# DETERMINING THE STRUCTURES OF HALOGENATED MARINE NATURAL PRODUCTS BY TOTAL SYNTHESIS


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*Linacre College, University of Oxford, 2011*

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# Determining the Structure of Marine Natural Products by Total Synthesis


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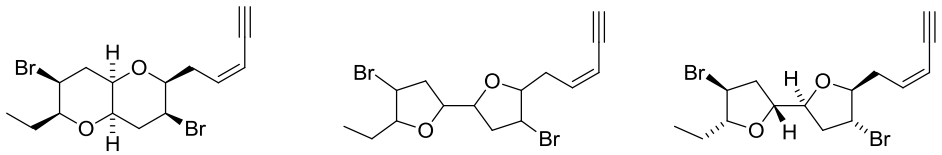
Elatenyne, a brominated $C_{15}$ acetogenin isolated from the red *Laurencia elata* marine algae, was originally assigned a pyranopyran structure (**20**). Previous total synthesis of the pyranopyran structure (**20**) has found this assignment to be incorrect. During this work the revised 2,2'-bifuranyl skeleton of elatenyne (**47**) was suggested, but this skeleton has 32 possible diastereomers. The most likely diastereomer of elatenyne (**60**) was predicted using computational $^{13}C$ NMR chemical shift calculation in combination with the possible stereochemical outcomes from the proposed biosynthesis.

Elatenyne (proposed structure) Revised skeleton of elatenyne Elatenyne




**20** **47** **60**

Chapter 1 introduces the structural misassignment of natural products and describes the misassignment of elatenyne as well as a related chloro enyne (not shown). The use of computational methods and biosynthetic postulates to aid structure elucidation are also discussed.

Chapter 2 describes the first generation synthesis of cross metathesis coupling partners required for the synthesis of elatenyne (**60**) from D-mannitol.

Chapter 3 describes the completed total synthesis of elatenyne (**60**), along with three derivatives and the (*E*)-isomer of elatenyne (not shown); itself a natural product. A comparison of the synthetic data with the isolation data for the natural products is presented, as well as comparison with the synthetic material of Kim and co-workers whose concurrent biomimetic total synthesis is also presented.

Chapter 4 describes the modular nature of the devised synthetic route to access any diastereomer of elatenyne and its application to related 2,2'-bifuranyl natural products.

## Declaration

Except where indicated to the contrary, either directly or by reference, the work described in this thesis is entirely the original work of the author and does not include any collaborative research.

This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Bryony S. Dyson

December 2011

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I am grateful to Professor Kim for sharing prepublication data and ideas and to Dr Urban for supplying NMR spectra of elatenyne.

Finally, I would like to thank the CRL service staff for their work and the EPSRC for funding.

BSD

## Abbreviation

| | |
|---|---|
| °C | degrees Celsius |
| Å | Ångström |
| Ac | acetyl |
| AD | asymmetric dihydroxylation |
| aq. | aqueous |
| Ar | aryl |
| Bn | benzyl |
| b.p. | boiling point |
| BPO | bromoperoxidase |
| BQ | benzoquinone |
| BRSM | based on recovered starting material |
| Bu | butyl |
| Bz | benzoyl |
| cat. | catalytic amount |
| COSY | correlated spectroscopy |
| CSA | (±)-camphor-10-sulfonic acid |
| CyHex | cyclohexyl |
| D | dimensional |
| dba | dibenzylideneacetone |
| DBB | 4,4'-di-*tert*-butylbiphenyl |
| DCC | *N*,*N'*-dicyclohexylcarbodiimide |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEPT | distortionless enhancement by polarisation transfer |
| DFT | density functional theory |
| $(DHQ)_2PHAL$ | hydroquinone 1,4-phthal-azinediyl diether |
| $(DHQD)_2PHAL$ | hydroquinidine 1,4-phthal-azinediyl diether |
| DIAD | diisopropyl azodicarboxylate |
| DiBAl | diisobutylaluminium hydride |
| DIPT | diisopropyltartrate |
| DMAP | 4-(dimethylamino)pyridine |
| DMDO | dimethyldioxirane |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMM | dimethoxymethane |
| DMP | 2,2-dimethoxypropane |
| DMSO | dimethyl sulfoxide |
| d.r. | diastereomeric ratio |
| EDTA | ethylenediaminetetraacetic acid |
| e.e. | enantiomeric excess |
| *ent* | enantiomer |
| ES | electrospray ionisation |
| Et | ethyl |
| eq. | equivalent(s) |

| | |
|---|---|
| FI | field ionisation |
| fod | 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate |
| GIAO | gauge including atomic orbital |
| h | hour(s) |
| HMDS | hexamethyldisilazane |
| HMQC | heteronuclear multiple-quantum correlation |
| HPLC | high pressure liquid chromatography |
| HSQCAD | heteronuclear single quantum coherence adiabatic |
| Hz | Hertz |
| *i* | *iso* |
| Im | imidazole |
| IPA | propan-2-ol |
| IR | infra-red |
| *J* | coupling constant |
| *L.* | *Laurencia* |
| LDA | Lithium diisopropylamide |
| lit. | literature |
| LUMO | lowest unoccupied molecular orbital |
| M | molar or metal |
| *m* | meta |
| MCMM | Monte Carlo multiple-minimum |
| *m*-CPBA | 3-chloroperbenzoic acid |
| Me | methyl |
| Mes | mesityl (2,4,6-trimethylphenyl) |
| min | minute(s) |
| MM2 | molecular mechanics Allinger force field version 2 |
| mmol | millimole(s) |
| mol | mole(s) |
| m.p. | melting point |
| Ms | methanesulfonyl |
| MS | molecular sieves |
| MTPA | α-methoxy-α-trifluoromethyl-phenylacetic acid |
| *m*/*z* | mass/charge ratio |
| *n* | normal |
| NBS | *N*-bromosuccinimide |
| NMO | *N*-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear Overhauser effect spectroscopy |
| P | protecting group |
| PBB | *para*-bromobenzyl |
| PDC | pyridinium dichromate |
| Ph | phenyl |
| PMB | *para*-methoxybenzyl |
| PMP | *para*-methoxyphenol |
| ppm | parts per million |

| | |
|---|---|
| Pr | propyl |
| *p*-TSA | *para*-toluenesulfonic acid |
| quant. | quantitative |
| R | generic group |
| RCM | ring-closing metathesis |
| ref. | reference |
| $R_f$ | retention factor |
| ROMP | ring-opening metathesis polymerisation |
| RT | room temperature |
| s | second(s) |
| SAD | Sharpless asymmetric dihydroxylation |
| SAE | Sharpless asymmetric epoxidation |
| sat. | saturated |
| sec | second(s) |
| SM | starting material |
| $S_N2$ | bimolecular nucleophilic substitution |
| sp. | species |
| syn. | synthetic |
| TASF | tris(dimethylamino)sulfonium difluorotrimethylsilicate |
| TBAF | tetrabutylammonium fluoride |
| TBAI | tetrabutylammonium iodide |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBHP | *tert*-butyl hydroperoxide |
| TBS | *tert*-butyldimethylsilyl |
| *tert* or *t* | tertiary |
| TES | triethylsilyl |
| Tf | trifluoromethane sulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMEDA | *N*,*N*,*N'*,*N'*-tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Tr | triphenylmethyl |
| Tris | 2,4,6-triisopropylphenylsulfonyl |
| Ts | *para*-toluenesulfonyl |
| UV | ultraviolet |
| wt | by weight |
| w.r.t. | with respect to |

## Contents

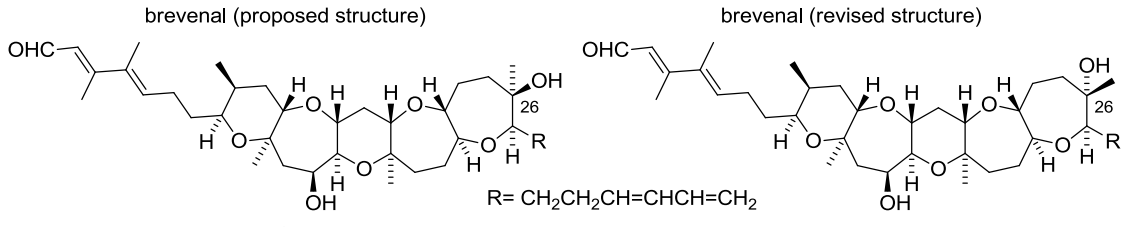
# CHAPTER 1: INTRODUCTION

The purpose of this thesis is to determine the structure of elatenyne and, in doing so, validate the use of computational $^{13}C$ NMR chemical shift calculation using the DFT-GIAO method in conformationally flexible systems.

This chapter will introduce the structural misassignment of natural products and then specifically, the misassignment of the natural products elatenyne and a chloro enyne from *Laurencia majuscula*. The use of computational methods and biosynthetic postulates to aid structure elucidation will also be discussed in relation to uncovering the structure of elatenyne.

## 1.1. Structural Revision of Natural Products by Total Synthesis

The nature of natural product structure elucidation has changed enormously from the 'classical' degradation and derivatisation approach with the introduction of modern spectroscopic techniques such as IR and UV spectroscopy, mass spectrometry and especially NMR spectroscopy.[1] These techniques have allowed the characterisation of milligram quantities of complex natural products to be carried out routinely, often including full stereochemical assignment. There are still, however, many cases in the chemical literature of structures proposed that have been subsequently revised following total synthesis.[2] Many of these corrections are minor, involving the correction of one stereocentre or the configuration of double bonds, for example Fuwa *et al.* completed the total synthesis of the proposed structure of brevenal (**1**) and then their revised structure (**2**) and found that the epimer at C26 was consistent with the natural product data (**Figure 1.1**).[3]




**1** **2**

**Figure 1.1 – The proposed and revised structure of brevenal.**

Sometimes, however, major constitutional revisions are necessary, for example Nicolaou and Li uncovered the true structure of α- and β-diversonolic esters after total syntheses of the proposed structures (**3** and **5**) and their revised structures (**4** and **6**) confirmed the originally assigned structural connectivity was incorrect (**Figure 1.2**).[4]

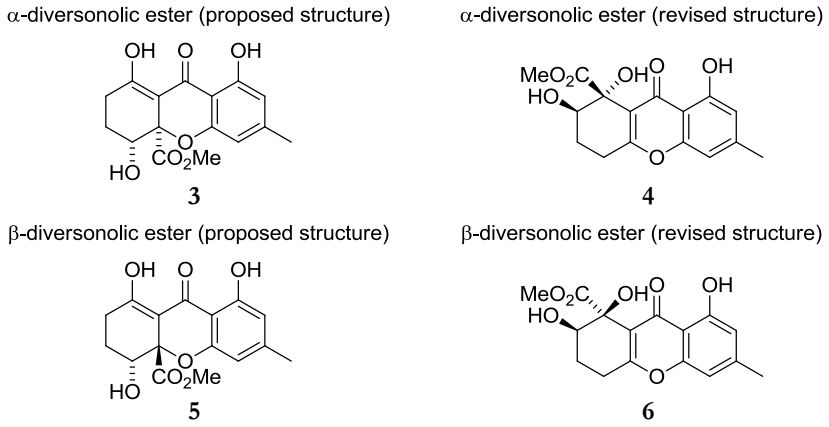



**Figure 1.2 – The proposed and revised structures of α- and β-diversonolic esters.**

Baran and co-workers found that a radical structure revision was required for the sarcodonin, sarcoviolin and hydnellin natural product family.[5] Representative examples (**7** to **10**) of the natural product family are shown in **Figure 1.3**.

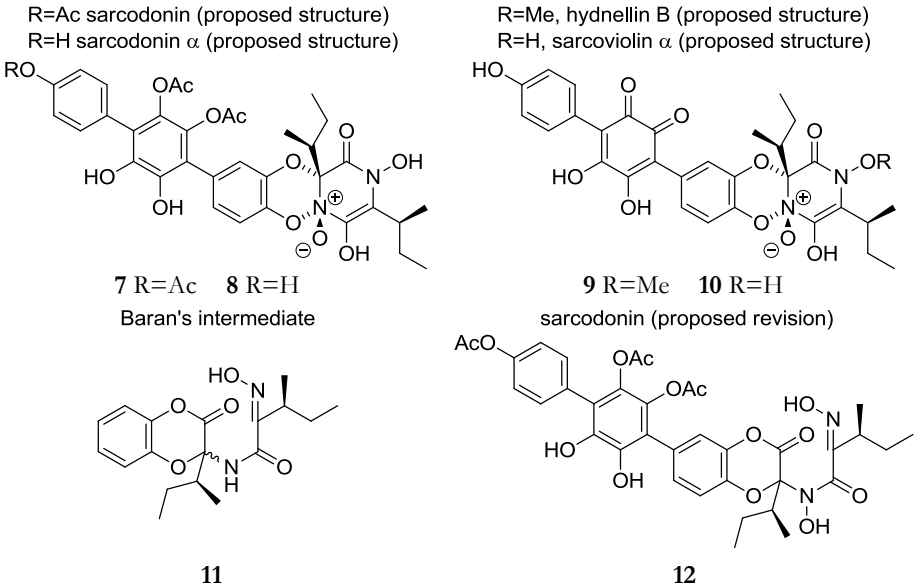



**Figure 1.3 – Baran's synthetic intermediate 11 and proposed structural revision demonstrated for sarcodonin.**

Three independent research groups assigned members of this family to have the unusual benzodioxazine core and an *N*,*N*-dioxide ring junction. During their synthetic efforts towards this

class of natural products Baran and co-workers synthesised intermediate **11** (**Figure 1.3**). Comparison of the $^{1}H$ and $^{13}C$ NMR spectra of intermediate **11** and natural product data for sarcodonin α revealed significant similarities. This observation, along with further considerations, led to the proposal of the benzodioxane aminal core for the natural product family, demonstrated in the proposed revised structure for sarcodonin (**12**, **Figure 1.3**).

## 1.2. Halogenated Marine Natural Products from the *Laurencia* Genus

The marine genus *Laurencia* is arguably the most studied of all algal genera. Between 1953 and Erickson's review in 1983[6] over 250 natural products, including numerous new structural types, were isolated from *Laurencia* algae and marine organisms which fed on *Laurencia* species. Many have been isolated since then and more are still being isolated today, for example marilzabicycloallene A (**13**) isolated in 2011 (**Figure 1.4**).[7] *Laurencia* species produce sesquiterpenoids (e.g. **14**[8]), diterpenoids (e.g. **15**[9]) and triterpenoids (e.g. **16**[10]), as well as a host of nonterpenoid $C_{15}$ acetogenins (e.g. **17**[11] and **18**[12]) and some miscellaneous substances (e.g. **19**[13]).

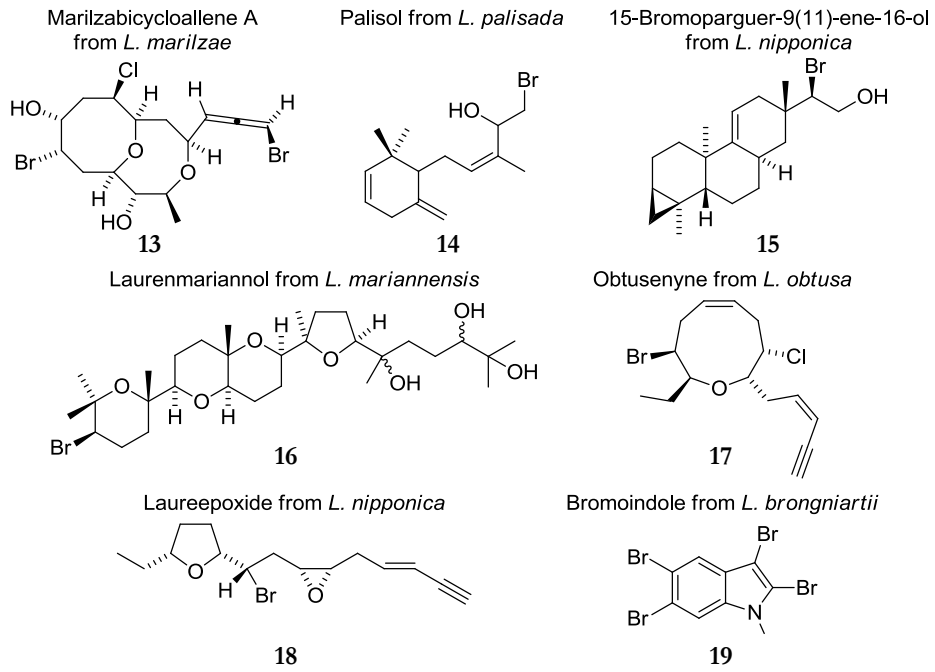
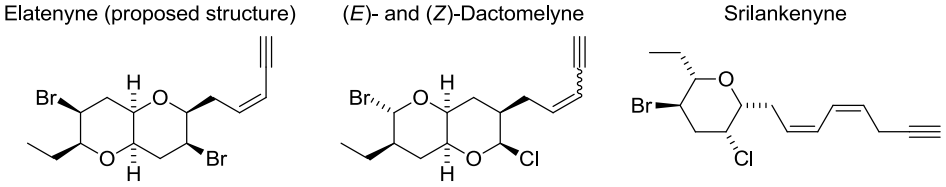



**Figure 1.4 – Examples of halogenated marine natural products from *Laurencia* species.**

## 1.3. Structural Revision of Elatenyne and *Laurencia majuscula* Enyne

### *1.3.1. Original Assignment of Elatenyne and* Laurencia majuscula *Enyne*

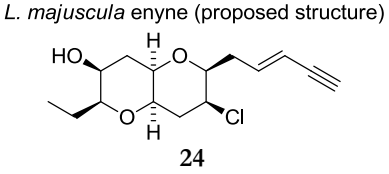
Elatenyne is a $C_{15}$ acetogenin isolated by Hall and Reiss[I] in 1986 from samples of *Laurencia elata*.[14] Elatenyne was assigned a pyrano[3,2-*b*]pyran structure (**20**) on the basis of extensive $^{1}H$ and $^{13}C$ NMR spectroscopic analysis and comparison with other similar known natural products, namely (*E*)- and (*Z*)-dactomelyne[15] (**21** and **22**) and srilankenyne[16] (**23**, **Figure 1.5**). The absolute configuration of (*E*)-dactomelyne (**21**) had been proven by X-ray crystallography.[15]




**20** **21** (*E*)- **22** (*Z*)- **23**

**Figure 1.5 – The proposed structure of elatenyne and the structures of the dactomelynes and srilankenyne.**

In 1993 Wright *et al.* isolated a chloro enyne from samples of *Laurencia majuscula*, which was assigned structure **24** (**Figure 1.6**).[17] The pyrano[3,2-*b*]pyran structure was assigned on the basis of $^{1}H$ and $^{13}C$ NMR spectroscopic analysis and comparison with elatenyne (**20**) and (*E*)-dactomelyne (**21**). Enyne **24** was assigned the same relative stereochemistry as elatenyne (**20**).




**24**

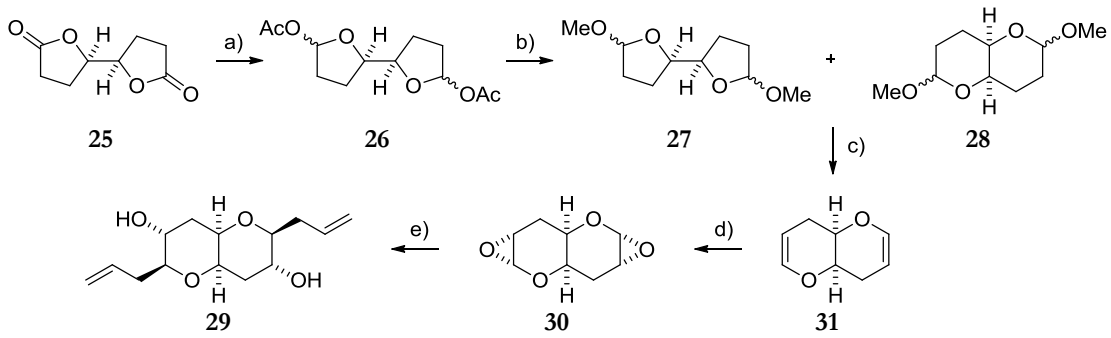
**Figure 1.6 – The proposed structure of the *L. majuscula* chloro enyne.**

### *1.3.2. Total Synthesis of the Proposed Structures*

Elatenyne (**20**) and *L. majuscula* enyne (**24**) were attractive targets for total synthesis due to their unknown biological activity, embedded $C_2$ symmetry and densely functionalised pyrano[3,2-*b*]pyran cores. Previous work in the Burton group resulted in the total synthesis of the proposed structures

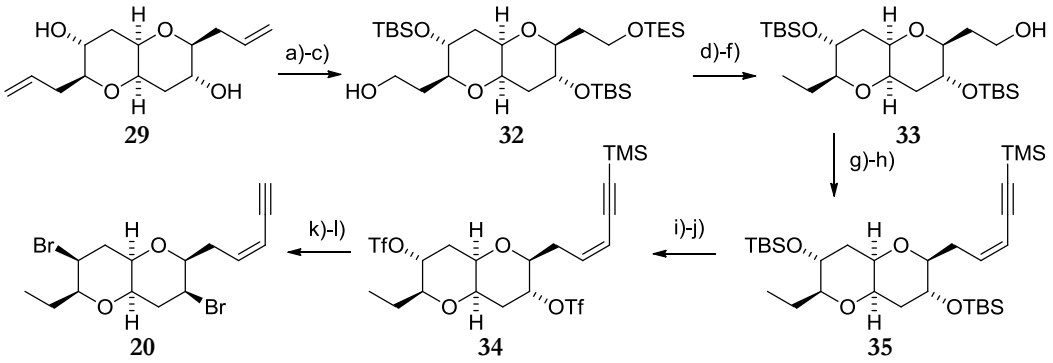
[I] Elatenyne has subsequently been isolated by both Wang and co-workers[134] and Dias and Urban[135]. These isolations will be discussed in **Chapter 3** (**Section 3.7.1**).

**20** and **24**.[18] The successful approach involved the synthesis of $C_2$-symmetric diol **29** from bislactone **25** as shown in **Scheme 1.1**. Bislactone **25** was reduced with DiBAl and the resulting aluminium alkoxides were trapped with acetic anhydride.[19] Treatment of the anomeric acetates **26** with acidic methanol gave a mixture of methyl acetals **27** and **28**, which were converted into pyrano[3,2-*b*]pyran **31** using iodotrimethylsilane in acetonitrile.[20] The bis-epoxide **30** was formed with DMDO and X-ray analysis confirmed the relative configuration at this stage. Bis-epoxide **30** was then opened with diallylmagnesium to provide $C_2$-symmetric diol **29** (**Scheme 1.1**).



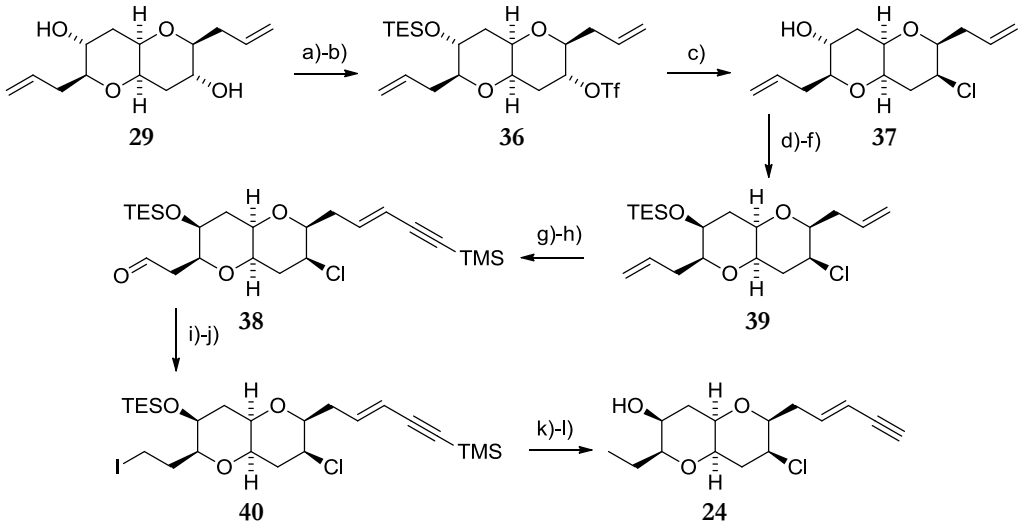

**Scheme 1.1 – Reagents and conditions: a) DiBAl, DCM, -78 °C, then $Ac_2O$, pyridine, DMAP, DCM, -78 °C, 14 h, then -78 to -20 °C, 83%; b) MeOH, HCl, 90%; c) $Me_3SiI$, MeCN, RT, then $(Me_3Si)_2NH$; d) DMDO, $NaHCO_3$, DCM; e) $(CH_2=CHCH_2)_2Mg$, $Et_2O$, THF -78 °C to RT, 57% (3 steps).**

Diol **29** was protected and the side chains differentiated to give desymmetrised alcohol **32** (**Scheme 1.2**). Alcohol **32** was converted into the ethyl side chain *via* reduction of the corresponding tosylate. The enyne side chain was installed *via* oxidation followed by a (*Z*)-selective Yamamoto-Peterson reaction (**33→35**).[21] Finally, deprotection, triflation and bromination followed by TBAF deprotection yielded the proposed structure of elatenyne (**20**) (**Scheme 1.2**).




**Scheme 1.2 - Reagents and conditions: a) TBSOTf, $Et_3N$, DCM, 99%; b) $O_3/O_2$, DCM, MeOH, -78 °C, then $PPh_3$, -78 °C, 2 h, then $NaBH_4$, -78 °C to RT, 2 h, 82%; c) 1 eq. TESCl, $Et_3N$, DCM, then recycle, 70%; d) TsCl, DMAP, $Et_3N$, DCM, 93%; e) $LiBHEt_3$, $Et_2O$, RT, 91%; f) $K_2CO_3$, MeOH, 98%; g) $^nPr_4NRuO_4$, NMO, DCM, 4 Å MS, 95%; h) $Me_3SiC{\equiv}CCH_2SiMe_2{}^tBu$, $^t$BuLi, $Ti(O^iPr)_4$, THF, -78 °C, add aldehyde, -78 °C to RT, 0.5 h, then $(Me_3Si)_2NK$, 75%; i) TsOH, MeOH, 22 h, 75%; j) $Tf_2O$, pyridine, DCM; k) $^nBu_4NBr$ toluene, reflux, 2 h, 14% 2 steps; l) TBAF, THF, -5 °C, 98%.**

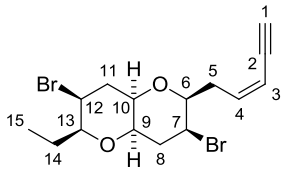
In the synthesis of *L. majuscula* enyne (**24**) diol **29** was desymmetrised and a chloride installed *via* displacement of the corresponding triflate to give **37**. Inversion of the other alcohol by an oxidation and reduction sequence, followed by protection gave **39** (**Scheme 1.3**). The enyne side chain was installed *via* addition of one equivalent of a pre-formed ylide to the bis-aldehyde derived from **39**. Aldehyde **38** was reduced and converted to the ethyl side chain *via* iodide **40**. TBAF deprotection of the enyne yielded the proposed structure of *L. majuscula* enyne **24** (**Scheme 1.3**).




**Scheme 1.3 – Reagents and conditions: a) TESCl, imidazole, DMF, 64% after 1 recycle; b) $Tf_2O$, pyridine, DCM; c) $^nBu_4NCl$, toluene, reflux, 2 h, then Amberlite™ resin IR-120, MeOH, 45% 2 steps; d) $^nPr_4NRuO_4$, NMO, DCM, 4 Å MS, 65%; e) $NaBH_4$, MeOH, 87%; f) $Et_3SiOTf$, $Et_3N$, DCM, 99%; g) $O_3/O_2$, DCM, -78 °C, then $PPh_3$, -78 °C, 0.5 h, then RT, 8 h, 95%; h) $Me_3SiC{\equiv}CCH_2PPh_3Br$, $^n$BuLi, THF, add aldehyde, -78 °C to 0 °C, 45% (60% BRSM) >7:1 *E*:*Z*; i) $NaBH_4$, MeOH, quant.; j) $I_2$, $PPh_3$, imidazole, $Et_2O$, MeCN, RT, 72%; k) Zn, AcOH, MeOH, $Et_2O$, RT, then HCl, 96%; l) TBAF, THF, RT, 92%.**

### *1.3.3. Data Comparison*

With the spectroscopic data in hand from the synthesised proposed structures for elatenyne (**20**) and *L. majuscula* enyne (**24**), a comparison could be made with the data reported in the literature for the natural products.[14, 17] It can be seen in the $^{1}$H and $^{13}$C NMR data tables below that there are significant discrepancies between the data for the natural product and synthetic elatenyne **20** (**Figure 1.7**, **Table 1.1**, **Table 1.2**).




**20**

**Figure 1.7 – The proposed structure of elatenyne.**

| Position | $\delta_H$ synthetic 20 ($CDCl_3$)[II] | $\delta_H$ synthetic 20 ($C_6D_6$) | $\delta_H$ literature ($C_6D_6$) |
|---|---|---|---|
| 1 | 3.10 | 2.08–2.88[c] | 2.81 |
| 2 | - | - | - |
| 3 | 5.55 | 5.47 | 5.37 |
| 4 | 6.13 | 6.04 | 5.74 |
| 5 | 2.80, 2.62 | 3.08, 2.78–2.88[c] | 2.36–2.48 |
| 6 | 3.27 | 2.78–2.88[c] | 4.06 |
| 7 | 4.03 | 3.58[d] | 3.68 |
| 8 | 2.61, 2.37[a] | 2.38, 1.54–1.67[e] | 1.98 |
| 9 | 3.54[b] | 2.08–2.88[c] | 3.84 |
| 10 | 3.52[b] | 2.08–2.88[c] | 3.84 |
| 11 | 2.61, 2.37[a] | 2.38, 1.54–1.67[e] | 1.98 |
| 12 | 4.05 | 3.56[d] | 3.55 |
| 13 | 3.04 | 2.52 | 3.92 |
| 14 | 1.79, 1.61 | 1.95, 1.54–1.67[e] | 1.22, 1.39 |
| 15 | 0.91 | 0.88 | 0.82 |

**Table 1.1 – Comparison of the $^{1}$H NMR for the synthetic pyranopyran 20 and the literature data for elatenyne. [a,b,d,f]assignments are interchangeable between pairs of signals, [c]part of 5H multiplet, [e]part of 3H multiplet.**

[II] A comparison has not been made with the literature $^{1}$H NMR spectra in $CDCl_3$ since we believe there are significant errors in these data (as discussed in **Chapter 3**, **Section 3.7.1**).

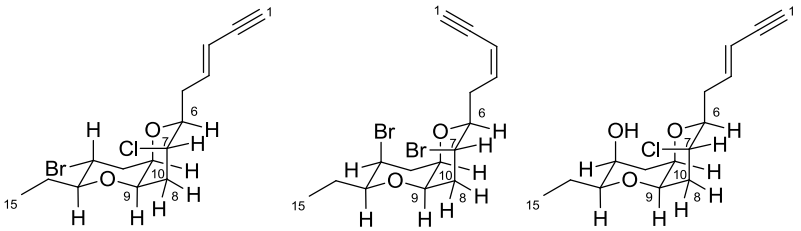
| Position | $\delta_C$ synthetic 20 ($CDCl_3$)/ppm | $\delta_C$ synthetic 20 ($C_6D_6$)/pmm | $\delta_C$ literature ($C_6D_6$)/pmm | $\Delta\delta_{(syn.-lit.)}$ /ppm |
|---|---|---|---|---|
| 1 | 82.5 | 82.7 | 83.0 | –0.3 |
| 2 | 80.5 | 80.4 | 80.0 | +0.4 |
| 3 | 110.7 | 110.6 | 111.2 | –0.6 |
| 4 | 141.2 | 141.3 | 140.1 | +1.2 |
| 5 | 36.6 | 36.7 | 34.7 | +2.0 |
| 6 | 78.9 | 78.7 | 86.4 | –7.7 |
| 7[III] | 46.9[a] | 46.4 | 49.2 | –2.8 |
| 8 | 37.8[b] | 37.4[d] | 39.0 | –1.6 |
| 9 | 71.8[c] | 71.4[e] | 80.0 | –8.6 |
| 10 | 71.6[c] | 71.2[e] | 79.5 | –8.3 |
| 11 | 37.7[b] | 37.3[d] | 39.3 | –2.0 |
| 12[III] | 46.8[a] | 46.4 | 48.9 | –2.5 |
| 13 | 82.1 | 80.9 | 88.6 | –7.7 |
| 14 | 28.5 | 28.7 | 26.8 | +1.9 |
| 15 | 9.8 | 9.7 | 10.2 | –0.5 |

**Table 1.2 – Comparison of the $^{13}C$ NMR for the synthetic pyranopyran 20 and the literature data for elatenyne. [a,b,c,d,e]assignments are interchangeable between pairs of signals.**

Large differences are highlighted in red and of particular note are the major differences in the $^{13}C$ NMR chemical shifts of all four carbons adjacent to oxygen (carbons 6, 9, 10 and 13, **Table 1.2**).

There were also significant differences observed between the coupling constants in the $^{1}H$ NMR spectra. A comparison of the $^{1}H,^{1}H$ NMR coupling constants of the ring protons for (*E*)-dactomelyne (**21**), the synthesised proposed structures of elatenyne (**20**) and *L. majuscula* enyne (**24**, **Figure 1.8**) and the natural product data is shown in **Table 1.3**. It can be seen that the coupling constants for the synthetic samples (**20** and **24**) match well with (*E*)-dactomelyne (**21**) due to their pyrano[3,2-*b*]pyran structures. The coupling constants reported for the isolated natural products, however, differ greatly from the synthetic samples as well as (*E*)-dactomelyne (**21**). This suggested, along with the mismatches in the chemical shifts in both $^{1}H$ and $^{13}C$ NMRs, that the natural products had been misassigned and were not pyrano[3,2-*b*]pyrans.

[III] The assignment of carbons 7 and 12 have since been reversed during the isolation and analysis by Dias and Urban.[135]



**21** **20** **24**

**Figure 1.8 – The structure of (*E*)-dactomelyne and the proposed structures of elatenyne and *L. majuscula* enyne.**

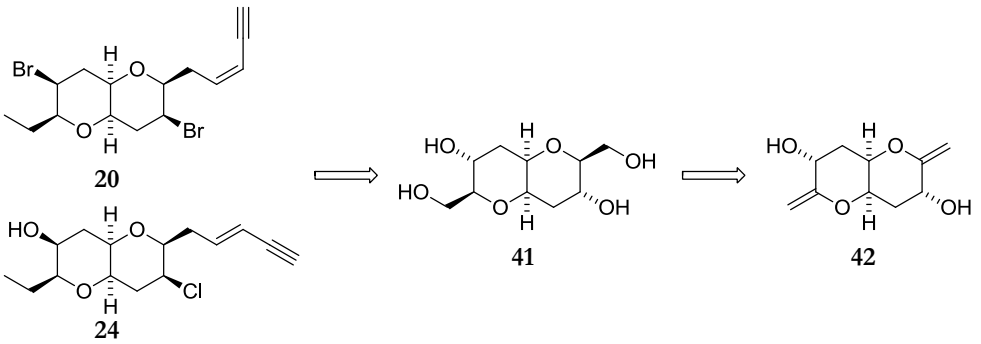
| Coupling Constant /Hz | (*E*)-Dactomelyne (**21**) | Synthetic **20** | Isolated elatenyne | Synthetic **24** | Isolated *L. majuscula* enyne |
|---|---|---|---|---|---|
| $J_{6,7}$ | 1.9 | 1.8 | 6.6 | 1.9 | 5.4 |
| $J_{7,8}$ | 1.9, 4.5 | 1.8, 4.4 | 7.1, 5.1 | 1.9, 4.3 | 7.8, 4.2 |
| $J_{8,9}$ | 1.5, 1.5 | 1.8, 4.4 | - | 1.9, 4.3 | 6.8, 9.1 |
| $J_{9,10}$ | 1.5 | 1.8 | 6.4 | - | 2.6 |

**Table 1.3 – Comparison of the $^{1}$H,$^{1}$H NMR coupling constants for (*E*)-dactomelyne, the synthetic pyranpyrans 20 and 24 and the natural product data for elatenyne and *L. majuscula* enyne.**

### *1.3.4. Structural Revision*

#### 1.3.4.1. $^{13}$C NMR Chemical Shift Trend

With the originally assigned structures for elatenyne (**20**) and *L. majuscula* enyne (**24**) in doubt, efforts were made to elucidate the true structures. The route to elatenyne (**20**) and *L. majuscula* enyne (**24**) shown previously (**Scheme 1.1** to **Scheme 1.3**, **Section 1.3.2**) was achieved after numerous attempted syntheses of bis-*exo*-cyclic enol ether **42**, which was a proposed intermediate in the initial retrosynthetic analysis (**Scheme 1.4**).[18b] In this analysis it was postulated that tetrol **41** would be accessible *via* intramolecular hydrosilation[22] or hydroboration[23] of bis-*exo*-cyclic enol ether **42**.



**20** **41** **42** **24**

**Scheme 1.4 – Initial retrosynthesis of the proposed structures of elatenyne and *L. majuscula* enyne.**

During these attempted syntheses a large number of pyrano[3,2-*b*]pyrans and 2,2'-bifuranyls were made and a trend was observed in the $^{13}C$ NMR chemical shifts of the central oxygen-bearing carbons. For the pyrano[3,2-*b*]pyrans the chemical shift was less than 76 ppm and for the 2,2'-bifuranyls the chemical shift was greater than 76 ppm (**Figure 1.9**). Over 98% of the 74 pyrano[3,2-*b*]pyrans and 27 2,2'-bifuranyl compounds synthesised in this work matched with the trend[18a] and the trend is particularly apparent with the anomeric sulfones (**43** to **46**, **Figure 1.9**).

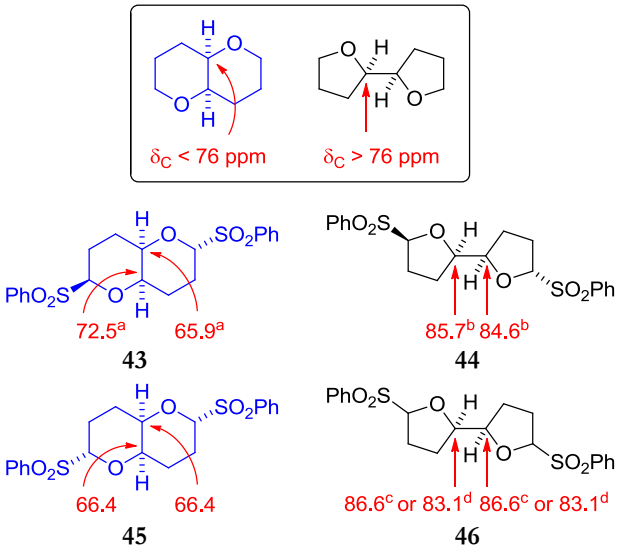



**Figure 1.9 – Observed $^{13}C$ NMR chemical shift trend. [a,b]Assignments could be reversed, [c,d]$C_2$-symmetric diastereomers.**

As can be seen in **Table 1.2** (**Section 1.3.3**), the central oxygen-bearing carbons in the natural product elatenyne lie at 80.0 and 79.5 ppm. The corresponding carbons in the synthetic data for the proposed structure of elatenyne (**20**) lie at 71.2 and 71.4 ppm. The synthetic data were consistent with the trend since it was a pyrano[3,2-*b*]pyran structure, but the values for the natural product suggested that elatenyne was in fact a 2,2'-bifuranyl structure (**47**, **Figure 1.10**).

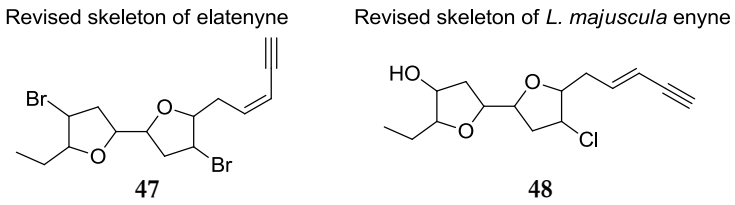



**Figure 1.10 – Revised skeletons of elatenyne and *L. majuscula* enyne.**

The same inconsistencies in data comparison between the natural product and the synthetic proposed structure were observed for *L. majuscula* enyne (**24**). In particular, the central oxygen-bearing carbons in the natural product enyne lie at 77.9 and 79.2 ppm. The corresponding carbons in the synthetic data for the proposed structure of *L. majuscula* enyne (**24**) lie at 70.5 and 73.9 ppm.[18] The synthetic data were again consistent with the trend since it is a pyrano[3,2-*b*]pyran structure, but the values for the natural product again suggested a 2,2'-bifuranyl structure (**48**, **Figure 1.10**).

In 1986, when elatenyne was isolated, there were no examples in the literature of natural products isolated from a *Laurencia* species with a 2,2'-bifuranyl skeleton. This changed in 1989 when Erickson and co-workers extracted a bromo enyne, assigned as 2,2'-bifuranyl **49**, from a collection of *Laurencia majuscula* off the coast of Hawaii (**Figure 1.11**).[24] The skeleton of Erickson's enyne **49** was assigned on the basis of NMR spectroscopy, although it is not stated why the pyrano[3,2-*b*]pyran skeleton was not considered, despite the 2,2'-bifuranyl and pyrano[3,2-*b*]pyran structures having the same carbon and hydrogen connectivity. The $^{13}C$ NMR chemical shifts match the observed trend detailed previously for 2,2'-bifuranyls, with the central oxygen bearing carbons in the natural product lying at 79.4 and 79.9 ppm.

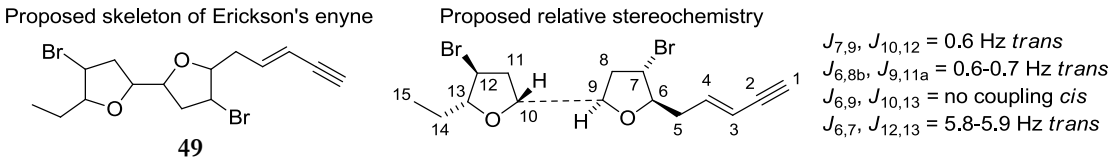


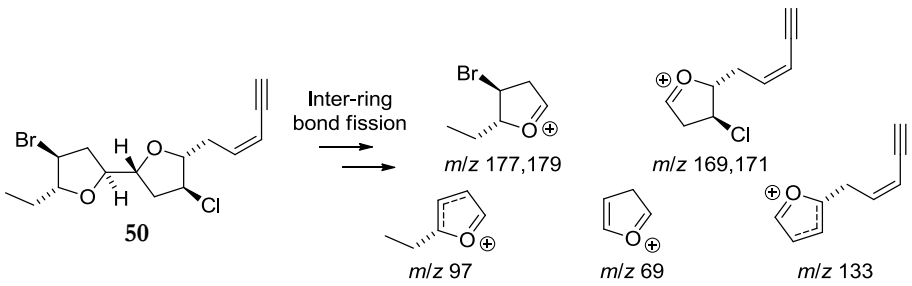

**Figure 1.11 – Proposed skeleton and relative stereochemistry for Erickson's enyne.**

Five-membered rings are conformationally mobile and their flexibility often makes assignment of stereochemistry difficult from NMR data alone. It is interesting therefore that the relative stereochemistry around the two rings of enyne **49** was assigned by analysis of the $^{1}H$ NMR coupling constants which are shown in **Figure 1.11**. Gagnaire and Vottero have shown, in a 2,5-disubstituted THF, that the values of $^{4}J_{HH}$*(trans)* are generally larger than those of $^{4}J_{HH}$*(cis)*, although both have a small magnitude (<1 Hz).[25] On the basis of this work, Erickson assigned the

stereochemistry in the 2,3,5-trisubstituted THFs of enyne **49**, but as this was the only method of stereochemical assignment the partial relative configuration may not be as published. Erickson stated that the stereochemical relationship between the two rings could not be unambiguously determined since the coupling constant ($J_{9,10}$ = 7.0 Hz) is consistent with either inter-ring diastereoisomer.[24]

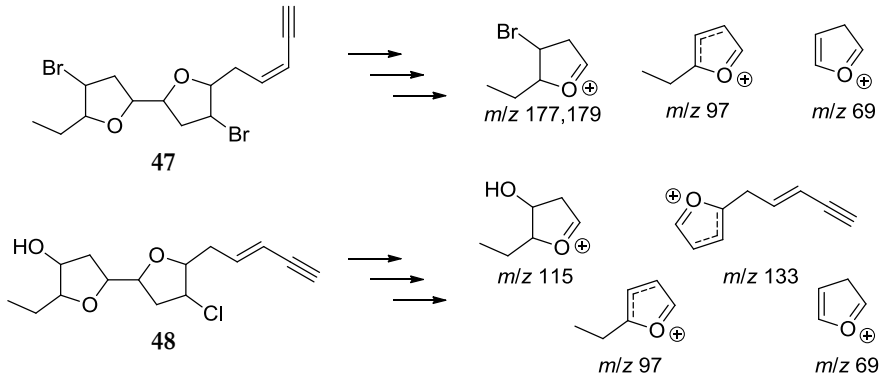
### 1.3.4.2. Mass Spectrometry Analysis

In 1991 Kikuchi *et al.* isolated notoryne (**50**) from the *Laurencia nipponica* alga (**Scheme 1.5**).[26] Notoryne (**50**) was assigned a 2,2'-bifuranyl rather than a pyrano[3,2-*b*]pyran structure based on extensive chemical degradation, synthetic correlation studies and mass spectral fragmentation patterns. Significant peaks at *m*/*z* 177, 179, 169, 171, 97, 69 and 133 were assigned to furan fragments as shown (**Scheme 1.5**).




**Scheme 1.5 – Mass spectral fragmentation patterns of notoryne.**

The spectroscopic data published for elatenyne shows peaks at *m*/*z* 177, 179, 97 and 69 in the mass spectrum, which, in an analogous way to notoryne (**50**), would be consistent with the revised 2,2'-bifuranyl skeleton (**47**, **Scheme 1.6**). The natural product data published for *L. majuscula* enyne shows peaks at *m*/*z* 133, 115, 97 and 69 in the mass spectrum, which again would be consistent with the revised 2,2'-bifuranyl skeleton (**48**, **Scheme 1.6**).




**Scheme 1.6 - Mass spectral fragmentation patterns of elatenyne and *L. majuscula* chloro enyne.**

## 1.4. Computational Prediction of the Stereochemistry of Elatenyne

### *1.4.1. Background*

The proposed 2,2'-bifuranyl skeletons of elatenyne (**47**) and *L. majuscula* enyne (**48**) have six stereocentres and hence there are 32 possible diastereoisomers for each of the natural products. As previously stated, five-membered rings are conformationally mobile and their flexibility often makes assignment of stereochemistry difficult from NMR data alone. 2,2'-Bifuranyl structures are very challenging to fully assign as there is free rotation about the central bond and each of the THF rings can adopt many envelope and twist conformations.[27] Synthesising all of the 32 possible diastereomers of elatenyne (**47**) and *L. majuscula* enyne (**48**) in order to determine the structure of the natural products would be some undertaking and very time consuming, although this approach to natural product assignment has been followed.[28] It would be much more efficient to highlight some likely diastereomers and focus on their total syntheses.

In the last decade there have been substantial developments in the area of quantum mechanical calculation of NMR parameters and their application to structure elucidation.[29] The calculation of $^{1}$H NMR coupling constants, chemical shifts and/or nOe intensities is becoming a powerful tool to aid the interpretation of experimental data. The calculation of $^{13}$C NMR chemical shifts using the

GIAO method[IV] was pioneered by Bifulco and co-workers.[30] $^{13}C$ NMR shifts are particularly suited to this type of prediction since they are comprised of sharp peaks spread over a wide chemical shift range and are highly sensitive to the steric and electronic environments within the molecule, but are relatively insensitive to shifts caused by changes in solvents *etc.*

The important role that this technique has acquired in the field of structure elucidation and structure revision can be exemplified with the natural product hexacyclinol. Hexacyclinol was isolated in 2002 from the basidiomycete *Panus rudis* by Schlegel *et al.* and was assigned structure **51** on the basis of NMR analysis (**Figure 1.12**).[31] La Clair reported a total synthesis of the complex structure **51** in 2006, which seemed to corroborate the assignment.[32] The proposed structure **51** was however disputed by Rychonovsky in the same year.[33] Rychonovsky noted that another natural product, panepophenanthrin (**53**, **Figure 1.12**), had also been isolated in 2002 from a different strain of *Panus rudis* and its structural assignment confirmed by X-ray crystallography.[34] Panepophenanthrin (**53**) has almost the same set of functional groups as the proposed structure of hexacyclinol (**51**) and has a similar molecular weight, but a very different ring system. Rychonovsky proposed a new structure for hexacyclinol (**52**, **Figure 1.12**), which had a similar skeleton to panepophenanthrin (**53**). He suggested hexacyclinol (**52**) could possibly be an isolation artefact produced by column chromatography of panepophenanthrin (**53**) with methanol.

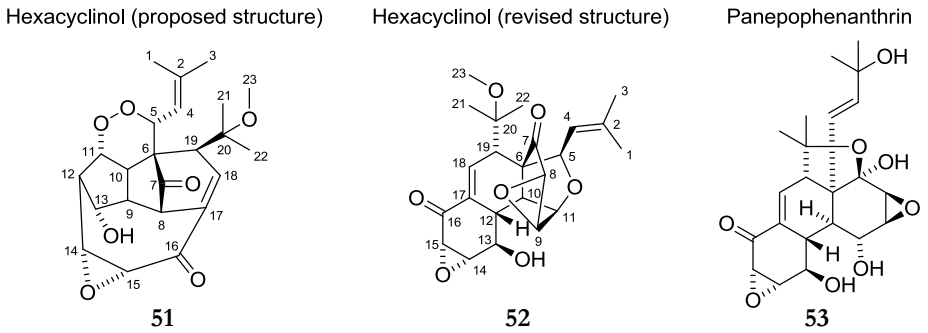



**Figure 1.12 – Proposed and revised structures of hexacyclinol and the structure of panepophenanthrin.**

[IV] GIAO stands for Gauge-Including Atomic Orbital and this method refers to the specific approach used to calculate the nuclear magnetic shielding tensors.

At the time Bifulco's approach to $^{13}C$ NMR shift prediction had not been validated with highly oxygenated compounds and did not perform well with unsaturated structures. As a result Rychonovsky developed a modified method, which performed well, with small differences between calculated and actual $^{13}C$ NMR chemical shifts, when tested on three highly oxygenated and unsaturated diterpene natural products. The method was therefore applied to the two proposed structures of hexacyclinol (**51** and **52**). **Figure 1.13** shows the parts per million (ppm) difference between the calculated and experimental $^{13}C$ NMR chemical shifts for the originally proposed structure **51** and the natural product. The ppm difference between the calculated and experimental $^{13}C$ NMR chemical shifts for two conformations of the revised structure **52** and the natural product are shown in **Figure 1.14**.

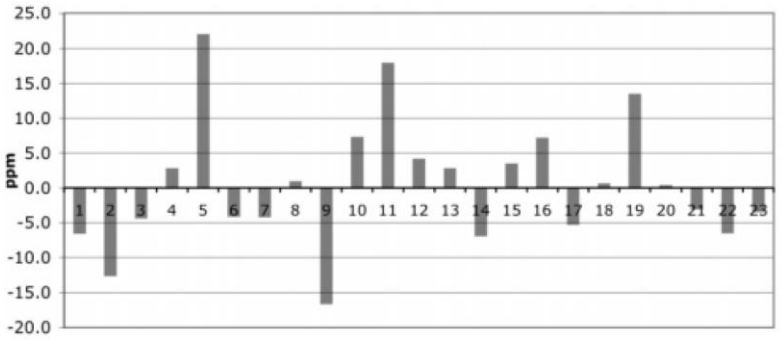



**Figure 1.13 – Reprinted with permission from 'Predicting NMR Spectra by Computational Methods: Structure Revision of Hexacyclinol, Scott D. Rychnovsky, *Org. Lett.*, 2006, *8*, 2895-2898'. Copyright 2006, American Chemical Society.[33] The plotted ppm difference between calculated and experimental $^{13}C$ NMR shifts for structure 51 and hexacyclinol. The average $|\Delta\delta|$ was 6.8 ppm and the maximum was 22.0 ppm.**

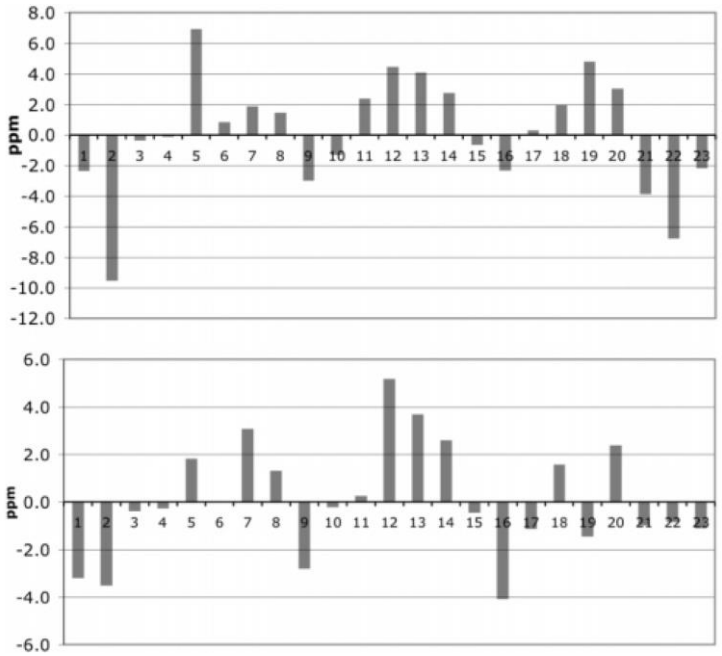



**Figure 1.14 – Reprinted with permission from 'Predicting NMR Spectra by Computational Methods: Structure Revision of Hexacyclinol, Scott D. Rychnovsky, *Org. Lett.*, 2006, *8*, 2895-2898'. Copyright 2006, American Chemical Society.[33] The plotted ppm difference between calculated and experimental $^{13}$C NMR shifts for two conformations of structure 52 and hexacyclinol. The lowest energy conformation (top) shows a H4-H5 dihedral angle of 65°, incompatible with the observed 10.1 Hz coupling constant. The conformation (bottom) shows a plausible 159° dihedral angle between H4 and H5. The average $|\Delta\delta|$ was 1.8 ppm and the maximum was 5.8 ppm for the second conformation.**

It can be seen from **Figure 1.13** and **Figure 1.14** that the correlation between calculated and experimental $^{13}$C NMR chemical shifts is much better for the revised structure **52**. The average $|\Delta\delta|$ was only 1.8 ppm compared with 6.8 ppm for the originally proposed structure **51** and the maximum difference was also significantly less (5.8 ppm compared to 22.0 ppm). This computational analysis therefore suggested that the revised structure of hexacyclinol **52** was more likely than structure **51** and this was confirmed by Porco *et al.*'s total synthesis and X-ray structure of compound **52**, which displayed identical NMR spectra to the natural product.[35] La Clair then postulated that he and Porco may have made two different molecules that happen to have very similar NMR spectra,[36] which led to further computational analysis by Saielli and Bagno in 2009.[37] An in-depth DFT computational investigation of the $^{1}$H and $^{13}$C NMR spectra, including proton couplings, for both of the proposed structures of hexacyclinol (**51** and **52**) was performed. The conclusion reached was that, despite the similarity of functional groups present in structures **51** and **52**, the two calculated spectra differ sufficiently to guarantee their distinction. Saielli and Bagno's

calculated spectra also showed a better correlation between structure **52** and the natural product and hence confirmed Rychnovsky's structural revision for hexacyclinol.

Many other research groups have also been able to use the calculation of GIAO $^{13}C$ NMR chemical shifts to aid structural assignment and reassignment, for example in the assignment of aplidinones A-C by Aiello *et al.*[38] and neofusapyrones by Honma *et al.*[39] and in the reassignment of obstusallenes V, VI and VII by Braddock and Rzepa[40] and in Nicoloau's investigation of the stereochemistry of maitotoxin (structures not shown).[41] In a recent publication Saielli *et al.* reflected in retrospect that the use of DFT-NMR predictions would have greatly aided and simplified the structural revision of vannusal B (**55**, **Figure 1.15**).[42] The originally proposed structure of vannusal B (**54**) was synthesised and the data were found not to match that of the natural product.[43] During their endeavours to solve the structure of this natural product by total synthesis, six further diastereoisomers were made before obtaining the correct, eighth diastereomer **55**.[44] The availability of all the experimental data for eight diastereoisomers of vannusal B allowed for direct comparison with $^{13}C$ NMR shifts and $^{1}H$ coupling constants predicted from DFT calculations. They were able to show that all the stereoisomers had subtle differences in their $^{13}C$ NMR spectra, which could have been exploited for their structural assignment and hence, would have allowed synthetic efforts to be concentrated on the most likely structures had the DFT-NMR predictions been carried out first.

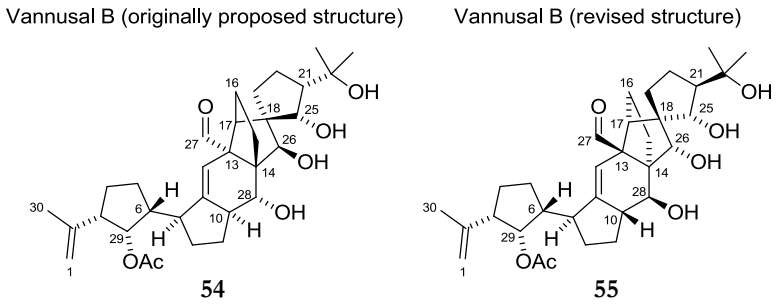



**Figure 1.15 – The proposed and revised structures of vannusal B.**

### *1.4.2. Computational Prediction for Elatenyne*

The studies described so far have been with molecules that are relatively conformationally rigid, which means that generally the only important conformer to consider when calculating NMR parameters is the global minimum. As previously stated, 2,2'-bifuranyls are extremely conformationally mobile and with flexible molecules computational prediction is more complex and there have been few investigations on these systems. Bifulco and co-workers have calculated the NMR chemical shift as a Boltzmann-weighted average of chemical shifts obtained for all low energy conformers.[30a] They were able to demonstrate the ability of this approach to predict stereochemistry by applying the method to four possible diastereomers of a model system (**56** to **59**, **Figure 1.16**). The Boltzmann weighting factors for this system suggested that over 90% of the conformational freedom was described by two or three lowest energy conformations, which means this was a limited model and the method has not been proven for use with very flexible systems.

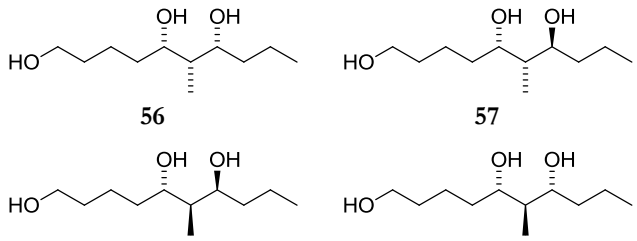



**Figure 1.16 – The four possibile diastereomers of Bifulco and co-workers' model system.**

Smith *et al.* completed computational analysis in order to predict the most likely stereoisomers of the 2,2'-bifuranyl skeleton of elatenyne (**47**, **Figure 1.10**).[45] In this study they subjected all of the 32 possible diastereomers of elatenyne (**47**) to conformational analysis (MCMM method[46] with MM2 force field[47]). The low energy conformers identified were further optimised by DFT calculations (B3LYP method[48]) and subjected to Boltzmann averaging over accessible conformers. The GIAO method was then used to calculate $^{13}C$ NMR chemical shifts for all 32 diastereomers, which were compared with the reported data for the natural product. **Figure 1.17** shows the mean and maximum values of $|\Delta\delta|$ for all 32 diastereomers as well as the originally proposed pyrano[3,2-*b*]pyran structure for elatenyne (**20**). $|\Delta\delta|$ is the modulus of the difference between the

natural product data and the computational data for the $^{13}C$ NMR chemical shifts of selected carbons in elatenyne. Carbons C2 (quaternary enyne carbon), C7 and C12 (carbons attached to bromide) were excluded from all stages of the analysis due to the large errors in the computed chemical shifts.

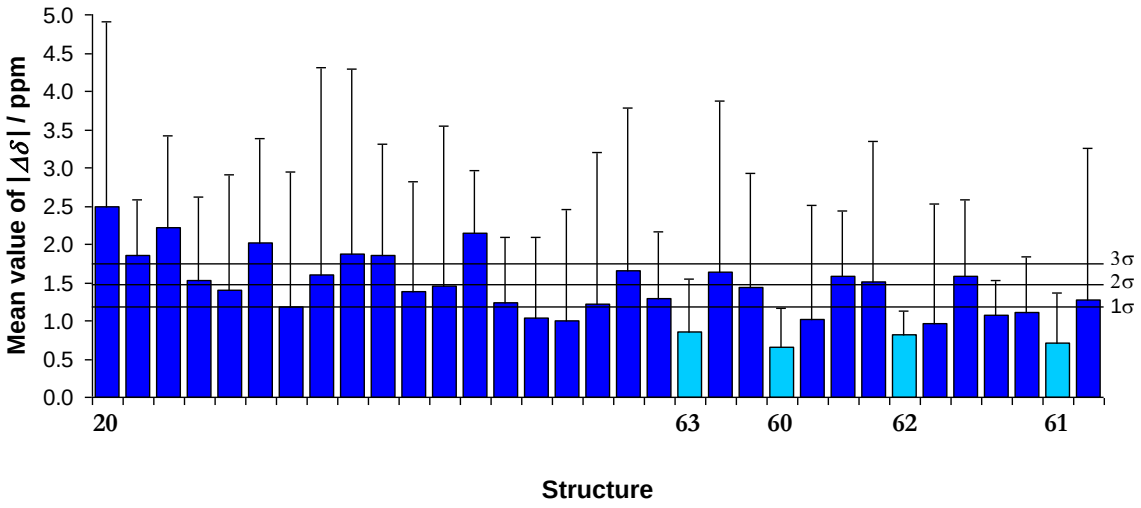



**Figure 1.17 - Mean (bars) and maximum (lines) values of |Δδ| for carbons C6, C8, C9, C10, C11 and C13 only. The horizontal lines represent the values of |Δδ| that are 1, 2 or 3 standard deviations above the expected value of the mean of |Δδ| for a correct structure. The smaller bars represent the best matches with the top four matches highlighted (60 to 63, Figure 1.18).**

The pyrano[3,2-*b*]pyran structure (**20**) gave the worst match with the natural product data, having the largest mean error and largest maximum error. The smaller bars represent the best matches and this analysis was able to highlight the four most likely diastereomers (**60** to **63**, **Figure 1.18**) for the structure of elatenyne, with the most likely shown first (**60**).

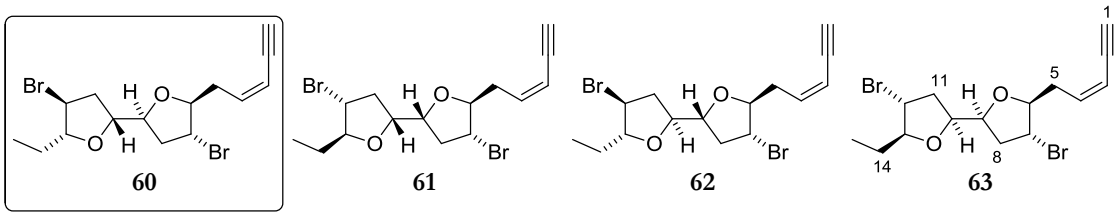
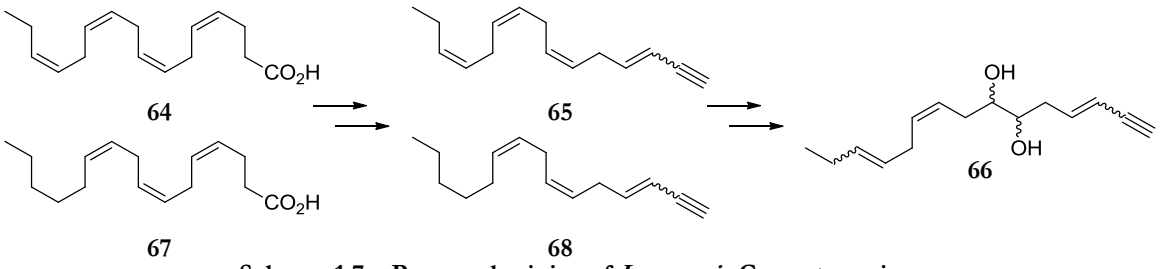



**Figure 1.18 – The four most likely diastereomers of elatenyne from computational prediction.**

## 1.5. Proposed Biosynthesis of Elatenyne

The study of the biosynthesis of natural products can often yield important and useful stereochemical information. Exploration of the biosynthetic pathway of *Laurencia* metabolites and similar structures to that of the proposed skeleton of elatenyne (**47**), was carried out in order to shed further light on the diastereomers upon which to focus synthetic efforts.

It is generally accepted that the wide range of $C_{15}$ acetogenins produced by the red algae of the *Laurencia* species trace their origin to hexadeca-4,7,10,13-tetraenoic acid (**64**) and/or hexadeca-4,7,10-trienoic acid (**67**, **Scheme 1.7**).[49] These fatty acids are thought to be metabolised into laurencenynes (**65**) and/or neolaurencenynes (**68**) and then epoxidation followed by ring opening is thought to produce laurediols (**66**, **Scheme 1.7**). A number of intermediates in this process including some of the laurencenyes (**65**), neolaurencenynes (**68**) and laurediols (**66**) have been isolated from *Laurencia* species which support this postulate.[50]




**Scheme 1.7 – Proposed origins of *Laurencia* $C_{15}$ acetogenins.**

Work by Murai has shown that cyclic brominated ethers of various ring sizes can be formed from (6*R*,7*R*)- or (6*S*,7*S*)-laurediols (**69** and **70**, **Figure 1.19**) *via* intramolecular attack of a hydroxyl group onto a bromonium ion formed on one of the alkenes.[49]

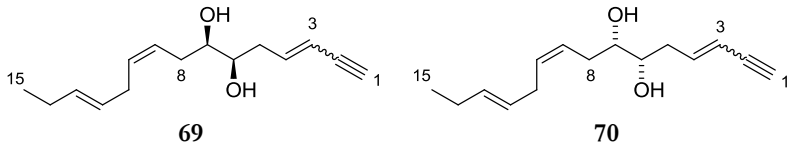
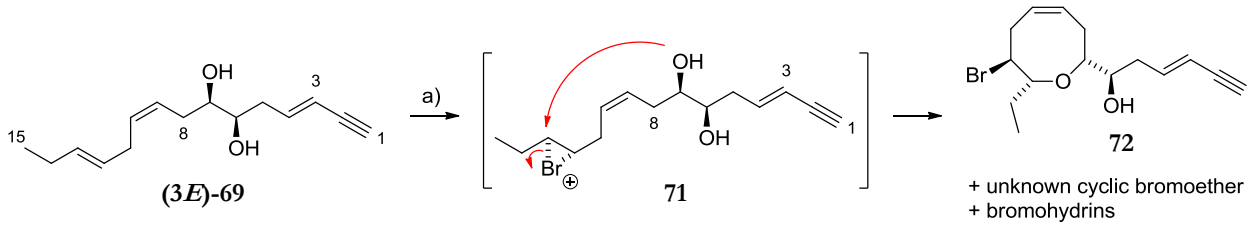



**Figure 1.19 – (6*R*,7*R*)- and (6*S*,7*S*)-laurediols.**

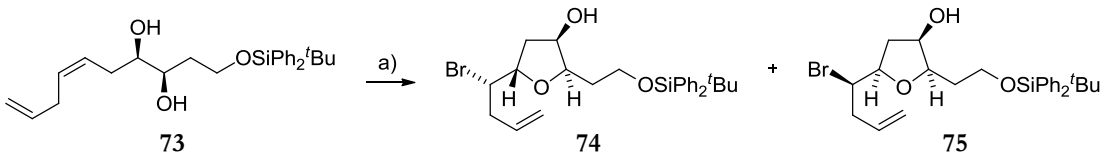
The bromonium ion is thought to be produced in the *Laurencia* algae by an enzyme called bromoperoxidase (BPO). Murai isolated BPO and was able to use this enzyme to convert

(3*E*,6*R*,7*R*)-laurediol ((3*E*)-**69**) into deacetyllaurencin (**72**) *via* bromonium ion **71**, albeit in low yield (**Scheme 1.8**).



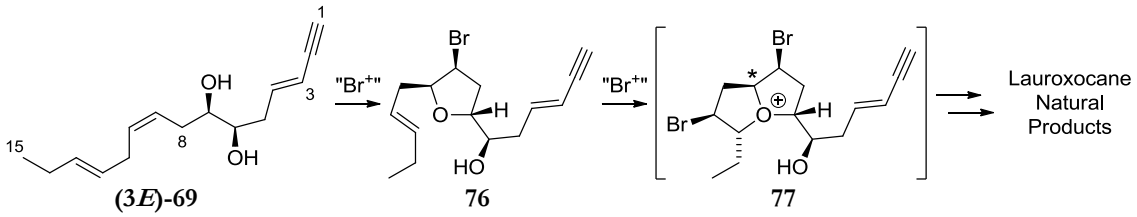

**Scheme 1.8 – Reagents and conditions: a) BPO, $H_2O_2$, NaBr, DMSO, phosphate buffer, 0.015%.**

The formation of a bromonium ion to initiate cyclisation resulting in brominated ethers has also been shown by Braddock *et al.* to be successful in the biomimetic synthesis of the THF core of some of the obtusallenes (**74**) from a laurediol 'surrogate' (**73**, **Scheme 1.9**).[51]




**Scheme 1.9 – Reagents and conditions: a) tetrabromocyclohexadienone, DCM, 87% 74, 7% 75 (12:1 d.r.).**

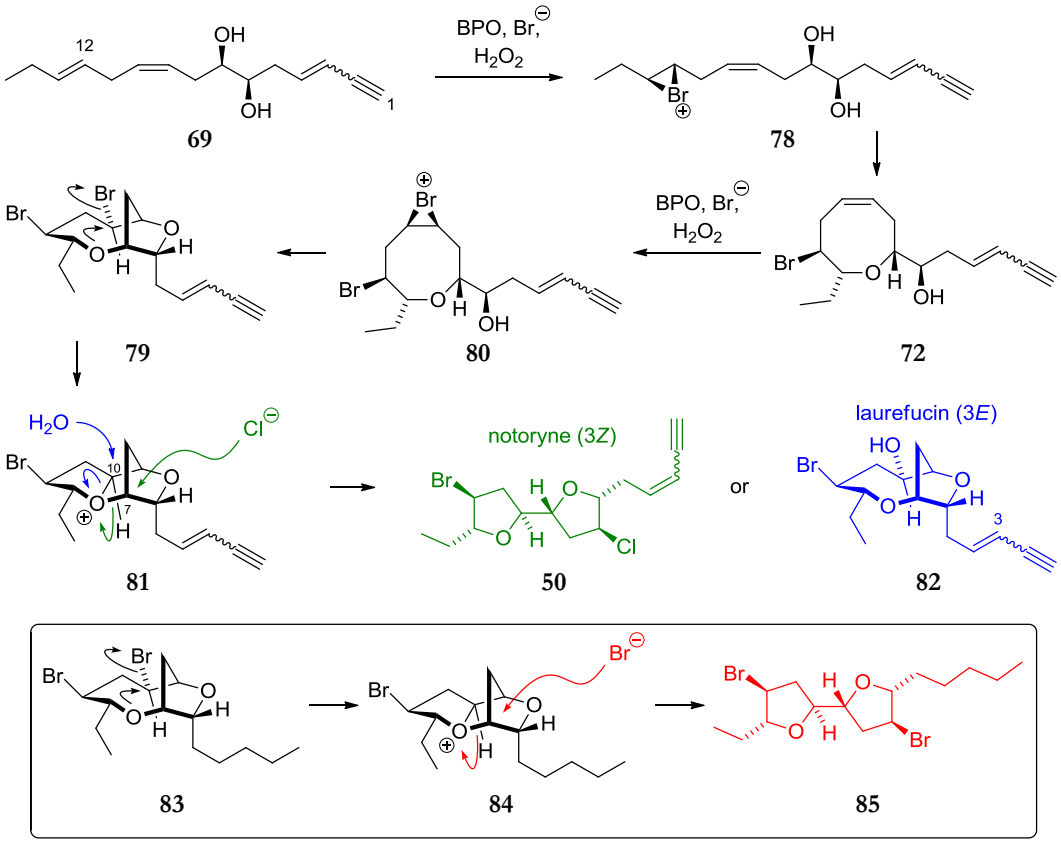
An alternative hypothesis for the biosynthesis of 8-membered cyclic lauroxocanes (such as **72**) from laurediols has recently been reported by Snyder and co-workers.[52] They propose that two 5-membered ring-forming steps could form oxonium ion **77**, and subsequent nucleophilic attack at the starred carbon could lead to lauroxocane natural products (**Scheme 1.10**).




**Scheme 1.10 – Snyder's proposed biosynthesis.[52]**

Notoryne (**50**) has a 2,2'-bifuranyl structure, which as described before, is analogous to the skeleton proposed for elatenyne (**47**, **Section 1.3.4.2**). Kikuchi *et al.* discussed the biosynthesis of notoryne (**50**) and proposed that it originates from (6*R*,7*R*)-laurediol (**69**) (**Scheme 1.11**).[26] They propose it to be the result of BPO induced cyclisation to form deacetyllaurencin (**72**) as tested experimentally

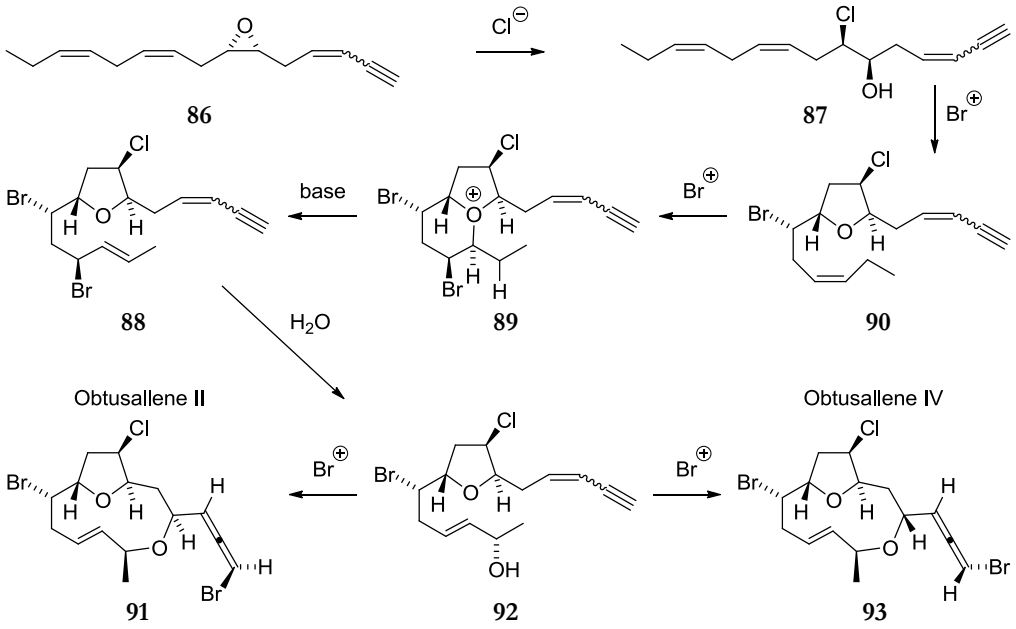
by Murai and previously discussed. Another BPO induced cyclisation onto bromonium ion **80** gives prelaurefucin **79** (not isolated as a natural product to date), which can form oxonium ion **81**. Attack by water onto the oxonium ion **81** at C10 would yield laurefucin (**82**), a metabolite isolated form *L. nipponica*[53] or attack by chloride at C7 would give notoryne (**50**, **Scheme 1.11**).




**Scheme 1.11 – Kikuchi *et al.*'s proposed biosynthesis of notoryne.**

Chemical evidence for the proposed biosynthesis of notoryne (**50**) comes from the work of Furusaki *et al.* who isolated the 2,2'-bifuranyl **85** on treatment of (10*R*)-10-bromo-10-deoxyhexahydrolaurefucin (**83**) with silica gel (**Scheme 1.11**).[53-54] Kikuchi *et al.* explained the formation of product **85** by an analogous mechanism to the notoryne (**50**) biosynthesis *via* saturated oxonium ion **84** (**Scheme 1.11**) and performed degradation and chemical comparison studies to confirm that rearrangement product **85** had an identical configuration to notoryne (**50**).[26]

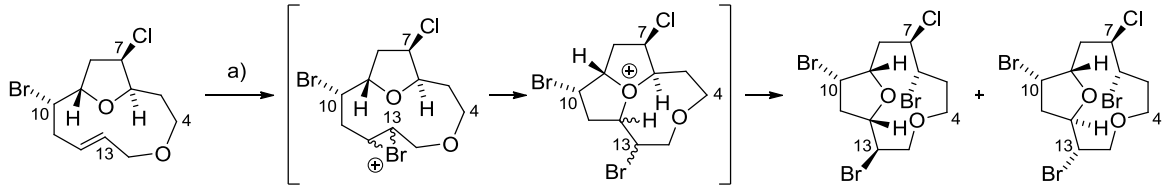
Related bi- and tricyclic oxonium ions have been proposed as intermediates in the biosynthesis of other *Laurencia* derived natural products. Braddock proposed that the obtusallene family of natural products (for example **91** and **93**) isolated from *L. obtusa* may originate from epoxide **86** (**Scheme 1.12**), thought to be the precursor to a laurediol (**69**, **Figure 1.19**).[51b] Chloride opening of the epoxide would give chlorohydrin **87**, which can undergo BPO induced cyclisation, as discussed previously, yielding THF **90**. Another BPO bromination followed by nucleophilic attack by the THF oxygen gives bicyclic oxonium ion **89**. This bicyclic oxonium ion **89** can fragment under basic conditions to yield allylic bromide **88**, which can undergo $S_N2$' displacement by water. Alcohol **92** can then cyclise during a fourth bromination event onto the enyne moiety to form the macrocycles and bromo-allenes of obtusallene II and IV (**91** and **93**, **Scheme 1.12**). Braddock postulated that other members of the natural product family are then accessible *via* bromonium ion formation on the alkene in these macrocycles and transannular attack of the THF oxygen to give further possible tricyclic oxonium ions. These oxonium ions could then undergo a variety of transformations to give other obtusallenes.




**Scheme 1.12 – Braddock's proposed biosynthesis of the obtusallenes.**

Braddock and co-workers were able to show experimentally the feasibility of this proposed bromonium ion induced transannular oxonium ion formation and subsequent fragmentation to

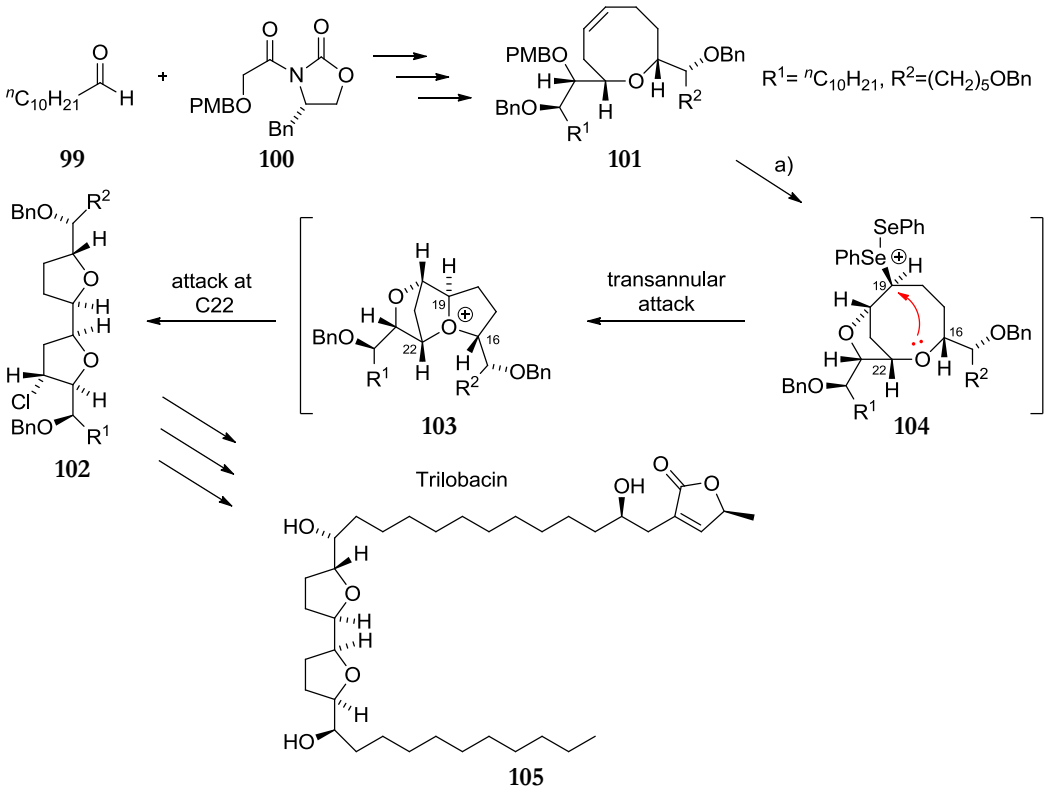
give other obtusallenes.[55] Treatment of an obtusallene II model substrate (**94**) with NBS gave a mixture of diastereomers **97** and **98** (**Scheme 1.13**). To form the mixture of diastereomers, initial bromonium ion formation must have occurred on both faces of the alkene in macrocycle **94** to give bromonium ion **95**. Formation of diastereomers **97** and **98** must have occurred *via* tricyclic oxonium ion **96** and subsequent nucleophilic attack of bromide at C-6 (**Scheme 1.13**).




**94** **95** **96** **97** **98**

**Scheme 1.13 – Reagents and conditions: a) NBS, chlorinated solvent saturated with water, 20 days, RT, 8% ~3:2 97:98.**

Kim and co-workers performed an asymmetric total synthesis of trilobacin (**105**), which contains a 2,2'-bifuranyl core, *via* a novel organoselenium-mediated oxonium ion formation/$SiO_2$-promoted fragmentation of α,α'-*cis*-oxocene **101** (**Scheme 1.14**).[56] Oxocene **101** was formed in 13 steps from **99** and **100**, beginning with an Evans *syn*-aldol reaction.[57] Treatment of oxocene **101** with phenylselenium chloride produced 2,2'-bifuranyl **102** in a stereo-, regio- and chemoselective fashion *via* tricyclic oxonium ion **103**. Global deprotection of 2,2'-bifuranyl **102** with removal of chloride, followed by side chain manipulations completed the total synthesis of trilobacin (**105**, **Scheme 1.14**).




**Scheme 1.14 – Reagents and conditions: a) PhSeCl, $SiO_2$, $K_2CO_3$, DCM, RT, 24 h, 83%.**

As has just been discussed, there is substantial evidence to support the postulated biosynthetic pathway for notoryne (**50**, **Scheme 1.11**) and this pathway is key when considering the origin of elatenyne. Product **85** (**Scheme 1.11**) is very similar to a diastereomer of the revised structure of elatenyne (**47**, **Figure 1.10**, **Section 1.3.4**), the only difference being a saturated side chain in place of the enyne moiety of elatenyne. Our proposed biosynthesis of elatenyne is therefore analogous to that shown for notoryne (**50**), and analogous to the formation of product **85**, by attack of bromide onto oxonium ion **81** (**Scheme 1.11**). A comparison of the natural product data for elatenyne with the data for product **85** showed that the stereochemistry of elatenyne is unlikely to match that of product **85** and that therefore elatenyne is unlikely to have the same configuration as notoryne (**50**). Previous work in the Burton group analysed the different possible stereochemical outcomes for elatenyne from this biosynthetic pathway.[58] Broadwith considered the four different diastereomers of laurediols that had been isolated[50c, 50d] (**(3*Z*)-69**, **(3*Z*,12*Z*)-69**, **(3*Z*)-70**, **(3*Z*,12*Z*)-70**, **Figure 1.20**) from which elatenyne could originate and also the different possible facial selectivities of the BPO. Diastereomers were removed from the analysis if cyclisation was geometrically impossible.

This biosynthetic analysis highlighted 4 possible stereochemical outcomes for elatenyne (**60**, **106**, **107**, **108**, **Figure 1.21**).

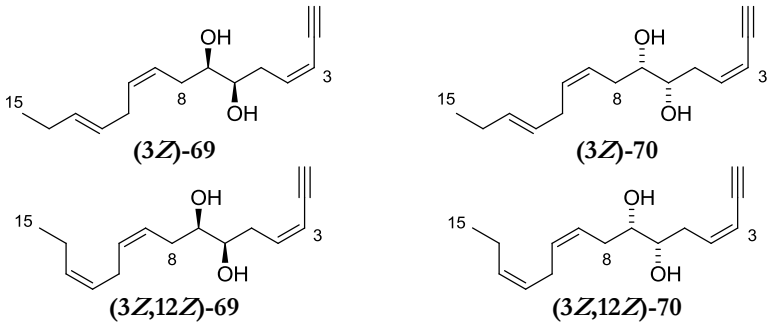



**Figure 1.20 – The four isolated laurediol diastereomers.**

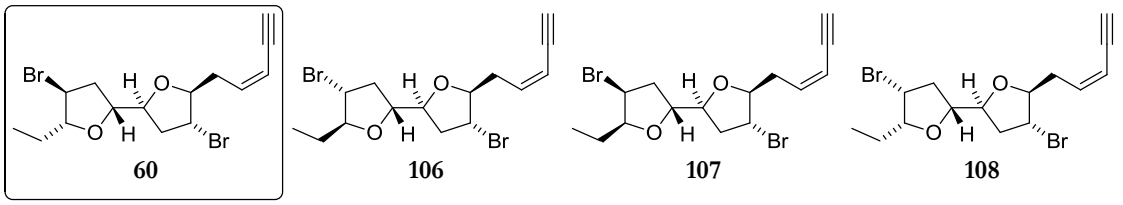
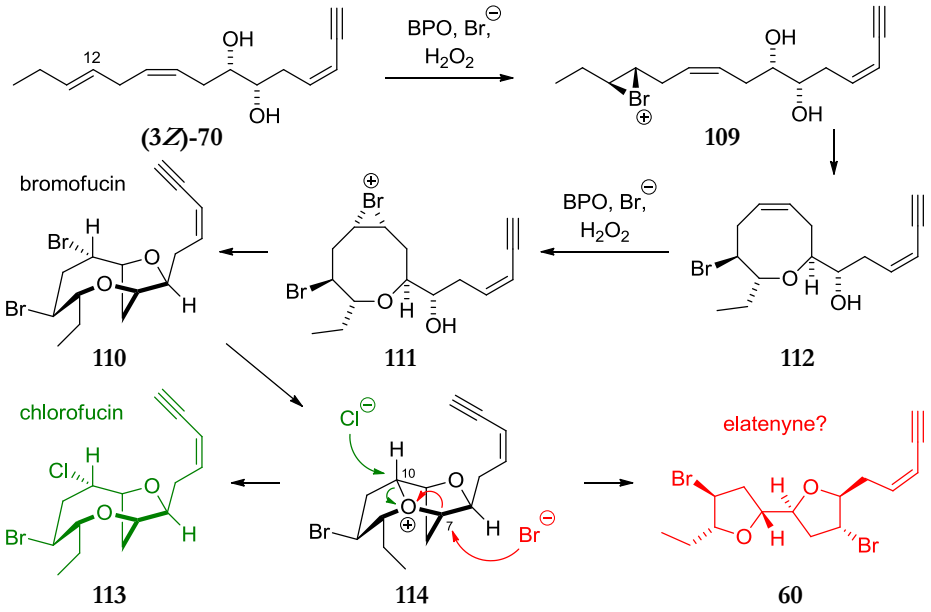



**Figure 1.21 – The four possible stereochemical outcomes for elatenyne from the proposed biosynthesis.**

Encouragingly one of the diastereomers highlighted (**60**) matched with the most likely diastereomer from the computational prediction (**Figure 1.18**, **Section 1.4**). The proposed biosynthetic pathway for this diastereomer (**60**) is shown in **Scheme 1.15**. (3*Z*,6*S*,7*S*)-Laurediol (**(3*Z*)-70**) could form bromonium ion **109** under the action of BPO and cyclisation would yield a diastereomer of deacetyllaurencin **112**. Another BPO induced bromination and cyclisation would produce (3*Z*)-bromofucin (**110**), which could undergo transannular oxonium ion formation to give oxonium ion **114**. Attack of bromide onto oxonium ion **114** at C7 would yield the most likely diastereomer of elatenyne (**60**). An intermediate in this biosynthetic pathway, (3*Z*)-bromofucin (**110**), has been isolated from a herbivorous sea hare, which feeds mainly on *Laurencia* algae.[59] (3*E*)-Chlorofucin (**(3*E*)-113**, $[\alpha]_D$ (20 °C) +12.0 (c=1.4 in $CHCl_3$)) was first isolated in 1980 from *L. synderae* and its structure and absolute configuration were determined by X-ray crystallography.[60] (3*Z*)-Chlorofucin (**113**, ($[\alpha]_D$ (24 °C) –11.3 (c=0.58 in $CHCl_3$)) was isolated from *L. pannosa* in 2001, but the optical rotation suggested it might be the enantiomer of (3*E*)-chlorofucin (**(3E)-113**).[61] Chlorofucin (**113**)

is also most likely derived from bromofucin (**110**) by attack of chloride onto the tricyclic oxonium ion **114** at C10, as shown in **Scheme 1.15**.




**Scheme 1.15 – The proposed biosynthesis of elatenyne.**

## 1.6. Previous Synthetic Work Towards Elatenyne

Previous work within the Burton group has achieved the synthesis of three simplified cores of elatenyne (**115** to **117**, **Figure 1.22**).[58]

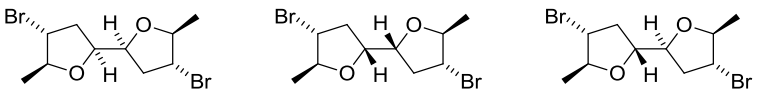
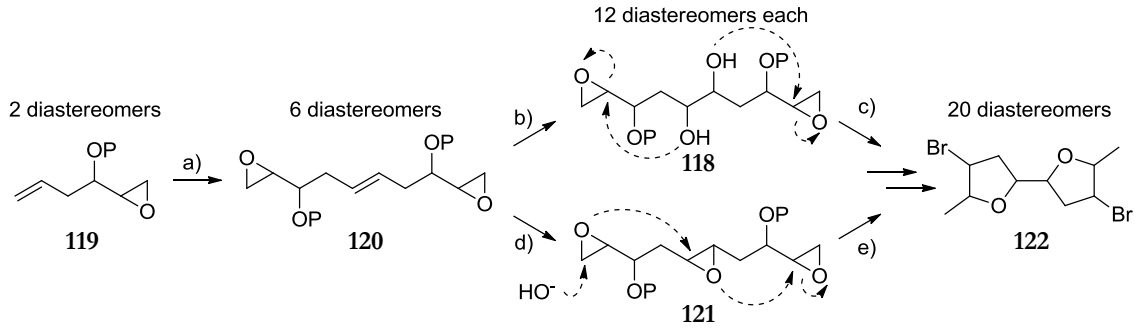


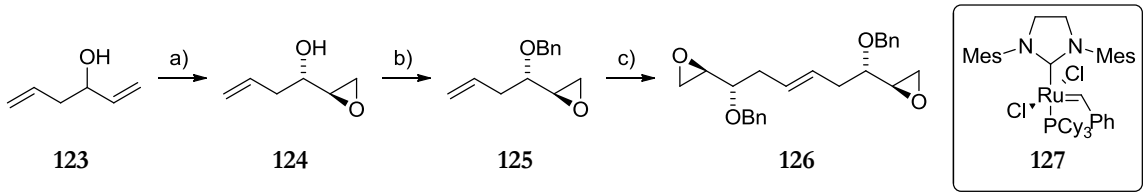

**Figure 1.22 – Simplified cores of elatenyne previously synthesised.**

A divergent strategy was developed for their synthesis, which potentially could enable access to any of the 20 diastereomers of the simplified core (**Scheme 1.16**). The strategy involved stereocontrolled synthesis of epoxyalcohols (**119**), which could undergo either homo- or hetero-coupling to form bis-epoxide structures (**120**). The alkene (**120**) could then be functionalised stereoselectively either by Sharpless asymmetric dihydroxylation (SAD)[62] or by Shi epoxidation.[63] The resultant diol (**118**) could cyclise into the epoxides, or alternatively the resultant tris-epoxide (**121**) could undergo cascade cyclisation to yield the core structures (**122**).



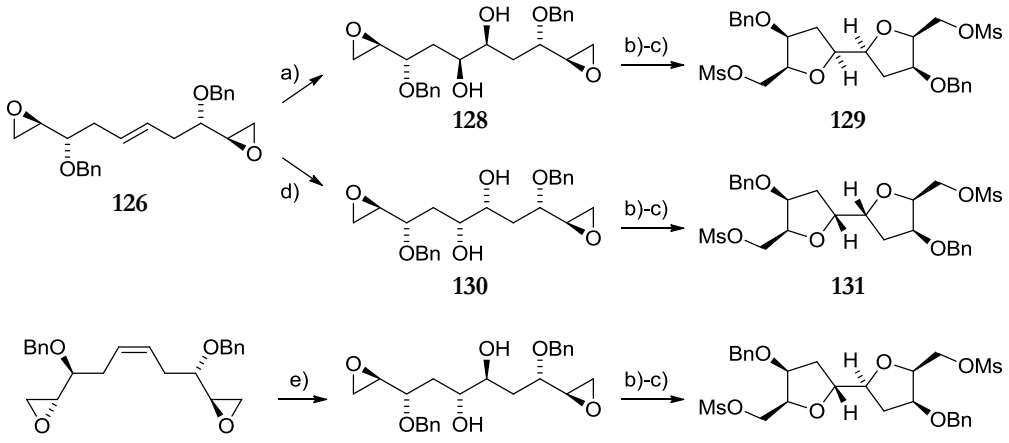

**Scheme 1.16 – Steps: a) homo- or hetero-coupling; b) Sharpless AD; c) acid mediated cyclisation; d) Shi epoxidation; e) base-promoted cyclisation sequence.**

The synthesis of all three cores (**115** to **117**) began from commercially available 1,5-hexadien-3-ol (**123**) with a kinetic resolution by Sharpless asymmetric epoxidation (**Scheme 1.17**).[64] The resulting epoxyalcohol **124** was benzyl protected using low temperature and TBAI in order to prevent the Payne rearrangement.[65] Homodimerisation of epoxide **125** using the Grubbs II catalyst (**127**), and acetic acid to prevent alkene isomerisation, yielded bis-epoxide **126**.[66]



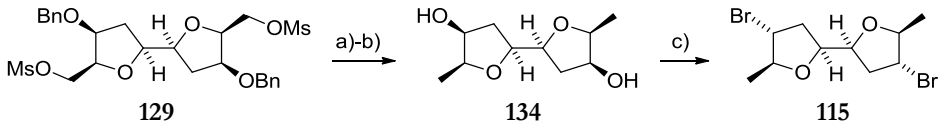

**Scheme 1.17 – Reagents and conditions: a) Ti(O$^i$Pr)$_4$, $^t$BuOOH, L-(+)-dicyclohexyl tartrate, 4 Å MS, DCM, -20 °C, 2 days, 30% (60% of max.), >95% e.e.; b) BnBr, TBAI, NaH, -78 °C to RT, 1 h, 95%; c) Grubbs II (1 mol%, slow addition), AcOH (10 mol%), DCM, reflux, 67%, 3:1 *E*:*Z*.**

Alkene **126** was subject to SAD conditions with $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ to yield two diastereomers of the diol (**128** and **130**, **Scheme 1.18**). Alkene **(*Z*)-126**, also formed in the cross metathesis, is $C_2$-symmetric and hence subjecting this alkene to simple dihydroxylation conditions yielded another single diastereomer, the *anti*-diol (**132**). All three diastereomeric diols (**128**, **130** and **132**) were treated with Amberlyst-15™ resin. The resultant 2,2'-bifuranyls were mesylated using standard conditions to yield the three bis-mesylates (**129**, **131** and **133**).




**Scheme 1.18 - Reagents and conditions: a) AD-mix α, $^t$BuOH/$H_2O$, 0 °C, 16 h, 97%; b) Amberlyst-15™, $CDCl_3$, RT, 40 min; c) MsCl, $Et_3N$, DCM, 16 h, 0 °C to RT; d) AD-mix β, $^t$BuOH/$H_2O$, 0 °C, 16 h, quant.; e) $K_2OsO_4.2H_2O$, NMO, acetone/$H_2O$, 0 °C to RT, 16 h, 97%.**

All three bis-mesylates (**129**, **131** and **133**) were converted in an identical fashion to the simplified core structures (**115** to **117**) as shown for bis-mesylate **129** in **Scheme 1.19**. The bis-mesylate (**129**) was reduced to give two methyl groups using SuperHydride® and the benzyl protecting groups were removed *via* hydrogenolysis to give diol **134**. The two bromides where introduced with inversion of configuration using triphenylphosphine and carbon tetrabromide to yield core **115**.



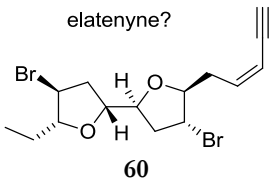

**Scheme 1.19 – Reagents and conditions: a) $Et_3BHLi$, THF, 16 h, 0 °C to RT, 80%; b) $H_2$, Pd/C, EtOH, RT, 16 h, 94%; c) $PPh_3$, $CBr_4$, PhMe, 80 °C, 2 h, 36%.**

These syntheses of the simplified core structures demonstrated an efficient route to 2,2'-bifuranyls and will form the basis of the retrosynthetic analysis in **Chapters 2** and **3**.

## 1.7. Conclusions and Project Aims

Total synthesis remains a key part of the structure elucidation of natural products, even with the significant advancement of analytical techniques, as shown by the numerous structural revisions still occurring today. There is substantial evidence for the structural revision of elatenyne and *L. majuscula* enyne from the originally proposed pyrano[3,2-*b*]pyrans to 2,2'-bifuranyl structures (**Figure 1.10**, **Section 1.3.4**). There are 32 possible diastereomers for the natural products with

these 2,2'-bifuranyl skeletons and there has been compelling evidence from computational analysis indicating the most likely diastereomers for elatenyne (**Figure 1.18**, **Section 1.4.2**). Biosynthetic analysis has also been used to highlight possible diastereomers (**Figure 1.21**, **Section 1.5**) and, encouragingly, one diastereomer (**60**, **Figure 1.23**) has been highlighted from both the biosynthesis and computational analysis.

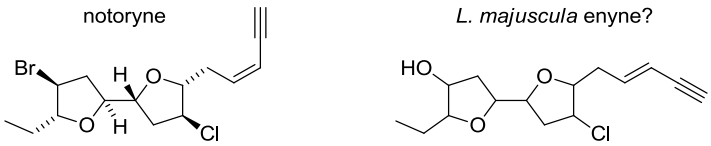



**60**

**Figure 1.23 – The most likely diastereomer of elatenyne.**

In this project we aimed to complete the total synthesis of the most likely diastereomer of elatenyne (**60**). We aimed to build upon the synthetic work towards the simplified cores completed in the Burton group (**Figure 1.22**, **Section 1.6**) and to use a divergent synthesis, which would allow access to any of the diastereomers if necessary. We required the stereochemistry to be unambiguous at every stage of the synthesis and, as such, planned to use well established methods when installing and manipulating stereocentres. The aim of this total synthesis was not only to confirm the structure of elatenyne, but to provide evidence for our biosynthetic proposal and most importantly to validate the use of the DFT-GIAO method with such flexible and conformationally demanding molecules. This validation would allow those involved in the structure determination of small organic molecules to use this computational method with confidence and therefore could have great impact.

The second aim of this project was to use the developed synthetic route to access similar natural products such as notoryne (**50**) and possible diastereomers of *L. majuscula* enyne (**48**, **Figure 1.24**).



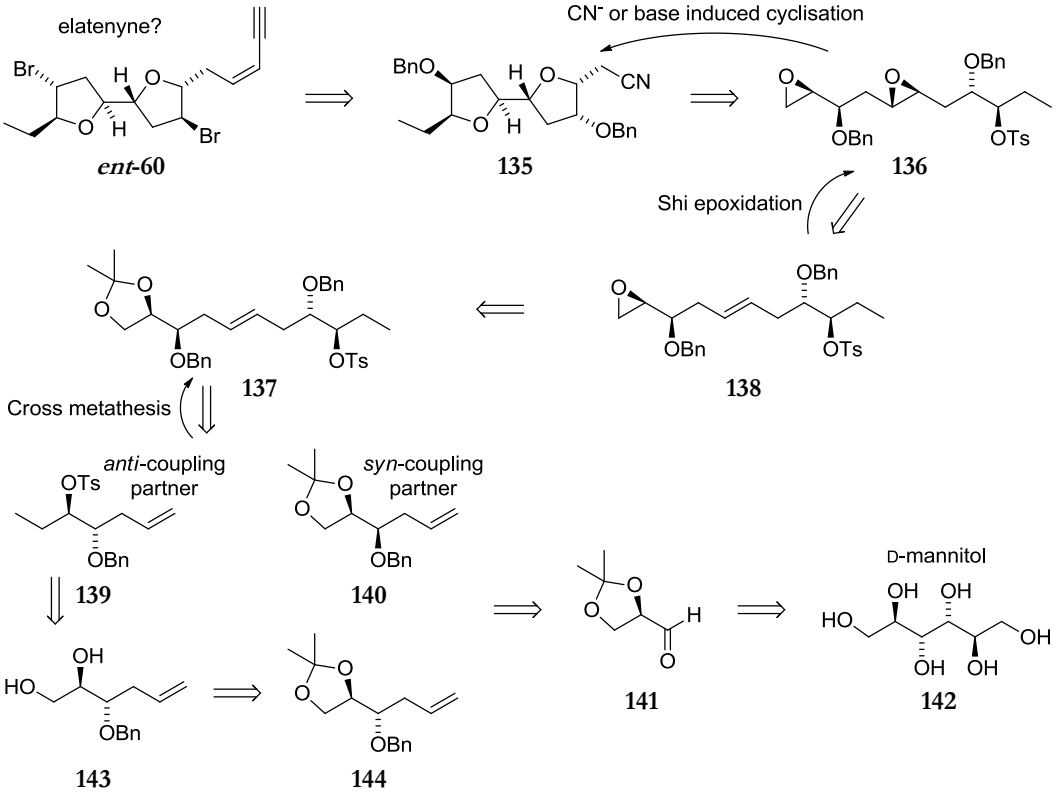

**50** **48**

**Figure 1.24 – The structure of notoryne and the proposed skeleton of *L. majuscula* enyne.**

# CHAPTER 2: FIRST GENERATION SYNTHESIS

## 2.1. Retrosynthetic Analysis

In our approach towards the most likely diastereomer of elatenyne (***ent*-60**)[V] we aimed to build upon the synthetic strategy developed within the group (**Chapter 1**, **Section 1.6**) and undertake a divergent synthesis, which would allow access to any diastereomer of elatenyne if necessary. Initially we decided, however, to avoid the kinetic resolution in the Sharpless asymmetric epoxidation (**Chapter 1**, **Section 1.6**) and make use of the stereochemistry already installed in cheap, readily available D-mannitol (**142**, **Scheme 2.1**). This would give rise to elatenyne with the absolute configuration shown for ***ent*-60**.




