Towards the Total Synthesis

of

Gambieric Acid A

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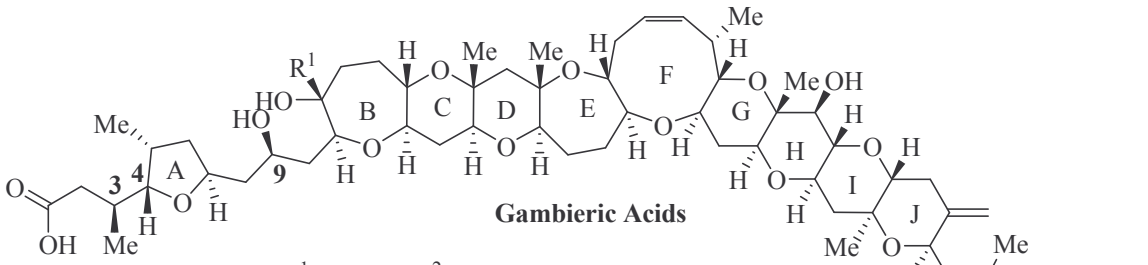
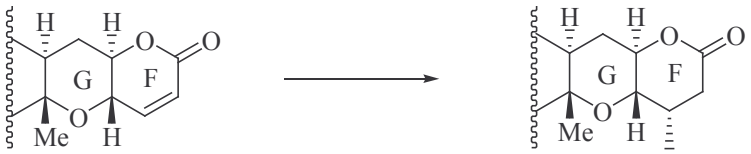
Abstract

Over the past three decades, numerous polycyclic ether natural products have been isolated from marine organisms. All of these unusual compounds possess a wide range of biological activities. In 1992, a new family of polyethers was discovered from the marine dinoflagellate *Gambierdiscus toxicus*: gambieric acids A–D, which show antifungal activity against a variety of filamentous fungi.

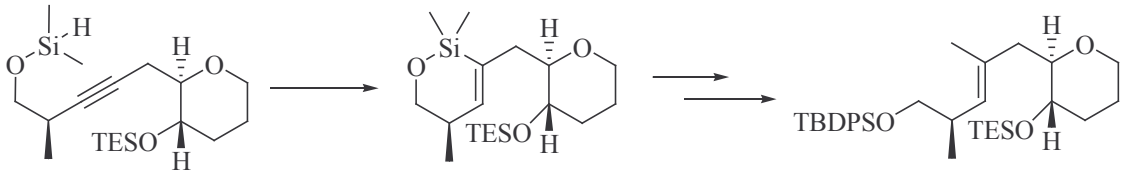


A $R^1 = H$; $R^2 = H$
B $R^1 = Me$; $R^2 = H$
C $R^1 = H$; $R^2 = (R)\text{-}COCH_2CH(Me)CH_2CO_2H$
D $R^1 = Me$; $R^2 = (R)\text{-}COCH_2CH(Me)CH_2CO_2H$

The purpose of this thesis is to show the progress towards the synthesis of F–J ring system of gambieric acid A. First, the large scale synthesis of I–G ring fragment using the two directional ring closing metathesis developed in the laboratory is described including the improvements made to the previous synthesis. Subsequently, the efficient introduction of the methyl group of the F ring using a 1,4 addition with a cuprate reagent to an α,β-unsaturated lactone is discussed in detail.



In addition, efficient introduction of the side chain to the J ring using a cyclic siloxane using a model system is also reported, after the exploration of ten different approaches. Finally, studies concerning the final stages of the synthesis are discussed.



Acknowledgements

I would like to express my sincere gratitude to my supervisor, Prof. Stephen Clark, for all his help, advice and support over the last three years. I would also like acknowledge my supervisor for letting me the freedom of exploring every single idea. It has been an immense source of learning during these three years.

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Finally, I would like to thank my family and friends (Benoît, Seb, Doris, Jérôme) for their encouragement and support throughout my time in United Kingdom. I also thank Anne-Valérie for her patience!

Declaration

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

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

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(J. Molette)

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(Professor J. S. Clark)

Abbreviations

ABSA	acetamidobenzenesulfonyl azide
ac	acetyl
acac	acetylacetonate
Bn	benzyl
br	broad
BTX	brevetoxin
Bu	butyl
calcd	calculated
CAN	ceric ammonium nitrate
Cat.	catalyst
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
dba	*trans, trans*-dibenzylideneacetone
DBU	1,5-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
Dibal-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	2,2-dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
eqn	equation
Et	ethyl
ether	diethyl ether
h	hour

HMPA	hexamethylphosphoric triamide
HRMS	high resolution mass spectrometry
Icp	diisopinocamphenyl
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
m	multiplet
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
min	minute(s)
MOM	methoxymethyl
NaHMDS	sodium bis(trimethylsilyl)amide
NAP	2-naphthylmethyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
P	protecting group
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
petrol	petroleum ether (bp 40-60 °C)
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
RCM	ring closing metathesis
RCEM	ring closing enyne metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
s	singlet
t	triplet

TBACN	*tetra*-*n*-butylammonium cyanide
TBAF	*tetra*-*n*-butylammonium fluoride
TBAI	*tetra*-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TEMPO	2,2,6,6-*tetra*-methyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
Tfacam	trifluoroacetamide
THF	tetrahydrofuran
Thx	tert-hexyl
TLC	thin layer chromatography
TMDS	1,1,3,3-tetramethyldisilazane
TMEDA	*N*, *N*, *N* ',*N* '-*tetra*-methylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

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1. Introduction

1.1. Origin: Gambierdiscus Toxicus

1.1.1. Discovery

Ciguatera fish poisoning is a neuro-digestive intoxication due to a small mollusc named "cigua" in Caribbean language. This phenomenon was first reported during the exploration of the Vanuata archipelago by Fernandes De Quieros in 1606 and Cook in 1776. Ciguatera fish poisoning is not only a health problem but also a socio-economic problem. Undeniably, an outbreak of ciguatera can result in the prohibition of fishing and selling sea food which can jeopardize the local economy. Moreover, intoxication can lead to a severe form of food poisoning that can result in absence from work and further economic loss. Consequently, identification of the agents responsible for the intoxication is a key element in developing an efficient treatment for affected populations and also to limit the environmental damage caused in areas of the ocean where toxic algal blooms occur. In 1977, Bagnis and a Japanese collaborator discovered one of the sources of the ciguatera poisoning: the alga *Gambierdiscus Toxicus* (**Figure 1**).[1]

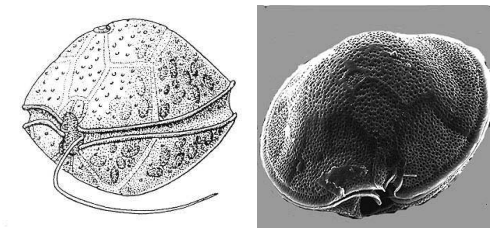
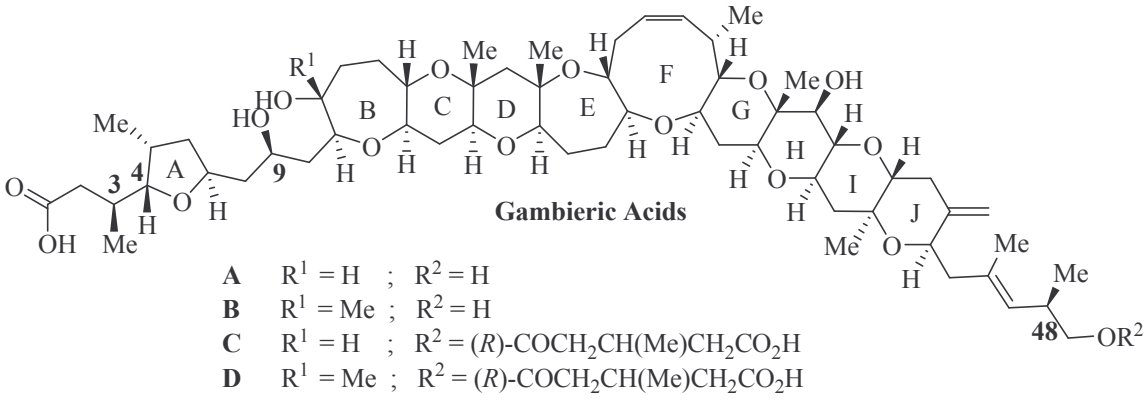


Figure 1: *Gambierdiscus Toxicus* (×2000)**.**

[1] (a) R. Bagnis, S. Chanteau, T. Yasumoto, *Revue Internationale d'Oceanographie Medicale* **1977**, *45-46*, 29; (b) R. Bagnis, S. Chanteau, T. Yasumoto, *Bulletin de la Societe de pathologie exotique et de ses filiales* **1977**, *70*, 320.

The name given to the ciguatera-producing organism refers to the location where the dinoflagellate was discovered: the area around the Gambier islands in French Polynesia. Marine algae produce different complex polyether structures such as ciguatoxins and maitotoxin. But it was only in 1992 that gambieric acids A–D were first isolated from *Gambierdiscus Toxicus* (**Scheme 1**).



Scheme 1: Structure of gambieric acids A–D.

1.1.2. Transmission

The dinoflagellate is usually present in small quantities around a coral reef because of the competition from other species. Nevertheless, a huge expansion in the numbers of algal cells can occur at any time. This event is known as an algal bloom (**Figure 2**).

Figure 2: Red algal bloom at Leigh near cape Rodney (New Zealand, © Miriam Gobfrey)

The reasons for the sudden expansion in the number of algal cells is not really known. However, several factors could be responsible for this proliferation. Natural phenomena (earthquake, cyclone) or artificial phenomena (pollution, ship wrecks, creation of a channel by dredging) generate free space for the algae to colonise. Consequently, herbivorous fish eat more of the toxic algae than usual, which leads to an increase of concentration of toxins all along the food chain. Accordingly, carnivorous fish present higher levels of toxins than herbivorous ones and this is the reason why most of human intoxications result from the consumption of carnivorous fish. In addition, no external or internal signs of intoxication are visible which increases the risk of contamination. Some tests have been developed but it is necessary to perform them in a laboratory environment. A diagnostic kit to test fish is commercially available but the results may have to be considered with caution.[2]

1.1.3. Symptoms

A wide range of symptoms can occur after eating fish contaminated by ciguatera toxins. However, symptoms are very dependent on the individual. For the same fish, a person could be heavily ill whereas another person could just have minor symptoms. There are three main manifestations of ciguatera poisoning:

- Gastrointestinal sickness (diarrhoea, abdominal cramps and vomiting).
- Neurological symptoms (paresthesias, pain, blurred vision).
- Cardiovascular signs (arrhythmias, heart attack).

The first symptoms appear generally 12 hours after ingestion. The persistence of the symptoms can vary from weeks to months. Several factors can reactivate the symptoms. Fish, alcohol, caffeine and nuts are foods to avoid even 3 to 6 months after the initial ingestion of the poisoned fish.

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[2] http://cigua.oceanit.com/.

1.1.4. Treatments

Treatments essentially deal with the symptoms and have limited effectiveness. Vitamins, antihistamines, anticholinesterases, steroids and tricyclic antidepressants are the most common drugs against ciguatera. Nevertheless, a new treatment was introduced by Palafox in 1988 with encouraging results.[3] The treatment consists of an injection of mannitol (1g/1kg over 30 minutes). The role played by the mannitol is yet to be clarified but it is probably linked to competitive binding of the mannitol with toxins at the cell membrane.

1.2. Structures and activities of gambieric acids

1.2.1. Biological activities

Over many decades, numerous polyether compounds have been isolated from marine organisms.[4] Most of these unusual compounds possess wide and varied biological activities. Gambieric acids A–D are no exception and have interesting antifungal activities.[5] However, limited studies have been carried out because of the difficulties in isolating gambieric acids A–D. A total of 5000 litres of media kept at 25 °C for 38 days produced only 0.6 mg of gambieric acid A, 0.15 mg of gambieric acid B and 5.8 mg of a mixture of gambieric acids C–D after a fastidious purification procedure.[5b] Gambieric acids A and B were tested against yeast, bacteria and filamentous fungi and their activities were compared with amphotericin B (**Table 1**).[5c] Gambieric acids were not active against the bacteria and yeasts tested, but significant activities were revealed against filamentous fungi in particular against *Aspergillus niger* and *Aspergillus fumigatus*. In general, gambieric acid A is more active than gambieric acid B. To further confirm the activity

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[3] N. A. Palafox, L. G. Jain, A. Z. Pinano, T. M. Gulick, R. K. Williams, I. J. Schatz, *J. Am. Med. Assoc.* **1988**, *259*, 2740.
[4] (a) T. Yasumoto, *Chem. Rec.* **2001**, *1*, 228; (b) H. Nagai, M. Satake, T. Yasumoto, *J. Appl. Phycol.* **1990**, *2*, 305; (c) P. Ciminiello, E. Fattorusso, *Eur. J. Org. Chem.* **2004**, 2533.
[5] (a) H. Nagai, M. Murata, K. Torigoe, M. Satake, T. Yasumoto, *J. Org. Chem.* **1992**, *57*, 5448; (b) H. Nagai, K. Torigoe, M. Satake, M. Murata, T. Yasumoto, H. Hirota, *J. Am. Chem. Soc.* **1992**, *114*, 1102; (c) H. Nagai, Y. Mikami, K. Yazawa, T. Gonoi, T. Yasumoto, *J. Antibiot.* **1993**, *46*, 520.

against *Aspergillus niger*, a paper disc assay was used. Paper disc 8 mm in diameter were soaked with gambieric acid A and was then placed in agar media with *Aspergillus niger* for 48 hours at 37 °C.

	Minimum inhibitory concentration (µg/mL)		
Microorganism	**Gambieric acid A**	**Gambieric acid B**	**Amphotericin B**
Aspergillus fumigatus No 184	0.39	0.78	3.13
Aspergillus niger IFM 40606	0.20	0.20	3.13
Aspergillus oryzae IFM 40607	3.13	6.25	6.25
Epidermophyton floccosum IFM 40770	3.13	1.56	3.13
Paecilomyces variotii IFM 30539	0.78	0.78	3.13
Penicillium chrysogenum Q176	1.56	1.56	6.25
Penicillium citrium IAM 7003	3.13	3.13	>12.5
Trchophyton mentagrophytes IFM 45110	0.78	0.78	1.56

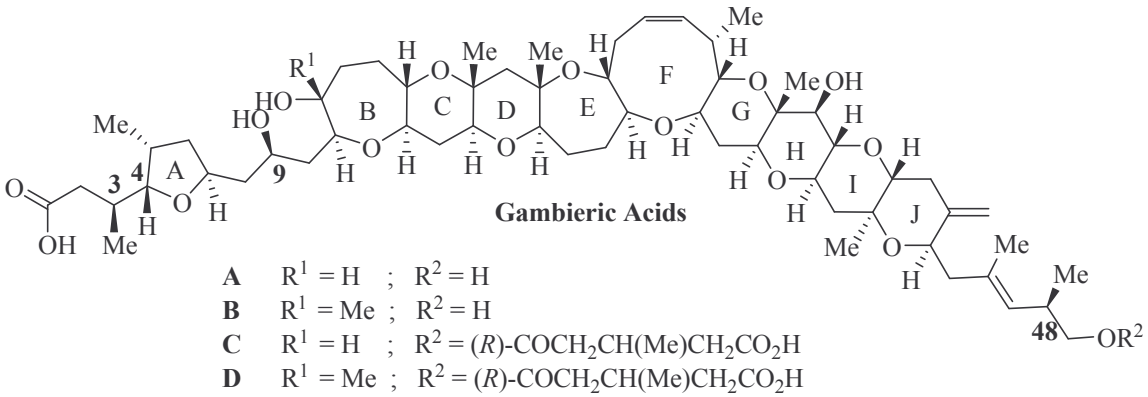
Table 1: Minimum inhibitory concentrations determined by Yasamoto and co-workers.[5c]

Gambieric acid A showed an inhibition zone as low as 10 ng/disc whereas 20 µg/disc are required for amphotericin B. Consequently, gambieric acid A is approximately 2000 times more active than amphotericin B against *Aspergillus niger*. During the study, the authors found that the antifungal activity of gambieric acids A and B were potentiated by ferric compound such as $FeCl_3$ or $Fe_2(SO_4)$. The role played by ferric ion needs to be elucidated and studies have been initiated by the authors. Additional studies have shown that gambieric acid A is the only member the family to be excreted into the aqueous media.[5a] However, gambieric acid A is poorly soluble in water suggesting that gambieric acid A stays on the surface of the dinoflagellate. Thus, gambieric acid A may act as a protective shield against external organisms. Yasamoto and co-workers also demonstrated that

gambieric acid A inhibits extremely toxic polyether compounds such as the brevetoxins (BTXs).[6] BTXs kill large numbers of fish and have been the origin of human intoxications. BTXs bind to the site 5 of voltage-sensitive sodium channels, which leads to a persistent activation of the channel. By competitive binding, gambieric acid A is one of the best inhibitors of the BTXs and has the advantage of being non-toxic towards mice and cultured mammalian cells. Indeed, gambieric acid A at a dose of 1 mg/kg showed no toxicity upon intraperitoneal injection to mice. Higher dose were not tested because of difficulties in isolating gambieric acid A in sufficient quantities. This value is very high compared to the other members of the polyether family such as CTX and gambierol, which respectively showed toxicities at 0.35µg/kg and 0.50µg/kg against mice.

1.2.2. Structures

Due to the complexity of their structures, the absolute configuration of gambieric acids was only fully determined many years after their discovery. The skeleton was first described in 1992 but stereochemical assignements at positions C3, C4, C9, C48 (**Scheme 2**) were not made.[5] In 2000, the absolute configuration was fully attributed using anisotropic reagents and a chiral fluorescent reagent.[7]



Scheme 2: Structure of gambieric acids A–D.

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[6] M. Inoue, M. Hirama, M. Satake, K. Sugiyama, T. Yasumoto, *Toxicon* **2003**, *41*, 469.
[7] A. Morohashi, M. Satake, H. Nagai, Y. Oshima, T. Yasumoto, *Tetrahedron* **2000**, *56*, 8995.

The framework is constituted of *trans/cis* polyether rings of various sizes: one 9-membered ring, two 7-membered rings, six 6-membered rings and one 5-membered ring (**Figure 3**).

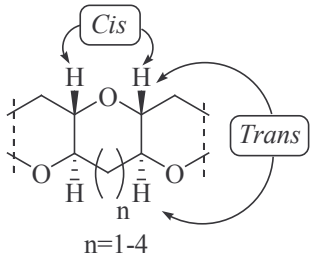


Figure 3: *Trans/cis* polyether structure.

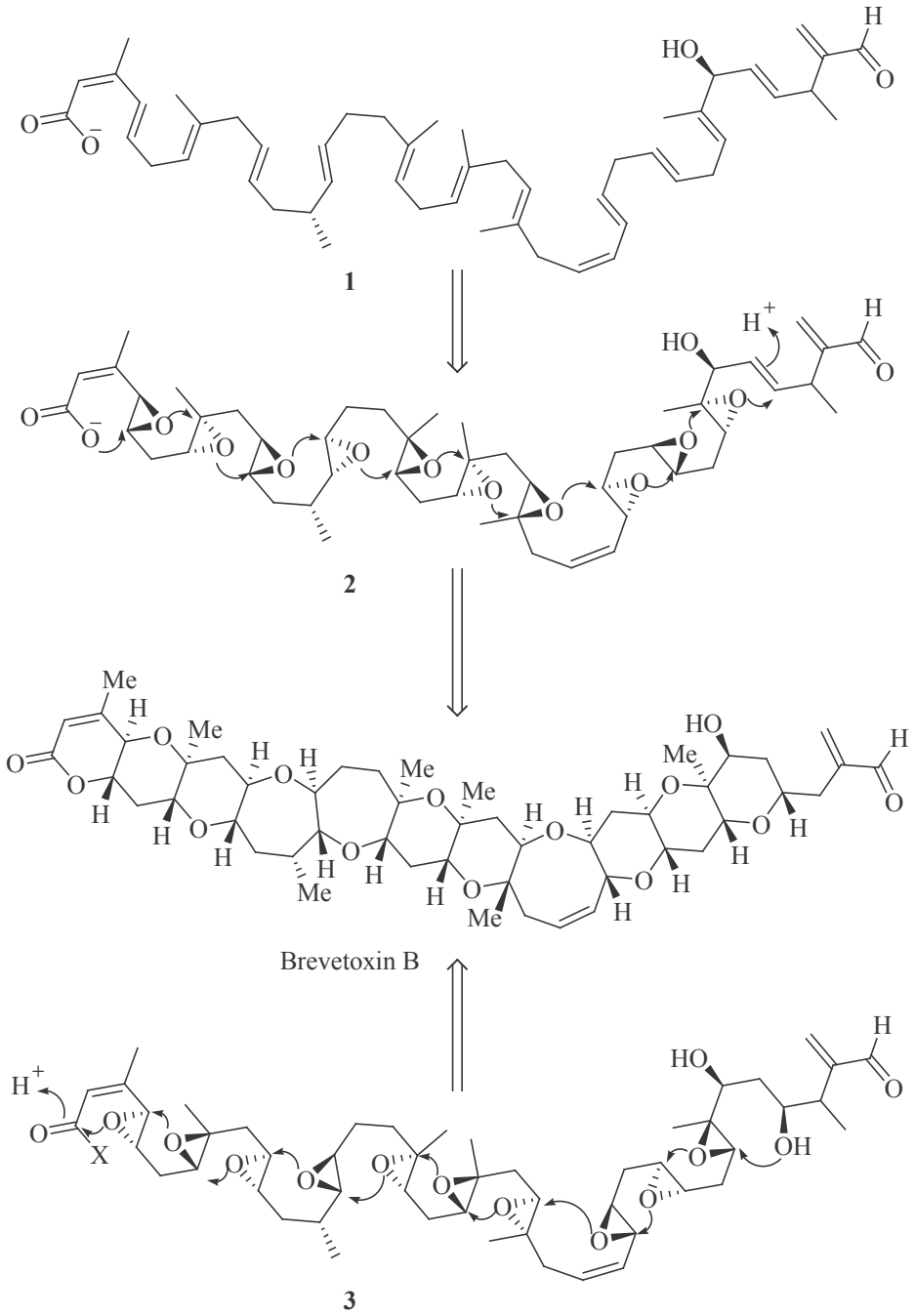
Appended to the main skeleton of the gambieric acids are two side chains one of which bears an isolated trisubstituted tetrahydrofuran (A ring unit) (**Scheme 2**). Gambieric acids A–E differ from one another by the substituent on the B ring (Me or H leading to a secondary or tertiary alcohol) and the terminal substituent on the side chain attached to the J ring (alcohol *versus* ester).

1.3. Biosynthesis of polyethers

Since the discovery of marine polycyclic ethers, scientists have been intrigued by the possible biosynthetic route leading to such complex structures. Shimizu and Nakanishi proposed a biosynthesis of brevetoxin B based on the results of an experiment in which C^{13}-labelled precursors were fed to the alga.[8,9] Thus, the biosynthetic origin of the carbon atoms in the structure was clearly identified. In addition, they postulated that the polyene **1** was formed by a condensation/decarboxylation/dehydration process of acetate units during the citric acid cycle and subsequent epoxidation by an epoxidase enzyme delivered the polyepoxide **2** or **3** (**Scheme 3**). The opening cascade of the polyepoxide can occur from left to right or from right to left. Therefore, the configuration of the epoxides produced

[8] (a) M. S. Lee, D. J. Repeta, K. Nakanishi, M. G. Zagorski, *J. Am. Chem. Soc.* **1986**, *108*, 7855; (b) M. S. Lee, G. Qin, K. Nakanishi, M. G. Zagorski, *J. Am. Chem. Soc.* **1989**, *111*, 6234; (c) H. N. Chou, Y. Shimizu, *J. Am. Chem. Soc.* **1987**, *109*, 2184.
[9] A. E. Gallimore, J. B. Spencer, *Angew. Chem., Int. Ed.* **2006**, *45*, 4406.

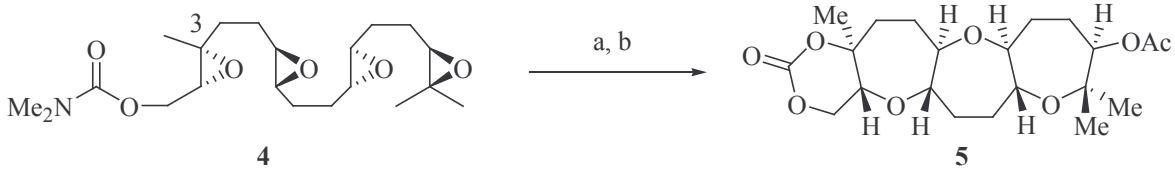
from the polyene **1** must be opposite one to each other to deliver the same configuration of brevetoxin B after the cyclisation process. In both cases, no experimental evidence has been presented to confirm the existence of polyepoxide **2** or **3**. Finally, *endo*-selective epoxide-opening affords brevetoxin B.



Scheme 3: Shimizu and Nakanishi's biosynthesis proposal.

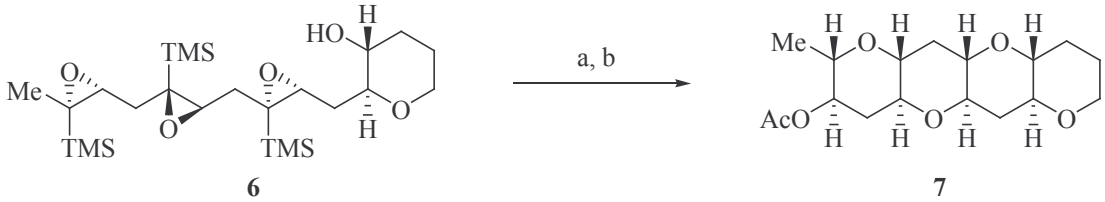
Interestingly, the hypothesis made by Shimizu and Nakanishi requires a mechanism in which Baldwin's rules for ring closure are contravened. Despite uncertainty about the exact mechanism, several groups worked to verify the Shimizu and Nakanishi proposal.

Three impressive examples of *endo*-selective epoxide-opening are shown below. Such progress was only possible thanks to the advent of Shi's enantiomeric epoxidation reaction, which allows the synthesis of polyepoxide cyclisation precursors with appropriate stereochemistry in a highly stereoselective manner. As a result, McDonald and co-workers managed to synthesise the polyether **5** *via* an *endo*-cyclisation of the trisepoxide **4** using $BF_3{\cdot}OEt_2$ as the promoter (**Scheme 4**).[10] The presence of the carbamate group, which acts as nucleophile, and the methyl group at the 3-position are vital for the success of the *endo*-reaction; in the absence of the methyl group *exo*-selectivity was obtained due to the reduced ring strained which favours kinetic products (*exo*).



Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -40 °C; (b) Ac_2O, pyridine (25% over 2 steps).
Scheme 4: McDonald's biomimetic polyether synthesis.

Jamison's group has worked on another type of cyclisation in which a directing group is not required to control the cascade process.[11] To perform their cyclisation reactions, they used a trimethylsilyl (TMS) group as temporary activating group at the epoxide junction to direct the *endo*-cyclisation process (**Scheme 5**).



Reagents and conditions: (a) Cs_2CO_3, CsF, MeOH, reflux; (b) Ac_2O, pyridine (15% over 2 steps).
Scheme 5: Jamison's polyether biosynthesis.

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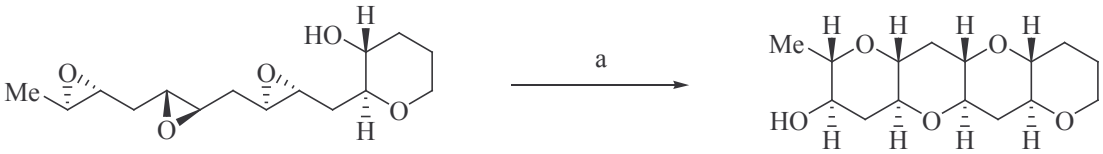
[10] (a) J. C. Valentine, F. E. McDonald, W. A. Neiwert, K. I. Hardcastle, *J. Am. Chem. Soc.* **2005**, *127*, 4586; (b) J. C. Valentine, F. E. McDonald, *Synlett* **2006**, 1816.
[11] (a) T. P. Heffron, T. F. Jamison, *Org. Lett.* **2003**, *5*, 2339; (b) G. L. Simpson, T. P. Heffron, E. Merino, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 1056.

During the cascade process, the TMS group was removed by treatment with CsF. Using this strategy, they were able to affect the cyclisation of three rings to give the tetracyclic product **7**. The presence of the first ring is important in order to obtain good yields.

More recently, Jamison's group managed to synthesise the same polyether **9** in water without using a TMS group to direct the reaction (**Scheme 6**).[12] Optimal conditions were found after studies of pH and solvent (mixture of H_2O/THF). They clearly showed the best results were obtained using 100% H_2O at pH 7 and the compound **9** was synthesised in an impressive 53% yield.



8 **9**

Reagents and conditions: (a) H_2O, 70 °C (53%).

Scheme 6: Jamison's polyether biosynthesis promoted in water.

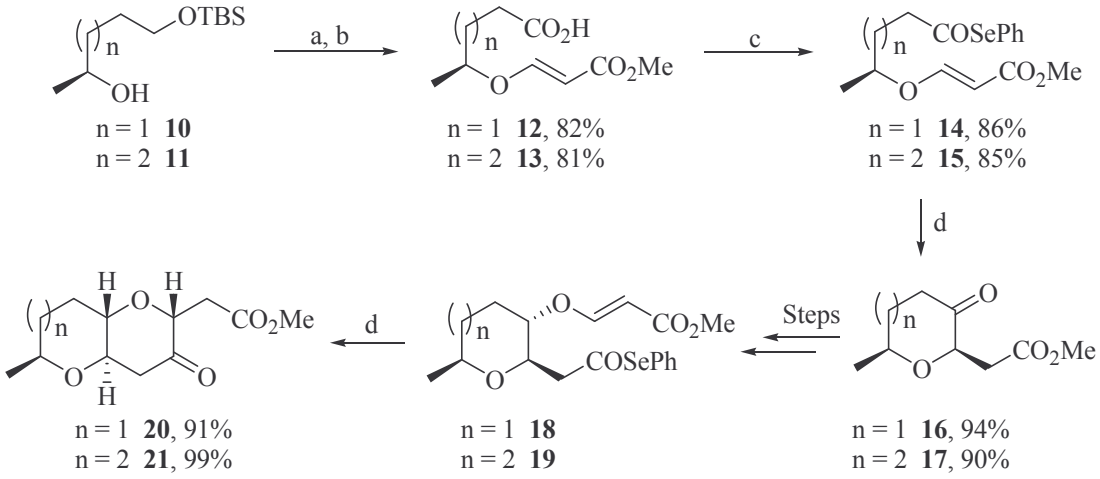
1.4. Previous synthesis of fragments of Gambieric acids

1.4.1. Evans' synthesis of BC and IJ ring fragments

Evans and co-workers were the first to report a study towards the synthesis of gambieric acids.[13] Evans developed an iterative acyl radical cyclisation strategy for the synthesis of BC and IJ ring fragments (**Scheme 7**). The synthesis of carboxylic acids **12** and **13** was achieved in two steps using methyl propionate and tributylphosphine followed by Jones oxidation. Carboxylic acids **12** and **13** were converted into the key acyl selenides **14** and **15**. Treatment of **14** and **15** with tris(trimethylsilyl)silane and triethylborane afforded

[12] I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189.
[13] P. A. Evans, J. D. Roseman, L. T. Garber, *J. Org. Chem.* **1996**, *61*, 4880.

desired ether rings **16** and **17** as a 5.7:1 and >19:1 mixture of diastereoisomers respectively. Then, the same strategy was applied to give the bicyclic ketones **20** and **21**.



Reagents and conditions: (a) methyl propionate, Bu_3P, CH_2Cl_2, rt; (b) Jones oxidation, –10 °C→rt; (c) (i) Et_3N, rt, 20 min (ii) PhSeBr, Bu_3P, rt; (d) $(Me_3Si)_3SiH$, Et_3B, toluene, air, rt.

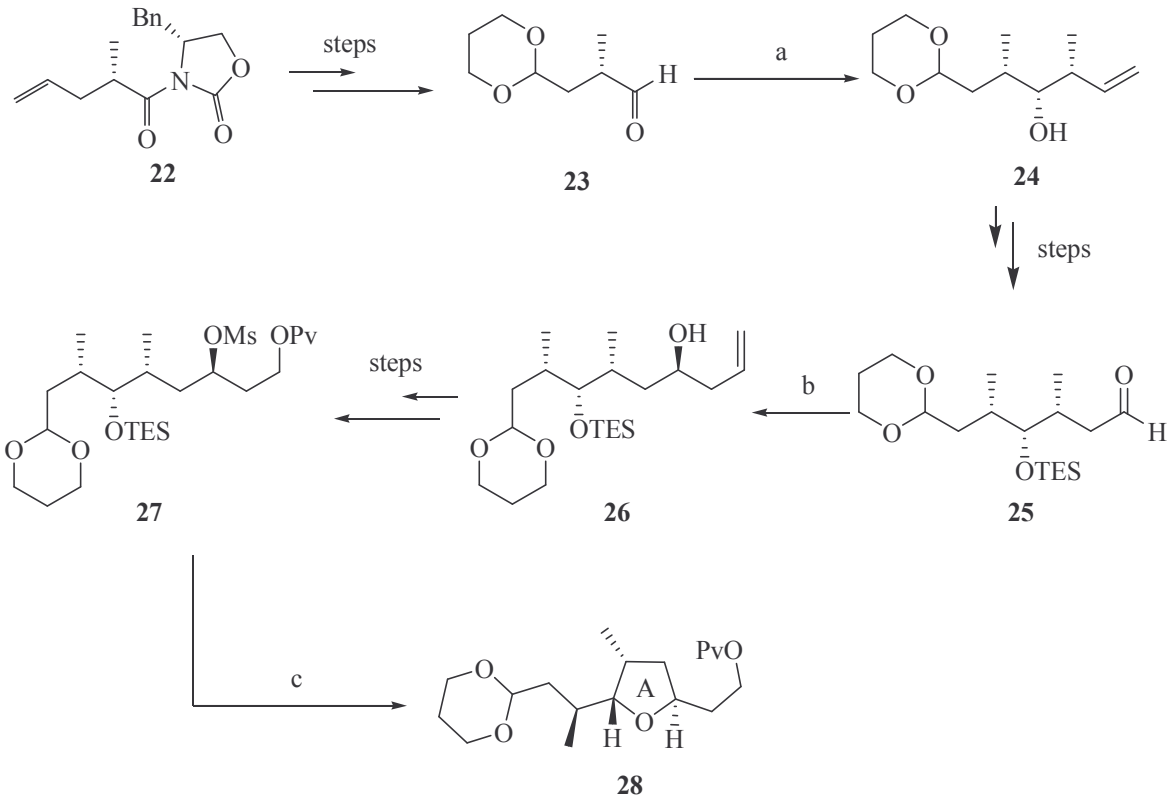
Scheme 7: Evan's iterative strategy.

1.4.2. Yamamoto's synthesis of A and J ring fragments

Yamamoto and co-workers reported the synthesis of the trisubstituted tetrahydrofuran (A-ring) of the gambieric acids (**Scheme 8**).[14] Yamamoto's approach required installation of four stereogenic centres. Therefore, the methyl and hydroxyl groups of the intermediate **24** were introduced using Brown's asymmetric crotylboration of the aldehyde **23**. Protection of the alcohol followed by a hydroboration/oxidation sequence delivered the desired aldehyde **25**. Finally, the last stereocentre was introduced by allylboration in highly diastereoselective manner (16:1). A few group manipulations gave key intermediate **27**. Deprotection of silyl ether **27** with TBAF furnished the free alcohol, which cyclised *in situ* to deliver the A-ring fragment by an intramolecular S_N2 reaction in 13 steps and 13.8% overall yield from **22**. Protection of the alcohol as a TES ether was found to be a key factor in the success of the route. Indeed, when a TBS ether was used, the rate of elimination of

[14] I. Kadota, N. Oguro, Y. Yamamoto, *Tetrahedron Lett.* **2001**, *42*, 3645.

the mesylate to give an alkene was higher than that of the desired cyclisation process. Consequently, the less robust TES ether was required to deliver the desired trisubtituted tetrahydrofuran **28** in good yield.



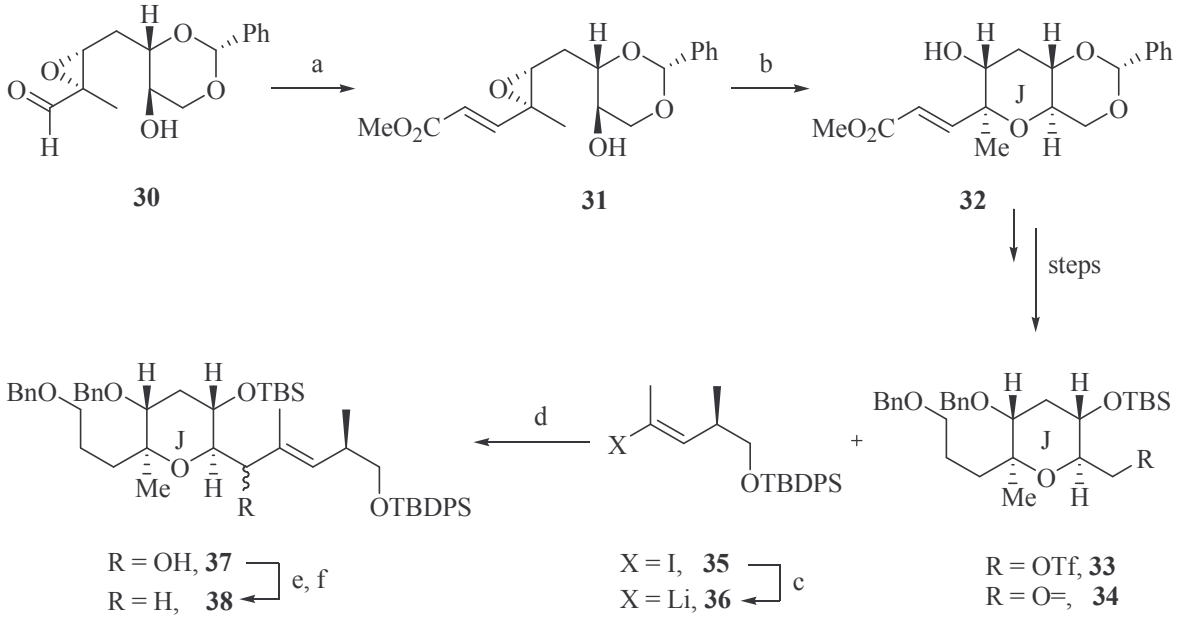
Reagents and conditions: (a) $^{d}Ipc_2B$-(*Z*)-crotyl, THF, –78 °C; H_2O_2, NaOH, 65 °C (72%); (b) $^{d}Ipc_2B$-allyl, ether, –78 °C; H_2O_2, NaOH, rt (88%); (c) TBAF, THF, rt (84%).

Scheme 8: Yamamoto's A-ring synthesis.

Yamamoto was also interested in the synthesis of the J-ring fragment (**Scheme 9**).[15] The synthesis started from the known aldehyde **30**. Wittig reaction delivered the α,β-unsaturated ester **31** and then acid catalysed 6-*endo* cyclisation afforded ether ring **32**. Yamamoto's first approach involved coupling between the alkynyl lithium reagent **36,** or the associated cuprate, and triflate **33**, which was synthesised from **32** after several steps (**Scheme 9**). Unfortunately, none of the desired coupling product was observed. Consequently, the authors devised a longer route involving the nucleophilic coupling

[15] I. Kadota, H. Takamura, Y. Yamamoto, *Tetrahedron Lett.* **2001**, *42*, 3649.

reaction of the aldehyde **34** with the alkenyl lithium **36**. The Barton deoxygenation protocol then gave a complex mixture of alkenes and only a 25% yield of the desired J-ring fragment **38** was obtained.



Reagents and conditions: (a) $Ph_3P{=}CHCO_2Me$, $PhCO_2H_{cat}$, Benzene, rt (89%); (b) $PPTS_{cat.}$, CH_2Cl_2, rt (78%); (c) *t*-BuLi, ether, –78 °C; (d) –78 °C, ether (76%); (e) CS_2, KH, ether, rt (98%); (f) Bu_3SnH, $AIBN_{cat.}$, benzene, reflux (25%).

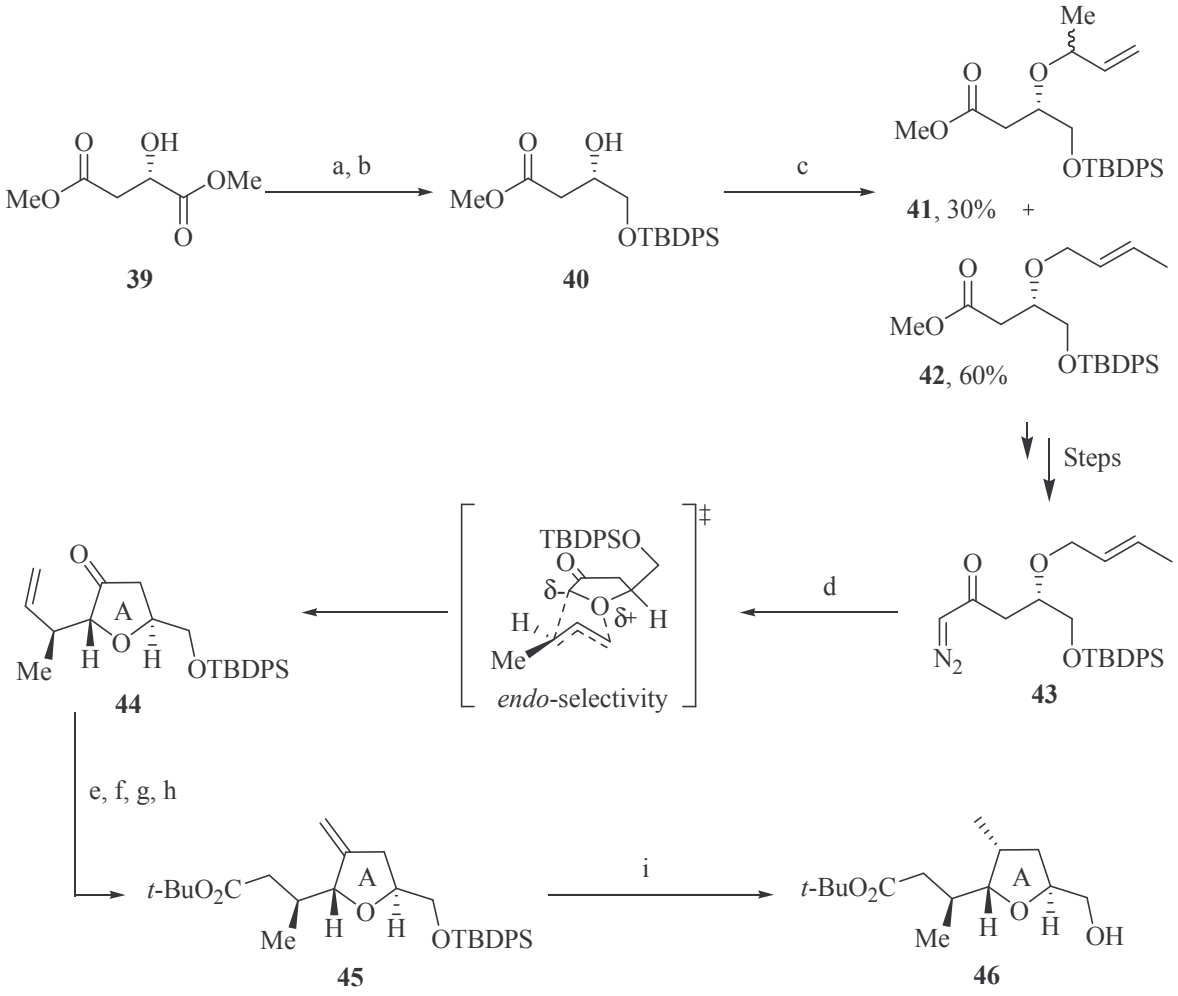
Scheme 9: Yamamoto's J-ring synthesis.

1.4.3. Clark's synthesis of A-ring fragment

The Clark synthesis was planned around a one-pot tandem catalytic carbenoid generation, ylide formation and [2,3] rearrangement sequence. Therefore, the synthesis began from the dimethyl malate **39** (**Scheme 10**).[16] Regioselective reduction of the ester **39** and subsequent protection of the resulting primary alcohol afforded the compound **40**. Ether formation using *E*-crotyl 2,2,2-trichloroacetimidate with a catalytic amount of acid gave a mixture of compounds arising from S_N2 and S_N2' reactions. Then, the desired S_N2 product **42** was converted into the diazoketone **43**. The key ylide formation and [2,3] rearrangement reaction was performed using copper(II) acetylacetonate to deliver the

[16] J. S. Clark, T. C. Fessard, C. Wilson, *Org. Lett.* **2004**, *6*, 1773.

3(2*H*)-dihydrofuranone **44** in 88% and with excellent diastereoselectivity (>98:2). Esterification and ketone methylenation provided the intermediate **45**. Ultimately, deprotection of the primary alcohol **45** allowed stereoselective hydrogenation using Wilkinson's catalyst to afford the A-ring in 12 steps starting from the dimethyl malonate **39**.

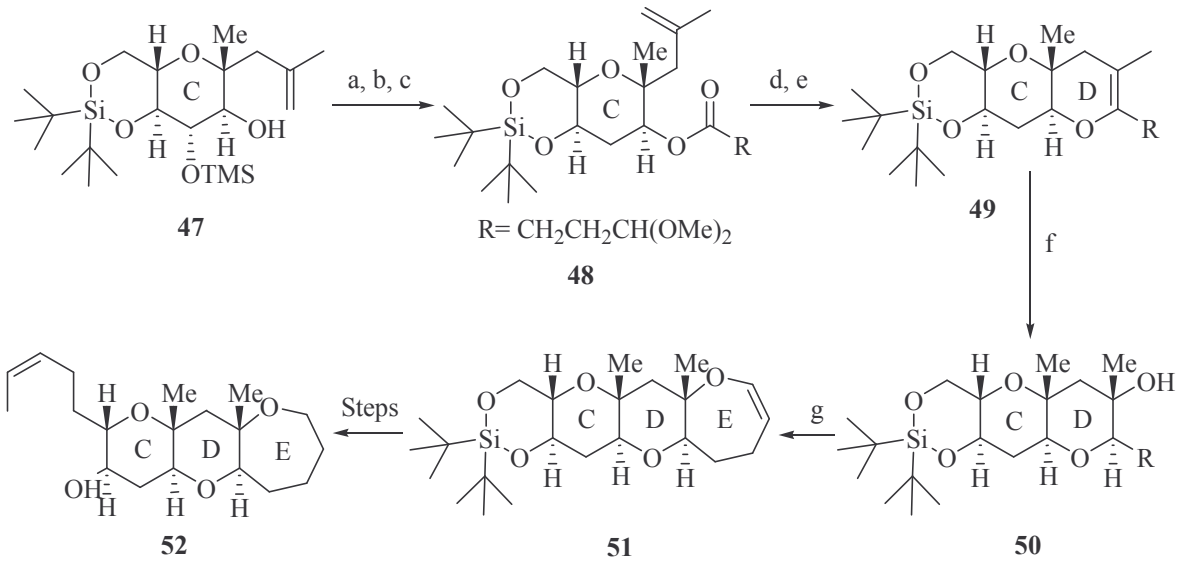


Reagents and conditions: (a) $NaBH_4$, $BH_3{\cdot}SMe_2$, THF, rt (92%); (b) TBDPSCl, imidazole, DMF, rt (88%); (c) *E*-crotyl 2,2,2-trichloroacetimidate, CF_3SO_3H, CH_2Cl_2, rt; (d) $Cu(acac)_2$, THF, reflux, (88%); (e) i) $(c\text{-}C_6H_{11})_2BH$, THF, 0 °C→rt; ii) H_2O_2, pH 7 buffer, (85%); (f) PDC, DMF, rt (74%); (g) $(COCl)_2$, DMF, CH_2Cl_2, rt then *t*-BuOH, rt (80%); (h) TBAF, THF, rt (99%); (i) H_2, $(Ph_3P)_3RhCl$, toluene, rt (92%).

Scheme 10: A-ring fragment synthesis.

1.4.4. Rainier's synthesis of AE-ring fragment

In 2007, Rainier and co-workers published the synthesis of A–E-ring fragment using three main reactions: the generation of carbon *C*-glucosides from glycal anhydride with nucleophiles, the synthesis of enol ether using RCM and acid catalysed cyclisations.[17] Synthesis of the advance compound **47** required 11 steps from L-glucose (**Scheme 11**). Completion of the C-ring involved esterification of the secondary alcohol **47** followed by deprotection/deoxygenation of the TMS alcohol. The bicyclic enol ether **49** was obtained by formation of an acyclic enol ether using the Takai-Utimoto reagent and subsequent RCM reaction. Functionalisation of the D-ring by DMDO oxidation followed by reductive opening of the epoxide at the anomeric position with Dibal-H gave alcohol **50**. Acid catalysed cyclisation then afforded a lactol, which was dehydrated *in situ* to deliver the E-ring. In order to study the coupling reaction between the A-ring and B–E-ring system, the enol ether **51** was hydrogenated and further transformations furnished the key tricyclic alcohol **52**.



Reagents and conditions: (a) $(MeO)_2CHCH_2CH_2COOH$, DCC, DMAP, CH_2Cl_2, rt (92%); (b) CSA, MeOH, rt (91%); (c) i) CS_2, NaH, MeI, ether, rt; ii) Bu_3SnH, AIBN, toluene, 110 °C (72%); (d) $TiCl_4$, Zn, $PbCl_2$, CH_2Br_2, TMEDA, THF, 65 °C; (e) Grubbs II catalyst, toluene, 80 °C (80% over 2 steps); (f) DMDO then Dibal-H (95%); (g) PPTS, pyridine, PhCl, 135 °C (80%).

Scheme 11: C−E-ring fragment synthesis

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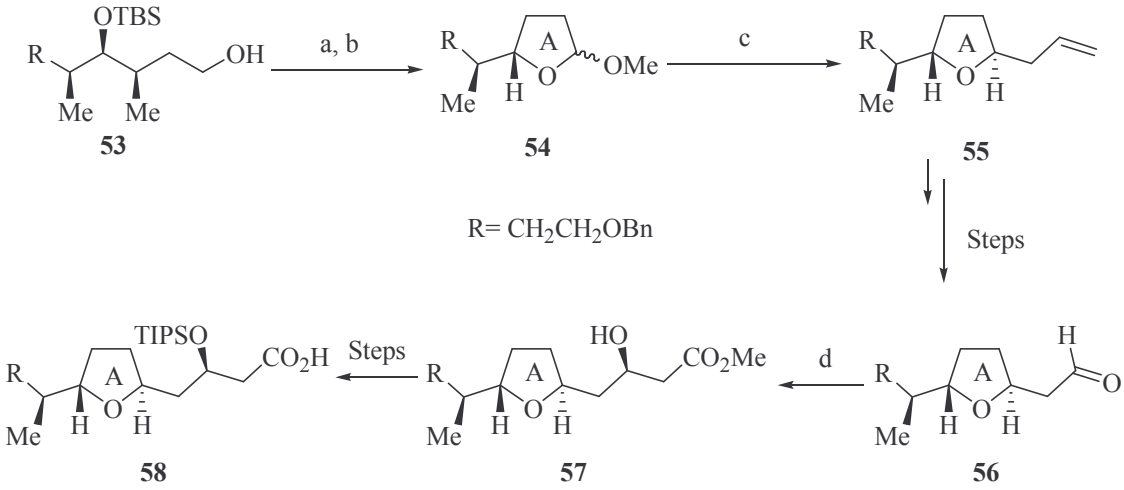
[17] S. W. Roberts, J. D. Rainier, *Org. Lett.* **2007**, *9*, 2227.

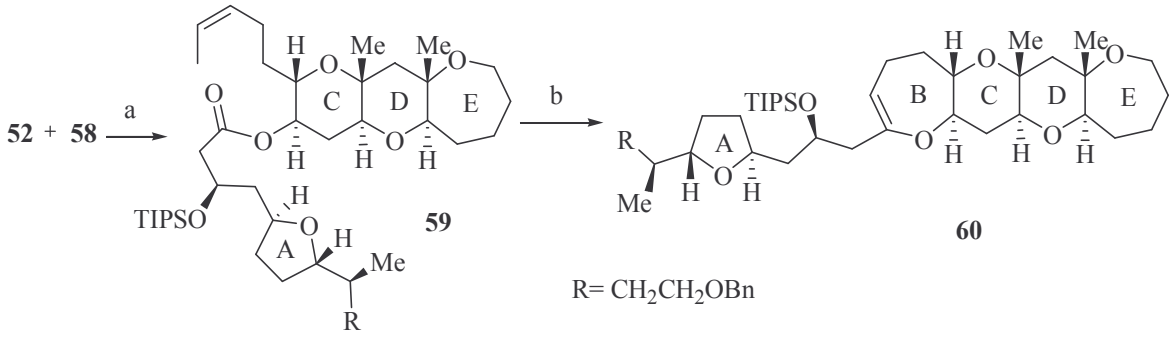
The other partner, the A-ring, was obtained starting from the known alcohol **53** (**Scheme 12**). Oxidation and subsequent acid cyclisation provided the cyclic acetal **54**. Introduction of the allyl side chain was achieved by addition of allylsilane promoted by $BF_3.Et_2O$. Further transformations furnished the aldehyde **56**. The last stereocentre was introduced with moderate selectivity (5.1:1) during a substrate-controlled aldol reaction to produce the alcohol **57**.



Reagents and conditions: (a) TPAP, NMO, rt (92%); (b) HCl/MeOH, rt (75% over 2 steps); (c) CH_2=$CHCH_2TMS$, $BF_3{\cdot}Et_2O$ (100%); (d) $TBSO(MeO)C{=}CH_2$, Me_2AlCl (86%).

Scheme 12: A-ring synthesis.

Further functional group transformations delivered the acid **58**, which was coupled with alcohol **52** using Yamaguchi's esterification conditions (**Scheme 13**). Finally, the use of Takai Utimoto protocol resulted in formation the E-ring in moderate yield. The presence of the methyl group on the alkene **59** is vital for the reaction to work. In the absence of the methyl group, the RCM reaction did not work and a mixture of compounds was obtained. The synthesis of A–E-ring fragment was achieved in 29 steps but further steps are required to functionalise the B-ring.

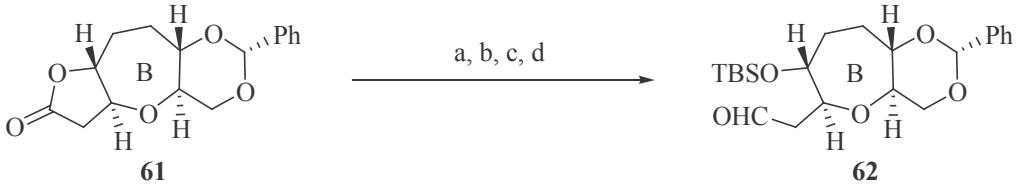


Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N (100%); (b) $TiCl_4$, Zn, $PbCl_2$, CH_3CHBr_2, TMEDA, THF, 65 °C (50%).

Scheme 13: A–E-ring fragment synthesis.

1.4.5. Sasaki's synthesis of AB-ring and CG-ring fragments

In 2007, Sasaki and co-workers published the synthesis of AB-ring fragment.[18] The strategy consisted of an acetylide-aldehyde coupling and a diastereoselective bromoetherification for construction of the A-ring. The synthesis began from the lactone **61**, which was converted into aldehyde **62** (**Scheme 14**).



Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C; (b) PivCl, pyridine, CH_2Cl_2, 0 °C → rt (90% over 2 steps); (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) Dibal-H, CH_2Cl_2, –78 °C (98% over 2 steps); (e) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (89%).

Scheme 14: B-ring synthesis.

The coupling partner was obtained starting from aldehyde **63** (**Scheme 15**). An Evans aldol reaction delivered the desired alcohol **65**, which was then transformed into the alcohol **66**. An alkyne was then introduced by displacement of the triflated alcohol **66** with lithium trimethylsilylacetylide followed by removal of the TMS group under basic conditions.

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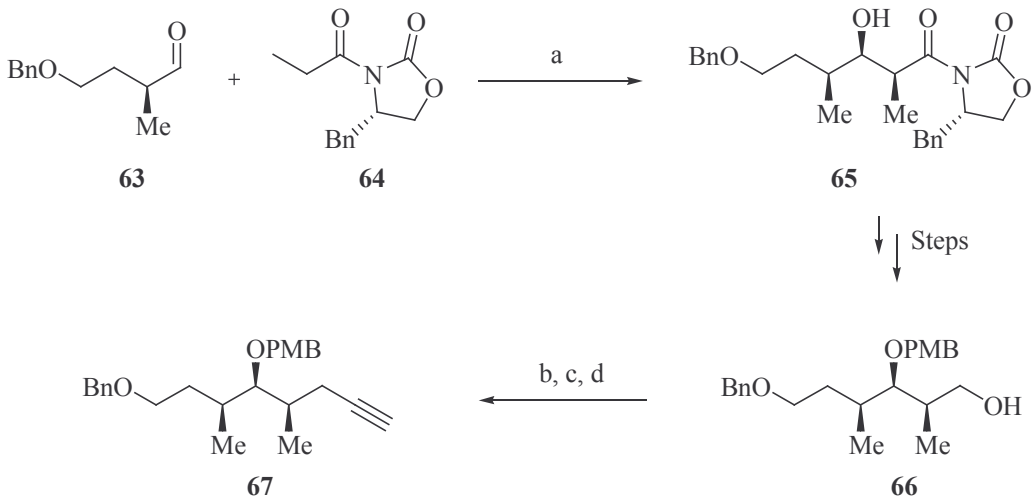
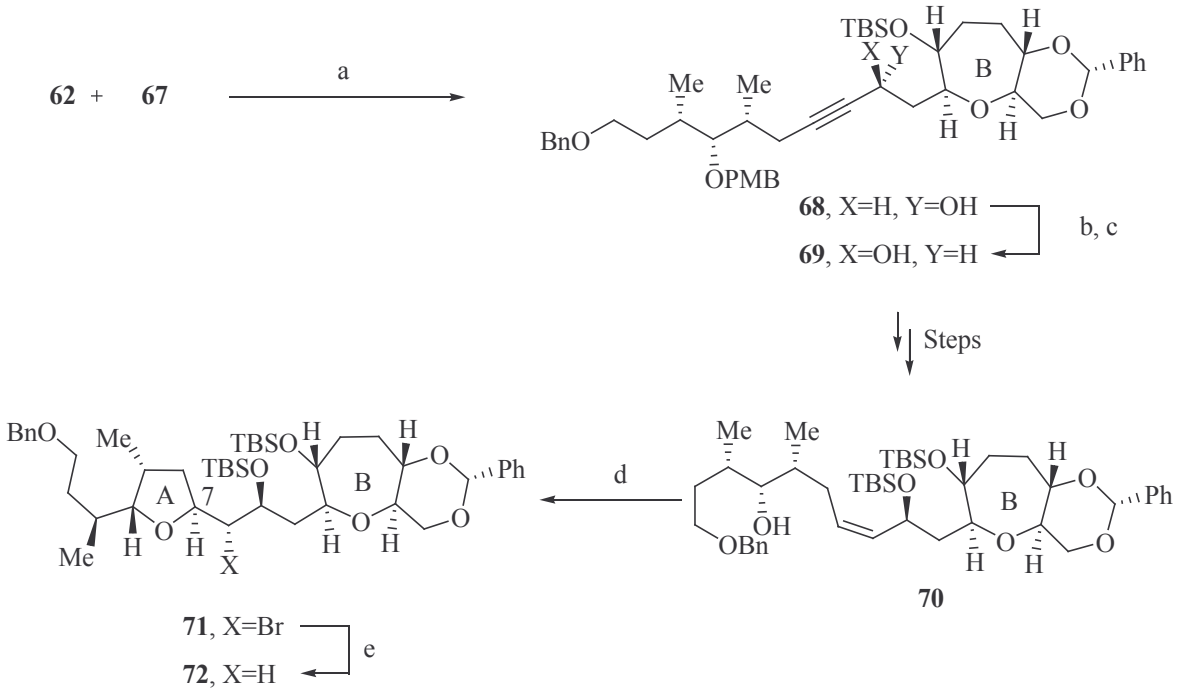
[18] H. Fuwa, A. Suzuki, K. Sato, M. Sasaki, *Heterocycles* **2007**, *72*, 139.



Reagents and conditions: (a) *n*-Bu_2OTf, Et_3N, CH_2Cl_2, –78 °C then pH 7 buffer, H_2O_2, MeOH, rt (87%); (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C; (c) TMS-acetylene, *n*-BuLi, HMPA, THF, –78 °C; (d) K_2CO_3, MeOH, rt (72% over 3 steps).

Scheme 15: Synthesis of acetylene **67**.

Nucleophilic addition of the corresponding lithium acetylene **67** to the aldehyde **62** afforded a diastereomeric separable mixture (3:2) of the propargyl alcohols **68** and **69** (**Scheme 16**). Fortunately, inversion of the hydroxyl-bearing stereogenic centre of the alcohol **68** using a Mitsunobu reaction delivered the desired isomer **69** in excellent yield. Partial hydrogenation with Lindlar catalyst afforded the alkene **70**. Key stereoselective bromoetherification was then achieved using NBS. Protection of the allylic hydroxyl group as a TBS ether is important. The bulky group limits directs formation of cyclic bromonium to the required face of the alkene. Finally, removal of the bromide using Barton's conditions gave the AB-ring fragment as a 4:1 mixture of diastereomers.



Reagents and conditions: (a) *n*-BuLi, THF, –78 °C (73%); (b) *p*-NO_2PhCO_2H, DEAD, Ph_3P, toluene, 0 °C; (c) Dibal-H, CH_2Cl_2, –78 °C (83% over 2 steps); (d) NBS, MeCN, rt; (e) *n*-Bu_3SnH, AIBN, toluene, 110 °C (87% over 2 steps, **72**/**7**-***epi*-72** = 4:1).

Scheme 16: AB-ring fragment synthesis.

Recently, Sasaki and Sato published the most advanced synthesis of the gambieric acid ring system: the B–J fragment.[19] The strategy was based on the disconnection at EF-rings to produce two equal fragments. This approach was successfully tested by the authors a few years earlier on a model system.[20] The synthesis of the BCD-ring system started from the known alcohol **73** (**Scheme 17**). Extension of the side chain allowed the formation of the key epoxy alcohol **74**. Cyclisation *via* a 6-*endo* mechanism furnished the C-ring in excellent yield. Then, further modifications delivered compound **76**. Reductive cyclisation using SmI_2 gave the D-ring as a single diasteoreomer. Synthesis of the B-ring used the same strategy as the D-ring. Finally, group manipulations provided the desired BCD fragment.

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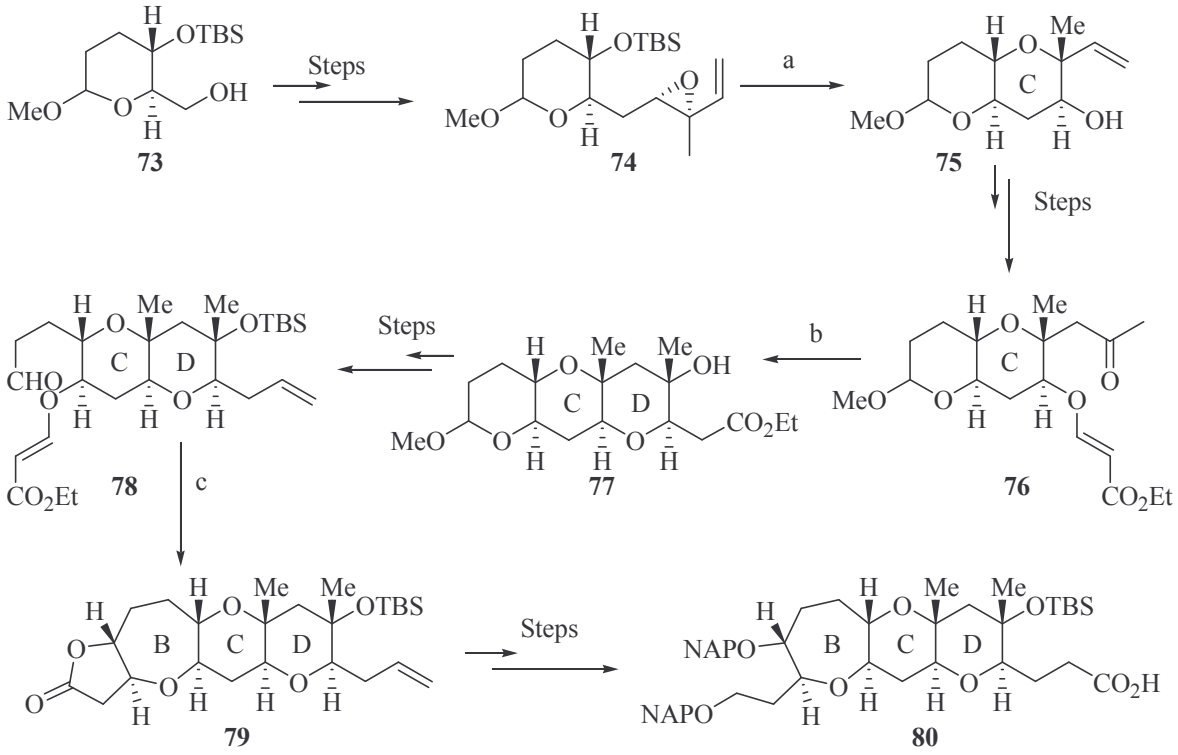
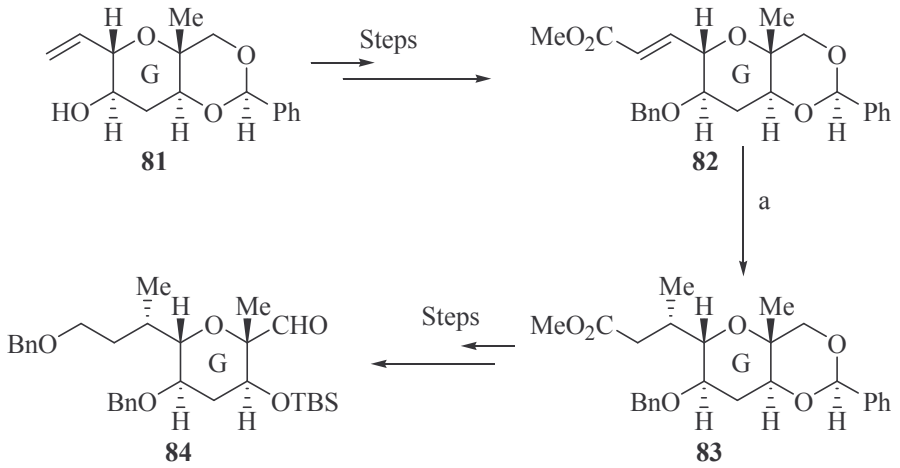
[19] (a) K. Sato, M. Sasaki, *Tetrahedron* **2007**, *63*, 5977; (b) K. Sato, M. Sasaki, *Angew. Chem., Int. Ed.* **2007**, *46*, 2518.
[20] K. Sato, M. Sasaki, *Org. Lett.* **2005**, *7*, 2441.



Reagents and conditions: (a) PPTS, CH_2Cl_2, 0 °C → rt (96%); (b) SmI_2, MeOH, THF, 0 °C → rt (81%); (b) SmI_2, MeOH, THF, rt.

