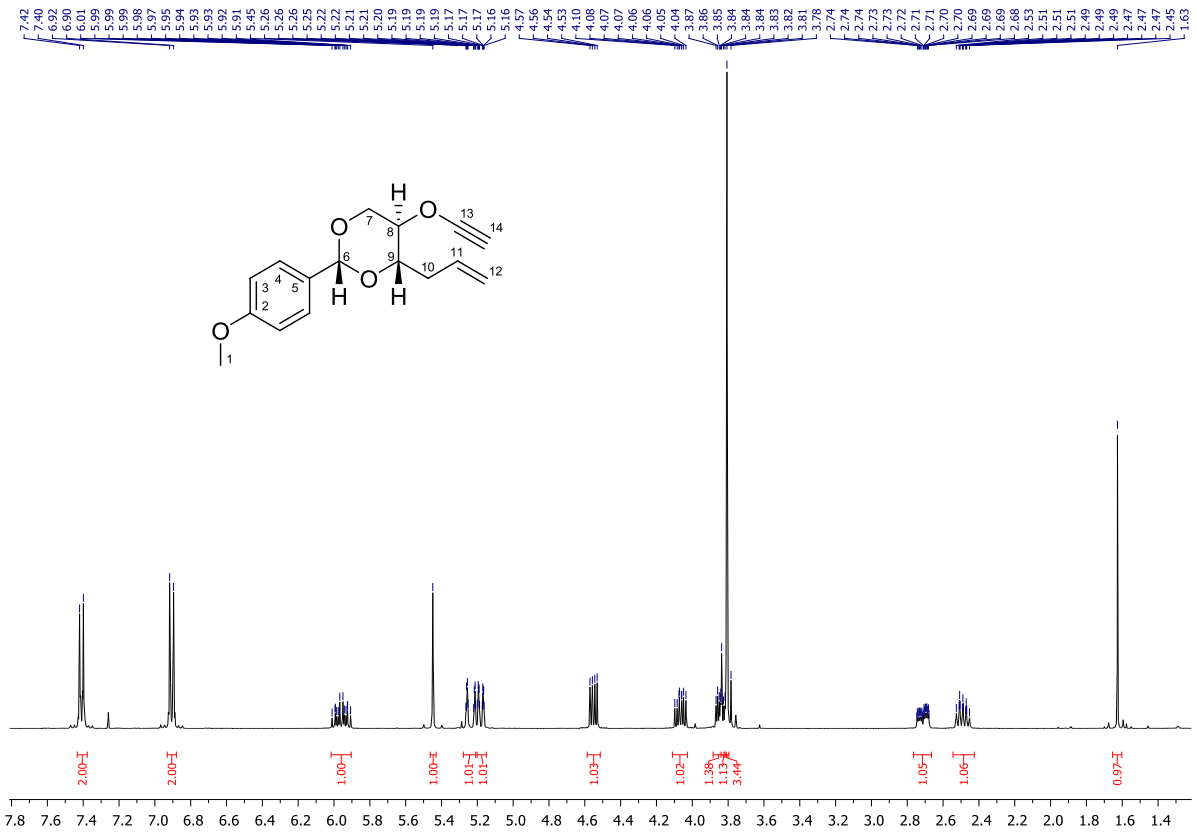
Method B

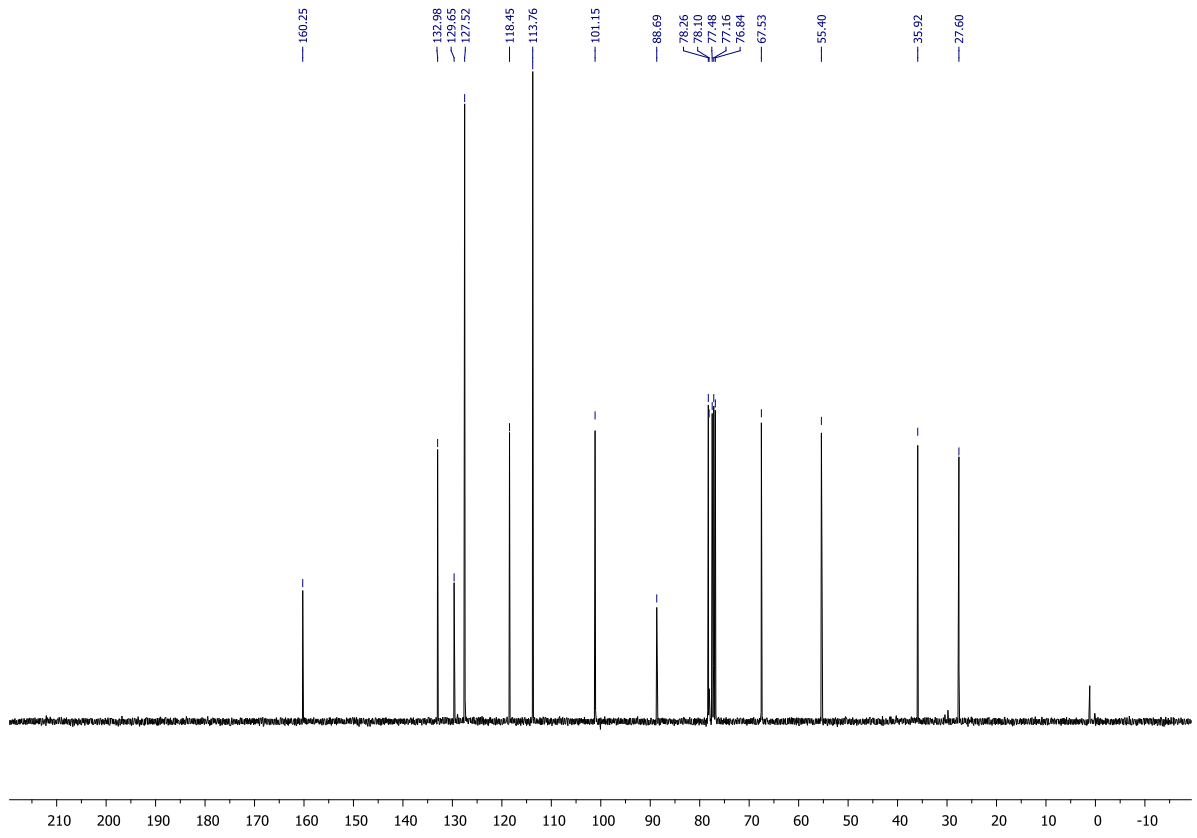
n-BuLi (0.10 mL of a 2.5 M solution in hexanes, 0.27 mmol) was added to a solution of diisopropylamine (37 µL, 0.26 mmol) in THF (1 mL) at −78 °C and the mixture was allowed to warm to room temperature over 1 h. This solution was then added dropwise to a solution of iodide **436** (37.9 mg, 0.0610 mmol) in THF (1 mL) at −78 °C and stirred at 0 °C for 1 h. The reaction was quenched with H_2O (2 mL) and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Unfortunately, this reaction led to decomposition of the starting material **436**.

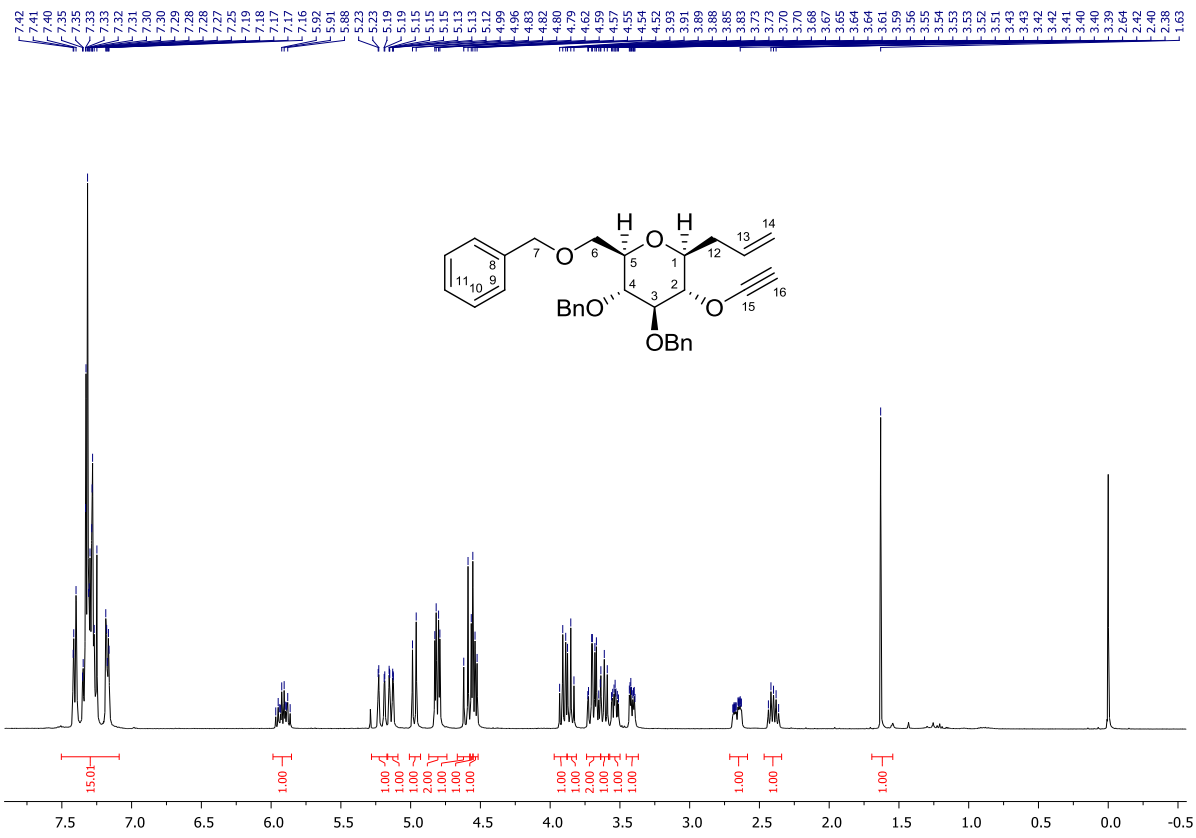
Method C

n-BuLi (0.19 mL of a 2.5 M solution in hexanes, 0.47 mmol) was added to a solution of di-iso-propylamine (60 µL, 0.42 mmol) in THF (1 mL) at −78 °C and the mixture was allowed to warm to room temperature over 1 h. This solution was then added dropwise to a solution of iodide **436** (66.2 mg, 0.106 mmol) in THF (1 mL) and hexamethylphosphoramide (22 µl, 0.13 mmol) at −78 °C and stirred at 0 °C for 1 h. The reaction was quenched with H_2O (2 mL) and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$

and concentrated *in vacuo*. Unfortunately, this reaction led to decomposition of the starting material **436**.



