Toward the Two-Directional Synthesis of the IJK-Ring System of the Marine Polyether CTX3C

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Thesis submitted in fulfilment of the requirements for
the degree of Doctor of Philosophy

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September 2014

Abstract

This thesis describes efforts made towards the two-directional synthesis of the IJK-tricyclic core of the H-M ring system of CTX3C.

The first chapter serves as an introduction to the complex marine polyether natural products and details their toxicology and biosynthetic origins. A literature review of the advances made by our research group, as well as in other laboratories, towards the iterative and convergent synthesis of polycyclic ethers, with particular emphasis on the ciguatoxins is also included. This is followed by a review of olefin metathesis and the use of double ring-closing metathesis reactions for the preparation of complex polycyclic systems.

The second chapter details the construction of two model systems to allow for investigation into the chemistry required for the synthesis of both the I- and K-rings. Following the successful construction of the two model systems, the chemistry developed was then employed in a two-directional strategy toward the synthesis of the target IJK-tricyclic core.

Declaration

I declare that the substance of this thesis has not been submitted, nor is concurrently being submitted in candidature for any other degree. I further declare that the work presented in this manuscript is the result of my own investigation. Where the work of others has been utilised, this has been acknowledged in the appropriate manner.

Helen Gibbard

Prof. J. Stephen Clark

Acknowledgements

First and foremost, I would like to thank Professor J. Stephen Clark for giving me the opportunity to work on such a challenging and rewarding project. I appreciate all the advice and support he has given me over the past three years. I would also like to extend my gratitude to Dr Alistair Boyer for all his help and advice.

The University of Glasgow and WestChem are acknowledged for financial support as well as the technical staff within the school; Dr David Adam (NMR spectroscopy), Jim Tweedie and Harry Jackson (mass spectroscopy) and Ted Easton (stores).

I would also like to thank all the people I have met and worked with in the Clark group over the past three years. Firstly, thank you to Euan, Ralph, Derek, Flavien, Paloma, Guang, Andy, Raphaëlle, Emelie and Alex for welcoming me into the group. I want to thank Alistair, Michael, Filo, Laura, Aurelien, Ludovic, Verena and Ian who made the time spent in the lab more fun and interesting. A special thank you goes to Emilie, Laetitia and Chao for always being around for cookies and hot chocolate. I must not forget to thank Tony, for always being able to make to smile.

Thanks to Geoff for all his patience, support and encouragement during the past couple of years.

Finally, I would like to thank my parents. I am fortunate to have such an understanding and supportive family.

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
AIBN	2,2′-azobis(2-methylpropionitrile)
aq	aqueous
Ar	aryl
BINOL	1,1′-bi-2-napthol
Bn	benzyl
brsm	based on recovered starting material
i-Bu	*iso*-butyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
°C	degrees Celsius
cat.	catalytic
CSA	10-camphorsulfonic acid
Cp	cyclopentadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicycano-1,4-benzoquinone
DIBAL	diisobutylaluminium hydride
DIPA	diisopropylamine
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyl dioxirane
DME	dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone
DMSO	dimethyl sulfoxide
dppf	diphenylphosphinoferrocene
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EC_{50}	half maximum effective concentration

EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EE	ethoxyether
Et	ethyl
g	gram(s)
h	hour(s)
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
L	litre
LD_{50}	median lethal dose
LDA	lithium diisopropylamide
M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
min	minute(s)
MOM	methoxymethyl
mol	mole(s)
MS	molecular sieves
NAP	2-napthylmethyl
NCS	*N*-chloro succinimide
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
i-Pr	*iso*-propyl
n-Pr	*n*-propyl
Py	pyridine

R	general substituents
RCM	ring-closing metathesis
RORCM	ring-opening ring-closing metathesis
rt	room temperature
SM	starting material
SO_3·py	sulfur trioxide pyridine complex
TBACl	tetra-*n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperdinyl)oxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
Thexyl	1,1,2-trimethylpropyl
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*para*-toluenesulfonyl

Contents

Chapter 1: Introduction

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1.0 Marine Natural Products

Marine organisms have proven to be rich reservoirs of structurally diverse natural products.[1] Many of these compounds display complex molecular architectures and potent toxicities. Several marine natural products have been identified as the causative agents in various seafood-related poisonings. These include compounds that cause diarrhetic shellfish poisoning (okadaic acid, **1**),[2] amnesic shellfish poisoning (domoic acid, **2**),[3] paralytic shellfish poisoning (saxitoxin, **3**)[4] and ciguatera (CTX3C, **4**) (**Figure 1**).[5]

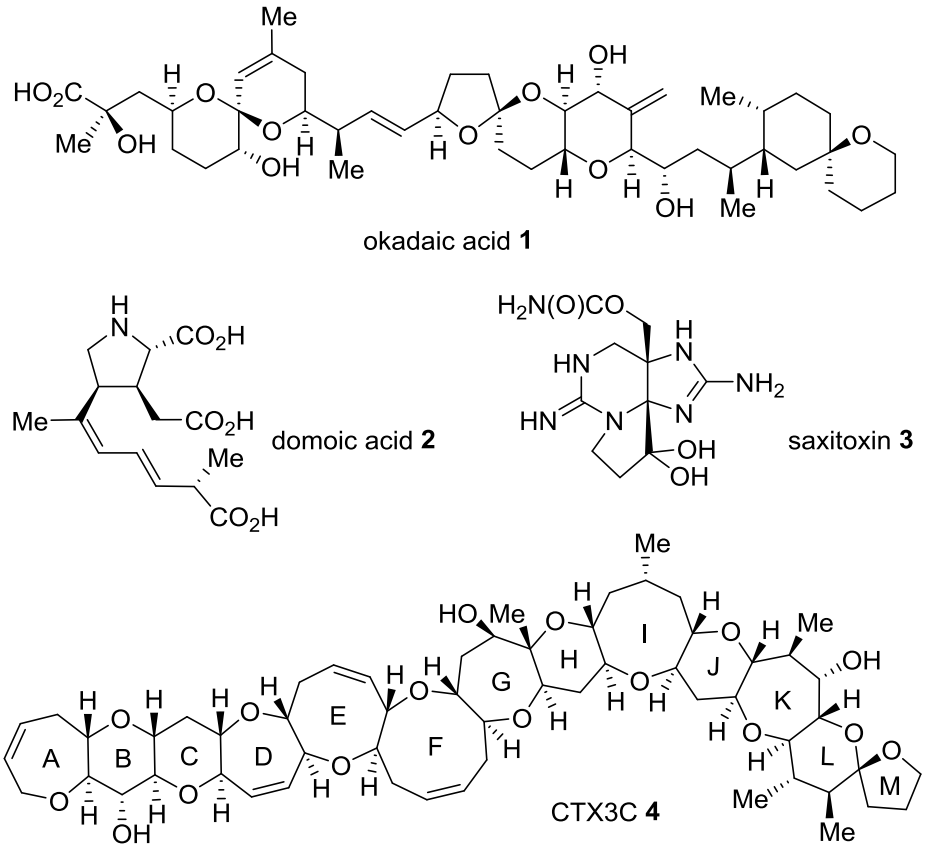


Figure 1

1.1 Ciguatera and the Ciguatoxins

Ciguatera is a form of food poisoning that results from the consumption of tropical and sub-tropical coral reef fish that have been contaminated with marine biotoxins. It is a debilitating disease that results in numerous disorders affecting the gastrointestinal, neurological and cardiovascular systems.[6] These symptoms can persist for weeks, months or even years.[7] It has been estimated, that worldwide around 10000—50000 individuals suffer from this form of poisoning every year.[8] With the rapid development of tourism and the growing international trade in seafood, poisoning of this type has become a potential threat on a global scale.[9] It has been estimated that only 2—10% of cases are documented by heath authorities as a consequence of misdiagnosis and under-reporting.[10]

In 1977, Yasumoto and co-workers discovered that ciguatoxins, the principle causative agents of ciguatera, were produced by the epiphytic dinoflagellate *Gambierdiscus toxicus*.[11] These biotoxins can be transferred to the herbivorous and carnivorous fish through the aquatic food chain. Over 400 species of coral reef fish have been identified as vectors of the ciguatera toxins, which accumulate in all fish tissues.

In 1989, the structure of ciguatoxin CTX1B (**5**) was successfully elucidated by Yasumoto and co-workers using 0.35 mg of the toxin extracted from moray eels (*Gymnthorax javanicus*) (**Figure 2**).[12] Shortly after, the structures of CTX3C (**4**) and 51-hydroxyCTX3C (**7**) were reported.[13] Studies have determined that ciguatoxins isolated from fish of the Pacific Ocean (**4**—**7**) show structural distinctions from those isolated from fish of the Caribbean Sea (**8**).[14] To date, over 20 different structural congeners of ciguatoxin have been isolated and characterised.

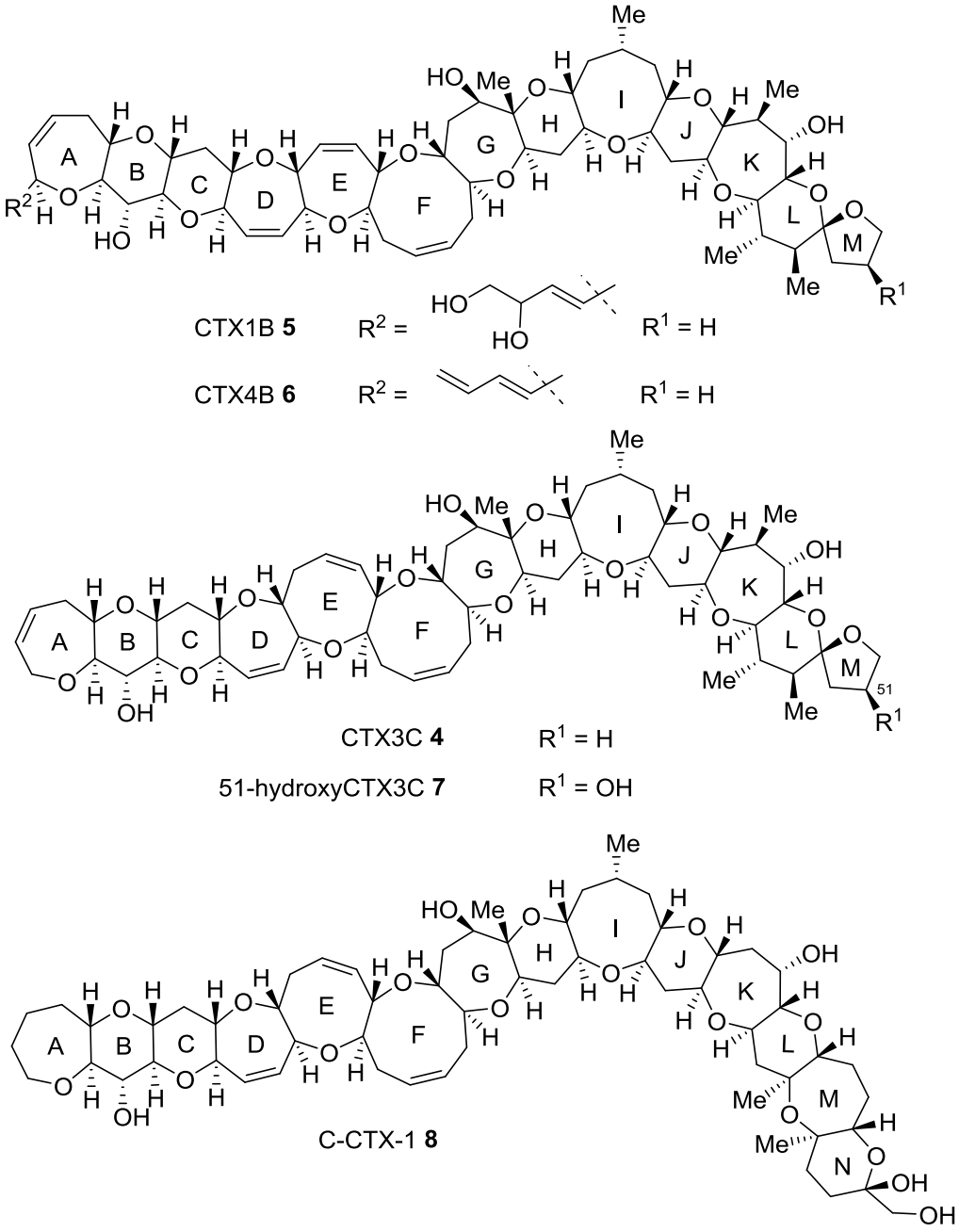


Figure 2

1.2 Marine Polycyclic Ethers

The ciguatoxins belong to the marine polyether class of natural products. Other members of the polycyclic ether family include hemibrevitoxin B (**9**),[15] brevetoxins A (**10**) and B (**11**),[16] and gambierol (**12**) (**Figure 3**).[17]

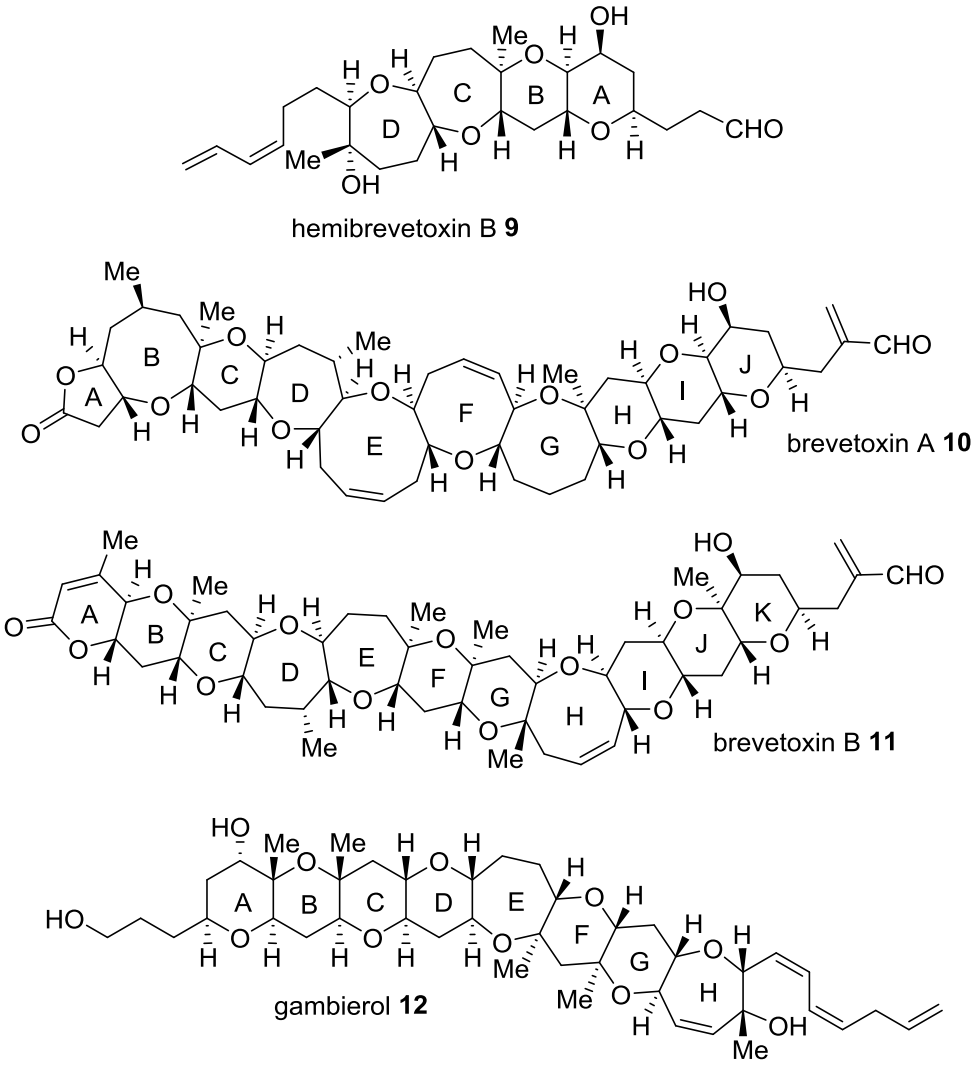


Figure 3

These polyether compounds are characterised by a single carbon chain locked into a long, semi-rigid, ladder-like structure. They contain distinctive extended arrays of *trans*-fused cyclic ethers that range in size from five- to nine-membered.[18] The oxygen atoms of the ether rings are placed alternatively on the northern and southern edges of the molecule. The stereochemistry of the carbon atoms adjacent to the oxygen strictly alternates between *R* and *S* configuration (**Figure 4**).[19]

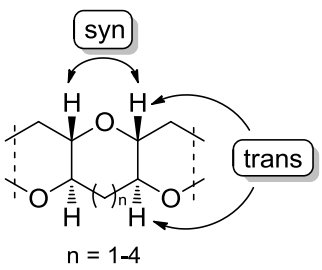


Figure 4

1.3 Toxicology and Therapy

Ciguatoxins and brevetoxins are known to affect the function of various cell types (nerve, heart and muscle cells) by binding to the voltage-sensitive sodium channels of excitable membranes. These transmembrane ion channels are heteromeric proteins consisting of α- and ß-subunits that are activated upon changes in electrical membrane potential.[19] Upon binding to the α-subunit of the ion channel protein, these toxins induce a conformational change resulting in the persistent activation of the channel. The resultant prolonged depolarization causes a continuous influx of sodium ions and neurotransmitter release, which ultimately leads to blockage of impulse conduction and a failure in transmitter release.[19] Binding of the toxins to the ion channel protein is believed to occur primarily through hydrogen bonding and/or electrostatic forces.[1] **Figure 5** highlights the possible interactions between the α-helix peptide and the ladder-like polyether. The average distance between the oxygen atoms on one side of the polyether structure matches the pitch of the α-helix.[20]

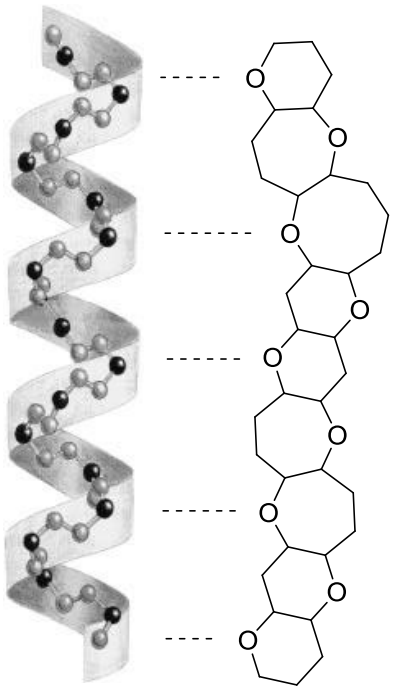
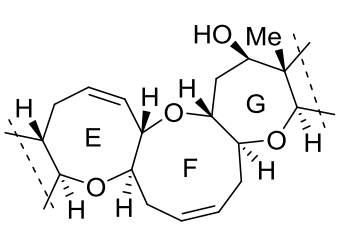


Figure 5[20]

Pharmacological studies have revealed that the toxicity of these molecules is associated with two main structural factors: the molecular size of the polyether and its conformational flexibility.[19] The first of these factors accounts for the low toxicity of tetracyclic hemibrevetoxin B (**9**). Conformational flexibility explains the lower toxicity of brevetoxin B (**11**) when compared to brevetoxin A (**10**) and CTX3C (**4**). Brevetoxin B (**11**) has a more rigid conformation imposed by the longer *trans*-fused sequence of six-membered rings. Both **10** and **4** have more flexible conformations due to the presence seven-, eight- and nine-membered rings in the central region of the molecules.

Through the biological evaluation of F-ring analogues of 51-hydroxyCTX3C (**7**), Hirama and co-workers demonstrated the structural importance of the nine-membered F-ring.[21] Synthetic analogues **13** and **14** were subjected to various biological assays: ligand-receptor interaction, *in vitro* activity and *in vivo* activity (**Table 1**). Both the *in vitro* and *in vivo* activities for analogues **13** and **14** were notably weaker than those observed for **7**, a finding that is consistent with the diminished affinities for the target receptor. Clearly, alterations in the F-ring structure have a significant effect of the bioactivity of the corresponding analogues.



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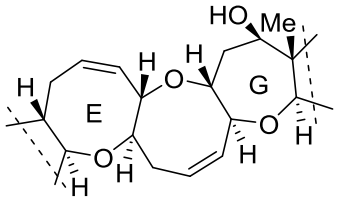

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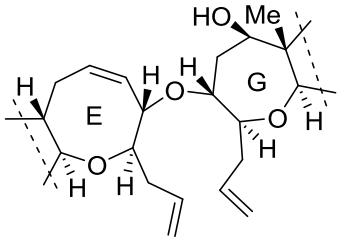


14

Polyether	Receptor interaction[a] K_i [nM]	Cytotoxicity[b] EC_{50} [nM]	Acute toxicity[c] LD_{50} [μg kg^{-1}]
7	0.0646	0.00326	0.31
13	11.2	103	> 667
14	125	170	> 667

[a] Dissociation constants measured against 5.0 nM [^{3}H]-**11**.

[b] Cytotoxicity determined as the EC_{50} value of mouse neuroblastoma cells Neuro-2A.

[c] Acute toxicity determined as the LD_{50} value in intraperitoneal injected mice.

Table 1[21]

A victim of ciguatera poisoning usually experiences the onset of symptoms within six to twenty four hours of eating the contaminated fish. Gastrointestinal problems common to other types of food poisoning such as nausea, vomiting and diarrhoea are followed by neurological symptoms that include dizziness, numbness, headaches and a sensation of temperature reversal.[22] Despite recent advances in the understanding of the pharmacological properties of ciguatoxins, no direct treatment for ciguatera poisoning has been identified. Treatment options focus primarily on the relief of symptoms: these include opiates for pain, along with antiemetic agents.[23]

Recently, attention has turned toward the development of new antibody-based therapeutic methods for the treatment of ciguatera poisoning. Hirama and co-workers have shown that CTX3C (**4**) can be effectively neutralized *in vitro* and *in vivo* through the simultaneous use of two anti-ciguatoxin monoclonal antibodies.[23] The monoclonal antibodies, specific against both ends of CTX3C (**4**), were prepared by immunization of mice with protein conjugates of two synthetic haptens **15** and **16** (**Figure 6**).[24] This work is the first step in a process leading toward the *in vivo* detoxification of ciguatoxins by the rational application of monoclonal antibodies. The next step is to produce effective and safe ciguatoxin antibodies suitable for human treatment.[25]

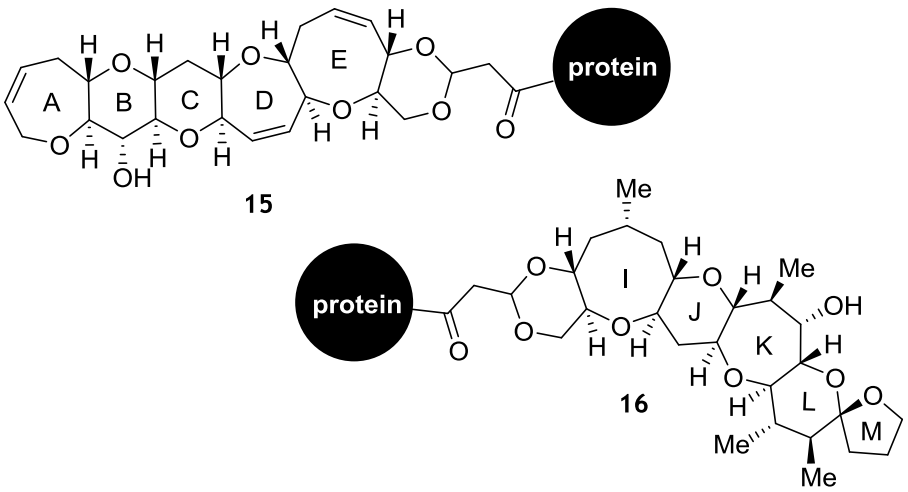
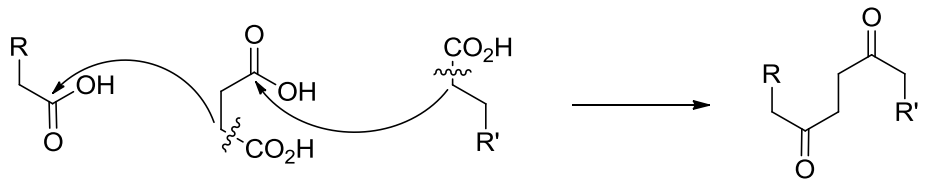


Figure 6

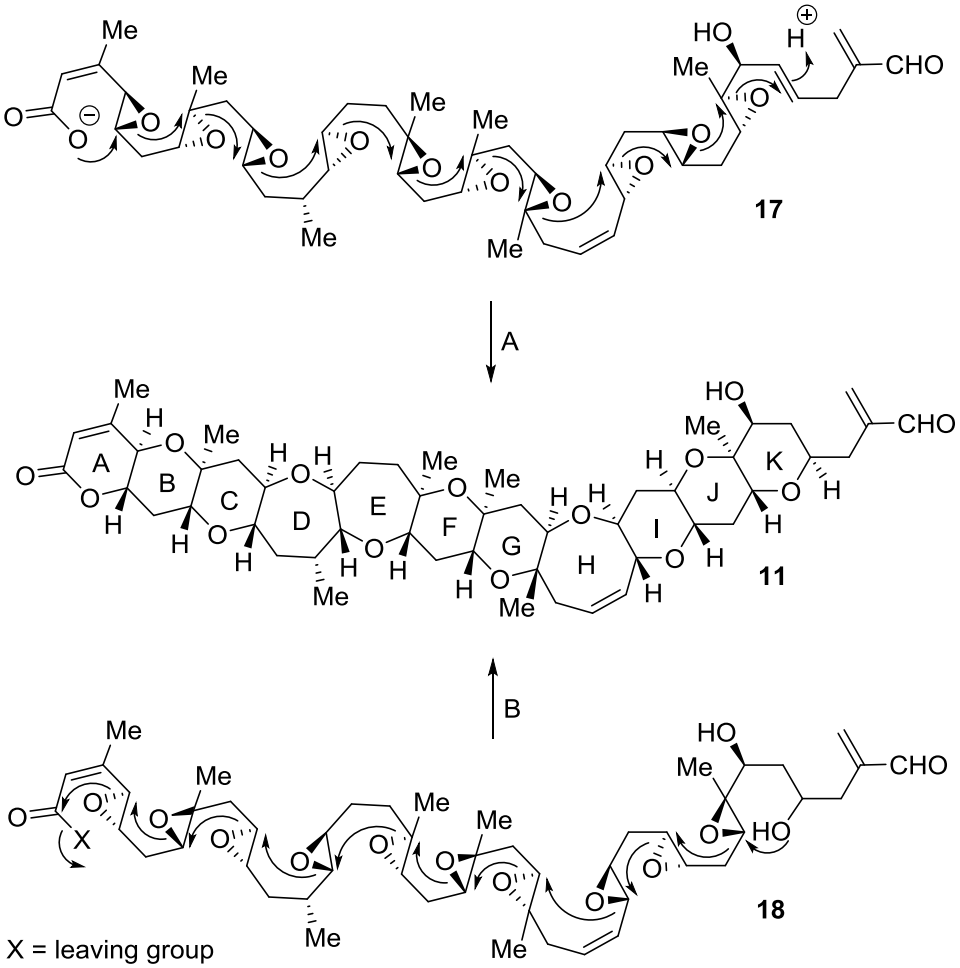
1.4 Biosynthesis of the Marine Polycyclic Ethers

To date, research into the biosynthetic origin of fused polycyclic ethers has focussed on the brevetoxins. The polycyclic ether skeleton was initially thought to be constructed through the standard polyketide pathway, in which linear Claisen-type condensations of acetate units form the carbon backbone.[26] Through ^{13}C-labelled studies, Nakanishi and Shimizu investigated the origin of the carbon atoms in the carbon backbone of both brevetoxins A (**10**) and B (**11**).[16a, 27] In the standard polyketide pathway, the acetate-derived carbons are expected to be arranged in head-to-tail linkage.[28] However, the ^{13}C-labelled studies of the brevetoxins revealed that some of the carboxyl-derived carbons were missing from the carbon skeleton. This data suggested that the brevetoxins were mixed polyketides whose biosynthesis required the use of dicarboxylic acids (**Scheme 1**).[26]



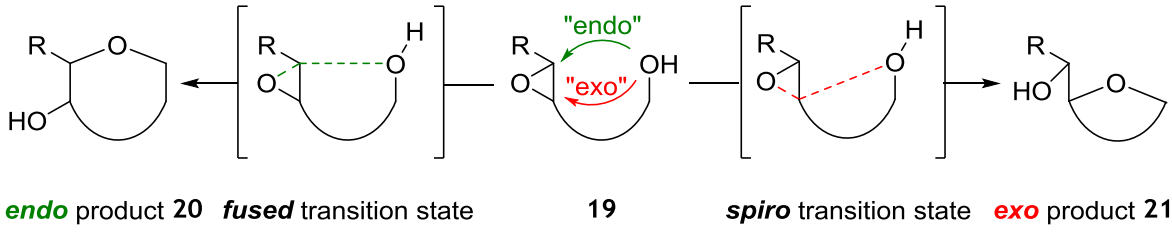
Scheme 1[26]

For several years, it has been postulated that nature synthesises the complex polycyclic ethers and other related natural products utilizing tandem oxacyclizations to construct several rings and multiple stereocentres in an efficient manner.[29] Nakanishi and co-workers proposed that a cascade reaction involving polyepoxide precursor **17** may be responsible for the enzymatic controlled biosynthesis of brevetoxin B (**11**) (**Scheme 2**).[1, 16a] Successive ring closure of polyepoxide **17** can be initiated upon attack of the carboxylate anion at the left terminus of the carbon chain (pathway A, **Scheme 2**). Shimizu and co-workers proposed an alternative pathway, involving intramolecular attack of a hydroxyl group on the right terminus of the carbon chain which triggers the cascade reaction of polyepoxide **18** in the opposite direction (pathway B, **Scheme 2**).[15a, 27] The cascade reaction of either polyepoxide precursor requires disfavoured *endo*-tet S_N2 reactions, which violate Baldwin's rules for ring closure.[30]



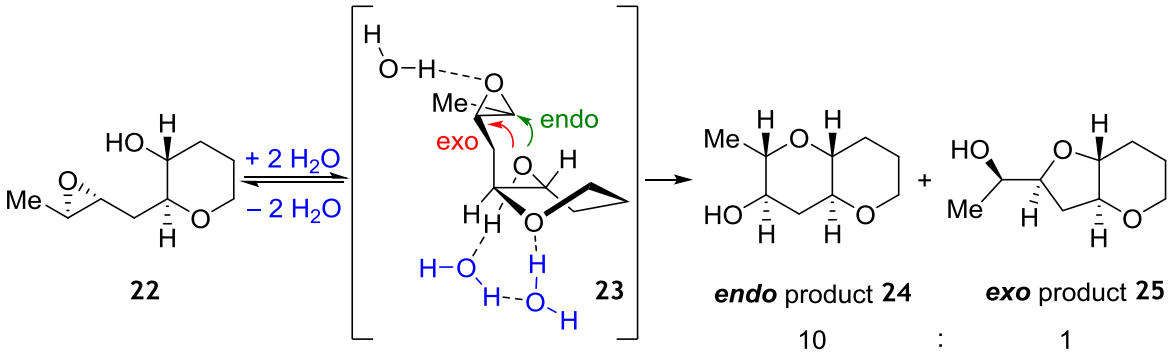
Scheme 2[1]

For those hoping to employ a cascade strategy in the synthesis of selected polyether subunits, work by Coxon and co-workers has shown that cyclization of simple epoxy alcohols **19** typically proceed through a spiro transition state to afford the corresponding *exo*-product **21** (**Scheme 3**).[31]



Scheme 3[32]

Recently, Jamison and co-workers have reported the development of *endo*-selective epoxide-opening cascades in water.[32] They have been able to utilise a THP template in order to alter the approach of the alcohol nucleophile to the epoxide electrophile and so bias the substrate towards *endo* cyclization (**Scheme 4**).[33] It is believed that the water molecules facilitate *endo* cyclization by forming a hydrogen-bonding network that bridges the oxygen atom within the THP template and the oxygen atom of the hydroxyl group attached to the template. These interactions encourage reorganization of the epoxy alcohol from an energetically favourable chair conformation into a higher energy twist boat conformation.[33] Reaction through conformer **23** significantly alters the trajectory of nucleophilic attack by the epoxy alcohol. Theoretical studies have indicated that the most important factor dictating regioselectivity in epoxy alcohol cyclizations is the angle with which the alcohol approaches the epoxide, with an incidence angle of 100° being optimal.[34] Such a trajectory is ideal because it allows for maximum overlap between the hydroxyl lone pair and the $C{-}O_{epox}$ σ* orbital.[32]



Scheme 4[33]

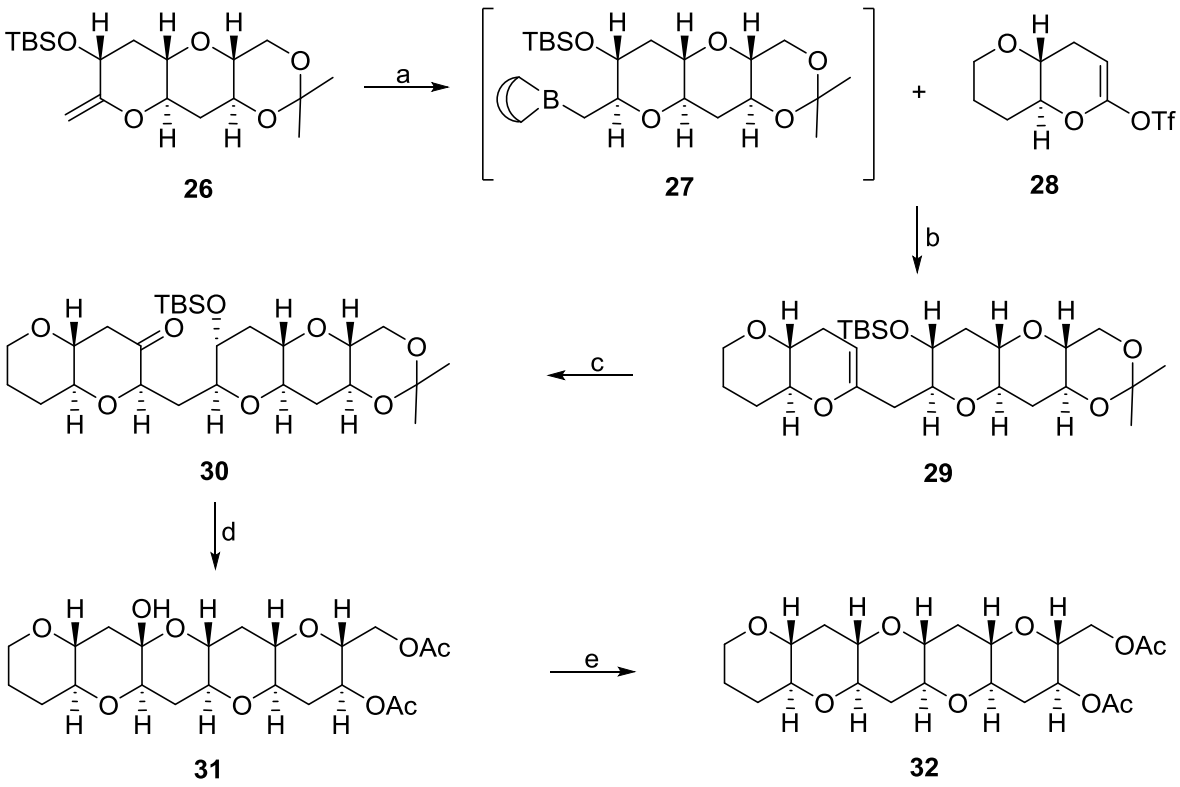
2.0 Strategies for the Synthesis of Ciguatoxins

The large and complex molecular architecture displayed by the marine polycyclic ethers dictates the need for highly efficient synthetic strategies. Numerous synthetic chemists have studied the development of new strategies and efficient methodologies for the construction of polycyclic ether ring systems. Nicolaou and co-workers have proven to be pioneers in the field of marine polyether synthesis. They reported the first total synthesis of a marine polyether, that of hemibrevetoxin B (**9**), in 1992 and have since completed the total syntheses of several larger members of this class of natural product.[35] The following section looks at the strategies employed by various research groups for the synthesis of CTX3C (**4**) and other ciguatoxins.

2.1 Sasaki Group Approach

2.1.1 Suzuki Coupling/Reductive Etherification

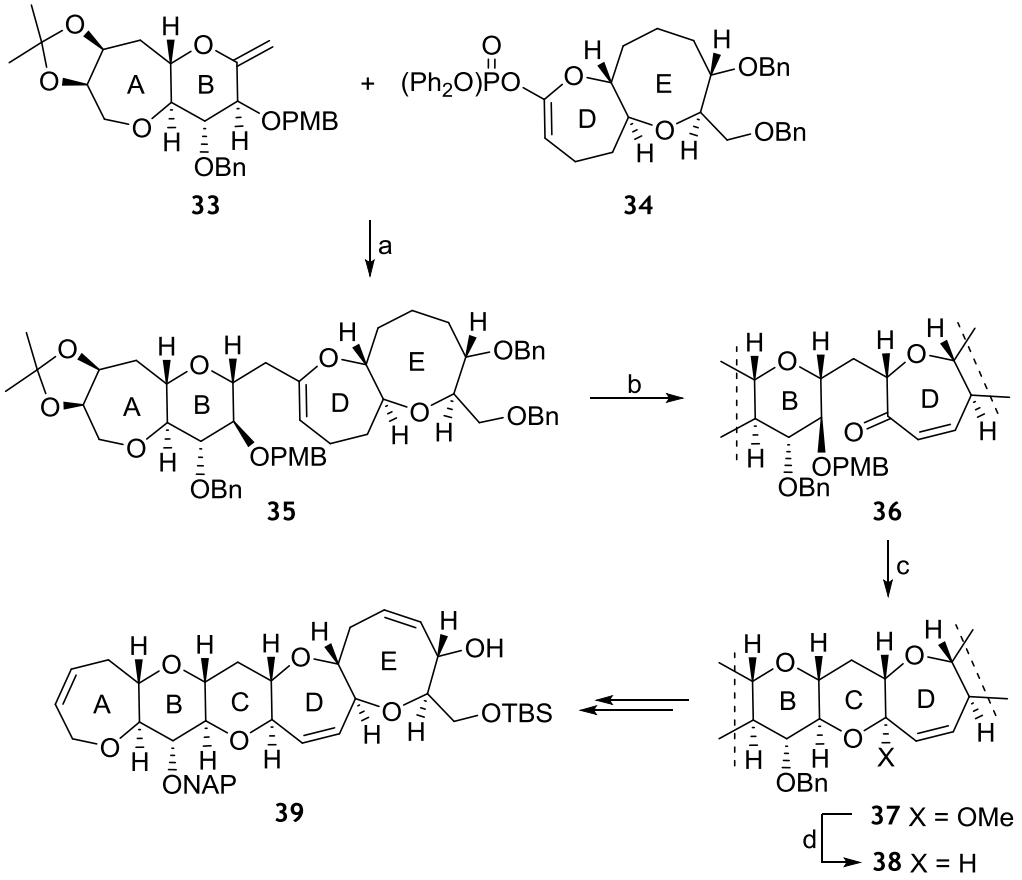
In 1998, Sasaki and co-workers reported a strategy for the convergent synthesis of *trans*-fused polyether arrays that used palladium(0)-catalysed cross-coupling of alkylboranes with enol triflates (**Scheme 5**).[36] Hydroboration of the exocyclic enol ether **26** using 9-BBN provided the corresponding alkylborane **27**. Reaction between **27** and enol triflate **28** under Suzuki-Miyaura coupling conditions furnished the desired cross-coupled product **29**. Stereoselective hydroboration of enol ether **29** with thexylborane followed by oxidative work-up and subsequent oxidation of the resultant secondary alcohol afforded ketone **30**. Acidic removal of the silyl and acetonide groups followed by acetylation provided hemiketal **31**. Finally, reductive etherification of **31** furnished the *trans*-fused pentacyclic ether **32**.



a) 9-BBN, THF; b) $PdCl_2(dppf)$, KBr, Ph_3As, DMF, 66% (2 steps); c) 1. thexylBH_2, THF, 0 °C; then H_2O_2, NaOH; 2. $(COCl)_2$, DMSO, Et_3N, −78 °C, 82% (2 steps); d) 1. CSA, CH_2Cl_2/MeOH; 2. Ac_2O, pyridine, 94% (2 steps); e) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −10 °C, 83%.

Scheme 5

Sasaki and co-workers utilized this methodology for the synthesis of the A-E ring system **39** of CTX3C (**4**) (**Scheme 6**).[37] Treatment of the AB-ring olefin **33** with 9-BBN afforded the corresponding alkylborane, which was then reacted *in situ* under Suzuki-Miyaura coupling conditions with phosphate **34** to afford the cross-coupled product **35**. Due to the chemical lability of medium-sized enol triflates, phosphate **34** was used as a stable alternative. From enol ether **35**, four synthetic steps furnished the seven-membered D-ring. The required double bond was introduced to the D-ring *via* Saegusa oxidation to afford enone **36**.[38] Cleavage of the 4-methoxybenzyl ether and subsequent treatment with methyl orthoformate under acidic conditions provided mixed ketal **37**. Acetal reduction then furnished the target pentacyclic array **38**. Elaboration of the intermediate to the target A-E ring system **39** required introduction of both the A- and E-ring olefins.



a) 9-BBN, THF; then **34**, Cs_2CO_3 aq., $PdCl_2(dppf)\cdot CH_2Cl_2$, DMF, 50 °C, 73%; b) 1. thexylBH_2, THF, 0 °C; then NaOH aq., H_2O_2, 78%; 2. TPAP, NMO, 4Å MS, CH_2Cl_2; 3. LiHMDS, THF, −78 °C, then TMSCl, Et_3N, −78 °C; 4. $Pd(OAc)_2$, MeCN, 89% (3 steps); c) 1. DDQ, pH 7 buffer/CH_2Cl_2, 85%; 2. $HC(OMe)_3$, PPTS, PhMe, 50 °C; d) Et_3SiH, $BF_3\cdot Et_2O$, CH_2Cl_2/MeCN, −15 °C, 73% (2 steps).

Scheme 6

Sasaki and co-workers have also reported a highly convergent synthetic route to the right-hand F-M ring system **40** of CTX1B (**5**).[39] Once again, their strategy relied upon the extensive use of the Suzuki-Miyaura coupling reaction (**Figure 7**).

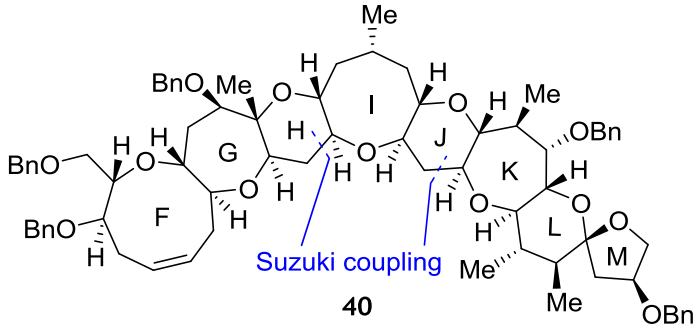
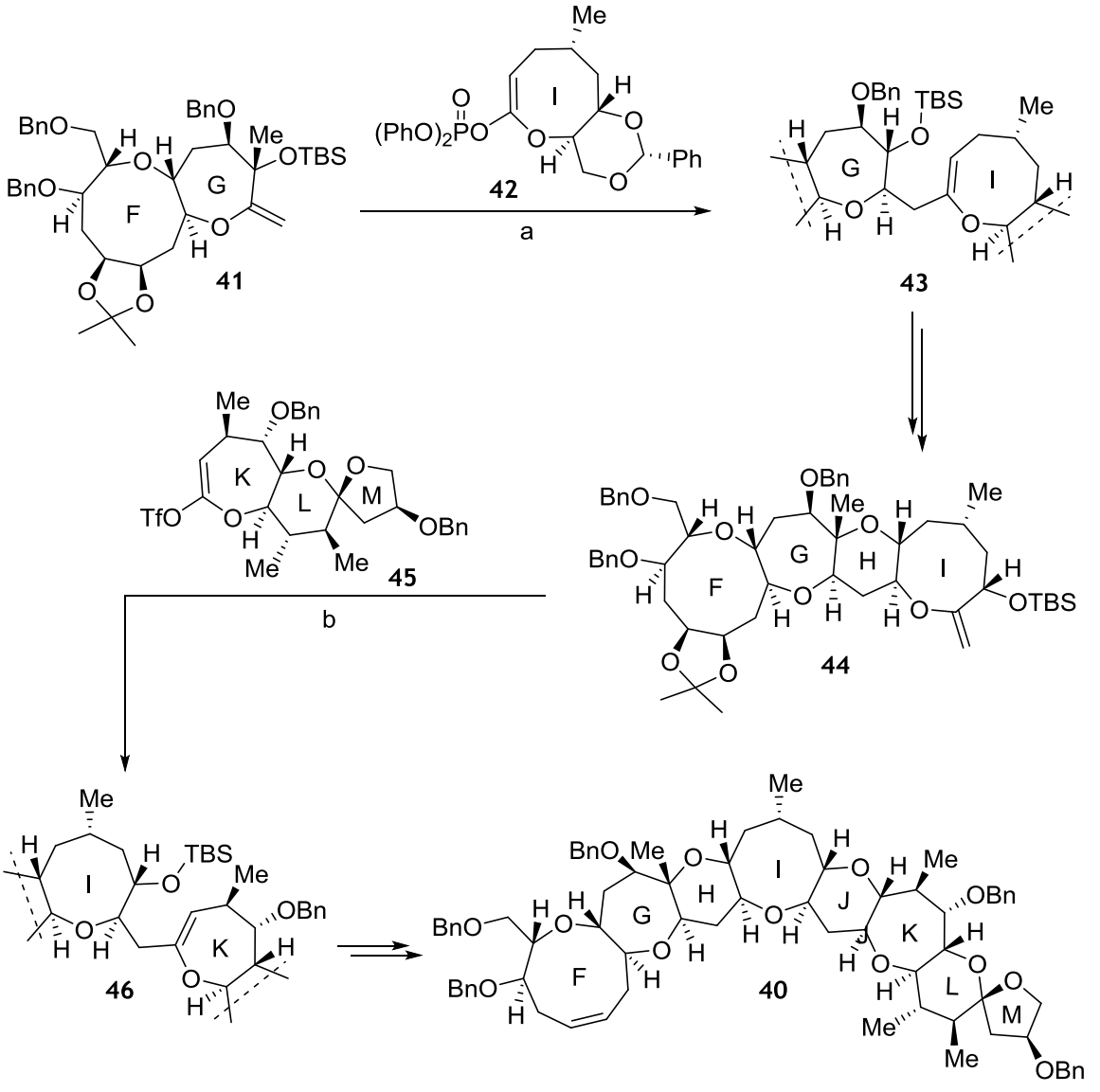


Figure 7

Utilizing their developed methodology, FG-ring olefin **41** and enol phosphate **42** were successfully coupled to afford enol ether **43** (**Scheme 7**). A short synthetic sequence furnished the tetracyclic ring system **44**. A second Suzuki coupling reaction between the exo-enol ether **44** and triflate **45** delivered the cross-coupled product **46**. Elaboration from enol ether **46** delivered the target F-M ring system **40** of CTX1B (**5**).

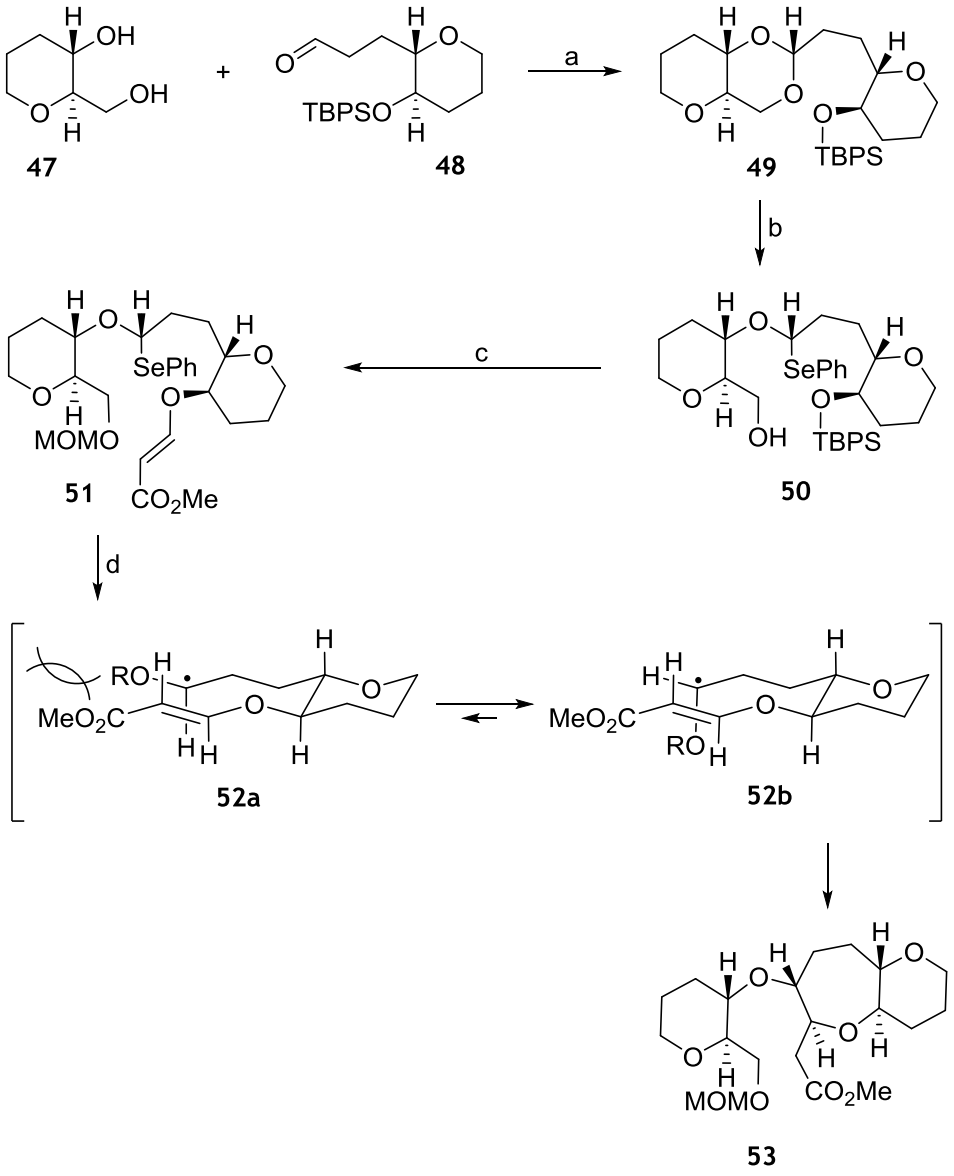


a) 9-BBN, THF; then **42**, $Pd(PPh_3)_4$, $NaHCO_3$ aq., DMF, 85%; b) 9-BBN, THF; then **45**, $Pd(PPh_3)_4$, Cs_2CO_3 aq., DMF, 61%.

Scheme 7

2.1.2 *O,O*-Acetalization/Intramolecular Radical Cyclization

Sasaki and co-workers have also reported a strategy for the synthesis of the *O*-linked oxepane ring system **53** based on an intramolecular radical cyclization reaction (**Scheme 8**).[40]

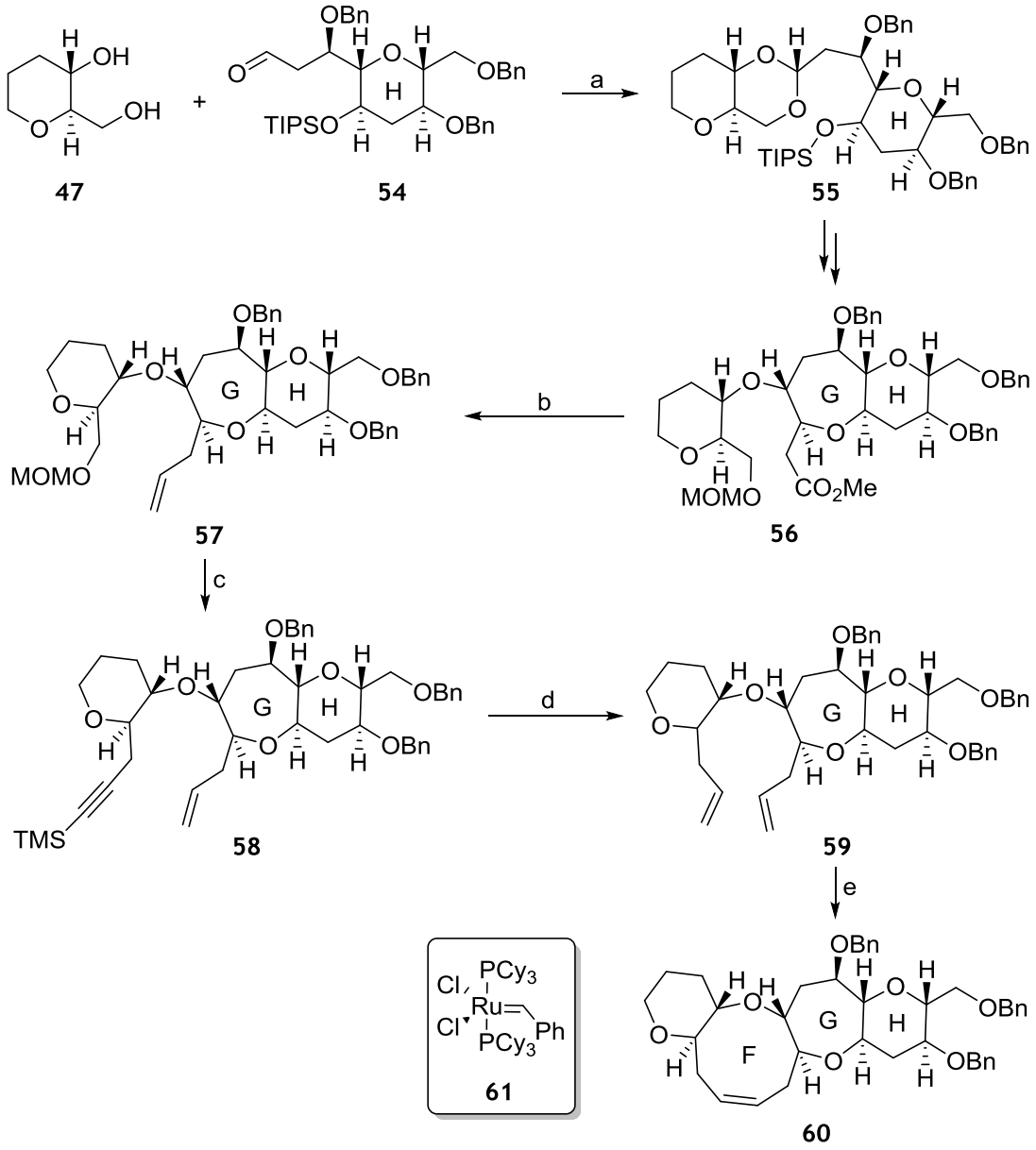


a) CSA, benzene, 80 °C, quant.; b) *i*-$Bu_2AlSePh$, PhMe, −20 °C, 94%; c) 1. MOMCl, *i*-Pr_2NEt, CH_2Cl_2; 2. TBAF, THF; 3. methyl propiolate, Bu_3P, CH_2Cl_2, 69% (3 steps); d) *n*- Bu_3SnH, Et_3B, benzene, 66%.

Scheme 8

Acetalization between diol **47** and aldehyde **48** afforded the six-membered acetal **49** (**Scheme 8**). Regioselective cleavage of the less hindered C—O acetal bond in **49** yielded the monoselenoacetal **50** as a single stereoisomer.[41] Protection of the hydroxyl group as the corresponding methoxymethyl ether followed by removal of the silyl ether and treatment with methyl propiolate in the presence of tributylphosphine furnished the desired ß-alkoxyacrylate **51**.[42] It was found that ß-alkoxyacrylate **51** favoured the extended *s-trans*- over the *s-cis*-conformation in order to avoid 1,3-diaxial-like interactions. Radical cyclization, upon treatment with tributyltin hydride in the presence of triethylborane, provided the *O*-linked oxacycle **53**.[43] The stereochemical outcome of the reaction was rationalized upon consideration of the transition state conformers **52a** and **52b**. In **52b** steric congestion between the acrylate unit and the bulky alkoxy group attached to the radical centre is avoided.

Sasaki and co-workers reported an efficient route to the FGH-ring system **60** of CTX1B (**5**) utilizing the developed intramolecular radical cyclization methodology combined with a RCM reaction (**Scheme 9**).[44] Treatment of diol **47** with ß-benzyloxyaldehyde **54** in the presence of scandium triflate afforded the desired six-membered acetal **55** as a single stereoisomer in good yield. Acetal **55** was then elaborated to the GH-ring system **56** upon conversion to the mixed selenoacetal and subsequent radical cyclization. Reduction of **56** followed by Wittig methylenation of the resultant aldehyde furnished olefin **57**. Removal of the methoxymethyl ether followed by activation of the primary alcohol by conversion to the triflate and subsequent displacement with lithium (trimethylsilyl)acetylide provided silylacetylene **58**. Removal of the trimethylsilyl group followed by partial hydrogenation using Lindlar catalyst furnished diene **59**. Finally, treatment of diene **59** with Grubbs first generation catalyst **61** led to the formation of the nine-membered F-ring and completion of the FGH-ring system **60** of CTX1B (**5**).[45]



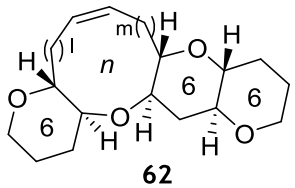
a) $Sc(OTf)_3$, benzene, 80%; b) 1. DIBAL, CH_2Cl_2, −78 °C; 2. Ph_3PCH_3Br, NaHMDS, 0 °C, 77% (2 steps); c) 1. $BF_3{\cdot}Et_2O$, Me_2S, CH_2Cl_2, 0 °C, 83%; 2. Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; 3. Me_3SiCCH, *n*-BuLi, THF/HMPA, −78 °C, 61% (2 steps); d) 1. K_2CO_3, THF/MeOH, 90%; 2. H_2, Lindlar catalyst, EtOAc, 86%; e) **61**, CH_2Cl_2, 35 °C, 61%.

Scheme 9

2.2 Hirama Group Approach

2.2.1 Intramolecular alkylation/RCM reaction

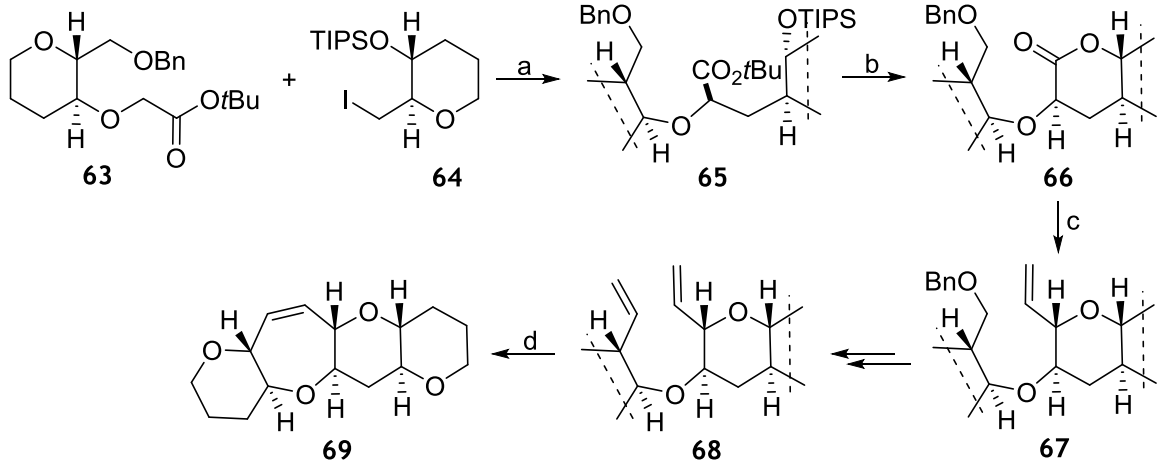
In 1998, Hirama and co-workers reported a new strategy for the synthesis of 6/*n*/6/6-tetracyclic polyether systems **62** (*n* = 7—10) (**Figure 8**).[46]



62

Figure 8

Coupling of *tert*-butyl ester **63** with iodide **64** using lithium diisopropylamide afforded the desired compound **65** as the major isomer (**Scheme 10**). Removal of the silyl ether and subsequent treatment with *p*-toluenesulfonic acid furnished the six-membered lactone **66**. Addition of vinylmagnesium bromide to **66** gave the corresponding hemiacetal which was then selectively reduced to give the *O*-linked oxacycle **67**.[47] Oxacycle **67** was then converted to diene **68** in three steps. Treatment of diene **68** with Grubbs first generation catalyst **61** delivered the target polyether system **69**.[46]

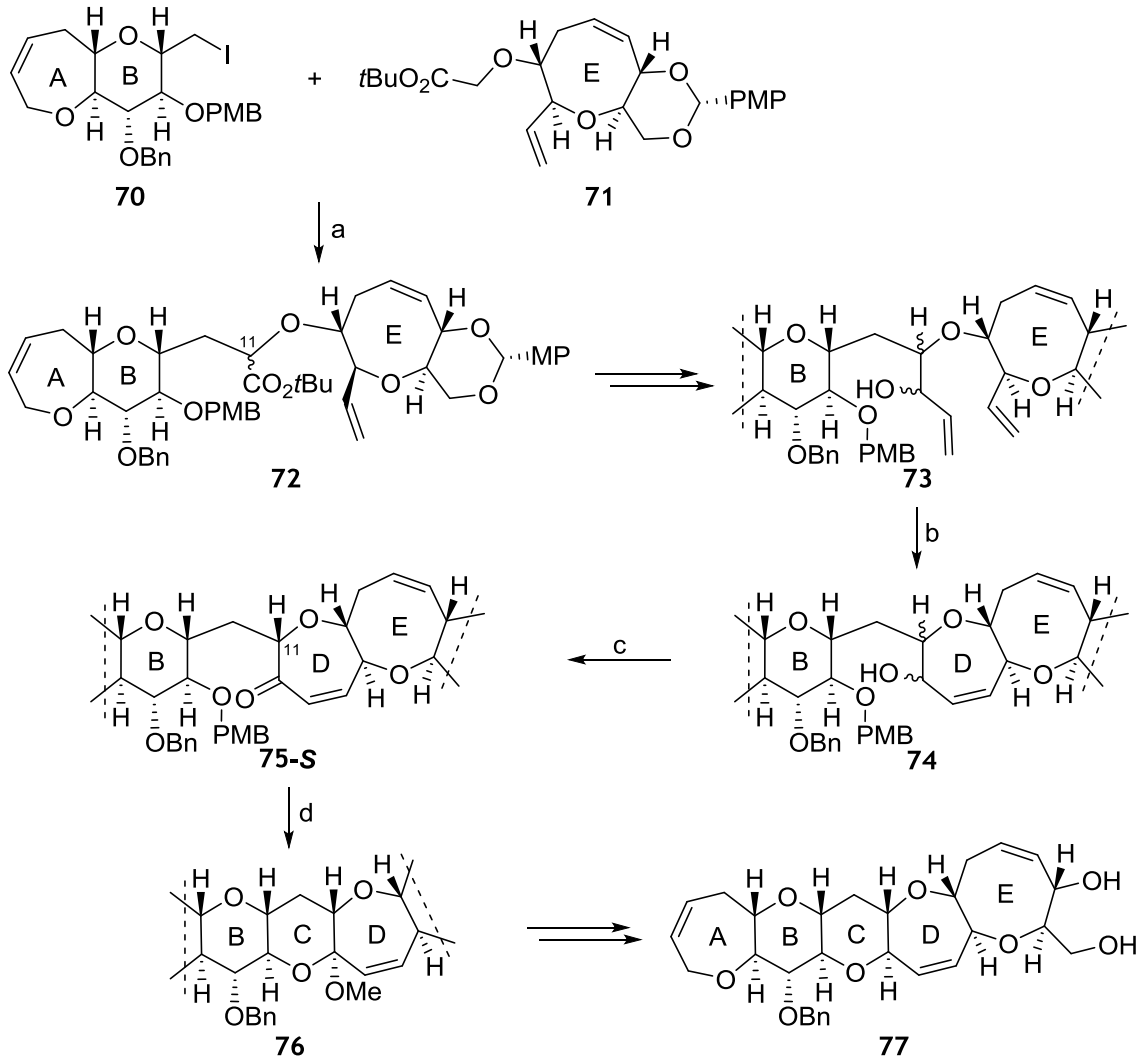


63 **64** **65** **66** **67** **68** **69**

a) LDA, HMPA, THF, 61%; b) TBAF, THF; then cat. TsOH, PhMe, 90 °C, 84%; c) 1. $CH_2CHMgBr$, THF, −78 °C, 80%; 2. Et_3SiH, $BF_3{\cdot}Et_2O$, MeCN, 71%; d) **61** (10 mol%), benzene, 81%.

Scheme 10

Hirama and co-workers demonstrated the versatility of their developed alkylation-metathesis strategy through the synthesis of the A-E ring system **77** of CTX3C (**4**) (**Scheme 11**).[48]



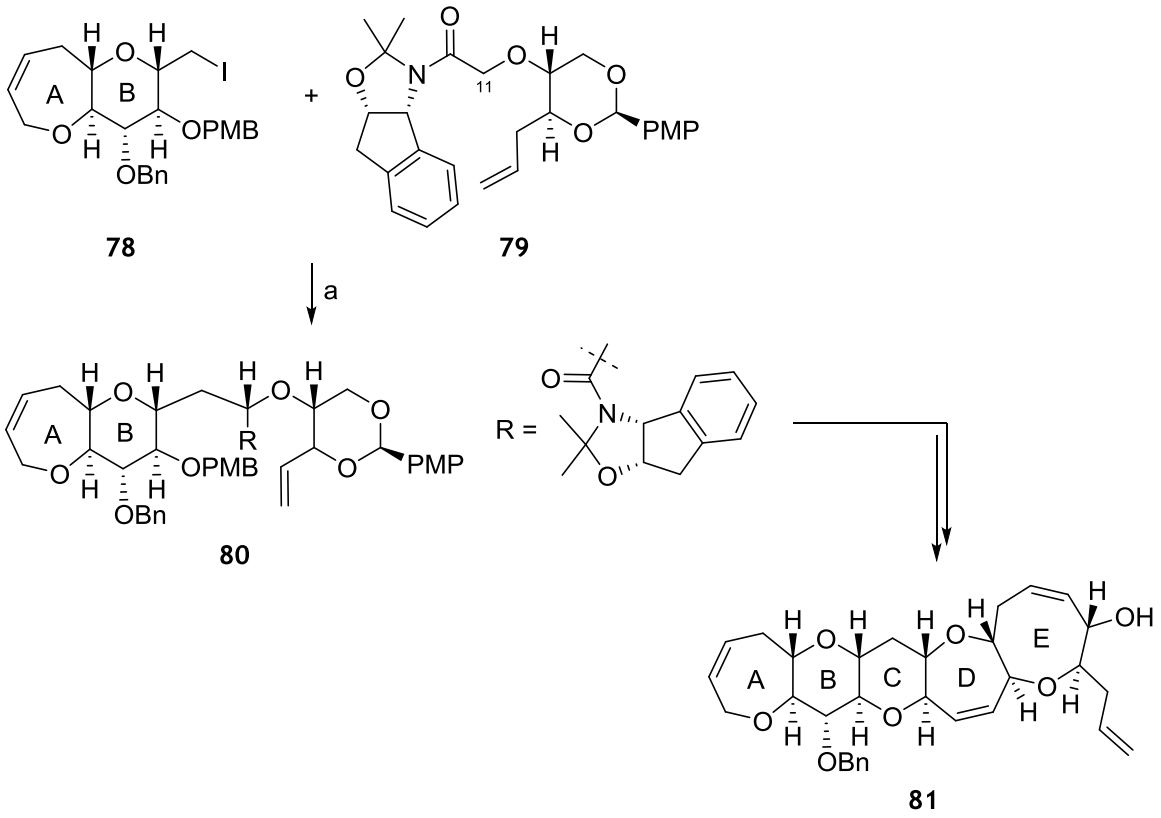
a) LDA, HMPA, THF, −78 °C, 51%; b) **61** (7 mol%), $CHCl_3$, 45 °C, 96%; c) 1. $(COCl)_2$, DMSO, Et_3N, −78 °C, 88%; 2. DBU, PhMe, 95 °C, 95%; d) 1. DDQ, CH_2Cl_2, 94%; 2. CSA, $CH(OMe)_3$, CH_2Cl_2, 64%.

Scheme 11

Unlike the model system detailed in **Scheme 10**,[46] intermolecular alkylation between *tert*-butyl ester **71** and iodide **70** afforded an inseparable mixture of epimers **72** in favour of the undesired stereoisomer ($C_{11}R$:$C_{11}S$ = 6:1). The undesired stereochemistry was addressed following the cyclization of diene **73** to alcohol **74**. Oxidation of alcohol **74** followed by DBU-mediated epimerization furnished the more thermodynamically stable pseudoequatorial isomer **75-*S*** as the major isomer. Removal of the 4-methoxybenzyl group, followed by

acetalization under acidic conditions afforded the pentacyclic polyether skeleton **76**. Reductive etherification and subsequent functional group manipulations provided the target A-E ring system **77** of CTX3C (**4**).

In order to avoid the base-mediated epimerisation step, Hirama and co-workers developed an alternative approach to the A-E ring system **81** of CTX3C (**4**) (**Scheme 12**).[49] The stereoselectivity of the alkylation step was successfully controlled through the incorporation of a chiral aminoindanol derivative into the substrate.[50] The coupling reaction between iodide **78** and amide **79** afforded the desired isomer **80** exclusively. The stereoselectivity of the coupling reaction resulted from the attack of iodide **78** from the less hindered C11-*si* face of the kinetically and thermodynamically favoured Z-enolate of **79**.[49] Amide **80** was successfully elaborated to afford the required A-E ring system **81** of CTX3C (**4**).