Scheme 17: B–D fragment synthesis.

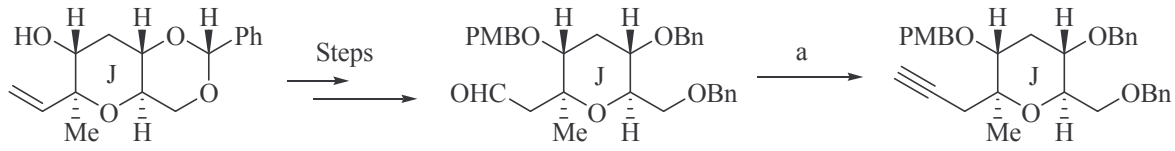
The GJ-ring fragment was synthesised by connecting the G-ring and J-ring. The synthesis of the G-ring started from the known alcohol **81** (**Scheme 18**). Functionalisation of the alkene gave the α,β-unsaturated ester **82**. A 1,4 addition of the methyl group was performed in good yield using methylmagnesium bromide, TMSCl and a copper(II) salt. Completion of the synthesis of the G-ring was achieved after several more steps.



Reagents and conditions: (a) MeMgBr, TMSCl, *i*-propylsalicylaldimine copper(II) complex, THF, –45 °C (92%).

Scheme 18: Synthesis of the G-ring.

The synthesis of the J-ring began from the alcohol **85** (**Scheme 19**). Modifications of the starting material delivered in 5 steps the aldehyde **86**. Next, the fully functionalised J-ring was synthesised by conversion of the aldehyde **86** into the alkyne **87** using the Ohira-Bestmann reagent.

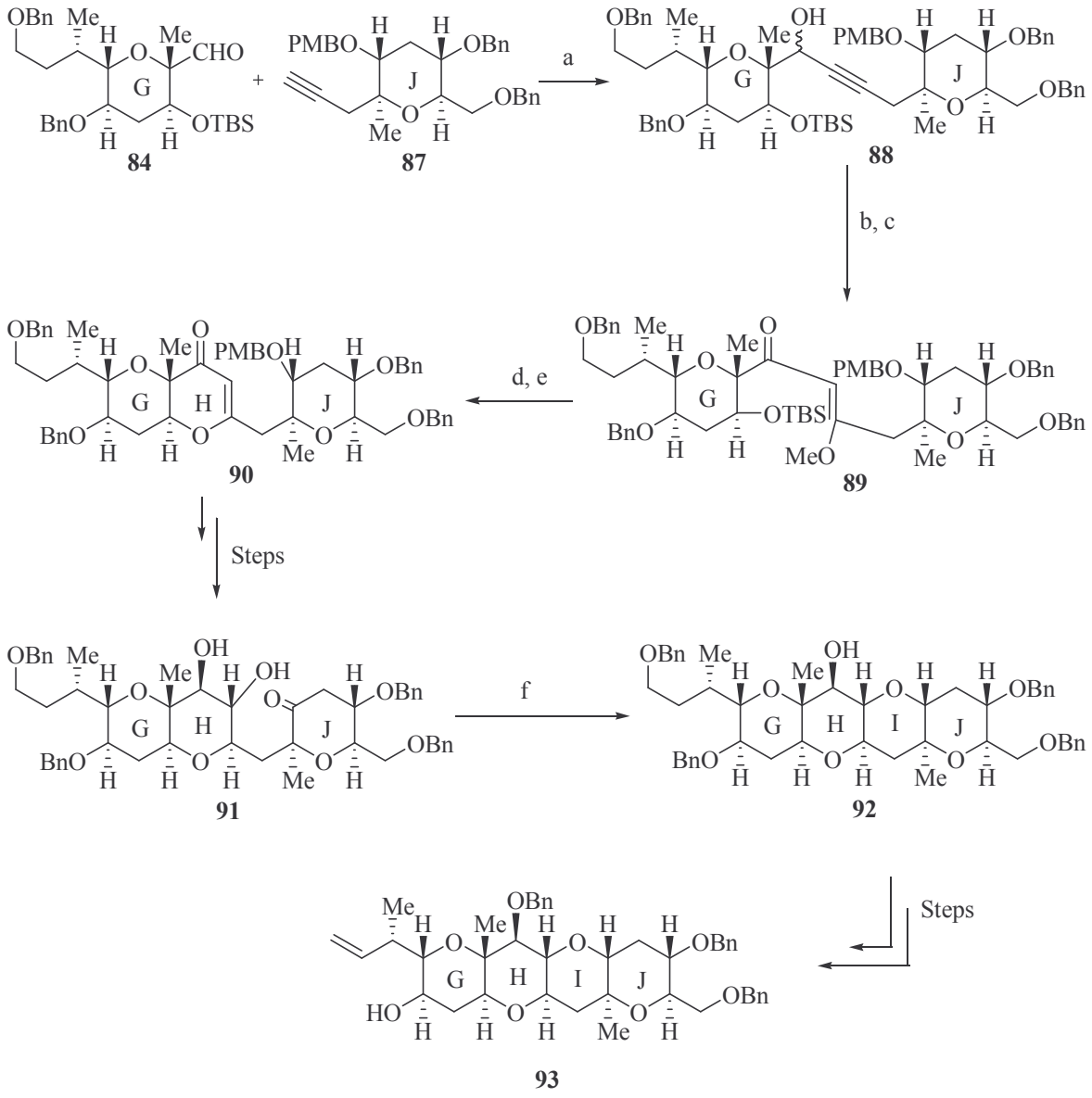


85 **86** **87**

Reagents and conditions: (a) $(MeO)_2P{=}OC(N_2)COCH_3$, Cs_2CO_3, *i*-PrOH, 0 °C → rt (93%).

Scheme 19: Synthesis of the J-ring.

The coupling reaction between the aldehyde **84** and the lithium acetylide generated from the alkyne **87** afforded the propargylic alcohol **88** (**Scheme 20)**. The alcohol **88** was then oxidised and treated with sodium methoxide to afford the β-methoxyenone **89**. Deprotection of the secondary TBS ether **89** followed by cyclisation under acidic conditions then delivered the H-ring. Further steps led to the advanced intermediate **91**, which was cyclised by addition of Et_3SiH and TMSOTf to afford the tetracyclic alcohol **92**. Finally, additional steps resulted in functionalisation of the G-ring and gave the complete G–J fragment **93**.

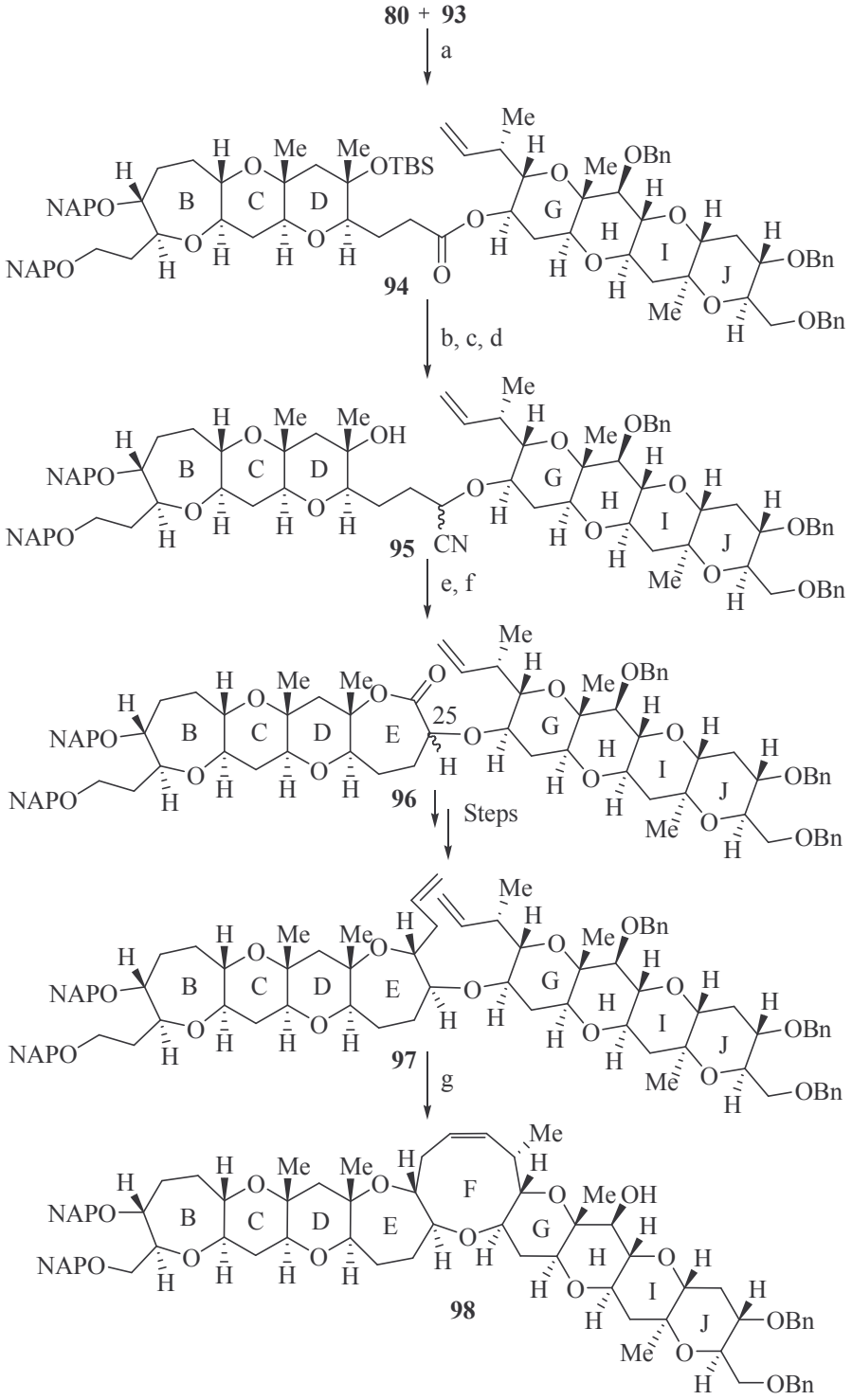


Reagents and conditions: (a) *t*-BuLi, THF/HMPA, –78 °C (95%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C (93%); (c)NaOMe, MeOH,/THF, rt (98%); (d) HF·Pyridine/pyridine/THF, 0 °C → rt (91%); (e) PPTS, toluene, 100 °C (87%); (f) TMSOTf, Et_3SiH/MeCN, –10 °C (83%).

Scheme 20: G–J fragment synthesis.

Esterification between fragments **80** and **93** using Yamaguchi's conditions provided the desired coupled ester **94** (**Scheme 21**). Reduction and protection of the ester **94** then gave the acetal, which was displaced with TMSCN to afford the α-cyano ether **95**. Hydrolysis of the cyanide followed by lactonisation delivered the E-ring. At this stage, a mixture of diastereoisomers was obtained at position 25 and only 37% of product was isolated. Unfortunately, all attempts to epimerise the stereocentre failed and the synthesis continued with the small amount of the required compound isolated. The allyl chain was introduced

using a three-step sequence: reduction of the lactone **96**, acetylation of lactol generated and subsequent displacement with allylsilane. Finally, RCM reaction with Grubbs second generation catalyst afforded the complete B–J fragment.



Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, THF, 0 °C → 40°C (92%); (b) Dibal-H, CH_2Cl_2, –78 °C; Ac_2O, DMAP, pyridine, CH_2Cl_2, –78 °C → 0 °C (54%); (c) TMSCN, TMSOTf, DTBMP, CH_2Cl_2, –78 °C → 0 °C; (d) TBAF, MeCN, 70 °C (89% over 2 steps); (e) KOH, ethylene glycol, 150 °C; (f) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, THF, reflux (37%+39% over 2 steps); (g) Grubbs II cat., CH_2Cl_2, 40 °C (67%).

Scheme 21: B–J fragment synthesis.

1.5. Metathesis reactions and polyether synthesis

Only small quantities of the gambieric acids are present in dinoflagellate and consequently, the total synthesis of these polyether compounds constitutes an important challenge for chemists. This is due to the fact that new methodologies must be developed in order to produce enough synthetic material to perform further biological evaluation.

1.5.1. Clark's strategy

In order to tackle the synthesis of complex polyether structures, the Clark group has developed a range of new methodologies in which ring-closing metathesis (RCM) is used to build small and medium rings.[21] Initially, RCM mediated by Schrock's catalyst (**A**) was used to build six- and seven-membered cyclic ethers (**Scheme 22**).[22] The RCM precursors were obtained by methylenation of the corresponding esters using the Takai protocol in moderate yield and subsequent RCM reaction delivered the desired bicyclic enol ethers **100**. The variations in the isolated yields were mainly due to the instability of the cyclic enol ethers towards purification. The enol ether **100** was further functionalised by hydroboration with thexyl borane at −25 °C of the remaining alkene to give the new alcohol **101**. The diastereoselectivity and regioselectivity of the hydroboration reaction is remarkable. Only a single diastereoisomer is obtained. Better yields could be obtained by a quick filtration of the reaction mixture through a plug of silica to remove catalyst debris followed by immediate hydroboration of the cyclic enol ethers. The preparation of tetrasubstituted enol ethers using Schrock's catalyst (**A**) was problematic. Indeed, significant steric interactions seem to inhibit the intramolecular RCM reaction.

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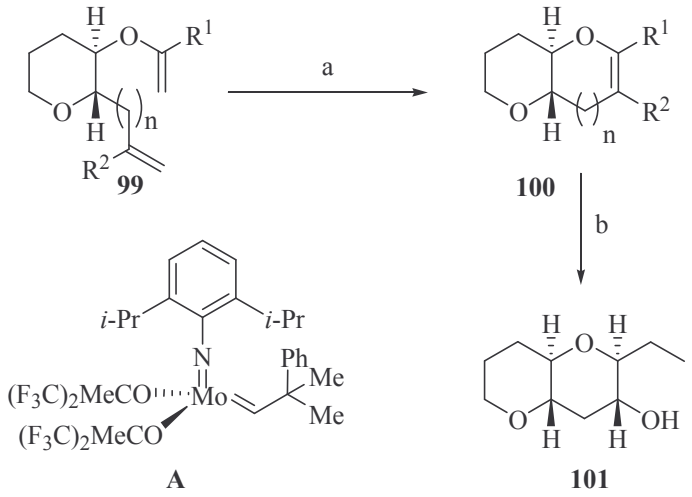
[21] J. S. Clark, *Chem. Commun.* **2006**, 3571.
[22] (a) J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 123; (b) J. S. Clark, J. G. Kettle, *Tetrahedron* **1999**, *55*, 8231.



n	R^1	R^2	Yield
1	Et	H	72%
1	H	Me	93%
2	Et	H	42%
2	H	Me	94%

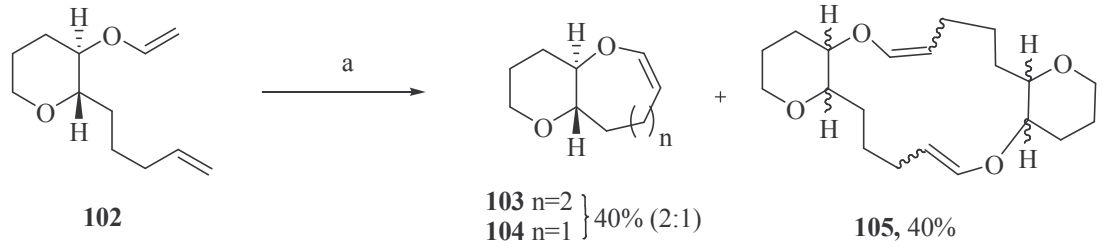
Reagents and conditions: (a) catalyst **A**, pentane, rt; (a) (i) $ThxBH_2$, THF, −20 °C (ii) NaOH, H_2O_2 (67%).

Scheme 22: RCM approach to six- and seven-membered rings.

The construction of eight- and nine-membered rings using the method described above was problematic because during the formation of eight- and nine-membered rings, unfavourable steric interactions occur. In addition, acyclic enol ethers are generally poor substrates for the RCM reaction because of the possible formation of stable Fisher-type carbene complexes. Consequently, the rate of the RCM reaction to form eight- and nine-membered rings is low and mixtures of starting material, product, ring-contracted product (*via* an isomerisation/RCM process) and cyclodimer product **105** were obtained (**Scheme 23**). The isomerisation/RCM process was unprecedented at this time but others later encountered the same process.[23] The isomerisation reaction is certainly due to the decomposition of the catalyst to a ruthenium hydride by mechanisms that have not been completely elucidated.[24] Nowadays, the isomerisation reaction can be totally controlled in certain circumstances. Grubbs was recently able to limit the isomerisation by addition of

[23] D. Joe, L. E. Overman, *Tetrahedron Lett.* **1997**, *38*, 8635.
[24] S. H. Hong, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc*. **2004**, *126*, 7414.

benzoquinone, whereas addition of catalytic amount of sodium borohydride promoted simultaneous RCM and isomerisation to give ring-contracted products in excellent yields.[25]



102

103 n=2
104 n=1
} 40% (2:1)

105, 40%

Reagents and conditions: (a) catalyst **A**, benzene, 60 °C.

Scheme 23: Isomerisation and dimerisation during construction of eight-membered rings

At this time, allylic ethers **106** were used to avoid these problems (**Scheme 24**).[26] The RCM precursors were synthesised as separable diastereoisomers and these can react at different rates. Indeed, reactivity proved to be highly different in the case of nine-membered rings (n = 2). This observation is certainly due to unfavourable steric interactions between the ethyl group and the acetal ring during the RCM process. Initially, the strategy for the functionalisation of the new ring relied on an isomerisation/hydroboration process to introduce the hydroxyl group. However, the isomerisation step proved to be ineffective and a new successful strategy was employed to functionalise the ring by epoxidation of the alkene **107**. Direct epoxidation with *m*-CPBA delivered the opposite diastereoisomer to that required but indirect epoxidation *via* a bromohydrin intermediate furnished the required product **108**. Regioselective opening with Super-Hydride® then yielded the alcohol **109**. Unsaturation of the medium rings is also frequently found in polyether systems. Thus, epoxide **108** was regioselectively opened with sodium phenylselenide to give selenide **110**. Subsequent oxidation and elimination gave the desired unsaturated cyclic ether in good yield.

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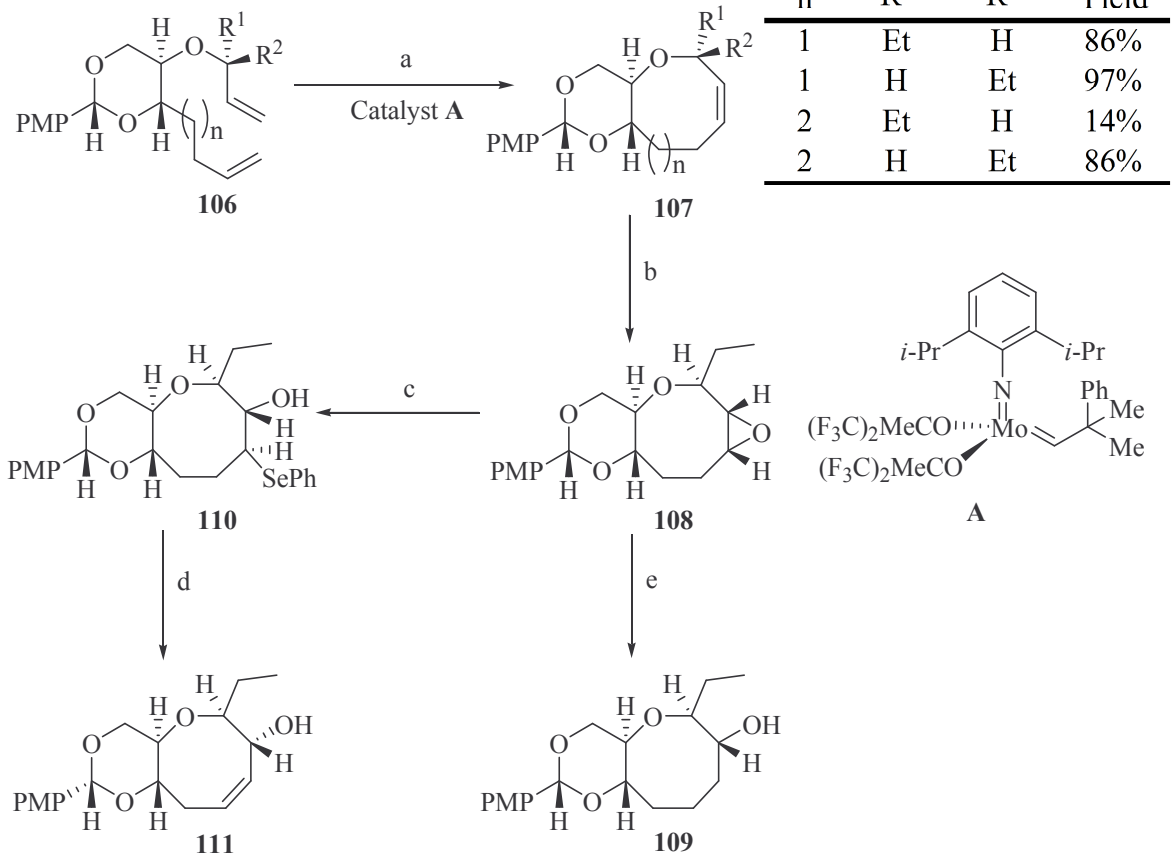
[25] (a) S. H. Hong, D. P. Sanders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160; (b) B. Schmidt, *J. Mol. Catal. A: Chem.* **2006**, *254*, 53.

[26] (a) J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 127; (b) J. S. Clark, O. Hamelin, R. Hufton, *Tetrahedron Lett.* **1998**, *39*, 8321.

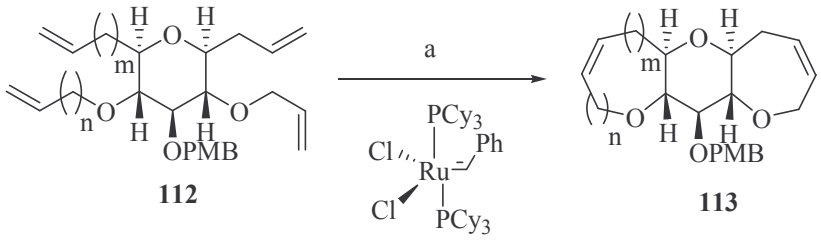


n	R^1	R^2	Yield
1	Et	H	86%
1	H	Et	97%
2	Et	H	14%
2	H	Et	86%

Reagents and conditions: (a) catalyst **A**, benzene, 60 °C, 3 h; (b) i) NBS, DME, H_2O, rt; ii) *t*-BuOK, C_6H_6, reflux (79% over 2 steps); (c) PhSeNa, EtOH, reflux; (d) H_2O_2, EtOH/THF, reflux (61% over 2 steps); (e) $LiEt_3BH$, THF, reflux (91%).

Scheme 24: RCM metathesis approach to the synthesis of eight and nine-membered rings.

These methods for the production of cyclic ethers were extended and a two-directional RCM strategy was employed.[27] A variety of different fused tricyclic ethers with different ring sizes were made in good yield (**Scheme 25**).



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

Reagents and conditions: (a) catalyst **B**, CH_2Cl_2, rt or reflux.

Scheme 25: Example of two-directional RCM.

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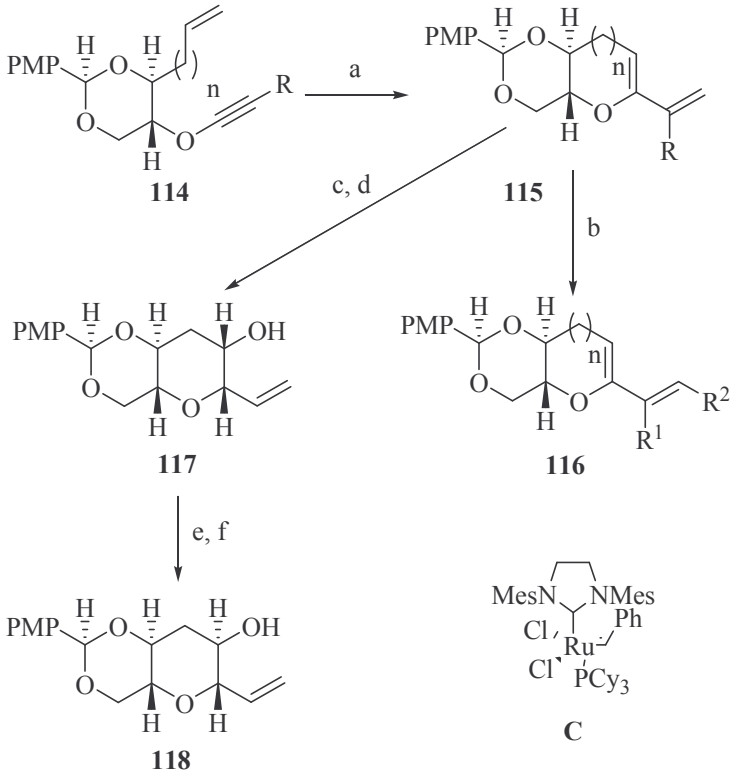
[27] J. S. Clark, O. Bamelin, *Angew. Chem., Int. Ed.* **2000**, *39*, 372.

The use of the ring closing enyne metathesis (RCEM) has also been utilised to synthesise six- and seven-membered alkenyl ethers in good yield using the Grubbs second generation catalyst (**C**) (**Scheme 26**).[28] In addition, extension of the side chain of the RCEM products could be achieved by cross-metathesis using the same catalyst employed for the ring closure. A functionalisation protocol was also explored, which consisted of a selective introduction of hydroxyl group to the diene **115**. Borane chemistry failed to give desired product in high yield. However, regioselective epoxidation and subsequent epoxide opening with Super-Hydride® delivered the alcohol **117** in good yield. Unfortunately, the product had incorrect configuration at hydroxyl-bearing centre and correction by oxidation/reduction steps needed to be performed.



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

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

Reagents and conditions: (a) catalyst **C**, toluene, 80 °C; (b) catalyst **C**, $H_2C{=}CHR^2$, toluene, 70 °C; (c) DMDO, CH_2Cl_2, 0 °C; (d) $LiEt_3BH$, THF, 0 °C (61% over 2 steps); (e) Dess-Martin periodinane, CH_2Cl_2, rt; (f) $NaBH_4$, CH_2Cl_2, MeOH, rt (79% over 2 steps).

Scheme 26: RCEM strategy.

[28] (a) J. S. Clark, F. Elustondo, G. P. Trevitt, D. Boyall, J. Robertson, A. J. Blake, C. Wilson, B. Stammen, *Tetrahedron* **2002**, *58*, 1973; (b) J. S. Clark, F. Elustondo, C. Kimber Marc, *Chem. Commun.* **2004**, 2470.

The Clark group has developed a variety of efficient tools using the RCM, two-directional RCM and the RCEM reactions to construct six- to nine-membered rings in a highly efficient manner. In addition, easy functionalisation of the cyclic products to give subunits found in the natural products can be performed. To demonstrate the viability of the methodology, the Clark group embarked on the total synthesis of various polyether compounds such as hemibrevetoxin B, ciguatoxin CTX3C and gambieric acid A.[29] Recently, construction of the complete core of hemibrevetoxin B has been achieved.[29a] The synthesis required the construction of four contiguous rings. A combination of enone RCM, RCEM and double RCM reactions was used and the synthesis commenced from the commercially available glucose derivative **119** (**Scheme 27**). Periodate cleavage and subsequent Wittig methylenation of the resulting aldehyde gave the alcohol **120**. Etherification of the alcohol followed by Wittig reaction yielded the RCM precursor **121**. Ring closing metathesis of enone **121** using Grubbs second generation catalyst provided the crystalline oxepenone **122** in 94% yield. Functionalisation of the ring was achieved using hydrazone chemistry. Indeed, selective deprotonation with *t*-BuLi and subsequent alkylation delivered the desired compound as 1:1 mixture of diastereoisomers in moderate yield. Epimerisation of the centre was then performed using DBU to furnish the required diastereoisomer and addition of methylmagnesium bromide delivered the tertiary alcohol. Hydrogenation of the alkene with concomitant hydrogenolysis of the benzyl ether furnished the diol **126**.

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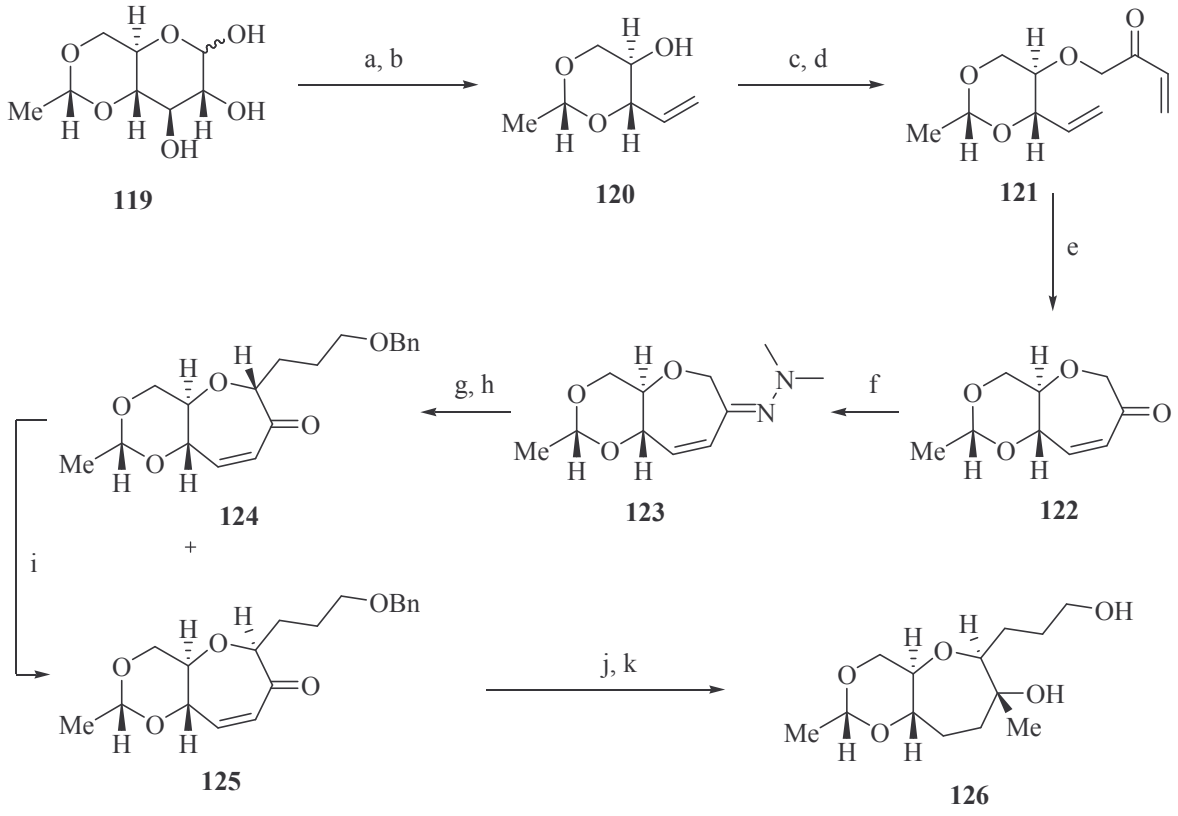
[29] J. S. Clark, D. M. Grainger, A. A. C. Ehkirch, A. J. Blake, C. Wilson, *Org. Lett.* **2007**, *9*, 1033; (b) J. S. Clark, J. Conroy, A. J. Blake, *Org. Lett.* **2007**, *9*, 2091; (c) J. S. Clark, M. C. Kimber, J. Robertson, C. S. P. McErlean, C. Wilson, *Angew. Chem., Int. Ed.* **2005**, *44*, 6157.



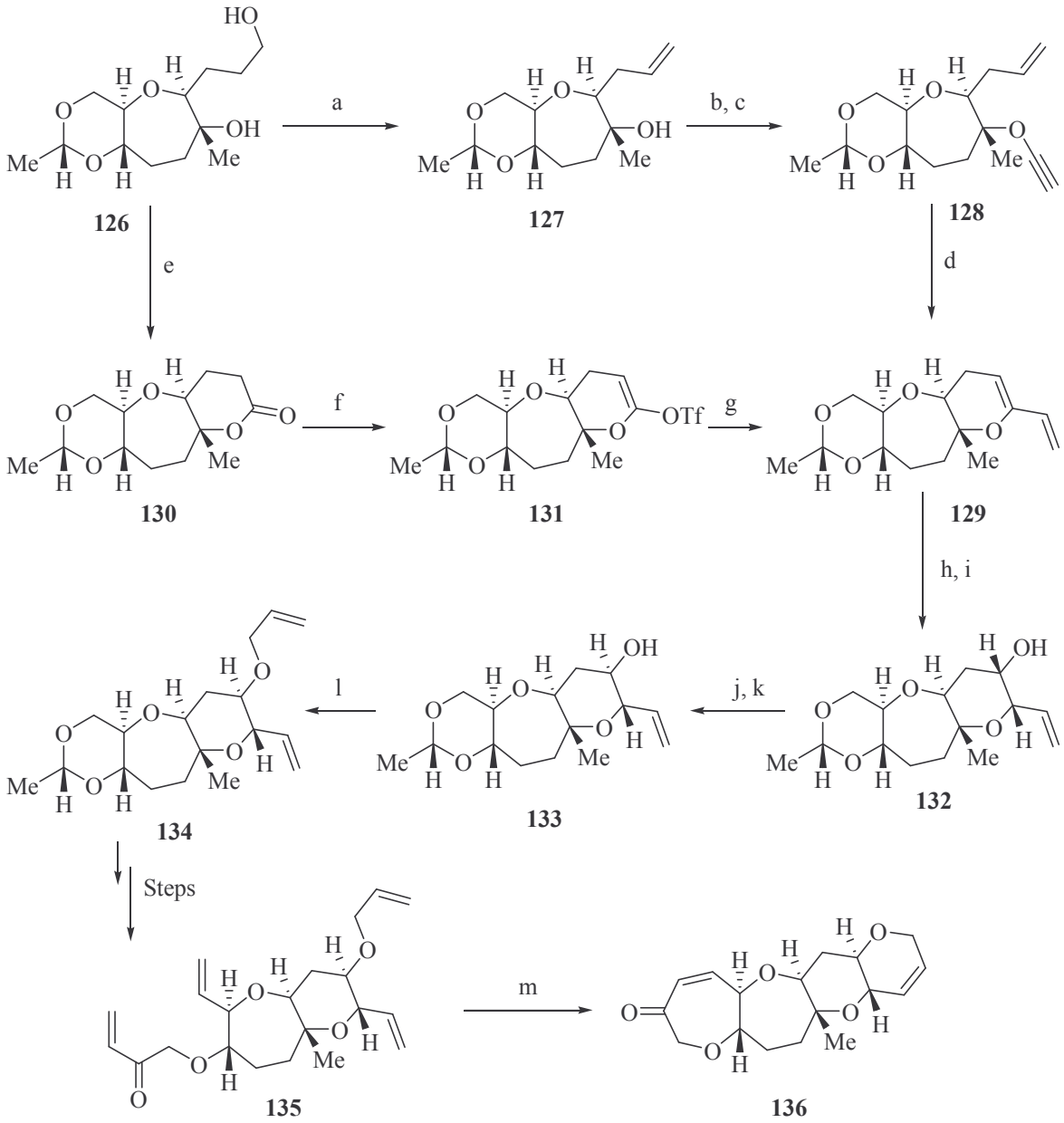
Reagents and conditions: (a) $NaIO_4$, $NaHCO_3$, CH_2Cl_2, H_2O, rt (85%); (b) PH_3PCH_2, THF, rt (91%); (c) NaH, TBAI, $ClCH_2COCH_2PPh_3$, THF, reflux (90%); (d) CH_2O, H_2O, pH 7 buffer (97%); (e) catalyst **C** (3 mol%), CH_2Cl_2, reflux (94%); (f) Me_2NNH_2, benzene, reflux (100%); (g) *t*-BuLi, $BnO(CH_2)_3I$, THF, −78 °C; (h) $CuCl_2$, THF_{aq}, (45% over 2 steps, **124/125** = 1:1); (i) DBU, benzene, rt (85%); (j) MeMgBr, THF, −78 °C (93%); (k) H_2, $Pd(OH)_2$, MeOH (99%).

Scheme 27: Synthesis of the C-ring of hemibrevetoxin B by enone RCM.

Introduction of the alkene was then achieved using selenium chemistry and alkynyl ether was synthesised from tertiary alcohol **127** using a modification of Greene's protocol (**Scheme 28**). The RCEM precursor **128** was cyclised with Grubbs second generation catalyst under an atmosphere of ethene to give triene **129** in 66% yield. In this particular case, the alkynyl ether **128** can undergo thermal retro-ene reaction resulting in fragmentation to give a cyclic allylic ether and ketene.[30] To avoid variable yields, an alternative route was successfully explored. The diol **126** was oxidised to give lactone **130**, which was converted into enol triflate **131**. Stille coupling between vinyl stannane and enol triflate **131** then delivered the same diene **129** than the RCEM product. Selective

[30] (a) A. Moyano, M. A. Pericas, F. Serratosa, E. Valenti, *J. Org. Chem.* **1987**, *52*, 5532; (b) R. M. Moslin, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 15106.

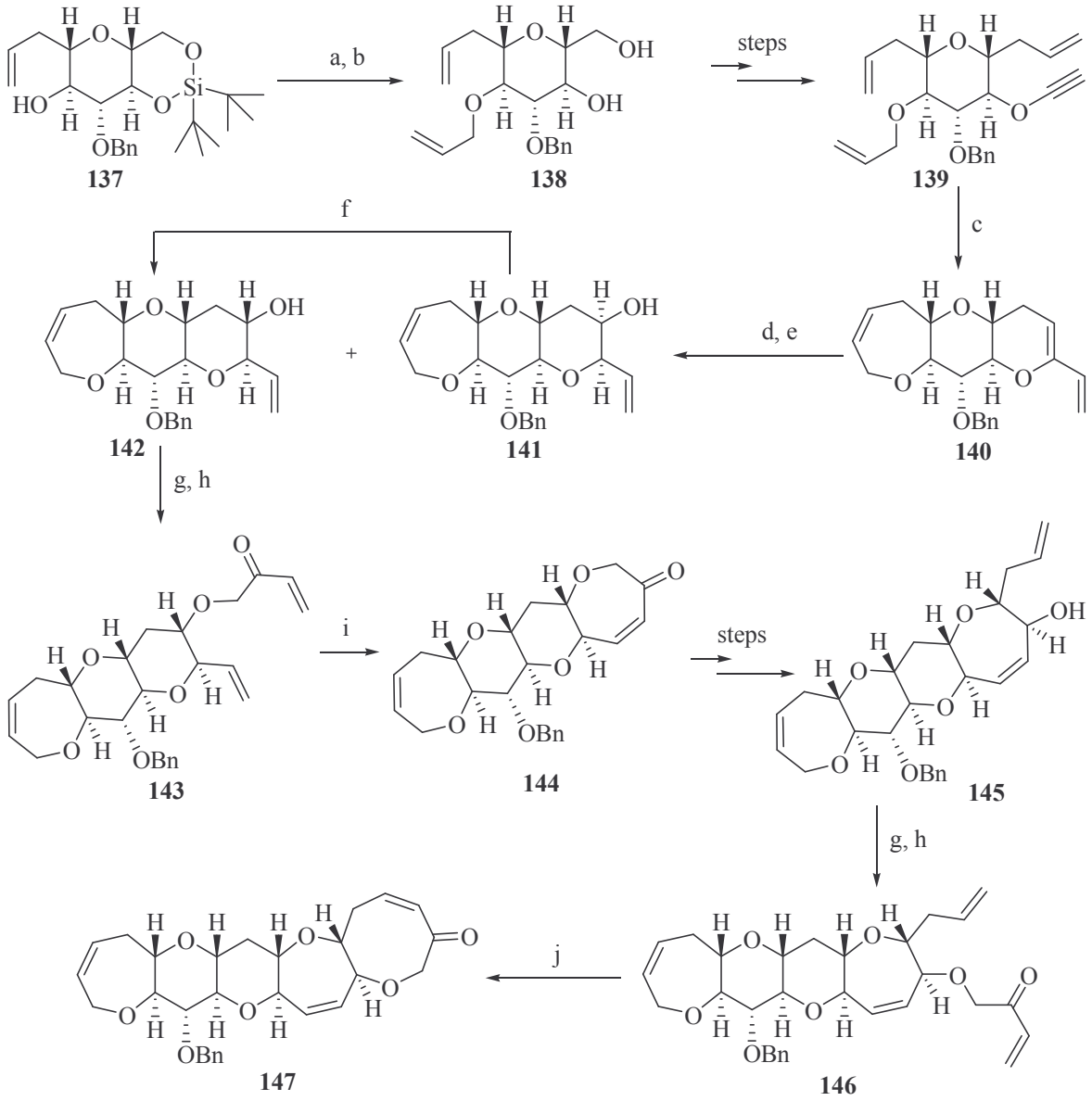
epoxidation with DMDO followed by ring opening with Super-Hydride® then yielded the alcohol **132**. At this step, it was necessary to correct the configuration at hydroxyl-bearing centre by a two-step oxidation and reduction sequence. Etherification and functionalisation of the acetal ring finally gave the tetraene **135**.



Reagents and conditions: (a) (i) *p*-$(O_2N)C_6H_4SeCN$, *n*-Bu_3P, THF, rt (ii) H_2O_2 (85%); (b) KH, Cl_2CCHCl, THF (98%); (c) *n*-BuLi, ether, –40 °C; (d) catalyst **C**, ethene, toluene, 70 °C (66% over 2 steps); (e) TEMPO, NaOCl, KBr, $NaHCO_3$, H_2O, CH_2Cl_2 (86%); (f) KHMDS, $PhNTf_2$, THF, DMPU, −78 °C (100%); (g) $CH_2CHSnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux (87% over 2 steps); (h) DMDO, CH_2Cl_2, 0 °C; (i) $LiHBEt_3$, THF, 0 °C; (j) Dess-Martin periodinane, CH_2Cl_2, rt; (k) $NaBH_4$, CH_2Cl_2, MeOH (68% over 4 steps); (l) NaH, TBAI, allylbromide, DMF, rt (80%); (m) catalyst **C** (10 mol%), CH_2Cl_2, reflux (73%).

Scheme 28: Synthesis of the core of hemibrevetoxin B by RCEM and double RCM reactions.

The key two-directional double RCM reaction was performed with Grubbs second generation catalyst to furnish the core of hemibrevetoxin B in high yield. Thanks to efficient RCM, RCEM and two-directional double RCM reactions, the core of hemibrevetoxin B was prepared in limited number of steps. Clark group also applied the metathesis strategy to the synthesis of A−E fragment of ciguatoxin CTX3C.[29b] The synthesis started from functionalised compound **137**, which was obtained from the commercially available tri-*O*-acetyl-D-glucal (**Scheme 29**). Etherification and subsequent deprotection of silylene group afforded diol **138**. Selective functionalisation of both alcohols delivered the RCM precursor **139**. Cyclisation with the Grubbs second generation catalyst under an ethene atmosphere by simultaneous diene and enyne RCM reactions provided the tricycle **140** in moderate yield (58%). Optimization of the reaction failed to give a better yield. The sequential process in which the RCEM reaction was performed prior to the diene RCM reaction did not improve the overall yield because it required more steps. However, in gram quantities, the sequential process was easier to perform. Selective epoxidation of enol ether **140** and subsequent reductive opening of epoxide gave a mixture of stereoisomers at the hydroxyl-bearing centre, which can be epimerized in good yield. Etherification and Wittig methylenation furnished the enone **143**, which was cyclised with the ruthenium catalyst to deliver the ABCD system **144** in 70% yield. Introduction of the side chain was achieved using the hydrazone chemistry described previously for the synthesis of hemibrevetoxin B. Functionalisation of secondary alcohol **145** by etherification and Wittig methylenation gave diene **146**. Finally, enone RCM reaction was applied and the pentacyclic enone **147** was synthesised in 50% yield. In summary, polyether compounds can be synthesised in a highly effective manner using the metathesis methodology developed in our laboratory.



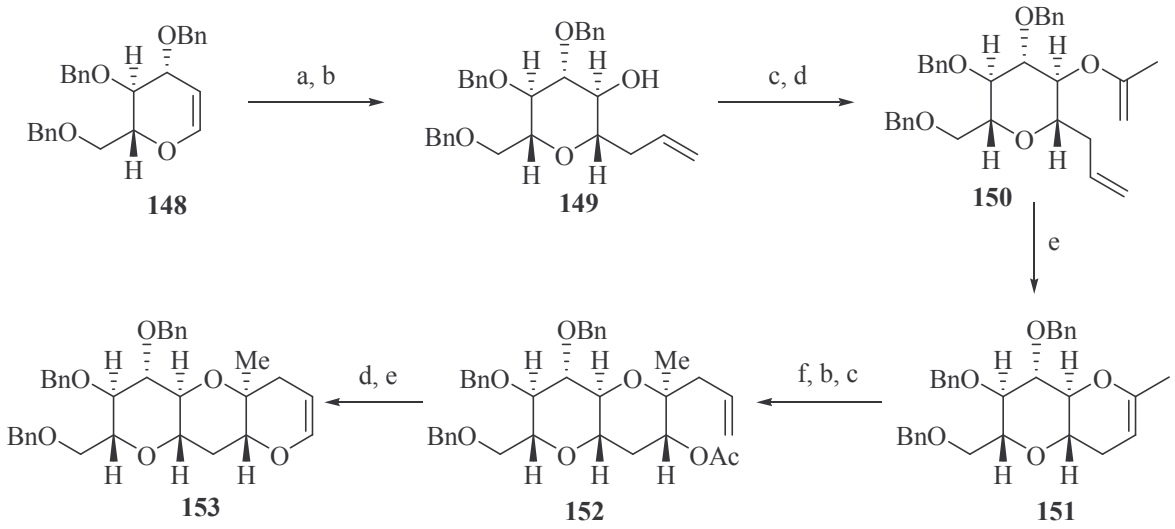
Reagents and conditions: (a) NaH, TBAI, 18-*c*-6, allylbromide, THF, rt (96%); (b) $(HF)_3{\cdot}Et_3N$, THF, rt (95%); (c) catalyst **C** (10 mol%), ethene, toluene, 70 °C (58%); (d) DMDO, CH_2Cl_2, 0 °C; (e) $BF_3{\bullet}OEt_2$, Et_3SiH, MeCN, −40 °C (71% over 2 steps, **141**/**142** = 1:1); (f) (i) Dess-Martin periodinane, CH_2Cl_2, rt (ii) $NaBH_4$, THF, −78 °C (88% over 2 steps); (g) NaH, TBAI, $ClCH_2COCH_2PPh_3$, THF, reflux; (h) CH_2O, H_2O, ether, rt (56% over 2 steps for **143**; 55% over 2 steps for **146**); (i) catalyst **C** (5 mol%), CH_2Cl_2, reflux (70%); (j) catalyst **C** (10 mol%), CH_2Cl_2, reflux (50%).

Scheme 29: Synthesis of the A−E fragment of ciguatoxin CTX3C by metathesis reactions.

1.5.2. Rainier's strategy

The Rainier group significantly contributed to the development of effective metathesis tools for the synthesis of fused polyether compounds. The approach of Rainier and co-workers consisted of enol ether epoxidation followed by addition of organometallic reagent

to introduce both hydroxyl group and side chain (**Scheme 30**).[31] Esterification of the alcohol and subsequent methylenation of the ester furnished the acyclic enol ether **150**. During his early work, Rainier used Schrock catalyst to effect the cyclisation reaction and he later demonstrated that the use of the Grubbs second generation catalyst was equally efficient for the RCM reaction of acyclic enol ethers.[31b] The same process can be applied again leading to an iterative approach. However, the use of DMDO for the epoxidation of enol ether **151** failed to give the desired diastereoisomer. Consequently, the author successfully used bromohydrins as epoxide precursors.



Reagents and conditions: (a) DMDO, CH_2Cl_2, 0 °C; (b) CH_2CHCH_2MgCl, THF, rt (82% over 2 steps for **149**); (c) Ac_2O, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 0 °C (37% over 3 steps for **152**); (d) $TiCl_4$, Zn, $PbCl_2$, CH_2Br_2, TMEDA, THF, 0 °C (62% over 2 steps for **150**); (e) catalyst **A**, hexane, 60 °C (76% for **151**; 46% over 2 steps for **153**); (f) (i) NBS, H_2O, DMF, −50 °C (ii) KH, 18-*c*-6, THF.

Scheme 30: Rainier's iterative strategy.

Later, Rainier studied nucleophilic epoxide opening using a variety of organometallic reagents.[32] Allylmagnesium chloride and propynylmagnesium bromide (**Entry 2,3 and 4**) gave the desired compounds in excellent yields as single diastereoisomers (**Scheme 31**).

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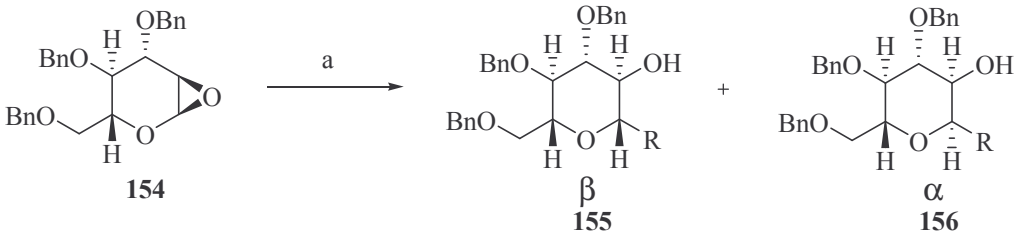
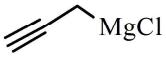
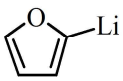
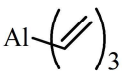
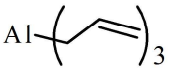
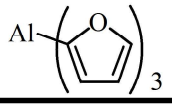
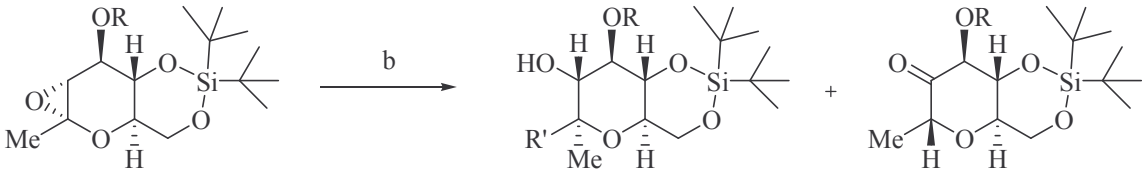
[31] (a) J. D. Rainier, S. P. Allwein, *J. Org. Chem.* **1998**, *63*, 5310; (b) J. D. Rainier, J. M. Cox, S. P. Allwein, *Tetrahedron Lett.* **2001**, *42*, 179.

[32] (a) J. D. Rainier, J. M. Cox, *Org. Lett.* **2000**, *2*, 2707; (b) S. P. Allwein, J. M. Cox, B. E. Howard, H. W. B. Johnson, J. D. Rainier, *Tetrahedron* **2002**, *58*, 199; (c) U. Majumder, J. M. Cox, J. D. Rainier, *Org. Lett.* **2003**, *5*, 913.

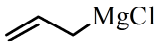
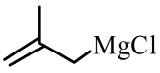
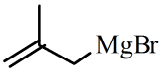
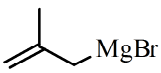


154 **β 155** **α 156**

Entry	Nucleophile	Temperature	ß/a	Yield
1	Me_2CuLi	0 °C	1:0	82%
2		0 °C	1:0	82%
3		0 °C	1:0	78%
4	$(MeO)_2CH(CH_2)_2MgBr$	0 °C	1:1	51%
5	$((MeO)_2CH(CH_2)_2)_2CuMgBr$	- 30 °C	6:1	74%
6	PhMgCl	- 60 °C	1:1	78%
7	Ph_2CuLi	0 °C	1:0	84%
8	 $ZnCl_2$	- 60 °C to rt	1:0	78%
9	$AlMe_3$	- 65 °C to rt	0:1	82%
10		- 65 °C to rt	0:1	76%
11		0 °C	2.3:1	73%
12	$AlPh_3$	- 65 °C to rt	0:1	79%
13		- 65 °C to rt	0:1	85%



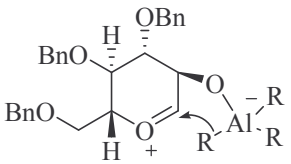
157 **158** **159**

Entry	R	Nucleophile	ß/a	158/159	Yield
14	TBDPS		1:0	>95:5	90%
15	TBDPS			>5:95	50%
16	TBDPS		1:0	>95:5	90%
17	TBS		2:1		80%

Reagents and conditions: (a) nucleophile, THF, temperature; (b) nucleophile, THF.

Scheme 31: Epoxide opening with nucleophiles.[32]

The use of 2-methylpropenylmagnesium chloride (**Entry 15**) failed to deliver the desired compound and led to pinacol rearrangement product **159**. Astonishingly, 2-methylpropenylmagnesium bromide delivered the desired diastereoisomer in high yield (**Entry 16**), highlighting the important role played by counterion. An important observation was also made concerning the nature of the protection group on the secondary hydroxyl group. Replacing the TBDPS group with a TBS group radically dropped the β/α selectivity (**Entry 16** *versus* **17**). This result can hardly be explained by the steric factors since the hindrance of both groups is similar and is probably due to electronic factors. The nature of the metal also influence the reaction, whereas the Grignard acetal (**Entry 4**) gave the desired compound in poor yield as 1:1 mixture of diastereoisomers, the use of the corresponding cuprate (**Entry 5**) gave the product in good yield and with excellent diastereoselectivity. Comparable results were observed with pheylmagnesium chloride and lithium diphenyl cuprate (**Entry 6** *versus* **7**). Another class of nucleophile – organoaluminium reagents – was studied by Rainier. Using trimethyl trivinyl, triphenyl, triallyl and trifuryl aluminium reagents the desired compounds were obtained in good yields (**Entries 9−13**). This time, high α selectivity was obtained except in the case of the triallylaluminium reagent (**Entry 13**). The α selectivity can be explained by intramolecular delivery of the alkyl chain, which occurs at the same face than the epoxide (**Figure 4**).

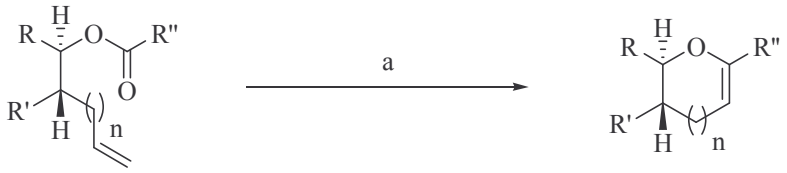


160

Figure 4: Possible explanation for the α selectivity of organoaluminium reagents.

By tuning the nature of the metal, both α and β selectivity are obtained in a highly diastereoselctive manner and introduction of a wide variety of side chains can be achieved

in excellent yield. Rainier was able to synthesise several polyether compounds using his methodology such as gambierol, fragments of gambieric acid A and hemibrevetoxin B.[33] Recently, Rainier used the ring closing metathesis using reduced titanium alkylidene reagent.[34] During the methylenation of ester with Takai protocol, some cyclised product was also isolated. Rainier discovered that the nature of titanium alkylidene reagent was a key factor. The titanium methylidene reagent gave mainly acyclic enol ether whereas titanium ethylidene reagent from dibromoethane gave only cyclic enol ether. A variety of esters **161** were synthesised and subjected to titanium ethylidene reagent (**Scheme 32**). Impressive results were obtained leading to cyclised compounds **162**. The reaction is tolerant to benzyl, acetal and silyl protecting groups and functionalised ester can be employed. Using this method, six-, seven- and eight-membered rings can be synthesised in good yields.



161 **162**

n	R	R'	R"	Yield
1	-CH(BnO)CH(BnO)CH(BnOCH$_2$)O-		Me	75%
1	Me	TBDPSO(CH$_2$)$_3$-	(MeO)$_2$CH(CH$_2$)$_3$-	70%
2	H	2,2-Dimethyl-[1,3]dioxolane	Me	78%
3	H	2,2-Dimethyl-[1,3]dioxolane	Me	82%

Reagents and conditions: (a) $TiCl_4$, Zn, $PbCl_2$, $CH_3CH_2Br_2$, TMEDA, THF, 65 °C.

Scheme 32: Rainier olefinic ester cyclisations.[34b]

They also studied the possibility of using a reduced titanium alkylidiene as the reagent for ring closing diene metathesis. Successful reactions were obtained with unstrained dienes

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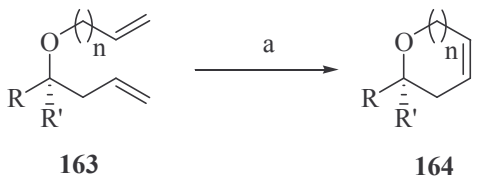
[33] (a) H. W. B. Johnson, U. Majumder, J. D. Rainier, *J. Am. Chem. Soc.* **2005**, *127*, 848; (b) S. W. Roberts, J. D. Rainier, *Org. Lett.* **2007**, *9*, 2227; (c) J. D. Rainier, S. P. Allwein, J. M. Cox, *Org. Lett.* **2000**, *2*, 231; (d) J. D. Rainier, S. P. Allwein, J. M. Cox, *J. Org. Chem.* **2001**, *66*, 1380.

[34] (a) U. Majumder, J. D. Rainier, *Tetrahedron Lett.* **2005**, *46*, 7209; (b) K. Iyer, J. D. Rainier, *J. Am. Chem. Soc.* **2007**, *129*, 12604.

even at room temperature (**Scheme 33**). A dihydropyran, oxepene and oxocene were synthesised in good yield. These impressive examples highlight the first use of a reduced titanium alkylidene for RCM reaction of unstrained dienes. Further investigations are under progress to study the scope of this reaction.



163 **164**

n	R	R'	Temperature	Yield
1	$-(CH_2)_6-$		65 °C or rt	100%
1	$PhCH_2CH_2$	H	rt	81%
2	$PhCH_2CH_2$	H	65 °C	72%
3	$PhCH_2CH_2$	H	65 °C	60%

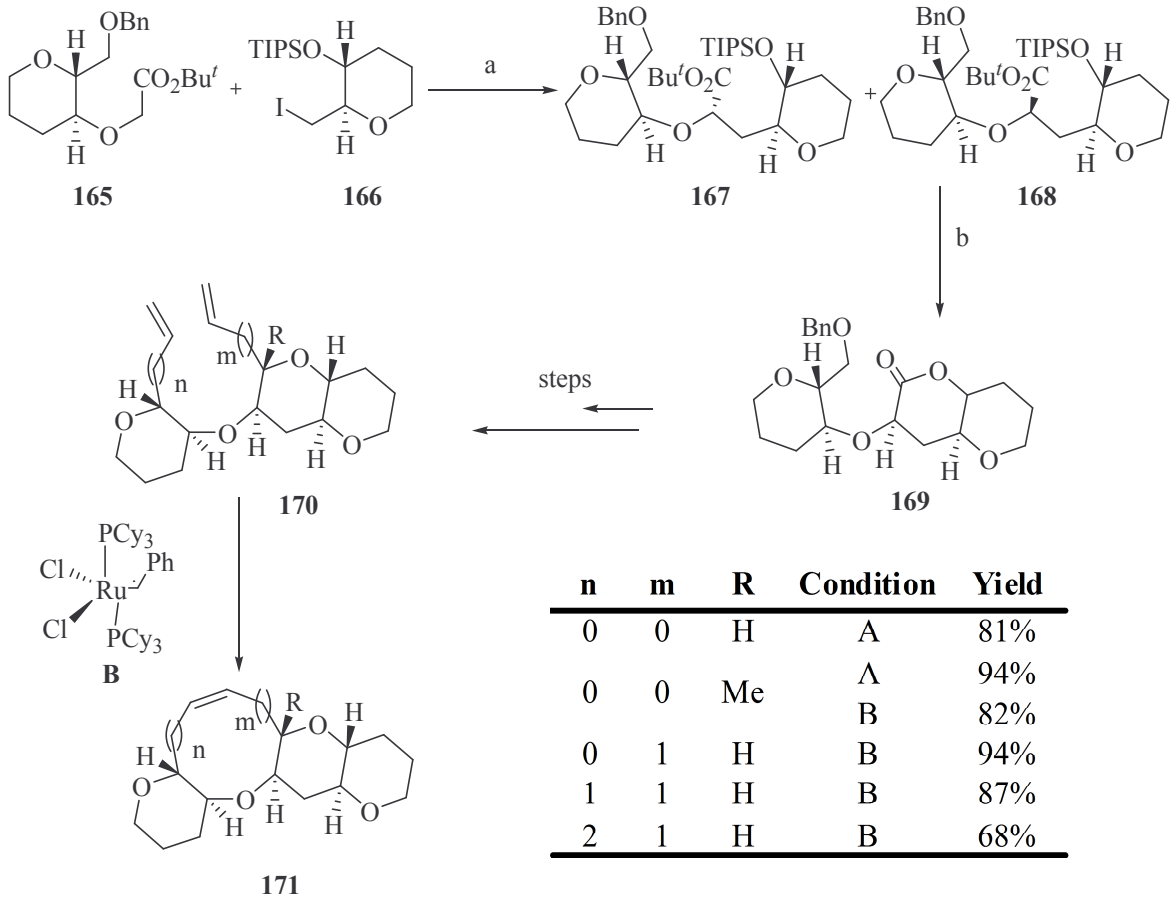
Reagents and conditions: (a) $TiCl_4$, Zn, $PbCl_2$, $CH_3CH_2Br_2$, TMEDA, THF, temperature.
Scheme 33: Reduced titanium-mediated diene RCM.[34b]

1.5.3. Hirama's Strategy

Hirama and collaborators studied the coupling of two polyether fragments by alkylation and subsequent RCM (**Scheme 34**).[35] This convergent approach reduced the number of steps compared to a linear synthesis. A range of RCM precursors **170** were synthesised to study the cyclisation of seven-, eight-, nine- and ten-membered rings. Alkylation of the ester **165** furnished the desired coupled fragment as 3:1 mixture of diastereoisomers. Deprotection of the alcohol in ether **168** and subsequent lactonisation gave the lactone **169**. After additional steps, several precursors were synthesised and were submitted to RCM reaction with the Grubbs first generation catalyst. The reaction was successful for compounds generating the seven-membered rings (n = 1, m = 1) but the reaction required between five and seven days to reach completion. However, by changing the solvent to dichloromethane, the reaction occurred within two days. The same conditions were applied to the other substrates and eight-, nine- and ten-membered rings were efficiently

[35] T. Oishi, Y. Nagumo, M. Hirama, *Chemical Communications (Cambridge)* **1998**, 1041.

synthesised in good to excellent yield. Using this highly convergent methodology, Hirima was able to synthesise the natural product ciguatoxin CTX3C.[36]



n	m	R	Condition	Yield
0	0	H	A	81%
0	0	Me	A	94%
			B	82%
0	1	H	B	94%
1	1	H	B	87%
2	1	H	B	68%

Reagents and conditions: (a) LDA, HMPA, THF, −78 °C→ 0 °C (61%, **168**/**167** = 3:1); (b) TBAF, THF, *p*-TsOH, toluene, 90 °C (84%); **condition A** : catalyst **B**, benzene (0.04 M), 50−60 °C, 5−7 days; **condition B** : catalyst **B**, CH_2Cl_2 (0.004 M−0.04 M), 35°C, 1−2 days.

Scheme 34: Hirima's convergent synthesis of tetracyclic polyethers using RCM reaction.[35]

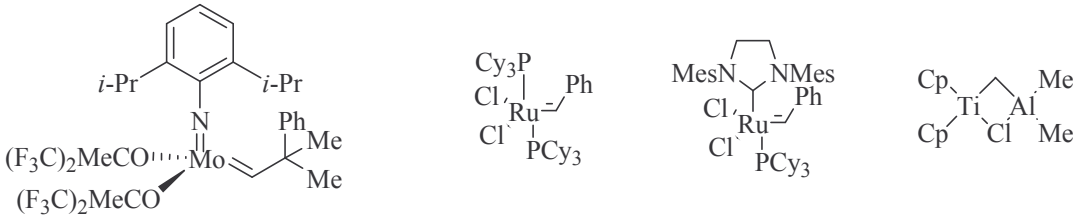
1.5.4. Ring closing metathesis reaction (RCM)

1.5.4.1. A short story of RCM reaction

The RCM reaction is one of the most powerful reactions available for the construction of carbon-carbon bonds. However, before having such an impact on total synthesis, the RCM reaction underwent a long period of development. The first example of the reaction appears in a patent filed by Eleuterio in 1960. In this case, molybdenum oxide on alumina

[36] M. Hirama, T. Oishi, H. Uehara, M. Inoue, M. Maruyama, H. Oguri, M. Satake, *Science* **2001**, *294*, 1904.

combined with lithium aluminium hydride was used as the catalyst.[37] At this time, the mechanism of the reaction was a total mystery. Many studies were performed to elucidate the mechanism, but it was only in 1964 that initial mechanistic findings were published. Indeed, E. O. Fisher and Maasböel isolated the first metal carbene in 1964 but it was not until 1971 that Chauvin proposed the currently accepted reaction mechanism.[38,39] With the advent of a rational mechanism, it was possible to design new catalysts without the requirement for the addition of a Lewis acidic co-catalyst. In 1978, Tebbe synthesised the titanium complex **D** which is efficient at catalysing alkene metathesis but does not tolerate certain important functional groups such as ketone, aldehyde, ester and hydroxyl groups (**Figure 5**).[40]



A **B** **C** **D**

Figure 5: Major catalysts for alkene metathesis.

Twelve years later, Schrock synthesised the highly efficient molybdenum catalyst **A** which is compatible with some functional groups (**Figure 5**).[41] Grubbs worked on the synthesis of a catalyst based on a less oxophilic metal than molybdenum. In 1988, he found that $RuCl_3$ can polymerise olefins in water.[42] A few years later, after systematically studying many

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[37] H. S. Eleuterio, (E. I. Du Pont de Nemours & Co.). DE 1072811, **1960**.
[38] E. O. Fischer, A. Maasboel, *Angew. Chem.* **1964**, *76*, 645.
[39] J. L. Herisson, Y. Chauvin, *Makromol. Chem.* **1971**, *141*, 161.
[40] F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611.
[41] (a) G. C. Bazan, E. Khosravi, R. R. Schrock, W. J. Feast, V. C. Gibson, M. B. O'Regan, J. K. Thomas, W. M. Davis, *J. Am. Chem. Soc.* **1990**, *112*, 8378; (b) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.* **1990**, *112*, 3875.
[42] B. M. Novak, R. H. Grubbs, *J. Am. Chem. Soc.* **1988**, *110*, 7542.

ligands,[43] he published a report concerning the potent ruthenium-based catalyst **B** which is now known as the Grubbs first generation catalyst (**Figure 5**).[44] The catalyst is tolerant of the nearly all major functional groups and can be stored under air at room temperature. Nevertheless, the catalyst **B** is not active enough to catalyse every conceivable RCM or cross-metathesis reaction. Further studies were carried out to replace one of the phosphine ligands with better σ-donor ligand. Finally, Grubbs introduced the catalyst **C,** known as the Grubbs second generation catalyst, bearing a new imidazoline-type ligand (**Figure 5**).[45] Nowadays, RCM, ring opening metathesis polymerisation (ROMP) and cross-metathesis are useful tools thanks to these highly reactive and tolerant catalysts.

