# Asymmetric Synthesis of Piperidine Alkaloids

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by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2008 until April 2012, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

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*April 2012*

# Abstract

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This thesis describes investigations into the total asymmetric synthesis of alkaloids from polysubstituted piperidines via iodolactonisation, resulting in the completion of an asymmetric synthesis of pseudodistomin D.

**Chapter 1** reviews the isolation, structural assignment and previous studies towards the total synthesis of the pseudodistomin alkaloids.

**Chapter 2** discusses the optimisation and scale-up of the synthesis of a key iodolactone intermediate in the synthesis of pseudodistomin D, via a sequence involving lithium amide conjugate addition, ring-closing metathesis and iodolactonisation as the key steps.

**Chapter 3** describes attempts to install the side chain of pseudodistomin D via $S_N2$-type displacement using a range of organometallic species.

**Chapter 4** describes attempts to install the side chain of pseudodistomin D via a cross coupling strategy to construct an (*E*,*E*)-diene unit.

**Chapted 5** describes the completion of the synthesis of pseudodistomin D utilising an olefination strategy for the installation of the (*E*,*E*)-diene unit within the side chain.

**Chapter 6** contains full experimental procedures and characterisation data for the compounds synthesised in Chapters 2, 3, 4 and 5.

# Acknowledgments

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# Abbreviations

The following abbreviations are used throughout this thesis.

| | |
|---|---|
| ((•)) | Sonication |
| ‡ | Transition state |
| $[\alpha]_D$ | Specific rotation |
| Å | Angstroms |
| Ac | Acetyl |
| app | Apparent |
| aq. | Aqueous |
| Ar | Aryl |
| atm | Atmosphere |
| ATR | Attenuated total reflectance |
| Bn | Benzyl |
| Boc | *tert*-Butoxycarbonyl |
| br | Broad |
| Bu | *n*-Butyl |
| $^t$Bu | *tert*-Butyl |
| Bz | Benzoyl |
| *c* | Concentration |
| C | Centigrade |
| cat | Catalytic |
| Cbz | Carboxybenzyl |
| CI | Chemical Ionisation |
| cm | Centimetres |
| $cm^{-1}$ | Wavenumber |
| COSY | Correlation spectroscopy |
| Cp | Cyclopentadienyl |
| D | Dextrorotatory |
| D | Dimensional |
| d | Doublet |
| dba | Dibenzylideneacetone |
| DEAD | Diethylazodicarboxylate |
| DIBAL-H | Di-isobutylaluminium hydride |
| DMAP | 4-Dimethylaminopyridine |
| DMB | 2,4-Dimethoxybenzyl |
| DMF | *N*,*N*-Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| DNA | Deoxyribonucleic acid |
| DPPA | Diphenyl phosphoryl azide |

| | |
|---|---|
| dr | Diastereoisomeric ratio |
| $\delta_H$ | Proton ($^1$H) NMR chemical shift |
| $\delta_C$ | Carbon ($^{13}$C) NMR chemical shift |
| ee | Enantiomeric excess |
| ESI | Electrospray ionisation |
| EXSY | Exchange spectroscopy |
| Et | Ethyl |
| FI | Field ionisation |
| FT | Fourier transform |
| g | Grams |
| GC | Gas chromatography |
| Grubbs I | Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium |
| h | Hours |
| HMDS | Hexamethyldisailazide |
| HMPA | Hexamethylphosphoramide |
| HMQC | Heteronuclear multiple quantum correlation |
| HPLC | High performance liquid chromatography |
| HRMS | High resolution mass spectrometry |
| *hν* | Light |
| Hz | Hertz |
| *i* | Ipso |
| $^3J$ | Vicinal coupling constant |
| K | Kelvin |
| L | Laevorotatory |
| L | Litres |
| LDA | Lithium diisopropylamide |
| lit. | Literature |
| μL | Microlitres |
| μmol | Micromoles |
| M | Molar |
| *m* | Meta |
| m | Multiplet |
| $M^+$ | Molecular ion |
| $[M+H]^+$ | Protonated molecular ion |
| $[M+Na]^+$ | Sodiated molecular ion |
| *m*-CPBA | *meta*-Chloroperoxybenzoic acid |
| *m*-CBA | *meta*-Chlorobenzoic acid |
| Me | Methyl |
| min | Minutes |
| mL | Millilitres |
| mol | Moles |
| mp | Melting point |

| | |
|---|---|
| MS | Mass spectrometry |
| Ms | Methanesulfonyl |
| *m/z* | Mass to charge ratio |
| NOE | Nuclear Overhauser effect |
| nm | nanometres |
| NMR | Nuclear magnetic resonance |
| *o* | Ortho |
| *p* | Para |
| Ph | Phenyl |
| PCC | Pyridinium chlorochromate |
| PMP | *p*-methoxyphenyl |
| ppm | Parts per million |
| Pr | Propyl |
| $^{i}$Pr | Isopropyl |
| PT | 1-Phenyl-1*H*-tetrazole |
| py | Pyridine |
| q | Quartet |
| quant | Quantitative |
| R | Alkyl |
| RCM | Ring-closing metathesis |
| rt | Room temperature |
| s | Singlet |
| satd | Saturated |
| $S_N2$ | Substitution nucleophilic bimolecular |
| *tert* | Tertiary |
| t | Triplet |
| TBAF | Tetrabutylammonium fluoride |
| TBS | *tert*-Butyldimethylsilyl |
| Tf | Trifluoromethanesulphonate |
| TFA | Trifluoroacetic acid |
| TIPS | Tri isopropylsilyl |
| THF | Tetrahydrofuran |
| TMS | Trimethylsilyl |
| Tof | Time of flight |
| Ts | *para*-Toluenesulfonyl |
| UV | Ultra-violet |
| $\nu_{max}$ | Infra red absorption |
| v | Volume |
| v/v | Volume per volume |
| w/w | Weight per weight |

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# Chapter 1: Introduction

## 1.1 Introduction

Countless alkaloids containing functionalised piperidine rings have been isolated from natural sources. Many such compounds exhibit potent biological activity and have attracted greatly the interest of biologists and chemists alike.[1] Piperidine alkaloids often present challenging targets for modern synthetic chemistry, and numerous total asymmetric syntheses have been published.[2] Many synthetic approaches to enantiopure piperidines can be seen in the literature, such as intramolecular reductive amination,[3] reduction of pyridines,[4] aza Diels-Alder cycloadditions,[5] and ring-closing metathesis reactions.[6] The pseudodistomins A–F **1**–**6** are a family of piperidine containing natural products isolated from two species of Urochordates found in shallow waters around the Okinawan islands[7,8] and Micronesia[9] (Figure 1).

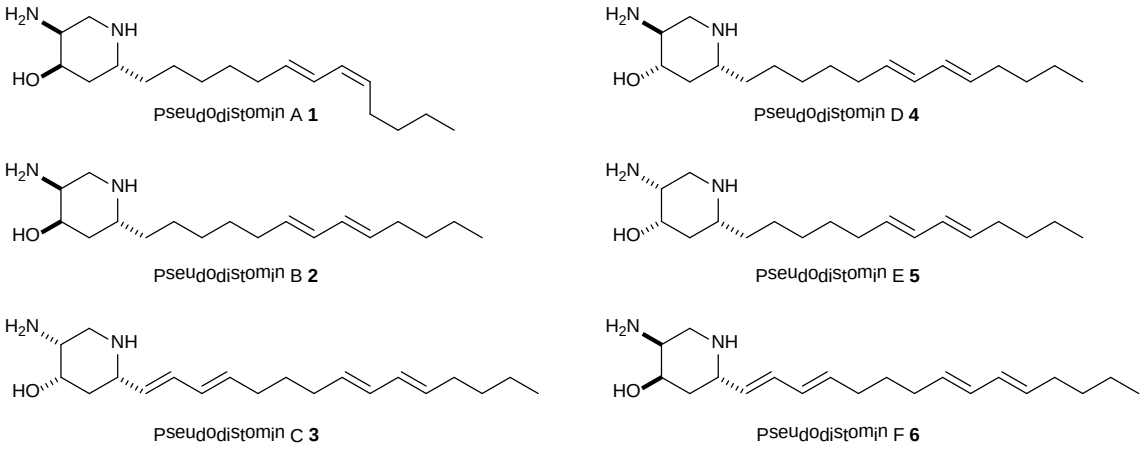



**Figure 1:** The pseudodistomins A–F **1**–**6**.

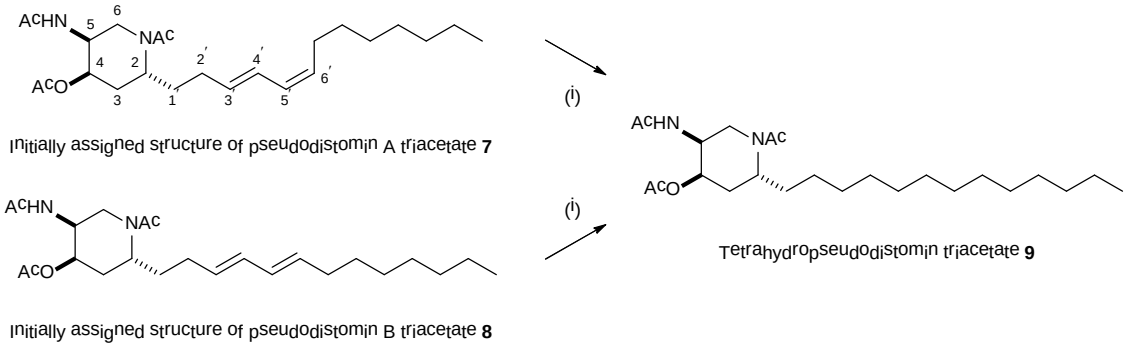
Although piperidine alkaloids are some of the most common metabolites found in terrestrial plants,[1] the pseudodistomins represent the first family of piperidine alkaloids isolated from a marine organism. Pseudodistomins A **1** and B **2** were observed to exhibit antagonistic activity towards the $Ca^{2+}$-calmodulin system, which has been linked with cellular proliferation and tumour formation, and all of the pseudodistomins **1**–**6** have shown potent DNA damaging activity, making them possible candidates for antitumor therapy.[7,8,9] It has been suggested that pseudodistomins A **1**, B **2** and F **6** are biosynthetically related to D-*erythro*-sphingosine, a derivative of L-serine, while pseudodistomins C **3** and E **5** are related to L-*erythro*-

sphingosine and in turn D-serine. The biological origins of pseudodistomin D **4** remain unknown.[9] To date, synthetic routes to pseudodistomins A **1**, B **2**, C **3**, D **4** and F **6** have been reported, with pseudodistomin E **5** yet to be synthesised in the laboratory. The following sections describe the isolation and structural assignment of the pseudodistomins **1**–**6**, as well as a review of their laboratory total syntheses.

### 1.2 The isolation of pseudodistomins A and B: initial structural assignment

Through several independent and collaborative efforts, Kobayashi *et al*. and Naito *et al*. have been largely responsible for the isolation and structural assignment of pseudodistomins A **1**, B **2** and C **3**, and both groups have published reviews on the subject.[10] Kobayashi *et al*. first isolated pseudodistomins A **1** and B **2** from the orange-coloured Okinawan tunicate *Pseudodistoma kanoko*, a member of the Urochordata subphylum of sac-like marine filter feeders, in 1987.[7] The sample of the organism from which the natural products were isolated was collected by SCUBA divers at Ie Island, Okinawa, and frozen prior to extraction. The methanol-toluene extract of *Pseudodistoma kanoko* was partitioned between water and toluene, and the resulting aqueous layer was then extracted with chloroform. This extract showed potent cytotoxicity and was chromatographed on silica gel, followed by reverse-phase HPLC. The products from this process were acetylated and then separated by extensive chromatography to give two compounds. These two products were analysed by a mixture of high-resolution mass spectrometry, IR and UV absorption spectroscopy, and extensive $^{1}$H and $^{13}$C NMR studies, including $^{1}$H–$^{1}$H and $^{1}$H–$^{13}$C shift correlation spectroscopy. Both products exhibited the same molecular weight, as shown by mass spectroscopy, and very similar retention times by HPLC. Pseudodistomin B triacetate was initially assigned the structure **8**, which included a piperidine "head group" with hydroxyl and amino substituents at the C(4) and C(5) positions on the ring, respectively, and an unsaturated alkyl "side chain" connected at the C(2) position. The side chain was assigned as containing a (3'*E*,5'*E*)-conjugated diene on the strength of 1D and 2D $^{1}$H NMR spectroscopic analysis. The relative configuration within the initially assigned structure of pseudodistomin B triacetate **8** was determined by $^{1}$H NMR NOE spectroscopy, while the absolute configuration was assigned by application of the

nonempirical dibenzoate chirality method.[11] The $^{1}H$ and $^{13}C$ NMR spectra of pseudodistomin A triacetate proved to be almost identical to those of **8** (the initially assigned structure of pseudodistomin B triacetate), except for the resonances associated with the conjugated diene system, leading the researchers to hypothesise that pseudodistomin A and pseudodistomin B were related as geometric isomers. On this basis, pseudodistomin A triacetate was assigned the structure **7**. Catalytic hydrogenation of **7** and **8** (the initially assigned structures of pseudodistomin A and B triacetates) yielded the same product, tetrahydropseudodistomin triacetate **9**, with both samples exhibiting identical spectroscopic properties, including specific rotations, supporting this proposal (Scheme 1).

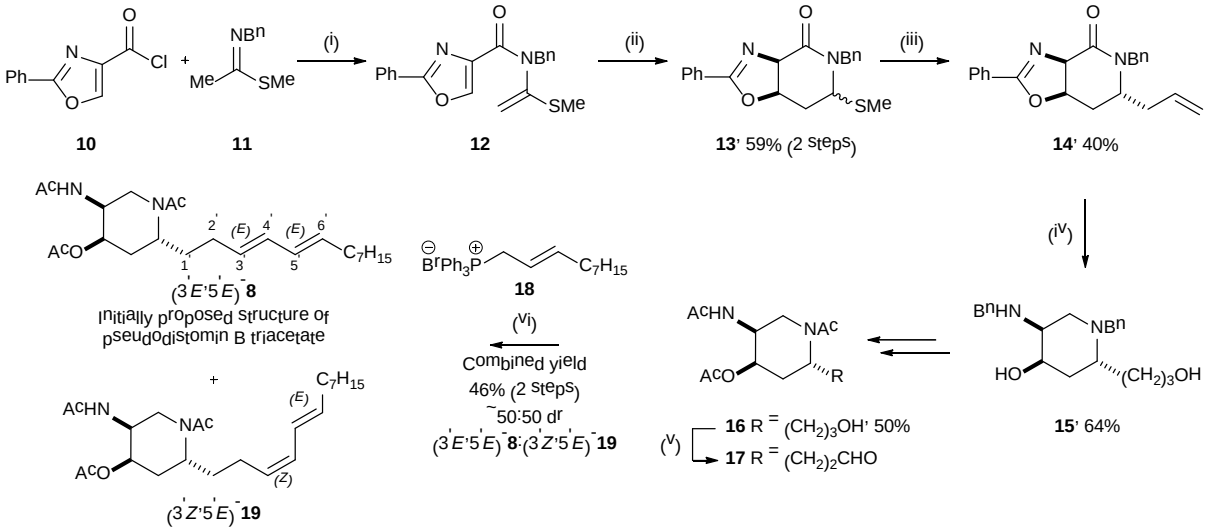



**Scheme 1:** *Reagents and conditions*: (i) $H_2$ (1 atm), 10% Pd/C, rt, 1 h.

### 1.3 The first synthesis of the proposed structures of pseudodistomins A and B

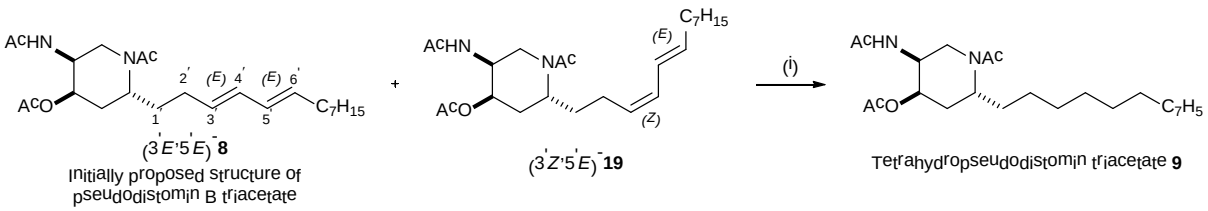
In 1992, Naito *et al*. published the first syntheses of the proposed structures of racemic pseudodistomin B triacetate **8** and tetrahydropseudodistomin triacetate **9**.[12] This synthetic approach utilised two photochemical reactions: a reductive photocyclisation of enamide **12**, and photoallylation of the resulting lactam **13** using allyltributyltin to give allyl lactam **14**. Treatment of **14** with borane-THF complex followed by alkaline hydrogen peroxide converted lactam **14** to a piperidine, opened the oxazoline and oxidised the allyl group to the terminal alcohol giving **15**, which possesses the correct configuration for the proposed structure of the piperidine core within pseudodistomins A and B, in 64% yield. The benzyl groups within **15** were then exchanged for acetates to give alcohol **16**, which was oxidised to aldehyde **17** followed by a Wittig olefination with phosphonium bromide **18** yielding an "almost equal"[12] mixture of alkene isomers **8** and **19**. These were separated by silica gel chromatography and reverse-phase HPLC and assigned as the (3'*E*,5'*E*)-diene **8** (i.e., the proposed structure of

pseudodistomin B triacetate) and (3'*Z*,5'*E*)-diene **19**. The spectra of synthetic product **8** did not exactly match those of the natural product, suggesting that an error may have been made in the initial structural assignment of the pseudodistomin side chains (Scheme 2).




**Scheme 2:** *Reagents and conditions*: (i) $Et_3N$; (ii) $NaBH_4$, hν, MeCN/MeOH; (iii) allyltributyltin, hν, PhMe/MeCN; (iv) $BH_3$•THF, then $H_2O_2$, NaOH; (v) PCC, NaOAc; (vi) **18**, NaH, THF.

Hydrogenation of a mixture of **8** and **19** yielded tetrahydropseudodistomin triacetate **9**. The spectroscopic properties of this synthetic product matched those of the sample of tetrahydropseudodistomin triacetate **9** derived from the natural source, confirming the initial structural assignment, with the exception of the position of the diene unit in the side chain (Scheme 3).

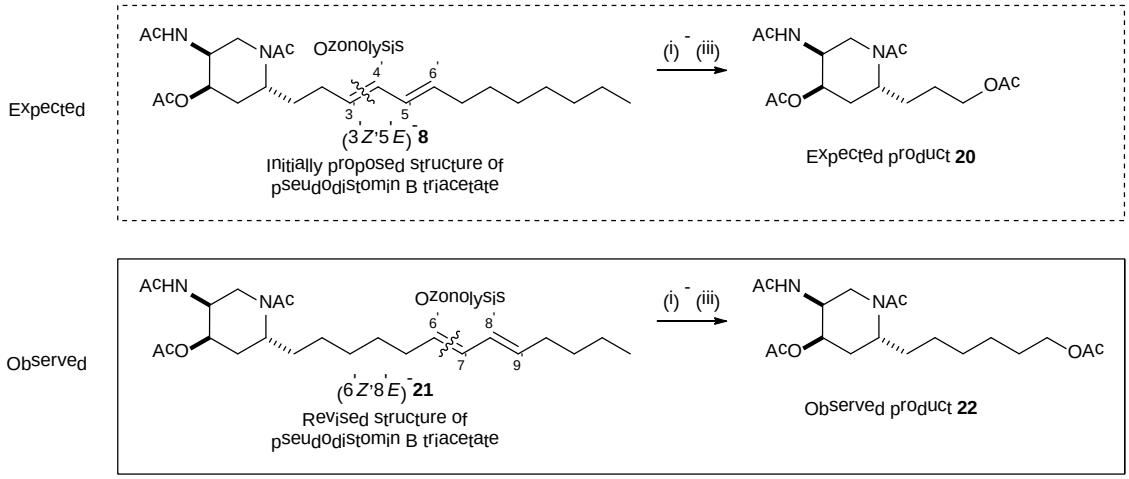



**Scheme 3:** *Reagents and conditions*: (i) $H_2$ (1 atm), 10% Pd/C, rt, 1 h.

### 1.4 Structural reassignment of pseudodistomins A and B

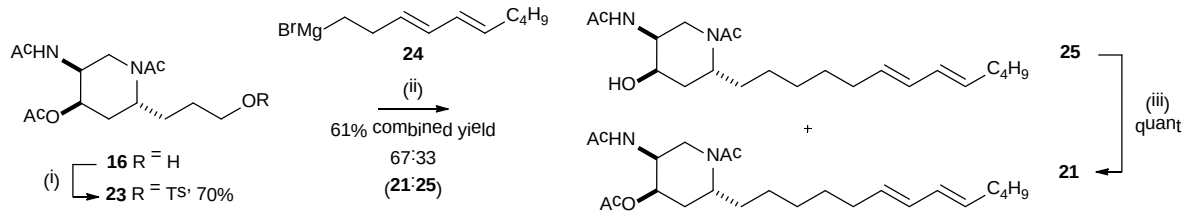
The structural and stereochemical assignment of tetrahydropseudodistomin **9** was further confirmed by two more total syntheses: one synthesis of racemic material reported by Natsume in 1992,[13] and one asymmetric synthesis reported by Knapp in 1993,[14] but this did nothing to elucidate the location of the diene units within the side chains of pseudodistomins

A and B. However, a collaborative effort by Naito and Kobayashi, which was published in 1992, resulted in a revision of the accepted structures of pseudodistomins A **1** and B **2**.[15] Naito's synthesis of the initially assigned structure of pseudodistomin B triacetate **8**,[12] prompted Kobayashi to perform an ozonolysis degradation experiment on a sample of pseudodistomin B triacetate **21** derived from the natural product. This yielded tetraacetate **22** rather than tetraacetate **20**, which would be expected had the initial assignment of a 3',5'-conjugated diene side chain been correct. The isolation of tetraacetate **22** therefore suggested that the diene was located at the 6',8'-position instead (Scheme 4).




**Scheme 4:** *Reagents and conditions*: (i) $O_3$; (ii) $NaBH_4$; (iii) $Ac_2O$, py.

Naito *et al*. were then able to use a racemic sample of intermediate **16** (available from their previous synthetic studies towards the initially proposed structure of pseudodistomin B triacetate **8**)[12] to complete the first racemic total synthesis of pseudodistomin B triacetate **21** by utilising a copper-mediated Grignard substitution with **24** to install the new (6'*E*,8'*E*)-diene unit in the side chain. This reaction gave a 67:33 mixture of triacetate **21** and alcohol **25** in 61% combined yield, resulting from partial loss of the *O*-acetate protecting group. However, this product was re-acetylated to give the triacetate **21** in quantitative yield. The spectroscopic data for this sample of synthetic triacetate **21** matched those for the sample derived from the natural source and confirmed the revised structural assignment of pseudodistomin B **2** (Scheme 5).



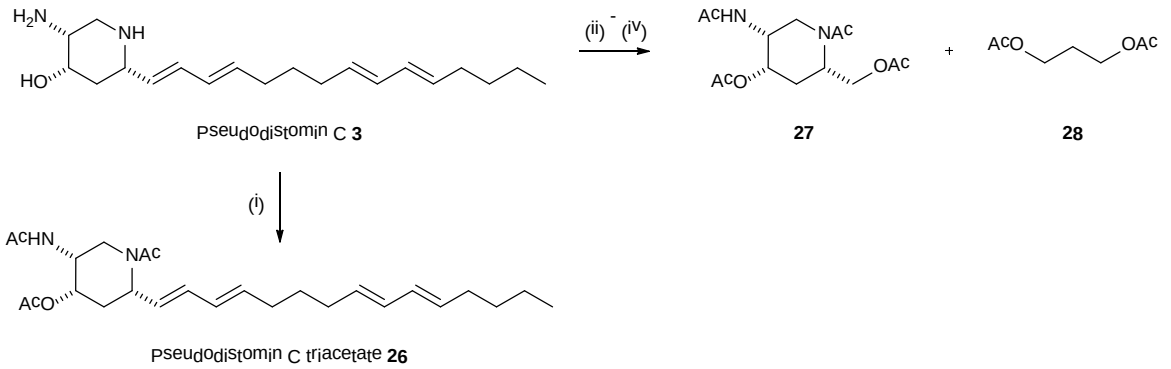

**Scheme 5:** *Reagents and conditions*: (i) TsCl, DMAP, $Et_3N$; (ii) **24**, $Li_2CuCl_4$, −20 °C; (iii) $Ac_2O$, py.

Kobayashi later revised the structure of pseudodistomin A **1**, as determined by an analogous ozonolysis degradation experiment.[16] Naito also published several more syntheses of pseudodistomins A **1** and B **2** and tetrahydropseudodistomin **9**.[17] This confirmed that pseudodistomins A **1** and B **2** were indeed geometric isomers.

### 1.5 The Isolation of pseudodistomin C

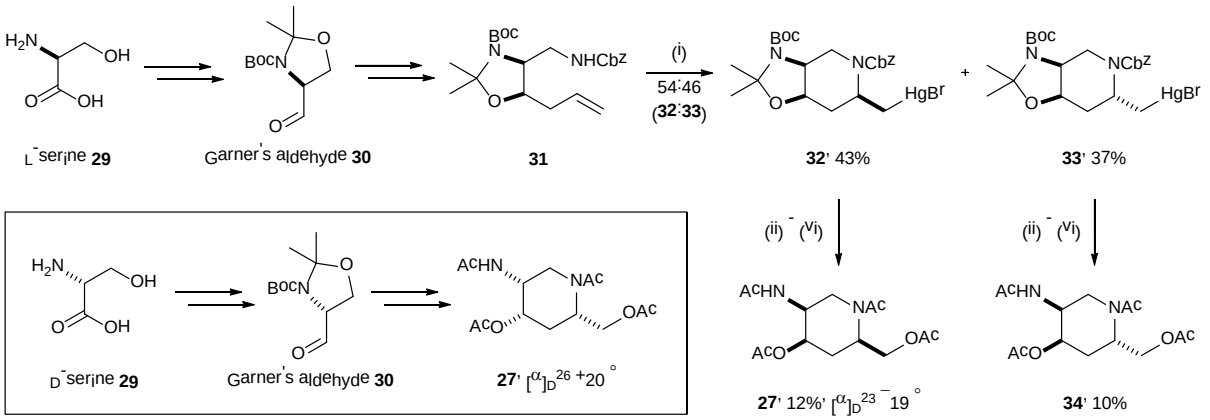
The third member of the pseudodistomin family, pseudodistomin C **3**, was isolated from *Pseudodistoma kanoko* in 1995 by Kobayashi.[8] A mixture of flash column chromatography and preparative TLC yielded pure pseudodistomin C **3** (along with samples of pseudodistomins A **1** and B **2**). Characterisation was mainly carried out on the triacetate derivative **26**, using a similar range of techniques to those employed for pseudodistomins A and B. Pseudodistomin C **3** appeared to have similar physical properties to those of pseudodistomins A **1** and B **2**: the molecular mass of pseudodistomin C triacetate **26** was shown to be higher by a factor of two carbon and two hydrogen atoms compared with triacetate **21** derived from pseudodistomins B **2**. $^1H$ and $^{13}C$ NMR studies suggested that pseudodistomin C **3** contained the same functionalised piperidine ring structure as pseudodistomins A **1** and B **2**, although differences in the $^1H$ NMR spectra of the corresponding triacetates suggested a different relative configuration within the piperidine core of pseudodistomin C **3**. Analysis of pseudodistomin C **3** by UV absorption spectroscopy suggested the presence of two diene units. The $^1H$-$^1H$ COSY spectrum of pseudodistomin C triacetate **26** indicated that there was a vicinal relationship between a proton on the piperidine ring and an olefinic proton in the side chain, suggesting the presence of a diene at the 1',3'-position. The position of the second diene was probed by an ozonolysis degradation reaction on pseudodistomin C **3** that produced diacetate **28**, which was recovered by reverse-phase

TLC and HPLC. This allowed the location of each diene in the side chain to be predicted, and their geometries were inferred to be "all (*E*)" from $^{1}$H NMR $^{3}J$ coupling constant analysis (Scheme 6).




**Scheme 6:** *Reagents and conditions*: (i) $Ac_2O$, py, rt, 16 h. (ii) $O_3$, MeOH, −78 °C, 4 min; (iii) $NaBH_4$, MeOH, 0 °C, 45 min; (iv) $Ac_2O$, py, rt, 1.5 h.

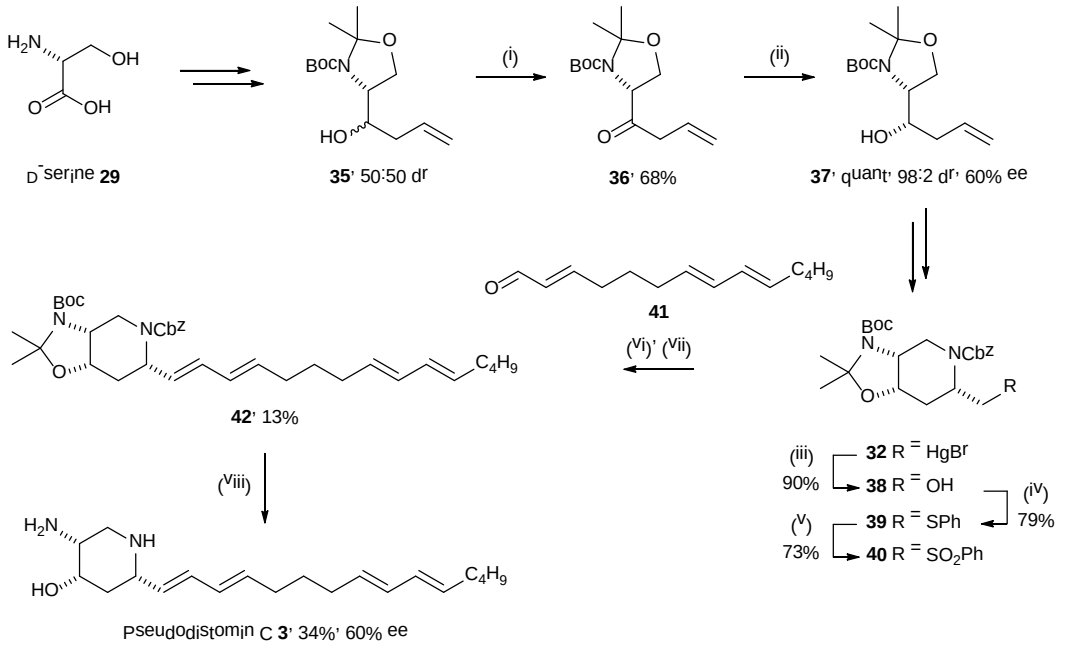
In order to confirm this structural assignment, Kobayashi *et al*. prepared tetraacetate **27** from Garner's aldehyde **30**, which is derived from L-serine **29**. Conversion of Garner's aldehyde **30** into benzyl carbamate **31** was followed by intramolecular amidomercuration providing a 54:46 mixture of separable diastereomeric piperidines **32** and **33**.[18] Piperidines **32** and **33** were further elaborated to the corresponding tetraacetates **27** and **34**, and their $^{1}$H NMR spectra were compared with that of the sample derived from natural pseudodistomin C **3** (Scheme 6). Piperidine **27**, with an "all-*cis*" relationship of substituents around the piperidine ring, proved to have identical spectroscopic properties to the sample of **27** derived from natural pseudodistomin C **3**. In addition, its specific rotation was equal in magnitude (within error) but opposite in sign. Therefore, the enantiomer of **27** was synthesised *via* the same route starting from D-serine **29**, and comparison with a sample of **27** derived from the natural source, allowed the absolute configuration within pseudodistomin C **3** to be assigned (Scheme 7).




**Scheme 7:** *Reagents and conditions*: (i) $Hg(OTFA)_2$, $CHCl_3$, rt, 20 h, then satd aq $NaHCO_3$, satd aq NaBr, rt, 3 h; (ii) $NaBH_4$, $O_2$, DMF, rt, 3 h; (iii) TFA, $CH_2Cl_2$, rt, 20 h; (iv) $Ac_2O$, py, rt, 2 h; (v) $H_2$ (1 atm), 5% Pd/C, EtOH, rt, 24 h; (vi) $Ac_2O$, py, rt, 1.5 h.

## 1.6 The first total synthesis and structural confirmation of pseudodistomin C

In 1996, Kobayashi *et al.* were able to complete the first total asymmetric synthesis of pseudodistomin C **3** from D-serine **29**.[19] In this synthesis, piperidine **32** was oxidatively demercurated to give alcohol **38** which was then converted to sulfide **39**, and oxidised to give sulfone **40**. This substrate was coupled with aldehyde **41** in a Julia olefination followed by treatment with sodium amalgam which gave **42**. Global deprotection under acidic conditions gave pseudodistomin C **3** in 34% yield and 60% ee, which displayed identical $^1H$ and $^{13}C$ NMR spectroscopic properties to that of the natural specimen, confirming the original structural assignment. The authors postulated that partial racemisation of ketone **36** was responsible for the degradation in the enantiopurity of their sample of pseudodistomin C **3** (Scheme 8).

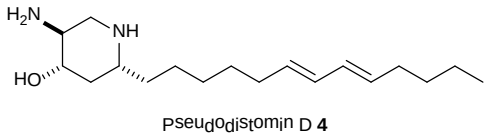



**Scheme 8:** *Reagents and conditions*: (i) Dess-Martin periodinane, DMF, rt, 4 h; (ii) $Zn(BH_4)_2$, $Et_2O$/PhH, rt, 15 min; (iii) $NaBH_4$, $O_2$, DMF, rt, 3 h; (vi) $(PhS)_2$, $PBu_3$, py, rt, 4.5 h; (v) $Ph_2Se_2$, 30% $H_2O_2$, $CH_2Cl_2/Et_2O$; (vi) BuLi, THF/HMPA, −78 °C, 10 min, then **41**, THF, −78 °C, 1.5 h; (vii) Na(Hg), MeOH/THF, −20 °C, 11 h; (viii) HCl, EtOAc, rt, 16 h.

### 1.7 The isolation and structural assignment of pseudodistomins D, E and F

In 1997, Freyer *et al*. published the discovery of three new pseudodistomins, this time extracted from the ascidian *Pseudodistoma megalarva* found near the tiny island of Palau in Micronesia.[9] The marine organism was freeze-dried prior to extraction with methanol and chloroform. These extracts were chromatographed, and several fractions with high DNA damaging activity were further purified through extensive preparative TLC. This yielded pseudodistomins B **2** and C **3**, (which were identified by comparison of their $^1H$ and $^{13}C$ NMR spectra with those reported in the literature)[7,8] as well as three new related compounds. Pseudodistomin D **4** was found to have the same molecular mass as pseudodistomin B **2**, and it also exhibited nearly identical resonances associated with the diene unit in its $^1H$ and $^{13}C$ NMR spectra. However, differences were observed for the resonances corresponding to the protons around the piperidine ring. Pseudodistomin D **4** was therefore assigned as being a diastereoisomer of pseudodistomin B **2**, differing only in the relative configuration within the piperidine ring: $^1H$ NMR NOE spectroscopic analysis suggested that each of the stereogenic protons occupied axial positions. This indicated a third “head” group, new to the pseudodistomin family, with a *trans*-relationship between the hydroxyl and primary amino

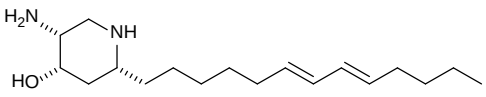
substituents, contrasting with the *cis*-amino alcohols seen in pseudodistomin A **1**, B **2** and C **3**. The absolute configuration within pseudodistomin D **4** was not determined as part of this study (Figure 2).



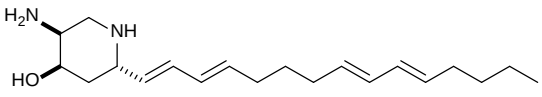

Pseudodistomin D **4**

**Figure 2:** Pseudodistomin D **4**.

Pseudodistomin E **5** was also found to have the same molecular weight as pseudodistomins B **2** and D **4**, and the $^{1}$H NMR resonances of its piperidine core were almost super imposable with those of pseudodistomin C **3**. Further NMR spectroscopic studies (including NOE analysis) suggested that pseudodistomin E **5** possessed the same piperidine core as pseudodistomin C **3** and the same side chain as pseudodistomins B **2** and D **4**. Pseudodistomin F **6** proved to have the same molecular mass as pseudodistomin C **3**, and similar IR and UV spectra suggested the presence of a bis-diene side chain, similar to that of pseudodistomin C **3**. The $^{1}$H NMR resonances of its piperidine ring appeared to match those of pseudodistomin B **2**, and further NMR and NOE analysis showed that pseudodistomin F **6** consisted of the same piperidine ring as pseudodistomin B **2** and the same side chain as pseudodistomin C **3**. Comparison of the specific rotations of pseudodistomins C **3** and E **5**, and also those of B **2** and F **6**, led the researchers to tentatively assign the absolute (2*R*,4*S*,5*R*)- and (2*S*,4*R*,5*S*)-configurations within pseudodistomins E **5** and F **6** respectively (Figure 3).




Pseudodistomin E **5**



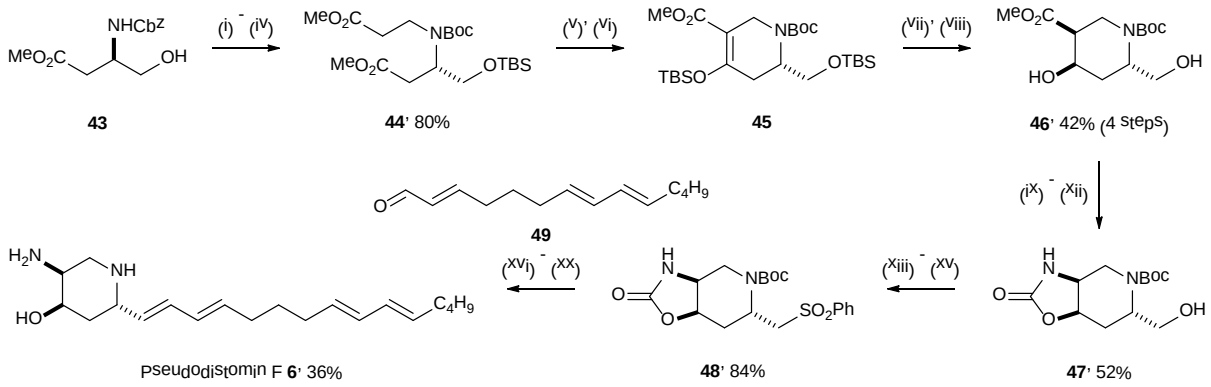

Pseudodistomin F **6**

**Figure 3:** Pseudodistomin E **5** and F **6**.

### 1.8 The first synthesis of pseudodistomin F

In 2000, Ma *et al*. published the first total synthesis of pseudodistomin F **6** (along with a synthesis of pseudodistomin B triacetate **21**).[20] The synthesis of pseudodistomin F **6** utilised enantiopure β-amino ester **43**, conveniently prepared using Davies's methodology for the highly diastereoselective conjugate addition of a lithium amide to an α,β-unsaturated ester.[21]

It was reported that ester **43** underwent *N*-deprotection, followed by conjugate addition to methyl acrylate and *N*-Boc protection, yielding diester **44**. Dieckmann condensation and silylation then gave silyl enol ether **45**. Treatment of **45** with Raney-Nickel at high temperature and pressure effected a diastereoselective hydrogenation, resulting in piperidine **46**. The side chain alcohol within **46** was protected prior to hydrolysis of the methyl ester moiety under basic conditions. Azidation of the resulting acid with diphenylphosphoryl azide (DPPA) was followed by *in situ* Curtius rearrangement and oxazolidinone formation. *O*-Silyl deprotection then furnished oxazolidinone **47**, possessing the correct configuration for the synthesis of pseudodistomin F **6**. Elaboration of **47** to pseudodistomin F **6** was then achieved in a series of olefinations that resulted in the (*E*,*E*,*E*,*E*)-alkene geometry of the required side chain[22] (Scheme 9).

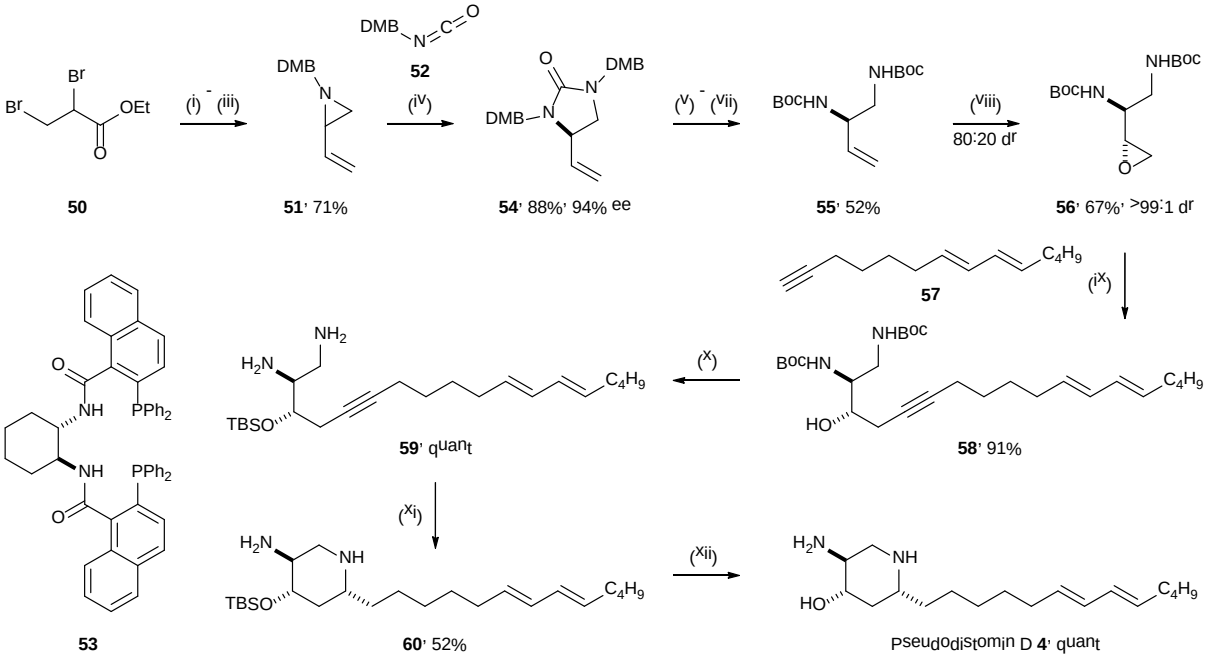



**Scheme 9:** *Reagents and conditions*: (i) TBSCl, DMAP, $Et_3N$, $CH_2Cl_2$, rt, 6 h; (ii) $H_2$ (1 atm), 10% Pd/C, MeOH, rt, 10 h; (iii) Methyl acrylate, MeOH, rt, 24–48 h; (iv) $(Boc)_2O$, $NaHCO_3$, 1,4-dioxane, 30 °C, 5 h; (v) Na, EtOH, PhH, rt, 48 h; (vi) TBSCl, DMAP, $Et_3N$, $CHCl_3$ rt, 24 h; (vii) $H_2$ (80 atm), Raney-Ni, $EtOAc/H_2O$,
80 °C, 24 h; (viii) TsOH, MeOH, rt, 1 h; (ix) TIPSCl, DMAP, $Et_3N$, $CH_2Cl_2$, rt, 6 h; (x) 10% aq NaOH, MeOH, rt, 6 h; (xi) DPPA, $Et_3N$, PhH, reflux, 16 h; (xii) TBAF, THF, rt, 6 h; (xiii) MsCl, DMAP, $Et_3N$, $CH_2Cl_2$, rt, 6 h; (xiv) PhSH, $Na_2CO_3$, 1,4-dioxane, rt, 24 h; (xv) *m*-CPBA, $CH_2Cl_2$, rt, 3 h; (xvi) BuLi, dimethoxyethane, −78 °C, 2 h, then **49**, −78 °C, 30 min; (xvii) BzCl, DMAP, $Et_3N$, $CH_2Cl_2$, rt, 3 h; (xviii) Na(Hg), MeOH/EtOAc, −25 °C, 1 h; (xix) KOH, MeOH, reflux, 3 h; (xx) HCl, MeOH/EtOAc, rt, 30 min.