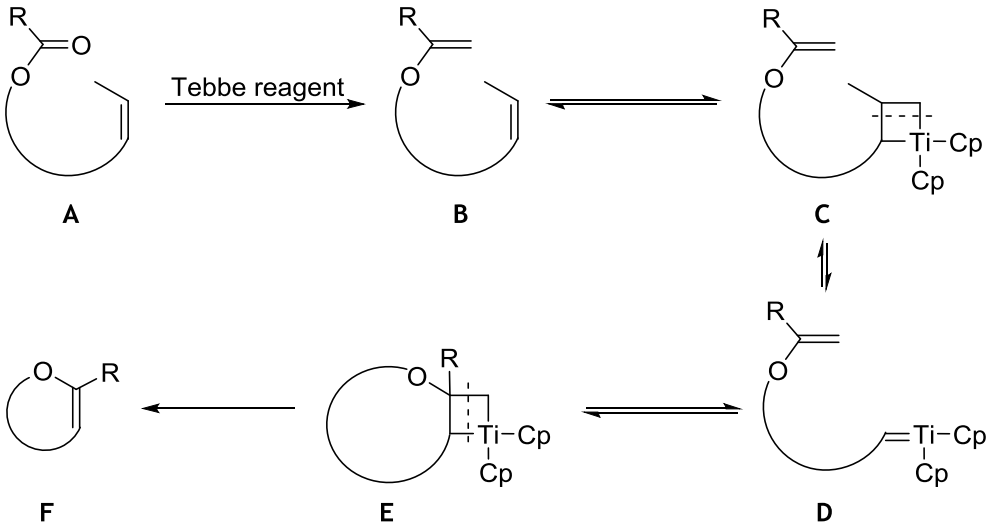


a) *n*-BuLi, DMPU, THF, 96%.

Scheme 12

2.2.2 Esterification/Intramolecular Enol Formation with RCM or Related Reaction

In 1996, Nicolaou and co-workers reported a new strategy for the synthesis of fused polyethers based on olefin metathesis,[51] which facilitated the generation of cyclic enol ethers directly from an olefinic ester using either the Tebbe ($Cp_2TiCH_2ClAlMe_2$) or Petasis (Cp_2TiMe_2) reagent (**Scheme 13**).[52] Olefinic ester **A** was converted to enol ether **B** upon treatment with the Tebbe reagent. It was proposed that the initially formed alkene then reacted with a second molecule of the Tebbe reagent to afford the titanacyclobutane **C**. Fragmentation of **C** afforded the titanium alkylidene **D** and intramolecular reaction of **D** then provided titancyclobutane **E**. Regioselective fragmentation furnished the desired cyclic enol ether **F** *via* olefin metathesis.



Scheme 13[51]

Nicolaou and co-workers employed their olefin metathesis based strategy for the construction of several key fragments (**82**—**84**) of the large marine polyether natural product maitotoxin (**Figure 9**).[53]

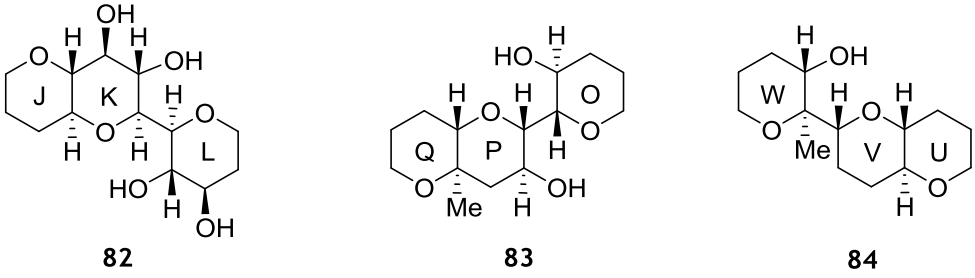
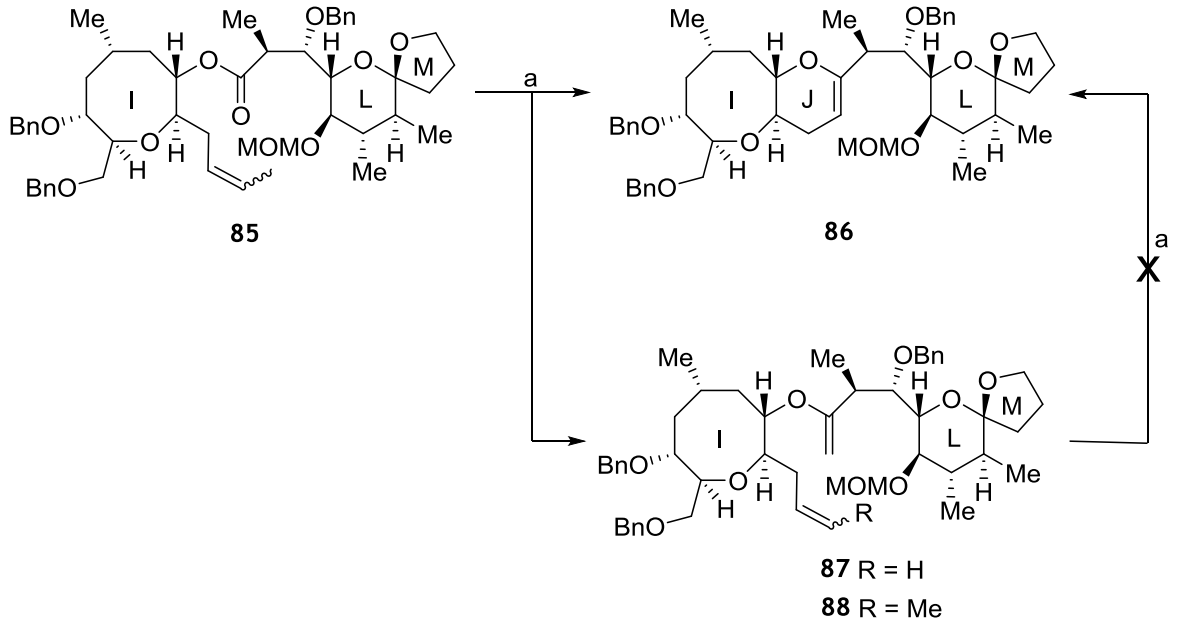


Figure 9

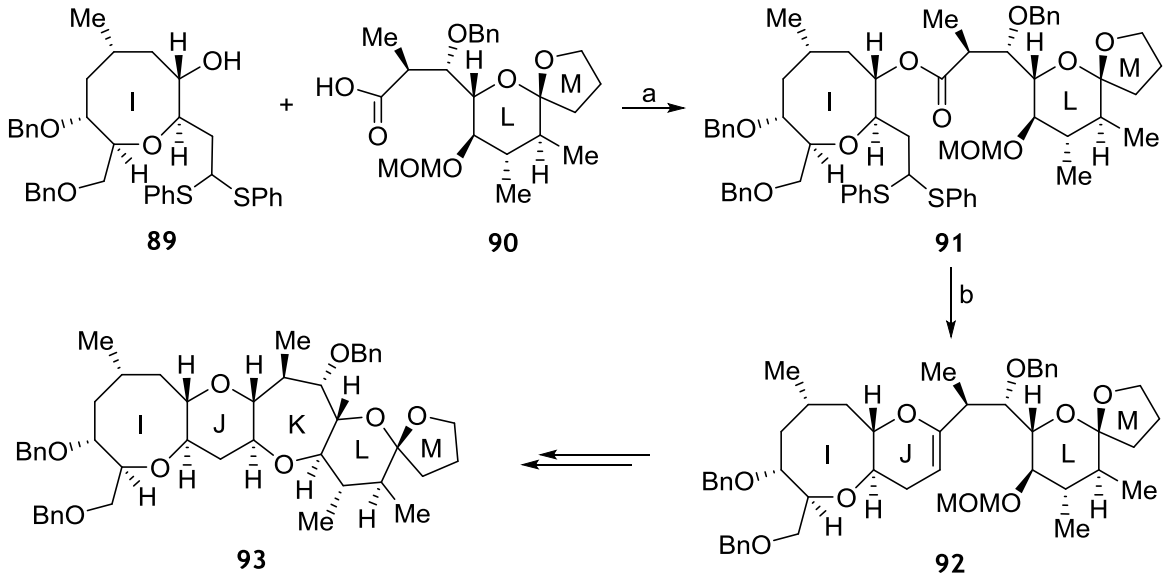
Hirama and co-workers attempted to utilize the developed metathesis strategy for the construction of the I-M ring system **93** of CTX3C (**4**) (**Scheme 14**).[54] Unfortunately, the reaction to provide the desired cyclic enol ether **86** proved unreliable. Significant amounts of uncyclized ethers **87** and **88** were isolated and treatment of these compounds with the Tebbe reagent did not afford the desired cyclic enol ether **86**. Steric hinderance around the diene system of **87**/**88** was blamed for the lack of cyclization observed.[54a]



a) Tebbe reagent, THF, 60 °C, **86**: trace—63%, **87**—**88**: 18—70%.

Scheme 14

As an alternative to the use of the Tebbe reagent, Hirama and co-workers employed the direct carbonyl olefination reaction of bis(phenylthio)acetals developed by Takeda (**Scheme 15**).[54b, 55] Treatment of dithioacetal **91** with the low-valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ generated the required enol ether **92** in a reproducible manner. Introduction of the seven-membered K-ring afforded the I-M ring system **93** of CTX3C (**4**).



a) EDC·HCl, DMAP, CSA, 40 °C, 76%; b) $Cp_2Ti[P(OEt)_3]_2$, THF, reflux, 67%.

Scheme 15

2.2.3 *O,O*-Acetalization/Intramolecular Radical Cyclization

In 2001, Hirama and co-workers were the first to report the total synthesis of a ciguatoxin, that of CTX3C (**4**).[56] Their synthesis employed a refined and modified version of Sasaki's intramolecular radical cyclization strategy (see **Ch 1. § 2.1.2**).[40] Their highly convergent strategy was based upon the coupling of the A-E ring system **94** and the H-M ring system **95** (**Figure 10**).

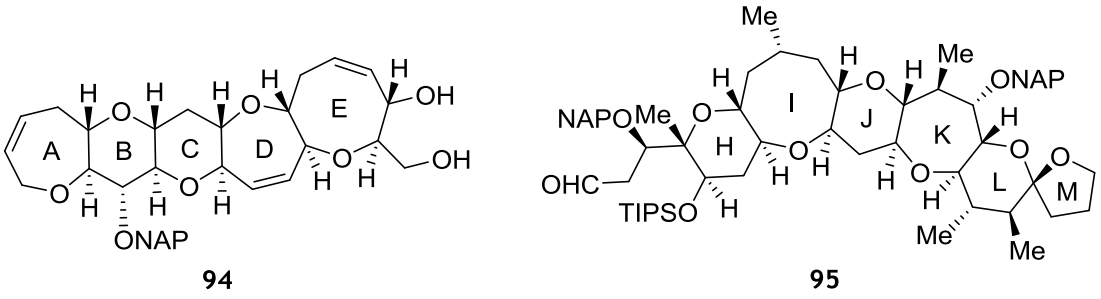
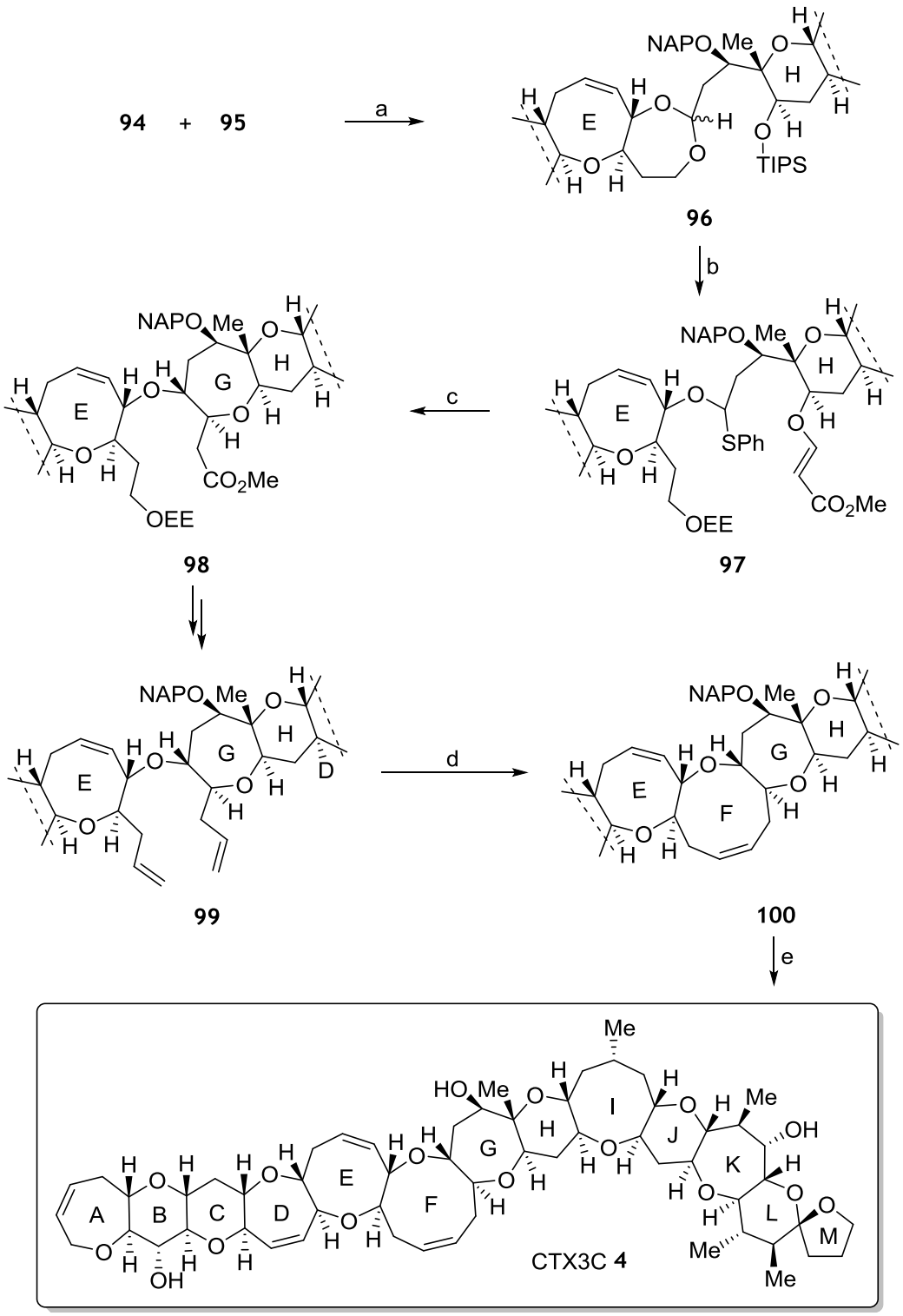


Figure 10

Scandium trifluoromethanesulfonate-promoted condensation between 1,4-diol **94** and ß-alkoxy aldehyde **95** afforded the seven-membered acetal **96** (**Scheme 16**).[57] Treatment of acetal **96** with phenylthiotrimethylsilane and trimethylsilyl trifluoromethanesulfonate furnished the linear *O,S*-acetal **97** without affecting the potentially reactive spiroketal. Construction of the seven-membered G-ring was realised upon stereoselective radical cyclization between the *O,S*-acetal and ß-alkoxyacrylate.[40, 44a, 58] Treatment of **97** with tributyltin hydride and AIBN furnished the desired G-ring oxepane **98**. Steric interactions between the bulky alkoxy group and ß-alkoxyacrylate favoured the formation of desired isomer **98** (see **Ch 1. § 2.1.2**).[59] Five steps were required for the conversion of **98** to the RCM precursor **99**. The critical chemoselective RCM reaction of **99** to form the F-ring, without affecting any of the pre-existing di-subsitituted double bonds, preceded smoothly using Grubbs first generation catalyst **61**.[56] Construction of the nine-membered F-ring provided the required polyether skeleton **100**. Global deprotection of **100** with DDQ completed the first total synthesis of CTX3C (**4**).

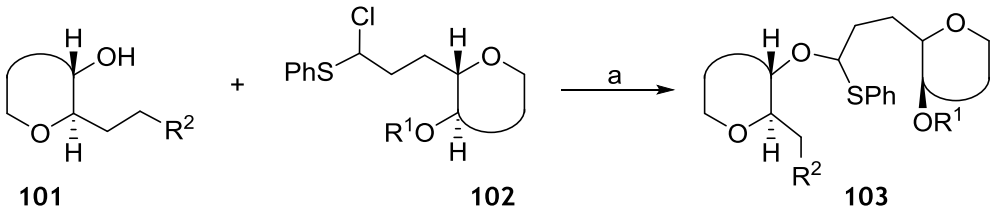


a) $Sc(OTf)_3$, benzene, 91%; b) 1. TMSSPh, TMSOTf, DTBMP, then K_2CO_3, MeOH, 74%; 2. ethyl vinyl ether, PPTS, 99%; 3. TBAF, THF; 4. methyl propiolate, NMM, 89% (2 steps); c) *n*-Bu_3SnH, AIBN, PhMe, 85 °C; d) **61** (20 mol%), CH_2Cl_2, 40 °C, 90%; e) DDQ, CH_2Cl_2/H_2O, 63%.

Scheme 16

2.2.4 Direct *O,S*-Acetal Formation/Intramolecular Radical Cyclization

The protecting group strategies that could be employed in the first generation synthesis of CTX3C (**4**) were restricted by the use of a Lewis acid in both the acetalization step to form the *O,O*-acetal **96** and the subsequent conversion to the *O,S*-acetal **97** (**Scheme 16**).[40, 56] This could potentially cause problems during the synthesis of other ciguatoxin congeners and so Hirama and co-workers developed a new, mild method for the construction of *O,S*-acetals that did not require strongly acidic conditions (**Scheme 17**).[60] *O,S*-Acetal **103** was obtained upon the coupling of secondary alcohol **101** and α-chlorosulfide **102** using AgOTf.[61] Halophilic activators, such as the silver cation, are highly chemoselective and non-acidic. This coupling strategy allows for the use of a wide variety of protecting groups.[60]

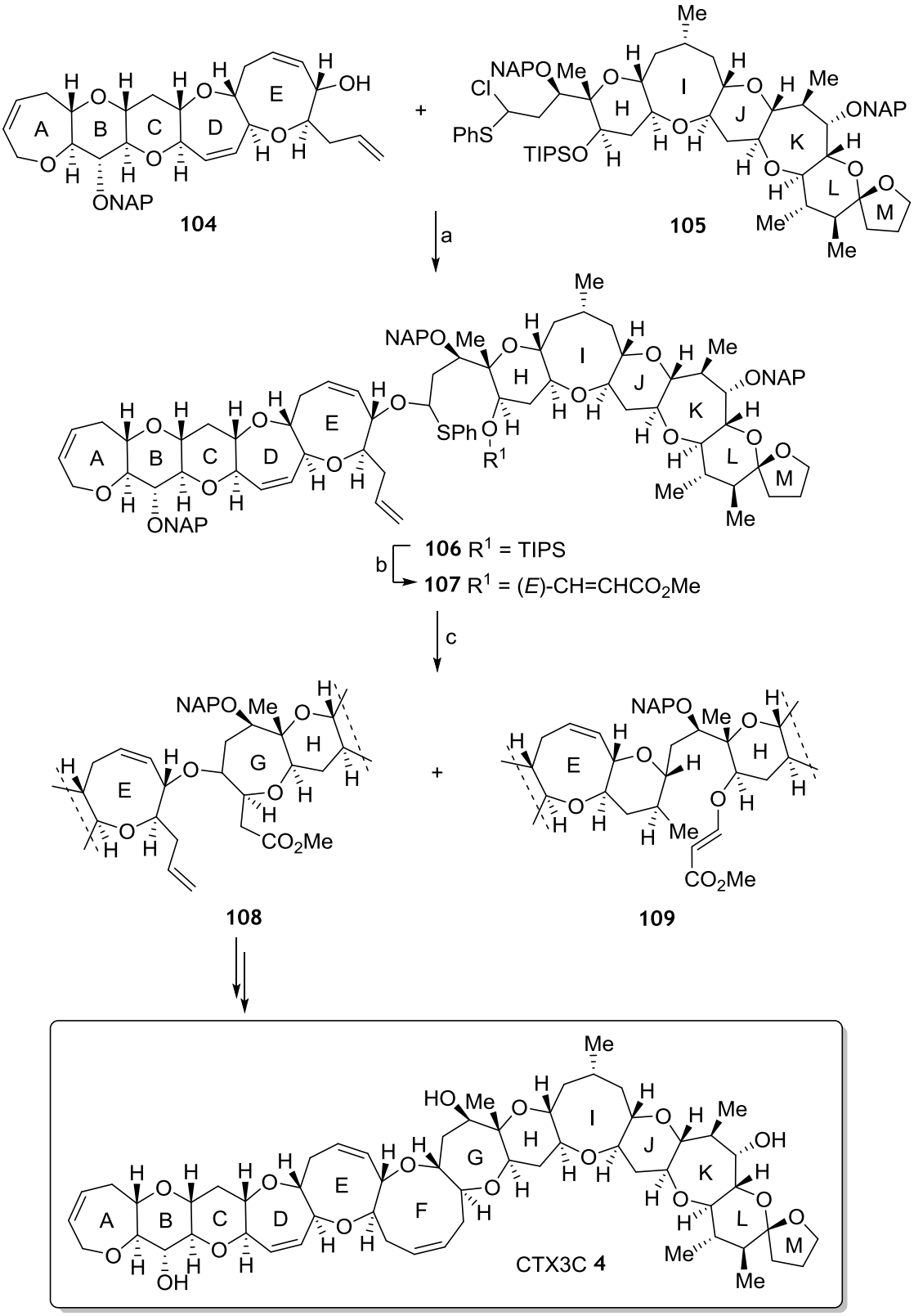


101 **102** **103**

a) AgOTf, DTBMP, 4Å MS, CH_2Cl_2, −60 °C to −30 °C.

Scheme 17

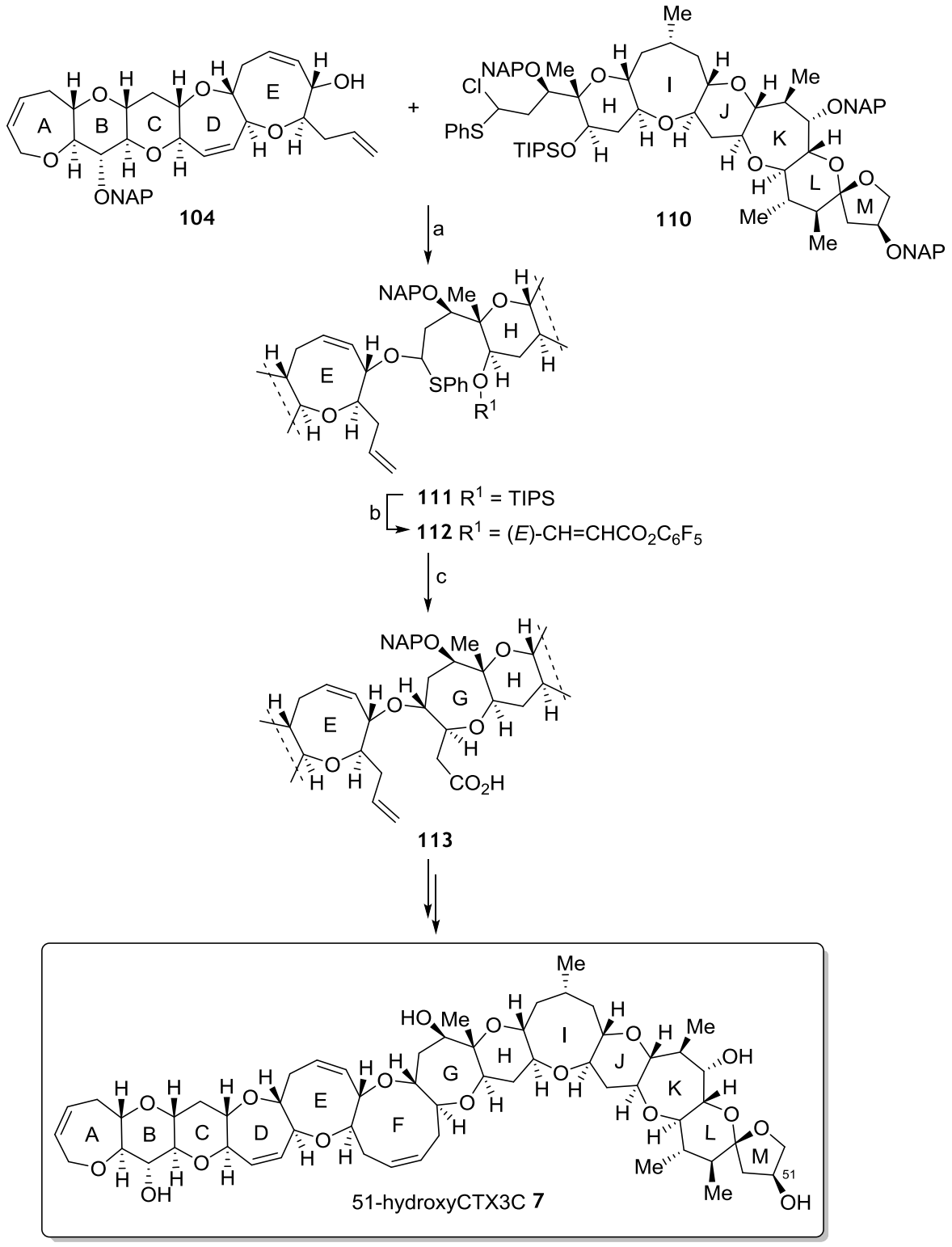
In 2004, Hirama and co-workers reported the second generation total synthesis of CTX3C (**4**).[59, 62] Coupling of alcohol **104** and α-chlorosulfide **105** facilitated the direct construction of *O,S*-acetal **106** (**Scheme 18**). As well as the ability to employ a wider range of protecting groups, this strategy also required fewer steps because it was no longer necessary to proceed *via* the *O,O*-acetal. Following the direct construction of *O,S*-acetal **106**, radical cyclization of **107** constructed the G-ring of **108** stereoselectively in 54% yield. By-product **109** arose from 6-*exo* cyclization of the radical onto the terminal olefin (27% yield).[59] The synthesis was then completed in the same manner as the first generation strategy. The nine-membered F-ring was constructed *via* RCM reaction and subsequent elaboration to CTX3C (**4**) proceeded smoothly.



a) AgOTf, DTBMP, CCl_4/CH_2Cl_2, −50 °C to −30 °C, 70%; b) 1. TBAF, THF, 35 °C, 85%; 2. methyl propiolate, NMM, CH_2Cl_2, quant.; c) *n*-Bu_3SnH, AIBN, PhMe, 85 °C, **108**: 54%, **109**: 27%.

Scheme 18

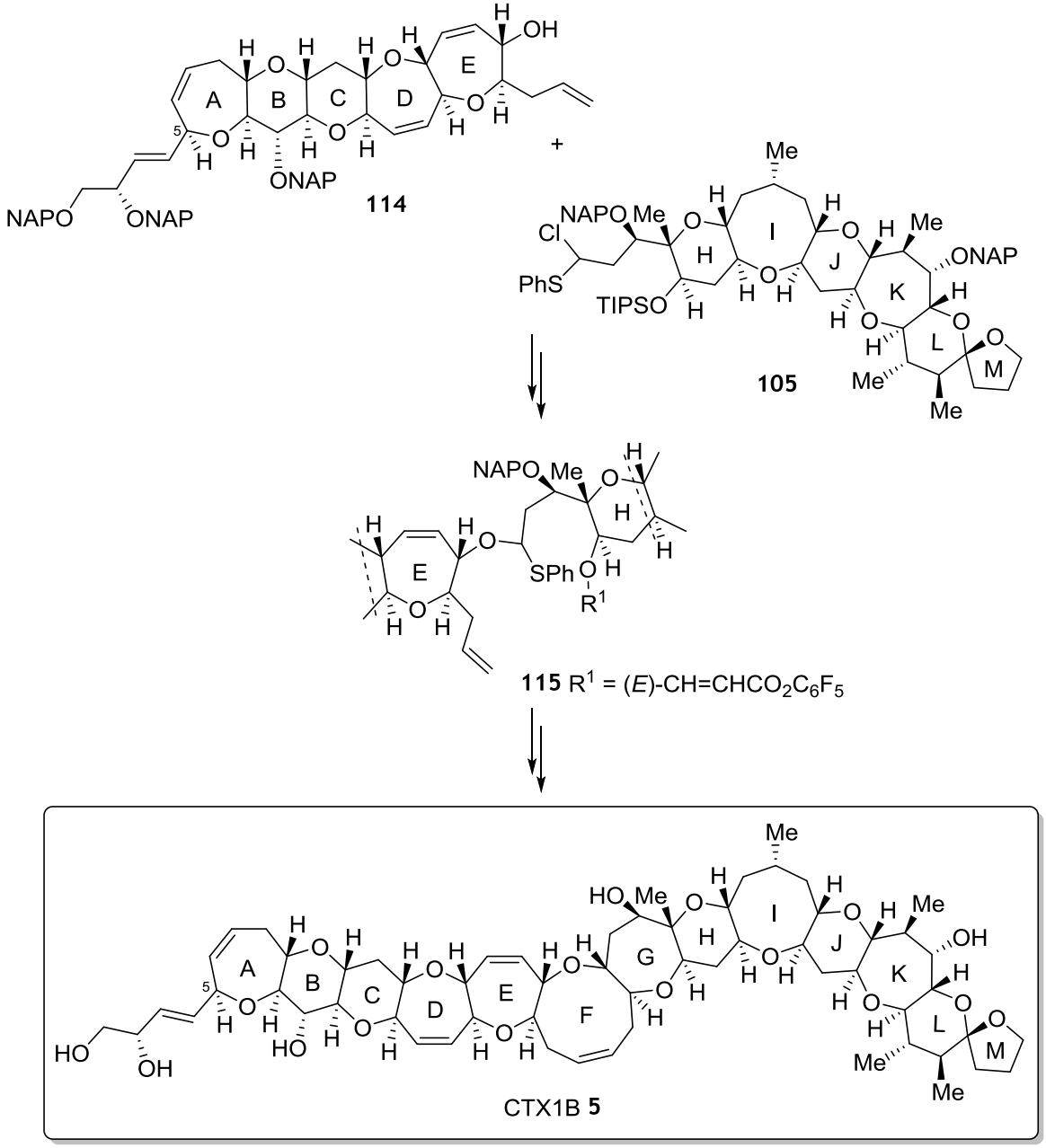
Following their successful synthesis of CTX3C (**4**), Hirama and co-workers focussed their attention on the synthesis of other ciguatoxin congeners.[63] Efforts to synthesise 51-hydroxyCTX3C (**7**) began with the coupling of the alcohol **104** and α-chlorosulfide **110** to afford *O,S*-acetal **111** (**Scheme 19**).[49] A modified radical cyclization precursor was employed in order to avoid the unwanted 6-*exo* cyclization by-product observed during the second generation synthesis of CTX3C (**4**). Model studies revealed that the incorporation of the pentafluorophenyl group significantly improved the selectivity for the desired 7-*exo* cyclization.[63c] The required cyclization precursor **112** was synthesised in two steps from acetal **111** with the silyl ether exchanged for the pentafluorophenyl acrylate. Stereoselective radical cyclization provided the desired seven-membered G-ring **113**. A short synthetic sequence allowed for elaboration of the acid **113** to the target 51-hydroxyCTX3C (**7**).



a) AgOTf, DTBMP, CH_2Cl_2:CCl_4 (5:1), −70 °C, 70%; b) 1. TBAF, THF, 35 °C, quant.; 2. pentafluorophenyl propiolate, PMe_3, CH_2Cl_2, 95%; c) *n*-Bu_3SnH, AIBN, PhMe, 85 °C, 74%.

Scheme 19

Having established a suitable synthetic route to 51-hydroxyCTX3C (**7**), attention turned toward the total synthesis of CTX1B (**5**) (**Scheme 20**).[63c] As well as displaying an additional dihydroxybutenyl side chain, CTX1B (**5**) possesses a seven-membered E-ring rather than the eight-membered E-ring present in both CTX3C (**4**) and 51-hydroxyCTX3C (**7**). The presence of the acid/base/oxidant-sensitive bisallylic C5-ether heightened the synthetic challenge posed by CTX1B (**5**).[64] Despite these challenges, CTX1B (**5**) was successfully synthesised upon the coupling of the A-E ring system **114** and the H-M ring system **105**.

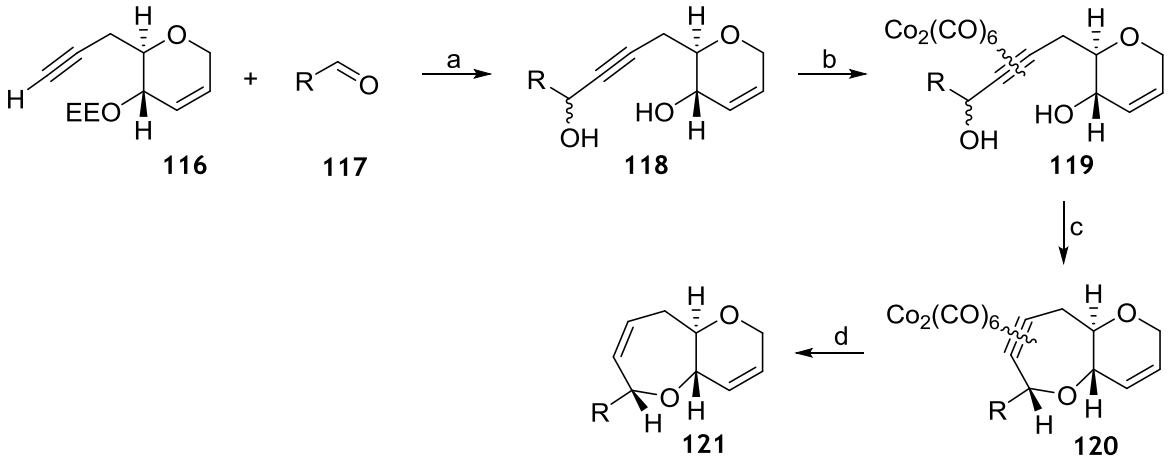


Scheme 20

2.3 Isobe Group Approach

2.3.1 Acetylide-Aldehyde Coupling/Cyclization of Acetylene Cobalt Complex

In 1994, Isobe and co-workers reported a novel approach to the synthesis of medium-sized cyclic ethers *via* cobalt-acetylene complexes (**Scheme 21**).[65] The use of cobalt-acetylene complexes is well established in synthetic chemistry as a result of the introduction of the Pauson-Khand and Nicholas reactions.[66] Coupling between the lithium acetylide generated from **116** and aldehyde **117** under Yamaguchi's protocol afforded diol **118**.[67] The acetylinic moiety of **118** was converted into the corresponding acetylene-dicobalthexacarbonyl complex **119**, which cyclized rapidly to give the *endo*-cobalt complex **120**. Decomplexation with tri-*n*-butyltin hydride afforded bicyclic ether **121**.[68]



a) 1. *n*-BuLi, $BF_3{\cdot}OEt_3$, THF, −78 °C, 63%; 2. PPTS cat., MeOH, 88%; b) $Co_2(CO)_8$, CH_2Cl_2, quant.; c) CSA, CH_2Cl_2, 0 °C, 90%; d) *n*-Bu_3SnH, benzene, 65 °C, 81%.

Scheme 21

Utilizing their cobalt-acetylene strategy, Isobe and co-workers reported the synthesis of several regions of CTX1B (**5**), **122**—**124** (**Figure 11**).[69] Following the successful synthesis of the B-E ring system **124** and H-M ring system **123**, Isobe and co-workers focussed on the coupling of these two fragments to complete the total synthesis of CTX1B (**5**).[70]

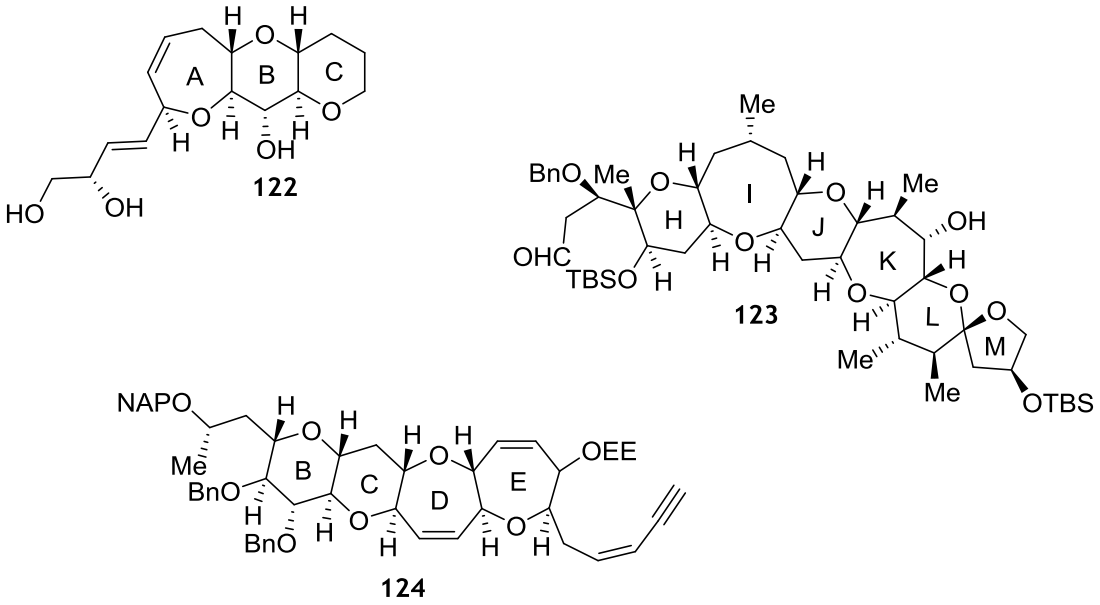
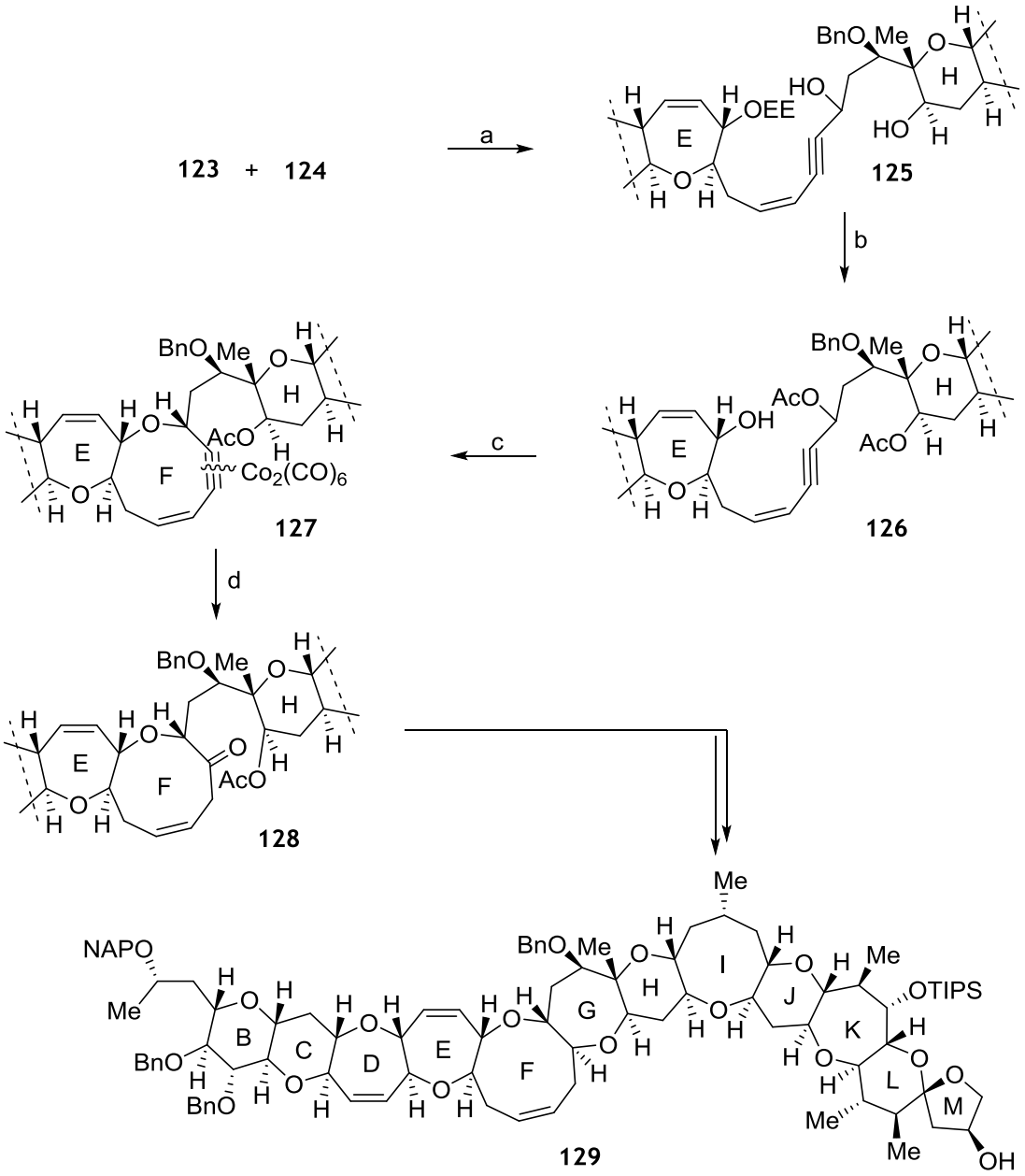


Figure 11

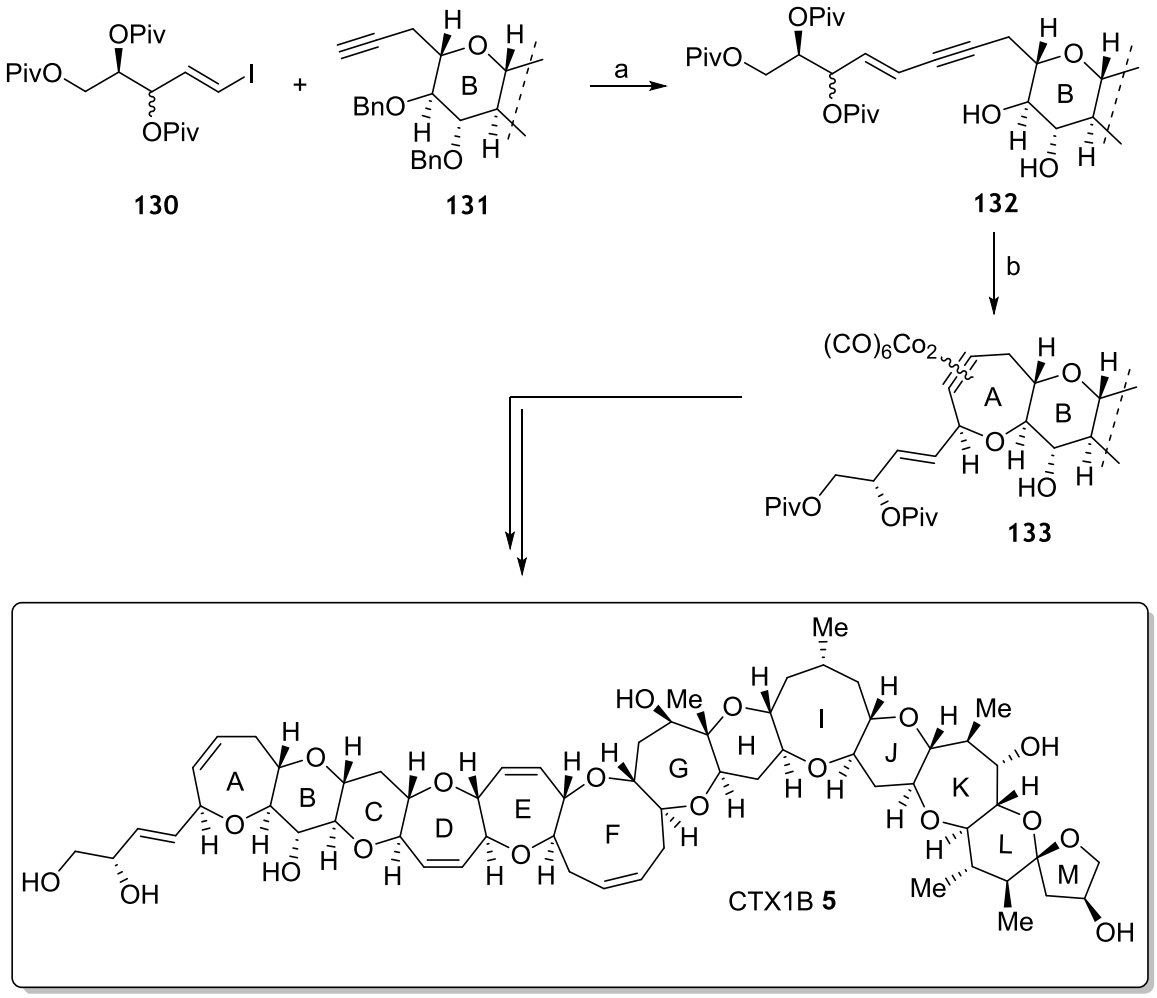
Coupling between the lithium acetylide of **124** and aldehyde **123** furnished enyne **125** (**Scheme 22**).[70] The hydroxyl groups of **125** were protected as acetates, and subsequent removal of the ethoxyethyl group provided the propargylic acetate **126**. The acetylenic moiety of **126** was then converted into the corresponding acetylene-dicobalthexacarbonyl complex. Cyclization upon treatment with *p*-toluenesulfonic acid afforded the desired nine-membered F-ring **127** as a single stereoisomer. Oxidative decomplexation of complex **127** afforded ketone **128** and subsequent introduction of the seven-membered G-ring afforded the B-M ring system **129** of CTX1B (**5**).[70-71]



a) 1. *n*-BuLi, THF, −78 °C; 2. TBAF, THF, 54% (2 steps); b) 1. Ac_2O, pyridine, DMAP; 2. Amberlyst 15, MeOH, 77% (2 steps); c) 1. $Co_2(CO)_8$, CH_2Cl_2; 2. $TsOH{\cdot}H_2O$, CH_2Cl_2, 72% (2 steps); d) $(Ph_2P)_2CH_2$, PhMe, N_2, 100 °C, then air, 100 °C, 48%.

Scheme 22

Sonogashira coupling between the B-M ring system **131** and the *trans*-vinyliodide **130** furnished enyne **132** (**Scheme 23**).[70] The seven-membered A-ring was then introduced *via* the developed acetylene-dicobalthexacarbonyl strategy. Reductive decomplexation of the *endo*-complex **133** followed by global deprotection afforded CTX1B (**5**).



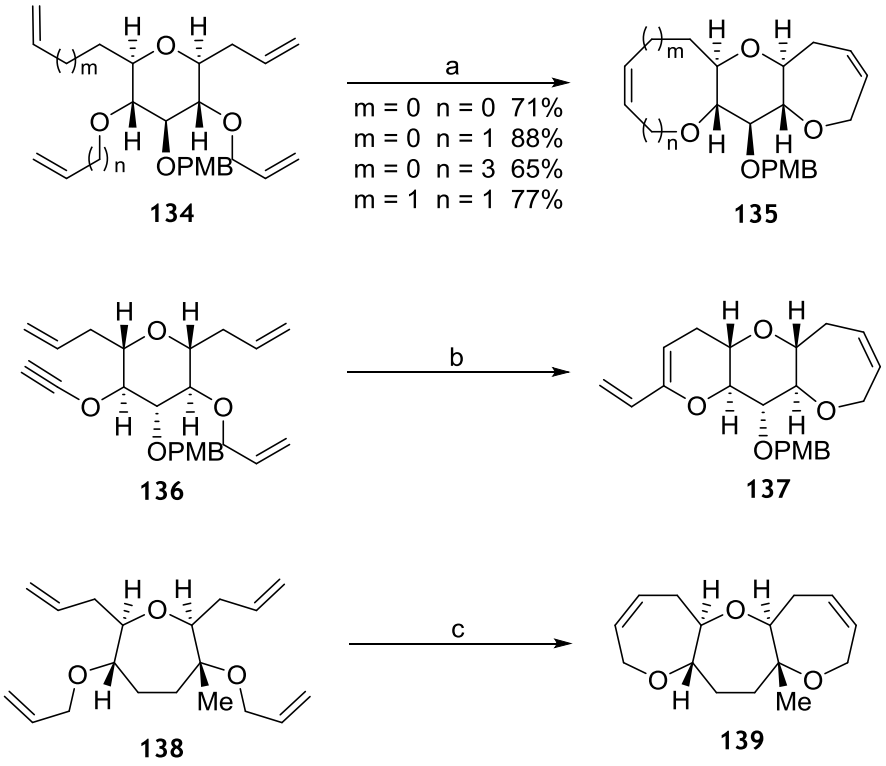
a) 1. DDQ, diallyl ether, $ClCH_2CH_2Cl$, 55 °C, 68%; 2. $Pd(PPh_3)_4$, CuI, *n*-$PrNH_2$, PhMe, 60%; b) 1. $Co_2(CO)_8$, CH_2Cl_2, 70%; 2. TMSOTf, CH_2Cl_2, −20 °C, then THF, 70%.

Scheme 23

2.4 Clark Group Approach

2.4.1 Two-Directional Double RCM

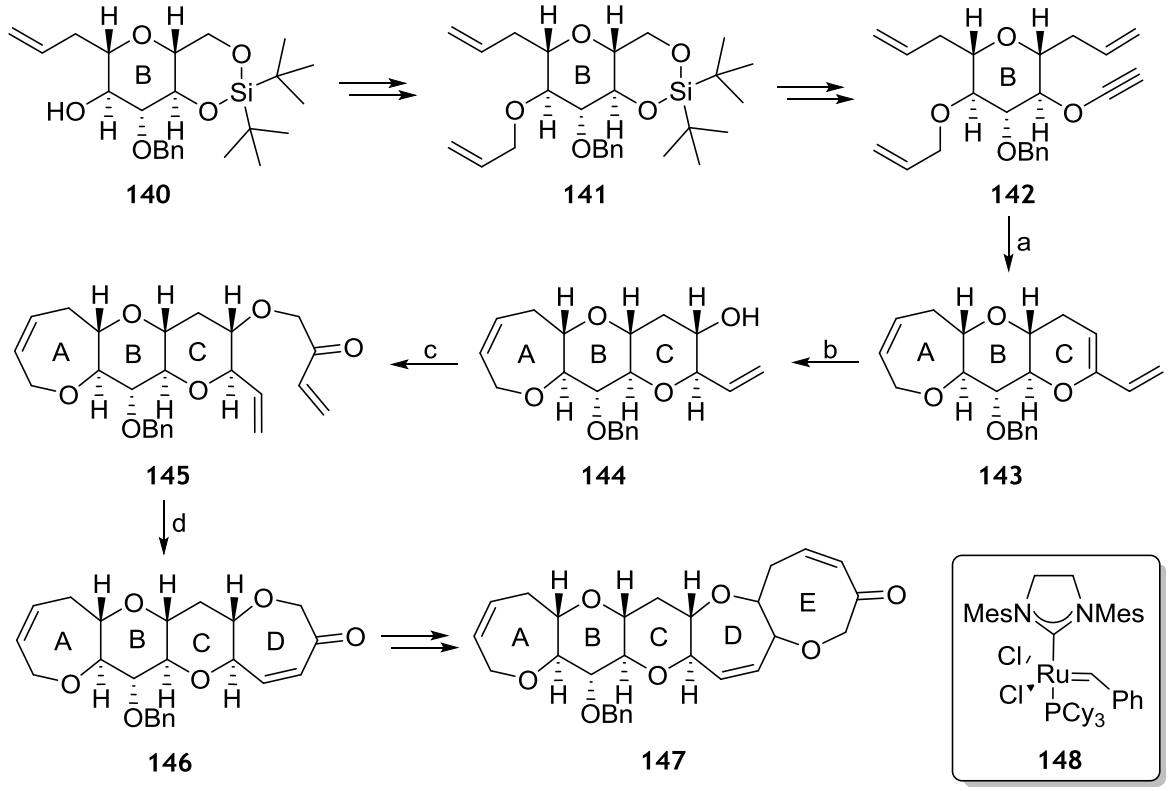
Clark and co-workers have reported several robust strategies for the synthesis of polycyclic ether systems utilizing RCM methodology.[72] The target cyclic ethers were constructed *via* RCM reaction of enol ethers,[73] allylic ethers,[74] or alkynyl ethers.[75] More recently, they have developed an efficient and flexible two-directional strategy for the construction of *trans*-fused polyether systems (**Scheme 24**).[76] Tricyclic ethers, containing rings of various sizes, were prepared in moderate to excellent yield by two-directional double RCM reaction of substrates containing combinations of enol, allylic and alkynyl ethers.



a) **61** (20—30 mol%), CH_2Cl_2, reflux; b) **61** (15 mol%), CH_2Cl_2, reflux, 50%; c) **61** (20 mol%), CH_2Cl_2, reflux, 75%.

Scheme 24

Clark and co-workers utilized their developed two-directional strategy for the synthesis of the A-E ring system **147** of CTX3C (**4**) (**Scheme 25**).[77] Preparation of the cyclization precursor **142** commenced with conversion of known alcohol **140** into allyl ether **141**. Following cleavage of the di-*tert*-butylsilylene group, the resultant diol was converted in five steps to the required double RCM precursor **142**. Simultaneous diene and enyne RCM reaction upon treatment of **142** with Grubbs second generation catalyst **148**, constructed both the A- and C-rings of the target system. Formation of the D-ring began with selective epoxidation of the electron-rich enol ether **143**. Regioselective reduction of the resulting epoxide provided alcohol **144**. Alkylation of alcohol **144** furnished RCM precursor **145**. Treatment of enone **145** with catalyst **148** provided tetracycle **146**. The E-ring was then introduced *via* the enone formation and RCM sequence to afford the A-E ring system **147** of CTX3C (**4**).



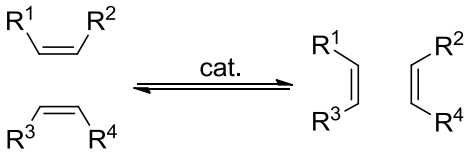
a) **148** (10 mol%), CH_2CH_2, PhMe, 70 °C, 58%; b) 1. DMDO, CH_2Cl_2, 0 °C; 2. $BF_3{\cdot}Et_2O$, Et_3SiH, MeCN, −40 °C, 71% (2 steps); c) 1. NaH, $ClCH_2COCHPPh_3$, TBAI, THF, reflux; 2. HCHO aq., Et_2O, 56% (2 steps); d) **148** (5 mol%), CH_2Cl_2, reflux, 70%.

Scheme 25

3.0 Double RCM

3.1 Olefin Metathesis

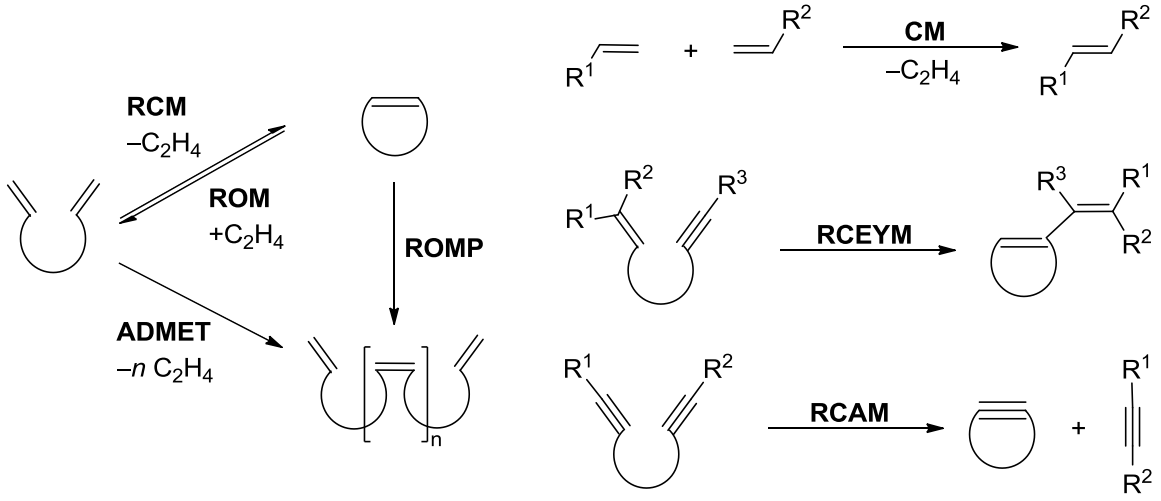
The word metathesis is derived from the Greek words *meta* (change) and *tithenai* (to place), and literally means to transpose. Olefin metathesis was discovered in the mid-1950s by workers at DuPont, Standard Oil of Indiana and Phillips Petroleum during their investigations into Ziegler—Natta polymerization catalysis.[78] Olefin metathesis is a catalytic process where two alkenes undergo bond reorganization in the presence of metal carbene complexes, resulting in the redistribution of the alkene moieties (**Scheme 26**).[79]



Scheme 26

Olefin metathesis represents a powerful transformation in chemical synthesis. Over the past two decades it has attracted a vast amount of interest from researchers in both industry and academia.[80] The importance of olefin metathesis was recognised in 2005 when Chauvin, Grubbs and Shrock were awarded the Nobel Prize in Chemistry "*for the development of the metathesis method in organic synthesis*".[81]

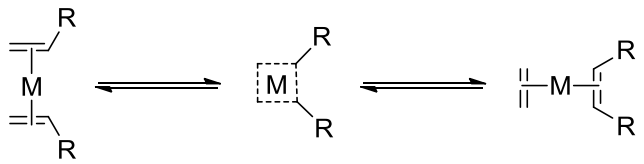
Olefin metathesis can be extended to different π-systems and has many applications: these include ring-opening methasis polymerisation (ROMP), ring-closing metathesis (RCM), acyclic diene metathesis (ADMET), cross-metathesis (CM), ring-closing enyne metathesis (RCEYM) and ring-closing alkyne metathesis (RCAM) (**Scheme 27**).



Scheme 27[82]

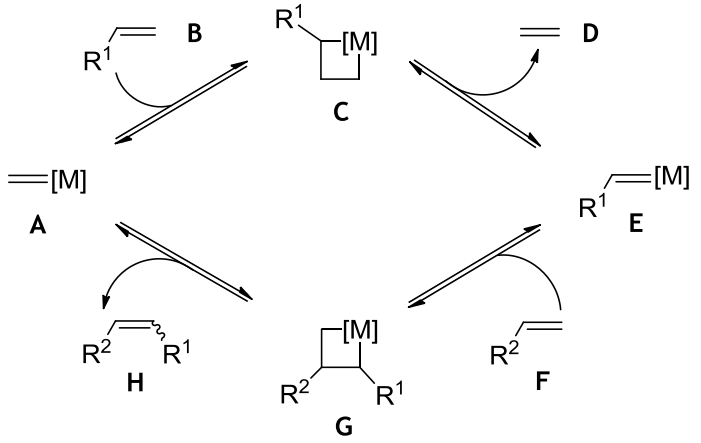
3.2 Olefin Metathesis Mechanism

The initial metathesis mechanism proposed by Calderon involved the pair-wise exchange of alkylidenes through a 'quasicyclobutane' mechanism (**Scheme 28**).[83] In this mechanism, two olefins coordinate to the metal centre and exchange alkylidene groups through a symmetrical intermediate. With a few assumptions, this mechanism can account for outcomes observed in most of the basic metathesis transformations.



Scheme 28

A later mechanism proposed by Chauvin was found to be more consistent with the experimental evidence, and even today remains the generally accepted metathesis mechanism (**Scheme 29**).[84] The proposed mechanism is believed to occur *via* a metallocyclobutane intermediate through alternating [2+2] cycloadditions and cycloreversions.



Scheme 29

The first step in the catalytic cycle is the formation of metallocyclobutane **C** *via* a [2+2] cycloaddition reaction between olefin **B** and the transition metal alkylidene complex **A**. This metallocycle then undergoes a [2+2] cycloreversion reaction to liberate ethene **D** and furnish the metal carbene **E**. A second [2+2] cycloaddition reaction between metal carbene **E** and olefin **F** provided metallocycle **G**. A further [2+2] cycloreversion reaction liberates alkene **H**; complex **A** is regenerated and re-enters the catalytic cycle.

Due to the reversible nature of the individual steps in the catalytic cycle, an equilibrium mixture of olefins is obtained. In order to make metathesis reactions productive in preparative terms, the equilibrium must be shifted in favour of the desired product.[82] In the case of RCM, the reaction is entropically driven as the alkene substrate is transformed into two products. Furthermore, if one of these two products is volatile, the cycloreversion step becomes irreversible. The substitution pattern of the alkene also proves to be an important factor because it dictates the kinetics of the reaction. In general, the more substituted the alkene, the less reactive it is.[85]

3.3 Catalysts

From the early discovery of Ta-based catalysts to the present-day *N*-heterocyclic carbene (NHC)-based catalysts, the design of metathesis catalysts has undergone a radical evolution.[78] At present, two main types of catalyst are in practical use. The molybdenum catalyst **149**, developed by Schrock and co-workers,[86] along with ruthenium complexes **61** and **148**, developed by Grubbs and co-workers,[87] have been crucial to the expansion of metathesis as general method in organic synthesis (**Figure 12**).

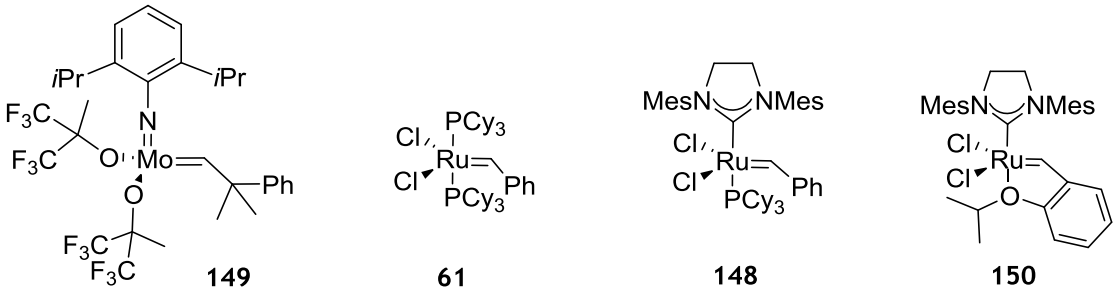


Figure 12

Molybdenum catalyst **149** is highly reactive towards a broad range of substrates and numerous derivatives are available with various steric and electronic modifications.[78] The drawbacks of the molybdenum-based catalysts are their poor functional group tolerance, along with their high sensitivity towards air, moisture and any impurities present in the solvent.[79]

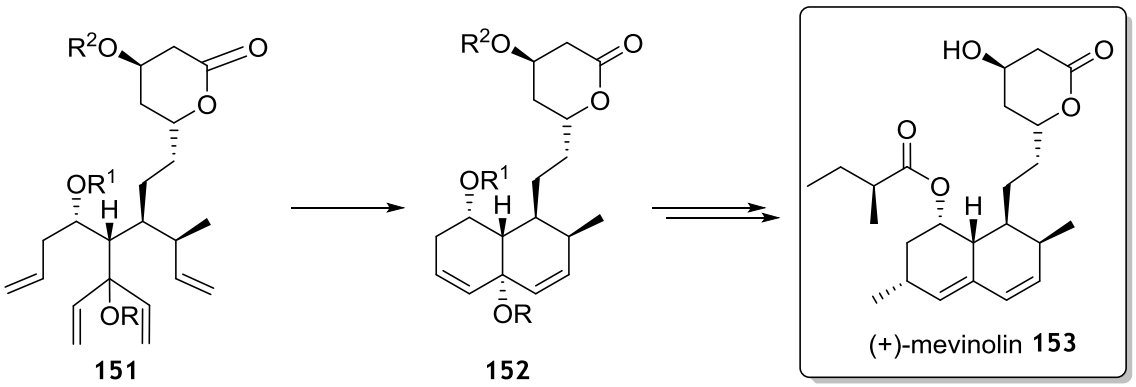
Ruthenium catalysts **61** and **148** have received a great deal of attention due to their excellent functional group tolerance combined with their significant stability towards both air and moisture. They can both be handled without the use of a glove box or Schlenk techniques. In recent years, Hoveyda and co-workers have developed a series of improved versions of Grubbs catalysts *e.g.* **150**.[88] These catalysts have been shown to display longer lifetimes, are reusable and, in cases where chiral ligands have been incorporated, show good enantioselectivity.[89]

3.4 Double RCM

Over the years, the RCM reaction has been employed for the construction of numerous complex cyclic compounds. Recently, several applications of double RCM reactions of tetraenes to furnish the corresponding cyclic systems have been reported. Double RCM provides an attractive strategy as it facilitates the rapid construction of various polycyclic systems.

3.4.1 Synthesis of Fused Bicyclic Compounds *via* Double RCM

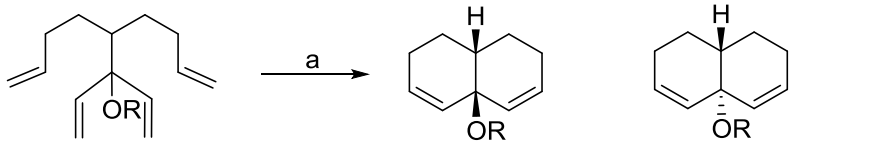
Lautens and co-workers became interested in using RCM methodology as a key step in their projected total synthesis of the HMG CoA reductase inhibitor (+)-mevinolin (**153**) (**Scheme 30**).[90] It was proposed that a diastereoselective double RCM strategy involving **151**, followed by an alkene selective sigmatropic rearrangement of **152**, would provide convenient access to the carbon skeleton of the hexahydronaphthalene portion of (+)-mevinolin (**153**).[91]



Scheme 30

Initial studies into the diastereoselective double RCM reaction were performed using unsubstituted tetraenes (**Scheme 31**). By analogy to fully saturated decalin systems, it was anticipated that the *trans*-fused decalins would be thermodynamically preferred. Treatment of tetraene **154** with Grubbs first generation catalyst **61** afforded a 1:2.8 mixture of diastereomers in favour of the *trans*-decalin **156**. When tetraene **155** was treated with catalyst **61** under an atmosphere of ethylene, an 8:1 mixture of diastereomers was formed with the *cis*-decalin **157** now predominanting. Computational studies suggested that the formation of the *cis*-decalin was a kinetic outcome, and that at least one of

the steps in the reaction sequence prior to the final bond formation was irreversible.[90] The diastereoselective double RCM strategy employed by Lautens and co-workers has provided access to a novel class of bicyclic diallylic alcohols and ethers.



154 R= H
155 R = PMB

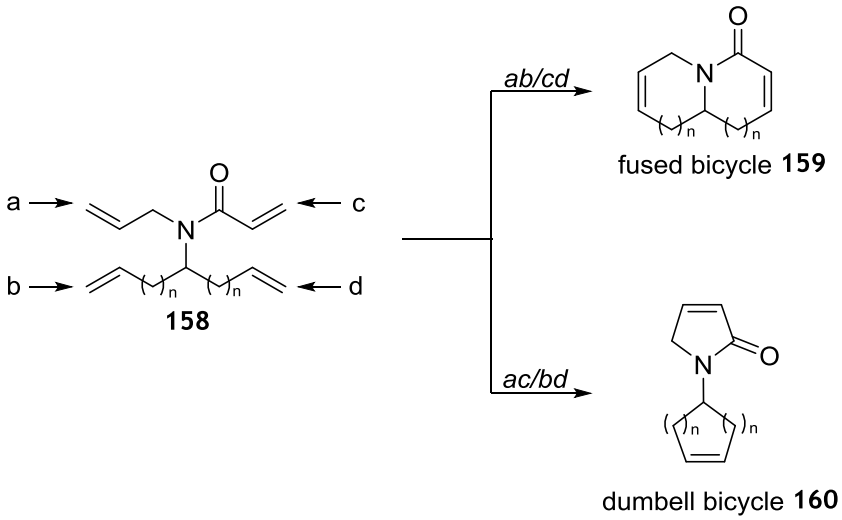
cis-**156** R = H
cis-**157** R = PMB

trans-**156** R = H
trans-**157** R = PMB

a) **61** (10—12 mol%), CH_2Cl_2, 23 °C, **156** = 84%, 1:2.8, **157** = 80%, 8:1, when R = PMB reactions performed under an ethylene atmosphere.

Scheme 31

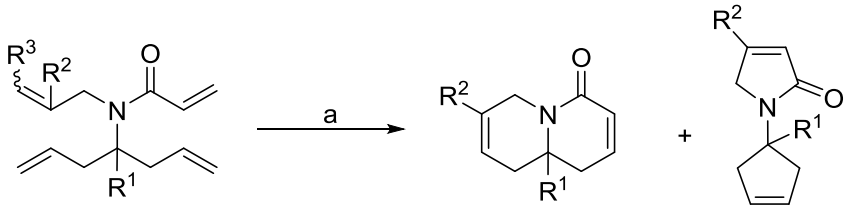
Ma and co-workers investigated the construction of bicyclic pyrrolizidine, indolizidine and quinolizidine alkaloid skeletons *via* a double RCM protocol.[92] These particular alkaloid skeletons are found in several natural products.[93] The proposed strategy relied upon the control of the RCM mode (*ab*/*cd vs ac*/*bd*) to provide the targeted fused bicycle **159** (**Scheme 32**).



Scheme 32[92a]

Treatment of **161a** and **161b** with ruthenium catalyst **61** afforded a mixture of *mode-ab*/*cd* and *mode-ac*/*bd* products in favour of the dumbell-type products **163** (**Table 2**). Reaction of **161c** under the same conditions furnished the corresponding products with a ratio of **162c**:**163c** as high as 21:1 in favour of

the desired fused product. Interestingly, it was noted that reaction of **161d** (with the methyl group in the terminal position of the carbon-carbon double bond), afforded fused bicycle **162d** as the only product, indicating a substituent effect on the selectivity of cyclization. This reaction was extended to the synthesis of substituted 6,6-bicyclic lactam **162e**.



161 **162** **163**

a) **61** (5 mol%), CH_2Cl_2, reflux.