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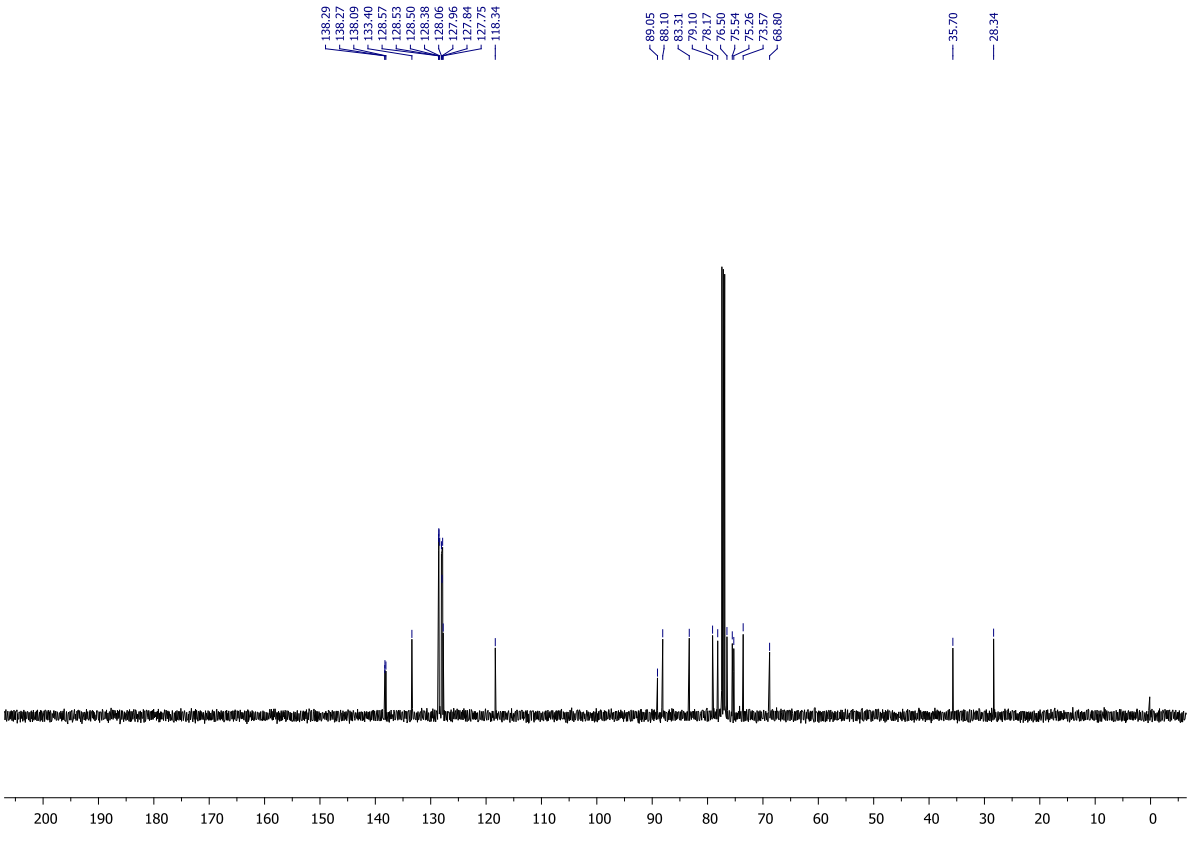
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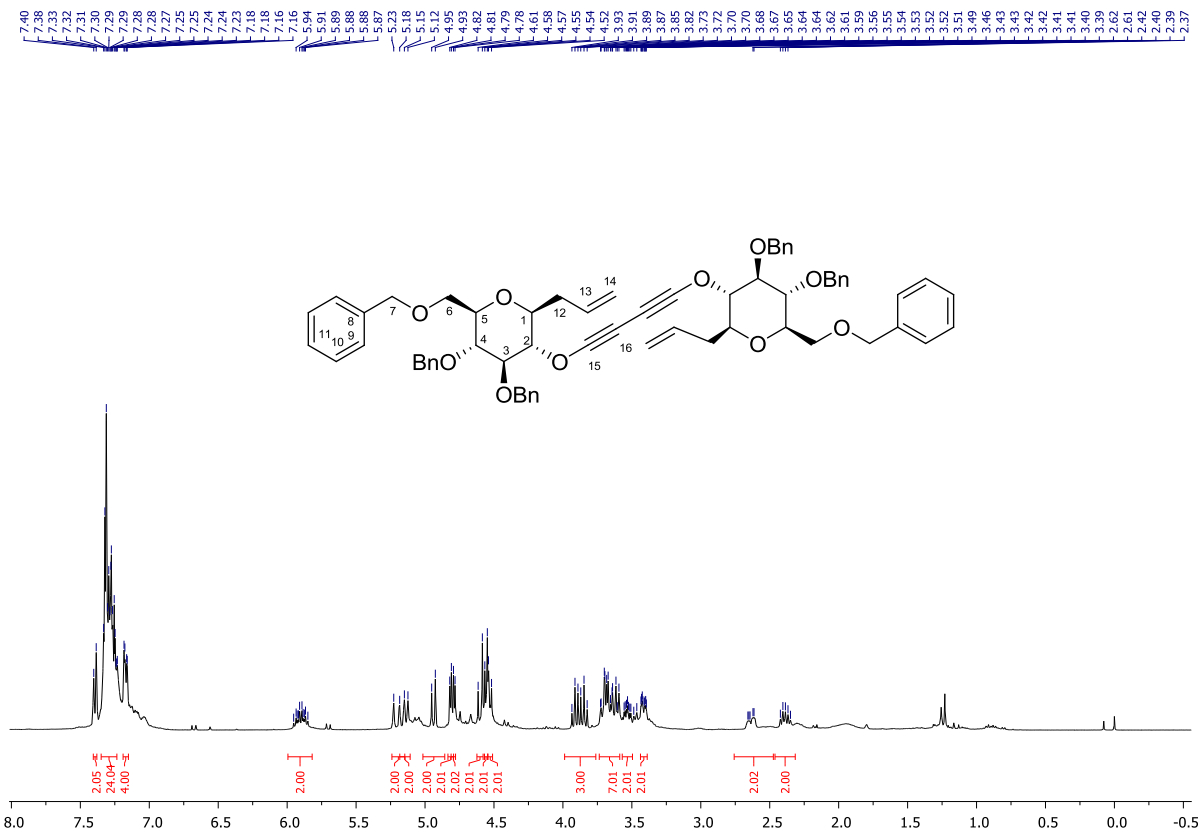
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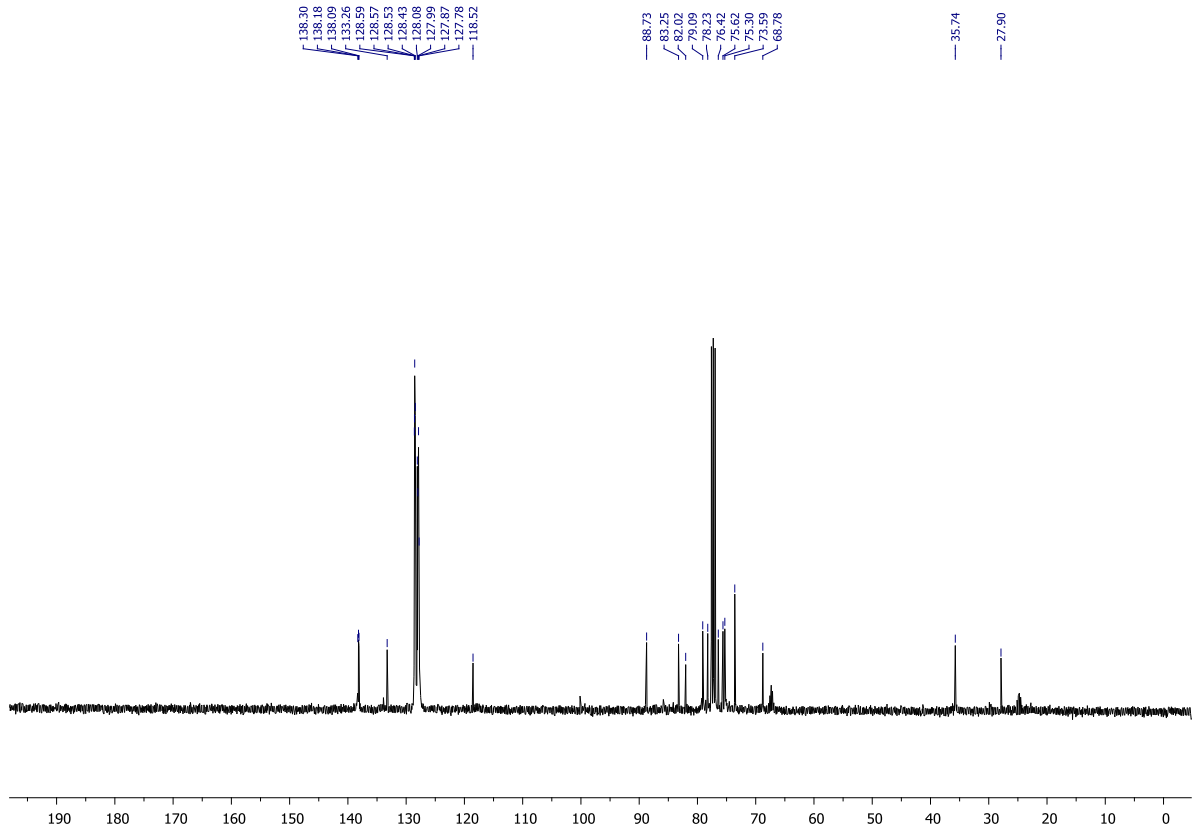