### 1.9 The first synthesis of pseudodistomin D

In 2005, Trost *et al*. completed the first total asymmetric synthesis of pseudodistomin D **4** using a dynamic kinetic resolution protocol in which the asymmetric cycloaddition of an isocyanate to a vinyl aziridine was used to give a chiral imidazolidinone:[23] in this synthesis, commercially available dibromide **50** was converted to dimethoxybenzyl protected vinyl aziridine **51** in three steps. The “dynamic kinetic asymmetric cycloaddition” of

dimethoxybenzyl isocyanate **52** to aziridine **51** proceeded in 88% yield to give imidazolidinone **54** in 94% ee. Imidazolidinone **54** was then reduced with $LiAlH_4$, yielding an imidazolidine which was hydrolysed with aqueous hydroxylamine under weakly acidic conditions. Subsequent protecting group exchange gave *N*-Boc protected diamine **55**, which was epoxidised with *m*-CPBA, giving an 80:20 mixture of diastereoisomers from which the major diastereoisomer **56** was isolated in 67% yield and >99:1 dr. Alkyne **57** was prepared in 4 steps utilising a modified Negishi coupling to install the conjugated (*E*,*E*)-diene with high diastereoselectivity. Lithiation of **57** with BuLi and a subsequent aluminium mediated addition to epoxide **56** gave **58** (essentially the backbone of pseudodistomin D **4**) in 91% yield. Subsequent *N*-deprotection and *O*-silyl protection yielded **59**. Silver tosylate was used to initiate a diastereoselective alkyne hydroamination leading to an intermediate imine which was reduced *in situ* to give piperidine **60**, with no detectable diastereoisomeric or pyrrolidine containing side-products. Subsequent *O*-deprotection with TBAF gave pseudodistomin D **4** in quantitative yield, which exhibited identical spectroscopic properties to those of the naturally acquired sample, thus supporting the initial structural assignment and determining the absolute (2*R*,4*S*,5*S*)-configuration within the natural product (Scheme 10).



**Scheme 10:** *Reagents and conditions*: (i) DMB-$NH_2$, $Et_3N$, EtOH, 0 °C to 50 °C, 20 h; (ii) DIBAL-H, $CH_2Cl_2$, −78 °C, 1.5 h; (iii) $[CH_3PPh_3]^+[Br]^-$, KHMDS, THF, −20 °C to rt; (iv) **52**, 2% $(\eta^3\text{-}C_3H_5PdCl)_2$, 6% (*S*,*S*)-**53**, 10% AcOH, $CH_2Cl_2$, rt, 18 h; (v) $LiAlH_4$, $Et_2O$, reflux, 19 h; (vi) $NH_2OH$-HCl, $H_2O$, 60 °C, 1 h; (vii) TsOH•$H_2O$, PhMe, 110 °C, 7 h, then $Boc_2O$, MeOH, $Et_3N$, 60 °C 2.5 h; (viii) *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$, reflux, 5 h; (ix) **57**, BuLi, $Me_2AlCl$, PhMe, then **56**, 0 °C, 2.75 h; (x) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, reflux, 2 h, then AcOH, MeOH, $H_2O$, THF, 50 °C, 2 h; (xi) 10% AgOTs, MeCN, 40 °C, 2 h, then $NaBH_3CN$, AcOH, MeOH, $H_2O$, THF; (xii) TBAF, THF, rt, 20 h.

## 1.10 Other synthetic approaches towards the pseudodistomins

The literature also contains formal syntheses of pseudodistomin C **3** by Langlois[24] and Tanaka *et al*.,[25] and a formal synthesis of pseudodistomin B triacetate **21** by Davis *et al*.[26] There have also been notable asymmetric approaches to the pseudodistomin piperidine cores published by Haddad[27] and Woerpel.[28] Trost's route remains the only published synthesis of pseudodistomin D **4**, and to date, no syntheses of pseudodistomin E **5** have been reported.

## 1.11 Project aim

This thesis describes synthetic studies towards the total asymmetric synthesis of pseudodistomin D **4** using the diastereoselective conjugate addition of lithium amide **62** to α,β,δ,ε-unsaturated ester **61** as one of the key steps (Figure 4).

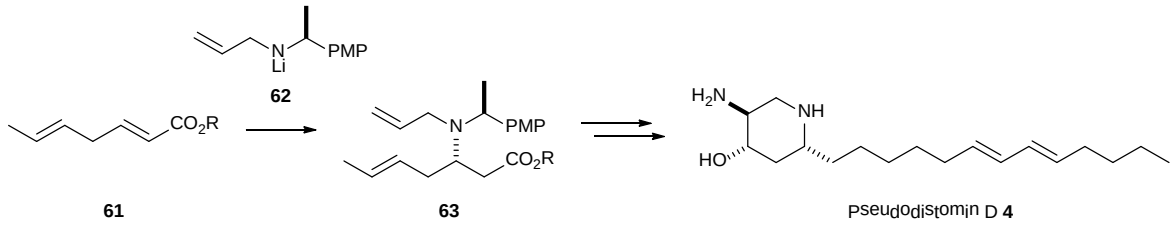



**Figure 4:** Pseudodistomin D **4**.

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# Chapter 2: Optimisation of the synthesis of key intermediates towards the pseudodistomins

## 2.1 Introduction

This chapter describes attempts to efficiently scale-up and optimise the synthesis of previously reported iodolactone **67**,[1] which was seen as a key intermediate in potential syntheses of the pseudodistomins, via a strategy utilising lithium amide conjugate addition, RCM, and iodolactonisation (Figure 5).

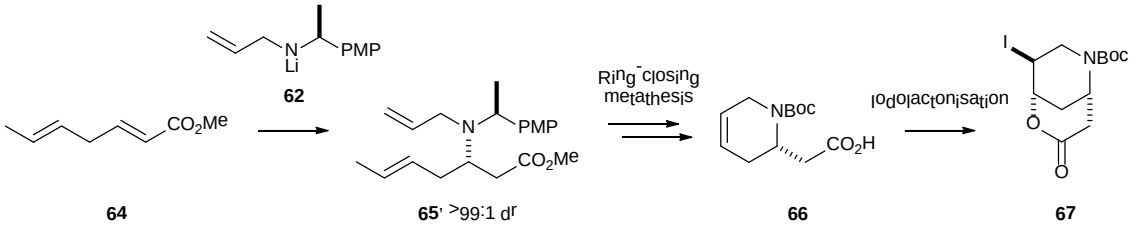



**Figure 5:** Synthetic strategy towards key iodolactone **67**.

## 2.2 Previous studies

It has been reported by Davies *et al*. that the conjugate addition of lithiated enantiopure amine **69** to α,β-unsaturated esters **68** proceeds in high yields (typically >85%) and diastereoselectivities (typically >99:1 dr) to give enantiopure β-amino esters **70** (Figure 6).

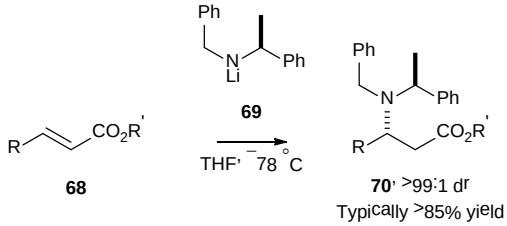
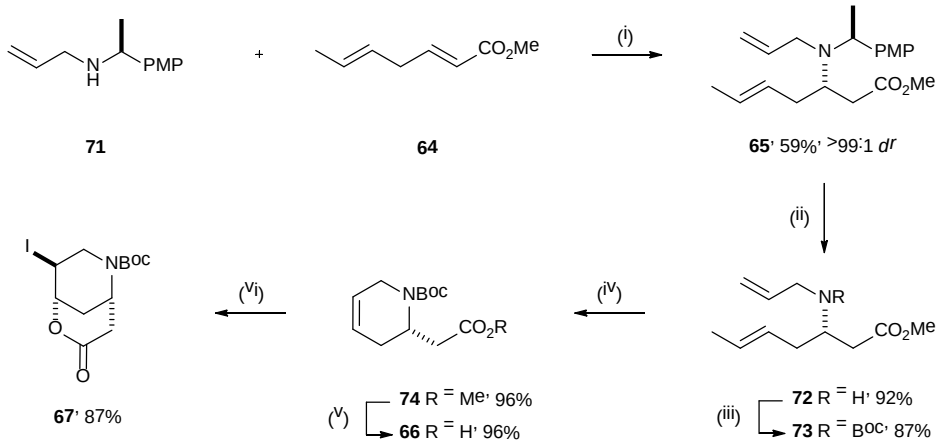



**Figure 6:** Lithium amide conjugate addition.

Previous work by Davies and Taylor[1] has sought to utilise a lithium amide conjugate addition as one of the key steps to access members of the pseudodistomin family. In this synthesis, construction of the polyfunctionalised piperidine core of the pseudodistomins was achieved by an iodolactonisation approach. The highly diastereoselective conjugate addition of the lithium amide derived from enantiopure amine **71** to α,β-unsaturated ester **64** gave β-amino ester **65** in 59% yield and >99:1 dr. The α-methyl-*p*-methoxybenzyl group within **65** was then

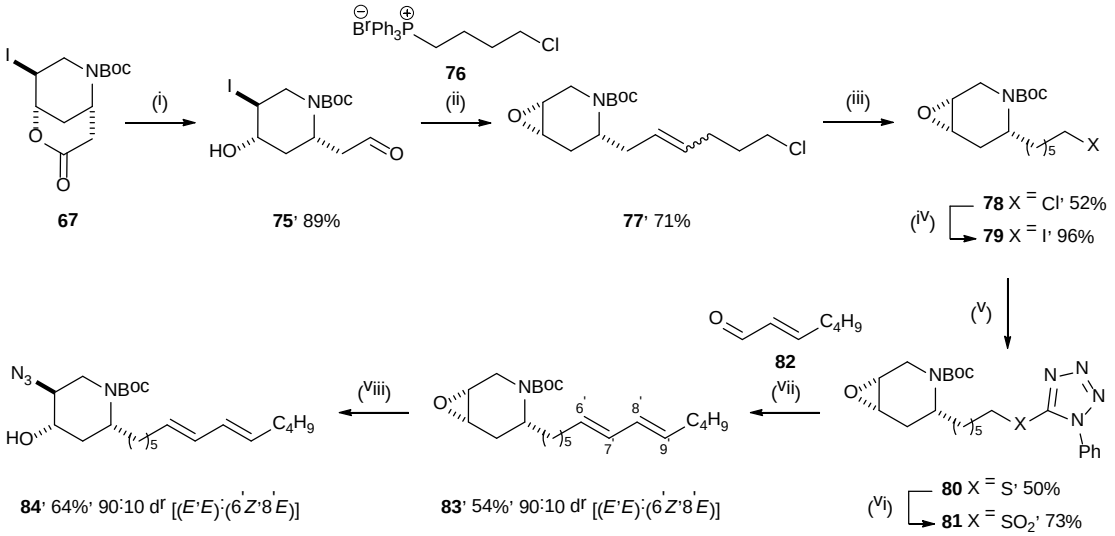
conveniently cleaved using refluxing formic acid and triethylsilane (i.e., without recourse to hydrogenolysis) in 92% yield. Secondary amine **72** was *N*-protected upon treatment with $Boc_2O$ to give **73** in 87% yield, which was subjected to RCM to give **74** in a yield of 96%. Saponification of the methyl ester within **74** yielded acid **66**, which was then treated with $I_2$ and $NaHCO_3$ to obtain bicyclic lactone **67** in 87% yield (Scheme 11).




**Scheme 11:** *Reagents and conditions:* (i) BuLi, THF, –78 °C, 2 h; (ii) $Et_3SiH$, $HCO_2H$, 90 °C, 16 h; (iii) $Boc_2O$, $NaHCO_3$, MeOH, rt, 16 h; (iv) Grubbs I, $CH_2Cl_2$, rt, 12 h, then $P(CH_2OH)_3$; (v) LiOH, THF/$H_2O$ (v/v 2:1), 50 °C, 16 h; (vi) $I_2$, $NaHCO_3$, $CH_3CN$, −20 °C to rt, 20 h.

It was proposed that iodolactone **67** represented a key intermediate in a stereodivergent strategy to access any of the pseudodistomin alkaloids, as it contained the 2,4,5-substituted piperidine motif common to all members of the family. To demonstrate this, studies towards the total synthesis of pseudodistomin D **4** were undertaken by Davies and co-workers.[2] Low temperature DIBAL-H reduction of **67** yielded aldehyde **75** in 89% yield, which was functionalised in a Wittig olefination to give **77** in 71% yield. Alkene **77** was saturated under hydrogenation in 52% yield, and a Finkelstein reaction gave iodide **79** in 96% yield. A sulfanyl tetrazole unit was installed in 50% yield, and **80** was subsequently oxidised to give sulfone **81** in 73% yield. A *trans*-selective Julia-Kocienski olefination was then effected, giving diene **83** as a 90:10 mixture of (6'*E*,8'*E*):(6'*Z*,8'*E*) isomers, which were inseparable by flash column chromatography and isolated in 54% combined yield. This mixture was then subjected to epoxide ring-opening to give azide **84** in 64% isolated yield. Azide **84** was therefore prepared in an overall yield of 1.1% over 15 linear steps from methyl acrylate. Due

to time constraints, no further progress was made and the total synthesis of pseudodistomin D **4** was not completed (Scheme 12).




**Scheme 12:** *Reagents and conditions*: (i) DIBAL-H, $CH_2Cl_2$, −78 °C, 1.5 h; (ii) **76**, KHMDS, THF, 0 °C to rt, 30 min, then **75**, −78 °C to rt, 1.5 h; (iii) Pd/C, $H_2$ (atm), EtOH, rt, 9 h; (iv) NaI, acetone, 50 °C, 5 days; (v) HSPT, KOH, EtOH, rt, 24 h; (vi) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt, 2 days; (vii) *trans*-hept-2-enal **82**, KHMDS, THF, −78 °C, 15 min; (viii) $NaN_3$, $NH_4Cl$, DMSO, 80 °C, 16 h.

## 2.3 Project aims

These previous investigations reveal a promising potential route to pseudodistomin D **4**, and an initial goal of this project was to complete this synthesis while optimising the attachment of the side chain, with a view to increasing the overall yield. Another aim was to attempt to optimise the yield of the lithium amide conjugate addition, possibly by utilising an α,β-unsaturated ester of a more sterically demanding alcohol. One of the main limitations of the previous route was its reliance on large-scale chromatography during the early stages of the synthesis, which posed a significant challenge when large quantities of material were required to enable development of the later steps of the synthesis. Therefore, another goal was to simplify and telescope some of the early purification steps on the way to producing large quantities of key iodolactone intermediate **67** (Figure 7).

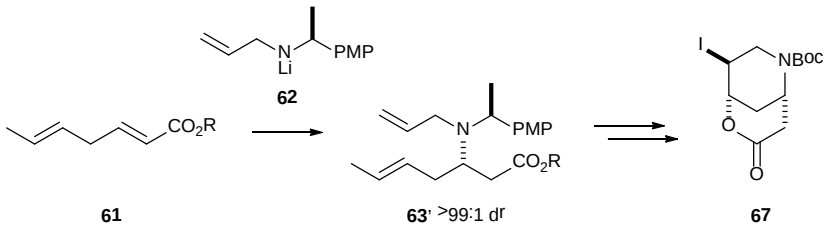
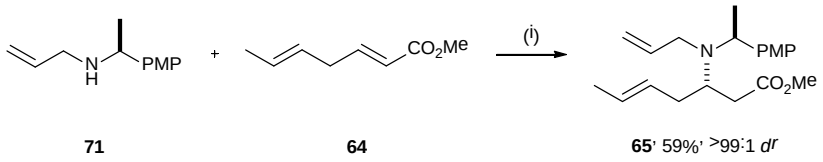



**Figure 7:** Strategy for the synthesis of key iodolactone intermediate **67**.

## 2.4 Optimisation of the lithium amide conjugate addition

The conjugate addition of the lithium amide derived from **71** to α,β,δ,ε-diunsaturated ester **64** proceeded in 59% yield (Scheme 13). This step was targeted for possible optimisation as many similar systems give significantly higher yields (>85%).[3] It was thought that the low yield in this case could be due to competing 1,2-addition of the lithium amide to the ester carbonyl group, or γ-deprotonation of α,β,δ,ε-diunsaturated ester **64** by the basic lithium amide reagent. In the case of **64**, the latter pathway may be promoted by the increased acidity of the γ-protons due to the adjacent alkene functionality.



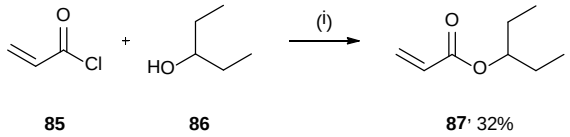

**Scheme 13:** *Reagents and conditions:* (i) BuLi, THF, –78 °C, 2 h.

It has been previously shown that it is possible to suppress competitive 1,2-addition by using a sterically demanding ester group,[4] whilst competing γ-deprotonation can be effectively suppressed when the reaction is carried out in $Et_2O$ at −20 °C.[5,6] In order to investigate these possibilities within this project, the synthesis of a sterically demanding ester of hepta-2,5-dienoic acid was targeted.

## 2.5 Synthesis of isopentyl hepta-2,5-dienoate

Unfortunately, previous attempts to synthesise *tert*-butyl (*E*,*E*)-hepta-2,5-dienoate by Davies and co-workers had failed.[1] Therefore, the synthesis of isopentyl (*E*,*E*)-hepta-2,5-dienoate **89** was investigated. It was proposed that **89** could be prepared in an analogous fashion to that of methyl (*E*,*E*)-hepta-2,5-dienoate **64**. Isopentyl acrylate **87** was synthesised from acryloyl

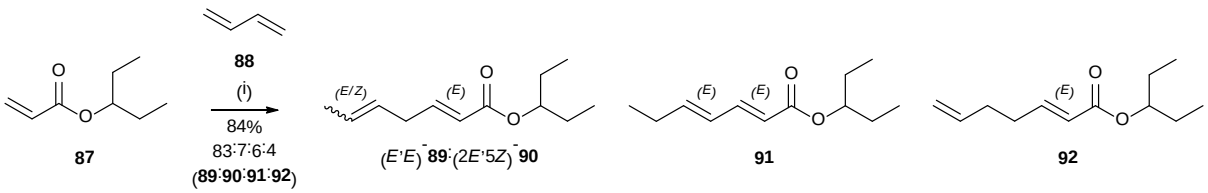
chloride **85** and isopentyl alcohol **86** in a modest isolated yield of 32%, due to the volatility of the product (Scheme 14).




**85** **86** **87**, 32%

**Scheme 14:** *Reagents and conditions:* (i) $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 16 h.

Coupling of isopentyl acrylate and 1,3-butadiene **88** gave the desired α,β,δ,ε-diunsaturated isopentyl ester **89** as the major product, along with a mixture of impurities, which were tentatively assigned as the isomers **90**, **91** and **92** by comparison of their $^1H$ and $^{13}C$ NMR spectroscopic data with those of the known methyl ester analogues.[7,8,9,10] The ratio of **89**:**90**:**91**:**92** was 83:7:6:4, with purification by flash column chromatography failing to separate these isomers, which were isolated in 84% combined yield (Scheme 15).



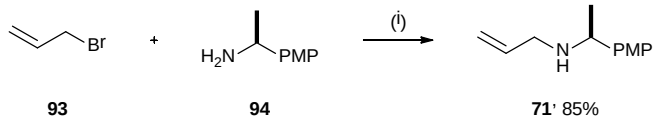

**Scheme 15:** *Reagents and conditions:* (i) $Pd_2(dba)_3$•$CHCl_3$, $HBF_4$, $PBu_3$, 80 °C, 5 h, sealed vessel.

Although this was not ideal, the sample of **89** was judged to be of sufficient purity to provide the required information upon conjugate addition of lithium amide **62**, and therefore investigations continued.

## 2.6 Amine synthesis

It was now necessary to synthesise enantiopure amine **71** for use in the conjugate addition of the corresponding lithium amide to α,β,δ,ε-diunsaturated ester **89**. Amine **71** was originally synthesised upon allylation of commercially available (*S*)-α-methyl-*p*-methoxybenzyl amine **94** with allyl bromide **93**, and subsequent purification by flash column chromatography giving **71** in 66% yield.[1] This reaction was repeated at the commencement of this project, yielding an orange/brown oil before purification. Flash column chromatography allowed separation of the desired product **71** from other impurities, but proved to be time consuming upon scale-up and

required large volumes of silica. In order to facilitate the convenient synthesis of **71** on a multigram scale (>50 g batches) a more streamlined process was developed. This involved an aqueous extraction of the product **71** from its impurities to avoid chromatography. Thus, deprotonation of amine **94** with BuLi and addition of allyl bromide **93** was followed by an aqueous quench. The product was then extracted into $Et_2O$ and the combined layers were washed with 10% citric acid, which carried protonated **71** into the aqueous layer. The citric acid layer was then neutralised with satd aq $NaHCO_3$ and extracted with $Et_2O$ to give the free base **71** in 85% yield (Scheme 16).



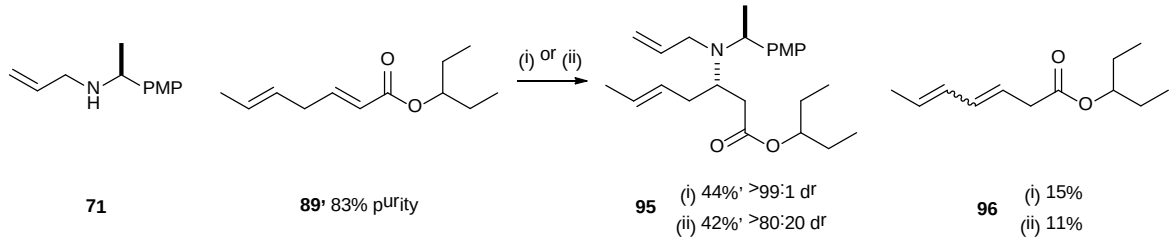

**93** **94** **71**, 85%

**Scheme 16:** *Reagents and conditions*: (i) BuLi, THF, 0 °C to rt, 16 h.

### 2.7 Conjugate addition to isopentyl hepta-2,5-dienoate

α,β,δ,ε-Diunsaturated ester **89** was then subjected to conjugate addition with the lithium amide derived from amine **71** in THF at −78 °C for 2 h. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy revealed formation of a mixture of products including β-amino ester **95** (in 97:3 dr), and a mixture of β,γ-unsaturated ester isomers **96**, the side products formed from γ-deprotonation followed by protonation upon aqueous work-up.[11] β-Amino ester **95** was isolated in 44% yield and >99:1 dr after flash column chromatography, alongside 15% yield of an impure sample of an approximately 55:45 mixture of two β,γ-unsaturated ester isomers **96**.[12,13] The isolated yield of β-amino ester **95** (44%) therefore proved to be lower than that of β-amino ester **65** derived from conjugate addition to methyl ester **64** (59% isolated yield of β-amino ester **65**). In an attempt to suppress the competing γ-deprotonation pathway, α,β-unsaturated ester **89** was then subjected to conjugate addition with the same lithium amide, this time in $Et_2O$ at −20 °C for 5 h.[5] Analysis of the crude reaction mixture again revealed formation of a mixture of products and indicated a reduction in the diastereoselectivity of the conjugate addition, which fell from 97:3 dr at −78 °C in THF to 75:25 dr at −20 °C in $Et_2O$. β-Amino ester **95** was this time isolated in 42% yield and 80:20 dr, along with 11% yield of an impure sample of β,γ-unsaturated esters **96** (~60:40 dr).[12,13]

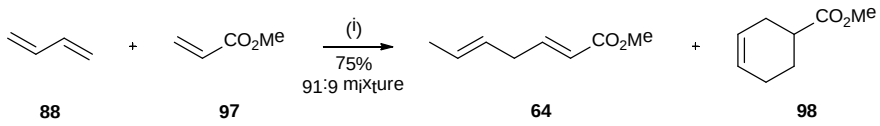
Therefore, this result did not represent an improvement over that recorded in THF at −78 °C, and due to the observed decrease in diastereoselectivity, this avenue of investigation was abandoned (Scheme 17).




**Scheme 17:** *Reagents and conditions:* (i) BuLi, THF, –78 °C, 2 h; (ii) BuLi, $Et_2O$, –20 °C, 5 h.

## 2.8 α,β-Unsaturated ester synthesis

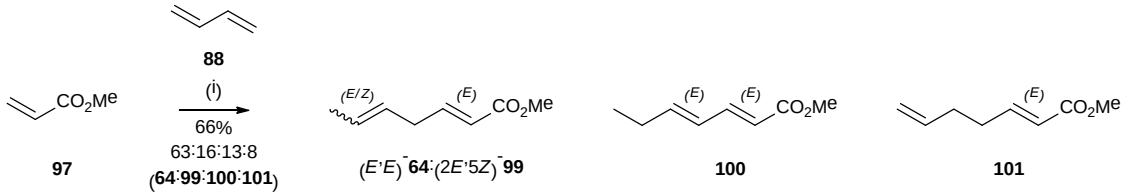
Investigations then reverted back to the use of methyl ester **64** in the conjugate addition reaction. α,β,δ,ε-Diunsaturated ester **64** was originally synthesised from commercially available methyl acrylate **97** and 1,3-butadiene **88** in a modification of a palladium catalysed coupling reaction initially reported by Tkatchenko *et al.*[14] The original publication reported the competing formation of diene **64** and Diels-Alder adduct **98** in a ratio of 89:11, respectively, and in 87% overall conversion with respect to 1,3-butadiene **88**. Previous results using a modification of this procedure performed by Davies and Kelly provided similar results,[15] with an isolated yield of 75% of an inseparable 91:9 mixture of diene **64** and Diels-Alder product **98** after flash column chromatography. This mixture was then utilised in the conjugate addition step (Scheme 18).




**Scheme 18:** *Reagents and conditions*: (i) $Pd_2(dba)_3$•$CHCl_3$, $HBF_4$, $PBu_3$, 80 °C, 5 h, sealed vessel.

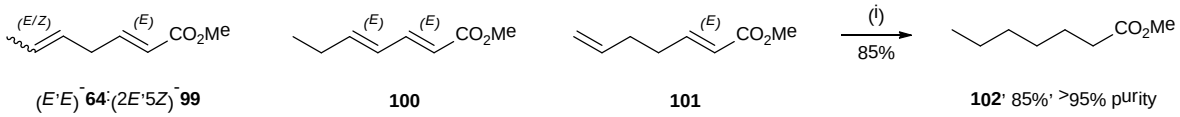
In order to provide material for the present synthesis, 1,3-butadiene **88**, methyl acrylate **97**, $Pd_2(dba)_3$•$CHCl_3$, $PBu_3$, and $HBF_4$ were heated at 80 °C for 5 h in a thick-walled, sealed vessel. Inspection of the $^1H$ and $^{13}C$ NMR spectra of the crude reaction mixture revealed the formation of a mixture of products. Comparison with the spectra of known compounds led to the assignment of these side-products as **99**,[7] **100**[8] and **101**[9,10] (structural and geometric

isomers of the major diene product **64**) present in the approximate ratio of 12:3:3:2. This mixture of products was isolated in 62% combined yield after flash column chromatography. However, a more efficient method of purification involved distillation, providing a 63:16:13:8 mixture of **64**:**99**:**100**:**101**, respectively, in 66% combined yield (Scheme 19).




**Scheme 19:** *Reagents and conditions*: (i) $Pd_2(dba)_3$•$CHCl_3$, $HBF_4$, $PBu_3$, 80 °C, 5 h, sealed vessel.

These assignments were supported by the results of a hydrogenation experiment carried out on a sample of the mixture of **64**, **99**, **100** and **101**, which yielded a single product **102** (>95%).[16] Trace amounts of an unidentified impurity in this sample (<5%) was consistent with the presence of small amounts of other impurities in the mixture of starting materials. This confirmed the assignment of **99**, **100** and **101** as regio- and stereoisomers of **64** (Scheme 20).

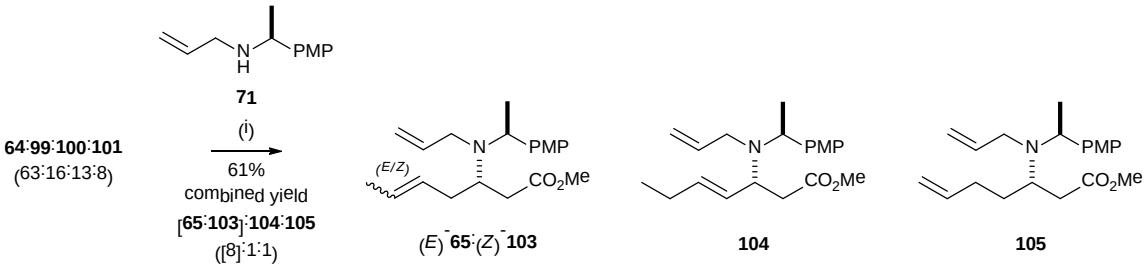



**Scheme 20:** *Reagents and conditions*: (i) $H_2$ (1 atm), 10% Pd/C, EtOAc, rt, 16 h.

### 2.9 Lithium amide conjugate addition

Conjugate addition of the lithium amide derived from amine **71** to the 63:16:13:8 mixture of α,β-unsaturated esters **64**, **99**, **100** and **101** could lead to four different β-amino esters: the desired **65**, as well as side-products **103**, **104**, and **105**. Indeed, conjugate addition to the mixture of Michael acceptors gave a mixture of conjugate addition products. Evidence of **104** and **105** was observed in the $^1$H NMR spectrum of the crude reaction mixture from this transformation. The presence of **104** was indicated by resonances in the $^1$H NMR spectrum associated with the terminal methyl moiety at $\delta_H$ 0.98 ppm, and a pair of resonances between $\delta_H$ 2.30–2.60 ppm corresponding to C(2)$H_A$ and C(2)$H_B$. The presence of **105** was suggested by distinctive terminal alkene resonances in the region $\delta_H$ 4.90–5.00 ppm. Distinct resonances

associated with **103** were not observable, presumably due to the similarity of its spectrum to that of **65**, however, its presence was assumed due to the presence of **99** in the starting material. The ratio of [**65**:**103**]:**104**:**105** was estimated as [8]:1:1, however, due to the similarity of the $^{1}$H NMR spectra of **65**, **103**, **104** and **105**, and the complex nature of the spectrum, it was not possible to obtain a more accurate ratio of their abundance. Careful and exhaustive flash column chromatography resulted in isolation of a sample enriched in **104** (in approximately 75:[25] **104**:[**65**:**103**:**105**]), although unsurprisingly, **65**, **103** and **105** appeared to be difficult to separate, especially on large scale, and were therefore isolated as a mixture in 48% combined yield (Scheme 21).




**Scheme 21:** *Reagents and conditions*: (i) BuLi, THF, –78 °C, 2 h.

It was recognised that both **65** and **103** would lead to the same product **74** after RCM later in the synthetic route. The other products **104** and **105** may lead to the corresponding 7- and 5-membered rings **106** and **107**, respectively, after RCM. Therefore, it was envisioned that the separation of the β-amino esters **65**, **103**, **104** and **105** could be postponed until later in the synthetic route when the polarity of such side products may aid their separation (Figure 8).

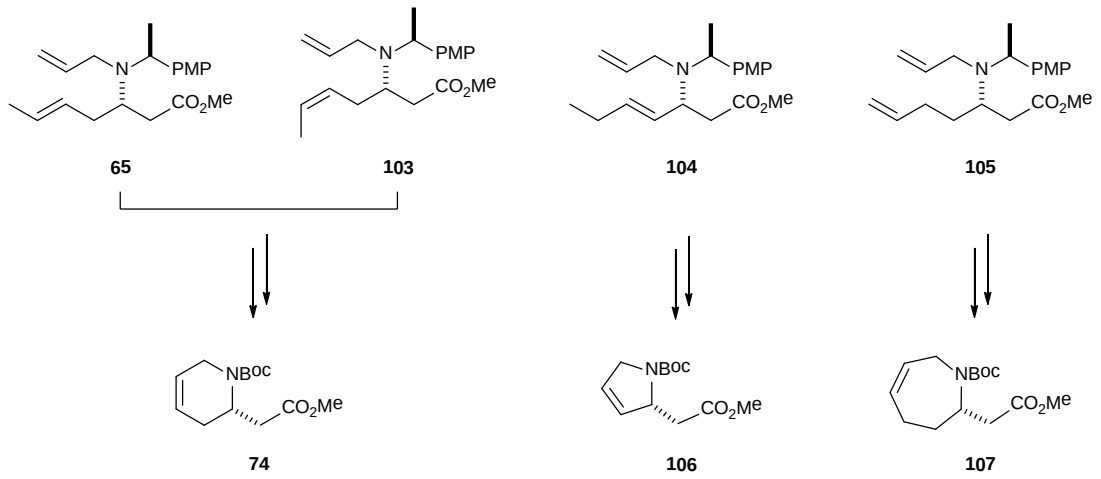
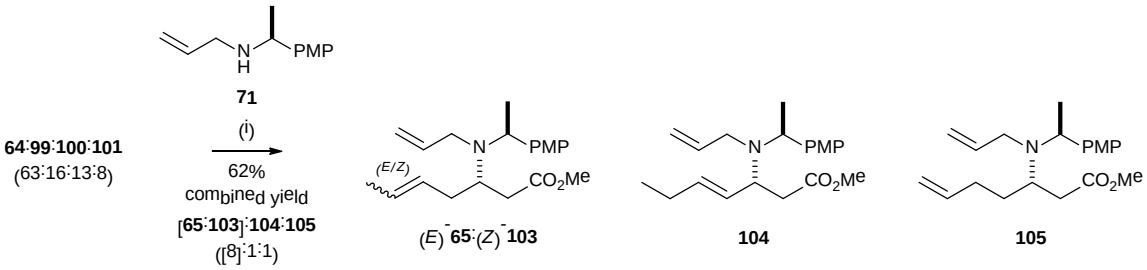



**Figure 8:** Prediction of the side-product derivatives after RCM.

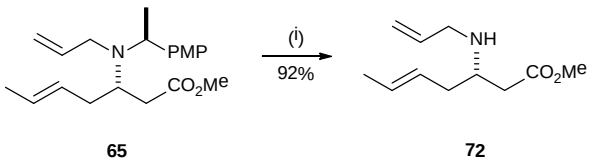
Given that **65**, **103** and **105** were inseparable by chromatography, a method for isolation of β-amino methyl ester **65** (together with associated β-amino ester side-products **103**–**105**) without chromatography was developed to aid in the efficient production of large quantities of material. The crude reaction mixture from the conjugate addition reaction was extracted with $Et_2O$, which was then washed with 10% aq citric acid to protonate and remove excess secondary amine **71**. The $Et_2O$ layers were then washed with 1.0 M aq HCl which was sufficiently acidic to carry protonated **65** (and β-amino ester side-products **103**–**105**) into the aqueous layer. The aqueous layer was then extracted with $CH_2Cl_2$ which was sufficiently solvating to carry protonated **65** (and **103**–**105**) into the organic layer. The $CH_2Cl_2$ layer was then neutralised with satd aq $NaHCO_3$ which yielded **65** (along with **103**–**105**) in 62% combined yield (Scheme 22).




**Scheme 22:** *Reagents and conditions:* (i) BuLi, THF, –78 °C, 2 h.

## 2.10 Secondary Amine

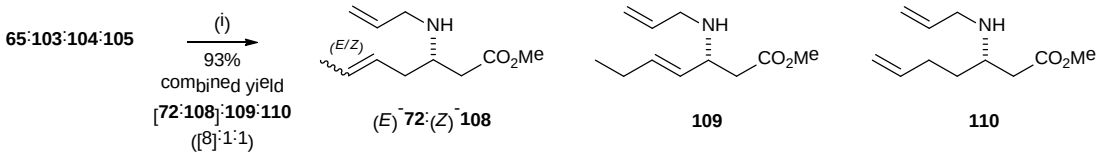
Davies and Taylor accessed secondary amine **72** in 92% yield by cleavage of the *p*-methoxybenzyl moiety within **65** under acidic, reducing conditions (Scheme 23).




**Scheme 23:** *Reagents and conditions*: (i) $Et_3SiH$, $HCO_2H$, 90 °C, 16 h.

This method was adapted in this synthesis, but it was decided to investigate methods to extract amine **72** (together with β-amino ester species **108**–**110**), without the need to use large-scale flash column chromatography. Attempts to extract **72** into both HCl and citric acid solutions were unsuccessful. Initially, a method was developed to utilise a commercial

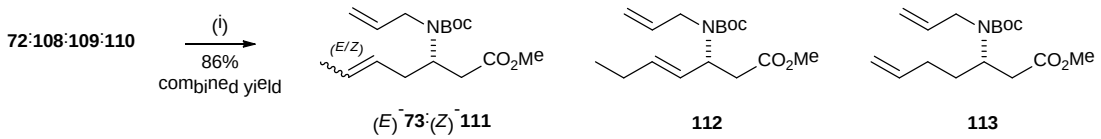
'capture-release' silica-based column to isolate **72**. These columns utilise silica impregnated with sulfonic acid residues which protonate and 'capture' the secondary amine **72**. Non-amine impurities were then washed out of the column using mixtures of $CH_2Cl_2$ and MeOH. The product was then 'released' as the free base using methanolic ammonia solution. However, this 'catch-release' method was not amenable to scale-up so other methods for the extraction of **72** were sought. A new method was developed that utilised the formate salt of **72** which was generated during the reaction due to the use of formic acid as a solvent. The majority of the formic acid was removed *in vacuo* and the residues were dissolved in water. Impurities were then extracted into $Et_2O$ while the protonated secondary amine **72** remained in the aqueous layer. The aqueous layer was then neutralised with satd aq $NaHCO_3$ and extracted with $CH_2Cl_2$ to give a 93% yield of **72** (together with **108**–**110**). Again, the similarity of the $^1$H NMR spectra of **72**, **108**, **109** and **110** precluded the determination of an accurate product ratio, however, an approximate ratio of [8]:1:1 [**72**:**108**]:**109**:**110** was observed (Scheme 24).




**Scheme 24:** *Reagents and conditions*: (i) $Et_3SiH$, $HCO_2H$, 90 °C, 16 h.

## 2.11 Ring-closing metathesis

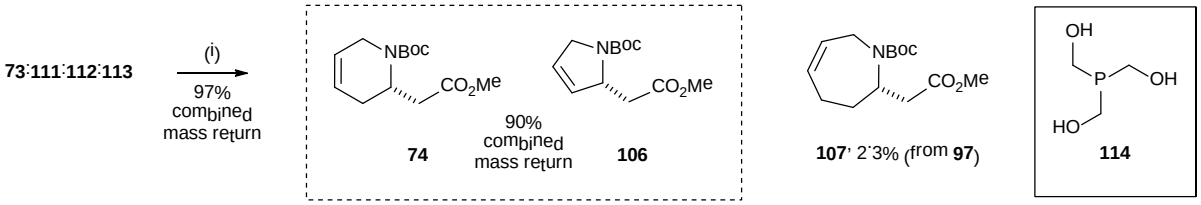
Secondary amine **72** (together with conjugate addition side-products **108**–**110**) was then *N*-Boc protected to give a mixture of **73**, **111**, **112** and **113** in a combined yield of 86%. Due to the rotameric nature of these *N*-Boc compounds at rt, no assessment of the ratio of the products **73**, **111**, **112**, and **113** could be made at this stage (Scheme 25).




**Scheme 25:** *Reagents and conditions*: (i) $Boc_2O$, $NaHCO_3$, MeOH, rt, 16 h.

This mixture of *N*-Boc compounds was then subjected to ring-closing metathesis with Grubbs 1$^{st}$ generation catalyst. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy again

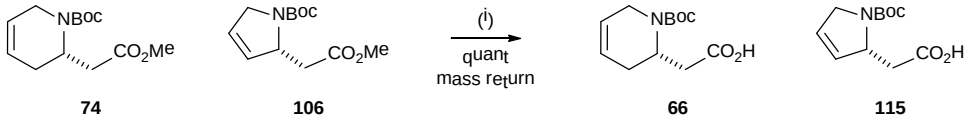
proved to be problematic due to the rotameric nature of the *N*-Boc compounds **74**, **106**, and **107**. The crude reaction mixture was treated with $P(CH_2OH)_3$ **114** to aid in the removal of ruthenium residues.[17] Subsequent purification via flash column chromatography gave 90% combined yield of a mixture of the desired 6-membered ring **74** and what was thought to be the corresponding 5-membered ring **106** (originating from conjugate addition of amine **71** to α,β-unsaturated ester **100**), a theory which was supported by mass spectrometry. The 7-membered ring **107** (originating from conjugate addition of amine **71** to α,β-unsaturated ester **101**) was separable from the other products at this stage, and was isolated in 2.3% yield from methyl acrylate **97** (Scheme 26).