1.5.4.2. Mechanism

The mechanism of the RCM consists of an initiation sequence to generate the active carbene complex **178**, which then enters the true catalytic cycle (**Scheme 35**). Both the initiation and the catalytic cycle are based on [2+2] cycloaddition and [2+2] retroaddition sequences. A [2+2] cycloaddition between alkene **172** and carbene catalyst **173** generates the metallocyclobutane intermediate **174**, which can then undergo retroaddition either towards products **176**, with the generation of ethane, or back to the starting material **172**. The intermediate **176** then undergoes the same sequence of reactions to afford the desired compound **179** and reform the carbene catalyst **178** which re-enters the catalytic cycle. In principle, all of the steps in the sequence are reversible. However, the driving force for RCM is the removal of ethene from the reaction mixture, which drives the reaction through the desired product **179**.

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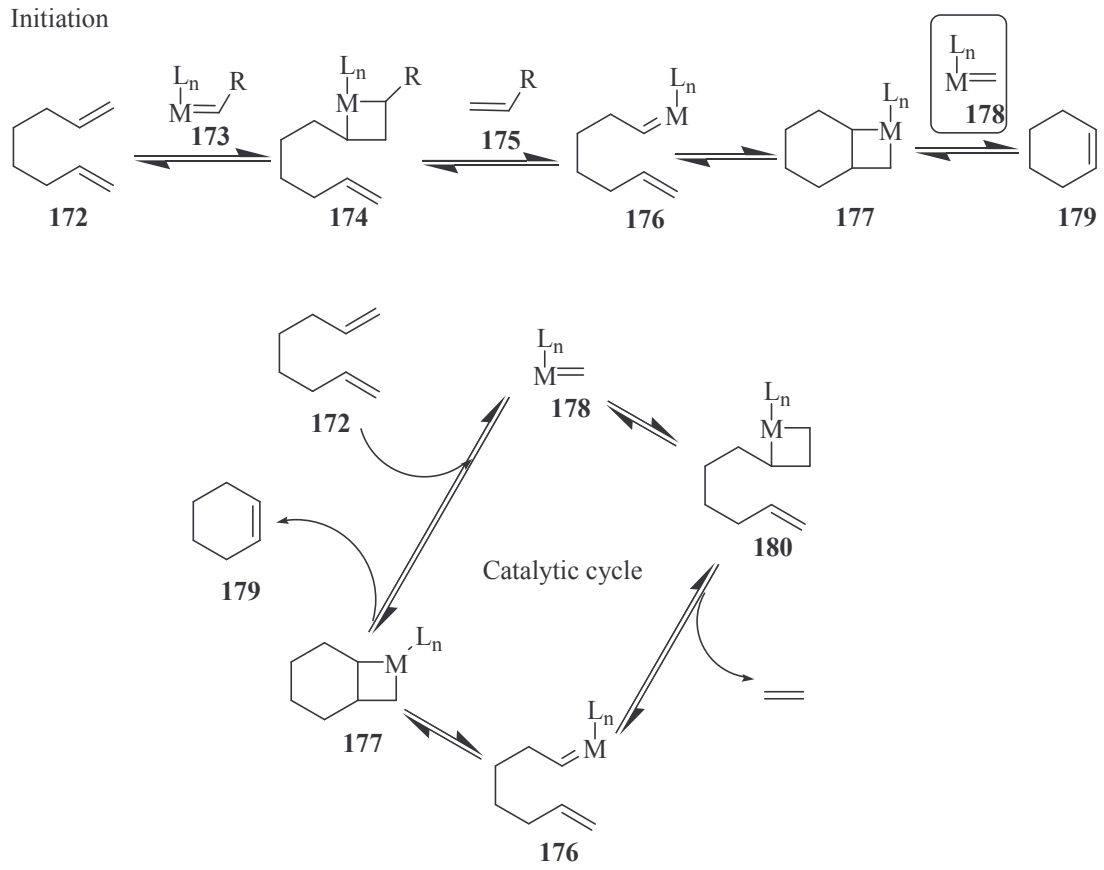
[43] (a) M. R. Gagne, R. H. Grubbs, J. Feldman, J. W. Ziller, *Organometallics* **1992**, *11*, 3933; (b) S. T. Nguyen, L. K. Johnson, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1992**, *114*, 3974; (d) S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1993**, *115*, 9858; (e) Z. Wu, S. T. Nguyen, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1995**, *117*, 5503.
[44] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.
[45] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.



Scheme 35: Ring closing metathesis mechanism.

In spite of the rather simple general mechanism, the course of events needs to be clarified. Many groups, and in particular the Grubbs group, intensively studied the metathesis mechanism with "ultimate goal of facilitating the rational design of new catalysts".[46] The mode of activation of ruthenium based catalyst was studied more precisely. Two pathways are possible for the activation of the ruthenium catalysts: the associative and dissociative pathways (**Scheme 36**). The associative pathway (**eqn 1**) consists of association of the olefin to the metal centre forming an 18-electron intermediate **182**. The loss of a phosphine ligand then gave the active 16-electron intermediate **183**. The dissociative pathway (**eqn 2**) requires initial loss of a phosphine ligand to form an 14-electron intermediate **184**. Alkene association finally gives the same 16-electron intermediate **183**. In order to prove which pathway controls the RCM reaction, Grubbs and co-workers performed intensive NMR,

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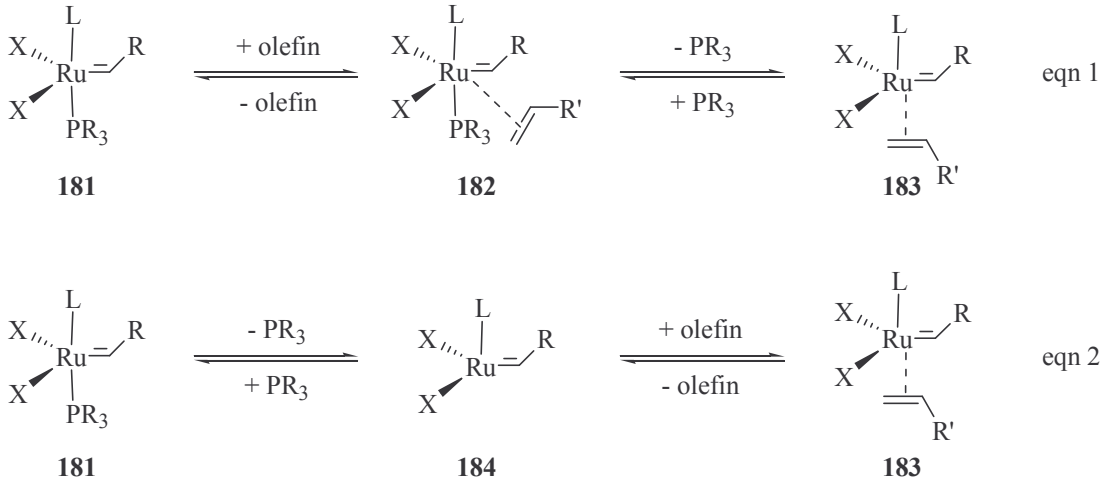
[46] (a) E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887; (b) M. Ulman, R. H. Grubbs, *Organometallics* **1998**, *17*, 2484; (c) M. S. Sanford, J. A. Love, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 6543.

theoretical studies and kinetic experiments. Grubbs concluded that the dissociative pathway should be the preferred mode of activation. Indeed, the reaction is independent of the concentration of the olefin. In addition, another group was able to detect a 14-electron intermediate for a ruthenium-based catalyst.[47] Consequently, the presence of ligands assisting the loss of the phosphine ligand, will result in an increase in the reactivity of the catalyst.



Scheme 36: Associative *versus* dissociative pathways

The high activity of the Grubbs second generation catalyst was originally attributed to the high lability of the phosphine ligand as a consequence of the strong σ-donor NHC ligand. However, Grubbs and co-workers discovered that the opposite effect was observed during their studies. The presence of the NHC ligand disfavoured the loss of the phosphine ligand. Nevertheless, when the phosphine ligand dissociates from the metal, the 14-electron intermediate **184** is stabilized by the NHC ligand. In addition, studies showed that competitive rebinding of ligand phosphine and association of the olefin favours association of the olefin resulting in a higher turnover of the catalyst. Other mechanistic problems such as the relative position of the olefin compared to other ligands and the existence of a

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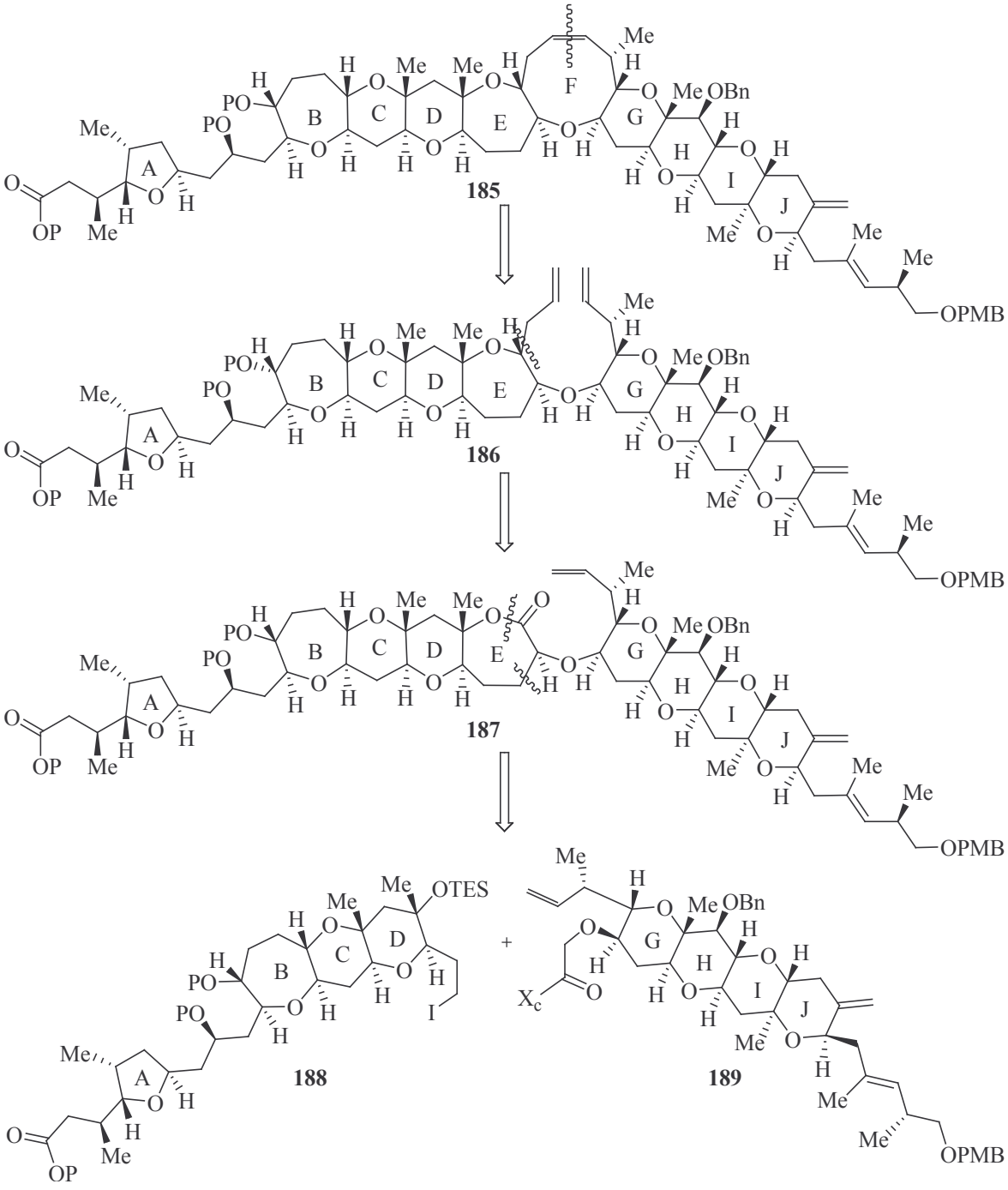
[47] J. N. Coalter, J. C. Bollinger, O. Eisenstein, K. G. Caulton, *New J. Chem.* **2000**, *24*, 925; (b) M. S. Sanford, L. M. Henling, M. W. Day, R. H. Grubbs, *Angew. Chem., Int. Ed.* **2000**, *39*, 3451.

metallacyclobutane as transition state or intermediate require further investigation. In spite of theses difficulties, Grubbs described the effect of each ligand on the activity of his ruthenium catalysts:

- Phosphine ligand: PCy_3 is better than PPh_3 because of the basicity of PCy_3 but steric interactions play an important role.
- NHC ligand: disfavours the labilisation of the phosphine ligand but stabilises the 14-electron intermediate.
- Halogen: Chloride is the best. Iodide favours the dissociation of the phosphine but steric factors decrease the RCM activity.

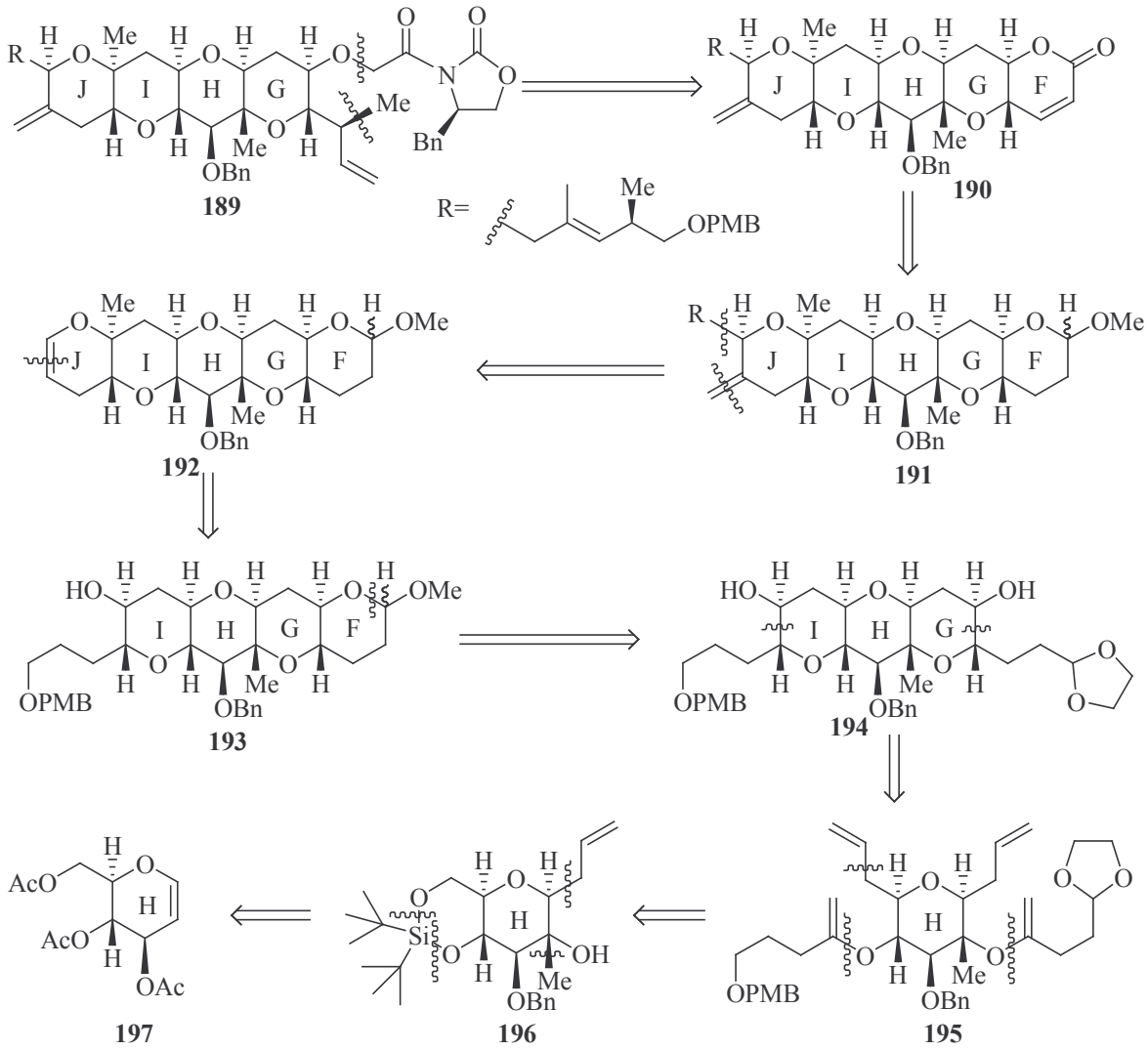
1.6. Retrosynthesis of F-J ring fragment of the gambieric acid A

The retrosynthesis of gambieric acid A was designed around the two-directional RCM strategy developed in our laboratory. Initial disconnection through the F ring of fully protected gambieric acid A gives *bis* allyl compound **186** (**Scheme 37**).



Scheme 37: Retrosynthetic approach.

Disconnection of the left-hand allyl chain reveals lactone **187**. Retro-lactonisation/alkylation delivers both fragment **188** and **189**, which are of approximately equal in size and complexity. Then, removal of the Evans chiral auxiliary and methyl group gives the α,β-unsaturated lactone **190**, which can be further disconnected to acetal **191** (**Scheme 38**).



Scheme 38: Retrosynthesis of F–J fragment.

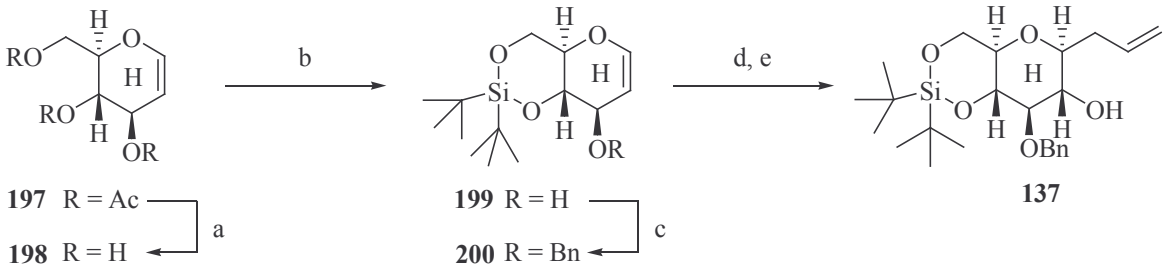
Retrosynthetic cleavage of the side chain affords cyclic enol ether **192**. Disconnection through the J-ring gives alcohol **193**, which can be further cleaved to deliver diol **194**. Subsequent retro double hydroboration/RCM reveals *bis* enol ether **195**. Double removal of enol ether and allyl group furnishes the tertiary alcohol **196**. Finally, disconnection of the methyl and allyl groups leads to tri-*O*-acetyl-D-glucal as starting material.

The first aim of this work is the large scale synthesis of the I−J ring fragment using the strategy developed in the laboratory as well as the improvement of the existing synthesis. Secondly, efficient methodology needs to be developed in order to introduce the methyl group to the F ring. The synthesis must be as short as possible with high yields and must be enantioselective. Finally, the remaining task is the introduction of the side chain to the J ring. This part of the work needs to reach the sames objectives in terms of efficiency than the introduction of the methyl group.

2. Results and discussion

2.1. Synthesis of the I–F fragment

The synthesis of the I–J fragment was designed around the methodology developed in the group and more precisely around the double RCM reaction. The work presented in this paragraph was previously published and developed by Doctor Kimber. [48]The synthesis started from commercially available tri-*O*-acetyl-D-glucal, which was converted into a tetraene in subsequent steps.



Reagents and conditions: (a) NaOMe, MeOH, rt, overnight; (b) $(t\text{-Bu})_2Si(OTf)_2$, pyridine, DMF, –40 °C, 3 h; (c) NaH, BnBr, DMF/THF (3/1), 0 °C then rt, overnight, (86% over three steps); (d) DMDO, CH_2Cl_2, 0 °C, 1 h; (e) AllylMgCl, THF, 0 °C, 1 h (80% over 2 steps).

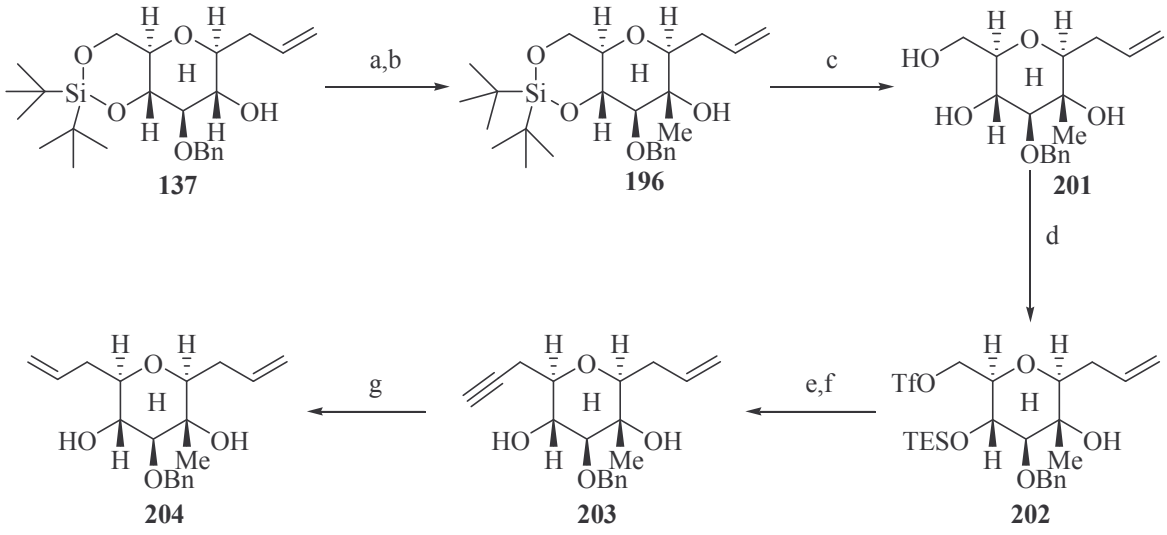
Scheme 39: Synthesis of compound **137**.

The tri-*O*-acetyl-D-glucal was first deprotected using a sub-stoichiometric amount of sodium methoxide in methanol to provide quantitatively D-glucal **198** (**Scheme 39**). The resulting triol, D-glucal **198**, was then protected with two different groups. Firstly, two of the hydroxyl groups were protected using a di-*tert*-butylsilylene group. The remaining secondary hydroxyl group of the alcohol **199** was then benzylated by treatment with sodium hydride and benzyl bromide to afford fully protected glucal **200** in 86% over three steps. Diastereoselective epoxidation of enol ether **200** with DMDO was followed by

[48] J. S. Clark, M. C. Kimber, J. Robertson, C. S. P. McErlean, C. Wilson, *Angew. Chem., Int. Ed.* **2005**, *44*, 6157.

subsequent regioselective opening with allylmagnesium chloride gave the alcohol **137** as the sole product.

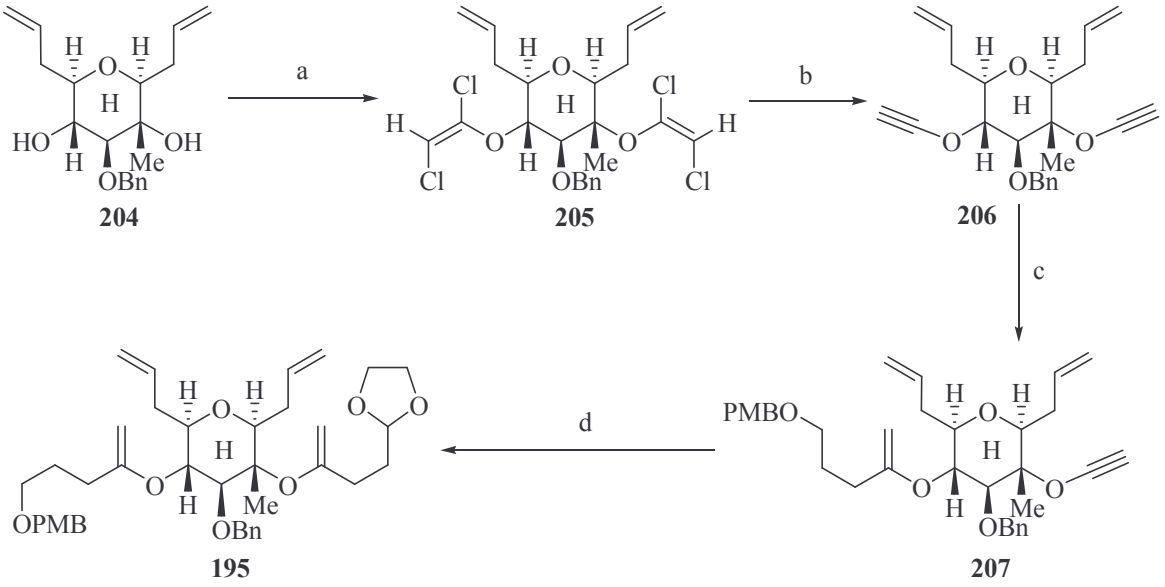
The gambieric acid possesses an angular methyl group in axial position between the G and H rings. This was introduced by oxidation of secondary alcohol **137** using Swern conditions followed by addition of methyl lithium under high dilution conditions, giving the tertiary alcohol **196** in good yield (**Scheme 40**). In addition to formation of the required diastereoisomer, 20% of the other diastereoisomer was also formed. The silyl protecting group in the compound **196** was smoothly removed by addition of $Et_3N{\cdot}(HF)_3$ to furnish the triol **201** in excellent yield (97%). Addition of triflic anhydride to the triol **201** followed by TESOTf resulted in selective triflation of the primary hydroxyl group and silyl protection of the hydroxyl group to afford the triflate **202**. Triflate displacement with lithium trimethylsilylacetylide afforded the TMS-protected acetylene and subsequent double deprotection of TES ether and TMS-protected acetylene using TBAF gave diol **203** in 77% over 3 steps. The acetylene **203** was then partially hydrogenated using Lindlar's catalyst in presence of quinoline to yield the diene **204**.



Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, –78 °C, 3.5 h (ii) Et_3N; (b) MeLi, toluene, –78 °C, 1 h (79% over two steps); (c) $(HF)_3{\cdot}Et_3N$, THF, 0 °C, overnight (97%); (d) (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min; (ii) TESOTf, CH_2Cl_2, –78 °C, 0.5 h; (e) *n*-BuLi, TMS-acetylene, DMPU, 0 °C, 1.5 h; (f) TBAF, 0 °C, 18 h (77% over 3 steps); (g) Lindlar's catalyst, quinoline, EtOAc, H_2, rt, 3 h (98%).

Scheme 40: Synthesis of diol **204**.

Introduction of *bis*-alkynyl ether functionality was achieved using a modified Greene's protocol (**Scheme 41**).[49] Normally, the reaction involves a one-step process and is performed in THF. However, we found that isolation of *bis*-dichloroenol ether **205** and changing the solvent to ether significantly improved the overall yield when the reaction was performed on a large scale. With a large quantity of **206** now available, the first enol ether **207** was introduced along with the side chain by cuprate addition to the less hindered of the two alkynyl ethers.[50] The regioselectivity of the addition reaction is remarkable; no addition to the tertiary alkynyl ether was observed. The tertiary alkynyl ether is substantially less reactive than the other alkynyl ether and so a more reactive cuprate was required to introduce the second side chain. As a result, copper cyanide and lithium chloride were used to achieve carbocupration and afford the tetraene **195** in good yield.

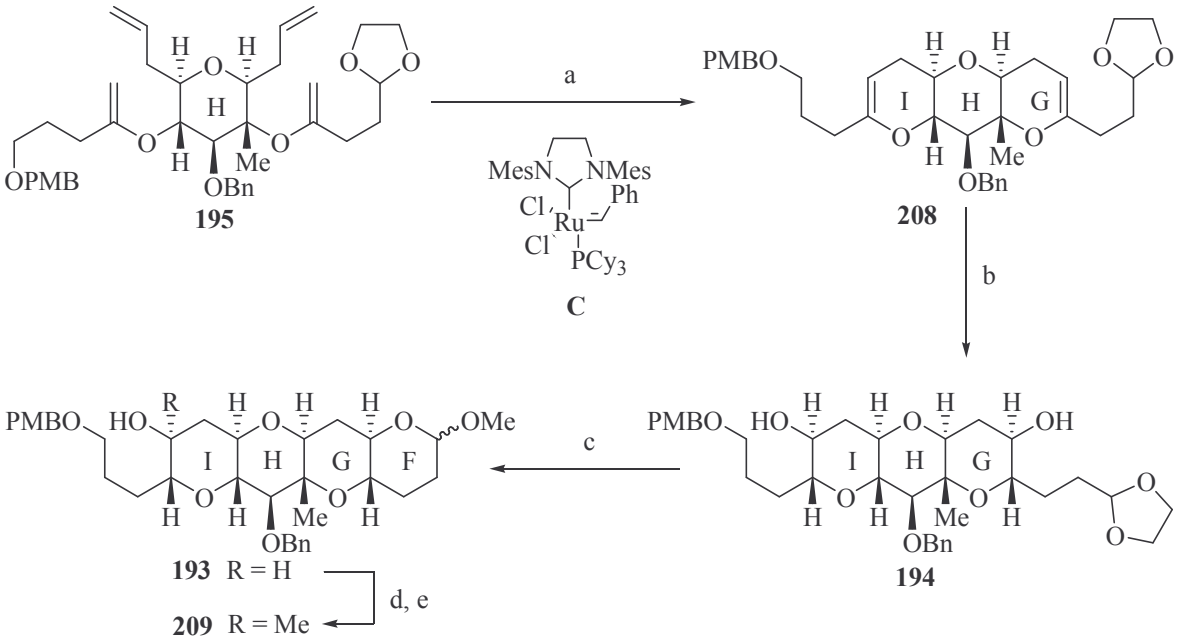


Reagents and conditions: (a) KH, Cl_2CCHCl, THF, 0 °C, 1.5 h, then rt, 1 h (78%); (b) *n*-BuLi, ether, –78 °C, 1 h, then –25 °C, 4 h (89%); (c) CuBr, LiBr, THF, $BrMg(CH_2)_3OPMB$, –95 °C, 1 h, then –78 °C, 2 h (84%); (d) CuCN, LiCl, THF, $BrMg(CH_2)_2CH(OCH_2CH_2O)$, –78 °C, 3 h (85%).

Scheme 41: Synthesis of *bis*-enolether **195**.

[49] A. Moyano, F. Charbonnier, A. E. Greene, *J. Org. Chem.* **1987**, *52*, 2919.
[50] S. E. Denmark, J. A. Dixon, *J. Org. Chem.* **1997**, *62*, 7086.

The key two directional RCM reaction was performed using the Grubbs second generation catalyst to provide the tricycle **208** in excellent yield (89%) (**Scheme 42**). Compared to the published work, the use of 3.6 mol% instead of 10 mol% was equally effective in performing the RCM reaction. Furthermore, addition of the catalyst to the reaction mixture at 70 °C improves the yield. The resulting *bis*-enol ether **208** was then hydroborated with thexyl borane to give diol **194** after oxidative workup.[51]



Reagents and conditions: (a) Catalyst **C**, toluene, 70 °C, overnight (86%); (b) (i) BH_3, 2,3-dimethylbut-2-ene, rt, 1 day; (ii) $NaBO_3$, H_2O, pH 7, rt, 18 h (70%); (c) *p*-TsOH., MeOH, rt, overnight (90%); (d) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; (e) MeMgI, toluene, –78 °C, 2 h (72% over 2 steps).

Scheme 42: Synthesis of alcohol **209**.

Regioselectivity and stereoselectivity during the hydroboration reaction are remarkable with the synthesis of only one diastereoisomer with little production of other isomers. Such a high level of stereoselection can be explained by steric interactions (**Figure 6**).[52] Indeed, the approach **E** of the thexyl borane to the enol generates two unfavourable interactions

[51] (a) J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 127; (b) A. P. Kozikowski, A. K. Ghosh, *J. Org. Chem.* **1985**, *50*, 3017.
[52] A. P. Kozikowski, A. K. Ghosh, *J. Org. Chem.* **1985**, *50*, 3017.

with the axial hydrogen 5 and the equatorial hydrogen 4, whereas the approach **F** generates only one critical steric interaction with axial hydrogen 4 and so is the preferred approach.

E **F**

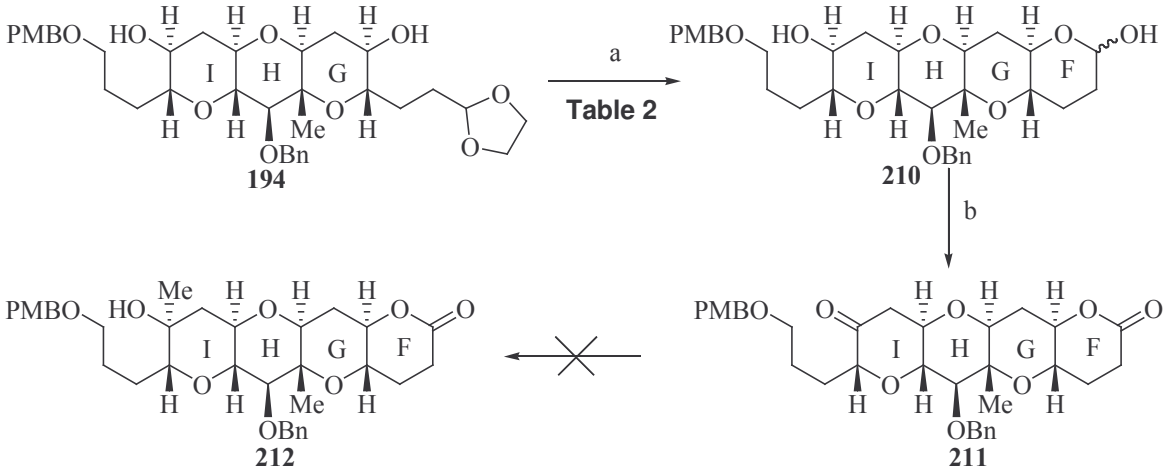
Figure 6: Approaches of thexyl borane to enol ether **208**.

Final construction of the I−F fragment then consisted of deprotection of the acetal **194** with sodium methoxide in methanol to produce an aldehyde, which cyclised *in situ* to afford new acetal **193**. Finally, the secondary hydroxyl goup was oxidised to give the corresponding ketone, which was converted into the tertiary alcohol **209** as single diastereoisomer in good yield.

In summary, large scale synthesis of the I−J ring fragment using our methodology proved to be robust to the scale up. Especially, improvement of the RCM conditions significantly contributed to the success.

2.2. Introduction of methyl group on the F ring

First, the possibility of reducing the initial synthesis by two steps was examined. Indeed, selective addition of a nucleophile to a ketone should be possible in presence of a lactone at low temperature and concentration to deliver the tertiary alcohol. This strategy avoids the deprotection of acetal **193** and allows the simultaneous oxidation of the secondary hydroxyl group and the lactol. Consequently, direct cyclisation of acetal **194** to lactol **210** was studied (**Scheme 43, Table 2**).



Reagents and conditions: (a) 1 M HCl, THF, Acetone, rt, 6 h (65%); (b) PCC, NaOAc, CH_2Cl_2, rt, 12 h (63%).

Scheme 43: Attempt of selective introduction of the ring junction methyl group.

The deprotection methods used were not satisfactory and seemed to be irreproducible (**Table 2**). The best results were obtained at low temperature otherwise there is an increased risk of dehydration of lactol **210** to form an enol ether, which is not stable under acidic conditions. Nevertheless, enough product was synthesised to explore the double oxidation reaction.

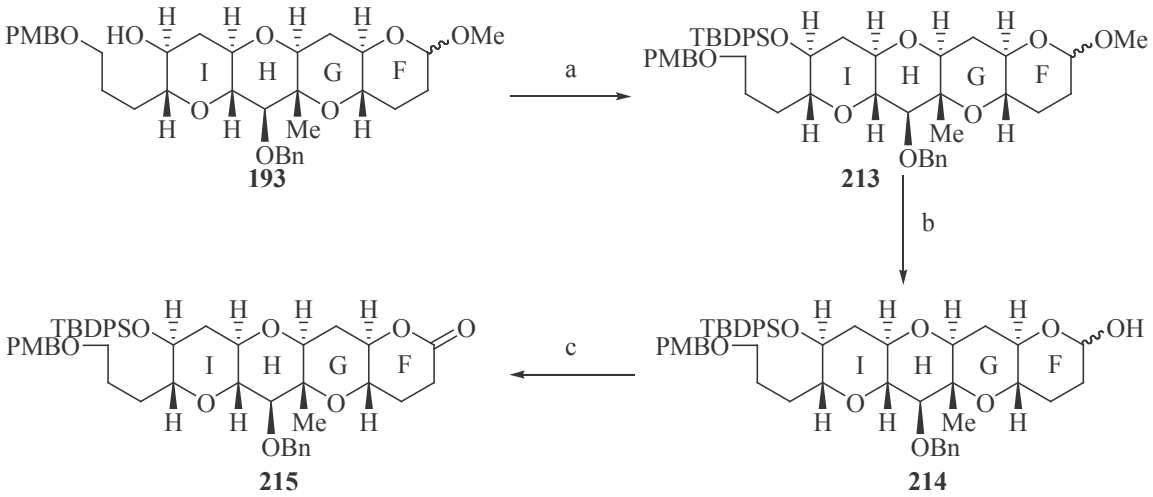
Entry	Conditions	Yield
1	*p*-TsOH/CH_3Cl/H_2O/rt/18 h	Traces
2	1 M HCl/CH_3Cl/rt/18 h	Traces
3	*p*-TsOH/toluene/H_2O/70°C/2 h (50 mg)	32%
4	*p*-TsOH/toluene/H_2O/70°C/2 h (186 mg)	decomposition
5	1 M HCl/THF/Acetone/rt/6 h (85.6 mg)	65%
6	1 M HCl/THF/Acetone/rt/18 h (220 mg)	32%

Table 2: Conditions for the cleavage of the acetal **194**.

The first reagent used in an attempt to oxidise both functionalities simultaneously was the Dess Martin periodinane, but the treatment of the lactol **210** with this reagent resulted in the recovery of unreacted starting material even when an excess of the oxidant was used.

Fortunately, the reaction occurred nicely when lactol **210** was treated with PCC and sodium acetate to give compound **211** in good yield.[53] However, despite attempts to add various nucleophiles such as methylmagnesium iodide or trimethylaluminium, the reaction delivered a mixture of starting material, mono and bis-Grignard addition products. As a result, we decided to return to the route described in **Scheme 42**.

The chemistry detailed below was designed to allow stereoselective introduction of the methyl group into the F-ring using an α,β-unsaturated lactone. Indeed, the rigidity of the structure should favour nucleophilic attack of a methyl cuprate in the *trans* position compared to the angular proton.[54] Thus, the secondary alcohol **193** was protected with a TBDPS group in good yield and acetal deprotection using acidic aqueous conditions then delivered the lactol **214** (**Scheme 44**). It should be noted that the TBDPS group was not removed in spite of the harsh conditions, such as reflux in 1 M HCl, used for acetal deprotection. Oxidation of lactol **214** with Fetizon's reagent then afforded lactone **215** in quantitative yield.[55] Since the decomposition of the lactone **215** on silica was observed, all the lactonic intermediates were used crude in the following steps.



Reagents and conditions: (a) TBDPSCl, imidazole, DMAP, DMF, rt, 18 h (98%); (b) THF/HCl (1M), reflux, 18 h (91%); (c) Ag_2CO_3 on Celite®, toluene, reflux, 3 h.

Scheme 44: Synthesis of lactone **215**.

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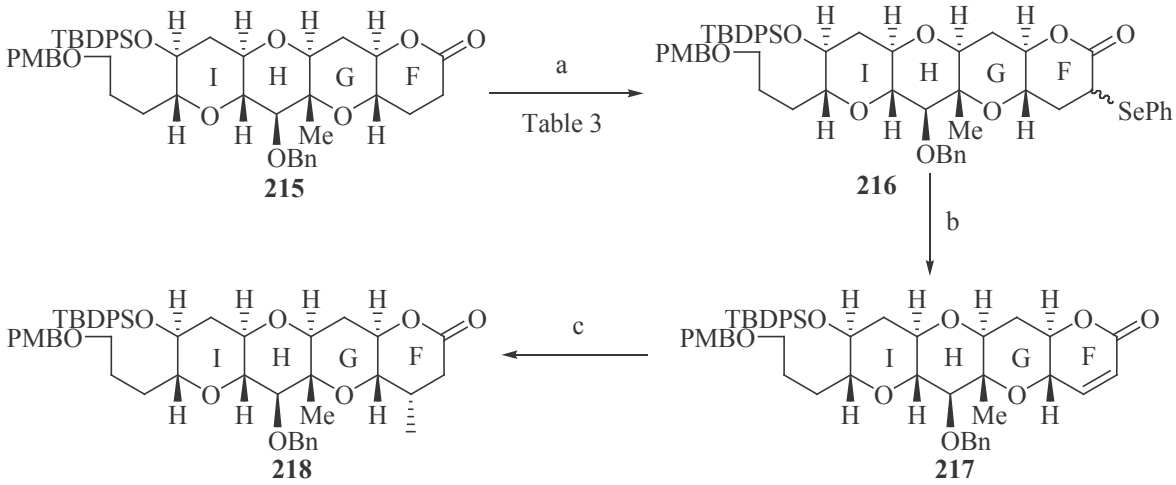
[53] Y. Shi, W. D. Wulff, *J. Org. Chem.* **1994**, *59*, 5122.
[54] D. Nicoll-Griffith, L. Weiler, *J. Chem. Soc., Chem. Commun.* **1984**, 659; (b) G. Matsuo, N. Hori, H. Matsukura, T. Nakata, *Tetrahedron Lett.* **2000**, 41, 7677.
[55] M. Fetizon, V. Balogh, M. Golfier, *J. Org. Chem.* **1971**, *36*, 1339.

The lactone **215** was converted into the α,β-unsaturated lactone **217** using a two-step strategy (**Scheme 45**). The phenyl selenide intermediate **216** was synthesised by quenching the enolate of the lactone **215** with phenylselenyl bromide (**Table 3**). Then, oxidation and selenoxide elimination afforded desired α,β-unsaturated lactone **217**.[56]



Reagents and conditions: (a) (i) TMSCl, NaHMDS, THF, –78 °C, 30 min (ii) PhSeBr, THF, –78 °C, 30 min; (b) (i) H_2O_2, $NaHCO_3$, EtOAc/THF, 0 °C, 15 min, (ii) rt, 15 min; (c) Me_2CuLi, ether, 0 °C, 15 min.

Scheme 45: Stereoselective carbocupration.

Before successful introduction of the unsaturation, a comprehensive study to identify the most appropriate base to deprotonate the lactone **215** was performed (**Table 3**). Surprisingly, the use of LDA (**Entry 1**) followed by addition of PhSeBr did not give satisfactory results. To confirm the inefficiency of LDA deprotonation, bromine was used as an electrophile (**Entry 2**). The use of *t*-BuLi (**Entry 3**) led to mixtures of product and starting material. However, the reaction was not satisfactory due to difficulties during purification and when forcing conditions were used in an attempt to consume all of the starting material, decomposition was observed (**Entry 4**). Reversible deprotonation using DBU was also attempted without success (**Entry 5**). The HMDS bases were then explored but deprotonation with LiHMDS delivered in poor yield the desired product (**Entry 7**). Addition of TMSCl to the reaction mixture significantly increased the yield (97% brsm)

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[56] (a) M. Chandrasekhar, K. L. Chandra, V. K. Singh, *J. Org. Chem.* **2003**, *68*, 4039; (b) K. Miyashita, M. Ikejiri, H. Kawasaki, S. Maemura, T. Imanishi, *J. Am. Chem. Soc.* **2003**, *125*, 8238.

and also reduced by-product formation (**Entry 8**). This observation can be explained by coordination of TMSCl to the lactone carbonyl group, which decreases the pKa of the α hydrogen of the lactone. *In situ* formation of silyl enol ether means that aggregation of enolate is avoided favouring the subsequent reaction with the electophilic selenium reagent. Delightfully, the combination of NaHMDS and TMSCl allowed the formation of phenyl selenide intermediate in quantitative yield (**Entry 8**).

Entry	Reagents	Yield
1	LDA/DMPU/PhSeBr	Traces
2	LDA/Br_2	Traces
3	*t*-BuLi/PhSeBr	55 % (70 % brsm)
4	*t*-BuLi (large excess)/PhSeBr	decomposition
5	DBU/PhSeBr	decomposition
6	LiHMDS/PhSeBr	35%
7	LiHMDS/TMSCl/PhSeBr	55 % (97% brsm)
8	NaHMDS/TMSCl/PhSeBr	quantitative

Table 3: Conditions for the deprotonation of lactone **215**.

Addition of hydrogen peroxide and $NaHCO_3$ converted the selenide into a selenoxide, which then underwent elimination when the temperature was raised to room temperature to provide the α,β-unsaturated lactone **217**. The methyl group was then introduced by stereoselective addition of dimethylcopper lithium to the α,β-unsaturated lactone **217**. Stereoselection was excellent and an 13:1 ratio of products in favour of the desired diastereoisomer **218** was obtained (**Figure 7**). Analysis of coupling constants and nOe effects in the ^1H NMR spectrum was used to confirm the configuration of the newly generated stereocentre (**Figure 7**). Indeed, a strong nOe effect was observed between the axial methyl group and the axial hydrogen 6, and a smaller value between the methyl group and the equatorial hydrogen 3. Coupling analysis between the axial hydrogen 5 and

hydrogens 4 and 6 gave values of 6.1 and 10.0 Hz respectively confirming the axial-equatorial and axial-axial relationships.

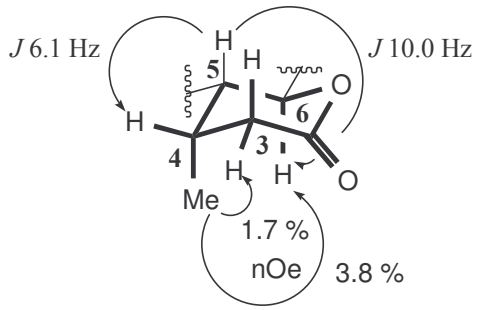
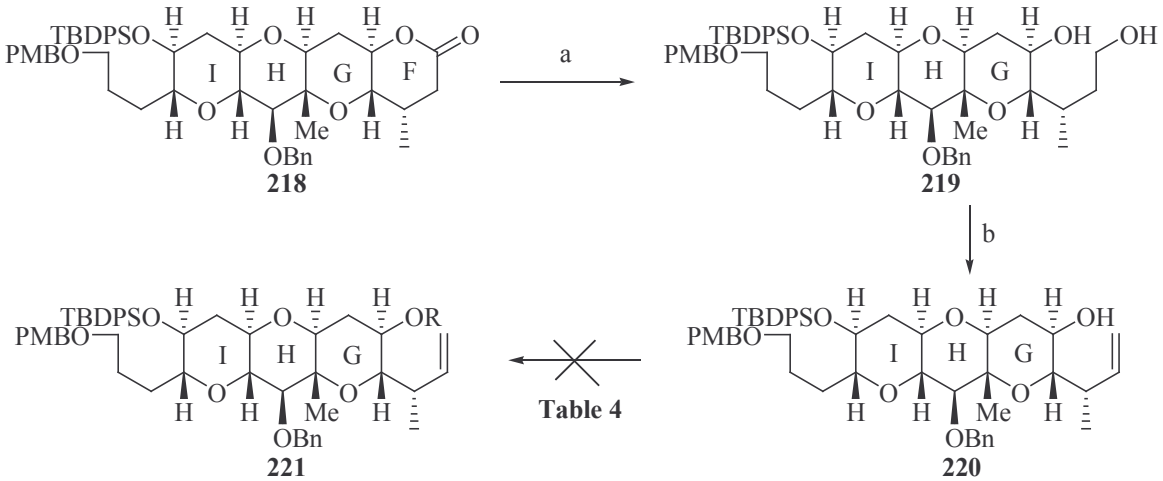


Figure 7: nOe effects and coupling constants in the lactone **218**.

The lactone **218** was then reduced to afford the diol **219** in good yield (**Scheme 46**). At this stage, compound **219** was purified by column chromatography on silica gel and a 53% yield over the 5-step sequence (an average of 88% yield per step) was obtained. Having successfully introduced the methyl group to the F-ring, studies toward the coupling of the two polyether fragments were started. Consequently, alkene functionality and a side chain on the secondary hydroxyl group needed to be introduced into the diol **219**. The primary hydroxyl group of the diol **219** was substituted by a nitrophenylselenyl group using tributylphosphine and PhSeCN.



Reagents and conditions: (a) (i) $LiAlH_4$, THF, 0 °C, 15 min (ii) rt, 30 min (53% over 5 steps); (b) (i) *p*-$(O_2N)C_6H_4SeCN$, *n*-Bu_3P, THF, rt, 30 min (ii) H_2O_2, $NaHCO_3$, 0 °C→ 40 °C, 1 h (66 %).

Scheme 46: Attempted alkylation of the alcohol **220**.

Oxidation of selenium using hydrogen peroxide and subsequent elimination of the selenoxide afforded the desired alkene **220** in moderate yield.[57]Alkylation of the secondary alcohol **220** was then explored (**Table 4**). Formation of the alcoholate using sodium hydride and displacement of (*R*)-4-benzyl-3-chloroacetyl-2-oxazolidinone unsurprisingly failed, since no examples of this reaction are known (**Entry 1**). However, etherification did not proceed even using known procedures, despite variation of electrophile (**Entries 2-5**, **Table 4**).[58] Surprisingly, an attempted carbenoid O–H-insertion reaction also gave unreacted starting material, even though alkene cyclopropanation should have occurred (**Entry 6**, **Table 4**).

Entry	Conditions	Solvent	Result
1	NaH, TBAI, (*R*)-4-benzyl-3-chloroacetyl-2-oxazolidinone, 0 °C → rt, 18 h	THF/DMF	Starting material
2	NaH, sodium bromoacetate, 0 °C → rt, 18 h	THF/DMF	Starting material
3	NaH, sodium iodoacetate, 0 °C → rt, 18 h	THF/DMF	Starting material
4	NaH, *tert*-butyl bromoacetate, 0 °C → rt, 18 h	DMF	Starting material
5	NaH (5 eq), bromo acetonitrile, 0 °C → rt, 18 h	MeCN	Starting material
6	Rh_2OAc_4, *tert*-butyl diazoacetate, reflux, 18 h	CH_2Cl_2	Starting material

Table 4: Conditions for the alkylation of the secondary alcohol **220**.

At the time, the connection reaction between the two fragments was not a priority and studies towards the introduction of the side chain to the J ring started.

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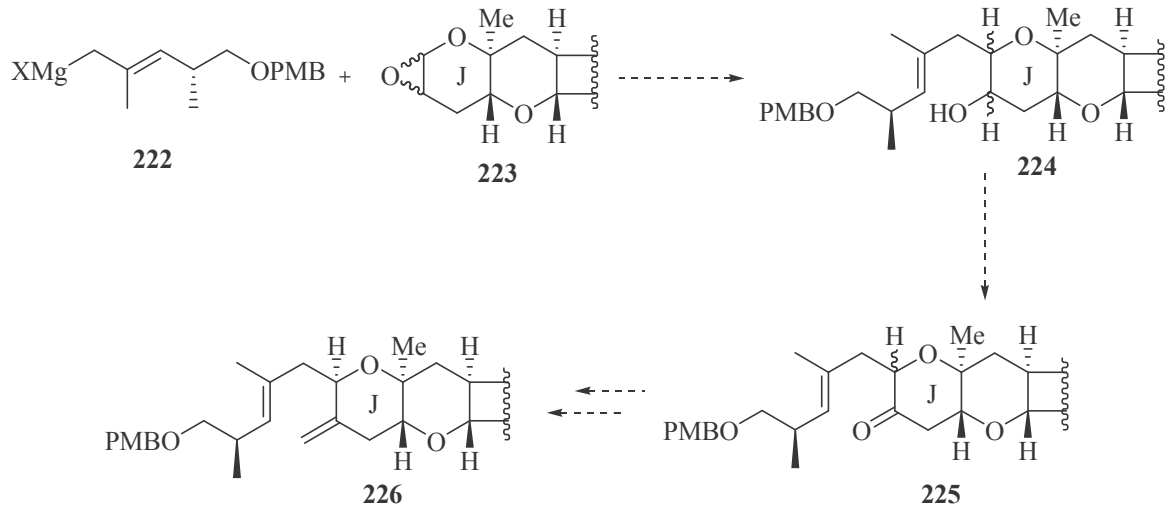
[57] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485.
[58] (a) M. T. Crimmins, C. J. Diaz, K. A. Emmitte, *Heterocycles* **2004**, *62*, 179 ; (b) R. Carrillo, L. G. Leon, T. Martin, V. S. Martin, J. M. Padron, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 780; (c) M. Pietraszkiewicz, J. Jurczak, *J. Carbohydr. Chem.* **1985**, *4*, 429; (d) A. Marinier, A. Martel, C. Bachand, S. Plamondon, B. Turmel, J.-P. Daris, J. Banville, P. Lapointe, C. Ouellet, P. Dextraze, M. Menard, J. J. K. Wright, J. Alford, D. Lee, P. Stanley, X. Nair, G. Todderud, K. M. Tramposch, *Bioorg. Med. Chem.* **2001**, *9*, 1395; (e)C. Malet, O. Hindsgaul, *J. Org. Chem.* **1996**, *61*, 4649; (f) K. Nagai, T. Sunazuka, S. Omura, *Tetrahedron Lett.* **2004**, *45*, 2507.

2.3. Introduction of the side chain onto the J ring

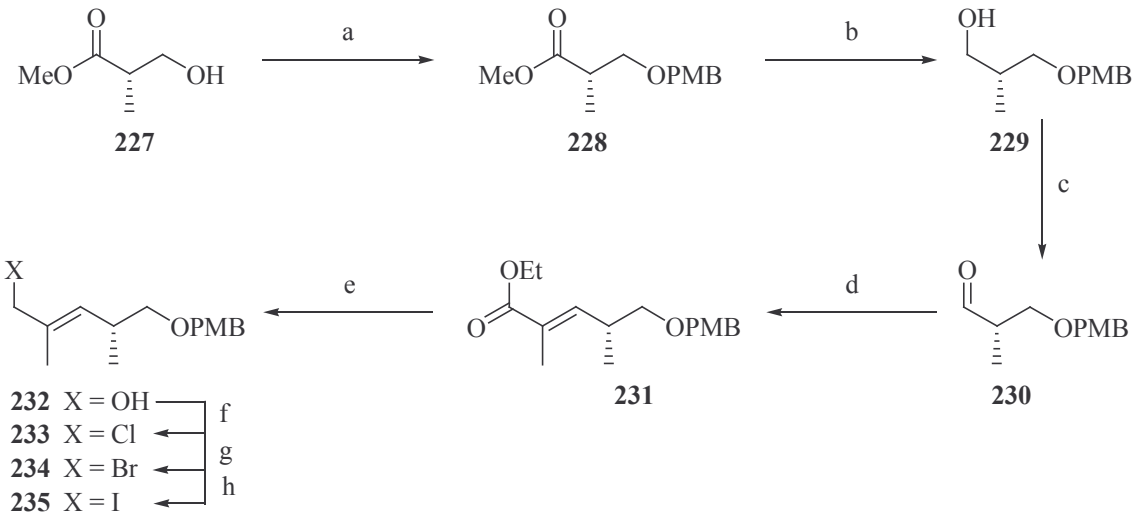
2.3.1. Grignard reagent approach

The strategy to introduce the side chain to the J-ring was planned around the RCM reaction. Indeed, the synthesis of the J-ring was to be achieved using the RCM reaction to deliver a cyclic enol ether. Careful analysis of the side chain revealed a possible C−C bond disconnection to give an allylic nucleophile. Rainier proved that it was possible to introduce a side chain to a pyranyl system by addition of an allylic Grignard reagent to an epoxide obtained from a dihydropyran (see § 1.5.2). This methodology should allow rapid introduction of the side chain to the J-ring and a hydroxyl group that will be converted into an alkene thereafter (**Scheme 47**). It was anticipated that a mixture of diastereoisomers would be produced during the epoxidation reaction because of the lack of directing group on the J−ring, but this problem would be addressed during the introduction of the alkene functionality. Indeed, the alkene **226** would be introduced via a ketone **225** and epimerisation of the stereocentre bearing the side chain would be performed to furnish the required diastereoisomer prior to methylenation.



Scheme 47: Grignard reagent strategy.

The first task was to synthesise the known allylic alcohol **232** (**Scheme 48**).[59] The commercially available alcohol **227** was protected as a PMB ether under mild acidic conditions in excellent yield and the aldehyde **230** was then obtained by reduction of the ester **228** followed by oxidation of the resulting alcohol **229**. A Wittig reaction delivered the desired ester **231** with good selectivity (10:1, *E*:*Z*), which was reduced with Dibal-H to furnish allylic alcohol **232**. The allyl chloride **233**, bromide **234** and iodide **235** were then synthesised in excellent yield.



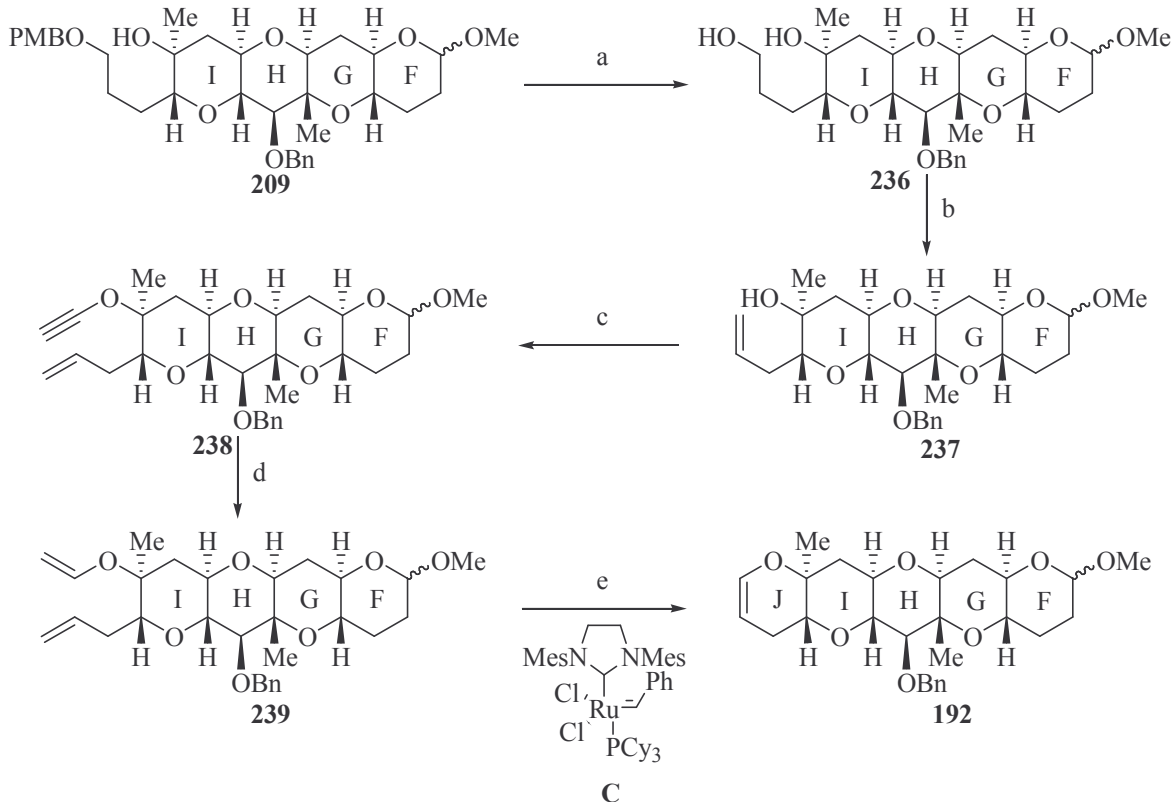
Reagents and conditions: (a) $PMBOC(=NH)CCl_3$, PPTS, CH_2Cl_2, rt, 24 h (98%); (b) Dibal-H, CH_2Cl_2, –10 °C, 1 h (86%); (c) Dess-Martin periodinane, CH_2Cl_2, 0 °C then rt, 1 h; (d) $EtO_2CC(=PPh_3)CH_3$, CH_2Cl_2, rt, 1 day (67% over 2 steps); (e) Dibal-H, CH_2Cl_2, –10 °C, 1 h (89%); (f) CCl_4, PPh_3, MeCN, 0 °C, 1 h (95%); (g) CBr_4, PPh_3, MeCN, 0 °C, 15 min (86%); (h) I_2, PPh_3, imidazole, CH_2Cl_2, –10 °C, 15 min (96%).

Scheme 48: Synthesis of allylic halides.

We next focused on the synthesis of the gambieric acid fragment containing the J-ring (**Scheme 49**). First, PMB ether **209** was treated with DDQ in wet DCM to afford primary alcohol **236** in good yield. The PMB ether could also be removed using CAN, but this reaction was slower and less clean than that in which DDQ was used. Conversion of primary alcohol **236** into an arylselenide followed by selenoxide elimination yielded the

[59] A. B. Smith, C. M. Adams, S. A. L. Barbosa, A. P. Degnan, *J. Am. Chem. Soc.* **2003**, *125*, 350.

desired alkene **237**,[60] and the tertiary hydroxyl group of this compound was then converted into the alkynyl ether **238** in excellent yield using Greene's protocol.[61]



Reagents and conditions: (a) DDQ, CH_2Cl_2/H_2O, 0 °C, 1 h then rt, 1 h (91%); (b) (i) *p*-$(O_2N)C_6H_4SeCN$, *n*-Bu_3P, THF, rt, 30 min (ii) H_2O_2, $NaHCO_3$, 0 °C→ 50 °C, 1 h (98%); (c) (i) KH, Cl_2CCHCl, THF, 0 °C (ii) *n*-BuLi, ether, –78 °C→0 °C, 2 h (74% over 2 steps); (d) Lindlar's catalyst, quinoline, EtOAc, H_2, rt, 18 h (78%); (e) Catalyst **C**, toluene, 70 °C, 1 h (92% over 2 steps).

Scheme 49: Synthesis of J-ring **192**.

Reduction of the alkynyl ether **238** in the presence of Lindlar's catalyst resulted in formation of the enol ether **239**. The reduction reaction was monitored by NMR spectroscopy since the starting material **238** and the product **239** have the same polarity by TLC. The cyclic enol ether **192** was obtained in good yield by RCM of the diene **239** using the Grubbs second generation catalyst.

Now that both the side chain and the fragment containing the J-ring had been prepared, the formation of the required Grignard reagent was studied. Despite numerous attempts using

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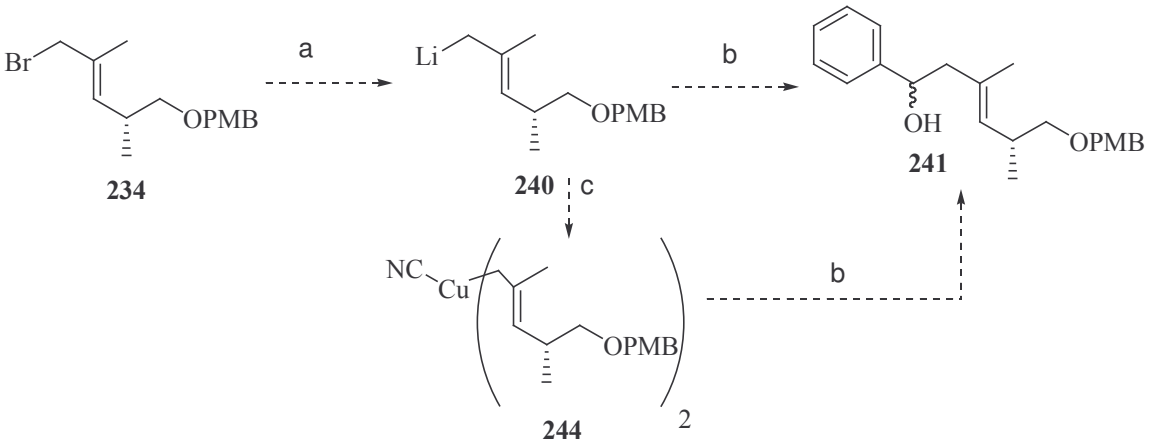
[60] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485.
[61] A. Moyano, F. Charbonnier, A. E. Greene, *J. Org. Chem.* **1987**, *52*, 2919.

various experimental conditions, the allylic Grignard reagent could not synthesised. First, effect of solvent was studied. For each allylic halides (**233–235**), ether, THF and hexane were used as solvent but in each case formation of the Grignard reagent was not successful. Generally, the starting material was recovered or the Wurtz coupling product was obtained when forcing conditions were applied. The magnesium source was also examined. Riecke magnesium was synthesised by reduction of $MgBr_2$ with lithium and naphthalene,[62] but this highly reactive source of magnesium was also ineffective for the formation of the corresponding Grignard reagent. The even more reactive magnesium anthracene also proved to be ineffective.[63]

Following the failure to make the Grignard reagent directly from the allylic halides **233–235**, a halogen metal exchange strategy was investigated (**Scheme 50**). Halogen/lithium exchange of bromide **234** followed by addition of either $MgBr_2.OEt_2$ or CuCN and then reaction with benzaldehyde did not result in formation of the desired alcohol **241**. A halogen/*iso*-propylmagnesium chloride exchange reaction was also attempted. Not surprisingly, the reaction failed since no examples of this transformation using allylic halides have been reported in the literature.



Reagents and conditions: (a) *t*-BuLi, THF, –78 °C, 1 h; (b) Benzaldehyde, –78 °C → rt, 3 h (c) CuCN, LiCl, –78 °C, 1 h.

Scheme 50: Attempted halogen/lithium exchange.

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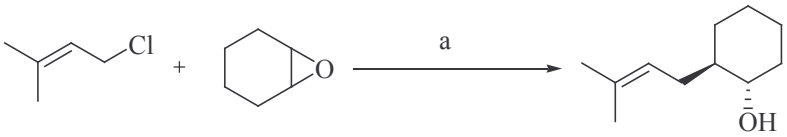
[62] R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhm, *J. Org. Chem.* **1981**, *46*, 4323.
[63] S. Harvey, P. C. Junk, C. L. Raston, G. Salem, *J. Org. Chem.* **1988**, *53*, 3134.

2.3.2. Organobarium reagent approach

It seemed to be impossible to generate the Grignard reagent from the allylic halides **233–235** and so the possibility of changing the metal and using other organometallic reagents was explored. Yamamoto and co-workers had reported an efficient synthesis of organobarium reagents and their use in organic synthesis.[64] They were able to access a wide range of these reagents starting with allylic chlorides on both small and large scale (**Scheme 51**). In addition, these organobarium reagents were reported to react in a S_N fashion compare to allyl Grignard reagent (mixture of S_N and S_N' products).

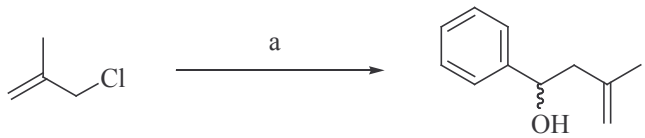


245 **246** **247**

Reagents and conditions: (a) (i) Ba, THF, –78 °C, 20 min (ii) rt, 12 h (78%).

Scheme 51: Yamamoto's addition of an organobarium reagent to an epoxide.

Barium metal was generated *in situ* by reduction of barium iodide with lithium and biphenyl under strictly anhydrous and oxygen-free conditions. We attempted the reaction with our side chain, but none of the desired compound was obtained. To verify the methodology and reactivity of an analogous barium reagent, methallyl chloride (**248**) was used and the reaction was quenched with benzaldehyde (**Scheme 52**).



248 **249**

Reagents and conditions: (a) (i) Ba, THF, –78 °C, 20 min (ii) rt, 12 h (25%).