**Scheme 2.1 – Retrosynthetic analysis of elatenyne.**

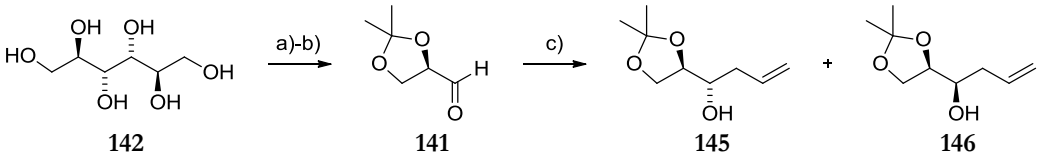
[V] The absolute configuration of elatenyne (**60**) is unknown. Due to the retrosynthetis strategy (see also **Chapter 3**, **Section 3.2.3**) we pursued the synthesis of both enantiomers of elatenyne, initially beginning with ***ent*-60**.

It was envisaged that the most likely diastereomer of elatenyne (***ent*-60**) would be accessed from 2,2'-bifuranyl **135** *via* benzyl-group deprotection, bromination and manipulation of the side chain (**Scheme 2.1**). The 2,2'-bifuranyl core would be formed in a key cyanide or base initiated cascade cyclisation of bis-epoxide **136**. Intermediate **136** could be reached *via* stereoselective Shi epoxidation of alkene **138**, which would originate from olefin cross metathesis product **137**. It was proposed that the two coupling partners for the cross metathesis (**139** and **140**) would be obtained, with manipulation of **144** to give **139**, from the allylation of D-glyceraldehyde acetonide (**141**), which itself would be easily accessible from D-mannitol (**142**, **Scheme 2.1**).

## 2.2. Coupling Partner Synthesis

### *2.2.1. Diastereomer Separation Difficulties*

The forward synthesis began with the protection of D-mannitol (**142**) and subsequent oxidative cleavage with sodium periodate to give D-glyceraldehyde acetonide **141** following the method of Schmid and Bryant (**Scheme 2.2**).[67] Barbier-type allylation using zinc dust, according to the procedure of Chattopadhyay, gave the two diastereomeric alcohols **145** and **146** which were inseparable by column chromatography in 5:1 to 7:1 d.r.[68] The diastereoselectivity was in keeping with some reported in the chemical literature, but much lower than others, all for the same substrate and conditions e.g. 77:23,[69] 9:1[70] and 96:4.[71]

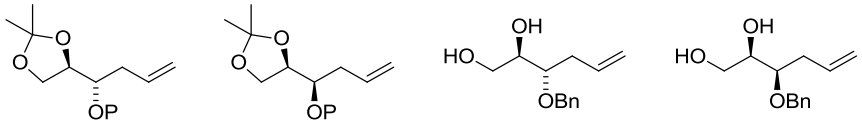



**142** **141** **145** **146**

**Scheme 2.2 – Reagents and conditions: a) $SnCl_2$, DMP, DME, reflux, 2 h; b) $NaIO_4$, $NaHCO_3$, DCM, RT, 2.5 h, 68% (2 steps); c) Allyl bromide, Zn, aq. $NH_4Cl$, THF, 10 °C, 3 h, 88%, 5:1 to 7:1 d.r.**

In order to be able to use both diastereomers formed during the allylation reaction their complete separation was essential. A range of different chromatography techniques, including use of a Biotage® and a Chromatotron®, were explored in order to separate the alcohols and a range of protected derivatives (**140**, **144**, **147** to **154**), as well as a diastereomeric mixture of diols **143** and **155**

(**Figure 2.1**, **Table 2.1**). There was literature precedent for the separation of protected derivatives of the diastereomers from this allylation for use in synthesis,[70, 72] but unfortunately in our hands only partial separation was achieved with the protecting groups used. Biotage® chromatography gave the best results for partial separation, but regrettably this was impractical for producing large quantities of material at this early stage of the total synthesis.



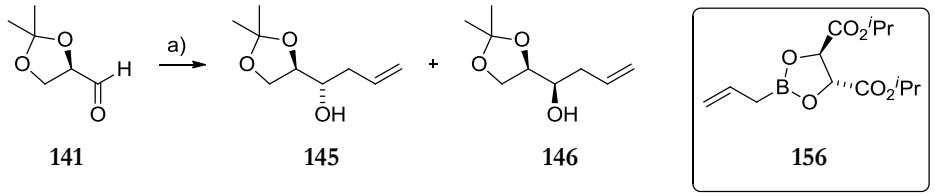

**144**, **140**, **147** to **154** **143** **155**

**Figure 2.1 – Range of protected derivatives synthesised.**

| Protecting Group | *Anti* | *Syn* | Procedure from **145** and **146** | Separation |
|---|---|---|---|---|
| Bn | **144** | **140** | a) | Partial |
| PMB | **147** | **148** | b) | Partial |
| Ac | **149** | **150** | c) | Partial |
| TES | **151** | **152** | d) | None |
| Bz | **153** | **154** | e) | None |
| Bn (deprotected) | **143** | **155** | f) from **144** and **140** | None |

**Table 2.1 – Range of protecting groups used and separation achieved. Reagents and conditions: a) BnBr, NaH, DMF, 0 °C to RT, 5 h, 99%; b) PMBCl, NaH, TBAI, DMF, 0 °C to RT, 16 h, 68%; c) $Ac_2O$, DMAP, $Et_3N$, DCM, RT, 30 min, 82%; d) TESCl, imidazole, DMAP, DMF, 0 °C to RT, 6 h, products not isolated; e) BzCl, pyridine, DCM, 67% (94% BRSM); f) 60% acetic acid, 50 °C, 7 h, products not isolated.**

It was postulated that the separation of diastereomers would be aided by an increase in the diastereomeric ratio of the allylation reaction. Roush and co-workers have developed the use of tartrate ester modified allylboronates with aldehydes to yield homoallylic alcohols with high stereoselectivity.[73] They achieved 96:4 or 98:2 d.r., depending on the solvent, when this protocol with allylboronate **156** was applied to D-glyceraldehyde acetonide (**141**, **Scheme 2.3**).




**141** **145** **146** **156**

**Scheme 2.3 – Roush and co-workers' results.[73] Reagents and conditions: a) 156, 4 Å MS, DCM, -78 °C, 96:4 d.r., 91% or toluene, 98:2 d.r.**

The selectivity is thought to originate from both an attractive electrostatic interaction between the lone pair of the tartrate carbonyl oxygen and the aldehyde carbonyl carbon in transition state **157** and the minimisation of lone-pair lone-pair interactions between the aldehyde and the tartrate carbonyl oxygens in transition state **157** when compared to transition state **158** (**Figure 2.2**).

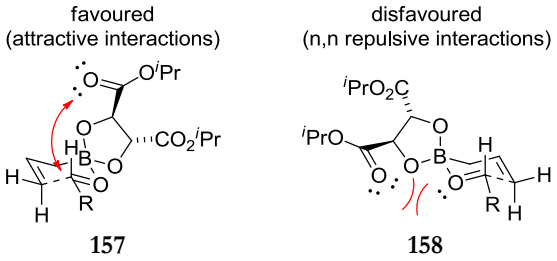
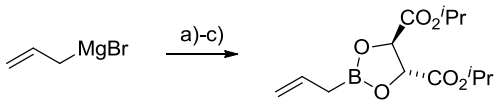


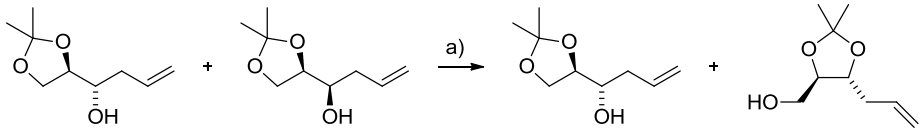

**Figure 2.2 – Transition states in the Roush allylation.**

This represented a significant improvement for our synthesis, and thus allylboronate **156** was synthesised according to Roush and co-workers' optimised procedure (**Scheme 2.4**).[73b] In this procedure the allylboronate **156** was obtained as a solution in toluene and a titration was performed by reaction of an aliquot with a known excess of cyclohexanecarboxaldehyde. Unfortunately we were unable to determine an exact concentration of the solution using $^{1}$H NMR analysis and reaction with D-glyceraldehyde acetonide (**141**) did not lead to any generation of product. The toluene was removed *in vacuo* and the crude material was purified by vacuum distillation. This ensured allylboronate **156** had been obtained, but surprisingly reaction of the distillate with D-glyceraldehyde acetonide (**141**), at best, gave homoallylic alcohols **145** and **146** in a disappointing 10:1 d.r. and 16% yield. With further work we believe this allylation would have been successful in our hands, however, other issues with the synthetic route resulted in further optimisation not being carried out.




**Scheme 2.4 – Reagents and conditions: a) ($^{i}$PrO)$_3$B, Et$_2$O, -78 °C to RT, 3 h; b) aq. HCl, 0 °C to RT, 10 min; c) (*R*,*R*)-DIPT, RT, ~41% (3 steps).**

An inspection of the literature concerning the use of homoallylic alcohol **145** in synthetic routes revealed Miranda *et al.*'s diastereomeric enrichment approach.[69] They stated that *anti*-diastereomer **145** was difficult to isolate and so used a selective transketalisation of the *syn*-isomer **146** into **160**, which gave diastereomerically enriched **145** (**Scheme 2.5**). Acetonides **145** and **160** were more easily separable by column chromatography and application of this methodology was successful giving *anti*-homoallylic alcohol **145** in >95:5 d.r. (**Scheme 2.5**).

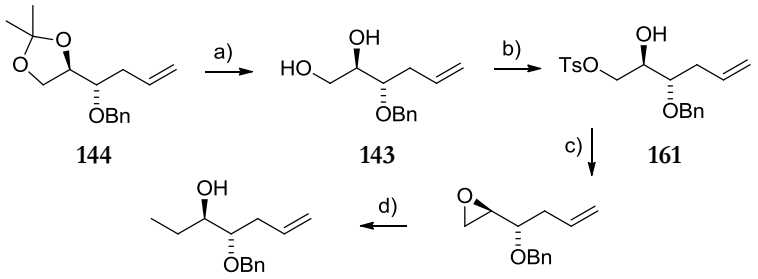



**145** **146** **145** **160**

**Scheme 2.5 – Reagents and conditions: a) CSA, acetone, -15 °C, 48 h, 91% 145 (>95:5 d.r.) and 160.**

### *2.2.2. Synthesis of the* Anti-*Coupling Partner*

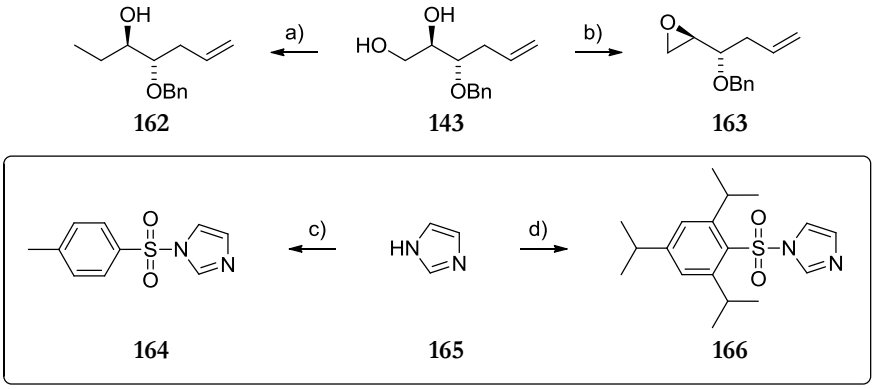
With homoallylic alcohol **145** in hand the preparation of the *anti*-coupling partner for the cross metathesis could proceed. Benzyl protected alcohol **144** was treated with acetic acid to remove the acetonide protecting group yielding diol **143** (**Scheme 2.6**). Mono-tosylation was not high yielding in pyridine (53%), due to the formation of bis-tosyl protected material, but the yield improved with the use of DMAP and triethylamine in DCM (75%). Deprotonation and intramolecular displacement of the tosylate was achieved with freshly prepared sodium methoxide and gave epoxide **163**.[72c] Attack of methylmagnesium bromide into epoxide **163** formed alcohol **162** and provided the ethyl group of elatenyne (***ent*-60**).




**144** **143** **161** **162** **163**

**Scheme 2.6 – Reagents and conditions: a) 60% acetic acid, 50 °C, 7 h, quant.; b) TsCl, pyridine, -5 °C to RT, 24 h, 53% with 10% bis-protected material or TsCl, DMAP, $Et_3N$, DCM, 0 °C to RT, 24 h, 75% with 17% bis-protected material and 8% SM; c) Na, MeOH, 0 °C to RT, 30 min, 58%; d) MeMgBr, CuI, THF/$Et_2O$, -23 °C, 1 h, 66%.**

The stepwise synthesis of alcohol **162** was not particularly high yielding. Cink and Forsyth have developed a one-pot reaction involving epoxide formation followed by nucleophilic epoxide opening.[74] Application of this procedure to our vicinal diol **143** using both *N*-(*p*-toluenesulfonyl)imidazole (*N*-TsIm, **164**) and *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole (*N*-TrisIm, **166**) was explored (**Scheme 2.7**). Initially it was confirmed that epoxide **163** was successfully formed in the reaction between diol **143** and *N*-TsIm (**164**) or *N*-TrisIm (**165**). It was found that *N*-TsIm (**164**) and *N*-TrisIm (**166**) freshly prepared by the procedure of Rad *et al.* (**Scheme 2.7**),[75] gave better results than commercially available *N*-TrisIm (**166**). The product (**163**) obtained from the reaction with *N*-TsIm (**164**) was always a single diastereomer, but with *N*-TrisIm (**166**) a small quantity of a second diastereomer could be seen (>10:1 d.r. by $^1$H NMR). This other epoxide diastereomer was thought to arise from sulfonylation of the secondary alcohol and subsequent deprotonation of the primary alcohol and trisyl displacement. Formation of bis-protected material was also a problem and lowered the yield with *N*-TsIm (**164**), but it was found that use of the more bulky *N*-TrisIm (**166**) prevented this. The higher yields and the fact that only trace amounts of the second diastereomer were observed meant that *N*-TrisIm (**166**) was the reagent of choice for the transformation. *N*-TrisIm (**166**) also performed better in the telescoped one-pot procedure with methylmagnesium bromide, giving alcohol **162** in 95% yield (**Scheme 2.7**).

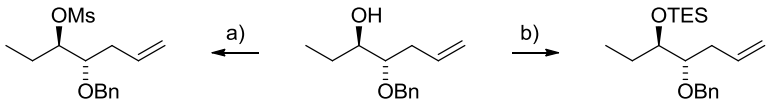



**162** **143** **163**

**164** **165** **166**

**Scheme 2.7 – Reagents and conditions: a) NaH, THF, 0 °C, 30 min, then *N*-TsIm (164), -78 °C to 0 °C, 5 h, then MeMgBr, CuI, 1.5 h, 37% (78% BRSM, 13% bis-tosylate); or NaH, THF, 0 °C 30 min, then *N*-TrisIm (166), -78 °C to 0 °C, 20 h then MeMgBr, CuI, 2 h, 95%; b) NaH, THF, 0 °C to RT, 40 min, then *N*-TrisIm (166), 0 °C to RT, 1 h, 83% (95% BRSM); c) TsCl, neat, ground, 2 min, 91%; d) TrisCl, neat, ground, 2 min, 98%.**

Protection of alcohol **162** proved more difficult than expected. Tosylation did not go to completion, even after 3 days at reflux, and the product co-eluted with the alcohol **162** on silica. Mesylation was successful, but product **167** proved very difficult to obtain free from impurities (**Scheme 2.8**). After 5 days the protection with TBSCl had gone to less than 50% conversion. The use of less bulky TESCl improved the reaction and pleasingly the protected alcohol **168** was obtained in 96% yield without purification difficulties (**Scheme 2.8**).

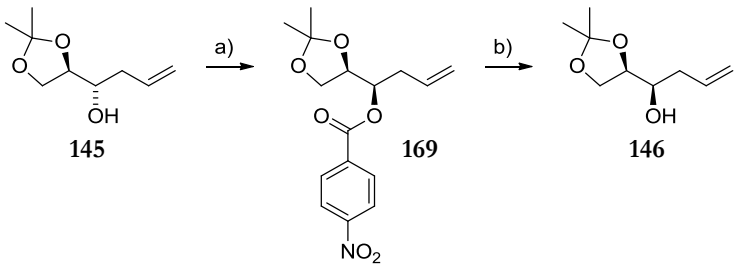



**167** **162** **168**

**Scheme 2.8 – Reagents and conditions: a) MsCl, $Et_3N$, DMAP, DCM, 0 °C, 1 h, <87%; b) TESCl, imidazole, DMAP, DCM, 0 °C, 5 h, 96%.**

### *2.2.3. Synthesis of the* Syn*-Coupling Partner*

The disadvantage of the diastereomeric enrichment route (**Scheme 2.5**, **Section 2.2.1**), was that instead of being able to isolate both alcohols (**145** and **146**) from the allylation, only the *anti*-alcohol **145** was obtainable. Thus, in order to synthesise the *syn*-coupling partner for the cross metathesis, an inversion of configuration of *anti*-alcohol **145** was required. Mitsunobu inversion[76] of alcohol **145**, with *p*-nitrobenzoic acid, gave ester **169** in low yield (40-50%, **Scheme 2.9**). Subsequent transesterification was successful with potassium carbonate in methanol and gave *syn*-alcohol **146**.

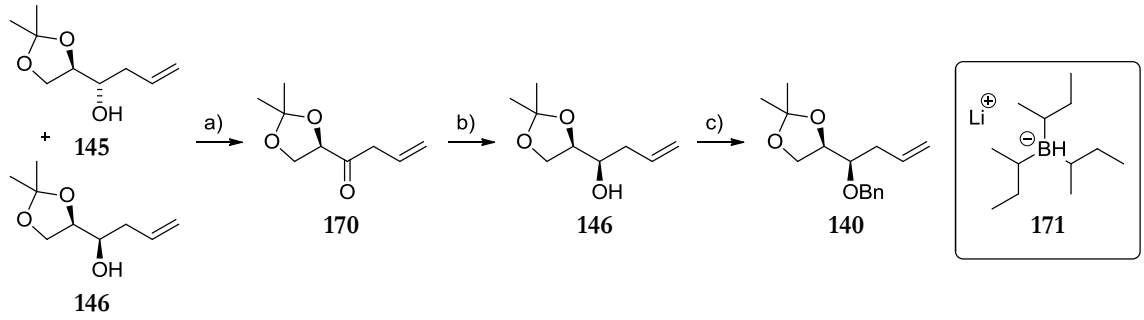



**145** **169** **146**

**Scheme 2.9 – Reagents and conditions: a) $PPh_3$, DIAD, THF, 0 °C, 15 min then alcohol 145, 0 °C, 15 min, then 4-nitrobenzoic acid, 0 °C to RT, 16 h, 40-55%; b) $K_2CO_3$, MeOH, 0 °C to RT, 16 h, 79%.**

Given the low yields, the Mitsunobu inversion was not a viable method for the formation of *syn*-alcohol **146** and hence an alternative oxidation/stereoselective reduction pathway was investigated. Dess-Martin oxidation[77] of a diastereomeric mixture of alcohols **145** and **146**, using the work-up

conditions published by Denmark and Edwards,[78] gave ketone **170** in 89% yield (**Scheme 2.10**). Stereoselective reduction of ketone **170** was initially attempted with K-Selectride®, following the procedure of Chattopadhyay and co-workers,[79] but no product was isolated after a simple aqueous work-up. It was postulated that the strong boron-oxygen bond was not being broken and hence a buffered oxidative work-up was employed. This was successful and produced *syn*-alcohol **146**, but in low yield (<57%) and purity. The reduction was then attempted with L-Selectride® (**171**), as used on an analogous substrate by White *et al.*,[80] which pleasingly improved the yield of the reaction to 80%. Subsequent protection gave benzyl ether **140** (**Scheme 2.10**).




**Scheme 2.10 – Reagents and conditions: a) Dess-Martin periodinane, DCM, RT, 18 h, 89%; b) L-Selectride® (171), THF, -78 °C to 0 °C, 3.5 h, 80%, 13:1 d.r.; c) BnBr, NaH, DMF, 0 °C to RT, 18 h, <67%.**

The *syn*-selectivity in the K- or L-Selectride® reduction can be explained using the polar Felkin-Anh model[81] where hydride addition takes place *via* conformation **172**, which is favoured due to orbital overlap of the C-O σ* and C=O π* leading to a new, lower energy LUMO (**Figure 2.3**).

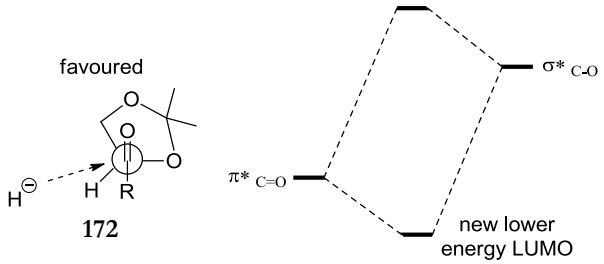
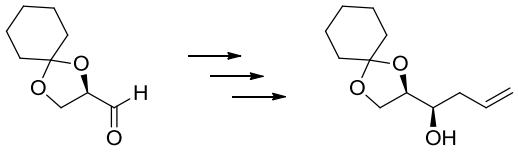



**Figure 2.3 – Polar Felkin-Ahn model.**

The yield shown for the benzylation step is poor for a simple protection (**Scheme 2.10**) and this was representative of decreased yields for nearly all of the steps in the synthesis shown so far (**Scheme 2.2**, **Scheme 2.5** to **Scheme 2.10**) when increasing the scale of the reaction. It was found

that the products were azeotroping with the solvents and hence material was being lost each time a crude or purified sample was concentrated *in vacuo*. Purification also became a major problem on scale. For example, in the L-Selectride® reduction shown in **Scheme 2.10** clean *syn*-alcohol **146** was obtained on small scale (0.59 mmol), whereas on a larger scale (23.8 mmol) no clean product was obtained after two column chromatography purifications. Additionally, benzyl protection of the impure *syn*-alcohol **146** did not yield any clean benzyl ether **140**.

The synthetic route, to obtain *syn*-alcohol **174** analogous to **146**, was repeated using (*R*)-2,3-O-cyclohexylideneglyceraldehyde (**173**, **Scheme 2.11**) in place of D-glyceraldehyde acetonide (**141**) in an attempt to improve the d.r. and avoid issues with azeotroping. This route had been demonstrated by Chattopadhyay and co-workers and had formed the basis of our original strategy.[68a, 79, 82] Disappointingly, this proved unsuccessful in our hands, with inseparable impurities causing issues and being carried through numerous steps from the beginning of the synthesis.




**173** **174**

**Scheme 2.11 – Synthetic route with (*R*)-2,3-O-cyclohexylideneglyceraldehyde.**

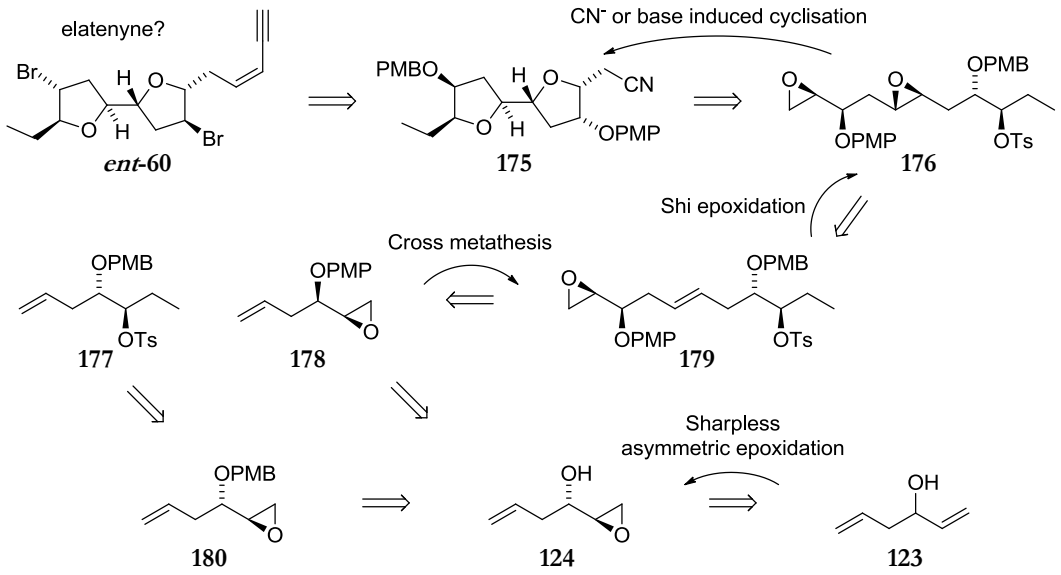
## 2.3. Conclusions

Although coupling partners **168** and **140** were successfully obtained after several optimisations, upon scale up there was great difficulty with purification and azeotroping of the products. The route was therefore not suitable to access the quantity of coupling partners **168** and **140** required for the total synthesis of the most likely diastereomer of elatenyne (***ent*-60**) and an alternative route was pursued.

# CHAPTER 3: SECOND GENERATION SYNTHESIS

## 3.1. Retrosynthetic Analysis

Following the ineffective D-mannitol (**142**) synthetic route to elatenyne (***ent*-60**, **Chapter 2**) we aimed to build upon this work and to access the equivalent alkene **179** for the previously proposed Shi epoxidation and cyclisation cascade (**Scheme 3.1**).




**Scheme 3.1 – Retrosynthetic analysis of elatenyne.**

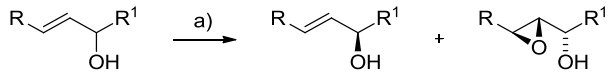
The olefin cross metathesis substrates **177** and **178** would be obtained using the Sharpless asymmetric epoxidation of 1,5-hexadien-3-ol (**123**, **Scheme 3.1**),[64] as previously demonstrated in the Burton group (**Chapter 1**, **Section 1.6**).[58] Coupling partner **178** would result from Mitsunobu inversion of epoxyalcohol **124** with *p*-methoxyphenol and coupling partner **177** would result from protection, epoxide opening and tosylation of epoxyalcohol **124**.

## 3.2. Coupling Partner Synthesis

### *3.2.1. Sharpless Asymmetric Epoxidation*

The reaction of an allylic alcohol with *tert*-butyl hydroperoxide in the presence of titanium(IV) isopropoxide and diethyl tartrate to form an epoxyalcohol with high enantioselectivity, namely the

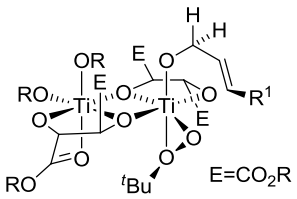
Sharpless asymmetric epoxidation, was introduced in 1980.[83] Since then, the process has been expanded to include the kinetic resolution of racemic allylic alcohols **181**, yielding enantioenriched allylic alcohols **182** and epoxyalcohols **183** with high enantioselectivity (**Scheme 3.2**).[84]




**181** **182** **183**

**Scheme 3.2 –Reagents and condition: a) Ti(O$^i$Pr)$_4$, (+)-DIPT, $^t$BuOOH.[64]**

When titanium(IV) isopropoxide, *tert*-butyl hydroperoxide, tartrate and allylic alcohol are mixed under the reaction conditions, rapid ligand exchange occurs and titanium complexes are formed. Based on X-ray analysis of these complexes, the structure of the asymmetric epoxidation intermediate has been proposed as **184** (**Figure 3.1**).[85]




**184**

**Figure 3.1 – Proposed structure of the asymmetric epoxidation intermediate.**

The selectivity in the kinetic resolution can be rationalised as demonstrated in **Figure 3.2**. Each tartrate enantiomer allows epoxidation preferentially on one face of the alkene, which can be predicted by drawing the allylic alcohol in the conformation shown on the 'tabletop' plane, with L-(+)-tartrates causing epoxidation from the bottom face and D-(–)-tartrates from the top.

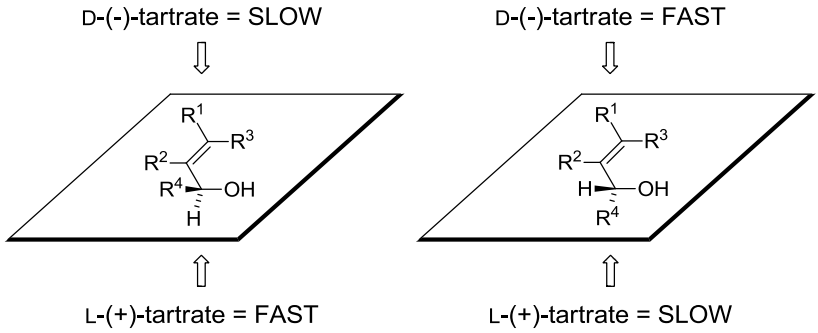
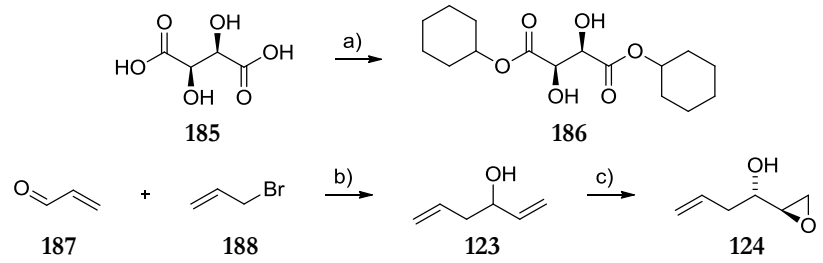



**Figure 3.2 – Selectivity of the kinetic resolution in the Sharpless asymmetric epoxidation.**

With secondary allylic alcohols the epoxidation is inhibited for one enantiomer of the alcohol due to unfavourable interactions of the catalyst complex with the alkyl substituent ($R^4$) on the alcohol carbon. The epoxidation of the other enantiomer involves delivery of the oxygen past the allylic hydrogen, which is not hindered. This leads to the epoxidation occurring much faster for one enantiomer and hence, if the reaction is controlled to 50% conversion, an efficient kinetic resolution occurs.

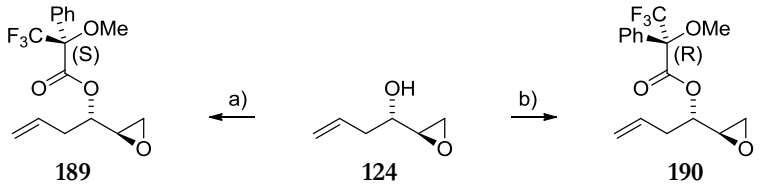
Sharpless and co-workers have performed studies and optimised the procedure for the epoxidation.[64, 86] They have shown that the presence of activated molecular sieves enables the reaction to proceed with substoichiometric (<10%) quantities of titanium(IV) isopropoxide and fewer equivalents of *tert*-butylhydroperoxide. Dicyclohexyl or dicyclododecyl tartrates were found to produce higher yields and enantioselectivities for the kinetic resolution compared to diisopropyl tartrate.

For our synthesis a dry, titrated solution of *tert*-butylhydroperoxide in DCM was prepared according to the procedure of Hanson and Sharpless.[86] L-(+)-Dicyclohexyl tartrate **186** was synthesised from L-(+)-tartaric acid (**185**) by a modified procedure of Gao *et al.* (**Scheme 3.3**).[64] 1,5-Hexadien-3-ol (**123**) is commercially available, but can be easily synthesised by Grignard addition of allyl bromide (**188**) into acrolein (**187**), as demonstrated by Barfield *et al.*[87] This procedure was successful yielding 1,5-hexadien-3-ol (**123**) in 60% yield (**Scheme 3.3**). The subsequent Sharpless asymmetric epoxidation, following the procedures of Crimmins *et al.*, produced the desired epoxyalcohol **124** in 38% yield (76% of maximum, **Scheme 3.3**).[88]




**Scheme 3.3 – Reagents and conditions: a) cyclohexanol, methanesulfonic acid, benzene, reflux, Dean-Stark apparatus, 16 h, 86%; b) Mg, diethyl ether, reflux, 5 h, 60%; c) 186, Ti(O$^i$Pr)$_4$, *tert*-butyl hydroperoxide, DCM, 4 Å MS, -20 °C, 43 h, 38% (76% of maximum).**

In order to determine the enantioselectivity of the epoxidation and to confirm the absolute configuration, Mosher's esters[89] **189** and **190** of epoxyalcohol **124** were synthesised (**Scheme 3.4**).




**Scheme 3.4 – Reagents and conditions: a) (*S*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, DCC, DMAP, DCM, RT, 20 h, 67%; b) As a) with (*R*)-(+)- α-methoxy-α-(trifluoromethyl)phenylacetic acid, 78%.**

Analysis of the crude $^{1}$H NMR spectra of the Mosher's esters (**189** and **190**) showed the e.e. to be greater than 95%, with the other diastereomers not visible in the NMR spectra. Ohtani *et al.* have developed a reliable method of using the difference in chemical shifts of each proton in the two Moshers esters ($\Delta\delta = \delta_S - \delta_R$) to determine the absolute configuration of secondary alcohols.[90] When drawn in the conformation shown in **Figure 3.3**, if the value of Δδ is negative to the left of the ester oxygen and positive to the right, the configuration of the alcohol is confirmed to be that drawn. When this procedure was applied to the Mosher's esters **189** and **190**, the (*S*)-configuration of the secondary alcohol of epoxyalcohol **124** was confirmed (**Figure 3.3**).

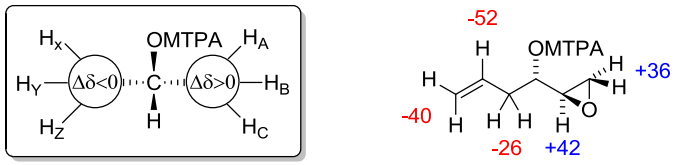
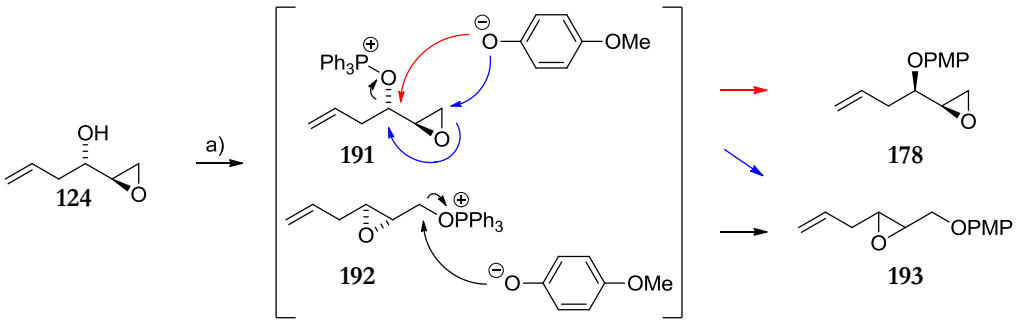



**Figure 3.3 – Mosher's ester analysis and confirmation of absolute configuration (Δδ quoted in Hz).**

### *3.2.2. Mitsunobu Inversion*

In order to achieve the required stereochemistry for the target diastereomer of elatenyne (***ent*-60**) an inversion of configuration of alcohol **124** was needed in one coupling partner. This was hoped to be achieved using a Mitsunobu reaction, but when this was attempted a mixture of the desired product (**178**) and isomer **193** were isolated (**Scheme 3.5**). This isomer (**193**) was thought to be formed by $S_N2$' attack on intermediate **191** and/or *via* intermediate **192** formed by initial Payne rearrangement.[65] Lowering of the initial temperature of the reaction to -78 °C did not inhibit

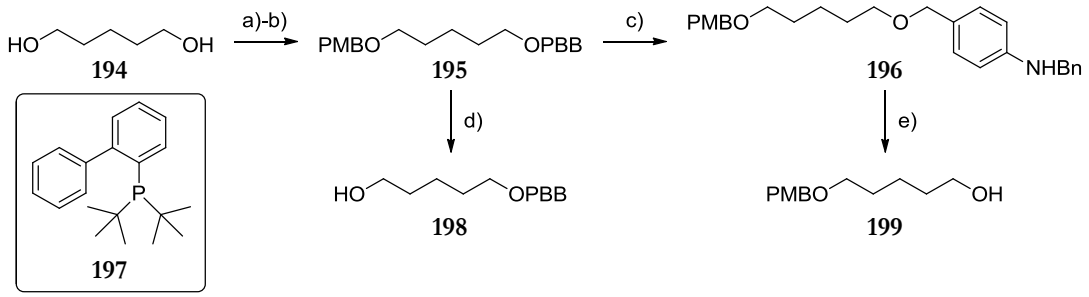
formation of isomer **193** and with the low yield of the desired product (**178**), this route was not feasible.




**Scheme 3.5 – Reagents and conditions: a) $PPh_3$, DIAD, *p*-methoxyphenol, DCM, 0 °C to RT, -78 °C to RT, 16 h, 41% 178 and 15% 193.**

### *3.2.3. Revised Retrosynthetic Analysis and Protecting Group Strategy*

Another approach to the synthesis would involve the use of orthogonal protecting groups, which would allow selective deprotection and inversion of the alcohol at a later stage in the synthesis. This approach would enable late stage diversity and, as such, would be very useful. The deprotection method for both protecting groups would need to be compatible with the unsaturated side chain, whether at the nitrile or enyne stage. Based on literature precedence, it was proposed that *p*-methoxybenzyl (PMB) and *p*-bromobenzyl (PBB) would be suitable and their orthogonal relationship was effectively demonstrated on a model system (**195**, **Scheme 3.6**).[91]

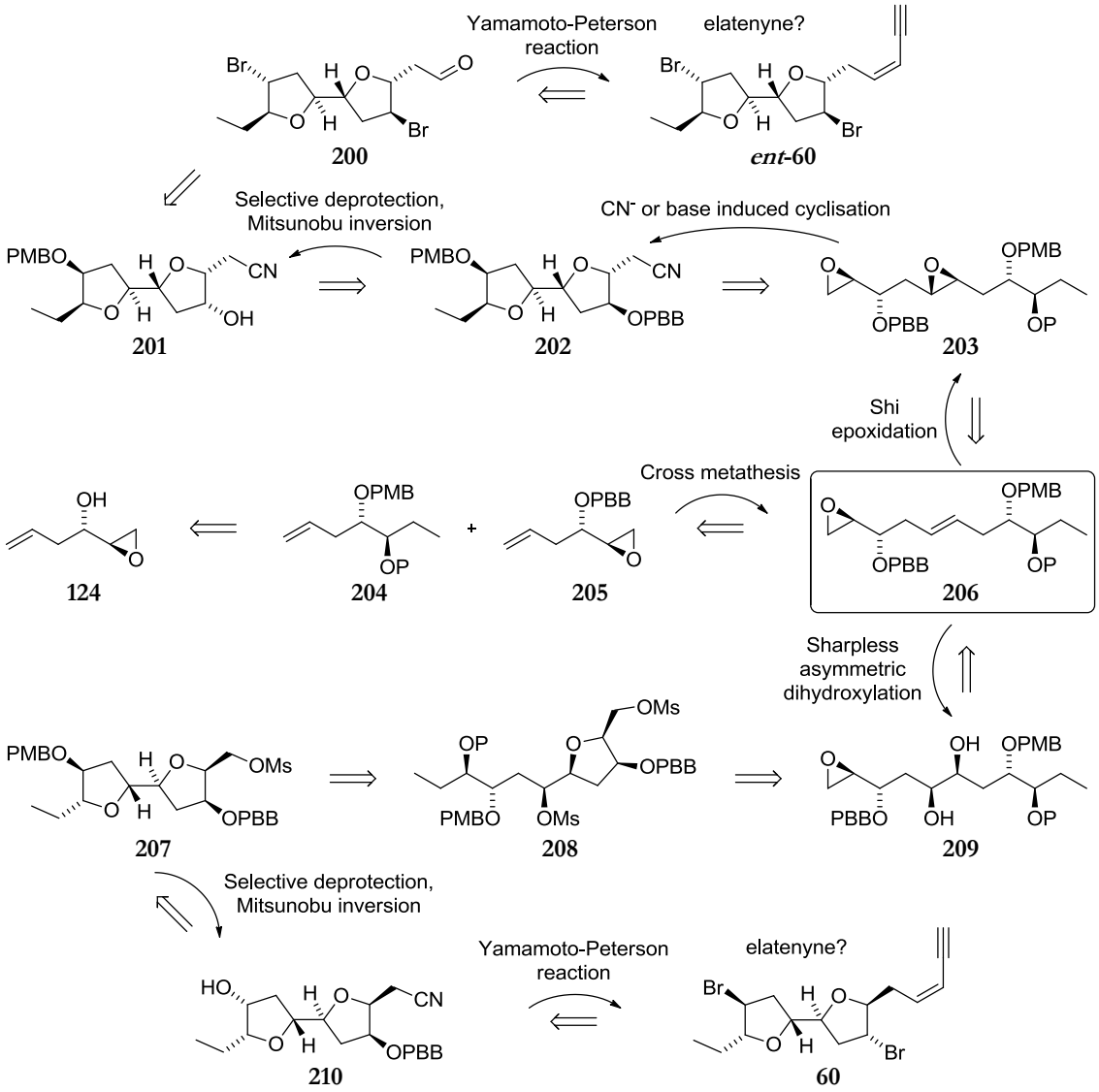



**Scheme 3.6 – Reagents and conditions: a) PBBBr, NaH, DMF, 0 °C to RT, 1.5 h, 60% (20% bis-protected); b) PMBBr, NaH, TBAI, THF, 0 °C to RT, 7 h, 84%; c) $Pd_2dba_3$ (1 mol%), 197 (2 mol%), NaO$^t$Bu, $BnNH_2$, toluene, 80 °C, 5 h, 20% (94% BRSM); d) DDQ, DCM, pH 7 buffer, 0 °C, 2.5 h or $BCl_3{\cdot}SMe_2$, DCM, RT, 5 min, 92%; e) $ZnCl_2$, DCM, RT, 2.5 h, 67%.**

The *p*-methoxybenzyl group was selectively deprotected using DDQ, but the product (**198**) was inseparable from impurities. Pleasingly, clean product (**198**) was obtained by deprotection with

$BCl_3 \cdot SMe_2$ following the method of Burton *et al.*[92] The *p*-bromobenzyl group was selectively deprotected using a Buchwald-Hartwig amination[93] followed by treatment with zinc(II) chloride according to the procedure of Plante *et al.* to yield compound **199** (**Scheme 3.6**).[91]

The use of an orthogonal protecting group strategy would enable greater flexibility in the synthetic route and potentially would allow access to either enantiomer of elatenyne (**60** and ***ent*-60**) from one olefin cross metathesis product (**206**, boxed in **Scheme 3.7**).



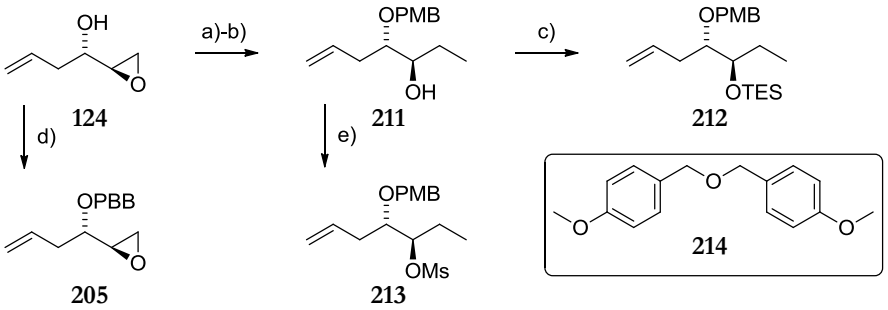

**Scheme 3.7 – Revised retrosynthetic analysis of elatenyne.**

The revised retrosynthesis (**Scheme 3.7**) shows formation of elatenyne (***ent*-60**) *via* a Shi epoxidation and cascade cyclisation pathway, with late stage selective deprotection of the PBB group and Mitsunobu inversion. Whereas, a Sharpless asymmetric dihydroxylation followed by two

cyclisations, late stage selective PMB deprotection, Mitsunobu inversion, bromination and side chain manipulation would give the other enantiomer of elatenyne (**60**, **Scheme 3.7**).

### *3.2.4. Coupling Partner Completion*

The Payne rearrangement needed to be avoided during the *p*-methoxybenzyl protection of epoxyalcohol **124** and so *p*-methoxybenzyl bromide[VI] was used in combination with tetrabutylammonium iodide at -78 °C with rapid warming to RT, as used previously in the Burton group (**Scheme 3.8**).[58, 88b] The protection was successful, but the product was obtained as an inseparable mixture with a derivative of *p*-methoxybenzyl bromide, which was thought to be 4,4'-oxybis(methylene)bis(methoxybenzene) (**214**). Distillation of the *p*-methoxybenzyl bromide prior to use and addition of TMEDA to quench any excess *p*-methoxybenzyl bromide before aqueous work-up did not prevent the formation of impurity **214**. However, after opening the impure *p*-methoxybenzyl protected epoxide with methylmagnesium bromide in the presence of catalytic copper(I), clean alcohol **211** was obtained in good yield (91% over 2 steps). Attempted tosylation of alcohol **211** gave mostly recovered starting material, which was in keeping with the results for tosylation of analogous alcohol **162** in **Chapter 2** (**Section 2.2.2**). Introduction of TES and mesyl groups was successful yielding substrates **212** and **213**. The *p*-bromobenzyl protection to give **205** was achieved again using tetrabutylammonium iodide at -78 °C with rapid warming to RT to avoid a Payne rearrangement (**Scheme 3.8**).




**Scheme 3.8 – Reagents and conditions: a) PMBBr, NaH, TBAI, THF, -78 °C to RT, 16 h; b) MeMgBr, CuI (10 mol%), THF/$Et_2O$, -23 °C, 1 h, 91% over 2 steps; c) TESCl, DMAP, imidazole, DCM, 0 °C to RT, 16 h, 97%; d) PBBBr, NaH, TBAI, -78 °C to RT, 17 h, 95%; e) MsCl, $Et_3N$, DMAP, DCM 0 °C, 1 h, 91%.**

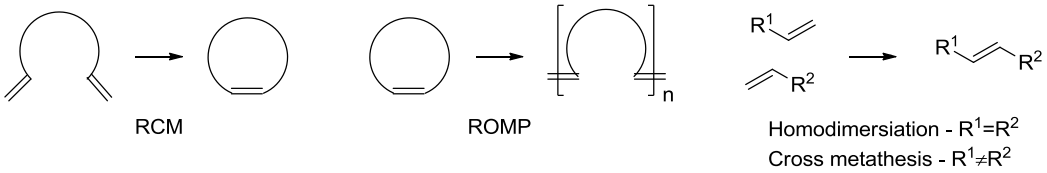
[VI] Freshly prepared from *p*-methoxybenzyl alcohol.

With the two coupling partners (**205** and **212** or **213**, **Scheme 3.8**) in hand the olefin cross metathesis was then investigated.

## 3.3. Cross Metathesis and Alkene Functionalisation

### *3.3.1. Cross Metathesis*

Metal alkylidene catalysed olefin metathesis has had an enormous impact on polymer chemistry and organic synthesis.[94] A range of transformations are possible including ring-closing metathesis (RCM), ring-opening metathesis polymerisation (ROMP), homodimerisation and cross metathesis (**Scheme 3.9**).




**Scheme 3.9 – Types of metathesis reactions.**

The development of commercially available, versatile, efficient catalysts (or precatalysts converted into metal alkylidenes *in situ*) has aided the progress and impact of this methodology. Among the most popular catalysts are the tungsten or molybdenum catalysts developed by Schrock (e.g. **215**) and the ruthenium carbene complexes introduced by Grubbs (e.g. **216** and **127**, **Figure 3.4**).[94a, 94c] Hoveyda has also made practical additions to the range of available catalysts by modifications to Grubbs catalysts to give, for example, the recyclable, robust and more active catalyst **217**.[95]

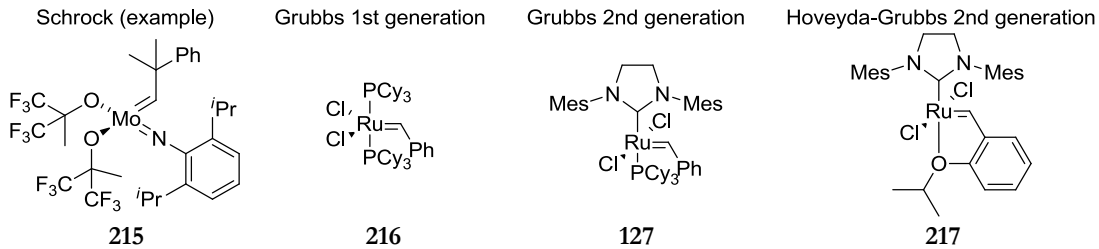
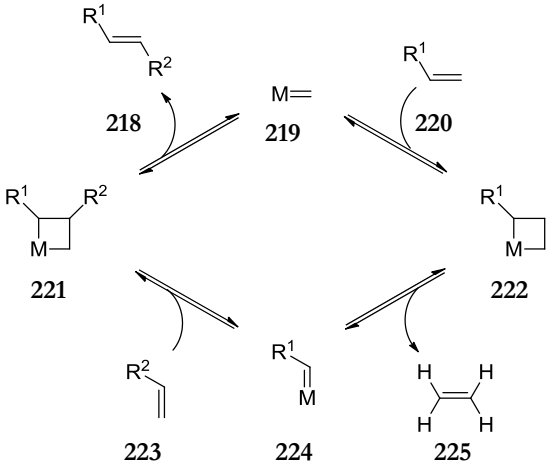



**Figure 3.4 – Metathesis catalysts.**

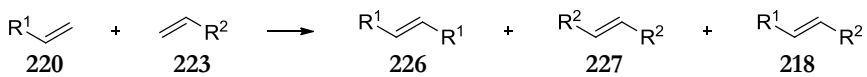
Many investigations have been made into the mechanism of olefin metathesis reactions and it is now generally accepted that the reactions proceed *via* metallocyclobutane intermediates (e.g. **221**

and **222**) formed by [2+2] cycloadditions between a metal alkylidene (e.g. **219** and **224**) and an olefin (**Scheme 3.10**). This mechanism was originally proposed by Hérisson and Chauvin in 1971 and since then has been supported by the observation of intermediates including metallocyclobutanes.[96] **Scheme 3.10** shows a simplified general mechanism for a homodimerisation (if $R^1=R^2$) or a cross metathesis reaction (if $R^1 \neq R^2$). The metal alkylidene **219** undergoes a formal [2+2] cycloaddition with alkene **220** to form metallocyclobutane **222**. This then collapses to release ethene (**225**) and gives a new metal alkylidene **224**. This process is then repeated *via* disubstituted metallocyclobutane **221** to regenerate the catalyst **219** and release product **218** (**Scheme 3.10**).




**Scheme 3.10 – Proposed mechanism of cross metathesis.**

During a cross metathesis reaction, homodimerisation of one or both olefins (**220** and/or **223**) can occur to give homodimers (**226** and/or **227**) rather than the desired product (**218**, **Scheme 3.11**). In some cases these homodimers (**226** and **227**) can go on to react with another metal alkylidene (**219** or **224**) making them still available for cross metathesis, but in some cases they are unreactive.




**Scheme 3.11 – Possible outcomes from a cross metathesis.**

Grubbs and co-workers have completed a study into a general model for selectivity in olefin cross metathesis.[97] They have classified olefins into the four types shown in **Table 3.1** and have investigated the product distribution for cross metathesis reactions. They found that reaction

between two type I olefins gives a statistical product distribution, reaction between two of the same type (not type I) gives a non-selective cross metathesis and the reaction between olefins of two different types gives a selective cross metathesis.

| Type | Reactivity | Examples (with Grubbs II (127)) |
|---|---|---|
| I | Rapid homodimerisation, homodimers consumable | Terminal olefins, allyl halides, esters |
| II | Slow homodimerisation, homodimers sparingly consumable | Acrolein, vinyl ketones, vinyl epoxides, perfluorinated alkane olefins |
| III | No homodimerisation | 1,1-disubstituted olefins, vinyl phosphonates |
| IV | Olefins inert to cross metathesis, but do not deactivate catalyst | vinyl nitro olefins, trisubstituted allyl alcohols (protected) |

**Table 3.1 – Grubbs' olefin classifications.[97]**

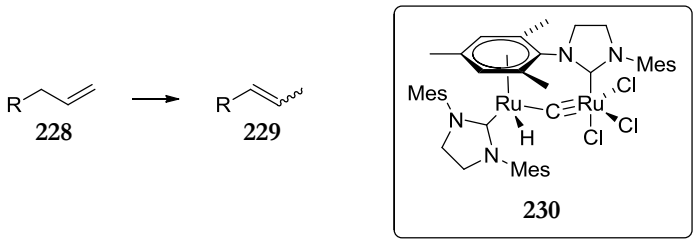
For our desired cross metathesis the two coupling partners (**205** and **204**) are terminal olefins and hence can both be classified as type I olefins. The statistical product distribution for the cross metathesis between two type I olefins means that 50% of the desired product can be obtained. Grubbs and co-workers, however, found that greater product selectivity could be achieved by using an excess of one coupling partner (**Table 3.2**).[97]

| $R^1$:$R^2$ (220:223) | Cross metathesis product selectivity |
|---|---|
| 1:1 | 50% |
| 2:1 | 66% |
| 4:1 | 80% |
| 10:1 | 91% |
| 20:1 | 95% |

**Table 3.2 – Cross metathesis product selectivity with varying substrate ratios.[97]**

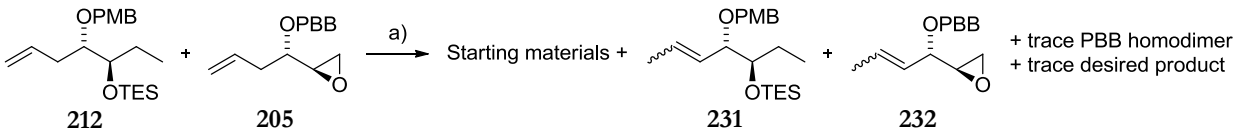
A known reaction, and an anticipated problem in our cross metathesis, was the isomerisation of the terminal olefin (**228**) to an internal olefin (**229**, **Scheme 3.12**). The exact mechanism responsible for the isomerisation is unknown, but it is suggested that ruthenium hydride species, such as **230**, formed from the decomposition of the ruthenium catalyst can catalyse the migrations.[66, 98] The ruthenium catalysed isomerisation of terminal olefins is well known and has been utilised in natural product synthesis, as highlighted by Donohoe *et al.*[99] Grubbs and co-workers have investigated the use of additives to prevent the undesired isomerisation and found that acetic acid or 1,4-

benzoquinones are particularly effective.[66] It is thought that either the additives prevent the formation of ruthenium hydrides or that they react rapidly with the hydrides generated from catalyst decomposition. 1,4-Hydroquinones were observed by $^1$H NMR during reactions with 1,4-benzoquinones to support this hypothesis.



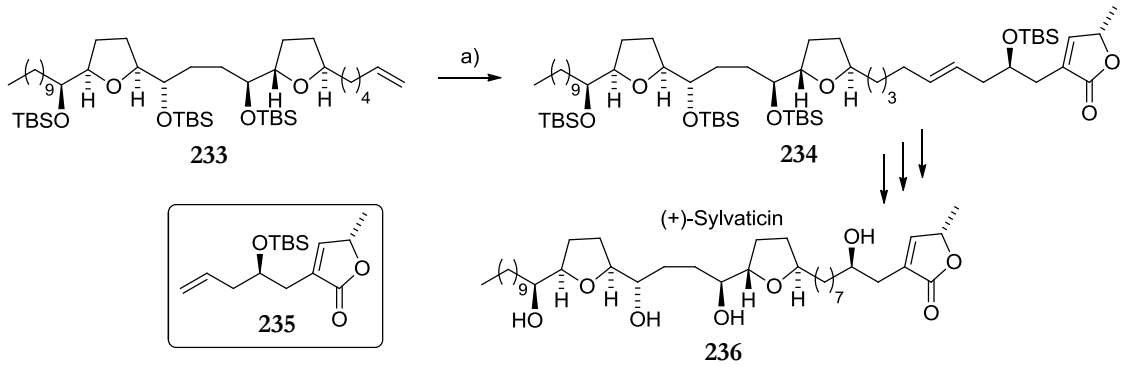

**Scheme 3.12 – Olefin isomerisation and proposed hydride species.**

An initial test reaction carried out using Hoveyda-Grubbs 2$^{nd}$ generation catalyst (**217**, **Figure 3.4**) showed that indeed isomerisation of our coupling partners **205** and **212** did occur to give internal olefins **231** and **232** (**Scheme 3.13**) and hence all subsequent reactions were carried out with an additive.



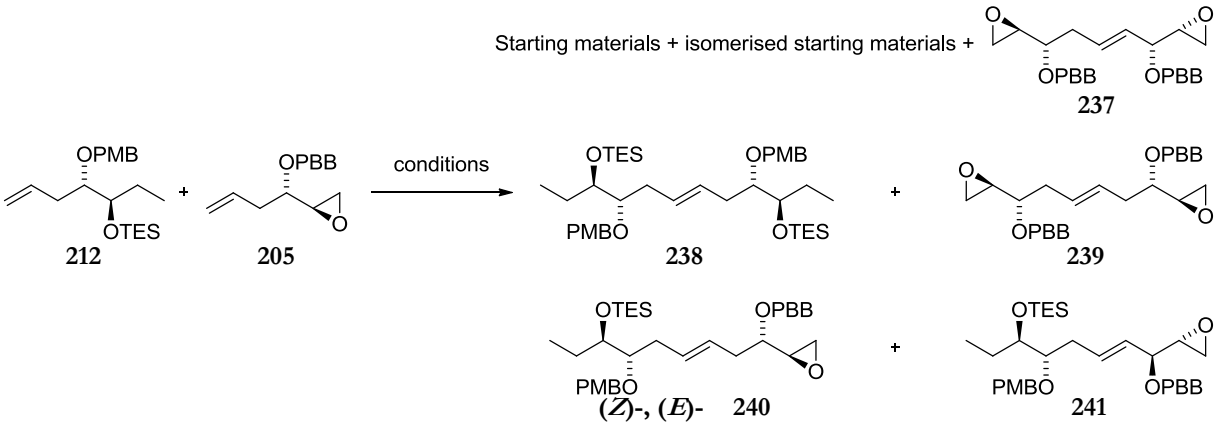

**Scheme 3.13 – Reagents and conditions: a) Hoveyda-Grubbs II (5 mol%), DCM (0.56 M), reflux, 16 h.**

Following conditions used previously within the Burton group for the homodimerisation of a similar substrate (**Chapter 1**, **Section 1.6**), only a trace of cross metathesis product (**240**, **Scheme 3.15**) was observed (**Entry 1**, **Table 3.3**).[58] At that time Donohoe *et al.* reported a cross metathesis of two type I olefins (**233** and **235**) using Hoveyda-Grubbs 2$^{nd}$ generation catalyst in a sealed tube at 70 °C in good yield (84%) to give intermediate **234** *en route* to (+)-sylvaticin (**236**, **Scheme 3.14**).[100]




**Scheme 3.14 – Reagents and conditions: a) Hoveyda-Grubbs II (10 mol%), 235 (4 eq.), DCM, 70 °C, 16 h, 84% (5:1 *E*:*Z*).**[100]

When these conditions were attempted on our system, with acetic acid or 1,4-benzoquinone additives, roughly 50% conversion was observed (**Entries 2 and 3**, **Table 3.3**). It could be seen from the mass recovery and colour of the products obtained from these reactions that ruthenium residues were being carried through the column chromatography. An oxidative work-up using hydrogen peroxide, developed by Knight *et al.*,[101] was therefore used subsequently to enable complete separation of the ruthenium residues during column chromatography. The cross metathesis reaction produced the variety of products (**237** to **241**) shown in **Scheme 3.15**. The use of either 1,4-benzoquinone or acetic acid did not entirely inhibit the isomerisation of the coupling partners (**205** and **212**), even when increased to 25 mol% additive loading. This resulted in the formation of the truncated cross metathesis product **241** from reaction of isomerised PBB-substrate **232** with substrate **212**. Product **241** was difficult to separate from the desired product (**240**) by column chromatography, as could be expected as they differ by only one $CH_2$ unit. The homodimers **238** and **239** of both coupling partners were also recovered, along with the cross metathesis product **237** from reaction of isomerised PBB-substrate **232** with substrate **205**. The PBB-homodimer **239** proved to be reactive when used in the cross metathesis (**Entry 5**, **Table 3.3**). There was not a significant observable difference between the two additives in the reaction and so eventually 1,4-benzoquinone became the additive of choice purely for ease of practical use in small scale reations.




**Scheme 3.15 – Conditions: 1:4 212:205, Hoveyda-Grubbs II (10 mol%), additive, DCM (see Table 3.3).**

| Entry | Additive (mol%) | Concentration /M | Catalyst addition | Temperature[a] /°C | Reaction time[b]/h | Product (240)/% |
|---|---|---|---|---|---|---|
| **1**[c] | 1,4-BQ (10) | 0.56 | solid at start | 40 | 16 | trace |
| **2** | acetic acid (25) | 0.01 | solution, quick | 70 | 16 | ~50[d,e] |
| **3** | 1,4-BQ (25) | 0.01 | solution, quick | 70 | 16 | ~50[d,e] |
| **4** | acetic acid (25) | 0.01 | solution, quick | 70 | 16 | 50[e] |
| **5**[f] | acetic acid (25) | 0.01 | solution, quick | 70 | 16 | 65[e] |
| **6** | acetic acid (25) | 0.017 | solution, quick | 70 | 16 | 64[e] |
| **7** | acetic acid (25) | 0.033 | solution, quick | 70 | 16 | 60[e] |
| **8**[g] | 1,4-BQ (25) | 0.017 | solution, quick | 70 | 16 | 61[e] (4:1 *E*:*Z*) |
| **9** | 1,4-BQ (25) | 0.017 | solution, 6 h | 40 | 130 | 55[j] |
| **10**[h] | 1,4-BQ (25) | 0.017 | solution, 6 h | 70 | 18 | 46[j] |
| **11** | 1,4-BQ (25) | 0.017 | solution, 12 h | 40 | 130 | 56[j] |
| **12**[i] | **1,4-BQ (25)** | **0.017** | **solution, 12 h** | **40** | **60** | **60[j] (3:1 *E*:*Z*)** |

**Table 3.3 – Cross metathesis results. [a]All reactions at 70 °C in sealed tube and at 40 °C in round bottomed flask unless otherwise stated, [b]after addition of catalyst, [c]5 mol% catalyst, [d]ruthenium residues present, [e]mix of (*E*)- and (*Z*)-240 and truncated product 241, [f]PBB-homodimer 239 used instead of substrate 205, [g]0.4 mmol largest scale successful, [h]toluene as solvent in round bottomed flask, [i]6.6 mmol largest scale successful, [j]mix of (*E*)- and (*Z*)-240 and trace of truncated product 241.**

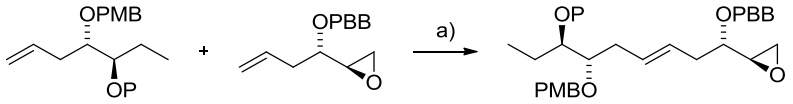
Many conditions were screened for the reaction, including increasing the ratio of subtrates **205**:**212** from 4:1 to 6:1 and 8:1 respectively, which did not have any significant impact on the yield of the products. Grubbs 2nd generation catalyst (**127**) gave a lower product yield than Hoveyda-Grubbs 2nd generation catalyst (**217**) and so the catalyst was not changed. It was found that the use of freeze-thaw degassing was the most effective method and gave more consistent yields than when the solvent was degassed by the bubbling through of argon gas. Increasing the concentration of the

reaction from 0.01 M to 0.017 M gave a slight improvement in yield, which dropped slightly upon an increase to 0.33 M (**Entries 4, 6 and 7**, **Table 3.3**).

The use of a sealed tube to enable the reaction in DCM to be heated to 70 °C was successful on small scale, but proved to be impractical on large scale (**Entry 8**, **Table 3.3**). The use of DCE and toluene at 70 °C was therefore investigated in in a round bottomed flask, but this resulted in a reduced yield (**Entry 10**, **Table 3.3**). The use of DCM at reflux in a round bottomed flask was not successful until it was found that adding the catalyst in solution to the reaction over 6 or 12 hours produced acceptable yields (**Entries 9, 11 and 12**, **Table 3.3**). A pleasing advantage of this method was that the isomerisation of the coupling partners **205** and **212** was reduced, which reduced the formation of compound **241** and therefore greatly eased purification. The slow addition of catalyst had been found to improve metathesis reactions previously both in the Burton group and in work by Sheddan and Mulzer.[102]

The (*E*)- and (*Z*)-isomers of the desired cross metathesis product **240** were only partially separable by normal silica column chromatography and better separation was enabled by the use of silver(I) nitrate impregnated silica following the method of Li *et al.*[103] Silver(I) ions have different affinities for different olefins and in this case a greater affinity for the (*Z*)-olefin, which allowed the (*E*)-olefin to be eluted first.

Unprotected and mesyl protected coupling partners (**211** and **213** respectively) were also used in cross metathesis reactions with the optimised conditions and substrate **205** (**Scheme 3.16**). The unprotected alcohol (**211**) gave a lower yield of product **242** (37%, mix of *E* and *Z*) and the mesyl substrate (**213**) a comparable yield of product **243** (67%, mix of *E* and *Z*). The synthesis was advanced with the TES protected material at this stage as this was compatible with both of our proposed routes.

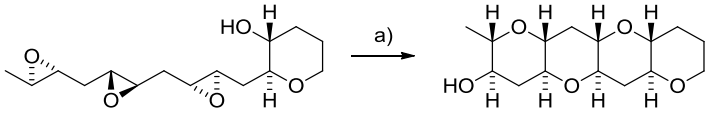



**211 P=H, 213 P=Ms** **205** **242 P=H, 243 P=Ms**

**Scheme 3.16 – Reagents and conditions: a) Hoveyda-Grubbs II (10 mol%, added over 12 h), 1,4-BQ, DCM, 40 °C, 60 h, 37% 242 (4:1 *E*:*Z*), 67% 243 (4:1 *E*:*Z*).**

### *3.3.2. Model Cyclisation*

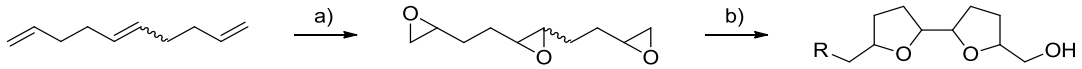
Jamison and co-workers have demonstrated the use of epoxide opening cascades promoted by water or acidic/basic conditions.[104] In this work they overcame the favoured pathway to form THFs by using a template or directing groups to force selectivity towards THP formation, for example in the cyclisation of tris-epoxide **244** to yield THP tetrad **245** (**Scheme 3.17**).




**244** **245**

**Scheme 3.17 – Reagents and conditions: a) $H_2O$, 70 °C, 72 h, 59% (71% corrected for purity of 244).**[104a]

Florence and Cadou formed 2,2'-bifuranyls *via* a one-pot alkyllithium addition/cyclisation of tris-epoxide **247**.[105] In order to study the feasibility of the proposed cascade cyclisation with initial cyanide opening to form THFs, the same tris-epoxide **247** was synthesised from triene **246** according to the procedure of Kakuchi *et al.* (**Scheme 3.18**).[106]




**246** **247** **248, R=CN 249, R=EtO**

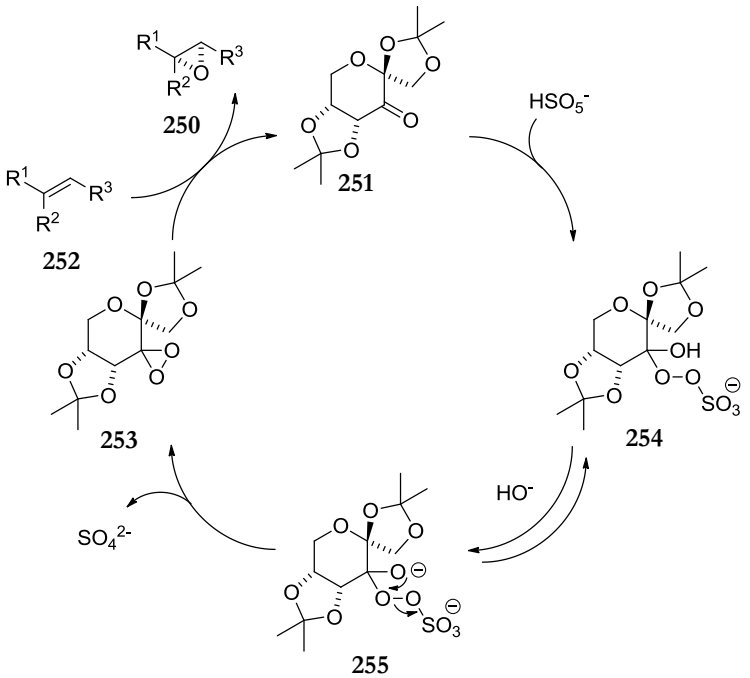
**Scheme 3.18 – Reagents and conditions: a) *m*-CPBA, $CHCl_3$, 0 °C, 4 days, 72%; b) NaCN, EtOH/$H_2O$, RT, 20 h, 46% 248, R=CN and 11% 249, R=EtO.**

A number of conditions were attempted and pleasingly, cyanide was successful in initiating the cascade cyclisation to produce the 2,2'-bifuranyl product **248** (**Scheme 3.18**). This product was unfortunately inseparable from another 2,2'-bifuranyl product **249**, which contained an ethoxy side chain. Lowering the reaction temperature to 0 °C still produced a mixture of the two products. It could not be determined whether use of DMF or DMSO as the reaction solvent was successful as no products were extracted from the aqueous work-up, although product formation was indicated by TLC analysis. This was thought to be due to the very polar nature of 2,2'-bifuranyl product **248**

and was postulated to be an issue with the model system rather than with the reaction on the required system. The $^{13}C$ NMR chemical shifts of the ring junction carbons in the isolation products **248** and **249** were at greater than 80 ppm (apart from those adjacent to the nitrile side chain). This therefore followed the trend previously observed for these carbons (**Chapter 1, Section 1.3.4.1**) and indicated that we had indeed formed the desired THF rather than THP rings.

### *3.3.3. Shi Epoxidation*

In order to perform the cascade cyclisation in the total synthesis of elatenyne (***ent*-60**) a bis-epoxide substrate was required, which could be accessed by stereoselective epoxidation of cross metathesis product **240** (**Scheme 3.15**). The Shi epoxidation was first introduced in 1996 and involves the use of fructose derived ketones (e.g. **251**) in combination with Oxone® (potassium peroxomonosulfate) to form dioxiranes (e.g. **253**) *in situ*.[107] These dioxiranes are used to perform an asymmetric epoxidation of *trans*-olefins (**252** to **250**) as shown in the catalytic cycle by utilising the chiral nature of the fructose sugar (**Scheme 3.19**).




**Scheme 3.19 – Proposed Shi epoxidation mechanism.**

The epoxidation has been studied since then and this has resulted in the development of optimised reaction conditions, a large variety of catalysts, use of hydrogen peroxide as an alternative oxidant

and the application to terminal and *cis*-olefins.[108] The reaction pH has been found to be a very important factor for the epoxidation.[109] Typically the initial epoxidations were carried out at pH 7–8 and at higher pH the autodecomposition of Oxone® was found to be a problem leading to poor epoxidation efficiency. The e.e. also had the potential to be reduced at higher pH if the uncatalysed background reaction became more significant. At pH 7–8, however, the ketone catalyst (**251**) was found to rapidly decompose, a process which is assumed to take place via Baeyer-Villiger reaction of intermediate **254** (**Scheme 3.19**). This decomposition pathway is suppressed by raising the pH and driving the equilibrium towards intermediate **255**. A study of the effect of pH on the reaction showed that addition of potassium carbonate to give a pH of 10.5 lay in the optimal pH range.

The selectivity in the epoxidation can be explained by considering the possible orientations in which the dioxirane and olefin can interact and the possible transition states for the reaction.[63] The dioxirane and olefin can interact in either a spiro or planar orientation, but calculations by Bach *et al.* show that the optimised transition state for oxygen transfer from DMDO to ethylene is the spiro transition state, which is suggested to be due to a stabilising interaction between the oxygen lone pair and the π* orbital of the olefin.[110] **Figure 3.5** shows the most favourable transition state in which the hydrogen projects into the most sterically hindered position and a CH-O dipole interaction can exist. $R^3$ is in the least hindered position and $R^1$ projects over the ring, which means that a higher e.e. can be obtained with smaller $R^1$ and larger $R^3$ groups. The bottom face of the dioxirane is blocked by the *cis*-fused acetonide.

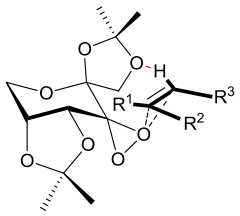
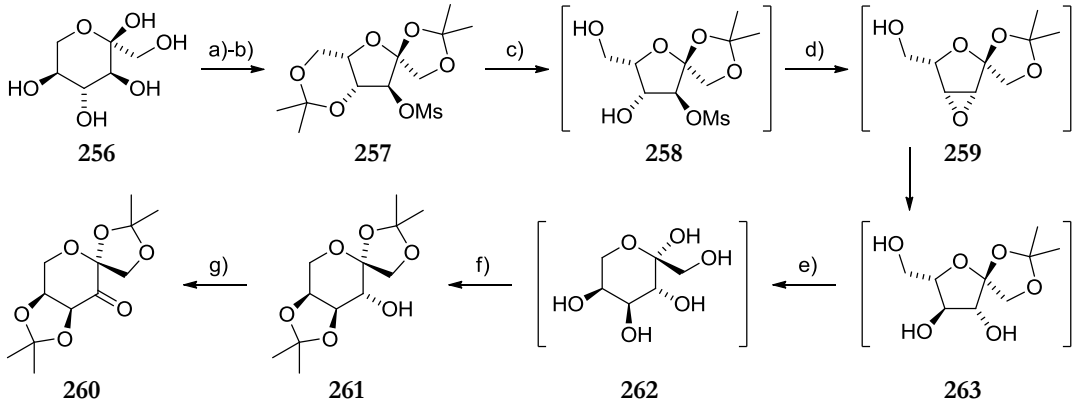



**Figure 3.5 – Most favourable transition state for the Shi epoxidation.**

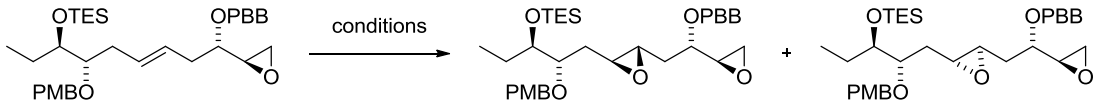
In order to form the correct stereochemistry in the epoxidation required for elatenyne (***ent*-60**), the Shi catalyst (**260**) derived from L-fructose (**262**) was required. Unnatural L-fructose (**262**) is

expensive but was successfully synthesised from L-sorbose (**256**) according to the procedure of Zhao and Shi (**Scheme 3.20**).[111] Formation of the acetonide of L-fructose (**261**) and subsequent PDC oxidation yielded the required catalyst (**260**).




**Scheme 3.20 – Reagents and conditions: a) $SnCl_2$, DMP, DME, 70 °C, 2.3 h; b) MsCl, pyridine, 0 °C, 4 h, 39% (55% BRSM); c) 4.5% aq. $H_2SO_4$, RT, 4 h; d) NaOH, 95 °C, 9 h; e) $H_2SO_4$, 75 °C, 30 min; f) DMP, acetone, $H_2SO_4$, 0 °C, 6 h, 40% over 4 steps; g) PDC, $Ac_2O$, DCM, reflux, 1.5 h, 77%.**

With the catalyst (**260**) in hand, attempts were made to perform the epoxidation of olefin **240** (**Scheme 3.21**). Initial experiments were carried out using a potassium carbonate/acetic acid buffer according to the procedure of Wang *et al.*, but no conversion was observed (**Entry 1**, **Table 3.4**).[112] The epoxidation was then attempted using a sodium tetraborate buffer, which showed some conversion to product (**Entry 2**, **Table 3.4**).[113] It was thought that trace metals present on the reaction glassware could be accelerating catalyst decomposition and therefore the glassware was soaked in a saturated aqueous potassium hydroxide bath for 24 hours before use (**Entry 3**, **Table 3.4**). This, however, did not improve the yield neither did a range of different addition and reaction times (**Entries 4 to 8**, **Table 3.4**). A control reaction with 5 equivalents of Oxone® in the absence of catalyst showed that no conversion took place, but that the starting material (**240**) was unstable in the oxidising conditions (**Entry 9**, **Table 3.4**). The formation of PMB-aldehyde was observed in small amounts in all of the reactions, indicating that the PMB-protecting group was not stable under the reaction conditions. A final experiment using stoichiometric **260** gave no improvement in yield (**Entry 10**, **Table 3.4**).




**240** **264** **265**

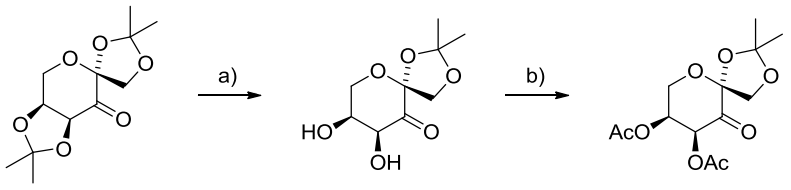
**Scheme 3.21 – Conditions: Catalyst 260 (0.3 eq.), buffer, $Bu_4NHSO_4$ (cat.), Oxone®, $Na_2(EDTA)$, $K_2CO_3$, DMM, MeCN, -10 °C, (See Table 3.4).**

| Entry[a] | Buffer | Eq. of Oxone® | Addition time[b]/h | Reaction time[c]/h | Product/% | SM/% |
|---|---|---|---|---|---|---|
| **1**[d,e] | $K_2CO_3$/AcOH | 1.75 | 2.5 | 2.5 | - | 100[f] |
| **2**[d,e] | $Na_2B_4O_7$[g] | 1.75 | 2 | 1 | 20 | 56 |
| **3**[e] | $Na_2B_4O_7$[g] | 1.75 | 2 | 1 | 16 | 64 |
| **4**[e] | $Na_2B_4O_7$[g] | 1.75 | 5.5 | 1 | 8 | 88 |
| **5** | $Na_2B_4O_7$[g] | 1.75 | 6.5 | 0.5 | 6 | 70 |
| **6**[e] | $Na_2B_4O_7$[g] | 1.75 | 1 | 1 | <14 | 64 |
| **7** | $Na_2B_4O_7$[g] | 1.38 | 2 | 46 | trace | <70 |
| **8** | $Na_2B_4O_7$[g] | 3.5 | 2 | 46 | <12 | 66 |
| **9**[h] | $Na_2B_4O_7$[g] | 5 | 2 | 1 | - | 72 |
| **10**[i] | $Na_2B_4O_7$[g] | 1.38 | 2 | 22 | <12 | 66 |

**Table 3.4 – Shi epoxidation results. [a]All reactions on a mixture of (*E*)- and (*Z*)-240 and 241, [b]Oxone® in aq. $Na_2(EDTA)$ and $K_2CO_3$ in $H_2O$ added via syringe pump, [c]After addition time, [d]Glassware not soaked – all other reactions glassware soaked for 24 h in base bath prior to use, [e]Reaction carried out with *ent*-260 catalyst to test reactivity, [f]From crude $^1$H NMR, [g]In $Na_2(EDTA)$ see ref.[113], [h]No catalyst, [i]Stoichiometric in catalyst 260.**

The catalyst activity was tested by epoxidation of 1-methylcyclohex-1-ene, a literature substrate,[63] and the crude $^1$H NMR showed full conversion to the epoxide, suggesting our substrate (**240**) was significantly less reactive.

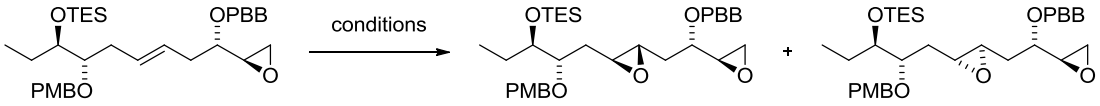
Shi introduced a more robust acetate modified catalyst (**267**) for the epoxidation of α,β-unsaturated esters in 2002.[114] Vidal-Ferran and co-workers demonstrated a practical synthesis of this catalyst and have shown it to be very effective with a broad substrate scope.[115] Synthesis of catalyst **267** was completed from the original catalyst **260** using the optimised procedures of Vidal-Ferran and co-workers (**Scheme 3.22**).[115a] Selective ketal cleavage was achieved with a mixture of acetic acid and water to give diol **266** and acetylation to give catalyst **267** was carried out under mild conditions to avoid elimination.




**260** **266** **267**

**Scheme 3.22 – Reagents and conditions: a) AcOH, $H_2O$, RT, 21 h, 87% (89% BRSM); b) $ZnCl_2$, $Ac_2O$, RT, 3 h, 83%.**

Catalyst **267** was then used in the epoxidation of olefin **240** using the conditions of Vidal-Ferran and co-workers (**Scheme 3.23**, **Conditions A**).[115a] Although catalyst **267** achieved good diastereomeric ratios (>15:1 d.r.) and greater conversion than previous results (**Table 3.5** *cf.* **Table 3.4**), yields were still low. Investigations altering the equivalents of Oxone®, the addition time of potassium carbonate and Oxone® and the subsequent reaction time showed only a small improvement in yield with a longer addition time (**Table 3.5**). When the epoxidation was carried out on pure (*E*)-**240** there was no significant difference in the results and therefore further optimisations were not pursued (**Entry 5**, **Table 3.5**). The products obtained from the epoxidation were often inseparable from impurities and in order to characterise epoxides **264** and **265** purification by semi-preparative HPLC was required.




**240** **264** **265**

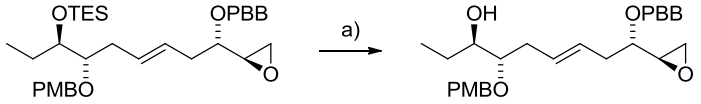
**Scheme 3.23 – Conditions: A) Catalyst 267 (30 mol%), pH 6 buffer ($KH_2PO_4$/KOH see ref.[115a]), $Bu_4NHSO_4$ (cat.), Oxone®, $K_2CO_3$, DMM, MeCN, 0 °C, (See Table 3.5); B) DMDO, $Na_2B_2O_7$ buffer, acetone, DCM, 0 °C to RT, 16 h, 50% (1:1 d.r., 55% BRSM) and 24% PMB deprotected product.**

| Entry[a] | Eq. of Oxone® | Addition time[b]/h | Reaction time[c]/h | Product/% | SM/% |
|---|---|---|---|---|---|
| **1** | 1.63 | 2 | 21 | <37 | 26 |
| **2** | 1.63 | 12 | 80 | ~40 | <40 |
| **3** | 3.26 | 2 | 16 | <28 | 36 |
| **4** | 1.63 | 36 | 12 | <31 | 56 |
| **5**[d] | 1.63 | 12 | 18 | ~42[e] | 57 |

**Table 3.5 – Shi epoxidation results. [a]All reactions using conditions A and glassware soaked for 24 h in base bath prior to use and on a mixture of (*E*)- and (*Z*)- 240 and 241 unless otherwise stated, [b]Oxone® in pH 6 buffer and $K_2CO_3$ in $H_2O$ added *via* syringe pump, [c]After addition time, [d]Reaction on pure (*E*)-240, [e]>15:1 d.r. 264:265.**

To test the reactivity of olefin **240**, and to be sure there was no bias in the system for one diastereomer to be formed, a racemic epoxidation was attempted. Use of DMDO under buffered conditions produced a 1:1 mixture of epoxides **264** and **265** in 50% yield (**Scheme 3.23**, **Conditions B**). A by-product isolated, which was identified as PMB deprotected product (*m/z* 539/537 ($M+Na^+$, 70%)), indicated again that there were stability issues under the oxidative epoxidation conditions.

In order to attempt the epoxidation on unprotected alcohol **242** before the cross metathesis had been attempted for this substrate, olefin **240** was deprotected with TBAF (**Scheme 3.24**). Epoxidation using the conditions of **Entry 5** (**Table 3.5**), however, produced no improvement in yield (<42%) and the same purification problems.



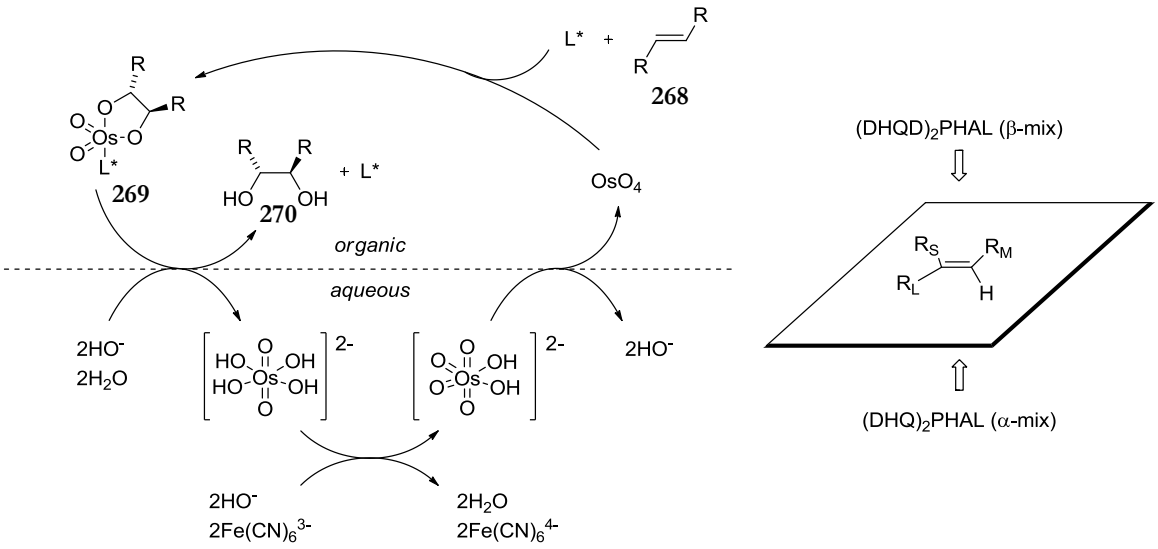

**240** **242**

**Scheme 3.24 – Reagent and conditions: a) TBAF, THF, RT, 3 h, 46% (10% PMB deprotected 242).**

### *3.3.4. Sharpless Asymmetric Dihydroxylation*

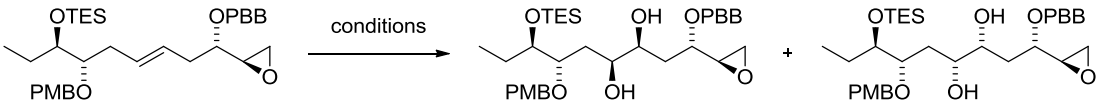
With the Shi epoxidation producing poor yields, efforts were focussed on the functionalisation of olefin **240** using the Sharpless asymmetric dihydroxylation. The Sharpless asymmetric dihydroxylation does not require any directing group to be present on the substrate and makes use of derivatives of cinchona alkaloids (e.g. $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$) as ligands to install the stereochemical information.[116] The optimised reaction conditions use substoichiometric amounts of potassium osmate(VI) dihydrate in a two phase mixture with potassium hexacyanoferrate(III) as the stoichiometric reoxidant. The catalytic cycle is shown in **Scheme 3.25** along with the mnemonic for predicting the selectivity of the dihydroxylation with the two commonly used ligands. The ligand (L*) and alkene (**268**) add to the osmium tetroxide to form an osmium glycolate (**269**). The glycolate **269** is then hydrolysed, releasing the ligand (L*) and product (**270**) into the organic layer and osmium(VI) into the aqueous layer before reoxidation can occur.

Sharpless and co-workers have found that addition of methanesulfonamide to the reaction results in an increased rate of reaction in most cases and this has been found to be due to the accelerated hydrolysis of the osmium glycolate **269**.[116-117] The practicality of this process has been greatly improved by the availability of AD-mix-α and AD-mix-β, premixes containing all the reagents including the catalyst.




**Scheme 3.25 – Proposed Sharpless asymmetric dihydroxylation mechanism and mnemonic.[116]**

When commercially available AD-mix-α was used in the reaction with olefin **240**, disappointingly, only a trace of the dihydroxylation products **271** and **272** were observed (**Scheme 3.26**, **Entry 1**, **Table 3.6**). Increasing the quantity of osmium catalyst and ligand present to 0.01 and 0.02 equivalents respectively improved the yield to 35% (**Entry 2**, **Table 3.6**). A vast improvement was found upon application of Nicolaou and co-worker's 'Super-AD-mix-α', which was used in their synthesis of Zaragozic Acid A/Squalestatin S1 (**Entry 3**, **Table 3.6**).[118] This 'Super-AD-mix-α' increased the equivalents of the ligand and methanesulfonamide to 0.1 and 3 respectively and achieved a greater conversion with a shorter reaction time.




**240** **271** **272**

**Scheme 3.26 – Conditions – $K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, $K_2Fe(CN)_6$ (3 eq.), $K_2CO_3$ (3 eq.), $MeSO_2NH_2$, $^tBuOH$, $H_2O$, 0 °C (See Table 3.6).**

| Entry | Eq. $K_2OsO_4 \cdot 2H_2O$ | Eq. $(DHQ)_2PHAL$ | Eq. $MeSO_2NH_2$ | Reaction time/days | Product/% | SM/% |
|---|---|---|---|---|---|---|
| **1**[a] | 0.002 | 0.01 | 1 | 5+3[b] | trace[c] | ~100[c] |
| **2** | 0.01 | 0.02 | 1 | 6 | 35 | 37 |
| **3**[d] | **0.01** | **0.1** | **3** | **4** | **88**[e] | **-** |
| **4**[f] | 0.01 | 0.1[f] | 3 | 5 | 62[g] | - |

**Table 3.6 – Sharpless asymmetric dihydroxylation results. [a]Using commercial AD-mix-α, [b]At RT, [c]By TLC analysis, [d]Nicolaou and co-workers 'Super AD-mix-α',[118] [e]271:272 4:1 d.r., [f]$(DHQD)_2PHAL$ used, [g]271:272 1:3.5 d.r. and ~27% cyclised product 279 (Scheme 3.29) obtained (89% overall yield).**

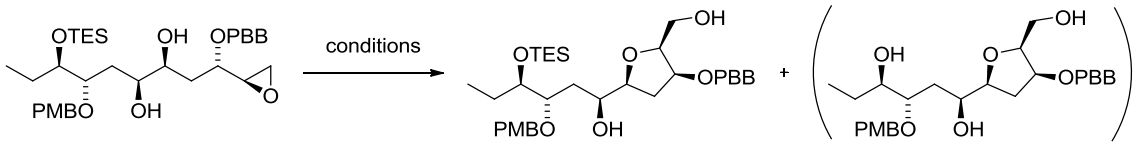
The diastereomers **271** and **272** were partially separable by column chromatography, allowing pure **271** to be obtained. A 'racemic' dihydroxylation was carried out according to the method of Eames *et al.*, along with a dihydroxylation using $(DHQD)_2PHAL$ (**Entry 4**, **Table 3.6**), in order to check for any stereoselective bias with olefin **240** and to help determine the diastereomeric ratio by isolating pure minor diastereomer.[119] The $^1H$ NMR of the crude racemic dihydroxylation indicated that the diastereomeric ratio of diols **271**:**272** was 1:1.3, showing no significant bias in the system for one diastereomer.

It was not possible to confirm the absolute configuration of the isolated diol products **271** and **272** from the dihydroxylation at this point in the synthesis by Mosher's ester analysis. It was seen, however, that the dihydroxylation using $(DHQD)_2PHAL$ produced the opposite diastereoselectivity so we continued with the synthesis and were able to perform Mosher's ester analysis on a later intermediate (**Section 3.4.2**).

## 3.4. Cyclisations and Side Chain Manipulation

### *3.4.1. Epoxide Ring Opening*

In order to form the first THF ring of elatenyne (**60**), one of the hydroxyl groups of **271** needed to cyclise and open the epoxide ring. Intramolecular cyclisations of this type are known in the literature using a range of acidic conditions, including CSA, zinc(II) chloride and hydrochloric acid.[120] Initial reactions with CSA and hydrochloric acid revealed that the cyclisation was successful, but that the TES-protecting group was not stable under the acidic conditions producing triol **274** (**Scheme 3.27**, **Entries 1 and 2**, **Table 3.7**). Use of zinc(II) chloride was less successful, causing no reaction at 0 °C and formation of an inseparable by-product at room temperature (**Entries 3 and 4**, **Table 3.7**).




**271** **273** **274**

**Scheme 3.27 – Conditions: See Table 3.7.**

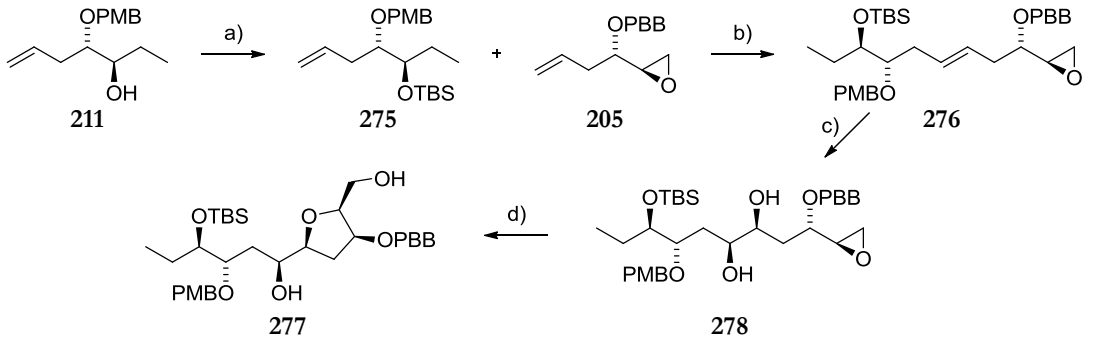
| Entry | Acid | Solvent | Temperature /°C | Reaction time/h | SM 271/% | Product 273/% | Triol 274/% |
|---|---|---|---|---|---|---|---|
| **1** | ~10 mol% CSA | DCM | RT | 0.25 | - | 50 | 40 |
| **2** | 1 drop HCl/$Et_2O$ | $CHCl_3$ | 0 | 2.5 | - | 70 | 25 |
| **3** | 3.5 eq. $ZnCl_2$ | $Et_2O$ | 0 | 24 | 100[a] | - | |
| **4** | 3.5 eq. $ZnCl_2$ | $Et_2O$ | RT | 24 | ?[b] | ?[b] | - |
| **5** | 1% HCl/$Et_2O$ in $CHCl_3$ | $CHCl_3$ | -20 then -5 | 1.5 then 4 days | ~95 | 5 | - |
| **6** | 2% HCl/$Et_2O$ in $CHCl_3$ | $CHCl_3$ | 0 | 20 | 50 | 36 | - |
| **7** | 2% HCl/$Et_2O$ in $CHCl_3$ | $CHCl_3$ | RT | 16 | 40 | 50 | - |
| **8** | 4% HCl/$Et_2O$ in $CHCl_3$ | $CHCl_3$ | 0 | 16 | 45 | 15 | - |
| **9[c]** | 1% CSA in DCM | DCM | 0 to ~5[d] | 2 then 16 | - | 55 | 18 |
| **10[c]** | 1% CSA in DCM | DCM | 0 | 7.5 | 14 | 64 | 18 |
| **11[c]** | **1% CSA in DCM** | **DCM** | **0** | **3** | **15** | **72** | **8** |

**Table 3.7 – Cyclisation results. [a]By TLC analysis, [b]Conversion to product observed by TLC, but inseparable milky deposit present, [c]Reaction mixture loaded cold directly onto column, [d]In refrigerator.**

In order to more accurately control the quantity of acid being added into the reactions, solutions of hydrochloric acid in chloroform and CSA in DCM were made. Reactions with hydrochloric acid at

a range of temperatures and loadings inhibited the formation of triol **274**, but greater conversion of starting material did not lead to higher product yields (**Entries 5 to 8**, **Table 3.7**). With CSA it was found that allowing the reaction to go to completion produced a lower yield of product than stopping the reaction early (**Entries 9 to 11**, **Table 3.7**). It was found that allowing the reaction to run for 3 hours, followed by immediate column chromatography of the cold reaction mixture produced an acceptable yield of THF **273** (72%, 87% BRSM, **Entry 10**, **Table 3.7**).

It was thought that an additional method of overcoming the instability of the TES-protecting group, was to use a more acid stable TBS-protecting group. The synthesis was therefore repeated from alcohol **211** using the TBS-protecting group to give diol **278** from the Sharpless asymmetric dihydroxylation (**Scheme 3.28**). Cyclisation of diol **278** with CSA was now more successful giving THF **277** in 85% yield with no silyl deprotection detectable.

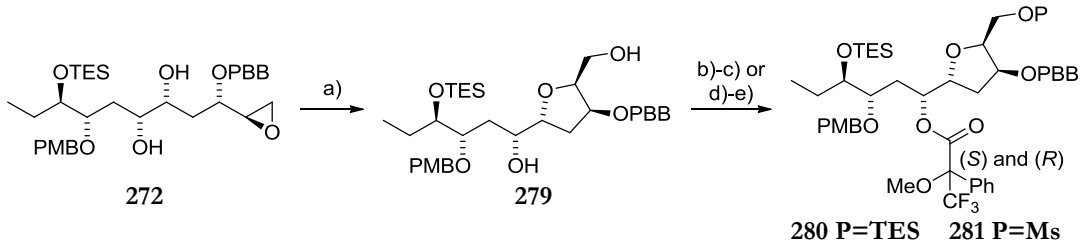



**Scheme 3.28 – Reagents and conditions: a) TBSCl, imidazole, DMF, RT, 18 h then 60 °C, 5 h, 92%; b) Hoveyda-Grubbs II, 1,4-BQ, DCM, 40 °C, 12+48 h, 58% (4:1 *E*:*Z*); c) $K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, $^tBuOH$, $H_2O$, 0 °C, 96 h, 70% (4.5:1 d.r.); d) CSA, DCM, 0 °C, 20.5 h, 85%.**

### *3.4.2. Mosher's Ester Analysis*

In order to confirm the absolute stereochemistry of the Sharpless asymmetric dihydroxylation, the minor diol diastereomer (**272**) was cyclised with catalytic CSA and the resulting THF **279** mono-mesylated (**Scheme 3.29**). Subsequent esterification using Mosher's acid chlorides with triethylamine and DMAP was successful yielding both esters (*S*)- and (*R*)-**281** in 78% yield. Initial attempts to form Mosher's esters (*S*)- and (*R*)-**280** by mono-TES protection of THF **279** and subsequent attempted Mosher's ester formation with DCC had failed (**Scheme 3.29**). This was thought to be due to removal of the TES groups during the attempted esterification and

subsequent side reactions occurring as the only compounds present ran on the baseline during TLC analysis. Esterification of the mono-mesylate derived from THF **279** using Mosher's acids with DCC did form the Mosher's esters, but they were inseparable from impurities.




**Scheme 3.29 – Reagents and conditions: a) CSA, DCM, 0 °C, 3 h, 40%; b) TESCl, imidazole, DMAP, DCM, 0 °C, 4 h, 24% (40% BRSM); c) (*S*)- and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, DCC, DMAP, DCM, RT, 20 h, 0%; d) MsCl, $Et_3N$, DCM, 0 °C, 10 min, 35%; e) (*S*)- or (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, $Et_3N$, DMAP, DCM, RT, 20 h, 78% (*S*)-281, 78% (*R*)-281.**

Analysis of the $^1$H NMR data for the two Mosher's esters (*S*)- and (*R*)-**281**, according to the method of Ohtani *et al.* (**Section 3.2.1**) confirmed the (*R*)-configuration of the hydroxyl installed during the Sharpless asymmetric epoxidation (**Figure 3.6**), which matched with that predicted for the minor diastereomer from the Sharpless mnemonic (**Scheme 3.25**, **Section 3.3.4**).[90]

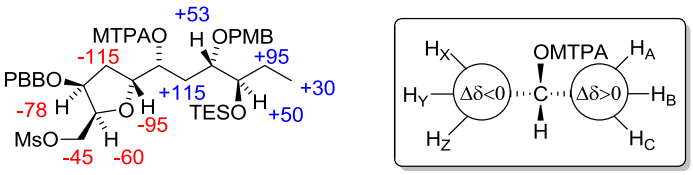
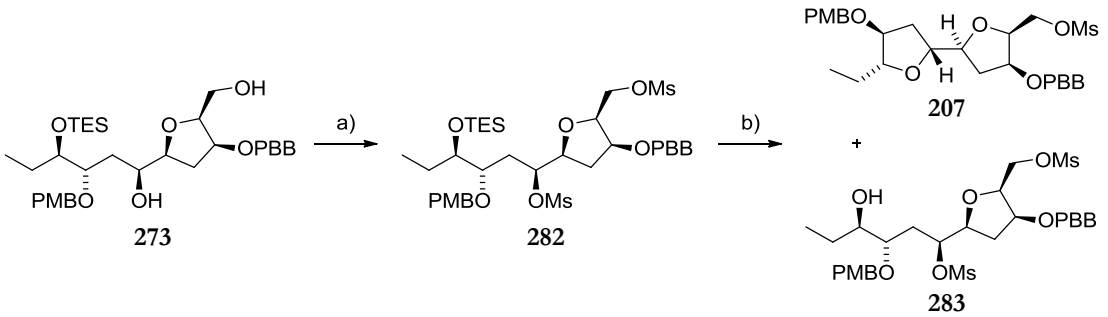



**Figure 3.6 - Mosher's ester analysis and confirmation of absolute configuration (Δδ quoted in Hz).**

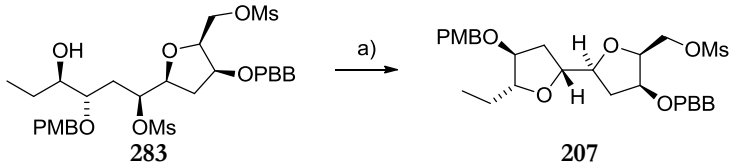
### *3.4.3. 2,2'-Bifuranyl Formation*

The next step in the synthesis involved formation of the second THF ring to give the 2,2'-bifuranyl core of elatenyne (**60**). This was done for the TES-protected substrate by bis-mesylation of cyclisation product **273** followed by one-pot TBAF deprotection and cyclisation, by displacement of the secondary mesylate, to give a mixture of 2,2'-bifuranyl **207** and uncyclised product **283** (**Scheme 3.30**). It was found that the yield over the two steps was higher when bis-mesylate **282** was used without purification.



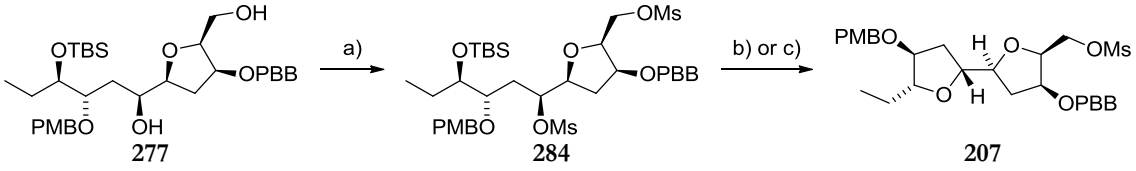

**Scheme 3.30 – Reagents and conditions: a) MsCl, $Et_3N$, DCM, 0 °C, 10 min; b) TBAF, THF, RT, 16 h, 66% 207 over 2 steps, 26% 283.**

It was postulated that the uncyclised product **283** was formed because of water present in the TBAF solution preventing cyclisation. The deprotection was therefore also attempted with TASF, an anhydrous fluoride source, but without improvement. The uncyclised product **283** could, however, be easily converted to the desired 2,2'-bifuranyl **207** in good yield by subjection to basic conditions (**Scheme 3.31**).




**Scheme 3.31 – Reagents and conditions: a) KHMDS, THF, RT, 20 min, 84%.**

When the 2,2'-bifuranyl formation was attempted with TBS-protected substrate **277** the one-pot deprotection/cyclisation was less successful. Bis-mesylate **284** was synthesised in 94% yield, but when subjected to the same TBAF conditions the deprotection was much slower and only 47% of 2,2'-bifuranyl **207** was formed after 2 days (**Scheme 3.32**). The deprotection was also attempted with hydrochloric acid, but after 5 days only 29% of product **207** was recovered with 52% of the uncyclised product **283**.