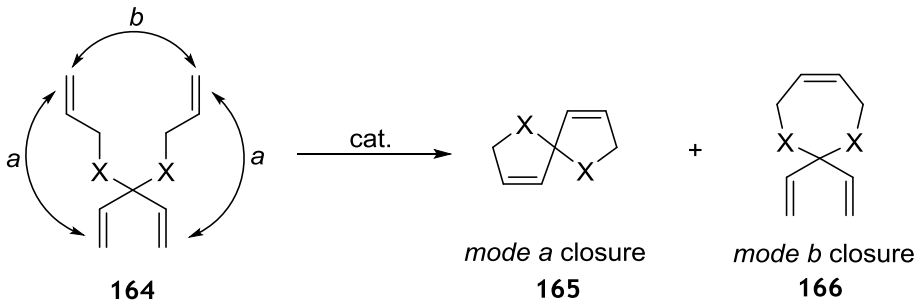
Compound	Result
161a (R^1= Me, R^2=R^3=H)	64% (**162a**:**163a**, 1:3.6)
161b (R^1= *n*-Pr, R^2=R^3=H)	41% (**162b**:**163b**, 1:3.8)
161c (R^1=R^2=R^3=H)	88% (**162c**:**163c**, 21:1)
161d (R^1=R^2= H R^3=Me)	86% (**162d**)
161e (R^1=R^3= H R^2=Me)	43% (**162e**)

Table 2[92]

Ma and co-workers have developed an efficient double RCM strategy for the construction of the target alkaloid skeletons. Reaction selectivity was tuned by the electronic and steric effects of the substituents on the *N*-containing tetraenes.

3.4.2 Synthesis of Spirocyclic Compounds *via* Double RCM

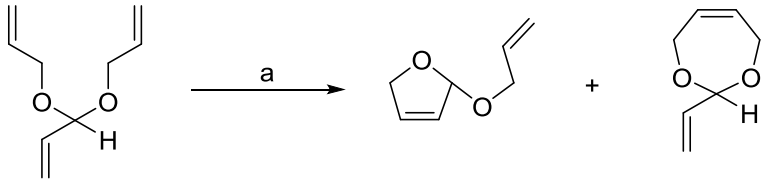
Harrity and co-workers employed a double RCM strategy for the novel construction of spirocyclic compounds such as **165**.[94] Tetraene **164** can undergo double RCM *via* two modes to afford two products (**Scheme 33**).The desired spirocyclization reaction would require selective metathesis of tetraene **164** through *mode a* to afford spirocycle **165**, whereas monocyclic product **166** would arise from cyclization through *mode b*.



164 **165** **166**

Scheme 33[94]

In order to establish the selectivity of *mode a* cyclization over *mode b*, model substrate **167** was prepared and its behaviour upon treatment with ruthenium catalyst **61** was investigated (**Scheme 34**). It was found that 5-membered ring cyclization proceeded with complete selectivity to afford dihydrofuran **168** with no detectable quantity of the acetal **169**.[94]



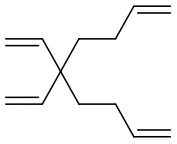
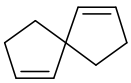
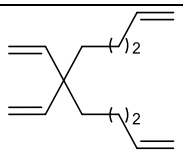
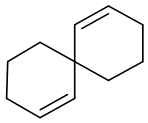
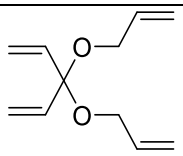
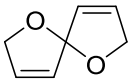
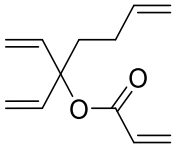
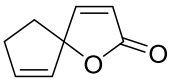
167 **168** **169**

>95 : <5

a) **61** (5 mol%), CH_2Cl_2.

Scheme 34[94]

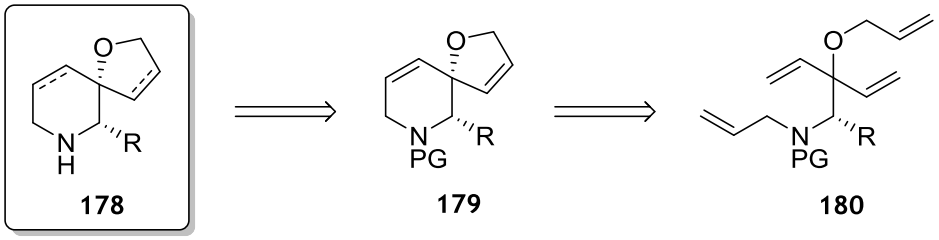
The double metathesis methodology was then applied to a range of tetraene precursors (**Table 3**).[94] The spirocyclic carbocycles **171** and **173** were both isolated in excellent yield from their corresponding tetraene precursors. Spiroacetal **175** was readily assembled from **174** under mild conditions. Interestingly, acetal **175** rapidly decomposed upon treatment with catalytic *p*-toluenesulfonic acid at room temperature. This result implies that functionalised [4,4]-spiroacetals such as **175** cannot be accessed from the corresponding open chain ketone or acetal using traditional acid-catalysed reactions.[95] The butenolide **177** was also successfully synthesised using the double RCM methodology.

Substrate	Product[a]	Yield
 **170**	 **171**	98%
 **172**	 **173**	92%
 **174**	 **175**	90%
 **176**	 **177**	62%

[a] reaction conditions: **61** (5—15 mol%), CH_2Cl_2, 25—40ºC.

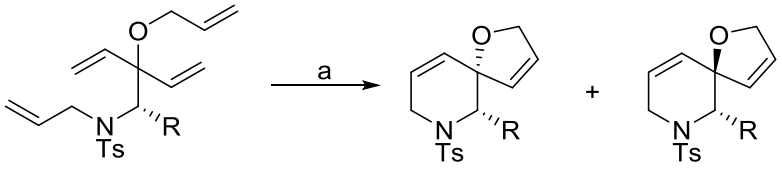
Table 3[94]

The double RCM strategy has also been employed for the diastereoselective synthesis of selected spirocycles.[96] In 2000, Wallace and co-workers reported the first diastereoselective double RCM reaction to afford a spirocyclic target.[97] While investigating the development of selective NK-1 receptor antagonists, a route to compounds with the general structure **178** was required. It was envisioned that a double RCM reaction of tetraene **180** would afford the desired spirocyclic system **179** (**Scheme 35**).



Scheme 35

A variety of *N*-tosyl protected metathesis precursors were prepared from commercially available amino acid esters (**Table 4**).[97] In all cases, the easily separable spirocycles **182a-d** and **183a-d** were isolated in good yield. The diastereoselectivity of the double RCM reaction was strongly in favour of the required 5*R*,6*S*-isomers **182a-d**, and appeared to be unaffected by the identity of alkyl substituent.



181 a-d **182 a-d** **183 a-d**

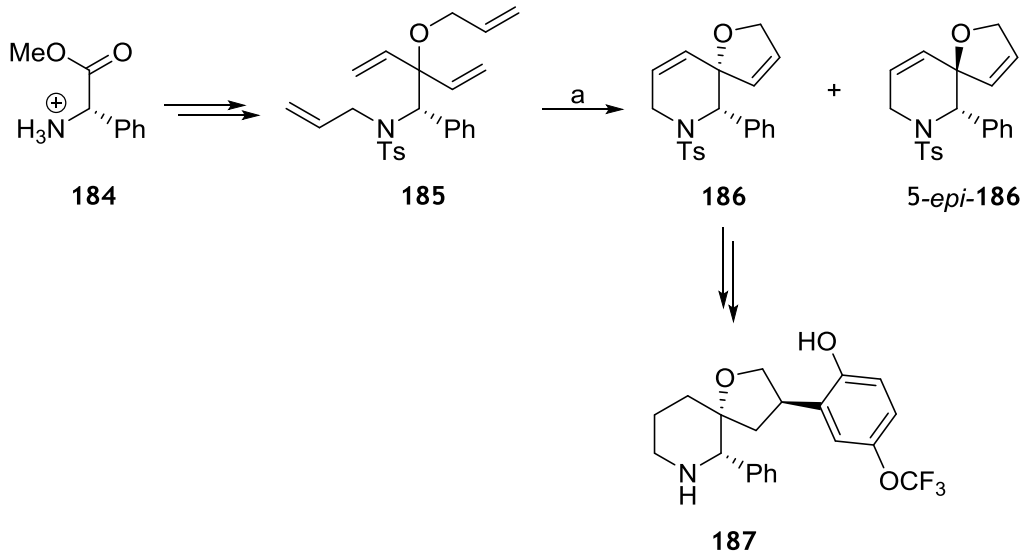
a) **61** (5—7 mol%), $CHCl_3$, 20 °C.

Tetraene	R	Yield	Diastereoselectivity[a]
181a	Me	74%	92%
181b	*i*-Pr	84%	92%
181c	*i*-Bu	76%	92%
181d	CH_2Ph	87%	92%

[a]Isomer ratio determined by HPLC analysis

Table 4[97]

Following their successful synthesis of spirocycles **182a-d**, Wallace and co-workers turned their attention to the synthesis of the selective NK-1 receptor antagonist 1-oxo-7-azaspirodecane **187** (**Scheme 36**).[98] The metathesis precursor **185** was synthesised in three steps from the commercially available phenylglycine ester (**184**). The key double RCM reaction of tetraene **185** proceeded smoothly upon treatment with ruthenium catalyst **61**. Diastereomers **186** and 5-*epi*-**186** were isolated in good yield and with 70% diastereoselectivity in favour of the desired isomer **186**. Selective functionalization of **186** furnished the target **187** in three further steps.

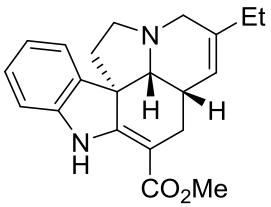


a) **61** (4 mol%), CH_3Cl, 86%, 70% ds.

Scheme 36

3.4.3 Synthesis of Natural Products *via* Double RCM

Martin and co-workers have pioneered the application of RCM to the synthesis of nitrogen heterocycles and a variety of alkaloid natural products.[99] Their concise total synthesis of the pentacyclic (±)-pseudotabersonine (**188**) employed a double RCM reaction to facilitate the rapid construction of the carbon skeleton of this natural product (**Figure 13**).[100]

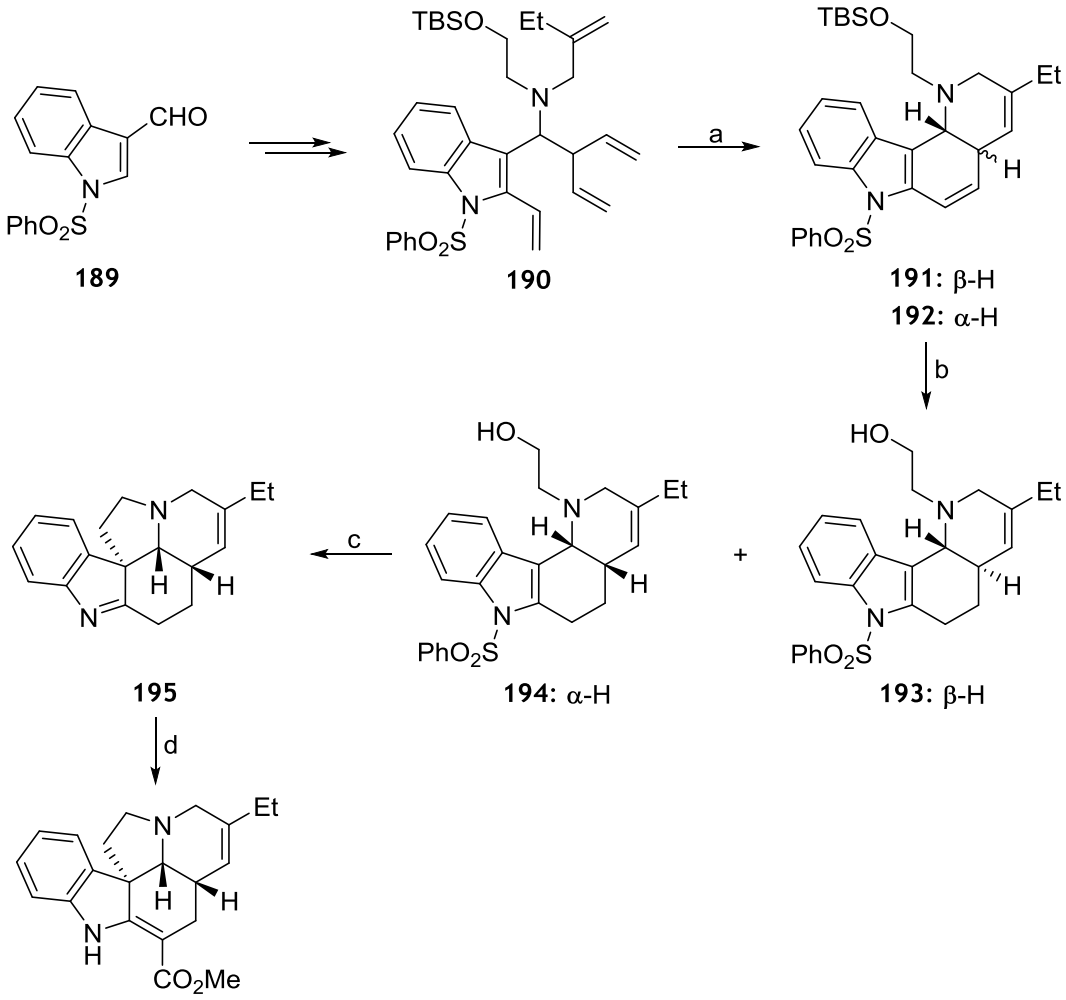


(±)-pseudotabersonine **188**

Figure 13

The metathesis precursor **190** was synthesised in six steps from the commercially available indole aldehyde **189** (**Scheme 37**).[100] The key double RCM reaction of the tetraene **190** proceeded smoothly upon treatment with ruthenium catalyst **150** to afford an inseparable mixture of the *cis*- and *trans*-fused tetracycles **191** and **192**. Catalytic hydrogenation of the crude mixture resulted in regioselective reduction of the less substituted alkene.

Subsequent removal of the silyl ether provided tetracycles **193** and **194** as a separable mixture in moderate yield over the three steps. Conversion of **194** into the pentacyclic intermediate **195** was achieved through the use of an *N*-deprotection/*O*-sulfonylation and cyclization process first reported by Bosch and co-workers.[101] Deprotonation of **195** followed by selective acylation with Mander's reagent furnished (±)-pseudotabersonine (**188**).[102]



(±)-pseudotabersonine **188**

a) **150** (5 mol%), PhMe, 100 °C, dr 7:10; b) 1. 10% PtO_2, EtOH, H_2; 2. HCl, MeOH, **193** = 26%, **194** = 44% (3 steps); c) KO*t*Bu, DME/THF, −20 to −5 °C, 66%; d) LDA, THF, −78 to −20 °C; then $NCCO_2Me$, −78 °C, 61%.

Scheme 37

Norcross and co-workers have employed double RCM methodology for the synthesis of several lupine alkaloids.[103] The lupine alkaloids constitute a structurally diverse group of natural products found in numerous varieties of leguminous plants and trees.[104] The sparteine subgroup of lupine alkaloids are characterized by a common 3,11-diazatetracyclo[7.7.1.0.0]heptadecane ring system (**Figure 14**). All three targets were synthesised from the common bisimide intermediate **196**.

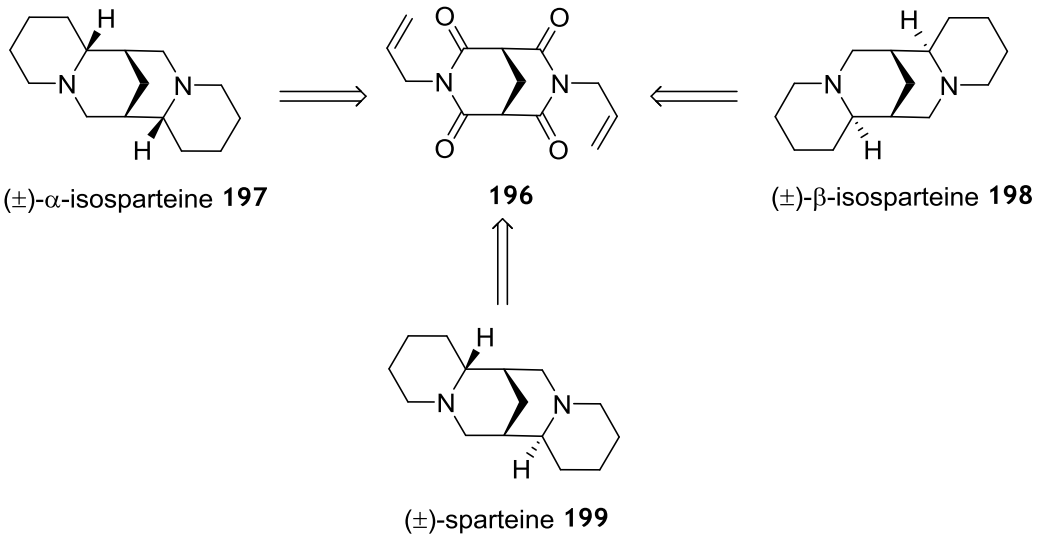
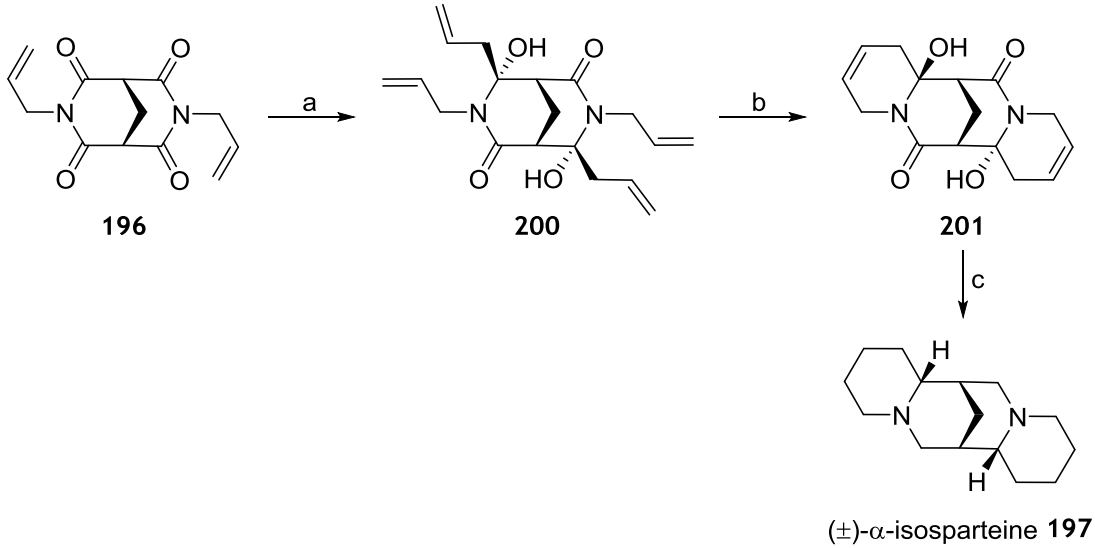


Figure 14

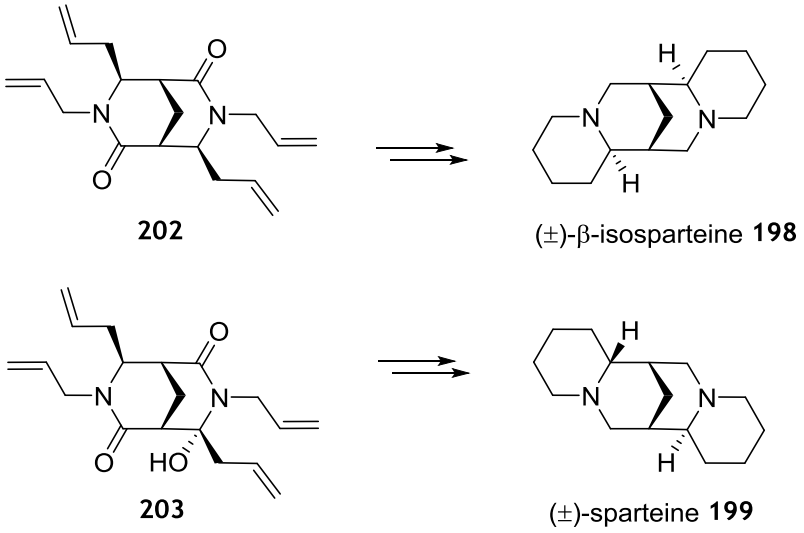
The synthesis of (±)-α-isosparteine **197** began with the addition of excess allylmagnesium bromide to bisimide **196** to generate tetraene **200** (**Scheme 38**).[105] Double RCM of tetraene **200** with ruthenium catalyst **61** proceeded smoothly to furnish the tetracyclic sparteine congener **201**. Completion of the total synthesis required hydrogenation followed by deoxygenation to afford (±)-α-isosparteine **197**.



a) CH_2CHCH_2MgBr, Et_2O/THF, −78 °C, 77%; b) **61** (4 mol%), CH_2Cl_2, 81%; c) 1. 5% Pd/C, H_2, MeOH:H_2O (5:1), 96%; 2. BH_3·THF, THF, 0 °C to rt, 47%.

Scheme 38

Alkaloids (±)-β-isosparteine **198** and (±)-sparteine **199** were synthesised in a similar manner from tetraene precursors **202** and **203** respectively (**Scheme 39**).



Scheme 39

Clark and co-workers have utilized the double RCM methodology in their two-directional synthesis of selected polycyclic ether fragments (see **Ch 1. § 2.4.1**).[77, 106] In 2005, they reported the rapid and efficient two-directional construction of the F-J ring system **214** of the gambieric acids **204**—**207** (**Figure 15**).[106a] The gambieric acids are marine polyethers (see **Ch 1. § 1.2**) that exhibit potent and selective antifungal activity.[107]

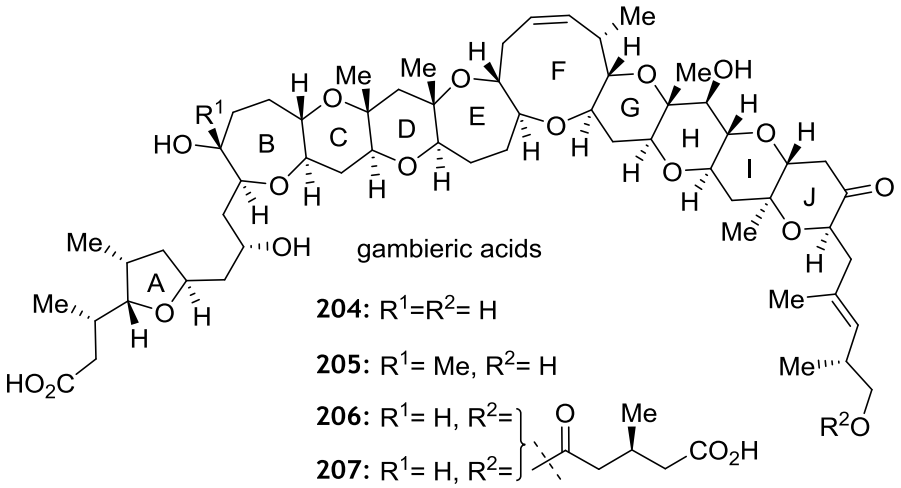
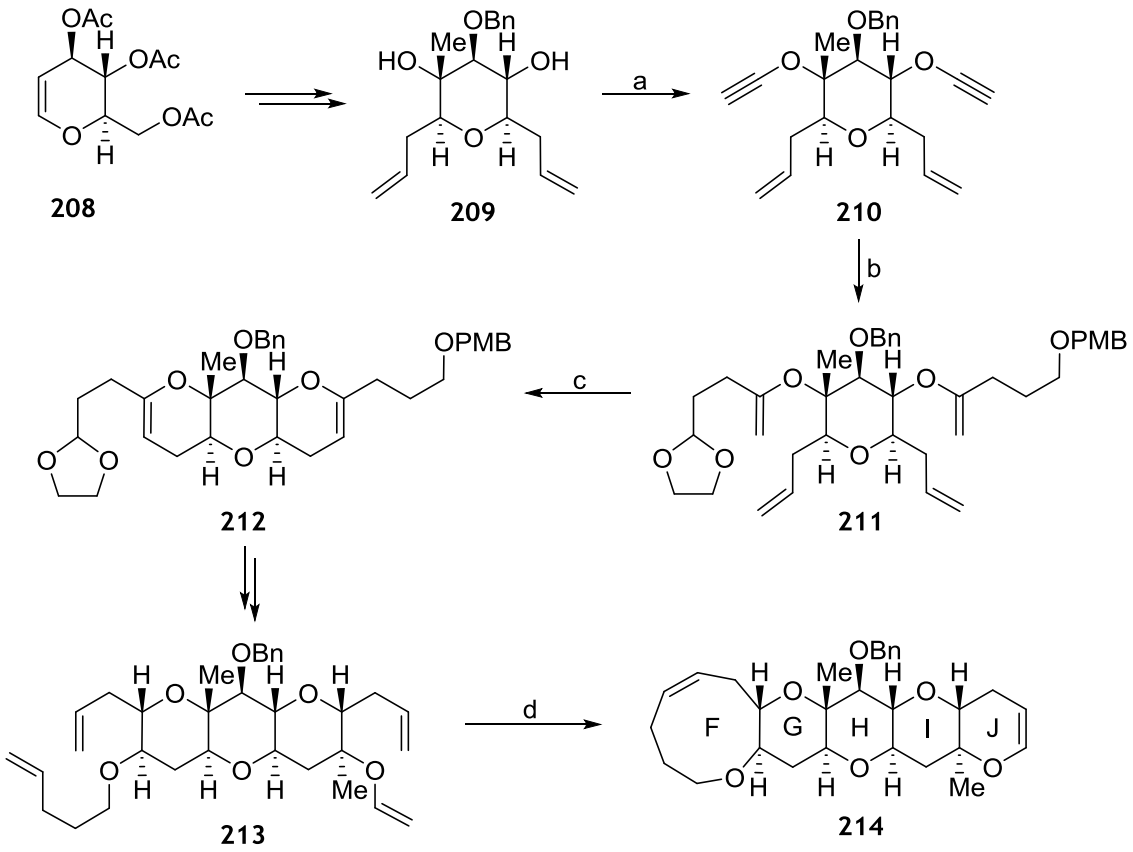


Figure 15

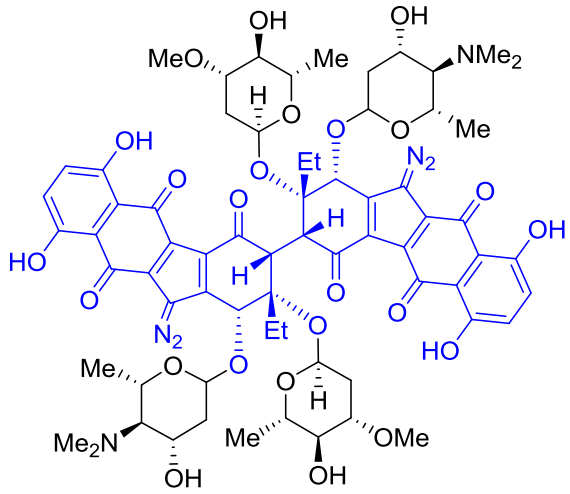
The synthesis of the pentacyclic target **214** began from the commercially available tri-*O*-acetyl-D-glucal **208** (**Scheme 40**). Diol **209** was prepared from **208** in ten synthetic steps and with an overall yield of 36%. Diol **209** was then converted into the corresponding bis(alkynyl ether) **210** using a one-pot alkynylation procedure developed by Greene and co-workers.[108] The first metathesis precursor **211** was prepared from **210** using sequential carbocupration reactions.[109] When bis(enol ether) **211** was treated with Grubbs second generation catalyst **148**, tricyclic product **212** was obtained in excellent yield. Following the double hydroboration of **212**, a series of functional group manipulations allowed for elaboration to the second metathesis precursor **213**. The final crucial double RCM reaction to construct the required nine- and six-membered rings proceeded smoothly to afford the target F-J ring system **214**. The synthesis of the pentacyclic F-J ring system **214** of the gambieric acids highlighted the advantages of employing a two-directional double RCM strategy for the synthesis of polyether natural products.



a) KH, Cl_2CCHCl. THF, 0 °C; then *n*-BuLi, Et_2O, −40 to −78 °C, 88% b) 1. $PMBO(CH_2)_3MgBr$, CuBr, LiBr, THF, −95 to −78 °C, 85%; 2. $(OCH_2CH_2O)CH(CH_2)_2MgBr$, CuCN, LiCl, THF, −78 °C, 84%; c) **148** (10 mol%), PhMe, 70 °C, 89%; d) **148** (10 mol%), PhMe, 80 °C, 60%.

Scheme 40

Feldman and co-workers have also exploited a two-directional strategy that incorporates the double RCM methodology for the synthesis of a targeted natural product.[110] Their approach to the central lomaiviticin A aglycone core **216** utilized a sequence involving double Ireland-Claisen ester enolate rearrangement and double RCM to deliver the central bis-cyclohexenone region (**Figure 16**). Lomaiviticin A (**215**) is a member of a small class of marine natural products which are characterized by the presence of the unusual diazoparaquinone moiety.[111]



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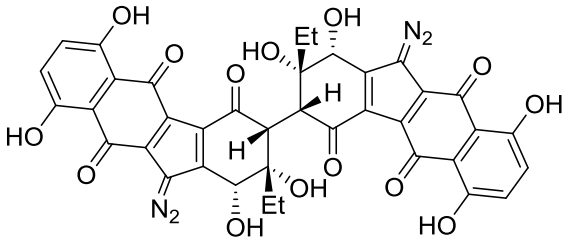
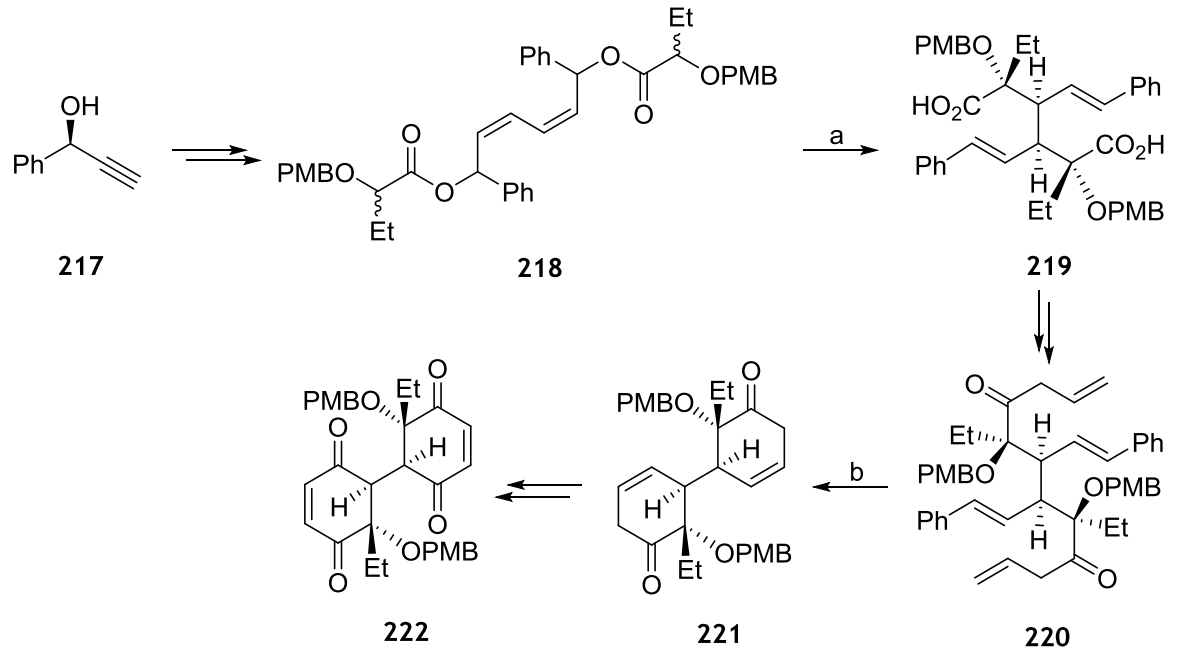


216

Figure 16

The synthesis of central bis-cyclohexenone region **222** began with the preparation of the Claisen rearrangement precursor **218** from chiral propargyl alcohol **217** (**Scheme 41**). Double Ireland-Claisen ester enolate rearrangement of dienyl glycolate **218** provided diacid **219** which possessed the desired stereochemistry.[112] Elaboration of **219** proceeded *via* two-directional chain extension of the carboxylic acid units to afford the allyl ketones required for the double RCM sequence. Bis-cyclohexene product **221** was obtained in good yield upon the treatment of metathesis precursor **220** with Grubbs second generation catalyst **148**. The bis-cyclohexene **221** was converted into the desired bis-cyclohexenone **222** following a short synthetic sequence. Feldman and co-workers successfully implemented a two-directional double RCM strategy for the completion of the core bicyclic system **222** of lomaiviticin A (**215**).



a) 1. $KN(TMS)_2$, TIPSOTf, Et_2O, −78 °C to rt; 2. TBAF, THF, 0 °C, 79% (from **217**); b) **148** (40 mol%), PhMe, 100 °C, 64%.

Scheme 41

3.5 Summary

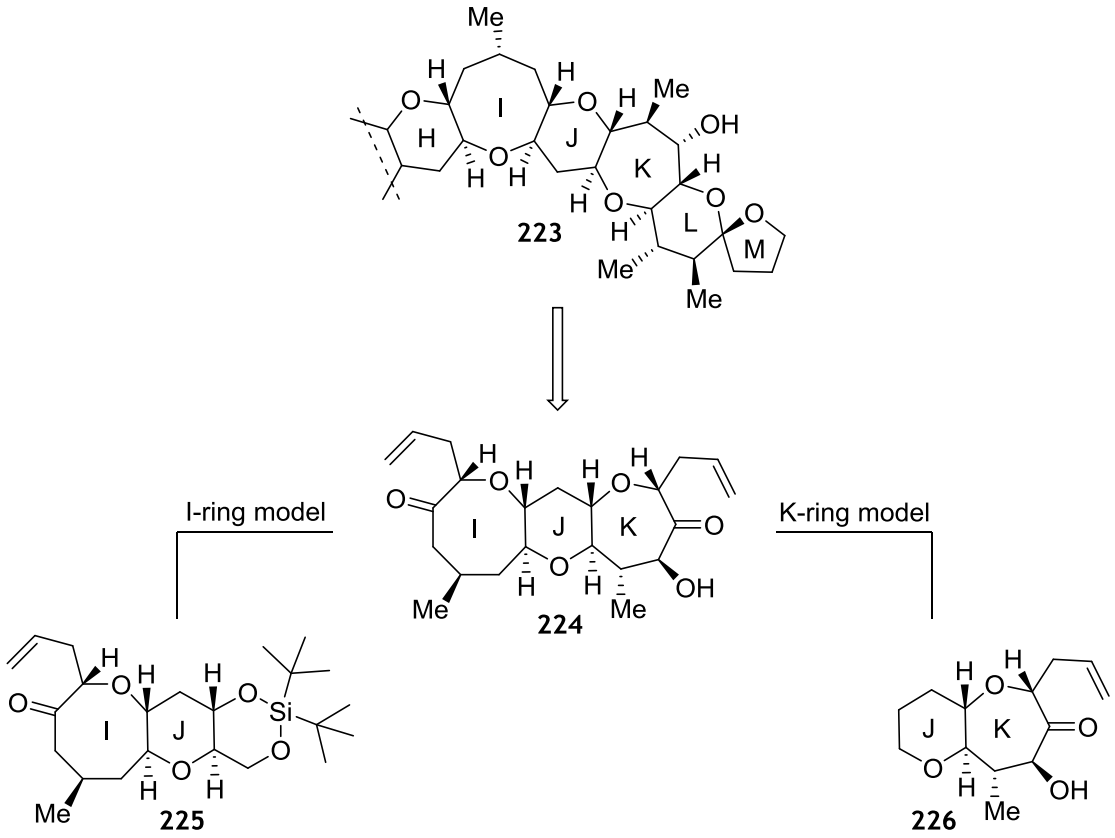
Olefin metathesis has emerged as one of the most powerful strategies for carbon-carbon bond construction. The development of well-defined catalysts which are able to combine high activity, durability and excellent tolerance towards a wide range of functional groups has revolutionised the field. Over the years, RCM has proven to be the most important olefin metathesis reaction. This methodology has been applied to the synthesis of numerous complex natural products. The development of the double RCM reaction has enabled the rapid construction of various structurally complex polycyclic systems.

Chapter 2: Results and Discussion

Chapter 2: Results and Discussion

1.0 Introduction

Previous work within the group had established an efficient two-directional strategy for the synthesis of various polycyclic ether systems (see **Ch 1. § 2.4.1**).[76] This two-directional methodology was employed for the synthesis of the A-E ring system **147** found in CTX3C (**4**).[77] It was proposed that a similar two-directional strategy could be developed for the construction of the IJK-tricyclic core **224** of the H-M ring system **223** of CTX3C (**4**). In order to allow for comprehensive investigation of the chemistry required to construct the IJK-tricyclic core **224**, two model systems were designed (**Scheme 42**). Both model systems were derived from tri-*O*-acetyl-D-glucal **208**, which was to provide the J-ring in each model compound. Our next challenge was to design a suitable two-directional strategy to the target IJK-tricycle **224**. Both model syntheses shared several common steps, which would be translated into a suitable two-directional approach to the tricyclic target **224**.



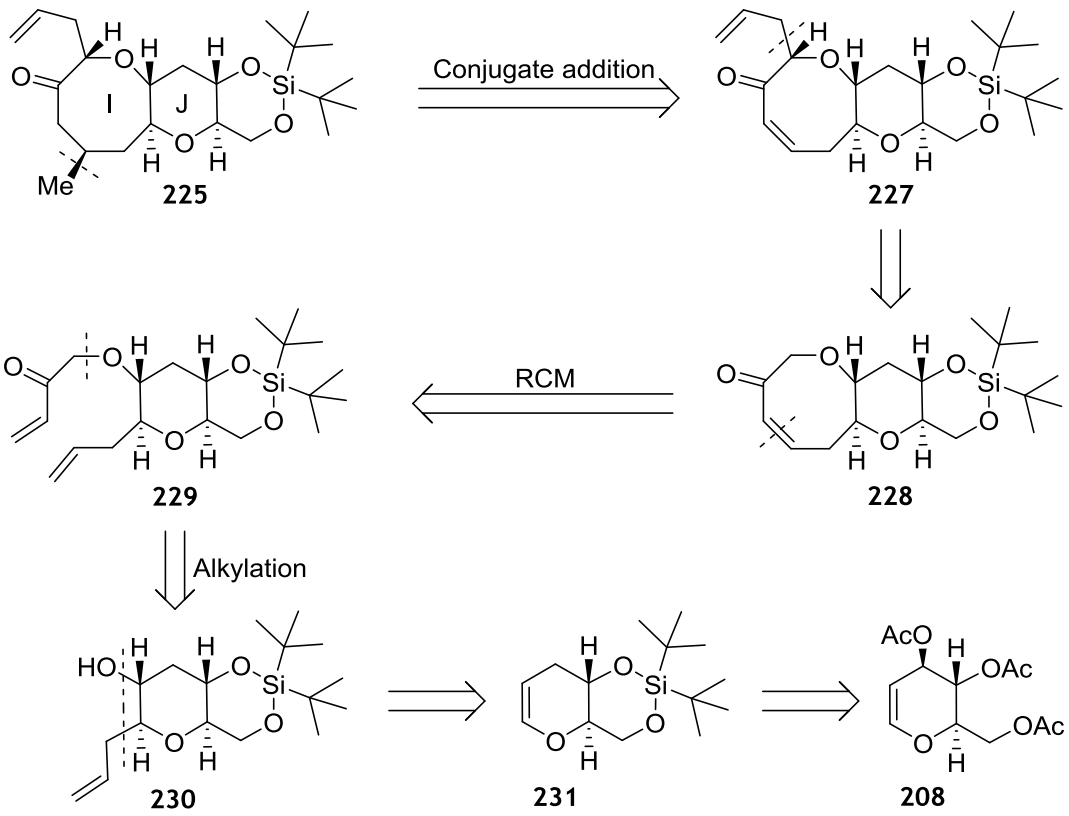
Scheme 42

2.0 Synthesis of the IJ-model 225

In order to investigate the chemistry required for the construction and functionalization of the eight-membered I-ring, the IJ-model system **225** was designed.

2.1 Retrosynthesis of the IJ-model 225

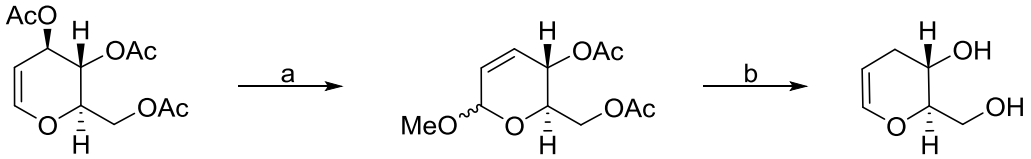
Retrosynthetic analysis of the IJ-model **225** is shown below (**Scheme 43**). Removal of the methyl group from ketone **225** implies conjugate addition to enone **227** to install this pendant methyl group in the forward direction. Disconnection of the allyl side chain to give **228** followed by scission of the alkene provides diene **229** and implies an RCM reaction in the forward direction. Removal of the ether linkage affords the secondary alcohol **230** which could be readily prepared from enol ether **231**. Deprotection affords the corresponding diol, which can be synthesised from commercially available tri-*O*-acetyl-D-glucal **208**.[113]



Scheme 43

2.2 Synthesis of Alcohol 230

The synthetic route toward the IJ-model system **225** began from commerically available tri-*O*-acetyl-D-glucal **208** (**Scheme 44**). Treatment with methanol in the presence of boron trifluoride diethyl etherate delivered the mixed acetal **232** by Ferrier rearrangement.[113] Displacement of the allylic methoxy group followed by simultaneous removal of the two acetate groups was achieved through reaction of acetal **232** with lithium aluminium hydride.[114] The diol **233** was obtained in high yield over the two steps.



208 **232** **233**

a) $BF_3 \cdot Et_2O$, MeOH, CH_2Cl_2, rt; b) $LiAlH_4$, dioxane, reflux, 81% (2 steps).

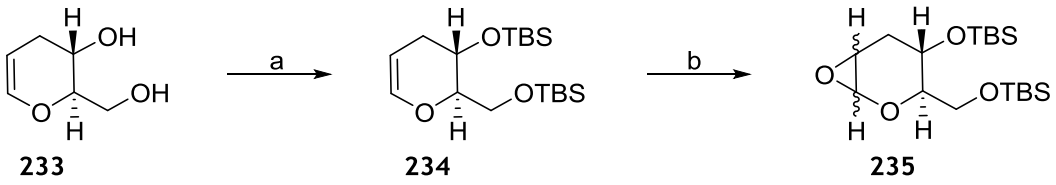
Scheme 44

2.2.1 Protection of Diol 233

Following the isolation of enol ether **233**, our next goal was the protection of the 1,3-diol. A variety of protecting group strategies were considered at this stage.

TBS-group Protection Strategy

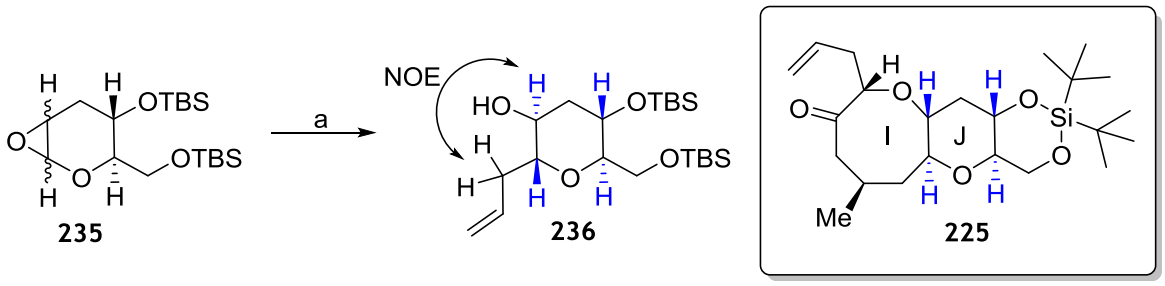
The first protection strategy investigated was the use of TBS-groups to protect the 1,3-diol. One benefit of this protection protocol is that it allows selective deprotection of the primary alcohol, if this should be required. TBS-groups were installed to afford cyclic enol ether **234** in 80% yield (**Scheme 45**). Epoxidation of the enol ether double bond using a preformed acetone solution of dimethyl dioxirane provided a diastereomeric mixture of the epoxides **235** (4:1 mixture of diastereomers).[115]



a) TBSCl, imidazole, DMF, 0 °C, 80%; b) DMDO (0.09 M in acetone), CH_2Cl_2, −78 °C, 95%, dr 4:1.

Scheme 45

Once isolated, epoxides **235** were treated directly with allylmagnesium chloride with the aim of affording the corresponding alcohol. Numerous attempts at this allylation step yielded only recovered starting material or decomposition products. Previous work carried out within the group has shown that the allylation of epoxides **235** was a challenging step, with the only successful attempt giving a 9% yield of alcohol **236**.[116] A variety of reaction conditions were explored. It was found that treatment of epoxides **235** with a freshly prepared solution of allylmagnesium bromide afforded alcohol **236** in good yield with a diastereomeric ratio > 20:1 (**Scheme 46**).

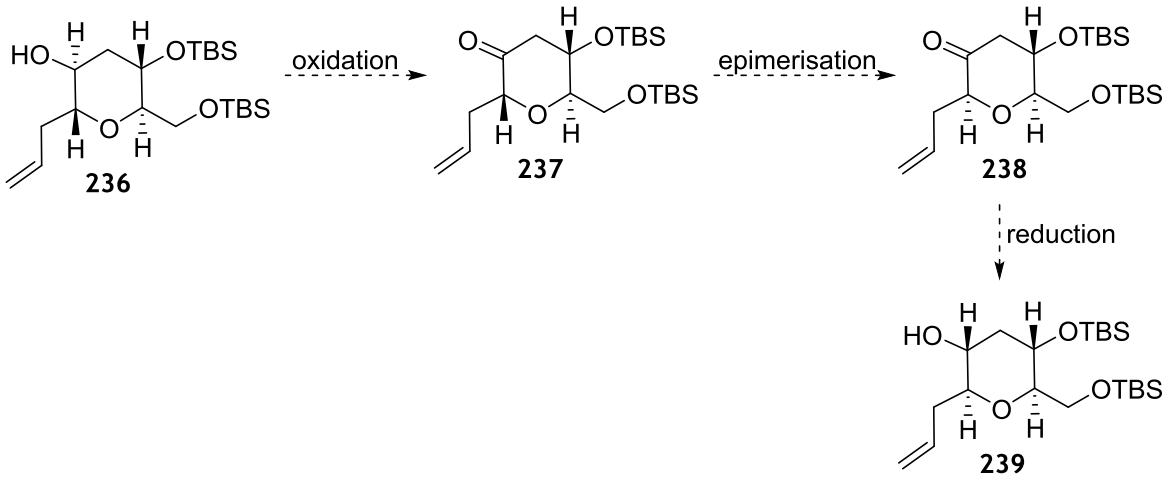


a) CH_2CHCH_2MgBr (0.7 M in Et_2O), THF, 0 °C to rt, 64%, dr > 20:1.

Scheme 46

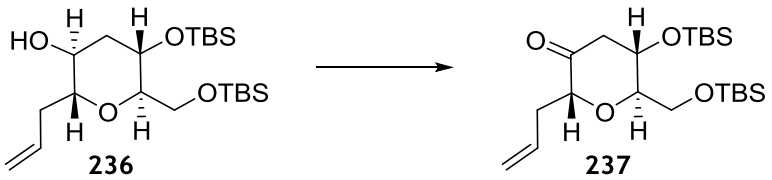
Although trans-diaxial ring opening of one diastereomer of epoxides **235** led to alcohol **236**, the remaining starting material afforded only decomposition products. The stereochemistry of alcohol **236** was confirmed through ^1H NMR NOE analysis (**see Appendix A**). Unfortunately, the stereochemistry observed in alcohol **236** was not that required for the formation of the target IJ-model system **225**. The highlighted hydrogens display a *trans*-relationship in alcohol **236** while in the target system **225** there is a *cis*-relationship across the polycyclic ether (**Scheme 46**).

Inversion of stereochemistry at the stereocentres bearing the alcohol and allyl functionalities was necessary in order to introduce the desired stereochemistry. It was envisioned that inversion to give the required stereochemistry could be accomplished through a simple three-step sequence (**Scheme 47**). Oxidation of alcohol **236**, followed by epimerisation of the allyl group to the more stable equatorial product would afford ketone **238**. Reduction of **238** would complete the sequence to provide the desired alcohol **239**.



Scheme 47

The first step in the sequence, oxidation of alcohol **236**, proved unexpectedly challenging. A wide selection of reaction conditions were screened for the oxidation of the TBS-protected alcohol **236** (**Table 5**). The use of an activated DMSO reagent (entries 1—3) was unsuccessful. Chromium oxidation reagents were also investigated with no success (entries 4—6) and the use of a hypervalent iodine reagent returned only starting material (entries 7). As a consequence of the failure to identify suitable conditions for the oxidation of alcohol **236**, it was decided that other protecting group strategies would be investigated.



236 **237**

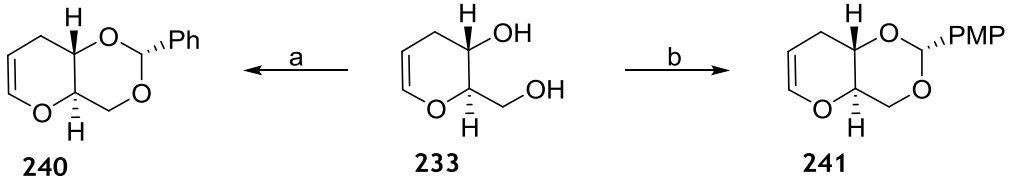
Entry	Reaction conditions	Temperature	Result[a]
1	$COCl_2$, DMSO, CH_2Cl_2	−78 °C	no reaction
2	$COCl_2$, DMSO, CH_2Cl_2	−45 °C	decomposition
3	SO_3·py, Et_3N, DMSO, CH_2Cl_2	0 °C	no reaction
4	PCC, CH_2Cl_2	rt	no reaction
5	PDC, CH_2Cl_2	rt	no reaction
6	PDC, CH_2Cl_2	reflux	no reaction
7	DMP, CH_2Cl_2	0 °C	no reaction
8	TEMPO, $PhI(OAc)_2$, CH_2Cl_2	rt	no reaction

[a]reaction progress followed by NMR.

Table 5

Acetal Protection Strategy

The next protection strategy to be investigated involved protection of diol **233** using either a benzylidene or a *p*-methoxybenzylidene acetal. As with the TBS-protection strategy, the use of a *p*-methoxybenzylidene acetal would allow for the selective deprotection of the primary alcohol if required.[117] Both acetal protecting groups were successfully installed to afford bicyclic enol ethers **240** and **241** (**Scheme 48**).[118]

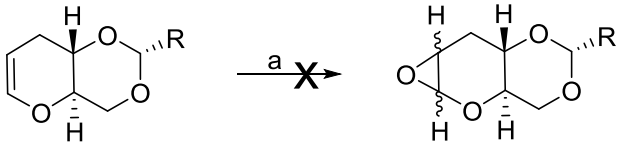


240 **233** **241**

a) benzaldehyde dimethylacetal, CSA (5 mol%), DMF, rt, 54%; b) *p*-anisaldehyde dimethylacetal, PPTS (20 mol%), CH_3CN, 0 °C to rt, 59%.

Scheme 48

Following the synthesis of compounds **240** and **241**, in moderate but acceptable yields, the next step was epoxidation using dimethyl dioxirane. Unfortunately, attempted epoxidation of the bicyclic enol ethers **240** and **241** under these reaction conditions resulted in decomposition of the starting material (**Scheme 49**). It is possible that the observed decomposition reaction might arise from oxidation at the activated benzylic position within the acetal protecting group.



240 R = Ph
241 R = PMP

244 R = Ph
245 R = PMP

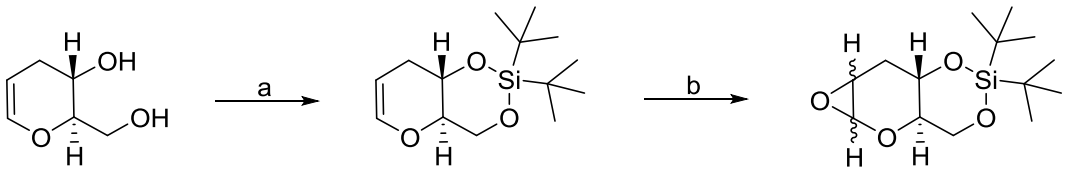
a) DMDO (0.09 M in acetone), CH_2Cl_2, −78 °C.

Scheme 49

Due to the difficulties encountered during the attempted epoxidation of both acetal-protected enol ethers, no further work was undertaken on these compounds.

Di-tert-butylsiloxane Protection Strategy

This strategy explored the suitability of employing the di-*tert*-butylsiloxane group for the protection of diol **233**. Upon reaction with di-*tert*-butylsilyl-bis(trifluoromethanesulfonate), diol **233** was protected as the corresponding bicyclic enol ether **231** in 94% yield (**Scheme 50**). Epoxidation of the enol ether with dimethyl dioxirane afforded a diastereomeric mixture of the epoxides **246** (1.2:1 mixture of diastereomers). It was discovered that in order to avoid epoxide decomposition, the reaction work-up was very important. Once the reaction had reached completion it was necessary to dry the reaction mixture with magnesium sulfate, and then concentrate the solution under reduced pressure at 4 °C. Following this work-up protocol, a diastereomeric mixture of epoxides **246** was obtained in quantitative yield (1.2:1 mixture of diastereomers).



233 **231** **246**

a) *t*-$Bu_2Si(OTf)_2$, pyridine, DMF, −45 °C, 94%; b) DMDO (0.1 M in acetone), CH_2Cl_2, −78 °C, quant, dr 1.2:1.

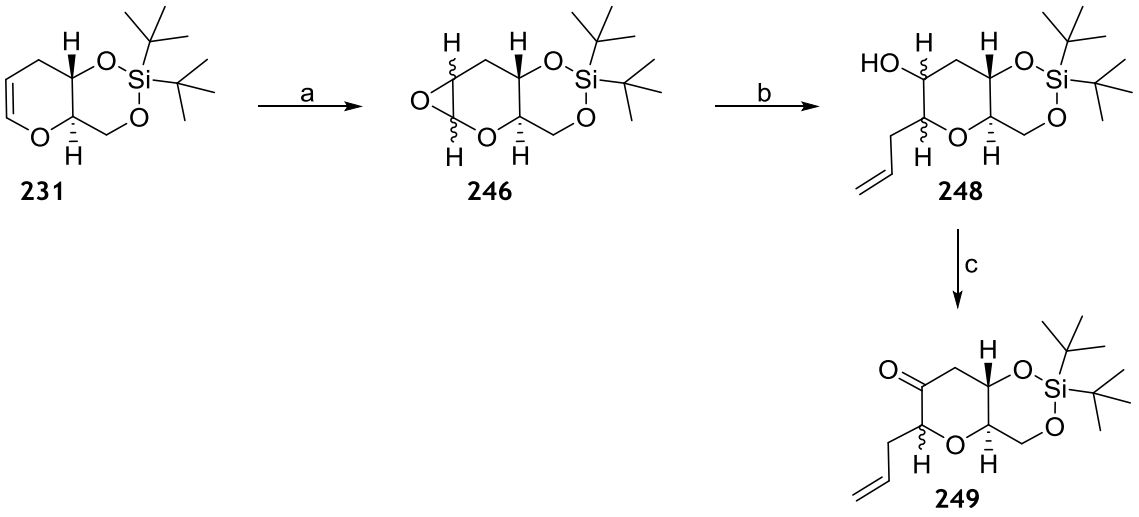
Scheme 50

The epoxides **246** were treated directly with allylmagnesium chloride to provide alcohols **248** as a mixture of diastereomers (**Scheme 51**). Purification of this mixture proved to be very difficult. However, a small amount of the main diastereomer was isolated and subjected to NMR analysis. Through ^{1}H NMR NOE correlations between CH-C2, CH-C5 and CH_2-C7 (**see Appendix A**), the main diastereomer was confirmed to be alcohol **247**. As was the case with alcohol **236**, alcohol **247** displayed the undesired *trans*-stereochemistry across the polycyclic ether (**Figure 17**).

247 **225**

Figure 17

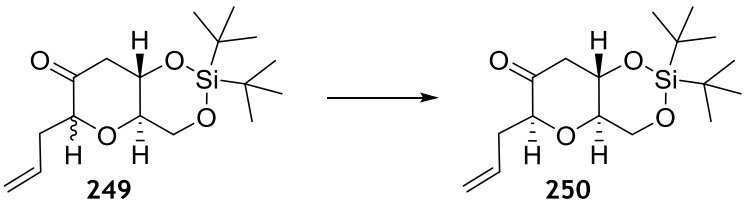
The decision was made to take the mixture on to the next stage rather than optimising the purification of alcohols **248** (**Scheme 51**). Oxidation of the crude mixture of alcohols **248** under Parikh-Doering conditions afforded ketones **249** as a 2.3:1 mixture of diastereomers.[119]



a) DMDO (0.1 M in acetone), CH_2Cl_2, −78 °C; b) CH_2CHCH_2MgCl (1.7 M in Et_2O), THF, 0 °C; c) SO_3·py, Et_3N, CH_2Cl_2:DMSO (1:1), 0 °C, 71% (3 steps), dr 2.3:1.

Scheme 51

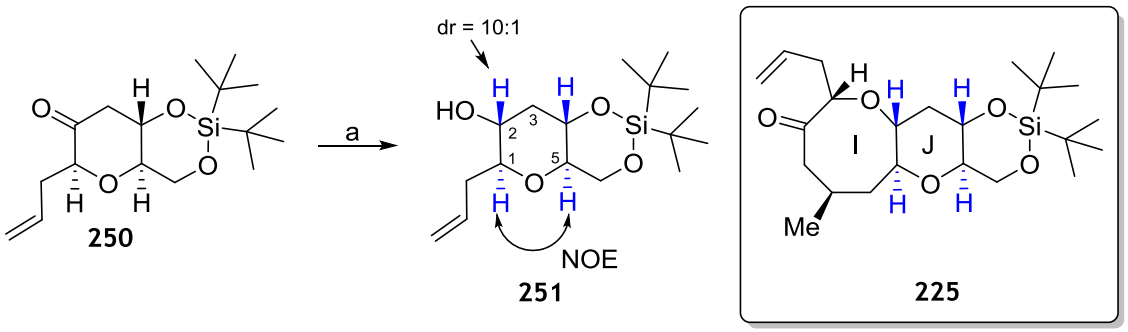
The next step was epimerisation of ketones **249** to give the desired equatorial configuration at the carbon bearing the allyl group. The use of either sodium hydroxide or potassium carbonate resulted in decomposition of the starting material (entries 1 and 2) (**Table 6**). When DBU was employed as the base at room temperature, 0 °C or at reflux, a mixture of recovered starting material and decomposition products was obtained (entries 3—5). It was found that performing the reaction in the dark had a surprising effect on the outcome of the reaction (entry 6). The exact reasons for the detrimental effect of light on the reaction remain unclear. Performing the reaction using DBU at room temperature with the reaction vessel carefully covered to exclude light resulted in a reproducible reaction yield of 60%.



Entry	Reaction conditions	Temperature	Result
1	NaOH, EtOH	rt	decomposition
2	K_2CO_3, MeOH	rt	decomposition
3	DBU, PhMe	rt	35% SM recovered/ decomposition
4	DBU, PhMe	0 °C to rt	43% SM recovered/ decomposition
5	DBU, PhMe	reflux	decomposition
6	DBU, PhMe, **in the dark**	rt	60% yield

Table 6

With the correct stereochemistry installed in ketone **250**, the next step was reduction to the desired alcohol **251** (**Scheme 52**). Pleasingly, treatment with sodium borohydride afforded **251** in high yield with a diastereomeric ratio of 10:1. The stereochemistry of alcohol **251** was confirmed by comparison to the known literature data,[120] along with ^{1}H NMR NOE correlations between CH-C1, CH-C5 and CH_2-$C3_{ax}$ (**see Appendix A**).



a) $NaBH_4$, CH_2Cl_2:MeOH (1:1), −78 °C, 88%.

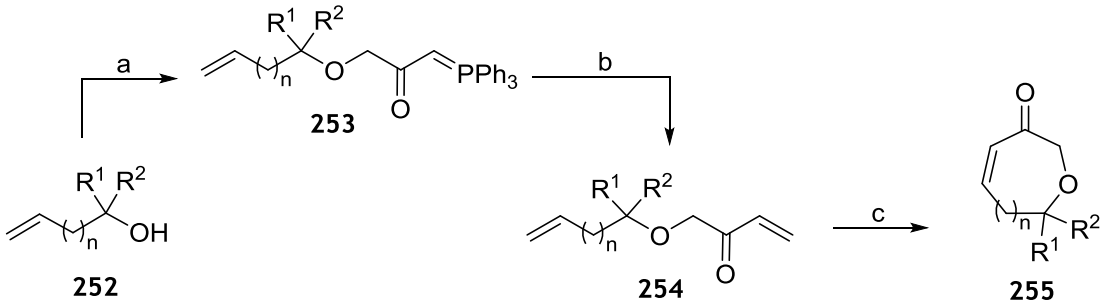
Scheme 52

2.3 Synthesis of Enone 228

With the correct stereochemistry installed around the J-ring, the next challenge was construction of the eight-membered I-ring utilizing an enone/RCM protocol.

2.3.1 Clark's Approach to Cyclic Enones

Cossy and co-workers have developed an efficient route to six-, seven-, and eight-membered 3-oxo oxacycloalkenes **255** from the corresponding α-alkoxy enones **254** (**Scheme 50**).[121] It was ascertained that these enones could be synthesised *via* the corresponding stabilized phosphoranes **253**. Alkylation using sodium hydride with triphenylchloroacetonylphosphorane afforded the required phosphoranes **253** in moderate to high yields. These compounds were then converted into the desired α-alkoxy enones **254** upon condensation with formaldehyde.



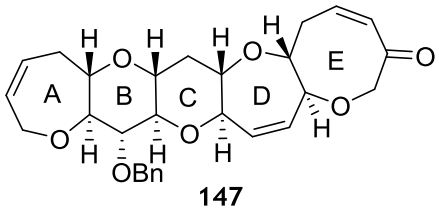
Entry	254	148 (mol%)	Yield of 255
1	n = 0, $R^1 = R^2 = H$	2.5	69%
2	n = 1, $R^1 = R^2 = H$	15	58%
3	n = 2, $R^1 = R^2 = H$	10	66%

a) NaH, $ClCH_2COCHPPh_3$, THF, rt or reflux, 48-94% (n=0—2); b) CH_2O aq., H_2O/Et_2O, rt, 49—73% (n=0—2); c) **148**, CH_2Cl_2, reflux.

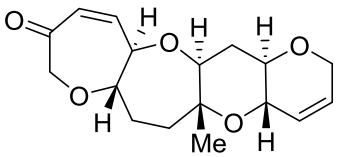
Scheme 53[121]

Treament of α-alkoxy enones **254** with Grubbs second-generation catalyst **148** allowed for the isolation of six-, seven-, and eight-membered cyclic enones **255** in good yield. It is worth noting the success of this protocol in the formation of eight-membered rings which are normally difficult to synthesize.

Clark and co-workers have previously utilized Cossy's approach to cyclic enones in the synthesis of several polycyclic ether targets.[77, 106a] Cossy's methodology was incorporated into the synthetic routes used to prepare the A-E ring system **147** of CTX3C (**4**),[77] and the fused tetracyclic polyether core **256** of hemibrevetoxin B (**9**) (**Figure 18**).[106b]



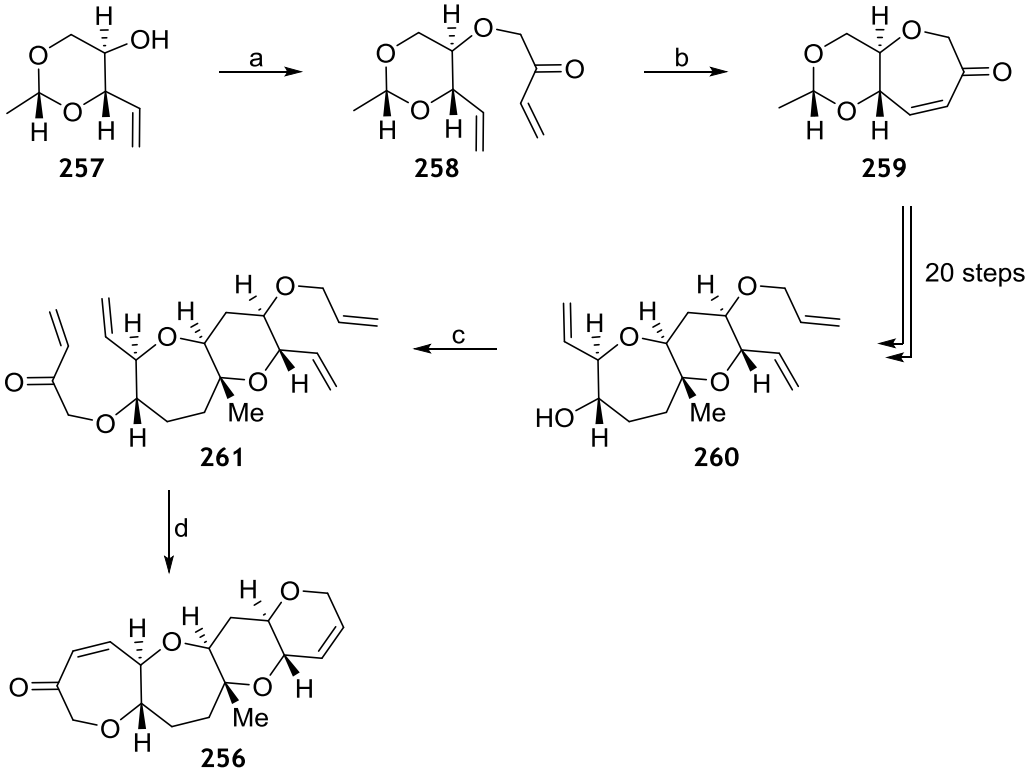
147



256

Figure 18

Both of the seven-membered rings in the tetracyclic polyether core **256** of hemibrevetoxin B (**9**) were constructed using a two-step sequence of enone formation and RCM reaction (**Scheme 54**). The alcohol **257** was alkylated using triphenylchloroacetonylphosphorane and condensation of the resulting phosphorane with formaldehyde then provided enone **258**. Construction of the seven-membered ring was completed upon treatment of **258** with ruthenium catalyst **148**. The second seven-membered ring was constructed by employing the same sequence of enone formation and subsequent RCM reaction to afford tetracycle **256**.[106b]



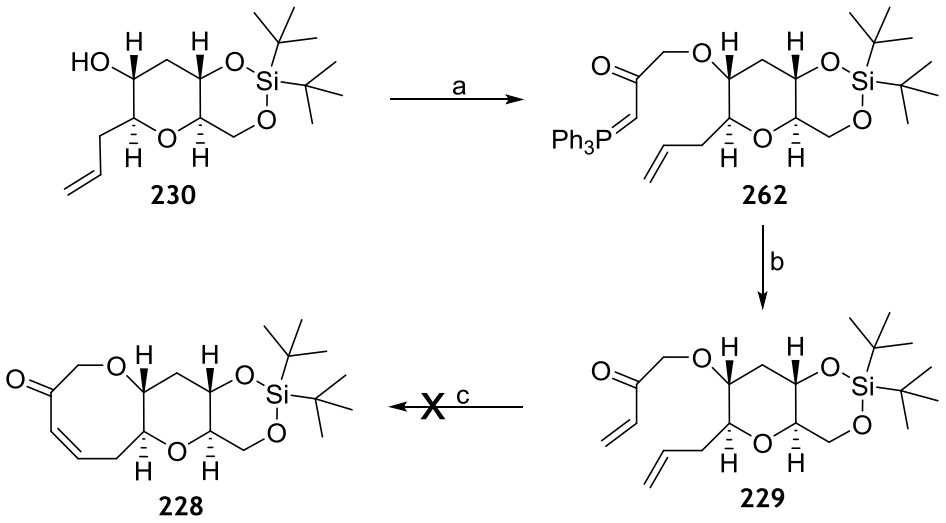
a) 1. NaH, $ClCH_2COCHPPh_3$, TBAI, THF, reflux, 90%; 2. CH_2O aq., Et_2O, pH 7 buffer, rt, 97%; b) **148** (3 mol%), CH_2Cl_2, reflux, 94%; c) 1. NaH, $ClCH_2COCHPPh_3$, DMF, rt; 2. CH_2O aq., Et_2O, pH 7 buffer, rt, 33% (2 steps); d) **148** (10 mol%), CH_2Cl_2, reflux, 73%.

Scheme 54[106b]

It is clear that this methodology provides a powerful tool that can be used to access various polyether systems. This efficient two-stage enone formation and RCM reaction sequence was investigated for the construction of the targeted eight-membered I-ring.

2.3.2 Initial Strategy for the Synthesis Enone 228

Alkyation of alcohol **229** with triphenylchloroacetonylphosphorane afforded the corresponding stabilized phosphorane **262** (**Scheme 55**). Subsequent condensation with formaldehyde yielded enone **229**.



a) NaH, $ClCH_2COCHPPh_3$, TBAI (5 mol%), THF, reflux; b) CH_2O aq., Et_2O, rt, 15—31% (2 steps); c) **148** (10 mol%), CH_2Cl_2, reflux.

Scheme 55

Unfortunately, low yields were observed for the transformation of alcohol **230** into enone **229** (15—31%, two steps). It was believed that the problem lay in the Wittig reaction between phosphorane **262** with aqueous formaldehyde.[122] The RCM reaction was then attempted using the small amount material that was isolated. Treatment of enone **229** with Grubbs' second-generation catalyst **148** resulted in the recovery of starting material without product formation. Attempts to achieve the RCM reaction by varying the metathesis catalyst employed, the catalyst loading or reaction concentration proved ineffective.

