Synthesis of the ABC Fragment of Pectenotoxin-4

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Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source. Text taken from another source will be enclosed in quotation marks and a reference given.

Radosław Michał Lipiński

Oxford, Michaelmas 2012

For Mum and Dad

Rodzicom

Contents

Abstract

Synthesis of the ABC fragment of pectenotoxin-4

Radosław M. Lipiński **Lincoln College** **D.Phil.** **Michaelmas 2012**

This thesis details the application of two synthetic methodologies, developed by the Donohoe group, to the synthesis of the ABC fragment of pectenotoxin-4, a macrolide marine natural product that consists of 19 stereogenic centres, three tetrahydrofuran rings, one spiroketal and one bicyclic ketal embedded within a 26-membered macrocycle.

Pivotal to the developed synthetic route was the utilisation of an unprecedented cascade osmium-catalysed oxidative cyclisation for the construction of two THF rings (the BC ring system). After successfully developing a model system for the synthesis of the AB anomeric 6,5-spiroketal, which involved the employment of a hydride shift initiated oxo-carbenium ion formation followed by intramolecular spiroketalisation, the developed system was then applied to the fully elaborated synthesis of the ABC fragment.

The synthesis of the ABC fragment of pectenotoxin-4 was completed in 20 linear steps, with an overall yield of 3.3%.

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Finally, I would like to thank Mum, Dad and Aneta for their continual and limitless love and support.

Abbreviations and Acronyms

AD	asymmetric dihydroxylation
aq	aqueous
Ac	acetyl
Ar	generic aromatic group
acac	acetylacetonato
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bt	benzothiazolyl
Bu	butyl
Bz	benzoyl
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
CSA	(±)-camphor-10-sulfonic acid
δ	NMR chemical shift in ppm downfield from a standard
DBB	4,4′-di-*tert*-butylbiphenyl
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMP	dimethoxypropane
DMPU	*N*,*N*′-dimethyl-*N*,*N*′-propylene urea
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionisation
Et	ethyl
h	hour
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry

Hz	Hertz
i	iso
IR	infra-red
J	coupling constant
L	generic ligand
LC_{50}	dose that is lethal to 50% of test subjects
LDA	lithium diisopropylamide
lit.	literature
LUMO	lowest unoccupied molecular orbital
M	metal or molar (mol dm^{-3})
Mc	chloromethanesulfonyl (chloromesyl)
m-CPBA	*meta*-chloroperoxybenzoic acid
Mes	2,4,6-trimethylphenyl (mesityl)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
NIS	*N*-iodosuccinimide
n	normal
NME	*N*-methylephedrine
NMO	*N*-methylmorpholine *N*-oxide
NMP	N-methylpyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NPNO	4-nitropyridine *N*-oxide
Ns	2-nitrobenzenesulfonyl (nosyl)
Nu	nucleophile
P	protecting group
Ph	phenyl
pH	$-\log_{10}[H_3O^+]$
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PNO	pyridine *N*-oxide
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
PTX	pectenotoxin
Py	pyridine
R	generic organic group
R_f	retention factor
rt	room temperature

ROESY	rotating frame Overhauser effect spectroscopy
rsm	recovered starting material
s/*sec*	secondary
t/*tert*	tertiary
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBDPS	*tert*-butyldiphenylsilyl
TBODPS	*tert*-butoxydiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TCA	*trans*-cinnamic acid
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
TMO	trimethylamine *N*-oxide
TMS	trimethylsilyl
TPS	triphenylsilyl
Ts	toluenesulfonyl (tosyl)
UV	ultraviolet
ν_{max}	infra-red absorption
wt %	weight percent
X	generic halogen

Chapter 1

Introduction

1.1 General introduction

This chapter provides an overview of the pectenotoxins, a family of marine natural products, describing their isolation, structure elucidation and biological activity. In addition, Section 1.3 reviews selected synthetic approaches to the synthesis of the ABC and related fragments. Particular focus is placed upon the construction of the AB spiroketal in both anomeric and non-anomeric form. This account summarises the key syntheses, but does not attempt to serve as a comprehensive review, however, a number of publications are available for more detailed reading, which are highlighted to the reader where appropriate. Finally, Section 1.4 provides an overview of our proposed synthetic approach to the northern hemisphere of pectenotoxin-4.

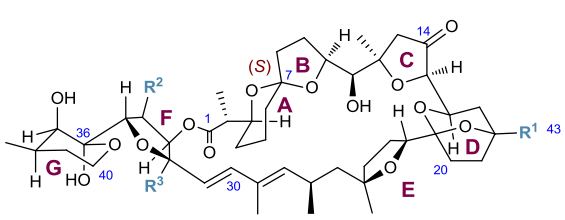
1.2 Introduction to the pectenotoxin family

1.2.1 Isolation of the pectenotoxins

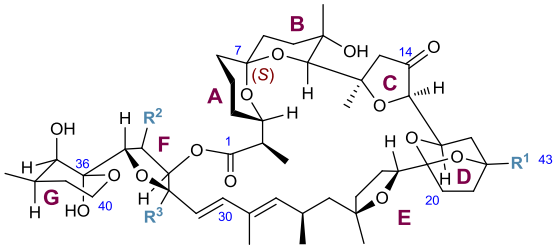
The pectenotoxins are a family of cyclic polyether macrolide toxins, first isolated in 1985 off the northeastern coast of Japan from the digestive glands of the toxic scallops *Patinopecten yessoensis*.[1] Together with okadaic acid and dinophysistoxin-1, the pectenotoxins were often associated with diarrhetic shellfish poisoning (DSP). The first member of the family to be characterised was pectenotoxin-1 (PTX-1), whose structure was determined by X-ray crystallography. However, it was not until 1997 that the absolute configuration of PTX-1 was deduced, through NMR studies conducted on phenylglycine methyl ester derivatives of PTX-6.[2]

Since 1985, more than twenty members of the pectenotoxin family have been isolated and characterised, largely by comparison of spectroscopic data with PTX-1 and PTX-6 (Figure 1).[3,4] The structures of PTX-5 and -10 have not yet been assigned, primarily due to their scarcity from natural sources, which limits a full spectral analysis.

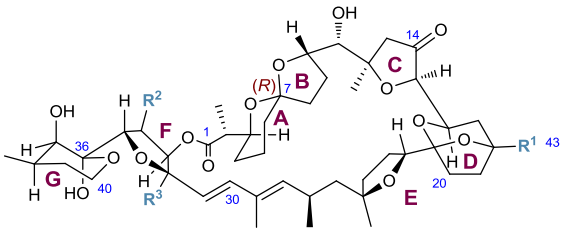
Figure 1 *Structures of the pectenotoxin family members*



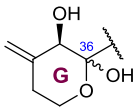
	R^1	R^2	R^3
PTX-2b	CH_3	H	H
PTX-4	CH_2OH	H	H
PTX-7	CO_2H	H	H
PTX-11b	CH_3	OH	H



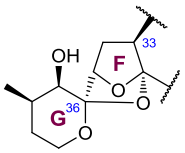
	R^1	R^2	R^3
PTX-2c	CH_3	H	H
PTX-8	CH_2OH	H	H
PTX-9	CO_2H	H	H
PTX-11c	CH_3	OH	H



	R^1	R^2	R^3
PTX-1	CH_2OH	H	H
PTX-2	CH_3	H	H
PTX-3	CHO	H	H
PTX-6	CO_2H	H	H
PTX-11	CH_3	OH	H
(36*S*)-PTX-12	CH_3	H	H
(36*R*)-PTX-12	CH_3	H	H
PTX-13	CH_3	H	OH
PTX-14	CH_3	H	--



(36*S*)-PTX-12 (C36 α-OH)
(36*R*)-PTX-12 (C36 β-OH)



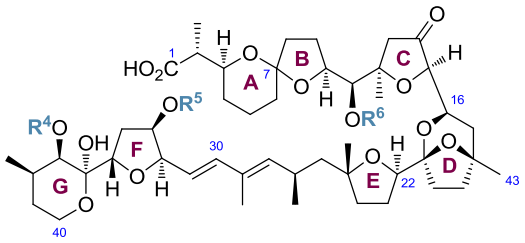
PTX-14

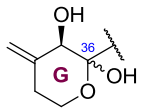
The pectenotoxins comprise three tetrahydrofuran rings, one spiroketal, one bicyclic ketal and 19 stereogenic centres (six of which are quaternary), embedded in a 34-membered macrolide ring. Major structural variation between the family members resides in the oxidation level of the C43 substituent, which can vary from a methyl group to the corresponding carboxylic acid, as well as the stereochemistry at the C7 anomeric spiroketal carbon, of which both epimers are known. Finally, the structure of the AB spiroketal can exist in either a 6,5- or a 6,6-form (Figure 1).

Although originally isolated from the digestive glands of scallops, it was later discovered that the actual producers of the pectenotoxins are dinoflagellate species of the genera *Dinophysis*, found in coastal areas worldwide.[5] It was reported that PTX-2 was the only congener secreted by *Dinophysis fortii*, suggesting that PTX-2 is the parent toxin (and a product of natural biosynthesis) and thus the pectenotoxin family is the result of secondary metabolism in toxic scallops. Further toxicological studies revealed that PTX-2 exhibited the highest lethality amongst the PTXs in tests with mice (LC_{50} = 219 μg/kg), indicating that conversion of PTX-2 to other congeners could be a result of a detoxification process.[6]

More recently, the open chain analogues of the pectenotoxins were isolated from New Zealand greenshell mussels (*Perna canaliculus*).[7-11] Through comparison of spectroscopic data it was possible to determine their structures as pectenotoxin seco acids (Figure 2). Moreover, a series of fatty acid esters of PTX-2 seco acid have been identified, which are similar to those found in derivatives of the brevetoxins.

Figure 2 *Structures of pectenotoxin seco acids*





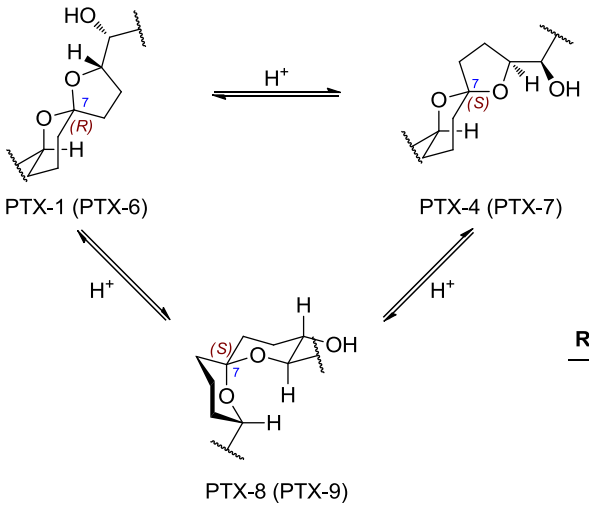
	R^4	R^5	R^6	C7
PTX-2sa and 7-epi-PTX-2sa	H	H	H	(*R*) and (*S*)
37-*O*-Acyl PTX-2sa	fatty acid ester	H	H	(*R*) and (*S*)
33-*O*-Acyl PTX-2sa	H	fatty acid ester	H	(*R*) and (*S*)
11-*O*-Acyl PTX-2sa	H	H	fatty acid ester	(*R*) and (*S*)
PTX-11sa	CH_3	OH	H	(*R*) and (*S*)
(36*S*)-PTX-12sa	CH_3	H	H	(*R*) and (*S*)
(36*R*)-PTX-12sa	CH_3	H	H	(*R*) and (*S*)

Interestingly, all of the seco acids appeared to be less toxic than their macrocyclic analogues. Toxicological studies of PTX-2 seco acid and 7-*epi*-PTX-2 seco acid showed that these analogues possessed no cytotoxicity against human KB cells at a dose of 1.8 μg/mL, whereas the parent PTX-2 exhibited cytotoxic activity at just 0.05 μg/mL. Based on these results it was concluded that the macrolide system was essential to maintaining potency.[10] It was later proposed that PTX-2 seco acid was produced as a result of an enzymatic hydrolysis of the PTX-2 lactone within the shellfish, likely as part of the detoxification process. Similar transformations also took place in the case of PTX-11 and PTX-12,[12] however, these analogues appeared to be more resistant to an enzymatic hydrolysis to the corresponding seco acids, likely due to the steric hindrance induced by the C34 hydroxyl group, and hydrogen bonding between the hydroxyl group and carboxylic moiety. Furthermore, the high resistance towards hydrolysis could rationalise the greater accumulation of PTX-11 in mussels compared to PTX-2.[13,14]

1.2.2 Acid sensitivity of the AB spiroketal

The configuration of the AB spiroketal present in the pectenotoxin macrolides is interconvertible by mild acid equilibration. In 1998, Yasumoto and co-workers reported that exposure of PTX-6 to a 0.1% solution of trifluoroacetic acid in an aqueous acetonitrile solution caused it to undergo a gradual conversion to PTX-7 and PTX-9 (Scheme 1).[3] The proportions of all isomers after 48 hours were PTX-6/PTX-7/PTX-9 40:16:44. Similar results were observed in case of PTX-1, which under the same conditions provided a mixture of PTX-1, PTX-4 and PTX-8 (29:14:57) respectively. Despite being produced under mildly acidic conditions during equilibration experiments, PTX-8 and PTX-9 were not found in extracts from the scallops and are only artificial products of the extraction process. Therefore, it was postulated that the spiroketal isomerisation occurs in the digestive gland of scallops and is catalysed by a scallop-derived enzyme, as opposed to an indiscriminate acid-catalysed process.[3]

Scheme 1 *Interconversion of the pectenotoxins under acidic conditions*



Relative abundance after 48 hours

PTX-1	**29**	**PTX-6**	**40**
PTX-4	**14**	**PTX-7**	**16**
PTX-8	**57**	**PTX-9**	**44**

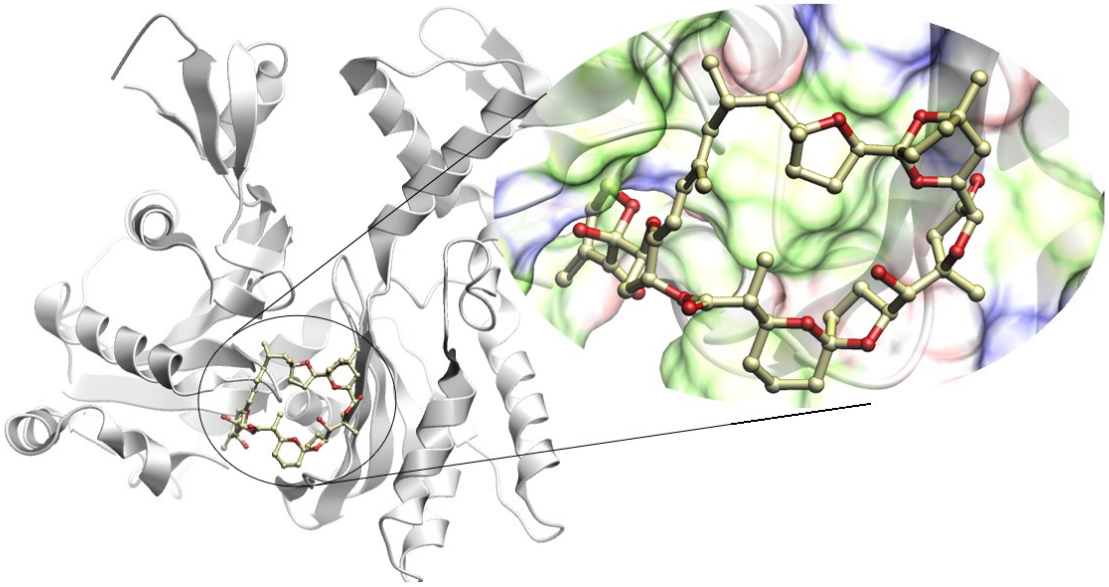
In contrast, only the two 6,5-AB spiroketals of the PTX-2 seco acid were isolated, with the (7*S*)-configuration being favoured in a 75:25 ratio, which suggested that this was the more thermodynamically favoured isomer in the open chain system. This information may have important implications for the design and implementation of viable synthetic routes to the pectenotoxins, since carrying through the 6,5-spiroketal with the (*S*)-configuration at C7 would likely minimise the risk of epimerisation prior to macrolide assembly. However, the equilibration data led to the conclusion that this is the least stable spiroketal form when embedded in a macrocyclic architecture.

1.2.3 Biological activity of the pectenotoxins

The pectenotoxins were initially classified and regulated with other DSP toxins, including okadaic acid, yessotoxins and dinophysistoxins, primarily due to their co-occurence and biological origin.[1] However, the inclusion of the PTXs in the DSP group was under debate until more recent studies demonstrated that different PTXs failed to show any signs of diarrhetic activity even at high doses (5 mg/kg).[15,16] It is likely that the classification of PTXs as causative agents for shellfish poisining was a result of the co-extraction of the PTXs with okadaic acid and its derivatives. Although the PTXs showed low toxicity following oral administration in mice, they exhibited high levels of toxicity when administered intraperitoneally, with PTX-2 being the most toxic (LC_{50} 216–260 μg/kg). However, subjecting mice to either route of administration did not induce diarrhoea, even at concentrations higher than 5000 μg/kg.[6,13]

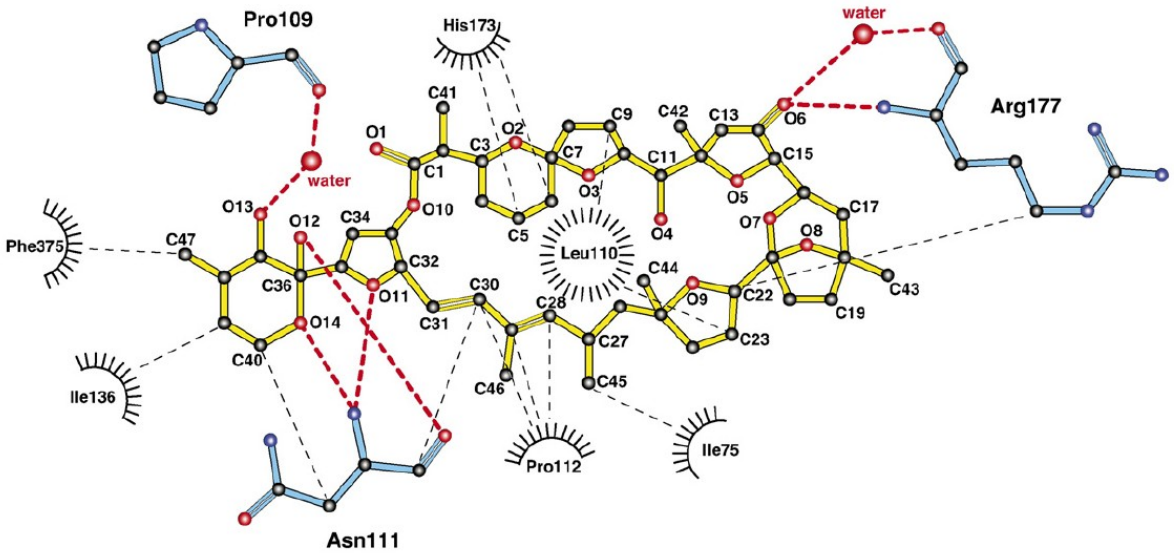
Initially reported to be hepatotoxic, the PTXs were later shown to display selective cytotoxicity against various cancer cell lines.[5,16] The most potent of this family, PTX-2, was discovered to be highly cytotoxic against a range of lung, colon and breast cancer cell lines. It was subsequently reported that the PTXs destabilise the cytoskeleton of actin, one of the most abudant proteins in eukaryotic cells, which controls cell shape, movement, cell division and adherens junctions between cells. Spector and co-workers showed that PTX-2 disrupts the organisation of actin in several cell types by sequestration of the G-actin monomer.[15,17,18] Further studies revealed that PTX-6 induced disruption of the F-actin cytoskeleton.[18] X-ray analysis of the crystal structure of PTX-2 bound to G-actin demonstrated a novel binding site between subdomain 1 and 3 (Figure 3). The position at which PTX-2 binds to actin had not previously been observed with other small natural products, revealing the PTXs ability to exhibit a unique mode of action.[19]

Figure 3 *X-ray crystal structure of PTX-2 in complex with actin*[19]



The C, F and G rings of the PTXs play important roles in binding by means of hydrogen bonds with actin residues or actin-coordinated molecules of water, while the AB spiroketal and 1,3-diene appear to serve as a scaffolding fragments to ensure proper orientation of the binding subunits to allow sufficient interaction with the approriate components of the actin surface (Figure 4). Notably, this role is significantly affected by the configuration at the C7 spiroketal centre, with the (7*R*) isomers demonstrating enhanced activites.

Figure 4 *Interactions between PTX-2 and actin. Thin dashed lines represent van der Waals interactions, while thick red dashed lines represent hydrogen bonding interactions. Actin residues involved in polar interactions are represented in blue.*[19]



Most recent studies on the mechanism of action have shown that PTX-2 efficiently inhibits F-actin polymerisation, as well as inhibiting the growth of leukemia cells, with a marked increase in apoptosis.[20,21] Furthermore, it has been discovered that cancerous cells exhibit a higher sensitivity to PTXs compared to normal cells, which is of great clinical importance in terms of development of new cancer chemotherapy agents.[22,23]

Given the promising anticancer properties of the PTXs, it has been speculated that this class of compound could serve as a promising lead in drug discovery. Analysis of the PTX-2/G-actin complexes have allowed better understanding of the structure-activity relationships within the pectenotoxin family and could assist in the further design of novel PTX analogues. However, the development of these marine natural products as potential therapeutics has remained in its infancy, mainly due to their low natural abundance (i.e. only 7 mg of PTX-4 was isolated from 200 kg of the digestive glands of the scallops).

1.3 Previous syntheses of ABC fragment of pectenotoxin-4

The unique architecture and molecular complexity of the pectenotoxins pose a very interesting synthetic challenge. As a result, and combined with their high cytotoxic activity, they have inspired many research groups to undertake studies directed towards the synthesis of these molecules. Although the isolation of the first pectenotoxin family members was reported in 1985,[1] it was not until 1997 that the first synthesis of the FG ring system was disclosed by Murai and Fujiwara.[24] Since this initial report, several research groups have disclosed their synthetic endeavours to different segments of the pectenotoxins, with only one total synthesis of pectenotoxin-4 and -8 reported to date.

Notably, the most potent member of this class of compounds, pectenotoxin-2, has received considerable attention. However, the presence of a less stable non-anomeric AB spiroketal in PTX-2 has made a configurationally-controlled synthesis highly challenging. Since PTX-2 (7*R*) and PTX-4 (7*S*) share the same carbon framework, with the only exceptions being the C7 stereochemistry and C43 oxidation state, the majority of synthetic approaches towards the ABC fragment of PTX-2 focus upon preparation of the thermodynamically more favoured AB ring system (a structure found in PTX-4) and rely on a late stage equilibration of the spiroketal fragment.

In line with the aims of this thesis, this section will provide an overview of synthetic approaches towards the ABC fragment of pectenotoxin-4, in the context of the synthesis of

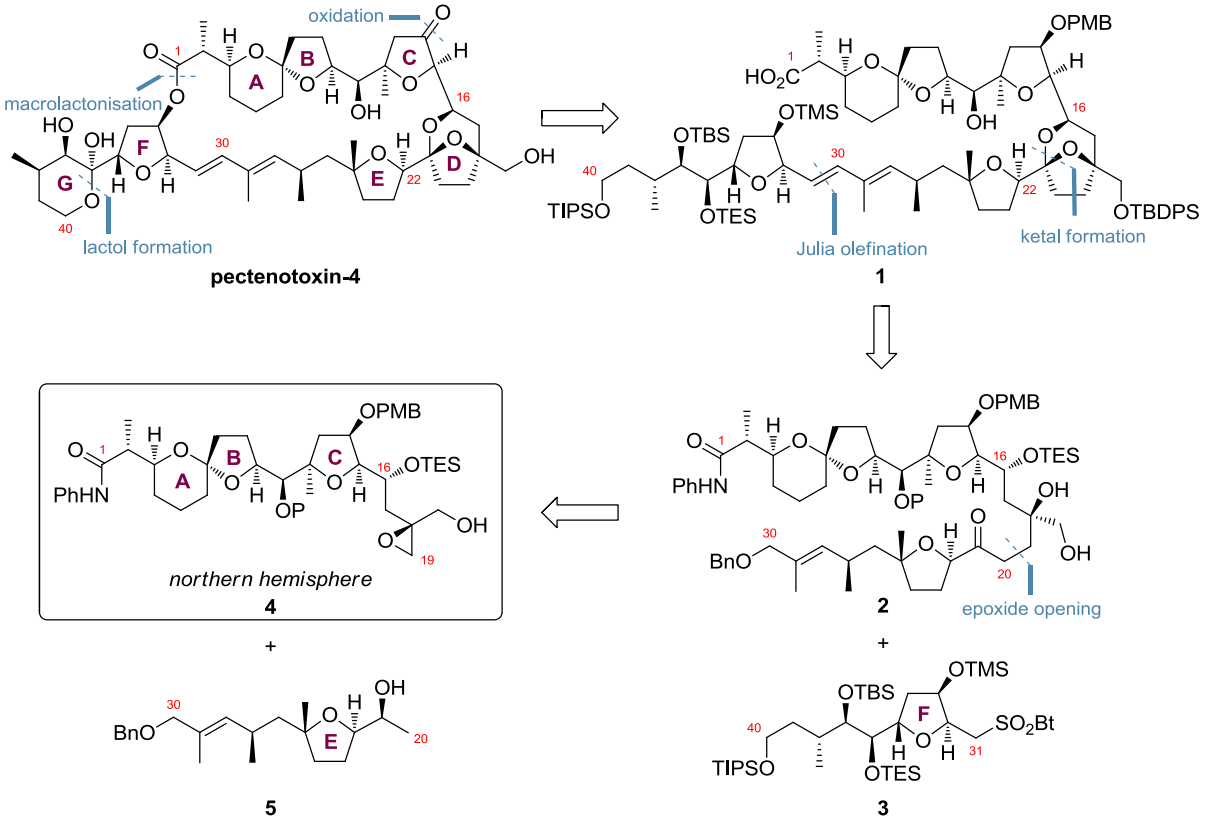
PTX-4 and PTX-8 by Evans and co-workers, with selected examples of syntheses of the non-anomeric AB spiroketal found in PTX-2.

1.3.1 Evans's total synthesis of pectenotoxin-4 and -8

In 2002, Evans and co-workers reported the first total synthesis of pectenotoxin-4 and -8.[25,26] Pectenotoxin-4, containing the anomerically favoured 6,5-spiroketal, was chosen as an initial target. As revealed in the equilibration studies of the PTXs and PTX seco acids, the (7*S*) spiroketal is the most stable isomer in the acyclic variants, but is the least stable when constrained within the macrolide framework. It is noteworthy that this choice allowed minimal spiroketal isomerisation prior to the macrolactonisation step.

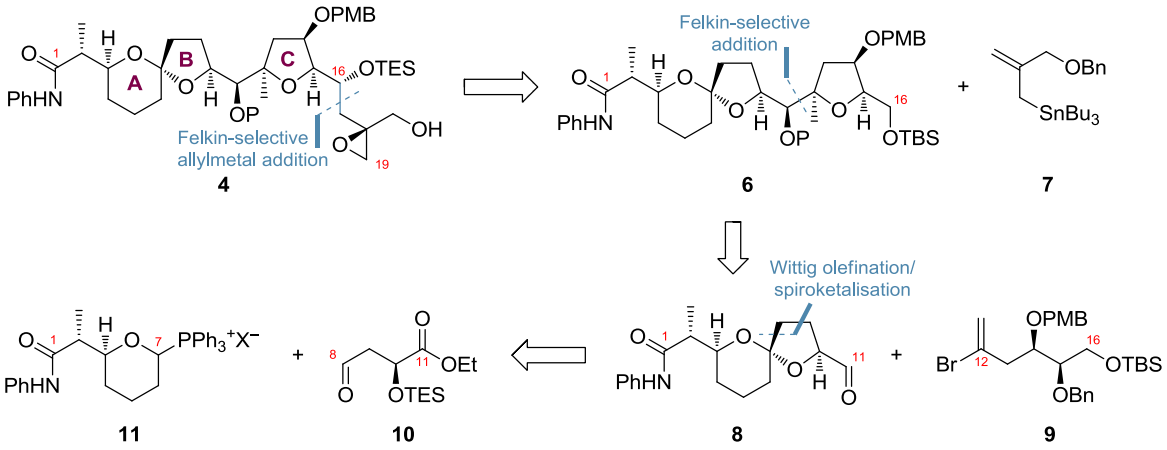
Evans and co-workers based their approach on the convergent coupling of several complex intermediates, as depicted in Figure 5. It was envisaged that pectenotoxin-4 could be accessed from seco acid **1**, *via* a late-macrolactonisation, followed by the formation of the G ring. Incorporation of the F ring fragment could be achieved by a Julia olefination of appropriate precursor **2** with fragment **3**. Retrosynthetic analysis of the D ring provided ketone **2**, which could be prepared from building block **4** (northern hemisphere) and fragment **5** *via* an epoxide-metalloenamine alkylation.

Figure 5 *Evans's retrosynthesis of pectenotoxin-4*



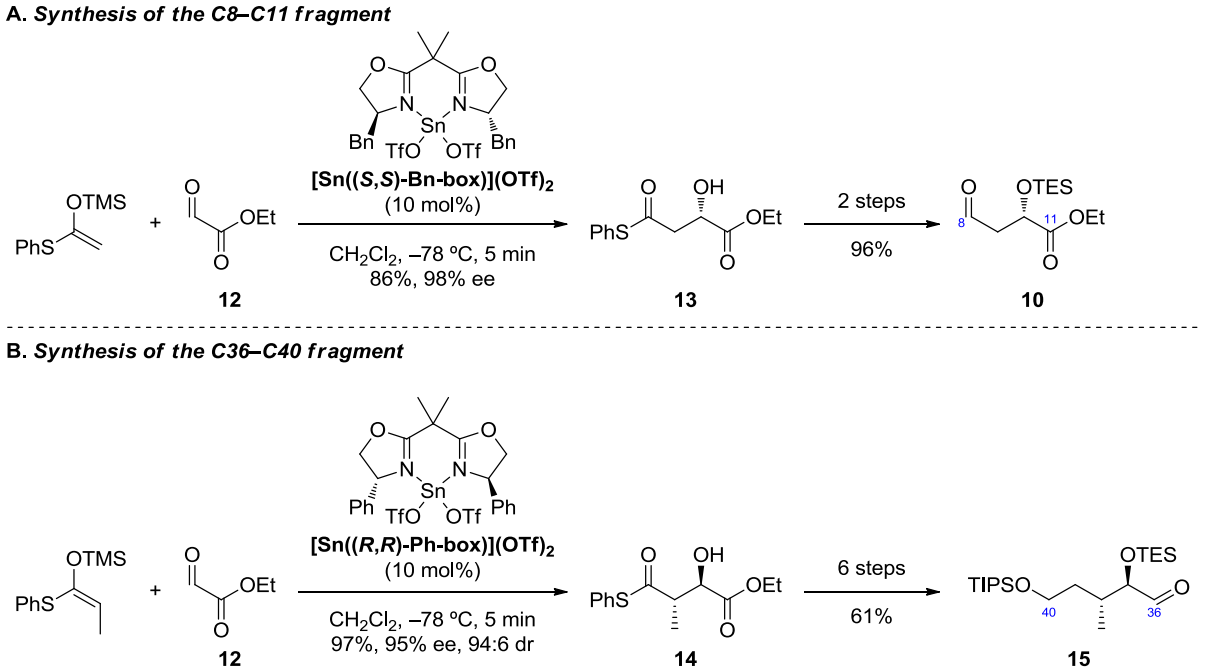
The strategic disconnections revealed three key fragments, **3** and **5** of approximately equal complexity and fragment **4** which constituted the northern hemisphere of PTX-4. **4** was further simplified to fragment **6**, which could be formed by a Felkin-selective allylation utilising 2-(benzyloxymethyl)allyltributyl stannane (**7**) (Figure 6). It was next envisioned that C1–C16 fragment **6** could be accessed through another Felkin-selective addition of vinylbromide **9** to the corresponding aldehyde **8**, which could in turn be constructed *via* a Wittig olefination/spiroketalisation sequence.

Figure 6 *Retrosynthesis of C1–C19 fragment*



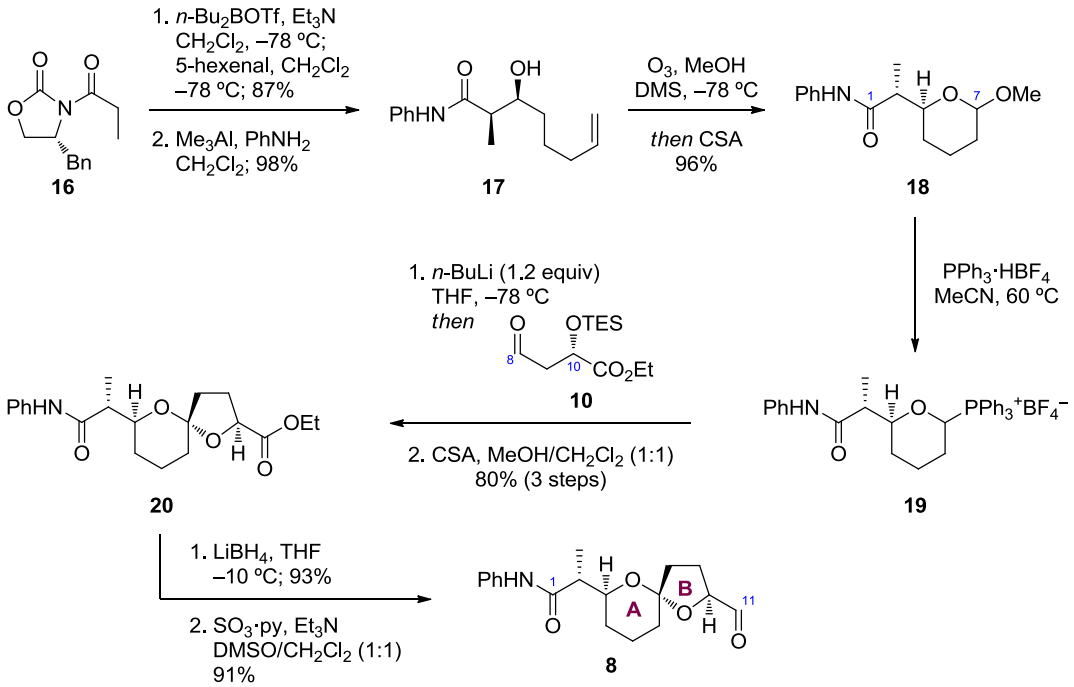
Evans's synthesis of pectenotoxin-4 was designed to incorporate the use of highly selective Sn(II)-catalysed asymmetric aldol reactions.[27] Bidentate chelation of ethyl glyoxylate (**12**) with the [Sn((*S*,*S*)-Bn-box)] or [Sn((*R*,*R*)-Ph-box)] complexes allowed for a high degree of stereocontrol, even on a large scale (Scheme 2). Subsequent chemoselective reduction of the (*S*)-phenyl thioester to the corresponding aldehyde was possible upon exposure to triethylsilane in the presence of palladium on carbon, which delivered aldehydes **10** and **15** in high yield.

Scheme 2 *Application of a Sn(II)-catalysed aldol reaction to the synthesis of pectenotoxin-4*



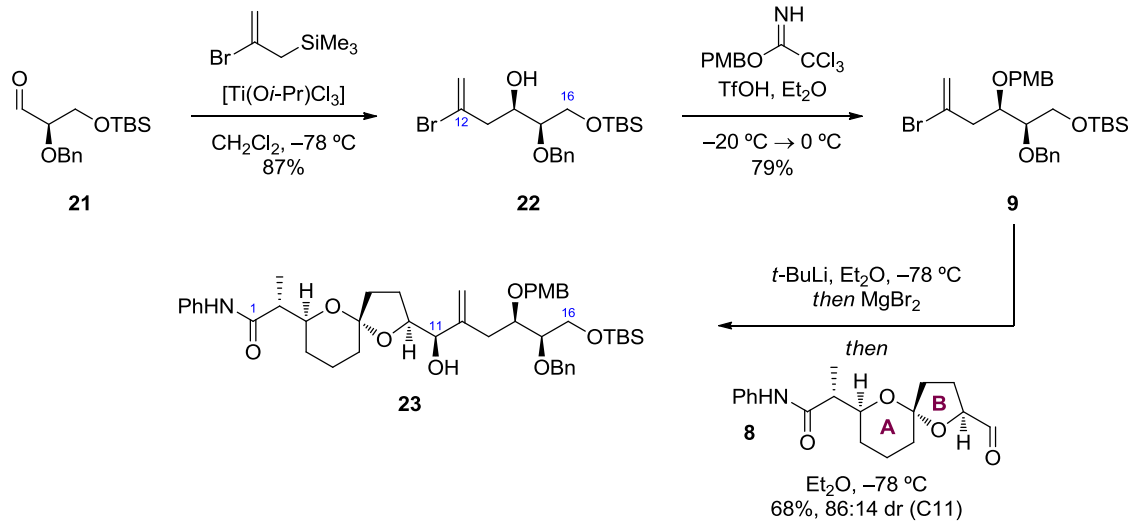
The synthesis of ABC segment **4** commenced by constructing AB spiroketal **8**. Evans's aldol reaction of 5-hexenal and *N*-propionyl oxazolidinone **16**, followed by transamidation with aniline in the presence of trimethylaluminium, delivered amide **17** in two steps (Scheme 3). A unique feature of the ABC fragment synthesis was the protection of the C1 carboxyl terminus as an *N*-phenylamide from an early stage until the projected macrolactonisation step.[28,29] This use of this functionality allowed for the preservation of the C1 carboxylate oxidation state throughout the synthesis.[30,31] Ozonolysis of **17**, followed by an *in situ* lactol formation (utilising CSA) yielded A ring coupling precursor **18**. Following the generation of the A ring phosphonium salt **19**, deprotonation with *n*-butyllithium and the addition of aldehyde **19** afforded the corresponding unstable enol ether. Immediate exposure of the coupled product to acidic methanol elicited a one-pot desilylation/spiroketalisation to provide AB ring system **20** in a high yield of 80% over three steps, with >95:5 diastereoselectivity for the formation of the anomerically favoured 6,5-spiroketal. Reduction of the ester functionality with lithium borohydride, followed by a Parikh–Doering oxidation delivered aldehyde **8**, which was ready to undergo a Felkin-controlled addition of a suitable nucleophile. It is worth noting that attempts to reduce the ester functionality directly to aldehyde **8** using DIBAL resulted in decomposition of the *N*-phenylamide.

Scheme 3 *Synthesis of the AB spiroketal*



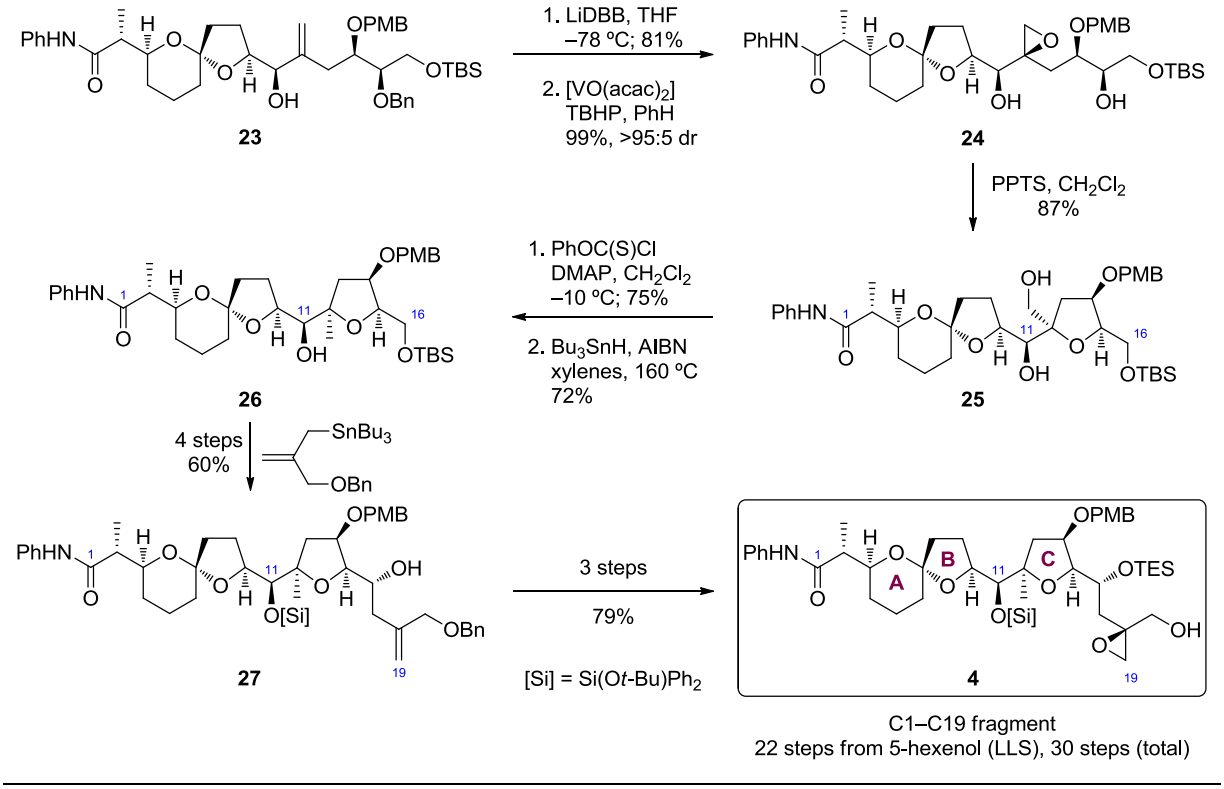
The synthesis of the C12–C16 coupling partner began with differentially protected glyceraldehyde **21**, which was prepared in 4 steps from commercially available 1,3:4,6-di-*O*-benzylidene-D-mannitol (Scheme 4). Upon subjecting **21** to Ti(O*i*-Pr)Cl_3 and 2-bromoallylsilane, chelation-controlled addition ensued to afford vinyl bromide **22** in 87% yield. Protection of the resulting C14 alcohol as the corresponding *p*-methoxybenzyl ether was achieved under acidic conditions using PMB-trichloroacetimidate. Subsequent treatment of **9** with *tert*-butyllithium, followed by transmetallation with magnesium bromide formed the corresponding Grignard reagent, which upon addition of aldehyde **8** afforded C1–C16 fragment **23** in 68% yield and 86:14 diastereomeric ratio at C11.

Scheme 4 *Synthesis of the C1–C16 fragment*



With the C1–C16 fragment in hand, the next task required the construction of the C ring tetrahydrofuran. This was achieved by employing a directed epoxidation/epoxide opening strategy (Scheme 5). Selective removal of the benzyl protecting group using lithium di-*tert*-butylbiphenyl, followed by the allylic 1,2-strain directed epoxidation of the olefin delivered the requisite epoxy alcohol **24** in high yield (99%) and good diastereoselectivity (>95:5 dr).

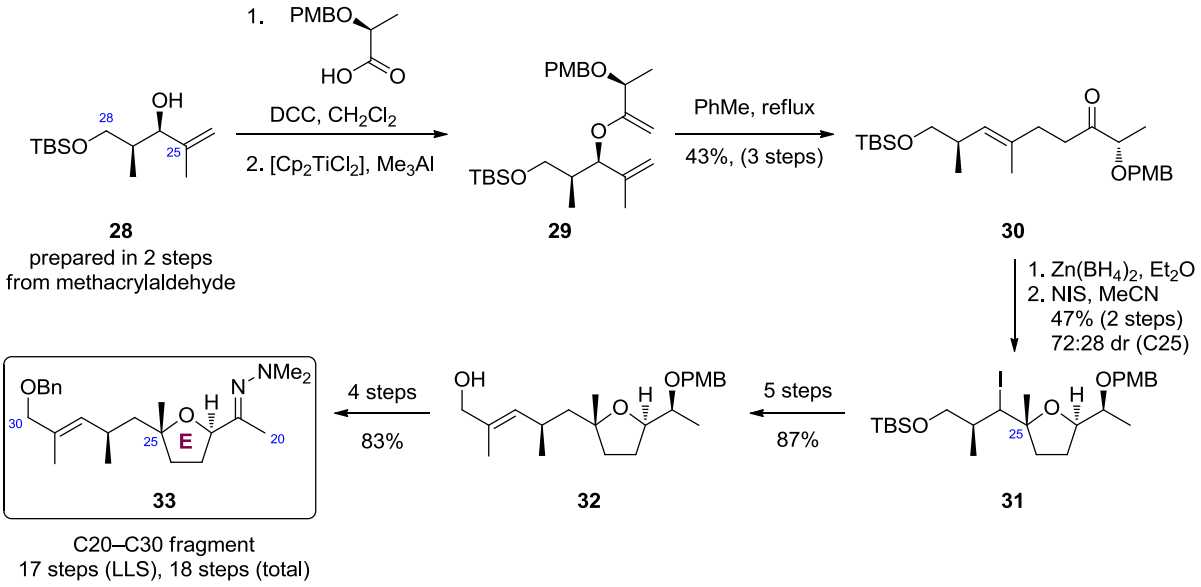
Scheme 5 *Completion of the synthesis of the northern hemisphere*



Treatment of **24** with pyridinium *p*-toluenesulfonate in dichloromethane elicited a 5-*exo*-tet cyclisation to form the desired C ring **25**. Acylation of the resulting primary alcohol with phenyl chlorothioformate, followed by a deoxygenation under Barton conditions completed the synthesis of the C ring **26**. The C11 hydroxyl group was next protected as a *tert*-butoxydiphenylsilyl ether. The choice of this unusual protecting group was dictated by its higher stability towards hydrolysis under acidic conditions and higher lability upon treatment with a source of fluoride than the corresponding TBS ether. Studies conducted by Evans and co-workers revealed that a TES protecting group at the C11 site did not offer the required stability throughout the synthesis, whereas a model deprotection of a C11–OTBS ether, with different fluoride reagents, led to irreproducible results. Subsequent selective deprotection of the C16–OTBS ether, followed by oxidation and Felkin-controlled allylation with 2-(benzyloxymethyl)allyltributylstannane provided **27**, which was advanced in three steps to epoxide **4**, completing the synthesis of the northern hemisphere.

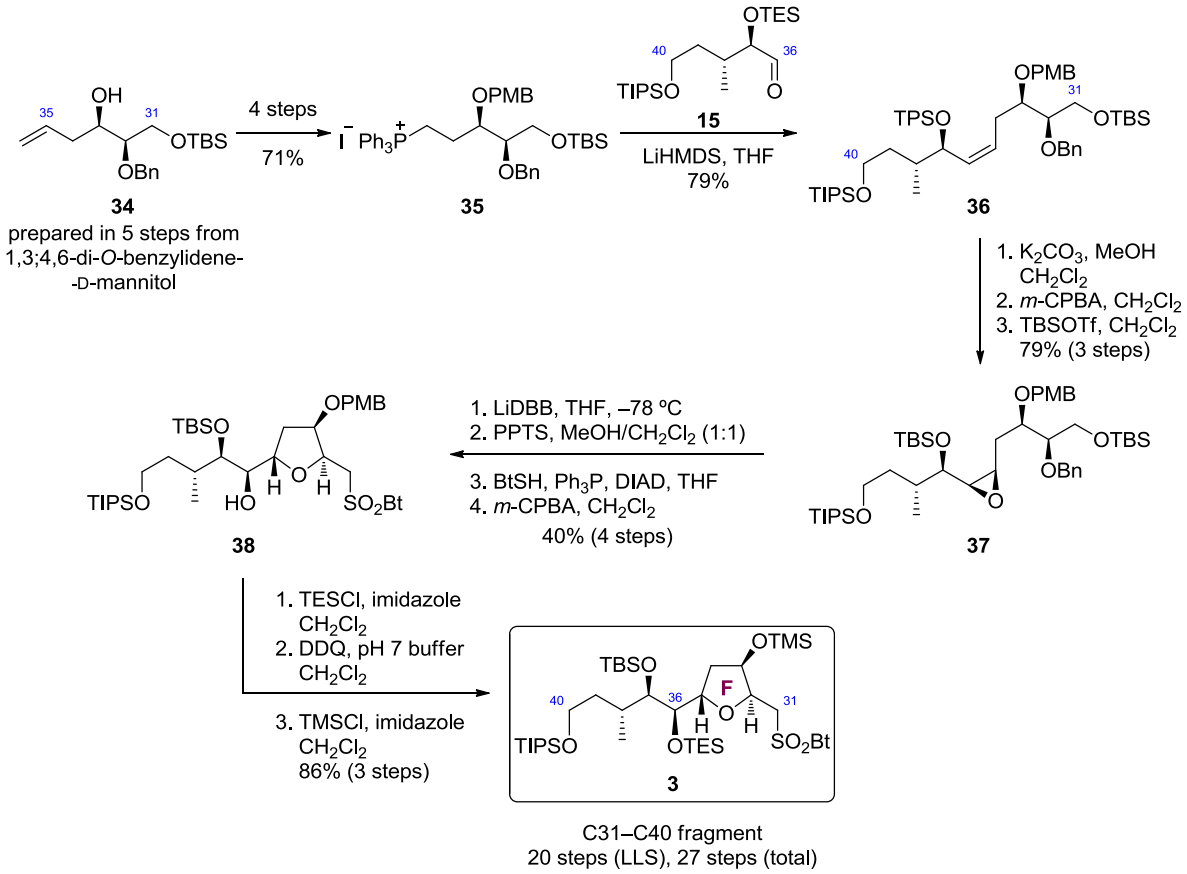
The synthesis of C20–C31 fragment **33** possessing the E ring began with acylation of allylic alcohol **28** (accessible in three steps) with PMB-protected lactic acid, followed by carbonyl olefination utilising the Tebbe reagent (Scheme 6). The resulting diene **29** underwent a Claisen rearrangement upon refluxing in toluene to afford the desired product **30**. Chelation-controlled reduction with zinc borohydride followed by treatment with *N*-iodosuccinimide resulted in the formation of the E ring **31** as a 72:28 mixture of diastereomers at C25. Successive radical dehalogenation and a chain elongation, using Wittig conditions, were utilised in the five step sequence to afford **32** in 87% yield. Necessary protecting group manipulations and hydrazone formation were accomplished in four steps (83% yield) delivering the C20–C30 subunit **33**.

Scheme 6 *Preparation of the E ring fragment*



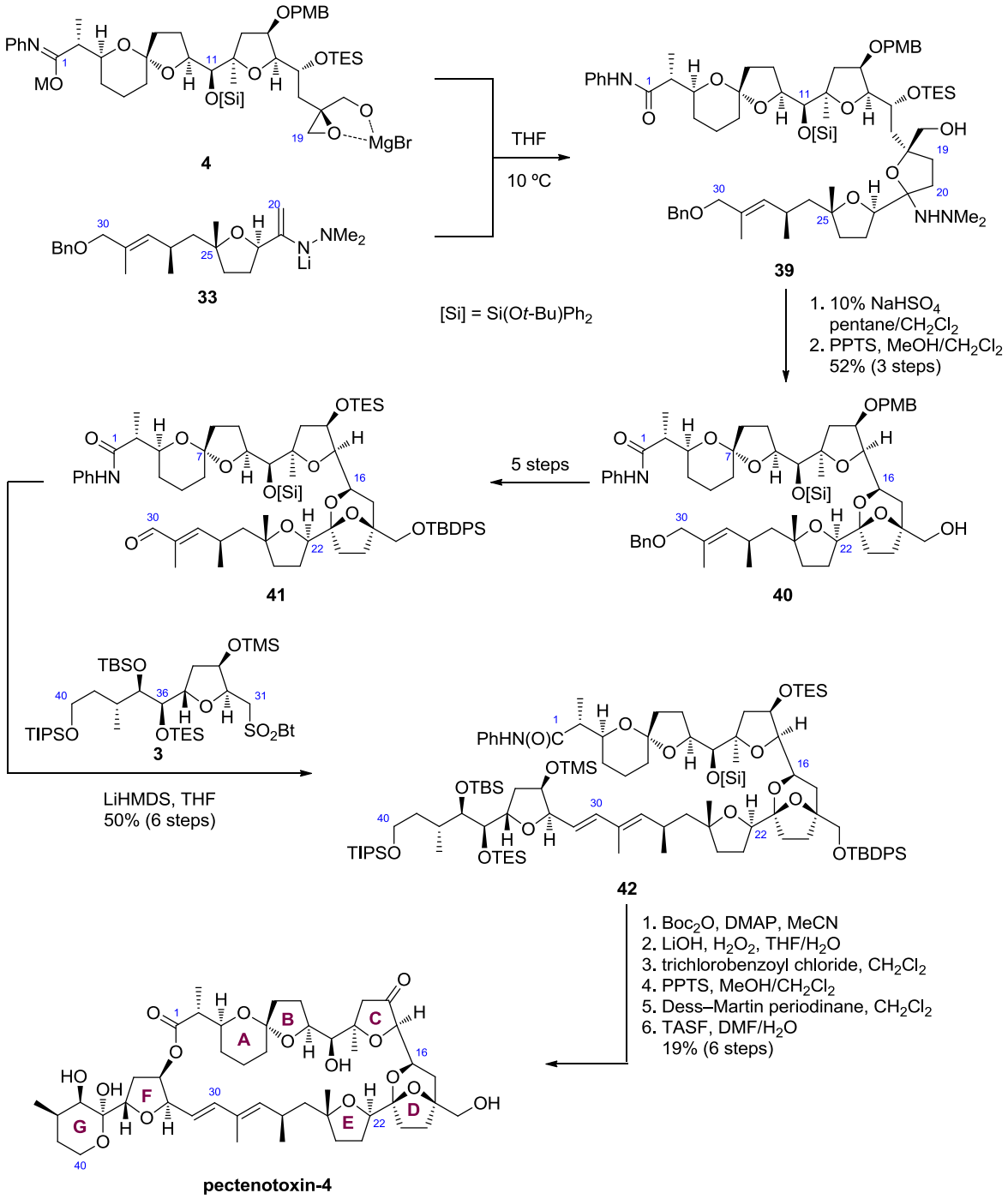
The construction of the C31–C40 fragment began with a convergent synthesis of (*Z*)-olefin **36**, which employed a Wittig reaction between phosphonium salt **35** (prepared from known protected triol **34** in four steps) and aldehyde **15** (Scheme 7). Hydroxyl-directed epoxidation and subsequent protecting group manipulation furnished epoxide **37** in good yield. Selective cleavage of the benzyl group at C32 followed by subjection of the resulting epoxy alcohol to mildly acidic conditions triggered a 5-*exo*-tet cyclisation/epoxide opening to give the *trans*-THF that constituted the F ring of PTX-4. Further elaboration to the C30 benzothiazole followed by protecting group manipulation afforded segment **3**, setting the stage for the key Julia olefination.

Scheme 7 *Synthesis of the C31–C40 portion*



With all three advanced intermediates in hand, completion of the synthesis began by coupling ABC fragment **4** with E ring fragment **33** (Scheme 8). The construction of the key C19–C20 bond was achieved *via* the addition of metalloenamine **33** to the magnesium-activated epoxide complex **4**. The resulting unstable hydrazinyl aminal **39** was converted to bicyclic ketal **40** *via* treatment with a mixture of aqueous $NaHSO_4$ in pentane and dichloromethane to access the corresponding lactol, followed by exposure to acidic conditions resulting in spontaneous ketalisation. Elaboration to aldehyde **41** and successive Julia olefination with the F ring segment **3** afforded the complete ABCDEF fragment **42**. In order to form the macrocyclic skeleton the *N*-phenyl amide was hydrolysed to the corresponding carboxylic acid, which was subsequently exposed to macrolactonisation under Yamaguchi conditions, furnishing the corresponding macrocycle. The installation of the remaining G ring was accomplished upon exposure to PPTS, which resulted in cleavage of the C14 and C36 OTES ethers, followed by oxidation to the corresponding diketone. Finally, global deprotection using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) delivered pectenotoxin-4 in 36 steps (longest linear sequence) and 0.3% overall yield.

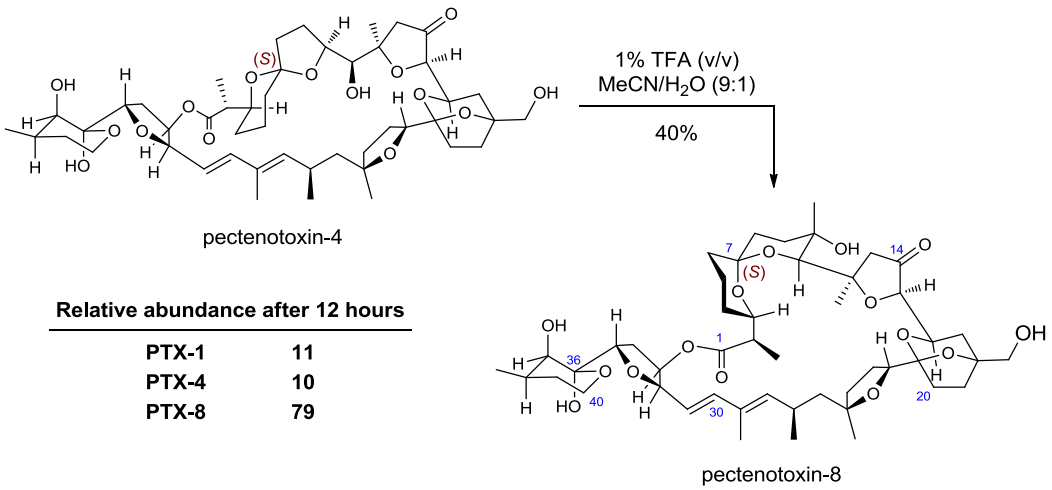
Scheme 8 *Completion of the synthesis of pectenotoxin-4*



Synthetic pectenotoxin-4 was found to be identical by ^{1}H NMR and specific rotation analysis to that of natural pectenotoxin-4. To obtain further proof of structure, pectenotoxin-4 was subjected to equilibration under identical conditions previously described by Yasumoto in the original isolation report (Scheme 9). Exposure to a 1% solution (v/v) of trifluoroacetic acid in aqueous acetonitrile provided pectenotoxin-8, possessing the 6,6-spiroketal stabilised

by two anomeric interactions, in 40% yield after 12 hours, along with pectenotoxin-1 and pectenotoxin-4, with the relative ratio PTX-1/PTX-4/PTX-8 11:10:79.

Scheme 9 *Acid-catalysed interconversion of pectenotoxin-4 to pectenotoxin-8*



Relative abundance after 12 hours	
PTX-1	11
PTX-4	10
PTX-8	79

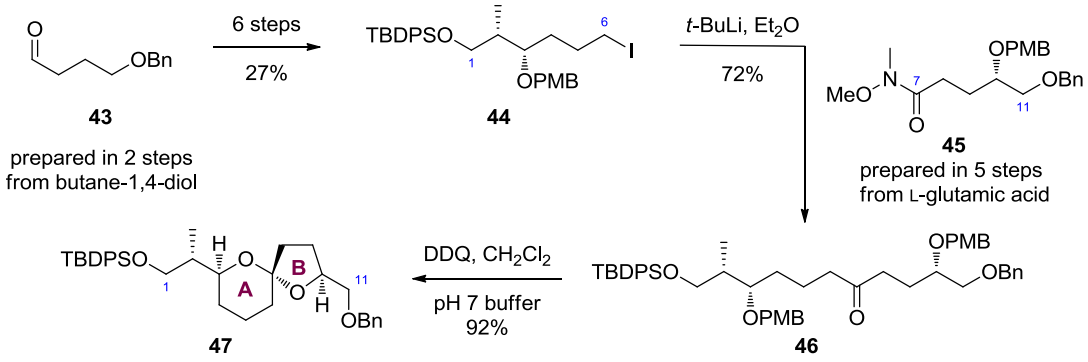
This experiment stands in contrast with Yasumoto's equilibration of natural PTX-1, which returned a 29:14:57 mixture of PTX-1 (7*R*), PTX-4 (7*S*) and PTX-8 (7*S*), respectively. The observed discrepancy led to speculation that one of these mixtures did not reach equilibrium. This may have potential synthetic implications, because if Evans's study represents a true distribution of spiroketal isomers at equilibrium, then the prognosis for a late-stage equilibration to access the (7*R*) pectenotoxins is rather poor.

1.3.2 Paquette's approach to the C1–C26 ABC–E fragment of pectenotoxin-2

In 2005, Paquette and co-workers disclosed their work on the synthesis of the C1–C15 fragment of pectenotoxin-2.[32] Similar to Evans's approach, Paquette's synthetic strategy concentrated upon the convergent construction of the AB spiroketal motif followed by elaboration to form the C ring *via* an epoxide opening.

Their synthesis began with setting the C2/C3 *syn* stereochemistry by exploiting an Evans aldol reaction (Scheme 10). Following several protecting group manipulations, iodide **44** was accessed from **43** in six steps and 27% yield. Subsequent coupling with Weinreb amide **45**, which was prepared in five steps from L-glutamic acid, afforded ketone **46** in a good yield of 72%. Oxidative deprotection of the C3 and C10 *p*-methoxybenzyl ethers with DDQ elicited a spiroketalisation, delivering the expected thermodynamically favoured 6,5-spiroketal **47** in a high yield of 92%.

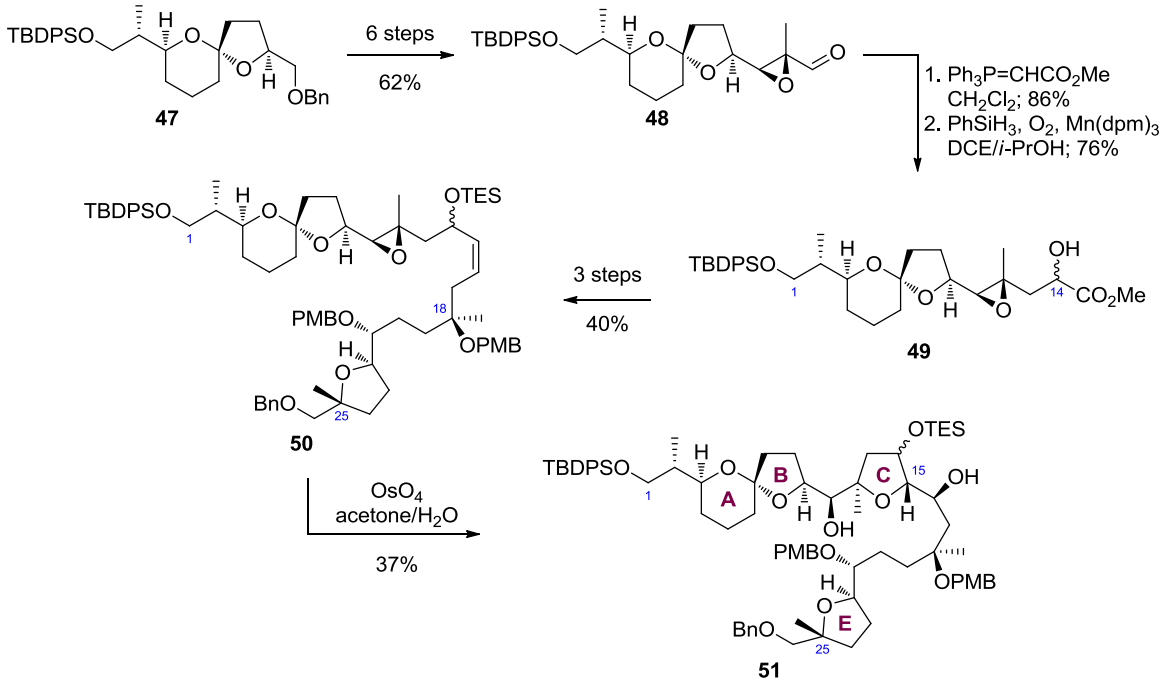
Scheme 10 *Paquette's synthesis of the AB spiroketal*



Although the configuration at C7 was assumed to be (*S*), identical to that found in pectenotoxin-4 and the opposite to that present in pectenotoxin-2, Paquette's strategy would therefore rely upon a late-stage equilibration to access the desired (7*R*) epimer.

In continuation of their efforts towards the synthesis of pectenotoxin-2, in 2007 Paquette and co-workers reported a route to the C1–C26 fragment, which also included the C ring (Scheme 11).[33] Elaboration of spiroketal **47** to aldehyde **48** was accomplished in six steps utilising a Wittig olefination and a Sharpless asymmetric epoxidation as the key steps. Another Wittig homologation, followed by installation of the C14 hydroxyl group *via* an oxidation catalysed by a bis(dipivaloylmethanato)manganese(III) complex, furnished epoxy alcohol **49** in a good yield. Incorporation of the E ring fragment was achieved under Wittig olefination conditions which furnished the C1–C26 carbon framework **50** with (*Z*)-geometry at the C15–C16 olefin. Finally, olefin dihydroxylation of **50** using osmium tetroxide, resulted in a spontaneous cyclisation/epoxide opening to form the fully elaborated ABC–E scaffold **51**.

Scheme 11 *Synthesis of the ABC–E ring system*

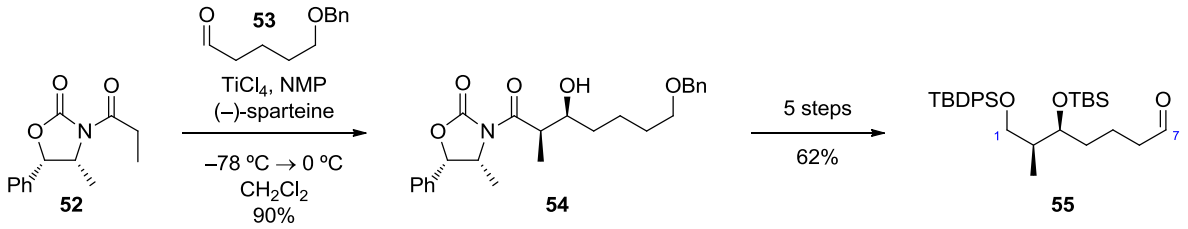


1.3.3 Brimble's approach to the C1–C16 ABC ring system of the pectenotoxins

Shortly after Paquette's initial report, Brimble and co-workers disclosed their synthetic endeavours towards the ABC ring system of the pectenotoxins in 2005.[34-36] Again, with the major aim of constructing pectenotoxin-2, Brimble's strategy concentrated on the synthesis of the C1–C16 portion bearing the anomerically stabilised spiroketal (possessing (7*S*)-configuration), which would isomerise to the correct C7 epimer after a late-stage macrolactonisation. It is important to note that the ABC fragment assembled by Brimble and co-workers was identical to that found in pectenotoxin-4 and -7.

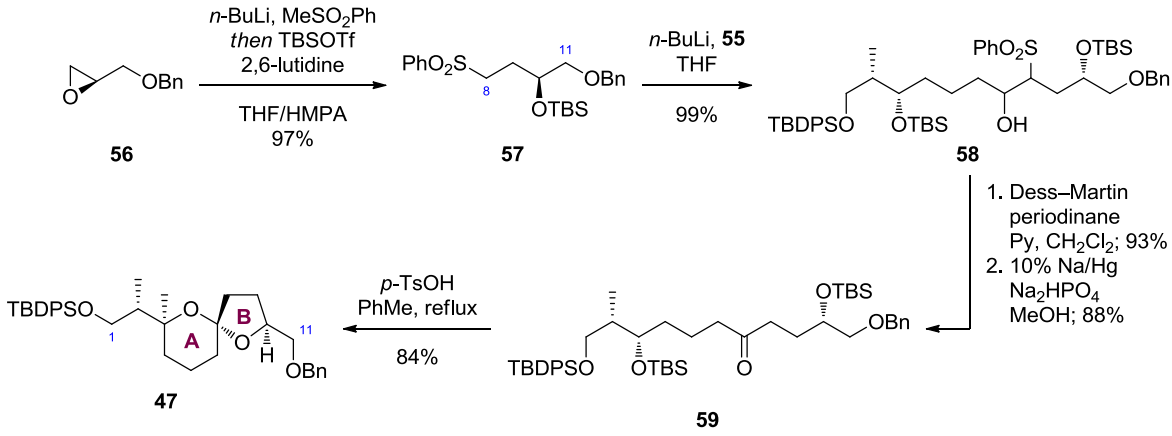
In a similar manner to Paquette, the synthesis commenced with a convergent formation of the 6,5-spiroketal, by means of a sulfone coupling. Installation of the required C2/C3 *syn* relationship was achieved by a titanium-catalysed aldol reaction developed by Crimmins[37,38] (Scheme 12). Subsequent functional group manipulations afforded aldehyde **55** over six steps from known aldehyde **53** and propionyl oxazolidinone **52**.

Scheme 12 *Synthesis of the C1–C7 aldehyde fragment*



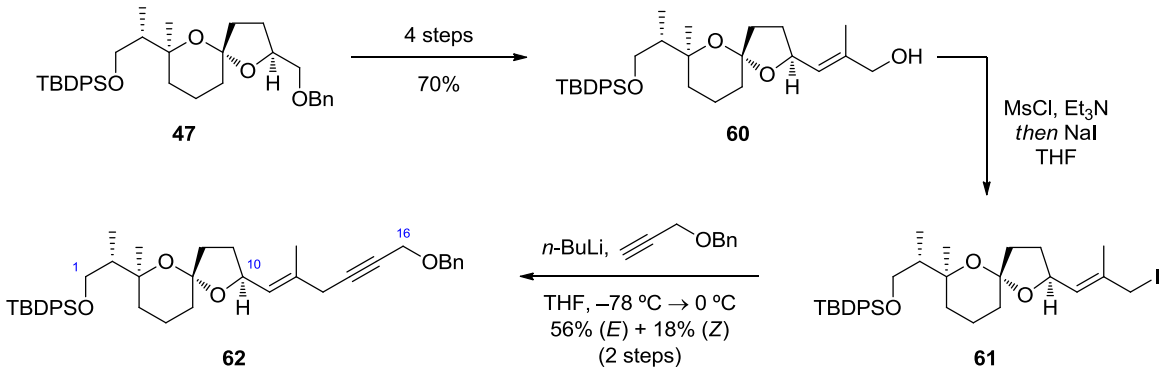
Sulfone coupling partner **57** was prepared from (*R*)-(+)-benzylglycidol (**56)** (Scheme 13). Treatment of epoxide **56** with methyl phenyl sulfone and butyllithium gave the corresponding sulfone which following trapping of the resulting alkoxide with *tert*-butyldimethylsilyl triflate furnished **57** in high yield (97%). Both partners were subsequently coupled together *via* an α-deprotonation of **57**, followed by the addition of **55**, which delivered the corresponding adduct **58** as a mixture of four diastereoisomers. Oxidation of **58** with Dess–Martin periodinane, and subsequent desulfurisation with a sodium/mercury amalgam afforded spirocylisation precursor **58**, which upon treatment with *p*-toluenesulfonic acid underwent a double desilylation, constructing the anomerically stabilised AB fragment **47**.

Scheme 13 *Construction of the AB spiroketal*



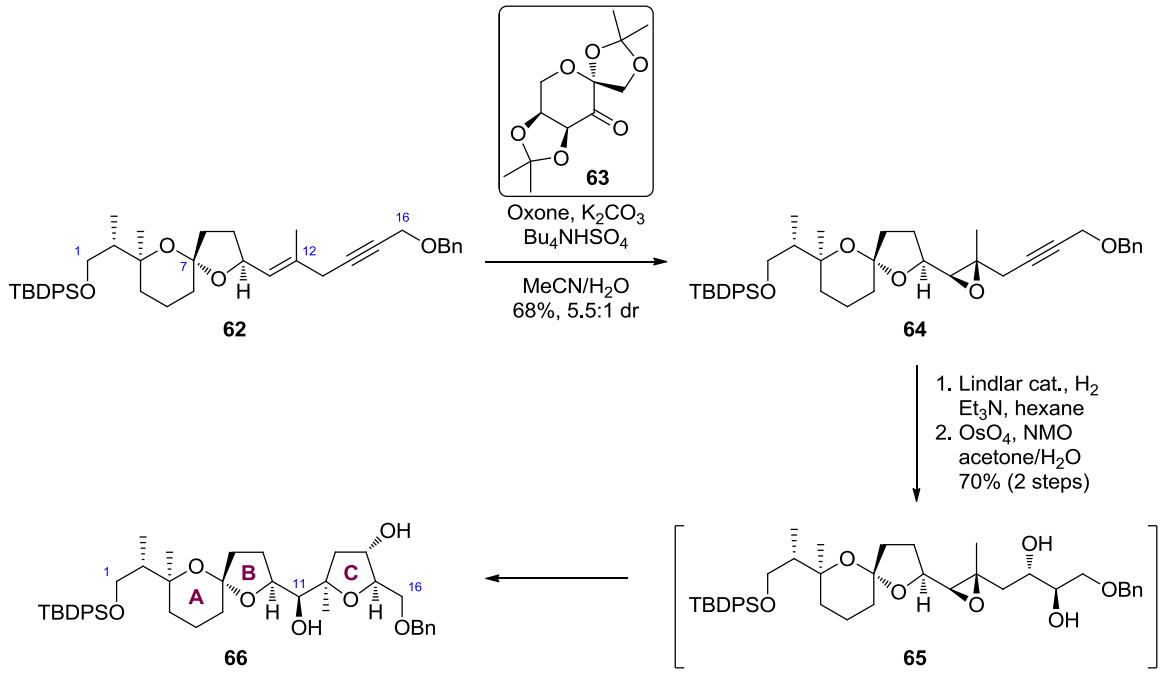
In order to incorporate the C11–C16 fragment, spiroketal **47** was elaborated to allylic alcohol **60** in four steps and 70% yield (Scheme 14). Sequential treatment with methanesulfonyl chloride and sodium iodide afforded iodide **61**, which upon exposure to lithium acetylide yielded the corresponding enyne, still as a mixture of (*E*) and (*Z*) isomers. Separation by flash column chromatography delivered the desired (*E*)-enyne **62** in 56% yield.

Scheme 14 *Elaboration of the AB spiroketal to C1–C16 fragment* ***62***



With the complete carbon framework in place, the construction of the C ring was achieved in three steps (Scheme 15). A Shi epoxidation of **62** in the presence of dioxirane **63** provided epoxy olefin **64** with the correct stereochemistry at C11/C12 (5.5:1 dr). Finally, a (*Z*)-selective reduction of the C14–C15 olefin, followed by substrate-controlled dihydroxylation generated the corresponding diol **65**, which underwent a spontaneous cyclisation to directly form the C ring and thus completed the synthesis of ABC fragment **66**.

Scheme 15 *Completion of the synthesis of the ABC C1–C16 fragment*

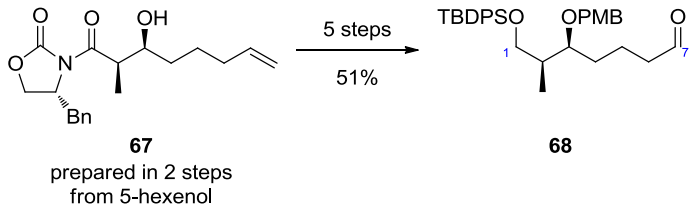


1.3.4 Williams's spirodiepoxide approach to the C1–C19 AB fragment of pectenotoxin-4

In 2007, the Williams group reported the synthesis of the AB ring system of pectenotoxin-4.[39] Their unusual approach exploited a previously developed spirodiepoxide-based strategy.[40]

The precursor for the final epoxidation/cyclisation was prepared in a convergent manner from two fragments of approximately equal complexity. Aldehyde **68** was accessed in five steps and 51% from aldol **67**, which was in turn obtained from commercially available 5-hexenol (Scheme 16).

Scheme 16 *Preparation of the C1–C7 aldehyde fragment*

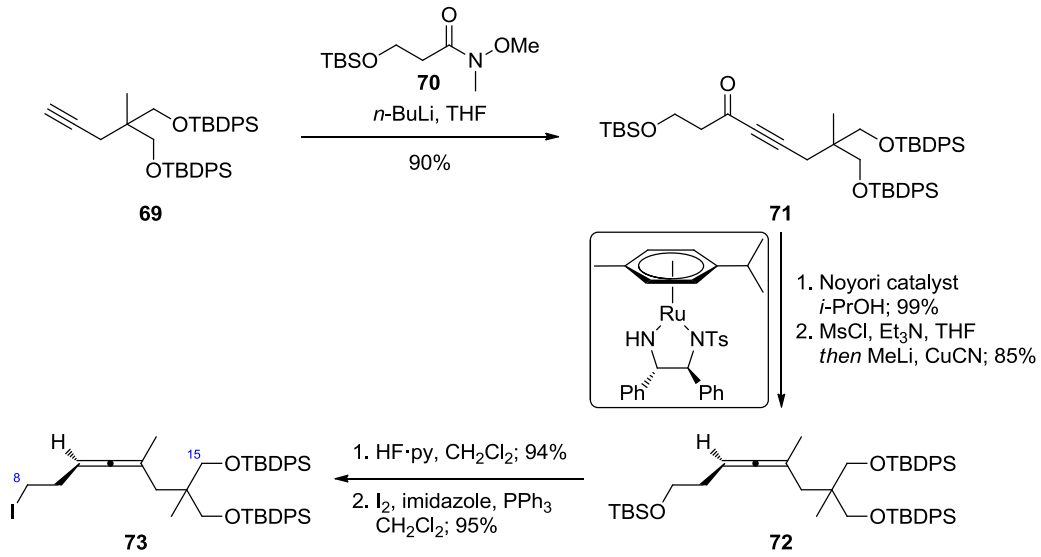


67
prepared in 2 steps
from 5-hexenol

68

The synthesis of the C8–C15 coupling partner began with the formation of ynone **71** by means of a lithium acetylide addition to Weinreb amide **70** (Scheme 17). An asymmetric reduction to the corresponding propargylic alcohol using Noyori's conditions, followed by sequential treatment with mesyl chloride and higher order methyl cuprate, yielded allene **72**. Removal of the *tert*-butyldimethylsilyl group and an Appel-type reaction afforded coupling partner **73**.

Scheme 17 *Synthesis of allene 73*



69

70

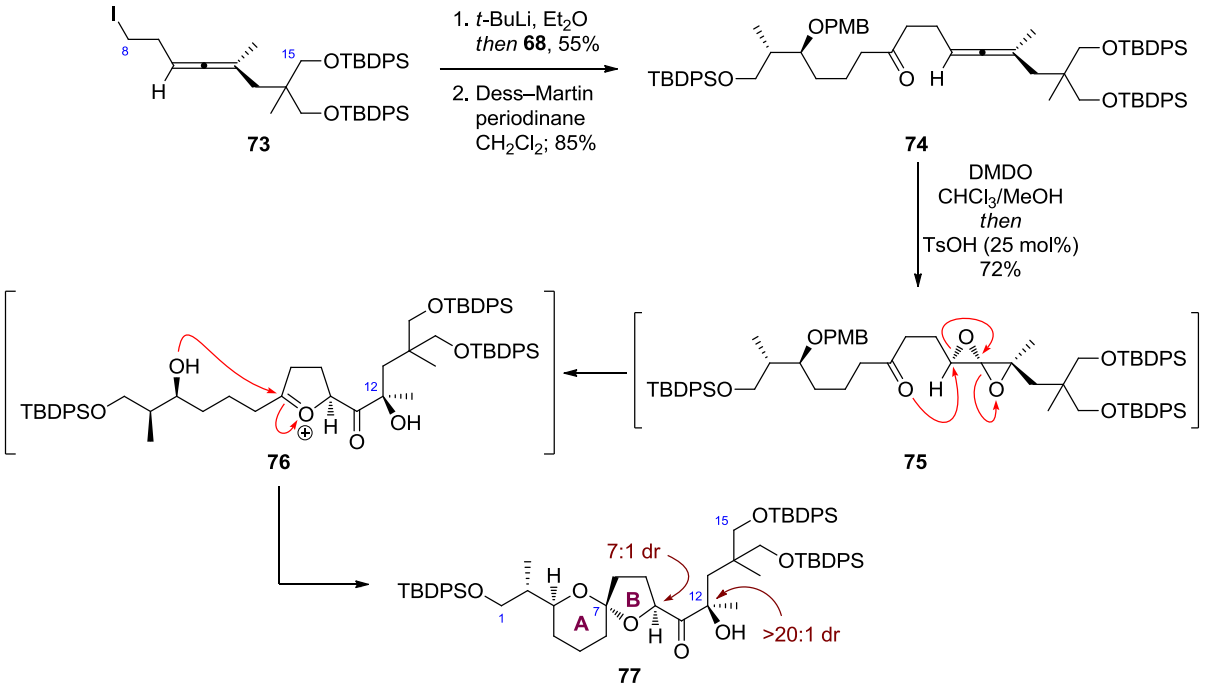
71

72

73

Key precursor **74** was assembled *via* a lithium halogen exchange of **73**, followed by addition to aldehyde **68** (Scheme 18). Subsequent oxidation, employing Dess–Martin periodinane, provided ketone **74**.

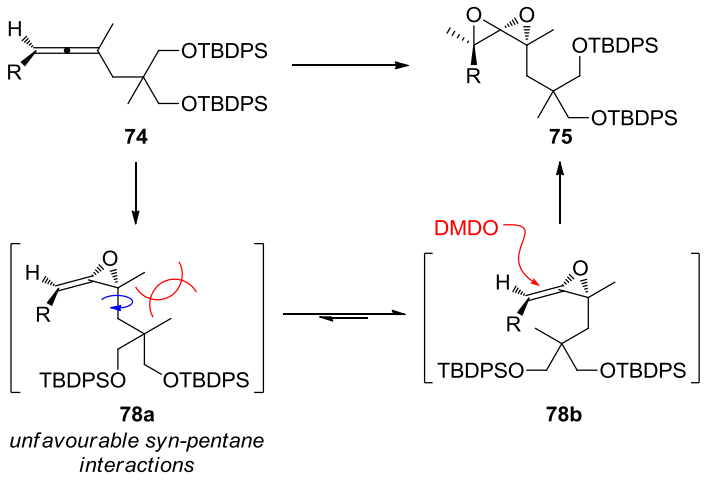
Scheme 18 *Completion of the synthesis of the AB spiroketal*



Upon oxidation with dimethyldioxirane (DMDO), in a mixture of chloroform and methanol, allene **74** was smoothly converted to the corresponding spirodiepoxide with concomitant cleavage of the C3 *p*-methoxybenzyl group, which when subsequently treated with a catalytic amount of acid triggered an intramolecular ketone addition to a spirodiepoxide, followed by trapping the intermediate oxocarbenium ion with the C3 pendent alcohol to form the expected AB spiroketal **77** in 72% yield as a 7:1 diastereomeric mixture at the C10 centre.

Whilst the first oxidation (on the more substituted double bond) was highly diastereoselective due to steric reasons, the second epoxidation was speculated to be less selective as a result of the increased reactivity of allene oxide **78a**, relative to the parent allene (Scheme 19). Williams and co-workers reasoned that the incorporation of a bulky neopentyl group, as a means to control the facial selectivity, would avoid the destabilising *syn*-pentane interaction expected in conformers closely related to **78a**, thus blocking the bottom face of olefin **78b** from attacking by dimethyldioxirane.

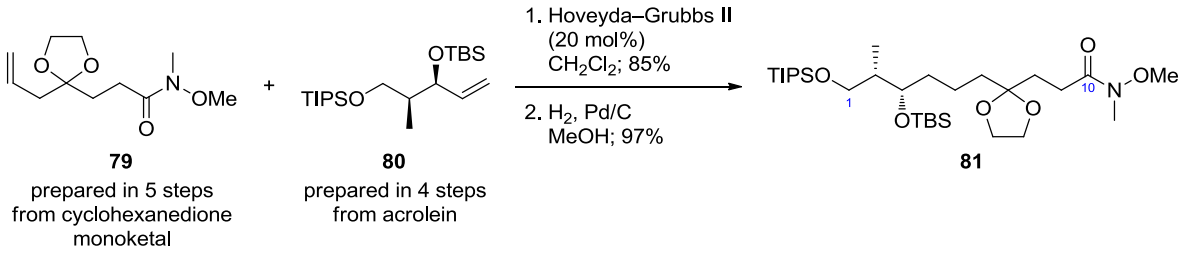
Scheme 19 *Stereoselectivity of allene **74** oxidation*



Following initial studies towards the synthesis of the northern hemisphere of PTX-4, Williams and co-workers later also reported their modified approach to the C1–C19 portion of PTX-4.[41] Key features of this strategy were again centred on the spirodiepoxide opening to fashion the C ring.

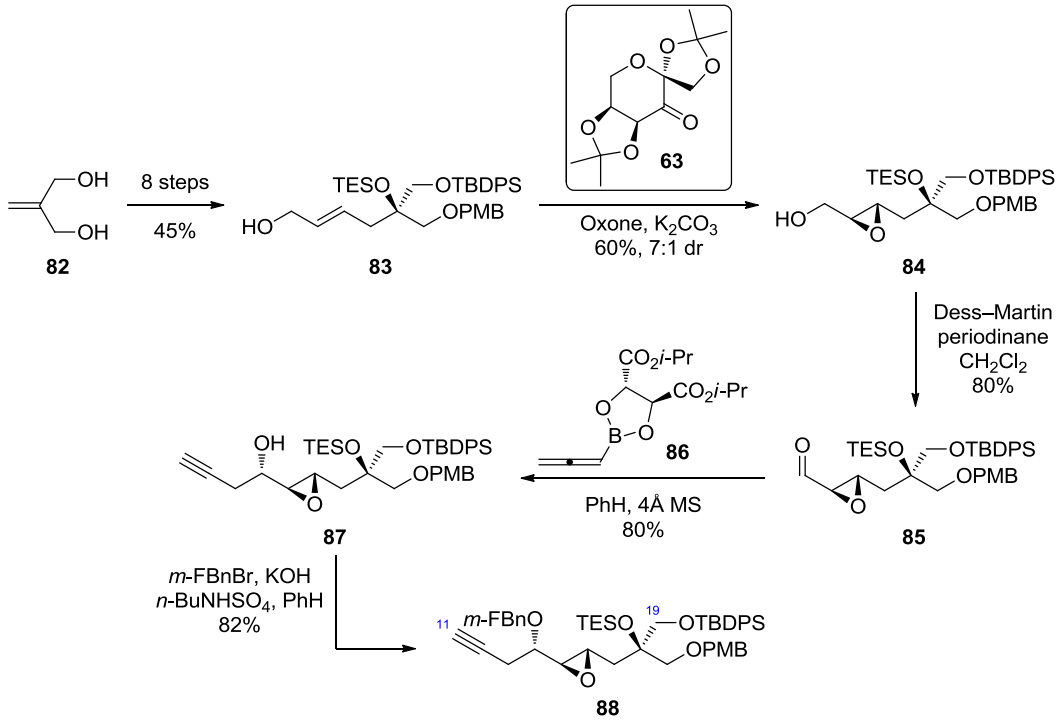
In contrast to the previous report, the synthesis of the C1–C10 portion exploited an olefin cross metathesis between aldol-derived alkene **80** and Weinreb amide **79** (Scheme 20). The use of the Hoveyda–Grubbs second generation catalyst was found to be best in this system. Subsequent hydrogenation of the newly formed olefin provided Weinreb amide **81** in high yield.