Scheme 52: Synthesis of alcohol **249**.

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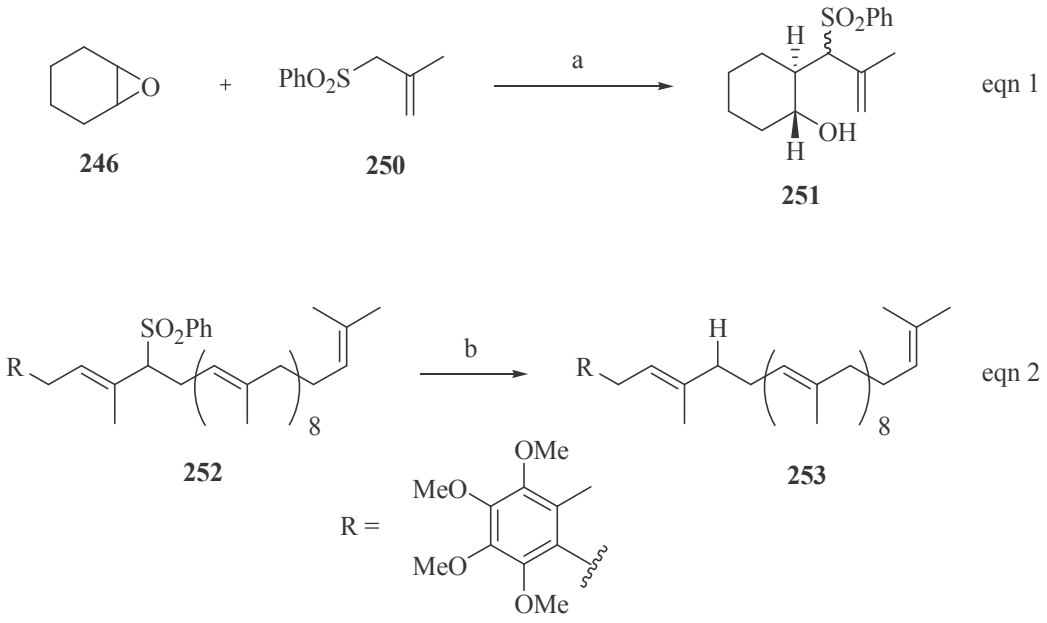
[64] (a) A. Yanagisawa, S. Habaue, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 8955; (b) A. Yanagisawa, S. Habaue, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 6130; (c) A. Yanagisawa, H. Hibino, S. Habaue, Y. Hisada, K. Yasue, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1263; (d) K. Yasue, A. Yanagisawa, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1995**, *70*, 493.

The reaction proved to be successful but the yield was low. The next step was to open an epoxide with organobarium reagent formed from the chloride **233**. Unfortunately, despite addition of $ZnCl_2$, none of the required compound was obtained from this reaction.

2.3.3. Allylsulfone approach

The organometallic reagents did not give the results expected. However, we demonstrated that it was possible to synthesise the J-ring as well as the corresponding epoxide. Our investigation led us to study another class of reagent, derived from allylic halides, that should be able to open epoxides: allylic sulfones. It is known that a sulfone-stablised anion can open epoxides (**Scheme 53**, **eqn 1**).[65] It is also known that regio- and stereoselective desulfonylation of allylic sulfones can be performed without significant alkene migration (**eqn 2**).[66]



Reagents and conditions: (a) *n*-BuLi, THF, −78 °C (58%); (b) $Pd(dppe)Cl_2$, $LiEt_3BH$, THF (77%).

Scheme 53: Examples of epoxide opening with an allylic sulfone and subsequent desulfonylation reaction.[65a, 66d]

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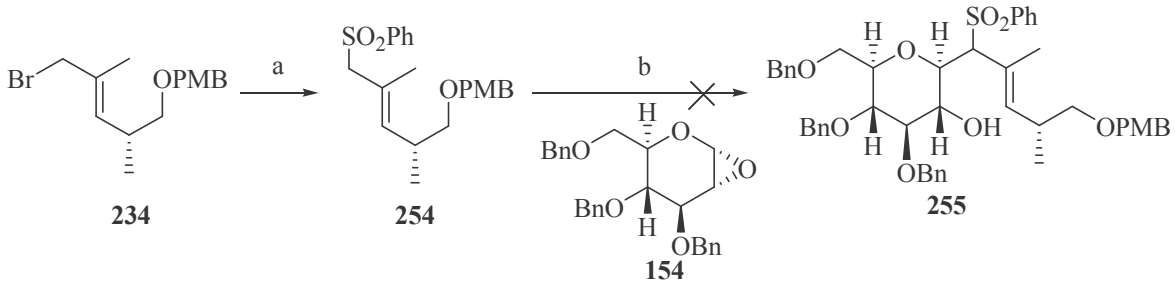
[65] J. A. Marshall, R. C. Andrews, *J. Org. Chem.* **1985**, *50*, 1602; (b) B. M. Trost, C. A. Merlic, *J. Am. Chem. Soc.* **1988**, *110*, 5216.

[66] (a) M. Mohri, H. Kinoshita, K. Inomata, H. Kotake, H. Takagaki, K. Yamazaki, *Chem. Lett.* **1986**, 1177; (b) H. Nagaoka, H. Miyaoka, Y. Yamada, *Tetrahedron Lett.* **1990**, *31*, 1573; (c) M. Kinoshita, M. Ohtsuka, D. Nakamura, H. Akita, *Chem. Pharm. Bull.* **2002**, *50*, 930; (d) J.-H. Min, J.-S. Lee, J.-D. Yang, S. Koo, *J. Org. Chem.* **2003**, *68*, 7925.

The allylsulfone **254** was synthesised by substitution of bromide **234** with the sodium salt of benzenethionosulfonic acid (**Scheme 54**). Deprotonation of the allylic sulfone was accomplished using *n*-BuLi in a mixture of THF and HMPA but the resulting deprotonated sulfone did not ring-open the epoxide **154**. In order to increase the electrophilicity of the epoxide, Bu_3SnOTf was added to the reaction, but none of the desired compound was obtained from this reaction either.



234 **254** **154** **255**

Reagents and conditions: (a) $PhSO_2Na$, $NaHCO_3$, DMF, rt, 24 h (84%); (b) (i) *n*-BuLi, THF/HMPA (6/1), –78 °C (ii) **154**, THF, –78 °C → rt **or** (ii) **154**, THF, - 78 °C (iii) Bu_3SnOTf, THF, –78 °C →.rt.

Scheme 54: Attempted epoxide opening with an allylic sulfone.

2.3.4. Lithium approach

In previous attempts to couple the side chain to the J-ring, a nucleophilic side chain was added to an electrophilic epoxide. However, the nucleophilicity and electrophilicity can be reversed. Indeed, deprotonation of cyclic enol ethers with alkyl lithium reagents and subsequent allylation of the deprotonated vinyl lithium intermediates with reactive allylic halides are known (**Scheme 55**).[67] It is also possible to generate the alkenyl lithium compound and then add copper iodide to give the corresponding cuprate which can then react with allylic bromide (**eqn 2**).[68]

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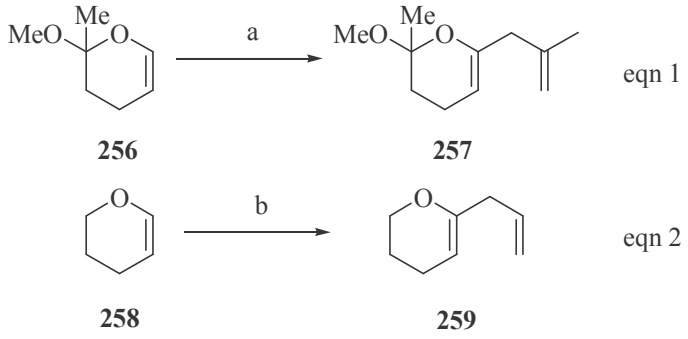
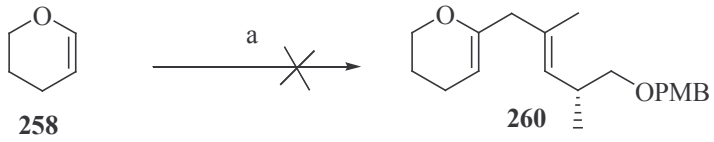
[67] R. K. Boeckman, Jr., K. J. Bruza, *Tetrahedron Lett.* **1977**, 4187.
[68] F. P. Marmsaeter, F. G. West, *J. Am. Chem. Soc.* **2001**, *123*, 5144.



Reagents and conditions: (a) (i) *t*-BuLi, THF, 0 °C (ii) methallyl bromide, −78 °C (80%); (b) (i) *t*-BuLi, THF, −78 °C (ii) CuI, −78 °C (iii) allylbromide, −78 °C.

Scheme 55: Functionalisation of alkenyl lithium intermediate.

Unfortunately, deprotonation of the model compound dihydropyran (**258**) using *t*-BuLi followed by addition of the allylic iodide **235** was not successful (**Scheme 56**). Generation of the cuprate derivative was attempted next but again without success. This approach requires a large excess of alkenyl lithium intermediate or cuprate to be used compared to the side chain and these reactions are reported to be capricious.[69] Consequently, this approach was not investigated further.



Reagents and conditions: (a) (i) *t*-BuLi, THF, –78 °C → rt, 1 h (ii) **235**, –78 °C → rt, 3 h.

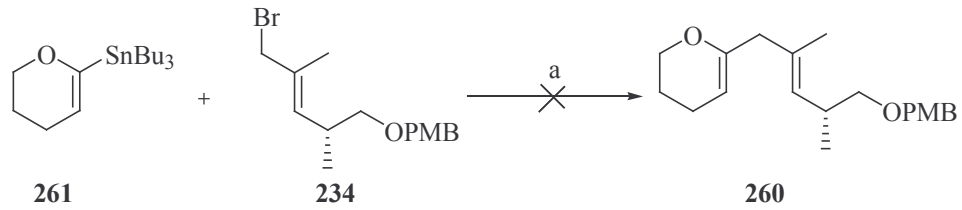
Scheme 56: A C1 lithiation and electrophile trapping approach.

2.3.5. The Stille coupling approach

The previous approach gave us a further opportunity to attch the side chain to the J-ring. Indeed, lithium alkenyl intermediates can be quenched with trialkylchlorostannane to afford vinylic stannanes, which are precursors of the Stille coupling reaction. The Stille coupling reaction was first explored by coupling the simple vinylic stannane **261** with the

[69] J. S. Potuzak, D. S. Tan, *Tetrahedron Lett.* **2004**, *45*, 1797.

allylic bromide **234** (**Scheme 57**).[70] The stannane **261** was easily prepared by deprotonation of 3,4-dihydro-2*H*-pyran with *t*-BuLi and subsequent addition of tributylchlorostannane.[71] The Stille coupling reaction catalysed by $(MeCN)_2PdCl_2$ in *N*-methylmorpholine gave none of the required product. Consequently, another source of palladium(0) – $[Pd(dba)_2]$ – was investigated. Unfortunately, none of the required coupled product was isolated and only isomerised allyl bromide **234** was isolated. This experiment showed that the palladium was able to insert into the allylic bromide but the transmetallation did not occur. Exploration of the reaction was abandoned at this stage because it was clear that the synthesis of the vinylic stannane required for the fully functionalised system would require too many steps.



261 **234** **260**

Reagents and conditions: (a) $(MeCN)_2PdCl_2$, NMP, rt, overnight.

Scheme 57: Stille coupling reaction.

An alternative sequence to the one outlined above, involving Stille coupling of an enol triflate with an allylic stannane, was studied.[72] The simple enol triflate **263** required for this study was synthesised by internal quenching of the enolate of lactone **262** with Comins' reagent (**Scheme 58)**.[73] In the case of the fully functionalised system, the required lactone could be synthesised by simple oxidation of diol **236**.

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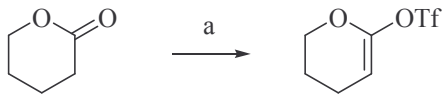
[70] (a) E. Dubois, J. M. Beau, *J. Chem. Soc., Chem. Commun.* **1990**, 1191; (b) E. Dubois, J. M. Beau, *J. Chem. Soc., Chem. Commun.* **1990**, 1191;(c) F. Yokokawa, T. Asano, T. Shioiri, *Tetrahedron* **2001**, *57*, 6311.
[71] S. Ghosal, G. P. Luke, K. S. Kyler, *J. Org. Chem.* **1987**, *52*, 4296.
[72] K. C. Nicolaou, P. M. Pihko, N. Diedrichs, N. Zou, F. Bernal, *Angew. Chem., Int. Ed.* **2001**, *40*, 1262.
[73] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299.

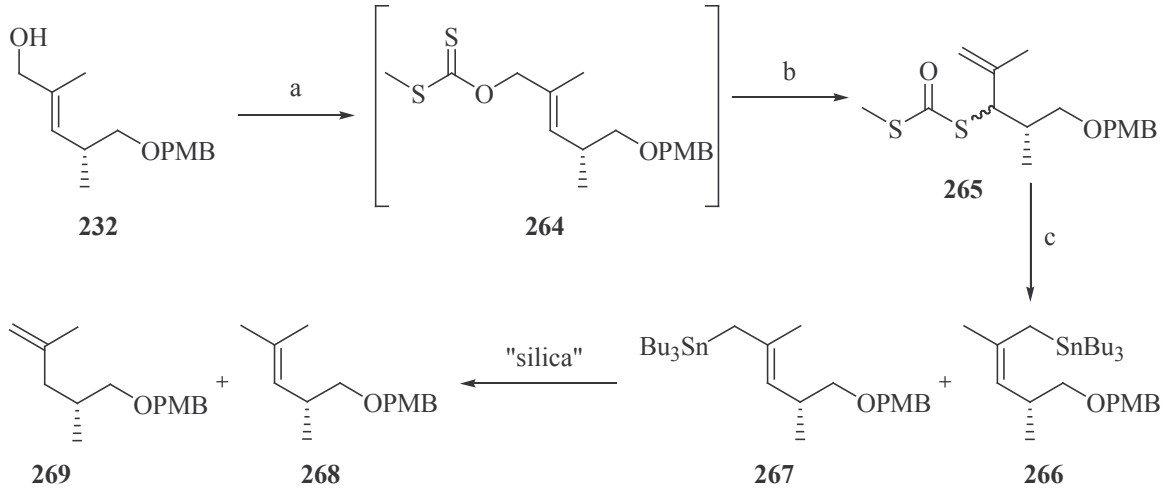


262 **263**

Reagents and conditions: (a) KHMDS, Cl-PyNTf$_2$, THF, –78 °C, 1 h (44%).

Scheme 58: Synthesis of the enol triflate **263**.

Synthesis of the allylic stannane **267** was attempted by formation of xanthate **264** followed by rearrangement to furnish compound **265** (**Scheme 59**).[74] Subsequent radical substitution gave a mixture (1:1) of *E* and *Z* allylic stannanes **267** and **266**. Unfortunately, the mixture could not be purified on silica gel because decomposition delivered a mixture of the alkenes **268** and **269**.



232 **264** **265** **269** **268** **267** **266**

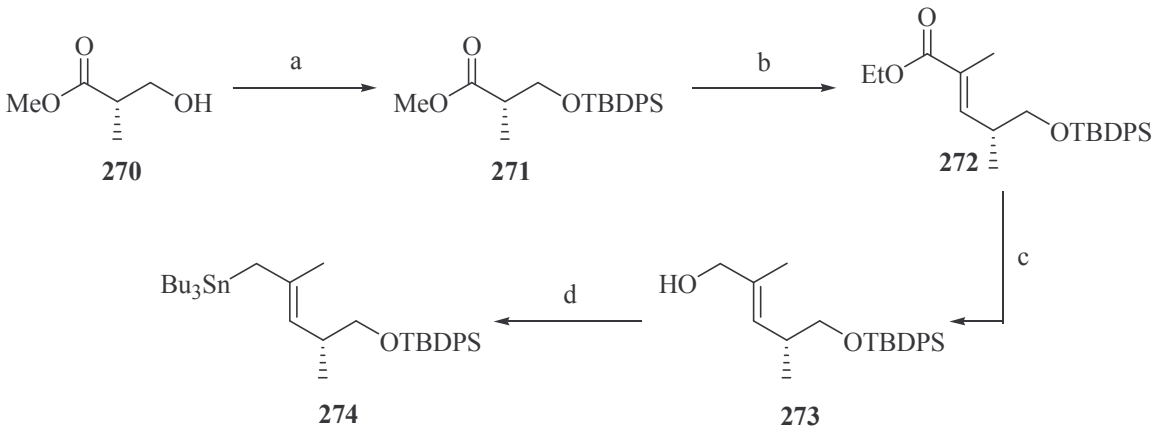
Reagents and conditions: (a) (i) NaH, CS_2, rt, 30 min (ii) MeI, rt, 10 min; (b) reflux, 18 h (90%); (c) Bu_3SnH, AIBN, benzene, reflux, 2 h (97% **268**+**269**).

Scheme 59: Synthesis of allylic stannanes **266** and **267**.

However, it was possible to prepare the required allylic stannane from the corresponding mesylate (**Scheme 60**). Deprotonation of alcohol **273** and addition of methanesulfonylchloride afforded the mesylate, which was smoothly displaced by $LiSnBu_3$

[74] (a) Y. Ueno, H. Sano, M. Okawara, *Tetrahedron Lett.* **1980**, *21*, 1767; (b) A. Teerawutgulrag, E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1993**, 2863.

to give the desired allylstannane **274** as sole product.[75] The yield was modest because quick filtration through a plug of silica was required to remove stannane wastes.



270 **271** **272** **273** **274**

Reagents and conditions: (a) TBDPSCl, imidazole, DMAP, DMF, rt, 2 h; (b) (i) Dibal-H, toluene, –78 °C, 1.5 h (ii) $EtOOCC(=PPh_3)CH_3$, CH_2Cl_2, reflux, 18 h (72% over 3 steps); (c) Dibal-H, ether, 0 °C, 15 min (85%); (d) (i) MsCl, *n*-BuLi, THF, –78 °C, 45 min (ii) Bu_3SnLi, –78 °C → rt, 18 h (57%).

Scheme 60: Successful synthesis of the allylic stannane **274**.

Stille coupling was first attempted using enol triflate **263**, allylstannane **274**, $Pd(dba)_2$ and triphenylarsine.[76] Unfortunately, the only the product isolated was that arising from dimerisation of the triflate. The use of $Pd_2(dba)_3.CHCl_3$ and allylstannane allowed us to obtain a coupled product, but it was contaminated with by-products. However, when the Stille reaction was repeated using the allylic stannane **274**, none of the required product was obtained.

2.3.6. Attempted synthesis of an allylic copper reagent

The availability of the allylic stannane **274** meant that a new option was possible. Lipshutz and co-workers have reported the synthesis of several allylic copper reagents from allylic stannanes (**Scheme 61**).[77] The first method involves the preparation of a dimethylcuprate followed by exchange with the allylic stannane. The second one involves tin-lithium

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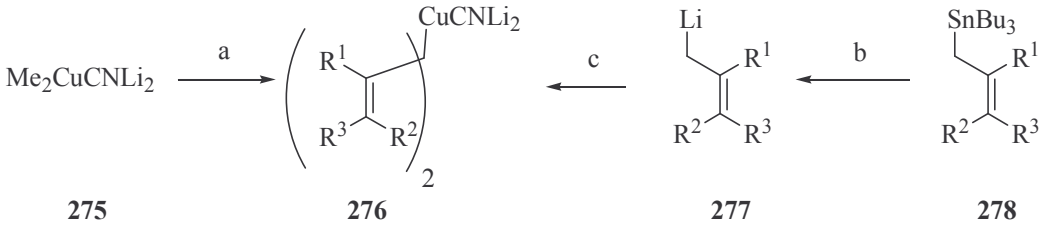
[75] S. Weigand, R. Brueckner, *Synthesis* **1996**, 475.
[76] V. Farina, B. Krishnan, *J. Am. Chem. Soc.* **1991**, *113*, 9585.
[77] (a) B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, R. A. J. Smith, *J. Org. Chem.* **1989**, *54*, 4977; (b) B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, R. A. J. Smith, *J. Am. Chem. Soc.* **1990**, *112*, 4404.

exchange followed by the addition of copper cyanide. Regrettably, we were unable to generate the cuprate using either of these methods and unreacted allylic stannane was usually recovered. This route was not investigated further because isomerisation of the alkene was a further potential complication.

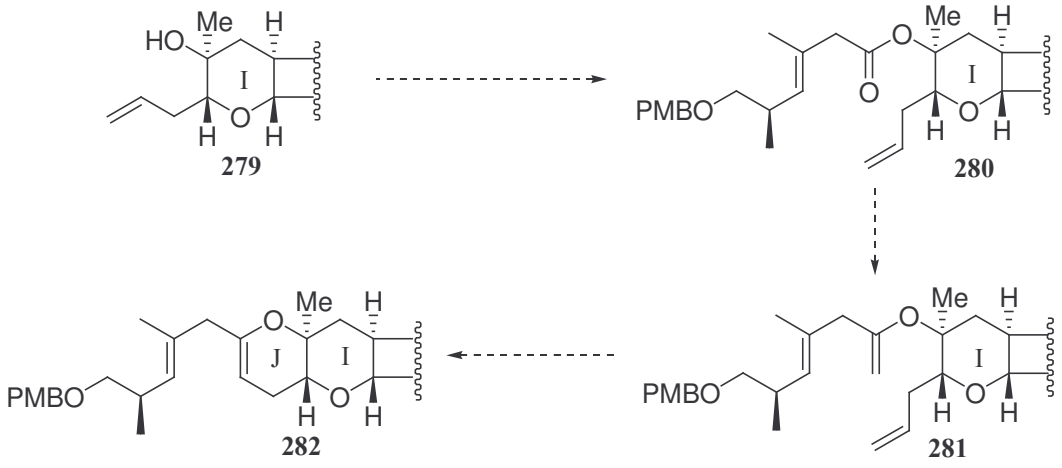


Reagents and conditions: (a) allylstannane; (b) MeLi or *n*-BuLi, THF, –78 °C; (c) CuCN, THF, –78 °C.

Scheme 61: Lipshutz' synthesis of allylic cuprates.

2.3.7. Ester approach

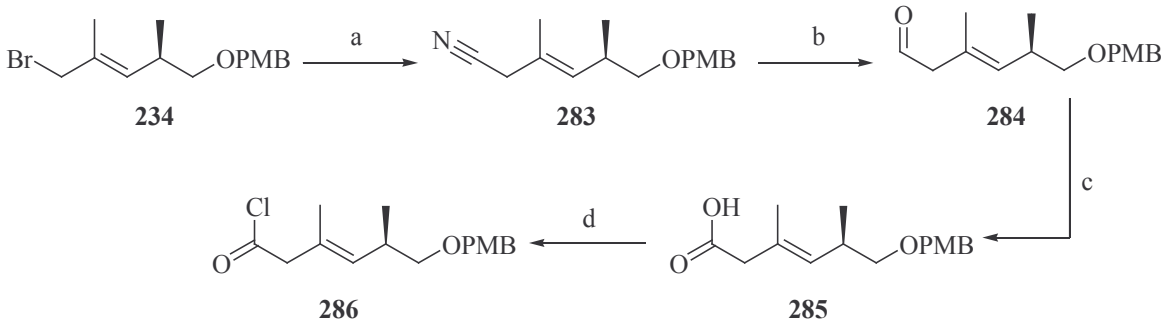
In all previous cases, attachment of the side chain to the intact J-ring had been attempted. Introduction of the side chain prior to the RCM offered a potential solution to our problem. In principle, a cyclic enol ether could be obtained by esterification of the tertiary alcohol **279** followed by ester methylenation and subsequent RCM of the enol ether (**Scheme 62**).



Scheme 62: Introduction of the J ring side chain by ester formation.

In order to explore this new approach, one-carbon homologation of the side chain was required. Thus, the bromide **234** was smoothly displaced with TBACN to afford nitrile **283**

in good yield without alkene isomerisation (**Scheme 63**).[78] Direct hydrolysis of the nitrile **283** with NaOH was possible but unfortunately this reaction resulted in unanticipated loss of the PMB group. As a result of this problem, the nitrile **283** was converted into the aldehyde **261** by reduction with Dibal-H and the carboxylic acid **285** was then obtained using Pinnick's conditions.[79] In addition, the acyl chloride **286** was prepared from the carboxylic acid **285** using standard conditions.



Reagents and conditions: (a) TBACN, MeCN, rt, 18 h (86%); (b) Dibal-H, THF, –78 °C, 1 h; (c) $NaClO_2$, $NaHPO_4.2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O (2/1), rt, 1 h (78% over 2 steps); (d) oxalyl chloride, DMF, benzene, rt, 15 min (quantitative).

Scheme 63: Synthesis of acyl chloride **286**.

A model coupling partner was then synthesised from benzylated glucal **148** (**Scheme 64**). Diastereoselective epoxidation of enol ether **148** with DMDO was followed by subsequent regioselective opening with allylmagnesium chloride to give alcohol **149** as the sole product. The tertiary alcohol **287** was then synthesised by oxidation of secondary alcohol **149** using the Dess Martin periodinane followed by addition of methyllithium under high dilution conditions. Unfortunately, a ratio of only 7:3, in favour of the desired diastereomer, was obtained. Confirmation of the structure was achieved by observation of nOe effects in the ^{1}H NMR spectrum. Interestingly, the other diastereomer was obtained as the major product (3.7:1 ratio) when methylmagnesium iodide was employed as nucleophile. The successful synthesis of both partners allowed the coupling reaction to be

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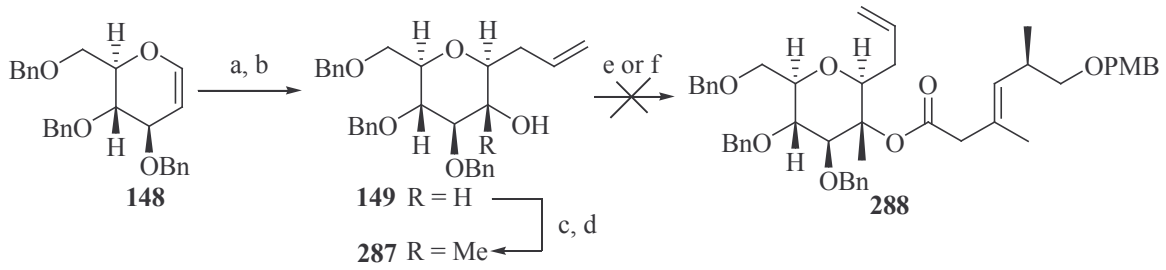
[78] D. V. Patel, R. J. Schmidt, *Synth. Commun.* **1995**, *25*, 413.
[79] B. S. Bal, W. E. Childers, Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.

explored. However, direct esterification between acyl chloride **286** and tertiary alcohol **287** was not successful. Furthermore, when the coupling was performed using Yamaguchi's conditions the desired ester was not obtained.[80]

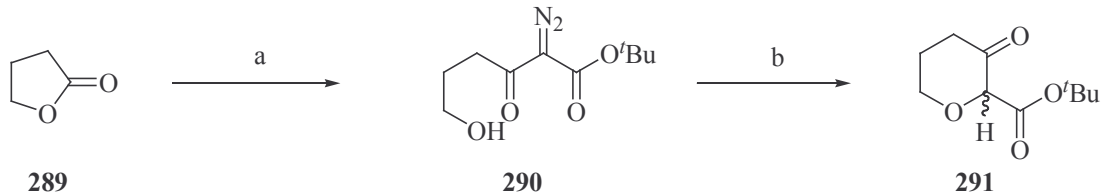


Reagents and conditions: (a) DMDO, CH_2Cl_2, 0 °C, 1 h; (b) CH_2CHCH_2MgCl, THF, 0 °C, 2 h (75% over 2 steps); (c) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; (d) MeLi, toluene, –78 °C, 1 h (75% over 2 steps); (e) **286**, DMAP, pyridine, reflux, overnight; (f) (i) **285**, Et_3N, 2,4,6-trichlorobenzoyl chloride, THF, rt, 15 min (ii) **287**, rt, 2 days.

Scheme 64: Ester synthesis attempted.

2.3.8. A carbenoid OH-insertion reaction

At this stage, a new route for the introduction of the side chain was required. Moody and co-workers have synthesised a six-membered cyclic ether using a carbenoid OH-insertion reaction and have then functionalised the product (**Scheme 65**).[81] This approach to the synthesis of the cyclic ethers appeared to be an attractive one for construction of the J ring.



Reagents and conditions: (a) $LiN_2CCO_2{}^tBu$, THF, –90 °C (47%); (b) $Rh_2(OAc)_4$, benzene, reflux, (57%).

Scheme 65: Synthesis of a six-membered cyclic ether by a carbenoid OH insertion reaction

The intramolecular carbenoid OH-insertion reaction was applied to the synthesis of the required ring system. First, we chose a model system on which to perform the reaction. A

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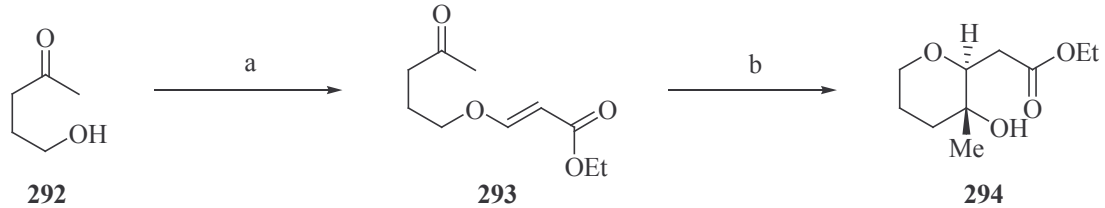
[80] I. Paterson, D. Y.-K. Chen, J. L. Acena, A. S. Franklin, *Org. Lett.* **2000**, *2*, 1513.
[81] (a) C. J. Moody, R. J. Taylor, *J. Chem. Soc., Perkin Trans. 1* **1989**, 721; (b) M. J. Davies, C. J. Moody, R. J. Taylor, *Synlett* **1990**, 93; (c) M. J. Davies, C. J. Moody, *Synlett* **1990**, 95.

simple two-step synthesis to produce the six-membered cyclic ether bearing a tertiary alcohol and an ester side chain was found in the literature.[82] The first step involved the formation of the α,β-unsaturated ethyl ester **293** (**Scheme 66**). Subsequent cyclisation of a ketyl radical, generated using samarium diiodide in THF/methanol, afforded the desired ring **294**. The stereochemical relationship C2 proton and the C3 methyl group was *trans* due to the chair transition state during the cyclisation reaction, as expected based on literature precedent.



292 **293** **294**

Reagents and conditions: (a) Ethyl propiolate, *N*-Methylmorpholine, CH_2Cl_2, rt, 18 h (66%); (b) SmI_2, THF/ MeOH, rt, 1 h (81%).

Scheme 66: Synthesis of the alcohol **294**.

The next step was lactonisation by reaction of the tertiary alcohol with the ethyl ester (**Scheme 67**). Unsurprisingly, the desired compound was not obtained, as a consequence of the relatively strained *trans*-fused six- and five-membered rings. Consequently, a two-step strategy was developed.[83] Firstly, saponification of the ethyl ester **294** with lithium hydroxide in refluxing THF afforded the desired carboxylic acid **296**. *In situ* activation of the acid with 2-chloro-1-methylpyridinium iodide then afforded the desired lactone **295** in a disappointing 19% yield. An attempt to open lactone **295** directly with lithium *tert*-butyl diazoacetate was also made using the method reported by Moody and co-workers,[84a] but unfortunately the required product was not obtained. As a consequence of the difficulties experienced when trying to synthesise the diazoester **297**, a longer route was selected, but with theoretically better yields.

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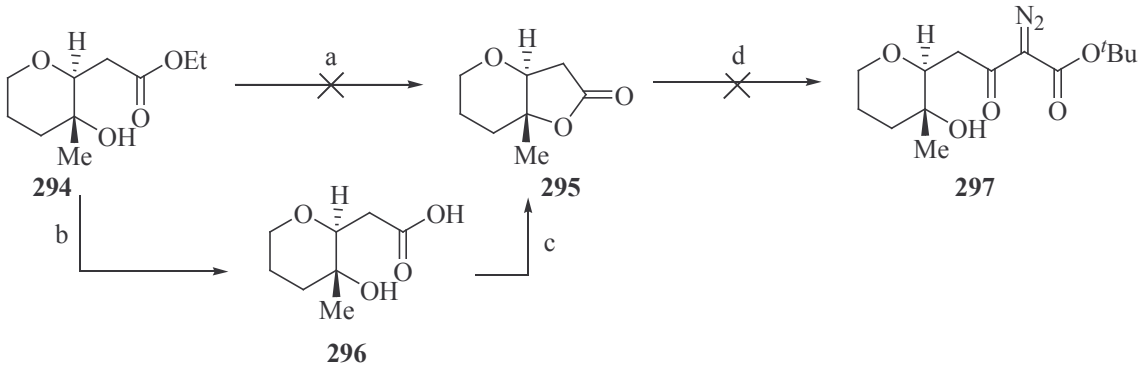
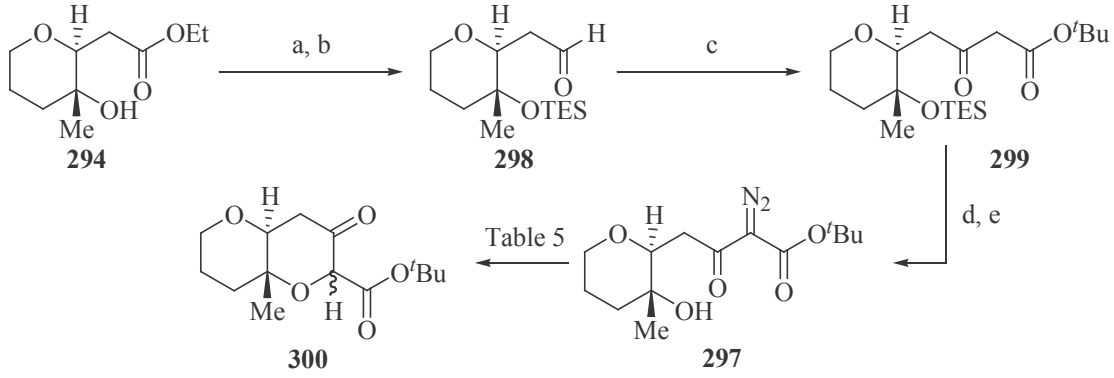
[82] K. Suzuki, H. Matsukura, G. Matsuo, H. Koshino, T. Nakata, *Tetrahedron Lett.* **2002**, *43*, 8653.
[83] L. Strekowski, M. Visnick, M. A. Battiste, *Synthesis* **1983**, 493.



Reagents and conditions: (a) PPTS, benzene, reflux; (b) LiOH, THF, H_2O, reflux, 1 h; (c) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, reflux, 3 h (19% over 2 steps); (d) $N_2LiCCO_2{}^tBu$, THF, –110 °C→–78 °C.

Scheme 67: Attempted direct synthesis of *tert*-butyl diazoacetate **297**.

The tertiary alcohol **294** was first protected as a triethylsilyl ether (**Scheme 68**). Careful addition of Dibal-H at –78 °C afforded the desired aldehyde **298**, which was then converted into the β-ketoester **299** by addition of *tert*-butyl diazoacetate and tin (II) chloride.[84] In our case, tin (II) chloride was not used sub-stoichiometrically because of the formation of a stable tin enolate. The product was used in the next step without purification since it was not possible to remove tin by-products by column chromatography. Deprotection of tertiary alcohol with TBAF yielded the desired β-keto ester and it was then transformed into the diazo β-keto ester **297** using the diazo transfer method.



Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min (94%); (b) Dibal-H, toluene, –78 °C, 3 h (84%); (c) *tert*-butyl diazoacetate, $SnCl_2$, CH_2Cl_2, rt, 1 h; (d) TBAF, THF, rt, 2 h (46% over 2 steps); (e) *p*-ABSA, Et_3N, MeCN, 0 °C, 2 h (74%).

Scheme 68: Synthesis of the diazo β-keto ester **297**.

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[84] C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258.

Treatment of the diazo ester **297** with several different catalysts was explored (**Table 5**). Generally, the reaction gave a very complex mixture of products as judged by ^{1}H NMR spectroscopic analysis. When the crude product was purified, very little material was isolated suggesting substantial decomposition of the products on silica gel. Nevertheless, rhodium (II) acetate seemed to give the cleanest reactions. The complexity of the NMR spectra could be explained by the equilibrium between the keto and enol forms. To simplify the spectrum, Moody and co-workers trapped the enol as a silyl enol ether. Unfortunately, this procedure did not help to simplify matters in our case. In spite of the unidentified mixture of products, the alkylation step was attempted, but none of the required compound was obtained.

Entry	Catalyst	Solvent	Temperature	Result
1	Rh_2OAc_4	Benzene	Reflux	Complex mixture
2	Rh_2OAc_4	Benzene	rt	Starting material
3	$Rh_2(tfacam)_4$	Benzene	rt	Complex mixture
4	$Cu(OTf)_2$	Benzene	50 °C	Decomposition

Table 5: Decomposition of β-ketodiazoester **297**.

2.3.9. Cross metathesis approach

The difficulties encountered when attempting to introduce the side chain *via* an allylic compound meant that a new retrosynthetic analysis had to be considered. Disconnection through the alkene of the side chain revealed two new alkene fragments; one of them bearing a methallyl group (**Scheme 69**). However, the methallyl group can be easily introduced by reaction of an epoxide with methallylmagnesium chloride and then alkene cross metathesis could be used to deliver the desired side chain. [85]

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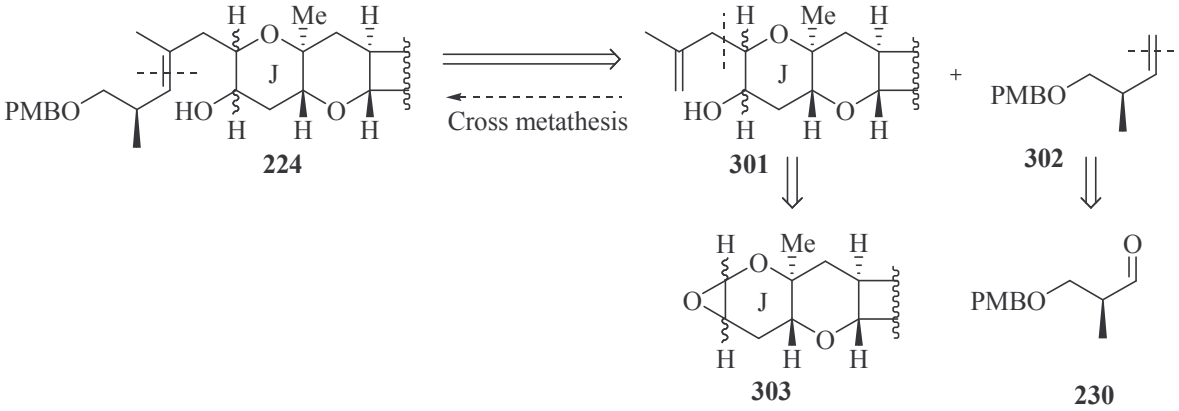
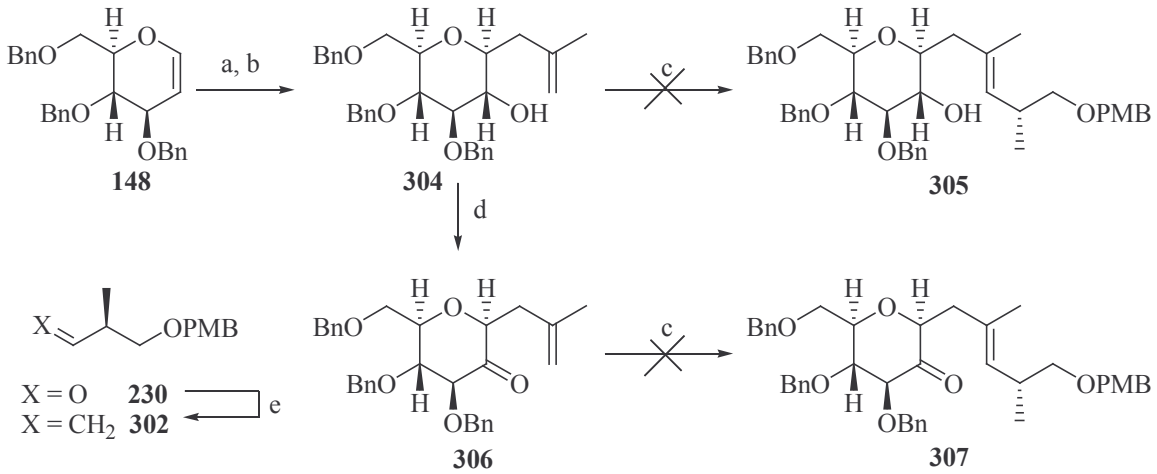
[85] A. K. Chatterjee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 1751.



Scheme 69: New retrosynthetic analysis of the side chain.

The intermediate **304** was first synthesised in moderate yield by opening of an epoxide with a Grignard reagent (**Scheme 70**). The other cross metathesis partner **308** was obtained by Wittig reaction of CH_2PPh_3 and the aldehyde **230**. The Grubbs second generation catalyst was then used to cross-couple alkenes **304** and **302**. Unfortunately, only the cross coupled dimer of **302** was isolated. The presence of the free hydroxyl group in the alkene **304** was deemed to be a possible cause of the failure of the cross metathesis reaction, so the alcohol **304** was converted into ketone **306**. However, cross metathesis of the alkenes **306** and **302** was also unsuccessful. These results were not surprising since 1,1-disubstituted alkenes are frequently poor substrates for cross metathesis reaction due to unfavourable steric interactions.[85]

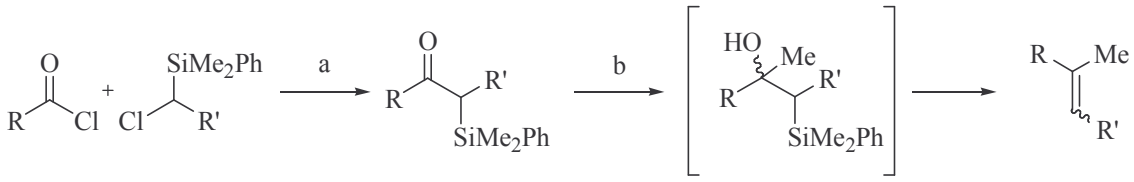


Reagents and conditions: (a) DMDO, CH_2Cl_2, 0 °C, 1 h; (b) $ClMgCH_2(CH_3)C{=}CH_2$, THF, 0 °C, 1 h (65% over 2 steps); (c) **308**, Grubbs second generation, CH_2Cl_2, reflux, 1 day; (d) Dess-Martin periodinane, CH_2Cl_2, rt, 2 h (96%); (e) $CH_2{=}PPh_3$, benzene, rt, 30 min (75% over 2 steps).

Scheme 70: A cross metathesis approach for introduction of the J ring side chain.

2.3.10. Peterson and Julia olefinations

The previous disconnection through the side chain alkene was further investigated. Indeed, the cross mletathesis is not the only reaction allowing the synthesis of alkenes. Of the possible alternatives, the Peterson and Julia olefination reactions were particularly appealing. Barrett's group has reported the synthesis of trisubstituted olefins using an improved version of the Peterson olefination reaction.[86] In this case an acyl chloride **309** and an α-chlorosilane **310** were used to form the key α-silylketone **311** (**Scheme 71**). Addition of methyllithium to the carbonyl group is controlled by the presence of the bulky silyl group and so a diastereoisomerically pure β-hydroxysilane **312** is synthesised due to the Cram controlled addition of the nucleophile. Consequently, they obtained the desired *E* or *Z* alkenes, with a high level of control using either a basic or acidic workup, in good yields over two steps.



309 **310** **311** **312** **313**

R	R'	Elimination	E:Z	Yield
C_4H_9	C_5H_{11}	TsOH	5:95	60%
		KH	95:5	61%
C_5H_{11}	C_5H_{11}	TsOH	8:92	67%
		KH	88:12	63%
C_7H_{15}	C_5H_{11}	TsOH	15:85	64%
		KH	94:6	62%
Ph	C_5H_{11}	TsOH	<2:>98	60%
		KH	>98:<2	69%
t-$BuPh_2SiO(CII_2)_4$	C_5II_{11}	TsOH	9:91	61%
		KH	99:1	62%
C_7H_{15}	C_7H_{15}	TsOH	10:90	54%
		KH	95:5	68%

Reagents and conditions: (a) i) Mg, ether, ii) $CuBr.Me_2S$; (b) i) MeLi, THF ii) KH or TsOH.

Scheme 71: Barrett's strategy for the synthesis of trisubstituted alkene.

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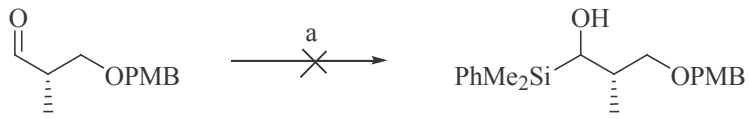
[86] (a) A. G. M. Barrett, J. A. Flygare, *J. Org. Chem.* **1991**, *56*, 638; (b) A. G. M. Barrett, J. M. Hill, E. M. Wallace, *J. Org. Chem.* **1992**, *57*, 386.

The main challenge in using this methodology was to synthesise the required α-chlorosilane (**Scheme 72**). Unfortunately, despite using several different experimental conditions, the desired α-hydroxysilane **314** could not be prepared. The aldehyde **230** was recovered from these reactions suggesting that competitive deprotonation of the aldehyde **230** might have been occurring. The failure of the reaction meant that Julia olefination was explored as an alternative.

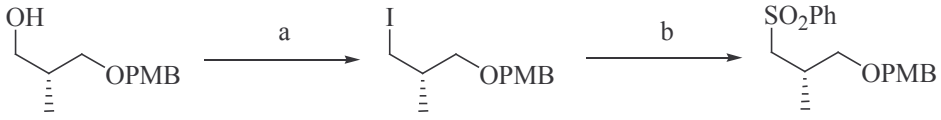


230 **314**

Reagents and conditions: (a) $PhMe_2SiLi$, THF, –78 °C→ rt, 18 h.

Scheme 72:Attempted synthesis of the α-hydroxysilane **314**.

In order to study the Julia olefination reaction, the sulfone and ketone precursors needed to be prepared. First, the sulfone **316** was synthesised according to a known procedure (**Scheme 73**).[87] The alcohol **229** was converted into the corresponding iodide **315**. Substitution of the iodide using sodium benzenesulfinate then gave the desired sulfone **316**.



229 **315** **316**

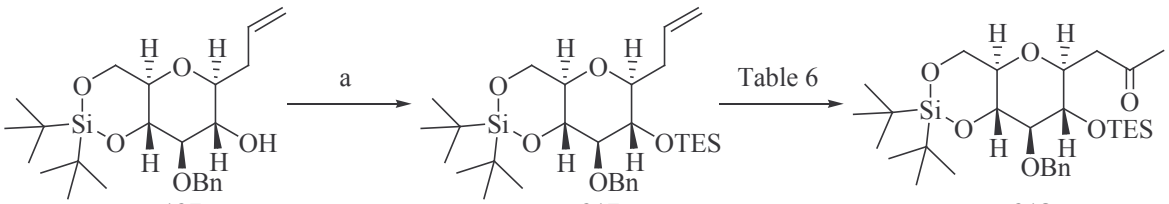
Reagents and conditions: (a) iodine, PPh_3, imidazole, benzene, rt, 3 h (88%); (b) $PhSO_2Na$, DMF, 60 °C, 18 h (85%).

Scheme 73: Synthesis of sulfone **316**.

The coupling partner **318** was synthesised using a sequence involving Wacker oxidation (**Scheme 74**). Indeed, the allylic side chain required for the Wacker reaction, could be easily introduced by opening an epoxide with allylmagnesium chloride and the secondary

[87] S. V. Ley, J. Norman, C. Pinel, *Tetrahedron Lett.* **1994**, *35*, 2095.

alcohol **137** was then protected as TES ether. Standard oxidation conditions (**Table 6, Entry 1**) were applied to the terminal alkene **317** to afford methyl ketone **318** in very low yield.[88] Increasing the reaction time or catalyst loading had little effect (**Entry 2**). The addition of copper acetate as co-catalyst was also studied, but again there was no improvement in the yield.[89] Fortunately, full conversion was obtained by pre-mixing the palladium catalyst, copper chloride and the oxygen for one hour before the addition of the alkene **317** (**Entry 4**). Nevertheless, the desired compound was not stable to silica gel and so a modest yield of the ketone **318** was isolated from the purified reaction mixture.



Reagents and conditions: (a) TESCl, imidazole, DMF, rt, 15 min (93%).

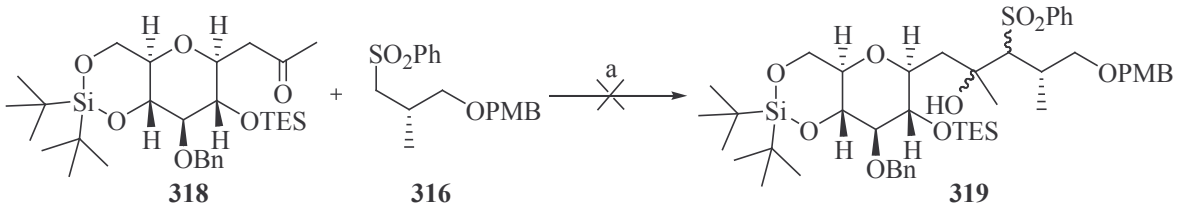
Scheme 74: Synthesis of the ketone **318**.

Entry	Conditions	Result
1	20 mol% $PdCl_2$, 1 eq CuCl, O_2, DMF, H_2O, rt, 2 days	24 %
2	1 eq $PdCl_2$, 1 eq CuCl, O_2, DMF, H_2O, rt, 2 days	Starting material
3	20 mol% $PdCl_2$, 1 eq $Cu(OAc)_2$, O_2, $AcNMe_2$, H_2O, rt, 2 days	Starting material
4	20 mol% $PdCl_2$, 1 eq CuCl, O_2, DMF, H_2O (pre-mixing 1 h), 60 °C, 1 h	100% by TLC, 40 % after purification

Table 6: Conditions for Wacker oxidation of the alkene **317**.

[88] J. S. Clark, T. C. Fessard, G. A. Whitlock, *Tetrahedron* **2005**, *62*, 73.
[89] A. B. Smith, III, Y. S. Cho, G. K. Friestad, *Tetrahedron Lett.* **1998**, *39*, 8765.

The Julia reaction was now attempted but it did not proceed as expected, despite varying the reaction conditions (**Scheme 75**).[90] A large excess of the sulfone **316** was added compared to the ketone **318** but unreacted starting materials were recovered. There are a few cases in which ketones have been used as substrates in Julia reactions. However, in the case of the relatively hindered ketone **318**, the rate of deprotonation of the methyl ketone appeared to be higher than nucleophilic attack leading to the recovery of unreacted starting materials after the reaction had been quenched.



318 **316** **319**

Reagents and conditions: (a) *n*-BuLi, THF, –78 °C → rt.

Scheme 75: Attempt of the synthesis of intermediate **319**.

2.3.11. Siloxane approach

The final approach to be explored involved the use of the side chain hydroxyl group to direct the addition of a methyl group onto an alkyne. Analogous cases of direct stereoselective addition of a methyl group to a substituted alkyne are not known and so the introduction of an alternative group, that could be converted into a methyl substituent, was studied.

Tributyltin reagents can add to homopropargylic alcohols but the regioselectivity of the reaction is usually poor (**Scheme 76, eqn 1**).[91] An iodide can be introduced directly into a homopropargylic alcohol, although there are only a limited number of literature examples of this reaction and harsh conditions are usually required (**eqn 2 and 3**).[92] Fortunately, Trost and co-workers have developed a ruthenium complex capable of promoting the

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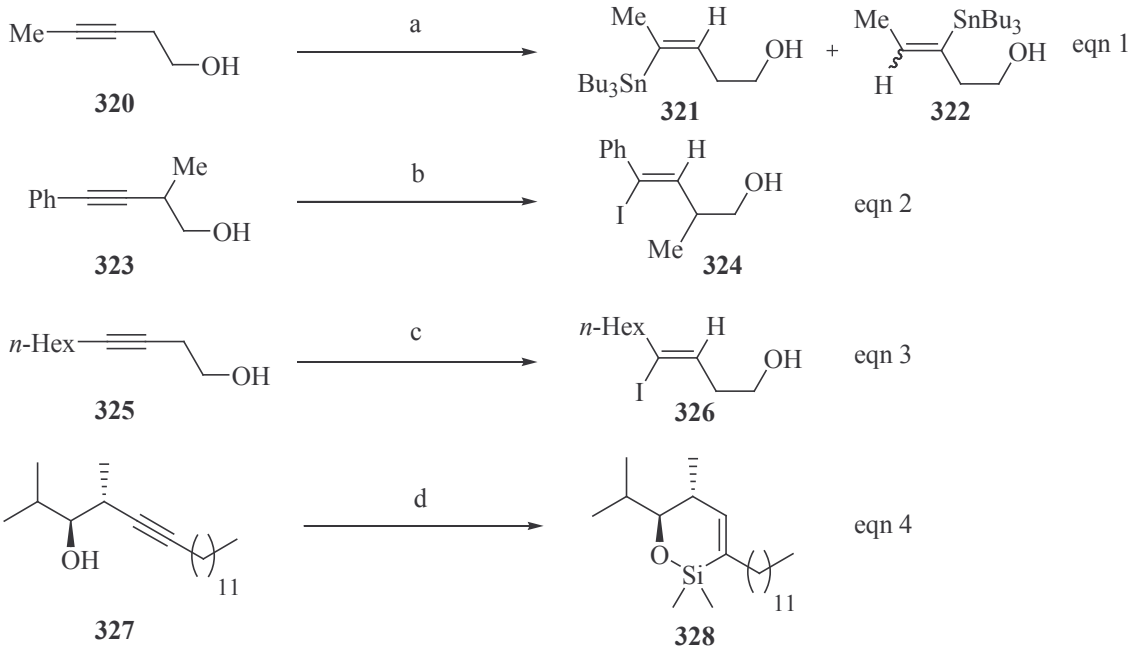
[90] J. Pospisil, I. E. Marko, *J. Am. Chem. Soc.* **2007**, *129*, 3516.
[91] K. Miura, D. Wang, Y. Matsumoto, A. Hosomi, *Org. Lett.* **2005**, *7*, 503.
[92] S. Ma, F. Liu, E.-i. Negishi, *Tetrahedron Lett.* **1997**, *38*, 3829.

synthesis of 6-membered siloxanes from secondary homopropargylic alcohol in high yield (**eqn 4**).[93]



Reagents and conditions: (a) (i) $Bu_2Sn(OTf)H$, hexane, rt, 3h; (ii) *n*-BuLi, ether, 0 °C (**321/322** = 59:41, 90%); (b) (i) Red-Al, THF, reflux, 2 h; (ii) I_2, THF, –78 °C (50%); (c) (i) $LiAlH_4$, diglyme, 140 °C, 42 h; (ii) EtOAc; (iii) I_2, THF, –78 °C → rt (74%); (d) (i) TMDS, 50 °C; (ii) 5 mol% $[Cp^*Ru(MeCN)_3]PF_6$, CH_2Cl_2, 30 min, rt (91%).

Scheme 76: Regioselective and stereoselective addition to homopropargylic alcohols.

To explore the strategy, we needed to synthesise a homopropargylic alcohol from a lithiated acetylene and a triflate. The precursors to both fragments were easily synthesised using known procedures, starting from tri-*O*-acetyl-D-glucal triacetate (**197**) and the protected ester **228** (**Scheme 77**).[94,95] Displacement of the allylic acetate in the triester **197** with hydride followed by removal of the remaining acetate groups delivered the diol **330**. Sequential hydrogenation of the alkene **330**, triflation of primary hydroxyl group and TES protection of secondary alcohol gave desired compound **331**. The coupling partner was obtained by reduction of the ester **228** to give an aldehyde, which was converted into the alkyne **333** using the Corey-Fuchs protocol. Deprotonation of the alkyne **333** followed by addition of the triflate **331** then furnished the protected homopropargylic alcohol **334** in

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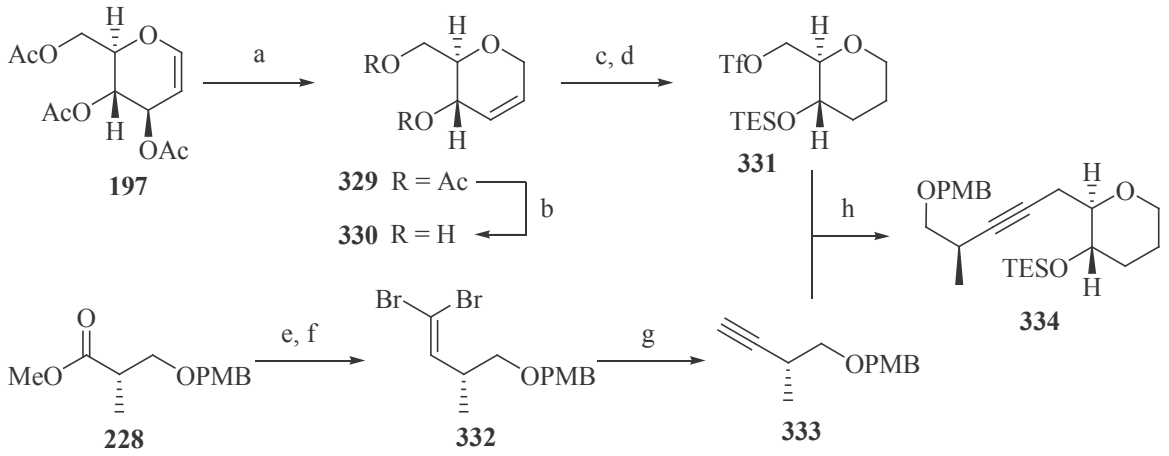
[93] (a) B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2003**, *125*, 30; (b) B. M. Trost, Z. T. Ball, K. M. Laemmerhold, *J. Am. Chem. Soc.* **2005**, *127*, 10028.
[94] K. C. Nicolaou, C. K. Hwang, B. E. Marron, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3040.
[95] A. B. Smith, III, D. Lee, *J. Am. Chem. Soc.* **2007**, *129*, 10957.

excellent yield. The use of ether as solvent was a key condition; the use of THF gave the desired product in only 27% yield.



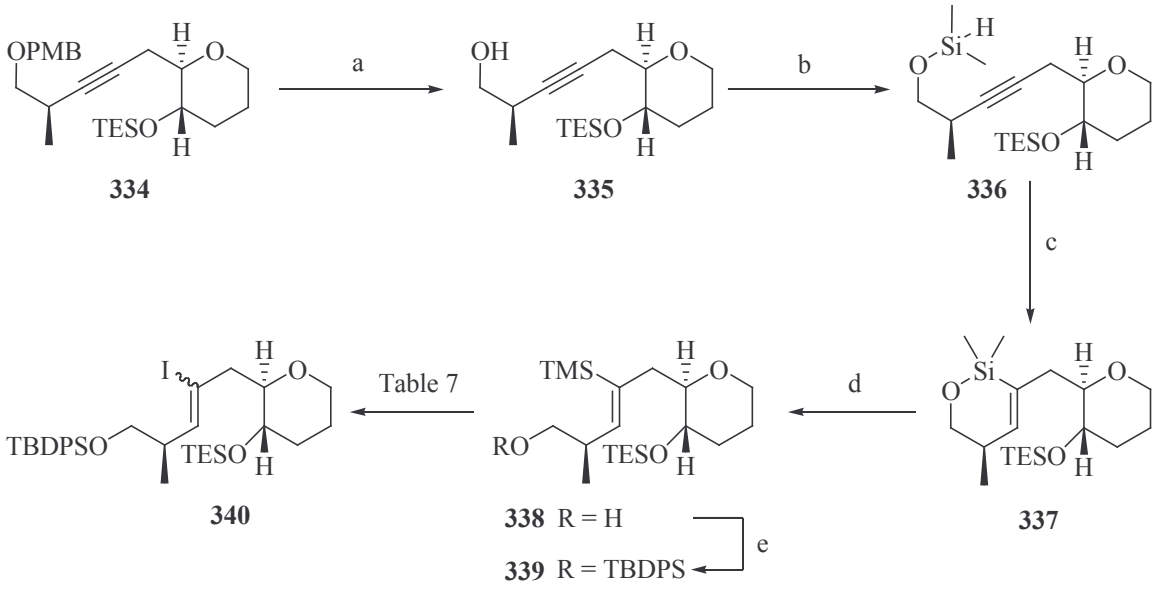
Reagents and conditions: (a) Et_3SiH, $BF_3{\cdot}OEt_2$, 0 °C, 3 h; (b) NaOMe, MeOH, 30 min, rt; (c) Pd/C, H_2, MeOH, rt, 18 h (94% over 3 steps); (d) (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min; (ii) TESOTf, CH_2Cl_2, –78 °C, 0.5 h; (69%); (e) Dibal-H, toluene, –78 °C, 2 h; (f) PPh_3, CBr_4, CH_2Cl_2, –78 °C, 1 h; (g) *n*-BuLi, ether, –78 °C, 1 h (92%); (h) *n*-BuLi, ether, –78 °C → rt, 18 h (87%).

Scheme 77: Synthesis of the alkyne **334**.

The next step consisted of removal of the PMB protecting group to yield the homopropargylic alcohol **335** (**Scheme 78**). Trost's strategy could now be employed to form a siloxane. Formation of silane **336** and subsequent cyclisation using the commercially available catalyst afforded the desired siloxane **337**. Direct iododesilylation was attempted, but treatment of the siloxane **337** with iodine in dichloromethane led to decomposition of starting material and reaction with NIS in acetonitrile gave mixture of compounds. Opening of the siloxane **337** with methyllithium to provide the vinylic silane **338** was also explored and was successful.[96] The use of THF as solvent was critical; the use of ether gave incomplete reaction and afforded decomposition products. Efforts to protect the alcohol **338** as its PMB ether failed and so the primary hydroxyl group was protected with the robust TBDPS group. It is worth noting that the method is highly efficient and that no chromatography is required from homopropargylic alcohol **335**

[96] M. Ahmed, A. G. M. Barrett, J. C. Beall, D. C. Braddock, K. Flack, V. C. Gibson, P. A. Procopiou, M. M. Salter, *Tetrahedron* **1999**, *55*, 3219.

onwards. The reaction times are also extremely short and vinylic silane **339** is produced in an impressive 73% yield over 4 steps (92% average).



Reagents and conditions: (a) DDQ, CH_2Cl_2/H_2O, 0 °C → rt, 1.5 h (92%); (b) TMDS, neat, 50 °C, 2 h; (c) 4 mol% $[Cp^*Ru(MeCN)_3]PF_6$, CH_2Cl_2, 10 min, rt; (d) MeLi, THF, –78 °C, 20 min; (e) TBDPSCl, DMAP, DMF, 0 °C → rt, 1 h (73% over 4 steps).

Scheme 78: Synthesis of vinylic iodide **340**.

At this stage, iododesilylation of vinylic silane **339** was studied (**Table 7**). Based on experimental observations, Kishi and co-workers have defined some guidelines to explain the retention (or not) of the configuration of vinylic silanes during replacement of silicon with iodine.[97] Retention of configuration is usually observed provided that solvent or functional groups in the compound do not attack the intermediate cyclic iodonium ion. In addition, steric effects can result in exceptions to this rule. First, the fluorinated solvent (HFIP), which is polar but has low nucleophilicity, was used.[98] In spite of a quick reaction time, product with the *Z* alkene geometry predominated signifying attack of the solvent (**Entry 1**). Interestingly, the product ratio could be modified in a dramatic way using acetonitrile as solvent (**Entry 2**). In order to reduce the reaction time, NIS was added portionwise (**Entry 3**) resulting in a higher ratio of desired product. Fascinatingly, a direct

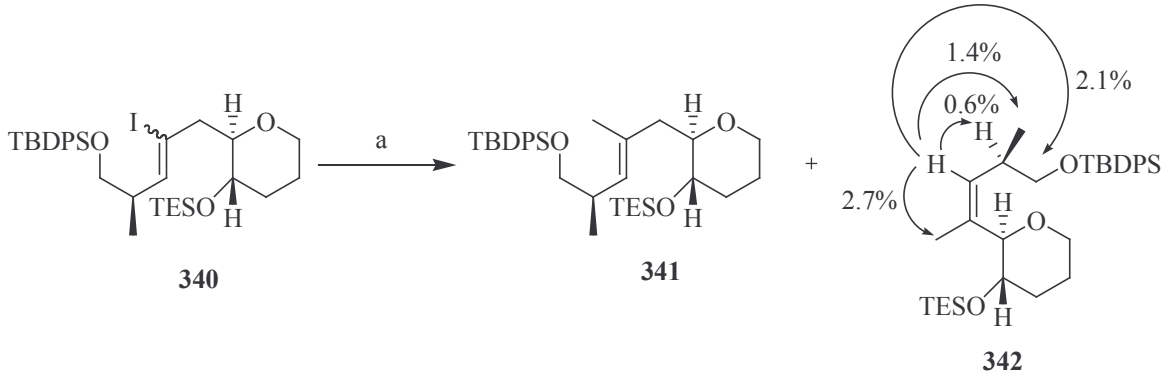
[97] D. P. Stamos, A. G. Taylor, Y. Kishi, *Tetrahedron Lett.* **1996**, *37*, 8647.
[98] A. Zakarian, A. Batch, R. A. Holton, *J. Am. Chem. Soc.* **2003**, *125*, 7822.

relationship between number of equivalents of NIS added and the ratio seemed to emerge from data (approximately 2 equiv. of NIS gave a 2:1 ratio whereas 4 equiv. of NIS gave a 4:1 ratio). To verify the hypothesis, 10 equivalents of NIS was added (**Entry 4**) but there was little improvement in the product ratio and the limit seemed to be 4:1 ratio. The use of iodine in dichloromethane was also investigated but without success (**Entry 5**).

Entry	Conditions	Ratio E/Z (determined by ^{1}H NMR)
1	1 eq NIS, hexafluoropropan-2-ol, 1 min	**1 : 2**
2	2eq NIS, MeCN, 1 day	2.4 : 1
3	2+1+1eq NIS, MeCN, 5h	**4 : 1**
4	10eq NIS, MeCN, 1h30	3.5 : 1 : 0.7 SM
5	1eq I_2, CH_2Cl_2	decomposition

Table 7: Results of iododesilylation studies.

Now that optimum reaction conditions (**Entry 3, Table 7**) for the iododesilylation reaction had been identified, Negishi coupling was performed to deliver the desired side chain in excellent yield (**Scheme 79**).[99] At this stage, the alkenes were separable and nOe studies confirmed the outcome of this key reaction.



340 **341** **342**

Reagents and conditions: (a) Me_2Zn, 5 mol% $Pd(dppf)Cl_2.CH_2Cl_2$, THF, 65 °C, 18 h (68% over 2 steps, **341/342** = 4:1).

Scheme 79: Negishi coupling.

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[99] K. C. Nicolaou, L. Nold Andrea, R. Milburn Robert, S. Schindler Corinna, P. Cole Kevin, J. Yamaguchi, *J. Am. Chem. Soc.* **2007**, *129*, 1760.