**Scheme 26:** *Reagents and conditions*: (i) Grubbs I, $CH_2Cl_2$, rt, 12 h.

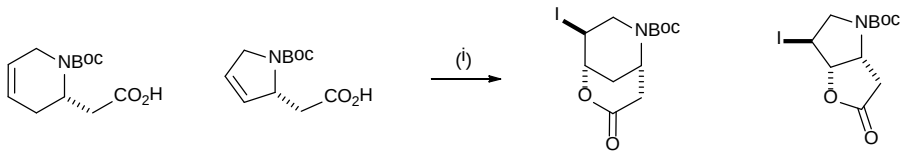
## 2.12 Iodolactonisation

The mixture of 6- and 5-membered rings **74** and **106** was then saponified with LiOH to give a mixture of acids **66** and **115** following the procedure of Davies and Taylor[1] (Scheme 27).




**Scheme 27:** *Reagents and conditions*: (i) LiOH, $THF/H_2O$, 50 °C, 16 h.

These compounds were then subjected to iodolactionisation to give a mixture of 6- and 5-membered ring iodolactones **67** and **116**. These products proved to be easily separable by flash column chromatography, giving 23% overall yield of the desired iodolactone **67** (from methyl acrylate **97**), and 1.8% overall yield of 5-membered iodolactone **116** (from methyl acrylate **97**), the identity of which was established by $^1H$, $^{13}C$, COSY, HMBC, and EXSY NMR spectroscopy (Scheme 28).




**66** **114** **67**, 23% (from **97**) **116**, 18% (from **97**)

**Scheme 28:** *Reagents and conditions*: (i) $I_2$, $NaHCO_3$, $CH_3CN$, −20 °C, 2 h, rt, 20 h.

Iodolactone **67** was obtained in a purity that allowed it to crystallise as colourless plates, despite being previously reported as "a viscous yellow oil".[1] Subsequent single crystal X-ray diffraction analysis of **67** allowed the relative configuration to be unambiguously assigned, with the absolute (1*S*,5*S*,8*S*)-configuration within **67** being assigned relative to the known configuration of the C(5)-stereocentre. Furthermore, the determination of a Flack *x* parameter[18,19] of –0.01(2) for the crystal structure of **67** allowed the absolute (1*S*,5*S*,8*S*)-configuration within **67** to be confirmed unambiguously (Figure 9).

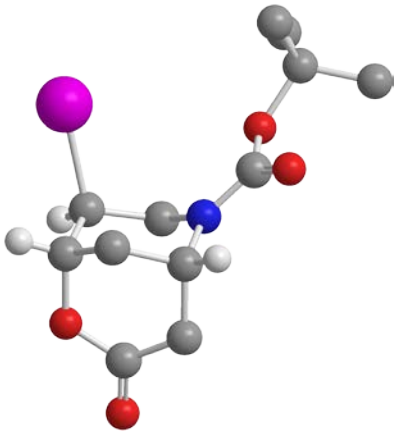
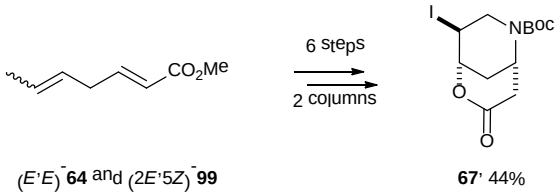


**Figure 9:** X-ray crystal structure of key 6-membered iodolactone **67**.

## 2.13 Conclusion

The overall yield of iodolactone **67** from α,β,δ,ε-diunsaturated ester **64** was originally reported as 42% over 6 steps,[1] however, when the purification was telescoped to avoid large-scale chromatography, iodolactone **67** was obtained in a comparable 44% yield from α,β,δ,ε-diunsaturated esters **64** and **99** (both of which give the same product). The original synthesis of iodolactone **67** from commercially available starting materials required a total of 6 steps requiring flash column chromatography, four of which were large-scale, time consuming, and suffered from poor separation. In the telescoped synthesis, this was reduced to only two small-scale, relatively simple chromatographic separations, and one distillation. This

represents a huge improvement in the time-efficiency and scalability of the synthesis and enables the large-scale (>10 g batches) production of lactone **67** with relative ease (Scheme 29).




**Scheme 29:** Telescoping of the purification in the synthesis of lactone **67**.

The following chapters explore the elaboration of key intermediate lactone **67** towards pseudodistomin D **4**.

## 2.14 References and notes

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[6] In these cases it is necessary to use an α,β-unsaturated ester with a sterically demanding ester substituent (e.g. *t*-Bu), as direct 1,2-addition is promoted at the higher temperature. Conjugate addition to α,β-unsaturated esters with less sterically demanding ester substituents (e.g. Me) have been shown to suffer from high levels of 1,2-addition, see: Taylor, R. J. *Part II Thesis*, University of Oxford, **2006**.

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[8] Ma, D.; Lu, X. *Tetrahedron* **1990**, *46*, 3189.

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[10] An authentic sample of **101** for comparison was kindly supplied by Miss E. A. Brock.

[11] Substantial peak overlap precluded a more accurate determination of the product ratio from this reaction.

[12] $^1$H NMR resonances were consistent with those of the β,γ,δ,ε-diunsaturated methyl ester analogues, see: Schlosser, M.; Zellner, A.; Leroux, F. *Synthesis* **2001**, 1830.

[13] This ratio was calculated by integration of characteristic CH=CHC*H*$_2$CO$_2$R signals at $\delta_H$ = 3.08 (d, *J* 7.5) ppm and $\delta_H$ = 3.21 (dd, *J* 6.8, 1.7) ppm, although the presence of other impurities in this region of the $^1$H NMR spectrum precluded determination of a more precise ratio.

[14] Grenouillet, P.; Neibecker, D.; Tkatchenko, I. *J. Chem. Soc., Chem. Commun.* **1983**, 542.

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[16] **102** is commercially available from the Sigma-Aldrich Company Ltd.

[17] Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137.

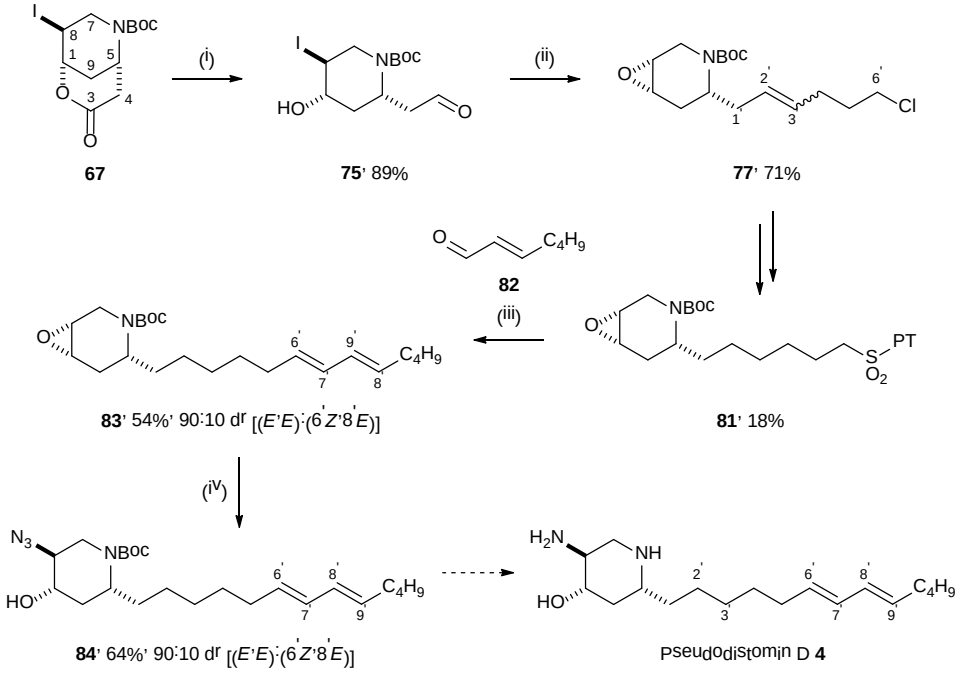
[18] Flack, H. D. *Acta. Cryst. A* **1983**, *39*, 876.

[19] Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143.

# Chapter 3: Side chain attachment via C(2')–C(3') bond formation

## 3.1 Introduction

With an efficient route to key iodolactone **67** in hand, it was necessary to devise a strategy for the elaboration of the piperidine core through installation of an amino functionality at C(5) and elaboration of the C(2)-side chain that would furnish pseudodistomin D **4**. The structure of key iodolactone **67** suggests a side chain attachment at the C(4) position. Previous studies by Davies and Taylor[1] had utilised a stepwise installation of the side chain, first forming the C(2')–C(3') bond within **77** using a Wittig olefination. Further elaborations allowed construction of the (6'*E*,8'*E*)-diene via a Julia-Kocienski olefination of **81** using *trans*-hept-2-enal **82** (i.e. construction of the C(6')–(7') bond). Nitrogen functionality was introduced via ring opening of epoxide **83** with sodium azide, which gave **84** in 64% yield. However, the required reduction and deprotection steps in this synthesis were not completed due to time constraints (Scheme 30).




**Scheme 30:** *Reagents and conditions*: (i) DIBAL-H, $CH_2Cl_2$, −78 °C, 1.5 h; (ii) $[Cl(CH_2)_4PPh_3]^+[Br]^-$ **76**, KHMDS, THF, −78 °C to rt, 1 h; (iii) **82**, KHMDS, THF, −78 °C, 15 min; (iv) $NaN_3$, $NH_4Cl$, DMSO, 80 °C, 16 h.

### 3.2 $S_N2$ Displacement to form the C(2')–C(3') bond of the side chain

It was envisioned that a more efficient synthesis might be possible if an undeca-4,6-diene unit such as **119** could be installed via formation of the C(2')–C(3') bond within **117**. This could be achieved, for example, by the $S_N2$ displacement of a leaving group at the C(2') position within **118**. This convergent approach might also allow an increased overall yield of pseudodistomin D to be obtained (Figure 10).

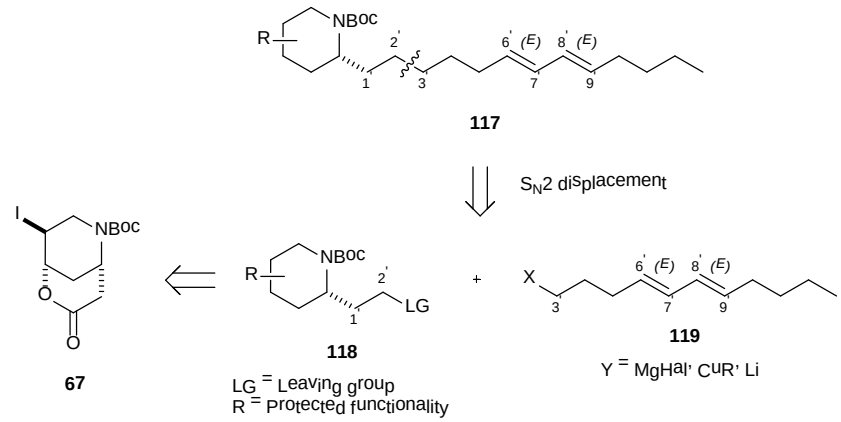
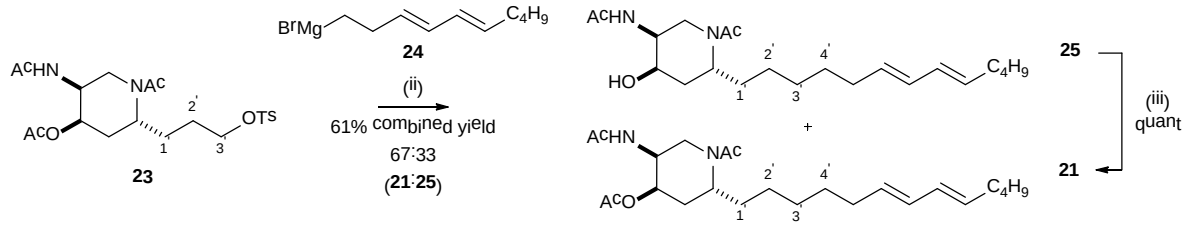



**Figure 10:** Side chain attachment via $S_N2$ displacement to form the C(2')–C(3') bond.

Naito *et al*. utilised a similar approach in their synthesis of pseudodistomin B **2**, involving a C(3')–(4') disconnection.[2] This strategy utilised a copper mediated Grignard displacement of a tosylate group at the C(3') position within **23** (Scheme 31).

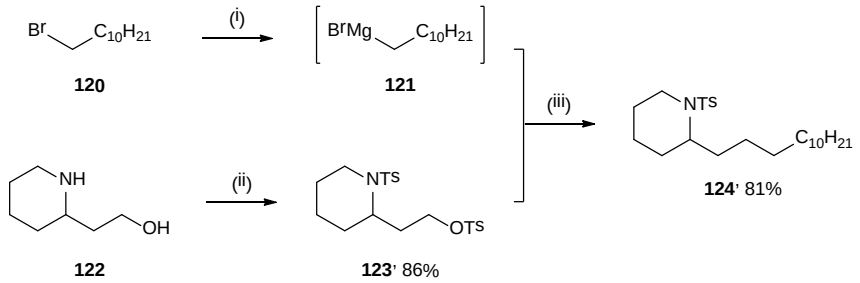



**Scheme 31:** *Reagents and conditions*: (i) TsCl, DMAP, $Et_3N$; (ii) **24**, $Li_2CuCl_4$, −20 °C; (iii) $Ac_2O$, py.

### 3.3 Proof of principle

A model system was devised to test the validity of this synthetic approach. *O*-Tosyl substituted piperidinol **123** (which was not rotameric at rt, unlike the analogous *N*-Boc compound) was conveniently prepared from 2-(piperidin-2'-yl)ethanol **122** in one step and subsequently used as the electrophilic component for a copper-mediated Grignard displacement.[2] 1-Bromoundecane **120** was heated with iodine-activated magnesium turnings

in dry THF to give Grignard reagent **121**, which was then added in excess to a solution of dilithium tetrachlorocuprate(II) and tosylate **123** at −78 °C. The reaction was warmed to −50 °C for 1 h before being allowed to warm to rt over a further 1 h, and then quenched by the addition of satd aq $NH_4Cl$. Following purification by flash column chromatography, the displacement product **124** was isolated in 81% yield (Scheme 32).




**Scheme 32:** *Reagents and conditions*: (i) Mg turnings, $I_2$, THF, reflux, 1 h; (ii) TsCl, py, $CH_2Cl_2$, rt, 16 h; (iii) $Li_2CuCl_4$, THF, −78 °C, to −50 °C, 1 h, then −50 °C to rt, 1 h.

### 3.4 Side chain synthesis

As the displacement of a tosylate leaving group at the C(2') position within model system **123** proved successful, it was next decided to attempt the synthesis of diene **119**. Davies and Taylor[1] had previously utilised a modified Julia olefination to form the C(6')–C(7') double bond in their attempted synthesis of pseudodistomin D **4**. This reaction proved to be (*E*)-selective, but only yielded a 90:10 mixture of geometrical isomers at this position. It was therefore decided to investigate other possible strategies for the formation of the (*E*,*E*)-diene within pseudodistomin D **4** with a view to increasing the (*E*)-diastereoselectivity. A search of the relevant literature suggested that one of the most effective strategies for the construction of (*E*,*E*)-dienes **125** involves palladium catalysed cross-couplings. This approach employs an (*E*)-vinyl halide **126** into which palladium(0) can oxidatively insert, and an (*E*)-vinyl organometallic species **127** (often boron, tin and zinc, in the Suzuki, Stille, and Negishi couplings, respectively) can then undergo transmetallation onto palladium(II). These (*E*)-vinyl organometallic species **127** can in turn be obtained from hydrometallation of a terminal alkyne **129**, a stereospecific process giving only the (*E*)-vinyl product **127** (Figure 11).

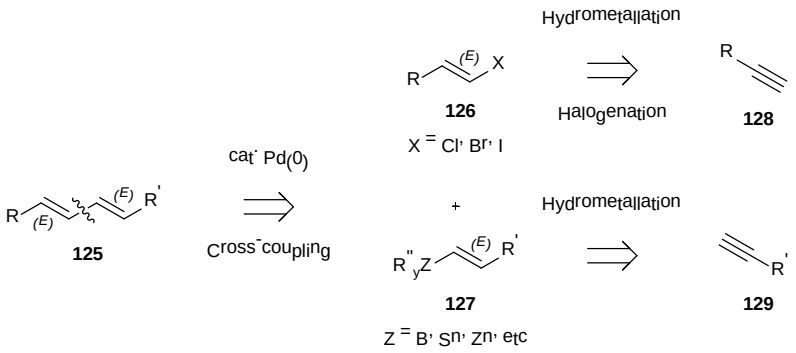
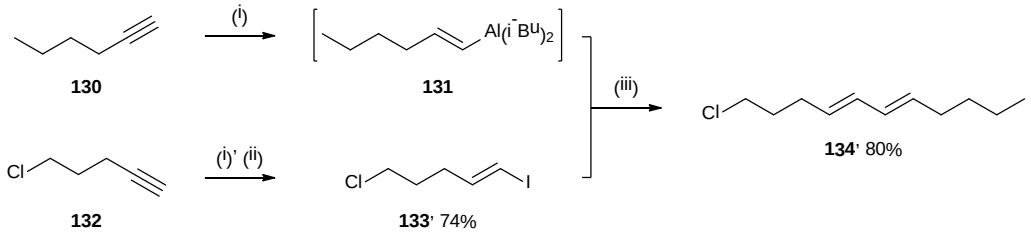



**Figure 11:** Installation of an (*E*,*E*)-diene via palladium $sp^2$-$sp^2$ cross coupling.

### 3.5 Modified Negishi coupling for the (*E*,*E*)-diene synthesis

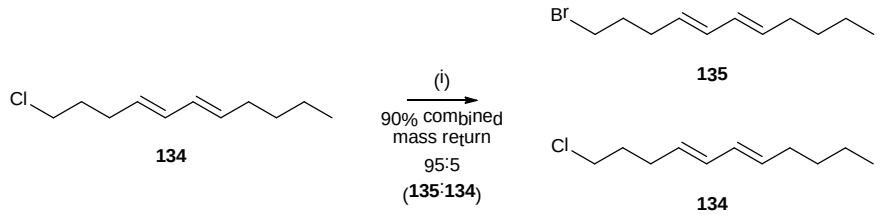
According to a modified procedure from the literature,[3] alkyne **132** was treated with DIBAL-H in hexanes at reflux to effect a stereoselective hydroalumination. The intermediate aluminated species was then cooled to −78 °C and quenched with iodine to give light-sensitive vinyl iodide **133**, which was distilled under reduced pressure and isolated in 74% yield. Vinyl iodide **133** was then used in a modified Negishi coupling to construct the desired (*E*,*E*)-diene. In this reaction, aluminated alkene **131** was prepared *in situ* upon treatment of alkyne **130** with DIBAL-H in hexanes at reflux. The resultant solution was cooled 0 °C and added to a mixture of vinyl iodide **133**, zinc chloride and $Pd(PPh_3)_4$ in THF. After 16 h the reaction was quenched, and gave **134** as the only detectable alkene product, which was purified by distillation under reduced pressure to give (*E*,*E*)-diene **134** in 80% yield and >99:1 dr (Scheme 33).




**Scheme 33:** *Reagents and conditions*: (i) DIBAL-H, hexanes, 50 °C, 16 h; (ii) $I_2$, THF, −78 °C to rt, 1 h; (iii) $Pd(PPh_3)_4$, $ZnCl_2$, THF, 0 °C to rt, 16 h.

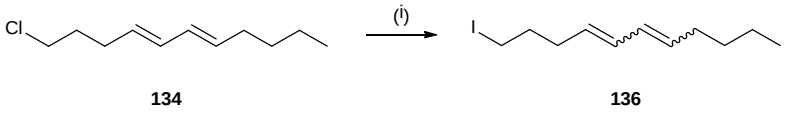
To enable the investigation of a range of coupling strategies, it was decided to attempt the synthesis of other halogen derivatives of chlorodiene **134**. The synthesis of the corresponding bromodiene **135** was then attempted from chlorodiene **134**. The most efficacious method found for this conversion was treatment with LiBr in butanone at 80 °C for 16 h. This yielded

a 95:5 mixture of the bromodiene **135** and chlorodiene **134**, respectively, in an overall mass return of 90%, which was deemed to be a high enough level of purity for use without further purification. No noticeable erosion of the (*E*,*E*)-diene stereochemistry was observed during this conversion (Scheme 34).



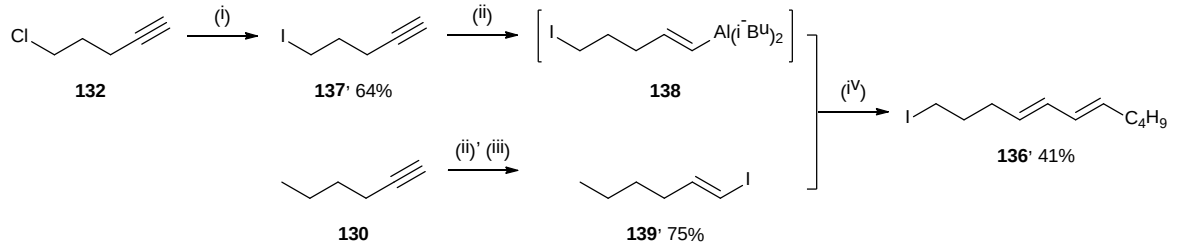

**Scheme 34:** *Reagents and conditions*: (i) LiBr, butanone, 80 °C, 16 h.

The synthesis of iododiene **136** was then attempted via a similar Finkelstein reaction in the presence of NaI. A range of conditions were trialled with different solvents, temperatures, and equivalents of NaI and $Na_2S_2O_3$ (used to quench the formation of $I_2$). However, although displacement was successful (as indicated by a distinctive shift in the $^1$H NMR resonances associated with protons at the C(1) position), significant scrambling of the diene stereochemistry was observed in all cases (Scheme 35). An alternative method for the synthesis of iododiene **136** was therefore sought.




**Scheme 35:** *Reagents and conditions*: (i) NaI (5/10/30 equiv), $Na_2S_2O_3$ (0/0.05/2 equiv), acetone/butanone, rt/60 °C/80 °C, 16 h.

It was thought that installation of the iodo-functionality prior to cross-coupling might furnish the desired iododiene **136**. A Finkelstein reaction was carried out on chloro alkyne **132** to yield iodo alkyne **137** in 64% yield. Hydroalumination of alkyne **137** with DIBAL-H gave intermediate **138**, which was reacted *in situ* with vinyl iodide **139** (derived from 1-hexyne **130**) in a similar procedure to that used in the synthesis of chloro diene **134**. Analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated high selectivity for formation of the (*E*,*E*)-diene. Careful flash column chromatography gave (*E*,*E*)-diene **136** in 41% yield, >99:1 dr, and approximately 95% purity (Scheme 36).

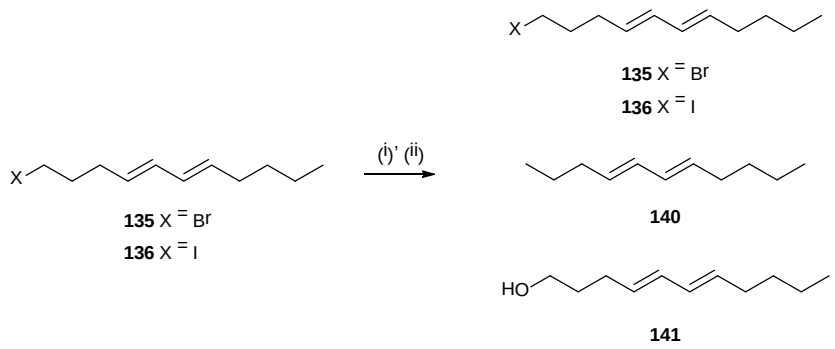



**Scheme 36:** *Reagents and conditions*: (i) NaI, acetone, 50 °C, 72 h; (ii) DIBAL-H, hexanes, 50 °C, 16 h; (iii) $I_2$, THF, −78 °C to rt, 1 h; (iv) $Pd(PPh_3)_4$, $ZnCl_2$, THF, 0 °C to rt, 16 h.

### 3.6 Attempted installation of the side chain via a Grignard displacement procedure

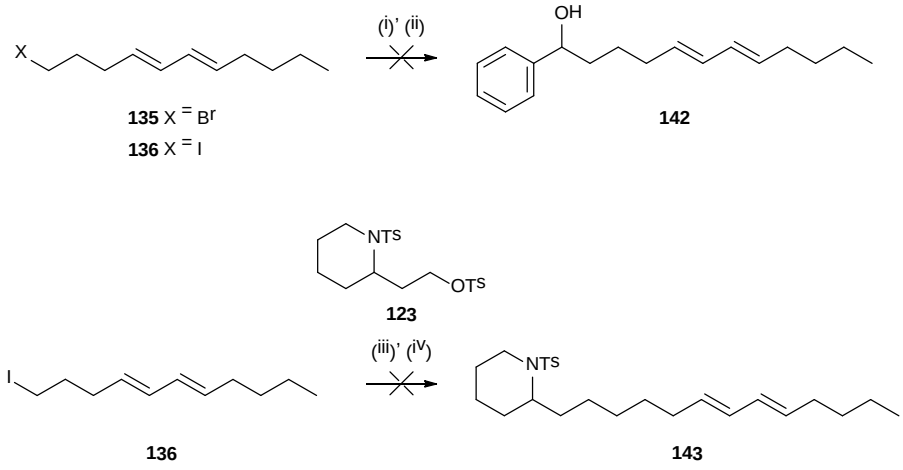
The formation of a Grignard reagent from each of the chlorodiene **134**, bromodiene **135** and iododiene **136** was attempted under a range of conditions. In these reactions, the use of both magnesium turnings and powder were investigated, along with iodine and 1,2-dibromoethane as activators. Magnesium turnings were washed with hexanes, dry heated, and stirred overnight under nitrogen prior to use.[4] Freshly distilled $Et_2O$ or THF were used as solvents for the Grignard formation. Initiation of the Grignard reaction was attempted by heating or sonication. Grignard formation was qualitatively gauged by decolouration (in the case of iodine initiation), ethene gas evolution (in the case of 1,2-dibromoethane), and the consumption of magnesium metal. A quantitative assessment was made by titration of the Grignard solution against salicylaldehyde phenylhydrazone,[5] and by analysis of the products arising from reaction of the Grignard solutions with either $H_2O$ or benzaldehyde. Chlorodiene **134** resisted all attempts to form its Grignard reagent, however, this might be expected due to the low reactivity of chlorinated species when compared to their brominated or iodinated analogues. Formation of Grignard reagents from bromodiene **135** and iododiene **136** was not successful under any conditions promoted by sonication or when heated with magnesium powder. Heating bromodiene **135** or iododiene **136** with magnesium turnings initiated with iodine or 1,2-dibromoethane gave reaction mixtures that appeared to decolourise (or release bubbles of ethene) and consume magnesium metal, suggesting that Grignard formation had been initiated. However, a persistent, grey precipitate quickly formed, possibly indicative of the facile oxidation of the long-chain Grignard formed.[6] Titration of these reaction mixtures did not indicate the presence of significant quantities of Grignard reagent. Aqueous work-up of these reaction mixtures and analysis of the $^1$H NMR spectra of the crude reaction mixtures

suggested the presence of hydrocarbon **140** and alcohol **141**, which would be the expected product of oxidation of Grignard reagents formed from **135** and **136**. Attempts at careful elimination of oxygen from the reaction system were unsuccessful in stopping the formation of alcohol **141** (Scheme 37).




**Scheme 37:** *Reagents and conditions*: (i) Mg turnings or Mg powder, $I_2$ or 1,2-dibromoethane, THF or $Et_2O$; (ii) reflux or ((•)) then $NH_4Cl$, $H_2O$, rt.

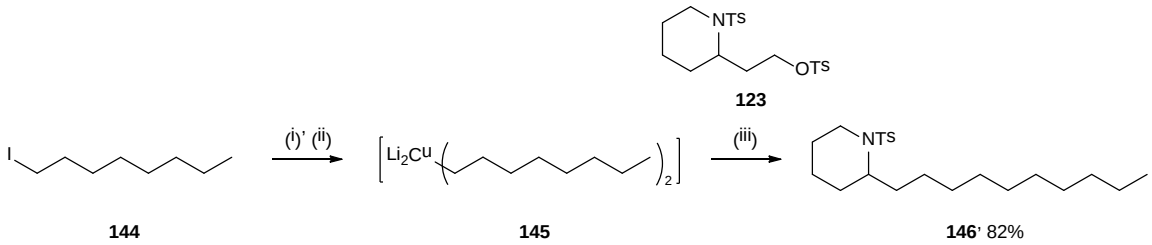
The presence of hydrocarbon **140** (together with unreacted starting material **135** and **136** and oxidation product **141**) in the crude reaction mixtures resulting from aqueous work-up after reaction of bromodiene **135** and iododiene **136** suggested the formation of a limited amount of Grignard reagent. However, quenching such reaction mixtures with benzaldehyde did not result in any observable addition product **142**. Addition of the Grignard reaction mixture derived from iododiene **136** to a mixture of tosylate **123** and dilithium tetrachlorocuprate(II) did not result in any observable addition product **143** (Scheme 38).




**Scheme 38:** *Reagents and conditions*: (i) Mg turnings, $I_2$ or 1,2-dibromoethane, THF or $Et_2O$, reflux; (ii) benzaldehyde, rt, 16 h; (iii) Mg turnings, $I_2$, $Et_2O$, reflux; (iv) **123**, $Li_2CuCl_4$, THF, −78 °C to rt, 16 h.

### 3.7 Side chain cuprate formation – proof of principle

In light of the poor results of Grignard formation, the copper-mediated Grignard strategy was abandoned. A more traditional approach to the formation of stoicheiometric cuprates from alkyl lithiums was investigated. Tosylate **123** was again used to test the validity of such an approach: 1-iodooctane **144** was treated with $^{t}$BuLi at −78 °C and then allowed to warm to rt for 1 h to facilitate full lithium-halogen exchange. The resultant mixture was then cooled to −78 °C and added to a suspension of CuI in $Et_2O$ at −30 °C. This mixture was maintained at −30 °C for 30 min and then cooled to −35 °C before the addition of a solution of tosylate **123** in THF. The resultant mixture was then allowed to warm to rt over 2 h, which resulted in full conversion to the displacement product **146**, which was isolated in 82% yield after purification (Scheme 39).

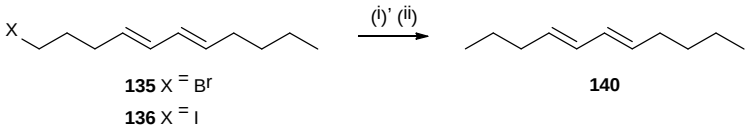



**Scheme 39:** *Reagents and conditions*: (i) $^{t}$BuLi (2.2 equiv), $Et_2O$, −78 °C to rt, 1 h; (ii) CuI, $Et_2O$, −30 °C, 30 min; (iii) **123**, THF, −35 °C to rt, 2 h.

### 3.8 Attempted side chain cuprate formation

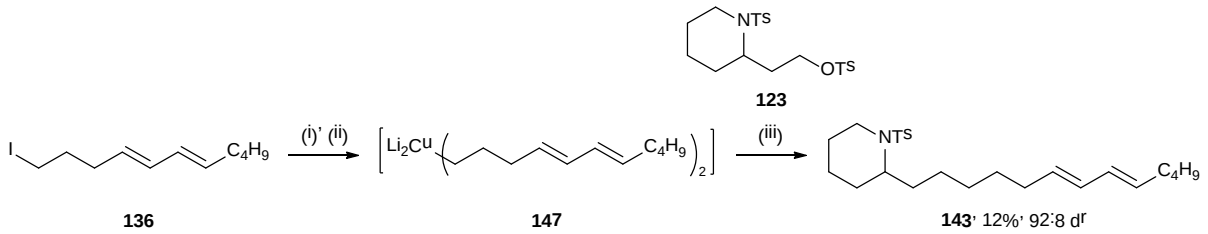
With these promising results in hand, a method for lithiation of chlorodiene **134** was sought, as **134** proved to be the easiest of the halodiene side chain precursors to synthesise. $^{t}$BuLi initiated lithium-halogen exchange was unsuccessful with chlorodiene **134**, as would be expected due to the low reactivity of chlorine in such reactions. Lithium naphthalide (prepared from lithium wire and naphthalene under an argon atmosphere) was unsuccessful in effecting a reductive lithiation of chlorodiene **134**. It was therefore decided to lithiate either bromodiene **135** or iododiene **136** via lithium-halogen exchange with $^{t}$BuLi. These experiments were carried out in an analogous fashion to the lithium-halogen exchange with 1-iodooctane **136**, and were quenched with satd aq $NH_4Cl$ to investigate the level of lithiation. Both experiments proceeded with a complete consumption of starting materials and resulted in an inseparable, complex mixture of hydrocarbon products. These products included the

expected (*E*,*E*)-diene **140**, together with several unidentified hydrocarbon products, possibly including alkene isomers, as indicated by $^1$H NMR resonances associated with these products in the region of $\delta_H$ 5.20–6.40 ppm. This alkene region in the $^1$H NMR spectrum of this mixture exhibited a lower than expected integration when compared with the aliphatic regions suggesting partial destruction of the diene moiety. These lithium-halogen exchange experiments were also carried out with a shorter time period, warming to rt over 15 min rather than 1 h, in an attempt to suppress side-reactions. These experiments also resulted in complete consumption of starting material, but unfortunately resulted in a similar mixture of products (Scheme 40).



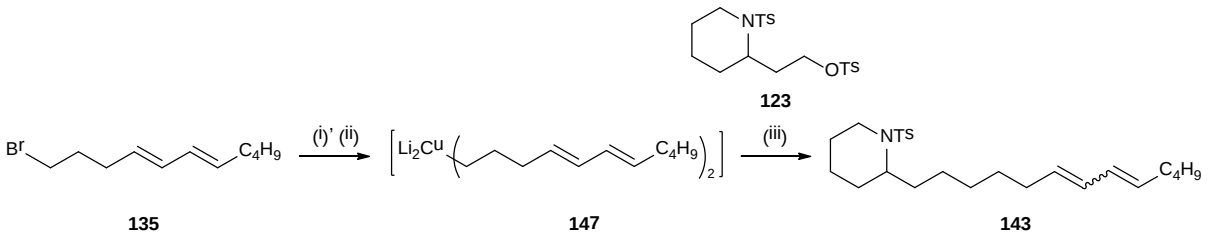

**Scheme 40:** *Reagents and conditions*: (i) $^t$BuLi (2.2 equiv), $Et_2O$, −78 °C to rt, 15 min or 1 h; (ii) $NH_4Cl$, $H_2O$, rt.

It was clear from these results that the lithium-halogen exchange was occurring, and so it was decided to attempt to form the stoicheiometric cuprate **147** and add it in excess to tosylate **123**. Two protocols were employed, the first of which used dilithium tetrachlorocuprate(II) as the copper source. Iododiene **136** was treated with $^t$BuLi under the lithium-halogen exchange conditions described above for 15 minutes. The resultant solution was cooled to −78 °C before the addition of a stoicheiometric dilithium tetrachlorocuprate(II) solution in THF. After a further 10 min at −78 °C, a solution of tosylate **123** was added in THF, and the reaction mixture was allowed to warm to rt over 30 min. After aqueous work-up the crude reaction mixture was purified by flash column chromatography to give a mixture of species, including a 26% yield of the returned starting material **123**, 12% yield of impure (*E*,*E*)-diene **143** in approximately 92:8 dr, and a similar mass return of a possibly isomeric, unknown product. Unfortunately, this result proved to be irreproducible (Scheme 41).




**Scheme 41:** *Reagents and conditions*: (i) $^{t}$BuLi (2.2 equiv), $Et_2O$, −78 °C to rt, 15 min; (ii) $Li_2CuCl_4$, THF, −78 °C, 10 min; (iii) **123**, THF, −78 °C to rt, 30 min.

The second protocol utilised CuI as the copper source. Bromodiene **135** was lithiated and transmetallated with CuI under identical conditions to those used for 1-iodooctane **144**. The resultant solution was stirred at −35 °C while a solution of tosylate **123** was added in $Et_2O$. The resultant mixture was allowed to warm to rt over 2 h before the addition of satd aq $NH_4Cl$. Flash column chromatography of the product gave approximately 85% mass return of an inseparable mixture of products that contained the desired product **143**. Analysis of the $^{1}$H and $^{13}$C NMR spectra of this mixture indicated a lower than expected integration in the alkene region when compared with aliphatic and aromatic regions. It was also observed that other alkene containing species were present, due to resonances in the alkene region. These observations suggested that the sensitive side chain diene had been partially destroyed under these reaction conditions (Scheme 42).




**Scheme 42:** *Reagents and conditions*: (i) $^{t}$BuLi (2.2 equiv), $Et_2O$, −78 °C to rt, 1 h; (ii) CuI, $Et_2O$, −30 °C, 30 min; (iii) **123**, THF, −35 °C to rt, 2 h.

The results of these studies imply that lithiation of halodienes **135** and **136** and transmetallation to copper to form the desired cuprate is accompanied by undesirable side reactions that result in scrambling or loss of the diene. This lack of selectivity greatly reduces the value of this reaction for installation of the side chain within pseudodistomin D **4**. The strategy of direct metallation of the side chain component was therefore abandoned.

### 3.9 Sulfur stabilised carbanions

In light of the poor results obtained from attempted direct organometallic formation for the installation of the side chain, it was decided to utilise deprotonation α to a sulfone to generate a more stable anionic species. It was thought that these more controllable organometallic species could be used to effect a displacement to install the side chain within pseudodistomin D **4**. Installation of a sulfone group at the C(2') position of a suitably protected head group **150** could enable deprotonation α to the sulfone, and subsequent displacement of a halogen from within side chains **135** or **136**. The sulfone could then be reductively cleaved from **149** to complete the side chain installation[7] (Figure 12).

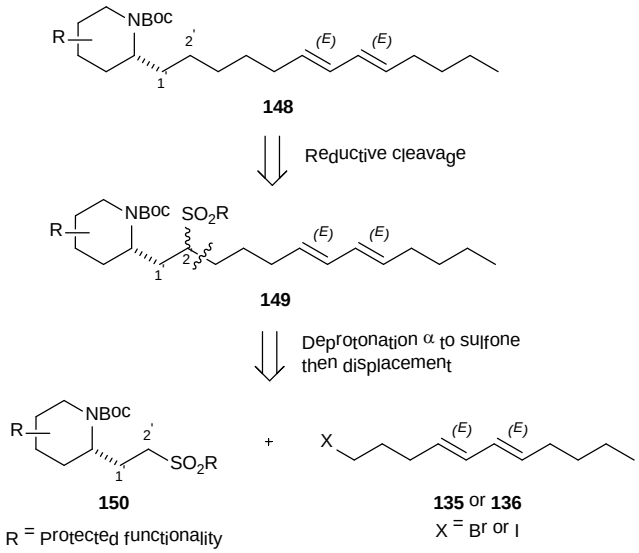
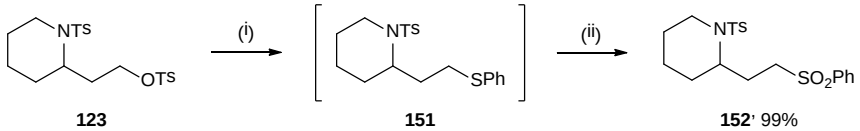



**Figure 12:** Sulfone anion $S_N2$ displacement strategy for the installation of the side chain.

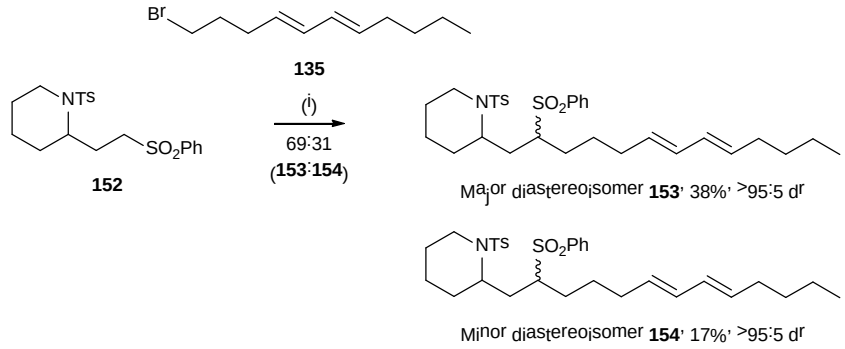
In order to furnish a model substrate to test this strategy, tosylate **123** was displaced with thiophenol and the resultant sulfide **151** was oxidised with *m*-CPBA to yield sulfone **152** in 99% yield over 2 steps (Scheme 43).




**Scheme 43:** *Reagents and conditions*: (i) PhSH, NaH, THF, rt, 30 min; (ii) *m*-CPBA, $CH_2Cl_2$, rt, 16 h.

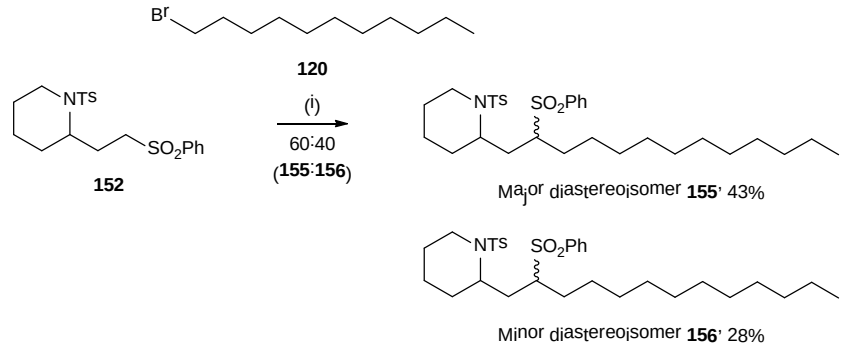
Deprotonation of sulfone **152** with BuLi at −78 °C followed by addition of bromodiene **135** led to only returned starting material after 1 h reaction time at −78 °C. When the same

reaction conditions were used and the reaction was allowed to warm to rt over 1 h, 82% conversion to a 69:31 mixture of two diastereoisomers **153** and **154** was produced. Flash column chromatography on silica allowed separation of the two diastereoisomers **153** and **154** which were isolated in 38 and 17% yield, respectively. No attempt was made to assign the relative configurations within either **153** or **154**. Both diastereoisomers **153** and **154** were isolated in >95:5 dr. This suggests that the reaction conditions are suitable for maintaining the stereochemistry of the side chain diene (Scheme 44).