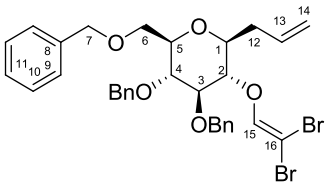
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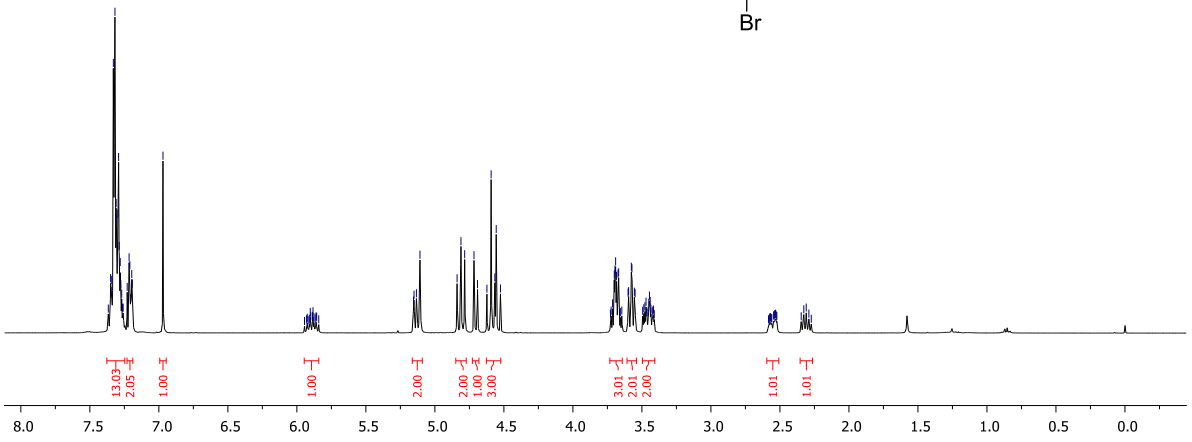
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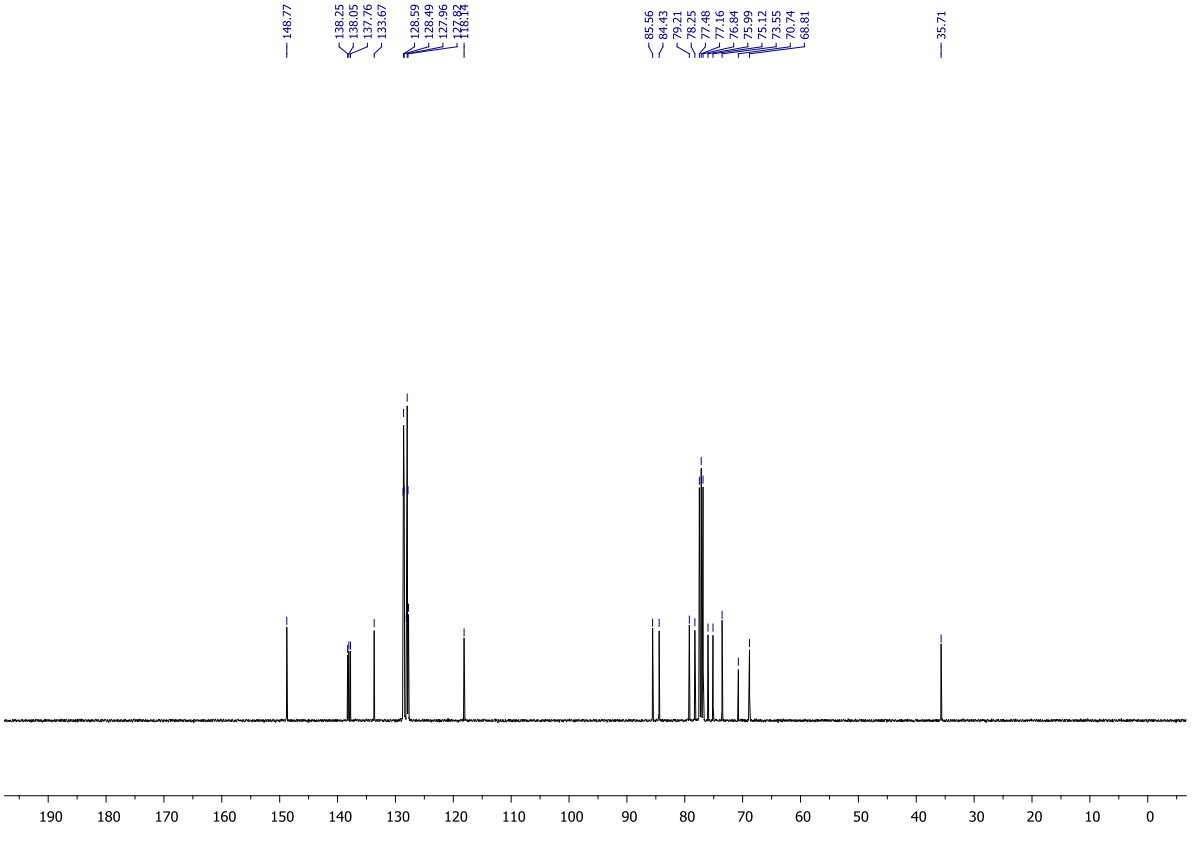
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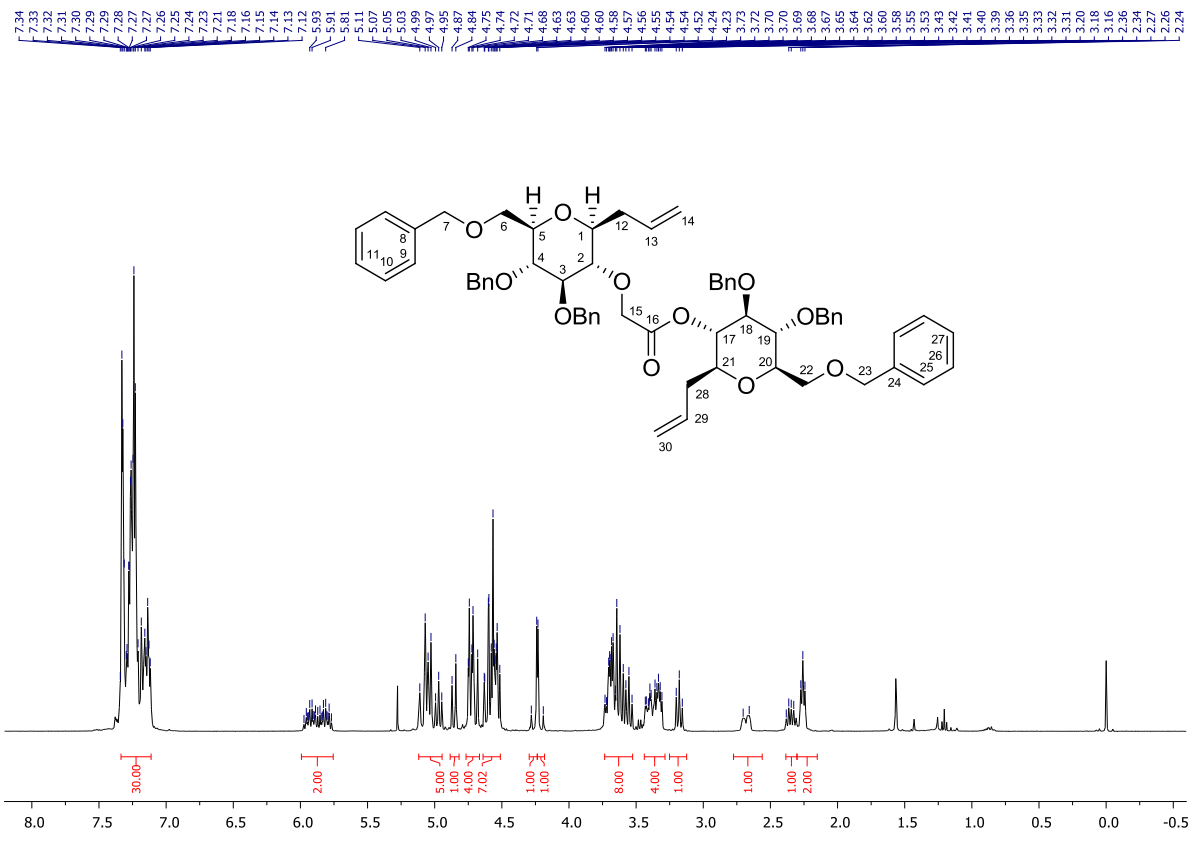