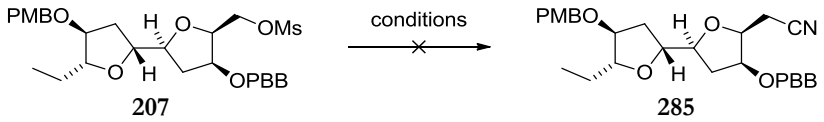



**Scheme 3.32 – Reagents and conditions: a) MsCl, $Et_3N$, DCM, 0 °C, 10 min, 94%; b) TBAF, THF, RT, 48 h, 47% (90% BRSM); c) HCl, EtOH, RT, 5 days, 29% (52% uncyclised product 283, Scheme 3.30).**

The slight improvement in yield for the CSA cyclisation with the TBS-protecting group did not compensate for the slow and poor yielding deprotection and therefore work with substrate **277** was not continued.

### *3.4.4. Cyanide Displacement*

In order to install a handle for later formation of the enyne side chain, a cyanide displacement of the primary mesylate **207** was attempted (**Scheme 3.33**). A range of conditions were attempted, but the formation of nitrile **285** was not observed (**Entries 1 to 6**, **Table 3.8**). The use of tetrabutylammonium cyanide in acetonitrile at reflux for 24 hours gave slight conversion to product by $^{1}$H NMR analysis (**Entry 7**, **Table 3.8**).




**207** **285**

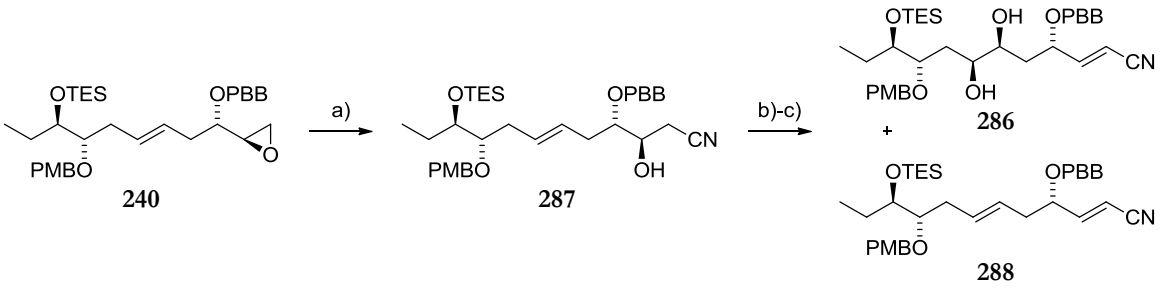
**Scheme 3.33 – Conditions: See Table 3.8.**

| Entry | Reagents | Solvent | Temperature /°C | Reaction time/h | Product/% |
|---|---|---|---|---|---|
| **1** | NaCN | DMF | 60 | 24 | -[a] |
| **2** | NaCN | DMSO | 90 | 63 | -[b] |
| **3** | NaCN | MeCN | 70 | 48 | -[a] |
| **4** | NaCN | EtOH | 70 | 48 | -[a] |
| **5** | KCN, crown ether | DMF | 155 | 24 | -[b] |
| **6** | KCN, NaI | DMSO | 80 | 24 | -[c] |
| **7** | $Bu_4NCN$ | MeCN | 70 | 24 | trace[d] |

**Table 3.8 – Cyanide displacement results. [a]Only SM present by crude $^{1}$H NMR, [b]No product or SM by crude $^{1}$H NMR, [c]SM and by-products by crude $^{1}$H NMR, [d]50% starting material recovered.**

Since 2,2'-bifuranyl mesylate **207** had been shown to be unreactive to cyanide displacement, it was thought that the nitrile group could be installed at an earlier stage in the synthesis. Cross metathesis product **240** was therefore treated with diethylaluminium cyanide according to the procedure of Fujimori *et al.* to give nitrile **287** (**Scheme 3.34**).[121] Nitrile **287** was then treated with methanesulfonyl chloride, but unfortunately, when the crude mesylate was submitted to Sharpless asymmetric dihydroxylation conditions, elimination of the mesylate occurred and a mixture of

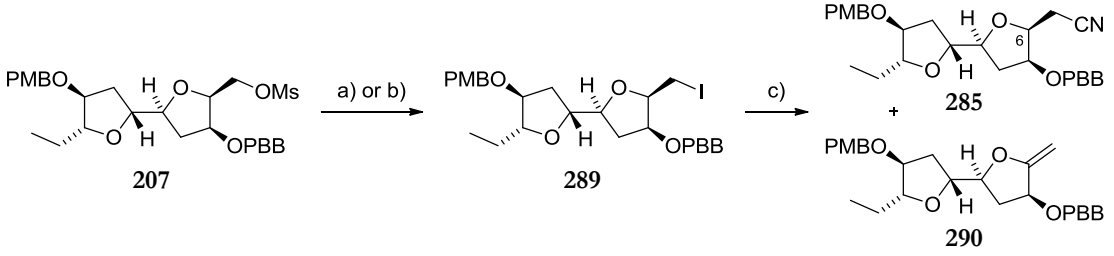
products **286** and **288** was obtained (**Scheme 3.34**). The loss of a stereocentre in products **286** and **288** meant that installation of the nitrile group at this early stage was not feasible.




**Scheme 3.34 – Reagents and conditions: a) $Et_2AlCN$, toluene, 0 °C to RT, 2 h, 84%; b) MsCl, $Et_3N$, 10 min; c) $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, $^tBuOH$, $H_2O$, 0 °C, 96 h, 50% 286 (4:1 d.r.), 19% 288.**

### *3.4.5. Iodide Formation and Grignard Displacement*

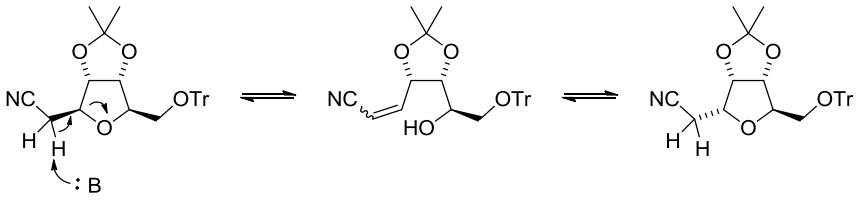
If the 2,2'-bifuranyl **207** was to be a viable intermediate in the synthesis of elatenyne (**60**) conditions were needed for the conversion of the mesylate into a handle for the enyne side chain. It was thought that conversion to a more reactive iodide might allow conversion to the nitrile group. Initially mesylate **207** was subjected to sodium iodide in refluxing acetone, but only 25% conversion to iodide **289** occurred (**Scheme 3.35**). Harsher conditions using 10 equivalents of tetrabutylammonium iodide in refluxing toluene gave a much better conversion of 83%. The greater reactivity of iodide **289** was demonstrated upon conversion to nitrile **285** using tetrabutylammonium cyanide in just 4 hours compared to the trace of product after 24 hours with mesylate **207** (**Scheme 3.35** and **Table 3.8**, **Section 3.4.4**).




**Scheme 3.35 – Reagents and conditions: a) NaI, acetone, RT, 18 h then reflux, 8 h, 25% (100% BRSM); b) $Bu_4NI$, toluene, reflux, 16 h, 83% (91% BRSM); c) $Bu_4NCN$, MeCN, reflux, 4 h, 71% 285, 21% 290.**

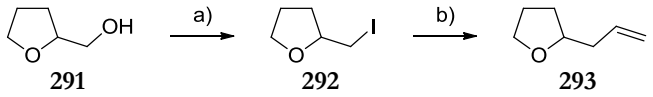
Disappointingly, the synthesis using the nitrile intermediate **285** was not continued further because of the additional formation of alkene **290** under the basic reaction conditions. This led to concern

about the stereochemical integrity of the C6 stereocentre of nitrile **285** because of possible epimerisation. Ohrui *et al.* observed that in the THF rings of some C-glycosyl nucleosides with a nitrile substituent, in the same position as our system, the acidity of the adjacent protons could cause an analogous epimerisation as shown in **Scheme 3.36**.[122]




**Scheme 3.36 – Epimerisation of C-glycosyl nucleosides.[122]**

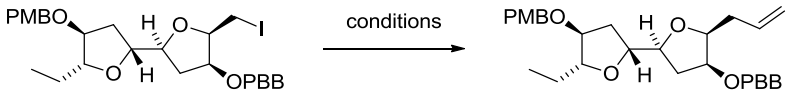
An alternative handle for later installation of the enyne side chain was to displace the iodide with a vinyl group and form an allyl side chain. The allyl group would be able to undergo cross metathesis as demonstrated by Kim and co-workers to form the required enyne (**Section 3.6.1**).[123] In order to test the proposed Grignard displacement, following the literature precedent on similar substrates of Takao *et al.* and Han and Lowary, a model iodide **292** was synthesised from tetrahydrofurfuryl alcohol (**291**, **Scheme 3.37**).[124] Grignard displacement with vinylmagnesium bromide was successful producing allyl-substituted compound **293**, but the isolated yields of both the iodide **292** and Grignard product **293** were very low, presumably due to their volatility.




**291** **292** **293**

**Scheme 3.37 – Reagents and conditions: a) $PPh_3$, $I_2$, imidazole, THF, 0 °C to RT, 2 h, 38%; b) vinylmagnesium bromide, THF, 0 °C to RT, 4 h, 19%.**

When the reaction was carried out using the same conditions in THF with iodide **289**, no formation of product **294** was observed (**Scheme 3.38**, **Entry 1**, **Table 3.9**). Changing the solvent to benzene and carrying out the reaction at room temperature for 24 hours also did not give any desired product **294** (**Entry 2**, **Table 3.9**). Increasing the temperature of the reaction to 60 °C achieved some product formation (**Entry 3**, **Table 3.9**).




**289** **294**

**Scheme 3.38 – Conditions: Vinylmagnesium bromide, benzene, see Table 3.9.**

| Entry | Eq. vinylmagnesium bromide | Temperature /°C | Reaction time/h | SM/% | Product/% |
|---|---|---|---|---|---|
| **1**[a] | 4 | 0 to RT | 22 | 88 | - |
| **2** | 4 | RT | 24 | 100[b] | - |
| **3** | 4 | 60 | 4 | ~25 | ~25 |
| **4** | 4 | 60 | 17 | 60 | - |
| **5** | 4 | 80 | 4 | 80 | - |
| **6** | 4 | 80 | 20 | 17 | - |
| **7** | 10 | 60 | 3 | 11 | 54 |
| **8** | 20 | 60 | 2 | - | 56 |
| **9** | **20** | **40** | **4** | **26** | **58** |
| **10** | 20 | RT | 24 | 60 | - |
| **11** | 20 | 40 | 7 | 14 | 37 |

**Table 3.9 – Grignard displacement results. [a]THF used as solvent, [b]From crude $^1$H NMR.**

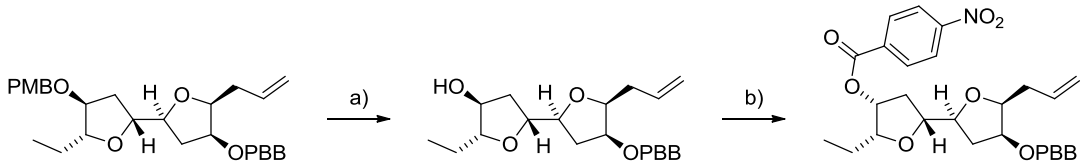
Investigations into the reaction temperature, time and number of equivalents of vinylmagnesium bromide suggested that iodide **289** and/or product **294** were not stable under the reaction conditions, with longer reaction times using the same conditions giving lower yields (**Entries 3 to 11**, **Table 3.9**). This meant that a balance was required between forcing the reaction with harsh conditions and limiting the reaction time to prevent decomposition. The optimal conditions found were using 20 equivalents of vinylmagnesium bromide at 40 °C for 4 hours, which gave 58% of product **294** and 26% recovered iodide **289** (**Entry 9**, **Table 3.9**).

## 3.5. Bromination

### *3.5.1. Selective Deprotection and Mitsunobu Inversion*

Application of the deprotection conditions using $BCl_3{\cdot}SMe_2$ for selective PMB removal, already tested on the model system (**Section 3.2.3**), to substrate **294** was successful to give alcohol **295** quantitatively (**Scheme 3.39**). Mitsunobu inversion of alcohol **295** required some optimisation of the reaction and purification conditions (**Table 3.10**).[76, 125] Initial experiments using 1.5 and 3

equivalents of the reagents produced only a trace of product **296** (**Entries 1 and 2**, **Table 3.10**). Increasing the number of equivalents to 10 gave full conversion of starting material and resulted in a yield of 40% (**Entry 3**, **Table 3.10**). Pleasingly, reduction of the reaction time to 2 hours and immediate dry-loading onto silica gel and column chromatography improved the yield to 85%, suggesting product **296** was unstable under the reaction conditions (**Entry 4**, **Table 3.10**). Removal of the excess reagents proved to be difficult, but it was found that use of a petrol/acetone solvent system for the column chromatography enabled clean product **296** to be obtained.




**294** **295** **296**

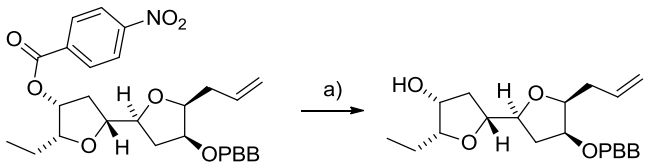
**Scheme 3.39 – Reagents and conditions: a) $BCl_3 \cdot SMe_2$, DCM, RT, 5 min, quant.; b) $PPh_3$, DIAD, 4-nitrobenzoic acid, THF, 0 °C to RT, See Table 3.10.**

| Entry | Eq. $PPh_3$, DIAD and 4-nitrobenzoic acid | Reaction time/h | SM/% | Product/% |
|---|---|---|---|---|
| **1** | 1.5 | 16 | 66 | trace |
| **2** | 3 | 16 | 50 | trace |
| **3** | 10 | 16 | - | 40 |
| **4**[a] | 10 | 2 | - | 85 |

**Table 3.10 – Mitsunobu results. [a]With immediate purification by column chromatography.**

### *3.5.2. Deprotections and Bromination*

In order to proceed towards elatenyne (**60**), the two alcohol groups needed to be deprotected and converted into bromides. The Mitsunobu product **296** was therefore treated with potassium carbonate in methanol to achieve transesterification to give alcohol **297** (**Scheme 3.40**).

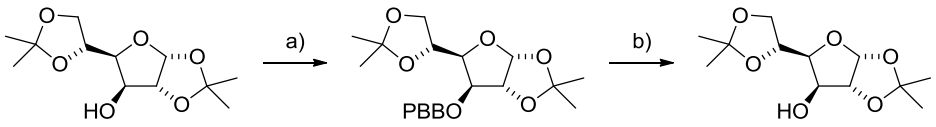



**296** **297**

**Scheme 3.40 – Reagents and conditions: a) $K_2CO_3$, MeOH, 0 °C to RT, 2 h, 94%.**

During the protecting group model studies the PBB-protecting group was selectively removed in the presence of the PMB-protecting group *via* a two step procedure (**Section 3.2.3**). Since the

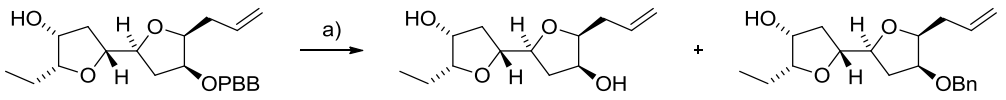
PMB-protecting group was not present in alcohol **297**, an investigation into a one step procedure was carried out. Kozikowski and Lee removed a PBB-protecting group successfully using lithium in ammonia.[126] It was thought that a similar deprotection *via* single electron reduction using LiDBB might be more practical on our small scale.[127] To test this method, a model system (**298**) was protected to give PBB-ether **299** and deprotected successfully using the procedure of Burton *et al.* (**Scheme 3.41**).[128]




**298** **299** **298**

**Scheme 3.41 – Reagents and conditions: a) PBBBr, NaH, TBAI, THF, -78 °C to RT, 16 h, 96%; b) LiDBB, THF, -78 °C, 3 min, quant.**

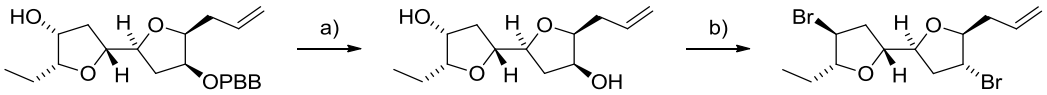
Upon application of this method to alcohol **297** it was found that, although the deprotection formed some of the required diol **300**, benzyl protected substrate **301** was also formed in equal quantity (**Scheme 3.42**). The benzyl protected substrate **301** was formed by removal of the bromide from alcohol **297**, and any attempts to modify the procedure and achieve full conversion through to diol **300** were unsuccessful.




**297** **300** **301**

**Scheme 3.42 – Reagents and conditions: a) LiDBB, THF, -78 °C, 10 min, ~50% 300, ~50% 301.**

The deprotection was attempted using $BCl_3 \cdot SMe_2$, as used for the PMB deprotection, with a longer reaction time, but only slight conversion was observed after 3 days. When the more reactive $BCl_3$ Lewis acid was used, pleasingly, the PBB group was removed in quantitative yield (**Scheme 3.43**). During previous synthetic efforts within the Burton group it was found that the most effective method for bromination of 2,2'-bifuranyls utilised triphenylphosphine and carbon tetrabromide under standard Appel conditions (**Chapter 1**, **Section 1.6**).[58, 129] Diol **300** was therefore converted to dibromide **302** in 70% yield with inversion of configuration using these standard Appel conditions (**Scheme 3.43**).

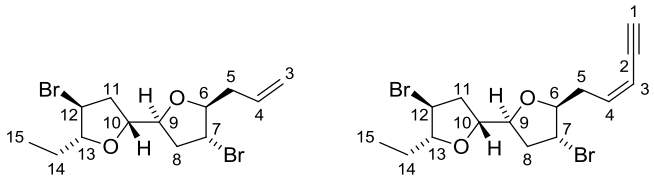



**297** **300** **302**

**Scheme 3.43 – Reagents and conditions: a) $BCl_3$, DCM, RT, 30 min, quant.; b) $PPh_3$, $CBr_4$, toluene, 80 °C, 75 min, 70%.**

### *3.5.3. Comparison of Dibromide 302 and Elatenyne*

A comparison of the $^{13}C$ NMR spectra of dibromide **302** and the natural product data for elatenyne (**60**)[14] at this stage of the synthesis suggested that we were approaching the correct diastereomer. Excluding the obviously different allyl and enyne side chains (C1 to C6, **Figure 3.7**), **Table 3.11** shows a good match between the $^{13}C$ NMR chemical shifts for all of the other carbons.




**302** **60**

**Figure 3.7 – Structures of dibromide intermediate and elatenyne.**

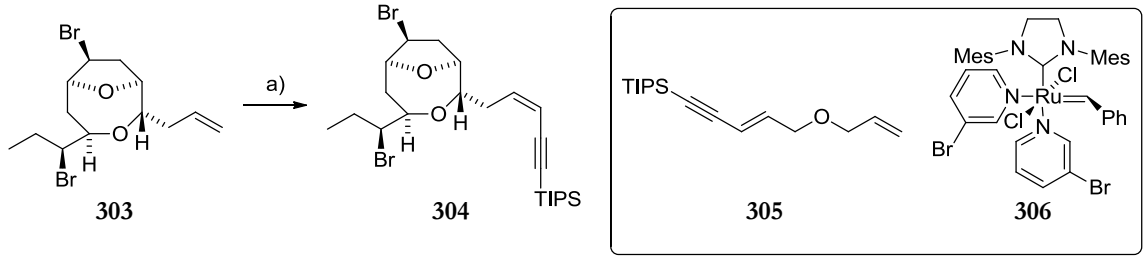
| Position | $\delta_C$ Synthetic dibromide 302 ($C_6D_6$)/pmm | $\delta_C$ Literature ($C_6D_6$)/pmm | $\Delta\delta_{(syn.-lit.)}$ /ppm |
|---|---|---|---|
| 1 | - | 83.0 | - |
| 2 | - | 80.0 | - |
| 3 | 117.8 | 111.2 | +6.6 |
| 4 | 133.8 | 140.1 | -6.3 |
| 5 | 38.0 | 34.7 | +3.3 |
| 6 | 86.8 | 86.4 | +0.4 |
| 7 | 49.3 | 49.2 | +0.1 |
| 8 | 39.1 | 39.0 | +0.1 |
| 9 | 80.0 | 80.0 | - |
| 10 | 79.6 | 79.5 | +0.1 |
| 11 | 39.4 | 39.3 | +0.1 |
| 12 | 48.9 | 48.9 | - |
| 13 | 88.7 | 88.6 | +0.1 |
| 14 | 26.9 | 26.8 | +0.1 |
| 15 | 10.2 | 10.2 | - |

**Table 3.11 – Comparison of $^{13}C$ NMR data for synthetic dibromide 302 and elatenyne natural product data.[14]**

## 3.6. Enyne installations

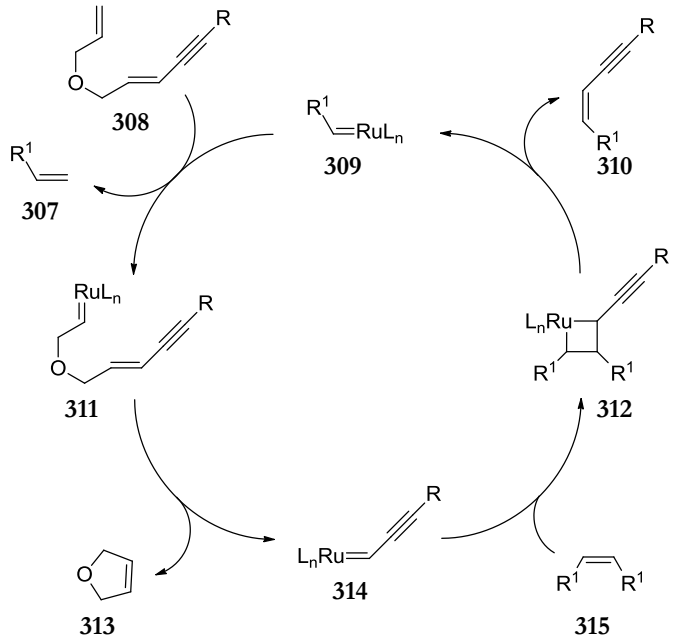
### *3.6.1. Cross Metathesis*

With dibromide **302** in hand, our attentions were focussed on the installation of the enyne side chain of elatenyne (**60**). Kim and co-workers demonstrated a (*Z*)-selective cross metathesis to install the enyne moiety of **304**, an intermediate in their synthesis of (+)-3-(*Z*)-isolaureatin (**Scheme 3.44**).[123] The procedure involved addition of enyne **305** and Grubbs catalyst **306** at regular intervals during the cross metathesis.



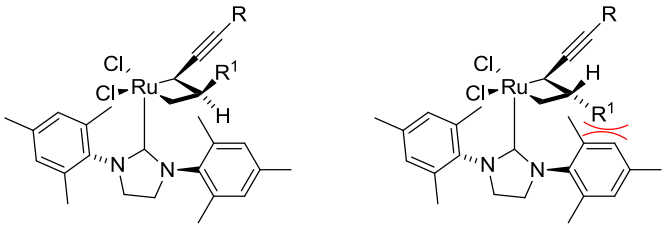

**Scheme 3.44 – Reagents and conditions: a) Enyne 305, Grubbs catalyst 306, benzene, 50 °C, 4 h, >76%, 7:1 *Z*:*E*.[123]**

The use of an allyl ether moiety to act as an intramolecular catalyst delivery vehicle for conjugated enynes in metathesis was developed by Hansen and Lee.[130] They propose a catalytic cycle in which the cross metathesis reaction selectively initiates at the terminal olefin of the allyl group of enyne **308** (**Scheme 3.45**). The conjugated alkynyl alkylidene **314** is then generated from alkylidene **311** with extrusion of dihydrofuran (**313**). Metallocyclobutane **312** is then formed upon formal [2+2] cycloaddition with alkene **315** and its subsequent collapse yields the cross metathesis product **310** and regenerates the catalyst **309**.




**Scheme 3.45 – Proposed catalytic cycle for enyne cross metathesis.**[130]

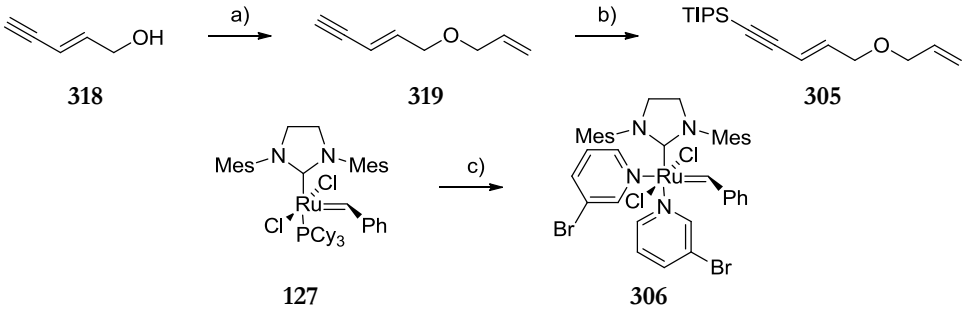
Chang and co-workers investigated substituent effects on the observed (*Z*)-selectivity in the cross metathesis of conjugated enynes.[131] Most cross metathesis reactions are under thermodynamic control, and therefore afford the (*E*)-olefin as the major product, but Chang and co-workers conclude that the cross metathesis of conjugated enynes is under kinetic control. They postulate that the low reactivity of the initially formed kinetic (*Z*)-enyne product means no further reversible metathesis cycles can take place and hence the initial *Z*:*E* ratio is maintained in the product. The initial (*Z*)-selectivity is proposed to originate from the relative energy differences of the corresponding metallocyclobutane adducts (**312**). It can be seen that proposed metallocyclobutane adduct **317** with the two substituents *trans* to each other, which leads to the *E*-olefin product, has significantly larger unfavourable steric interactions (**Figure 3.8**). The proposed metallocyclobutane adduct **316** with the two substituents *cis* to each other is consequently lower in energy and predominates.



**316** **317**

**Figure 3.8 – Proposed metallocyclobutane adducts.**[131b]

Before the cross metathesis protocol could be attempted, enyne **305** and Grubbs catalyst **306** needed to be synthesised. 2-Pentene-4-yn-1-ol (**318**) was treated with sodium hydride and allyl bromide according to the procedure of Yun *et al.* to give enyne **319**, albeit in poor yield, presumably due to its volatility (**Scheme 3.46**).[132] This enyne **319** was then protected with TIPSCl to produce the desired enyne **305**. Grubbs catalyst **306** was synthesised according to the method of Love *et al.* from Grubbs 2nd generation catalyst (**127**).[133]

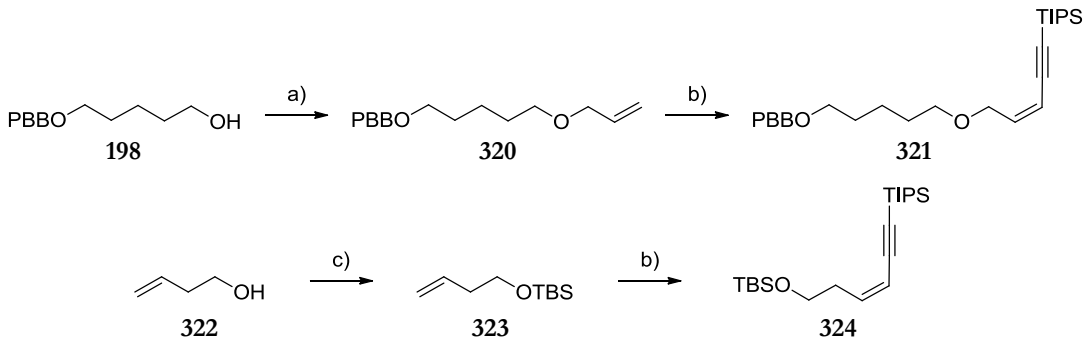


**318** **319** **305**

**127** **306**

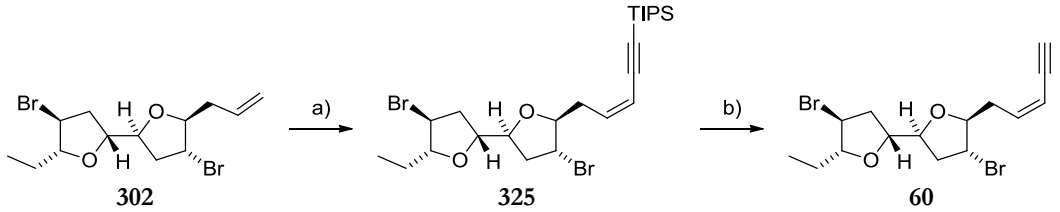
**Scheme 3.46 – Reagents and conditions: a) Allyl bromide, NaH, DMF, RT, 16 h, 30%; b) $^{n}$BuLi, TIPSCl, THF, -78 °C to -30 °C to 0 °C, 2 h, 76%; c) 3-bromopyridine, RT, 5 min, 82%.**

In order to test the cross metathesis reaction, two model substrates **320** and **323** were synthesised from **198** (**Section 3.2.3**) and 3-buten-1-ol (**322**) respectively (**Scheme 3.47**). When the cross metathesis was carried out with model substrate **320** only a trace of enyne product **321** was visible by $^{1}$H NMR analysis. Use of model substrate **323** and a slightly higher temperature gave roughly 60% conversion to enyne **324** by $^{1}$H NMR analysis. Difficulties with volatility and purification of enyne **324** meant that, unfortunately, the selectivity could not be determined, but it was concluded that the protocol had shown sufficient promise to be applied to the natural product synthesis.




**Scheme 3.47 – Reagents and conditions: a) Allyl bromide, NaH, DMF, RT, 16 h, 47%; b) enyne 305, Grubbs catalyst 306, benzene, for 321: 50 °C, trace product (~100% SM by $^1$H NMR), for 324: 65 °C, 1.75 h, ~60% (~40% SM by $^1$H NMR); c) TBSCl, imidazole, DMF, RT 16 h, 82%.**

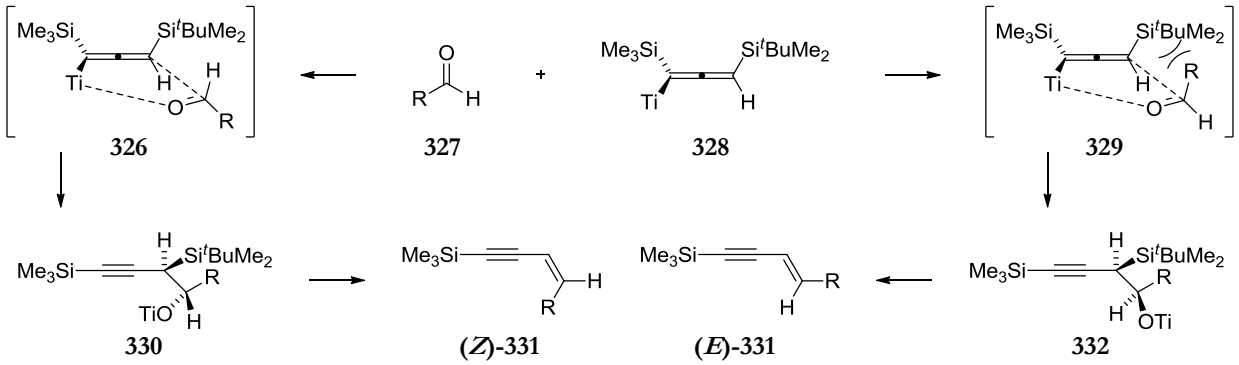
When the cross metathesis was performed on dibromide **302**, even with a total of 16.5 equivalents of enyne **305** and 0.9 equivalents of Grubbs catalyst **306** added over 2.5 hours, only 33% of enyne **325** was produced with roughly 5:1 *Z*:*E* selectivity (**Scheme 3.48**). The reaction was repeated with continuous rather than batch addition of the enyne **305** and Grubbs catalyst **306** over 1.5 hours *via* syringe pump, but only a trace of enyne **325** was observed by $^1$H NMR analysis. The dibromide **302** and enyne **325** were difficult to separate and this was only achieved when a petrol/toluene mixture was used as the column chromatography eluent. The very small quantity of enyne **325** obtained (1.5 mg) was deprotected with TBAF to yield elatenyne (**60**). $^1$H and $^{13}$C NMR data were obtained at this stage, which pleasingly confirmed that the synthetic elatenyne (**60**) matched the natural product, as shown later (**Section 3.7**), but insufficient mass meant that further analytical data was not obtainable. The cross metathesis did not appear a feasible method for accessing any more than trace quantities of elatenyne (**60**) in our hands and so an alternate strategy was sought.




**Scheme 3.48 – Reagents and conditions: a) Enyne 305, Grubbs catalyst 306, benzene, 65 °C, 2.5 h, 33% (~5:1 *Z*:*E*, 97% BRSM); b) TBAF, THF, -20 °C, 30 min, 48%.**

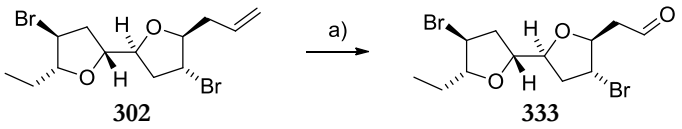
### *3.6.2. Ozonolysis and Yamamoto-Peterson Olefination*

The Yamamoto-Peterson olefination was successfully utilised during the synthesis of the originally proposed structure of elatenyne (**20**) to install the (*Z*)-enyne moiety (**Chapter 1, Section 1.3.2**).[18] This reaction involves addition of an allenic titanium reagent (**328**) to an aldehyde (**327**), followed by basic *syn*-elimination of the resulting β-titanium alkoxysilane intermediate (**330** or **332, Scheme 3.49**). The selectivity in this reaction can be explained by considering the two transition states (**326** and **329**) for the initial aldehyde addition. Transition state **329** is disfavoured due to the steric clash between the TBS group and the R group of the aldehyde, whereas in transition state **326** the R group is eclipsing a hydrogen atom. Transition state **326** is therefore favoured and after *syn*-elimination yields enyne **(*Z*)-331** selectively.




**Scheme 3.49 – Proposed mechanism of the Yamamoto-Peterson olefination.**[21]

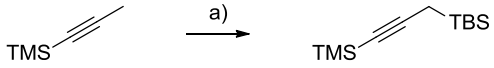
Before performing the Yamamoto-Peterson olefination, aldehyde **333** needed to be prepared from dibromide **302**, which was achieved by ozonolysis (**Scheme 3.50**). The reaction was successful when quenched with triphenylphosphine followed by rapid purification by column chromatography. When the reaction was attempted with a dimethylsulfide quench no aldehyde **333** was obtained, but instead unidentified by-products were observed. Aldehyde **333** was also a derivative of elatenyne (**60**) characterised by Hall and Reiss and as such provided additional data comparison as shown later (**Section 3.7**).[14]




**302** **333**

**Scheme 3.50 – Reagents and conditions: a) $O_3/O_2$, DCM -78 °C, 2 min, then $PPh_3$, -78 °C to RT, 15 h, 85%.**

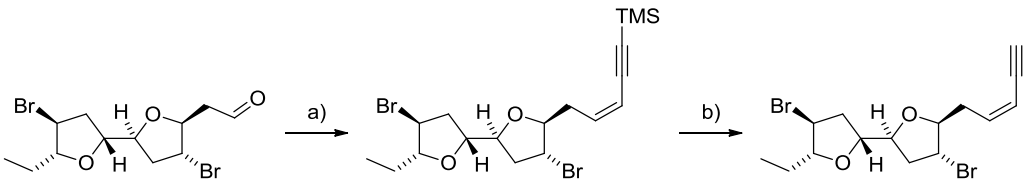
The required allenic titanium reagent (**328**, **Scheme 3.49**) is formed in the Yamamoto-Peterson olefination by addition of $^t$BuLi to silane **335**, followed by transmetallation with titanium(IV) isopropoxide. Silane **335** was therefore synthesised according to the procedure of Yamamoto and co-workers from 1-(trimethylsilyl)propyne (**334**, **Scheme 3.51**).[21]




**334** **335**

**Scheme 3.51 – Reagents and conditions: a) $^t$BuLi, $Et_2O$, -10 °C, 1 h, then TBSCl, -10 °C to -5 °C, 30 min, then RT, 1 h, 56%.**

With the required aldehyde (**333**) and silane (**335**) in hand the Yamamoto-Peterson olefination was first tested on cyclohexanecarboxaldehyde and full conversion was observed by crude $^1$H NMR analysis. The reaction was also successful with aldehyde **333**, following the procedure of Sheldrake *et al.*,[18] and gave the required (*Z*)-enyne **336** in a pleasing 83% yield with >30:1 *Z*:*E* selectivity (**Scheme 3.52**). TBAF deprotection yielded elatenyne (**60**) in sufficient quantity for full characterisation.




**333** **336** **60**

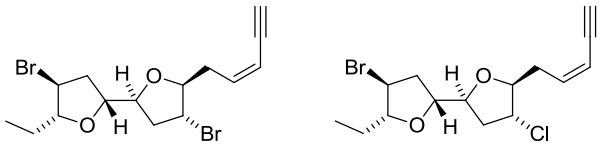
**Scheme 3.52 – Reagents and conditions: a) 335, $^t$BuLi, THF, -78 °C, 1 h, then $Ti(O^iPr)_4$, 10 min, then aldehyde 333 in THF, -78 °C, 30 min, then RT, 30 min, 83% (>30:1 *Z*:*E*); b) TBAF, THF, -20 °C, 5 min, 80%.**

## 3.7. Data Comparison of Elatenyne and Derivatives

### *3.7.1. Elatenyne Data Comparison*

It was noted in the introduction that, since Hall and Reiss' isolation of elatenyne in 1986,[14] elatenyne has also been isolated by both Wang and co-workers[134] and Dias and Urban.[135] Wang

isolated an inseparable 1:1 mixture of two compounds from *Laurencia decumbens* in 2007,[134] which have ultimately been shown to be elatenyne (**60**) by comparison with Hall and Reiss' and Dias and Urban's data[14] and the other, laurendecumenyne B (**337**), an analogous structure containing one bromide and one chloride substituent (**Figure 3.9**).

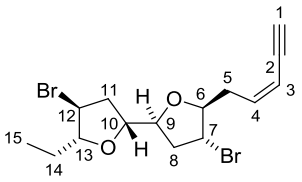



**60** **337**

**Figure 3.9 – Structures of elatenyne and laurendecumenyne B.**

Dias and Urban isolated elatenyne (**60**) in 2011 during their studies of the *Laurencia elata* algae.[135] They noted that all of their spectral data were in agreement with Hall and Reiss apart from the $^{1}H$ NMR in $CDCl_3$, which showed significant differences, whereas the $^{1}H$ and $^{13}C$ NMR spectra in $C_6D_6$ were an excellent match. They also concluded on the basis of direct proton to carbon correlations observed in the HSQCAD NMR spectrum, that the carbon chemical shifts previously assigned to positions 7 and 12 by Hall and Reiss should be reversed (**See Table 3.12**).

Pleasingly, there was excellent correlation between the $^{1}H$ and $^{13}C$ NMR spectra of our synthetic elatenyne (**60**, **Figure 3.10**) and the literature data for the natural product as shown in **Table 3.12** and **Figure 3.11** to **Figure 3.15**. Our $^{1}H$ NMR spectrum in $CDCl_3$ matched with that of Dias and Urban (not shown) and was in agreement with Wang's data (**Figure 3.15**), and therefore we also noted in agreement with Dias and Urban[135] that there were differences compared to the listed data of Hall and Reiss (**Table 3.13**).[14]




**60**

**Figure 3.10 – Structure of elatenyne.**

| Position | $\delta_C$ Synthetic elatenyne (60) ($C_6D_6$)/pmm | $\delta_C$ Hall and Reiss ($C_6D_6$)/pmm | $\Delta\delta_{(syn.-Hall\ and\ Reiss)}$/ppm | $\delta_C$ Dias and Urban ($C_6D_6$)/pmm | $\Delta\delta_{(syn.-Dias\ and\ Urban)}$/ppm |
|---|---|---|---|---|---|
| 1 | 82.9 | 83.0 | -0.1 | 82.9 | - |
| 2 | 80.2 | 80.0 | +0.2 | 80.2 | - |
| 3 | 111.2 | 111.2 | - | 111.2 | - |
| 4 | 140.1 | 140.1 | - | 140.1 | - |
| 5 | 34.7 | 34.7 | - | 34.7 | - |
| 6 | 86.5 | 86.4 | +0.1 | 86.5 | - |
| 7 | 49.0 | 48.9[a] | +0.1 | 48.9 | +0.1 |
| 8 | 39.1 | 39.0 | +0.1 | 39.1 | - |
| 9 | 80.1 | 80.0 | +0.1 | 80.1 | - |
| 10 | 79.6 | 79.5 | +0.1 | 79.5 | +0.1 |
| 11 | 39.3 | 39.3 | - | 39.3 | - |
| 12 | 49.3 | 49.2[a] | +0.1 | 49.2 | +0.1 |
| 13 | 88.7 | 88.6 | +0.1 | 88.6 | +0.1 |
| 14 | 26.8 | 26.8 | - | 26.8 | - |
| 15 | 10.1 | 10.2 | -0.1 | 10.1 | - |

**Table 3.12 – Comparison of the $^{13}C$ NMR data for elatenyne synthesised by the author and the natural product data for elatenyne. [a]Carbons 7 and 12 reversed from Hall and Reiss' original assignment.**

**The spectrum originally shown here cannot be made freely available via ORA because of copyright. The spectrum was sourced from J. G. Hall's Ph.D. thesis made available to Dr J. W. Burton by Dr J. A. Reiss relating to the publication J. G. Hall, J. A. Reiss, *Aust. J. Chem.* 1986, *39*, 1401-1409.**

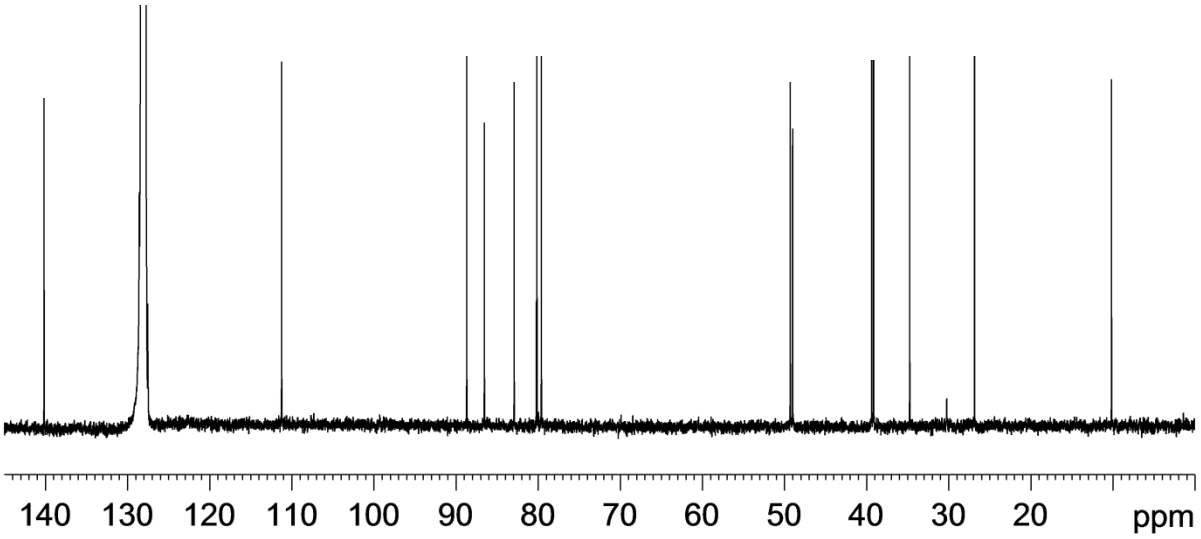



**Figure 3.11 – Comparison of $C_6D_6$ $^{13}C$ NMR spectra of Hall and Reiss' natural product (50 MHz, top) and elatenyne (60) synthesised by the author (125 MHz, bottom).**

**The spectrum originally shown here cannot be made freely available via ORA because of copyright. The spectrum was sourced from supporting information in the publication N. Y. Ji, X. M. Li, K. Li, B. G. Wang, *J. Nat. Prod.* 2007, *70*, 1499-1502.**

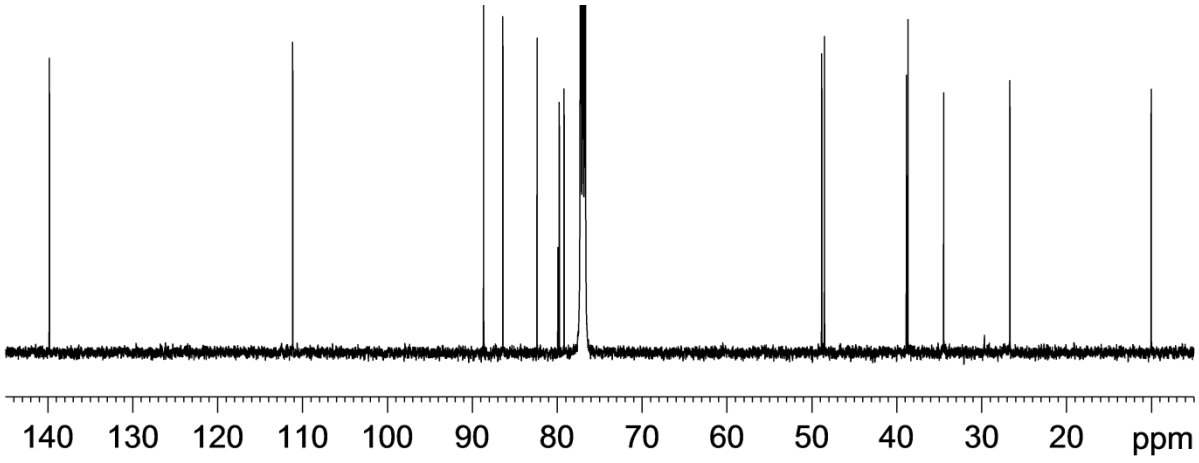



**Figure 3.12 - Comparison of $CDCl_3$ $^{13}C$ NMR spectra of Wang's 1:1 mixture of natural products (125 MHz, top) and elatenyne (60) synthesised by the author (125 MHz, bottom).**

**The spectrum originally shown here cannot be made freely available via ORA because of copyright. The spectrum was sourced from J. G. Hall's Ph.D. thesis made available to Dr J. W. Burton by Dr J. A. Reiss relating to the publication J. G. Hall, J. A. Reiss, *Aust. J. Chem.* 1986, *39*, 1401-1409.**

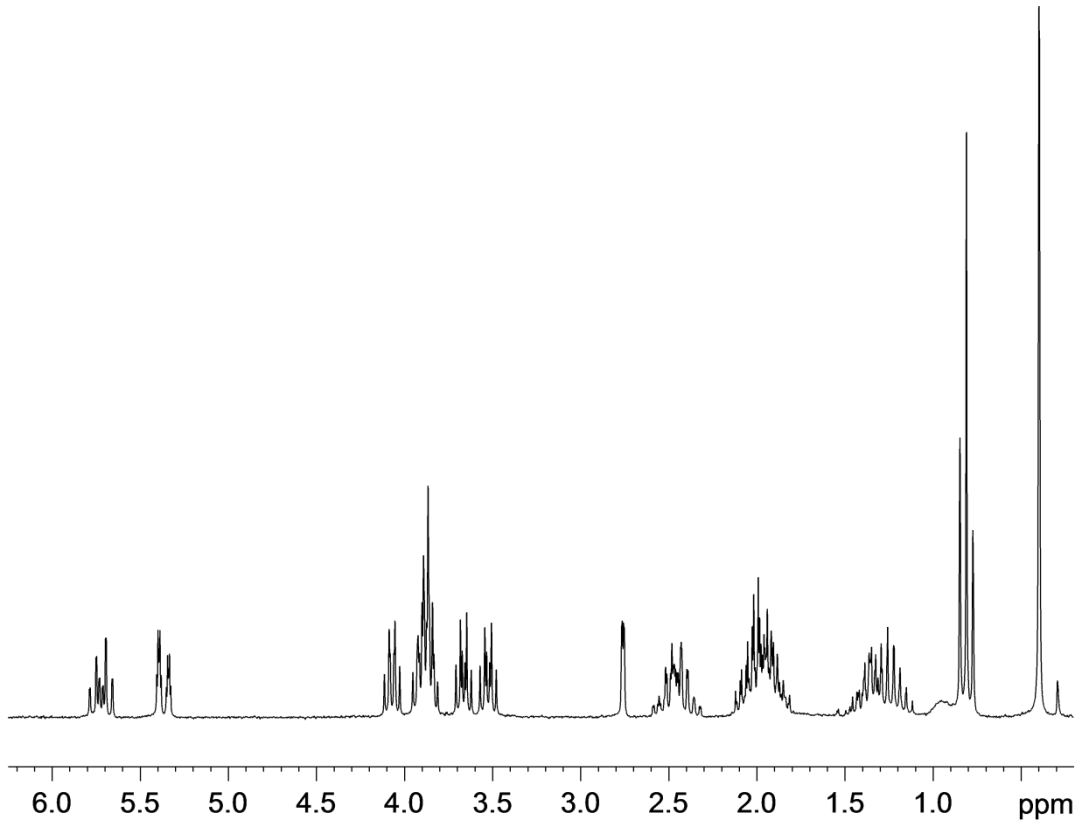



**Figure 3.13 – Comparison of $C_6D_6$ 200 MHz $^1H$ NMR spectra of Hall and Reiss' natural product (top) and elatenyne (60) synthesised by the author (bottom).**

**The spectrum originally shown here cannot be made freely available via ORA because of copyright. The spectrum was sourced from J. G. Hall's Ph.D. thesis made available to Dr J. W. Burton by Dr J. A. Reiss relating to the publication J. G. Hall, J. A. Reiss, *Aust. J. Chem.* 1986, *39*, 1401-1409.**

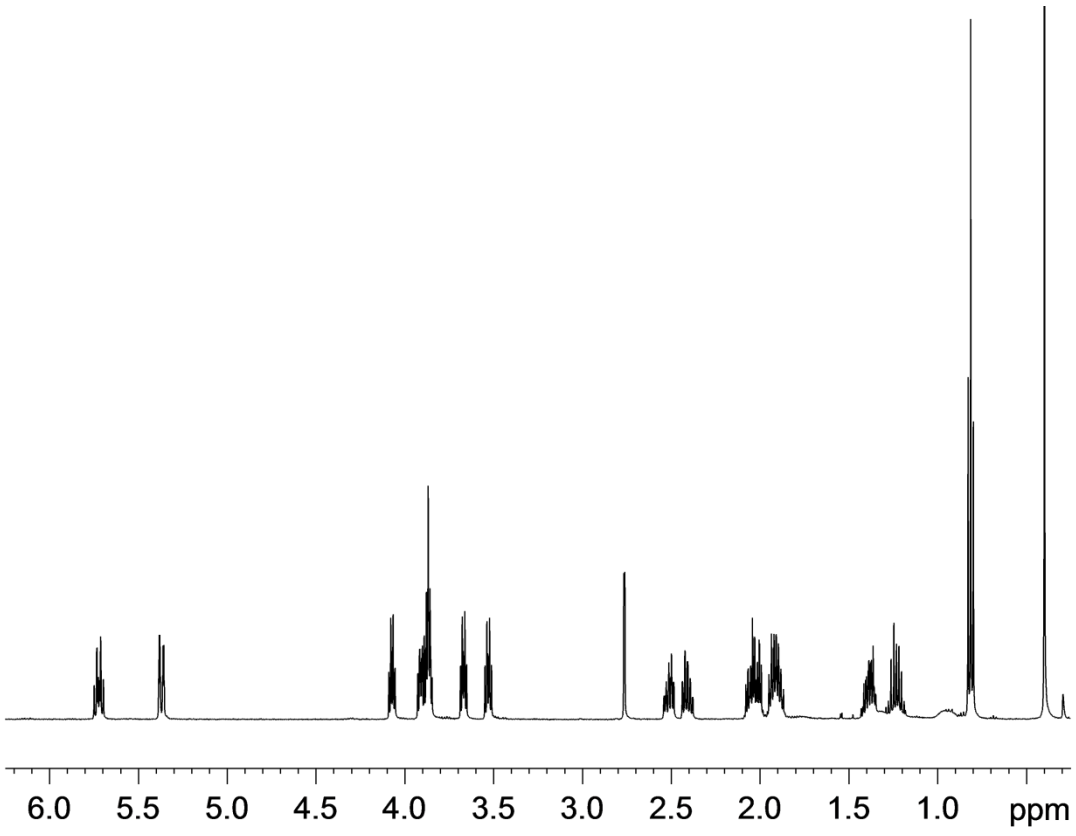



**Figure 3.14 - Comparison of $C_6D_6$ $^1H$ NMR spectra of Hall and Reiss' natural product (top, 200 MHz) and elatenyne (60) synthesised by the author (bottom, 500 MHz).**

**The spectrum originally shown here cannot be made freely available via ORA because of copyright. The spectrum was sourced from supporting information in the publication N. Y. Ji, X. M. Li, K. Li, B. G. Wang, *J. Nat. Prod.* 2007, *70*, 1499-1502.**

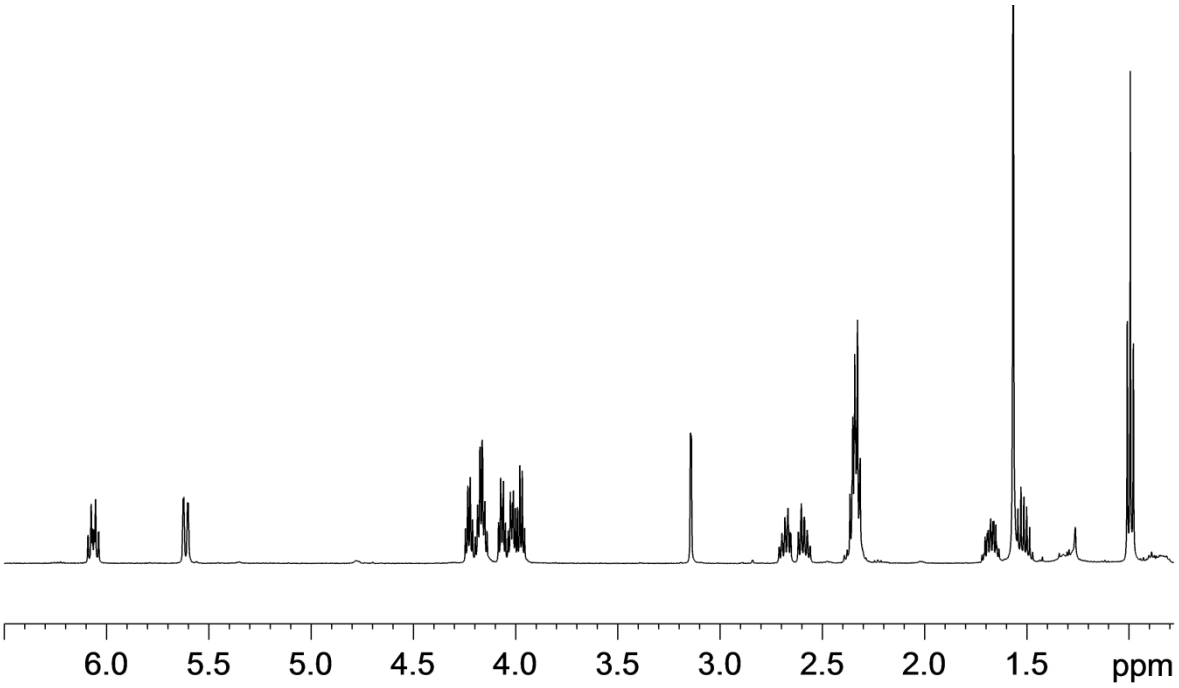



**Figure 3.15 - Comparison of 500 MHz $CDCl_3$ $^1H$ NMR spectra of Wang's 1:1 mixture of natural products (top) and elatenyne (60) synthesised by the author (bottom).**

| Position | $\delta_H$ (multiplicity, *J* in Hz) | | | |
|---|---|---|---|---|
| | **Synthetic 60 (200 MHz, $CDCl_3$)** | **Hall and Reiss (200 MHz, $CDCl_3$)[VII]** | **Synthetic 60 (500 MHz, $CDCl_3$)** | **Dias and Urban (500 MHz, $CDCl_3$)** |
| 1 | 3.14 (dd, 2.0, 0.5) | 3.09 | 3.14 (br d, 2.0) | 3.14 (dd, 2.5, 0.5) |
| 2 | - | - | - | - |
| 3 | 5.61 (ddt, 11.0, 2.0, 1.5) | 5.49 | 5.61 (ddt, 11.0, 2.0, 1.0) | 5.60 (ddt, 11.0, 2.5, 1.0) |
| 4 | 6.07 (dtd, 11.0, 7.5, 1.0) | 5.94 | 6.06 (dtd, 11.0, 7.5, 1.0) | 6.05 (ddt, 11.0, 7.5, 1.0)[a] |
| 5 | 2.48–2.78 (m) | 2.51 | 2.55–2.62 (m) | 2.57 (m) |
| 5’ | 2.48–2.78 (m) | 2.51 | 2.64–2.72 (m) | 2.66 (ddd, 8.5, 5.5, 1.0) |
| 6 | 3.91–4.29 (m) | 3.89 | 4.23 (q, 6.0) | 4.22 (dt, 6.0, 5.5) |
| 7 | 3.91–4.29 (m) | 3.82 | 4.07 (dt, 7.0, 5.5) | 4.05 (dt, 7.0, 5.5) |
| 8[b] | 2.26–2.41 (m) | 2.32 | 2.30–2.37 (m) | 2.33 (m) |
| 9[c] | 3.91–4.29 (m) | 3.87 | 4.17 (ddd, 12.0, 7.0, 5.5) | 4.15 (ddd, 12.0, 7.0, 5.5) |
| 10[c] | 3.91–4.29 (m) | 3.87 | 4.17 (ddd, 12.0, 7.0, 5.5) | 4.15 (ddd, 12.0, 7.0, 5.5) |
| 11[b] | 2.26–2.41 (m) | 2.32 | 2.30–2.37 (m) | 2.33 (m) |
| 12 | 3.91–4.29 (m) | 3.77 | 3.97 (q, 5.5) | 3.96 (dt, 5.5, 5.5) |
| 13 | 3.91–4.29 (m) | 3.77 | 4.02 (dt, 7.5, 5.5) | 4.00 (dt, 7.5, 5.5) |
| 14 | 1.37–1.78 (m) | 1.51 | 1.46–1.59 (m) | 1.50 (ddq, 14.0, 7.5, 7.5) |
| 14’ | 1.37–1.78 (m) | 1.51 | 1.63–1.72 (m) | 1.66 (ddq, 14.0, 5.0, 7.5) |
| 15 | 0.99 (t, 7.5) | 0.87 | 0.99 (t, 7.5) | 0.98 (t, 7.5) |

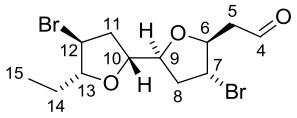
**Table 3.13 – Comparison of the $^1$H NMR data for elatenyne synthesised by the author and the natural product data for elatenyne. [a]Multiplicity misassigned in literature, [b,c]assignments interchangeable between pairs of signals.**

Unfortunately we were not able to confirm the absolute configuration of elatenyne (**60**) from the optical rotation. Hall and Reiss quote an optical rotation of $[\alpha]_D^{25}$ +16.83° (c = 1.401 in DCM),[14] but when taken with the sodium D line (λ = 589 nm) the optical rotation of our synthetic material was much smaller with the polarimeter readings very close to zero (**See Table 3.22**, **Section 3.9**). The optical rotations were also measured at a variety of wavelengths using a mercury lamp so that accurate comparisons could be made with this work in any future syntheses or isolations of elatenyne (**60**). It was also found that a variance in the level of contamination of (*Z*)-elatenyne (**60**) by the (*E*)-isomer had a large effect on the optical rotation, which suggested that the magnitude of the rotation for the (*E*)-isomer is much larger than the (*Z*)-isomer and this hypothesis was later confirmed upon synthesis (**Section 3.8** and **Table 3.22**, **Section 3.9**).

[VII] We believe there are significant errors in these data as noted by Dias and Urban.

### *3.7.2. Aldehyde Data Comparison as Part of the Structure Elucidation of Elatenyne*

Comparison of the synthetic data for aldehyde **333** (**Figure 3.16**) with the literature data for the elatenyne aldehyde derivative synthesised by Hall and Reiss confirmed that they have the same structure.[14] The $^{13}C$ NMR data were almost identical; with only two carbons (C8 and C12) having a difference of 0.1 ppm (**Table 3.14**). The $^{1}H$ NMR data of our synthetic aldehyde **333** were a reasonable match with the listed data of Hall and Reiss (**Figure 3.17**, **Table 3.15**); the $^{1}H$ NMR data of Hall and Reiss in $CDCl_3$ did not report two protons. Unfortunately there was no optical rotation reported in the literature for aldehyde **333** and therefore this could not aid assignment of the absolute configuration of elatenyne (**60**).




**333**

**Figure 3.16 – Structure of the aldehyde derivative of elatenyne.**

| Position | $\delta_C$ Synthetic 333 ($C_6D_6$)/ppm | $\delta_C$ Hall and Reiss ($C_6D_6$[VIII])/ppm | $\Delta\delta_{(syn.-lit.)}$ /ppm | $\delta_C$ Synthetic 333 ($CDCl_3$)/pmm |
|---|---|---|---|---|
| 1 | - | - | - | - |
| 2 | - | - | - | - |
| 3 | - | - | - | - |
| 4 | 197.8 | 197.8 | - | 199.4 |
| 5 | 46.8 | 46.8 | - | 46.6 |
| 6 | 82.1 | 82.1 | - | 81.9 |
| 7 | 48.4 | 48.4 | - | 47.6 |
| 8 | 38.3 | 38.2 | +0.1 | 37.8 |
| 9 | 80.1 | 80.1 | - | 79.9 |
| 10 | 79.3 | 79.3 | - | 78.9 |
| 11 | 39.2 | 39.2 | - | 38.9 |
| 12 | 49.1 | 49.0 | +0.1 | 48.6 |
| 13 | 88.7 | 88.7 | - | 88.8 |
| 14 | 26.8 | 26.8 | - | 26.7 |
| 15 | 10.1 | 10.1 | - | 10.0 |

**Table 3.14 - Comparison of the $^{13}C$ NMR data for the aldehyde derivative synthesised by the author and Hall and Reiss' data.**

[VIII] This spectrum was reported to be in $CDCl_3$ in J. G. Hall's Ph.D. thesis, but comparison of the spectra in the two solvents strongly suggests it was run in $C_6D_6$.

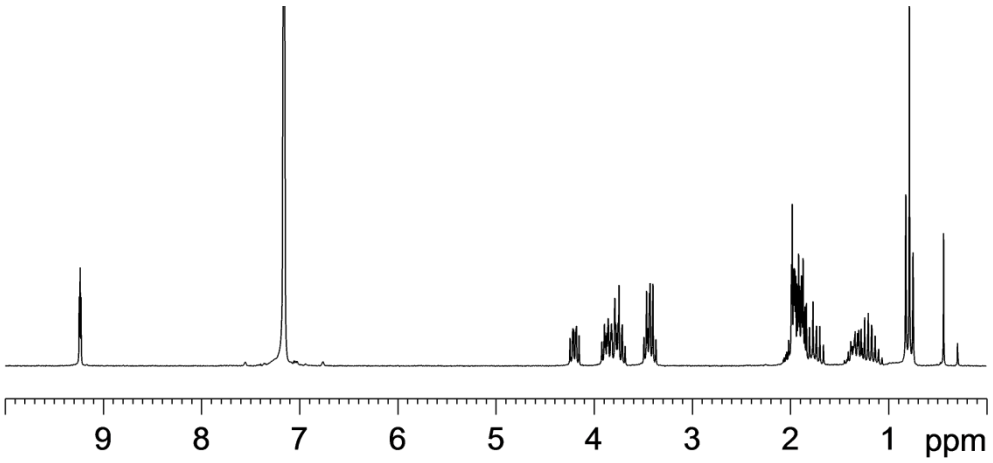


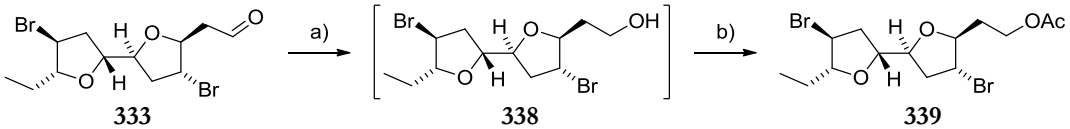

**Figure 3.17 - $^1$H NMR spectra of synthetic aldehyde 333 (200 MHz, $C_6D_6$).**

| | **$\delta_H$ (multiplicity, *J* in Hz)** |
|---|---|
| **Hall and Reiss (200 MHz, $CDCl_3$)[IX]** | 0.92 (3H, t, 7.3), 1.1–1.4 (2H, m), 2.2–2.3 (4H, m), 3.8–4.0 (3H, m), 4.0–4.2 (2H, m), 4.43 (1H, ddd, 7.9, 6.4, 4.3), 9.73 (1H, t, 1.8) |
| **Synthetic 333 (200 MHz, $CDCl_3$)** | 0.98 (3H, t, 7.5), 1.36–1.80 (2H, m), 2.13–2.89 (6H, m), 3.88–4.08 (3H, m), 4.10–4.25 (2H, m), 4.48 (1H, ddd, 8.0, 6.5, 4.5), 9.79 (1H, dd, 2.0, 1.5) |
| **Hall and Reiss (200 MHz, $C_6D_6$)** | 0.78 (3H, t, 7.4), 1.8–2.0 (2H, m), 1.8–2.5 (6H, m), 3.6–3.7 (2H, m), 3.9–4.2 (3H, m), 4.19 (1H, ddd, 7.5, 6.0, 5.1), 9.23 (1H, dd, 2.1, 1.6) |
| **Synthetic 333 (200 MHz, $C_6D_6$)** | 0.79 (3H, t, 7.5), 1.05–1.46 (2H, m), 1.64–2.08 (6H, m), 3.35–3.51 (2H, m), 3.67–3.92 (3H, m), 4.20 (1H, ddd, 7.5, 6.0, 5.0), 9.24 (1H, dd, 2.0, 1.5) |

**Table 3.15 – Comparison of the $^1$H NMR data for the aldehyde synthesised by the author and Hall and Reiss' data.**

### *3.7.3. Acetate Data Comparison as Part of the Structure Elucidation of Elatenyne*

Hall and Reiss had also characterised an acetate derivative of elatenyne (**339**), which they synthesised by reducing aldehyde **333** and subsequent acetylation.[14] Acetate **339** was successfully synthesised from aldehyde **333**, according to the procedures of Hall and Reiss, in order to obtain further data for comparison (**Scheme 3.53**).[14]




**333** **338** **339**

**Scheme 3.53 – Reagents and conditions: a) $NaBH_4$, MeOH, RT, 20 min, b) $Ac_2O$, pyridine, DMAP, DCM, RT, 1.5 h, 89% over 2 steps.**

[IX] There are 2 protons missing in these literature data.

Pleasingly, the $^1$H NMR at 200 MHz of our synthetic acetate **339** in $C_6D_6$ matched the printed $^1$H NMR reported in J. G. Hall's Ph.D. thesis with good agreement between both the chemical shifts and line shapes (**Figure 3.18**), although comparison of the listed $^1$H NMR data in $CDCl_3$ between the Hall and Reiss data and our own data showed some discrepancies (**Table 3.16**).

**The spectrum originally shown here cannot be made freely available via ORA because of copyright. The spectrum was sourced from J. G. Hall's Ph.D. thesis made available to Dr J. W. Burton by Dr J. A. Reiss relating to the publication J. G. Hall, J. A. Reiss, *Aust. J. Chem.* 1986, *39*, 1401-1409.**

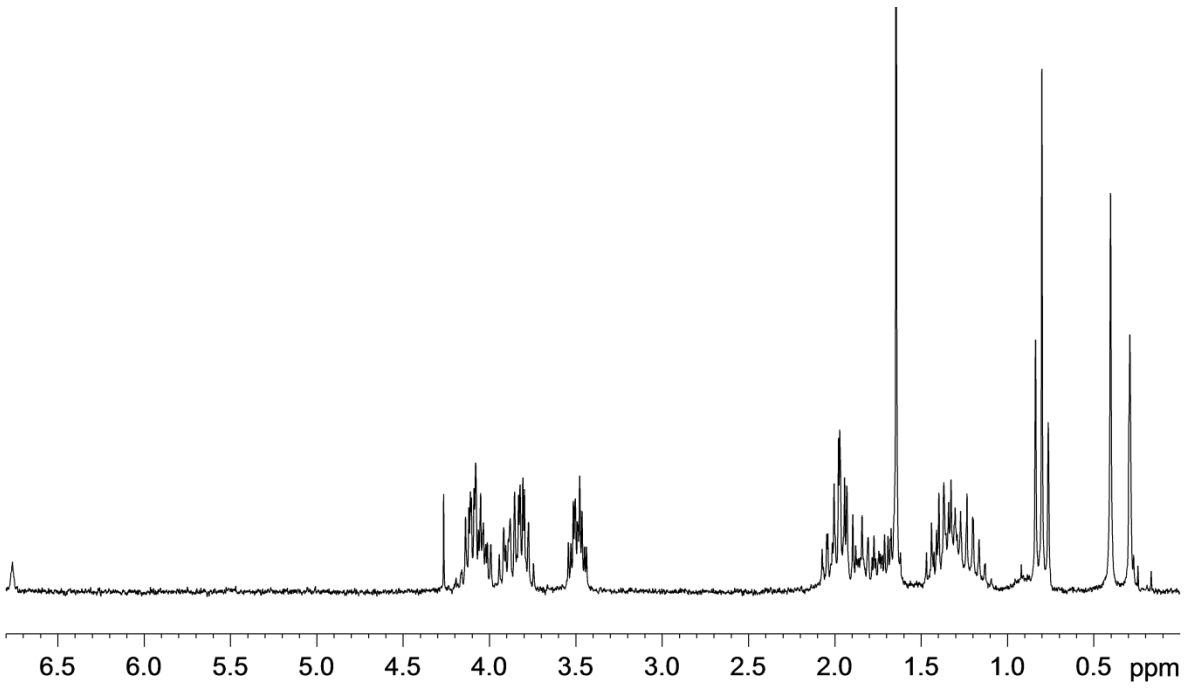
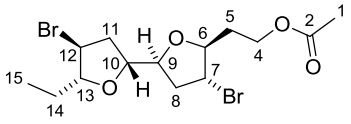



**Figure 3.18 – Comparison of 200 MHz $C_6D_6$ $^1$H NMR spectra of Hall and Reiss' acetate (top) and synthetic acetate 339 (bottom).**

| | **$\delta_H$ (multiplicity, *J* in Hz)** |
|---|---|
| **Hall and Reiss (200 MHz, $CDCl_3$)** | 0.97 (3H, t, 7.3), 1.4–1.7 (2H, m), 1.99 (1H, m), 2.2–2.4 (5H, m), 2.48 (3H, s), 4.01 (3H, m), 4.23 (2H, m), 4.29 (1H, m), 4.67 (2H, m) |
| **Synthetic 339 (200 MHz, $CDCl_3$)** | 0.99 (3H, t, 7.5), 1.39–1.88 (3H, m), 1.93–2.15 (1H, m), 2.07 (3H, s), 2.23–2.43 (4H, m), 3.90–4.32 (8H, m) |
| **Synthetic 339 (200 MHz, $C_6D_6$)** | 0.80 (3H, t, 7.5), 1.08–1.50 (3H, m), 1.60–2.10 (5H, m), 1.65 (3H, s), 3.41–3.55 (2H, m), 3.72–3.96 (3H, m), 3.98–4.16 (3H, m) |

**Table 3.16 – Comparison of the $^1$H NMR data for the acetate synthesised by the author and Hall and Reiss' data.**

Hall and Reiss used a number of different NMR experiments on elatenyne (**60**) and derivatives (**333**, **339** and **340**) in an attempt to assign a full stereostructure to the natural product. As part of this exercise they reported both $^1$H and $^{13}$C NMR spectra of acetate **339** in the presence of the lanthanide shift reagent Eu(fod)$_3$. Their listed $^{13}$C NMR data of acetate **339** (**Figure 3.19**) contains no resonance for the carbonyl carbon (**Table 3.17**); this is surprising given that the carbonyl carbon of the aldehyde **333** is reported (**Table 3.14**). The $^{13}$C NMR spectrum of our synthetic acetate **339** clearly shows the resonance for the carbonyl carbon, however, there are many small discrepancies between our $^{13}$C NMR data and the data listed by Hall and Reiss (**Table 3.17**). It is possible that the $^{13}$C NMR data listed by Hall and Reiss for acetate **339** was from a $^{13}$C NMR spectrum acquired in the presence of a lanthanide shift reagent, which would readily account for the chemical shift discrepancies and the absence of the carbonyl carbon.



**339**

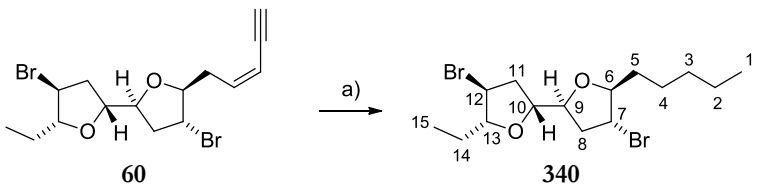
**Figure 3.19 – Structure of the acetate derivative of elatenyne.**

| Position | $\delta_C$ Synthetic 339 ($C_6D_6$)/pmm | $\delta_C$ Hall and Reiss ($C_6D_6$)/pmm | $\Delta\delta_{(syn.-lit.)}$ /ppm |
|---|---|---|---|
| 1[a] | 20.4 | 23.1 | -2.7 |
| 2 | 169.9 | [b] | [c] |
| 3 | - | - | - |
| 4 | 61.0 | 62.9 | -1.9 |
| 5 | 32.9 | 33.1 | -0.2 |
| 6 | 84.3 | 84.7 | -0.4 |
| 7 | 49.2 | 48.7 | +0.5 |
| 8 | 38.9 | 38.7 | +0.2 |
| 9 | 79.9 | 80.0 | -0.1 |
| 10 | 79.5 | 79.4 | +0.1 |
| 11 | 39.3 | 39.1 | +0.2 |
| 12 | 49.2 | 48.9 | +0.3 |
| 13 | 88.7 | 88.9 | -0.2 |
| 14 | 26.8 | 26.9 | -0.1 |
| 15 | 10.1 | 10.0 | +0.1 |

**Table 3.17 – Comparison of the $^{13}C$ NMR data for the acetate synthesised by the author and Hall and Reiss' data. [a]$CH_3$ of OAc, [b]C=O of OAc not observed, [c]C=O clearly observed in our spectum.**

### *3.7.4. Elatane Data Comparison as Part of the Structure Elucidation of Elatenyne*

Hall and Reiss reported the reduction of the enyne side chain of elatenyne in the isolation paper to give elatane (**340**). In order to compare the data for this compound we hydrogenated elatenyne (**60**) using Adam's catalyst to yield elatane (**340, Scheme 3.54**). The $^{13}C$ and $^{1}H$ NMR data matched well with the listed NMR data of Hall and Reiss as shown in **Table 3.18** and **Table 3.19**.



**60** **340**

**Scheme 3.54 – Reagents and conditions: a) $PtO_2$, $H_2$, EtOH, RT, 2 h, quant.**

| Position | $\delta_C$ Synthetic 340 ($C_6D_6$)/pmm | $\delta_C$ Hall and Reiss ($C_6D_6$)/pmm | $\Delta\delta_{(syn.-lit.)}$ /ppm |
|---|---|---|---|
| 1 | 14.2 | 14.2 | - |
| 2 | 22.9 | 22.9 | - |
| 3 | 32.0 | 32.0 | - |
| 4 | 25.9 | 25.8 | +0.1 |
| 5 | 34.0 | 33.9 | +0.1 |
| 6 | 87.5 | 87.5 | - |
| 7 | 49.3 | 49.2 | +0.1 |
| 8 | 39.4 | 39.5 | -0.1 |
| 9 | 79.8 | 79.8 | - |
| 10 | 79.8 | 79.8 | - |
| 11 | 39.3 | 39.4 | -0.1 |
| 12 | 49.9 | 49.8[X] | +0.1 |
| 13 | 88.7 | 88.6 | +0.1 |
| 14 | 26.9 | 26.8 | +0.1 |
| 15 | 10.1 | 10.1 | - |

**Table 3.18 - Comparison of the $^{13}C$ NMR data for elatane synthesised by the author and Hall and Reiss' data.**

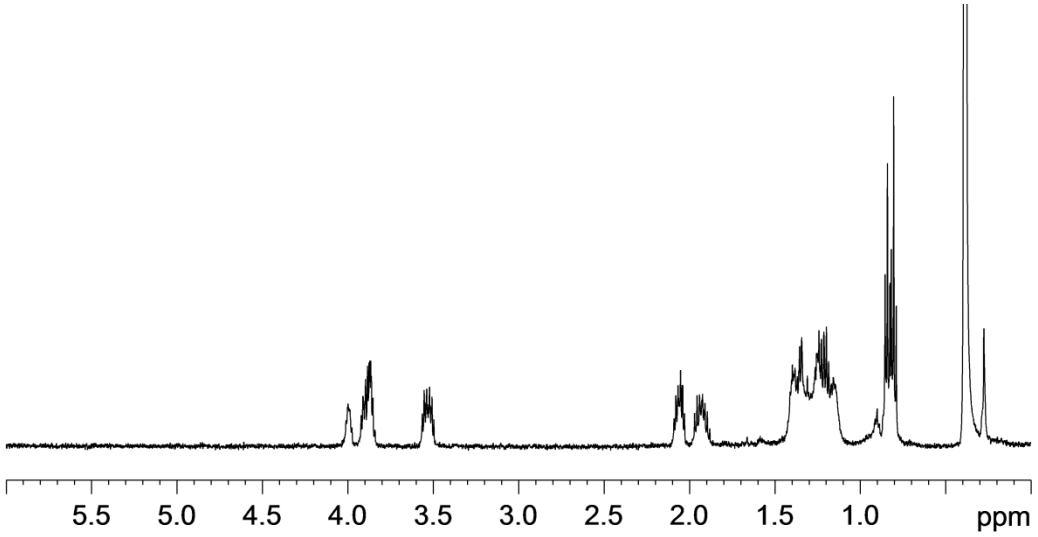



**Figure 3.20 – 500 MHz $C_6D_6$ $^1H$ NMR spectrum of elatane (340).**

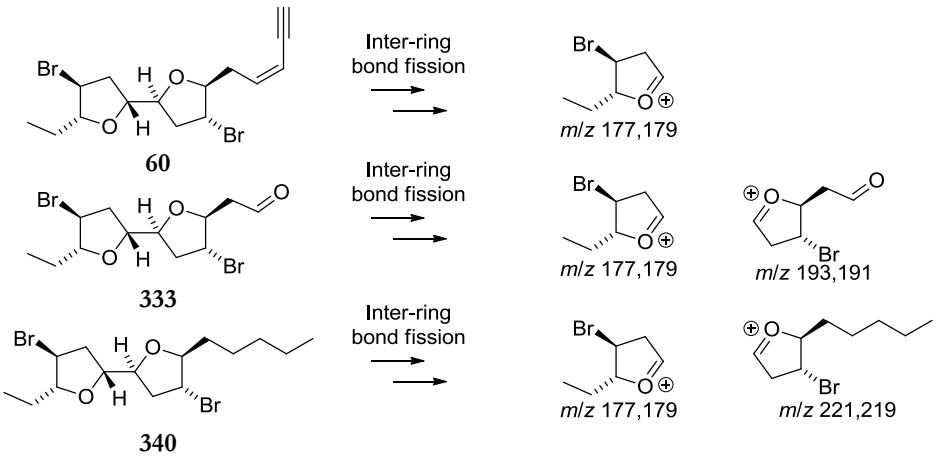
| | $\delta_H$ (multiplicity, *J* in Hz) |
|---|---|
| **Hall and Reiss (200 MHz, $C_6D_6$)** | 0.87 (3H, t, 7.4), 0.91 (3H, t, 7.4), 1.1–1.6 (10H, m), 2.0–2.1 (4H, m), 3.6 (2H, m), 3.9 (4H, m) |
| **Synthetic 340 (200 MHz, $C_6D_6$)** | 0.82 (3H, t, 7.5), 0.86 (3H, t, 7.5), 1.10–1.47 (10H, m), 1.85–2.15 (4H, m), 3.46–3.63 (2H, m), 3.81–4.07 (4H, m) |

**Table 3.19 - Comparison of the $^1H$ NMR data for elatane synthesised by the author and Hall and Reiss' data.**

[X] The chemical shift for C12 is reported as 48.8 ppm in the literature, but 49.8 ppm in J. G. Hall's Ph.D. thesis.

### *3.7.5. Mass Spectrometry Analysis*

It was discussed in **Chapter 1** (**Section 1.3.4.2**), that some of the evidence for the structural revision of elatenyne (**60**) to a 2,2'-bifuranyl structure came from the presence of furan fragments in the mass spectrum. Analysis of the FI mass spectra of synthetic elatenyne (**60**), aldehyde **333** and elatane (**340**) showed peaks corresponding to these furan fragments as shown in **Scheme 3.55**.



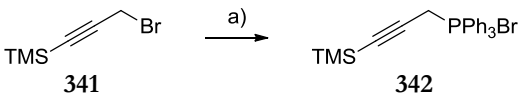

**60** **333** **340**

**Scheme 3.55 – Mass spectral fragmentation patterns of elatenyne, aldehyde 333 and elatane.**

## 3.8. Erickson's Enyne

### *3.8.1. Wittig Reaction*

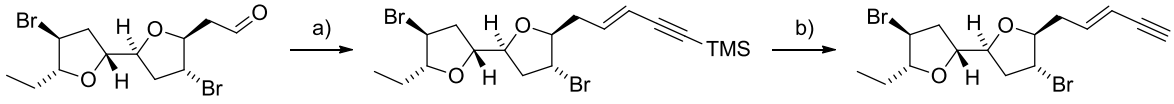
It was thought that a Wittig reaction with aldehyde **333** would provide access to the thermodynamic (*E*)-isomer of elatenyne, which is one of the proposed diastereomers of Erickson's enyne discussed in **Chapter 1** (**Section 1.3.4**).[24] When the Wittig reaction was attempted using commercial phosphonium salt **342** with addition of the aldehyde into the pre-formed ylide, some enyne **343** was produced but mixed with an inseparable impurity. It was thought that the impurity may have originated from commercial phosphonium salt **342** and so fresh salt was synthesised from TMS-propargyl bromide (**341**, **Scheme 3.56**).




**341** **342**

**Scheme 3.56 – Reagents and conditions: a) $PPh_3$, *o*-xylene, 0 °C to RT, 24 h, 58%.**

The reaction was successful when the fresh phosphonium salt **342** was used with an altered procedure involving addition of the pre-formed ylide into a solution of aldehyde **333** until consumption of starting material was observed by TLC analysis. (*E*)-Enyne **343** was produced in 80% yield with 8:1 *E*:*Z* selectivity (**Scheme 3.57**). Deprotection with TBAF yielded enyne **344**, which, matched the literature data for Erickson's enyne (**Section 3.8.2**).

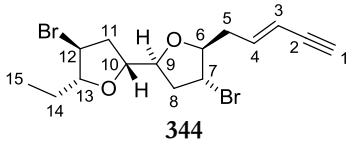



**333** **343** **344**

**Scheme 3.57 – Reagents and conditions: a) $Me_3SiC{\equiv}CCH_2PPh_3Br$ (342), $^n$BuLi, THF, -78 °C to between -40 °C and -30 °C, 30 min, then -78 °C, add to aldehyde 333 in THF, -78 °C to 0 °C, 2 h, 80% (8:1 *E*:*Z*); b) TBAF, THF -20 °C, 5 min, 81%.**

### *3.8.2. Erickon's Enyne Data Comparison*

Both the $^1$H and $^{13}$C NMR data showed no significant discrepancies between synthetic enyne **344** (**Figure 3.21**) and the enyne isolated by Erickson and co-workers (**Table 3.20** and **Table 3.21**). These data therefore confirm the structure of Erickson's enyne (**344**). It is surprising that Erickson and co-workers were able to predict the correct relative stereochemistry for the 2,2'-bifuranyl considering their method as discussed in **Chapter 1** (**Section 1.3.4**).




**344**

**Figure 3.21 – Structure of Erickson's enyne.**

| Position | $\delta_C$ Synthetic 344 ($C_6D_6$)/pmm | $\delta_C$ Erickson ($C_6D_6$)/pmm | $\Delta\delta_{(syn.-lit.)}$ /ppm |
|---|---|---|---|
| 1 | 77.32 | 77.31 | +0.01 |
| 2 | 82.13 | 82.13 | - |
| 3 | 112.16 | 112.18 | -0.02 |
| 4 | 140.83 | 140.82 | +0.01 |
| 5 | 36.55 | 36.56 | -0.01 |
| 6 | 85.92 | 85.91 | +0.01 |
| 7 | 48.36 | 48.34 | +0.02 |
| 8 | 38.75 | 38.76 | -0.01 |
| 9 | 79.87 | 79.88 | -0.01 |
| 10 | 79.35 | 79.36 | -0.01 |
| 11 | 39.22 | 39.22 | - |
| 12 | 49.10 | 49.09 | +0.01 |
| 13 | 88.60 | 88.60 | - |
| 14 | 26.77 | 26.76 | +0.01 |
| 15 | 10.10 | 10.10 | - |

**Table 3.20 - Comparison of the $^{13}C$ NMR data for Erickson's enyne synthesised by the author and Erickson's data.**

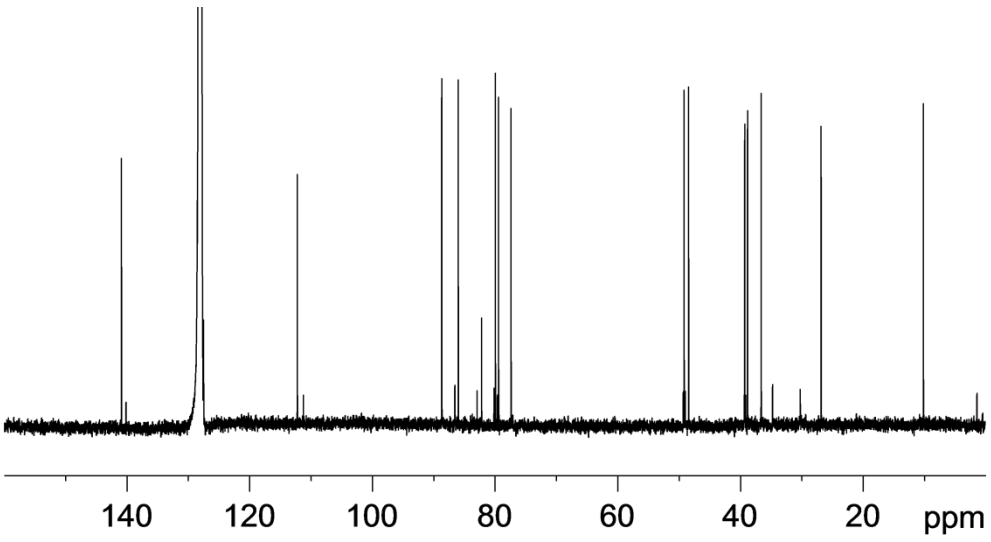



**Figure 3.22 – $C_6D_6$ 125 MHz $^{13}C$ NMR spectrum of Erickson's enyne (344, mix 9:1 *E*:*Z*) synthesised by the author.**

| Position | $\delta_H$ (multiplicity, *J* in Hz) | | |
|---|---|---|---|
| | **Synthetic 344 (500 Hz, $C_6D_6$)** | **Synthetic 344 (400 Hz, $C_6D_6$)** | **Erickson[a] (400 MHz, $C_6D_6$)** |
| 1 | 2.53–2.55 (m) | 2.54 (br d, 2.2) | 2.54 (ddt, 2.3, 0.9, 0.8) |
| 2 | - | - | - |
| 3 | 5.35 (ddt, 16.1, 2.2, 1.6) | 5.35 (ddt, 16.0, 2.2, 1.5) | 5.35 (ddt, 16.0, 2.3, 1.5) |
| 4 | 6.12 (dt, 16.1, 7.3) | 6.12 (dt, 16.0, 7.2) | 6.11 (dddd, 16.0, 7.2, 7.0, 0.9) |
| 5a | 1.90–2.02 (m) | 1.90–2.03 (m) | 1.99 (ddddd, 14.9, 7.2, 4.7, 1.5, 0.8) |
| 5b | 1.77–1.90 (m) | 1.75–1.89 (m) | 1.83 (ddddd, 14.9, 7.3, 7.0, 1.5, 0.8) |
| 6 | 3.84–3.91 (m) | 3.84–3.92 (m) | 3.86 (dddd, 7.3, 5.8, 4.7, 0.6) |
| 7 | 3.44 (dt, 7.6, 5.7) | 3.44 (dt 7.5, 5.6) | 3.44 (dddd, 7.5, 5.8, 5.4, 0.6) |
| 8a | 1.90–2.02 (m) | 1.90–2.03 (m) | 1.94 (ddd, 13.8, 6.9, 5.4) |
| 8b | 1.77–1.90 (m) | 1.75–1.89 (m) | 1.84 (dddd, 13.8, 7.5, 6.8, 0.6) |
| 9 | 3.73–3.83 (m) | 3.73–3.83 (m) | 3.75 (6.9, 6.8, 7.0, 0.6) |
| 10 | 3.73–3.83 (m) | 3.73–3.83 (m) | 3.79 (7.1, 7.0, 6.8, 0.6) |
| 11a | 1.77–1.90 (m) | 1.75–1.89 (m) | 1.80 (dddd, 13.8, 7.6, 7.1, 0.7) |
| 11b | 1.90–2.02 (m) | 1.90–2.03 (m) | 1.98 (ddd, 13.8, 6.8, 5.0) |
| 12 | 3.48 (dt, 7.6, 5.7) | 3.48 (dt, 7.5, 5.5) | 3.48 (dddd, 7.6 5.9, 5.0, 0.6) |
| 13 | 3.84–3.91 (m) | 3.84–3.92 (m) | 3.88 (dddd, 7.6, 5.9, 4.6, 0.7) |
| 14a | 1.33–1.43 (m) | 1.31–1.43 (m) | 1.37 (ddd, 13.8, 7.5, 4.6) |
| 14b | 1.16–1.28 (m) | 1.15–1.28 (m) | 1.21 (ddd, 13.8, 7.6, 7.4) |
| 15 | 0.82 (t, 7.6) | 0.81 (t, 7.5) | 0.8 (dd, 7.5, 7.4) |

**Table 3.21 – Comparison of the $^1$H NMR data for Erickson's enyne synthesised by the author and the natural product data. [a]Multiplets resolved using extensive NMR experiments.[24]**

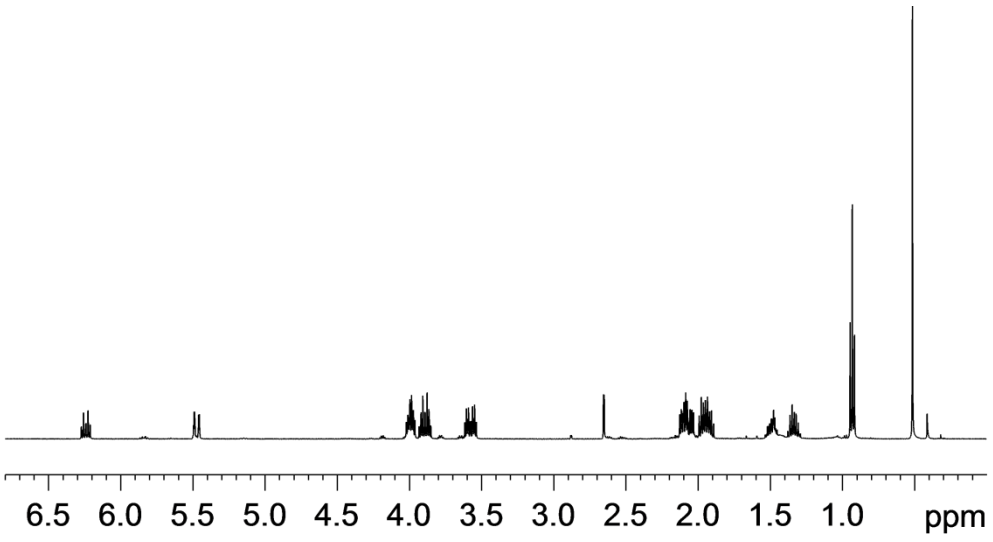
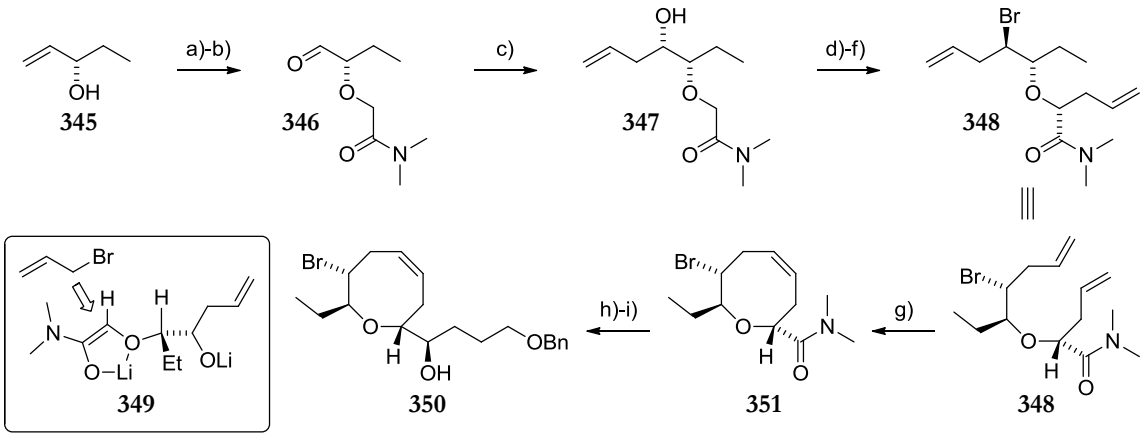



**Figure 3.23 – 500 MHz $C_6D_6$ $^1$H NMR spectrum of Erickson's enyne (344, mix 9:1 *E*:*Z*) synthesised by the author.**

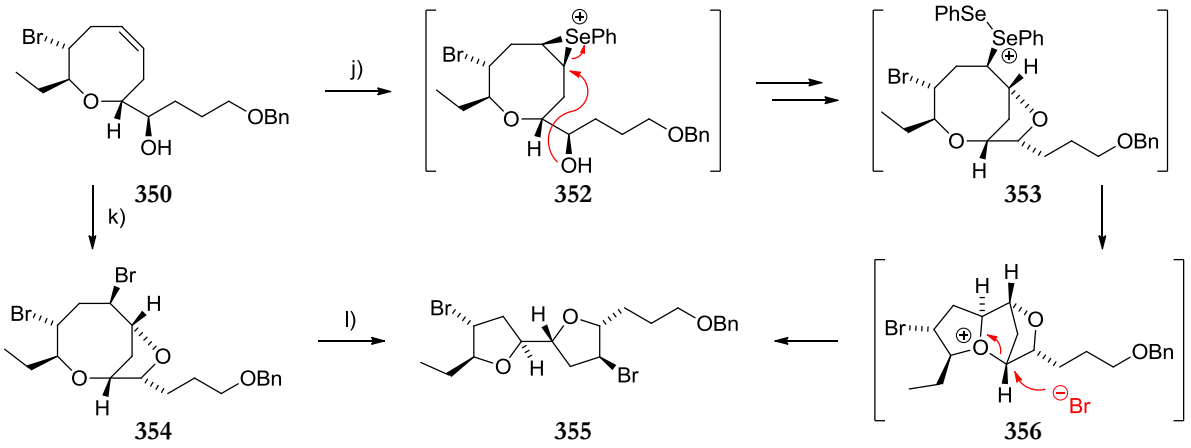
## 3.9. Kim and Co-workers Synthetic Route

During the course of our synthesis of elatenyne and Erickson's enyne, Kim and co-workers were also working on the synthesis of elatenyne (**60**) and Erickson's enyne (**344**). They completed the total syntheses of both natural products in the opposite enantiomeric series to our syntheses using a biomimetic approach as shown in **Scheme 3.58** to **Scheme 3.60**.[136] Their synthesis began from the known alcohol **345** and utilised proven methodology established within the Kim group and demonstrated in other natural product syntheses.[56, 137] Alcohol **345** was alkylated and the alkene cleaved by a modified Lemieux-Johnson oxidation to give the desired aldehyde **346**. Chemoselective chelation controlled nucleophilic addition of allyltributylstannane to the aldehyde in the presence of the α-alkoxy amide yielded alcohol **347** in 18:1 d.r.[138] Dianion alkylation using LiHMDS and allylbromide gave the desired isomer with 9.3:1 *anti*:*syn* selectivity, which was then brominated *via* the corresponding chloromesylate to give bromide **348**.[137a, 137b] The stereocontrol is thought to arise by alkylation of the (*Z*)-enolate *via* pretransition state assembly **349** with the electrophile approaching from the least hindered side in the H,H-eclipsed conformation. Ring closing metathesis of bromide **348** followed by ketone formation and reduction with L-Selectride® produced the required oxocene **350** (**Scheme 3.58**).



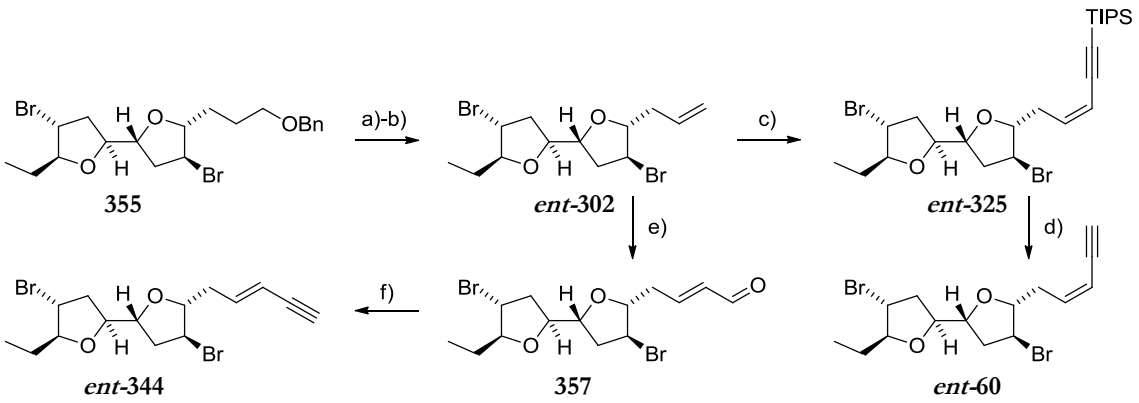

**Scheme 3.58 – Reagents and conditions: a) $ClCH_2CONMe_2$, NaH, THF, 0 °C to RT, 3 h, 93%; b) (i) $OsO_4$, NMO, acetone, RT, 18 h; (ii) $NaIO_4$, acetone/$H_2O$ (3:1), RT, 3 h; c) allyltributyltin, $MgBr_2 \cdot Et_2O$, DCM, -78 °C to RT, 15 h, 18:1 d.r., 92% (2 steps); d) LiHMDS, $CH_2=CHCH_2Br$, THF, -78 °C to -40 °C, 2 h, 85%, 9.3:1 d.r.; e) $ClSO_2CH_2Cl$, 2,6-lutidine, DCM, 0 °C, 1.5 h; f) LiBr, $Et_2O$/THF (10:1), RT, 6 h, 72% (2 steps); g) Grubbs 1st generation catalyst (216), DCM, 40 °C, 2 h, then DMSO, RT, 12 h, 94%; h) $BnO(CH_2)_5MgBr$, THF, RT, 1 h, 94%; i) L-Selectride® (171), THF, -78 °C, 1 h, 99%.**

Oxocene **350** was then subjected to the organoselenium-mediated oxonium ion formation/$SiO_2$-promoted fragmentation strategy discussed in **Chapter 1** (**Section 1.5**), which successfully gave the desired 2,2'-bifuranyl **355**.[56, 137c] The reaction proceeded by selenium ion formation (**352**), cyclisation and subsequent activation of the phenylselenyl group by phenylselenium bromide (**353**), followed by transannular displacement to give the tricyclic oxonium ion **356**, which was then opened with bromide (**Scheme 3.59**). The conversion of oxocene **350** to 2,2'-bifuranyl **355** was also demonstrated in a two-step process *via* dibromide **354** using NBS followed by heating in acetonitrile (**Scheme 3.59**).




**Scheme 3.59 – Reagents and conditions: j) PhSeBr, $SiO_2$, $K_2CO_3$, DCM, RT, 20 h, 70%; k) NBS, DCM, RT, 2 h, 91%; l) MeCN, 80 °C, 10 h, 93%.**

With the 2,2'-bifuranyl **355** in hand, side chain manipulation was completed by benzyl deprotection and subsequent conversion to alkene ***ent*-302** using Grieco's protocol.[139] From the allyl dibromide intermediate ***ent*-302** the synthesis of elatenyne (***ent*-60**) was completed using the previously demonstrated cross metathesis to install the (*Z*)-enyne moiety, as discussed in **Section 3.6.1**.[123] The (*E*)-enyne for Erickson's enyne (***ent*-344**) was accessed using a cross metathesis with crotonaldehyde and subsequent conversion of the aldehyde with TMS-diazomethane (**Scheme 3.60**).




**Scheme 3.60 – Reagents and conditions: a) $Pd(OH)_2$, $H_2$, THF, 10 min, RT, 95%; b) (i) *o*-$NO_2$-PhSeCN, *n*-$Oct_3P$, THF, RT, 30 min, (ii) 30% $H_2O_2$, THF, RT, 12 h, 97%; c) enyne 305 (see Section 3.6.1), Hoveyda-Grubbs 2nd generation catalyst (217), benzene, 70 °C, 6 h, 78%, 4.6:1 *Z*:*E*; d) TBAF, THF, 0 °C, 30 min, 98%; e) crotonaldehyde, Grubbs 2nd generation catalyst (127), 40 °C, 1.5 h, then DMSO, RT, 12 h, 91%; f) $TMSCH_2N_2$, LDA, THF, -78 °C to 0 °C, 1.5 h, 82%.**

The $^{1}H$ and $^{13}C$ NMR spectra of our synthetic material and Kim's synthetic material were in excellent agreement for elatenyne (**60**), Erickson's enyne (**344**) and the common allyl dibromide intermediate **302** (**Scheme 3.59**) as shown in **Figure 3.24** to **Figure 3.31**.