Scheme 20 *Synthesis of C1–C10 fragment **81***



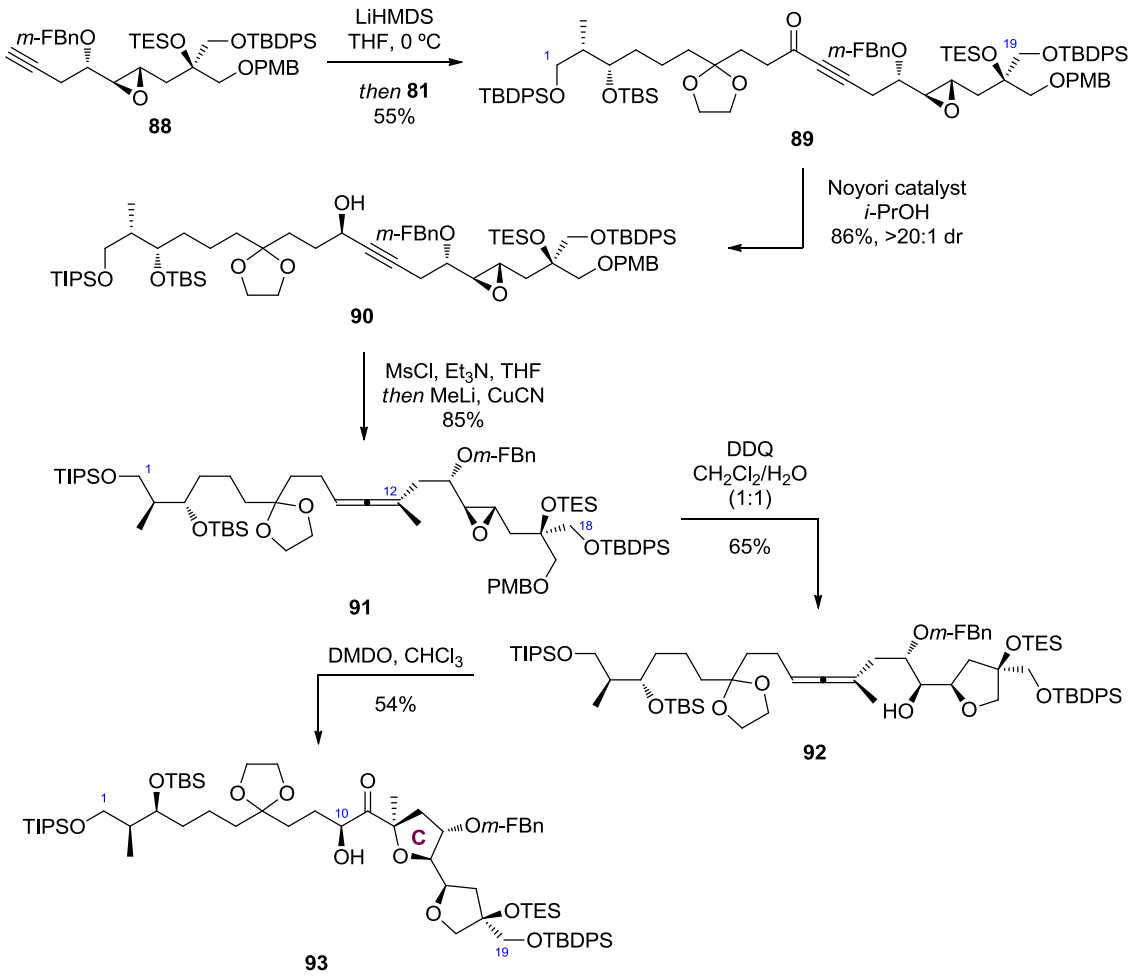
The preparation of the C11–C19 section commenced with commercially available diol **82**, which was advanced in eight steps and high overall yield to allylic alcohol **83**. A Shi epoxidation followed by oxidation of the primary alcohol furnished aldehyde **85**, which was subjected to a Yamamoto propargylation using chiral allenyl boronate **86**. The resulting secondary alcohol was protected with 3-fluorobenzyl bromide to deliver alkyne **88**.

Scheme 21 *Preparation of alkyne fragment* ***88***



The union of both fragments was achieved by the addition of a lithium acetylide (derived from **88**) to Weinreb amide **81**, providing ynone **89** which possessed the complete C1–C19 carbon framework (Scheme 22). Preparation of allene **91**, a precursor to final cyclisation, was accomplished in a similar manner to previous studies. Thus, a Noyori asymmetric hydrogenation delivered propargylic alcohol **90** in high yield and diastereoselectivity. Subsequent treatment with mesyl chloride and then methyl cuprate addition afforded allene **91** in good yield. Treatment of **91** with DDQ effected cleavage of the PMB group and spontaneous epoxide opening to provide **92** in a yield of 65%. The key formation of the C ring *via* a spirodiepoxide opening was accomplished by exposure of **92** to DMDO in chloroform, which provided **93** in 54% yield, as a single isomer. The C10 epimer, the expected minor diastereoisomer of this reaction resulting from less selective second epoxidation of the allene moiety, was not evident.

Scheme 22 *Synthesis of the C1–C19 fragment and construction of the C ring*



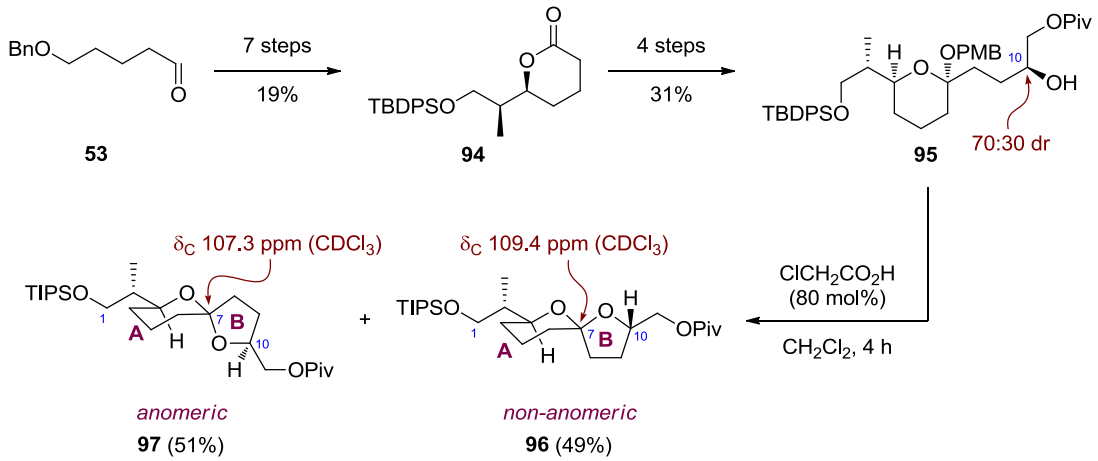
1.3.5 Pihko's approach to the ABCD fragment of pectenotoxin-2

Although the (7*R*) AB spiroketal present in pectenotoxin-2 is less favoured due to the lack of anomeric stabilisation, access to this motif had not been addressed until 2004, when Pihko and co-workers demonstrated their approach to the generation of both C7 anomers of the 6,5-spiroketal.[42]

Starting with aldehyde **53**, lactone **94** was prepared in seven steps and 19% overall yield (Scheme 23). Subsequent elaboration, which involved treatment with 4-butenylmagnesium bromide and Sharpless asymmetric dihydroxylation of the terminal olefin, provided the key spirocyclisation precursor **95** in a 70:30 diastereomeric ratio. Interestingly, the use of *p*-methoxybenzyl alcohol was crucial to attain the required stability of the corresponding ketal. The key spiroketalisation was performed in the presence of several different acids. Whilst the use of strong acids, such as *p*-toluenesulfonic or methanesulfonic acids, resulted in predominant formation of the anomeric product **96**, weaker acids gave

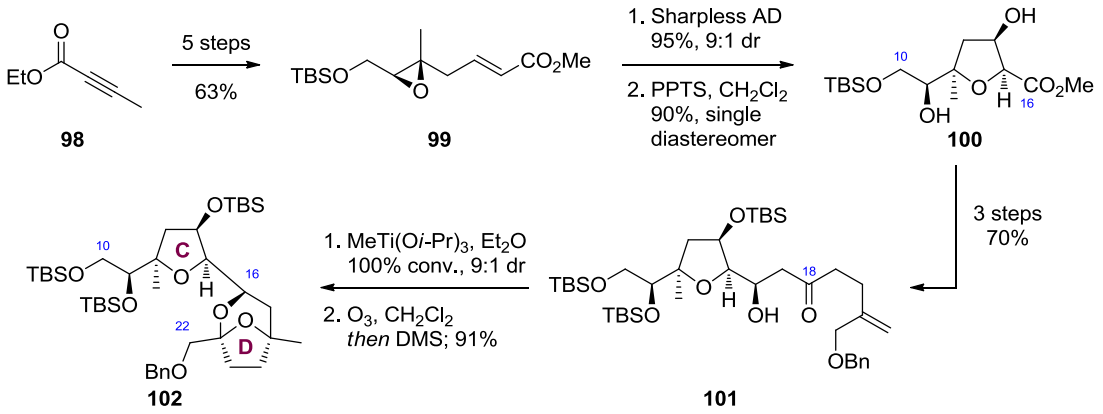
comparatively higher yields of the non-anomeric spiroketal **97**, with the best result obtained with a substoichiometric amount of chloroacetic acid (49% yield for both C10 epimers). The formation of the non-anomeric AB spiroketal was confirmed by the presence of the characteristic 109.4 ppm peak in the ^{13}C NMR spectrum.

Scheme 23 *Kinetic spiroketalisation to access non-anomeric AB spiroketal* ***96***



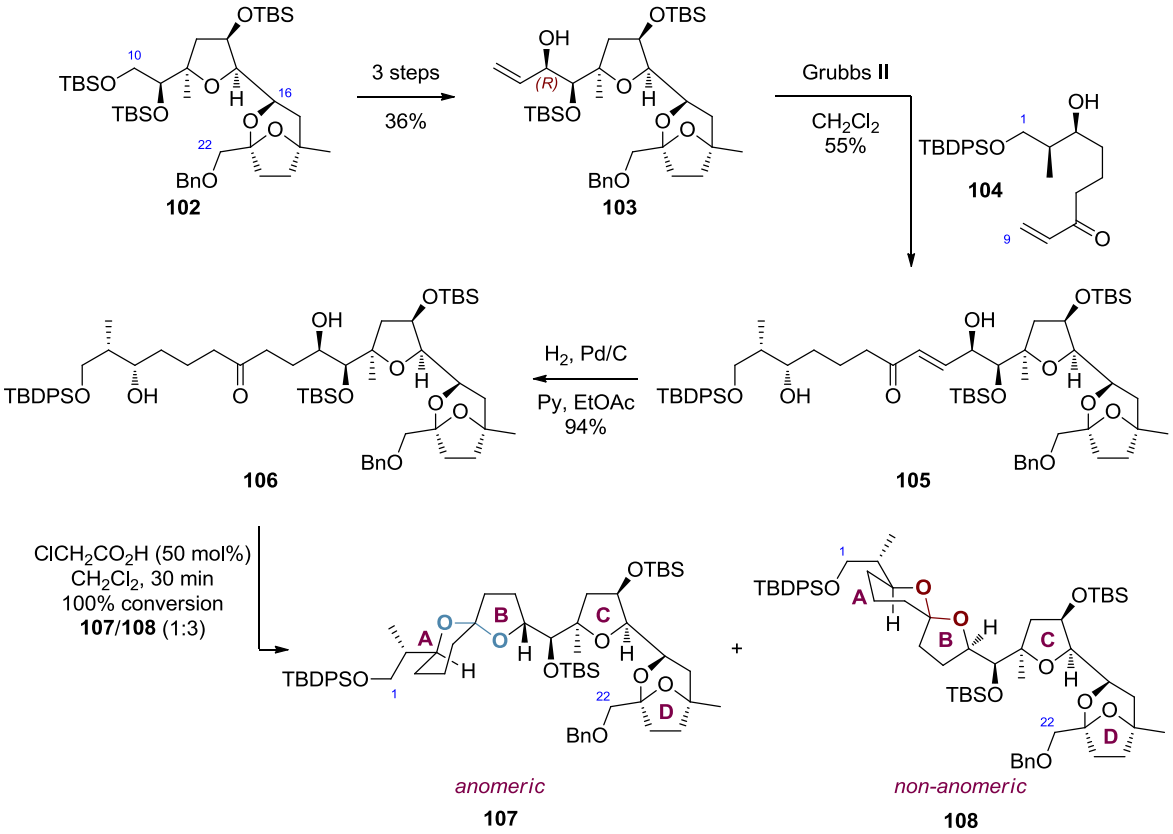
In 2011, Pihko and co-workers disclosed further efforts directed towards the synthesis of the 10-*epi*-ABCD ring system of pectenotoxin-2, which relied on a previously developed kinetic spiroketalisation to set the correct stereochemistry at the C7 spiroketal centre.[43] The synthesis began with construction of the C ring, starting from commercially available ethyl tetrolate (**98**), which was advanced to epoxy olefin **99** in five steps and 63% yield (Scheme 24).[44] A Sharpless asymmetric dihydroxylation of **99** afforded the corresponding diol, which upon treatment with pyridinium *p*-toluenesulfonate elicited a cyclisation/epoxide opening sequence, providing the C ring **101** in high yield and a 9:1 diastereomeric ratio. Installation of the C17–C22 ketone fragment was achieved *via* an *anti*-selective addition to the corresponding C16 aldehyde to afford **101**.[44,45] Hydroxyl-directed methyl addition to the C18 ketone, using MeTi(O*i*-Pr)$_3$, furnished the corresponding tertiary alcohol with a 9:1 diastereomeric ratio, which after ozonolysis underwent a spontaneous spiroketalisation to fashion the D ring fragment **102** of pectenotoxin-2.

Scheme 24 *Construction of the CD ring system*



Incorporation of the remaining C1–C9 fragment began by elaborating **102** to the requisite alkene **103**. This alkene was subsequently coupled with enone **104** by means of an olefin cross metathesis reaction (Scheme 25). Hydrogenation of the alkene **105** yielded ketodiol **106**, setting the stage for the final spiroketalisation activated with chloroacetic acid, to provide **108** and **107** as a 3:1 mixture of isomers in favour of the non-anomeric spiroketal.

Scheme 25 *Preparation of the ABCD fragment of pectenotoxin-2*

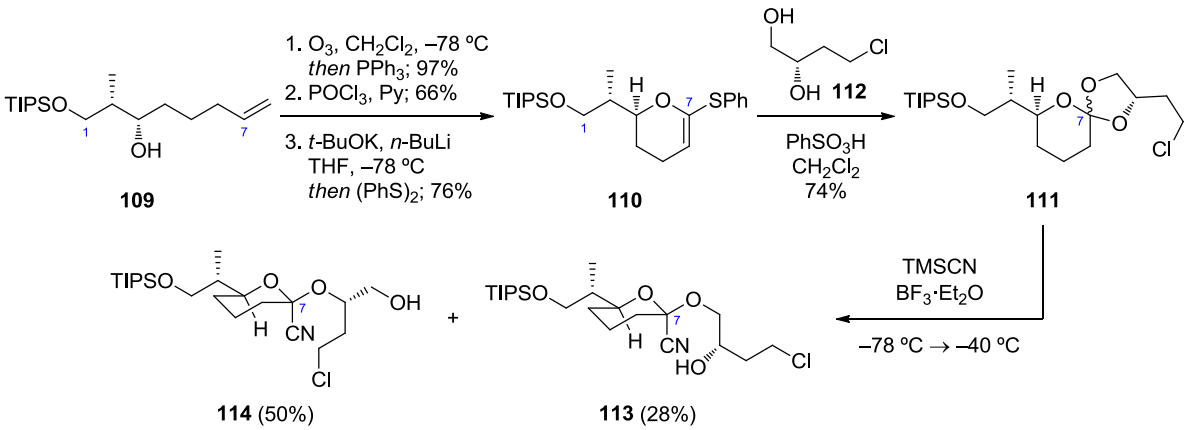


1.3.6 Rychnovsky's synthesis of the non-anomeric AB ring system of pectenotoxin-2

In 2007, Rychnovsky reported the first highly diastereoselective generation of the non-anomeric 6,5-spiroketal of the pectenotoxins (pectenotoxin-2).[46] Their elegant approach was designed around a reductive lithation and cyclisation of 2-cyanotetrahydropyrans. This efficient strategy was employed in the preparation of non-anomeric 6,5- and 6,6-spiroketals with excellent selectivity, and was later also applied to the synthesis of the core of spirofungin B.

The synthesis of the reductive cyclisation precursor commenced with alkene **109** (Scheme 26), which was prepared in four steps from 5-hexenal *via* an Evans aldol reaction, followed by appropriate protecting group manipulations. Ozonolysis of alkene **109** resulted in *in situ* lactol formation in a high yield of 97%. Subsequent dehydration of the resultant lactol with $POCl_3$ in pyridine at elevated temperature generated the corresponding dihydropyran, which was then treated with Schlosser's base and diphenyl disulfide to afford 2-thiophenyl dihydropyran **110** in good yield. With **110** in hand, orthoester **111** was prepared as a 1:1 mixture of diastereoisomers at C7 by the treatment with diol **112** with benzenesulfonic acid under anhydrous conditions. Exposure of **111** to trimethylsilyl cyanide and trifluoroborane led to the cleavage of the orthoester, with the desired regioisomer **114** formed in 50% yield.

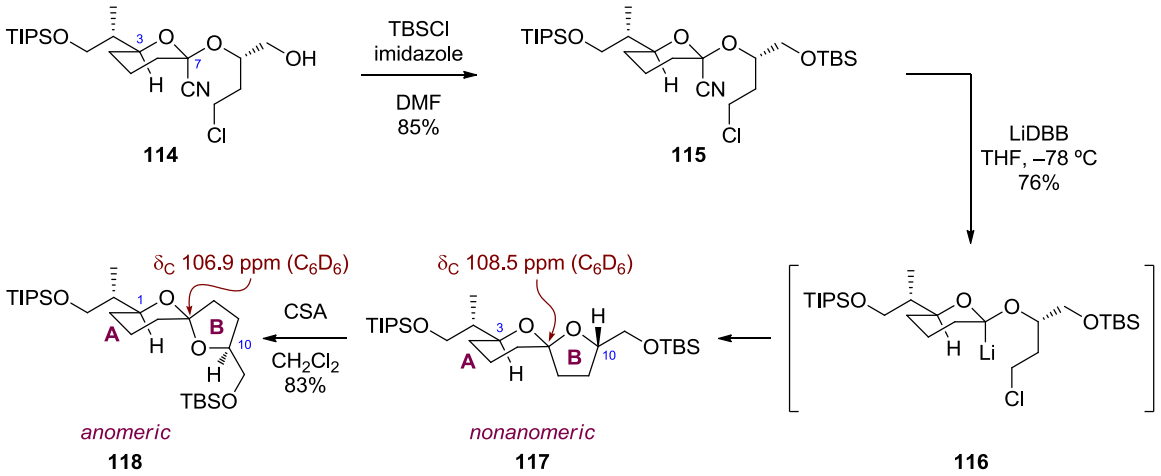
Scheme 26 *Synthesis of AB spiroketal precursors **113** and **114***



Isolation of **114**, followed by TBS protection set the stage for the key reductive cyclisation (Scheme 27). Subjecting acetal **115** to lithium di-*tert*-butylbiphenyl at low temperature generated an axial alkyllithium reagent, which subsequently cyclised with

retention of configuration onto the primary alkyl chloride, providing **117** as a single diastereoisomer and completing the synthesis of non-anomeric AB spiroketal.

Scheme 27 *Diastereoselective synthesis of the AB spiroketal of pectenotoxin-2*

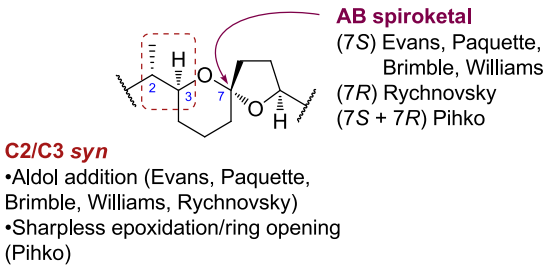


The non-anomeric configuration of the AB spiroketal **117** was confirmed by the characteristic chemical shift of 108.5 ppm in the ^{13}C NMR spectrum (Scheme 27). Additionally, treatment of **117** with camphorsulfonic acid in dichloromethane resulted in complete isomerisation to the favoured anomeric spiroketal with a ^{13}C NMR signal at 106.9 ppm, which was consistent with other chemical shifts observed for the pectenotoxin spiroketals.

1.3.7 Comparison of the syntheses

Although there are several different approaches to the northern hemisphere of the pectenotoxins, there exists a certain level of commonality. Most strategies rely on early stage construction of the AB spiroketal, often with further elaboration to the complete ABC ring system. In all cases except Pihko, the C2/C3 *syn* relationship was introduced *via* an aldol addition (Figure 7).[36]

Figure 7 *Summary of the approaches to the AB spiroketal of the pectenotoxins*



A higher degree of variety was reported in the synthesis of the 6,5-spiroketal subunit. While most approaches used a thermodynamically controlled spiroketalisation under acidic conditions to form the (7*S*)-configuratoin, Pikho exploited acid-catalysed spirocyclisation under kinetic conditions to access both C7 epimers. The only diastereoselective synthesis of the (7*R*)-spiroketal was accomplished by Rychnovsky, by means of reductive lithiation, followed by cyclisation under kinetic conditions.

In summary, and as has been discussed, the synthetic endeavours towards the ABC ring system of the pectenotoxins have constituted a number of approaches to this complex framework. For comparison, a summary of the synthetic strategies to the northern hemisphere is presented below, highlighting carbon fragment length, rings assembled and steps, both longest linear sequence (LLS) and total (Table 1).

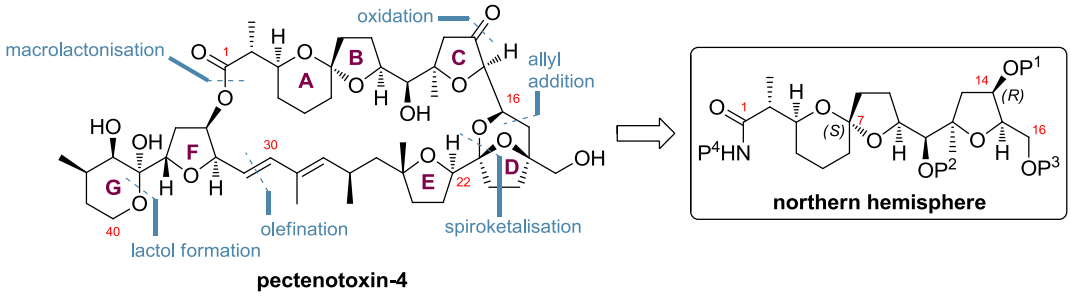
Table 1 *Summary of the discussed approaches to the particular subunits of the pectenotoxins*

Research Group	Fragment	Rings assembled	Number of steps
Evans	pectenotoxin-4	ABCDEFG	36 steps (LLS)
Paquette	C1–C15	AB	18 steps (LLS), 23 steps (total)
	C1–C26	ABC–E	21 steps (LLS), 44 steps (total)
Brimble	C1–C16	ABC	17 steps (LLS), 23 steps (total)
Williams	C1–C15	AB	12 steps (LLS), 19 steps (total)
	C1–C19	C	18 steps (LLS), 29 steps (total)
Pihko	C1–C11	AB	15 steps (LLS), 15 steps (total)
	C1–C22	ABCD	18 steps (LLS), 32 steps (total)
Rychnovsky	C1–C11	AB	12 steps (LLS), 14 steps (total)

1.4 Research outline

The pectenotoxins have been demonstrated to be very challenging synthetic targets, reflected by a sole total synthesis. Their complexity and structural features provide a great opportunity to design novel and creative approaches to access these complex natural products. As part of ongoing research in the Donohoe group directed towards the synthesis of a wide variety of heterocyclic compounds, with subsequent applications to the synthesis of natural products, focus was placed upon the synthesis of the pectenotoxins. Of particular interest was the ABC fragment of pectenotoxin-4, which consists of two tetrahydrofuran rings, one 6,5-spiroketal moiety and eight stereogenic centres (two quaternary) (Figure 8). The target of choice was pectenotoxin-4. This was dictated by the presence of the anomerically stabilised 6,5-spiroketal, which could be carried though the synthesis with minimal risk involved with epimerisation of the C7 stereogenic centre.

Figure 8 *Northern hemisphere of pectenotoxin-4*



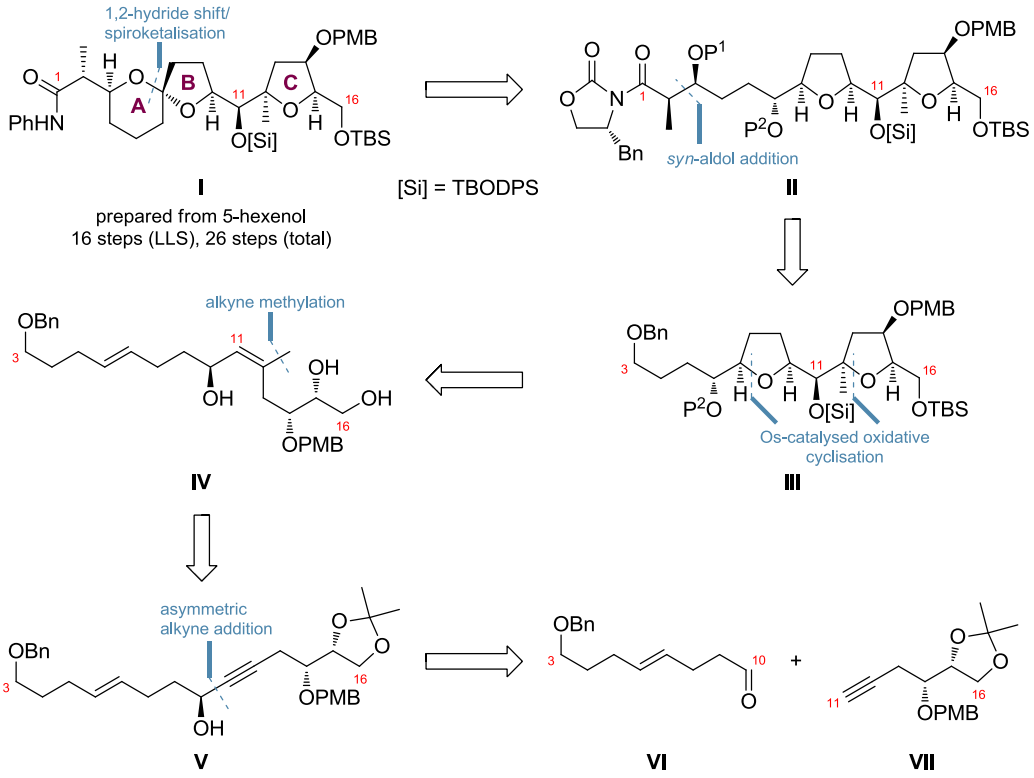
Following studies by Evans and co-workers,[25,26] it was envisioned that the total synthesis would be accomplished by gradual elaboration the ABC fragment by sequential installation of the DE and FG ring systems, followed by a late-stage macrocyclisation. Such an order of events afforded the C1–C16 fragment **I**, a known intermediate in Evans's synthesis, as the primary synthetic target. The retrosynthetic analysis of northern hemisphere outlines an alternative approach to this fragment of pectenotoxin-4 (Scheme 28). Key to the approach is the use of two methods developed in the Donohoe laboratories, namely:

- osmium-catalysed oxidative cyclisation to form tetrahydrofurans
- 1,2-hydride shift of tetrahydrofuran rings

In contrast to previous syntheses, as discussed in Section 1.3, our approach would rely on a late construction of the A ring by elaboration of the BC ring system. It was envisaged that the A ring could be formed *via* key late-stage 1,2-hydride shift, followed by intramolecular

spiroketalisation. The selection of the P^1 and P^2 protecting group, as well as development of this methodology is discussed in Chapter 2.2.

Scheme 28 *Retrosynthetic analysis of the northern hemisphere (fragment **I**) of pectenotoxin-4*



In order to compare the northern hemisphere spectroscopically (Figure 8) with Evans's intermediate fragment **I** (Scheme 28), it was decided to select the same protecting group at the C1, C11, C14 and C16 sites. The choice of a *p*-methoxybenzyl ether was dictated by its orthogonality required for later deprotection and oxidation to the corresponding ketone. Although the configuration at C14 was inconsequential, the (*R*)-configuration at this site was preferred in order to enable the potential late stage comparison with Evans. The C11 and C16 silyl ether would provide necessary stability through the synthesis and the possibility for selective deprotection of the C16 hydroxyl group required for further functionalisation. Precursor **II** could be accessed by employing a *syn*-aldol reaction and suitable protecting group manipulation, which revealed bis-THF **III**. It was envisaged that this fragment, containing the BC ring system could be formed using a tandem osmium-catalysed oxidative cyclisation of triol **IV**. This powerful method was developed in the Donohoe group and is further discussed in Section 2.1.2. In order to access oxidative cyclisation precursor **IV** it would be necessary to introduce a methyl group in a regio- and stereoselective fashion. This transformation could be achieved *via* carbometallation of propargylic alcohol **V**. Further

disconnection of alcohol **V** revealed two fragments **VI** and **VII**, which could be afforded from commercially available starting materials. To secure required stability at the C3 site throughout the synthesis, it was decided to employ a benzyl group. Utilising this potentially competitive route would provide a unique opportunity to validate and demonstrate the versatility of two methods developed in our laboratories in context of the synthesis of complex molecules.

Chapter 2

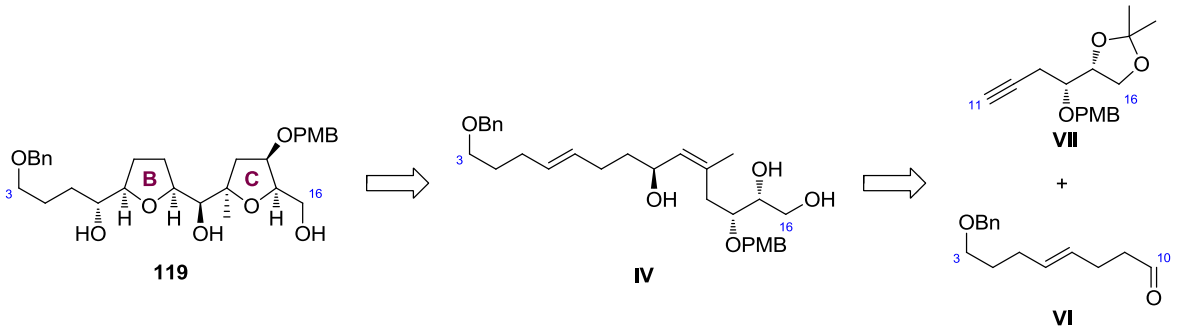
Results and Discussion

2.1 Synthesis of the BC ring system of pectenotoxin-4

2.1.1 Synthesis of the C3–C16 oxidative cyclisation precursor

Initial investigations into the synthesis of the ABC fragment of pectenotoxin-4 concentrated upon the preparation of the BC bis-THF fragment **119**. Key to these studies would be an exploitation of the osmium-catalysed oxidative cyclisation, a methodology previously developed in the Donohoe group, which would allow a rapid construction of two THF rings.

Scheme 29 *Retrosynthetic analysis of the BC ring system **119***

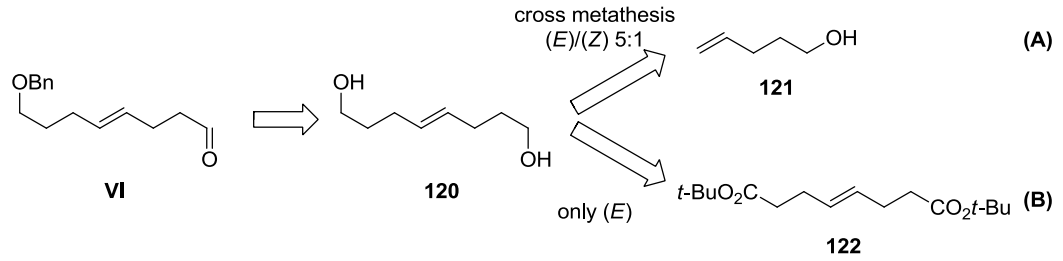


This chapter will detail efforts towards the synthesis of the oxidative cyclisation precursor with subsequent application of the osmium-catalysed oxidative cyclisation to the formation of the BC ring system of pectenotoxin-4.

2.1.1.1 Synthesis of the C3–C10 aldehyde fragment

In order to access the C3–C10 aldehyde fragment several strategies are in principle available. A promising approach may proceed *via* the desymmetrisation of (*E*)-oct-4-ene-1,8-diol (**120**), followed by oxidation to the aldehyde. In order to access **120** in an efficient manner, it was reasoned that dimerisation of commercially available pent-4-en-1-ol (**121**) *via* an olefin cross metathesis reaction could be utilised. However, modest literature precedent for the formation of oct-4-ene-1,8-diol (**120**) *via* cross metathesis revealed that whilst the reaction of pent-4-en-1-ol (**121**) delivers the desired product in high yield, it is formed as an inseparable 5:1 mixture of *E*/*Z* isomers.[47]

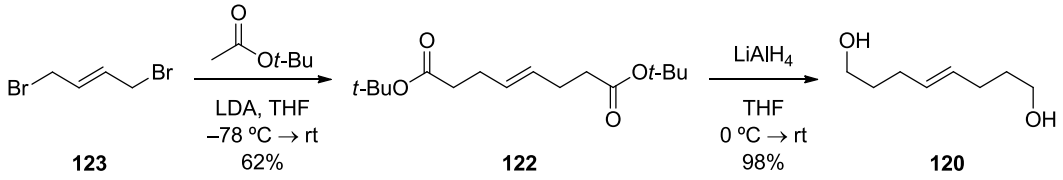
Scheme 30 *Retrosynthetic analysis of aldehyde* ***VI***



Given the modest selectivity of this transformation, an alternative strategy was adopted in which the starting material would already possess the required (*E*) olefin geometry. Therefore, we considered utilising diester **122** (Route B), which may be easily accessed from commercially available (*E*)-1,4-dibromobut-2-ene (**123**).

Following a literature procedure,[48] (*E*)-1,4-dibromobut-2-ene (**123**) was thus treated with *in situ* generated *tert*-butyl acetate enolate to afford corresponding diester **122** in a modest yield of 46% (Scheme 31). However, the formation of several side-products was also noted in this reaction. It was postulated that a slower addition of **123** to the solution of the enolate might be beneficial towards the yield of the desired product. Gratifyingly, the slow addition of **123** to the reaction mixture over 5 hours resulted in a much cleaner reaction, which furnished diester **122** in 62% yield.

Scheme 31 *Synthesis of diol* ***120*** *from dibromide* ***123***

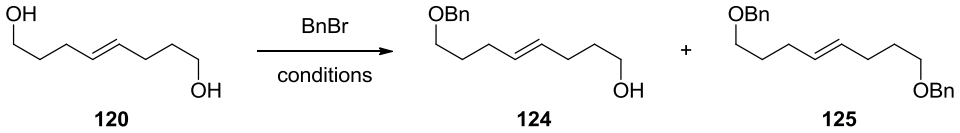


Subsequent reduction of the two ester functionalities was achieved using $LiAlH_4$ to provide the corresponding diol **120** in 98% yield. The formation of **120** was confirmed by the absence of the *tert*-butyl singlet at 1.44 ppm in the ^{1}H NMR spectrum, as well as the loss of the carbonyl and *tert*-butyl peaks in the ^{13}C NMR spectrum.

With diol **120** in hand, it was now possible to attempt a desymmetrisation by protecting one of the hydroxyl groups. As this protecting group was to be carried through the majority of the synthesis, a benzyl ether was chosen due to its stability towards both acidic and basic conditions. Typically monoprotection of symmetrical 1,n-diols can be accomplished by employing an equimolar amount of protecting group reagent.[49] However, the use of such

conditions in the case of a benzylation reaction often leads to a statistical 2:1:1 mixture of the product, the bisprotected diol and the unreacted diol, respectively. According to literature precedent, it is possible to achieve an efficient monobenzylation of certain symmetrical 1,n-diols by utilising stoichiometric benzyl bromide and silver(I) oxide.[50] Hence, attempts to prepare benzyl ether **124** began by exposing **120** to 1.1 equivalents of benzyl bromide, combined with 1.5 equivalents of silver(I) oxide in CH_2Cl_2 (Table 2, entry 1).

Table 2 *Monobenzylation of diol **120***



120 **124** **125**

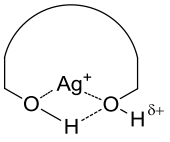
Entry	Conditions/equiv	Solvent	Yield 124/%
1	Ag_2O (1.5), BnBr (1.1)	CH_2Cl_2	traces
2	Ag_2O (1.5), BnBr (1.1)	EtOAc	39
3	Ag_2O (1.5), BnBr (1.1)	Et_2O	55
4	Ag_2O (1.5), BnBr (1.1)	DMF	traces
5	NaH (1.0), BnBr (1.0)	DMF	47
6[a]	NaH (0.5), BnBr (0.33)	DMF	90

[a] Yield based on benzyl bromide

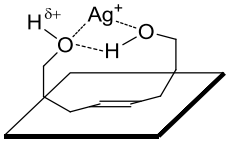
Disappointingly, only partial conversion of diol **120** into the desired monobenzylated product was observed, with most of the starting material being recovered. It was suspected that this result was a consequence of the relatively low solubility of diol **120** in CH_2Cl_2. Since it has been reported that monobenzylation of 1,8-octanediol similarly led to a lower yield of the monobenzylated product due to solubility issues,[50] the reaction was repeated in EtOAc, which provided the product in a modest yield (39%), with significant amounts of the unreacted diol and bisprotected side-product being observed (entry 2). The use of Et_2O as a solvent improved the yield to 55%, whereas in the case of DMF only traces of the monobenzylated product were isolated (<10%, entries 3 and 4). Examination of the proposed mechanism of the silver(I) oxide-mediated reaction suggested that the high selectivity of monobenzylation stems from chelation of the silver(I) cation by both hydroxyl groups of the 1,n-diol. This results in an increase in the lability (acidity) of the hydrogen atom not involved in the hydrogen bonding therefore allowing faster benzylation at this position (Figure 9A). Due to the (*E*)-geometry of the alkene in diol **120**, it is likely that the distance between two hydroxyl groups is too large for the effective chelation of the silver(I) cation to occur, which may account for the reduced selectivity and lower yield of **124**.

Figure 9 *Proposed mechanism of Ag-catalysed monobenzylation*

A. *Proposed mechanism of Ag-catalysed monobenzylation*



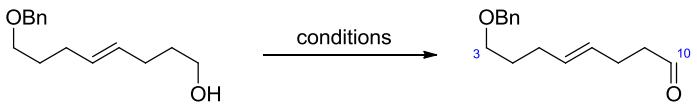
B. *Proposed transient structure of monobenzylation*



Given the difficulties encountered in the attempted monoalkylation of **120**, an alternative approach for the installation the benzyl group was sought. In order to suppress the formation of bisbenzylated side-product **125**, which could not be easily transformed into the desired product, it was decided to use an excess of the diol with respect to benzyl bromide (Table 2, entries 5 and 6). After further optimization of the reaction, it was found that the use of 3 equivalents of diol **120** delivered the monoprotected **124** in 90% yield (based on benzyl bromide), with only traces of dibenzyl ether **125** being observed (entry 6). The recovered diol **120** was subsequently resubjected to the reaction conditions a further four times, increasing the overall yield of the monobenzylated diol to 80%.

In order to access aldehyde **VI**, the final compound of this sequence, several oxidation procedures were examined (Table 3), which ultimately led to the identification of Dess–Martin periodinane as the most effective oxidation conditions (entry 3). Treatment of alcohol **124** with 2 equivalents of Dess–Martin periodinane delivered the desired aldehyde **VI** in 91% yield. Swern and Parikh–Doering conditions also converted **124** to the desired product in similar yields with the latter procedure chosen due to its simplicity of execution on a large scale, and use of inexpensive reagents (entries 1 and 2).

Table 3 *Oxidation of alcohol **124** to aldehyde **VI***



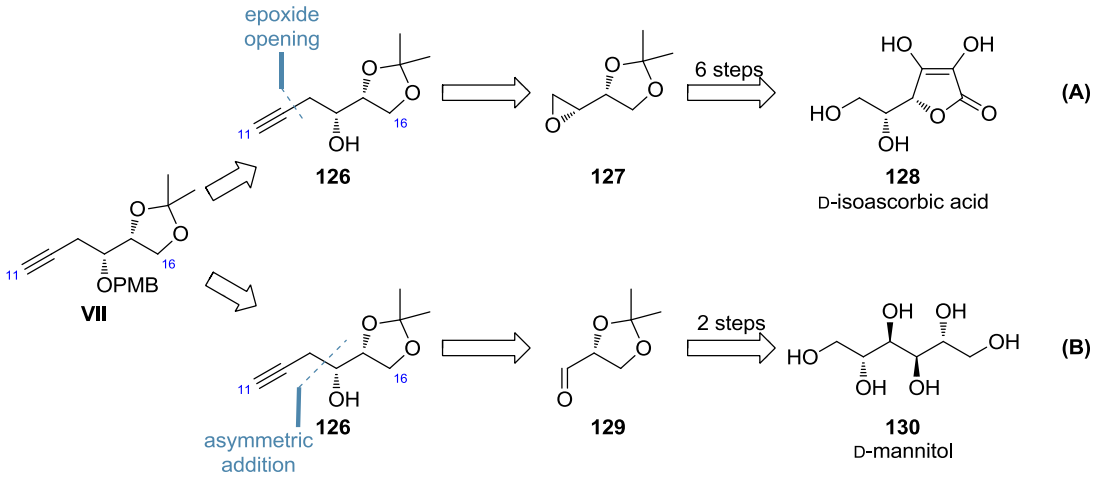
124 **VI**

Entry	Conditions	Yield VI/%
1	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt	85
2	SO_3·py, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0 °C	88
3	Dess–Martin periodinane, CH_2Cl_2, 0 °C → rt	91

2.1.1.2 Synthesis of the C11–C16 alkyne fragment

With the C3–C10 aldehyde fragment in hand, attentions were turned to the synthesis of the complementary C11–C16 fragment. With the hope that it would be possible to spectroscopically compare the resulting ABC fragment to that synthesised by Evans and co-workers,[26] it was decided to set the stereogenic centre at C14 in the (*R*)-configuration. The retrosynthetic analysis of key intermediate **VII** is outlined in Scheme 32. Analysis of **VII** suggested that a disconnection at the C12–C13 bond would reveal an epoxide fragment, which could be prepared from D-ascorbic acid and acetylene. However, D-ascorbic acid, which is the unnatural enantiomer, was not an ideal starting material for a long synthetic route (due to its cost).

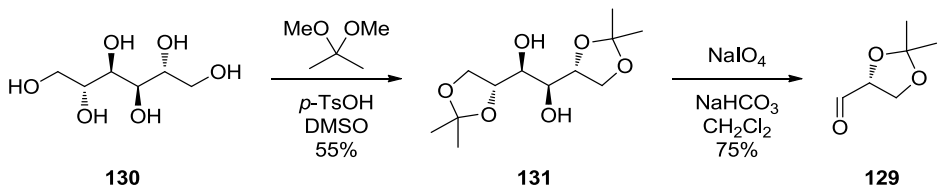
Scheme 32 *Retrosynthetic analysis of the C11–C16 fragment*



Although relatively inexpensive D-isoascorbic acid could alternatively be used to generate suitable epoxide (Route A), the sequence would potentially consist of 6 steps, which was also undesired. Secondly, the use of isoascorbic acid as a building block would lead to poor atom economy. With these considerations in mind, an alternative strategy was forged (Route B). It was envisioned that alkyne **126** could be prepared *via* an asymmetric organometallic addition to glyceraldehyde acetonide **129**, which could in turn be generated from commercially available D-mannitol bisacetonide. It is noteworthy that this approach requires a fewer number of steps than the route employing isoascorbic acid. Moreover, due to C_2 symmetry of D-mannitol and its bisacetonide derivative, the sequence would proceed in an atom-economical manner.

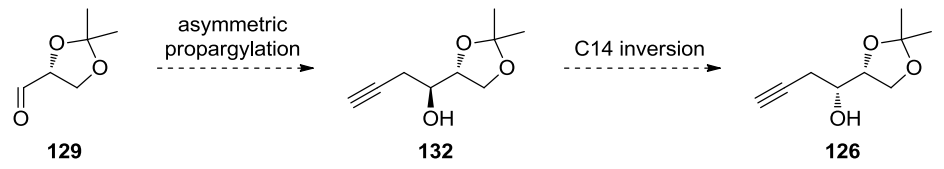
In order to pursue this potential construction of fragment **VII**, commercially available D-mannitol was treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to yield the corresponding bisacetonide **131** in 55% yield (Scheme 33).[51] Despite the fact that bisacetonide **131** is commercially available, due to its relatively high cost this procedure was employed on a regular basis and could be used reliably to produce multigram quantities of bisacetonide **131**. The next step required oxidative cleavage of **131** to deliver the desired protected glyceraldehyde. This transformation is well documented in the literature[52] and after examining several procedures it was found that the use of 2 equivalents of sodium periodate was optimal for this transformation, affording glyceraldehyde **129** in 75% yield.[53] Although **129** is usually purified by vacuum distillation,[52] it was found that the crude product could be used in the next step without further purification.

Scheme 33 *Preparation of glyceraldehyde acetonide **129** from D-mannitol **130***



With a convenient route in place to access to glyceraldehyde **129** on a multigram scale, attention turned to exploring the asymmetric addition of an organometallic species to this intermediate. It was envisaged that selective addition of a propargylmetal species would result in the direct formation of the desired homopropargylic moiety **132** (Scheme 34).

Scheme 34 *Propargylation approach to homopropargylic alcohol **126***

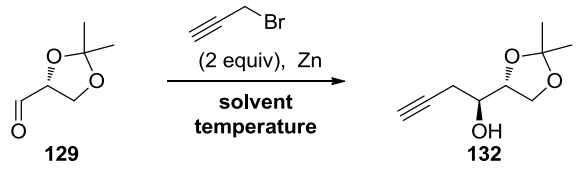


Although there was a limited literature precedent for diastereoselective propargylation of glyceraldehydes, it has been reported that a Barbier-type addition of propargyl bromide in the presence of zinc dust delivers the corresponding homopropargylic alcohol **132**.[54-56] This reaction proceeds with high *anti*-diastereoselectivity, whose origin can be explained *via* Felkin–Anh transition state. Unfortunately, propargylation of protected glyceraldehydes

proceeding with *syn* diastereoselectivity was notably lacking in literature precedent. Since this transformation gives the undesired stereochemical outcome at C14, it was reasoned the Mitsunobu protocol could be employed to furnish the desired *syn*-stereoisomer.

To examine the Zn-mediated propargylation reaction, aldehyde **129** was treated with 2 equivalents of propargyl bromide and activated zinc dust at 0 °C in a 1:1 mixture of DMF and Et_2O (Table 4, entry 1).[55] Pleasingly, the corresponding product was formed after 8 hours in 73% yield as an inseparable 86:14 mixture of *anti* and *syn* diastereoisomers, as determined by ^{19}F NMR analysis of the corresponding Mosher's esters.

Table 4 *Propargylation of aldehyde **129***



129 **132**

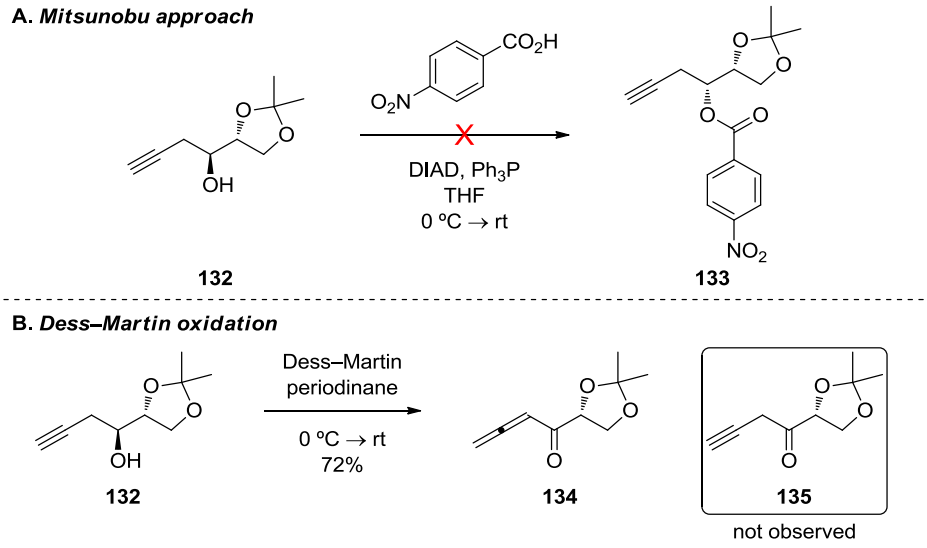
Entry	Solvent	Temperature	Yield/%	*anti*/*syn*
1	DMF/Et_2O 1:1	0 °C → rt	73	86:14[a]
2	THF/NH_4Cl (sat. aq.) 4:1	0 °C → rt	68	89:11[a]
3	THF	−78 °C → rt	75	92:8

[a] Determined by ^{19}F NMR of the corresponding Mosher esters

Changing the solvent to a 4:1 mixture of THF and a saturated aqueous solution of NH_4Cl provided slightly higher level of diastereoselectivity, furnishing **132** in 68% yield and as a 89:11 mixture of diastereoisomers (entry 2).[56] It was also discovered that carrying out the reaction in THF at low temperature (−78 °C) resulted in a further increase in selectivity for the desired product (entry 3). The formation of alcohol **132** with *anti*-selectivity was verified by comparison of its specific rotation with previously reported data. Furthermore, in all cases, only traces of the potential allene side-product were observed.

The next objective in advancing homopropargylic alcohol **132** to alkyne **126** was inversion of the C14 stereogenic centre. Based on literature precedent, a Mitsunobu protocol was attempted using DIAD, *p*-nitrobenzoic acid and triphenylphosphine.[57] Surprisingly, despite extensive experimentation involving different diazo reagents, reaction time and temperature, it was not possible to promote this esterification (Scheme 35A).

Scheme 35 *Attempts to invert the C14 stereochemistry of alkyne* ***132***



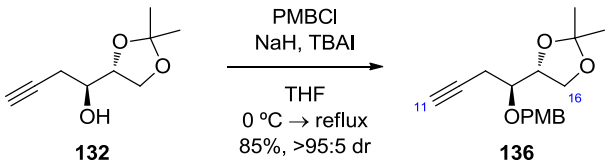
It was reasoned that this problem could by circumvented by carrying out an oxidation/asymmetric reduction sequence to achieve the desired stereochemistry at C14. To pursue this plan, homopropargylic alcohol **132** was subjected to several mild oxidation conditions. Whilst in the case of Swern and Parikh–Doering protocols, no evidence of the desired ketone was observed, the use of Dess–Martin periodinane led to complete oxidation of the C14 alcohol to the corresponding ketone. Disappointingly, analysis of ^{1}H and ^{13}C NMR spectra established that isomerisation of the alkyne to ketoallene **135** had also taken place (Scheme 35B).[58] Similar results of the attempted oxidation of **132** were observed by Gademann and co-workers in their synthesis of the sporolides.[59]

Given the unexpected difficulties encountered in attempting to invert the stereogenic centre at C14, we opted to continue studies with alkyne **132**. As alluded to earlier, it was preferential to have the same stereochemistry at C14 as Evans so as to compare the ABC fragment **I** to the intermediate prepared by Evans and co-workers, however, the stereochemistry at this centre is inconsequential for the synthesis since the corresponding secondary alcohol would later be oxidised to the ketone in the final stages of the synthesis. Furthermore, the use of alcohol **132** instead of **126** did not necessitate inversion of C14 which would therefore not elongate the sequence.

With a reliable route to the C11–C16 carbon framework now in place, attempts were made to introduce a *p*-methoxybenzyl protecting group which, as discussed earlier, allows potential later comparison. Exposure of **132** to sodium hydride and *p*-methoxybenzyl chloride, using a catalytic amount of tetrabutylammonium iodide (THF, 0 °C to room

temperature) provided the desired product in a modest yield of 56%. Pleasingly, increasing the reaction temperature to 40 °C led to the isolation of **136** in 78% yield. This observation ultimately led to further optimisation, which revealed that refluxing the reaction in THF gave a good yield of 85% (Scheme 36).

Scheme 36 *Protection of **132** and completion of the C11–C16 fragment*



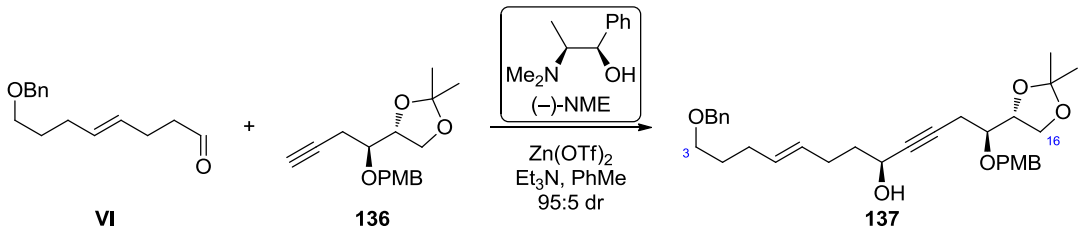
2.1.1.3 Assembly of the C3–C16 fragment

With routes to both aldehyde **VI** and alkyne **136** now established, attention turned to coupling the fragments in an asymmetric fashion. The most common methods that have been reported for the asymmetric synthesis of propargylic alcohols involve either nucleophilic addition of metallated acetylenes to aldehydes, or the reduction of ynones.[60-73] The enantioselective addition of terminal acetylenes to aldehydes has received widespread attention in recent years. The advantage of this transformation is that direct access to chiral propargylic alcohols can be achieved, obviating the need for subsequent oxidation and asymmetric reduction. As a result of this, a number of methods have been developed over the past decade, which have exploited a Zn-mediated alkynylation. In 2000, Carreira and co-workers introduced a very facile process for the synthesis of optically active propargylic alcohols from terminal alkynes and aldehydes, which employs zinc triflate and *N*-methylephedrine as a chiral additive.[74-76] The salient features of this transformation are: (1) reaction conditions are mild compared to alternative protocols and the reaction procedure is comparatively simple to execute; (2) terminal alkynes are used without a separate activation or refunctionalisation prior to the reaction; and (3) both enantiomers of *N*-methylephedrine, as well as zinc triflate, are inexpensive and commercially available. Although the reaction possesses a wide scope with respect to both starting materials, both lower yields and lower enantiomeric inductions were recorded in the case of α-unsubstituted aldehydes.

In order to examine the feasibility of this methodology, alkyne **136** and aldehyde **VI** were subjected to the reaction (Table 5). However, treatment of alkyne **136** with stoichiometric amounts of zinc triflate, (−)-*N*-methylephedrine and triethylamine, followed by aldehyde **VI** provided the desired product in only 26% yield after 24 hours. However, an

excellent diastereomeric ratio of 95:5 was achieved (as evidenced by ^{19}F NMR analysis of the corresponding Mosher's esters, entry 1). Whilst the majority of the remaining alkyne could be recovered, only a small amount of the unreacted aldehyde was isolated. Although the yield of this reaction was modest, this approach appeared promising and thus attentions focussed on optimising this process. According to Carreira's observations, this transformation exhibits reasonable tolerance with respect to water content in the solvent and reagents.[76] However, it has been reported that traces of moisture have a detrimental effect on the reaction and its strict exclusion often helps achieve better yields.[77] Accordingly, the reaction was repeated with the strict exclusion of moisture by azeotroping the starting materials with toluene, followed by drying under high vacuum for 12 hours. It was gratifying to find that the reaction now delivered the desired product in 43% yield with the same level of selectivity (Table 4, entry 2).

Table 5 *Optimisation of the Carreira alkynylation of aldehyde **VI** with alkyne **136***



VI **136** **137**

Entry	Alkyne 136 (equiv)	(−)-NME (equiv)	$Zn(OTf)_2$ (equiv)	Temperature	Yield/%
1	1.2	1.2	1.1	rt	26
2[a]	1.2	1.2	1.1	rt	43
3	1.2	1.2	1.1	60 °C	39
4	2.1	2.1	2.0	rt	36
5	1.2	0.22	0.20	rt	22
6[b]	1.2	1.2	1.1	rt	48

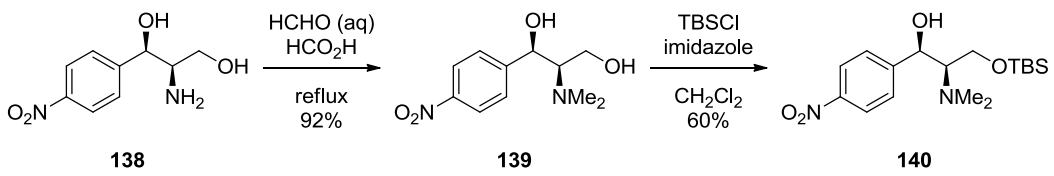
[a] Reaction carried out under scrupulously dry conditions. [b] Slow addition of aldehyde **VI** over 7 hours.

Encouraged by this promising result we next examined the influence of temperature on the reaction. Unfortunately, carrying out the reaction at 60 °C led to a slight depreciation in yield (39%, Table 5, entry 3) and it was found that the mass recovery of aldehyde **VI** was very low, which suggested that the aldehyde **VI** might be unstable under the reaction conditions. With this observation in mind, three potential solutions were conceived. Firstly, it was hypothesised that if the aldehyde slowly decomposed when exposed to the reaction conditions, a higher concentration of the alkyne partner should increase the reaction rate enough to allow **VI** to fully react before decomposition occurred. Therefore, the alkylidene addition was carried out

employing 2 equivalents of alkyne **136**. However, no improvement in the yield of **137** was observed (36%, entry 4). Secondly, it was questioned whether the use of lesser quantities of the reagents in the process would improve the stability of **VI**. To probe this hypothesis we examined a catalytic variant of the asymmetric addition. Unfortunately, employing catalytic amounts of $Zn(OTf)_2$, (−)-*N*-methylephedrine and triethylamine led to a significant erosion in the yield of **137** (22%, entry 5). Thirdly, it was reasoned that the slow addition of aldehyde **VI** to the reaction mixture may be advantageous as it could limit the exposure of **VI** to the reaction mixture. Gratifyingly, addition of aldehyde **VI** to the reaction over 7 hours afforded the desired product in 48% yield (Table 4, entry 6). In all cases, the formation of **137** was verified by the loss of the aldehyde and C(11)H alkyne signals in ^{1}H NMR spectrum, as well as the appearance of new peak at 4.36 ppm corresponding to the newly formed C(11)H propargylic alcohol. The high level of diastereoselectivity was confirmed in an independent experiment, in which the opposite enantiomer of chiral additive was used. Thus, carrying out the reaction in the presence of (+)-*N*-methylephedrine afforded propargylic alcohol 10-*epi*-**137** as a 5:95 mixture of diastereomers (as verified by ^{19}F NMR analysis of the corresponding Mosher esters).

In 2002, Jiang reported the development of a new chiral aminoalcohol-based ligand **140** for the enantioselective alkynylation of aldehydes (Scheme 37).[78,79] Studies carried out by Jiang and co-workers showed that employing this new chiral additive instead of *N*-methylephedrine in Carreira's protocol often led to both higher yields and enantioselectivities of the isolated products. Its application in total synthesis has been demonstrated by Smith in the synthesis of (−)-indolizidine 223AB in which an addition of a linear alkyne to a linear aldehyde was achieved with higher yield and asymmetric induction than in the case of *N*-methylephedrine.[80,81] Although **140** was not commercially available, it could be readily prepared in a two-step procedure from (1*R*,2*R*)-(−)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (**138**). To investigate this method, chiral ligand **140** was prepared by reductive methylation of aminoalcohol **138**, followed by selective TBS protection of the primary hydroxyl group (Scheme 37).

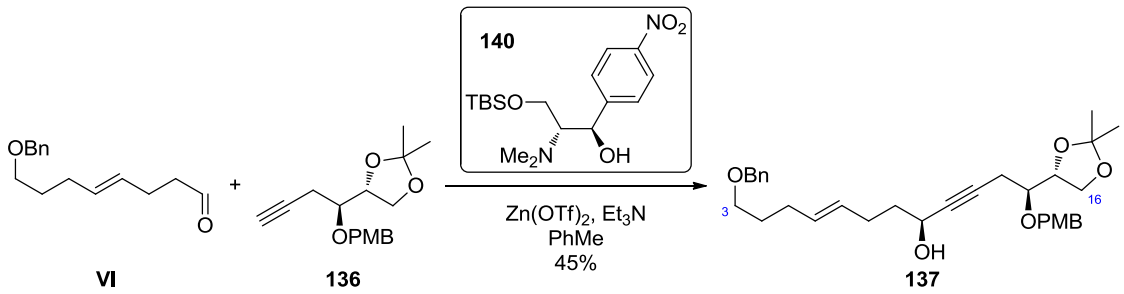
Scheme 37 *Preparation of ligand **140***



138 **139** **140**

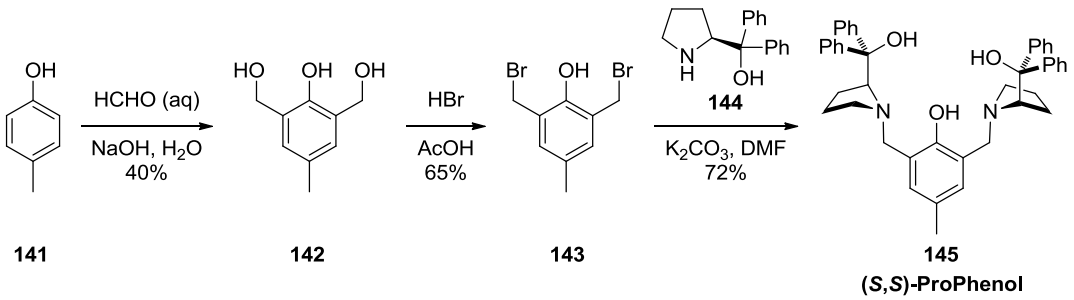
With ligand **140** in hand, we attempted to couple alkyne **136** with aldehyde **VI**. Disappointingly, employing our previous best conditions we were able to isolate the desired product in 45% yield (Scheme 38).

Scheme 38 *Alkynylation of aldehyde **VI** using ligand **140***



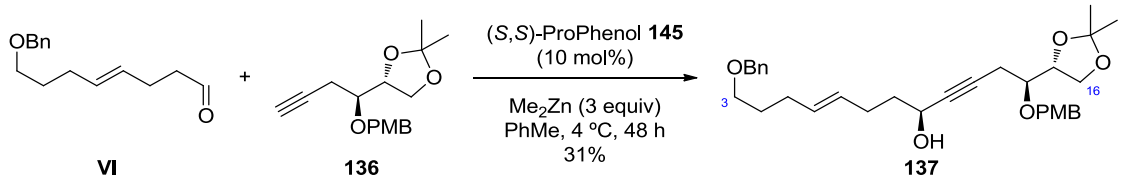
As the efficient coupling of both fragments proved difficult, an alternative method was sought to gain access to **137**. More recently Trost and co-workers disclosed an enantioselective alkynylation of aldehydes, catalysed by dinuclear zinc complex with ProPhenol (Scheme 39).[82-87] Although initially used for α,β-unsaturated aldehydes, it has also been applied to linear aliphatic aldehydes, furnishing products in high yields and enantioselectivities. It was necessary to prepare ProPhenol ligand **145** in a three step sequence from *p*-cresol (Scheme 39). The synthesis commenced with the condensation of 4-methylphenol (**141)** with formaldehyde in the presence of formic acid to furnish phenol **142**. Subsequent exposure of **142** to HBr in acetic acid afforded dibromide **143** in 65% yield, which was ready to undergo a substitution reaction with prolinol. Pleasingly, treatment of **143** with an excess of prolinol **144** provided (*S*,*S*)-ProPhenol **145** in 72% yield.

Scheme 39 *Preparation of ligand ProPhenol ligand **145***



Having prepared (*S*,*S*)-ProPhenol **145**, it was now possible to attempt the asymmetric alkenylation of aldehyde **VI**. Unfortunately, the reaction, when carried out in the presence of Me_2Zn (toluene, 4 °C), provided product **137** in only 31% yield after 48 hours (Scheme 40).

Scheme 40 *Alkynylation using ligand **145***

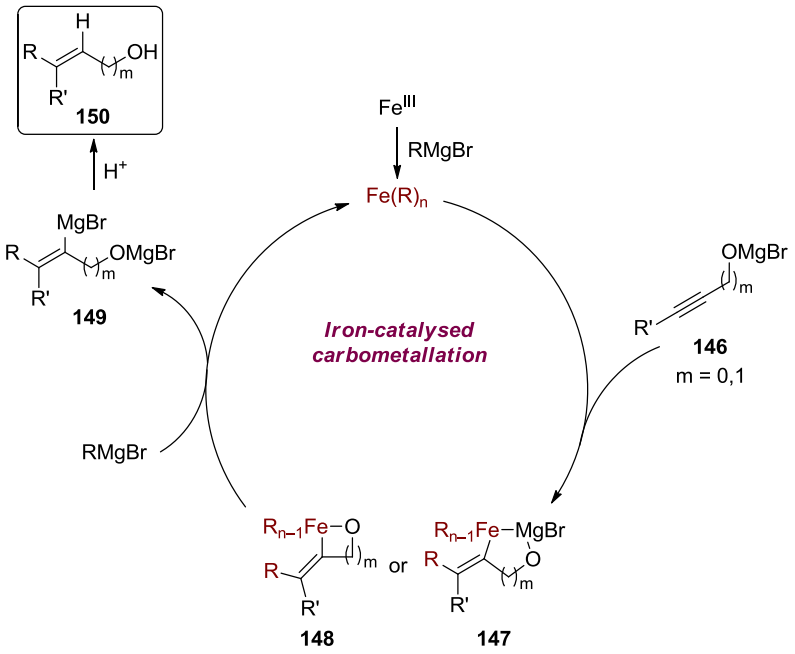


As the alternative approaches investigated to obtain propargylic alcohol **137** offered no improvement in yield, we elected to continue studies using the highest-yielding optimised Carreira conditions. Despite the modest yield, this reaction proved reliable on a multigram scale with no erosion in yield and stereoisomeric purity.

2.1.1.4 Elaboration to the oxidative cyclisation precursor

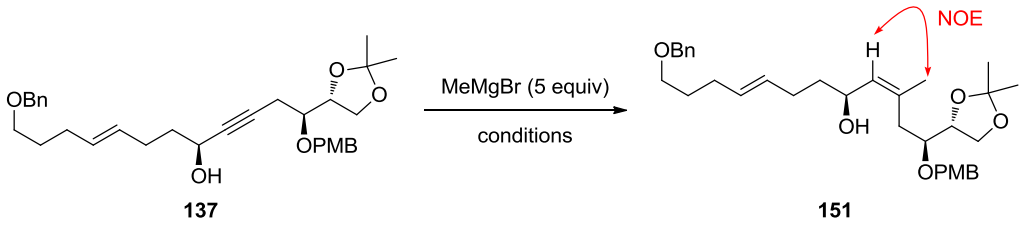
The next transformation required stereo- and regioselective installation of a methyl group to propargylic alcohol **137**, in order to deliver the desired allylic alcohol **151** (*vide infra* Table 6), which possessed a (*Z*)-trisubstituted C11–C12 olefin. In 2006, Ready and co-workers reported a facile iron-catalysed carbometallation of propargylic and homopropargylic alcohols, which afforded tri- and tetrasubstituted olefins with high regio- and stereoselectivity.[88] This transformation appeared to be an attractive method for the methylation of **137**, potentially allowing rapid access to the desired alkene. Moreover, the carbometallation was reported to proceed with complete conservation of stereochemistry. The proposed mechanism for this transformation is depicted in Figure 10. Iron(III) salts are thought to undergo ligand exchange at 0 °C, and reduction with methylmagnesium bromide has been shown to yield complexes of a general structure $L_nFe^{II}(CH_3)_2$. Subsequent alkoxide-directed carbometallation generates intermediate (vinyl)FeR species **147** and/or **148**, which can undergo metathesis with a Grignard reagent to form carbometallated intermediate **149**, with concomitant regeneration of the iron catalyst. Upon aqueous workup, intermediate **149** is protonated to yield alcohol **150**. Alternatively, **149** can be trapped with a variety of electrophiles providing entry to a range of tetrasubstituted allylic alcohols.

Figure 10 *Mechanism of iron-catalysed carbometallation*



In accordance with Ready's protocol, propargylic alcohol **137** was treated with a catalytic amount of $Fe(acac)_3$ and 1,2-bis(diphenylphosphino)ethane (dppe), followed by 5 equivalents of methylmagnesium bromide (THF, −78 °C). After 8 hours at 0 °C, the reaction yielded an approximately 1:1 mixture of **151** and starting material (Table 6, entry 1). An increase in the amount of the iron catalyst and the ligand surprisingly yielded an identical mixture of **151** and unreacted **137**, whilst changing the solvent to toluene had a detrimental effect on the reaction (Table 6, entries 2 and 3). It was eventually discovered that when conducted at room temperature, the reaction resulted in complete conversion of alcohol **137**, affording allylic alcohol **151** in 51% yield (entry 4).

Table 6 *Optimisation of carbometallation of alcohol **137***

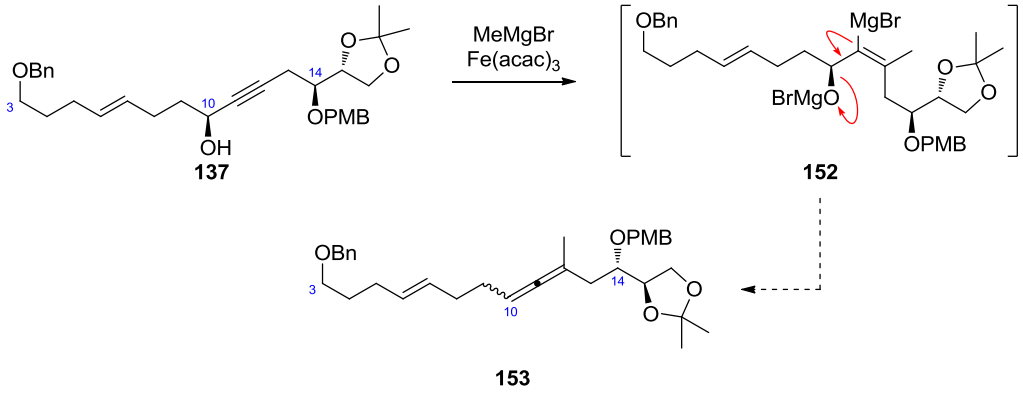


137 **151**

Entry	$Fe(acac)_3$ (mol%)	dppe (mol%)	Solvent	Temperature	Yield 151
1	20	20	THF	−78 °C→ 0 °C	1:1 mixture (**137**/**151**)
2	100	100	THF	−78 °C→ 0 °C	1:1 mixture (**137**/**151**)
3	20	20	PhMe	−78 °C→ 0 °C	traces of **151**
4	20	20	THF	−78 °C→ rt	51%

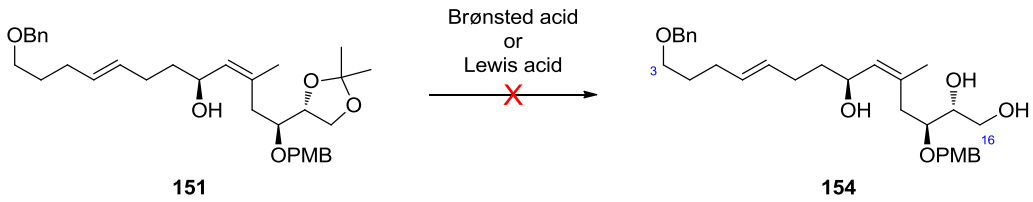
It is noteworthy that the conversion to the product proceeded with complete stereoselectivity, which was subsequently confirmed by NOE analysis. The most telling interaction was observed between the vinyl hydrogen atom at C11 and a methyl group at C12, indicating the desired (*Z*)-geometry of the olefin. The regioselectivity of the reaction was verified by the presence of a doublet at 5.30 ppm ($J = 8.6$ Hz) in the ^{1}H NMR spectrum, corresponding to the C11–H. Moreover, the reaction proceeded with complete conservation of the stereoisomeric purity of **137** as indicated by ^{19}F NMR analysis of the corresponding C14 Mosher's ester. To the best of our knowledge an application of this method in synthesis of complex natural products has not been reported. Although alcohol **151** was obtained in a satisfactory yield, the formation of a significant amount of a side-product was observed under the reaction conditions. Analysis of ^{1}H and ^{13}C NMR spectra revealed that the C-OH carbon signal was absent, along with the appearance of 3 new signals at 202, 96 and 91 ppm. As a result, this compound was tentatively assigned as allene **153** (Scheme 41). Considering the reaction mechanism we hypothesised that **153** could arise from elimination of magnesium halide at the vinyl position, to produce the corresponding allene moiety. Since the formation of allenic by-products was not reported in the seminal work by Ready, it suggested that this process would only be likely to occur at temperatures above 0 °C.

Scheme 41 *Proposed mechanism for the formation of allene **153***



With the key stereogenic centres and functional groups now in place for the double oxidative cyclisation, cleavage of the acetonide group was required. Therefore, allylic alcohol **151** was subjected to a range of acidic conditions typically employed to effect this transformation, such as HCl and TFA in aqueous methanol or tetrahydrofuran. Surprisingly, in all cases a complex mixture of products was formed. Analysis of the reaction mixture by mass spectrometry did not indicate the presence of the product or starting material. Since initial attempts were unsuccessful, attention turned to the use of a wide range of mild conditions, including catalytic PPTS in MeOH, and iodine in MeOH. Unfortunately, these conditions still led to the formation of a non-specific and complex mixture of products.

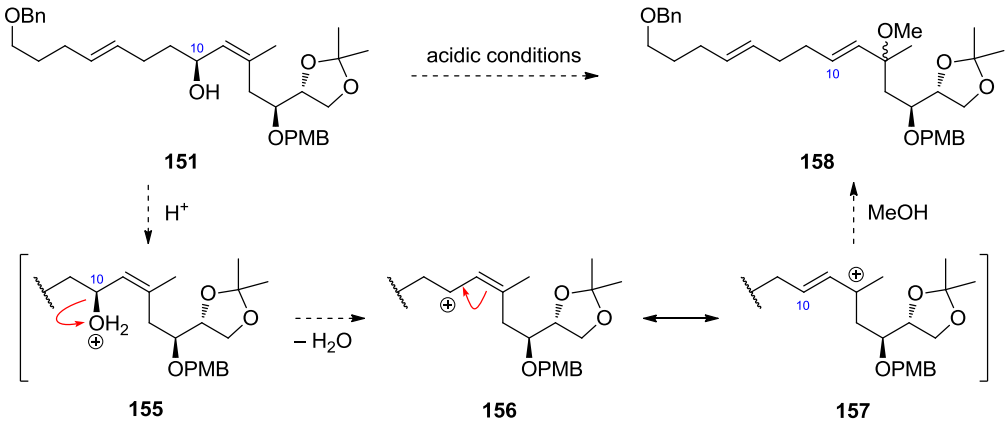
Scheme 42 *Unsuccessful attempts to form **154** via acidic hydrolysis*



Analysis of the ^{1}H NMR spectra of the crude reaction mixtures revealed that the C11 vinyl hydrogen atom was absent in most cases. It was also noted that new alkene signals appeared at 5.45–5.30 ppm. Moreover, analysing the mass spectrum of the reaction conducted in acidic methanol revealed the presence of a peak at 575 Da, which could correspond to the adduct of alcohol **151** and methanol with simultaneous elimination of H_2O. Based on these observations, it was reasoned that even under mildly acidic conditions decomposition occurred, which could be predominantly attributed to the elimination of the allylic alcohol. This observation may be rationalised by the mechanism depicted in Figure 11. In the presence

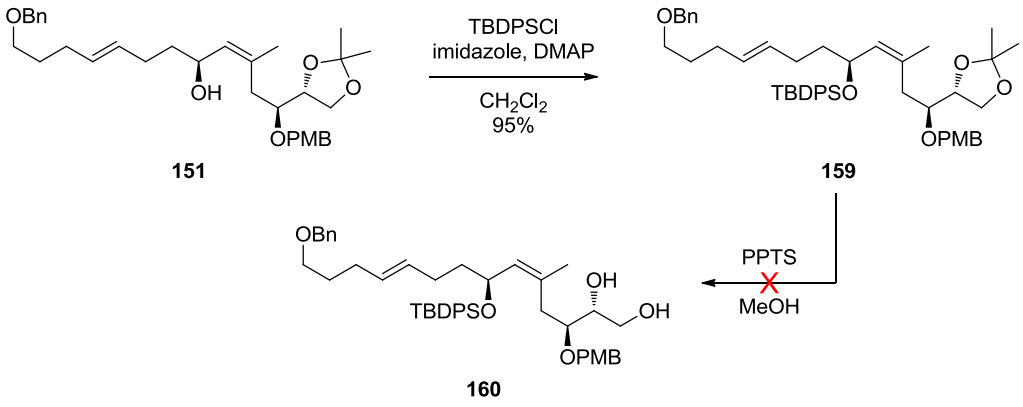
of either Brønsted or Lewis acid, the C10 hydroxyl group can undergo an elimination to form a stabilised allylic secondary carbocation **156**, which precedes a rearrangement to the more stable tertiary carbocation **157**. This newly formed carbocation **157** could, over the course of the reaction, be captured by a molecule of the solvent, delivering product **158**.

Figure 11 *Possible allylic alcohol rearrangement*



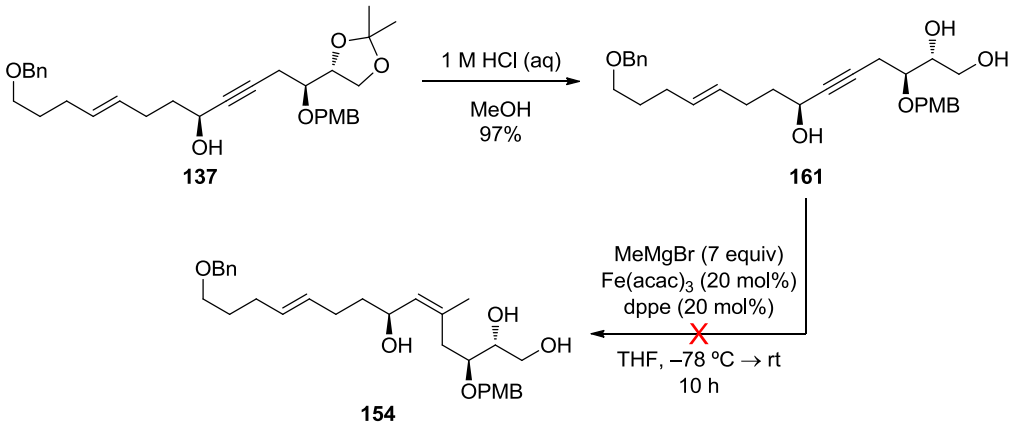
In order to overcome this problem it was reasoned that protection of the allylic alcohol might suppress the undesired decomposition. It was clear that any potential protecting group for the C15–C16 diol should be cleavable under non-acidic conditions. To this end, alcohol **151** was protected as a *tert*-butyldiphenylsilyl ether and was subsequently exposed to a catalytic amount of PPTS in MeOH. Disappointingly, this attempt to cleave the acetonide protecting group was also unsuccessful, resulting in a complex mixture of products. Further attempts to apply literature procedures (which were applied to similar systems) led to no improvement.[89,90]

Scheme 43 *Alternative acetonide deprotection*



Although this deprotection was met with a serious setback, it was felt that these problems could be avoided by modifying the protecting group strategy earlier in the synthesis. As all attempts to effect the cleavage of the acetonide functionality under acidic conditions failed, resulting in undesired decomposition, thus, two alternative strategies were conceived to obviate the acidic deprotection step at this point in the synthesis. The first approach was to remove the acetonide from coupled product **137** as a prelude to Ready carbometallation step. Although no examples of the carbometallation reaction have been reported where multiple free hydroxyl groups are present, if successful, the transformation would readily give access to the key double oxidative cyclisation precursor **154**. In order to test this potential solution, propargylic alcohol **137** was treated with a 10:1 mixture of methanol and a 1 M aqueous solution of HCl to furnish triol **161** in 97% yield (Scheme 44). Triol **161** was subsequently exposed to 7 equivalents of MeMgBr (an additional 2 equivalents were added due to the presence of two free hydroxyl groups), 20 mol% of $Fe(acac)_3$ and dppe. Unfortunately, no evidence of the desired product **154** was encountered, with the mass balance largely constituting of recovered starting material.

Scheme 44 *Unsuccessful carbometallation of triol **161***

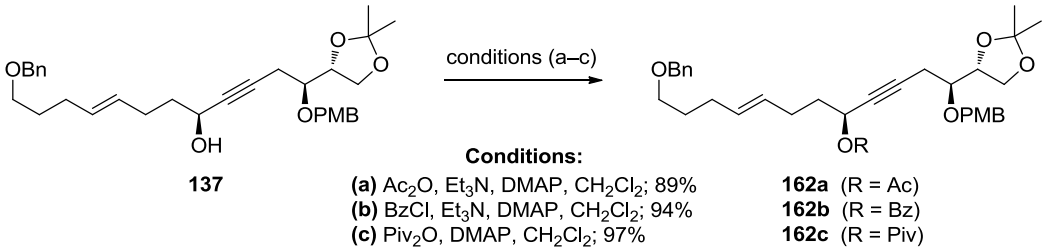


A further increase in the amount of the Grignard component or $Fe(acac)_3$ only led to recovery of triol **161**. These results led to speculation that the trianion arising from the low-temperature deprotonation of the hydroxyl groups under the reaction conditions might be insoluble in tetrahydrofuran, which would result in no reaction being observed. Thus, this strategy was abandoned.

The second potential approach to avoid acidic hydrolysis of **151** would be to replace the acetonide functionality with a different protecting group, which could be cleaved under non-acidic conditions, after undergoing the carbometallation step. It was reasoned that this

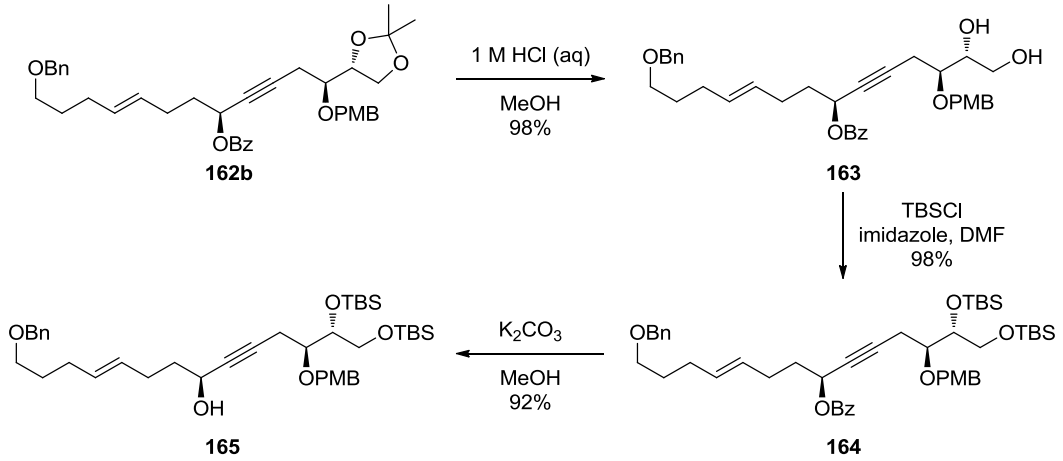
would allow for the deprotection of the bisprotected diol without affecting the allylic alcohol moiety. The *tert*-butyldimethylsilyl group was strategically chosen as it has been shown by Ready to be stable under the carbometallation reaction conditions. In order to manipulate the protecting groups of the C15–C16 diol, it was necessary to protect the C10 hydroxyl group in an orthogonal manner. It was decided that protecting the C10 alcohol as an ester would allow sufficient orthogonality to the acetonide group. Therefore, three typical ester derivatives 1**62a–c** groups were prepared according to standard procedures, in order to examine their relative stability to acetonide deprotection conditions (Scheme 45).

Scheme 45 *Protection of C10 hydroxyl group of alcohol **137***



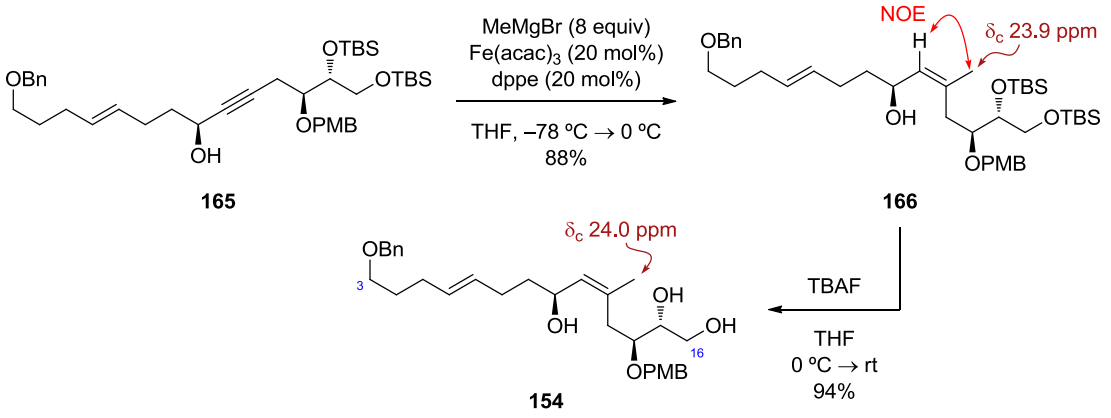
Exposure of acetate **162a** to previous successful acidic conditions proved to be non-selective, as partial hydrolysis of the acetate group occurred. In contrast, the reaction with pivalate **162c** and benzoate **162b** proceeded smoothly resulting solely in the formation of the corresponding vicinal diols. The benzoate protecting group was chosen for subsequent studies. Treatment of diol **163** with *tert*-butyldimethylsilyl chloride in DMF provided bis-TBS ether **164** in 98% yield (Scheme 46). The synthesis of bis-TBS protected propargylic alcohol **165** was accomplished by basic removal of the benzoyl group using K_2CO_3 in methanol (92%).

Scheme 46 *Preparation of alcohol **165***



With a reliable route to bis-TBS propargylic alcohol **165** now established, attention turned to the critical selective methylation of the triple bond. Upon applying the previously optimised conditions to **165**, the desired allylic alcohol was generated in 64% yield. However, contrary to the reactivity of **165**, it was found that when the reaction was carried out according to the literature protocol at 0 °C, alcohol **166** was delivered in an excellent yield of 88%, with only traces of the allenic side-product being observed (Scheme 47). This fact supported the hypothesis that the formation of the allenic side-products occurs at temperatures above 0 °C. The regioselectivity of the carbometallation was confirmed by the presence of a doublet at 5.34 ppm (J = 8.3 Hz) in the ^{1}H NMR spectrum, corresponding to the C(11)H group. With the appropriate substrate in hand, it was now necessary to remove the two TBS groups in order to liberate the corresponding diol moiety, which was essential for the oxidative cyclisation step. Pleasingly, this transformation was accomplished by the treatment of alcohol **166** with 3 equivalents of TBAF in THF solution, providing the desired triol **154** in 94% yield (Scheme 47). It was gratifying that no decomposition or by-products were observed under the reaction conditions.