In summary, the side chain was efficiently introduced in 8 steps and 40% overall yield (89% average) using intramolecular hydrosilylation as the key reaction. At this point, studies on the real system started and so a fragment bearing the J-ring that is analogous to the triflate **331** was required. The use of RCM reaction to build the J-ring and its functionalisation would require too many steps. So, we considered using an alternative route in which epoxide cyclisation would be used to afford the J-ring (**Scheme 80**). Oxidation of primary hydroxyl group of the diol **236** using Swern conditions furnished a mixture of lactol **343** and the corresponding hydroxy aldehyde. Subsequent methylenation using standard conditions gave alkene **344** in good yield over 2 steps and a hydroxyl group was introduced by allylic oxidation to give the diol **345**.[100] During the reaction, the over-oxidised product (enone) was also obtained. In order to minimise the amount of enone produced, the reaction time was reduced and under optimum conditions only a 10% yield of the enone was obtained. Submission of alkene **345** to *N*-phenylselenophtalimide was expected to deliver the cyclised product **346** *via* a cyclic selenium ion.[101] Initially, ^{1}H NMR spectroscopic analysis showed disappearance of the alkene signals, suggesting formation of the desired cyclic product. However, after oxidation, the starting material **345** was recovered suggesting that the epoxide **348** was formed from the diol **345** rather than the required cyclised product.

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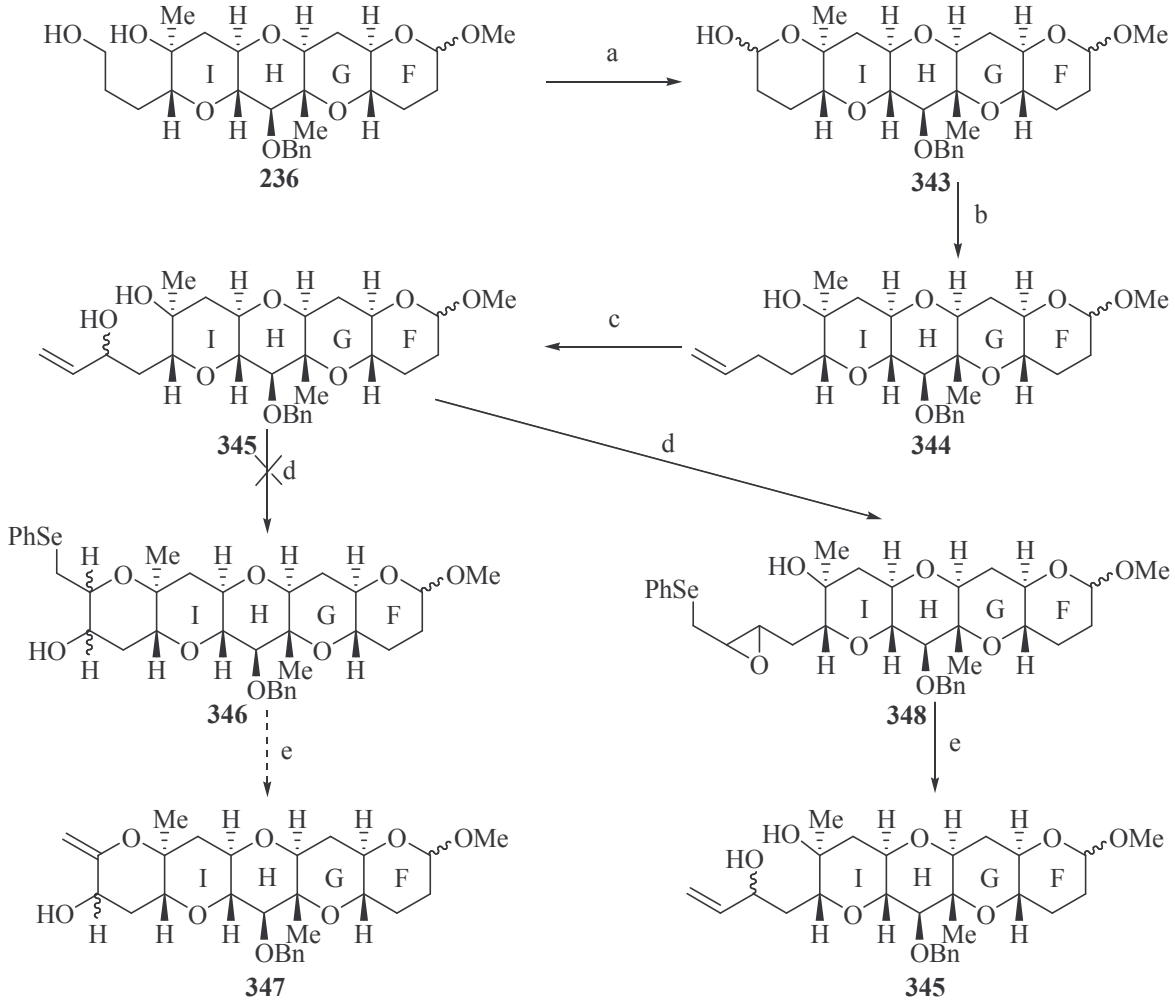
[100] J. D. Winkler, M. B. Rouse, M. F. Greaney, S. J. Harrison, Y. T. Jeon, *J. Am. Chem. Soc.* **2002**, *124*, 9726.
[101] (a) J. M. Lancelin, J. R. Pougny, P. Sinay, *Carbohydr. Res.* **1985**, *136*, 369; (b) H. M. Zhong, J.-H. Sohn, V. H. Rawal, *J. Org. Chem.* **2007**, *72*, 386.

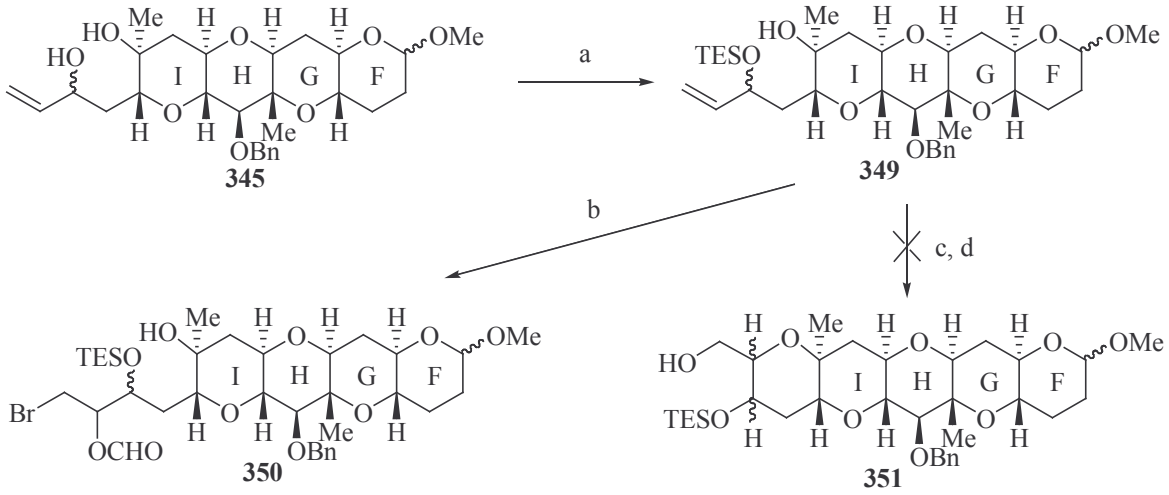


Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, –78 °C, 3.5 h (ii) Et_3N; (b) $CH_2{=}PPh_3$, benzene, rt, 20 min (74% over 2 steps); (c) SeO_2, TBHP, salicylic acid, CH_2Cl_2, reflux, 4 h; (d) NSPhSe, CSA, CH_2Cl_2, rt; (e) H_2O_2, $NaHCO_3$, 0 °C→ 40 °C, 1 h.

Scheme 80: Attempted of selenium mediated cyclisation to form the J ring.

The result above demonstrated that protection of allylic alcohol was necessary and that separation of the allylic alcohol **345** from enone by-product is desirable. Protection of the allylic alcohol as the MOM ether failed and so a TES protecting group was selected (**Scheme 81**). The strategy previously described could not be applied to this new substrate because the reaction required acidic conditions and direct cyclisation *via* a bromonium intermediate was explored instead.[102b] Treatment of the alkene **349** with NBS following a literature procedure afforded the compound **350** rather than the cyclised product, as confirmed by mass spectrometry, so cyclisation by oxymecuration was investigated

instead.[102] In this case, despite the disappearance of the NMR signals corresponding to the alkene, none of the desired product was obtained. A possible problem with the cyclisation reaction could be steric hindrance of the tertiary alcohol and in all literature examples cyclisation was affected using a secondary hydroxyl group.



Reagents and conditions: (a) TESCl, imidazole, DMAP, DMF, rt, 18 h (41% over 2 steps); (b) NBS, propylene oxide, DMF, rt, 1 day (42%); (c) (i) $Hg(OAc)_2$, THF, rt, 18 h (ii) KCl (aq.), 30 min; (d) $NaBH_4$, O_2, DMF, rt, 2 h.

Scheme 81: Alternative routes for cyclisation of the alkene **345**.

In parallel, studies were made to improve the allylic oxidation step. In principle, a terminal allylic secondary alcohol can be synthesised by rearrangement of an allylic selenoxide.[103] However, such procedures usually involve substitution of a primary allylic alcohol with a selenide followed by oxidation and rearrangement of the allylic selenoxide. In order to minimise the number of steps, cross metathesis between the alkene **287** and the allylic selenide **353** was undertaken (**Scheme 82**). The yield for the synthesis of the allylic selenide was good but the reaction was performed only once and it should be possible to achieve a higher yield. To our delight, the reaction gave the desired product in good yield with moderate *E*/*Z* selectivity (3:1 ratio). To the best of our knowledge, this is the first

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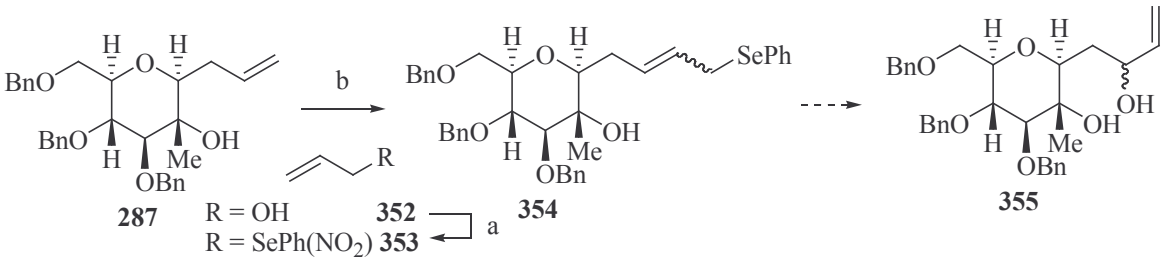
[102] (a) J. R. Pougny, M. A. M. Nassr, P. Sinay, *J. Chem. Soc., Chem. Commun.* **1981**, 375; (b) K. Hori, N. Hikage, A. Inagaki, S. Mori, K. Nomura, E. Yoshii, *J. Org. Chem.* **1992**, *57*, 2888; (c) E. G. Nolen, A. J. Kurish, J. M. Potter, L. A. Donahue, M. D. Orlando, *Org. Lett.* **2005**, *7*, 3383.
[103] B. J. Albert, A. Sivaramakrishnan, T. Naka, N. L. Czaicki, K. Koide, *J. Am. Chem. Soc.* **2007**, *129*, 2648.

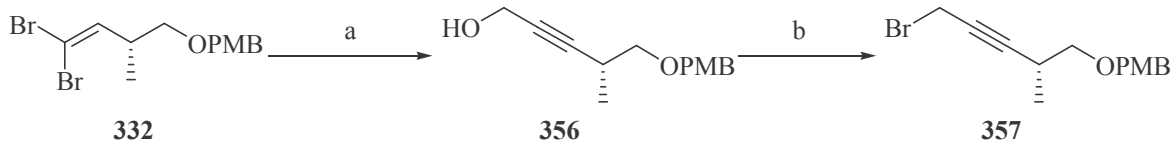
example of cross metathesis involving allyl selenide. This reaction was attempted only once and higher yields should be achievable. Subsequent oxidation of the selenides should give the desired compound in high yield based on literature precedent.[103]



Reagents and conditions: (a) *p*-$(O_2N)C_6H_4SeCN$, *n*-Bu_3P, THF, rt, 1 h (69%); (b) Catalyst **C**, toluene, 70 °C, 18 h (66%, 3:1 *E*/*Z*).

Scheme 82: Cross metathesis using an allyl selenide.

As a consequence of the difficulties experienced when attempting to form the J-ring, an alternative route using enol ether **192** (already synthesised, see paragraph 2.3.1) was explored. Opening of cyclic epoxides using simple propargylic Grignard reagents had been reported in literature.[104] In our case, a more elaborate propargylic Grignard reagent, generated from the propargylic bromide **357**, was required (**Scheme 83**). The synthesis of propargylic bromide **357** was accomplished by *in situ* quenching of the lithiated alkyne, generated from the 1,1-dibromo alkene **332**, with paraformaldehyde and subsequent substitution of propargylic alcohol.



Reagents and conditions: (a) (i) *n*-BuLi, THF, –78 °C, 1 h (ii) paraformaldehyde, –78 °C → rt, 18 h (59%); (b) CBr_4, PPh_3, K_2CO_3, ether, rt, 2 h. (42%).

Scheme 83: Synthesis of the propargylic bromide **357**.

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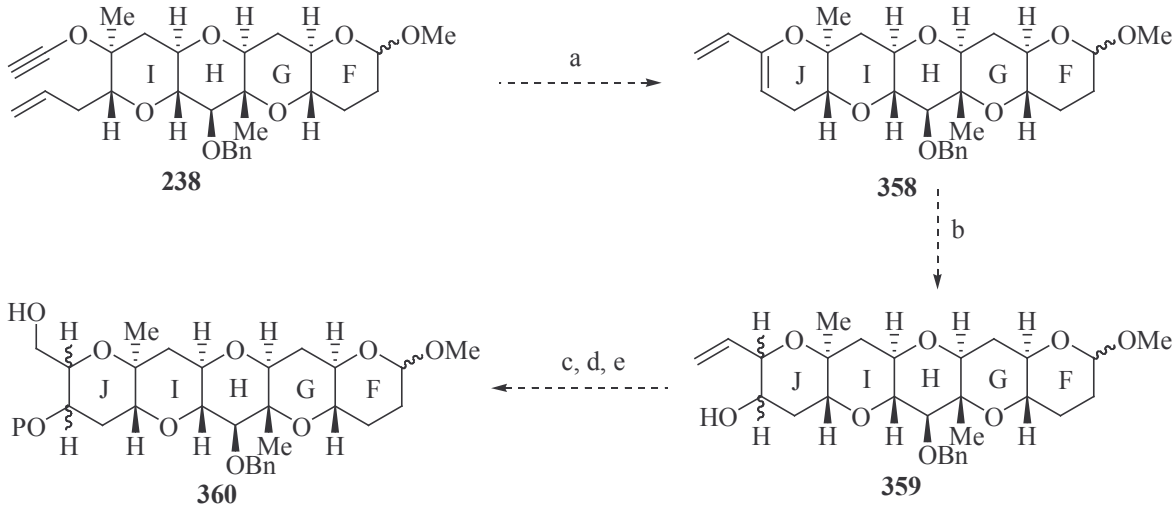
[104] M. Barry Trost, H. Rhee Young, *Org. Lett.* **2004**, *6*, 4311.

In preliminary studies, the Grignard reagent generated from the propargylic bromide **357** failed to open the epoxide. However, attempts to prepare the Grignard reagent were performed on very small scale, which might have been the source of problem. Encouragingly, the debrominated methyl alkyne was obtained suggesting at least partial formation of the Grignard reagent.

3. Conclusions

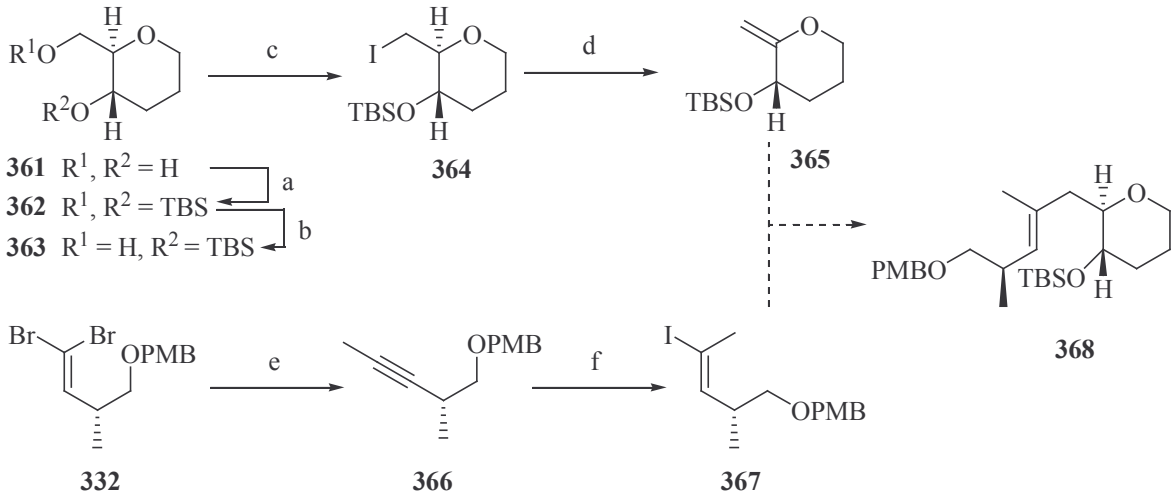
The side chain was introduced efficiently into a model system using the cyclic siloxane strategy. Future efforts will focus on applying this methodology to the complete polycyclic system. In this case, the alkynyl ether **238** will be cyclised under an atmosphere of ethene with Grubbs catalyst to deliver the diene **358** (**Scheme 84**). Selective epoxidation with DMDO and subsequent opening of epoxide with Dibal-H should deliver the alcohol **359**. Protection of this alcohol and dihydroxylation/cleavage will afford an aldehyde, which will be converted into alcohol **360**. The chemistry already developed will then be applied to obtain the required compound. If the strategy fails, further studies will be undertaken regarding formation of the Grignard reagent derived from the propargylic bromide (see § 2.3.11).



Reagents and conditions: (a) Catalyst **C**, toluene, 70 °C; (b) (i) DMDO, CH_2Cl_2, 0 °C (ii) Dibal-H, 0 °C; (c) TESCl, Imidazole, DMAP., DMF, rt; (d) OsO_4, $NaIO_4$, 2,6-lutidine, *t*-BuOH, H_2O, dioxane, rt; (e) Dibal-H, ether, 0 °C.

Scheme 84: Altenative synthesis of J ring.

Another shorter alternative route involving B-alkyl Suzuki coupling is also probably worth investigating.[105] Preliminary studies have been performed using a model system (**Scheme 85**). Both coupling partners (**365** and **367**) were synthesised using known procedures.[106,107] Sodium hydroxide and cesium carbonate were used as the bases but the reaction was not successful. Systematic studies of catalysts, solvents and bases will need to be performed to investigate this route thoroughly. An alternative to the use of borane is conceivable involving epoxide opening using $BrZnCH_2B(OCMe_2)_2$.[108]



Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 18 h (90%); (b) TFA, H_2O, 0 °C, 10 min (77%); (c) I_2, PPh_3, imidazole, benzene, rt, 45 min (93%); (d) *t*-BuOK, THF, 0 °C, 4 h (57%); (e) (i) *n*-BuLi, THF, –78 °C, 1 h (ii) MeI, –78 °C → rt, 18 h (77%); (f) (i) Cp_2ZrHCl, THF, rt, 1 day (ii) I_2, 0 °C, 30 min (66%).

Scheme 85: Suzuki coupling approach to side chain introduction.

The successful synthesis of an α,β-unsaturated lactone allowed the introduction of methyl group to F ring with a high degree of diastereoselection using substrate control. In addition, all the reactions were highly efficient and did not required purification at each stage over 4 steps. In spite of the disappointing results obtained when attempting to alkylate the

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[105] (a) M. Sasaki, H. Fuwa, M. Inoue, K. Tachibana, *Tetrahedron Lett.* **1998**, *39*, 9027; (b) M. Sasaki, M. Ishikawa, H. Fuwa, K. Tachibana, *Tetrahedron* **2002**, *58*, 1889; (c) C. Tsukano, M. Ebine, M. Sasaki, *J. Am. Chem. Soc.* **2005**, *127*, 4326.

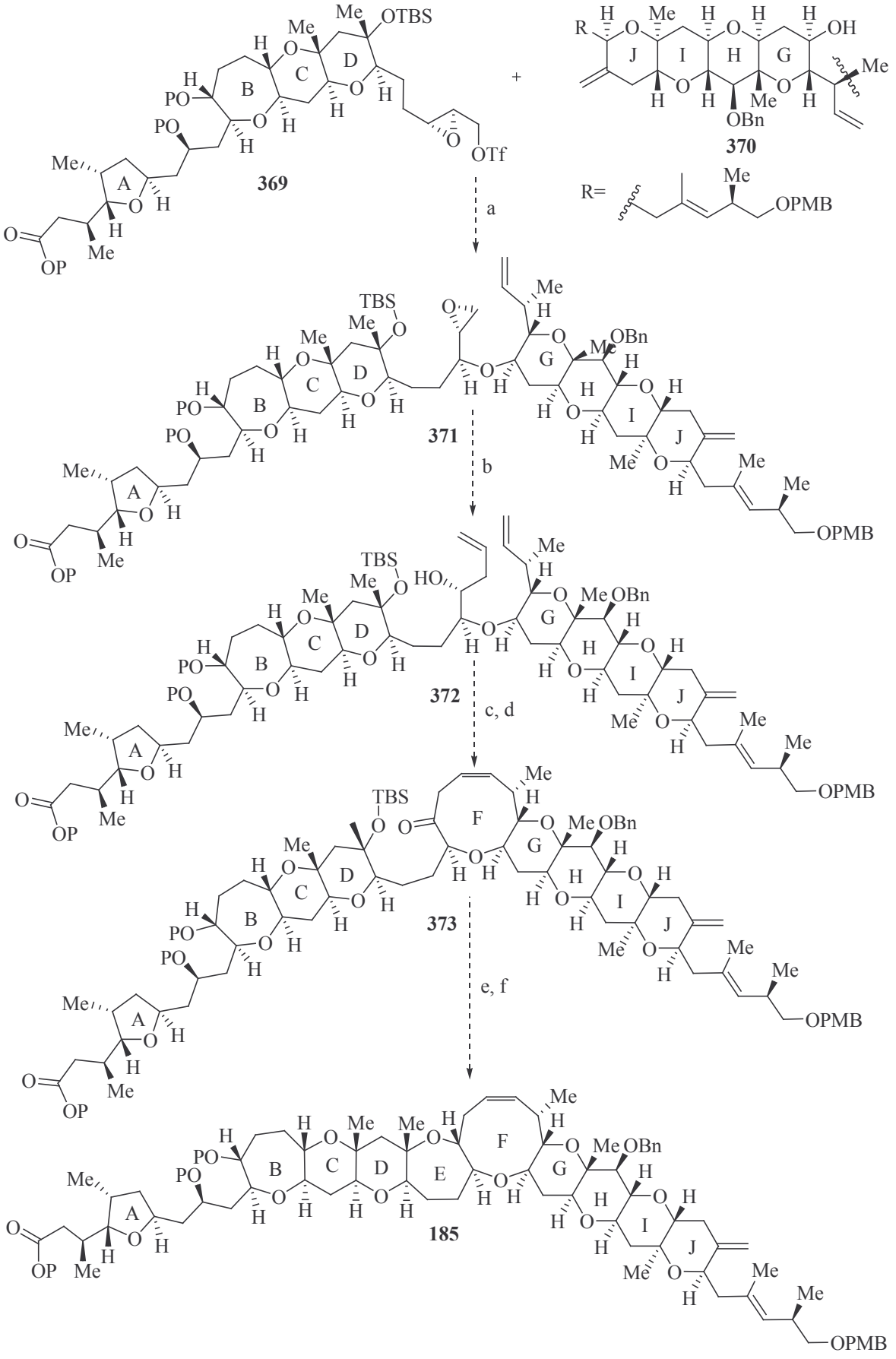
[106] K. C. Nicolaou, C. K. Hwang, B. E. Marron, S. A. DeFrees, E. A. Couladouros, Y. Abe, P. J. Carroll, J. P. Snyder, *J. Am. Chem. Soc.* **1990**, *112*, 3040.

[107] M. G. Organ, J. Wang, *J. Org. Chem.* **2003**, *68*, 5568.

[108] (a) P. Knochel, *J. Am. Chem. Soc.* **1990**, *112*, 7431; (b) M. Sakai, S. Saito, G. Kanai, A. Suzuki, N. Miyaura, *Tetrahedron* **1996**, *52*, 915.

secondary alcohol, a new route will be explored. Hoffmann and co-workers were able to alkylate a secondary alcohol with triflated epoxy alcohol in presence of boron trifluoride.[109] To apply this approach to our synthesis, the new epoxide **369** will be synthesised and then converted into alcohol **372** by reaction of the coupled product **371** with a vinyl cuprate (**Scheme 86**). A RCM reaction followed by oxidation of the alcohol will then deliver the desired ketone **373**. Deprotection of the alcohol and subsequent reductive ring closure will then give fully protected gambieric acid A (**185**).

[109] (a) A. Brandes, U. Eggert, H. M. R. Hoffmann, *Synlett* **1994**, 745; (b) H. M. R. Hoffmann, A. Brandes, *Tetrahedron* **1995**, *51*, 155; (c) S. M. Berberich, R. J. Cherney, J. Colucci, C. Courillon, L. S. Geraci, T. A. Kirkland, M. A. Marx, M. F. Schneider, S. F. Martin, *Tetrahedron* **2003**, *59*, 6819.



Reagents and conditions: (a) (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –20 °C → rt (ii) K_2CO_3, MeOH, rt; (b) $CH_2CHMgBr$, CuI, THF, rt, –78 °C; (c) Catalyst **C**, toluene, 70 °C; (d) Dess-Martin periodinane, CH_2Cl_2, 0 °C; (e) TBAF, THF, 0 °C; (f) Et_3SiH, TMSOTf, CH_2Cl_2, –10 °C.

Scheme 86: An alternative end-game synthesis of protected gambieric acid A.

4. Experimental section

4.1. General Information

4.1.1. Characterisation

Proton NMR spectra were recorded on Bruker DRX 500, DPX 400, AM 400 and AV 400 instruments at room temperature. All spectra were run in deuterochloroform unless otherwise stated, using chloroform as the internal standard (δ 7.26 and 77.0 ppm respectively). *J* values are given in Hertz. Signals in NMR spectra are described as singlets (s), doublets (d), triplets (t), quartets (q), multiplets (m), broad (br) or combination of these, which refers to the spin-spin coupling pattern observed. The multiplicity of each carbon signal was obtained using DEPT sequences and is described as C, CH, CH_2, CH_3.

IR spectra were recorded in the range 4000–600 cm^{-1} on a Perkin-Elmer 1600 series FT-IR spectrometer or JASCO FTIR 410 spectrometer with internal calibration using solution cells unless otherwise stated. Melting points were determined using a Mel-Temp II melting point apparatus. Elemental analyses were carried out on an Exeter analytical Inc. CE-440 Elemental analyzer. Mass spectra and accurate mass measurements were recorded under EI, FAB, CI and ES conditions on a FISSONS VG Autospec instrument or JEOL JMS-700 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line (λ= 589 nm) using an AA series Automatic polarimeter or a Jasco DIP-370 digital polarimeter. $[\alpha]_D$ values are given in units $10^{-1}degcm^2g^{-1}$.

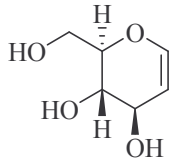
4.1.2. Purification of Reagents and Solvents

Reagents were used as supplied unless otherwise stated. Air and/or moisture sensitive reactions were performed in flame-dried glassware under nitrogen or argon. THF and toluene were distilled from sodium-benzophenone ketyl and dichloromethane was distilled

from calcium hydride. Dry benzene, methanol, Et_2O and acetonitrile were purchased from Fluka and used as supplied.

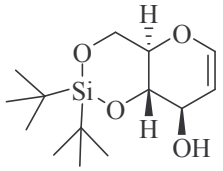
4.2. Protocols

2-Hydroxymethyl-3,4-dihydro-2*H*-pyran-3,4-diol 198 [48]



To a solution of tri-*O*-acetyl-D-glucal (29.80 g, 108.3 mmol) in MeOH (200 mL) at rt was added sodium methoxide (0.14 g, 2.60 mmol). After 16 h, the MeOH was removed *in vacuo*. Then, the crude oil was dissolved in $CHCl_3$ (200 mL). The solvent was removed under reduced pressure and the procedure was repeated three more times. The oil was dried under high vacuum for one day. The crude glucal **198** was used to the next step without further purification.

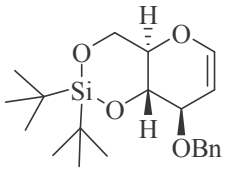
2,2-Di-*tert*-butyl-4,4a,8,8a-tetrahydro-1,3,5-trioxa-2-sila-naphthalen-8-ol 199 [48]



To a solution of glucal **198** (27.70g, 108.3 mmol) in DMF (120 mL) at –40 °C was added di-*tert*-butylsilylditrifluoromethane sulfonate (50.00g, 113.6 mmol) by a syringe pump over a period of 1.5 h. After an additional 1.5 h at –40 °C, pyridine (10 mL) was added and the reaction mixture was allowed to warm to rt. Then, the solution was diluted with ether

(400 mL), washed with water (150 mL) and brine (150 mL). The organic layer was then dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude solid was used without further purification to the next step.

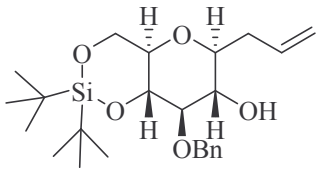
8-Benzyloxy-2,2-di-*tert*-butyl-4,4a,8,8a-tetrahydro-1,3,5-trioxa-2-sila-naphthalene 200[48]



To a solution of alcohol **199** in THF-DMF (200 mL/60 mL) at 0 °C was added in three portions, sodium hydride (6.65 g, 162 mmol, 60% dispersion in oil). After 0.5 h at 0 °C, benzyl bromide (15.5 mL, 130 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred overnight. The reaction mixture was cooled to 0 °C and carefully quenched by the addition of sat. aqueous NH_4Cl (120 mL). Then, the solution was diluted with ether (400 mL), washed with sat. aqueous NH_4Cl (200 mL) and brine (120 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave protected glucal **200** as a colourless oil (35.23 g, 86% over 3 steps). R_f = 0.45 (petrol/EtOAc, 9:1); $[\alpha]_D^{24}$ –22.4 (*c* = 1.00, $CHCl_3$); Lit.[48] $[\alpha]_D^{27}$ –19.5 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2962, 2933, 2889, 2858, 1648, 1472, 1233, 1159, 1121, 869, 826; δ_H (400 MHz, $CDCl_3$) 7.41–7.28 (5H, m, ***Ph***), 6.29 (1H, dd, *J* 6.0, 1.6, OC***H***=*C*H), 4.92 (1H, d, *J* 12.4, PhC***H***H), 4.79 (1H, d, *J* 12.4, PhCH***H***), 4.77 (1H, dd, *J* 6.0, 2.0, OCH=*C****H***), 4.23 (1H, dd, *J* 10.0, 7.2, SiOC***H***), 4.18 (1H, dd, *J* 10.4, 4.8, SiOC***H***H), 4.16 (1H, ddd, *J* 7.2, 2.0, 1.6, BnOC***H***), 4.01 (1H, dd, *J* 10.4, 10.4, SiOCH***H***), 3.83 (1H, ddd, *J* 10.4, 10.0, 4.8, $SiOCH_2C$***H***O), 1.13 (9H, s, C(C***H₃***)₃), 1.03 (9H, s, C(C***H₃***)₃); δ_c (100 MHz, $CDCl_3$) 143.9 (CH), 138.8 (C), 128.3 (CH),

127.6 (CH), 127.4 (CH), 102.3 (CH), 76.8 (CH), 76.3 (CH), 72.6 (CH), 72.0 (CH_2), 65.9 (CH_2), 27.4 (CH_3), 26.9 (CH_3), 22.7 (C), 19.8 (C); HRMS (CI+) calcd. for $C_{21}H_{33}O_4Si$, $(M+H)^+$: 377.2148, found 377.2150.

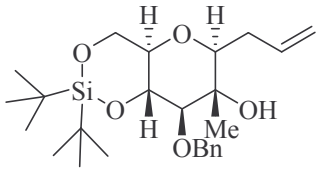
6-Allyl-8-benzyloxy-2,2-di-*tert*-butyl-hexahydro-1,3,5-trioxa-2-sila-naphthalen-7-ol 137 [48]



To a solution of fully protected glucal **200** (13.26 g, 35.21 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added DMDO (575 mL of a ~0.08 M solution in acetone, 46 mmol) was added by a dropping funnel over a period of 0.5 h. After an additional 0.5 h, the solvent was removed under reduced pressure **without exceeding 5 °C**. The crude oil was diluted with CH_2Cl_2 (100 mL) then washed with water (20 mL) and brine (20 mL). The organic layer was then dried (Na_2SO_4), filtered and the solvent removed *in vacuo* **without exceeding 5 °C**. The crude oil was dried under high-reduced pressure for 1 h. To a solution of crude epoxide in THF (250 mL) at 0 °C was added allylmagnesium chloride (35.2 mL, 70.4 mmol, 2 M in THF) by a syringe pump over a period of 15 min. After 2 h at 0 °C, the reaction was quenched by the addition of sat. aqueous NH_4Cl (120 mL) and the solution was allowed to warm to rt. Then, the reaction was diluted with ether (350 mL), washed with sat. aqueous NH_4Cl (100 mL) and brine (100 mL). The organic layer was then dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave compound **137** as a colourless oil (12.40 g, 80% over 2 steps). R_f= 0.55 (petrol/EtOAc, 9:1); $[\alpha]_D^{25}$ +2.4 (*c* = 1.0, $CHCl_3$); Lit.[48] $[\alpha]_D^{27}$ +6.9 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3464 (br), 2933, 2885, 2859, 1473, 1483, 1161, 1095,

1032, 1009, 827, 767, 652; δ_H (400 MHz, $CDCl_3$) 7.46–7.34 (5H, m, ***Ph***), 5.90 (1H, dddd, *J* 17.1, 10.1, 6.9, 6.9, CH_2=C***H***), 5.16 (1H, d, *J* 11.4, PhC***H***H), 5.13 (2H, m, C***H₂***=CH), 4.80 (1H, d, *J* 11.4, PhCH***H***), 4.22 (1H, dd, *J* 10.2, 5.0, SiOC***H***H), 3.95 (1H, dd, *J* 8.7, 8.7, SiOC***H***), 3.90 (1H, dd, *J* 10.2, 10.2, SiOCH***H***), 3.48–3.32 (4H, m, $SiOCH_2C$***H***O, BnOC***H***, CH_2=$CHCH_2C$***H***), 2.60 (2H, m, CH_2=CHC***H***H, OH), 2.27 (1H, ddd, *J* 14.7, 7.3, 6.9, CH_2=CHCH***H***), 1.14 (9H, s, C(C***H₃***)***₃***), 1.09 (9H, s, C(C***H₃***)***₃***); δ_c (100 MHz, $CDCl_3$) 138.6 (C), 134.1 (CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 117.1 (CH_2), 85.3 (CH), 79.0 (CH), 78.3 (CH), 74.7 (CH_2), 74.5 (CH), 72.4 (CH), 66.5 (CH_2), 36.0 (CH_2), 27.4 (CH_3), 27.0 (CH_3), 22.6 (C), 19.9 (C); HRMS (EI+) calcd. for $C_{24}H_{38}O_5Si$, M^+: 434.2489, found 434.2487.

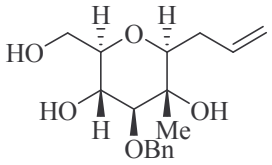
6-Allyl-8-benzyloxy-2,2-di-*tert*-butyl-7-methyl-hexahydro-1,3,5-trioxa-2-sila-naphthalen-7-ol 196 [48]



To a solution of oxalyl chloride (8.8 mL, 0.10 mol) in CH_2Cl_2 (300 mL) at –78 °C was slowly added DMSO (15.0 mL, 0.211 mol). After 0.5 h at –78 °C, alcohol **137** (24.79 g, 57.00 mmol) in CH_2Cl_2 (200 mL) was added by cannula and the reaction mixture was stirred at –78 °C for 3 h. Then, Et_3N (40.0 mL, 0.285 mol) was added and the reaction mixture was allowed to warm to rt. The solution was diluted with CH_2Cl_2 (300 mL) and washed with water (400 mL). The aqueous layer was further extracted with CH_2Cl_2 (300 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) filtered and the solvent removed *in vacuo*.

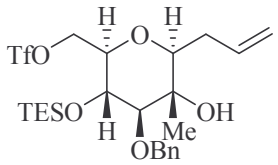
The crude oil was dried under high vacuum for 1 h. To a solution of ketone in toluene (1 L) at –78 °C was slowly added methyl lithium (72.0 mL, 0.114 mol, 1.6 M in ether) by a syringe pump over a period of 0.5 h. After an additional 0.5 h, the reaction was carefully quenched by the addition of MeOH (50 mL). A solution of sat. aqueous NH_4Cl (300 mL) was added and washed several times with ether (3 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over ($MgSO_4$) filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 95:5) gave compound **196** as a colourless oil (20.19 g, 79% over 2 steps). R_f = 0.39 (petrol/EtOAc, 95:5); $[\alpha]_D^{24}$ –5.9 (*c* = 1.0, $CHCl_3$); Lit.[48] $[\alpha]_D^{27}$ –3.3 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3565 (br), 2962, 2933, 2891, 2858, 1473, 1109, 1089, 826, 652; δ_H (400 MHz, $CDCl_3$) 7.41–7.28 (5H, m, ***Ph***), 5.87 (1H, dddd, *J* 17.0, 10.1, 7.2, 6.5, CH_2=C***H***), 5.11 (1H, d, *J* 11.7, PhC***H***H), 5.10 (1H, dddd, *J* 17.0, 3.2, 1.4, 1.4, C***H***H=CH), 5.06−5.02 (1H, m, CH***H***=CH), 4.74 (1H, d, *J* 11.7, PhCH***H***), 4.18 (1H, dd, *J* 10.0, 4.8, SiOC***H***H), 3.89−3.84 (2H, m, SiOCH***H***, SiOC***H***), 3.43 (1H, ddd, *J* 10.2, 9.5, 4.9, $SiOCH_2C$***H***O), 3.35 (1H, d, *J* 9.2, BnOC***H***), 3.29 (1H, dd, *J* 10.0, 2.8, CH_2=$CHCH_2C$***H***), 2.42 (1H, ddddd, *J* 14.6, 7.2, 2.8, 1.4, 1.4, CH_2=CHCH***H***), 2.13 (1H, ddddd, *J* 14.6, 10.0, 6.3, 1.4, 1.4, CH_2=CHCH***H***), 1.18 (3H, s, Me), 1.08 (9H, s, C(C***H₃***)₃), 1.04 (9H, s, C(C***H₃***)₃); δ_c (100 MHz, $CDCl_3$) 139.0 (C), 135.6 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 116.5 (CH_2), 87.7 (CH), 82.2 (CH), 77.7 (CH), 75.8 (CH), 75.1 (CH_2), 73.8 (C), 66.8 (CH_2), 32.7 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 22.7 (C), 19.9 (C), 16.4 (CH_3); HRMS (EI+) calcd. for $C_{25}H_{40}O_5Si$, M^+: 448.2645, found 448.2648.

2-Allyl-4-benzyloxy-6-hydroxymethyl-3-methyl-tetrahydro-pyran-3,5-diol 201 [48]



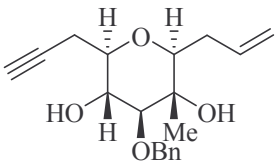
To a solution of alcohol **196** (20.17 g, 44.95 mmol) in THF (350 mL) at 0 °C was added $(HF)_3.Et_3N$ (18.0 mL, 113 mmol). After 18 h at rt, the solution was cooled to 0 °C and the reaction was quenched by the careful addition of sat. aqueous $NaHCO_3$ (100 mL). The aqueous layer was washed several times with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), and filtered and the solvent was then removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 7:3) gave compound **139** as a colourless oil (13.42 g, 97%). R_f = 0.06 (petrol/EtOAc, 9:1); $[\alpha]_D^{24}$ –26.0 (*c* = 1.00, $CHCl_3$); Lit.[48] $[\alpha]_D^{27}$ –30.7 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3409 (br), 2869, 1369, 1103, 1037; δ_H (400 MHz, $CDCl_3$) 7.40–7.28 (5H, m, Ph), 5.90 (1H, dddd, *J* 16.6, 10.2, 7.3, 6.2, CH_2=C***H***), 5.12–5.07 (2H, m, C***H***$_2$=CH), 4.93 (1H, d, *J* 11.9, PhC***H***H), 4.83 (1H, d, *J* 11.9, PhCH***H***), 3.85 (1H, dd, *J* 11.6, 3.5, HOC***H***H), 3.71 (1H, dd, *J* 11.6, 5.2, HOCH***H***), 3.49 (1H, dd, *J* 9.4, 9.3, HOC***H***), 3.35 (1H, d, *J* 9.3, BnOC***H***), 3.35–3.30 (1H, m, $HOCH_2C$***H***O), 3.29 (1H, dd, *J* 9.5, 3.2, CH_2CHCH_2C***H***), 2.44–2.41 (1H, m, CH_2=CHC***H***H), 2.22 (3H, brs, O***H***), 2.18 (1H, m, CH_2=CHCH***H***), 1.21 (3H, s, Me); δ_c (100 MHz, $CDCl_3$) 138.6 (C), 135.5 (CH), 128.7 (CH), 128.0 (CH), 127.7 (CH), 116.7 (CH_2), 88.9 (CH), 81.6 (CH), 79.4 (CH), 75.5 (CH_2), 74.9 (C), 70.1 (CH), 62.9 (CH_2), 32.8 (CH_2), 16.0 (CH_3); HRMS (EI+) calcd. for $C_{17}H_{24}O_5$, M^+: 308.1624, found 308.1620.

Trifluoro-methanesulfonic acid 6-allyl-4-benzyloxy-5-hydroxy-5-methyl-3-triethylsilanyloxy-tetrahydro-pyran-2-ylmethyl ester 202 [48]



To a solution of triol **201** (13.42 g, 43.54 mmol) in CH_2Cl_2 (350 mL) at –78 °C was added 2,6-lutidine (22.0 mL, 191 mmol) followed by Tf_2O (7.7 mL, 46 mmol). After 0.5 h at –78 °C, TfOTES (11.0 mL, 47.9 mmol) was added and stirred at –78 °C for 0.5 h.. The reaction mixture was then diluted with EtOAc (100 mL) and allowed to warm to rt. The solution was diluted with further EtOAc (300 mL) and the mixture was washed with sat. aqueous $NaHCO_3$ (200 mL). The aqueous layer was extracted with EtOAc (200 mL) and the combined organic layers were washed with sat. aqueous $CuSO_4$ (3 × 500 mL), brine (200 mL), dried ($MgSO_4$) and filtered and the solvent was then removed *in vacuo* to give an oil. The crude product was used **immediately** to the next step without further purification.

2-Allyl-4-benzyloxy-3-methyl-6-prop-2-ynyl-tetrahydro-pyran-3,5-diol 203 [48]

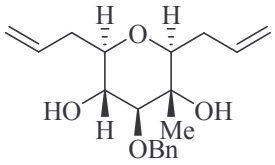


To a solution of TMS-acetylene (23.0 mL, 167 mmol) in THF (400 mL) at –78 °C was added *n*-BuLi (68 mL of a 2.5 M solution in hexane, 0.17 mol). After 0.5 h at 0 °C, the triflate **202** (~43 mmol) in THF (300 mL) was added by cannula followed by the addition of DMPU (66 mL). After 1 h at 0 °C, EtOAc (100 mL) was added and the reaction mixture was allowed to warm to rt. The solution was diluted with Et_2O (300 mL), washed with sat.

aqueous NH_4Cl (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*.

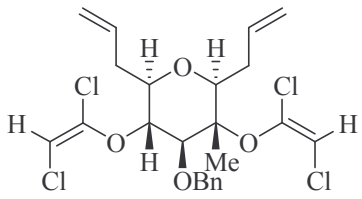
The protected acetylene was dissolved in THF (500 mL) at 0 °C and TBAF (152 mL, 152.00 mmol, 1 M in THF) was added. After 18 h at rt, the solution was cooled to 0 °C and the reaction was quenched by the careful addition of sat. aqueous NH_4Cl (100 mL). The reaction mixture was diluted with EtOAc (400 mL), washed with brine (200 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 7:3) gave compound **203** as a pale yellow oil (10.58 g, 77% over 3 steps), which need to be used **immediately** to the next step. R_f = 0.50 (petrol/EtOAc, 7:3); $[\alpha]_D^{25}$ –34.7 (*c* = 1.00, $CHCl_3$); Lit.[48] $[\alpha]_D^{27}$ –27.5 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3542 (br), 3442 (br), 3296 (br), 2919, 2856, 1103, 1029; δ_H (400 MHz, $CDCl_3$) 7.39–7.30 (5H, m, ***Ph***), 5.95 (1H, m, CH_2=C***H***), 5.14 (1H, m, C***H***H=CH), 5.06 (1H, m, CH***H***=CH), 4.94 (1H, d, *J* 11.8, PhC***H***H), 4.82 (1H, d, *J* 11.8, PhCH***H***), 3.51 (1H, ddd, *J* 9.3, 9.3, 2.7, HOC***H***), 3.35 (1H, ddd, *J* 9.3, 5.9, 3.8, HC≡CCH_2C***H***O), 3.34 (1H, d, *J* 9.3, BnOC***H***), 3.26 (1H, dd, *J* 9.3, 3.5, OC***H***COHMe), 2.65 (1H, ddd, *J* 17.1, 3.8, 2.7, HC≡CC***H***H), 2.53(1H, ddd, *J* 17.1, 5.9, 2.7, HC≡CCH***H***), 2.41 (1H, ddddd, *J* 14.6, 8.0, 3.5, 1.0, 1.0, CH_2=CHC***H***H), 2.32 (1H, d, *J* 2.7, ***H***OCH), 2.25 (1H, ddddd, *J* 14.6, 9.3, 5.6, 1.7, 1.7, CH_2=CHCH***H***), 2.01 (1H, dd, *J* 2.7, 2.7, ***H***C≡C), 1.72 (1H, s, ***H***OMeC), 1.23 (3H, s, Me); δ_c (100 MHz, $CDCl_3$) 138.6 (C), 135.7 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 116.5 (CH_2), 88.6 (CH), 81.8 (CH), 80.3 (C), 77.3 (CH), 75.5 (CH_2), 75.0 (C), 72.2 (CH), 70.1 (CH), 32.8 (CH_2), 22.2 (CH_2), 16.1 (CH_3); HRMS (EI+) calcd. for $C_{19}H_{24}O_4$, M^+: 316.1675, found 316.1678.

2,6-Diallyl-4-benzyloxy-3-methyl-tetrahydro-pyran-3,5-diol 204 [48]



To a solution of acetylene **203** (10.58 g, 33.44 mmol) in EtOAc (230 mL) were added Lindlar's catalyst (272 mg) and quinoline (630 μL). The reaction vessel was purged of air and filled with hydrogen, then stirred at rt for 3 h. Then, the hydrogen was purged from the reaction vessel and the solution was filtered through celite®, which was washed several times with EtOAc (3 × 100 mL). The solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 75:25) gave compound **204** as an oil (10.44 g, 98%). R_f = 0.56 (petrol/EtOAc, 7:3); $[\alpha]_D^{24}$ –30.4 (*c* =1.00, $CHCl_3$); Lit.[48] $[\alpha]_D^{27}$ –31.9 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3534 (br), 3450 (br), 2980, 2908, 1643, 1455, 1361, 1102, 1028, 997, 915, 736, 700, 439; δ_H (400 MHz, $CDCl_3$) 7.39–7.30 (5H, m, ***Ph***), 5.91 (2H, m, 2 × CH_2=C***H***), 5.14–5.12 (2H, m, 2 × CH=C***H***H), 5.08–5.04 (2H, m, 2 × CH=CH***H***), 4.93 (1H, d, *J* 12.0, PhC***H***H), 4.80 (1H, d, *J* 12.0, PhCH***H***), 3.31–3.26 (3H, m, HOC***H,*** CH_2=CHCH_2C***H***O, BnOC***H***), 3.21 (1H, dd, *J* 9.6, 3.2, Me(OH)COC***H***), 2.58–2.52 (1H, m, CH_2=CHC***H***H), 2.42–2.36 (1H, m, CH_2=CHCH***H***), 2.28–2.16 (2H, m, CH_2=CHC***H*****$_2$**), 2.12 (1H, s, O***H***), 1.64 (1H, s, O***H***), 1.20 (3H, s, Me); δ_c (100 MHz, $CDCl_3$) 138.7 (C), 135.8 (CH), 134.6 (CH), 128.7 (CH), 128.0 (CH), 127.8 (CH), 116.9 (CH_2), 116.5 (CH_2), 89.0 (CH), 81.7 (CH), 79.3 (CH), 75.5 (C), 75.2 (CH_2), 72.9 (CH), 36.3 (CH_2), 32.9 (CH_2), 16.2 (CH_3). HRMS (EI+) calcd. for $C_{19}H_{26}O_4$, M^+: 318.1831, found 318.1827.

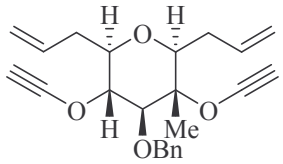
2,6-Diallyl-4-benzyloxy-3,5-bis-(1,2-dichloro-vinyloxy)-3-methyl-tetrahydro-pyran 205 [48]



To a washed suspension of KH (28.10 g, 210.8 mmol, 30% dispersion in oil) in THF (800 mL) at 0 °C was added diol **204** (16.80 g, 52.76 mmol) in THF (200 mL) by cannula. After 0.5 h at 0 °C, the solution was allowed to warm at rt. After 0.5 h at rt, the reaction was cooled to 0 °C. Trichloroethylene (10.4 mL, 116 mmol) was slowly added, stirred at 0 °C for 1 h and finally 1 h at rt. The reaction mixture was cooled to 0 °C, quenched by the careful addition of MeOH (50 mL) and allowed to warm to rt. The solution was diluted with Et_2O (500 mL) and washed with water (300 mL). The aqueous layer was further extracted with Et_2O (500 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$) then filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/Et_2O, 9:1) gave compound **205** as a pale yellow semi-solid (20.95 g, 78%). R_f = 0.57 (petrol/Et_2O, 95:5); $[\alpha]_D^{24}$ –7.2 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3444 (br), 3105, 2868, 1621, 1455, 1275, 1088; δ_H (400 MHz, $CDCl_3$) 7.39–7.28 (5H, m, ***Ph***), 5.95–5.83 (2H, m, 2 × CH_2=C***H***), 5.64 (1H, s, CCl***H***=C), 5.37 (1H, s, CCl***H***=C), 5.17–5.08 (4H, m, 2 × C***H₂***=CH), 4.80 (2H, s, PhC***H₂***), 4.21 (1H, dd, *J* 9.6, 8.8, CClH=CClOC***H***), 4.08 (1H, d, *J* 8.8, BnOC***H***), 3.65 (1H, dd**,** *J* 10.2, 1.6, CClH=CClOCMeC***H***O), 3.57 (1H, ddd, *J* 9.7, 7.9, 2.9, CH_2=CHCH_2C***H***O), 2.56–2.49 (2H, m, 2 × CH_2=CHC***H***H), 2.27–2.17 (2H, m, 2 × CH_2=CHCH***H***), 1.55 (3H, s, Me); δ_c (100 MHz, $CDCl_3$) 138.1 (C), 138.2 (C), 135.0 (CH), 133.2 (CH), 128.0 (CH), 127.4 (CH), 127.3 (CH), 118.0 (CH_2), 116.9 (CH_2), 101.3 (CH), 95.8 (CH), 90.1 (C), 84.0 (CH), 81.2

(CH), 80.4 (CH), 77.7 (CH), 74.4 (CH_2), 35.5 (CH_2), 32.9 (CH_2), 14.2 (CH_3); HRMS Mass not found.

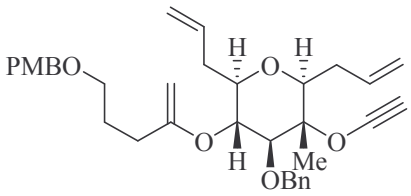
2,6-Diallyl-4-benzyloxy-3,5-bis-ethynyloxy-3-methyl-tetrahydro-pyran 206 [48]



To a solution of *bis*-dichloroenol ether **205** (20.95 g, 41.22 mmol) in Et_2O (500 mL) at –78 °C was added dropwise *n*-BuLi (61.0 mL of a 2.7 M solution in hexane, 165 mmol,). After 1 hour at –78 °C, the reaction mixture was warmed to –25 °C over a period of 4 h. The reaction was quenched by the addition of MeOH (50 mL) and allowed to warm to rt. Sat. aqueous NH_4Cl (200 mL) was added and was extracted several with ether (3 × 200 mL). The combined organic layers was washed with brine (200 mL), dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/Et_2O/Et_3N, 95:5:5) gave compound **206** as a colourless oil (13.45 g, 89%). R_f = 0.35 (petrol/Et_2O, 95:5); $[\alpha]_D^{25}$ +11.6 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3316, 3077, 2946, 2916, 2869, 2153, 1102; δ_H (400 MHz, $CDCl_3$) 7.49–7.29 (5H, m, ***Ph***), 5.94–5.82 (2H, m, 2 × CH_2=C***H***), 5.22–5.09 (4H, m, 2 × C***H₂***=CH), 4.93 (1H, d, *J* 10.8, PhC***H***H), 4.88 (1H, d, *J* 10.8, PhCH***H***), 4.24 (1H, d, *J* 9.2, BnOC***H***), 3.76 (1H, dd, *J* 10.0, 9.2, HC≡COC***H***), 3.59 (1H, dd**,** *J* 10.4, 2.4, HC≡COMeCC***H***O), 3.55 (1H, ddd, *J* 10.0, 7.2, 3.2, CH_2=CHCH_2C***H***O), 2.67–2.61 (1H, m, CH_2=CHC***H***HCHOC≡CH), 2.43 (1H, dd, *J* 14.7, 7.4, CH_2=CHC***H***HCHCMeOC≡CH), 2.33 (1H, ddd, *J* 14.7, 7.3, 7.3, CH_2=CHCH***H***CHOC≡C***H***), 2.24–2.17 (1H, m, CH_2=CHCH***H***CHCMeOC≡CH), 1.72 (1H, s, ***H***C≡C), 1.66 (1H, s, ***H***C≡C), 1.35 (3H, s, Me); δ_c (100 MHz, $CDCl_3$) 138.0 (C), 134.3 (CH), 132.8 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 118.4 (CH_2), 117.3 (CH_2), 88.9

(C), 88.6 (C), 87.6 (CH), 85.6 (C), 80.4 (CH), 78.7 (CH), 76.8 (CH), 75.1 (CH_2), 35.5 (CH_2), 32.3 (CH_2), 31.5 (C), 28.2 (C), 12.7 (CH_3).(2 × H**C**≡C appeared as C) HRMS (CI+) calcd. for $C_{23}H_{26}O_4$, M^+: 367.1909, found 367.1908.

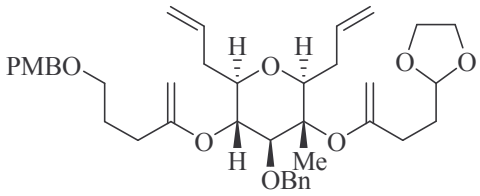
2,6-Diallyl-4-benzyloxy-3-ethynyloxy-5-[4-(4-methoxy-benzyloxy)-1-methylene-butoxy]-3-methyl-tetrahydro-pyran 207 [48]



CuBr (7.90 g, 55.1 mmol) and LiBr (4.78 g, 55.1 mmol) were dried 18 h at 70 °C. THF (170 mL) was added (exothermic) and stirred until complete dissolution. Then, the reaction mixture was cooled to –95 °C and $PMBO(CH_2)_3MgBr$ (100 mL, 44.04 mmol) [Grignard was prepared using 14.26 g of bromide and 1.47 g of magnesium] cooled to –78 °C was added dropwise by an insulated cannula. Then, the cuprate was added by an insulated cannula into a stirred solution of *bis*-alkynyl ether **206** (13.45 g, 36.70 mmol) in THF (100 mL) at –95 °C. After 1 h, the reaction was warmed to –78 °C and stirred for 2 h. Then, the reaction was quenched by the addition of 10% aqueous NH_4OH (200 mL) and the reaction mixture was allowed to warm to rt. A 10% aqueous solution of NH_4OH (100 mL) was added and the aqueous layer was extracted several times with ether (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered and then the solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc/Et_3N, 90:10:1) gave compound **207** as a colourless oil (16.95 g, 84%). R_f = 0.37 (petrol/EtOAc, 9:1); $[\alpha]_D^{25}$ +21.6 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3312, 2950, 2857, 2139, 1613, 1247, 1100, 1035; δ_H (400 MHz, $CDCl_3$) 7.41–7.27 (7H, m, ***Ph***, ***Ph***OMe), 6.92–6.90 (2H, m, ***Ph***OMe), 5.99–5.83 (2H, m, 2 × CH_2=C***H***), 5.21–5.09 (4H,

m, 2 × CH=C***H₂***), 4.83 (1H, d, *J* 10.8, PhC***H***H), 4.73 (1H, d, *J* 10.8, PhCH***H***), 4.73 (2H, s, MeOPhC***H₂***), 4.20 (1H, d, *J* 2.4, C***H***H=CO), 4.03 (1H, d, *J* 2.4, CH***H***=CO), 4.01 (1H, d, *J* 9.2, BnOC***H***), 3.93 (1H, dd, *J* 9.2, 9.2, CH_2=COC***H***), 3.83 (3H, s, ***Me***O), 3.63 (1H, dd**,** *J* 10.0, 2.4, HC≡COCMeC***H***O), 3.48 (2H, t**,** *J* 6.4, PMBOC***H₂***), 3.88 (1H, ddd, *J* 9.2, 8.8, 2.8, CH_2=CHCH_2C***H***O), 2.49–2.40 (2H, m, 2 × CH_2=CHC***H***H), 2.29–2.13 (4H, m, 2 ×CH_2=CHC***H***H, PMBO(CH_2)$_2$C***H₂***), 1.88–1.81 (2H, m, PMBOCH_2C***H₂***), 1.70 (1H, s, ***H***C≡C), 1.40 (3H, s, Me); δ_c (100 MHz, $CDCl_3$) 161.5 (C), 159.1 (C), 138.5 (C), 134.7 (CH), 134.0 (CH), 130.6 (C), 129.2 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 117.2 (CH_2), 117.0 (CH_2), 113.7 (CH), 88.6 (C), 86.0 (C), 83.5 (CH_2), 82.9 (CH), 79.0 (CH), 78.7 (CH), 77.4 (CH), 74.8 (CH_2), 72.6 (CH_2), 69.3 (CH_2), 55.2 (CH_3), 35.9 (CH_2), 32.5 (CH_2), 32.1 (CH_2), 30.9 (C), 27.5 (CH_2), 12.8 (CH_3). (H**C**≡C appeared as C) HRMS (ES+) calcd. for $C_{34}H_{42}O_6Na$, $(M+Na)^+$: 367.1909, found 569.2844.

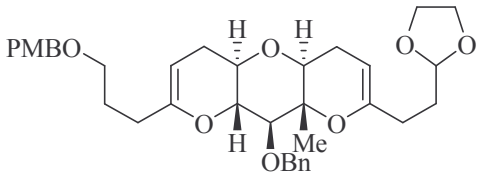
2,6-Diallyl-4-benzyloxy-3-(3-[1,3]dioxolan-2-yl-1-methylene-propoxy)-5-[4-(4-methoxy-benzyloxy)-1-methylene-butoxy]-3-methyl-tetrahydro-pyran 195 [48]



CuCN (13.88 g, 155.0 mmol) and LiCl (13.14 g, 310.0 mmol) were dried 18 h at 70 °C. THF (500 mL) was added and stirred until complete dissolution. The reaction mixture was cooled to –78 °C and the $(OCH_2CH_2O)CH(CH_2)_2MgBr$ (250 mL, 155.00 mmol) [Grignard was prepared using 19.6 mL of bromide and 4.44 g of magnesium] cooled to –78 °C was added dropwise by an insulated cannula. Then, the cuprate was stirred at –40 °C for 10 min and cooled to –78 °C. Compound **207** (16.95 g, 31.00 mmol) in THF (200 mL) cooled to –78 °C was added by an insulated cannula into the cuprate. After 3 h at –78 °C, the reaction

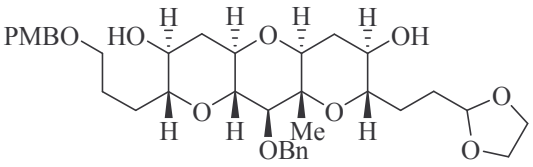
was stirred at –40 °C for 1 h. The reaction was quenched by the addition of 10% aqueous NH_4OH (100 mL) and the reaction was allowed to warm to rt. 10% aqueous NH_4OH (400 mL) was added and the mixture was extracted several with ether (3 × 400 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc/Et_3N, 50:50:1) gave compound **195** as a colourless oil (17.06 g, 85%). R_f = 0.46 (petrol/Et_2O, 1:1); $[\alpha]_D^{24}$ +1.1 (*c* = 1.0, $CHCl_3$); Lit.[48] $[\alpha]_D^{26}$ +4.1 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2952, 2857, 1642, 1613, 1512, 1247, 1101, 1035; δ_H (400 MHz, $CDCl_3$) 7.33–7.24 (7H, m, ***Ph***, MeO***Ph***), 6.89–6.87 (2H, m, MeO***Ph***), 5.96–5.83 (2H, m, 2 × CH_2=C***H***), 5.13–5.04 (4H, m, 2 × CH=C***H₂***), 4.85 (1H, t, *J* 4.7, (OCH_2CH_2O)C***H***), 4.68 (1H, d, *J* 10.8, PhC***H***H), 4.62 (1H, d, *J* 10.8, PhCH***H***), 4.40 (2H, s, MeOPhC***H₂***), 4.33 (1H, d, *J* 1.3, C***H***H=CO), 4.19 (1H, d, *J* 2.1, C***H***H=CO), 4.16 (1H, d, *J* 1.3, CH***H***=CO), 4.00 (1H, d, *J* 2.1, CH***H***=CO), 3.86–3.82 (4H, m, OC***H₂***CH_2O, BnOC***H***, BnOCHC***H***), 3.86–3.82 (2H, m, OCH_2C***H₂***O), 3.81 (3H, s, ***Me***O), 3.66 (1H, dd**,** *J* 10.1, 1.8, CH_2=COCMeC***H***O), 3.44 (2H, t, *J* 6.4, PMBOC***H₂***), 3.88 (1H, ddd, *J* 8.1, 8.1, 1.7, CH_2=$CHCH_2$C***H***O), 2.42–2.44 (2H, m, 2 × CH_2=CHC***H***H), 2.22–2.07 (6H, m), 1.91–1.77 (4H, m), 1.37 (3H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 161.5 (C), 159.1 (C), 157.9 (C), 138.8 (C), 138.5 (CH), 134.5 (CH), 130.6 (C), 129.2 (CH), 128.0 (CH), 127.7 (CH), 127.1 (CH), 117.0 (CH_2), 116.2 (CH_2), 113.7 (CH), 103.9 (CH), 90.5 (CH_2), 84.0 (CH), 83.3 (CH_2), 82.9 (C), 80.2 (CH), 79.2 (CH), 77.8 (CH), 74.3 (CH_2), 72.6 (CH_2), 69.4 (2 × CH_2), 64.9 (CH_2), 55.2 (CH_3), 48.0 (CH_2), 32.6 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 31.5 (CH_2), 27.4 (CH_2), 14.4 (CH_3); HRMS (ES+) calcd. for $C_{39}H_{52}O_8Na$, $(M+Na)^+$: 671.3560, found 671.3514.

9-Benzyloxy-7-(2-[1,3]dioxolan-2-yl-ethyl)-2-[3-(4-methoxy-benzyloxy)-propyl]-8a-methyl-4a,5,8a,9,9a,10a-hexahydro-4H-1,8,10-trioxa-anthracene 208 [48]



To a solution of *bis*-enolether **195** (8.53 g, 13.2 mmol) in toluene (2 L) at 70 °C was added the Grubbs second generation catalyst (440 mg, 0.490 mmol). The reaction was stirred for 18 h at 70 °C. Then, the solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 3:2; silica was treated with 2% Et_3N) gave compound **208** as a colourless oil (7.79 g, 86%). R_f = 0.26 (petrol/Et_2O, 1:1); $[\alpha]_D^{24}$ –26.5 (*c* = 1.00, $CHCl_3$); Lit.[48] $[\alpha]_D^{27}$ –29.6 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2855, 1675, 1512, 1247, 1108, 1072, 1052, 1036; δ_H (400 MHz, $CDCl_3$) 7.47–7.25 (7H, m, ***Ph***, MeO***Ph***), 6.87 (2H, d, *J* 8.7, MeO***Ph***), 4.95 (1H, d, *J* 12.1, PhC***H***H), 4.93 (1H, t, *J* 4.8, (OCH_2CH_2O)C***H***), 4.87 (1H, d, *J* 12.1, PhCH***H***), 4.49 (1H, d, *J* 3.7, C***H***=CO), 4.49–4.27 (3H, m, MeOPhC***H₂***, C***H***=CO), 3.98–3.95 (2H, m, OC***H₂***CH_2O), 3.88–3.82 (2H, m, OCH_2C***H₂***O), 3.79 (3H, s, ***Me***O), 3.61 (1H, d**,** *J* 9.0, BnOC***H***), 3.55–3.42 (5H, m), 2.30–1.99 (8H, m), 1.93–1.77 (4H, m) 1.23 (3H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 158.9 (C), 153.6 (C), 150.4 (C), 139.0 (C), 130.6 (C), 129.0 (CH), 128.0 (CH), 127.6 (CH), 127.2 (CH), 113.6 (CH), 103.8 (CH), 93.1 (CH), 92.4 (CH), 83.4 (CH), 78.2 (C), 77.8 (CH), 74.9 (CH), 74.3 (CH_2), 73.8 (CH), 72.3 (CH_2), 69.1 (CH_2), 64.7 (2 ×CH_2), 55.1 (CH_3), 31.4 (CH_2), 30.0 (CH_2), 28.3 (CH_2), 27.5 (CH_2), 26.9 (CH_2), 23.6 (CH_2), 10.7 (CH_3); HRMS (EI+) calcd. for $C_{35}H_{44}O_8$, M^+: 592.3036, found 592.3040.