It has been reported that polar groups such as ethers, ketones and esters can act to position the reacting sites within the co-ordination sphere of the metal (**A**).[123] It was proposed that this directing behaviour favours ring closure (**B**). However, if complexation confers a high degree of stability, the catalyst can become trapped in the form of an unproductive complex (**C**) (**Figure 19**).

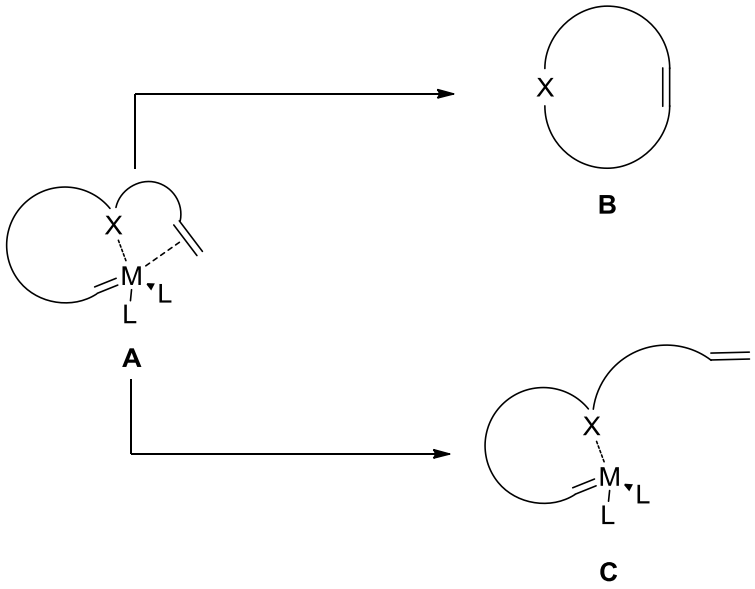
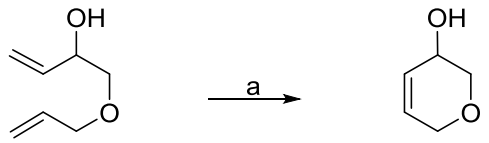


Figure 19

This unproductive complexation between substrate and catalyst may be to blame for the lack of ring closure observed upon treatment of enone **229** with the Grubbs second-generation catalyst **148**. The utilization of a Lewis acid additive, such as Ti(O*i*-Pr)$_4$, to overcome unwanted complexation between the polar group and metal centre is well documented in the literature.[124] However, previous studies within the group have found that the optimisation of reaction conditions with these additives can prove challenging.[125] For this reason, alternative reaction conditions were investigated.

The effect of allylic substituents in RCM reactions has been well studied.[126] It was widely believed that an allylic alcohol adversely effects metathesis reactions that involve the adjacent double bond.[127] However, recent reports suggest that this functionality is not only tolerated, but may even assist the metathesis reaction (**Scheme 56**).[128]

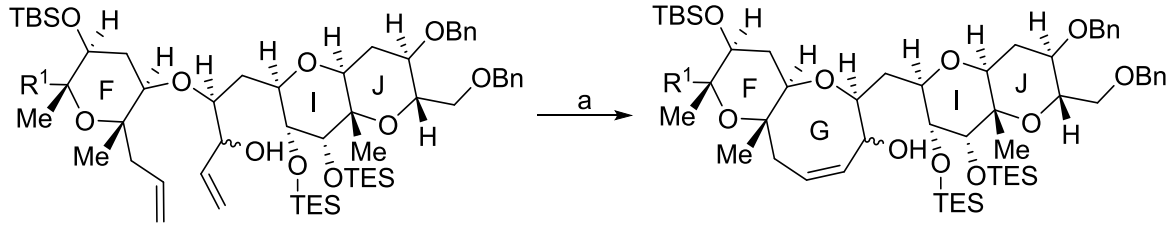


263 **264**

a) **148** (2.5 mol%), CH_2Cl_2, rt, 87%.

Scheme 56[128c]

Construction of eight-membered rings by RCM in substrates containing an unprotected allylic alcohol has been achieved in the synthesis of several polyether fragments.[49, 129] Oishi and co-workers demonstrated the viability of such ring construction in the synthesis of the F-J ring system **266** of yessotoxin.[129] In this case, treatment of diene **265** with ruthenium catalyst **148** afforded alcohol **266** in 68% yield (**Scheme 57**).

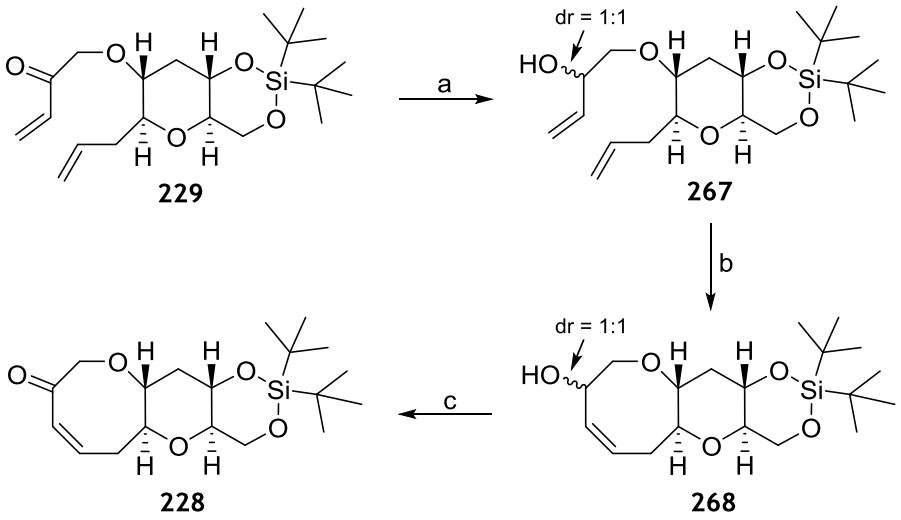


265 **266**

a) **148** (8 mol%), PhMe, reflux, 68%.

Scheme 57[129]

Based on these reports, it was decided to reduce enone **229** to the corresponding diastereomeric alcohols **267** before attempting the RCM reaction. Luche reduction of enone **229** afforded alcohols **267** (1:1 mixture of diastereomers) (**Scheme 58**). To prevent the unwanted isomeration of allylic alcohols to the corresponding ketones, the use of the more reactive metathesis catalysts, such as **150**, was required.[130] Pleasingly, treatment of **267** using Hoveyda-Grubbs second generation catalyst **150** effected ring closure to provide alcohols **268**. It was observed that the concentration of the RCM reaction had a significant effect on the reaction yield: increasing the dilution by a factor of 10 almost doubled the yield obtained for the reaction. The hydroxyl group was oxidised upon treatment with Dess-Martin periodinane, to afford the target enone **228** in 82% yield.



229 267 268 228

a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 80%, dr 1:1; b) **150** (5 mol%), CH_2Cl_2, reflux, 0.01 M, 37% or 0.001 M, 68%, dr 1:1; c) DMP, CH_2Cl_2, 0 °C, 82%.

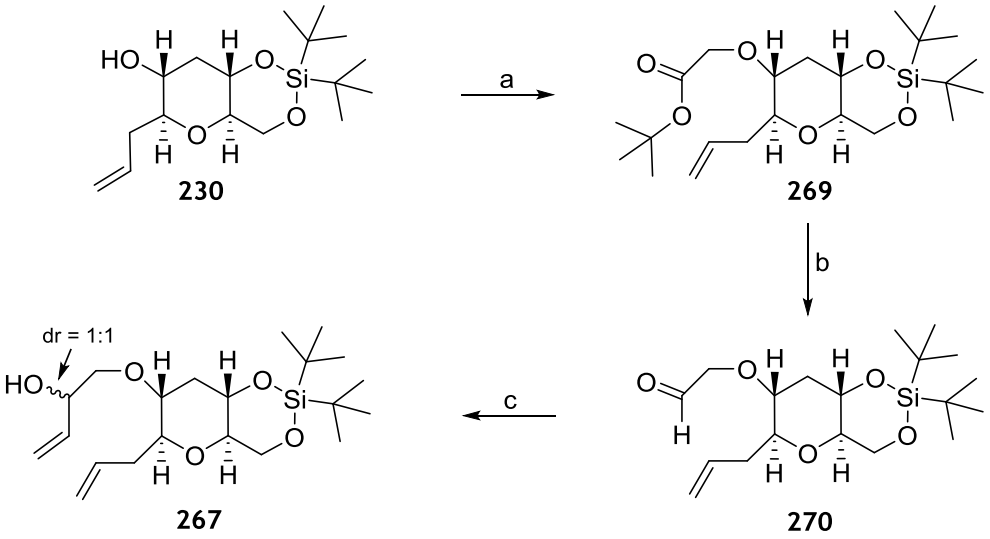
Scheme 58

Subjection of enone **229** to the three-step Luche reduction, RCM and oxidation sequence delivered the target tricyclic enone **228** in good yield. However, the poor yield obtained for the formation of enone **229**, the precursor required for this sequence, meant this approach was not a viable synthetic option. For this reason, other strategies were investigated.

2.3.3 Alternative Strategies for the Synthesis of Enone 228

tert-Butyl Ester Strategy

The first alternative strategy focussed on the formation of alcohols **267** from the corresponding *tert*-butyl ester **269** (**Scheme 59**). Treatment of alcohol **230** with *tert*-butyl bromoacetate afforded ester **269**, which was then converted into aldehyde **270** upon DIBAL reduction. Direct treatment of aldehyde **270** with vinylmagnesium bromide afforded the required alcohols **267**. Although this reaction sequence was effective on a small scale, it proved to be more challenging when performed on a large scale due to the unreliable nature of the esterification reaction.



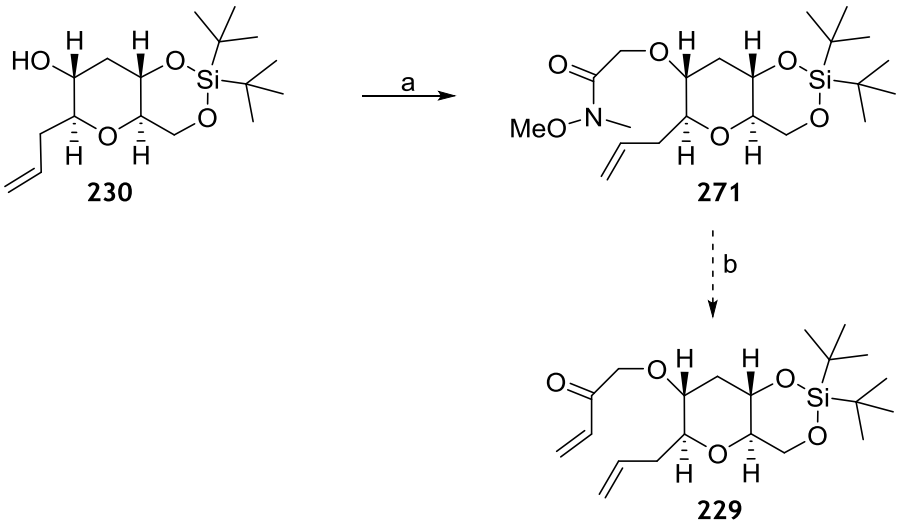
a) *tert*-butyl bromoacetate, 30% aq. NaOH, TBAI (50 mol%), PhMe, rt, 11—82%; b) DIBAL (1 M in CH_2Cl_2), CH_2Cl_2, −78 °C; c) $CH_2CHMgBr$ (1 M in THF), THF, 0 °C, 87% (2 steps), dr 1:1.

Scheme 59

The synthesis of desired enone **228** from the alcohols **267** can be achieved through a simple two-step sequence involving RCM reaction and subsequent oxidation, as had been demonstrated in the initial strategy (see **Scheme 58**).

Weinreb Amide Approach

Another approach toward the synthesis of enone **228** was *via* the weinreb amide **271** (**Scheme 60**). Treatment of alcohol **230** with 2-bromo-*N*-methoxy-*N*-methylacetamide afforded **271**. Unfortunately, the synthesis of amide **271** proved to be problematic with a significant proportion of starting material being recovered from the reaction.



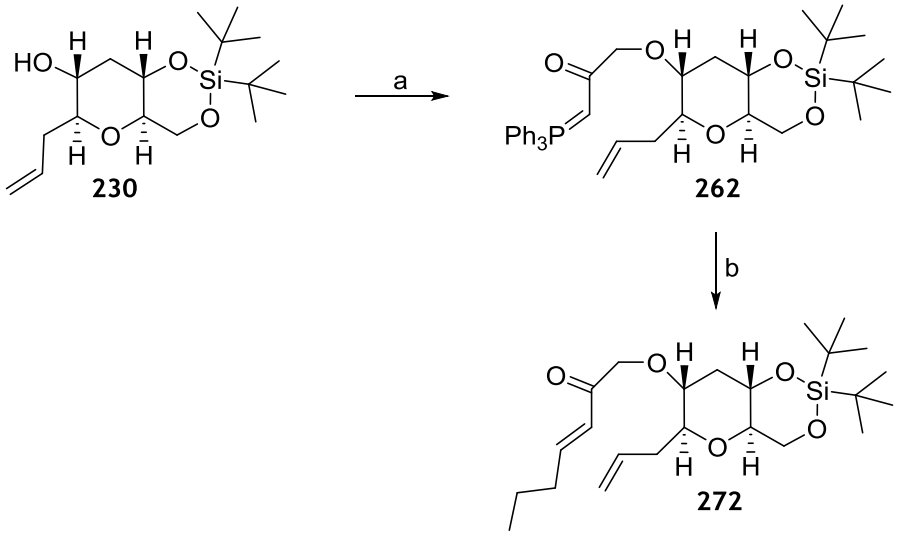
a) KHMDS (0.5 M in THF), 2-bromo-*N*-methoxy-*N*-methylacetamide, THF, −78 °C, 32% (66% brsm); b) $CH_2CHMgBr$, THF, 0 °C.

Scheme 60

Modification of the Initial Wittig Strategy

As a consequence of the challenges encountered in both alternative strategies, it was decided to investigate the possibility of improving the initial Wittig sequence. It was believed that the problems with the initial strategy were encountered during the Wittig reaction of formaldehyde with the stabilized phosphorane **262** (see **Scheme 55**). The problems with the Wittig reaction were attributed to the aqueous conditions that resulted from the use of a 48% aqueous solution of formaldehyde. A selection of alternative aldehydes were considered.

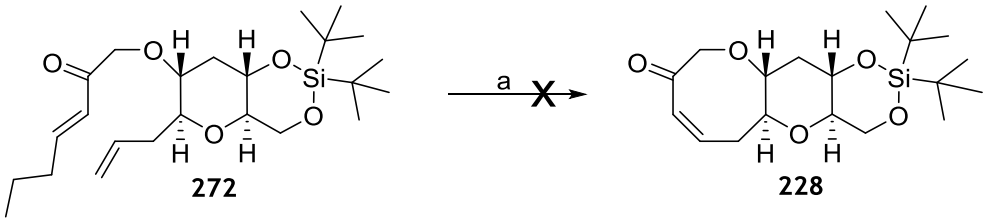
Butyraldehyde was deemed to be a suitable alternative, with literature reports suggesting that the presence of a small alkyl chain should not interfere with the subsequent RCM reaction.[131] Alcohol **230** was alkylated by sequential deprotonation using sodium hydride and treatment of the alkoxide with triphenylchloroacetonylphosphorane to afford phosphorane **262** (**Scheme 61**). Pleasingly, Wittig reaction between butyraldehyde and the stabilized phosphorane **262** afforded enone **272** in 86% yield over the two steps. This synthetic sequence provided reliable reaction yields.



a) NaH, $ClCH_2COCHPPh_3$, TBAI (5 mol%), THF, reflux; b) butyraldehyde, CH_2Cl_2, reflux, 86% (2 steps).

Scheme 61

Following the synthesis of **272**, the next step was ring closure to form tricyclic enone **228**. It was hoped that direct treatment of **272** with the Grubbs second-generation catalyst **148** would afford the target enone **228**. However, as with enone **229**, ring closure was not observed (**Scheme 62**). This result was not entirely unexpected due to the structural similarities between enones **229** and **272**.

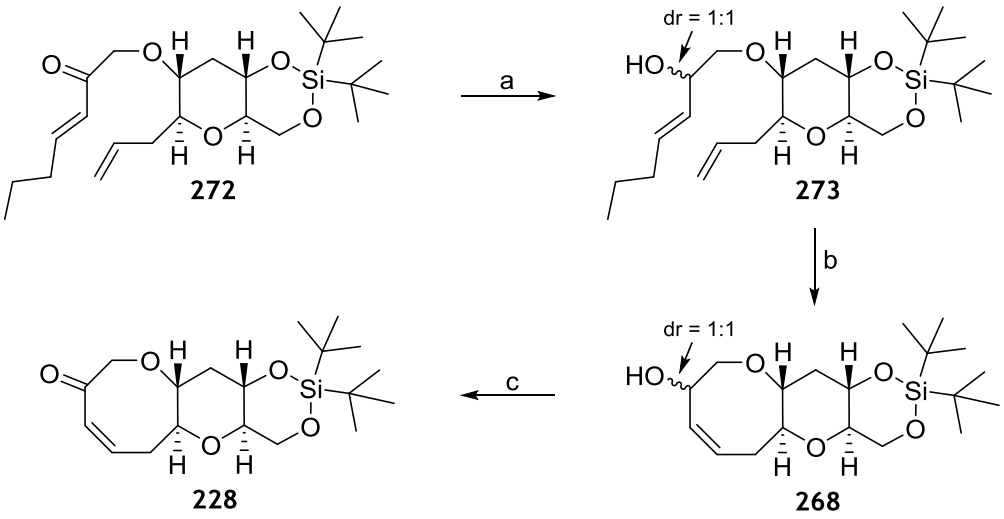


a) **148** (10 mol%), CH_2Cl_2, reflux.

Scheme 62

The problem was circumvented by the use of a three-step reduction, RCM and oxidation sequence (**Scheme 63**). Luche reduction of enone **272** afforded alcohols **273** (1:1 mixture of diastereomers). Treatment of **273** with the Hoveyda-Grubbs second generation catalyst **150** effected ring closure to afford alcohols **268** in excellent yield. Pleasingly, the substitution of butyraldehyde for formaldehyde did not have an adverse effect upon the outcome of the RCM

reaction. Finally, oxidation with Dess-Martin periodinane afforded target enone **228** in good yield.



a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, −78 °C, 93%, dr 1:1; b) **150** (5 mol%), CH_2Cl_2, 0.001 M, 96%, dr 1:1; c) DMP, CH_2Cl_2, 0 °C, 78%.

Scheme 63

2.4 Functionalization of Enone 228

Completion of the IJ-model system **225** required functionalization of the eight-membered I-ring. This functionalization entailed the stereoselective incorporation of an allyl side chain followed by 1,4-conjugate addition (**Figure 20**).

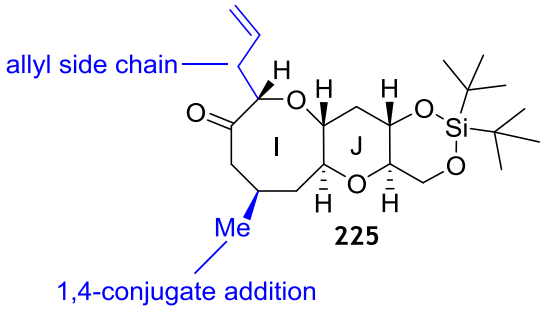
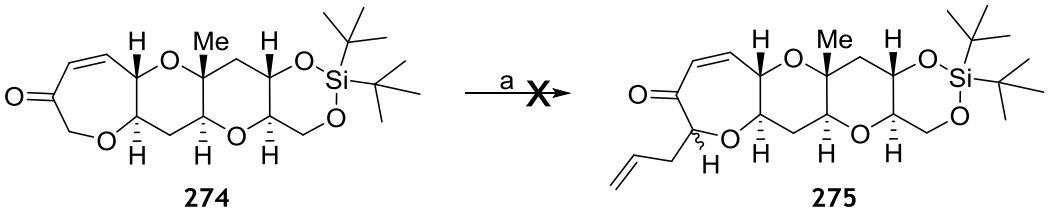


Figure 20

Direct alkylation of enones is notoriously difficult to perform under standard conditions, but has been reported by Cossy and co-workers.[121] Previous work performed in the group towards the use of these reaction conditions for the allylation of enone **274** has proved unsuccessful (**Scheme 64**).[116]

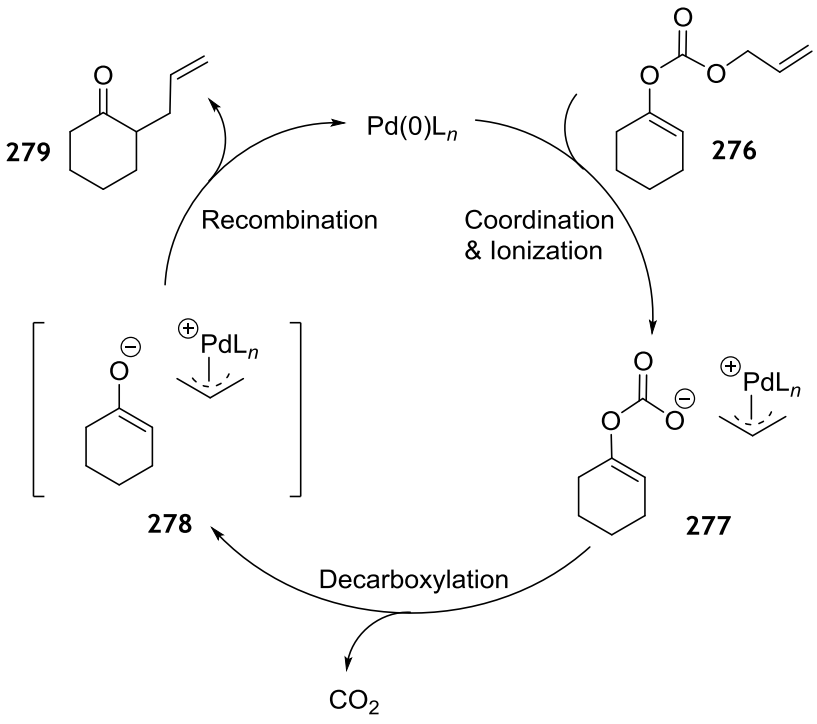


274 **275**

a) LDA, CH_2CHCH_2Br, HMPA, THF, −78 °C.

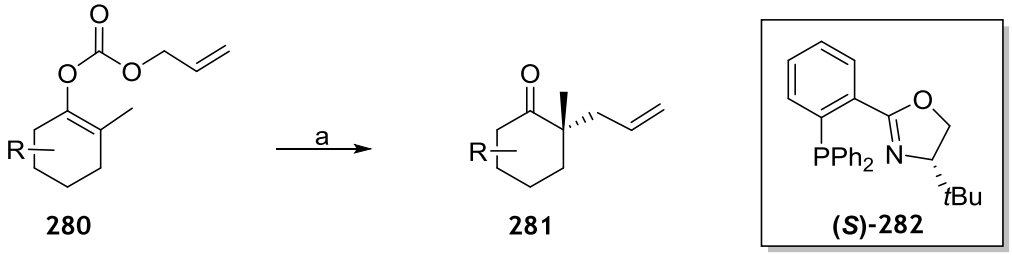
Scheme 64[116]

Tsuji and co-workers have reported the α-allylation of ketones and aldehydes *via* a decarboxylative palladium-catalyzed rearrangement.[132] The proposed mechanism for this palladium-catalyzed rearrangement reaction is shown below (**Scheme 65**). Treatment of allyl enol carbonate **276** with a Pd^0 source furnishes the corresponding π-allyl palladium complex **277**. Decarboxylation of **277** affords intermediate **278**. Alkylated product **279** is delivered upon attack of the electrophilic π-allyl complex by the nucleophilic enolate.[133]



Scheme 65[133]

Stoltz and co-workers reported the first catalytic enantioselective Tsuji allylation from allyl enol carbonate substrates.[134] A screen of chiral ligands revealed that the phosphinooxazoline ligand (*S*)-*t*Bu-PHOX **(*S*)-282**, a chelating P/N ligand, was especially effective in terms of both yield and enantioselectivity (**Scheme 66**).[135] The mild and operationally straightforward reaction conditions allowed for the formation of quaternary stereocentres at the α-position in excellent yield with high enantiopurity. It is worth noting that the reaction displayed good tolerance to a variety of substituents and functional groups, as well as differing ring sizes.



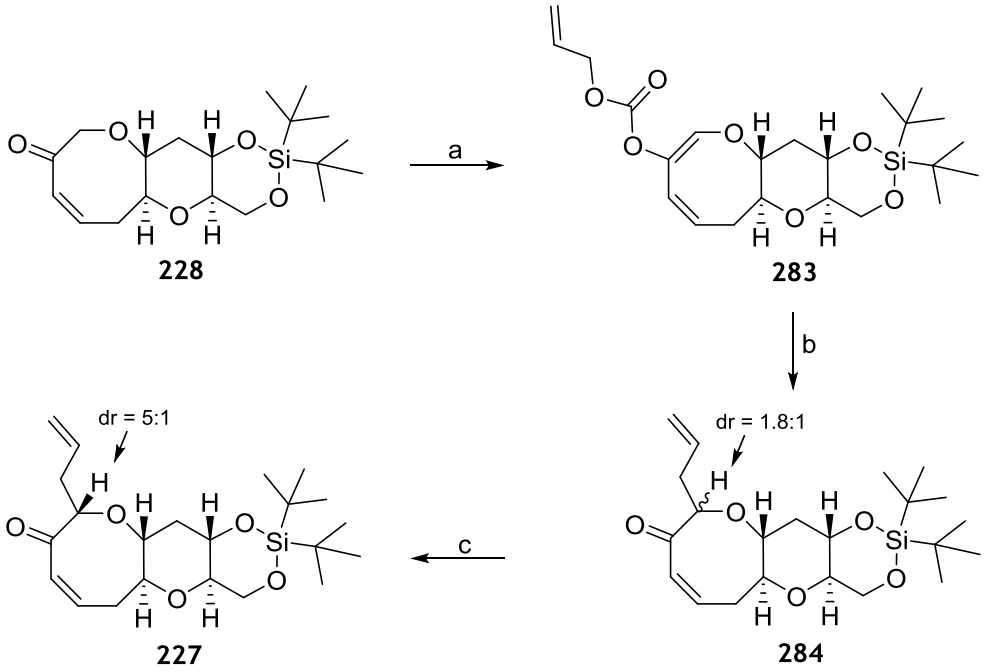
280 **281** **(*S*)-282**

85-96% (82-92% *ee*)

a) $Pd_2(dba)_3$ (2.5 mol%), (*S*)-*t*Bu-PHOX **(*S*)-282** (12.5 mol%), THF, rt.

Scheme 66[135]

Based on these results, enone **228** was converted to the corresponding allyl enol carbonate **283** (**Scheme 67**). It was known that Barbier-type conditions, in which enone **228** and allylchloroformate were cooled to −78 °C before addition of the base, were optimal for this reaction.[116] When these conditions were employed, the carbonate **283** was obtained in 89% yield. The next step was the palladium-catalyzed rearrangement of **283**. Initially, the reaction was performed using conditions previously optimised within the group.[136] When a chiral ligand was not employed and $Pd(PPh_3)_4$ was selected as the Pd^0 source, the alkylated enone **284** was isolated in 75% yield with a diastereomeric ratio of 1.8:1 in favour of the required diastereomer. Epimerisation of alkylated enone **284** with DBU improved the diastereomeric ratio from 1.8:1 to 5:1 in favour of the *cis*-diastereomer **227**.

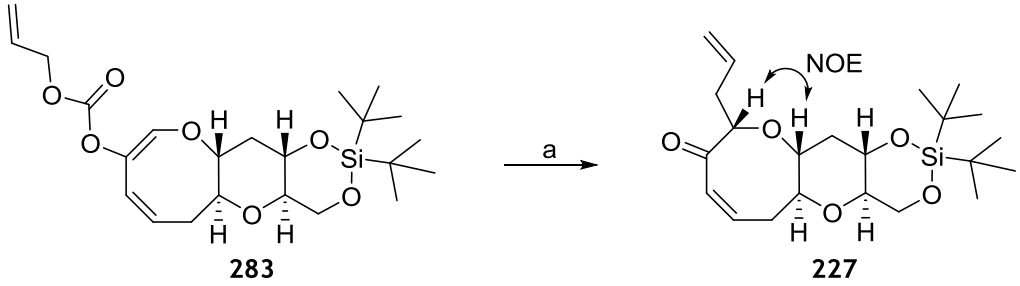


228 **283** **284** **227**

a) allylchloroformate, NaHMDS (2 M in THF), THF, −78 °C, 89%; b) $Pd(PPh_3)_4$ (10 mol%), THF, rt, 75%, dr 1.8:1; c) DBU, PhMe, rt, 73%, dr 5:1.

Scheme 67

The use of the phosphinooxazoline (*S*)-*t*Bu-PHOX ligand **(*S*)-282** in the rearrangement was then investigated. Treatment of allyl enol carbonate **283** with $Pd(PPh_3)_4$ and (S)-*t*Bu-PHOX ligand **(*S*)-282** afforded alkylated enone **227** in 85% yield with a diastereomeric ratio of >20:1 in favour of the desired *cis*-diastereomer (**Scheme 68**). The absolute configuration at the newly created stereocentre was confirmed through ^{1}H NMR NOE analysis (**see Appendix A**).

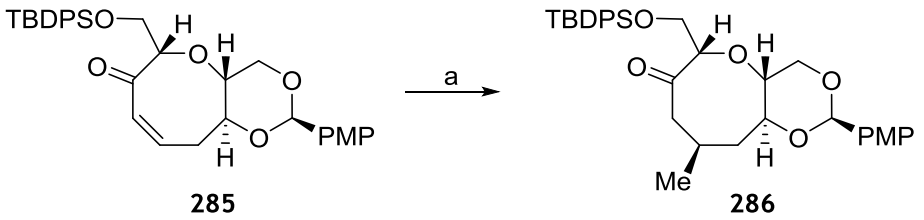


283 **227**

a) $Pd(PPh_3)_4$ (10 mol%), (*S*)-*t*Bu-PHOX **(*S*)-282** (25 mol%), THF, rt, 85%, dr >20:1.

Scheme 68

The successful preparation of the alkylated enone **227** meant that installation of the methyl group by 1,4-conjugate addition could be explored. Previous reports regarding similar polycyclic ether fragments had shown that the stereoselective introduction of a methyl group is possible (**Scheme 69**).[54] Reaction of enone **285** with $Me_2Cu(CN)Li_2$ afforded the desired product **286** as a single isomer in good yield.

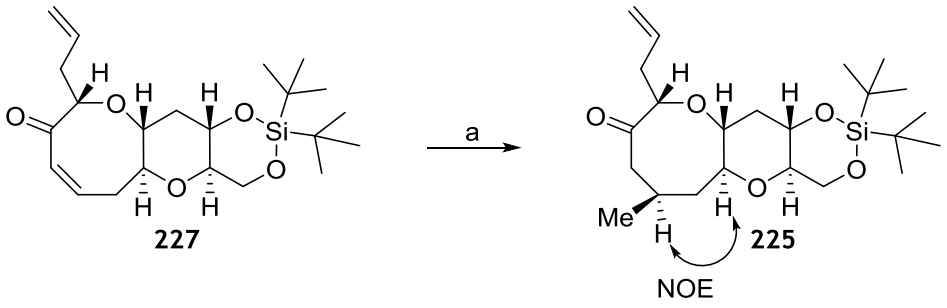


285 **286**

a) $Me_2Cu(CN)Li_2$, Et_2O, −78 °C, 74%.

Scheme 69[54]

The same reaction conditions were employed for the stereoselective installation of the methyl group to alkylated enone **227** (**Scheme 70**). Treatment of **227** with $Me_2Cu(CN)Li_2$ effected 1,4-conjugate addition to afford the targeted methylated product **225** in 89% yield. The stereochemistry of the methyl-bearing stereogenic centre was confirmed through ^1H NMR NOE analysis (**see Appendix A**).



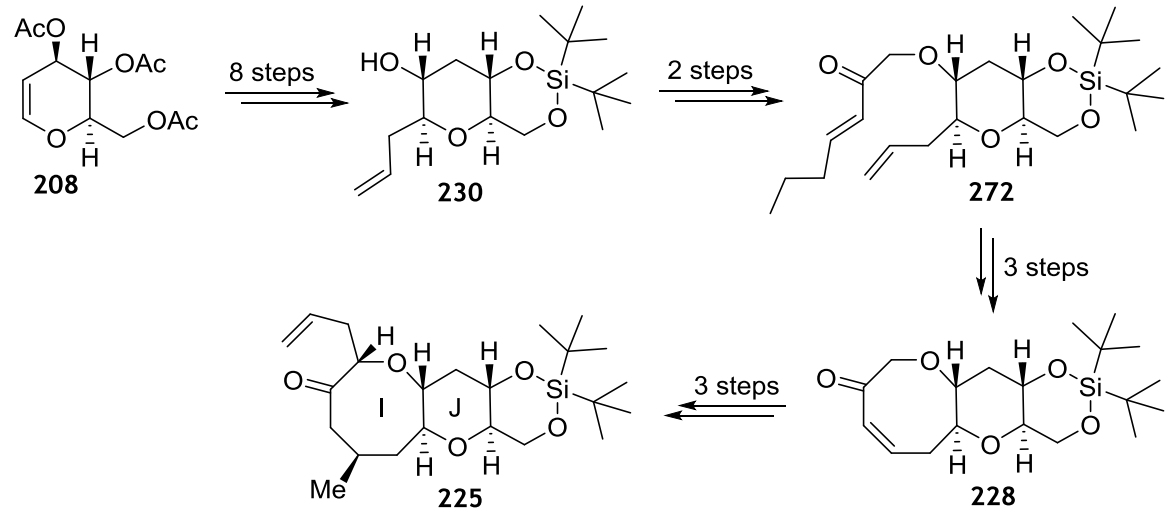
227 **225**

a) $Me_2Cu(CN)Li_2$, Et_2O, −78 °C, 89%, dr >20:1.

Scheme 70

2.5 Summary

Alcohol **230** was synthesised from the commercially available tri-*O*-acetyl-D-glucal **208** in eight steps (**Scheme 71**). The di-*tert*-butylsiloxane group was identified as the optimal protecting group for this synthetic sequence. By employing an improved version of the initial Wittig strategy, enone **272** was obtained from alcohol **230** in two steps. Although the RCM reaction of enone **272** proved to be unsuccessful, RCM of the alcohols **273** provided a suitable route to the tricyclic enone **228**. Pleasingly, it was found that enone **228** could be transformed into the desired IJ-model system **225**. Side-chain introduction was accomplished by Tsuji allylation and the secondary methyl group installed stereoselectively upon treatment of the resulting enone with $Me_2Cu(CN)Li_2$. Overall, the synthesis of the IJ-model system **225** was completed in sixteen steps from tri-*O*-acetyl-D-glucal **208**. The synthesis of the IJ-model system **225** allowed the transformations required for the successful construction and functionalisation of the eight-membered I-ring to be tested.



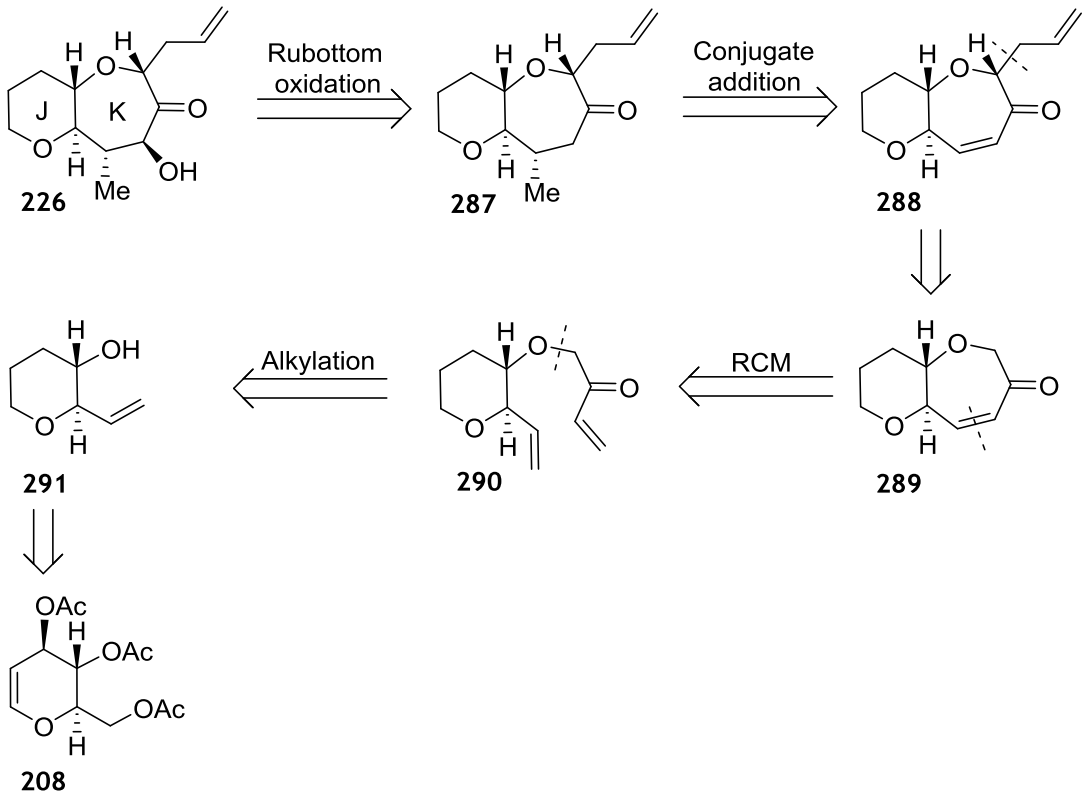
Scheme 71

3.0 Synthesis of the JK-model 226

A second model system was designed in order to investigate the chemistry required for the construction and functionalization of the seven-membered K-ring.

3.1 Retrosynthesis of the JK-model 226

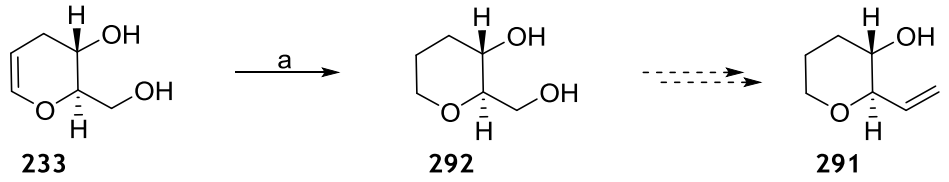
The retrosynthetic analysis of the JK-model **226** is shown below (**Scheme 72**). Disconnection of the hydroxyl group leads to ketone **287** and implies that the hydroxyketone functionality will be introduced by Rubottom oxidation in the forward synthesis. Subsequent retro 1,4-conjugate addition affords bicyclic enone **288**. Removal of the allyl side chain and subsequent alkene disconnection provides diene **290** and implies an RCM reaction in the forward direction. Disconnection of the ether linkage affords the secondary alcohol **291**. Alcohol **291** can be readily prepared in several synthetic steps tri-*O*-acetyl-D-glucal **208**.



Scheme 72

3.2 Synthesis of Alcohol 291

As before (see **Ch 2. § 2.2**), diol **233** was prepared from tri-*O*-acetyl-D-glucal **208** (see **Scheme 44**). Ferrier rearrangement followed by treatment with lithium aluminium hydride afforded diol **233** in good yield over the two steps. The next step was hydrogenation of the double bond to remove the labile enol ether. Treatment with a sub-stiochiometric amount of palladium on carbon under an atmosphere of hydrogen afforded diol **292** in excellent yield. Following the successful hydrogenation reaction, introduction of the required vinyl group was required. From diol **292**, oxidation of the primary alcohol followed by Wittig methylenation with methyltriphenylphosphonium bromide was expected to afford alcohol **291** (**Scheme 73**).

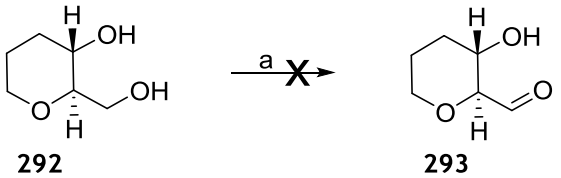


233 **292** **291**

a) 10% Pd/C (5 mol%), EtOAc, H_2 (1 atm), rt, 94%.

Scheme 73

The chemoselective oxidation of a primary alcohol in the presence of a secondary one was investigated.[137] A *N*-oxoammonium salt based oxidation using a catalytic amount of (2,2,6,6-tetramethyl-1-piperidinyl)oxy (TEMPO) in conjunction with *N*-chlorosuccinimide (NCS) as the stoichiometric oxidant was reported to display the required degree of chemoselectivity. Unfortunately, when diol **292** was subjected to these reaction conditions, selective oxidation was not observed (**Scheme 74**).

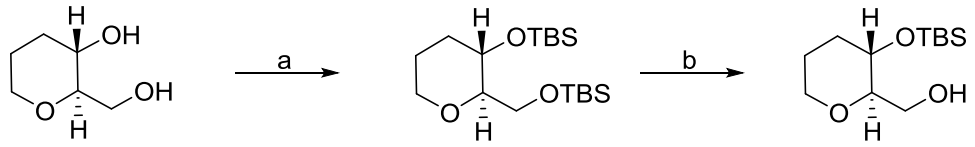


292 **293**

a) TEMPO, TBACl, NCS, CH_2Cl_2:$NaHCO_3$ aq.:K_2CO_3 aq. (2:1:1).

Scheme 74

The unsuccessful chemoselective oxidation of diol **292** meant that an alternative protection/deprotection strategy was necessary. The TBS-protection of diol **292** proceeded smoothly to afford the corresponding cyclic ether **294** in excellent yield. Selective deprotection of the primary alcohol to afford **295** was achieved upon treatment of **294** with camphorsulfonic acid (**Scheme 75**).

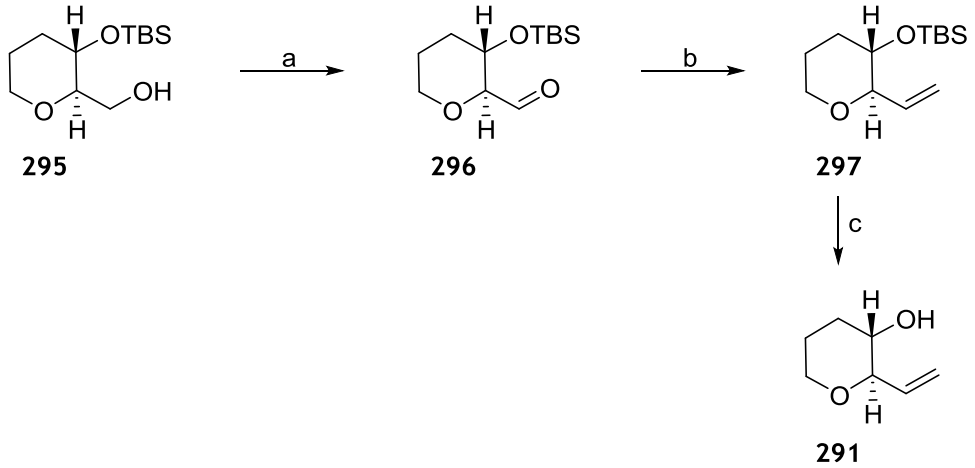


292 **294** **295**

a) TBSCl, DMAP (20 mol%), imidazole, DMF, 0 °C, 93%; b) CSA (30 mol%), CH_2Cl_2:MeOH (1:1), 0 °C, 89%.

Scheme 75

Following preparation of alcohol **295**, the vinyl group could be introduced. A two-step sequence of oxidation, followed by Wittig methylenation was selected for this functional group modification (**Scheme 76**). Oxidation was performed under Parikh-Doering conditions to afford aldehyde **296**. Subsequent Wittig reaction with methyltriphenylphosphonium bromide furnished alkene **297** in good yield over the two steps. Complete silyl ether cleavage upon treatment with camphorsulfonic acid then afforded the corresponding alcohol **291**.



295 **296** **297** **291**

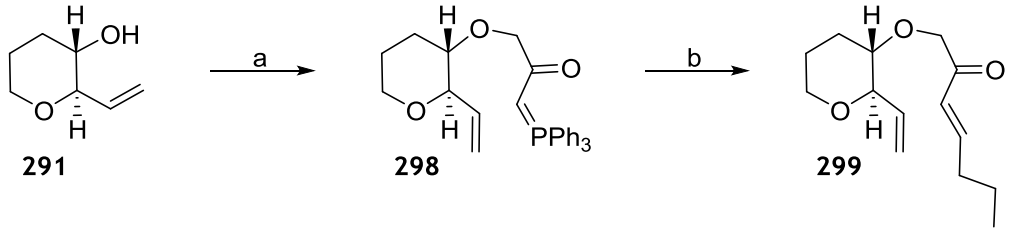
a) SO_3·py, Et_3N, DMSO, CH_2Cl_2, 0 °C; b) NaHMDS (2 M in THF), Ph_3PCH_3Br, THF, 0 °C, 76% (2 steps); c) CSA, CH_2Cl_2:MeOH (1:1), 0 °C, 96%.

Scheme 76

Following the successful introduction of the vinyl group to afford alcohol **291**, the next challenge was the construction the seven-membered K-ring utilizing the previously described enone/RCM protocol (see **Ch 2. § 2.3.3**).

3.3 Synthesis of Enone 289

The first step in the enone/RCM strategy was the introduction of the ether side chain. Following the optimisation work undertaken during the synthesis of the IJ-model system **225**, it had been found that Wittig reaction of a stabilized phosphorane with butyraldehyde allowed for the successful incorporation of the ether side chain (see **Scheme 63**). These conditions for the introduction of the required ether side chain were utilized in the synthesis of enone **299** (**Scheme 77**). Alcohol **291** was alkylated upon treatment with sodium hydride and triphenylchloroacetonylphosphorane to afford the stabilized phosphorane **298**. Pleasingly, as noted in the IJ-model system **225**, the Wittig reaction between butyraldehyde and phosphorane **298** furnished the desired enone **299** in 70% yield over the two steps.

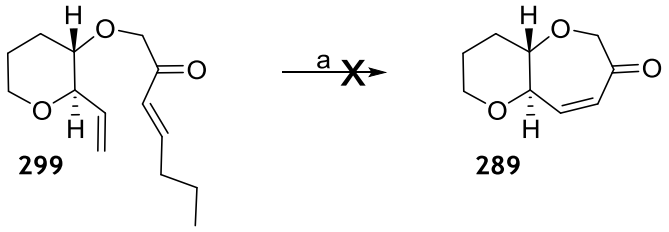


291 **298** **299**

a) NaH, $ClCH_2COCHPPh_3$, TBAI (5 mol%), THF, rt; b) butyraldehyde, CH_2Cl_2, reflux, 70% (2 steps).

Scheme 77

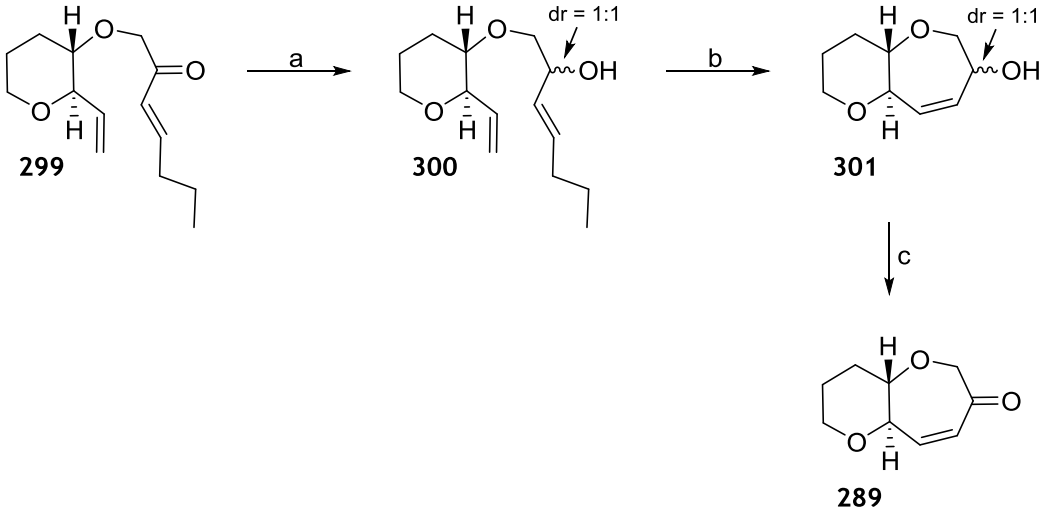
Following isolation of the enone **299**, the next step was ring closure to form the targeted seven-membered ring. Initial investigations into ring closure focussed on the use of the Grubbs second-generation catalyst **148**. Unfortunately, treatment of enone **299** with ruthenium catalyst **148** resulted in no reaction (**Scheme 78**). As observed for the IJ-model system **225**, the enone moiety appeared to render the ruthenium catalyst **148** unreactive.



a) **148** (10 mol%), CH_2Cl_2, reflux.

Scheme 78

The synthesis of the IJ-model system **225** utilized a three-step reduction, RCM and oxidation sequence to afford the desired bicyclic enone **228** (see **Scheme 63**). The same sequence was employed for the synthesis of bicyclic enone **289** (**Scheme 79**). Reduction of enone **299** under Luche conditions afforded alcohols **300** in good yield (1:1 mixture of diastereomers). Treatment of alcohols **300** with Hoveyda-Grubbs second-generation catalyst **150** initiated ring closure to provide alcohols **301** in 81% yield. Alcohols **301** were isolated as a separable mixture (1:1) of diastereomers. It was noted in this case, that more concentrated reaction conditions provided the best yields for the construction of the seven-membered ring. Following successful ring construction, oxidation of alcohols **301** with Dess-Martin periodinane furnished the bicyclic enone **289** in good yield.



a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 99%, dr 1:1; b) **150** (7.5 mol%), CH_2Cl_2, reflux, 0.01 M, 81%, dr 1:1; c) DMP, CH_2Cl_2, 0 °C, 64%.

Scheme 79

Pleasingly, the use of the modified methodology developed during the synthesis of the IJ-model system **225** allowed the target bicyclic enone **289** to be synthesised. The next step was to investigate the installation of the required functionality for the completion of the target bicyclic ketone **226**.

3.4 Functionalization of Enone 289

Completion of the JK-model system **226** required functionalization of the seven-membered ring in enone **289**. This functionalization entailed the incorporation of an allyl side chain followed by 1,4-conjugate addition and Rubottom oxidation to install the K-ring methyl and hydroxyl substituents (**Figure 21**).[138]

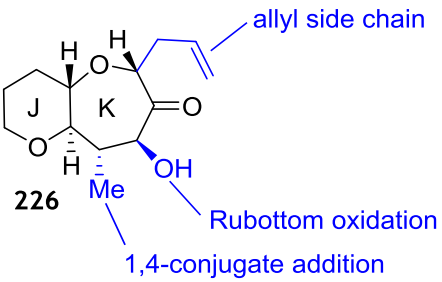
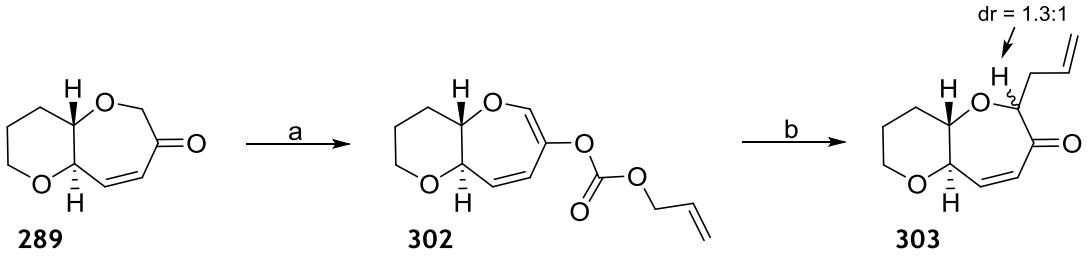


Figure 21

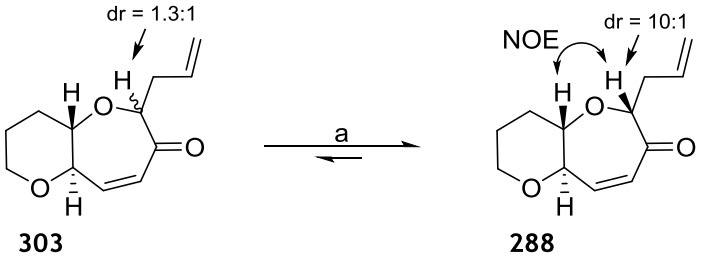
As discussed previously (see **Ch 2. § 2.4**), the direct alkylation of systems similar to enone **289** is extremely difficult to perform under standard conditions. For this reason, the allyl side chain was introduced to the eight-membered ring of the IJ-model system **225** using the palladium-catalyzed Tsuji rearrangement of enol carbonate **283** (see **Scheme 68**). It was proposed that the required allyl side chain could be introduced to the seven-membered ring of the JK-model system **226** in a similar manner (**Scheme 80**). Treatment of bicyclic enone **289** with allylchloroformate and NaHMDS afforded the corresponding enol carbonate **302** in 76% yield. Upon isolation, the enol carbonate **302** was found to be unstable. After a quick purification, the enol carbonate **302** was used directly in the palladium-catalyzed rearrangement reaction. Initial attempts were made to perform the rearrangement reaction using $Ph(PPh_3)_4$ as the Pd^0 source in the absence of any chiral ligand. These conditions afforded a diastereomeric mixture (1.3:1) of alkylated enones **303** favouring the desired diastereomer.



a) allylchloroformate, NaHMDS (1 M in THF), THF, −78 °C, 76%; b) $Pd(PPh_3)_4$ (10 mol%), THF, rt, 64%, dr 1.3:1.

Scheme 80

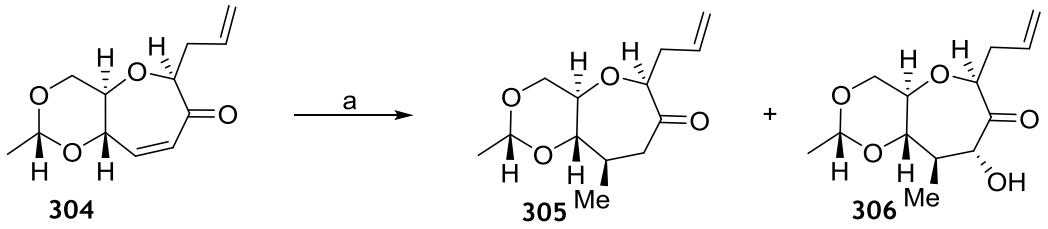
Epimerisation of the diastereomeric mixture of alkylated enones **303** with DBU improved the diastereomeric ratio from 1.3:1 to 10:1 (**Scheme 81**). Epimerised product **288** was confirmed to be the desired *cis*-diastereomer by ^{1}H NMR NOE analysis (**see Appendix A**).



a) DBU, PhMe, 77%, dr 10:1.

Scheme 81

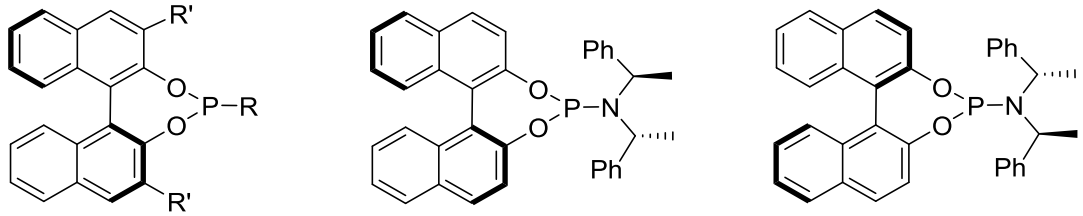
Following the isolation of alkylated enone **288**, the next step to functionalize the seven-membered K-ring was the stereoselective introduction of the required methyl group. In previous studies within the group, copper-catalysed conjugate addition of dimethylzinc had been used to install a methyl group in a similar cyclic ether system (**Scheme 82**).[125] In this case, the chiral phosphoramidite ligand (S_a,*R*,*R*)-**307** had been employed to control the stereochemical outcome of the reaction. Unexpected direct oxidation of the intermediate zinc enolate to hydroxyketone **306** was observed and had been attributed to the action of copper salts in the presence of oxygen.[125, 139]



a) Me_2Zn, $CuOTf_2$ (2 mol%), (S_a,*R*,*R*)-**307**, PhMe, 42% **305**, 32% **306**.

Scheme 82[125]

Feringa and co-workers have shown that phosphoramidites, such as (S_a,*R*,*R*)-**307** and (R_a,*S*,*S*)-**308**, are excellent ligands for the asymmetric copper-catalysed conjugate addition of dialkylzinc reagents to enones (**Figure 22**).[140] Excellent enantioselectivities, in both cyclic and acyclic substrates, have been achieved utilizing these chiral ligands for conjugate addition reactions.[141]

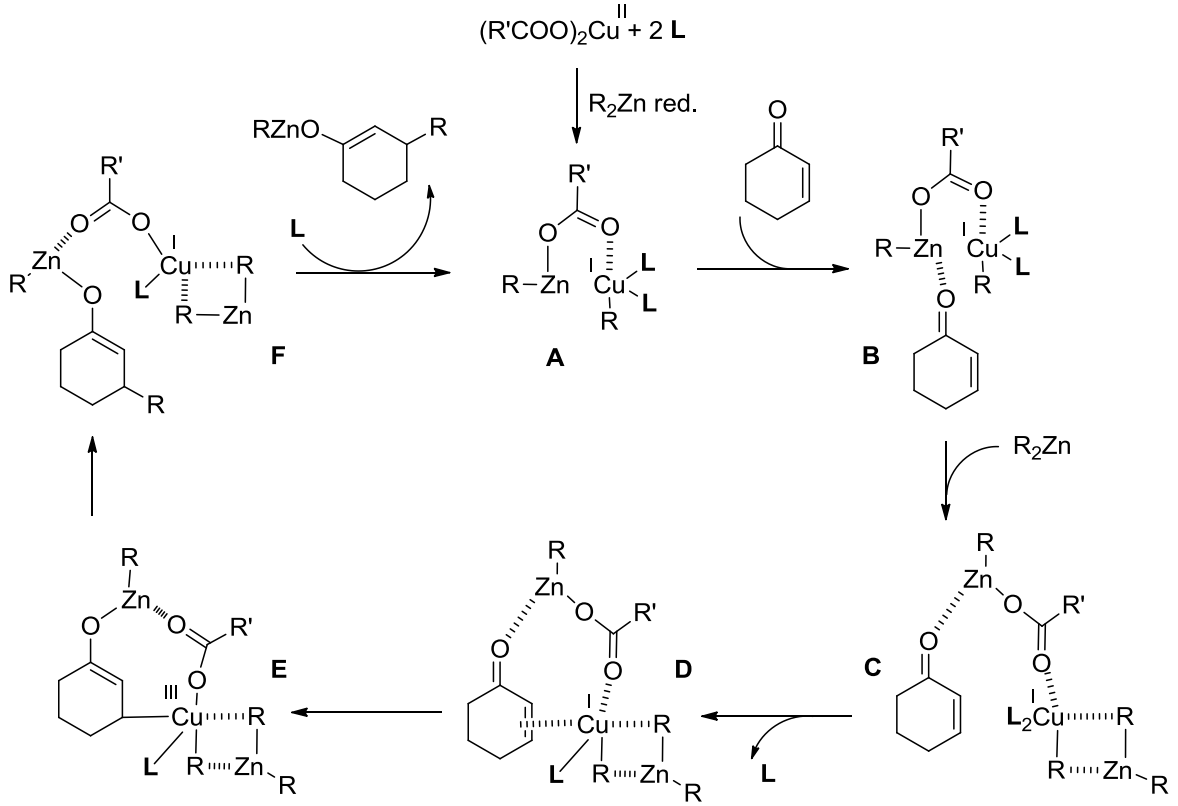


(S_a,*R*,*R*)-**307** (R_a,*S*,*S*)-**308**

Figure 22

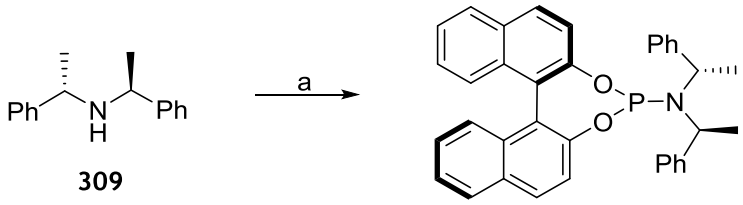
The copper-catalysed conjugate addition of dialkylzinc reagents follows the generally accepted mechanism of cuprate reactions.[142] A tentative general scheme can be drawn, although no intermediates have been isolated (**Scheme 83**).[143] The copper(II) salt is reduced to corresponding copper(I) salt upon treatment with the dialkylzinc reagent. Reaction of the copper(I) salt with the primary organometallic reagent affords organocopper reagent **A**. Intermediate **B** arises as a result of strong coordination between the most oxophilic metal (zinc) in complex **A** and the oxygen atom of the enone. This complex is unable to react further and so must be transformed into the higher order cuprate **C**. The formation of π-complex **D** is the first step toward the conjugate addition. It is this step that determines the absolute configuration of the adduct. Following this π-complexation, oxidative addition affords the copper(III) intermediate **E**. Reductive elimination results in the formation of zinc enolate **F**. The copper species is then released to re-enter the catalytic cycle. Detailed investigations

revealed reductive elimination to be the rate-determing step.[144] The nature of the substituents on the phosphorus ligand plays a key role in this step. It was noted that the higher the number of P—O bonds, the higher the rate of addition.[143a, 145]



Scheme 83[143]

For the JK-model system **226**, the carbon bearing the methyl group displays the opposite absolute configuration to that observed in the previously synthesised ketone **305**. For this reason, it was necessary to employ the antipodal ligand (R_a,*S*,*S*)-**308** for the copper-catalysed conjugate addition reaction. Although ligand (R_a,*S*,*S*)-**308** is not commercially available, it was readily synthesised in moderate yield from chiral amine **309** upon treatment with phosphorus trichloride and (*R*)-BINOL (**Scheme 84**).[146]

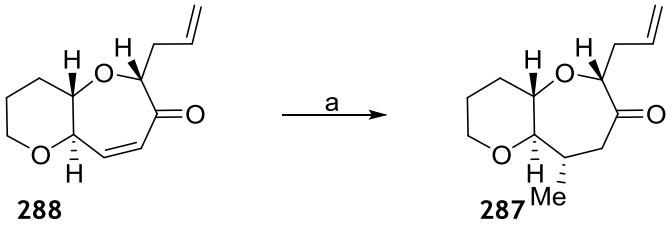


309 (R_a,*S*,*S*)-**308**

a) PCl_3, (*R*)-BINOL, Et_3N, PhMe, 46%.

Scheme 84

Treatment of alkylated enone **288** with dimethylzinc and copper(II) triflate in the presence of the ligand (R_a,*S*,*S*)-**308** afforded ketone **287** in 30% yield (45% brsm). The low yield obtained for the reaction was attributed to the small scale (18 mg) on which the reaction was performed (**Scheme 85**).

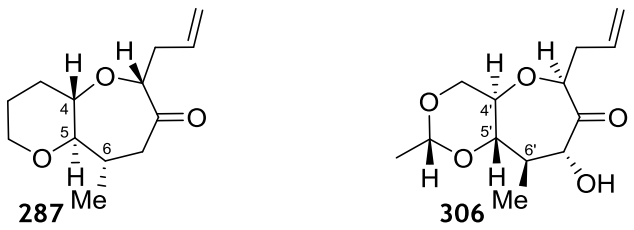


288 **287**

a) Me_2Zn, $CuOTf_2$ (6 mol%), (R_a,*S*,*S*)-**308** (12 mol%), PhMe, −40 °C to rt, 30% (45% brsm).

Scheme 85

Unfortunately, due to a lack of material, no useful NOE data was collected to confirm the configuration of the methyl group. The configuration was assigned based on the high stereoselectivity of the ligand (R_a,*S*,*S*)-**308**, along with a comparison between the NMR data obtained for ketone **287** and the previously synthesised hydroxyketone **306** (**Figure 23**).[125]



287 **306**

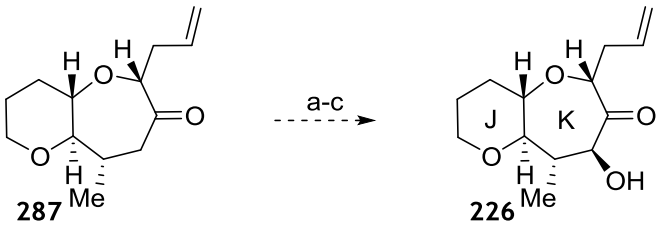
Figure 23

It was proposed that if the relationship between the H5 and H6 in ketone **287** was comparable to that between H5' and H6' in hydroxyketone **306**, then the coupling constants of H5 in ketone **287** and H5' in hydroxyketone **306** should be similar. It is clear, from the reported NMR data, that the splitting patterns and coupling constants of the two selected signals are similar (**Table 7**). This suggests that the methyl group is indeed on the same face as H5 in ketone **287**.

Hydrogen	Chemical shift (ppm)	Coupling constant (Hz)
H5' (**306**)	3.24	dd, *J* = 9.6, 9.5
H5 (**287**)	2.83	dd, *J* = 9.4, 9.3

Table 7

The final step in the synthesis of the JK-model system **226** was Rubottom oxidation of ketone **287** to afford the corresponding hydroxyketone **306**. It is known from previous studies, that the hydroxyl group would be introduced on the opposite face to the methyl group in the ß-position.[125] This pattern of reactivity would afford the desired JK-model system **226** (**Scheme 86**). Unfortunately, due to a lack of material this reaction was not investigated.

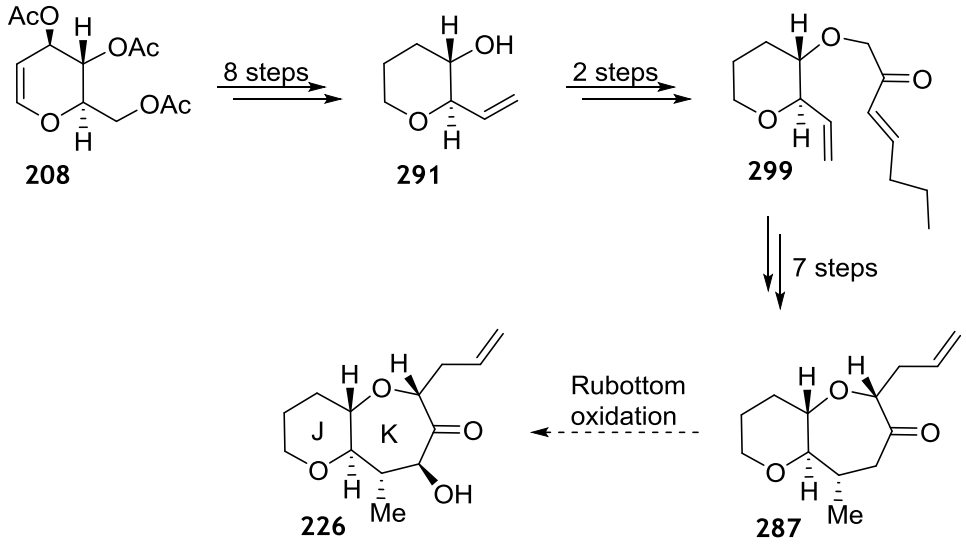


a) DIPA, *n*-BuLi, TESCl, Et_3N, THF, −78 °C; b) *m*-CPBA, $NaHCO_3$, PhMe, 0 °C; c) THF/H_2O/AcOH (4:2:1), rt.

Scheme 86

3.5 Summary

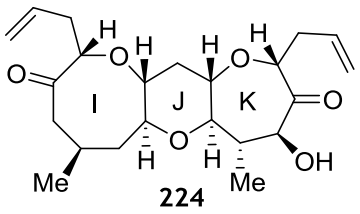
Alcohol **291** was synthesised from the commercially available tri-*O*-acetyl-D-glucal **208** in eight steps (**Scheme 87**). As in the IJ-model system **225**, by employing an improved version of the initial Wittig strategy, enone **299** was obtained from alcohol **291** in two steps. Pleasingly, it was found that enone **299** could be transformed into ketone **287**. Side chain introduction was accomplished by Tsuji allylation and the methyl group was installed stereoselectively upon copper-catalysed conjugate addition in the presence of the ligand (R_a,*S*,*S*)-**308**. The completion of the JK-model system **226** requires only Rubottom oxidation of ketone **287**. Previous work indicates that this step should proceed smoothly to afford the desired target **226**.[125]



Scheme 87

4.0 Two-directional approach to the IJK-ring system 224

With investigations into both model systems successfully completed, attention turned toward the development of a two-directional strategy for the synthesis of the IJK-ring system **224** of CTX3C (**4**) (**Figure 24**). Two-directional synthesis by simultaneous homologation has received significant attention over the past two decades.[147] This type of strategy involves homologating both ends of the chain at the same time, followed by desymmetrization of the ends as required. When applied to appropriate target molecules, a two-directional approach offers an efficient route that requires significantly fewer steps than the corresponding linear route. The two-directional strategy designed for the synthesis of the IJK-ring system **224** featured chemistry developed during the synthesis of both model systems.