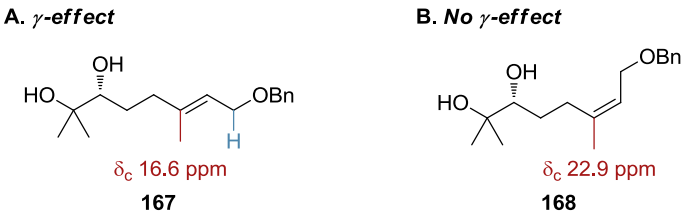
Scheme 47 *Completion of the synthesis of the cyclisation precursor **154***



The geometry of the C11–C12 olefin was confirmed by NOE analysis and also by the lack of the γ-effect in the case of a methyl group at C10. In (*Z*)-alkenes the van der Waals radii of the synperiplanar allylic C–H groups overlap with each other, resulting in a sterically induced polarisation of these bonds. This moves the electron density of the σ_{C-H} bonding electrons towards the allylic carbon atoms, causing greater shielding. Therefore the chemical shift of the allylic carbon atoms in (*Z*)-olefins is usually lower than that of (*E*)-olefins. Since the allylic methyl group in geraniol derivative **167** (Figure 12A) is in a *cis*-relationship with the CH_2OBn moiety, it suffers from the γ-effect, resulting in the chemical shift of 16.6 ppm. In contrast, the allylic methyl in nerol derivative **168** (Figure 12B) rests in a *trans*-relationship

with the CH_2OBn moiety causing a downfield shift of the methyl group to 22.9 ppm. The presence of a chemical shift of 23.9 ppm in **166** and 24.0 ppm in **154**, corresponding to the C12 methyl group strongly suggested a lack of the γ-effect and thus the (*Z*)-geometry of the C11–C12 alkene.

Figure 12 *Correlation of γ-effect with the chemical shift*

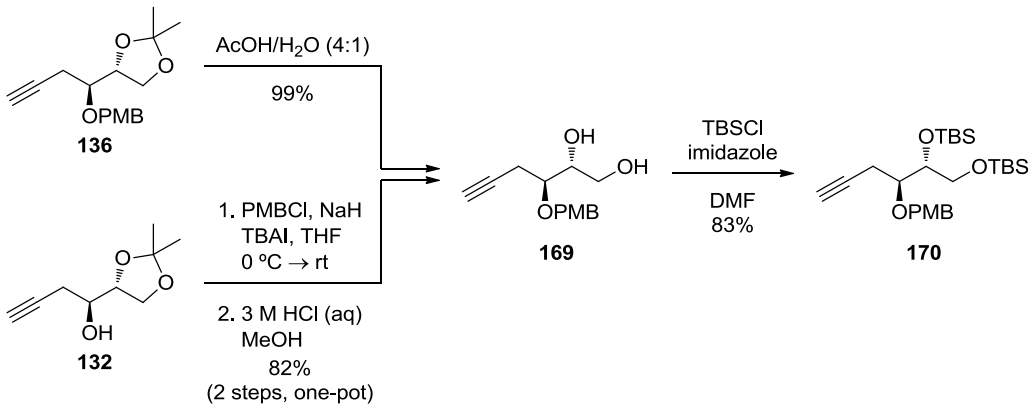


2.1.1.5 Optimisation of the route to the linear precursor

With a reliable route to key precursor **154** now established we directed attention to optimising the sequence to obtain this intermediate in a shorter sequence. To avoid excessive protecting group manipulation *en route* to propargylic alcohol **165**, it was envisaged that alcohol **165** could be prepared *via* a Carreira alkyne addition of alkyne **170** to already prepared aldehyde **VI**. Such an approach would necessitate the reprotection of the C15–C16 diol at an earlier stage of the synthesis, which would save two steps in the sequence by obviating the need for protection/deprotection manipulation of the C10 hydroxyl group.

In order to pursue this potential route, several acetonide deprotection conditions were examined. Pleasingly, treatment of alkyne **136** with aqueous acetic acid or 3 M hydrochloric acid in methanol resulted in a successful reaction that delivered the desired diol **169** in up to 99% yield (Scheme 48).

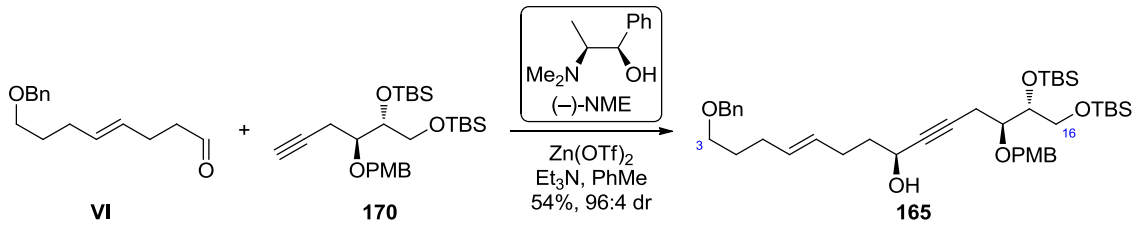
Scheme 48 *Preparation of alkyne **170***



Preparation of diol **169** could be carried out in a more efficient manner by combining the PMB protection with the acetonide deprotection. Careful quenching of the PMB protection reaction of alcohol **132** with methanol and a 3 M solution of HCl gave diol **169** in a high yield of 82%. Diol **169** was next exposed to 2.5 equivalents of TBSCl in DMF, which furnished the corresponding bis-TBS ether in 83% yield. To minimise handling and purification of diol **169**, the crude reaction mixture of the PMB-protection/acetonide deprotection could directly be subjected to the subsequent TBS protection reaction conditions to deliver alkyne **170** in 68% yield (from **132**). These modifications appeared particularly attractive as they allowed for the convenient execution of a 6-step sequence from D-mannitol **130** to afford **170** with only two flash column chromatography purifications.

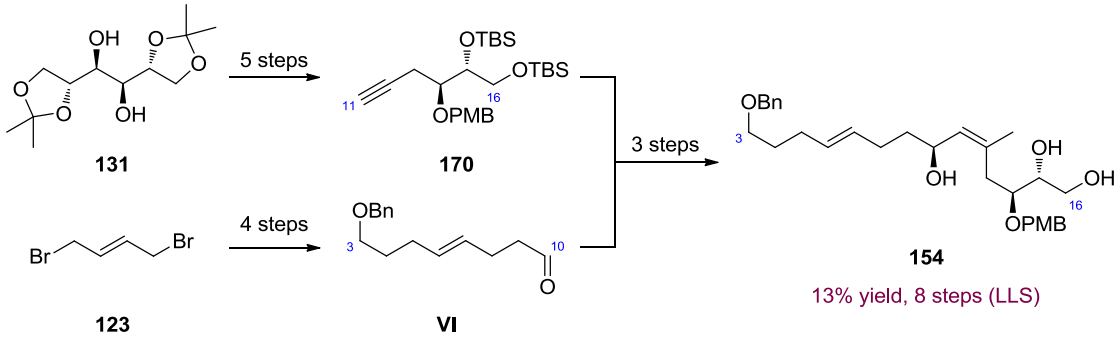
With a high-yielding route to alkyne **170** secured, it was possible to attempt the coupling reaction with aldehyde **VI,** utilising a Carreira asymmetric alkynylation reaction. Initially, it was decided that attempting the reaction under the previously developed optimal stoichiometric reaction conditions would be the best course of action (Scheme 49). Pleasingly, the slow addition of the aldehyde partner over 7 hours to the reaction mixture provided desired propargylic alcohol **165** in 54% yield and 96:4 diastereomeric ratio. The ratio was determined by analysis of the corresponding Mosher esters and comparison to a 1:1 diastereomeric mixture (at C10). Further examination of the reaction conditions, including alteration of the amount of alkyne **170**, $Zn(OTf)_2$ and the ligand, did not improve the yield. Therefore, it was decided to utilise the developed conditions for this reaction, which pleasingly was found to be reliable on a large scale.

Scheme 49 *Synthesis of alcohol **165***



As a result of this optimised sequence, oxidative cyclisation precursor **154** was prepared in 8 steps (longest linear sequence, 12 total steps) from commercially available D-mannitol bisacetonide **131** in an overall yield of 13% (Figure 13). This route provided reliable access to the oxidative cyclisation precursor **154** on a multigram scale.

Figure 13 *Summary of the synthesis of the oxidative cyclisation precursor*

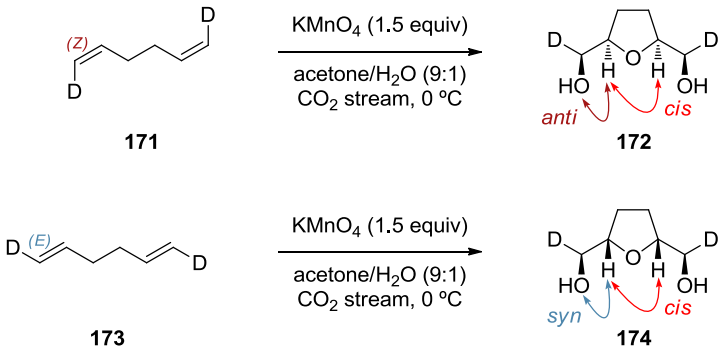


2.1.2 Oxidative cyclisation to form the BC fragment

2.1.2.1 Introduction to osmium-catalysed oxidative cyclisation

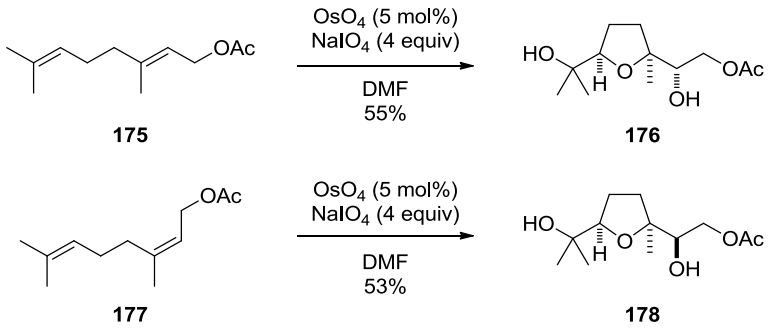
The oxidative cyclisation of 1,5-dienes to generate tetrahydrofurans has been known for almost 50 years. In 1965 Klein and Rojahn discovered that the treatment of 1,5-hexadiene with $KMnO_4$ resulted in the formation of *cis*-THFs flanked with two hydroxyl groups.[91] The reaction is particularly useful, as it proceeds with complete stereoselectivity with respect to the formation of *cis*-THFs, as well as being *syn*-stereospecific with respect to the addition across both alkenes, as later demonstrated by Baldwin (Scheme 50).[92]

Scheme 50 *Confirmation of the oxidative cyclisation stereospecificity by Baldwin*



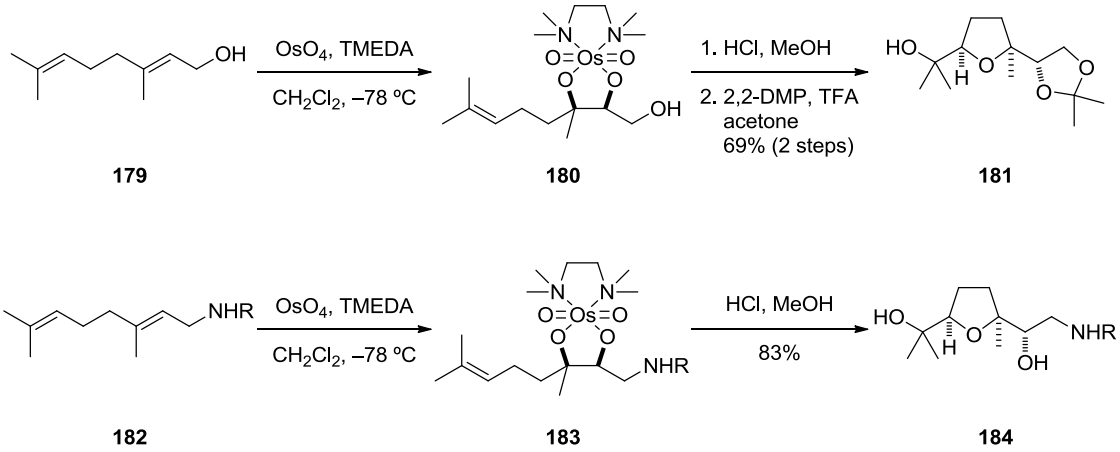
Since this initial report a variety of other metal-oxo species have been shown to accomplish this transformation. In 1998, Piccialli reported that exposure of nerol- and geraniol-derived dienes **177** and **175** to a catalytic amount of OsO_4 in the presence of a stoichiometric amount of sodium periodate resulted in the formation of THF **178** and **176**, however in modest yields (Scheme 51).[93,94]

Scheme 51 *Piccialli's catalytic osmium oxidative cyclisation*



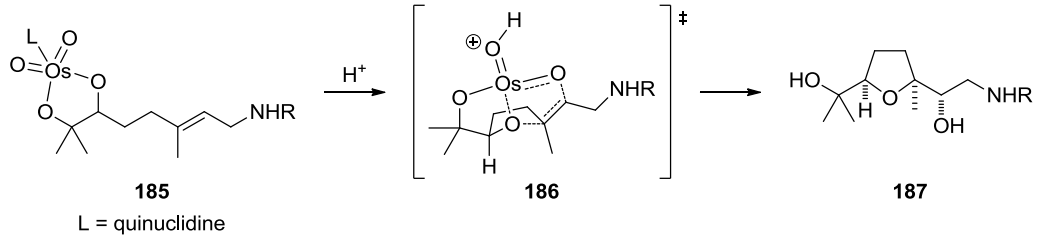
Shortly after Piccialli's report, Donohoe and co-workers discovered that the selective dihydroxylation of 1,5-dienes using stoichiometric OsO_4 and TMEDA, followed by exposure to acid, resulted in a second oxidation at the pendent alkene, to deliver *cis*-THFs in high yields (Scheme 52).[95,96]

Scheme 52 *Donohoe's oxidative cyclisation*



It was proposed that the cyclisation proceeds through transition state structure **186** (Figure 14). Given that the formation of the THF product only occurred under acidic conditions, Donohoe postulated that the cyclisation proceeded *via* a (3+2) inverse electron demand cycloaddition, facilitated by the protonation of an oxo-ligand.

Figure 14 *The proposed role of acid in the oxidative cyclisation*



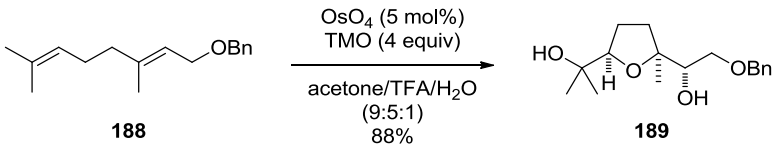
185
L = quinuclidine

186

187

Subsequently, Donohoe revealed a catalytic variant of this method, employing a large excess of trifluoroacetic acid in combination with a stoichiometric amount of trimethylamine *N*-oxide (TMO) as a reoxidant for osmium.[97] Catalytic OsO_4 promoted the oxidative cyclisation reaction of various 1,5-dienes producing solely *cis*-THFs in increased yields (Scheme 53).

Scheme 53 *Donohoe's aqueous osmium oxidative cyclisation*

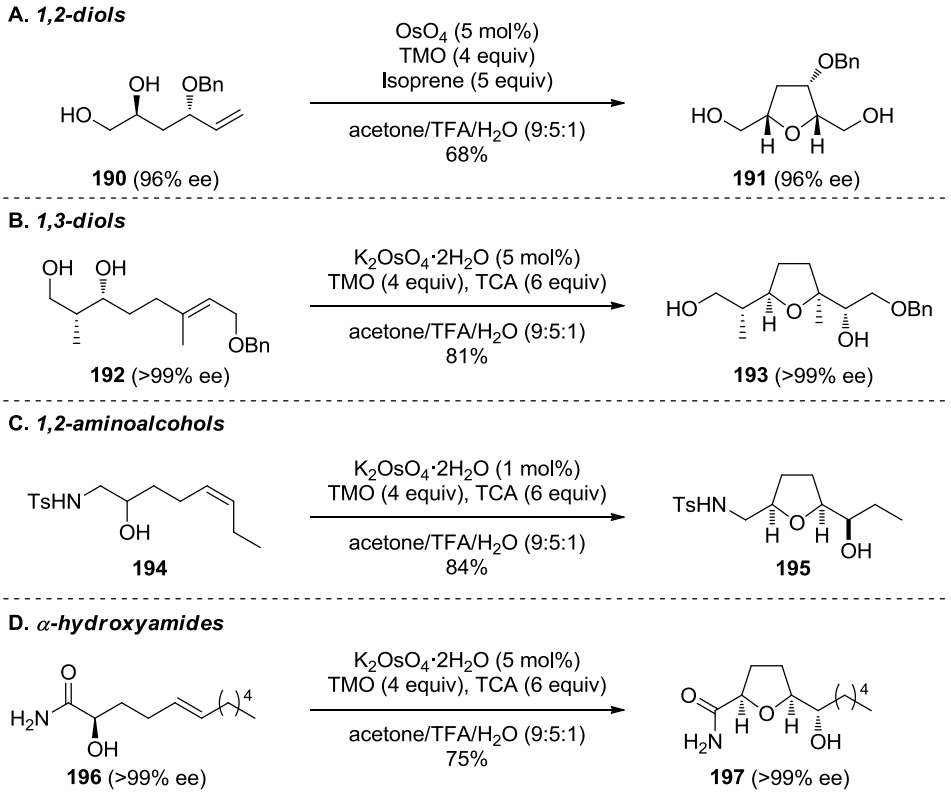


188

189

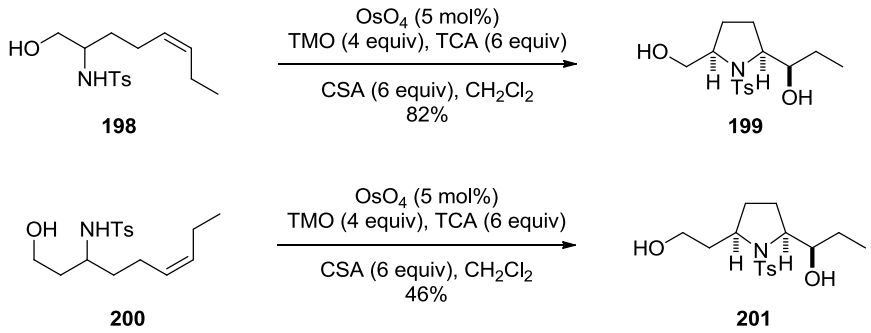
A significant improvement to the methodology was realised in 2005 to access enantioenriched THFs.[97] Donohoe and co-workers developed an alternative strategy demonstrating that enantiomerically pure vicinal diols generated from 1,5-dienes will form the THF when subjected to oxidative cyclisation conditions. In this novel approach condensation of the 1,2-diol with the osmium catalyst provides an intermediate osmate ester, which subsequently undergoes the oxidative cyclisation to deliver the corresponding THF (Scheme 54A). Notably, because the reaction proceeded with complete stereoselectivity, with respect to the formation of *cis*-THFs, as well as complete stereospecificity for *syn*-addition across the olefin, it was now possible to generate up to two stereogenic centres. In this early report, in order to avoid unwanted dihydroxylation of the pendent alkene by the Os(VIII) catalyst, the diol cyclisation required the use of a sacrificial alkene, typically isoprene or *trans*-cinnamic acid (TCA), which could undergo dihydroxylation at a faster rate than the pendent alkyne in the starting material. This process generated the catalytically active Os(VI) species, which subsequently form the osmate ester with the 1,2-diol and cyclised under acidic conditions. Due to the avoidance of a 1,5-diene precursor, the discovery of these conditions allowed the scope of the cyclisation reaction to encompass 1,3-diols,[98] aminoalcohols and α-hydroxyamides to form a range of functionalised THFs (Scheme 54B–D).[99]

Scheme 54 *Scope of oxidative cyclisation iniciators*



Furthermore, in 2006 Donohoe and co-workers reported that the oxidative cyclisation of aminoalcohols possessing reversed functionalisation (relative to the hydroxyl and amino groups) resulted in the formation of the corresponding *cis*-pyrrolidines.[99]

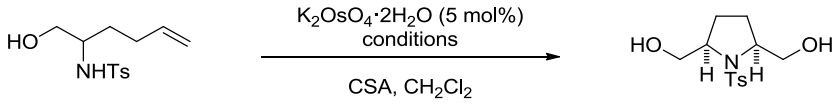
Scheme 55 *Oxidative cyclisation to generate pyrrolidines*



Despite the initial success of the oxidative cyclisation methodology in terms of direct entry to a variety of functionalised tetrahydrofurans and pyrrolidines from simple precursor, the reaction utilised a large excess of a sacrificial alkene. After the discovery that osmium(VI) was the active catalytic species, Donohoe and co-workers turned attentions to the developing a reoxidant, which would be able to oxidise osmium(IV) to osmium(VI), but not to unwanted

osmium(VIII). Screening a number of *N*-oxide-based reoxidants revealed that pyridine *N*-oxide (PNO) was an effective alternative to TMO, allowing aminoalcohol **202** to cyclise to the corresponding pyrrolidine in 85% yield (Table 7, entry 3) in the absence of a sacrificial alkene.[100] The reaction with PNO proceeded smoothly with no dihydroxylated side-products being observed, which suggested that no osmium(VIII) was present in the reaction mixture.

Table 7 *Improvements in the oxidative cyclisation*



202 **203**

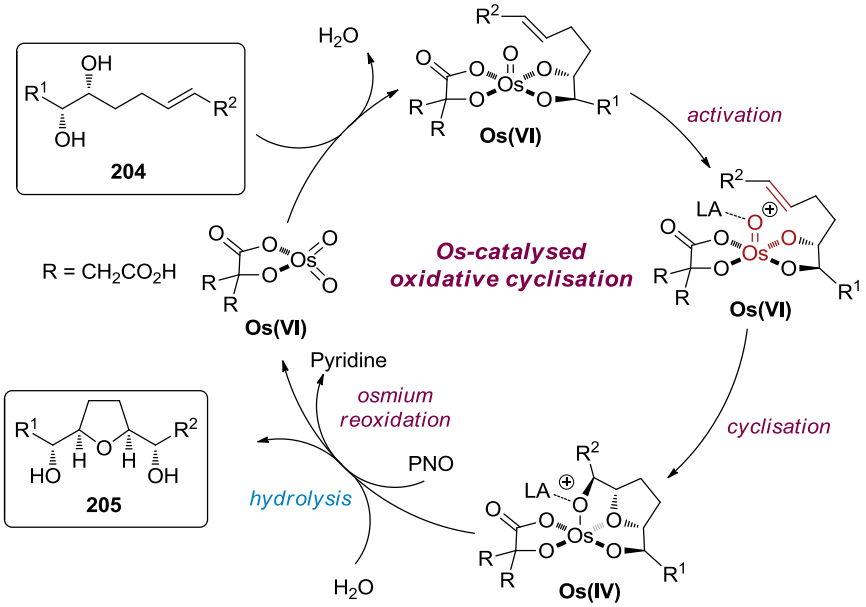
Entry	Reoxidant	Additive (equiv)	Time/h	Yield/%
1	triethylamine *N*-oxide	---	48	69
2	triethylamine *N*-oxide	*trans*-cinnamic acid (6.0)	16	79
3	pyridine *N*-oxide	---	4	85
4	pyridine *N*-oxide	citric acid (0.75)	2	98

Furthermore, the addition of a catalytic amount of citric acid to the reaction was found to result in a significant increase in the yield of **203** (98%, entry 4). It should be noted that the reaction also proceeded at a faster rate, which was attributed to several factors. According to studies by Sharpless and co-workers, the addition of citric acid might facilitate the hydrolysis of the osmate ester to liberate the product and thus enable the osmium species to return to the catalytic cycle.[101] Based on these results Donohoe and co-workers postulated that citrate stabilised Os(VI) with respect to disproportionation and aided the hydrolysis of the intermediate osmate ester, similar to observations reported by Sharpless. It was later demonstrated that a range of aminoalcohols would successfully undergo the oxidative cyclisation reaction under the new conditions. Applying the pyridine *N*-oxide/citric acid conditions to a range of substrates increased yield in the formation of THFs compared to the TMO/TCA cyclisation system.[100]

Whilst the osmium-catalysed oxidative cyclisation has been shown to be a powerful synthetic tool, its use in synthesis was limited by the strongly acidic conditions required for the reaction to proceed. Therefore, studies in the group focussed on developing more viable reaction conditions that may be applicable to a wider range of substrates, by reducing the acidity of the reaction. Although the exact role of the acid in the cyclisation was not known, it has been postulated that the protonation of the oxo-ligand on Os(VI) leads to a more electron-deficient osmium-centre, which in turn allows it to undergo an inverse electron demand (3+2)

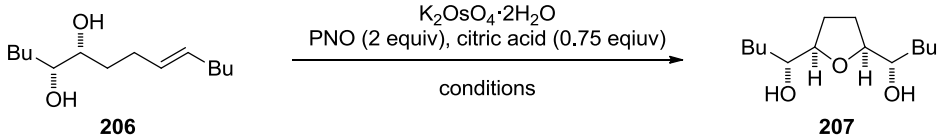
cycloaddition with an electron-rich alkene (Figure 15). Therefore, Donohoe envisaged that the Brønsted acid could be replaced with a Lewis acid to render a less acidic oxidative cyclisation.

Figure 15 *Proposed catalytic cycle for the oxidative cyclisation*



After examination of a range of Lewis acids for the oxidative cyclisation with model substrate **206**, Donohoe and co-workers found that utilising a substoichiometric amount of either zinc or copper trifluoromethanesulfonate resulted in a formation of THF **207** in high yield (Table 8).[102] Screening of various solvents revealed that a mixture of acetonitrile and water was most effective, generating THF **207** in 87% yield (entry 2).

Table 8 *The use of Lewis acid in the oxidative cyclisation*

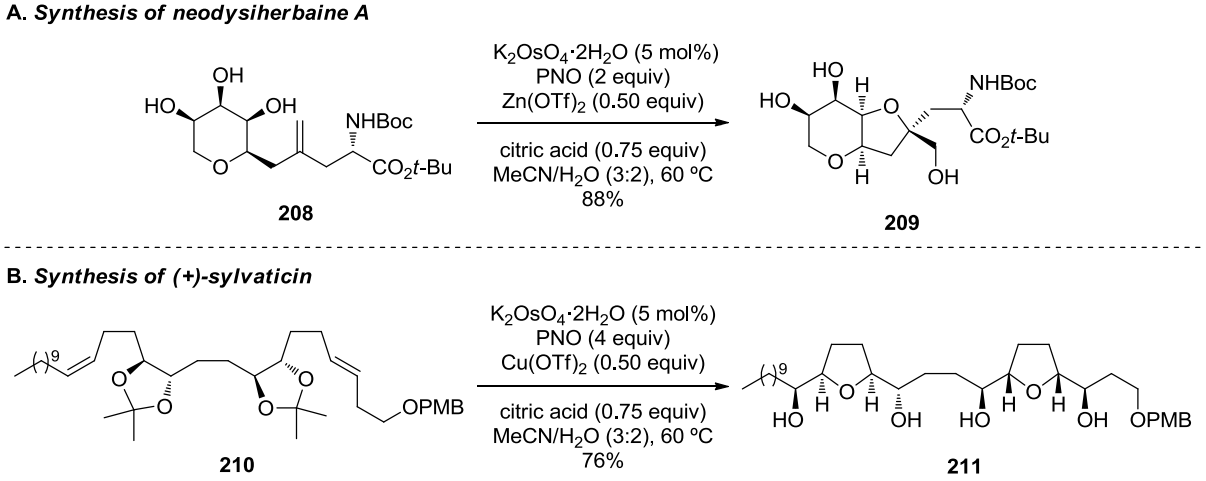


Entry	$K_2OsO_4 \cdot 2H_2O$	Conditions	Time/h	Yield/%
1	5 mol%	TFA, acetone/H_2O (9:1)	16	78
2	5 mol%	$Cu(OTf)_2$ (0.5 equiv), MeCN/H_2O (4:1), 60 °C	8	87
3	5 mol%	$Zn(OTf)_2$ (0.5 equiv), MeCN/H_2O (3:2), 60 °C	2	89
4	1 mol%	$Zn(OTf)_2$ (0.5 equiv), MeCN/H_2O (3:2), 60 °C	6	92
5	0.2 mol%	$Zn(OTf)_2$ (0.5 equiv), MeCN/H_2O (3:2), 60 °C	72	90

This optimised set of conditions allowed the reaction of **206** in the presence of 5 mol% $K_2OsO_4 \cdot 2H_2O$ to reach completion in only 2 hours (entry 3), which is almost an order of magnitude shorter than in the reaction in the presence of TFA (entry 1). Moreover, when the catalyst loading was reduced to as low as 0.2 mol%, no depreciation in yield was noted; however, the cyclisation required an extension of the reaction time to 72 hours (entry 5).

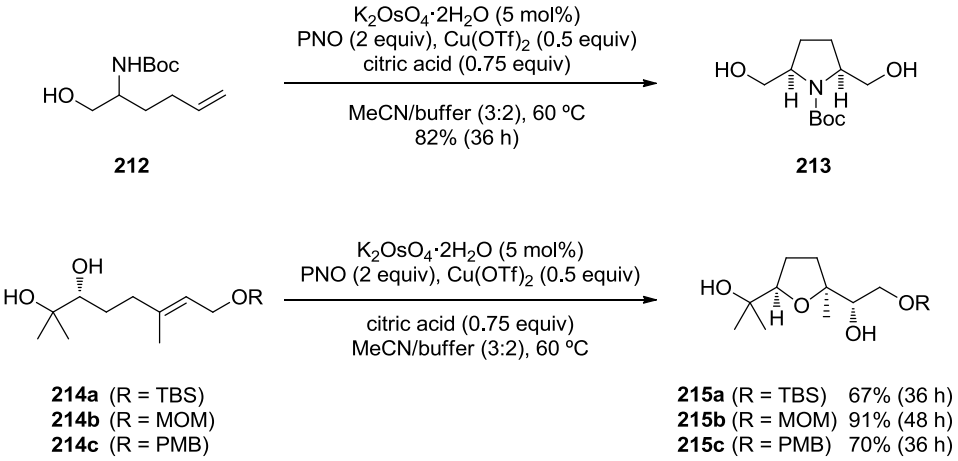
With the optimised conditions in hand, Donohoe successfully applied the Lewis acid-promoted oxidative cyclisation to the total synthesis of (+)-sylvaticin[103,104] and neodysiherbaine A[105] (Scheme 56).

Scheme 56 *Applications of the oxidative cyclisation to total synthesis*



The main benefit of removing TFA from the oxidative cyclisation procedure was to provide conditions which were compatible with a range of functional groups that would otherwise not undergo reaction under acidic conditions (with TFA). By utilising a pH 6.5 phosphate buffer instead of water, it was possible to cyclise substrates containing a range of acid-sensitive *N*- and *O*-protecting groups in high yields (Scheme 57). Despite the comparatively long reaction times, presumably due to the biphasic reaction mixture (as opposed to the monophasic unbuffered conditions), this modification allowed the cyclisation of vicinal diols and aminoalcohols to the corresponding THFs and pyrrolidines. This set of reaction conditions should allow the oxidative cyclisation to become a valuable synthetic tool for the synthesis of complex molecules.[102]

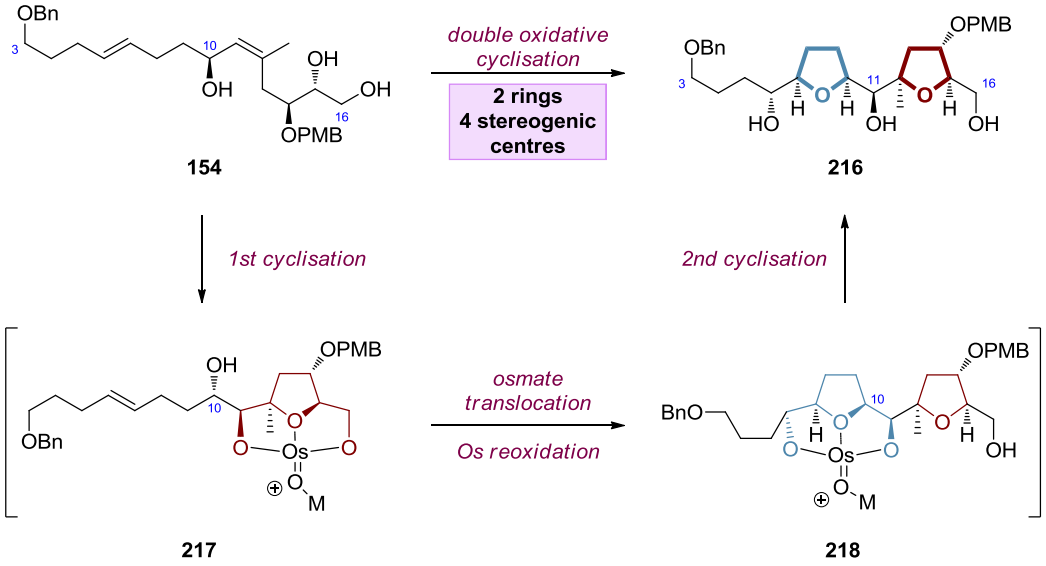
Scheme 57 *The development of the buffered oxidative cyclisation*



2.1.2.2 Application of the oxidative cyclisation to the construction of the BC ring system

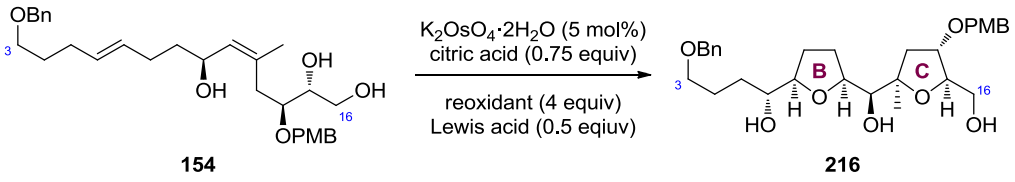
Having successfully prepared the key precursor **154**, the stage was set for the osmium-mediated oxidative cyclisation, in order to construct the BC fragment of pectenotoxin-4. Several features regarding this cyclisation should be noted. Firstly, if successful, this transformation would be the first example of a double oxidative cyclisation, whereby the initial cyclisation would install a second 1,2-diol, which in turn would facilitate a further oxidative cyclisation to take place. As described in Figure 16, we anticipated that the initial cyclisation would form the C ring whilst installing the C11 hydroxyl group (structure **217**); this cyclisation is crucial for translocation of the osmate ester (structure **218**) and a subsequent cyclisation (after reoxidation of osmium) to now afford the B ring of pectenotoxin-4 (**216**). This cascade cyclisation approach had not previously been investigated during the methodology studies and if successful, could serve as an excellent demonstration of the versatility of the method. Secondly, the planned transformation would be highly productive as it would construct two new rings and set four new stereogenic centres in one operation. Finally, this process could test the stability of acid-labile moieties, such as PMB protecting group and notably the sensitive allylic alcohol, under the reaction conditions.

Figure 16 *Proposed pathway for double oxidative cyclisation*



Whilst it was envisaged that the allylic alcohol moiety may be sensitive to the Lewis acidic nature of the oxidative cyclisation reaction, we first examined the use of standard conditions in order to determine whether precursor **154** would exhibit sufficient stability to successfully undergo the cyclisation. Pleasingly, treatment of **154** with 5 mol% of $K_2OsO_4{\cdot}2H_2O$ in combination with either $Cu(OTf)_2$ or $Zn(OTf)_2$ provided the desired bis-THF **216** in 29% and 37% yield respectively, after 48 hours (Table 9, entries 1 and 2).

Table 9 *Optimisation of the double oxidative cyclisation*

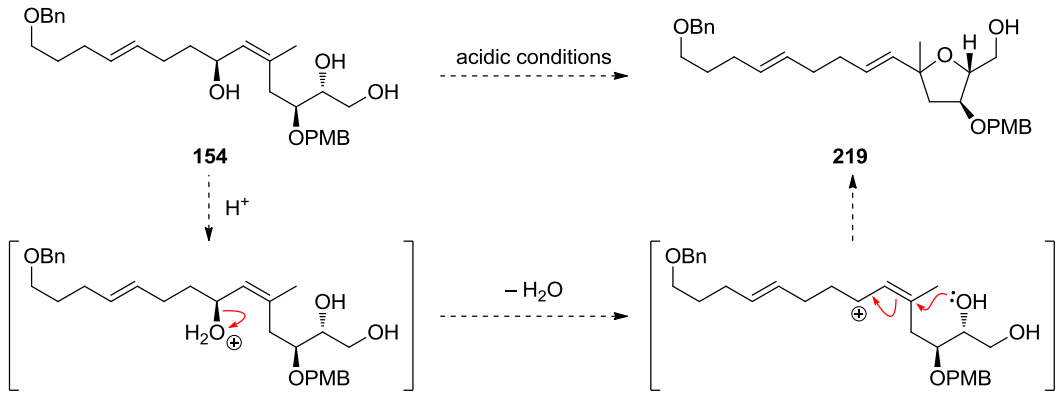


Entry	Lewis acid	Reoxidant	Solvent	Temp./°C	Yield/%
1	$Cu(OTf)_2$	PNO	MeCN/H_2O	60	29
2	$Zn(OTf)_2$	PNO	MeCN/H_2O	60	37
3	$Zn(OTf)_2$	PNO	MeCN/buffer	60	33
4	$Sc(OTf)_3$	PNO	MeCN/buffer	60	traces
5	$Cu(OTf)_2$	PNO	MeCN/buffer	80	55
6	$Zn(OTf)_2$	NPNO	MeCN/buffer	60	<20
7	$Zn(OTf)_2$	PNO	MeCN/buffer	80	69%

It was also noted that upon employing the unbuffered conditions, the desired bis-THF product was accompanied by a major side-product. Upon analysis of the ^{1}H NMR spectrum of this

product, it was revealed that the C6–C7 olefin remained intact, which suggested that the double oxidative cyclisation had not occurred. Secondly, both the peak corresponding to the C11 vinyl proton, as well as the allylic C10 proton signal had disappeared. Furthermore, the concomitant appearance of a new singlet at 5.64 ppm, integrating to two vinyl protons, indicated the formation of a new alkene moiety. Further analysis of the ^{13}C NMR spectrum revealed the loss of the C10 allylic carbon signal and the appearance of a new peak at 82.5 ppm, which was absent in ^{13}C DEPT experiment (indicative of a quaternary carbon atom). This observation led to the conclusion that under the unbuffered conditions the reaction mixture exhibits sufficient acidity to slowly decompose the sensitive allylic alcohol moiety. On the basis of these diagnostic observations we were able to assign the major by-product as mono-THF **219** (Scheme 58). It was proposed that under the more acidic (unbuffered) conditions that allylic alcohol **154** underwent rearrangement, with subsequent formation of a tetrahydrofuran ring. The formation of this side-product again reflected the acid-sensitive nature of **154**.

Scheme 58 *Proposed mechanism for the formation of side-product **219***



Considering the sensitive nature of the key precursor **154** (as highlighted in Section 2.1.1.4) it was decided that the oxidative cyclisation would potentially be most successful under the buffered conditions. Treatment of **154** with 5 mol% of $K_2OsO_4 \cdot 2H_2O$ in combination with $Zn(OTf)_2$ under the buffered reaction conditions (MeCN/pH 6.5 buffer) at 60 °C resulted in a slow reaction that afforded desired product **216** in 33% yield after 48 hours (Table 9, entry 3). It was noted that the desired product was accompanied by a significant amount of a side-product (20% yield). Although the nature of this product could not be fully identified, analysis of its ^{1}H NMR spectrum revealed the loss of the C11 olefin proton signal. It was also clear from the ^{1}H NMR spectrum that the C6–C7 alkene functionality remained intact. These

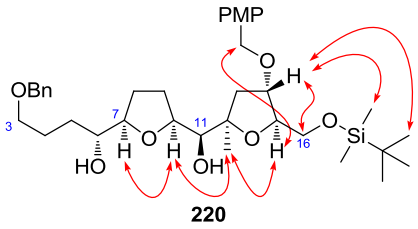
observations led to the conclusion that under the Lewis acidic buffered conditions, the rate of reaction was slow, resulting in only one oxidative cyclisation taking place. Furthermore, it was hypothesised that the second cyclisation would be inherently slower as the C10–C11 vicinal diol is sterically more hindered, thus, the formation of the corresponding osmate ester would be slower. It was therefore decided to employ more potent $Sc(OTf)_3$, however, the reaction under the buffered conditions disappointingly delivered a mixture of products (entry 4). This setback, however, was remedied by using more forcing conditions. Pleasingly, increasing the temperature to 80 °C in the presence of $Cu(OTf)_2$ provided the desired bis-THF **216** in 55% yield after 36 hours (entry 5). It should also be noted that the PMB protecting group remained intact under the reaction conditions.

Although the yield of the cascade oxidative cyclisation was satisfactory given the complexity of the transformation, we were drawn to gain more insight into the reaction as the formation of very polar by-products was observed. Previous work in our group showed that when an oxidative cyclisation was carried out at 90 °C, competing dihydroxylation of the starting material was observed. This is presumably due to an accelerated disproportionation of Os(VI) to Os(VIII) and Os(IV), or PNO being able to oxidise Os(VI) to Os(VIII) at high temperatures. In order to negate this problem, 4-nitropyridine *N*-oxide (NPNO) was alternatively employed as a reoxidant.[106] Previous studies within the group have shown that when utilising NPNO, higher yields of cyclised products were obtained, most likely as a result of the nitro group diminishing the oxidising power of the *N*-oxide species. Disappointingly, when NPNO was used instead of PNO the cyclisation of **154** afforded **216** in a very low yield of 20% along with other by-products (entry 6). Based on these results it was postulated to employ less potent $Zn(OTf)_2$ at higher temperature. To our delight, the reaction carried out at 80 °C provided desired bis-THF **216** as a single diastereoisomer in 69% yield after 36 hours (entry 7).

The formation of the BC ring system was verified by the absence of three olefin proton signals in the ^{1}H NMR spectrum with concurrent appearance of four new carbon peaks (out of which one was quaternary) in the region from 85–70 ppm in the ^{13}C NMR spectrum. Further evidence for the formation of two tetrahydrofuran rings was provided by NOE correlations of C16–OTBS derivative **220** (Figure 17). The strong interactions between the C(7)H and C(10)H, as well as C(12)CH_3 and C(15)H confirmed that both B and C THF rings were formed with complete stereoselectivity for the desired *cis*-2,5-relationship. Moreover, a correlation between the C(14)H and both C(16)H_2 and the *tert*-butyldimethylsilyl group indicated the (*S*)-stereochemistry at C14, which confirmed the *anti* selectivity of the

propargylation of glyceraldehyde acetonide **129**. This was further confirmed by an interaction between the C(15)H and benzylic CH_2 group of the *p*-methoxybenzyl moiety.

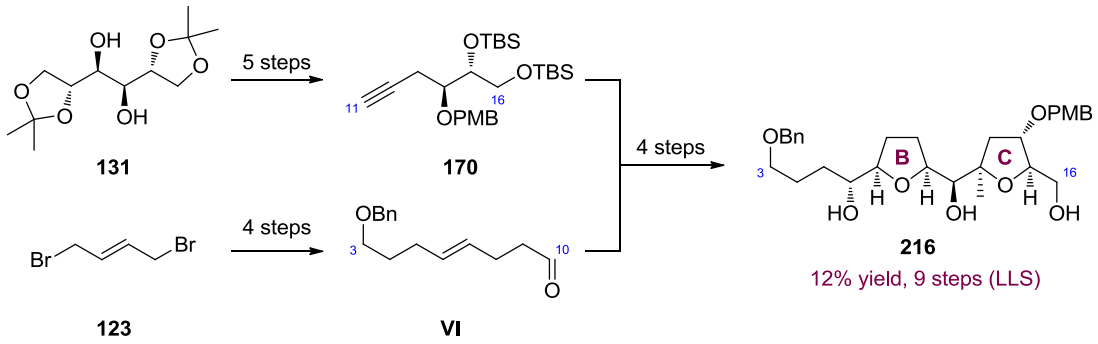
Figure 17 *Key NOE enhancements of bis-THF* ***220***



2.1.3 Summary

In summary, the C3–C16 BC fragment of pectenotoxin-4 was prepared in 9 linear steps from D-mannitol bisacetonide **131** (longest linear sequence, 13 steps total) and an overall yield of 12% (Scheme 59).

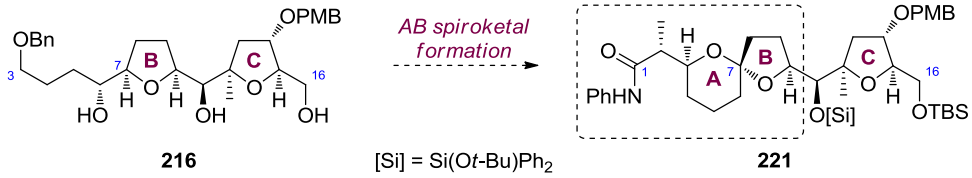
Scheme 59 *Summary of the synthesis of the BC ring system of pectenotoxin-4*



2.2 Development of hydride shift initiated spiroketalisation methodology and synthesis of the AB spiroketal of pectenotoxin-4

Having completed the synthesis of the BC fragment of pectenotoxin-4, we set out to investigate the formation of the AB spiroketal using simplified model systems. That could later be implemented to the fully elaborated construction of the ABC ring system (Figure 18).

Figure 18 *Projected installation of the AB spiroketal*

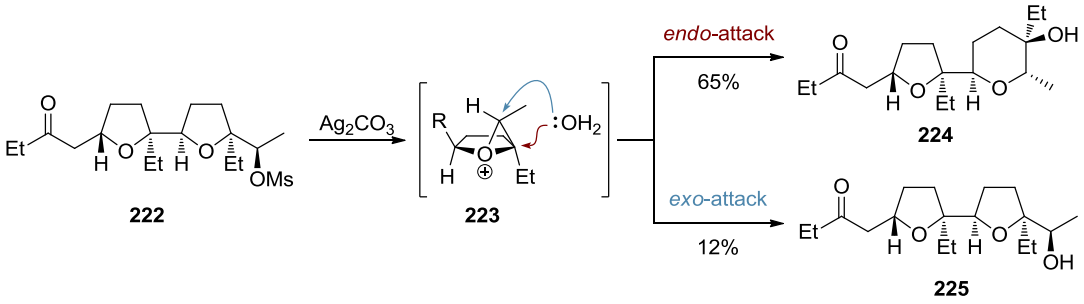


Key to these investigations would be the expansion of previously developed methodology by the Donohoe group, which utilised a hydride shift mediated rearrangement of *cis*-THFs to *trans*-THFs *via* the intermediacy of an *in situ* generated oxocarbenium ion. This chapter will provide discussion of precedent for rearrangement of 2,5-disubstituted THFs and the development of the hydride shift methodology to provide a novel entry to spiroketals.

2.2.1 Literature Precedent for the Rearrangement of 2,5-substituted THFs

The first example of a rearrangement of *cis*-2,5-THFs, bearing an activated alcohol adjacent to the ring, was a ring expansion to a tetrahydropyran (THP) reported by Kishi in 1978.[107] In this original protocol, exposure of mesylate **222** to silver carbonate in aqueous acetone resulted in the formation of bicyclic oxonium ion **223** which was solvolysed to a mixture of THP **224** and THF **225**, arising from *endo* and *exo*-attack, respectively (Scheme 60). This transformation was used in Kocienski's synthesis of salinomycin, whereby a similarly 2,2,5-trisubstituted THF was cleanly transformed into the corresponding THP.[108]

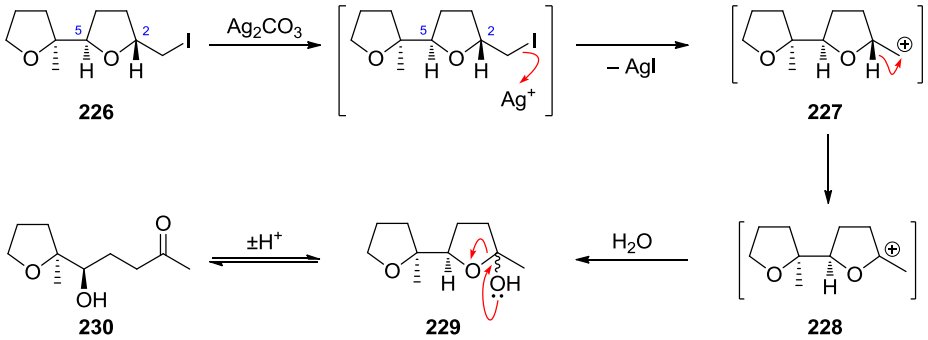
Scheme 60 *The first report of the rearrangement of THFs with activated alcohols*



Nakata subsequently showed, following an extensive screening of reaction conditions, that the use of zinc acetate in aqueous acetic acid at reflux improved yields of the isolated THPs, and that a bromine could serve as the leaving group.[109]

Following Kishi's work, Brimble reported that attempts to effect a similar rearrangement of *syn*-α-iodo THF **226** containing a tertiary carbon at the C2 ring junction resulted in the exclusive formation of ketone **230** (Scheme 61).[110] It was proposed that the hydrogen at the C2 junction underwent a [1,2]-hydride shift onto the primary carbocation **227**, generated by the abstraction of the iodide. The resulting tertiary carbocation **228** was trapped with water to form hemiketal **229**, which subsequently opened to the corresponding ketone. Therefore, Brimble postulated that the success of the ring expansion to a THP was reliant on the presence of a quaternary ring junction α to the leaving group, as present in that of Kishi (Scheme 60).

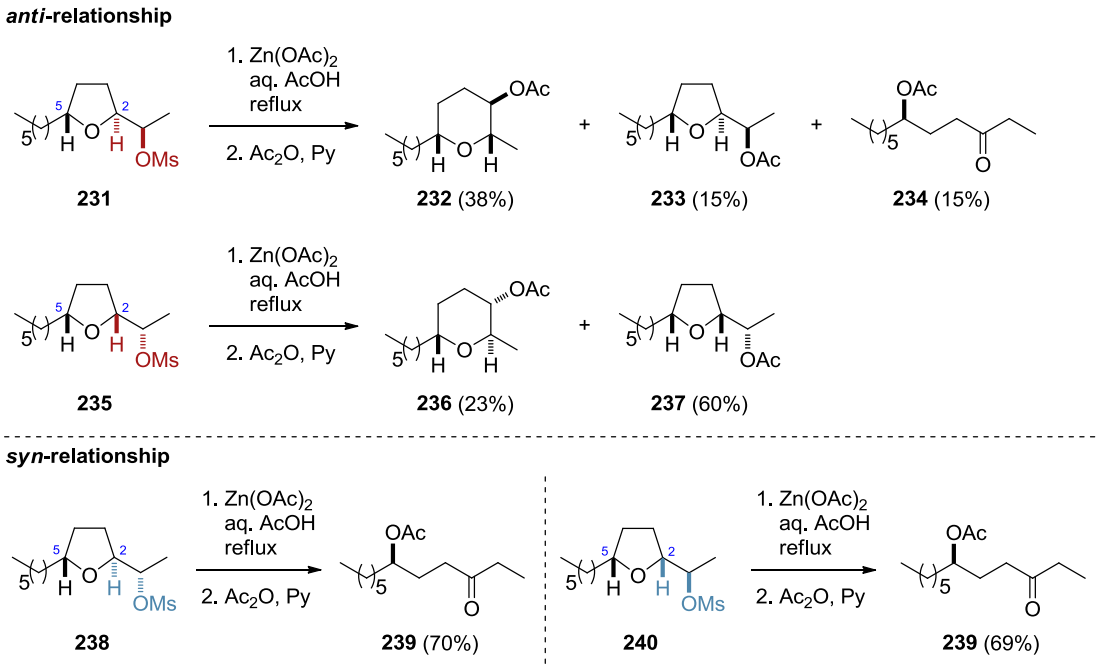
Scheme 61 *Brimble's Ag-promoted ketone formation*



In 1999 Nakata disclosed further investigations into the rearrangement of α-mesyloxy THFs.[111] Similar to Brimble's findings, attempts to trigger an analogous ring expansion upon exposure to $Zn(OAc)_2$ in refluxing aqueous acetic acid resulted in the formation of the corresponding ketones rather than THPs. Analysis of the obtained results revealed a

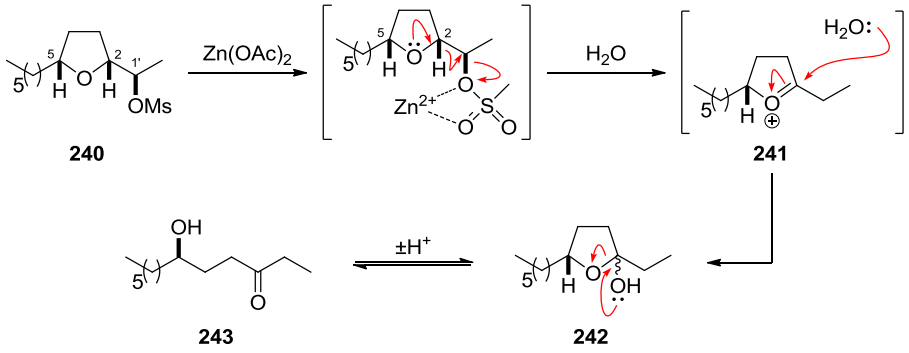
dependence on the relative stereochemical relationship between the carbon at the ring junction and the leaving group centre. When the mesylate and the hydrogen atom at the adjacent centre rest in an *anti*-relationship the ring expansion reaction proceeds in an analogous manner to that reported by Kishi, forming THPs and THFs (Scheme 62). In contrast, when the mesylate and the hydrogen have a *syn*-relationship, ketone formation dominates over ring expansion.

Scheme 62 *The role of stereochemistry in the rearrangement of THFs*



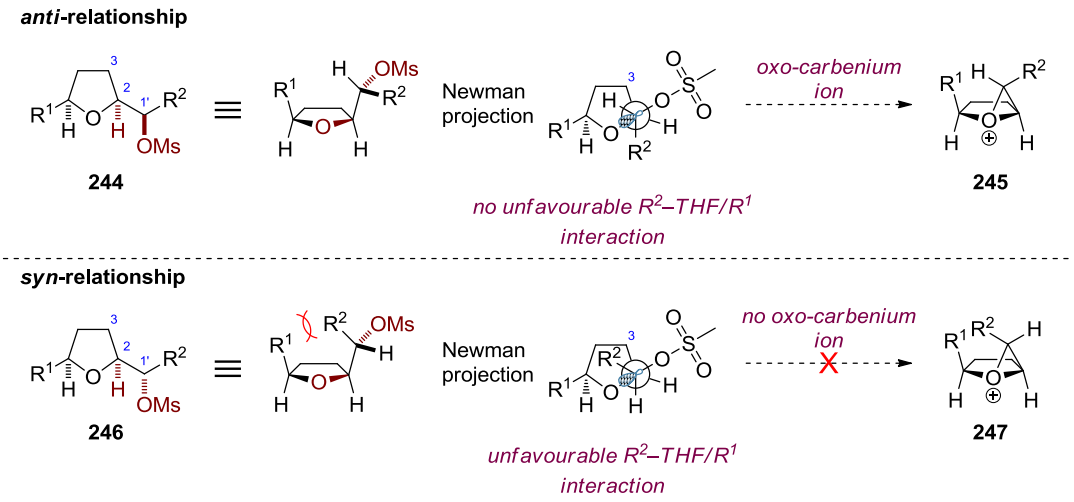
It was proposed that the ketone products were formed by a concerted hydride shift/mesylate displacement mechanism whereby the C2 hydrogen atom undergoes a [1,2]-shift onto the neighbouring C(1') carbon, breaking the C–OMs bond in the process (Scheme 63). This is facilitated by the lone pair on the oxygen atom that generates oxocarbenium ion **241**. This ion can be trapped by water to form lactol **242**, which opens to the keto form **243**.

Scheme 63 *Proposed mechanism of ketone formation*



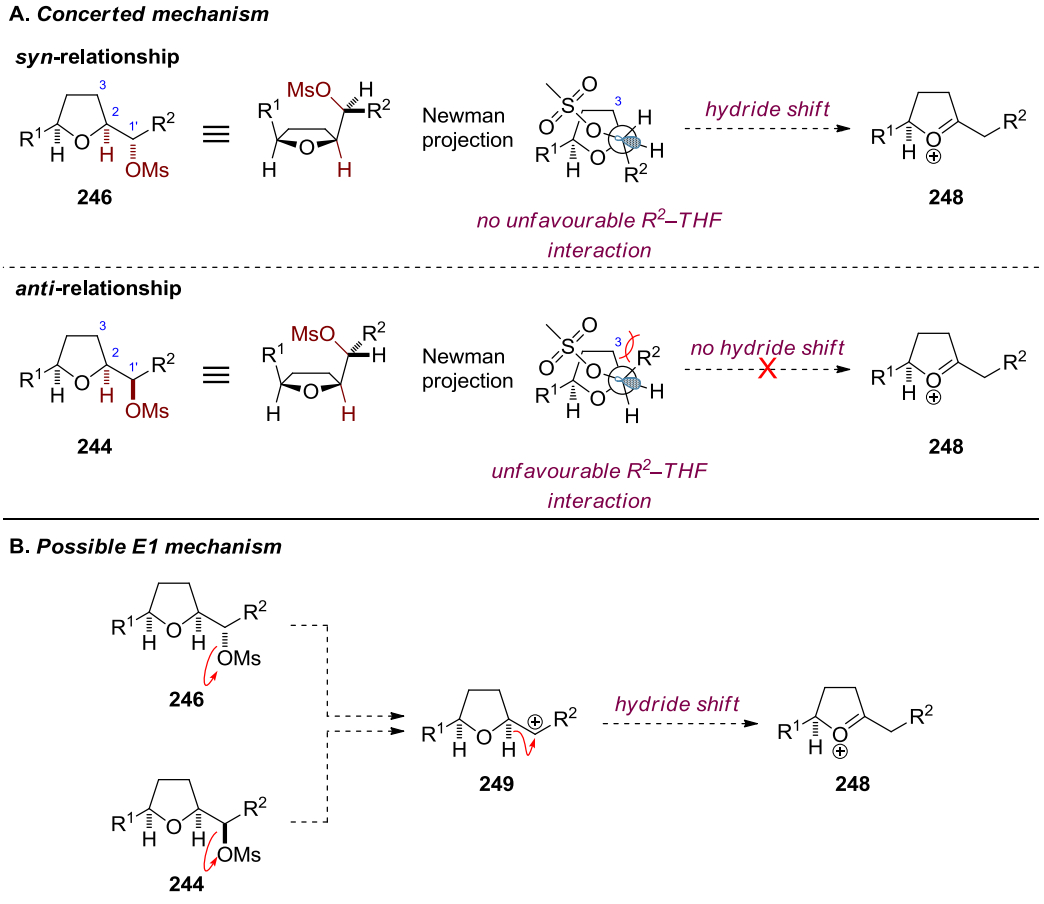
As mentioned, the relative stereochemistry of the hydrogen atom at the ring juncture and leaving group at the adjacent carbon influences the product distribution in the ring expansion reaction. This difference in reactivity can be rationalised by plausible transition states for the two pathways (Figure 19). In order for the ring expansion to take place the oxygen lone pair and the mesyloxy group are required to be in an antiperiplanar relationship to one another. This positioning allows for efficient overlap between the HOMO orbital of the tetrahydrofuran oxygen lone pair and the LUMO (σ* orbital) of the C–OMs group. To allow this orbital interaction substrate **244** possessing *anti* stereochemistry adopts a conformation in which the C(1')–H bond is positioned over the tetrahydrofuran ring and the C(1') substituent (R^2) points away from the ring. Such a conformation is easily accessible for **244** as there are no unfavourable steric interactions.

Figure 19 *Conformations leading to ring expansion*



In contrast, mesylate **246** with a *syn* stereochemistry does not react *via* this pathway as the required conformation produces a transition state significantly higher in energy due to unfavourable interaction between the THF backbone and the side chain. Instead, mesylate **246** undergoes a concerted hydride shift/mesylate displacement process which demands an antiperiplanar relationship between C(2)–H σ orbital and the C–OMs σ* orbital (Figure 20A). Such a conformation allows the hydrogen to undergo a [1,2]-shift by feeding its electron density into the σ* orbital of C–OMs to displace the bond. However, this conformation is disfavoured in *anti* substrate **244** as the required conformer of **244** places the side chain over the THF ring and thus the reaction suffers from unfavourable steric interactions with the C3–H substituent.

Figure 20 *Conformations leading to hydride shift and possible E1 mechanism*



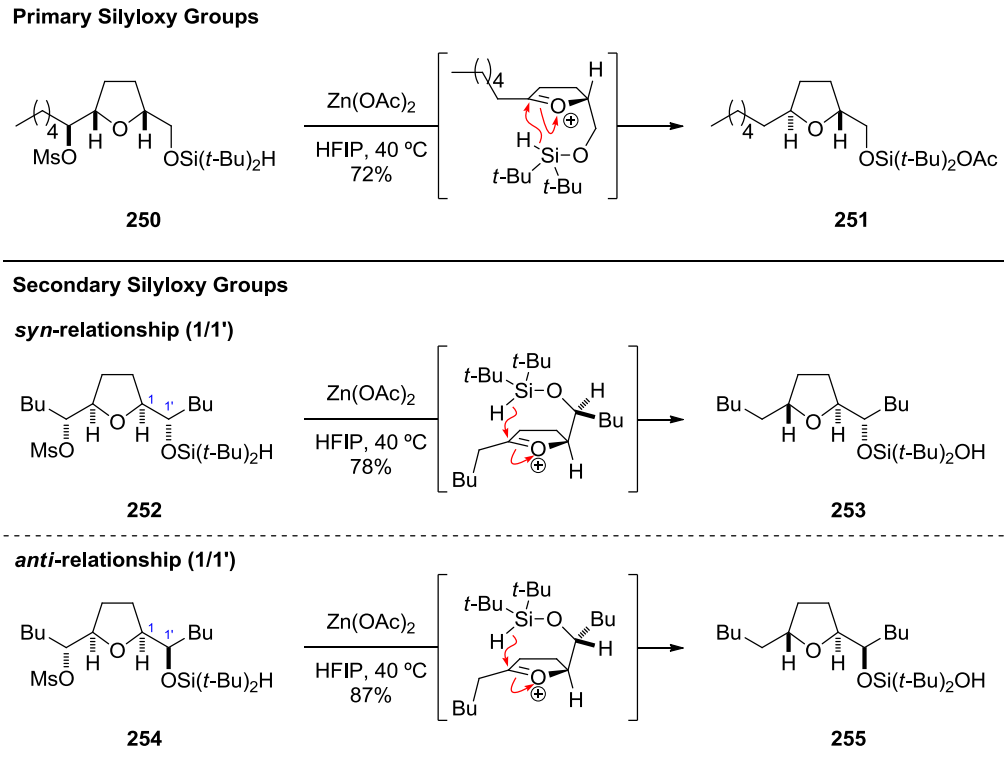
Notably, these observations did not concur with the stepwise elimination/hydride shift mechanism previously proposed by Brimble.[110] If an E1 mechanism were operative, a [1,2]-hydride shift onto planar carbocation should take place regardless of the relative stereochemistry in the substrate (Figure 20B). This would lead to a common intermediate **249**

and thus it should not affect the reaction outcome (with the assumption that the two diastereomers generate cation **249** at comparable rates).

2.2.1.1 Previous work on hydride shift in the Donohoe group

Although the groups of Brimble and Nakata have reported the generation of ketone products from the rearrangement of THFs bearing an activated adjacent hydroxyl group, the use of these motifs in synthesis has not been exploited. Inspired by these results, Donohoe and co-workers investigated the synthetic utility of this process concentrating upon the intramolecular trapping of the transient oxocarbenium ion generated in the reaction.[112] Of particular interest was the idea of exploiting this transformation in order to modify the stereochemistry of the ring juncture of parent *cis*-THFs produced in the oxidative cyclisation reaction. Since initial attempts to generate *trans*-2,5-THFs employing external hydride sources to trap the oxocarbenium ion, such as Et_3SiH, proved fruitless,[113] Donohoe turned attention to exploiting an intramolecular reduction by the use of tethered silicon hydride, such as on a di-*tert*-butylsilyloxyl group. It was found that treatment of a range of *cis*-THFs, which bore a tethered silane (primary or secondary), with $Zn(OAc)_2$ in a polar protic solvent (1,1,1,3,3,3-hexafluoroisopropanol (HFIP)) afforded the corresponding *trans*-2,5-THFs in good yields (Scheme 64).[114]

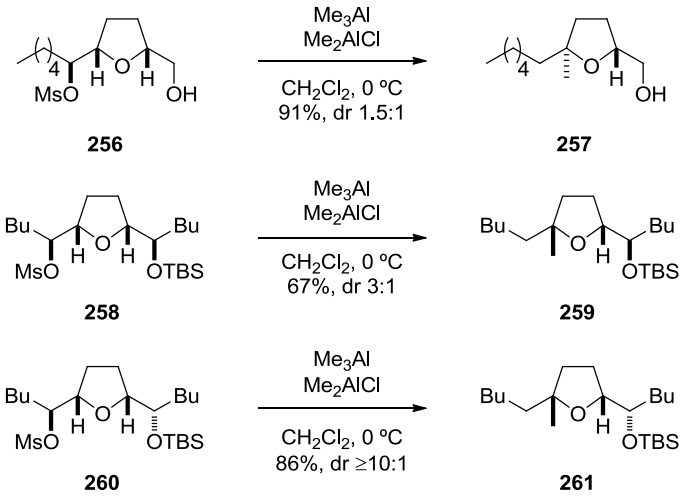
Scheme 64 *Donohoe's application of hydride shift in the formation of trans-THFs*



Hexafluoroisopropanol is an extremely polar solvent which has a very high ionising power and is an excellent hydrogen bond donor.[115] As a result the reaction could take place at temperatures as low as 40 °C in comparison to those of Nakata and Brimble which usually utilised high temperatures. Notably, the use of anhydrous conditions prevented the trapping of the oxocarbenium ion with water and the consequential formation of the open chain form. The obtained results showed that this methodology can be used in the synthesis of *trans*-THFs from the corresponding *cis*-THFs which bear either a *syn* or *anti* relationship between the hydrogen atom at the ring juncture and the adjacent silicon hydride functionality.

Donohoe and co-workers next attempted to extend the range of groups that could be installed at the C2 position by evaluating intramolecular organometallic addition onto the transient oxocarbenium ion. Although the use of *cis*-THF **256** bearing a free hydroxyl group to direct the addition was met with failure, delivering desired product **257** in only 1.5:1 diastereomeric ration, subjecting a range of THFs possessing *tert*-butyldimethylsilyl protected hydroxyl groups adjacent to the ring to the reaction with Me_3Al and Me_2AlCl resulted in predominantly intermolecular addition providing the corresponding *cis*-THFs with good yields and good to excellent diastereoselectivities (Scheme 65). The use of more potent Lewis acids enabled the experiments to be conducted at low temperature (0 °C) and in a less polar solvent (CH_2Cl_2).[114]

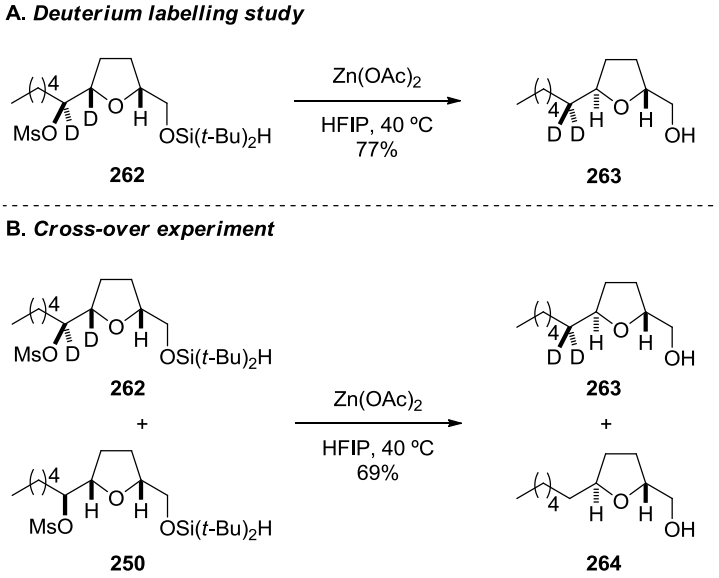
Scheme 65 *Introduction of an external nucleophile at the ring junction*



In order to conclusively prove that the transformation proceeded through a hydride shift mechanism, Donohoe and co-workers elected to conduct studies on deuterium labelled compounds. Subjecting **262** to the reaction with $Zn(OAc)_2$ in HFIP led to the formation of

trans-THF **263**, possessing the expected geminal deuteration pattern as the sole product (Scheme 66A). The reaction required 72 hours to reach completion, which was three times longer than in the case of **250**. This behaviour was consistent with a primary kinetic isotope effect, which served as circumstantial evidence in favour of a concerted mechanism, whereby the hydride shift is involved in the rate determining step, rather than the reduction of the oxocarbenium ion.

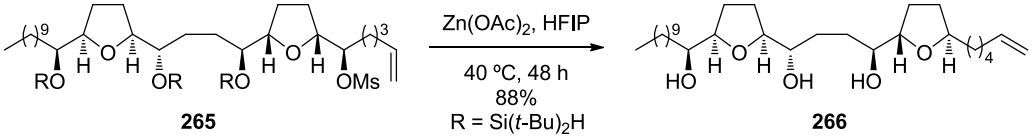
Scheme 66 *Deuterium labelling study of the hydride shift mechanism*



This result, however, did not preclude an elimination-type mechanism in which elimination of mesylic acid (MsOD), followed by deuteration of the resulting enol ether might give a similar result. Donohoe disproved this mechanism by conducting a crossover experiment. When a mixture of doubly deuterated *trans*-THF **262** and *trans*-THF **250** was exposed to the reaction conditions, only products **263** and **264** were detected, which strongly implied that the proposed mechanism was in operation (Scheme 66B).

This methodology was later applied to the first total synthesis of (+)-sylvaticin (Scheme 67).[104]

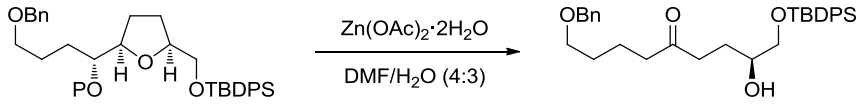
Scheme 67 *Application of the hydride shift methodology to the synthesis of (+)-sylvaticin*



2.2.1.2 Recent studies on the hydride shift methodology in the Donohoe group

Having demonstrated the possibility of trapping the oxocarbenium ion generated by a [1,2]-hydride shift with a selection of nucleophiles, work in the Donohoe group concentrated upon exploiting an intramolecular addition of pendent nucleophiles in order to provide a versatile entry to a range of spirocyclic scaffolds.[112,116] As part of the studies detailed in this thesis, initial forays were conducted into the application of the hydride shift methodology for the construction of spiroketals by a Part II student under my guidance. Studies were initiated by evaluating the formation of 6,5-spiroketals from *cis*-THFs, generated from the oxidative cyclisation. Subjecting *cis*-THF **267a**, bearing a benzyl ether and mesylate as a leaving group, to the hydride shift conditions previously employed by Nakata[109,111,117] (5 equivalents of $Zn(OAc)_2$ in a mixture of DMF and H_2O) at a range of temperatures, pleasingly afforded the desired ketone **268**, however in only poor yields (Table 10, entries 1–2).[116]

Table 10 *Initial attempts to generate ketone **268** via hydride shift*



267a–c **268**

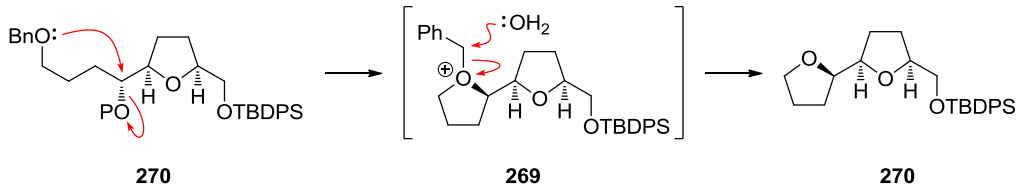
Entry	Leaving Group (P)	Substrate	Temperature/°C	Yield/%
1	Ms	**267a**	100	33
2	Ms	**267a**	80	34
3	Mc	**267b**	40	no reaction
4	Mc	**267b**	60	41
5	Ns	**267c**	40	53

In an effort to develop milder reaction conditions the use of alternative leaving groups was examined. During studies on ring expansion reactions, Nakata found that using chloromesylate (Mc) in place of mesylate often allowed the transformation to proceed under milder conditions and in a higher yield.[118] To explore this result chloromesylate **267b** was subjected to the hydride shift reaction at 60 °C delivering ketone **268** in 41% yield, while the reaction at 40 °C returned only starting material (Table 10, entries 3 and 4). Using even more reactive 2-nitrobenzenesulfonate (Ns) **267c** led to the formation of **268** in 53% yield at 40 °C (entry 5).

Conducting the experiments revealed that the overall yield of the hydride shift was largely limited by the formation of multiple side-products under the reaction conditions.

Examination of the reaction mixtures allowed the identification of the major impurity as unexpected bis-THF **270**, isolated in every instance as a single diastereoisomer. It was hypothesised that this compound arose from intramolecular S_N2-type displacement of the leaving group by the tethered oxygen nucleophile, followed by the loss of the benzyl group, presumably *via* nucleophilic attack by water (Figure 21).

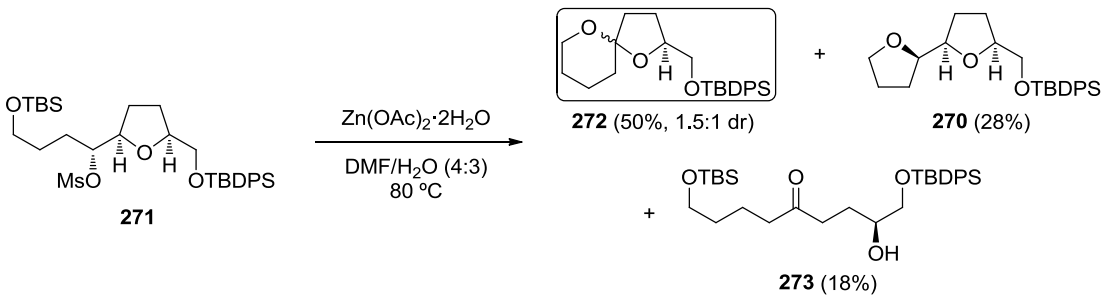
Figure 21 *Formation of bis-THF side product **270***



270 **269** **270**

Despite significant improvements to the conditions for this transformation, the yield remained relatively low as a result of the formation of the bis-THF **270** (up to 32% yield). To circumvent this problem it was therefore hypothesised that the use of an alternative protecting group may temper the reactivity of the pendent oxygen nucleophile. Therefore, focus was directed towards developing suitable reaction conditions that would allow direct access to the spiroketal **272** by means of a three-step one-pot hydride shift/spiroketalisation procedure. This approach required the employment of a protecting group which was deactivating with respect to bis-THF formation, but could also be cleaved *in situ* following the hydride shift. The formation of **272** in a one-pot sequence was achieved by utilising a TBS group. Subjecting THF **271** to the hydride shift reaction led to the direct formation of spiroketal **272** in a moderate yield of 50%; both bis-THF **270** (28% yield) and ketone **273** (18% yield) were also isolated as side-products (Scheme 68).[116]

Scheme 68 *One-pot hydride shift/spiroketalisation approach to spiroketal **272***



These preliminary results confirmed the validity of the novel strategy for constructing spiroketals by utilising the osmium-catalysed oxidative cyclisation and subsequent hydride shift reaction.

2.2.2 Development of hydride shift conditions towards the synthesis of 6,5-spiroketals

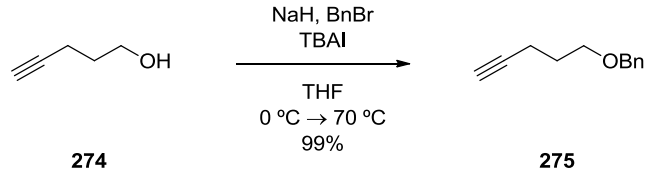
As discussed, previous work from within the group demonstrated an entirely novel concept for the construction of spiroketals and provided the foundations for developing the hydride shift/spiroketalisation sequence. The ultimate goal of these studies would be to test the validity of this novel approach in the synthesis of the AB spiroketal fragment of pectenotoxin-4.

The preliminary results revealed that the overall yield of the hydride shift/spiroketalisation sequence was predominantly restricted by inefficiencies associated with the hydride shift step. In order to develop this tandem transformation into a more general process it was necessary to further optimise the hydride shift conditions. The successful three-step one-pot procedure provided a convenient starting point from which investigations could continue. Since the use of a benzyl group to protect the pendent alcohol nucleophile led to the formation of the unwanted bis-THF compounds, we chose to explore the use of a silicon-based protecting group at this site. It was shown that the chloromesylate leaving group offered the best balance between maximising the yield and minimising the temperature required for the hydride shift to occur, therefore we elected to use this activating group in further optimisation. To initiate the studies it was first necessary to prepare a suitable hydride shift precursor, based on the skeleton of **271** that would be employed in the initial investigations.

2.2.2.1 Synthesis of the model system

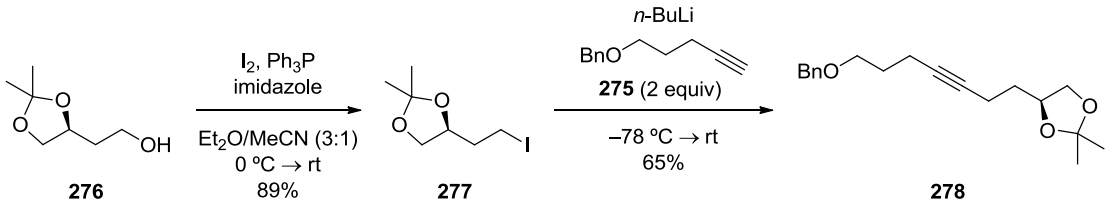
The synthesis of the model system began with the benzyl protection of commercially available 4-pentyn-1-ol (**274**) (Scheme 69). Although this protecting group was not to be used in our studies, we chose to temporarily employ it given its necessary stability towards all oxidative cyclisation conditions. Thus, treatment of **274** with benzyl bromide in the presence of catalytic TBAI afforded the desired benzyl ether in near-quantitative yield (99%).

Scheme 69 *Synthesis of benzyl ether **275** from alcohol **274***



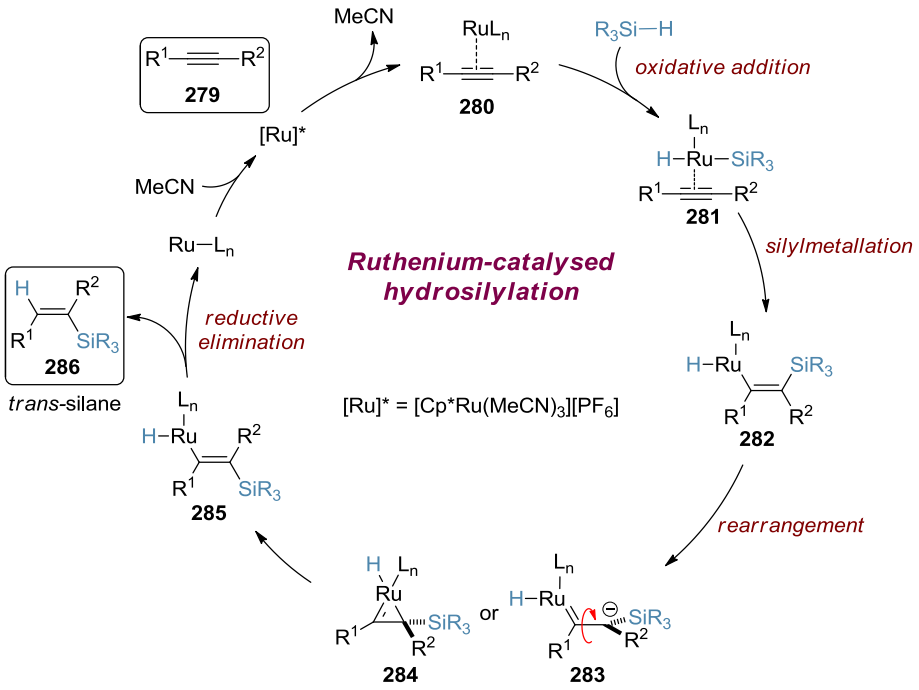
The synthesis of the second fragment commenced from alcohol **276**, which was transformed into iodide **277** *via* an Appel-type reaction in a good yield of 89% (Scheme 70). With both fragments in hand, attempts were made to couple them together to fashion internal alkyne **278**. Pleasingly, lithiation of **275**, followed by the slow addition of iodide **277** delivered the desired product in a good yield of 65%.

Scheme 70 *Synthesis of alkyne **278***



The next step required an (*E*)-selective reduction of alkyne **278** to provide the desired oxidative cyclisation precursor. Since the dissolving metal reduction (Li or Na in liquid ammonia), which is typically used for this transformation, would result in the cleavage of the benzyl group, attention focussed on alternative methods capable of delivering the desired reduction. The task was achieved by utilising a hydrosilylation/protodesilylation procedure developed by Trost.[119,120] The ruthenium complex $[Cp^*Ru(MeCN)_3][PF_6]$ has been shown to catalyse the *trans*-hydrosilylation of an alkyne to yield a mixture of vinylsilane regioisomers; the mixture is then protodesilylated with retention of the (*E*)-geometry using TBAF. The mechanism for the hydrosilylation process in not well understood, but a plausible explanation is provided by the modified Chalk–Harrod mechanism (Figure 22).[121]

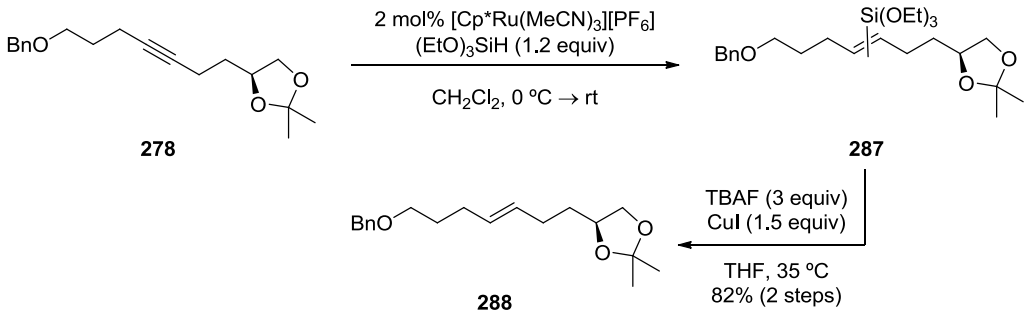
Figure 22 *Mechanism of hydrosilylation of alkynes*



It is proposed that alkyne **279** coordinates to the ruthenium catalyst displacing a labile MeCN ligand to form complex **280** which subsequently undergoes an oxidative addition of silane SiR_3–H to generate intermediate **281**. Following *syn*-silylmetallation of **281**, isomerisation takes place *via* complex **283** or **284** to form the (*E*)-olefin. This process in conceivably driven by the greater thermodynamic stability of the (*E*)-isomer, where steric interactions between the metal centre and the silicon substituent (–SiR_3) are minimised. Reductive elimination, which is postulated to be the rate-determining step, provides vinylsilane **286** with concomitant release of the catalyst. The regiochemistry of the hydrosilylation is governed by the preference of the metal catalyst to bind to the least hindered position of the alkyne.

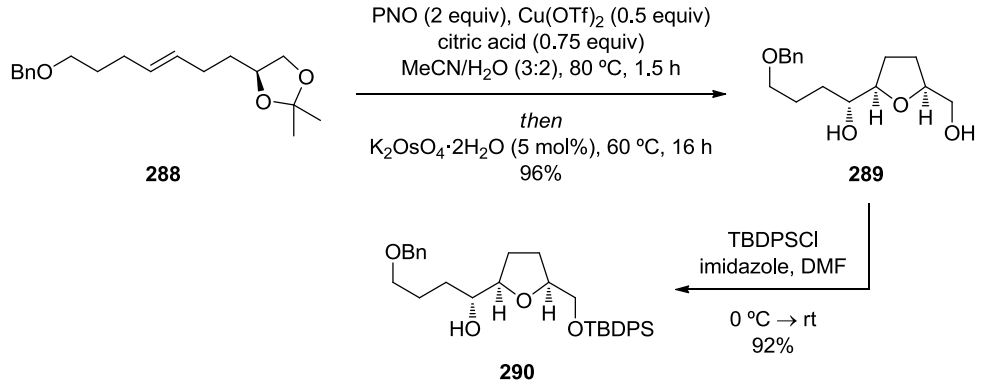
To this end, treatment of alkyne **278** with 1.2 equivalents of $(EtO)_3SiH$ in the presence of 2 mol% of $[Cp^*Ru(MeCN)_3][PF_6]$ catalyst afforded a 1:1 mixture of vinylsilane regioisomers, however, this result was inconsequential, as the silyl group would ultimately be replaced by hydrogen (Scheme 71). The crude mixture was subsequently exposed to 3 equivalents of TBAF along with a stoichiometric amount of copper(I) iodide (THF, 35 °C) furnishing the desired product in 82% yield over two steps.[122] The expected (*E*)-olefin geometry was verified by analysis of the coupling constants between the vinyl protons (10.2 Hz).

Scheme 71 *Application of hydrosilylation/protodesilylation to the formation of alkene **288***



Having obtained alkene **288**, it was then possible to access *cis*-THF **289** by employing the osmium-catalysed oxidative cyclisation reaction. Based on previous precedent in the group, instead of using a stepwise approach to remove the acetonide prior to cyclisation, we opted to utilise a one-pot procedure which allowed *in situ* deprotection to furnish the desired vicinal diol.[104] Pleasingly, subjecting **288** to the Lewis acid promoted oxidative cyclisation conditions provided *cis*-THF **289** in excellent yield (96%) (Scheme 72). The relative and absolute stereochemistry was assigned based on ample literature precedent. Subsequent protection of the primary hydroxyl group as a TBDPS ether delivered **290** in 92% yield.

Scheme 72 *Preparation of THF **290** employing an osmium-catalysed oxidative cyclisation*

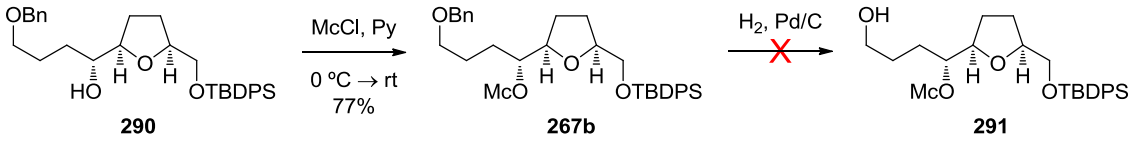


With a robust route to THF **290** established, we could initiate optimisation of the hydride shift conditions. It was envisaged that activation of the C4 hydroxyl group as a chloromesylate, followed by reductive removal of the benzyl group would provide alcohol **291**, which could serve as a platform for further modification of the C1 site. As may be expected, this transformation was anticipated to be nontrivial. To pursue this potential approach THF **290** was treated with chloromethanesulfonyl chloride (McCl) in pyridine to furnish chloromesylate **267b** in good yield (77%) (Scheme 73). The formation of the chloromesylate

moiety was verified by a diagnostic downfield shift of the C(6)H proton in the ^{1}H NMR spectrum, from 3.41 to 4.68 ppm, as well as downfield shift of the C6 carbon peak in the ^{13}C NMR spectrum, from 74.4 to 89.4 ppm.