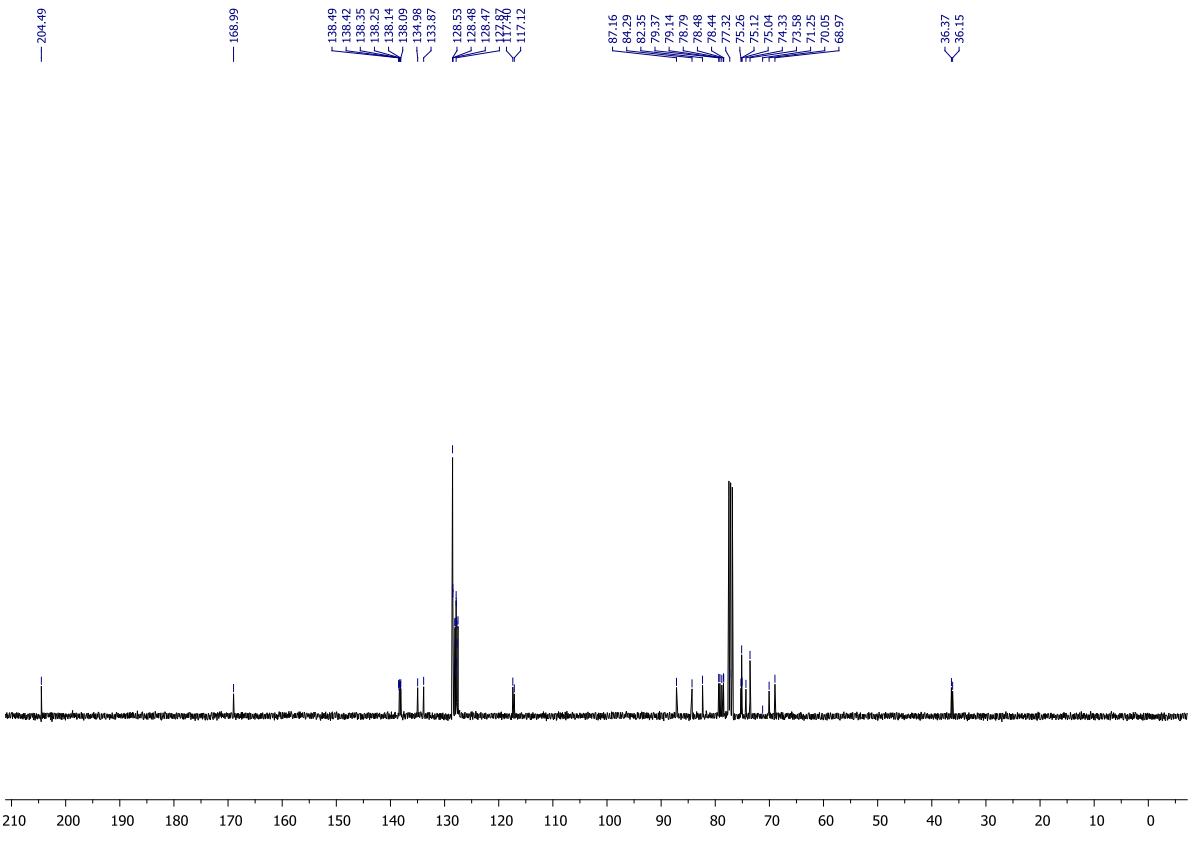

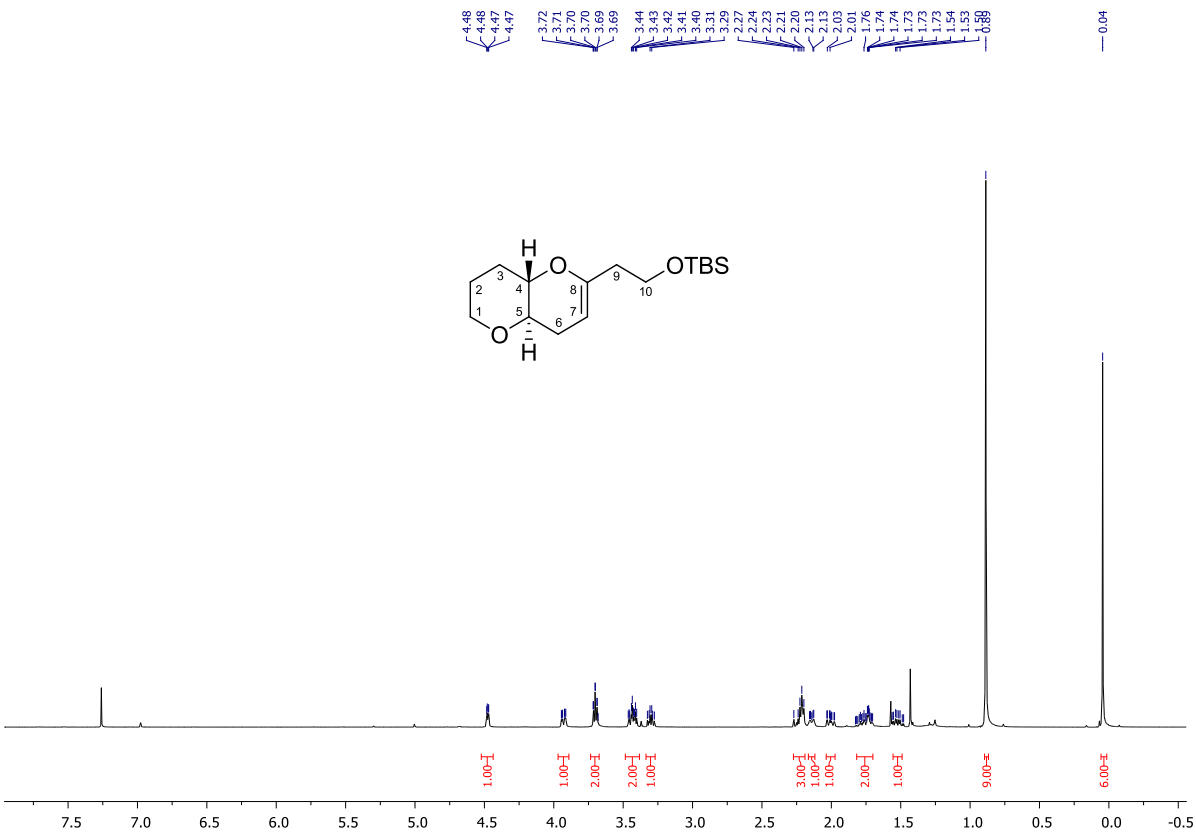
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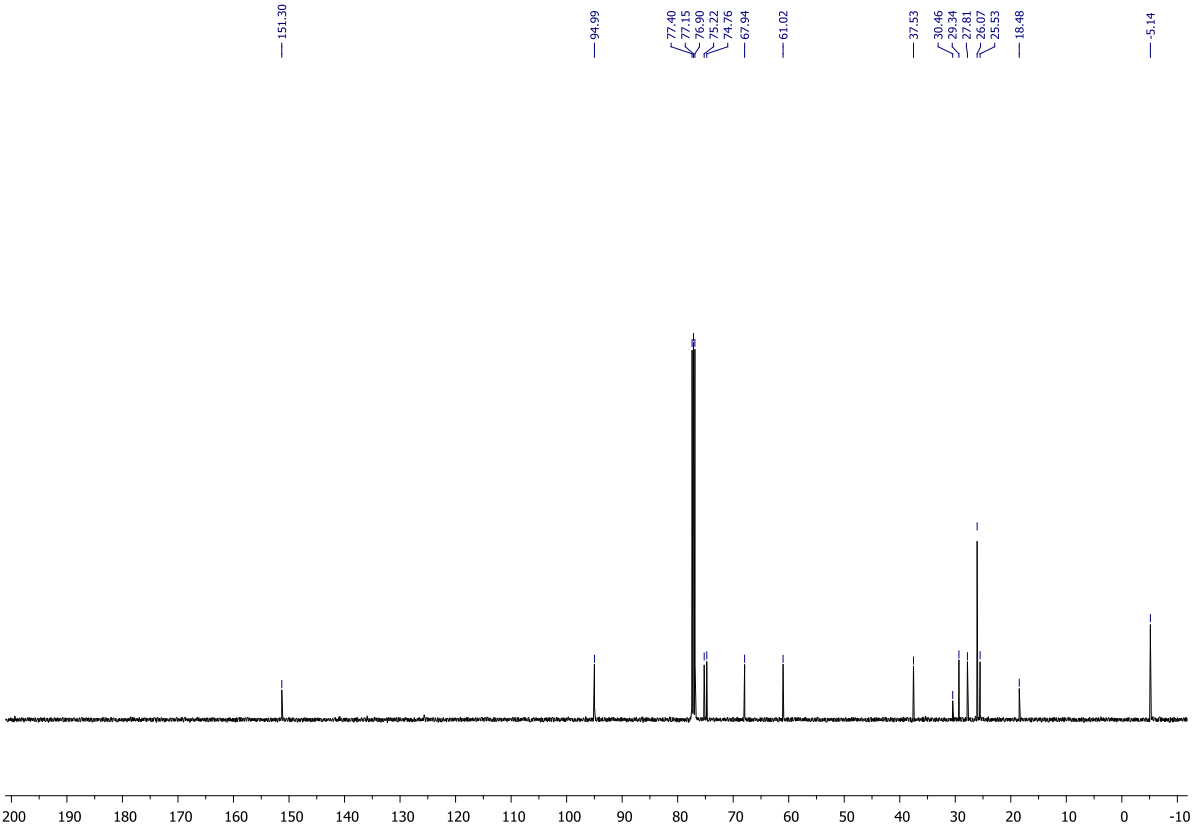
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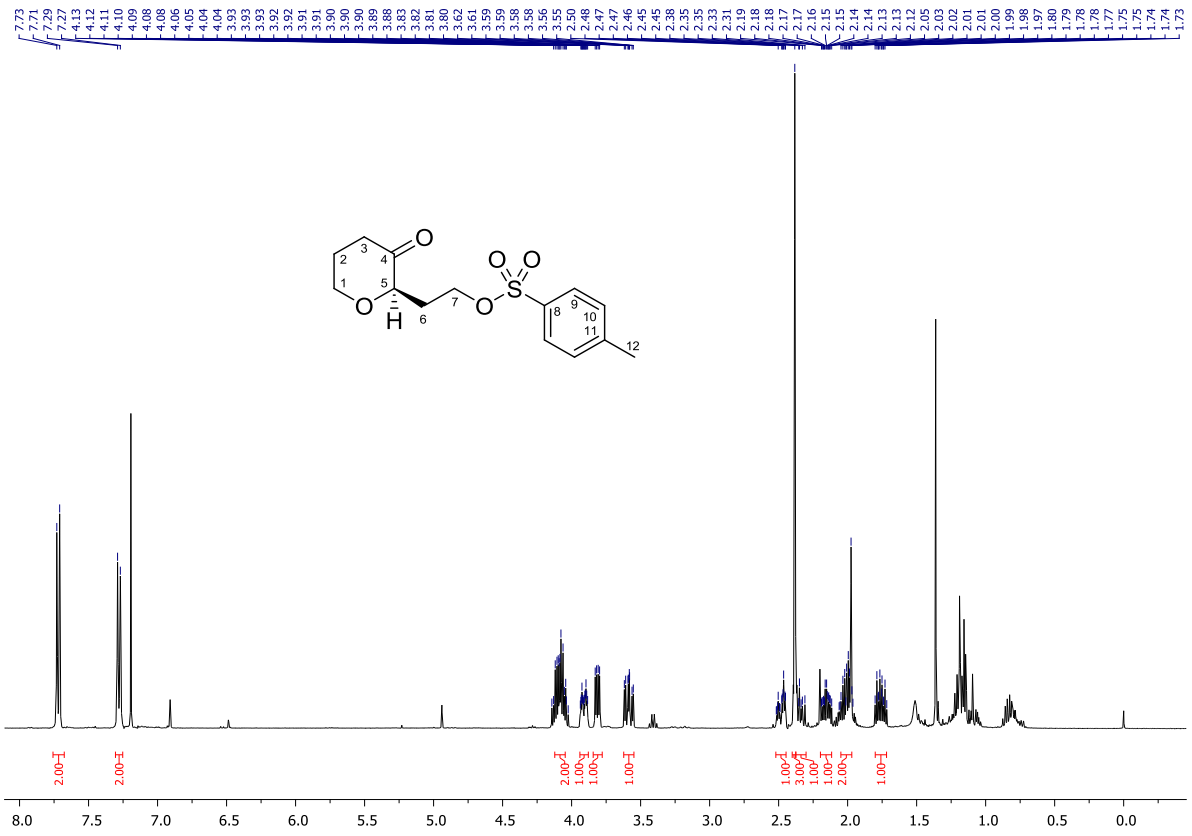