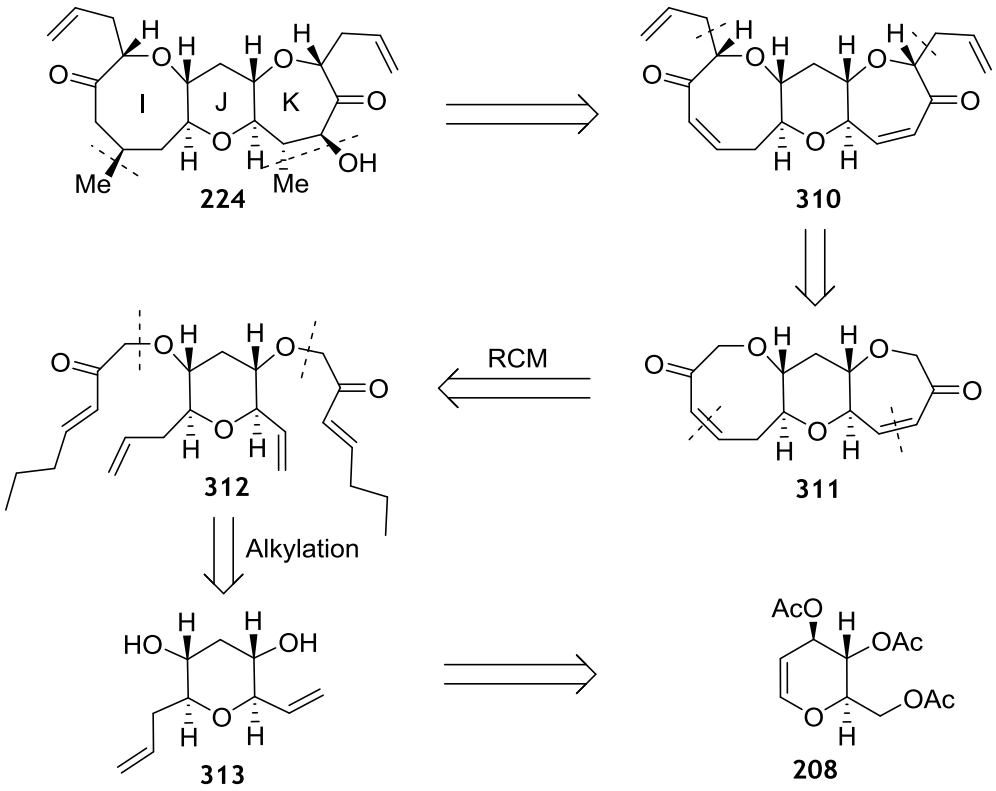


224

Figure 24

4.1 Retrosynthesis of the IJK-ring System 224

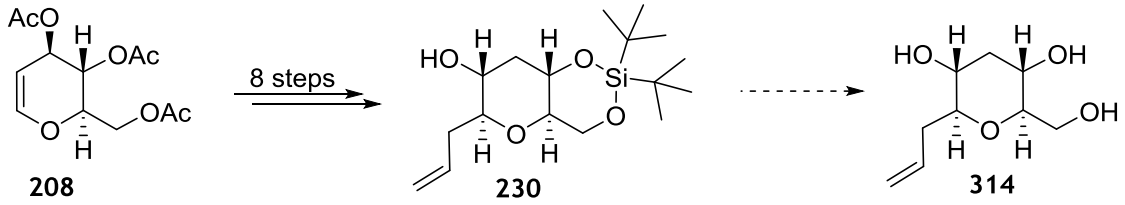
Our retrosynthetic analysis of the IJK-ring system **224** is shown below (**Scheme 88**). Functional group modifications followed by double retro 1,4-conjugate addition afford the alkylated tricyclic enone **310**. Disconnection of both allyl side chains and subsequent alkene scission provides tetraene **312**. Removal of both ether linkages affords diol **313**. Using the chemistry developed during the synthesis of the two model systems, diol **313** was to be synthesised from the commercially available tri-*O*-acetyl-D-glucal **208**.



Scheme 88

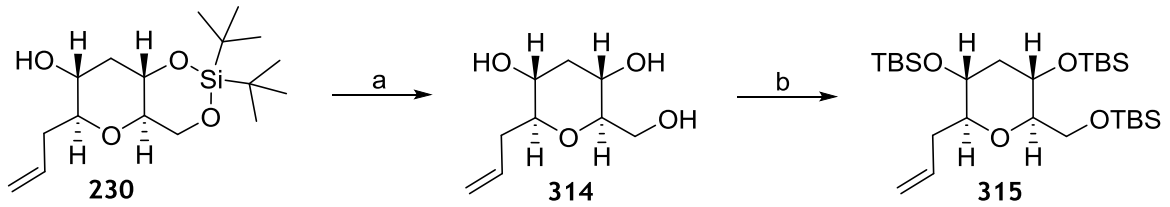
4.2 Synthesis of Diol 313

As described previously (see **Ch 2. § 2.2**), alcohol **230** was prepared from the commercially available tri-*O*-acetyl-D-glucal **208** in eight steps. Alcohol **230** afforded easy access to triol **314**; the first key target in the two-directional synthesis of the IJK-tricycle **224** (**Scheme 89**).



Scheme 89

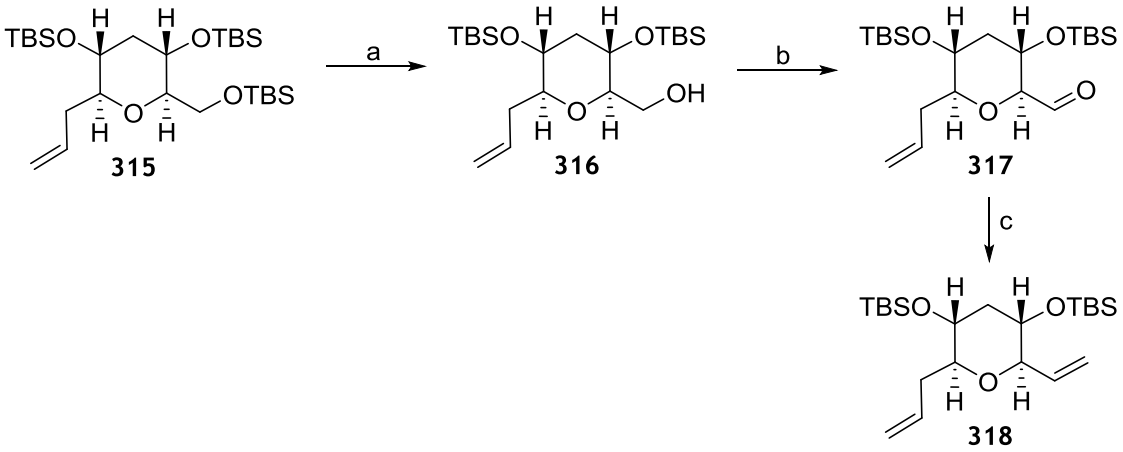
Treatment of alcohol **230** with TBAF afforded triol **314**. Purification of triol **314** proved to be difficult, but filtration through a short plug of silica gel provided material of sufficient purity. Complete TBS-protection of triol **314** proceeded smoothly to afford the alkene **315** in 88% yield over the two steps (**Scheme 90**).



a) TBAF (1 M in THF), THF, 0 °C to rt; b) Imidazole, TBSCl, DMAP (25 mol%), DMF, 0 °C, 88% (2 steps).

Scheme 90

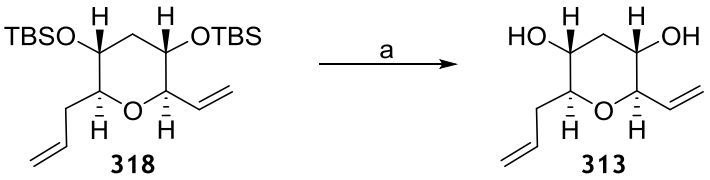
Following the successful isolation of alkene **315**, the next challenge was selective deprotection of the primary alcohol and subsequent installation of the required vinyl group (**Scheme 91**). Treatment of alkene **315** with camphorsulfonic acid resulted in selective deprotection of the primary alcohol to afford **316**. Oxidation of alcohol **316** was performed under Parikh-Doering conditions to provide the corresponding aldehyde **317**. Subsequent Wittig reaction with the ylide generated from methyltriphenylphosphonium bromide furnished diene **318** in excellent yield over the two steps.



a) CSA (30 mol%), CH_2Cl_2:MeOH (1:1), 0 °C, 89%; b) SO_3·py, Et_3N, DMSO, CH_2Cl_2, 0 °C; c) NaHMDS (1 M in THF), Ph_3PCH_3Br, THF, 0 °C, 91% (2 steps).

Scheme 91

Following the isolation of diene **318**, the next step was removal of the remaining silyl ether protecting groups. Deprotection by treatment of the diene **318** with camphorsulfonic acid afforded the corresponding diol **313** in 95% yield (**Scheme 92**).



a) CSA, CH_2Cl_2:MeOH (1:1), 0 °C, 95%.

Scheme 92

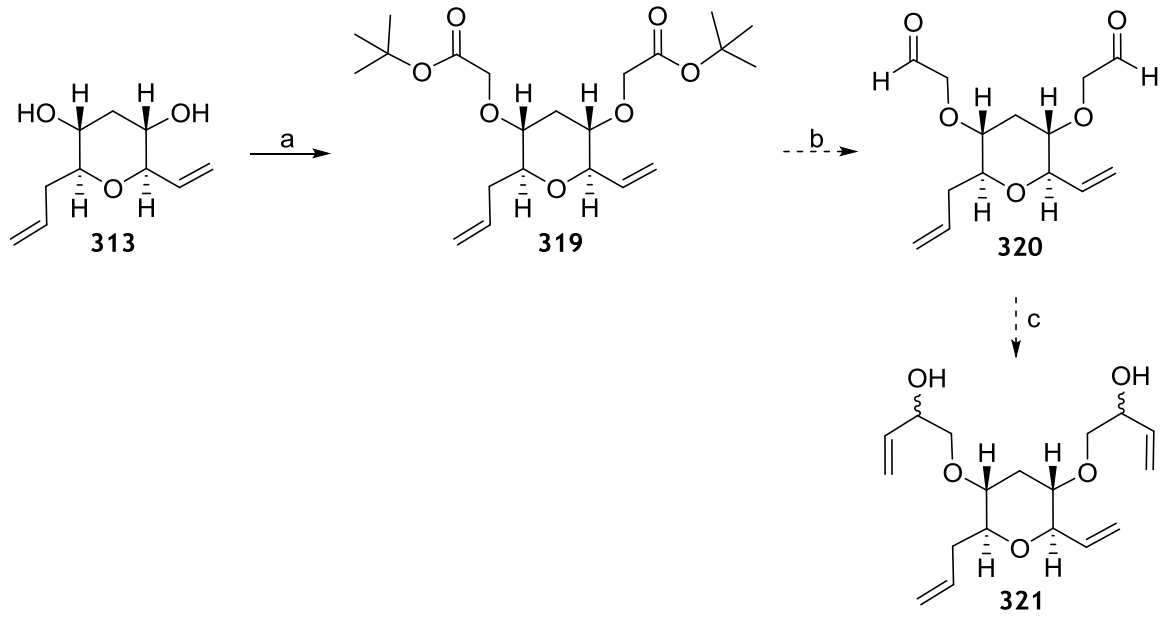
Following the successful introduction of the vinyl group to afford diol **313**, the next challenge was to construct both the eight- and seven-membered rings simultaneously utilizing the enone/RCM protocol. It was hoped that a double enone/RCM reaction sequence would allow for the two-directional synthesis of the target tricycle **224**.

4.3 Synthesis of Tricyclic Enone 311

The first step in the double enone/RCM protocol was the introduction of the two ether side chains. During the synthesis of the two model systems, various strategies were considered for the introduction of the required ether side chains. Two separate methodologies were selected for consideration in the two-directional approach to enone **311**.

tert-Butyl Ester Strategy

The first strategy considered was to introduce the ether side chains from the corresponding *tert*-butyl diester **319**. As detailed earlier (see **Ch 2. § 2.3.3**), this method was employed during the synthesis of the IJ-model system **225**. Treatment of diol **313** with *tert*-butyl bromoacetate afforded the corresponding diester **319** in moderate yield (**Scheme 93**). Due to the moderate yield obtained upon extended and lengthy reaction times, no further work on this sequence was undertaken.

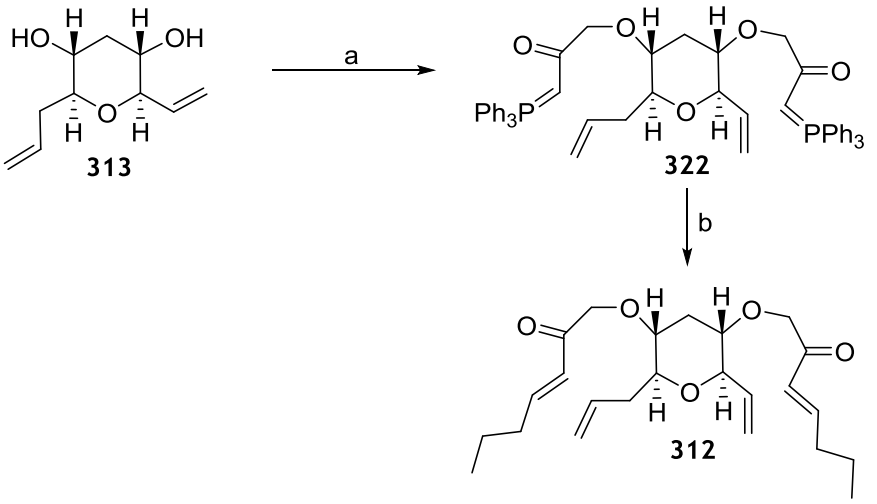


a) *tert*-butyl bromoacetate, 30% aq. NaOH, TBAI (50 mol%), PhMe, rt, 5 days, 53%; b) DIBAL; c) $CH_2CHMgBr$.

Scheme 93

Modification of the Initial Wittig Strategy

As seen in the synthesis of both the IJ- and JK-model systems, an improved version of the initial Wittig methodology allowed for the successful introduction of the required ether side chains (see **Ch 2. § 2.3.3**, **§ 3.3**). It was believed that these reaction conditions could be employed for the two-directional synthesis of tetraene **312**. First, diol **313** was alkylated upon treatment with sodium hydride and triphenylchloroacetonylphosphorane to afford phosphorane **322**. Pleasingly, the Wittig reaction between butyraldehyde and the stabilized phosphonium ylide **322** afforded the desired tetraene **312** in 86% yield over the two steps (**Scheme 94**).

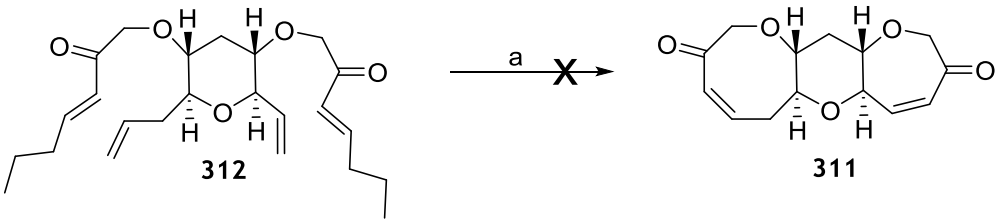


a) NaH, $ClCH_2COCHPPh_3$, TBAI (5 mol%), THF, rt; b) butyraldehyde, CH_2Cl_2, reflux, 86% (2 steps).

Scheme 94

Following the successful synthesis of the tetraene **312**, the next challenge was simultaneous ring closure to form the eight-membered I-ring and seven-membered K-ring. During earlier studies performed in the group, the construction of rings in a two-directional manner *via* the double RCM reaction of allylic ethers, enol ethers or alkynyl ethers had been explored (see **Ch 1. § 2.4.**).[76] With these results in mind, ring closure to form the required tricyclic carbon skeleton of the IJK-ring system **224** was investigated. Treatment of tetraene **312** with either Grubbs first or second generation catalyst **61** or **148**, resulted in the recovery of starting material without formation of the required

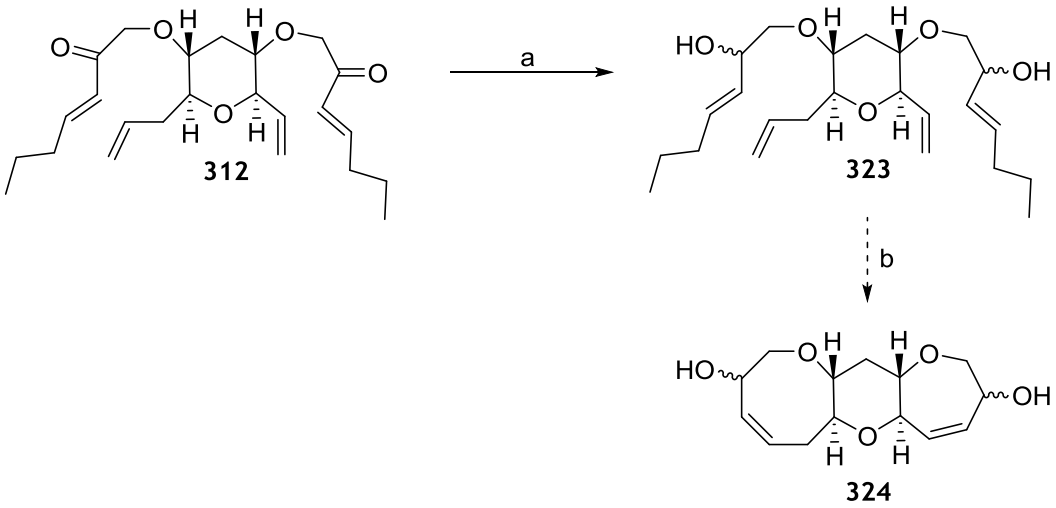
product (**Scheme 95**). This result was not unexpected because in both model systems neither the eight- nor seven-membered ring was closed upon treatment of the corresponding enone with these ruthenium catalysts. The lack of reactivity toward ring closure was attributed to unproductive complexation between the substrate and the catalyst (see **Ch 2. § 2.3.2**).



a) **61** or **148** (20 mol%), CH_2Cl_2, reflux.

Scheme 95

During the synthesis of the two model systems it had been shown that RCM of the corresponding allylic alcohol precursors **273** and **300** resulted in successful ring construction. A three-step reduction, RCM and oxidation sequence was employed for the construction of both the eight-membered I-ring and the seven-membered K-ring (**Scheme 96**). It was believed that this three-step sequence could be employed for the two-directional synthesis of the tricyclic enone **311**. The first step in the sequence was Luche reduction of both enones in the tetraene **312** to give the corresponding diol **323**. Diol **323** was isolated in excellent yield as a statistical mixture of diastereomers.



a) $NaBH_4$,$CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 96%, dr 1:1:1:1; b) RCM.

Scheme 96

Following the synthesis of diol **323**, the next step in the sequence was double RCM reaction to afford the desired tricyclic ether **324.** This step necessitated some optimisation of the reaction conditions. During the model syntheses, it was discovered that reaction concentration had a significant effect on the yield of the RCM reaction. The optimum reaction conditions for the construction of the eight- and seven-membered rings, differ in terms of both reaction concentration and catalyst loading (**Table 8**). In the case of the eight-membered ring, low concentration (0.001 M) and a catalyst loading of 5 mol% afforded the desired alcohol **268** in 96% yield. For the construction of the seven-membered ring, the best yields were observed at a higher concentration (0.01 M) and a slightly higher catalyst loading of 7.5 mol%.

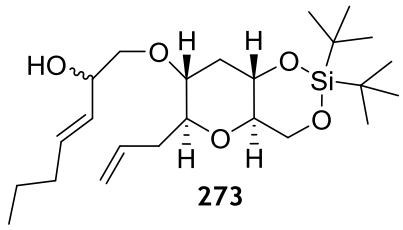
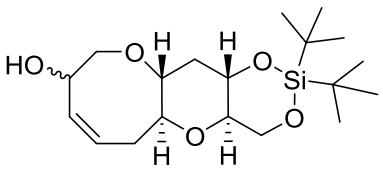
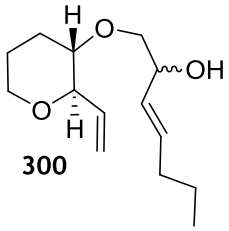
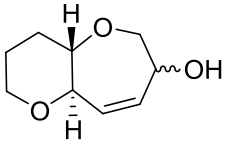
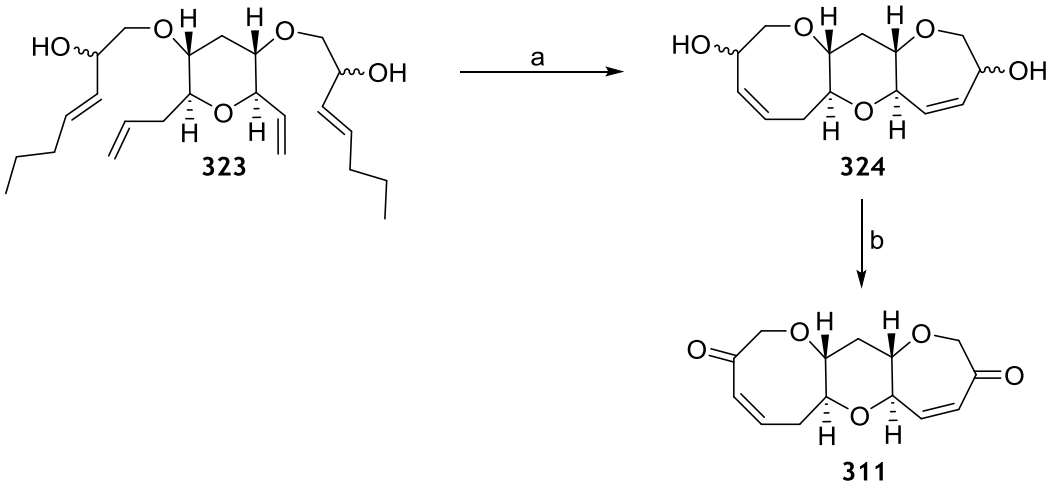
Starting material	Reaction concentration (M)	150 (mol%)	Result
 **273**			 **268**
	0.001	5	96% yield (dr 1:1)
	0.01	5	53% yield (dr 1:1)
 **300**			 **301**
	0.01	7.5	81% yield (dr 1:1)
	0.001	7.5	~80% rsm

Table 8

These results suggested that some optimisation of both the reaction concentration and catalyst loading would be required to obtain a high yield from the double RCM reaction. Initial studies revealed a catalyst loading of 20 mol% afforded the highest conversion of starting material. This requirement for a higher catalyst loading was not unexpected because the double RCM reaction constructs two rings simultaneously. With regard to reaction concentration, complete conversion of starting material was only observed for the two higher concentrations investigated, 0.01 M and 0.005 M. Unfortunately, purification of diol **324** proved to be problematic due to decomposition on silica. For this reason, the conversion was noted and the crude reaction mixture was then taken directly on to the next step (**Scheme 97**). Oxidation of diol **324** with Dess-Martin periodinane afforded tricyclic ether **311** in 39% yield over the two steps. It is believed, that with further investigation, the reaction conditions could be optimised further and yields comparable to those achieved for the corresponding steps in the two model syntheses could be obtained.



a) **150** (20 mol%), CH_2Cl_2, reflux, 0.01 M, full conversion; b) DMP, CH_2Cl_2, 0 °C, 39% (2 steps).

Scheme 97

4.4 Functionalization of Tricyclic Ether 311

With the core of the polycyclic carbon skeleton now in place, the remaining challenge was efficient functionalization of the eight- and seven-membered rings to afford the IJK-ring system **224**. Functionalization entailed the incorporation of an allyl side chain by alkylation and introduction of a methyl substituent by conjugate addition to each ring, followed by Rubottom oxidation on the seven-membered ring. (**Figure 25**).

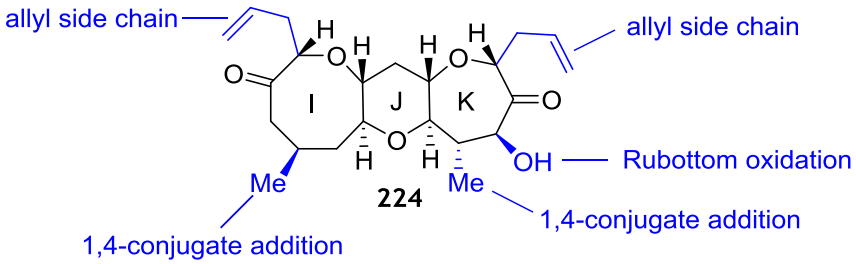
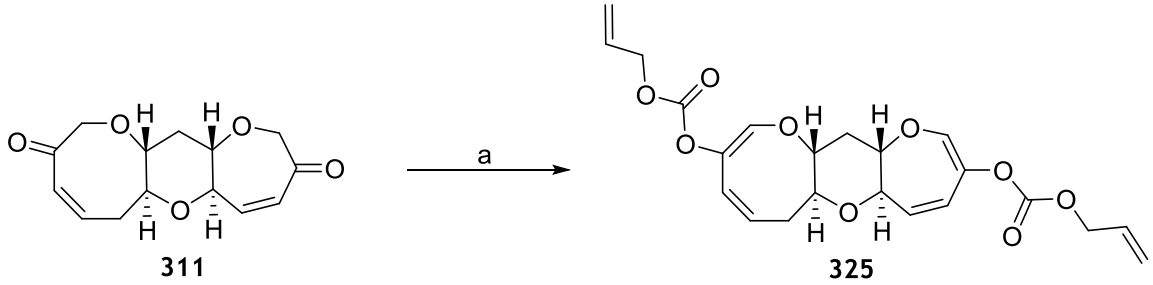


Figure 25

The first step in the sequence used to functionalize the IJK-ring system **224** was the simultaneous incorporation of the two allyl side chains. Ether **311** was first treated with allylchloroformate and sodium bis(trimethylsilyl)amide solution to afford carbonate **325** in good yield (**Scheme 98**).

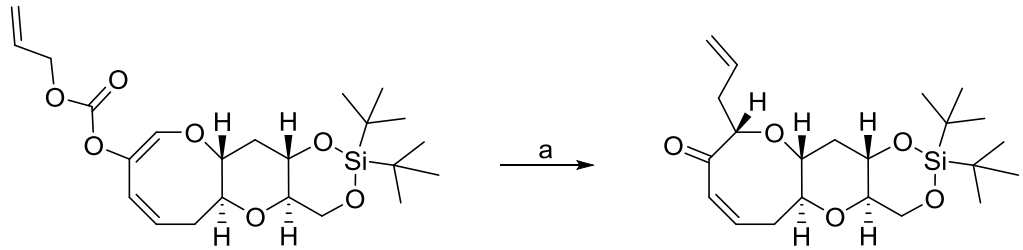


311 **325**

a) allylchloroformate, NaHMDS (1 M in THF), THF, −78 °C, 69%.

Scheme 98

It was proposed that palladium-catalysed rearrangement of **325** would afford the desired alkylated tricyclic ether **310**. During the synthesis of both model systems palladium-catalysed rearrangement had been employed to introduce the requisite allyl side chain (see **Ch 2. § 2.4**, **§ 3.4**). In the case of the eight-membered I-ring, it was found that performing the rearrangement in the presence of the (*S*)-*t*Bu-PHOX ligand **(*S*)-282** afforded the desired alkylated enone **227** with a diastereomeric ratio of >20:1 (**Scheme 99**).

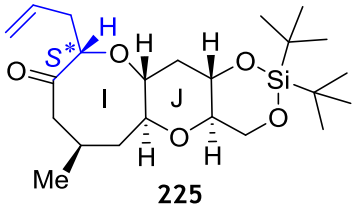


283 **227**

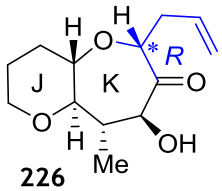
a) $Pd(PPh_3)_4$ (10 mol%), (*S*)-*t*Bu-PHOX **(*S*)-282** (25 mol%), THF, rt, 85%, dr >20:1.

Scheme 99

The highlighted stereocentre (*) in the IJ-model system **227** has *S*-configuration (**Figure 26**). The desired configuration was installed through the use of the chiral (*S*)-*t*Bu-PHOX ligand **(*S*)-282** in the palladium-catalyzed rearrangement. The corresponding highlighted stereocentre (*) in the JK-model system **226** has *R*-configuration.



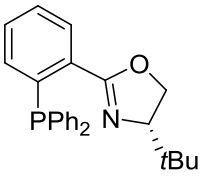
225



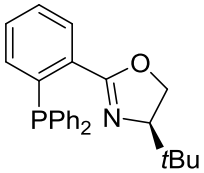
226

Figure 26

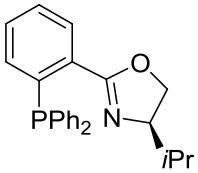
Ideally, the palladium-catalyzed rearrangement reaction used to install the allyl side chain in the JK-model system **226** would have been performed using the (*R*)-*t*Bu-PHOX ligand **(*R*)-282**. Unfortunately the (*R*)-*t*Bu-PHOX ligand **(*R*)-282** is not commercially available and, unlike the (*S*)-*t*Bu-PHOX ligand **(*S*)-282**, cannot be synthesised readily from straightforward starting materials.[148] An alternative option would have been to utilize the commercially available (*R*)-*i*Pr-PHOX ligand **326** (**Figure 27**).



(*S*)-282



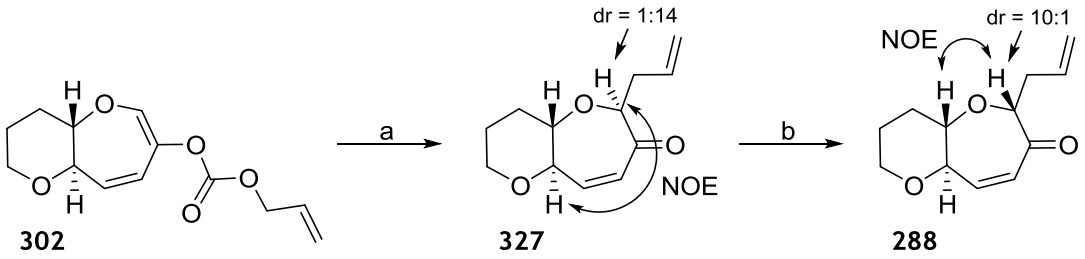
(*R*)-282



326

Figure 27

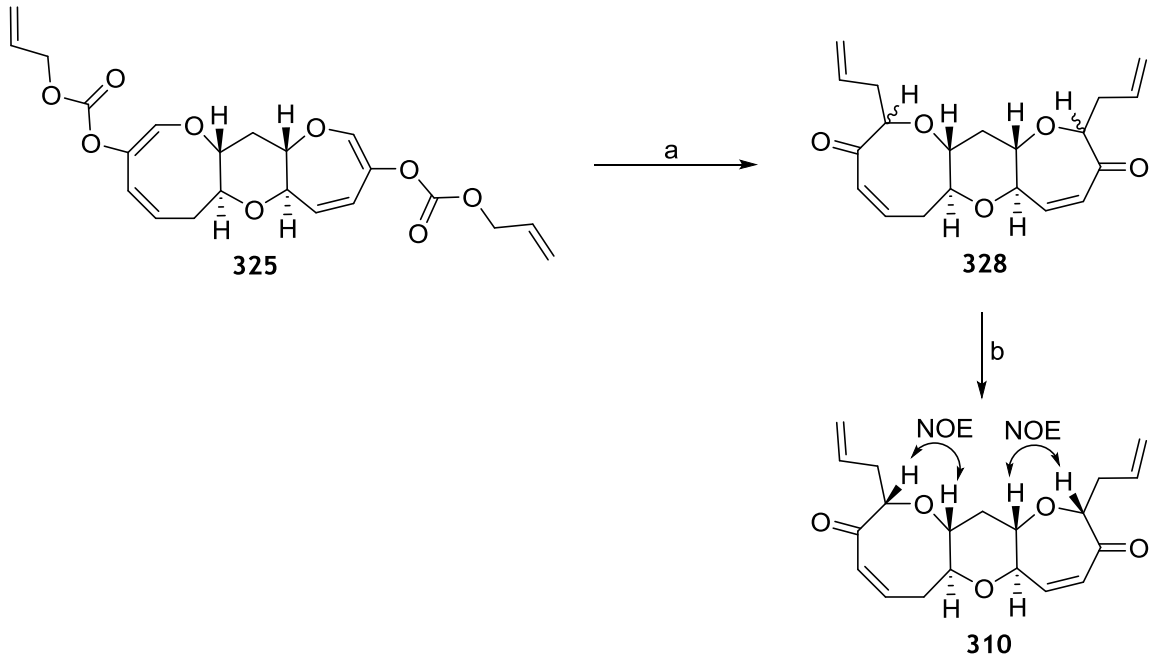
The use of the (*R*)-*i*Pr-PHOX ligand **326** was discounted because the two-directional approach to the IJK-ring system **224** requires the simultaneous alkylation of both the eight- and seven-membered rings. Consequently, it was only possible to employ one chiral ligand in the palladium-catalysed rearrangement of carbonate **325**. The (*S*)-*t*Bu-PHOX ligand **(*S*)-282** was selected for use in the rearrangement because the epimerisation at the stereocentre bearing the allyl side chain in the seven-membered ring (dr 1.3:1 to 10:1) was far more successful than epimerisation at the corresponding stereocentre in eight-membered ring (dr 1.8:1 to 5:1). The palladium-catalysed rearrangement of bicyclic carbonate **302** in the presence of the (*S*)-*t*Bu-PHOX ligand **(*S*)-282** was investigated (**Scheme 100**). Treatment of carbonate **302** with $Pd(PPh_3)_4$ and (*S*)-*t*Bu-PHOX ligand **(*S*)-282** afforded alkylated enone **327** as a 1:14 mixture of diastereomers, favouring the undesired diastereomer. Epimerisation of **327** with DBU afforded the desired *cis*-product **288** in 83% yield with a diastereomeric ratio of 10:1.



a) $Pd(PPh_3)_4$ (10 mol%), (*S*)-*t*Bu-PHOX **(*S*)-282** (25 mol%), THF, rt, 88%, dr 1:14; b) DBU, PhMe, rt, 83%, dr 10:1.

Scheme 100

Following successful epimerisation of the alkylated enone **327**, it was decided to perform the double palladium-catalysed rearrangement of carbonate **325** in the presence of the (*S*)-*t*Bu-PHOX ligand **(*S*)-282**. It was expected that this reaction would allow the allyl side chain on the eight-membered ring to be installed with the correct stereochemistry at the newly created stereocentre and that subsequent epimerisation with DBU should correct the stereochemistry at the stereocentre bearing the allyl side chain in the seven-membered ring. The palladium-catalysed rearrangement of carbonate **325** afforded alkylated tricyclic ethers **328** in good yield as a complex mixture of diastereomers (**Scheme 101**). Epimerisation of **328** using DBU afforded the target tricyclic ether **310**. The disappointingly low yield obtained for the epimerisation reaction was likely due to a combination of two factors: decomposition of the starting material and the small scale on which the reaction was performed.



325 328 310

a) $Pd(PPh_3)_4$ (10 mol%), (*S*)-*t*Bu-PHOX **(*S*)-282** (25 mol%), THF, rt, 84%; b) DBU, PhMe, 31%, dr 6:1.

Scheme 101

The next stage in the functionalization of the tricyclic ring system **310** was introduction of the methyl substituents by 'double' 1,4-conjugate addition. Again, data obtained from the model studies allowed suitable reaction conditions to be identified for the two-directional approach. In an effort to discover conditions that would allow for the stereoselective 'double' 1,4-conjugate addition on both rings, the two sets of reaction conditions developed in the model studies were applied to both the eight- and seven-membered rings. **Table 9** details the 1,4-conjugate addition reaction conditions developed for the synthesis of the JK-model system **226**. These conditions were found to introduce the methyl group on the seven-membered K-ring with the desired stereochemical outcome and with good selectivity. However, when these conditions were applied to the eight-membered enone **227**, ketones **329** were isolated as a 1:1 mixture of diastereomers. Consequently, due to the lack of selectivity observed in the case of addition to eight-membered cyclic enone, these reaction conditions proved unsuitable for use in the two-directional strategy.

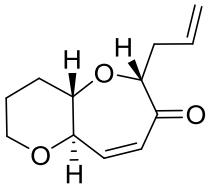
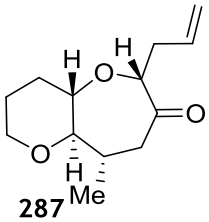
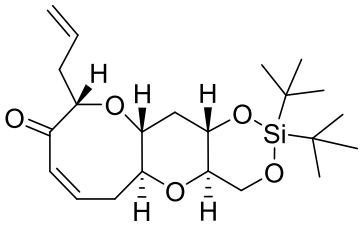
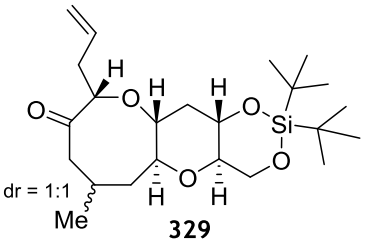
Starting material	Reaction conditions	Product
 **288**	Me_2Zn, $CuOTf_2$ (6 mol%), (R_a,*S*,*S*)-**308** (12 mol%), PhMe.	 **287** 30% yield (45% brsm)
 **227**	Me_2Zn, $CuOTf_2$ (6 mol%), (R_a,*S*,*S*)-**308** (12 mol%), PhMe.	 **329** 53% yield (dr 1:1)

Table 9

Table 10 details the 1,4-conjugate addition reaction conditions developed during the synthesis of the IJ-model system **225**. Under these conditions, the methyl group could be installed on the eight-membered I-ring with the desired stereochemical outcome in a highly stereoselective manner. When these conditions were applied to conjugate addition to the seven-membered enone **288**, ketone **287** was isolated in low yield. Pleasingly, the reaction conditions appear to allow for the simultaneous stereoselective introduction of the methyl group to both rings. The disappointing yield observed for the reaction, was attributed to the low conversion of the starting material. It is believed that with further studies this poor conversion could be improved.

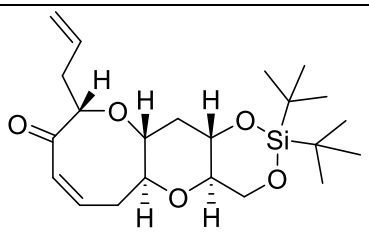
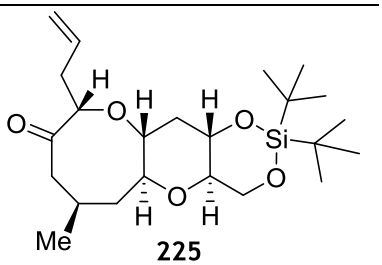
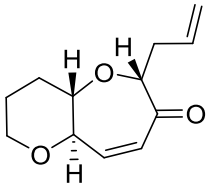
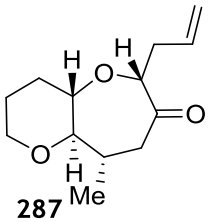
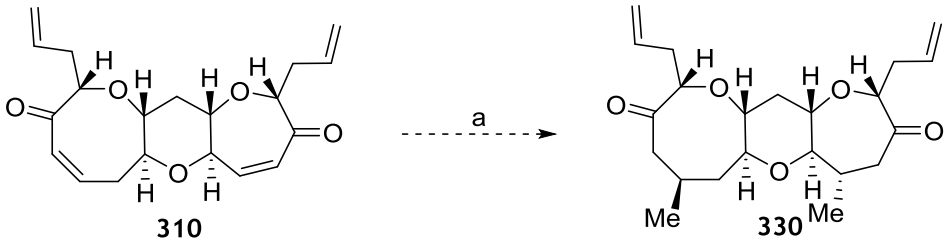
Starting material	Reaction conditions	Product
 **227**	$Me_2Cu(CN)Li_2$, Et_2O, −78 °C.	 **225** 89% yield
 **288**	$Me_2Cu(CN)Li_2$, Et_2O, −78 °C.	 **287** 12% yield (52% brsm)

Table 10

Based on the results noted in **Tables 9** and **10**, it appears that the use of a higher order cuprate reagent, $Me_2Cu(CN)Li_2$, should allow stereoselective introduction of the required methyl groups to both the eight- and seven-membered rings. The stereoselectivity of the 1,4-conjugate addition reaction was attributed to substrate control. Unfortunately, due to a lack of material and time this reaction could not be investigated on the alkylated tricyclic ether **310** (**Scheme 102**).



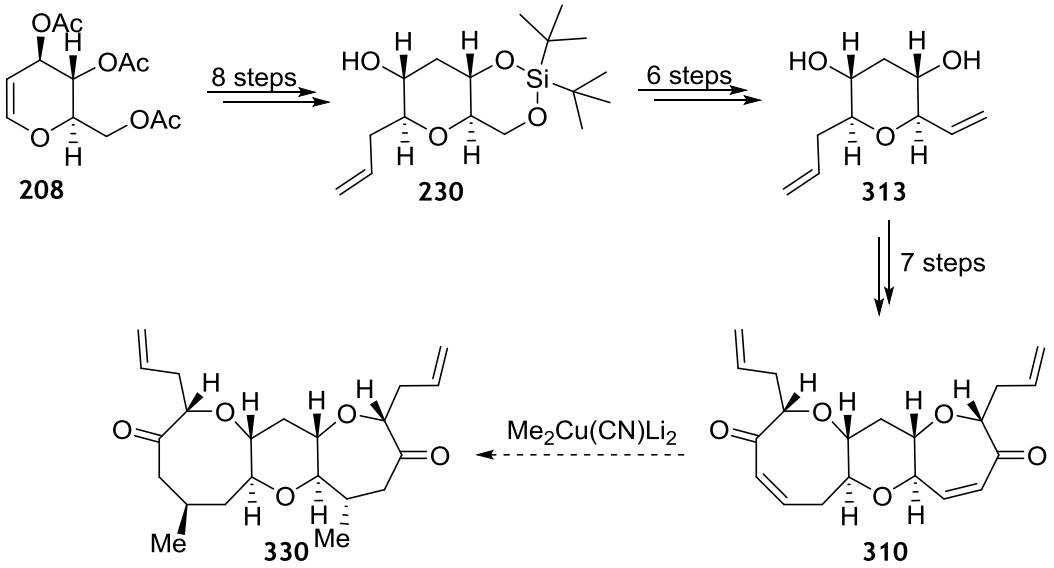
310 **330**

a) $Me_2Cu(CN)Li_2$, Et_2O, −78 °C.

Scheme 102

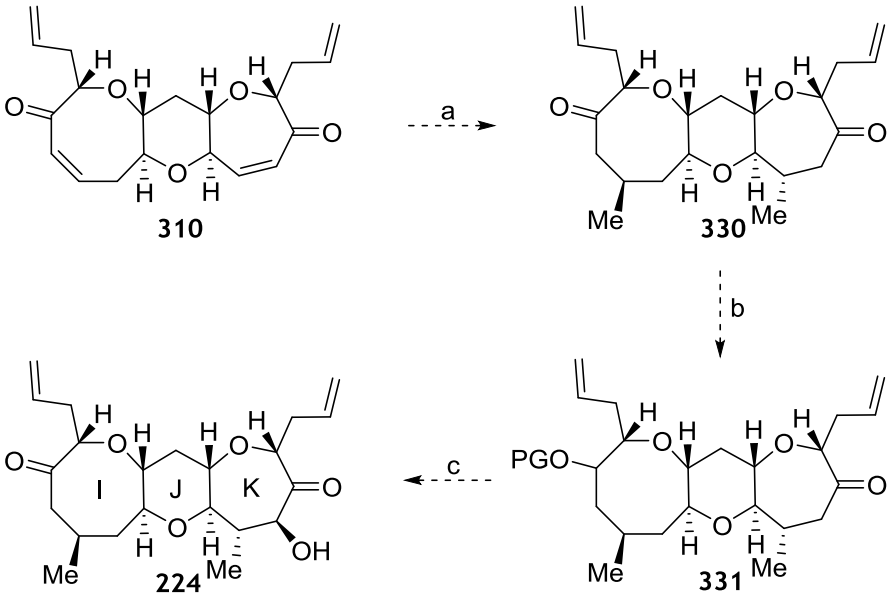
4.5 Summary

Alcohol **230** was synthesised from the commercially available tri-*O*-acetyl-D-glucal **208** in eight steps. Utilizing chemistry developed during the synthesis of the JK-model system, alcohol **230** was converted into the diol **313** in six steps. Diol **313** proved to be a key target in the synthesis of the IJK-tricyclic system **224**. From diol **313**, alkylated tricyclic ether **310** was synthesised *via* a two-directional strategy based on the chemistry developed during the two model syntheses. Conditions that allow the simultaneous 1,4-conjugate addition to both the eight- and seven-membered rings have been identifed by performing studies on the corresponding model systems (**Scheme 103**).



Scheme 103

Completion of the IJK-ring system **224** from the alkylated tricyclic ether **330** requires some further functionalization. Rubottom oxidation of the seven-membered ring is the final step required to afford the desired target **224**. Unfortunately, this reaction is unlikely to be fully chemoselective and affect only the seven-membered ring. For this reason, reduction of the eight-membered ring ketone and subsequent protection is likely to be required before the Rubottom oxidation (**Scheme 104**). Depending on the differing reactivities of the two ketones, it is possible that reduction and protection of the seven-membered ring ketone will be required.

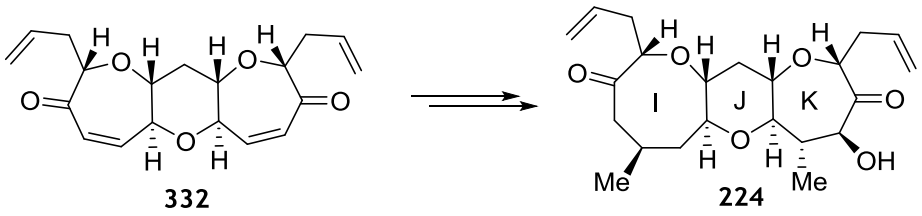


a) $Me_2Cu(CN)Li_2$, Et_2O, −78 °C; b) 1. Selective reduction; 2. Protection; c) 1. Rubottom oxidation; 2. Deprotection; 3. Oxidation.

Scheme 104

5.0 Alternative Two-directional Strategy

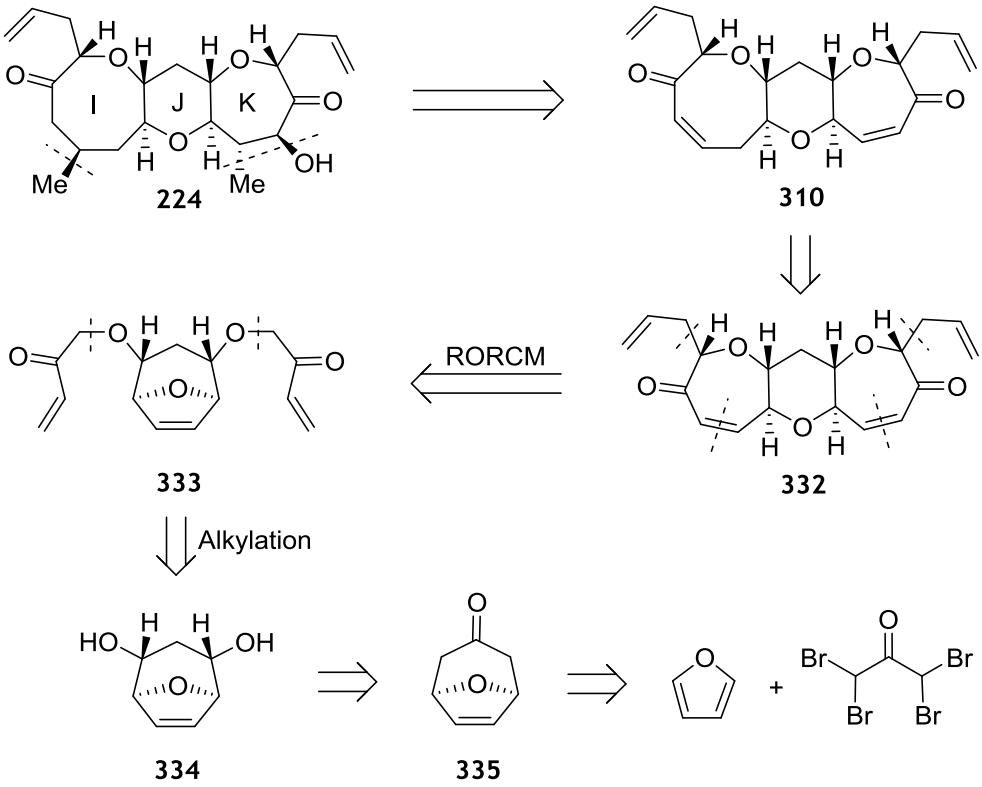
While working toward the synthesis of the IJK-ring system **224** (see **Ch 2. § 4.0**), an alternative two-directional approach that employed a completely symmetrical strategy was also investigated. This novel strategy would rely on the late-stage desymmetrisation of the *meso* tricyclic intermediate **332** (**Scheme 105**).



Scheme 105

5.1 Alternative Retrosynthetic Analysis of the IJK-ring System 224

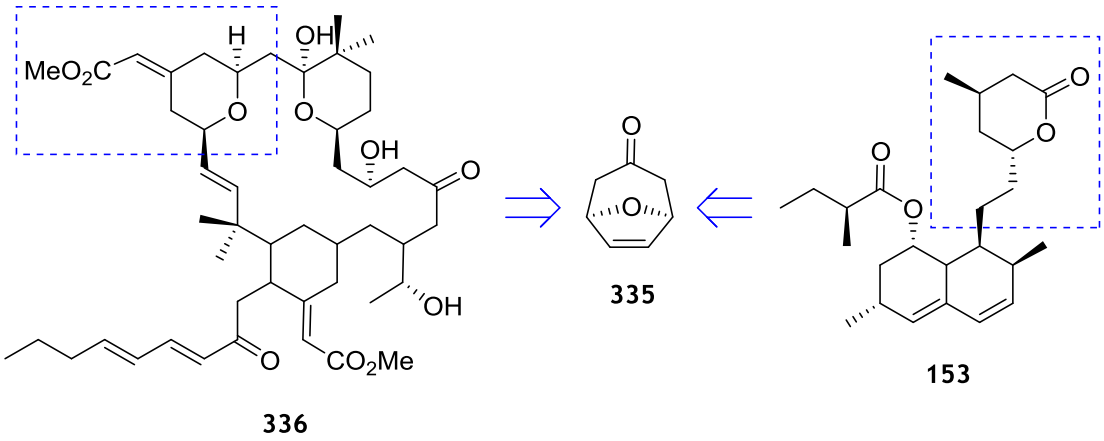
Our retrosynthetic analysis of the IJK-ring system **224** following the alternative two-directional strategy is shown below (**Scheme 106**). Functional group modifications followed by double retrosynthetic 1,4-conjugate addition afford the tricyclic *bis*-enone **310**. Retrosynthetic ring contraction of the eight-membered ring affords the key *meso* tricyclic *bis*-enone **332**. Disconnection of both allyl side chains, followed by a retrosynthetic RORCM reaction provides bicycle **333**. Removal of both ether linkages affords diol **334** and further functional group modifications provide the known oxabicyclic ketone **335**. Retro [4+3] cycloaddition delivers furan and tetrabromoacetone.



Scheme 106

5.2 Synthesis of Oxabicycle 335

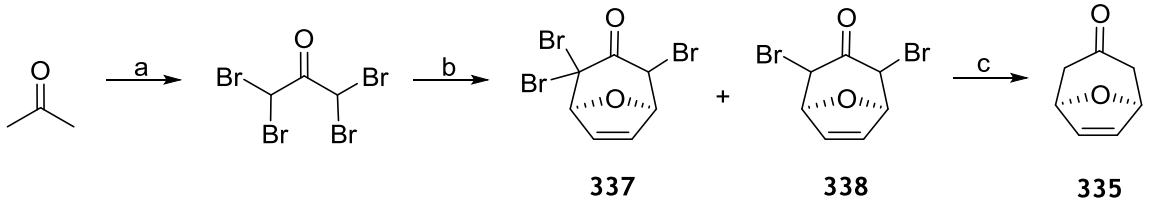
The [4+3] cycloaddition reaction of allylic cations and dienes provides a convenient route to bicyclo[3.2.1]ketones such as oxabicycle **335**. Oxabicycle **335** has been known in the literature for over four decades.[149] It has proven to be a useful and highly versatile building block in organic synthesis. Recent applications include the synthesis of various tetrahydropyran units that appear in marine natural products, pseudo-C-glycosides and other bioactive substances e.g. bryostatin 1 (**336**) and (+)-mevinolin (**153**) (**Scheme 107**).[150]



336 **335** **153**

Scheme 107

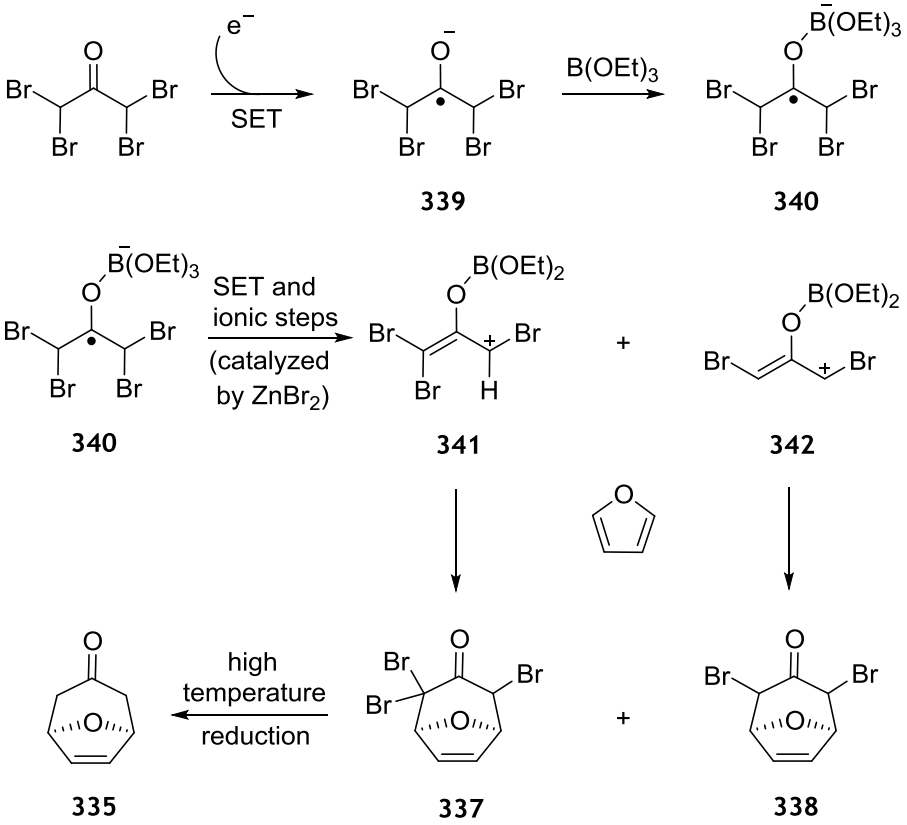
Bicyclic ketone **335** was originally prepared by the reaction of 2-methyoxy allyl bromide with silver trifluoroacetate in the presence of furan.[151] More recently, Hoffmann and co-workers have reported an inexpensive and scalable synthesis of oxabicycle **335** from furan and tetrabromoacetone.[152] Our synthesis began with the preparation of tetrabromoacetone (**Scheme 108**). Acetone was treated with bromine and an aqueous solution of hydrogen bromide to afford tetrabromoacetone in moderate yield. The next step was the [4+3] cycloaddition reaction with furan. The cycloaddition reaction was performed in the presence of activated zinc and triethyl borate to afford a mixture of brominated adducts **337** and **338**. It was noted, that the addition of a catalytic amount of bromine was required for the initiation of the cycloaddition reaction. Debromination of cycloadducts **337** and **338** was achieved using a suspension of zinc-copper couple and ammonium chloride in methanol to afford the target bicycle **335** in 45% yield over the two steps.



a) Br_2, HBr (48% aq.), 0 °C to rt, 41%; b) furan, activated Zn dust, $B(OEt)_3$, cat. Br_2, THF, 40 °C; c) Zn-Cu couple, NH_4Cl, MeOH, −78 °C to 0 °C, 45% (2 steps).

Scheme 108

It is known that **335** is prone to decomposition under acidic conditions.[152] In an attempt to avoid decomposition, the bicyclic ketone **335** was filtered through a short plug of potassium carbonate to ensure the removal of any remaining traces of hydrogen bromide. Hoffmann has proposed that the cycloaddition reaction can be visualized as a single electron transfer (SET) process (**Scheme 109**).

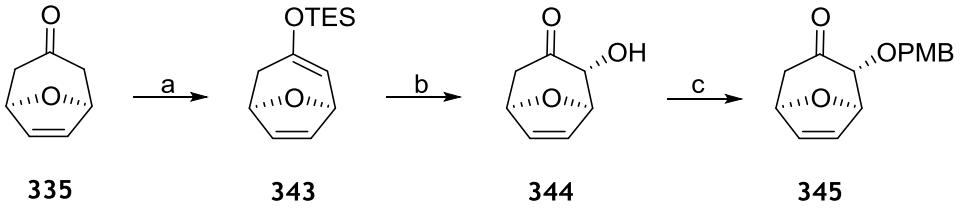


Scheme 109[152]

SET and Lewis acid mediated ionic steps, facilitated by triethyl borate, generate the crucial boron oxyallyl cation **341**/**342**. The cation is then captured by furan to afford the corresponding brominated bicyclic ether **337**/**338**. High temperature reduction then delivers the target bicycle **335**. Following the synthesis of **335**, the next challenge was functionalization of the scaffold to afford diol **334**.

5.3 Towards the Synthesis of Diol 334

Efforts to synthesise the diol **334** began by once more following procedures detailed by Hoffmann and co-workers.[152] Oxabicycle **335** was deprotonated with lithium diisopropylamine, and the resulting enolate trapped with triethylsilyl chloride to afford silyl enol ether **343** (**Scheme 110**). Oxidation with *m*-CPBA effected Rubottom oxidation to provide α-hydroxyketone **344**. PMB-protection of hydroxyketone **344** afforded ketone **345** in 84% yield. Due to the base sensitivity of hydroxyketone **344**, the protection reaction was performed under acid catalysis using 4-methoxybenzyltrichloroacetamidate and a catalytic amount of camphorsulfonic acid.



335 **343** **344** **345**

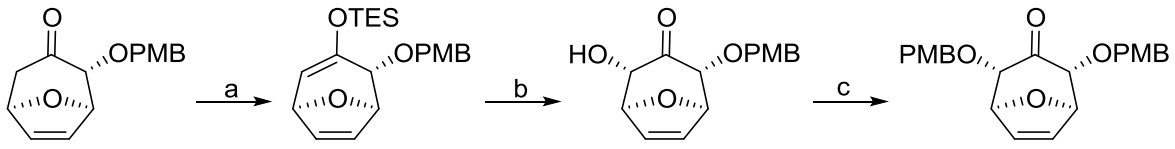
a) LDA, THF, −78 °C, then **335**, TESCl, Et_3N, THF, −78 °C; b) *m*-CPBA, THF/H_2O (1:1), 0 °C, then TFA, 0 °C, 36% (2 steps); c) 4-methoxybenzyltrichloroacetamidate, CSA (10 mol%), CH_2Cl_2, 0 °C to rt, 84%.

Scheme 110

Unfortunately, the yield obtained for the formation of hydroxyketone **344** was disappointingly low. The problem appeared to arise from the incomplete conversion of the silyl enol ether **343** into the hydroxyketone **344** and because the enol ether **343** was unstable to purification on silica gel, a significant

amount of material was lost due to decomposition on the column. All attempts to improve the yield obtained for this sequence were unsuccessful.

The reaction sequence was then repeated to afford ketone **348** (**Scheme 111**). Ketone **345** was deprotonated with lithium diisopropylamine and the resulting enolate trapped with triethylsilyl chloride to afford silyl enol ether **346**. Oxidation with dimethyl dioxirane furnished the rearranged Rubottom product, which was desilylated *in situ* to provide α-hydroxyketone **347**. PMB-protection of hydroxyketone **347** afforded ketone **348** in 63% yield.



345 **346** **347** **348**

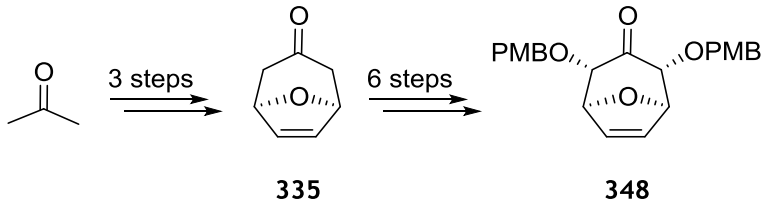
a) LDA, THF, −78 °C, then **345**, TESCl, Et_3N, THF, −78 °C; b) DMDO (0.09 M in acetone), CH_2Cl_2, −78 °C, then AcOH, THF:H_2O (1:1), 0 °C, 48% (2 steps); c) 4-methoxybenzyltrichloroacetamidate, CSA, CH_2Cl_2, 0 °C to rt, 63%.

Scheme 111

Unfortunately, the yield from the Rubottom oxidation reaction was only slightly improved upon the replacement of *m*-CPBA with dimethyl dioxirane. As before, incomplete conversion of the silyl enol ether **346** into the hydroxyketone **348** led to a significant loss of material during purification. The low-yielding Rubottom oxidation steps made it very difficult to bring significant quantities of material through this sequence. Consequently, it was decided that no further work would be undertaken on this route and efforts would be focused on the initial two-directional strategy.

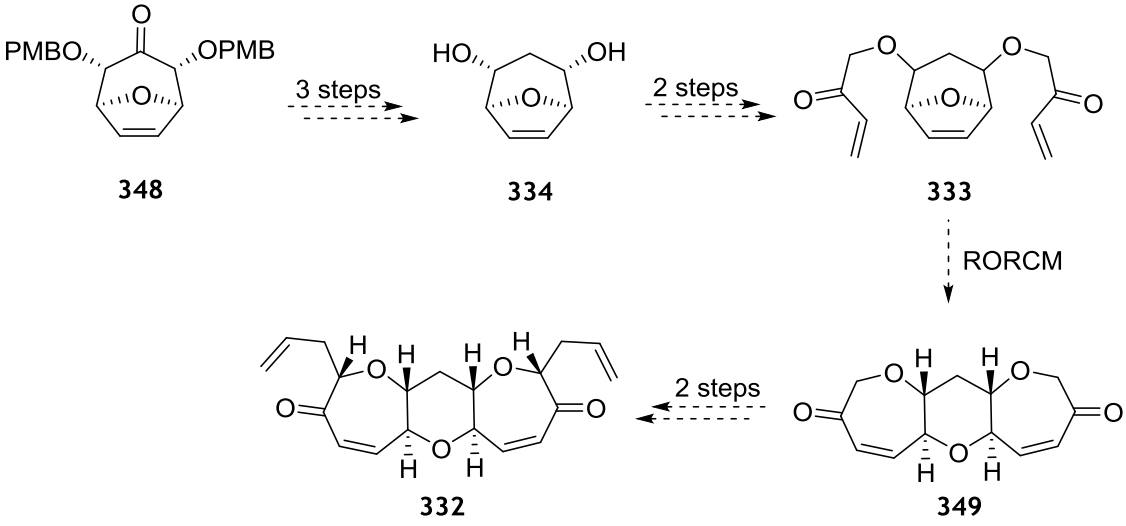
5.4 Summary

The oxabicyclic ketone **335** was synthesised from acetone in three steps. Functionalization to afford ketone **348** using sequential Rubottom oxidation reactions was completed in six steps. Unfortunately, due to the poor yields observed during the sequence no further investigation into this route was undertaken (**Scheme 112**).



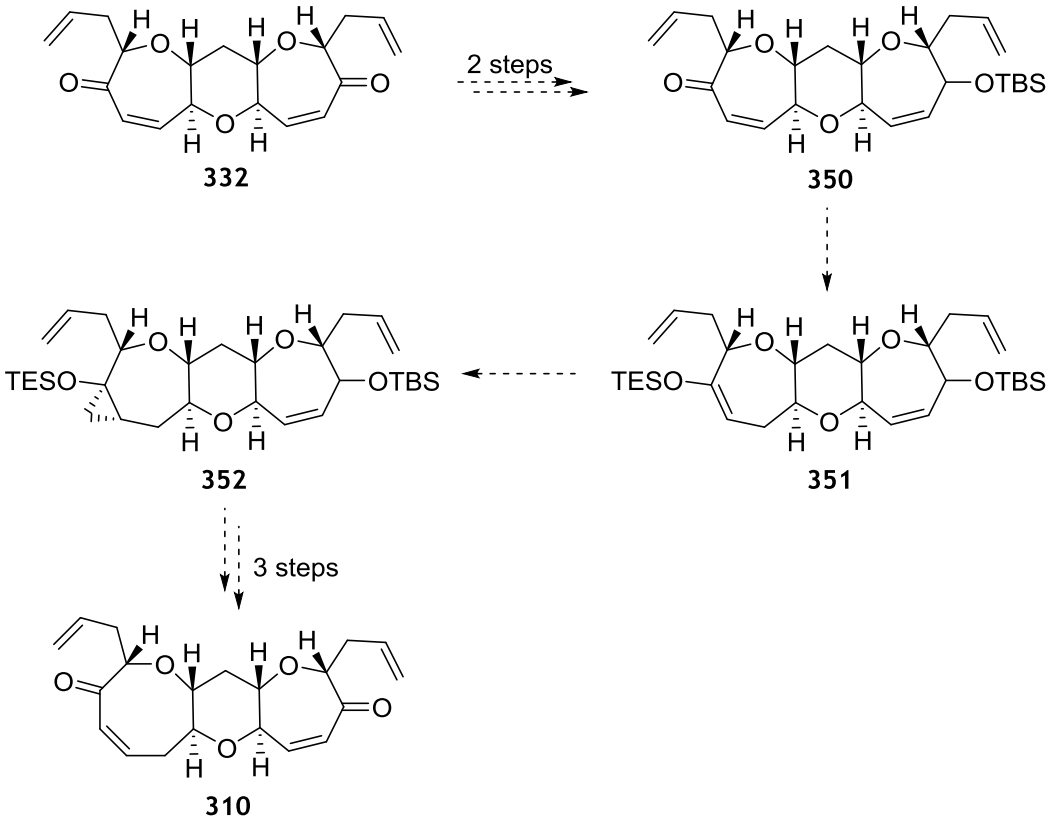
Scheme 112

The next step in the alternative two-directional approach would have been deoxgenation of ketone **348** followed by the subsequent deprotection of the resulting bicyclic ether to afford diol **334** (**Scheme 113**). The metathesis precursor **333** would be obtained utilizing the enone formation protocol detailed earlier (see **Ch 2. § 2.3**). RORCM reaction of **333** should afford the tricyclic ether **349**. There is literature precedent for the use of a similar RORCM process to construct a tricyclic system.[153] Alkylation of tricycle **349**, upon palladium-catalysed rearrangement of the corresponding enol carbonate, should afford the *meso*-intermediate **332**.



Scheme 113

The next challenge would be desymmetrisation and ring expansion to form the eight-membered carbon skeleton of the I-ring (**Scheme 114**). For this approach to be successful, it would be necessary to identify conditions for the selective reduction of one of the carbonyl groups. The resulting alcohol would be protected as the corresponding TBS ether and susbequent 1,4-conjugate reduction of enone **350** with enolate trapping should deliver silyl enol ether **351**.[154] Cyclopropane **352** could be obtained *via* the regio- and stereoselective cyclopropanation of the electron-rich silyl enol ether **351**.[155] Treatment of cyclopropane **352** with iron(III) chloride and triethylamine should deliver the desired ring-expanded enone. Removal of the TBS ether and subsequent oxidation would then deliver the tricyclic ether **310**. At this point, the route intersects with the initial two-directional strategy.

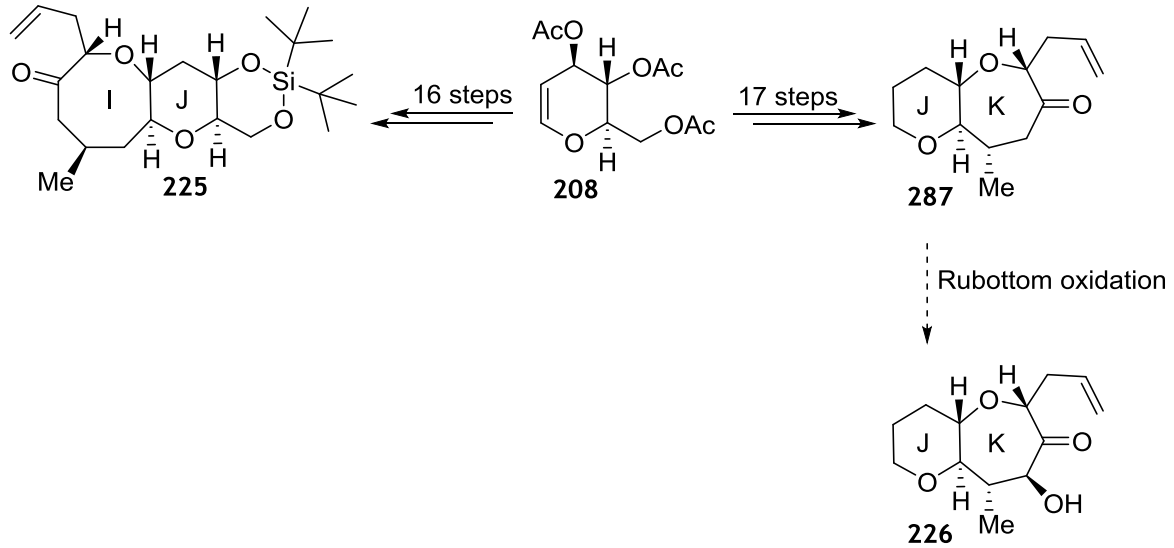


332 **350** **352** **351** **310**

Scheme 114

6.0 Conclusions

In order to investigate the chemistry required for the synthesis of the IJK-ring system **224** two separate model systems were designed and investigated. The IJ-model **225** was constructed in sixteen steps from tri-*O*-acetyl-D-glucal **208** (**Scheme 115**). Completion of the model system allowed the construction and functionalization of the eight-membered I-ring to be explored. The ketone **287** was obtained in seventeen steps from tri-*O*-acetyl-D-glucal **208**. Rubottom oxidation of ketone **287** should afford the targeted JK-model system **226**. Precedent shows that the Rubottom oxidation should proceed with the desired stereochemistry.[125]



Scheme 115

Both model systems employed a two-stage enone formation/RCM protocol for ring construction. After some optimisation, suitable RCM precursors for both model systems were synthesised (**Figure 28**). It was noted that by using an allylic alcohol as the RCM precursor, instead of the corresponding enone, the yields for ring construction by RCM were markedly improved.