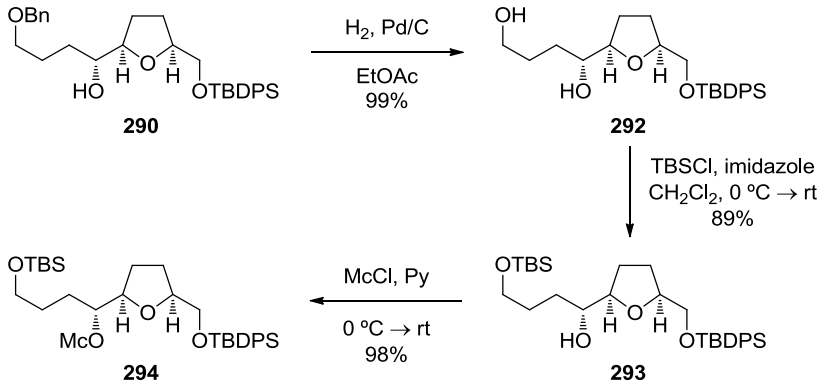
The isolated chloromesylate **267b** was then subjected to the hydrogenation reaction. Unfortunately, despite many attempts, including different catalysts, solvents and concentrations, all efforts to remove the benzyl group resulted in the formation of a complex mixture of products.

Scheme 73 *Unsuccessful generation of chloromesylate **291***



Given the difficulties encountered in the attempted hydrogenation of the benzyl group, we chose to pursue an alternate strategy for installation of the C3 and C6 functionalities. It was envisaged that initial deprotection of the Bn group would provide diol **292**, which could in turn give access to a range of differentially protected scaffolds. Therefore, THF **290** was exposed to hydrogenolysis using palladium on carbon as a catalyst (Scheme 74). Pleasingly, the reaction proceeded smoothly delivering diol **292** in near-quantitative yield (99%). The next step required selective TBS protection of the C3 hydroxyl group. This was achieved by utilising a stoichiometric amount of *tert*-butyldimethylsilyl chloride, affording the expected product in 89% yield. The regioselectivity was confirmed by a diagnostic downfield shift of the CH_2 carbon adjacent to the TBS ether in the ^{13}C NMR spectrum (from 62.8 to 63.1 ppm). Subsequent activation of the remaining hydroxyl group using chloromethanesulfonyl chloride delivered THF **294** in an excellent yield of 98%.

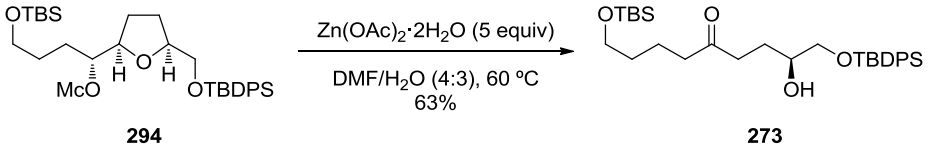
Scheme 74 *Synthesis of hydride shift precursor* ***294***



2.2.2.2 Model studies on hydride shift methodology

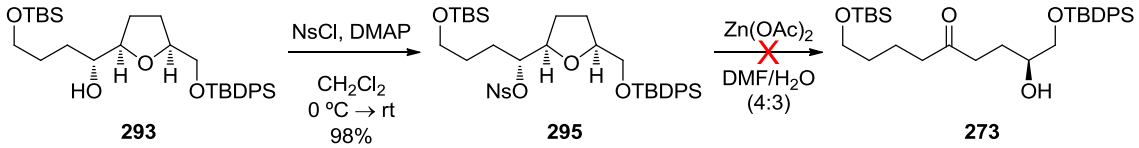
With model THF **294** in hand, hydride shift experiments could be attempted. Following previous work, **294** was treated with 5 equivalents of $Zn(OAc)_2$ in an aqueous DMF solution. When the reaction was conducted at 40 °C, only unreacted starting material was observed in the reaction mixture. Increasing the temperature to 50 °C resulted in a slow conversion of the starting material to the desired ketone. Best results were obtained when **294** was subjected to the reaction conditions at 60 °C, delivering ketone **273** in a good yield of 63% (Scheme 75). Unfortunately, attempts to effect ketone formation at higher temperatures (>80 °C) delivered complex mixtures of ketone **273**, bis-THF **270**, spiroketal **272** and other unidentified side-products.

Scheme 75 *Formation of ketone* ***273*** *using hydride shift methodology*



In an attempt to further lower the temperature, we examined the use of the even more reactive 2-nitrobenzenesulfonyl (nosyl, Ns) leaving group. Thus, alcohol **293** was treated with nosyl chloride to deliver the expected product in a high yield of 98% (Scheme 76).

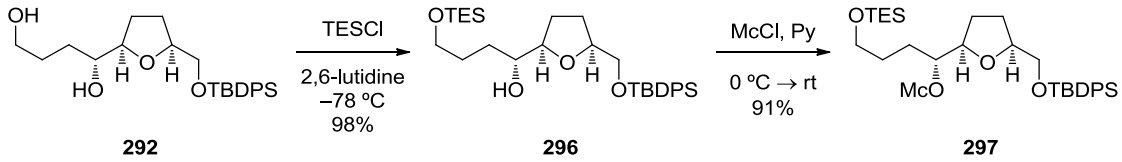
Scheme 76 *Attempts to utilise a nosyl group in the formation of ketone **273***



The enhanced reactivity of this system was evident from its decomposition when left to stand at room temperature, or even at 4 °C over several days. Nosylate **295** was subjected to the hydride shift conditions at several temperatures. Disappointingly, whilst the reaction at room temperature returned the majority of starting material after 12 hours, reactions conducted at 40 °C and higher yielded complex mixtures. This observation again confirmed that the use of chloromesylate leaving group at this site was most promising.

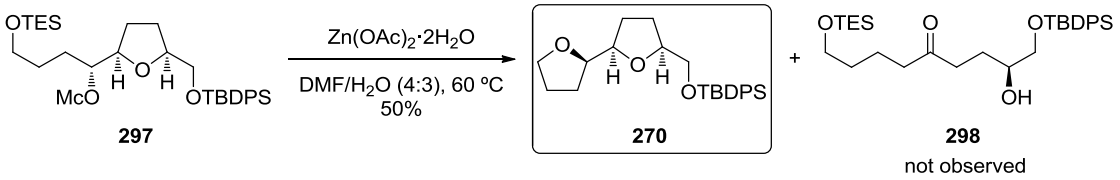
It was next pertinent to explore the use of a more labile TES group for the protection of the pendent C3 hydroxyl group. In order to prepare the required substrate, diol **292** was treated with a stoichiometric amount of TESCl at −78 °C to yield the desired mono-TES product **296** in 98% yield (Scheme 77). Subsequent activation of the C4 secondary alcohol using chloromethanesulfonyl chloride delivered THF **297** in a high yield of 91%. The formation of the primary TES ether in **296** was verified by a diagnostic downfield shift of the *C*H_2OTES carbon peak in the ^{13}C NMR spectrum.

Scheme 77 *Preparation of THF **297***



Chloromesylate **297** was then subjected to the hydride shift reaction at various temperatures. Similar to the analogous TBS example, the reaction at 40 °C led only to the recovery of the starting material. Further increase in the temperature to 50 °C resulted in a slow conversion of **297** to a new compound, while the reaction at 60 °C yielded a new product (50% yield), with only trace amounts of the desired ketone **298** (Scheme 78). Unfortunately, the isolated new product in both cases appeared to be the undesired bis-THF **270** resulting from an internal S_N2-type displacement of the leaving group. This could possibly be rationalised by a higher rate of cleavage of the TES group under the reaction conditions relative to the hydride shift process. The identity of **270** was determined by comparison to previously obtained data.[112,116]

Scheme 78 *Formation of bis-THF side product under hydride shift conditions*



2.2.3 Synthesis of the AB spiroketal of pectenotoxin-4

Having established suitable hydride shift conditions on model substrate **294**, it was pertinent to investigate whether this transformation could be improved by employing a substrate relevant to the synthesis of the AB fragment of pectenotoxin-4, where the pendent hydroxyl group is attached to a secondary carbon centre. It was reasoned that additional substitution at this site might decrease the rate of *in situ* deprotection of the protecting group on the pendent hydroxyl, as well as reduce the nucleophilicity of its oxygen atom and thus would suppress the formation of unwanted bis-THF derived side-products. Moreover, the use of substrates bearing a defined absolute configuration at this carbon atom could serve as a means to control installation of the quaternary spiroketal carbon stereocenter, formed under thermodynamic control.

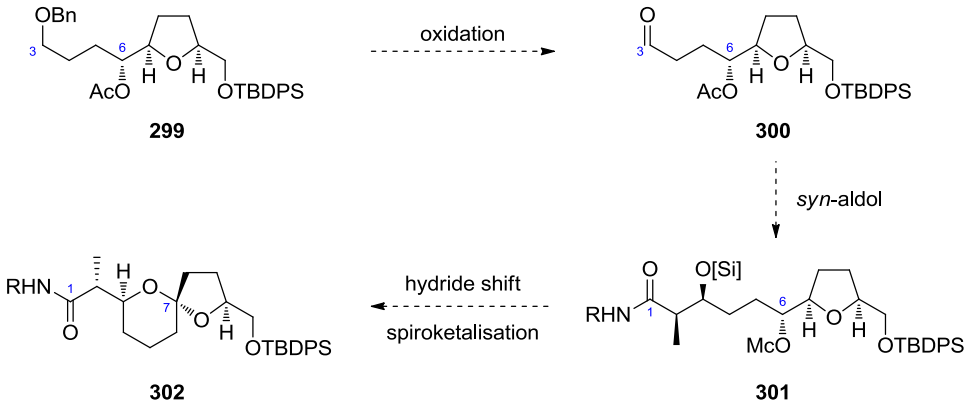
2.2.3.1 Preparation of the hydride shift precursor

With these considerations in mind, our attention turned to the preparation of a more elaborate system which would ultimately culminate in a synthesis of model AB spiroketal fragment **302**. This would serve as an ideal example to test the viability of this new methodology as well as to allude to the potential challenges that might be encountered in the implementation of this method to the synthesis of the ABC ring system of pectenotoxin-4.

In our synthetic planning it was anticipated that following the hydride shift reaction, the spiroketal **302** would adopt, on the basis of anomeric stabilisation and steric effects, its most thermodynamically favoured configuration (Scheme 79). We envisaged that the hydride shift precursor could be accessed *via* a *syn*-aldol reaction of aldehyde **300**, which could in turn be traced back to the corresponding protected alcohol **299**. Similar to previous studies, THF **290** would provide a suitable starting point for this new sequence. However, the main obstacle encountered during the investigations on simpler systems was an inability to cleave the benzyl ether in the presence of a chloromesylate ester. This problem could be addressed by introducing a temporary protecting group at the C6 site that would be removed prior to the

hydride shift/spiroketalisation sequence. Therefore, an acetyl group was chosen as it provided an orthogonal protection *en route* to spiroketal **302**.

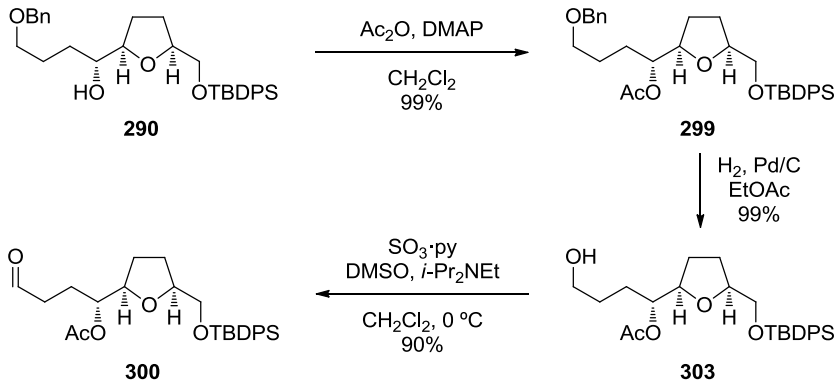
Scheme 79 *Plan for elaboration of THF **299** to the AB spiroketal fragment of pectenotoxin-4*



2.2.3.1.1 Installation of the C1–C2 fragment

Thus, our efforts to elaborate THF **290** to the complete C1–C11 fragment commenced with acetylation of the C6 hydroxyl group (Scheme 80). Treatment with acetic anhydride delivered the corresponding acetate (99% yield), which was then subjected to hydrogenation conditions providing primary alcohol **303** in near-quantitative yield over two steps. Subsequent Parikh–Doering oxidation afforded the corresponding aldehyde in an excellent yield of 90%.

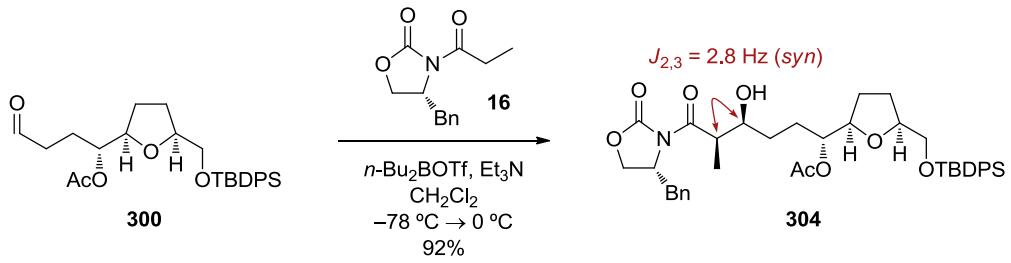
Scheme 80 *Formation of aldehyde **300** from THF **290***



With the aim of fashioning aldol **304** from aldehyde **300**, attention turned to installation of the C2 and C3 stereogenic centres *via* an Evans aldol reaction. Following the literature procedure,[123] *N*-propionyl oxazolidinone **16** was treated with dibutylboron triflate at

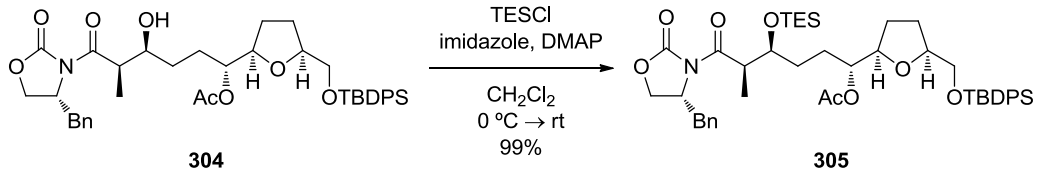
0 °C and the resulting enol borane was then allowed to react with aldehyde **300** at −78 °C, affording the desired aldol in high yield (92%) and as a single *syn*-diastereoisomer, as evidenced by ^{19}F NMR of the corresponding Mosher esters, and coupling constant analysis ($J_{2,3}$ = 2.8 Hz) (Scheme 81).

Scheme 81 *Generation of **304** using Evans aldol reaction*



Keen to build upon by the results obtained during initial optimisation studies of the hydride shift using a TES-protected substrate, we sought an explanation whether the hydride shift reaction would be successful by employing OTES ether attached to the secondary C3 centre. In order to protect the C3 hydroxyl group aldol **304** was treated with TESCl in the presence of imidazole and catalytic DMAP to afford TES ether **305** in 99% yield (Scheme 82).

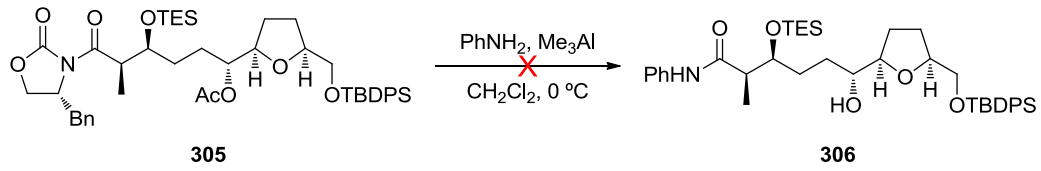
Scheme 82 *Protection of the C3 hydroxyl group of **304** to form **305***



During studies on total synthesis of pectenotoxin-4, following the aldol addition Evans and co-workers replaced the chiral auxiliary fragment with a phenyl amide moiety which offered the necessary stability under a range of conditions employed in their synthetic approach.[25,26,30,31] It also provided the carboxylic acid group handle required for a late-stage macrolactonisation to close the macrocyclic system of pectenotoxin-4. Based on this work, we attempted to elicit an analogous transformation in our system. It was hypothesised that exposure to aniline and trimethylaluminium would not only result in transamidation of the oxazolidinone, but could also remove the acetyl group from the C6 hydroxyl. If successful, this strategy could give access to alcohol **306** which after necessary activation could be subjected to the hydride shift reaction.

To this end, TES-protected aldol **305** was treated with aniline and trimethylaluminium (Scheme 83). Unfortunately, the reaction provided only a complex mixture of products. Further attempts to trigger the desired transformation by variation of the reagent quantities and conditions were met with failure.

Scheme 83 *Unsuccessful transamidation of **305** to form amide **306***

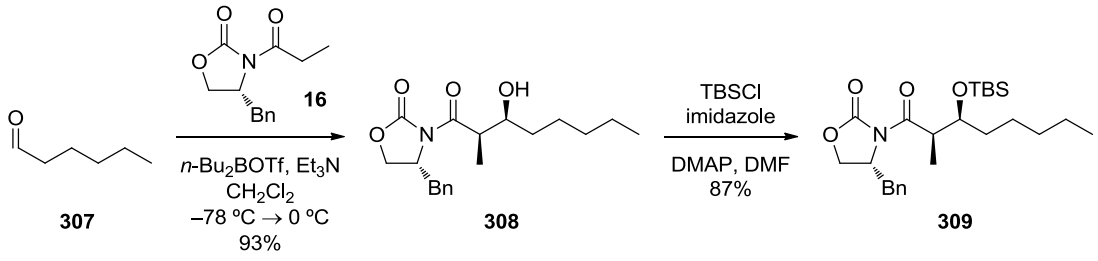


305 **306**

2.2.3.1.2 Model studies on transamidation of the chiral auxiliary

Intrigued by these unsuccessful results we decided to investigate the transamidation process on a simple protected aldol model system. Therefore aldol **308** was prepared from commercially available hexanal (**307**), utilising an Evans aldol reaction that provided the expected *syn*-product in 93% yield (Scheme 84). Subsequent TBS-protection using TBSCl afforded product **309** in a high yield of 87%.

Scheme 84 *Synthesis of model system **309***

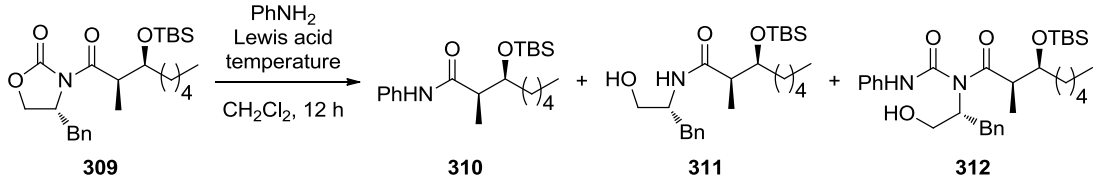


307 **308** **309**

With a suitable model substrate in hand, we attempted the transamidation under a range of conditions. Whilst exposure of **309** to either 1 or 2 equivalents of aniline and Me_3Al at room temperature resulted in no reaction (Table 11, entries 1 and 2), the use of 5 equivalents of both reagents delivered a mixture of three major products after 24 hours (entry 3). Careful inspection of the spectroscopic data showed that desired phenylamide **310** (21% yield) was accompanied by amide **311** (26% yield) and diamide **312** (23%). Increasing the amount of aniline and Me_3Al led to a slight improvement in yield of the desired product (42%) (entry 4). The best result was achieved when **309** was treated with 5 equivalents of $PhNH_2$ and Me_3Al at 40 °C furnishing phenylamide **310** in 50% yield after 24 hours, although

the desired product was still accompanied by a significant amount of diamide **312** (47% yield, entry 5). Interestingly, the use of more reactive Me_2AlCl resulted in exclusive formation of amide **311** in 68% yield with only trace amounts of phenylamide **310** (entry 6).

Table 11 *Screening of transamidation conditions on protected aldol **309***

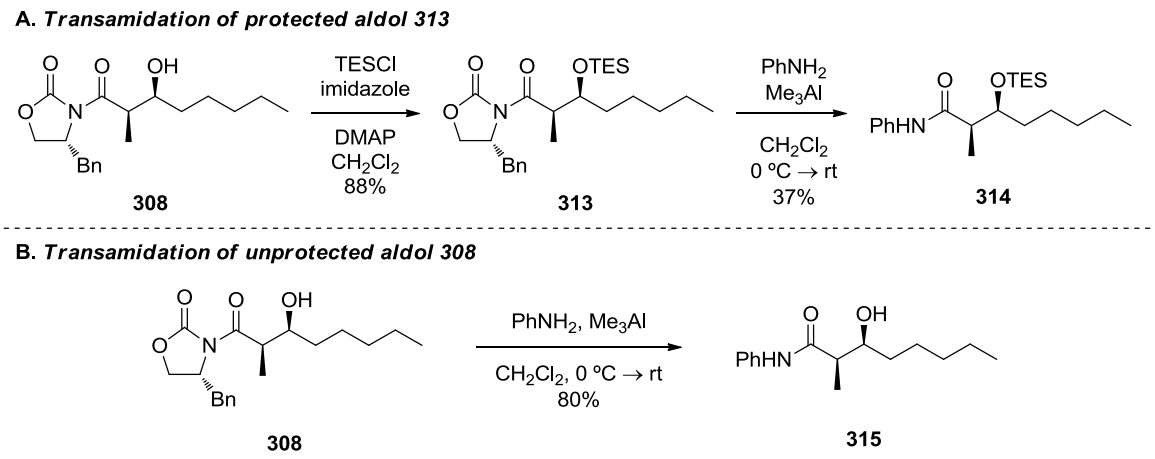


309 310 311 312

Entry	Aniline (equiv)	Lewis acid (equiv)	Temperature	Yield/%		
				310	311	312
1	1.0	Me_3Al (1.0)	rt	---	---	---
2	2.0	Me_3Al (2.0)	rt	---	---	---
3	5.0	Me_3Al (5.0)	rt	21	26	23
4	10.0	Me_3Al (10.0)	rt	42	---	---
5	5.0	Me_3Al (5.0)	reflux	52	---	47
6	5.0	Me_2AlCl (5.0)	rt	traces	68	---

In order to compare the effect of a TES group on the transamidation process, aldol **308** was reacted with TESCl to provide **313** in 88% yield (Scheme 85A). Subjecting TES protected aldol **313** to the transamidation conditions (Me_3Al (10 equiv), aniline (10 equiv), room temperature) afforded phenylamide **314** in only 37% yield.

Scheme 85 *Transamidation of protected aldol **313** and unprotected aldol **314***



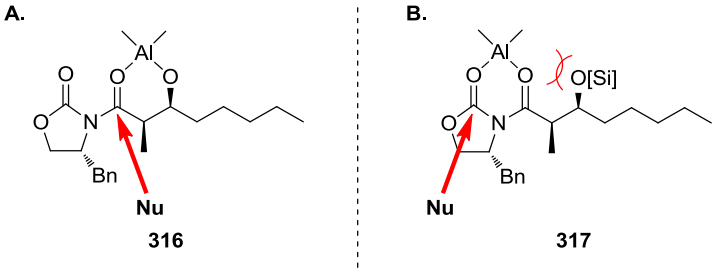
308 313 314

308 315

In contrast, when unprotected aldol **308** was exposed to a mixture of aniline and Me_3Al a clean transamidation ensued affording the corresponding phenylamide **315** in a high yield of

82% (Scheme 85B). These results led to the conclusion that in the case of unprotected aldol **308**, Me_3Al chelates to the hydroxyl group forming chelate **316** and thus directs the attack of nucleophiles at C1 (Figure 23A), whereas in the presence of a sterically encumbering protecting group, the Lewis acid preferentially forms complex **317** which activates both carbonyl groups (Figure 23B). As a result a mixture of products is observed.

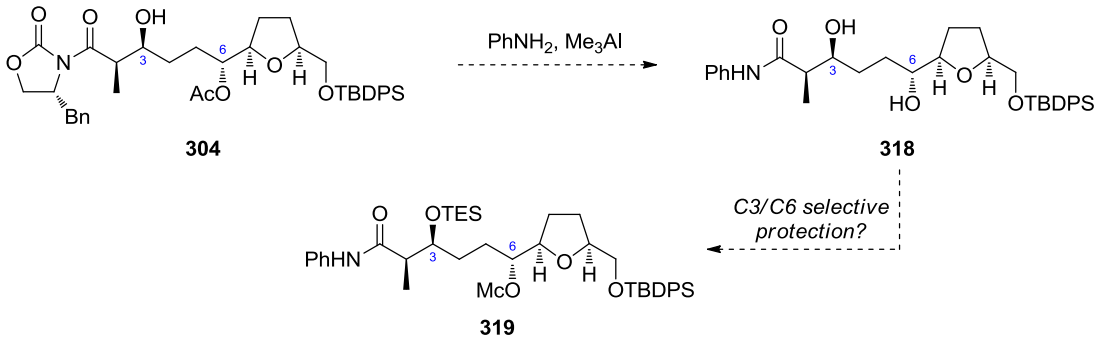
Figure 23 *Proposed rationale for a difference in regioselectivity of transamidation*



2.2.3.1.3 Completion of the preparation of the hydride shift precursor

From these model results it became evident that in order to obtain high yields, the desired transamidation should be carried out on aldol **304** rather than its C3-protected derivatives. This potential strategy change, however, might lead to concomitant cleavage of the acetyl group which would generate diol **318** (Scheme 86). Consequently, the formation of **319** possessing two secondary hydroxyl groups would likely preclude orthogonal protection. Moreover, considering the rather harsh conditions required for the desired transamidation, we decided to abandon the use of phenylamide as a protecting group.

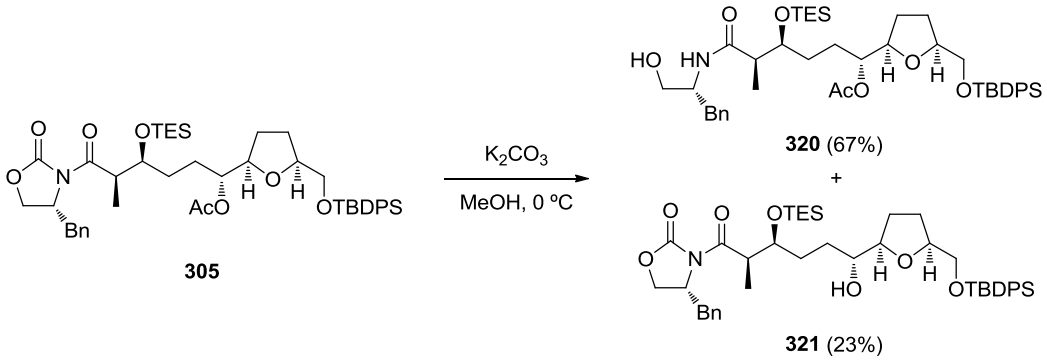
Scheme 86 *Possible complications after transamidation of THF **304***



Instead, attention turned to selective removal of the acetyl group to fashion alcohol **321**. It was anticipated that exposure of **305** to basic hydrolysis should selectively cleave the

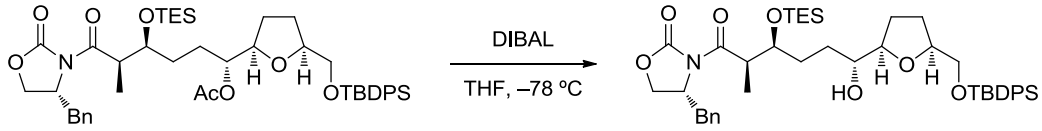
ester functionality. Thus, acetate **305** was subjected to basic conditions employing K_2CO_3 in methanol (0 °C) (Scheme 87). Unfortunately, the major product observed under these conditions was amide **320** resulting from hydrolysis of the carbamate moiety with only trace amounts of the desired alcohol being observed. Attempts to utilise other bases were found to offer no improvements.

Scheme 87 *Attempts to facilitate hydrolysis the acetate group of **305** under basic conditions*



We therefore sought to explore reductive conditions in order to effect the desired transformation. Although the use of aluminium or boron hydrides is known to reduce oxazolidinone-type chiral auxiliaries, it was reasoned that lowering the reaction temperature might allow for sufficient discrimination in order to selectively reduce the C6 acetyl group. In an initial screen we investigated the use of DIBAL in a dilute THF solution. Exposure of **305** to 1 equivalent of DIBAL at −78 °C resulted in selective removal of the acetyl group, however the product was isolated in a very low yield with most of the starting material recovered (Table 12, entry 1). Satisfyingly, the use of 2 equivalents of DIBAL afforded the desired product in 53% yield (entry 2). Further increase in the amount of DIBAL led to higher yields, with the best result obtained using 5 equivalents of DIBAL (83% yield, entry 4). Attempts to utilise a greater excess of DIBAL or higher concentrations led to no improvement in yield of **321**.

Table 12 *Optimisation of reductive removal of the acetate group of THF **305***

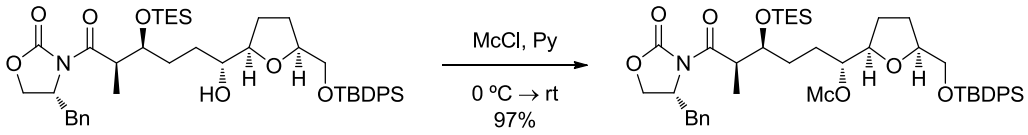


305 **321**

Entry	DIBAL (equiv)	Yield 321/%
1	1.0	35
2	2.0	53
3	3.0	72
4	5.0	83

Following an efficient approach to furnish alcohol **321**, the required activation of the C6 hydroxyl group was achieved by treating **321** with chloromesyl chloride to provide chloromesylate **322** in 97% yield (Scheme 88).

Scheme 88 *Preparation of hydride shift precursor **322** from alcohol **321***



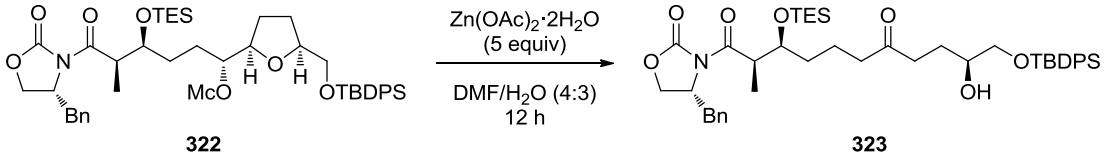
321 **322**

2.2.3.2 Application of the hydride shift methodology to the synthesis of the AB spiroketal

With the necessary precursor **322** in hand, the stage was set for the key hydride shift reaction. Results of our screening are presented in Table 13. Given the lability of the primary OTES group under the reaction conditions in previous studies, chloromesylate **322** was subjected to the previous best set of conditions. Pleasingly, the reaction at 60 °C yielded desired ketone **323** in modest yield (34%) with a considerable amount of unreacted **322** also recovered (36% yield) (entry 1). Elevation of the reaction temperature to 70 °C led to a slight increase in yield (42%), while execution of the same transformation at 75 °C provided the desired product in 53% yield, which was accompanied only by trace amounts of unreacted **323**. It was gratifying to note that no evidence of the bis-THF side-product was ever encountered, which supported the notion that the increased steric hindrance surrounding the C3–OTES moiety effectively retarded the unwanted TES deprotection. The formation of **323**

was confirmed by the appearance of a carbon peak at 210.8 ppm in the ^{13}C NMR spectrum and the absence of the proton and carbon signals corresponding to the chloromesylate moiety.

Table 13 *Optimisation of hydride shift conditions to generate ketone **323** from THF **322***

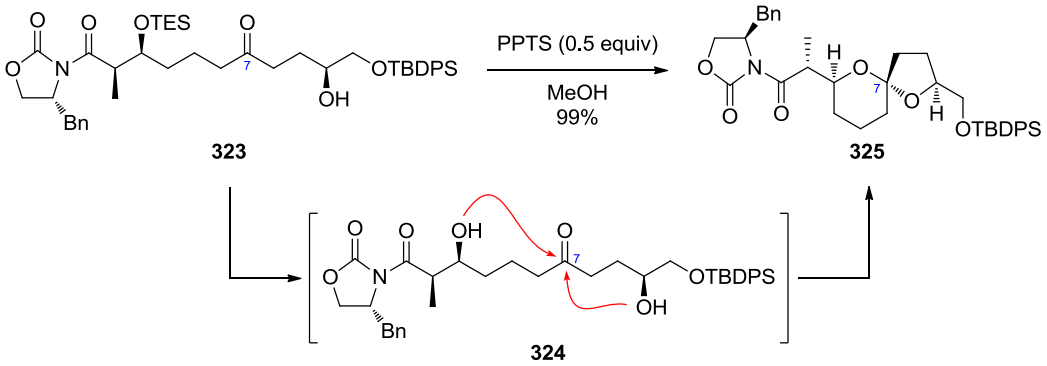


322 **323**

Entry	Temperature/°C	Yield 323/%
1	60	34 (36 rsm)
2	70	42
3	75	53

With a suitable set of conditions to trigger an efficient hydride shift process, attention focused upon construction of AB spiroketal model fragment **325**. Based on substantial literature precedent for deprotection of a secondary TES ether in the presence of a primary TBDPS ether, we anticipated that cleavage of the TES group would trigger *in situ* spiroketalisation furnishing **325**. To this end, ketone **323** was treated with a substoichiometric amount of PPTS in MeOH. To our delight, these reaction conditions resulted in fast formation of desired spiroketal **325** in near-quantitative yield (99%).

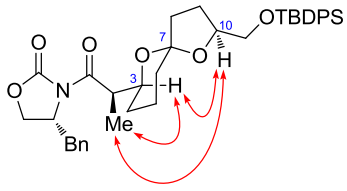
Scheme 89 *Spiroketalisation of ketone **323** to form AB spiroketal **325***



Analysis of the spectral data indicated the presence of only one diastereoisomer, which strongly suggested that spiroketal **325** had adopted the most thermodynamically favoured conformation. This was confirmed by diagnostic NOE enhancements (Figure 24). It was assumed that the configuration of the 6,5-spiroketal would stem from anomeric stabilisation as well as an inherent preference to adopt a conformation in which the C1–C2 side chain

occupies the more sterically-favoured equatorial position. Accordingly, the most telling NOE interactions were noted between C10–H and C3–H, as well as between C10–H and the methyl group at C2.

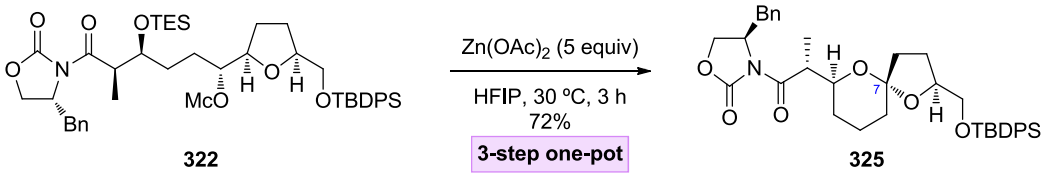
Figure 24 *Key NOE enhancements of* ***325***



325

Since it was previously shown that the hydride shift could be achieved at temperatures as low as 40 °C using hexafluoroisopropanol as a solvent, we speculated whether the reaction temperature could further be lowered, and potentially improved, by utilising these conditions. Our investigation began with treating chloromesylate **322** with 5 equivalents of $Zn(OAc)_2$ in HFIP. Since the chloromethanesulfonyl group proved more reactive than the mesyl group we decided to initiate the reaction at a lower temperature of 30 °C. Complete conversion of starting material was observed after only 3 hours. It was gratifying to find that the isolated product identified was not the expected ketone **323**, but spiroketal **325**, which likely arose from the hydride shift reaction, followed by *in situ* deprotection of the C3–OTES ether and subsequent spontaneous spiroketalisation to fashion **325** in a good yield of 72%. It is likely that the acetate anion attacked the silicon centre of the triethylsilyl group to form an "ate" complex prior to spiroketalisation, facilitating *in situ* cleavage of this group.

Scheme 90 *One-pot formation of the AB spiroketal of pectenotoxin-4 from THF* ***325***



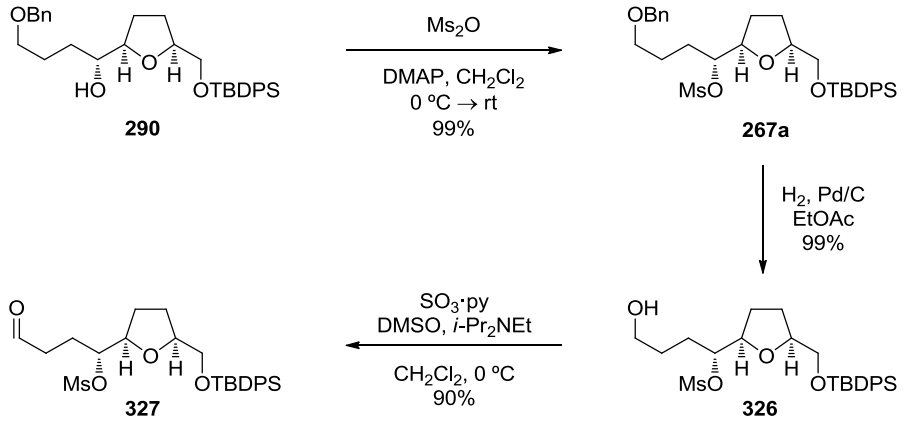
322 **325**

Analysis of the ^{1}H and ^{13}C NMR data revealed that the product, as expected, was identical to that obtained *via* a stepwise approach.

Having demonstrated the efficiency of the hydride shift/spiroketalisation strategy for constructing spiroketal motifs, we next turned to improving the operational simplicity of this

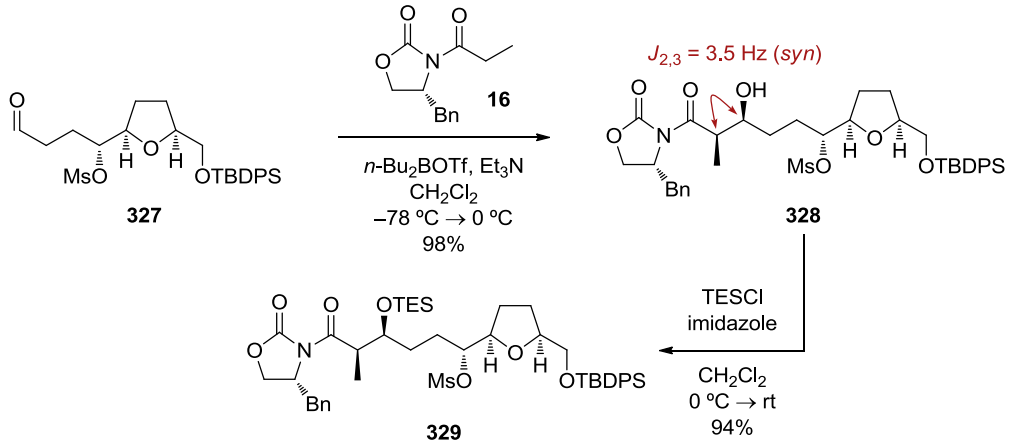
tandem sequence. In order to reduce the overall number of steps we questioned whether the need for interim acetate protection could be obviated by employing the less reactive methanesulfonyl group (in comparison to chloromethanesulfonyl group) as an activating group. To probe this potential strategy, a modified synthetic route was forged (Scheme 91). Thus, alcohol **290**, previously obtained *via* oxidative cyclisation, was directly activated using methanesulfonic anhydride, affording mesylate **267a** in an excellent yield of 99%. Pleasingly, exposure of **267a** to hydrogenation conditions resulted in a clean reaction, providing primary alcohol **326** in 99% yield. Subsequent oxidation to the corresponding aldehyde **327** was achieved using either Parikh–Doering (90% yield) or Dess–Martin periodinane oxidation (86% yield).

Scheme 91 *Synthesis of aldehyde **327** from THF **290***



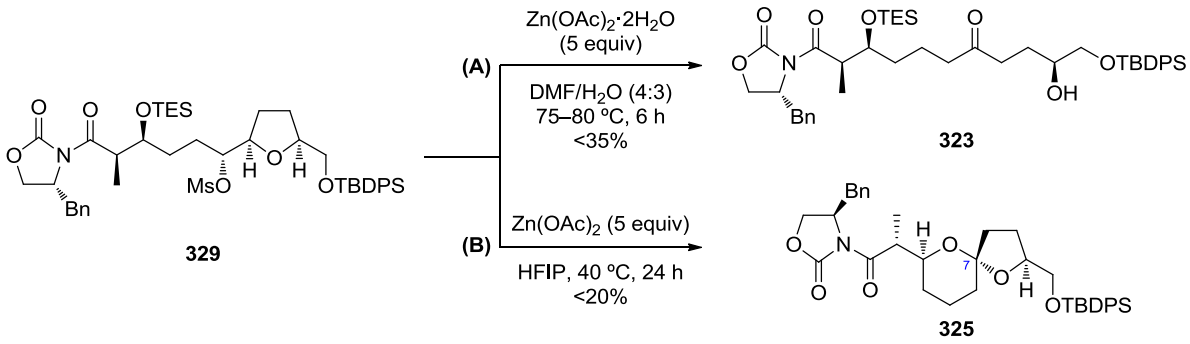
Aldehyde **327** was then transformed into *syn*-aldol **328** *via* an Evans aldol addition (Scheme 92). The installation of the *syn* diastereoisomer was verified by coupling constant analysis, which revealed a characteristic vicinal coupling constant $J_{2,3}$ = 3.5 Hz. The preparation of the hydride shift precursor **329** was accomplished by treating **328** with TESCl to give the desired product in high yield (94%).

Scheme 92 *Preparation of hydride shift precursor* ***329***



With mesylate **329** hand, we attempted to effect the hydride shift transformation. Surprisingly, employing optimal aqueous conditions resulted in a very poor conversion to desired ketone **323**, even at higher temperatures and with increased amounts of the Lewis acid (Scheme 93A). The reaction usually yielded a mixture of products with variable amounts of the starting material being recovered.

Scheme 93 *Attempts to facilitate hydride shift on chloromesylate* ***329***

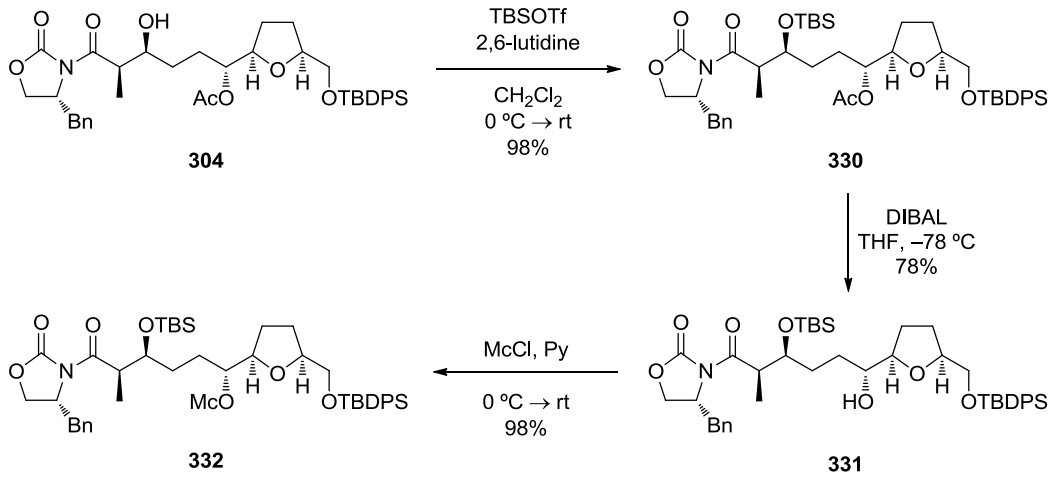


Therefore our attention turned to utilising the one-pot hydride shift initiated spiroketalisation (Scheme 93B). Unfortunately, the reaction with $Zn(OAc)_2$ in HFIP at 40 °C resulted in a low yield of spiroketal **325** after 24 hours. It was also noted that the formation of ketone **323** was often accompanied by the formation of small amounts the corresponding bis-THF side-product (analogous to that formed in the case of the primary C3–OTES, Scheme 78), as well as more polar side-products. These observations indicated that the mesylate leaving group required more forcing conditions to undergo the Lewis acid-promoted 1,2-hydride shift. In the case of **329** the relative rate of deprotection of the triethylsilyl group was faster than the

rate of hydride shift process. It may be speculated that formation of polar side-products, upon treatment with HFIP under prolonged reaction times resulted in cleavage of the TBDPS group, leading to complex mixtures.

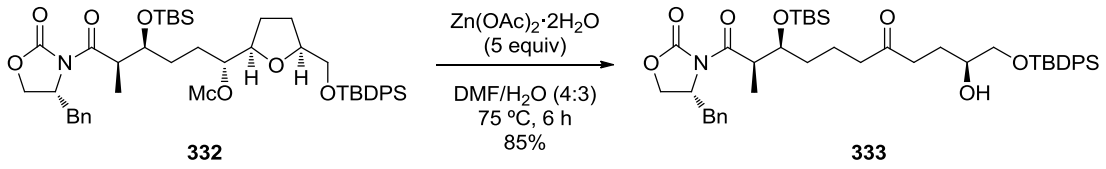
Although the synthesis of the AB spiroketal portion successfully demonstrated the feasibility of constructing spiroketal scaffolds using the hydride shift/spiroketalisation approach, it was pertinent to examine the effect of a more stable TBS group on the hydride shift step. Based on previous studies concerning the construction of the simplified model AB spiroketal **272**, we anticipated that the use of a TBS group would provide better yields for the hydride shift sequence than the more labile TES group (*vide supra* Scheme 78). To this end, TBS ether **330** was prepared from aldol **304** in an excellent yield of 98% by treatment with TBSOTf (Scheme 89). Subsequent acetate removal was achieved under the action of DIBAL in an analogous manner to previous work, providing alcohol **331** in a good yield of 78%. Activation of the resultant alcohol upon exposure to chloromesyl chloride afforded chloromesylate **332** in high yield (98%).

Scheme 94 *Synthesis of hydride shift precursor **332** from aldol **304***



Again, to accomplish the synthesis of AB spiroketal **325**, chloromesylate **332** was subjected to the optimal hydride shift conditions previously developed for the analogous TES ether (Table 13, entry 3). To our delight, the reaction furnished ketone **333** in a high yield of 85% in only 6 hours (Scheme 95).

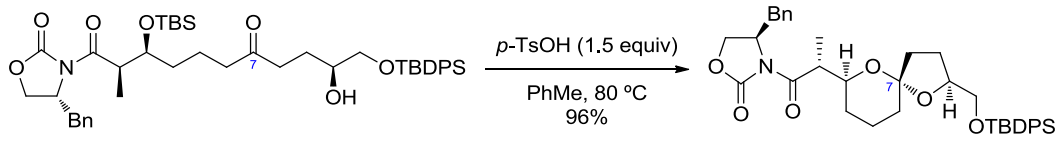
Scheme 95 *Formation of ketone **333** from precursor **332***



332 **333**

With the aim of constructing the 6,5-spiroketal, we first attempted to cleave the C3–OTBS group. Although seemingly straightforward, the projected deprotection proved to be surprisingly laborious. With little literature precedent for selective cleavage of a secondary TBS ether over a primary TBDPS ether, we set out using the previously employed conditions for the cleavage of the C3–OTES group in compound **323** (*vide supra* Scheme 89). Thus, treatment of **333** with PPTS in methanol (or ethanol) was undertaken, however this failed to deliver spiroketal **325**, even under extended reaction times and elevated temperatures. Varying the amount of PPTS was also unsuccessful. The use of previously reported conditions that were developed for a similar system (TMSOTf, CH_2Cl_2, 0 °C) resulted in extensive decomposition. Partial conversion into the desired spiroketal, however, was observed upon treatment with stoichiometric amount of *p*-toluenesulfonic acid in toluene at room temperature. To our delight, exposure of **333** to *p*-toluenesulfonic acid at elevated temperature resulted in a very clean deprotection providing desired spiroketal **325** in an excellent yield of 96% (Scheme 96). The spectroscopic and specific rotation data were in complete accordance with those obtained for the TES protected series.

Scheme 96 *Spiroketalisation of **333** to generate the AB fragment of pectenotoxin-4*



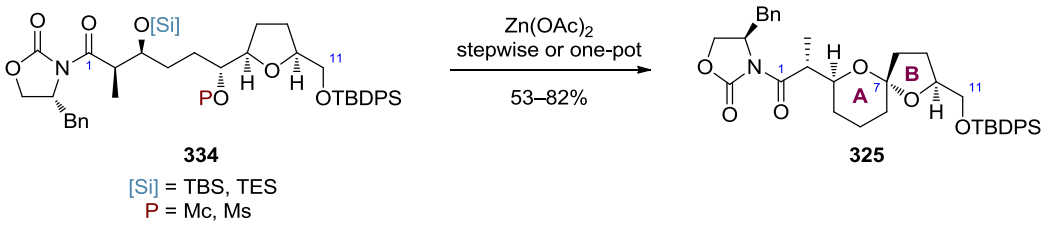
333 **325**

2.2.3.3 Summary

In conclusion, investigations detailed in this section have led to the development of a hydride shift initiated spiroketalisation to provide a direct entry to the 6,5-spiroketal moiety by modification the products of the oxidative cyclisation. This allowed retention of all of the benefits of the parent reaction, such as the generation of products as single enantiomers and the control of both exo- and endocyclic stereochemistry. It has been demonstrated that the use

of a chloromesylate leaving group led to better yields of the initial 1,2-hydride shift process, under milder conditions in comparison to a mesylate group (Scheme 97). Furthermore, employment of HFIP as a solvent allowed a rapid access the desired the 6,5-spiroketal moiety in a one-pot procedure. Finally, the viability of this method was successfully demonstrated in the synthesis of the model AB spiroketal.

Scheme 97 *Summary of hydride shift/spiroketalisation approach to the synthesis of* ***325***



334

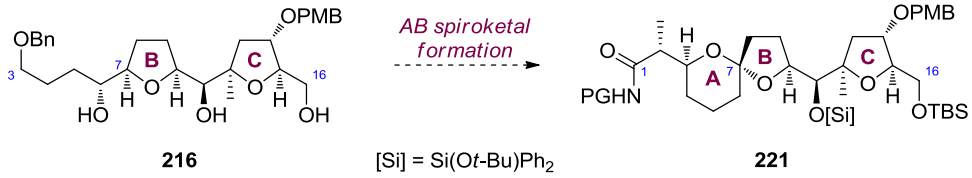
[Si] = TBS, TES
P = Mc, Ms

325

2.3 Completion of the synthesis of the ABC fragment of pectenotoxin-4

With a robust route to the BC fragment (Section 2.1) and reliable methodology to access the AB spiroketal (Section 2.2) in hand, we directed attention towards implementation of the hydride shift/spiroketalisation sequence in the synthesis of the ABC fragment of pectenotoxin-4 (Scheme 98).

Scheme 98 *Plan for elaboration to the ABC fragment*



216 [Si] = Si(O*t*-Bu)Ph$_2$ **221**

2.3.1 Synthesis of the hydride shift precursor

2.3.1.1 Preparation of orthogonally protected fragment 335

Our initial task required selective orthogonal protection of each of the three hydroxyl groups present in bis-THF **216**. The C16 hydroxyl protecting group was to be eventually removed to allow further manipulation during the later assembly of pectenotoxin-4; it therefore necessitated an orthogonal protection to the C6 and C11 centres, yet it had to exhibit necessary stability in the final hydride shift/spiroketalisation sequence. Based on precedent by Evans a *tert*-butyldimethylsilyl group was chosen at this position.[25,26]

Scheme 99 *Selective protection of the C6, C11 and C16 hydroxyl groups of* ***216***

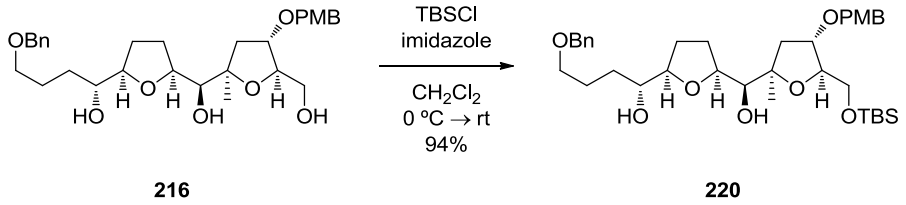
216 **335** [Si] = Si(O*t*-Bu)Ph$_2$

The ability to selectively protect the two remaining secondary hydroxyl groups was anticipated to be a significant challenge. However, after considering steric factors it was reasoned that the secondary C6 hydroxyl group would be more easily accessible than the neopentyl C11 alcohol. The C6 alcohol was later to be activated as a chloromesylate prior to the hydride shift reaction; however, based on our previous attempts to remove a benzyl group

under hydrogenation conditions in the presence of the chloromesylate moiety were unsuccessful (Section 2.2.2.1, Scheme 73), it was therefore not feasible to carry the chloromesylate as a protecting group forward at this site. As such, it was therefore decided to temporarily protect C6 alcohol as an acetate in a similar fashion to previous studies (Section 2.2.3.1). With two alcohols selectively protected the remaining C11 neopentyl hydroxyl group would be finally protected as TBODPS ether, in line with studies by Evans and co-workers.

The synthesis sequence commenced with a selective TBS protection of the primary hydroxyl group. Pleasingly, treatment of triol **216** with 1.05 equivalents of *tert*-butyldimethylsilyl chloride in DMF provided the desired mono-TBS product **220** in a high yield of 94% (Scheme 100).

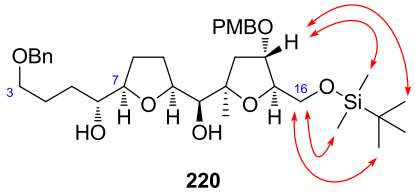
Scheme 100 *Selective protection of **216** with TBSCl*



216 **220**

The regioselective formation of the C16–OTBS ether was verified by NOESY correlations since the analysis of the ^{1}H and ^{13}C NMR chemical shifts of C4, C9 and C14 was not conclusive (Figure 25).

Figure 25 *Key NOE interactions confirming selective protection of **220***

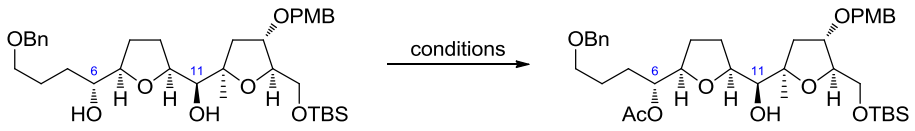


220

The next step required selective acetylation of the C6 hydroxyl group. Although precedent for selective acetyl protection of two secondary alcohols existed in the literature, often the conditions utilised for this transformation are substrate-dependent. Initial attempts using a stoichiometric amount of acetyl chloride with pyridine, or 2,6-lutidine, in dichloromethane resulted in a mixture of monoacetylated regioisomers as well as bisacetylated side-product. It

was therefore reasoned that a better selectivity might be achieved utilising less reactive acetic anhydride. Whilst using pyridine as a solvent delivered again a mixture of regioisomers and bisacetylated by-product (Table 14, entry 1), acetylation in dichloromethane in the presence of 10 equivalents of pyridine resulted in a slower reaction, however, relatively less of the unwanted products were observed (entry 2). Thus it was reasoned that by conducting the reaction at high dilution this may suppress the formation of the undesired regioisomer as well as the bisacetylated side-product. Pleasingly, exposure of **220** to 1.5 equivalents of Ac_2O and 10 equivalents of pyridine in a 0.02 M dichloromethane solution yielded the desired monoacetate **336** in 54% yield with the remaining mass balance attributed to the recovered starting material **220** (entry 3). It was gratifying that under these conditions only traces of the bisprotected side-product and the undesired regioisomer were noted, although the reaction did require 36 hours. In order to increase the yield and rate of this transformation a catalytic amount of DMAP was employed. Pleasingly, the reaction conducted in the presence of 10 mol% of DMAP provided monoacetate **336** in a high yield of 80% after 18 hours (entry 4). It was also noteworthy that despite considerable acceleration of the process, the use of DMAP did not affect the selectivity of the reaction. The formation of monoacetate **336** was confirmed on the basis of a chemical shift of the diagnostic multiplet signal of the C(4)H group in the ^{1}H NMR spectrum (δ_H 3.37 to 4.94 ppm) and by further analysis of the COSY spectrum.

Table 14 *Selective acetylation of the C6 hydroxyl group of **320***



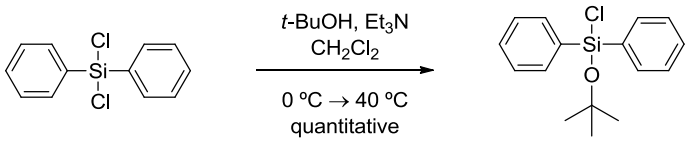
220 **336**

Entry	Conditions (equiv)	Solvent	Conc. [M]	Yield/%
1	Ac_2O (1.5)	Pyridine	0.1	mixture
2	Ac_2O (1.5), Py (10)	CH_2Cl_2	0.1	mixture
3	Ac_2O (1.5), Py (10)	CH_2Cl_2	0.02	54
4	Ac_2O (1.5), Py (10), DMAP (0.1)	CH_2Cl_2	0.02	80

Finally, having successfully prepared monoacetate **336**, we set out to protect the remaining neopentyl hydroxyl group. The C11 hydroxyl protecting group would have to be stable under acidic conditions required for the key hydride shift/spiroketalisation sequence and late deprotection of the C16–OTBS ether. On the basis of the work by Evans and co-workers it was chosen to utilise the *tert*-butoxydiphenylsilyl group. This unusual

protecting group offers a 20 times higher stability under acidic conditions than the *tert*-butyldimethyl silyl group, but it is less stable than the *tert*-butyldiphenylsilyl group.[124] Although *tert*-butoxydiphenylsilyl chloride is commercially available, analysis of the purity of the reagent purchased from several different suppliers showed that it was not acceptable. Therefore it was necessary to freshly prepare the reagent prior to use by reacting dichlorodiphenylsilane with *tert*-butanol in the presence of triethylamine (Scheme 101).

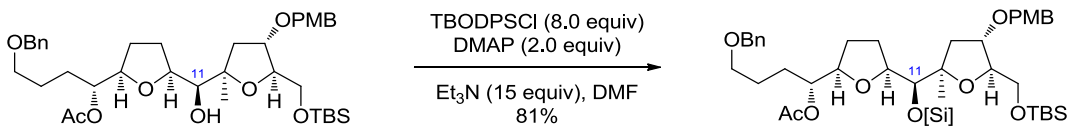
Scheme 101 *Preparation of tert-butyoxydiphenyl chloride **338***



220 **336**

In an initial attempt to protect the C11 hydroxyl group, monoacetate **336** was treated, according to the literature conditions, with 2 equivalents of *tert*-butoxychlorodiphenylsilane **338** with the addition of 1 equivalent of DMAP in DMF at room temperature. Disappointingly, after 12 hours only a small amount of the desired product was observed. Considering the relatively large size of the protecting group, as well as the fact that C11 alcohol rested in a sterically encumbered environment, it became apparent that the use of more forcing conditions would be required. Thus, the reaction was carried out employing a large excess (8 equivalents) of TBODPSCl in combination with 2 equivalents of DMAP in DMF at room temperature. Satisfyingly, the desired product was obtained in a good yield of 81%.[125]

Scheme 102 *Protection of C11 hydroxyl group of **336** with TBODPSCl*



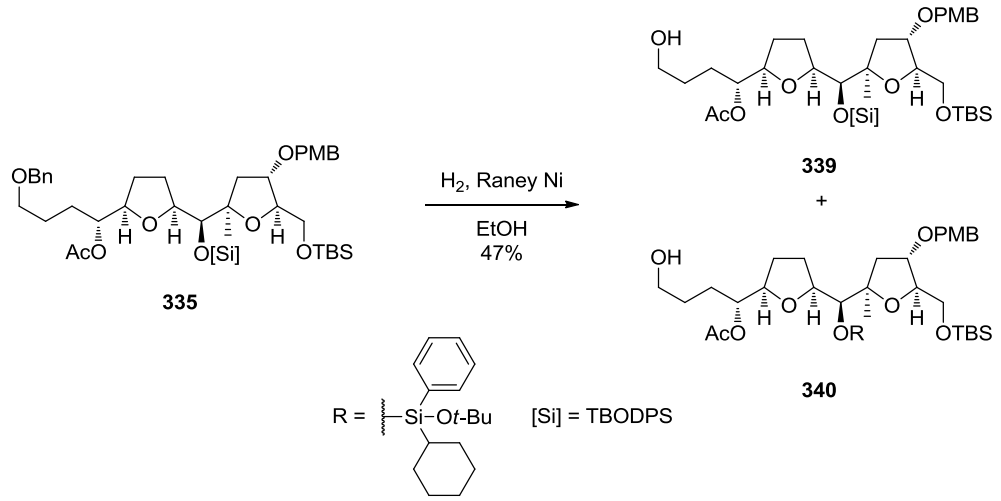
336 [Si] = TBODPS **335**

2.3.1.2 Elaboration to the C3 aldehyde

With each hydroxyl group orthogonally protected now in place we next focussed on elaboration of the bis-THF **335** towards the aldol intermediate possessing the full carbon

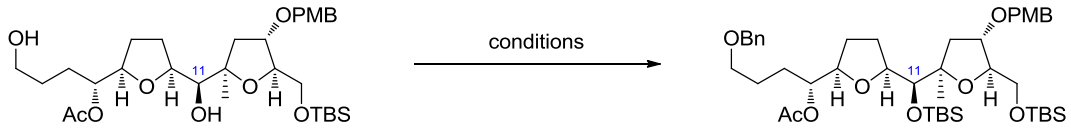
skeleton of the ABC fragment of pectenotoxin-4. Our projected approach relied upon selective deprotection of the benzyl ether with preservation of the C14–OPMB ether, to provide a functional group handle for the subsequent installation of the aldol fragment. Selective debenzylation in the presence of the *p*-methoxybenzyl group is well documented in the literature, with the most exploited conditions being reduction using LiDBB or hydrogenation using Raney nickel. Since the use of LiDBB may have a detrimental effect (such as cleavage of the acetate moiety) on the starting material **335**, initial attempts to cleave the benzyl group concentrated on employing Raney nickel. However, treatment of **335** with an excess of Raney nickel at high dilution (0.005 M) under an atmosphere of hydrogen (balloon pressure) resulted in a sluggish reaction that delivered only trace amounts of the desired alcohol **339**. Increasing the concentration of the reaction mixture (to 0.05 M) led to a moderate conversion to alcohol **339**, however reaction times were often found to be irreproducible (Scheme 103). Interestingly, over multiple runs it was found that under these conditions the isolated product was always contaminated with an inseparable side-product, which by ^{1}H and ^{13}C NMR analysis bore a very close structural resemblance to alcohol **339**. At a larger scale we were able to observe the appearance of a new spot on a TLC plate largely overlapping with the spot of the desired product. Careful purification using flash column chromatography allowed for isolation a small amount of the by-product **340**. Although it was not possible to fully assign the obtained contamination, extensive inspection of the ^{1}H NMR spectra showed subtle changes in the aromatic region, which were tentatively attributed to reduction of one phenyl ring of the TBODPS group. Furthermore, the mass spectrometry analysis revealed the appearance of a molecular peak of 873 Da, which corresponded to the desired product ($M + Na^{+}$), as well as a peak of 879 Da corresponding to the mass of the desired alcohol and 6 hydrogen atoms ($M + 6 + Na^{+}$). These observations supported our supposition regarding possible reduction of the phenyl group to the cyclohexyl ring. An extensive literature search revealed one precedent whereby a selective hydrogenation of a benzyl group in the presence of *tert*-butyldiphenylsilyl protecting group using Raney nickel effected full reduction of one phenyl group of a TBDPS moiety.[126] This unexpected difficulty to perform a clean debenzylation led us to abandon the use of the TBODPS group.

Scheme 103 *Deprotection of the C3 benzyl ether of **335** with Raney nickel*



We next turned to examine several typical silicon-based protecting groups for use at the C11 site. Disappointingly, despite substantial experimentation, attempts to utilise a triisopropylsilyl group were met with failure. The reaction of alcohol **336** with various amounts of TIPSCl or TIPSOTf returned only unreacted starting material. This outcome stood in marked contrast to our previous results employing the TBODPS group, conceivably due to the greater size of the triisopropylsilyl group compared to the *tert*-butoxydiphenylsilyl group. Thus, we directed attention to protecting the neopentyl alcohol as a sterically smaller TBS ether. The first attempt using 3 equivalents of *tert*-butyldimethylsilyl chloride in combination with imidazole and a catalytic amount of DMAP resulted in no reaction being observed (Table 15, entry 1). The use of more forcing conditions, analogous to the TBODPS protection (8 equiv. of TBSCl, 2 equiv. of DMAP in DMF), again did not provide any appreciable amount of the desired product **341** (entry 2). It was after considerable screening that the successful conditions of 5 equivalents of *tert*-butyldimethylsilyl triflate in dichloromethane at room temperature were discovered to successfully produce bis-THF **341** in 97% yield (entry 3).

Table 15 *Protection of C11 hydroxyl group of **336** with TBS reagents*

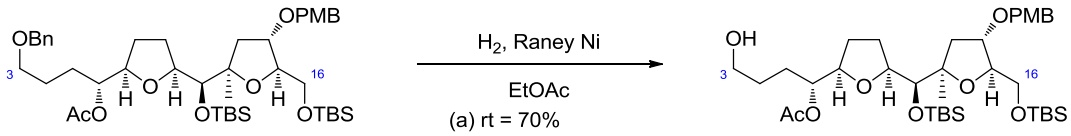


336 **341**

Entry	Conditions (equiv)	Solvent	Temperature	Yield/%
1	TBSCl (3.0), DMAP (0.2), imidazole (5.0)	DMF (0.1 M)	0 °C → rt	no reaction
2	TBSCl (8.0), Et_3N (15), DMAP (2.0)	DMF (0.1 M)	0 °C → rt	traces
3	TBSOTf (5.0), 2,6-lutidine (10),	CH_2Cl_2 (0.1 M)	0 °C → rt	97

With the appropriate substrate in hand we returned to the task of selective removal of the C3 benzyl group in bis-THF **341**. Pleasingly, attempted hydrogenation using an excess of Raney Ni in ethyl acetate (0.05 M) furnished alcohol **342** in 70% yield after 12 hours (Scheme 104). It was later found that the yield significantly improved when the reaction was carried out at 35–40 °C delivering the desired product in 84% yield after 8 hours, with no side-products being observed under this set of conditions. Notably, the reaction carried out in ethyl acetate proceeded cleaner and faster than when ethanol was used as a solvent.

Scheme 104 *Successful deprotection of the C3 benzyl ether of **341** with Raney nickel*



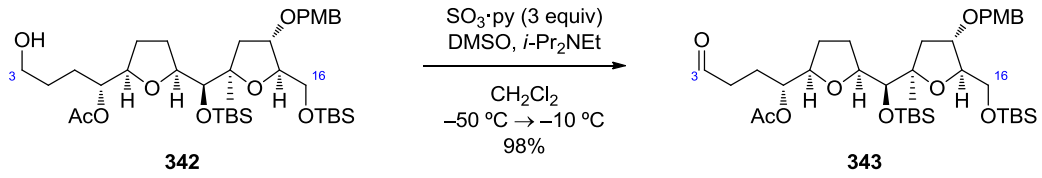
341 **342**

2.3.1.3 Elaboration to the hydride shift precursor

Successful removal of the benzyl group allowed us to examine the required oxidation to arrive at the corresponding aldehyde. Two set of conditions were examined for this transformation. Exposure of primary alcohol **342** to Dess–Martin periodinane in dichloromethane gratifyingly delivered aldehyde **343** in very high yield (91%). Although the yield obtained was high enough to carry material forward without further optimisation, we decided to examine the Parikh–Doering oxidation. This mild oxidation had previously worked very well in our hands and given the low cost of the reagent it appeared an attractive alternative. Thus, treatment of alcohol **342** with 3 equivalents of sulfur trioxide pyridine complex at 0 °C provided the desired aldehyde in a good yield of 77%, however, the

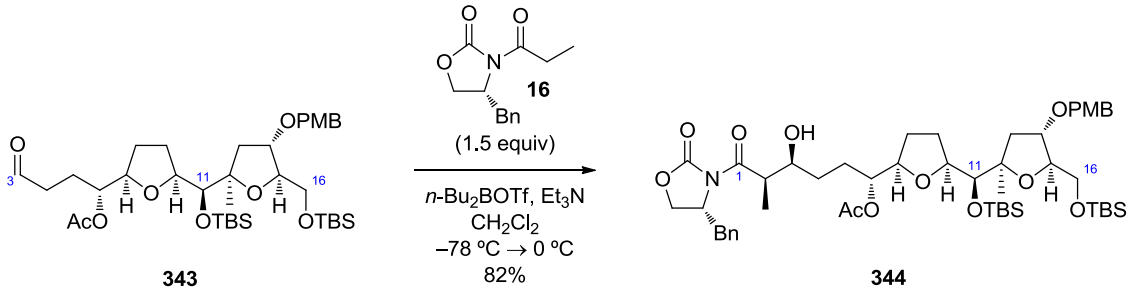
formation of small amounts of side-products were also noted. Therefore it was reasoned that lowering the temperature may prevent the starting material undergoing side reactions, leading to a cleaner reaction. Pleasingly, carrying out the reaction from −50 °C to −10 °C led to a cleaner transformation, affording the desired aldehyde **343** in almost quantitative yield (98%) in only 1 hour (Scheme 105).

Scheme 105 *Oxidation of **342** to aldehyde **343***



With convenient access to aldehyde **343** in hand, focus turned to installation of the C1–C2 fragment and setting the C2 and C3 stereogenic centres. As discussed earlier, it was anticipated that the *syn*-aldol moiety could be constructed *via* the established Evans aldol reaction of aldehyde **343** and an *N*-propionyl derivative of chiral auxiliary **16**. To pursue the planned construction of aldol **344**, oxazolidinone **16** was treated with dibutylboron triflate at 0 °C and the resulting enol borane was allowed to react at −78 °C with aldehyde **343** (Scheme 106). However, this transformation proved to be more challenging than the standard conditions previously employed in the synthesis of the AB spiroketal model (1.0 equiv. of oxazolidinone **16**, 1.1 equiv. of aldehyde **16**), providing the desired aldol only in moderate yields (varying from 45% to 60%), with most of the remaining aldehyde **343** being recovered. Furthermore, under no circumstances was the yield of the desired aldol **344** improved using this set of conditions, despite extensive investigation, including repurification of starting materials, strict exclusion of moisture and the use of new batches of the reagents. Numerous attempts to improve the conversion of aldehyde **343** to aldol **344** revealed that use of an excess of both *N*-propionyl oxazolidinone and dibutylboron triflate was crucial for the reaction to proceed in higher yields. When aldehyde **343** was subjected to the modified conditions (1.5 equiv. of oxazolidinone **16**, 1.7 equiv. of Bu_2BOTf) a cleaner reaction took place pleasingly affording the desired *syn*-aldol in 82% yield as a single diastereoisomer.

Scheme 106 *Evans aldol reaction of aldehyde **343** to access aldol **344***

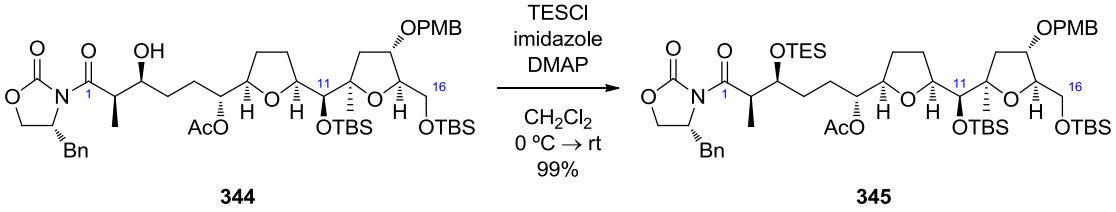


Analysis of the C2/C3 vicinal coupling constant in the ^{1}H NMR spectrum of **344** ($J_{2,3}$ = 2.6 Hz) and comparison with the literature data confirmed that the aldol reaction had established the *syn* relationship between C2 and C3 (typically J_{syn} = 2.5–4.0 Hz, J_{anti} = 7.0–10.0 Hz).

With the complete C1–C16 carbon chain now assembled our attention turned to preparation of the precursor required for the key hydride shift step. Our envisaged approach relied on a sequence previously developed for the preparation of the model AB spiroketal, which included protection of the C3 hydroxyl group, followed by reductive removal of the acetate to unmask the C6 alcohol, which would in turn be activated as a chloromesylate. Notably, the nature of the protecting group at the C3 site may have a critical effect on the efficiency of the projected spiroketalisation step as our approach necessitated selective removal of this group. Model studies showed (Section 2.2.3) that the use of a *tert*-butyldimethylsilyl group allowed the key hydride shift to proceed in higher yields compared to the triethylsilyl group, however, we opted to utilise the latter group in our initial investigation for several reasons. To facilitate the desired spiroketalisation, the C3 hydroxyl group was to be deprotected in the presence of the C11–OTBS and C16–OTBS groups. If the C3 hydroxyl was masked as a TBS ether, the deprotection/spiroketalisation step may likely result in concomitant cleavage of the C16–OTBS group (and potentially the C11–OTBS). This may in turn lead to the formation of different spiroketal side-products. Thus, the strategy employing the triethylsilyl group to mask the C3 hydroxyl appeared more promising.

The synthesis of the key hydride shift precursor commenced with a triethylsilyl protection group of aldol **344**. Treatment of **344** with triethylchlorosilane and a catalytic amount of DMAP resulted in a near-quantitative conversion into C3–OTES ether (99% yield) (Scheme 107).

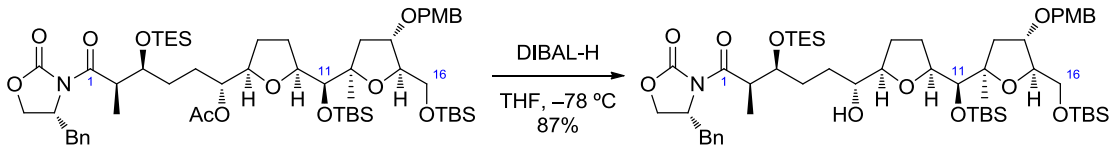
Scheme 107 *Protection of the C3 hydroxyl group of **344** to form TES ether **345***



344 **345**

The next step required selective reduction of the acetate group in the presence of the oxazolidinone. Following the general strategy developed earlier for the synthesis of the AB fragment, acetate **345** was treated with 5 equivalents of diisobutylaluminum hydride (DIBAL) at −78 °C affording the desired alcohol in 77% yield (Scheme 108). Further optimisation showed that the use of a greater excess of DIBAL led to the formation of side-products and a noticeable depreciation in the yield of **346**. The best results were obtained by employing sequential addition of the reducing agent. Thus, exposure of acetate **345** to 3 equivalents of DIBAL at −78 °C, followed by addition of further 2 equivalents of DIBAL after 1.5 hours led to a clean removal of the acetate group furnishing alcohol **346** in a very high yield of 87%.

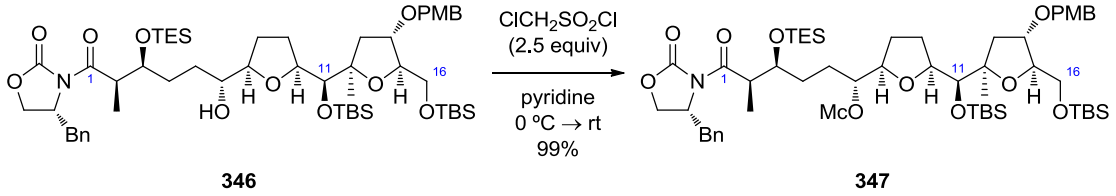
Scheme 108 *Reduction of C6 acetate group to form alcohol **346***



345 **346**

To complete the synthesis of the hydride shift precursor **347**, alcohol **346** was to be activated as a chloromesylate. Pleasingly, treatment of **346** with 2.5 equivalents of chloromethanesulfonyl chloride in pyridine delivered expected chloromesylate **347** in a very high yield of 99%.

Scheme 109 *Preparation of hydride shift precursor **346** from alcohol **346***

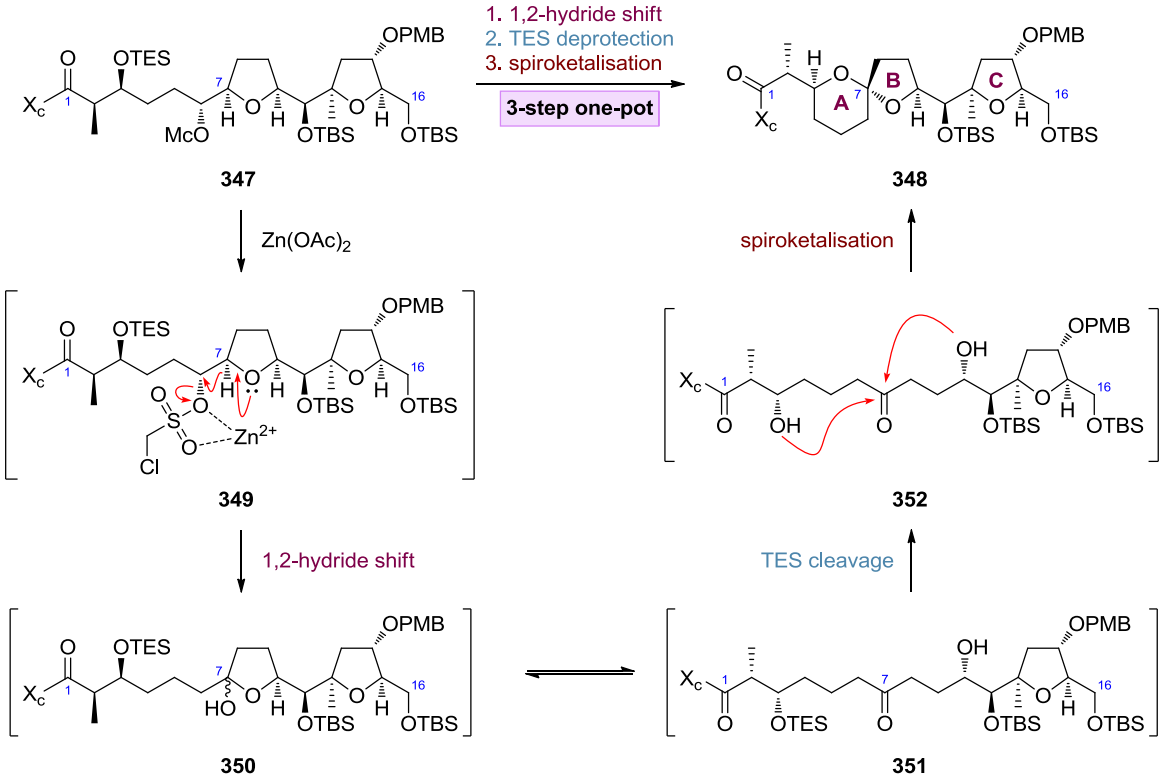


346 **347**

2.3.2 Completion of the synthesis

With the reliable sequence to chloromesylate **347** now established, the stage was set for examining the pivotal hydride shift reaction. Our initial forays to fashion the ABC fragment focussed upon utilising the three-step one-pot approach successfully employed in previous studies. It was envisaged that in the event, following the hydride shift, the reaction conditions allowed for *in situ* deprotection of the TES group to form diol **352**, which could then undergo spiroketalisation to yield **348** (Scheme 110). This procedure proved efficient in the synthesis of the AB spiroketal fragment (Section 2.2.3.2) and successful implementation of this concept would provide a direct entry to the ABC fragment of pectenotoxin-4, but it remained to be seen whether this result would translate to a more complex system such as **348**. As alluded to earlier, the potential success of the one-pot approach in this case also relied on sufficient tolerance of the reaction conditions by the C11–OTBS and C16–OTBS groups.

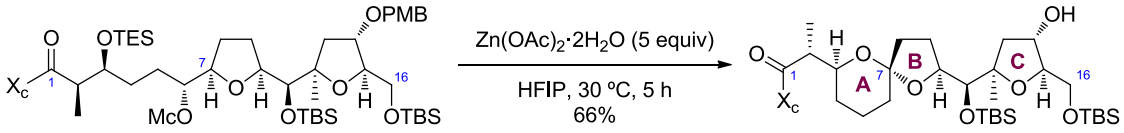
Scheme 110 *Proposed pathway for one-pot approach to the ABC fragment **348***



In order to probe the strategy delineated in Scheme 110, chloromesylate **347** was treated with 5 equivalents of $Zn(OAc)_2 \cdot 2H_2O$ in hexafluoroisopropanol at 30 °C, which resulted in a relatively fast formation of a new compound in good yield (66%). Pleasingly, inspection of ^{1}H and ^{13}C NMR spectra verified the formation of the expected anomerically

stabilised 6,5-spiroketal, as evidenced by the appearance of diagnostic C7 (105.2 ppm, C_6D_6) signal and the loss all signals attributed to the triethylsilyl as well as chloromesylate groups. However, it was also noted that the reaction disappointingly proceeded with a concurrent cleavage of the *p*-methoxybenzyl group. Since the pH of the reaction mixture was close to neutral, it was postulated that *in situ* deprotection of the PMB group was likely a result of the Lewis acidic reaction conditions.

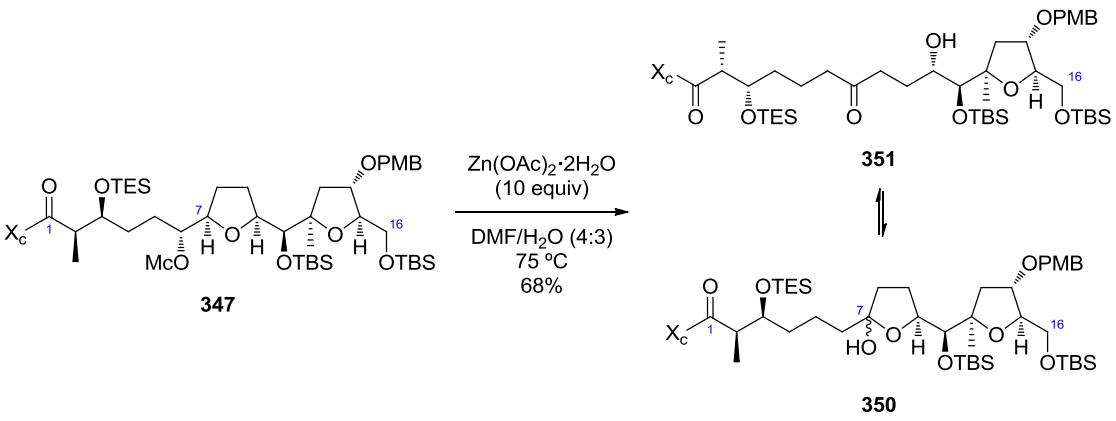
Scheme 111 *Three-step one-pot approach to form ABC fragment* ***353***



347 **353**

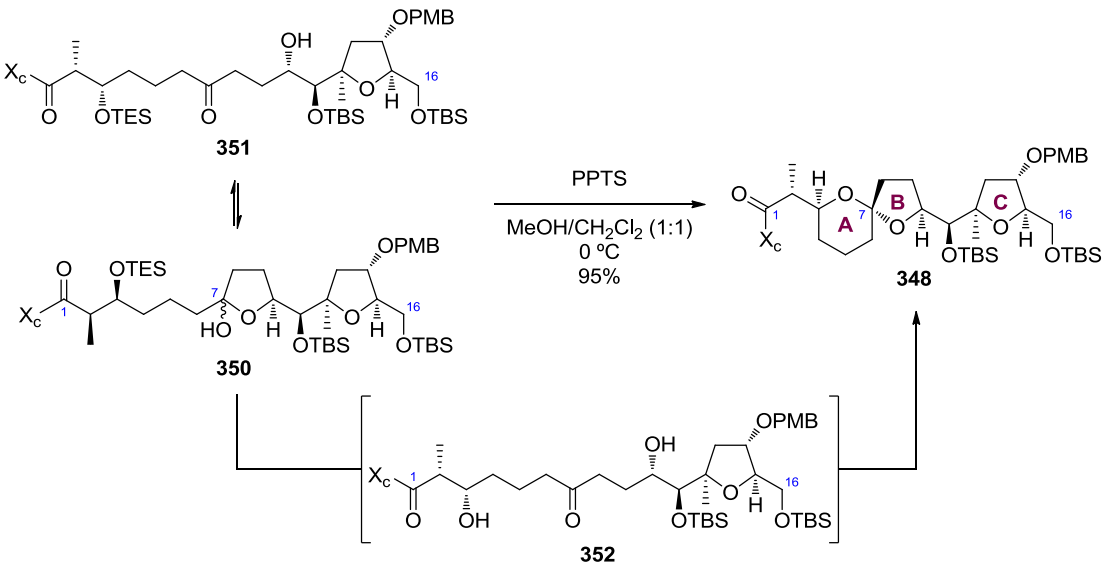
Having successfully demonstrated the versatility of the hydride shift initiated spiroketalisation in a complex system, we elected to investigate whether the desired ABC ring system **348** could be accessed by utilising a stepwise approach (Scheme 112) with maintenance of the C14–OPMB functionality. The stepwise hydride shift sequence, under aqueous conditions, would furnish ketone **351**, which could then be appropriately converted to the desired spiroketal **348** in a subsequent step. To this end, employing our previous best conditions, treatment of chloromesylate **347** with 6 equivalents of $Zn(OAc)_2 \cdot 2H_2O$ in aqueous DMF at 75 °C disappointingly resulted in a sluggish reaction that yielded only trace amounts of the desired ketone. As the elevation of the temperature could have a detrimental effect on the transformation, it was reasoned that increasing the amount of the Lewis acid used in the reaction might prove fruitful, leading to a better conversion to the desired product. Pleasingly, upon exposure to 10 equivalents of $Zn(OAc)_2 \cdot 2H_2O$ at 75 °C chloromesylate **347** yielded the desired product **351** in 68% yield after 8 hours. Disappointingly, no further improvements were observed upon prolonged reaction times, even using a greater excess of the Lewis acid. Analysis of the ^{1}H and ^{13}C NMR data of the isolated product indicated that the obtained material existed as a mixture of ketone **351** and lactol **350**, thus the full assignment was very difficult.

Scheme 112 *Zinc-promoted 1,2-hydride shift of **347** to form a mixture of **350** and **351***



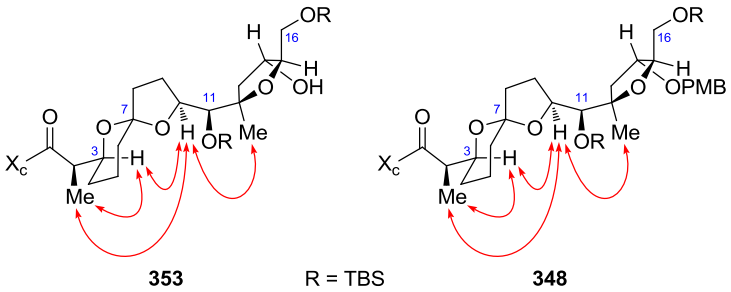
With a mixture of the hydride shift-derived products **350** and **351** in hand, we next directed attention to completion of the synthesis by effecting a selective TES deprotection with subsequent *in situ* spiroketalisation. A detailed survey of the literature provided limited precedent of a selective secondary OTES removal in the presence of a primary OTBS moiety, however, we were able to select several methods that seemed most promising when applied to our complex system. To our delight, treatment of ketone **351** with 0.5 equivalents of PPTS in a 1:1 mixture of methanol and dichloromethane (0 °C) elicited a selective cleavage of the triethylsilyl group, yielding diol **352**, followed by *in situ* spiroketalisation that constructed the desired 6,5-spiroketal cementing the synthesis of the northern hemisphere of pectenotoxin-4 (Scheme 113). The reaction proceeded in only 30 minutes delivering product **348** in 95% yield as a single diastereoisomer, as evidenced by ^{1}H and ^{13}C NMR analysis.