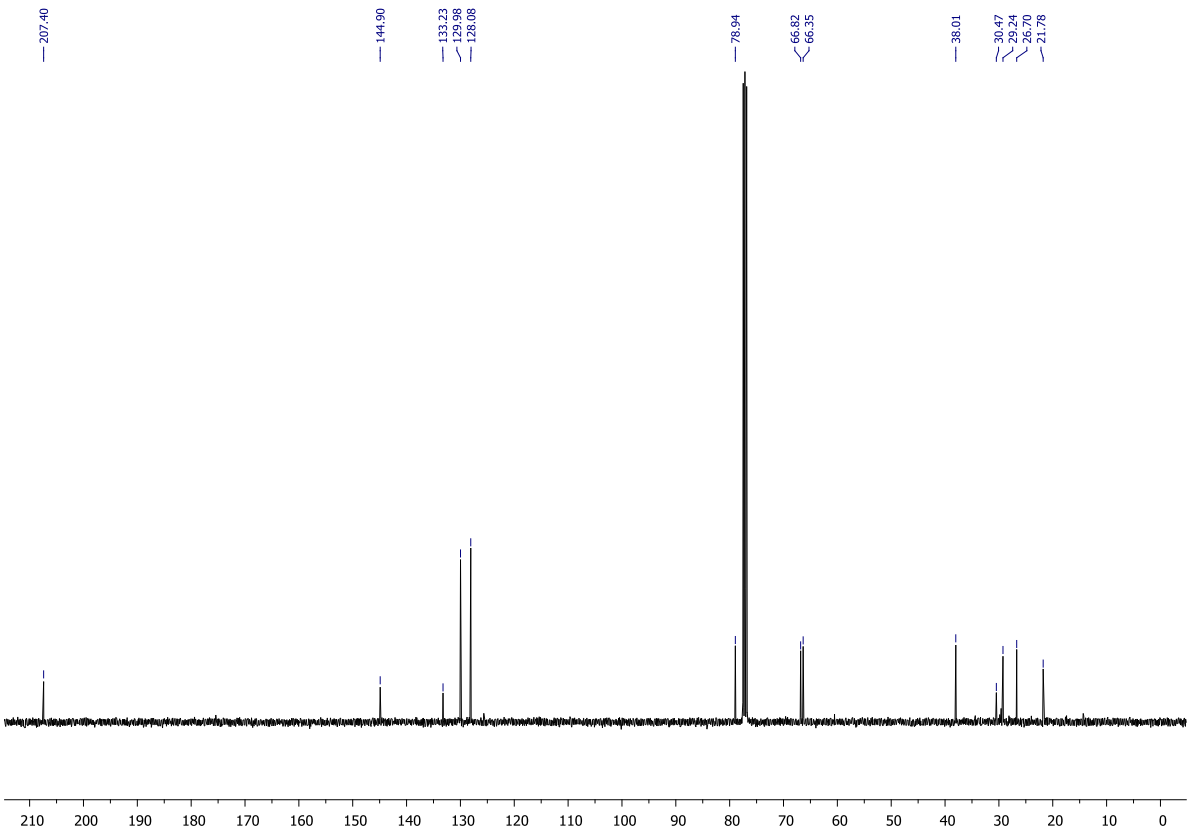

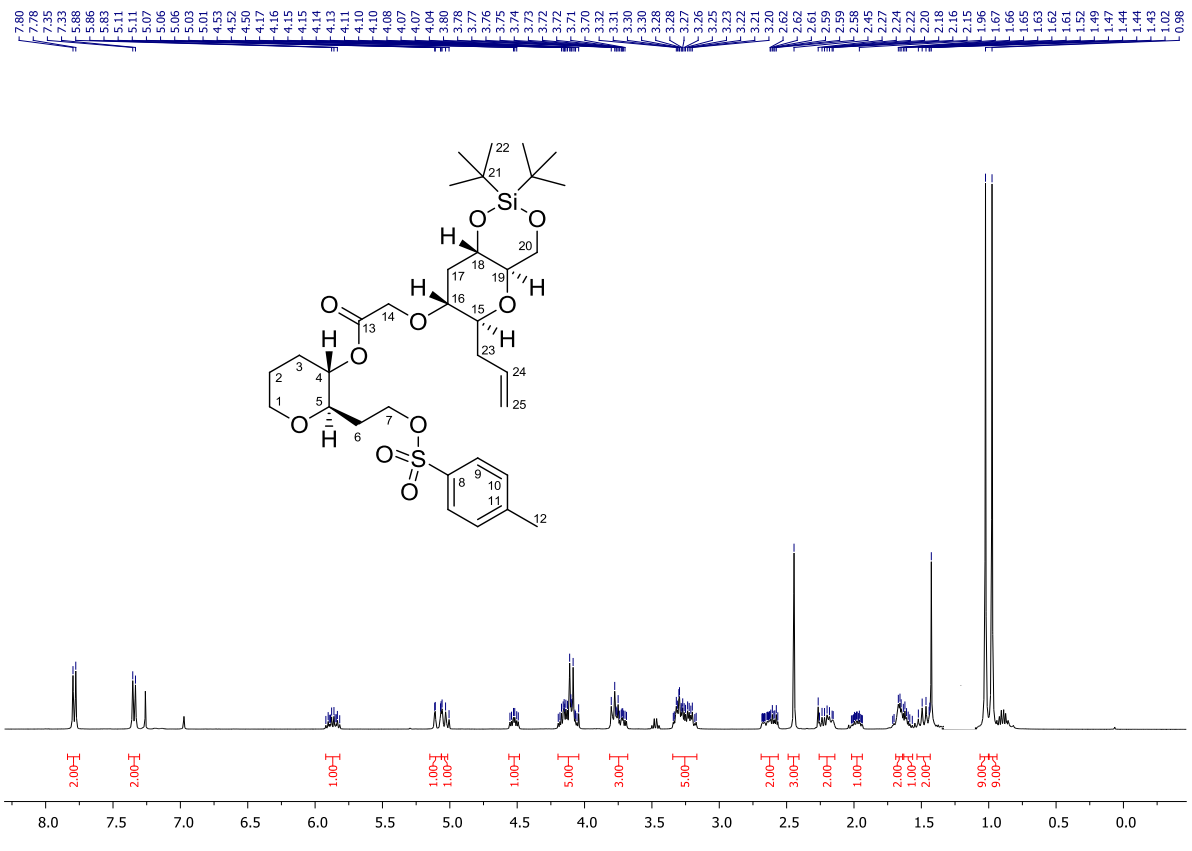

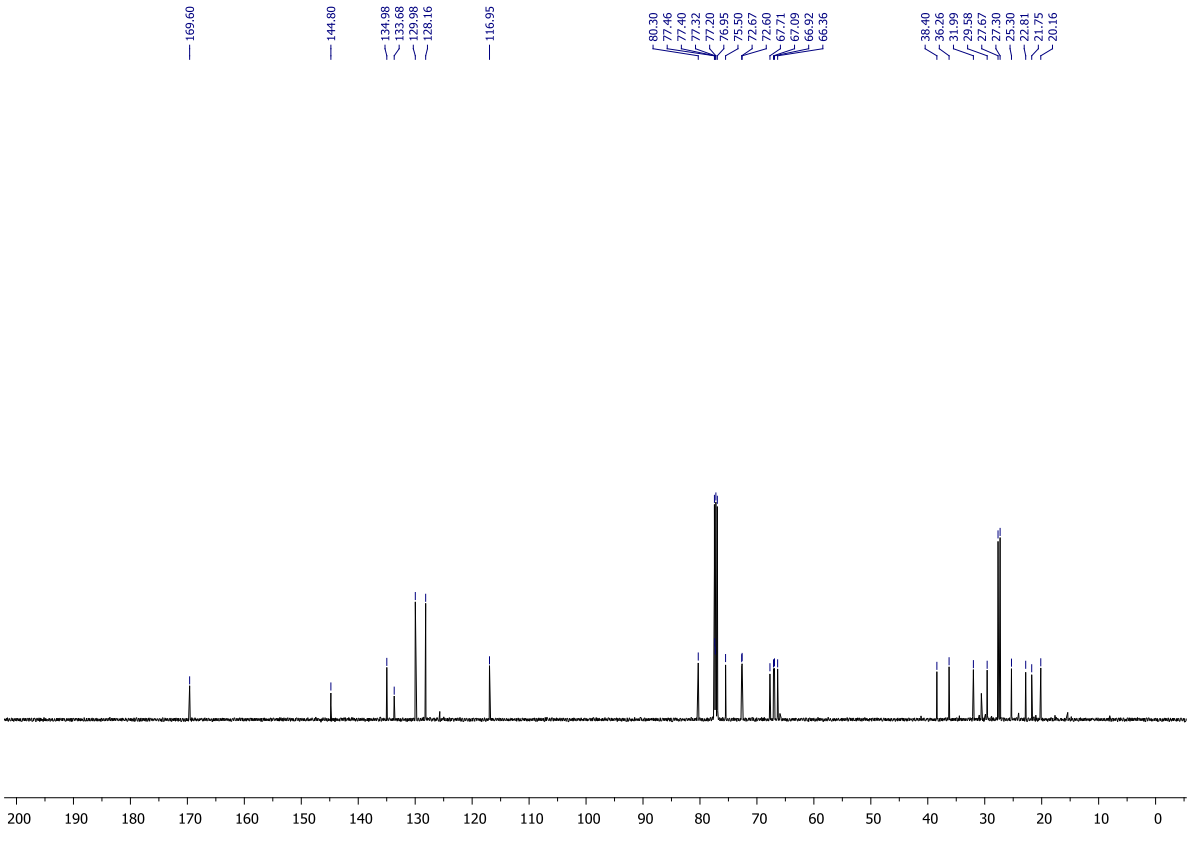

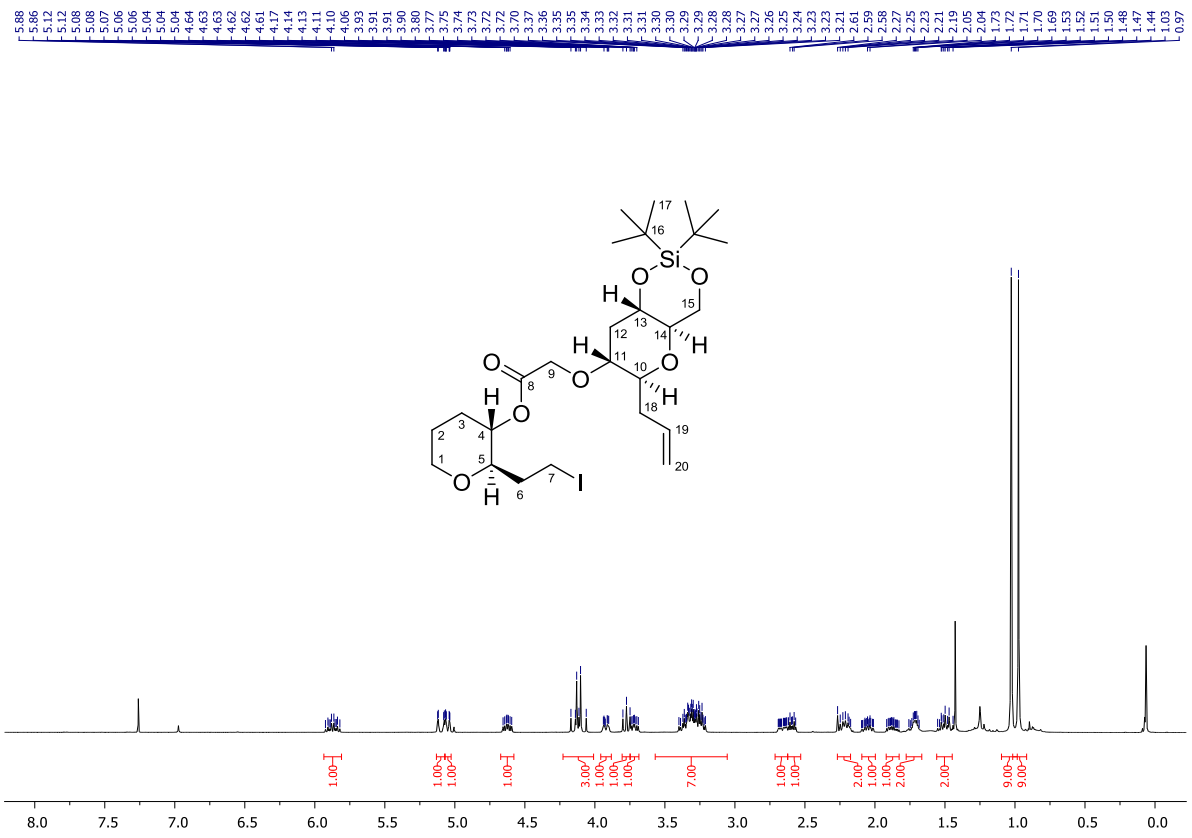

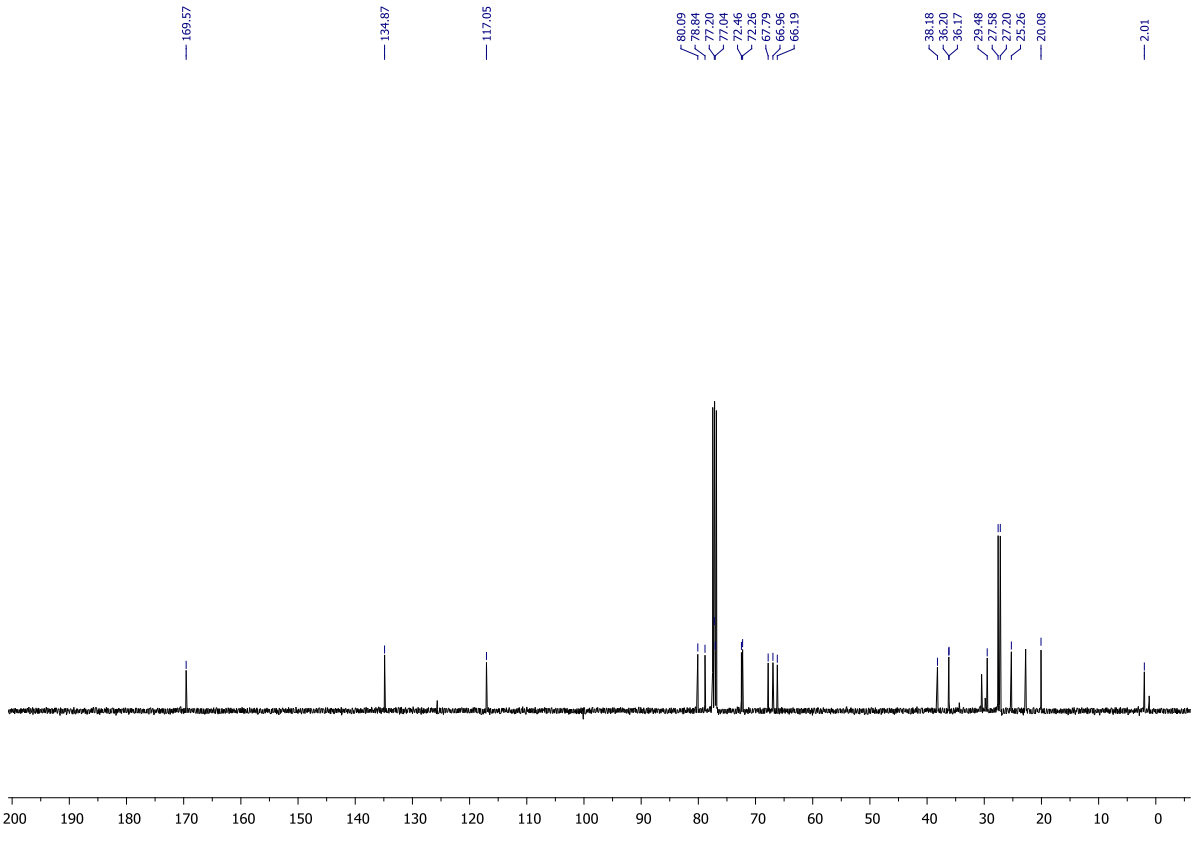

References

1 T. Yasumoto, M. Murata, *Chem. Rev.* **1993**, *93*, 1897-1909.
2 M. S. Lee, G. Qin, K. Nakanishi, M. G. Zagorski, *J. Am. Chem. Soc.* **1989**, *111*, 6234-6241.
3 M. Satake, M. Shoji, Y. Oshima, H. Naoki, T. Fujita, T. Yasumoto, *Tetrahedron Lett.* **2002**, *43*, 5829-5832.
4 K. Nakanishi, *Toxicon* **1985**, *23*, 473-479.
5 Y.-Y. Lin, M. Risk, S. M. Ray, D. Van Engen, J. Clardy, J. Golik, J. C. James, K. Nakanishi, *J. Am. Chem. Soc.* **1981**, *103*, 6773-6775.
6 H. Nagai, K. Torigoe, M. Satake, M. Murata, T. Yasumoto, H. Hirota, *J. Am. Chem. Soc.* **1992**, *114*, 1102-1103.
7 H. Nagai, M. Murata, K. Torigoe, M. Satake, T. Yasumoto, *J. Org. Chem.* **1992**, *57*, 5448-5453.
8 M. Satake, M. Murata, T. Yasumoto, *J. Am. Chem. Soc.* **1993**, *115*, 361-362.
9 M. Murata, A. M. Legrand, Y. Ishibashi, M. Fukui, T. Yasumoto, *J. Am. Chem. Soc.* **1990**, *112*, 4380-4386.
10 M. Murata, H. Naoki, T. Iwashita, S. Matsunaga, M. Sasaki, A. Yokoyama, T. Yasumoto, *J. Am. Chem. Soc.* **1993**, *115*, 2060-2062.
11 M. Murata, T. Yasumoto, *Nat. Prod. Rep.* **2000**, *17*, 293-314.
12 Y. Mori, K. Yaegashi, H. Furukawa, *J. Am. Chem. Soc.* **1996**, *118*, 8158-8159.
13 Y. Mori, H. Furuta, T. Takase, S. Mitsuoka, H. Furukawa, *Tetrahedron Lett.* **1999**, *40*, 8019-8022.
14 Y. Mori, K. Yaegashi, H. Furukawa, *Tetrahedron* **1997**, *53*, 12917-12932.
15 Y. Mori, K. Yaegashi, H. Furukawa, *J. Org. Chem.* **1998**, *63*, 6200-6209.
16 H. Furuta, M. Hase, R. Noyori, Y. Mori, *Org. Lett.* **2005**, *7*, 4061-4064.