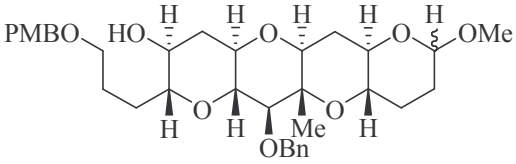
9-Benzyloxy-7-(2-[1,3]dioxolan-2-yl-ethyl)-2-[3-(4-methoxy-benzyloxy)-propyl]-8a-methyl-decahydro-1,8,10-trioxa-anthracene-3,6-diol 194 [48]



To a solution of borane (50 mL, 50 mmol, 1 M in THF) in THF (250 mL) at 0 °C was added 2,3-dimethyl butene (50 mL, 50 mmol, 1 M in THF). The reaction was stirred for 1 h at 0 °C. The tricyclic compound **208** (6.56 g, 11.1 mmol) in THF (100 mL) was added by cannula and the reaction mixture was stirred at rt for 24 h. The reaction was cooled to 0 °C and carefully quenched by the addition of pH 7 buffer (200 mL). $NaBO_3$ (31.0 g, 200 mmol) was added and the reaction was vigorously stirred at rt for 18 h. H_2O (400 mL) was added and the mixture was extracted several times with Et_2O (3 × 300 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (EtOAc/MeOH/Et_3N, 100:2:1) gave the diol **194** as a white foam (4.87 g, 70%). R_f = 0.33 (EtOAc); $[\alpha]_D^{23}$ –15.2 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3695, 3617, 2956, 2882, 2361, 1610, 1455, 1360, 1089; δ_H (400 MHz, $CDCl_3$) 7.41–7.22 (7H, m, ***Ph***, MeO***Ph***), 6.87 (2H, d, *J* 8.7, MeO***Ph***), 4.93 (1H, t, *J* 4.3, ([OCH_2CH_2O]C***H***), 4.84 (1H, d, *J* 12.1, PhC***H***H), 4.75 (1H, d, *J* 12.1, PhCH***H***), 4.43 (2H, s, MeOPhC***H₂***), 3.99–3.93 (2H, m, OC***H₂***CH_2O), 3.87–3.83 (2H, m, OCH_2C***H₂***O), 3.80 (3H, s, ***Me***O), 3.51 (2H, t, *J* 6.0, PMBOC***H₂***), 3.44–3.33 (3H, m), 3.34 (1H, d**,** *J* 8.8, BnOC***H***), 3.19–3.06 (4H, m), 2.40–2.33 (3H, m, 2 × ***H***O), 2.15 (1H, ddd, *J* 11.6, 4.3, 4.3), 2.01–1.88 (4H, m), 1.83–1.66 (3H, m), 1.56–1.42 (3H, m), 1.27 (3H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 139.1 (C), 130.4 (C), 129.3 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 113.7 (CH), 104.4 (CH), 84.5 (CH), 82.0 (CH), 80.9 (CH), 77.5 (C), 77.4 (CH), 76.4 (CH), 74.2 (CH_2), 73.3 (CH), 72.4 (CH_2), 70.3 (CH), 69.9 (CH_2), 69.7

(CH), 64.9 (CH_2), 64.8 (CH_2), 55.2 (CH_3), 38.6 (CH_2), 33.2 (CH_2), 29.6 (CH_2), 28.6 (CH_2), 26.3 (CH_2), 25.3 (CH_2), 10.8 (CH_3); HRMS (FAB+) calcd. for $C_{35}H_{48}O_{10}Na$, $(M+Na)^+$: 651.3145, found 651.3148.

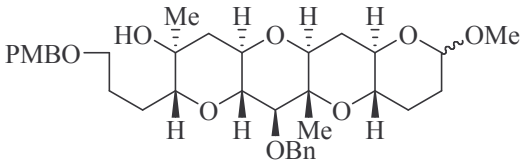
12-Benzyloxy-8-methoxy-2-[3-(4-methoxy-benzyloxy)-propyl]-11a-methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-ol 193 [48]



To a solution of acetal **194** (6.93 g, 11.0 mmol) in MeOH (200 mL) at rt was added *p*-TsOH (104 mg, 0.547 mmol). The reaction was stirred for 18 h at rt. Sat. aqueous $NaHCO_3$ (400 mL) was added and extracted several times with Et_2O (3 × 400 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (EtOAc/petrol, 8:2) gave compound **193** as a white foam (5.95 g, 90%). R_f = 0.68 (EtOAc); υ_{max}/cm^{-1} (neat) 3449, 2949, 2880, 2361, 1512, 1247, 1089, 1034; δ_H (400 MHz, $CDCl_3$, mixture of diastereomers) 7.41–7.22 (7H, m, ***Ph***, MeO***Ph***), 6.87 (2H, d, *J* 8.7, MeO***Ph***), 4.84 (0.5H, d, *J* 12.1, PhC***H***H), 4.83 (0.5H, d, *J* 12.1, PhC***H***H), 4.79 (0.5H, d, *J* 12.1, PhC***H***H), 4.78 (0.5H, d, *J* 12.1, PhCH***H***), 4.68 (0.6H, m, MeOC***H***O), 4.42–4.39 (2.4H, s, MeOPhC***H₂***, MeOC***H***O), 3.81 (3H, s, ***Me***O), 3.52–3.35 (9H, m), 3.24–3.07 (4H, m), 2.44–2.38 (1H, m), 2.15–1.47 (12H, m), 1.32 (1.5H, s, ***Me***), 1.32 (1.5H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 159.1 (C), 139.2 (C), 130.5 (C), 129.3 (CH), 128.0 (CH), 127.7 (CH), 127.2 (CH), 113.7 (CH), 103.1 (CH), 97.59 (CH), 84.4 (CH), 84.3 (CH), 82.1 (CH), 81.1 (CH), 78.5 (CH), 78.3 (2 × CH), 77.2 (C), 76.6 (2 × CH), 75.0 (CH), 74.3 (2 × CH_2), 72.4 (CH_2), 69.9 (CH), 69.9 (CH_2), 69.8 (CH), 69.4 (CH), 68.6 (CH), 56.6 (CH_3), 55.3 (CH_3), 54.6 (CH_3), 38.7 (CH_2),

30.7 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 28.0 (CH_2), 25.4 (CH_2), 24.9 (CH_2), 11.1 (CH_3); HRMS (FAB+) calcd. for $C_{34}H_{46}O_9Na$, $(M+Na)^+$: 621.3040, found 621.3041.

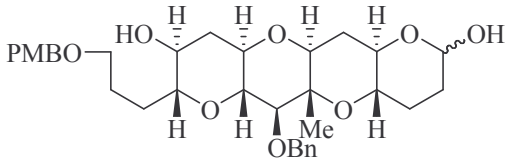
12-Benzyloxy-8-methoxy-2-[3-(4-methoxy-benzyloxy)-propyl]-3,11a-dimethyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-ol 209 [48]



To a solution of alcohol **193** (940 mg, 1.62 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added Dess-Martin periodinane (1.03 g, 2.43 mmol) portionwise. After 1 h at rt, the reaction mixture was quenched with sat. aqueous $Na_2S_2O_3$ (30 mL). After 15 min of vigorous stirring, the mixture was extracted with ether (3 × 20 mL). The combined organics were washed with sat. aqueous K_2CO_3 (2 × 60 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dried for 1 h under high vaccum. To a solution of crude ketone in toluene (16 mL) at –78 °C was added methylmagnesium iodide (747 µL, 2.24 mmol, ~3 M in ether) [Grignard was prepared using 1.9 mL of methyliodide and 802 mg of magnesium in 10 mL of ether]. After 2 h at –78 °C, sat. aqueous solution NH_4Cl (60 mL) was added and the reaction was allowed to warm to rt. The aqueous phase was extracted several times with EtOAc (3 × 50 mL). The combined organics were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 7:3) gave alcohol **209** as a white foam (719 mg, 72% over 2 steps). R_f = 0.47 (petrol/EtOAc, 1:1); υ_{max}/cm^{-1} ($CHCl_3$) 3604 (br), 2954, 2895,1612, 1462, 1381, 1089, 1052; δ_H (400 MHz, $CDCl_3$, mixture of diastereomers) 7.42–7.40 (2H, m, ***Ph***), 7.32–7.22 (5H, m, ***Ph***, MeO***Ph***), 6.88 (2H, d, *J* 8.7, MeO***Ph***), 4.86 (1H, d, *J* 12.0, PhC***H***H), 4.79

(1H, d, *J* 12.0, PhCH***H***), 4.67 (0.7H, s, MeOC***H***O), 4.45–4.39 (2.3H, m, MeOPhC***H₂***, MeOC***H***O), 3.81 (3H, s, ***Me***O), 3.56–3.35 (8H,m), 3.27–3.11 (4H, m), 2.18–1.38 (13H, m), 1.33 (2.1H, s, BnOCHC***Me***), 1.32 (0.9H, s, BnOCHC***Me***), 1.23 (3H, s, HOC***Me***); δ_c (100 MHz, $CHCl_3$) 159 (C), 139.2 (C), 130.7 (C), 129.2 (CH), 128.0 (CH), 127.5 (CH), 127.5 (CH), 127.1 (CH), 113.7 (CH), 103.1 (CH), 97.8 (CH), 85.0 (CH), 84.5 (CH), 82.2 (CH), 78.6 (CH), 78.3 (CH), 76.6 (CH), 75.0 (CH), 74.3 (CH_2), 72.2 (CH_2), 71.1 (CH_2), 69.8 (CH), 69.3 (CH), 68.6 (CH), 56.6 (CH_3), 55.2 (CH_3), 54.5 (CH_3), 45.6 (CH_2), 30.7 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 28.0 (CH_2), 26.7 (CH_2), 25.4 (CH_2), 24.9 (CH_2), 21.9 (CH_3), 11.2 (CH_3); HRMS (ES+) calcd. for $C_{35}H_{46}O_8$, $(M–H_2O)^+$: 594.3132, found 594.3184.

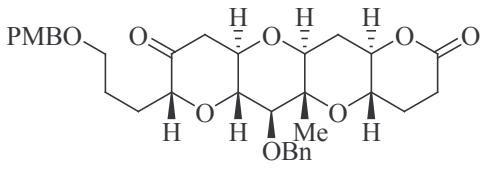
6-Benzyloxy-8-[3-(4-methoxy-benzyloxy)-propyl]-5a-methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacene-2,9-diol 210



To a solution of acetal **194** (85.9 mg, 0.137 mmol) in THF (2 mL) at rt was added acetone (0.5 mL) followed by 1 M HCl (2 mL). The reaction was vigourosly stirred for 6 h at rt. H_2O (5 mL) was added and extracted several times with EtOAc (2 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (EtOAc/MeOH/Et_3N, 100:4:1) gave compound **210** as a white foam (52.0 mg, 65%). R_f = 0.53 (EtOAc/MeOH, 100:4); υ_{max}/cm^{-1} (neat) 3396 (br), 2949, 2878, 1513, 1247, 1060, 1035; δ_H (400 MHz, $CDCl_3$, mixture of diastereomers) 7.35–7.15 (7H, m, Ph, **Ph**OMe), 6.80–6.78 (2H, d, *J* 6.9, **Ph**OMe), 5.16 (0.5H, brs, HOC***H***O), 4.78–4.70 (2.5H, m, C***HH***Ph, OC***H***OH), 4.35 (2H, s,

C***HH***PhOMe), 3.74–3.62 (4H, m), 3.44–2.98 (10H, m), 2.34–2.30 (1H, m), 2.08–1.39 (14H, m), 1.24 (3H, 2s, Me); δ_c (100 MHz, $CDCl_3$) 159.1 (C), 139.3 (C), 130.5 (C), 129.4 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 113.8 (CH), 91.2 (CH), 84.4 (CH), 84.2 (CH), 81.2 (CH), 78.5 (CH), 78.3 (CH), 78.2 (CH), 77.4 (CH), 75.2 (CH), 74.3 (CH_2), 72.4 (CH_2), 70.0 (CH_2), 69.7 (CH), 69.2 (CH), 68.8 (CH), 55.3 (CH_3), 38.7 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 28.0 (CH_2), 25.4 (CH_2), 24.3 (CH_2), 11.2 (CH_3); HRMS (ES+) calcd. for $C_{33}H_{45}O_9$, $(M+H)^+$: 585.3064, found 585.2919; calcd. for $C_{33}H_{48}N_1O_9$, $(M+NH_4)^+$: 602.3329, found 602.3196; calcd. for $C_{33}H_{44}O_9Na$, $(M+Na)^+$: 607.2883, found 607.2696.

6-Benzyloxy-8-[3-(4-methoxy-benzyloxy)-propyl]-5a-methyl-decahydro-1,5,7,11-tetraoxa-naphthacene-2,9-dione 211

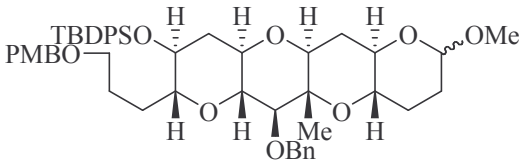


33

To a solution of lactol **210** (50.0 mg, 0.086 mmol) in CH_2Cl_2 (2 mL) at rt were added NaOAc (70.0 mg, 0.855 mmol) and PCC (92.1 mg, 0.427 mmol). After 12 h at rt, the reaction mixture was filtered through a plug of silica, which was washed with EtOAc (3 × 10 mL). The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 1:1) gave compound **211** as a white foam (31.3 mg, 63%). R_f = 0.38 (petrol/EtOAc, 1:1); $[\alpha]_D^{24}$ +20.5 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2870, 1731, 1612, 1455, 1358, 1326, 1303, 1065; δ_H (400 MHz, $CDCl_3$) 7.40–7.24 (7H, m, ***Ph***, MeO***Ph***), 6.88–6.86 (2H, m, MeO***Ph***), 4.85 (1H, d, *J* 12.1, PhC***H***H), 4.81 (1H, d, *J* 12.1, PhCH***H***), 4.41 (2H, s, MeOPhC***H*****$_2$**), 3.96 (1H, ddd, *J* 11.4, 9.7, 4.9), 3.82–3.78 (4H, m, ***Me***O), 3.73 (1H, ddd, *J* 10.2, 5.9), 3.59–3.45 (5H, m), 3.24 (1H, dd, *J* 12.8, 4.3), 2.93 (1H,

dd, *J* 15.6, 4.6), 2.82 (1H, ddd, *J* 18.2, 9.4, 4.3), 2.67 (1H, ddd, *J* 18.1, 8.5, 8.5), 2.50–2.44 (1H, m), 2.35 (1H, ddd, *J* 11.7, 4.1, 4.1), 2.21–2.13 (1H, m), 2.05–1.66 (6H, m), 1.39 (3H, s, Me); δ_c (100 MHz, $CDCl_3$) 204.7 (C), 170.1 (C), 159.1 (C), 138.7 (C), 130.7 (C), 129.3 (CH), 128.2 (CH), 127.7 (CH), 127.5 (CH), 113.8 (CH), 83.9 (CH), 83.4 (CH), 80.3 (CH), 78.4 (C), 76.6 (CH), 76.5 (2 × CH), 74.6 (CH_2), 72.4 (CH_2), 69.6 (CH_2), 67.0 (CH), 55.3 (CH_3), 45.0 (CH_2), 30.0 (CH_2), 27.8 (CH_2), 26.9 (CH_2), 25.4 (CH_2), 24.8 (CH_2), 10.9 (CH_3); HRMS (ES+) calcd. for $C_{33}H_{43}N_1O_9$, $(M+NH_4)^+$: 598.3016, found 598.2886; calcd. for $C_{33}H_{40}NaO_9$, $(M+Na)^+$: 603.2570, found 603.2259.

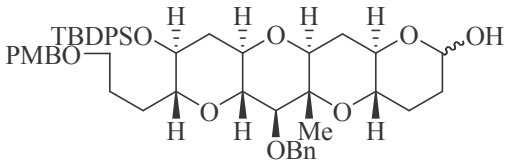
{12-Benzyloxy-8-methoxy-2-[3-(4-methoxy-benzyloxy)-propyl]-11a-methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-yloxy}-*tert*-butyl-diphenyl-silane 213



To a solution of alcohol **193** (94.0 mg, 0.156 mmol) and imidazole (32.0 mg, 0.188 mmol) in DMF (1 mL) at rt were added TBDPSCl (53.4 mg, 0.188 mmol) and DMAP (5.0 mg, 0.041 mmol). The reaction mixture was stirred for 18 h at rt. H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 75:25) gave protected alcohol **213** as a white foam (129.0 mg, 98%). R_f = 0.47 (petrol/EtOAc, 7:3); υ_{max}/cm^{-1} ($CHCl_3$) 2933, 2858, 1089, 1052; 7.70; δ_H (400 MHz, $CDCl_3$, mixture of diastereomers) 7.72−7.67 (4H, m, ***Ph*****$_2$**Si), 7.48−7.37 (8H, m, ***Ph***CH_2O**,** ***Ph*****$_2$**Si), 7.32−7.22 (5H, m, ***Ph***CH_2O, MeO***Ph***), 6.82 (2H, d, *J* 9.6, MeO***Ph***), 4.52 (1H, d, *J* 13.3, PhC***H***HO), 4.46 (1H, d, *J* 13.4, PhCH***H***O), 4.34 (1H, s, MeOC***H***), 4.09 (2H, s, MeOPhC***H*****$_2$**O), 3.43 (3H, s, ***Me***O), 3.51−2.90 (13H, m,

MeOCHOCHC***H***, MeOCHOC***H***, PMBO***CH₂***, TBDPSOC***H***, BnOC***H***, TBDPSOCHC***H***, BnOCHC***H***, BnOCHCMeC***H***, BnOCHCHC***H***, ***Me***OCH), 2.24−1.58 (12H, m, MeOCHC***H₂***, MeOCHOCHC***H₂***, MeOCHCH$_2$C***H₂***, PMBOCH$_2$CH$_2$C***H₂***, TBDPSOCHC***H₂***, PMBOCH$_2$C***H₂***), 1.31 (3H, s, BnOCHC***Me***), 1.06 (9H, s, {C***H₃***}$_3$CSi); δ_c (100 MHz, $CDCl_3$) 158.9 (C), 139.1 (C), 135.9 (CH), 135.8 (CH), 133.8 (C), 130.8 (C), 130.1 (C), 129.8 (C), 129.7 (CH), 129.6 (CH), 129.1 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.1 (CH), 113.6 (CH), 103.0 (CH), 97.8 (CH), 84.3 (CH), 82.3 (CH), 81.0 (CH), 78.3 (CH), 78.1 (CH), 76.4 (CH), 74.9 (CH), 74.2 (CH_2), 72.2 (CH_2), 71.5 (CH), 69.8 (CH_2), 69.7 (CH), 69.3 (CH), 68.5 (CH), 56.5 (CH_3), 55.2 (CH_3), 54.5 (CH_3), 39.1 (CH_2), 30.7 (CH_2), 29.6 (CH_2), 28.5 (CH_2), 28.0 (CH_2), 27.0 (CH_3), 25.6 (CH_2), 24.8 (CH_2), 19.2 (C), 11.1 (CH_3); HRMS (ES+) calcd. for $C_{50}H_{64}O_9SiNa$, $(M+Na)^+$: 859.4212, found 859.4248 and calcd. for $C_{50}H_{68}NO_9Si$, $(M+NH_4)^+$: 854.4658, found 854.4687.

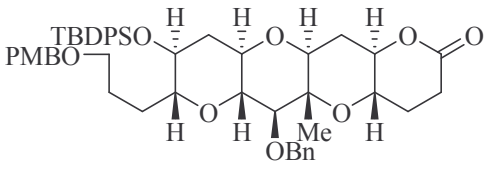
6-Benzyloxy-9-(*tert*-butyl-diphenyl-silanyloxy)-8-[3-(4-methoxy-benzyloxy)-propyl]-5a-methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-2-ol 214



To a solution of acetal **213** (2.00 g, 2.39 mmol) in THF (20 mL) at rt was added HCl (1M, 20 mL). The reaction mixture was heated at reflux for 18 h. The reaction was cooled to rt and H_2O (40 mL) was added. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 6:4) gave lactol **214** as a white foam (1.79 g, 91%). R_f = 0.25 (petrol/EtOAc, 7:3); υ_{max}/cm^{-1} ($CHCl_3$) 3595, 2933, 2859, 1090, 1065; δ_H (400 MHz, $CDCl_3$, mixture of diastereomers)

7.70−7.64 (4H, m, ***Ph₂***Si), 7.46−7.35 (8H, m, ***Ph***CH_2O***, Ph₂***Si), 7.32−7.20 (5H, m, ***Ph***CH_2O, MeO***Ph***), 6.88 (2H, d, *J* 8.6, MeO***Ph***), 5.19 (0.5H, brs, HOC***H***), 4.78 (2.5H, m, PhC***H₂***O), 4.41 (2H, s, MeOPhC***H₂***O), 3.81 (3H, s, ***Me***O), 3.69−2.80 (10H, m, HOCHOCHC***H***, HOCHOC***H***, PMBO***CH₂***, TBDPSOC***H***, BnOC***H***, TBDPSOCHC***H***, BnOCHC***H***, BnOCHCMeC***H***, BnOCHCHC***H***), 2.21−1.46 (12H, m, MeOCHC***H₂***, MeOCHOCHC***H₂***, MeOCHCH_2C***H₂***, PMBOCH$_2$CH$_2$C***H₂***, TBDPSOCHC***H₂***, PMBOCH$_2$C***H₂***), 1.29 (3H, s, BnOCHC***Me***), 1.04 (9H, s, {C***H₃***}$_3$CSi); δ_c (100 MHz, $CDCl_3$) 158.9 (C), 139.1 (C), 135.9 (CH), 135.8 (CH), 133.9 (C), 133.1 (C), 130.8 (C), 129.8 (CH), 129.6 (CH), 129.1 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 113.6 (CH), 96.3 (CH), 91.2 (CH), 84.4 (CH), 84.3 (CH), 82.3 (CH), 81.0 (CH), 78.2 (C), 78.0 (CH), 76.4 (CH), 75.1 (CH), 74.2 (CH_2), 72.2 (CH_2), 71.4 (CH), 69.8 (CH_2), 69.1 (CH), 68.7 (CH), 55.2 (CH_3), 39.1 (CH_2), 32.3 (CH_2), 30.2 (CH_2), 29.8 (CH_2), 28.5 (CH_2), 27.9 (CH_2), 27.0 (CH_3), 25.6 (CH_2), 24.2 (CH_2), 19.2 (C), 11.1 (CH_3); HRMS (ES+) calcd. for $C_{49}H_{62}O_9SiNa$, $(M+Na)^+$: 845.4055, found 845.4062 and calcd. for $C_{49}H_{66}NO_9Si$, $(M+NH_4)^+$: 840.4501, found 840.4503.

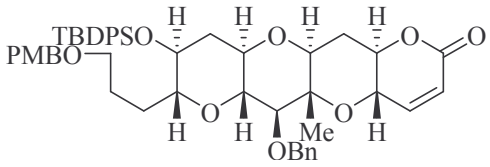
6-Benzyloxy-9-(*tert*-butyl-diphenyl-silanyloxy)-8-[3-(4-methoxy-benzyloxy)-propyl]-5a-methyl-dodecahydro-1,5,7,11-tetraoxa-naphthacen-2-one 215



To a solution of lactol **214** (1.68 g, 2.04 mmol) in toluene (168 mL) at rt was added Fetizon's reagent (3.06 g, 6.12 mmol). The reaction mixture was refluxed for 3 h. The reaction was cooled to rt, filtered through a plug of celite®, which was washed with EtOAc (3 × 50 mL) and concentrated *in vacuo*. The white foam (1.62 g, 97% crude) was used

without further purification. R_f = 0.25 (petrol/EtOAc, 7:3); $[\alpha]_D^{31}$ +28.2 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2932, 2858, 1742, 1088, 1061; δ_H (400 MHz, $CDCl_3$) 7.72−7.66 (4H, m, ***Ph*****$_2$**Si), 7.49−7.37 (8H, m, ***Ph***CH_2O**,** ***Ph*****$_2$**Si), 7.33−7.24 (5H, m, ***Ph***CH_2O, MeO***Ph***), 6.89 (2H, d, *J* 8.7, MeO***Ph***), 4.78 (2H, s, PhC***H*****$_2$**O), 4.13 (2H, s, MeOPhC***H*****$_2$**O), 3.93 (1H, ddd, *J* 11.3, 10.0, 4.9, O=COC***H***), 3.83 (3H, s, ***Me***O), 3.70 (1H, ddd, *J* 10.0, 10.0, 5.9, O=COCHC***H***), 3.47−3.44 (2H, m, PMBOC***H*****$_2$**), 3.43−3.48 (1H, m, TBDPSOC***H***), 3.31−3.26 (1H, m, TBDPSOCHC***H***), 3.29 (1H, d, *J* 9.3, BnOC***H***), 3.18 (1H, dd, *J* 9.3, 9.3, BnOCHC***H***), 3.08 (1H, dd, *J* 12.3, 3.8, BnOCHCMeC***H***), 2.94 (1H, ddd, *J* 11.9, 9.4, 3.7, BnOCHCHC***H***), 2.81 (1H, ddd, *J* 18.0, 9.3, 4.2, O=CC***H***H), 2.66 (1H, ddd, *J* 18.0, 8.2, 8.2, O=CCH***H***), 2.27 (1H, ddd, *J* 11.6, 4.2, 4.2, O=COCHC***H***H), 2.22−2.05 (3H, m, O=CCH_2C***H***H, PMBOCH_2CH_2C***H***H, TBDPSOCHC***H***H), 1.92−1.59 (5H, m, O=CCH_2CH***H***, O=COCHCH***H***, PMBOCH_2C***H*****$_2$**, TBDPSOCHCH***H***), 1.34 (3H, s, BnOCHC***Me***), 1.31−1.21 (1H, m, PMBOCH_2CH_2CH***H***), 1.06 (9H, s, {C***H*****$_3$**$\}_3$CSi); δ_c (100 MHz, $CDCl_3$) 170.2 (C), 159.0 (C), 139.9 (C), 135.9 (CH), 135.8 (CH), 133.8 (C), 131.1 (C), 130.8 (C), 129.8 (CH), 129.7 (CH), 129.1 (CH), 128.0 (CH), 127.7 (CH), 127.5 (2 × CH), 127.3 (CH), 113.6 (CH), 84.0 (CH), 82.4 (CH), 81.0 (CH), 78.4 (C), 77.0 (CH), 76.6 (CH), 76.5 (CH), 74.3 (CH_2), 72.3 (CH_2), 71.4 (CH), 69.8 (CH_2), 66.7 (CH), 55.2 (CH_3), 39.0 (CH_2), 30.0 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 27.0 (CH_3), 25.8 (CH_2), 24.7 (CH_2), 19.2 (C), 10.9 (CH_3); HRMS mass not found.

6-Benzyloxy-9-(*tert*-butyl-diphenyl-silanyloxy)-8-[3-(4-methoxy-benzyloxy)-propyl]-5a-methyl-5a,6,6a,8,9,10,10a,11a,12,12a-decahydro-4aH-1,5,7,11-tetraoxa-naphthacen-2-one 217

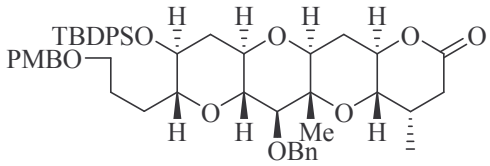


To a solution of lactone **215** (661.6 mg, 0.8058 mmol) and TMSCl (514 μL, 4.03 mmol) in THF (8 mL) at –78 °C was added NaHMDS (1.21 mL of a 1M solution in THF, 1.21 mmol). After 30 min, a solution of PhSeBr (227.9 mg, 0.9668 mmol) in THF (4 mL) was added by cannula. The reaction mixture was stirred at –78 °C for 30 min. The reaction was quenched with sat. aqueous $NaHCO_3$ (15 mL) and allowed to warm to rt. The aqueous phase was extracted with EtOAc (3 ×10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

The foam was dissolved in THF (5 mL) and EtOAc (4 mL). $NaHCO_3$ (609.0 mg, 7.245 mmol) followed by H_2O_2 (274 μL, 2.42 mmol, 30% in water) were added at 0 °C. After 15 min, the reaction mixture was warmed to rt and sirred for 15 min. The reaction was quenched with water (20 mL) and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo*. The light brown foam was used without further purification. R_f = 0.32 (petrol/EtOAc, 7:3); $[\alpha]_D^{23}$ +21.3 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2932, 2858, 1743, 1111, 1086, 1063; δ_H (400 MHz, $CDCl_3$) 7.68−7.62 (4H, m, ***Ph*****$_2$**Si), 7.52−7.22 (13H, m, ***Ph***CH_2O**,** ***Ph*****$_2$**Si, MeO***Ph***), 6.88−6.84 (3H, m, MeO***Ph***, O=CC***H***=), 5.95 (1H, dd, *J* 9.8, 2.5, O=CCH=C***H***), 4.79 (1H, d, *J* 11.9, PhC***H***HO), 4.74 (1H, d, *J* 11.9, PhCH***H***O), 4.40 (2H, s, MeOPhC***H*****$_2$**O), 4.39−4.34 (1H, m, O=COCHC***H***), 3.99 (1H, ddd, *J* 11.7, 11.7, 4.5, O=COC***H***), 3.81 (3H, s, ***Me***O), 3.42 (2H, ddd, *J* 6.4, 6.4, 1.6, PMBO***CH*****$_2$**), 3.48 (1H, ddd, *J* 10.5, 9.0, 4.6, TBDPSOC***H***), 3.30 (1H, d, *J* 9.2, BnOC***H***), 3.230−3.23 (1H, m,

TBDPSOCHC***H***), 3.17 (1H, dd, *J* 9.3, 9.3, BnOCHC***H***), 3.07 (1H, dd, *J* 12.1, 3.8, BnOCHCMeC***H***), 2.91 (1H, ddd, *J* 11.8, 9.4, 3.7, BnOCHCHC***H***), 2.25 (1H, ddd, *J* 11.4, 4.0, 4.0, O=COCHC***H***H), 2.17 (1H, ddd, *J* 8.5, 4.4, 4.4, TBDPSOCHC***H***H), 2.10−1.92 (2H, m, O=COCHCH***H***, PMBOCH$_2$CH$_2$C***H***H), 1.81−1.74 (1H, m, PMBOCH$_2$C***H***H), 1.69−1.55 (2H, m, PMBOCH$_2$CH***H***, TBDPSOCHCH***H***), 1.33 (3H, s, BnOCHC***Me***), 1.28−1.18 (1H, m, PMBOCH$_2$CH$_2$CH***H***), 1.03 (9H, s, {C***H$_3$***}$_3$CSi); δ_c (100 MHz, $CDCl_3$) 162.9 (C), 159.0 (C), 148.9 (CH), 138.8 (C), 135.9 (CH), 135.8 (CH), 133.8 (C), 131.1 (C), 130.8 (C), 129.8 (CH), 129.7 (CH), 129.1 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.5 (CH), 127.4 (CH), 120.2 (CH), 113.7 (CH), 84.1 (CH), 82.5 (CH), 81.2 (CH), 79.2 (C), 77.2 (CH), 76.9 (CH), 76.7 (CH), 74.5 (CH_2), 72.3 (CH_2), 71.4 (CH), 69.8 (CH_2), 66.6 (CH), 55.2 (CH_3), 39.0 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 27.0 (CH_3), 25.7 (CH_2), 19.2 (C), 10.7 (CH_3); HRMS (ES+) calcd. for $C_{49}H_{58}O_9SiNa$, $(M+Na)^+$: 841.3742, found 841.3744 and calcd. for $C_{49}H_{62}NO_9Si$, $(M+NH_4)^+$: 836.4188, found 836.4181.

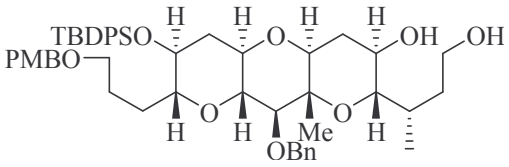
6-Benzyloxy-9-(*tert*-butyl-diphenyl-silanyloxy)-8-[3-(4-methoxy-benzyloxy)-propyl]-4,5a-dimethyl-dodecahydro-1,5,7,11-tetraoxa-naphthacen-2-one 218



To a solution of dried CuI (460.0 mg, 2.415 mmol) in ether (20 mL) at 0 °C was added MeLi (3.22 mL of a 1.5 M solution in ether, 4.83 mmol,). After 15 min, the α,β-unsaturated lactone **217** (659.3 mg, 0.8058 mmol) in ether (10 mL) was added at 0 °C by cannula. After 15 min, the reaction was quenched with sat. aqueous NH_4Cl (20 mL) and allowed to warmed to rt. The aqueous phase was extracted with ether (3 × 20 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The light green foam was used without further purification. R_f =

0.31 (7:3 petrol/EtOAc); $[\alpha]_D^{31}$ +28.2 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2962, 2858, 1743, 1602, 1265, 1089; δ_H (400 MHz, $CDCl_3$) 7.71−7.65 (4H, m, ***Ph*****$_2$**Si), 7.47−7.48 (8H, m, ***Ph***CH_2O**,** ***Ph*****$_2$**Si), 7.32−7.22 (5H, m, ***Ph***CH_2O, MeO***Ph***), 6.88 (2H, d, *J* 8.6, MeO***Ph***), 4.79 (1H, d, *J* 12.1, PhC***H***HO), 4.75 (1H, d, *J* 12.1, PhCH***H***O), 4.42 (2H, s, MeOPhC***H*****$_2$**O), 4.09 (1H, ddd, *J* 11.0, 10.0, 4.9, O=COC***H***), 3.82 (3H, s, ***Me***O), 3.76 (1H, dd, *J* 10.0, 6.1, O=COCHC***H***), 3.44 (2H, t, *J* 6.5, PMBO***CH*****$_2$**), 3.37 (1H, ddd, *J* 10.4, 9.1, 4.6, TBDPSOC***H***), 3.29 (1H, d, *J* 9.3, BnOC***H***), 3.27 (1H, ddd, *J* 9.2, 9.1, 2.2, TBDPSOCHC***H***), 3.16 (1H, dd, *J* 9.3, 9.3, BnOCHC***H***), 3.00 (1H, dd, *J* 12.4, 3.7, BnOCHCMeC***H***), 2.91 (1H, ddd, *J* 11.8, 9.4, 3.7, BnOCHCHC***H***), 2.82 (1H, dd, *J* 12.4, 8.4, O=CC***H***H), 2.42−2.34 (2H, m, O=CCH***H***, O=CCH_2C***H***Me), 2.27 (1H, ddd, *J* 11.5, 4.4, 4.4, O=COCHC***H***H), 2.18 (1H, ddd, *J* 11.3, 4.2, 4.2, TBDPSOCHC***H***H), 2.10−2.02 (1H, m, PMBOCH_2CH_2C***H***), 1.89−1.56 (4H, m, O=COCHCH***H***, PMBOCH_2C***H*****$_2$**, TBDPSOCHCH***H***), 1.33 (3H, s, BnOCHC***Me***), 1.28−1.19 (1H, m, PMBOCH_2CH_2CH***H***), 1.05 (9H, s, {C***H*****$_3$**}$_3$CSi), 1.02 (3H, d, *J* 6.8, O=CCH_2CH***Me***); δ_c (100 MHz, $CDCl_3$) 170.4 (C), 159.0 (C), 138.8 (C), 135.9 (CH), 135.8 (CH), 133.8 (C), 131.1 (C), 130.9 (C), 129.8 (CH), 129.7 (CH), 129.1 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 113.7 (CH), 83.9 (CH), 82.4 (CH), 80.9 (CH), 78.3 (C), 77.2 (CH), 76.7 (CH), 74.3 (CH_2), 72.3 (CH_2), 71.4 (CH), 71.3 (CH), 69.9 (CH_2), 68.7 (CH), 55.3 (CH_3), 39.0 (CH_2), 48.9 (CH_2), 29.9 (CH_2), 28.5 (CH_2), 27.8 (CH), 27.0 (CH_3), 25.7 (CH_2), 19.2 (C), 14.5 (CH_3), 10.8 (CH_3); HRMS (ES+) calcd. for $C_{50}H_{62}O_9SiNa$, $(M+Na)^+$: 857.4055, found 857.4065 and calcd. for $C_{50}H_{66}NO_9Si$, $(M+NH_4)^+$: 852.4501, found 852.4514.

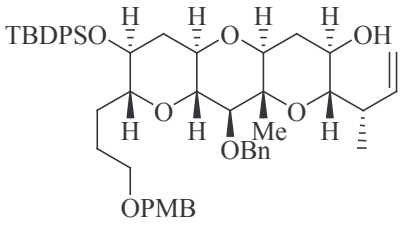
9-Benzyloxy-6-(*tert*-butyl-diphenyl-silanyloxy)-2-(3-hydroxy-1-methyl-propyl)-7-[3-(4-methoxy-benzyloxy)-propyl]-9a-methyl-decahydro-1,8,10-trioxa-anthracen-3-ol 219



To a solution of lactone **218** (672.9 mg, 0.8058 mmol) in THF (8 mL) at 0 °C was added $LiAlH_4$ (2.42 mL of a 1M solution in THF, 2.42 mmol,). After 15 min, the reaction mixture was warmed to rt and stirred for an additional 30 min. The reaction was carefully quenched at 0 °C with a saturated solution of Rochelle's salt (30 mL) and allowed to warmed to rt. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5) gave diol **219** as a white foam (357.0 mg, 53 % over 5 steps). R_f = 0.24 (petrol/EtOAc, 7:3); $[\alpha]_D^{27}$ –0.4 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3621, 3424 (br), 2932, 2858, 1621, 1455, 1362, 1084, 1051; δ_H (400 MHz, $CDCl_3$) 7.69−7.63 (4H, m, ***Ph*****$_2$**Si), 7.45−7.34 (8H, m, ***Ph***CH_2O**,** ***Ph*****$_2$**Si), 7.29−7.21 (5H, m, ***Ph***CH_2O, MeO***Ph***), 6.87 (2H, d, *J* 8.7, MeO***Ph***), 4.79 (1H, d, *J* 11.9, PhC***H***HO), 4.69 (1H, d, *J* 11.9, PhCH***H***O), 4.41 (2H, s, MeOPhC***H*****$_2$**O), 3.81 (3H, s, ***Me***O), 3.73 (1H, ddd, *J* 10.2, 5.1, 5.1, HOC***H***H), 3.63−3.52 (2H, m, HOCH***H***, HOC***H***), 3.44 (2H, ddd, *J* 6.4, 6.4, 1.0, PMBO***CH*****$_2$**), 3.39−3.31 (2H, m, HOCHC***H***, TBDPSOC***H***), 3. 27−3.22 (1H, m, TBDPSOCHC***H***), 3.23 (1H, d, *J* 9.2, BnOC***H***), 3.12 (1H, dd, *J* 9.3, 9.2, BnOCHC***H***), 2.97 (1H, dd, *J* 12.4, 3.8, BnOCHCMeC***H***), 2.90 (1H, ddd, *J* 11.8, 9.4, 3.7, BnOCHCHC***H***), 2.16 (1H, ddd, *J* 11.2, 4.2, 4.2, TBDPSOCHC***H***H), 2.10−2.02 (3H, m, PMBOCH_2CH_2C***H***, HOCH_2CH_2CMe***H***), 1.85−1.55 (5H, m, HOCHCH***H***, PMBOCH_2C***H*****$_2$**, TBDPSOCHCH***H***, HOCH_2C***H***H), 1.40−1.31 (1H, m, HOCH_2CH***H***), 1.26−1.17 (1H, m, PMBOCH_2CH_2CH***H***), 1.24 (3H, s, BnOCHC***Me***), 1.06 (3H, d, *J* 6.8, HOCH_2CH_2CH***Me***),

1.04 (9H, s, {C***H*****3**}$_3$CSi); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 139.1 (C), 136.0 (CH), 135.9 (CH), 133.9 (C), 133.2 (C), 130.9 (C), 129.8 (CH), 129.6 (CH), 129.1 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 113.7 (CH), 84.6 (CH), 82.3 (CH), 80.8 (CH), 77.7 (CH), 77.6 (CH), 77.4 (C), 76.4 (CH), 74.3 (CH_2), 72.3 (CH_2), 71.5 (CH), 69.9 (CH_2), 66.5 (CH), 60.5 (CH_2), 55.3 (CH_3), 39.2 (CH_2), 33.0 (CH_2), 31.8 (CH_2), 29.0 (CH), 28.5 (CH_2), 27.0 (CH_3), 25.6 (CH_2), 19.2 (C), 17.6 (CH_3), 10.8 (CH_3); HRMS (ESI+) calcd. for $C_{50}H_{66}O_9SiNa$, $(M+Na)^+$: 861.4369, found 861.4368 and calcd. for $C_{50}H_{70}NO_9Si$, $(M+NH_4)^+$: 856.4814, found 856.4814.

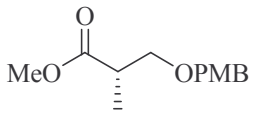
9-Benzyloxy-6-(*tert*-butyl-diphenyl-silanyloxy)-7-[3-(4-methoxy-benzyloxy)-propyl]-9a-methyl-2-(1-methyl-allyl)-decahydro-1,8,10-trioxa-anthracen-3-ol 220



To a solution of diol **219** (206.3 mg, 0.2458 mmol) and recrystallized 2-nitrophenyl selenocyanate (139.6 mg, 0.6148 mmol) in THF (5 mL) at 0 °C was added *n*-Bu_3P (152 µL, 0.615 mmol). After 30 min, $NaHCO_3$ (165.5 mg, 1.968 mmol) followed by H_2O_2 (0.9 mL, 30 % in H_2O) were added. The reaction mixture was stirred at 40 °C for 1 h, then cooled to rt. Sat. aqueous Na_2CO_3 (20 mL) was added and the aqueous layer was extracted with ether (3 × 25 mL). The combined organics were washed with brine (20mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 8:2) gave alkene **158** as a white foam (133.0 mg, 66%). R_f = 0.30 (petrol/EtOAc, 8:2); $[\alpha]_D^{26}$ +42.0 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3459, 2955, 2930, 2857, 1247, 1090, 702; δ_H (400 MHz, $CDCl_3$) 7.68–7.62 (4H, m, ***Ph*****$_2$**Si), 7.44–7.34 (8H, m, ***Ph***CH_2O**,** ***Ph*****$_2$**Si), 7.30–7.32 (5H, m, ***Ph***CH_2O, MeO***Ph***), 6.87 (2H, d, *J* 8.6, MeO***Ph***),

5.77 (1H, ddd, *J* 17.4, 10.2, 8.9, CH_2=C***H***), 5.04 (1H, dd, *J* 17.4, 1.3, C***H***H=), 5.02 (1H, dd, *J* 10.2, 1.9, CH***H***=), 4.84 (1H, d, *J* 12.1, PhC***H***HO), 4.71 (1H, d, *J* 12.1, PhCH***H***O), 4.41 (2H, s, MeOPhC***H₂***O), 3.81 (3H, s, ***Me***O), 3.46–3.43 (3H, m), 3.94–3.91 (2H, m, CH_2=CHCHMeC***H***), 3.27–3.22 (2H, m, BnOC***H***), 3.11 (1H, dd, *J* 9.4, 9.4, BnOCHC***H***), 2.93 (1H, dd, *J* 12.6, 3.9, BnOCHCMeC***H***), 2.88 (1H, ddd, *J* 12.0, 9.1, 3.4, BnOCHCHC***H***), 2.65–2.57 (1H, m, CH_2=CHC***H***Me), 2.15 (1H, ddd, *J* 11.3, 4.1, 4.1, TBDPSOCHC***H***H), 2.13–2.02 (2H, m), 1.84–1.75 (1H, m), 1.73–1.55 (4H, m), 1.27− 1.22 (4H, m + s, BnOCHC***Me***), 1.15 (3H, d, *J* 7.0, $HOCH_2CH_2CH$***Me***), 1.03 (9H, s, {C***H₃***}$_3$CSi); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 139.5 (CH), 139.1 (C), 135.9 (2 × CH), 133.9 (C), 133.1 (C), 130.9 (C), 129.8 (CH), 129.6 (CH), 129.1 (CH), 128.1 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 115.6 (CH_2), 113.6 (CH), 84.3 (CH), 82.2 (CH), 80.6 (CH), 77.3 (CH), 76.5 (CH), 76.3 (CH), 74.2 (CH_2), 72.3 (CH_2), 71.5 (CH), 69.9 (CH_2), 67.4 (CH), 55.2 (CH_3), 39.1 (CH_2), 38.7 (CH), 33.0 (CH_2), 29.7 (C), 28.5 (CH_2), 27.0 (CH_3), 25.6 (CH_2), 19.2 (C), 17.9 (CH_3), 10.5 (CH_3); HRMS mass not found.

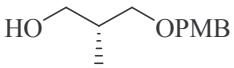
(*S*)-Methyl 3-(4-methoxybenzyloxy)-2-methylpropanoate 228 [59]



To a solution of NaH (152.0 mg, 3.802 mmol) in ether (30 mL) at rt was added PMBOH (5.25 g, 38.0 mmol). After 1 h, the reaction mixture was cooled to 0 °C and CCl_3CN (3.86 mL, 38.0 mmol) was slowly added and stirred at rt for 30 min. The mixture was diluted with ether (40 mL) and the organic layer was washed with sat. aqueous $NaHCO_3$ (50 mL), brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To a solution of the oil in CH_2Cl_2 (45 mL) at rt was added (*S*)-methyl 3-hydroxy-2-methylpropanoate (2.50 g, 21.1 mmol) followed by PPTS (234 mg, 0.373 mmol). After 24 h, the reaction mixture was

washed with sat. aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The solid was triturated with petrol-CH_2Cl_2 (1:1), filtered through a plug of celite® and the solution was concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 5:1) gave protected alcohol **228** as a colourless oil (4.96 g, 98%). R_f = 0.31 (petrol/EtOAc, 5:1); $[\alpha]_D^{25}$ +9.3 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2953, 2863, 1731, 1612, 1089; δ_H (400 MHz, $CDCl_3$) 7.24 (2H, d, *J* 9.6, ***Ph***), 6.83 (2H, d, *J* 9.6, ***Ph***), 4.14 (2H, s, PhC***H*****$_2$**), 3.42 (3H, s), 3.30 (3H, s), 3.23 (1H, dd, *J* 10.1, 8.1, PMBOC***H***H), 3.04 (1H, dd, *J* 10.1, 6.5, PMBOCH***H***), 2.34−2.20 (1H, m, MeC***H***), 0.5 (3H, d, *J* 7.8, ***Me***); δ_c (100 MHz, $CDCl_3$) 175.3 (C), 159.1 (C), 130.2 (C), 129.2 (CH), 113.7 (CH), 72.7 (CH_2), 71.6 (CH_2), 55.2 (CH_3), 51.7 (CH_3), 40.1 (CH), 14.0 (CH_3); HRMS (ES+) calcd. for $C_{13}H_{18}O_4Na$, $(M+Na)^+$: 261.1097, found 261.1092.

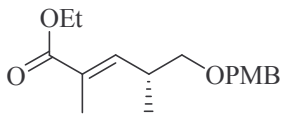
(*R*)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol 229 [59]



To a solution of methyl ester **228** (2.00 g, 8.39 mmol) in CH_2Cl_2 (40 mL) at –10 °C was added Dibal-H (21 mL of a 1M solution in CH_2Cl_2, 21 mmol). After 1 h, the reaction mixture was carefully quenched with MeOH (5 mL). A saturated solution of Rochelle's salt (50 mL) was added and the mixture was stirred vigorously for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 1:1) gave alcohol **229** as a colourless oil (1.51 g, 86%). R_f = 0.15 (petrol/EtOAc, 8:2); $[\alpha]_D^{23}$ +16.4 (*c* = 1.00, $CHCl_3$): υ_{max}/cm^{-1} ($CHCl_3$) 3625, 3513, 2958, 2910, 2863, 1612, 1463, 1361, 1302, 1087, 1037; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, d, *J* 8.7, ***Ph***), 6.92 (2H, d, *J* 8.7, ***Ph***), 4.47 (2H, s, PhC***H*****$_2$**), 3.82 (3H, s, ***Me***OPh),

3.61 (2H, d, *J* 5.8, PMBOC***H*****$_2$**), 3.52 (1H, dd, *J* 9.0, 5.1, HOC***H***H), 3.44 (1H, dd, *J* 9.0, 7.6, HOCH***H***), 3.08 (1H, brs, ***H***O), 2.10−2.01 (1H, m, MeC***H***), 0.92 (3H, d, *J* 7.0, ***Me***); δ_c(100 MHz, $CDCl_3$) 159.0 (C), 130.0 (C), 129.0 (CH), 113.6 (CH), 74.3 (CH_2), 72.7 (CH_2), 66.8 (CH_2), 55.0 (CH_3), 35.4 (CH), 13.4 (CH_3); HRMS (ES+) calcd. for $C_{12}H_{18}O_3Na$, $(M+Na)^+$: 233.1148, found 233.1143.

(*R*,*E*)-Ethyl 5-(4-methoxybenzyloxy)-2,4-dimethylpent-2-enoate 231 [59]

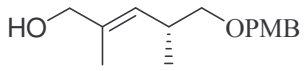


To a solution of alcohol **229** (526.1 mg, 2.526 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Dess-Martin periodinane (1.16 g, 2.75 mmol) portionwise. After 1 h at 0 °C, the reaction mixture was allowed to warm to rt and stirring continued for a further1 h. The reaction was quenched with sat. aqueous $Na_2S_2O_3$ (30 mL). After 30 min of vigorous stirring, the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with sat. aqueous K_2CO_3 (60 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dried 15 min under high vacuum.

To a solution of crude aldehyde **230** in CH_2Cl_2 (15 mL) at rt was added ethyl 2-(triphenylphosphoranylidene)propionate (1.81 g, 5.00 mmol) portionwise. The reaction was stirred at rt for one day. H_2O (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave alkene **231** as a colourless oil (492.3 mg, 67% over 2 steps). R_f= 0.20 (petrol/EtOAc, 9:1); $[\alpha]_D^{23}$ –2.8 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2960, 2933, 2860, 1702, 1084; δ_H (400 MHz, $CDCl_3$) 7.24 (2H, d, *J* 8.7, ***Ph***), 6.87 (2H, d, *J* 8.7, ***Ph***), 6.59 (1H, dd, *J* 9.6, 1.4, ***H***C=), 4.44 (2H, s, PhC***H*****$_2$**), 4.19 (2H, q, *J* 7.1, CH_3C***H*****$_2$**O), 3.79

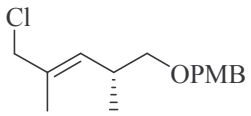
(3H, s, ***Me***O), 3.33 (2H, dd, *J* 6.7, 0.8, PMBOC***H*****$_2$**), 2.86−2.79 (1H, m, MeC***H***), 1.86 (3H, d, *J* 1.4, C***H*****$_3$**C=), 1.29 (3H, t, *J* 7.1, C***H*****$_3$**CH_2O), 1.03 (3H, d, *J* 6.7, C***H*****$_3$**CH); δ_c (100 MHz, $CDCl_3$) 168.1 (C), 159.0 (C), 144.2 (CH), 130.3 (C), 129.0 (CH), 128.0 (C), 113.6 (CH), 73.8 (CH_2), 72.6 (CH_2), 60.3 (CH_2), 55.1 (CH_3), 33.8 (CH), 16.5 (CH_3), 14.2 (CH_3), 12.5 (CH_3); HRMS (ES+) calcd. for $C_{17}H_{24}O_4Na$, $(M+Na)^+$: 315.1567, found 315.1566.

(*R*,*E*)-5-(4-Methoxybenzyloxy)-2,4-dimethylpent-2-en-1-ol 232 [59]



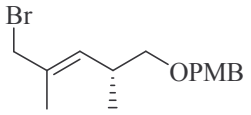
To a solution of ethyl ester **231** (4.30 g, 14.7 mmol) in CH_2Cl_2 (147 mL) at –10 °C was added Dibal-H (37 mL of a 1M solution in CH_2Cl_2, 37 mmol,). After 1 h, the reaction mixture was carefully quenched with MeOH (10 mL). A saturated solution of Rochelle's salt (150 mL) was then added and stirred vigorously for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 7:3) gave alcohol **232** as a colourless oil (3.26 g, 89%). R_f = 0.15 (petrol/EtOAc, 8:2); $[\alpha]_D^{23}$ –17.3 *(c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3608, 2931, 2860, 1612, 1456, 1370, 1302, 1083, 1039, 997; δ_H (270 MHz, $CDCl_3$) 7.28 (2H, d, *J* 9.5, ***Ph***), 6.87 (2H, d, *J* 9.5, ***Ph***), 5.02 (1H, dd, *J* 10.2, 1.1, C***H***=), 4.15 (2H, s, PhC***H*****$_2$**), 3.59 (2H, s, HOC***H*****$_2$**), 3.43 (3H, s, ***Me***O), 2.90 (1H, dd, *J* 10.3, 7.5, PMBOCH***H***), 2.83 (1H, dd, *J* 10.3, 8.0, PMBOC***H***H), 2.39 (1H, brs, ***H***O), 2.48−2.18 (1H, m, MeC***H***), 1.09 (3H, d, *J* 1.1, C***H*****$_3$**C=), 0.32 (3H, d, *J* 6.7, C***H*****$_3$**CH); δ_c (68 MHz, $CDCl_3$) 158.8 (C), 135.2 (C), 130.3 (C), 128.9 (CH), 128.1 (CH), 113.5 (CH), 74.6 (CH_2), 72.3 (CH_2), 68.1 (CH_2), 55.1 (CH_3), 32.3 (CH), 17.4 (CH_3), 13.7 (CH_3); HRMS (ES+) calcd. for $C_{15}H_{22}O_3Na$, $(M+Na)^+$: 273.1461, found 273.1457.

(*R*,*E*)-1-((5-Chloro-2,4-dimethylpent-3-enyloxy)methyl)-4-methoxybenzene 233



To a solution of alcohol **232** (250.3 mg, 1.000 mmol) and triphenylphosphine (524.6 mg, 2.000 mmol) in CH_3CN (3 mL) at –20 °C were carbon tetrachloride (390 μL, 4.00 mmol) was added portionwise. After 1 h, the reaction was concentrated *in vacuo*. The residue was triturated with petrol and filtered. The process was repeated three times. The combined layers were concentrated *in vacuo*. Purification by flash column chromatography (petrol/Et_2O, 95:5) gave chloride **233** as a colourless oil (256.0 mg, 95%). R_f = 0.71 (petrol/EtOAc, 8:2); $[\alpha]_D^{26}$ –15.9 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2957, 2931, 2855, 1613, 1512, 1247, 1091, 1035, 818, 684; δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* 8.7, ***Ph***), 6.89 (2H, d, *J* 8.7, ***Ph***), 5.37 (1H, dd, *J* 9.2, 0.9, C***H***=), 4.45 (2H, s, PhC***H₂***), 4.02 (2H, d, *J* 0.6, ClC***H₂***), 3.82 (3H, s, ***Me***O), 3.31 (1H, dd, *J* 9.1, 6.6, PMBOC***H***H), 3.27 (1H, dd, *J* 9.1, 6.8, PMBOCH***H***), 2.78–2.67 (1H, m, MeC***H***), 1.78 (3H, d, *J* 1.3, C***H₃***C=), 1.00 (3H, d, *J* 6.8, C***H₃***CH); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 133.5 (CH), 132.0 (C), 130.5 (C), 129.0 (CH), 113.6 (CH), 74.4 (CH_2), 72.5 (CH_2), 55.2 (CH_3), 52.3 (CH_2), 33.1 (CH), 17.2 (CH_3), 14.3 (CH_3); HRMS mass not found.

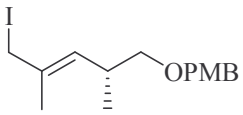
(*R*,*E*)-1-((5-Bromo-2,4-dimethylpent-3-enyloxy)methyl)-4-methoxybenzene 234



To a solution of alcohol **232** (1.89 g, 4.70 mmol) in CH_3CN (60 mL) at 0 °C were added triphenylphosphine (2.46 g, 9.40 mmol) and carbon tetrabromide (3.10 g, 9.40 mmol).

After 15 min, the reaction mixture was filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave bromide **234** as a colourless oil (1.27 g, 86%). R_f = 0.70 (petrol/EtOAc, 7:3); $[\alpha]_D^{24}$ –14.4 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2959, 2933, 2859, 1612, 1456, 1302, 1085, 1036; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.5, ***Ph***), 6.90 (2H, d, *J* 8.5, ***Ph***), 5.43 (1H, d, *J* 9.3, C***H***=), 4.46 (2H, s, PhC***H₂***), 3.98 (2H, s, BrC***H₂***), 3.82 (3H, s, ***Me***O), 3.32 (1H, dd, *J* 7.8, 5.4, PMBOC***H***H), 3.29 (1H, dd, *J* 7.8, 5.4, PMBOCH***H***), 2.75−2.65 (1H, m, MeC***H***), 1.81 (3H, d, *J* 1.2, C***H₃***C=), 1.01 (3H, d, *J* 6.7, C***H₃***CH); δ_c (100 MHz, $CDCl_3$) 158.9 (C), 133.9 (CH), 132.2 (C), 130.4 (C), 128.9 (CH), 113.6 (CH), 74.2 (CH_2), 72.5 (CH_2), 53.1 (CH_3), 41.4 (CH_2), 33.3 (CH), 17.0 (CH_3), 14.8 (CH_3); HRMS (ES+) calcd. for $C_{15}H_{21}BrO_2Na$, $(M+Na)^+$: 337.0617, found 337.0623.

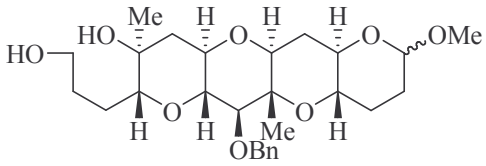
(*R*,*E*)-1-((5-Iodo-2,4-dimethylpent-3-enyloxy)methyl)-4-methoxybenzene 235



To a solution of alcohol **232** (250.3 mg, 1.000 mmol) in CH_2Cl_2 (2 mL) at –10 °C were added triphenylphosphine (288.5 mg, 1.100 mmol) and imidazole (81.7 mg, 1.20 mmol). Iodine (266.5 mg, 1.050 mmol) was added portionwise. After 15 min, sat. aqueous $Na_2S_2O_8$ (5 mL) was added and extracted several times with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 95:5) gave iodide **235** as a pale yellow oil (345.6 mg, 96%). R_f = 0.71 (8:2 petrol/EtOAc); $[\alpha]_D^{26}$ –39.4 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2956, 2929, 2853, 1612, 1511, 1245, 1087, 1034, 819; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.7, ***Ph***), 6.89 (2H, d, *J* 8.7, ***Ph***), 5.50 (1H, d, *J* 9.2, C***H***=), 4.44 (2H, s, PhC***H₂***), 3.94 (2H, s, IC***H₂***), 3.82 (3H, s, ***Me***O), 3.29 (1H, dd, *J* 9.1, 6.6, PMBOC***H***H), 3.25 (1H, dd, *J* 9.1, 6.5, PMBOCH***H***), 2.71–2.60 (1H, m, MeC***H***),

1.81 (3H, d, *J* 1.3, C***H*****3**C=), 0.96 (3H, d, *J* 6.7, C***H*****3**CH); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 133.3 (C), 132.4 (CH), 130.5 (C), 129.1 (CH), 113.7 (CH), 74.1 (CH_2), 72.5 (CH_2), 55.2 (CH_3), 33.6 (CH), 16.8 (CH_3), 16.6 (CH_2), 15.7 (CH_3); HRMS Mass not found.

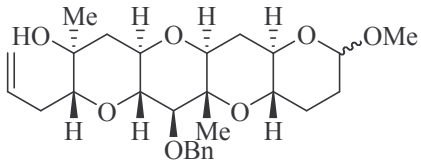
12-Benzyloxy-2-(3-hydroxy-propyl)-8-methoxy-3,11a-dimethyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-ol 236



To a solution of alcohol **209** (436.8 mg, 0.7128 mmol) in CH_2Cl_2 (50 mL) and H_2O (2.5 mL) at 0 °C was added DDQ (242.8 mg, 1.069 mmol) portionwise. After 1 h at 0 °C, the reaction mixture was allowed to warm to rt and stirring continued for 1 h. The reaction was quenched with sat. aqueous $NaHCO_3$ (100 mL). After 15 min of vigorous stirring, the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (CH_2Cl_2/MeOH, 9:1) gave alcohol **236** as a white foam (320.8 mg, 91%). R_f = 0.10 (petrol/EtOAc, 1:1); υ_{max}/cm^{-1} ($CHCl_3$) 3607, 3491, 2951, 2888, 1052; δ_H (400 MHz, C_6D_6, mixture of diastereomers) 7.58 (2H, d, *J* 7.6, ***Ph***), 7.30−7.25 (2H, m, ***Ph***), 7.16−7.12 (1H, m, ***Ph***), 5.02 (0.7H, d, *J* 11.9, PhC***H***H), 4.98 (0.3H, d, *J* 11.9, PhC***H***H), 4.95 (0.7H, d, *J* 11.9, PhCH***H***), 4.94 (0.3H, d, *J* 11.9, PhC***H***H), 4.45 (0.8H, d, *J* 3.2, MeOC***H***O), 4.45 (0.2H, dd, *J* 9.1, 2.1, MeOC***H***O), 3.67−3.46 (4H, m), 3..34−3.01 (7H, m), 2.93 (1H, dd, *J* 12.2, 3.8), 2.64 (1H, brs, ***H***OCH$_2$), 2.23−2.18 (1H, m), 2.16 (1H, dd, *J* 11.5, 3.9), 2.09 (1H, ddd, *J* 11.2, 4.0, 4.0), 1.97−1.61 (7H, m), 1.53−1.39 (2H, m), 1.48 (2.1H, s, BnOCHC***Me***), 1.32 (0.9H, s, BnOCHC***Me***), 1.17 (2.1H, s, HOC***Me***), 1.13 (09H, s, HOC***Me***); δ_c (100 MHz, C_6D_6) 139.8 (C), 128.4 (CH), 128.3 (2 × CH), 128.2

(CH), 127.6 (CH), 103.4 (CH), 97.9 (CH), 85.8 (CH), 84.8 (CH), 84.7 (CH), 82.6 (CH), 79.1 (C), 79.0 (C), 78.8 (CH), 78.7 (CH), 77.0 (CH), 76.9 (CH), 75.4 (CH), 74.5 (CH_2), 70.9 (2 × C), 70.3 (CH), 69.9 (CH), 69.0 (CH), 62.5 (2 × CH_2), 51.6 (CH_3), 54.2 (CH_3), 46.3 (CH_2), 31.2 (CH_2), 31.0 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 28.5 (CH_2), 25.8 (CH_2), 25.5 (CH_2), 21.8 (2 × CH_3), 11.4 (CH_3); HRMS (ES+) calcd. for $C_{27}H_{40}O_8Na$, $(M+Na)^+$: 515.2615, found 515.2602.

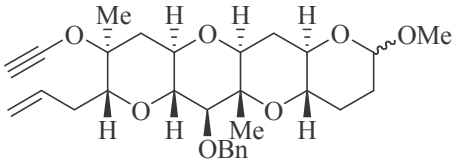
2-Allyl-12-benzyloxy-8-methoxy-11a-methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-ol 237



To a solution of diol **236** (50.2 mg, 0.102 mmol) and recrystallized 2-nitrophenyl selenocyanate (30.2 mg, 0.133 mmol) in THF (2 mL) at rt was added *n*-Bu_3P (33 μL, 1.1 mmol). After 30 min, the reaction mixture was cooled to 0 °C and $NaHCO_3$ (100 mg, 1.19 mmol) followed by H_2O_2.(58 μL, 0.51 mmol, 30 % in water) were added. The reaction mixture was stirred at 50 °C for 1 h, then cooled to rt. Sat. aqueous Na_2CO_3 (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 1:1) gave alkene **237** as a light brown foam (46.9 mg, 98%). R_f = 0.33 (petrol/EtOAc, 1:1); $[\alpha]_D^{24}$ +45.6 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3605, 2953, 2896, 1092, 1053; δ_H (400 MHz, C_6D_6, major diastereomer) 7.58 (2H, d, *J* 7.6, ***Ph***), 7.25 (2H, dd, *J* 7.6, 7.6, ***Ph***), 7.13−7.11 (1H, m, ***Ph***), 6.05 (1H, dddd, *J* 17.1, 10.2, 6.6, 6.6, H_2C=C***H***), 5.18 (1H, dd, *J* 17.1, 1.6, ***H***HC=), 5.10 (1H, d, *J* 10.2, H***H***C=), 5.03 (1H, d, *J* 12.2, PhC***H***H), 4.99 (1H, d, *J* 12.2,

PhCH***H***), 4.45 (1H, d, *J* 3.3, MeOC***H***O), 3.53 (1H, ddd, *J* 11.5, 9.8, 4.6, MeOCHOC***H***), 3.46 (1H, d, *J* 9.3, BnOC***H***), 3.34 (1H, ddd, *J* 11.0, 11.0, 3.9, $MeOCHCH_2CH_2C$***H***), 3.20 (1H, dd, *J* 9.4, 9.3, BnOCHC***H***), 3.18 (3H, s, O***Me***), 3.07–3.01 (2H, m, BnOCHCHC***H***, H_2C=$CHCH_2C$***H***), 2.93 (1H, dd, *J* 12.1, 3.8, BnOCHCMeC***H***), 2.42 (1H, brdd, *J* 14.7, 7.1, H_2C=CHCH***H***), 2.19−2.13 (1H, m, H_2C=CHC***H***H), 2.09 (1H, ddd, *J* 11.2, 4.1, 4.1, MeOCHOCHC***H***H), 2.03 (1H, dd, *J* 11.4, 3.9, HOCMeC***H***H), 1.95–1.89 (2H, m, MeOCHOCHCH***H***, $MeOCHCH_2C$***H***H), 1.74–1.65 (2H, m, $MeOCHCH_2CH$***H***, MeOCHC***H***H), 1.52–1.40 (2H, m, MeOCHCH***H***, HOCMeCH***H***), 1.38 (3H, s, BnOCHC***Me***), 1.06 (3H, s, HOC***Me***); δ_c (100 MHz, C_6D_6) 140.3 (C), 136.7 (CH), 128.3 (CH), 127.9 (CH), 127.4 (CH), 111.4 (CH_2), 98.0 (CH), 85.2 (CH), 84.6 (CH), 83.3 (CH), 79.0 (CH), 78.6 (C), 76.7 (CH), 74.5 (CH_2), 70.7 (CH), 70.3 (C), 69.1 (CH), 54.2 (CH_3), 46.2 (CH_2), 33.7 (CH_2), 30.8 (CH_2), 30.1 (CH_2), 25.5 (CH_2), 21.9 (CH_3), 11.3 (CH_3); HRMS (ES+) calcd. for $C_{27}H_{38}O_7Na$, $(M+Na)^+$: 497.2510, found 497.2501.

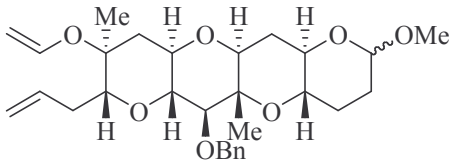
2-Allyl-12-benzyloxy-3-ethynyloxy-8-methoxy-11a-methyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacene 238



To a solution of dry potassium hydride (140.0 mg, 1.050 mmol) in THF (3 mL) at 0 °C was added alcohol **237** (49.8 mg, 0.105 mmol). After 30 min at 0 °C, the reaction mixture was warmed to rt and stirring continued for 30 min. The reaction was cooled to 0 °C and freshly distilled trichloroethylene (11 μL, 0.13 mmol) was added. The resulting mixture was allowed to warm to rt for 1 h. Then, *n*-BuLi (525 μL of a 1.6M solution in hexane, 0.315 mmol,) was added at –78 °C and the reaction mixture was slowly warmed to 0 °C.