Scheme 113 *Spiroketalisation of a mixture of **350** and **351** to access the ABC fragment **348***



The stereochemistry of the AB spiroketal of **348** and **353** was subsequently verified by key NOESY and ROESY correlations that are depicted in Figure 26.

Figure 26 *Key NOE interactions confirming the configuration of the AB spiroketal of **348** and **353***



The most telling proton interactions between C(10)H and C(3)H, as well as C(10)H and the methyl group at C2 confirmed the formation of the thermodynamically favoured spiroketal. Moreover, a strong interproton correlation between the methyl group at C12 and C(10)H proved that the hydride shift did not occur from C10 to C11, as well as that the stereochemistry at C10 had not been affected during the hydride shift reaction. The stereochemistry of the AB spiroketal was further confirmed by analysis of the chemical shift of C7. The presence of a peak at 105.2 ppm in the ^{13}C NMR spectrum of **353** and a peak at 105.1 ppm in the case of **348** indicated the formation of the anomeric configuration at the C7 centre in both cases. These chemical shifts were consistent with those observed for the anomeric pectenotoxins, while the pectenotoxins with the non-anomeric spiroketals displayed a chemical shift at the C7 centre in the range 107.0–110.0 ppm.

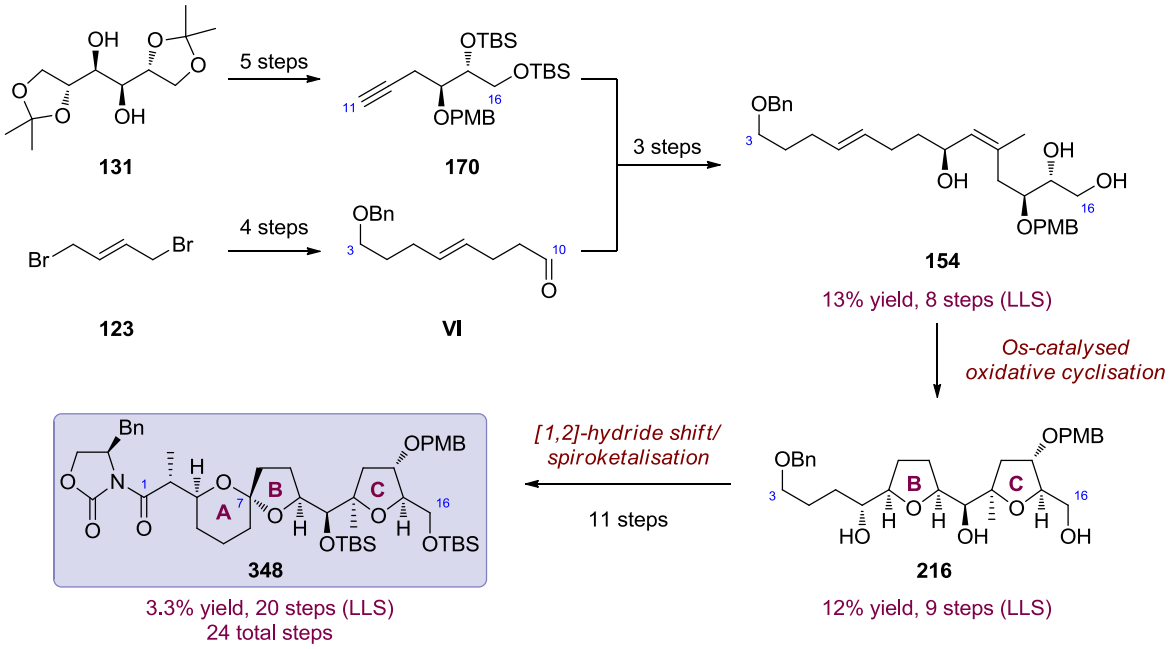
2.4 Conclusions and future work

In conclusion, an efficient synthesis of the C1–C16 ABC fragment of pectenotoxin-4 has been accomplished. Key to the success of our approach was the use of two methods developed in the Donohoe group:

- an osmium-mediated cascade oxidative cyclisation, which provided rapid access to the BC bis-THF fragment of the northern hemisphere from a linear precursor
- a hydride shift initiated spiroketalisation to construct the AB spiroketal.

The utilised sequence was completed in 20 steps (longest linear sequence) and with a total of 24 chemical transformations, in an overall yield of 3.3% (84.3% per step) (Scheme 114). The approach described in this thesis represents a competitive route to the northern hemisphere of pectenotoxin-4.

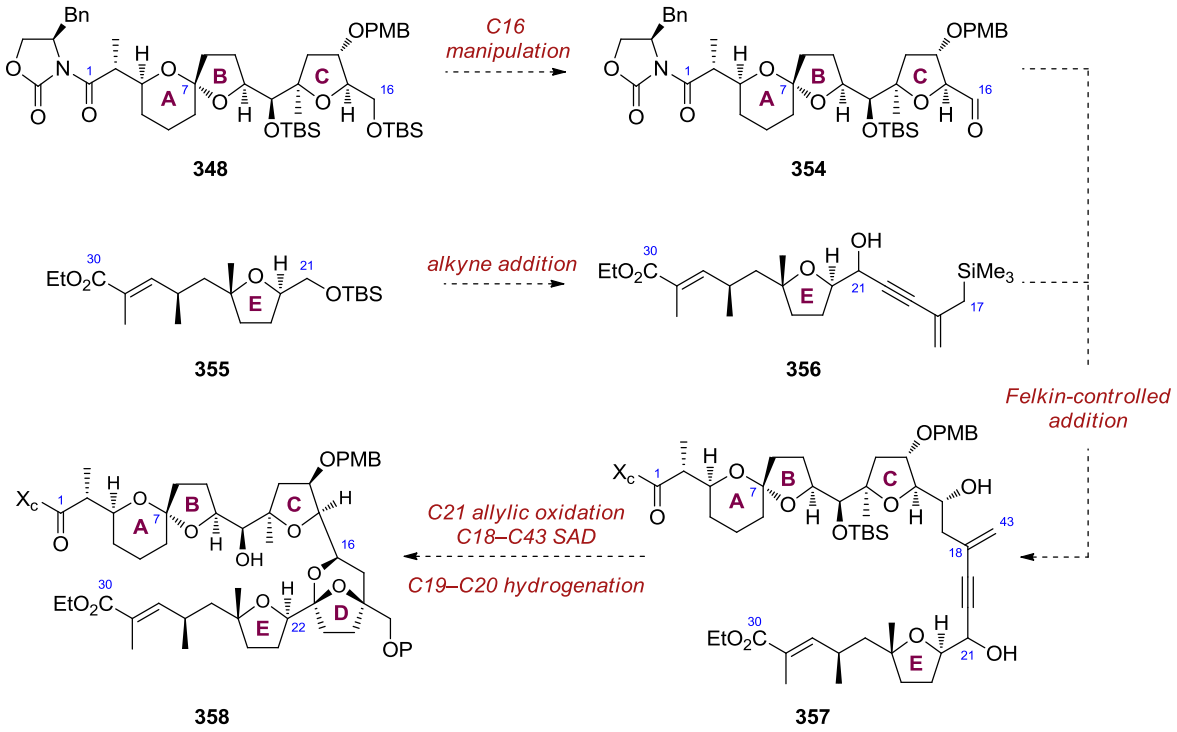
Scheme 114 *Synthesis of the ABC fragment of pectenotoxin-4*



The next challenge for the total synthesis of pectenotoxin-4 would be the construction of the D ring. It was envisaged that the formation of this bicyclic spiroketal could arise from a Felkin-controlled addition of intermediate **356** (possessing the E ring) to aldehyde **354**, which could be accessed from the ABC fragment **348** through deprotection and oxidation of the primary hydroxyl group at C16 (Scheme 115). Intermediate **356** could be prepared from the E ring fragment **355**, which has previously been synthesised in the Donohoe group. Subsequent

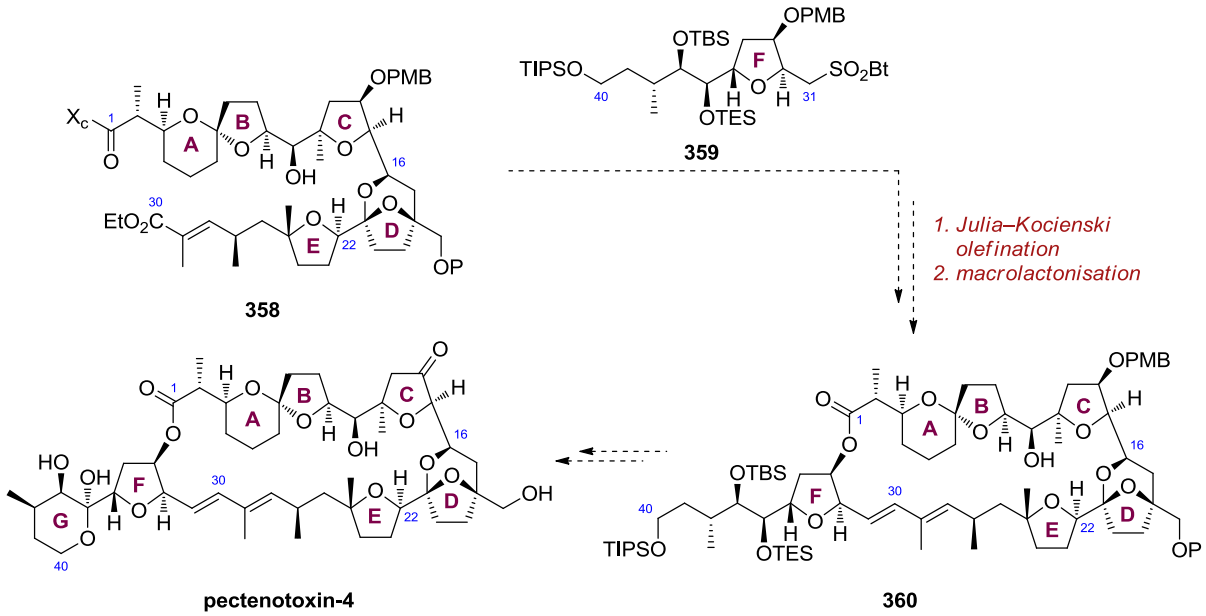
allylic oxidation, followed by Sharpless asymmetric dihydroxylation and hydrogenation of the C19–C20 alkyne could afford ABCDE fragment **358**.

Scheme 115 *Elaboration of fragment **348** to the ABCDE ring system **358***



The resulting C1–C30 fragment **358**, after necessary manipulation at C30, would be set up to undergo a Julia–Kocienski olefination with the F ring fragment **359**, which has also been prepared in the group (Scheme 116). It is envisaged that the chiral auxiliary at C1 may serve as a protecting group at this site until final macrolactonisation. Subsequently, employment of conditions similar to that used by Evans could allow a deprotection/oxidation at the C14 and C36 centres. Finally, selective cleavage of the C40–OTIPS group would install the remaining G ring *via* intramolecular hemiacetal formation. With all the rings established, the synthesis would be completed after global deprotection to deliver pectenotoxin-4.

Scheme 116 *Completion of the synthesis of pectenotoxin-4*



Chapter 3

Experimental

3.1 Experimental techniques

Reagents obtained from Acros, Aldrich, Alfa Aesar, Avocado, BDH, Fluorochem, Lancaster or Strem fine chemicals suppliers were used directly as supplied or following purification according to procedures described by Armarego and Chai.[127]

Reactions were carried out under an inert atmosphere of argon if anhydrous conditions were required. Syringes and needles, for the transfer of moisture-sensitive reagents, were oven-dried and cooled in a dessicator over self-indicating silica gel. Flasks were flame-dried under vacuum prior to use. All reactions were carried out at room temperature unless otherwise stated.

Acetonitrile, dichloromethane, diethyl ether, methanol, tetrahydrofuran and toluene were dried by filtration through two activated alumina, purification columns. Petrol refers to petroleum ether in the boiling range 30–60 °C.

^{1}H NMR spectra were recorded either on a Bruker DPX200 (200 MHz), Bruker Avance AV400 (400 MHz), Bruker DRX500 (500 MHz), Bruker AVII500 (500 MHz) in $CDCl_3$, $(CD_3)_2CO$ or C_6D_6.^{13}C NMR spectra were recorded either on a Bruker Avance AV400 (100 MHz), Bruker DRX500 (125 MHz) or a Bruker AVII500 (125 MHz) spectrometers in $CDCl_3$, $(CD_3)_2CO$ or C_6D_6. ^{19}F NMR were recorded on a Bruker DPX250 or Bruker AV400 spectrometers in $CDCl_3$. Chemical shifts are quoted to two decimal places in ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). Coupling constants, *J*, are quoted to one decimal place in Hz. All NMR chemical shifts were referenced to residual solvent peaks.

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analysed as thin films or pressed solids using the Infra-red Diamond ATR Module. Selected absorption peaks are given in cm^{-1}.

Accurate mass spectra (HRMS) were recorded on a Bruker MicroTof spectrometer under conditions of electrospray ionisaiton (ESI). Values are reported as ratio of mass to charge in Daltons.

Specific optical rotations were recorded on a Perkin Elmer 241 Polarimeter at the sodium line (589.3 nm) in $CHCl_3$ or ACS photo spectroscopic grade CH_2Cl_2 and are quoted in the units of 10^{-1} deg cm^2 g^{-1}. Solution concentrations are given in units of 10^{-2} g mL^{-1}.

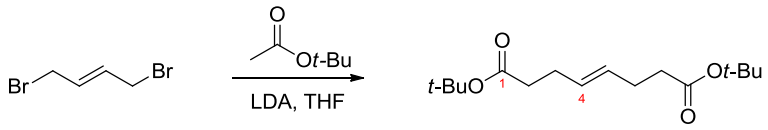
Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

Thin layer chromatography (TLC) was performed on Merck Kiesegel 60 F254 0.25 mm precoated aluminium plates. Compunds were visualised under UV light (λ_{max}) and by staining with potassium permanganate, phosphomolybdic acid or vanilin solution. Flash column chromatography was performed using silica gel 60 (0.033–0.070 mm, BDH) or alumina gel (Fluka aluminium oxide for chromatography) using head pressure by means of a positive pressure from a nitrogen line, according to Still.[128]

Atoms have been numbered according to a self-consistent system used for clarity of assignment, which does not reflect the IUPAC rules used in naming the compunds.

3.2 Experimental procedures

(*E*)-Di-*tert*-butyl oct-4-enedioate (122)

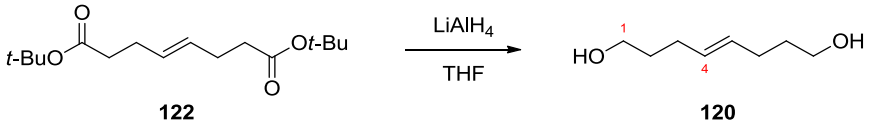


123 **122**

To a stirred solution of diisopropylamine (45.0 mL, 322 mmol) in tetrahydrofuran (600 mL) at –78 °C was added *n*-butyllithium (1.6 M solution in hexanes, 200 mL, 316 mmol) dropwise over a period of 10 minutes. The resulting mixture was stirred for 15 minutes before *tert*-butyl acetate (38.2 mL, 293 mmol) was added dropwise using a syringe pump (40 mL/h). The resulting solution was stirred at –78 ºC for 30 minutes. A solution of (*E*)-1,4-dibromobutene (**123**) (25.0 g, 117 mmol) in tetrahydrofuran (100 mL) was added dropwise using a syringe pump (20 mL/h) and the resulting mixture was stirred at –78 ºC for 5 hours and then allowed to warm slowly to room temperature and left stirring for 16 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (500 mL) and the resultant mixture extracted with ethyl acetate (4 × 250 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/EtOAc 92.5:7.5) gave diester **122** (20.6 g, 72.5 mmol, 62%) as a white solid. R_f = 0.80 (petrol/EtOAc 85:15); mp 58–60 °C (lit.[48] 59–60 °C);IR ν_{max} (KBr)/cm^{-1} 2979, 1720, 1369, 1257, 1161, 1003; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.45 (2 H, br. s, C(4)H × 2), 2.26 (8 H, s, C(2)H_2 × 2 and C(3)H_2 × 2), 1.44 (18 H, s, C(CH_3)$_3$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.5

(C1 × 2), 129.4 (C4 × 2), 80.1 (*C*(CH_3)$_3$), 35.4 (C2 × 2), 28.1, 28.0 (C3 × 2 and C(*C*H_3)$_3$ × 2). Data were consistent with those previously reported.[48]

(*E*)-Oct-4-ene-1,8-diol (120)



122 **120**

To a stirred solution of diester **122** (14.0 g, 49.0 mmol) in tetrahydrofuran (300 mL) was added lithium aluminium hydride (7.84 g, 196 mmol) at 0 °C in 5 portions over 15 minutes. The resulting mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction was carefully quenched by the sequential addition of water (8 mL), an aqueous solution of NaOH (15% w/v, 8 mL) and water (24 mL). The mixture was then poured into 100 mL of ether and stirred for 30 minutes. The insoluble material was removed by filtration through a plug of celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, EtOAc) to give diol **120** (6.95 g, 48.3 mmol, 98%) as a colourless oil. $R_f = 0.40$ (EtOAc); IR ν_{max} (film)/cm^{-1} 3500-3100, 2944, 1668, 1445, 1057; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.47 (2 H, t, $J = 3.7$, C(4)H × 2), 3.65 (4 H, t, $J = 6.4$, C(1)H_2 × 2), 2.13-2.05 (4 H, m, C(3)H_2 × 2), 1.63 (4 H, quin, $J = 6.9$, C(2)H_2 × 2), 1.55 (2 H, s, OH × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 130.2 (C4 × 2), 62.5 (C1 × 2), 32.4 (C2 × 2), 28.9 (C3 × 2). Data were consistent with those previously reported.[47]

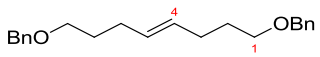
(*E*)-8-(Benzyloxy)oct-4-en-1-ol (124)

120 **124**

To a solution of diol **120** (8.25 g, 57.0 mmol) in dimethylformamide (120 mL) was added sodium hydride (60% dispersion in mineral oil, 1.14 g, 28.5 mmol) at 0 °C. The reaction mixture was stirred for 1 hour at 0 ºC before benzyl bromide (3.25 g, 19.0 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 1 hour and stirred for a further 4 hours before being quenched with water (100 mL). The resulting mixture was extracted with ethyl acetate (4 × 200 mL) and the combined organic layers were

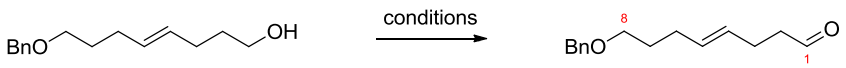
washed with an aqueous solution of $CuSO_4$ (2 M, 200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/EtOAc 50:50) afforded monoether **124** (3.90 g, 16.7 mmol, 88%) and diether **125** (585 mg, 1.80 mmol, 9%). $R_f = 0.55$ (petrol/EtOAc 50:50); IR ν_{max} (film)/cm^{-1} 3385, 3030, 2934, 1453, 1364, 1205, 1102; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.24 (5 H, m, Ph*H* × 5), 5.44 (2 H, t, *J* = 5.1, C(4)H and C(5)H), 4.51 (2 H, s, C*H*$_2$Ph), 3.63 (2 H, t, *J* = 6.4, C(1)H$_2$), 3.48 (2 H, t, *J* = 6.6, C(8)H$_2$), 2.17–2.00 (4 H, m, C(3)H$_2$ and C(6)H$_2$), 1.74–1.58 (4 H, m, C(2)H$_2$ and C(7)H$_2$), 1.57 (1 H, s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.6 (PhC$_q$), 130.6, 130.0 (C4 and C5), 128.4 (PhC), 127.7 (PhC), 127.5 (PhC), 72.9 (*C*H$_2$Ph), 69.7 (C8), 62.5 (C1), 32.4 (C2), 29.6 (C7), 29.2 (C6), 28.9 (C3). Data were consistent with those previously reported.[129,130]

(*E*)-1,8-Bis(benzyloxy)oct-4-ene (125)



$R_f = 0.90$ (petrol/EtOAc 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43–7.25 (10 H, m, Ph*H* × 10), 5.43 (2 H, t, *J* = 3.5, C(4)H × 2), 4.52 (4 H, s, C*H*$_2$Ph × 2), 3.48 (4 H, t, *J* = 6.6, C(1)H$_2$ × 2), 2.19–2.04 (4 H, m, C(3)H$_2$ × 2), 1.69 (4 H, quin, *J* = 6.9, C(2)H$_2$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.7 (PhC$_q$), 130.1 (C4 × 2), 128.4 (PhC), 127.7 (PhC), 127.5 (PhC), 72.9 (C5 × 2), 69.8 (C1 × 2), 29.6 (C2 × 2), 29.2 (C3 × 2). Data were consistent with those previously reported.[131]

(*E*)-8-(Benzyloxy)oct-4-enal (VI)



124 **VI**

Procedure A (Swern):

To a solution of oxalyl chloride (2.14 g, 16.8 mmol) in dichloromethane (50 mL) was added dimethylsulfoxide (2.63 g, 33.7 mmol) dropwise at –78 °C. The resulting mixture was stirred for 15 minutes before a solution of alcohol **124** (1.97 g, 8.42 mmol) in dichloromethane (15 mL and 5 mL rinse) was added dropwise over 10 minutes. The reaction mixture was

stirred for 30 minutes before triethylamine (3.41 g, 33.7 mmol) was added. The mixture was stirred for a further 30 minutes before being allowed to warm to room temperature. The reaction was quenched with a saturated solution of NH_4Cl (50 mL), the layers were separated and the aqueous phase extracted with dichloromethane (4 × 50 mL). The combined organic extracts were washed with an aqueous solution of $CuSO_4$ (2 M, 50 mL), water (30 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 85:15) to afford aldehyde **VI** (1.66 g, 7.20 mmol, 85%) as an oil.

Procedure B (Dess–Martin):

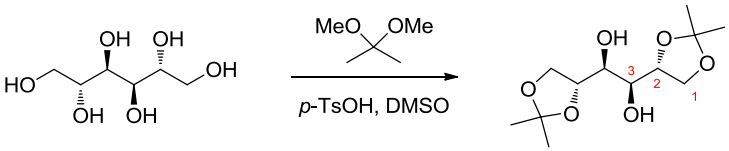
To a solution of alcohol **124** (840 mg, 3.59 mmol) in dichloromethane (30 mL) was added Dess-Martin periodinane (2.28 g, 5.38 mmol) in one portion and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane (10 mL), petrol (25 mL), a saturated aqueous solution of $NaHCO_3$ (10 mL) and the biphasic mixture was cooled to 0 °C. A saturated aqueous solution of $Na_2S_2O_3$ (10 mL) was added dropwise and the resulting mixture was stirred vigorously for 30 minutes before being diluted with ethyl acetate (80 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 mL), water (2 × 5 mL), brine (2 × 5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 85:15) to afford aldehyde **VI** (758 mg, 3.26 mmol, 91%) as an oil.

Procedure C (Parikh–Doering):

To a stirred solution of alcohol **124** (13.2 g, 56.4 mmol) in dichloromethane (280 mL) were added dimethyl sulfoxide (12.0 mL, 169 mmol) and diisopropylethylamine (29.4 mL, 169 mmol) and the resulting mixture was cooled to 0 °C. Sulfur trioxide pyridine complex (26.9 g, 169 mmol) was added in one portion, the resultant mixture was stirred for 2 hours at 0 °C. The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (100 mL), followed by a saturated aqueous solution of $NaHCO_3$ (100 mL). The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 85:15) to give aldehyde **VI** (11.5 g, 49.6 mmol, 88%) as a colourless oil.

$R_f = 0.75$ (petrol/EtOAc 60:40); IR ν_{max} (film)/cm^{-1} 3030, 2852, 2721, 1725, 1453, 1364, 1103; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.75 (1 H, s, C(1)H), 7.41–7.23 (5 H, m, Ph*H* × 5), 5.52–5.37 (2 H, m, C(4)H and C(5)H), 4.50 (2 H, s, C*H*$_2$Ph), 3.47 (2 H, t, $J = 6.6$, C(8)H$_2$), 2.52–2.45 (2 H, m, C(2)H$_2$), 2.37–2.29 (2 H, m, C(3)H$_2$), 2.13–2.06 (2 H, m, C(6)H$_2$), 1.68 (2 H, quin, $J = 7.0$, C(7)H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.4 (C1), 138.6 (PhC$_q$), 131.2, 128.4 (C4 and C5), 128.3, 127.7, 127.5 (PhC × 5), 72.9 (*C*H$_2$Ph), 69.6 (C8), 43.5 (C2), 29.4 (C7), 29.1 (C6), 25.1 (C3); HRMS (ESI$^+$, *m/z*) for $C_{15}H_{20}NaO_2$ calculated 255.1356, found 255.1353.

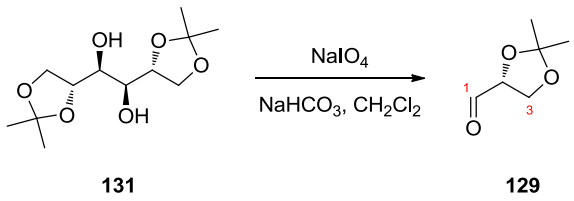
(1*S*,2*S*)-1,2-*Bis*((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (131)



130 **131**

To a solution of D-mannitol (50.0 g, 303 mmol) in dimethylsulfoxide (82 mL) were added 2,2-dimethoxypropane (78.7 g, 757 mmol) and *para*-toluenesulfonic acid (275 mg) at room temperature. Within 2 hours the suspended solids had dissolved and the resulting solution was stirred for 16 hours. The reaction mixture was poured into an aqueous solution of $NaHCO_3$ (3% w/v, 300 mL) and the resulting mixture was extracted with ethyl acetate (4 × 400 mL). The combined extracts were washed with water (3 × 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Ethyl acetate (150 mL) was added to the residue and the mixture was heated to reflux to redissolve the solids. The resulting solution was diluted with hot hexane (450 mL) and the mixture was allowed to cool to room temperature. The resulting crystalline material was collected by filtration, washed with a 1:3 mixture of ether and hexane and dried to give bisacetonide **131** (43.7 g, 16.7 mmol, 55%) as a white solid. mp 119–120 ºC; IR ν_{max} (KBr)/cm^{-1} 3403, 3288, 2934, 2894, 1385, 1373, 1264, 1211, 1069; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.20 (2 H, q, $J = 6.3$, C(2)H × 2), 4.17–4.10 (2 H, m, C(1)*H*$_A$H$_B$ × 2), 3.98 (2 H, dd, $J = 8.5$ and 5.7, C(1)H$_A$*H*$_B$ × 2), 3.76 (2 H, t, $J = 6.2$, C(3)H × 2), 2.60 (2 H, d, $J = 6.3$, OH × 2), 1.43 (6 H, s, C(CH$_3$)$_2$ × 2), 1.37 (6 H, s, C(CH$_3$)$_2$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 109.4 (*C*(CH$_3$)$_2$), 76.3 (C2 × 2), 71.2 (C3 × 2), 66.7 (C1 × 2), 26.7 (C(*C*H$_3$)CH$_3$ × 2), 25.2 (C(CH$_3$)*C*H$_3$ × 2). Data were consistent with those previously reported.[132]

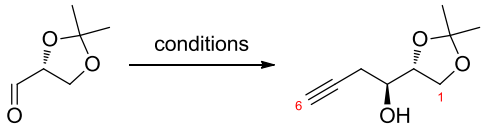
(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (129)



131 **129**

To a stirred solution of diol **131** (5.00 g, 19.1 mmol) in dichloromethane (50 mL) were added sodium periodate (8.1 g, 38 mmol) and a saturated aqueous solution of $NaHCO_3$ (4 mL) and the resulting mixture was stirred vigorously at room temperature for 2 hours. Magnesium sulfate (3.0 g) was then added and stirring was continued for 20 minutes. The resultant slurry was filtered through a plug of celite and the filtrate was subsequently concentrated *in vacuo* to afford crude aldehyde **129** (3.72 g, 2.90 mmol, 75%) which was used in the next step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 9.70 (1 H, d, J = 1.7, C(1)H), 4.42–4.32 (1 H, m,C(2)H), 4.23–4.02 (2 H, m, C(3)H_2), 1.47 (3 H, s, C(CH_3)CH_3), 1.40 (3 H, s, C(CH_3)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 201.8 (C1), 111.2 (*C*(CH_3)$_2$), 79.8 (C2), 65.5 (C3), 26.2 (C(CH_3)*C*H_3), 25.1 (C(*C*H_3)CH_3). Data were consistent with those previously reported.[132]

(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-yn-1-ol (132)



129 **132**

Procedure A:

Activated zinc dust (5.28 g, 80.7 mmol) was added carefully to a vigorously stirred solution of aldehyde **129** (3.50 g, 26.9 mmol) and propargyl bromide (80% w/v solution in toluene, 6.00 mL, 53.8 mmol) in a 1:1 mixture of *N*,*N*-dimethylformamide (30 mL) and ether (30 mL) at 0 °C. The flask was then quickly fitted with an air condenser. The water/ice bath was removed and after 5 minutes the reaction brought itself to reflux. The mixture was stirred for 8 hours at room temperature before being quenched with a saturated aqueous solution of NH_4Cl (50 mL). The aqueous layer was separated and extracted with ethyl acetate

(3 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to afford alcohol **132** (3.34 g, 19.6 mmol, 73%) as a thick colourless oil and as a 86:14 mixture of diastereoisomers.

Procedure B:

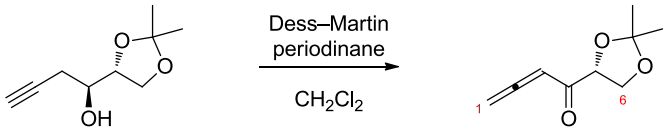
To a suspension of aldehyde **129** (5.00 g, 38.4 mmol) and activated zinc dust (4.99 g, 76.9 mmol) in tetrahydrofuran (60 mL) at 0 ºC was added propargyl bromide (80% w/v solution in toluene, 8.57 mL, 76.9 mmol) dropwise (a vigorous exotherm). The resulting suspension was stirred vigorously for 10 minutes at 0 °C and a saturated aqueous solution of NH_4Cl (15 mL) was added dropwise over a period of 30 minutes. The resulting mixture was warmed to room temperature and stirred for 12 hours before being filtered through a plug of celite. The precipitate was thoroughly washed with chloroform (3 × 25 mL). The aqueous layer was separated and treated with a cold aqueous solution of HCl (5%, 10 mL) to dissolve the suspended material. The aqueous phase was extracted with chloroform (3 × 100 mL) and the combined organic extracts were washed with an aqueous solution of $NaHCO_3$ (10%, 30 mL), brine (25 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to afford alcohol **132** (4.43 g, 26.0 mmol, 68%) as a thick colourless oil and as a 89:11 mixture of diastereoisomers.

Procedure C:

Zinc dust (10.0 g, 153 mmol) was activated by stirring with an aqueous solution of HCl (1 M, 200 mL) for 30 minutes, before being washed with water (2 × 100 mL), absolute ethanol (2 × 100 mL), ether (2 × 100 mL) and dried under high vacuum. To a stirred suspension of activated zinc dust (8.63 g, 132 mmol) in tetrahydrofuran (30 mL) at 0 °C was added propagyl bromide (80% w/v solution in toluene, 14.2 mL, 132 mmol) dropwise (a vigorous exotherm). The resulting mixture was cooled to –78 °C before a solution of aldehyde **129** (8.60 g, 66.2 mmol) in tetrahydrofuran (15 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 2 hours before it was warmed to room temperature and stirred for a further 6 hours. The mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and filtered through a plug of celite. The layers were separated and the aqueous layer was extracted with chloroform (3 × 100 mL). the combined organic extracts were washed with brine (100 mL), dried over dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude

product was purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to afford alcohol **132** (8.45 g, 49.7.0 mmol, 75%) as a thick colourless oil and as a 92:8 mixture of diastereoisomers. $[\alpha]_D^{20}$ +3.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.11–4.05 (2 H, m, C(1)H_AH$_B$ and C(2)H), 4.01–3.94 (1 H, m, C(1)H$_A$$H_B$), 3.77 (1 H, d, J = 5.3, C(3)H), 2.50 (2 H, ddd, J = 8.7, 5.9 and 2.5, C(4)H_2), 2.33 (1 H, br. s, OH), 2.08 (1 H, t, J = 2.5, C(6)H), 1.41 (3 H, s, C(CH_3)CH$_3$), 1.35 (3 H, s, C(CH$_3$)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 109.4 (C(CH$_3$)$_2$), 80.1 (C5), 77.3 (C2), 71.2 (C6), 70.1 (C3), 65.9 (C1), 26.6 (C(CH$_3$)CH$_3$), 25.1 (C(CH$_3$)CH$_3$), 23.6 (C4). Spectroscopic data were consistent with those previously reported.[133]

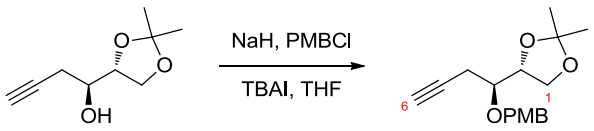
(*R*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)buta-2,3-dien-1-one (134)



132 **134**

To a suspension of Dess–Martin periodinane (636 mg, 1.50 mmol) in dichloromethane (6.0 mL) was added a solution of alcohol **132** (170 mg, 1.0 mmol) in dichloromethane (4.0 mL) dropwise. The reaction mixture was stirred at room temperature for 2 hours before being quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous layer was separated, extracted with ethyl acetate (3 × 75 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 75:25) to give ketone **134** (121 mg, 0.72 mmol, 72%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.10 (1 H, t, J = 6.5, C(3)H), 5.30 (2 H, dd, J = 6.5 and 1.0, C(1)H_2), 4.85 (1 H, dd, J = 7.5 and 6.1, C(5)H), 4.26 (1 H, t, J = 8.0, C(6)H_AH$_B$), 4.01 (1 H, dd, J = 8.5 and 6.1, C(6)H$_A$$H_B$), 1.49 (3 H, s, C(C$H_3$)CH$_3$), 1.42 (3 H, s, C(CH$_3$)C$H_3$). Data were consistent with those previously reported.[134]

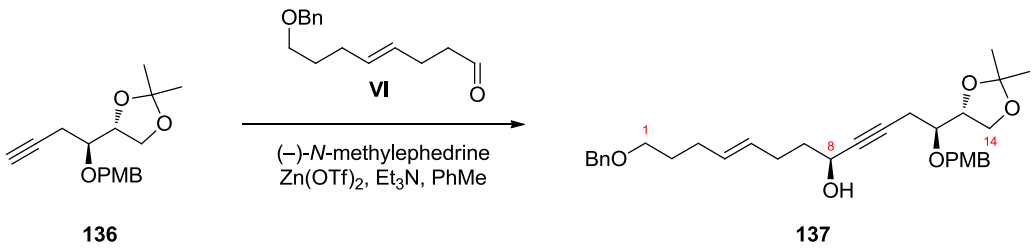
(*R*)-4-((*S*)-1-(4-Methoxybenzyloxy)but-3-ynyl)-2,2-dimethyl-1,3-dioxolane (136)



132 **136**

To a stirred solution of alcohol **132** (2.38 g, 14.0 mmol) in tetrahydrofuran (50 mL) was added sodium hydride (60% dispersion in mineral oil, 644 mg, 16.1 mmol) in one portion at 0 °C and the resulting mixture was stirred at this temperature for 1 hour. Tetrabutylammonium iodide (264 mg, 0.70 mmol) was added, followed by the slow dropwise addition of *para*-methoxybenzyl chloride (2.35 mL, 16.8 mmol). The resulting mixture was stirred for 30 minutes at 0 °C and then heated to 60 °C and stirred for a further 16 hours. The reaction mixture was cooled to room temperature and quenched with a saturated aqueous solution of NH_4Cl (25 mL) and water (25 mL). The aqueous layer was separated, extracted with ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 95:5) to afford alkyne **136** (3.45 g, 11.9 mmol, 85%) as a pale yellow oil. $[\alpha]_D^{20}$ +37.3 (*c* 1.64, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3290, 2987, 2936, 1613, 1514, 1464, 1371, 1249, 1076, 849; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.29 (2 H, d, *J* = 8.6, Ar*H* × 2), 6.89 (2 H, d, *J* = 8.6, Ar*H* × 2), 4.72 (1 H, d, *J* = 11.1, C*H*$_A$H$_B$C$_6$H$_4$OCH$_3$), 4.53 (1 H, d, *J* = 11.1, CH$_A$*H*$_B$C$_6$H$_4$OCH$_3$), 4.18 (1 H, q, *J* = 6.5, C(2)H), 4.06 (1 H, dd, *J* = 8.2 and 6.4, C(1)*H*$_A$H$_B$), 3.88 (1 H, dd, *J* = 8.6 and 5.6, C(1)H$_A$*H*$_B$), 3.81 (3 H, s, C$_6$H$_4$OC*H*$_3$), 3.55 (1 H, dt, *J* = 7.0 and 4.8, C(3)H), 2.69–2.58 (1 H, m, C(4)*H*$_A$H$_B$), 2.55–2.46 (1 H, m, C(4)H$_A$*H*$_B$), 2.07–2.03 (1 H, m, C(6)H), 1.40 (3 H, s, C(C*H*$_3$)CH$_3$), 1.35 (3 H, s, C(CH$_3$)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.4 (ArC$_q$), 130.0 (ArC$_q$), 129.6 (ArC), 113.8 (ArC), 109.3 (*C*(CH$_3$)$_2$), 80.6 (C5), 77.2 (C3), 76.4 (C2), 72.0 (*C*H$_2$C$_6$H$_4$OCH$_3$), 70.4 (C6), 66.7 (C1), 55.3 (C$_6$H$_4$O*C*H$_3$), 26.8 (C(*C*H$_3$)CH$_3$), 25.3 (C(CH$_3$)*C*H$_3$), 21.0 (C4); HRMS (ESI$^+$, *m/z*) for $C_{17}H_{22}NaO_4$ calculated 313.1410, found 313.1409.

(1*S*,5*S*,8*E*)-12-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxybenzyloxy)dodec-8-en-3-yn-5-ol (137)



Procedure A:

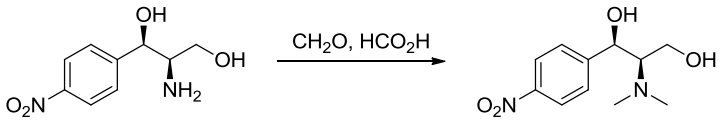
To a stirred solution of alkyne **136** (100 mg, 0.340 mmol) in tetrahydrofuran (5.0 mL) was added *n*-butyllithium (1.6 M solution in hexanes, 0.21 mL, 0.34 mmol) dropwise at –78 °C. The resulting mixture was stirred for 45 minutes before a solution of aldehyde **VI** (80 mg, 0.34 mmol) in tetrahydrofuran (2.0 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), the aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/EtOAc 70:30) gave alcohol **137** (113 mg, 0.22 mmol, 63%) as a pale yellow oil and as a 1:1 mixture of diastereoisomers.

Procedure B:

$Zn(OTf)_2$ (2.58 g, 7.10 mmol) was placed in a 100 mL flask and dried at 125 °C under high vacuum for 48 hours. (–)-*N*-methylephedrine (1.39 g, 7.75 mmol) was dried at room temperature under high vacuum for 48 hours in a separate flask. The (–)-*N*-methylephedrine was dissolved in toluene (18 mL) and transferred *via* cannula to the flask containing $Zn(OTf)_2$. Triethylamine (1.08 mL, 7.75 mmol) was added and the reaction mixture was stirred at room temperature for 3 hours under argon. The alkyne **136** (2.25 g, 7.75 mmol) was dissolved in toluene (9.0 mL) and added dropwise over 15 minutes. The resultant mixture was stirred for 1 hour before a solution of aldehyde **VI** (1.50 g, 6.46 mmol) in toluene (3.0 mL) was added slowly over 7 hours. The reaction mixture was stirred for a further 24 hours before being diluted with ether (20 mL) and quenched with a saturated NH_4Cl solution (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with brine (75 mL), dried over Na_2SO_4 and

concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to give alcohol **137** (1.62 g, 3.10 mmol, 48%) as a colourless oil. Spectroscopic data for 95:5 mixture of diastereoisomers. IR ν_{max} (film)/cm^{-1} 3443, 2935, 1613, 1586, 1514, 1454, 1371, 1302, 1249; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.31 (4 H, m, Ph*H* × 4), 7.28 (3 H, d, *J* = 8.6, Ph*H* and Ar*H* × 2), 6.88 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.43 (2 H, q, *J* = 5.4, C(4)H and C(5)H), 4.70 (1 H, d, *J* = 11.1, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.53 (1 H, d, *J* = 11.4, CH$_A$$H_BC_6H_4OCH_3$), 4.50 (2 H, s, C$H_2$Ph), 4.36 (1 H, t, *J* = 6.3, C(8)H), 4.15 (1 H, quin, *J* = 6.1, C(13)H), 4.09–4.03 (1 H, m, C(14)H_AH$_B$), 3.89 (1 H, dd, *J* = 8.3 and 5.6, C(14)H$_A$$H_B$), 3.80 (3 H, s, C$_6H_4OCH_3$), 3.58–3.51 (1 H, m, C(12)H), 3.47 (2 H, t, *J* = 6.6, C(1)H$_2$), 2.70–2.60 (1 H, m, C(11)H_AH$_B$), 2.58–2.48 (1 H, m, C(11)H$_A$$H_B$), 2.19–2.14 (2 H, m, C(7)H$_2$), 2.07 (2 H, dd, *J* = 7.5 and 5.9, C(3)H$_2$), 1.76–1.70 (2 H, m, C(6)H$_2$), 1.70–1.65 (2 H, m, C(2)H$_2$), 1.41 (3 H, s, C(CH_3)CH$_3$), 1.35 (3 H, s, C(CH$_3$)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.3 (ArC$_q$), 138.6 (PhC$_q$), 130.6 (C4/C5), 130.0 (ArC$_q$), 129.5 (C4/C5), 129.5 (ArC), 128.3 (PhC), 127.6 (PhC), 127.5 (PhC), 113.8 (ArC), 109.3 (*C*(CH$_3$)$_2$), 83.0 (C10), 81.6 (C9), 77.4 (C12), 76.6 (C13), 72.8 (*C*H$_2$Ph), 72.0 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.7 (C1), 66.6 (C14), 62.2 (C8), 55.3 (C$_6$H$_4$O*C*H$_3$), 37.7 (C7), 29.5 (C6), 29.1 (C2), 28.3 (C3), 26.7 (C(*C*H$_3$)CH$_3$), 25.2 (C(CH$_3$)*C*H$_3$), 21.3 (C11); HRMS (ESI$^+$, *m/z*) for $C_{32}H_{42}NaO_6$ calculated 545.2874, found 545.2871.

(1*R*,2*R*)-2-(Dimethylamino)-1-(4-nitrophenyl)propane-1,3-diol (139)

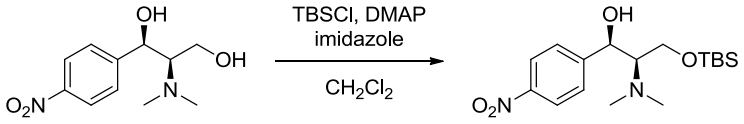


138 **139**

To a mixture of formaldehyde (37–40% in H_2O, 30 mL) and formic acid (98%, 40 mL) was added (1*R*,2*R*)-2-amino-3-(*p*-nitrophenyl)propane-1,3-diol (**138**) (4.00 g, 18.8 mmol) and the resulting mixture was refluxed for 10 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was neutralised with an aqueous solution of NaOH (2 M, 50 mL) and extracted with dichloromethane (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Al_2O_3, CH_2Cl_2/MeOH 95:5) to give diol **139** (4.10 g, 17.1 mmol, 92%) as a yellow solid.

mp 87 °C (lit.[79] 88.9–89.1 °C); $[\alpha]_D^{20}$ +24.1 (*c* 0.50, MeOH), lit.[78,79] +25.7 (*c* 0.505, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.19–8.10 (2 H, m, Ar*H* × 2), 7.59–7.51 (2 H, m, Ar*H* × 2), 4.54 (1 H, d, *J* = 9.6, C*H*(OH)CHN), 3.56–3.49 (2 H, m, C*H*$_2$OH), 2.54 (1 H, dd, *J* = 9.7 and 4.9, C*H*N(CH$_3$)$_2$), 2.49 (6 H, s, NCH$_3$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 150.1 (ArC$_q$), 147.4 (ArC$_q$), 128.0 (ArC), 123.5 (ArC), 71.2 (*C*H(OH)CHN), 69.8 (NCH), 57.5 (CH_2OH), 41.5 (NCH$_3$ × 2). Spectroscopic data were consistent with those previously reported.[78]

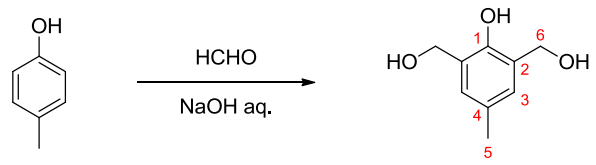
(1*R*,2*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-(dimethylamino)-1-(4-nitrophenyl)propan-1-ol (140)



139 **140**

To a stirred solution of diol **139** (4.10 g, 17.0 mmol) in dichloromethane (60 mL) were added imidazole (2.89 g, 42.5 mmol) and 4-(dimethylamino)pyridine (21 mg, 0.17 mmol) and the resulting mixture was stirred until all the reagents had dissolved. *tert*-Butyldimethysilylchloride (2.77 g, 17.8 mmol) was added in one portion and the mixture was stirred for 20 hours. The reaction mixture was poured into water (40 mL) and a cold aqueous solution of HCl (0.5 M) was added until pH = 8. The aqueous phase was separated and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with a saturated aqueous solution of Na_2CO_3 (50 mL), brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, CH_2Cl_2/MeOH 20:1) afforded alcohol **140** (3.63 g, 10.2 mmol, 60%) as a yellow oil. $[\alpha]_D^{20}$ −17.2 (*c* 1.00, $CHCl_3$), lit.[78,79] −15.8 (*c* 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.19 (2 H, d, *J* = 8.6, Ar*H* × 2), 7.59 (2 H, d, *J* = 8.6, Ar*H* × 2), 4.62 (1 H, d, *J* = 9.6, C*H*(OH)CHN), 3.69–3.60 (1 H, m, C*H*$_A$H$_B$OTBS), 3.51–3.42 (1 H, m, CH$_A$*H*$_B$OTBS), 2.49 (7 H, s, NCH$_3$ × 2 and OH), 0.86 (9 H, s, SiC(CH$_3$)$_3$), –0.04 (6 H, br. s, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 150.3 (ArC$_q$), 147.4 (ArC$_q$), 128.1 (ArC), 123.4 (ArC), 71.4 (*C*H(OH)CHN), 69.1 (NCH), 57.1 (*C*H$_2$OTBS), 41.7 (NCH$_3$ × 2), 25.8 (SiC(*C*H$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), –5.8 (Si(CH$_3$)$_2$). Data were consistent with those previously reported.[78]

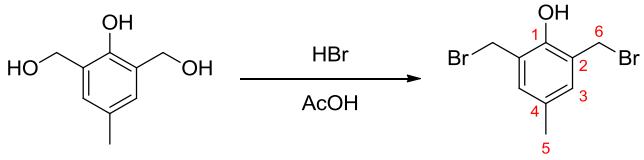
(2-Hydroxy-5-methyl-1,3-phenylene)dimethanol (142)



141 **142**

To a stirred solution of *p*-cresol (**141**) (5.40 g, 50.0 mmol) in an aqueous solution of NaOH (25% w/v, 10 mL) was added an aqueous solution of formaldehyde (37%, 10 mL) and the resulting mixture was stirred for 15 hours before being filtered. The collected solid was dissolved in water, followed by the slow addition of acetic acid inducing crystallisation of the product. The resultant white solid was filtered, washed with water and dried under vacuum to give diol **142** (3.41 g, 20.3 mmol, 40%) as a white solid. mp 126–128 °C (lit.[87] 130 °C); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ_H 6.92 (2 H, s, C(3)H × 2), 4.72 (4 H, s, C(6)H_2 × 2), 3.06 (3 H, br. s, OH × 3), 2.21 (3 H, s, C(5)H_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ_C 152.4 (C1), 128.5 (C4), 127.6 (C2 × 2), 127.6 (C3 × 2), 62.2 (C6 × 2), 20.6 (C5). Data were consistent with those previously reported.[87]

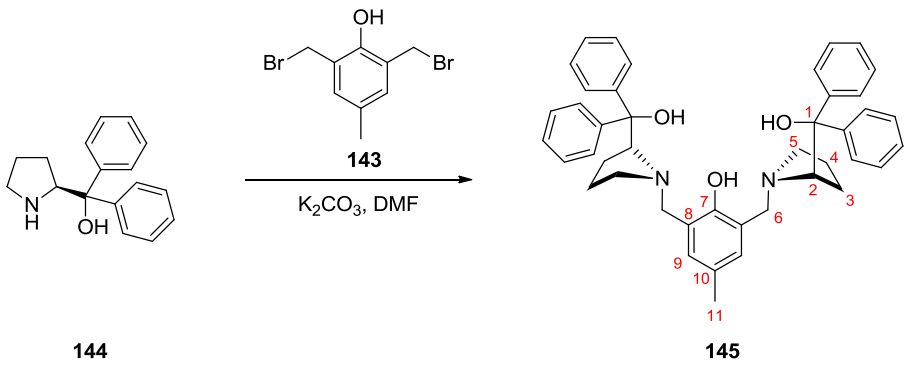
2,6-Bis(bromomethyl)-4-methylphenol (143)



142 **143**

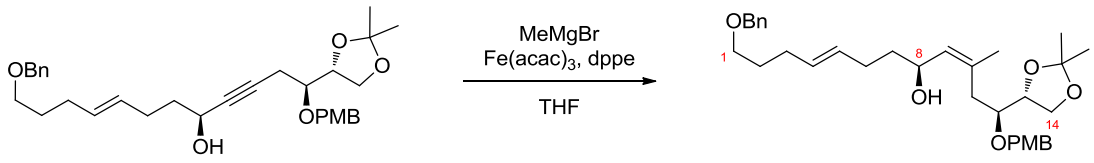
To a solution of HBr in acetic acid (33% w/w, 5.4 mL) was added diol **142** (1.00 g, 5.95 mmol) and the resulting suspension was stirred for 24 hours before being diluted with water (20 mL). The resulting mixture was filtered, the crystals washed with water and dried under vaccum to give dibromide **143** (1.14 g, 3.87 mmol, 65%) as white crystals. mp 84–86 °C (lit.[87] 85–93 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 7.09 (2 H, s, C(3)H × 2), 5.50 (1 H, br. s, OH), 4.55 (4 H, s, C(6)H_2 × 2), 2.27 (3 H, s, C(5)H_3). Data were consistent with those previously reported.[87]

((2*R*,2'*S*)-1,1'-((2-Hydroxy-5-methyl-1,3-phenylene)bis(methylene))bis(pyrrolidine-2,1-diyl))bis(diphenylmethanol) (145)



To a stirred solution of prolinol **144**[135] (1.32 g, 5.22 mmol) in *N*,*N*-dimethylformamide (10 mL) was added K_2CO_3 (2.88 g, 20.8 mmol). The resulting mixture was cooled to 0 °C and dibromide **143** (760 mg, 2.60 mmol) was added in one portion. The mixture was warmed to room temperature and stirred for 12 hours before being diluted with water (50 mL) and ether (50 mL). The phases were separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Al_2O_3, petrol/EtOAc 80:20) to yield an yellow oil which was dissolved in ether and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was azeotroped with anhydrous benzene (2 × 5 mL) to give ProPhenol **145** (1.20 g, 1.88 mmol, 72%) as a pale yellow crusty foam. $[\alpha]_D^{25}$ +46.5 (*c* 2.50, $CHCl_3$), lit.[87] $[\alpha]_D^{25}$ +49.8 (*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (4 H, d, *J* = 6.8, Ph*H* × 4), 7.56 (4 H, d, *J* = 7.6, Ph*H* × 4), 7.40–7.23 (12 H, m, Ph*H* × 12), 6.59 (2 H, br. s, C(9)H × 2), 4.01 (2 H, dd, *J* = 9.0 and 4.7, C(2)H × 2), 3.39 (2 H, d, *J* = 12.6, C(6)H_AH_B × 2), 3.22 (2 H, d, *J* = 12.1, C(6)H_AH_B × 2), 2.89–2.82 (2 H, m, C(5)H_AH_B × 2), 2.47–2.38 (2 H, m, C(5)H_AH_B × 2), 2.15 (3 H, s, C(11)H_3), 2.09–1.95 (2 H, m, C(3)H_AH_B × 2), 1.89–1.79 (2 H, m, C(3)H_AH_B × 2.), 1.70–1.60 (2 H, m, C(4)H_AH_B × 2), 1.56–1.43 (2 H, m, C(4)H_AH_B × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 152.7 (C7), 146.9 and 146.4 (PhC_q), 130.0 (C9 × 2), 128.9 (PhC), 128.3 (PhC), 128.2 (PhC), 127.9 (PhC), 127.1 (C10), 126.6 (PhC), 126.4 (PhC), 126.0 (PhC), 125.9 (PhC), 123.8 (C8 × 2), 78.9 (C1 × 2), 71.4 (C2 × 2), 57.7 (C6 × 2), 54.9 (C5 × 2), 29.6 (C3 × 2), 24.0 (C4 × 2), 20.3 (C11). Data were consistent with those previously reported.[87]

(1*S*,3*Z*,5*S*,8*E*)-12-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxybenzyloxy)-3-methyldodeca-3,8-dien-5-ol (151)

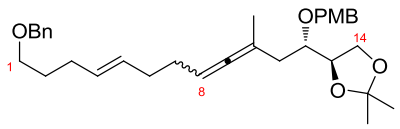


137 **151**

To a stirred solution of alcohol **137** (360 mg, 0.690 mmol) in tetrahydrofuran (7.0 mL) were added iron(III) acetylacetonate (48.7 mg, 0.140 mmol) and 1,2-bis(diphenylphosphino)ethane (56.7 mg, 0.140 mmol). The resulting mixture was cooled to −78 °C and stirred for 10 minutes. Methylmagnesium bromide (3.0 M solution in Et_2O, 1.15 mL, 3.45 mmol) was added dropwise and the resulting mixture was stirred for 2 hours before being warmed to 0 °C and stirred for a further 8 hours. The reaction mixture was cooled to −78 °C and quenched by the dropwise addition of a saturated aqueous solution of NH_4Cl (10 mL). The mixture was warmed to room temperature and diluted with ether (10 mL). The layers were separated and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 75:25) to give alcohol **151** (189 mg, 0.350 mmol, 51%) as a colourless oil. $[\alpha]_D^{20}$ +10.7 (*c* 0.84, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3458, 2934, 2360, 1613, 1586, 1514, 1455, 1371, 1249, 1072; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.26 (5 H, m, Ph*H* × 5), 7.24 (2 H, d, *J* = 8.3, Ar*H* × 2), 6.87 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.41 (2 H, br. s, C(4)H and C(5)H), 5.30 (1 H, d, *J* = 8.6, C(9)H), 4.61–4.55 (1 H, m, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.54–4.47 (3 H, m, CH_2Ph and CH$_A$H$_B$C$_6$H$_4$OCH$_3$), 4.36–4.27 (1 H, m, C(8)H), 4.11–4.01 (2 H, m, C(13)H and C(14)H_AH$_B$), 3.87–3.82 (1 H, m, C(14)H$_A$H$_B$), 3.80 (3 H, s, C$_6$H$_4$OCH_3), 3.60 (1 H, q, *J* = 5.7, C(12)H), 3.47 (2 H, t, *J* = 6.4, C(1)H$_2$), 2.51–2.43 (1 H, m, C(11)H_AH$_B$), 2.41–2.32 (1 H, m, C(11)H$_A$H$_B$), 2.12–1.95 (4 H, m, C(3)H$_2$ and C(6)H$_2$), 1.79 (3 H, s, C(10)CH$_3$), 1.70–1.64 (2 H, m, C(2)H$_2$), 1.62–1.55 (1 H, m, C(7)H_AH$_B$), 1.52–1.44 (1 H, m, C(7)H$_A$H$_B$), 1.40 (3 H, s, C(CH_3)CH$_3$), 1.34 (3 H, s, C(CH$_3$)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.3 (ArC$_q$), 138.6 (ArC$_q$), 134.9 (C10), 131.2 (ArC$_q$) , 130.3 (C9), 130.0, 129.8 (C4 and C5), 129.6 (ArC), 128.3 (PhC), 127.6 (PhC), 127.5 (PhC), 113.8 (ArC), 109.4 (*C*(CH$_3$)$_2$), 78.3 (C13), 77.2 (C12), 72.8 (*C*H$_2$Ph), 72.2 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.8 (C1), 67.5 (C8), 66.7 (C14), 55.2 (C$_6$H$_4$O*C*H$_3$), 37.0 (C7), 34.8 (C11),

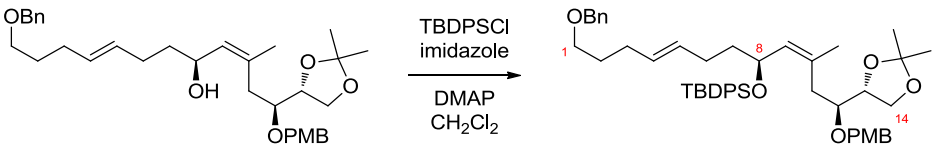
29.6 (C2), 29.1, 28.7 (C3 and C6), 26.5 (C(*C*H$_3$)CH$_3$), 25.3 (C(CH$_3$)*C*H$_3$), 24.4 (C(10)*C*H$_3$); HRMS (ESI$^+$, *m/z*) for $C_{33}H_{46}NaO_6$ calculated 561.3187, found 561.3189.

(4*R*)-4-((1*S*,*E*)-12-(Benzyloxy)-1-((4-methoxybenzyl)oxy)-3-methyldodeca-3,4,8-trien-1-yl)-2,2-dimethyl-1,3-dioxolane (153)



Allene **153** was isolated as a side-product in the synthesis of allylic alcohol **151**.
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43–7.26 (7 H, m, Ar*H* × 7), 6.95–6.86 (2 H, m, Ar*H* × 2), 5.53–5.39 (2 H, m, C(4)H and C(5)H), 5.13–5.05 (1 H, m, C(8)H), 4.65 (2 H, s, C*H*$_2$C$_6$H$_4$OCH$_3$), 4.56–4.49 (2 H, m, C*H*$_2$Ph), 4.24–4.16 (1 H, m, C(13)H), 4.09–4.03 (1 H, m, C(14)*H*$_A$H$_B$), 4.00–3.93 (1 H. m, C(14)H$_A$*H*$_B$), 3.85–3.74 (4 H, m, C(12)H and C$_6$H$_4$OC*H*$_3$), 3.55–3.46 (2 H, m, C(1)H$_2$), 2.36–2.00 (8 H, m, C(3)H$_2$, C(6)H$_2$, C(7)H$_2$ and C(11)H$_2$), 1.78–1.67 (5 H, m, C(2)H$_2$ and C(10)CH$_3$), 1.48 (3 H, s, C(C*H*$_3$)CH$_3$), 1.40 (3 H, s, C(CH$_3$)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 202.2 (C9), 159.1 (ArC$_q$), 138.7 (ArC$_q$), 132.9 (ArC), 132.8 (ArC), 132.7 (ArC), 130.9 (ArC$_q$), 130.1 (C4/C5), 129.3 (C4/C5), 128.7 (ArC), 128.5 (ArC), 128.5 (ArC), 128.4 (ArC), 128.4 (ArC), 127.6 (ArC), 127.5 (ArC), 113.7 (ArC), 109.0 (*C*(CH$_3$)$_2$), 96.3 (C10), 90.2 (C8), 77.9 (C13), 77.2 (C12), 72.9 (*C*H$_2$Ph), 72.6 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.8 (C1), 65.8 (C14), 55.2 (C$_6$H$_4$O*C*H$_3$), 36.6, 32.4, 29.6, 29.2 and 29.2 (C2, C3 and C6), 26.6 (C(CH$_3$)*C*H$_3$), 25.5 (C(*C*H$_3$)CH$_3$), 23.9 and 23.9 (C7), 20.0 (C(10)CH3).

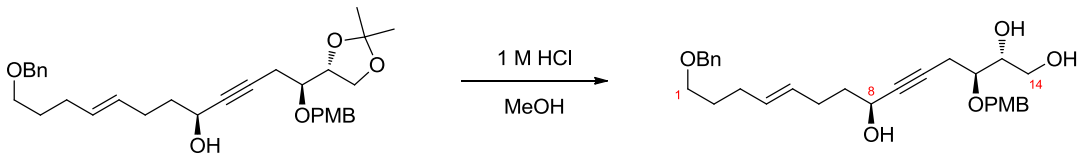
(((1*S*,3*Z*,5*S*,8*E*)-12-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((4-methoxybenzyl)oxy)-3-methyldodeca-3,8-dien-5-yl)oxy)(*tert*-butyl)diphenylsilane (159)



151 **159**

To a stirred solution of alcohol **151** (180 mg, 0.333 mmol) in *N*,*N*-dimethylformamide (3.3 mL) was added imidazole (79.7 mg, 1.17 mmol), followed by the dropwise addition of *tert*-butyl(chloro)diphenylsilane (128 μL, 0.500 mmol). The resulting mixture was stirred at room temperature for 12 hours before being quenched with water (10 mL) and stirred for a further 10 minutes. The resultant mixture was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 85:15) to afford ether **159** (245 mg, 0.316 mmol, 95%) as an oil. $R_f = 0.65$ (petrol/Et_2O 80:20); $[\alpha]_D^{20}$ +9.1 (*c* 0.35, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2932, 2856, 1614, 1514, 1428, 1370, 1248, 1110, 1072; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.79–7.68 (4 H, m, Ph*H* × 4), 7.48–7.34 (11 H, m, Ph*H* × 11), 7.16 (2 H, d, *J* = 8.6, Ar*H* × 2), 6.85 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.38–5.28 (3 H, m, C(4)H, C(5)H and C(9)H), 4.53 (2 H, s, CH_2Ph), 4.47–4.36 (3 H, m, C(8)H and C$H_2C_6H_4OCH_3$), 3.83–3.75 (5 H, m, C(12)H, C(14)H_AH_B and $C_6H_4OCH_3$), 3.72–3.65 (1 H, m, C(14)H_AH_B), 3.52–3.42 (3 H, m, C(1)H_2 and C(13)H), 2.14–1.97 (4 H, m, C(3)H_2 and C(6)H_2), 1.82 (1 H, dd, *J* = 14.1 and 8.8, C(11)H_AH_B), 1.72–1.60 (3 H, m, C(2)H_2 and C(7)H_AH_B), 1.58 (3 H, s, C(10)CH_3), 1.54–1.42 (2 H, m, C(7)H_AH_B and C(11)H_AH_B), 1.37 (3 H, s, C(CH_3)CH_3), 1.32 (3 H, s, C(CH_3)CH_3), 1.11 (9 H, s, SiC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.1 (ArC_q), 138.8 (PhC_q), 136.1 (PhC), 136.0 (PhC), 135.4 (C10), 134.9 (PhC), 134.8 (PhC_q), 134.6 (PhC_q), 132.1 (PhC_q), 131.9 and 130.9 (C4 and C9), 130.7 (ArC_q), 129.7 (ArC), 129.6 (C5), 129.4 (PhC), 129.3 (PhC), 128.4 (PhC), 127.8 (PhC), 127.7 (PhC), 127.7 (PhC), 127.3 (PhC), 113.7 (ArC), 109.0 (*C*(CH_3)$_2$), 78.2 (C12), 76.8 (C13), 72.9 (*C*H_2Ph), 72.7 (*C*$H_2C_6H_4OCH_3$), 70.0 (C1), 69.8 (C8), 65.7 (C14), 55.3 ($C_6H_4OCH_3$), 38.5 (C7), 34.3 (C11), 29.7 (C2), 29.3, 28.3 (C3 and C6), 26.7 (SiC(*C*H_3)$_3$), 26.6 (C(*C*H_3)CH_3), 25.4 (C(CH_3)*C*H_3), 23.8 (C(10)*C*H_3), 19.1 (Si*C*(CH_3)$_3$); HRMS (ESI^+, *m/z*) for $C_{49}H_{64}NaO_6Si$ calculated 799.4364, found 799.4349.

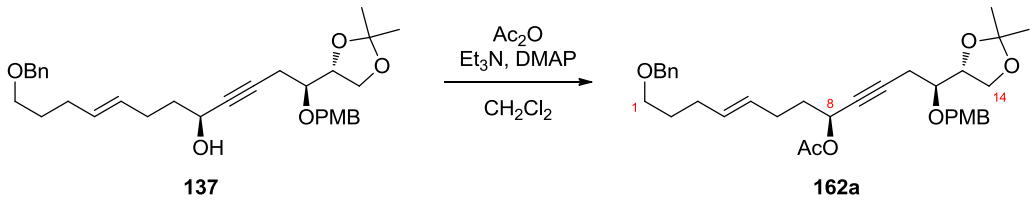
(2*R*,3*S*,7*S*,*E*)-14-(Benzyloxy)-3-((4-methoxybenzyl)oxy)tetradec-10-en-5-yne-1,2,7-triol (161)



137 **161**

To a stirred solution of alcohol **137** (100 mg, 0.191 mmol) in methanol (5.0 mL) was added an aqueous solution of HCl (1 M, 0.4 mL). The resultant mixture was stirred for 12 hours before being quenched with a saturated aqueous solution of $NaHCO_3$ (1.0 mL). The mixture was diluted with ethyl acetate (5.0 mL) and water (5.0 mL), the aqueous layer was separated and extracted with ethyl acetate (3 × 5.0 mL). The combined organic extracts were washed with brine (5.0 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 60:40) to give triol **161** (89.2 mg, 0.185 mmol, 97%) as an oil. $R_f = 0.30$ (petrol/acetone 40:60); $[\alpha]_D^{20}$ +31.0 (*c* 0.70, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3600–3200, 2933, 1613, 1514, 1250, 1175, 1087; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.32 (4 H, m, Ph*H* × 4), 7.31–7.24 (3 H, m, Ar*H* × 2 and Ph*H*), 6.88 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.44 (2 H, q, *J* = 5.6, C(4)H and C(5)H), 4.66 (1 H, d, *J* = 11.1, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.50 (2 H, s, CH_2Ph), 4.49–4.43 (1 H, m, CH$_A$H$_B$C$_6$H$_4$OCH$_3$), 4.34 (1 H, t, *J* = 6.4, C(8)H), 3.86–3.78 (4 H, m, C(13)H and C$_6$H$_4$OCH_3), 3.77–3.68 (2 H, m, C(14)H$_2$), 3.62 (1 H, q, *J* = 5.6, C(12)H), 3.47 (2 H, t, *J* = 6.4, C(1)H$_2$), 2.67–2.40 (5 H, m, C(11)H$_2$ and OH × 3), 2.19–2.11 (2 H, m, C(6)H$_2$), 2.11–2.04 (2 H, m, C(3)H$_2$), 1.78–1.62 (4 H, m, C(2)H$_2$ and C(7)H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.4 (ArC$_q$), 138.6 (PhC$_q$), 130.6 (C4/C5), 129.7 (ArC$_q$), 129.6 (C4/C5), 129.4 (ArC), 128.3 (PhC), 127.6 (PhC), 127.5 (PhC), 113.9 (ArC), 83.4 (C9), 81.3 (C10), 78.0 (C12), 72.8 (*C*H$_2$Ph), 72.2 (C13), 72.0 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.7 (C1), 63.3 (C14), 62.0 (C8), 55.3 (C$_6$H$_4$O*C*H$_3$), 37.6 (C7), 29.5 (C2), 29.1 (C3), 28.3 (C6), 20.6 (C11); HRMS (ESI$^+$, *m/z*) for $C_{29}H_{39}NaO_6$ calculated 505.2566, found 505.2557.

(1*S*,5*S*,*E*)-12-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((4-methoxybenzyl)oxy)dodec-8-en-3-yn-5-yl acetate (162a)

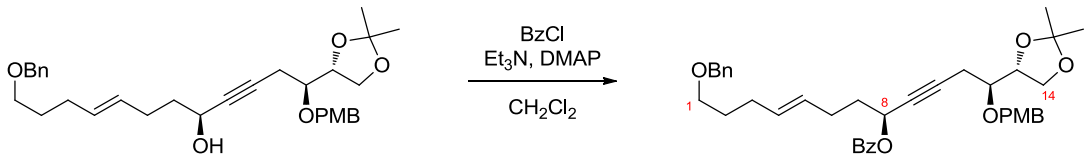


137 **162a**

To a stirred solution of alcohol **137** (50 mg, 0.096 mmol) in dichloromethane (0.5 mL) was added triethylamine (40 µL, 0.29 mmol), followed by 4-(dimethylamino)pyridine (1.2 mg, 0.01 mmol) at 0 °C. Acetic anhydride (13 µL, 0.14 mmol) was added dropwise and the resulting mixture was warmed to room temperature and left stirring for 10 hours. The reaction

mixture was diluted with dichloromethane (5.0 mL) and quenched with a saturated aqueous solution of NH_4Cl (2.0 mL). The layers were separated and the aqueous layer extracted with dichloromethane (3 × 2 mL). The combined organic extracts were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/EtOAc 80:20) afforded acetate **162a** (48 mg, 0.085 mmol, 89%) as an oil. $R_f = 0.70$ (petrol/EtOAc 70:30); $[\alpha]_D^{25}$ −3.6 (*c* 1.65, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3342, 2935, 1740, 1613, 1586, 1514, 1454, 1371, 1302, 1236, 1174, 1076; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.32 (4 H, m, Ph*H* × 4), 7.28 (3 H, d, *J* = 9.1, Ar*H* × 2, Ph*H* × 1), 6.88 (2 H, d, *J* = 8.3, Ar*H* × 2), 5.49–5.32 (3 H, m, C(4)H, C(5)H and C(8)H), 4.72 (1 H, d, *J* = 11.1, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.56–4.48 (3 H, m, CH_2Ph and CH$_A$$H_BC_6H_4OCH_3$), 4.11 (1 H, q, *J* = 6.1, C(13)H), 4.08–4.02 (1 H, m, C(14)H_AH$_B$), 3.87 (1 H, dd, *J* = 7.8 and 5.6, C(14)H$_A$$H_B$), 3.80 (3 H, s, C$_6H_4OCH_3$), 3.56 (1 H, q, *J* = 5.8, C(12)H), 3.47 (2 H, t, *J* = 6.4, C(1)H$_2$), 2.71–2.60 (1 H, m, C(11)H_AH$_B$), 2.57–2.46 (1 H, m, C(11)H$_A$$H_B$), 2.20–1.99 (7 H, m, C(3)H$_2$, C(6)H$_2$ and C(O)CH$_3$), 1.80 (2 H, dt, *J* = 13.8 and 6.9, C(7)H$_2$), 1.67 (2 H, quin, *J* = 6.9, C(2)H$_2$), 1.41 (3 H, s, C(CH_3)CH$_3$), 1.35 (3 H, s, C(CH$_3$)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.0 (*C*(O)CH$_3$), 159.3 (ArC$_q$), 138.6 (PhC$_q$), 130.8 (C4/C5), 130.1 (ArC$_q$), 129.5 (PhC), 128.8 (C4/C5), 128.3 (ArC), 127.6 (PhC), 127.5 (PhC), 113.8 (ArC), 109.3 (*C*(CH$_3$)$_2$), 82.5 (C10), 79.3 (C9), 77.5 (C12), 76.8 (C13), 72.8 (*C*H$_2$Ph), 72.2 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.7 (C1), 66.6 (C14), 63.9 (C8), 55.2 (C$_6$H$_4$O*C*H$_3$), 34.8 (C7), 29.5 (C2), 29.1 (C3), 28.1 (C6), 26.7 (C(*C*H$_3$)CH$_3$), 25.2 (C(CH$_3$)*C*H$_3$), 21.6 (C11), 21.0 (C(O)*C*H$_3$); HRMS (ESI$^+$, *m/z*) for $C_{34}H_{44}NaO_7$ calculated 587.2985, found 587.2980.

(1*S*,5*S*,*E*)-12-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((4-methoxybenzyl)oxy)dodec-8-en-3-yn-5-yl benzoate (162b)

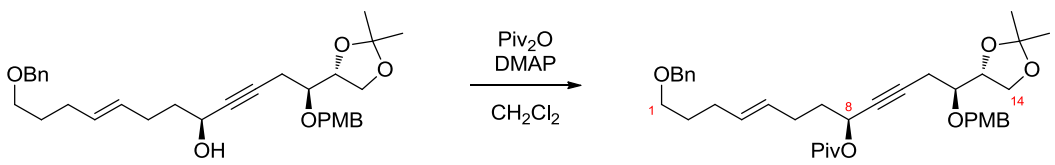


137 **162b**

To a stirred solution of alcohol **137** (6.48 g, 12.40 mmol) in dichloromethane (100 mL) was added triethylamine (2.59mL, 18.6 mmol), followed by 4-(dimethylamino)pyridine (303 mg, 2.48 mmol) and the resultant mixture was cooled to 0 °C. Benzoyl chloride (1.73 mL,

14.9 mmol) was added dropwise and the resulting mixture was warmed to room temperature and stirred for 6 hours. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL) and the mixture was stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to give benzoate **162b** (7.26 g, 11.6 mmol, 94%) as an oil. $R_f = 0.50$ (petrol/ethyl acetate 80:20); $[\alpha]_D^{25}$ +6.0 (*c* 0.91, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3200–2800, 1721, 1613, 1586, 1514, 1453, 1370, 1266, 1175, 1106; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.11 (2 H, d, $J = 7.3$, Ph*H* × 2), 7.63–7.55 (1 H, m, Ph*H*), 7.51–7.43 (2 H, m, Ph*H* × 2), 7.38 (3 H, d, $J = 4.3$, Ph*H* × 3), 7.34–7.25 (4 H, m, Ar*H* × 2 and Ph*H* × 2), 6.85 (2 H, d, $J = 8.6$, Ar*H* × 2), 5.68 (1 H, t, $J = 6.4$, C(8)H), 5.49 (2 H, t, $J = 5.1$, C(4)H and C(5)H), 4.76 (1 H, d, $J = 11.1$, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.59–4.50 (3 H, m, CH_2Ph and CH$_A$H$_B$C$_6$H$_4$OCH$_3$), 4.16 (1 H, q, $J = 6.3$, C(13)H), 4.09 (1 H, t, $J = 7.3$, C(14)H_AH$_B$), 3.91 (1 H, dd, $J = 8.2$ and 5.7, C(14)H$_A$H$_B$), 3.80 (3 H, s, C$_6$H$_4$OCH_3), 3.65–3.57 (1 H, m, C(12)H), 3.50 (2 H, t, $J = 6.4$, C(1)H$_2$), 2.77–2.67 (1 H, m, C(11)H_AH$_B$), 2.62–2.52 (1 H, m, C(11)H$_A$H$_B$), 2.32–2.23 (2 H, m, C(6)H$_2$), 2.17–2.09 (2 H, m, C(3)H$_2$), 2.07–1.94 (2 H, m, C(7)H$_2$), 1.71 (2 H, quin, $J = 6.9$, C(2)H$_2$), 1.44 (3 H, s, C(CH_3)CH$_3$), 1.38 (3 H, s, C(CH$_3$)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.5 (*C*(O)Ph), 159.3 (ArC$_q$), 138.7 (PhC$_q$), 133.0 (PhC), 131.0 (C4), 130.2 (ArC$_q$), 130.1 (PhC$_q$), 129.8 (ArC), 129.5 (ArC), 128.9 (C5), 128.4 (PhC), 128.4 (PhC), 127.7 (PhC), 127.5 (PhC), 113.8 (ArC), 109.3 (*C*(CH$_3$)$_2$), 82.8 (C10), 79.4 (C9), 77.6 (C12), 76.8 (C13), 72.9 (*C*H$_2$Ph), 72.3 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.7 (C1), 66.7 (C14), 64.5 (C8), 55.2 (C$_6$H$_4$O*C*H$_3$), 35.0 (C7), 29.5 (C2), 29.2 (C3), 28.2 (C6), 26.7 (C(*C*H$_3$)CH$_3$), 25.3 (C(CH$_3$)*C*H$_3$), 21.7 (C11); HRMS (ESI$^+$, *m/z*) for $C_{39}H_{46}O_7$ calculated 649.3141, found 649.3142.

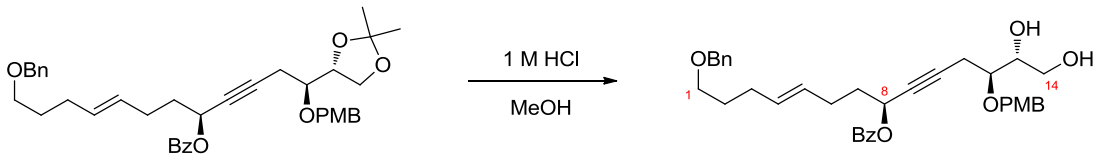
(1*S*,5*S*,*E*)-12-(Benzyloxy)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-((4-methoxybenzyl)oxy)dodec-8-en-3-yn-5-yl pivalate (162c)



137 **162c**

To a stirred solution of alcohol **137** (50 mg, 0.096 mmol) in dichloromethane (1.0 mL) was added 4-(dimethylamino)pyridine (71 mg, 0.58 mmol), followed by trimethylacetic anhydride (60 µL, 0.29 mmol). The reaction mixture was stirred at room temperature for 10 hours before methanol (1.0 mL) was added. The resulting mixture was stirred for 15 minutes before being concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to afford pivalate **162c** (56 mg, 0.093 mmol, 97%) as an oil. $R_f = 0.65$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −1.0 (*c* 2.0, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2935, 1732, 1614, 1514, 1456, 1369, 1249, 1148, 1078, 1035; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.33 (4 H, m, Ph*H* × 4), 7.28 (3 H, d, *J* = 8.1, Ar*H* × 2 and Ph*H*), 6.88 (2 H, d, *J* = 8.1, Ar*H* × 2), 5.42 (2 H, q, *J* = 4.8, C(4)H and C(5)H), 5.36 (1 H, t, *J* = 6.3, C(8)H), 4.72 (1 H, d, *J* = 11.1, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.53 (1 H, d, *J* = 8.0, CH$_A$$H_BC_6H_4OCH_3$), 4.51 (2 H, s, C$H_2$Ph), 4.12 (1 H, q, *J* = 6.1, C(13)H), 4.05 (1 H, t, *J* = 7.3, C(14)H_AH$_B$), 3.87 (1 H, dd, *J* = 7.6 and 6.3, C(14)H$_A$$H_B$), 3.80 (3 H, s, C$_6H_4OCH_3$), 3.56 (1 H, q, *J* = 5.3, C(12)H), 3.47 (2 H, t, *J* = 6.4, C(1)H), 2.65 (1 H, dd, *J* = 16.9 and 3.5, C(11)H_AH$_B$), 2.52 (1 H, dd, *J* = 17.2 and 5.8, C(11)H$_A$$H_B$), 2.18–2.04 (4 H, m, C(3)H$_2$ and C(6)H$_2$), 1.89–1.73 (2 H, m, C(7)H$_2$), 1.68 (2 H, quin, *J* = 6.8, C(2)H$_2$), 1.41 (3 H, s, C(CH_3)CH$_3$), 1.35 (3 H, s, C(CH$_3$)CH_3), 1.21 (9 H, s, C(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.4 (*C*(O)C(CH$_3$)$_3$), 159.4 (ArC$_q$), 138.7 (PhC$_q$), 130.9 (C4/C5), 130.3 (ArC$_q$), 129.6 (ArC), 129.0 (C4/C5), 128.4 (PhC), 127.7 (PhC), 127.6 (PhC), 113.9 (ArC), 109.4 (*C*(CH$_3$)$_2$), 82.2, 79.7 (C9 and C10), 77.6 (C12), 76.9 (C13), 72.9 (*C*H$_2$Ph), 72.3 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.8 (C1), 66.7 (C14), 63.7 (C8), 55.3 (C$_6$H$_4$O*C*H$_3$), 38.8 (*C*(CH$_3$)$_3$), 34.9 (C7), 29.6 (C2), 29.2, 28.2 (C3 and C6), 27.2 (C(*C*H$_3$)$_3$), 26.8 (C(*C*H$_3$)CH$_3$), 25.4 (C(CH$_3$)*C*H$_3$), 21.7 (C11); HRMS (ESI$^+$, *m/z*) for $C_{37}H_{50}NaO_7$ calculated 629.3454, found 629.3454.

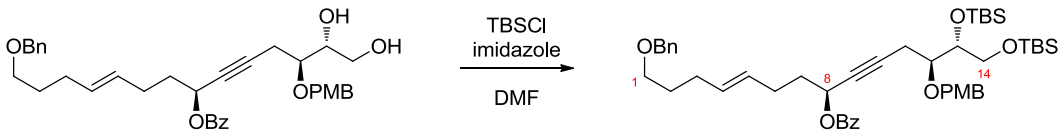
(2*R*,3*S*,7*S*,*E*)-14-(Benzyloxy)-1,2-dihydroxy-3-((4-methoxybenzyl)oxy)tetradec-10-en-5-yn-7-yl benzoate (163)



162b **163**

To a stirred solution of benzoate 1**62b** (6.89 g, 11.0 mmol) in methanol (150 mL) was added an aqueous solution of HCl (1 M, 6.0 mL) and the resulting mixture was stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL) and the resultant mixture was stirred for 30 minutes before being diluted with water (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 60:40) to afford diol **163** (6.33 g, 10.8 mmol, 98%) as an oil. $R_f = 0.45$ (petrol/acetone 60:40); $[\alpha]_D^{20}$ +1.0 (*c* 0.68, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3600–3200, 2935, 1716, 1613, 1586, 1514, 1453, 1249, 1176, 1107; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.07 (2 H, d, *J* = 7.6, Ph*H* × 2), 7.55 (1 H, d, *J* = 7.3, Ph*H*), 7.48–7.40 (2 H, m, Ph*H* × 2), 7.39–7.20 (7 H, m, Ph*H* × 5 and Ar*H* × 2), 6.82 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.60 (1 H, t, *J* = 6.2, C(8)H), 5.52–5.39 (2 H, m, C(4)H and C(5)H), 4.68 (1 H, d, *J* = 11.1, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.54–4.45 (3 H, m, CH_2Ph and CH$_A$H$_B$C$_6$H$_4$OCH$_3$), 3.81–3.66 (6 H, m, C(13)H, C(14)H$_2$ and C$_6$H$_4$OCH_3), 3.65–3.60 (1 H, m, C(12)H), 3.48 (2 H, t, *J* = 6.4, C(1)H$_2$), 2.70–2.53 (2 H, m, C(11)H$_2$), 2.29–2.19 (2 H, m, C(6)H$_2$), 2.13–2.06 (2 H, m, C(3)H$_2$), 2.04–1.91 (2 H, m, C(7)H$_2$), 1.68 (2 H, quin, *J* = 6.9, C(2)H$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.5 (*C*(O)Ph), 159.1 (ArC$_q$), 138.4 (PhC$_q$), 133.0 (PhC), 130.8 (C4), 129.8 (PhC$_q$), 129.8 (PhC$_q$), 129.6 (PhC), 129.3(ArC), 128.6 (C5), 128.2 (PhC), 128.2 (PhC), 127.5 (PhC), 127.3 (PhC), 113.6 (ArC), 82.9 (C10), 79.2 (C9), 77.9 (C12), 72.6 (*C*H$_2$Ph), 72.3 (C13), 72.0 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.5 (C1), 64.4 (C8), 63.1 (C14), 55.0 (C$_6$H$_4$O*C*H$_3$), 34.6 (C7), 29.2 (C2), 28.9 (C3), 28.0 (C6), 20.8 (C11); HRMS (ESI$^+$, *m/z*) for $C_{36}H_{42}NaO_7$ calculated 609.2828, found 609.2828.

(2*R*,3*S*,7*S*,*E*)-14-(Benzyloxy)-1,2-bis((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)tetradec-10-en-5-yn-7-yl benzoate (164)



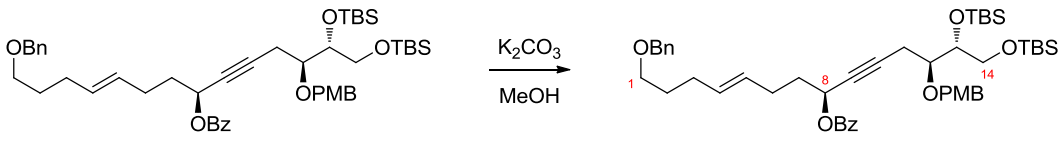
163 **164**

To a stirred solution of diol **163** (6.15 g, 10.5 mmol) in *N*,*N*-dimethylformamide (70 mL) was added imidazole (2.86 g, 42.0 mmol) and the resultant mixture was stirred until all reagents had dissolved. *tert*-Butyldimethylsilyl chloride (3.16 g, 21.0 mmol) was added in one portion

and the resulting mixture was stirred for 12 hours before water (100 mL) and ether (300 mL) were added. The layers were separated and the aqueous layer was extracted with ether (4 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 90:10) to give benzoate **164** (8.38 g, 10.3 mmol, 98%) as a pale yellow oil. $R_f = 0.45$ (petrol/Et_2O 80:20); $[\alpha]_D^{20}$ −4.4 (*c* 1.40, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2929, 2856, 2361, 2341, 1722, 1613, 1514, 1453, 1249, 1174, 1096, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.07 (2 H, d, *J* = 7.8, Ph*H* × 2), 7.61-7.53 (1 H, m, Ph*H*), 7.49-7.40 (2 H, m, Ph*H* × 2), 7.35 (4 H, m, Ph*H* × 4), 7.31-7.23 (3 H, m, Ph*H* and Ar*H* × 2), 6.81 (2 H, d, *J* = 8.3, Ar*H* × 2), 5.66 (1 H, t, *J* = 6.2, C(8)H), 5.44 (2 H, br. s, C(4)H and C(5)H), 4.64 (1 H, d, *J* = 11.2, $CH_AH_BC_6H_4OCH_3$), 4.56 (1 H, d, *J* = 11.2, $CH_AH_BC_6H_4OCH_3$), 4.51 (2 H, s, CH_2Ph), 3.85-3.79 (1 H, m, C(13)H), 3.77 (3 H, s, $C_6H_4OCH_3$), 3.71-3.67 (1 H, m, C(12)H), 3.64 (2 H, t, *J* = 4.7, C(14)H_2), 3.47 (2 H, t, *J* = 6.6, C(1)H_2), 2.66-2.57 (1 H, m, C(11)H_AH_B), 2.56-2.46 (1 H, m, C(11)H_AH_B), 2.28-2.17 (2 H, m, C(6)H_2), 2.12-2.05 (2 H, m, C(3)H_2), 2.03-1.87 (2 H, m, C(7)H_2), 1.72-1.63 (2 H, m, C(2)H_2), 0.89 (18 H, s, $SiC(CH_3)_3$ × 2), 0.08 (6 H, s, $SiCH_3$ × 2), 0.05 (6 H, s, $SiCH_3$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.5 (*C*(O)Ph), 159.0 (ArC_q), 138.6 (PhC_q), 133.0 (PhC), 130.8 (C4), 130.7 (PhC_q), 130.2 (ArC_q), 129.8 (PhC), 129.4 (ArC), 129.0 (C5), 128.3 (PhC), 128.3 (PhC), 127.6 (PhC), 127.5 (PhC), 113.6 (ArC), 84.2 (C10), 78.6 (C9), 78.2 (C12), 74.5 (C13), 72.8 (CH_2Ph), 72.3 ($CH_2C_6H_4OCH_3$), 69.7 (C1), 64.6 (C8), 64.5 (C14), 55.2 ($C_6H_4OCH_3$), 35.0 (C7), 29.5 (C2), 29.1 (C3), 28.2 (C6), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 21.0 (C11), 18.3 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.4 ($SiCH_3$), −4.8 ($SiCH_3$), −5.4 ($SiCH_3$ × 2); HRMS (ESI^+, *m/z*) for $C_{48}H_{70}NaO_7Si_2$ calculated 837.4558, found 837.4558.