17 T. Sakai, A. Sugimoto, Y. Mori, *Org. Lett.* **2011**, *13*, 5850-5853.
18 T. P. Heffron, T. F. Jamison, *Org. Lett.* **2003**, *5*, 2339-2342.
19 J. D. Warren, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7675-7677.
20 G. L. Simpson, T. P. Heffron, E. Merino, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 1056-1057.
21 N. Hayashi, K. Fujiwara, A. Murai, *Tetrahedron* **1997**, *53*, 12425-12468.
22 F. E. McDonald, X. Wang, B. Do, K. I. Hardcastle, *Org. Lett.* **2000**, *2*, 2917-2919.
23 F. Bravo, F. E. McDonald, W. A. Neiwert, B. Do, K. I. Hardcastle, *Org. Lett.* **2003**, *5*, 2123-2126.
24 I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189-1192.
25 Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807.
26 K. C. Nicolaou, C. A. Veale, C. K. Hwang, J. Hutchinson, C. V. C. Prasad, W. W. Ogilvie, *Angew. Chem. Int. Ed.* **1991**, *30*, 299-303.
27 H. Fuwa, M. Sasaki, K. Tachibana, *Tetrahedron Lett.* **2000**, *41*, 8371-8375.
28 M. B. Sassaman, K. D. Kotian, G. K. S. Prakash, G. A. Olah, *J. Org. Chem.* **1987**, *52*, 4314-4319.
29 K. Sato, M. Sasaki, *Tetrahedron* **2007**, *63*, 5977-6003.
30 P. A. Evans, J. Cui, S. J. Gharpure, R. J. Hinkle, *J. Am. Chem. Soc.* **2003**, *125*, 11456-11457.
31 G. Matsuo, H. Hinou, H. Koshino, T. Suenaga, T. Nakata, *Tetrahedron Lett.* **2000**, *41*, 903-906.
32 K. Fujiwara, H. Morishita, K. Saka, A. Murai, *Tetrahedron Lett.* **2000**, *41*, 507-508.
33 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440-467.
34 Y. Mori, S. Mitsuoka, H. Furukawa, *Tetrahedron Lett.* **2000**, *41*, 4161-4164.
35 J. Yamada, T. Asano, I. Kadota, Y. Yamamoto, *J. Org. Chem.* **1990**, *55*, 6066-6068.
36 Y. Yamamoto, J.-i. Yamada, I. Kadota, *Tetrahedron Lett.* **1991**, *32*, 7069-7072.