After 2 h, the reaction was quenched with MeOH (2 mL). H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 8:2; silica treated with 1% Et_3N) gave alkynyl ether **238** as a colourless glass (38.8 mg, 74% over 2 steps). R_f = 0.15 (petrol/EtOAc, 9:1); $[\alpha]_D^{24}$ +66.8 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3321, 2954, 2898, 2137, 1731, 1089, 1051; δ_H (400 MHz, C_6D_6, major diastereomer) 7.52 (2H, d, *J* 7.1, ***Ph***), 7.23 (2H, dd, *J* 7.5, 7.5, ***Ph***), 7.13−7.11 (1H, m, ***Ph***), 5.92 (1H, dddd, *J* 17.0, 10.3, 6.6, 6.6, H_2C=C***H***), 5.13 (1H, dd, *J* 17.0, 1.7, ***H***HC=), 5.06 (1H, dd, *J* 10.3, 1.7, H***H***C=), 4.94 (2H, s, PhC***H*****$_2$**), 4.44 (1H, d, *J* 3.2, MeOC***H***), 3.55–3.48 (2H, m, MeOCHOC***H***, H_2C=CHCH_2C***H***), 3.35 (1H, d, *J* 9.3, BnOC***H***), 3.30 (1H, ddd, *J* 13.6, 9.6, 3.9, MeOCHC$H_2C$$H_2$C***H***), 3.17 (3H, s, ***Me***O), 3.15 (1H, dd, *J* 9.4, 9.3, BnOCHC***H***), 2.92 (1H, ddd, *J* 12.0, 9.6, 4.0, BnOCHCHC***H***), 2.85 (1H, dd, *J* 12.2, 3.8, BnOCHCMeC***H***), 2.38-2.34 (2H, m, H_2C=CHC***H***H, HC≡COCMeC***H***H), 2.10–2.02 (3H, m, H_2C=CHCH***H***, HC≡COCMeCH***H***, MeOCHOCHC***H***H), 1.95–1.81 (2H, m, MeOCHOCHCH***H***, MeOCHCH_2C***H***H), 1.74–1.62 (2H, m, MeOCHCH_2CH***H,*** MeOCHC***H***H), 1.49 (1H, s, ***H***C≡C), 1.53−1.43 (1H, m, MeOCHCH***H***), 1.26 (3H, s, BnOCHC***Me***), 1.19 (3H, s, HC≡COC***Me***); δ_c (100 MHz, C_6D_6) 140.0 (C), 135.3 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 117.0 (CH_2), 98.0 (CH), 85.9 (CH), 85.9 (C), 84.8 (CH), 84.4 (CH), 83.1 (CH), 81.7 (CH), 79.1 (CH), 78.6 (C), 76.4 (CH), 74.4 (CH_2), 70.3 (CH), 69.1 (CH), 54.2 (CH_3), 41.0 (CH_2), 33.5 (CH_2), 31.1 (C), 30.7 (CH_2), 30.1 (CH_2), 25.5 (CH_2), 18.6 (CH_3), 11.2 (CH_3); HRMS (ES+) calcd. for $C_{29}H_{38}O_7Na$, $(M+Na)^+$: 521.2510, found 521.2494.

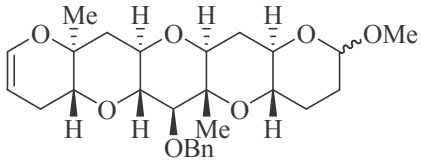
2-Allyl-12-benzyloxy-8-methoxy-3,11a-dimethyl-3-vinyloxy-tetradecahydro-1,5,7,11-tetraoxa-naphthacene 239



To a solution of alkynylether **238** (60.1 mg, 0.120 mmol) in EtOAc (1 mL) at rt were added Lindlar's catalyst (5.3 mg) and quinoline (1.5 μL). The reaction was purged of air, filled with hydrogen and stirred at rt for 18 h. The hydrogen was purged and the solution was filtered through celite®, which was washed several times with EtOAc (3 × 10 mL). The solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1; silica treated with 1% Et_3N) gave compound **239** as a white foam (47.1 mg, 78%). R_f = 0.15 (petrol/EtOAc, 9:1); $[\alpha]_D^{27}$ +44.0 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (liquid film) 2949, 2888, 1633, 1379, 1098, 1054, 1023; δ_H (400 MHz, C_6D_6, major diastereomer) 7.52 (2H, d, *J* 7.6, ***Ph***), 7.23 (2H, dd, *J* 7.4, 7.4, ***Ph***), 7.15–7.11 (1H, m, ***Ph***), 6.18 (1H, dd, *J* 13.5, 6.1, CH_2=C***H***O), 6.01 (1H, dddd, *J* 17.1, 10.2, 6.6, 6.6, H_2C=C***H***CH_2), 5.17 (1H, dd, *J* 17.1, 1.9, ***H***HC=$CHCH_2$), 5.09 (1H, dd, *J* 10.2, 1.9, H***H***C=$CHCH_2$), 5.02 (1H, d, *J* 12.3, PhC***H***H), 4.97 (1H, d, *J* 12.3, PhCH***H***), 4.61 (1H, dd, *J* 13.5, 0.4, ***H***HC=CHO), 4.44 (1H, d, *J* 3.2, MeOC***H***), 4.07 (1H, dd, *J* 6.1, 0.4, H***H***C=CHO), 3.52 (1H, ddd, *J* 11.6, 9.6, 4.5, MeOCHOC***H***), 3.42 (1H, d, *J* 9.3, BnOC***H***), 3.37–3.30 (2H, m, H_2C=$CHCH_2$C***H***, MeOCHCH_2CH_2C***H***), 3.18 (1H, dd, *J* 9.5, 9.3, BnOCHC***H***), 3.17 (3H, s, ***Me***O), 2.97 (1H, ddd, *J* 12.0, 9.7, 4.0, BnOCHCHC***H***), 2.90 (1H, dd, *J* 12.2, 3.8, BnOCHCMeC***H***), 2.52 (1H, ddd, *J* 14.5, 6.7, 1.5, H_2C=CHC***H***H), 2.15–2.07 (3H, m, CH_2=CHOCMeC***H***H, H_2C=CHCH***H***, MeOCHOCHC***H***H), 1.97–1.82 (2H, m, MeOCHOCHC***H***H, MeOCHCH_2C***H***H), 1.73–1.62 (3H, m, CH_2=CHOCMeCH***H***, MeOCHCH_2CH***H***, MeOCHC***H***H), 1.49 (1H, dddd, *J* 13.2, 13.2, 3.9, 3.9, MeOCHCH***H***), 1.31 (3H, s,

BnOCHC***Me***), 1.09 (3H, s, CH_2=CHOC***Me***); δ_c (100 MHz, C_6D_6) 145.0 (CH), 140.2 (C), 136.2 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 116.6 (CH_2), 98.0 (CH), 92.7 (CH_2), 84.5 (CH), 83.3 (CH), 83.2 (CH), 79.0 (CH), 78.6 (C), 77.1 (C), 76.3 (CH), 74.4 (CH_2), 70.3 (CH), 69.1 (CH), 54.2 (CH_3), 42.1 (CH_2), 33.5 (CH_2), 30.8 (CH_2), 30.1 (CH_2), 25.5 (CH_2), 19.2 (CH_3), 11.2 (CH_3); HRMS (EI+) calcd. for $C_{29}H_{40}O_7$, $(M+H)^+$: 500.2774, found 500.2775.

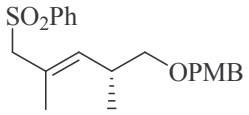
6-Benzyloxy-2-methoxy-5a,11a-dimethyl-3,4,4a,5a,6,6a,7a,8,11a,12,12a,13a,14,14a-tetradecahydro-2*H*-1,5,7,11,13-pentaoxa-pentacene 192



To a solution of enolether **239** (43.8 mg, 0.0875 mmol) in toluene (9 mL) at 70 °C was added Grubbs second generation catalyst (7.5 mg, 0.00875 mmol). After 1 h at 70 °C, the reaction mixture was cooled to rt and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1; silica treated with 1% Et_3N) gave compound **192** as a white foam (38.2 mg, 92%). R_f= 0.15 (petrol/EtOAc, 9:1); $[\alpha]_D^{23}$ +26.2 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (liquid film) 2948, 2889, 1100, 1074, 1053, 1022; δ_H (400 MHz, C_6D_6, major diastereomer) 7.52 (2H, d, *J* 7.6, ***Ph***), 7.22 (2H, dd, *J* 7.4, 7.4, ***Ph***), 7.15–7.10 (1H, m, ***Ph***), 6.07−6.04 (1H, m, OC***H***=CH), 5.03 (1H, d, *J* 12.3, PhC***H***H), 4.94 (1H, d, *J* 12.3, PhCH***H***), 4.44 (1H, d, *J* 3.3, MeOC***H***), 4.48 (1H, ddd, *J* 5.7, 5.7, 1.9, OCH=C***H***), 3.51 (1H, ddd, *J* 11.5, 9.6, 4.4, MeOCHOC***H***), 3.46 (1H, d, *J* 9.3, BnOC***H***), 3.32 (1H, ddd, *J* 11.1, 9.6, 4.0, MeOCHCH$_2$CH$_2$C***H***), 3.27 (1H, dd, *J* 9.3, 9.3, BnOCHC***H***), 3.22 (1H, dd, *J* 10.7, 5.9, OCH=CHCH$_2$C***H***), 3.19–3.12 (1H, m, BnOCHCHC***H***), 3.18 (3H, s, ***Me***O), 2.91 (1H, dd, *J* 12.2, 3.9, BnOCHCMeC***H***), 2.31 (1H, dd, *J* 11.4, 4.0, =CHOCMeC***H***H), 2.09–2.01 (2H,

m, OCH=CHC***H***H, MeOCHOCHC***H***H), 1.94–1.61 (6H, m, =CHOCMeCH***H***, OCH=CHCH***H***, MeOCHOCHCH***H***, MeOCHCH$_2$C***H$_2$***, MeOCHC***H***H), 1.47 (1H, dddd, *J* 13.4, 13.4, 4.1, 4.1, MeOCHCH***H***), 1.35 (3H, s, BnOCHC***Me***), 1.20 (3H, s, =CHOC***Me***); δ_c (100 MHz, C_6D_6) 141.4 (CH), 140.2 (C), 128.3 (CH), 127.8 (CH), 127.4 (CH), 98.0 (CH), 97.9 (CH), 84.9 (CH), 83.4 (CH), 79.1 (CH), 78.8 (C), 78.0 (CH), 76.7 (CH), 74.6 (CH_2), 74.2 (C), 70.3 (CH), 69.1 (CH), 54.2 (CH_3), 43.1 (CH_2), 30.7 (CH_2), 30.1 (CH_2), 25.5 (CH_2), 24.1 (CH_2), 17.1 (CH_3), 11.3 (CH_3); HRMS (EI+) calcd. for $C_{27}H_{37}O_7$, $(M+H)^+$: 472.2461, found 472.2462.

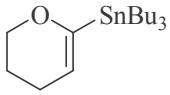
(*R,E*)-1-((2,4-dimethyl-5-(phenylsulfonyl)pent-3-enyloxy)methyl)-4-methoxybenzene 254



To a solution of bromide **234** (1.00 g, 3.20 mmol) and $NaHCO_3$ (40.0 mg, 0.482 mmol) in DMF (20 mL) at rt was added $PhSO_2Na$ (1.05 g, 6.40 mmol). The reaction mixture was stirred for 24 hours at rt. Saturated aqueous solution of $NaHCO_3$ (30 mL) was added and extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 7:3) gave the allylsulfone **254** as a colourless oil (1.00 g, 84 %). R_f = 0.23 (petrol/EtOAc, 7:3); δ_H (400 MHz, $CDCl_3$) 7.83 (2H, m, ***Ph***SO_2), 7.61 (1H, m, ***Ph***SO_2), 7.49 (2H, m, ***Ph***SO_2), 7.22 (2H, d, *J* 8.5, MeO***Ph***), 6.88 (2H, d, *J* 8.5, MeO***Ph***), 4.82 (1H, d, *J* 9.0, C=C***H***), 4.38 (2H, m, MeOPhC***H$_2$***), 3.80 (3H, s, ***Me***O), 3.73 (2H, s, $PhSO_2$C***H$_2$***), 3.07 (2H, m, PMBOC***H$_2$***), 2.62 (1H, m, PMBOCH$_2$CMe***H***), 1.78 (3H, d, *J* 1.2, $PhSO_2CH_2$CC***H$_3$***), 0.78 (3H, d, *J* 6.7, PMBOCH$_2$CH***Me***); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 138.9 (CH), 138.0 (C), 133.4 (CH), 130.3 (C), 128.9 (CH), 128.7 (CH), 128.5

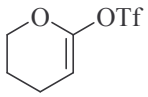
(CH), 123.7 (C), 113.6 (CH), 74.0 (CH_2), 72.4 (CH_2), 66.0 (CH_2), 55.2 (CH_3), 33.2 (CH), 16.8 (CH_3), 16.7 (CH_3).

Tributyl(5,6-dihydro-4*H*-pyran-2-yl)stannane 261 [71]



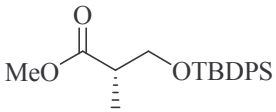
To a solution of 3,4-dihydro-2*H*-pyran (2.67 mL, 29.3 mmol) in THF (100 mL) at –78 °C was added *t*-BuLi (19.0 mL of a 1.7 M solution in ether, 32.3 mmol). After 15 min, the reaction mixture was allowed to warm to –20 °C for 30 min. The reaction mixture was cooled to –78 °C and Bu_3SnCl (12.0 mL, 44.0 mmol) was added slowly. After being stirred at –20 °C for 2 h, a sat. solution of NH_4Cl (50 mL) was carefully added and the mixture was extracted with ether (3 × 20 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by distillation (103 °C at 0.1 mmHg) gave the stannane **261** as a colourless oil (11.4 g, 100%). υ_{max}/cm^{-1} (neat) 2959, 2924, 2871, 2854, 1462, 1069, 1052; δ_H (400 MHz, $CDCl_3$) 4.74 (1H, t, *J* 4.0, OC=C***H***), 3.91−3.87 (2H, m, OC***H₂***), 2.02−1.98 (2H, m, OC=CHC***H₂***), 1.87−1.81 (2H, m, OCH_2C***H₂***), 1.70–0.80 (27H, m, Sn***Bu₃***); δc (100 MHz, $CDCl_3$) 162.6 (C), 112.4 (CH), 66.0 (CH_2), 29.0 (CH_2), 27.8 (CH_2), 27.2 (CH_2), 26.9 (CH_2), 23.2 (CH_2), 21.2 (CH_2), 17.5 (CH_2), 13.7 (CH_3), 13.6 (CH_3), 9.3 (CH_2); HRMS mass not found.

5,6-Dihydro-4*H*-pyran-2-yl trifluoromethanesulfonate 263



To a solution of δ-valerolactone (186 μL, 2.00 mmol) and Commins' reagent (1.18 g, 3.00 mmol) in THF (5 mL) at –78 °C was added KHMDS (8.0 mL of a 0.5 M solution in THF, 4 mmol). After 1 h, the reaction mixture was allowed to warm to rt. The reaction mixture was concentrated *in vacuo*. The residue was triturated with petrol (10 mL) and filtered. The filtrate was concentrated *in vacuo* and the same procedure was repeated to afford the enol triflate **263** as a colourless oil (206.2 mg, 44%). υ_{max}/cm^{-1} (neat) 2940, 2891, 2858, 1699, 1425, 1213, 1140, 1116, 903, 832, 807, 623, 597; δ_H (400 MHz, $CDCl_3$) 4.73 (1H, t, *J* 3.8, OC=C***H***), 4.24–4.22 (2H, m, OC***H₂***), 2.23–2.25 (2H, m, OC=CHC***H₂***), 1.91–1.85 (2H, m, OCH_2C***H₂***); δc (100 MHz, $CDCl_3$) 150.1 (C), 118.4 (C, $J_{C\text{-}F}$ 321), 87.9 (CH), 69.4 (CH_2), 21.3 (CH_2), 19.6 (CH_2); HRMS mass not found.

(*S*)-Methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanoate 271 [110]

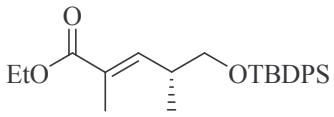


To a solution of (*S*)-methyl 3-hydroxy-2-methylpropanoate (1.18 g, 10.0 mmol) and imidazole (1.48 g, 20.0 mmol) in DMF (10 mL) at 0 °C was added TBDPSCl (2.9 mL, 11 mmol). After 2 h at rt, H_2O (50 mL) was added and the aqueous phase was extracted with ether (150 mL). The organic layer was washed with 1 M HCl (100 mL), sat. aqueous $NaHCO_3$ (100 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The

[110] C. H. Heathcock, S. D. Young, J. P. Hagen, R. Pilli, U. Badertscher, *J. Org. Chem.* **1985**, *50*, 2095.

colourless oil was used to the next step without further purification (quantitative). R_f= 0.57 (petrol/EtOAc, 9:1); $[\alpha]_D^{26}$ +16.0 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2952, 2932, 2857, 1741, 1428, 1111, 702, 505; δ_H (400 MHz, $CDCl_3$) 7.68–7.66 (4H, m, ***Ph***), 7.45–7.38 (6H, m ***Ph***), 3.84 (1H, dd, *J* 9.7, 6.9, TBDPSOC***H***H), 3.72 (1H, dd, *J* 9.7, 5.8, TBDPSOCH***H***), 3.70 (3H, s, ***Me***O), 2.78–2.79 (1H, m, MeC***H***), 1.17 (3H, d, *J* 7.0, ***Me***CH), 1.04 (9H, s, {C***H₃***}$_3$CSi); δ_c (100 MHz, $CDCl_3$) 175.4 (C), 135.5 (CH), 134.8 (C), 133.5 (C), 129.6 (CH), 127.6 (CH), 65.9 (CH_2), 51.5 (CH_3), 42.4 (CH), 26.7 (CH_3), 19.2 (C), 13.5 (CH_3); HRMS (CI+) calcd. for $C_{21}H_{29}O_3Si$, $(M+H)^+$: 357.1886, found 357.1884.

(*R*,*E*)-Ethyl 5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-enoate 272

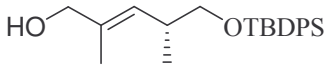


To a solution of methyl ester **271** (10.0 mmol) in toluene (50 mL) at –78 °C was added Dibal-H (10 mL of a 1.0 M solution in cyclohexane, 10 mmol) by a syringe pump over a period of 15 min. After 1.5 h, the reaction mixture was carefully quenched with a saturated solution of Rochelle's salt (300 mL). Ether (300 mL) was then added and the mixture was stirred vigorously for 30 min at rt. The aqueous phase was extracted with ether (2 × 100 mL). The combined organics were washed with brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

To a solution of crude aldehyde (10.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added ethyl 2-(triphenylphosphoranylidene)propionate (5.43 g, 15.0 mmol) portionwise and the reaction was then heated at reflux for 18 h. The reaction was allowed to cooled to rt and the solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 95:5) gave alkene **272** as a colourless oil contaminated with 18% of starting material (2.97 g, 72% over 3 steps). R_f= 0.42 (petrol/EtOAc, 95:5); $[\alpha]_D^{26}$ +4.7 (*c* = 1.0,

$CHCl_3$); υ_{max}/cm^{-1} (neat) 2959, 2931, 2857, 1713, 1235, 1111, 702; δ_H (400 MHz, $CDCl_3$) 7.68–7.67 (4H, m, ***Ph***), 7.44–7.37 (6H, m ***Ph***), 6.61 (1H, dd, *J* 9.9, 1.4, C***H***=), 4.24–4.18 (2H, m, $CH_3C\boldsymbol{H_2}O$), 3.57–3.53 (2H, m, TBDPSOC***H*****$_2$**), 2.81–2.71 (1H, m, MeC***H***), 1.82 (3H, d, *J* 1.4, ***CH*****$_3$**C=), 1.31 (3H, t, *J* 7.1, C***H*****$_3$**CH_2O), 1.07–1.05 (12H, m, ***Me***CH, {C***H*****$_3$**$\}_3$CSi); δ_c (100 MHz, $CDCl_3$) 168.2 (C), 144.4 (CH), 135.6 (3 × CH), 133.6 (2 × C), 129.6 (2 × CH), 127.9 (C), 127.6 (CH), 67.7 (CH_2), 60.4 (CH_2), 48.1 (CH), 26.8 (CH_3), 19.2 (C), 16.3 (CH_3), 14.3 (CH_3), 12.6 (CH_3); HRMS (CI+) calcd. for $C_{25}H_{35}O_3Si$, $(M+H)^+$: 411.2355, found 411.2357.

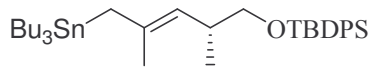
(*R*,*E*)-5-(*Tert*-butyldiphenylsilyloxy)-2,4-dimethylpent-2-en-1-ol 273



To a solution of ethyl ester **272** (2.97 g, 7.23 mmol) in ether (50 mL) at 0 °C was added Dibal-H (18 mL of a 1.0 M solution in cyclohexane, 18 mmol). After 15 min, the reaction mixture was carefully quenched with a saturated solution of Rochelle's salt (200 mL) and stirred vigorously for 1 h at rt. The aqueous phase was extracted with ether (3 × 100 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave alcohol **273** as a colourless oil (2.27 g, 85%). R_f = 0.14 (petrol/EtOAc, 9:1); $[\alpha]_D^{26}$ – 16.3 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3341 (br), 3608, 2958, 2930, 2857, 1428, 1112, 701; δ_H (400 MHz, $CDCl_3$) 7.68–7.67 (4H, m, ***Ph***), 7.46–7.37 (6H, m ***Ph***), 5.17 (1H, d, *J* 9.4, C***H***=), 3.96 (2H, s, HOC***H*****$_2$**), 3.51 (1H, dd, *J* 9.7, 6.3, TBDPSOC***H***H), 3.48 (1H, dd, *J* 9.7, 6.7, TBDPSOCH***H***), 2.68–2.59 (1H, m, MeC***H***), 1.62 (3H, d, *J* 1.0, ***CH*****$_3$**C=), 1.07 (9H, s, {C***H*****$_3$**$\}_3$CSi), 1.01 (3H, d, *J* 6.7, ***Me***CH); δ_c (100 MHz, $CDCl_3$) 135.6 (2 × CH), 135.1 (C), 133.9 (2 × C), 129.5 (2 × CH), 128.9 (CH), 127.6 (CH), 127.5 (CH), 68.8

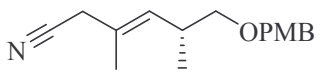
(CH_2), 68.4 (CH_2), 35.0 (CH), 26.8 (CH_3), 19.3 (C), 17.2 (CH_3), 13.9 (CH_3); HRMS (CI+) calcd. for $C_{23}H_{33}O_2Si$, $(M+H)^+$: 369.2250, found 369.2257.

(*R*,*E*)-Tributyl(5-(4-methoxybenzyloxy)-2,4-dimethylpent-2-enyl)stannane 274



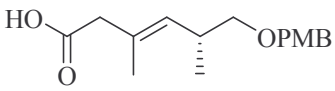
To a solution of allylic alcohol **273** (1.12 g, 3.00 mmol) in THF (2.5 mL) at –78 °C was added *n*-BuLi (2.3 mL of a 1.3 M in hexane, 3.0 mmol). After 25 min, MsCl (292 μL, 3.00 mmol) was added and the mixture was stirred for 30 min at –78 °C. A freshly prepared solution of $LiSnBu_3$ (2.5 mL, 3.0 mmol) was then added and the reaction mixture was allowed to warm to rt. After being stirred at rt overnight, H_2O (50 mL) was carefully added and the mixture was extracted with ether (3 × 20 mL). The combined organics were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by filtration through a plug of deactivated silica (petrol/Et_3N, 100:3) gave allylic stannane **274** as a colourless oil (1.34 g, 57 %). R_f decomposiotion; $[\alpha]_D^{26}$ +4.4 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2956, 2926, 2857, 1111, 700; δ_H (400 MHz, $CDCl_3$) 7.71–7.68 (4H, m, ***Ph***), 7.45–7.48 (6H, m, ***Ph***), 4.72 (2H, dd, *J* 9.9, 0.9, C=C***H***), 3.52 (1H, dd, *J* 9.7, 5.3, TBDPSOCH***H***), 3.35 (1H, dd, *J* 9.7, 8.4, TBDPSOC***H***H), 2.59–2.49 (1H, m, $TBDPSOCH_2CMe$***H***), 1.73 (1H, dd, *J* 11.3, 0.6, Bu_3SnC***H***H), 1.67 (1H, dd, *J* 11.3, 0.6, Bu_3SnCH***H***), 1.54–1.42 (6H, m, ***Bu₃***Sn), 1.52 (3H, d, *J* 1.2, ***CH₃***C=), 1.35–1.24 (8H, m, ***Bu₃***Sn), 1.08 (9H, s, {C***H₃***}$_3$Si), 1.02 (3H, d, *J* 6.7, ***CH₃***CH), 0.88 (9H, t, *J* 7.2, ***Bu₃***Sn), 0.84–0.80 (4H,m, ***Bu₃***Sn); δ_c (100 MHz, $CDCl_3$) 135.6 (2 × CH), 135.6 (C), 134.1 (2 × C), 129.4 (2 × CH), 127.5 (br CH), 122.8 (CH), 68.9 (CH_2), 35.7 (CH), 29.1 (CH_2), 27.4 (CH_2), 26.9 (CH_3), 22.1 (CH_2), 19.3 (C), 18.7 (CH_3), 18.0 (CH_3), 13.7 (CH_3), 9.4 (CH_2); HRMS Mass not found.

(*R*,*E*)-6-(4-Methoxybenzyloxy)-3,5-dimethylhex-3-enenitrile 283



To a solution of bromide **234** (195.6 mg, 0.6245 mmol) in MeCN (0.3 mL) at 0 °C was added TBACN (176.3 mg, 0.6245 mmol). After 18 h at rt, the reaction was concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 8:2) gave compound **283** as a pale yellow oil (139.5 mg, 86%). R_f = 0.53 (ether/petrol, 7:3); $[\alpha]_D^{24}$ –11.1 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2958, 2934, 2859, 2838, 2251, 1612, 1087, 1038; δ_H (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.7, ***Ph***), 6.89 (2H, d, *J* 8.7, ***Ph***), 5.32 (1H, dddd, *J* 9.2, 2.7, 1.3, 1.2, C***H***=), 4.44 (2H, s, MeOPhC***H*****$_2$**), 3.82 (3H, s, ***Me***O), 3.29–3.27 (2H, m, PMBOC***H*****$_2$**), 3.03 (2H, d, *J* 0.9, N≡CC***H*****$_2$**), 2.76–2.68 (1H, m, PMBOCH$_2$CMe***H***), 1.76 (3H, d, *J* 1.2, C***H*****$_3$**C=), 1.10 (3H, d, *J* 6.8, PMBOCH$_2$C***Me***H); δ_c (100 MHz, $CDCl_3$) 158.9 (C), 132.4 (CH), 130.3 (C), 128.9 (CH), 124.6 (C), 117.6 (C), 113.5 (CH), 74.3 (CH_2), 72.4 (CH_2), 55.0 (CH_3), 33.1 (CH), 27.0 (CH_2), 17.1 (CH_3), 16.1 (CH_3); HRMS (ES+) calcd. for $C_{16}H_{21}NO_2Na$, $(M+Na)^+$: 282.1465, found 282.1466.

(*R*,*E*)-6-(4-Methoxybenzyloxy)-3,5-dimethylhex-3-enoic acid 285

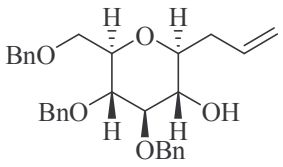


To a solution of nitrile **283** (100.0 mg, 0.3856 mmol) in CH_2Cl_2 (2 mL) at –78 °C was added Dibal-H (579 μL of a 1.0 M solution in CH_2Cl_2, 0.56 mmol,). After 1 h at –78 °C, EtOH (1 mL) was slowly added. Then, the reaction mixture was poured into a solution of EtOAc/sat. NH_4Cl (20 mL, 1:1). After 1 h at rt, a saturated solution of Rochelle's salt was

added and stirring continued for 30 min at rt. Brine (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

To a solution of crude aldehyde **284** (0.386 mmol) in *t*-BuOH (4 mL) at rt was added 2-methylbut-2-ene (328 μL, 3.09 mmol). A solution of $NaClO_2$ (261.8 mg, 2.895 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (391.4 mg, 2.506 mmol) in H_2O (2 mL) was added dropwise. After 1 h at rt, brine (10 mL) was added and the aqueous phase was extracted with ether (2 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc/AcOH, 7:3:0.1) gave compound **285** as a colourless oil (83.2 mg, 78% over 2 steps). R_f = 0.10 (ether/petrol, 8:2); $[\alpha]_D^{26}$ –2.3 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (liquid film) 3469 (br), 2958, 2930, 2855, 2838, 1712, 1612, 1512, 1248, 1033; δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* 8.5, ***Ph***), 6.89 (2H, d, *J* 8.5, ***Ph***), 5.15 (1H, d, *J* 9.0, C***H***=), 4.48 (1H, d, *J* 11.8, MeOPhC***H***H), 4.45 (1H, d, *J* 11.8, MeOPhCH***H***), 3.82 (3H, s, ***Me***O), 3.33 (1H, dd, *J* 9.1, 6.5, PMBOC***H***H), 3.28 (1H, dd, *J* 9.1, 7.1, PMBOCH***H***), 3.04 (2H, s, HOOCC***H₂***), 2.78–2.72 (1H, m, PMBOCH$_2$CMe***H***), 1.76 (3H, d, *J* 0.9, C***H₃***C=), 1.00 (3H, d, *J* 6.7, PMBOCH$_2$C***Me***H); δ_c (100 MHz, $CDCl_3$) 177.8 (C), 159.0 (C), 132.7 (CH), 130.5 (C), 129.1 (CH), 128.3 (C), 113.6 (CH), 74.6 (CH_2), 72.4 (CH_2), 55.1 (CH_3), 44.7 (CH_2), 33.0 (CH), 17.4 (CH_3), 16.4 (CH_3); HRMS Mass not found.

(2*S*,3*S*,4*R*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-tetrahydro-2*H*-pyran-3-ol 149 [111]



To a solution of protected glucal **148** (874.7 mg, 2.100 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DMDO (29 mL of a ~0.08 M solution in acetone, 2.3 mmol) was added carefully by addition funnel over a period of 0.5 h. After an additional 0.5 h, the solvent was removed under reduced pressure **without exceeding 5 °C**. The crude oil was diluted with CH_2Cl_2 (10 mL), washed with water (10 mL) and brine (10 mL). The organic layer was then dried (Na_2SO_4), filtered and the solvent removed *in vacuo* **without exceeding 5 °C**. The crude oil was dried under high-reduced pressure for 1 h.

To a solution of crude epoxide in THF (4 mL) at 0 °C was added allylmagnesium chloride (2.1 mL of a 2 M solution in THF, 4.2 mmol,) by a syringe pump over a period of 15 min. After 2 h at 0 °C, the reaction was quenched by the addition of sat. aqueous NH_4Cl (20 mL). Then, the reaction was diluted with ether (30 mL), washed with sat. aqueous NH_4Cl (20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/Ether, 6:4) gave compound **149** as a solid (747.3 mg, 75% over 2 steps). R_f = 0.55 (petrol/Ether, 1:1); $[\alpha]_D^{26}$ +42.3 (*c* = 1.00, $CHCl_3$); M.P. 66.2–67.0 °C; υ_{max}/cm^{-1} (liquid film) 3314 (br), 3206 (br), 3065, 3025, 2903, 2861, 1493, 1453, 1358, 1145, 1093, 1026, 729, 695; δ_H (400 MHz, $CDCl_3$) 7.39–7.22 (15H, m, ***Ph***), 5.96 (1H, dddd, *J* 17.1, 10.1, 7.0, 7.0, CH_2=C***H***), 5.15 (1H, dddd, *J* 17.1, 2.0, 1.4, 1.4, C***H***H=), 5.10 (1H, dddd, *J* 10.1, 2.0, 1.0, 1.0, CH***H***=), 4.96 (1H, d, *J* 11.6, PhC***H***H), 4.82 (1H, d, *J* 10.8, PhC***H***H), 4.76 (1H, d, *J* 11.6, PhCH***H***), 4.66

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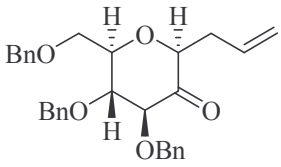
[111] J. D. Rainier, S. P. Allwein, *J. Org. Chem.* **1998**, *63*, 5310.

(1H, d, *J* 12.3, PhC***H***H), 4.62 (1H, d, *J* 10.8, PhCH***H***), 4.60 (1H, d, *J* 12.3, PhCH***H***), 3.78–3.70 (2H, m, BnOC***H₂***), 3.63 (1H, dd, *J* 9.3, 9.3, $BnOCH_2CHC\boldsymbol{H}$), 3.50 (1H, dd, *J* 8.8, 8.8, $BnOCH_2CHCHC\boldsymbol{H}$), 3.45 (1H, ddd, *J* 9.7, 4.0, 2.2, $BnOCH_2C\boldsymbol{H}$), 3.39 (1H, ddd, *J* 9.2, 9.2, 2.6, HOC***H***), 3.28 (1H, ddd, *J* 9.4, 7.3, 3.4, $CH_2{=}CHCH_2C\boldsymbol{H}$), 2.59 (1H, m, $CH_2{=}CHC\boldsymbol{H}$H), 3.33 (1H, ddd, *J* 14.6, 7.3, 7.3, $CH_2{=}CHCH\boldsymbol{H}$), 2.13 (1H, d, *J* 2.1, ***H***O); δ_c (100 MHz, $CDCl_3$) 138.5 (C), 138.2 (C), 138.0 (C), 134.6 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (3 × CH), 127.5 (CH), 117.1 (CH_2), 86.7 (CH), 79.1 (CH), 78.7 (CH), 78.4 (CH), 75.2 (CH_2), 74.8 (CH_2), 73.4 (CH), 73.4 (CH_2), 68.8 (CH_2), 48.2 (CH_2); HRMS (CI+) calcd. for $C_{30}H_{35}O_5$, $(M+H)^+$: 475.2484, found 475.2485.

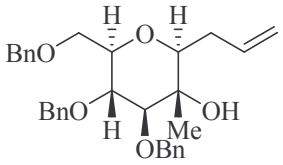
(2*S*,4*S*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-dihydro-2*H*-pyran-3(4*H*)-one



To a solution of alcohol **149** (747.3 mg, 1.575 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Dess-Martin periodinane (734.8 mg, 1.732 mmol) portionwise. The reaction mixture was allowed to warm to rt and stirring continued for 1 h. The reaction was quenched with sat. aqueous $Na_2S_2O_3$ (30 mL). After 30 min of vigorous stirring, the mixture was extracted with ether (2 × 70 mL). The combined organics were washed with sat. aqueous K_2CO_3 (3× 50 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo*. The crude solid was used without further purification (700.0 mg, 94%). R_f = 0.45 (petrol/ether, 1:1); $[\alpha]_D^{26}$ –29 (c 1.0, $CHCl_3$); M.P. 65.6–66.2 °C; υ_{max}/cm^{-1} (neat) 3314 (br), 3206 (br), 3064, 3030, 2911, 2865, 1454, 1106, 736, 698; δ_H (400 MHz, $CDCl_3$) 7.45–7.20 (15H, m, ***Ph***), 5.91 (1H, dddd, *J* 17.0, 10.2, 7.0, 7.0, $CH_2{=}C\boldsymbol{H}$), 5.20 (1H, d, *J* 17.0, C***H***H=), 5.13 (1H, d, *J* 10.2,

CH***H***=), 5.03 (1H, d, *J* 11.3, PhC***H***H), 4.88 (1H, d, *J* 10.8, PhC***H***H), 4.64 (1H, d, *J* 12.3, PhC***H***H), 4.63 (1H, d, *J* 11.3, PhCH***H***), 4.59 (1H, d, *J* 12.3, PhCH***H***), 4.58 (1H, d, *J* 10.8, PhCH***H***), 4.22 (1H, d, *J* 8.8, BnOCH$_2$CHCHC***H***), 3.91 (1H, dd, *J* 9.3, 9.3, BnOCH$_2$CHC***H***), 3.86–3.78 (3H, m, BnOC***H***H, BnOCH$_2$C***H***, CH$_2$=CHCH$_2$C***H***), 3.74 (1H, dd, *J* 10.7, 4.6, BnOCH***H***), 2.66 (1H, ddd, *J* 14.5, 6.0, 6.0, CH$_2$=CHC***H***H), 2.44 (1H, ddd, *J* 14.5, 7.0, 7.0, CH$_2$=CHCH***H***); δ_c (100 MHz, $CDCl_3$) 201.9 (C), 138.0 (C), 138.7 (C), 137.5 (C), 133.7 (CH), 128.4 (2 × CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 117.6 (CH$_2$), 86.7 (CH), 80.4 (CH), 80.2 (CH), 79.2 (CH), 75.0 (CH$_2$), 73.7 (CH$_2$), 73.4 (CH$_2$), 68.7 (CH$_2$), 32.9 (CH$_2$); HRMS (FAB+) calcd. for $C_{30}H_{33}O_5$, $(M+H)^+$: 473.2328, found 473.2323.

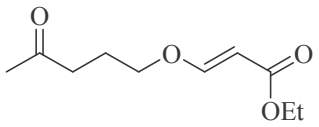
(2*S*,3*S*,4*S*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-methyl-tetrahydro-2*H*-pyran-3-ol 287



To a solution of ketone (163.5 mg, 0.3460 mmol) in toluene (7 mL) at –78 °C was slowly added methyl lithium (432 μL of a 1.6 M solution in ether, 0.69 mmol,). After 1 h at –78 °C, the reaction was carefully quenched by the addition of MeOH (5 mL). A solution of sat. aqueous NH_4Cl (30 mL) was added and washed several times with ether (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether, 6:4) gave compound **287** (73.0 mg), minor diastereomer (28.4 mg) and mixture of diastereomers (26.0 mg) as colourless oils (75% over 2 steps). **Major diastereomer**: R_f= 0.41 (petrol/ether, 1:1); $[\alpha]_D^{26}$ +18.0 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (liquid film) 3564 (br),

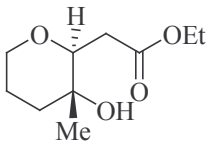
3466 (br), 3064, 3030, 2980, 2904, 2862, 1454, 1111, 1059, 735, 698; δ_H (400 MHz, $CDCl_3$) 7.42–7.22 (15H, m, ***Ph***), 5.96 (1H, dddd, *J* 16.4, 10.2, 7.6, 6.1, CH_2=C***H***), 5.20–5.15 (1H, m, C***H***H=), 5.12–5.09 (1H, m, CH***H***=), 5.00 (1H, d, *J* 11.7, PhC***H***H), 4.84 (1H, d, *J* 10.8, PhC***H***H), 4.83 (1H, d, *J* 11.7, PhCH***H***), 4.70 (1H, d, *J* 12.2, PhC***H***H), 4.60 (1H, d, *J* 10.7, PhCH***H***), 4.57 (1H, d, *J* 10.6, PhCH***H***), 3.80 (1H, dd, *J* 11.1, 2.2, BnOC***H***H), 3.75 (1H, dd, *J* 11.1, 4.1, BnOCH***H***), 3.62 (1H, dd, *J* 9.5, 9.5, $BnOCH_2CHC$***H***), 3.53 (1H, d, *J* 9.5, $BnOCH_2CHCHC$***H***), 3.49 (1H, ddd, *J* 9.7, 4.0, 2.1, $BnOCH_2C$***H***), 3.26 (1H, dd, *J* 9.5, 3.0, CH_2=$CHCH_2C$***H***), 2.48 (1H, ddddd, *J* 14.6, 7.6, 3.0, 1.6, 1.6, CH_2=CHC***H***H), 2.39–2.25 (1H, m, CH_2=CHCH***H***), 1.87 (1H, brs, ***H***O), 1.29 (3H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 138.8 (C), 138.3 (C), 138.1 (C), 135.9 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 127.7 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 116.4 (CH_2), 89.2 (CH), 81.8 (CH), 79.7 (CH), 77.6 (CH), 75.5 (CH_2), 74.9 (CH_2), 74.6 (C), 73.3 (CH_2), 68.9 (CH_2), 48.9 (CH_2), 16.1 (CH_3); HRMS (FAB+) calcd. for $C_{31}H_{37}O_5$, $(M+H)^+$: 489.2641, found 489.2638; **Minor diastereomer**: R_f= 0.17 (petrol/ether, 1:1); $[\alpha]_D^{26}$ –7.2 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (liquid film) 3564 (br), 3466 (br), 3064, 3030, 2980, 2904, 2862, 1454, 1111, 1059, 735, 698; δ_H (400 MHz, $CDCl_3$) 7.37–7.20 (15H, m, ***Ph***), 5.98 (1H, dddd, *J* 17.2, 10.1, 7.4, 6.3, CH_2=C***H***), 5.14 (1H, dd, *J* 17.2, 1.6, C***H***H=), 5.07 (1H, d, *J* 10.1, CH***H***=), 4.99 (1H, d, *J* 11.0, PhC***H***H), 4.80 (1H, d, *J* 10.9, PhC***H***H), 4.71 (1H, d, *J* 11.0, PhC***H***H), 4.64–4.57 (3H, m, PhCH***H***), 3.84 (1H, dd, *J* 9.5, 9.5, $BnOCH_2CHC$***H***), 3.79 (1H, dd, *J* 11.0, 2.0, BnOC***H***H), 3.72 (1H, dd, *J* 11.0, 4.9, BnOCH***H***), 3.44 (1H, ddd, *J* 9.9, 4.9, 2.0, $BnOCH_2C$***H***), 3.32 (1H, d, *J* 9.1, $BnOCH_2CHCHC$***H***), 3.24 (1H, dd, *J* 9.4, 3.2, CH_2=$CHCH_2C$***H***), 2.53–2.45 (1H, m, CH_2=CHC***H***H), 2.40–2.35 (1H, m, CH_2=CHCH***H***), 2.30 (1H, brs, ***H***O), 1.19 (3H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 138.3 (C), 138.0 (C), 137.9 (C), 136.0 (CH), 128.4 (2 × CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (2 × CH), 127.5 (CH), 116.3 (CH_2), 86.4 (CH), 81.9 (CH), 79.6 (CH), 77.2 (CH), 76.2 (CH_2), 74.9 (CH_2), 74.3 (C), 73.5 (CH_2), 69.1 (CH_2), 32.8 (CH_2), 16.1 (CH_3); HRMS (FAB+) calcd. for $C_{31}H_{37}O_5$, $(M+H)^+$: 489.2641, found 489.2646.

(*E*)-Ethyl 3-(4-oxopentyloxy)acrylate 293 [82]



To a solution of 3-acetyl-1-propanol (3.57 g, 35.0 mmol) and *N*-methylmorpholine (7.7 mL, 70 mmol) in CH_2Cl_2 (100 mL) at rt was added ethyl propiolate (5.3 mL, 53 mmol). After 18 h, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 8:2) gave compound **293** as a colourless oil (4.60 g, 66%). R_f = 0.22 (petrol/EtOAc, 8:2); δ_H (400 MHz, $CDCl_3$) 7.54 (1H, d, *J* 12.6, $EtO_2CC\boldsymbol{H}$), 5.16 (1H, d, *J* 12.6, $EtO_2CCH{=}C\boldsymbol{H}$), 4.14 (2H, q, *J* 7.1, $CH_3C\boldsymbol{H_2}O$), 3.83 (2H, t, *J* 6.1, $=CHOC\boldsymbol{H_2}$), 2.55 (2H, t, *J* 6.1, $CH_3COC\boldsymbol{H_2}$), 2.14 (3H, s, $C\boldsymbol{H_3}CO$), 1.95 (2H, m, $CH_3COCH_2C\boldsymbol{H_2}$), 1.24 (3H, t, *J* 7.1, $C\boldsymbol{H_3}CH_2O_2C$); δ_c (100 MHz, $CDCl_3$) 207.5 (C), 167.7 (C), 162.1 (CH), 96.7 (CH), 69.8 (CH_2), 59.8 (CH_2), 39.3 (CH_2), 29.9 (CH_3), 22.8 (CH_2), 14.3 (CH_3).

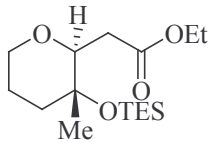
Ethyl 2-(3-hydroxy-3-methyl-tetrahydro-2*H*-pyran-2-yl)acetate 294 [82]



To a solution of ethyl ester **293** (2.00 g, 10.0 mmol) and MeOH (1.2 mL) in THF (100 mL) at rt was added SmI_2 (300 mL of a 0.1 M solution in THF, 30.0 mmmol,). After 1 h, the reaction was quenched with sat. aqueous sodium thiosulphate (100 mL). Then, the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organics were washed with

brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 6:4) gave compound **294** as a colourless oil (1.64 g, 81%). R_f= 0.48 (petrol/EtOAc, 6:4); δ_H (400 MHz, $CDCl_3$) 4.15–4.07 (2H, m, $CH_3C\boldsymbol{H_2}O$), 3.87 (1H, dd, *J* 11.3, 4.3, OC***H***H), 3.58 (1H, dd, *J* 9.7, 3.0, OC***H***), 3.37 (1H, m, OCH***H***), 2.69 (1H, dd, *J* 15.4, 3.0, $CH_3CH_2O_2CC\boldsymbol{H}H$), 2.31 (1H, dd, *J* 15.4, 9.7, $CH_3CH_2O_2CCH\boldsymbol{H}$), 1.84 (1H, brd, *J* 11.6, $OCH_2C\boldsymbol{H}H$), 1.70–1.62 (1H, m, $OCH_2CH\boldsymbol{H}$), 1.57–1.49 (2H, m, HOMeC$\boldsymbol{C H_2}$), 1.23–1.19 (3H, m, $C\boldsymbol{H_3}CH_2O$), 1.15 (3H, s, HOC$\boldsymbol{H_3}$).

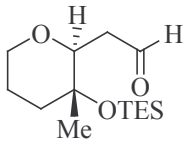
Ethyl 2-(3-methyl-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)acetate



To a solution of ethyl ester **294** (1.49 g, 7.37 mmol) and 2,6-lutidine (1.9 mL, 16 mmol) in CH_2Cl_2 (100 mL) at –78 °C was added TESOTf (1.8 mL, 8.1 mmol). After 30 min, the reaction was quenched with sat. aqueous $NaHCO_3$ (30 mL) and allowed to warm to rt. Then, the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were washed with brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave compound as a colourless oil (2.33 g, 94%). R_f = 0.30 (petrol/EtOAc, 9:1); υ_{max}/cm^{-1} (neat) 2955, 2930, 2876, 1742, 1141, 744, 725; δ_H (400 MHz, $CDCl_3$) 4.16–4.06 (2H, m, $CH_3C\boldsymbol{H_2}O$), 3.85 (1H, brd, *J* 11.2, OC***H***H), 3.54 (1H, dd, *J* 12.2, 10.3, OC***H***), 3.35 (1H, dd, *J* 11.0, 10.0, OCH***H***), 2.68 (1H, dd, *J* 15.4, 2.0, $CH_3CH_2O_2CC\boldsymbol{H}H$), 2.20 (1H, dd, *J* 15.4, 10.4, $CH_3CH_2O_2CCH\boldsymbol{H}$), 1.84 (1H, dd, *J* 9.8, 2.7, $OCH_2C\boldsymbol{H}H$), 1.70–1.51 (3H, m, $OCH_2CH\boldsymbol{H}$, TESOCMeC$\boldsymbol{H_2}$), 1.20 (3H, t, *J* 7.1, $C\boldsymbol{H_3}CH_2O$), 1.14 (3H, s, TESOC***Me***), 0.89 (9H, t, *J* 8.0, $\{C\boldsymbol{H_3}CH_2\}_3Si$), 0.53 (6H, t, *J* 8.0, $\{CH_3C\boldsymbol{H_2}\}_3Si$); δ_c (100 MHz, $CDCl_3$) 172.4 (C),

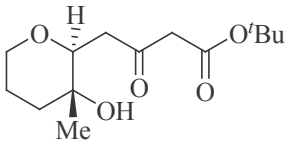
81.6 (CH), 71.5 (C), 68.2 (CH_2), 60.2 (CH_2), 39.9 (CH_2), 34.8 (CH_2), 24.8 (CH_2), 20.6 (CH_3), 14.0 (CH_3), 6.9 (CH_3), 6.6 (CH_2); HRMS (FAB+) calcd. for $C_{16}H_{32}O_4Si$, $(M+H)^+$: 317.2148, found 317.2145.

2-(3-Methyl-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)acetaldehyde 298



To a solution of protected ethyl ester (1.09 g, 3.44 mmol) in toluene (50 mL) at –78 °C was added Dibal-H (3.44 mL of a 1.0 M solution in cyclohexane, 3.4 mmol). After 3 h, the reaction was quenched with a saturated solution of Rochelle's salt (30 mL) and stirred at rt for 30 min. Then, the aqueous phase was extracted with ether (3 × 50 mL). The combined organics were washed with brine (50mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 8:2) gave compound **298** as a colourless oil (786.3 mg, 84%). R_f = 0.30 (petrol/EtOAc, 9:1); υ_{max}/cm^{-1} (neat) 2954, 2873, 1713, 1142, 744, 725, 456; δ_H (400 MHz, $CDCl_3$) 9.70 (1H, dd, *J* 2.1, 2.1, ***H***CO), 3.87 (1H, ddd, *J* 11.1, 2.2, 2.2, OC***H***H), 3.60 (1H, dd, *J* 9.2, 3.8, OC***H***), 3.38 (1H, ddd, *J* 11.6, 11.6, 2.6, OCH***H***), 2.66 (1H, dddd, *J* 16.0, 3.8, 2.2, 0.6, HCOC***H***H), 2.35 (1H, dddd, *J* 16.0, 9.2, 2.8, 0.6, HCOCH***H***), 1.89 (1H, dd, *J* 8.7, 2.7, OCH_2C***H***H), 1.70–1.52 (3H, m, OCH_2CH***H***, TESOMeCC***H₂***), 1.18 (3H, s, TESOC***Me***), 0.90 (9H, t, *J* 8.0, {C***H₃***CH_2}$_3$Si), 0.54 (6H, t, *J* 8.0, {CH_3C***H₂***}$_3$Si); δ_c (100 MHz, $CDCl_3$) 201.4 (CH), 80.0 (CH), 71.6 (C), 68.2 (CH_2), 39.8 (CH_2), 24.7 (CH_2), 20.7 (CH_3), 6.9 (CH_3), 6.6 (CH_2); HRMS (CI+) calcd. for $C_{14}H_{29}O_3Si$, $(M+H)^+$: 273.1886, found 273.1885.

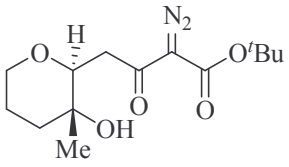
***Tert*-butyl 4-(3-hydroxy-3-methyl-tetrahydro-2*H*-pyran-2-yl)-3-oxobutanoate**



To a solution of aldehyde **298** (1.43 g, 5.42 mmol) and *tert*-butyl diazoacetate (809 mg, 5.69 mmol) in CH_2Cl_2 (50 mL) at rt was added $SnCl_2$ (103.1 mg, 0.5438 mmol). After 15 min, another portion of $SnCl_2$ (103.1 mg, 0.5438 mmol) was added. The process was repeated until complete consumption of starting material was observed by TLC. Brine (30 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

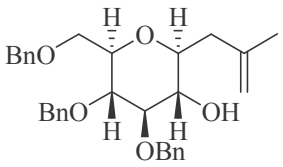
The crude compound was dissolved in THF (25 mL) and TBAF (8.1 mL of a 1.0 M in THF, 8.1 mmol) was added. After 2 h, brine (25 mL) was added and the aqueous phase was extracted with ether (3 × 50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (ether/petrol/MeOH, 7:3:0.1) gave compound as a colourless oil (675.2 mg, 46% over 2 steps). R_f = 0.14 (7:3:0.1 ether/petrol /MeOH); υ_{max}/cm^{-1} (neat) 3444 (br), 2977, 2938, 2858, 1735, 1714, 1369, 1323, 1147, 1103; δ_H (400 MHz, $CDCl_3$) 3.81 (1H, d, *J* 11.2, OC***H***H), 3.55 (1H, dd, *J* 9.3, 2.8, OC***H***), 3.40–3.30 (2H, m, OCH***H***, $(CH_3)_3COCOCH_2$), 2.77 (1H, dd, *J* 16.1, 2.8, OCHC***H***H), 2.69 (1H, brs, ***H***O), 2.55 (1H, m, OCHCH***H***), 1.81 (1H, d, *J* 11.4, OCH_2CHH), 1.64 (1H, ddd, *J* 14.5, 8.0, 3.7, HOCMeC***H***H), 1.55–1.52 (3H, m, OCH_2CH***H***, HOCMeCH***H***), 1.40 (9H, s, $\{CH_3\}_3C$), 1.11 (3H, s, HOC***Me***); δ_c (100 MHz, $CDCl_3$) 202.6 (C), 166.4 (C), 81.7 (C), 80.3 (CH), 68.9 (C), 67.9 (CH_2), 51.0 (CH_2), 42.8 (CH_2), 39.5 (CH_2), 27.7 (CH_3), 24.6 (CH_2), 19.7 (CH_3); HRMS (FAB+) calcd. for $C_{14}H_{25}O_5$, $(M+H)^+$: 273.1702, found 273.1708.

***Tert*-butyl 4-(3-hydroxy-3-methyl-tetrahydro-2*H*-pyran-2-yl)-3-oxobutanoate 297**



To a solution of β-ketoester (136.0 mg, 0.4886 mmol) and Et_3N (155 μL, 1.10 mmol) in MeCN (2 mL) at 0 °C was added *p*-ASBA (132.0 mg, 0.5495 mmol). After 2 h, brine (5 mL) was added and the aqueous phase was extracted with ether (3 × 5 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (ether/petrol, 8:2) gave compound **297** as a colourless oil (110.0 mg, 74%). R_f = 0.33 (ether/petrol, 8:2); υ_{max}/cm^{-1} (neat) 3451, 2976, 2938, 2131,1714, 1318; δ_H (400 MHz, $CDCl_3$) 3.87 (1H, ddd, *J* 11.8, 3.0, 1.7, OC***H***H), 3.70 (1H, dd, *J* 8.3, 3.6, OC***H***), 3.38 (2H, ddd, *J* 11.8, 10.1, 2.6, OCH***H***), 3.16–2.99 (2H, m, OCHC***H₂***), 1.92–1.82 (1H, m, HOCMeC***H***H), 1.73–1.65 (1H, m, OCH_2CH***H***), 1.60–1.54 (2H, m, OCH_2CH***H***, HOCMeC***H***H), 1.50 (9H, s, {C***H₃***}$_3$C), 1.21 (3H, s, HOC***Me***); δ_c (100 MHz, $CDCl_3$) 191.5 (C), 160.4 (C), 83.2 (C), 80.0 (CH), 69.4 (C), 68.0 (CH_2), 55.8 (C), 40.2 (CH_2), 39.7 (CH_2), 20.2 (CH_3), 24.8 (CH_2), 20.1 (CH_3); HRMS (CI+) calcd. for $C_{14}H_{23}N_2O_5$, $(M+H)^+$: 299.1607, found 299.1604.

(2*S*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(2-methylallyl)-tetrahydro-2*H*-pyran-3-ol 198 [112]



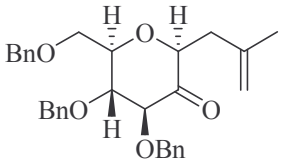
To a solution of fully protected glucal **194** (1.45 g, 3.47 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added DMDO (56 mL of a ~0.08 M solution in acetone, 4.51 mmol) was added carefully from an addition funnel over a period of 0.5 h. After an additional 0.5 h, the solvent was removed under reduced pressure **without exceeding 5 °C**. The crude oil was diluted with CH_2Cl_2 (10 mL), washed with water (10 mL) and brine (10 mL). The organic layer was then dried (Na_2SO_4), filtered and the solvent removed *in vacuo* **without exceeding 5 °C**. The crude oil was dried under high-reduced pressure for 1 h.

To a solution of crude epoxide in THF (5 mL) at –78 °C was added (2-methylallyl)magnesium chloride (14 mL of a 0.5 M in THF, 6.94 mmol) by a syringe pump over a period of 15 min. Then, the reaction was allowed to warm to rt over 2 h. The reaction was cooled to 0 °C, quenched by the addition of sat. aqueous NH_4Cl (20 mL) and the solution was allowed to warm to rt. Then, the reaction was diluted with ether (30 mL), washed with sat. aqueous NH_4Cl (20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/ether, 6:4) gave compound **198** as a solid (1.10 g, 65% over 2 steps). R_f = 0.53 (petrol/ether, 1:1); $[\alpha]_D^{27}$ +34.5 (*c* = 1.00, $CHCl_3$); M.P. 55.0–55.6 °C; υ_{max}/cm^{-1} (neat) 3450 (br), 3064, 3030, 2899, 2864, 1454, 1102, 1069, 735, 698; δ_H (400 MHz, $CDCl_3$) 7.43–7.27 (15H, m, ***Ph***), 5.02 (1H, d, *J* 11.5, PhC***H***H), 4.89 (2H, brs, C***H₂***=), 4.88 (1H, d, *J* 10.8, PhC***H***H), 4.83 (1H, d, *J* 11.5, PhCH***H***), 4.69 (1H, d, *J* 12.3,

[112] Unpublished result

PhC***H***H), 4.67 (1H, d, *J* 10.8, PhCH***H***), 4.63 (1H, d, *J* 12.3, PhCH***H***), 3.82–3.66 (3H, m), 3.59–3.56 (1H, m), 3.50 (1H, ddd, *J* 9.7, 4.2, 2.1), 3.44–3.40 (2H, m), 2.60 (1H, d, *J*, 14.2, CH_2=CCH$_3$C***H***H), 2.35–2.29 (2H, m, ***H***O, CH_2=CCH$_3$CH***H***), 1.87 (3H, s, CH_2=CC***H$_3$***); δ_c (100 MHz, $CDCl_3$) 143.0 (C), 138.5 (C), 138.2 (C), 138.0 (C), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.9 (2 × CH), 127.8 (CH), 127.7 (2 × CH), 127.5 (CH), 112.5 (CH_2), 86.7 (CH), 79.0 (CH), 78.3 (CH), 78.1 (CH), 75.2 (CH_2), 74.7 (CH_2), 74.1 (CH), 73.3 (CH_2), 68.9 (CH_2), 40.1 (CH_2), 23.2 (CH_3); HRMS (CI+) calcd. for $C_{31}H_{37}O_5$, $(M+H)^+$: 489.2641, found 489.2638.

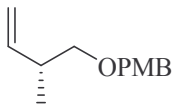
(2*S*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(2-methylallyl)-dihydro-2*H*-pyran-3(4*H*)-one 200



To a solution of alcohol **198** (500.0 mg, 1.156 mmol) in CH_2Cl_2 (23 mL) at 0 °C was added Dess-Martin periodinane (539.1 mg, 1.271 mmol) portionwise. The reaction mixture was allowed to warm to rt and stirring continued for 2 h. The reaction was quenched with sat. aqueous $Na_2S_2O_3$ (30 mL). After 30 min of vigorous stirring, the mixture was extracted with ether (2 × 70 mL). The combined organics were washed with sat. aqueous K_2CO_3 (3 × 50 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo*. The crude solid was used without further purification (539.5 mg, 96%). R_f = 0.55 (petrol/ether, 1:1); $[\alpha]_D^{26}$ –43.3 (*c* = 1.00, $CHCl_3$); M.P. 72.7–73.6 °C; υ_{max}/cm^{-1} (neat) 3067, 3027, 2942, 2913, 2874, 1730, 1452, 1117, 1052, 731, 693; δ_H (400 MHz, $CDCl_3$) 7.44–7.20 (15H, m, ***Ph***), 5.02 (1H, d, *J* 11.3, PhC***H***H), 4.88 (1H, d, *J* 11.0, PhC***H***H), 4.86 (1H, brs, C***H***H=), 4.81 (1H, d, *J* 0.9, CH***H***=), 4.64–4.55(4H, m, PhC***H$_2$***), 4.21 (1H, dd, *J* 8.8, 0.7, BnOCH$_2$CHCHC***H***), 3.95 (1H, ddd, *J* 8.6, 3.9, 0.7, O=CC***H***O), 3.90 (1H, dd, *J* 8.9, 8.8, BnOCH$_2$CHC***H***), 3.82–3.77

(2H, m, $BnOCH_2C\boldsymbol{H}$, $BnOC\boldsymbol{H}H$), 3.71 (1H, dd, *J* 10.8, 4.7, $BnOCH\boldsymbol{H}$), 2.64 (1H, dd, *J*, 15.5, 3.9, $CH_2{=}CCH_3C\boldsymbol{H}H$), 2.33 (1H, dd, *J*, 15.5, 8.6, $CH_2{=}CCH_3CH\boldsymbol{H}$), 1.81 (3H, s, $CH_2{=}CC\boldsymbol{H_3}$); δ_c (100 MHz, $CDCl_3$) 201.8 (C), 141.6 (C), 138.1 (C), 137.8 (C), 137.5 (C), 128.4 (2 × CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 112.4 (CH_2), 86.6 (CH), 80.3 (CH), 79.8 (CH), 79.3 (CH), 74.9 (CH_2), 73.7 (CH_2), 73.4 (CH_2), 68.8 (CH_2), 35.9 (CH_2), 23.2 (CH_3); HRMS (CI+) calcd. for $C_{31}H_{35}O_5$, $(M+H)^+$: 487.2484, found 487.2487.

(*R*)-1-Methoxy-4-((2-methylbut-3-enyloxy)methyl)benzene 302

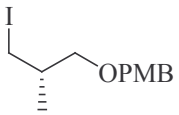


To a solution of methyl ester **166** (1.14 g, 4.80 mmol) in toluene (50 mL) at –78 °C was added Dibal-H (5 mL of a 1 M in cyclohexane, 5 mmol) by a syringe pump over a period of 15 min. After 2 h at –78 °C, the reaction mixture was carefully quenched with MeOH (2 mL). Ether (100 mL) and a saturated solution of Rochelle's salt (100 mL) were added and the mixture was stirred vigorously for 30 min at rt. The aqueous phase was extracted with ether (3 × 100 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

To a solution of methyltriphenylphosphonium bromide (5.14 g, 14.4 mmol) in benzene (20 mL) at rt was added *t*-BuOK (1.62 g, 14.4 mmol). The reaction was heated at reflux for 1 h. The reaction was cooled to rt and a solution of aldehyde in benzene (5 mL) was added. After 30 min at rt, acetone (10 mL) was added and stirred for 10 min at rt. Sat aqueous NH_4Cl (100 mL) was added and the mixture was extracted several times with ether (2 × 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was triturated with petrol (30 mL), filtered and concentrated *in vacuo*.

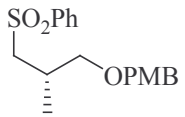
Purification by flash column chromatography (petrol/ether, 100:2) gave alkene **302** as a colourless oil (509.0 mg, 51% over 2 steps). R_f= 0.53 (petrol/EtOAc, 9:1); $[\alpha]_D^{27}$ +6.7 (*c* = 1.0, $CHCl_3$): υ_{max}/cm^{-1} (neat) 2958, 2933, 2855, 1613, 1513, 1247, 1095, 1037, 819; δ_H (400 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.7, ***Ph***), 6.91 (2H, d, *J* 8.7, ***Ph***), 5.83 (1H, ddd, *J* 17.3, 10.4, 6.9, CH_2=C***H***), 5.11 (1H, ddd, *J* 17.3, 1.5, 1.5, C***H***H=CH), 5.05 (1H, ddd, *J* 10.4, 1.6, 1.2, CH***H***=CH), 4.49 (2H, s, PhC***H₂***), 3.82 (3H, s, ***Me***O), 3.39 (1H, dd, *J* 9.1, 6.6, PMBOC***H***H), 3.31 (1H, dd, *J* 9.1, 6.8, PMBOCH***H***), 2.57–2.49 (1H, m, MeC***H***), 1.07 (3H, d, *J* 6.8, ***Me***); δ_c(100 MHz, $CDCl_3$) 159.0 (C), 141.2 (CH), 130.5 (C), 129.0 (CH), 113.9 (CH_2), 113.6 (CH), 74.6 (CH_2), 72.5 (CH_2), 55.1 (CH_3), 37.7 (CH), 16.5 (CH_3); HRMS (EI+) calcd. for $C_{13}H_{18}O_2$, M^+: 206.1307, found 206.1308.

(*S*)-1-((3-Iodo-2-methylpropoxy)methyl)-4-methoxybenzene 315 [87]



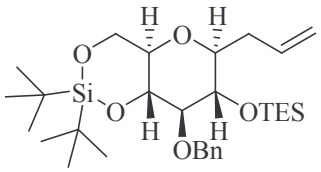
To a solution of alcohol **229** (420.0 mg, 2.000 mmol), imidazole (340.0 mg, 5.000 mmol) and PPh_3 (1.31 g, 5.00 mmol) in benzene (17 mL) at 0 °C was added iodine (1.01 g, 4.00 mmol). After 3 h at rt, sat. aqueous $Na_2S_2O_3$ (20 mL) was added and the aqueous phase was extracted with ether (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 95:5) gave compound **315** as a colourless oil (562.0 mg, 88%), which needs to be used directly in the next step. R_f= 0.70 (petrol/EtOAc, 7:3).

(*S*)-1-Methoxy-4-((2-methyl-3-(phenylsulfonyl)propoxy)methyl)benzene 316 [87]



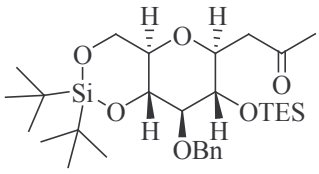
To a solution of iodide **315** (562.0 mg, 1.755 mmol) in DMF (6 mL) at rt was added $PhSO_2Na$ (866.0 mg, 5.275 mmol). After 18 h at 60 °C, H_2O (15 mL) was added and the aqueous phase was extracted with ether (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave compound **316** as a colourless oil (500.0 mg, 85%). R_f = 0.26 (petrol/EtOAc, 7:3); $[\alpha]_D^{23}$ +2.5 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2928, 1512, 1303, 458; δ_H (400 MHz, $CDCl_3$) 7.90 (2H, d, *J* 7.7, ***Ph***SO_2), 7.63 (1H, dd, *J* 7.7, 7.0, ***Ph***), 7.53 (2H, dd, *J* 7.7, 7.7, ***Ph***SO_2), 7.17 (2H, d, *J* 8.6, MeO***Ph***), 6.85 (2H, d, *J* 8.6, MeO***Ph***), 4.35 (1H, d, *J* 11.6, MeOPhC***H***H), 4.31 (1H, d, *J* 11.6, MeOPhCH***H***), 3.78 (3H, s, ***Me***O), 3.38 (1H, dd, *J* 14.2, 4.5), 3.37 (1H, dd, *J* 9.3, 5.1), 3.26 (1H, dd, *J* 9.3, 6.5), 2.91 (1H, dd, *J* 14.2, 7.9), 2.44−2.33 (1H, m, PMBOCH_2C***H***Me), 1.10 (3H, d, *J* 6.9, $PhSO_2CH_2CH$***Me***); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 139.8 (C), 133.4 (CH), 130.0 (C), 129.1 (CH), 129.0 (CH), 127.7 (CH), 113.6 (CH), 73.0 (CH_2), 72.3 (CH_2), 59.0 (CH_2), 55.1 (CH_3), 29.2 (CH), 17.0 (CH_3); HRMS (EI+) calcd. for $C_{18}H_{22}O_4S$, M^+: 334.1239, found 334.1237.