(2*R*,3*S*,7*S*,*E*)-14-(Benzyloxy)-1,2-bis((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)tetradec-10-en-5-yn-7-ol (165)

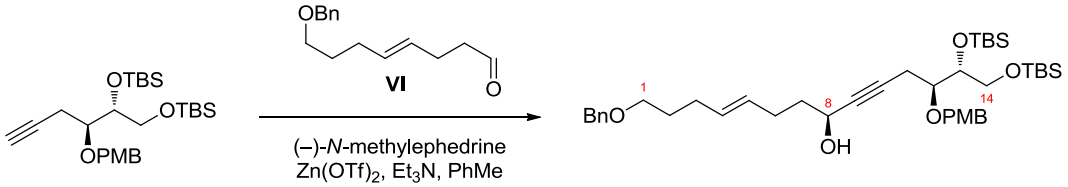
Procedure A:



164 **165**

To a stirred solution of benzoate **164** (8.22 g, 10.1 mmol) in methanol (100 mL) was added potassium carbonate (2.79 g, 20.2 mmol). The resulting mixture was stirred for 4 hours being concentrated *in vacuo*. The residue was dissolved in ether (100 mL) and the resulting solution washed with water (2 × 25 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 85:15) to give alcohol **165** (6.52 g, 9.19 mmol, 91%) as an oil.

Procedure B:

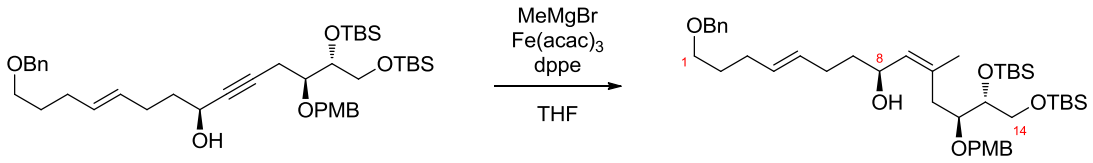


170 **165**

Zinc trifluoromethanesulfonate (5.98 g, 16.13 mmol) was dried at 130 ºC under high vacuum for 12 hours before the reaction flask was allowed to cool to room temperature and purged with argon. (–)-*N*-methylephedrine (3.15 g, 17.59 mmol) was added and the reaction flask was evacuated and purged with argon. The mixture was suspended in toluene (20 mL) and to the stirred mixture was added triethylamine (2.45 mL, 17.59 mmol) dropwise. The reaction mixture was stirred vigorously at room temperature for 3 hours. A solution of alkyne **170** (8.41 g, 17.90 mmol) in toluene (10 mL) was added dropwise over 15 minutes and the resultant mixture was stirred for 1 hour before a solution of aldehyde **VI** (3.40 g, 14.66 mmol) in toluene (15 mL) was added dropwise over 7 hours *via* a syringe pump. The reaction mixture was stirred vigorously for 14 hours at room temperature before being diluted with ether (50 mL) and quenched with a saturated aqueous solution of NH_4Cl (75 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to give alcohol **165** (5.62 g, 7.92 mmol, 54%) as a colourless oil. $R_f = 0.50$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −2.4 (*c* 1.08, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3600–3300, 2929, 1613, 1587, 1514, 1463, 1361, 1302, 1250, 1096; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.40–7.33 (4 H, m, Ph*H* × 4), 7.31 (3 H, d, $J = 8.3$, Ph*H* and Ar*H* × 2), 6.88 (2 H, d, $J = 8.6$, Ar*H* × 2), 5.51–5.38 (2 H, m, C(4)H and C(5)H), 4.64 (1 H, d, $J = 11.2$, $CH_AH_BC_6H_4OCH_3$),

4.60 (1 H, d, J = 11.2, $CH_AH_BC_6H_4OCH_3$), 4.51 (2 H, s, CH_2Ph), 4.35 (1 H, br. s, C(8)H), 3.87–3.82 (1 H, m, C(13)H), 3.80 (3 H, s, $C_6H_4OCH_3$), 3.72–3.61 (3 H, m, C(12)H and $C(14)H_2$), 3.48 (2 H, t, J = 6.6, $C(1)H_2$), 2.63–2.55 (1 H, m, $C(11)H_AH_B$), 2.55–2.46 (1 H, m, $C(11)H_AH_B$), 2.16 (2 H, d, J = 5.6, $C(6)H_2$), 2.09 (2 H, d, J = 6.1, $C(3)H_2$), 1.88 (1 H, br. s, OH), 1.77–1.64 (4 H, m, $C(2)H_2$ and $C(7)H_2$), 0.92 (9 H, s, $SiC(CH_3)_3$), 0.91 (9 H, s, $SiC(CH_3)_3$), 0.11 (3 H, s, $SiCH_3$), 0.10 (3 H, s, $SiCH_3$), 0.08 (6 H, s $SiCH_3$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.1 (ArC_q), 138.6 (PhC_q), 130.7 (ArC_q), 130.5 (C4), 129.6 (C5), 129.4 (ArC), 128.3 (PhC), 127.6 (PhC), 127.5 (PhC), 113.7 (ArC), 83.1 (C9), 82.3 (C10), 78.2 (C12), 74.4 (C13), 72.8 (CH_2Ph), 72.1 ($CH_2C_6H_4OCH_3$), 69.7 (C1), 64.5 (C14), 62.2 (C8), 55.2 ($C_6H_4OCH_3$), 37.8 (C7), 29.5 (C2), 29.1 (C3), 28.3 (C6), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 20.7 (C11), 18.3 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.3 ($SiCH_3$), −4.7($SiCH_3$), −5.3 ($SiCH_3$ × 2); HRMS (ESI^+, *m/z*) for $C_{41}H_{66}O_6Si_2$ calculated 733.4296, found 733.4295.

(2*R*,3*S*,5*Z*,7*S*,10*E*)-14-(Benzyloxy)-1,2-bis((*tert*-butyldimethylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-5-methyltetradeca-5,10-dien-7-ol (166)

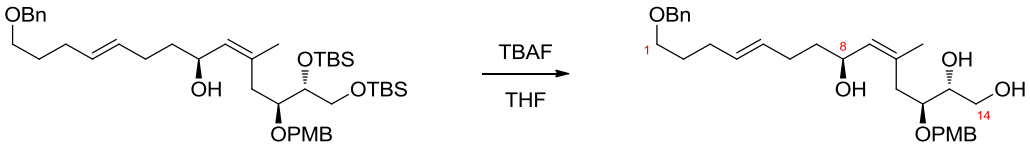


165 **166**

To a stirred solution of alcohol **165** (4.00 g, 5.63 mmol) in tetrahydrofuran (50 mL) were added iron(III) acetylacetonate (400 mg, 1.13 mmol) and 1,2-bis(diphenylphosphino)ethane (450 mg, 1.13 mmol). The resulting mixture was cooled to −78 °C and stirred for 10 minutes. Methylmagnesium bromide (3.0 M in Et_2O, 15.0 mL, 45.0 mmol) was added dropwise over 10 minutes and the resulting mixture was stirred for 2 hours before being warmed to 0 °C and stirred for a further 18 hours. The reaction mixture was cooled to −78 °C and quenched by the dropwise addition of a saturated aqueous solution of NH_4Cl (20 mL). The mixture was warmed to room temperature and diluted with ether (50 mL). The layers were separated and the aqueous layer was extracted with ether (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 85:15) to give alcohol **166** (3.59 g, 4.95 mmol, 88%) as an oil. R_f = 0.40 (petrol/EtOAc 90:10); $[\alpha]_D^{20}$ −6.6

(*c* 0.90, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3600–3300, 3050–2800, 1613, 1514, 1471, 1250, 1102; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 (4 H, d, *J* = 4.5, Ph*H* × 4), 7.32–7.26 (3 H, m, Ph*H*, Ar*H* × 2), 6.89 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.44 (2 H, br. s, C(4)H and C(5)H), 5.34 (1 H, d, *J* = 8.3, C(9)H), 4.63 (1 H, d, *J* = 11.5, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.54 (2 H, s, CH_2Ph), 4.46 (1 H, d, *J* = 11.5, CH$_A$$H_BC_6H_4OCH_3$), 4.44–4.36 (1 H, m, C(8)H), 3.98 (1 H, td, *J* = 5.9 and 1.8, C(13)H), 3.81 (3 H, s, C$_6$H$_4$OCH_3), 3.79–3.74 (1 H, m, C(12)H), 3.67 (2 H, d, *J* = 6.3, C(14)H$_2$), 3.51 (2 H, t, *J* = 6.6, C(1)H$_2$), 2.54 (1 H, dd, *J* = 13.8 and 8.7, C(11)H_AH$_B$), 2.36–2.27 (1 H, m, C(11)H$_A$$H_B$), 2.19–2.01 (4 H, m, C(3)H$_2$ and C(6)H$_2$), 1.80–1.68 (5 H, m, C(2)H$_2$ and C(10)CH$_3$), 1.65–1.52 (2 H, m, C(7)H$_2$), 0.99 (9 H, s, SiC(CH$_3$)$_3$), 0.97 (9 H, s, SiC(CH$_3$)$_3$), 0.18 (3 H, s, SiCH$_3$), 0.17 (3 H, s, SiCH$_3$), 0.13 (6 H, s, SiCH$_3$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 158.9 (ArC$_q$), 138.5 (PhC$_q$), 135.2 (C10), 130.9 (C9), 130.5 (ArC$_q$), 130.5 and 129.4 (C4 and C5), 129.2 (ArC), 128.1 (PhC), 127.4 (PhC), 127.3 (PhC), 113.4 (ArC), 77.5 (C12), 74.7 (C13), 72.6 (*C*H$_2$Ph), 71.6 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.6 (C1), 67.7 (C8), 64.4 (C14), 54.9 (C$_6$H$_4$O*C*H$_3$), 37.1 (C7), 32.7 (C11), 29.4 (C2), 29.0 (C3), 28.6 (C6), 25.8 (SiC(*C*H$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 23.9 (C(10)*C*H$_3$), 18.1 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), −4.7 (SiCH$_3$), −4.7 (SiCH$_3$), −5.5 (SiCH$_3$), −5.6 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for $C_{42}H_{70}NaO_6Si_2$ calculated 749.4609, found 749.4609.

(2*R*,3*S*,5*Z*,7*S*,10*E*)-14-(Benzyloxy)-3-((4-methoxybenzyl)oxy)-5-methyltetradeca-5,10-diene-1,2,7-triol (154)



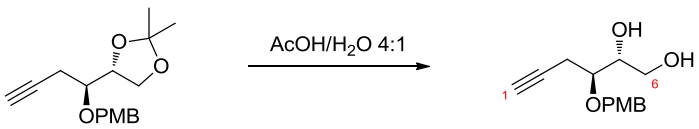
166 **154**

To a stirred solution of bis-TBS ether **166** (3.49 g, 4.81 mmol) in tetrahydrofuran (40 mL) was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 14.5 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 3 hours before being quenched with a saturated aqueous solution of NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (5 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 50:50) to give triol **154** (2.25 g, 4.52 mmol, 94%) as an oil. R_f = 0.45 (petrol/acetone 50:50);

$[\alpha]_D^{20}$ +13.5 (*c* 1.0, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3600–3100, 2933, 1613, 1514, 1454, 1302, 1249, 1175, 1077; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39–7.31 (4 H, m, Ph*H* × 4), 7.31–7.21 (3 H, m, Ph*H* and Ar*H* × 2), 6.87 (2 H, d, *J* = 8.1, Ar*H* × 2), 5.41 (2 H, br. s, C(4)H and C(5)H), 5.27 (1 H, d, *J* = 8.3, C(9)H), 4.57–4.52 (1 H, m, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.52–4.46 (3 H, m, CH_2Ph and CH$_A$$H_BC_6H_4OCH_3$), 4.39–4.30 (1 H, m, C(8)H), 3.79 (3 H, s, C$_6$H$_4$OCH_3), 3.75–3.60 (4 H, m, C(12)H, C(13)H and C(14)H$_2$), 3.48 (2 H, t, *J* = 6.4, C(1)H$_2$), 2.50 (1 H, d, *J* = 6.6, C(11)H_AH$_B$), 2.39–2.30 (1 H, m, C(11)H$_A$$H_B$), 2.12–2.04 (2 H, m, C(3)H$_2$), 2.04–1.95 (2 H, m, C(6)H$_2$), 1.77 (3 H, s, C(10)CH$_3$), 1.73–1.57 (4 H, m, C(2)H$_2$, C(7)H_AH$_B$ and OH), 1.54–1.42 (1 H, m, C(7)H$_A$$H_B$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.2 (ArC_q), 138.5 (PhC_q), 135.8 (C10), 130.4 (C9), 130.0 (ArC_q), 130.0 and 129.9 (C4 and C5), 129.5 (ArC), 128.2 (PhC), 127.6 (PhC), 127.4 (PhC), 113.7 (ArC), 78.0 (C12), 74.1 (C13), 72.7 (*C*H$_2$Ph), 71.9 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.7 (C1), 67.4 (C8), 63.3 (C14), 55.1 (C$_6$H$_4$O*C*H$_3$), 37.2 (C7), 34.4 (C11), 29.4 (C2), 29.0 (C3), 28.5 (C6), 24.0 (C(10)*C*H$_3$); HRMS (ESI$^+$, *m/z*) for $C_{30}H_{42}NaO_6$ calculated 521.2874, found 521.2879.

(2*R*,3*S*)-3-((4-Methoxybenzyl)oxy)hex-5-yne-1,2-diol (169)

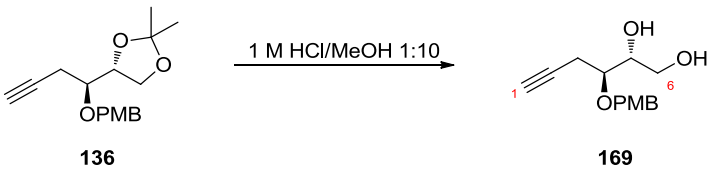
Procedure A:



136 **169**

To a stirred mixture of acetonide **136** (11.6 g, 40.0 mmol) and water (25 mL) was added acetic acid (100 mL) and the resulting mixture was stirred for 14 hours. The reaction mixture was diluted with ethyl acetate (100 mL), solid $NaHCO_3$ (50 g) was added portionwise and the resultant mixture was stirred for a further 30 minutes. The phases were separated and the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 50:50) to give diol **169** (9.90 g, 39.6 mmol, 99%) as an oil.

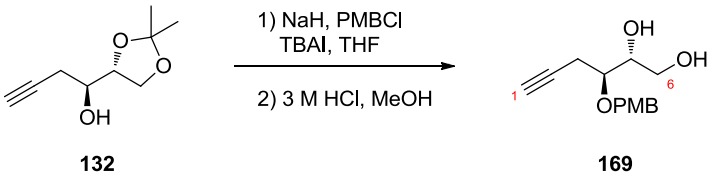
Procedure B:



136 **169**

To a stirred solution of acetonide **136** (4.64 g, 16.0 mmol) in methanol (145 mL) was added an aqueous solution of HCl (1 M, 15 mL). The resulting mixture was stirred for 12 hours before solid $NaHCO_3$ (2 g) was added and the mixture was stirred for a further 15 minutes. Methanol was removed *in vacuo* and the residue diluted with water (50 mL) and ethyl acetate (100 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (4 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 50:50) to give diol **169** (9.90 g, 39.6 mmol, 99%) as an oil.

Procedure C:

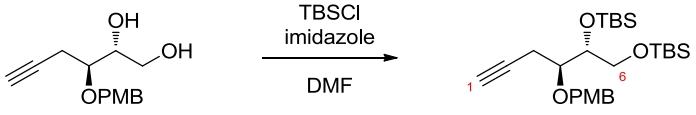


132 **169**

To a stirred solution of alcohol **132** (5.29 g, 31.1 mmol) in tetrahydrofuran (90 mL) was added sodium hydride (60% dispersion in mineral oil, 1.37 g, 34.2 mmol) in one portion at 0 °C and the resulting mixture was stirred for 1 hour. Tetrabutylammonium iodide (576 mg, 1.56 mmol) was added followed by the slow dropwise addition of *p*-methoxybenzyl chloride (4.42 mL, 32.6 mmol). The resulting mixture was stirred for 30 minutes at 0 °C and then heated to 60 °C and stirred for a further 16 hours. The reaction mixture was cooled to room temperature, quenched with water (20 mL) and left stirring for 10 minutes. The mixture was diluted with methanol (60 mL) and an aqueous solution of HCl (3 M, 10 mL) was added. The resultant mixture was stirred for 8 hours before a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The mixture was stirred for 20 minutes and concentrated *in vacuo*. The residue was diluted with ethyl acetate (100 mL) and water (100 mL) and the layers were

separated. The aqueous layer was extracted with ethyl acetate (4 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give diol **169** (6.38 g, 25.5 mmol, 82%) as a light yellow oil, which was used in the next step without further purification. $R_f = 0.40$ (petrol/acetone 60:40); $[\alpha]_D^{20}$ +39.5 (*c* 1.1, CH_2Cl_2), IR ν_{max} (film)/cm^{-1} 3600–3250, 2935, 1613, 1513, 1302, 1247, 1175, 1077, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 (2 H, d, *J* = 8.1, Ar*H* × 2), 6.89 (2 H, d, *J* = 8.3, Ar*H* × 2), 4.69 (1 H, d, *J* = 11.1, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.48 (1 H, d, *J* = 11.1, CH$_A$$H_BC_6H_4OCH_3$), 3.86–3.78 (4 H, m, C(5)H and C$_6$H$_4$OCH_3), 3.77–3.69 (2 H, m, C(6)H$_2$), 3.64 (1 H, q, *J* = 5.6, C(4)H), 2.78 (1 H, br. s, OH), 2.57 (2 H, dd, *J* = 4.9 and 2.4, C(3)H$_2$), 2.33 (1 H, br. s, OH), 2.05 (1 H, s, C(1)H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.4 (ArC_q), 129.8 (ArC_q), 129.7 (ArC), 113.9 (ArC), 80.6 (C2), 77.8 (C4), 72.2 (C5), 72.1 (*C*H$_2$C$_6$H$_4$OCH$_3$), 70.6 (C1), 63.2 (C6), 55.3 (C$_6$H$_4$O*C*H$_3$), 20.4 (C3); HRMS (ESI$^+$, *m/z*) for $C_{14}H_{18}NaO_4$ calculated 273.1097, found 273.1103.

(*R*)-5-((*S*)-1-((4-Methoxybenzyl)oxy)but-3-yn-1-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (170)

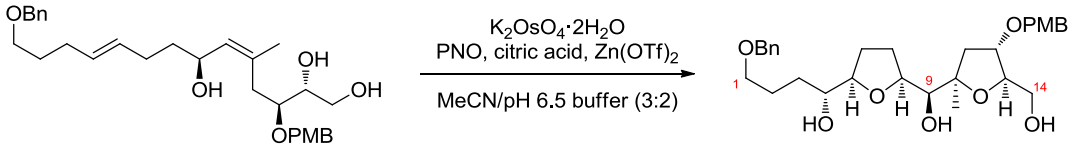


169 **170**

To a stirred solution of diol **169** (9.0 g, 36 mmol) in *N*,*N*-dimethylformamide (110 mL) was added imidazole (14.7 g, 216 mmol) and the resultant mixture was stirred until all reagents had dissolved. *tert*-Butyldimethylsilyl chloride (16.2 g, 108 mmol) was added in one portion and the resulting mixture was stirred for 12 hours before water (100 mL) and ether (300 mL) were added. The layers were separated and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were washed with water (3 × 50 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 90:10) to give alkyne **170** (14.3 g, 29.9 mmol, 83%) as an oil. $R_f = 0.65$ (petrol/Et_2O 80:20); $[\alpha]_D^{20}$ −5.3 (*c* 1.25, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3313, 2930, 1614, 1514, 1471, 1250, 1095; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.33 (2 H, d, *J* = 8.3, Ar*H* × 2), 6.90 (2 H, d, *J* = 8.6, Ar*H* × 2), 4.68 (1 H, d, *J* = 11.0, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.59 (1 H, d, *J* = 11.0, CH$_A$$H_BC_6H_4OCH_3$), 3.88 (1 H, q, *J* = 4.6, C(5)H),

3.82 (3 H, s, $C_6H_4OCH_3$), 3.75–3.64 (3 H, m, C(4)H and $C(6)H_2$), 2.64–2.55 (1 H, m, $C(3)H_AH_B$), 2.55–2.46 (1 H, m, $C(3)H_AH_B$), 2.01 (1 H, br. s, C(1)H), 0.95 (9 H, s, $SiC(CH_3)_3$), 0.94 (9 H, s, $SiC(CH_3)_3$), 0.14 (3 H, s, $SiCH_3$), 0.13 (3 H, s, $SiCH_3$), 0.10 (6 H, s, $SiCH_3 \times 2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.2 (ArC_q), 130.6 (ArC_q), 129.5 (ArC), 113.7 (ArC), 82.1 (C2), 77.7 (C4), 74.3 (C5), 72.2 (C7), 69.6 (C1), 64.5 (C6), 55.2 ($C_6H_4OCH_3$), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 20.4 (C3), 18.3 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −4.3 ($SiCH_3$), −4.8 ($SiCH_3$), −5.3 ($SiCH_3 \times 2$). HRMS (ESI^+, *m/z*) for $C_{26}H_{46}NaO_4Si$ calculated 501.2827, found 501.2831.

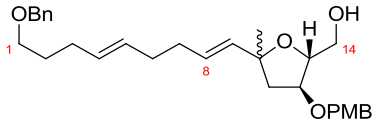
(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-hydroxy((2*R*,4*S*,5*R*)-5-(hydroxymethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butan-1-ol (216)



To a stirred solution of triol **154** (4.98 g, 10.0 mmol), pyridine *N*-oxide (95% purity, 4.00 g, 40.0 mmol) and citric acid (1.44 g, 7.50 mmol) in a mixture of acetonitrile (120 mL) and pH 6.5 phosphate buffer (80 mL) was added potassium osmate dihydrate (184 mg, 0.500 mmol), followed by zinc trifluoromethanesulfonate (1.82 g, 5.00 mmol). The reaction flask was fitted with a water condenser and the resulting mixture was warmed to 60 °C and stirred for 12 hours before being heated to 80 °C and stirred for a further 24 hours. The reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of Na_2SO_3 (50 mL). The resultant mixture was stirred vigorously for 30 minutes before water (100 mL) and ethyl acetate (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (5 × 100 mL). The combined organic extracts were washed with brine (100 mL), then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 50:50) to give bis-THF **216** (3.66 g, 6.90 mmol, 69%) as a viscous oil. $R_f = 0.45$ (petrol/acetone 50:50); $[\alpha]_D^{25}$ +13.5 (*c* 1.0, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3500–3250, 2868, 1613, 1514, 1455, 1363, 1247, 1174, 1097, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.36–

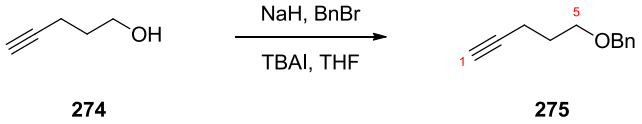
7.26 (5 H, m, Ph*H* × 5), 7.24 (2 H, d, *J* = 8.3, Ar*H* × 2), 6.87 (2 H, d, *J* = 8.3, Ar*H* × 2), 4.49 (2 H, s, CH_2Ph), 4.45 (1 H, d, *J* = 11.4, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.42 (1 H, d, *J* = 11.4, CH$_A$$H_BC_6H_4OCH_3$), 4.17–4.12 (2 H, m, C(12)H and C(13)H), 4.06–3.99 (1 H, m, C(8)H), 3.95 (1 H, d, *J* = 3.0, C(9)H), 3.87–3.81 (1 H, m, C(5)H), 3.80–3.72 (4 H, m, C(14)H_AH$_B$ and C$_6$H$_4$OCH_3), 3.56–3.47 (3 H, m, C(1)H$_2$ and C(14)H$_A$$H_B$), 3.39 (1 H, td, *J* = 7.6 and 4.1, C(4)H), 2.38 (1 H, dd, *J* = 13.3 and 6.4, C(11)H_AH$_B$), 2.07–1.92 (2 H, m, C(6)H_AH$_B$ and C(7)H_AH$_B$), 1.91–1.83 (1 H, m, C(6)H$_A$$H_B$), 1.79 (1 H, dd, *J* = 13.8 and 6.9, C(2)H_AH$_B$), 1.73–1.64 (3 H, m, C(2)H$_A$$H_B$, C(7)H$_A$$H_B$ and C(11)H$_A$$H_B$), 1.63–1.55 (2 H, m, C(3)H$_2$), 1.35 (3 H, s, C(10)CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 159.1 (ArC$_q$), 138.3 (PhC$_q$), 130.2 (ArC$_q$), 129.1 (ArC), 128.4 (PhC), 127.7 (PhC), 127.6 (PhC), 113.8 (ArC), 85.9 (C10), 84.0 (C13), 82.0 (C12), 81.3 (C5), 80.0 (C8), 77.3 (C9), 73.9 (C4), 72.9 (*C*H$_2$Ph), 71.0 (*C*H$_2$C$_6$H$_4$OCH$_3$), 70.4 (C1), 63.8 (C14), 55.2 (C$_6$H$_4$OCH$_3$), 37.7 (C11), 31.5 (C3), 28.9 (C6), 26.2 (C2), 25.0 (C7), 24.6 (C(10)*C*H$_3$); HRMS (ESI$^+$, *m/z*) for C$_{30}$H$_{42}$NaO$_8$ calculated 553.2772, found 553.2779.

((2*R*,3*S*)-5-((1*E*,5*E*)-9-(Benzyloxy)nona-1,5-dien-1-yl)-3-((4-methoxybenzyl)oxy)-5-methyltetrahydrofuran-2-yl)methanol (219)



Diene **219** was isolated as a side-product in the oxidative cyclisation reaction of **154** under the unbuffered conditions. ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.39–7.20 (7 H, m, Ar*H* × 7), 6.88 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.64 (2 H, s, C(8)H and C(9)H), 5.42 (2 H, br. s, C(4)H and C(5)H), 4.50 (2 H, s, CH_2Ph), 4.49–4.44 (1 H, d, *J* = 11.3, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.44–4.38 (1 H, d, *J* = 11.3, CH$_A$$H_BC_6H_4OCH_3$), 4.08 (1 H, d, *J* = 7.1, C(12)H), 4.03–3.97 (1 H, m, C(13)H), 3.81 (3 H, s, C$_6$H$_4$OCH_3), 3.78 (1 H, dd, *J* = 11.8 and 3.0, C(14)H_AH$_B$) 3.60 (1 H, dd, *J* = 11.9 and 3.8, C(14)H$_A$$H_B$), 3.47 (2 H, t, *J* = 6.6, C(1)H$_2$), 2.13–1.95 (m, 6 H), 1.68 (quin, *J* = 6.9 Hz, 2 H), 1.33 (3 H, s, C(10)CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 159.3 (ArC$_q$), 138.8 (ArC$_q$), 135.5 (C9), 130.4 (ArC$_q$), 130.2 (C4/C5), 130.1 (C4/C5), 129.3 (ArC), 128.5 (ArC), 127.8 (ArC), 127.8 (C8), 127.6 (ArC), 113.9 (ArC), 83.3 (C13), 82.5 (C10), 79.7 (C12), 73.0 (*C*H$_2$Ph), 71.6 (*C*H$_2$C$_6$H$_4$OCH$_3$), 69.9 (C1), 63.0 (C14), 55.4 (C$_6$H$_4$O*C*H$_3$), 44.2 (C11), 32.5, 32.4, 29.7 and 29.2 (C2, C3, C6 and C7), 28.1 (C10).

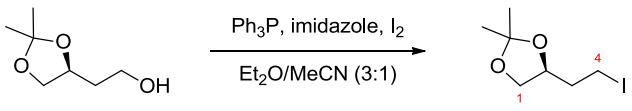
((Pent-4-yn-1-yloxy)methyl)benzene (275)



274 **275**

To a stirred solution of 4-pentyn-1-ol (**274**) (16.6 mL, 178 mmol) in tetrahydrofuran (270 mL) was added sodium hydride (60% dispersion in mineral oil, 7.84 g, 196 mmol) at 0 °C and the resulting mixture was stirred for 1 hour. Benzyl bromide (22.2 mL, 187 mmol) was added dropwise, followed by tetrabutylammonium iodide (2.63 g, 7.12 mmol) and the resulting mixture was stirred at 70 °C for 16 hours. The mixture was cooled to room temperature before being diluted with ethyl acetate (300 mL). The The resulting mixture was washed with water (2 × 200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 90:10) to give benzyl ether **275** (30.6 g, 176 mmol, 99%) as a pale yellow oil. $R_f = 0.40$ (petrol/Et_2O 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.25 (5 H, m, Ph*H* × 5), 4.55 (2 H, s, C*H*$_2$Ph), 3.60 (2 H, t, $J = 6.1$, C(5)H_2), 2.35 (2 H, td, $J = 7.1$ and 2.5, C(3)H_2), 1.96 (1 H, t, $J = 2.8$, C(1)H), 1.88 (2 H, quin, $J = 6.6$, C(4)H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.7 (PhC_q), 128.3 (PhC), 127.5 (PhC), 127.8 (PhC), 84.1 (C2), 73.1 (*C*H_2Ph), 68.8 (C1), 68.6 (C5), 28.8 (C4), 15.3 (C3). Spectroscopic data were consistent with those previously reported.[136]

(*S*)-4-(2-Iodoethyl)-2,2-dimethyl-1,3-dioxolane (277)

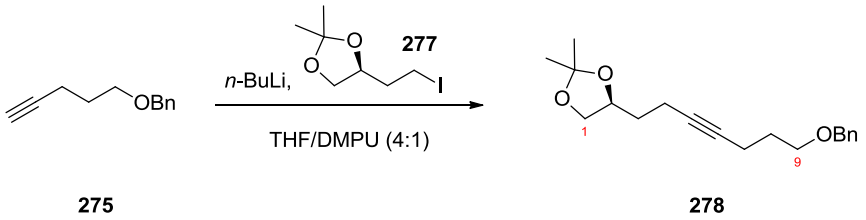


276 **277**

To a vigorously stirred solution of alcohol **276** (5.00 g, 33.6 mmol) in a 3:1 mixture of diethyl ether and acetonitrile (180 mL) were added imidazole (4.56 g, 67.0 mmol) and triphenylphosphine (12.3 g, 47.0 mmol) at 0 °C and the mixture was stirred for 10 minutes. Iodine (11.9 g, 47.0 mmol) was added portionwise over 45 minutes, the reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction was then cooled to 0 °C and quenched with methanol (50 mL). The resulting mixture was concentrated onto

silica gel and purified by flash column chromatography (petrol/Et_2O 90:10) to give iodoacetonide **277** (7.68 g, 30.0 mmol, 89%) as a pale yellow oil. $R_f = 0.80$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −22.7 (*c* 1.05, $CHCl_3$), lit.[137] $[\alpha]_D^{25}$ −23.99 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.14–4.04 (1 H, m, C(2)H), 3.99 (1 H, dd, *J* = 7.9 and 6.2, C(1)H_AH_B), 3.48 (1 H, dd, *J* = 7.9 and 6.6, C(1)H_AH_B), 3.24–3.08 (2 H, m, C(4)H_2), 2.07–1.88 (2 H, m, C(3)H_2), 1.31 (3 H, s, C(CH_3)CH_3), 1.26 (3 H, s, C(CH_3)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 109.0 (*C*(CH_3)$_2$), 75.6 (C2), 68.6 (C1), 37.8 (C3), 27.0 (C(*C*H_3)CH_3), 25.6 (C(CH_3)*C*H_3), 1.4 (C4). Data were consistent with those previously reported.[137]

(*S*)-4-(7-(Benzyloxy)hept-3-yn-1-yl)-2,2-dimethyl-1,3-dioxolane (278)

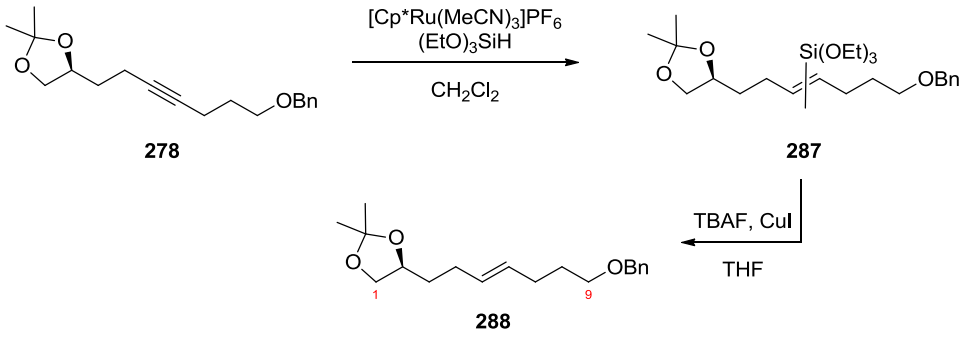


275 **278**

To a stirred solution of alkyne **275** (9.93 g, 57.0 mmol) in tetrahydrofuran (60 mL) was added *n*-butyllithium (2.5 M solution in hexanes, 25.1 mL, 62.7 mmol) dropwise over 10 minutes at –78 °C. The resulting solution was stirred at –78 °C for 3 hours before a solution of iodoacetonide **277** (7.30 g, 28.5 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (15 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction was quenched with a saturated, aqueous solution of NH_4Cl (50 mL) and the resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with a saturated, aqueous solution of NH_4Cl (100 mL), water (2 × 100 mL) and brine (2 × 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 95:5) to give alkyne **278** (5.59 g, 18.5 mmol, 65%) as a colourless oil. $R_f = 0.35$ (petrol/EtOAc 90:10); $[\alpha]_D^{20}$ –9.0 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49–7.22 (5 H, m, Ph*H* × 5), 4.51 (2 H, s, C(10)H_2), 4.18 (1 H, dt, *J* = 12.6 and 6.5, C(2)H), 4.05 (1 H, dd, *J* = 7.8 and 6.1, C(1)H_AH_B), 3.64–3.50 (3 H, m, C(1)H_AH_B and C(9)H_2), 2.40–2.19 (4 H, m, C(4)H_2 and C(10)H_2), 1.78 (3 H, td, *J* = 6.6 and 4.0, C(3)H_AH_B and C(8)H_2), 1.75–1.59 (1 H, m, C(3)H_AH_B), 1.41 (3 H, s, OC(CH_3)CH_3), 1.36 (3 H, s, OC(CH_3)CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.7 (PhC_q), 128.5 (PhC), 127.6 (PhC), 127.5 (PhC), 108.7

($C(CH_3)_2$), 80.2 (C5), 79.3 (C6), 75.1 (C2), 72.9 (CH_2Ph), 69.2 (C1), 68.9 (C9), 33.2 (C3), 29.2 (C8), 27.0 ($C(CH_3)CH_3$), 25.7 ($C(CH_3)CH_3$), 15.6 C(7), 15.3 (C4). Data were consistent with those previously reported.[116]

(*S*,*E*)-4-(7-(Benzyloxy)hept-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane (288)

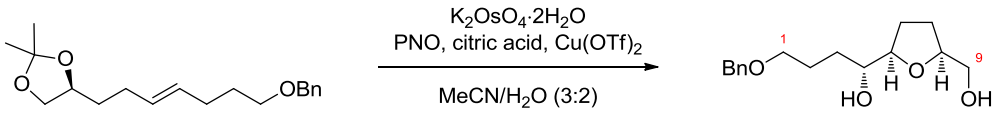


278 287 288

A stirred solution of alkyne **278** (3.90 g, 12.9 mmol) in dichloromethane (26 mL) was cooled to 0 °C and degassed with argon for 30 minutes. Triethoxysilane (95% purity, 3.01 mL, 15.5 mmol) was added at 0 °C, followed by $[Cp^*Ru(MeCN)_3]PF_6$ (131 mg, 0.260 mmol) and the resulting mixture was warmed to room temperature. After stirring for 1.5 hours the mixture was diluted with ether (50 mL) and filtered twice through a plug of florisil. The filtrate was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford an inseparable 1:1 mixture of regioisomers of vinyl silanes **287** (5.41 g, 11.6 mmol, 90%) as a pale yellow oil which was used in the next step without further purification. $R_f = 0.50$ (petrol/ethyl acetate 80:20). To a stirred solution of vinyl silanes **287** (6.33 g, 13.6 mmol) in tetrahydrofuran (70 mL) was added copper(I) iodide (3.88 g, 20.4 mmol), followed by the dropwise addition of tetrabutylammonium fluoride (1.0 M solution in THF, 41.0 mL, 40.8 mmol) at room temperature. The reaction was heated to 35 °C and stirred in the dark for 24 hours. The reaction mixture was then filtered twice through a plug of silica, eluting with ether, before the filtrate was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 90:10) to give alkene **288** (3.56 g, 11.7 mmol, 86%) as a pale yellow oil. $R_f = 0.55$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ +10.0 (*c* 1.08, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.25 (5 H, m, Ph*H* × 5), 5.50–5.38 (2 H, m, C(5)H and C(6)H), 4.50 (2 H, s, C*H*$_2$Ph), 4.12–4.05 (1 H, m, C(2)H), 4.05–4.00 (1 H, m, C(1)H_AH_B), 3.54–3.44 (3 H, m, C(1)H_AH_B and C(9)H_2), 2.19–1.96 (4 H, m, C(4)H_2 and C(7)H_2), 1.76–1.64 (3 H, m, C(3)H_AH_B and C(8)H_2), 1.60–1.51 (1 H, m, C(3)H_AH_B), 1.42 (3 H, s, C(C*H*$_3$)CH_3), 1.35 (3 H, s, C(CH_3)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.7

(PhC_q), 130.3, 129.8 (C5 and C6), 128.3 (PhC), 127.6 (PhC), 127.5 (PhC), 108.6 ($C(CH_3)_2$), 75.6 (C2), 72.9 (CH_2Ph), 69.7 (C9), 69.5 (C1), 33.4 (C3), 29.6, 29.2, 28.8 (C4, C7 and C8), 27.0 ($C(CH_3)CH_3$), 25.9 ($C(CH_3)CH_3$). Data were consistent with those previously reported.[116]

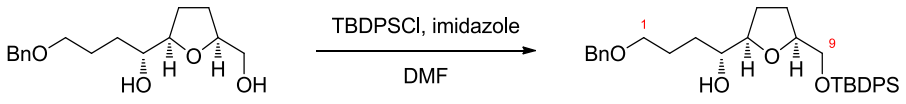
(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-(hydroxymethyl)tetrahydrofuran-2-yl)butan-1-ol (289)



288 **289**

To a stirred solution of alkene **288** (3.91 g, 12.8 mmol) in acetonitrile (100 mL) was added a solution of pyridine *N*-oxide (95% purity, 2.56 g, 25.6 mmol) in acetonitrile (56 mL) followed by a solution of citric acid (1.85 g, 9.60 mmol) in water (52 mL). Copper(II) trifluoromethanesulfonate (2.31 g, 6.40 mmol) was added and the resulting mixture was stirred at 80 °C for 1.5 hours. After cooling to room temperature, a solution of potassium osmate dihydrate (236 mg, 0.640 mmol) in water (52 mL) was added and the resulting mixture was heated to 60 °C and stirred for 16 hours. The reaction was cooled to room temperature before a saturated, aqueous solution of Na_2SO_3 (50 mL) was added. The resultant mixture was stirred for 20 minutes before being diluted with water (100 mL) and the resulting mixture was extracted with ethyl acetate (4 × 200 mL). The combined organic extracts were washed sequentially with an aqueous solution of NaOH (1 M, 2 × 400 mL), an aqueous solution of HCl (1 M, 2 × 400 mL) and brine (400 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 70:30) to afford tetrahydrofuran **289** (3.44 g, 12.3 mmol, 96%) as a pale yellow oil. $R_f = 0.35$ (petrol/acetone 50:50); $[\alpha]_D^{20}$ +0.82 (*c* 1.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41–7.22 (5 H, m, Ph*H* × 5), 4.51 (2 H, s, CH_2Ph), 4.07 (1 H, d, *J* = 3.8, C(8)H), 3.82 (1 H, d, *J* = 6.0, C(5)H), 3.74 (1 H, dd, *J* = 11.6 and 2.9, C(9)H_AH_B), 3.51 (2 H, t, *J* = 6.1, C(1)H_2), 3.48–3.43 (2 H, m, C(4)H and C(9)H_AH_B), 1.96–1.87 (2 H, m, C(6)H_AH_B and C(7)H_AH_B), 1.87–1.68 (4 H, m, C(2)H_2, C(6)H_AH_B and C(7)H_AH_B), 1.66–1.47 (2 H, m, C(3)H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.4 (PhC_q), 128.5 (PhC), 127.7 (PhC), 127.7 (PhC), 83.2 (C5), 80.0 (C8), 74.1 (C4), 73.0 (CH_2Ph), 70.4 (C1), 65.2 (C9), 31.3 (C3), 28.3 (C6), 27.4 (C7), 26.1 (C2). Data were consistent with those previously reported.[116]

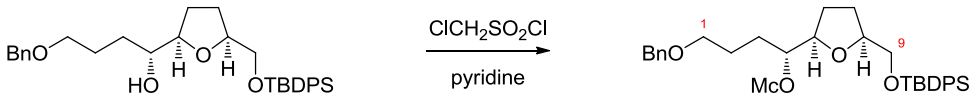
(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butan-1-ol (290)



289 **290**

To a stirred solution of tetrahydrofuran **289** (3.44 g, 12.3 mmol) in *N*,*N*-dimethylformamide (50 mL) at 0 °C was added imidazole (1.67 g, 24.6 mmol), followed by the dropwise addition of *tert*-butyl(chloro)diphenylsilane (3.31 mL, 12.9 mmol). The resulting mixture was stirred at room temperature for 4 hours before being quenched with water (25 mL) and stirred for a further 20 minutes. The resultant mixture was extracted with ether (4 × 50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to give tetrahydrofuran **290** (5.86 g, 11.3 mmol, 92%) as a pale yellow oil. R_f = 0.55 (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ +10.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.66 (4 H, m, Ph*H* × 4), 7.45–7.37 (6 H, m, Ph*H* × 6), 7.36–7.24 (5 H, m, Ph*H* × 5), 4.52 (2 H, s, CH_2Ph), 4.09 (1 H, t, *J* = 3.9, C(8)H), 3.83 (1 H, q, *J* = 6.1, C(5)H), 3.76 (1 H, dd, *J* = 10.7 and 4.1, C(9)H_AH$_B$), 3.62 (1 H, dd, *J* = 10.7 and 3.9, C(9)H$_A$$H_B$), 3.57–3.48 (2 H, m, C(1)H_2), 3.45–3.37 (1 H, m, C(4)H), 2.67 (1 H, d, *J* = 5.6, OH), 2.03–1.68 (6 H, m, C(2)H_2, C(6)H_2, C(7)H_2), 1.67–1.48 (2 H, m, C(3)H_2), 1.08 (9 H, s, SiC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.7 (PhC_q), 135.8 (PhC), 135.7 (PhC), 133.5 (PhC_q), 129.8 (PhC), 129.8 (PhC), 128.5 (PhC), 127.8 (PhC), 127.8 (PhC), 127.8 (PhC), 127.6 (PhC), 82.8 (C5), 80.0 (C8), 74.4 (C4), 73.1 (*C*H_2Ph), 70.6 (C1), 66.0 (C9), 31.0 (C3), 28.3 (C6), 27.5 (C7), 26.9 (SiC(*C*H_3)$_3$), 26.2 (C2), 19.3 (Si*C*(CH$_3$)$_3$). Data were consistent with those previously reported.[116]

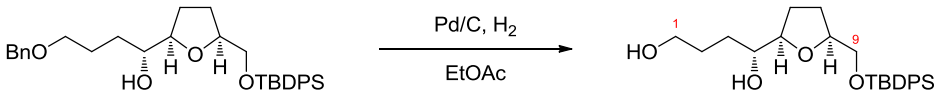
(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*tert*-butyldiphenylsilyloxy)methyl)tetrahydrofuran-2-yl)butyl chloromethanesulfonate (267b)



290 **267b**

To a stirred solution of tetrahydrofuran **290** (109 mg, 0.211 mmol) in pyridine (1.2 mL) at 0 °C was added chloromethanesulfonyl chloride (0.0533 mL, 0.528 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2.5 hours. The solution was diluted with ethyl acetate (3.0 mL) and the mixture was washed sequentially with an aqueous solution of HCl (1 M, 3 × 5.0 mL), water (2 × 5.0 mL) and brine (5.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, petrol/EtOAc 80:20) afforded chloromesylate **291** (102 mg, 0.162 mmol, 77%) as a colourless oil. $R_f = 0.70$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ –21.9 (*c* 0.90, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2858, 1430, 1365, 1179, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72–7.65 (4 H, m, Ph*H* × 4), 7.50–7.38 (6 H, m, Ph*H* × 6), 7.38–7.24 (5 H, m, Ph*H* × 5), 5.05 (1 H, d, *J* = 12.0, SCH_AH$_B$Cl), 4.72–4.65 (1 H, m, C(4)H), 4.61 (1 H, d, *J* = 12.0, SCH$_A$$H_B$Cl), 4.51 (2 H, s, C$H_2$Ph), 4.17–4.08 (1 H, m, C(8)H), 4.09–4.01 (1 H, m, C(5)H), 3.68–3.62 (2 H, m, C(9)H$_2$), 3.60–3.48 (2 H, m, C(1)H$_2$), 2.03–1.92 (2 H, m, C(6)H_AH$_B$ and C(7)H_AH$_B$), 1.91–1.72 (5 H, m, C(2)H$_2$, C(3)H$_2$ and C(7)H$_A$$H_B$), 1.66–1.54 (1 H, m, C(6)H$_A$$H_B$), 1.08 (9 H, s, SiC(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.6 (PhC$_q$), 135.6 (PhC), 133.3 (PhC$_q$), 133.2 (PhC$_q$), 129.7 (PhC), 128.4 (PhC), 127.9 (PhC), 127.7 (PhC), 127.6 (PhC), 89.4 (C4), 80.9 (C5), 80.3 (C8), 72.9 (*C*H$_2$Ph), 69.2 (C1), 66.4 (C9), 54.5 (SCH$_2$Cl), 28.6 (C3), 28.2 (C6), 27.4 (C7), 26.9 (SiC(*C*H$_3$)$_3$), 25.1 (C2), 19.2 (Si*C*(CH$_3$)$_3$). Data were consistent with those previously reported.[116]

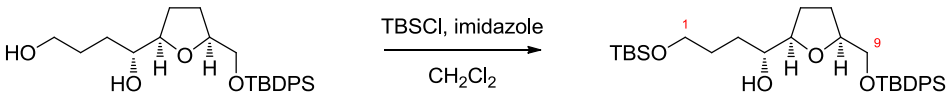
(*R*)-1-((2*R*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butane-1,4-diol (292)



290 **292**

A solution of tetrahydrofuran **290** (1.57 g, 3.03 mmol) in ethyl acetate (100 mL) was evacuated and purged with argon three times. To this solution palladium on carbon (10 wt.%, 1.00 g) was added and the reaction flask was evacuated and purged with hydrogen five times. The resulting mixture was stirred vigorously under an atmosphere of hydrogen for 5 hours before being filtered through a pad of celite, eluting with ethyl acetate (150 mL). The combined organic phases were concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 50:50) to afford diol **292** (1.28 g, 3.00 mmol, 99%) as a colourless oil. $R_f = 0.20$ (petrol/EtOAc 50:50); $[\alpha]_D^{20}$ +8.1 (*c* 0.95, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3385, 2930, 2858, 1427, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (4 H, t, *J* = 6.4, Ph*H* × 4), 7.46–7.35 (6 H, m, Ph*H* × 6), 4.10–4.04 (1 H, m, C(8)H), 3.83 (1 H, q, *J* = 6.0, C(5)H), 3.75 (1 H, dd, *J* = 10.7 and 4.2, C(9)H_AH$_B$), 3.68–3.59 (3 H, m, C(1)H$_2$ and C(9)H$_A$$H_B$), 3.43 (1 H, dt, *J* = 5.6 and 3.0, C(4)H), 3.06 (2 H, br. s, OH × 2), 1.99–1.88 (3 H, m, C(6)H_AH$_B$ and C(7)H$_2$), 1.78–1.68 (3 H, m, C(2)H$_2$ and C(6)H$_A$$H_B$), 1.66–1.57 (1 H, m, C(3)H_AH$_B$), 1.57–1.46 (1 H, m, C(3)H$_A$$H_B$), 1.08 (9 H, s, SiC(CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.6 (PhC), 135.6 (PhC), 133.3 (PhC$_q$), 129.8 (PhC$_q$), 129.8 (PhC), 127.8 (PhC), 127.8 (PhC), 82.8 (C5), 79.9 (C8), 74.6 (C4), 65.9 (C9), 62.8 (C1), 31.0, 29.4, 28.2, 27.5 (C2, C3, C6 and C7), 26.9 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{25}H_{36}NaO_4Si$ calculated 451.2275, found 451.2279.

(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butan-1-ol (293)

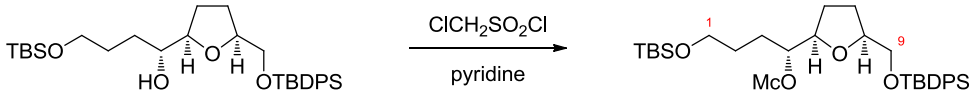


292 **293**

To a stirred solution of diol **292** (1.35 g, 3.15 mmol) in dichloromethane (50 mL) at 0 °C was added imidazole (643 mg, 9.45 mmol) the resultant mixture was stirred until all reagents had dissolved. *tert*-Butyldimethylsilyl chloride (514 mg, 3.31 mmol) was added in one portion and the resulting mixture was warmed to room temperature and stirred for 8 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL), the layers were separated and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc

80:20) to give alcohol **293** (1.53 g, 2.80 mmol, 89%) as a colourless oil. $R_f = 0.85$ (petrol/EtOAc 50:50); $[\alpha]_D^{20}$ +5.2 (*c* 0.87, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2929, 2856, 1472, 1428, 1254, 1104, 1006; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (4 H, t, *J* = 6.7, Ph*H* × 4), 7.47–7.35 (6 H, m, Ph*H* × 6), 4.12–4.04 (1 H, m, C(8)H), 3.89–3.82 (1 H, m, C(5)H), 3.76 (1 H, dd, *J* = 10.9 and 4.3, C(9)H_AH$_B$), 3.69–3.60 (3 H, m, C(1)H$_2$ and C(9)H$_A$$H_B$), 3.43 (2 H, dt, *J* = 8.8 and 4.3, C(4)H), 2.75–2.70 (1 H, m, OH), 2.04–1.89 (3 H, m, C(6)H_AH$_B$ and C(7)H$_2$), 1.82–1.70 (2 H, m, C(2)H_AH$_B$ and C(6)H$_A$$H_B$), 1.67–1.55 (2 H, m, C(2)H$_A$$H_B$ and C(3)H_AH$_B$), 1.54–1.41 (1 H, m, C(3)H$_A$$H_B$), 1.08 (9 H, s, SiC(CH$_3$)$_3$), 0.91 (9 H, s, SiC(CH$_3$)$_3$), 0.06 (6 H, s, SiCH$_3$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.6 (PhC), 135.6 (PhC), 133.3 (PhC$_q$), 129.7 (PhC), 129.6 (PhC), 127.7 (PhC), 127.7 (PhC), 82.6 (C5), 79.8 (C8), 74.3 (C4), 65.8 (C9), 63.1 (C1), 30.5 (C3), 29.0 (C2), 28.1 (C7), 27.5 (C6), 26.8 (SiC(*C*H$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 18.3 (Si*C*(CH$_3$)$_3$), −5.3 (Si*C*H$_3$ × 2); HRMS (ESI$^+$, *m/z*) for $C_{31}H_{50}NaO_4Si_2$ calculated 565.3140, found 565.3144.

(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butyl chloromethanesulfonate (294)

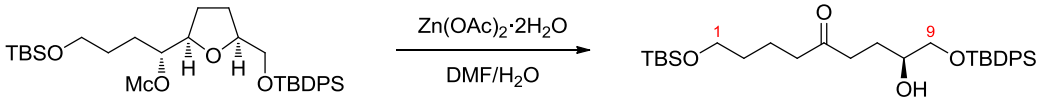


293 **294**

To a stirred solution of alcohol **293** (150 mg, 0.277 mmol) in pyridine (2.2 mL) at 0 °C was added chloromethanesulfonyl chloride (90% purity, 55.9 µL, 0.554 mmol). The resulting mixture was warmed to room temperature and stirred for 3 hours before water (5.0 mL) and ethyl acetate (5.0 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extracts were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 85:15) to give chloromesylate **294** (177 mg, 0.271 mmol, 98%) as a colourless oil, which was used immediately in the next step. $R_f = 0.90$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −10.8 (*c* 1.01, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2929, 2857, 1739, 1472, 1428, 1368, 1254, 1179, 1104; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72–7.64 (4 H, m, Ph*H* × 4), 7.48–7.38 (6 H, m, Ph*H* × 6), 5.05 (1 H, d, *J* = 12.1, SCH_AH$_B$Cl), 4.72–4.64 (1 H, m, C(4)H), 4.61 (1 H, d, *J* = 12.1, SCH$_A$$H_B$Cl), 4.17–4.09 (1 H, m, C(8)H), 4.04

(1 H, td, J = 8.4 and 6.2, C(5)H), 3.71–3.61 (4 H, m, C(2)H_2 and C(9)H_2), 2.00–1.90 (2 H, m, C(6)H_AH$_B$ and C(7)H_AH$_B$), 1.85–1.74 (3 H, m, C(2)H_AH$_B$, C(3)H_AH$_B$ and C(7)H$_A$$H_B$), 1.72–1.59 (3 H, m, C(2)H$_A$$H_B$, C(3)H$_A$$H_B$ and C(6)H$_A$$H_B$), 1.07 (9 H, s, SiC(CH$_3$)$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.05 (6 H, s, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 135.8 (PhC), 135.7 (PhC), 133.4 (PhC$_q$), 133.3 (PhC$_q$), 129.9 (PhC), 129.9 (PhC), 127.9 (PhC), 127.9 (PhC), 89.7 (C4), 81.1 (C5), 80.4 (C8), 66.6 (C9), 62.1 (C1), 54.7 (SCH$_2$Cl), 28.4, 28.3, 28.1, 27.5 (C2, C3, C6 and C7), 27.0 (SiC(*C*H$_3$)$_3$), 26.0(SiC(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), −5.2 (SiCH$_3$), −5.2 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for $C_{32}H_{51}ClNaO_6SSi_2$ calculated 677.2531, found 677.2526.

(*S*)-6-Hydroxy-2,2,15,15,16,16-hexamethyl-3,3-diphenyl-4,14-dioxa-3,15-disilaheptadecan-9-one (273)

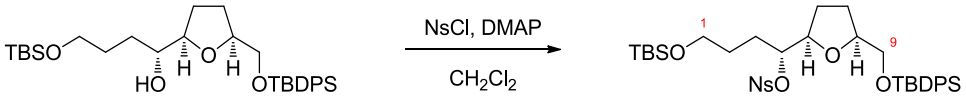


294 **273**

To a stirred solution of chloromesylate **294** (50.0 mg, 0.0765 mmol) in *N*,*N*-dimethylformamide (1.10 mL) was added water (0.84 mL), followed by zinc trifluoromethanesulfonate dihydrate (84.1 mg, 0.383 mmol). The resulting mixture was heated to 60 °C and stirred for 12 hours, before it was cooled to room temperature and diluted with brine (5.0 mL). The resultant mixture was extracted with ether (4 × 5.0 mL) and the combined organic extracts were dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO$_2$, petrol/EtOAc 90:10) to afford ketone **273** (26.1 mg, 0.0482 mmol, 63%) as a colourless oil. R_f = 0.50 (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ +1.3 (*c* 1.00, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.66 (4 H, td, J = 7.7 and 1.5, Ph*H* × 4), 7.49–7.36 (6 H, m, Ph*H* × 6), 3.73–3.68 (1 H, m, C(8)H), 3.67 (1 H, t, J = 3.5, C(9)H_AH$_B$), 3.61 (2 H, t, J = 6.5, C(1)H$_2$), 3.50 (1 H, dd, J = 10.1 and 7.1, C(9)H$_A$$H_B$), 2.62–2.51 (2 H, m, C(6)H$_2$), 2.43 (2 H, t, J = 7.1, C(4)H$_2$), 1.70–1.58 (4 H, m, C(3)H$_2$ and C(7)H$_2$), 1.56–1.46 (2 H, m, C(2)H$_2$), 1.07 (9 H, s, SiC(CH$_3$)$_3$), 0.90 (9 H, s, SiC(CH$_3$)$_3$), 0.05 (6 H, s, Si(CH$_3$)$_2$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 211.2 (C5), 135.8 (PhC), 135.7 (PhC), 133.2 (PhC$_q$), 130.0 (PhC), 127.9 (PhC), 71.4 (C8), 68.0 (C9), 63.0 (C1), 42.8 (C4), 38.8 (C6), 32.4

(C2), 27.0 (SiC(CH_3)$_3$), 26.7 (C7), 26.1 (SiC(CH_3)$_3$), 20.4 (C3), 19.4 (SiC(CH_3)$_3$), 18.5 (SiC(CH_3)$_3$), −5.2 (Si(CH_3)$_2$). Data were consistent with those previously reported.[116]

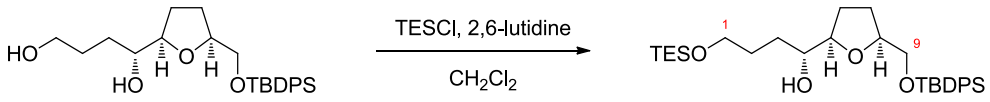
(*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butyl 2-nitrobenzenesulfonate (295)



293 **295**

To a stirred solution of THF **293** (150 mg, 0.277 mmol) in dichloromethane (2.8 mL) at 0 °C was added 4-(dimethylamino)pyridine (203 mg, 1.66 mmol), followed by the addition of 2-nitrobenzenesulfonyl chloride (190 mg, 0.831 mmol). The resulting mixture was warmed to room temperature and stirred for 3 hours before being diluted with dichloromethane (20 mL). The resulting suspension was washed with water (2 × 10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 50:50) to afford THF **295** (197 mg, 0.271 mmol, 98%) as a colourless oil. R_f = 0.48 (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −8.8 (*c* 1.3, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3734, 2929, 1544, 1472, 1363, 1254, 1185, 1104; ^{1}H NMR (500 MHz, $CDCl_3$) 8.03 (1 H, dd, *J* = 7.9 and 0.9, Ar*H*), 7.68 (4 H, dd, *J* = 15.6 and 6.8, Ph*H* × 4), 7.61 (1 H, d, *J* = 7.9, Ar*H*), 7.54–7.33 (8 H, m, Ar*H* × 2 and Ph*H* × 6), 4.77–4.70 (1 H, m, C(4)H), 3.99 (1 H, q, *J* = 7.3, C(5)H), 3.89–3.83 (1 H, m, C(8)H), 3.67 (2 H, t, *J* = 5.5, C(1)H_2), 3.29–3.19 (2 H, m, C(9)H_2), 2.03–1.85 (4 H, m) and 1.78–1.62 (4 H, m) (C(2)H_2, C(3)H_2, C(6)H_2 and C(7)H_2), 1.08 (9 H, s, SiC(CH_3)$_3$), 0.93 (9 H, s, SiC(CH_3)$_3$), 0.09 (6 H, s, SiCH_3 × 2); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 148.2 (ArC_q), 135.7 (PhC), 135.7 (PhC), 133.8 (PhC_q), 133.6 (PhC_q), 133.6 (ArC), 131.8 (ArC), 131.6 (ArC), 131.1 (ArC_q), 129.9 (PhC), 129.9 (PhC), 127.9 (PhC), 127.8 (PhC), 124.3 (ArC), 89.1 (C4), 80.0 (C5), 79.5 (C8), 65.8 (C9), 62.3 (C1), 28.2, 28.1, 28.0, 27.6 (C2, C3, C6 and C7), 26.9 (SiC(CH_3)$_3$), 26.0 (SiC(CH_3)$_3$), 19.3 (SiC(CH_3)$_3$), 18.4 (SiC(CH_3)$_3$), −5.2 (SiCH_3), −5.2 (SiCH_3); HRMS (ESI$^+$, *m/z*) for $C_{37}H_{53}NNaO_8SSi_2$ calculated 750.2923, found 750.2919.

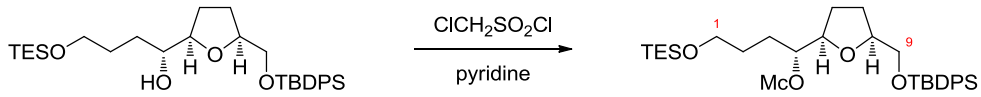
(*R*)-1-((2*R*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-((triethylsilyl)oxy)butan-1-ol (296)



292 **296**

To a stirred solution of diol **292** (206 mg, 0.481 mmol) and 2,6-lutidine (0.223 mL, 1.92 mmol) in dichloromethane (4.8 mL) was added chlorotriethylsilane (0.097 mL, 0.58 mmol) dropwise at −78 °C and the resulting mixture was stirred for 40 min. The reaction was quenched by the addition of methanol (1.0 mL) before being allowed to warm to room temperature. The resulting mixture was diluted with dichloromethane (10 mL) and a cold aqueous solution of HCl (1 M, 10 mL), the layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give alcohol **296** (255 mg, 0.471 mmol, 98%) as an oil, which was used in the next step without further purification. $R_f = 0.57$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ +6.8 (*c* 1.12, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3734, 2954, 1428, 1106; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.66 (4 H, m, Ph*H* × 4), 7.47–7.35 (6 H, m, Ph*H* × 6), 4.08 (1 H, t, *J* = 4.2, C(8)H), 3.85 (1 H, q, *J* = 6.2, C(5)H), 3.75 (1 H, dd, *J* = 10.9 and 4.3, C(9)H_AH_B), 3.69–3.59 (3 H, m, C(1)H_2 and C(9)H_AH_B), 3.42 (1 H, d, *J* = 3.0, C(4)H), 2.81–2.72 (1 H, m, OH), 2.01–1.89 (3 H, m, C(6)H_AH_B and C(7)H_2), 1.81–1.72 (2 H, m, C(6)H_AH_B and C(2)H_AH_B), 1.69–1.56 (2 H, m, C(2)H_AH_B and C(3)H_AH_B), 1.54–1.43 (1 H, m, C(3)H_AH_B), 1.08 (9 H, s, SiC(CH_3)$_3$), 0.97 (9 H, t, *J* = 7.8, Si(CH_2CH_3)$_3$), 0.61 (6 H, q, *J* = 7.8, Si(CH_2CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.8 (PhC), 135.7 (PhC), 133.5 (PhC_q), 129.8 (PhC), 129.8 (PhC), 127.8 (PhC), 127.8 (PhC), 82.8 (C5), 79.9 (C8), 74.5 (C4), 66.0 (C9), 63.0 (C1), 30.7 (C3), 29.3 (C2), 28.2 (C6), 27.7 (C7), 26.9 (SiC(CH_3)$_3$), 19.3 (SiC(CH_3)$_3$), 6.9 (Si(CH_2CH_3)$_3$), 4.5 (Si(CH_2CH_3)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{31}H_{50}NaO_4Si_2$ calculated 565.3145, found 565.3139.

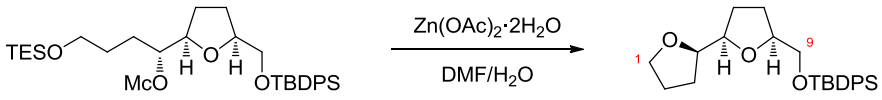
(*R*)-1-((2*R*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-((triethylsilyl)oxy)butyl chloromethanesulfonate (297)



296 **297**

To a stirred solution of alcohol **296** (100 mg, 0.185 mmol) in pyridine (1.5 mL) at 0 °C was added chloromethanesulfonyl chloride (90% purity, 37.4 µL, 0.370 mmol). The resulting mixture was warmed to room temperature and stirred for 4 hours before water (3.0 mL) and ethyl acetate (3.0 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The combined organic extracts were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 80:20) to give chloromesylate **297** (110 mg, 0.168 mmol, 91%) as a colourless oil, which was used immediately in the next step. $R_f = 0.60$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −12.0 (*c* 1.00, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2955, 1472, 1428, 1369, 1179, 1112, 1006; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72–7.64 (4 H, m, Ph*H* × 4), 7.48–7.36 (6 H, m, Ph*H* × 6), 5.05 (1 H, d, *J* = 12.1, SCH_AH$_B$Cl), 4.69 (1 H, d, *J* = 7.1, C(4)H), 4.62 (1 H, d, *J* = 12.1, SCH$_A$$H_B$Cl), 4.16–4.10 (1 H, m, C(8)H), 4.08–4.00 (1 H, m, C(5)H), 3.75–3.67 (2 H, m, C(1)H_2), 3.66–3.63 (2 H, m, C(9)H_2), 2.01–1.91 (3 H, m, C(6)H_AH$_B$ and C(7)H_2), 1.85–1.58 (5 H, m, C(2)H_2, C(3)H_2 and C(6)H$_A$$H_B$), 1.08 (9 H, s, SiC(C$H_3$)$_3$), 0.95 (9 H, t, *J* = 7.8, Si(CH$_2$CH_3)$_3$), 0.54 (6 H, q, *J* = 7.8, Si(CH_2CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.7 (PhC), 135.6 (PhC), 133.3 (PhC$_q$), 133.3 (PhC$_q$), 129.9 (PhC), 127.9 (PhC), 89.5 (C4), 81.0 (C5), 80.4 (C8), 66.6 (C9), 62.0 (C1), 54.6 (SCH_2Cl), 28.3, 28.2, 28.0, 27.5 (C2, C3, C6 and C7), 26.9 (SiC(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 6.5 (Si(*C*H$_2$CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{32}H_{51}ClNaO_6SSi_2$ calculated 677.2526, found 677.2538.

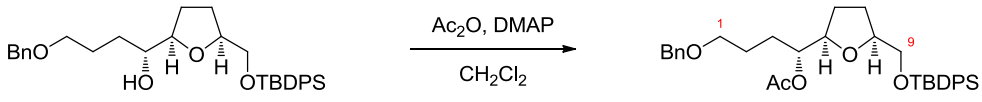
***tert*-Butyl(((2*R*,2'*R*,5*S*)-octahydro-[2,2'-bifuran]-5-yl)methoxy)diphenylsilane (270)**



297 **270**

To a stirred solution of chloromesylate **297** (40 mg, 0.061 mmol) in *N*,*N*-dimethylformamide (0.92 mL) was added water (0.67 mL), followed by zinc trifluoromethanesulfonate dihydrate (67 mg, 0.31 mmol). The resulting mixture was heated to 60 °C and stirred for 12 hours, before it was cooled to room temperature and diluted with brine (3.0 mL). The resultant mixture was extracted with ether (4 × 3.0 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 90:10) to afford bis-THF **270** (12.5 mg, 0.0305 mmol, 50%) as a colourless oil. $R_f = 0.70$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ +1.0 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.74–7.55 (4 H, m, Ph*H* × 4), 7.49–7.38 (6 H, m, Ph*H* × 6), 4.17–4.05 (1 H, m, C(8)H), 3.96–3.85 (2 H, m, C(1)H_AH$_B$ and C(4)H), 3.84–3.75 (2 H, m, C(1)H$_A$$H_B$ and C(5)H), 3.72 (2 H, d, $J = 4.9$, C(9)H_2), 2.11–1.77 (8 H, m, C(2)H_2, C(3)H_2, C(6)H_2 and C(7)H_2), 1.11 (9 H, s, SiC(CH_3)$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 135.8 (PhC), 133.8 (PhC_q), 129.7 (PhC), 129.7 (PhC), 127.8 (PhC), 81.8 (C4), 81.4 (C5), 80.0 (C8), 68.6 (C1), 66.1 (C9), 28.7 (C6), 28.3 (C3), 27.5 (C7), 27.0 (SiC(*C*H$_3$)$_3$), 26.0 (C2), 19.4 (Si*C*(CH$_3$)$_3$). Data were consistent with those previously reported.[112]

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butyl acetate (299)

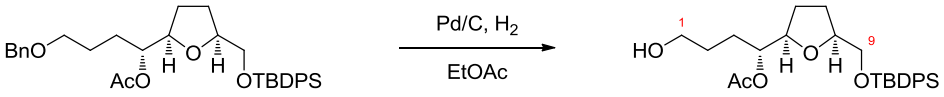


290 **299**

To a stirred solution of alcohol **290** (1.00 g, 1.93 mmol) and 4-(dimethylamino)pyridine (1.42 g, 11.6 mmol) in dichloromethane (20 mL) was added acetic anhydride (0.547 mL, 5.79 mmol) dropwise. The resulting mixture was stirred at room temperature for 4 hours before being quenched with methanol (5.0 mL) and stirred for a further 10 minutes. The mixture was concentrated *in vacuo* and the crude product purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to give acetate **299** (6.44 g, 11.5 mmol, 99%) as an oil. $R_f = 0.70$ (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ +8.9 (*c* 1.35, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2931, 2857, 1735, 1428, 1364, 1240, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76–7.69 (4 H, m, Ph*H* × 4), 7.48–7.26 (11 H, m, Ph*H* × 11), 4.99–4.91 (1 H, m, C(4)H), 4.51 (2 H, s, CH_2Ph),

4.11 (1 H, quin, J = 5.7, C(8)H), 4.04–3.97 (1 H, m, C(5)H), 3.74 (1 H, dd, J = 10.5 and 4.9, C(9)H_AH$_B$), 3.62 (1 H, dd, J = 10.4 and 5.8, C(9)H$_A$$H_B$), 3.49 (2 H, t, J = 6.1, C(1)H$_2$), 1.99 (3 H, s, C(O)CH$_3$), 1.95–1.82 (3 H, m, C(6)H_AH$_B$ and C(7)H$_2$), 1.79–1.59 (5 H, m, C(2)H$_2$, C(3)H$_2$ and C(6)H$_A$$H_B$), 1.09 (9 H, s, SiC(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 170.8 (*C*(O)CH$_3$), 138.6 (PhC$_q$), 135.7 (PhC), 133.8 (PhC$_q$), 133.7 (PhC$_q$), 129.7 (PhC), 129.7 (PhC), 128.4 (PhC), 127.7 (PhC), 127.6 (PhC), 80.2 (C5), 79.8 (C8), 75.1 (C4), 73.0 (*C*H$_2$Ph), 70.0 (C1), 66.2 (C9), 28.0, 27.9, 27.4 (C3, C6 and C7), 26.9 (SiC(*C*H$_3$)$_3$), 25.8 (C2), 21.1 (C(O)*C*H$_3$), 19.4 (Si*C*(CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{34}H_{44}NaO_5Si$ calculated 583.2856, found 583.2859.

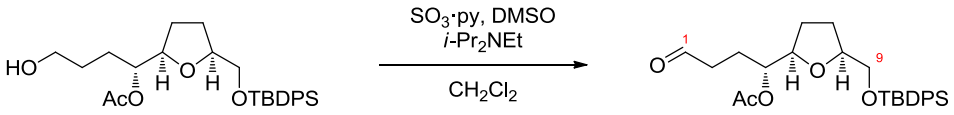
(*R*)-1-((2*R*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-hydroxybutyl acetate (303)



299 **303**

A solution of acetate **299** (1.08 g, 1.93 mmol) in ethyl acetate (100 mL) was evacuated and purged with argon three times. To this solution palladium on carbon (10 wt.%, 1.0 g) was added and the reaction flask was evacuated and purged with hydrogen five times. The resulting mixture was stirred under an atmosphere of hydrogen for 24 hours before being filtered through a plug of celite and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO$_2$, petrol/EtOAc 50:50) to afford alcohol **303** (898 mg, 1.91 mmol, 99%) as a colourless oil. R_f = 0.32 (petrol/EtOAc 50:50); $[\alpha]_D^{20}$ +9.5 (*c* 1.1, CH$_2$Cl$_2$); IR ν_{max} (film)/cm^{-1} 3735, 3629, 2931, 1735, 1428, 1242, 1112; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.75–7.65 (4 H, m, Ph*H* × 4), 7.47–7.34 (6 H, m, Ph*H* × 6), 4.97–4.89 (1 H, m, C(4)H), 4.09 (1 H, td, J = 11.6 and 5.8, C(8)H), 4.03–3.96 (1 H, m, C(5)H), 3.71 (1 H, dd, J = 10.5 and 4.9, C(9)H_AH$_B$), 3.66–3.56 (3 H, m, C(1)H$_2$ and C(9)H$_A$$H_B$), 1.98 (3 H, s, C(O)CH$_3$), 1.95–1.80 (3 H, m, C(6)H_AH$_B$ and C(7)H$_2$), 1.73–1.55 (5 H, m, C(2)H$_2$, C(3)H$_2$ and C(6)H$_A$$H_B$), 1.07 (9 H, s, SiC(CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 171.0 (*C*(O)CH$_3$), 135.7 (PhC), 133.8 (PhC$_q$), 133.7 (PhC$_q$), 129.7 (PhC), 127.8 (PhC), 80.2 (C5), 79.8 (C8), 75.2 (C4), 66.1 (C9), 62.6 (C1), 28.5 (C2), 28.0, 27.5, 27.4 (C3, C6 and C7), 26.9 (SiC(*C*H$_3$)$_3$), 21.2 (C(O)*C*H$_3$), 19.4 (Si*C*(CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{27}H_{38}NaO_5Si$ calculated 493.2381, found 493.2379.

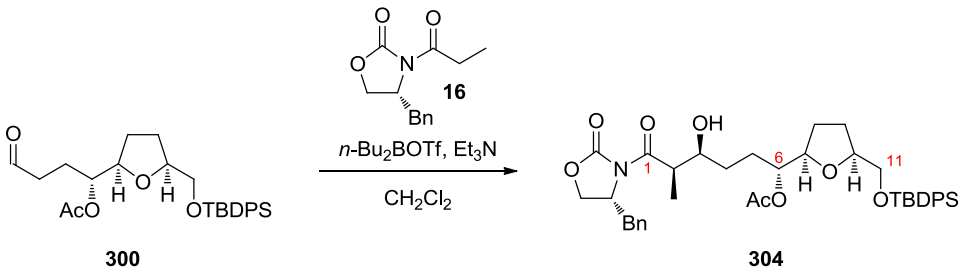
(*R*)-1-((2*R*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-oxobutyl acetate (300)



303 **300**

To a stirred solution of alcohol **303** (810 mg, 1.72 mmol) in dichloromethane (5.2 mL) at 0 °C were added dimethylsulfoxide (366 µL, 5.16 mmol) and *N*,*N*-diisopropylethylamine (900 µL, 5.16 mmol) and the resultant solution was stirred for 5 minutes. Sulfur trioxide pyridine complex (821 mg, 5.16 mmol) was added in one portion and the resulting mixture was stirred at 0 °C for 1 hour before being quenched with a saturated aqueous solution of $Na_2S_2O_3$ (3.0 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to afford aldehyde **300** (730 mg, 1.56 mmol, 90%) as a colourless oil. $R_f = 0.59$ (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ +11.3 (*c* 1.15, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2858, 2360, 2341, 1734, 1428, 1372, 1237, 1110; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.73 (1 H, s, C(1)H), 7.69 (4 H, d, $J = 7.3$, Ph*H* × 4), 7.49–7.33 (6 H, m, Ph*H* × 6), 4.92 (1 H, dt, $J = 8.9$ and 4.5, C(4)H), 4.11–4.04 (1 H, m, C(8)H), 3.98 (1 H, q, $J = 6.5$, C(5)H), 3.70 (1 H, dd, $J = 10.6$ and 5.1, C(9)H_AH_B), 3.60 (1 H, dd, $J = 10.4$ and 5.6, C(9)H_AH_B), 2.54–2.43 (2 H, m, C(2)H_2), 2.03–1.79 (8 H, m, C(3)H_2, C(6)H_AH_B, C(7)H_2 and C(O)CH_3), 1.68–1.57 (1 H, m, C(6)H_AH_B), 1.07 (9 H, s, SiC$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 201.4 (C1), 170.8 (*C*(O)CH_3), 135.7 (PhC), 133.7 (PhC_q), 133.7 (PhC_q), 129.7 (PhC), 129.7 (PhC), 127.8 (PhC), 80.1 (C5), 79.9 (C8), 74.4 (C4), 66.1 (C9), 40.0 (C2), 27.9, 27.4 (C6 and C7), 26.9 (SiC(*C*$H_3)_3$), 23.7 (C3), 21.0 (C(O)*C*H_3), 19.4 (Si*C*$(CH_3)_3$); HRMS (ESI$^+$, *m/z*) for $C_{27}H_{36}NaO_5Si$ calculated 491.2230, found 491.2228.

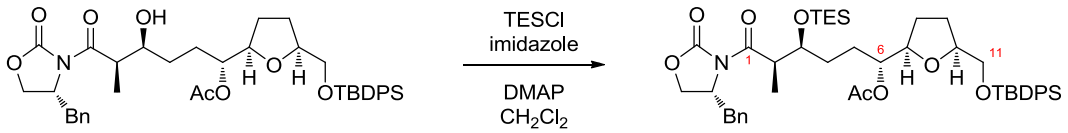
(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-hydroxy-5-methyl-6-oxohexyl acetate (304)



To a stirred solution of (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone (**16**) (348 mg, 1.49 mmol) in dichloromethane (2.5 mL) at 0 °C was added dibutylboron trifluoromethanesulfonate (1.0 M solution in CH_2Cl_2, 1.94 mL, 1.94 mmol), followed by triethylamine (364 µL, 2.61 mmol). The resulting mixture was cooled to −78 °C and stirred for 5 minutes before a solution of aldehyde **300** (800 mg, 1.71 mmol) in dichloromethane (2.0 mL) was added dropwise. The reaction mixture was stirred for 45 minutes before being warmed to 0 °C and stirred for a further 2 hours. The reaction was quenched by the addition of pH 7 phosphate buffer (3.0 mL) and methanol (4.5 mL). To the resultant slurry was added a 2:1 mixture of methanol and a 30% aqueous solution of hydrogen peroxide (4.5 mL) and the mixture was stirred vigorously for 1 hour. The reaction mixture was then extracted with ether (3 × 25 mL). The combined organic extracts were washed with water (20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 60:40) to afford aldol **304** (960 mg, 1.37 mmol, 92%) as an oil. $R_f = 0.55$ (petrol/EtOAc 50:50); $[\alpha]_D^{20}$ −26.5 (*c* 0.90, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2931, 1778, 1732, 1428, 1382, 1238, 1110; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (5 H, d, $J = 7.3$, Ph*H* × 5), 7.46–7.25 (8 H, m, Ph*H* × 8), 7.21 (2 H, d, $J = 7.1$, Ph*H* × 2), 4.91 (1 H, td, $J = 8.6$ and 4.3, C(6)H), 4.74–4.66 (1 H, m, NCH), 4.26–4.16 (2 H, m, OCH_2CHN), 4.10–4.04 (1 H, m, C(10)H), 3.97 (1 H, q, $J = 6.1$, C(7)H), 3.94–3.88 (1 H, m, C(3)H), 3.74 (1 H, dq, $J = 7.0$ and 2.8, C(2)H), 3.71 (1 H, dd, $J = 10.4$ and 4.9, C(11)H_AH$_B$), 3.57 (1 H, dd, $J = 10.4$ and 6.1, C(11)H$_A$$H_B$), 3.24 (1 H, dd, $J = 13.4$ and 3.0, CH_AH$_B$Ph), 3.01 (1 H, br. s, OH), 2.80 (1 H, dd, $J = 13.4$ and 9.3, CH$_A$$H_B$Ph), 1.98 (3 H, s, C(O)CH$_3$), 1.87 (4 H, m, C(5)H_AH$_B$, C(8)H_AH$_B$ and C(9)H$_2$), 1.68–1.51 (3 H, m, C(4)H_AH$_B$, C(5)H$_A$$H_B$ and C(8)H$_A$$H_B$), 1.49–1.37 (1 H, m, C(4)H$_A$$H_B$), 1.25

(3 H, d, J = 7.1, C(2)CH_3), 1.06 (9 H, s, SiC$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.3 (C1), 171.0 (C(O)CH_3), 153.1 (OC(O)N), 135.7 (PhC), 135.1 (PhC_q), 133.8 (PhC_q), 133.7 (PhC_q), 129.7 (PhC), 129.5, 129.1 (PhC), 127.7 (PhC), 127.5 (PhC), 80.3 (C7), 79.8 (C10), 75.4 (C6), 71.5 (C3), 66.3 (OCH_2CHN), 66.1 (C11), 55.2 (NCH), 42.4 (C2), 37.8 (CH_2Ph), 29.8 (C4), 28.1, 28.1, 27.4 (C5, C8 and C9), 26.9 (SiC$(CH_3)_3$), 21.2 (C(O)CH_3), 19.3 (Si$C(CH_3)_3$), 10.6 (C(2)CH_3); HRMS (ESI$^+$, *m/z*) for $C_{40}H_{51}NNaO_8Si$ calculated 724.3276, found 724.3280.

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl acetate (305)

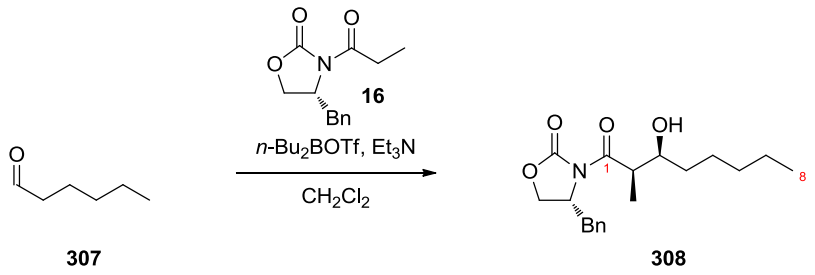


304 **305**

To a stirred solution of aldol **304** (475 mg, 0.678 mmol) in dichloromethane (4.8 mL) was added imidazole (92.6 mg, 1.36 mmol), followed by 4-(dimethylamino)pyridine (8.3 mg, 0.068 mmol). The resultant solution was cooled to 0 °C and chlorotriethylsilane (174 µL, 1.02 mmol) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 2 hours before a saturated aqueous solution of $NaHCO_3$ (5.0 mL) was added. The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to afford aldol **305** (547 mg, 0.671 mmol, 99%) as a viscous colourless oil. R_f = 0.60 (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −42.6 (*c* 0.71, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2955, 1780, 1735, 1698, 1456, 1428, 1381, 1237, 1111, 1016; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (4 H, dt, J = 4.2 and 2.4, PhH × 4), 7.43–7.26 (9 H, m, PhH × 9), 7.22 (2 H, d, J = 7.1, PhH × 2), 4.86–4.78 (1 H, m, C(6)H), 4.60 (1 H, tdd, J = 9.5, 6.3 and 3.1, NCH), 4.15–4.11 (2 H, m, OCH_2CHN), 4.09–3.99 (2 H, m, C(3)H and C(10)H), 3.93 (1 H, q, J = 6.6, C(7)H), 3.85 (1 H, quin, J = 6.4, C(2)H), 3.69 (1 H, dd, J = 10.4 and 4.8, C(11)H_AH$_B$), 3.54 (1 H, dd, J = 10.2 and 6.4, C(11)H$_A$$H_B$), 3.26 (1 H, dd, J = 13.3 and 2.9, CH_AH$_B$Ph), 2.77 (1 H, dd, J = 13.4 and 9.6, CH$_A$$H_B$Ph), 1.98 (3 H, s, C(O)$CH_3$), 1.96–1.78

(3 H, m, C(8)H_AH_B and C(9)H_2), 1.70–1.65 (1 H, m, C(5)H_AH_B), 1.64–1.47 (4 H, m, C(4)H_2, C(5)H_AH_B and C(8)H_AH_B), 1.21 (3 H, d, J = 6.6, C(2)CH_3), 1.05 (9 H, s, SiC$(CH_3)_3$), 0.94 (9 H, t, J = 8.0, Si$(CH_2CH_3)_3$), 0.58 (6 H, q, J = 7.5, Si$(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.3 (C1), 170.9 (C(O)CH_3), 153.2 (OC(O)N), 135.7 (PhC), 135.5 (PhC$_q$), 133.8 (PhC$_q$), 133.8 (PhC$_q$), 129.7 (PhC), 129.6 (PhC), 129.1 (PhC), 127.8 (PhC), 127.5 (PhC), 80.4 (C7), 79.8 (C10), 75.8 (C6), 72.8 (C3), 66.2 (C11), 66.2 (OCH_2CHN), 55.8 (NCH), 42.7 (C2), 37.8 (CH_2Ph), 31.1 (C4), 28.2 (C9), 27.5 (C8), 26.9 (SiC$(CH_3)_3$), 26.6 (C5), 21.2 (C(O)CH_3), 19.4 (Si$C(CH_3)_3$), 12.3 (C(2)CH_3), 7.0 (Si$(CH_2CH_3)_3$), 5.2 (Si$(CH_2CH_3)_3$); HRMS (ESI$^+$, *m/z*) for $C_{46}H_{65}NNaO_8Si_2$ calculated 838.4141, found 838.4144.