**Scheme 44:** *Reagents and conditions*: (i) BuLi, THF, −78 °C, 10 min, then **135**, THF, −78 °C to rt, 1 h.

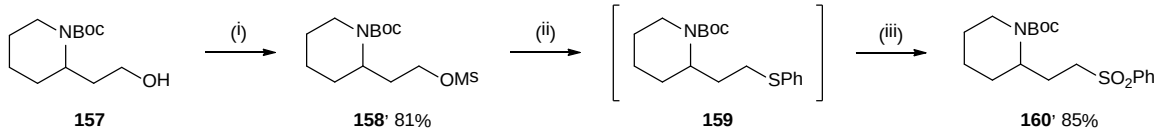
In a control experiment, reaction of 1-bromoundecane **120** with sulfone **152** under the same conditions gave nearly complete conversion to a 60:40 mixture of two diastereoisomers **155** and **156**, which were isolated in 43 and 28% yield, respectively. Once again, no attempt was made to assign the relative configurations within **155** or **156** (Scheme 45).




**Scheme 45:** *Reagents and conditions*: (i) BuLi, THF, −78 °C, 10 min, then **120**, THF, −78 °C to rt, 1 h.

Before any further optimisation was carried out it was decided to investigate the compatibility of the *N*-Boc protecting group with this chemistry. *N*-Boc sulfone **160** was synthesised from

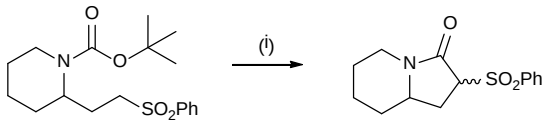
**157** in 69% yield over 3 steps and used as a model system to probe this compatibility (Scheme 46).




**157** **158**, 81% **159** **160**, 85%

**Scheme 46:** *Reagents and conditions*: (i) MsCl, $Et_3N$, 0 °C, 1 h; (ii) PhSH, NaH, THF, rt, 30 min; (iii) *m*-CPBA, $CH_2Cl_2$, rt, 16 h.

Deprotonation of **160** with BuLi at −78 °C for 1 h followed by addition of satd aq $NH_4Cl$ yielded a complex mixture of products. However, treatment of *N*-Boc sulfone **160** with KHMDS to generate the desired α-sulfone anion led to incomplete conversion of the starting material to a number of products. Flash column chromatography of this mixture gave 20% yield of returned starting material and 34% yield of bicyclic compound **161** as a single diasteroisomer in 95% purity. It was hypothesised that this was the result of intramolecular attack onto the *N*-Boc carbonyl group (Scheme 47). Other fractions yielded complex mixtures of minor products that were not identifiable. Due to this apparent incompatibility of the *N*-Boc protecting group with the generation of the required anion, it was decided to abandon this strategy.




**160** **161**, 34%

**Scheme 47:** *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 1 h, then satd aq $NH_4Cl$.

### 3.10 Conclusion

Attempts to devise a convergent route to pseudodistomin D **4**, by installation of the full side chain in one step via a sigma bond formation at the C(2')–C(3') position, proved to be unsuccessful. It was hypothesised that the sensitivity of the (6'*E*,8'*E*)-diene towards isomerisation or other side reactions is the major cause for the observed difficulties in this approach. It is thought that the specific disconnection at the C(2')–C(3') position and its proximity to the side chain diene leads to a range of pathways resulting in destruction of the desired diene. It is noted that the literature contains an example of the alternative C(3')–C(4')

displacement being successful in the direct side chain metallation strategy utilised by Naito *et al*. in their synthesis of pseudodistomin B **2**.[2] By contrast, the methodology used to install the (*E*,*E*)-diene in the side chain via C(7')–C(8') cross coupling has proved successful, furnishing the desired diene geometry in high diastereoselectivity and good yield. This approach has proved more efficient and selective than the C(6')–C(7') olefination strategy utilised in previous studies. It is hoped that this approach to diene synthesis could be utilised in further studies towards pseudodistomin D **4**. It was decided to next pursue a strategy of forming the C(2')-(3') bond prior to the construction of the side chain diene via C(7')–C(8') cross coupling (Figure 13).

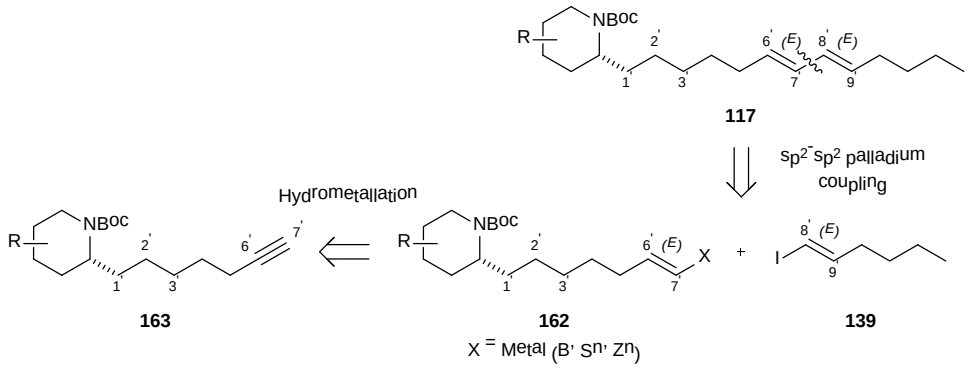



**Figure 13:** Cross-coupling strategy for the installation of the side chain within pseudodistomin D **4**.

### 3.11 References and notes

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[2] Kiguchi, T.; Yuumoto, Y.; Ninomiya, I.; Naito, T.; Deki, K.; Ishibashi, M.; Kobayashi, J. *Tetrahedron Lett.* **1992**, *33*, 7389.

[3] Sammakia, T.; Johns, D. M.; Kim, G.; Berliner, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 6504.

[4] Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698.

[5] B. E. Love, E. G. Jones, *J. Org. Chem.* **1999**, *64*, 3755.

[6] Previous studies by Davies and co-workers indicated similar problems with long-chain aliphatic Grignard reagents.

[7] Suzuki, T.; Tanaka, N.; Matsumura, T.; Hosoya, Y.; Nakada, M. *Tetrahedron Lett.* **2006**, *47*, 1593.

# Chapter 4: Side chain attachment via C(7')–C(8') cross coupling

## 4.1 Introduction

As shown in the previous chapter, the direct installation of the completed, diene-containing side chain at the C(2')–C(3') position was problematic. Therefore, an alternative route was sought for the side chain synthesis and it was thought that installation of the diene at a later stage could circumvent some of the problems encountered thus far. The success of cross coupling for the highly selective construction of (*E*,*E*)-dienes through the formation of the C(7')–C(8') bond suggested that this strategy would be suitable. Therefore, it was decided to construct the side chain in a stepwise fashion by first forming the C(2')–C(3') bond and later installing the diene via a cross coupling reaction to construct the C(7')–C(8') bond. It was envisioned that a suitably protected alkyne **163** could be hydrometallated *in situ* to enable its coupling to vinyl iodide **119** to complete the side chain with high diastereoselectivity. A range of alkyne hydrometallation conditions could be investigated, including hydroboration[1] (for Suzuki cross coupling), hydrostannation (for Stille cross coupling), and hydroalumination or hydrozirconation (for modified Negishi cross couplings). It was thought that alkyne **163** could be furnished via homologation of aldehyde **164**, which could be formed from the corresponding alcohol **165**. Wittig olefination of aldehyde **167** (derived from key intermediate lactone **67**) with *O*-benzyl protected phosphonium bromide salt **168** could allow subsequent, concomitant alkene hydrogenation and hydrogenolytic removal of the *O*-benzyl group in a single operation to give alcohol **165** (Figure 14). A similar strategy can be seen in the previous studies towards pseudodistomin D **4**, with a C(2')–C(3') bond formation followed by a C(6')–C(7') olefination to install the desired diene. It was also hoped that the yield and selectivity of this previous strategy could be improved further.

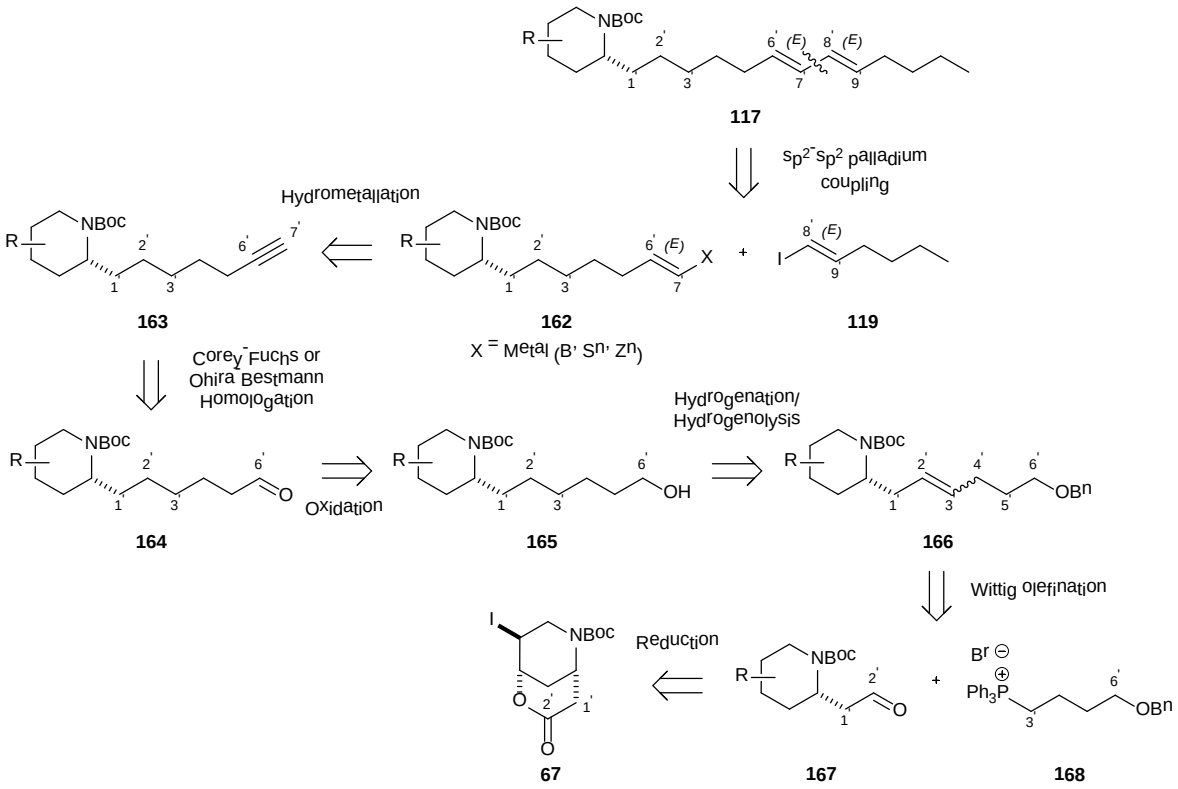
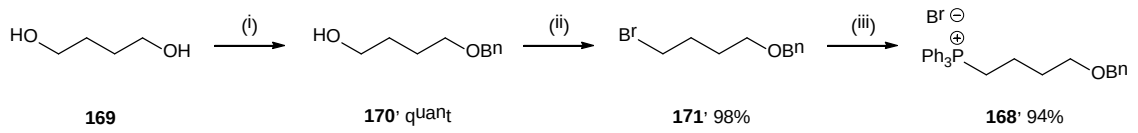



**Figure 14:** Cross-coupling strategy for the installation of the pseudodistomin D **4** side-chain.

## 4.2 Synthesis of phosphonium bromide salt

In order to investigate this route, it was decided to attempt the synthesis of phosphonium bromide salt **168**. An excess of butane-1,4-diol **169** was mono-deprotonated with sodium hydride before the addition of BnBr to effect mono-*O*-benzylation. This gave **170** in quantitative yield (after purification to remove the excess butane-1,4-diol **169**), which was converted to bromide **171** via an Appel reaction in 98% yield. Phosphonium bromide **168** was then generated by reaction of **171** at 120 °C in molten $PPh_3$, and recrystallised from $CH_2Cl_2$ in 94% yield, and an overall yield of 92% from BnBr over 3 steps (Scheme 48).

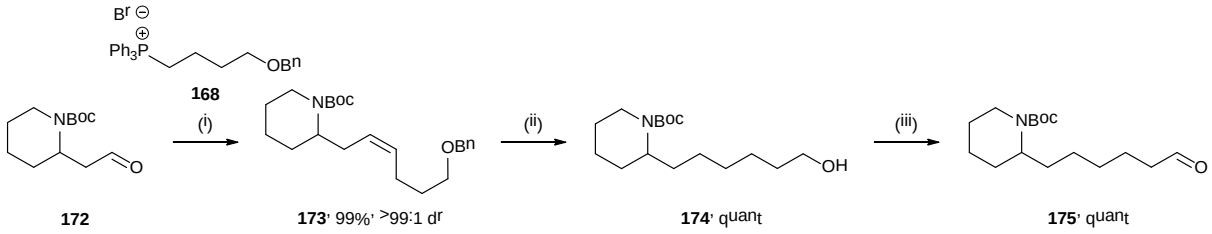



**Scheme 48:** *Reagents and conditions*: (i) NaH, THF, 0 °C, 30 min, then BnBr, 0 °C to rt, 16 h; (ii) $PPh_3$, $CBr_4$, $CH_2Cl_2$, rt, 20 min; (iii) $PPh_3$, 120 °C, 2 h.

## 4.3 Synthesis of model alkyne

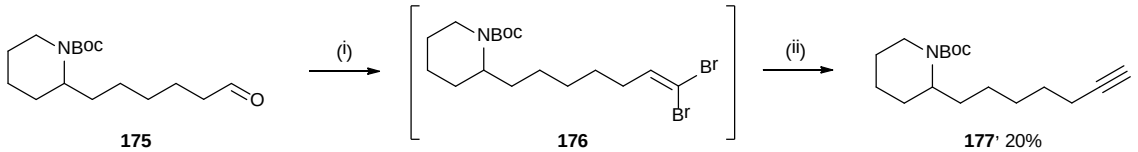
The synthesis of a model alkyne was then attempted starting from known aldehyde **172**,[2] derived from 2-(piperidin-2'-yl)ethanol **122**. According to a literature procedure,[3] the Wittig

olefination of aldehyde **172** and phosphonium bromide **168** was effected using NaHMDS as a base to give **173** in 99% yield. No evidence of a minor diastereoisomer was observed by $^{1}H$ or $^{13}C$ NMR spectroscopy, therefore the diastereoselectivity of the reaction was tentatively assigned as >99:1 dr. The major isomer was assigned the (*Z*)-configuration on the basis of $^{1}H$ NMR $^{3}J$ coupling constant analysis ($J_{2',3'}$ = 10.7 Hz). Alkene hydrogenation and hydrogenolytic removal of the *O*-benzyl group was then achieved with Pearlman's catalyst under an atmosphere of hydrogen to give alcohol **174** in quantitative yield. A Swern oxidation was then carried out on alcohol **174** to give the corresponding aldehyde **175**, again in quantitative yield (Scheme 49).




**Scheme 49:** *Reagents and conditions*: (i) **168**, NaHMDS, THF, 0 °C to rt, 40 min, then **172**, 0 °C to rt, 16 h; (ii) $H_2$ (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 2 h; (iii) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 1 h, then $Et_3N$, −78 °C to rt, 15 min.

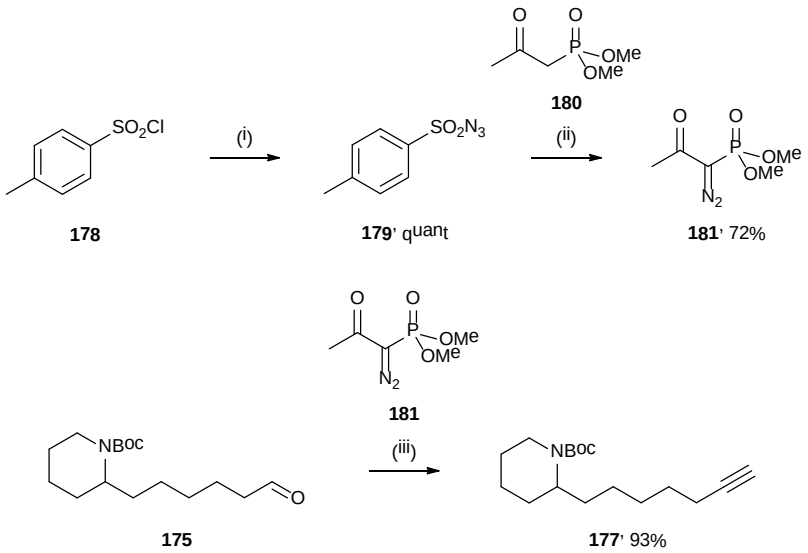
Corey-Fuchs homologation was attempted on aldehyde **175**, using conditions reported in the literature.[4] A modest 20% yield of alkyne **177** was obtained after treatment of the intermediate dibromide **176** with BuLi. Analysis of intermediate dibromide **176** suggested the presence of an unknown side product and therefore another homologation strategy was sought (Scheme 50).




**Scheme 50:** *Reagents and conditions*: (i) $PPh_3$, $CBr_4$, $CH_2Cl_2$, 0 °C, 30 min; (ii) BuLi, THF, −78 °C, 1 h.

It was decided to attempt an Ohira-Bestmann modification of the Seyferth-Gilbert homologation that converts aldehydes to terminal alkynes.[5] For this purpose, the Ohira-Bestmann reagent **181** was synthesised in 72% yield from commercially available starting

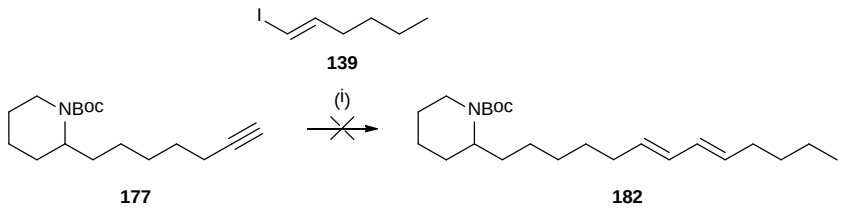
materials.[6] Aldehyde **175** was treated with **181** and potassium carbonate according to a literature procedure[5] giving, after purification by flash column chromatography, alkyne **177** in 93% yield (Scheme 51).




**Scheme 51:** *Reagents and conditions*: (i) $NaN_3$, $^{i}PrOH/H_2O$ (v/v 2:1), rt, 2 h; (ii) NaH, PhMe/THF (v/v 3:2), 0 °C to rt, 16 h; (iii) $K_2CO_3$, MeOH, 0 °C to rt, 16 h.

### 4.4 Hydrometallation and cross-coupling of model systems

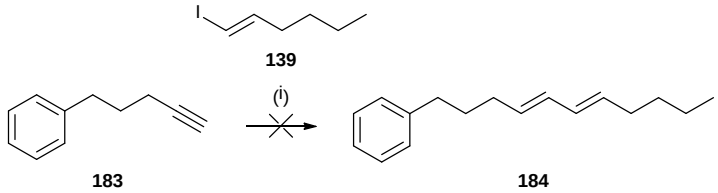
With alkyne **177** in hand, it was decided to investigate conditions for its *in situ* hydrometallation and subsequent coupling to vinyl iodide **139**, to furnish the desired (*E*,*E*)-diene containing side chain within **182**. An initial attempt to hydroaluminate alkyne **177** with DIBAL-H and transmetallate with zinc chloride before palladium coupling to vinyl iodide **139** returned near quantitative yield of starting material, suggesting a failure in the hydroalumination step (Scheme 52).




**Scheme 52:** *Reagents and conditions*: (i) DIBAL-H, hexanes, 50 °C, 2 h, then, **139**, $ZnCl_2$, $Pd(PPh_3)_4$, THF, 0 °C to rt, 16 h.

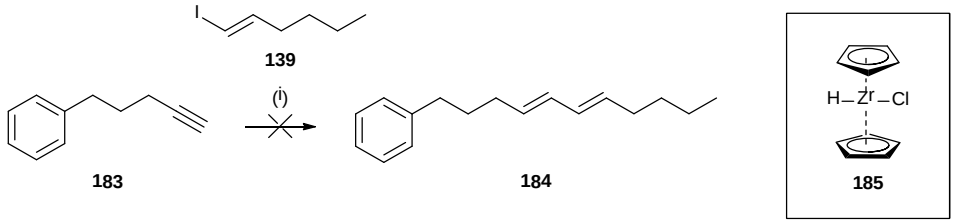
It was decided to use another model alkyne to determine if the nature of substrate **177** was causing the failure of the hydroalumination. Commercially available 5-phenyl-1-pentyne **183**

was selected as a suitable test alkyne. The above hydroalumination and coupling conditions were used on 5-phenyl-1-pentyne **183**, again with poor results, giving only trace amounts of product, and mainly starting material. Due to the presence of starting material, it was assumed that hydroalumination had not been successful, and another method of hydrometalation was therefore sought (Scheme 53).



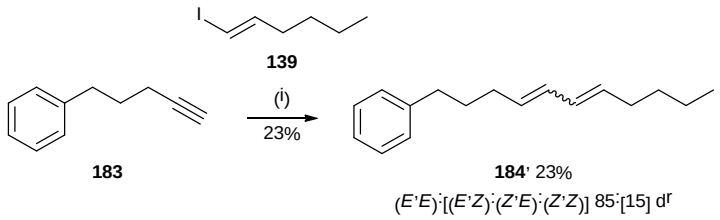

**Scheme 53:** *Reagents and conditions*: (i) DIBAL-H, hexanes, 50 °C, 2 h, then **139**, $ZnCl_2$, $Pd(PPh_3)_4$, THF, 0 °C to rt, 16 h.

To facilitate screening of hydrometallation conditions, 5-phenyl-1-pentyne **183** was used to identify a viable protocol. It was decided to attempt to hydrozirconate alkyne **183** using the Schwartz reagent **185** according to a literature procedure,[7] with $Pd(OAc)_2$ and DavePhos[8] as the ligand. Initial attempts using commercially available Schwartz reagent **185** were unsuccessful with full return of starting material (Scheme 54).



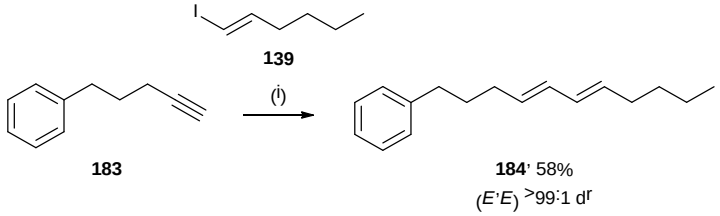

**Scheme 54:** *Reagents and conditions*: (i) Schwartz reagent **185**, $Pd(OAc)_2$, DavePhos, THF, rt, 16 h.

The above reaction conditions were then modified to generate the Schwartz reagent **185** *in situ* using zirconocene dichloride and DIBAL-H in hexanes. This resulted in a 23% yield of the desired coupling product **184**. However, the diastereoselectivity of the coupling was only modest, giving an approximate 85:15 dr of the (*E*,*E*)-diene to other geometrical isomers (Scheme 55).



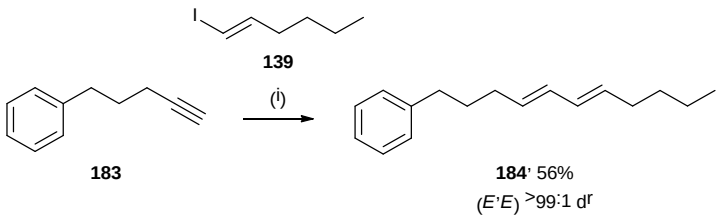

**Scheme 55:** *Reagents and conditions*: (i) DIBAL-H, $ZrCp_2Cl_2$, THF, 0 °C, 1 h, then **183**, 0 °C to rt, 1 h, then **139**, $Pd(OAc)_2$, DavePhos, rt, 16 h.

A change of DIBAL-H solvent from hexanes to THF with the above conditions greatly improved the reaction yield and diastereoselectivity giving the desired (*E*,*E*)-diene **184** in 58% yield and >99:1 dr (Scheme 56).



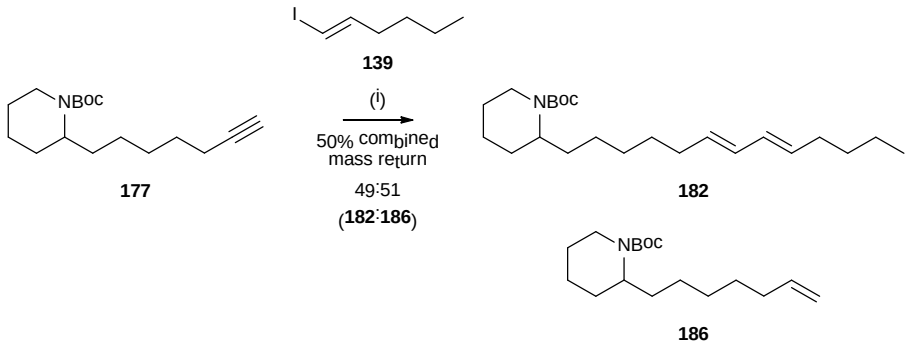

**Scheme 56:** *Reagents and conditions*: (i) DIBAL-H, $ZrCp_2Cl_2$, THF, 0 °C, 1 h, then **183**, 0 °C to rt, 1 h, then **139**, $Pd(OAc)_2$, DavePhos, rt, 16 h.

Replacement of $Pd(OAc)_2$ and DavePhos with $Pd(PPh_3)_4$ under the same reaction conditions gave an almost identical yield of 56% and the same high diastereoselectivity for formation of (*E*,*E*)-**184** (Scheme 57).




**Scheme 57:** *Reagents and conditions*: (i) DIBAL-H, $ZrCp_2Cl_2$, THF, 0 °C, 1 h, then **183**, 0 °C to rt, 1 h, then **139**, $Pd(PPh_3)_4$, rt, 16 h.

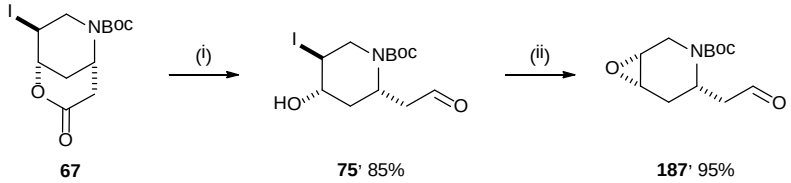
These conditions were then used on the model piperidine **177**, and resulted in an inseparable 49:51 mixture of desired diene **182** and terminal alkene side product **186** (presumably derived from proto-dezirconation of the hydrozirconated alkyne), in 50% combined mass return. The diastereoselectivity for the (*E*,*E*)-diene was again seen to be >99:1 dr. A further 21% of the starting material was isolated, alongside 13% mass return of another unknown product (Scheme 58).




**Scheme 58:** *Reagents and conditions*: (i) DIBAL-H, $ZrCp_2Cl_2$, THF, 0 °C, 1 h, then **177**, 0 °C to rt, 1 h, then **139**, $Pd(PPh_3)_4$, rt, 16 h.

### 4.5 Synthesis of pseudodistomin D alkyne precursor

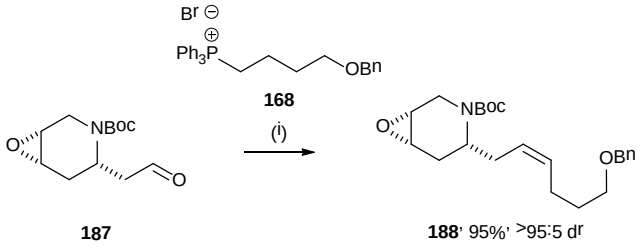
With a promising strategy available, attention next turned to the task of synthesising a suitable alkyne precursor to pseudodistomin D **4** from iodolactone **67**, to investigate its compatibility with the above reaction conditions before any further optimisation was carried out. Iodolactone **67** was converted to aldehyde **75** in 85% yield under the conditions reported by Davies and Taylor.[2] It was then decided to find conditions for the transformation of iodohydrin **75** to epoxide **187**. A range of basic conditions were investigated for this epoxide formation. The use of amine bases or strong bases at low temperature resulted in a mixture of products. Use of aqueous NaOH at rt provided the best results: under these conditions, epoxide **187** was isolated in 95% yield (Scheme 59).




**Scheme 59:** *Reagents and conditions*: (i) DIBAL-H, $CH_2Cl_2$, −78 °C, 1.5 h; (ii) 1.0 M aq NaOH, $CH_2Cl_2$, rt, 1 h.

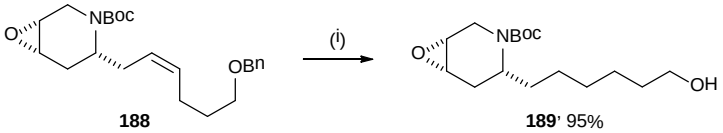
Aldehyde **187** was olefinated with the ylide derived from phosphonium bromide salt **168** to give alkene **188** in 95% yield. Due to peak overlap in the $^1$H NMR spectrum of the crude reaction mixture the diastereoselectivity could not be accurately assessed, but was tentatively assigned as >95:5 dr based on resonances in the region $\delta_H$ 5.22–5.54 ppm, and on the absence of any observable minor isomer in the corresponding $^{13}$C NMR spectrum. The major isomer

was assigned the (*Z*)-configuration on the basis of $^{1}$H NMR $^{3}J$ coupling constant analysis ($J_{2',3'}$ = 10.7 Hz) (Scheme 60).



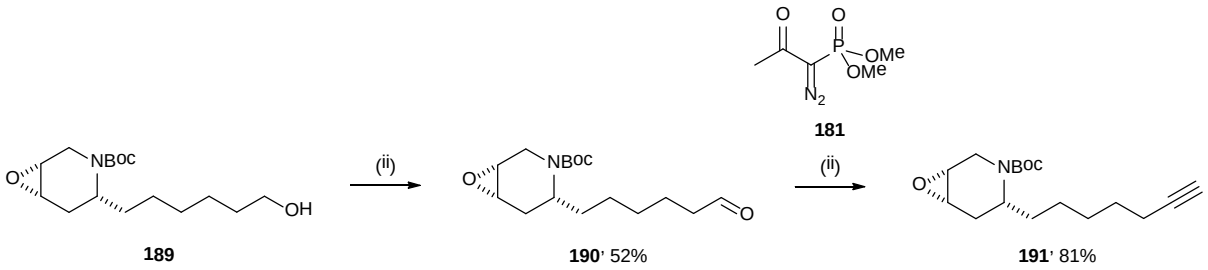

**Scheme 60:** *Reagents and conditions*: (i) **168**, NaHMDS, THF, 0 °C to rt, 40 min, then **187**, 0 °C to rt, 16 h.

Alkene **188** was then exposed to the same hydrogenation/hydrogenolysis conditions as used for the model system. This gave alcohol **189** in a yield of 95% after purification via flash column chromatography (Scheme 61).




**Scheme 61:** *Reagents and conditions*: (i) $H_2$ (1 atm), $Pd(OH)_2$/C, EtOAc, rt, 2 h.

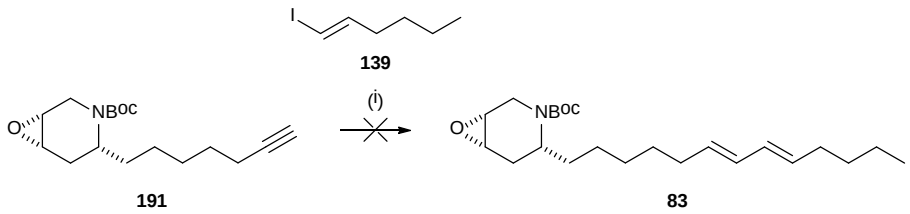
Alcohol **189** was subjected to Swern oxidation which yielded 52% of aldehyde **190**. Unreacted alcohol **189** was also recovered from the reaction in 40% yield, which could then be recycled to increase the effective yield of the oxidation. Aldehyde **190** appeared to be quite sensitive to decomposition, and so was immediately subjected to homologation with the Ohira-Bestmann reagent **181**. This gave alkyne **191** in 81% yield after purification via flash column chromatography (Scheme 62).




**Scheme 62:** *Reagents and conditions*: (i) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 1 h, then $Et_3N$, −78 °C to rt, 15 min; (ii) $K_2CO_3$, MeOH, 0 °C to rt, 16 h.

### 4.6 Attempted coupling of pseudodistomin D precursor

With alkyne **191** in hand it was decided to attempt a cross-coupling with vinyl iodide **139** under the conditions previously investigated on the model systems **177** and **183**. The product of such a coupling would be diene **83**, which is known from the previous studies by Davies and Taylor.[2] Alkyne **191** was hydrozirconated with zirconocene dichloride and DIBAL-H in THF, before the addition of $Pd(PPh_3)_4$ and vinyl iodide **139**. $^1$H NMR spectroscopic analysis of the crude reaction mixture showed complete consumption of the starting material. Distinctive resonances corresponding to an (*E*,*E*)-diene unit and terminal alkene from proto-dezirconation could be seen in the $^1$H NMR spectrum of the crude reaction mixture in an approximate 30:70 ratio. However, comparison of this spectrum with that of known compound **83**, suggested that the desired product was not present. Resonances associated with the piperidine core and epoxide of **191**, were also altered considerably in the spectrum of the crude reaction mixture, suggesting that an undesired reaction had occurred. It is likely that the reducing conditions required to generate the Swartz reagent **185** in situ are incompatible with the epoxide functionality within alkyne **191** (Scheme 63).




**Scheme 63:** *Reagents and conditions*: (i) DIBAL-H, $ZrCp_2Cl_2$, THF, 0 °C, 1 h, then **191**, 0 °C to rt, 1 h, then **139**, $Pd(PPh_3)_4$, rt, 16 h.

### 4.7 Conclusion

Due to time constraints, it was not possible to further pursue this avenue of investigation, however, epoxide opening and suitable *N*- and *O*-protection at an earlier stage could circumvent the problems seen here using an approach based upon hydrozirconation. Other methods of alkyne functionalisation (e.g. hydroboration) followed by alternative cross coupling protocols (e.g. Suzuki reaction) could also then be investigated. The next chapter discusses an alternative strategy for completion of the synthesis of pseudodistomin D **4** based upon Julia-Kocienski olefination for the construction of the side chain diene.

### 4.8 References and notes

[1] There is some precedent for the hydroboration of alkynes in the presence of epoxides, see: (a) Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem.* **2001**, 1873. (b) Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem Soc.* **2010**, *132*, 6941.

[2] Taylor, R. J. *MSc(Res) Thesis*, University of Oxford, **2008**.

[3] Yagi, K.; Nonaka, H.; Acharya, H. P.; Furukawa, K.; Ainai, T.; Kobayashi, Y. *Tetrahedron* **2006**, *62*, 4933.

[4] Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960.

[5] (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Muller, S.; Liepold, B.; Roth, B.; Bestmann, H. J. *Synlett* **1996**, 521.

[6] Bélanger, D.; Tong, X.; Soumaré, S.; Dory, Y. L.; Zhao, Y. *Chem. Eur. J.* **2009**, *15*, 4428.

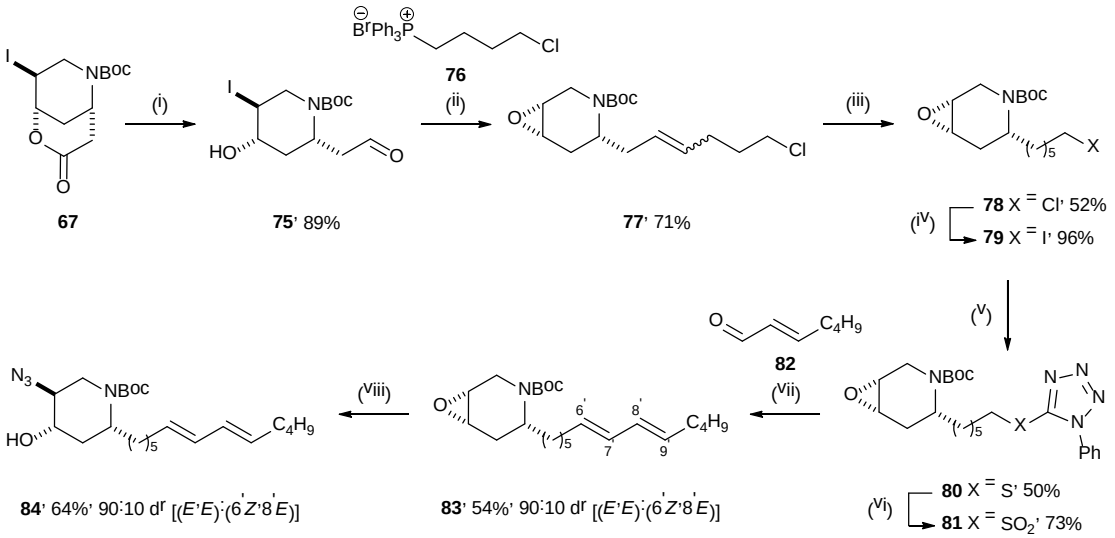
[7] Falck, J. R.; He, A.; Fukui, H.; Tsutsui, H.; Radha, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4527.

[8] Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885.

# Chapter 5: Synthesis of pseudodistomin D via C(6')–C(7') olefination

## 5.1 Introduction

It was decided to return to the C(6')–C(7') olefination strategy for the installation of the pseudodistomin D side chain, as investigated during the previous studies towards pseudodistomin D **4** by Davies and Taylor.[1] As part of the previous study, the Julia-Kocienski olefination of **81** yielded a 90:10 mixture of the desired (6'*E*,8'*E*)-diene **83**, together with the corresponding (6'*Z*,8'*E*)-diene. It was envisioned that this previous route could be improved by optimisation of some the lower yielding steps, particularly hydrogenation of the C=C bond within chloro-compound **77** (52% yield) and nucleophilic substitution of iodo-compound **79** with PTSH (50% yield) (Scheme 64).




**Scheme 64:** *Reagents and conditions*: (i) DIBAL-H, $CH_2Cl_2$, −78 °C, 1.5 h; (ii) **76**, KHMDS, THF, 0 °C to rt, 30 min, then **75**, −78 °C to rt, 1.5 h; (iii) Pd/C, $H_2$ (atm), EtOH, rt, 9 h; (iv) NaI, acetone, 50 °C, 5 days; (v) HSPT, KOH, EtOH, rt, 24 h; (vi) *m*-CPBA, $CH_2Cl_2$, 0 °C to rt, 2 days; (vii) *trans*-hept-2-enal **82**, KHMDS, THF, −78 °C, 15 min; (viii) $NaN_3$, $NH_4Cl$, DMSO, 80 °C, 16 h.

It was envisioned that the synthesis of the side chain could be completed in fewer steps if sulfone **193** was synthesised and used to effect two Julia-Kocienski olefination reactions, the first forming the C(2')–C(3') bond within **192** (followed by hydrogenation of the resultant C=C bond and oxidation to give known sulfone **81**), and the second forming the C(6')–C(7') bond within **83** (Figure 15).

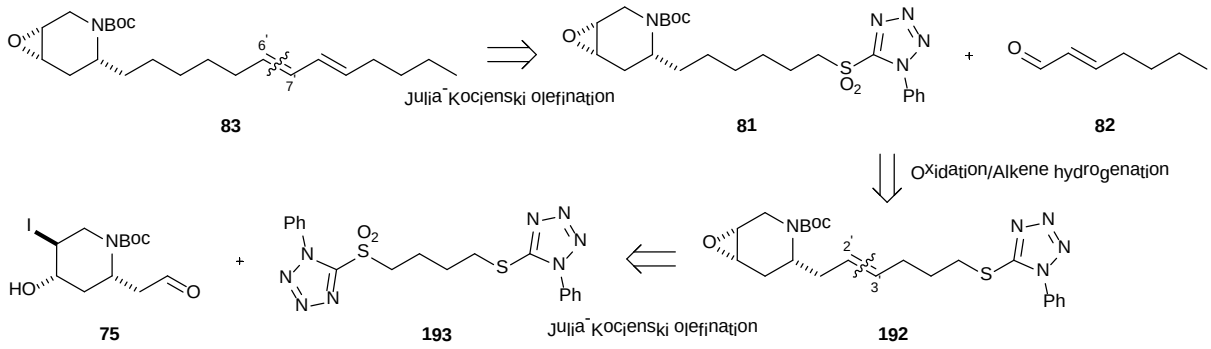
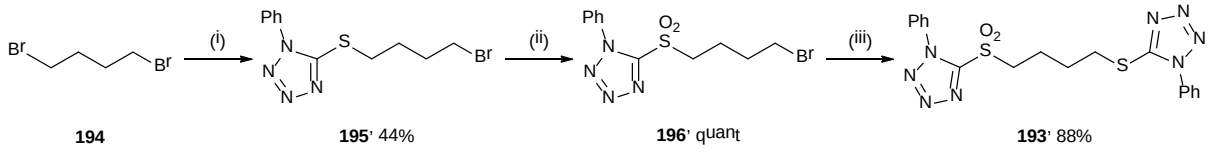



**Figure 15:** Retrosynthetic analysis of the side chain attachment of pseudodistomin D **4**.

## 5.2 Sulfone synthesis

The synthesis of sulfone **193** was completed in three steps in an overall yield of 39% from PTSH. Under the conditions reported by Davies and Taylor,[1] 1,4-dibromobutane **194** was mono-substituted with PTSH to give **195** in 44% yield, with subsequent *m*-CPBA oxidation proceeding in quantitative yield to give **196**. Bromide **196** was then displaced with PTSH to give **193** in 88% yield after recrystallisation from $CH_2Cl_2$ (Scheme 65).

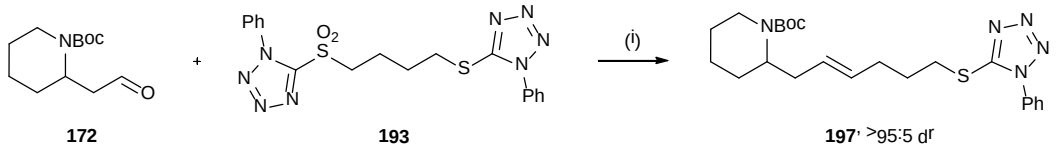



**Scheme 65:** *Reagents and conditions*: (i) PTSH, KO$^t$Bu, DMF, 0 °C, 15 min; (ii) *m*-CPBA, $CH_2Cl_2$, rt, 48 h; (iii) HSPT, KOH, $CH_2Cl_2$/EtOH (v/v 6:1), rt, 16 h.