37 I. Kadota, A. Ohno, K. Matsuda, Y. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 6702-6703.
38 N. Hori, H. Matsukura, G. Matsuo, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 2811-2814.
39 N. Hori, H. Matsukura, T. Nakata, *Org. Lett.* **1999**, *1*, 1099-1101.
40 G. Matsuo, N. Hori, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 8859-8862.
41 N. Hori, H. Matsukura, G. Matsuo, T. Nakata, *Tetrahedron* **2002**, *58*, 1853-1864.
42 Y. Sakamoto, G. Matsuo, H. Matsukura, T. Nakata, *Org. Lett.* **2001**, *3*, 2749-2752.
43 G. Matsuo, K. Kawamura, N. Hori, H. Matsukura, T. Nakata, *J. Am. Chem. Soc.* **2004**, *126*, 14374-14376.
44 K. C. Nicolaou, C. K. Hwang, M. E. Duggan, K. B. Reddy, B. E. Marron, D. G. McGarry, *J. Am. Chem. Soc.* **1986**, *108*, 6800-6802.
45 K. C. Nicolaou, C. K. Hwang, B. E. Marron, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3040-3054.
46 K. C. Nicolaou, C. K. Hwang, M. E. Duggan, P. J. Carroll, *J. Am. Chem. Soc.* **1987**, *109*, 3801-3802.
47 K. C. Nicolaou, C. K. Hwang, S. DeFrees, N. A. Stylianides, *J. Am. Chem. Soc.* **1988**, *110*, 4868-4869.
48 K. C. Nicolaou, S. A. DeFrees, C. K. Hwang, N. Stylianides, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3029-3039.
49 H. Z. Lecher, R. A. Greenwood, K. C. Whitehouse, T. H. Chao, *J. Am. Chem. Soc.* **1956**, *78*, 5018-5022.
50 S. Scheibye, B. S. Pedersen, S. O. Lawesson, *Bull. Soc. Chim. Belg.* **1978**, *87*, 229-238.
51 K. C. Nicolaou, C. K. Hwang, D. A. Nugiel, *J. Am. Chem. Soc.* **1989**, *111*, 4136-4137.
52 K. C. Nicolaou, C. K. Hwang, D. A. Nugiel, *Angew. Chem. Int. Ed.* **1988**, *27*, 1362-1364.
53 M. Sasaki, M. Inoue, T. Noguchi, A. Takeichi, K. Tachibana, *Tetrahedron Lett.* **1998**, *39*, 2783-2786.
54 M. Sasaki, T. Noguchi, K. Tachibana, *Tetrahedron Lett.* **1999**, *40*, 1337-1340.
55 F. P. Marmsäter, F. G. West, *J. Am. Chem. Soc.* **2001**, *123*, 5144-5145.
56 F. P. Marmsäter, F. G. West, *Chem. Eur. J.* **2002**, *8*, 4346-4353.
57 F. P. Marmsäter, J. A. Vanecko, F. G. West, *Tetrahedron* **2002**, *58*, 2027-2040.
58 O. Fujimura, G. C. Fu, R. H. Grubbs, *J. Org. Chem.* **1994**, *59*, 4029-4031.
59 G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1993**, *115*, 9856-9857.
60 G. C. Fu, R. H. Grubbs, *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427.
61 F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613.
62 S. H. Pine, R. Zahler, D. A. Evans, R. H. Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 3270-3272.
63 N. A. Petasis, E. I. Bzowej, *J. Am. Chem. Soc.* **1990**, *112*, 6392-6394.
64 K. C. Nicolaou, M. H. D. Postema, C. F. Claiborne, *J. Am. Chem. Soc.* **1996**, *118*, 1565-1566.
65 K. C. Nicolaou, M. H. D. Postema, E. W. Yue, A. Nadin, *J. Am. Chem. Soc.* **1996**, *118*, 10335-10336.
66 J. D. Rainier, S. P. Allwein, *J. Org. Chem.* **1998**, *63*, 5310-5311.
67 J. D. Rainier, S. P. Allwein, J. M. Cox, *Org. Lett.* **2000**, *2*, 231-234.
68 J. D. Rainier, J. M. Cox, S. P. Allwein, *Tetrahedron Lett.* **2001**, *42*, 179-181.
69 S. P. Allwein, J. M. Cox, B. E. Howard, H. W. B. Johnson, J. D. Rainier, *Tetrahedron* **2002**, *58*, 1997-2009.
70 K. Takai, T. Kakiuchi, Y. Kataoka, K. Utimoto, *J. Org. Chem.* **1994**, *59*, 2668-2670.
71 S. W. Roberts, J. D. Rainier, *Org. Lett.* **2007**, *9*, 2227-2230.
72 K. Iyer, J. D. Rainier, *J. Am. Chem. Soc.* **2007**, *129*, 12604-12605.
73 H. W. B. Johnson, U. Majumder, J. D. Rainier, *J. Am. Chem. Soc.* **2005**, *127*, 848-849.
74 C. Osei Akoto, J. D. Rainier, *Angew. Chem. Int. Ed.* **2008**, *47*, 8055-8058.
75 Y. Zhang, J. Rohanna, J. Zhou, K. Iyer, J. D. Rainier, *J. Am. Chem. Soc.* **2011**, *133*, 3208-3216.
76 J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 123-126.
77 J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 127-130.
78 J. S. Clark, O. Hamelin, R. Hufton, *Tetrahedron Lett.* **1998**, *39*, 8321-8324.

79 J. S. Clark, R. P. Freeman, M. Cacho, A. W. Thomas, S. Swallow, C. Wilson, *Tetrahedron Lett.* **2004**, *45*, 8639-8642.
80 J. S. Clark, G. P. Trevitt, D. Boyall, B. Stammen, *Chem. Commun.* **1998**, 2629-2630.
81 J. S. Clark, F. Elustondo, G. P. Trevitt, D. Boyall, J. Robertson, A. J. Blake, C. Wilson, B. Stammen, *Tetrahedron* **2002**, *58*, 1973-1982.
82 J. S. Clark, F. Elustondo, M. C. Kimber, *Chem. Commun.* **2004**, 2470-2471.
83 J. S. Clark, O. Hamelin, *Angew. Chem. Int. Ed.* **2000**, *39*, 372-374.
84 J. S. Clark, M. C. Kimber, J. Robertson, C. S. P. McErlean, C. Wilson, *Angew. Chem. Int. Ed.* **2005**, *44*, 6157-6162.
85 A. Moyano, F. Charbonnier, A. E. Greene, *J. Org. Chem.* **1987**, *52*, 2919-2922.
86 S. E. Denmark, V. Guagnano, J. A. Dixon, A. Stolle, *J. Org. Chem.* **1997**, *62*, 4610-4628.
87 G. W. Kabalka, J. T. Maddox, T. Shoup, *Org. Synth.* **1996**, *73*, 116-122.
88 K. C. Nicolaou, D. G. McGarry, P. K. Sommers, *J. Am. Chem. Soc.* **1990**, *112*, 3696-3697.
89 J. S. Clark, D. M. Grainger, A. A. C. Ehkirch, A. J. Blake, C. Wilson, *Org. Lett.* **2007**, *9*, 1033-1036.
90 J. S. Clark, J. Conroy, A. J. Blake, *Org. Lett.* **2007**, *9*, 2091-2094.
91 T. Nakata, S. Nomura, H. Matsukura, *Tetrahedron Lett.* **1996**, *37*, 213-216.
92 T. Sakai, S. Ito, H. Furuta, Y. Kawahara, Y. Mori, *Org. Lett.* **2012**, *14*, 4564-4567.
93 R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413-4450.
94 K. Ziegler, E. Holzkamp, H. Breil, H. Martin, *Angew. Chem.* **1955**, *67*, 541-547.
95 K. Ziegler, *Angew. Chem.* **1964**, *76*, 545-553.
96 R. L. Banks, G. C. Bailey, *Ind. Eng. Chem., Prod. Res. Dev.* **1964**, *3*, 170-173.
97 R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117-7140.
98 A. Fürstner, *Angew. Chem. Int. Ed.* **2000**, *39*, 3012-3043.
99 N. Calderon, H. Y. Chen, K. W. Scott, *Tetrahedron Lett.* **1967**, *8*, 3327-3329.
100 J.-L. P. Hérisson, Y. Chauvin, *Makromol. Chem.* **1971**, *141*, 161-176.
101 F. N. Tebbe, G. W. Parshall, D. W. Ovenall, *J. Am. Chem. Soc.* **1979**, *101*, 5074-5075.
102 T. R. Howard, J. B. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **1980**, *102*, 6876-6878.
103 R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886.
104 R. R. Schrock, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2003**, *42*, 4592-4633.
105 G. C. Bazan, J. H. Oskam, H. N. Cho, L. Y. Park, R. R. Schrock, *J. Am. Chem. Soc.* **1991**, *113*, 6899-6907.
106 S. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975.
107 Z. Wu, A. D. Benedicto, R. H. Grubbs, *Macromolecules* **1993**, *26*, 4975-4977.
108 Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503-5511.
109 P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem. Int. Ed.* **1995**, *34*, 2039-2041.
110 M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953-956.
111 S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.
112 E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887-3897.
113 M. S. Sanford, J. A. Love, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.
114 M. E. Maier, *Angew. Chem. Int. Ed.* **2000**, *39*, 2073-2077.
115 M. W. Peczuh, N. L. Snyder, *Tetrahedron Lett.* **2003**, *44*, 4057-4061.
116 A. Mortreux, M. Blanchard, *J. Chem. Soc., Chem. Commun.* **1974**, 786-787.
117 M. L. Listemann, R. R. Schrock, *Organometallics* **1985**, *4*, 74-83.
118 A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, *121*, 9453-9454.
119 A. Mortreux, O. Coutelier, *J. Mol. Catal. A: Chem.* **2006**, *254*, 96-104.
120 J. H. Wengrovius, J. Sancho, R. R. Schrock, *J. Am. Chem. Soc.* **1981**, *103*, 3932-3934.
121 A. Fürstner, G. Seidel, *Angew. Chem. Int. Ed.* **1998**, *37*, 1734-1736.
122 A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307-2320.
123 A. Fürstner, C. Mathes, K. Grela, *Chem. Commun.* **2001**, 1057-1059.