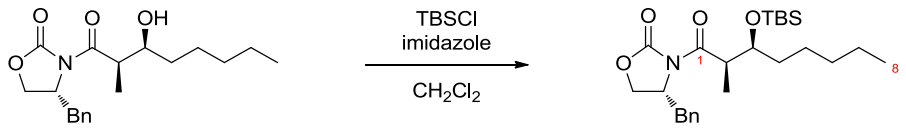
(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methyloctanoyl)oxazolidin-2-one (308)



To a stirred solution of (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone (**16**) (400 mg, 1.71 mmol) in dichloromethane (5.1 mL) at 0 °C was added dibutylboron trifluoromethanesulfonate (1.0 M solution in CH_2Cl_2, 2.22 mL, 2.22 mmol), followed by triethylamine (420 µL, 3.00 mmol). The resulting mixture was cooled to −78 °C and stirred for 5 minutes before hexanal (**307**) (245 µL, 1.97 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes at −78 °C before being warmed to 0 °C and stirred for a further 2 hours. The reaction was quenched by the addition of pH 7 phosphate buffer (4.0 mL) and methanol (5.0 mL). To the resultant slurry was added a 2:1 mixture of methanol and a 30% aqueous solution of hydrogen peroxide (5.0 mL) and the mixture was stirred vigorously for 1 hour. The reaction mixture was then extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (10 mL), a saturated aqueous solution of $NaHCO_3$ (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to afford aldol **308** (530 mg, 1.59 mmol, 93%) as a viscous colourless oil. R_f = 0.50 (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −53.2 (*c* 1.82, $CHCl_3$), lit.[138] +51.6 ((*S*)-enantiomer, *c* 1.82, $CHCl_3$); ^{1}H NMR

(400 MHz, $CDCl_3$) δ_H 7.38–7.24 (3 H, m, Ph*H* × 3), 7.20 (2 H, d, *J* = 7.3, Ph*H* × 2), 4.74–4.66 (1 H, m, NCH), 4.26–4.15 (1 H, m, OC*H*$_2$CHN), 3.95 (1 H, br. s, C(3)H), 3.76 (1 H, dq, *J* = 7.0 and 2.5, C(2)H), 3.25 (1 H, dd, *J* = 13.4 and 3.0, C*H*$_A$H$_B$Ph), 2.92 (1 H, br. s, OH), 2.79 (1 H, dd, *J* = 13.3 and 9.5, CH$_A$*H*$_B$Ph), 1.60–1.37 (3 H, m, C(4)H$_2$ and C(6)*H*$_A$H$_B$), 1.36-1.28 (5 H, m, C(5)H$_2$, C(6)H$_A$*H*$_B$ and C(7)H$_2$), 1.25 (3 H, d, *J* = 7.1, C(2)CH$_3$), 0.89 (3 H, t, *J* = 6.4, C(8)H$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.6 (C1), 153.1 (PhC$_q$), 135.1 (PhC), 129.5 (PhC), 129.0 (PhC), 127.5 (PhC), 71.6 (C3), 66.2 (O*C*H$_2$CHN), 55.2 (NCH), 42.2 (C2), 37.8 (*C*H$_2$Ph), 33.9 (C4), 31.8 (C6), 25.8 (C7), 22.7 (C5), 14.1 (C8), 10.5 (C(2)*C*H$_3$). Data were consistent with those previously reported.[138]

(*R*)-4-Benzyl-3-((2*R*,3*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-methyloctanoyl)oxazolidin-2-one (309)

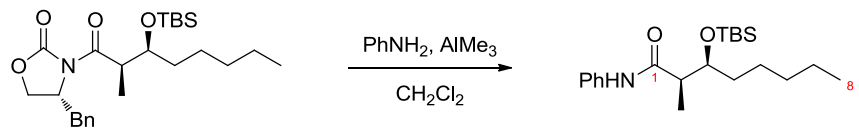


308 **309**

To a stirred solution of aldol **308** (266 mg, 0.798 mmol), imidazole (217 mg, 3.19 mmol) and 4-(dimethylamino)pyridine (9.8 mg, 0.080 mmol) in *N*,*N*-dimethylformamide (2.4 mL) was added *tert*-butyldimethylsilyl chloride (245 mg, 1.60 mmol) in one portion. The reaction mixture was stirred for 12 hours at room temperature before being quenched with water (5.0 mL). The resultant mixture was extracted with ethyl acetate (3 × 5.0 mL), the combined organics were washed sequentially with water (5.0 mL) and brine (5.0 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 80:20) to afford ether **309** (312 mg, 0.694 mmol, 87%) as a viscous colourless oil. R_f = 0.70 (petrol/Et_2O 70:30); mp 58 °C (lit.[138] 61–62 °C); $[\alpha]_D^{20}$ −57.5 (*c* 1.26, $CHCl_3$), lit.[138] +58.2 ((*S*)-enantiomer, *c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38-7.25 (3 H, m, Ph*H* × 3), 7.23 (2 H, d, *J* = 7.1, Ph*H* × 2), 4.61 (1 H, tdd, *J* = 9.6, 6.5 and 2.9, NCH), 4.22–4.12 (2 H, m, OC*H*$_2$CHN), 4.01 (1 H, q, *J* = 5.6, C(3)H), 3.91–3.82 (1 H, m, C(2)H), 3.30 (1 H, dd, *J* = 13.3 and 2.9, C*H*$_A$H$_B$Ph), 2.78 (1 H, dd, *J* = 13.1 and 9.6, CH$_A$*H*$_B$Ph), 1.57–1.48 (2 H, m, C(4)H$_2$), 1.38–1.24 (6 H, m, C(5)H$_2$, C(6)H$_2$ and C(7)H$_2$), 1.21 (3 H, d, *J* = 6.8, C(2)CH$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.05 (3 H, s, SiCH$_3$), 0.00 (3 H, s, SiCH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.4 (C1), 153.2 (OC(O)N), 135.5

(PhC_q), 129.6 (PhC), 129.0 (PhC), 127.4 (PhC), 73.0 (C3), 66.1 (O*C*H_2CHN), 56.0 (NCH), 42.9 (C2), 37.7 (*C*H_2Ph), 35.6 (C4), 32.2 (C5), 25.9 (SiC(*C*H_3)$_3$), 24.8 (C6), 22.7 (C7), 18.2 (Si*C*$(CH_3)_3$), 14.2 (C8), 11.6 (C(2)*C*H_3), −4.0 ($SiCH_3$), −4.7 ($SiCH_3$). Data were consistent with those previously reported.[138]

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-*N*-phenyloctanamide (310)

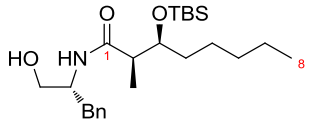


309 **310**

To a stirred solution of aniline (51 μL, 0.56 mmol) in dichloromethane (0.7 mL) at 0 °C was added trimethylaluminium (2.0 M solution in heptane, 0.28 mL, 0.56 mmol) dropwise and the resulting solution was stirred for 10 minutes before it was warmed to room temperature and stirred for a further 30 minutes. The mixture was cooled to 0 °C and a solution of ether **309** (50 mg, 0.11 mmol) in dichloromethane (0.3 mL) was added dropwise. The reaction tube was sealed, the mixture was heated to 40 °C and stirred for 24 hours. The reaction mixture was cooled to room temperature before being transferred *via* a syringe into an ice-cold vigorously stirred 1:1 mixture of dichloromethane (3.0 mL) and an aqueous solution of HCl (1 M, 3.0 mL). The resultant mixture was stirred at 0 °C for 30 minutes, then the layers were separated and the aqueous layer was extracted with chloroform (3 × 3.0 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (3.0 mL), brine (3.0 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 90:10) to afford amide **310** (21 mg, 0.058 mmol, 52%) as a viscous colourless oil. $R_f = 0.80$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −60.2 (*c* 0.85, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3400, 2930, 2857, 1659, 1600, 1538, 1500, 1441, 1379, 1306, 1253, 1056; ^{1}H NMR (400 MHz ,$CDCl_3$) δ_H 8.61 (1 H, br. s, NH), 7.52 (2 H, d, *J* = 8.1, Ph*H* × 2), 7.32 (2 H, t, *J* = 7.8, Ph*H* × 2), 7.12–7.04 (1 H, m, Ph*H*), 3.85–3.78 (1 H, m, C(3)H), 2.70 (1 H, dq, *J* = 7.1 and 3.4, C(2)H), 1.52–1.43 (3 H, m, C(4)H_2 and C(6)H_AH$_B$), 1.30–1.20 (5 H, m, C(5)H_2, C(6)H$_A$*H*$_B$ and C(7)H_2), 1.17 (3 H, d, *J* = 7.1, C(9)H_3), 1.00 (9 H, s, SiC$(CH_3)_3$), 0.87 (3 H, t, *J* = 6.9, C(8)H_3), 0.17 (6 H, s, $SiCH_3$ × 2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.1 (C1), 138.5 (PhC_q), 129.1 (PhC), 123.8 (PhC), 119.8 (PhC), 75.9 (C3), 46.8 (C2), 32.2 (C4), 31.9 (C5), 26.2 (C6), 26.1 (SiC(*C*H_3)$_3$), 22.7 (C7),

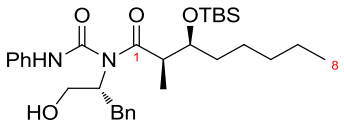
18.2 (Si*C*$(CH_3)_3$), 14.1 (C8), 13.0 (C9), −4.4 ($SiCH_3$), −4.4 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{21}H_{37}NNaO_2Si$ calculated 386.2486, found 386.2481.

(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-*N*-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-2-methyloctanamide (311)



Amide **311** was isolated as a side product in the synthesis of **310** as a viscous colourless oil. R_f = 0.50 (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −8.0 (*c* 1.25, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3314, 2930, 2857, 1638, 1598, 1543, 1498, 1462, 1379, 1254, 1114, 1058; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.32–7.26 (2 H, m, Ph*H* × 2), 7.25–7.19 (3 H, m, Ph*H* × 3), 6.54 (1 H, d, *J* = 7.3, NH), 4.26–4.16 (1 H, m, NCH), 3.76–3.65 (2 H, m, C(3)H and OCH_AH_BCHN), 3.60–3.51 (1 H, m, OCH_AH_BCHN), 2.86 (2 H, dq, *J* = 13.6 and 7.6, CH_2Ph), 2.78 (1 H, br. s, OH), 2.49–2.40 (1 H, m, C(2)H), 1.49–1.35 (3 H, m, C(4)H_2 and C(5)H_AH_B), 1.35–1.18 (5 H, m, C(5)H_AH_B, C(6)H_2 and C(7)H_2), 1.06 (3 H, d, *J* = 7.1, C(2)CH_3), 0.92–0.85 (12 H, m, C(8)H_3 and Si$C(CH_3)_3$), 0.09 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.7 (C1), 137.9 (PhC_q), 129.3 (PhC), 128.7 (PhC), 126.7 (PhC), 75.3 (C3), 64.6 (O*C*H_2CHN), 53.1 (NCH), 46.1 (C2), 37.3 (*C*H_2Ph), 32.7 (C4), 32.0 (C6), 26.0 (Si$C(CH_3)_3$), 25.8 (C5), 22.7 (C7), 18.2 (Si*C*$(CH_3)_3$), 14.1 (C8), 13.2 (C(2)*C*H_3), −4.3 ($SiCH_3$), −4.4 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{24}H_{43}NNaO_3Si$ calculated 444.2904, found 444.2910.

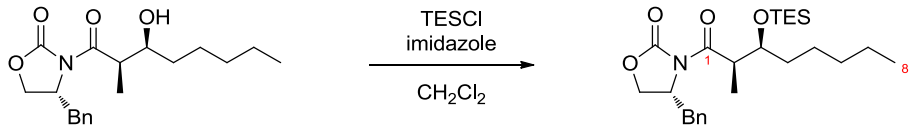
(2*R*,3*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-*N*-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-2-methyl-*N*-(phenylcarbamoyl)octanamide (312)



Compound **312** was isolated as a side product in the synthesis of **310** as a light yellow foam. R_f = 0.30 (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ +8.0 (*c* 1.35, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3282, 2930, 2857, 1700, 1597, 1521, 1492, 1458, 1372, 1254, 1167, 1107, 1053; ^1H NMR (400 MHz,

$(CD_3)_2CO$) δ_H 8.14 (1 H, br. s, NH), 7.54 (2 H, d, J = 7.8, Ph*H* × 2), 7.32–7.23 (6 H, m, Ph*H* × 6), 7.22–7.14 (1 H, m, Ph*H*), 6.98 (1 H, t, J = 7.3, Ph*H*), 4.23–4.12 (1 H, m, NCH), 4.00 (1 H, t, J = 4.8, OH), 3.89–3.82 (1 H, m, C(3)H), 3.61–3.47 (2 H, m, OCH_2CHN), 2.98 (1 H, dd, J = 13.6 and 6.3, CH_AH$_B$Ph), 2.77 (1 H, dd, J = 13.6 and 7.8, CH$_A$$H_B$Ph), 2.42 (1 H, quin, J = 6.9, C(2)H), 1.52–1.40 (3 H, m, C(4)H_2 and C(5)H_AH$_B$), 1.38–1.20 (5 H, m, C(5)H$_A$$H_B$, C(6)$H_2$ and C(7)H_2), 1.02 (3 H, d, J = 6.8, C(2)CH_3), 0.91 (9 H, s, SiC$(CH_3)_3$), 0.88 (3 H, t, J = 7.1, C(8)H_3), 0.09 (3 H, s, SiCH_3), 0.08 (3 H, s, SiCH_3); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ_C 174.8 (C1), 153.4 (NC(O)N), 141.0 (PhC_q), 140.0 (PhC_q), 130.2 (PhC), 129.6 (PhC), 129.1 (PhC), 126.9 (PhC), 123.0 (PhC), 119.5 (PhC), 75.2 (C3), 64.1 (OCH$_2$CHN), 53.3 (NCH), 47.0 (C2), 37.8 (CH$_2$Ph), 35.2 (C4), 33.0 (C6), 26.4 (SiC(CH$_3$)$_3$), 25.0 (C5), 23.3 (C7), 18.7 (SiC(CH$_3$)$_3$), 15.0 (C(2)CH$_3$), 14.4 (C8), −4.0 (SiCH_3), −4.1 (SiCH_3); HRMS (ESI$^+$, *m/z*) for $C_{31}H_{48}N_2NaO_4Si$ calculated 563.3276, found 563.327.

(*R*)-4-Benzyl-3-((2*R*,3*S*)-2-methyl-3-((triethylsilyl)oxy)octanoyl)oxazolidin-2-one (313)

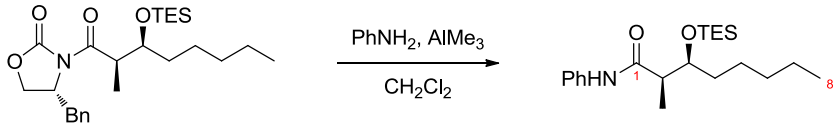


308 **313**

To a stirred solution of aldol **308** (150 mg, 0.450 mmol), imidazole (61 mg, 0.90 mmol) and 4-(dimethylamino)pyridine (5.5 mg, 0.045 mmol) in dichloromethane (3.2 mL) was added chlorotriethylsilane (115 μL, 0.675 mmol). The reaction mixture was stirred for 12 hours at room temperature before being quenched with water (5.0 mL). The resultant mixture was extracted with ether (3 × 5.0 mL), the combined organics were washed sequentially with water (5.0 mL) and brine (5.0 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 85:15) to afford ether **313** (177 mg, 0.396 mmol, 88%) as a viscous colourless oil. R_f = 0.70 (petrol/Et_2O 70:30); $[\alpha]_D^{20}$ −52.6 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.25 (3 H, m, Ph*H* × 3), 7.23 (2 H, d, J = 7.1, Ph*H* × 2), 4.66–4.58 (1 H, m, NCH), 4.21–4.12 (2 H, m, OCH_2CHN), 4.02 (1 H, q, J = 5.6, C(3)H), 3.91–3.83 (1 H, m, C(2)H), 3.30 (1 H, dd, J = 13.3 and 2.9, CH_AH$_B$Ph), 2.78 (1 H, dd, J = 13.3 and 9.7, CH$_A$$H_B$Ph), 1.57–1.47 (2 H, m, C(4)H_2), 1.40–1.25 (6 H, m, C(5)H_2, C(6)H_2 and C(7)H_2), 1.22 (3 H, d, J = 7.1, C(2)CH_3), 0.96 (9 H, t, J = 8.0, Si(CH$_2$CH_3)$_3$), 0.89 (3 H, t, J = 6.8, C(8)H_3), 0.63–0.55 (6 H, m,

$Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.5 (C1), 153.2 (PhC_q), 135.5 (PhC), 129.6 (PhC), 129.0 (PhC), 127.4 (PhC), 73.3 (C3), 66.1 (OCH_2CHN), 55.9 (NCH), 43.1 (C2), 37.8 (CH_2Ph), 35.8 (C4), 32.2 (C5), 25.0 (C6), 22.7 (C7), 14.1 (C8), 11.8 ($C(2)CH_3$), 7.0 ($Si(CH_2CH_3)_3$), 5.2 ($Si(CH_2CH_3)_3$).

(2*R*,3*S*)-2-Methyl-*N*-phenyl-3-((triethylsilyl)oxy)octanamide (314)

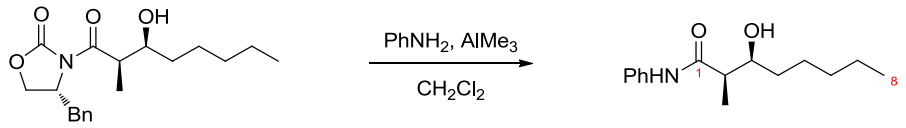


313 **314**

To a stirred solution of aniline (102 μL, 1.1 mmol) in dichloromethane (0.7 mL) at 0 °C was added trimethylaluminium (2.0 M solution in heptane, 0.56 mL, 1.1 mmol) dropwise and the resulting solution was stirred for 10 minutes before it was warmed to room temperature and stirred for a further 30 minutes. The mixture was cooled to 0 °C and a solution of ether **313** (50 mg, 0.11 mmol) in dichloromethane (0.3 mL) was added dropwise. The reaction tube was sealed, the mixture was warmed to room temperature stirred for 24 hours. The reaction transferred *via* a syringe into an ice-cold vigorously stirred 1:1 mixture of dichloromethane (3.0 mL) and an aqueous solution of HCl (1 M, 3.0 mL). The resultant mixture was stirred at 0 °C for 30 minutes, then the layers were separated and the aqueous layer was extracted with chloroform (3 × 3.0 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (3.0 mL), brine (3.0 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 90:10) to afford amide **313** (15 mg, 0.041 mmol, 37%) as a viscous colourless oil. $R_f = 0.80$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −62.2 (*c* 1.00, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3300, 2940, 2866, 1659, 1601, 1540, 1500, 1441, 1307, 1256, 1056; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.76 (1 H, br. s, NH), 7.51 (2 H, d, $J = 7.8$, C(11)H × 2), 7.32 (2 H, t, $J = 8.0$, C(12)H × 2), 7.12-7.04 (1 H, m, C(13)H), 3.88-3.80 (1 H, m, C(3)H), 2.69 (1 H, dq, $J = 7.2$ and 3.5, C(2)H), 1.55-1.38 (2 H, m, $C(4)H_AH_B$ and $C(6)H_AH_B$), 1.34-1.21 (6 H, m, $C(4)H_AH_B$, $C(5)H_2$, $C(6)H_AH_B$ and $C(7)H_2$), 1.17 (3 H, d, $J = 7.3$, $C(9)H_3$), 1.04 (9 H, t, $J = 8.1$, $Si(CH_2CH_3)_3$), 0.87 (3 H, t, $J = 6.9$, $C(8)H_3$), 0.72 (6 H, q, $J = 7.8$, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.2 (C1), 138.6 (PhC_q), 129.1 (PhC), 123.7 (PhC), 119.6 (PhC), 75.8 (C3), 46.9 (C2), 32.3 (C4), 31.9 (C6), 26.2 (C5), 22.7 (C7), 14.1 (C8), 12.9 (C9),

7.1 ($Si(CH_2\mathit{C}H_3)_3$), 5.2 ($Si(\mathit{C}H_2CH_3)_3$); HRMS (ESI^+, *m/z*) for $C_{21}H_{37}NNaO_2Si$ calculated 386.2486, found 386.2483.

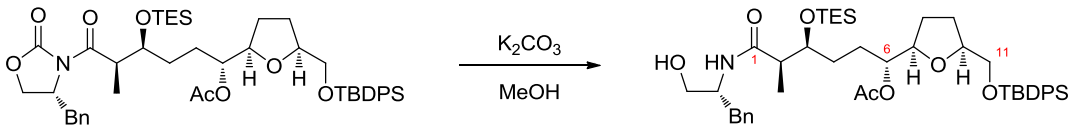
(2*R*,3*S*)-3-Hydroxy-2-methyl-*N*-phenyloctanamide (315)



308 **315**

To a stirred solution of aniline (68 μL, 0.75 mmol) in dichloromethane (1.0 mL) at 0 °C was added trimethylaluminium (2.0 M solution in heptane, 0.38 mL, 0.75 mmol) dropwise and the resulting solution was stirred for 10 minutes before it was warmed to room temperature and stirred for a further 30 minutes. The mixture was cooled to 0 °C and a solution of aldol **308** (50 mg, 0.15 mmol) in dichloromethane (0.5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours before it was transferred *via* a syringe into an ice-cold vigorously stirred 1:1 mixture of dichloromethane (5.0 mL) and an aqueous solution of HCl (1 M, 5.0 mL). The resultant mixture was stirred at 0 °C for 30 minutes before the layers were separated and the aqueous layer was extracted with chloroform (3 × 5.0 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (5.0 mL), brine (5.0 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 60:40) to afford amide **315** (30 mg, 0.12 mmol, 80%) as a viscous colourless oil. $R_f = 0.55$ (petrol/EtOAc 50:50); $[\alpha]_D^{20}$ −14.0 (*c* 1.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3281, 2929, 1650, 1599, 1533, 1443; ^1H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (1 H, br. s, NH), 7.52 (2 H, d, $J = 7.8$, Ph*H* × 2), 7.37–7.21 (3 H, m, Ph*H* × 3), 4.00–3.89 (1 H, m, C(3)H), 2.53 (1 H, dq, $J = 7.2$ and 2.8, C(2)H), 1.58–1.39 (3 H, m, $C(4)H_2$ and $C(6)H_AH_B$), 1.37–1.19 (8 H, m, $C(5)H_2$, $C(6)H_AH_B$, $C(7)H_2$ and $C(2)CH_3$), 0.89 (3 H, t, $J = 6.6$, $C(8)H_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.6 (C1), 137.9 (PhC_q), 129.1 (PhC), 124.4 (PhC), 120.2 (PhC), 72.6 (C3), 46.0 (C2), 33.6 (C4), 31.8 (C5), 25.9 (C6), 22.7 (C7), 14.1 (C8), 11.5 ($C(2)\mathit{C}H_3$); HRMS (ESI^+, *m/z*) for $C_{15}H_{23}NNaO_2$ calculated 272.1621, found 272.1624.

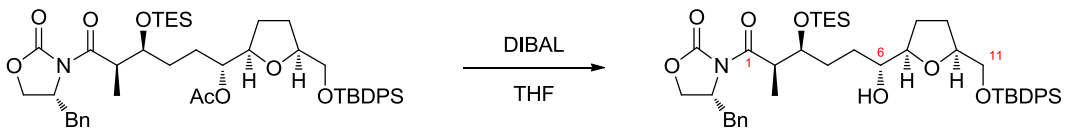
(1*R*,4*S*,5*R*)-1-((2*R*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(((*R*)-1-hydroxy-3-phenylpropan-2-yl)amino)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl acetate (320)



305 **320**

To a stirred solution of acetate **305** (10.0 mg, 0.0123 mmol) in methanol (0.25 mL) at 0 °C was added K_2CO_3 (2.6 mg, 0.019 mmol) and the resulting mixture was stirred at this temperature for 1 hour. The reaction was diluted with ether (5.0 mL) and washed with water (2 × 1.0 mL), brine (2.0 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography afforded amide **320** (6.5 mg, 0.0082 mmol, 67%) as a viscous colourless oil and a major product along with THF **321** (2.2 mg, 0.0029 mmol, 23%). $R_f = 0.35$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ +1.6 (*c* 0.25, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3300, 2955, 1646, 1541, 1242, 1112; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.69 (4 H, d, *J* = 6.9, Ph*H* × 4), 7.46–7.33 (7 H, m, Ph*H* × 7), 7.29 (1 H, m, Ph*H* × 1), 7.23–7.16 (3 H, m, Ph*H* × 3), 6.50 (1 H, d, *J* = 8.2, NH), 4.82–4.76 (1 H, m, C(6)H), 4.25–4.16 (1 H, m, NCH), 4.12–4.06 (1 H, m, C(10)H), 4.02–3.95 (1 H, m, C(7)H), 3.75 (1 H, q, *J* = 4.9, C(3)H), 3.71 (1 H, dd, *J* = 10.3 and 5.0, C(11)H_AH_B), 3.65 (1 H, dd, *J* = 3.0 and 11.2, OCH_AH_BCHN), 3.55 (1 H, dd, *J* = 10.3 and 6.1, C(11)H_AH_B), 3.46 (1 H, dd, *J* = 11.2 and 4.6, OCH_AH_BCHN), 2.86 (1 H, dd, *J* = 14.2 and 7.9, CH_AH_BPh), 2.78 (1 H, dd, *J* = 13.9 and 7.6, CH_AH_BPh), 2.39–2.32 (1 H, m, C(2)H), 1.92 (3 H, s, C(O)CH_3), 1.90–1.71 (4 H, m, C(5)H_AH_B, C(8)H_AH_B and C(9)H_2), 1.65–1.54 (2 H, m, C(5)H_AH_B and C(8)H_AH_B), 1.51–1.43 (2 H, m, C(4)H_2), 1.06 (9 H, s, SiC(CH_3)$_3$), 1.03 (3 H, d, *J* = 6.9, C(2)CH_3), 0.98–0.91 (9 H, m, Si(CH_2CH_3)$_3$), 0.60 (6 H, q, *J* = 7.9, Si(CH_2CH_3)$_3$); ^{13}C NMR (125 MHz, CDCl3) δ_C 174.2 (C1), 171.1 (*C*(O)CH_3), 138.1 (PhC_q), 135.8 (PhC), 133.8 (PhC_q), 133.7 (PhC_q), 129.8 (PhC), 129.3 (PhC), 128.6 (PhC), 127.8 (PhC), 126.6 (PhC), 79.9 (C10), 79.7 (C7), 75.6 (C6), 74.4 (C3), 66.2 (C11), 63.6 (OCH_2CHN), 52.3 (NCH), 46.2 (C2), 37.2 (*C*H_2Ph), 28.9 (C4), 28.2 (C9), 27.3 (C8), 27.0 (SiC(*C*H_3)$_3$), 26.8 (C5), 21.2 (C(O)*C*H_3), 19.4 (Si*C*(CH_3)$_3$), 13.9 (C(2)*C*H_3), 7.0 (Si(CH_2CH_3)$_3$), 5.1 (Si(*C*H_2CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{45}H_{67}NNaO_7Si_2$ calculated 812.4348, found 812.4351.

(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*)-6-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-hydroxy-2-methyl-3-((triethylsilyl)oxy)hexanoyl)oxazolidin-2-one (321)

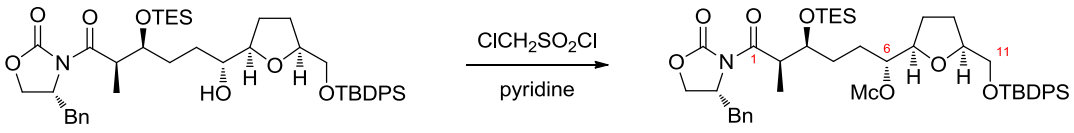


305 **321**

To a stirred solution of acetate **305** (716 mg, 0.879 mmol) in tetrahydrofuran (35 mL) at −78 °C was added diisobutylaluminium hydride (1.0 M solution in hexanes, 4.40 mL, 4.40 mmol) dropwise. The reaction mixture was stirred at −78 °C for 3 hours before a saturated aqueous solution of Rochelle's salt (30 mL) was slowly added. The resultant mixture was stirred vigorously for 1 hour while being allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 50:50) to afford alcohol **321** (564 mg, 0.730 mmol, 83%) as a viscous colourless oil. $R_f = 0.35$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −31.5 (*c* 1.00, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3500, 2955, 2876, 1781, 1699, 1457, 1428, 1383, 1210, 1112, 1010; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.73–7.64 (4 H, m, Ph*H* × 4), 7.47–7.31 (9 H, m, Ph*H* × 9), 7.22 (2 H, d, *J* = 6.9, Ph*H* × 2), 4.60 (1 H, dt, *J* = 6.5 and 3.6, NCH), 4.17–4.10 (2 H, m, OCH_2CHN), 4.09–4.00 (2 H, m, C(3)H and C(10)H), 3.89 (1 H, quin, *J* = 6.6, C(2)H), 3.81 (1 H, q, *J* = 5.7, C(7)H), 3.74 (1 H, dd, *J* = 10.7 and 4.1, C(11)H_AH_B), 3.60 (1 H, dd, *J* = 10.7 and 4.1, C(11)H_AH_B), 3.36 (1 H, d, *J* = 4.4, C(6)H), 3.29 (1 H, dd, *J* = 13.2 and 2.8, CH_AH_BPh), 2.77 (1 H, dd, *J* = 13.4 and 9.6, CH_AH_BPh), 2.58 (1 H, d, *J* = 4.7, OH), 2.00–1.88 (3 H, m, C(8)H_AH_B and C(9)H_2), 1.86–1.71 (2 H, m, C(4)H_AH_B, and C(8)H_AH_B), 1.61–1.53 (2 H, m, C(4)H_AH_B and C(5)H_AH_B), 1.50–1.39 (1 H, m, C(5)H_AH_B), 1.22 (3 H, d, *J* = 6.6, C(2)CH_3), 1.06 (9 H, s, SiC$(CH_3)_3$), 0.95 (9 H, t, *J* = 8.0, Si$(CH_2CH_3)_3$), 0.63–0.55 (6 H, m, Si$(CH_2CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.4 (C1), 153.2 (OC(O)N), 135.8 (PhC), 135.7 (PhC), 135.6 (PhC_q), 133.5 (PhC_q), 133.5 (PhC_q), 129.8 (PhC), 129.8 (PhC), 129.6 (PhC), 129.1 (PhC), 127.9 (PhC), 127.8 (PhC), 127.4 (PhC), 82.8 (C7), 80.0 (C10), 74.8 (C6), 73.4 (C3), 66.2 (OCH_2CHN), 66.0 (C11), 56.0 (NCH), 43.0 (C2), 37.8 (CH_2Ph), 31.7 (C4), 29.8 (C5), 28.3 (C8), 27.7 (C9), 27.0 (SiC$(CH_3)_3$), 19.4 (Si$C(CH_3)_3$), 12.0 (C(2)CH_3), 7.1

($Si(CH_2CH_3)_3$), 5.3 ($Si(CH_2CH_3)_3$); HRMS (ESI^+, *m/z*) for $C_{44}H_{63}NNaO_7Si_2$ calculated 796.4035, found 796.4041.

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl chloromethanesulfonate (322)

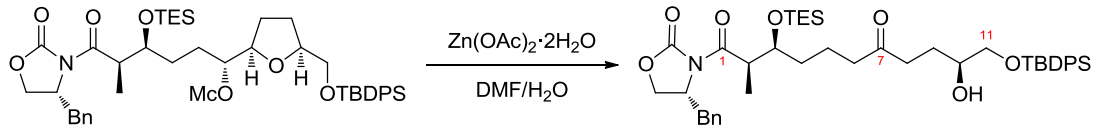


321 **322**

To a stirred solution of alcohol **321** (100 mg, 0.129 mmol) in pyridine (1.0 mL) at 0 °C was added chloromethanesulfonyl chloride (90% purity, 26.0 µL, 0.258 mmol). The resulting mixture was stirred for 30 minutes at 0 °C before being warmed to room temperature and stirred for a further 3 hours. The reaction mixture was quenched with water (2.0 mL) and diluted with ethyl acetate (5.0 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The combined organic extracted were washed with water (5.0 mL), brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 70:30) to give chloromesylate **322** (20 mg, 0.125 mmol, 97%) as a viscous, colourless oil. $R_f = 0.65$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −43.0 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2955, 1776, 1694, 1456, 1370, 1179, 1111, 1008; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.63 (4 H, m, Ph*H* × 4), 7.47–7.19 (11 H, m, Ph*H* × 11), 5.02 (1 H, d, *J* = 11.9, SCH_AH_BCl), 4.71–4.63 (1 H, m, NCH), 4.58 (2 H, d, *J* = 12.1, C(6)H and SCH_AH_BCl), 4.25 (1 H, t, *J* = 8.2, OCH_AH_BCHN), 4.16–4.09 (2 H, m, C(10)H and OCH_AH_BCHN), 4.07–3.97 (2 H, m, C(3)H and C(7)H), 3.92 (1 H, quin, *J* = 6.8, C(2)H), 3.64 (2 H, d, *J* = 4.8, $C(11)H_AH_B$), 3.49 (1 H, q, *J* = 7.0, $C(11)H_AH_B$), 3.27 (1 H, dd, *J* = 13.4 and 2.8, CH_AH_BPh), 2.79 (1 H, dd, *J* = 13.4 and 9.6, CH_AH_BPh), 1.99–1.89 (2 H, m, $C(8)H_AH_B$ and $C(9)H_AH_B$), 1.83–1.76 (2 H, m, $C(4)H_AH_B$ and $C(9)H_AH_B$), 1.69–1.54 (4 H, m, $C(4)H_AH_B$, $C(5)H_2$ and $C(8)H_AH_B$), 1.26 (3 H, d, *J* = 6.6, $C(2)CH_3$), 1.06 (9 H, s, $SiC(CH_3)_3$), 0.97 (9 H, t, *J* = 8.0, $Si(CH_2CH_3)_3$), 0.62 (6 H, q, *J* = 8.0, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.4 (C1), 153.4 (OC(O)N), 135.7 (PhC), 135.7 (PhC), 135.5 (PhC_q), 133.4 (PhC_q), 133.3 (PhC_q), 129.9 (PhC), 129.9 (PhC), 129.6 (PhC), 129.0 (PhC), 127.9 (PhC), 127.9 (PhC), 127.4 (PhC), 90.1 (C6), 81.0 (C7), 80.4 (C10),

73.1 (C3), 66.7 (O*C*H$_2$CHN), 66.3 (C11), 55.7 (NCH), 54.6 (SCH$_2$Cl), 42.8 (C2), 37.8 (*C*H$_2$Ph), 30.6 (C4), 28.3 (C8), 27.6, 27.2 (C5 and C9), 27.0 (SiC(*C*H$_3$)$_3$), 22.8, 19.3 (Si*C*(CH$_3$)$_3$), 13.4 (C2)*C*H$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 5.2 (Si(*C*H$_2$CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{45}H_{64}ClNNaO_9SSi_2$ calculated 908.3421, found 908.3426.

(2*R*,3*S*,10*S*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-11-((*tert*-butyldiphenylsilyl)oxy)-10-hydroxy-2-methyl-3-((triethylsilyl)oxy)undecane-1,7-dione (323)



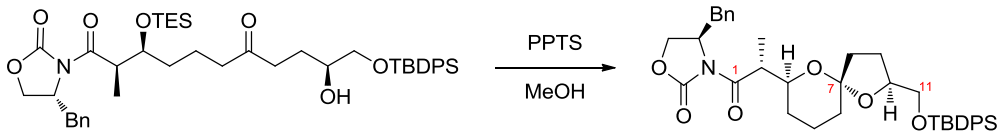
322 **323**

To a stirred solution of chloromesylate **322** (36 mg, 41 μmol) in *N*,*N*-dimethylformamide (0.61 mL) was added water (0.45 mL), followed by zinc trifluoromethanesulfonate dihydrate (46 mg, 0.21 mmol). The resulting mixture was heated to 70 °C and stirred for 16 hours, before it was cooled to room temperature and diluted with brine (5.0 mL). The resultant mixture was extracted with ether (4 × 5.0 mL) and the combined organic extracts were dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO$_2$, petrol/EtOAc 70:30) to afford ketone **323** (16.8 mg, 21.7 μmol, 53%) as a viscous oil. $R_f = 0.35$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −37.0 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2955, 1782, 1704, 1384, 1210, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (4 H, d, *J* = 7.1, Ph*H* × 4), 7.47–7.19 (11 H, m, Ph*H* × 11), 4.70–4.61 (1 H, m, NCH), 4.31–4.24 (1 H, m, OC*H*$_A$H$_B$CHN), 4.18–4.09 (1 H, m, OCH$_A$*H*$_B$CHN), 4.03 (1 H, q, *J* = 5.6, C(3)H), 3.94 (1 H, quin, *J* = 6.8, C(2)H), 3.72–3.60 (2 H, m, C(10)H and C(11)*H*$_A$H$_B$), 3.49 (1 H, dd, *J* = 9.9 and 6.8, C(11)H$_A$*H*$_B$), 3.27 (1 H, dd, *J* = 13.1 and 2.8, C*H*$_A$H$_B$Ph), 2.79 (1 H,. dd, *J* = 13.1 and 9.6, CH$_A$*H*$_B$Ph), 2.61 (1 H, br. s, OH), 2.56–2.49 (2 H, m, C(8)H$_2$), 2.45–2.38 (2 H, m, C(6)H$_2$), 1.75–1.54 (4 H, m, C(5)H$_2$ and C(9)H$_2$), 1.53–1.46 (2 H, m, C(4)H$_2$), 1.25 (3 H, d, *J* = 6.8, C(2)CH$_3$), 1.07 (9 H, s, SiC(CH$_3$)$_3$), 0.96 (9 H, t, *J* = 8.0, Si(CH$_2$C*H*$_3$)$_3$), 0.60 (6 H, q, *J* = 8.0, Si(C*H*$_2$CH$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 210.8 (C7), 175.6 (C1), 153.3 (OC(O)N), 135.7 (PhC), 135.6 (PhC), 135.6 (PhC$_q$), 133.2 (PhC$_q$), 129.9 (PhC), 129.6 (PhC), 129.0 (PhC), 127.9 (PhC), 127.7 (PhC), 127.4 (PhC), 73.1 (C3), 71.3 (C10), 68.0 (C11), 66.2 (O*C*H$_2$CHN), 55.8 (NCH), 42.6 (C2), 42.5 (C6), 38.8 (C8), 37.8 (*C*H$_2$Ph), 35.0 (C4), 26.9 (SiC(*C*H$_3$)$_3$), 26.7 (C9), 19.3 (Si*C*(CH$_3$)$_3$), 18.8 (C5), 12.9

(C(2)CH_3), 7.0 (Si(CH_2CH_3)$_3$), 5.2 (Si(CH_2CH_3)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{44}H_{63}NNaO_7Si_2$ calculated 796.4041, found 796.4035.

(*R*)-4-Benzyl-3-((*R*)-2-((2*S*,5*S*,7*S*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1,6-dioxaspiro[4.5]decan-7-yl)propanoyl)oxazolidin-2-one (325)

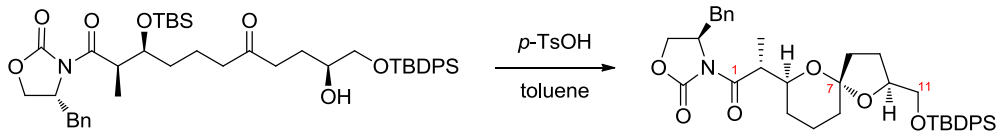
Procedure A:



323 **325**

To a stirred solution of ketone **323** (23 mg, 30 µmol) in methanol (1.2 mL) was added pyridinium *para*-toluenesulfonate (3.8 mg, 15 µmol). The resulting mixture was stirred at room temperature for 10 hours before being quenched with a saturated aqueous solution of $NaHCO_3$ (0.5 mL). The resulting mixture was diluted with ether (25 mL) and washed with water (5.0 mL), brine (5.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 90:10) to afford spiroketal **325** (19.0 mg, 29.7 µmol, 99%) as a colourless oil.

Procedure B:

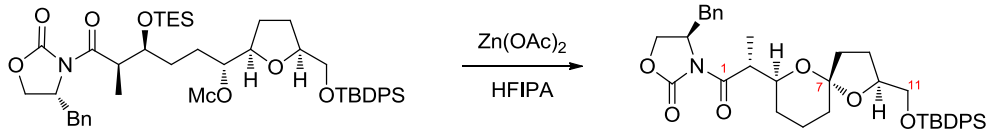


333 **325**

To a stirred solution of ketone **333** (16 mg, 21 µmol) in toluene (0.21 mL) was added *para*-toluenesulfonic acid monohydrate (6.1 mg, 32 µmol) and the resulting solution was heated to 80 °C and stirred for 8 hours. The reaction mixture was cooled to room temperature and diluted with ether (5.0 mL) and washed with brine (1.0 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash

column chromatography (SiO_2, petrol/EtOAc 90:10) to afford spiroketal **325** (12.9 mg, 20.2 μmol, 96%) as a colourless oil.

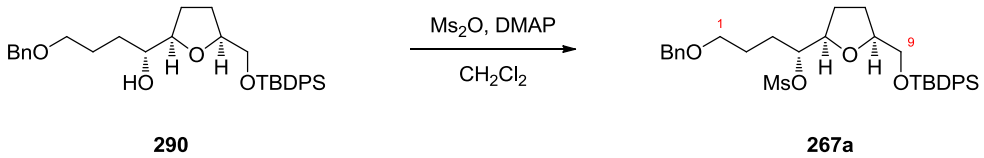
Procedure C:



322 **325**

To a stirred solution of chloromesylate **322** (40.0 mg, 0.0452 mmol) in hexafluoroisopropanol (0.45 mL) was added zinc acetate (41.5 mg, 0.226 mmol). The reaction tube was sealed and the mixture was warmed to 30 °C and stirred for 3 hours before being diluted with ethyl acetate (5.0 mL). The resulting mixture was washed with water (2.0 mL), brine (2.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 90:10) to afford spiroketal **325** (20.2 mg, 0.0316 mmol, 70%) as a colourless oil. $[\alpha]_D^{20}$ −28.6 (*c* 0.75, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2932, 1783, 1698, 1457, 1382, 1281, 1112; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.74–7.67 (4 H, m, Ph*H* × 4), 7.45–7.20 (11 H, m, Ph*H* × 11), 4.67–4.59 (1 H, m, NCH), 4.14 (3 H, d, *J* = 5.4, C(10)H and OC*H*$_2$CHN), 4.07–4.00 (1 H, m, C(3)H), 3.94 (1 H, quin, *J* = 6.9, C(2)H), 3.72–3.63 (2 H, m, C(11)H_2), 3.30 (1 H, dd, *J* = 13.4 and 3.0, CH_AH$_B$Ph), 2.77 (1 H, dd, *J* = 13.6 and 9.8, CH$_A$*H*$_B$Ph), 2.17–2.07 (1 H, m, C(9)H_AH$_B$), 1.94–1.78 (3 H, m, C(5)H_AH$_B$, C(8)H_AH$_B$ and C(9)H$_A$*H*$_B$), 1.71–1.59 (6 H, m, C(4)H_2, C(5)H$_A$*H*$_B$, C(6)H_2 and C(8)H$_A$*H*$_B$), 1.25 (3 H, d, *J* = 6.6, C(2)CH_3), 1.05 (9 H, s, SiC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.3 (C1), 153.3 (OC(O)N), 135.8 (PhC), 135.8 (PhC), 135.6 (PhC), 133.9 (PhC_q), 133.8 (PhC_q), 129.7 (PhC), 129.7 (PhC), 129.6 (PhC), 129.1 (PhC), 127.7 (PhC), 127.4 (PhC), 106.8 (C7), 78.6 (C10), 71.5 (C3), 66.4 (C11), 66.1 (O*C*H$_2$CHN), 55.8 (NCH), 42.3 (C2), 38.1 (*C*H$_2$Ph), 37.6 (C8), 32.7 (C6), 27.9 (C4), 26.9 (SiC(*C*H$_3$)$_3$), 25.9 (C9), 20.4 (C5), 19.4 (Si*C*(CH$_3$)$_3$), 13.0 (C(2)*C*H$_3$); HRMS (ESI$^+$, *m/z*) for $C_{38}H_{47}NNaO_6Si$ calculated 664.3070, found 664.3084.

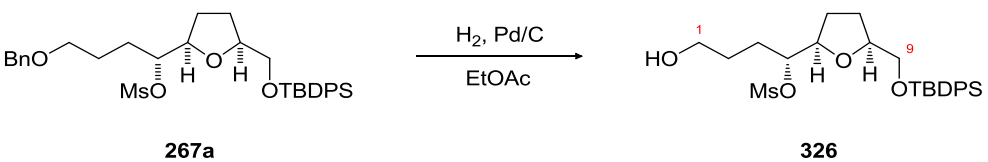
(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)butyl methanesulfonate (267a)



290 **267a**

To a stirred solution of tetrahydrofuran **290** (500 mg, 0.963 mmol) in dichloromethane (10 mL) at 0 °C was added 4-(dimethylamino)pyridine (706 mg, 5.78 mmol) followed by methanesulfonic anhydride (503 mg, 2.89 mmol). The reaction mixture was warmed to room temperature and stirred for 5 hours before an aqueous solution of HCl (1 M, 10 mL) was added. The layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield mesylate **267a** (569 mg, 0.953 mmol, 99%) as a colourless oil which was used without further purification. $R_f = 0.65$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ +5.2 (*c* 0.95, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.67 (4 H, m, Ph*H* × 4), 7.52–7.39 (6 H, m, Ph*H* × 6), 7.39–7.24 (5 H, m, Ph*H* × 5), 4.64–4.60 (1 H, m, C(4)H), 4.52 (2 H, s, C*H*$_2$Ph), 4.17–4.08 (1 H, m, C(8)H), 4.07–3.97 (1 H, m, C(5)H), 3.71–3.63 (2 H, m, C(9)H_2), 3.60–3.47 (2 H, m, C(1)H_2), 3.10 (3 H, s, SCH_3), 2.05–1.91 (2 H, m, C(6)H_AH$_B$ and C(7)H_AH$_B$), 1.91–1.77 (4 H, m, C(2)H_2, C(3)H_AH$_B$ and C(7)H$_A$*H$_B$*,), 1.77–1.69 (1 H, m, C(3)H$_A$*H$_B$*), 1.69–1.58 (1 H, m, C(6)H$_A$*H$_B$*), 1.09 (9 H, s, SiC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.5 (PhC$_q$), 135.6 (PhC), 133.4 (PhC$_q$), 133.3 (PhC$_q$), 129.8 (PhC), 128.4 (PhC), 127.8 (PhC), 127.7 (PhC), 127.6 (PhC), 86.7 (C4), 80.9 (C5), 80.1 (C8), 72.8 (*C*H$_2$Ph), 69.5 (C1), 66.4 (C9), 38.9 (SCH_3), 28.6 (C3), 28.2 (C6), 27.6 (C7), 26.9 (SiC(*C*H$_3$)$_3$), 25.2 (C2), 19.2 (Si*C*(CH_3)$_3$). Data were consistent with those previously reported.[116]

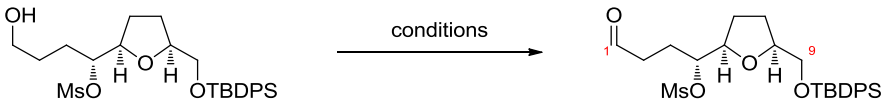
(*R*)-1-((2*R*,5*S*)-5-((*tert*-Butyldiphenylsilyloxy)methyl)tetrahydrofuran-2-yl)-4-hydroxybutyl methanesulfonate (326)



267a **326**

A solution of mesylate **267a** (575 mg, 0.963 mmol) in ethyl acetate (50 mL) was evacuated and purged with argon three times. To this solution palladium on carbon (10 wt.%, 500 mg) was added and the reaction flask was evacuated and purged with hydrogen five times. The resulting mixture was stirred vigorously under an atmosphere of hydrogen for 8 hours before being filtered through a pad of celite, eluting with ethyl acetate (50 mL). The combined organics were concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 50:50) to afford alcohol **326** (482 mg, 0.953 mmol, 99%) as a colourless oil. $R_f = 0.35$ (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ +3.4 (*c* 1.07, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3381, 2932, 2858, 1472, 1428, 1348, 1171, 1112; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.72–7.64 (4 H, m, Ph*H* × 4), 7.48–7.36 (6 H, m, Ph*H* × 6), 4.67–4.57 (1 H, m, C(4)H), 4.16–4.06 (1 H, m, C(8)H), 4.05–3.97 (1 H, m, C(5)H), 3.73–3.60 (4 H, m, $C(1)H_2$, $C(9)H_2$), 3.08 (3 H, s, SCH_3), 2.00–1.92 (3 H, m, OH, $C(6)H_AH_B$ and $C(7)H_AH_B$), 1.87–1.58 (6 H, m, $C(2)H_2$, $C(3)H_2$, $C(6)H_AH_B$ and $C(7)H_AH_B$), 1.07 (9 H, s, $SiC(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.6 (PhC), 133.3 (PhC_q), 129.8 (PhC), 127.8 (PhC), 86.7 (C4), 80.8 (C5), 80.0 (C8), 66.4 (C9), 62.1 (C1), 38.9 (SCH_3), 28.2 (C2), 28.1 (C6), 27.9 (C3), 27.6 (C7), 26.8 ($SiC(CH_3)_3$), 19.2 ($SiC(CH_3)_3$); HRMS (ESI^+, *m/z*) for $C_{26}H_{38}NaO_6SSi$ calculated 529.5051, found 529.2042.

(*R*)-1-((2*R*,5*S*)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-oxobutyl methanesulfonate (327)



326 **327**

Procedure A (Parikh–Doering):

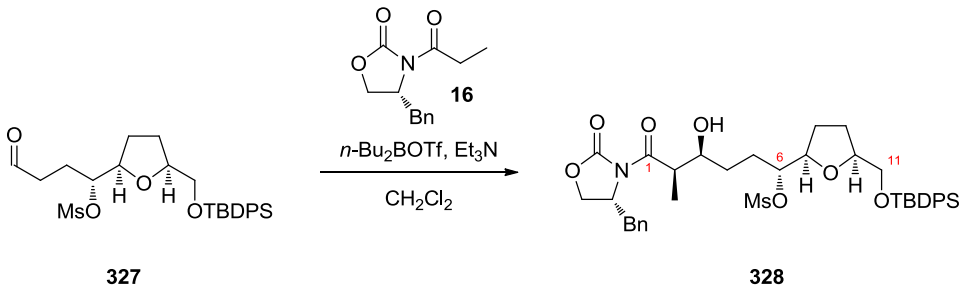
To a stirred solution of alcohol **326** (487 mg, 0.962 mmol) in dichloromethane (4.8 mL) were added dimethylsulfoxide (205 µL, 2.89 mmol) and *N*,*N*-diisopropylethylamine (205 µL, 2.89 mmol) and the resulting solution was cooled to 0 °C. Sulfur trioxide pyridine complex (460 mg, 2.89 mmol) was added in one portion and the resulting mixture was stirred at 0 °C for 1 hour before being quenched with a saturated aqueous solution of $NaHCO_3$ (5.0 mL). The layers were separated and the aqueous phase was extracted with dichloromethane

(3 × 5.0 mL). The combined organic extracts were washed with brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to afford aldehyde **327** (436 mg, 0.866 mmol, 90%) as a colourless oil.

Procedure B (Dess–Martin):

To a stirred solution of alcohol **326** (100 mg, 0.198 mmol) in dichloromethane (2.0 mL) at 0 °C was added Dess–Martin periodinane (168 mg, 0.396 mmol) in one portion. The resulting suspension was warmed to room temperature and stirred for 3 hours before a saturated aqueous solution of $NaHCO_3$ (2.0 mL) was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 2.0 mL). The combined organic extracts were washed with brine (2.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to afford aldehyde **327** (85.7 mg, 0.170 mmol, 86%) as a colourless oil. $R_f = 0.55$ (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ +6.2 (*c* 1.45, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2930, 1724, 1428, 1350, 1172, 1111, 1082; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.84–9.76 (1 H, m, C(1)H), 7.71–7.60 (4 H, m, Ph*H* × 4), 7.49–7.31 (6 H, m, Ph*H* × 6), 4.61–4.50 (1 H, m, C(4)H), 4.17–4.06 (1 H, m, C(8)H), 3.97 (1 H, q, *J* = 6.7, C(5)H), 3.70–3.58 (2 H, m, C(9)H_2), 3.07 (3 H, s, SCH_3), 2.85–2.63 (2 H, m, C(2)H_2), 2.02–1.91 (3 H, m, C(3)H_AH$_B$, C(6)H_AH$_B$ and C(7)H_AH$_B$), 1.82 (2 H, m, C(3)H$_A$$H_B$ and C(7)H$_A$$H_B$), 1.69 (1 H, m, C(6)H$_A$$H_B$), 1.05 (9 H, s, SiC($CH_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 200.9 (C1), 135.7 (PhC), 135.7 (PhC), 133.4 (PhC$_q$), 133.4 (PhC$_q$), 129.9 (PhC), 129.9 (PhC), 127.9 (PhC), 85.8 (C4), 81.0 (C5), 80.3 (C8), 66.5 (C9), 39.4 (C2), 38.9 (S*C*H$_3$), 28.3 (C6), 27.6 (C7), 26.9 (SiC(*C*H$_3$)$_3$), 24.1 (C3), 19.3 (Si*C*(CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for $C_{26}H_{36}NaO_6SSi$ calculated 527.1900, found 527.1892.

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-hydroxy-5-methyl-6-oxohexyl methanesulfonate (328)

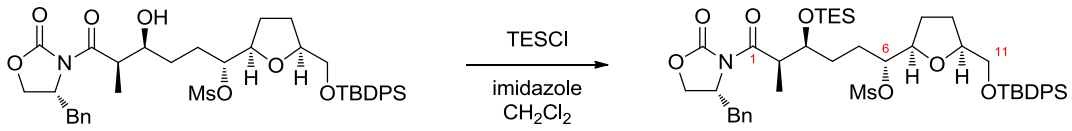


327 **328**

To a stirred solution of (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone (**16**) (195 mg, 0.836 mmol) in dichloromethane (1.5 mL) at 0 °C was added dibutylboron trifluoromethanesulfonate (1.0 M solution in CH_2Cl_2, 1.10 mL, 1.09 mmol), followed by triethylamine (205 µL, 1.46 mmol). The resulting mixture was cooled to −78 °C and stirred for 5 minutes before a solution of aldehyde **327** (484 mg, 0.961 mmol) in dichloromethane (1.0 mL) was added dropwise. The reaction mixture was stirred for 45 minutes before being warmed to 0 °C and stirred for a further 2 hours. The reaction was quenched by the addition of pH 7 phosphate buffer (2.0 mL) and methanol (2.5 mL). To the resultant slurry was added a 2:1 mixture of methanol and a 30% aqueous solution of hydrogen peroxide (2.5 mL) and the mixture was stirred vigorously for 1 hour. The reaction mixture was then extracted with ether (3 × 25 mL). The combined organic extracts were washed with water (20 mL), a saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/acetone 70:30) to afford aldol **328** (604 mg, 0.819 mmol, 98%) as a viscous colourless oil. $R_f = 0.70$ (petrol/acetone 60:40); $[\alpha]_D^{20}$ −19.3 (*c* 1.05, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2932, 1778, 1694, 1455, 1427, 1388, 1349, 1212, 1171, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.64 (4 H, m, Ph*H* × 4), 7.47–7.19 (11 H, m, Ph*H* × 11), 4.75–4.67 (1 H, m, NCH), 4.63–4.56 (1 H, m, C(6)H), 4.30–4.23 (1 H, m, OCH_AH$_B$CHN), 4.17 (1 H, dd, *J* = 9.1 and 2.5, OCH$_A$$H_B$CHN), 4.10 (1 H, quin, *J* = 5.7, C(10)H), 4.02–3.95 (1 H, m, C(7)H), 3.92 (1 H, br. s, C(3)H), 3.79 (1 H, dq, *J* = 6.9 and 3.5, C(2)H), 3.69–3.58 (2 H, m, C(11)H_2), 3.25 (1 H, dd, *J* = 13.4 and 3.0, CH_AH$_B$Ph), 3.07 (3 H, s, SCH_3), 2.88 (1 H, br. s, OH), 2.81 (1 H, dd, *J* = 13.4 and 9.3, CH$_A$$H_B$Ph), 2.00–1.89 (3 H, m, C(5)H_AH$_B$, C(8)H_AH$_B$ and C(9)H_AH$_B$), 1.85–1.76 (1 H, m, C(9)H$_A$$H_B$), 1.72–1.59 (4 H, dd, *J* = 11.0 and 6.2, C(4)H_2, C(5)H$_A$$H_B$ and C(8)H$_A$$H_B$), 1.29

(3 H, d, J = 7.1, C(2)CH_3), 1.06 (9 H, s, SiC$(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 177.1 (C1), 153.2 (OC(O)N), 135.7 (PhC), 135.6 (PhC), 135.2 (PhC_q), 133.4 (PhC_q), 133.4 (PhC_q), 129.9 (PhC), 129.8 (PhC), 129.5 (PhC), 129.0 (PhC), 127.8 (PhC), 127.5 (PhC), 87.2 (C6), 81.0 (C7), 80.2 (C10), 71.9 (C3), 66.5 (C11), 66.3 (OCH_2CHN), 55.2 (NCH), 42.6 (C2), 39.0 (SCH_3), 37.8 (CH_2Ph), 29.7 (C4), 28.7, 28.2 (C5 and C8), 27.6 (C9), 26.9 (SiC$(CH_3)_3$), 19.3 (Si$C(CH_3)_3$), 11.0 (C(2)CH_3); HRMS (ESI$^+$, *m/z*) for $C_{39}H_{51}NNaO_9SSi$ calculated 760.2946, found 760.2949.

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl methanesulfonate (329)

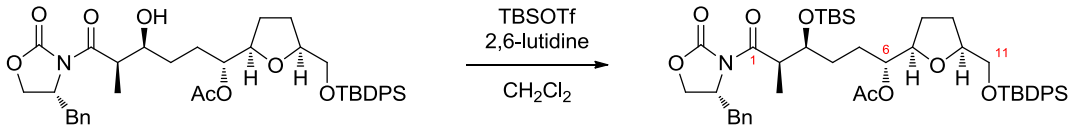


328 **329**

To a stirred solution of aldol **328** (330 mg, 0.448 mmol) in dichloromethane (3.2 mL) was added imidazole (61.0 mg, 0.896 mmol). The resultant solution was cooled to 0 °C and chlorotriethylsilane (115 µL, 0.672 mmol) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 2 hours before being quenched with methanol (2.0 mL), followed by a saturated aqueous solution of $NaHCO_3$ (5.0 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to afford mesylate **329** (358 mg, 0.421 mmol, 94%) as a viscous colourless oil. R_f = 0.62 (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ −32.6 (*c* 1.5, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2956, 2877, 1779, 1694, 1456, 1428, 1383, 1351, 1211, 1173, 1112, 1009; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.63 (4 H, m, PhH × 4), 7.47–7.19 (11 H, m, PhH × 11), 4.72–4.63 (1 H, m, NCH), 4.54–4.45 (1 H, m, C(6)H), 4.26 (1 H, t, J = 8.3, OCH_AH$_B$CHN), 4.17–4.02 (3 H, m, C(3)H, C(10)H and OCH$_A$$H_B$CHN), 4.01–3.88 (2 H, m, C(2)H and C(7)H), 3.69–3.57 (2 H, m, C(11)H_2), 3.26 (1 H, dd, J = 13.3 and 2.7, CH_AH$_B$Ph), 3.04 (3 H, s, SCH_3), 2.79 (1 H, dd, J = 13.3 and 9.5, CH$_A$$H_B$Ph), 2.02–1.88 (2 H, m, C(8)H_AH$_B$ and C(9)H_AH$_B$), 1.85–1.72 (3 H, m, C(4)H_AH$_B$, C(5)H_AH$_B$ and C(9)H$_A$$H_B$), 1.71–1.57 (3 H, m, C(4)H$_A$$H_B$, C(5)H$_A$$H_B$ and

C(8)H$_A$*H$_B$*), 1.27 (3 H, d, *J* = 6.8, C(2)CH$_3$), 1.05 (9 H, s, SiC(CH$_3$)$_3$), 0.98 (9 H, dt, *J* = 8.0 and 4.3, Si(CH$_2$C*H*$_3$)$_3$), 0.67–0.56 (6 H, m, Si(C*H*$_2$CH$_3$)$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 175.4 (C1), 153.4 (OC(O)N), 135.7 (PhC), 135.6 (PhC$_q$), 133.4 (PhC$_q$), 133.4 (PhC$_q$), 129.9 (PhC), 129.6 (PhC), 129.0 (PhC), 127.8 (PhC), 127.3 (PhC), 87.4 (C6), 80.8 (C7), 80.1 (C10), 73.2 (C3), 66.6 (C11), 66.2 (O*C*H$_2$CHN), 55.7 (NCH), 42.7 (C2), 38.8 (CH$_2$Ph), 37.8 (SCH$_3$), 30.4, 28.2, 27.7, 27.2 (C4, C5, C8 and C9), 26.9 (SiC(*C*H$_3$)$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 13.5 (C(2)*C*H$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 5.2 (Si(*C*H$_2$CH$_3$)$_3$); HRMS (ESI$^+$, *m/z*) for C$_{45}$H$_{65}$NNaO$_9$SSi$_2$ calculated 874.3811, found 874.3821.

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-4-((*tert*-butyldimethylsilyl)oxy)-1-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxohexyl acetate (330)

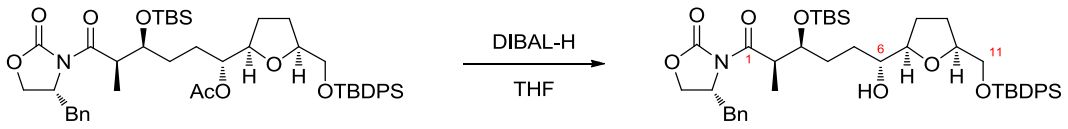


304 **330**

To a stirred solution of aldol **304** (150 mg, 0.214 mmol) in dichloromethane (1.1 mL) at 0 °C was added 2,6-lutidine (125 µL, 1.07 mmol), followed by the dropwise addition of *tert*-butyldimethylsilyl trifluromethanesulfonate (98 µL, 0.428 mmol). The resulting mixture was warmed to room temperature and stirred for 1 hour before a saturated aqueous solution of NaHCO$_3$ (1.0 mL) was added dropwise. The layers were separated and the aqueous layer was extracted with ether (3 × 2.0 mL). The combined organic extracts were washed with brine (2.0 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO$_2$, petrol/EtOAc 85:15) to afford acetate **330** (171 mg, 0.210 mmol, 98%) as a viscous colourless oil. R_f = 0.60 (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ −30.5 (*c* 1.0, CH$_2$Cl$_2$); IR ν_{max} (film)/cm^{-1} 2931, 2858, 1781, 1736, 1704, 1462, 1428, 1382, 1239, 1112; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.75–7.66 (4 H, m, Ph*H* × 4), 7.46–7.18 (11 H, m, Ph*H* × 11), 4.91–4.82 (1 H, m, C(6)H), 4.65–4.57 (1 H, m, NCH), 4.19–4.10 (2 H, m, OC*H*$_2$CHN), 4.06 (2 H, tq, *J* = 10.7 and 5.4, C(3)H and C(10)H), 3.99–3.93 (1 H, m, C(7)H), 3.93–3.85 (1 H, m, C(2)H), 3.72 (1 H, dd, *J* = 10.4 and 4.8, C(11)*H$_A$*H$_B$), 3.58 (1 H, dd, *J* = 10.2 and 6.2, C(11)H$_A$*H$_B$*), 3.27 (1 H, dd, *J* = 13.4 and 2.8, C*H$_A$*H$_B$Ph), 2.80 (1 H, dd, *J* = 13.3 and 9.5, CH$_A$*H$_B$*Ph), 1.99 (3 H, s, C(O)CH$_3$), 1.97–1.80 (3 H, m, C(8)*H$_A$*H$_B$ and

C(9)H_2), 1.76–1.52 (5 H, m, C(4)H_2, C(5)H_2 and C(8)H_AH_B), 1.24 (3 H, d, J = 6.8, C(2)CH_3), 1.08 (9 H, s, SiC(CH_3)$_3$), 0.91 (9 H, s, SiC(CH_3)$_3$), 0.06 (3 H, s, SiCH_3), 0.03 (3 H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.1 (C1), 170.7 (*C*(O)CH_3), 153.1 (OC(O)N), 135.6 (PhC), 135.4 (PhC_q), 133.7 (PhC_q), 133.7 (PhC_q), 129.6 (PhC), 129.5 (PhC), 128.9 (PhC), 127.7 (PhC), 127.3 (PhC), 80.4 (C7), 79.7 (C10), 75.6 (C6), 72.5 (C3), 66.2 (C11), 66.0 (O*C*H_2CHN), 55.7 (NCH), 42.4 (C2), 37.6 (*C*H_2Ph), 30.8 (C4), 28.1 (C9), 27.4 (C8), 26.9 (SiC(*C*H_3)$_3$), 26.2 (C5), 25.9 (SiC(*C*H_3)$_3$), 21.1 (C(O)*C*H_3), 19.3 (Si*C*(CH_3)$_3$), 18.1 (Si*C*(CH_3)$_3$), 12.1 (C(2)*C*H_3), −4.1 (SiCH_3), −4.8 (SiCH_3); HRMS (ESI$^+$, *m/z*) for $C_{46}H_{65}NNaO_8Si_2$ calculated 838.4141, found 838.4144.

(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)-6-((2*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-hydroxy-2-methylhexanoyl)oxazolidin-2-one (331)

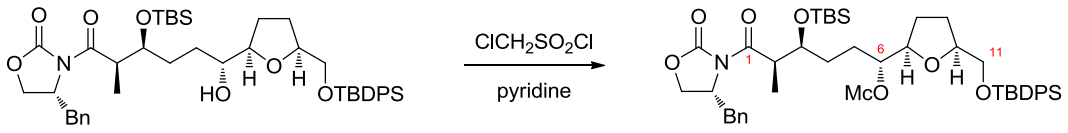


330 **331**

To a stirred solution of acetate **330** (250 mg, 0.307 mmol) in tetrahydrofuran (12 mL) at −78 °C was added diisobutylaluminium hydride (1.0 M solution in hexanes, 1.54 mL, 1.54 mmol) dropwise. The reaction mixture was stirred at −78 °C for 5 hours before being quenched by the dropwise addition of ethyl acetate (3.0 mL). The resultant mixture was stirred for 10 minutes before a saturated aqueous solution of Rochelle's salt (15 mL) was slowly added and the mixture was stirred vigorously for 1 hour while being allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 50:50) to afford alcohol **331** (185 mg, 0.239 mmol, 78%) as a viscous colourless oil. R_f = 0.46 (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −31.5 (*c* 1.0, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2931, 2857, 1781, 1704, 1462, 1428, 1383, 1210, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73–7.65 (4 H, m, Ph*H* × 4), 7.47–7.19 (11 H, m, Ph*H* × 11), 4.59 (1 H, dt, J = 6.4 and 3.4, NCH), 4.18–4.10 (2 H, m, OC*H*$_2$CHN), 4.09–4.00 (2 H, m, C(3)H and C(10)H), 3.93–3.85 (1 H, m, C(2)H), 3.81 (1 H, q, J = 6.0, C(7)H), 3.74 (1 H, dd,

J = 10.9 and 4.3, C(11)H_AH$_B$), 3.60 (1 H, dd, J = 10.6 and 4.0, C(11)H$_A$$H_B$), 3.37 (1 H, dd, J = 8.3 and 3.3, C(6)H), 3.30 (1 H, dd, J = 13.3 and 2.7, CH_AH$_B$Ph), 2.78 (1 H, dd, J = 13.3 and 9.7, CH$_A$$H_B$Ph), 2.58 (1 H, d, J = 5.3, OH), 2.01–1.87 (3 H, m, C(8)H_AH$_B$ and C(9)H$_2$), 1.87–1.71 (2 H, m, C(4)H_AH$_B$ and C(8)H$_A$$H_B$), 1.69–1.51 (2 H, m, C(4)H$_A$$H_B$ and C(5)H_AH$_B$), 1.50–1.39 (1 H, m, C(5)H$_A$$H_B$), 1.22 (3 H, d, J = 6.8, C(2)CH$_3$), 1.07 (9 H, s, SiC(CH$_3$)$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.06 (3 H, s, SiCH$_3$), 0.01 (3 H, s, SiCH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 175.4 (C1), 153.2 (OC(O)O), 135.8 (PhC), 135.7 (PhC), 135.6 (PhC$_q$), 133.5 (PhC$_q$), 133.5 (PhC$_q$), 129.8 (PhC), 129.6 (PhC), 129.1 (PhC), 127.9 (PhC), 127.8 (PhC), 127.4 (PhC), 82.8 (C7), 80.0 (C10), 74.8 (C6), 73.0 (C3), 66.1 (O*C*H$_2$CHN), 66.0 (C11), 56.0 (NCH), 42.8 (C2), 37.8 (*C*H$_2$Ph), 31.5 (C4), 29.6 (C5), 28.3 (C8), 27.6 (C9), 27.0 (SiC(*C*H$_3$)$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 11.6 (C(2)*C*H$_3$), −3.9 (SiCH$_3$), −4.7 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for C$_{44}$H$_{63}$NNaO$_7$Si$_2$ calculated 796.4035, found 796.4057.

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-4-((tert-butyldimethylsilyl)oxy)-1-((2*R*,5*S*)-5-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxohexyl chloromethanesulfonate (332)

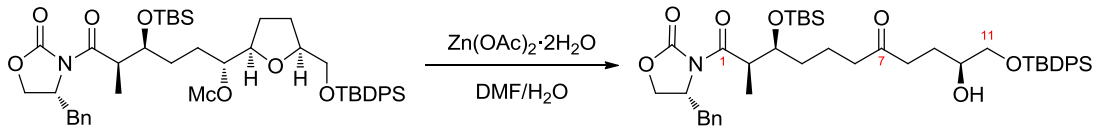


331 **332**

To a stirred solution of alcohol **331** (269 mg, 0.348 mmol) in pyridine (2.8 mL) was added chloromethanesulfonyl chloride (90% purity, 70.3 µL, 0.696 mmol) at 0 °C. The resulting mixture was stirred for 30 minutes at 0 °C, before being warmed to room temperature and stirred for a further 4 hours. The reaction mixture was quenched with water (5.0 mL) and diluted with ethyl acetate (25 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The combined organic extracted were washed with water (10 mL), brine (10 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO$_2$, petrol/EtOAc 80:20) to give chloromesylate **332** (302 mg, 0.341 mmol, 98%) as a viscous oil. R_f = 0.70 (petrol/EtOAc 80:20), $[\alpha]_D^{20}$ −42.2 (*c* 0.45, CH$_2$Cl$_2$); IR ν_{max} (film)/cm^{-1} 2931, 2858, 1779, 1699, 1473, 1374, 1180, 1112; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.69 (4 H, t, J = 5.9, Ph*H* × 4), 7.50–7.15 (11 H, m, Ph*H* × 11), 5.04 (1 H, d, J = 12.1, SCH_AH$_B$Cl), 4.72–4.65 (1 H, m,

NCH), 4.65–4.57 (2 H, m, C(6)H and SCH_AH_BCl), 4.27 (1 H, t, $J = 8.2$, OCH_AH_BCHN), 4.19–4.10 (2 H, m, C(10)H and OCH_AH_BCHN), 4.04 (2 H, m, C(3)H and C(7)H), 3.95 (1 H, t, $J = 6.8$, C(2)H), 3.66 (2 H, d, $J = 4.8$, $C(11)H_2$), 3.28 (1 H, dd, $J = 13.4$ and 2.8, CH_AH_BPh), 2.81 (1 H, dd, $J = 13.3$ and 9.5, CH_AH_BPh), 2.02–1.90 (2 H, m, $C(8)H_AH_B$ and $C(9)H_AH_B$), 1.86–1.75 (3 H, m, $C(4)H_AH_B$, $C(5)H_AH_B$ and $C(9)H_AH_B$), 1.74–1.57 (3 H, m, $C(4)H_AH_B$, $C(5)H_AH_B$ and $C(8)H_AH_B$), 1.28 (3 H, d, $J = 6.8$, $C(2)CH_3$), 1.09 (9 H, s, $SiC(CH_3)_3$), 0.93 (9 H, s, $SiC(CH_3)_3$), 0.10 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.3 (C1), 153.4 (OC(O)N), 135.7 (PhC), 135.7 (PhC), 135.5 (PhC_q), 133.4 (PhC_q), 133.3 (PhC_q), 129.9 (PhC), 129.9 (PhC), 129.6 (PhC), 129.0 (PhC), 127.9 (PhC), 127.9 (PhC), 127.4 (PhC), 90.0 (C6), 80.9 (C8), 80.4 (C10), 72.6 (C3), 66.6 (C11), 66.3 (OCH_2CHN), 55.7 (NCH), 54.6 (SCH_2Cl), 42.6 (C2), 37.8 (CH_2Ph), 30.2 (C4), 28.2 (C8), 27.5 (C9), 27.0 (C5), 27.0 ($SiC(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 19.3 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 13.3 ($C(2)CH_3$), −3.9 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{45}H_{64}ClNNaO_9Si_2$ calculated 908.3427, found 796.3396.

(2*R*,3*S*,10*S*)-1-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-11-((*tert*-butyldiphenylsilyl)oxy)-10-hydroxy-2-methylundecane-1,7-dione (333)

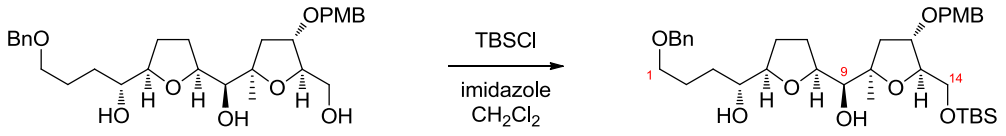


332 **333**

To a stirred solution of chloromesylate **332** (125 mg, 0.141 mmol) in *N*,*N*-dimethylformamide (2.1 mL) was added water (1.6 mL), followed by zinc trifluoromethanesulfonate dihydrate (186 mg, 0.846 mmol). The resulting mixture was heated to 75 °C and stirred for 6 hours, before it was cooled to room temperature and diluted with brine (10 mL). The resultant mixture was extracted with ether (4 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to afford ketone **333** (92.8 mg, 0.120 mmol, 85%) as a viscous colourless oil. $R_f = 0.35$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −36.4 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2950, 1760, 1701, 1383, 1211, 1115; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65 (4 H, d, $J = 7.1$, Ph*H* × 4), 7.48–7.18 (11 H, m, Ph*H* × 11), 4.69–4.61 (1 H, m, NCH), 4.28 (1 H, t, $J = 8.2$, OCH_AH_BCHN), 4.16 (1 H, dd, $J = 9.1$ and 1.8,

OCH$_A$*H$_B$*CHN), 4.01 (1 H, q, *J* = 5.6, C(3)H), 3.94 (1 H, quin, *J* = 6.6, C(2)H), 3.71–3.60 (2 H, m, C(10)H and C(11)*H$_A$*H$_B$), 3.52–3.45 (1 H, m, C(11)H$_A$*H$_B$*), 3.27 (1 H, dd, *J* = 13.3 and 2.9, C*H$_A$*H$_B$*Ph), 2.79 (1 H, dd, *J* = 13.4 and 9.6, CH$_A$*H$_B$*Ph), 2.60–2.56 (1 H, m, OH), 2.55–2.48 (2 H, m, C(8)H$_2$), 2.44–2.37 (2 H, m, C(6)H$_2$), 1.73–1.55 (4 H, m, C(5)H$_2$ and C(9)H$_2$), 1.54–1.45 (2 H, m, C(4)H$_2$), 1.24 (3 H, d, *J* = 6.8, C(2)CH$_3$), 1.06 (9 H, m, SiC(CH$_3$)$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.05 (3 H, s, SiCH$_3$), 0.02 (3 H, s, SiCH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ_C 210.8 (C7), 175.6 (C1), 153.4 (OC(O)N), 135.6 (PhC), 135.6 (PhC$_q$), 133.2 (PhC$_q$), 130.0 (PhC), 129.6 (PhC), 129.0 (PhC), 127.9 (PhC), 127.4 (PhC), 72.9 (C3), 71.4 (C10), 68.0 (C11), 66.3 (O*C*H$_2$CHN), 55.9 (NCH), 42.5 (C2), 42.5 (C6), 38.9 (C8), 37.8 (*C*H$_2$Ph), 34.8 (C4), 27.0 (SiC(*C*H$_3$)$_3$), 26.7 (C9), 26.0 (SiC(*C*H$_3$)$_3$), 19.4 (Si*C*(CH$_3$)$_3$), 18.6 (C5), 18.2 (Si*C*(CH$_3$)$_3$), 12.8 (C(2)*C*H$_3$), −4.0 (SiCH$_3$), −4.7 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for C$_{44}$H$_{63}$NNaO$_7$Si$_2$ calculated 796.4041, found 796.4021.

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)(hydroxy)methyl)tetrahydrofuran-2-yl)butan-1-ol (220)

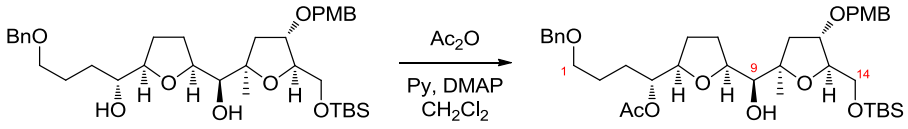


216 **220**

To a stirred solution of triol **216** (1.11 g, 2.09 mmol) in dichloromethane (21 mL) at 0 °C was added imidazole (355 mg, 5.22 mmol), followed by *tert*-butyldimethylsilyl chloride (330 mg, 2.19 mmol). The reaction mixture was warmed to room temperature and stirred for 12 hours before being quenched with an aqueous saturated solution of NH$_4$Cl (15 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO$_2$, petrol/EtOAc 50:50) to give diol **220** (1.32 g, 2.05 mmol, 94%) as a viscous oil. R$_f$ = 0.50 (petrol/EtOAc 50:50); $[\alpha]_D^{20}$ +14.0 (*c* 1.30, CH$_2$Cl$_2$); IR ν_{max} (film)/cm^{-1} 3500–3300, 2931, 1614, 1514, 1457, 1249, 1099; ^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.34 (4 H, d, *J* = 4.3, Ph*H* × 4), 7.28–7.22 (3 H, m, Ar*H* × 2 and Ph*H*), 6.88 (2 H, d, *J* = 8.3, Ar*H* × 2), 4.50 (2 H, s, C*H$_2$*Ph), 4.47 (1 H, d, *J* = 11.4, C*H$_A$*H$_B$C$_6$H$_4$OCH$_3$), 4.41 (1 H, d, *J* = 11.1,

$CH_AH_BC_6H_4OCH_3$), 4.19-4.14 (1 H, m, C(12)H), 4.10-4.04 (1 H, m, C(13)H), 4.03–3.96 (1 H, m, C(8)H), 3.90–3.86 (1 H, m, C(5)H), 3.84 (1 H, d, J = 3.8, C(9)H), 3.82–3.75 (4 H, m, C(14)H_AH_B and $C_6H_4OCH_3$), 3.66 (1 H, dd, J = 10.9 and 1.5, C(14)H_AH_B), 3.55–3.47 (2 H, m, C(1)H_2), 3.37 (1 H, quin, J = 4.0, C(4)H), 2.34 (1 H, dd, J = 13.0 and 7.2, C(11)H_AH_B), 2.20–2.09 (1 H, m, C(7)H_AH_B), 2.03–1.89 (2 H, m, C(6)H_2), 1.89–1.79 (1 H, m, C(2)H_AH_B), 1.79–1.69 (2 H, m, C(2)H_AH_B and C(7)H_AH_B), 1.67 (1 H, dd, J = 13.1 and 3.0, C(11)H_AH_B), 1.63-1.51 (2 H, m, C(3)H_2), 1.37 (3 H, s, C(10)CH_3), 0.90 (9 H, s, $SiC(CH_3)_3$), 0.06 (6 H, s, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.3 (ArC_q), 138.7 (PhC_q), 130.2 (ArC_q), 129.3 (ArC), 128.4 (PhC), 127.7 (PhC), 127.5 (PhC), 113.9 (ArC), 86.2 (C10), 83.3 (C13), 81.6 (C5), 81.0 (C12), 79.8 (C8), 78.2 (C9), 74.6 (C4), 72.9 (CH_2Ph), 71.3 ($CH_2C_6H_4OCH_3$), 70.5 (C1), 63.5 (C14), 55.3 ($CH_2C_6H_4OCH_3$), 37.4 (C11), 31.3 (C3), 29.2 (C6), 26.3 (C2), 25.9 ($SiC(CH_3)_3$), 25.9 (C7), 25.0 (C(10)CH_3), 18.4 ($SiC(CH_3)_3$), −5.5 ($SiCH_3$), −5.6 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{36}H_{56}NaO_8Si$ calculated 667.3642, found 667.3637.

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)(hydroxy)methyl)tetrahydrofuran-2-yl)butyl acetate (336)

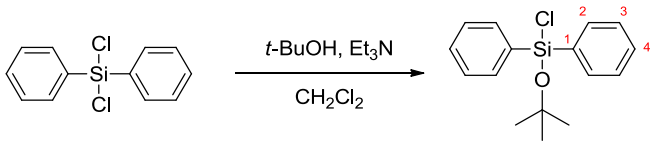


220 **336**

To a stirred solution of bis-THF **220** (770 mg, 1.20 mmol) in dichloromethane (72 mL) were added pyridine (968 µL, 12.0 mmol) and 4-(dimethylamino)pyridine (14.7 mg, 0.120 mmol). The resulting solution was cooled to 0 °C and acetic anhydride (170 µL, 1.80 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours before being quenched with an aqueous, saturated solution of $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 75:25) to give acetate **336** (658 mg, 0.96 mmol, 80%) as a colourless oil. R_f = 0.67 (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ +18.9 (*c* 1.20, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3500, 2930, 2857, 1737, 1613, 1514, 1456, 1369, 1247, 1099; ^{1}H NMR (500 MHz

,$CDCl_3$) δ_H 7.42–7.36 (4 H, m, Ph*H* × 4), 7.35–7.28 (3 H, m, Ar*H* × 2 and Ph*H* × 1), 6.93 (2 H, d, *J* = 8.5, Ar*H* × 2), 4.97–4.90 (1 H, m, C(4)H), 4.57–4.50 (3 H, m, $CH_AH_BC_6H_4OCH_3$ and CH_2Ph), 4.47 (1 H, d, *J* = 11.3, $CH_AH_BC_6H_4OCH_3$), 4.19 (1 H, td, *J* = 7.3 and 3.7, C(12)H), 4.11 (1 H, d, *J* = 3.5, C(13)H), 3.98 (1 H, q, *J* = 5.9, C(5)H), 3.91 (1 H, q, *J* = 6.4, C(8)H), 3.85 (3 H, s, $C_6H_4OCH_3$), 3.76 (1 H, dd, *J* = 10.7 and 4.1, $C(14)H_AH_B$), 3.72 (1 H, dd, *J* = 10.7 and 2.5, $C(14)H_AH_B$), 3.57 (1 H, d, *J* = 6.0, C(9)H), 3.52 (2 H, t, *J* = 5.5, $C(1)H_2$), 2.41 (1 H, dd, *J* = 13.1 and 7.4, $C(11)H_AH_B$), 2.11 (3 H, s, $C(O)CH_3$), 2.06–1.92 (3 H, m, $C(6)H_AH_B$ and $C(7)H_2$), 1.82 (1 H, dd, *J* = 12.9 and 3.5, $C(11)H_AH_B$), 1.77–1.66 (5 H, m, $C(2)H_2$, $C(3)H_2$ and $C(6)H_AH_B$), 1.45 (3 H, s, $C(10)CH_3$), 0.94 (9 H, s, $Si(CH_3)_3$), 0.11 (6 H, s, $Si(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 171.2 ($C(O)CH_3$), 159.3 (ArC_q), 138.5 (PhC_q), 130.5 (ArC_q), 129.3 (ArC), 128.4 (PhC), 127.7 (PhC), 127.6 (PhC), 113.9 (ArC), 86.1 (C10), 83.4 (C13), 80.5 (C12), 80.2 (C8), 80.0 (C5), 77.8 (C9), 75.5 (C4), 73.0 (CH_2Ph), 71.3 ($CH_2C_6H_4OCH_3$), 69.9 (C1), 63.4 (C14), 55.3 ($C_6H_4OCH_3$), 38.1 (C11), 28.0, 27.8, 27.8 (C3, C6 and C7), 26.0 ($SiC(CH_3)_3$), 25.7 (C2), 24.8 ($C(10)CH_3$), 21.3 ($C(O)CH_3$), 18.4 ($SiC(CH_3)_3$), −5.4 ($SiCH_3$), −5.5 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{38}H_{58}NaO_9Si$ calculated 709.3748, found 709.3730.

tert-Butoxychlorodiphenylsilane (338)

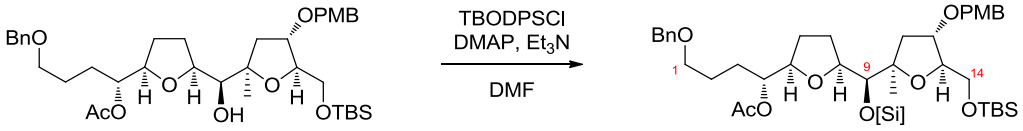


337 **338**

To a stirred solution of dichlorodiphenylsilane (**337**) (3.00 mL, 14.6 mmol) and triethylamine (2.25 mL, 16.1 mmol) in dichloromethane (22 mL) at 0 °C was added *tert*-butanol (1.40 mL, 14.6 mmol) dropwise. The resulting mixture was warmed to room temperature and stirred for 6 hours and then heated to 40 °C and stirred for a further 36 hours. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The resultant oil was dissolved in a 1:1 mixture of hexane and ether (36 mL) and the resulting suspension was filtered and concentrated *in vacuo* to furnish *tert*-butoxychlorodiphenylsilane (**338**) as a pale yellow oil which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (4 H, d, *J* = 7.1, C(2)H × 4), 7.51–7.39 (6 H, m, C(3) ×4 and C(4) × 2), 1.42 (9 H, s,

$C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.0 (C1 × 2), 134.4 (C2 × 4), 130.7 (C4 × 2), 128.0 (C3 × 4), 76.5 ($C(CH_3)_3$), 31.8 ($C(CH_3)_3$).