## 5.3 Model system

Known piperidinyl aldehyde **172** was initially used to investigate the viability of the proposed double Julia-Kocienski olefination approach. Under the conditions previously reported by Davies and Taylor,[1] sulfone **193** was deprotonated with KHMDS at −78 °C before the addition of aldehyde **172**. No conversion was observed when the reaction was quenched at −78 °C. However, when the reaction was allowed to warm to rt over 1 h, 95% consumption of starting aldehyde **172** was observed, giving alkene **197** as the major product. In this case, a 72% yield of alkene **197** was isolated upon chromatography of the crude reaction mixture. No evidence of a minor diastereoisomer could be observed by $^1$H NMR spectroscopic analysis, so the diastereoselectivity of this reaction was tentatively assigned as being >95:5 dr. The major product was assigned the (*E*)-configuration on the basis of the known stereochemical outcome

of this reaction.[2] LiHMDS, BuLi, LDA, NaH, and KO$^t$Bu were also investigated as bases for the deprotonation of sulfone **193**; however, KHMDS proved to be the most effective choice. Again, no minor diastereoisomer was observed by $^1$H NMR spectroscopic analysis in any of these reactions, therefore the dr was again tentatively assigned as >95:5 in each case (Scheme 66).

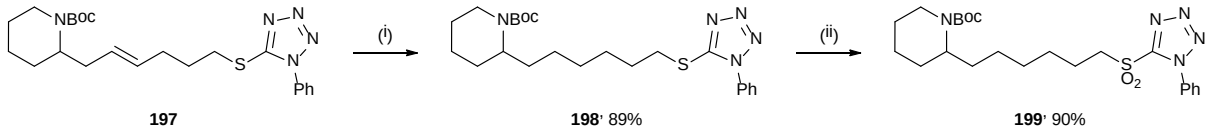



**172** **193** **197**, >95:5 dr

| Base | Conversion | Yield |
|---|---|---|
| LiHMDS | 89% | 69% |
| KHMDS | 95% | 72% |
| $^n$BuLi | 55% | - |
| LDA | 95% | 65% |
| NaH | 33% | - |
| KO$^t$Bu | 0% | - |

**Scheme 66:** *Reagents and conditions*: (i) Base, THF, −78 °C, 1 h, to rt, 1 h.

Hydrogenation of alkene **197** in the presence of Pd/C under 1 atmosphere of hydrogen failed. This was likely due to the poisoning effect of sulfides on palladium catalysts.[3] An alternative hydrogenation method was therefore investigated, and it was found that Adam's catalyst ($PtO_2$) under 5 atmospheres of hydrogen gave saturated sulfide **198** in 89% yield. Sulfide **198** was then oxidised to sulfone **199** with *m*-CPBA in 90% yield using a previously reported procedure[1] (Scheme 67).

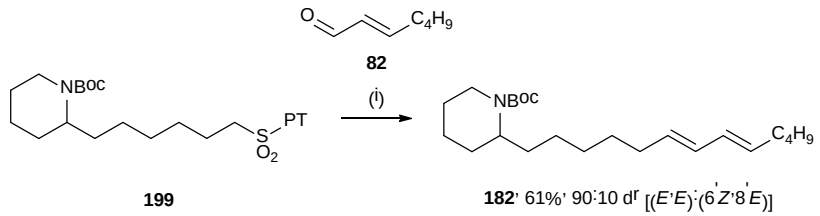



**197** **198**, 89% **199**, 90%

**Scheme 67:** *Reagents and conditions*: (i) $PtO_2$, $H_2$ (5 atm), EtOH, rt, 4 h; (ii) *m*-CPBA, $CH_2Cl_2$, rt, 48 h.

The Julia-Kocienski olefination of model sulfone **199** with *trans*-hept-2-enal **82** was then carried out under the conditions laid down during the previous synthetic studies towards pseudodistomin D **4** by Davies and Taylor.[1] Thus, KHMDS was added to a mixture of **199** and **82** in THF at −78 °C, followed by the addition of $H_2O$ after 15 min. Analysis of the crude reaction mixture by $^1$H NMR spectroscopy showed a 90:10 ratio of (*E*,*E*):(6'*Z*,8'*E*) geometric

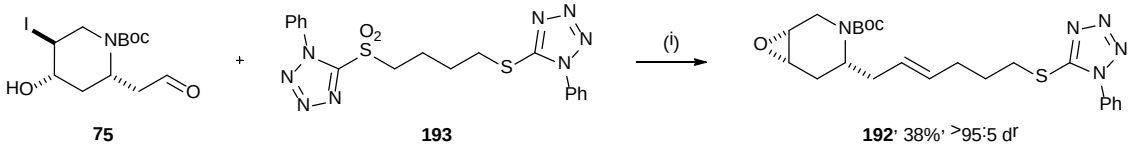
isomers of **182**. Purification via flash column chromatography gave 61% combined yield of an inseparable, 90:10 mixture of (*E*,*E*):(6'*Z*,8'*E*) isomers of **182**. The minor isomer was assigned as containing an (*E*,*Z*)-diene on the basis of $^{3}J$ $^{1}$H NMR coupling constant analysis, exhibiting $^{3}J$ couping constants of ~15 Hz for the (*E*)-alkene and ~10 Hz for the (*Z*)-alkene. The configuration of the (8'*E*)-alkene was assigned due to the known configuration of *trans*-hept-2-enal **82** (which was purchased in >97% purity), leading to the (6'*Z*,8'*E*)-diene assignment of the minor isomer of **182** (Scheme 68).




**Scheme 68:** *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 15 min.

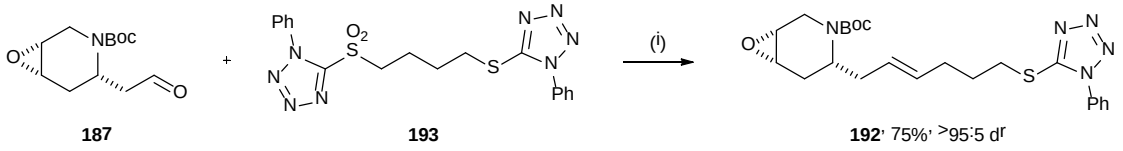
### 5.4 C(2')–C(3') Julia-Kocienski olefination

With these promising results on the model system in hand, it was decided to attempt this synthetic route with aldehyde **75**. Aldehyde **75** was then subjected to Julia-Kocienski olefination with sulfone **193** and KHMDS. It was also hoped that the iodohydrin functionality within **75** would be converted to the corresponding epoxide functionality within **192** under the Julia-Kocienski olefination reaction conditions if the sulfone anion were present in excess; unfortunately, the isolated yield of **192** from this reaction was only 38%. No evidence of a minor diastereoisomer could be observed by $^{1}$H NMR spectroscopic analysis, so the diastereoselectivity of the reaction was tentatively assigned as >95:5 dr, with the (*E*)-configuration being assigned to **192** on the basis of $^{1}$H NMR $^{3}J$ coupling constant analysis and the known stereochemical outcome of this reaction[2] (Scheme 69).




**Scheme 69:** *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 1 h, to rt, 1 h.

It was hoped that Julia-Kocienski olefination of epoxide **187** would give a higher yield in this reaction than iodohydrin **75**. Julia-Kocienski olefination of **187** with sulfone **193** was performed under the optimised conditions developed with the model aldehyde **172**. This time, alkene **192** was isolated in 75% yield, nearly a two-fold increase in the yield over the analogous reaction with iodohydrin **75** (Scheme 70).

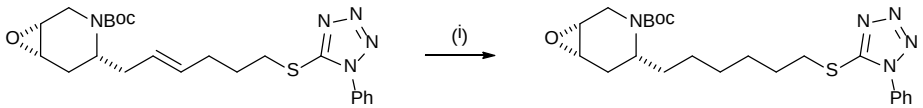



**187** **193** **192**, 75%, >95:5 dr

**Scheme 70:** *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 1 h, to rt, 1 h.

## 5.5 Alkene hydrogenation

Hydrogenation of the C=C bond within sulfide **192** with Adam's catalyst under 5 atmospheres of hydrogen gave saturated sulfide **80** in 80% yield. Saturated sulfide **80** was a known compound from the previous synthetic study by Davies and Taylor which was accessed in 18% over 4 steps from aldehyde **75**.[1] This new route enabled the same transformation to be achieved in only 2 steps with an overall yield of 60% (Scheme 71).




**192** **80**, 80%

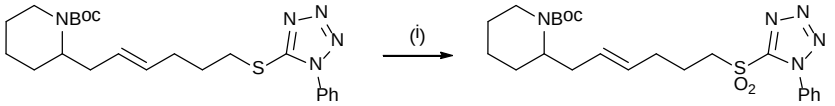
**Scheme 71:** *Reagents and conditions*: (i) 20% $PtO_2$, $H_2$ (5 atm), EtOH, rt, 4 h.

However, upon scale-up of this reaction to quantities of 1 gram or larger, the reaction conversion decreased, and longer reaction times were required. To obtain full conversion it was often necessary to increase the reaction time to 24–48 h, and to use up to 40% $PtO_2$ catalyst, while yields would often fall below 80%. Other routes that might avoid alkene hydrolysis in the presence of a sulfide were therefore investigated.

## 5.6 Sulfide oxidation

It was decided to reverse the order of the alkene hydrogenation and sulfide oxidation steps, by attempting the oxidation step first. This would require the use of an oxidant that would not

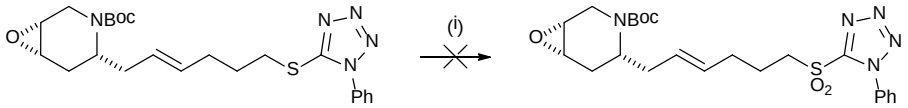
oxidise the alkene at the C(2') position of sulfide **192**. This eliminated the use of *m*-CPBA, the oxidant successfully used to oxidise model sulfide **198**. Hydrogen peroxide and ammonium molybdate was successfully trialled on the model system, sulfide **197**, giving an isolated yield of 70% of sulfone **200** (Scheme 72).




**197** **200**, 70%

**Scheme 72:** *Reagents and conditions*: (i) 30% aq. $H_2O_2$, $(NH_4)_6Mo_7O_{24}$•$4H_2O$, EtOH, 0 °C to rt, 16 h.

However, when these conditions were used on sulfide **192**, they led to a complex mixture of products. $^1$H NMR spectroscopic analysis of these products showed significant changes to the resonances associated with the piperidine epoxide, suggesting that this functionality had not survived these reaction conditions (Scheme 73). An alternative route was therefore sought.

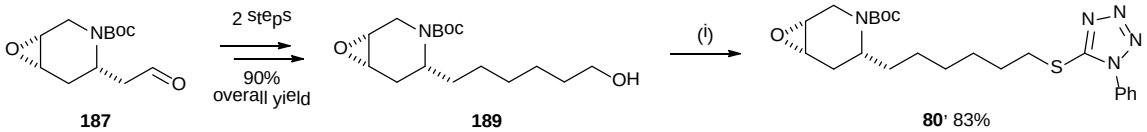



**192** **201**

**Scheme 73:** *Reagents and conditions*: (i) 30% aq. $H_2O_2$, $(NH_4)_6Mo_7O_{24}$•$4H_2O$, EtOH, 0 °C to rt, 16 h.

### 5.7 Alternative route via Wittig olefination at C(2')–(3')

During the studies into side chain installation via C(7')–(8') cross-coupling (*vida supra*, Chapter 4), alcohol **189** was formed in 90% yield over 2 steps from aldehyde **187**, utilising a Wittig olefination to form the C(2')=(3') bond. Alcohol **189** was now investigated as a possible precursor to sulfide **80**. The transformation of **189** to **80** was effected using a Mitsunobu displacement with PTSH under literature conditions[4] to give sulfide **80** in 83% yield (Scheme 74).




**187** **189** **80**, 83%

**Scheme 74:** *Reagents and conditions*: (i) PTSH, DEAD, $PPh_3$, THF, 0 °C to rt, 16 h.

When compared with the two step route from aldehyde **187** to sulfide **80** in the previous strategy, which was reliant on Julia-Kocienski olefination and proceeded in an overall yield of 60%, this new three step protocol yielded the product **80** in an improved overall yield of 75%. In addition to this increased yield, the steps in the Mitsunobu route proved to be more scalable, and gave reliably high yields in each case (Figure 16).

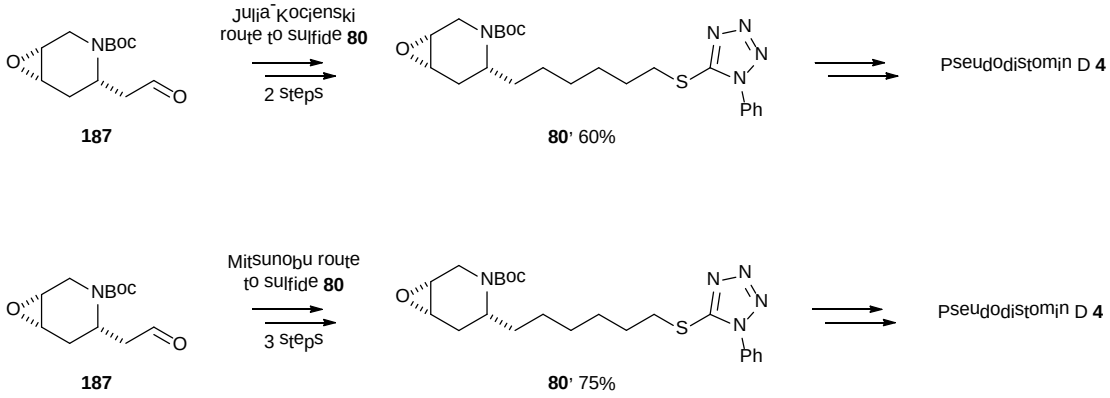
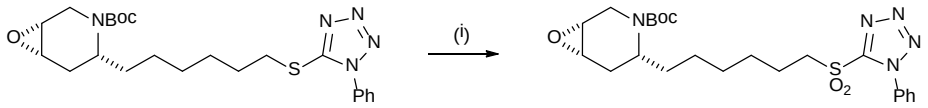



**Figure 16:** Comparison of the two routes to sulfide **80**.

### 5.8 Sulfide oxidation

Oxidation of saturated sulfide **80** with *m*-CPBA gave incomplete crude mass return and an isolated yield of 71% for sulfone **81** after flash column chromatography. The oxidation was repeated with the addition of satd aq $NaHCO_3$ to buffer the pH of the reaction media, but these conditions proved to be detrimental to the crude mass return, and $^1H$ NMR spectroscopic analysis of the crude reaction mixture revealed the presence of a mixture of products. Flash column chromatography gave an isolated yield of only 42% of the desired sulfone **81** in this case. Due to the incomplete crude mass return seen after the aqueous work-up of the unbuffered *m*-CPBA oxidation of sulfide **80**, it was decided to investigate alternative work-up conditions. Cyclohexene was added to the reaction mixture to quench excess *m*-CPBA before the removal of volatiles *in vacuo*. The residues were dissolved in $Et_2O$ and washed with satd aq $NaHCO_3$ to remove *m*-CBA, before purification by flash column chromatography. This allowed the isolation of **81** in a slightly improved yield of 78% (Scheme 75).

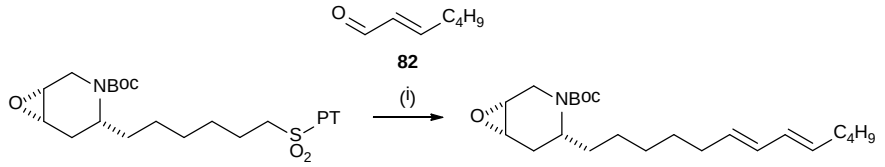



**80** **81**, 78%

**Scheme 75:** *Reagents and conditions*: (i) *m*-CPBA, $CH_2Cl_2$, rt, 16 h.

### 5.9 C(6')–C(7') Julia-Kocienski olefination

With an improved route to sulfone **81** available, the previously reported Julia-Kocienski olefination with *trans*-hept-2-enal **82** was performed to give a 90:10 mixture of (*E*,*E*):(6'*Z*,8'*E*) geometric isomers of **83**. These compounds were known from the previous work by Davies and Taylor,[1] and their assignment was supported by $^3J$ $^1$H NMR coupling constant analysis which confirmed the identity of the minor isomer. These alkenes proved to be inseparable by flash column chromatography and were therefore isolated as a mixture in 77% combined yield. Flash column chromatography on silver nitrate doped silica[5] was also used to attempt to separate the diastereoisomers, but without success (Scheme 76).



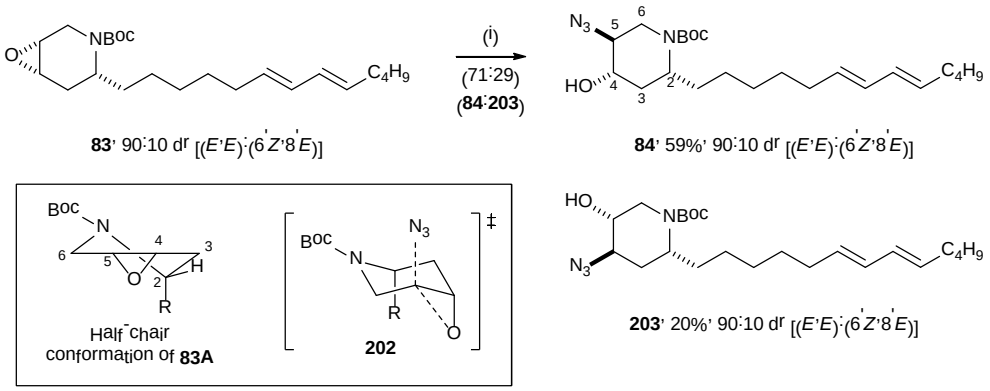

**81** **83**, 77%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]

**Scheme 76:** *Reagents and conditions*: (i) KHMDS, THF, −78 °C, 15 min.

### 5.10 Azide epoxide opening

With the side chain installed, the amino alcohol stereochemistry of the pseudodistomin D head group could be set with a regioselective ring-opening of epoxide **83**. Epoxide **83** was treated with $NaN_3$ in DMSO at 80 °C; analysis of the crude reaction mixture indicated that two products were formed in the ratio 71:29. Careful flash column chromatography enabled isolation of the major product **84** in 59% yield, and the minor product **203** in 20% yield. The identity of the major product was determined by $^1$H, $^{13}$C, COSY and HMBC NMR spectroscopic analyses, which allowed the regiochemistry of **84** to be assigned. The stereochemistry was inferred from $^1$H NMR $^3J$ coupling constant analysis of the protons around the piperidine ring: C(2)*H*, C(4)*H* and C(5)*H* showed $^3J$ coupling constants consistent with them occupying equatorial positions of a chair conformation of the piperidine ring

(Figure 17). This stereochemistry was consistent with the expected result of the $S_N2$-type ring-opening of epoxide **83** proceeding via half-chair conformation **83A**, in which 1,2-strain between the *N*-Boc and C(2)-substituent is minimised with the C(2)-substituent adopting a pseudo-axial position.[6] Attack of the azide ion at C(5) results in a chair-like transition state **202** leading to **84**. The regiochemistry of the minor product **203** was ascertained from $^1$H, $^{13}$C, COSY and HMQC NMR spectroscopic analysis. Peak overlap and broadening in the $^1$H NMR spectrum of **203** due to its rotameric nature, precluded any meaningful coupling constant analysis to aid with stereochemical assignment, and therefore **203** was tentatively assigned as the alternative regioisomer resulting from $S_N2$-type epoxide ring-opening upon attack of the azide ion at the C(4) position within **83** (Scheme 77).




**Scheme 77:** *Reagents and conditions*: (i) $NaN_3$, $NH_4Cl$, DMSO, 80 °C, 16 h.

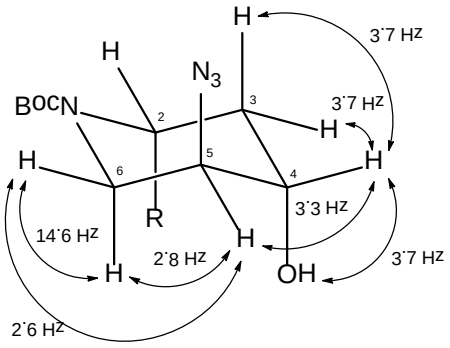
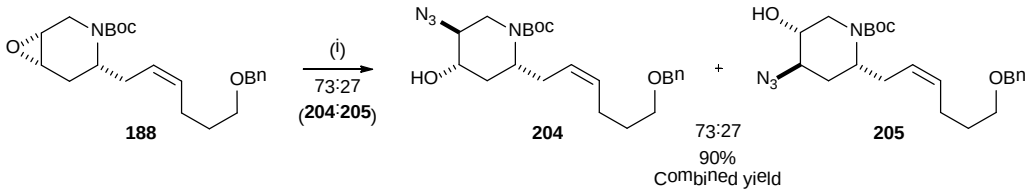



**Figure 17:** $^3J$ $^1$H NMR Coupling constant analysis of **84**.

During the course of these studies it was of interest to investigate the regioselectivity of ring-opening of other epoxide intermediates to determine if a regioisomeric ratio better than 71:29 could be obtained. *O*-Benzyl protected alcohol **188** was subjected to the above conditions, which led to a 73:27 mixture of regioisomers **204** and **205**. Flash column chromatography was

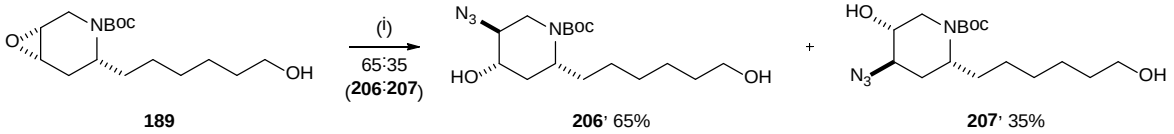
unsuccessful in separating these products which were isolated in 90% combined yield (73:27 ratio). The regio- and stereochemistry within major and minor products **204** and **205** were assigned by comparison with **84** and **203**, respectively, which exhibited very similar $^1$H NMR resonances associated with the protons around the piperidine ring (Scheme 78).




**188** **204** **205**

**Scheme 78:** *Reagents and conditions*: (i) $NaN_3$, $NH_4Cl$, DMSO, 80 °C, 16 h.

Epoxide opening of **189** was also attempted with $NaN_3$ under the same conditions, which gave a 65:35 crude ratio of two products, assigned as regioisomers **206** and **207**. The desired azide **206** was isolated in 65% yield via flash column chromatography. The other regioisomer **207** was recovered in 35% yield. Again, the regio- and stereochemical assignments of major and minor products **206** and **207** were made by comparison with **84** and **203**, respectively (Scheme 79).



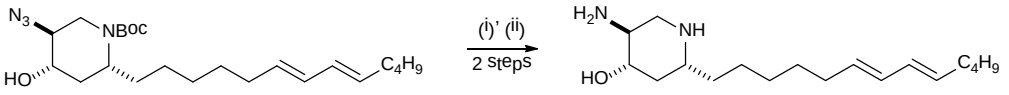

**189** **206**, 65% **207**, 35%

**Scheme 79:** *Reagents and conditions*: (i) $NaN_3$, $NH_4Cl$, DMSO, 80 °C, 16 h.

### 5.11 Finalising the synthesis of pseudodistomin D

Azide **84** was then treated with $PPh_3$ at rt for 16 h followed by addition of water before being heated at 50 °C for a further 16 h, under a two-step Staudinger reduction.[1] The crude reaction mixture was heated in methanolic HCl at 60 °C for 3 h to affect an *N*-Boc deprotection. The reaction mixture was then passed through a commercial silica-based 'capture-release' column impregnated with sulfonic acid residues. $PPh_3$ impurities were then eluted from the column with MeOH and $CH_2Cl_2$, before the product **4** was eluted using methanolic ammonia. The product was then purified by careful flash column chromatography and characterised as the free-base of pseudodistomin D **4** which was obtained in 51% over 2 steps, in an isomeric ratio

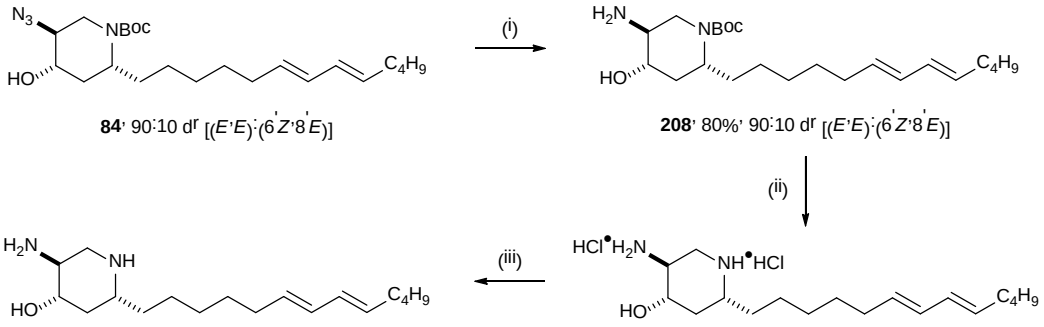
of (*E*,*E*):(6'*Z*,8'*E*) 90:10 dr. All data matched those previously reported for the sample isolated from the natural source[7] and the sample obtained via total synthesis[8] (Scheme 80).




**84**, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)] **4**, 51%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]

**Scheme 80:** *Reagents and conditions*: (i) $PPh_3$, THF, rt, 16 h, then $H_2O$, 50 °C, 16 h; (ii) HCl, MeOH, 60 °C, 3 h.

The use of polymer supported $PPh_3$ in the Staudinger reduction of azide **84** enabled the convenient isolation of primary amine **208** after careful flash column chromatography. This allowed amine **208** to be isolated and characterised in 80% yield. The use of pure **208** in a subsequent *N*-Boc deprotection step using methanolic HCl resulted in a 79% yield of the HCl salt of pseudodistomin D **4**•2HCl. Pseudodistomin D free base **4** was then isolated in 92% yield after **4**•2HCl was washed with 2.0 M aq KOH (Scheme 81).



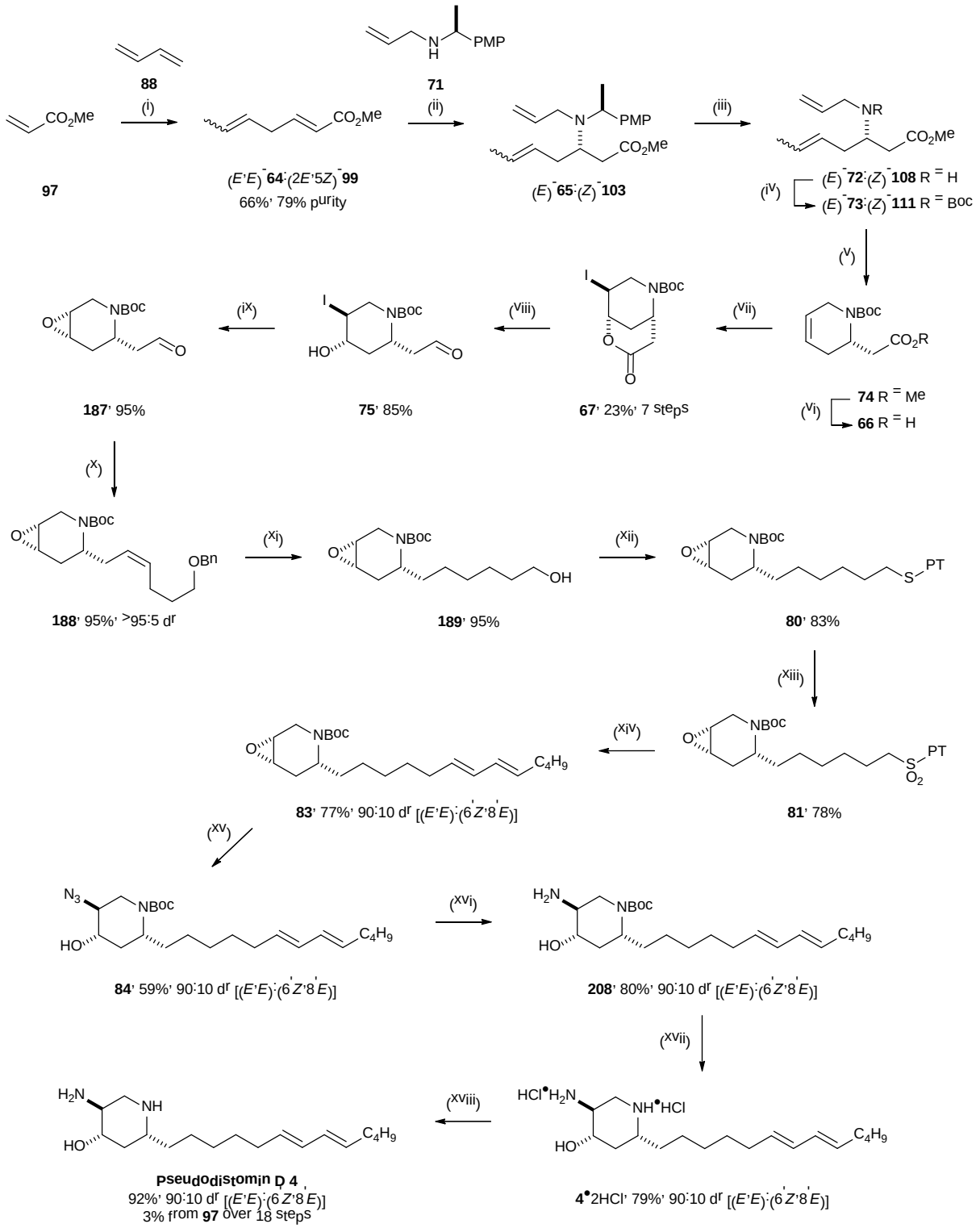

**84**, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)] **208**, 80%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]

**4**, 92%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)] **4**•2HCl, 79%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]

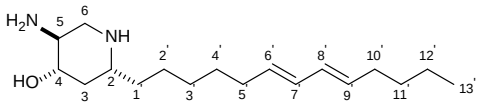
**Scheme 81:** *Reagents and conditions*: (i) polymer-supported $PPh_3$, THF/$H_2O$, rt, 16 h; (ii) HCl, MeOH, 60 °C, 1 h; (iii) 2.0 M aq KOH.

## 5.12 Conclusion

This completed the synthesis of pseudodistomin D **4** in 3% overall yield, >90:10 dr and >99% ee over a total of 18 steps from methyl acrylate **97** (Scheme 82). The spectroscopic data, including $[\alpha]_D$, $^1H$ and $^{13}C$ NMR, of this sample of pseudodistomin D **4** {$[\alpha]_D^{25}$ +5.6 (*c* 0.3 in MeOH)}[9] were identical to those for the natural sample {$[\alpha]_D^{25}$ +5 (*c* 0.26 in MeOH)},[7] and those reported by Trost and Fandrick in their synthesis {$[\alpha]_D^{25}$ +6 (*c* 0.2 in MeOH)}[8] (Figure 18 and 19).

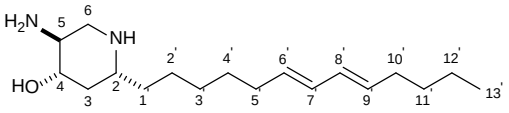



**Scheme 82:** *Reagents and conditions*: (i) $Pd_2(dba)_3$•$CHCl_3$, $HBF_4$, $PBu_3$, 80 °C, 5 h, sealed vessel; (ii) BuLi, THF, –78 °C, 2 h; (iii) $Et_3SiH$, $HCO_2H$, 90 °C, 16 h; (iv) $Boc_2O$, $NaHCO_3$, MeOH, rt, 16 h; (v) Grubbs I, $CH_2Cl_2$, rt, 12 h; (vi) LiOH, THF/$H_2O$, 50 °C, 16 h; (vii) $I_2$, $NaHCO_3$, $CH_3CN$, −20 °C, 2 h, rt, 20 h; (viii) DIBAL-H, $CH_2Cl_2$, −78 °C, 1.5 h; (ix) 1.0 M aq NaOH, $CH_2Cl_2$, rt, 1 h; (x) **168**, NaHMDS, THF, 0 °C to rt, 40 min, then **187**, 0 °C to rt, 16 h; (xi) $H_2$ (1 atm), $Pd(OH)_2$/C, EtOAc, rt, 2 h; (xii) PTSH, DEAD, $PPh_3$, THF, 0 °C to rt, 16 h; (xiii) *m*-CPBA, $CH_2Cl_2$, rt, 48 h; (xiv) KHMDS, THF, −78 °C, 15 min; (xv) $NaN_3$, $NH_4Cl$, DMSO, 80 °C, 16 h; (xvi) polymer-supported $PPh_3$, THF/$H_2O$, rt, 16 h; (xvii) HCl, MeOH, 60 °C, 1 h; (xviii) 2.0 M aq KOH.



| | Sample from natural source[7] | | | Trost and Fandrick[8] | | | This work[9] | | |
|---|---|---|---|---|---|---|---|---|---|
| Proton | $\delta_H$ (ppm) | Multiplicity | Coupling constant (Hz) | $\delta_H$ (ppm) | Multiplicity | Coupling constant (Hz) | $\delta_H$ (ppm) | Multiplicity | Coupling constant (Hz) |
| C(2)*H* | 2.50 | 1H, m | | 2.52–2.58 | 1H, m | | 2.52–2.61 | 1H, m | |
| C(3)$H_A$ | 1.07 | 1H, ddd | 12.1, 11.3, 11.1 | 1.09 | 1H, ddd | 11.4, 11.4, 11.4 | 1.12 | 1H, ddd | 12.2, 11.7, 11.7 |
| C(3)$H_B$ | 1.96 | 1H, ddd | 12.1, 4.6, 4.6 | 1.98 | 1H, ddd | 12.7, 4.7, 2.5 | 2.00 | 1H, ddd | 12.2, 4.6, 2.4 |
| C(4)*H* | 3.20 | 1H, ddd | 11.1, 9.5, 4.6 | 3.24 | 1H, ddd | 11.2, 9.3, 4.6 | 3.23–3.29 | 1H, m | |
| C(5)*H* | 2.50 | 1H, m | | 2.52–2.58 | 1H, m | | 2.52–2.61 | 1H, m | |
| C(6)$H_A$ | 2.31 | 1H, dd | 12.1, 10.9 | 2.35 | 1H, dd | 12.1, 11.1 | 2.37 | 1H, dd | 12.0, 11.2 |
| C(6)$H_B$ | 3.04 | 1H, dd | 12.1, 4.5 | 3.07 | 1H, dd | 12.2, 4.5 | 3.09 | 1H, dd | 12.0, 4.6 |
| C(1')$H_2$ | 1.35 | 2H, m | | 1.27–1.47 | 2H, m | | 1.28–1.52 | 2H, m | |
| C(2')$H_2$ | 1.35 | 2H, m | | 1.27–1.47 | 2H, m | | 1.28–1.52 | 2H, m | |
| C(3')$H_2$ | 1.35 | 2H, m | | 1.27–1.47 | 2H, m | | 1.28–1.52 | 2H, m | |
| C(4')$H_2$ | 1.35 | 2H, m | | 1.27–1.47 | 2H, m | | 1.28–1.52 | 2H, m | |
| C(5')$H_2$ | 2.04 | 2H, dt | 7.1, 7.0 | 2.02–2.08 | 2H, m | | 2.04–2.11 | 2H, m | |
| C(6')*H* | 5.53 | 1H, dm | 14.4 | 5.47–5.56 | 1H, m | | 5.51–5.59 | 1H, m | |
| C(7')*H* | 5.96 | 1H, dm | 14.4 | 5.93–6.01 | 1H, m | | 5.96–6.04 | 1H, m | |
| C(8')*H* | 5.96 | 1H, dm | 14.4 | 5.93–6.01 | 1H, m | | 5.96–6.04 | 1H, m | |
| C(9')*H* | 5.53 | 1H, dm | 14.4 | 5.47–5.56 | 1H, m | | 5.51–5.59 | 1H, m | |
| C(10')$H_2$ | 2.04 | 2H, dt | 7.1, 7.0 | 2.02–2.08 | 2H, m | | 2.04–2.11 | 2H, m | |
| C(11')$H_2$ | 1.35 | 2H, m | | 1.27–1.47 | 2H, m | | 1.28–1.52 | 2H, m | |
| C(12')$H_2$ | 1.35 | 2H, m | | 1.27–1.47 | 2H, m | | 1.28–1.52 | 2H, m | |
| C(13')$H_3$ | 0.90 | 3H, t | 7.1 | 0.90 | 3H, t | 7.1 | 0.93 | 3H, t | 7.1 |

**Figure 18:** Comparison of the $^1$H NMR shifts of pseudodistomin D **4** from three different sources.



| | Sample from natural source[7] | Trost and Fandrick[8] | This work[9] |
|---|---|---|---|
| Carbon | $\delta_C$ (ppm) | $\delta_C$ (ppm) | $\delta_C$ (ppm) |
| *C*(2) | 56.7 | 56.8 | 56.7 |
| *C*(3) | 41.2 | 41.2 | 41.1 |
| *C*(4) | 75.5 | 75.0 | 75.1 |
| *C*(5) | 56.4 | 56.3 | 56.3 |
| *C*(6) | 51.9 | 51.4 | 51.4 |
| *C*(1') | 37.3 | 37.2 | 37.1 |
| *C*(2') | 26.9 | 27.0 | 26.9 |
| *C*(3') | 30.3 | 30.4 | 30.3 |
| *C*(4') | 30.5 | 30.6 | 30.5 |
| *C*(5') | 33.3 | 33.5 | 33.3 |
| *C*(6') | 132.9 | 133.0 | 132.9 |
| *C*(7') | 132.0 | 132.1 | 132.0 |
| *C*(8') | 131.8 | 132.0 | 131.8 |
| *C*(9') | 133.1 | 133.2 | 133.1 |
| *C*(10') | 33.5 | 33.6 | 33.5 |
| *C*(11') | 32.8 | 33.0 | 32.9 |
| *C*(12') | 23.3 | 23.4 | 23.3 |
| *C*(13') | 14.3 | 14.4 | 14.3 |

**Figure 19:** Comparison of the $^{13}$C NMR shifts of pseudodistomin D **4** from three different sources.

### 5.13 Future work

Future work in this project could include the extension of this methodology to the synthesis of other members of the pseudodistomin family. It is thought that the 2,4,5-substituted piperidine ring within lactone **209**[10] represents a useful starting material for the synthesis of the other pseudodistomins, all of which contain a 2,4,5-substituted piperidine ring motif. The other pseudodistomins all display *cis*-vicinal amino alcohol motifs, which could result from strategies involving tethered nucleophiles to control the stereochemical outcome of a displacement reaction.[11] For example, a possible approach to the stereochemistry of pseudodistomins A **1**, B **2** and F **6** could entail the formation of **210** from **209**, followed by activation of the alcohol as a leaving group to facilitate cyclisation of the carbonate carbonyl onto the C(4) position of the piperidine within **211**.[12] A route to pseudodistomins C **3** and E **5** could involve formation of a bromohydrin, available from **209** via reductive or hydrolytic lactone opening,[1] followed by reaction with an isocyanate. The resultant carbamate **212** could then displace the bromide ion and cyclise, directing nitrogen functionality onto the C(5) position of the piperidine ring, providing an oxozolidin-2-one which could be hydrolysed to give the desired substitution pattern.[13] The side-chains of pseudodistomins A **1**, B **2** and E **5** could be installed in an analogous manner to that of pseudodistomin D **4**, while those of pseudodistomins C **3** and F **6** could possibly be installed using a palladium-catalysed cross-coupling strategy (Figure 20).

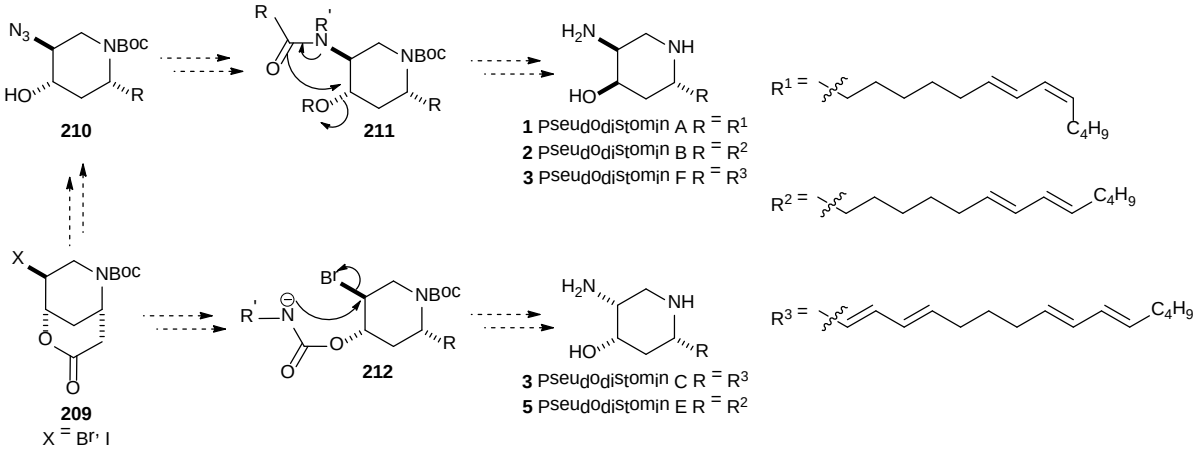



**Figure 20**: Possible strategies for the synthesis of pseudodistomins A **1**, B **2**, C **3**, E **5** and F **6**.

## 5.14 References and notes

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## 6.1 General experimental

**General techniques:** Reactions involving air or moisture sensitive reagents were carried out under nitrogen using standard vacuum line techniques. All glassware for these reactions was flame-dried and allowed to cool under vacuum. Reactions described as being performed at −78 °C were cooled by means of an acetone/dry ice bath whilst reactions described as being performed between −78 °C and 0 °C were cooled by means of an acetone bath incompletely saturated with dry ice, or an ice-salt water bath, as appropriate. Organic layers were dried with $MgSO_4$.

**Solvents:** Solvents were dried by passing them through a column of basic alumina, according to the procedure detailed by Grubbs and co-workers.[1] In the case of $Et_2O$ and $CH_2Cl_2$ this was Brockman 1 standard grade *ca*. 150 mesh alumina, whilst for THF it was Alcoa Grade DD-2 alumina. In some cases $Et_2O$ and THF were distilled from sodium/benzophenone ketyl radical under nitrogen prior to use. $H_2O$ was purified by either Millipore Mill-Q® or Elix® UV-10 systems. Solvent ratios are quoted as v/v.

**Reagents:** BuLi was supplied as a solution in hexanes (Aldrich) and titrated against diphenylacetic acid prior to use. *m*-CPBA was supplied as a damp solid (70–77% with $H_2O$) (Aldrich) and titrated prior to use.[2] All other reagents were used as supplied, without further purification.

**Chromatography:** Column chromatography was performed either isocratically using a glass column on silica gel (Kieselgel 60), or via gradient elution using a Biotage SP4 flash chromatography platform. Thin layer chromatography was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 $F_{254}$. Plates were visualised either by UV light (254 nm) or potassium permanganate (1% in 2% NaOH solution, containing 7% potassium carbonate).