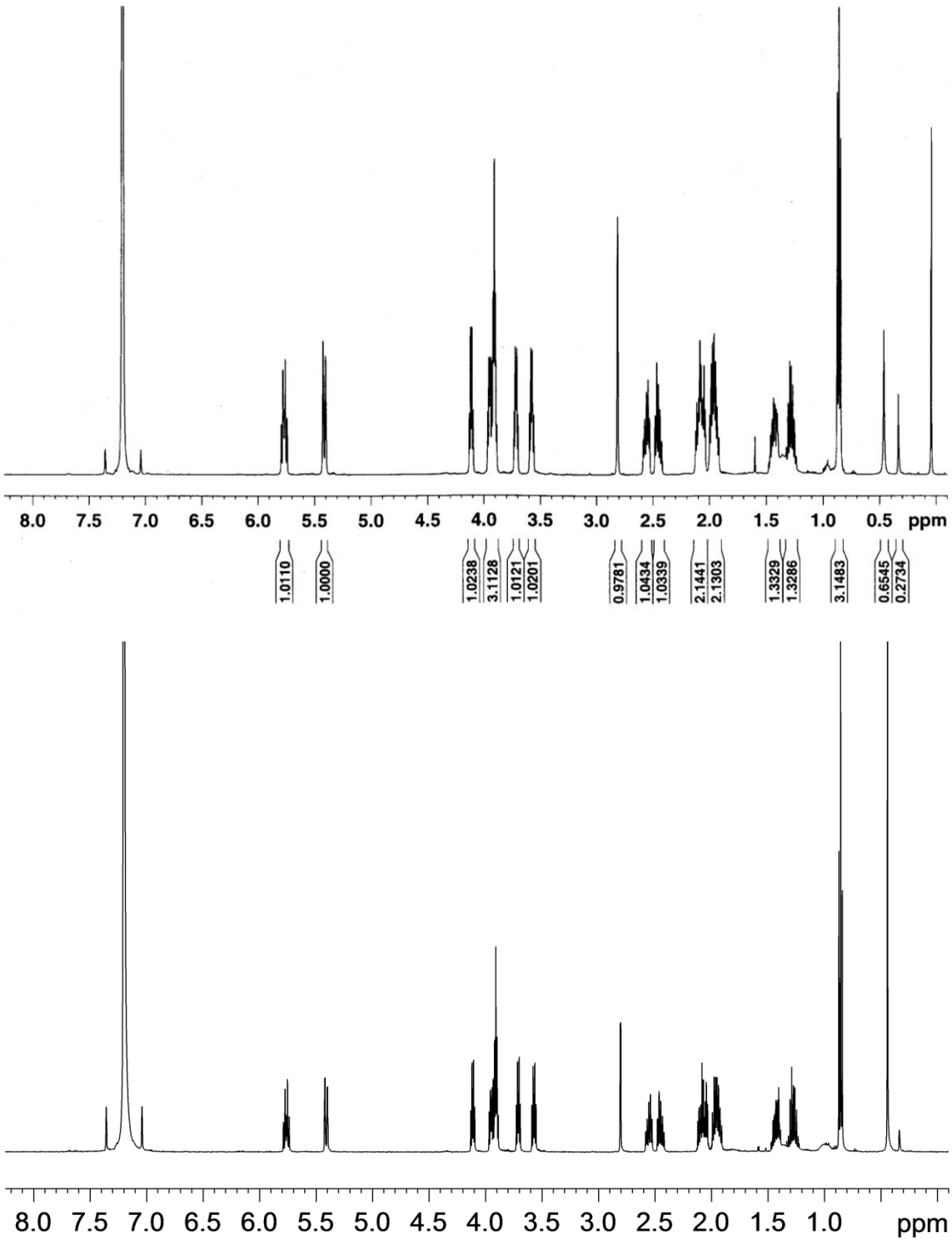



**Figure 3.24 – Comparison of 500 MHz $C_6D_6$ $^1H$ NMR spectra of Kim's synthetic elatenyne (*ent*-60) (top) and elatenyne (60) synthesised by the author (bottom).**

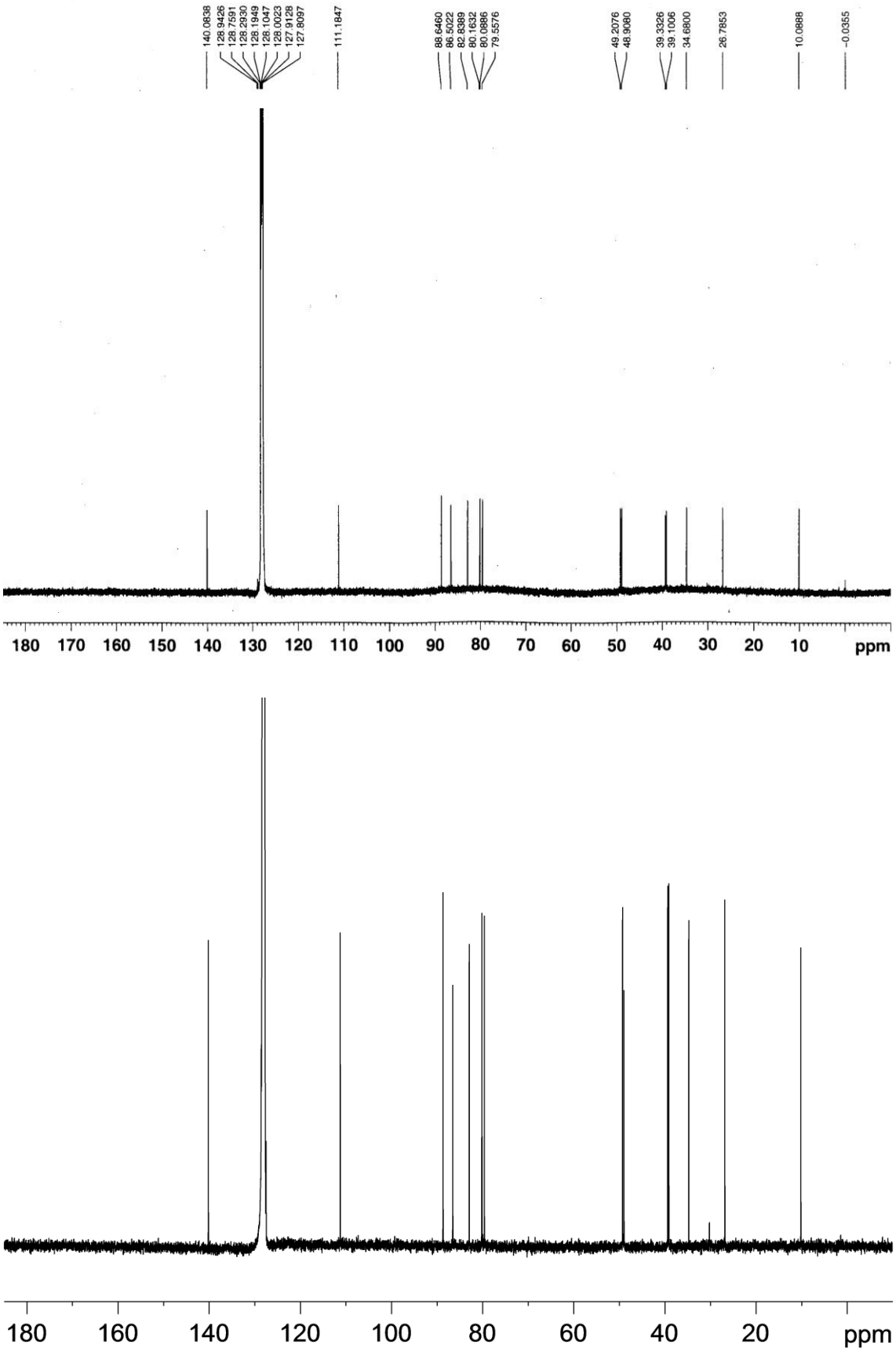



**Figure 3.25 – Comparison of 125 MHz $C_6D_6$ $^{13}C$ NMR spectra of Kim's synthetic elatenyne (*ent*-60) (top) and elatenyne (60) synthesised by the author (bottom).**

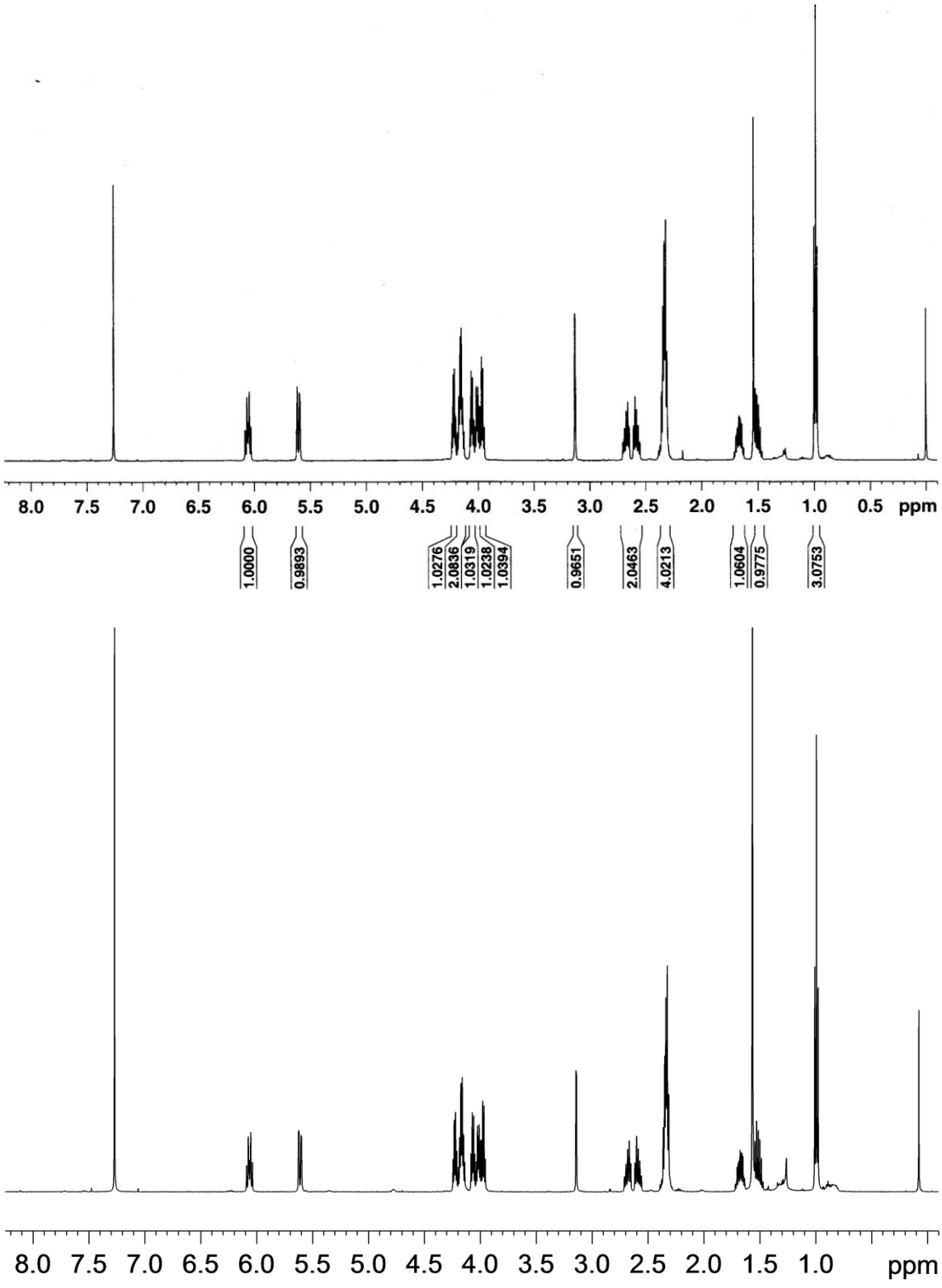



**Figure 3.26 – Comparison of 500 MHz $CDCl_3$ $^1H$ NMR spectra of Kim's synthetic elatenyne (*ent*-60) (top) and elatenyne (60) synthesised by the author (bottom).**

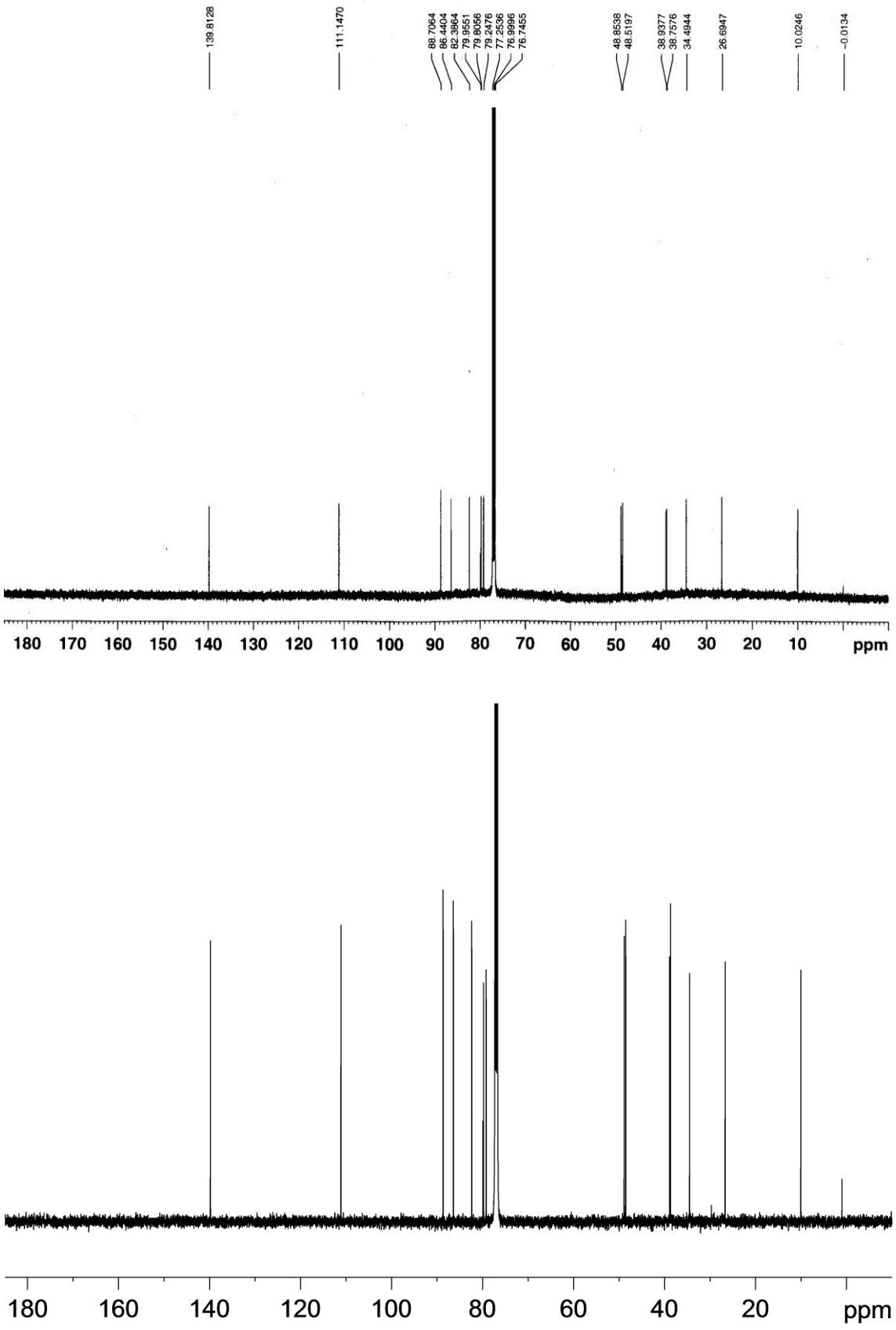



**Figure 3.27 – Comparison of 125 MHz $CDCl_3$ $^{13}C$ NMR spectra of Kim's synthetic elatenyne (*ent*-60) (top) and elatenyne (60) synthesised by the author (bottom).**

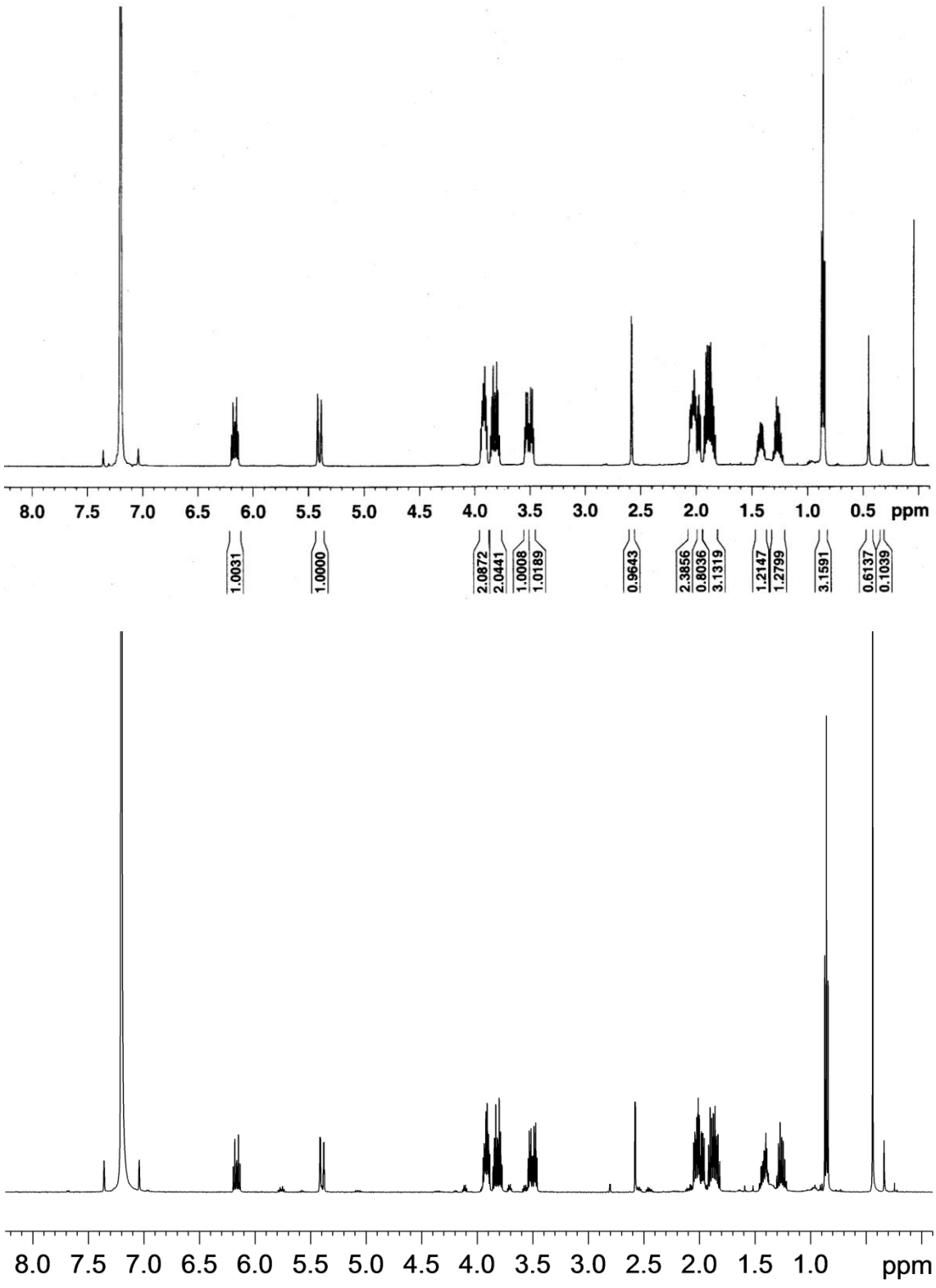



**Figure 3.28 – Comparison of 500 MHz $C_6D_6$ $^1H$ NMR spectra of Kim's synthetic Erickson's enyne (*ent*-344) (top) and Erickson's enyne (344, mix 9:1 *E*:*Z*) synthesised by the author (bottom).**

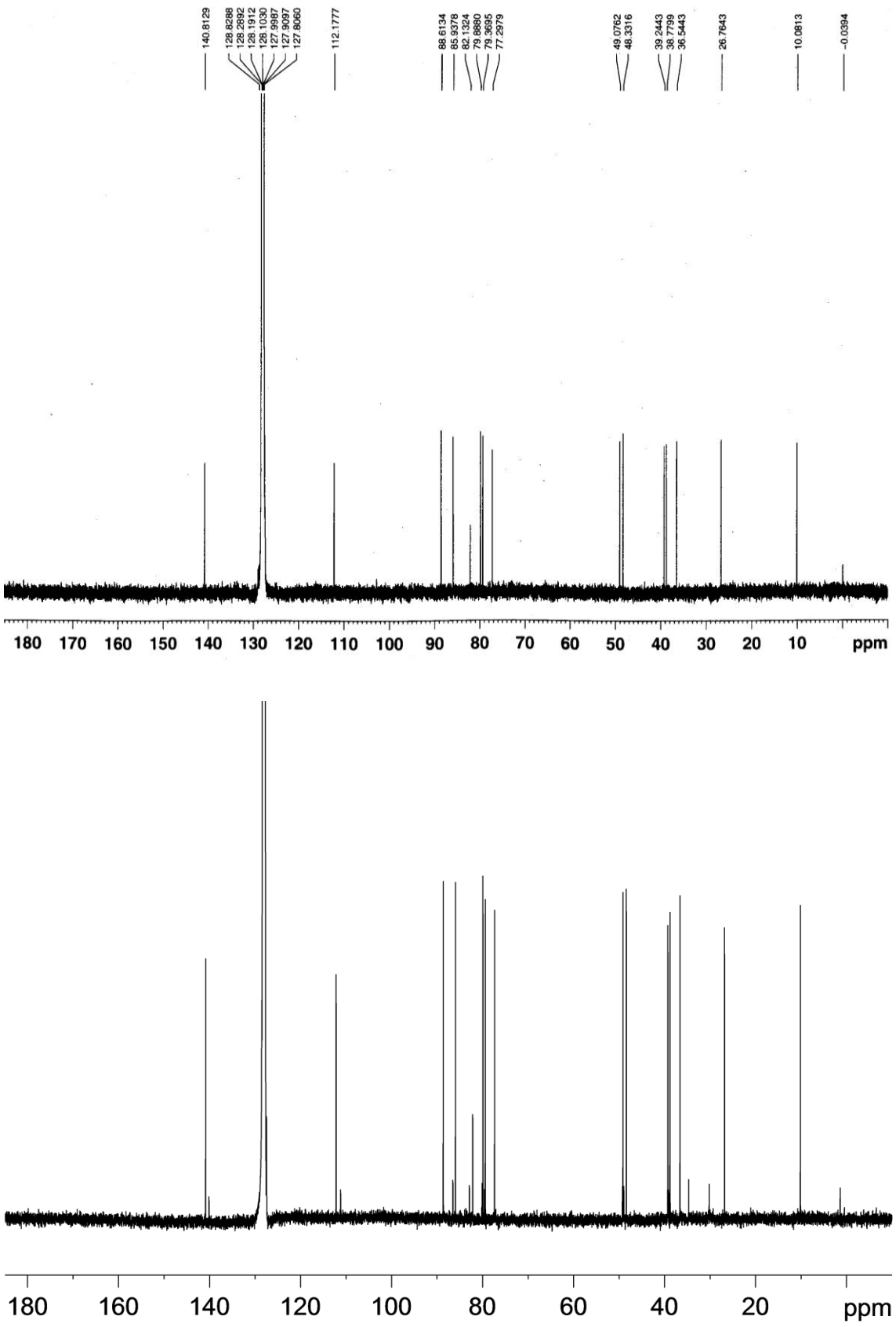



**Figure 3.29 – Comparison of 125 MHz $C_6D_6$ $^{13}C$ NMR spectra of Kim's synthetic Erickson's enyne (*ent*-344) (top) and Erickson's enyne (344, mix 9:1 *E*:*Z*) synthesised by the author (bottom).**

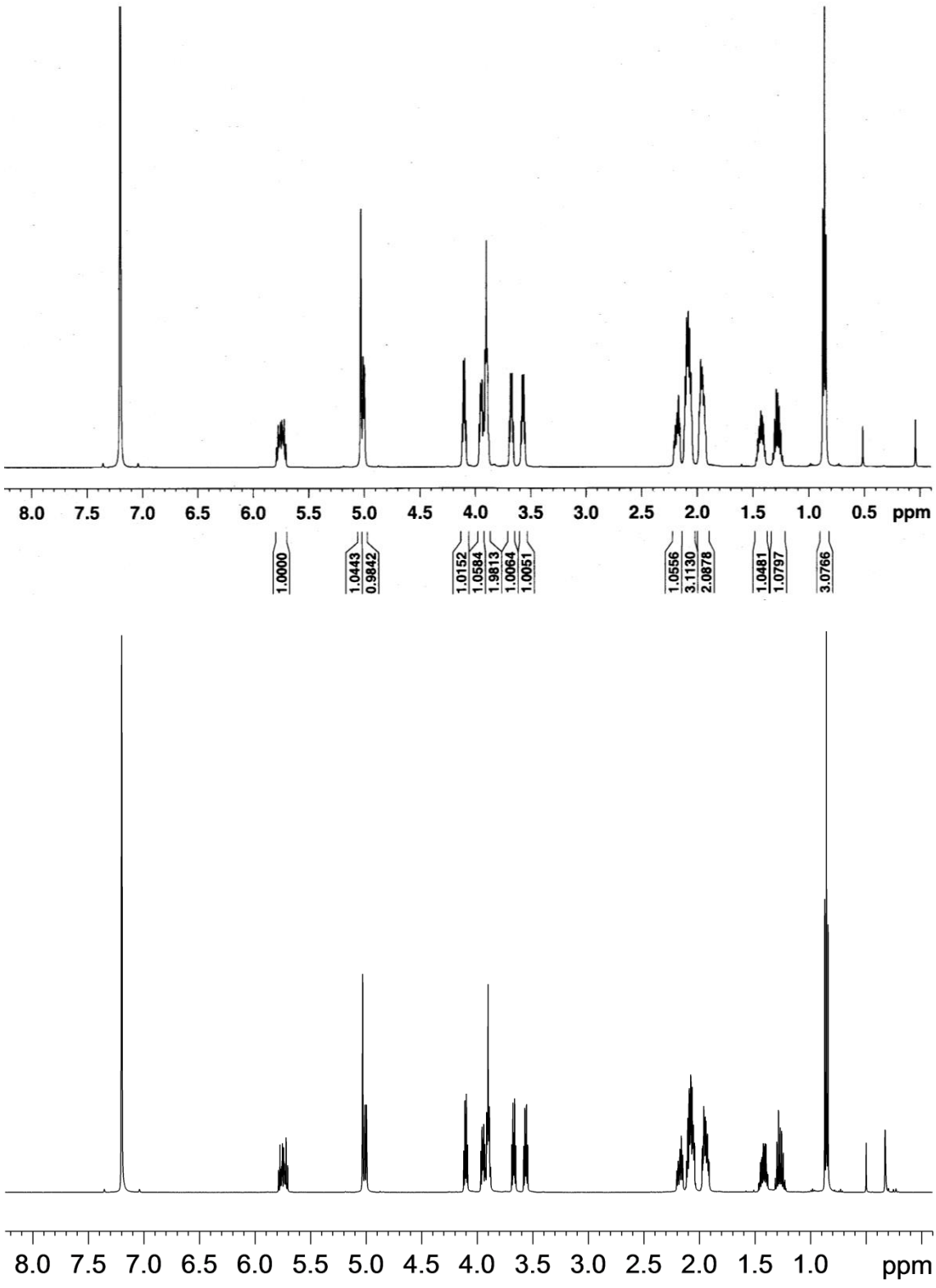



**Figure 3.30 – Comparison of 500 MHz $C_6D_6$ $^1H$ NMR spectra of Kim's synthetic allyl dibromide *ent*-302 (top) and allyl dibromide 302 synthesised by the author (bottom).**

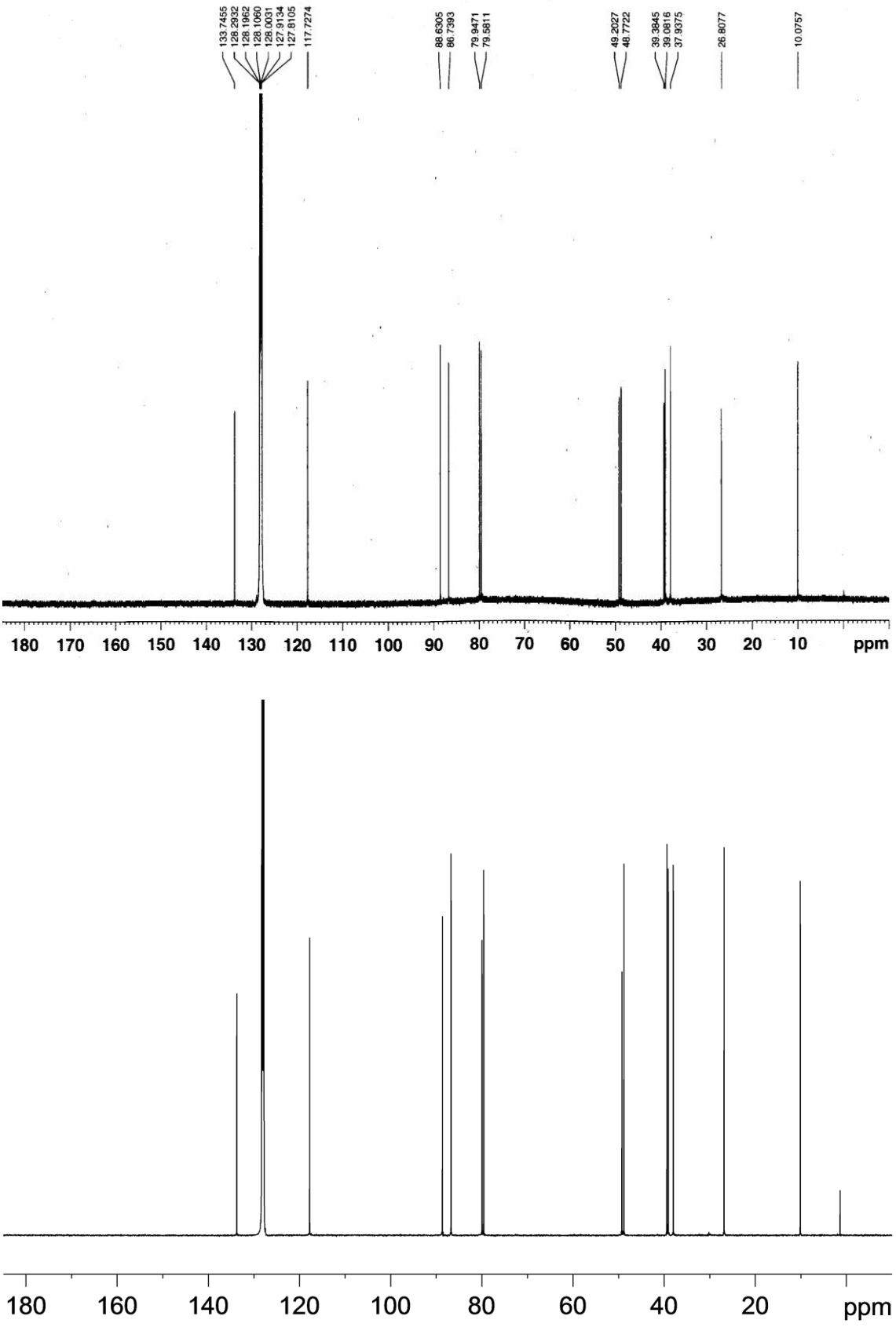



**Figure 3.31 – Comparison of 125 MHz $C_6D_6$ $^{13}C$ NMR spectra of Kim's synthetic allyl dibromide *ent*-302 (top) and allyl dibromide 302 synthesised by the author (bottom).**

The optical rotations of our synthetic material and Kim's synthetic material were in good agreement (**Table 3.22**), which means that Kim's optical rotation of elatenyne (***ent*-60**) at the sodium D line (λ = 589 nm) was also much smaller than Hall and Reiss' reported optical rotation of $[\alpha]_D^{25}$ +16.83° (c = 1.401 in DCM).[14] When Kim's optical rotation was taken using a mercury lamp (λ = 365 nm) it was also much larger and was in agreement with the value we obtained, showing we had indeed synthesised enantiomers of elatenyne, but does not allow us to determine the absolute configuration of the natural product (**Table 3.22**).

$[\alpha]_D^{25}$

| **Allyl dibromide 302/*ent*-302** | **Elatenyne 60/*ent*-60** | **Erickson's enyne 344/*ent*-344** |
|---|---|---|
| Dyson (c 0.66, DCM) -5.1 | Dyson (c 0.25, DCM) -1.6 | Dyson (c 0.09, DCM) -33.0 |
| Kim (c 1.15, DCM) +5.3 | Kim (c 0.714, DCM) +0.80 | Kim (c 0.35, DCM) +29.5 |
| | Dyson (c 0.25, $CHCl_3$) -4.0 | |
| | Kim (c 0.714, $CHCl_3$) +0.85 | |
| | Dyson (c 0.25, DCM) -17.4<br>λ=365 nm, Hg lamp | |
| | Kim (c 0.64, DCM) +18.97<br>λ=365 nm, Hg lamp | |

**Table 3.22 – Comparison of the optical rotations for Kim's synthetic material and the synthetic material synthesised by the author.**

## 3.10. Conclusions

A stereoselective total synthesis of elatenyne (**60**) has been completed, which has confirmed the structure of the natural product and has therefore validated the use of the computational $^{13}C$ NMR chemical shift prediction in structure determination with highly flexible small molecules, as discussed in **Chapter 1** (**Section 1.4.2**). The key steps in the synthesis include a Sharpless asymmetric epoxidation, cross metathesis and a Sharpless asymmetric dihydroxylation. Cyclisations were achieved using epoxide opening and mesylate displacement and the (*Z*)-enyne moiety was installed using a Yamamoto-Peterson olefination. A summary of the total synthesis can be seen in **Appendix A**. The absolute configuration of elatenyne (**60**) has not been determined, but comparison of optical rotations with Kim's synthetic enantiomer of our synthetic elatenyne has

shown good correlation. The structure of an enyne isolated by Erickson and co-workers has also been confirmed as structure **344**, an (*E*)-enyne isomer with the same stereochemistry as elatenyne.

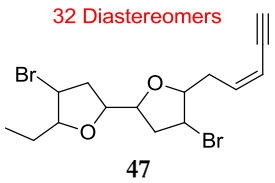
Additionally, three derivatives of elatenyne, aldehyde **333**, acetate **339** and elatane (**340**), were synthesised and their data compared with that published by Hall and Reiss.[14] This highlighted significant errors in the published characterisation of acetate **339**, however the confirmed structures of aldehyde **333** and elatane (**340**) supported the structure determination of elatenyne (**60**).

# CHAPTER 4: OTHER MARINE NATURAL PRODUCTS

## 4.1. Diastereoisomers of Elatenyne

### *4.1.1. Strategy to Access Any Diastereomer*

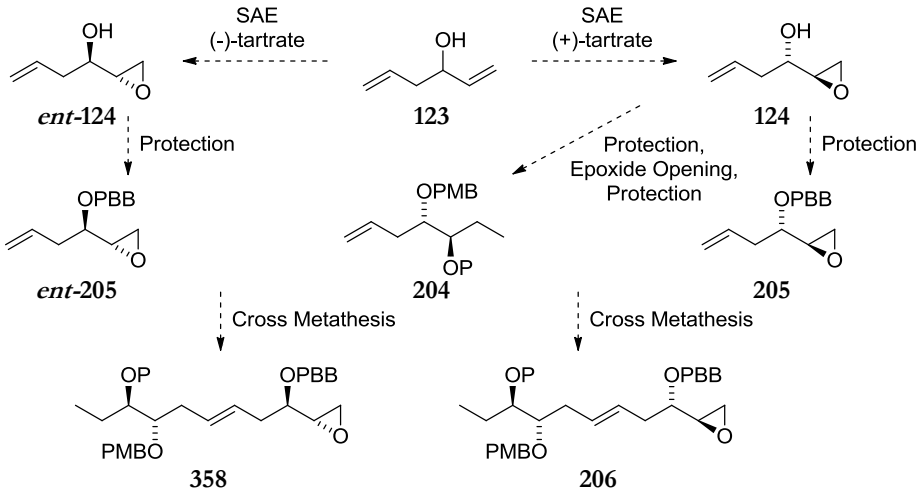
The synthetic route to elatenyne (**60**) discussed in **Chapter 3** and summarised in **Appendix A** was designed to be divergent and to allow access to any desired diastereomer of elatenyne. This section will illustrate how the synthetic route can potentially be utilised to gain access to any of the 32 possible diastereomers of the 2,2'-bifuranyl skeleton of elatenyne (**47**, **Figure 4.1**).




**47**

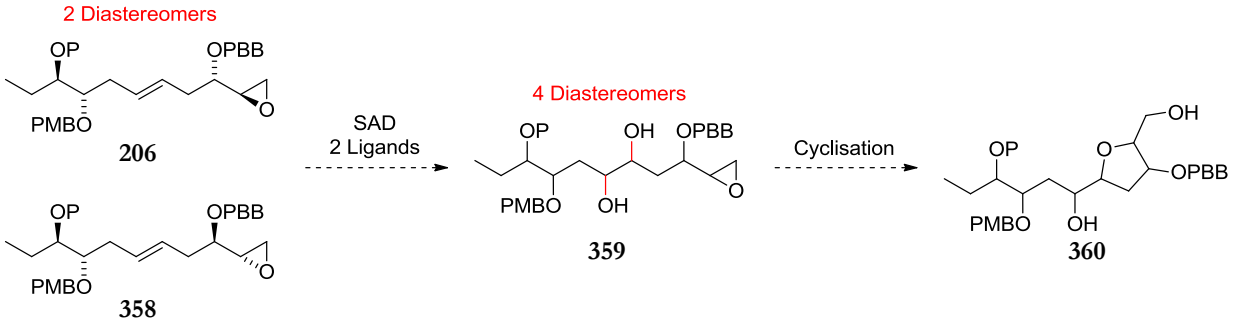
**Figure 4.1 – 2,2'-Bifuranyl skeleton of elatenyne.**

The use of the two enantiomeric tartrates in the Sharpless asymmetric epoxidation allows access to both enantiomers of epoxyalcohol **124** (**Scheme 4.1**). These two enantiomers can be converted into three coupling partners (***ent*-205**, **204** and **205**), which may be used in two different cross metathesis reactions to yield the two diastereomeric products **358** and **206** from which all 32 diastereomers of elatenyne can be synthesised.



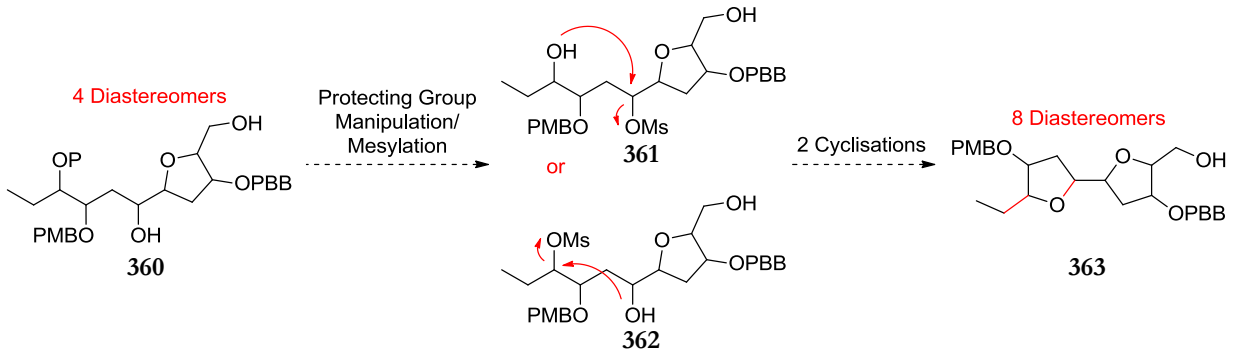

**Scheme 4.1 – Synthesis of two diastereomeric cross metathesis products.**

The first stereodivergent step from the two cross metathesis product diastereomers (**206** and **358**) is the Sharpless asymmetric dihydroxylation, utilising the two pseudo-enantiomeric ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$, to give four diastereomers of diol **359** (**Scheme 4.2**). These diols (**359**) can then be cyclised to form the first THF ring (**360**).




**Scheme 4.2 – Synthesis of four diastereomers of cyclised SAD products.**

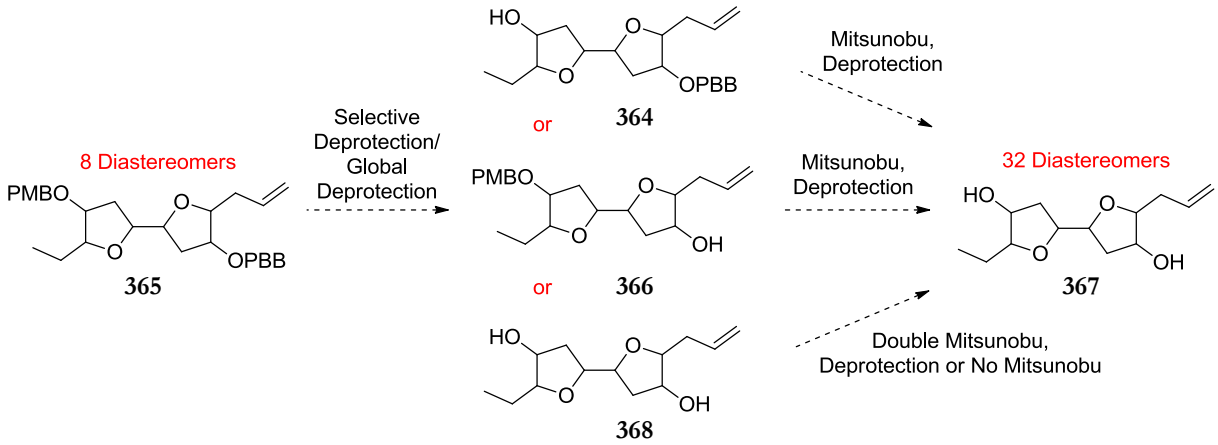
The THF (**360**) can, after protecting group manipulation, give two isomeric mesylates (**361** and **362**, **Scheme 4.3**). This allows for two different ring closures, which occur with inversion of configuration at the mesylate centres, therefore giving rise to eight possible diastereomers of the 2,2'-bifuranyl backbone of elatenyne (**363**).




**Scheme 4.3 – Two possible ring closures to form eight diastereomers of the 2,2'-bifuranyl backbone.**

The use of the orthogonal PMB and PBB protecting groups in the synthesis allows for late stage divergence with the eight diastereomers of the 2,2'-bifuranyl **365** being converted into 32 possible diastereomers of diol **367** (**Scheme 4.4**). This is achievable since four pathways are possible; either of the PMB or PBB protecting groups can be selectively removed and the hydroxyl group inverted, or both protecting groups can be removed and then both hydroxyls may be inverted or left with

the original stereochemistry. Thus, each 2,2'-bifuranyl diastereomer (**365**) can be converted into four different diol diastereomers (**367**, **Scheme 4.4**).

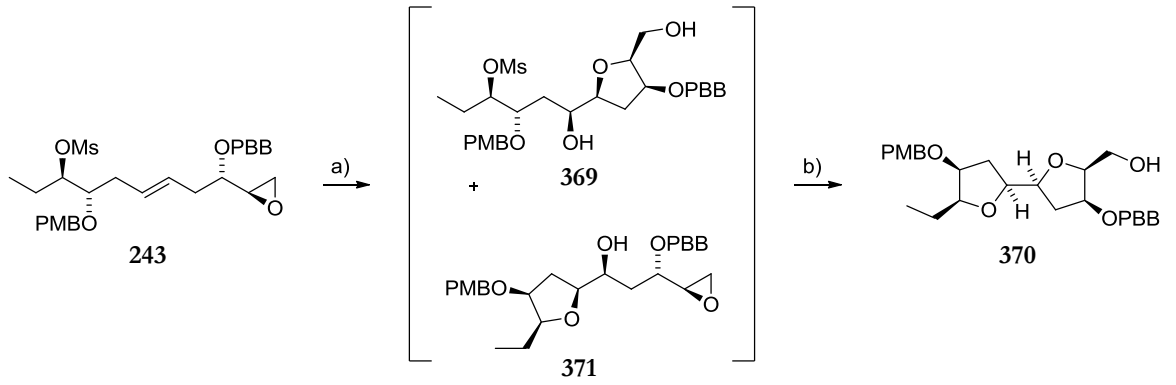



**Scheme 4.4 – Late stage protecting group strategy to convert eight diastereomers of the 2,2'-bifuranyl backbone into 32 diol diastereomers.**

The 32 diol diastereomers (**367**) could then be brominated and the allyl side chain converted into the enyne, as shown for elatenyne (**Chapter 3**, **Sections 3.5.2** and **3.6.2**), to yield all of the 32 possible diastereomers of elatenyne (**60**, **Figure 4.1**).

### *4.1.2. Demonstration of Second Ring Closure*

The completed total synthesis of elatenyne (**60**) demonstrated the viability of the divergent route discussed, but only demonstrated one of the two possible ring closures to the 2,2'-bifuranyl core (**Scheme 4.3**). In order to show the viability of the second ring closure, cross metathesis product **243**, with the mesylate already in place, was subjected to the dihydroxylation conditions established in the elatenyne synthesis (**Scheme 4.5**). The uncyclised dihydroxylation product was not observed, but instead a mixture of mesylate **369** and epoxide **371** were isolated. It was found that upon exposure to KHMDS both of these compounds (**369** and **371**) were converted to the desired 2,2'-bifuranyl **370** and hence a simple two step procedure was performed, without isolation after the dihydroxylation, to successfully yield 2,2'-bifuranyl **370** in 76% yield (**Scheme 4.5**).



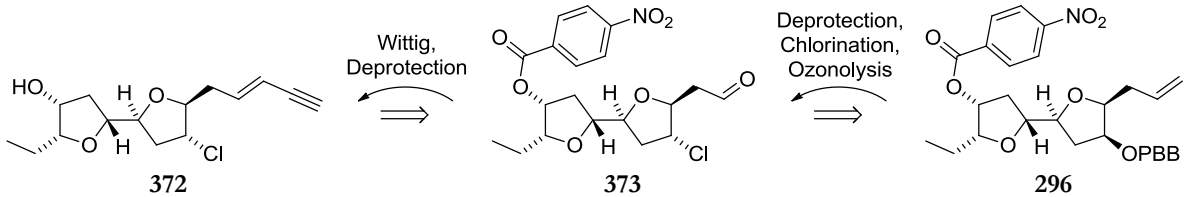

**Scheme 4.5 – Reagents and conditions: a) $K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, $^tBuOH$, $H_2O$, 0 °C, 48 h, (6:1 d.r. from isolated intermediates); b) KHMDS, THF, RT, 15 min, 76% (2 steps, 98% BRSM).**

## 4.2. *Laurencia Majuscula* Enyne

The late stage divergence in the developed synthetic route to elatenyne (**60**) allows manipulation of each hydroxyl group independently (**Scheme 4.4**) and therefore enables the route to be applied to other 2,2'-bifuranyl natural products with different substituents. One such natural product is the reassigned 2,2'-bifuranyl structure proposed for the *Laurencia majuscula* enyne (**48**) discussed in **Chapter 1** (**Section 1.3.4**).[17-18] The most likely diastereomer of the natural product has yet to be investigated computationally, but access to synthetic data for any diastereomer of the 2,2'-bifuranyl skeleton would be useful and would aid stereochemical prediction.

### *4.2.1. Retrosynthetic Analysis*

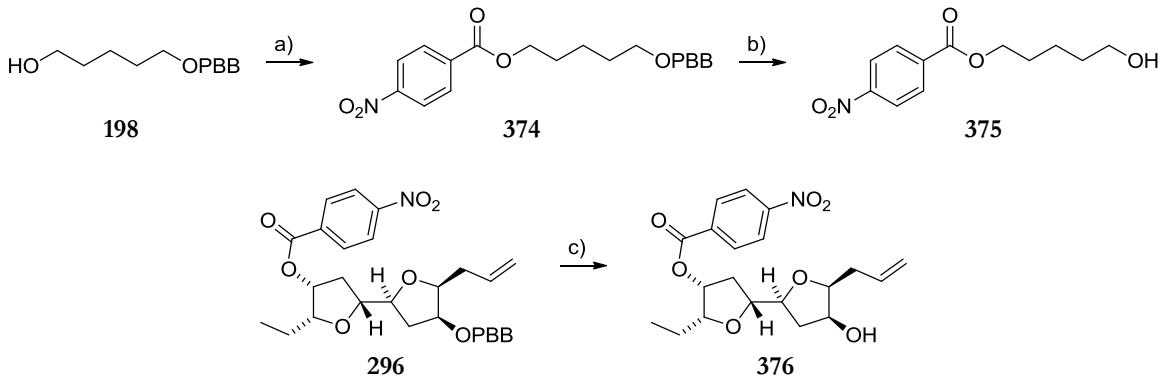
It was proposed that we could access a diastereomer of the *L. majuscula* enyne (**372**) from the *p*-nitrobenzoate intermediate (**296**) in the synthesis of elatenyne (**60**), which was the product from the Mitsunobu inversion (**Scheme 4.6**, also see **Chapter 3**, **Section 3.5.1**). Removal of the PBB group of **296**, followed by chlorination and ozonolysis would yield chloride **373**, which could be converted to enyne **372** by Wittig olefination and deprotection.




**Scheme 4.6 – Retrosynthetic analysis of a diastereomer of *L. majuscula* enyne to the elatenyne intermediate.**

### 4.2.2. PBB Deprotection

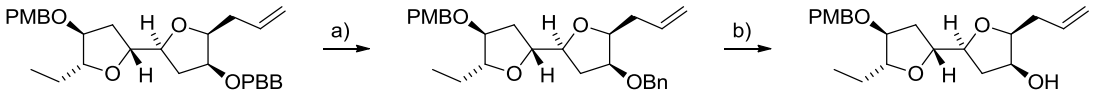
In order to test the PBB deprotection in the presence of the *p*-nitrobenzoate functionality, a model system (**374**) was synthesised (**Scheme 4.7**). Deprotection of the model system (**374**) with boron trichloride at room temperature gave a quantitative yield of alcohol **375**. Unfortunately, when the same conditions were attempted on substrate **296** no product (**376**) was observed, no starting material was recovered and only unidentified material was obtained. Lowering the reaction temperature to -50 °C allowed the formation of alcohol **376**, but this was obtained in low yield along with a significant quantity of unidentified side products (**Scheme 4.7**).




**Scheme 4.7 – Reagents and conditions: a) 4-nitrobenzoic acid, DCC, DMAP, 0 °C to RT, 20 h, 90%; b) $BCl_3$, DCM, RT, 10 min, quant.; c) $BCl_3$, DCM, -50 °C, 45 min, 22%.**

### 4.2.3. Alternative Diastereomer Synthesis

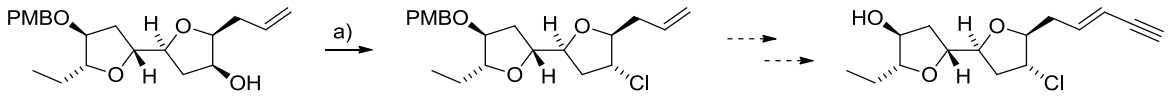
Since we were not targeting a particular diastereomer of *L. majuscula* enyne based on any stereochemical prediction, we decided to use intermediate **294** with both the PMB and PBB groups present before the Mitsunobu inversion in the synthesis of elatenyne (**Chapter 3, Section 3.5.1**). We knew that the PMB and PBB groups were orthogonal and successfully used lithium-halogen exchange to form Bn protected substrate **377** in an unoptimised 59% yield, followed by LiDBB to selectively remove the benzyl group (**Scheme 4.8**). If excess LiDBB was used in the reaction then doubly deprotected diol was isolated in addition to product **378**. However, simple titration of the LiDBB and monitoring by TLC analysis for consumption of starting material was successful to give a good yield of alcohol **378** and no diol was observed.




**294** **377** **378**

**Scheme 4.8 – Reagents and conditions: a) $^{n}$BuLi, THF, -78 °C, 10 min, 59%; b) LiDBB, THF, -78 °C, 1 h, quant.**

With alcohol **378** in hand we were able to install the chloride with inversion using Appel conditions (**Scheme 4.9**) in an analogous reaction to the bromination in the elatenyne synthesis (**Chapter 3**, **Section 3.5.2**).[129] Due to time restraints we were unable to progress chloride **379** through to *L. majuscula* diastereomer **380** (**Scheme 4.9**), but are confident this would be successful (See **Chapter 5**).



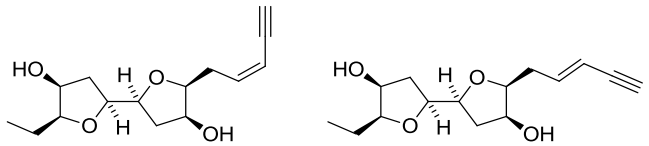

**378** **379** **380**

**Scheme 4.9 – Reagents and conditions: a) $CCl_4$, $PPh_3$, 70 °C, 18 h, quant.**

## 4.3. Laurefurenynes A and B

### *4.3.1. Isolation and Retrosynthetic Analysis*

Two 2,2'-bifuranyl diols, laurefurenynes A and B (**381** and **382**), were isolated in 2010 from aqueous extracts of a red marine alga *Laurencia* sp. collected in the Phillipines.[140] They were assigned a 2,2'-bifuranyl skeleton on the basis of the NMR chemical shifts of the ring junction carbons lying at >76 ppm (**Chapter 1**, **Section 1.3.4.1**). The relative stereochemistry was assigned on the basis of 2D NOESY correlations and molecular modelling.

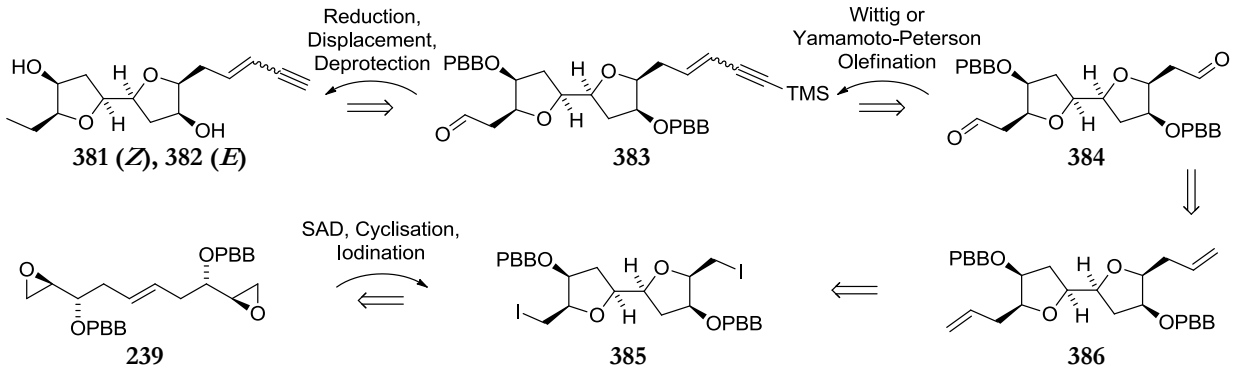



**381** **382**

**Figure 4.2 – Laurefurenynes A and B.**

Laurefurenynes A and B (**381** and **382**) were attractive synthetic targets as we envisaged being able to rapidly access the $C_2$-symmetric 2,2'-bifuranyl core as demonstrated previously in the Burton group (**Chapter 1**, **Section 1.6**).[58] We envisaged that desymmetrisation using one equivalent of

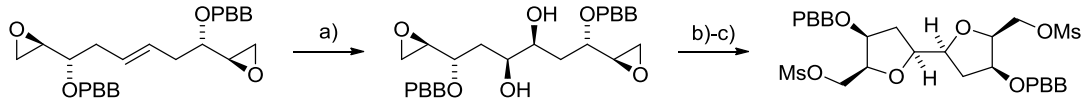
reagent in the Wittig or Yamamoto-Peterson olefination with dialdehyde **384** would allow installation of the enyne side chain (**Scheme 4.10**). Reduction of the remaining aldehyde **383**, conversion of the alcohol into a leaving group and subsequent reductive removal would install the ethyl side chain. $C_2$-symmetric dialdehyde **384** would be easily accessible using ozonolysis of diallyl substrate **386**, which was proposed to be synthesised by double Grignard displacement of diiodide **385**. It was thought that the diiodide **385** could be easily accessed using a Sharpless asymmetric dihydroxylation of PBB-homodimer **239** already in hand from the cross metathesis in the elatenyne synthesis (**Chapter 3**, **Section 3.3.1**). Subsequent cyclisation and conversion of the hydroxyl groups would give diiodide **385** (**Scheme 4.10**).




**Scheme 4.10 – Retrosynthetic analysis of laurefurenynes A and B.**

### *4.3.2. Synthesis of $C_2$-Symmetric Intermediates*

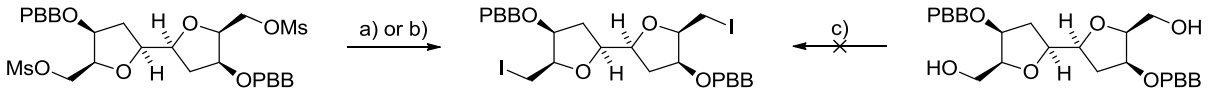
Following the work of Broadwith on a similar substrate (**126**, as discussed in **Chapter 1**, **Section 1.6**), the PPB homodimer **239** was subjected to Sharpless asymmetric dihydroxylation conditions to yield a 5:1 mixture of diastereomeric diols (**387** and **(3*R*,4*R*)-387**, **Scheme 4.11**). The mixture of diols (**387** and **(3*R*,4*R*)-387**) were cyclised to form the 2,2'-bifuranyl core using Amberlyst-15® resin and then the bis-mesylates (**388** and **(2*R*,2'*R*)-388**) were formed. At this stage the two diastereomers were easily separated by column chromatography.




**239** **387** **388**

**Scheme 4.11 – Reagents and conditions: a) $K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, $^tBuOH$, $H_2O$, 0 °C, 96 h, quant. (5:1 d.r.); b) Amberlyst-15® resin, DCM, RT, 4 h; c) MsCl, $Et_3N$, DCM, 0 °C, 10 min, 94% (2 steps).**

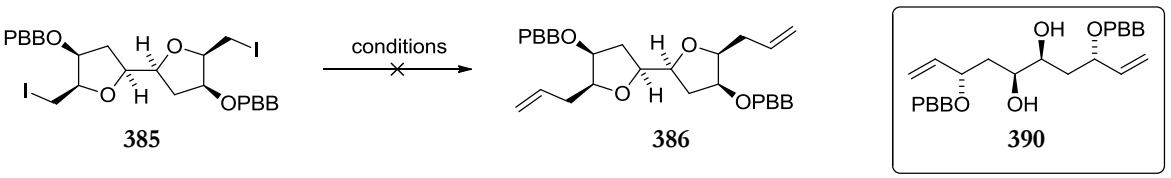
The major bis-mesylate diastereomer (**388**) was subjected to the optimised tetrabutylammonium iodide conditions for iodide formation from the elatenyne synthesis (**Chapter 3**, **Section 3.4.5**), but unfortunately diiodide **385** was not isolated (**Scheme 4.12**). Conversion of diol **389** directly to diiodide **385** using triphenylphosphine and iodine was also unsuccessful, but it was found that reacting the bis-mesylate **388** in refluxing butanone with sodium iodide for two days gave a good yield of diiodide **385** (**Scheme 4.12**). When this reaction was stopped before two days the mono-iodide from a single substitution was isolated in addition to a lower yield of diiodide **385**.




**388** **385** **389**

**Scheme 4.12 – Reagents and conditions: a) $Bu_4NI$, toluene, reflux, 16 h, 0%; b) NaI, butanone, reflux, 40 h, 92%; c) $I_2$, $PPh_3$, imidazole, THF, 0 °C to RT, 72 h, 0%.**

With diiodide **385** in hand, attention was focussed on the Grignard displacement reaction to synthesise diallyl compound **386** (**Scheme 4.13**). Unfortunately with a range of conditions only a trace of product formation was observed (**Table 4.1**).




**385** **386** **390**

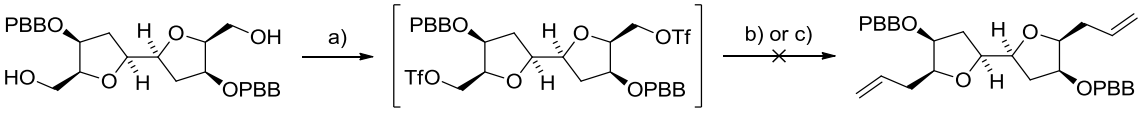
**Scheme 4.13 – Conditions: See Table 4.1.**

| Entry | Eq. Vinylmagnesium bromide | Temperature /°C | Reaction Time/h | Additive | Solvent | Yield of 386/% |
|---|---|---|---|---|---|---|
| **1** | 20 | 40 | 4 | - | benzene/THF (2:1) | trace[a,b] |
| **2** | 20 | 40 | 4 | - | THF | trace[b,c] |
| **3** | 10 | 25 | 8 | - | benzene/THF (1:1) | trace[b,d] |
| **4** | 5 | 0 to 25 | 5 | CuI | benzene (2:1) | -[e] |
| **5** | 10 | 0 to 40 | 5 min | CuI | benzene/THF (2:1) | trace[b] |
| **6** | 10 | 0 to 25 | 1.5 | CuI | benzene/THF (2:1) | trace[f] |
| **7** | 5 | -5 | 18 | $Li_2CuCl_4$ | THF | -[g] |

**Table 4.1 – Double Grignard displacement reactions. [a]Mixture of SM (385), mono-displacement product and product 386 by mass spectroscopy, [b]Mostly unidentified side product isolated, [c]15% SM (385) isolated, [d]55% SM (385) isolated, [e]SM (385) only identifiable compound isolated but in poor yield, [f]Isolated 390 in 40% yield, [g]SM (385) and trace mono-displacement product by mass spectroscopy.**

The optimised conditions for the Grignard displacement in the synthesis of elatenyne (**Chapter 3**, **Section 3.4.5**) gave limited reaction to diallyl **386** and altering the solvent, temperature and reaction time did not produce any improvement (**Entries 1-3**, **Table 4.1**). Use of copper(I) iodide in the reaction resulted in elimination of the iodides and opening of the THF rings (**Entry 6**, **Table 4.1**). The use of Kochi's catalyst has been found to be successful previously in the Burton group,[141] but use of this catalyst resulted in only a trace of the mono-displacement product by mass spectrometry after 18 hours (**Entry 7**, **Table 4.1**).

The Grignard displacement was also attempted with ditriflate **391** synthesised from diol **389** and used crude in the reactions. The Grignard displacement without any additive or with copper(I) iodide did not result in any observable formation of product **386** (**Scheme 4.14**).

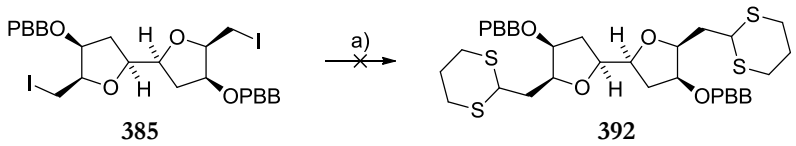



**389** **391** **386**

**Scheme 4.14 – Reagents and conditions: a) $Tf_2O$, pyridine, DCM, -78 °C, 20 min; b) vinylmagnesium bromide, benzene, 40 °C, 4 h, 0%; c) vinylmagnesium bromide, CuI, THF, -30 °C to RT, 2 h, 0%.**

Dithianes have been used synthetically as masked aldehydes and it was thought that if diiodide **385** could be displaced by 1,3-dithiane then an alternative route to the desired dialdehyde **384** (**Scheme 4.10**) could be developed. A displacement of an iodide in a similar system by 1,3-dithiane was achieved by Bates *et al.* in their synthesis of a fragment of amphidinolide C.[142] Diiodide **385** was

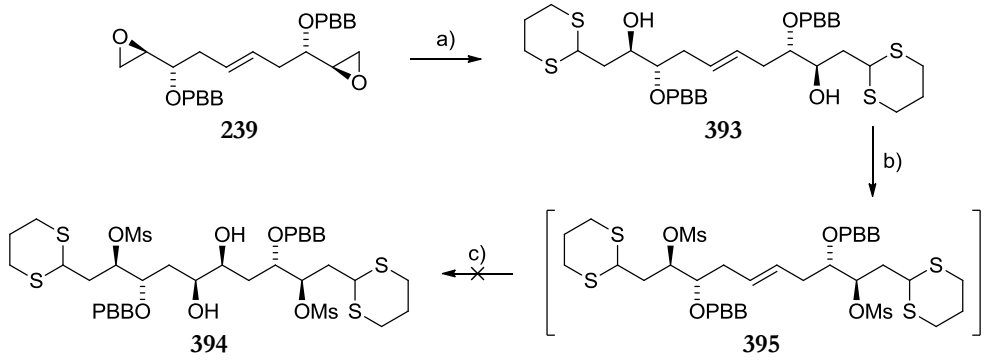
therefore subjected to preformed solution of lithiated 1,3-dithiane, but unfortunately no displacement product (**392**) was observed (**Scheme 4.15**).




**385** **392**

**Scheme 4.15 – Reagents and conditions: a) 1,3-dithiane, $^{n}$BuLi, THF/HMPA (4:1), -30 °C to RT, 3 h, 0%.**

We briefly investigated whether the 1,3-dithiane functionality could be installed earlier in the synthesis to avoid any displacement reactions of diiodide **385**. PBB homodimer **239** successfully underwent double epoxide opening with the conditions of Smith III *et al.* to give bis-dithiane **393** in an unoptimised yield of 57% (**Scheme 4.16**)[143] The bis-mesylate **395** was then formed and subjected to the Sharpless asymmetric dihydroxylation conditions, but disappointingly after five days only starting material (**395**) was recovered.




**239** **393** **394** **395**

**Scheme 4.16 – Reagents and conditions: a) 1,3-dithiane, $^{n}$BuLi, THF/HMPA (4:1), -30 °C to RT, 3 h, 57%; b) MsCl, $Et_3N$, DCM, 0 °C, 10 min; c) $K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, $^{t}$BuOH, $H_2O$, 0 °C, 120 h, 0% (100% BRSM).**

## 4.4. Conclusions

The strategy for the application of the completed total synthesis of elatenyne (**60**) to any of the 32 diastereomers of the 2,2'-bifuranyl skeleton has been presented. The late stage divergence in this synthetic route allows for its expansive application to other 2,2'-bifuranyl natural products with different substituent patterns to elatenyne, for example the revised 2,2'-bifuranyl structure of *Laurencia majuscula* enyne (**48**). The synthesis of a hydroxychloride substituted 2,2'-bifuranyl (**379**) from an intermediate (**294**) in the synthesis of elatenyne (**60**) has been demonstrated, which could

be elaborated to a diastereomer of *L. majuscula* enyne (**380**). The synthesis of the $C_2$-symmetric core of laurefurenynes A and B (**381** and **382**) has also been completed, but unfortunately installation of the side chains has so far been unsuccessful.

# CHAPTER 5: CONCLUSIONS AND FUTURE WORK

## 5.1. Elatenyne and Erickson's Enyne

The stereoselective total synthesis of elatenyne (**60**, **Figure 5.1**) has been completed, which has not only confirmed the structure of the natural product, but has shown that the relative stereochemistry was correctly predicted by computational and biosynthetic analysis. The use of the GIAO method for $^{13}C$ NMR chemical shift calculations and its application for stereochemical prediction has therefore been validated with these highly flexible 2,2'-bifuranyl systems, which could have great impact in the field of structure determination. The absolute configuration of the natural product has not been determined, but the optical rotation has been shown to be in accordance with the value obtained from the Kim and co-worker's synthetic elatenyne (***ent*-60**) and has been recorded using a mercury lamp ($\lambda$ = 589 nm) for comparison with any future isolation or synthesis.

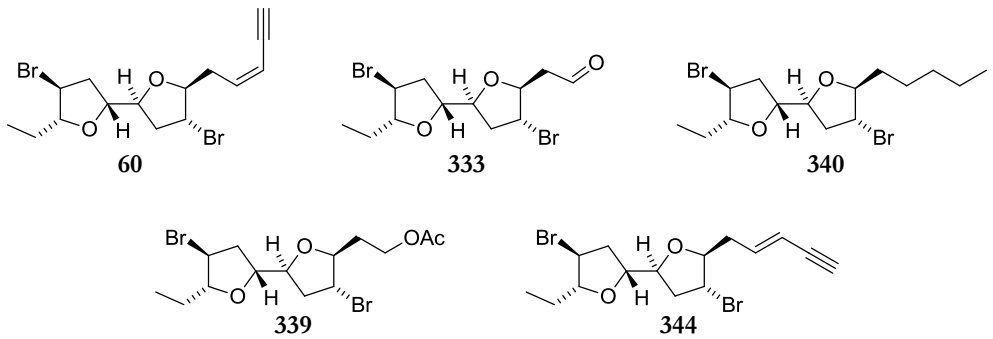



**Figure 5.1 – Elatenyne, derivatives of elatenyne and Erickson's enyne.**

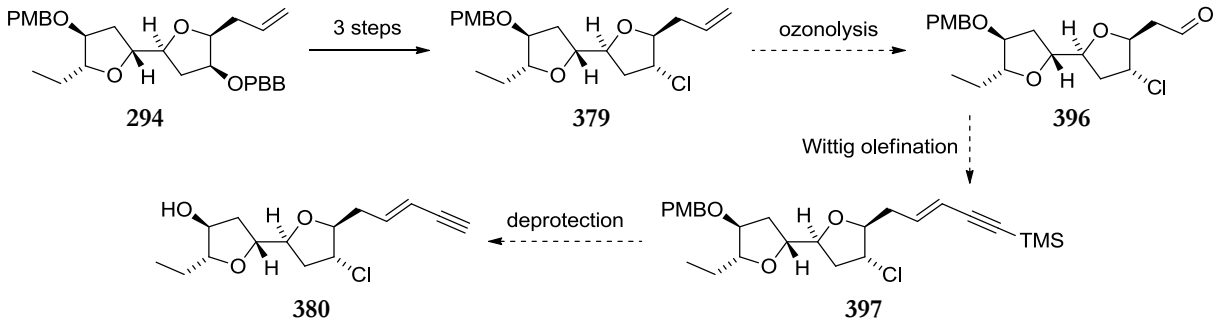
Three derivatives of elatenyne (**333**, **340** and **339**, **Figure 5.1**) were also synthesised and the data compared with that of the derivatives synthesised by Hall and Reiss to support the structure determination of elatenyne.

The completed synthesis of the (*E*)-enyne isomer of elatenyne (**344**, **Figure 5.1**) has also confirmed the structure of a dibrominated enyne natural product isolated by Erickson and co-workers.

## 5.2. Other Marine Natural Products

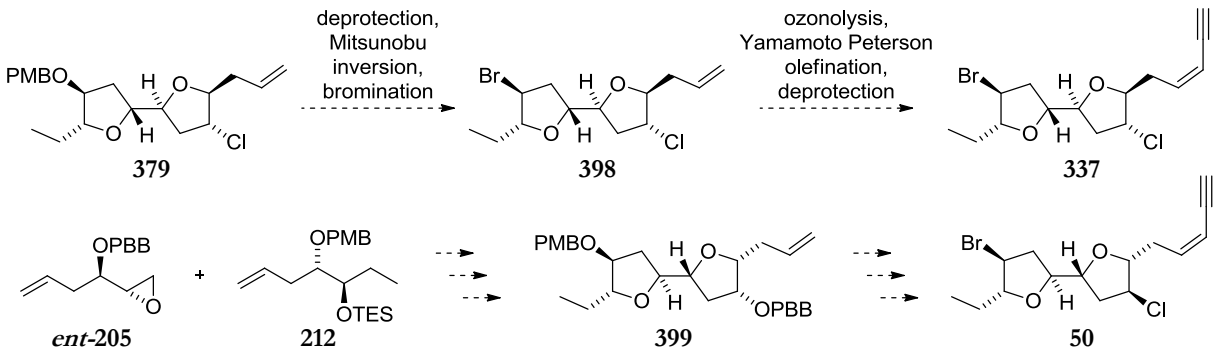
The developed synthetic route to elatenyne has been shown to be divergent and to allow access not only to any of the 32 possible diastereomers of the 2,2'-bifuranyl skeleton of elatenyne, but also to other 2,2'-bifuranyl natural products with differing substitutions on the THF rings. The key divergent steps in the synthesis include the use of either tartrate in the Sharpless asymmetric epoxidation, the use of either pseudo-enantiomeric ligand in the Sharpless asymmetric dihydroxylation, two possible 2,2'-bifuranyl ring closures and an orthogonal protecting group strategy allowing manipulation of each hydroxyl group independently.

The synthesis of a diastereomer of the revised 2,2'-bifuranyl structure of the *Laurencia majuscula* enyne (**48**) has been started from an intermediate in the synthesis of elatenyne (**294**, **Scheme 5.1**). Chloride **379** could be easily converted to the *L. majuscula* enyne diastereomer (**380**) by ozonolysis, Wittig olefination and deprotection (**Scheme 5.1**).



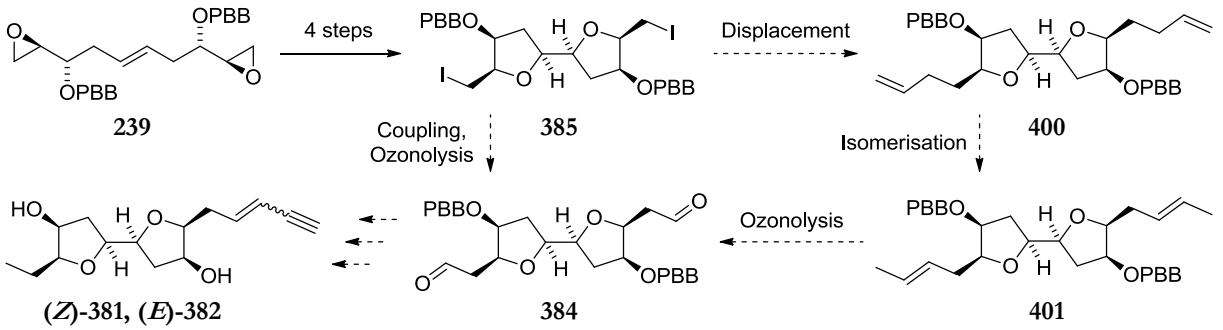

**Scheme 5.1 – Synthesis of *L. majuscula* enyne diastereomer.**

This synthetic route could be easily applied to the synthesis of laurendecumenyne B (**337**) from chloride **379** by deprotection, Mitsunobu inversion, bromination and installation of the enyne side chain in the same manner as in the synthesis of elatenyne (**Scheme 5.2**).[134] Use of the presented synthetic strategy could also be used to synthesise notoryne (**50**) from coupling partners ***ent*-205** and **212** (**Scheme 5.2**).[26]




**Scheme 5.2 – Synthesis of laurendecumenyne B and notoryne.**

The synthesis of the $C_2$-symmetric core of laurefurenynes A and B (**381** and **382**) from PBB homodimer **239** has also been completed, but so far installation of the side chains from diiodide **385** has not been successful (**Scheme 5.3**). Future work could involve the investigation of metal catalysed coupling of the Grignard reagent and the diiodide **385** to install the vinyl group. There is some literature precedence for this kind of coupling reaction with cobalt,[144] silver[145] or low-valent iron complexes.[146] Alternatively, displacement with allylmagnesium bromide, which should be more reactive than its vinyl equivalent, could be investigated to give diene **400**. The alkenes could be isomerised using the procedure of Donohoe and co-workers to give diene **401**,[99] and then ozonolysis would yield the desired bis-aldehyde **384** for the proposed synthesis (**Scheme 5.3**).




**Scheme 5.3 – Synthesis of laurefurenynes A and B.**

# CHAPTER 6: EXPERIMENTAL

## 6.1. General Experimental

*NMR spectra:* Proton ($^{1}$H), carbon ($^{13}$C) and fluorine ($^{19}$F) NMR spectra were recorded on a Bruker AV 500 (500/125 MHz), Bruker AV 400 (400/100 MHz) or Bruker DPX 200 (200/50 MHz) spectrometer. Proton and carbon chemical shifts ($\delta_H$, $\delta_C$) are quoted in ppm and referenced to tetramethylsilane ($\delta$ = 0 ppm) with residual protonated solvent as internal standard. Fluorine chemical shifts ($\delta_F$) are quoted in ppm and referenced to trichlorofluoromethane. Assignments were made on the basis of chemical shifts, coupling constants, COSY, DEPT, HMQC data and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), app. (apparent), br (broad), dd (double doublet) and so on. Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.5 Hz. H and H' refer to diastereotopic protons attached to the same carbon and imply no particular stereochemistry.

*Mass spectra:* Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ES). High resolution mass spectra were recorded by the mass spectrometry service at the Chemistry Research Laboratory, University of Oxford, using a Bruker Daltronics microTOF spectrometer (ES) or a Micromass GCT (FI). *m/z* values are reported in Daltons with their percentage abundances and, where known, the relevant fragment ions in parentheses. High resolution values are calculated to four decimal places from the molecular formula, all found values being within a tolerance of 5 ppm.

*Infrared spectra:* Infrared spectra were recorded on a Bruker Tensor 27 Fourier Transform spectrometer, as a thin film on NaCl plates or using diamond ATR. Absorption maxima ($\nu_{max}$) are described as s (strong), m (medium), w (weak) and br (broad) and quoted in wavenumbers ($cm^{-1}$).

*Melting points:* Melting points were determined using a Griffin heated metal block apparatus and are uncorrected.

*Optical rotations:* Optical rotations were measured using a Perkin-Elmer 241 polarimeter in a cell of 1 dm path length (l). The concentration (c) is expressed in g/0.1 $dm^3$ (equivalent to mg/0.1 $cm^3$). Specfic rotations denoted as $[\alpha]_D^T$ (T = temperature in °C, D refers to the D line of a sodium lamp, where the wavelength of light = 589 nm unless otherwise stated) imply units of $°dm^2g^{-1}$ and are calculated according to the equation below where α is the observed rotation:

$$[\alpha]_D^T = \frac{100 \propto}{lc}$$

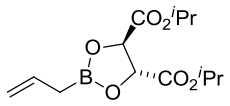
*Chromatography techniques:* TLC was performed on Merck DC-Alufolien 60 $F_{254}$ 0.2 mm precoated plates and visualised using acidic vanillin or basic potassium permanganate dips. Retention factors ($R_f$) are reported with the solvent system used in parentheses. Flash column chromatography was performed on Merck 60 silica (particle size 40–63 μm, pore diameter 60 Å) and the solvent system used is recorded in parentheses.

*Reactions:* All non-aqueous reactions were carried out in oven-dried glassware under an inert atmosphere of nitrogen and employing standard techniques for handling air-sensitive materials. Solvents and commercially available reagents were dried and purified before use, as appropriate according to standard techniques.[147] In particular carbon tetrabromide was sublimed (70 °C, 17 mbar), dissolved in DCM and passed through a column of deactivated alumina (with 6% $H_2O$), concentrated *in vacuo* and dried in a desiccator over KOH for at least 16 h. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40–60 °C unless otherwise stated. All water used experimentally was distilled and the term 'brine' refers to a saturated solution of sodium chloride in water. pH 2 buffer was prepared using concentrated sulfuric acid and sodium sulfate in water. pH 7 buffer was prepared from pH 7 buffer tablets dissolved in water. pH 6 buffer was prepared using monobasic potassium phosphate and potassium hydroxide in water.

## 6.2. Experimental Procedures

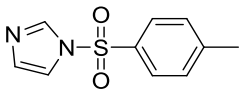
### *6.2.1. Reagent Synthesis*

**(4*R*,5*R*)-Diisopropyl 2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylate[73] (156)**



*According to the procedure of Roush et al.*[73b]: To dry diethyl ether (75 mL) at -78 °C was added dropwise, simultaneously but separately, solutions of triisopropyl borate (6.92 mL, 5.64 g, 30.0 mmol) in dry diethyl ether (7.5 mL) and allyl magnesium bromide (30 mL, 1.0 M solution in diethyl ether, 30.0 mmol). The reaction mixture was stirred at -78 °C for 30 min and then allowed to warm to RT and stirred for 3 h. The slurry was cooled to 0 °C and a solution of aq. HCl (30 mL, 1 M solution sat. with NaCl) was added dropwise over a 15 min period. The reaction mixture was warmed to RT and stirred for 10 min. The organic layer was separated, placed under an atmosphere of $N_2$ and treated with (+)-diisopropyl L-tartrate (6.31 mL, 7.03 g, 30.0 mmol). The aqueous layer was extracted with 5:1 diethyl ether:DCM (3 × 40 mL). The combined organic layers, under an atmosphere of $N_2$, were stirred over $MgSO_4$ for 2.5 h and then filtered under an atmosphere of $N_2$. The filtrate was concentrated *in vacuo*. Purification by vacuum fractional distillation (b.p. 122–128 °C/0.7 mmHg (lit. 88–90 °C/0.03 mmHg)[73b]) gave the title compound (**156**) as a colourless oil (3.5 g, 12.3 mmol, 41%); $\delta_H$ (400 MHz, $CDCl_3$) 1.30 (12H, d, *J*=6.0 Hz, 4 × C**H**$_3$), 1.93 (2H, d, *J*=7.5 Hz, C**H**$_2$CH=CH$_2$), 4.78 (2H, s, 2 × BOC**H**), 4.97–5.22 (4H, m, CH$_2$CH=C**H**$_2$, 2 × C**H**(CH$_3$)$_2$), 5.90 (1H, ddt, *J*=17.5, 10.0, 7.5 Hz, CH$_2$C**H**=CH$_2$).

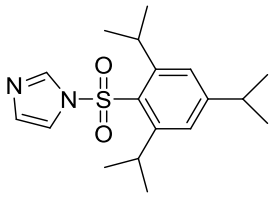
**1-(*p*-Toluenesulfonyl)imidazole[75] (164)**



*According to the procedure of Rad et al.*[75]: In a well dried mortar a mixture of *p*-toluenesulfonyl chloride (1.72 g, 9.00 mmol) and imidazole (**165**) (1.35 g, 19.8 mmol) was ground vigorously at RT. The

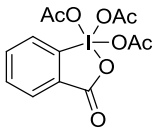
reaction mixture melted and solidified after 2 min. The resulting white solid was dissolved in chloroform (50 mL) and washed with $H_2O$ (3 × 50 mL). The organic layer was dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to give the title compound (**164**) as white crystals (1.82 g, 8.20 mmol, 91%); m.p. 72–74 °C (lit. 75–77 °C)[148]; $\delta_H$ (400 MHz, MeOD-$d_4$) 2.46 (3H, s, C**H**$_3$), 7.10 (1H, s, Im**H**), 7.49 (2H, d, *J*=8.0 Hz, Tos**H**), 7.59 (1H, s, Im**H**), 7.98 (2H, d, *J*=8.0 Hz, Tos**H**), 8.29 (1H, s, Im**H**).

**1-(2,4,6-Triisopropylbenzenesulfonyl)imidazole**[149] **(166)**



Prepared according to the procedure for 1-(*p*-toluenesulfonyl)imidazole using 2,4,6-triisopropylbenzenesulfonyl chloride (2.72 g, 8.97 mmol) to give the title compound (**166**) as white crystals (2.93 g, 8.76 mmol, 98%); m.p. 108–122 °C (lit. 122–124 °C)[149]; $\delta_H$ (200 MHz, MeOD-$d_4$) 1.22 (12H, d, *J*=7.0 Hz, C**H**$_3$), 1.31 (6H, d, *J*=7.0 Hz, C**H**$_3$), 3.02 (1H, sept, *J*=7.0 Hz, C**H**(Me$_2$)), 4.16 (2H, sept, *J*=7.0 Hz, C**H**(Me$_2$)), 7.15 (1H, s, Im**H**), 7.41 (3H, br s, Im**H**, Tris**H**), 8.27 (1H, s, Im**H**).

**Dess-Martin periodinane**[77]



*According to the procedures of Dess and Martin*[77] and *Frigerio et al.*[150]: 2-Iodobenzoic acid (50 g, 200 mmol) was added in one portion to a solution of Oxone® (181 g, 290 mmol) in $H_2O$ (650 mL) with overhead stirring. The reaction was heated to 70 °C over 20 min and stirred for 3 h. The suspension was cooled to 5 °C, slowly stirred for 1.5 h and then filtered through a sinter. The white IBX crystals were washed with $H_2O$ (6 × 100 mL) and acetone (2 × 100 mL) and dried under high

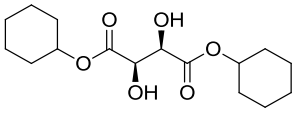
vacuum at RT. To a suspension of these crystals (41.7 g, 149 mmol) in acetic anhydride (209 mL, 226 g, 2.20 mol) was added *p*-toluenesulfonic acid monohydrate (283 mg, 1.49 mmol). The resulting mixture was heated to 85 °C for 2.5 h during which time the white solid dissolved. The reaction mixture was cooled to 0 °C and the precipitate was filtered, washed with diethyl ether (3 × 100 mL) and dried under high vacuum for 18 h to give the title compound as a white powder (43.8 g, 103 mmol, 52% over two steps).

**_tert_-Butyl hydroperoxide solution preparation**

*According to the procedure of Hanson and Sharpless*[86]: *tert*-Butyl hydroperoxide solution (100 mL, 70% in $H_2O$) was extracted with DCM (100 mL). The organic layer was placed in a 250 mL round bottomed flask fitted with reverse phase Dean-Stark apparatus and heated to reflux for 18 h (10 mL water collected). The organic solution was transferred to a plastic bottle containing cooled, activated 3 Å molecular sieves (20 g) and stored in the fridge for 24 h before titration. NaI (6.0 g) was dissolved in IPA (30 mL) with heating to ensure dissolution. After cooling, 10 mL of this solution was added to a 250 mL conical flask containing IPA (25 mL) and glacial acetic acid (1 mL). 0.25 mL of *tert*-butyl hydroperoxide in DCM was added and the solution heated to reflux with stirring for 30–45 sec. The solution was diluted with distilled $H_2O$ (100 mL) and titrated with 0.1 M $Na_2S_2O_3$ solution (average 19.7 mL) to the disappearance of the yellow iodine colour. The concentration of the *tert*-butyl hydroperoxide solution was determined according to the equation:

$$concentration = \frac{molarity\ of\ titrant \times mL\ of\ titrant}{2 \times mL\ of\ TBHP\ solution} = \frac{0.1 \times 19.7}{2 \times 0.25} = 3.94\ \text{M}$$

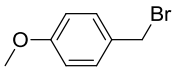
**(2*R*,3*R*)-Dicyclohexyl 2,3-dihydroxysuccinate[64] (186)**




*According to the modified procedure of Gao et al.*[64]: L-(+)-Tartaric acid (**185**) (20.0 g, 0.133 mol) and cyclohexanol (35.2 mL, 33.2 g, 0.333 mol) were suspended in benzene (140 mL) and

methanesulfonic acid (0.86 mL, 1.27 g, 13.3 mmol) was added. The reaction mixture was heated at reflux with azeotropic removal of water *via* Dean-Stark apparatus for 16 h (14 mL water collected). The reaction mixture was cooled to RT and washed sequentially with 5% aq. $NaHCO_3$ (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The solvent and excess cyclohexanol were removed by distillation under high vacuum using a rotary evaporator and the resulting viscous brown oil was slowly crystallised from hot hexane (40 mL) to give the title compound (**186**) as a white powder (36.1 g, 0.115 mol, 86%); m.p. 67–68 °C (lit. 69.5–70.5 °C)[64]; $\delta_H$ (400 MHz, $CDCl_3$) 1.20–1.63 (12H, m, 6 × CyHex C**H**$_2$), 1.69–1.82 (4H, m, 4 × CyHex C**H**H'), 1.85–1.96 (4H, m, 4 × CyHex CH**H'**), 3.13 (2H, dd, *J*=7.5, 1.5 Hz, 2 × CHO**H**), 4.51 (2H, dd, *J*=7.5, 1.5 Hz, 2 × C**H**OH), 4.94 (2H, tt, *J*=9.0, 4.0 Hz, 2 × CyHex C**H**O); $\delta_C$ (100 MHz, $CDCl_3$) 23.5 (CyHex), 23.5 (CyHex), 25.2 (CyHex), 31.3 (CyHex), 31.4 (CyHex), 72.1 (**C**HOH), 75.2 (CyHex **C**HO), 171.1 (**C**=O); *m/z* (ES$^+$) 373 (M+MeCN+$NH_4^+$, 15%), 337 (M+$Na^+$, 40), 315 (M+$H^+$, 5); $[\alpha]_D^{25}$ +14.7 (c = 1.0 in EtOH), literature value $[\alpha]_D^{25}$ +14.97 (c = 1.71 in EtOH).[64]

**4-Methoxybenzyl bromide**[151]




*According to the modified procedure of Burke et al.*[151b]: 4-Methoxybenzyl alcohol (9.00 g, 65.1 mmol) in diethyl ether (15 mL) was added slowly to HBr (9.95 mL 48% aq. solution) in diethyl ether (15 mL) and stirred for 1 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ (15 mL), the aqueous layer was separated and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by vacuum distillation (b.p. 85–92 °C/0.4 mmHg (lit. 92–95 °C/0.2 mmHg)[152]) gave the title compound as a colourless oil (7.30 g, 36.3 mmol, 56%), although the crude was often used without further purification; $\delta_H$ (400 MHz, $CDCl_3$) 3.82 (3H, s, C**H**$_3$), 4.52 (2H, s, C**H**$_2$Br), 6.88 (2H, d, *J*=8.5 Hz, Ar**H**), 7.34 (2H, d, *J*=8.5 Hz, Ar**H**).

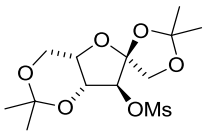
**Silver(I) nitrate impregnated silica**

*According to the modified procedure of Li et al.*[103]: A solution of silver(I) nitrate (16.5 g, 97.1 mmol) in $H_2O$ (90 mL) was poured over silica gel (150 g) in a 500 mL conical flask whilst excluding as much light as possible and shaken. The silica gel was ground in portions until it was free flowing and then dried in an oven in the dark for at least 72 h. The silica gel was cooled to RT before use.

**Silver(I) nitrate TLC plates**

*According to the modified procedure of Li et al.*[103]: TLC plates were dipped into a solution of silver(I) nitrate (2.0 g, 11.8 mmol) in $H_2O$ (5 mL) whilst excluding as much light as possible and then dried in the dark on top of an oven for at least 16 h. When used for TLC, the plates were visualised using an ammonium molybdate dip.

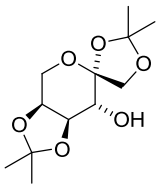
**(4*S*,4a'*S*,7'*S*,7a'*R*)-2,2,2',2'-Tetramethyltetrahydrospiro[[1,3]dioxolane-4,6'-furo[3,2-*d*][1,3]dioxin]-7'-yl methanesulfonate**[111] **(257)**




*According to the procedure of Zhao et al.*[111]: A solution of tin(II) chloride (100 mg, 0.51 mmol) in dry 1,2-dimethoxyethane (4 mL) was added to a suspension of pulverised L-sorbose (**256**) (20.0 g, 111 mmol) in 2,2-dimethoxypropane (60 mL, 50.8 g, 488 mmol) with vigorous stirring. The reaction mixture was refluxed gently (70 °C) under $N_2$ for 2.3 h. The reaction mixture was quenched immediately with triethylamine (0.5 mL), filtered to remove the remaining L-sorbose (**256**) (3.10 g, 17 mmol) and washed through with EtOAc (5 mL). The filtrate was concentrated *in vacuo* to give a syrup which was dissolved in pyridine (45 mL) and cooled to 0 °C. Methanesulfonyl chloride (10.6 mL, 15.7 g, 138 mmol) was added dropwise *via* an addition funnel over 1 h. The reaction mixture was stirred at 0 °C for a further 3 h, poured into ice water (300 mL), stirred for 30 min and filtered. The filter cake was washed with $H_2O$ (3 × 100 mL), recrystallized from hot

ethanol (100 mL) and dried under vacuum overnight to give the title compound (**257**) as a white powder (14.5 g, 42.9 mmol, 39%); m.p. 114–116 °C (lit. 120–122 °C)[111]; $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (3H, s, C**H**$_3$), 1.42 (3H, s, C**H**$_3$), 1.47 (3H, s, C**H**$_3$), 1.54 (3H, s, C**H**$_3$), 3.16 (3H, s, SC**H**$_3$), 3.92 (1H, dd, *J*=13.0, 3.0 Hz, C**H**H'OC($Me_2$)), 4.01 (1H, dd, *J*=13.0, 3.0 Hz, CH**H'**OC($Me_2$)), 4.20 (1H, d, *J*=10.0 Hz, C**H**H'OC($Me_2$)), 4.21–4.25 (1H, m, C**H**$CH_2$OC($Me_2$)), 4.25 (1H, d, *J*=10.0 Hz, CH**H'**OC($Me_2$)), 4.44–4.47 (1H, m, C**H**OC($Me_2$)), 4.87–4.89 (1H, m, C**H**OMs); $\delta_C$ (100 MHz, $CDCl_3$) 19.9 (**C**H$_3$), 25.7 (**C**H$_3$), 25.9 (**C**H$_3$), 28.1 (**C**H$_3$), 38.8 (S**C**H$_3$), 60.3 (**C**$H_2$OC($Me_2$)), 72.1 (**C**H$CH_2$OC($Me_2$)), 73.2 (**C**$H_2$OC($Me_2$)), 73.3 (**C**HOC($Me_2$)), 84.2 (**C**HOMs), 98.2 (**C**(C)(O)OC($Me_2$)), 109.8 (**C**($Me_2$)), 111.5 (**C**($Me_2$)); *m/z* ($ES^+$) 361 ($M+Na^+$, 70%), 356 ($M+NH_4^+$, 10); $[\alpha]_D^{25}$ –26.3 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{25}$ -28.0 (c = 1.06 in $CHCl_3$).[111]

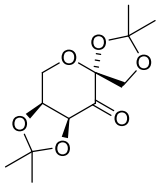
**(3a*S*,4'*R*,7*R*,7a*R*)-2,2,2',2'-Tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-*c*]pyran-6,4'-[1,3]dioxolan]-7-ol[111] (261)**




*According to the procedure of Zhao et al.*[111]: A suspension of pulverised (4*S*,4a'*S*,7'*S*,7a'*R*)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolane-4,6'-furo[3,2-*d*][1,3]dioxin]-7'-yl methanesulfonate (**257**) (35.4 g, 106 mmol) in 4.5% (wt) $H_2SO_4$ (350 mL) was stirred for 4 h until the starting material was consumed as observed by TLC. The reaction mixture was made alkaline with 9 M NaOH (70 mL) and heated at 95 °C for 9 h. The reaction mixture was allowed to cool and then acidified to pH 1 with 9 M $H_2SO_4$ (25 mL) and heated at 75 °C for 30 min. The reaction mixture was then neutralised with 9 M NaOH (20 mL) and concentrated *in vacuo*. Ethanol (200 mL) was added to the resulting residue, heated to reflux and then filtered. The filter cake was then added to ethanol (200 mL), heated to reflux and filtered and this process was repeated once. The combined filtrate solutions were concentrated *in vacuo* to give a syrup. To a suspension of this syrup in acetone

(175 mL) was added 2,2-dimethoxypropane (39.0 mL, 33.0 g, 318 mmol). After cooling to 0 °C concentrated $H_2SO_4$ (1.41 mL, 26.5 mmol) was added dropwise under $N_2$. The reaction mixture was then stirred at 0 °C for 6 h. Concentrated $NH_4OH$ (8.75 mL) was added and the reaction mixture was concentrated *in vacuo* to give a solid. The solid was dissolved in DCM (120 mL) and washed with $H_2O$ (2 × 60 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1→3:1 hexane:EtOAc) gave the title compound (**261**) as a white powder (11.0 g, 42.3 mmol, 40%); m.p. 106–108 °C (lit. 115–116 °C)[111]; $R_f$ 0.48 (1:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (3H, s, C**H**$_3$), 1.45 (3H, s, C**H**$_3$), 1.52 (3H, s, C**H**$_3$), 1.54 (3H, s, C**H**$_3$), 2.00 (1H, br s, O**H**), 3.67 (1H, d, *J*=7.0 Hz, C**H**OH), 3.96–4.05 (1H, m, 2 × C**H**H'O), 4.09–4.16 (2H, m, CH**H'**O, C**H**CHOH), 4.19 (1H, d, *J*=9.0 Hz, CH**H'**O), 4.20–4.24 (1H, m, C**H**CH$_2$O); $\delta_C$ (100 MHz, $CDCl_3$) 25.9 (**C**H$_3$), 26.2 (**C**H$_3$), 26.4 (**C**H$_3$), 27.9 (**C**H$_3$), 60.7 (**C**H$_2$O), 70.4 (**C**HOH), 72.3 (**C**H$_2$O), 73.3 (**C**HCH$_2$O), 77.3 (**C**HCHOH), 104.5 (**C**(C)(O)OC(Me$_2$)), 109.4 (**C**(Me$_2$)), 111.9 (**C**(Me$_2$)); *m/z* (ES$^-$) 259 ((M–H)$^-$, 55%); $[\alpha]_D^{25}$ +125.1 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{25}$ +142.4 (c = 1.05 in $CHCl_3$).[111]

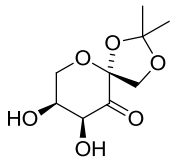
**(3a*S*,4'*R*,7a*S*)-2,2,2',2'-Tetramethyldihydrospiro[[1,3]dioxolo[4,5-*c*]pyran-6,4'-[1,3]dioxolan]-7(7a*H*)-one[111] (260)**



*According to the procedure of Zhao et al.*[111]: To a stirred solution of (3a*S*,4'*R*,7*R*,7a*R*)-2,2,2',2'-tetramethyltetrahydrospiro[[1,3]dioxolo[4,5-*c*]pyran-6,4'-[1,3]dioxolan]-7-ol (**261**) (5.31 g, 20.4 mmol) in dry DCM (43 mL) were added acetic anhydride (6.36 mL, 6.87 g, 67.3 mmol) and pyridinium dichromate (4.60 g, 12.2 mmol). The reaction mixture was heated at reflux for 1.5 h before being cooled to RT and concentrated *in vacuo*. EtOAc (30 mL) was added and the mixture applied to a pad of silica and washed through with EtOAc (150 mL). The filtrate was concentrated

*in vacuo* and the resulting solid recrystallized from hot hexane (20 mL) to give the title compound (**260**) as white crystals (4.06 g, 15.7 mmol, 77%); m.p. 89–96 °C (lit. 99–100 °C)[111]; $\delta_H$ (400 MHz, $CDCl_3$) 1.40 (6H, s, 2 × C**H**$_3$), 1.47 (3H, s, C**H**$_3$), 1.55 (3H, s, C**H**$_3$), 4.00 (1H, d, *J*=9.5 Hz, C**H**H'OC(Me)$_2$), 4.13 (1H, d, *J*=13.5 Hz, CHC**H**H'O), 4.40 (1H, dd, *J*=13.5, 2.0 Hz, CHCH**H'**O), 4.53–4.57 (1H, m, C**H**CH$_2$O), 4.62 (1H, d, *J*=9.5 Hz, CH**H'**OC(Me)$_2$), 4.73 (1H, d, *J*=5.5 Hz, C**H**C(O)); $\delta_C$ (100 MHz, $CDCl_3$) 26.0 (**C**H$_3$), 26.1 (**C**H$_3$), 26.5 (**C**H$_3$), 27.1 (**C**H$_3$), 60.0 (CH**C**H$_2$O), 70.0 (**C**H$_2$OC(Me)$_2$), 75.9 (**C**HC(O)), 77.9 (**C**HCH$_2$O), 104.1 (**C**(C)(O)OC(Me$_2$)), 110.6 (**C**(Me$_2$)), 113.8 (**C**(Me$_2$)), 196.9 (**C**=O); *m/z* (ES$^+$) 539 (2M+Na$^+$, 100%), 281 (M+Na$^+$, 30), 259 (M+H$^+$, 10); $[\alpha]_D^{25}$ +110.1 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{25}$+120.0 (c = 1.0 in $CHCl_3$).[111]

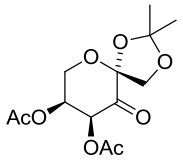
***(5R,8S,9S)-8,9-Dihydroxy-2,2-dimethyl-1,3,6-trioxaspiro[4.5]decan-10-one*[114] (266)**




*According to the modified procedure of Nieto et al.*[115a]: Acetic acid (3.2 mL) and $H_2O$ (0.8 mL) were added to (3a*S*,4'*R*,7a*S*)-2,2,2',2'-tetramethyldihydrospiro[[1,3]dioxolo[4,5-*c*]pyran-6,4'-[1,3]dioxolan]-7(7a*H*)-one (**260**) (400 mg, 1.55 mmol) and the reaction mixture was stirred at RT for 21 h. The reaction mixture was concentrated *in vacuo*, dissolved in DCM (1 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1→0:1 petrol:EtOAc) gave recovered starting material (11 mg, 0.04 mmol, 3%) and the title compound (**266**) as a white powder (294 mg, 1.35 mmol, 87%); m.p. 98–103 °C (lit. 107–110 °C)[114]; $R_f$ 0.14 (1:1 petrol:EtOAc); $\nu_{max}$/cm$^{-1}$ (thin film) 3466s (OH), 3400s (OH), 2994s (CH), 2903s, 1747s (CO), 1375s, 1212s, 1067s, 868m; $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (3H, s, C**H**$_3$), 1.55 (3H, s, C**H**$_3$), 3.98 (1H, m, CHC**H**H'O), 4.00 (1H, d, *J*=9.5 Hz, C**H**H'OC(Me)$_2$), 4.33 (1H, d, *J*=13.0 Hz, CHCH**H'**O), 4.38–4.41 (1H, m, C**H**CH$_2$O), 4.68 (1H, d, *J*=9.5 Hz, CH**H'**OC(Me)$_2$), 4.73 (1H, d, *J*=4.0 Hz, C**H**C(O)); $\delta_C$ (100 MHz, $CDCl_3$) 26.1 (**C**H$_3$), 26.3 (**C**H$_3$), 63.3 (CH**C**H$_2$O), 69.5 (**C**H$_2$OC(Me)$_2$), 73.6 (**C**HC(O)), 74.2 (**C**HCH$_2$O), 104.3 (**C**(C)(O)OC(Me$_2$)), 113.5 (**C**(Me$_2$)), 199.0 (**C**=O); *m/z*

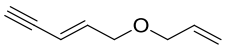
(ES$^-$) 217 (M–H$^-$, 35%); Accurate mass (FI$^+$): Found 218.0793, $C_9H_{14}O_6$ (M$^+$) requires 218.0790; $[\alpha]_D^{25}$ +128.1 (c = 1.0 in MeOH), literature value for enantiomer $[\alpha]_D^{25}$ -140.0 (c = 1.0 in MeOH).[114]

***(5R,8S,9S)-2,2-Dimethyl-10-oxo-1,3,6-trioxaspiro[4.5]decane-8,9-diyl diacetate*[114] (267)**



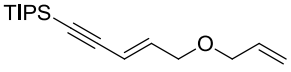

*According to the procedure of Nieto et al.*[115a]: Tin(II) chloride (1.6 mg, 0.01 mmol) was added to a suspension of (5*R*,8*S*,9*S*)-8,9-dihydroxy-2,2-dimethyl-1,3,6-trioxaspiro[4.5]decan-10-one (**266**) (100 mg, 0.46 mmol) in acetic anhydride (0.17 mL, 187 g, 1.83 mmol) and the reaction mixture was stirred at RT under $N_2$ for 3 h. EtOAc (1 mL) was added and the reaction mixture was filtered through a pad of silica, washing through with EtOAc (15 mL). The filtrate was concentrated *in vacuo* and purification by flash column chromatography (1:0→2:1 hexane:EtOAc) gave the title compound (**267**) as a colourless oil (116 mg, 0.38 mmol, 83%). $R_f$ 0.73 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2993s (CH), 2940s, 1768s (CO), 1756s (CO), 1747s (CO), 1373s, 1214s, 1068s, 851m; $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (3H, s, C**H**$_3$), 1.52 (3H, s, C**H**$_3$), 2.09 (3H, s, C(O)C**H**$_3$), 2.14 (3H, s, C(O)C**H**$_3$), 3.93 (1H, dd, *J*=13.0, 2.0 Hz, CHC**H**H'O), 3.96 (1H, d, *J*=9.5 Hz, C**H**H'OC(Me)$_2$), 4.41 (1H, d, *J*=13.0 Hz, CHCH**H'**O), 4.67 (1H, *J*=9.5 Hz, CH**H'**OC(Me)$_2$), 5.56–5.61 (1H, m, C**H**CH$_2$O), 5.86 (1H, d, *J*=4.0 Hz, C**H**C(O)); $\delta_C$ (100 MHz, $CDCl_3$) 20.4 (**C**H$_3$), 20.8 (**C**H$_3$), 26.0 (**C**H$_3$), 26.4 (**C**H$_3$), 62.5 (CH**C**H$_2$O), 69.4 (**C**H$_2$OC(Me)$_2$), 72.1 (**C**HC(O)), 74.0 (**C**HCH$_2$O), 105.0 (**C**(C)(O)OC(Me$_2$)), 113.8 (**C**(Me$_2$)), 169.3 (**C**(O)Me), 170.1 (**C**(O)Me), 191.8 (**C**=O); *m/z* (ES$^+$) 325 (M+Na$^+$, 20%); Accurate mass (ES$^+$): Found 325.0892, $C_{13}H_{18}NaO_8$ (M+Na$^+$) requires 325.0894; $[\alpha]_D^{25}$ +93.0 (c = 1.0 in $CHCl_3$), literature value for enantiomer $[\alpha]_D^{25}$ -103.0 (c = 1.0 in $CHCl_3$).[114]

**(*E*)-5-(Allyloxy)pent-3-en-1-yne**[132] **(319)**



*According to the modified procedure of Yun et al.*[132]: To a stirred solution of 2-pentene-4-yn-1-ol (**318**) (400 mg, 4.87 mmol) in DMF (16 mL) was added sodium hydride (234 mg, 60% dispersion in mineral oil, 5.84 mmol). The suspension was stirred at RT for 30 min and then allyl bromide (0.55 mL, 766 mg, 6.33 mmol) was added. The reaction mixture was stirred at RT for 16 h and then quenched by addition of $H_2O$ (10 mL). The aqueous layer was extracted with diethyl ether (3 × 40 mL) and the combined organics were washed with $H_2O$ (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**319**) as a colourless oil (180 mg, 1.47 mmol, 30%); $R_f$ 0.30 (30:1 petrol:diethyl ether); $\delta_H$ (400 MHz, $CDCl_3$) 2.89 (1H, d, *J*=2.0 Hz, C≡C**H**), 4.00 (2H, dt, *J*=5.5, 1.5 Hz, C**H**$_2$CH=CH$_2$), 4.04 (2H, dd, *J*=5.5, 2.0 Hz, C**H**$_2$CH=CH), 5.20 (1H, dq, *J*=10.5, 1.5 Hz, CH=C**H**H'), 5.29 (1H, dq, *J*=17.0, 1.5 Hz, CH=CH**H'**), 5.74 (1H, dq, *J*=16.0, 2.0 Hz, CH$_2$CH=C**H**), 5.91 (1H, ddt, *J*=17.0, 10.5, 5.5 Hz, C**H**=CH$_2$), 6.28 (1H, dt, *J*=16.0, 5.5 Hz, CH$_2$C**H**=CH); $\delta_C$ (100 MHz, $CDCl_3$) 69.5 (**C**H$_2$CH=CH), 71.4 (**C**H$_2$CH=CH$_2$), 77.7 (C≡**C**H), 81.6 (**C**≡CH), 110.3 (CH$_2$CH=**C**H), 117.3 (CH$_2$CH=**C**H$_2$), 134.3 (CH$_2$CH=**C**H), 141.4 (CH$_2$**C**H=CH$_2$).