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butoxydiphenylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butyl acetate (335)

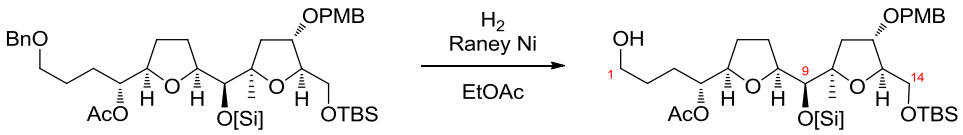


336 [Si] = Si(O*t*-Bu)Ph_2 **335**

To a stirred solution of bis-THF **336** (315 mg, 0.459 mmol) in *N*,*N*-dimethylformamide (4.6 mL) were added triethylamine (960 µL, 6.89 mmol) and 4-(dimethylamino)pyridine (112 mg, 0.918 mmol). The resulting solution was cooled to 0 °C and *tert*-butoxy(chloro)diphenylsilane (**338**) (1.01 mL, 3.72 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 14 hours before being quenched with an aqueous, saturated solution of $NaHCO_3$ (5.0 mL). The mixture was diluted with water (10 mL), the aqueous layer was separated and extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 85:15) to give acetate **336** (350 mg, 0.372 mmol, 81%) as a colourless oil. $R_f = 0.72$ (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −6.8 (*c* 0.75, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2930, 2857, 1737, 1613, 1514, 1430, 1246, 1196, 1115, 1050; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.83 (2 H, d, *J* = 6.6, Ph*H* × 2), 7.72 (2 H, d, *J* = 6.6, Ph*H* × 2), 7.48–7.33 (11 H, m, Ph*H* × 11), 7.29 (2 H, d, *J* = 8.5, C(18)H × 2), 6.94 (2 H, d, *J* = 8.2, C(19)H × 2), 4.92–4.85 (1 H, m, C(4)H), 4.55 (2 H, s, CH_2Ph), 4.43 (2 H, s, C$H_2C_6H_4OCH_3$), 4.19 (1 H, t, *J* = 8.0, C(8)H), 4.09–4.04 (1 H, m, C(13)H), 3.93–3.89 (2 H, m, C(9)H and C(12)H), 3.87 (3 H, s, C(21)H_3), 3.75–3.68 (1 H, m, C(5)H), 3.55 (1 H, dd, *J* = 10.6 and 4.3, C(14)H_AH_B), 3.49 (2 H, t, *J* = 5.0, C(1)H_2), 3.33 (1 H, dd, *J* = 10.4 and 6.3, C(14)H_AH_B), 2.35–2.27 (2 H, m, C(7)H_AH_B and C(11)H_AH_B), 1.90 (1 H, d, *J* = 3.8, C(7)H_AH_B), 1.88–1.85 (2 H, m, C(6)H_AH_B and C(11)H_AH_B), 1.84 (3 H, s, C(O)CH_3), 1.70–1.63 (4 H, m, C(2)H_2 and C(3)H_2), 1.52–1.46 (1 H, m, C(6)H_AH_B), 1.42 (3 H, s, C(10)CH_3), 1.32 (9 H, s, SiOC$(CH_3)_3$), 0.91 (9 H, s, SiC$(CH_3)_3$), 0.05 (3 H, s, SiCH_3), 0.03 (3 H, s, SiCH_3); ^{13}C NMR (100 MHz,

$CDCl_3$) δ_C 170.7 (*C*(O)CH_3), 159.2 (ArC_q), 138.6 (PhC_q), 136.2 (PhC_q), 136.1 (PhC), 135.4 (PhC), 134.1 (PhC_q), 130.7 (ArC_q), 129.9 (PhC), 129.7 (ArC), 129.1 (PhC), 128.4 (PhC), 127.9 (PhC), 127.6 (PhC), 127.5 (PhC), 127.5 (PhC), 113.8 (ArC), 84.6 (C10), 84.3 (C13), 80.3 (C12), 79.7 (C8), 79.6 (C9), 78.8 (C5), 74.5 (C4), 73.9 (SiO*C*$(CH_3)_3$), 73.0, 71.0, 70.1 (C1), 63.7 (C14), 55.3 ($C_6H_4OCH_3$), 42.9 (C11), 32.1 (SiOC(*C*$H_3)_3$), 28.1 (C2), 27.9 (C6), 26.0 (SiC(*C*$H_3)_3$), 25.6 (C3), 25.4 (C7), 22.4 (C(10)*C*H_3), 20.8 (C(O)*C*H_3), 18.4 (Si*C*$(CH_3)_3$), −5.3 ($SiCH_3$), −5.4 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{54}H_{76}NaO_{10}Si_2$ calculated 963.4869, found 963.4863.

(*R*)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-Butoxydiphenylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-4-hydroxybutyl acetate (339)

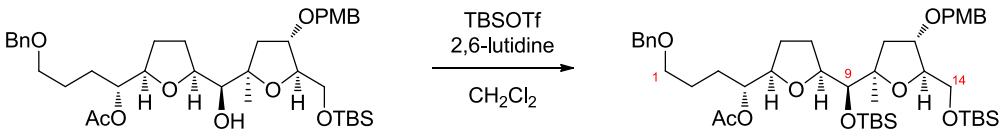


335 [Si] = Si(O*t*-Bu)Ph_2 **339**

Raney nickel (2800, slurry in H_2O, 3.0 mL) was washed sequentially with water (2 × 2.0 mL) and ethanol (3 × 2.0 mL). A solution of benzyl ether **335** (135 mg, 0.143 mmol) in ethanol (7.0 mL) was added and the reaction flask was evacuated and purged with hydrogen five times. The resulting mixture was stirred vigorously for 12 hours under an atmosphere of hydrogen (balloon pressure). The reaction mixture was carefully filtered through a plug celite, eluting with a 1:1 mixture of ethanol and ethyl acetate (3 × 5.0 mL) and the combined organics were concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 50:50) to give alcohol **339** (57.1 mg, 0.0672 mmol, 47%) as a colourless oil. R_f = 0.35 (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ −14.0 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3464, 3017, 2971, 2574, 1740, 1538, 1437, 1422, 1371, 1228, 1216, 1092; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (2 H, d, *J* = 6.6, Ph*H* × 2), 7.64 (2 H, d, *J* = 6.6, Ph*H* × 2), 7.42–7.30 (6 H, m, Ph*H* × 6), 7.22 (2 H, d, *J* = 8.6, Ar*H* × 2), 6.87 (2 H, d, *J* = 8.6, Ar*H* × 2), 4.84–4.76 (1 H, m, C(4)H), 4.35 (2 H, s, $CH_2C_6H_4OCH_3$), 4.15–4.08 (1 H, m, C(8)H), 4.02–3.96 (1 H, m, C(13)H), 3.88–3.77 (5 H, m, C(9)H, C(12)H and $C_6H_4OCH_3$), 3.70–3.62 (1 H, m, C(5)H), 3.57 (2 H, t, *J* = 5.8, C(1)H_2), 3.48 (1 H, dd, *J* = 10.5 and 4.4, C(14)H_AH_B), 3.24 (1 H, dd, *J* = 10.5 and 6.4, C(14)H_AH_B), 2.22 (2 H, dd, *J* = 13.6 and 6.8,

C(7)H_AH_B and C(11)H_AH_B), 1.86–1.75 (6 H, m, C(3)H_AH_B, C(7)H_AH_B, C(11)H_AH_B and C(O)CH_3), 1.63–1.47 (4 H, m, C(2)H_2, C(3)H_AH_B and C(6)H_AH_B), 1.46–1.38 (1 H, m, C(6)H_AH_B), 1.35 (3 H, s, C(10)CH_3), 1.24 (9 H, s, SiOC$(CH_3)_3$), 0.83 (9 H, s, SiC$(CH_3)_3$), −0.03 (3 H, s, SiCH_3), −0.05 (3 H, s, SiCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.9 (*C*(O)CH_3), 159.2 (ArC_q), 136.3 (PhC_q), 136.1 (PhC), 135.4 (PhC), 134.1 (PhC_q), 130.7 (ArC_q), 130.0 (PhC), 129.8 (PhC), 129.2 (ArC), 127.6 (PhC), 127.5 (PhC), 113.9 (ArC), 84.7 (C10), 84.3 (C13), 80.4 (C12), 79.9 (C8), 79.7 (C9), 78.8 (C5), 74.6 (C4), 73.9 (SiO*C*$(CH_3)_3$), 71.0 (*C*$H_2C_6H_4OCH_3$), 63.7 (C14), 62.6 (C1), 55.4 ($C_6H_4OCH_3$), 42.9 (C11), 32.1 (SiOC(*C*$H_3)_3$), 28.4 (C2), 27.8 (C6), 27.6 (C3), 26.1 (SiC(*C*$H_3)_3$), 25.5 (C7), 22.4 (C(10)*C*H_3), 20.9 (C(O)*C*H_3), 18.4 (Si*C*$(CH_3)_3$), −5.3 (SiCH_3), −5.3 (SiCH_3); HRMS (ESI$^+$, *m/z*) for $C_{47}H_{70}NaO_{10}Si_2$ calculated 873.4405, found 873.4374.

(*R*)-4-(Benzyloxy)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(4-methoxyphenoxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)butyl acetate (341)

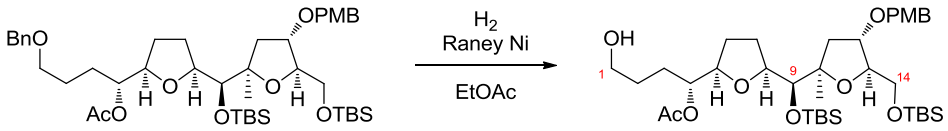


336 **341**

To a stirred solution of bis-THF **336** (550 mg, 0.802 mmol) in dichloromethane (8.0 mL) was added 2,6-lutidine (933 µL, 8.02 mmol) and the resulting solution was cooled to −78 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (940 µL, 4.01 mmol) was added dropwise, the reaction mixture was allowed to warm to room temperature and stirred for 12 hours before an saturated aqueous solution of $NaHCO_3$ (15 mL) was added. The layers were separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 75:25) to give acetate **341** (622 mg, 0.778 mmol, 97%) as a colourless oil. R_f = 0.70 (petrol/Et_2O 80:20); $[\alpha]_D^{20}$ +4.8 (*c* 0.80, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2929, 2856, 1738, 1613, 1514, 1463, 1369, 1247, 1100, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.31 (4 H, m, Ph*H* × 4), 7.31–7.23 (3 H, m, Ar*H* × 2 and Ph*H*), 6.88 (2 H, d, *J* = 8.6, Ar*H* × 2), 5.04–4.96 (1 H, m, C(4)H), 4.50 (2 H, s, C*H*$_2$Ph), 4.48 (1 H, d, *J* = 11.4, C*H*$_A$H$_B$C$_6$H$_4$OCH$_3$), 4.40 (1 H, d, *J* = 11.4,

$CH_AH_BC_6H_4OCH_3$), 4.09 (1 H, quin, $J = 3.0$, C(13)H), 4.06–4.01 (1 H, m, C(12)H), 3.97 (1 H, t, $J = 8.0$, C(8)H), 3.81 (4 H, s, C(9)H and $C_6H_4OCH_3$), 3.70–3.61 (2 H, m, C(5)H and $C(14)H_AH_B$), 3.52–3.44 (3 H, m, $C(1)H_2$ and $C(14)H_AH_B$), 2.11–2.04 (4 H, m, $C(11)H_AH_B$ and $C(O)CH_3$), 1.99–1.89 (1 H, m, $C(7)H_AH_B$), 1.88–1.78 (2 H, m, $C(6)H_AH_B$ and $C(11)H_AH_B$), 1.74–1.61 (5 H, m, $C(2)H_2$, $C(3)H_2$ and $C(7)H_AH_B$), 1.48–1.37 (1 H, m, $C(6)H_AH_B$), 1.25 (3 H, s, $C(10)CH_3$), 0.90 (9 H, s, $SiC(CH_3)_3$), 0.89 (9 H, s, $SiC(CH_3)_3$), 0.09 (3 H, s, $SiCH_3$), 0.06 (6 H, s, 2 × $SiCH_3$), 0.04 (3 H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 170.7 ($C(O)CH_3$), 159.2 (ArC_q), 138.6 (PhC_q), 130.7 (ArC_q), 129.2 (ArC), 128.5 (PhC), 127.8 (PhC), 127.7 (PhC), 113.9 (ArC), 85.1, (C10), 84.6 (C13), 81.3 (C12), 80.0 (C8), 78.9 (C5), 78.1 (C9), 74.7 (C4), 73.1 (CH_2Ph), 71.2 ($CH_2C_6H_4OCH_3$), 70.1 (C1), 64.2 (C14), 55.4 ($C_6H_4OCH_3$), 42.6 (C11), 28.4 (C3), 28.2 (C6), 26.3 ($SiC(CH_3)_3$), 26.1 ($SiC(CH_3)_3$), 25.4 (C2), 24.0 (C7), 22.1 ($C(10)CH_3$), 21.3 ($C(O)CH_3$), 18.5 ($SiC(CH_3)_3$), 18.4 ($SiC(CH_3)_3$), −3.2 ($SiCH_3$), −4.6 ($SiCH_3$), −5.2 ($SiCH_3$), −5.3 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{44}H_{72}NaO_9Si_2$ calculated 823.4607, found 823.4600.

(*R*)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-Butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-4-hydroxybutyl acetate (342)



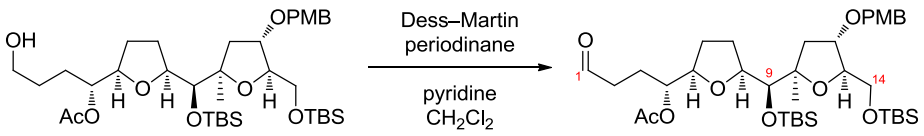
341 **342**

Raney nickel (2800, slurry in H_2O, 10 mL) was washed sequentially with water (2 × 10 mL), ethanol (3 × 10 mL) and ethyl acetate (2 × 10 mL). A solution of benzyl ether **341** (770 mg, 0.963 mmol) in ethyl acetate (19 mL) was added and the reaction flask was evacuated and purged with hydrogen five times. The resulting mixture was warmed to 30 °C and stirred vigorously for 8 hours under an atmosphere of hydrogen (balloon pressure). The reaction mixture was carefully filtered through a plug celite, eluting with a 1:1 mixture of ethanol and ethyl acetate (3 × 20 mL) and the combined organics were concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 55:45) to give alcohol **342** (574 mg, 0.809 mmol, 84%) as a colourless oil. $R_f = 0.35$ (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ −17.4 (*c* 0.80, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3250–2900, 2575, 1736, 1541, 1411, 1361,

1221; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.24 (2 H, d, J = 8.5, Ar*H* × 2), 6.86 (2 H, d, J = 8.5, Ar*H* × 2), 5.01–4.96 (1 H, m, C(4)H), 4.46 (1 H, d, J = 11.3, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.38 (1 H, d, J = 11.7, CH$_A$$H_BC_6H_4OCH_3$), 4.10–4.05 (1 H, m, C(13)H), 4.02 (1 H, td, J = 6.9 and 2.8, C(12)H), 3.97 (1 H, t, J = 8.0, C(8)H), 3.79 (4 H, s, C(9)H and C$_6$H$_4$OCH_3), 3.68–3.61 (4 H, m, C(1)H$_2$, C(5)H and C(14)H_AH$_B$), 3.48 (1 H, dd, J = 10.4 and 6.3, C(14)H$_A$$H_B$), 2.09–2.03 (4 H, m, C(11)H_AH$_B$ and C(O)CH$_3$), 1.98–1.89 (1 H, m, C(7)H_AH$_B$), 1.87–1.78 (2 H, m, C(6)H_AH$_B$ and C(11)H$_A$$H_B$), 1.77–1.64 (3 H, m, C(3)H$_2$ and C(7)H$_A$$H_B$), 1.63–1.56 (2 H, m, C(2)H$_2$), 1.49–1.39 (1 H, m, C(6)H$_A$$H_B$), 1.24 (3 H, s, C(10)CH$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.88 (9 H, s, SiC(CH$_3$)$_3$), 0.08 (3 H, s, SiCH$_3$), 0.05 (6 H, s, 2 × SiCH$_3$), 0.03 (3 H, s, SiCH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 170.9 (*C*(O)CH$_3$), 159.2 (ArC$_q$), 130.7 (ArC$_q$), 129.2 (ArC), 113.9 (ArC), 85.1 (C10), 84.6 (C13), 81.2 (C12), 80.0 (C8), 78.8 (C5), 78.1 (C9), 74.7 (C4), 71.2 (*C*H$_2$C$_6$H$_4$OCH$_3$), 64.1 (C14), 62.7 (C1), 55.4 (C$_6$H$_4$O*C*H$_3$), 42.6 (C11), 28.3, 28.1, 28.1 (C2, C3 and C6), 26.3 (SiC(*C*H$_3$)$_3$), 26.1 (SiC(*C*H$_3$)$_3$), 24.0 (C7), 22.1 (C(10)*C*H$_3$), 21.3 (C(O)*C*H$_3$), 18.5 (Si*C*(CH$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), −3.2 (SiCH$_3$), −4.6 (SiCH$_3$), −5.2 (SiCH$_3$), −5.3 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for $C_{37}H_{66}NaO_9Si_2$ calculated 733.4138, found 733.4138.

(*R*)-1-((2*R*,5*S*)-5-((*S*)-((2*R*,4*S*,5*R*)-5-(2-(*tert*-Butyldimethylsilyl)ethyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-oxobutyl acetate (343)

Procedure A:

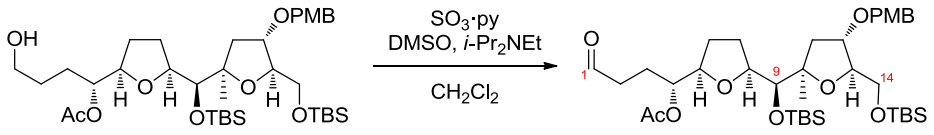


342 **343**

To a stirred solution of alcohol **342** (255 mg, 0.359 mmol) in dichloromethane (3.6 mL) at 0 °C was added pyridine (0.4 mL), followed by Dess–Martin periodinane (458 mg, 1.08 mmol). The resulting mixture was warmed to room temperature and stirred for 3 hours before being quenched with a saturated aqueous solution of $NaHCO_3$ (2.0 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (2.0 mL). The mixture was stirred for 10 minutes, then the layers were separated and the aqueous layer was extracted with ether (3 × 5.0 mL). The combined organic phases were washed with brine (5.0 mL), then dried over Na_2SO_4, filtered and

concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to give aldehyde **343** (232 mg, 0.327 mmol, 91%) as a colourless oil.

Procedure B:

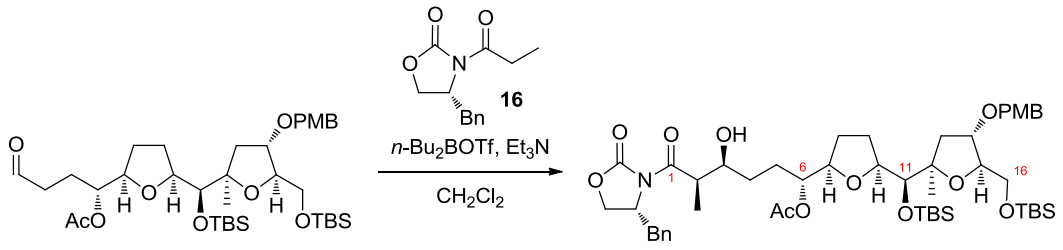


342 **343**

To a stirred solution of alcohol **342** (306 mg, 0.431 mmol) in dichloromethane (4.3 mL) were added dimethyl sulfoxide (306 µL, 4.31 mmol) and diisopropylethylamine (300 µL, 1.72 mmol) and the resulting mixture was cooled to −50 °C. Sulfur trioxide pyridine complex (210 mg, 1.29 mmol) was added in one portion, the resultant mixture was warmed to −10 °C and stirred for 1 hour. The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$, followed by a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 70:30) to give aldehyde **343** (299 mg, 0.422 mmol, 98%) as a colourless oil. $R_f = 0.65$ (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ +2.6 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2930, 2856, 1739, 1613, 1514, 1463, 1372, 1249, 1129, 1040; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.80 (1 H, s, C(1)H), 7.30 (2 H, d, $J = 8.5$, Ar*H* × 2), 6.92 (2 H, d, J =8.5, Ar*H* × 2), 5.03 (1 H, ddd, $J = 8.6$, 6.4 and 3.9, C(4)H), 4.52 (1 H, d, $J = 11.3$, C$H_AH_BC_6H_4OCH_3$), 4.45 (1 H, d, $J = 11.7$, C$H_AH_BC_6H_4OCH_3$), 4.13 (1 H, td, $J = 6.3$ and 3.5, C(13)H), 4.10–4.06 (1 H, m, C(12)H), 4.03 (1 H, t, $J = 8.0$, C(8)H), 3.84 (4 H, s, C(9)H and $C_6H_4OCH_3$), 3.74–3.66 (2 H, m, C(5)H and C(14)H_AH_B), 3.54 (1 H, dd, $J = 10.4$ and 6.3, C(14)H_AH_B), 2.63–2.47 (2 H, m, C(2)H_2), 2.14–2.09 (4 H, m, C(11)H_AH_B and C(O)CH_3), 2.05–1.94 (2 H, m, C(3)H_AH_B and C(7)H_AH_B), 1.93–1.85 (3 H, m, C(3)H_AH_B, C(6)H_AH_B and C(11)H_AH_B), 1.78–1.69 (1 H, m, C(7)H_AH_B), 1.57–1.45 (1 H, m, C(6)H_AH_B), 1.30 (3 H, s, C(10)CH_3), 0.95 (9 H, s, SiC$(CH_3)_3$), 0.94 (9 H, s, SiC$(CH_3)_3$), 0.13 (3 H, s, SiCH_3), 0.11 (6 H, s, SiCH_3 × 2), 0.09 (3 H, s, SiCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 201.3 (C1), 170.7 (*C*(O)CH_3), 159.2 (ArC_q), 130.6 (ArC_q), 129.2 (ArC), 113.9 (ArC), 85.0 (C10), 84.6 (C13), 81.2 (C12), 80.1 (C8), 78.7 (C5), 78.1 (C9), 73.8 (C4), 71.1

($CH_2C_6H_4OCH_3$), 64.1 (C14), 55.4 ($C_6H_4OCH_3$), 42.6 (C11), 39.9 (C2), 28.0 (C6), 26.2 SiC(CH_3)$_3$), 26.1 SiC(CH_3)$_3$), 24.2 (C3), 23.9 (C7), 22.0 (C(10)CH_3), 21.2 (C(O)CH_3), 18.4 (SiC(CH_3)$_3$), 18.4 (SiC(CH_3)$_3$), −3.3 ($SiCH_3$), −4.6 ($SiCH_3$), −5.3 ($SiCH_3$), −5.3 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{37}H_{64}NaO_9Si_2$ calculated 731.3981, found 731.3979.

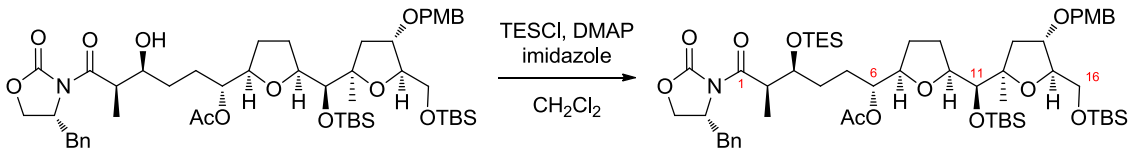
(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-4-hydroxy-5-methyl-6-oxohexyl acetate (344)



To a stirred solution of (*R*)-4-benzyl-*N*-propionyl-2-oxazolidinone (**16**) (70.0 mg, 0.297 mmol) in dichloromethane (0.2 mL) at 0 °C was added dibutylboron trifluoromethanesulfonate (1.0 M solution in CH_2Cl_2, 0340 µL, 0.337 mmol), followed by triethylamine (55 µL, 0.396 mmol). The resulting mixture was stirred for 10 minutes, then cooled to −78 °C and stirred for 5 minutes before a solution of aldehyde **343** (140 mg, 0.198 mmol) in dichloromethane (0.4 mL) was added dropwise. The reaction mixture was stirred for 1 hour before being warmed to 0 °C and stirred for a further 2 hours. The reaction was quenched by the addition of pH 7 phosphate buffer (0.6 mL) and methanol (0.6 mL). To the resultant slurry was added a 2:1 mixture of methanol and a 30% aqueous solution of hydrogen peroxide (0.6 mL) and the mixture was stirred vigorously at 0 °C for 1 hour. The reaction mixture was then extracted with ether (3 × 3.0 mL). The combined organic extracts were washed with water (2.0 mL), a saturated aqueous solution of $NaHCO_3$ (2.0 mL), brine (2.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 60:40) to afford aldol **344** (152 mg, 0.162 mmol, 82%) as a viscous colourless oil. R_f = 0.42 (petrol/EtOAc 60:40); $[\alpha]_D^{20}$ −16.1 (*c* 0.60, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2930, 2857, 1782, 1735, 1613, 1514, 1462, 1372, 1249, 1111, 1039; ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.42–7.36 (2 H, m, PhH × 2), 7.36–

7.28 (2 H, m, Ph*H* × 2), 7.25 (2 H, d, *J* = 7.6, Ar*H* × 2), 6.92 (2 H, d, *J* = 8.5, Ar*H* × 2), 5.09–5.00 (1 H, m, C(6)H), 4.79–4.71 (1 H, m, NCH), 4.52 (1 H, d, *J* = 11.3, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.44 (1 H, d, *J* = 11.7, CH$_A$$H_BC_6H_4OCH_3$), 4.31–4.21 (2 H, m, OC$H_2$CHN)), 4.13 (1 H, td, *J* = 6.3 and 3.5, C(15)H), 4.10–4.05 (1 H, m, C(14)H), 4.02 (1 H, t, *J* = 7.9, C(10)H), 3.98–3.94 (1 H, m, C(3)H), 3.87–3.83 (4 H, m, C(11)H and C$_6$H$_4$OCH_3), 3.81–3.75 (1 H, m, C(2)H), 3.75–3.64 (2 H, m, C(7)H and C(16)H_AH$_B$), 3.53 (1 H, dd, *J* = 10.4 and 6.3, C(16)H$_A$$H_B$), 3.30 (1 H, dd, *J* = 13.6 and 3.2, PhCH_AH$_B$), 2.84 (1 H, dd, *J* = 13.6 and 9.5, PhCH$_A$$H_B$), 2.15–2.08 (4 H, m, C(13)H_AH$_B$ and C(O)CH$_3$)), 2.03–1.96 (1 H, m, C(9)H_AH$_B$), 1.94–1.83 (3 H, m, C(5)H_AH$_B$, C(8)H_AH$_B$ and C(13)H$_A$$H_B$), 1.72 (1 H, dd, *J* = 10.2 and 5.5, C(9)H$_A$$H_B$), 1.67–1.58 (2 H, m, C(4)H_AH$_B$ and C(5)H$_A$$H_B$), 1.54–1.44 (2 H, m, C(4)H$_A$$H_B$ and C(8)H$_A$$H_B$), 1.30 (3 H, d, *J* = 6.3, C(2)CH$_3$), 1.29 (3 H, s, C(12)CH$_3$), 0.95 (9 H, s, SiC(CH$_3$)$_3$), 0.94 (9 H, s, SiC(CH$_3$)$_3$), 0.14 (3 H, s, SiCH$_3$), 0.11 (6 H, s, SiCH$_3$ × 2), 0.08 (3 H, s, SiCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ_C 177.5 (C1), 170.9 (*C*(O)CH$_3$), 159.2 (ArC$_q$), 153.1 (OC(O)N), 135.1 (PhC$_q$), 130.7 (ArC$_q$), 129.6 (ArC), 129.2 (PhC), 129.1 (PhC), 127.6 (PhC), 113.9 (ArC), 85.1 (C12), 84.5 (C15), 81.3 (C14), 80.0 (C10), 79.1 (C7), 78.1 (C11), 75.1 (C6), 71.6 (C3), 71.2 (*C*H$_2$C$_6$H$_4$OCH$_3$), 66.3 (O*C*H$_2$CHN), 64.2 (C16), 55.4 (C$_6$H$_4$O*C*H$_3$), 55.2 (N*C*HCH$_2$Ph), 42.5 (C13)), 42.4 (C2), 37.9 (*C*H$_2$Ph), 29.6, 28.7, 28.3 (C4, C5 and C8), 26.3 (SiC(*C*H$_3$)$_3$), 26.1 (SiC(*C*H$_3$)$_3$), 24.0 (C9), 22.1 (C(12)*C*H$_3$), 21.4 (C(O)*C*H$_3$), 18.5 (Si*C*(CH$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 10.5 (C(2)*C*H$_3$), −3.2 (SiCH$_3$), −4.7 (SiCH$_3$), −5.2 (SiCH$_3$), −5.3 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for C$_{50}$H$_{79}$NNaO$_{12}$Si$_2$ calculated 964.5038, found 964.5027.

(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl acetate (345)

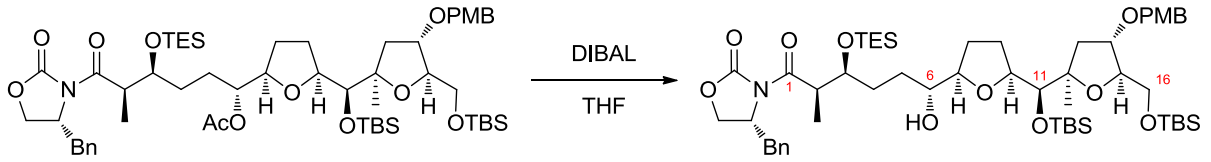


344 **345**

To a stirred solution of aldol **344** (114 mg, 0.121 mmol) in dichloromethane (1.0 mL) at 0 °C was added imidazole (33.0 mg, 0.484 mmol), followed by 4-(dimethylamino)pyridine

(1.5 mg, 0.012 mmol). The resulting solution was cooled to 0 °C and chlorotriethylsilane (41 μL, 0.24 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours before being quenched with a saturated aqueous solution of $NaHCO_3$ (2.0 mL). The mixture was diluted with water (2.0 mL), the aqueous layer was separated and extracted with ether (3 × 5.0 mL). The combined organic extracts were washed with brine (5.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 85:15) to give acetate **345** (127 mg, 0.120 mmol, 99%) as a colourless oil. $R_f = 0.74$ (petrol/EtOAc 70:30); $[\alpha]_D^{20}$ −18.4 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2954, 2810, 1783, 1737, 1699, 1514, 1460, 1374, 1248, 1113, 1040; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.37–7.32 (2 H, m, Ph*H* × 2), 7.31–7.24 (3 H, m, Ph*H* × 2), 7.22 (2 H, d, *J* = 7.3, Ar*H* × 2), 6.87 (2 H, d, *J* = 8.8, Ar*H* × 2), 4.95–4.90 (1 H, m, C(6)H), 4.61 (1 H, tdd, *J* = 9.7, 6.5 and 3.1, NCH), 4.48 (1 H, d, *J* = 11.7, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.39 (1 H, d, *J* = 11.7, CH$_A$$H_BC_6H_4OCH_3$), 4.22–4.15 (2 H, m, OC$H_2$CHN), 4.09 (1 H, td, *J* = 6.5 and 3.5, C(15)H), 4.04–3.99 (2 H, m, C(3)H and C(14)H), 3.96 (1 H, t, *J* = 7.9, C(10)H), 3.89–3.82 (1 H, m, C(2)H), 3.81 (3 H, s, C$_6$H$_4$OCH_3), 3.79 (1 H, s, C(11)H), 3.67 (1 H, dd, *J* = 10.4 and 4.1, C(16)H_AH$_B$), 3.65–3.60 (1 H, m, C(7)H), 3.47 (1 H, dd, *J* = 10.4 and 6.6, C(16)H$_A$$H_B$), 3.28 (1 H, dd, *J* = 13.2 and 3.2, CH_AH$_B$Ph), 2.77 (1 H, dd, *J* = 13.2 and 9.5, CH$_A$$H_B$Ph), 2.10–2.04 (4 H, m, C(13)H_AH$_B$ and C(O)CH$_3$), 1.99–1.89 (1 H, m, C(9)H_AH$_B$), 1.88–1.82 (1 H, m, C(8)H_AH$_B$), 1.82 (1 H, dd, *J* = 13.2 and 2.2, C(13)H$_A$$H_B$), 1.74–1.62 (2 H, m, C(5)H_AH$_B$ and C(9)H$_A$$H_B$), 1.61–1.50 (3 H, m, C(4)H$_2$ and C(5)H$_A$$H_B$), 1.47–1.37 (1 H, m, C(8)H$_A$$H_B$), 1.25 (3 H, s, C(12)CH$_3$), 1.21 (3 H, d, *J* = 6.9, C(2)CH$_3$), 0.96 (9 H, t, *J* = 8.0, Si(CH$_2$CH_3)$_3$), 0.90 (9 H, s, SiC(CH$_3$)$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.58 (6 H, dq, *J* = 7.9 and 1.4, Si(CH_2CH$_3$)$_3$), 0.08 (3 H, s, SiCH$_3$), 0.06 (6 H, s, SiCH$_3$ × 2), 0.03 (3 H, s, SiCH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 175.3 (C1), 170.7 (*C*(O)CH$_3$), 159.2 (ArC_q), 153.2 (OC(O)N), 135.5 (PhC_q), 130.7 (ArC_q), 129.6 (ArC), 129.2 (PhC), 129.1 (PhC), 127.5 (PhC), 113.9 (ArC), 85.1 (C12), 84.5 (C15), 81.4 (C14), 80.0 (C10), 79.0 (C7), 78.1 (C11), 75.2 (C6), 72.9 (C3), 71.1 (*C*H$_2$C$_6$H$_4$OCH$_3$), 66.2 (O*C*H$_2$CHN), 64.2 (C14), 55.9 (NCH), 55.4 (C$_6$H$_4$O*C*H$_3$), 42.8 (C2), 42.4 (C13), 37.8 (*C*H$_2$Ph), 30.9 (C4), 28.3 (C8), 27.1 (C5), 26.3 (SiC(*C*H$_3$)$_3$), 26.1 (SiC(*C*H$_3$)$_3$), 24.0 (C9), 22.1 (C(12)*C*H$_3$), 21.3 (C(O)*C*H$_3$), 18.5 (Si*C*(CH$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 12.1 (C(2)*C*H$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 5.2 (Si(*C*H$_2$CH$_3$)$_3$), −3.2 (SiCH$_3$), −4.7 (SiCH$_3$), −5.2 (SiCH$_3$), −5.3 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for $C_{56}H_{93}NNaO_{12}Si_3$ calculated 1078.5898, found 1078.5880.

(*R*)-4-Benzyl-3-((2*R*,3*S*,6*R*)-6-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-6-hydroxy-2-methyl-3-((triethylsilyl)oxy)hexanoyl)oxazolidin-2-one (346)

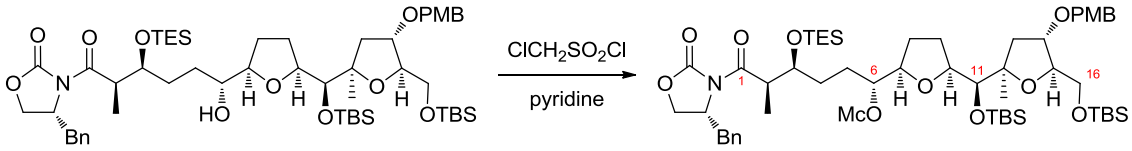


345 **346**

To a stirred solution of acetate **345** (120 mg, 0.114 mmol) in tetrahydrofuran (4.6 mL) at −78 °C was added diisobutylaluminium hydride (1.0 M in hexanes, 0.34 mL, 0.342 mmol) dropwise. The resulting mixture was stirred for 90 minutes and a further diisobutylaluminium hydride (1.0 M in hexanes, 0.23 mL, 0.228 mmol) was added. The reaction mixture was stirred for a further 2 hours at −78 °C before being quenched by the dropwise addition of ethyl acetate (3.0 mL). The resultant mixture was stirred for 10 minutes before a saturated aqueous solution of Rochelle's salt (5.0 mL) was added and the mixture was stirred vigorously for 45 minutes while being allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with ether (4 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/Et_2O 50:50) to give bis-THF **346** (100 mg, 0.0992 mmol, 87%) as a viscous, colourless oil. $R_f = 0.34$ (petrol/Et_2O 60:40); $[\alpha]_D^{20}$ −21.6 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3502, 2954, 2820, 1783, 1700, 1613, 1514, 1462, 1382, 1249, 1107, 1043; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.37–7.31 (2 H, m, Ph*H* × 2), 7.30–7.24 (3 H, m, Ph*H* × 3), 7.24–7.20 (2 H, m, Ar*H* × 2), 6.88 (2 H, d, *J* = 8.5, Ar*H* × 2), 4.62 (1 H, tdd, *J* = 9.5, 6.3 and 3.3, NCH), 4.48 (1 H, d, *J* = 11.3, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.40 (1 H, d, *J* = 11.3, CH$_A$$H_BC_6H_4OCH_3$), 4.19–4.14 (2 H, m, OC$H_2$CHN), 4.11 (1 H, td, *J* = 6.3 and 3.5, C(15)H), 4.07–3.99 (3 H, m, C(3)H, C(10)H and C(14)H), 3.94–3.87 (1 H, m, C(2)H), 3.81 (3 H, s, C$_6$H$_4$OCH_3), 3.72 (1 H, d, *J* = 1.9, C(11)H), 3.68 (1 H, dd, *J* = 10.6 and 3.9, C(16)H_AH$_B$), 3.55–3.47 (2 H, m, C(7)H and C(16)H$_A$$H_B$), 3.47–3.41 (1 H, m, C(6)H), 3.29 (1 H, dd, *J* = 13.2 and 3.2, CH_AH$_B$Ph), 2.77 (1 H, dd, *J* = 13.2 and 9.8, CH$_A$$H_B$Ph), 2.04 (1 H, dd, *J* = 13.2 and 6.9, C(13)H_AH$_B$), 2.01–1.91 (1 H, m, C(9)H_AH$_B$), 1.89–1.81 (3 H, m, C(4)H_AH$_B$, C(8)H_AH$_B$ and C(13)H$_A$$H_B$), 1.80–1.74 (1 H, m, C(9)H$_A$$H_B$), 1.63–1.52 (2 H, m, C(4)H$_A$$H_B$ and C(5)H_AH$_B$), 1.51–1.44 (1 H, m,

C(8)H$_A$*H$_B$*), 1.41–1.34 (1 H, m, C(5)H$_A$*H$_B$*), 1.29 (3 H, s, C(12)CH$_3$), 1.23 (3 H, d, *J* = 6.9, C(2)CH$_3$), 0.96 (9 H, t, *J* = 8.0, Si(CH$_2$C*H$_3$*)$_3$), 0.90 (9 H, s, SiC(CH$_3$)$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.60 (6 H, q, *J* = 8.0, Si(C*H$_2$*CH$_3$)$_3$), 0.07 (3 H, s, SiCH$_3$), 0.07 (3 H, s, SiCH$_3$), 0.07 (3 H, s, SiCH$_3$), 0.06 (3 H, s, SiCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ_C 175.4 (C1), 159.2 (ArC$_q$), 153.2 (OC(O)N), 135.6 (PhC$_q$), 130.7 (ArC$_q$), 129.6 (ArC), 129.2 (PhC), 129.1 (PhC), 127.5 (PhC), 113.9 (ArC), 85.4 (C12), 84.7 (C15), 82.1 (C7), 81.0 (C14), 80.1 (C10), 78.8 (C11), 74.5 (C6), 73.5 (C3), 71.2 (*C*H$_2$C$_6$H$_4$OCH$_3$), 66.1 (O*C*H$_2$CHN), 64.0 (C16), 55.9 (NCH), 55.4 (C$_6$H$_4$O*C*H$_3$), 43.1 (C2), 42.8 (C13), 37.8 (*C*H$_2$Ph), 31.4 (C4), 29.3 (C5), 28.0 (C8), 26.2 (SiC(*C*H$_3$)$_3$), 26.1 (SiC(*C*H$_3$)$_3$), 25.5 (C9), 21.7 (C(12)*C*H$_3$), 18.5 (Si*C*(CH$_3$)$_3$), 18.4 (Si*C*(CH$_3$)$_3$), 12.2 (C(2)*C*H$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 5.3 Si(*C*H$_2$CH$_3$)$_3$), −3.0 (SiCH$_3$), −4.1 (SiCH$_3$), −5.2 (SiCH$_3$), −5.3 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for C$_{54}$H$_{91}$NNaO$_{11}$Si$_3$ calculated 1036.5792, found 1036.5745.

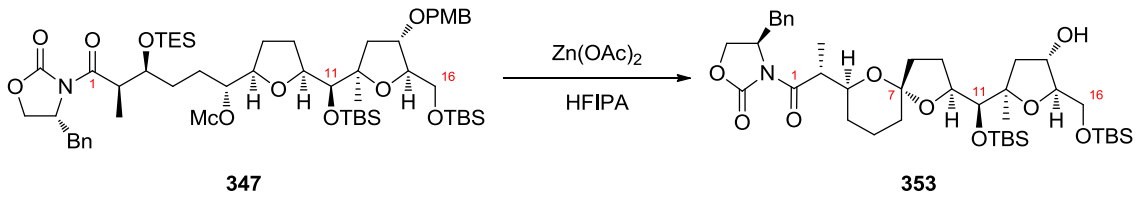
(1*R*,4*S*,5*R*)-6-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-((2*R*,5*S*)-5-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)tetrahydrofuran-2-yl)-5-methyl-6-oxo-4-((triethylsilyl)oxy)hexyl chloromethanesulfonate (347)



To a stirred solution of alcohol **346** (70.0 mg, 0.0691 mmol) in pyridine (0.55 mL) at 0 °C was added chloromethanesulfonyl chloride (90% purity, 18 µL, 0.173 mmol). The resulting mixture was stirred for 30 minutes at 0 °C before being warmed to room temperature and stirred for a further 2 hours. The reaction mixture was quenched with water (1.0 mL) and diluted with ether (2.0 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 2.0 mL). The combined organic extracted were washed with water (2.0 mL), brine (2.0 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO$_2$, petrol/EtOAc 80:20) to give chloromesylate **347** (77.0 mg, 0.0684 mmol, 99%) as a viscous, pale yellow oil. R_f = 0.60 (petrol/EtOAc 80:20); $[\alpha]_D^{20}$ −40.8 (*c* 0.25, CH$_2$Cl$_2$); IR ν_{max} (film)/cm^{-1} 2955, 2850, 1781, 1712, 1615, 1515, 1471, 1384, 1250, 1105; ^{1}H NMR (500 MHz, CDCl$_3$) δ_H 7.36–7.31 (2 H, m, Ph*H* × 2), 7.30–

7.24 (3 H, m, Ph*H* × 3), 7.21 (2 H, d, *J* = 6.9, Ar*H* × 2), 6.88 (2 H, d, *J* = 8.5, Ar*H* × 2), 4.87 (1 H, d, *J* = 12.0, SC$H_A$$H_B$Cl), 4.73 (1 H, d, *J* = 12.0, SCH$_A$$H_B$Cl), 4.71–4.64 (2 H, m, C(6)H and NCH), 4.47 (1 H, d, *J* = 11.7, C$H_A$$H_BC_6H_4OCH_3$), 4.40 (1 H, d, *J* = 11.3, CH$_A$$H_BC_6H_4OCH_3$), 4.25 (1 H, t, *J* = 8.4, OC$H_A$$H_B$CHN), 4.17–4.10 (3 H, m, C(10)H, C(15)H and OCH$_A$$H_B$CHN), 4.06–4.00 (2 H, m, C(3)H and C(14)H), 3.91 (1 H, quin, *J* = 6.8, C(2)H), 3.81 (3 H, s, C$_6$H$_4$OCH_3), 3.72 (1 H, ddd, *J* = 10.6, 8.4 and 5.8, C(7)H), 3.67–3.62 (2 H, m, C(11)H and C(16)$H_A$$H_B$), 3.47 (1 H, dd, *J* = 10.6 and 6.1, C(16)H$_A$$H_B$), 3.26 (1 H, dd, *J* = 13.2 and 3.2, C$H_A$$H_B$Ph), 2.79 (1 H, dd, *J* = 13.4 and 9.6, CH$_A$$H_B$Ph), 2.12–2.06 (1 H, m, C(9)$H_A$$H_B$), 1.92–1.85 (3 H, m, C(8)$H_A$$H_B$ and C(13)H$_2$), 1.84–1.72 (3 H, m, C(4)$H_A$$H_B$, C(5)$H_A$$H_B$ and C(9)H$_A$$H_B$), 1.70–1.61 (2 H, m, C(4)H$_A$$H_B$ and C(5)H$_A$$H_B$), 1.45–1.36 (1 H, m, C(8)H$_A$$H_B$), 1.26 (3 H, d, *J* = 7.1, C(2)CH$_3$), 1.25 (3 H, s, C(12)CH$_3$), 0.97 (9 H, t, *J* = 7.9, Si(CH$_2$CH_3)$_3$), 0.90 (9 H, s, SiC(CH$_3$)$_3$), 0.89 (9 H, s, SiC(CH$_3$)$_3$), 0.61 (6 H, q, *J* = 7.9, Si(CH_2CH$_3$)$_3$), 0.08 (3 H, s, SiCH$_3$), 0.06 (3 H, s, SiCH$_3$), 0.05 (3 H, s, SiCH$_3$), 0.05 (3 H, s, SiCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ_C 175.4 (C1), 159.3 (ArC$_q$), 153.4 (OC(O)N), 135.5 (PhC$_q$), 130.6 (ArC$_q$), 129.6 (ArC), 129.3 (PhC), 129.0 (PhC), 127.4 (PhC), 113.9 (ArC), 88.8 (C(6)H), 85.1 (C12), 84.9 (C15), 81.2 (C14), 80.8 (C10), 79.8 (C7), 79.6 (C11), 73.2 (C3), 71.2 (*C*H$_2$C$_6$H$_4$OCH$_3$), 66.3 (O*C*H$_2$CHN), 64.2 (C16), 55.7 (NC6H), 55.4 (C$_6$H$_4$O*C*H$_3$), 54.5 (SCH$_2$Cl), 43.4 (C13), 42.9 (C2), 37.8 (*C*H$_2$Ph), 30.5, 28.6, 27.7 (C4, C5 and C8), 26.1 (SiC(*C*H$_3$)$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 24.2 (C9), 21.3 (C(12)*C*H$_3$), 18.4 Si*C*(CH$_3$)$_3$), 18.4 Si*C*(CH$_3$)$_3$), 13.4 (C(2)*C*H$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 5.3 (Si(*C*H$_2$CH$_3$)$_3$), −2.9 (SiCH$_3$), −4.6 (SiCH$_3$), −5.1 (SiCH$_3$), −5.3 (SiCH$_3$); HRMS (ESI$^+$, *m/z*) for C$_{55}$H$_{92}$ClNNaO$_{13}$SSi$_3$ calculated 1148.5178, found 1148.5151.

(*R*)-4-Benzyl-3-((*R*)-2-((2*S*,5*S*,7*S*)-2-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxy-2-methyltetrahydrofuran-2-yl)methyl)-1,6-dioxaspiro[4.5]decan-7-yl)propanoyl)oxazolidin-2-one (353)

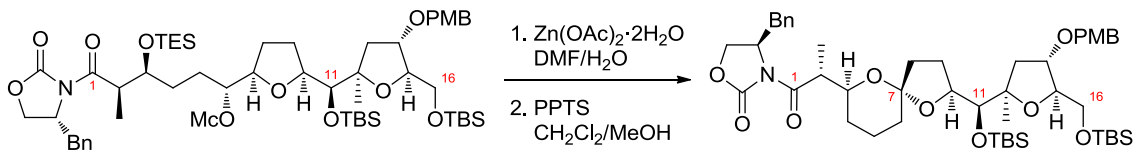


347 **353**

To a stirred solution of chloromesylate **347** (18 mg, 0.016 mmol) in hexafluoroisopropanol (0.16 mL) was added zinc acetate (15 mg, 0.080 mmol). The reaction tube was sealed and the

mixture was warmed to 30 °C and stirred for 6 hours before being diluted with ethyl acetate (5.0 mL). The resulting mixture was washed with water (2.0 mL), brine (2.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 80:20) to afford spiroketal **353** (8.4 mg, 0.011 mmol, 66%) as a colourless oil. $[\alpha]_D^{20}$ −2.8 (*c* 0.25, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 3100–3000, 1777, 1691, 1515, 1387; ^{1}H NMR (700 MHz, C_6D_6) δ_C 7.19–7.10 (5 H, m, Ph*H* × 5), 4.69 (1 H, t, *J* = 7.7, C(10)H), 4.48–4.39 (3 H, m, C(2)H, C(3)H and NCH), 4.35 (1 H, quin, *J* = 3.7, C(14)H), 4.16 (1 H, s, C(11)H), 4.09 (1 H, td, *J* = 6.4 and 4.2, C(15)H), 3.91 (1 H, dd, *J* = 10.2 and 4.1, C(16)H_AH_B), 3.75 (1 H, dd, *J* = 10.2 and 6.5, C(16)H_AH_B), 3.61 (1 H, dd, *J* = 8.9 and 2.5, OCH_AH_BCHN), 3.48 (1 H, t, *J* = 8.4, OCH_AH_BCHN), 3.12 (1 H, dd, *J* = 13.3 and 3.1, CH_AH_BPh), 2.45–2.40 (2 H, m, C(13)H_AH_B and CH_AH_BPh), 2.20 (1 H, ddt, *J* = 11.7, 7.7 and 4.1, C(9)H_AH_B), 2.16–2.10 (2 H, m, C(5)H_AH_B and C(8)H_AH_B), 2.02–1.96 (1 H, m, C(9)H_AH_B), 1.89–1.82 (2 H, m, C(4)H_AH_B and C(6)H_AH_B), 1.80 (1 H, dd, *J* = 12.9 and 3.7, C(13)H_AH_B), 1.77–1.70 (2 H, m, C(6)H_AH_B and C(8)H_AH_B), 1.69–1.67 (1 H, m, C(5)H_AH_B), 1.62 (3 H, d, *J* = 6.3, C(2)CH_3), 1.54–1.52 (1 H, m, C(4)H_AH_B), 1.51 (3 H, s, C(12)CH_3), 1.14 (9 H, s, SiC$(CH_3)_3$), 1.09 (9 H, s, SiC$(CH_3)_3$), 0.32 (3 H, s, SiCH_3), 0.31 (3 H, s, SiCH_3), 0.26 (3 H, s, SiCH_3), 0.23 (3 H, s, SiCH_3); ^{13}C NMR (126 MHz, C_6D_6) δ_C 175.0 (C1), 153.1 (OC(O)N), 136.0 (PhC_q), 129.6 (PhC), 129.0 (PhC), 127.5 (PhC), 105.2 (C7), 86.7 (C12), 84.9 (C15), 79.0 (C10), 78.1 (C11), 75.1 (C14), 71.4 (C3), 65.4 (C16), 65.0 (O*C*H_2CHN), 55.4 (NCH), 45.4 (C2), 43.0 (C13), 38.4 (C8), 37.8 (*C*H_2Ph), 32.4 (C6), 28.3 (C4), 26.4 (SiC(*C*$H_3)_3$), 26.2 (SiC(*C*$H_3)_3$), 23.3 (C9), 22.8 (C(12)*C*H_3), 20.8 (C5), 18.6 (Si*C*$(CH_3)_3$), 18.5 (Si*C*$(CH_3)_3$), 14.1 (C(2)CH_3), −3.0 (SiCH_3), −4.1 (SiCH_3), −5.1 (SiCH_3), −5.2 (SiCH_3); HRMS (ESI^+, *m/z*) for $C_{40}H_{67}NNaO_9Si_2$ calculated 784.4247, found 784.4256.

(*R*)-4-Benzyl-3-((*R*)-2-((2*S*,5*S*,7*S*)-2-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,4*S*,5*R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-((4-methoxybenzyl)oxy)-2-methyltetrahydrofuran-2-yl)methyl)-1,6-dioxaspiro[4.5]decan-7-yl)propanoyl)oxazolidin-2-one (348)



347 **348**

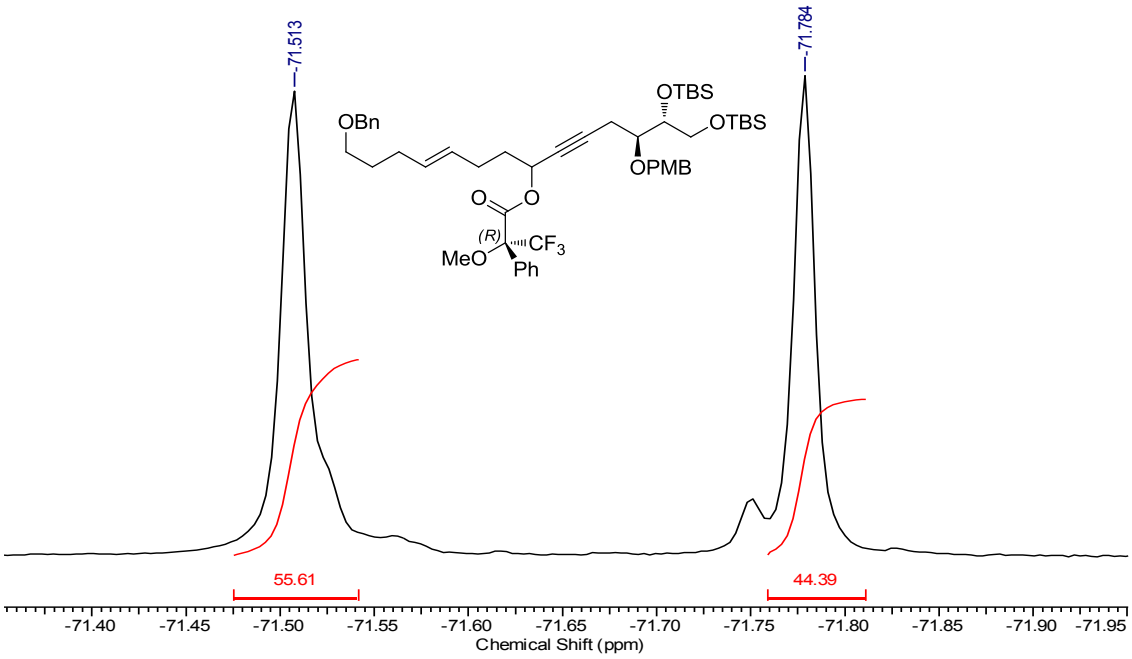
To a stirred solution of chloromesylate **347** (40.0 mg, 0.0356 mmol) in *N*,*N*-dimethylformamide (0.54 mL) was added water (0.40 mL), followed by zinc trifluoromethanesulfonate dihydrate (80.0 mg, 0.356 mmol). The resulting mixture was heated to 75 °C and stirred for 12 hours, before it was cooled to room temperature and diluted with brine (5.0 mL). The resultant mixture was extracted with ether (4 × 5.0 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 75:25) to afford a mixture of ketone **351** and lactol **350** (24.5 mg, 0.0242 mmol, 68%) as an oil. $R_f = 0.45$ (petrol/EtOAc 80:20). The mixture of **350** and **351** (24.5 mg, 0.0242 mmol) was dissolved in methanol (1.2 mL) and dichloromethane (1.2 mL) and the resultant mixture was cooled to 0 °C. Pyridinium *p*-toluenesulfonate (3.0 mg, 0.012 mmol) was added and the resulting mixture was stirred at 0 °C for 2 hours before being quenched with a saturated aqueous solution of $NaHCO_3$ (1.5 mL). The resulting mixture was diluted with ether (10 mL) and washed with water (5.0 mL), brine (5.0 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, petrol/EtOAc 90:10) to afford spiroketal **348** (20.3 mg, 0.0230 μmol, 95%) as a colourless oil. $[\alpha]_D^{20}$ −8.5 (*c* 0.50, CH_2Cl_2); IR ν_{max} (film)/cm^{-1} 2929, 1782, 1699, 1514, 1386, 1037; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H 7.36–7.32 (2 H, m, Ph*H* × 2), 7.30–7.24 (3 H, m, Ph*H* × 3), 7.22 (2 H, d, *J* = 7.2, Ar*H* × 2), 6.88 (2 H, d, *J* = 8.7, Ar*H* × 2), 4.66–4.62 (1 H, m, NCH), 4.49 (1 H, d, *J* = 11.4, CH_AH$_B$C$_6$H$_4$OCH$_3$), 4.40 (1 H, d, *J* = 11.6, CH$_A$$H_BC_6H_4OCH_3$), 4.24 (1 H, t, *J* = 8.3, OCH_AH$_B$CHN), 4.18 (1 H, t, *J* = 7.6, C(10)H), 4.14 (1 H, dd, *J* = 8.9 and 2.3, OCH$_A$$H_B$CHN), 4.07 (1 H, td, *J* = 7.0 and 3.5, C(15)H), 4.04 (1 H, dt, *J* = 7.0 and 1.9, C(14)H), 3.99 (ddd, *J* = 11.2, 7.6 and 1.7, C(3)H), 3.88 (1 H, quin, *J* = 7.0, C(2)H), 3.82 (3 H, s, C$_6$H$_4$OCH_3), 3.81 (1 H, s, C(11)H), 3.69 (1 H, dd, *J* = 10.3 and 4.0, C(16)H_AH$_B$), 3.45 (1 H, dd, *J* = 10.4, and 7.2, C(16)H$_A$$H_B$), 3.28 (1 H, dd, *J* = 13.5 and 3.1, CH_AH$_B$Ph), 2.78 (1 H, dd, *J* = 13.4 and 9.6, CH$_A$$H_B$Ph), 2.09 (1 H, dd, *J* = 13.4 and 7.2, C(13)H_AH$_B$), 1.97 (1 H, ddt, *J* = 11.6, 7.6 and 3.9, C(9)H_AH$_B$), 1.90–1.83 (2 H, m, C(5)H_AH$_B$ and C(8)H_AH$_B$), 1.79 (1 H, dd, *J* = 13.4 and 1.4, C(13)H$_A$$H_B$), 1.78–1.73 (1 H, m, C(9)H$_A$$H_B$), 1.71–1.68 (1 H, m, C(6)H_AH$_B$), 1.67–1.63 (1 H, m, C(5)H$_A$$H_B$), 1.63–1.56 (4 H, m, C(4)H_AH$_B$, C(6)H$_A$$H_B$ and C(8)H$_A$$H_B$), 1.27 (1 H, m, C(4)H$_A$$H_B$), 1.27 (3 H, s, C(12)CH$_3$), 1.25 (3 H, d, *J* = 6.8, C(2)CH$_3$), 0.92 (9 H, s, SiC(CH$_3$)$_3$), 0.90 (9 H, s, SiC(CH$_3$)$_3$), 0.10 (3 H, s, SiCH$_3$), 0.09 (3 H, s, SiCH$_3$), 0.07 (3 H, s, SiCH$_3$), 0.05 (3 H, s, SiCH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 175.3 (C1), 159.2 (ArC$_q$), 153.2 (OC(O)N), 135.6 (PhC$_q$), 130.8 (ArC$_q$), 129.6 (ArC), 129.2 (PhC), 129.1 (PhC), 127.4 (PhC), 113.9 (ArC), 105.1 (C7), 85.2 (C12), 84.5 (C15), 78.2 (C11), 78.0 (C10), 71.1

(*C*$H_2C_6H_4OCH_3$), 71.0 (C3), 66.0 (O*C*H_2CHN), 64.3 (C16), 55.7 (NCH), 55.4 ($C_6H_4OCH_3$), 42.6 (C2), 41.6 (C13), 38.1 (C8), 38.0 (*C*H_2Ph), 32.2 (C6), 28.1 (C4), 26.2 (SiC(*C*H_3)$_3$), 26.1 (SiC(*C*H_3)$_3$), 22.8 (C9), 22.4 (C(12)*C*H_3), 20.3 (C5), 18.5 (Si*C*$(CH_3)_3$), 18.4 (Si*C*$(CH_3)_3$), 13.5 (C(2)*C*H_3), −3.3 ($SiCH_3$), −4.1 ($SiCH_3$), −5.1 ($SiCH_3$), −5.2 ($SiCH_3$); HRMS (ESI^+, *m/z*) for $C_{48}H_{75}NNaO_{10}Si_2$ calculated 904.4822, found 904.4789.

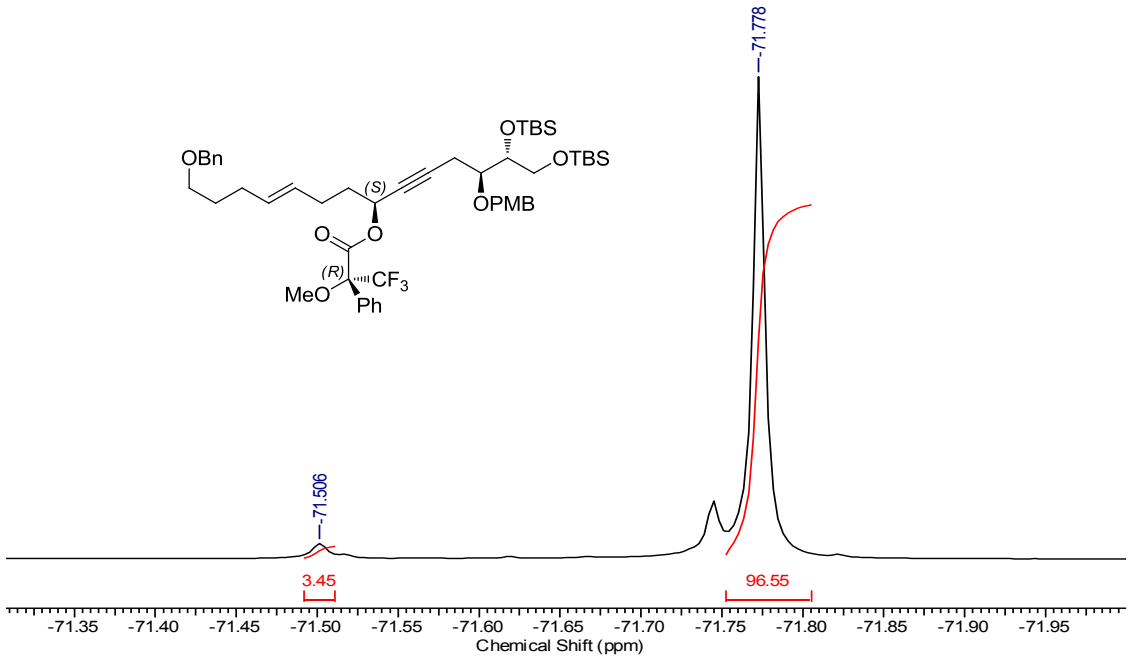
3.3 Mosher's esters analysis and relevant spectra

3.3.1 Mosher's esters analysis for alcohol 165

- ^{19}F NMR spectrum of Mosher esters of a C10 epimeric mixture of alcohols **165** and 10-*epi*-**165**

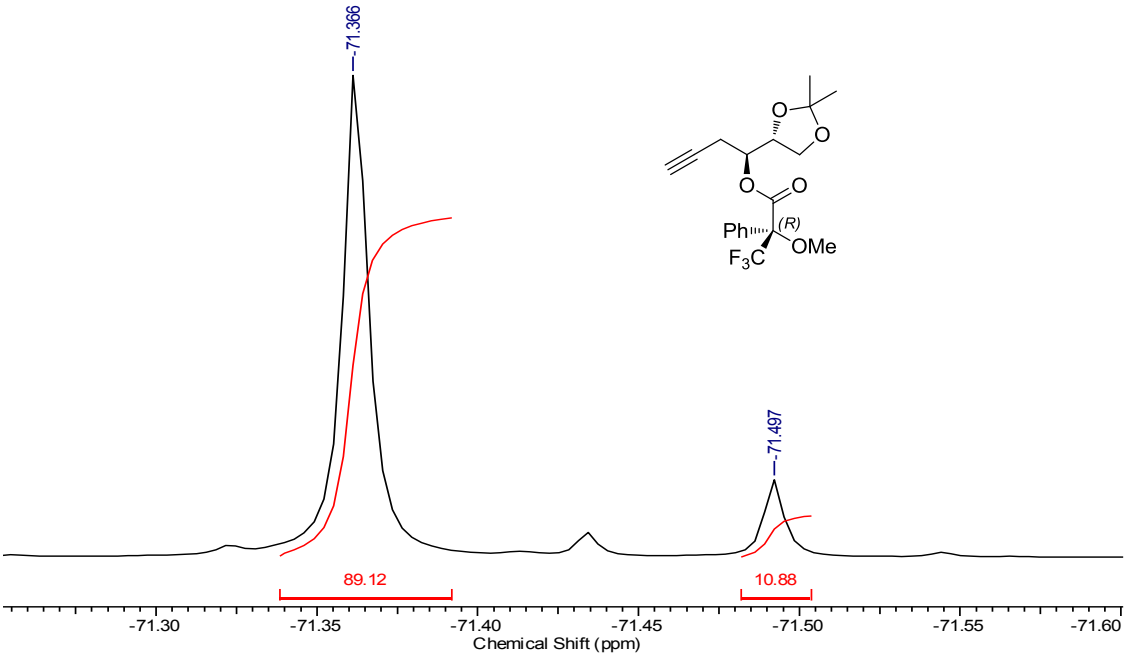


- ^{19}F NMR spectrum of Mosher ester of alcohol **165**



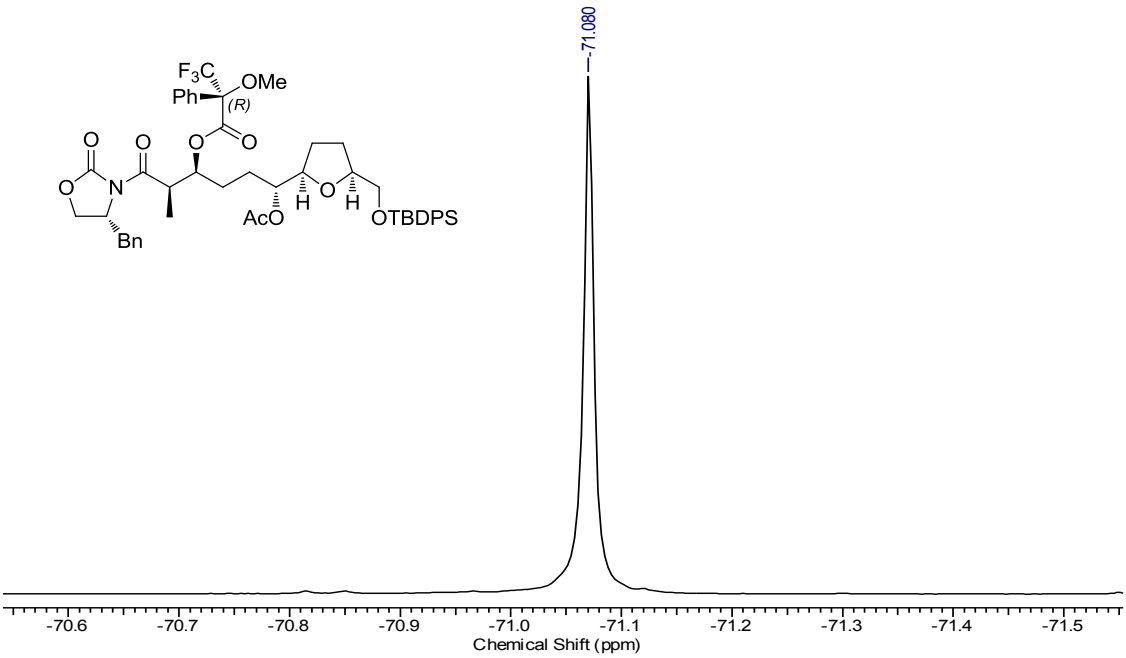
3.3.2 Mosher's ester analysis for homopropargylic alcohol 132

- ^{19}F NMR spectrum of Mosher ester of alcohol **132**



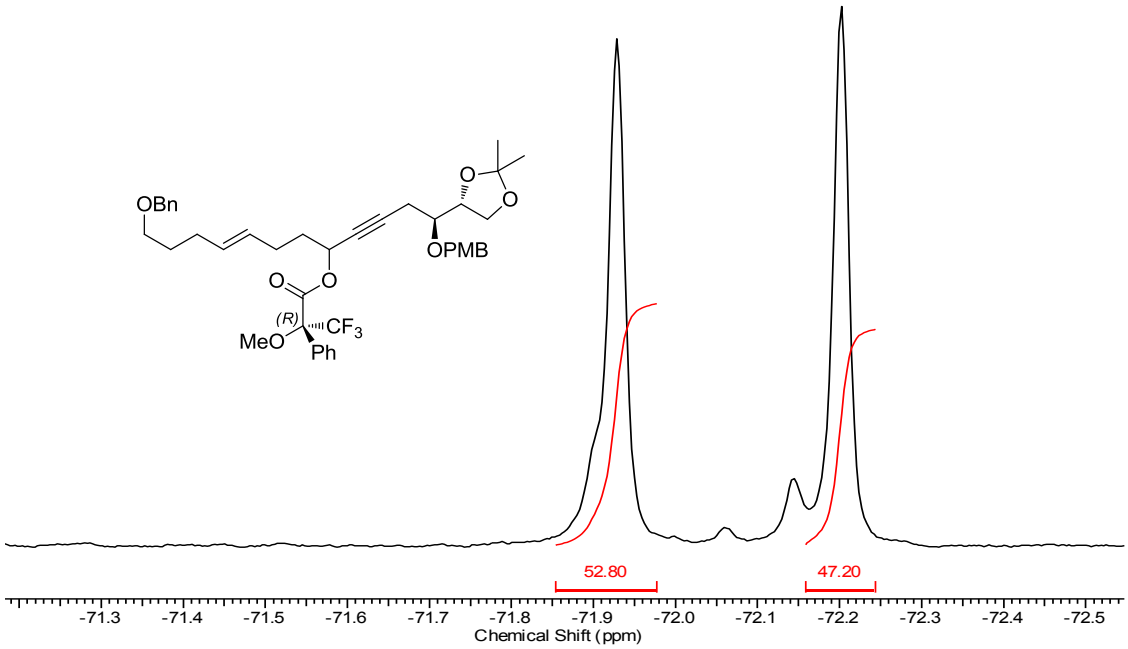
3.3.3 Mosher's ester analysis for aldol 304

- ^{19}F NMR spectrum of Mosher ester of aldol **304**

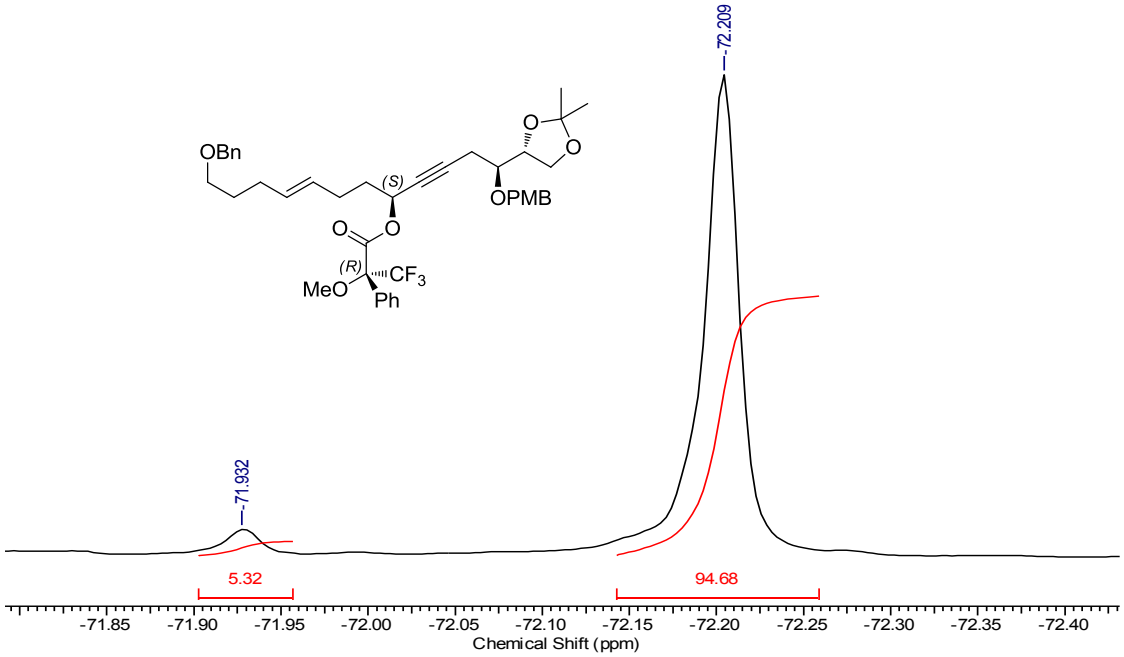


3.3.4 Mosher ester analysis for alcohol 137

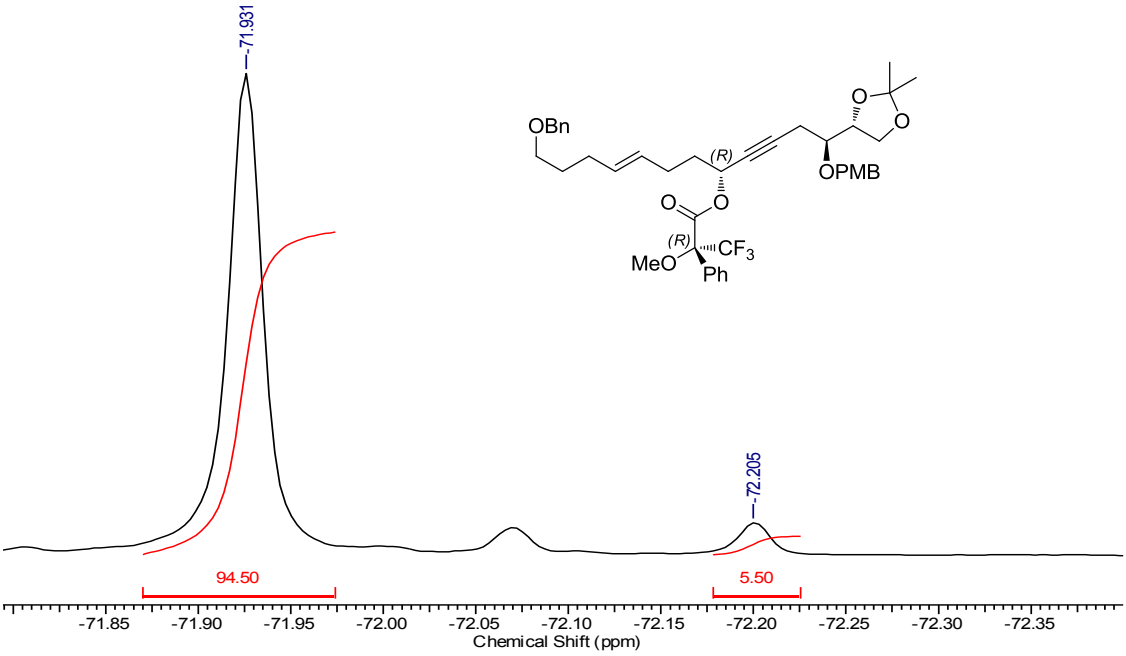
- ^{19}F NMR spectrum of Mosher esters of a C10 epimeric mixture of alcohols **137** and 10-*epi*-**137**



- ^{19}F NMR spectrum of Mosher ester of alcohol **137**

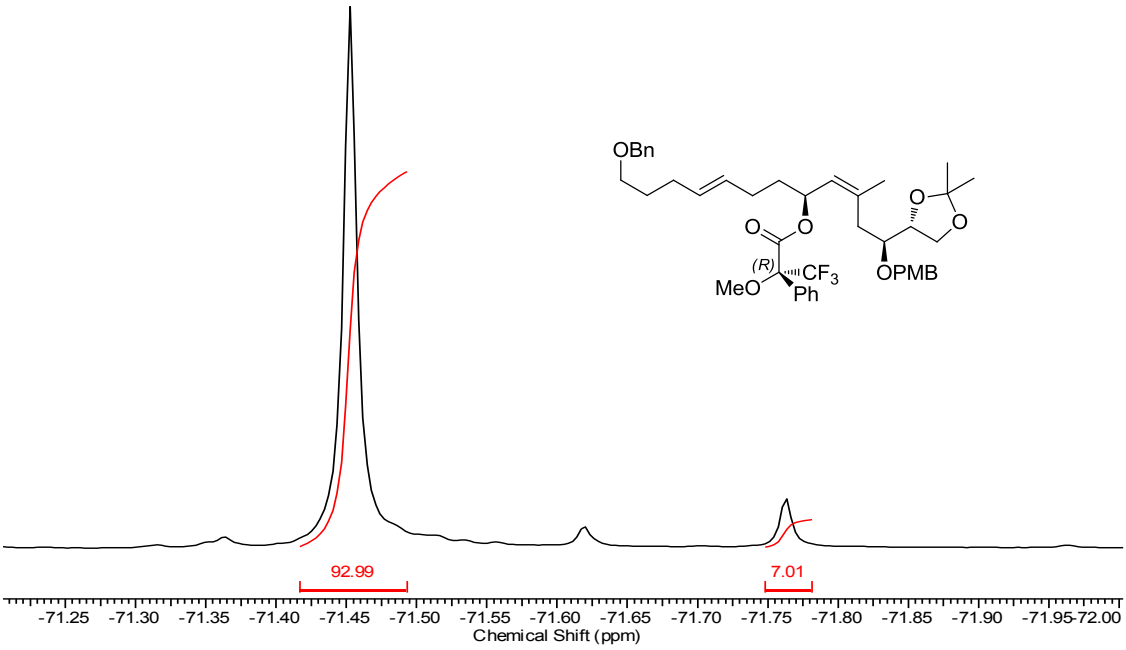


- ^{19}F NMR spectrum of Mosher ester of alcohol 10-*epi*-**137**

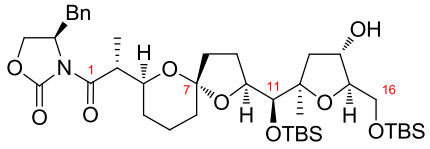


3.3.5 Mosher ester analysis for alcohol 151

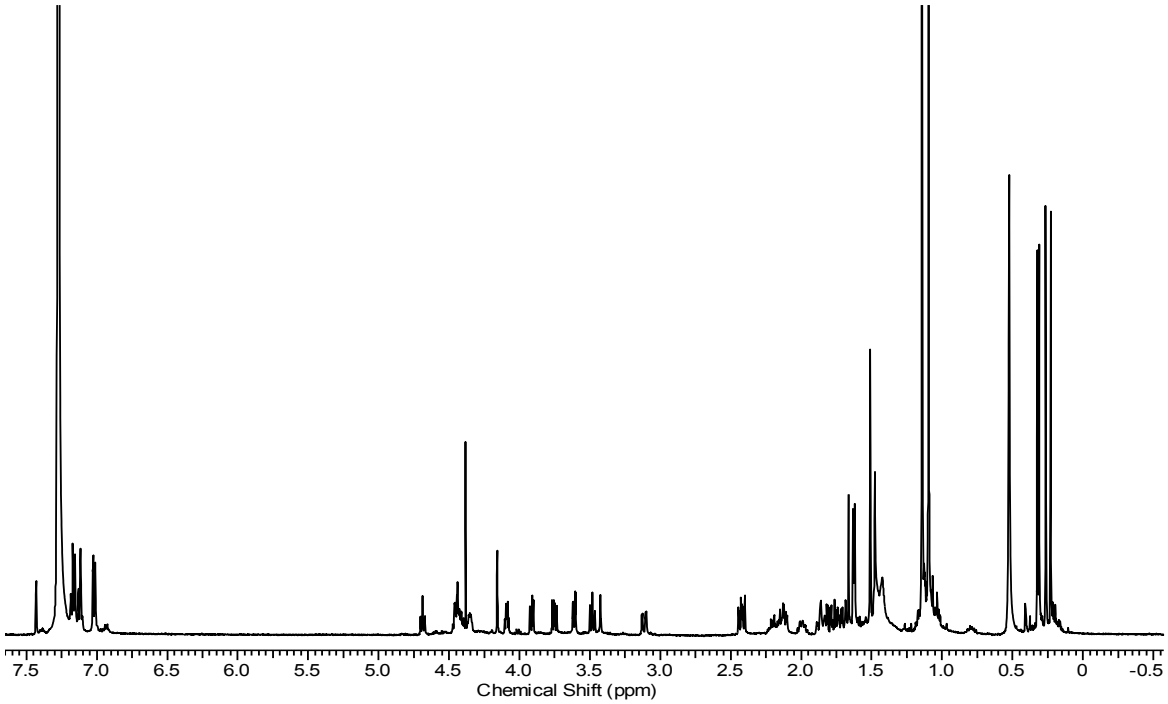
- ^{19}F NMR spectrum of the Mosher ester of alcohol **151**

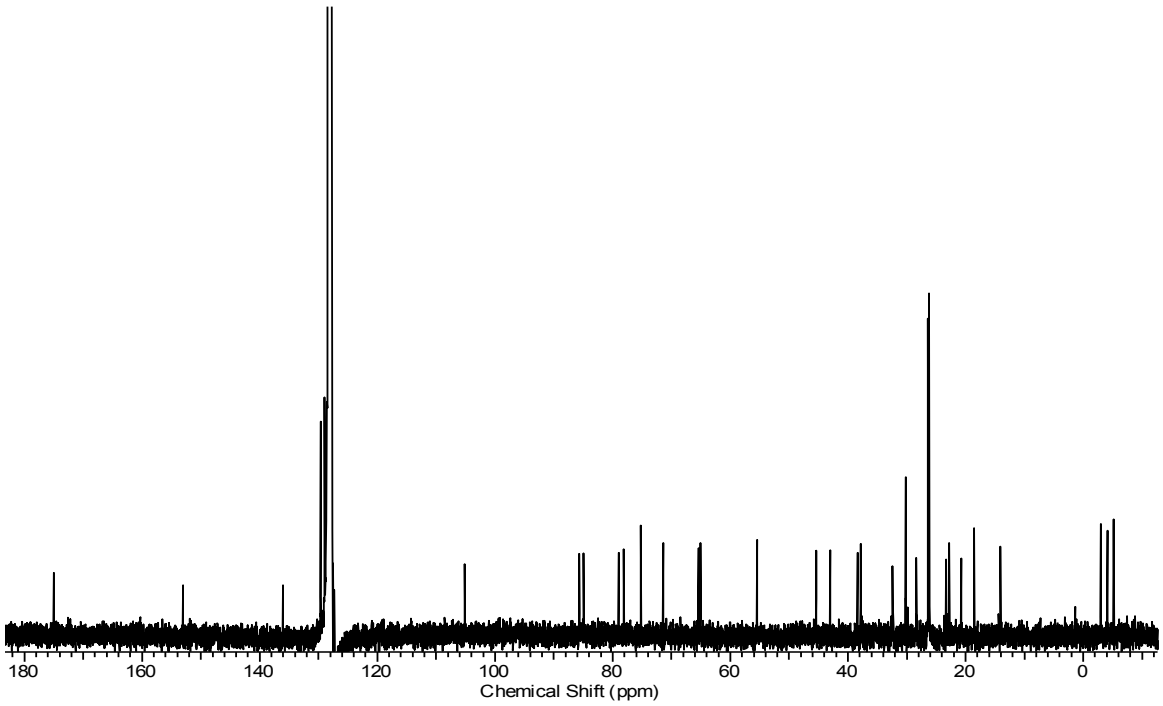


3.3.6 ^{1}H NMR and ^{13}C NMR spectra of ABC fragment 353

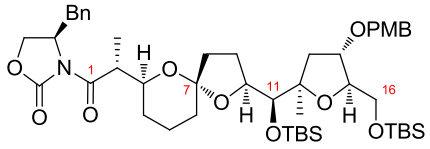


353

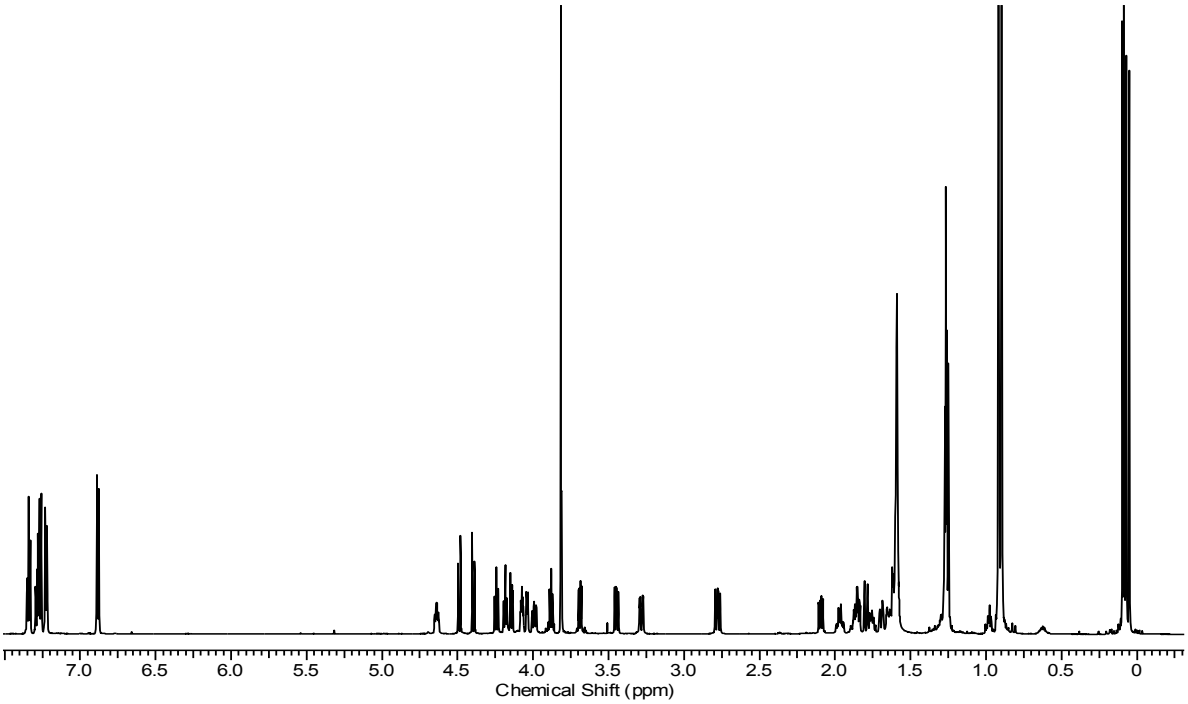


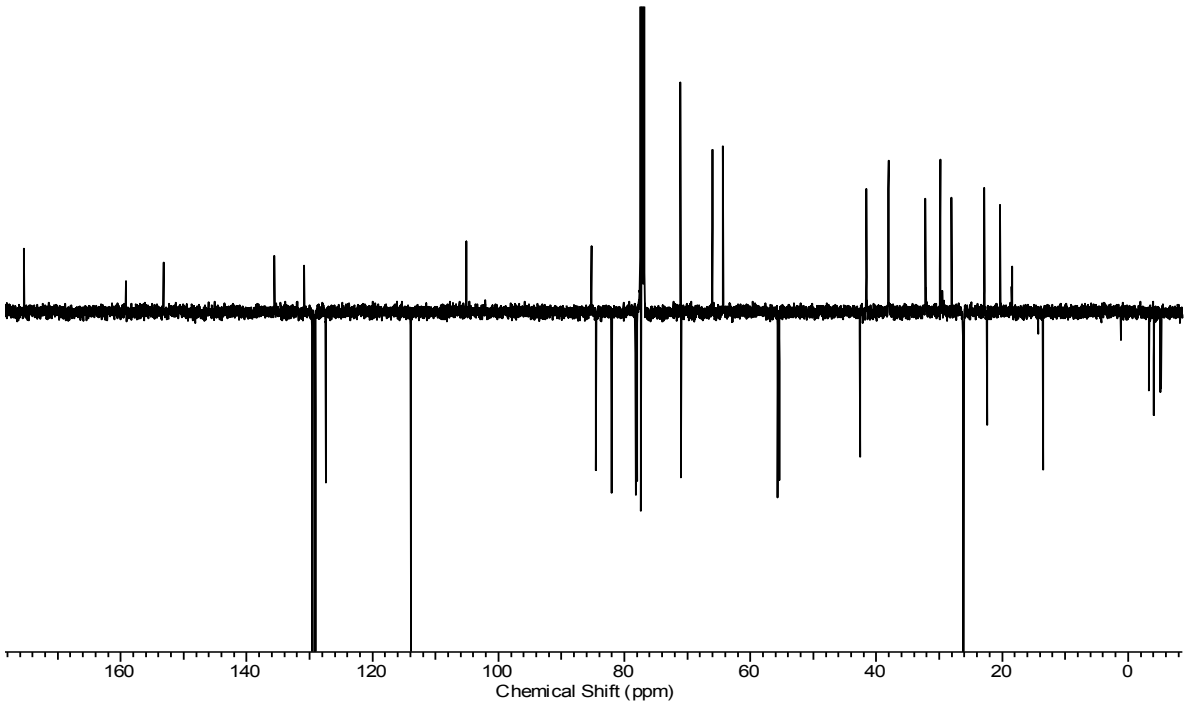


3.3.7 ^{1}H NMR and ^{13}C NMR spectra of ABC fragment 348



348





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