(4a*R*,6*S*,7*S*,8*R*,8a*R*)-6-Allyl-8-(benzyloxy)-2,2-di-*tert*-butyl-7-(triethylsilyloxy)-hexahydropyrano[3,2-*d*][1,3,2]dioxasiline 317



To a solution of alcohol **137** (592.0 mg, 1.362 mmol) and imidazole (277.0 mg, 4.068 mmol) in DMF (3 mL) at rt was added TESCl (225.0 mg, 1.493 mmol). After 15 min, H_2O (15 mL) was added and the aqueous phase was extracted with ether (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 8:2) gave compound **317** as a colourless oil (698.3 mg, 93%). R_f = 0.76 (petrol/EtOAc, 8:2); $[\alpha]_D^{24}$ +26.1 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2957, 2934, 2878, 1472, 1113, 802; δ_H (400 MHz,$CDCl_3$) 7.26 (1H, brd, *J* 7.3, ***Ph***), 7.20–7.16 (2H, m, ***Ph***), 7.13–7.10 (1H, m, ***Ph***), 5.72 (1H, dddd, *J* 17.0, 10.2, 6.8, 6.8, CH_2=C***H***), 5.03 (1H, d, *J* 11.0, PhC***H***H), 4.94 (1H, dd, *J* 17.0, 1.8, C***H***H=CH), 4.91 (1H, dd, *J* 9.9, 1.8, CH***H***=CH), 4.52 (1H, d, *J* 11.0, PhCH***H***), 4.01 (1H, dd, J 10.1, 4.9, SiOC***H***H), 3.77–3.71 (1H, m), 3.69 (1H, dd, *J* 10.2, 10.2, OSiOC***H***), 3.28–3.14 (4H, m, $SiOCH_2C$***H***, BnOC***H***, TESOC***H***, CH_2=$CHCH_2C$***H***), 2.41 (1H, dd, *J* 14.8, 6.7, CH_2=CHC***H***H), 1.97 (1H, ddd, *J* 14.8, 8.1, 7.1, CH_2=CHCH***H***), 0.87 (9H, s, {C***H*****3**}**3**C), 0.85 (9H, s, {C***H*****3**}**3**C), 0.77 (9H, t, *J* 7.9, {C***H*****3**CH_2}**3**Si), 0.45 (6H, ddd, *J* 11.8, 7.9, 3.3, {CH_3C***H*****2**}**3**Si); δ_c (100 MHz, $CDCl_3$) 139.2 (C), 134.8 (CH), 128.1 (CH), 127.6 (CH), 127.2 (CH), 116.8 (CH_2), 86.2 (CH), 80.5 (CH), 79.2 (CH), 74.8 (CH_2), 74.3 (CH), 74.2 (CH), 66.6 (CH_2), 48.1 (CH_2), 27.4 (CH_3), 27.1 (CH_3), 22.6 (C), 19.9 (C), 7.0 (CH_3), 5.3 (CH_2); HRMS (CI+) calcd. for $C_{30}H_{53}O_5Si_2$, $(M+H)^+$: 549.3432, found 549.3438.

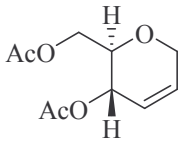
1-((4aR,6S,7S,8R,8aR)-8-(Benzyloxy)-2,2-di-tert-butyl-7-(triethylsilyloxy)-hexahydropyrano[3,2-d][1,3,2]dioxasilin-6-yl)propan-2-one 318



To a solution of $PdCl_2$ (2.4 mg, 0.014 mmol) in DMF (2.5 mL) and H_2O (0.13 mL) at rt was added CuCl (67.4 mg, 0.681 mmol). Then, the reaction vessel was purged of air and filled with oxygen. The process was repeated three times and the reaction was stirred for 1 h. The alkene **317** (373.8 mg, 0.6809 mmol) was dissolved in DMF (0.3 mL) and was added by cannula. After 1 h at 60 °C, the reaction vessel was purged of oxygen and filled with air. Brine (5 mL) was then added and the aqueous phase was extracted with ether (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 95:5) gave compound **318** as a colourless oil (154.0 mg, 40%). R_f = 0.19 (petrol/EtOAc, 95:5); $[\alpha]_D^{23}$ –32.8 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2957, 2934, 2878, 1725, 1472, 1100, 800; δ_H (400 MHz,$CDCl_3$) 7.40–7.24 (5H, m, ***Ph***), 5.18 (1H, d, *J* 11.0, PhC***H***H), 4.66 (1H, d, *J* 11.0, PhCH***H***), 4.10 (1H, dd, J 10.1, 5.0, SiOC***H***H), 3.87 (1H, dd, *J* 9.3, 8.5, OSiOC***H***), 3.78 (1H, ddd, *J* 9.3, 9.3, 2.4, $CH_3C{=}OCH_2C$***H***), 3.76 (1H, dd, *J* 10.1, 10.1, SiOCH***H***), 3.44 (1H, ddd, *J* 9.9, 9.9, 4.9, $SiOCH_2C$***H***), 3.42–3.28 (2H, m, BnOC***H***, TESOC***H***), 2.76 (1H, dd, *J* 15.8, 2.4, $CH_3C{=}OC$***H***H), 2.48 (1H, dd, *J* 15.8, 9.8, $CH_3C{=}OCH$***H***), 2.17 (3H, s, C***H₃***C=O), 1.00 (9H, s, {C***H₃***}₃C), 0.99 (9H, s, {C***H₃***}₃C), 0.89 (9H, t, *J* 7.9, {C***H₃***CH_2}₃Si), 0.57 (6H, ddd, *J* 11.6, 7.9, 3.0, {CH_3C***H₂***}₃Si); δ_c (100 MHz, $CDCl_3$) 206.7 (C), 139.1 (C), 128.1 (CH), 127.6 (CH), 127.2 (CH), 85.9 (CH), 79.1 (CH), 77.2 (CH), 74.8 (CH_2), 74.4 (CH), 74.1 (CH), 68.5 (CH_2), 46.1 (CH_2), 30.8 (CH_3), 27.4 (CH_3), 27.0 (CH_3), 22.6 (C), 19.9 (C), 6.9

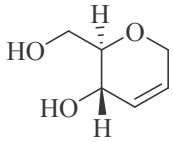
(CH_3), 5.2 (CH_2); HRMS (CI+) calcd. for $C_{30}H_{53}O_6Si_2$, $(M+H)^+$: 565.3381, found 565.3383.

Acetic acid 3-acetoxy-3,6-dihydro-2*H*-pyran-2-ylmethyl ester 329 [94]



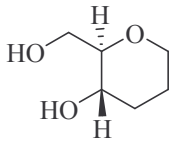
To a solution of tri-*O*-acetyl-D-glucal (15.00 g, 55.00 mmol) in CH_2Cl_2 (500 mL) at 0 °C was added triethylsilane (17.6 mL, 110 mmol) followed by $BF_3{\cdot}OEt_2$ (12.6 mL, 102 mmol). After 3 h at 0 °C, sat. aqueous $NaHCO_3$ (300 mL) was added. Then, the reaction mixture was allowed to warm to rt. The aqueous phase was extracted with $CHCl_3$ (300 mL). The combined organics were extracted with sat. aqueous $NaHCO_3$ (300 mL), brine (300 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude compound **329** was used to the next step without further purification.

(2*R*,3*S*)-2-(Hydroxymethyl)-3,6-dihydro-2*H*-pyran-3-ol 330 [94]



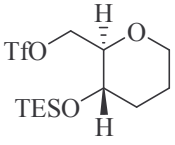
To a solution of acetate **329** (~55 mmol) in MeOH (500 mL) at rt was added sodium methoxide (2.97 g, 55.0 mmol). After 0.5 h, Amberlsyt 15® was added and stirred for 15 min. The reaction was filtered through a plug of celite®, which was washed several times with MeOH (3 × 200 mL). The combined organics was concentrated *in vacuo*. The crude diol **330** was used to the next step without further purification.

(2*R*,3*S*)-2-(Hydroxymethyl)-tetrahydro-2*H*-pyran-3-ol 361 [94]



To a solution of diol **330** (~55 mmol) in MeOH (300 mL) was added Pd/C (410.0 mg). The reaction vessel was purged of air, filled with hydrogen and stirred at rt for 18 h. The hydrogen was then purged from the reaction vessel and the solution was filtered through celite®, which was washed with further MeOH (3 × 200 mL). The solvent was removed *in vacuo*. Purification by flash column chromatography (EtOAc/MeOH, 7:3) gave compound **361** as an oil (6.84 g, 94% over 3 steps). R_f = 0.19 (EtOAc); $[\alpha]_D^{24}$ +24.3 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3375 (br), 2938, 2857, 1098, 1076, 1046; δ_H (400 MHz, $CDCl_3$) 3.95−3.90 (1H, m, OC***H***H), 3.81 (1H, dd, *J* 11.6, 3.9, HOC***H***H), 3.76 (1H, dd, *J* 11.6, 4.8, HOCH***H***), 3.54 (1H, ddd, *J* 10.8, 9.4, 4.7), 3.41−3.34 (1H, m), 3.11 (1H, ddd, *J* 9.0, 4.3, 4.3), 2.96 (2H, brs, 2 × ***H***O), 2.14−2.10 (1H, m), 1.72−1.65 (2H, m), 1.50−1.39 (1H, m); δ_c (100 MHz, $CDCl_3$) 81.8 (CH), 67.6 (CH_2), 67.2 (CH), 63.1 (CH_2), 32.4 (CH_2), 25.3 (CH_2); HRMS (CI+) calcd. for $C_6H_{13}O_3$, $(M+H)^+$: 133.0865, found 133.0862.

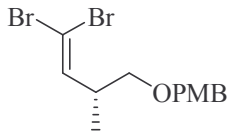
((2*R*,3*S*)-3-(Triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)methyl trifluoromethanesulfonate 331



To a solution of diol **361** (127.9 mg, 4.751 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added 2,6-lutidine (1.7 mL, 14 mmol) followed by Tf_2O (880 μL, 5.23 mmol). After 0.5 h at –78

°C, TESOTf (1.3 mL, 5.7 mmol) was added and stirred at –78 °C for 0.5 h. The reaction was quenched by the addition of sat. aqueous $NaHCO_3$ (50 mL) and allowed to warm to rt. The mixture was diluted with ether (200 mL) and washed with sat. aqueous $CuSO_4$ (3 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/ether, 85:25; silica treated with 1% Et_3N) gave triflate **331** as a pale yellow oil (1.37 g, 69%). The crude oil was used **immediately** to the next step.

(*R*)-1-((4,4-Dibromo-2-methylbut-3-enyloxy)methyl)-4-methoxybenzene 332 [95]

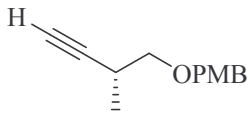


To a solution of methyl ester **228** (6.67 g, 28.0 mmol) in toluene (300 mL) at –78 °C was added Dibal-H (30 mL of a 1.0 M solution in cyclohexane, 30 mmol,) by a syringe pump over a period of 15 min. After 2 h at –78 °C, the reaction was quenched by careful addition of MeOH (20 mL). Ether (300 mL) and a saturated solution of Rochelle's salt (300 mL) were added and the mixture was stirred vigorously for 30 min at rt. The aqueous phase was extracted with ether (3 × 200 mL) and the combined organics were washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

To a solution of PPh_3 (29.37 g, 112.0 mmol) in CH_2Cl_2 (200 mL) at rt was added CBr_4 (18.57 g, 56.00 mmol) portionwise. The reaction was stirred for 1 h at rt and then cooled to –78 °C before a solution of the crude aldehyde in CH_2Cl_2 (50 mL) was added slowly by cannula. After 1 h at –78 °C, petrol (250 mL) was added and the reaction mixture was filtered. The solvent was removed *in vacuo* and the crude was triturated with petrol/EtOAC (250 mL, 98:2) at –40 °C. Filteration and removal of the solvent *in vacuo* followed by purification by flash column chromatography (petrol/EtOAc, 95:5) gave alkene **332** as a

colourless oil (6.22 g, 61% over 2 steps). R_f = 0.62 (petrol/EtOAc, 8:2); $[\alpha]_D^{25}$ –20.2 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2961, 2931, 2855, 1612, 1512, 1247, 1095, 1036, 785; δ_H (400 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.7, ***Ph***), 6.94 (2H, d, *J* 8.7, ***Ph***), 6.37 (1H, d, *J* 9.1, CBr_2=C***H***), 4.50 (1H, d, *J* 11.7, PhC***H***H), 4.47 (1H, d, *J* 11.7, PhCH***H***), 3.82 (3H, s, ***Me***O), 3.40 (1H, dd, *J* 9.2, 6.2, PMBOC***H***H), 3.37 (1H, dd, *J* 9.2, 3.8, PMBOC***H***H), 2.87−2.76 (1H, m, MeC***H***), 1.11 (3H, d, *J* 6.9, ***Me***CH); δ_c (100 MHz, $CDCl_3$) 158.9 (C), 141.0 (CH), 130.0 (C), 128.9 (CH), 113.5 (CH), 88.6 (C), 72.4 (CH_2), 72.3 (CH_2), 54.9 (CH_3), 38.5 (CH), 15.7 (CH_3); HRMS (CI+) calcd. for $C_{13}H_{17}O_2Br_2$, $(M+H)^+$: 362.9595 found 362.9601; 364.9575 found 364.9569; 366.9557 found 366.9684.

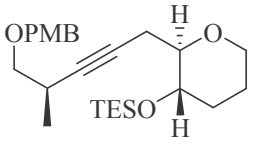
(*R*)-1-Methoxy-4-((2-methylbut-3-ynyloxy)methyl)benzene 333



To a solution of dibromoalkene **332** (1.73 g, 4.75 mmol) in ether (60 mL) at –78 °C was slowly added *n*-BuLi (7.4 mL of a 1.4 M solution in ether, 10 mmol,). After 1 h at –78 °C, the reaction was quenched with sat. aqueous NH_4Cl (100 mL) and the mixture was allowed to warm to rt. The aqueous phase was extracted several times with ether (2 × 100 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/ether, 9:1) gave alkyne **333** as a colourless oil (889.4 mg, 92%). R_f = 0.41 (petrol/EtOAc, 9:1); $[\alpha]_D^{24}$ +2.6 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3291, 2936, 2905, 2858, 1613, 1513, 1247, 1090, 1035; δ_H (400 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.7, ***Ph***), 6.90 (2H, d, *J* 8.7, ***Ph***), 4.54 (1H, d, *J* 11.8, PhC***H***H), 4.50 (1H, d, *J* 11.8, PhCH***H***), 3.82 (3H, s, ***Me***O), 3.53 (1H, dd, *J* 9.0, 6.2, PMBOC***H***H), 3.38 (1H, dd, *J* 9.0, 7.8, PMBOC***H***H), 2.79−2.70 (1H, m, MeC***H***), 2.10 (1H, d, *J* 2.4, ***H***C≡C), 1.24 (3H, d, *J* 6.9, ***Me***CH); δ_c (100 MHz, $CDCl_3$) 159.1 (C), 130.1 (C),

129.2 (CH), 113.6 (CH), 88.4 (C), 73.4 (CH_2), 72.6 (CH_2), 68.9 (CH), 55.1 (CH_3), 26.4 (CH), 17.6 (CH_3); HRMS mass not found.

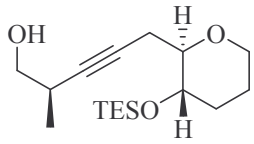
Triethyl((2*R*,3*S*)-2-((*R*)-5-(4-methoxybenzyloxy)-4-methylpent-2-ynyl)-tetrahydro-2*H*-pyran-3-yloxy)silane 334



To a solution of alkyne **333** (889.4 mg, 4.354 mmol) in ether (8 mL) at –78 °C was slowly added *n*-BuLi (3.4 mL of a 1.4 M solution in ether, 4.79 mmol). After 1 h at –78 °C, a solution of triflate **331** (915.6 mg, 2.177 mmol) in ether (2 mL) was slowly added by cannula. Then, the reaction was allowed to warm to rt over 18 h. The reaction was cooled to 0 °C, quenched with sat. aqueous NH_4Cl (50 mL) and the reaction was allowed to warm to rt. The aqueous phase was extracted several times with ether (2 × 100 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 9:1) gave compound **334** as a colourless oil (822.2 mg, 87%) and alkyne **333** (285.6 mg). R_f = 0.26 (9:1 petrol/EtOAc); $[\alpha]_D^{24}$ +23.7 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2953, 2911, 2875, 1613, 1513, 1459, 1247, 1172, 1127, 1097, 1044, 1011, 814, 744, 727; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.5, ***Ph***), 6.88 (2H, d, *J* 8.5, ***Ph***), 4.51 (1H, d, *J* 11.7, PhC***H***H), 4.47 (1H, d, *J* 11.7, PhCH***H***), 3.93 (1H, dd, *J* 11.0, 1.7, OC***H***H), 3.80 (3H, s, ***Me***O), 3.71 (1H, dd, *J* 9.2, 5.5, PMBOC***H***H), 3.52 (1H, ddd, *J* 10.4, 8.8, 4.6, TESOC***H***), 3.37–3.31 (2H, m, PMBOC***H***H, OCH***H***), 3.12 (1H, ddd, *J* 8.9, 5.9, 3.3, OC***H***), 2.80−2.72 (1H, m, MeC***H***), 2.63 (1H, ddd, *J* 16.8, 2.5, 2.5, OCHC***H***H), 2.48 (1H, ddd, *J* 16.8, 5.9, 2.2, OCHCH***H***), 2.03 (1H, dd, *J* 9.3, 3.0, TESOCHC***H***H), 1.70–1.41 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.51−1.41 (1H, m, TESOCHCH***H***), 1.22 (3H, d, *J* 6.9, ***Me***CH), 0.99 (9H, t, *J* 7.9, $\{C\boldsymbol{H_3}CH_2\}_3Si$), 0.64

(6H, q, *J* 7.9, {$CH_3C\boldsymbol{H_2}$}$_3$Si); δ_c (100 MHz, $CDCl_3$) 158.8 (C), 130.2 (C), 128.9 (CH), 113.4 (CH), 82.9 (C), 80.5 (CH), 77.3 (C), 73.8 (CH_2), 72.3 (CH_2), 69.2 (CH), 67.5 (CH_2), 54.8 (CH_3), 33.2 (CH_2), 26.5 (CH), 25.2 (CH_2), 22.0 (CH_2), 17.9 (CH_3), 6.6 (CH_3), 4.8 (CH_2); HRMS (CI+) calcd. for $C_{25}H_{41}O_4Si$, $(M+H)^+$: 433.2774, found 433.2777.

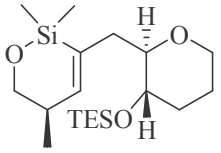
(*R*)-2-Methyl-5-((2*R*,3*S*)-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)pent-3-yn-1-ol 335



To a solution of compound **334** (813.0 mg, 1.879 mmol) in CH_2Cl_2 (30 mL) and H_2O (0.6 mL) at 0 °C was added DDQ (513.0 mg, 2.260 mmol) portionwise. After 1.5 h at rt, sat. aqueous K_2CO_3 (150 mL) was added and stirred for 15 min at rt. The aqueous phase was extracted with ether (2 × 150 mL). The combined organics were washed with sat. aqueous K_2CO_3 (150 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 7:3) gave alcohol **335** as a pale yellow oil (540.8 mg, 92%). R_f= 0.29 (petrol/EtOAc, 7:3); $[\alpha]_D^{25}$ +34.5 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3438 (br), 2954, 2876, 1131, 1098, 1045, 1006, 813, 744; δ_H (400 MHz, $CDCl_3$) 3.88 (1H, dddd, *J* 11.6, 4.1, 2.1, 2.1, OC***H***H), 3.50–3.41 (3H, m, HOC$\boldsymbol{H_2}$, TESOC***H***), 3.31 (1H, ddd, *J* 14.8, 11.2, 11.2, OCH***H***), 3.10 (1H, ddd, *J* 9.1, 5.9, 3.5, OC***H***), 2.67–2.56 (3H, m, MeC***H***, ***H***O, OCHC***H***H), 2.42 (1H, ddd, *J* 16.8, 5.9, 2.1, OCHCH***H***), 2.00−1.97 (1H, m, TESOCHC***H***H), 1.69–1.59 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.46−1.37 (1H, m, TESOCHCH***H***), 1.11 (3H, d, *J* 6.9, ***Me***CH), 0.93 (9H, t, *J* 7.9, {$C\boldsymbol{H_3}CH_2$}$_3$Si), 0.58 (6H, q, *J* 7.9, {$CH_3C\boldsymbol{H_2}$}$_3$Si); δ_c (100 MHz, $CDCl_3$) 83.1 (C), 80.6 (CH), 79.1 (C), 69.5 (CH), 67.8 (CH_2), 66.9 (CH_2), 33.2 (CH_2), 29.6 (CH), 25.4 (CH_2), 22.0 (CH_2), 17.0

(CH_3), 6.7 (CH_3), 4.9 (CH_2); HRMS (FAB+) calcd. for $C_{17}H_{33}O_3Si$, $(M+H)^+$: 313.2199, found 313.2195.

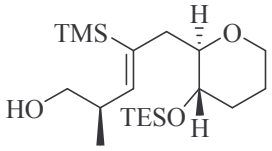
(*R*)-2,2,5-Trimethyl-3-(((2*R*,3*S*)-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)methyl)-5,6-dihydro-2*H*-1,2-oxasiline 337



A solution of alcohol **335** (191.5 mg, 0.6127 mmol) in TMDS (1 mL) was heated at 50 °C for 2 h. Then, the reaction mixture was concentrated and dried under high vacuum for 1 h. CH_2Cl_2 (2 mL) was added and cooled to 0 °C. $[Cp^*Ru(MeCN)_3]PF_6$ (12.6 mg, 0.0249 mmol) was added and the reaction was stirred for 10 min at rt. Ether (10 mL) was added and the reaction was filtered through a plug of florisil®, which was washed with ether (3 × 10 mL). The combined organics were dried *in vacuo* and the resulting oil was used in the next step without further purification (210.7 mg). R_f= 0.68 (petrol/EtOAc, 7:3); $[\alpha]_D^{24}$ +16.0 (*c* = 0.50, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2955, 2876, 1725, 1244, 1098, 846, 815, 783, 727; δ_H (400 MHz, $CDCl_3$) 6.29 (1H, d, *J* 2.5, C***H***=), 3.87 (1H, ddd, *J* 10.6, 4.2, 0.6, $Me_2SiOC\boldsymbol{H}H$), 3.81 (1H, dddd, *J* 11.0, 4.1, 1.8, 1.8, OC***H***H), 3.51 (1H, dd, *J* 10.8, 8.1, $Me_2SiOCH\boldsymbol{H}$), 3.28 (1H, ddd, *J* 10.6, 8.7, 6.4, OCH***H***), 3.23 (1H, ddd, *J* 11.3, 11.3, 3.4, TESOC***H***,), 3.00 (1H, ddd, *J* 10.4, 8.6, 1.9, OC***H***), 2.68 (1H, dddd, *J* 14.6, 3.2, 1.6, 1.6, OCHC***H***H), 2.48−2.39 (1H, m, MeC***H***), 2.07 (1H, dddd, *J* 14.6, 9.8, 1.4, 1.4, OCHCH***H***), 2.04−1.99 (1H, m, TESOCHC***H***H), 1.74–1.52 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.43 (1H, dddd, *J* 12.5, 12.5, 10.6, 5.0, TESOCHCH***H***), 0.98 (9H, t, *J* 7.9, $\{C\boldsymbol{H_3}CH_2\}_3Si$), 0.97 (3H, d, *J* 6.2, ***Me***CH), 0.62 (6H, q, *J* 7.9, $\{CH_3C\boldsymbol{H_2}\}_3Si$), 0.22 (3H, s, ***Me***Si), 0.18 (3H, s, ***Me***Si); δ_c (100 MHz, $CDCl_3$) 148.2 (CH), 135.9 (C), 82.4 (CH), 71.1 (CH), 67.7 (CH_2), 67.2 (CH_2), 39.8

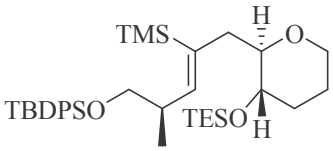
(CH_2), 34.6 (CH), 33.6 (CH_2), 25.6 (CH_2), 17.3 (CH_3), 6.9 (CH_3), 5.1 (CH_2), –0.8 (CH_3), –1.3 (CH_3); HRMS (CI+) calcd. for $C_{19}H_{39}O_3Si_2$, $(M+H)^+$: 371.2438, found 371.2437.

(*R*,*Z*)-2-Methyl-5-((2*R*,3*S*)-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)-4-(trimethylsilyl)pent-3-en-1-ol 338



To a solution of siloxane **337** (210.7 mg, 0.5684 mmol) in THF (5 mL) at 0 °C was added MeLi (533 μL of a 1.6 M solution in ether, 0.85 mmol). After 15 min at 0 °C, an additional volume of MeLi (100 μL) was added. After 5 min, sat. aqueous NH_4Cl (20 ml) was added and the reaction was allowed to warm to rt. Ether (60 mL) was added and the organic layer was washed with sat. aqueous $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The alcohol **338** was used to the next step without further purification. R_f= 0.62 (petrol/EtOAc, 7:3); $[\alpha]_D^{23}$ +65.2 (*c* = 0.50, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3479 (br), 2954, 2876, 1247, 1095, 836, 813; δ_H (400 MHz, $CDCl_3$) 5.57 (1H, d, *J* 10.8, C***H***=), 3.87 (1H, dddd, *J* 11.1, 3.8, 2.0, 2.0, OC***H***H), 3.54–3.43 (1H, m, HOC***H***H), 3.27 (1H, ddd, *J* 10.5, 8.6, 4.6, TESOC***H***), 3.26–3.18 (1H, m, OCH***H***), 3.17 (1H, dd, *J* 10.1, 10.1, HOCH***H***), 2.99 (1H, dddd, *J* 12.9, 2.0, 1.1, 1.1, OCHC***H***H), 2.90 (1H, ddd, *J* 10.8, 8.6, 2.2, OC***H***), 2.69–2.57 (1H, m, MeC***H***), 2.46 (1H, brd, *J* 10.3, ***H***O), 2.03–1.99 (1H, m, TESOCHC***H***H), 1.90 (1H, dd, *J* 12.8, 11.0, OCHCH***H***), 1.68–1.52 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.49–1.43 (1H, m, TESOCHCH***H***), 0.97 (9H, t, *J* 7.9, $\{C\boldsymbol{H_3}CH_2\}_3Si$), 0.91 (3H, d, *J* 6.6, ***Me***CH), 0.61 (6H, q, *J* 7.7, $\{CH_3C\boldsymbol{H_2}\}_3Si$), 0.19 (9H, s, $\boldsymbol{\{CH_3\}_3}Si$); δ_c (100 MHz, $CDCl_3$) 148.1 (CH), 135.8 (C), 81.0 (CH), 72.0 (CH), 67.7 (CH_2), 69.9 (CH_2), 42.6 (CH_2), 39.6 (CH), 33.9 (CH_2), 25.6 (CH_2), 16.0 (CH_3), 6.9 (CH_3), 5.1 (CH_2), 0.7 (CH_3); HRMS (CI+) calcd. for $C_{20}H_{43}O_3Si_2$, $(M+H)^+$: 387.2751, found 387, 2747.

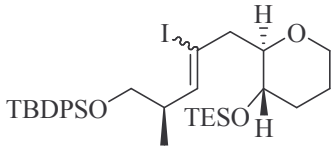
***Tert*-butyl((*R*,*Z*)-2-methyl-5-((2*R*,3*S*)-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)-4-(trimethylsilyl)pent-3-enyloxy)diphenylsilane 339**



To a solution of alcohol **338** (204.0 mg, 0.5275 mmol) and imidazole (107.8 mg, 1.584 mmol) in DMF (0.5 mL) at 0 °C were added TBDPSCl (207 μL, 0.792 mmol) and DMAP (13.0 mg, 0.106 mmol). The reaction mixture was stirred for 1 h at rt. H_2O (10 mL) was added and extracted with ether (3 × 15 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether/Et_3N, 95:5:1) gave protected alcohol **339** as a colourless oil (270.1 mg, 73% over 4 steps). R_f= 0.80 (petrol/EtOAc, 9:1); $[\alpha]_D^{23}$ +3.0 (*c* = 0.5, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2955, 2876, 2857, 1098, 836, 816, 739, 701; δ_H (400 MHz, $CDCl_3$) 7.73–7.70 (4H, m, ***Ph***), 7.46–7.38 (6H, m, ***Ph***), 5.81 (1H, d, *J* 10.4, C***H***=), 3.77 (1H, m, OC***H***H), 3.56 (1H, dd, *J* 9.7, 5.8, TBDPSOC***H***H), 3.46 (1H, dd, *J* 9.7, 7.3, TBDPSOCH***H***), 3.29 (1H, ddd, *J* 10.3, 8.7, 4.6, TESOC***H***), 3.17 (1H, ddd, *J* 11.3, 11.3, 3.2, OCH***H***), 3.00 (1H, ddd, *J* 10.1, 8.7, 1.8, OC***H***), 2.77–2.66 (2H, m, OCHC***H***H, MeC***H***), 2.02–1.98 (1H, m, TESOCHC***H***H), 1.94 (1H, dd, *J* 14.2, 10.1, OCHCH***H***), 1.70–1.58 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.49–1.38 (1H, m, TESOCHCH***H***), 1.08 (9H, s, $\{C\boldsymbol{H_3}\}_3CSi$), 1.05 (3H, d, *J* 6.6, ***Me***CH), 1.00 (9H, t, *J* 7.9, $\{C\boldsymbol{H_3}CH_2\}_3Si$), 0.63 (6H, q, *J* 7.9, $\{CH_3C\boldsymbol{H_2}\}_3Si$), 0.15 (9H, s, $\boldsymbol{\{CH_3\}_3}Si$); δ_c (100 MHz, $CDCl_3$) 146.8 (CH), 135.6 (C), 135.7 (CH), 135.6 (CH), 133.9 (C), 129.4 (CH), 127.5 (CH), 83.3 (CH), 71.4 (CH), 68.7 (CH_2), 67.4 (CH_2), 40.2 (CH_2), 39.1 (CH), 33.8 (CH_2), 26.8 (CH_3), 25.8 (CH_2), 19.3 (C), 17.7

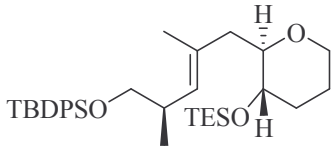
(CH_3), 6.9 (CH_3), 5.1 (CH_2), 0.7 (CH_3); HRMS (CI+) calcd. for $C_{36}H_{61}O_3Si_3$, $(M+H)^+$: 625.3929, found 625.3931.

***Tert*-butyl((*R,Z*)-4-iodo-2-methyl-5-((2*R*,3*S*)-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)pent-3-enyloxy)diphenylsilane 340**



To a solution of vinyl silane **339** (39.8 mg, 0.064 mmol) in MeCN/THF (0.6:0.1 mL) at 0 °C protected from light was added NIS (31.4 mg, 0.070 mmol). The reaction mixture was stirred for 2 h at rt. An additional portion of NIS (11.5 mg, 0.051 mmol) was added and stirred for 2 h at rt. An other portion of NIS (14.4 mg, 0.064 mmol) was added and stirred for 1 h at rt. Sat. aqueous $Na_2S_2O_3$ (5 mL) was added and vigorously stirred for 15 min. The aqueous phase was extracted several times with ether (3 × 5 mL). The combined organics were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The oil was used to the next step without further purification.

***Tert*-butyl((*R,E*)-2,4-dimethyl-5-((2*R*,3*S*)-3-(triethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)pent-3-enyloxy)diphenylsilane 341**

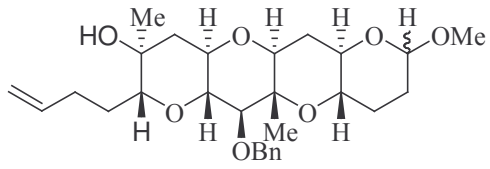


To a degassed solution of vinyl iodide **340** (138.6 mg, 0.2042 mmol) and Me_2Zn (204 µL, 0.408 mmol) in THF (1.1 mL) at rt was added Pd(dppf)Cl_2·CH_2Cl_2 (8.3 mg, 0.010 mmol).

The reaction mixture was degassed with nitrogen 2 times and stirred at 65 °C for 12 h. The reaction was cooled to 0 °C and sat. aqueous NH_4Cl (5 mL) was added. The aqueous phase was extracted several times with ether (2 × 5 mL). The combined organics were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether, 98:2) gave compound **341** (63.7 mg) and compound **342** (15.3 mg) as colourless oils (68% over 2 steps). ***E* alkene** R_f = 0.32 (petrol/ether, 98:2); $[\alpha]_D^{23}$ +3.8 (*c* = 0.5, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2956, 2934, 2875, 2857, 1125, 1098, 739, 701; δ_H (400 MHz, $CDCl_3$) 7.71–7.70 (4H, m, ***Ph***), 7.46–7.37 (6H, m, ***Ph***), 4.99 (1H, d, *J* 8.7, C***H***=), 3.82 (1H, m, OC***H***H), 3.54 (1H, dd, *J* 9.7, 6.0, TBDPSOC***H***H), 3.43 (1H, dd, *J* 9.7, 7.6, TBDPSOCH***H***), 3.29 (1H, ddd, *J* 10.3, 8.7, 4.6, TESOC***H***), 3.24 (1H, ddd, *J* 11.3, 11.3, 3.3, OCH***H***), 3.16 (1H, ddd, *J* 9.9, 8.7, 2.0, OC***H***), 2.69–2.58 (2H, m, OCHC***H***H, MeC***H***), 2.05–1.99 (1H, m, TESOCHC***H***H), 1.92 (1H, dd, *J* 14.5, 9.9, OCHCH***H***), 1.72–1.58 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.63 (3H, d, *J* 1.1, $C\boldsymbol{H_3}C$=), 1.53–1.41 (1H, m, TESOCHCH***H***), 1.07 (9H, s, $\{C\boldsymbol{H_3}\}_3CSi$), 1.02 (3H, d, *J* 6.7, ***Me***CH), 0.98 (9H, t, *J* 7.9, $\{C\boldsymbol{H_3}CH_2\}_3Si$), 0.62 (6H, q, *J* 7.9, $\{CH_3C\boldsymbol{H_2}\}_3Si$); δ_c (100 MHz, $CDCl_3$) 135.7 (CH), 135.6 (CH), 134.1 (2 × C), 133.3 (C), 129.4 (CH), 128.9 (CH), 127.5 (CH), 81.5 (CH), 71.3 (CH), 68.8 (CH_2), 67.6 (CH_2), 42.3 (CH_2), 35.4 (CH), 33.7 (CH_2), 26.8 (CH_3), 25.7 (CH_2), 19.2 (C), 17.5 (CH_3), 16.7 (CH_3), 6.9 (CH_3), 5.1 (CH_2); HRMS (CI+) calcd. for $C_{34}H_{55}O_3Si_2$, $(M+H)^+$: 567.3690, found 567.3688; ***Z* alkene** R_f = 0.34 (petrol/ether, 98:2); $[\alpha]_D^{27}$ –4.8 (*c* = 0.5, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2955, 2934, 2875, 2857, 1097, 738, 700; δ_H (400 MHz, $CDCl_3$) 7.70–7.67 (4H, m, ***Ph***), 7.44–7.48 (6H, m, ***Ph***), 5.05 (1H, d, *J* 9.7, C***H***=), 3.83 (1H, ddd, *J* 11.3, 2.1, 2.1, OC***H***H), 3.49 (1H, dd, *J* 9.6, 6.3, TBDPSOC***H***H), 3.43 (1H, dd, *J* 9.6, 6.0, TBDPSOCH***H***), 3.29 (1H, ddd, *J* 10.4, 8.7, 4.6, TESOC***H***), 3.23 (1H, ddd, *J* 11.5, 11.5, 2.9, OCH***H***), 3.11 (1H, ddd, *J* 10.4, 8.7, 1.7, OC***H***), 2.78–2.29 (1H, m, MeC***H***), 2.52 (1H, d, *J* 13.8, OCHC***H***H), 2.12 (1H, dd, *J* 13.8, 10.4, OCHCH***H***), 2.03–1.99 (1H, m, TESOCHC***H***H), 1.75 (3H, d, *J* 1.1, $C\boldsymbol{H_3}C$=), 1.70–1.58 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.49–1.39 (1H, m, TESOCHCH***H***), 1.05 (9H, s, $\{C\boldsymbol{H_3}\}_3CSi$), 0.98–0.95 (12H, m,

{C***H₃***CH_2}$_3$Si, ***Me***CH), 0.61 (6H, q, *J* 7.9, {CH_3C***H₂***}$_3$Si); δ_c (100 MHz, $CDCl_3$) 135.7 (CH), 135.6 (CH), 134.1 (2 × C), 133.4 (C), 130.1 (CH), 129.4 (CH), 127.5 (CH), 81.2 (CH), 71.6 (CH), 68.8 (CH_2), 67.7 (CH_2), 35.1 (CH), 34.9 (CH_2), 33.7 (CH_2), 26.8 (CH_3), 25.7 (CH_2), 24.3 (CH_3), 19.3 (C), 17.6 (CH_3), 6.9 (CH_3), 5.1 (CH_2); HRMS (CI+) calcd. for $C_{34}H_{55}O_3Si_2$, $(M+H)^+$: 567.3690, found 567.3682.

12-Benzyloxy-2-but-3-enyl-8-methoxy-3,11a-dimethyl-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-ol 344

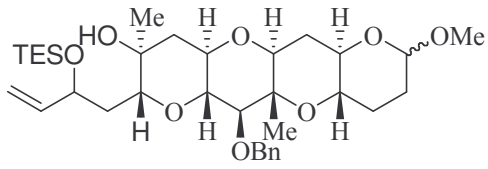


To a solution of oxalyl chloride (86 μL, 1.0 mmol) in CH_2Cl_2 (3 mL) at –78 °C was slowly added DMSO (142 μL, 2.00 mmol). After 0.5 h at –78°C, alcohol **236** (197.0 mg, 0.4000 mmol) in CH_2Cl_2 (1 mL) was added by cannula and the reaction mixture was stirred at –78 °C for 1 h. Then, Et_3N (1 mL) was added and the reaction mixture was allowed to warm to rt. The solution was diluted with CH_2Cl_2 (10 mL) and washed with water (400 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude foam was then dried under high vacuum for 1 h.

To a solution of methyltriphenylphosphonium bromide (107.2 mg, 0.3000 mmol) in benzene (1 mL) at rt was added *t*-BuOK (33.6 mg, 0.300 mmol). Then, mixture was heated at reflux for 1 h and then cooled to rt. A solution of crude lactol (0.1 mmol) in benzene (1 mL) was added to the solution of phosphonium ylide. After 10 min at rt, acetone (1 mL) was added and the mixture was stirred for 10 min at rt. The reaction mixture was then concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/petrol, 7:3) gave alkene **344** as a colourless glass (48.1 mg, 74% over 2 steps, mixture of

diastereomers). R_f = 0.59 (EtOAc/petrol, 7:3); υ_{max}/cm^{-1} (neat) 3454 (br), 2949, 2885, 1091, 1068, 1054, 1024; δ_H (400 MHz, $CDCl_3$) 7.43–7.41 (2H, m, ***Ph***), 7.33–7.29 (3H, m, ***Ph***), 5.87 (1H, dddd, *J* 17.0, 10.2, 6.6, 6.6, H_2C=C***H***), 5.04 (1H, dd, *J* 17.0, 1.4, ***H***HC=), 4.97 (1H, dddd, *J* 10.2, 2.0, 1.1, 1.1, H***H***C=), 4.87 (0.55H, d, *J* 12.1, PhC***H***H), 4.85 (0.45H, d, *J* 12.1, PhC***H***H), 4.81 (1H, brd, *J* 11.9, PhCH***H***), 4.66 (0.56H, d, *J* 1.5, MeOC***H***O), 4.40 (0.44H, dd, *J* 9.5, 2.0, MeOC***H***O), 3.51–3.35 (6H, m), 3.27–3.07 (4H, m), 2.44–2.48 (1H, m, H_2C=CHC***H***H), 2.20–1.41 (12H, m), 1.33 (1.33H, s, BnOCHC***Me***), 1.31 (1.67H, s, BnOCHC***Me***), 1.24 (1.33H, s, HOC***Me***), 1.23 (1.67H, s, HOC***Me***); δ_c (100 MHz, $CDCl_3$) 139.2 (C), 138.4 (CH), 128.0 (CH), 127.5 (2 × CH), 127.2 (2 × CH), 114.8 (CH_2), 103.1 (CH), 97.8 (CH), 84.6 (2 × CH), 84.5 (CH), 82.2 (CH), 78.6 (CH), 78.4 (CH), 76.5 (CH), 75.0 (CH), 74.3 (CH_2), 71.1 (C), 69.7 (CH), 69.3 (CH), 68.6 (CH), 56.5 (CH_3), 54.5 (CH_3), 45.7 (CH_2), 30.7 (2 × CH_2), 30.2 (CH_2), 30.1 (CH_2), 29.7 (CH_2), 28.0 (CH_2), 27.9 (CH_2), 24.9 (CH_2), 21.9 (CH_3), 11.2 (CH_3); HRMS (EI+) calcd. for $C_{28}H_{40}O_7$, M^+: 488.2774, found 488.2776.

12-Benzyloxy-8-methoxy-3,11a-dimethyl-2-(2-triethylsilanyloxy-but-3-enyl)-tetradecahydro-1,5,7,11-tetraoxa-naphthacen-3-ol 349

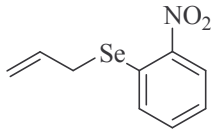


To a solution of alkene **344** (78.9 mg, 0.161 mmol) and salicylic acid (8.8 mg, 0.064 mmol) in CH_2Cl_2 (1.6 mL) at rt was added TBHP (129 μL of a 5.0 M solution in dodecane, 0.644 mmol) followed by SeO_2 (35.7 mg, 0.322 mmol). After heating for 4 h under reflux, the reaction was cooled to rt and sat. aqueous NH_4Cl (10 mL) was added. The aqueous

layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude allylic alcohol (contaminated with 10% of enone) was dried under high vacuum for 1 h.

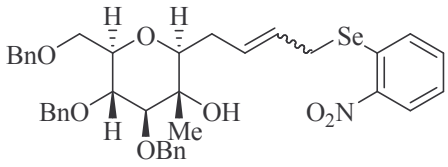
To a solution of crude alcohol **345** (0.161 mmol), imidazole (32.9 mg, 0.483 mmol) and DMAP (2.0 mg, 0.016 mmol) in DMF (0.8 mL) at 0 °C was added TESCl (27 μL, 0.16 mmol). After 18 h at rt, sat. aqueous NH_4Cl (10 mL) was added and the aqueous phase was extracted with ether (3 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/petrol, 6:4) gave compound **274** as a colourless glass (40.8 mg, 41% over 2 steps). R_f = 0.45 (EtOAc/petrol, 7:3); υ_{max}/cm^{-1} (neat) 3472 (br), 2953, 2876, 1461, 1379, 1069, 1024, 740; δ_H (400 MHz, $CDCl_3$) 7.41–7.39 (2H, m, ***Ph***), 7.34–7.23 (3H, m, ***Ph***), 5.87 [RANGE!] (1H, m, H_2C=C***H***), 5.21–5.16 (1H, m, ***H***HC=), 5.13–5.10 (0.3H, m, H***H***C=), 5.04–5.02 (0.7H, m, H***H***C=), 4.90–4.78 (2H, PhC***H₂***), 4.67(0.7H, d, *J* 1.7, MeOC***H***O), 4.44-4.31 (1.3H, m, MeOC***H***O, CH_2C=CHC***H***O), 3.51–3.05 (10H, m), 2.22–1.29 (11H, m), 1.33–1.29 (6H, m, BnOCHC***Me***, HOC***Me***), 0.97–0.87 (9H, m, {C***H₃***CH_2}$_3$Si), 0.64–0.53 (6H, m, {CH_3C***H₂***}$_3$Si); δ_c (100 MHz, $CDCl_3$) 142.0 (CH), 139.4 (C), 139.3 (CH), 139.3 (C), 128.0 (CH), 127.9 (CH), 127.5 (2 × CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 115.6 (CH_2), 113.8 (CH_2), 103.1 (CH), 97.8 (CH), 84.6 (2 × CH), 84.3 (2 × CH), 82.2 (2 × CH), 81.8 (CH), 81.7 (2 × CH), 81.2 (CH), 81.1 (CH), 81.0 (CH), 78.7 (2 × CH), 78.5 (C), 78.4 (CH), 76.6 (CH), 75.0 (CH), 74.3 (CH_2), 74.1 (CH_2), 71.7 (2 × CH), 70.4 (C), 70.1 (C), 69.8 (CH), 69.4 (CH), 68.6 (CH), 56.5 (CH_3), 54.5 (CH_3), 45.4 (CH_2), 44.7 (CH_2), 38.3 (CH_2), 38.0 (CH_2), 30.7 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 29.7 (CH_2), 28.0 (CH_2), 24.9 (CH_2), 22.5 (CH_3), 21.9 (CH_3), 11.1 (CH_3), 11.0 (CH_3), 6.9 (CH_3), 6.8 (CH_3), 6.7 (CH_3), 4.8 (CH_2), 4.7 (CH_2), 4.6 (CH_2); HRMS (EI+) calcd. for $C_{34}H_{54}O_8Si$, M^+: 618.3588, found 618.3589.

Allyl(2-nitrophenyl)selane 353



To a solution of allylalcohol (133 μL, 1.95 mmol) and recrystallized 2-nitrophenyl selenocyanate (577 mg, 2.54 mmol) in THF (4 mL) at rt was added *n*-Bu_3P (627 μL, 2.54 mmol). After 1 h, sat. aqueous $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with ether (3 × 20 mL). The combined organics were washed with brine (20mL), dried ($MgSO_4$) filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether, 9:1) gave compound **353** as a yellow solid (324.8 mg, 69%). R_f = 0.35 (petrol/ether, 9:1); m.p. 55.1–55.8 °C; υ_{max}/cm^{-1} (neat) 2979, 2931, 1587, 1504, 1329, 940, 728; δ_H (400 MHz, $CDCl_3$) 8.30 (1H, m, ***Ph***), 7.56–7.50 (2H, m, ***Ph***), 7.32 (1H, ddd, *J* 8.4, 5.9, 2.6, ***Ph***), 5.98 (1H, dddd, *J* 17.2, 10.0, 7.3, 7.3, CH_2=C***H***), 5.34 (1H, dddd, *J* 17.0, 1.3, 1.3, 1.3, C***H***H=CH), 5.18 (1H, dd, *J* 10.0, 1.0, CH***H***=CH), 3.62 (2H, ddd, *J* 7.3, 1.0, 1.0, CH_2=CHC***H₂***); δ_c (100 MHz, $CDCl_3$) 146.6 (C), 133.5 (C), 133.5 (CH), 132.2 (CH), 129.2 (CH), 126.3 (CH), 125.5 (CH), 119.1 (CH_2), 29.1 (CH_2); HRMS (EI+) calcd. for $C_9H_9O_2NSe$, M^+: 240.9808, found 240.9814; 242.9799, found 242.9802;

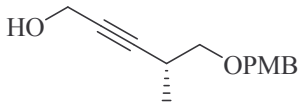
(2*S*,3*S*,4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-3-methyl-2-(4-(2-nitrophenylselanyl)but-2-enyl)-tetrahydro-2*H*-pyran-3-ol 354



To a solution of alcohol **287** (57.0 mg, 0.117 mmol) in benzene (120 μL) at 70 °C was added Grubbs second generation catalyst (5 mg, 0.006 mmol). Then, a solution of allyl selenide **353** (113.3 mg, 0.4680 mmol) was added over 1 h at 70 °C. The reaction was stirred at 70 °C for a further 18 h and the solvent was then removed *in vacuo*. Purification by flash column chromatography (petrol/ether, 1:1) gave compound **354** as a yellow oil (54.2 mg, 66%, 3:1 mixture of *E*/*Z* isomers); R_f= 0.15 (petrol/ether, 1:1); υ_{max}/cm^{-1} (neat) 3553 (br), 3470 (br), 3029, 2920, 2854, 1590, 1512, 1453, 1330, 1303, 1105, 1066, 730, 698; δ_H (400 MHz, $CDCl_3$) 8.28 (1H, dd, *J* 8.3, 1.3, NO_2***Ph***), 7.56–7.46 (2H, m), 7.38–7.22 (14H, m), 7.21–7.20 (1.76H, m), 6.92–6.90 (0.24H, m), 5.91–5.84 (0.87H, m, CH_2=C***H***H), 5.82–5.75 (0.24H, m, CH_2=C***H***H), 5.73–5.66 (0.89H, m, CH_2=C***H***H), 5.01–4.96 (1H, m, PhC***H***H), 4.82–4.76 (2H, m, PhC***H***H), 4.68–4.53 (3H, m, PhCH***H***), 3.76–3.40 (7H, BnOC***H₂***, $BnOCH_2CHC$***H***, $BnOCH_2CHCHC$***H***, $BnOCH_2C$***H***, $PhSeC$***H₂***), 3.20 (0.17H, dd, *J* 9.5, 1.8, $PhSeCH_2CH$=$CHCH_2C$***H***), 3.18 (0.75H, dd, *J* 9.8, 2.4, $PhSeCH_2CH$=$CHCH_2C$***H***), 2.62–2.49 (0.15H, m, $PhSeCH_2CH$=CHC***H***H), 2.41 (0.15H, dd, *J* 13.3, 7.4, $PhSeCH_2CH$=CHC***H***H), 2.34–2.28 (0.22H, m, $PhSeCH_2CH$=CHCH***H***), 2.25– 2.18 (0.79H, m, $PhSeCH_2CH$=CHCH***H***), 1.86 (0.15H, brs, ***H***O), 1.78 (0.79H, brs, ***H***O), 1.27 (0.58H, s, ***Me***), 1.22 (2.41H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 146.7 (C), 138.8 (C), 138.3 (C), 138.0 (C), 133.9 (C), 133.4 (CH), 132.6 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.3 (CH), 125.6 (CH), 125.3 (CH), 113.9 (CH), 89.2 (CH), 81.9 (CH), 79.8 (CH), 77.7 (CH),

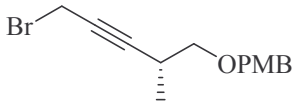
75.5 (CH_2), 74.9 (CH_2), 74.4 (C), 73.4 (CH_2), 69.0 (CH_2), 31.4 (CH_2), 28.5 (CH_2), 16.1 (CH_3); HRMS (FAB+) calcd. for $C_{38}H_{41}NO_7SeNa$, $(M+Na)^+$: 726.1946, found 726.1943.

(*R*)-5-(4-methoxybenzyloxy)-4-methylpent-2-yn-1-ol 356



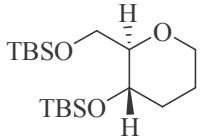
To a solution of alkene **352** (1.35 g, 3.70 mmol) in THF (3 mL) at –78 °C was slowly added *n*-BuLi (3.7 mL of a 2.5 M solution in hexane, 9.25 mmol). After 1 h at –78 °C, paraformaldehyde (3.33 g, 111 mmol) was added portionwise. The reaction was allowed to warm to rt over 18 h. The reaction was cooled to 0 °C, quenched with sat. aqueous NH_4Cl (50 mL) and the reaction was allowed to warm to rt. The aqueous phase was extracted several times with ether (2 × 50 mL) and the combined organics were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was then removed *in vacuo*. Purification by flash column chromatography (petrol/EtOAc, 6:4) gave alkyne **281** as a colourless oil (515.7 mg, 59%). R_f= 0.13 (petrol/EtOAc, 7:3); $[\alpha]_D^{26}$ +8.4 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3414 (br), 2969, 2934, 2904, 2863, 1613, 1513, 1248, 1090, 1035, 819; δ_H (400 MHz, $CDCl_3$) 7.27 (2H, d, *J* 8.7, ***Ph***), 6.88 (2H, d, *J* 8.7, ***Ph***), 4.49 (2H, s, PhC***H₂***), 4.22 (2H, dd, *J* 5.6, 1.7, HOC***H₂***), 3.80 (3H, s, ***Me***O), 3.47 (1H, dd, *J* 9.1, 6.4, PMBOC***H***H), 3.33 (1H, dd, *J* 9.1, 7.1, PMBOCH***H***), 2.76 (1H, m, MeC***H***), 2.41 (1H, brs, ***H***O), 1.18 (3H, d, *J* 6.9, ***Me***CH); δ_c (100 MHz, $CDCl_3$) 159.1 (C), 130.0 (C), 129.2 (CH), 113.7 (CH), 87.8 (C), 79.3 (C), 73.4 (CH_2), 72.6 (CH_2), 55.2 (CH_3), 51.0 (CH_2), 26.5 (CH), 17.6 (CH_3); HRMS (EI+) calcd. for $C_{14}H_{18}O_3$, M^+: 234.1256, found 234.1254.

(*R*)-1-((5-bromo-2-methylpent-3-ynyloxy)methyl)-4-methoxybenzene 357



To a solution of alcohol **356** (497.0 mg, 2.121 mmol), PPh_3 (1.53 g, 4.24 mmol) and K_2CO_3 (44 mg) in ether (20 mL) at 0 °C was added carbon tetrabromide (1.40 g, 4.24 mmol) portionwise. The reaction was stirred for 2 h at rt. Petrol (50 ml) was then added and the reaction mixture was filtered. Purification by flash column chromatography (petrol/ether, 9:1) gave bromide **357** as a colourless oil (263.5 mg, 42%). R_f= 0.30 (petrol/ether, 9:1); $[\alpha]_D^{26}$ +6.5 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2934, 2902, 2857, 2835, 2237, 1612, 1512, 1246, 1092, 1034, 819; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, d, *J* 8.6, ***Ph***), 6.90 (2H, d, *J* 8.6, ***Ph***), 4.50 (2H, s, PhC***H₂***), 3.94 (2H, d, *J* 2.2, BrC***H₂***), 3.81 (3H, s, ***Me***O), 3.48 (1H, dd, *J* 9.1, 6.3, PMBOC***H***H), 3.35 (1H, dd, *J* 9.1, 7.1, PMBOCH***H***), 2.80 (1H, m, MeC***H***), 1.20 (3H, d, *J* 6.7, ***Me***CH); δ_c (100 MHz, $CDCl_3$) 159.1 (C), 130.1 (C), 129.1 (CH), 113.7 (CH), 89.5 (C), 76.1 (C), 73.2 (CH_2), 72.6 (CH_2), 55.2 (CH_3), 26.9 (CH), 17.3 (CH_3), 15.4 (CH_2); HRMS (EI+) calcd. for $C_{14}H_{17}O_2Br$, M^+: 296.0412, found 296.0413; 298.0393 found 298.0388.

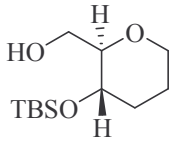
***Tert*-butyl(((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)methoxy)dimethylsilane 362 [106]**



To a solution of diol **3611** (1.10 g, 8.32 mmol) and imidazole (2.27 g, 33.3 mmol) in DMF (20 mL) at 0 °C was added TBSCl (2.88 g, 19.1 mmol). The reaction mixture was stirred for 18 h at rt. Sat. aqueous $NaHCO_3$ (200 mL) was added and extracted with CH_2Cl_2 (3 ×

200 mL). The combined organics were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether, 97:3) gave protected alcohol **362** as a colourless oil (2.70 g, 90%). R_f= 0.41 (petrol/ether, 1:1); $[\alpha]_D^{25}$ +27.9 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2955, 2929, 2857, 1472, 1462, 1252, 1102, 836, 776; δ_H (400 MHz, $CDCl_3$) 3.88–3.84 (2H, m, OC***H***H, TBSOC***H***H), 3.66 (1H, dd, *J* 11.2, 5.8, TBSOCH***H***), 3.45 (1H, ddd, *J* 10.3, 9.4, 4.8, TBSOC***H***), 3.28 (1H, ddd, *J* 11.0, 11.0, 4.0, OCH***H***), 3.07–3.03 (1H, m, $TBSOCH_2C$***H***), 1.97 (1H, dd, *J* 12.2, 3.0, TBSOCHC***H***H), 1.66–1.1.56 (2H, m, OCH_2***CH_2***), 1.45–1.35 (1H, m, TBSOCHCH***H***), 0.87 (9H, s, {C***H_3***}$_3$C), 0.86 (9H, s, {C***H_3***}$_3$C), 0.04 (12H, s, C***H_3***Si); δ_c (100 MHz, $CDCl_3$) 83.6 (CH), 67.4 (CH_2), 67.0 (CH), 63.6 (CH_2), 33.4 (CH_2), 26.0 (CH_3), 25.7 (CH_3), 25.5 (CH_2), 18.5 (C), 17.8 (C), –4.2 (CH_3), –4.9 (CH_3), –5.0 (CH_3), –5.2 (CH_3); HRMS (CI+) calcd. for $C_{18}H_{41}O_3Si_2$, $(M+H)^+$: 361.2594, found 361.2591.

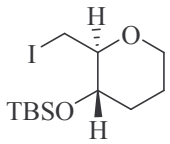
((2*R*,3*S*)-3-(*Tert*-butyldimethylsilyloxy)-tetrahydro-2*H*-pyran-2-yl)methanol 363 [106]



To a solution of protected alcohol **362** (2.70 g, 7.48 mmol) in THF/H_2O (16 mL, 1/1) at 0 °C wad added TFA (8 mL). After 10 min of vigourous stirring, sat. aqueous $NaHCO_3$ (150 mL) was added **carefully**. Then, the aqueous phase was extracted several times with ether (2 × 100 mL). The combined organics were washed with sat. aqueous NH_4Cl (2 × 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether, 1:1) gave alcohol **363** as a colourless oil (1.42 g, 77%). R_f = 0.50 (petrol/ether, 1:1); $[\alpha]_D^{24}$ +39 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3177,

2953, 2930, 2857, 1252, 1039, 876, 837, 776; δ_H (400 MHz, $CDCl_3$) 3.92 (1H, dddd, *J* 11.2, 3.7, 1.9, 1.9, OC***H***H), 3.84 (1H, ddd, *J* 11.2, 6.7, 3.1, HOC***H***H), 3.62 (1H, ddd, *J* 11.5, 5.9, 5.9, HOCH***H***), 3.49 (1H, ddd, *J* 10.6, 9.0, 4.7, TBSOC***H***), 3.40–3.38 (1H, m, OCH***H***), 3.15 (1H, ddd, *J* 9.0, 6.0, 3.1, $HOCH_2C$***H***), 2.06–1.99 (2H, m, TBSOCHC***H***H, ***H***O), 1.70–1.63 (2H, m, OCH_2C***H*****$_2$**), 1.51–1.49 (1H, m, TBSOCHCH***H***), 0.88 (9H, s, {C***H*****$_3$**$\}_3$C), 0.07 (6H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 82.5 (CH), 67.4 (CH_2), 67.5 (CH), 62.7 (CH_2), 33.1 (CH_2), 25.6 (CH_3), 25.3 (CH_2), 17.7 (C), –4.3 (CH_3), –5.1 (CH_3); HRMS (CI+) calcd. for $C_{12}H_{27}O_3Si_1$, $(M+H)^+$: 247.1729, found 247.1726.

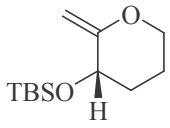
Tert-butyl((2*S*,3*S*)-2-(iodomethyl)-tetrahydro-2*H*-pyran-3-yloxy)dimethylsilane 364[106]



To a solution of alcohol **363** (1.42 g, 5.76 mmol), imidazole (588.0 mg, 8.636 mmol) and PPh_3 (2.27 g, 8.64 mmol) in benzene (90 mL) at rt was added iodine (1.90 g, 7.49 mmol). After 45 min at rt, sat. aqueous $Na_2S_2O_3$ (100 mL) was added and the aqueous phase was extracted with ether (3 × 100 mL). The combined organics were dried ($MgSO_4$) filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether, 95:5) gave compound **364** as a colourless oil (1.90 g, 93%). R_f= 0.39 (petrol/ether, 95:5); $[\alpha]_D^{24}$ +39.3 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2953, 2929, 2856, 1252, 1010, 837, 776; δ_H (400 MHz, $CDCl_3$) 3.96 (1H, dddd, *J* 11.4, 4.4, 2.2, 2.2, OC***H***H), 3.50 (1H, dd, *J* 10.4, 2.7, IC***H***H), 3.47–3.48 (2H, m, TBSOC***H***, OCH***H***), 3.33 (1H, ddd, *J* 10.4, 5.7, ICH***H***), 2.82 (1H, ddd, *J* 8.5, 5.7, 2.7, ICH_2C***H***), 2.02 (1H, m, TBSOCHC***H***H), 1.76–1.61 (2H, m, OCH_2C***H*****$_2$**), 1.48 (1H, dddd, *J* 12.8, 12.8, 10.7, 4.6, TBSOCHCH***H***), 0.88 (9H, s, {C***H*****$_3$**$\}_3$C), 0.11 (3H, s, ***Me***) , 0.09 (3H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 80.8 (CH), 71.2

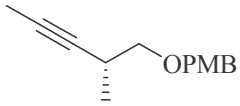
(CH), 68.0 (CH_2), 33.1 (CH_2), 25.8 (CH_3), 25.5 (CH_2), 18.0 (C), 9.4 (CH_2), –3.8 (CH_3), –4.5 (CH_3); HRMS (CI+) calcd. for $C_{12}H_{26}O_2SiI$, $(M+H)^+$: 357.0747, found 357.0746.

(*S*)-*Tert*-butyldimethyl(2-methylene-tetrahydro-2*H*-pyran-3-yloxy)silane 365



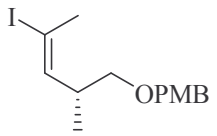
To a solution of iodide **364** (1.90 g, 5.33 mmol) in THF (60 mL) at 0 °C was added *t*-BuOK (1.50 g, 13.3 mmol). After 4 h at 0 °C, brine (200 mL) was added and the aqueous phase was extracted with ether (3 × 100 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (petrol/ether, 98:2) gave compound **365** as a colourless oil (700.2 mg, 57%). R_f = 0.39 (petrol/ether, 95:5); $[\alpha]_D^{24}$ –25.5 (*c* = 1.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2952, 2930, 2857, 1656, 1253, 1129, 1106, 1074, 851, 837, 775; δ_H (400 MHz, $CDCl_3$) 4.49 (1H, d, *J* 1.4, C***H***H=), 4.47 (1H, d, *J* 1.2, CH***H***=), 4.06 (1H, dddd, *J* 9.7, 4.9, 1.4, 1.4, TBSOC**H**), 3.96 (1H, dddd, *J* 10.8, 4.0, 4.0, 1.4, OC***H***H), 3.66–3.60 (1H, m, OCH***H***), 2.00–1.93 (1H, m, TBSOCHC***H***H), 1.86–1.53 (2H, m, $OCH_2C\boldsymbol{H_2}$), 1.66–1.56 (1H, m, TBSOCHCH***H***), 0.91 (9H, s, $\{C\boldsymbol{H_3}\}_3C$), 0.08 (3H, s, ***Me***) , 0.08 (3H, s, ***Me***); δ_c (100 MHz, $CDCl_3$) 163.2 (C), 91.6 (CH_2), 69.9 (CH_2), 68.2 (CH), 33.5 (CH_2), 25.8 (CH_3), 24.2 (CH_2), 18.2 (C), –5.0 (2 × CH_3); HRMS (CI+) calcd. for $C_{12}H_{25}O_2Si$, $(M+H)^+$: 229.1624 found 229.1628.

(*R*)-1-Methoxy-4-((2-methylpent-3-ynyloxy)methyl)benzene 366 [107]



To a solution of alkene **352** (6.22 g, 17.0 mmol) in THF (100 mL) at –78 °C was slowly added *n*-BuLi (30 mL of a 1.4 M solution in ether, 43 mmol). After 1 h at rt, the reaction was cooled to –78 °C and MeI (4.2 mL, 68 mmol) was added. The reaction was allowed to warm to rt over 18 h. The reaction was cooled to 0 °C, quenched with sat. aqueous NH_4Cl (100 mL) and the reaction was allowed to warm to rt. The aqueous phase was extracted several times with ether (2 × 100 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent was then removed *in vacuo*. Purification by flash column chromatography (petrol/ether, 95:5) gave alkyne **366** as a colourless oil (2.85 g, 77%). R_f = 0.33 (petrol/EtOAc, 95:5); $[\alpha]_D^{23}$ +3.1 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2968, 2934, 2917, 2902, 2857, 1613, 1513, 1247, 1092, 1036, 820; δ_H (400 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8.7, ***Ph***), 6.90 (2H, d, *J* 8.7, ***Ph***), 4.53 (1H, d, *J* 11.8, PhC***H***H), 4.50 (1H, d, *J* 11.8, PhCH***H***), 3.82 (3H, s, ***Me***O), 3.49 (1H, dd, *J* 9.0, 6.1, PMBOC***H***H), 3.32 (1H, dd, *J* 9.0, 7.5, PMBOCH***H***), 2.76-2.66(1H, m, MeC***H***), 1.82 (3H, d, *J* 2.4, C***H₃***C≡C), 1.20 (3H, d, *J* 6.9, ***Me***CH); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 130.3 (C), 129.1 (CH), 113.6 (CH), 81.1 (C), 76.3 (C), 74.0 (CH_2), 72.5 (CH_2), 55.1 (CH_3), 26.6 (CH), 18.0 (CH_3), 3.4 (CH_3); HRMS (CI+) calcd. for $C_{14}H_{19}O_2$, $(M+H)^+$: 219.1885, found 219.1387.

(*R,E*)-1-((4-Iodo-2-methylpent-3-enyloxy)methyl)-4-methoxybenzene 367 [107]



To a solution of Schwartz' reagent (1.00 g, 3.88 mmol) in THF (3.5 mL) at rt protected from light, was added a solution of alkynyl **366** (338.0 mg, 1.548 mmol) in THF (3.5 mL). After 1 day at rt, the reaction was cooled to 0 °C and a solution of I_2 (786.8 mg, 3.100 mmol) in THF (1 mL) was added. The reaction was allowed to warm to rt and stirred for 30 min. Sat. aqueous $Na_2S_2O_3$ (10 mL) was added and vigorously stirred for 10 min. The aqueous phase was extracted several times with ether (2 × 20 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by flash column chromatography (petrol/ether, 95:5) gave alkyne **291** as a colourless oil (354.2 mg, 66%). R_f = 0.33 (petrol/EtOAc, 95:5); $[\alpha]_D^{23}$ +7.6 (*c* = 1.0, $CHCl_3$); υ_{max}/cm^{-1} (neat) 2957, 2929, 2853, 2835, 1612, 1512, 1247, 1094, 1037, 819; δ_H (400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.7, ***Ph***), 6.92 (2H, d, *J* 8.7, ***Ph***), 6.03 (1H, dq, *J* 9.4, 1.4, C***H***=), 4.47 (2H, s, ArC***H₂***), 3.84 (3H, s, ***Me***O), 3.31 (1H, dd, *J* 9.1, 6.7, PMBOC***H***H), 3.28 (1H, dd, *J* 9.1, 6.7, PMBOCH***H***), 2.80–2.60 (1H, m, MeC***H***), 2.43 (3H, d, *J* 1.4, C***H₃***C≡C), 1.02 (3H, d, *J* 6.8, ***Me***CH); δ_c (100 MHz, $CDCl_3$) 159.0 (C), 143.8 (CH), 130.4 (C), 129.1 (CH), 113.7 (CH), 94.5 (C), 73.8 (CH_2), 72.6 (CH_2), 55.2 (CH_3), 48.0 (CH), 27.9 (CH_3), 17.0 (CH_3); HRMS mass not found.