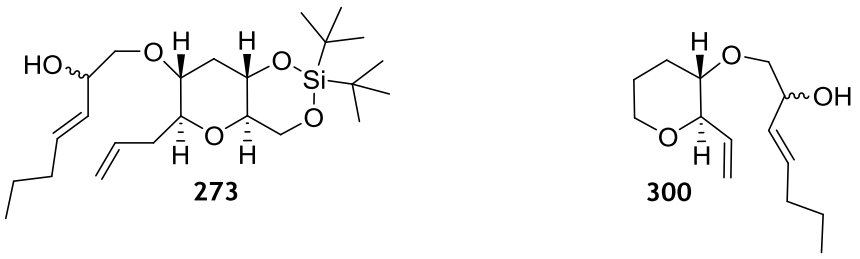
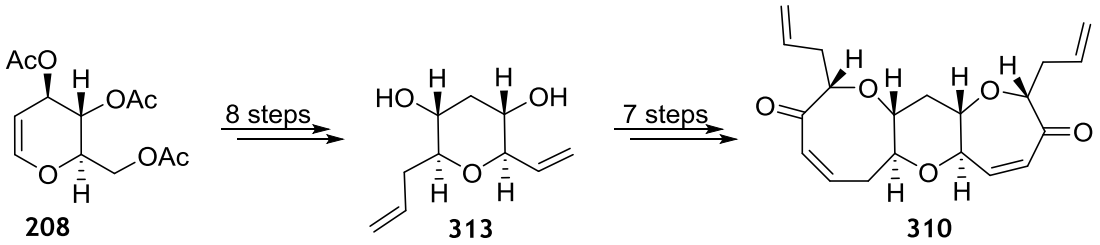


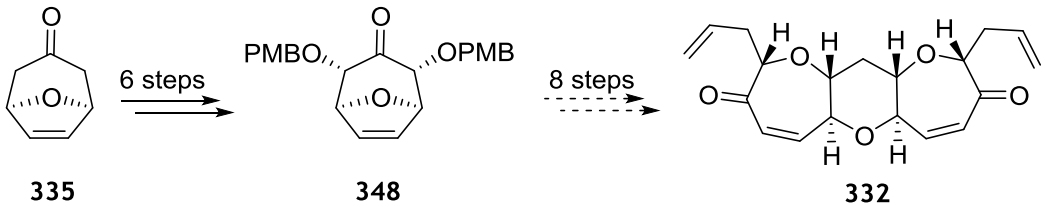
Figure 28

Finally, after studies towards the model systems were complete, a two-directional strategy towards the IJK-ring system **224** was considered (**Scheme 116**). The initial two-directional approach built upon the chemistry developed during the synthesis of the two model systems. Pleasingly, a suitable route that allowed for the successful isolation of alkylated tricyclic ether **310** was developed. The two-directional nature of the strategy was observed in the conversion of diol **313** to tricyclic ether **310**.



Scheme 116

An alternative two-directional strategy, employing late stage desymmeterisation of *meso*-intermediate **332**, was also considered. Unfortunately, due to the low yields encountered in the initial stages of the sequence, further optimisation will be required before this strategy can be considered to be synthetically viable (**Scheme 117**).



Scheme 117

Chapter 3: Experimental

Chapter 3: Experimental Section

Apparatus

1H NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at ambient temperature. The spectra are reported as follows: chemical shift in ppm relative to $CDCl_3$ (δ = 7.26), integration, multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad (br), apparent (app) or a combination of these], coupling constant(s) *J* (Hz) and assignment. ^{13}C NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at 101 MHz and 126 MHz at ambient temperature. The spectra are reported as follows: chemical shift in ppm relative to the central resonance of $CDCl_3$ (δ = 77.16) and assignment. DEPT 135 and two-dimensional NMR spectroscopy (COSY, HSQC) were used, where appropriate, to assist with the assignment of signals in the ^{1}H and ^{13}C NMR spectra. IR spectra were recorded using a type IIa diamond single reflection element on a Shimadzu FTIR-8400 instrument. The IR spectrum of the compound (solid or liquid) was detected directly as a thin layer, without any sample preparation, at ambient temperature. High resolution mass spectra (HRMS) were obtained under EI, CI and ESI conditions by the analytical services of the University of Glasgow. Melting points were recorded with an Electrothermal IA 9100 apparatus. Specific rotations ($[\alpha]_D$) were measured on an Autopol V Automatic polarimeter.

Chromatography

Column chromatography was performed under pressure using silica gel (Flurochem LC60A, 35—70 micron, 60A) as solid support and HPLC grade solvent as eluent. Petroleum ether (40—60 ºC) was used for column chromatography. Reactions were monitored by thin layer chromatography using Merck F_{254} silca gel covered aluminium plates. Thin layer chromatography plates were viewed under UV-light and/or developed using either a potassium permanganate solution (3 g of $KMnO_4$, 20 g of K_2CO_3, 5 mL 5% NaOH aq. and 300 mL H_2O) or an acidic ethanolic anisaldehyde solution (15 g anisaldehyde, 250 mL ethanol, 2.5 mL conc. H_2SO_4).

Nomenclature

The numbering which appears on the structures corresponds to the assignments of NMR spectra.

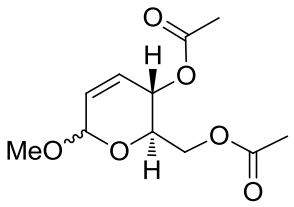
Reagents

Liquid reagents were distilled prior to use if necessary. All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated.

General reaction conditions

Air and/or moisture sensitive reactions were performed in glassware that was flame dried prior to use, under an atmosphere of argon. Organic solvents were dried using a Pure Solv™ purification system.

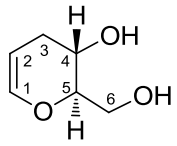
[(2*R*,3*S*)-3-Acetoxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl]methylacetate (232)



$C_{11}H_{18}O_6$
Molecular weight: 244.24 g.mol^{-1}

Boron trifluoride diethyl etherate (5.00 mL, 40.4 mmol) and anhydrous MeOH (4.10 mL, 101 mmol) were added to a solution of **208** (25.0 g, 91.8 mmol) in anhydrous CH_2Cl_2 (120 mL). The reaction mixture was stirred for 3 h at rt, then the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (175 mL). The solution was diluted with H_2O:CH_2Cl_2 (1:1, 400 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residual crude product was filtered through a short pad of silica gel (petroleum ether—Et_2O, 1:1) to afford **232** (18.4 g) as a pale yellow oil that was used without further purification.

(2*R*,3*S*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-pyran-3-ol (233)[156]

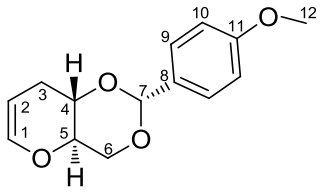


$C_6H_{10}O_3$
Molecular weight: 130.14 g.mol^{-1}

A solution of crude acetal **232** [56.3 mmol] in anhydrous dioxane (100 mL) was added dropwise to a suspension of lithium aluminium hydride (4.27 g, 113 mmol) in anhydrous dioxane (300 ml) at reflux. The reaction mixture was stirred for 1 h at reflux, then cooled to rt and diluted with Et_2O (175 mL). The solution was cooled to 0 ºC, then the reaction was quenched by the addition of H_2O (10 mL), 6 M NaOH (10 mL) and H_2O (20 mL). The reaction mixture was warmed to rt and $MgSO_4$ (*ca* 15 g) was added. After 45 min, the solution was filtered through a pad of Celite and the pad washed with Et_2O (4 x 150 mL). The resulting filtrate was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—EtOAc, 3:5) to afford diol **233** (5.96 g, 81% yield over two steps) as a colourless oil.

R_f = 0.48 (EtOAc);
$[\alpha]_D$ (26.7 ºC, $CHCl_3$) = +89.9 (*c* = 1.05);
{Lit.[157] $[\alpha]_D$ (26 ºC, $CHCl_3$) = +80.4 (*c* = 1.10)};
IR: ν_{max} 3351, 2924, 1652, 1444, 1234, 1133, 1063 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.32 (1H, ddd, *J* = 5.9, 1.9, 1.9 Hz, CH–C1), 4.67 (1H, ddd, *J* = 5.9, 5.2, 2.6 Hz, CH–C2), 3.98 (1H, dddd, *J* = 8.6, 8.6, 5.6, 5.6 Hz, CH–C4), 3.94—3.84 (2H, m, CH_2–C6), 3.67 (1H, ddd, *J* = 8.6, 4.1, 4.1 Hz, CH–C5), 2.83 (1H, d, *J* = 5.6 Hz, OH), 2.47 (1H, dd, *J* = 7.0, 5.7 Hz, OH), 2.38—2.29 (1H, m, CH_2-C3), 2.06 (1H, dddd, *J* = 16.5, 8.6, 2.6, 2.6 Hz, CH_2–C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 142.9 (CH–C1), 98.5 (CH–C2), 78.7 (CH–C5), 64.6 (CH–C4), 62.4 (CH_2–C6), 29.3 (CH_2–C3);
HRMS: (EI^+) for $C_6H_{10}O_3$ ($[M]^+$) calculated 130.0630, found 130.0627, Δ −2.5 ppm.

(4a*R*,8a*R*)-2-(4-Methoxyphenyl)-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3] dioxine (241)

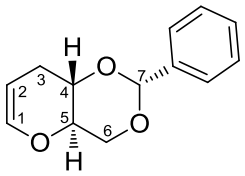


$C_{14}H_{16}O_4$
Molecular weight: 248.27 g.mol^{-1}

Pyridinium *p*-toluenesulfonate (116 mg, 0.460 mmol) was added to an ice-cooled solution of **233** (300 mg, 2.31 mmol) and *p*-anisaldehyde dimethylacetal (0.60 mL, 3.5 mmol) in anhydrous acetonitrile (5 mL). The reaction mixture was stirred for 30 min at 0 °C, then warmed to rt and stirred overnight. The solution was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous solution of NH_4Cl (10 mL). The two phases were separated and the organic phase was dried ($MgSO_4$) then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 98:2) afforded enol ether **241** (339 mg, 59% yield) as a colourless solid.

R_f = 0.72 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (24.7 °C, $CHCl_3$) = +56.6 (*c* = 1.16);
{Lit.[118a] $[\alpha]_D$ (25 °C, CH_2Cl_2) = +40.9 (*c* = 0.2)};
m.p. = 104—106 °C;
IR: ν_{max} 2980, 2872, 1641, 1614, 1587, 1518, 1372, 1247, 1174, 1034, 1014 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 7.46—7.41 (2H, m, CH-C10), 6.92—6.88 (2H, m, CH-C9), 6.33 (1H, ddd, *J* = 5.8, 2.2, 1.6 Hz, CH-C1), 5.59 (1H, s, CH-C7), 4.74 (1H, ddd, *J* = 5.8, 5.8, 2.2 Hz, CH-C2), 4.42—4.34 (1H, m, CH-C5), 3.96—3.89 (1H, m, CH-C4), 3.82—3.76 (5H, m, CH_3-C12 and CH_2-C6), 2.35 (1H, dddd, *J* = 16.2, 5.8, 5.8, 1.9 Hz CH_2-C3), 2.25 (1H, dddd, *J* = 16.2, 9.7, 2.2, 2.2 Hz, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 160.3 (C-C11), 143.2 (CH-C1), 130.1 (C-C8), 127.6 (2 x CH-C10), 113.9 (2 x CH-C9), 101.8 (CH-C7), 98.8 (CH-C2), 75.2 (CH-C4), 70.1 (CH-C5), 69.0 (CH_2-C6), 55.5 (CH_3-C12), 26.5 (CH_2-C3);
HRMS: (EI$^+$) for $C_{14}H_{16}O_4$ ([M]$^+$) calculated 248.1049, found 248.1046, Δ −1.2 ppm.

(4a*R*,8a*S*)-2-Phenyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3]dioxine (240)[118b]

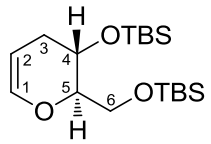


$C_{13}H_{14}O_3$
Molecular weight: 218.25 g.mol^{-1}

Camphorsulfonic acid (23.3 mg, 0.100 mmol) was added to a solution of **233** (250 mg, 1.92 mmol) and benzaldehyde dimethylacetal (0.15 mL, 1.0 mmol) in anhydrous DMF (5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The solution was neutralised with solid $NaHCO_3$ (until gas evolution ceased), diluted with EtOAc (15 mL) and washed with brine (15 mL). The two phases were separated and the organic phase was dried ($MgSO_4$) then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded **240** (224 mg, 54% yield) as a colourless solid.

R_f = 0.80 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (25.4 °C, $CHCl_3$) = +29.6 (*c* = 0.93);
m.p. = 107—109 °C;
IR: ν_{max} 3063, 2986, 2876, 1640, 1380, 1236, 1130, 1084, 1072, 1003 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 7.54—7.49 (2H, m, CH-Ar), 7.42—7.34 (3H, m, CH-Ar), 6.34 (1H, d, *J* = 5.9 Hz, CH-C1), 5.63 (1H, s, CH-C7), 4.75 (1H, ddd, *J* = 5.9, 5.9, 2.2 Hz, CH-C2), 4.45—4.36 (1H, m, CH-C5), 3.95 (1H, dddd, *J* = 15.8, 7.3, 1.6, 1.6 Hz, CH-C4), 3.85—3.75 (2H, m, CH_2-C6), 2.41—2.32 (1H, m, CH_2-C3), 2.32—2.22 (1H, m, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 143.2 (CH-C1), 137.6 (C-Ar), 129.2 (2 x CH-Ar), 128.5 (2 x CH-Ar), 126.3 (CH-Ar), 101.9 (CH-C7), 98.8 (CH-C2), 75.2 (CH-C4), 70.1 (CH-C5), 69.1 (CH_2-C6), 26.5 (CH_2-C3);
HRMS: (EI$^+$) for $C_{13}H_{14}O_3$ ([M]$^+$) calculated 218.0943, found 218.0947, Δ +2.1 ppm.

***tert*-Butyl{[(2*R*,3*S*)-3-[(*tert*-butyldimethylsilyl)oxy]-3,4-dihydro-2*H*-pyran-2-yl]methoxy}dimethylsilane (234)**[114]

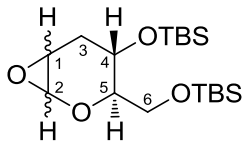


$C_{18}H_{38}O_3Si_2$
Molecular weight: 358.66 g.mol^{-1}

TBSCl (1.84 g, 12.2 mmol) and imidazole (1.30 g, 19.0 mmol) were added to a solution of **233** (500 mg, 3.80 mmol) in anhydrous DMF (15 mL) at 0 °C. The reaction mixture was warmed to rt, stirred overnight then diluted with Et_2O (30 mL). The organic phase was washed with H_2O (5 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 99:1) afforded enol ether **234** (1.09 g, 80% yield) as a colourless oil.

R_f = 0.73 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (26.1 °C, $CHCl_3$) = +76.3 (*c* = 1.09);
{Lit.[116] $[\alpha]_D$ (22.6 °C, $CHCl_3$) = +75.3 (*c* = 1.02)};
IR: ν_{max} 2955, 2929, 2858, 1657, 1473, 1254, 1240, 1106, 1089, 1051 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.32 (1H, d, *J* = 5.8 Hz, CH-C1), 4.57 (1H, ddd, *J* = 5.8, 5.8, 2.4 Hz, CH-C2), 3.94—3.88 (2H, m, CH-C4 and CH_2-C6), 3.84 (1H, dd, *J* = 11.3, 4.8 Hz, CH_2-C6), 3.56 (1H, ddd, *J* = 8.6, 4.8, 2.4 Hz, CH-C5), 2.26—2.20 (1H, m, CH_2-C3), 2.03 (1H, ddd, *J* = 16.4, 8.8, 2.4, 2.4 Hz, CH_2-C3), 0.90 (9H, s, CH_3-*t*Bu), 0.89 (9H, s, CH_3-*t*Bu), 0.09 (3H, s, CH_3-Me), 0.08 (3H, s, CH_3-Me), 0.07 (6H, s, CH_3-Me);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 143.4 (CH-C1), 97.6 (CH-C2), 80.0 (CH-C5), 64.4 (CH-C4), 62.7 (CH_2-C6), 30.6 (CH_2-C3), 26.2 (CH_3-*t*Bu), 25.9 (CH_3-*t*Bu), 18.7 (C-*t*Bu), 18.1 (C-*t*Bu), −4.1 (CH_3-Me), −4.8 (CH_3-Me), −4.9 (CH_3-Me), −5.1 (CH_3-Me);
HRMS: (ESI) for $C_{18}H_{38}NaO_3Si_2$ ($[M+Na]^+$) calculated 381.2257, found 381.2252, Δ +2.8 ppm.

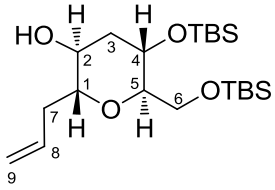
***tert*-Butyl{[(3*R*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2,7-dioxabicyclo[4.1.0] heptan-3-yl]methoxy}dimethylsilane (235)**



$C_{18}H_{38}O_4Si_2$
Molecular weight: 374.66 g.mol^{-1}

A freshly distilled solution of dimethyl dioxirane (28.0 mL of a 0.09 M solution in acetone, 2.42 mmol) was added to a solution of **234** (668 mg, 1.86 mmol) in CH_2Cl_2 (25 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. The organic phase was then washed with a saturated aqueous solution of $NaHCO_3$ (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure at 4 °C to afford a diastereomeric mixture of epoxides **235** (687 mg, dr 4:1) as a colourless oil. Epoxides **235** were then used directly without further purification.

(2*R*,3*S*,5*S*,6*R*)-2-Allyl-5-[(*tert*-butyldimethylsilyl)oxy]-6-{[(*tert*-butyldimethyl silyl)oxy]methyl}tetrahydro-2*H*-pyran-3-ol (236)



$C_{21}H_{44}O_4Si_2$
Molecular weight: 416.74 g.mol^{-1}

Allylmagnesium bromide (5.31 mL of a 0.7 M solution in Et_2O, 3.72 mmol) was added to a solution of crude epoxide **235** [1.86 mmol] in anhydrous THF (35 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, then the reaction was quenched with a saturated aqueous solution of NH_4Cl (40 mL). The two phases were separated and the aqueous phase extracted with Et_2O (3 x 40 mL). The organic extracts were combined, washed with brine (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded alcohol **236** (488 mg, 64% yield, dr > 20:1) as a colourless solid.

R_f = 0.39 (petroleum ether—Et_2O, 1:1);

$[\alpha]_D$ (24.4 °C, $CHCl_3$) = +18.7 (*c* = 0.95);

m.p. = 41—43 °C;

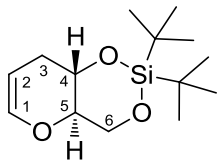
IR: ν_{max} 3307, 2929, 2856, 1473, 1462, 1250, 1165, 1142, 1096, 1032, 1018 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.88 (1H, dddd, *J* = 17.1, 10.2, 7.4, 7.4 Hz, CH-C8), 5.20—5.16 (1H, m, CH_2-C9), 5.16—5.10 (1H, m, CH_2-C9), 3.84—3.77 (2H, m, CH-C4 and CH_2-C6), 3.72 (1H, dd, *J* = 11.0, 4.8 Hz, CH_2-C6), 3.58 (1H, dd, *J* = 11.1, 1.7 Hz, CH-C2), 3.30—3.22 (2H, m, CH-C1 and CH-C5), 2.56 (1H, s, OH), 2.29 (2H, d, *J* = 7.4 Hz, CH_2-C7), 2.01 (1H, ddd, *J* = 12.7, 4.3, 1.7 Hz, CH_2-C3), 1.57 (1H, dd, *J* = 12.7, 8.7 Hz, CH_2-C3), 0.89 (9H, s, CH_3-*t*Bu), 0.88 (9H, s, CH_3-*t*Bu), 0.07 (6H, s, CH_3-Me), 0.06 (3H, s, CH_3-Me), 0.05 (3H, s, CH_3-Me);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 133.0 (CH-C8), 119.3 (CH_2-C9), 81.8 (CH-C5), 73.6 (CH-C1), 69.9 (CH-C2), 65.4 (CH-C4), 62.5 (CH_2-C6), 42.2 (CH_2-C7), 42.1 (CH_2-C3), 26.1 (3 x CH_3-*t*Bu), 25.9 (3 x CH_3-*t*Bu), 18.5 (C-*t*Bu), 18.0 (C-*t*Bu), −4.4 (CH_3-Me), −4.8 (CH_3-Me), −5.1 (CH_3-Me), −5.2 (CH_3-Me);

HRMS: (CI, isobutane) for $C_{21}H_{45}O_4Si_2$ ($[M+H]^+$) calculated 417.2856, found 417.2852, Δ −0.9 ppm.

(4a*R*,8a*S*)-2,2-Di-*tert*-butyl-4,4a,8,8a-tetrahydropyrano[3,2-*d*][1,3,2] dioxasiline (231)[116]

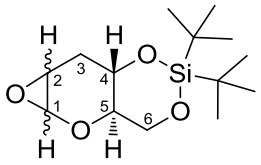


$C_{14}H_{26}O_3Si$
Molecular weight: 270.44 g.mol^{-1}

Di-*tert*-butylsilyl-bis(trifluoromethanesulfonate) (12.7 mL, 39.1 mmol) was added dropwise to a solution of diol **233** (5.03 g, 38.7 mmol) in anhydrous DMF (102 mL) at −45 °C. The reaction mixture was stirred for 1 h at −45 °C, then the reaction was quenched with pyridine (4.30 mL, 53.2 mmol). The solution was warmed to rt and diluted with Et_2O (125 mL). The organic phase was washed with H_2O (5 x 150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 99:1) afforded enol ether **231** (9.82 g, 94% yield) as a colourless solid.

R_f = 0.91 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (29.8 °C, $CHCl_3$) = +39.3 (*c* = 1.03);
{Lit.[157] $[\alpha]_D$ (25 °C, $CHCl_3$) = +37.9 (*c* = 1.10)};
m.p. = 38—40 °C;
IR: ν_{max} 2933, 2860, 1653, 1473, 1387, 1239, 1129, 1078 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.26 (1H, ddd, *J* = 5.9, 2.2, 1.4 Hz, CH-C1), 4.69 (1H, ddd, *J* = 5.9, 5.9, 2.2 Hz, CH-C2), 4.18 (1H, dd, *J* = 10.4, 4.8 Hz, CH_2-C6), 4.11 (1H, ddd, *J* = 9.6, 9.6, 5.9 Hz, CH-C4), 3.92 (1H, dd, *J* = 10.4, 10.4 Hz, CH_2-C6), 3.71—3.65 (1H, m, CH-C5), 2.38 (1H, dddd, *J* = 16.5, 5.9, 5.9, 1.4 Hz, CH_2-C3), 2.07 (1H, dddd, *J* = 16.5, 9.6, 2.2, 2.2 Hz, CH_2-C3), 1.06 (9H, s, CH_3-*t*Bu), 0.99 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 142.7 (CH-C1), 99.0 (CH-C2), 74.1 (CH-C5), 71.5 (CH-C4), 66.5 (CH_2-C6), 30.3 (CH_2-C3), 27.6 (3 x CH_3-*t*Bu), 27.1 (3 x CH_3-*t*Bu), 22.9 (C-*t*Bu), 20.0 (C-*t*Bu);
HRMS: (EI$^+$) for $C_{14}H_{26}O_3Si$ ([M]$^+$) calculated 270.1651, found 270.1650, Δ −0.3 ppm.

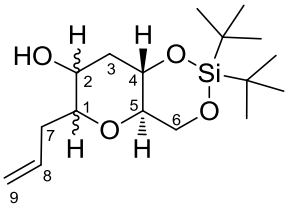
(4a*R*,7a*S*)-2,2-Di-*tert*-butylhexahydrooxireno[2',3':5,6]pyrano[3,2-*d*][1,3,2] dioxasiline (246)



$C_{14}H_{26}O_4Si$
Molecular weight: 286.44 g.mol^{-1}

A freshly distilled solution of dimethyl dioxirane (160 mL of a 0.1 M solution in acetone, 16.0 mmol) was added to a solution of enol ether **231** (3.32 g, 12.3 mmol) in anhydrous CH_2Cl_2 (160 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. The solution was dried ($MgSO_4$) and concentrated under reduced pressure at 4 °C to afford a diastereomeric mixture of epoxides **246** (3.52 g, dr 1.2:1) as a colourless solid. Epoxides **246** were then used without further purification.

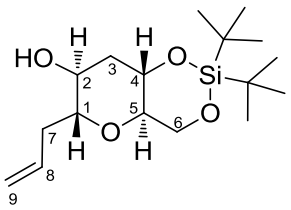
(4a*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (248)



$C_{17}H_{32}O_4Si$
Molecular weight: 328.52 g.mol^{-1}

Allylmagnesium chloride (14.5 mL of a 1.7 M solution in Et_2O, 24.6 mmol) was added to a solution of epoxides **246** [12.3 mmol] in anhydrous THF (250 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (200 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 150 mL). The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford alcohols **248** as a mixture of diastereomers. The crude mixture was then used without further purification. (Purification was attempted on a small scale to separate the diastereomers. A small amount of the major diastereomer **247** was isolated and is characterised below.)

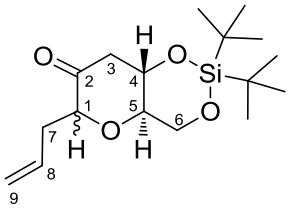
(4a*R*,6*R*,7*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2] dioxasilin-7-ol (247)



$C_{17}H_{32}O_4Si$
Molecular weight: 328.52 g.mol^{-1}

R_f = 0.52 (petroleum ether—Et_2O, 1:1);
IR: ν_{max} 3225, 2942, 2857, 1473, 1127, 1084, 1009 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.77 (1H, dddd, *J* = 17.3, 10.4, 7.0, 7.0 Hz, CH-C8), 5.17—5.08 (2H, m, CH_2-C9), 4.13 (1H, ddd, *J* = 11.3, 9.6, 4.9 Hz, CH-C4), 4.01 (1H, dd, *J* = 10.0, 4.9 Hz, CH_2-C6), 3.89 (1H, m, CH-C2), 3.83 (1H, dd, *J* = 10.0, 10.0 Hz, CH_2-C6), 3.82—3.77 (1H, m, CH-C1), 3.54 (1H, ddd, *J* = 10.0, 9.6, 4.9 Hz, CH-C5), 2.61—2.49 (1H, m, CH_2-C7), 2.30 (1H, ddd, *J* = 14.3, 7.0, 7.0 Hz, CH_2-C7), 2.24—2.17 (1H, m, CH_2-C3), 1.74 (1H, ddd, *J* = 13.7, 11.3, 2.9 Hz, CH_2-C3), 1.03 (9H, s, CH_3-*t*Bu), 0.99 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 133.8 (CH-C8), 117.8 (CH_2-C9), 78.4 (CH-C1), 70.1 (CH-C5), 69.9 (CH-C4), 69.2 (CH-C2), 67.5 (CH_2-C6), 35.5 (CH_2-C7), 34.2 (CH_2-C3), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.8 (C-*t*Bu), 20.1 (C-*t*Bu).

(4a*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butyltetrahydropyrano[3,2-*d*][1,3,2]dioxsilin-7(6*H*)-one (249)

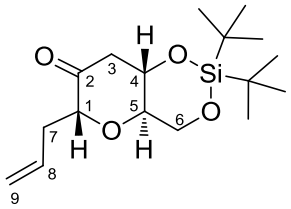


$C_{17}H_{30}O_4Si$
Molecular weight: 326.52 g.mol^{-1}

Sulfur trioxide pyridine complex (7.83 g, 49.2 mmol) and Et_3N (8.60 mL, 61.5 mmol) were added to a solution of alcohols **248** [12.3 mmol] in anhydrous CH_2Cl_2:DMSO (1:1, 136 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, then diluted with Et_2O (150 mL). The mixture was washed with a solution of 1 M HCl (125 mL), a saturated aqueous solution of $NaHCO_3$ (125 mL) and brine (125 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O,

19:1) afforded a diastereomeric mixture of ketones **249** (2.86 g, 71% yield over three steps, dr 2.3:1) as a colourless solid. Ketones **249** were taken on to the next step without further purification. (Purification was attempted on a small scale to separate the diastereomers. The undesired diastereomer **249a** was isolated and is characterised below.)

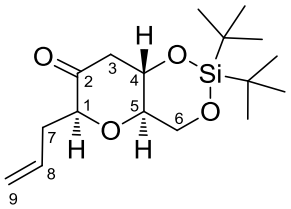
(4a*R*,6*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butyltetrahydropyrano[3,2-*d*][1,3,2] dioxasilin-7(6*H*)-one (249a)



$C_{17}H_{30}O_4Si$
Molecular weight: 326.52 g.mol^{-1}

R_f = 0.86 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (26.5 °C, $CHCl_3$) = +80.0 (*c* = 0.99);
m.p. = 73—75 °C;
IR: ν_{max} 2932, 2859, 1722, 1474, 1238, 1109, 1067, 1007 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.76 (1H, dddd, *J* = 16.9, 9.8, 7.0, 7.0 Hz, CH-C8), 5.18—5.15 (1H, m, CH_2-C9), 5.15—5.13 (1H, m, CH_2-C9), 4.17 (1H, dd, *J* = 10.2, 4.8 Hz, CH_2-C6), 4.15—4.12 (1H, m, CH-C4), 4.06 (1H, dd, *J* = 9.8, 5.5 Hz, CH-C1), 3.87 (1H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6), 3.76 (1H, ddd, *J* = 10.2, 9.7, 4.8 Hz, CH-C5), 2.97 (1H, dd, *J* = 16.4, 5.6 Hz, CH_2-C3), 2.65—2.57 (1H, m, CH_2-C7), 2.48 (1H, dd, *J* = 16.4, 11.1 Hz, CH_2-C3), 2.41 (1H, ddd, *J* = 13.4, 6.7, 5.5 Hz, CH_2-C7), 1.05 (9H, s, CH_3-*t*Bu), 1.01 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 207.1 (C-C2), 132.5 (CH-C8), 118.7 (CH_2-C9), 81.1 (CH-C1), 72.7 (CH-C4), 69.7 (CH-C5), 67.1 (CH_2-C6), 46.4 (CH_2-C3), 34.3 (CH_2-C7), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.8 (C-*t*Bu), 20.1 (C-*t*Bu);
HRMS: (CI, isobutane) for $C_{17}H_{31}O_4Si$ ($[M+H]^+$) calculated 327.1992, found 327.1996, Δ +1.2 ppm.

(4a*R*,6*S*,8a*S*)-6-Allyl-2,2-di-*tert*-butyltetrahydropyrano[3,2-*d*][1,3,2] dioxasilin-7(6*H*)-one (250)[120]

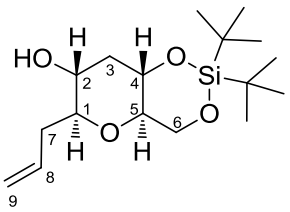


$C_{17}H_{30}O_4Si$
Molecular weight: 326.52 g.mol^{-1}

DBU (0.30 mL, 2.0 mmol) was added to a solution of ketones **249** (2.58 g, 7.90 mmol) in anhydrous toluene (92 mL) at rt. The reaction mixture was stirred for 24 h in the dark, then the reaction was quenched with a saturated aqueous solution of NH_4Cl (85 mL). The two phases were separated and the aqueous phase extracted with Et_2O (3 x 75 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 99:1) afforded the desired ketone **250** (1.55 g, 60% yield) as a colourless solid

R_f = 0.86 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (27.5 °C, $CHCl_3$) = −22.0 (*c* = 1.16);
{Lit.[116] $[\alpha]_D$ (24.5 °C, $CHCl_3$) = −24.1 (*c* = 1.07)};
m.p. = 83—85 °C;
IR: ν_{max} 2934, 2861, 1724, 1476, 1364, 1146, 1115, 1099 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.80 (1H, dddd, *J* = 17.1, 10.2, 7.0, 7.0 Hz, CH-C8), 5.11 (1H, dddd, *J* = 17.1, 1.7, 1.4, 1.4 Hz, CH_2-C9), 5.08—5.03 (1H, m, CH_2-C9), 4.26 (1H, dd, *J* = 10.3, 5.0 Hz, CH_2-C6), 4.12 (1H, ddd, *J* = 11.1, 9.4, 5.7 Hz, CH-C4), 3.90 (1H, dd, *J* = 10.3, 10.3 Hz, CH_2-C6), 3.85 (1H, dd, *J* = 7.6, 4.3 Hz, CH-C1), 3.61 (1H, ddd, *J* = 10.3, 9.4, 5.0 Hz, CH-C5), 3.01 (1H, dd, *J* = 15.7, 5.7 Hz, CH_2-C3), 2.65—2.58 (1H, m, CH_2-C7), 2.45 (1H, dd, *J* = 15.7, 11.1 Hz, CH_2-C3), 2.30 (1H, ddd, *J* = 14.6, 7.6, 7.0 Hz, CH_2-C7), 1.05 (9H, s, CH_3-*t*Bu), 1.01 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 204.8 (C-C2), 133.8 (CH-C8), 117.7 (CH_2-C9), 82.7 (CH-C1), 76.5 (CH-C5), 73.3 (CH-C4), 66.7 (CH_2-C6), 48.4 (CH_2-C3), 33.6 (CH_2-C7), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.8 (C-*t*Bu), 20.1 (C-*t*Bu);
HRMS: (CI, isobutane) for $C_{17}H_{31}O_4Si$ ($[M+H]^+$) calculated 327.1992, found 327.1993, Δ +0.4 ppm.

(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-ol (251)[120]

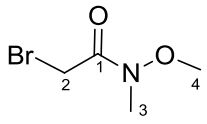


$C_{17}H_{32}O_4Si$
Molecular weight: 328.52 g.mol^{-1}

Sodium borohydride (984 mg, 26.0 mmol) was added to a solution of ketone **250** (2.12 g, 6.50 mmol) in anhydrous CH_2Cl_2:MeOH (1:1, 232 mL) at −78 ºC. The reaction mixture was stirred for 2 h at −78 ºC and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (150 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts were combined, washed with brine (175 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 17:1 to 7:3) afforded alcohol **251** (1.89 g, 88% yield) as a colourless solid.

R_f = 0.74 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (25.6 ºC, $CHCl_3$) = +25.1 (*c* = 1.02);
{Lit.[120] $[\alpha]_D$ (29 ºC, $CHCl_3$) = +27.3 (*c* = 1.00)};
m.p. = 65—67 ºC;
IR: ν_{max} 3382, 2835, 2861, 2362, 1474, 1360, 1092, 1033, 1010 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.90 (1H, dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, CH-C8), 5.13 (1H, dddd, *J* = 17.2, 1.8, 1.6, 1.6 Hz, CH_2-C9), 5.09—5.07 (1H, m, CH_2-C9), 4.13 (1H, dd, *J* = 10.2, 5.0 Hz, CH_2-C6), 3.79 (1H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6), 3.78—3.73 (1H, m, CH-C4), 3.50—3.44 (1H, m, CH-C2), 3.27 (1H, ddd, *J* = 10.2, 9.2, 5.0 Hz, CH-C5), 3.19 (1H, ddd, *J* = 9.5, 7.2, 4.0 Hz, CH-C1), 2.57—2.51 (1H, m, CH_2-C7), 2.46 (1H, ddd, *J* = 11.6, 5.0, 4.5 Hz, CH_2-C3), 2.27 (1H, ddd, *J* = 14.3, 7.2, 7.0 Hz, CH_2-C7), 1.55 (1H, d, *J* = 4.5 Hz, OH), 1.49 (1H, app q, *J* = 11.6 Hz, CH_2-C3), 1.04 (9H, s, CH_3-*t*Bu), 0.99 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 134.8 (CH-C8), 117.3 (CH_2-C9), 81.5 (CH-C1), 77.3 (CH-C5), 72.5 (CH-C4), 69.5 (CH-C2), 67.0 (CH_2-C6), 42.0 (CH_2-C3), 36.6 (CH_2-C7), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.8 (C-*t*Bu), 20.1 (C-*t*Bu);
HRMS: (CI, isobutane) for $C_{17}H_{33}O_4Si$ ($[M+H]^+$) calculated 329.2148, found 329.2154, Δ +1.7 ppm.

2-Bromo-*N*-methoxy-*N*-methylacetamide[158]

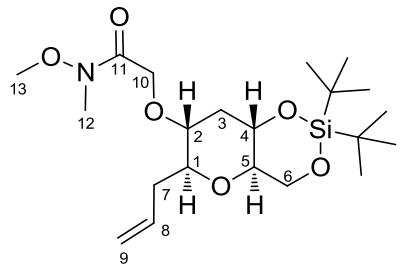


$C_4H_8BrNO_2$
Molecular weight: 182.02 g.mol^{-1}

An ice-cooled solution of K_2CO_3 (6.24 g, 45.0 mmol) in H_2O (25 mL) was added to a solution of *N*-methylhydroxylamine hydrochloride (2.00 g, 20.5 mmol) in Et_2O (25 mL) at 0 °C. Bromoacetyl bromide (2.14 mL, 24.6 mmol) was added dropwise and the reaction mixture stirred for 30 min at rt. The phases were separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The organic extracts were combined, washed with brine (75 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was distilled under reduced pressure (100 °C, 30 mbar) to afford 2-bromo-*N*-methoxy-*N*-methylacetamide (2.42 g, 65% yield) as a colourless oil.

R_f = 0.27 (petroleum ether—Et_2O, 1:1);
IR: ν_{max} 2977, 2942, 1668, 1462, 1431, 1386, 1180 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 3.99 (2H, s, CH_2–C2), 3.77 (3H, s, CH_3–C4), 3.22 (3H, s, CH_3–C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 167.8 (C–C1), 61.8 (CH_3–C4), 32.7 (CH_2–C2), 25.2 (CH_3–C3).

2-{[(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2] dioxasilin-7-yl]oxy}-*N*-methoxy-*N*-methylacetamide (271)



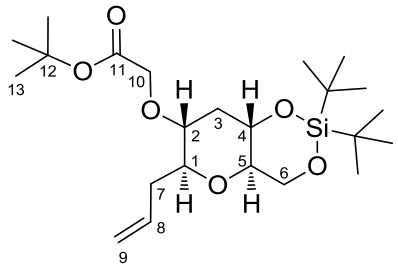
$C_{21}H_{39}NO_6Si$
Molecular weight: 429.62 g.mol^{-1}

KHMDS (0.69 mL of 0.5 M solution in THF, 0.35 mmol) was added to a solution of **230** (100 mg, 0.300 mmol) in anhydrous THF (1.5 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 5 min, then cooled to −78 °C. 2-Bromo-*N*-methoxy-*N*-methylacetamide (81.9 mg, 0.450 mmol) in anhydrous THF (1 mL)

was added dropwise and the reaction mixture stirred for 3 h at −78 °C, then overnight at rt. The reaction was quenched with a saturated aqueous solution of NH_4Cl (2 mL) then diluted with H_2O (5 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. NaOAc (66.0 mg, 0.800 mmol) was added to a solution of crude residue **271** [0.300 mmol] in DMSO (3 mL). The reaction mixture was stirred for 1.5 h at rt, then diluted with Et_2O (5 mL) and washed with H_2O (3 x 5 mL). The phases were separated and the organic phase was dried ($MgSO_4$) then concentrated under reduced pressure to afford amide **271** (43.0 mg, 32% yield) as a colourless oil and alcohol **230** (64.0 mg, 50% recovered starting material).

R_f = 0.44 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (27.1 °C, $CHCl_3$) = −49.5 (*c* = 1.00);
IR: ν_{max} 2934, 2860, 2363, 1692, 1473, 1092, 1033, 1000 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.87 (1H, dddd, *J* = 17.1, 10.2, 7.0, 7.0 Hz, CH-C8), 5.09 (1H, dddd, *J* = 17.1, 1.8, 1.5, 1.5 Hz, CH_2-C9), 5.05—5.01 (1H, m, CH_2-C9), 4.34 (1H, d, *J* = 15.5 Hz, CH_2-C10), 4.29 (1H, d, *J* = 15.5 Hz, CH_2-C10), 4.11 (1H, dd, *J* = 10.2, 4.9 Hz, CH_2-C6), 3.77 (1H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6), 3.74—3.69 (1H, m, CH-C4), 3.68 (3H, s, CH_3-C13), 3.36—3.31 (1H, m, CH-C5), 3.30—3.24 (2H, m, CH-C1, CH-C2), 3.18 (3H, s, CH_3-C12), 2.72—2.66 (1H, m, CH_2-C7), 2.64 (1H, ddd, *J* = 11.7, 4.4, 4.4 Hz, CH_2-C3), 2.23 (1H, ddd, *J* = 14.9, 7.0, 7.0 Hz, CH_2-C7), 1.49 (1H, ddd, *J* = 11.7, 11.4, 11.3 Hz, CH_2-C3), 1.02 (9H, s, CH_3-*t*Bu), 0.97 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 170.8 (C-C11), 135.1 (CH-C8), 116.9 (CH_2-C9), 80.3 (CH-C5), 77.2 (CH-C1), 76.9 (CH-C2), 72.6 (CH-C4), 67.0 (CH_2-C6), 66.2 (CH_2-C10), 61.6 (CH_3-C13), 38.2 (CH_2-C3), 36.1 (CH_2-C7), 32.4 (CH_3-C12), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.7 (C-*t*Bu), 20.1 (C-*t*Bu);
HRMS: (ESI) for $C_{21}H_{39}NNaO_6Si$ ($[M+Na]^+$) calculated 452.2444, found 452.2439, Δ −0.2 ppm.

***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-yl]oxy}acetate (269)**[157]



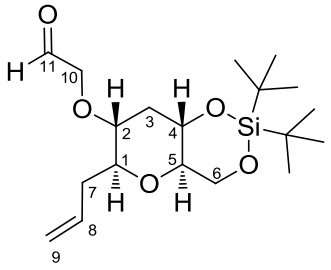
$C_{23}H_{42}O_6Si$
Molecular weight: 442.66 g.mol^{-1}

A 30% aqueous solution of NaOH (2 mL) was added to a solution of **230** (100 mg, 0.300 mmol) in toluene (2 mL) at 0 ºC. After 5 min, *tert*-butyl bromoacetate (0.09 mL, 0.6 mmol) and TBAI (55.0 mg, 0.150 mmol) were added and the reaction mixture stirred overnight at rt. The solution was diluted with toluene (5 mL) and H_2O (5 mL), then the two phases were separated and the aqueous phase extracted with toluene (3 x 10 mL). The organic extracts were combined, washed with 1 M HCl (10 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded ester **269** (109 mg, 82% yield) as a colourless oil.

R_f = 0.84 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (25.1 ºC, $CHCl_3$) = −31.0 (*c* = 1.49);
IR: ν_{max} 2933, 2860, 1751, 1474, 1368, 1225, 1090 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.88 (1H, dddd, *J* = 17.2, 10.2, 6.9, 6.9 Hz, CH-C8), 5.10 (1H, dddd, *J* = 17.2, 1.9, 1.5, 1.5 Hz, CH_2-C9), 5.06—5.02 (1H, m, CH_2-C9), 4.12 (1H, dd, *J* = 10.2, 4.9 Hz, CH_2-C6), 4.03 (1H, d, *J* = 16.1 Hz, CH_2-C10), 3.98 (1H, d, *J* = 16.1 Hz, CH_2-C10), 3.78 (1H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6), 3.71 (1H, ddd, *J* = 11.2, 9.2, 4.5 Hz, CH-C4), 3.33—3.25 (2H, m, CH-C1, CH-C5), 3.21 (1H, ddd, *J* = 10.9, 9.2, 4.5 Hz, CH-C2), 2.72—2.66 (1H, m, CH_2-C7), 2.60 (1H, ddd, *J* = 11.8, 4.5, 4.5 Hz, CH_2-C3), 2.22 (1H, ddd, *J* = 15.0, 7.6, 6.9 Hz, CH_2-C7), 1.48 (9H, s, CH_3-C13), 1.52—1.43 (1H, m, CH_2-C3), 1.03 (9H, s, CH_3-*t*Bu), 0.98 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 169.5 (C-C11), 135.1 (CH-C8), 116.9 (CH_2-C9), 81.9 (C-C12), 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-C10), 38.3 (CH_2-C3), 36.2 (CH_2-C7), 28.3 (3 x CH_3-C13), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.8 (C-*t*Bu), 20.1 (C-*t*Bu);

HRMS: (EI^+) for $C_{23}H_{42}O_6Si$ ($[M]^+$) calculated 442.2751, found 442.2738, Δ −2.9 ppm.

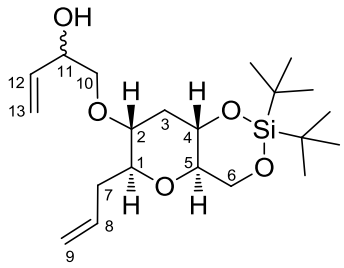
2-{[(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yl]oxy}acetaldehyde (270)



$C_{19}H_{34}O_5Si$
Molecular weight: 370.56 g.mol^{-1}

DIBAL (0.46 mL of a 1 M solution in CH_2Cl_2, 0.46 mmol) was added to a solution of **269** (99.7 mg, 0.230 mmol) in anhydrous CH_2Cl_2 (2 mL) at −78 °C. The reaction mixture was stirred for 3 h at −78 °C, then diluted with MeOH (4 mL) and 1 M HCl (4 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts were combined, washed with a 5% aqueous solution of $NaHCO_3$ (20 mL) and brine (20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude aldehyde **270** was then used without further purification.

1-{[(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yl]oxy}but-3-en-2-ol (267)



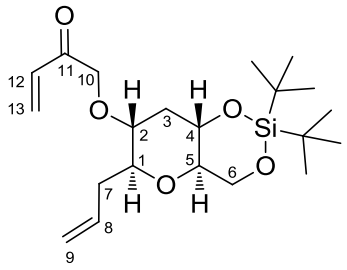
$C_{21}H_{38}O_5Si$
Molecular weight: 398.61 g.mol^{-1}

Vinylmagnesium bromide (0.46 mL of a 1 M solution in THF, 0.46 mmol) was added to a solution of crude aldehyde **270** [0.230 mmol] in anhydrous THF (5 mL) at 0 °C. The mixture was stirred for 45 min at 0 °C and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (7 mL). The phases

were separated and the aqueous phase extracted with Et_2O (3 x 15 mL). The organic extracts were combined, washed with brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 4:1) afforded an inseparable mixture of the diastereomeric alcohols **267** (80.0 mg, 87% over two steps, dr 1:1) as a colourless oil.

R_f = 0.76 (petroleum ether—Et_2O, 1:1);
IR: ν_{max} 3459, 2934, 2860, 1474, 1365, 1089, 1010 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.91—5.79 (4H, m, CH-C8/C8′ and CH-C12/12′), 5.36 (2H, ddd, *J* = 17.3, 3.5, 1.6 Hz, CH_2-C13/C13′), 5.21 (2H, d, *J* = 10.6 Hz, CH_2-C13/C13′), 5.12—5.03 (4H, m, CH_2-C9/C9′), 4.27 (2H, br s, CH-C11/C11′), 4.12 (2H, dd, *J* = 10.2, 4.9 Hz, CH_2-C6/C6′), 3.78 (2H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6/C6′), 3.72 (2H, dddd, *J* = 13.8, 9.3, 4.6, 2.5 Hz, CH-C4/C4′), 3.68 (1H, dd, *J* = 9.4, 3.5 Hz, CH_2-C10), 3.51 (1H, dd, *J* = 9.4, 7.5 Hz, CH_2-C10′), 3.44 (1H, dd, *J* = 9.4, 3.7 Hz, CH_2-C10′), 3.32—3.23 (5H, m, CH-C1/C1′ and CH-C5/C5′ and CH_2-C10), 3.18 (2H, dddd, *J* = 11.4, 9.2, 4.4, 2.5 Hz, CH-C2/C2′), 2.61 (2H, ddd, *J* = 12.0, 8.0, 4.4 Hz, CH_2-C3/C3′), 2.57—2.51 (2H, m, CH_2-C7/C7′), 2.32 (1H, d, *J* = 3.5 Hz, OH), 2.26 (1H, d, *J* = 3.7 Hz, OH), 2.25—2.19 (2H, m, CH_2-C7/C7′), 1.48—1.38 (2H, m, CH_2-C3/C3′), 1.03 (18H, s, CH_3-*t*Bu), 0.98 (18H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 136.7 and 136.6 (CH-C12/12′), 134.9 and 134.8 (CH-C8/C8′), 117.0 and 116.9 (CH_2-C9/C9′), 116.8 (CH_2-C13/C13′), 80.0 (CH-C1/C1′), 77.2 (CH-C5/C5′), 76.5 (CH-C2/C2′), 72.8 and 72.6 (CH_2-C10/C10′), 72.5 and 72.4 (CH-C4/C4′), 72.0 and 71.7 (CH-C11/C11′), 67.0 (CH_2-C6/C6′), 38.6 and 38.4 (CH_2-C3/C3′), 36.5 and 36.4 (CH_2-C7/C7′), 27.6 (6 x CH_3-*t*Bu), 27.2 (6 x CH_3-*t*Bu), 22.8 (2 x C-*t*Bu), 20.1 (2 x C-*t*Bu);
HRMS: (EI^+) for $C_{21}H_{38}O_5Si$ ($[M]^+$) calculated 398.2489, found 398.2489, Δ +0.2 ppm.

1-{[(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yl]oxy}but-3-en-2-one (229)



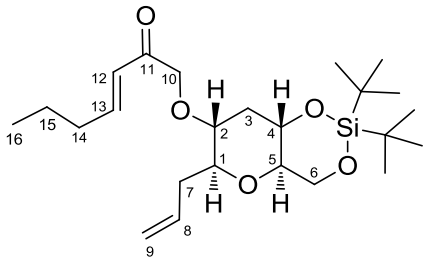
$C_{21}H_{36}O_5Si$
Molecular weight: 396.59 g.mol^{-1}

Dess-Martin periodinane (212 mg, 0.500 mmol) was added to a solution of the alcohols **267** (100 mg, 0.250 mmol) in CH_2Cl_2 (10 mL) at 0 ºC. The reaction mixture was stirred for 2 h at 0 ºC, then the reaction was quenched with a solution of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ (1:1, 20 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 15 mL). The organic extracts were combined, washed with brine (25 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 9:1) afforded enone **229** (90.6 mg, 92% yield) as a colourless solid.

R_f = 0.74 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (26.9 ºC, $CHCl_3$) = −51.4 (*c* = 0.96);
m.p. = 39—41 ºC;
IR: ν_{max} 2934, 2860, 1703, 1614, 1474, 1090 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.54 (1H, dd, *J* = 17.6, 10.7 Hz, CH-C12), 6.35 (1H, dd, *J* = 17.6, 1.2 Hz, CH_2-C13), 5.91—5.82 (2H, m, CH-C8 and CH_2-C13), 5.11—5.03 (2H, m, CH_2-C9), 4.35 (1H, d, *J* = 16.6 Hz, CH_2-C10), 4.24 (1H, d, *J* = 16.6 Hz, CH_2-10), 4.12 (1H, dd, *J* = 10.2, 5.0 Hz, CH_2-C6), 3.77 (1H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6), 3.71 (1H, ddd, *J* = 11.2, 9.2, 4.4 Hz, CH-C4), 3.37—3.33 (1H, m, CH-C1), 3.28 (1H, ddd, *J* = 10.2, 9.2, 5.0 Hz, CH-C5), 3.21 (1H, ddd, *J* = 11.0, 9.2, 4.5 Hz, CH-C2), 2.66—2.61 (1H, m, CH_2-C7), 2.61—2.56 (1H, m, CH_2-C3), 2.24 (1H, ddd, *J* = 14.9, 7.4, 7.4 Hz, CH_2-C7), 1.48 (1H, app q, *J* = 11.2 Hz, CH_2-C3), 1.02 (9H, s, CH_3-*t*Bu), 0.97 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 196.7 (C-C11), 134.7 (CH-C8), 132.5 (CH-C12), 129.5 (CH_2-C13), 117.1 (CH_2-C9), 80.0 (CH-C1), 77.2 (CH-C5), 77.0 (CH-C2), 73.0 (CH_2-C10), 72.5 (CH-C4), 67.0 (CH_2-C6), 38.2 (CH_2-C3), 36.2 (CH_2-C7), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.8 (C-*t*Bu), 20.1 (C-*t*Bu);

HRMS: (ESI) for $C_{21}H_{36}NaO_5Si$ ($[M+Na]^+$) calculated 419.2230, found 419.2224, Δ +3.3 ppm.

(*E*)-1-{[(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2] dioxasilin-7-yl]oxy}hept-3-en-2-one (272)



$C_{24}H_{42}O_5Si$
Molecular weight: 438.67 g.mol^{-1}

To a suspension of sodium hydride (146 mg of a 60% suspension in mineral oil, 6.08 mmol) in anhydrous THF (25 mL) at 0 °C was added a solution of **230** (500 mg, 1.52 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred at 0 °C for 10 min then warmed to rt before triphenylchloroacetonylphosphorane (642 mg, 1.82 mmol) and TBAI (28.0 mg, 0.0760 mmol) were added. The reaction mixture was heated to reflux and stirred for 3 h. The solution was cooled to rt, and the reaction was quenched with H_2O (10 mL) and concentrated under reduced pressure. The phases were separated and the aqueous phase extracted with EtOAc (4 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude phosphorane **262** was isolated as a yellow foam and used without further purification.

Butyraldehyde (1.40 mL, 15.2 mmol) was added to a solution of crude phosphorane **262** [1.52 mmol] in anhydrous CH_2Cl_2 (50 mL). The reaction mixture was heated to reflux and stirred overnight. Further butyraldehyde (1.40 mL, 15.2 mmol, 10 equiv.) was added and the reaction mixture stirred at reflux for 24 h. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) to afford enone **272** (573 mg, 86% yield over two steps) as a yellow oil.

R_f = 0.85 (petroleum ether—Et_2O, 1:1);

$[\alpha]_D$ (26.1 °C, $CHCl_3$) = −52.0 (*c* = 0.97);

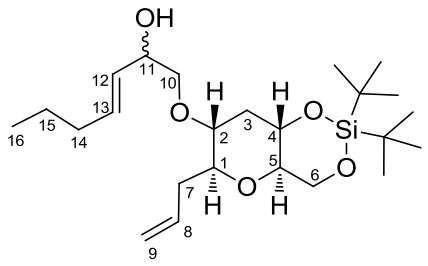
IR: ν_{max} 2961, 2933, 2860, 1696, 1625, 1473, 1089, 1055 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.97 (1H, ddd, *J* = 15.8, 7.0, 7.0 Hz, CH–C13), 6.28 (1H, ddd, *J* = 15.8, 1.5, 1.5 Hz, CH–C12), 5.87 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH–C8), 5.08 (1H, dddd, *J* = 17.1, 1.8, 1.6, 1.6 Hz, CH_2–C9), 5.06—5.03 (1H, m, CH_2–C9), 4.29 (1H, d, *J* = 16.3 Hz, CH_2–C10), 4.18 (1H, d, *J* = 16.3 Hz, CH_2–C10), 4.12 (1H, dd, *J* = 10.2, 4.9 Hz, CH_2–C6), 3.78 (1H, dd, *J* = 10.2, 10.2 Hz, CH_2–C6), 3.71 (1H, ddd, *J* = 11.2, 9.2, 4.5 Hz, CH–C4), 3.35 (1H, ddd, *J* = 9.2, 7.8, 3.1 Hz, CH–C1), 3.32—3.26 (1H, m, CH–C5), 3.21 (1H, ddd, *J* = 11.4, 9.2, 4.5 Hz, CH–C2), 2.67—2.61 (1H, m, CH_2–C7), 2.59 (1H, ddd, *J* = 11.4, 4.5, 4.5 Hz, CH_2-C3), 2.27—2.19 (3H, m, CH_2–C7 and CH_2–C14), 1.55—1.43 (3H, m, CH_2–C15 and CH_2–C3), 1.03 (9H, s, CH_3–*t*Bu), 0.98 (9H, s, CH_3–*t*Bu), 0.95 (3H, t, *J* = 7.4 Hz, CH_3–C16);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 196.6 (C–C11), 149.0 (CH–C13), 134.8 (CH–C8), 126.2 (CH–C12), 117.1 (CH_2–C9), 80.1 (CH–C2), 77.2 (CH–C5), 76.9 (CH–C1), 73.1 (CH_2–C10), 72.5 (CH–C4), 67.0 (CH_2–C6), 38.2 (CH_2–C3), 36.2 (CH_2–C7), 34.8 (CH_2-C14), 27.6 (3 x CH_3–*t*Bu), 27.2 (3 x CH_3–*t*Bu), 22.8 (C–*t*Bu), 21.4 (CH_2–C15), 20.1 (C–*t*Bu), 13.9 (CH_3–C16);

HRMS: (EI^+) for $C_{24}H_{42}O_5Si$ ($[M]^+$) calculated 438.2802, found 438.2805, Δ +0.8 ppm.

(*E*)-1-{[(4a*R*,6*S*,7*R*,8a*S*)-6-Allyl-2,2-di-*tert*-butylhexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yl]oxy}hept-3-en-2-ol (273)



$C_{24}H_{44}O_5Si$
Molecular weight: 440.69 g.mol^{-1}

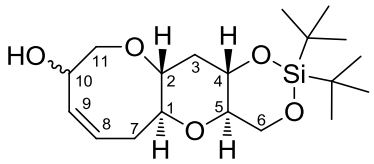
Cerium trichloride heptahydrate (484 mg, 1.30 mmol) and sodium borohydride (60.0 mg, 1.56 mmol) were added to a solution of enone **272** (570 mg, 1.30 mmol) in MeOH (70 mL) at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C, then the reaction was quenched with a saturated aqueous solution of NH_4Cl (75 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The organic extracts were combined, washed with brine (125 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford an inseparable mixture of the diastereomeric alcohols **273** (533 mg, 93% yield, dr 1:1) as a colourless oil.

R_f = 0.76 (petroleum ether—Et_2O, 1:1);
IR: ν_{max} 3457, 2934, 2861, 2364, 1474, 1365, 1092, 1012 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.91—5.81 (2H, m, CH-C8/C8′), 5.81—5.73 (2H, m, CH-13/C13′), 5.43 (1H, ddd, *J* = 6.7, 2.7, 1.3 Hz, CH-C12), 5.40 (1H, ddd, *J* = 6.7, 2.7, 1.3 Hz, CH-C12′), 5.11—5.03 (4H, m, CH_2-C9/C9′), 4.26—4.19 (2H, m, CH-C11/C11′), 4.12 (2H, dd, *J* = 10.2, 4.9 Hz, CH_2-C6/C6′), 3.78 (2H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6/C6′), 3.75—3.69 (2H, m, CH-C4/C4′), 3.63 (1H, dd, *J* = 9.4, 3.0 Hz, CH_2-C10), 3.51—3.46 (1H, m, CH_2-C10′), 3.39 (1H, dd, *J* = 9.4, 3.2 Hz, CH_2 C10′), 3.28 (4H, m, CH-C5/C5′ and CH-C1/C1′), 3.23 (1H, dd, *J* = 9.4, 8.2 Hz, CH_2-C10), 3.21—3.14 (2H, m, CH_2-C2/C2′), 2.61 (2H, app dq, *J* = 11.8, 4.6 Hz, CH_2-C3/C3′), 2.54 (2H, m, CH_2-C7/C7′), 2.29 (1H, d, *J* = 3.0 Hz, OH), 2.27—2.22 (2H, m, CH_2-C7/C7′), 2.21 (1H, d, *J* = 3.2 Hz, OH), 2.02 (4H, dd, *J* = 14.5, 7.3 Hz, CH_2-C14/C14′), 1.48—1.36 (6H, m, CH_2-C3/C3′ and CH_2-C15/C15′), 1.03 (18H, s, CH_3-*t*Bu), 0.98 (18H, s, CH_3-*t*Bu), 0.90 (6H, 2 x t, *J* = 7.4 Hz and *J* = 7.4 Hz, CH_3-C16/C16′);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 134.9 and 134.8 (CH-C8/C8′), 134.2 and 134.1 (CH-C13/C13′), 128.3 and 128.2 (CH-C12/C12′), 117.0 and 116.9 (CH_2-C9/C9′),

80.1 and 80.0 (CH-C5/C5′), 77.3 (2 x CH-C1/C1′), 76.5 (2 x CH-C2/C2′), 73.3 and 73.0 (CH-C10/C10′), 72.6 and 72.5 (CH-C4/C4′), 71.9 and 71.5 (CH-C11/C11′), 67.0 (CH_2-C6/C6′), 38.7 and 38.4 (CH_2-C3/C3′), 36.5 and 34.6 (CH_2-C7/C7′), 27.6 (6 x CH_3-*t*Bu), 27.2 (6 x CH_3-*t*Bu), 22.8 (2 x C-*t*Bu), 22.3 (CH_2-C15/C15′), 20.1 (2 x C-*t*Bu), 13.8 (2 x CH_3-C16/16′);

HRMS: (EI^+) for $C_{24}H_{44}O_5Si$ ($[M]^+$) calculated 440.2958, found 440.2960, Δ +0.4 ppm.

(4a*R*,5a*S*,11a*R*,12a*S*,*Z*)-2,2-Di-*tert*-butyl-4a,5a,6,9,10,11a,12,12a-octahydro-4*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*b*]oxocin-9-ol (268)



$C_{19}H_{34}O_5Si$
Molecular weight: 370.56 g.mol^{-1}

Hoveyda-Grubbs second generation catalyst **150** (21.0 mg, 0.0340 mmol) was added to a solution of **273** (299 mg, 0.680 mmol) in degassed anhydrous CH_2Cl_2 (680 mL). The reaction mixture was heated to reflux and stirred overnight. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—Et_2O, 4:1) to afford an inseparable mixture of the diastereomeric alcohols **268** (240 mg, 96% yield, dr 1:1) as a colourless oil.

R_f = 0.41 (petroleum ether—Et_2O, 1:1);

IR: ν_{max} 3318, 2932, 2859, 1474, 1366, 1101, 1061, 1042 cm^{-1};

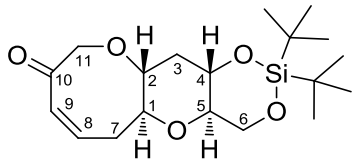
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.86—5.75 (2H, m, CH-C8 and CH-C9′), 5.71—5.64 (1H, m, CH-C8′), 5.59 (1H, ddd, *J* = 10.7, 7.2, 1.3 Hz, CH-C9), 4.71—4.63 (1H, m, CH-C10), 4.58—4.52 (1H, m, CH-C10′), 4.13—4.08 (2H, m, CH_2-C6/C6′), 3.87 (1H, dd, *J* = 11.6, 3.8 Hz, CH_2-C11′), 3.74 (2H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6/C6′), 3.69—3.63 (3H, m, CH_2-C11 and CH-C4/C4′), 3.42—3.34 (3H, m, CH_2-C11′ and CH-C1′ and CH-C2′), 3.31—3.11 (5H, m, CH_2-C11 and CH-C5/C5′ and CH-C1 and CH-C2), 2.70—2.63 (1H, m, CH_2-C7′), 2.45 (1H, ddd, *J* = 13.2, 8.7, 2.8 Hz, CH_2-C7), 2.39 (1H, app dt, *J* = 11.5, 4.3 Hz, CH_2-C3 or C3′), 2.36—2.29 (2H, m,

CH_2-C3 or 3′ and CH_2-C7′), 2.25—2.17 (1H, m, CH_2-C7), 1.58—1.46 (2H, m, CH_2-C3/C3′), 1.02 (18H, s, CH_3-*t*Bu), 0.97 (18H, s, CH_3-*t*Bu);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 137.4 and 134.1 (CH-C9/C9′), 126.6 and 126.4 (CH-C8/C8′), 83.0 (CH-C2 or CH-C1), 79.7 and 79.4 (CH-C1′ and CH-C2′), 78.0 and 77.3 (CH-C5/C5′), 76.2 (CH-C2 or CH-1), 75.4 (CH_2-C11), 73.0 and 72.5 (CH-C4/C4′), 71.5 (CH_2-C11), 69.4 (CH-C10′), 67.6 (CH-C10), 67.1 and 67.0 (CH_2-C6/C6′), 41.0 and 40.0 (CH_2-C3/C3′), 33.4 (CH_2-C7′), 30.4 (CH_2-C7), 27.6 (6 x CH_3-*t*Bu), 27.2 (6 x CH_3-*t*Bu), 22.8 (2 x C-*t*Bu), 20.1 (2 x C-*t*Bu);

HRMS: (EI^+) for $C_{19}H_{34}O_5Si$ ($[M]^+$) calculated 370.2176, found 370.2177, Δ +0.5 ppm.

(4a*R*,5a*S*,11a*R*,12a*S*,*Z*)-2,2-Di-*tert*-butyl-5a,6,10,11a,12,12a-hexahydro-4*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*b*]oxocin-9(4a*H*)-one (228)

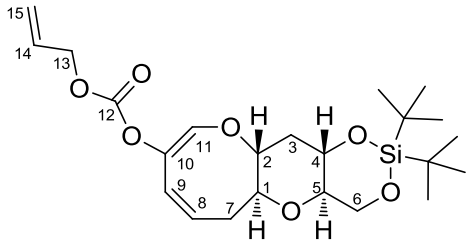


$C_{19}H_{32}O_5Si$
Molecular weight: 368.54 g.mol^{-1}

Dess-Martin periodinane (687 mg, 1.62 mmol) was added to a solution of alcohols **268** (300 mg, 0.810 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, then the reaction was quenched with a solution of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ (1:1, 50 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 4:1) afforded the desired enone **228** (231 mg, 78% yield) as a colourless solid.

R_f = 0.63 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (25.3 °C, $CHCl_3$) = −97.8 (*c* = 1.10);
m.p. = 161—163 °C;
IR: ν_{max} 2957, 2933, 2860, 2364, 1672, 1666, 1473, 1095, 1036 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.43 (1H, ddd, *J* = 12.4, 8.9, 7.6 Hz, CH-C8), 5.86 (1H, d, *J* = 12.4 Hz, CH-C9), 4.52 (1H, dd, *J* = 17.8, 0.9 Hz, CH_2-C11), 4.20 (1H, d, *J* = 17.8 Hz, CH_2-C11), 4.13 (1H, dd, *J* = 10.3, 5.0 Hz, CH_2-C6), 3.81 (1H, ddd, *J* = 11.2, 9.2, 4.3 Hz, CH-C4), 3.78 (1H, dd, *J* = 10.3, 10.3 Hz, CH_2-C6), 3.43 (1H, ddd, *J* = 11.6, 9.1, 4.3 Hz, CH-C2), 3.35—3.26 (2H, m, CH-C1 and CH-C5), 2.69—2.60 (1H, m, CH_2-C7), 2.52 (1H, ddd, *J* = 15.0, 8.9, 0.9 Hz, CH_2-C7), 2.43 (1H, ddd, *J* = 11.8, 4.3, 4.3 Hz, CH_2-C3), 1.68 (1H, ddd, *J* = 11.8, 11.6, 11.2 Hz, CH_2-C3), 1.04 (9H, s, CH_3-*t*Bu), 0.99 (9H, s, CH_3-*t*Bu);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 203.6 (C-C10), 137.7 (CH-C8), 129.1 (CH-C9), 84.8 (CH-C2), 78.6 (CH_2-C11), 77.7 (CH-C5), 77.4 (CH-C1), 72.7 (CH-C4), 66.8 (CH_2-C6), 39.6 (CH_2-C3), 34.8 (CH_2-C7), 27.5 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.7 (C-*t*Bu), 20.1 (C-*t*Bu);
HRMS: (EI^+) for $C_{19}H_{32}O_5Si$ ($[M]^+$) calculated 368.2019, found 368.2015, Δ −1.2 ppm.

Allyl[(4a*R*,5a*S*,7*Z*,9*E*,11a*R*,12a*S*)-2,2-di-*tert*-butyl-4a,5a,6,11a,12,12a-hexahydro-4*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*b*]oxocin-9-yl] carbonate (283)



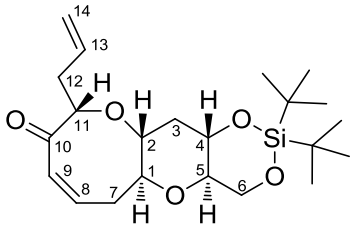
$C_{23}H_{36}O_7Si$
Molecular weight: 452.61 g.mol^{-1}

Allylchloroformate (25 µL, 0.25 mmol) was added to a solution of enone **228** (78.0 mg, 0.210 mmol) in anhydrous THF (5 mL) at −78 °C. The reaction mixture stirred for 10 min at −78 °C, then NaHMDS (0.12 mL of a 2 M solution in THF, 0.25 mmol) was added dropwise. The solution was stirred for 2.5 h at −78 °C, then the reaction was quenched with a 5% aqueous solution of KH_2PO_4 (10 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded carbonate **283** (84.5 mg, 89% yield) as a colourless solid.

R_f = 0.81 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (29.3 °C, $CHCl_3$) = +119.8 (*c* = 1.01);
m.p. = 111—113 °C;
IR: ν_{max} 2934, 2861, 1759, 1651, 1474, 1366, 1244, 1221, 1094 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.57 (1H, s, CH-C11), 5.98—5.90 (2H, m, CH-C14, CH-C9), 5.71 (1H, ddd, *J* = 10.8, 8.6, 7.3 Hz, CH-C8), 5.37 (1H, dddd, *J* = 17.2, 1.4, 1.4, 1.4 Hz, CH_2-C15), 5.29 (1H, dddd, *J* = 10.4, 1.4, 1.4, 1.4 Hz, CH_2-C15), 4.64 (2H, ddd, *J* = 5.8, 1.4, 1.2 Hz, CH_2-C13), 4.40 (1H, ddd, *J* = 11.8, 9.1, 4.4 Hz, CH-C2), 4.13 (1H, dd, *J* = 10.2, 4.9 Hz, CH_2-C6), 3.77 (1H, dd, *J* = 10.2, 10.2 Hz, CH_2-C6), 3.76—3.71 (1H, m, CH-C4), 3.36—3.28 (2H, m, CH-C1 and CH-C5), 2.82 (1H, dddd, *J* = 14.1, 8.6, 3.8, 1.4 Hz, CH_2-C7), 2.52 (1H, ddd, *J* = 14.1, 7.3, 2.8 Hz, CH_2-C7), 2.43 (1H, ddd, *J* = 11.5, 4.4, 4.4 Hz, CH_2-C3), 1.63 (1H, app q, *J* = 11.5 Hz, CH_2-C3), 1.03 (9H, s, CH_3-*t*Bu), 0.98 (9H, s, CH_3-*t*Bu);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 154.7 (C–C12), 141.6 (CH–C11), 131.3 (CH–C14), 129.9 (C–C10), 128.0 (CH–C8), 126.3 (CH–C9), 119.4 (CH_2–C15), 77.9 (CH–C5), 73.9 (CH–C1), 72.6 (CH–C4), 72.6 (CH–C2), 69.1 (CH_2–C13), 66.9 (CH_2–C6), 39.3 (CH_2–C3), 31.3 (CH_2–C7), 27.6 (3 x CH_3–*t*Bu), 27.2 (3 x CH_3–*t*Bu), 22.7 (C–*t*Bu), 20.1 (C–*t*Bu);
HRMS: (CI, isobutane) for $C_{23}H_{37}O_7Si$ ($[M+H]^+$) calculated 453.2309, found 453.2313, Δ +1.0 ppm.