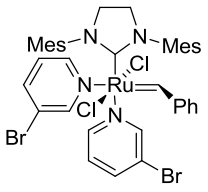
**(*E*)-(5-(Allyloxy)pent-3-en-1-yn-1-yl)triisopropylsilane**[123] **(305)**




*According to the modified procedure of Kim et al.*[123]: To a stirred solution of (*E*)-5-(allyloxy)pent-3-en-1-yne (**319**) (110 mg, 0.90 mmol) in THF (1.13 mL) at -78 °C was added *n*-butyllithium (0.84 mL, 1.6 M in hexanes, 1.35 mmol) dropwise. The reaction mixture was stirred for 1 h and allowed to warm to -30 °C, during which time an orange colour was observed. After this time, at -30 °C, chlorotriisopropylsilane (0.29 mL, 260 mg, 1.35 mmol) was added dropwise and the reaction

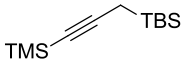
mixture was allowed to warm to RT over 1 h. The reaction mixture was quenched by addition of sat. aq. $NH_4Cl$ (5 mL). The aqueous layer was extracted with diethyl ether (3 × 15 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**305**) as a colourless oil (190 mg, 0.68 mmol, 76%); $R_f$ 0.30 (50:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3082w, 2943s (CH), 2865s, 2174w, 2130m (C≡C), 1463s, 1116s, 1071s, 883s, 677s; $\delta_H$ (400 MHz, $CDCl_3$) 1.08 (21H, s, Si(C**H**($CH_3$)$_2$)$_3$), 4.00 (2H, dt, *J*=5.5, 1.5 Hz, C**H**$_2$CH=$CH_2$), 4.04 (2H, dd, *J*=5.5, 2.0 Hz, C**H**$_2$CH=CH), 5.18–5.23 (1H, m, CH=C**H**H'), 5.30 (1H, dq, *J*=17.0, 1.5 Hz, CH=CH**H'**), 5.79 (1H, dq, *J*=16.0, 2.0 Hz, $CH_2$CH=C**H**), 5.91 (1H, ddt, *J*=17.0, 10.5, 5.5 Hz, C**H**=$CH_2$), 6.24 (1H, dt, *J*=16.0, 5.5 Hz, $CH_2$C**H**=CH); $\delta_C$ (100 MHz, $CDCl_3$) 11.3 (Si(**C**H($CH_3$)$_2$)$_3$), 18.6 (Si(CH(**C**$H_3$)$_2$)$_3$), 69.7 (**C**$H_2$CH=CH), 71.3 (**C**$H_2$CH=$CH_2$), 91.4 (**C**≡C), 104.9 (C≡**C**), 112.0 ($CH_2$CH=**C**H), 117.2 ($CH_2$CH=**C**$H_2$), 134.4 ($CH_2$CH=**C**H), 140.2 ($CH_2$**C**H=$CH_2$); *m/z* ($ES^+$) 301 (M+$Na^+$, 100%), 279 (M+$H^+$, 50); Accurate mass ($ES^+$): Found 301.1956, $C_{17}H_{30}NaOSi$ (M+$Na^+$) requires 301.1958.

**Bis(pyridine) substituted Grubbs catalyst**[133] **(306)**



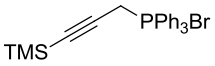

*According to the procedure of Grubbs and co-workers*[133]: 3-Bromopyridine (0.11 mL, 186 mg, 1.18 mmol) was added to Grubbs 2nd generation catalyst (**127**) (100 mg, 0.12 mmol) in a 7 mL vial with a screw cap. The reaction mixture was stirred at RT for 5 min, during which time a colour change from red to bright green was observed. Pentane (4 mL) was added and the vial was capped under air and cooled to ~5 °C in a refrigerator for 18 h. The green precipitate was vacuum filtered, washed with pentane (4 × 2 mL at RT) and dried under high vacuum for 24 h to give the title compound (**306**) as a bright green powder (86 mg, 0.10 mmol, 82%).

**3-(*tert*-Butyldimethylsilyl)-1-(trimethylsilyl)-propyne[21] (335)**




*According to the procedure of Yamakado et al.*[21]: To a stirred solution of 1-(trimethylsilyl)propyne (**334**) (1.27 g, 11.3 mmol) in diethyl ether (20 mL) at -10 °C was added dropwise *tert*-butyllithium (6.65 mL, 1.7 M in pentane, 11.3 mmol). The reaction mixture was stirred at -10 °C for 1 h, during which time a colour change from yellow to deep orange was observed. A solution of *tert*-butylchlorodimethylsilane (1.71 g, 11.3 mmol) in diethyl ether (5 mL) was added dropwise and the resulting cloudy suspension was stirred at -5 °C for 30 min and then at RT for 1 h. The reaction mixture was poured into a separating funnel containing sat. aq. $NH_4Cl$ (50 mL), the layers were separated and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by Kugelrohr distillation (b.p. 110–120 °C/53 mbar (lit. 106 °C/31 mmHg)[21]) gave the title compound (**335**) as a pale yellow oil (1.34 g, 6.31 mmol, 56%); $\delta_H$ (400 MHz, $CDCl_3$) 0.07 (6H, s, Si(C**H**$_3$)$_2$), 0.13 (9H, s, Si(C**H**$_3$)$_3$), 0.92 (9H, s, SiC(C**H**$_3$)$_3$), 1.57 (2H, s, C**H**$_2$TBS).

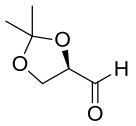
**3-(Trimethylsilyl-2-propynyl)-triphenylphosphonium bromide[153] (342)**




*According to the procedure of Zürcher et al.*[153]: To a solution of triphenylphosphine (161 mg, 0.61 mmol) in *o*-xylene (0.3 mL) at 0 °C was added 3-bromo-1-(trimethylsilyl)-1-propyne (**341**) (0.10 mL, 117 mg, 0.61 mmol). The reaction mixture was allowed to warm to RT and stirred for 24 h. The white precipitate was filtered off, washed with cold hexane (3 × 2 mL) and dried under high vacuum for 24 h to give the title compound (**342**) as a white powder (160 mg, 0.35 mmol, 58%); $\delta_H$ (400 MHz, $CDCl_3$) –0.03 (9H, s, Si(C**H**$_3$)$_3$), 5.26 (2H, d, *J*=15.0 Hz, C**H**$_2$PPh$_3$), 7.64–7.77 (6H, m, Ar**H**), 7.78–7.87 (3H, m, Ar**H**), 7.88–8.00 (6H, m, Ar**H**).

### *6.2.2. Compound Synthesis*

**(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde[67] (141)**

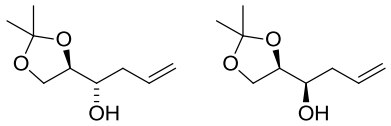


*According to the procedure of Schmid and Bryant*[67]: To a 1 L three necked flask equipped with an overhead stirrer and a condenser with a drying tube, was added D-mannitol (**142**) (100 g, 549 mmol), distilled 1,2-dimethoxyethane (240 mL) and 2,2-dimethoxypropane (160 mL). The mixture was stirred and tin(II) chloride (100 mg, 0.5 mmol) was added. The stirred slurry was heated to reflux for 80 min until the mixture went colourless and heating was continued for a further 30 min. The heat was removed and the solution was allowed to cool below reflux. Pyridine (0.2 mL, 196 mg, 2.47 mmol) was added and the solution cooled to RT. The reaction mixture was concentrated *in vacuo* beginning at RT and increasing to 60 °C and then placed under high vacuum to give the crude diacetonide (192 g of 69% purity by $^1$H NMR analysis: comparison of the doublet at 2.67 ppm with the DCM peak in a $CDCl_3$ sample of crude diacetonide (47 mg) and DCM (10 μL)). The crude mixture was heated to reflux in DCM (1.3 L) until the solids were dissolved to an even consistency. The heat was removed and the slurry cooled below reflux. Celite™ (16 g) was added with stirring and the reaction mixture was cooled to RT, filtered through a pad of Celite™ and concentrated *in vacuo*. To a three necked flask equipped with an overhead stirrer, thermometer and water bath was added crude reaction mixture (18.3 g, 48.4 mmol of diacetonide) in DCM (120 mL). A solution of sat. aq. $NaHCO_3$ (5 mL) was added with stirring followed by sodium metaperiodate (20.5 g, 96.1 mmol) added portion wise over 2–3 min. The reaction mixture was stirred whilst the internal temperature was maintained below 35 °C with water bath cooling. After 2 h, $MgSO_4$ (6 g) was added and the reaction mixture was stirred for a further 30 min. The slurry was filtered and the filter cake was transferred back to the reaction vessel. DCM (30 mL) was added and the slurry stirred for 10 min and then filtered. The combined filtrates were concentrated

*in vacuo*. Purification by vacuum fractional distillation (b.p. 60–63 °C/39 mbar (lit. 67–73 °C/40 mbar)[67]) gave the title compound (**141**) as a colourless oil (8.59 g, 66.0 mmol, 68% over two steps); $\delta_H$ (400 MHz, $CDCl_3$) 1.43 (3H, s, C**H**$_3$), 1.50 (3H, s, C**H**$_3$), 4.11 (1H, dd, *J*=9.0, 5.0 Hz, C**H**H'OC), 4.18 (1H, dd, *J*=9.0, 7.5 Hz, CH**H'**OC), 4.39 (1H, ddd, *J*=7.5, 5.0, 2.0 Hz, C**H**OC), 9.73 (1H, d, J=2.0 Hz, C(O)**H**); $\delta_C$ (100 MHz, $CDCl_3$) 25.1 (**C**H$_3$), 26.2 (**C**H$_3$), 65.6 (**C**H$_2$OC), 79.8 (**C**HOC), 111.3 (**C**(CH$_3$)$_2$), 201.9 (**C**=O); *m*/*z* (ES$^-$) 165 (M+Cl$^-$, 40%); $[\alpha]_D^{23}$ +58.5 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{20}$ +53.8 (c = 2.0 in $CHCl_3$).[154]

**(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol**[72c] **(145)**

**(*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol**[72c] **(146)**



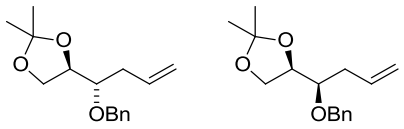

**Allylation method 1:** *According to the modified procedure of Chattopadhyay*[68a]: To a mixture of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**141**) (7.15 g, 54.9 mmol), zinc powder (7.18 g, 110 mmol), and allyl bromide (9.50 mL, 13.3 g, 110 mmol) in THF (100 mL) at 10 °C was added sat. aq. $NH_4Cl$ (27.5 mL) dropwise over 30 min with care (large exotherm after an induction period). The mixture was stirred at RT for 3 h and then filtered, washing through with DCM (100 mL). The aqueous layer was separated and treated with aq. HCl (1 M) until the suspended material dissolved. The aqueous layer was extracted with DCM (3 × 60 mL) and the combined organic layers washed sequentially with 10% aq. $NaHCO_3$ (100 mL), $H_2O$ (100 mL) and concentrated *in vacuo*. Purification by flash column chromatography (7:1 petrol:EtOAc with 1.5% IPA) gave the two inseparable diastereomeric title compounds (**145** and **146**) as a colourless oil in a 5:1 ratio of diastereomers by NMR integration (8.28 g, 47.6 mmol, 88%).

**Allylation method 2:** *According to the procedure of Roush et al.*[73a]: To a stirred solution of (4*R*,5*R*)-diisopropyl 2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylate (**141**) (292 mg, 1.03 mmol) in distilled

toluene (19 mL) over powdered activated 4 Å molecular sieves at -78 °C was added dropwise a precooled solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (200 mg, 1.54 mmol) in distilled toluene (2 mL). The reaction mixture was stirred at -78 °C for 24 h. A precooled solution of sodium borohydride (63 mg, 1.70 mmol) in ethanol (3 mL) was added. After 5 min, aq. NaOH (15 mL, 1.0 M) and diethyl ether (15 mL) were added and the two phase mixture was stirred vigorously for 2 h. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (6:1 petrol:EtOAc) gave recovered starting material (27 mg, 0.21 mmol, 13%) and the two inseparable diastereomeric title compounds (**145** and **146**) as a colourless oil in a 10:1 ratio of diastereomers by NMR integration (28 mg, 0.16 mmol, 16% w.r.t. (4*R*,5*R*)-diisopropyl 2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylate (**156**)); characterisation of the individual components are shown later (**Page 146 and 155**).

**(*R*)-4-((*S*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane**[72c] **(144)**

**(*R*)-4-((*R*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane**[72c] **(140)**




To a stirred solution of 7:1 (*S*)-:(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**:**146**) (1.20 g, 6.97 mmol) in dry DMF (4 mL) at 0 °C was added sodium hydride (556 mg, 60% dispersion in mineral oil, 13.9 mmol). The reaction mixture was stirred for 20 min and benzyl bromide (0.99 mL, 1.43 g, 8.36 mmol) was added and the reaction mixture was stirred for 5 h at RT. TMEDA (1.57 mL, 1.22 g, 10.5 mmol) was added to the reaction mixture at 0 °C and the mixture was stirred for 1 h at RT. EtOAc (20 mL) and pH 2 buffer (30 mL) were added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed sequentially with $H_2O$ (3 × 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petrol:EtOAc with 1.0% IPA) gave the two

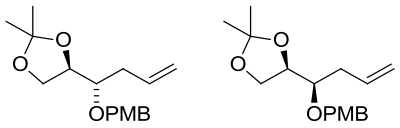
partially separable product diastereomers (**144** and **140**) as colourless oils (overall 1.81 g, 6.90 mmol, 99%, 7:1 (*S*):(*R*) from crude $^1$H NMR analysis).

1. (*R*)-4-((*S*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (**144**): $R_f$ 0.62 (9:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 1.37 (3H, s, C**H**$_3$), 1.43 (3H, s, C**H**$_3$), 2.31–2.41 (1H, m, C**H**H'CH=CH$_2$), 2.41–2.51 (1H, m, CH**H'**CH=CH$_2$), 3.59 (1H, td, *J*=6.0, 5.0 Hz, C**H**OBn), 3.91 (1H, dd, *J*=8.0, 6.5 Hz, C**H**H'OC(Me$_2$)), 4.01–4.16 (2H, m, CH**H'**OC(Me$_2$), C**H**OC(Me$_2$)), 4.61 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.67 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 5.07–5.22 (2H, m, CH$_2$CH=C**H**$_2$), 5.91 (1H, ddt, *J*=17.5, 10.5, 7.5 Hz, CH$_2$C**H**=CH$_2$), 7.24–7.39 (5H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 25.4 (**C**H$_3$), 26.7 (**C**H$_3$), 35.6 (**C**H$_2$CH=CH$_2$), 66.4 (**C**HOC(Me$_2$)), 72.5 (**C**H$_2$Ar), 77.2 (**C**H$_2$OC(Me$_2$)), 78.9 (**C**HOBn), 109.1 (**C**(Me)$_2$), 117.6 (CH$_2$CH=**C**H$_2$), 127.7 (Ar), 127.8 (Ar), 128.4 (Ar), 134.2 (CH$_2$**C**H=CH$_2$), 138.4 (Ar); *m/z* (ES$^+$) 285 (M+Na$^+$, 100%); $[\alpha]_D^{23}$ +35.4 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{20}$ +33.8 (c = 1.25 in $CHCl_3$).[72c]

2. (*R*)-4-((*R*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (**140**): $R_f$ 0.56 (9:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 1.38 (3H, s, C**H**$_3$), 1.45 (3H, s, C**H**$_3$), 2.19–2.38 (2H, m, C**H**$_2$CH=CH$_2$), 3.52 (1H, dt, *J*=7.0, 4.5 Hz, C**H**OBn), 3.72 (1H, app. t, *J*=8.0 Hz, C**H**H'OC(Me$_2$)), 4.00 (1H, dd, *J*=8.5, 6.5 Hz, CH**H'**OC(Me$_2$)), 4.23 (1H, app. q, *J*=7.0 Hz, C**H**OC(Me$_2$)), 4.68 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.74 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 5.05–5.17 (2H, m, CH$_2$CH=C**H**$_2$), 5.89 (1H, ddt, *J*=17.0, 10.5, 7.0 Hz, CH$_2$C**H**=CH$_2$), 7.26–7.41 (5H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 25.4 (**C**H$_3$), 26.5 (**C**H$_3$), 35.3 (**C**H$_2$CH=CH$_2$), 65.8 (**C**H$_2$OC(Me$_2$)), 72.7 (**C**H$_2$Ar), 77.9 (**C**HOC(Me$_2$)), 79.3 (**C**HOBn), 109.1 (**C**(Me)$_2$), 117.6 (CH$_2$CH=**C**H$_2$), 127.7 (Ar), 127.8 (Ar), 128.3 (Ar), 134.5 (CH$_2$**C**H=CH$_2$), 138.6 (Ar); *m/z* (ES$^+$) 285 (M+Na$^+$, 60%); $[\alpha]_D^{23}$ +13.1 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{20}$ +13.9 (c = 1.1 in $CHCl_3$).[155]

**(*R*)-4-((*S*)-1-(4-Methoxybenzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane**[156] **(147)**

**(*R*)-4-((*R*)-1-(4-Methoxybenzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane**[72b] **(148)**




To a stirred solution of 7:1 (*S*)-:(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**:**146**) (300 mg, 1.74 mmol) and tetrabutylammonium iodide (709 mg, 1.92 mmol) in dry DMF (2 mL) at 0 °C was added sodium hydride (77 mg, 60% dispersion in mineral oil, 1.92 mmol). After 20 min, *p*-methoxybenzyl chloride (0.26 mL, 300 mg, 1.92 mmol) was added and the reaction mixture stirred at RT for 16 h. Starting material was still present by TLC analysis so the reaction mixture was stirred at 40 °C for 1.5 h. The reaction mixture was quenched with sat. aq. $NH_4Cl$ (5 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed sequentially with $H_2O$ (10 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10:1 petrol:EtOAc with 1.0% IPA) gave the two partially separable product diastereomers (**147** and **148**) as colourless oils (overall 345 mg, 1.18 mmol, 68%, 7:1 (*S*):(*R*) from crude $^1$H NMR analysis).

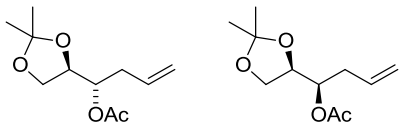
1. (*R*)-4-((*S*)-1-(4-Methoxybenzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (**147**): $R_f$ 0.53 (6:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3494w, 3076m, 2986s (CH), 2936s, 1641s (C=C), 1514s, 1370m, 1249s, 1174s, 1075s, 823m, 757m; $\delta_H$ (400 MHz, $CDCl_3$) 1.36 (3H, s, C**H**$_3$), 1.43 (3H, s, C**H**$_3$), 2.27–2.51 (2H, m, C**H**$_2$CH=CH$_2$), 3.47–3.64 (1H, m, C**H**OPMB), 3.81 (3H, s, OC**H**$_3$), 3.88 (1H, dd, *J*=8.0, 6.0 Hz, C**H**H'OC(Me$_2$)), 4.03 (1H, dd, *J*=8.0, 6.5 Hz, CH**H'**OC(Me$_2$)), 4.06–4.14 (1H, m, C**H**OC(Me$_2$)), 4.53 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.60 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 5.07–5.22 (2H, m, CH$_2$CH=C**H**$_2$), 5.91 (1H, ddt, *J*=17.0, 10.5, 7.0 Hz, CH$_2$C**H**=CH$_2$), 6.83–6.95 (2H, m, Ar**H**), 7.23–7.35 (2H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 25.4 (**C**H$_3$), 26.7 (**C**H$_3$), 35.6 (**C**H$_2$CH=CH$_2$), 55.3 (O**C**H$_3$), 66.5 (**C**H$_2$OC(Me$_2$)), 72.1 (**C**H$_2$Ar), 77.2 (**C**HOC(Me$_2$)), 78.5 (**C**HOPMB), 109.0 (**C**(Me)$_2$), 113.8 (Ar), 117.5 (CH$_2$CH=**C**H$_2$), 129.5 (Ar), 130.5 (Ar), 134.3

($CH_2$**C**H=$CH_2$), 159.2 (Ar); *m/z* ($ES^+$) 310 ($M+NH_4^+$, 30%), 315 ($M+Na^+$, 35), 356 ($M+Na+MeCN^+$, 25); Accurate mass ($ES^+$): Found 315.1566, $C_{17}H_{24}NaO_4$ ($M+Na^+$) requires 315.1567; $[\alpha]_D^{23}$ +36.6 (c = 1.0 in $CHCl_3$).

2. (*R*)-4-((*R*)-1-(4-Methoxybenzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (**148**): $R_f$ 0.47 (6:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3519w, 3076m, 2986s (CH), 1739s, 1613s (C=C), 1514s, 1371s, 1245s, 1174s, 1075s, 916s, 823s, 757m; $\delta_H$ (400 MHz, $CDCl_3$) 1.37 (3H, s, C**H**$_3$), 1.44 (3H, s, C**H**$_3$), 2.17–2.36 (2H, m, C**H**$_2$CH=$CH_2$), 3.50 (1H, ddd, *J*=7.5, 6.5, 4.5 Hz, C**H**OPMB), 3.71 (1H, dd, *J*=8.5, 7.0 Hz, C**H**H'OC(Me)$_2$), 3.81 (3H, s, OC**H**$_3$), 3.98 (1H, dd, *J*=8.5, 6.5 Hz, CH**H'**OC(Me)$_2$), 4.20 (1H, dt, *J*=7.0, 6.5 Hz, C**H**OC(Me)$_2$), 4.57 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.67 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 5.05–5.14 (2H, m, $CH_2CH=CH$**H**$_2$), 5.87 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2$C**H**=$CH_2$), 6.85–6.92 (2H, m, Ar**H**), 7.27–7.31 (2H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 25.4 (**C**H$_3$), 26.5 (**C**H$_3$), 35.3 (**C**H$_2$CH=$CH_2$), 55.3 (O**C**H$_3$), 65.8 (**C**H$_2$OC(Me)$_2$), 72.2 (**C**H$_2$Ar), 77.9 (**C**HOC(Me)$_2$), 78.8 (**C**HOPMB), 109.3 (**C**(Me)$_2$), 113.7 (Ar), 113.8 (Ar), 117.2 ($CH_2CH=$**C**H$_2$), 129.4 (Ar), 129.5 (Ar), 130.7 (Ar), 134.6 ($CH_2$**C**H=$CH_2$), 159.1 (Ar); *m/z* ($ES^+$) 310 ($M+NH_4^+$, 100%), 315 ($M+Na^+$, 40), 356 ($M+Na+MeCN^+$, 70); Accurate mass ($ES^+$): Found 315.1577, $C_{17}H_{24}NaO_4$ ($M+Na^+$) requires 315.1567; $[\alpha]_D^{23}$ +33.7 (c = 1.0 in $CHCl_3$).

**(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyl acetate**[157] **(149)**

**(*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyl acetate**[157] **(150)**

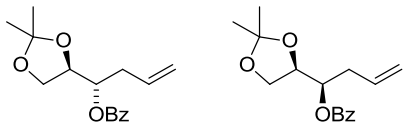



To a stirred solution of 7:1 (*S*)-:(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**:**146**) (100 mg, 0.58 mmol) in dry DCM (15 mL) at RT were added sequentially acetic anhydride (0.55 mL, 593 mg, 5.81 mmol), DMAP (71 mg, 0.58 mmol) and triethylamine (0.81 mL, 588 mg, 5.81 mmol). The reaction mixture was stirred at RT for 30 min and then quenched by addition of

brine (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (10:1 petrol:EtOAc with 1.0% IPA) gave the two partially separable product diastereomers (**149** and **150**) as a colourless oil (102 mg, 0.48 mmol, 82% 7:1 (*S*):(*R*) from crude $^1$H NMR analysis), with only the major diastereomer (**149**) isolated for characterisation; $R_f$ 0.51 (6:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3080m, 2988s (CH), 1745s (C=O), 1644w (C=C), 1373s, 1234s, 1159m, 1064s, 919m, 853m; $\delta_H$ (400 MHz, $CDCl_3$) 1.34 (3H, s, C**H**$_3$), 1.40 (3H, s, C**H**$_3$), 2.05 (3H, s, C(O)C**H**$_3$), 2.26–2.37 (1H, m, C**H**H'CH=CH$_2$), 2.38–2.47 (1H, m, CH**H'**CH=CH$_2$), 3.79 (1H, dd, *J*=8.0, 6.5 Hz, C**H**H'OC(Me)$_2$), 4.02 (1H, dd, *J*=8.0, 6.5 Hz, CH**H'**OC(Me)$_2$), 4.14 (1H, q, *J*=6.5 Hz, C**H**OC(Me)$_2$), 4.98–5.13 (3H, m, C**H**OAc, CH$_2$CH=C**H**$_2$), 5.75 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 21.0 (C(O)**C**H$_3$), 25.2 (**C**H$_3$), 26.4 (**C**H$_3$), 35.0 (**C**H$_2$CH=CH$_2$), 65.9 (**C**H$_2$OC(Me)$_2$), 72.6 (**C**HOAc), 76.2 (**C**HOC(Me)$_2$), 109.6 (**C**(Me)$_2$), 118.1 (CH$_2$CH=**C**H$_2$), 133.1 (CH$_2$**C**H=CH$_2$), 170.3 (**C**=O); *m/z* (ES$^+$) 278 (M+Na+MeCN$^+$, 10%), 429 (2M+H$^+$, 35); Accurate mass (ES$^+$): Found 237.1098, $C_{11}H_{18}NaO_4$ (M+Na$^+$) requires 237.1097; $[\alpha]_D^{23}$ +21.2 (c = 1.0 in $CHCl_3$).

**(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyl benzoate**[158] **(153)**

***(R)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyl benzoate*** **(154)**

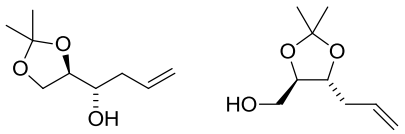



To a stirred solution of 7:1 (*S*)-:(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**:**146**) (100 mg, 0.58 mmol) in pyridine (2.5 mL) was added a solution of benzoyl chloride (81 μL, 98 mg, 0.70 mmol) in DCM (1.2 mL). The reaction mixture was stirred at RT for 2 h and then diethyl ether (15 mL) was added and the organic layer washed with $H_2O$ (4 × 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petrol:EtOAc with 1.0% IPA) gave recovered starting material (27 mg, 0.16 mmol, 27%) and

a mixture of the two title compounds (**153** and **154**) as a colourless oil (108 mg, 0.39 mmol, 67%, 7:1 (*S*):(*R*) ratio from $^1$H NMR integration); $R_f$ 0.5 (18:1 petrol:EtOAc); $\delta_H$ as a mixture of diastereomers $D_S$ (major) and $D_R$ (minor) (400 MHz, $CDCl_3$) 1.37 (3H, s, C**H**$_3$ $D_S$) 1.38 (3H, s, C**H**$_3$ $D_R$), 1.39 (3H, s, C**H**$_3$ $D_S$), 1.47 (3H, s, C**H**$_3$ $D_R$), 1.45–1.62 (4H, m, C**H**$_2$CH=CH$_2$ $D_S$ + $D_R$), 3.82 (1H, dd, *J*=8.5, 6.5 Hz, C**H**H'OC(Me)$_2$ $D_R$), 3.95 (1H, dd, *J*=8.5, 6.0 Hz, C**H**H'OC(Me)$_2$ $D_S$), 4.07 (1H, dd, *J*=8.5, 6.5 Hz, CH**H'**OC(Me)$_2$ $D_R$), 4.10 (1H, dd, *J*=8.5, 6.5 Hz, CH**H'**OC(Me)$_2$ $D_S$), 4.30 (1H, dt, *J*=6.5, 6.0 Hz, C**H**OC(Me)$_2$ $D_S$), 4.34 (1H, td, *J*=6.5, 5.0 Hz, C**H**OC(Me)$_2$ $D_R$), 5.04–5.20 (4H, m, CH$_2$CH=C**H**$_2$ $D_S$ + $D_R$), 5.22–5.33 (2H, m, C**H**OBz $D_S$ + $D_R$), 5.77–5.91 (2H, m, CH$_2$C**H**=CH$_2$ $D_S$ + $D_R$), 7.41–7.51 (4H, m, Ar**H** $D_S$ + $D_R$), 7.54–7.65 (2H, m, Ar**H** $D_S$ + $D_R$), 8.01–8.14 (4H, m, Ar**H** $D_S$ + $D_R$); $\delta_C$ (100 MHz, $CDCl_3$) 25.3 (**C**H$_3$ $D_S$), 25.4 (**C**H$_3$ $D_R$), 26.3 (**C**H$_3$ $D_R$), 26.5 (**C**H$_3$ $D_S$), 35.4 (**C**H$_2$CH=CH$_2$ $D_S$ + $D_R$), 65.6 (**C**H$_2$OC(Me)$_2$ $D_R$), 66.1 (**C**H$_2$OC(Me)$_2$ $D_S$), 72.9 (**C**HOBz $D_R$), 73.3 (**C**HOBz $D_S$), 76.1 (**C**HOC(Me)$_2$ $D_R$), 76.3 (**C**HOC(Me)$_2$ $D_S$), 109.6 (**C**(Me)$_2$ $D_R$), 109.7 (**C**(Me)$_2$ $D_S$), 118.4 (CH$_2$CH=**C**H$_2$ $D_S$ + $D_R$), 128.4 (Ar $D_S$), 128.5 (Ar $D_R$), 129.7 (Ar $D_S$), 129.7 (Ar $D_R$), 130.0 (Ar $D_S$), 130.1 (Ar $D_R$), 132.9 (Ar $D_S$ + $D_R$), 133.0 (CH$_2$**C**H=CH$_2$ $D_R$), 133.1 (CH$_2$**C**H=CH$_2$ $D_S$), 165.8 (**C**=O $D_S$ + $D_R$); *m*/*z* (ES$^+$) 299 (M+Na$^+$, 35%).

**(*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol**[72c] **(145)**

**((4*R*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol**[159] **(160)**



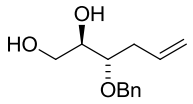

*According to the modified procedure of Miranda et al.*[69]: To a stirred solution of 6:1 (*S*)-:(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**:**146**) (130 mg, 0.76 mmol) in dry acetone (2 mL) was added in one portion (±)-camphor-10-sulfonic acid (11 mg, 0.05 mmol). The reaction mixture was stirred at -15 °C for 48 h and was then concentrated *in vacuo*. Purification by flash column

chromatography (20:1→8:1 petrol:acetone with 1.0% IPA) gave the two title compounds (**145** and **160**) as colourless oils (118 mg, 0.69 mmol, 91%).

1. (*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**): (106 mg, 0.62 mmol, 82% >95:5 (*S*):(*R*) from $^1$H NMR integration); $R_f$ 0.60 (1:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 1.36 (3H, s, C**H**$_3$), 1.42 (3H, s, C**H**$_3$), 2.11 (1H, br s, O**H**), 2.11–2.24 (1H, m, C**H**H'CH=CH$_2$), 2.28–2.38 (1H, m, CH**H'**CH=CH$_2$), 3.78 (1H, ddt, *J*=8.0, 1.5, 4.5 Hz, C**H**OH), 3.90–3.98 (1H, m, C**H**H'OC), 3.99–4.07 (2H, m, CH**H'**OC, C**H**OC), 5.11–5.21 (2H, m, CH$_2$CH=C**H**$_2$), 5.84 (1H, ddt, *J*=17.5, 10.5, 7.5 Hz, CH$_2$C**H**=CH$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 25.3 (**C**H$_3$), 26.5 (**C**H$_3$), 37.6 (**C**H$_2$CH=CH$_2$), 65.2 (**C**H$_2$OC), 70.3 (**C**HOH), 78.1 (**C**HOC), 109.1 (**C**(Me)$_2$), 118.4 (CH$_2$CH=**C**H$_2$), 134.0 (CH$_2$**C**H=CH$_2$); *m/z* (ES$^-$) 171 ((M–H)$^-$, 35%); $[a]_D$ (23 °C) +16.9 (c = 1.0 in $CHCl_3$), literature value $[a]_D$ (20 °C) +17.0 (c = 3.4 in $CHCl_3$).[72c]

2. ((4*R*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (**160**): (12 mg, 0.07 mmol, 9%); $R_f$ 0.18 (9:1 petrol:acetone with 1.0% IPA); $\delta_H$ (400 MHz, $CDCl_3$) 1.34 (3H, s, C**H**$_3$), 1.50 (3H, s, C**H**$_3$), 2.09–2.23 (1H, m, C**H**H'CH=CH$_2$), 2.23–2.49 (2H, m, CH**H'**CH=CH$_2$, O**H**), 3.46–3.70 (2H, m, C**H**$_2$OH), 3.96–4.13 (2H, m, 2 × C**H**OC), 5.04–5.18 (2H, m, CH$_2$CH=C**H**$_2$), 5.82–5.97 (1H, m, CH$_2$C**H**=CH$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 25.4 (**C**H$_3$), 28.2 (**C**H$_3$), 34.0 (**C**H$_2$CH=CH$_2$), 61.6 (**C**H$_2$OH), 76.7 (**C**HOC), 78.2 (**C**HOC), 108.0 (**C**(Me)$_2$), 116.8 (CH$_2$CH=**C**H$_2$), 135.2 (CH$_2$**C**H=CH$_2$); *m/z* (ES$^+$) 173 (M+H$^+$, 20%); $[\alpha]_D^{23}$ +14.8 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{23}$ +25.2 (c = 0.9 in $CHCl_3$).[159]

**(2*R*,3*S*)-3-(Benzyloxy)hex-5-ene-1,2-diol**[72c] **(143)**

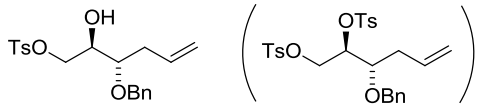



(*R*)-4-((*S*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (**144**) (1.00 g, 3.81 mmol) was dissolved in 60% aq. acetic acid (10 mL) and stirred at 50 °C for 7 h. The reaction mixture was concentrated *in vacuo* and subsequent purification by flash column chromatography (1:1→1:2

petrol:EtOAc) gave the title compound (**143**) as a colourless oil (848 mg, 3.81 mmol, quant.); $R_f$ 0.25 (1:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 2.33–2.52 (2H, m, C**H**$_2$CH=CH$_2$), 2.64 (1H, br s, O**H**), 2.92 (1H, br s, O**H**), 3.56–3.65 (1H, m, C**H**OBn), 3.68–3.78 (3H, m, C**H**$_2$OH, C**H**OH), 4.53 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.67 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 5.08–5.21 (2H, m, CH$_2$CH=C**H**$_2$), 5.88 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 7.28–7.40 (5H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 35.0 (**C**H$_2$CH=CH$_2$), 63.3 (**C**H$_2$OH), 72.4 (**C**HOH), 72.4 (**C**H$_2$Ar), 80.3 (**C**HOBn), 117.7 (CH$_2$CH=**C**H$_2$), 127.9 (Ar), 127.9 (Ar), 128.5 (Ar), 134.2 (CH$_2$**C**H=CH$_2$), 138.0 (Ar); *m/z* ($ES^+$) 245 ($M+Na^+$, 53%), 286 ($M+Na+MeCN^+$, 10); $[\alpha]_D^{23}$ +36.9 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{25}$ +4.28 (c = 0.92 in $CHCl_3$).[70]

**(2*R*,3*S*)-3-(Benzyloxy)-2-hydroxyhex-5-enyl 4-methylbenzenesulfonate**[72c] **(161)**

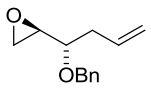
By-product: (2*R*,3*S*)-3-(Benzyloxy)hex-5-ene-1,2-diyl bis(4-methylbenzenesulfonate)




To a stirred solution of (2*R*,3*S*)-3-(benzyloxy)hex-5-ene-1,2-diol (**143**) (100 mg, 0.45 mmol) in DCM (11.5 mL) was added triethylamine (0.16 mL, 114 mg, 1.13 mmol) followed by DMAP (8 mg, 0.07 mmol). The reaction mixture was cooled to 0 °C and *p*-toluenesulfonyl chloride (86 mg, 0.45 mmol) was added. The reaction mixture was allowed to warm to RT and stirred for 24 h. The reaction mixture was diluted with DCM (100 mL) and washed sequentially with $H_2O$ (20 mL) and brine (20 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (8:1→4:1 petrol:EtOAc with 1% IPA) gave recovered starting material (**143**) (8 mg, 0.04 mmol, 8%), (2*R*,3*S*)-3-(benzyloxy)hex-5-ene-1,2-diyl bis(4-methylbenzenesulfonate) (40 mg, 0.08 mmol, 17%) and the title compound (**161**) as a colourless oil (127 mg, 0.34 mmol, 75%); $R_f$ 0.17 (6:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3520s br (OH), 2920s (CH), 1670s, 1598s, 1496s, 1455s; $\delta_H$ (400 MHz, $CDCl_3$) 2.32 (1H, br s, O**H**), 2.36–2.52 (5H, m, ArC**H**$_3$, C**H**$_2$CH=CH$_2$), 3.55 (1H, dt, *J*=6.5, 5.5 Hz, C**H**OBn), 3.87 (1H, ddt, *J*=9.0, 3.0, 6.5 Hz, C**H**OH),

4.13 (1H, dd, *J*=10.5, 6.5 Hz, C**H**H'OTos), 4.23 (1H, dd, *J*=10.5, 3.0 Hz, CH**H'**OTos), 4.43 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.61 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 5.07–5.18 (2H, m, $CH_2CH=C\mathbf{H}_2$), 5.85 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2C\mathbf{H}=CH_2$), 7.22–7.37 (7H, m, Ar**H**), 7.77–7.83 (2H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 21.7 (**C**$H_3$), 34.4 (**C**$H_2CH=CH_2$), 70.6 (**C**HOH), 71.4 (**C**$H_2$OTos), 72.1 (**C**$H_2$Ar), 78.2 (**C**HOBn), 118.1 ($CH_2CH=\mathbf{C}H_2$), 127.8 (Ar), 127.8 (Ar), 128.0 (Ar), 128.4 (Ar), 129.9 (Ar), 132.5 (Ar), 133.6 ($CH_2\mathbf{C}H=CH_2$), 137.8 (Ar), 145.1 (Ar); *m/z* ($ES^+$) 394 ($M+NH_4^+$, 100%), 399 ($M+Na^+$, 30); Accurate mass ($ES^+$): Found 399.1227, $C_{20}H_{24}NaO_5S$ ($M+Na^+$) requires 399.1237; $[\alpha]_D^{23}$ +43.5 (c = 1.0 in $CHCl_3$). By-product (2*R*,3*S*)-3-(benzyloxy)hex-5-ene-1,2-diyl bis(4-methylbenzenesulfonate); $R_f$ 0.26 (6:1 petrol:EtOAc); *m/z* ($ES^+$) 394 ($M+NH_4^+$, 85%), 399 ($M+Na^+$, 35); Accurate mass ($ES^+$): Found 533.1318, $C_{27}H_{30}NaO_7S_2$ ($M+Na^+$) requires 533.1325.

**(*R*)-2-((*S*)-1-(Benzyloxy)but-3-enyl)oxirane**[71, 72c] **(163)**

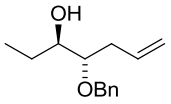



**Method 1:** *According to the procedure of Mulzer et al.*[160]: To a solution of (2*R*,3*S*)-3-(benzyloxy)-2-hydroxyhex-5-enyl 4-methylbenzenesulfonate (**161**) (281 mg, 0.75 mmol) in methanol (0.5 mL) at 0 °C was added dropwise a solution of sodium methoxide (prepared by addition of sodium (21 mg, sodium sticks in paraffin washed with hexane, 0.91 mmol) in methanol (0.5 mL)) over 10 min. The reaction mixture was warmed to RT, stirred for 30 min and then neutralised with sat. aq. $NH_4Cl$ (1 mL). The aqueous layer was extracted with diethyl ether (3 × 1 mL) and the combined organic extracts were concentrated *in vacuo*. Purification by flash column chromatography (10:1 petrol:EtOAc) gave the title compound (**163**) as a colourless oil (89 mg, 0.44 mmol, 58%); $R_f$ 0.32 (7:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 2.40–2.54 (2H, m, $C\mathbf{H}_2CH=CH_2$), 2.75 (1H, dd, *J*=5.5, 3.0 Hz, C**H**H'O(CH)), 2.81 (1H, dd, *J*=5.5, 4.0 Hz, CH**H'**O(CH)), 3.00 (1H, ddd, *J*=5.5, 4.0, 3.0 Hz, CHH'O(C**H**)), 3.36 (1H, dt, *J*=7.0, 5.5 Hz, C**H**OBn), 4.57 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.67 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 5.11–5.23 (2H, m, $CH_2CH=C\mathbf{H}_2$), 5.94 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2C\mathbf{H}=CH_2$), 7.28–7.40 (5H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 37.3 (**C**$H_2CH=CH_2$), 45.7

(**C**$H_2$O(CH)), 53.1 ($CH_2$O(**C**H)), 72.2 (**C**$H_2$Ar), 77.7 (**C**HOBn), 117.5 ($CH_2$CH=**C**$H_2$), 127.7 (Ar), 127.7 (Ar), 128.4 (Ar), 134.0 ($CH_2$**C**H=$CH_2$), 138.4 (Ar); Accurate mass ($FI^+$): Found 204.1148, $C_{13}H_{16}O_2$ ($M^+$) requires 204.1150; $[\alpha]_D^{23}$ +5.0 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{25}$ +5.44 (c = 0.8 in $CHCl_3$).[71]

**Method 2:** *According to the modified procedure of Vintonyak et al.*[161]: To a solution of (2*R*,3*S*)-3-(benzyloxy)hex-5-ene-1,2-diol (**143**) (0.10 g, 0.45 mmol) in dry THF (5.5 mL) at 0 °C was added sodium hydride (90 mg, 60% dispersion in mineral oil, 2.25 mmol). The reaction mixture was stirred at 0 °C for 0.5 h before cooling to -78 °C. 1-(2,4,6-Triisopropylbenzenesulfonyl)imidazole (0.23 g, 0.68 mmol) in dry THF (3 mL + 0.5 mL rinse) was added dropwise and the reaction mixture was warmed to 0 °C over 1 h. The reaction mixture was then stirred at 0 °C for 22 h and then quenched by slow addition of sat. aq. $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1→1:1 petrol:acetone) gave recovered starting material (**143**) (12 mg, 0.05 mmol, 12%) and the title compound (**163**) as a colourless oil (76 mg, 0.37 mmol, 83%); data as shown above.

**(3*R*,4*S*)-4-(Benzyloxy)hept-6-en-3-ol**[72c] **(162)**



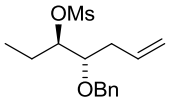

**Method 1:** *According to the modified procedure of Crimmins and Powell*[88b]: To a solution of copper(I) iodide (6 mg, 0.03 mmol) in THF (2 mL) at -23 °C was added methylmagnesium bromide (1.61 mL, 1.0 M in diethyl ether, 1.61 mmol) dropwise over 15 min and the reaction mixture was stirred for 10 min. A solution of (*R*)-2-((*S*)-1-(benzyloxy)but-3-enyl)oxirane (**163**) (67 mg, 0.33 mmol) in THF (0.5 mL) was added dropwise over 10 min and the reaction mixture stirred at -23 °C for 1 h. The reaction mixture was quenched by slow addition of sat. aq. $NH_4Cl$ (0.3 mL) and diluted with EtOAc (10 mL) and $H_2O$ (10 mL). The aqueous layer was extracted with EtOAc

(3 × 15 mL) and the combined organic layers were washed sequentially with sat. aq. $NH_4Cl$ (20 mL), $H_2O$ (20 mL), brine (20 mL) and concentrated *in vacuo*. Purification by flash column chromatography (9:1 petrol:EtOAc) gave the title compound (**162**) as a colourless oil (48 mg, 0.22 mmol, 66%); $R_f$ 0.31 (7:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3444s br (OH), 3068m, 2965s (CH), 1705w, 1641m (C=C), 1497s, 1094s, 914s, 738s, 698s; $\delta_H$ (400 MHz, $CDCl_3$) 1.01 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.43–1.62 (2H, m, $C\mathbf{H}_2CH_3$), 2.18 (1H, br s, O**H**), 2.28–2.38 (1H, m, C**H**H'$CH=CH_2$), 2.40–2.50 (1H, m, CH**H'**$CH=CH_2$), 3.45 (1H, dt, *J*=7.5, 4.5 Hz, C**H**OBn), 3.67–3.74 (1H, m, C**H**OH), 4.58 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.63 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 5.10 (1H, ddt, *J*=10.0, 2.0, 1.0 Hz, $CH_2CH=C\mathbf{H}H'$), 5.10 (1H, dq, *J*=17.0, 2.0 Hz, $CH_2CH=CH\mathbf{H'}$), 5.93 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2C\mathbf{H}=CH_2$), 7.28–7.40 (5H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 10.5 ($CH_2\mathbf{C}H_3$), 25.1 ($\mathbf{C}H_2CH_3$), 33.7 ($\mathbf{C}H_2CH=CH_2$), 71.9 ($\mathbf{C}H_2Ar$), 73.5 (**C**HOH), 81.7 (**C**HOBn), 116.9 ($CH_2CH=\mathbf{C}H_2$), 127.7 (Ar), 127.8 (Ar), 128.4 (Ar), 135.4 ($CH_2\mathbf{C}H=CH_2$), 138.4 (Ar); *m/z* ($ES^+$) 203 ($M–OH^+$, 30%), 243 ($M+Na^+$, 60); Accurate mass ($ES^+$): Found 243.1360, $C_{14}H_{20}NaO_2$ ($M+Na^+$) requires 243.1356; $[\alpha]_D^{23}$ +3.0 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{20}$ +10.1 (c = 1.0 in $CHCl_3$).[72c]

**Method 2:** *According to the modified procedures of Sabes et al.*[162] *and Cink and Forsyth*[74]: To a stirred solution of (2*R*,3*S*)-3-(benzyloxy)hex-5-ene-1,2-diol (**143**) (576 mg, 2.59 mmol) in dry THF (30 mL) at 0 °C was added sodium hydride (518 mg, 60% dispersion in mineral oil, 13.0 mmol). The reaction mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. To this mixture was added a solution of 1-(2,4,6-triisopropylbenzenesulfonyl)imidazole (1.30 g, 3.89 mmol) in dry THF (20 mL + 3 mL rinse). The reaction mixture was warmed to 0 °C over 1 h and then stirred at 0 °C for 20 h. To the *in situ* formed epoxide were added copper(I) iodide (99 mg, 0.52 mmol) and methylmagnesium bromide (7.77 mL, 1.0 M solution in diethyl ether, 7.77 mmol). The reaction mixture was stirred for 2 h and then quenched by slow addition of sat. aq. $NH_4Cl$ (30 mL). The reaction mixture was diluted with EtOAc (50 mL) and $H_2O$ (30 mL). The aqueous layer was

separated, extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed sequentially with sat. aq. $NH_4Cl$ (50 mL), $H_2O$ (50 mL), brine (50 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1→5:1 petrol:acetone) gave the title compound (**162**) as a colourless oil (540 g, 2.45 mmol, 95%, >20:1 mixture of diastereomers); data as shown above.

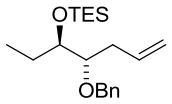
***(3R,4S)-4-(Benzyloxy)hept-6-en-3-yl methanesulfonate* (167)**




**General Mesylation Procedure:** To a stirred solution of (3*R*,4*S*)-4-(benzyloxy)hept-6-en-3-ol (**162**) (100 mg, 0.45 mmol) in dry DCM (24 mL) at 0 °C were added triethylamine (0.3 mL, 220 mg, 2.17 mmol), methanesulfonyl chloride (67 μL, 99 mg, 0.87 mmol) and DMAP (53 mg, 0.45 mmol). The reaction mixture was stirred for 1 h at 0 °C and then quenched with sat. aq. $NH_4Cl$ (25 mL) and allowed to warm to RT. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (15:1→5:1 petrol b.p. 30–40 °C:acetone) gave the title compound (**167**) as a colourless oil (113 mg, 0.38 mmol, 87%); $R_f$ 0.38 (5:1 petrol:acetone); $\nu_{max}/cm^{-1}$ (thin film) 3067m, 3032s, 2975s (CH), 1642m (C=C), 1497m, 1456s, 1350s, 1174s, 1074s, 929s, 778s, 740s, 700s; $\delta_H$ (400 MHz, $CDCl_3$) 1.05 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.59–1.71 (1H, m, C**H**H'$CH_3$), 1.75–1.89 (1H, m, CH**H'**$CH_3$), 2.27–2.45 (2H, m, $C\mathbf{H}_2CH{=}CH_2$), 3.02 (3H, s, $SC\mathbf{H}_3$), 3.63 (1H, ddd, *J*=8.0, 5.0, 2.5 Hz, C**H**OBn), 4.56 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.70 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.83 (1H, ddd, *J*=9.0, 4.0, 2.5 Hz, C**H**OMs), 5.08–5.19 (2H, m, $CH_2CH{=}C\mathbf{H}_2$), 5.87 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2C\mathbf{H}{=}CH_2$), 7.28–7.39 (5H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 10.3 ($CH_2\mathbf{C}H_3$), 23.6 ($\mathbf{C}H_2CH_3$), 34.4 ($\mathbf{C}H_2CH{=}CH_2$), 38.8 ($S\mathbf{C}H_3$), 72.3 ($\mathbf{C}H_2Ar$), 79.8 (**C**HOBn), 85.8 (**C**HOMs), 117.6 ($CH_2CH{=}\mathbf{C}H_2$), 127.8 (Ar), 128.0 (Ar), 128.4 (Ar), 134.4 ($CH_2\mathbf{C}H{=}CH_2$), 137.7

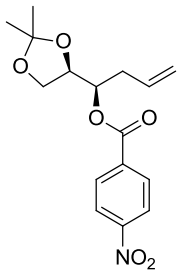
(Ar); *m/z* ($ES^+$) 357 ($M+MeCN+NH_4^+$, 100%), 321 ($M+Na^+$, 60); Accurate mass ($ES^+$): Found 321.1130, $C_{15}H_{22}NaO_4S$ ($M+Na^+$) requires 321.1131; $[\alpha]_D^{23}$ -14.3 (c = 1.0 in $CHCl_3$).

***((3R,4S)-4-(Benzyloxy)hept-6-en-3-yloxy)triethylsilane* (168)**




To a stirred solution of (3*R*,4*S*)-4-(benzyloxy)hept-6-en-3-ol (**162**) (100 mg, 0.45 mmol) in dry DCM (5 mL) at 0 °C were added imidazole (68 mg, 0.68 mmol), DMAP (11 mg, 0.09 mmol) and chlorotriethylsilane (0.11 mL, 103 mg, 0.68 mmol). The reaction mixture was allowed to warm to RT and stirred for 5 h and then quenched with $H_2O$ (15 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50:1→20:1 petrol b.p. 30–40 °C:acetone) gave the title compound (**168**) as a colourless oil (146 mg, 0.44 mmol, 96%); $R_f$ 0.75 (20:1 petrol:acetone); $\nu_{max}/cm^{-1}$ (thin film) 3474m br, 3067m, 3031m, 2957s (CH), 2877s, 1641m (C=C), 1497s, 1239m, 1064s, 1009s, 912m, 739s, 697s; $\delta_H$ (400 MHz, $CDCl_3$) 0.63 (6H, q, *J*=8.0 Hz, $Si(C\mathbf{H}_2CH_3)_3$), 0.88–1.02 (12H, m, $Si(CH_2C\mathbf{H}_3)_3$, $CH_2C\mathbf{H}_3$), 1.48–1.71 (2H, m, $C\mathbf{H}_2CH_3$), 2.36 (2H, td, *J*=7.0, 1.5 Hz, $C\mathbf{H}_2CH{=}CH_2$), 3.39–3.45 (1H, m, C**H**OBn), 3.72 (1H, dt, *J*=6.5, 4.0 Hz, C**H**OTES), 4.58 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.65 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 5.01–5.18 (2H, m, $CH_2CH{=}C\mathbf{H}_2$), 5.91 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2C\mathbf{H}{=}CH_2$), 7.22–7.43 (5H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 5.1 ($Si(\mathbf{C}H_2CH_3)_3$), 6.9 ($Si(CH_2\mathbf{C}H_3)_3$), 9.7 ($CH_2\mathbf{C}H_3$), 25.7 ($\mathbf{C}H_2CH_3$), 35.3 ($\mathbf{C}H_2CH{=}CH_2$), 72.3 ($\mathbf{C}H_2Ar$), 75.1 (**C**HOTES), 81.8 (**C**HOBn), 116.5 ($CH_2CH{=}\mathbf{C}H_2$), 127.4 (Ar), 127.8 (Ar), 128.2 (Ar), 135.9 ($CH_2\mathbf{C}H{=}CH_2$), 138.9 (Ar); *m/z* ($ES^+$) 393 ($M+MeCN+NH_4^+$, 80%), 357 ($M+Na^+$, 100), 335 ($M+H^+$, 55); Accurate mass ($ES^+$): Found 357.2214, $C_{20}H_{34}NaO_2Si$ ($M+Na^+$) requires 357.2220; $[\alpha]_D^{23}$ -9.4 (c = 1.0 in $CHCl_3$).

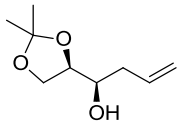
***(R)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-enyl 4-nitrobenzoate* (169)**



*According to the modified procedure of Proctor et al.*[125]: To a stirred solution of triphenylphosphine (343 mg, 1.31 mmol) in THF (4 mL) at 0 °C was added diisopropyl azodicarboxylate (0.21 mL, 211 mg, 1.05 mmol) dropwise. This mixture was stirred at 0 °C for 15 min and then a solution of (*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**) (150 mg, 0.87 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 15 min. 4-Nitrobenzoic acid (175 mg, 1.05 mmol) was added in a single portion and the cooling bath was removed. The reaction mixture was stirred at RT for 16 h and then diluted with diethyl ether (10 mL). The reaction mixture was washed with 15% aq. $H_2O_2$ (5 mL) and the aqueous layer extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1→6:1 petrol:EtOAc) gave the title compound (**169**) as a colourless oil (154 mg, 0.48 mmol, 55%); $R_f$ 0.13 (6:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3113m, 3081m, 2987s (CH), 1730s (C=O), 1644s (C=C), 1608s, 1531s ($NO_2$), 1373s ($NO_2$), 1274s, 1103s, 841s, 719s; $\delta_H$ (400 MHz, $CDCl_3$) 1.37 (3H, s, C**H**$_3$), 1.46 (3H, s, C**H**$_3$), 2.45–2.61 (2H, m, C**H**$_2$CH=CH$_2$), 3.81 (1H, dd, *J*=8.5, 6.0 Hz, C**H**H'OC(Me)$_2$), 4.09 (1H, dd, *J*=8.5, 7.0 Hz, CH**H'**OC(Me)$_2$), 4.34 (1H, app. q, *J*=6.0 Hz, C**H**OC(Me)$_2$), 5.06–5.20 (2H, m, CH$_2$CH=C**H**$_2$), 5.27 (1H, dt, *J*=7.5, 5.0 Hz, C**H**OC(O)Ar), 5.81 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 8.23 (2H, d, *J*=9.0 Hz, Ar**H**), 8.31 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 25.3 (**C**H$_3$), 26.4 (**C**H$_3$), 35.5 (**C**H$_2$CH=CH$_2$), 65.7 (**C**H$_2$OC(Me)$_2$), 74.4 (**C**HOC(Me)$_2$), 76.1 (**C**HOC(O)Ar), 109.8 (**C**(Me)$_2$), 118.8 (CH$_2$CH=**C**H$_2$), 123.6 (Ar), 130.8 (Ar), 132.5 (CH$_2$**C**H=CH$_2$), 135.6 (Ar), 150.6 (**C**NO$_2$), 164.3 (**C**=O); Accurate mass (FI$^+$): Found

321.1212, $C_{16}H_{19}NO_6$ ($M^+$) requires 321.1212; $[\alpha]_D^{23}$ +8.8 (c = 1.0 in $CH_2Cl_2$), literature value for enantiomer $[\alpha]_D^{25}$ -23.8 (c = 0.5 in $CH_2Cl_2$).[163]

**(*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol**[72c] **(146)**

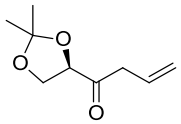



**Method 1:** To a stirred solution of (*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-enyl 4-nitrobenzoate (**169**) (90 mg, 0.28 mmol) in methanol (5 mL) at 0 °C was added $K_2CO_3$ (194 mg, 1.40 mmol). The reaction mixture was allowed to warm to RT, stirred for 16 h, diluted with $H_2O$ (7 mL) and extracted with DCM (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (6:1 petrol:EtOAc) gave the title compound (**146**) as a colourless oil (38 mg, 0.22 mmol, 79%); $R_f$ 0.60 (1:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 1.37 (3H, s, C**H**$_3$), 1.44 (3H, s, C**H**$_3$), 2.20–2.32 (3H, m, C**H**$_2$CH=CH$_2$, O**H**), 3.56–3.63 (1H, m, C**H**OH), 3.70–3.80 (1H, m, C**H**H'OC), 3.97–4.08 (2H, m, CH**H'**OC, C**H**OC), 5.08–5.20 (2H, m, CH$_2$CH=C**H**$_2$), 5.86 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 25.3 (**C**H$_3$), 26.6 (**C**H$_3$), 38.3 (**C**H$_2$CH=CH$_2$), 66.0 (**C**H$_2$OC), 71.5 (**C**HOH), 78.4 (**C**HOC), 109.4 (**C**(Me)$_2$), 117.9 (CH$_2$CH=**C**H$_2$), 134.0 (CH$_2$**C**H=CH$_2$); *m/z* (ES$^+$) 173 ((M+H)$^+$, 20%); $[\alpha]_D^{23}$ +14.1 (c = 1.0 in $CHCl_3$), literature value $[\alpha]_D^{20}$ +14.2 (c = 1.5 in $CHCl_3$).[155]

**Method 2:** *According to the modified procedure of Dhotare et al.*[79]: To a stirred solution of (*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-one (**170**) (0.1 g, 0.59 mmol) in dry THF (2.9 mL) at -78 °C was added a solution of L-selectride® (1.2 mL of 1.0 M solution in THF, 1.2 mmol) over 45 min. The reaction mixture was stirred at -78 °C for a further 2 h and then warmed to 0 °C over 1 h. The reaction mixture was quenched with pH 7 buffer solution (1.5 mL), methanol (1.5 mL) and 30% aq. $H_2O_2$ (0.75 mL). The mixture was transferred to a conical flask and stirred at 0 °C with

dropwise addition of sat. aq. $Na_2S_2O_3$ until no peroxide was present by starch iodide test. The mixture was diluted with EtOAc (20 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($Na_2SO_4$) for 5 min, filtered and concentrated *in vacuo*. Purification by flash column chromatography (15:1→5:1 petrol b.p. 30–40 °C:acetone with 1% IPA) gave the title compound (**146**) as a colourless oil (81 mg, 0.47 mmol, 80%, 13:1 (*R*):(*S*) from crude $^1$H NMR analysis); data as shown above.

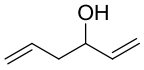
***(R)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-one* (170)**



*According to the modified procedure of Denmark et al.*[78]: Dess-Martin periodinane (3.55 g, 8.36 mmol) was suspended in moist DCM (5.3 mL) with stirring. A solution of 10:1 (*S*)-:(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**145**:**146**) (1.20 g, 6.97 mmol) in moist DCM (7.0 mL) was added dropwise and the reaction mixture was stirred at RT for 18 h. The reaction mixture was poured into a mixture of diethyl ether (80 mL) and aq. $Na_2S_2O_3$/$NaHCO_3$ solution (17 g $Na_2S_2O_3$ in 170 mL sat. aq. $NaHCO_3$) and stirred until both layers were clear. The mixture was separated and the aqueous layer extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10:1 petrol b.p. 30–40 °C:acetone) gave the title compound (**170**) as a colourless oil (1.06 g, 6.23 mmol, 89%); $R_f$ 0.43 (10:1 petrol:acetone); $\nu_{max}$/cm$^{-1}$ (thin film) 3082w, 2989s (CH), 2893m, 1721s (C=O), 1644m (C=C), 1383s, 1260s, 1214s, 1153s, 1068s, 922m, 848s; $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (3H, s, C**H**$_3$), 1.50 (3H, s, C**H**$_3$), 3.37–3.43 (2H, m, C**H**$_2$CH=CH$_2$), 4.01 (1H, dd, *J*=8.5, 5.5 Hz, C**H**H'OC(Me)$_2$), 4.20 (1H, dd, *J*=8.5, 8.0 Hz, CH**H'**OC(Me)$_2$), 4.47 (1H, dd, *J*=8.0, 5.5 Hz, C**H**OC(Me)$_2$), 5.11–5.25 (2H, m, CH$_2$CH=C**H**$_2$), 5.93 (1H, ddt, *J*=17.0, 10.5, 7.0 Hz, CH$_2$C**H**=CH$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 24.9 (**C**H$_3$), 26.0 (**C**H$_3$), 43.3 (**C**H$_2$CH=CH$_2$), 66.5 (**C**H$_2$OC(Me)$_2$), 80.0 (**C**HOC(Me)$_2$), 111.0 (**C**(Me)$_2$), 119.1

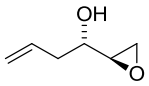
($CH_2CH=\mathbf{C}H_2$), 129.7 ($CH_2\mathbf{C}H=CH_2$), 208.7 (**C**=O); *m/z* ($ES^-$) 169 ($(M–H)^-$, 100%); Accurate mass ($ES^+$): Found 193.0834, $C_9H_{14}NaO_3$ ($M+Na^+$) requires 193.0835; $[\alpha]_D^{23}$ +90.0 (c = 1.0 in $CHCl_3$).

**1,5-Hexadien-3-ol**[87, 164] **(123)**




*According to the procedure of Barfield et al.*[87]: To an initiated Grignard reaction (prepared by adding allyl bromide (**188**) (0.40 mL, 559 mg, 4.62 mmol) in diethyl ether (25 mL) to magnesium (17.7 g, 0.73 mol) under $N_2$) was added a solution of allyl bromide (**188**) (52.0 mL, 72.6 g, 0.60 mol) and acrolein (**187**) (33 mL, 27.7 g, 0.50 mol) in diethyl ether (150 mL) dropwise over 3.25 h whilst maintaining a gentle reflux. The reaction mixture was then heated to reflux for 1.75 h and then cooled to 0 °C. Sat. aq. $NH_4Cl$ (125 mL) was added dropwise, followed by $H_2O$ (200 mL) and the suspension was stirred for 16 h. The solution was acidified to pH 2 by the addition of aq. HCl (2 M) and then the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by vacuum fractional distillation (b.p. 62–66 °C/67 mbar (lit. 60–70 °C/67 mbar)[87]) gave the title compound (**123**) as a colourless oil (29.0 g, 0.30 mol, 60%); $R_f$ 0.38 (6:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 1.86 (1H, br s, O**H**), 2.23–2.40 (2H, m, $C\mathbf{H}_2CH=CH_2$), 4.14–4.21 (1H, m, C**H**OH), 5.09–5.30 (4H, m, 2 × $CH=C\mathbf{H}_2$), 5.75–5.94 (2H, m, 2 × $C\mathbf{H}=CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 41.6 ($\mathbf{C}H_2CH=CH_2$), 71.8 (**C**HOH), 114.8 ($CH=\mathbf{C}H_2$), 118.3 ($CH=\mathbf{C}H_2$), 134.1 ($\mathbf{C}H=CH_2$), 140.3 ($\mathbf{C}H=CH_2$); Accurate mass ($FI^+$): Found 98.0731, $C_6H_{10}O$ ($M^+$) requires 98.0732.

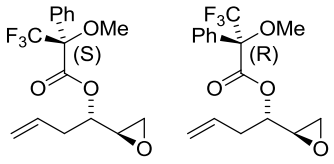
**(*S*)-1-((*R*)-Oxiran-2-yl)but-3-en-1-ol**[165] **(124)**




*According to the procedure of Crimmins et al.*[88]: To a 500 mL dry round bottomed flask were added powdered activated 4 Å molecular sieves (4.6 g), L-(+)-dicyclohexyl tartrate (**186**) (4.80 g, 15.3 mmol), 1,5-hexadien-3-ol (**123**) (11.4 mL, 10.0 g, 102 mmol) and distilled DCM (115 mL). The flask was cooled to -20 °C and the reaction mixture stirred for 30 min. Distilled titanium(IV) isopropoxide (3.0 mL, 2.90 g, 10.2 mmol) was added and the reaction mixture stirred for 30 min. *tert*-Butyl hydroperoxide (15.5 mL, 3.94 M solution in DCM, 61.1 mmol) was added dropwise over 30 min and the reaction mixture stirred at -20 °C for a further 42 h. The reaction was quenched at -20 °C with a 0 °C $FeSO_4$/citric acid solution (33 g $FeSO_4$ heptahydrate and 10.3 g citric acid monohydrate in 100 mL $H_2O$). The reaction mixture was warmed to RT and stirred for 30 min before filtering through a pad of Celite™. The layers were separated and the aqueous layer, with addition of $H_2O$ (100 mL), was extracted with DCM (6 × 50 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**124**) as a colourless oil (4.38 g, 38.4 mmol, 38%, (76% of maximum)); $R_f$ 0.08 (2:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3424s br (OH), 3077m, 3000s (CH), 2930s, 1643s (C=C), 1434s, 1254s, 1072s, 993s, 919s, 858s; $\delta_H$ (400 MHz, $CDCl_3$) 2.12 (1H, br s, O**H**), 2.26–2.36 (1H, m, C**H**H'CH=$CH_2$), 2.36–2.45 (1H, m, CH**H'**CH=$CH_2$), 2.75 (1H, dd, *J*=5.0, 4.0 Hz, C**H**H'O(CH)), 2.81 (1H, dd, *J*=5.0, 3.0 Hz, CH**H'**O(CH)), 3.03 (1H, ddd, *J*=6.5, 4.0, 3.0 Hz, $CH_2O$(C**H**)), 3.83 (1H, m, C**H**OH), 5.10–5.22 (2H, m, $CH_2CH$=C$\mathbf{H}_2$), 5.87 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2$C**H**=$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 38.1 (**C**$H_2$CH=$CH_2$), 43.8 (**C**$H_2$O(CH)), 54.1 ($CH_2$O(**C**H)), 68.2 (**C**HOH), 118.2 ($CH_2CH$=**C**$H_2$), 133.6 ($CH_2$**C**H=$CH_2$); Accurate mass ($FI^+$): Found 114.0681, $C_6H_{10}O_2$ ($M^+$) requires 114.0681; $[\alpha]_D^{25}$ +30.1 (c = 1.0 in $CH_2Cl_2$), literature value for enantiomer $[\alpha]_D^{24}$ -28.0 (c = 9.65 in $CH_2Cl_2$).[88a]

***(S)-((S)-1-((R)-Oxiran-2-yl)but-3-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* (189)**

***(R)-((S)-1-((R)-Oxiran-2-yl)but-3-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* (190)**

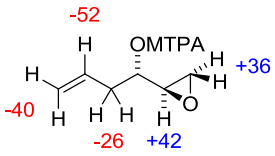


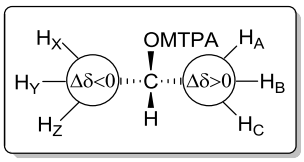

(*S*)-ester: To a solution of (*S*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (41 mg, 0.18 mmol) in DCM (1.5 mL) were added (*S*)-1-((*R*)-oxiran-2-yl)but-3-en-1-ol (**124**) (10 mg, 0.09 mmol), DCC (54 mg, 0.26 mmol), and DMAP (11 mg, 0.09 mmol). The reaction mixture was stirred at RT for 20 h and then diluted with diethyl ether (5 mL). The organic layer was washed sequentially with aq. HCl (5 mL, 2 M), sat. aq. $NaHCO_3$ (5 mL), brine (5 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**189**) as a colourless oil (21 mg, 0.06 mmol, 67%); $R_f$ 0.32 (2:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2953w (CH), 2850w, 1752s (C=O), 1644w (C=C), 1252s, 1171s, 1123m, 1020m, 766w, 719m; $\delta_H$ (400 MHz, $CDCl_3$) 2.41–2.58 (2H, m, C**H**$_2$CH=CH$_2$), 2.74–2.80 (2H, m, C**H**$_2$O(CH)), 3.11 (1H, ddd, *J*=7.0, 4.0, 3.0 Hz, CH$_2$O(C**H**)), 3.55 (3H, s, OC**H**$_3$), 5.04–5.13 (2H, m, CH$_2$CH=C**H**$_2$), 5.17 (1H, dt, *J*=7.5, 4.5 Hz, C**H**OC(O)R), 5.68 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 7.38–7.44 (3H, m, Ar**H**), 7.52–7.57 (2H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 35.7 (**C**H$_2$CH=CH$_2$), 44.7 (**C**H$_2$O(CH)), 51.5 (CH$_2$O(**C**H)), 55.4 (O**C**H$_3$), 73.5 (**C**HOC(O)), 119.1 (CH$_2$CH=**C**H$_2$), 127.4 (Ar), 128.4 (Ar), 129.7 (Ar), 131.6 (CH$_2$**C**H=CH$_2$), 132.1 (Ar), 165.9 (**C**=O), (**C**(CF$_3$) and C(**C**F$_3$) carbons were not resolved); $\delta_F$ (400 MHz, $CDCl_3$) –71.4 (C**F**$_3$); *m/z* (ES$^+$) 353 (M+Na$^+$, 75%), 348 (M+NH$_4^+$, 20), 331 (M+H$^+$, 10); Accurate mass (ES$^+$): Found 353.0976, $C_{16}H_{17}F_3NaO_4$ (M+Na$^+$) requires 353.0971; $[\alpha]_D^{25}$ -21.5 (c = 1.0 in $CHCl_3$).

(*R*)-ester: Procedure as for (*S*)-ester but with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. Purification by flash column chromatography (2:1 petrol b.p. 30–40 °C:diethyl ether) gave the

title compound (**190**) as a colourless oil (24 mg, 0.07 mmol, 78%); $R_f$ 0.32 (2:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2953w (CH), 2851w, 1753s (C=O), 1645w (C=C), 1452m, 1253s, 1171s, 1018s, 995s, 720s; $\delta_H$ (400 MHz, $CDCl_3$) 2.48–2.64 (2H, m, C**H**$_2$CH=CH$_2$), 2.65 (1H, dd, *J*=5.0, 2.5 Hz, C**H**H'O(CH)), 2.71 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 3.00 (1H, ddd, *J*=8.0, 4.0, 2.5 Hz, CH$_2$O(C**H**)), 3.56 (3H, s, OC**H**$_3$), 5.11 (1H, dt, *J*=8.0, 5.0 Hz, C**H**OC(O)), 5.14–5.23 (2H, m, CH$_2$CH=C**H**$_2$), 5.81 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 4.37–4.45 (3H, m, Ar**H**), 7.51–7.57 (2H, m, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 35.8 (**C**H$_2$CH=CH$_2$), 45.0 (**C**H$_2$O(CH)), 51.5 (CH$_2$O(**C**H)), 55.6 (O**C**H$_3$), 74.0 (**C**HOC(O)R), 119.1 (CH$_2$CH=**C**H$_2$), 127.4 (Ar), 128.3 (Ar), 129.7 (Ar), 132.1 (CH$_2$**C**H=CH$_2$), 132.1 (Ar), 165.9 (**C**=O), (**C**(CF$_3$) and C(**C**F$_3$) carbons were not resolved); $\delta_F$ (400 MHz, $CDCl_3$) –71.5 (C**F**$_3$); *m/z* (ES$^+$) 353 (M+Na$^+$, 80%), 348 (M+NH$_4^+$, 20), 331 (M+H$^+$, 10); Accurate mass (ES$^+$): Found 353.0975, $C_{16}H_{17}F_3NaO_4$ (M+Na$^+$) requires 353.0971; $[\alpha]_D^{25}$ +50.1 (c = 1.0 in $CHCl_3$).

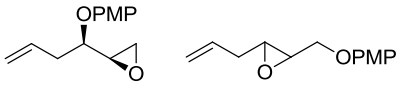
The e.e. was determined to be >95% by analysis of the $^1$H NMR spectra of the crude Mosher esters and, as shown below, the absolute configuration was confirmed by the method of Ohtani *et al.* (values quoted in Hz).[90]




***(R)-2-((R)-1-(4-Methoxyphenoxy)but-3-enyl)oxirane* (178)**

***2-Allyl-3-((4-methoxyphenoxy)methyl)oxirane* (193)**




*According to the modified procedure of Jung et al.*[166]: A solution of diisopropyl azodicarboxylate (112 μL, 115 mg, 0.57 mmol) in DCM (0.6 mL) was added slowly to a stirred solution of (*S*)-1-((*R*)-oxiran-2-yl)but-3-en-1-ol (**124**) (50 mg, 0.44 mmol), 4-methoxyphenol (163 mg, 1.31 mmol) and

triphenylphosphine (149 mg, 0.57 mmol) in DCM (0.6 mL) at -78 °C. The reaction mixture was stirred for 16 h and then washed with aq. NaOH solution (1.5 mL, 2 M), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (8:1 petrol:diethyl ether) gave the title compounds (**178** and **193**) as partially separable colourless oils.

1. (*R*)-2-((*R*)-1-(4-Methoxyphenoxy)but-3-enyl)oxirane (**178**) (40 mg, 0.18 mmol, 41%); $R_f$ 0.63 (1:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3074m, 2999m (CH), 2934m, 2835m, 1642m (C=C), 1507s, 1225s, 1038s, 920s, 889s, 829s, 744m; $\delta_H$ (400 MHz, $CDCl_3$) 2.45–2.63 (2H, m, C**H**$_2$CH=CH$_2$), 2.68 (1H, dd, *J*=5.0, 3.0 Hz, C**H**H'O(CH)), 2.85 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 3.19 (1H, ddd, *J*=6.5, 4.0, 3.0 Hz, CH$_2$O(C**H**)), 3.77 (3H, s, OC**H**$_3$), 3.90 (1H, q, *J*=6.5 Hz, C**H**OPMP), 5.08–5.23 (2H, m, CH$_2$CH=C**H**$_2$), 5.89 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 6.82 (2H, d, *J*=9.0 Hz, Ar**H**), 6.94 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 36.7 (**C**H$_2$CH=CH$_2$), 44.7 (**C**H$_2$O(CH)), 53.9 (CH$_2$O(**C**H)), 55.6 (O**C**H$_3$), 79.9 (**C**HOPMP), 114.6 (Ar), 117.9 (Ar), 118.1 (CH$_2$CH=**C**H$_2$), 133.3 (CH$_2$**C**H=CH$_2$), 152.3 (Ar), 154.4 (Ar); *m/z* (ES$^+$) 243 (M+Na$^+$, 35%), 238 (M+NH$_4^+$, 10); Accurate mass (ES$^+$): Found 243.0987, $C_{13}H_{16}NaO_3$ (M+Na$^+$) requires 243.0992; $[\alpha]_D^{25}$ +16.5 (c = 1.0 in $CHCl_3$).

2. 2-Allyl-3-((4-methoxyphenoxy)methyl)oxirane (**193**) (15 mg, 0.07 mmol, 15%); $R_f$ 0.69 (1:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3077m, 2927s (CH), 2837s, 1641m (C=C), 1508s, 1462s, 1232s, 1040s, 918s, 827s; $\delta_H$ (400 MHz, $CDCl_3$) 2.37–2.43 (2H, m, C**H**$_2$CH=CH$_2$), 3.05 (1H, td, *J*=5.5, 2.0 Hz, C**H**CH$_2$CH=CH$_2$), 3.14 (1H, ddd, *J*=5.5, 3.5, 2.0 Hz, C**H**CH$_2$OPMP), 3.77 (3H, s, OC**H**$_3$), 3.97 (1H, dd, *J*=11.0, 5.5 Hz, C**H**H'OPMP), 4.15 (1H, dd, *J*=11.0, 3.5 Hz, CH**H'**OPMP), 5.09–5.24 (2H, m, CH$_2$CH=C**H**$_2$), 5.84 (1H, ddt, *J*=17.0, 10.5, 7.0 Hz, CH$_2$C**H**=CH$_2$), 6.83 (2H, d, *J*=9.0 Hz, Ar**H**), 6.87 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 35.7 (**C**H$_2$CH=CH$_2$), 55.4 (C**H**CH$_2$CH=CH$_2$), 55.7 (O**C**H$_3$), 55.7 (C**H**CH$_2$OPMP), 68.9 (**C**H$_2$OPMP), 114.6 (Ar), 115.7 (Ar), 117.8 (CH$_2$CH=**C**H$_2$), 132.7 (CH$_2$**C**H=CH$_2$), 152.6 (Ar), 154.1 (Ar); *m/z* (ES$^+$) 243 (M+Na$^+$, 45%),

238 (M+$NH_4^+$, 10); Accurate mass ($ES^+$): Found 243.0993, $C_{13}H_{16}NaO_3$ (M+$Na^+$) requires 243.0992; $[\alpha]_D^{25}$ +5.0 (c = 1.0 in $CHCl_3$). Absolute stereochemistry is not known.

***5-(4-Bromobenzyloxy)pentan-1-ol* (198)**

***1,5-Bis(4-bromobenzyloxy)pentane***


**Method 1:** *According to the modified procedure of Plante et al.*[91]: To a stirred solution of 1,5-pentanediol (**194**) (0.20 mL, 200 mg, 1.92 mmol) in dry DMF (19 mL) was added sodium hydride (84 mg, 60% dispersion in mineral oil, 2.11 mmol) and 4-bromobenzyl bromide (527 mg, 2.11 mmol) at 0 °C. The reaction mixture was stirred at RT for 1.5 h before being quenched by slow addition of $H_2O$ (15 mL). The reaction mixture was diluted with EtOAc (25 mL) and washed sequentially with $H_2O$ (2 × 10 mL) and brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1→0:1 petrol b.p. 30–40 °C:diethyl ether) gave the two title compounds (**198**) as colourless oils.

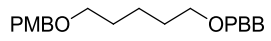
1. 5-(4-Bromobenzyloxy)pentan-1-ol (**198**): (316 mg, 1.16 mmol, 60%); $R_f$ 0.53 (diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3383s br (OH), 2937s (CH), 1593m, 1487s, 1396m, 1360m, 1095s, 1011s, 823s, 734m; $\delta_H$ (400 MHz, $CDCl_3$) 1.40–1.75 (7H, m, C**H**$_2$CH$_2$CH$_2$O, O**H**, 2 × C**H**$_2$CH$_2$O), 3.47 (2H, t, *J*=6.5 Hz, C**H**$_2$OPBB), 3.65 (2H, t, *J*=6.5 Hz, C**H**$_2$OH), 4.45 (2H, s, C**H**$_2$Ar), 7.21 (2H, d, *J*=8.5 Hz, Ar**H**), 7.47 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 22.4 (**C**H$_2$CH$_2$CH$_2$O), 29.4 (**C**H$_2$CH$_2$OPBB), 32.4 (**C**H$_2$CH$_2$OH), 62.6 (**C**H$_2$OH), 70.4 (**C**H$_2$OPBB), 72.1 (**C**H$_2$Ar), 121.4 (Ar), 129.3 (Ar), 131.5 (Ar), 137.5 (Ar); *m*/*z* ($ES^+$) 297 (M+$Na^+$, 100%), 295 (M+$Na^+$, 95), 273 (M+$H^+$, 15); Accurate mass ($ES^+$): Found 297.0285, $C_{12}H_{17}{}^{81}BrNaO_2$ (M+$Na^+$) requires 297.0285, found 295.0308, $C_{12}H_{17}{}^{79}BrNaO_2$ (M+$Na^+$) requires 295.0304.

2. 1,5-Bis(4-bromobenzyloxy)pentane: (166 mg, 0.38 mmol, 20%); $R_f$ 0.84 (diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2858s, 1592m, 1487s, 1396m, 1359s, 1096s, 1011s, 803s, 734m; $\delta_H$ (400 MHz, $CDCl_3$) 1.40–1.50 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.59–1.68 (4H, m, 2 × C**H**$_2$CH$_2$O), 3.47 (4H, t, *J*=6.5 Hz

2 × C**H**$_2$OPBB), 4.44 (4H, s, 2 × C**H**$_2$Ar), 7.21 (4H, d, *J*=8.5 Hz, Ar**H**), 7.47 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 22.8 (**C**H$_2$CH$_2$CH$_2$O), 29.5 (**C**H$_2$CH$_2$OPBB), 70.4 (**C**H$_2$OPBB), 72.1 (**C**H$_2$Ar), 121.3 (Ar), 129.2 (Ar), 131.4 (Ar), 137.6 (Ar); *m/z* (ES$^+$) 467 (M+Na$^+$, 55%), 465 (M+Na$^+$, 100), 463 ((M+Na$^+$, 60), 462 (M+NH$_4^+$, 10), 460 (M+NH$_4^+$, 20), 458 (M+NH$_4^+$, 10); Accurate mass (ES$^+$): Found 466.9831, $C_{19}H_{22}{}^{81}Br_2NaO_2$ (M+Na$^+$) requires 466.9842, found 464.9853, $C_{19}H_{22}{}^{81}Br^{79}BrNaO_2$ (M+Na$^+$) requires 464.9859, found 462.9875, $C_{19}H_{22}{}^{79}Br_2NaO_2$ (M+Na$^+$) requires 462.9879.

**Method 2:** To a stirred solution of 1-bromo-4-((5-(4-methoxybenzyloxy)pentyloxy)methyl)benzene (**195**) (30 mg, 0.08 mmol) in DCM (7.6 mL) was added boron trichloride-dimethyl sulfide complex (0.19 mL, 2 M in DCM, 0.38 mmol). The reaction mixture was stirred at RT for 5 min and then quenched by addition of sat. aq. $NaHCO_3$ (6 mL). The reaction mixture was diluted with $H_2O$ (5 mL) and the aqueous layer was extracted with DCM (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1→0:1 petrol b.p. 30–40 °C:diethyl ether) gave 5-(4-bromobenzyloxy)pentan-1-ol (**198**) as a colourless oil (19 mg, 0.07 mmol, 92%); data as shown above.

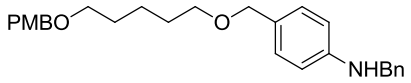
***1-Bromo-4-((5-(4-methoxybenzyloxy)pentyloxy)methyl)benzene* (195)**




5-(4-Bromobenzyloxy)pentan-1-ol (**198**) (190 mg, 0.70 mmol), 4-methoxybenzyl bromide (0.15 mL, 210 mg, 1.04 mmol) and tetrabutylammonium iodide (26 mg, 0.07 mmol) were dissolved in dry THF (5 mL) and cooled to 0 °C. Sodium hydride (70 mg, 60% dispersion in mineral oil, 1.74 mmol) was added and the reaction mixture was warmed to RT and stirred for 7 h. The reaction mixture was cooled to 0 °C, quenched by slow addition of sat. aq. $NH_4Cl$ (5 mL) and diluted with diethyl ether (10 mL). The aqueous layer was separated, extracted with diethyl ether (3 × 10 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (8:1 petrol b.p. 30–40 °C:diethyl ether) gave the

title compound (**195**) as a colourless oil (231 mg, 0.58 mmol, 84%); $R_f$ 0.26 (8:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2936s (CH), 2858s, 1699m, 1613s, 1514s, 1247s, 1096s, 1035s, 1012s, 805s; $\delta_H$ (400 MHz, $CDCl_3$) 1.40–1.50 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.58–1.68 (4H, m, 2 × C**H**$_2$CH$_2$O), 3.45 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 3.46 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 3.81 (3H, s, OC**H**$_3$), 4.43 (2H, s, C**H**$_2$Ar), 4.44 (2H, s, C**H**$_2$Ar), 6.88 (2H, d, *J*=8.5 Hz, Ar**H**), 7.21 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=8.5 Hz, Ar**H**), 7.47 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 22.9 (**C**H$_2$CH$_2$CH$_2$O), 29.5 (**C**H$_2$CH$_2$O), 29.5 (**C**H$_2$CH$_2$O), 55.3 (O**C**H$_3$), 70.0 (**C**H$_2$O), 70.4 (**C**H$_2$O), 72.1 (**C**H$_2$Ar), 72.5 (**C**H$_2$Ar), 113.7 (Ar), 121.3 (Ar), 129.2 (Ar), 129.2 (Ar), 130.7 (Ar), 131.4 (Ar), 137.7 (Ar), 159.1 (Ar); *m*/*z* ($ES^+$) 417 ($M+Na^+$, 100%), 415 ($M+Na^+$, 95); Accurate mass ($ES^+$): Found 417.0863, $C_{20}H_{25}{}^{81}BrNaO_3$ ($M+Na^+$) requires 417.0861, found 415.0885, $C_{20}H_{25}{}^{79}BrNaO_3$ ($M+Na^+$) requires 415.0879.

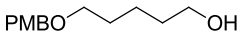
**N-*Benzyl-4-((5-(4-methoxybenzyloxy)pentyloxy)methyl)aniline* (196)**




*According to the procedure of Plante et al.*[91]: 1-Bromo-4-((5-(4-methoxybenzyloxy)pentyloxy)methyl)benzene (**195**) (100 mg, 0.25 mmol) was azeotropically dried with dry toluene (3 × 1 mL) and then dried for 1 h under high vacuum. The flask was purged with $N_2$, benzylamine (34 μL, 33 mg, 0.36 mmol) was added and the residue was dissolved in dry toluene (0.5 mL). This solution was added *via* cannula to tris(dibenzylideneacetone)dipalladium (2 mg, 3 μmol), sodium *tert*-butoxide (34 mg, 0.36 mmol) and (2-biphenyl)di-*tert*-butylphosphine (2 mg, 5 μmol) in a dry Schlenk tube. The reaction mixture was heated to 80 °C for 5 h with vigorous stirring. The reaction mixture was cooled to RT and diluted with diethyl ether (2 mL), filtered through a pad of Celite™ and concentrated *in vacuo*. Purification by flash column chromatography (5:1 petrol b.p. 30–40 °C:diethyl ether) gave recovered starting material (**195**) (74 mg, 0.19 mmol, 74%) and the title compound (**196**) as a yellow oil (21 mg, 0.05 mmol, 20%); $R_f$ 0.14 (4:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3414s br (NH), 2936s (CH), 2857s, 1701m, 1614s, 1516s,

1247s, 1094s, 1034s, 911s, 816s; $\delta_H$ (500 MHz, $CDCl_3$) 1.39–1.48 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.58–1.68 (4H, m, 2 × C**H**$_2$CH$_2$O), 3.43 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 3.45 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 3.81 (3H, s, OC**H**$_3$), 4.13 (1H, br s, N**H**), 4.34 (2H, s, NC**H**$_2$Ar), 4.38 (2H, s, C**H**$_2$Ar), 4.43 (2H, s, C**H**$_2$Ar), 6.62 (2H, d, *J*=8.5 Hz, Ar**H**), 6.89 (2H, d, *J*=8.5 Hz, Ar**H**), 7.15 (2H, d, *J*=8.5 Hz, Ar**H**), 7.24–7.32 (3H, m, Ar**H**), 7.33–7.40 (4H, m, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 22.9 (**C**H$_2$CH$_2$CH$_2$O), 29.6 (**C**H$_2$CH$_2$O), 29.6 (**C**H$_2$CH$_2$O), 48.4 (N**C**H$_2$Ar), 55.3 (O**C**H$_3$), 70.0 (**C**H$_2$O), 70.1 (**C**H$_2$O), 72.5 (**C**H$_2$Ar), 72.9 (**C**H$_2$Ar), 112.7 (Ar), 113.7 (Ar), 127.2 (Ar), 127.5 (Ar), 127.5 (Ar), 128.6 (Ar), 129.2 (Ar), 129.4 (Ar), 130.8 (Ar), 139.3 (Ar), 147.7 (Ar), 159.1 (Ar); *m*/*z* ($ES^+$) 442 ($M+Na^+$, 100%), 420 ($M+H^+$, 25); Accurate mass ($ES^+$): Found 442.2356, $C_{27}H_{33}NNaO_3$ ($M+Na^+$) requires 442.2353.

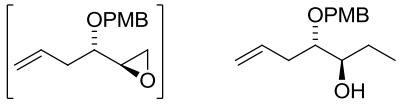
**5-(4-Methoxybenzyloxy)pentan-1-ol**[167] **(199)**




*According to the procedure of Plante et al.*[91]: To a solution of *N*-benzyl-4-((5-(4-methoxybenzyloxy)pentyloxy)methyl)aniline (**196**) (11 mg, 0.03 mmol) in DCM (1 mL) was added zinc(II) chloride (4 mg, 0.03 mmol). The reaction mixture was stirred for 2.5 h and then diluted with DCM (4 mL). This solution was washed sequentially with $H_2O$ (5 mL) and sat. aq. $NaHCO_3$ (5 mL), dried ($Na_2SO_4$), filtered through a pad of Celite™ and concentrated *in vacuo*. Purification by flash column chromatography (6:1→1:1 petrol b.p. 30–40 °C:EtOAc) gave the title compound (**199**) as a yellow oil (4 mg, 0.02 mmol, 67%); $R_f$ 0.20 (1:1 petrol:diethyl ether); $\delta_H$ (500 MHz, $CDCl_3$) 1.40–1.49 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.55–1.68 (5H, m, 2 × C**H**$_2$CH$_2$O, O**H**), 3.46 (2H, t, *J*=6.5 Hz, C**H**$_2$OPMB), 3.65 (2H, t, *J*=6.5 Hz, C**H**$_2$OH), 3.81 (3H, s, OC**H**$_3$), 4.44 (2H, s, C**H**$_2$Ar), 6.88 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 22.4 (**C**H$_2$CH$_2$CH$_2$O), 29.4 (**C**H$_2$CH$_2$OPMB), 32.5 (**C**H$_2$CH$_2$OH), 55.3 (O**C**H$_3$), 62.9 (**C**H$_2$OH), 70.0 (**C**H$_2$OPMB), 72.6 (**C**H$_2$Ar), 113.7 (Ar), 129.2 (Ar), 130.6 (Ar), 159.1 (Ar); *m*/*z* ($ES^+$) 247 ($M+Na^+$, 100%), 225 ($M+H^+$, 30).

**(R)-2-((S)-1-(4-Methoxybenzyloxy)but-3-en-1-yl)oxirane**

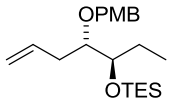
***(3*R*,4*S*)-4-(4-Methoxybenzyloxy)hept-6-en-3-ol* (211)**




*According to the procedure of Broadwith*[58] *and Crimmins and Powell*[88b]: (*S*)-1-((*R*)-Oxiran-2-yl)but-3-en-1-ol (**124**) (600 mg, 5.26 mmol), freshly prepared 4-methoxybenzyl bromide (1.15 mL, 1.59 g, 7.89 mmol) and tetrabutylammonium iodide (196 mg, 0.53 mmol) were dissolved in dry THF (18 mL) and the solution was cooled to -78 °C. Sodium hydride (526 mg, 60% dispersion in mineral oil, 13.2 mmol) was added and the reaction mixture was allowed to warm rapidly to RT and stirred for 16 h. TMEDA (1.20 mL, 930 mg, 8.00 mmol) was added to the reaction mixture at 0 °C and the mixture was stirred for 1 h at RT. The reaction mixture was cooled to 0 °C, quenched by slow addition of sat. aq. $NH_4Cl$ (15 mL) and diluted with diethyl ether (30 mL). The aqueous layer was separated, extracted with diethyl ether (3 × 30 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1 petrol b.p. 30–40 °C:diethyl ether) gave an inseparable mixture of the (*R*)-2-((*S*)-1-(4-methoxybenzyloxy)but-3-en-1-yl)oxirane and a *p*-methoxybenzyl bromide derivative thought to be 4,4'-oxybis(methylene)bis(methoxybenzene) (**214**) (1.68 g). This crude mixture was dissolved in dry THF (10 mL) and added dropwise over 10 min to a solution of copper(I) iodide (137 mg, 0.72 mmol) and methylmagnesium bromide (35.0 mL, 1 M solution in diethyl ether, 35.0 mmol) in dry THF (40 mL) at -23 °C (prepared by dropwise addition of the methylmagnesium bromide over 15 min to a solution of copper(I) iodide in THF at -23 °C). The reaction mixture was stirred for 1 h at -23 °C and then quenched by slow addition of sat. aq. $NH_4Cl$ (10 mL) and diluted with EtOAc (100 mL) and $H_2O$ (100 mL). The aqueous layer was separated and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed sequentially with sat. aq. $NH_4Cl$ (100 mL) and brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column

chromatography (2:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**211**) as a colourless oil (1.19 g, 4.75 mmol, 91% over two steps); $R_f$ 0.41 (2:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3456s br (OH), 3074m, 2963s (CH), 2935s, 1640m (C=C), 1463s, 1249s, 1082s, 915s, 823s; $\delta_H$ (400 MHz, $CDCl_3$) 0.98 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.40–1.60 (2H, m, $C\mathbf{H}_2CH_3$), 1.81 (1H, br s, O**H**), 2.25–2.35 (1H, m, C**H**H'CH=$CH_2$), 2.35–2.47 (1H, m, CH**H'**CH=$CH_2$), 3.43 (1H, dt, *J*=7.5, 4.0 Hz, C**H**OPMB), 3.68 (1H, dt, *J*=8.5, 4.0 Hz, C**H**OH), 3.81 (3H, s, $OC\mathbf{H}_3$), 4.49 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.55 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 5.04–5.18 (2H, m, $CH_2CH=C\mathbf{H}_2$), 5.90 (1H, ddt, *J*=17.0, 10.5, 7.0 Hz, $CH_2C\mathbf{H}=CH_2$), 6.89 (2H, d, *J*=8.5 Hz, Ar**H**), 7.27 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 10.5 ($CH_2\mathbf{C}H_3$), 25.0 ($\mathbf{C}H_2CH_3$), 33.7 ($\mathbf{C}H_2CH=CH_2$), 55.3 ($O\mathbf{C}H_3$), 71.6 ($\mathbf{C}H_2Ar$), 73.5 (**C**HOH), 81.2 (**C**HOPMB), 113.8 (Ar), 116.8 ($CH_2CH=\mathbf{C}H_2$), 129.4 (Ar), 130.5 (Ar), 135.4 ($CH_2\mathbf{C}H=CH_2$), 159.2 (Ar); *m/z* ($ES^+$) 273 ($M+Na^+$, 50%); Accurate mass ($ES^+$): Found 273.1461, $C_{15}H_{22}NaO_3$ ($M+Na^+$) requires 273.1461; $[\alpha]_D^{25}$ +1.9 (c = 1.0 in $CHCl_3$).

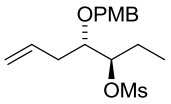
***Triethyl(((3R,4S)-4-(4-methoxybenzyloxy)hept-6-en-3-yl)oxy)silane* (212)**




To a stirred solution of (3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-ol (**211**) (3.35 g, 13.4 mmol) in dry DCM (170 mL) at 0 °C were added imidazole (2.00 g, 29.4 mmol), DMAP (327 mg, 2.68 mmol) and chlorotriethylsilane (3.40 mL, 3.03 g, 20.1 mmol). The reaction mixture was allowed to warm to RT and stirred for 16 h and then quenched by addition of $H_2O$ (100 mL). The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**212**) as a colourless oil (4.74 g, 13.0 mmol, 97%). $R_f$ 0.63 (10:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3075m, 2956s (CH), 2911s, 2877s, 1641m (C=C), 1614s, 1514s, 1248s, 1094s, 1010s, 912s, 821s, 742s; $\delta_H$ (400 MHz, $CDCl_3$) 0.63 (6H, q, *J*=8.0 Hz, $Si(C\mathbf{H}_2CH_3)_3$), 0.93 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$),

0.97 (9H, t, *J*=8.0 Hz, Si($CH_2C\mathbf{H}_3)_3$), 1.47–1.70 (2H, m, $C\mathbf{H}_2CH_3$), 2.34 (2H, t, *J*=6.5 Hz, $C\mathbf{H}_2CH{=}CH_2$), 3.40 (1H, td, *J*=6.5, 4.5 Hz, C**H**OPMB), 3.70 (1H, dt, *J*=6.5, 4.5 Hz, C**H**OTES), 3.81 (3H, s, $OC\mathbf{H}_3$), 4.50 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.58 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 5.02–5.19 (2H, m, $CH_2CH{=}C\mathbf{H}_2$), 5.90 (1H, ddt, *J*=17.0, 10.5, 6.5 Hz, $CH_2C\mathbf{H}{=}CH_2$), 6.88 (2H, d, *J*=8.5 Hz, Ar**H**), 7.28 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 5.2 (Si($\mathbf{C}H_2CH_3)_3$), 7.0 (Si($CH_2\mathbf{C}H_3)_3$), 9.7 ($CH_2\mathbf{C}H_3$), 25.7 ($\mathbf{C}H_2CH_3$), 35.3 ($\mathbf{C}H_2CH{=}CH_2$), 55.3 ($O\mathbf{C}H_3$), 72.0 ($\mathbf{C}H_2Ar$), 75.0 (**C**HOTES), 81.4 (**C**HOPMB), 113.6 (Ar), 116.5 ($CH_2CH{=}\mathbf{C}H_2$), 129.4 (Ar), 131.0 (Ar), 135.9 ($CH_2\mathbf{C}H{=}CH_2$), 159.0 (Ar); *m*/*z* ($ES^+$) 387 ($M+Na^+$, 100%); Accurate mass ($ES^+$): Found 387.2329, $C_{21}H_{36}NaO_3Si$ ($M+Na^+$) requires 387.2326; $[\alpha]_D^{25}$ -7.9 (c = 1.0 in $CHCl_3$).

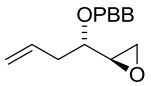
***(3R,4S)-4-(4-Methoxybenzyloxy)hept-6-en-3-yl methanesulfonate* (213)**




Prepared according to the **general mesylation procedure** (**Page 152**) with (3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-ol (**211**) (150 mg, 0.60 mmol). Purification by flash column chromatography (2:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**213**) as a colourless oil (180 mg, 0.55 mmol, 91%); $R_f$ 0.53 (1:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3077m, 2974s (CH), 2939s, 2880s, 1642m (C=C), 1613s, 1514s, 1348s, 1248s, 1173s, 1034s, 928s, 824s, 778s; $\delta_H$ (400 MHz, $CDCl_3$) 1.04 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.58–1.69 (1H, m, C**H**H'$CH_3$), 1.74–1.87 (1H, m, CH**H'**$CH_3$), 2.25–2.42 (2H, m, $C\mathbf{H}_2CH{=}CH_2$), 3.02 (3H, s, $SC\mathbf{H}_3$), 3.60 (1H, ddd, *J*=7.5, 4.5, 2.5 Hz, C**H**OPMB), 3.81 (3H, s, $OC\mathbf{H}_3$), 4.48 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.62 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.82 (1H, ddd, *J*=9.0, 3.0, 2.5 Hz, C**H**OMs), 5.06–5.18 (2H, m, $CH_2CH{=}C\mathbf{H}_2$), 5.85 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2C\mathbf{H}{=}CH_2$), 6.88 (2H, d, *J*=8.5 Hz, Ar**H**), 7.29 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 10.3 ($CH_2\mathbf{C}H_3$), 23.7 ($\mathbf{C}H_2CH_3$), 34.3 ($\mathbf{C}H_2CH{=}CH_2$), 38.8 ($S\mathbf{C}H_3$), 55.3 ($O\mathbf{C}H_3$), 71.9 ($\mathbf{C}H_2Ar$), 79.3 (**C**HOPMB), 85.8 (**C**HOMs), 113.8 (Ar), 117.5 ($CH_2CH{=}\mathbf{C}H_2$), 129.7 (Ar), 129.8 (Ar), 134.5 ($CH_2\mathbf{C}H{=}CH_2$), 159.3 (Ar); *m*/*z* ($ES^+$)

351 ($M+Na^+$, 80%), 346 ($M+NH_4^+$, 35); Accurate mass ($ES^+$): Found 351.1240, $C_{16}H_{24}NaO_5S$ ($M+Na^+$) requires 351.1237; $[\alpha]_D^{25}$ -18.6 (c = 1.0 in $CHCl_3$).