**Melting points:** Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected.

**Polarimetry:** Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water jacketed 10 cm cell, with concentrations (*c*) given in g/100 $cm^3$, solvent and temperature as recorded. Specific rotations are quoted in units of $10^{-1}$ deg $cm^2$ $g^{-1}$.

**Infra-red spectroscopy:** Infra-red spectra were recorded as a film, KBr disc, or ATR module using a Bruker Tensor 27 FT-IR spectrometer, with selected characteristic peaks are reported in $cm^{-1}$.

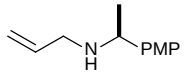
**NMR spectroscopy:** $^{1}H$ NMR spectra were recorded on Bruker AVANCE DPX-400 (400 MHz), AV-400 (400 MHz), DRX-500 (500 MHz) and AV-500 (500 MHz) spectrometers and $^{13}C$ NMR spectra were recorded at 100 MHz on the Bruker AVANCE AV-400 spectrometer and at 125 MHz on the Bruker AVANCE DRX-500 and AV-500 spectrometers. Chemical shifts (δ) are quoted in ppm and referenced using residual solvent signals. Coupling constants (*J*) are measured in Hz. The spectra recorded on the Bruker AVANCE DRX-500 and AV-500 spectrometers were obtained by Dr. B. Odell of the Chemistry Research Laboratory, University of Oxford.

**Mass spectrometry:** Low resolution mass spectra (*m/z*) were recorded on either a VG Autospec instrument ($CI^{+}$, $NH_3$), a VG MassLab 20-250 instrument (ESI) or a Micromass Platform I instrument (ESI). Major peaks are listed with intensities quoted as percentages of the principal peak. Accurate mass measurements were recorded by Dr. J. McCullagh, Mr. C. Sparrow, Mr. L. Gong or Mr. R. Procter of the Chemistry Research Laboratory. Accurate Mass ESI measurements were run on a Bruker MicroTof and were internally calibrated with polyalanine in positive and negative modes. Accurate mass ESI measurements were also carried out on a Micromass LCT instrument using a lock-spray source. Positive ion spectra were calibrated relative to PEG using tetraoctylammonium bromide as a lock mass. GC Tof measurements ($CI^{+}$) were run on a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m x 0.25 mm), using amyl acetate as a lock mass.

**Diastereoisomeric ratios:** Diastereoisomeric ratios were assessed by peak integration of the corresponding $^{1}H$ NMR spectra.

## 6.2 Experimental for Chapter 2

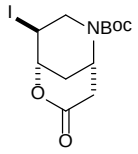
### (*S*)-*N*-Allyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 71




*Method A*: BuLi (1.45 M in hexanes, 199 mL, 289 mmol) was added dropwise to a stirred solution of **94** (39.8 g, 263 mmol) in THF (480 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. A solution of freshly distilled allyl bromide **93** (22.7 mL, 263 mmol) in THF (20 mL) was then added dropwise over 30 min, and the reaction mixture was then allowed to warm to rt over 16 h. Satd aq $NH_4Cl$ (250 mL) and brine (120 mL) were added sequentially, the aqueous layer extracted with EtOAc (3 × 120 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (eluent 30–40 °C petrol increased to 30–40 °C petrol/$Et_2O$/$Et_3N$, 90:9:1) gave **71** as a colourless oil (48.6 g, 61%, >99% ee);[3,4] $[\alpha]_D^{22}$ +12.3 (*c* 1.0 in $CHCl_3$); {lit.[3] $[\alpha]_D^{25}$ +11.0 (*c* 1.0 in $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.55 (1H, br s, N*H*), 3.05–3.16 (2H, m, NC*H*$_2$CH=$CH_2$), 3.73–3.89 (4H, m, C(α)*H*, O*Me*), 5.04–5.19 (2H, m, $NCH_2CH$=C*H*$_2$), 5.84–5.96 (1H, m, $NCH_2$C*H*=$CH_2$), 6.84–6.93 (2H, m, *Ar*), 7.20–7.31 (2H, m, *Ar*).

*Method B*: BuLi (2.34 M in hexanes, 156 mL, 364 mmol) was added dropwise to a stirred solution of **94** (50.0 g, 331 mmol) in THF (600 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. A solution of freshly distilled allyl bromide **93** (28.6 mL, 331 mmol) in THF (25 mL) was then added dropwise over 30 min, and the reaction mixture was allowed to warm to rt over 16 h. Satd aq $NH_4Cl$ (310 mL) and brine (150 mL) were added sequentially, the aqueous layer was extracted with EtOAc (3 × 150 mL), and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in $Et_2O$ (400 mL) and the resultant solution was extracted with 10% aq citric acid (2 × 500 mL). The combined aqueous extracts were neutralized with solid $NaHCO_3$, extracted with $Et_2O$ (3 × 200 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give **71** as a pale yellow oil (53.8 g, 85%, >99% ee);[3,4] $[\alpha]_D^{22}$ +11.5 (*c* 1.0 in $CHCl_3$).

**(1*S*,5*R*,8*S*)-*N*(6)-*tert*-Butoxycarbonyl-8-iodo-2-oxa-6-azabicyclo[3.3.0]octan-3-one 67**




*Step 1*: Methyl acrylate **97** (20.9 mL, 232 mmol), $Pd_2(dba)_3$•$CHCl_3$ (480 mg, 0.46 mmol), $PBu_3$ (0.23 mL, 0.92 mmol) and $HBF_4$ (6.15 M in $Et_2O$, 0.30 mL, 1.84 mmol) were added to a thick-walled glass vessel under a nitrogen atmosphere. The solution was cooled to −20 °C and condensed 1,3-butadiene **88** (20.3 mL, 232 mmol) was added to the vessel, which was subsequently sealed, and the resultant mixture was heated at 80 °C for 5 h. The reaction vessel was then cooled to 0 °C and opened to permit evaporation of any remaining 1,3-butadiene **88**. The reaction mixture was then filtered through a plug of Celite® (eluent $Et_2O$) and concentrated *in vacuo*. Purification via distillation under reduced pressure gave a 63:16:13:8 mixture of **64**, **99**, **100** and **101** as a colourless oil (21.5 g, 66% combined yield). Data for **64**:[5] $\delta_H$ (400 MHz, $CDCl_3$) 1.62–1.66 (3H, m, C(7)$H_3$), 2.81–2.86 (2H, m, C(4)$H_2$), 3.74 (3H, s, O*Me*), 5.37–5.58 (2H, m, C(5)*H*, C(6)*H*), 5.83 (1H, d, *J* 15.7, C(2)*H*), 6.96 (1H, dt, *J* 15.7, 6.5, C(3)*H*). Data for **99**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 1.57–1.60 (3H, m, C(7)$H_3$), 2.89–2.94 (2H, m, C(4)$H_2$); $\delta_C$ (100 MHz, $CDCl_3$) 12.8 (*C*(7)), 29.5 (*C*(4)), 51.3 (O*Me*), 120.9 (*C*(2)), 124.9 (*C*(6)), 126.9 (*C*(5)), 147.3 (*C*(3)), 167.0 (*C*(1)). Data for **100**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 1.02 (3H, t, *J* 7.5, C(7)$H_3$), 2.13–2.23 (2H, m, C(6)$H_2$), 6.02–6.21 (2H, m, C(4)*H*, C(5)*H*), 7.19–7.29 (1H, m, C(3)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 12.7 (*C*(7)), 26.0 (*C*(6)), 51.3 (O*Me*), 118.7 (*C*(2)), 127.3 (*C*(4)), 145.3, 146.1 (*C*(3), (*C*(5)), 167.0 (*C*(1)). Data for **101**: $\delta_H$ (400 MHz, $CDCl_3$) 2.15–2.22 (2H, m, C(5)$H_2$), 2.24–2.31 (2H, m, C(4)$H_2$), 3.69 (3H, s, O*Me*), 4.95–5.05 (2H, m, C(7)$H_2$), 5.76 (1H, ddt, *J* 16.9, 10.4, 6.3, C(6)*H*), 5.81 (1H, dt, *J* 15.8, 1.5, C(2)*H*), 6.93 (1H, dt, *J* 15.8, 6.7, C(3)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 31.4, 32.0 (*C*(4), *C*(5)), 51.3 (O*Me*), 115.5 (*C*(7)), 121.2 (*C*(2)), 136.9 (*C*(6)), 148.5 (*C*(3)), 166.9 (*C*(1)).

*Step 2*: BuLi (2.31 M in hexanes, 33.5 mL, 77.5 mmol) was added dropwise over 5 min to a stirred solution of **71** (15.3 g, 80.0 mmol) in THF (140 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 30 min. A solution of a 63:16:13:8 mixture of **64**, **99**, **100**

and **101** (7.00 g, 49.9 mmol) in THF (35 mL) was added via canula over 10 min and the reaction mixture was then stirred for 2 h at −78 °C. Satd aq $NH_4Cl$ (30 mL) was added, the aqueous layer was extracted with $Et_2O$ (3 × 175 mL), and the combined organic extracts were washed with 10% aq citric acid (280 mL), then extracted with 1.0 M aq HCl (280 mL). The aqueous extract was then extracted with $CH_2Cl_2$ (2 × 140 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (280 mL), then dried and concentrated *in vacuo* to give a mixture of **65**, **103**, **104** and **105** as a pale yellow oil (10.3 g).[6,7,8] Data for **65**: $\delta_H$ (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.0, C(α)*Me*), 1.65 (3H, d, *J* 5.3, C(7)$H_3$), 1.91–2.00 (1H, m, C(4)$H_A$), 2.20–2.29 (3H, m, C(2)$H_2$, C(4)$H_B$), 3.11 (1H, ddt, *J* 15.3, 6.2, 1.4, NC$H_A$CH=$CH_2$), 3.19 (1H, ddt, *J* 15.3, 6.2, 1.4, NC$H_A$CH=$CH_2$), 3.34–3.41 (1H, m, C(3)*H*), 3.57 (3H, s, $CO_2$*Me*), 3.80 (3H, s, ArO*Me*), 3.93 (1H, q, *J* 6.9, C(α)*H*), 5.01–5.18 (2H, m, $NCH_2$CH=C$H_2$), 5.33–5.49 (2H, m, C(5)*H*, C(6)*H*), 5.82 (1H, ddt, *J* 17.2, 10.1, 6.2, $NCH_2$C*H*=$CH_2$), 6.83 (2H, d, *J* 8.6, *Ar*), 7.22 (2H, d, *J* 8.6, *Ar*). Data for **104**: $\delta_H$ (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.5, C(7)$H_3$), 1.34 (3H, d, *J* 6.8, C(α)*Me*), 2.05 (2H, dq, *J* 7.1, 7.1, C(6)$H_2$), 2.36 (1H, dd, *J* 14.2, 7.8, C(2)$H_A$), 2.52 (1H, dd, *J* 14.2, 7.3, C(2)$H_B$), 3.07–3.23 (3H, m, C(3)*H*, NC$H_2$CH=$CH_2$), 3.58 ($CO_2$*Me*), 3.80 (ArO*Me*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 5.00–5.17 (2H, m, $NCH_2$CH=C$H_2$), 5.33–5.49 (2H, m, C(4)*H*, C(5)*H*), 5.73–5.87 (1H, m, $NCH_2$C*H*=$CH_2$), 6.84 (2H, m, *J* 8.6, *Ar*), 7.27 (2H, d, *J* 8.6, *Ar*); $\delta_C$ (100 MHz, $CDCl_3$) 13.7 (*C*(7)), 17.8 (C(α)*Me*), 25.6 (*C*(6)), 39.0 (*C*(2)), 49.3 ($NCH_2$CH=$CH_2$), 51.3 ($CO_2$*Me*), 55.2 (ArO*Me*), 56.1, 56.8 (*C*(3), *C*(α)), 113.3 (*Ar*), 115.6 ($NCH_2$CH=*C*$H_2$), 128.3 (*C*(4)), 128.6 (*Ar*), 134.1 (*C*(5)), 137.1 (*Ar*), 138.8 ($NCH_2$*C*H=$CH_2$), 158.2 (*Ar*), 172.4 (*C*(1)). Data for **105**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 4.91–5.00 (1H, m, C(7)$H_A$).

*Step 3*: $Et_3SiH$ (13.3 mL, 83.0 mmol) was added to a stirred solution of **65**, **103**, **104** and **105** (18.3 g)[8] in $HCO_2H$ (350 mL) and the resultant mixture was heated at 90 °C for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in $H_2O$ (800 mL), and the resultant mixture was washed with $E_2O$ (3 × 400 mL), neutralised with solid $NaHCO_3$ until pH 7 was reached, and extracted with $CH_2Cl_2$ (3 × 400 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a mixture of **72**, **108**, **109** and **110** as a pale yellow oil (10.1 g).[6,9,10] Data for **72**: $\delta_H$ (400 MHz, $CDCl_3$) 1.61 (1H, br s, N*H*), 1.64–

1.74 (3H, m, C(7)$H_3$), 2.13–2.25 (2H, m, C(4)$H_2$), 2.43 (2H, app d, *J* 6.1, C(2)$H_2$), 2.99–3.10 (1H, m, C(3)*H*), 3.24–3.31 (2H, m, NC$H_2$CH=$CH_2$), 3.69 (3H, s, O*Me*), 5.06–5.14 (1H, m, CH=C$H_A$), 5.14–5.23 (1H, m, NCH$_2$CH=C$H_B$), 5.32–5.58 (2H, m, C(5)*H*, C(6)*H*), 5.82–5.96 (1H, m, NCH$_2$C*H*=CH$_2$). Data for **109**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 0.99 (3H, t, *J* 7.5, C(7)$H_3$), 2.00–2.09 (2H, m, C(6)$H_2$), 3.44–3.51 (1H, m, C(3)*H*), 5.59–5.68 (1H, m, C(5)*H*). Data for **110**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 2.00–2.09 (2H, m, C(4)$H_2$), 4.91–5.00 (1H, m, C(7)$H_A$).

*Step 4*: $NaHCO_3$ (4.16 g, 49.5 mmol) and $Boc_2O$ (10.3 g, 47.3 mmol) were added to a stirred solution of **72**, **108**, **109** and **110** (8.84 g)[10] in MeOH (600 mL) and the resultant mixture was stirred at rt for 16 h, then filtered and concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (600 mL), and the resultant solution was sequentially washed with $H_2O$ (300 mL) and satd aq $NaHCO_3$ (300 mL), then dried and concentrated *in vacuo*. Purification via passage through a short plug of silica (eluent 30–40 °C petrol/$Et_2O$, 1:1) gave a mixture of **73**, **111**, **112** and **113** as a colourless oil (11.5 g).[6,11] Data for **73**: $\delta_H$ (400 MHz, $CDCl_3$) 1.34–1.55 (9H, m, C*Me*$_3$), 1.59–1.68 (3H, m, C(7)$H_3$), 2.16–2.28 (1H, m, C(4)$H_A$), 2.28–2.41 (1H, m, C(4)$H_B$), 2.46–2.58 (1H, m, *J* 15.3, 6.1, C(2)$H_A$), 2.67 (1H, dd, *J* 15.3, 8.5, C(2)$H_B$), 3.61–3.80 (2H, m, NC$H_2$CH=$CH_2$), 3.66 (3H, s, O*Me*), 3.94–4.26 (1H, m, C(3)*H*), 5.02–5.22 (2H, m, NCH$_2$CH=C$H_2$), 5.28–5.39 (1H, m, C(5)*H*), 5.42–5.53 (1H, m, C(6)*H*), 5.72–5.88 (1H, m, NCH$_2$C*H*=CH$_2$).

*Step 5*: Grubbs I (1.60 g, 1.94 mmol) was added to a solution of **73**, **111**, **112** and **113** (11.5 g)[11] in $CH_2Cl_2$ (1.6 L) at rt and the resultant mixture was stirred for 16 h then concentrated *in vacuo*. The residue was then dissolved in $CH_2Cl_2$ (800 mL), **114** (23.8 g, 192 mmol) and $Et_3N$ (13.0 mL, 93.2 mmol) were added, and the resultant mixture was stirred at rt for 10 min. Excess silica (120 g) was then added and the resultant mixture was stirred at rt for 2 h. The mixture was then filtered through a pad of Celite® (eluent $CH_2Cl_2$) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→50% $Et_2O$ in 30–40 °C petrol) gave a mixture of **74** and **106** as a colourless oil (8.85 g);[6,12] Data for **74**: $\delta_H$ (400 MHz, $CDCl_3$) 1.47 (9H, s, C*Me*$_3$), 1.91–2.04 (1H, m, C(3')$H_A$), 2.40–2.58 (3H, m, C(3')$H_B$, C(2)$H_2$), 3.45–3.70 (1H, m, C(6')$H_A$), 3.66 (3H, s, O*Me*), 4.06–4.34 (1H, m, C(6')$H_B$), 4.71–

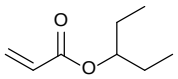
4.91 (1H, m, C(2')*H*), 5.61–5.76 (2H, m, C(4')*H*, C(5')*H*). Data for mixture: *m/z* ($ESI^+$) 533 ([2M(**74**)+Na]$^+$, 100%), 519 ([M(**74**)+M(**106**)+Na]$^+$, 75%), 278 ([M(**74**)+Na]$^+$, 80%), 264 ([M(**106**)+Na]$^+$, 25%). Further elution gave **107** as a colourless oil [729 mg, 2.3% (from methyl acrylate **97**), >99:1 dr]; $[\alpha]_D^{20}$ −47.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3024 (C–H, alkene), 2976, 2930 (C–H), 1738 (C=O, ester), 1689 (C=O, carbamate, C=C); $\delta_H$ (500 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), *1.45* (9H, s, C*Me*$_3$), 1.69–1.79 (1H, m, C(3')$H_A$), 1.92–2.03 (1H, m, C(3')$H_B$), 2.08–2.26 (2H, m, C(4')$H_2$), 2.39–2.55 (2H, m, C(2)$H_2$), 3.49–3.57 (1H, m, C(7')$H_A$), 3.64 (3H, s, O*Me*), *3.66* (3H, s, O*Me*), 4.01 (1H, dd, *J* 17.3, 5.7, C(7')$H_B$), *4.14–4.21* (1H, m, C(7')$H_B$), 4.48 (1H, dddd, *J* 12.2, 6.2, 6.2, 6.2, C(2')*H*), *4.64* (1H, dddd, *J* 12.2, 6.2, 6.2, 6.2, C(2')*H*), 5.58–5.70 (2H, m, C(5')*H*, C(6')*H*);[13] $\delta_C$ (125 MHz, $CDCl_3$) 26.5 (*C*(4')), 28.3, 28.4 (C*Me*$_3$), 31.9, 32.2 (*C*(3')), 39.0, 39.2, 39.7, 40.2 (*C*(7'), *C*(2)), 51.6 (O*Me*), 52.9, 54.0 (*C*(2')), 79.4, 79.7 (*C*Me$_3$), 127.9, 127.9 (*C*(6')), 130.8, 131.0 (*C*(5')), 155.1, 155.5 (N*C*O), 171.5, 171.6 (*C*(1));[14] *m/z* ($ESI^+$) 561 ([2M+Na]$^+$, 100%), 292 ([M+Na]$^+$, 95%), 270 ([M+H]$^+$, 55%); HRMS ($ESI^+$) $C_{14}H_{23}NNaO_4^+$ [M+Na]$^+$ requires 292.1519; found 292.1519.

*Step 6*: A solution of LiOH•$H_2O$ (8.83 g, 210 mmol) in $H_2O$ (180 mL) was added to a solution of **74** and **106** (8.85 g)[13] in THF (360 mL) and the resultant mixture was heated at 50 °C for 16 h. The reaction mixture was then allowed to cool to rt, acidified to pH 4 using satd aq $KHSO_4$ and filtered. The aqueous layer was extracted with $CHCl_3$ (3 × 360 mL) and the combined organic extracts were washed with brine (360 mL), then dried and concentrated *in vacuo* to give a mixture of **66** and **115** as a viscous yellow oil (8.61 g);[6,15] Data for **66**: $\delta_H$ (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 1.96–2.08 (1H, m, C(3')$H_A$), 2.44–2.62 (3H, m, C(3')$H_B$, C(2)$H_2$), 3.49–3.63 (1H, m, C(6')$H_A$), 4.10–4.31 (1H, m, C(6')$H_B$), 4.75–4.92 (1H, m, C(2')*H*)), 5.64–5.78 (2H, m, C(4')*H*, C(5')*H*). Data for mixture: *m/z* ($ESI^+$) 505 ([2M(**66**)+Na]$^+$, 60%), 491 ([M(**66**)+M(**115**)+Na]$^+$, 10%), 264 ([M(**66**)+Na]$^+$, 100%), 250 ([M(**115**)+Na]$^+$, 20%).

*Step 7*: $NaHCO_3$ (547 mg, 6.51 mmol) and $I_2$ (1.67 g, 6.51 mmol) were added sequentially to a stirred solution of **66** and **115** (479 mg)[15] in MeCN (20 mL) at −20 °C, and the resultant mixture was stirred for 2 h at −20 °C. The reaction mixture was then allowed to warm to rt over 20 h, $Et_2O$ (30 mL) was added, and the organic layer was washed sequentially with satd

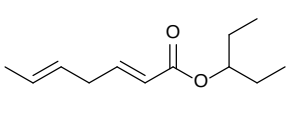
aq $Na_2S_2O_3$ (30 mL) and $H_2O$ (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 20%→80% EtOAc in 30–40 °C petrol) gave **116** as a colourless gum [40 mg, 1.8% (from methyl acrylate **97**), >99:1 dr]; $[\alpha]_D^{20}$ −93.8 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 2976, 2931 (C–H), 1791 (C=O, ester), 1695 (C=O, carbamate); $\delta_H$ (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), *1.50* (9H, s, C*Me*$_3$), 2.78–2.95 (2H, m, C(4)*H*$_2$), 3.87–4.13 (2H, m, C(7)*H*$_2$), 4.42–4.48 (1H, m, C(8)*H*), 4.74–4.78 (1H, m, C(5)*H*), *4.83–4.88* (1H, m, C(5)*H*), 5.16–5.20 (1H, m, C(1)*H*);[13] $\delta_C$ (100 MHz, $CDCl_3$) 14.1 (*C*(8)), 28.3 (C*Me*$_3$), 28.4 (C*Me*$_3$), 35.4 (*C*(4)), 36.1 (*C*(4)), 54.3 (*C*(7), 54.9 (*C*(7)), 56.6 (*C*(5)), 81.3 (*C*Me$_3$), 88.3 (*C*(1)), 156.6 (N*C*O), 168.6 (*C*(3)); *m/z* (ESI$^+$) 376 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{16}INNaO_4^+$ [M+Na]$^+$ requires 376.0016; found 376.0010. Further elution gave **67** as a white solid [566 mg, 23% (from methyl acrylate **97**), >99:1 dr]; mp 80–82 °C;[16] $[\alpha]_D^{18}$ −26.1 (*c* 1.0 in $CHCl_3$); {lit.[6] $[\alpha]_D^{18}$ −26.3 (*c* 1.3 in $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 1.89–1.97 (1H, m, C(9)*H*$_A$), 2.57–2.67 (1H, m, C(4)*H*$_A$), 2.79–2.95 (2H, m, C(4)*H*$_B$, C(9)*H*$_B$), 3.30–3.51 (1H, m, C(7)*H*$_A$), 4.21–4.47 (2H, m, C(7)*H*$_B$, C(8)*H*), 4.77–4.91 (1H, m, C(1)*H*, C(5)*H*).

**3-Pentyl acrylate 87**

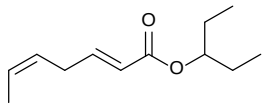


Acryloyl chloride **85** (4.50 mL g, 55.3 mmol) was added dropwise to a stirred solution of 3-pentanol **86** (8.70 mL, 83.0 mmol) and $Et_3N$ (15.5 mL, 110 mmol) in $CH_2Cl_2$ (125 mL) at 0 °C, and the resultant solution was allowed to warm to rt over 16 h. $H_2O$ (125 mL) was then added dropwise, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 125 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→20% $Et_2O$ in 30–40 °C petrol) gave **87** as a colourless oil (2.54 g, 32%);[17,18] $\delta_H$ (400 MHz, $CDCl_3$) 0.90 (6H, t, *J* 7.5, OCH(CH$_2$C*H*$_3$)$_2$), 1.57–1.64 (4H, m, OCH(C*H*$_2$CH$_3$)$_2$), 4.85 (1H, quintet, *J* 6.1, OC*H*(CH$_2$CH$_3$)$_2$), 5.81 (1H, dd, *J* 10.3, 1.5, C(3)*H*$_A$), 6.13 (1H, dd, *J* 17.2, 10.3, C(2)*H*), 6.40 (1H, dd, *J* 17.2, 1.5, C(3)*H*$_B$).

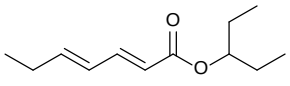
**3-Pentyl (*E*,*E*)-hepta-2,5-dienoate 89, 3-pentyl (2*E*,5*Z*)-hepta-2,5-dienoate 90, 3-pentyl (*E*,*E*)-hepta-2,4-dienoate 91 and 3-pentyl (*E*)-hepta-2,6-dienoate 92**



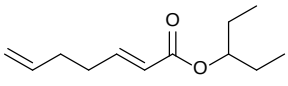
**89**



**90**



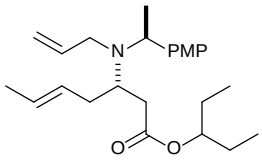
**91**



**92**

3-Pentyl acrylate **87** (2.00 g, 14.1 mmol), $Pd_2(dba)_3$•$CHCl_3$ (31 mg, 0.03 mmol), $PBu_3$ (12 mL, 0.06 mmol) and $HBF_4$ (6.15 M in $Et_2O$, 20 μL, 0.12 mmol) were added to a thick-walled glass vessel under a nitrogen atmosphere. The solution was cooled to −20 °C and condensed 1,3-butadiene **88** (1.25 mL, 14.1 mmol) was added to the vessel, which was subsequently sealed, and the resultant mixture was heated at 80 °C for 5 h. The reaction vessel was then cooled to 0 °C and opened to permit evaporation of any remaining 1,3-butadiene **88**. The reaction mixture was then filtered through a short plug of Celite® (eluent $Et_2O$) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→20% $Et_2O$ in 30–40 °C petrol) gave an 83:7:6:4 mixture of **89**, **90**, **91** and **92** as a colourless oil (2.32 g, 84%). Data for **89**: $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (6H, t, *J* 7.3, $OCH(CH_2C\mathit{H}_3)_2$), 1.55–1.64 (4H, m, $OCH(C\mathit{H}_2CH_3)_2$), 1.67–1.71 (3H, m, C(7)$\mathit{H}_3$), 2.85–2.91 (2H, m, C(4)$\mathit{H}_2$), 4.78–4.86 (1H, m, $OC\mathit{H}(CH_2CH_3)_2$), 5.39–5.58 (2H, m, C(5)*H*, C(6)*H*), 5.83 (1H, dt, *J* 15.7, 1.7, C(2)*H*), 6.96 (1H, dt, *J* 15.7, 6.4, C(3)*H*). Data for **90**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 2.93–2.99 (2H, m, C(4)$\mathit{H}_2$). Data for **91**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 1.97–2.14 (2H, m, C(6)$\mathit{H}_2$), 6.13–6.22 (2H, m, C(4)*H*, C(5)*H*), 7.21–7.31 (1H, m, C(3)*H*). Data for **92**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 1.97–2.14 (2H, m, C(5)$\mathit{H}_2$), 2.15–2.35 (2H, m, C(4)$\mathit{H}_2$), 5.04–5.10 (2H, m, C(7)$\mathit{H}_2$).

**3-Pentyl (*S*,*S*,*E*)-3-[*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]hept-5-enoate 95**

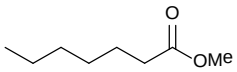



*Method A*: BuLi (2.4 M in hexanes, 0.66 mL, 1.58 mmol), was added dropwise to a stirred solution of **71** (312 mg, 1.63 mmol) in THF (7.5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 30 min. A solution of **89** (200 mg, 1.02 mmol, 83% purity) in THF (2.5 mL) was then added via canula and the resultant solution was stirred at −78 °C for 2 h. Satd aq $NH_4Cl$ (20 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 20 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→5% EtOAc in 30–40 °C petrol) gave an impure sample of **96** as a colourless oil (29 mg, 15%, 55:45 dr); first diastereoisomer; $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 0.84–0.92 (6H, m, OCH($CH_2CH_3$)$_2$), 1.52–1.62 (4H, m, OCH($CH_2CH_3$)$_2$), 1.63–1.83 (3H, m *C*(7)*H*$_3$), 3.21 (2H, dd, *J* 6.8, 1.7, C(2)*H*$_2$), 4.72–4.82 (1H, m, OC*H*($CH_2CH_3$)$_2$), 5.33–6.5 (4H, m, C(3)*H*, C(4)*H*, C(5)*H*, C(6)*H*); second diastereoisomer; $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 3.09 (2H, d, *J* 7.5, C(2)*H*$_2$). Further elution **95** as a colourless oil (172 mg, 44%, >99:1 dr); $[\alpha]_D^{20}$ +6.1 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3075 (C–H, alkene), 2967, 2935, 2880, (C–H), 1725 (C=O), 1640, 1681 (C=C); $\delta_H$ (400 MHz, $CDCl_3$) 0.82–0.89 (6H, m, OCH($CH_2CH_3$)$_2$), 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.47–1.59 (4H, m, OCH($CH_2CH_3$)$_2$), 1.66 (3H, d, *J* 4.1, C(7)*H*$_3$), 1.97 (1H, dddd, *J* 14.3, 6.6, 4.4, 1.7, C(4)*H*$_A$), 2.12–2.23 (1H, m, C(4)*H*$_B$), 2.17 (2H, app d, *J* 6.7, C(2)*H*$_2$), 3.06 (1H, dd, *J* 15.4, 6.7, NC*H*$_A$CH=$CH_2$), 3.23 (1H, app dddd, *J* 15.4, 5.5, 1.7, 1.7, NC*H*$_B$CH=$CH_2$), 3.42 (1H, app dtd, *J* 6.9, 6.7, 6.6, C(3)*H*), 3.78 (3H, s, ArO*Me*), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.72 (1H, quintet, *J* 6.1, OC*H*($CH_2CH_3$)$_2$), 5.04 (1H, dd, *J* 10.2, 1.5, $NCH_2CH$=C*H*$_A$), 5.16 (1H, dd, *J* 17.1, 1.5, $NCH_2CH$=C*H*$_B$), 5.39–5.44 (2H, m, C(5)*H*, C(6)*H*), 5.84 (1H, dddd, *J* 17.1, 10.2, 6.7, 5.5, $NCH_2C$*H*=$CH_2$), 6.82 (2H, d, *J* 8.9, *Ar*), 7.23 (2H, d, *J* 8.9, *Ar*); $\delta_C$ (100 MHz, $CDCl_3$) 9.6 (OCH($CH_2$*C*$H_3$)$_2$), 18.0 (*C*(7)), 20.5 (C(α)*Me*), 26.3 (OCH(*C*$H_2CH_3$)$_2$), 36.0 (*C*(4)), 37.3 (*C*(2)), 48.8 (N*C*$H_2CH$=$CH_2$), 55.2 (O*Me*), 55.3 (*C*(3)), 57.7 (*C*(α)), 76.3 (O*C*H($CH_2CH_3$)$_2$), 113.3 (*Ar*), 115.3 ($NCH_2CH$=*C*$H_2$), 126.5 (*C*(6)), 128.6 (*Ar*), 129.2

(*C*(5)), 136.5 (*Ar*), 139.2 ($NCH_2CH=CH_2$), 158.3 (*Ar*), 172.7 (*C*(1)); *m/z* ($ESI^+$) 410 ($[M+Na]^+$, 25%), 388 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_{24}H_{38}NO_3^+$ ($[M+Na]^+$) requires 388.2846; found 388.2842.

*Method B*: BuLi (2.4 M in hexanes, 0.66 mL, 1.58 mmol), was added dropwise to a stirred solution of **71** (312 mg, 1.63 mmol) in $Et_2O$ (7.5 mL) at −20 °C, and the resultant solution was stirred at −20 °C for 30 min. A solution of **89** (200 mg, 1.02 mmol, 83% purity) in $Et_2O$ (2.5 mL) was then added via canula and the resultant solution was stirred at −20 °C for 5 h. Satd aq $NH_4Cl$ (20 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 20 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→5% EtOAc in 30–40 °C petrol) gave an impure sample of **96** as a colourless oil (21 mg, 11%, 60:40 dr). Further elution **95** as a colourless oil (166 mg, 42%, >80:20 dr); $[\alpha]_D^{20}$ +5.9 (*c* 1.0 in $CHCl_3$).

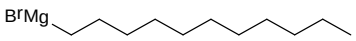
**Methyl heptanoate 102**




Pd/C (10% w/w of substrate, 12 mg) was added to a stirred solution of a 63:16:13:8 mixture of **64**, **99**, **100** and **101** (40 mg, 0.29 mmol) in degassed EtOAc (0.5 mL) at rt. The resultant mixture was saturated with $H_2$ then stirred under an atmosphere of $H_2$ (1 atm) for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo* to give **102** as a colourless oil (36 mg, 85%, >95% purity);[19] $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.6, C(7)$H_3$), 1.22–1.37 (6H, m, C(4)$H_2$, C(5)$H_2$, C(6)$H_2$), 1.62 (2H, tt, *J* 7.6, 7.6, C(3)$H_2$), 2.30 (2H, t, *J* 7.6, C(2)$H_2$), 3.67 (3H, s, O*Me*).

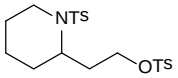
## 6.3 Experimental for Chapter 3

### 1-Undecylmagnesium bromide 121




One drop of **120** was added to a stirred mixture of magnesium turnings (729 mg, 30.0 mmol) and $I_2$ (cat.) in THF (2 mL) at reflux. Once the solution had decolourised, a solution of **120** (2.35 g, 10.0 mmol) in THF (18 mL) was added dropwise at such a rate so as to maintain a steady reflux, and the resultant mixture was then heated at reflux for 1 h. The reaction mixture was then allowed to cool to rt and the supernatant was decanted from the excess magnesium via canula and used immediately.

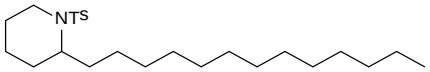
### (*RS*)-*N*(1)-*p*-Toluenesulfonyl-2-[2'-(*p*-toluenesulfonate)eth-1'-yl]piperidine 123




TsCl (14.8 g, 77.4 mmol) was added portionwise to a stirred solution of **122** (5.00 g, 38.7 mmol) and pyridine (12.5 mL, 155 mmol) in $CH_2Cl_2$ (200 mL) at rt, and the resultant mixture was stirred at rt for 16 h. $H_2O$ (200 mL) was then added dropwise, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 200 mL), and the combined organic extracts were sequentially washed with satd aq $CuSO_4$ (500 mL), 2.0 M aq NaOH (500 mL), $H_2O$ (500 mL), and brine (500 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→80% EtOAc in 30–40 °C petrol) gave **123** as a white solid (14.6 g, 86%); mp 69–71 °C; $\nu_{max}$ (ATR) 2941 (C–H); $\delta_H$ (400 MHz, $CDCl_3$) 1.07–1.22 (1H, m, C(5)$H_A$), 1.31–1.52 (6H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_B$), 1.78 (1H, m, C(1')$H_A$), 2.03–2.14 (1H, m, C(1')$H_B$), 2.42 (3H, s, *Me*), 2.45 (3H, s, *Me*), 2.92 (1H, m, C(6)$H_A$), 3.73–3.81 (1H, m, C(6)$H_B$), 4.00–4.12 (3H, m, C(2)*H*, C(2')$H_2$), 7.27 (2H, d, *J* 8.2, *Ar*), 7.35 (2H, d, *J* 8.2, *Ar*), 7.67 (2H, d, *J* 8.2, *Ar*), 7.80 (2H, d, *J* 8.2, *Ar*); $\delta_C$ (100 MHz, $CDCl_3$) 18.3, 21.5 (*Me*), 21.7 (*C*(4)), 24.0 (*C*(5)), 27.6 (*C*(3)), 29.4 (*C*(1')), 40.6 (*C*(6)), 49.6 (*C*(2)), 68.1 (*C*(2')), 126.9, 127.9, 129.8, 129.9, 132.9, 138.4, 143.1, 144.8 (*Ar*); *m/z* ($ESI^+$) 897 ($[2M+Na]^+$, 95%),

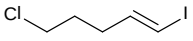
460 ([M+Na]$^+$, 100%), 438 ([M+H]$^+$, 30%); HRMS (ESI$^+$) $C_{21}H_{27}NNaO_5S_2^+$ [M+Na]$^+$ requires 460.1223; found 460.1224.

**(*RS*)-*N*(1)-*p*-Toluenesulfonyl-2-tridecylpiperidine 124**




A solution of **121** (0.5 M in THF, 2.30 mL, 1.15 mmol) was added dropwise to a stirred solution of **123** (100 mg, 0.23 mmol) and $Li_2CuCl_4$ (0.1 M in THF, 0.23 mL, 0.02 mmol) in THF (5 mL) at −78 °C. The resultant solution was allowed to warm to −50 °C and stirred for 1 h, then allowed to warm to rt over a further 1 h. Satd aq $NH_4Cl$ (20 mL) was then added, the aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→20% $Et_2O$ in 30–40 °C petrol) gave **124** as a white solid (79 mg, 81%); mp 50–51 °C; $\nu_{max}$ (ATR) 2923, 2853 (C–H); $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.6, C(13')$H_3$), 1.15–1.61 (30H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(5')$H_2$, C(6')$H_2$, C(7')$H_2$, C(8')$H_2$, C(9')$H_2$, C(10')$H_2$, C(11')$H_2$, C(12')$H_2$), 2.41 (3H, s, Ar*Me*), 2.92–3.02 (1H, m, C(6)$H_A$), 3.71–3.78 (1H, m, C(6)$H_B$), 3.94–4.03 (1H, m, C(2)*H*), 7.26 (2H, d, *J* 8.2, *Ar*), 7.71 (2H, d, *J* 8.2, *Ar*); $\delta_C$ (100 MHz, $CDCl_3$) 14.1 (*C*(13')), 18.4, 21.5, 22.7, 24.5, 26.5, 27.4, 29.4, 29.4, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 31.9 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(5'), *C*(6'), *C*(7'), *C*(8'), *C*(9'), *C*(10'), *C*(11'), *C*(12'), Ar*Me*), 40.6 (*C*(6)), 53.0 (*C*(2)), 126.9, 129.5, 139.0, 142.6 (*Ar*); *m/z* (ESI$^+$) 866 ([2M+Na]$^+$, 65%), 444 ([M+Na]$^+$, 100%), 422 ([M+H]$^+$, 20%); HRMS (ESI$^+$) $C_{25}H_{43}NNaO_2S^+$ [M+Na]$^+$ requires 444.2907; found 444.2904.

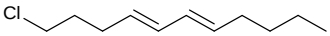
**(*E*)-1-Iodo-5-chloro-1-pentene 133**




**132** (4.82 mL, 45.5 mmol) was added dropwise to a stirred solution of DIBAL-H (1.0 M in hexanes, 50.0 mL, 50.0 mmol) at 0 °C and the resultant solution was heated at 50 °C for 16 h. The reaction mixture was then cooled to −78 °C, a solution of $I_2$ (13.9 g, 54.6 mmol) THF

(100 mL) was added via canula and the resultant solution was stirred at −78 °C for 15 min, then allowed to warm to rt over 45 min. The reaction mixture was then added via canula to a stirred mixture of 2.0 M aq HCl (50 mL) and 30–40 °C petrol (50 mL) at 0 °C. The aqueous layer was then extracted with 30–40 °C petrol (2 × 50 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL), satd aq $Na_2S_2O_3$ (25 mL), and brine (25 mL), then dried and concentrated *in vacuo*. Purification via distillation under reduced pressure gave **133** as a colourless, light sensitive oil (7.74 g, 74%, >99:1 dr);[20] $\delta_H$ (400 MHz, $CDCl_3$) 1.87 (2H, tt, *J* 7.2, 6.4, C(4)$H_2$), 2.24 (2H, dtd, *J* 7.2, 7.2, 1.3, C(3)$H_2$), 3.54 (2H, t, *J* 6.4, C(5)$H_2$), 6.10 (1H, dt, *J* 14.3, 1.3, C(1)*H*), 6.49 (1H, dt, *J* 14.3, 7.2, C(2)*H*).

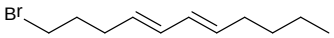
**(*E*,*E*)-1-Chloroundeca-4,6-diene 134**




1-Hexyne **130** (9.70 mL, 84.7 mmol) was added dropwise to a stirred solution of DIBAL-H (1.0 M in hexanes, 80.0 mL, 80.0 mmol) at 0 °C and the resultant solution was heated at 50 °C for 16 h. The reaction mixture was allowed to cool to rt then added via canula to a stirred mixture of ZnCl (7.16 g, 52.6 mmol), **133** (10.5 g, 45.7 mmol), $Pd(PPh_3)_4$ (2.65 g, 2.29 mmol) in THF (220 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 16 h. The reaction mixture was then added via canula to a stirred mixture of 2.0 M aq HCl (90 mL) and 30–40 °C petrol (180 mL) at 0 °C. The aqueous layer was then extracted with 30–40 °C petrol (3 × 90 mL) and the combined organic extracts were washed sequentially with 2.0 M aq HCl (90 mL), satd aq $NaHCO_3$ (90 mL), and $H_2O$ (90 mL), then dried and concentrated *in vacuo*. Purification via distillation under reduced pressure gave **134** as a colourless oil (6.78 g, 80%, >99:1 dr); $\nu_{max}$ (ATR) 2957, 2928 (C–H), 1659, 1625 (C=C); $\delta_H$ (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8, C(11)$H_3$), 1.26–1.43 (4H, m, C(9)$H_2$, C(10)$H_2$), 1.86 (2H, tt, *J* 7.3, 6.7, C(2)$H_2$), 2.07 (2H, dt, *J* 7.1, 7.1, C(8)$H_2$), 2.22 (2H, dt, *J* 7.3, 7.1, C(3)$H_2$), 3.54 (2H, t, *J* 6.7, C(1)$H_2$), 5.51 (1H, dt, *J* 14.3, 7.1, C(7)*H*), 5.61 (1H, dt, *J* 14.7, 7.1, C(4)*H*), 5.95–6.11 (2H, m, C(5)*H*, C(6)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 13.9 (*C*(11)), 22.2 (*C*(10)), 29.6, 31.5, 32.2, 32.3 (*C*(2), *C*(3), *C*(8), *C*(9)), 44.3 (*C*(1)), 129.6, 129.9 (*C*(5), *C*(6)), 131.8 (*C*(7)), 133.3 (*C*(4));

*m/z* (FI$^+$) 186 ([M($^{35}$Cl)]$^+$, 100%); HRMS (FI$^+$) $C_{11}H_{19}{}^{35}Cl^+$ [M($^{35}$Cl)]$^+$ requires 186.1170; found 186.1173.