(4a*R*,5a*S*,10*S*,11a*R*,12a*S*,*Z*)-10-Allyl-2,2-di-*tert*-butyl-5a,6,10,11a,12,12a-hexahydro-4*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*b*]oxocin-9(4a*H*)-one (227)



$C_{22}H_{36}O_5Si$
Molecular weight: 408.60 g.mol^{-1}

(*S*)-*t*Bu-PHOX ligand **(*S*)-282** (19.0 mg, 0.0480 mmol) was added to a suspension of tetrakis(triphenylphosphine)palladium (22.0 mg, 0.0200 mmol) in anhydrous THF (11 mL) at rt. After 30 min, a solution of carbonate **283** (84.5 mg, 0.190 mmol) in anhydrous THF (4 mL) was added and the reaction mixture stirred for 2.5 h at rt. The solution was filtered through a pad of Celite and the pad washed with Et_2O (3 x 25 mL). The resulting filtrate was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) to afford enone **227** as a colourless oil (66.3 mg, 85% yield, dr > 20:1).

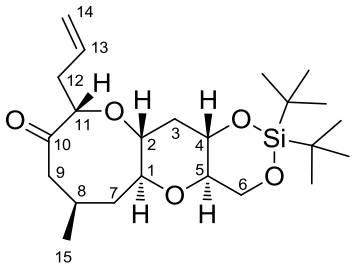
R_f = 0.78 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (27.1 °C, $CHCl_3$) = −124.0 (*c* = 1.00);
IR: ν_{max} 2935, 2860, 1678, 1474, 1387, 1185, 1094 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.41 (1H, ddd, *J* = 12.3, 9.8, 8.3 Hz, CH–C8), 5.88—5.78 (2H, m, CH–C9 and CH–C13), 5.20—5.14 (2H, m, CH_2–C14), 4.19 (1H, dd, *J* = 9.2, 3.6 Hz, CH–C11), 4.12 (1H, dd, *J* = 10.1, 4.9 Hz, CH_2–C6), 3.82—3.75 (2H, m, CH–C4 and CH_2–C6), 3.38 (1H, ddd, *J* = 11.6, 9.2, 4.1 Hz, CH–C2), 3.28 (1H,

ddd, *J* = 10.5, 9.7, 4.9 Hz, CH–C5), 3.26—3.21 (1H, m, CH–C1), 2.71—2.61 (2H, m, CH_2–C7 and CH_2–C12), 2.49—2.43 (2H, m, CH_2–C7 and CH_2–C3), 2.34—2.27 (1H, m, CH_2-C12), 1.64 (1H, app q, *J* = 11.6 Hz, CH_2–C3), 1.04 (9H, s, CH_3–*t*Bu), 0.98 (9H, s, CH_3–*t*Bu);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 202.5 (C–C10), 136.4 (CH–C8), 134.0 (CH–C13), 130.7 (CH–C9), 118.5 (CH_2–C14), 88.2 (CH–C11), 85.6 (CH–C2), 77.9 (CH–C5), 77.8 (CH–C1), 72.8 (CH–C4), 66.8 (CH_2–C6), 40.5 (CH_2–C3), 37.1 (CH_2–C12), 33.9 (CH_2-C7), 27.5 (3 x CH_3–*t*Bu), 27.1 (3 x CH_3–*t*Bu), 22.7 (C–*t*Bu), 20.0 (C–*t*Bu);

HRMS: (ESI) for $C_{22}H_{36}O_5SiNa$ ($[M+Na]^+$) calculated 431.2230, found 431.2224, Δ +4.3 ppm.

(4a*R*,5a*S*,7*R*,10*S*,11a*R*,12a*S*)-10-Allyl-2,2-di-*tert*-butyl-7-methylocatahydro-4*H*-[1,3,2]dioxasilino[4',5':5,6]pyrano[3,2-*b*]oxocin-9(4a*H*)-one (225)



$C_{23}H_{40}O_5Si$
Molecular weight: 424.65 g.mol^{-1}

Methyl lithium (0.45 mL of a 1.4 M solution in Et_2O, 0.60 mmol) was added to a suspension of copper (I) cyanide (27.0 mg, 0.300 mmol) in anhydrous Et_2O (2.5 mL) at −78 °C. The reaction mixture was warmed to 0 °C, stirred until the solution turned colourless and then cooled back down to −78 °C. A solution of enone **227** (40.0 mg, 0.100 mmol) in anhydrous Et_2O (2.5 mL) was added and the reaction mixture stirred for 1.5 h at −78 °C. The reaction was quenched with a solution of saturated aqueous NH_4Cl and NH_4OH (5:1, 12 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 15 mL). The organic extracts were combined, washed with brine (45 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded **225** (38 mg, 89% yield) as a colourless oil.

R_f = 0.85 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (28.0 °C, $CHCl_3$) = −122.0 (*c* = 1.00);

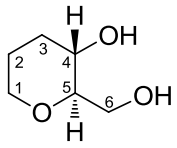
IR: ν_{max} 2934, 2860, 1715, 1472, 1457, 1094 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.80 (1H, dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, CH-C13), 5.14—5.08 (2H, m, CH_2-C14), 4.11 (1H, dd, *J* = 10.1, 5.0 Hz, CH_2-C6), 3.79—3.72 (2H, m, CH_2-C6 and CH-C4), 3.64 (1H, dd, *J* = 9.2, 3.9 Hz, CH-C11), 3.44 (1H, dd, *J* = 10.9, 6.8 Hz, CH_2-C9), 3.33 (1H, dd, *J* = 8.9, 8.9 Hz, CH-C1), 3.26 (1H, ddd, *J* = 10.1, 10.1, 5.0 Hz, CH-C5), 3.05 (1H, ddd, *J* = 11.5, 8.9, 4.4 Hz, CH-C2), 2.47 (1H, ddd, *J* = 12.2, 4.4, 4.4 Hz, CH_2-C3), 2.45—2.38 (1H, m, CH_2-C12), 2.30—2.22 (2H, m, CH_2-C12 and CH-C8), 1.84 (2H, m, CH_2-C9 and CH_2-C7), 1.64 (1H, ddd, *J* = 12.2, 11.5, 11.3 Hz, CH_2-C3), 1.33 (1H, ddd, *J* = 15.2, 12.4, 8.9 Hz, CH_2-C7), 1.04—0.97 (21H, m, CH_3-*t*Bu and CH_3-C15);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 216.1 (C-C10), 133.7 (CH-C13), 118.2 (CH_2-C14), 89.0 (CH-C11), 82.8 (CH-C2), 81.3 (CH-C5), 77.3 (CH-C1), 72.6 (CH-C4), 67.0 (CH_2-C6), 41.9 (CH_2-C7), 41.5 (CH_2-C9), 40.6 (CH_2-C3), 38.2 (CH_2-C12), 30.6 (CH-C8), 27.6 (3 x CH_3-*t*Bu), 27.2 (3 x CH_3-*t*Bu), 22.8 (C-*t*Bu), 22.3 (C-*t*Bu), 20.1 (CH_3-C15);

HRMS: (CI, isobutane) for $C_{23}H_{41}O_5Si$ ($[M+H]^+$) calculated 425.2723, found 425.2719, Δ −0.9 ppm.

(2*R*,3*S*)-2-(Hydroxymethyl)tetrahydro-2*H*-pyran-3-ol (292)[159]

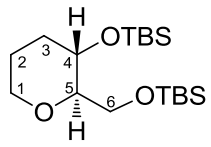


$C_6H_{12}O_3$
Molecular weight: 132.16 g.mol^{-1}

Pd/C (5%, 391 mg) was added to a solution of diol **233** (4.78 g, 36.7 mmol) in EtOAc (180 mL). The flask was flushed with H_2 three times before the reaction mixture was placed under an atmosphere of H_2 and stirred overnight at rt. The suspension was filtered through a pad of Celite and the pad washed with EtOAc (4 x 100 mL). The resulting filtrate was concentrated under reduced pressure to afford diol **292** (4.54 g, 94% yield) as a colourless oil.

R_f = 0.28 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (26.8 °C, $CHCl_3$) = +29.6 (*c* = 1.11);
{Lit.[159] $[\alpha]_D$ (20 °C, CH_2Cl_2) = +33.3 (*c* = 5.2)};
IR: ν_{max} 3378, 2937, 2856, 1452, 1274, 1098, 1074, 1045, 1028 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 3.94—3.88 (1H, m, CH_2-C1), 3.79 (2H, dddd, *J* = 15.4, 13.8, 11.6, 4.3 Hz, CH_2-C6), 3.54 (1H, ddd, *J* = 10.5, 10.5, 4.7 Hz, CH-C4), 3.39—3.32 (1H, m, CH_2-C1), 3.11 (1H, ddd, *J* = 8.9, 4.7, 4.3 Hz, CH-C5), 3.00 (1H, br s, OH), 2.85 (1H, br s, OH), 2.13—2.07 (1H, m, CH_2-C3), 1.70—1.63 (2H, m, CH_2-C2), 1.47—1.37 (1H, m, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 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 $C_6H_{13}O_3$ ($[M+H]^+$) calculated 133.0865, found 133.0875, Δ +4.6 ppm.

***tert*-Butyl{[(2*R*,3*S*)-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}tetrahydro-2*H*-pyran-3-yl]oxy}dimethylsilane (294)[159]**

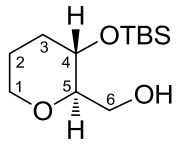


$C_{18}H_{40}O_3Si_2$
Molecular weight: 360.68 g.mol^{-1}

TBSCl (14.4 g, 95.6 mmol), DMAP (773 mg, 6.33 mmol) and imidazole (8.68 g, 0.128 mol) were added to a solution of diol **292** (4.21 g, 31.9 mmol) in anhydrous DMF (110 mL) at 0 ºC. The reaction mixture was stirred overnight at rt, cooled to 0 ºC and then the reaction was quenched with H_2O (100 mL). The phases were separated and the aqueous phase extracted with Et_2O (4 x 125 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 9:1) afforded **294** (10.7 g, 93% yield) as a colourless oil.

R_f = 0.91 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (22.0 ºC, $CHCl_3$) = +49.4 (*c* = 0.99);
{Lit.[159] $[\alpha]_D$ (20 ºC, CH_2Cl_2) = +36.4 (*c* = 6.7)};
IR: ν_{max} 2928, 2857, 1471, 1462, 1362, 1252, 1099 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 3.92—3.88 (1H, m, CH_2-C1), 3.88 (1H, dd, *J* = 11.2, 1.9 Hz, CH_2-C6), 3.67 (1H, dd, *J* = 11.2, 6.0 Hz, CH_2-C6), 3.46 (1H, ddd, *J* = 10.6, 8.9, 4.8 Hz, CH-C4), 3.31 (1H, ddd, *J* = 11.2, 4.8, 3.6 Hz, CH_2-C1), 3.08 (1H, ddd, *J* = 8.9, 6.0, 1.9 Hz, CH-C5), 2.03—1.96 (1H, m, CH_2-C3), 1.66—1.57 (2H, m, CH_2-C2), 1.47—1.38 (1H, m, CH_2-C3), 0.90 (9H, s, CH_3-*t*Bu), 0.88 (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: (126 MHz, $CDCl_3$) δ_C 83.9 (CH-C5), 67.6 (CH-C4), 67.4 (CH_2-C1), 63.9 (CH_2-C6), 33.7 (CH_2-C3), 26.2 (3 x CH_3-*t*Bu), 25.9 (3 x CH_3-*t*Bu), 25.7 (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 $C_{18}H_{41}O_3Si_2$ ($[M+H]^+$) calculated 361.2594, found 361.2593, Δ −0.3 ppm.

{(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]tetrahydro-2*H*-pyran-2-yl}methanol (295)[159]

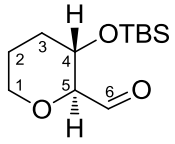


$C_{12}H_{26}O_3Si$
Molecular weight: 246.42 g.mol^{-1}

Camphorsulfonic acid (966 mg, 4.16 mmol) was added to a solution of **294** (5.00 g, 13.9 mmol) in CH_2Cl_2:MeOH (1:1, 160 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with Et_3N (0.95 mL, 6.7 mmol) and the mixture was concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—EtOAc, 2:1) afforded **295** (3.05 g, 89% yield) as a colourless oil.

R_f = 0.48 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (21.8 °C, $CHCl_3$) = +51.3 (*c* = 0.99);
{Lit.[160] $[\alpha]_D$ (21 °C, $CHCl_3$) = +50.3 (*c* = 1.01)};
IR: ν_{max} 3485, 2930, 2857, 1462, 1362, 1094 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 3.94—3.89 (1H, m, CH_2-C1), 3.83 (1H, ddd, *J* = 11.3, 6.7, 3.1 Hz, CH_2-C6), 3.61 (1H, app dt, *J* = 11.3, 5.9 Hz, CH_2-C6), 3.48 (1H, ddd, *J* = 10.7, 9.0, 4.7 Hz, CH-C4), 3.37 (1H, ddd, *J* = 11.2, 7.9, 4.7 Hz, CH_2-C1), 3.14 (1H, ddd, *J* = 9.0, 5.9, 3.1 Hz, CH-C5), 2.05—2.00 (1H, m, CH_2-C3), 1.98 (1H, dd, *J* = 6.7, 5.9 Hz, OH), 1.70—1.61 (2H, m, CH_2-C2), 1.50—1.41 (1H, m, CH_2-C3), 0.88 (9H, s, CH_3-*t*Bu), 0.07 (6H, s, CH_3-Me);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 82.5 (CH-C5), 68.1 (CH-C4), 67.8 (CH_2-C1), 63.3 (CH_2-C6), 33.5 (CH_2-C3), 25.9 (3 x CH_3-*t*Bu), 25.6 (CH_2-C2), 18.1 (C-*t*Bu), −4.0 (CH_3-Me), −4.8 (CH_3-Me);
HRMS: (CI, isobutane) for $C_{12}H_{27}O_3Si$ ($[M+H]^+$) calculated 247.1729, found 247.1732, Δ +1.2 ppm.

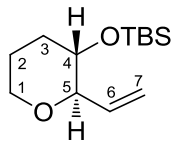
(2*S*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carbaldehyde (296)[161]



$C_{12}H_{24}O_3Si$
Molecular weight: 244.40 g.mol^{-1}

Et_3N (8.50 mL, 60.9 mmol) was added to a solution of **295** (3.00 g, 12.2 mmol) in anhydrous CH_2Cl_2 (45 mL) at 0 °C. A solution of sulfur trioxide pyridine complex (5.82 g, 36.5 mmol) in anhydrous DMSO (13 mL) was added dropwise and the reaction mixture stirred for 2 h at 0 °C. The resulting solution was diluted with H_2O (40 mL), the phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 80 mL). The organic extracts were combined, washed with a saturated aqueous solution of $CuSO_4$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (petroleum ether—Et_2O, 1:1) then used without further purification.

***tert*-Butyldimethyl{[(2*R*,3*S*)-2-vinyltetrahydro-2*H*-pyran-3-yl]oxy}silane (297)[159]**

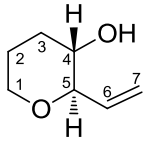


$C_{13}H_{26}O_2Si$
Molecular weight: 242.43 g.mol^{-1}

NaHMDS (24.4 mL of a 2 M solution in THF, 48.7 mmol) was added to a suspension of methyltriphenylphosphonium bromide (20.0 g, 56.1 mmol) in anhydrous THF (60 mL) at 0 °C. The reaction mixture was stirred for 45 min at 0 °C, then a solution of **296** [12.2 mmol] in anhydrous THF (135 mL) was added. The resulting mixture was stirred for 45 min at 0 °C and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (150 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 99:1) afforded **297** (2.23 g, 76% yield over two steps) as a colourless oil.

R_f = 0.85 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (23.3 °C, $CHCl_3$) = +40.9 (*c* = 0.96);
{Lit.[157] $[\alpha]_D$ (26 °C, $CHCl_3$) = +40.5 (*c* = 1.0)};
IR: ν_{max} 2930, 2857, 1471, 1362, 1254, 1125, 1094 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.92 (1H, ddd, *J* = 17.2, 10.7, 5.8 Hz, CH-C6), 5.31 (1H, ddd, *J* = 17.2, 1.8, 1.3 Hz, CH_2-C7), 5.18 (1H, ddd, *J* = 10.7, 1.8, 1.3 Hz, CH_2-C7), 3.96—3.91 (1H, m, CH_2-C1), 3.53—3.48 (1H, m, CH-C5), 3.38 (1H, ddd, *J* = 11.3, 11.3, 3.5 Hz, CH_2-C1), 3.31 (1H, ddd, *J* = 10.5, 8.8, 4.6 Hz, CH-C4), 2.07—1.99 (1H, m, CH_2-C3), 1.72—1.62 (2H, m, CH_2-C2), 1.49 (1H, ddd, *J* = 12.5, 10.5, 5.1 Hz, CH_2-C3), 0.87 (9H, s, CH_3-*t*Bu), 0.05 (3H, s, CH_3-Me), 0.03 (3H, s, CH_3-Me);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 137.1 (CH-C6), 116.6 (CH_2-C7), 83.4 (CH-C5), 71.5 CH-C4), 67.7 (CH_2-C1), 33.9 (CH_2-C3), 26.0 (3 x 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 $C_{13}H_{27}O_2Si$ ($[M+H]^+$) calculated 243.1780, found 243.1777, Δ −1.4 ppm.

(2*R*,3*S*)-2-Vinyltetrahydro-2*H*-pyran-3-ol (291)[162]

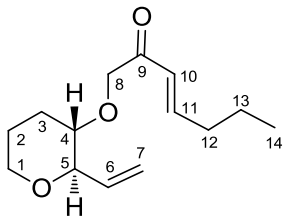


$C_7H_{12}O_2$
Molecular weight: 128.17 g.mol^{-1}

Camphorsulfonic acid (3.15 g, 13.6 mmol) was added to a solution of **297** (2.20 g, 9.08 mmol) in CH_2Cl_2:MeOH (1:1, 90 mL) at 0 °C. The resulting mixture was warmed to rt and stirred overnight. The reaction was quenched with Et_3N (2.25 mL, 16.3 mmol) and the resulting mixture was concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 4:1 to 7:3) afforded alcohol **291** (1.12 g, 96% yield) as a colourless oil.

R_f = 0.34 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (25.3 °C, $CHCl_3$) = +4.04 (*c* = 1.14);
{Lit.[163] $[\alpha]_D$ (25 °C, $CHCl_3$) = +6.5 (*c* = 1.2)};
IR: ν_{max} 3411, 2940, 2856, 1427, 1264, 1085, 1027 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.87 (1H, ddd, *J* = 17.4, 10.5, 7.1 Hz, CH-C6), 5.39 (1H, ddd, *J* = 17.4, 1.7, 1.1 Hz, CH_2-C7), 5.32 (1H, ddd, *J* = 10.5, 1.7, 0.8 Hz, CH_2-C7), 3.94 (1H, dddd, *J* = 11.4, 4.2, 2.0, 2.0 Hz, CH_2-C1), 3.50—3.46 (1H, m, CH-C5), 3.39 (1H, ddd, *J* = 11.4, 4.7, 3.6 Hz, CH_2-C1), 3.36—3.29 (1H, m, CH-C4), 2.19—2.12 (1H, m, CH_2-C3), 1.76—1.66 (3H, m, CH_2-C2 and OH), 1.49—1.40 (1H, m, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 136.3 (CH-C6), 119.1 (CH_2-C7), 84.2 (CH-C5), 69.7 (CH-C4), 67.6 (CH_2-C1), 31.7 (CH_2-C3), 25.5 (CH_2-C2);
HRMS: (CI, isobutane) for $C_7H_{13}O_2$ ($[M+H]^+$) calculated 129.0916, found 129.0920, Δ +3.4 ppm.

(*E*)-1-{[(2*R*,3*S*)-2-Vinyltetrahydro-2*H*-pyran-3-yl]oxy}hept-3-en-2-one (299)



$C_{14}H_{22}O_3$
Molecular weight: 238.32 g.mol^{-1}

A solution of alcohol **291** (500 mg, 3.90 mmol) in anhydrous THF (62 mL) was slowly added to a suspension of sodium hydride (374 mg of a 60% dispersion in mineral oil, 15.6 mmol) in anhydrous THF (62 mL) at 0 °C. The reaction mixture was warmed to rt, then triphenylchloroacetonylphosphorane (1.65 g, 4.68 mmol) and TBAI (74.0 mg, 0.200 mmol) were added. The resulting solution was heated to reflux and stirred for 3 h. The reaction mixture was cooled to rt and the reaction was quenched with H_2O (10 mL). The mixture was concentrated under reduced pressure and the aqueous phase was extracted with EtOAc (4 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product **298** was used without any further purification.

Butyraldehyde (3.55 mL, 39.0 mmol) was added to a solution of crude phosphorane **298** [3.90 mmol] in anhydrous CH_2Cl_2 (145 mL). The reaction mixture was heated to reflux, stirred for 48 h then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1 to 9:1) afforded the desired enone **299** (650 mg, 70% yield over two steps) as a colourless oil.

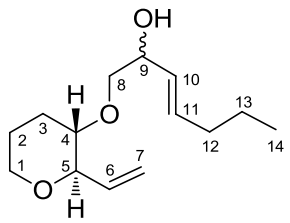
R_f = 0.48 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (27.1 °C, $CHCl_3$) = +35.1 (*c* = 1.09);
IR: ν_{max} 2934, 2864, 1738, 1713, 1694, 1624, 1217, 1138, 1088 cm^{-1};
^{1}**H NMR**: (500 MHz, $CDCl_3$) δ_H 6.96 (1H, ddd, *J* = 15.8, 6.9, 6.9 Hz, CH-C11), 6.30 (1H, ddd, *J* = 15.8, 1.5, 1.5 Hz, CH-C10), 6.01 (1H, ddd, *J* = 17.4, 10.7, 6.0 Hz, CH-C6), 5.39 (1H, ddd, *J* = 17.4, 1.5, 1.5 Hz, CH_2-C7), 5.24 (1H, ddd, *J* = 10.7, 1.5, 1.5 Hz, CH_2-C7), 4.25 (1H, d, *J* = 16.5 Hz, CH_2-C8), 4.20 (1H, d, *J* = 16.5 Hz, CH_2-C8), 3.96—3.92 (1H, m, CH_2-C1), 3.69—3.64 (1H, m, CH_2-C5), 3.40 (1H, ddd, *J* = 11.5, 11.5, 2.7 Hz, CH_2-C1), 3.09 (1H, ddd, *J* = 10.6, 8.9, 4.5 Hz, CH-C4),

2.29—2.23 (1H, m, CH_2-C3), 2.20 (2H, dddd, *J* = 7.7, 7.4, 7.2, 1.5 Hz, CH_2-C12), 1.74—1.67 (1H, m, CH_2-C2), 1.68—1.59 (1H, m, CH_2-C2), 1.54—1.45 (3H, m, CH_2-C3 and CH_2-C13), 0.94 (3H, t, *J* = 7.4 Hz, CH_3-C14);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 197.3 (C-C9), 148.4 (CH-C11), 136.7 (CH-C6), 126.2 (CH-C10), 117.3 (CH_2-C7), 81.4 (CH-C5), 79.2 (CH-C4), 74.0 (CH_2-C8), 67.5 (CH_2-C1), 34.8 (CH_2-C12), 29.6 (CH_2-C3), 25.3 (CH_2-C2), 21.4 (CH_2-C13), 13.9 (CH_3-C14);

HRMS: (CI, isobutane) for $C_{14}H_{23}O_3$ ($[M+H]^+$) calculated 239.1647, found 239.1645, Δ −0.9 ppm.

(*E*)-1-{[(2*R*,3*S*)-2-Vinyltetrahydro-2*H*-pyran-3-yl]oxy}hept-3-en-2-ol (300)



$C_{14}H_{24}O_3$
Molecular weight: 240.34 g.mol^{-1}

Cerium trichloride heptahydrate (484 mg, 1.30 mmol) and sodium borohydride (59.0 mg, 1.56 mmol) were added to a solution of enone **299** (309 mg, 1.30 mmol) in MeOH (70 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, then the reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 75 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford an inseparable diastereomeric mixture of alcohols **300** (310 mg, 99% yield, dr 1:1) as a colourless oil

R_f = 0.39 (petroleum ether—Et_2O; 1:1);

IR: ν_{max} 3453, 2956, 2929, 2861, 1464, 1269, 1216, 1110, 1088 cm^{-1};

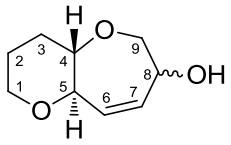
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.96 (2H, dddd, *J* = 17.3, 10.6, 6.5, 6.5 Hz, CH-C6/C6′), 5.75 (2H, app dtt, *J* = 15.0, 6.8, 1.2 Hz, CH-C11/C11′), 5.42—5.36 (2H, m, CH-C10/C10′), 5.37 (2H, d, *J* = 17.3 Hz, CH_2-C7/C7′), 5.25 (2H, dddd, *J* = 10.6, 5.0, 1.8, 1.1 Hz, CH_2-C7/C7′), 4.19 (2H, br s, CH-C5/C5′), 3.96—3.91 (2H, m, CH_2-C1/C1′), 3.63 (1H, dd, *J* = 9.4, 3.2 Hz, CH_2-C8), 3.61—3.57 (2H, m, CH-C4/C4′), 3.46—3.40 (2H, m, CH_2-C8′), 3.41—3.36 (2H, m, CH_2-C1/C1′), 3.19

(1H, dd, *J* = 9.4, 8.7 Hz, CH_2-C8), 3.10—3.04 (2H, m, CH-C9/C9′), 2.48 (1H, s, OH), 2.39 (1H, s, OH), 2.26—2.20 (2H, m, CH_2-C3/C3′), 2.01 (4H, dd, *J* = 14.5, 7.1 Hz, CH_2-C12/C12′), 1.75—1.59 (4H, m, CH_2-C2/C2′), 1.44—1.36 (6H, m, CH_2-C13/C13′ and CH_2-C3/C3′), 0.89 (6H, t, *J* = 7.4 Hz, CH_3-C14/C14′);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 136.9 and 136.8 (CH-C6/C6′), 134.1 and 134.0 (CH-C11/C11′), 128.2 and 128.0 (CH-C10/C10′), 117.7 and 117.5 (CH_2-C7/C7′), 81.6 and 81.5 (CH-C4/C4′), 78.7 and 78.2 (CH-C9/C9′), 73.9 (CH_2-C8), 73.4 (CH_2-C8′), 71.9 and 71.2 (CH-C5/C5′), 67.5 (CH_2-C1/C1′), 34.6 (CH_2-C12/C12′), 29.8 and 29.6 (CH_2-C3/C3′), 25.3 and 25.2 (CH_2-C2/C2′), 22.3 and 22.2 (CH_2-C13/C13′), 13.8 (CH_3-C14/C14′);

HRMS: (EI^+) for $C_{14}H_{24}O_3$ ($[M]^+$) calculated 240.1725, found 240.1721, Δ −1.6 ppm.

(4a*S*,9a*R*)-3,4,4a,6,7,9a-Hexahydro-2*H*-pyrano[3,2-*b*]oxepin-7-ol (301)



$C_9H_{14}O_3$
Molecular weight: 170.21 g.mol^{-1}

Hoveyda-Grubbs second generation catalyst **150** (61.4 mg, 0.0980 mmol) was added to a solution of alcohols **300** (312 mg, 1.30 mmol) in degassed anhydrous CH_2Cl_2 (130 mL). The reaction mixture was heated to reflux and stirred overnight. The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—Et_2O, 1:1) to afford the desired alcohols **301** (178 mg, 81% yield, dr 1:1) as a separable mixture of diastereomers.(N.B. The two diastereomers were separated for characterisation but were usually taken on to the next step as a mixture.)

<u>Diastereomer A</u>

R_f = 0.28 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (27.2 °C, $CHCl_3$) = −20.9 (*c* = 1.04);
m.p. = 101—103 °C;
IR: ν_{max} 3420, 2938, 2857, 2817, 1738, 1381, 1267, 1126, 1072 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.73 (1H, ddd, *J* = 12.7, 3.9, 2.4 Hz, CH-C7), 5.55 (1H, ddd, *J* = 12.7, 2.2, 2.2 Hz, CH-C6), 4.45—4.40 (1H, m, CH-C8), 3.95 (1H, ddd, *J* = 11.5, 4.3, 1.4 Hz, CH_2-C9), 3.90—3.85 (1H, m, CH_2-C1), 3.75 (1H, ddd, *J* = 9.0, 4.6, 2.2 Hz, CH-C5), 3.38 (1H, dd, *J* = 11.5, 10.1 Hz, CH_2-C9), 3.32—3.26 (1H, m, CH_2-C1), 3.15 (1H, ddd, *J* = 11.0, 9.0, 4.6 Hz, CH-C4), 2.14 (1H, d, *J* = 5.7 Hz, OH), 2.08—2.02 (1H, m, CH_2-C3), 1.68—1.62 (2H, m, CH_2-C2), 1.47—1.38 (1H, m, CH_2-C3);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 134.3 (CH-C7), 132.4 (CH-C6), 81.6 (CH-C5), 80.0 (CH-C4), 75.5 (CH_2-C9), 70.7 (CH-C8), 67.6 (CH_2-C1), 31.1 (CH_2-C3), 25.5 (CH_2-C2);

HRMS: (CI, isobutane) for $C_9H_{13}O_2$ ($[M\text{-}OH]^+$) calculated 153.0916, found 153.0912, Δ −2.5 ppm.

<u>Diastereomer B</u>

R_f = 0.13 (petroleum ether—Et_2O, 1:1);

$[\alpha]_D$ (27.1 °C, $CHCl_3$) = −105.3 (*c* = 1.06);

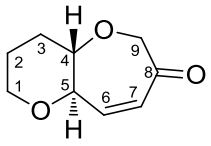
IR: ν_{max} 3426, 2944, 2861, 1740, 1370, 1216, 1148, 1096, 1059 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.94 (1H, dddd, *J* = 12.4, 7.2, 2.8, 0.9 Hz, CH-C7), 5.69 (1H, dd, *J* = 12.4, 1.7 Hz, CH-C6), 4.12 (1H, ddd, *J* = 12.8, 3.0, 0.9 Hz, CH_2-C9), 3.98—3.94 (1H, m, CH-C8), 3.93—3.86 (2H, m, CH-C5 and CH_2-C1), 3.70 (1H, dd, *J* = 12.8, 1.3 Hz, CH_2-C9), 3.35—3.29 (1H, m, CH-C4), 3.17 (1H, ddd, *J* = 10.8, 9.3, 4.6 Hz, CH_2-C1), 2.23 (1H, d, *J* = 8.5 Hz, OH), 2.16—2.08 (1H, m, CH_2-C3), 1.72—1.61 (2H, m, CH_2-C2), 1.59—1.47 (1H, m, CH_2-C3);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 136.5 (CH-C6), 128.5 (CH-C7), 81.5 (CH-C5), 80.3 (CH-C4), 75.8 (CH_2-C9), 68.4 (CH-C8), 67.8 (CH_2-C1), 31.3 (CH_2-C3), 25.4 (CH_2-C2);

HRMS: (CI, isobutane) for $C_9H_{13}O_2$ ($[M\text{-}OH]^+$) calculated 153.0916, found 153.0920, Δ +3.1 ppm.

(4a*S*,9a*R*)-4,4a,6,9a-Tetrahydro-2*H*-pyrano[3,2-*b*]oxepin-7(3*H*)-one (289)

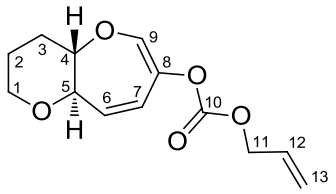


$C_9H_{12}O_3$
Molecular weight: 168.19 g.mol^{-1}

Dess-Martin periodinane (891 mg, 2.10 mmol) was added to a solution of alcohols **301** (178 mg, 1.05 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The resulting mixture was warmed to rt and stirred overnight. The reaction was quenched with a solution of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 50 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 75 mL). The organic extracts were combined, washed with brine (125 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 4:1) afforded enone **289** (113 mg, 64% yield) as a colourless solid.

R_f = 0.47 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (28.9 °C, $CHCl_3$) = −54.8 (*c* = 1.06);
m.p. = 66—68 °C;
IR: ν_{max} 2945, 2851, 2361, 2330, 1668, 1260, 1138, 1092 cm^{-1};
^{1}**H NMR**: (500 MHz, $CDCl_3$) δ_H 6.47 (1H, dd, *J* = 12.9, 2.5 Hz, CH-C7), 5.98 (1H, dd, *J* = 12.9, 2.5 Hz, CH-C6), 4.36 (1H, d, *J* = 18.3 Hz, CH_2-C9), 4.25 (1H, d, *J* = 18.3 Hz, CH_2-C9), 3.94 (1H, dddd, *J* = 6.0, 4.3, 4.2, 1.8 Hz, CH_2-C1), 3.86 (1H, ddd, *J* = 9.0, 2.5, 2.5 Hz, CH-C5), 3.44—3.39 (1H, m, CH_2-C1), 3.37 (1H, ddd, *J* = 11.0, 9.0, 4.8 Hz, CH-C4), 2.21—2.14 (1H, m, CH_2-C3), 1.75—1.68 (2H, m, CH_2-C2), 1.60—1.50 (1H, m, CH_2-C3);
^{13}**C NMR**: (126 MHz, $CDCl_3$) δ_C 201.8 (C-C8), 146.3 (CH-C7), 127.8 (CH-C6), 81.1 (CH-C5), 79.8 (CH-C4), 77.4 (CH_2-C9), 68.3 (CH_2-C1), 30.7 (CH_2-C3), 25.5 (CH_2-C2);
HRMS: (CI, isobutane) for $C_9H_{13}O_3$ ($[M+H]^+$) calculated 169.0865, found 169.0861, Δ −2.4 ppm.

Allyl[(4a*S*,9a*R*)-3,4,4a,9a-tetrahydro-2*H*-pyrano[3,2-*b*]oxepin-7-yl]carbonate (302)

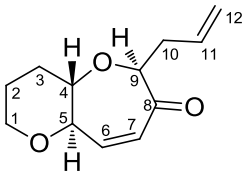


$C_{13}H_{16}O_5$
Molecular weight: 252.26 g.mol^{-1}

Allylchloroformate (0.12 mL, 1.1 mmol) was added to a solution of enone **289** (153 mg, 0.910 mmol) in anhydrous THF (15 mL) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C, then NaHMDS (2.28 mL of a 1 M solution in THF, 2.28 mmol) was added. The reaction mixture was stirred for 2 h at −78 °C, then the reaction was quenched with a 5% aqueous solution of KH_2PO_4 (20 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 30 mL). The organic extracts were combined, washed with brine (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded carbonate **302** (173 mg, 76% yield) as a colourless oil.

R_f = 0.83 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (24.7 °C, $CHCl_3$) = +64.1 (*c* = 0.98);
IR: ν_{max} 2945, 2851, 1759, 1252, 1225, 1162, 1092 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.72 (1H, s, CH-C9), 5.95 (1H, dddd, *J* = 17.2, 10.4, 5.8, 5.8 Hz, CH-C12), 5.79—5.69 (2H, m, CH-C7 and CH-C6), 5.39 (1H, dddd, *J* = 17.2, 1.5, 1.4, 1.4 Hz, CH_2-C13), 5.30 (1H, dddd, *J* = 10.4, 1.5, 1.4, 1.4 Hz, CH_2-C13), 4.66 (2H, ddd, *J* = 5.8, 1.4, 1.4 Hz, CH_2-C11), 3.95—3.90 (1H, m, CH_2-C1), 3.78—3.75 (1H, m, CH-C5), 3.52 (1H, ddd, *J* = 11.3, 7.4, 5.0 Hz, CH-C4), 3.38 (1H, ddd, *J* = 11.4, 11.3, 3.1 Hz, CH_2-C1), 2.39—2.31 (1H, m, CH_2-C3), 1.78—1.66 (2H, m, CH_2-C2), 1.64—1.55 (1H, m, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 154.7 (C-C10), 142.5 (CH-C9), 133.8 (C-C8), 131.3 (CH-C12), 130.5 (CH-C7), 121.1 (CH-C6), 120.0 (CH_2-C13), 78.0 (CH-C5), 76.8 (CH-C4), 69.3 (CH_2-C11), 67.2 (CH_2-C1), 30.6 (CH_2-C3), 25.2 (CH_2-C2);
HRMS: (CI, isobutane) for $C_{13}H_{17}O_5$ ($[M+H]^+$) calculated 253.1076, found 253.1073, Δ −1.4 ppm.

(4a*S*,6*S*,9a*R*)-6-Allyl-4,4a,6,9a-tetrahydro-2*H*-pyrano[3,2-*b*]oxepin-7(3*H*)-one (327)

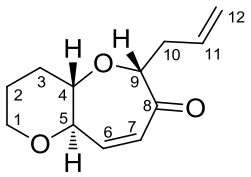


$C_{12}H_{16}O_3$
Molecular weight: 208.25 g.mol^{-1}

(*S*)-*t*Bu-PHOX ligand **(*S*)-282** (66.0 mg, 0.170 mmol) was added to a suspension of tetrakis(triphenylphosphine)palladium (80.0 mg, 0.0690 mmol) in anhydrous THF (11 mL) at rt. The reaction mixture was stirred for 30 min and then a solution of carbonate **302** (173 mg, 0.690 mmol) in anhydrous THF (12 mL) was added. The reaction mixture was stirred for 2.5 h at rt, then concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (petroleum ether—Et_2O, 19:1) to afford **327** (128 mg, 88% yield, dr 1:14) as a colourless solid.

R_f = 0.57 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (27.9 °C, $CHCl_3$) = −122.3 (*c* = 0.94);
m.p. = 47—49 °C;
IR: ν_{max} 2944, 2917, 2849, 1663, 1260, 1135, 1126, 1090, 1057 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.46 (1H, dd, *J* = 12.6, 2.6 Hz, CH-C7), 6.00 (1H, dd, *J* = 12.6, 2.6 Hz, CH-C6), 5.87 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH-C11), 5.16 (1H, dddd, *J* = 17.1, 1.6, 1.5, 1.5 Hz, CH_2-C12), 5.13—5.09 (1H, m, CH_2-C12), 4.26 (1H, dd, *J* = 10.0, 3.7 Hz, CH-C9), 3.96—3.91 (1H, m, CH_2-C1), 3.88 (1H, ddd, *J* = 8.9, 2.6, 2.6 Hz, CH-C5), 3.51 (1H, ddd, *J* = 10.9, 8.9, 4.6 Hz, CH-C4), 3.43—3.37 (1H, m, CH_2-C1), 2.74—2.68 (1H, m, CH_2-C10), 2.53—2.45 (1H, m, CH_2-C10), 2.14—2.08 (1H, m, CH_2-C3), 1.75—1.66 (2H, m, CH_2-C2), 1.61—1.52 (1H, m, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 202.4 (C-C8), 145.4 (CH-C7), 134.6 (CH-C11), 128.3 (CH-C6), 117.8 (CH_2-C12), 83.2 (CH-C9), 80.5 (CH-C5), 73.5 (CH-C4), 68.2 (CH_2-C1), 35.4 (CH_2-C10), 30.6 (CH_2-C3), 25.6 (CH_2-C2);
HRMS: (EI$^+$) for $C_{12}H_{16}O_3$ ([M]$^+$) calculated 208.1099, found 208.1100, Δ +0.2 ppm.

(4a*S*,6*R*,9a*R*)-6-Allyl-4,4a,6,9a-tetrahydro-2*H*-pyrano[3,2-*b*]oxepin-7(3*H*)-one (288)

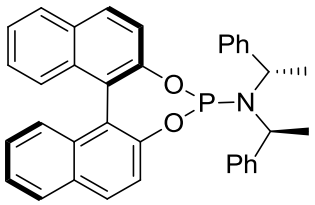


$C_{12}H_{16}O_3$
Molecular weight: 208.25 g.mol^{-1}

DBU (64 µL, 0.43 mmol) was added to a solution of **327** (88.8 mg, 0.430 mmol) in anhydrous toluene (5 mL). The reaction mixture was stirred for 48 h at rt, then the reaction was quenched with a saturated aqueous solution of NH_4Cl (7 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was quickly filtered through a short pad of silica gel (petroleum ether—Et_2O, 1:1) to afford **288** (73.8 mg, 83% yield, dr 10:1) as a colourless oil.

R_f = 0.57 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (26.5 °C, $CHCl_3$) = −8.30 (*c* = 1.00);
IR: ν_{max} 2944, 2925, 2852, 1664, 1261, 1127, 1092 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.41 (1H, dd, *J* = 12.8, 2.5 Hz, CH-C7), 5.95 (1H, dd, *J* = 12.8, 2.5 Hz, CH-C6), 5.82 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH-C11), 5.09 (1H, dddd, *J* = 17.1, 1.6, 1.5, 1.5 Hz, CH_2-C12), 5.06—5.03 (1H, m, CH_2-C12), 4.23 (1H, dd, *J* = 7.4, 4.2 Hz, CH-C9), 3.97—3.92 (1H, m, CH_2-C1), 3.83 (1H, ddd, *J* = 8.9, 2.5, 2.5 Hz, CH-C5), 3.42 (1H, ddd, *J* = 11.3, 11.3, 3.2 Hz, CH_2-C1), 3.34 (1H, ddd, *J* = 10.7, 8.9, 4.8 Hz, CH-C4), 2.59—2.53 (1H, m, CH_2-C10), 2.40 (1H, ddd, *J* = 14.7, 7.4, 6.9 Hz, CH_2-C10), 2.20—2.14 (1H, m, CH_2-C3), 1.74—1.66 (2H, m, CH_2-C2), 1.63—1.56 (1H, m, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 203.7 (C-C8), 144.8 (CH-C7), 133.7 (CH-C11), 128.0 (CH-C6), 117.7 (CH_2-C12), 86.8 (CH-C9), 80.6 (CH-C5), 78.6 (CH-C4), 68.3 (CH_2-C1), 37.9 (CH_2-C10), 30.6 (CH_2-C3), 25.5 (CH_2-C2);
HRMS: (EI$^+$) for $C_{12}H_{16}O_3$ ([M]$^+$) calculated 208.1099, found 208.1103, Δ +1.9 ppm.

***N*,*N*-bis[(*S*)-1-Phenylethyl]dinaphto[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-amine (*R_a*,*S*,*S*-308)**[146]

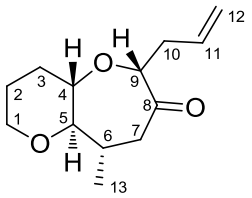


$C_{36}H_{30}NO_2P$
Molecular weight: 539.60 g.mol^{-1}

A solution of amine **309** (0.25 mL, 1.1 mmol) and Et_3N (0.17 mL, 1.3 mmol) in anhydrous toluene (2 mL) was added dropwise to a solution of phosphorus trichloride (97 µL, 1.1 mmol) in anhydrous toluene (15 mL) at rt. The reaction mixture was heated to 70 °C and stirred for 6 h. The solution was cooled to rt and then Et_3N (0.28 mL, 2.05 mmol) was added. The reaction mixture was cooled to −78 °C and (*R*)-BINOL (318 mg, 1.11 mmol) in anhydrous toluene:THF (4:1, 3.75 mL) was added dropwise. The solution was warmed slowly to rt then stirred overnight. The reaction mixture was filtered, then concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—EtOAc, 19:1) afforded *R_a*,*S*,*S*-**308** (275 mg, 46% yield) as a colourless solid.

R_f = 0.31 (petroleum ether—CH_2Cl_2, 3:1);
$[\alpha]_D$ (27.7 °C, $CHCl_3$) = −449 (*c* = 0.94);
{Lit.[146] $[\alpha]_D$ (20 °C, $CHCl_3$) = −456 (*c* = 0.79)};
m.p. = 96—98 °C
IR: ν_{max} 3059, 2973, 1591, 1463, 1376, 1327, 1231, 1204, 1071, 949 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 7.97—7.87 (4H, m, Ar), 7.62—7.07 (18H, m, Ar), 4.51 (2H, dq, *J* = 13.9, 7.0 Hz, 2 x CH), 1.73 (6H, d, *J* = 7.0 Hz, 2 x CH_3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 150.3—121.1 (Ar), 52.48 (CH), 52.38 (CH), 21.6 (CH_3, taken from HSQC);
HRMS: (ESI) for $C_{36}H_{30}NNaO_2P$ ($[M+Na]^+$) calculated 562.1912, found 562.1906, Δ +4.5 ppm.

(4a*S*,6*R*,9*S*,9a*R*)-6-Allyl-9-methylhexahydro-2*H*-pyrano[3,2-*b*]oxepin-7(3*H*)-one (287)

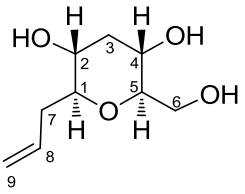


$C_{13}H_{20}O_3$
Molecular weight: 224.30 g.mol^{-1}

R$_a$,*S*,*S*-**308** (6 mg, 0.01 mmol) was added to a solution of copper (II) triflate (2 mg, 0.005 mmol) in anhydrous toluene (0.75 mL) at rt. The reaction mixture was stirred at rt for 30 min, then cooled to −40 °C. Dimethylzinc (0.2 mL of a 2 M solution in toluene, 0.4 mmol) was added dropwise, followed by a solution of **288** (18 mg, 0.087 mmol) in anhydrous toluene (0.75 mL). The solution was warmed to rt and allowed to stir overnight. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The phases were separated and the aqueous phase extracted with Et_2O (3 x 2 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded **287** (5.8 mg, 30% yield) as a colourless oil.

R_f = 0.55 (petroleum ether—Et_2O, 1:1);
^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 5.81 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH-C11), 5.13—5.04 (2H, m, CH_2-C12), 3.94—3.88 (1H, m, CH_2-C7), 3.83 (1H, dd, *J* = 7.7, 5.1 Hz, CH-C9), 3.30 (1H, ddd, *J* = 11.3, 11.3, 3.6 Hz, CH_2-C7), 2.96 (1H, ddd, *J* = 10.4, 9.3, 4.7 Hz, CH-C4), 2.88 (1H, dd, *J* = 12.0, 11.8 Hz, CH_2-C1), 2.83 (1H, dd, *J* = 9.4, 9.3 Hz, CH-C5), 2.43—2.30 (2H, m, CH_2-C10), 2.13 (1H, dd, *J* = 11.8, 1.9 Hz, CH_2-C1), 2.10—2.06 (1H, m, CH_2-C3), 1.73—1.62 (3H, m, CH_2-C2 and CH-C6), 1.53—1.47 (1H, m, CH_2-C3), 1.12 (3H, d, *J* = 6.6 Hz, CH_3-C13);
^{13}C NMR: (101 MHz, $CDCl_3$) δ_C 133.2 (CH-C11), 117.7 (CH_2-C12), 86.2 (CH-C5), 86.1 (CH-C9), 80.5 (CH-C4), 67.8 (CH_2-C7), 45.3 (CH_2-C1), 37.2 (CH_2-C10), 36.1 (CH-C6), 31.3 (CH_2-C3), 25.9 (CH_2-C2), 20.1 (CH_3-C13) (C-C8 not observed).

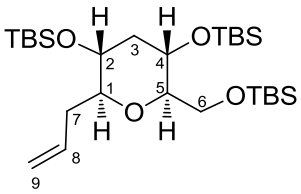
(2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,5-diol (314)



$C_9H_{16}O_4$
Molecular weight: 188.22 g.mol^{-1}

TBAF (9.15 mL of a 1.0 M solution in THF, 9.15 mmol) was added to a solution of **230** (1.00 g, 3.05 mmol) in anhydrous THF (50 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 48 h and then concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (CH_2Cl_2—MeOH, 19:1) to afford triol **314** which was used without further purification.

{[(2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-{[(*tert*-butyldimethylsilyl)oxy]methyl}tetrahydro-2*H*-pyran-3,5-diyl]bis(oxy)}bis(*tert*-butyldimethylsilane) (315)



$C_{27}H_{58}O_4Si_3$
Molecular weight: 531.00 g.mol^{-1}

Imidazole (2.50 g, 36.6 mmol), TBSCl (4.60 g, 30.5 mmol) and DMAP (187 mg, 1.53 mmol) were added to a solution of **314** (1.03 g, 6.10 mmol) in anhydrous DMF (100 mL) at 0 °C. The reaction mixture was warmed to rt, stirred overnight and then the reaction was quenched with H_2O (100 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 125 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded **315** (2.85 g, 88% yield over two steps) as a colourless oil.

R_f = 0.91 (petroleum ether—Et_2O, 1:1);

$[\alpha]_D$ (27.5 °C, $CHCl_3$) = −0.30 (*c* = 1.01);

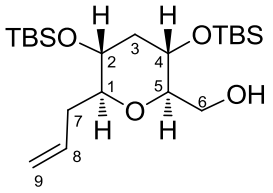
IR: ν_{max} 2928, 2857, 1472, 1462, 1362, 1252, 1080, 1005 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.91 (1H, dddd, *J* = 17.1, 10.2, 7.0, 7.0 Hz, CH-C8), 5.07 (1H, dddd, *J* = 17.1, 1.9, 1.5, 1.5 Hz, CH_2-C9), 5.04—5.00 (1H, m, CH_2-C9), 3.81 (1H, dd, *J* = 11.4, 1.8 Hz, CH_2-C6), 3.69 (1H, dd, *J* = 11.4, 4.8 Hz, CH_2-C6), 3.57 (1H, ddd, *J* = 11.3, 9.1, 4.7 Hz, CH-C4), 3.30 (1H, ddd, *J* = 11.0, 8.9, 4.7 Hz, CH-C2), 3.09 (1H, ddd, *J* = 8.9, 8.6, 2.8 Hz, CH-C1), 3.04 (1H, ddd, *J* = 9.1, 4.8, 1.8 Hz, CH-C5), 2.55—2.48 (1H, m, CH_2-C7), 2.20 (1H, ddd, *J* = 11.9, 4.7, 4.7 Hz, CH_2-C3), 2.10 (1H, ddd, *J* = 15.0, 8.6, 7.0 Hz, CH_2-C7), 1.46 (1H, app q, *J* = 11.9, 11.3, 11.0 Hz, CH_2-C3), 0.90—0.87 (27H, m, CH_3-*t*Bu), 0.07—0.04 (18H, m, CH_3-Me);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 135.7 (CH-C8), 116.4 (CH_2-C9), 82.8 (CH-C5), 81.6 (CH-C1), 69.9 (CH-C2), 65.9 (CH-C4), 62.9 (CH_2-C6), 43.5 (CH_2-C3), 36.3 (CH_2-C7), 26.1 (3 x CH_3-*t*Bu), 26.0 (3 x CH_3-*t*Bu), 25.9 (3 x CH_3-*t*Bu), 18.6 (C-*t*Bu), 18.1 (C-*t*Bu), 18.1 (C-*t*Bu), −3.8 (CH_3-Me), −4.2 (CH_3-Me), −4.5 (CH_3-Me), −4.7 (CH_3-Me), −4.9 (CH_3-Me), −5.1 (CH_3-Me);

HRMS: (CI, isobutane) for $C_{27}H_{59}O_4Si_3$ ($[M+H]^+$) calculated 531.3721, found 531.3728, Δ +1.3 ppm.

[(2*R*,3*S*,5*R*,6*S*)-6-Allyl-3,5-bis[(*tert*-butyldimethylsilyl)oxy]tetrahydro-2*H*-pyran-2-yl]methanol (316)

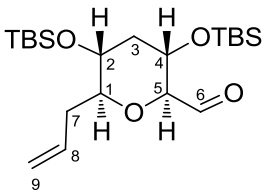


$C_{21}H_{44}O_4Si_2$
Molecular weight: 416.74 g.mol^{-1}

Camphorsulfonic acid (367 mg, 1.58 mmol) was added to a solution of **315** (2.79 g, 5.25 mmol) in CH_2Cl_2:MeOH (1:1, 200 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C, then the reaction was quenched with Et_3N (0.40 mL, 2.6 mmol). The solution was concentrated under reduced pressure and the crude product purified by flash column chromatography on silica gel (petroleum ether—Et_2O, 9:1) to afford alcohol **316** (1.95 g, 89% yield) as a colourless oil.

R_f = 0.83 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (25.9 °C, $CHCl_3$) = −0.50 (*c* = 1.01);
IR: ν_{max} 3497, 2955, 2930, 2886, 2859, 1471, 1252, 1078, 1005 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.87 (1H, dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, CH-C8), 5.11—5.02 (2H, m, CH_2-C9), 3.81 (1H, ddd, *J* = 10.6, 7.3, 3.1 Hz, CH_2-C6), 3.60—3.54 (1H, m, CH_2-C6), 3.51 (1H, ddd, *J* = 11.1, 9.0, 4.5 Hz, CH-C4), 3.34 (1H, ddd, *J* = 11.1, 9.0, 4.5 Hz, CH-C2), 3.20—3.13 (2H, m, CH-C1 and CH-C5), 2.59—2.53 (1H, m, CH_2-C7), 2.22 (1H, ddd, *J* = 12.0, 4.5, 4.5 Hz, CH_2-C3), 2.13—2.07 (1H, m, CH_2-C7), 1.98 (1H, dd, *J* = 7.3, 5.6 Hz, OH), 1.51 (1H, ddd, *J* = 12.0, 11.1, 11.1 Hz, CH_2-C3), 0.89 (9H, s, CH_3-*t*Bu), 0.88 (9H, s, CH_3-*t*Bu), 0.07 (6H, s, CH_3-Me), 0.06 (6H, s, CH_3-Me);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 135.2 (CH-C8), 116.8 (CH_2-C9), 81.7 (CH-C5), 81.3 (CH-C1), 69.8 (CH-C2), 67.0 (CH-C4), 63.1 (CH_2-C6), 43.4 (CH_2-C3), 36.2 (CH_2-C7), 25.9 (3 x CH_3-*t*Bu), 25.8 (3 x CH_3-*t*Bu), 18.1 (C-*t*Bu), 18.0 (C-*t*Bu), −3.9 (CH_3-Me), −4.1 (CH_3-Me), −4.5 (CH_3-Me), −4.8 (CH_3-Me);
HRMS: (CI, isobutane) for $C_{21}H_{45}O_4Si_2$ ($[M+H]^+$) calculated 417.2856, found 417.2851, Δ −1.4 ppm.

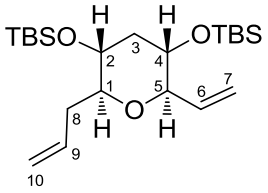
(2*S*,3*S*,5*R*,6*S*)-6-Allyl-3,5-bis((*tert*-butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-2-carbaldehyde (317)



$C_{21}H_{42}O_4Si_2$
Molecular weight: 414.73 g.mol^{-1}

Et_3N (3.14 mL, 22.6 mmol) was added to a solution of **316** (1.88 g, 4.51 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred for 5 min then sulfur trioxide pyridine complex (2.15 g, 13.5 mmol) in anhydrous DMSO (4.80 mL) was added dropwise. The solution was stirred for 3 h at 0 °C and then the reaction was quenched with H_2O (50 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 75 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was filtered through a short pad of silica gel (petroleum ether—Et_2O, 1:1) to afford aldehyde **317** that was used without further purification.

{[(2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-vinyltetrahydro-2*H*-pyran-3,5-diyl]bis(oxy)}bis*tert*-butyldimethylsilane (318)



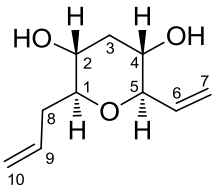
$C_{22}H_{44}O_3Si_2$
Molecular weight: 412.75 g.mol^{-1}

NaHMDS (18.1 mL of a 1 M solution in THF, 18.1 mmol) was added to a suspension of methyltriphenylphosphonium bromide (7.40 g, 20.8 mmol) in anhydrous THF (30 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then a solution of crude **317** [4.51 mmol] in anhydrous THF (60 mL) was added. The reaction mixture was stirred for 1 h at 0 °C and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (100 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 125 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$) and concentrated

under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 99:1) afforded diene **318** (1.69 g, 91% yield over two steps) as a colourless oil.

R_f = 0.94 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (26.6 °C, $CHCl_3$) = +1.14 (*c* = 1.10);
IR: ν_{max} 2954, 2930, 2885, 2858, 1642, 1473, 1362, 1251, 1082, 1005 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.97—5.86 (2H, m, CH-C9 and CH-6), 5.33 (1H, ddd, *J* = 17.4, 1.9, 1.6, CH_2-C7), 5.17 (1H, ddd, *J* = 10.7, 2.2, 1.6 Hz, CH_2-C7), 5.09 (1H, dddd, *J* = 17.2, 1.9, 1.5, 1.5 Hz, CH_2-C10), 5.06—5.03 (1H, m, CH_2-C10), 3.52 (1H, dd, *J* = 8.9, 5.4 Hz, CH-C5), 3.38 (1H, ddd, *J* = 11.0, 9.0, 4.5 Hz CH-C2), 3.34 (1H, ddd, *J* = 11.2, 8.9, 4.5 Hz, CH-C4), 3.16 (1H, ddd, *J* = 9.0, 8.5, 2.9 Hz, CH-C1), 2.59—2.52 (1H, m, CH_2-C8), 2.23 (1H, ddd, *J* = 12.0, 4.5, 4.5 Hz, CH_2-C3), 2.20—2.12 (1H, m, CH_2-C8), 1.52 (1H, ddd, *J* = 12.0, 11.2, 11.0 Hz, CH_2-C3), 0.89 (9H, s, CH_3-*t*Bu), 0.87 (9H, s, CH_3-*t*Bu), 0.07 (6H, s, CH_3-Me), 0.04 (6H, s, CH_3-Me);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 136.3 (CH-C9), 135.4 (CH-C6), 116.6 (CH_2-C7), 116.4 (CH_2-C10), 82.3 (CH-C5), 81.3 (CH-C1), 70.6 (CH-C4), 69.8 (CH-C2), 43.8 (CH_2-C3), 36.3 (CH_2-C8), 26.0 (3 x CH_3-*t*Bu), 25.9 (3 x CH_3-*t*Bu), 18.2 (C-*t*Bu), 18.1 (C-*t*Bu), −3.8 (CH_3-Me), −4.1 (CH_3-Me), −4.4 (CH_3-Me), −4.5 (CH_3-Me);
HRMS: (CI, isobutane) for $C_{22}H_{45}O_3Si_2$ ($[M+H]^+$) calculated 413.2907, found 413.2911, Δ +1.0 ppm.

(2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-vinyltetrahydro-2*H*-pyran-3,5-diol (313)

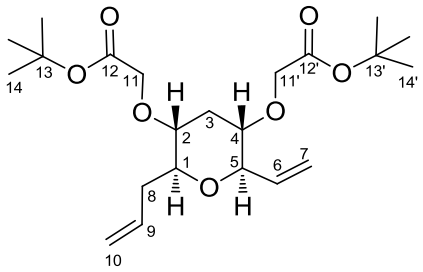


$C_{10}H_{16}O_3$
Molecular weight: 184.23 g.mol^{-1}

Camphorsulfonic acid (2.18 g, 9.40 mmol) was added to a solution of **318** (1.55 g, 3.76 mmol) in CH_2Cl_2:MeOH (1:1, 60 mL) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with Et_3N (2.00 mL, 15.1 mmol) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—EtOAc, 3:7) afforded diol **313** (655 mg, 95% yield) as a colourless solid.

R_f = 0.13 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (22.2 °C, $CHCl_3$) = +2.20 (*c* = 1.00);
m.p. = 39—41 °C;
IR: ν_{max} 3356, 2924, 2859, 1641, 1431, 1354, 1080, 1030 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 5.95 (1H, dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, CH-C9), 5.85 (1H, ddd, *J* = 17.4, 10.5, 6.9 Hz, CH-C6), 5.41 (1H, ddd, *J* = 17.4, 1.6, 1.1 Hz, CH_2-C7), 5.33 (1H, ddd, *J* = 10.5, 1.6, 0.9 Hz, CH_2-C7), 5.15 (1H, dddd, *J* = 17.2, 1.9, 1.9, 1.5 Hz, CH_2-C10), 5.09 (1H, ddd, *J* = 10.2, 1.9, 1.0 Hz, CH_2-C10), 3.56—3.46 (2H, m, CH-C5 and CH-C2), 3.41—3.34 (1H, m, CH-C4), 3.20 (1H, ddd, *J* = 9.1, 6.9, 4.3 Hz, CH-C1), 2.61—2.52 (1H, m, CH_2-C8), 2.46 (1H, ddd, *J* = 11.6, 4.6, 4.6 Hz, CH_2-C3), 2.40—2.30 (1H, m, CH_2-C8), 1.71 (1H, d, *J* = 3.5 Hz, OH), 1.65 (1H, d, *J* = 5.2 Hz, OH), 1.49 (1H, app q, *J* = 11.6 Hz, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 135.7 (CH-C6), 134.9 (CH-C9), 119.3 (CH_2-C7), 117.3 (CH_2-C10), 83.5 (CH-C5), 80.9 (CH-C1), 69.4 (CH-C2), 68.8 (CH-C4), 40.9 (CH_2-C3), 36.8 (CH_2-C8);
HRMS: (CI, isobutane) for $C_{10}H_{17}O_3$ ($[M+H]^+$) calculated 185.1178, found 185.1174, Δ −2.2 ppm.

Di-*tert*-butyl-2,2'-{[(2*S*,3*R*,5*S*,6*R*)-2-allyl-6-vinyltetrahydro-2*H*-pyran-3,5-diyl]bis(oxy)}diacetate (319)



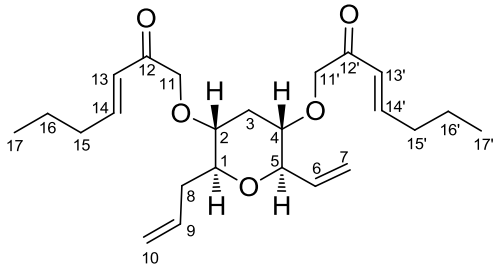
$C_{22}H_{36}O_7$
Molecular weight: 412.52 g.mol^{-1}

A 30% aqueous solution of NaOH (6 mL) was added to a solution of **313** (176 mg, 0.960 mmol) in toluene (6 mL) at 0 °C. After 5 min, *tert*-butyl-bromoacetate (0.60 mL, 3.8 mmol) and TBAI (355 mg, 0.960 mmol) were added and the reaction mixture was stirred overnight at rt. A further 1 eq of TBAI (355 mg, 0.960 mmol) and 3 eq of *tert*-butyl-bromoacetate (0.60 mL, 3.8 mmol) were added and the reaction mixture was stirred overnight. The solution was diluted with toluene (10 mL) and H_2O (10 mL). The phases were separated and the aqueous phase extracted with toluene (3 x 15 mL). The organic extracts were combined, washed with 1 M HCl (30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 19:1) afforded ester **319** (210 mg, 53% yield) as a colourless oil.

R_f = 0.63 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (26.8 °C, $CHCl_3$) = −8.78 (*c* = 0.95);
IR: ν_{max} 2980, 2931, 1749, 1730, 1369, 1303, 1252, 1226, 1126 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.00 (1H, ddd, *J* = 17.1, 10.7, 5.5 Hz, CH-C6), 5.97—5.88 (1H, m, CH-C9), 5.41 (1H, ddd, *J* = 17.1, 1.5, 1.5 Hz, CH_2-C7), 5.23 (1H, ddd, *J* = 10.7, 1.5, 1.5 Hz, CH_2-C7), 5.11 (1H, dd, *J* = 17.2, 1.9, 1.5, 1.5 Hz, CH_2-C10), 5.07—5.02 (1H, m, CH_2-C10), 4.06—3.96 (4H, m, CH_2-C11 and CH_2-C11'), 3.64 (1H, dd, *J* = 9.3, 5.6 Hz, CH-C4), 3.30 (1H, ddd, *J* = 9.7, 7.6, 3.2, CH-C1), 3.18 (1H, ddd, *J* = 12.0, 9.7, 5.0 Hz, CH-C2), 3.13 (1H, ddd, *J* = 11.2, 9.3, 4.6 Hz, CH-C5), 2.73 (1H, ddd, *J* = 12.0, 5.0, 4.7 Hz, CH_2-C3), 2.70—2.65 (1H, m, CH_2-C8), 2.28 (1H, ddd, *J* = 14.8, 7.6, 7.6 Hz, CH_2-C8), 1.48 (9H, s, CH_3-C14) 1.47 (9H, s, CH_3-C14'), 1.51—1.44 (1H, m, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 169.7 and 169.5 (C-C12/C12'), 135.8 (CH-C6), 135.1 (CH-C9), 117.3 (CH_2-C7), 116.9 (CH_2-C10), 81.8 and 81.7 (C-C13/C13'),

80.7 (CH–C4), 79.6 (CH–C1), 78.1 (CH–C2), 77.0 (CH–C5), 67.9 and 67.1 (CH_2-C11/C11′), 36.3 (CH_2–C8), 35.6 (CH_2–C3), 28.3 (3 x CH_3–C14 and 3 x CH_3-C14′).

(3*E*,3'*E*)-1,1'-{[(2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-vinyltetrahydro-2*H*-pyran-3,5-diyl]bis(oxy)}bis(hept-3-en-2-one) (312)



$C_{24}H_{36}O_5$
Molecular weight: 404.54 g.mol^{-1}

A solution of **313** (300 mg, 1.63 mmol) in anhydrous THF (30 mL) was added to a suspension of sodium hydride (313 mg of a 60% suspension in mineral oil, 13.1 mmol) in anhydrous THF (30 mL) at 0 °C. The reaction mixture was warmed to rt, then triphenylchloroacetonylphosphorane (1.38 g, 3.91 mmol) and TBAI (60.0 mg, 0.160 mmol) were added. The reaction mixture was heated to reflux, stirred for 3 h then cooled to rt and the reaction was quenched with H_2O (15 mL). The solution was concentrated under reduced pressure and the aqueous phase extracted with EtOAc (4 x 75 mL). The organic extracts were combined, washed with brine (125 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude phosphorane **322** was then used without further purification.

Butyraldehyde (4.40 mL, 48.9 mmol) was added to a solution of crude **322** [1.63 mmol] in anhydrous CH_2Cl_2 (60 mL). The reaction mixture was heated to reflux and stirred for 48 h. The solution was concentrated under reduced pressure and the crude residue product purified by flash column chromatography on silica gel (petroleum ether—Et_2O, 8:2) to afford enone **312** (570 mg, 86% yield over two steps) as a pale yellow oil.

R_f = 0.65 (petroleum ether—Et_2O, 1:1);

$[\alpha]_D$ (23.4 °C, $CHCl_3$) = +1.55 (*c* = 0.97);

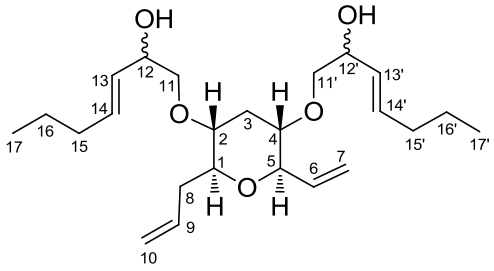
IR: ν_{max} 2959, 2932, 2905, 2872, 1694, 1624, 1456, 1433, 1339, 1290, 1085 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.95 (2H, dddd, *J* = 15.9, 9.1, 6.9, 6.9 Hz, CH-C14/C14′), 6.26 (2H, dddd, *J* = 15.9, 5.7, 1.5, 1.5 Hz, CH-C13/C13′), 6.00—5.89 (2H, m, CH-C6 and CH-C9), 5.41 (1H, ddd, *J* = 17.2, 1.9, 1.6 Hz, CH_2-C7), 5.24 (1H, ddd, *J* = 10.7, 1.9, 1.6 Hz, CH_2-C7), 5.09 (1H, ddd, *J* = 17.3, 3.3, 1.4 Hz, CH_2-C10), 5.07—5.03 (1H, m, CH_2-C10), 4.30 (1H, d, *J* = 16.4 Hz, CH_2-C11), 4.26 (1H, d, *J* = 16.6 Hz, CH_2-C11′), 4.22 (1H, d, *J* = 16.6 Hz, CH_2-C11′), 4.19 (1H, d, *J* = 16.4 Hz, CH_2-C11), 3.69 (1H, dd, *J* = 9.2, 5.7 Hz, CH-C5), 3.36 (1H, ddd, *J* = 9.2, 7.4, 3.3 Hz, CH-C1), 3.16 (1H, ddd, *J* = 11.1, 9.2, 4.5 Hz, CH-C2), 3.09 (1H, ddd, *J* = 11.2, 9.2, 4.5 Hz, CH-C4), 2.71 (1H, ddd, *J* = 11.8, 4.5, 4.5 Hz, CH_2-C3), 2.67—2.61 (1H, m, CH_2-C8), 2.29 (1H, ddd, *J* = 14.6, 7.4, 7.3 Hz, CH_2-C8), 2.20 (4H, 2 x app p, *J* = 7.3 Hz and *J* = 7.3 Hz, CH_2-C15/C15′), 1.54—1.46 (5H, m, CH_2-C16/C16′ and CH_2-C3), 0.94 (6H, 2 x t, *J* = 7.4 Hz and *J* = 7.4 Hz, CH_3-C17/C17′);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 196.8 and 196.5 (C-C12/C12′), 149.0 (CH-C14/C14′), 135.8 (CH-C6), 134.8 (CH-C9), 126.2 and 126.1 (CH-C13/C13′), 117.5 (CH_2-C7), 117.0 (CH_2-C10), 80.7 (CH-C5), 79.4 (CH-C1), 78.2 (CH-C4), 76.9 (CH-C2), 74.1 and 73.4 (CH_2-C11/C11′), 36.3 (CH_2-C8), 35.3 (CH_2-C3), 34.8 (CH_2-C15/15′), 21.4 (CH_2-C16/C16′), 13.8 (CH_3-C17/C17′);

HRMS: (EI^+) for $C_{24}H_{36}O_5$ ($[M]^+$) calculated 404.2563, found 404.2566, Δ +0.7 ppm.