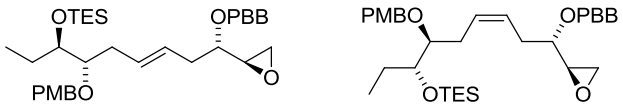
***(R)-2-((S)-1-(4-Bromobenzyloxy)but-3-enyl)oxirane* (205)**




*According to the modified procedure of Plante et al.*[91]: (*S*)-1-((*R*)-Oxiran-2-yl)but-3-en-1-ol (**124**) (1.50 g, 13.1 mmol), 4-bromobenzyl bromide (4.93 g, 19.7 mmol) and tetrabutylammonium iodide (485 mg, 1.31 mmol) were dissolved in dry THF (45 mL) and cooled to -78 °C. Sodium hydride (1.31 g, 60% dispersion in mineral oil, 32.9 mmol) was added and the reaction mixture was allowed to warm rapidly to RT and stirred for 17 h. The reaction mixture was quenched by slow addition of $H_2O$ (30 mL). The aqueous layer was separated, extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed sequentially with $H_2O$ (40 mL), brine (40 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (6:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**205**) as a colourless oil (3.50 g, 12.4 mmol, 95%); $R_f$ 0.52 (5:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3075m, 2985s (CH), 2924s, 2868s, 1641m (C=C), 1487s, 1249m, 1074s, 1010s, 918s, 805s; $\delta_H$ (400 MHz, $CDCl_3$) 2.36–2.51 (2H, m, C**H**$_2$CH=CH$_2$), 2.74 (1H, dd, *J*=5.0, 3.0 Hz, C**H**H'O(CH)), 2.80 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.96–3.01 (1H, m, CH$_2$O(C**H**)), 3.37 (1H, dt, *J*=6.5, 5.0 Hz, C**H**OPBB), 4.49 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.60 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 5.08–5.21 (2H, m, CH$_2$CH=C**H**$_2$), 5.90 (1H, ddt, *J*=17.5, 10.0, 7.0 Hz, CH$_2$C**H**=CH$_2$), 7.21 (2H, d, *J*=8.5 Hz, Ar**H**), 7.47 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 37.2 (**C**H$_2$CH=CH$_2$), 45.5 (**C**H$_2$O(CH)), 53.1 (CH$_2$O(**C**H)), 71.5 (**C**H$_2$Ar), 77.7 (**C**HOPBB), 117.6 (CH$_2$CH=**C**H$_2$), 121.5 (Ar), 129.2 (Ar), 131.5 (Ar), 133.8 (CH$_2$**C**H=CH$_2$) 137.4 (Ar); *m/z* ($ES^+$) 307 ($M+Na^+$, 100%), 305 ($M+Na^+$, 100), 300 ($M+NH_4^+$, 10); Accurate mass ($ES^+$): Found 307.0131, $C_{13}H_{15}{}^{81}BrNaO_2$ ($M+Na^+$) requires 307.0128, found 305.0151, $C_{13}H_{15}{}^{79}BrNaO_2$ ($M+Na^+$) requires 305.0148; $[\alpha]_D^{25}$ +1.1 (c = 1.0 in $CHCl_3$).

***(((3R,4S,9S,E)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((R)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane* (*E*-240)**

***(((3R,4S,9S,Z)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((R)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane* (*Z*-240)**



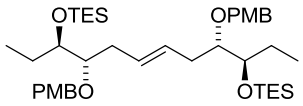

**General Cross Metathesis Procedure:** *According to the modified procedure of Donohoe et al.*[100] *and Knight et al.*[101]: To a solution of triethyl(((3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-yl)oxy)silane (**212**) (800 mg, 2.19 mmol), (*R*)-2-((*S*)-1-(4-bromobenzyloxy)but-3-enyl)oxirane (**205**) (2.48 g, 8.76 mmol) and 1,4-benzoquinone (59 mg, 0.55 mmol) in dry, freeze-thaw degassed DCM (110 mL) under Ar was added a solution of Hoveyda-Grubbs 2nd generation catalyst (**127**) (137 mg, 0.22 mmol) in DCM (20 mL) over 12 h. During this time the reaction mixture was stirred at 40 °C and after the addition the reaction mixture was stirred at 40 °C for a further 60 h. The reaction mixture was cooled to 0 °C and then 15% aq. $H_2O_2$ (50 mL) was added with care (exothermic and oxygen released) and the reaction mixture was stirred for 30 min and allowed to warm to RT. The aqueous layer was separated and extracted with DCM (3 × 100 mL). The combined organic layers, after testing negative with starch-iodide paper, were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (20:1→15:1→10:1→5:1→0:1 petrol:EtOAc) gave the title compounds (***E*-** and ***Z*-240**) as colourless oils (821 g, 1.32 mmol, 60%, 3:1 (*E*):(*Z*)) along with some of the homodimer compounds (**238** and **239**), truncated products (**241** and **237**) and recovered starting materials; triethyl(((3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-yl)oxy)silane (**212**) (190 mg, 0.52 mmol, 24%) and (*R*)-2-((*S*)-1-(4-bromobenzyloxy)but-3-enyl)oxirane (**205**) (364 mg, 1.31 mmol, 15%). Further purification using flash column chromatography with $AgNO_3$ impregnated silica (1:0→50:1→25:1→10:1 DCM:EtOAc) enabled separation of the (*E*) and (*Z*) isomers.

1. (((3*S*,4*R*,9*S*,*E*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane (***E*-240**) (614 mg, 0.99 mmol, 45%): $R_f$ 0.33 (4:1 petrol:diethyl ether); $R_f$ 0.87 ($AgNO_3$ impregnated TLC plates 6:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2957s (CH), 1613m (C=C), 1513s, 1463s, 1248s, 1012s, 972s, 822s, 742s; $\delta_H$ (500 MHz, $CDCl_3$) 0.62 (6H, q, *J*=8.0 Hz, Si(C**H**$_2$CH$_3$)$_3$), 0.91 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 0.97 (9H, t, *J*=8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$), 1.46–1.66 (2H, m, C**H**$_2$CH$_3$), 2.29 (2H, dd, *J*=6.5, 6.0 Hz, C**H**$_2$CHOPMB), 2.32–2.43 (2H, m, C**H**$_2$CHOPBB), 2.73 (1H, dd, *J*=5.0, 3.0 Hz, C**H**H'O(CH)), 2.76 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.96 (1H, ddd, *J*=7.5, 4.0, 3.0 Hz, CH$_2$O(C**H**)), 3.28–3.37 (2H, m, C**H**OPMB, C**H**OPBB), 3.69 (1H, dt, *J*=6.5, 4.0 Hz, C**H**OTES), 3.80 (3H, s, OC**H**$_3$), 4.45 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.46 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.55 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.57 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 5.56 (1H, dt, *J*=15.5, 6.5 Hz, C**H**=CH), 5.62 (1H, dt, *J*=15.5, 6.5 Hz, CH=C**H**), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.0 Hz, Ar**H**), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=8.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 5.2 (Si(**C**H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$**C**H$_3$)$_3$), 9.8 (CH$_2$**C**H$_3$), 25.8 (**C**H$_2$CH$_3$), 34.0 (**C**H$_2$CHOPMB), 36.0 (**C**H$_2$CHOPBB), 45.3 (**C**H$_2$O(CH)), 53.1 (CH$_2$O(**C**H)), 55.3 (O**C**H$_3$), 71.4 (**C**H$_2$Ar), 71.9 (**C**H$_2$Ar), 75.0 (**C**HOTES), 77.9 (**C**HOPBB), 81.5 (**C**HOPMB), 113.6 (Ar), 121.4 (Ar), 127.0 (**C**H=CH), 129.1 (Ar), 129.3 (Ar), 130.4 (CH=**C**H), 131.0 (Ar), 131.4 (Ar), 137.5 (Ar) 159.0 (Ar); *m*/*z* (ES$^+$) 643 (M+Na$^+$, 100%), 641 (M+Na$^+$, 100), 638 (M+NH$_4^+$, 45), 636 (M+NH$_4^+$, 40); Accurate mass (ES$^+$): Found 643.2243, $C_{32}H_{47}{}^{81}BrNaO_5Si$ (M+Na$^+$) requires 643.2254, Found 641.2261, $C_{32}H_{47}{}^{79}BrNaO_5Si$ (M+Na$^+$) requires 641.2268; $[\alpha]_D^{25}$ –13.8 (c = 1.0 in $CHCl_3$).

2. (((3*S*,4*R*,9*S*,*Z*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane (***Z*-240**) (210 mg, 0.34 mmol, 15%): $R_f$ 0.33 (4:1 petrol:diethyl ether); $R_f$ 0.77 ($AgNO_3$ impregnated TLC plates 6:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2957s (CH), 2911s, 2876s, 1613m (C=C), 1513s, 1462s, 1248s, 973s, 822s, 741s; $\delta_H$ (500 MHz, $CDCl_3$) 0.62 (6H, q, *J*=8.0 Hz, Si(C**H**$_2$CH$_3$)$_3$), 0.92 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 0.97 (9H, t, *J*=8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$),

1.45–1.68 (2H, m, C**H**$_2$CH$_3$), 2.32 (2H, dd, *J*=7.0, 6.5 Hz, C**H**$_2$CHOPMB), 2.40–2.45 (2H, m, C**H**$_2$CHOPBB), 2.73 (1H, dd, *J*=5.0, 3.0 Hz, C**H**H'O(CH)), 2.76 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.96 (1H, ddd, *J*=7.5, 4.0, 3.0 Hz, CH$_2$O(C**H**)), 3.33–3.39 (2H, m, C**H**OPMB, C**H**OPBB), 3.70 (1H, dt, *J*=7.0, 4.0 Hz, C**H**OTES), 3.80 (3H, s, OC**H**$_3$), 4.44 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.46 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.57 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.57 (1H, *J*=11.0 Hz, CH**H'**Ar), 5.58 (1H, dt, *J*=10.5, 7.0 Hz C**H**=CH), 5.64 (1H, dt, *J*=10.5, 7.0 Hz CH=C**H**), 6.86 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.0 Hz, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz, Ar**H**), 7.45 (2H, d, *J*=8.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 5.1 (Si**C**H$_2$CH$_3$), 7.0 (SiCH$_2$**C**H$_3$), 10.0 (CH$_2$**C**H$_3$), 25.9 (**C**H$_2$CH$_3$), 28.9 (**C**H$_2$CHOPMB), 30.7 (**C**H$_2$CHOPBB), 45.2 (**C**H$_2$O(CH)), 53.2 (CH$_2$O(**C**H)), 55.3 (O**C**H$_3$), 71.5 (**C**H$_2$Ar), 72.1 (**C**H$_2$Ar), 75.2 (**C**HOTES), 77.7 (**C**HOPBB), 81.7 (**C**HOPMB), 113.7 (Ar), 121.4 (Ar), 125.7 (**C**H=CH), 129.1 (CH=**C**H), 129.1 (Ar), 129.2 (Ar), 131.0 (Ar), 131.4 (Ar), 137.5 (Ar) 159.0 (Ar); *m/z* (ES$^+$) 643 (M+Na$^+$, 100%), 641 (M+Na$^+$, 100); Accurate mass (ES$^+$): Found 643.2256, $C_{32}H_{47}{}^{81}BrNaO_5Si$ (M+Na$^+$) requires 643.2254, Found 641.2272, $C_{32}H_{47}{}^{79}BrNaO_5Si$ (M+Na$^+$) requires 641.2268; $[\alpha]_D^{25}$ -4.8 (c = 1.0 in $CHCl_3$).

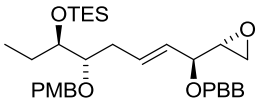
***(5R,6S,11S,12R,E)-3,3,5,12,14,14-Hexaethyl-6,11-bis(4-methoxybenzyloxy)-4,13-dioxa-3,14-disilahexadec-8-ene* (238)**




Isolated as a by-product during cross metathesis reactions and contaminated with a trace of the *Z*-isomer; $R_f$ 0.68 (4:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2961s (CH), 2911s, 2876s, 1613m (C=C), 1514s, 1463s, 1248s, 1097s, 1010s, 822s, 741s; $\delta_H$ (400 MHz, $CDCl_3$) 0.62 (12H, q, *J*=8.0 Hz, 2 × Si(C**H**$_2$CH$_3$)$_3$), 0.92 (6H, t, *J*=7.5 Hz, 2 × CH$_2$C**H**$_3$), 0.97 (18H, t, *J*=8.0 Hz, 2 × Si(CH$_2$C**H**$_3$)$_3$), 1.44–1.67 (4H, m, 2 × C**H**$_2$CH$_3$), 2.22–2.40 (4H, m, 2 × C**H**$_2$CHOPMB), 3.32–3.41 (2H, m, 2 × C**H**OPMB), 3.66–3.72 (2H, m, 2 × C**H**OTES), 3.80 (6H, s, 2 × OC**H**$_3$), 4.48 (2H, d, *J*=11.0 Hz, 2 × C**H**H'Ar), 4.56 (2H, d, *J*=11.0 Hz, 2 × CH**H'**Ar), 5.53–5.59 (2H, m,

C**H**=C**H**), 6.86 (4H, d, *J*=8.5 Hz, Ar**H**), 7.26 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 5.2 (Si(**C**$H_2CH_3)_3$), 7.0 (Si($CH_2$**C**$H_3)_3$), 9.8 ($CH_2$**C**$H_3$), 25.7 (**C**$H_2CH_3$), 34.0 (**C**$H_2$CHOPMB), 55.2 (O**C**$H_3$), 71.9 (**C**$H_2$Ar), 75.1 (**C**HOTES), 81.9 (**C**HOPMB), 113.6 (Ar), 127.9 (**C**H=**C**H), 129.3 (Ar), 131.1 (Ar), 159.0 (Ar); *m/z* ($ES^+$) 723 ($M+Na^+$, 100%), 718 ($M+NH_4^+$, 100); Accurate mass ($ES^+$): Found 718.4889, $C_{40}H_{72}NO_6Si_2$ ($M+NH_4^+$) requires 718.4893; $[\alpha]_D^{25}$ -16.3 (c = 1.0 in $CHCl_3$).

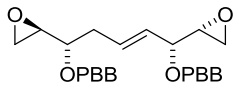
***(((3R,4S,8S,E)-8-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-8-((R)-oxiran-2-yl)oct-6-en-3-yl)oxy)triethylsilane* (241)**




Isolated as a by-product during cross metathesis reactions; $R_f$ 0.34 (4:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2957s (CH), 2913s, 2876s, 1613m (C=C), 1514s, 1463s, 1248s, 1071s, 1012s, 974s, 822s, 807, 742s; $\delta_H$ (400 MHz, $CDCl_3$) 0.62 (6H, q, *J*=8.0 Hz, Si(C**H**$_2$$CH_3)_3$), 0.93 (3H, t, *J*=7.5 Hz, $CH_2$C**H**$_3$), 0.97 (9H, t, *J*=8.0 Hz, Si($CH_2$C**H**$_3)_3$), 1.47–1.68 (2H, m, C**H**$_2$$CH_3$), 2.35–2.40 (2H, m, C**H**$_2$CHOPMB), 2.68 (1H, dd, *J*=5.5, 3.0 Hz, C**H**H'O(CH)), 2.75 (1H, dd, *J*=5.5, 4.0 Hz, CH**H'**O(CH)), 3.06 (1H, ddd, *J*=6.5, 4.0, 3.0 Hz, $CH_2$O(C**H**)), 3.35–3.41 (1H, m, C**H**OPMB), 3.71 (1H, dt, *J*=6.5, 4.5 Hz, C**H**OTES), 3.78 (3H, s, OC**H**$_3$), 3.79–3.82 (1H, m, C**H**OPBB), 4.35 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.46 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.50 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.57 (1H, *J*=11.0 Hz, CH**H'**Ar), 5.48 (1H, dd, *J*=15.5, 8.0 Hz, CHOPBBC**H**=C), 5.82 (1H, dt, *J*=15.5, 7.0 Hz $CH_2$C**H**=C), 6.84 (2H, d, *J*=8.5 Hz, Ar**H**), 7.16 (2H, d, *J*=8.5 Hz, Ar**H**), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**), 7.44 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 5.1 (Si(**C**$H_2CH_3)_3$), 7.0 (Si($CH_2$**C**$H_3)_3$), 9.7 ($CH_2$**C**$H_3$), 26.0 (**C**$H_2CH_3$), 33.6 (**C**$H_2$CHOPMB), 44.5 (**C**$H_2$O(CH)), 53.3 ($CH_2$O(**C**H)), 55.2 (O**C**$H_3$), 69.5 (**C**$H_2$Ar), 71.8 (**C**$H_2$Ar), 74.9 (**C**HOTES), 79.0 (**C**HOPBB), 81.2 (**C**HOPMB), 113.6 (Ar), 121.3 (Ar), 127.6 (CHOPBB**C**H=C), 129.2 (Ar), 129.3 (Ar), 130.8 (Ar), 131.4 (Ar), 134.1 ($CH_2$**C**H=C), 137.5 (Ar) 159.0 (Ar); *m/z* ($ES^+$) 629 ($M+Na^+$, 100%), 627 ($M+Na^+$, 100), 624 ($M+NH_4^+$, 15), 622 ($M+NH_4^+$, 10); Accurate mass ($ES^+$): Found 629.2097,

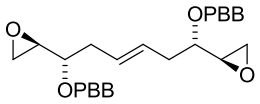
$C_{31}H_{45}{}^{81}BrNaO_5Si$ (M+$Na^+$) requires 629.2093, Found 627.2112, $C_{31}H_{45}{}^{79}BrNaO_5Si$ (M+$Na^+$) requires 627.2112; $[\alpha]_D^{25}$ +1.8 (c = 0.73 in $CHCl_3$).

***(2R,2'R)-2,2'-((1S,5S,E)-1,5-Bis(4-bromobenzyloxy)pent-2-ene-1,5-diyl)bis(oxirane)* (237)**




Isolated as a by-product during cross metathesis reactions; $R_f$ 0.10 (4:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2992s (CH), 2923s, 2865s, 1639m (C=C), 1593s, 1488s, 1070s, 1012s, 804s; $\delta_H$ (400 MHz, $CDCl_3$) 2.37–2.56 (2H, m, C**H**$_2$CHOPBB), 2.66 (1H, dd, *J*=5.0, 2.5 Hz, C**H**H'O(CH)), 2.74 (1H, dd, *J*=5.0, 2.5 Hz, C**H**H'O(CH)), 2.77 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.82 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.95–2.98 (1H, m, $CH_2O$(C**H**)), 3.04–3.08 (1H, m, $CH_2O$(C**H**)), 3.34 (1H, dt, *J*=7.0, 5.0 Hz, $CH_2$C**H**OPBB), 3.77 (1H, dd, *J*=8.0, 4.0 Hz, C=CHC**H**OPBB), 4.38 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.47 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.53 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.61 (1H, *J*=12.0 Hz, CH**H'**Ar), 5.56 (1H, dd, *J*=15.5, 8.0 Hz, C=C**H**CHOPBB), 5.81 (1H, dt, *J*=15.5, 7.0 Hz, C=C**H**$CH_2$), 7.17 (2H, d, *J*=8.0 Hz, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**), 7.45 (2H, d, *J*=8.0 Hz, Ar**H**), 7.45 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 35.6 (**C**$H_2$CHOPBB), 44.7 (**C**$H_2$O(CH)), 45.6 (**C**$H_2$O(CH)), 53.0 ($CH_2$O(**C**H)), 53.3 ($CH_2$O(**C**H)), 69.6 (**C**$H_2$Ar), 71.4 (**C**$H_2$Ar), 77.7 ($CH_2$**C**HOPBB), 79.0 (C=CH**C**HOPBB), 121.4 (Ar), 121.6 (Ar), 129.0 (C=**C**HCHOPBB), 129.2 (Ar), 129.2 (Ar), 131.5 (Ar), 131.5 (Ar), 131.6 (C=**C**H$CH_2$), 137.2 (Ar), 137.2 (Ar); *m/z* (ES$^+$) 549 (M+$Na^+$, 55%), 547 (M+$Na^+$, 100), 545 (M+$Na^+$, 60), 542 (M+$NH_4^+$, 15); Accurate mass (ES$^+$): Found 548.9886, $C_{23}H_{24}{}^{81}Br_2NaO_4$ (M+$Na^+$) requires 548.9894, found 546.9901, $C_{23}H_{24}{}^{81}Br^{79}BrNaO_4$ (M+$Na^+$) requires 546.9915, found 544.9926, $C_{23}H_{24}{}^{79}Br_2NaO_4$ (M+$Na^+$) requires 544.9934; $[\alpha]_D^{25}$ +15.3 (c = 0.91 in $CHCl_3$).

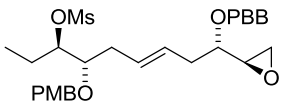
***(1S,6S,E)-1,6-Bis(4-bromobenzyloxy)-1,6-di((R)-oxiran-2-yl)hex-3-ene* (239)**

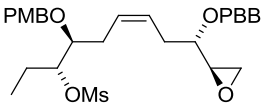



Isolated as a by-product during cross metathesis reactions; $R_f$ 0.09 (2:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2993s (CH), 2923s, 2869s, 1640m (C=C), 1592s, 1487s, 1267s, 1070s, 1011s, 927s, 804s, 736s; $\delta_H$ (400 MHz, $CDCl_3$) 2.32–2.47 (4H, m, 2 × C**H**$_2$CH=C), 2.71 (2H, dd, *J*=5.0, 2.5 Hz, 2 × C**H**H'O(CH)), 2.77 (2H, dd, *J*=5.0, 4.0 Hz, 2 × CH**H'**O(CH)), 2.93–2.99 (2H, m, 2 × CH$_2$O(C**H**)), 3.26–3.33 (2H, m, 2 × C**H**OPBB), 4.45 (2H, d, *J*=12.0 Hz, 2 × C**H**H'Ar), 4.58 (2H, d, *J*=12.0 Hz, 2 × CH**H'**Ar), 5.59–5.69 (2H, m, C**H**=C**H**), 7.18 (4H, d, *J*=8.0 Hz, Ar**H**), 7.45 (4H, d, *J*=8.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 36.0 (**C**H$_2$CH=C), 45.5 (**C**H$_2$O(CH)), 53.1 (CH$_2$O(**C**H)), 71.3 (**C**H$_2$Ar), 77.9 (**C**HOPBB), 121.4 (Ar), 128.4 (**C**H=**C**H), 129.2 (Ar), 131.4.5 (Ar), 137.4 (Ar); *m/z* ($ES^+$) 563 ($M+Na^+$, 65%), 561 ($M+Na^+$, 100), 559 ($M+Na^+$, 75), 558 ($M+NH_4^+$, 15), 556 ($M+NH_4^+$, 25), 554 ($M+NH_4^+$, 15); Accurate mass ($ES^+$): Found 563.0035, $C_{24}H_{26}{}^{81}Br_2NaO_4$ ($M+Na^+$) requires 563.0056, found 561.0059, $C_{24}H_{26}{}^{81}Br^{79}BrNaO_4$ ($M+Na^+$) requires 561.0071, found 559.0081, $C_{24}H_{26}{}^{79}Br_2NaO_4$ ($M+Na^+$) requires 559.0090; $[\alpha]_D^{25}$ -2.1 (c = 1.0 in $CHCl_3$).

***(3R,4S,9S,E)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((R)-oxiran-2-yl)non-6-en-3-yl methanesulfonate* (*E*-243)**

***(3R,4S,9S,Z)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((R)-oxiran-2-yl)non-6-en-3-yl methanesulfonate* (*Z*-243)**




Prepared according to the **general cross metathesis procedure** (**Page 170**) with (3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-yl methanesulfonate (**213**) (109 mg, 0.33 mmol) and heating at 40 °C for 60 h after catalyst addition. Purification by flash column chromatography

(10:1→7:1→5:1→3:1→1:1→1:2→0:1 petrol:diethyl ether) gave the two title compounds (***E*-** and ***Z*-243**) as a colourless oil (128 mg, 0.22 mmol, 67% mixture of 4:1 (*E*):(*Z*)), along with some of the homodimer compounds and recovered starting materials; (3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-yl methanesulfonate (**213**) (12 mg, 0.04 mmol, 11%) and (*R*)-2-((*S*)-1-(4-bromobenzyloxy)but-3-enyl)oxirane (**205**) (207 mg, 0.74 mmol, 56%). Further purification using flash column chromatography with $AgNO_3$ impregnated silica (50:1→25:1→10:1→5:1 DCM:EtOAc) enabled separation of the (*E*) and (*Z*) isomers.

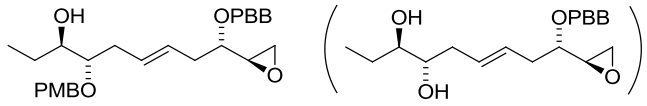
1. (3*R*,4*S*,9*S*,*E*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl methanesulfonate (***E*-243**) (90 mg, 0.15 mmol, 46%): $R_f$ 0.83 (1:1 petrol:diethyl ether); $R_f$ 0.73 ($AgNO_3$ impregnated TLC plates 6:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2971s (CH), 2936s, 2878s, 1613m (C=C), 1514s, 1344s, 1248s, 1172s, 1071s, 906s, 808s; $\delta_H$ (400 MHz, $CDCl_3$) 1.03 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.56–1.69 (1H, m, C**H**H'$CH_3$), 1.72–1.86 (1H, m, CH**H'**$CH_3$), 2.22–2.45 (4H, m, $C\mathbf{H}_2$CHOPMB, $C\mathbf{H}_2$CHOPBB), 2.71 (1H, dd, *J*=5.5, 2.5 Hz, C**H**H'O(CH)), 2.78 (1H, dd, *J*=5.5, 4.0 Hz, CH**H'**O(CH)), 2.95 (1H, ddd, *J*=6.5, 4.0, 2.5 Hz, $CH_2O(C\mathbf{H})$), 3.00 (3H, s, $SC\mathbf{H}_3$), 3.28 (1H, dt, *J*=6.5, 5.5 Hz, C**H**OPBB), 3.55 (1H, ddd, *J*=8.0, 5.0, 2.5 Hz, C**H**OPMB), 3.80 (3H, s, $OC\mathbf{H}_3$), 4.45 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.46 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.58 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.60 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.80 (1H, ddd, *J*=9.0, 4.0, 2.5 Hz, C**H**OMs), 5.52–5.64 (2H, m, C**H**=C**H**), 6.86 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=8.5 Hz, Ar**H**), 7.44 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 10.3 ($CH_2\mathbf{C}H_3$), 23.6 ($\mathbf{C}H_2CH_3$), 33.2 ($\mathbf{C}H_2$CHOPMB), 36.0 ($\mathbf{C}H_2$CHOPBB), 38.8 ($S\mathbf{C}H_3$), 45.6 ($\mathbf{C}H_2O$(CH)), 53.0 ($CH_2O(\mathbf{C}H)$), 55.3 ($O\mathbf{C}H_3$), 71.3 ($\mathbf{C}H_2$Ar), 71.9 ($\mathbf{C}H_2$Ar), 78.0 (**C**HOPBB), 79.5 (**C**HOPMB), 85.8 (**C**HOMs), 113.8 (Ar), 121.4 (Ar), 128.1 (**C**H=CH), 129.0 (CH=**C**H), 129.2 (Ar), 129.6 (Ar), 129.9 (Ar), 131.4 (Ar), 137.5 (Ar) 159.3 (Ar); *m/z* ($ES^+$) 607 ($M+Na^+$, 100%), 605 ($M+Na^+$, 95); Accurate mass ($ES^+$): Found 607.1155, $C_{27}H_{35}{}^{81}BrNaO_7S$ ($M+Na^+$) requires

607.1160, found 605.1170, $C_{27}H_{35}{}^{79}BrNaO_7S$ ($M+Na^+$) requires 605.1179; $[\alpha]_D^{25}$ -13.8 (c = 1.0 in $CHCl_3$).

2. (3*R*,4*S*,9*S*,*Z*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl methanesulfonate (***Z*-143**) (23 mg, 0.04 mmol, 12%): $R_f$ 0.83 (1:1 petrol:diethyl ether); $R_f$ 0.62 ($AgNO_3$ impregnated TLC plates 6:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2971s (CH), 2935s, 2878s, 1613m (C=C), 1513s, 1346s, 1248s, 1172s, 1071s, 906s, 808s; $\delta_H$ (400 MHz, $CDCl_3$) 1.03 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.54–1.66 (1H, m, C**H**H'$CH_3$), 1.71–1.85 (1H, m, CH**H'**$CH_3$), 2.26–2.47 (4H, m, $C\mathbf{H}_2$CHOPMB, $C\mathbf{H}_2$CHOPBB), 2.69 (1H, dd, *J*=5.5, 2.5 Hz, C**H**H'O(CH)), 2.77 (1H, dd, *J*=5.5, 4.0 Hz, CH**H'**O(CH)), 2.93 (1H, ddd, *J*=6.5, 4.0, 2.5 Hz, $CH_2O(C\mathbf{H})$), 3.01 (3H, s, $SC\mathbf{H}_3$), 3.28 (1H, dt, *J*=6.5, 5.5 Hz, C**H**OPBB), 3.56 (1H, dt, *J*=7.5, 5.0, 2.5 Hz, C**H**OPMB), 3.80 (3H, s, $OC\mathbf{H}_3$), 4.43 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.44 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.57 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.61 (1H, *J*=11.0 Hz, CH**H'**Ar), 4.81 (1H, ddd, *J*=9.5, 4.0, 2.5 Hz, C**H**OMs), 5.58 (1H, ddd, *J*=11.0, 6.5, 3.0 Hz C**H**=CH), 5.64 (1H, ddd, *J*=11.0, 6.5, 3.0 Hz CH=C**H**), 6.87 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**), 7.27 (2H, d, *J*=8.5 Hz, Ar**H**), 7.46 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 10.3 ($CH_2\mathbf{C}H_3$), 23.7 ($\mathbf{C}H_2CH_3$), 27.9 ($\mathbf{C}H_2$CHOPMB), 30.8 ($\mathbf{C}H_2$CHOPBB), 38.8 ($S\mathbf{C}H_3$), 45.7 ($\mathbf{C}H_2O$(CH)), 53.0 ($CH_2O(\mathbf{C}H)$), 55.3 ($O\mathbf{C}H_3$), 71.5 ($\mathbf{C}H_2$Ar), 72.0 ($\mathbf{C}H_2$Ar), 78.1 (**C**HOPBB), 79.6 (**C**HOPMB), 85.9 (**C**HOMs), 113.8 (Ar), 121.5 (Ar), 127.0 (**C**H=CH), 127.7 (CH=**C**H), 129.2 (Ar), 129.7 (Ar), 129.8 (Ar), 131.5 (Ar), 137.4 (Ar) 159.3 (Ar); *m/z* ($ES^+$) 607 ($M+Na^+$, 100%), 605 ($M+Na^+$, 95); Accurate mass ($ES^+$): Found 607.1155, $C_{27}H_{35}{}^{81}BrNaO_7S$ ($M+Na^+$) requires 607.1160, found 605.1173, $C_{27}H_{35}{}^{79}BrNaO_7S$ ($M+Na^+$) requires 605.1179; $[\alpha]_D^{21}$ +1.6 (c = 1.0 in $CHCl_3$).

***(3*R*,4*S*,9*S*,E)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-ol* (242)**

By-product: (3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-ene-3,4-diol



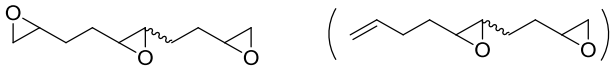

**Method 1:** To a solution of (((3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane (***E*-240**) (200 mg, 0.32 mmol) in dry THF (1.7 mL) was added tetrabutylammonium fluoride solution (0.38 mL, 1.0 M in THF, 0.38 mmol). The reaction mixture was stirred for 3 h and then quenched by slow addition of sat. aq. $NH_4Cl$ (2 mL) and diluted with EtOAc (6 mL). The aqueous layer was separated, extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed sequentially with $H_2O$ (10 mL), brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:1 petrol:EtOAc) gave (3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-ene-3,4-diol (12 mg, 0.03 mmol, 10%) and the title compound (**242**) as a colourless oil (75 mg, 0.15 mmol, 46%); $R_f$ 0.62 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3473m br (OH), 2962s (CH), 2933s, 2874s, 1612m (C=C), 1514s, 1249m, 1071s, 1011s, 808s; $\delta_H$ (400 MHz, $CDCl_3$) 0.97 (3H, t, *J*=7.0 Hz, $CH_2C\mathbf{H}_3$), 1.39–1.59 (2H, m, $C\mathbf{H}_2CH_3$), 2.10 (1H, br s, O**H**), 2.21–2.45 (4H, m, 2 × $C\mathbf{H}_2CH$=C), 2.70–2.74 (1H, m, C**H**H'O(CH)), 2.75–2.80 (1H, m, CH**H'**O(CH)), 2.93–2.99 (1H, m, $CH_2O(C\mathbf{H})$), 3.29 (1H, q, *J*=5.5 Hz, C**H**OPBB), 3.34–3.40 (1H, m, C**H**OPMB), 3.65 (1H, dt, *J*=8.0, 4.0 Hz, C**H**OH), 3.80 (3H, s, $OC\mathbf{H}_3$), 4.46 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.47 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.51 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.57 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 5.53–5.67 (2H, m, C**H**=C**H**), 6.87 (2H, d, *J*=7.0 Hz, Ar**H**), 7.19 (2H, d, *J*=7.5 Hz, Ar**H**), 7.24 (2H, d, *J*=7.5 Hz, Ar**H**), 7.45 (2H, d, *J*=7.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 10.5 ($CH_2\mathbf{C}H_3$), 25.1 ($\mathbf{C}H_2CH_3$), 32.5 ($\mathbf{C}H_2CH$=C), 36.0 ($\mathbf{C}H_2CH$=C), 45.5 ($\mathbf{C}H_2O(CH)$), 53.1 ($CH_2O(\mathbf{C}H)$), 55.3 ($O\mathbf{C}H_3$), 71.3 ($\mathbf{C}H_2Ar$), 71.5 ($\mathbf{C}H_2Ar$), 73.5 (**C**HOH), 78.0 (**C**HOPBB), 81.4 (**C**HOPMB), 113.8

(Ar), 121.4 (Ar), 127.5 (C=**C**H), 129.2 (Ar), 129.4 (Ar), 129.9 (C=**C**H), 130.5 (Ar), 131.4 (Ar), 137.5 (Ar), 159.2 (Ar); $m/z$ ($ES^+$) 529 ($M+Na^+$, 100%), 527 ($M+Na^+$, 100); Accurate mass ($ES^+$): Found 529.1384, $C_{26}H_{33}{}^{81}BrNaO_5$ ($M+Na^+$) requires 529.1385, found 527.1405, $C_{26}H_{33}{}^{79}BrNaO_5$ ($M+Na^+$) requires 527.1404; $[\alpha]_D^{25}$ -0.8 (c = 1.0 in $CHCl_3$). By-product (3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-ene-3,4-diol; $R_f$ 0.20 (1:1 petrol:EtOAc); $m/z$ ($ES^+$) 409 ($M+Na^+$, 100%), 407 ($M+Na^+$, 100%).

**Method 2:** Cross metathesis according to the **general cross metathesis procedure** (**Page 170**) with (3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-ol (**211**) (150 mg, 0.60 mmol) and purification by flash column chromatography (10:1 petrol:EtOAc) gave the title compound (**242**) as a colourless oil (112 mg, 0.22 mmol, 36% mixture of (*E*) and (*Z*)); data for (*E*)-isomer as above.

**2,3-Bis(2-(oxiran-2-yl)ethyl)oxirane[106] (247)**

By-product: 2-(but-3-en-1-yl)-3-(2-(oxiran-2-yl)ethyl)oxirane



*According to the modified procedure of Kakuchi et al.*[106]: To a solution of *m*-chloroperbenzoic acid (8.22 g, 47.7 mmol) in chloroform (90 mL) was added a solution of 1,5,9-decatriene (**246**) (2.15 mL, 1.65 g, 12.1 mmol) in chloroform (30 mL) at 0 °C. The reaction mixture was stirred for 4 days at 0 °C and then 10% aq. $Na_2SO_3$ (20 mL) was added until no peracid was present (as indicated by starch-iodide paper). The layers were separated and the aqueous layer was extracted with chloroform (3 × 100 mL). The combined organic layers were washed sequentially with 5% aq. $Na_2CO_3$ (100 mL) and water (100 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by vacuum distillation (b.p. 80–86 °C/0.15 mmHg (lit. 135–136 °C/1.0 mmHg)[106]) and then flash column chromatography (2:1→0:1 30–40 petrol:diethyl ether) gave 2-(but-3-en-1-yl)-3-(2-(oxiran-2-yl)ethyl)oxirane (220 mg, 1.31 mmol, 11%) and the title compound (**247**) as a colourless oil (1.60 g, 8.69 mmol, 72%); $R_f$ 0.05 (5:1 petrol:diethyl ether); $\delta_H$ as a mixture of diastereomers

(500 MHz, $CDCl_3$) 1.46–1.62 (8H, m, 2 × C**H**$_2$C**H**$_2$), 2.37–2.48 (2H, m, 2 × C**H**H'O(CH)), 2.64–2.75 (3H, m, 2 × CH**H'**O(CH), C**H**O(CH)), 2.82–2.97 (3H, m, 2 × CHH'O(C**H**), CHO(C**H**)); $\delta_C$ as an incomplete assignment of a mixture of diastereomers (125 MHz, $CDCl_3$) 24.1 (**C**H$_2$CH$_2$), 24.1 (**C**H$_2$CH$_2$), 24.5 (**C**H$_2$CH$_2$), 28.3 (**C**H$_2$CH$_2$), 28.7 (**C**H$_2$CH$_2$), 29.2 (**C**H$_2$CH$_2$), 29.4 (**C**H$_2$CH$_2$), 29.7 (**C**H$_2$CH$_2$), 47.0 (**C**H$_2$O(CH)), 47.1 (**C**H$_2$O(CH)), 51.5 (CH$_2$O(**C**H)), 51.5 (CH$_2$O(**C**H)), 51.5 (CH$_2$O(**C**H)), 51.8 (CH$_2$O(**C**H)), 56.4 (**C**HO(CH)), 56.5 (**C**HO(CH)), 56.7 (**C**HO(CH)), 56.7 (**C**HO(CH)), 57.9 (**C**HO(CH)), 58.0 (**C**HO(CH)), 58.2 (**C**HO(CH)), 58.3 (**C**HO(CH)); *m*/*z* (ES$^+$) 207 (M+Na$^+$, 100%). By-product: 2-(but-3-en-1-yl)-3-(2-(oxiran-2-yl)ethyl)oxirane; *m*/*z* (ES$^+$) 191 (M+Na$^+$, 100%).

***2-(5'-(Hydroxymethyl)octahydro-[2,2'-bifuran]-5-yl)acetonitrile* (248)**

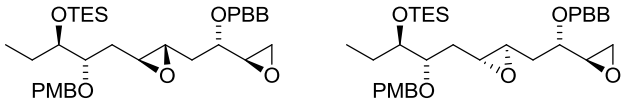
***(5'-(Ethoxymethyl)octahydro-[2,2'-bifuran]-5-yl)methanol* (249)**


To a solution of 2,3-bis(2-(oxiran-2-yl)ethyl)oxirane (**247**) (50 mg, 0.27 mmol) in ethanol (0.2 mL) were added $H_2O$ (0.4 mL) and sodium cyanide (13 mg, 0.27 mmol). The reaction mixture was stirred at RT for 20 h and then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (2 mL) and filtered through a pad of silica, washing with EtOAc. The filtrate was concentrated *in vacuo* and purification by flash column chromatography (EtOAc→EtOAc+10% IPA→EtOAc+10% MeOH) gave a inseparable mixture of the two title compounds (**248** and **249**) as a colourless oil (33 mg total; 0.12 mmol cyano 46%; 0.03 mmol ethoxy 11%); $R_f$ 0.24 (EtOAc); $\delta_H$ as a 4:1 mixture of **248**:**249** and a mixture of diastereomers (500 MHz, $CDCl_3$) 1.20 (3H, t, *J*=7.0 Hz, CH$_2$C**H**$_3$ ethoxy), 1.57–2.33 (18H, m, 2 × C**H**$_2$C**H**$_2$, O**H** cyano + ethoxy), 2.53–2.71 (2H, m, C**H**$_2$CN cyano), 3.38–3.57 (6H, m, C**H**H'OH cyano + ethoxy, C**H**$_2$OC**H**$_2$ ethoxy), 3.69–3.81 (2H, m, CH**H'**OH cyano + ethoxy), 3.84–4.32 (8H, m, 2 × C**H**OC**H** cyano + ethoxy); $\delta_C$ a tentative, incomplete assignment of a 4:1 mixture of **248**:**249** and a mixture of diastereomers (125 MHz, $CDCl_3$) 15.1 (CH$_2$**C**H$_3$ ethoxy), 15.1 (CH$_2$**C**H$_3$ ethoxy), 24.1 (**C**H$_2$CN cyano), 24.1

(**C**$H_2$CN cyano), 24.2 (**C**$H_2$CN cyano), 24.3 (**C**$H_2$CN cyano), 27.1 (**C**$H_2CH_2$), 27.1 (**C**$H_2CH_2$), 27.2 (**C**$H_2CH_2$), 27.3 (**C**$H_2CH_2$), 27.4 (**C**$H_2CH_2$), 27.4 (**C**$H_2CH_2$), 27.4 (**C**$H_2CH_2$), 27.5 (**C**$H_2CH_2$), 27.7 (**C**$H_2CH_2$), 28.4 (**C**$H_2CH_2$), 28.5 (**C**$H_2CH_2$), 28.7 (**C**$H_2CH_2$), 28.8 (**C**$H_2CH_2$), 28.9 (**C**$H_2CH_2$), 29.7 (**C**$H_2CH_2$), 30.3 (**C**$H_2CH_2$), 30.5 (**C**$H_2CH_2$), 31.5 (**C**$H_2CH_2$), 64.5 (**C**$H_2$OH), 64.5 (**C**$H_2$OH), 64.9 (**C**$H_2$OH), 65.1 (**C**$H_2$OH), 65.3 (**C**$H_2$OH), 65.4 (**C**$H_2$OH), 66.8 (**C**$H_2CH_3$ ethoxy), 66.8 (**C**$H_2CH_3$ ethoxy), 74.2 (**C**H$CH_2$CN cyano), 74.5 (**C**H$CH_2$CN cyano), 74.6 (**C**$H_2$OEt ethoxy), 74.6 (**C**H$CH_2$CN cyano), 74.7 (**C**H$CH_2$CN cyano), 74.7 (**C**$H_2$OEt ethoxy), 80.0 (**C**HO(CH)), 80.1 (**C**HO(CH)), 80.1 (**C**HO(CH)), 80.2 (**C**HO(CH)), 80.7 (**C**HO(CH)), 80.9 (**C**HO(CH)), 81.1 (**C**HO(CH)), 81.5 (**C**HO(CH)), 81.6 (**C**HO(CH)), 81.7 (**C**HO(CH)), 81.7 (**C**HO(CH)), 81.9 (**C**HO(CH)), 82.0 (**C**HO(CH)), 82.0 (**C**HO(CH)), 82.1 (**C**HO(CH)), 82.3 (**C**HO(CH)), 82.6 (**C**HO(CH)), 82.7 (**C**HO(CH)), 83.1 (**C**HO(CH)), 117.3 (**C**≡N cyano), 117.4 (**C**≡N cyano), 117.4 (**C**≡N cyano), 117.5 (**C**≡N cyano); *m/z* ($ES^+$) 253 ($M+Na^+$ ethoxy, 100%), 234 ($M+Na^+$ cyano, 85), 212 ($M+H^+$ cyano, 10).

***(((2S,3R)-1-((2S,3S)-3-((S)-2-(4-Bromobenzyloxy)-2-((R)-oxiran-2-yl)ethyl)oxiran-2-yl)-2-(4-methoxybenzyloxy)pentan-3-yl)oxy)triethylsilane*** **(264)**

***(((2S,3R)-1-((2R,3R)-3-((S)-2-(4-Bromobenzyloxy)-2-((R)-oxiran-2-yl)ethyl)oxiran-2-yl)-2-(4-methoxybenzyloxy)pentan-3-yl)oxy)triethylsilane*** **(265)**




*According to the modified procedure of Nieto et al.*[115a]: (((3*R*,4*S*,9*S*,*E*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane (**240**) (23 mg, 0.04 mmol) and (5*R*,8*S*,9*S*)-2,2-dimethyl-10-oxo-1,3,6-trioxaspiro[4.5]decane-8,9-diyl diacetate (**267**) (3.4 mg, 0.01 mmol) were dissolved in acetonitrile (0.23 mL) and dimethoxymethane (0.46 mL). Tetrabutylammonium hydrogensulfate (cat.) and pH 6 buffer (0.14 mL) were added slowly with stirring and the reaction mixture was cooled to 0 °C. Oxone® (37 mg, 0.06 mmol) in pH 6 buffer

(0.24 mL) and potassium carbonate (12 mg, 0.09 mmol) in $H_2O$ (0.24 mL) were added simultaneously *via* syringe pumps over 12 h and the reaction mixture was stirred at 0 °C for a further 18 h. The reaction mixture was quenched by addition of $H_2O$ (1 mL) and pentane (1 mL) and then diluted with DCM (5 mL). The layers were separated and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Flash column chromatography (10:1 petrol:EtOAc) gave recovered starting material (15 mg, 0.02 mmol, 57%) and an inseparable, impure mixture of the two title compounds (**264** and **265**) as a colourless oil (10 mg, <0.02 mmol, <42%, >15:1 2*S*,3*S*:2*R*,3*R*). Further purification by semi-preparative HPLC provided 3 mg of the major (2*S*,3*S*)-diastereomer for characterisation and a trace of the minor (2*R*,3*R*)-diastereomer for partial characterisation.

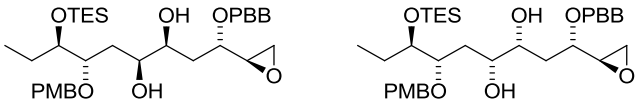
1. (((2*S*,3*R*)-1-((2*S*,3*S*)-3-((*S*)-2-(4-Bromobenzyloxy)-2-((*R*)-oxiran-2-yl)ethyl)oxiran-2-yl)-2-(4-methoxybenzyloxy)pentan-3-yl)oxy)triethylsilane (**264**): $R_f$ 0.73 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2957s (CH), 2912s, 2876s, 1514s, 1463s, 1248s, 1105s, 1071s, 1012s, 822s, 807s, 742s; $\delta_H$ (400 MHz, $CDCl_3$) 0.61 (6H, q, *J*=8.0 Hz, Si(C**H**$_2$CH$_3$)$_3$), 0.92 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 0.96 (9H, t, *J*=8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$), 1.40–1.48 (2H, m, C**H**H'CH$_3$, C**H**H'CHO), 1.49–1.56 (1H, m, CH**H'**CH$_3$), 1.60–1.67 (1H, m, C**H**H'CHO), 1.90–2.00 (2H, m, 2 × CH**H'**CHO), 2.73 (1H, dd, *J*=5.0, 3.0 Hz, C**H**H'O(CH)), 2.79 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.90–2.95 (2H, m, C**H**O(C**H**)), 2.98 (1H, ddd, *J*=6.5, 4.0, 3.0 Hz, CH$_2$O(C**H**)), 3.52–3.58 (2H, m, C**H**OPMB, C**H**OPBB), 3.74 (1H, ddd, *J*=7.5, 5.0, 3.0 Hz, C**H**OTES), 3.80 (3H, s, OC**H**$_3$), 4.47 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.51 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.65 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 4.66 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.87 (2H, d, *J*=9.0 Hz, Ar**H**), 7.21 (2H, d, *J*=8.0 Hz, Ar**H**), 7.27 (2H, d, *J*=9.0 Hz, Ar**H**), 7.46 (2H, d, *J*=8.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 5.1 (Si(**C**H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$**C**H$_3$)$_3$), 10.2 (CH$_2$**C**H$_3$), 26.3 (**C**H$_2$CH$_3$), 33.4 (**C**H$_2$CHO(CH)), 35.6 (**C**H$_2$CHO(CH)), 45.3 (**C**H$_2$O(CH)), 53.2 (CH$_2$O(**C**H)), 55.3 (O**C**H$_3$), 56.1 (**C**HO(CH)), 57.1 (CHO(**C**H)), 71.9 (**C**H$_2$Ar), 72.2 (**C**H$_2$Ar), 75.2 (**C**HOTES), 76.0 (**C**HOPBB), 79.8 (**C**HOPMB), 113.7 (Ar), 121.6 (Ar), 129.2

(Ar), 129.3 (Ar), 130.8 (Ar), 131.5 (Ar), 137.3 (Ar) 159.1 (Ar); *m/z* ($ES^+$) 695 ($M+MeCN+NH_4^+$, 20%), 693 ($M+MeCN+NH_4^+$, 20), 659 ($M+Na^+$, 100), 657 ($M+Na^+$, 100), 654 ($M+NH_4^+$, 20), 652 ($M+NH_4^+$, 15), 265 (25); Accurate mass ($ES^+$): Found 659.2199, $C_{32}H_{47}{}^{81}BrNaO_6Si$ ($M+Na^+$) requires 659.2199, found 657.2216, $C_{32}H_{47}{}^{79}BrNaO_6Si$ ($M+Na^+$) requires 657.2217; $[\alpha]_D^{25}$ -34.4 (c = 0.36 in $CHCl_3$).

2. (((2*S*,3*R*)-1-((2*R*,3*R*)-3-((*S*)-2-(4-Bromobenzyloxy)-2-((*R*)-oxiran-2-yl)ethyl)oxiran-2-yl)-2-(4-methoxybenzyloxy)pentan-3-yl)oxy)triethylsilane (**265**): $R_f$ 0.73 (1:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 0.61 (6H, q, *J*=8.0 Hz, $Si(C\mathbf{H}_2CH_3)_3$), 0.90 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 0.96 (9H, t, *J*=8.0 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 1.40–1.70 (4H, m, 2 × $C\mathbf{H}_2$), 1.74–1.96 (2H, m, $C\mathbf{H}_2$), 2.73 (1H, dd, *J*=5.0, 2.5 Hz, C**H**H'O(CH)), 2.81 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.82–2.88 (2H, m, C**H**O(C**H**)), 2.98 (1H, ddd, *J*=6.5, 4.0, 2.5 Hz, $CH_2O(C\mathbf{H})$), 3.37–3.52 (2H, m, C**H**OPMB, C**H**OPBB), 3.72–3.77 (1H, m, C**H**OTES), 3.80 (3H, s, $OC\mathbf{H}_3$), 4.41 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.45 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.56 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.60 (1H, *J*=12.0 Hz, CH**H'**Ar), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz, Ar**H**), 7.45 (2H, d, *J*=8.5 Hz, Ar**H**); *m/z* ($ES^+$) 695 ($M+MeCN+NH_4^+$, 35%), 693 ($M+MeCN+NH_4^+$, 30), 659 ($M+Na^+$, 100), 657 ($M+Na^+$, 95); Accurate mass ($ES^+$): Found 659.2203, $C_{32}H_{47}{}^{81}BrNaO_6Si$ ($M+Na^+$) requires 659.2199, found 657.2213, $C_{32}H_{47}{}^{79}BrNaO_6Si$ ($M+Na^+$) requires 657.2217.

***(1S,3S,4S,6S,7R)-1-(4-Bromobenzyloxy)-6-(4-methoxybenzyloxy)-1-((R)-oxiran-2-yl)-7-(triethylsilyloxy)nonane-3,4-diol* (271)**

***(1S,3R,4R,6S,7R)-1-(4-Bromobenzyloxy)-6-(4-methoxybenzyloxy)-1-((R)-oxiran-2-yl)-7-(triethylsilyloxy)nonane-3,4-diol* (272)**




**General SAD Procedure:** *According to the modified procedure of Nicolaou et al.*[118]: (((3*R*,4*S*,9*S*,*E*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane (***E*-240**) (553 mg, 0.89 mmol), methanesulfonamide (170 mg, 1.78 mmol), $(DHQ)_2PHAL$ (69 mg, 0.09 mmol), potassium hexacyanoferrate(III) (880 mg, 2.68 mmol) and potassium carbonate (370 mg, 2.68 mmol) were dissolved in a mixture of $^tBuOH/H_2O$ (20 mL, 1:1) and cooled to 0 °C with vigorous stirring. Potassium osmate(VI) dihydrate (3 mg, 9 μmol) was added and the reaction mixture was stirred for 96 h at 0 °C. Sodium sulfite (560 mg, 4.44 mmol) was added and the reaction mixture was stirred for 30 min at RT. $H_2O$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with aq. NaOH (10 mL, 0.1 M) and the aqueous layer was back extracted with EtOAc (15 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:1 petrol:EtOAc) gave the title compounds (**271** and **272**) as a partially separable mixture of colourless oils (511 mg, 0.78 mmol, 88%, 4:1 3*S*,4*S*:3*R*,4*R* diastereomers from crude $^1H$ NMR analysis).

1. (1*S*,3*S*,4*S*,6*S*,7*R*)-1-(4-Bromobenzyloxy)-6-(4-methoxybenzyloxy)-1-((*R*)-oxiran-2-yl)-7-(triethylsilyloxy)nonane-3,4-diol (**271**) (412 mg, 0.63 mmol, 71%); $R_f$ 0.38 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3443m br (OH), 2957s (CH), 2912s, 2875s, 1514s, 1463s, 1249m, 1012s, 808s, 741s; $\delta_H$ (400 MHz, $C_6D_6$) 0.60–0.75 (6H, m, $Si(C\mathbf{H}_2CH_3)_3$), 0.94 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.04 (9H, t, *J*=8.0 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 1.37–1.50 (1H, m, C**H**H'$CH_3$), 1.54–1.97 (5H, m, CH**H'**$CH_3$,

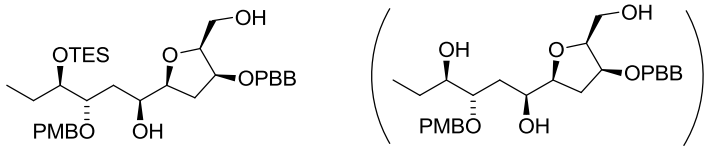
2 × C**H**$_2$CHOH), 2.30 (1H, dd, *J*=5.5, 4.0 Hz, C**H**H'O(CH)), 2.39 (1H, dd, *J*=5.5, 2.5 Hz, CH**H'**O(CH)), 2.61–2.66 (1H, m, CH$_2$O(C**H**)), 2.74 (1H, br s, O**H**), 2.86 (1H, br s, O**H**), 3.28 (3H, s, OC**H**$_3$), 3.58 (1H, ddd, *J*=8.5, 4.5, 3.5 Hz, C**H**OPBB), 3.74 (1H, dt, *J*=8.5, 2.5 Hz, C**H**OPMB), 3.77–3.85 (3H, m, 2 × C**H**OH, C**H**OTES), 4.17 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.36 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 4.43 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.62 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 6.91 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=8.5 Hz, Ar**H**), 7.28 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $C_6D_6$) 6.0 (Si(**C**H$_2$CH$_3$)$_3$), 7.7 (Si(CH$_2$**C**H$_3$)$_3$), 10.9 (CH$_2$**C**H$_3$), 27.3 (**C**H$_2$CH$_3$), 34.1 (**C**H$_2$CHOH), 37.2 (**C**H$_2$CHOH), 45.4 (**C**H$_2$O(CH)), 53.7 (CH$_2$O(**C**H)), 55.1 (O**C**H$_3$), 72.0 (**C**HOH), 72.4 (**C**HOH), 72.6 (**C**H$_2$Ar), 72.7 (**C**H$_2$Ar), 75.9 (**C**HOTES), 76.3 (**C**HOPBB), 80.0 (**C**HOPMB), 114.5 (Ar), 122.1 (Ar), 129.9 (Ar), 130.1 (Ar), 131.5 (Ar), 132.1 (Ar), 138.5 (Ar), 160.2 (Ar); *m/z* (ES$^+$) 677 (M+Na$^+$, 100%), 675 (M+Na$^+$, 100); Accurate mass (ES$^+$): Found 677.2311, $C_{32}H_{49}{}^{81}BrNaO_7Si$ (M+Na$^+$) requires 677.2305, found 675.2325, $C_{32}H_{49}{}^{79}BrNaO_7Si$ (M+Na$^+$) requires 675.2323; $[\alpha]_D^{25}$ -29.8 (c = 1.0 in $CHCl_3$).

2. (1*S*,3*R*,4*R*,6*S*,7*R*)-1-(4-Bromobenzyloxy)-6-(4-methoxybenzyloxy)-1-((*R*)-oxiran-2-yl)-7-(triethylsilyloxy)nonane-3,4-diol (**272**) (99 mg, 0.15 mmol, 17%); $R_f$ 0.50 (1:1 petrol:EtOAc); $\nu_{max}$/cm$^{-1}$ (thin film) 3464m br (OH), 2956s (CH), 2912s, 1514s, 1463s, 1071s, 1012s, 807s, 742s; $\delta_H$ (500 MHz, $C_6D_6$) 0.60–0.74 (6H, m, Si(C**H**$_2$CH$_3$)$_3$), 0.91 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.04 (9H, t, *J*=8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$), 1.32–1.42 (1H, m, C**H**H'CH$_3$), 1.51–1.64 (1H, m, CH**H'**CH$_3$), 1.86–2.05 (4H, m, 2 × C**H**$_2$CHOH), 2.29 (1H, dd, *J*=5.5, 4.0 Hz, C**H**H'O(CH)), 2.38 (1H, dd, *J*=5.5, 2.5 Hz, CH**H'**O(CH)), 2.69 (1H, ddd, *J*=7.5, 4.0, 2.5 Hz, CH$_2$O(C**H**)), 3.12 (1H, d, *J*=3.5 Hz, O**H**), 3.28 (3H, s, OC**H**$_3$), 3.41 (1H, dt, *J*=7.5, 5.0 Hz, C**H**OPBB), 3.56 (1H, ddd, *J*=8.0, 4.0, 2.0 Hz, C**H**OPMB), 3.76 (1H, ddd, *J*=7.5, 5.0, 2.0 Hz, C**H**OTES), 3.88–3.93 (2H, m, 2 × C**H**OH), 4.06 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.07 (1H, d, *J*=1.5 Hz, O**H**), 4.13 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.33 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.57 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.78 (2H, d, *J*=9.0 Hz, Ar**H**), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.23 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (125 MHz,

$C_6D_6$) 5.9 ($Si(\mathbf{C}H_2CH_3)_3$), 7.6 ($Si(CH_2\mathbf{C}H_3)_3$), 11.3 ($CH_2\mathbf{C}H_3$), 27.3 ($\mathbf{C}H_2CH_3$), 32.5 ($\mathbf{C}H_2CHOH$), 36.3 ($\mathbf{C}H_2CHOH$), 45.1 ($\mathbf{C}H_2O(CH)$), 53.4 ($CH_2O(\mathbf{C}H)$), 55.1 ($O\mathbf{C}H_3$), 72.0 ($\mathbf{C}H_2Ar$), 72.1 ($\mathbf{C}H_2Ar$), 72.8 (**C**HOH), 73.1 (**C**HOH), 76.1 (**C**HOTES), 78.1 (**C**HOPBB), 82.2 (**C**HOPMB), 114.6 (Ar), 122.2 (Ar), 130.0 (Ar), 130.3 (Ar), 131.0 (Ar), 132.1 (Ar), 138.1 (Ar), 160.3 (Ar); *m/z* ($ES^+$) 1331 ($2M+Na^+$, 65%), 1329 ($2M+Na^+$, 85), 1328 ($2M+Na^+$, 55), 677 ($M+Na^+$, 100), 675 ($M+Na^+$, 95); Accurate mass ($ES^+$): Found 677.2309, $C_{32}H_{49}{}^{81}BrNaO_7Si$ ($M+Na^+$) requires 677.2305, found 675.2309, $C_{32}H_{49}{}^{79}BrNaO_7Si$ ($M+Na^+$) requires 675.2323; $[\alpha]_D^{25}$ -21.9 (c = 1.0 in $CH_2Cl_2$).

***(1S,3S,4R)-1-((2S,4S,5S)-4-(4-Bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexan-1-ol* (273)**

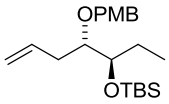
By-product: (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)hexane-1,4-diol (**274**)




**General CSA Cyclisation Procedure:** *According to the modified procedure of Wang et al.*[120a]: (1*S*,3*S*,4*S*,6*S*,7*R*)-1-(4-Bromobenzyloxy)-6-(4-methoxybenzyloxy)-1-((*R*)-oxiran-2-yl)-7-(triethylsilyloxy)nonane-3,4-diol (**271**) (347 mg, 0.53 mmol) was dissolved in DCM (8.5 mL) and cooled to 0 °C using a salt-ice bath. A cold solution of (±)-camphor-10-sulfonic acid (1.2 mg, 5 μmol) in DCM (1.2 mL) was added and the reaction mixture stirred at 0 °C for 3 h. Immediate purification by flash column chromatography by direct loading of the cold reaction mixture (1:1 petrol:EtOAc) gave recovered starting material (52 mg, 0.08 mmol, 15%), (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)hexane-1,4-diol (**274**) (22 mg, 0.04 mmol, 8%) and the title compound (**273**) as a colourless oil (246 mg, 0.38 mmol, 72%); $R_f$ 0.18 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3425s br (OH), 2956s (CH),

2911s, 2875s, 1514s, 1463m, 1248s, 1070s, 1012s, 821s, 7412s; $\delta_H$ (500 MHz, $C_6D_6$) 0.67–0.80 (6H, m, Si(C**H**$_2$CH$_3$)$_3$), 1.00 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.08 (9H, t, *J*=8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$), 1.47–1.57 (1H, m, C**H**H'CH$_3$), 1.57–1.73 (2H, m, C**H**H'CHOPBB, CH**H'**CH$_3$), 1.81–1.88 (3H, m, CH**H'**CHOPBB, C**H**$_2$CHOH), 2.45 (1H, br s, O**H**), 3.31 (3H, s, OC**H**$_3$), 3.34 (1H, br s, O**H**), 3.56–3.60 (1H, m, C**H**OPBB), 3.68 (1H, q, *J*=5.0 Hz, C**H**CH$_2$OH), 3.72 (1H, td, *J*=7.5, 5.0 Hz, CH(OH)C**H**OC), 3.75 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.79–3.84 (2H, m, C**H**$_2$OH), 3.88 (1H, ddd, *J*=7.5, 5.0, 2.0 Hz, C**H**OTES), 3.97 (1H, td, *J*=6.0, 2.0 Hz, C**H**OPMB), 3.99–4.06 (1H, m, C**H**OH), 4.02 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.58 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.74 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.78 (2H, d, *J*=8.5 Hz, Ar**H**), 6.81 (2H, d, *J*=8.5 Hz, Ar**H**), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**), 7.36 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 6.0 (Si(**C**H$_2$CH$_3$)$_3$), 7.8 (Si(CH$_2$**C**H$_3$)$_3$), 11.3 (CH$_2$**C**H$_3$), 27.5 (**C**H$_2$CH$_3$), 34.6 (**C**H$_2$CHOPBB), 35.4 (**C**H$_2$CHOH), 55.1 (O**C**H$_3$), 62.5 (**C**H$_2$OH), 70.8 (**C**H$_2$Ar), 70.9 (**C**HOH), 73.3 (**C**H$_2$Ar), 76.5 (**C**HOTES), 80.1 (**C**HOPMB), 80.4 (**C**HOPBB), 82.2 (**C**HCH$_2$OH), 82.4 (CH(OH)**C**HOC), 114.4 (Ar), 122.2 (Ar), 128.7 (Ar), 129.8 (Ar), 130.1 (Ar), 132.2 (Ar), 137.5 (Ar), 160.0 (Ar); *m/z* (ES$^+$) 1331 (2M+Na$^+$, 70%), 1329 (2M+Na$^+$, 100), 1327 (2M+Na$^+$, 100), 677 (M+Na$^+$, 100), 675 (M+Na$^+$, 100), 655 (M+H$^+$, 10), 653 (M+H$^+$, 10); Accurate mass (ES$^+$): Found 677.2312, $C_{32}H_{49}{}^{81}BrNaO_7Si$ (M+Na$^+$) requires 677.2305, found 675.2325, $C_{32}H_{49}{}^{79}BrNaO_7Si$ (M+Na$^+$) requires 675.2323; $[\alpha]_D^{25}$ -0.7 (c = 1.0 in $CH_2Cl_2$). By-product: (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)hexane-1,4-diol (**274**); $R_f$ 0.10 (1:1 petrol:EtOAc); *m/z* (ES$^+$) 563 (M+Na$^+$, 80%), 561 (M+Na$^+$, 80), 541 (M+H$^+$, 10), 539 (M+H$^+$, 10).

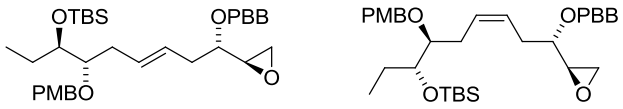
***tert*-Butyl(((3R,4S)-4-(4-methoxybenzyloxy)hept-6-en-3-yl)oxy)dimethylsilane (275)**




To a stirred solution of (3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-ol (**211**) (300 mg, 1.20 mmol) in dry DMF (10 mL) were added imidazole (245 mg, 3.60 mmol) and *tert*-butylchlorodimethylsilane (271 mg, 1.80 mmol). The reaction mixture was stirred at RT for 18 h and then heated to 60 °C for 5 h. The reaction mixture was allowed to cool to RT, quenched with $H_2O$ (20 mL) and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed sequentially with $H_2O$ (5 × 30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**275**) as a colourless oil (403 mg, 1.11 mmol, 92%); $R_f$ 0.47 (20:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3076m, 2957s (CH), 2931s (CH), 2857s (CH), 1641m (C=C), 1614s, 1514s, 1249s, 1095s, 1006s, 836s, 775s; $\delta_H$ (400 MHz, $CDCl_3$) 0.06 (3H, s, Si(C**H**$_3$)($CH_3$)), 0.07 (3H, s, Si($CH_3$)(C**H**$_3$)), 0.92 (9H, s, SiC(C**H**$_3$)$_3$), 0.92 (3H, t, *J*=7.5 Hz, $CH_2$C**H**$_3$), 1.43–1.71 (2H, m, C**H**$_2$$CH_3$), 2.33 (2H, dd, *J*=7.0, 6.0 Hz, C**H**$_2$CH=$CH_2$), 3.41 (1H, td, *J*=6.0, 4.0 Hz, C**H**OPMB), 3.69 (1H, dt, *J*=6.5, 4.0 Hz, C**H**OTBS), 3.81 (3H, s, OC**H**$_3$), 4.49 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.59 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 5.01–5.15 (2H, m, $CH_2$CH=C**H**$_2$), 5.90 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2$C**H**=$CH_2$), 6.87 (2H, d, *J*=8.5 Hz, Ar**H**), 7.28 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) -4.5 (Si(**C**$H_3$)($CH_3$)), -4.3 (Si($CH_3$)(**C**$H_3$)), 9.7 ($CH_2$**C**$H_3$), 18.2 (Si**C**($CH_3$)$_3$), 25.5 (**C**$H_2CH_3$), 26.0 (SiC(**C**$H_3$)$_3$), 35.4 (**C**$H_2$CH=$CH_2$), 55.3 (O**C**$H_3$), 72.0 (**C**$H_2$Ar), 74.9 (**C**HOTBS), 81.4 (**C**HOPMB), 113.6 (Ar), 116.4 ($CH_2$CH=**C**$H_2$), 129.3 (Ar), 131. 1(Ar), 136.0 ($CH_2$**C**H=$CH_2$), 159.0 (Ar); *m*/*z* ($ES^+$) 388 (95%), 387 (M+$Na^+$, 100); Accurate mass ($ES^+$): Found 387.2326, $C_{21}H_{36}NaO_3Si$ (M+$Na^+$) requires 387.2326; $[\alpha]_D^{25}$ -12.8 (c = 1.0 in $CHCl_3$).

***(((3*R*,4*S*,9*S*,E)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((R)-oxiran-2-yl)non-6-en-3-yl)oxy)(tert-butyl)dimethylsilane* (*E*-276)**

***(((3*R*,4*S*,9*S*,Z)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((R)-oxiran-2-yl)non-6-en-3-yl)oxy)(tert-butyl)dimethylsilane* (*Z*-276)**




Prepared according to the **general cross metathesis procedure** (**Page 170**) with *tert*-butyl(((3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-yl)oxy)dimethylsilane (**275**) (373 mg, 1.02 mmol) and heating at 40 °C for 48 h after catalyst addition. Purification by flash column chromatography (20:1→15:1→10:1→5:1→1:2 petrol:EtOAc) gave the two title compounds (***E*-** and ***Z*-276**) as a colourless oil (364 mg, 0.59 mmol, 58% mixture of 4:1 (*E*):(*Z*)), along with some of the homodimer compounds and recovered starting materials; *tert*-butyl(((3*R*,4*S*)-4-(4-methoxybenzyloxy)hept-6-en-3-yl)oxy)dimethylsilane (**275**) (110 mg, 0.30 mmol, 30%) and (*R*)-2-((*S*)-1-(4-bromobenzyloxy)but-3-enyl)oxirane (**205**) (170 mg, 0.60 mmol, 15%). Further purification using flash column chromatography with $AgNO_3$ impregnated silica (1:0→50:1→25:1→10:1 DCM:EtOAc) enabled separation of the (*E*) and (*Z*) isomers.

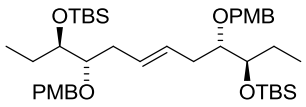
1. (((3*R*,4*S*,9*S*,*E*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (***E*-276**) (283 mg, 0.46 mmol, 45%): $R_f$ 0.30 (10:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2956s (CH), 2930s, 2857s, 1613m (C=C), 1513s, 1463s, 1248s, 1070s, 836s, 775s; $\delta_H$ (400 MHz, $CDCl_3$) 0.05 (3H, s, Si(C**H**$_3$)($CH_3$)), 0.06 (3H, s, Si($CH_3$)(C**H**$_3$)), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 0.88–0.92 (3H, m, $CH_2$C**H**$_3$), 1.43–1.69 (2H, m, C**H**$_2$$CH_3$), 2.28 (2H, t, *J*=6.0 Hz, C**H**$_2$CHOPMB), 2.32–2.43 (2H, m, C**H**$_2$CHOPBB), 2.73 (1H, dd, *J*=5.0, 2.5 Hz, C**H**H'O(CH)), 2.76 (1H, dd, *J*=5.0, 4.0 Hz, CH**H'**O(CH)), 2.94–2.99 (1H, m, $CH_2$O(C**H**)), 3.28–3.39 (2H, m, C**H**OPMB, C**H**OPBB), 3.68 (1H, dt, *J*=6.5, 4.0 Hz, C**H**OTBS), 3.80 (3H, s, OC**H**$_3$), 4.44 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.46 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.57 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.57

(1H, *J*=12.0 Hz, CH**H'**Ar), 5.55 (1H, dt, *J*=15.5, 6.5 Hz, C**H**=CH), 5.62 (1H, dt, *J*=15.5, 6.5 Hz, CH=C**H**), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**), 7.46 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) -4.5 (Si(**C**$H_3$)($CH_3$)), -4.2 (Si($CH_3$)(**C**$H_3$)), 9.7 ($CH_2$**C**$H_3$), 18.2 (Si**C**($CH_3$)$_3$), 25.7 (**C**$H_2CH_3$), 25.9 (SiC(**C**$H_3$)$_3$), 34.0 (**C**$H_2$CHOPMB), 36.0 (**C**$H_2$CHOPBB), 45.3 (**C**$H_2$O(CH)), 53.1 ($CH_2$O(**C**H)), 55.3 (O**C**$H_3$), 71.4 (**C**$H_2$Ar), 71.9 (**C**$H_2$Ar), 74.9 (**C**HOTBS), 77.9 (**C**HOPBB), 81.6 (**C**HOPMB), 113.6 (Ar), 121.4 (Ar), 127.0 (**C**H=CH), 129.2 (Ar), 129.2 (Ar), 130.6 (CH=**C**H), 131.1 (Ar), 131.4 (Ar), 137.5 (Ar) 159.0 (Ar); *m/z* ($ES^+$) 643 ($M+Na^+$, 100%), 641 ($M+Na^+$, 100), 638 ($M+NH_4^+$, 15), 636 ($M+NH_4^+$, 10); Accurate mass ($ES^+$): Found 643.2243, $C_{32}H_{47}{}^{81}BrNaO_5Si$ ($M+Na^+$) requires 643.2250, Found 641.2267, $C_{32}H_{47}{}^{79}BrNaO_5Si$ ($M+Na^+$) requires 641.2268; $[\alpha]_D^{25}$ -12.3 (c = 1.0 in $CHCl_3$).

2. (((3*R*,4*S*,9*S*,*Z*)-9-(4-Bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (***Z*-276**) (70 mg, 0.11 mmol, 11%): $R_f$ 0.30 (10:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2956s (CH), 2930s, 2857s, 1613m (C=C), 1587s, 1463s, 1248s, 1070s, 836s; $\delta_H$ (400 MHz, $CDCl_3$) 0.07 (6H, s, Si(C**H**$_3$)$_2$), 0.92 (9H, s, SiC(C**H**$_3$)$_3$), 0.92 (3H, t, *J*=7.5 Hz, $CH_2$C**H**$_3$), 1.43–1.55 (1H, m, C**H**H'$CH_3$), 1.55–1.71 (1H, m, CH**H'**$CH_3$), 2.32 (2H, t, *J*=6.5 Hz, C**H**$_2$CHOPMB), 2.39–2.46 (2H, m, C**H**$_2$CHOPBB), 2.71–2.79 (2H, m, C**H**$_2$O(CH)), 2.96 (1H, ddd, *J*=6.5, 4.0, 3.0 Hz, $CH_2$O(C**H**)), 3.32–3.42 (2H, m, C**H**OPMB, C**H**OPBB), 3.69 (1H, dt, *J*=6.5, 4.0 Hz, C**H**OTBS), 3.80 (3H, s, OC**H**$_3$), 4.44 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.46 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.57 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.59 (1H, *J*=11.0 Hz, CH**H'**Ar), 5.58 (1H, dt, *J*=11.0, 7.0 Hz C**H**=CH), 5.64 (1H, dt, *J*=11.0, 7.0 Hz CH=C**H**), 6.86 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz, Ar**H**), 7.45 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) –4.6 (Si(**C**$H_3$)($CH_3$)), –4.2 (Si($CH_3$)(**C**$H_3$)), 10.0 ($CH_2$**C**$H_3$), 18.2 (Si**C**($CH_3$)$_3$), 25.7 (**C**$H_2CH_3$), 26.0 (SiC(**C**$H_3$)$_3$), 29.0 (**C**$H_2$CHOPMB), 30.7 (**C**$H_2$CHOPBB), 45.2 (**C**$H_2$O(CH)), 53.2 ($CH_2$O(**C**H)), 55.3 (O**C**$H_3$), 71.5 (**C**$H_2$Ar), 72.1 (**C**$H_2$Ar), 75.2 (**C**HOTBS), 77.8 (**C**HOPBB), 81.8 (**C**HOPMB), 113.7 (Ar), 121.4 (Ar), 125.7 (**C**H=CH), 129.2 (CH=**C**H), 129.2 (Ar), 129.2 (Ar),

131.0 (Ar), 131.4 (Ar), 137.6 (Ar) 159.0 (Ar); *m/z* ($ES^+$) 643 ($M+Na^+$, 95%), 641 ($M+Na^+$, 100); Accurate mass ($ES^+$): Found 643.2254, $C_{32}H_{47}{}^{81}BrNaO_5Si$ ($M+Na^+$) requires 643.2250, found 641.2269, $C_{32}H_{47}{}^{79}BrNaO_5Si$ ($M+Na^+$) requires 641.2268; $[\alpha]_D^{25}$ -6.1 (c = 1.0 in $CHCl_3$).

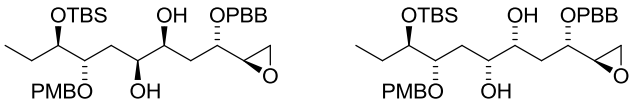
***(5R,6S,11S,12R,E)-5,12-Diethyl-6,11-bis(4-methoxybenzyloxy)-2,2,3,3,14,14,15,15-octamethyl-4,13-dioxa-3,14-disilahexadec-8-ene***




Isolated as a by-product during cross metathesis reactions; $R_f$ 0.73 (10:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2931s (CH), 1587s, 1249s, 1096s, 1012s, 836s, 775s; $\delta_H$ (500 MHz, $CDCl_3$) 0.06 (6H, s, 2 × Si(C**H**$_3$)($CH_3$)), 0.07 (6H, s, 2 × Si($CH_3$)(C**H**$_3$)), 0.92 (18H, s, 2 × SiC(C**H**$_3$)$_3$), 0.92 (6H, t, *J*=7.5 Hz, 2 × $CH_2$C**H**$_3$), 1.44–1.55 (2H, m, 2 × C**H**H'$CH_3$), 1.56–1.68 (2H, m, 2 × CH**H'**$CH_3$), 2.25–2.34 (4H, m, 2 × C**H**$_2$CH=CH), 3.34–3.42 (2H, m, 2 × C**H**OPMB), 3.68 (2H, dt, *J*=6.5, 4.0 Hz, 2 × C**H**OTBS), 3.80 (6H, s, 2 × OC**H**$_3$), 4.47 (2H, d, *J*=11.5 Hz, 2 × C**H**H'Ar), 4.58 (2H, d, *J*=11.0 Hz, 2 × CH**H'**Ar), 5.54–5.59 (2H, m, C**H**=C**H**), 6.86 (4H, d, *J*=8.5 Hz, Ar**H**), 7.26 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) –4.5 (Si(**C**H$_3$)($CH_3$)), –4.3 (Si($CH_3$)(**C**H$_3$)), 9.7 ($CH_2$**C**H$_3$), 18.2 (Si**C**($CH_3$)$_3$), 25.4 (**C**H$_2$CH$_3$), 26.0 (SiC(**C**H$_3$)$_3$), 34.2 (**C**H$_2$CH=CH), 55.2 (O**C**H$_3$), 71.9 (**C**H$_2$Ar), 75.0 (**C**HOTBS), 81.8 (**C**HOPMB), 113.6 (Ar), 129.2 (**C**H=**C**H) 129.3 (Ar), 131.1 (Ar), 159.0 (Ar); *m/z* ($ES^+$) 723 ($M+Na^+$, 50%), 350 (100); Accurate mass ($ES^+$): Found 723.4441, $C_{40}H_{68}NaO_6Si_2$ ($M+Na^+$) requires 723.4447; $[\alpha]_D^{25}$ -18.4 (c = 1.0 in $CH_2Cl_2$).

***(1S,3S,4S,6S,7R)-1-(4-Bromobenzyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-(4-methoxybenzyloxy)-1-((R)-oxiran-2-yl)nonane-3,4-diol* (278)**

***(1S,3R,4R,6S,7R)-1-(4-Bromobenzyloxy)-7-((tert-butyldimethylsilyl)oxy)-6-(4-methoxybenzyloxy)-1-((R)-oxiran-2-yl)nonane-3,4-diol* (3*R*,4*R*-278)**



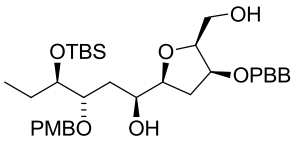

Prepared according to the **general SAD procedure** (**Page 184**) with (((3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (224 mg, 0.36 mmol). Purification by flash column chromatography (2.5:1→2:1→1:1 petrol:EtOAc) gave the two partially separable title compounds (**278** and ***3R*,4*R*-278**) as colourless oils (166 mg, 0.25 mmol, 70%, 4.5:1 3*S*,4*S*:3*R*,4*R*)

1. (1*S*,3*S*,4*S*,6*S*,7*R*)-1-(4-Bromobenzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-6-(4-methoxybenzyloxy)-1-((*R*)-oxiran-2-yl)nonane-3,4-diol (**278**) (136 mg, 0.21 mmol 57%); $R_f$ 0.56 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3451s br (OH), 2956s (CH), 2930s, 2857s, 1613m (C=C), 1514s,, 1249m, 1070s, 1012s, 836s, 776s; $\delta_H$ (400 MHz, $C_6D_6$) 0.09 (3H, s, Si(C**H**$_3$)(CH$_3$)), 0.15 (3H, s, Si(CH$_3$)(C**H**$_3$)), 0.92 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.00 (9H, s, SiC(C**H**$_3$)$_3$), 1.35–1.48 (1H, m, C**H**H'CH$_3$), 1.55–1.79 (3H, m, CH**H'**CH$_3$, 2 × C**H**H'CHOH), 1.80–1.94 (2H, m, 2 × CH**H'**CHOH), 2.33 (1H, dd, *J*=5.5, 4.0 Hz, C**H**H'O(CH)), 2.41 (1H, dd, *J*=5.5, 2.5 Hz, CH**H'**O(CH)), 2.64–2.69 (1H, m, CH$_2$O(C**H**)), 3.02 (1H, br s, O**H**), 3.09 (1H, br s, O**H**), 3.31 (3H, s, OC**H**$_3$), 3.58 (1H, ddd, *J*=8.5, 5.0, 3.0 Hz, C**H**OPBB), 3.72–3.85 (4H, m, C**H**OPMB, 2 × C**H**OH, C**H**OTES), 4.20 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.38 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.42 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.63 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 6.93 (2H, d, *J*=8.0 Hz, Ar**H**), 7.27 (2H, d, *J*=8.0 Hz, Ar**H**), 7.28 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $C_6D_6$) –4.5 (Si(**C**H$_3$)(CH$_3$)), –3.9 (Si(CH$_3$)(**C**H$_3$)), 10.6 (CH$_2$**C**H$_3$), 18.4 (Si**C**(CH$_3$)$_3$), 26.2 (SiC(**C**H$_3$)$_3$), 26.7 (**C**H$_2$CH$_3$), 33.7 (**C**H$_2$CHOH), 36.9 (**C**H$_2$CHOH), 45.2 (**C**H$_2$O(CH)), 53.4

($CH_2O(\mathbf{C}H)$), 54.8 ($O\mathbf{C}H_3$), 71.6 (**C**HOH), 72.0 (**C**HOH), 72.2 ($\mathbf{C}H_2Ar$), 72.3 ($\mathbf{C}H_2Ar$), 75.6 (**C**HOTBS), 76.0 (**C**HOPBB), 79.7 (**C**HOPMB), 114.1 (Ar), 121.6 (Ar), 129.5 (Ar), 129.7 (Ar), 131.1 (Ar), 131.6 (Ar), 138.1 (Ar), 159.7 (Ar); *m/z* ($ES^+$) 677 ($M+Na^+$, 100%), 675 ($M+Na^+$, 100); Accurate mass ($ES^+$): Found 677.2307, $C_{32}H_{49}{}^{81}BrNaO_7Si$ ($M+Na^+$) requires 677.2305, found 675.2322, $C_{32}H_{49}{}^{79}BrNaO_7Si$ ($M+Na^+$) requires 675.2323; $[\alpha]_D^{25}$ -31.3 (c = 1.0 in $CH_2Cl_2$).

2. (1*S*,3*R*,4*R*,6*S*,7*R*)-1-(4-Bromobenzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-6-(4-methoxybenzyl-oxy)-1-((*R*)-oxiran-2-yl)nonane-3,4-diol (**3*R*,4*R*-278**) (30 mg, 0.05 mmol 13%); $R_f$ 0.64 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3474s br (OH), 3047w, 2956s (CH), 2930s, 2857s, 1613m (C=C), 1514s, 1463s, 1249s, 1038s, 806s, 776s; $\delta_H$ (500 MHz, $C_6D_6$) 0.10 (3H, s, $Si(C\mathbf{H}_3)(CH_3)$), 0.17 (3H, s, $Si(CH_3)(C\mathbf{H}_3)$), 0.90 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.02 (9H, s, $SiC(C\mathbf{H}_3)_3$), 1.30–1.41 (1H, m, C**H**H'$CH_3$), 1.52–1.63 (1H, m, CH**H'**$CH_3$), 1.83–2.04 (4H, m, 2 × $C\mathbf{H}_2CHOH$), 2.29 (1H, dd, *J*=5.5, 4.0 Hz, C**H**H'O(CH)), 2.37 (1H, dd, *J*=5.5, 2.5 Hz, CH**H'**O(CH)), 2.68 (1H, ddd, *J*=7.5, 4.0, 2.5 Hz, $CH_2O(C\mathbf{H})$), 3.09 (1H, d, *J*=4.0 Hz, O**H**), 3.28 (3H, s, $OC\mathbf{H}_3$), 3.37–3.42 (1H, dt, *J*=7.5, 5.0 Hz, C**H**OPBB), 3.57 (1H, ddd, *J*=8.0, 4.0, 2.0 Hz, C**H**OPMB), 3.72 (1H, ddd, *J*=8.0, 5.0, 2.0 Hz, C**H**OTBS), 3.85–3.91 (2H, m, 2 × C**H**OH), 3.96 (1H, d, *J*=2.0 Hz, O**H**), 4.06 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.30 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.31 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.58 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.78 (2H, d, *J*=9.0 Hz, Ar**H**), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.23 (2H, d, *J*=8.5 Hz, Ar**H**), 7.35 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) –4.6 ($Si(\mathbf{C}H_3)(CH_3)$), –4.1 ($Si(CH_3)(\mathbf{C}H_3)$), 11.0 ($CH_2\mathbf{C}H_3$), 18.5 ($Si\mathbf{C}(CH_3)_3$), 26.1 ($SiC(\mathbf{C}H_3)_3$), 26.8 ($\mathbf{C}H_2CH_3$), 32.2 ($\mathbf{C}H_2CHOH$), 36.0 ($\mathbf{C}H_2CHOH$), 44.8 ($\mathbf{C}H_2O(CH)$), 53.4 ($CH_2O(\mathbf{C}H)$), 54.8 ($O\mathbf{C}H_3$), 71.6 ($\mathbf{C}H_2Ar$), 71.8 ($\mathbf{C}H_2Ar$), 72.6 (**C**HOH), 72.7 (**C**HOH), 75.8 (**C**HOTBS), 77.7 (**C**HOPBB), 82.0 (**C**HOPMB), 114.2 (Ar), 121.8 (Ar), 128.3 (Ar), 129.6 (Ar), 130.0 (Ar), 131.8 (Ar), 137.8 (Ar) 159.0 (Ar); *m/z* ($ES^+$) 677 ($M+Na^+$, 100%), 675 ($M+Na^+$, 100); Accurate mass ($ES^+$): Found 677.2313, $C_{32}H_{49}{}^{81}BrNaO_7Si$ ($M+Na^+$) requires 677.2305, found 675.2325, $C_{32}H_{49}{}^{79}BrNaO_7Si$ ($M+Na^+$) requires 675.2323; $[\alpha]_D^{25}$ -24.4 (c = 0.55 in $CH_2Cl_2$).

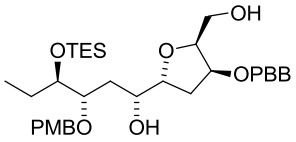
***(1S,3S,4R)-1-((2S,4S,5S)-4-(4-Bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-((tert-butyldimethylsilyl)oxy)-3-(4-methoxybenzyloxy)hexan-1-ol* (277)**




Prepared according to the **general CSA cyclisation procedure** (**Page 186**) with (1*S*,3*S*,4*S*,6*S*,7*R*)-1-(4-bromobenzyloxy)-7-((*tert*-butyldimethylsilyl)oxy)-6-(4-methoxybenzyloxy)-1-((*R*)-oxiran-2-yl)nonane-3,4-diol (**278**) (59 mg, 0.09 mmol). Immediate purification by flash column chromatography by direct loading of the cold reaction mixture (1:1 petrol:EtOAc) gave the title compound (**277**) as a colourless oil (50 mg, 0.08 mmol, 85%); $R_f$ 0.20 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3425s br (OH), 2956s (CH), 2856s, 1587m, 1245s, 1070s, 1012s, 835s, 775s; $\delta_H$ (500 MHz, $C_6D_6$) 0.14 (3H, s, Si(C**H**$_3$)(CH$_3$)), 0.22 (3H, s, Si(CH$_3$)(C**H**$_3$)), 0.98 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.05 (9H, s, SiC(C**H**$_3$)$_3$), 1.44–1.54 (1H, m, C**H**H'CH$_3$), 1.57–1.72 (2H, m, C**H**H'CHOPBB, CH**H'**CH$_3$), 1.79–1.91 (3H, m, CH**H'**CHOPBB, C**H**$_2$CHOH), 2.39 (1H, br s, O**H**), 3.31 (3H, s, OC**H**$_3$), 3.58 (1H, td, *J*=6.0, 5.0 Hz, C**H**OPBB), 3.67 (1H, q, *J*=5.0 Hz, C**H**CH$_2$OH), 3.71 (1H, td, *J*=7.0, 5.0 Hz, CH(OH)C**H**OC), 3.74 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.81 (2H, d, *J*=5.0 Hz, C**H**$_2$OH), 3.84 (1H, ddd, *J*=7.0, 5.0, 2.0 Hz, C**H**OTBS), 3.94–3.99 (1H, m, C**H**OPMB), 3.99–4.04 (1H, m, C**H**OH), 4.01 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.56 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.73 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.78 (2H, d, *J*=8.0 Hz, Ar**H**), 6.81 (2H, d, *J*=8.5 Hz, Ar**H**), 7.24 (2H, d, *J*=8.0 Hz, Ar**H**), 7.36 (2H, d, *J*=8.5 Hz, Ar**H**), (one O**H** was not resolved); $\delta_C$ (125 MHz, $CDCl_3$) –4.5 (Si(**C**H$_3$)(CH$_3$)), –3.7 (Si(CH$_3$)(**C**H$_3$)), 11.0 (CH$_2$**C**H$_3$), 18.6 (Si**C**(CH$_3$)$_3$), 26.3 (SiC(**C**H$_3$)$_3$), 27.0 (**C**H$_2$CH$_3$), 34.2 (**C**H$_2$CHOPBB), 35.1 (**C**H$_2$CHOH), 54.8 (O**C**H$_3$), 62.2 (**C**H$_2$OH), 70.4 (**C**HOH), 70.5 (**C**H$_2$Ar), 72.9 (**C**H$_2$Ar), 76.1 (**C**HOTBS), 79.8 (**C**HOPMB), 80.1 (**C**HOPBB), 81.8 (**C**HCH$_2$OH), 82.0 (CH(OH)**C**HOC), 114.0 (Ar), 121.9 (Ar), 128.3 (Ar), 129.4 (Ar), 129.7 (Ar), 131.8 (Ar), 137.2 (Ar), 159.7 (Ar); *m/z* (ES$^+$) 1331 (2M+Na$^+$, 70%), 1329 (2M+Na$^+$, 100), 1327 (2M+Na$^+$, 50), 677 (M+Na$^+$, 20), 675 (M+Na$^+$, 20); Accurate

mass ($ES^+$): Found 677.2312, $C_{32}H_{49}{}^{81}BrNaO_7Si$ ($M+Na^+$) requires 677.2305, found 675.2325, $C_{32}H_{49}{}^{79}BrNaO_7Si$ ($M+Na^+$) requires 675.2323; $[\alpha]_D^{25}$ -1.4 (c = 1.0 in $CH_2Cl_2$).

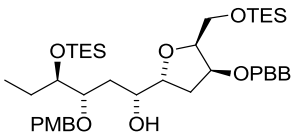
***(1R,3S,4R)-1-((2R,4S,5S)-4-(4-Bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexan-1-ol*** **(279)**




Prepared according to the **general CSA cyclisation procedure** (**Page 186**) with (1*S*,3*R*,4*R*,6*S*,7*R*)-1-(4-bromobenzyloxy)-6-(4-methoxybenzyloxy)-1-((*R*)-oxiran-2-yl)-7-(triethylsilyloxy)nonane-3,4-diol (**272**) (10 mg, 0.02 mmol). Immediate purification by flash column chromatography by direct loading of the cold reaction mixture (1:1 petrol:EtOAc) gave recovered starting material **272** (2 mg, 3 μmol, 15%) and the title compound (**279**) as a colourless oil (4 mg, 0.01 mmol, 40%); $R_f$ 0.13 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3442s br (OH), 2956s (CH), 2934s, 2876s, 1515s, 1463m, 1240s, 1070s, 1004s, 806s, 741s; $\delta_H$ (500 MHz, $C_6D_6$) 0.63–0.77 (6H, m, $Si(C\mathbf{H}_2CH_3)_3$), 0.95 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.06 (9H, t, *J*=8.0 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 1.40–1.50 (1H, m, C**H**H'$CH_3$), 1.60–1.70 (1H, m, CH**H'**$CH_3$), 1.84 (1H, dt, *J*=15.0, 3.5 Hz, C**H**H'CHOH), 1.87–1.92 (2H, m, $C\mathbf{H}_2$CHOPBB), 2.09 (1H, dt, *J*=15.0, 8.0 Hz, CH**H'**CHOH), 3.27 (3H, s, $OC\mathbf{H}_3$), 3.49 (1H, d, *J*=2.0 Hz, O**H**), 3.65 (1H, ddd, *J*=8.0, 4.0, 2.0 Hz, C**H**OPMB), 3.75–3.89 (7H, m, O**H**, C**H**OH, C**H**OTES, C**H**H'Ar, $C\mathbf{H}_2$OH, C**H**OPBB), 4.00–4.05 (1H, m, C**H**$CH_2$OH), 4.03 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 4.23 (1H, td, *J*=7.5, 4.0 Hz, CH(OH)C**H**OC), 4.37 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.60 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.77 (2H, d, *J*=9.0 Hz, Ar**H**), 6.80 (2H, d, *J*=8.0 Hz, Ar**H**), 7.26 (2H, d, *J*=8.0 Hz, Ar**H**), 7.27 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 5.9 ($Si(\mathbf{C}H_2CH_3)_3$), 7.7 ($Si(CH_2\mathbf{C}H_3)_3$), 11.2 ($CH_2\mathbf{C}H_3$), 27.2 ($\mathbf{C}H_2CH_3$), 33.8 ($\mathbf{C}H_2$CHOH), 34.1 ($\mathbf{C}H_2$CHOPBB), 55.1 ($O\mathbf{C}H_3$), 62.6 ($\mathbf{C}H_2$OH), 70.9 ($\mathbf{C}H_2$Ar), 72.1 ($\mathbf{C}H_2$Ar), 72.2 (**C**HOH), 76.3 (**C**HOTES), 81.1 (**C**HOPBB), 81.3 (CH(OH)**C**HOC), 81.4 (**C**HOPMB), 82.7 (**C**H$CH_2$OH), 114.5 (Ar), 122.1 (Ar), 128.9 (Ar), 129.5 (Ar), 130.2 (Ar), 132.1 (Ar), 138.4 (Ar), 160.2 (Ar); *m/z* ($ES^+$)

1331 (2M+$Na^+$, 70%), 1329 (2M+$Na^+$, 100), 1327 (2M+$Na^+$, 60), 677 (M+$Na^+$, 70), 675 (M+$Na^+$, 70); Accurate mass ($ES^+$): Found 677.2306, $C_{32}H_{49}{}^{81}BrNaO_7Si$ (M+$Na^+$) requires 677.2305, found 675.2321, $C_{32}H_{49}{}^{79}BrNaO_7Si$ (M+$Na^+$) requires 675.2323; $[\alpha]_D^{25}$ +11.2 (c = 0.64 in $CH_2Cl_2$).

***(1R,3S,4R)-1-((2R,4S,5S)-4-(4-Bromobenzyloxy)-5-((triethylsilyloxy)methyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexan-1-ol***

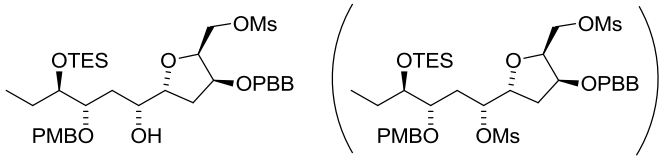



To a stirred solution of (1*R*,3*S*,4*R*)-1-((2*R*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexan-1-ol (**279**) (6.3 mg, 9.6 μmol) in DCM (0.12 mL) at 0 °C was added imidazole (1 mg, 13.4 μmol), DMAP (0.1 mg, 9.6 μmol) and chlorotriethylsilane (1.6 μL, 1.5 mg, 9.6 μmol). The reaction mixture was stirred at 0 °C for 4 h and then quenched by addition of $H_2O$ (1 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1→1:1→0:1 petrol:EtOAc) gave recovered starting material (1.0 mg, 1.5 μmol, 16%) and the title compound as a colourless oil (1.8 mg, 2.3 μmol, 24%); $R_f$ 0.85 (1:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3424s br (OH), 2956s (CH), 2934s, 2876s, 1613s, 1514s, 1463s, 1249s, 1072s, 1012s, 806s, 741s; $\delta_H$ (500 MHz, $CDCl_3$) 0.55–0.66 (12H, m, 2 × Si($CH_2CH_3$)$_3$), 0.90–1.00 (21H, m, 2 × Si($CH_2CH_3$)$_3$, $CH_2CH_3$), 1.41–1.61 (3H, m, $CH_2CH_3$, OH), 1.65 (1H, ddd, *J*=15.0, 4.0, 3.0 Hz, CHH'CHOH), 1.72–1.89 (2H, m, CHH'CHOH, CHH'CHOPBB), 2.02–2.11 (1H, m, CHH'CHOPBB), 3.54–3.58 (1H, m, CHOPMB), 3.59–3.63 (1H, m, CHOH), 3.68–3.81 (2H, m, CHOTES, CHH'OTES), 3.79 (3H, s, $OCH_3$), 3.88 (1H, dd, *J*=10.0, 7.5 Hz, CHH'OTES), 3.96–4.02 (1H, m, $CHCH_2OTES$), 4.05–4.15 (2H, m, CH(OH)CHOC, CHOPBB), 4.42 (1H, d, *J*=11.0 Hz, CHH'Ar), 4.45 (1H, d, *J*=12.5 Hz, CHH'Ar), 4.55 (1H, d, *J*=12.5 Hz,

CH**H'**Ar), 4.67 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.20 (2H, d, *J*=8.5 Hz, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz, Ar**H**), 7.45 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 5.1 ($Si(\mathbf{C}H_2CH_3)_3$), 5.8 ($Si(\mathbf{C}H_2CH_3)_3$), 6.8 ($Si(CH_2\mathbf{C}H_3)_3$), 6.9 ($Si(CH_2\mathbf{C}H_3)_3$), 10.5 ($CH_2\mathbf{C}H_3$), 26.1 ($\mathbf{C}H_2CH_3$), 32.8 ($\mathbf{C}H_2CHOH$), 33.4 ($\mathbf{C}H_2CHOPBB$), 55.2 ($O\mathbf{C}H_3$), 60.9 ($\mathbf{C}H_2OTES$), 70.6 ($\mathbf{C}H_2Ar$), 71.5 ($\mathbf{C}H_2Ar$), 71.8 (**C**HOH), 75.7 (**C**HOTES), 79.1 (**C**HOPBB), 80.6 (CH(OH)**C**HOC), 81.2 (**C**HOPMB), 82.9 ($\mathbf{C}HCH_2OH$), 113.8 (Ar), 122.2 (Ar), 128.9 (Ar), 129.5 (Ar), 130.4 (Ar), 131.3 (Ar), 137.7 (Ar), 159.1 (Ar); *m/z* ($ES^+$) 791 ($M+Na^+$, 100%), 769 ($M+Na^+$, 95), 769 ($M+H^+$, 15), 767 ($M+H^+$, 10); Accurate mass ($ES^+$): Found 791.3180, $C_{38}H_{63}{}^{81}BrNaO_7Si_2$ ($M+Na^+$) requires 791.3170, found 789.3189, $C_{38}H_{63}{}^{79}BrNaO_7Si_2$ ($M+Na^+$) requires 789.3188; $[\alpha]_D^{25}$ +13.4 (c = 0.16 in $CHCl_3$).

***((2S,3S,5R)-3-(4-Bromobenzyloxy)-5-((1R,3S,4R)-1-hydroxy-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexyl)tetrahydrofuran-2-yl)methyl methanesulfonate***

By-product: (1R,3S,4R)-1-((2R,4S,5S)-4-(4-bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-(triethylsilyloxy)-3-(4-methoxybenzyloxy)hexyl methanesulfonate

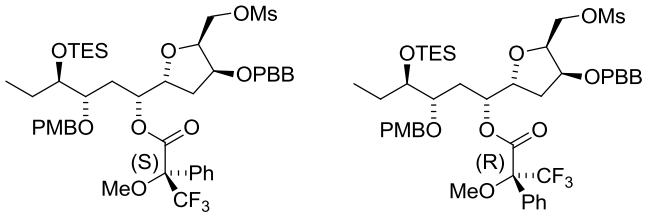



Prepared according to the **general mesylation procedure** (**Page 152**) with (1*R*,3*S*,4*R*)-1-((2*R*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexan-1-ol (**279**) (12 mg, 0.02 mmol), triethylamine (3 μL, 2 mg, 0.02 mmol) and methanesulfonyl chloride (2 μL, 2 mg, 0.02 mmol) in DCM (0.5 mL). Purification by flash column chromatography (2:1→1:1 petrol:EtOAc) gave bis-mesylate (5 mg, 6 μmol, 30%) and the title compound as a colourless oil (5 mg, 7 μmol, 35%); $R_f$ 0.53 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3489s br (OH), 2955s (CH), 2876s, 1613m, 1514s, 1356s, 1248s, 1175s, 1071s, 1011s, 961s, 821s, 742s; $\delta_H$ (500 MHz, $C_6D_6$) 0.63–0.76 (6H, m, $Si(C\mathbf{H}_2CH_3)_3$),

0.92 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.05 (9H, t, *J*=8.0 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 1.35–1.46 (1H, m, C**H**H'$CH_3$), 1.55–1.66 (1H, m, CH**H'**$CH_3$), 1.77 (1H, dt, *J*=15.0, 3.5 Hz, C**H**H'CHOH), 1.78–1.89 (2H, m, $C\mathbf{H}_2$CHOPBB), 2.06 (1H, dt, *J*=15.0, 8.5 Hz, CH**H'**CHOH), 2.25 (3H, s, $SC\mathbf{H}_3$), 3.27 (3H, s, $OC\mathbf{H}_3$), 3.55 (1H, br s, O**H**), 3.59 (1H, ddd, *J*=8.0, 4.0, 2.0 Hz, C**H**OPBB), 3.67–3.71 (1H, m, C**H**OPMB), 3.71–3.81 (2H, m, C**H**OH, C**H**OTES), 3.79 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.98 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.14 (1H, dt, *J*=6.5, 4.5 Hz, C**H**$CH_2$OMs), 4.18 (1H, td, *J*=7.5, 4.0 Hz, CH(OH)C**H**OC), 4.33 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.33–4.40 (2H, m, $C\mathbf{H}_2$OMs), 4.57 (1H, *J*=11.0 Hz, CH**H'**Ar), 6.78 (2H, d, *J*=8.5 Hz, Ar**H**), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz, Ar**H**), 7.27 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 5.5 ($Si(\mathbf{C}H_2CH_3)_3$), 7.3 ($Si(CH_2\mathbf{C}H_3)_3$), 10.9 ($CH_2\mathbf{C}H_3$), 27.0 ($\mathbf{C}H_2CH_3$), 33.2 ($\mathbf{C}H_2$CHOH), 33.2 ($\mathbf{C}H_2$CHOPBB), 36.8 ($S\mathbf{C}H_3$), 54.8 ($O\mathbf{C}H_3$), 69.0 ($\mathbf{C}H_2$OMs), 70.5 ($\mathbf{C}H_2$Ar), 71.5 (**C**HOH), 71.7 ($\mathbf{C}H_2$Ar), 75.8 (**C**HOTES), 79.8 (**C**HOPBB), 80.0 (**C**H$CH_2$OMs), 81.1 (**C**HOPMB), 81.4 (CH(OH)**C**HOC), 114.2 (Ar), 122.8 (Ar), 129.3 (Ar), 129.9 (Ar), 130.7 (Ar), 131.8 (Ar), 137.4 (Ar), 159.9 (Ar); *m/z* ($ES^+$) 1487 ($2M+Na^+$, 90%), 1485 ($2M+Na^+$, 100), 1483 ($2M+Na^+$, 70), 755 ($M+Na^+$, 100), 753 ($M+Na^+$, 95); Accurate mass ($ES^+$): Found 755.2073, $C_{33}H_{51}{}^{81}BrNaO_9SSi$ ($M+Na^+$) requires 755.2080, found 753.2093, $C_{33}H_{51}{}^{79}BrNaO_9SSi$ ($M+Na^+$) requires 753.2099; $[\alpha]_D^{25}$ -0.3 (c = 0.36 in $CH_2Cl_2$). By-product: (1R,3S,4R)-1-((2R,4S,5S)-4-(4-bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetra-hydrofuran-2-yl)-4-(triethylsilyloxy)-3-(4-methoxybenzyloxy)hexyl methanesulfonate; *m/z* ($ES^+$) 833 ($M+Na^+$, 100%), 831 ($M+Na^+$, 85).