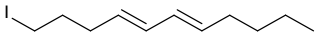
**(*E*,*E*)-1-Bromoundeca-4,6-diene 135**




*Method A*: KHMDS (0.5 M in PhMe, 1.34 mL, 0.67 mmol) was added dropwise to a stirred solution of **196** (200 mg, 0.56 mmol) and **82** (0.08 mL, 0.56 mmol) in THF (6 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. $H_2O$ (10 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 10 mL), and the combined organic extracts were washed sequentially with satd aq $NH_4Cl$ (40 mL) and brine (40 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol) gave **135** as a colourless oil (39 mg, 30%, 90:10 dr [(*E*,*E*):(4'*Z*,6'*E*)]);[21] $\delta_H$ (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(11)*H*$_3$), 1.25–1.46 (4H, m, C(9)*H*$_2$, C(10)*H*$_2$), 1.87 (2H, tt, *J* 7.0, 6.7, C(2)*H*$_2$), 2.07 (2H, dt, *J* 7.1, 7.0, C(8)*H*$_2$), 2.23 (2H, dt, *J* 7.1, 7.0, C(3)*H*$_2$), 3.55 (2H, t, *J* 6.7, C(1)*H*$_2$), 5.52 (1H, dt, *J* 14.1, 7.1, C(7)*H*), 5.61 (1H, dt, *J* 14.1, 7.1, C(4)*H*), 5.96–6.11 (2H, m, C(5)*H*, C(6)*H*). Data for (4'*Z*,6'*E*)-isomer: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.25 (1H, dt, *J* 10.7, 7.8, C(4')*H*), 5.70 (1H, dt, *J* 15.4, 6.8, C(7')*H*), 6.32 (1H, app ddq, *J* 15.0, 10.9, 1.4, C(6')*H*).

*Method B*: LiBr (2.78 g, 32.1 mmol) was added to a stirred solution of **134** (200 mg, 1.07 mmol, >99:1 dr) in butanone (10 mL) at rt, and the resulant solution was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. $H_2O$ (125 mL) was then added, the aqueous layer was extracted with 30–40 °C petrol (3 × 100 mL), and the combined organic extracts were washed with satd aq $Na_2S_2O_3$ (100 mL), brine (150 mL), and $H_2O$ (150 mL), then dried and concentrated *in vacuo* to give a 95:5 mixture of **135** and **134** as a colourless oil (120 mg, 90% mass return, >99:1 dr).[21]

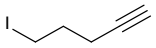
**(*E*,*E*)-1-Iodoundeca-4,6-diene 136**



*Method A*: $Na_2S_2O_3$ (250 mg, 1.08 mmol) and NaI (2.40 g, 16.2 mmol) were added to a stirred solution of **134** (100 mg, 0.54 mmol, >99:1 dr) in butanone (5 mL) at rt, and the resulant mixture was heated at reflux for 16 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. $H_2O$ (50 mL) was then added, the aqueous layer was extracted with 30–40 °C petrol (3 × 25 mL), and the combined organic extracts were sequentially washed with satd aq $Na_2S_2O_3$ (25 mL), brine (30 mL), and $H_2O$ (50 mL), then dried and concentrated *in vacuo* to give **136** as a pale yellow oil (144 mg, 96%, >85:15 dr); $\nu_{max}$ (ATR) 3015, 2956, 2926, 2871, 2858 (C–H), 1695, 1626 (C=C); $\delta_H$ (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, C(11)$H_3$), 1.26–1.45 (4H, m, C(9)$H_2$, C(10)$H_2$), 1.91 (2H, tt, *J* 7.2, 7.0, C(2)$H_2$), 2.07 (2H, dt, *J* 7.1, 7.1, C(8)$H_2$), 2.18 (2H, dt, *J* 7.2, 7.2, C(3)$H_2$), 3.19 (2H, t, *J* 7.0, C(1)$H_2$), 5.49 (1H, dt, *J* 14.3, 7.1, C(7)*H*), 5.61 (1H, dt, *J* 14.7, 7.2, C(4)*H*), 5.95–6.12 (2H, m, C(5)*H*, C(6)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 6.5 (*C*(1)), 13.9 (*C*(11)), 22.2 (*C*(10)), 31.5, 32.3, 33.0, 33.1 (*C*(2), *C*(3), *C*(8), *C*(9)), 129.3, 129.9 (*C*(5), *C*(6)), 131.9 (*C*(7)), 133.4 (*C*(4)).[22] Data for minor diastereoisomers: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.20–5.28 (1H, m), 5.32–5.40 (1H, m), 5.66–5.74 (1H, m), 6.26–6.43 (1H, m).

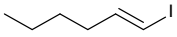
*Method B*: **137** (2.50 g, 12.9 mmol) was added dropwise to a stirred solution of DIBAL-H (1.0 M in hexanes, 12.3 mL, 12.3 mmol) at 0 °C and the resultant solution was heated at 50 °C for 16 h. The reaction mixture was allowed to cool to rt then added via canula to a stirred mixture of $ZnCl_2$ (981 mg, 7.20 mmol), **139** (1.30 g, 6.30 mmol), $Pd(PPh_3)_4$ (380 mg, 0.33 mmol) in THF (30 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 16 h. The reaction mixture was then added via canula to a stirred mixture of 2.0 M aq HCl (12 mL) and 30–40 °C petrol (25 mL) at 0 °C. The aqueous layer was then extracted with 30–40 °C petrol (3 × 12 mL) and the combined organic extracts were washed sequentially with 2.0 M aq HCl (12 mL), satd aq $NaHCO_3$ (12 mL), and $H_2O$ (12 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol) gave **136** as a colourless oil (720 mg, 41%, >99:1 dr, >95% purity).

**5-Iodo-1-pentyne 137**



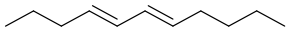
NaI (21.8 g, 146 mmol) and $Na_2S_2O_3$ (15 mg, 0.09 mmol) were added to a stirred solution of **132** (3.00 g, 29.2 mmol) in acetone (100 mL) at rt, and the resulant solution was heated at 50 °C for 72 h. The reaction mixture was then allowed to cool to rt and 30–40 °C petrol (200 mL) was added. The reaction mixture was then filtered and the filter cake was washed further with 30–40 °C petrol (2 × 200 mL). The combined organic washings were washed with $H_2O$ (2 × 100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification via distillation under reduced pressure gave **137** as a colourless oil (3.63 g, 64%);[23] $\delta_H$ (400 MHz, $CDCl_3$) 2.00 (1H, t, *J* 2.7, C(1)*H*), 2.01 (2H, app quintet, *J* 6.8, C(4)$H_2$), 2.35 (2H, td, *J* 6.8, 2.7, C(3)$H_2$), 3.32 (2H, t, *J* 6.8, C(5)$H_2$).

**(*E*)-1-Iodo-1-hexene 139**



1-Hexyne **130** (5.20 mL, 45.5 mmol) was added dropwise to a stirred solution of DIBAL-H (1.0 M in hexanes, 50.0 mL, 50.0 mmol) at 0 °C and the resultant solution was heated at 50 °C for 16 h. The reaction mixture was then cooled to −78 °C, a solution of $I_2$ (13.9 g, 54.6 mmol) THF (100 mL) was added via canula and the resultant mixture was stirred at −78 °C for 15 min, then allowed to warm to rt over 45 min. The reaction mixture was then added via canula to a stirred mixture of 1.0 M aq HCl (50 mL) and 30–40 °C petrol (50 mL) at 0 °C. The aqueous layer was extracted with 30–40 °C petrol (2 × 50 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (25 mL), satd aq $Na_2S_2O_3$ (25 mL), and brine (25 mL), then dried and concentrated *in vacuo*. Purification via distillation under reduced pressure gave **139** as a colourless, light sensitive oil (7.13 g, 75%, >99:1 dr);[24] $\delta_H$ (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, C(6)$H_3$), 1.27–1.43 (4H, m, C(4)$H_2$, C(5)$H_2$), 2.06 (2H, dtd, *J* 7.2, 7.2, 1.4, C(3)$H_2$), 5.98 (1H, dt, *J* 14.3, 1.4, C(1)*H*), 6.52 (1H, dt, *J* 14.3, 7.2, C(2)*H*).

**(*E*,*E*)-Undeca-4,6-diene 140**

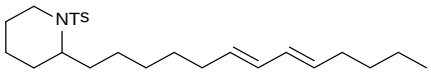


*Method A*: One drop of **135** was added to a stirred mixture of magnesium turnings (73 mg, 3.00 mmol) and $I_2$ (cat.) in THF (1 mL) at reflux. Once the solution had decolourised, a solution of **135** (231 mg, 1.00 mmol) in THF (2 mL) was added dropwise at such a rate so as to maintain a steady reflux, and the resultant mixture was then heated at reflux for 1 h. The reaction mixture was then allowed to cool to rt and satd aq $NH_4Cl$ (5 mL) was added dropwise. The aqueous layer was extracted with 30–40 °C petrol (3 × 10 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give a mixture of products thought to include **140** and **141**. Data for **140**:[25] $\delta_H$ (400 MHz, $CDCl_3$) 0.86–0.94 (6H, m, C(1)$H_3$, C(11)$H_3$), 1.25–1.60 (6H, m, C(2)$H_2$, C(9)$H_2$, C(10)$H_2$), 2.01–2.10 (4H, m, C(3)$H_2$, C(8)$H_2$), 5.52–5.64 (2H, m, C(4)*H*, C(7)*H*), 5.95–6.08 (2H, m, C(5)*H*, C(6)*H*). Data for **141**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 1.67 (2H, tt, *J* 7.3, 6.5, C(2)$H_2$), 2.16 (2H, app q, *J* 7.3, C(3)$H_2$), 3.67 (2H, t, *J* 6.5, C(1)$H_2$).

*Method B*: $^t$BuLi (1.8 M in hexanes, 0.53 mL, 0.95 mmol) was added dropwise to a stirred solution of **135** (100 mg, 0.43 mmol) in $Et_2O$ (1 mL) at −78 °C and the resultant solution was allowed to warm to rt over 15 min, then cooled to −78 °C. Satd aq $NH_4Cl$ (5 mL) was then added, the aqueous layer was extracted with 30–40 °C petrol (3 × 5 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give a complex mixture of products, including **140** (53 mg).[25,26]

*Method C*: $^t$BuLi (1.8 M in hexanes, 0.44 mL, 0.79 mmol) was added dropwise to a stirred solution of **136** (100 mg, 0.36 mmol) in $Et_2O$ (1 mL) at −78 °C and the resultant solution was allowed to warm to rt over 15 min, then cooled to −78 °C. Satd aq $NH_4Cl$ (5 mL) was then added, the aqueous layer was extracted with 30–40 °C petrol (3 × 5 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give a complex mixture of products, including **140** (40 mg).[25,26]

**(*RS*,*E*,*E*)-*N*(1)-*p*-toluenesulfonyl-2-(trideca-6',8'-dien-1'-yl)piperidine 143**

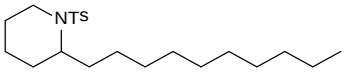



*Method A*: $^{t}$BuLi (1.6 M in hexanes, 0.50 mL, 0.79 mmol) was added dropwise to a stirred solution of **136** (100 mg, 0.36 mmol) in $Et_2O$ (2 mL) at −78 °C and the resultant solution was allowed to warm to rt over 15 min, then cooled to −78 °C. $Li_2CuCl_4$ (1.0 M in THF, 0.72 mL, 0.72 mmol) was added dropwise and the resultant solution was stirred at −78 °C for 10 min. A solution of **123** (79 mg, 0.18 mmol) in THF (2 mL) was then added dropwise and the resultant solution was stirred at −78 °C for 10 min, then allowed to warm to rt over 30 min. Satd aq $NH_4Cl$ (10 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→30% $Et_2O$ in 30–40 °C petrol) gave **143** as a colourless gum (9 mg, 12%, 92:8 dr); $\delta_H$ (400 MHz, $CDCl_3$) 0.82–0.94 (3H, m, C(13')$H_3$), 1.16–1.60 (18H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.99–2.10 (4H, m, C(5')$H_2$, C(10')$H_2$), 2.42 (3H, s, Ar*Me*), 2.93–3.02 (1H, m, C(6)$H_A$), 3.72–3.80 (1H, m, C(6)$H_B$), 3.96–4.04 (1H, m, C(2)*H*), 5.50–5.62 (2H, m, C(6')*H*, C(9')*H*), 5.94–6.06 (2H, m, C(7')*H*, C(8')*H*), 7.28 (2H, d, *J* 8.2, *Ar*), 7.72 (2H, d, *J* 8.2, *Ar*); $\delta_C$ (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 18.4, 21.5, 22.2, 24.4, 24.5, 27.4, 28.9, 29.2, 29.4, 29.4, 31.6, 32.3, (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(5'), *C*(10'), *C*(11'), *C*(12'), Ar*Me*), 40.6 (*C*(6)), 53.0 (*C*(2)), 126.9, 129.5 (*Ar*), 130.3, 130.4 (*C*(7'), *C*(8')), 132.1, 132.4 (*C*(6'), *C*(9'),), 139.0, 142.7 (*Ar*).[27] Further elution gave **123** as a white solid (13 mg, 26%).

*Method B*: $^{t}$BuLi (1.8 M in hexanes, 5.3 mL, 9.53 mmol) was added dropwise to a stirred solution of **135** (1.00 g, 4.33 mmol) in $Et_2O$ (11 mL) at −78 °C and the resultant solution was allowed to warm to rt over 1 h. Titration of the resultant solution against diphenylacetic acid indicated a 0.17 M solution of lithiated species. This solution was added dropwise to a stirred suspension of CuI (238 mg, 1.25 mmol) in $Et_2O$ (3 mL) at −30 °C, and the resultant mixture was stirred at −30 °C for 30 min, then cooled to −35 °C. A solution of **123** (109 mg, 0.25 mmol) in $Et_2O$ (2 mL) was then added dropwise and the resultant solution was stirred at −35 °C for 2 h. Satd aq $NH_4Cl$ (20 mL) was then added, the aqueous layer was extracted with

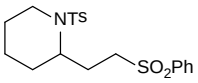
$Et_2O$ (3 × 30 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→50% $Et_2O$ in 30–40 °C petrol) gave a complex mixture of products containing **143** as a colourless oil (88 mg, 85% mass return).

**(*RS*)-*N*(1)-*p*-Toluenesulfonyl-2-decylpiperidine 146**




$^t$BuLi (1.7 M in hexanes, 3.0 mL, 5.06 mmol) was added dropwise to a stirred solution of 1-iodooctane **144** (553 mg, 2.30 mmol) in $Et_2O$ (5 mL) at −78 °C and the resultant solution was allowed to warm to rt over 1 h. The resultant solution was added dropwise to a stirred suspension of CuI (219 mg, 1.15 mmol) in $Et_2O$ (3 mL) at −30 °C, and the resultant mixture was stirred at −30 °C for 30 min, then cooled to −35 °C. A solution of **123** (100 mg, 0.23 mmol) in THF (2 mL) was then added dropwise and the resultant solution was stirred at −35 °C for 2 h. Satd aq $NH_4Cl$ was then added, the aqueous layer was extracted with $Et_2O$ (3 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→20% $Et_2O$ in 30–40 °C petrol) gave **146** as a colourless gum (72 mg, 82%); $\nu_{max}$ (ATR) 2924, 2854 (C–H); $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8, C(10')$H_3$), 1.16–1.60 (24H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(5')$H_2$, C(6')$H_2$, C(7')$H_2$, C(8')$H_2$, C(9')$H_2$), 2.41 (3H, s, Ar*Me*), 2.92–3.02 (1H, m, C(6)$H_A$), 3.71–3.78 (1H, m, C(6)$H_B$), 3.95–4.02 (1H, m, C(2)*H*), 7.26 (2H, d, *J* 8.2, *Ar*), 7.71 (2H, d, *J* 8.2, *Ar*); $\delta_C$ (100 MHz, $CDCl_3$) 14.1 (*C*(10')), 18.4, 21.5, 22.7, 24.5, 26.5, 27.4, 29.3, 29.4, 29.4, 29.5, 29.6, 29.6, 31.9 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(5'), *C*(6'), *C*(7'), *C*(8'), *C*(9'), Ar*Me*), 40.6 (*C*(6)), 53.0 (*C*(2)), 127.0, 129.5, 139.0, 142.6 (*Ar*); *m/z* (ESI$^+$) 781 ([2M+Na]$^+$, 100%), 402 ([M+Na]$^+$, 95%), 380 ([M+H]$^+$, 35%); HRMS (ESI$^+$) $C_{22}H_{37}NNaO_2S^+$ [M+Na]$^+$ requires 402.2437; found 402.2439.

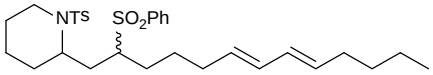
**(*RS*)-*N*(1)-*p*-Toluenesulfonyl-2-[2'-(phenylsulfonyl)eth-1'-yl]piperidine 152**



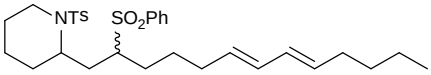

*Step 1*: A solution of PhSH (0.35 mL, 3.42 mmol) in THF (12 mL) was added dropwise to a stirred suspension of NaH (126 mg, 60% w/w in mineral oil, 3.14 mmol) in THF (75 mL) at rt, and the resultant mixture was stirred at rt for 5 min. A solution of **123** (500 mg, 1.14 mmol) in THF (25 mL) was then added dropwise and the resultant mixture was stirred at rt for 30 min. 1.0 M aq NaOH (75 mL) was then added and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **151**.

*Step 2*: The residue was then dissolved in $CH_2Cl_2$ (50 mL) and the resultant solution was stirred at 0 °C. *m*-CPBA (1.06 g, 74% w/w in $H_2O$, 4.56 mmol) was then added portionwise and the resultant mixture was allowed to warm to rt over 16 h. 0.5 M aq $Na_2S_2O_3$ (100 mL) and 10% aq NaOH (100 mL) were then added and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were washed with brine (250 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→80% EtOAc in 30–40 °C petrol) gave **152** as a white solid (460 mg, 99%); mp 119–120 °C; $\nu_{max}$ (ATR) 2940 (C–H); $\delta_H$ (400 MHz, $CDCl_3$) 0.96–1.10 (1H, m, C(5)$H_A$), 1.24–1.51 (5H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_B$), 1.74–1.84 (1H, m, C(1')$H_A$), 2.29–2.40 (1H, m, C(1')$H_B$), 2.41 (3H, s, Ar*Me*), 2.92 (1H, ddd, *J* 14.9, 13.1, 2.8, C(6)$H_A$), 3.17 (2H, dt, *J* 11.2, 5.2, C(2')$H_2$), 3.79 (1H, app dd, *J* 14.9, 3.4, C(6)$H_B$), 4.05 (1H, app dt, *J* 11.1, 4.0, C(2)*H*), 7.27 (2H, d, *J* 8.3, *Ph*), 7.55–7.61 (2H, m, *Ar*), 7.64–7.70 (3H, m, *Ar*), 7.90–7.94 (2H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 18.3 (*C*(4)), 21.5, 22.4 (*C*(1'), Ar*Me*), 23.6 (*C*(5)), 27.8 (*C*(3)), 40.6 (*C*(6)), 51.7 (*C*(2')), 53.6 (*C*(2)), 126.8, 127.9, 129.3, 129.8, 133.8, 138.4, 139.3, 143.3 (*Ar*); *m/z* ($ESI^+$) 837 ($[2M+Na]^+$, 100%), 430 ($[M+Na]^+$, 100%), 408 ($[M+H]^+$, 35%); HRMS ($ESI^+$) $C_{20}H_{25}NNaO_4S_2^+$ $[M+Na]^+$ requires 430.1117; found 430.1118.

**(2*RS*,2'*RS**,6'*E*,8'*E*)-*N*(1)-*p*-Toluenesulfonyl-2-[2'-(phenylsulfonyl)trideca-6,8-dien-1'-yl]piperidine 153 and (2*RS*,2'*RS**,6'*E*,8'*E*)-*N*(1)-*p*-toluenesulfonyl-2-[2'-(phenylsulfonyl)trideca-6,8-dien-1'-yl]piperidine 154**[28]




**153**

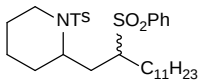



**154**

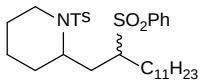
BuLi (2.4 M in hexanes, 0.07 mL, 0.17 mmol) was added dropwise to a stirred solution of **152** (60 mg, 0.15 mmol) in THF (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. A solution of **135** (42 mg, 0.18 mmol) in THF (1 mL) was then added dropwise, and the reaction mixture was allowed to warm to rt over 1 h. Satd aq $NH_4Cl$ (5 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→30% $Et_2O$ in 30–40 °C petrol) gave **154** as a colourless oil (14 mg, 17%, >95:5 dr); $\nu_{max}$ (ATR) 3064 (C–H, alkene), 2926, 2855 (C–H), 1597 (C=C), 1337, 1303 (S=O); $\delta_H$ (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, C(13')$H_3$), 1.01–1.67 (14H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.88–2.18 (6H, m, C(1')$H_2$, C(5')$H_2$, C(10')$H_2$), 2.44 (3H, s, Ar*Me*), 2.96–3.04 (1H, m, C(6)$H_A$), 3.37–3.45 (1H, m, C(2')*H*), 3.89–3.96 (1H, m, C(6)$H_B$), 4.28–4.35 (1H, m, C(2)*H*), 5.38 (1H, dt, *J* 14.0, 6.9, C(6')*H*), 5.55 (1H, dt, *J* 14.1, 7.0, C(9')*H*), 5.87–5.96 (2H, m, C(7')*H*, C(8')*H*), 7.30 (2H, d, *J* 8.0, *Ar*), 7.58 (2H, dd, *J* 7.3, 7.3, *m-Ph*), 7.66 (1H, tt, *J* 7.3, 1.3, *p-Ph*), 7.74 (2H, d, *J* 8.0, *Ar*), 8.02 (2H, dd, *J* 7.3, 1.3, *o-Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 13.9 (*C*(13')), 18.3, 21.5, 22.2, 23.8, 25.9, 27.5, 28.2, 28.8, 31.5, 31.8, 32.2, (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(3'), *C*(4'), *C*(5'), *C*(10'), *C*(11'), *C*(12'), Ar*Me*), 40.9 (*C*(6)), 52.1 (*C*(2)), 60.2 (*C*(2')), 127.0, 128.9, 129.1, 129.8, 130.0, 130.4, 131.3, 133.0, 133.5, 138.2, 138.5, 143.1 (*C*(6'), *C*(7'), *C*(8'), *C*(9'), *Ar*, *Ph*); *m/z* ($ESI^+$) 580 ($[M+Na]^+$, 100%), 558 ($[M+H]^+$, 40%); HRMS ($ESI^+$) $C_{31}H_{43}NNaO_4S_2^+$ ($[M+Na]^+$) requires 580.2526; found 580.2516. Further elution gave **153** as a colourless oil (32 mg, 38%, >95:5 dr); $\nu_{max}$ (ATR) 3063 (C–H, alkene), 2933, 2869 (C–H), 1598 (C=C), 1336, 1303 (S=O); $\delta_H$ (500 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.9, C(13')$H_3$), 1.22–1.74 (14H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_A$, C(3')$H_A$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.83–1.93 (1H, m,

C(3')$H_B$), 2.02–2.11 (4H, m, C(5')$H_2$, C(10')$H_2$), 2.43 (3H, s, Ar*Me*), 2.55–2.65 (2H, m, C(6)$H_A$, C(1')$H_B$), 3.22–3.28 (1H, m, C(2')*H*), 3.61 (1H, app dd, *J* 15.1, 3.2 C(6)$H_B$), 4.04–4.12 (1H, m, C(2)*H*), 5.49 (1H, dt, *J* 14.2, 6.9, C(6')*H*), 5.58 (1H, dt, *J* 14.0, 7.1, C(9')*H*), 5.93–6.02 (2H, m, C(7')*H*, C(8')*H*), 7.29 (2H, d, *J* 8.2, *Ar*), 7.58 (2H, dd, *J* 7.6, 7.3, *m-Ph*), 7.65 (1H, tt, *J* 7.6, 1.9 *p-Ph*), 7.70 (2H, d, *J* 8.2, *Ar*), 7.93 (2H, dd, *J* 7.3, 1.9, *o-Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 13.9 (*C*(13')), 18.3, 21.5, 22.2, 23.3, 25.6, 27.9, 28.0, 28.1, 30.9, 31.6, 32.3, (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(3'), *C*(4'), *C*(5'), *C*(10'), *C*(11'), *C*(12'), Ar*Me*), 40.1 (*C*(6)), 50.4 (*C*(2)), 60.8 (*C*(2')), 126.9, 128.8, 129.2, 129.8, 130.1, 131.0, 131.1, 132.8, 133.5, 138.0, 138.6, 143.2 (*C*(6'), *C*(7'), *C*(8'), *C*(9'), *Ar*, *Ph*); *m/z* ($ESI^+$) 580 ($[M+Na]^+$, 100%), 558 ($[M+H]^+$, 35%); HRMS ($ESI^+$) $C_{31}H_{43}NNaO_4S_2^+$ ($[M+Na]^+$) requires 580.2526; found 580.2518.

**(2*RS*,2'*RS**)-*N*(1)-*p*-Toluenesulfonyl-2-[2'-(phenylsulfonyl)tridec-1'-yl]piperidine 155 and (2*RS*,2'*RS**)-*N*(1)-*p*-toluenesulfonyl-2-[2'-(phenylsulfonyl)tridec-1'-yl]piperidine 156**[28]




**155**

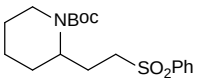



**156**

BuLi (2.4 M in hexanes, 0.07 mL, 0.17 mmol) was added dropwise to a stirred solution of **152** (60 mg, 0.15 mmol) in THF (1 mL) at −78 °C, and the resultant mixture was stirred at −78 °C for 10 min. A solution of **120** (42 mg, 0.18 mmol) in THF (1 mL) was then added dropwise, and the reaction mixture was allowed to warm to rt over 1 h. Satd aq $NH_4Cl$ (5 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→30% $Et_2O$ in 30–40 °C petrol) gave **156** as a colourless oil (24 mg, 28%, >99:1 dr); $\nu_{max}$ (ATR) 2931, 2861 (C–H), 1337, 1303 (S=O); $\delta_H$ (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9, C(13')$H_3$), 1.04–1.65 (26H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(3')$H_2$, C(4')$H_2$, C(5')$H_2$, C(6')$H_2$, C(7')$H_2$, C(8')$H_2$, C(9')$H_2$, C(10')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.98 (1H, ddd, *J* 15.4, 9.9, 3.0, C(1')$H_A$), 2.09 (1H, ddd, *J* 15.4, 7.3, 4.1, C(1')$H_B$),

2.44 (3H, s, Ar*Me*), 2.97–3.04 (1H, m, C(6)$H_A$), 3.37–3.43 (1H, m, C(2')*H*), 3.90–3.96 (1H, m, C(6)$H_B$), 4.29–4.35 (1H, m, C(2)*H*), 7.30 (2H, d, *J* 8.2, *Ar*), 7.59 (2H, dd, *J* 7.4, 7.4, *m-Ph*), 7.66 (1H, t, *J* 7.4, *p-Ph*), 7.74 (2H, d, *J* 8.2, *Ar*), 8.03 (2H, d, *J* 7.4, *o-Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 14.1 (*C*(13')), 18.3, 21.5, 22.7, 23.8, 26.1, 27.5, 28.3, 29.0, 29.1, 29.3, 29.3, 29.4, 29.6, 29.6, 31.9 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(3'), *C*(4'), *C*(5'), *C*(6'), *C*(7'), *C*(8'), *C*(9'), *C*(10'), *C*(11'), *C*(12'), Ar*Me*), 40.9 (*C*(6)), 52.1 (*C*(2)), 60.4 (*C*(2')), 127.0, 128.9, 129.1, 129.8, 133.4, 138.3, 138.5, 143.1 (*Ar*, *Ph*); *m/z* ($ESI^+$) 584 ($[M+Na]^+$, 100%), 562 ($[M+H]^+$, 35%); HRMS ($ESI^+$) $C_{31}H_{47}NNaO_4S_2^+$ ($[M+Na]^+$) requires 584.2839; found 584.2836. Further elution gave **155** as a colourless oil (36 mg, 43%, >99:1 dr); $\nu_{max}$ (ATR) 2926, 2855 (C–H), 1337, 1303 (S=O); $\delta_H$ (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9, C(13')$H_3$), 0.91–1.55 (25H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_A$, C(4')$H_2$, C(5')$H_2$, C(6')$H_2$, C(7')$H_2$, C(8')$H_2$, C(9')$H_2$, C(10')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.62–1.70 (1H, m, C(3')$H_A$), 1.83–1.92 (1H, m, C(3')$H_B$), 2.43 (3H, s, Ar*Me*), 2.53–2.65 (2H, m, C(6)$H_A$, C(1')$H_A$), 3.24 (1H, app dtd, *J* 9.1, 5.7, 2.2, C(2')*H*), 3.60 (1H, app dd, *J* 15.0, 3.0 C(6)$H_B$), 4.08–4.14 (1H, m, C(2)*H*), 7.29 (2H, d, *J* 8.1, *Ar*), 7.59 (2H, dd, *J* 7.9, 7.6, *m-Ph*), 7.66 (1H, tt, *J* 7.6, 1.6 *p-Ph*), 7.71 (2H, d, *J* 8.1, *Ar*), 7.93 (2H, dd, *J* 7.9, 1.6, *o-Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 14.1 (*C*(13')), 18.3, 21.5, 22.7, 23.3, 25.9, 28.0, 28.0, 28.5, 29.3, 29.3, 29.3, 29.6, 29.6, 29.9, 31.9 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(3'), *C*(4'), *C*(5'), *C*(6'), *C*(7'), *C*(8'), *C*(9'), *C*(10'), *C*(11'), *C*(12'), Ar*Me*), 40.1 (*C*(6)), 50.4 (*C*(2)), 60.9 (*C*(2')), 126.9, 128.8, 129.2, 129.8, 133.5, 138.1, 138.6, 143.2 (*Ar*, *Ph*); *m/z* ($ESI^+$) 584 ($[M+Na]^+$, 100%), 562 ($[M+H]^+$, 35%); HRMS ($ESI^+$) $C_{31}H_{47}NNaO_4S_2^+$ ($[M+Na]^+$) requires 584.2839; found 584.2834.

**(*RS*)-*N*(1)-*tert*-Butoxycarbonyl-2-[2'-(phenylsulfonyl)eth-1'-yl]piperidine 160**



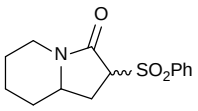

*Step 1*: MsCl (1.01 g, 13.1 mmol) was added dropwise to a stirred solution of **157** (2.00 g, 8.72 mmol)[29] and $Et_3N$ (2.43 mL, 14.7 mL) in $CH_2Cl_2$ (40 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 16 h. Satd aq $NH_4Cl$ (40 mL) was then added dropwise, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL), and the combined

organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→80% EtOAc in 30–40 °C petrol) gave **158** as a white gum (2.17 g, 81%); $\delta_H$ (400 MHz, $CDCl_3$) 1.34–1.49 (1H, m, C(5)$H_A$), 1.47 (9H, s, C$Me_3$), 1.53–1.67 (5H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_B$), 1.76–1.87 (1H, m, C(1')$H_A$), 2.18–2.29 (1H, m, C(1')$H_B$), 2.71–2.81 (1H, m, C(6)$H_A$), 3.03 (3H, s, $SO_2Me$), 3.95–4.06 (1H, m, C(6)$H_B$), 4.22 (2H, t, *J* 6.1, C(2')$H_2$), 4.37–4.48 (1H, m, C(2)*H*).

*Step 2*: A solution of PhSH (0.35 mL, 3.42 mmol) in THF (12 mL) was added dropwise to a stirred suspension of NaH (126 mg, 60% w/w in mineral oil, 3.14 mmol) in THF (75 mL) at rt, and the resultant mixture was stirred at rt for 5 min. A solution of **158** (350 mg, 1.14 mmol) in THF (25 mL) was then added dropwise and the resultant mixture was stirred at rt for 30 min. 1.0 M aq NaOH (75 mL) was then added and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **159**.

*Step 3*: The residue was then dissolved in $CH_2Cl_2$ (50 mL) and the resultant solution was stirred at 0 °C. *m*-CPBA (1.06 g, 74% w/w in $H_2O$, 4.56 mmol) was then added portionwise and the resultant mixture was allowed to warm to rt over 16 h. 0.5 M aq $Na_2S_2O_3$ (100 mL) and 10% aq NaOH (100 mL) were then added and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic extracts were washed with brine (250 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→80% EtOAc in 30–40 °C petrol) gave **160** as a colourless gum (343 mg, 85%); $\nu_{max}$ (ATR) 2934 (C–H), 1683 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.27–1.44 (1H, m, C(5)$H_A$), 1.38 (9H, s, C$Me_3$), 1.45–1.64 (5H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_B$), 1.66–1.76 (1H, m, C(1')$H_A$), 2.15–2.28 (1H, m, C(1')$H_B$), 2.55–2.67 (1H, m, C(6)$H_A$), 2.94 (1H, ddd, *J* 13.9, 12.4, 4.3, C(2')$H_A$), 3.10 (1H, ddd, *J* 13.9, 12.1, 4.3, C(2')$H_B$), 3.87–3.97 (1H, m, C(6)$H_B$), 4.18–4.28 (1H, m, C(2)*H*), 7.56 (2H, dd, *J* 7.6, 7.3, *m-Ph*), 7.65 (1H, t, *J* 7.3, *p-Ph*), 7.89 (2H, d, *J* 7.6, *o-Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 18.9 (*C*(4)), 22.9 (*C*(1')), 25.3 (*C*(5)), 28.4 (C$Me_3$), 28.8 (*C*(3)), 38.7 (*C*(6)), 49.1 (*C*(2)), 53.7 (*C*(2')), 79.7 (*C*$Me_3$), 127.9, 129.3, 133.7, 139.1 (*Ph*), 154.9 (N*C*O); *m/z* ($ESI^+$) 729 ($[2M+Na]^+$, 100%), 376 ($[M+Na]^+$, 100%), 354 ($[M+H]^+$, 20%); HRMS ($ESI^+$) $C_{18}H_{27}NNaO_4S^+$ $[M+Na]^+$ requires 376.1553; found 376.1554.

**(2*RS*,9*RS**)-2-(phenylsulfonyl)hexahydroindolizin-3(2*H*)-one 161**[28]

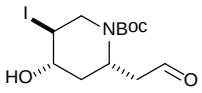



*Method A*: BuLi (2.40 M in hexanes, 63 μL, 0.15 mmol) was added dropwise to a stirred solution of **160** (50 mg, 0.14 mmol) in THF (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 1 h. Satd aq $NH_4Cl$ (5 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), then dried and concentrated *in vacuo* to give a complex mixture of products.

*Method B*: KHMDS (0.5 M in PhMe, 0.30 mL, 0.15 mmol) was added dropwise to a stirred solution of **160** (50 mg, 0.14 mmol) in THF (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 1 h. Satd aq $NH_4Cl$ (5 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 5 mL), and the combined organic extracts were washed with brine (5 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→60% $Et_2O$ in 30–40 °C petrol) gave **160** as a colourless gum (10 mg, 20%). Further elution gave **161** as an off-white gum (13 mg, 34%, >99:1 dr, 95% purity); $\nu_{max}$ (ATR) 2938, 2858 (C–H), 1693 (C=O); $\delta_H$ (500 MHz, $CDCl_3$) 1.08 (1H, dddd, *J* 13.2, 13.1, 11.5, 3.2, C(8)$H_A$), 1.30 (1H, ddddd, *J* 12.6, 12.6, 12.6, 4.7, 3.6, C(6)$H_A$), 1.40 (1H, ddddd, *J* 13.4, 13.2, 13.1, 3.2, 3.2, C(7)$H_A$), 1.71 (1H, app d, *J* 13.1, C(6)$H_B$), 1.87 (1H, app dddd, *J* 13.4, 3.2, 3.2, 1.4, C(7)$H_B$), 1.98 (1H, app dd, *J* 13.2, 3.4, C(8)$H_B$), 2.03 (1H, ddd, *J* 14.8, 10.2, 7.4, C(1)$H_A$), 2.66 (1H, ddd, *J* 13.3, 13.1, 3.6, C(5)$H_A$), 2.99 (1H, ddd, *J* 14.8, 7.2, 2.8, C(1)$H_B$), 3.51 (1H, dddd, *J* 11.5, 7.4, 7.2, 3.4, C(9)*H*), 3.92 (1H, dd, *J* 10.2, 2.8, C(2)*H*), 4.08 (1H, app dd, *J* 13.3, 4.7, C(5)$H_B$), 7.58 (2H, dd, *J* 8.4, 7.5, *m-Ph*), 7.69 (1H, tt, *J* 7.5, 1.3, *p-Ph*), 7.94 (2H, dd, *J* 8.4, 1.3, *o-Ph*); $\delta_C$ (125 MHz, $CDCl_3$) 23.2 (*C*(7)), 24.1 (*C*(6)), 25.9 (*C*(1)), 33.7 (*C*(8)), 40.7 (*C*(5)), 55.3 (*C*(9)), 66.0 (*C*(2)), 128.8, 129.3 (*o,m-Ph*), 134.1 (*p-Ph*), 137.8 (*i-Ph*), 163.9 (*C*(3)); *m/z* ($ESI^+$) 581 ($[2M+Na]^+$, 100%), 302 ($[M+Na]^+$, 60%), 280 ($[M+H]^+$, 30%); HRMS ($ESI^+$) $C_{14}H_{17}NNaO_3S^+$ ($[M+Na]^+$) requires 302.0821; found 302.0818.

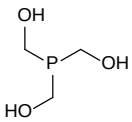
## 6.4 Experimental for Chapter 4

### (*S*,*S*,*S*)-*N*(1)-*tert*-Butoxycarbonyl-2-(2'-oxoethyl)-4-hydroxy-5-iodopiperidine 75



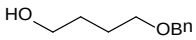

DIBAL-H (1.0 M in $CH_2Cl_2$, 39.2 mL, 39.2 mmol) was added dropwise to a stirred solution of **67** (7.20 g, 19.6 mmol, >99:1 dr) in $CH_2Cl_2$ (210 mL) at −78 °C and the resultant solution was stirred for 1.5 h at −78 °C. $CH_2Cl_2$ (210 mL) and satd aq Rochelle salt (550 mL) were then added subsequently and the reaction mixture was allowed to warm to rt and stirred for 16 h. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 420 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 20%→80% EtOAc in 30–40 °C petrol) gave **75** as a colourless gum (6.16 g, 85%, >99:1 dr);[21] $[\alpha]_D^{20}$ +1.3 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{20}$ +0.7 (*c* 1.0 in $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 1.67–1.74 (1H, m, C(3)*H*$_A$), 2.51–2.59 (1H, m, C(3)*H*$_B$), 2.90 (1H, ddd, *J* 16.4, 7.0, 1.8, C(1')*H*$_A$), 3.02 (1H, ddd, *J* 16.4, 8.0, 2.5, C(1')*H*$_B$), 3.67 (1H, dd, *J* 15.1, 2.7, C(6)*H*$_A$), 4.00 (1H, dd, *J* 15.1, 3.6, C(6)*H*$_B$), 4.09–4.16 (1H, m, C(5)*H*), 4.21–4.26 (1H, m, C(4)*H*), 4.67–4.75 (1H, m, C(2)*H*), 9.75 (1H, dd, *J* 2.5, 1.8, C(2')*H*).

### Tris(hydroxymethyl)phosphine 114



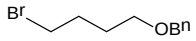

Dry $[P(CH_2OH)_4]^+[Cl]^-$ (114 g, 596 mmol) was dissolved in $Et_3N$ (500 mL) and the resultant mixture was stirred with an over-head stirrer at 60 °C for 1 h. The reaction mixture was then filtered through a pad of Celite® (eluent $Et_3N$) and concentrated *in vacuo* to give **114** as a colourless oil (56.4 g, 76%);[30] $\delta_H$ (400 MHz, MeOD-$d_4$) 4.13 (6H, d, *J* 6.1, P(C*H*$_2$OH)$_3$).

**4-(Benzyloxy)butan-1-ol 170**



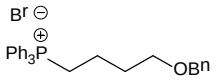

A solution of butan-1,4-diol **169** (39.4 mL, 444 mmol) in THF (80 mL) was added dropwise to a stirred suspension of NaH (4.26 g, 60% w/w in mineral oil, 106 mmol) in THF (150 mL) at 0 °C and the resultant mixture was stirred for 30 min at 0 °C. A solution of BnBr (10.6 mL, 88.8 mmol) in THF (20 mL) was then added dropwise and the resultant mixture was allowed to warm to rt over 16 h. Satd aq $NH_4Cl$ (400 mL) was added, the aqueous layer was extracted with EtOAc (3 × 200 mL), and the combined organic extracts were washed with brine (400 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 50%→100% $Et_2O$ in 30–40 °C petrol) gave **170** as a colourless oil (16.0 g, quant); [31] $\delta_H$ (400 MHz, $CDCl_3$) 1.65–1.78 (4H, m, C(2)$H_2$, C(3)$H_2$), 2.16 (1H, t, *J* 5.6, O*H*), 3.54 (2H, t, *J* 5.8, C(4)$H_2$), 3.66 (2H, app q, *J* 5.8, C(1)$H_2$), 4.54 (2H, s, OC$H_2$Ph), 7.22–7.40 (5H, m, *Ph*).

**1-Bromo-4-(benzyloxy)butane 171**



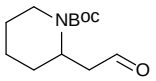

$PPh_3$ (36.8 g, 140 mmol) and $CBr_4$ (22.5 g, 68.0 mmol) were added to a stirred solution of **170** (8.00 g, 42.5 mmol) in $CH_2Cl_2$ (500 mL) at 0 °C and the resultant solution was allowed to warm to rt over 1 h, then concentrated in vacuo. Purification via flash chromatography (gradient elution, 0%→10% $Et_2O$ in 30–40 °C petrol) gave **171** as a colourless oil (10.1 g, 98%);[32] $\delta_H$ (400 MHz, $CDCl_3$) 1.74–1.81 (2H, m, C(2)$H_2$), 1.95–2.03 (2H, m, C(3)$H_2$), 3.45 (2H, t, *J* 8.8, C(1)$H_2$), 3.51 (2H, t, *J* 6.3, C(4)$H_2$), 4.51 (2H, s, OC$H_2$Ph), 7.27–7.39 (5H, m, *Ph*).