(3*E*,3'*E*)-1,1'-{[(2*S*,3*R*,5*S*,6*R*)-2-Allyl-6-vinyltetrahydro-2*H*-pyran-3,5-diyl]bis(oxy)}bis(hept-3-en-2-ol) (323)

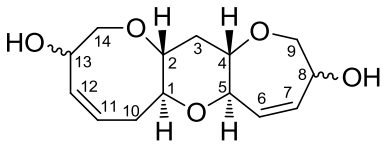


$C_{24}H_{40}O_5$
Molecular weight: 408.57 g.mol^{-1}

Cerium trichloride heptahydrate (428 mg, 1.15 mmol) and sodium borohydride (44.0 mg, 1.15 mmol) were added to a solution of **312** (200 mg, 0.480 mmol) in MeOH (25 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (35 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford alcohols **323** (188 mg, 96% yield, dr 1:1) as a colourless oil. Alcohols **323** were used in the next step without further purification.

R_f = 0.39 (petroleum ether—Et_2O, 1:1)
IR: ν_{max} 3430, 2957, 2926, 2870, 1458, 1344, 1288, 1107, 970 cm^{-1}.
HRMS: (CI, isobutane) for $C_{24}H_{41}O_5$ ($[M+H]^+$) calculated 409.2954, found 409.2955, Δ +0.2 ppm.

(5a*R*,6a*S*,12a*R*,13a*S*,*Z*)-2,3,5a,6a,7,10,11,12a,13,13a-Decahydrooxepino [2',3':5,6]pyrano[3,2-*b*]oxocine-3,10-diol (324)

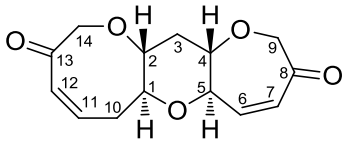


$C_{14}H_{20}O_5$
Molecular weight: 268.31 g.mol^{-1}

Hoveyda-Grubbs second generation catalyst **150** (12.0 mg, 0.0190 mmol) was added to a solution of **323** (76.0 mg, 0.190 mmol) in degassed anhydrous CH_2Cl_2 (20 mL). The reaction mixture was heated to reflux and stirred overnight. The solution was concentrated under reduced pressure and the crude product used without further purification.

R_f = 0.10 (petroleum ether—Et_2O, 1:1)

(5a*R*,6a*S*,12a*R*,13a*S*,*Z*)-6a,7,11,12a,13,13a-Hexahydrooxepino[2',3':5,6] pyrano[3,2-*b*]oxocine-3,10(2*H*,5a*H*)-dione (311)



$C_{14}H_{16}O_5$
Molecular weight: 264.27 g.mol^{-1}

Dess-Martin periodinane (161 mg, 0.380 mmol) was added to a solution of crude **324** [0.190 mmol] in CH_2Cl_2 (10 mL) at 0 ºC. The reaction mixture was stirred for 2 h at 0 °C, then the reaction was quenched with a solution of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 20 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 1:1) afforded enone **311** (19.7 mg, 39% yield over two steps) as a colourless solid.

R_f = 0.21 (petroleum ether—Et_2O, 1:1);

$[\alpha]_D$ (25.6 °C, $CHCl_3$) = −87.3 (*c* = 1.00);

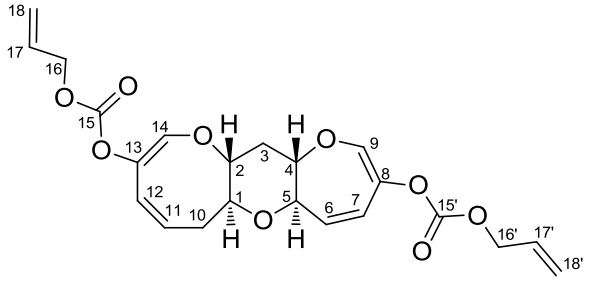
m.p. = 175—177 °C;

IR: ν_{max} 2959, 2922, 2872, 2356, 1684, 1669, 1465, 1281, 1120, 1077, 1014 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.50 (1H, dd, *J* = 12.9, 2.0 Hz, CH–C6), 6.46 (1H, ddd, *J* = 12.3, 9.0, 8.0 Hz, CH–C11), 6.03 (1H, dd, *J* = 12.9, 2.6 Hz, CH–C7), 5.89 (1 H, d, *J* = 12.3 Hz, CH–C12), 4.53 (1H, dd, *J* = 17.7, 0.9 Hz, CH_2–C14), 4.39 (1H, d, *J* = 18.2 Hz, CH_2–C9), 4.26 (1H, d, *J* = 18.2 Hz, CH_2–C9), 4.22 (1H, d, *J* = 17.7 Hz, CH_2–C14), 3.97 (1H, ddd, *J* = 9.0, 2.6, 2.0 Hz, CH–C5), 3.49 (1H, ddd, *J* = 11.2, 9.0, 4.8 Hz, CH–C4), 3.43 (1H, ddd, *J* = 11.6, 9.2, 4.1 Hz, CH–C2), 3.36 (1H, ddd, *J* = 9.2, 9.0, 1.3 Hz, CH–C1), 2.73—2.65 (1H, m, CH_2–C10), 2.60 (1H, ddd, *J* = 14.8, 9.0, 1.1 Hz, CH_2–C10), 2.48 (1H, ddd, *J* = 12.2, 4.8, 4.1 Hz, CH_2-C3), 1.80 (1H, ddd, *J* = 12.2, 11.6, 11.2 Hz, CH_2–C3);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 203.2 (C–C8), 201.2 (C–C13), 144.6 (CH–C6), 137.2 (CH–C11), 129.5 (CH–C12), 128.4 (CH–C7), 84.6 (CH–C2), 80.8 (CH–C5), 79.0 (CH_2-C14), 78.7 (CH–C4), 77.8 (CH–C1), 77.5 (CH_2–C9), 37.6 (CH_2–C3), 34.6 (CH_2-C10).

Diallyl[(5a*R*,6a*S*,8*Z*,10*E*,12a*R*,13a*S*)-5a,6a,7,12a,13,13a-hexahydrooxepino [2',3':5,6]pyrano[3,2-*b*]oxocine-3,10-diyl]dicarbonate (325)



$C_{22}H_{24}O_9$
Molecular weight: 423.42 $g.mol^{-1}$

Allylchloroformate (0.05 mL, 0.4 mmol) was added to a solution of **311** (47.9 g, 0.180 mmol) in anhydrous THF (3 mL) at −78 °C. The reaction mixture was stirred for 10 min, then NaHMDS (0.90 mL of a 1 M solution in THF, 0.90 mmol) was added. The reaction mixture was stirred for 3 h at −78 °C, then the reaction was quenched with a 5% solution of KH_2PO_4 (5 mL). The phases were separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$) and concentrated

under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 9:1) afforded carbonate **325** (53.5 g, 69% yield) as an unstable colourless solid.

R_f = 0.74 (petroleum ether—Et_2O, 1:1);

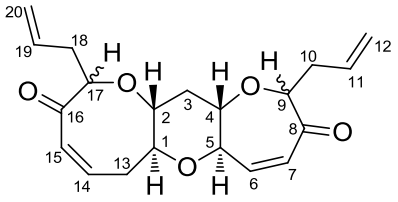
IR: ν_{max} 2949, 2360, 1758, 1246, 1221, 1160, 1053, 1032 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.68 (1H, s, CH-C9 or CH-C14), 6.56 (1H, s, CH-9 or CH-14), 5.99—5.87 (4H, m, CH-C17/C17′ and CH-C7 and CH-C12), 5.78—5.70 (2H, m, CH-C11 and CH-C6), 5.39 (1H, dddd, *J* = 6.8, 1.5, 1.3, 1.3 Hz, CH_2-C18 or C18′), 5.35 (1H, dddd, *J* = 6.8, 1.5, 1.3, 1.3 Hz, CH_2-C18 or 18′), 5.32—5.26 (2H, m, CH_2-C18/C18′), 4.65 (2H, d, *J* = 5.8 Hz, CH_2-C16 or C16′), 4.63 (2H, d, *J* = 5.8 Hz, CH_2-C16 or C16′), 4.47—4.38 (1H, m, CH-C2), 3.87 (1H, d, *J* = 7.4 Hz, CH-C5), 3.67—3.60 (1H, m, CH-C4), 3.33 (1H, ddd, *J* = 8.8, 3.2, 3.2 Hz, CH-C1), 2.90—2.82 (1H, m, CH_2-C10), 2.62—2.54 (2H, m, CH_2-C10 and CH_2-C3), 1.79 (1H, app q, *J* = 11.8 Hz, CH_2-C3).

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 154.7 and 154.6 (C-C15/C15′), 142.1 (CH-C9 or CH-C14), 141.3 (CH-C9 or CH-C14), 133.5 (CH-C12 or CH-C7), 133.0 (C-C8 or C-C13), 131.3 and 131.2 (CH-C17/C17′), 130.0 (C-C8 or C-C13), 129.5 (CH-C11 or CH-C6), 128.1 (CH-C12 or CH-C7), 121.3 (CH-C11 or CH-C6), 119.6 and 119.4 (CH_2-C18/C18′), 77.9 (CH-C5), 76.3 (CH-C4), 72.7 (CH-C1), 72.3 (CH-C2), 69.3 and 69.1 (CH_2-C16/C16′), 36.9 (CH_2-C3), 31.3 (CH_2-C10);

HRMS: (EI$^+$) for $C_{22}H_{24}O_9$ ([M]$^+$) calculated 432.1420, found 432.1419, Δ −0.4 ppm.

(5a*R*,6a*S*,12a*R*,13a*S*,*Z*)-2,11-Diallyl-6a,7,11,12a,13,13a-hexahydrooxepino [2',3':5,6]pyrano[3,2-*b*]oxocine-3,10(2*H*,5a*H*)-dione (328)

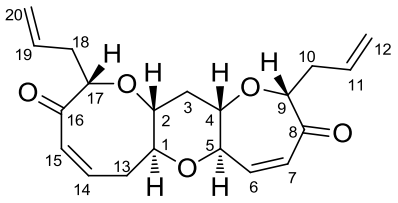


$C_{20}H_{24}O_5$
Molecular weight: 344.40 g.mol^{-1}

(*S*)-*t*Bu-PHOX ligand **(*S*)-282** (19.4 mg, 0.0500 mmol) was added to a solution of tetrakis(triphenylphosphine)palladium (23.0 mg, 0.0200 mmol) in degassed anhydrous THF (5.5 mL) at rt. The reaction mixture was stirred for 30 min at rt, then a solution of **325** (43.9 g, 0.100 mmol) in degassed anhydrous THF (2.5 mL) was added. The reaction was stirred for 2.5 h at rt, then concentrated under reduced pressure. The crude product was filtered through a small pad of silica (petroleum ether—Et_2O, 3:1) to afford enone **328** (29.0 mg, 84% yield) as a mixture of diastereomers. (Mixture of diastereomers identified by crude 1H NMR analysis.)

R_f = 0.36 (petroleum ether—Et_2O, 1:1);
IR: ν_{max} 2917, 2873, 1674, 1660, 1297, 1275, 1103, 1075, 1020 cm^{-1};
HRMS: (EI$^+$) for $C_{20}H_{24}O_5$ ([M]$^+$) calculated 344.1624, found 344.1620, Δ −1.2 ppm.

(2*R*,5a*R*,6a*S*,11*S*,12a*R*,13a*S*,*Z*)-2,11-Diallyl-6a,7,11,12a,13,13a-hexahydro oxepino[2',3':5,6]pyrano[3,2-*b*]oxocine-3,10(2*H*,5a*H*)-dione (310)



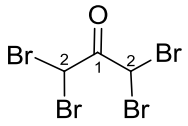
$C_{20}H_{24}O_5$
Molecular weight: 344.40 g.mol^{-1}

DBU (12.5 µL, 0.0840 mmol) was added to a solution of **328** (29.0 mg, 0.084 mmol) in anhydrous toluene (1.5 mL) at rt. The reaction mixture was stirred at rt in the dark for 24 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (2 mL), then the phases were separated and the aqueous phase extracted with Et_2O (3 x 5 mL). The organic extracts were

combined, washed with brine (7.5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. A quick filtration through a small pad of silica gel (petroleum ether—Et_2O, 1:1) afforded the desired enone **310** (8.9 mg, 31% yield, dr 6:1) as a colourless oil.

R_f = 0.37 (petroleum ether—Et_2O, 1:1);
$[\alpha]_D$ (25.4 °C, $CHCl_3$) = −87.6 (*c* = 0.28);
IR: ν_{max} 2926, 2864, 2357, 2341, 1669, 1660, 1107, 1087, 1058, 1034, 1016 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.47—6.40 (2H, m, CH-14 and CH-6), 5.98 (1H, dd, *J* = 12.8, 2.6 Hz, CH-C7), 5.91 (1H, d, *J* = 12.3 Hz, CH-C15), 5.87—5.78 (2H, m, CH-C19 and CH-C11), 5.20—5.05 (4H, m, CH_2-C20 and CH_2-C12), 4.25 (1H, dd, *J* = 7.4, 4.3 Hz, CH-C9), 4.19 (1H, dd, *J* = 9.2, 3.6 Hz, CH-C17), 3.92 (1H, ddd, *J* = 9.0, 2.4, 2.4 Hz, CH-C5), 3.44 (1H, ddd, *J* = 11.3, 9.0, 4.8 Hz, CH-C4), 3.39—3.34 (1H, m, CH-C2), 3.28 (1H, ddd, *J* = 10.1, 9.5, 1.1 Hz, CH-C1), 2.75—2.69 (1H, m, CH_2-C13), 2.68—2.62 (1H, m, CH_2-C18), 2.59—2.53 (2H, m, CH_2-C13 and CH_2-C3), 2.50—2.45 (1H, m, CH_2-C10), 2.45—2.38 (1H, m, CH_2-C10), 2.34—2.27 (1H, m, CH_2-C18), 1.77 (1H, ddd, *J* = 12,2, 11.6, 11.3 Hz, CH_2-C3);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 203.2 and 202.3 (C-16 and C-8), 143.2 (CH-C15), 136.2 (CH-C7), 134.0 and 133.4 (CH-C19 and CH-C11), 130.9 (CH-C6), 128.5 (CH-C14), 118.7 and 118.0 (CH_2-C20 and CH_2-C12), 88.2 (CH-C17), 86.9 (CH-C9), 85.2 (CH-C2), 80.4 (CH-C5), 77.9 (CH-C1), 77.5 (CH-C4), 38.2 (CH_2-C10), 37.9 (CH_2-C3), 37.1 (CH_2-C18), 33.9 (CH_2-C13);
HRMS: (ESI) for $C_{20}H_{24}NaO_5$ ($[M+Na]^+$) calculated 367.1521, found 367.1516, Δ +4.3 ppm.

1,1,3,3-Tetrabromopropan-2-one[152]



$C_3H_2Br_4O$
Molecular weight: 373.66 g.mol^{-1}

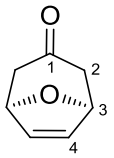
Bromine (65.0 mL, 1.27 mol) was added dropwise over 4 h to a stirred solution of acetone (25.0 mL, 0.340 mol) in hydrogen bromide (30.0 mL of a 48% aqueous solution, 0.270 mol) at 0 ºC. The reaction mixture was warmed to rt and stirred overnight. The solution was cooled to 0 ºC then diluted with H_2O (200 mL) and CH_2Cl_2 (300 mL). A saturated aqueous solution of $NaHCO_3$ (300 mL) was added, then the two phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 200 mL). The organic extracts were combined, washed with a saturated aqueous solution of $Na_2S_2O_3$ (50 mL) and H_2O (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was distilled under reduced pressure (130 ºC, 15 mbar) to deliver a yellow oil. Crystallization using petroleum ether and EtOAc afforded tetrabromoacetone (52.2 g, 41% yield) as a colourless solid.

R_f = 0.71 (petroleum ether—Et_2O, 1:1);
IR: ν_{max} 3011, 1728, 1244, 1088, 1044 cm^{-1};
m.p. = 37—39 ºC;
^{1}**H NMR**: (400 MHz, $CDCl_3$) δ_H 6.37 (2H, s, CH–C2);
^{13}**C NMR**: (101 MHz, $CDCl_3$) δ_C 183.6 (C–C1), 34.0 (2 x CH–C2).

Preparation of Zn/Cu couple[164]

A suspension of activated zinc dust (20.2 g, 309 mmol) in degassed H_2O (80 mL) was treated with copper (II) sulfate (3.45 g, 21.6 mmol) and lead (II) chloride (433 mg, 1.50 mmol). The reaction mixture was stirred under an argon atmosphere for 45 min. The reaction mixture was filtered under argon and the black solid obtained washed with degassed H_2O (200 mL) and degassed acetone (200 mL). The Zn/Cu couple was dried at 100 ºC under vacuum for 6 h, then stored under argon.

(1*R,5*S**)-8-Oxabicyclo[3.2.1]oct-6-en-3-one (335)**[152]



$C_7H_8O_2$
Molecular weight: 124.14 g.mol^{-1}

Furan (11.1 mL, 153 mmol) was added to a suspension of activated zinc dust (7.40 g, 112 mmol) in anhydrous THF (25 mL). A solution of tetrabromoacetone (30.0 g, 102 mmol) and triethyl borate (22.5 mL, 132 mmol) in anhydrous THF (15 mL) was added dropwise over 15 min. After the addition of 80% of the tetrabromoacetone solution, bromine (0.3 mL) was added and then the addition was completed. The reaction mixture was warmed to 40 °C until the exothermic reaction started, then the oil bath was removed and the reaction stirred overnight at rt. The solution was cooled to −15 °C, the reaction was quenched with H_2O (30 ml) and the resulting mixture was stirred for 30 min at rt. The reaction mixture was filtered through a short pad of Celite and the pad washed with Et_2O (5 x 100 mL). The solution was washed with H_2O (2 x 150 mL) and brine (250 mL). The phases were separated and the aqueous phase extracted with Et_2O (2 x 150 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure.

A solution of the residue material [64.4 mmol] in MeOH (30 mL) was added to a suspension of Zn/Cu couple (16.8 g) and NH_4Cl (10.3 g, 193 mmol) in MeOH (30 mL) at −78 °C. After 10% of the solution was added, the reaction mixture was stirred for 15 min at −78 °C then warmed to 0 °C. Addition of the solution was completed and the mixture was warmed to rt and stirred overnight. The resulting solution was filtered through a small pad of Celite and the pad washed with Et_2O (3 x 150mL). The combined filtrate was washed with brine (200 mL), then the phases were separated and the aqueous phase extracted with $CHCl_3$ (4 x 100 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Any remaining traces of HBr were removed by filtration through a small pad of K_2CO_3 and the pad washed with $CHCl_3$ (3 x 30 mL). Flash column chromatography (petroleum ether—Et_2O, 9:1 to 1:1) afforded **335** (3.59 g, 45% yield over two steps) as a pale yellow solid.

R_f = 0.32 (petroleum ether—Et_2O, 1:1);

m.p. = 39—41 °C;

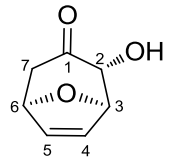
IR: ν_{max} 2990, 2969, 2011, 2895, 1707, 1400, 1343, 1180, 1123, 1030 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 6.26 (2H, s, CH–C4), 5.04 (2H, d, *J* = 5.1 Hz, CH-C3), 2.76 (2H, dd, *J* = 17.0, 5.1 Hz, CH_2–C2), 2.33 (2H, d, *J* = 17.0 Hz, CH_2-C2);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 205.4 (C–C1), 133.4 (CH–C4), 77.3 (CH-C3), 46.8 (CH_2–C2);

HRMS: (EI^+) for $C_7H_8O_2$ ($[M]^+$) calculated 124.0524, found 124.0522, Δ −1.5 ppm.

(1*S,2*S**,5*S**)-2-Hydroxy-8-oxabicyclo[3.2.1]oct-6-en-3-one (344)[152]**



$C_7H_8O_3$
Molecular weight: 140.14 g.mol^{-1}

n-Butyl lithium (13.0 mL, 2.5 M solution in hexanes, 32.6 mmol) was added to a freshly distilled solution of diisopropylamine (4.40 mL, 31.5 mmol) in anhydrous THF (20 mL) at −78 °C. The solution was warmed to rt, stirred for 30 min, then cooled to −78 °C. A solution of **335** (1.30 g, 10.5 mmol) in anhydrous THF (10 mL) was added, followed by the dropwise addition of TESCl (2.92 mL, 17.9 mmol) and Et_3N (3.80 mL, 27.3 mmol). The solution was stirred for 30 min at −78 °C and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (110 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with brine (125 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting silyl enol ether **343** was used without further purification.

A freshly distilled solution of dimethyl dioxirane (130 mL of a 0.09 M solution in acetone, 11.6 mmol) was added to a solution of crude **343** [10.5 mmol] in anhydrous CH_2Cl_2 (120 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h, concentrated under reduced pressure then diluted in THF:H_2O (2:1, 60 mL). The solution was cooled to 0 °C and AcOH (4 mL) was added. The reaction mixture was stirred for 1 h at 0 °C, then for 1 h at rt. The reaction was

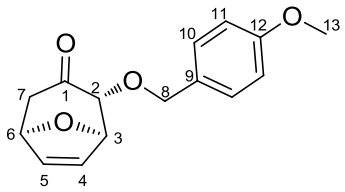
quenched with saturated aqueous $NaHCO_3$ (75 mL) and solid $NaHCO_3$ (until gas evolution ceased). The phases were separated and the aqueous phase extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with brine (250 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 3:1) afforded the hydroxyketone **344** (529 mg, 36% yield over two steps) as a colourless solid.

R_f = 0.21 (petroleum ether—Et_2O, 1:1);
m.p. = 47—49 °C;
IR: ν_{max} 3397, 2963, 1717, 1404, 1335, 1180, 1065, 1040, 1009 cm^{-1};
^{1}H NMR: (400 MHz, $CDCl_3$) δ_H 6.40 (1H, ddd, *J* = 6.1, 1.7, 0.7 Hz, CH–C5), 6.21 (1H, dd, *J* = 6.1, 1.9 Hz, CH–C4), 5.05—5.00 (1H, m, CH–C6), 4.93 (1H, br s, CH-C3), 3.69 (1H, d, *J* = 7.2 Hz, CH–C2), 3.20 (1H, d, *J* = 7.2 Hz, OH), 3.05 (1H, dd, *J* = 16.6, 5.1 Hz, CH_2–C7), 2.32 (1H, d, *J* = 16.6 Hz, CH_2–C7);
^{13}C NMR: (101 MHz, $CDCl_3$) δ_C 204.9 (C–C3), 136.7 (CH–C6), 129.6 (CH–C7), 82.5 (CH–C1), 77.5 (CH-C5), 75.5 (CH–C2), 44.6 (CH_2–C4);
HRMS: (EI^+) for $C_7H_8O_3$ ($[M]^+$) calculated 140.0473, found 140.0470, Δ −2.2 ppm.

Preparation of 4-methoxybenzyltrichloroacetamidate[165]

A solution of 4-methoxybenzyl alcohol (5.80 mL, 46.7 mmol) was added to a suspension of sodium hydride (200 mg of a 60% dispersion in mineral oil, 8.33 mmol) in anhydrous Et_2O (40 mL). The reaction mixture was cooled to 0 °C and stirred for 15 min. Trichloroacetonitrile (5.00 mL, 50.0 mmol) was added dropwise and the solution stirred for 30 min at 0 °C, then for 45 min at rt. The solution was diluted with Et_2O (150 mL) and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (150 mL). The phases were separated and the organic phase washed with brine (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude acetamidate (11.7 g) was used without further purification.

(1*S,2*S**,5*S**)-2-(4-Methoxyphenoxy)-8-oxabicyclo[3.2.1]oct-6-en-3-one (345)**[125]

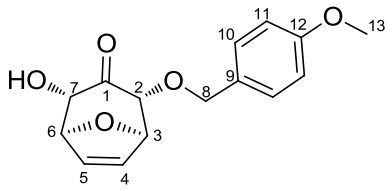


$C_{15}H_{16}O_4$
Molecular weight: 260.29 g.mol^{-1}

Camphorsulfonic acid (671 mg, 2.89 mmol) and a solution of **344** (4.02 g, 28.9 mmol) in anhydrous CH_2Cl_2 (35 mL) were added to a solution of 4-methoxybenzyltrichloroacetamidate (7.24 g, 31.2 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 ºC. The reaction mixture was warmed to rt and stirred overnight. The solution was diluted with Et_2O (300 mL) and the organic phase washed with a saturated aqueous solution of $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 9:1 to 3:2) afforded **345** (6.32 g, 84% yield) as a colourless solid.

R_f = 0.43 (petroleum ether—Et_2O, 1:1);
m.p. = 61—63 ºC;
IR: ν_{max} 2957, 2841, 1707, 1613, 1512, 1470, 1331, 1238, 1173, 1086, 1059 cm^{-1};
^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 7.29 (2H, d, *J* = 8.6 Hz, CH–11), 6.88 (2H, d, *J* = 8.6 Hz, CH–10), 6.39 (1H, dd, *J* = 6.0, 1.2 Hz, CH–C5), 6.11 (1H, dd, *J* = 6.0, 1.8 Hz, CH–C4), 5.02 (1H, ddd, *J* = 4.8, 1.2, 1.2 Hz, CH–C6), 4.91 (1H, br s, CH-C3), 4.67 (1H, d, *J* = 11.9 Hz, CH_2–C8), 4.44 (1H, d, *J* = 11.9 Hz, CH_2–C8), 3.80 (3H, s, CH_3–C13), 3.39 (1H, s, CH–C2), 3.07 (1H, dd, *J* = 16.1, 4.8 Hz, CH_2-C7), 2.32 (1H, d, *J* = 16.1 Hz, CH_2–C7);
^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 203.7 (C–C1), 159.6 (C–C12), 137.3 (CH–C5), 130.1 (2 x CH–11), 129.5 (CH–C4), 129.4 (C–C9), 114.0 (2 x CH–10), 81.4 (CH–C3), 79.9 (CH–C2), 77.5 (CH–C6), 71.9 (CH_2–C8), 55.4 (CH_3–C13), 45.5 (CH_2–C7);
HRMS: (EI$^+$) for $C_{15}H_{16}O_4$ ([M]$^+$) calculated 260.1049, found 260.1046, Δ −0.9 ppm.

(1*S,2*S**,4*R**,5*R**)-2-Hydroxy-4-((4-methoxybenzyl)oxy)-8-oxabicyclo[3.2.1] oct-6-en-3-one (347)**[125]



$C_{15}H_{16}O_5$
Molecular weight: 276.28 g.mol^{-1}

n-Butyl lithium (0.80 mL 2.5 M solution in hexanes, 2.0 mmol) was added to a freshly distilled solution of diisopropylamine (0.27 mL, 1.9 mmol) in anhydrous THF (5 mL) at −78 °C. The solution was warmed to rt, stirred for 30 min then cooled to −78 °C. A solution of **345** (251 mg, 0.960 mmol) in anhydrous THF (3 mL) was added, followed by the dropwise addition of TESCl (0.27 mL, 1.6 mmol) and Et_3N (0.35 mL, 2.5 mmol). The solution was stirred for 30 min at −78 °C and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 25 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting silyl enol ether **346** was used without further purification.

A freshly distilled solution of dimethyl dioxirane (11.8 mL of a 0.09 M solution in acetone, 1.06 mmol) was added to a solution of crude **346** [0.960 mmol] in anhydrous CH_2Cl_2 (15 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 3 h, concentrated under reduced pressure and then diluted in THF:H_2O (2:1, 9 mL). The solution was cooled to 0 °C and AcOH (0.4 mL) was added. The reaction mixture was stirred for 1 h at 0 °C, then warmed to rt and stirred for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and solid $NaHCO_3$ (until gas evolution ceased). The phases were separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 9:1 to 1:1) afforded hydroxyketone **347** (154 mg, 58% over two steps) as a colourless solid.

R_f = 0.21 (petroleum ether—Et_2O, 1:1);

m.p. = 105—107 °C;

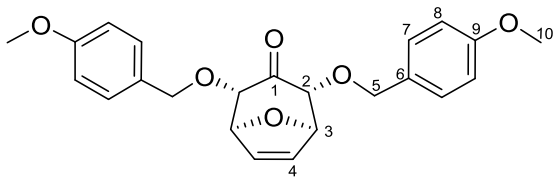
IR: ν_{max} 3403, 1722, 1614, 1514, 1398, 1250, 1177, 1074, 1044, 1032, 1005 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 7.29 (2H, d, *J* = 8.6 Hz, CH–11), 6.89 (2H, d, *J* = 8.6 Hz, CH–C10), 6.32 (1H, dd, *J* = 6.1, 1.7 Hz, CH–C5), 6.23 (1H, dd, *J* = 6.1, 1.7 Hz, CH–C4), 4.95—4.92 (2H, m, CH–C3 and CH–C6), 4.68 (1H, d, *J* = 11.4 Hz, CH_2–C8), 4.45 (1H, d, *J* = 11.4 Hz, CH_2–C8), 3.81 (3H, s, CH_3–C13), 3.80—3.75 (1H, m, CH–C7), 3.56 (1H, dd, *J* = 1.4, 1.3 Hz, CH–C2), 3.45 (1H, d, *J* = 10.8 Hz, OH);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 202.1 (C–C1), 159.8 (C–C12), 132.9 (CH–C5), 132.4 (CH–C4), 130.3 (CH–11), 128.9 (C–C9), 114.1 (CH–10), 83.1 (CH–C6), 81.8 (CH–C2), 81.6 (CH–C3), 77.3 (CH–C7), 72.2 (CH_2–C8), 55.4 (CH_3–C13);

HRMS: (EI_+) for $C_{15}H_{16}O_5$ ($[M]^+$) calculated 276.0998, found 276.0997, Δ −0.2 ppm.

(1*R,2*R**,4*S**,5*S**)-2,4-Bis[(4-methoxybenzyl)oxy]-8-oxabicylo-[3.2.1]oct-6-en-3-one (348)[125]**



$C_{23}H_{24}O_6$
Molecular weight: 396.43 $g.mol^{-1}$

Camphorsulfonic acid (19.0 mg, 0.0800 mmol) and a solution of **347** (220 mg, 0.810 mmol) in anhydrous CH_2Cl_2 (5 mL) were added to a solution of 4-methoxybenzyltrichloroacetamidate (230 mg, 0.920 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was warmed to rt and stirred overnight. The solution was diluted with Et_2O (20 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography on silica gel (petroleum ether—Et_2O, 9:1 to 1:1) afforded **348** (202 mg, 63% yield) as a colourless solid.

R_f = 0.37 (petroleum ether—Et_2O, 1:1);

m.p. = 87—89 °C;

IR: ν_{max} 2955, 2891, 1713, 1613, 1512, 1458, 1302, 1238, 1175, 1065, 1034 cm^{-1};

^{1}H NMR: (500 MHz, $CDCl_3$) δ_H 7.31 (4H, d, *J* = 8.6 Hz, CH–C8), 6.87 (4H, d, *J* = 8.6 Hz, CH–C7), 6.21 (2H, s, CH–C4), 4.93 (2H, s, CH–C3), 4.74 (2H, d, *J* = 11.9 Hz, CH_2–C5), 4.49 (2H, d, *J* = 11.9 Hz, CH_2–C5), 3.80 (6H, s, CH_3–C10), 3.43 (2H, s, CH–C2);

^{13}C NMR: (126 MHz, $CDCl_3$) δ_C 202.6 (C–C1), 159.6 (2 x C–C9), 133.0 (2 x CH–C4), 130.1 (4 x CH–C8), 129.5 (2 x C–C6), 114.0 (4 x CH–C7), 81.4 (2 x CH–C3), 79.9 (2 x CH–C2), 71.8 (2 x CH_2–C5), 55.4 (2 x CH_3–C10);

HRMS: (ESI) for $C_{23}H_{24}NaO_6$ ($[M+Na]^+$) calculated 419.1471, found 419.1465, Δ +0.2 ppm.

Chapter 4: References

Chapter 4: References

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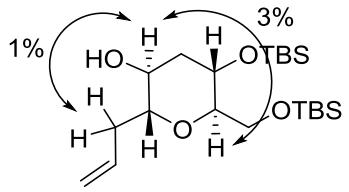
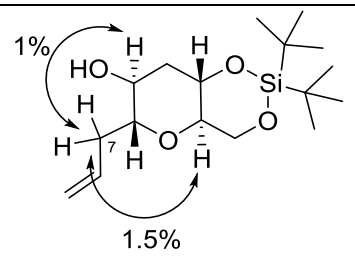
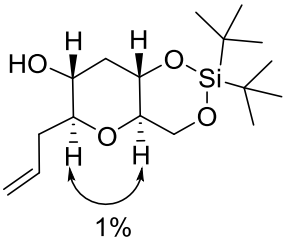
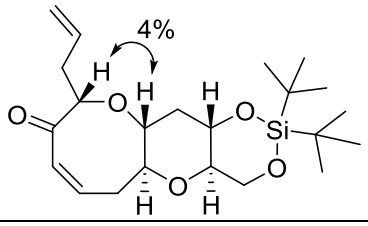
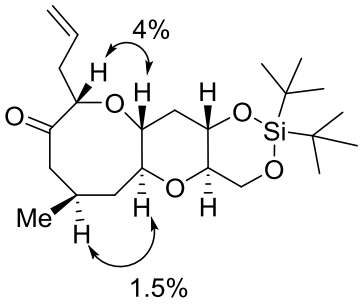
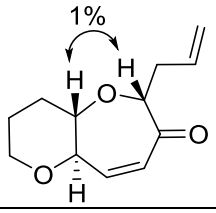
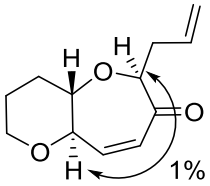
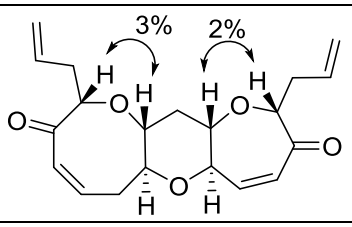
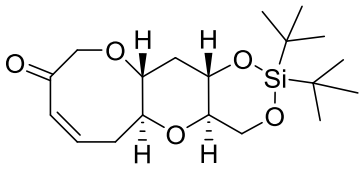
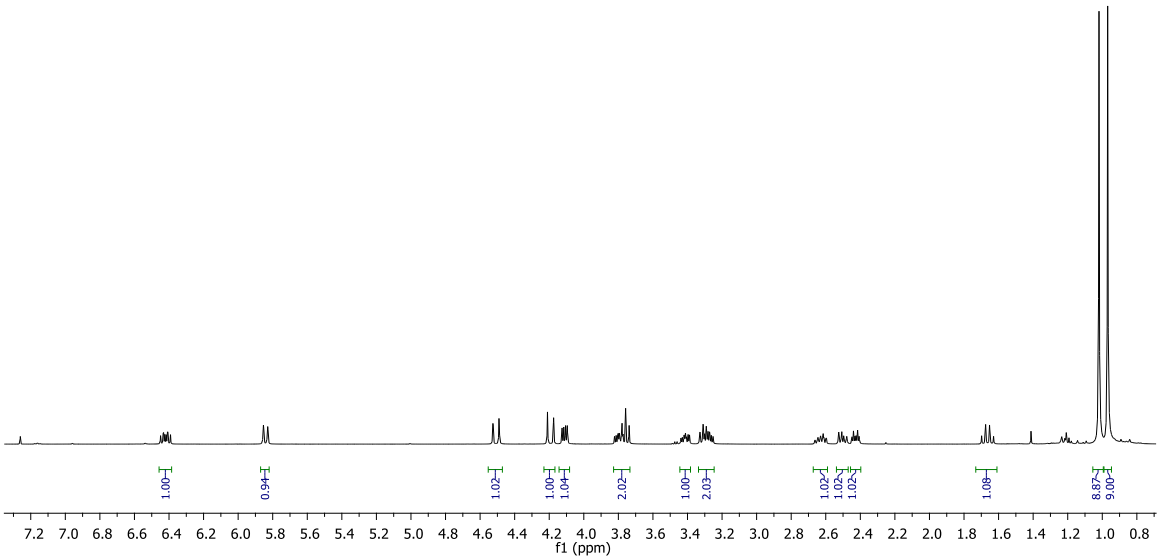
Appendix A: NOE correlations

Compound	% NOE enhancements
236	
247	
251	
227	
225	
288	
327	
310	

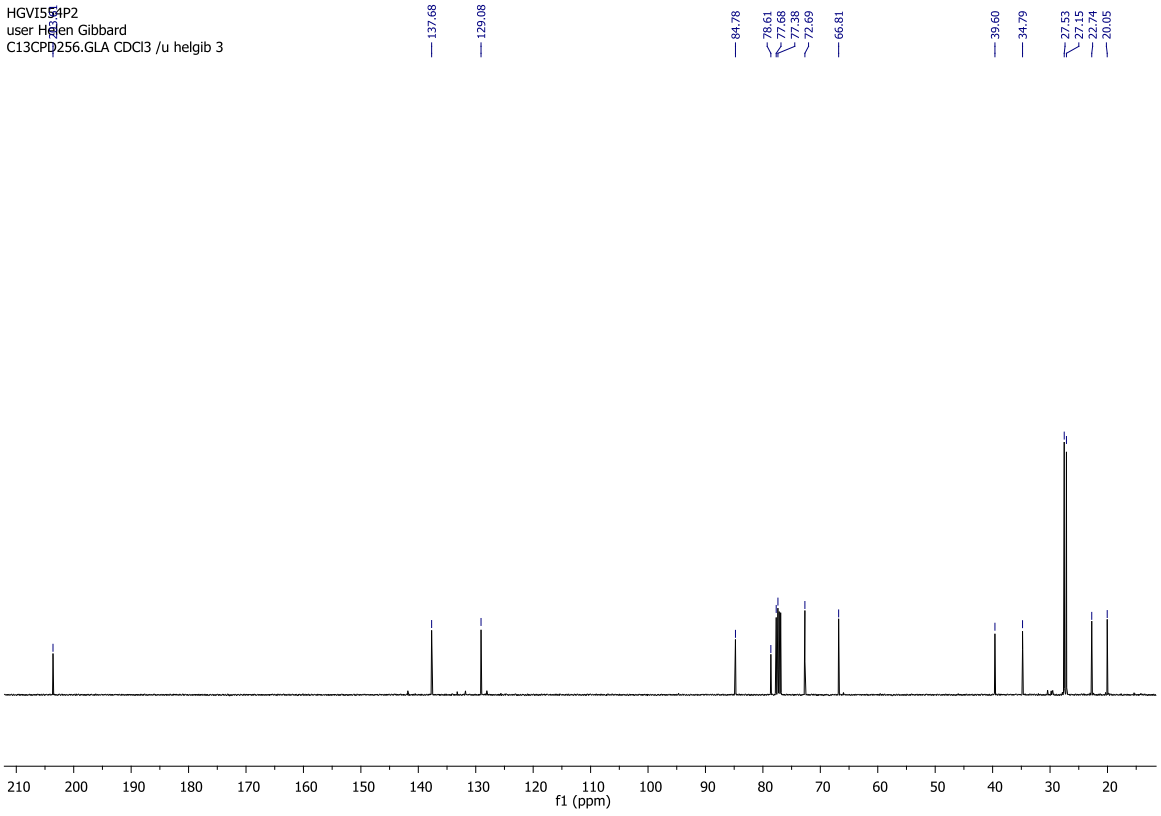
Appendix B: Selected ^{1}H and ^{13}C spectra

HGVI554P2
user Helen Gibbard
proton.gla CDCl3 /u helgib 3

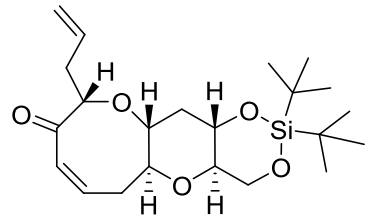




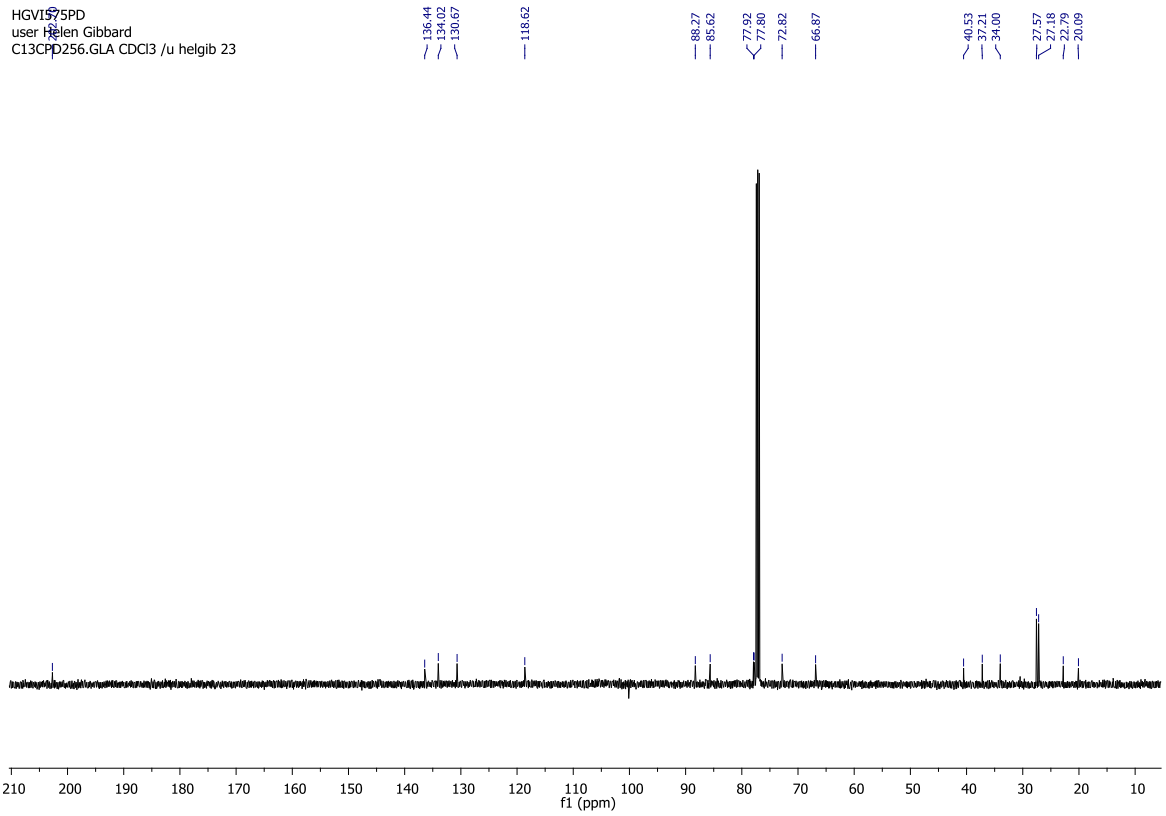
HGVI554P2
user Helen Gibbard
C13CPD256.GLA CDCl3 /u helgib 3



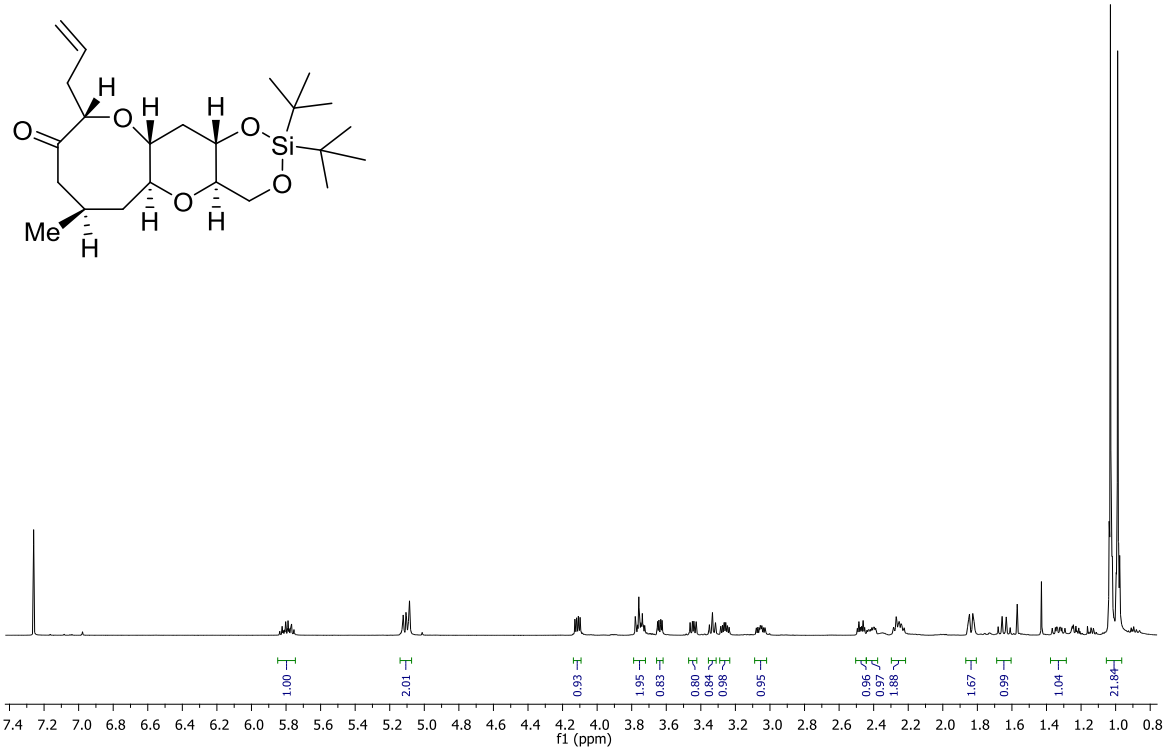
HGVIII575PD
user Helen Gibbard
proton.gla CDCl3 /u helgib 25



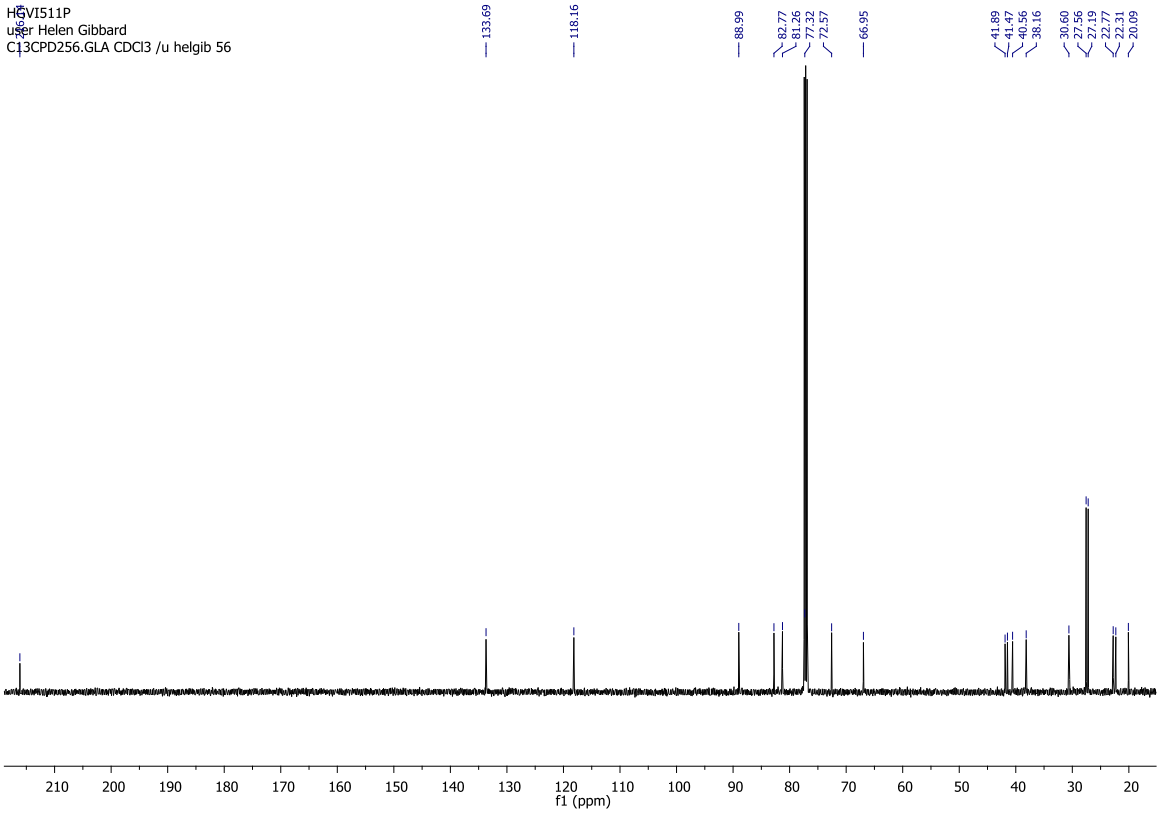
HGVI575PD
user Helen Gibbard
C13CPD256.GLA CDCl3 /u helgib 23



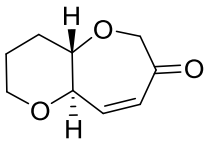
HGVI511P
user Helen Gibbard
proton.gla CDCl3 /u helgib 56

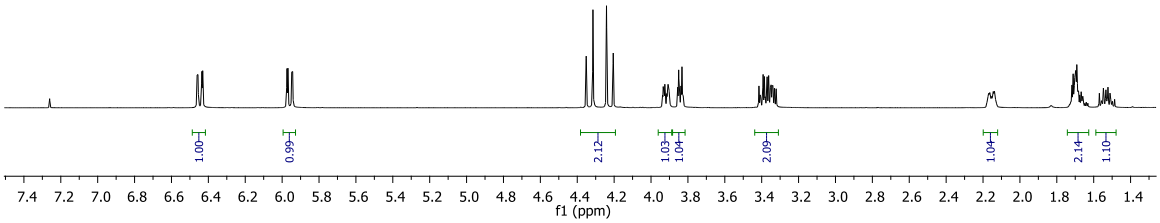


HGVI511P
user Helen Gibbard
C13CPD256.GLA CDCl3 /u helgib 56



HGVIII713PD
user Helen Gibbard
proton.gla CDCl3 /u helgib 31





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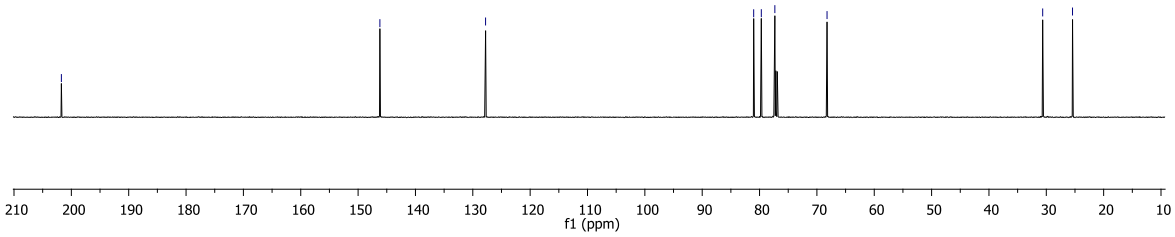
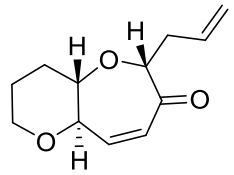
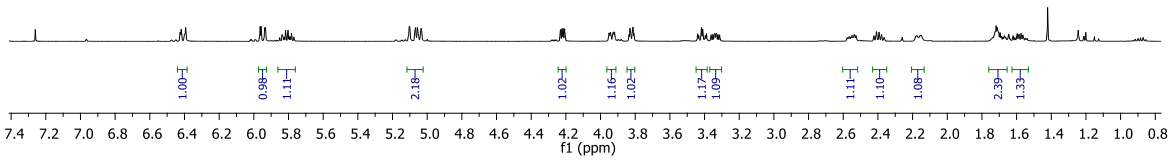
user Helen Gibbard
C13CPD256.GLA CDCl3 /u helgib 31



HGVIII756PD
user Helen Gibbard
proton.gla CDCl3 /u helgib 12





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user Helen Gibbard
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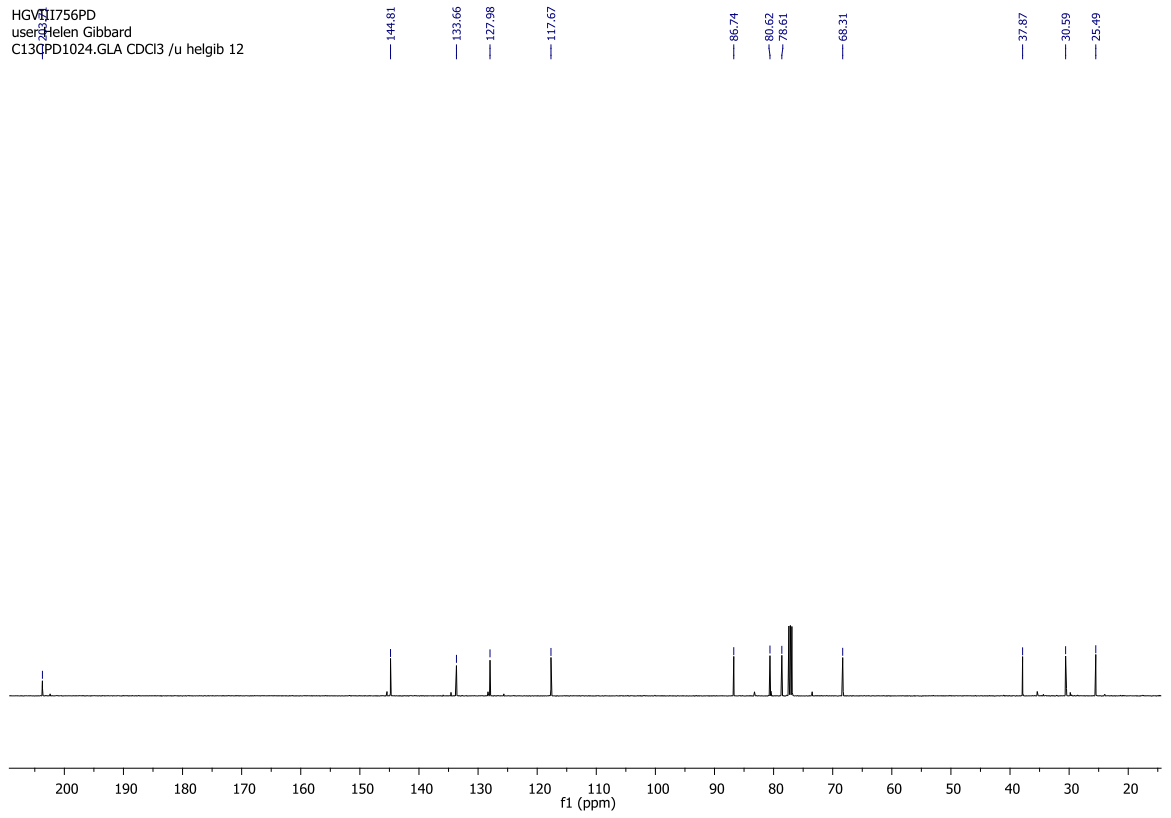

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user Helen Gibbard
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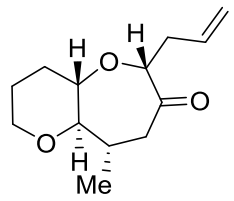

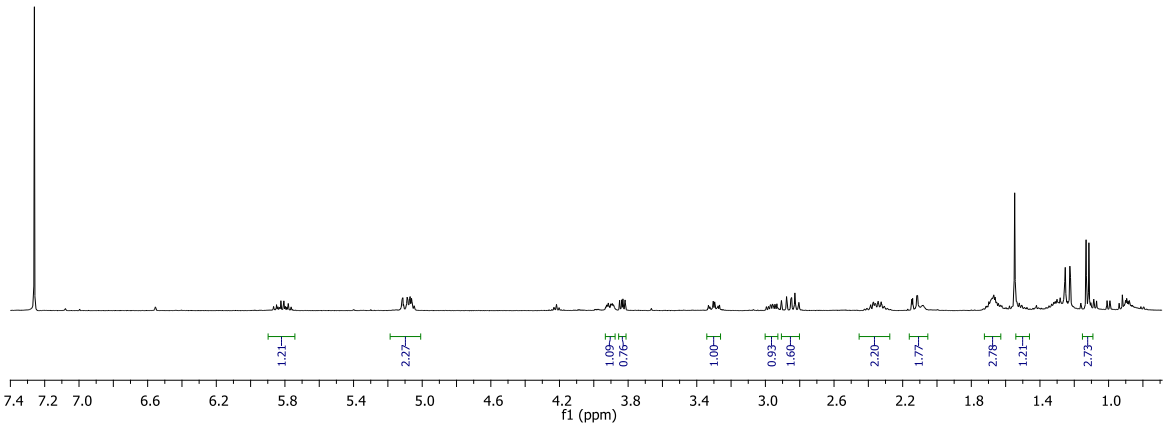

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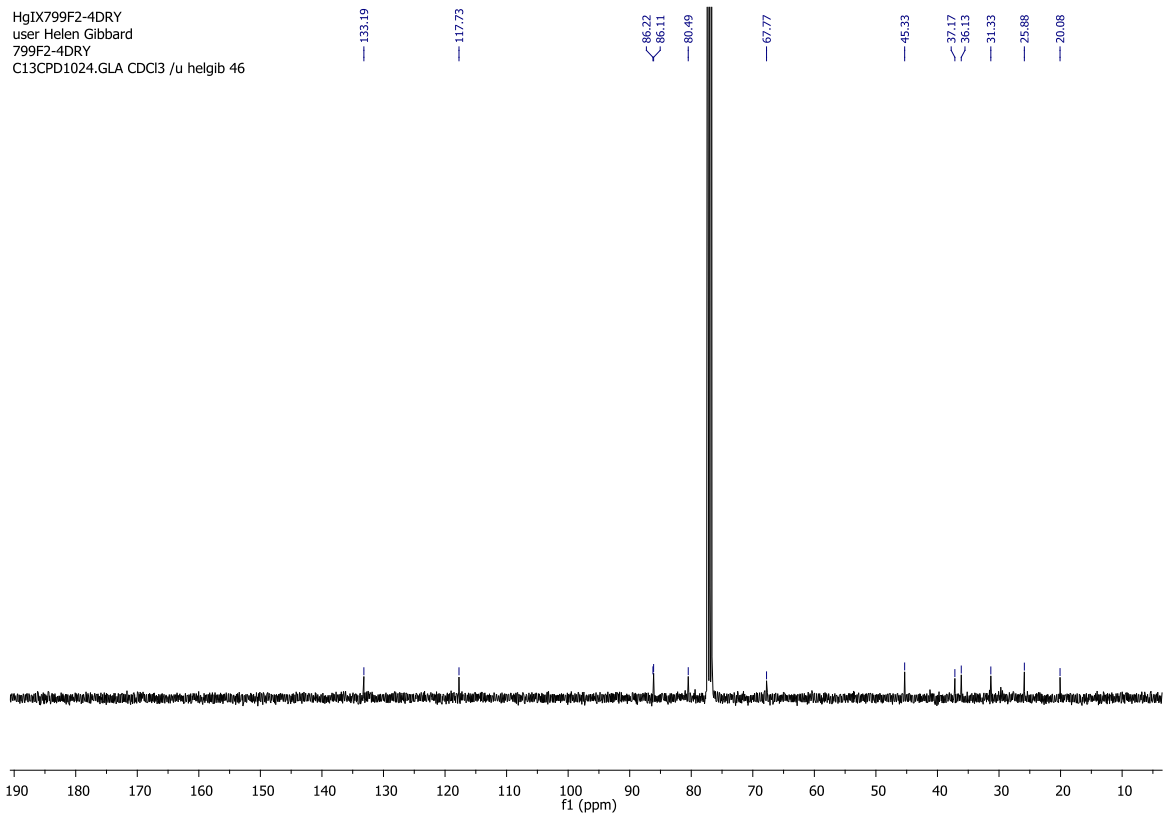

HGVII625P
User Helen Gibbard
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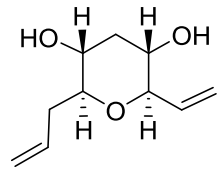

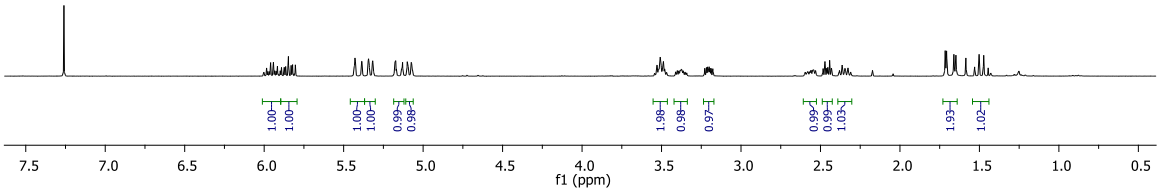

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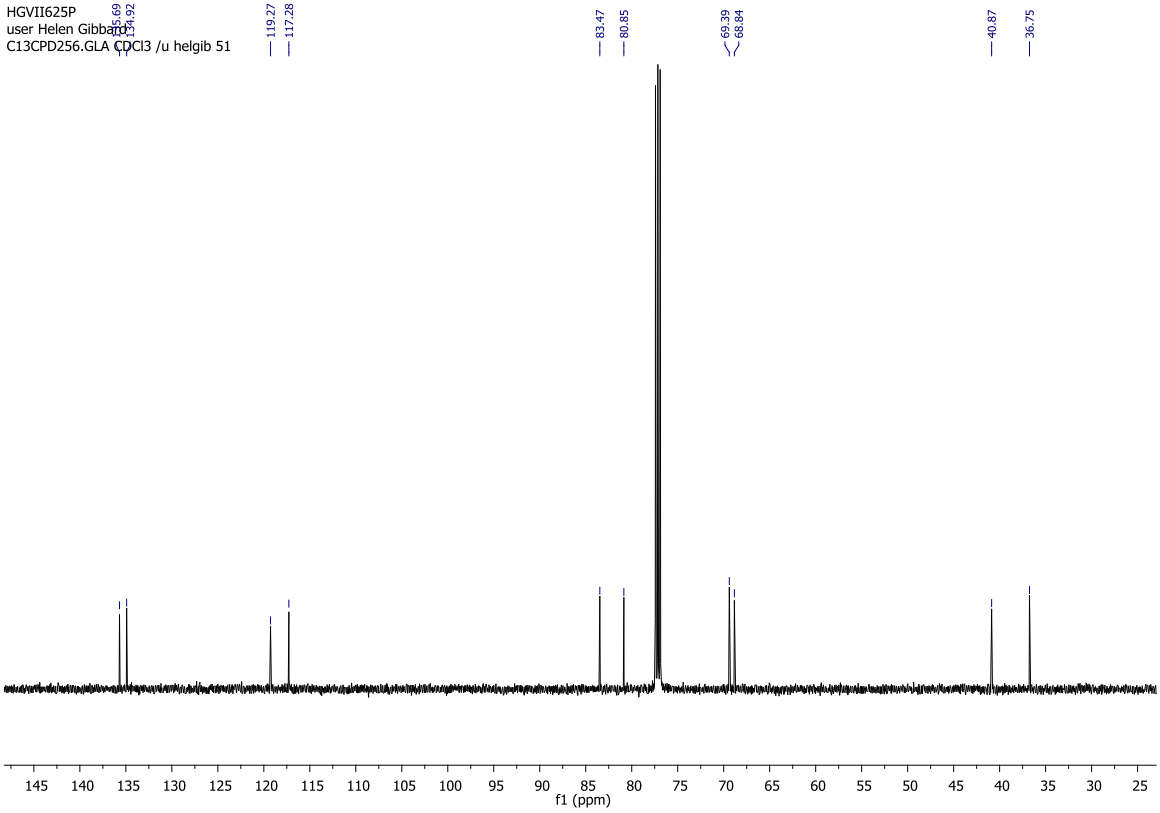
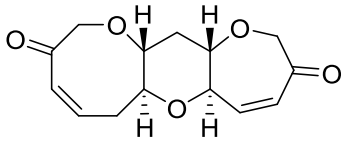
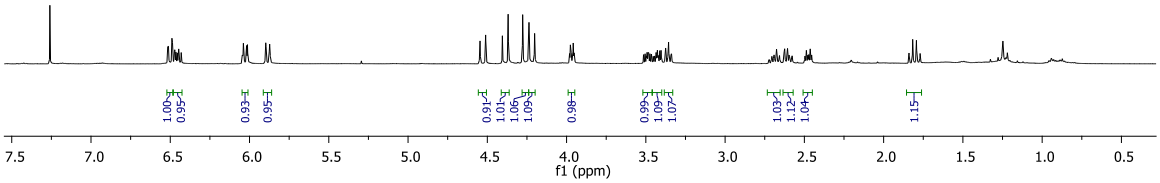


HGIX792PD
user Helen Gibbard
proton.gla CDCl3 /u helgib 6





HGIX792PD
user Helen Gibbard
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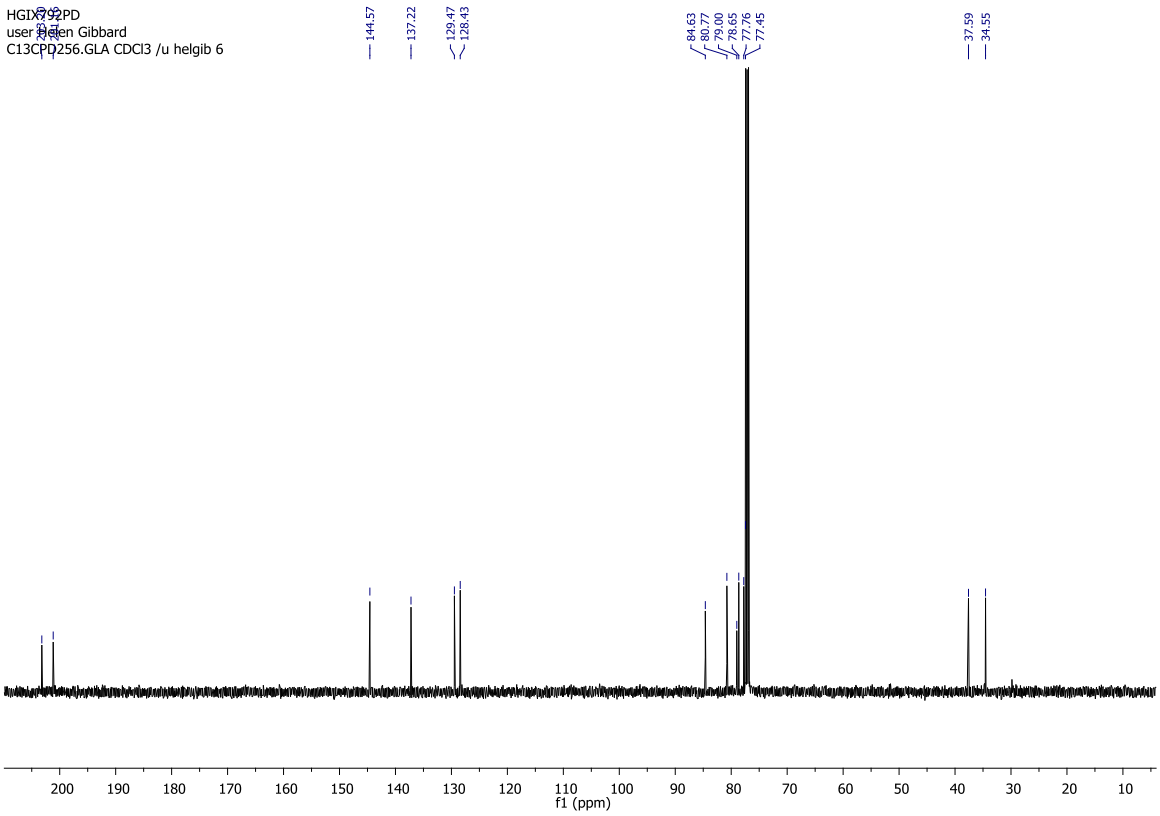

HGIX798F21-30PD
user Helen Gibbard
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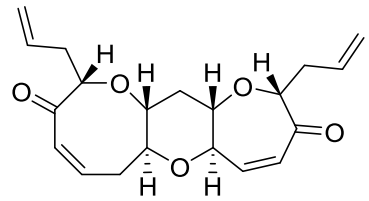

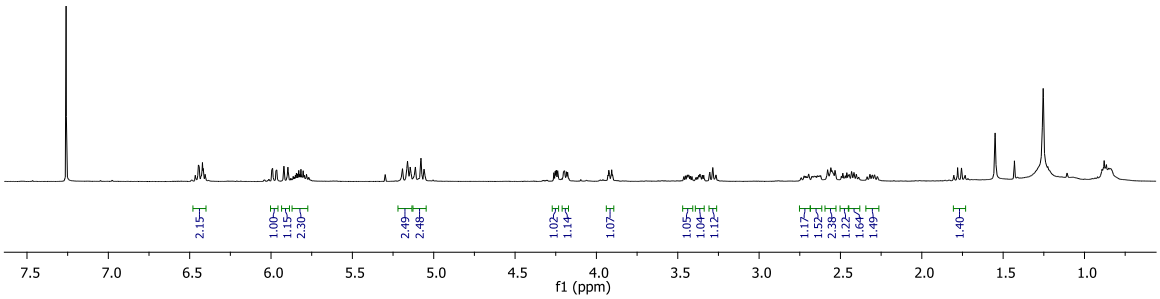

HGIX798F21-30PD
user Helen Gibbard
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