***(S)-(1R,3S,4R)-1-((2R,4S,5S)-4-(4-Bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* (S-281)**

***(R)-(1R,3S,4R)-1-((2R,4S,5S)-4-(4-Bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate* (R-281)**



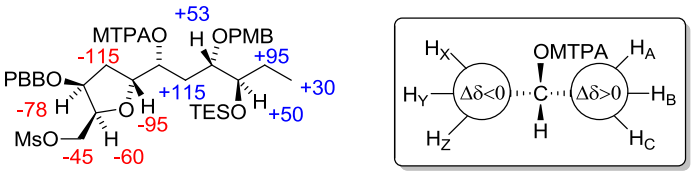

(*S*)-ester: To a stirred solution of ((2*S*,3*S*,5*R*)-3-(4-bromobenzyloxy)-5-((1*R*,3*S*,4*R*)-1-hydroxy-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexyl)tetrahydrofuran-2-yl)methyl methanesulfonate (2.0 mg, 2.7 μmol) in DCM (0.1 mL) was added triethylamine (1 drop), DMAP (flake) and (*R*)-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1 drop). The reaction mixture was stirred at RT for 16 h and then concentrated *in vacuo*. Purification by flash column chromatography (5:1 petrol:EtOAc) gave the title compound (***S*-281**) as a colourless oil (2 mg, 2.1 μmol, 78%); $R_f$ 0.81 (2:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2956s (CH), 2877s, 1748s (C=O), 1612m, 1358s, 1249s, 1175s, 1071m, 1013m, 961m, 822s, 743s, 723s; $\delta_H$ (500 MHz, $C_6D_6$) 0.64–0.76 (6H, m, Si(C**H**$_2$CH$_3$)$_3$), 0.96 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.07 (9H, t, *J*=8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$), 1.26 (1H, ddd, *J*=13.5, 8.5, 5.0 Hz, C**H**H'CHOPBB), 1.38–1.49 (1H, m, C**H**H'CH$_3$), 1.54–1.65 (1H, m, CH**H'**CH$_3$), 1.70 (1H, ddd, *J*=13.5, 7.0, 1.5 Hz, CH**H'**CHOPBB), 2.16 (2H, t, *J*=6.0 Hz, C**H**$_2$CHOPMB), 2.19 (3H, s, SC**H**$_3$), 3.27 (3H, s, OC**H**$_3$), 3.38–3.42 (1H, m, C**H**OPBB), 3.49–3.55 (1H, m, C**H**OPMB), 3.51 (3H, s, OC**H**$_3$), 3.69 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.84 (1H, ddd, *J*=7.5, 5.5, 2.0 Hz, C**H**OTES), 3.88–3.92 (1H, m, C**H**CH$_2$OMs), 3.91 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.23–4.29 (3H, m, C**H**$_2$OMs, CH(OC(O))C**H**OC) 4.23 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.55 (1H, *J*=11.5 Hz, CH**H'**Ar), 5.38–5.43 (1H, m, C**H**OC(O)), 6.76 (2H, d, *J*=8.5 Hz, Ar**H**), 6.79 (2H, d, *J*=8.5 Hz, Ar**H**), 7.04 (1H, tt,

*J*=7.5, 1.5 Hz, Ar**H**), 7.10–7.21 (2H, m, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz, Ar**H**), 7.29 (2H, d, *J*=8.5 Hz, Ar**H**), 7.77 (2H, d, *J*=8.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 5.6 (Si(**C**$H_2CH_3)_3$), 7.3 (Si($CH_2$**C**$H_3)_3$), 10.8 ($CH_2$**C**$H_3$), 27.4 (**C**$H_2CH_3$), 30.7 (**C**$H_2$CHOPMB), 33.4 (**C**$H_2$CHOPBB), 36.8 (S**C**$H_3$), 54.8 (O**C**$H_3$), 55.5 (O**C**$H_3$), 68.2 (**C**$H_2$OMs), 70.4 (**C**$H_2$Ar), 71.1 (**C**$H_2$Ar), 74.8 (**C**HOTES), 76.4 (**C**HOC(O)), 77.5 (CH(OC(O))**C**HOC), 78.2 (**C**HOPMB), 85.0 (**C**HOPBB), 85.3 (**C**H$CH_2$OMs), 114.2 (Ar), 121.9 (Ar), 127.5 (Ar), 128.7 (Ar), 129.3 (Ar), 129.8 (Ar), 130.0 (Ar), 130.7 (Ar), 131.8 (Ar), 133.0 (Ar), 137.1 (Ar), 159.8 (Ar), 166.2 (**C**=O), (**C**($CF_3$) and C(**C**$F_3$) carbons were not resolved); $\delta_F$ (235 MHz, $CDCl_3$) -71.64 (C**F**$_3$); *m/z* ($ES^+$) 1917 ($2M+Na^+$, 30%), 971 ($M+Na^+$, 100), 969 ($M+Na^+$, 90); Accurate mass ($ES^+$): Found 971.2499, $C_{43}H_{58}{}^{81}BrF_3NaO_{11}SSi$ ($M+Na^+$) requires 971.2479, found 969.2498, $C_{43}H_{58}{}^{79}BrF_3NaO_{11}SSi$ ($M+Na^+$) requires 969.2497; $[\alpha]_D^{25}$ -19.5 (c = 0.19 in $CH_2Cl_2$).

(*R*)-ester: Procedure as for (*S*)-ester but with (*S*)-methoxy-α-(trifluoromethyl)phenylacetyl chloride. Purification by flash column chromatography (5:1 petrol:EtOAc) gave the title compound (***R*-281**) as a colourless oil (2 mg, 2.1 μmol, 78%); $R_f$ 0.81 (2:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2956s (CH), 2876s, 1747s (C=O), 1651m, 1514m, 1359s, 1249s, 1176s, 1013m, 961m, 822s, 743s, 723s; $\delta_H$ (500 MHz, $C_6D_6$) 0.63–0.73 (6H, m, Si(C**H**$_2CH_3)_3$), 0.90 (3H, t, *J*=7.5 Hz, $CH_2$C**H**$_3$), 1.05 (9H, t, *J*=8.0 Hz, Si($CH_2$C**H**$_3)_3$), 1.15–1.34 (2H, m, C**H**H'CHOPBB, C**H**H'$CH_3$), 1.38–1.48 (1H, m, CH**H'**$CH_3$), 1.89–1.97 (2H, m, CH**H'**CHOPBB, C**H**H'CHOPMB), 2.05 (1H, ddd, *J*=15.5, 7.0, 2.0 Hz, CH**H'**CHOPMB), 2.21 (3H, s, SC**H**$_3$), 3.26 (3H, s, OC**H**$_3$), 3.39–3.44 (1H, m, C**H**OPMB), 3.48–3.53 (1H, m, C**H**OPBB), 3.61 (3H, s, OC**H**$_3$), 3.70 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.74 (1H, ddd, *J*=7.0, 5.0, 1.5 Hz, C**H**OTES), 3.93 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.02 (1H, dt, *J*=7.0, 4.5 Hz, C**H**$CH_2$OMs), 4.10 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.29 (1H, dd, *J*=10.5, 7.0 Hz, C**H**H'OMs), 4.35 (1H, dd, *J*=10.5, 4.5 Hz, CH**H'**OMs), 4.39 (1H, *J*=11.0 Hz, CH**H'**Ar), 4.45 (1H, dt, *J*=9.0, 7.0 Hz, CH(OC(O))C**H**OC), 5.36 (1H, td, *J*=7.0, 3.5 Hz, C**H**OC(O)), 6.71 (2H, d, *J*=8.5 Hz, Ar**H**), 6.77 (2H, d, *J*=8.5 Hz, Ar**H**), 7.07–7.24 (3H, m, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**), 7.29 (2H, d,

*J*=8.5 Hz, Ar**H**), 7.87 (2H, d, *J*=7.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 5.6 (Si(**C**$H_2$CH$_3$)$_3$), 7.3 (Si(CH$_2$**C**H$_3$)$_3$), 10.8 (CH$_2$**C**H$_3$), 27.4 (**C**H$_2$CH$_3$), 30.5 (**C**H$_2$CHOPMB), 34.0 (**C**H$_2$CHOPBB), 36.8 (S**C**H$_3$), 54.8 (O**C**H$_3$), 55.6 (O**C**H$_3$), 68.1 (**C**H$_2$OMs), 70.4 (**C**H$_2$Ar), 71.1 (**C**H$_2$Ar), 74.8 (**C**HOTES), 77.0 (**C**HOC(O)), 78.1 (**C**HOPMB), 78.4 (CH(OC(O))**C**HOC), 79.4 (**C**HOPBB), 79.5 (**C**HCH$_2$OMs), 114.1 (Ar), 121.9 (Ar), 127.5 (Ar), 128.8 (Ar), 129.3 (Ar), 129.8 (Ar), 129.9 (Ar), 130.6 (Ar), 131.8 (Ar), 132.9 (Ar), 137.1 (Ar), 159.7 (Ar), 166.5 (**C**=O), (**C**(CF$_3$) and C(**C**F$_3$) carbons were not resolved); $\delta_F$ (235 MHz, $CDCl_3$) -71.60 (C**F**$_3$); *m*/*z* (ES$^+$) 1919 (2M+Na$^+$, 40%), 1917 (2M+Na$^+$, 50), 1915 (2M+Na$^+$, 20), 971 (M+Na$^+$, 100), 969 (M+Na$^+$, 95); Accurate mass (ES$^+$): Found 971.2496, $C_{43}H_{58}{}^{81}BrF_3NaO_{11}SSi$ (M+Na$^+$) requires 971.2479, found 969.2501, $C_{43}H_{58}{}^{79}BrF_3NaO_{11}SSi$ (M+Na$^+$) requires 969.2497; $[\alpha]_D^{25}$ +1.3 (c = 0.15 in $CH_2Cl_2$).

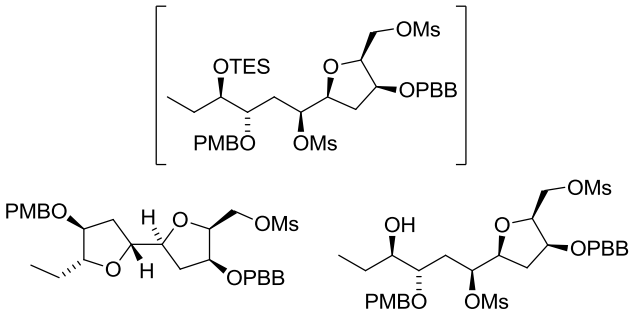
The absolute configuration was confirmed by the method of Ohtani *et al.* as shown below (values quoted in Hz).[90]



***(1S,3S,4R)-1-((2S,4S,5S)-4-(4-Bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-(triethylsilyloxy)-3-(4-methoxybenzyloxy)hexyl methanesulfonate*** **(282)**

***((2S,2'R,4S,4'S,5S,5'R)-4-(4-Bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-5-yl)methyl methanesulfonate*** **(207)**

***(1S,3S,4R)-1-((2S,4S,5S)-4-(4-Bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-hydroxy-3-(4-methoxybenzyloxy)hexyl methanesulfonate*** **(283)**




*According to the modified procedure of Kadota et al.*[168]: Intermediate prepared according to the **General Mesylation Procedure II**: To a stirred solution of (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3-(4-methoxybenzyloxy)-4-(triethylsilyloxy)hexan-1-ol (**273**) (205 mg, 0.31 mmol) in DCM (3.1 mL) at 0 °C was added triethylamine (0.13 mL, 95 mg, 0.94 mmol) and methanesulfonyl chloride (58 μL, 86 mg, 0.75 mmol). The reaction mixture was stirred at 0 °C for 10 min and then quenched with sat. aq. $NH_4Cl$ (5 mL) and allowed to warm to RT. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. to yield a crude oil of (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-(triethylsilyloxy)-3-(4-methoxybenzyloxy)hexyl methanesulfonate (**282**) (254 mg, 0.31 mmol, quant.); $R_f$ 0.55 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3030m, 2957s (CH), 2912s, 2876s, 1613m, 1587s, 1349s, 1173s, 1069s, 823s, 740s; $\delta_H$ (500 MHz, $C_6D_6$) 0.64–0.75 (6H, m, $Si(CH_2CH_3)_3$), 1.00

(3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.04 (9H, t, *J*=8.0 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 1.35–1.48 (2H, m, C**H**H'$CH_3$, C**H**H'CHOPBB), 1.49–1.63 (2H, m, CH**H'**$CH_3$, CH**H'**CHOPBB), 1.66–1.74 (1H, m, C**H**H'CHOPMB), 1.77–1.85 (1H, m, CH**H'**CHOPMB) 2.21 (3H, s, $SC\mathbf{H}_3$), 2.78 (3H, s, $SC\mathbf{H}_3$), 3.28 (3H, s, $OC\mathbf{H}_3$), 3.38 (1H, ddd, *J*=8.0, 5.5, 3.5 Hz, C**H**OPBB), 3.68–3.74 (1H, m, C**H**CHOMs), 3.69 (1H, d, *J*=12.5 Hz, C**H**H'Ar), 3.78 (1H, q, *J*=5.5 Hz, C**H**$CH_2$OMs), 3.85–3.89 (1H, m, C**H**OTES), 3.89–4.93 (1H, m, C**H**OPMB), 3.94 (1H, d, *J*=12.5 Hz, CH**H'**Ar), 4.33 (2H, d, *J*=5.5 Hz, $C\mathbf{H}_2$OMs), 4.66 (1H, d, *J*=10.0 Hz, C**H**H'Ar), 4.73 (1H, *J*=10.0 Hz, CH**H'**Ar), 5.24–5.29 (1H, m, C**H**OMs), 6.74–6.79 (4H, m, Ar**H**), 7.23 (2H, d, *J*=8.5 Hz, Ar**H**), 7.48 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 5.6 ($Si(\mathbf{C}H_2CH_3)_3$, 7.4 ($Si(CH_2\mathbf{C}H_3)_3$), 11.0 ($CH_2\mathbf{C}H_3$), 27.6 ($\mathbf{C}H_2CH_3$), 32.9 ($\mathbf{C}H_2$CHOPMB), 34.0 ($\mathbf{C}H_2$CHOPBB), 36.6 ($S\mathbf{C}H_3$), 38.8 ($S\mathbf{C}H_3$), 54.8 ($O\mathbf{C}H_3$), 68.8 ($\mathbf{C}H_2$OMs), 70.5 ($\mathbf{C}H_2$Ar), 72.5 ($\mathbf{C}H_2$Ar), 74.7 (**C**HOTES), 78.4 (**C**HOPBB), 78.9 (**C**HOPMB), 79.9 (**C**H$CH_2$OMs), 80.6 (**C**HCHOMs), 83.3 (**C**HOMs), 114.0 (Ar), 122.1 (Ar), 129.5 (Ar), 130.5 (Ar), 131.3 (Ar), 131.9 (Ar), 136.8 (Ar), 159.8 (Ar); *m/z* ($ES^+$) 833 ($M+Na^+$, 90%), 831 ($M+Na^+$, 85), 828 ($M+NH_4^+$, 15), 826 ($M+NH_4^+$, 10); Accurate mass ($ES^+$): Found 833.1863, $C_{34}H_{53}{}^{81}BrNaO_{11}S_2Si$ ($M+Na^+$) requires 833.1855, found 831.1876, $C_{34}H_{53}{}^{79}BrNaO_{11}S_2Si$ ($M+Na^+$) requires 831.1874; $[\alpha]_D^{25}$ -4.3 (c = 1.0 in $CH_2Cl_2$). The crude oil of (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-(triethylsilyloxy)-3-(4-methoxybenzyloxy)hexyl methanesulfonate (**282**) (254 mg, 0.31 mmol) was dissolved in THF (2.9 mL) and tetrabutylammonium fluoride (0.47 mL, 1.0 M in THF, 0.47 mmol) was added. The reaction mixture was stirred at RT for 16 h and then $H_2O$ (3 mL) was added and the aqueous was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1→0:1 petrol:EtOAc) gave the two title compounds (**207** and **283**) as colourless oils.

1. ((2*S*,2'*R*,4*S*,4'*S*,5*S*,5'*R*)-4-(4-Bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-5-yl)methyl methanesulfonate (**207**) (128 mg, 0.21 mmol, 66%); $R_f$ 0.48 (1:

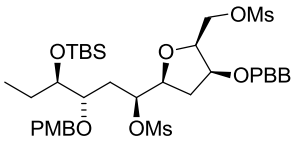
petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2957s (CH), 2934s, 2876s, 1512s, 1463m, 1356s, 1248s, 953s, 809s; $\delta_H$ (500 MHz, $C_6D_6$) 0.93 (3H, t, *J*=7.5 Hz, $CH_2CH_3$), 1.38–1.54 (2H, m, $CH_2CH_3$), 1.64–1.79 (2H, m, CHH'CHOPBB, CHH'CHOPMB), 1.93 (1H, ddd, *J*=14.0, 5.5, 3.0 Hz, CH**H'**CHOPBB), 2.16–2.22 (1H, m, CH**H'**CHOPMB), 2.24 (3H, s, $SCH_3$), 3.32 (3H, s, $OCH_3$), 3.43 (1H, ddd, *J*=8.0, 5.0, 3.0 Hz, CHOPBB), 3.60–3.65 (1H, m, CHOPMB), 3.70 (1H, d, *J*=12.0 Hz, CHH'Ar), 3.71–3.77 (1H, m, $CHCH_2$CHOPMB), 3.80 (1H, dt, *J*=7.0, 4.5 Hz, $CHCH_2$OMs), 3.95 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.00 (1H, td, *J*=6.5, 3.0 Hz, CHEt), 4.21–4.28 (1H, m, $CHCH_2$CHOPMB), 4.23 (1H, d, *J*=11.5 Hz, CHH'Ar), 4.30 (1H, *J*=11.5 Hz, CH**H'**Ar), 4.32–4.41 (2H, m, $CH_2$OMs), 6.76 (2H, d, *J*=8.5 Hz, ArH), 6.81 (2H, d, *J*=9.0 Hz, ArH), 7.18 (2H, d, *J*=9.0 Hz, ArH), 7.24 (2H, d, *J*=8.5 Hz, ArH); $\delta_C$ (125 MHz, $C_6D_6$) 10.5 ($CH_2CH_3$), 27.9 ($CH_2CH_3$), 34.6 ($CH_2$CHOPBB), 35.8 ($CH_2$CHOPMB), 36.7 ($SCH_3$), 54.8 ($OCH_3$), 69.0 ($CH_2$OMs), 70.2 ($CH_2$Ar), 73.3 ($CH_2$Ar), 78.9 (CHOPBB), 79.9 ($CHCH_2$OMs), 80.8 ($CHCH_2$CHOPMB), 81.7 ($CHCH_2$CHOPBB), 83.0 (CHOPMB), 86.0 (CHEt), 114.2 (Ar), 121.9 (Ar), 129.5 (Ar), 129.5 (Ar), 130.9 (Ar), 131.8 (Ar), 137.1 (Ar), 159.8 (Ar); *m/z* ($ES^+$) 1223 ($2M+Na^+$, 35%), 1221 ($2M+Na^+$, 75), 1219 ($2M+Na^+$, 35), 623 ($M+Na^+$, 100), 621 ($M+Na^+$, 100), 618 ($M+NH_4^+$, 15), 616 ($M+NH_4^+$, 15); Accurate mass ($ES^+$): Found 623.1111, $C_{27}H_{35}{}^{81}BrNaO_8S$ ($M+Na^+$) requires 623.1109, found 621.1128, $C_{27}H_{35}{}^{79}BrNaO_8S$ ($M+Na^+$) requires 621.1128; $[\alpha]_D^{26}$ +27.8 (c = 0.73 in $CH_2Cl_2$).

2. (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-Bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-hydroxy-3-(4-methoxybenzyloxy)hexyl methanesulfonate (**283**) (53 mg, 0.08 mmol, 26%); $R_f$ 0.08 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3545s br (OH), 2963s (CH), 2936s, 2870s, 1464m, 1348s, 1249s, 11.73s, 1070s, 1012s, 820s; $\delta_H$ (500 MHz, $C_6D_6$) 0.99 (3H, t, *J*=7.5 Hz, $CH_2CH_3$), 1.20–1.48 (4H, m, $CH_2CH_3$, $CH_2$CHOPBB), 1.60–1.67 (1H, m, CHH'CHOPMB), 1.71–1.78 (1H, m, CH**H'**CHOPMB), 1.87 (1H, br s, OH), 2.19 (3H, s, $SCH_3$), 2.77 (3H, s, $SCH_3$), 3.29 (3H, s, $OCH_3$), 3.32 (1H, td, *J*=5.5, 3.5 Hz, CHOPBB), 3.61 (1H, d, *J*=12.0 Hz, CHH'Ar), 3.65 (1H, td, *J*=8.0, 6.5 Hz, CHCHOMs), 3.69–3.74 (1H, m, CHOH), 3.75 (1H, q, *J*=5.5 Hz, $CHCH_2$OMs),

3.78–3.93 (1H, m, C**H**OPMB), 3.85 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.30 (2H, d, *J*=5.5 Hz, C**H**$_2$OMs), 4.45 (1H, d, *J*=10.5 Hz, C**H**H'Ar), 4.72 (1H, *J*=10.5 Hz, CH**H'**Ar), 5.20–5.26 (1H, m, C**H**OMs), 6.75 (2H, m, *J*=8.0 Hz, Ar**H**), 6.76 (2H, m, *J*=9.0 Hz, Ar**H**), 7.23 (2H, d, *J*=8.0 Hz, Ar**H**), 7.34 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.9 ($CH_2$**C**$H_3$), 25.8 (**C**$H_2CH_3$), 31.4 (**C**$H_2$CHOPMB), 34.0 (**C**$H_2$CHOPBB), 36.6 (S**C**$H_3$), 38.8 (S**C**$H_3$), 54.8 (O**C**$H_3$), 68.7 (**C**$H_2$OMs), 70.5 (**C**$H_2$Ar), 71.7 (**C**$H_2$Ar), 72.0 (**C**HOH), 78.2 (**C**HOPMB), 78.4 (**C**HOPBB), 79.9 (**C**HCH$_2$OMs), 80.5 (**C**HCHOMs), 82.8 (**C**HOMs), 114.2 (Ar), 122.1 (Ar), 129.5 (Ar), 130.3 (Ar), 131.1 (Ar), 131.9 (Ar), 136.8 (Ar), 159.9 (Ar); *m/z* (ES$^+$) 719 (M+Na$^+$, 100%), 717 (M+Na$^+$, 100), 714 (M+NH$_4^+$, 10), 712 (M+NH$_4^+$, 10); Accurate mass (ES$^+$): Found 719.0986, $C_{28}H_{39}{}^{81}BrNaO_{11}S_2$ (M+Na$^+$) requires 719.0992, found 717.1007, $C_{28}H_{39}{}^{79}BrNaO_{11}S_2$ (M+Na$^+$) requires 717.1009; $[\alpha]_D^{25}$ -5.2 (c = 0.15 in $CH_2Cl_2$).

**Method 2:** To a stirred solution of (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-hydroxy-3-(4-methoxybenzyloxy)hexyl methanesulfonate (**283**) (60 mg, 86 μmol) in THF (0.9 mL) was added potassium bis(trimethylsilyl)amide (0.52 mL, 0.5 M in toluene, 0.26 mmol). The reaction mixture was stirred at RT for 20 min and then quenched by addition of sat. aq. $NH_4Cl$ (3 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1 petrol:EtOAc) gave ((2*S*,2'*R*,4*S*,4'*S*,5*S*,5'*R*)-4-(4-bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-5-yl)methyl methanesulfonate (**207**) as a colourless oil (43 mg, 72 μmol, 84%); data as shown above.

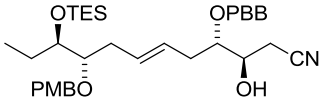
***(1S,3S,4R)-1-((2S,4S,5S)-4-(4-Bromobenzyloxy)-5-((methylsulfonyloxy)methyl)tetrahydrofuran-2-yl)-4-((tert-butyldimethylsilyl)oxy)-3-(4-methoxybenzyloxy)hexyl methanesulfonate*** **(284)**




Prepared according to the **general mesylation procedure II** (**Page 202**) with (1*S*,3*S*,4*R*)-1-((2*S*,4*S*,5*S*)-4-(4-bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-((*tert*-butyldimethylsilyl)oxy)-3-(4-methoxybenzyloxy)-hexan-1-ol (**277**) (50 mg, 0.08 mmol), triethylamine (32 μL, 23 mg, 0.23 mmol) and methanesulfonyl chloride (14 μL, 21 mg, 0.18 mmol). Purification by flash column chromatography (2:1 petrol:EtOAc) gave the title compound (**284**) as a colourless oil (58 mg, 0.07 mmol, 94%); $R_f$ 0.60 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2955s (CH), 2934s, 2857s, 1463s, 1348s, 1248s, 1069s, 1012s, 835s, 776s; $\delta_H$ (400 MHz, $C_6D_6$) 0.11 (3H, s, Si(C**H**$_3$)(CH$_3$)), 0.17 (3H, s, Si(CH$_3$)(C**H**$_3$)), 0.97 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.01 (9H, s, SiC(C**H**$_3$)$_3$), 1.31–1.84 (6H, m, C**H**$_2$CH$_3$, C**H**$_2$CHOPBB, C**H**$_2$CHOPMB), 2.26 (3H, s, SC**H**$_3$), 2.80 (3H, s, SC**H**$_3$), 3.30 (3H, s, OC**H**$_3$), 3.40–3.46 (1H, m, C**H**OPBB), 3.68–3.76 (1H, m, CH(OMs)C**H**OC), 3.72 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.78–3.86 (2H, m, C**H**CH$_2$OMs, C**H**OTBS), 3.86–3.94 (1H, m, C**H**OPMB), 3.96 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.34 (2H, d, *J*=5.5 Hz, C**H**$_2$OMs), 4.65 (1H, d, *J*=10.0 Hz, C**H**H'Ar), 4.70 (1H, *J*=10.0 Hz, CH**H'**Ar), 5.25 (1H, t, *J*=9.0 Hz, C**H**OMs), 6.76 (2H, d, *J*=8.5 Hz, Ar**H**), 6.78 (2H, d, *J*=8.5 Hz, Ar**H**), 7.23 (2H, d, *J*=8.5 Hz, Ar**H**), 7.46 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) –4.6 (Si(**C**H$_3$)(CH$_3$)), –3.8 (Si(CH$_3$)(**C**H$_3$)), 11.0 (CH$_2$**C**H$_3$), 18.5 (Si**C**(CH$_3$)$_3$), 26.2 (SiC(**C**H$_3$)$_3$), 27.3 (**C**H$_2$CH$_3$), 32.8 (**C**H$_2$CHOPBB), 34.0 (**C**H$_2$CHOMs), 36.7 (S**C**H$_3$), 38.7 (S**C**H$_3$), 54.7 (O**C**H$_3$), 68.8 (**C**H$_2$OMs), 70.5 (**C**H$_2$Ar), 72.4 (**C**H$_2$Ar), 74.8 (**C**HOTBS), 78.4 (**C**HOPBB), 78.9 (**C**HOPMB), 79.9 (**C**HCH$_2$OMs), 80.5 (CH(OMs)**C**HOC), 83.2 (**C**HOMs), 114.0 (Ar), 122.0 (Ar), 129.5 (Ar), 130.4 (Ar), 131.2 (Ar), 131.8 (Ar), 136.7 (Ar), 159.7 (Ar); *m*/*z* (ES$^+$) 833 (M+Na$^+$, 100%), 831 (M+Na$^+$,

90); Accurate mass ($ES^+$): Found 833.1866, $C_{34}H_{53}{}^{81}BrNaO_{11}S_2Si$ ($M+Na^+$) requires 833.1855, found 831.1884, $C_{34}H_{53}{}^{79}BrNaO_{11}S_2Si$ ($M+Na^+$) requires 831.1874; $[\alpha]_D^{25}$ -5.0 (c = 1.0 in $CH_2Cl_2$).

***(3R,4S,9S,10R,E)-4-(4-Bromobenzyloxy)-3-hydroxy-9-(4-methoxybenzyloxy)-10-(triethylsilyloxy)dodec-6-enenitrile* (287)**




*According to the modified procedure of Fujimori et al.*[121]: To a stirred solution of (((3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl)oxy)triethylsilane (**240**) (100 mg, 0.16 mmol) in toluene (0.2 mL) at 0 °C was added diethylaluminium cyanide (0.18 mL, 1 M in toluene, 0.18 mmol). The reaction mixture was allowed to warm to RT and stirred for 2 h. The reaction mixture was diluted with diethyl ether (0.5 mL), quenched with a mixture of sat. aq. $NH_4Cl$ and Rochelle salt (1:1, 1 mL) and stirred for 1 h. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organics were washed with brine (5 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1 petrol:EtOAc) gave the title compound (**287**) as a colourless oil (87 mg, 0.13 mmol, 84%); $R_f$ 0.17 (5:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3456s br (OH), 2956s (CH), 2877s, 1614m (C=C), 1514s, 1248s, 1091s, 1071s, 1011s, 806s, 742s; $\delta_H$ (500 MHz, $C_6D_6$) 0.64–0.75 (6H, m, $Si(C\mathbf{H}_2CH_3)_3$), 0.98 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.06 (9H, t, *J*=8.0 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 1.43–1.55 (1H, m, C**H**H'$CH_3$), 1.66–1.77 (1H, m, CH**H'**$CH_3$), 1.85–1.94 (1H, m, C**H**H'CN), 1.99–2.12 (2H, m, CH**H'**CN, C**H**H'CHOPBB), 2.16–2.25 (1H, m, CH**H'**CHOPBB), 2.31–2.40 (1H, m, C**H**H'CHOPMB), 2.47–2.56 (1H, m, CH**H'**CHOPMB), 3.13 (1H, q, *J*=6.5 Hz, C**H**OPBB), 3.31 (3H, s, $OC\mathbf{H}_3$), 3.36 (1H, dt, *J*=7.5, 4.0 Hz, C**H**OPMB), 3.44 (1H, ddd, *J*=10.5, 6.5, 4.0 Hz, C**H**OH), 3.80 (1H, dt, *J*=6.5, 4.0 Hz, C**H**OTES), 3.98 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.13 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 4.44 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.53 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 5.44 (1H, dt, *J*=15.0, 7.5 Hz, C**H**=CH), 5.66 (1H, dt, *J*=15.0, 7.5 Hz, CH=C**H**), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 6.84 (2H, d,

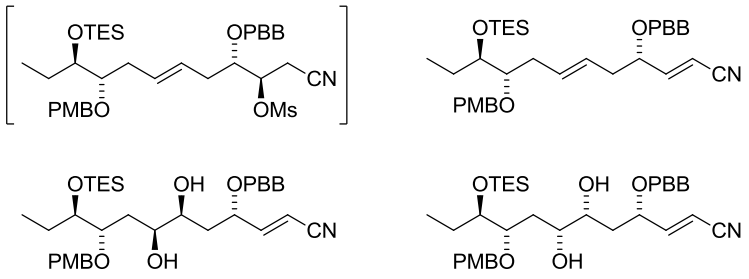
*J*=8.5 Hz, Ar**H**), 7.29 (2H, d, *J*=8.5 Hz, Ar**H**), 7.30 (2H, d, *J*=8.5 Hz, Ar**H**), (one O**H** was not resolved); $\delta_C$ (125 MHz, $C_6D_6$) 5.6 (Si(**C**$H_2CH_3)_3$), 7.4 (Si($CH_2$**C**$H_3)_3$), 10.2 ($CH_2$**C**$H_3$), 22.1 (**C**$H_2$CN), 26.8 (**C**$H_2CH_3$), 33.4 (**C**$H_2$CHOPBB), 33.7 (**C**$H_2$CHOPMB), 54.8 (O**C**$H_3$), 68.8 (**C**HOH), 71.2 (**C**$H_2$Ar), 71.8 (**C**$H_2$Ar), 75.1 (**C**HOTES), 80.6 (**C**HOPBB), 81.5 (**C**HOPMB), 114.1 (Ar), 118.0 (**C**≡N), 121.9 (Ar), 126.9 (**C**H=CH), 129.6 (Ar), 129.6 (Ar), 131.3 (CH=**C**H), 131.4 (Ar), 131.8 (Ar), 137.5 (Ar) 159.7 (Ar); *m/z* ($ES^+$) 670 ($M+Na^+$, 100%), 668 ($M+Na^+$, 100), 665 ($M+NH_4^+$, 35), 663 ($M+NH_4^+$, 25); Accurate mass ($ES^+$): Found 670.2364, $C_{33}H_{48}{}^{81}BrNNaO_5Si$ ($M+Na^+$) requires 670.2359, found 668.2383, $C_{33}H_{48}{}^{79}BrNNaO_5Si$ ($M+Na^+$) requires 668.2377; $[\alpha]_D^{25}$ +20.4 (c = 0.46 in $CHCl_3$).

***(2R,3S,8S,9R,E)-3-(4-Bromobenzyloxy)-1-cyano-8-(4-methoxybenzyloxy)-9-(triethylsilyloxy)undec-5-en-2-yl methanesulfonate***

***(2E,4S,6E,9S,10R)-4-(4-Bromobenzyloxy)-9-(4-methoxybenzyloxy)-10-(triethylsilyloxy)dodeca-2,6-dienenitrile* (288)**

***(4S,6S,7S,9S,10R,E)-4-(4-Bromobenzyloxy)-6,7-dihydroxy-9-(4-methoxybenzyloxy)-10-(triethylsilyloxy)dodec-2-enenitrile* (286)**

***(4S,6R,7R,9S,10R,E)-4-(4-Bromobenzyloxy)-6,7-dihydroxy-9-(4-methoxybenzyloxy)-10-(triethylsilyloxy)dodec-2-enenitrile* (6*R*,7*R*-286)**

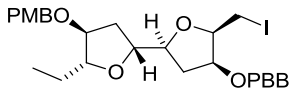



Intermediate prepared according to the **general mesylation procedure II** (**Page 202**) with (3*R*,4*S*,9*S*,10*R*,*E*)-4-(4-bromobenzyloxy)-3-hydroxy-9-(4-methoxybenzyloxy)-10-(triethylsilyloxy)dodec-6-enenitrile (**287**) (40 mg, 0.06 mmol), triethylamine (13 μL, 9.4 mg,

0.09 mmol) and methanesulfonyl chloride (6 μL, 8.9 mg, 0.07 mmol) to yield crude (2*R*,3*S*,8*S*,9*R*,*E*)-3-(4-bromobenzyloxy)-1-cyano-8-(4-methoxybenzyloxy)-9-(triethylsilyloxy)undec-5-en-2-yl methanesulfonate (44 mg, 0.06 mmol, 98%; *m*/*z* ($ES^+$) 748 ($M+Na^+$, 100%), 746 ($M+Na^+$, 95), 743 ($M+NH_4^+$, 40), 741 ($M+NH_4^+$, 35)). This crude oil (44 mg, 0.06 mmol) was subjected to the **general SAD procedure** (**Page 184**). Purification by flash column chromatography (4:1 petrol:EtOAc) gave recovered starting material (2 mg, 3 μmol, 5%), (2*E*,4*S*,6*E*,9*S*,10*R*)-4-(4-bromobenzyloxy)-9-(4-methoxybenzyloxy)-10-(triethylsilyloxy)dodeca-2,6-dienenitrile (**288**) (7 mg, 0.01 mmol, 19%; $R_f$ 0.83 (2:1 petrol:EtOAc); *m*/*z* ($ES^+$) 652 ($M+Na^+$, 100%), 650 ($M+Na^+$,100), 647 ($M+NH_4^+$, 30), 645 ($M+NH_4^+$, 30)) and a mixture of the two partially separable diol title compounds (**286** and **6*R*,7*R*-286**) as colourless oils (20 mg, 0.03 mmol, 50%, ~4:1 6*S*,7*S*:6*R*,7*R*), with only the major diastereomer obtained pure for full characterisation. (4*S*,6*S*,7*S*,9*S*,10*R*,*E*)-4-(4-Bromobenzyloxy)-6,7-dihydroxy-9-(4-methoxybenzyloxy)-10-(triethylsilyloxy)dodec-2-enenitrile (**286**): $R_f$ 0.17 (2:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3470s br (OH), 2934s (CH), 2911s, 2876s, 2226s (C≡N), 1616s (C=C), 1514s, 1248s, 1071s, 1011s, 808s, 742s; $\delta_H$ (500 MHz, $C_6D_6$) 0.63–0.71 (6H, m, $Si(C\mathbf{H}_2CH_3)_3$), 0.93 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.03 (9H, t, *J*=8.0 Hz, $Si(CH_2C\mathbf{H}_3)_3$), 1.29–1.47 (3H, m, C**H**H'$CH_3$, C$\mathbf{H}_2$CHOPBB), 1.56–1.72 (2H, m, CH**H'**$CH_3$, C**H**H'CHOPMB), 1.83 (1H, ddd, *J*=15.0, 8.5, 3.0 Hz, CH**H'**CHOPMB), 2.44 (1H, d, *J*=4.5 Hz, O**H**), 2.73 (1H, d, *J*=5.0 Hz, O**H**), 3.28 (3H, s, $OC\mathbf{H}_3$), 3.58–3.71 (3H, m, 2 × C**H**OH, C**H**OPMB), 3.77–3.86 (2H, m, C**H**OTES, C**H**OPBB), 3.83 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.93 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.35 (1H, d, *J*=11.0 Hz, C**H**H'Ar), 4.57 (1H, d, *J*=11.0 Hz, CH**H'**Ar), 4.92 (1H, dd, *J*=16.5, 1.5 Hz, CH=C**H**CN), 5.95 (1H, dd, *J*=16.5, 5.5 Hz, C**H**=CHCN), 6.79 (2H, d, *J*=8.5 Hz, Ar**H**), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz, Ar**H**), 7.27 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 5.6 ($Si(\mathbf{C}H_2CH_3)_3$), 7.3 ($Si(CH_2\mathbf{C}H_3)_3$), 10.4 ($CH_2\mathbf{C}H_3$), 27.0 ($\mathbf{C}H_2CH_3$), 33.4 ($\mathbf{C}H_2$CHOPMB), 39.0 ($\mathbf{C}H_2$CHOPBB), 54.8 ($O\mathbf{C}H_3$), 70.9 ($\mathbf{C}H_2$Ar), 71.0 (**C**HOH), 72.2 ($\mathbf{C}H_2$Ar), 72.2 (**C**HOH), 75.3 (**C**HOTES), 75.9 (**C**HOPBB), 79.4 (**C**HOPMB), 100.3 (CH=**C**HCN), 114.3 (Ar), 118.0 (**C**≡N), 122.0 (Ar), 129.5 (Ar), 129.8 (Ar), 130.8 (Ar), 131.8

(Ar) 137.1 (Ar), 154.1 (**C**H=CHCN), 160.0 (Ar); *m/z* ($ES^+$) 1349 ($2M+Na^+$, 60%), 1347 ($2M+Na^+$, 100), 1345 ($2M+Na^+$, 50), 686 ($M+Na^+$, 60), 684 ($M+Na^+$, 60); Accurate mass ($ES^+$): Found 686.2308, $C_{33}H_{48}{}^{81}BrNNaO_6Si$ ($M+Na^+$) requires 686.2308, found 684.2308, $C_{33}H_{48}{}^{79}BrNNaO_6Si$ ($M+Na^+$) requires 684.2326; $[\alpha]_D^{25}$ -34.5 (c = 1.0 in $CH_2Cl_2$).

***(2S,2'R,4S,4'S,5R,5'R)-4-(4-Bromobenzyloxy)-5'-ethyl-5-(iodomethyl)-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran* (289)**

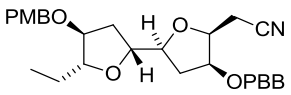


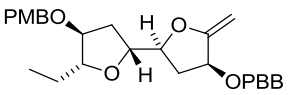

*According to the modified procedure of Han and Lowary*[124b]: To a stirred solution of ((2*S*,2'*R*,4*S*,4'*S*,5*S*,5'*R*)-4-(4-bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-5-yl)methyl methanesulfonate (**207**) (217 mg, 0.36 mmol) in dry toluene (1.8 mL) was added tetrabutylammonium iodide (1.32 g, 3.62 mmol) and the reaction mixture was heated to 110 °C for 16 h. The reaction mixture was then cooled to RT and filtered through a sinter washing with diethyl ether (50 mL). The filtrate was concentrated *in vacuo* and purification by flash column chromatography (5:1→3:1→1:1 petrol:EtOAc) gave recovered starting material (**207**) (15 mg, 0.03 mmol, 8%) and the title compound (**289**) as a colourless oil (191 mg, 0.30 mmol, 83%); $R_f$ 0.79 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2961s (CH), 2930s, 2875s, 1513s, 1248s, 1069s, 809s; $\delta_H$ (400 MHz, $C_6D_6$) 0.93 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.38–1.57 (2H, m, $C\mathbf{H}_2CH_3$), 1.68–1.84 (2H, m, C**H**H'CHOPBB, C**H**H'CHOPMB), 2.04 (1H, ddd, *J*=14.0, 5.0, 2.0 Hz, CH**H'**CHOPBB), 2.23 (1H, ddd, *J*=13.0, 6.0, 2.5 Hz, CH**H'**CHOPMB), 3.17 (1H, dd, *J*=9.5, 6.0 Hz, C**H**H'I), 3.24–3.29 (1H, m, CH**H'**I), 3.33 (3H, s, $OC\mathbf{H}_3$), 3.56–3.60 (1H, m, C**H**OPBB), 3.62 (1H, dt, *J*=6.5, 3.5 Hz, C**H**OPMB), 3.78–3.87 (2H, m, C**H**$CH_2$I, C**H**$CH_2$CHOPBB), 3.84 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 3.99 (1H, td, *J*=6.5, 3.5 Hz, C**H**Et), 4.06 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 4.19 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.21–4.27 (1H, m, C**H**$CH_2$CHOPMB), 4.27 (1H, *J*=11.5 Hz, CH**H'**Ar), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 6.86 (2H, d, *J*=8.0 Hz, Ar**H**), 7.13–7.18 (2H, m, Ar**H**), 7.25 (2H, d, *J*=8.5 Hz,

Ar**H**); $\delta_C$ (100 MHz, $C_6D_6$) 2.1 (**C**$H_2$I), 10.6 ($CH_2$**C**$H_3$), 28.0 (**C**$H_2CH_3$), 34.7 (**C**$H_2$CHOPBB), 36.0 (**C**$H_2$CHOPMB), 54.9 (O**C**$H_3$), 70.4 (**C**$H_2$Ar), 70.8 (**C**$H_2$Ar), 78.9 (**C**HOPBB), 81.1 (**C**$HCH_2$CHOPMB), 82.3 (**C**$HCH_2$CHOPBB), 83.0 (**C**$HCH_2$I), 83.4 (**C**HOPMB), 85.9 (**C**HEt), 114.1 (Ar), 121.8 (Ar), 129.5 (Ar), 129.7 (Ar), 131.0 (Ar), 131.8 (Ar), 137.4 (Ar), 159.8 (Ar); *m/z* ($ES^+$) 1287 ($2M+Na^+$, 20%), 1285 ($2M+Na^+$, 40), 1283 ($2M+Na^+$, 20), 655 ($M+Na^+$, 90), 653 ($M+Na^+$, 100), 650 ($M+NH_4^+$, 20), 648 ($M+NH_4^+$, 20); Accurate mass ($ES^+$): Found 655.0361, $C_{26}H_{32}{}^{81}BrINaO_5$ ($M+Na^+$) requires 655.0351, found 653.0370, $C_{26}H_{32}{}^{79}BrINaO_5$ ($M+Na^+$) requires 653.0370; $[\alpha]_D^{25}$ +50.7 (c = 0.45 in $CH_2Cl_2$).

***2-((2S,2'R,4S,4'S,5S,5'R)-4-(4-Bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-5-yl)acetonitrile* (285)**

***(2S,2'R,4S,4'S,5'R)-4-(4-Bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)-5-methyleneoctahydro-2,2'-bifuran* (290)**




To a stirred solution of (2*S*,2'*R*,4*S*,4'*S*,5*R*,5'*R*)-4-(4-bromobenzyloxy)-5'-ethyl-5-(iodomethyl)-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran (**289**) (3 mg, 4.8 μmol) in acetonitrile (0.05 mL) was added a solution of tetrabutylammonium cyanide (16 mg, 59 μmol) in acetonitrile (0.1 mL + 0.1 mL rinse). The reaction mixture was heated to reflux for 4 h and then cooled to RT and quenched by addition of $H_2O$ (2 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50:1→25:1→5:1 DCM:EtOAc) gave the two title compounds (**285** and **290**) as colourless oils.

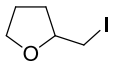
1. 2-((2*S*,2'*R*,4*S*,4'*S*,5*S*,5'*R*)-4-(4-Bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-5-yl)acetonitrile (**285**) (1.8 mg, 3.4 μmol, 71%); $R_f$ 0.38 (20:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2960s (CH), 2926s, 2875s, 2251m (C≡N), 1513s, 1248s, 1099s, 1071s, 811s; $\delta_H$

(500 MHz, $C_6D_6$) 0.93 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.34–1.55 (2H, m, $C\mathbf{H}_2CH_3$), 1.63–1.79 (2H, m, C**H**H'CHOPBB, C**H**H'CHOPMB), 1.89 (1H, ddd, *J*=13.5, 6.0, 3.0 Hz, CH**H'**CHOPMB), 2.12 (2H, d, *J*=6.5 Hz, $C\mathbf{H}_2CN$), 2.19 (1H, ddd, *J*=13.0, 5.5, 2.0 Hz, CH**H'**CHOPBB), 3.32 (3H, s, $OC\mathbf{H}_3$), 3.35 (1H, ddd, *J*=8.0, 5.0, 3.0 Hz, C**H**OPMB), 3.48 (1H, td, *J*=6.5, 5.0 Hz, C**H**$CH_2CN$), 3.60–3.64 (1H, m, C**H**OPBB), 3.67 (1H, td, *J*=7.5, 6.0 Hz, C**H**$CH_2$CHOPMB), 3.76 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.95–4.01 (1H, m, C**H**Et), 3.98 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.16–4.21 (1H, m, C**H**$CH_2$CHOPBB), 4.21 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.29 (1H, *J*=11.5 Hz, CH**H'**Ar), 6.81 (2H, d, *J*=8.5 Hz, Ar**H**), 6.82 (2H, d, *J*=8.5 Hz, Ar**H**), 7.18 (2H, d, *J*=8.5 Hz, Ar**H**), 7.27 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.5 ($CH_2\mathbf{C}H_3$), 18.5 ($\mathbf{C}H_2CN$), 27.9 ($\mathbf{C}H_2CH_3$), 34.4 ($\mathbf{C}H_2$CHOPMB), 35.7 ($\mathbf{C}H_2$CHOPBB), 54.8 ($O\mathbf{C}H_3$), 70.4 ($\mathbf{C}H_2Ar$), 70.9 ($\mathbf{C}H_2Ar$), 77.6 ($\mathbf{C}HCH_2CN$), 78.6 (**C**HOPMB), 80.8 ($\mathbf{C}HCH_2$CHOPBB), 81.6 ($\mathbf{C}HCH_2$CHOPMB), 82.9 (**C**HOPBB), 85.9 (**C**HEt), 114.1 (Ar), 117.7 (**C**≡N), 122.0 (Ar), 129.4 (Ar), 129.6 (Ar), 130.9 (Ar), 131.8 (Ar), 137.0 (Ar), 159.8 (Ar); $m/z$ ($ES^+$) 1085 ($2M+Na^+$, 65%), 1083 ($2M+Na^+$, 90), 1081 ($2M+Na^+$, 40), 554 ($M+Na^+$, 100), 552 ($M+Na^+$, 95), 549 ($M+NH_4^+$, 40), 547 ($M+NH_4^+$, 40); Accurate mass ($ES^+$): Found 554.1345, $C_{27}H_{32}{}^{81}BrNNaO_5$ ($M+Na^+$) requires 554.1337, found 552.1356, $C_{27}H_{32}{}^{79}BrNNaO_5$ ($M+Na^+$) requires 552.1356; $[\alpha]_D^{25}$ +33.1 (c = 0.14 in $CH_2Cl_2$).

2. (2*S*,2'*R*,4*S*,4'*S*,5'*R*)-4-(4-Bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)-5-methylene-octahydro-2,2'-bifuran (**290**) (0.5 mg, 1.0 μmol, 21%); $R_f$ 0.76 (20:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3052w, 2959s (CH), 2916s, 2852s, 1613s (C=C), 1514s, 1248s, 1101s, 1070s, 1037s, 808s; $\delta_H$ (500 MHz, $C_6D_6$) 0.91 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.33–1.55 (2H, m, $C\mathbf{H}_2CH_3$), 1.79 (1H, ddd, *J*=13.0, 9.0, 6.5 Hz, C**H**H'CHOPMB), 1.79 (1H, dt, *J*=13.0, 7.0 Hz, C**H**H'CHOPBB), 2.04 (1H, dt, *J*=13.0, 5.0 Hz, CH**H'**CHOPBB), 2.23 (1H, ddd, *J*=13.0, 6.0, 2.5 Hz, CH**H'**CHOPMB), 3.33 (3H, s, $OC\mathbf{H}_3$), 3.58–3.62 (1H, m, C**H**OPMB), 3.94–4.02 (2H, m, C**H**Et, C**H**OPBB), 4.05 (1H, d, *J*=12.5 Hz, C**H**H'Ar), 4.07 (1H, td, *J*=7.0, 5.0 Hz, C**H**$CH_2$CHOPBB), 4.14 (1H, t, *J*=1.0 Hz, C=C**H**H'), 4.17 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.19 (1H, d, *J*=12.5 Hz, CH**H'**Ar), 4.26 (1H,

*J*=11.5 Hz, CH**H'**Ar), 4.37 (1H, ddd, *J*=9.0, 7.0, 6.0 Hz, C**H**$CH_2$CHOPMB), 4.66 (1H, t, *J*=1.0 Hz, C=CH**H'**), 6.82 (2H, d, *J*=9.0 Hz, Ar**H**), 6.86 (2H, d, *J*=8.5 Hz, Ar**H**), 7.11–7.19 (2H, m, Ar**H**), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.4 ($CH_2$**C**$H_3$), 27.8 (**C**$H_2CH_3$), 34.8 (**C**$H_2$CHOPBB), 35.5 (**C**$H_2$CHOPMB), 54.8 (O**C**$H_3$), 69.9 (**C**$H_2$Ar), 70.8 (**C**$H_2$Ar), 77.9 (**C**HOPBB), 80.2 (**C**H$CH_2$CHOPMB), 82.9 (**C**HOPMB), 83.2 (C=**C**$H_2$), 83.2 (**C**H$CH_2$CHOPBB), 85.9 (**C**HEt), 114.1 (Ar), 121.6 (Ar), 127.5 (Ar), 129.4 (Ar), 130.9 (Ar), 131.7 (Ar), 137.6 (Ar), 159.8 (Ar), 162.2 (**C**=$CH_2$); *m/z* ($ES^+$) 1031 (2M+$Na^+$, 65%), 1029 (2M+$Na^+$, 75), 1027 (2M+$Na^+$, 65), 527 (M+$Na^+$, 100), 525 (M+$Na^+$, 100), 522 (M+$NH_4^+$, 15), 520 (M+$NH_4^+$, 15); Accurate mass ($ES^+$): Found 527.1232, $C_{26}H_{31}{}^{81}BrNaO_5$ (M+$Na^+$) requires 527.1228, found 525.1245, $C_{26}H_{31}{}^{79}BrNaO_5$ (M+$Na^+$) requires 525.1247; $[\alpha]_D^{25}$ +44.0 (c = 0.06 in $CH_2Cl_2$).

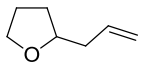
**2-(Iodomethyl)tetrahydrofuran**[169] **(292)**



*According to the modified procedure of Deng et al.*[170]: To a solution of tetrahydrofurfuryl alcohol (**291**) (1.2 g, 11.8 mmol) in THF (160 mL) at 0 °C was added triphenylphosphine (9.3 g, 35.3 mmol) and imidazole (4.8 g, 70.5 mmol). The reaction mixture was stirred at 0 °C for 10 min and then iodine (9.0 g, 35.3 mmol) was added in 3 portions. The reaction mixture was stirred at 0 °C for 10 min and then allowed to warm to RT and stirred for 2 h. The reaction mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ (80 mL) and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was filtered to remove most of the triphenylphosphine oxide, washing through with diethyl ether. The filtrate was concentrated *in vacuo* and purification by fractional vacuum distillation (b.p. 68–72 °C/17 mbar (lit. 97–100 °C/17 torr (=23 mbar)[171]) gave the title compound (**292**) as a colourless oil (935 mg, 4.43 mmol, 38%); $\delta_H$ (400 MHz, $CDCl_3$) 1.61–1.72 (1H, m, C**H**H'$CH_2CH_2O$), 1.85–2.02 (2H, m, $CH_2$C**H**$_2CH_2O$), 2.05–2.15 (1H, m, CH**H'**$CH_2CH_2O$), 3.20 (1H, dd, *J*=10.0, 6.5 Hz, C**H**H'I), 3.20

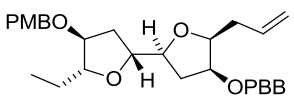
(1H, dd, *J*=10.0, 5.0 Hz, CH**H'**I), 3.79–3.86 (1H, m, $CH_2CH_2CHH'O$), 3.91–4.03 (2H, m, $CH_2CH_2CHH'O$, $CHCH_2I$); $\delta_C$ (100 MHz, $CDCl_3$) 10.5 ($CH_2I$), 26.1 ($CH_2CH_2CH_2O$), 31.9 ($CH_2CH_2CH_2O$), 68.9 ($CH_2CH_2CH_2O$), 78.5 ($CHCH_2I$); Accurate mass ($FI^+$): Found 211.9691, $C_5H_9OI$ ($M^+$) requires 211.9698.

**2-Allyltetrahydrofuran**[172] **(293)**



*According to the modified procedure of Han and Lowary*[124b]: To a stirred solution of 2-(iodomethyl)tetrahydrofuran (**292**) (222 mg, 1.05 mmol) in THF (5.6 mL) at 0 °C was added vinylmagnesium bromide (4.2 mL, 1.0 M in THF, 4.19 mmol). The reaction mixture was allowed to warm to RT and stirred for 4 h before being quenched by slow addition of sat. aq. $NH_4Cl$ (5 mL). The reaction mixture was diluted with $H_2O$ (5 mL) and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by fractional vacuum distillation (b.p. 95–110 °C/133 mbar (lit. 102–105 °C/100 mmHg (=133 mbar)[172]) gave the title compound (**293**) as a colourless oil (22 mg, 0.20 mmol, 19%); $\delta_H$ (400 MHz, $CDCl_3$) 1.45–1.56 (1H, m, $CHH'CH_2CH_2O$), 1.78–2.01 (3H, m, $CH_2CH_2CH_2O$, $CHH'CH_2CH_2O$), 2.25 (1H, dtt, *J*=14.0, 6.5, 1.5 Hz, $CHH'CH=CH_2$), 2.33 (1H, dtt, *J*=14.0, 7.0, 1.5 Hz, $CHH'CH=CH_2$), 3.72 (1H, td, *J*=8.0, 6.5 Hz, $CH_2CH_2CHH'O$), 3.82–3.92 (2H, m, $CH_2CH_2CHH'O$, $CHCH_2CH=CH_2$), 5.02–5.13 (2H, m, $CH_2CH=CH_2$), 5.82 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, $CH_2CH=CH_2$).

***(2S,2'R,4S,4'S,5S,5'R)-5-Allyl-4-(4-bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran*** **(294)**

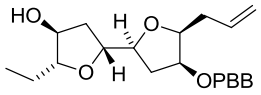



*According to the modified procedure of Han and Lowary*[124b]:(2*S*,2'*R*,4*S*,4'*S*,5*R*,5'*R*)-4-(4-Bromobenzyloxy)-5'-ethyl-5-(iodomethyl)-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran (**289**) (120 mg, 0.19 mmol)

was dried three times *via* azeotroping with dry benzene and then dissolved in dry benzene (2.7 mL). To this stirred solution was added vinylmagnesium bromide (3.8 mL, 1.0 M in THF, 3.8 mmol) and the reaction mixture was stirred for 4 h at 40 °C, cooled to 0 °C and quenched by slow addition of sat. aq. $NH_4Cl$ (2 mL). The reaction mixture was diluted with $H_2O$ (3 mL) and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50:1→25:1 DCM:EtOAc) gave recovered starting material (31 mg, 0.05 mmol, 26%) and the title compound (**294**) as a colourless oil (57 mg, 0.11 mmol, 58%); $R_f$ 0.67 (20:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3071m, 2960s (CH), 2933s, 2875s, 1621m (C=C), 1513s, 1256s, 1070s, 919m, 806s; $\delta_H$ (500 MHz, $C_6D_6$) 0.95 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.44–1.60 (2H, m, $C\mathbf{H}_2CH_3$), 1.83–1.96 (2H, m, C**H**H'CHOPBB, C**H**H'CHOPMB), 2.05 (1H, ddd, *J*=14.0, 5.5, 2.0 Hz, CH**H'**CHOPBB), 2.31 (1H, ddd, *J*=13.0, 6.0, 2.5 Hz, CH**H'**CHOPMB), 2.56 (1H, dt, *J*=14.0, 7.0 Hz, C**H**H'$CH{=}CH_2$), 2.66 (1H, dt, *J*=14.0, 7.0 Hz, CH**H'**$CH{=}CH_2$), 3.32 (3H, s, $OC\mathbf{H}_3$), 3.45–3.49 (1H, m, C**H**OPBB), 3.61 (1H, td, *J*=7.0, 4.0 Hz, C**H**$CH_2CH{=}CH_2$), 3.66 (1H, dt, *J*=6.0, 3.0 Hz, C**H**OPMB), 3.81 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.84 (1H, td, *J*=7.5, 5.5 Hz, C**H**$CH_2$CHOPBB), 4.03 (1H, td, *J*=6.5, 3.0 Hz, C**H**Et), 4.10 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.20 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.29 (1H, *J*=11.5 Hz, CH**H'**Ar), 4.30–4.36 (1H, m, C**H**$CH_2$CHOPMB), 5.03–5.07 (1H, m, CH=C**H**H'), 5.10–5.16 (1H, m, CH=CH**H'**), 5.94 (1H, ddt, *J*=17.5, 10.0, 7.0 Hz, C**H**=$CH_2$), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.10–7.20 (2H, m, Ar**H**), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.6 ($CH_2\mathbf{C}H_3$), 28.0 ($\mathbf{C}H_2CH_3$), 34.4 ($\mathbf{C}H_2CH{=}CH_2$), 35.3 ($\mathbf{C}H_2$CHOPBB), 35.9 ($\mathbf{C}H_2$CHOPMB), 54.8 ($O\mathbf{C}H_3$), 70.0 ($\mathbf{C}H_2$Ar), 70.8 ($\mathbf{C}H_2$Ar), 79.4 (**C**HOPBB), 81.1 (**C**H$CH_2$CHOPBB), 81.5 (**C**H$CH_2$CHOPMB), 82.6 (**C**H$CH_2CH{=}CH_2$), 83.1 (**C**HOPMB), 85.9 (**C**HEt), 114.1 (Ar), 116.6 ($CH{=}\mathbf{C}H_2$), 121.6 (Ar), 129.4 (Ar), 129.4 (Ar), 131.1 (Ar), 131.7 (Ar), 136.0 (**C**H=$CH_2$), 137.9 (Ar), 159.7 (Ar); *m*/*z* ($ES^+$) 1087 ($2M+Na^+$, 30%), 1085 ($2M+Na^+$, 55), 1083 ($2M+Na^+$, 35), 555 ($M+Na^+$, 100), 553 ($M+Na^+$, 100), 550 ($M+NH_4^+$, 25), 548 ($M+NH_4^+$,

25); Accurate mass ($ES^+$): Found 555.1531, $C_{28}H_{35}{}^{81}BrNaO_5$ ($M+Na^+$) requires 555.1541, found 553.1543, $C_{28}H_{35}{}^{79}BrNaO_5$ ($M+Na^+$) requires 553.1560; $[\alpha]_D^{25}$ +47.1 (c = 0.31 in $CH_2Cl_2$).

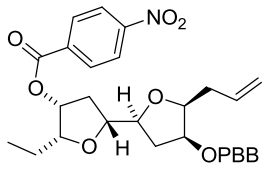
***(2R,2'S,4S,4'S,5R,5'S)-5'-Allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-ol* (295)**




*According to the modified procedure of Burton et al.*[92]: To a stirred solution of (2*S*,2'*R*,4*S*,4'*S*,5*S*,5'*R*)-5-allyl-4-(4-bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran (**294**) (32 mg, 0.06 mmol) in DCM (6 mL) was added boron trichloride-methyl sulfide complex (0.15 mL, 2.0 M in DCM, 0.3 mmol). The reaction mixture was stirred at RT for 5 min and then quenched by addition of sat. aq. $NaHCO_3$ (5 mL). After stirring vigorously for 10 min, the reaction mixture was diluted with $H_2O$ (5 mL) and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1 petrol:EtOAc) gave the title compound (**295**) as a colourless oil (25 mg, 0.05 mmol, quant.); $R_f$ 0.42 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3433s br (OH), 3074m, 2972s (CH), 2926s, 2880s, 1639m (C=C), 1487s, 1345m, 1071s, 918m, 805m; $\delta_H$ (500 MHz, $C_6D_6$) 0.72 (1H, d, *J*=4.0 Hz, O**H**), 0.93 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.31–1.51 (2H, m, $C\mathbf{H}_2CH_3$), 1.80–2.02 (4H, m, $C\mathbf{H}_2CHOH$, $C\mathbf{H}_2CHOPBB$), 2.51–2.59 (1H, m, C**H**H'CH=$CH_2$), 2.60–2.68 (1H, m, CH**H'**CH=$CH_2$), 3.44–3.48 (1H, m, C**H**OH), 3.56–3.64 (2H, m, $C\mathbf{H}CH_2CH=CH_2$, C**H**Et), 3.65–3.69 (1H, m, C**H**OPBB), 3.77 (1H, td, *J*=7.5, 5.5 Hz, $C\mathbf{H}CH_2CHOH$), 3.82 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.10 (1H, *J*=12.0 Hz, CH**H'**Ar), 4.22 (1H, dt, *J*=7.5, 7.0 Hz, $C\mathbf{H}CH_2CHOPBB$), 5.03–5.08 (1H, m, CH=C**H**H'), 5.10–5.16 (1H, m, CH=CH**H'**), 5.93 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, C**H**=$CH_2$), 6.85 (2H, d, *J*=8.0 Hz, Ar**H**), 7.25 (2H, d, *J*=8.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.5 ($CH_2\mathbf{C}H_3$), 27.6 ($\mathbf{C}H_2CH_3$), 34.4 ($\mathbf{C}H_2CH=CH_2$), 35.2 ($\mathbf{C}H_2CHOH$), 39.0 ($\mathbf{C}H_2CHOPBB$), 70.0 ($\mathbf{C}H_2Ar$), 76.1 (**C**HOPBB), 79.4 (**C**HOH), 80.9

(**C**HCH$_2$CHOPBB), 81.0 (**C**HCH$_2$CHOH), 82.5 (**C**HCH$_2$CH=CH$_2$), 88.0 (**C**HEt), 116.6 (CH=**C**H$_2$), 121.6 (Ar), 129.4 (Ar), 131.7 (Ar), 136.0 (**C**H=CH$_2$), 137.9 (Ar); *m*/*z* (ES$^+$) 847 (2M+Na$^+$, 20%), 845 (2M+Na$^+$, 35), 843 (2M+Na$^+$, 20), 435 (M+Na$^+$, 100), 433 (M+Na$^+$, 100), 430 (M+NH$_4^+$, 20), 428 (M+NH$_4^+$, 20); Accurate mass (ES$^+$): Found 435.0969, $C_{20}H_{27}{}^{81}BrNaO_4$ (M+Na$^+$) requires 435.0965, found 433.0988, $C_{20}H_{27}{}^{79}BrNaO_4$ (M+Na$^+$) requires 433.0985; $[\alpha]_D^{25}$ +46.0 (c = 0.45 in $CH_2Cl_2$).

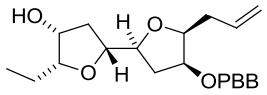
***(2R,2'S,4R,4'S,5R,5'S)-5'-Allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-yl 4-nitrobenzoate* (296)**




*According to the modified procedures of Broadwith*[58] *and Proctor et al.*[125]: To a stirred solution of (2*R*,2'*S*,4*S*,4'*S*,5*R*,5'*S*)-5'-allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-ol (**295**) (31 mg, 0.08 mmol) and triphenylphosphine (198 mg, 0.75 mmol) in THF (0.86 mL) at 0 °C was added diisopropyl azodicarboxylate (0.15 mL, 152 mg, 0.75 mmol). The reaction mixture was stirred at 0 °C for 30 min and then 4-nitrobenzoic acid (126 mg, 0.75 mmol) was added. The cooling bath was removed and the reaction was stirred for 2 h before being transferred to a separating funnel (washing with EtOAc) and being washed sequentially with 15% aq. $H_2O_2$ (5 mL) and sat. aq. $Na_2S_2O_3$ (5 mL). The aqueous layers were sequentially re-extracted with EtOAc (10 mL) and then the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid purification by flash column chromatography (15:1 petrol:acetone) gave the title compound (**296**) as a colourless oil (36 mg, 0.06 mmol 85%); $R_f$ 0.48 (2:1 petrol:EtOAc); $\nu_{max}$/cm$^{-1}$ (thin film) 3056m, 2978s (CH), 2936s, 2877s, 1721s (C=O), 1529s ($NO_2$), 1375s ($NO_2$), 1270s, 1071s, 916m, 720m; $\delta_H$ (500 MHz, $C_6D_6$) 0.93 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.53–1.62 (1H, m, C**H**H'CH$_3$), 1.70–1.81 (1H, m, CH**H'**CH$_3$), 1.95 (1H, ddd, *J*=14.0, 8.0, 5.5 Hz, C**H**H'CHOPBB),

2.13 (1H, ddd, *J*=14.0, 4.5, 2.0 Hz, CH**H'**CHOPBB), 2.20–2.31 (2H, m, C**H**$_2$CHOC(O)Ar), 2.46–2.54 (1H, m, C**H**H'CH=CH$_2$), 2.55–2.62 (1H, m, CH**H'**CH=CH$_2$), 3.35 (1H, ddd, *J*=9.0, 5.5, 3.5 Hz, C**H**Et), 3.48 (1H, ddd, *J*=5.5, 4.0, 2.0 Hz, C**H**OPBB), 3.61 (1H, td, *J*=7.0, 4.0 Hz, C**H**CH$_2$CH=CH$_2$), 3.87 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.92–4.02 (2H, m, C**H**CH$_2$CHOC(O)Ar, C**H**CH$_2$CHOPBB), 4.13 (1H, *J*=12.0 Hz, CH**H'**Ar), 4.99–5.02 (1H, m, CH=C**H**H'), 5.06–5.12 (1H, m, CH=CH**H'**), 5.26 (1H, ddd, *J*=5.5, 3.5, 2.0 Hz, C**H**OC(O)Ar), 5.86 (1H, ddt, *J*=17.0, 10.5, 7.0 Hz, C**H**=CH$_2$), 6.88 (2H, d, *J*=8.0 Hz, Ar**H**), 7.29 (2H, d, *J*=8.0 Hz, Ar**H**), 7.64 (2H, d, *J*=9.0 Hz, Ar**H**), 7.78 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.9 (CH$_2$**C**H$_3$), 22.8 (**C**H$_2$CH$_3$), 34.4 (**C**H$_2$CH=CH$_2$), 35.3 (**C**H$_2$CHOPBB), 36.9 (**C**H$_2$CHOC(O)Ar), 70.2 (**C**H$_2$Ar), 76.5 (**C**HOC(O)Ar), 79.5 (**C**HOPBB), 80.6 (**C**HCH$_2$CHOC(O)Ar), 80.7 (**C**HCH$_2$CHOPBB), 82.7 (**C**HCH$_2$CH=CH$_2$), 83.6 (**C**HEt), 116.8 (CH=**C**H$_2$), 121.7 (Ar), 123.5 (Ar), 129.4 (Ar), 130.5 (Ar), 131.8 (Ar), 135.4 (Ar), 135.7 (**C**H=CH$_2$), 137.8 (Ar), 150.7 (Ar), 164.0 (C=O); *m/z* (ES$^+$) 584 (M+Na$^+$, 55%), 582 (M+Na$^+$, 60); Accurate mass (ES$^+$): Found 584.1077, $C_{27}H_{30}{}^{81}BrNNaO_7$ (M+Na$^+$) requires 584.1079, found 582.1099, $C_{27}H_{30}{}^{79}BrNNaO_7$ (M+Na$^+$) requires 582.1098; $[\alpha]_D^{25}$ +42.2 (c = 1.0 in $CH_2Cl_2$).

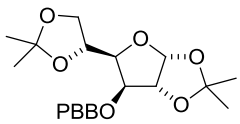
***(2R,2'S,4R,4'S,5R,5'S)-5'-Allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-ol* (297)**




To a solution of (2*R*,2'*S*,4*R*,4'*S*,5*R*,5'*S*)-5'-allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-yl 4-nitrobenzoate (**296**) (45 mg, 80 μmol) in methanol (1.4 mL) at 0 °C was added potassium carbonate (55 mg, 0.40 mmol). The reaction mixture was allowed to warm to RT and stirred for 2 h before being diluted with $H_2O$ (4 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1 petrol:EtOAc) gave the title

compound (**297**) as a colourless oil (31 mg, 75 μmol, 94%); $R_f$ 0.52 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3444s br (OH), 2957s (CH), 2925s, 2853s, 1641m, 1484s, 1069s, 948s, 918m; $\delta_H$ (500 MHz, $C_6D_6$) 1.05 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.25 (1H, ddd, *J*=14.0, 7.5, 2.0 Hz, C**H**H'CHOPBB), 1.53 (1H, ddd, *J*=14.0, 8.5, 6.5 Hz, CH**H'**CHOPBB), 1.85 (1H, ddd, *J*=13.5, 10.0, 5.0 Hz, C**H**H'CHOH), 1.88–2.02 (2H, m, $C\mathbf{H}_2CH_3$), 2.18 (1H, dd, *J*=13.5, 2.5 Hz, CH**H'**CHOH), 2.38–2.46 (1H, m, C**H**H'$CH=CH_2$), 2.52–2.60 (1H, m, CH**H'**$CH=CH_2$), 3.28 (1H, ddd, *J*=6.5, 4.0, 2.0 Hz, C**H**OPBB), 3.38–3.45 (2H, m, C**H**$CH_2CH=CH_2$, C**H**Et), 3.65 (1H, d, *J*=10.5 Hz, O**H**), 3.76 (1H, d, *J*=12.5 Hz, C**H**H'Ar), 3.88–3.97 (2H, m, C**H**OH, C**H**$CH_2$CHOH), 3.98 (1H, *J*=12.5 Hz, CH**H'**Ar), 3.99–4.04 (1H, m, C**H**$CH_2$CHOPBB), 5.00–5.04 (1H, m, CH=C**H**H'), 5.05–5.15 (1H, m, CH=CH**H'**), 5.78 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, C**H**$=CH_2$), 6.84 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 11.0 ($CH_2\mathbf{C}H_3$), 22.8 ($\mathbf{C}H_2CH_3$), 33.7 ($\mathbf{C}H_2CH=CH_2$), 34.7 ($\mathbf{C}H_2$CHOH), 34.8 ($\mathbf{C}H_2$CHOPBB), 70.0 ($\mathbf{C}H_2$Ar), 71.3 (**C**HOH), 79.0 (**C**HOPBB), 79.4 (**C**H$CH_2$CHOPBB), 79.6 (**C**H$CH_2$CHOH), 82.5 (**C**H$CH_2CH=CH_2$), 86.4 (**C**HEt), 117.2 ($CH=\mathbf{C}H_2$), 121.7 (Ar), 129.2 (Ar), 131.8 (Ar), 135.1 (**C**H$=CH_2$), 137.6 (Ar); *m/z* ($ES^+$) 435 ($M+Na^+$, 100%), 433 ($M+Na^+$, 100); Accurate mass ($ES^+$): Found 435.0951, $C_{20}H_{27}{}^{81}BrNaO_4$ ($M+Na^+$) requires 435.0965, found 433.0969, $C_{20}H_{27}{}^{79}BrNaO_4$ ($M+Na^+$) requires 433.0985; $[\alpha]_D^{25}$ +26.8 (c = 1.0 in $CH_2Cl_2$).

**(3a*R*,5*R*,6*S*,6a*R*)-6-(4-Bromobenzyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole[173] (299)**

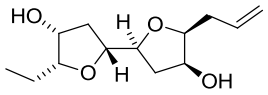


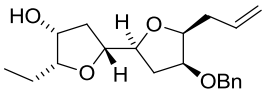

Diacetone-D-glucose (**298**) (1.0 g, 3.84 mmol), 4-bromobenzylbromide (1.44 g, 5.76 mmol) and tetrabutylammonium iodide (142 mg, 0.38 mmol) were dissolved in THF (15 mL) and cooled to -78 °C. To this stirred solution was added sodium hydride (384 mg, 60% dispersion in mineral oil, 9.60 mmol) and the reaction mixture was allowed to warm to RT, stirred for 16 h and then

cooled to 0 °C. The reaction mixture was quenched by addition of $H_2O$ (20 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine (20 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1 petrol:EtOAc) gave the title compound (**299**) as a colourless oil (1.58 g, 3.68 mmol, 96%); $R_f$ 0.28 (5:1 petrol:EtOAc); $\delta_H$ (400 MHz, $CDCl_3$) 1.32 (3H, s, C**H**$_3$), 1.38 (3H, s, C**H**$_3$), 1.43 (3H, s, C**H**$_3$), 1.50 (3H, s, C**H**$_3$), 3.98–4.03 (2H, m, CHC**H**H'O, C**H**OPBB), 4.10–4.15 (2H, m, CHCH**H'**O, C**H**CHCH$_2$O) 4.34 (1H, dt, *J*=8.0, 6.0 Hz, C**H**CH$_2$O), 4.57–4.62 (2H, m, C**H**H'Ar, C**H**CHOPBB), 4.65 (1H, *J*=12.0 Hz, CH**H'**Ar), 5.90 (1H, d, *J*=3.5 Hz, OC**H**O), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**), 7.48 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 25.4 (**C**H$_3$), 26.2 (**C**H$_3$), 26.8 (**C**H$_3$), 26.8 (**C**H$_3$), 67.5 (CH**C**H$_2$O), 71.6 (**C**H$_2$Ar), 72.4 (**C**HCH$_2$O), 81.3 (**C**HCHCH$_2$O), 81.8 (**C**HOPBB), 82.6 (**C**HCHOPBB), 105.3 (O**C**HO), 109.1 (**C**(CH$_3$)$_2$), 111.9 (**C**(CH$_3$)$_2$), 121.7 (Ar), 129.3 (Ar), 131.5 (Ar), 136.7 (Ar); *m/z* (ES$^+$) 453 (M+Na$^+$, 100%), 451 (M+Na$^+$, 95), 448 (M+NH$_4^+$, 10), 446 (M+NH$_4^+$, 10); $[\alpha]_D^{25}$ -27.4 (c = 1.0 in $CH_2Cl_2$).

***(2S,2'R,4S,4'R,5S,5'R)-5-Allyl-5'-ethyloctahydro-[2,2'-bifuran]-4,4'-diol*** **(300)**

***(2R,2'S,4R,4'S,5R,5'S)-5'-Allyl-4'-(benzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-ol*** **(301)**




**Method 1:** *According to the modified procedure of Burton et al.*[128]: To a stirred solution of (2*R*,2'*S*,4*R*,4'*S*,5*R*,5'*S*)-5'-allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-ol (**297**) (0.7 mg, 1.7 μmol) in THF (0.1 mL) at -78 °C was added freshly prepared LiDBB (8 μL of a solution prepared by sonicating 4,4'-di-*tert*-butylbiphenyl (1.00 g, 3.8 mmol) and lithium (26 mg, 3.8 mmol) in THF (4 mL) for 2 h). The reaction mixture was stirred at -78 °C for 2 min, during which time the reaction mixture changed from green/brown to colourless. Further LiDBB (4 μL) was added 5 times, but with the reaction mixture returning to colourless each time. Analysis by TLC showed no starting material present and so the reaction mixture was quenched by addition of

sat. aq. $NH_4Cl$ (1 mL). After warming to RT the aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organics were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:1→2:1→1:1 petrol:EtOAc) gave the two title compounds (**300** and **301**) as colourless oils.

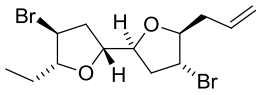
1. (2*S*,2'*R*,4*S*,4'*R*,5*S*,5'*R*)-5-Allyl-5'-ethyloctahydro-[2,2'-bifuran]-4,4'-diol (**300**) (<1 mg, ~50%): $R_f$ 0.13 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3408s br (OH), 3077w, 2966s (CH), 2940s, 2878s, 1642m, 1445s, 1051s, 920m; $\delta_H$ (500 MHz, $C_6D_6$) 0.94 (3H, t, *J*=7.5 Hz, $CH_2CH_3$), 1.64–1.85 (6H, m, 2 × $CH_2CHOH$, $CH_2CH_3$), 2.46–2.53 (1H, m, CH**H'**$CH=CH_2$), 2.55–2.63 (1H, m, CH**H'**$CH=CH_2$), 2.89 (1H, d, *J*=8.0 Hz, O**H**), 3.11 (1H, d, *J*=8.0 Hz, O**H**), 3.25 (1H, td, *J*=7.0, 3.0 Hz, C**H**Et), 3.42 (1H, td, *J*=7.0, 3.0 Hz, C**H**$CH_2CH=CH_2$), 3.72–3.82 (2H, m, 2 × C**H**OH), 3.92–4.99 (2H, m, 2 × C**H**$CH_2CHOH$), 5.00–5.05 (1H, m, CH=C**H**H'), 5.12–5.18 (1H, m, CH=CH**H'**), 5.90 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, C**H**$=CH_2$); $\delta_C$ (125 MHz, $C_6D_6$) 10.9 ($CH_2CH_3$), 22.1 ($CH_2CH_3$), 34.0 ($CH_2CH=CH_2$), 36.0 ($CH_2CHOH$), 36.3 ($CH_2CHOH$), 71.4 (**C**HOH), 71.6 (**C**HOH), 79.2 (**C**H$CH_2CHOH$), 79.5 (**C**H$CH_2CHOH$), 83.8 (**C**H$CH_2CH=CH_2$), 85.8 (**C**HEt), 116.9 ($CH=CH_2$), 135.5 ($CH=CH_2$); *m/z* ($ES^+$) 265 ($M+Na^+$, 100%), 243 ($M+H^+$, 25); Accurate mass ($ES^+$): Found 265.1412, $C_{13}H_{22}NaO_4$ ($M+Na^+$) requires 265.1410; $[\alpha]_D^{25}$ -5.9 (c = 0.37 in $CH_2Cl_2$).

2. (2*R*,2'*S*,4*R*,4'*S*,5*R*,5'*S*)-5'-Allyl-4'-(benzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-ol (**301**) (<1 mg, ~50%): $R_f$ 0.64 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3442s br (OH), 2960s (CH), 2918s, 2850s, 1617m, 1457s, 1261s, 1088s, 1019s, 802s; $\delta_H$ (500 MHz, $C_6D_6$) 1.05 (3H, t, *J*=7.5 Hz, $CH_2CH_3$), 1.20–1.40 (1H, m, C**H**H'CHOH), 1.50–1.61 (1H, m, CH**H'**CHOH), 1.80–1.89 (1H, m, C**H**H'CHOBn), 1.81–2.02 (2H, m, $CH_2CH_3$), 2.25 (1H, dd, *J*=14.0, 3.0 Hz, CH**H'**CHOBn), 2.44–2.51 (1H, m, C**H**H'$CH=CH_2$), 2.56–2.65 (1H, m, CH**H'**$CH=CH_2$), 3.34–3.45 (3H, m, C**H**OH, C**H**$CH_2CH=CH_2$, C**H**Et), 3.72 (1H, d, *J*=11.0 Hz, O**H**), 3.88–4.04 (3H, m, C**H**OBn, C**H**$CH_2CHOBn$, C**H**$CH_2CHOH$), 3.97 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.20 (1H, *J*=12.0 Hz,

CH**H'**Ar), 5.00–5.05 (1H, m, CH=C**H**H'), 5.11–5.17 (1H, m, CH=CH**H'**), 5.80 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, C**H**=$CH_2$), 7.02–7.26 (5H, m, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 11.0 ($CH_2$**C**$H_3$), 22.8 (**C**$H_2CH_3$), 33.7 (**C**$H_2CH$=$CH_2$), 34.6 (**C**$H_2$CHOBn), 34.7 (**C**$H_2$CHOH), 70.9 (**C**$H_2$Ar), 71.3 (**C**HOBn), 78.8 (**C**HOH), 79.4 (**C**H$CH_2$CHOH), 79.6 (**C**H$CH_2$CHOBn), 82.6 (**C**H$CH_2$CH=$CH_2$), 86.4 (**C**HEt), 117.1 (CH=**C**$H_2$), 127.5 (Ar), 128.5 (Ar), 138.6 (Ar), 135.2 (**C**H=$CH_2$), 138.7 (Ar); *m/z* ($ES^+$) 355 ($M+Na^+$, 100%), 333 ($M+H^+$, 20); Accurate mass ($ES^+$): Found 355.1875, $C_{20}H_{28}NaO_4$ ($M+Na^+$) requires 355.1880; $[\alpha]_D^{25}$ +22.0 (c = 0.009 in $CH_2Cl_2$).

**Method 2:** *According to the modified procedure of Burton et al.*[92]: To a stirred solution of (2*R*,2'*S*,4*R*,4'*S*,5*R*,5'*S*)-5'-allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-ol (**297**) (24 mg, 0.06 mmol) in DCM (5.7 mL) was added boron trichloride (0.29 mL, 1.0 M in DCM, 0.29 mmol). The reaction mixture was stirred at RT for 30 min and then quenched by addition of sat. aq. $NaHCO_3$ (2 mL). After stirring vigorously for 10 min, the reaction mixture was diluted with $H_2O$ (3 mL) and the aqueous layer was extracted with DCM (4 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 petrol:EtOAc) gave (2*S*,2'*R*,4*S*,4'*R*,5*S*,5'*R*)-5-allyl-5'-ethyloctahydro-[2,2'-bifuran]-4,4'-diol (**300**) as a colourless oil (14 mg, 0.06 mmol, quant.); data as shown above.

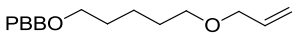
***(2S,2'R,4R,4'S,5S,5'R)-5-Allyl-4,4'-dibromo-5'-ethyloctahydro-2,2'-bifuran* (302)**




*According to the modified procedure of Broadwith*[58]: To a solution of (2*S*,2'*R*,4*S*,4'*R*,5*S*,5'*R*)-5-allyl-5'-ethyloctahydro-[2,2'-bifuran]-4,4'-diol (**300**) (17 mg, 0.07 mmol) in dry toluene (2.8 mL) was added carbon tetrabromide (114 mg, 0.34 mmol) and triphenylphosphine (90 mg, 0.34 mmol). The reaction mixture was heated to 80 °C and stirred for 75 min. The reaction mixture was then cooled to RT, diluted with DCM (2 mL) and dry-loaded onto silica. Purification by flash column chromatography (20:1 petrol:diethyl ether) gave the title compound (**302**) as a colourless oil (18 mg,

0.05 mmol, 70%); $R_f$ 0.51 (20:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2962s (CH), 2925s, 2873s, 1643m, 1454s, 1074s. 1066s, 918m, 798m; $\delta_H$ (500 MHz, $C_6D_6$) 0.82 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.17–1.28 (1H, m, C**H**H'$CH_3$), 1.33–1.43 (1H, m, CH**H'**$CH_3$), 1.85–1.95 (2H, m, 2 × C**H**H'CHBr), 1.99–2.09 (3H, m, C**H**H'CH=$CH_2$, 2 × CH**H'**CHBr), 2.10–2.17 (1H, m, CH**H'**CH=$CH_2$), 3.52 (1H, dt, *J*=7.5, 5.5 Hz, EtCHC**H**Br), 3.63 (1H, dt, *J*=7.5, 5.5 Hz, AllylCHC**H**Br), 3.83–3.89 (2H, m, 2 × C**H**$CH_2$CHBr), 3.91 (1H, dt, *J*=7.5, 5.5 Hz, C**H**Et), 4.06 (1H, dt, *J*=6.5, 5.5 Hz, C**H**$CH_2$CH=$CH_2$), 4.94–5.00 (2H, m, CH=C**H**$_2$), 5.71 (1H, ddt, *J*=17.5, 11.0, 7.0 Hz, C**H**=$CH_2$); $\delta_C$ (125 MHz, $C_6D_6$) 10.2 ($CH_2\mathbf{C}H_3$), 26.9 (**C**$H_2CH_3$), 38.0 (**C**$H_2$CH=$CH_2$), 39.1 (**C**$H_2$CHBr), 39.4 (**C**$H_2$CHBr), 48.9 (**C**HBr), 49.3 (**C**HBr), 79.6 (**C**H$CH_2$CHBr), 80.0 (**C**H$CH_2$CHBr), 86.8 (**C**H$CH_2$CH=$CH_2$), 88.7 (**C**HEt), 117.8 (CH=**C**$H_2$), 133.8 (**C**H=$CH_2$); *m/z* ($FI^+$) 329 (M–$C_3H_5^+$, 50%), 327 (M–$C_3H_5^+$, 100), 325 (M–$C_3H_5^+$, 50), 288 (M–$HBr^+$, 10), 286 (M–$HBr^+$, 10), 191 (M–$C_6H_{10}BrO^+$, 10), 189 (M–$C_6H_{10}BrO^+$, 10), 179 (M–$C_7H_{10}BrO^+$, 10), 177 (M–$C_7H_{10}BrO^+$, 10); Accurate mass ($FI^+$): Found 328.9418, $C_{10}H_{15}O_2{}^{81}Br_2$ (M–$C_3H_5^+$) requires 328.9419, found 326.9403, $C_{10}H_{15}O_2{}^{81}Br^{79}Br$ (M–$C_3H_5^+$) requires 326.9419, found 324.9426, $C_{10}H_{15}O_2{}^{79}Br_2$ (M–$C_3H_5^+$) requires 324.9439; $[\alpha]_D^{25}$ -3.9 (c = 1.0 in $CHCl_3$), -5.1 (c = 0.66 in $CH_2Cl_2$).

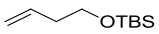
***1-(((5-(Allyloxy)pentyl)oxy)methyl)-4-bromobenzene* (320)**




To a stirred solution of 5-(4-bromobenzyloxy)pentan-1-ol (**198**) (52 mg, 0.22 mmol) in DMF (0.73 mL) was added sodium hydride (18 mg, 60% dispersion in mineral oil, 0.44 mmol). The suspension was stirred for 30 min at RT and then allyl bromide (28 μL, 40 mg, 0.33 mmol) was added. The reaction mixture was stirred for 16 h and then quenched by addition of $H_2O$ (2 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with $H_2O$ (3 × 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**320**) as a colourless oil (31 mg, 0.10 mmol, 47%); $R_f$ 0.19 (20:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin

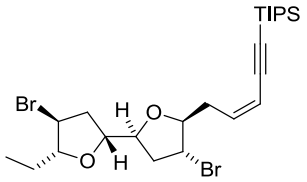
film) 3014w, 2937s (CH), 2858s, 1358s, 1298s, 1070s, 1011s, 802s, 735s; $\delta_H$ (500 MHz, $CDCl_3$) 1.39–1.49 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.55–1.68 (4H, m, 2 × C**H**$_2$CH$_2$O), 3.43 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 3.47 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 3.96 (2H, dt, *J*=5.5, 1.5 Hz, C**H**$_2$CH=CH$_2$), 4.45 (2H, s, C**H**$_2$Ar), 5.17 (1H, dq, *J*=10.5, 1.5 Hz, CH=C**H**H'), 5.27 (1H, dq, *J*=17.0, 1.5 Hz, CH=CH**H'**), 5.92 (1H, ddt, *J*=17.0, 10.5, 5.5 Hz, C**H**=CH$_2$), 7.21 (2H, d, *J*=8.5 Hz, Ar**H**), 7.47 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 22.8 (**C**H$_2$CH$_2$CH$_2$O), 29.5 (**C**H$_2$CH$_2$O), 29.5 (**C**H$_2$CH$_2$O), 70.2 (**C**H$_2$O), 70.4 (**C**H$_2$O), 71.8 (**C**H$_2$CH=CH$_2$), 72.1 (**C**H$_2$Ar), 116.7 (CH$_2$CH=**C**H$_2$), 121.3 (Ar), 129.2 (Ar), 131.4 (Ar), 135.0 (CH$_2$**C**H=CH$_2$), 137.7 (Ar); *m*/*z* ($ES^+$) 337 ($M+Na^+$, 100%), 335 ($M+Na^+$, 100), 315 ($M+H^+$, 95), 313 ($M+H^+$, 95); Accurate mass ($ES^+$): Found 337.0591, $C_{15}H_{21}{}^{81}BrNaO_2$ ($M+Na^+$) requires 337.0597, found 335.0608, $C_{15}H_{21}{}^{79}BrNaO_2$ ($M+Na^+$) requires 335.0617.

**(But-3-en-1-yloxy)(*tert*-butyl)dimethylsilane**[174] **(323)**




To a stirred solution of 3-buten-1-ol (**322**) (100 mg, 1.39 mmol) in DMF (3 mL) was added imidazole (284 mg, 4.17 mmol) and *tert*-butylchlorodimethylsilane (251 mg, 1.66 mmol). The reaction mixture was stirred at RT for 16 h before being diluted with diethyl ether (20 mL). The organic layer was washed sequentially with $H_2O$ (4 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**323**) as a colourless oil (212 mg, 1.14 mmol, 82%); $R_f$ 0.89 (20:1 petrol:diethyl ether); $\delta_H$ (400 MHz, $CDCl_3$) 0.06 (6H, s, Si(C**H**$_3$)$_2$), 0.91 (9H, s, SiC(C**H**$_3$)$_3$), 2.29 (2H, q, *J*=7.0 Hz, C**H**$_2$CH=CH$_2$), 3.67 (2H, t, *J*=7.0 Hz, C**H**$_2$OTBS), 5.01–5.11 (2H, m, CH=C**H**$_2$), 5.83 (1H, ddt, *J*=17.0, 10.5, 7.0 Hz, C**H**=CH$_2$); $\delta_C$ (100 MHz, $CDCl_3$) -5.3 (Si(**C**H$_3$)$_2$), 18.3 (Si**C**(CH$_3$)$_3$), 25.9 (SiC(**C**H$_3$)$_3$), 37.5 (**C**H$_2$CH=CH$_2$), 62.8 (**C**H$_2$OTBS), 116.3 (CH$_2$CH=**C**H$_2$), 135.4 (CH$_2$**C**H=CH$_2$).

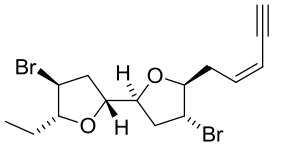
***((Z)-5-((2S,2'R,4R,4'S,5S,5'R)-4,4'-Dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)pent-3-en-1-yn-1-yl)triisopropylsilane* (325)**




To a stirred solution of (2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-5-allyl-4,4'-dibromo-5'-ethyloctahydro-2,2'-bifuran (**302**) (3 mg, 8.1 μmol) in dry, freeze-thaw degassed benzene (0.85 mL) was added a solution of (*E*)-(5-(allyloxy)pent-3-en-1-yn-1-yl)triisopropylsilane (**305**) (0.1 mL of solution of 37 mg (0.13 mmol) in 0.6 mL benzene) and a solution of bis(pyridine) substituted Grubbs catalyst (**306**) (0.1 mL of 6.6 mg (7.5 μmol) in 0.6 mL benzene). The reaction mixture was stirred at 65 °C and addition of the enyne and catalyst was repeated 5 times with 25 min intervals. The reaction mixture was then dry-loaded onto silica and purification by flash column chromatography (5:1→3:1→1:1→0:1 petrol:toluene) gave recovered starting material (**302**) (1.9 mg, 5.2 μmol, 64%) and the title compound (**325**) as a colourless oil (1.5 mg, 2.7 μmol, 33%, ~5:1 *Z*:*E*); $R_f$ 0.55 (20:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2942s (CH), 2865s, 2146m (C≡C), 1462s, 1070s, 882s; $\delta_H$ (500 MHz, $C_6D_6$) 0.82 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.09–1.26 (1H, m, C**H**H'$CH_3$), 1.18 (18H, s, $Si(CH(C\mathbf{H}_3)_2)_3$), 1.20 (3H, s, $Si(C\mathbf{H}(CH_3)_2)_3$), 1.30–1.43 (1H, m, CH**H'**$CH_3$), 1.77–2.12 (4H, m, 2 × C**H**$_2$CHBr), 2.49–2.57 (1H, m, C**H**H'CH=CH), 2.64–2.72 (1H, m, CH**H'**CH=CH), 3.53 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHEt), 3.79 (1H, dt, *J*=7.0, 5.0 Hz, C**H**BrCHCH$_2$CH=CH), 3.84–3.94 (3H, m, 2 × C**H**CH$_2$CHBr, C**H**Et), 4.14 (1H, dt, *J*=6.0, 5.5 Hz, C**H**CH$_2$CH=CH), 5.52 (1H, dt, *J*=11.0, 1.5 Hz, CH$_2$CH=C**H**), 5.76 (1H, dt, *J*=11.0, 7.5 Hz, CH$_2$C**H**=CH); $\delta_C$ (125 MHz, $C_6D_6$) 10.1 ($CH_2C\mathbf{H}_3$), 11.7 ($Si(\mathbf{C}H(CH_3)_2)_3$), 19.0 ($Si(CH(\mathbf{C}H_3)_2)_3$), 26.8 (**C**H$_2$CH$_3$), 34.9 (**C**H$_2$CH=CH), 39.4 (**C**H$_2$CHBr), 39.4 (**C**H$_2$CHBr), 48.9 (**C**HBr), 49.2 (**C**HBr), 79.6 (**C**HCH$_2$CHBr), 80.1 (**C**HCH$_2$CHBr), 86.7 (**C**HCH$_2$CH=CH), 88.7 (**C**HEt), 96.4 (**C**≡C), 104.0 (C≡**C**), 112.5 (CH$_2$CH=**C**H), 139.3 (CH$_2$**C**H=CH); *m*/*z* (ES$^+$) 573 (M+Na$^+$, 55%), 571 (M+Na$^+$, 100), 569 (M+Na$^+$, 55); Accurate mass (ES$^+$): Found 573.1035, $C_{24}H_{40}{}^{79}Br_2NaO_2Si$ (M+Na$^+$) requires

573.1017, found 571.1036, $C_{24}H_{40}{}^{81}Br_2NaO_2Si$ ($M+Na^+$) requires 571.1038, found 569.1057, $C_{24}H_{40}{}^{81}Br_2NaO_2Si$ ($M+Na^+$) requires 569.1057; $[\alpha]_D^{25}$ -5.5 (c = 0.13 in $CH_2Cl_2$).

**Elatenyne:** ***(2R,2'S,4S,4'R,5R,5'S)-4,4'-Dibromo-5-ethyl-5'-((Z)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran*** **(60)**



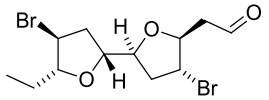

**Method 1:** *According to the modified procedure of Kim et al.*[123]: To a stirred solution of ((*Z*)-5-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4,4'-dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)pent-3-en-1-yn-1-yl)triisopropylsilane (**325**) (1.5 mg, 2.7 μmol, ~5:1 *Z*:*E*) in THF (0.1 mL) at -20 °C was added tetrabutylammonium fluoride (5.5 μL) dropwise. The reaction mixture was stirred at -20 °C for 30 min, quenched by addition of sat. aq. $NH_4Cl$ (2 mL) and poured into a separating funnel with diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**60**) as a colourless oil (~0.5 mg, 1.3 μmol, 48%, ~13:1 *Z*:*E* mixture after purification).

**Method 2:** To a solution of ((*Z*)-5-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4,4'-dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)pent-3-en-1-yn-1-yl)trimethylsilane (**336**) (4.5 mg, 10 μmol, >30:1 *Z*:*E*) in dry THF (2 mL) at -20 °C was added tetrabutylammonium fluoride (28 μL, 1.0 M in THF, 28 μmol) dropwise. The reaction mixture was stirred at -20 °C for 5 min and then poured into a separatory funnel containing sat. aq. $NH_4Cl$ (3 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**60**) as a colourless oil (3.0 mg, 8 μmol, 80%, characterised as a >30:1 *Z*:*E* mixture); $R_f$ 0.45 (20:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3294s (C≡C–H), 3029w, 2962s (CH), 2921s,

2851s, 2095w (C≡C), 1733s, 1615w, 1461s, 1072s, 751m; $\delta_H$ (500 MHz, $C_6D_6$) 0.82 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.18–1.29 (1H, m, C**H**H'$CH_3$), 1.34–1.44 (1H, m, CH**H'**$CH_3$), 1.85–1.97 (2H, m, C**H**$_2$CHBr), 1.97–2.09 (2H, m, C**H**$_2$CHBr), 2.37–2.44 (1H, m, C**H**H'CH=CH), 2.47–2.55 (1H, m, CH**H'**CH=CH), 2.76–2.77 (1H, m, C≡C**H**), 3.53 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHEt), 3.67 (1H, dt, *J*=7.5, 5.0 Hz, C**H**BrCHCH$_2$CH=CH), 3.84–3.93 (3H, m, 2 × C**H**CH$_2$CHBr, C**H**Et), 4.07 (1H, dt, *J*=6.5, 5.5 Hz, C**H**CH$_2$CH=CH), 5.37 (1H, ddt, *J*=11.0, 2.0, 1.5 Hz, CH$_2$CH=C**H**), 5.72 (1H, dtd, *J*=11.0, 7.5, 0.5 Hz, CH$_2$C**H**=CH); $\delta_H$ (200 MHz, $C_6D_6$) 0.81 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.09–1.51 (2H, m, C**H**$_2$CH$_3$), 1.78–2.16 (4H, m, 2 × C**H**$_2$CHBr), 2.29–2.61 (2H, m, C**H**$_2$CH=CH), 2.76 (1H, ddt, *J*=2.0, 1.0, 0.5 Hz, C≡C**H**), 3.53 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHEt), 3.67 (1H, dt, *J*=7.0, 5.0 Hz, C**H**BrCHCH$_2$CH=CH), 3.79–3.97 (3H, m, 2 × C**H**CH$_2$CHBr, C**H**Et), 4.07 (1H, dt, *J*=6.5, 5.5 Hz, C**H**CH$_2$CH=CH), 5.36 (1H, ddt, *J*=11.0, 2.5, 1.5 Hz, CH$_2$CH=C**H**), 5.72 (1H, dtd, *J*=11.0, 7.5, 1.0 Hz, CH$_2$C**H**=CH); $\delta_H$ (200 MHz, $CDCl_3$) 0.99 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.37–1.78 (2H, m, C**H**$_2$CH$_3$), 2.26–2.41 (4H, m, 2 × C**H**$_2$CHBr), 2.48–2.78 (2H, m, C**H**$_2$CH=CH), 3.14 (1H, ddt, *J*=2.5, 1.0 0.5 Hz, C≡C**H**), 3.91–4.29 (6H, m, 2 × C**H**Br, 2 × C**H**CH$_2$CHBr, C**H**Et, C**H**CH$_2$CH=CH), 5.61 (1H, ddt, *J*=11.0, 2.0, 1.5 Hz, CH$_2$CH=C**H**), 6.07 (1H, dtd, *J*=11.0, 7.5, 1.0 Hz, CH$_2$C**H**=CH); $\delta_H$ (500 MHz, $CDCl_3$) 0.99 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.46–1.59 (1H, m, C**H**H'$CH_3$), 1.63–1.72 (1H, m, CH**H'**$CH_3$), 2.30–2.37 (4H, m, 2 × C**H**$_2$CHBr), 2.55–2.62 (1H, m, C**H**H'CH=CH), 2.64–2.72 (1H, m, CH**H'**CH=CH), 3.14 (1H, br d, *J*=2.0 Hz, C≡C**H**), 3.97 (1H, q, *J*=5.5 Hz, C**H**Br), 4.02 (1H, dt, *J*=7.5, 5.5 Hz, C**H**Et), 4.07 (1H, dt, *J*=7.0, 5.5 Hz, C**H**Br), 4.17 (2H, ddd, *J*=12.0, 7.0, 5.5 Hz, 2 × C**H**CH$_2$CHBr), 4.23 (1H, q, *J*=6.0 Hz, C**H**CH$_2$CH=CH), 5.61 (1H, ddt, *J*=11.0, 2.0, 1.0 Hz, CH$_2$CH=C**H**), 6.06 (1H, dtd, *J*=11.0, 7.5, 1.0 Hz, CH$_2$C**H**=CH); $\delta_C$ (125 MHz, $C_6D_6$) 10.1 ($CH_2\mathbf{C}H_3$), 26.8 (**C**H$_2$CH$_3$), 34.7 (**C**H$_2$CH=CH), 39.1 (**C**H$_2$CHBr), 39.3 (**C**H$_2$CHBr), 49.0 (**C**HBr), 49.3 (**C**HBr), 79.6 (**C**HCH$_2$CHBr), 80.1 (**C**HCH$_2$CHBr), 80.2 (**C**≡CH), 82.9 (C≡**C**H), 86.5 (**C**HCH$_2$CH=CH), 88.7 (**C**HEt), 111.2 (CH$_2$CH=**C**H), 140.1 (CH$_2$**C**H=CH); $\delta_C$ (125 MHz, $CDCl_3$) 10.3 ($CH_2\mathbf{C}H_3$), 27.0 (**C**H$_2$CH$_3$), 34.8 (**C**H$_2$CH=CH), 39.0 (**C**H$_2$CHBr), 39.2 (**C**H$_2$CHBr), 48.8 (**C**HBr), 49.2 (**C**HBr), 79.5 (**C**HCH$_2$CHBr), 80.1 (**C**HCH$_2$CHBr), 80.2 (**C**≡CH),

82.7 (C≡**C**H), 86.7 (**C**HCH$_2$CH=CH), 89.0 (**C**HEt), 111.4 (CH$_2$CH=**C**H), 140.1 (CH$_2$**C**H=CH); *m/z* (FI$^+$) 394 (M$^+$, 10%), 392 (M$^+$, 20), 390 (M$^+$, 10), 329 (M–C$_5$H$_5^+$, 45), 327 (M–C$_5$H$_5^+$, 100), 325 (M–C$_5$H$_5^+$, 45), 313 (M–Br$^+$, 35), 312 (M–HBr$^+$, 10), 311 (M–Br$^+$, 35), 310 (M–HBr$^+$, 10), 179 (M–C$_9$H$_{10}$BrO$^+$, 15), 177 (M–C$_9$H$_{10}$BrO$^+$, 10); Accurate mass (FI$^+$): Found 389.9811, C$_{15}$H$_{20}$$^{79}$Br$_2$O$_2$ (M$^+$) requires 389.9830; $[\alpha]^{25}$ (Hg 365 nm) -17.4 (c = 0.25 in CH$_2$Cl$_2$), $[\alpha]^{25}$ (Hg 365 nm) -10.6 (c = 0.25 in CHCl$_3$).