124 A. Fürstner, C. Mathes, C. W. Lehmann, *Chem. Eur. J.* **2001**, *7*, 5299-5317.
125 D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1997**, *119*, 10073-10092.
126 K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem. Int. Ed.* **1998**, *37*, 2014-2045.
127 A. Fürstner, K. Radkowski, *Chem. Commun.* **2002**, 2182-2183.
128 F. Lacombe, K. Radkowski, G. Seidel, A. Fürstner, *Tetrahedron* **2004**, *60*, 7315-7324.
129 B. M. Trost, Z. T. Ball, T. Jöge, *J. Am. Chem. Soc.* **2002**, *124*, 7922-7923.
130 B. M. Trost, M. R. Machacek, Z. T. Ball, *Org. Lett.* **2003**, *5*, 1895-1898.
131 A. Fürstner, M. Bonnekessel, J. T. Blank, K. Radkowski, G. Seidel, F. Lacombe, B. Gabor, R. Mynott, *Chem. Eur. J.* **2007**, *13*, 8762-8783.
132 K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064-14066.
133 J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045-11057.
134 S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317-1382.
135 T. J. Katz, T. M. Sivavec, *J. Am. Chem. Soc.* **1985**, *107*, 737-738.
136 A. Kinoshita, M. Mori, *Synlett* **1994**, *1994*, 1020-1022.
137 G. C. Lloyd-Jones, R. G. Margue, J. G. de Vries, *Angew. Chem. Int. Ed.* **2005**, *44*, 7442-7447.
138 L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136.
139 T. R. Hoye, C. S. Jeffrey, M. A. Tennakoon, J. Wang, H. Zhao, *J. Am. Chem. Soc.* **2004**, *126*, 10210-10211.
140 M. Kim, D. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 18024-18025.
141 M. Kim, R. L. Miller, D. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12818-12819.
142 W. A. L. van Otterlo, E. Lindani Ngidi, C. B. de Koning, M. A. Fernandes, *Tetrahedron Lett.* **2004**, *45*, 659-662.
143 J. Li, S. Park, R. L. Miller, D. Lee, *Org. Lett.* **2008**, *11*, 571-574.
144 E. J. Cho, D. Lee, *Org. Lett.* **2008**, *10*, 257-259.
145 H. Villar, M. Frings, C. Bolm, *Chem. Soc. Rev.* **2007**, *36*, 55-66.
146 D. A. Kummer, J. B. Brenneman, S. F. Martin, *Org. Lett.* **2005**, *7*, 4621-4623.
147 F. Royer, C. Vilain, L. Elkaïm, L. Grimaud, *Org. Lett.* **2003**, *5*, 2007-2009.
148 P. Dewi, S. Randl, S. Blechert, *Tetrahedron Lett.* **2005**, *46*, 577-580.
149 S.-H. Kim, N. Bowden, R. H. Grubbs, *J. Am. Chem. Soc.* **1994**, *116*, 10801-10802.
150 A. Niethe, D. Fischer, S. Blechert, *J. Org. Chem.* **2008**, *73*, 3088-3093.
151 T. R. Hoye, H. Zhao, *Org. Lett.* **1999**, *1*, 1123-1125.
152 S. Michaelis, S. Blechert, *Org. Lett.* **2005**, *7*, 5513-5516.
153 F.-D. Boyer, I. Hanna, *Tetrahedron Lett.* **2002**, *43*, 7469-7472.
154 F.-D. Boyer, I. Hanna, L. Ricard, *Org. Lett.* **2004**, *6*, 1817-1820.
155 L. T. Truxal, A. J. Bourdelais, H. Jacocks, W. M. Abraham, D. G. Baden, *J. Nat. Prod.* **2010**, *73*, 536-540.
156 W. Zheng, J. A. DeMattei, J.-P. Wu, J. J. W. Duan, L. R. Cook, H. Oinuma, Y. Kishi, *J. Am. Chem. Soc.* **1996**, *118*, 7946-7968.
157 T. Nonomura, M. Sasaki, N. Matsumori, M. Murata, K. Tachibana, T. Yasumoto, *Angew. Chem. Int. Ed.* **1996**, *35*, 1675-1678.
158 K. C. Nicolaou, M. O. Frederick, *Angew. Chem. Int. Ed.* **2007**, *46*, 5278-5282.
159 T. Igarashi, M. Satake, T. Yasumoto, *J. Am. Chem. Soc.* **1999**, *121*, 8499-8511.
160 A. Bayle, University of Glasgow (Glasgow), **2011**.
161 B. Sieng, University of Glasgow (Glasgow), **2011**.
162 J. Jurczak, S. Pikul, T. Bauer, *Tetrahedron* **1986**, *42*, 447-488.
163 H. Sörensen, A. E. Greene, *Tetrahedron Lett.* **1990**, *31*, 7597-7598.
164 L.-O. Pålsson, C. Wang, A. S. Batsanov, S. M. King, A. Beeby, A. P. Monkman, M. R. Bryce, *Chem. Eur. J.* **2010**, *16*, 1470-1479.
165 J. K. Stille, *Angew. Chem.* **1986**, *98*, 504-519.
166 P. Cheshev, A. Marra, A. Dondoni, *Carbohydr. Res.* **2006**, *341*, 2714-2716.
167 Q. Zhang, Z.-Y. Jiang, J. Luo, J.-F. Liu, Y.-B. Ma, R.-H. Guo, X.-M. Zhang, J. Zhou, J.-J. Chen, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2148-2153.

168 E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769-3772.
169 H. J. Bestmann, H. Frey, *Liebigs Ann. Chem.* **1980**, *1980*, 2061-2071.
170 R. J. P. Corriu, J. P. Masse, *J. Chem. Soc., Chem. Commun.* **1972**, 144-145.
171 M. Braun, A. Hohmann, J. Rahematpura, C. Bühne, S. Grimme, *Chem. Eur. J.* **2004**, *10*, 4584-4593.
172 E. Valenti, M. A. Pericas, F. Serratosa, *J. Am. Chem. Soc.* **1990**, *112*, 7405-7406.
173 J. R. Sosa, A. A. Tudjarian, T. G. Minehan, *Org. Lett.* **2008**, *10*, 5091-5094.
174 M. T. Crimmins, J. M. Ellis, K. A. Emmitte, P. A. Haile, P. J. McDougall, J. D. Parrish, J. L. Zuccarello, *Chem. Eur. J.* **2009**, *15*, 9223-9234.
175 R. Cheaib, A. Listkowski, S. Chambert, A. Doutheau, Y. Queneau, *Tetrahedron: Asymmetry* **2008**, *19*, 1919-1933.
176 M. T. Crimmins, J. M. Stevens, G. M. Schaaf, *Org. Lett.* **2009**, *11*, 3990-3993.
177 D. Crich, F. Cai, *Org. Lett.* **2007**, *9*, 1613-1615.
178 B. Neises, W. Steglich, *Angew. Chem. Int. Ed.* **1978**, *17*, 522-524.
179 A. G. Myers, R. Glatthar, M. Hammond, P. M. Harrington, E. Y. Kuo, J. Liang, S. E. Schaus, Y. Wu, J.-N. Xiang, *J. Am. Chem. Soc.* **2002**, *124*, 5380-5401.
180 G. Campiani, V. Nacci, I. Fiorini, M. P. De Filippis, A. Garofalo, S. M. Ciani, G. Greco, E. Novellino, D. C. Williams, D. M. Zisterer, M. J. Woods, C. Mihai, C. Manzoni, T. Mennini, *J. Med. Chem.* **1996**, *39*, 3435-3450.
181 G. Pruckmayr, T. K. Wu, *Macromolecules* **1978**, *11*, 662-668.
182 R. J. Ferrier, W. G. Overend, A. E. Ryan, *J. Chem. Soc.* **1962**, 3667-3670.
183 M. Okabe, R.-C. Sun, *Tetrahedron Lett.* **1989**, *30*, 2203-2206.
184 E. Alvarez, M. Delgado, M. Teresa Díaz, L. Hanxing, R. Pérez, J. D. Martín, *Tetrahedron Lett.* **1996**, *37*, 2865-2868.
185 K. C. Nicolaou, M. O. Frederick, A. C. B. Burtoloso, R. M. Denton, F. Rivas, K. P. Cole, R. J. Aversa, R. Gibe, T. Umezawa, T. Suzuki, *J. Am. Chem. Soc.* **2008**, *130*, 7466-7476.
186 J. Qi, A. R. Blanden, S. Bane, D. G. I. Kingston, *Biorg. Med. Chem.* **2011**, *19*, 5247-5254.
187 E. J. Corey, G. Schmidt, *Tetrahedron Lett.* **1979**, *20*, 399-402.
188 U. Majumder, J. D. Rainier, *Tetrahedron Lett.* **2005**, *46*, 7209-7211.
189 J. Ramza, A. Zamojski, *Carbohydr. Res.* **1992**, *228*, 205-216.
190 K. A. Stein, P. L. Toogood, *J. Org. Chem.* **1995**, *60*, 8110-8112.
191 T.-Z. Liu, J.-M. Li, M. Isobe, *Tetrahedron* **2000**, *56*, 10209-10219.
192 K. Sato, M. Sasaki, *Angew. Chem. Int. Ed.* **2007**, *46*, 2518-2522.
193 J. Bi, V. K. Aggarwal, *Chem. Commun.* **2008**, 120-122.
194 A. Kamal, S. R. Vangala, *Tetrahedron* **2011**, *67*, 1341-1347.
195 J. Mulzer, A. Angermann, W. Münch, *Liebigs Ann. Chem.* **1986**, *1986*, 825-838.
196 H. Uehara, T. Oishi, M. Inoue, M. Shoji, Y. Nagumo, M. Kosaka, J.-Y. Le Brazidec, M. Hirama, *Tetrahedron* **2002**, *58*, 6493-6512.
197 Z. Chen, H. Jiang, A. Wang, S. Yang, *J. Org. Chem.* **2010**, *75*, 6700-6703.
198 F. Leonelli, M. Capuzzi, V. Calcagno, P. Passacantilli, G. Piancatelli, *Eur. J. Org. Chem.* **2005**, 2671-2676.
199 P. Lesimple, J.-M. Beau, P. Sinaÿ, *Carbohydr. Res.* **1987**, *171*, 289-300.
200 S. Kobayashi, Y. Takahashi, K. Komano, B. H. Alizadeh, Y. Kawada, T. Oishi, S.-i. Tanaka, Y. Ogasawara, S.-y. Sasaki, M. Hirama, *Tetrahedron* **2004**, *60*, 8375-8396.
201 L. Cipolla, L. Lay, F. Nicotra, *J. Org. Chem.* **1997**, *62*, 6678-6681.
202 O. Frey, M. Hoffmann, V. Wittmann, H. Kessler, P. Uhlmann, A. Vasella, *Helv. Chim. Acta* **1994**, *77*, 2060-2069.
203 A. R. Banaag, M. A. Tius, *J. Am. Chem. Soc.* **2007**, *129*, 5328-5329.
204 T. Oishi, Y. Nagumo, M. Hirama, *Synlett* **1997**, *1997*, 980-982.
205 E. Alvarez, R. Pérez, M. Rico, R. M. Rodríguez, J. D. Martín, *J. Org. Chem.* **1996**, *61*, 3003-3016.
206 M. Delgado, J. D. Martín, *J. Org. Chem.* **1999**, *64*, 4798-4816.
207 O. J. Donadel, T. Martín, V. S. Martín, J. Villar, J. M. Padrón, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3536-3539.

208 K. Fujiwara, H. Morishita, K. Saka, A. Murai, *Tetrahedron Lett.* **2000**, *41*, 507-508.
209 K. Fujiwara, K. Saka, D. Takaoka, A. Murai, *Synlett* **1999**, *1999*, 1037-1040.
210 B. W. Gung, R. M. Fox, *Tetrahedron* **2004**, *60*, 9405-9415.
211 H. Furuta, Y. Hasegawa, M. Hase, Y. Mori, *Chem. Eur. J* **2010**, *16*, 7586-7595.