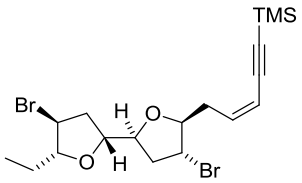
***2-((2S,2'R,4R,4'S,5S,5'R)-4,4'-Dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)acetaldehyde* (333)**




*According to the modified procedure of Sheldrake et al.*[18a]: A mixture of ozone and oxygen was gently bubbled through a stirred solution of (2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-5-allyl-4,4'-dibromo-5'-ethyloctahydro-2,2'-bifuran (**302**) (7 mg, 19.0 μmol) in DCM (3 mL) at -78 °C until the solution became pale blue (approx. 2 min). The excess ozone was purged from the solution by bubbling oxygen through for a further 5 min. Triphenylphosphine (48 mg, 0.19 mmol) was added and the reaction mixture was allowed to warm to RT over 15 h. The reaction mixture was dry-loaded onto silica and rapid purification by flash column chromatography (10:1→5:1→3:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**333**) as a colourless oil (6 mg, 16.2 μmol, 85%); $R_f$ 0.13 (3:1 petrol:diethyl ether); $\nu_{max}$/cm$^{-1}$ (thin film) 3054m, 2964s (CH), 2918s, 2849s, 1786s (C=O), 1265s, 1071s, 737s; $\delta_H$ (500 MHz, C$_6$D$_6$) 0.79 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.13–1.23 (1H, m, C**H**H'CH$_3$), 1.29–1.39 (1H, m, CH**H'**CH$_3$), 1.74 (1H, dt, *J*=14.0, 7.5 Hz, C**H**H'CHBr), 1.81–2.03 (5H, m, C**H**$_2$COH, CH**H'**CHBr, C**H**$_2$CHBr), 3.40–3.47 (2H, m, 2 × C**H**Br), 3.73 (1H, td, *J*=7.0, 5.5 Hz, C**H**CH$_2$CHBr), 3.80 (1H, td, *J*=7.0, 5.5 Hz, C**H**CH$_2$CHBr), 3.87 (1H, dt, *J*=7.5, 5.5 Hz, C**H**Et), 4.20 (1H, ddd, *J*=8.0, 6.0, 4.5 Hz, C**H**CH$_2$COH), 9.24 (1H, dd, *J*=2.0, 1.5 Hz, CO**H**); $\delta_H$ (200 MHz, C$_6$D$_6$) 0.79 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.05–1.46 (2H, m, C**H**$_2$CH$_3$), 1.64–2.08 (6H, m,

C**H**$_2$COH, 2 × C**H**$_2$CHBr), 3.35–3.51 (2H, m, 2 × C**H**Br), 3.67–3.92 (3H, m, 2 × C**H**CH$_2$CHBr, C**H**Et), 4.20 (1H, ddd, *J*=7.5, 6.0, 5.0 Hz, C**H**CH$_2$COH), 9.24 (1H, dd, *J*=2.0, 1.5 Hz, CO**H**); $\delta_H$ (200 MHz, $CDCl_3$) 0.98 (3H, t, *J*=7.5 Hz, CH$_2$C**H**$_3$), 1.36–1.80 (2H, m, C**H**$_2$CH$_3$), 2.13–2.89 (6H, m, C**H**$_2$COH, 2 × C**H**$_2$CHBr), 3.88–4.08 (3H, m, C**H**Et, 2 × C**H**Br), 4.10–4.25 (2H, m, 2 × C**H**CH$_2$CHBr), 4.48 (1H, ddd, *J*=8.0, 6.5, 4.5 Hz, C**H**CH$_2$COH), 9.79 (1H, dd, *J*=2.0, 1.5 Hz, CO**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.1 (CH$_2$**C**H$_3$), 26.8 (**C**H$_2$CH$_3$), 38.3 (**C**H$_2$CHBr), 39.2 (**C**H$_2$CHBr), 46.8 (**C**H$_2$COH), 48.4 (**C**HBr), 49.1 (**C**HBr), 79.3 (**C**HCH$_2$CHBr), 80.1 (**C**HCH$_2$CHBr), 82.1 (**C**HCH$_2$COH), 88.7 (**C**HEt), 197.8 (**C**=O); $\delta_C$ (125 MHz, $CDCl_3$) 10.0 (CH$_2$**C**H$_3$), 26.7 (**C**H$_2$CH$_3$), 37.8 (**C**H$_2$CHBr), 38.9 (**C**H$_2$CHBr), 46.6 (**C**H$_2$COH), 47.6 (**C**HBr), 48.6 (**C**HBr), 78.9 (**C**HCH$_2$CHBr), 79.9 (**C**HCH$_2$CHBr), 81.9 (**C**HCH$_2$COH), 88.8 (**C**HEt), 199.4 (**C**=O); *m*/*z* (FI$^+$) 373 (M+H$^+$, 50), 371 (M+H$^+$, 100), 369 (M+H$^+$, 50), 291 (M–Br$^+$, 50), 290 (M–HBr$^+$, 30), 289 (M–Br$^+$, 60), 288 (M–HBr$^+$, 30), 193 (M–$C_6H_{10}BrO^+$, 15), 191 (M–$C_6H_{10}BrO^+$, 30), 179 (M–$C_6H_8BrO_2^+$, 50), 177 (M–$C_6H_8BrO_2^+$, 60); Accurate mass (FI$^+$): Found 372.9653, $C_{12}H_{19}O_3{}^{81}Br_2$ (M+H$^+$) requires 372.9662; $[\alpha]_D^{25}$ -2.5 (c = 0.81 in $CH_2Cl_2$).

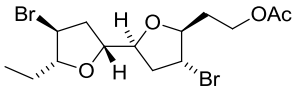
***((Z)-5-((2S,2'R,4R,4'S,5S,5'R)-4,4'-Dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)pent-3-en-1-yn-1-yl)trimethylsilane* (336)**




*According to the modified procedure of Sheldrake et al.*[18a]: To a solution of 3-(*tert*-butyldimethylsilyl)-1-(trimethylsilyl)-propyne (**335**) (135 mg, 0.63 mmol) in dry THF (1 mL) at -78 °C was added dropwise *tert*-butyllithium (0.37 mL, 1.7 M in pentane) and this solution was stirred at -78 °C for 1 h. A solution of titanium(IV) isopropoxide (0.19 mL, 0.63 mmol) in dry THF (0.5 mL) was added dropwise to the reaction mixture, the resulting solution was stirred for 10 min and then 1.94 mL was removed and discarded. To the remaining 0.12 mL (36 μmol) was added dropwise a solution

of 2-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4,4'-dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)acetaldehyde (**333**) (4.5 mg, 12 μmol) in dry THF (0.5 mL + 0.5 mL rinse). The reaction mixture was stirred at -78 °C for 30 min and then the cooling bath was removed and the reaction mixture was stirred at RT for 30 min. The reaction mixture was then poured into a separatory funnel containing 0.1 M aqueous HCl (2 mL) and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**336**) as a colourless oil (4.5 mg, 10 μmol, 83%, >30:1 (*Z*):(*E*) from crude $^1$H NMR analysis and characterised as such a mixture); $R_f$ 0.38 (20:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2963s (CH), 2938s, 2900s, 2149s (C≡C), 1716s, 1654s, 1558s, 1540s, 1250s, 1076s, 843s; $\delta_H$ (500 MHz, $C_6D_6$) 0.22 (9H, s, Si(C**H**$_3$)$_3$), 0.82 (3H, t, *J*=7.5 Hz, $CH_2C$**H**$_3$), 1.18–1.28 (1H, m, C**H**H'$CH_3$), 1.34–1.44 (1H, m, CH**H'**$CH_3$), 1.89–2.10 (4H, m, 2 × C**H**$_2$CHBr), 2.45–2.52 (1H, m, C**H**H'CH=CH), 2.58–2.65 (1H, m, CH**H'**CH=CH), 3.52 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHEt), 3.75 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHCH$_2$CH=CH), 3.83–3.93 (3H, m, 2 × C**H**CH$_2$CHBr, C**H**Et), 4.11 (1H, dt, *J*=6.5, 5.5 Hz, C**H**CH$_2$CH=CH), 5.51 (1H, dt, *J*=10.5, 1.5 Hz, $CH_2CH$=C**H**), 5.75 (1H, dt, *J*=10.5, 7.5 Hz, $CH_2C$**H**=CH); $\delta_C$ (125 MHz, $C_6D_6$) 0.05 (Si(C**H**$_3$)$_3$), 10.1 ($CH_2$**C**$H_3$), 26.8 (**C**H$_2$CH$_3$), 34.6 (**C**H$_2$CH=CH), 39.2 (**C**H$_2$CHBr), 39.4 (**C**H$_2$CHBr), 48.9 (**C**HBr), 49.2 (**C**HBr), 79.6 (**C**HCH$_2$CHBr), 80.1 (**C**HCH$_2$CHBr), 86.7 (**C**HCH$_2$CH=CH), 88.6 (**C**HEt), 100.0 (**C**≡C), 102.2 (C≡**C**), 112.5 ($CH_2CH$=**C**H), 139.5 ($CH_2$**C**H=CH); *m*/*z* (ES$^+$) 489 (M+Na$^+$, 55%), 487 (M+Na$^+$, 100), 485 (M+Na$^+$, 55); Accurate mass (ES$^+$): Found 485.0123, $C_{18}H_{28}{}^{79}Br_2NaO_2Si$ (M+Na$^+$) requires 485.0118; $[\alpha]_D^{25}$ +1.8 (c = 0.4 in $CH_2Cl_2$).

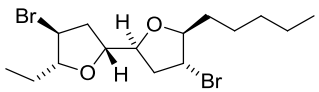
***2-((2S,2'R,4R,4'S,5S,5'R)-4,4'-Dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)ethyl acetate* (339)**




*According to the modified procedure of Hall and Reiss*[14]: To a stirred solution of 2-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4,4'-dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)acetaldehyde (**333**) (2 mg, 5.4 μmol) in methanol (0.54 mL) was added sodium borohydride (1.2 mg, 32 μmol). The reaction mixture was stirred for 20 min and then quenched by addition of aq. HCl (4 mL, 0.5 M). The aqueous layer was extracted sequentially with diethyl ether (10 mL) and DCM (10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was dissolved in DCM (0.7 mL) and pyridine (0.16 mL, 0.17 g, 1.69 mmol), acetic anhydride (0.16 mL, 0.16 g, 1.98 mmol) and DMAP (1.5 mg, 12 μmol) were added. The reaction mixture was stirred at RT for 1.5 h and then quenched by addition of $H_2O$ (5 mL). The aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20:1→5:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**339**) as a colourless oil (2.0 mg, 4.8 μmol, 89%); $R_f$ 0.65 (1:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2964s (CH), 2923s, 2878s, 1739s (C=O), 1457m, 1366s, 1241s, 1049s; $\delta_H$ (500 MHz, $C_6D_6$) 0.80 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.15–1.26 (1H, m, C**H**H'$CH_3$), 1.28–1.43 (2H, m, CH**H'**$CH_3$, C**H**H'$CH_2$OAc), 1.65 (3H, s, C(O)C$\mathbf{H}_3$), 1.70 (1H, dtd, *J*=14.0, 6.5, 4.0 Hz, CH**H'**$CH_2$OAc), 1.82 (1H, dt, *J*=14.0, 7.0 Hz, C**H**H'CHBr), 1.91 (1H, dt, *J*=14.0, 7.0 Hz, C**H**H'CHBr), 1.96–2.03 (2H, m, 2 × CH**H'**CHBr), 3.46–3.52 (2H, m, 2 × C**H**Br), 3.77–3.86 (2H, m, 2 × C**H**$CH_2$CHBr), 3.87 (1H, dt, *J*=7.5, 5.0 Hz, C**H**Et), 4.01–4.16 (3H, m, C**H**$CH_2CH_2$OAc, $CHCH_2C\mathbf{H}_2$OAc); $\delta_H$ (200 MHz, $C_6D_6$) 0.80 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.08–1.50 (3H, m, C$\mathbf{H}_2CH_3$, C**H**H'$CH_2$OAc), 1.60–2.10 (5H, m, CH**H'**$CH_2$OAc, 2 × C$\mathbf{H}_2$CHBr), 1.65 (3H, s, C(O)C$\mathbf{H}_3$), 3.41–3.55 (2H, m, 2 × C**H**Br), 3.72–3.96 (3H, m, 2 × C**H**$CH_2$CHBr, C**H**Et), 3.98–4.16 (3H, m, C**H**$CH_2CH_2$OAc,

$CHCH_2C\mathbf{H}_2OAc$); $\delta_H$ (200 MHz, $CDCl_3$) 0.99 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.39–1.88 (3H, m, $C\mathbf{H}_2CH_3$, $C\mathbf{H}H'CH_2OAc$), 1.93–2.15 (1H, m, $CH\mathbf{H'}CH_2OAc$), 2.07 (3H, s, $C(O)C\mathbf{H}_3$), 2.23–2.43 (4H, m, 2 × $C\mathbf{H}_2CHBr$), 3.90–4.32 (8H, m, 2 × $C\mathbf{H}Br$, 2 × $C\mathbf{H}CH_2CHBr$, $C\mathbf{H}Et$, $C\mathbf{H}CH_2CH_2OAc$, $CHCH_2C\mathbf{H}_2OAc$); $\delta_C$ (125 MHz, $C_6D_6$) 10.1 ($CH_2\mathbf{C}H_3$), 20.4 ($C(O)\mathbf{C}H_3$), 26.8 ($\mathbf{C}H_2CH_3$), 32.9 ($\mathbf{C}H_2CH_2OAc$), 38.9 ($\mathbf{C}H_2CHBr$), 39.3 ($\mathbf{C}H_2CHBr$), 49.2 ($\mathbf{C}HBr$), 49.2 ($\mathbf{C}HBr$), 61.0 ($CH_2\mathbf{C}H_2OAc$), 79.5 ($\mathbf{C}HCH_2CHBr$), 79.9 ($\mathbf{C}HCH_2CHBr$), 84.3 ($\mathbf{C}HCH_2CH_2OAc$), 88.7 ($\mathbf{C}HEt$), 169.9 ($\mathbf{C}$=O); *m/z* 439 ($M+Na^+$, 50%), 437 ($M+Na^+$, 100), 435 ($M+Na^+$, 50); Accurate mass ($ES^+$): Found 436.9749, $C_{14}H_{22}{}^{79}Br^{81}BrNaO_4$ ($M+Na^+$) requires 436.9757, found 434.9769, $C_{14}H_{22}{}^{81}Br_2NaO_4$ ($M+Na^+$) requires 434.9777; $[\alpha]_D^{25}$ -20.3 (c = 0.12 in $CH_2Cl_2$).

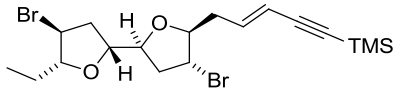
***(2R,2'S,4S,4'R,5R,5'S)-4,4'-Dibromo-5-ethyl-5'-pentyloctahydro-2,2'-bifuran* (340)**




*According to the modified procedure of Hall and Reiss*[14]: A solution of (2*R*,2'*S*,4*S*,4'*R*,5*R*,5'*S*)-4,4'-dibromo-5-ethyl-5'-((*Z*)-pent-2-en-4-yn-1-yl)octa-hydro-2,2'-bifuran (**60**) (~0.5 mg, 1.3 μmol) in ethanol (0.5 mL + 0.5 mL rinse) was added to a suspension of activated platinum(IV) oxide (cat.) in ethanol (2 mL) and hydrogenated for 2 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**340**) as a colourless oil (~0.5 mg, ~1.3 μmol, quant.); $R_f$ 0.45 (20:1 petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 2959s (CH), 2928s, 2856s, 1457m, 1261s, 1071s, 802s; $\delta_H$ (500 MHz, $C_6D_6$) 0.82 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 0.86 (3H, t, *J*=7.0 Hz, $CH_2C\mathbf{H}_3$), 1.11–1.47 (10H, m, $C\mathbf{H}_2$), 1.89–2.01 (2H, m, 2 × $C\mathbf{H}H'CHBr$), 2.04–2.13 (2H, m, 2 × $CH\mathbf{H'}CHBr$), 3.51–3.59 (2H, m, 2 × $C\mathbf{H}Br$), 3.85–3.95 (3H, m, 2 × $C\mathbf{H}CH_2CHBr$, $C\mathbf{H}Et$), 3.98–4.05 (1H, m, $C\mathbf{H}((CH_2)_4CH_3)$; $\delta_H$ (200 MHz, $C_6D_6$) 0.82 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 0.86 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.10–1.47 (10H, m, $C\mathbf{H}_2$), 1.85–2.15 (4H, m, 2 × $C\mathbf{H}_2CHBr$), 3.46–3.63 (2H, m, 2 × $C\mathbf{H}Br$), 3.81–4.07 (4H, m, 2 × $C\mathbf{H}CH_2CHBr$, $C\mathbf{H}Et$, $C\mathbf{H}((CH_2)_4CH_3)$; $\delta_C$ (125 MHz, $C_6D_6$) 10.1 ($CHCH_2\mathbf{C}H_3$), 14.2 ($(CH_2)_4\mathbf{C}H_3$), 22.9 ($(CH_2)_3\mathbf{C}H_2CH_3$), 25.9

(**C**$H_2(CH_2)_2CH_3$), 26.9 (CH**C**$H_2CH_3$), 32.0 (**C**$H_2CH_2CH_3$), 34.0 (CH**C**$H_2(CH_2)_3$), 39.3 (**C**$H_2$CHBr), 39.4 (**C**$H_2$CHBr), 49.3 (**C**HBr), 49.9 (**C**HBr), 79.8 (**C**$HCH_2$CHBr), 79.8 (**C**$HCH_2$CHBr), 87.5 (**C**H$((CH_2)_4CH_3$), 88.7 (**C**HEt); *m/z* ($FI^+$) 400 ($M^+$, 40), 398 ($M^+$, 100), 396 ($M^+$, 40), 318 (M–$HBr^+$, 35), 316 (M–$HBr^+$, 40), 221 (M–$C_6H_{10}BrO^+$, 10), 219 (M–$C_6H_{10}BrO^+$, 10), 179 (M–$C_9H_{16}BrO^+$, 20), 177 (M–$C_9H_{16}BrO^+$, 10); Accurate mass ($FI^+$): Found 398.0262, $C_{15}H_{26}{}^{79}Br^{81}BrO_2$ ($M^+$) requires 398.0280; $[\alpha]_D^{25}$ -6.6 (c = 0.05 in $CH_2Cl_2$).

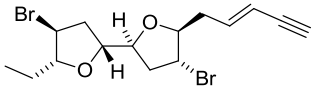
***((E)-5-((2S,2'R,4R,4'S,5S,5'R)-4,4'-Dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)pent-3-en-1-yn-1-yl)trimethylsilane* (343)**




3-(Trimethylsilyl-2-propynyl)-triphenylphosphonium bromide (**342**) (80 mg, 0.18 mmol) was weighed into a dry Schlenk tube and stirred vigorously under vacuum for 1.5 h. The vacuum was quenched to $N_2$ and dry THF (2 mL) was added. The suspension was stirred vigorously, cooled to -78 °C and *n*-butyllithium (0.11 mL, 1.6 M in THF, 0.18 mmol) was added rapidly. The reaction mixture was stirred at -40 °C to -30 °C for 30 min, which gave a yellow solution, and then cooled back to -78 °C. 70 μL of this solution was added to a solution of 2-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4,4'-dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)acetaldehyde (**333**) (2.0 mg, 5.4 μmol) in dry THF (0.5 mL) at -78 °C. After 5 min there was still starting material present as indicated by TLC, so a further 35 μL of the ylide solution was added. After 5 min TLC indicated there was no starting material in the reaction mixture so the reaction mixture was allowed to warm to 0 °C over 2 h. The reaction mixture was quenched by addition of sat. aq. $NH_4Cl$ (5 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 petrol:DCM) gave the title compound (**343**) as a colourless oil (2.0 mg, 4.3 μmol, 80%, 8:1 (*E*):(*Z*) from crude $^1$H NMR analysis, characterized as a 9:1 mixture of (*E*):(*Z*)); $R_f$ 0.43 (1:1 petrol:DCM); $\nu_{max}/cm^{-1}$ (thin film)

3033m, 2963s (CH), 2925s, 2898s, 2135m (C≡C), 1737m, 1356m, 1276s, 1079s, 956s, 843s, 791s; $\delta_H$ (500 MHz, $C_6D_6$) 0.20 (9H, s, Si(C**H**$_3$)$_3$), 0.82 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.17–1.27 (1H, m, C**H**H'$CH_3$), 1.33–1.42 (1H, m, CH**H'**$CH_3$), 1.76–2.06 (6H, m, 2 × C**H**$_2$CHBr, C**H**$_2$CH=CH), 3.46 (1H, dt, *J*=7.5, 5.5 Hz, C**H**Br), 3.75 (1H, dt, *J*=7.5, 5.5 Hz, C**H**Br), 3.73–3.81 (2H, m, 2 × C**H**$CH_2$CHBr,), 3.84–3.92 (2H, m, C**H**$CH_2$CH=CH, C**H**Et), 5.52 (1H, dt, *J*=16.0, 1.5 Hz, $CH_2$CH=C**H**), 6.16 (1H, dt, *J*=16.0, 7.5 Hz, $CH_2$C**H**=CH); $\delta_C$ (125 MHz, $C_6D_6$) 0.04 (Si(C**H**$_3$)$_3$), 10.2 ($CH_2\mathbf{C}H_3$), 26.8 (**C**$H_2CH_3$), 36.6 (**C**$H_2$CH=CH), 38.8 (**C**$H_2$CHBr), 39.3 (**C**$H_2$CHBr), 48.3 (**C**HBr), 49.2 (**C**HBr), 79.4 (**C**H$CH_2$CHBr), 79.9 (**C**H$CH_2$CHBr), 86.0 (**C**H$CH_2$CH=CH), 88.6 (**C**HEt), 94.0 (**C**≡C), 104.3 (C≡**C**), 113.4 ($CH_2$CH=**C**H), 140.3 ($CH_2$**C**H=CH); *m*/*z* (ES$^+$) 489 (M+Na$^+$, 55%), 487 (M+Na$^+$, 100), 485 (M+Na$^+$, 55); Accurate mass (ES$^+$): Found 489.0081, $C_{18}H_{28}{}^{81}Br_2NaO_2Si$ (M+Na$^+$) requires 489.0077, found 487.0099, $C_{18}H_{28}{}^{81}Br^{79}BrNaO_2Si$ (M+Na$^+$) requires 487.0098, found 485.0114, $C_{18}H_{28}{}^{79}Br_2NaO_2Si$ (M+Na$^+$) requires 485.0118; $[\alpha]_D^{21}$ -34.6 (c = 0.13 in $CH_2Cl_2$).

***(2R,2'S,4S,4'R,5R,5'S)-4,4'-Dibromo-5-ethyl-5'-((E)-pent-2-en-4-yn-1-yl)octahydro-2,2'-bifuran* (344)**

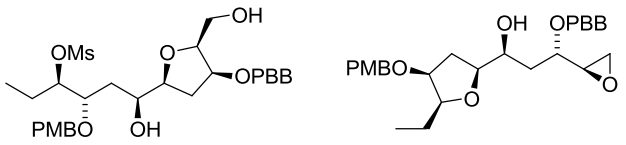



To a solution of ((*E*)-5-((2*S*,2'*R*,4*R*,4'*S*,5*S*,5'*R*)-4,4'-dibromo-5'-ethyloctahydro-[2,2'-bifuran]-5-yl)pent-3-en-1-yn-1-yl)trimethylsilane (**343**) (1.5 mg, 3.2 μmol) in dry THF (2 mL) at -20 °C was added tetrabutylammonium fluoride (10 μL, 1.0 M in THF, 10 μmol) dropwise. The reaction mixture was stirred at -20 °C for 5 min and then poured into a separatory funnel containing sat. aq. $NH_4Cl$ (3 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (30:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**344**) as a colourless oil (1.0 mg, 2.6 μmol, 81%, characterized as a 9:1 mixture of (*E*):(*Z*)); $R_f$ 0.2 (30:1

petrol:diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3294s (C≡C–H), 3033w, 2965s (CH), 2923s, 2878s, 2103w (C≡C), 1738s, 1460s, 1377s, 1276s, 1202s, 1072s, 958s; $\delta_H$ (500 MHz, $C_6D_6$) 0.82 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.16–1.28 (1H, m, C**H**H'$CH_3$), 1.33–1.43 (1H, m, CH**H'**$CH_3$), 1.77–1.90 (3H, m, 2 × C**H**H'CHBr, C**H**H'CH=CH), 1.90–2.02 (3H, m, 2 × CH**H'**CHBr, CH**H'**CH=CH), 2.53–2.55 (1H, m, C≡C**H**), 3.44 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHC$H_2$CH=CH), 3.48 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHEt), 3.73–3.83 (2H, m, 2 × C**H**C$H_2$CHBr), 3.84–3.91 (2H, m, C**H**C$H_2$CH=CH, C**H**Et), 5.35 (1H, ddt, *J*=16.0, 2.0, 1.5 Hz, $CH_2CH$=C**H**), 6.12 (1H, dt, *J*=16.0, 7.5 Hz, $CH_2C\mathbf{H}$=CH); $\delta_H$ (400 MHz, $C_6D_6$) 0.81 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.15–1.28 (1H, m, C**H**H'$CH_3$), 1.31–1.43 (1H, m, CH**H'**$CH_3$), 1.75–1.89 (3H, m, 2 × C**H**H'CHBr, C**H**H'CH=CH), 1.90–2.03 (3H, m, 2 × CH**H'**CHBr, CH**H'**CH=CH), 2.54 (1H, br d, *J*=2.0 Hz, C≡C**H**), 3.44 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHC$H_2$CH=CH), 3.48 (1H, dt, *J*=7.5, 5.5 Hz, C**H**BrCHEt), 3.73–3.83 (2H, m, 2 × C**H**C$H_2$CHBr), 3.84–3.92 (2H, m, C**H**C$H_2$CH=CH, C**H**Et), 5.35 (1H, ddt, *J*=16.0, 2.0, 1.5 Hz, $CH_2CH$=C**H**), 6.12 (1H, dt, *J*=16.0, 7.0 Hz, $CH_2C\mathbf{H}$=CH); $\delta_C$ (125 MHz, $C_6D_6$) 10.1 ($CH_2\mathbf{C}H_3$), 26.8 ($\mathbf{C}H_2CH_3$), 36.6 ($\mathbf{C}H_2CH$=CH), 38.8 ($\mathbf{C}H_2CHBr$), 39.2 ($\mathbf{C}H_2CHBr$), 48.4 (**C**HBr), 49.1 (**C**HBr), 77.3 (C≡**C**H), 79.4 (**C**HC$H_2$CHBr), 79.9 (**C**HC$H_2$CHBr), 82.1 (**C**≡CH), 85.9 (**C**HEt), 88.6 (**C**HC$H_2$CH=CH), 112.2 ($CH_2CH$=**C**H), 140.8 ($CH_2\mathbf{C}H$=CH); *m/z* ($FI^+$) 394 (M+$Na^+$, 10%), 392 (M+$Na^+$, 20), 390 (M+$Na^+$, 10), 329 (M–$C_5H_5^+$, 50), 327 (M–$C_5H_5^+$, 100), 325 (M–$C_5H_5^+$, 50), 313 (M–$Br^+$, 20), 311 (M–$Br^+$, 20), 179 (M–$C_9H_{10}BrO^+$, 10), 177 (M–$C_9H_{10}BrO^+$, 10); Accurate mass ($FI^+$): Found 326.9431, $C_{10}H_{15}O_2{}^{81}Br^{79}Br$ (M–$C_5H_5^+$) requires 326.9419, found 324.9432, $C_{10}H_{15}O_2{}^{79}Br_2$ (M–$C_5H_5^+$) requires 324.9439; $[\alpha]_D^{22}$ -33.0 (c = 0.09 in $CH_2Cl_2$).

***(3R,4S,6S)-6-((2S,4S,5S)-4-(4-Bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-hydroxy-4-(4-methoxybenzyloxy)hexan-3-yl methanesulfonate* (369)**

***(1S,3S)-3-(4-Bromobenzyloxy)-1-((2S,4S,5S)-5-ethyl-4-(4-methoxybenzyloxy)tetrahydrofuran-2-yl)-3-((R)-oxiran-2-yl)propan-1-ol* (371)**




Prepared according to the **general SAD procedure** (**Page 184**) with (3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl methanesulfonate (**243**) (24 mg, 0.04 mmol), purification by flash column chromatography (2:1→1:1→0:1 petrol:EtOAc) gave the two title compounds (**369** and **371**) as colourless oils.

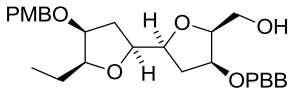
1. (3*R*,4*S*,6*S*)-6-((2*S*,4*S*,5*S*)-4-(4-Bromobenzyloxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-hydroxy-4-(4-methoxybenzyloxy)hexan-3-yl methanesulfonate (**369**) (12 mg, 19 μmol, 49%): $R_f$ 0.40 (EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3417s br (OH), 2937s (CH), 2877s, 1612m, 1513s, 1339s, 1248s, 1172s, 1070s, 1035s, 905s, 812s; $\delta_H$ (500 MHz, $C_6D_6$) 0.93 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.27–1.38 (1H, m, C**H**H'$CH_3$), 1.54–1.72 (3H, m, CH**H'**$CH_3$, C**H**H'CHOPBB, C**H**H'CHOPMB), 1.74–1.87 (2H, m, CH**H'**CHOPBB, CH**H'**CHOPMB), 2.55 (3H, s, $SC\mathbf{H}_3$), 2.71 (2H, br s, 2 × O**H**), 3.30 (3H, s, $OC\mathbf{H}_3$), 3.58 (1H, dt, *J*=6.0, 4.5 Hz, C**H**OPBB), 3.61–3.67 (2H, m, C**H**$CH_2$CHOPBB, C**H**$CH_2$OH), 3.75 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.79 (2H, d, *J*=4.5 Hz, $C\mathbf{H}_2$OH), 3.91 (1H, ddd, *J*=10.5, 4.0, 2.0 Hz, C**H**OH), 3.95–3.99 (1H, m, C**H**OPMB), 3.99 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.43 (1H, d, *J*=10.5 Hz, C**H**H'Ar), 4.66 (1H, *J*=10.5 Hz, CH**H'**Ar), 4.97 (1H, ddd, *J*=9.5, 4.5, 2.0 Hz, C**H**OMs), 6.78 (2H, d, *J*=8.0 Hz, Ar**H**), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 7.25 (2H, d, *J*=8.0 Hz, Ar**H**), 7.34 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.5 ($CH_2\mathbf{C}H_3$), 24.5 ($\mathbf{C}H_2CH_3$), 34.2 ($\mathbf{C}H_2$CHOPBB), 34.8 ($\mathbf{C}H_2$CHOPMB), 38.5 ($S\mathbf{C}H_3$), 54.8 ($O\mathbf{C}H_3$), 62.1 ($\mathbf{C}H_2$OH), 69.7 (**C**HOH), 70.6 ($\mathbf{C}H_2$Ar), 72.6 ($\mathbf{C}H_2$Ar), 77.5 (**C**HOPMB), 79.9 (**C**HOPBB), 81.5 (**C**H$CH_2$CHOPBB), 81.8 (**C**H$CH_2$OH), 85.8 (**C**HOMs), 114.2 (Ar), 122.0 (Ar), 129.4 (Ar), 130.3

(Ar), 130.7 (Ar), 131.9 (Ar), 137.0 (Ar), 160.0 (Ar); *m/z* ($ES^+$) 1259 ($2M+Na^+$, 70%), 1257 ($2M+Na^+$, 100), 1255 ($2M+Na^+$, 50), 641 ($M+Na^+$, 70), 639 ($M+Na^+$, 65); Accurate mass ($ES^+$): Found 641.1228, $C_{27}H_{37}{}^{81}BrNaO_9S$ ($M+Na^+$) requires 641.1215, found 639.1237, $C_{27}H_{37}{}^{79}BrNaO_9S$ ($M+Na^+$) requires 639.1234; $[\alpha]_D^{25}$ +18.7 (c = 1.0 in $CH_2Cl_2$).

2. (1*S*,3*S*)-3-(4-Bromobenzyloxy)-1-((2*S*,4*S*,5*S*)-5-ethyl-4-(4-methoxybenzyloxy)tetrahydrofuran-2-yl)-3-((*R*)-oxiran-2-yl)propan-1-ol (**371**) (7 mg, 13 μmol, 34% 2:1 $D_1$:$D_2$ mixture of diastereomers (**371**:**(1*R*,2*R*)-371**) formed in the dihydroxylation): $R_f$ 0.79 (EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3463s br (OH), 2966s (CH), 2933s, 2874s, 1613m, 1514s, 1248s, 1070s, 1012s, 807s; $\delta_H$ (500 MHz, $C_6D_6$) 0.91 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$ $D_1$), 0.94 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$ $D_2$), 1.55–2.05 (12H, m, $C\mathbf{H}_2CH_3$, $C\mathbf{H}_2$CHOPMB, $C\mathbf{H}_2$CHOPBB $D_1$ + $D_2$), 2.32 (1H, dd, *J*=5.5, 4.0 Hz, C**H**H'O(CH) $D_1$), 2.33 (1H, dd, *J*=5.5, 4.0 Hz, C**H**H'O(CH) $D_2$), 2.39 (1H, dd, *J*=5.5, 2.5 Hz, CH**H'**O(CH) $D_2$), 2.44 (1H, dd, *J*=5.5, 2.5 Hz, CH**H'**O(CH) $D_1$), 2.64 (1H, d, *J*=4.5 Hz, O**H** $D_2$), 2.71–2.76 (2H, m, $CH_2O(C\mathbf{H})$ $D_1$ + $D_2$), 2.95 (1H, d, *J*=6.0 Hz, O**H** $D_1$), 3.28–3.35 (1H, m, C**H**Et $D_1$), 3.31 (3H, s, $OC\mathbf{H}_3$ $D_1$), 3.32 (3H, s, $OC\mathbf{H}_3$ $D_2$), 3.41–3.48 (2H, m, C**H**OPMB $D_1$, C**H**OPBB $D_2$), 3.63–3.75 (4H, m, C**H**Et $D_2$, C**H**OPMB $D_2$, C**H**OH $D_2$, C**H**CHOH $D_1$), 3.83 (1H, ddd, *J*=10.5, 5.0, 2.5 Hz, C**H**OPBB $D_1$), 3.89–3.97 (1H, m, C**H**OH $D_1$), 3.97 (1H, d, *J*=11.0 Hz, C**H**H'Ar $D_1$), 4.06 (1H, d, *J*=11.5 Hz, C**H**H'Ar $D_2$), 4.10 (1H, d, *J*=11.5 Hz, C**H**H'Ar $D_2$), 4.14 (1H, ddd, *J*=9.0, 6.0, 4.5 Hz, C**H**CHOH $D_2$), 4.29 (2H, m, C**H**H'Ar $D_1$, CH**H'**Ar $D_2$), 4.34 (1H, d, *J*=11.0 Hz, CH**H'**Ar $D_1$), 4.35 (1H, d, *J*=11.5 Hz, CH**H'**Ar $D_2$), 4.48 (1H, *J*=12.0 Hz, CH**H'**Ar $D_1$), 6.79 (2H, d, *J*=8.5 Hz, Ar**H** $D_1$), 6.83 (2H, d, *J*=9.0 Hz, Ar**H** $D_2$), 6.87 (2H, d, *J*=8.0 Hz, Ar**H** $D_2$), 6.97 (2H, d, *J*=8.0 Hz, Ar**H** $D_1$), 7.19 (2H, d, *J*=8.0 Hz, Ar**H** $D_1$), 7.21 (2H, d, *J*=9.0 Hz, Ar**H** $D_2$), 7.24 (2H, d, *J*=8.0 Hz, Ar**H** $D_2$), 7.25 (2H, d, *J*=8.5 Hz, Ar**H** $D_1$); $\delta_C$ (125 MHz, $C_6D_6$) 10.9 ($CH_2\mathbf{C}H_3$ $D_2$), 10.9 ($CH_2\mathbf{C}H_3$ $D_1$), 22.4 ($\mathbf{C}H_2CH_3$ $D_1$), 22.9 ($\mathbf{C}H_2CH_3$ $D_2$), 33.5 ($\mathbf{C}H_2$CHOPMB $D_2$), 33.8 ($\mathbf{C}H_2$CHOPMB $D_1$), 37.1 ($\mathbf{C}H_2$CHOPBB $D_2$), 37.9 ($\mathbf{C}H_2$CHOPBB $D_1$), 44.7 ($\mathbf{C}H_2O(CH)$ $D_1$), 45.0 ($\mathbf{C}H_2O(CH)$ $D_2$), 53.5 ($CH_2O(\mathbf{C}H)$ $D_2$), 53.7 ($CH_2O(\mathbf{C}H)$ $D_1$), 54.8 ($O\mathbf{C}H_3$ $D_1$ + $D_2$), 69.7 (**C**HOH $D_1$), 70.6 (**C**$H_2$Ar

$D_1$), 70.9 (**C**$H_2$Ar $D_2$), 71.4 (**C**$H_2$Ar $D_2$), 71.5 (**C**HOH $D_2$), 72.3 (**C**$H_2$Ar $D_1$), 75.6 (**C**HOPBB $D_1$), 76.6 (**C**HOPBB $D_2$), 78.5 (**C**HOPMB $D_1$), 80.0 (**C**HOPMB $D_2$), 80.2 (**C**HCHOH $D_2$), 81.0 (**C**HCHOH $D_1$), 84.5 (**C**HEt $D_2$), 84.7 (**C**HEt $D_1$), 114.1 (Ar $D_2$), 114.2 (Ar $D_1$), 121.5 (Ar $D_1$), 121.7 (Ar $D_2$), 129.3 (Ar $D_2$), 129.6 (Ar $D_1$ + $D_2$), 129.7 (Ar $D_1$), 130.4 (Ar $D_1$), 131.1 (Ar $D_2$), 131.6 (Ar $D_1$), 131.7 (Ar $D_2$), 137.9 (Ar $D_2$), 138.7 (Ar $D_1$), 159.8 (Ar $D_2$), 159.9 (Ar $D_1$); *m/z* ($ES^+$) 1067 ($2M+Na^+$, 60%), 1065 ($2M+Na^+$, 100), 1063 ($2M+Na^+$, 55), 545 ($M+Na^+$, 55), 543 ($M+Na^+$, 50); Accurate mass ($ES^+$): Found 545.1319, $C_{26}H_{33}{}^{81}BrNaO_6$ ($M+Na^+$) requires 545.1334, found 543.1334, $C_{26}H_{33}{}^{79}BrNaO_6$ ($M+Na^+$) requires 543.1353; $[\alpha]_D^{25}$ +4.3 (c = 1.0 in $CH_2Cl_2$).

***((2S,2'S,4S,4'S,5S,5'S)-4-(4-Bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-5-yl)methanol* (370)**

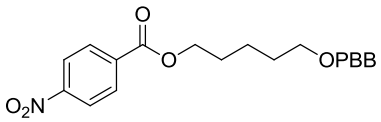



**Method 1:** To a stirred solution of (1*S*,3*S*)-3-(4-bromobenzyloxy)-1-((2*S*,4*S*,5*S*)-5-ethyl-4-(4-methoxybenzyloxy)tetrahydrofuran-2-yl)-3-((*R*)-oxiran-2-yl)propan-1-ol (**371**) (7 mg, 17 μmol) in THF (0.17 mL) was added potassium bis(trimethylsilyl)amide (0.1 mL, 0.5 M in toluene, 52 μmol). The reaction mixture was stirred at RT for 15 min and then quenched by addition of sat. aq. $NH_4Cl$ (3 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 petrol:EtOAc) gave the title compound (**370**) as a colourless oil (6 mg, 15 μmol, 87% mixture of diastereomers from starting material).

**Method 2:** Prepared according to the **general SAD procedure** (**Page 184**) but stirring for 48 h with (3*R*,4*S*,9*S*,*E*)-9-(4-bromobenzyloxy)-4-(4-methoxybenzyloxy)-9-((*R*)-oxiran-2-yl)non-6-en-3-yl methanesulfonate (**243**) (32 mg, 55 μmol), followed by subjection of the crude residue in THF (0.55 mL) to potassium bis(trimethylsilyl)amide (0.33 mL, 0.5 M in toluene, 0.17 mmol). The reaction mixture was stirred at RT for 15 min and then quenched by addition of sat. aq. $NH_4Cl$

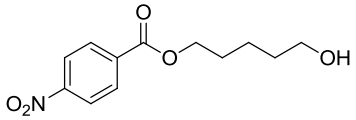
(3 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 petrol:EtOAc) gave recovered starting material (**243**) (7 mg, 12 μmol, 22%) and the title compound as a mixture of diastereomers (**370** and **(2*R*,2'*R*)-370**) (17 mg, 42 μmol, 76%, d.r. not determined) with only the major diastereomer (**370**) obtained pure for characterisation as a colourless oil; $R_f$ 0.19 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3460s br (OH), 2930s (CH), 2873s, 1612m, 1514s, 1247s, 1070s, 808s; $\delta_H$ (500 MHz, $C_6D_6$) 0.97 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.68 (1H, ddd, *J*=14.0, 9.0, 6.5 Hz, C**H**H'CHOPBB), 1.79 (1H, dt, *J*=12.5, 7.0 Hz, C**H**H'CHOPMB), 1.83–1.94 (1H, m, C**H**H'$CH_3$), 1.95–2.06 (1H, m, CH**H'**$CH_3$), 2.07–2.21 (2H, m, CH**H'**CHOPBB, CH**H'**CHOPMB), 3.16 (1H, br s, O**H**), 3.27–3.34 (1H, m, C**H**Et), 3.29 (3H, s, OC**H**$_3$), 3.54–3.58 (1H, m, C**H**OPMB), 3.75–3.91 (3H, m, C**H**$CH_2$CHOPBB, C**H**$CH_2$CHOPMB, C**H**H'OH), 3.90 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 3.94 (1H, ddd, *J*=10.0, 7.0, 3.0 Hz, C**H**OPBB), 4.00 (1H, d, *J*=12.0 Hz, CH**H'**Ar), 4.00–4.10 (2H, m, C**H**$CH_2$OH, CH**H'**OH), 4.12 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.47 (1H, *J*=11.5 Hz, CH**H'**Ar), 6.79 (2H, d, *J*=8.5 Hz, Ar**H**), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 7.20 (2H, d, *J*=8.5 Hz, Ar**H**), 7.24 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 11.1 ($CH_2\mathbf{C}H_3$), 22.3 ($\mathbf{C}H_2CH_3$), 32.9 ($\mathbf{C}H_2$CHOPBB), 33.3 ($\mathbf{C}H_2$CHOPMB), 54.8 (O$\mathbf{C}H_3$), 62.0 ($\mathbf{C}H_2$OH), 70.5 ($\mathbf{C}H_2$Ar), 71.0 ($\mathbf{C}H_2$Ar), 78.1 (**C**HOPBB), 78.1 (**C**H$CH_2$CHOPMB), 78.5 (**C**HOPMB), 79.7 (**C**H$CH_2$CHOPBB), 80.2 (**C**H$CH_2$OH), 84.9 (**C**HEt), 114.1 (Ar), 121.6 (Ar), 129.2 (Ar), 129.6 (Ar), 130.5 (Ar), 131.7 (Ar), 137.7 (Ar), 159.8 (Ar); $m/z$ ($ES^+$) 545 ($M+Na^+$, 100%), 543 ($M+Na^+$, 100); Accurate mass ($ES^+$): Found 545.1333, $C_{26}H_{33}{}^{81}BrNaO_6$ ($M+Na^+$) requires 545.1334, found 543.1345, $C_{26}H_{33}{}^{79}BrNaO_6$ ($M+Na^+$) requires 543.1353; $[\alpha]_D^{25}$ +31.5 (c = 0.27 in $CH_2Cl_2$).

***5-(4-Bromobenzyloxy)pentyl 4-nitrobenzoate* (374)**



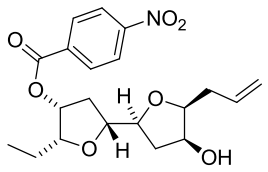

To a stirred solution of 5-(4-bromobenzyloxy)pentan-1-ol (**198**) (100 mg, 0.37 mmol) in DCM (6 mL) at 0 °C was added DCC (230 mg, 1.10 mmol), DMAP (45 mg, 0.37 mmol) and 4-nitrobenzoic acid (120 mg, 0.73 mmol). The reaction mixture was allowed to warm to RT and stirred for 20 h and then diluted with diethyl ether (20 mL). The organic layer was washed sequentially with aq. HCl (10 mL, 2 M), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL) before being dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5:1→2:1→1:1→0:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**374**) as a white solid (140 mg, 0.33 mmol, 90%); $R_f$ 0.81 (diethyl ether); m.p. 38–41 °C; $\nu_{max}/cm^{-1}$ (thin film) 2940s (CH), 2861s, 1722s (C=O), 1526s, 1348m, 1272s, 1101s, 1012m, 719s; $\delta_H$ (400 MHz, $CDCl_3$) 1.50–1.62 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.65–1.76 (2H, m, C**H**$_2$CH$_2$O), 1.79–1.88 (2H, m, C**H**$_2$CH$_2$O), 3.50 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 4.38 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 4.46 (2H, s, C**H**$_2$Ar), 7.20 (2H, d, *J*=8.5 Hz, Ar**H**), 7.46 (2H, d, *J*=8.5 Hz, Ar**H**), 8.20 (2H, d, *J*=9.0 Hz, Ar**H**), 8.28 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 22.8 (**C**H$_2$CH$_2$CH$_2$O), 28.4 (**C**H$_2$CH$_2$O), 29.3 (**C**H$_2$CH$_2$O), 65.8 (**C**H$_2$O), 70.1 (**C**H$_2$O), 72.2 (**C**H$_2$Ar), 121.4 (Ar), 123.5 (Ar), 129.2 (Ar), 130.7 (Ar), 131.5 (Ar), 135.8 (Ar), 137.5 (Ar), 150.5 (Ar), 164.7 (**C**=O); *m*/*z* (ES$^+$) 869 (2M+Na$^+$, 20%), 867 (2M+Na$^+$, 30), 865 (2M+Na$^+$, 20), 446 (M+Na$^+$, 100), 444 (M+Na$^+$, 95); Accurate mass (ES$^+$): Found 446.0387, $C_{19}H_{20}{}^{81}BrNNaO_5$ (M+Na$^+$) requires 446.0398, found 444.0413, $C_{19}H_{20}{}^{79}BrNNaO_5$ (M+Na$^+$) requires 444.0417.

**5-Hydroxypentyl 4-nitrobenzoate**[175] **(375)**



To a stirred solution of 5-(4-bromobenzyloxy)pentyl 4-nitrobenzoate (**374**) (20 mg, 0.05 mmol) in DCM (4.7 mL) was added boron trichloride (0.24 mL, 1.0 M in DCM, 0.24 mmol). The reaction mixture was stirred at RT for 10 min and then quenched by addition of sat. aq. $NaHCO_3$ (2 mL). After stirring vigorously for 10 min, the reaction mixture was diluted with $H_2O$ (3 mL) and the aqueous layer was extracted with DCM (4 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1→0:1 petrol b.p. 30–40 °C:diethyl ether) gave the title compound (**375**) as a colourless oil (14 mg, 0.05 mmol, quant.); $R_f$ 0.64 (diethyl ether); $\nu_{max}/cm^{-1}$ (thin film) 3363s br (OH), 2939s (CH), 2866s, 1722s (C=O), 1526s, 1349m, 1275s, 1103s, 719s; $\delta_H$ (400 MHz, $CDCl_3$) 1.39 (1H, br s, O**H**), 1.49–1.61 (2H, m, C**H**$_2$CH$_2$CH$_2$O), 1.61–1.71 (2H, m, C**H**$_2$CH$_2$O), 1.79–1.90 (2H, m, C**H**$_2$CH$_2$O), 3.70 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 4.40 (2H, t, *J*=6.5 Hz, C**H**$_2$O), 8.21 (2H, d, *J*=9.0 Hz, Ar**H**), 8.29 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (100 MHz, $CDCl_3$) 22.3 (**C**H$_2$CH$_2$CH$_2$O), 28.4 (**C**H$_2$CH$_2$O), 32.2 (**C**H$_2$CH$_2$O), 62.6 (**C**H$_2$O), 65.9 (**C**H$_2$O), 123.5 (Ar), 130.7 (Ar), 135.8 (Ar), 150.5 (Ar), 164.7 (**C**=O); *m*/*z* (ES$^+$) 276 (M+Na$^+$, 100%); Accurate mass (ES$^+$): Found 276.0843, $C_{12}H_{15}NNaO_5$ (M+Na$^+$) requires 276.0842.

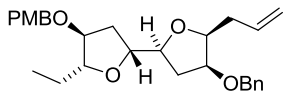
***(2R,2'S,4R,4'S,5R,5'S)-5'-Allyl-5-ethyl-4'-hydroxyoctahydro-[2,2'-bifuran]-4-yl 4-nitrobenzoate* (376)**



*According to the modified procedure of Burton et al.*[92]: To a stirred solution of (2*R*,2'*S*,4*R*,4'*S*,5*R*,5'*S*)-5'-allyl-4'-(4-bromobenzyloxy)-5-ethyloctahydro-[2,2'-bifuran]-4-yl 4-nitrobenzoate (**296**) (4 mg,

7.1 μmol) in DCM (0.7 mL) was added boron trichloride (36 μL, 1.0 M in DCM, 36 μmol). The reaction mixture was stirred at -50 °C for 45 min and then quenched by addition of methanol (2 mL) and concentrated *in vacuo*. Purification by flash column chromatography (5:1→2:1 petrol:EtOAc) gave the title compound (**376**) as a colourless oil (0.6 mg, 1.6 μmol, 22%); $R_f$ 0.39 (2:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3676m br (OH), 3077m, 2968s (CH), 2925s, 2876s, 1726s (C=O), 1529s ($NO_2$), 1350s ($NO_2$), 1274s, 1104s, 917m; $\delta_H$ (500 MHz, $C_6D_6$) 0.80 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.27 (1H, ddd, *J*=15.0, 7.0, 1.5 Hz, C**H**H'CHOH), 1.41–1.51 (1H, m, C**H**H'$CH_3$), 1.61–1.71 (1H, m, CH**H'**$CH_3$), 1.77 (1H, ddd, *J*=14.0, 10.0, 5.5 Hz, C**H**H'CHOC(O)Ar), 1.86 (1H, ddd, *J*=15.0, 9.0, 7.0 Hz, CH**H'**CHOH), 1.96 (1H, dd, *J*=14.0, 2.5 Hz, CH**H'**CHOC(O)Ar), 2.64–2.75 (2H, m, C**H**$_2$CH=$CH_2$), 3.15 (1H, ddd, *J*=7.5, 5.5, 3.5 Hz, C**H**Et), 3.57 (1H, td, *J*=7.0, 2.5 Hz, C**H**$CH_2$CH=$CH_2$), 3.74 (1H, d, *J*=10.5 Hz, O**H**), 3.83 (1H, dt, *J*=10.0, 2.5 Hz, C**H**$CH_2$CHOC(O)Ar), 3.90–3.96 (2H, m, C**H**OH, C**H**$CH_2$CHOH), 5.06–5.11 (2H, m, CH=C**H**H', C**H**OC(O)Ar), 5.18–5.23 (1H, m, CH=CH**H'**), 6.03 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, C**H**=$CH_2$), 7.64 (2H, d, *J*=9.0 Hz, Ar**H**), 7.85 (2H, d, *J*=9.0 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.7 ($CH_2\mathbf{C}H_3$), 22.0 (**C**$H_2CH_3$), 34.4 (**C**$H_2$CH=$CH_2$), 34.7 (**C**$H_2$CHOC(O)Ar), 36.0 (**C**$H_2$CHOH), 71.4 (**C**HOH), 75.7 (**C**HOC(O)Ar), 78.9 (**C**H$CH_2$CHOH), 79.2 (**C**H$CH_2$CHOC(O)Ar), 83.6 (**C**HEt), 84.4 (**C**H$CH_2$CH=$CH_2$), 116.8 (CH=**C**$H_2$), 123.8 (Ar), 128.5 (Ar), 134.9 (Ar), 135.7 (**C**H=$CH_2$), 150.8 (Ar), 163.9 (**C**=O); *m/z* ($ES^+$) 414 ($M+Na^+$, 100%); Accurate mass ($ES^+$): Found 414.1534, $C_{20}H_{25}NNaO_7$ ($M+Na^+$) requires 414.1523; $[\alpha]_D^{25}$ -18.3 (c = 0.05 in $CH_2Cl_2$).

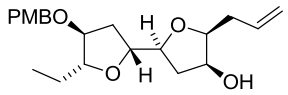
***(2S,2'R,4S,4'S,5S,5'R)-5-Allyl-4-(benzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran* (377)**




*According to the modified procedure of Smith III et al.*[176]: To a stirred solution of (2*S*,2'R,4*S*,4'*S*,5*S*,5'R)-5-allyl-4-(4-bromobenzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran (**294**) (5 mg,

9.4 μmol) in dry THF (0.1 mL) at -78 °C was added *n*-butyllithium (1 drop, 1.6 M in hexanes). The reaction mixture was stirred at -78 °C for 10 min and then quenched by addition of sat. aq. $NH_4Cl$ (2 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10:1→5:1 petrol:EtOAc) gave the title compound (**377**) as a colourless oil (2.5 mg, 55 μmol, 59%); $R_f$ 0.85 (2:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2969s (CH), 2875s, 1612m, 1513s, 1248s, 1094s, 1066s, 820m; $\delta_H$ (500 MHz, $C_6D_6$) 0.96 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.45–1.62 (2H, m, $C\mathbf{H}_2CH_3$), 1.89 (1H, ddd, *J*=14.0, 8.0, 5.5 Hz, C**H**H'CHOBn), 1.98 (1H, ddd, *J*=13.0, 9.0, 6.5 Hz, C**H**H'CHOPMB), 2.07 (1H, ddd, *J*=14.0, 5.5, 2.0 Hz, CH**H'**CHOBn), 2.28 (1H, ddd, *J*=13.0, 6.5, 2.5 Hz, C**H**H'CHOPMB), 2.58–2.65 (1H, m, C**H**H'CH=$CH_2$), 2.65–2.73 (1H, m, CH**H'**CH=$CH_2$), 3.31 (3H, s, OC$\mathbf{H}_3$), 3.57 (1H, ddd, *J*=6.5, 4.5, 2.5 Hz, C**H**OBn), 3.60–3.65 (1H, m, C**H**$CH_2$CH=$CH_2$), 3.66–3.70 (1H, m, C**H**OPMB), 3.83–3.88 (1H, m, C**H**$CH_2$CHOBn), 4.00–4.06 (1H, m, C**H**Et), 4.04 (1H, d, *J*=12.0 Hz, C**H**H'Ar), 4.20 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.31 (1H, d, *J*=11.5 Hz, CH**H'**Ar), 4.32 (1H, *J*=12.0 Hz, CH**H'**Ar), 4.36 (1H, dt, *J*=8.5, 6.5 Hz, C**H**$CH_2$CHOPMB), 5.04–5.09 (1H, m, CH=C**H**H'), 5.11–5.18 (1H, m, CH=CH**H'**), 5.97 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, C**H**=$CH_2$), 6.80 (2H, d, *J*=8.5 Hz, Ar**H**), 7.08–7.20 (5H, m, Ar**H**), 7.23 (2H, d, *J*=7.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.5 ($CH_2\mathbf{C}H_3$), 27.9 ($\mathbf{C}H_2CH_3$), 34.5 ($\mathbf{C}H_2CH=CH_2$), 35.3 ($\mathbf{C}H_2CHOBn$), 35.7 ($\mathbf{C}H_2CHOPMB$), 54.8 ($O\mathbf{C}H_3$), 70.8 ($\mathbf{C}H_2Ar$), 70.9 ($\mathbf{C}H_2Ar$), 79.2 (**C**HOBn), 81.0 (**C**H$CH_2$CHOBn), 81.4 (**C**H$CH_2$CHOPMB), 82.6 (**C**H$CH_2$CH=$CH_2$), 83.0 (**C**HOPMB), 85.8 (**C**HEt), 114.0 (CH=$\mathbf{C}H_2$), 116.5 (Ar), 127.5 (Ar), 127.6 (Ar), 128.6 (Ar), 129.4 (Ar), 131.1 (Ar), 136.2 (**C**H=$CH_2$), 139.0 (Ar), 159.7 (Ar); *m/z* ($ES^+$) 475 ($M+Na^+$, 100%); Accurate mass ($ES^+$): Found 475.2451, $C_{28}H_{36}NaO_5$ ($M+Na^+$) requires 475.2455; $[\alpha]_D^{25}$ +58.7 (c = 0.11 in $CH_2Cl_2$).

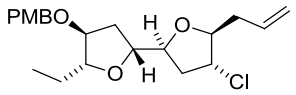
***(2S,2'R,4S,4'S,5S,5'R)-5-Allyl-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-4-ol* (378)**




*According to the modified procedure of Burton et al.*[128]: To a stirred solution of (2*S*,2'*R*,4*S*,4'*S*,5*S*,5'*R*)-5-allyl-4-(benzyloxy)-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran (**377**) (2.5 mg, 5.5 μmol) in THF (0.2 mL) at -78 °C was added freshly prepared LiDBB (20 μL of a solution prepared by sonicating 4,4'-di-*tert*-butylbiphenyl (0.50 g, 1.9 mmol) and lithium (13 mg, 1.9 mmol) in THF (2 mL) for 2 h). The reaction mixture was stirred at -78 °C for 2 min, during which time the reaction mixture changed from green/brown to colourless. Further LiDBB (1 drop, 6 times) was added until analysis by TLC showed no starting material present and then the reaction mixture was quenched by addition of sat. aq. $NH_4Cl$ (1 mL). After warming to RT the aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2:1→1:1 petrol:EtOAc) gave the title compound (**378**) as a colourless oil (2 mg, 5.5 μmol, quant.); $R_f$ 0.31 (2:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3437m br (OH), 3074w, 2961s (CH), 2934s, 2876s, 1613m, 1514s, 1249s, 1036s, 821m; $\delta_H$ (500 MHz, $C_6D_6$) 0.83 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.12 (1H, ddd, *J*=13.0, 10.5, 6.5 Hz, C**H**H'CHOPMB), 1.29 (1H, ddd, *J*=13.5, 7.5, 7.0 Hz, C**H**H'$CH_3$), 1.39–1.48 (1H, m, CH**H'**$CH_3$), 1.65 (1H, ddd, *J*=13.0, 5.5, 2.0 Hz, CH**H'**CHOPMB), 1.70 (1H, dd, *J*=13.5, 3.0 Hz, C**H**H'CHOH), 1.78 (1H, ddd, *J*=13.5, 10.0, 5.0 Hz, CH**H'**CHOH), 2.67–2.78 (2H, m, $C\mathbf{H}_2CH{=}CH_2$), 3.31 (3H, s, $OC\mathbf{H}_3$), 3.40–3.44 (1H, m, C**H**OPMB), 3.55 (1H, td, *J*=7.0, 2.5 Hz, C**H**$CH_2CH{=}CH_2$), 3.76 (1H, d, *J*=10.5 Hz, O**H**), 3.85–3.95 (3H, m, C**H**Et, C**H**$CH_2$CHOH, C**H**OH), 4.14 (1H, d, *J*=11.5 Hz, C**H**H'Ar), 4.19 (1H, *J*=11.5 Hz, CH**H'**Ar), 4.46 (1H, ddd, *J*=10.5, 5.5, 2.0 Hz, C**H**$CH_2$CHOPMB), 5.08 (1H, ddt, *J*=10.0, 2.0, 1.0 Hz, CH=C**H**H'), 5.20 (1H, ddt, *J*=17.0, 2.0, 1.5 Hz, CH=CH**H'**), 6.07 (1H, ddt, *J*=17.0, 10.0, 7.0 Hz, C**H**=$CH_2$), 6.81 (2H, d, *J*=9.0 Hz, Ar**H**), 7.13–7.18 (2H, m, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.4 ($CH_2\mathbf{C}H_3$), 27.4 (**C**$H_2CH_3$),

34.5 (**C**$H_2$CH=$CH_2$), 34.8 (**C**$H_2$CHOPMB), 34.9 (**C**$H_2$CHOH), 54.8 (O**C**$H_3$), 70.8 (**C**$H_2$Ar), 71.4 (**C**HOH), 78.9 (**C**HCH$_2$CHOH), 79.9 (**C**HCH$_2$CHOPMB), 82.2 (C**H**OPMB), 84.0 (**C**HCH$_2$CH=$CH_2$), 86.3 (**C**HEt), 114.1 (CH=**C**$H_2$), 127.5 (Ar), 129.3 (Ar), 130.7 (Ar), 136.0 (**C**H=$CH_2$), 159.8 (Ar); $m/z$ ($ES^+$) 747 ($2M+Na^+$, 100%), 385 ($M+Na^+$, 85); Accurate mass ($ES^+$): Found 385.1985, $C_{21}H_{30}NaO_5$ ($M+Na^+$) requires 385.1985; $[\alpha]_D^{25}$ +42.2 (c = 0.11 in $CH_2Cl_2$).

***(2S,2'R,4R,4'S,5S,5'R)-5-Allyl-4-chloro-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-2,2'-bifuran* (379)**



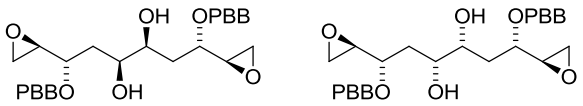

*According to the modified procedure of Kikuchi et al.*[26]: (2*S*,2'*R*,4*S*,4'*S*,5*S*,5'*R*)-5-Allyl-5'-ethyl-4'-(4-methoxybenzyloxy)octahydro-[2,2'-bifuran]-4-ol (**378**) (1.0 mg, 2.8 μmol) and triphenylphosphine (7.0 mg, 27.6 μmol) were dissolved in carbon tetrachloride (0.2 mL) and the reaction mixture was heated to 70 °C for 18 h. The reaction mixture was then cooled to RT and concentrated *in vacuo*. Purification by flash column chromatography (10:1→5:1 petrol:EtOc) gave the title compound (**379**) as a colourless oil (1.1 mg, 2.8 μmol, quant.); $R_f$ 0.89 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3080m, 2961s (CH), 2930s, 2877s, 1613m, 1514s, 1248s, 1098s, 1062s, 1037s, 918m, 822m; $\delta_H$ (500 MHz, $C_6D_6$) 0.90 (3H, t, *J*=7.5 Hz, $CH_2C\mathbf{H}_3$), 1.32–1.48 (2H, m, $C\mathbf{H}_2CH_3$), 1.57 (1H, ddd, *J*=13.0, 9.0, 6.5 Hz, C**H**H'CHOPMB), 2.04 (1H, ddd, *J*=13.0, 6.0, 2.5 Hz, CH**H'**CHOPMB), 2.05–2.21 (4H, m, $C\mathbf{H}_2$CHCl, $C\mathbf{H}_2$CH=$CH_2$), 3.30 (3H, s, O$C\mathbf{H}_3$), 3.55 (1H, ddd, *J*=6.5, 3.0, 2.5 Hz, C**H**OPMB), 3.77 (1H, dt, *J*=7.0, 5.0 Hz, C**H**Cl), 3.96 (1H, ddd, *J*=7.0, 6.5, 3.0 Hz, C**H**Et), 4.00–4.13 (3H, m, C**H**$CH_2$CH=$CH_2$, C**H**$CH_2$CHCl, C**H**$CH_2$CHOPMB), 4.21 (1H, d, *J*=11.5 Hz, C**H**H'Ar,), 4.27 (1H, *J*=11.5 Hz, CH**H'**Ar), 4.96–4.99 (1H, m, CH=C**H**H'), 4.99–5.02 (1H, m, CH=CH**H'**), 5.78 (1H, ddt, *J*=16.5, 10.0, 7.0 Hz, C**H**=$CH_2$), 6.81 (2H, d, *J*=8.5 Hz, Ar**H**), 7.19 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 10.5 ($CH_2\mathbf{C}H_3$), 27.8 (**C**$H_2CH_3$), 35.7 (**C**$H_2$CHOPMB), 38.3 (**C**$H_2$CH=$CH_2$), 38.9 (**C**$H_2$CHCl), 54.8 (O**C**$H_3$), 59.8 (**C**HCl), 70.9 (**C**$H_2$Ar),

80.4 (**C**HCH$_2$CHOPMB), 80.8 (**C**HCH$_2$CHCl), 82.8 (**C**HOPMB), 85.9 (**C**HEt), 86.7 (**C**HCH$_2$CH=CH$_2$), 114.1 (CH=**C**H$_2$), 127.5 (Ar), 129.4 (Ar), 130.9 (Ar), 134.1 (**C**H=CH$_2$), 159.8 (Ar); *m/z* (ES$^+$) 405 (M+Na$^+$, 50%), 403 (M+Na$^+$, 100); Accurate mass (ES$^+$): Found 405.1621, $C_{21}H_{29}{}^{37}ClNaO_4$ (M+Na$^+$) requires 405.1619, found 403.1638, $C_{21}H_{29}{}^{35}ClNaO_4$ (M+Na$^+$) requires 403.1647; $[\alpha]_D^{25}$ +5.5 (c = 0.07 in $CH_2Cl_2$).

***(1S,3S,4S,6S)-1,6-Bis(4-bromobenzyloxy)-1,6-di((R)-oxiran-2-yl)hexane-3,4-diol* (387)**

***(1S,3R,4R,6S)-1,6-Bis(4-bromobenzyloxy)-1,6-di((R)-oxiran-2-yl)hexane-3,4-diol***

**((3*R*,4*R*)-387)**



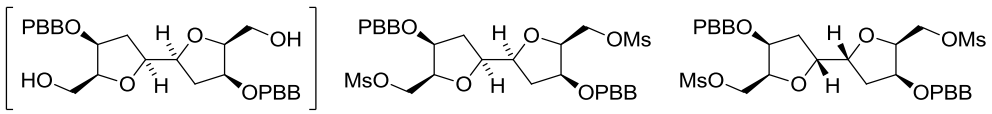

Prepared according to the **general SAD procedure** (**Page 184**) with (1*S*,6*S*,*E*)-1,6-bis(4-bromobenzyloxy)-1,6-di((*R*)-oxiran-2-yl)hex-3-ene (**239**) (0.74 g, 1.37 mmol), purification through a plug of silica (EtOAc) gave a mixture of the two title compounds (**387** and **(3*R*,4*R*)-387**) in 5:1 d.r. as a colourless oil (0.79 g, 1.37 mmol, quant.); $R_f$ (3*S*,4*S*) 0.40, (3*R*,4*R*) 0.3 (1:2 petrol:EtOAc); $\nu_{max}$/cm$^{-1}$ (thin film) 3445s br (OH), 2921s (CH), 2872s, 1487s, 1406m, 1330m, 1261m, 1069s, 1011s, 804s; $\delta_H$ as a mixture of diastereomers $D_1$ (major 3*S*,4*S*) and $D_2$ (minor 3*R*,4*R*) (500 MHz, $C_6D_6$) 1.70 (4H, ddd, *J*=14.0, 9.5, 2.0 Hz, C**H**H'CHOPBB $D_1$ + $D_2$), 1.82–1.92 (4H, m, CH**H'**CHOPBB $D_1$ + $D_2$), 2.35–2.40 (4H, m, C**H**H'O(CH) $D_1$ + $D_2$), 2.42 (4H, dd, *J*=5.5, 2.5 Hz, CH**H'**O(CH) $D_1$ + $D_2$), 2.67–2.73 (4H, m, $CH_2O$(C**H**) $D_1$ + $D_2$), 3.23 (2H, d, *J*=5.0 Hz, O**H** $D_1$), 4.37 (2H, d, *J*=3.5 Hz, O**H** $D_2$), 3.52 (4H, ddd, *J*=8.5, 5.5, 3.0 Hz, C**H**OPBB $D_1$ + $D_2$), 3.71–3.82 (4H, m, C**H**OH $D_1$ + $D_2$), 4.09 (2H, d, *J*=12.0 Hz, C**H**H'Ar $D_2$), 4.22 (2H, d, *J*=12.0 Hz, C**H**H'Ar $D_1$), 4.31 (2H, d, *J*=12.0 Hz, CH**H'**Ar $D_2$), 4.40 (2H, d, *J*=12.0 Hz, CH**H'**Ar $D_1$), 6.89 (4H, d, *J*=8.5 Hz, Ar**H** $D_2$), 6.96 (4H, d, *J*=8.5 Hz, Ar**H** $D_1$), 7.27 (4H, d, *J*=8.5 Hz, Ar**H** $D_2$), 7.30 (4H, d, *J*=8.5 Hz, Ar**H** $D_1$); $\delta_C$ (125 MHz, $C_6D_6$) 36.1 (**C**H$_2$CHOPBB $D_2$), 36.9 (**C**H$_2$CHOPBB $D_1$), 45.5 (**C**H$_2$O(CH) $D_2$), 45.7 (**C**H$_2$O(CH) $D_1$), 55.2 ($CH_2O$(**C**H) $D_2$), 55.3 ($CH_2O$(**C**H) $D_1$), 71.3 (**C**HOH

$D_2$), 71.4 (**C**HOH $D_1$), 71.8 (**C**$H_2$Ar $D_1$), 72.3 (**C**$H_2$Ar $D_2$), 76.3 (**C**HOPBB $D_1$), 77.7 (**C**HOPBB $D_2$), 121.7 (Ar $D_1$), 121.9 (Ar $D_2$), 129.5 (Ar $D_1$), 129.7 (Ar $D_2$), 131.7 (Ar $D_1$), 131.8 (Ar $D_2$), 137.6 (Ar $D_2$), 138.1 (Ar $D_1$); *m/z* ($ES^+$) 1169 (2M+$Na^+$, 70%), 1167 (2M+$Na^+$, 100), 1165 (2M+$Na^+$, 65), 597 (M+$Na^+$, 15), 595 (M+$Na^+$, 30), 593 (M+$Na^+$, 15); Accurate mass ($ES^+$): Found 597.0099, $C_{24}H_{28}{}^{81}Br_2NaO_6$ (M+$Na^+$) requires 597.0138, found 595.0114, $C_{24}H_{28}{}^{81}Br^{79}BrNaO_6$ (M+$Na^+$) requires 595.0126, found 593.0130, $C_{24}H_{28}{}^{79}Br_2NaO_6$ (M+$Na^+$) requires 593.0145.

***((2S,2'S,4S,4'S,5S,5'S)-4,4'-Bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)dimethanol* (389)**

***((2S,2'S,4S,4'S,5S,5'S)-4,4'-Bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)bis(methylene) dimethanesulfonate* (388)**

***((2R,2'R,4S,4'S,5S,5'S)-4,4'-Bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)bis(methylene) dimethanesulfonate* ((2*R*,2'*R*)-388)**




To a stirred solution of ((1*S*,3*S*,4*S*,6*S*)- and (1*S*,3*R*,4*R*,6*S*)-1,6-bis(4-bromobenzyloxy)-1,6-di((*R*)-oxiran-2-yl)hexane-3,4-diol (**387**) (0.79 g, 1.37 mmol) in dry DCM (2 mL) was added Amberlyst-15® resin (cat.). The reaction mixture was stirred at RT for 4 h and then loaded onto silica. Purification by flash column chromatography (EtOAc + 1% MeOH) gave a partitally separable mixture of ((2*S*,2'*S*,4*S*,4'*S*,5*S*,5'*S*)- and ((2*R*,2'*R*,4*S*,4'*S*,5*S*,5'*S*)-4,4'-bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)dimethanol (**389**) with only the major diastereomer being characterised (760 mg); $R_f$ 0.20 (EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3412s br (OH), 2929s (CH), 2870s, 1487s, 1069s, 1011s, 804s; $\delta_H$ (400 MHz, $C_6D_6$) 1.79–1.89 (2H, m, 2 × C**H**H'CHOPBB), 1.89–2.00 (2H, m, 2 × CH**H'**CHOPBB), 3.83–3.96 (4H, m, 2 × C**H**OPBB, 2 × C**H**$CH_2$CHOPBB), 3.97–3.27 (12H, m, 2 × C**H**$CH_2$OH, 2 × O**H**, 2 × C**H**$_2$OH, 2 × C**H**$_2$Ar), 7.01 (4H, d, *J*=8.5 Hz, Ar**H**), 7.41 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 33.9

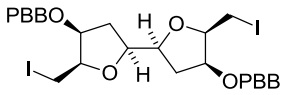
(**C**$H_2$CHOPBB), 61.8 (**C**$H_2$OH), 70.9 (**C**$H_2$Ar), 79.0 (**C**HCH$_2$CHOPBB), 79.5 (**C**HOPBB), 82.0 (**C**HCH$_2$OH), 121.7 (Ar), 129.4 (Ar), 131.7 (Ar), 137.6 (Ar); *m/z* ($ES^+$) 1169 (2M+$Na^+$, 75%), 1167 (2M+$Na^+$, 100), 1165 (2M+$Na^+$, 70), 597 (M+$Na^+$, 20), 595 (M+$Na^+$, 35), 593 (M+$Na^+$, 20); Accurate mass ($ES^+$): Found 597.0113, $C_{24}H_{28}{}^{81}Br_2NaO_6$ (M+$Na^+$) requires 597.0105, found 595.0128, $C_{24}H_{28}{}^{81}Br^{79}BrNaO_6$ (M+$Na^+$) requires 595.0126, found 593.0138, $C_{24}H_{28}{}^{79}Br_2NaO_6$ (M+$Na^+$) requires 593.0145; $[\alpha]_D^{25}$ +29.6 (c = 1.0 in $CH_2Cl_2$).

A portion of the mixture of ((2*S*,2'*S*,4*S*,4'*S*,5*S*,5'*S*)- and ((2*R*,2'*R*,4*S*,4'*S*,5*S*,5'*S*)-4,4'-bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)dimethanol (**389**) (99 mg, 0.17 mmol) was subjected to the **general mesylation procedure II** (**Page 202**). Purification by flash column chromatography (20:1→15:1→10:1 DCM:EtOAc) gave the two title compounds (**388** and **(2*R*,2'*R*)-388**) as a colourless oils.

1. ((2*S*,2'*S*,4*S*,4'*S*,5*S*,5'*S*)-4,4'-Bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)bis(methylene) dimethanesulfonate (**388**) (95 mg, 0.13 mmol, 76%): $R_f$ 0.40 (10:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3027m, 2937s (CH), 2875s, 1350s, 1172s, 1071s, 958s, 813s; $\delta_H$ (400 MHz, $C_6D_6$) 1.57–1.70 (4H, m, 2 × C**H**$_2$CHOPBB), 2.42 (6H, s, 2 × SC**H**$_3$), 3.56 (2H, dt, *J*=5.5, 5.0 Hz, 2 × C**H**CH$_2$CHOPBB), 3.80–3.92 (6H, m, 2 × C**H**OPBB, 2 × C**H**CH$_2$OMs, 2 × C**H**H'Ar), 4.00 (2H, d, *J*=12.0 Hz, 2 × CH**H'**Ar), 4.37–4.43 (4H, m, 2 × C**H**$_2$OMs), 6.85 (4H, d, *J*=8.5 Hz, Ar**H**), 7.30 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (100 MHz, $C_6D_6$) 33.5 (**C**$H_2$CHOPBB), 36.9 (S**C**$H_3$), 69.0 (**C**$H_2$OMs), 70.6 (**C**$H_2$Ar), 78.9 (**C**HCH$_2$CHOPBB), 79.4 (**C**HOPBB), 79.7 (**C**HCH$_2$OMs), 121.9 (Ar), 129.3 (Ar), 131.8 (Ar), 137.1 (Ar); *m/z* ($ES^+$) 1481 (2M+$Na^+$, 80%), 1479 (2M+$Na^+$, 100), 1477 (2M+$Na^+$, 70), 753 (M+$Na^+$, 30), 751 (M+$Na^+$, 50), 749 (M+$Na^+$, 30); Accurate mass ($ES^+$): Found 752.9677, $C_{26}H_{32}{}^{81}Br_2NaO_{10}S_2$ (M+$Na^+$) requires 752.9656, found 750.9691, $C_{26}H_{32}{}^{81}Br^{79}BrNaO_{10}S_2$ (M+$Na^+$) requires 750.9677, found 748.9711, $C_{26}H_{32}{}^{79}Br_2NaO_{10}S_2$ (M+$Na^+$) requires 748.9696; $[\alpha]_D^{25}$ +13.2 (c = 1.0 in $CH_2Cl_2$).

2. ((2*R*,2'*R*,4*S*,4'*S*,5*S*,5'*S*)-4,4'-Bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)bis(methylene) dimethanesulfonate (**(2*R*,2'*R*)-388**) (22 mg, 0.03 mmol, 18%): $R_f$ 0.60 (10:1 DCM:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2936s (CH), 1487s, 1352s, 1172s, 1071s, 960s, 826s; $\delta_H$ (500 MHz, $CDCl_3$) 2.01–2.09 (2H, m, 2 × C**H**H'CHOPBB), 2.10–2.17 (2H, m, 2 × CH**H'**CHOPBB), 3.00 (6H, s, 2 × SC**H**$_3$), 4.15–4.21 (2H, m, 2 × C**H**OPBB), 4.22–4.28 (4H, m, 2 × C**H**$CH_2$CHOPBB, 2 × C**H**$CH_2$OMs), 4.33–4.44 (6H, m, 2 × C**H**$_2$OMs, 2 × C**H**H'Ar), 4.54 (2H, d, *J*=12.0 Hz, 2 × CH**H'**Ar), 7.18 (4H, d, *J*=8.5 Hz, Ar**H**), 7.48 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 33.6 (**C**$H_2$CHOPBB), 37.5 (S**C**$H_3$), 68.7 (**C**$H_2$OMs), 70.8 (**C**$H_2$Ar), 79.3 (**C**H$CH_2$CHOPBB), 79.6 (**C**H$CH_2$OMs), 79.7 (**C**HOPBB), 121.8 (Ar), 129.2 (Ar), 131.6 (Ar), 136.6 (Ar); *m*/*z* ($ES^+$) 1481 (2M+$Na^+$, 30%), 1479 (2M+$Na^+$, 40), 1477 (2M+$Na^+$, 20), 753 (M+$Na^+$, 30), 751 (M+$Na^+$, 50), 749 (M+$Na^+$, 30); Accurate mass ($ES^+$): Found 752.9666, $C_{26}H_{32}{}^{81}Br_2NaO_{10}S_2$ (M+$Na^+$) requires 752.9656, found 750.9688, $C_{26}H_{32}{}^{79}Br^{81}BrNaO_{10}S_2$ (M+$Na^+$) requires 750.9677, found 748.9702, $C_{26}H_{32}{}^{79}Br_2NaO_{10}S_2$ (M+$Na^+$) requires 748.9696; $[\alpha]_D^{25}$ +23.8 (c = 1.0 in $CH_2Cl_2$).

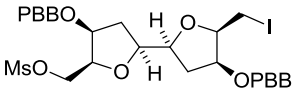
***(2S,2'S,4S,4'S,5R,5'R)-4,4'-Bis(4-bromobenzyloxy)-5,5'-bis(iodomethyl)octahydro-2,2'-bifuran* (385)**




To a stirred solution of ((2*S*,2'*S*,4*S*,4'*S*,5*S*,5'*S*)-4,4'-bis(4-bromobenzyloxy)octahydro-[2,2'-bifuran]-5,5'-diyl)bis(methylene) dimethanesulfonate (**388**) (95 mg, 0.13 mmol) in 2-butanone (1.3 mL) was added sodium iodide (98 mg, 0.65 mmol). The reaction mixture was heated to 80 °C for 40 h and then cooled to RT and $H_2O$ (5 mL) was added. The aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (10:1→5:1 petrol:EtOAc) gave the title compound (**385**) as a colourless oil (95 mg, 0.12 mmol, 92%); $R_f$ 0.78 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 2966s (CH), 2867s, 1487s, 1347s, 1069s, 1011s, 804s; $\delta_H$ (500 MHz, $C_6D_6$) 1.59 (2H,

ddd, *J*=14.0, 6.5, 1.5 Hz, 2 × C**H**H'CHOPBB), 1.76 (2H, ddd, *J*=14.0, 6.5, 2.0 Hz, 2 × CH**H'**CHOPBB), 3.21 (2H, dd, *J*=9.5, 6.0 Hz, 2 × C**H**H'I), 3.21 (2H, dd, *J*=9.5, 7.5 Hz, 2 × CH**H'**I), 3.50 (2H, ddd, *J*=6.5, 4.0, 2.5 Hz, 2 × C**H**OPBB), 3.65 (2H, ddd, *J*=7.5, 6.0, 4.0 Hz, 2 × C**H**$CH_2$I), 3.84 (2H, d, *J*=12.0 Hz, 2 × C**H**H'Ar), 3.97 (2H, d, *J*=12.0 Hz, 2 × CH**H'**Ar), 3.97–4.04 (2H, m, 2 × C**H**$CH_2$CHOPBB), 6.82 (4H, d, *J*=8.5 Hz, Ar**H**), 7.27 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 1.5 (**C**$H_2$I), 33.0 (**C**$H_2$CHOPBB), 70.5 (**C**$H_2$Ar), 78.9 (**C**HOPBB), 79.5 (**C**H$CH_2$CHOPBB), 83.1 (**C**H$CH_2$I), 121.8 (Ar), 129.2 (Ar), 131.7 (Ar), 137.4 (Ar); *m*/*z* ($ES^+$) 1609 (2M+$Na^+$, 70%), 1607 (2M+$Na^+$, 100), 1605 (2M+$Na^+$, 70), 617 (M+$Na^+$, 35), 615 (M+$Na^+$, 65), 613 (M+$Na^+$, 35); Accurate mass ($ES^+$): Found 816.8154, $C_{24}H_{26}{}^{81}Br_2I_2NaO_4$ (M+$Na^+$) requires 816.9140, found 814.8161, $C_{24}H_{26}{}^{81}Br^{79}BrI_2NaO_4$ (M+$Na^+$) requires 814.8161, 812.8189, found $C_{24}H_{26}{}^{79}Br_2I_2NaO_4$ (M+$Na^+$) requires 812.8179; $[\alpha]_D^{25}$ +56.9 (c = 1.0 in $CH_2Cl_2$).

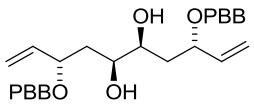
***((2S,2'S,4S,4'S,5S,5'R)-4,4'-Bis(4-bromobenzyloxy)-5'-(iodomethyl)octahydro-[2,2'-bifuran]-5-yl)methyl methanesulfonate***




Isolated in sodium iodide reactions stirred for less than 40 h as a colourless oil; $R_f$ 0.50 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3027m, 2869s (CH), 1487s, 1350s, 1172s, 1069s, 958s, 806s; $\delta_H$ (500 MHz, $C_6D_6$) 1.50–1.71 (4H, m, 2 × C**H**$_2$CHOPBB), 2.32 (3H, s, SC**H**$_3$), 3.19 (1H, dd, *J*=9.5, 6.0 Hz, C**H**H'I), 3.27 (1H, dd, *J*=9.5, 8.0 Hz, CH**H'**I), 3.40 (1H, ddd, *J*=6.5, 5.0, 4.0 Hz, C**H**OPBB), 3.53 (1H, *J*=6.5, 4.5, 2.5 Hz, C**H**OPBB), 3.66–3.75 (3H, m, C**H**$CH_2$I, C**H**$CH_2$OMs, C**H**H'Ar), 3.86–3.91 (3H, m, C**H**$CH_2$CHOPBB, CH**H'**Ar, C**H**H'Ar), 3.93–4.03 (2H, m, C**H**$CH_2$CHOPBB, CH**H'**Ar), 4.34 (1H, dd, *J*=11.0, 4.0 Hz, C**H**H'OMs), 4.39 (1H, dd, *J*=11.0, 7.0 Hz, CH**H'**OMs), 6.75 (2H, d, *J*=8.5 Hz, Ar**H**), 6.85 (2H, d, *J*=8.5 Hz, Ar**H**), 7.26 (2H, d, *J*=8.5 Hz, Ar**H**), 7.27 (2H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$) 1.4 (**C**$H_2$I), 33.2 (**C**$H_2$CHOPBB), 33.3 (**C**$H_2$CHOPBB), 37.0 (S**C**$H_3$), 68.8 (**C**$H_2$OMs), 70.4 (**C**$H_2$Ar), 70.6 (**C**$H_2$Ar),

78.8 (**C**HOPBB), 78.8 (**C**HOPBB), 79.4 (**C**HCH$_2$OMs), 79.6 (**C**HCH$_2$CHOPBB), 79.8 (**C**HCH$_2$CHOPBB), 83.2 (**C**HCH$_2$I), 121.8 (Ar), 121.9 (Ar), 129.1 (Ar), 129.2 (Ar), 131.8 (Ar), 131.8 (Ar), 137.1 (Ar), 137.3 (Ar); $m/z$ (ES$^+$) 1545 (2M+Na$^+$, 60%), 1543 (2M+Na$^+$, 80), 1541 (2M+Na$^+$, 50), 785 (M+Na$^+$, 25), 783 (M+Na$^+$, 40), 781 (M+Na$^+$, 25); Accurate mass (ES$^+$): Found 784.8882, $C_{25}H_{29}{}^{81}Br_2INaO_7S$ (M+Na$^+$) requires 784.8898, found 782.8914, $C_{25}H_{29}{}^{81}Br^{79}BrINaO_7S$ (M+Na$^+$) requires 782.8919, found 780.8941, $C_{25}H_{29}{}^{79}Br_2INaO_7S$ (M+Na$^+$) requires 780.8938; $[\alpha]_D^{25}$ +31.1 (c = 1.0 in $CH_2Cl_2$).

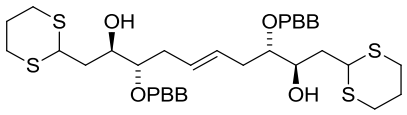
***(3S,5S,6S,8S)-3,8-Bis(4-bromobenzyloxy)deca-1,9-diene-5,6-diol* (390)**




To a stirred solution of copper(I) iodide (12 mg, 65 μmol) in dry benzene (0.2 mL) at 0 °C was added vinylmagnesium bromide (0.13 mL, 1.0 M in THF, 0.13 mmol) and this solution was stirred at 0 °C for 30 min. To this solution was added a solution of (2*S*,2'*S*,4*S*,4'*S*,5*R*,5'*R*)-4,4'-bis(4-bromobenzyloxy)-5,5'-bis(iodomethyl)octahydro-2,2'-bifuran (**385**) (10 mg, 14 μmol) in dry benzene (0.2 mL + 0.5 mL rinse) and the reaction mixture was stirred for 1.5 h and allowed to warm to RT. The reaction mixture was quenched with sat. aq. $NH_4Cl$ (5 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:0→10:1→0:1 DCM:EtOAc) gave the title compound (**390**) as a colourless oil (3 mg, 5.6 μmol, 40%); $R_f$ 0.68 (5:1 DCM:EtOAc); $\nu_{max}$/cm$^{-1}$ (thin film) 3433s br (OH), 2916s (CH), 2867s, 1488s, 1070s, 1012s, 803s; $\delta_H$ (500 MHz, $C_6D_6$) 1.64 (2H, ddd, *J*=14.0, 8.5, 2.5 Hz, 2 × C**H**H'CHOH), 1.75 (2H, ddd, *J*=14.0, 9.0, 3.0 Hz, 2 × CH**H'**CHOH), 2.62–2.67 (2H, m, 2 × O**H**), 3.74–3.81 (2H, m, 2 × C**H**OH), 3.97–4.03 (4H, m, 2 × C**H**H'Ar, 2 × C**H**OPBB), 4.27 (2H, d, *J*=12.0 Hz, 2 × CH**H'**Ar), 4.98–5.02 (2H, m, 2 × CH=C**H**H'), 5.02–5.07 (2H, m, 2 × CH=CH**H'**), 5.60 (2H, ddd, *J*=17.5, 10.5, 7.5 Hz, 2 × C**H**=CH$_2$), 6.89 (4H, d, *J*=8.5 Hz, Ar**H**), 7.26 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $C_6D_6$)

39.8 (**C**$H_2$CHOH), 69.9 (**C**$H_2$Ar), 71.4 (**C**HOH), 78.3 (**C**HOPBB), 116.8 (CH=**C**$H_2$), 121.7 (Ar), 129.5 (Ar), 131.7 (Ar), 138.0 (Ar), 138.7 (**C**H=$CH_2$); *m/z* ($ES^+$) 565 ($M+Na^+$, 60%), 563 ($M+Na^+$, 100), 561 ($M+Na^+$, 60); Accurate mass ($ES^+$): Found 565.0218, $C_{24}H_{28}{}^{81}Br_2NaO_4$ ($M+Na^+$) requires 565.0207, found 563.0222, $C_{24}H_{28}{}^{81}Br^{79}BrNaO_4$ ($M+Na^+$) requires 563.0228, found 561.0264, $C_{24}H_{28}{}^{79}Br_2NaO_4$ ($M+Na^+$) requires 561.0247; $[\alpha]_D^{25}$ -13.8 (c = 0.22 in $CH_2Cl_2$).

***(2R,3S,8S,9R,E)-3,8-Bis(4-bromobenzyloxy)-1,10-di(1,3-dithian-2-yl)dec-5-ene-2,9-diol* (393)**




*According to the modified procedure of Smith III et al.*[143]: To a stirred solution of 1,3-dithiane (85 mg, 0.71 mmol) in dry THF/HMPA (3.3 mL, 10:1) at -30 °C was added *n*-butyllithium (0.44 mL, 1.6 M in hexanes, 0.71 mmol) dropwise. The resulting solution was stirred at -30 °C for 1 h during which time a yellow colour was produced. To a stirred solution of (1*S*,6*S*,*E*)-1,6-bis(4-bromobenzyloxy)-1,6-di((*R*)-oxiran-2-yl)hex-3-ene (**239**) (30 mg, 56 μmol) in dry THF (0.5 mL) at -30 °C was added the solution of lithiated 1,3-dithiane (0.70 mL, 0.13 mmol) dropwise. The reaction mixture was stirred at -30 °C for 20 min and then a further two portion of lithiated dithiane solution (0.18 mL, 0.03 mmol) were added until TLC analysis indicated complete consumption of SM. The reaction mixture was allowed to warm to 0 °C over 2 h and then quenched with sat. aq. $NH_4Cl$ (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with $H_2O$ (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:1→2:1→1:1 petrol:EtOAc) gave the title compound (**393**) as a colourless oil (25 mg, 32 μmol, 57%); $R_f$ 0.53 (1:1 petrol:EtOAc); $\nu_{max}/cm^{-1}$ (thin film) 3448s br (OH), 2932s (CH), 2899s, 1487s, 1422s, 1243s, 1070s, 1011s, 804s; $\delta_H$ (500 MHz, $CDCl_3$) 1.83–1.98 (6H, m, 2 × C**H**$_2$CHS$_2$, 2 × C**H**H'$CH_2$S), 2.08–2.16 (2H, m, 2 × CH**H'**$CH_2$S), 2.19–2.31 (4H, m, 2 × C**H**H'CHOPBB, 2 × O**H**), 2.34–2.42 (2H, m, 2 × CH**H'**CHOPBB), 2.79–2.96 (8H, m,

4 × C**H**$_2$S), 3.43 (2H, td, *J*=6.0, 4.0 Hz, 2 × C**H**OPBB), 3.99–4.07 (2H, m, 2 × C**H**OH), 4.26 (2H, dd, *J*=9.0, 5.0 Hz, 2 × C**H**S$_2$), 4.50 (2H, d, *J*=11.5 Hz, 2 × C**H**H'Ar), 4.56 (2H, d, *J*=11.5 Hz, 2 × CH**H'**Ar), 5.52–5.56 (2H, m, C**H**=C**H**), 7.20 (4H, d, *J*=8.5 Hz, Ar**H**), 7.46 (4H, d, *J*=8.5 Hz, Ar**H**); $\delta_C$ (125 MHz, $CDCl_3$) 25.9 (**C**H$_2$CH$_2$S), 30.0 (**C**H$_2$S), 30.4 (**C**H$_2$S), 33.1 (**C**H$_2$CHOPBB), 37.6 (**C**H$_2$CHS$_2$), 44.2 (**C**HS$_2$), 69.0 (**C**HOH), 71.2 (**C**H$_2$Ar), 81.8 (**C**HOPBB), 121.6 (Ar), 128.7 (**C**H=**C**H), 129.3 (Ar), 131.5 (Ar), 137.3 (Ar); $m/z$ (ES$^+$) 803 (M+Na$^+$, 70%), 801 (M+Na$^+$, 100), 799 (M+Na$^+$, 60); Accurate mass (ES$^+$): Found 803.0185, $C_{32}H_{42}{}^{81}Br_2NaO_4S_4$ (M+Na$^+$) requires 803.0185, found 801.0207, $C_{32}H_{42}{}^{81}Br^{79}BrNaO_4S_4$ (M+Na$^+$) requires 801.0205, found 799.0229, $C_{32}H_{42}{}^{79}Br_2NaO_4S_4$ (M+Na$^+$) requires 799.0225; $[\alpha]_D^{25}$ +14.3 (c = 1.0 in $CH_2Cl_2$).

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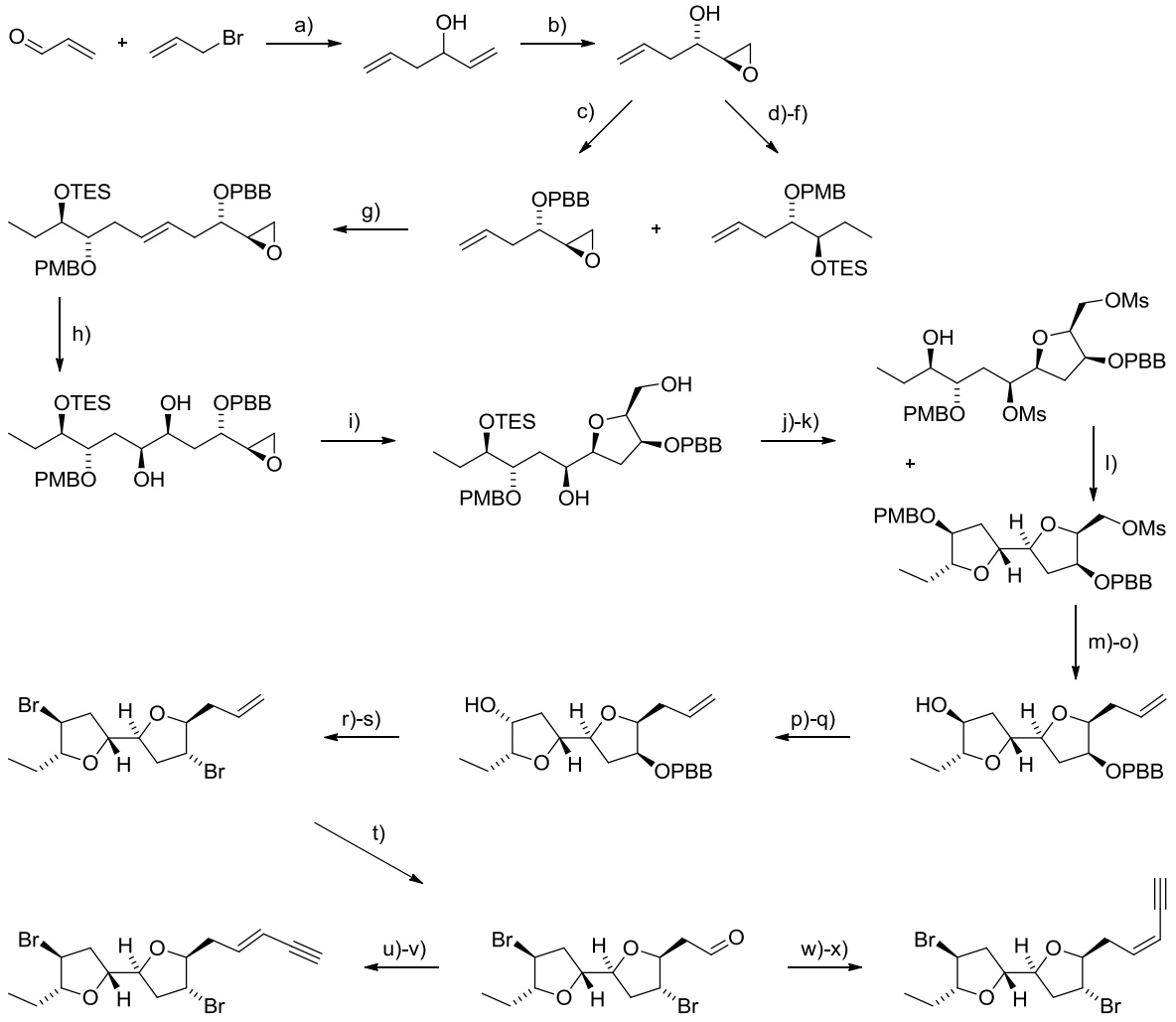
**PLEASE NOTE: Since submission of the hard copy of this thesis reference [136] no longer refers to unpublished work but to the joint publication B. S. Dyson, J. W. Burton, T. I. Sohn, B. Kim, H. Bae, D. Kim, *J. Am. Chem. Soc.* 2012, *134*, 11781-11790. [Available at http://dx.doi.org/10.1021/ja304554e]**

# APPENDIX A – Summary of Elatenyne and Erickson's Enyne Total Syntheses




**Scheme A.4 – Reagents and conditions: a) Mg, diethyl ether, reflux, 5 h, 60%; b) dicyclohexyl tartrate, $Ti(O^iPr)_4$, *tert*-butyl hydroperoxide, DCM, 4 Å MS, -20 °C, 43 h, 38% (76% of maximum, >95% e.e.); c) PBBBr, NaH, TBAI, -78 °C to RT, 17 h, 95%; d) PMBBr, NaH, TBAI, THF, -78 °C to RT, 16 h; e) MeMgBr, CuI, THF/$Et_2O$, -23 °C, 1 h, 91% over 2 steps; f) TESCl, DMAP, imidazole, DCM, 0 °C to RT, 16 h, 97%; g) Hoveyda-Grubbs II (added over 12 h), 1,4-BQ, DCM, 40 °C, 60 h, 60% (3:1 *E*:*Z*); h) $K_2OsO_4.2H_2O$, $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, $MeSO_2NH_2$, $^tBuOH$, $H_2O$, 0 °C, 96 h, 88% (4:1 d.r.); i) CSA, DCM, 0 °C, 3 h, 72%, (87% BRSM); j) MsCl, $Et_3N$, DCM, 0 °C, 10 min; k) TBAF, THF, RT, 16 h, 66% over 2 steps (with 26% uncyclised product); l) KHMDS, THF, RT, 20 min, 84%; m) $Bu_4NI$, toluene, reflux, 16 h, 83% (91% BRSM); n) vinylmagnesium bromide, benzene, 40 °C, 4 h, 58% (84% BRSM); o) $BCl_3$:$SMe_2$, DCM, RT, 5 min, quant.; p) $PPh_3$, DIAD, 4-nitrobenzoic acid, THF, 0 °C to RT, 2 h, 85%; q) $K_2CO_3$, MeOH, 0 °C to RT, 2 h, 94%; r) $BCl_3$, DCM, RT, 30 min, quant.; s) $PPh_3$, $CBr_4$, toluene, 80 °C, 75 min, 70%; t) $O_3/O_2$, DCM -78 °C, 2 min, then $PPh_3$, -78 °C to RT, 15 h, 85%; u) $Me_3SiC{\equiv}CCH_2PPh_3Br$, $^nBuLi$, THF, -78 °C to between -40 °C and -30 °C, 30 min, then -78 °C, add to aldehyde in THF, -78 °C to 0 °C, 2 h, 80% (8:1 *E*:*Z*); v) TBAF, THF -20 °C, 5 min, 81%, w) $Me_3SiC{\equiv}CCH_2Si^tBuMe_2$, $^tBuLi$, THF, -78 °C, 1 h, then $Ti(O^iPr)_4$, 10 min, then aldehyde in THF, -78°C, 30 min, then RT, 30 min, 83% (>30:1 *Z*:*E*); x) TBAF, THF, -20 °C, 5 min, 80%.**

# APPENDIX B – Summary of $^{13}$C NMR Data for 2,2-Bifuranyls

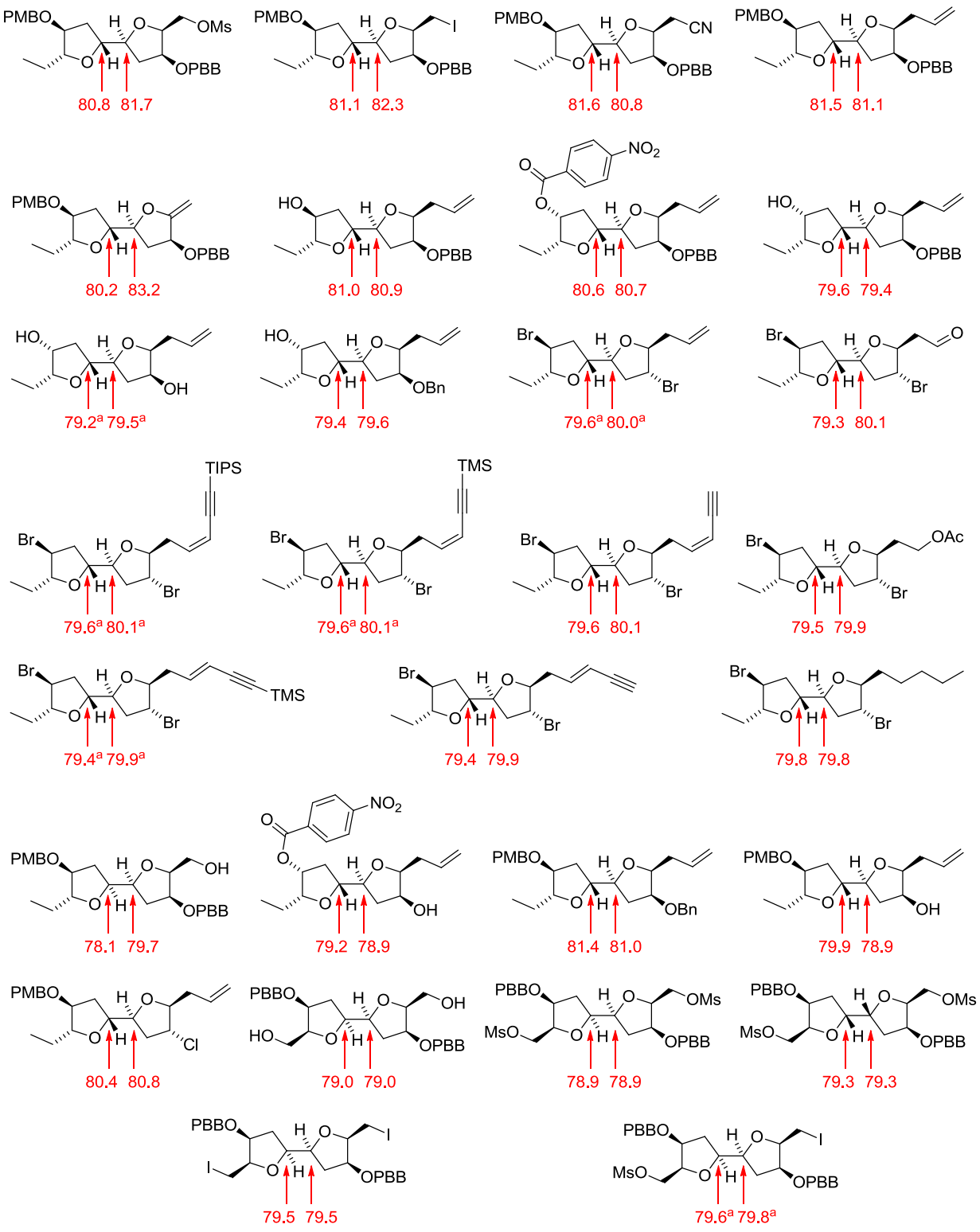



**Figure B.2 – Summary of ring junction $^{13}$C NMR chemical shifts for 2,2'-bifuranyls synthesised. Values quoted in ppm. [a]Assignment could be reversed.**