**[4-(Benzyloxy)butyl]triphenylphosphonium bromide 168**



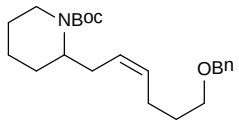
A stirred mixture of **171** (665 mg, 2.74 mmol) and $PPh_3$ (718 mg, 2.74 mmol) was heated to 120 °C for 2 h and then allowed to cool to rt. Purifiction via recrystallisation from $CH_2Cl_2$ gave **168** as a white solid (1.30 g, 94%);[33] mp 161–163 °C ($CH_2Cl_2$); {lit.[33] mp 159–160 °C}; $\nu_{max}$ (ATR) 3055, 2861 (C–H); $\delta_H$ (400 MHz, $CDCl_3$) 1.66–1.78 (2H, m, C(2)$H_2$), 1.89–2.98 (2H, m, C(3)$H_2$), 3.53 (2H, t, *J* 5.7, C(4)$H_2$), 3.63–3.72 (2H, m, C(1)$H_2$), 4.39 (2H, s, OC$H_2$Ph), 7.14–7.24 (5H, m, *Ph*), 7.55–7.76 (15H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 19.5 (*C*(2)), 22.3 (*C*(1)), 29.6 (*C*(3)), 68.8 (*C*(4)), 72.7 (O*C*$H_2$Ph), 118.6, 127.5, 127.6, 128.3, 130.1, 133.6, 135.0, 138.4 (*Ph*); *m/z* ($ESI^+$) 425 ($[M–Br]^+$, 100%); HRMS ($ESI^+$) $C_{29}H_{30}OP^+$ ($[M–Br]^+$) requires 425.2029; found 425.2028.

**(*RS*)-[*N*(1')-*tert*-Butoxycarbonyl-piperidin-2'-yl]ethanal 172**



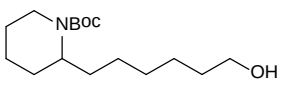
DMSO (10.3 mL, 145.2 mmol) was added to a solution of $(COCl)_2$ (6.7 mL, 79.2 mmol) in $CH_2Cl_2$ (150 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 10 min. A solution of **157** (10.0 g, 44 mmol)[29] in $CH_2Cl_2$ (150 mL) was then added and the resultant mixture was stirred at −78 °C for 1 h. $Et_3N$ (25.2 mL, 180.4 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 15 min, then allowed to warm to rt over 15 min. The reaction mixture was then filtered through a plug of deactivated silica (eluent 30–40 °C petrol/EtOAc/$Et_3N$, 9:9:2) and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→80% $Et_2O$ in 30–40 °C petrol) gave **172** as a colourless oil (8.60 g, 86%);[21] $\delta_H$ (400 MHz, $CDCl_3$) 1.33–1.79 (6H, m, C(3')$H_2$, C(4')$H_2$, C(5')$H_2$), 1.46 (9H, s, C$Me_3$) 2.49–2.58 (1H, m, C(2)$H_A$) 2.69–2.84 (2H, m, C(6')$H_A$, C(2)$H_B$) 3.89–4.07 (1H, m, C(6')$H_B$), 4.87–4.91 (1H, m, C(2')*H*) 9.73–9.75 (1H, m, C(1)*H*).

**(*RS*,*Z*)-*N*(1)-*tert*-Butoxycarbonyl-2-[6'-(benzyloxy)hex-2'-en-1'-yl]piperidine 173**




NaHMDS (1.0 M in THF, 1.32 mL, 1.32 mmol) was added dropwise to a stirred suspension of **168** (667 mg, 1.32 mmol) in THF (1 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 40 min. The reaction mixture was then cooled to 0 °C, a solution of **172** (100 mg, 0.44 mmol) in THF (3 mL) was added dropwise via canula, and the resultant mixture was allowed to warm to rt over 16 h. Satd aq $NH_4Cl$ (5 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→50% $Et_2O$ in 30–40 °C petrol) gave **173** as a colourless oil (163 mg, 99%, >99:1 dr); $\nu_{max}$ (ATR) 3064 (C–H, alkene), 2973, 2932, 2856 (C–H), 1687 (C=O, C=C); $\delta_H$ (400 MHz, $CDCl_3$) 1.31–1.46 (1H, m, C(5)$H_A$), 1.45 (9H, s, C$Me_3$), 1.47–1.63 (5H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_B$), 1.69 (2H, tt, *J* 7.4, 6.5, C(5')$H_2$), 2.16 (2H, dt, *J* 7.4, 7.2, C(4')$H_2$), 2.30 (2H, app dt, *J* 7.0, 6.8, C(1')$H_2$), 2.75 (1H, ddd, *J* 13.3, 13.0, 2.0, C(6)$H_A$), 3.49 (2H, t, *J* 6.5, C(6')$H_2$), 3.97 (1H, app d, *J* 13.3, C(6)$H_B$), 4.17–4.27 (1H, m, C(2)*H*), 4.51 (2H, s, OC$H_2$Ph), 5.35 (1H, app dt, *J* 10.7, 7.0, C(2')*H*), 5.43 (1H, dt, *J* 10.7, 7.2, C(3')*H*), 7.25–7.38 (5H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 19.0 (*C*(4)), 24.0, 25.5, 27.6 (*C*(3), *C*(5), *C*(4')), 28.5 (C$Me_3$), 29.7 (*C*(5')), 69.7 (*C*(6')), 72.9 (O$CH_2$Ph), 79.1 (*C*$Me_3$), 126.9 (*C*(2')), 127.5, 127.6, 128.3 (*o*,*m*,*p*-*Ph*), 130.8 (*C*(3')), 138.6 (*i*-*Ph*), 155.1 (N*C*O);[34] *m/z* ($ESI^+$) 769 ($[2M+Na]^+$, 95%), 396 ($[M+Na]^+$, 100%), 374 ($[M+H]^+$, 35%); HRMS ($ESI^+$) $C_{23}H_{35}NNaO_3^+$ ($[M+Na]^+$) requires 396.2509; found 396.2503.

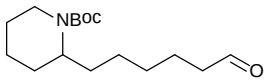
**(*RS*)-*N*(1)-*tert*-Butoxycarbonyl-2-(6'-hydroxyhex-1'-yl)piperidine 174**




$Pd(OH)_2$/C (20% w/w of substrate, 43 mg) was added to a stirred solution of **173** (163 mg, 0.43 mmol) in degassed EtOAc (5 mL) at rt. The resultant mixture was saturated with $H_2$ then

stirred under an atmosphere of $H_2$ (1 atm) at rt for 2 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→80% EtOAc in 30–40 °C petrol) gave **174** as a colourless oil (123 mg, quant); $\nu_{max}$ (ATR) 3433 (O–H), 2930, 2857 (C–H), 1687 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.15–1.71 (16H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(5')$H_2$), 1.42 (9H, s, C$Me_3$), 2.29 (1H, br s, O*H*), 2.67–2.76 (1H, m, C(6)$H_A$), 3.60 (2H, t, *J* 6.6, C(6')$H_2$), 3.88–4.97 (1H, m, C(6)$H_B$), 4.12–4.21 (1H, m, C(2)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 19.0 (*C*(4)), 25.6, 25.7, 26.2 (*C*(5), *C*(2'), *C*(4')), 28.3 (C$Me_3$), 29.2, 29.5 (*C*(3), *C*(3')), 32.7 (*C*(5')), 38.6 (*C*(6)), 50.2 (*C*(2)), 62.8 (*C*(6')), 79.0 (*C*Me$_3$), 155.2 (N*C*O);[35] *m/z* (ESI$^+$) 593 ([2M+Na]$^+$, 100%), 308 ([M+Na]$^+$, 95%), 286 ([M+H]$^+$, 25%); HRMS (ESI$^+$) $C_{16}H_{31}NNaO_3^+$ ([M+Na]$^+$) requires 308.2196; found 308.2195.

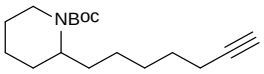
**(*RS*)-*N*(1)-*tert*-Butoxycarbonyl-2-(6'-oxohex-1'-yl)piperidine 175**




DMSO (0.82 mL, 11.6 mmol) was added to a solution of $(COCl)_2$ (0.53 mL, 6.30 mmol) in $CH_2Cl_2$ (14 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of **174** (1.00 g, 3.50 mmol) in $CH_2Cl_2$ (14 mL) was then added via canula and the resultant mixture was stirred at −78 °C for 1 h. $Et_3N$ (2.00 mL, 14.4 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 15 min, then allowed to warm to rt over 15 min. The reaction mixture was then filtered through a column of deactivated silica (eluent 30–40 °C petrol/EtOAc/$Et_3N$, 9:9:2) and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→80% $Et_2O$ in 30–40 °C petrol) gave **175** as a colourless oil (991 mg, quant); $\nu_{max}$ (ATR) 2931, 2859 (C–H), 1725 (C=O, aldehyde) 1687 (C=O, carbamate); $\delta_H$ (400 MHz, $CDCl_3$) 1.19–1.72 (14H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.43 (9H, s, C$Me_3$), 2.41 (2H, td, *J* 7.3, 1.8, C(5')$H_2$), 2.67–2.76 (1H, m, C(6)$H_A$), 3.89–3.99 (1H, m, C(6)$H_B$), 4.13–4.22 (1H, m, C(2)*H*), 9.74 (1H, t, *J* 1.8, C(6')*H*); $\delta_C$ (100 MHz, $CDCl_3$) 19.0 (*C*(4)), 22.0, (*C*(4')), 25.6, 26.1 (*C*(5), *C*(2')), 28.5 (C$Me_3$), 29.0, 29.4 (*C*(3), *C*(3')), 38.7 (*C*(6)), 43.8 (*C*(5')), 50.2 (*C*(2)), 79.0

(*C*Me$_3$), 155.1 (N*C*O), 202.7 (*C*(6'));[35] *m/z* (ESI$^+$) 653 ([2M+2MeOH+Na]$^+$, 100%), 621 ([2M+MeOH+Na]$^+$, 55%), 338 ([M+MeOH+Na]$^+$, 95%), 306 ([M+Na]$^+$, 60%), 284 ([M+H]$^+$, 10%); HRMS (ESI$^+$) $C_{16}H_{29}NNaO_3^+$ ([M+Na]$^+$) requires 306.2040; found 306.2038.

**(*RS*)-*N*(1)-*tert*-Butoxycarbonyl-2-(hept-6'-yn-1'-yl)piperidine 177**



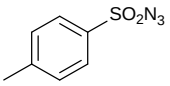

*Method A*: *Step 1*: $CBr_4$ (186 mg, 0.56 mmol) was added to a stirred solution of $PPh_3$ (294 mg, 1.12 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 30 min. The reaction mixture was then cooled to 0 °C, a solution of **175** (122 mg, 0.43 mmol) in $CH_2Cl_2$ (1 mL) was added dropwise, and the resultant solution was stirred at 0 °C for 30 min. Hexane (10 mL) was then added, causing a white precipitate ($OPPh_3$) to form, and the resultant suspension was filtered through a plug of Celite® (eluent hexane) and concentrated *in vacuo*. The residue was dissolved in hexane (10 mL) and the resultant suspension was again filtered through a plug of Celite® (eluent hexane) and concentrated *in vacuo* to give **176**.

*Step 2*: BuLi (2.30 M in hexanes, 0.38 mL, 0.88 mmol) was added dropwise to a stirred solution of **176** in THF (2 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 1 h. Satd aq $NH_4Cl$ (10 mL) was then added dropwise and the aqueous layer was extracted with EtOAc (3 × 10 mL), then the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→50% $Et_2O$ in 30–40 °C petrol) gave **177** as a colourless oil (24 mg, 20%); $\nu_{max}$ (ATR) 3311 (C–H, alkyne), 2974, 2934, 2860, (C–H), 2118 (C≡C), 1686 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.17–1.72 (14H, m, C(3)*H*$_2$, C(4)*H*$_2$, C(5)*H*$_2$, C(1')*H*$_2$, C(2')*H*$_2$, C(3')*H*$_2$, C(4')*H*$_2$), 1.43 (9H, s, C*Me*$_3$), 1.91 (1H, t, *J* 2.7, C(7')*H*), 2.15 (2H, td, *J* 7.0, 2.7, C(5')*H*$_2$), 2.67–2.75 (1H, m, C(6)*H*$_A$), 3.90–3.98 (1H, m, C(6)*H*$_B$), 4.14–4.21 (1H, m, C(2)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 18.3 (*C*(5')), 19.0 (*C*(4)), 25.6, 25.8 (*C*(5), *C*(2')), 28.5 (*C*(4')), 28.5 (C*Me*$_3$), 28.7 (*C*(3')), 29.5 (*C*(3)), 38.8 (*C*(6)), 50.3 (*C*(2)), 68.1 (*C*(7')), 78.9 (*C*Me$_3$), 84.6 (*C*(6')), 155.1 (N*C*O);[35] *m/z* (ESI$^+$) 581 ([2M+Na]$^+$,

35%), 302 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{29}NNaO_2^+$ ([M+Na]$^+$) requires 302.2091; found 302.2088.

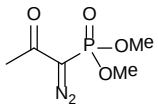
*Method B*: A solution of **181** (294 mg, 1.53 mmol) in dry MeOH (2 mL) was added to a solution of **175** (173 mg, 0.61 mmol) and $K_2CO_3$ (253 mg, 1.83 mmol) in dry MeOH (5 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h. $Et_2O$ (40 mL) was then added and the organic layer was washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→50% $Et_2O$ in 30–40 °C petrol) gave **177** as a colourless oil (158 mg, 93%).

**_p_-Toluenesulfonyl azide 179**




A solution of $NaN_3$ (4.10 g, 63.0 mmol) in $H_2O$ (17 mL) was added to a stirred suspension of TsCl (10.0 g, 52.5 mmol) in $^i$PrOH (30 mL) at rt, and the resultant mixture was stirred at rt for 1 h. $H_2O$ (300 mL) was then added and the resultant mixture was stirred for 1 h. The reaction mixture was then extracted with $CH_2Cl_2$ (4 × 100 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give **179** as a colourless oil (10.4 g, quant);[36] $\delta_H$ (400 MHz, $CDCl_3$) 2.49 (3H, s, *Me*), 7.42 (2H, d, *J* 8.5, *Ar*), 7.86 (2H, d, *J* 8.5, *Ar*).

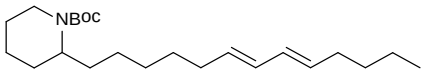
**(1-Diazo-2-oxo-propyl)-phosphonic acid dimethyl ester [Ohira-Bestmann's reagent] 181**




A solution of **180** (5.33 mL, 50.7 mmol) in THF (25 mL) was added dropwise to a stirred suspension of NaH (60% w/w in mineral oil, 2.03 g, 50.7 mmol) in THF (45 mL) and PhMe (90 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1.5 h. A solution of **179** (10.0 g, 50.7 mmol) in PhMe (25 mL) was then added and the resultant mixture was allowed to warm to rt over 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc), then dried and concentrated *in vacuo*. Purification via flash column

chromatography (gradient elution, 20%→80% EtOAc in 30–40 °C petrol) gave **181** as a colourless oil (7.01 g, 72%);[36] $\delta_H$ (400 MHz, $CDCl_3$) 2.28 (3H, s, C(3)$H_3$), 3.86 (6H, d, *J* 11.9, P(O*Me*)$_2$).

**(6'*E*,8'*E*)-*N*(1)-*tert*-Butoxycarbonyl-2-(trideca-6',8'-dienyl)piperidine 182**

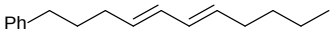



*Method A*: KHMDS (0.5 M in PhMe, 0.30 mL, 0.15 mmol) was added dropwise to a solution of **199** (60 mg, 0.126 mmol) and **82** (0.016 mL, 0.126 mmol) in THF (3 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. $H_2O$ (3 mL) was added dropwise, the aqueous layer was extracted with $Et_2O$ (3 × 3 mL), and the combined organic extracts were washed sequentially with satd aq $NH_4Cl$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 4:1) gave **182** as a colourless oil (28 mg, 61%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]); $\delta_H$ (400 MHz, $CDCl_3$) 0.88–0.92 (3H, m, C(13')$H_3$), 1.18–1.73 (18H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.46 (9H, s, C*Me*$_3$), 2.00–2.10 (4H, m, C(5')$H_2$, C(10')$H_2$), 2.71–280 (1H, m, C(6)$H_A$), 3.92–4.00 (1H, m, C(6)$H_B$), 4.15–4.22 (1H, C(2)*H*), 5.51–5.61 (2H, m, C(6')*H*, C(9')*H*), 5.96–6.02 (2H, m, C(7')*H*, C(8')*H*). Data for (6'*Z*,8'*E*)-isomer: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.28 (1H, dt, *J* 10.7, 7.3, C(6')*H*), 5.64 (1H, dt, *J* 14.9, 7.1, C(9')*H*), 6.29 (1H, ddd, *J* 14.9, 11.2, 1.1, C(8')*H*).

*Method B*: DIBAL-H (1.0 M in THF, 0.40 mL, 0.40 mmol) was added dropwise to a stirred solution of $ZrCp_2Cl_2$ (117 mg, 0.40 mmol) in THF (1 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. A solution of **177** (100 mg, 0.36 mmol) in THF (1 mL) was then added dropwise and the resultant mixture was allowed to warm to rt over 1 h. A solution of **139** (76 mg, 0.36 mmol) and $Pd(PPh_3)_4$ (42 mg, 36 μmol) in THF (1 mL) was added dropwise and the reaction mixture was stirred at rt for 16 h. $H_2O$ (10 mL) was then added dropwise, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution,

0%→50% $Et_2O$ in 30–40 °C petrol) gave a 49:51 mixture of **182** and **186** as a colourless oil (59 mg, 50% combined mass return, >99:1 dr). Data for **186**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 4.94 (1H, ddt, *J* 10.2, 2.2, 1.2, C(7')$H_A$), 5.00 (1H, app dq, *J* 17.1, 1.8, C(7')$H_B$), 5.81 (1H, ddt, *J* 17.1, 10.2, 6.7, C(6')*H*).

**(4*E*,6*E*)-(Undeca-4,6-dien-1-yl)benzene 184**



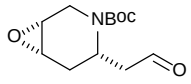

*Method A*: DIBAL-H (1.0 M in hexanes, 0.83 mL, 0.83 mmol) was added dropwise to a stirred solution of $ZrCp_2Cl_2$ (243 mg, 0.83 mmol) in THF (1.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. A solution of **183** (100 mg, 0.69 mmol) in THF (1 mL) was then added dropwise and the resultant mixture was allowed to warm to rt over 1 h. A solution of **139** (132 mg, 0.63 mmol), $Pd(OAc)_2$ (13 mg, 13 μmol) and DAVEPHOS (7 mg, 18 μmol) in THF (1.5 mL) was added dropwise and the reaction mixture was stirred at rt for 16 h. $H_2O$ (10 mL) was then added dropwise, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→10% $Et_2O$ in 30–40 °C petrol) gave **184** as a colourless oil (33 mg, 23%, 85:15 dr); $\nu_{max}$ (ATR) 3085, 3062 (C–H, alkene), 2956, 2926, 2857 (C–H), 1604 (C=C); $\delta_H$ (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, C(11)$H_3$), 1.27–1.42 (4H, m, C(9)$H_2$, C(10)$H_2$), 1.69–1.79 (2H, m, C(2)$H_2$), 2.04–2.15 (4H, m, C(3)$H_2$, C(8)$H_2$), 2.63 (2H, t, *J* 7.6, C(1)$H_2$), 5.55–5.64 (2H, m, C(4)*H*, C(7)*H*), 5.98–6.08 (2H, m, C(5)*H*, C(6)*H*), 7.16–7.23 (3H, m, *Ph*), 7.26–7.32 (2H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 14.0 (*C*(11)), 22.3 (*C*(10)), 31.1, 31.6, 32.1, 35.0, 35.4 (*C*(1), *C*(2), *C*(3), *C*(8), *C*(9)), 125.6, 128.3, 128.4 (*o,m,p-Ph*), 130.2, 130.8 (*C*(5), *C*(6)), 131.7, 132.7 (*C*(4), *C*(7)), 142.5 (*i-Ph*).[22] Data for minor diastereoisomers: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.29–5.37 (1H, m), 5.63–5.76 (1H, m), 6.22–6.37 (1H, m).

*Method B*: DIBAL-H (1.0 M in THF, 0.83 mL, 0.83 mmol) was added dropwise to a stirred solution of $ZrCp_2Cl_2$ (243 mg, 0.83 mmol) in THF (1.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. A solution of **183** (100 mg, 0.69 mmol) in THF (1 mL) was then added dropwise and the resultant mixture was allowed to warm to rt over 1 h. A solution of

**139** (132 mg, 0.63 mmol), $Pd(OAc)_2$ (13 mg, 13 μmol) and DAVEPHOS (7 mg, 18 μmol) in THF (1.5 mL) was added dropwise and the reaction mixture was stirred at rt for 16 h. $H_2O$ (10 mL) was then added dropwise, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→10% $Et_2O$ in 30–40 °C petrol) gave **184** as a colourless oil (83 mg, 58%, >99:1 dr).

*Method C*: DIBAL-H (1.0 M in THF, 0.83 mL, 0.83 mmol) was added dropwise to a stirred solution of $ZrCp_2Cl_2$ (243 mg, 0.83 mmol) in THF (1.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. A solution of **183** (100 mg, 0.69 mmol) in THF (1 mL) was then added dropwise and the resultant mixture was allowed to warm to rt over 1 h. A solution of **139** (132 mg, 0.63 mmol) and $Pd(PPh_3)_4$ (69 mg, 63 μmol) in THF (1.5 mL) was added dropwise and the reaction mixture was stirred at rt for 16 h. $H_2O$ (10 mL) was then added dropwise, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→10% $Et_2O$ in 30–40 °C petrol) gave **184** as a colourless oil (82 mg, 56%, >99:1 dr).

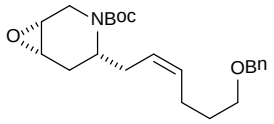
**(2*S*,4*S*,5*R*)-*N*(1)-*tert*-Butoxycarbonyl-2-(2'-oxoethyl)-4,5-epoxypiperidine 187**




1.0 M aq NaOH (280 mL) was added to a stirred solution of **75** (3.80 g, 10.3 mmol, >99:1 dr) in $CH_2Cl_2$ (280 mL) at rt and the resultant mixture was stirred at rt for 1 h. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 280 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→50% EtOAc in 30–40 °C petrol) gave **187** as a colourless gum (2.36 g, 95%, >99:1 dr); $[\alpha]_D^{25}$ +3.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (film) 2978, 2932 (C–H), 1724 (C=O, aldehyde), 1691 (C=O, carbamate); $\delta_H$ (400 MHz, $CDCl_3$) 1.45 (9H, s, C$Me_3$), 2.07–2.25 (2H, m, C(3)$H_2$), 2.82–2.93 (2H, m, C(1')$H_2$), 3.27–3.38 (2H, m, C(4)*H*, C(5)*H*), 3.48–3.67 (1H, m, C(6)$H_A$), 3.96–4.24 (1H, m, C(6)$H_B$), 4.57–4.72 (1H, m, C(2)*H*), 9.86–9.71 (1H, m, C(2')*H*); $\delta_C$ (100 MHz,

$CDCl_3$) 28.3 (C*Me*$_3$), 39.2 (*C*(3)), 42.9 (*C*(6)), 47.9 (*C*(1')), 50.3, 50.6 (*C*(4), *C*(5)), 80.5 (*C*Me$_3$), 154.5 (N*C*O), 200.8 (*C*(2'));[37] *m/z* (ESI$^+$) 505 ([2M+Na]$^+$, 100%), 264 ([M+Na]$^+$, 37%); HRMS (ESI$^+$) $C_{13}H_{23}NNaO_5^+$ [M+Na+MeOH]$^+$ requires 296.1468; found 296.1467.

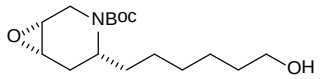
**(2*R*,4*S*,5*R*,*Z*)-*N*(1)-*tert*-Butoxycarbonyl-2-[6'-(benzyloxy)hex-2'-en-1'-yl]-4,5-epoxypiperidine 188**




NaHMDS (1.0 M in THF, 16.6 mL, 16.6 mmol) was added dropwise to a stirred suspension of **168** (8.40 g, 16.6 mmol) in THF (22 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 40 min. The reaction mixture was then cooled to 0 °C, a solution of **187** (2.67 g, 11.1 mmol, >99:1 dr) in THF (40 mL) was added dropwise via canula, and the resultant mixture was allowed to warm to rt over 16 h. Satd aq $NH_4Cl$ (120 mL) was then added, the aqueous layer was extracted with $Et_2O$ (3 × 240 mL), and the combined organic extracts were washed with brine (240 mL) then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 10%→60% $Et_2O$ in 30–40 °C petrol) gave **188** as a colourless oil (4.07 g, 95%, >95:5 dr); $[\alpha]_D^{25}$ −19.5 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 2976, 2931, 2859 (C–H), 1687 (C=O, C=C); $\delta_H$ (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 1.68 (2H, tt, *J* 7.0, 6.6, C(5')*H*$_2$), 2.02 (1H, ddd, *J* 15.4, 6.3, 1.8, C(3)*H*$_A$) 2.09 (1H, app d, *J* 15.4, C(3)*H*$_B$), 2.17 (2H, dt, *J* 7.2, 7.0, C(4')*H*$_2$), 2.28–2.40 (1H, m, C(1')*H*$_A$), 2.48 (1H, ddd, *J* 13.9, 7.6, 7.6, C(1')*H*$_B$), 3.22–3.31 (2H, m, C(4)*H*, C(5)*H*), 3.42–3.51 (1H, m, C(6)*H*$_A$), 3.48 (2H, t, *J* 6.6, C(6')*H*$_2$), 3.98–4.31 (2H, m, C(2)*H*, C(6)*H*$_B$), 4.50 (2H, s, OC*H*$_2$Ph), 5.28 (1H, dt, *J* 10.7, 7.6, C(2')*H*), 5.43 (1H, dt, *J* 10.7, 7.2, C(3')*H*), 7.23–7.37 (5H, m, *Ph*); $\delta_H$ (500 MHz, PhMe-$d_8$, 363 K) 1.44 (9H, s, C*Me*$_3$), 1.66 (2H, tt, *J* 7.0, 6.6, C(5')*H*$_2$), 1.63–1.69 (1H, m, C(3)*H*$_A$), 1.87 (1H, app d, *J* 15.1, C(3)*H*$_B$), 2.22 (2H, dt, *J* 7.4, 7.0, C(4')*H*$_2$), 2.41 (1H, ddd, *J* 14.5, 7.6, 7.4, C(1')*H*$_A$), 2.56 (1H, ddd, *J* 14.4, 7.4, 7.4, C(1')*H*$_B$), 2.76–2.80 (2H, m, C(4)*H*, C(5)*H*), 3.38–3.43 (1H, m, C(6)*H*$_A$), 3.40 (2H, t, *J* 6.6, C(6')*H*$_2$), 3.95–4.02 (2H, m, C(6)*H*$_B$), 4.06–4.12 (1H, m, C(2)*H*), 4.37 (2H, s, OC*H*$_2$Ph), 5.35 (1H, ddd, *J* 10.7, 7.4, 7.4, C(2')*H*), 5.44

(1H, dt, *J* 10.7, 7.4, C(3')*H*), 7.08–7.29 (5H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 24.0 (*C*(4')), 28.3 (C*Me*$_3$), 28.4 (*C*(3)), 29.7 (*C*(5')), 30.9 (*C*(1')), 39.3 (*C*(6)), 48.0 (*C*(2)), 50.2 (*C*(4)), 50.8 (*C*(5)), 69.9 (*C*(6')), 72.9 (O*C*H$_2$Ph), 79.8 (*C*Me$_3$), 126.8 (*C*(2')), 127.4, 127.6, 128.3 (*o*,*m*,*p*-*Ph*), 131.3 (*C*(3')), 138.7 (*i*-*Ph*), 154.9 (N*C*O); $\delta_C$ (125 MHz, PhMe-$d_8$, 363 K) 24.5 (*C*(4')), 27.3 (*C*(3)), 28.5 (C*Me*$_3$), 30.1 (*C*(5')), 31.5 (*C*(1')), 40.2 (*C*(6)), 49.0 (*C*(2)), 49.9 (*C*(4)), 50.3 (*C*(5)), 70.1 (*C*(6')), 73.0 (O*C*H$_2$Ph), 79.2 (*C*Me$_3$), 127.3 (*C*(2')), 127.4, 127.6, 128.3 (*o*,*m*,*p*-*Ph*), 131.5 (*C*(3')), 139.7 (*i*-*Ph*), 154.7 (N*C*O); *m/z* (ESI$^+$) 797 ([2M+Na]$^+$, 30%), 410 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{33}NNaO_4^+$ ([M+Na]$^+$) requires 410.2302; found 410.2292.

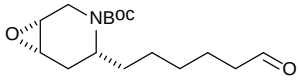
**(2*R*,4*S*,5*R*)-*N*(1)-*tert*-Butoxycarbonyl-2-(6'-hydroxyhex-1'-yl)-4,5-epoxypiperidine 189**




$Pd(OH)_2$/C (20% w/w of substrate, 77 mg) was added to a stirred solution of **188** (300 mg, 0.77 mmol, >99:1 dr) in degassed EtOAc (9 mL) at rt. The resulting mixture was saturated with $H_2$ then stirred under an atmosphere of $H_2$ (1 atm) at rt for 2 h. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→80% EtOAc in 30–40 °C petrol) gave **189** as a colourless oil (219 mg, 95%, >99:1 dr); $[\alpha]_D^{20}$ +4.7 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3422 (O–H), 2930, 2859 (C–H), 1689 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.06–1.16 (2H, m, C(3')$H_2$), 1.20–1.30 (4H, m, C(2')$H_2$, C(4')$H_2$), 1.38 (9H, s, C*Me*$_3$), 1.42–1.51 (3H, m, C(1')$H_A$, C(5')$H_2$), 1.72–1.84 (1H, m, C(1')$H_B$), 1.92–2.06 (2H, m, C(3)$H_2$), 2.29 (1H, br s, O*H*), 3.16–3.26 (2H, m, C(4)*H*, C(5)*H*), 3.27–3.40 (1H, m, C(6)$H_A$), 3.52 (2H, t, *J* 6.6, C(6')$H_2$), 3.93–4.25 (2H, m, C(2)*H*, C(6)$H_B$); $\delta_H$ (500 MHz, PhMe-$d_8$, 363 K) 1.17–1.33 (6H, m, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.38–1.48 (3H, m, C(1')$H_A$, C(5')$H_2$), 1.44 (9H, s, C*Me*$_3$), 1.72 (1H, ddd, *J* 15.0, 6.6, 1.9, C(3)$H_A$), 1.78 (1H, app d, *J* 15.0, C(3)$H_B$), 1.86–1.96 (1H, m, C(1')$H_B$), 2.79–2.84 (2H, m, C(4)*H*, C(5)*H*), 3.35 (1H, app d, *J* 15.4, C(6)$H_A$), 3.43 (2H, t, *J* 6.5, C(6')$H_2$), 4.00–4.08 (2H, m, C(2)*H*, C(6)$H_B$); $\delta_C$ (100 MHz, $CDCl_3$) 25.7 (*C*(4')), 26.6 (*C*(2')), 28.3 (C*Me*$_3$), 29.0 (*C*(3')), 32.6 (*C*(5')), 38.7 (*C*(6)), 48.1 (*C*(2)), 50.3,

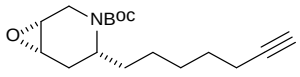
50.7 (*C*(4), *C*(5)), 62.6 (*C*(6')), 79.7 (*C*Me$_3$), 154.9 (N*C*O);[38] $\delta_C$ (125 MHz, PhMe-$d_8$, 363 K) 26.1 (*C*(4')), 27.0 (*C*(2')), 28.0 (*C*(3)), 28.2 (C*Me*$_3$), 29.4 (*C*(3')), 33.2, 33.2 (*C*(1'), *C*(5')), 39.9 (*C*(6)), 48.9 (*C*(2)), 50.0, 50.2 (*C*(4), *C*(5)), 62.6 (*C*(6')), 79.2 (*C*Me$_3$), 154.9 (N*C*O); *m/z* (ESI$^+$) 621 ([2M+Na]$^+$, 75%), 322 ([M+Na]$^+$, 100%), 300 ([M+H]$^+$, 20%); HRMS (ESI$^+$) $C_{16}H_{29}NNaO_4^+$ ([M+Na]$^+$) requires 322.1989; found 322.1988.

**(2*R*,4*S*,5*R*)-*N*(1)-*tert*-Butoxycarbonyl-2-(6'-oxohex-1'-yl)-4,5-epoxypiperidine 190**




DMSO (0.08 mL, 1.09 mmol) was added to a solution of $(COCl)_2$ (0.05 mL, 0.59 mmol) in $CH_2Cl_2$ (1.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 10 min. A solution of **189** (100 mg, 0.33 mmol) in $CH_2Cl_2$ (1.5 mL) was then added and the resultant mixture was stirred at −78 °C for 1 h. $Et_3N$ (0.19 mL, 1.35 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 15 min, then allowed to warm to rt over 15 min. The reaction mixture was then filtered through a plug of deactivated silica (eluent 30–40 °C petrol/EtOAc/$Et_3N$, 9:9:2) and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→80% $Et_2O$ in 30–40 °C petrol) gave **190** as a colourless oil (51 mg, 52%, >99:1 dr); $[\alpha]_D^{25}$ +9.0 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 2931 (C–H), 1724 (C=O, aldehyde), 1687 (C=O, carbamate); $\delta_H$ (400 MHz, $CDCl_3$) 1.10–1.38 (7H, m, C(1')$H_A$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.42 (9H, s, C*Me*$_3$), 1.58 (2H, tt, *J* 7.5, 7.4, C(4')$H_2$), 1.42–1.51 (3H, m, C(1')$H_A$), 1.78–1.90 (1H, m, C(1')$H_B$), 1.96–2.11 (2H, m, C(3)$H_2$), 2.38 (2H, td, *J* 7.4, 1.8, C(5')$H_2$), 3.20–3.30 (2H, m, C(4)*H*, C(5)*H*), 3.32–3.45 (1H, m, C(6)$H_A$), 3.95–4.33 (2H, m, C(2)*H*, C(6)$H_B$), 9.72 (1H, t, *J* 1.8, C(6')*H*); $\delta_C$ (100 MHz, $CDCl_3$) 22.0 (*C*(4')), 26.4 (*C*(2')), 28.3 (C*Me*$_3$), 28.8 (*C*(3')), 32.6 (*C*(3)), 43.8 (*C*(5')), 50.3, 50.7 (*C*(4), *C*(5)), 79.8 (*C*Me$_3$), 154.8 (N*C*O), 202.7 (*C*(6'));[39] *m/z* (ESI$^+$) 681 ([2M+2MeOH+Na]$^+$, 649 ([2M+MeOH+Na]$^+$, 45%), 352 ([M+MeOH+Na]$^+$, 100%), 320 ([M+Na]$^+$, 45%); HRMS (ESI$^+$) $C_{16}H_{27}NNaO_4^+$ ([M+Na]$^+$) requires 320.1832; found 320.1841. Further elution gave **189** as a colourless gum (40 mg, 40%, >99:1 dr); $[\alpha]_D^{20}$ +5.0 (*c* 1.0 in $CHCl_3$).

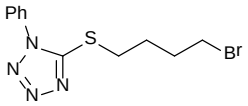
**(2*R*,4*S*,5*R*)-*N*(1)-*tert*-Butoxycarbonyl-2-(hept-6'-yn-1'-yl)-4,5-epoxypiperidine 191**




A solution of **181** (82 mg, 0.43 mmol) in dry MeOH (1 mL) was added to a solution of **190** (50 mg, 0.17 mmol) and $K_2CO_3$ (70 mg, 0.51 mmol) in dry MeOH (1 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h. $Et_2O$ (10 mL) was then added and the organic layer was washed with satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→50% $Et_2O$ in 30–40 °C petrol) gave **191** as a colourless oil (40 mg, 81%, >99:1 dr); $[\alpha]_D^{25}$ +5.2 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3293 (C–H, alkyne), 2976, 2932, 2860 (C–H), 2117 (C≡C), 1685 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.09–1.26 (2H, m, C(3')$H_2$), 1.28–1.54 (5H, m, C(3)$H_A$, C(2')$H_2$, C(4')$H_2$), 1.43 (9H, s, C$Me_3$), 1.77–1.91 (1H, m, C(3)$H_B$), 1.91 (1H, t, *J* 2.7, C(7')*H*), 1.97–2.10 (2H, m, C(1')$H_2$), 2.14 (2H, td, *J* 7.0, 2.7, C(5')$H_2$), 3.20–3.31 (2H, m, C(4)*H*, C(5)*H*), 3.30–3.50 (1H, m, C(6)$H_A$), 3.97–4.33 (2H, m, C(2)*H*, C(6)$H_B$); $\delta_C$ (100 MHz, $CDCl_3$) 18.3 (*C*(5')), 26.2 (*C*(3')), 28.3, 28.4 (*C*(2'), *C*(4')), 28.4 (C$Me_3$), 32.6 (*C*(3)), 50.4, 50.7 (*C*(4), *C*(5)), 68.2 (*C*(7')), 79.7 (*C*Me$_3$), 84.5 (*C*(6')), 155.0 (N*C*O);[39] *m/z* ($ESI^+$) 609 ($[2M+Na]^+$, 100%), 316 ($[M+Na]^+$, 75%); HRMS ($ESI^+$) $C_{17}H_{27}NNaO_3^+$ ($[M+Na]^+$) requires 316.1883; found 316.1886.

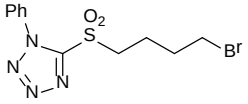
## 6.5 Experimental for Chapter 5

### *N*(1)-Phenyl-5-(4'-bromobutylsulfanyl)-1*H*-tetrazole 195



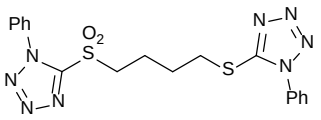

KO$^t$Bu (5.20 g, 46.3 mmol) and 1,4-dibromobutane **194** (5.50 mL, 46.3 mmol) were added to a stirred solution of PTSH (8.25 g, 46.3 mmol) in DMF (100 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 15 min. Satd aq $NH_4Cl$ (240 mL), $Et_2O$ (360 mL) and $H_2O$ (480 mL) were then added, and the resultant mixture was filtered. The aqueous layer was extracted with $Et_2O$ (3 × 300 mL) and the combined organic extracts were washed with brine (800 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 9:1 increased to 3:1) gave **195** as a colourless oil (6.33 g, 44%);[21] $\delta_H$ (400 MHz, $CDCl_3$) 1.98–2.09 (4H, m, C(2')$H_2$), C(3')$H_2$), 3.39–3.50 (4H, m, C(1')$H_2$, C(4')$H_2$), 7.53–7.64 (5H, m, *Ph*).

### *N*(1)-Phenyl-5-(4'-Bromobutylsulfonyl)-1*H*-tetrazole 196



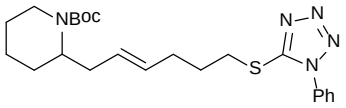

*m*-CPBA (19.6 g, 73% w/w in $H_2O$, 80.8 mmol) was added portionwise to a stirred solution of **195** (6.33 g, 20.2 mmol) in $CH_2Cl_2$ (300 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 48 h. 10% aq NaOH (400 mL) and 0.5 M aq $Na_2SO_3$ (400 mL) were added sequentially. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 300 mL) and the combined organic extracts were washed with brine (800 mL), then dried and concentrated *in vacuo* to give **196** as a white solid (7.09 g, quant);[21] mp 73–75 °C; {lit.[21] mp 74–76 °C}; $\delta_H$ (400 MHz, $CDCl_3$) 2.04–2.24 (4H, m, C(2')$H_2$, C(3')$H_2$), 3.45 (2H, t, *J* 6.5, C(4')$H_2$), 3.78–3.84 (2H, m, C(1')$H_2$), 7.59–7.74 (5H, m, *Ph*).

**_N_(1)-Phenyl-5-({4'-[_N_(1'')-phenyl-1''_H_-tetrazol-5''-yl]sulfanyl}butylsulfonyl)-1_H_-tetrazole 193**



A solution of **196** (4.75 g, 13.8 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise to a stirred solution of PTSH (4.92 g, 27.6 mmol) and KOH (1.55 g, 27.6 mmol) in EtOH (125 mL) at rt, and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered and washed with cold $Et_2O$ (30 mL), giving **193** as a white solid. Purification via recrystallisation ($CH_2Cl_2$) gave **193** as a while solid (5.77 g, 88%); mp 131–133 °C ($CH_2Cl_2$); $\nu_{max}$ (KBr) 2946, 2927, 2904 (C−H), 1498, 1338, 1187, 768, 695; $\delta_H$ (400 MHz, $CDCl_3$) 2.07–2.22 (4H, m, C(2')$H_2$, C(3')$H_2$), 3.45 (2H, t, *J* 6.8, C(4')$H_2$), 3.82 (2H, t, *J* 7.5, C(1')$H_2$) 7.51–7.73 (10H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 21.3 (*C*(3')), 27.7 (*C*(2')), 32.1 (*C*(4')), 55.3 (*C*(1')), 123.8, 125.0, 129.8, 129.9, 130.3, 131.5 (*o*,*m*,*p*-*Ph*), 132.9, 133.5 (*i*-*Ph*), 153.3, 153.8 (*C*(5), *C*(5'')); *m/z* ($ESI^+$) 465 ($[M+Na]^+$, 100%); HRMS ($ESI^+$) $C_{18}H_{18}N_8NaO_2S_2^+$ $[M+Na]^+$ requires 465.0889; found 465.0886.

**(_E_)-_N_(1)-_tert_-Butyoxycarbonyl-2-{6'-[_N_(1'')-phenyl-1"_H_-tetrazol-5"-ylsulfanyl]hex-2'-en-1'-yl}piperidine 197**



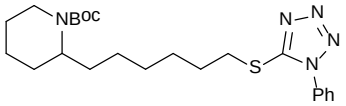
*Method A*: KHMDS (0.5 M in PhMe, 1.02 mL, 0.51 mmol) was added dropwise to a stirred solution of **172** (100 mg, 0.44 mmol) and **193** (235 mg, 0.53 mmol) in THF (20 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h, then allowed to warm to rt over 1 h. Satd aq $NH_4Cl$ (1 mL) was then added and the resultant mixture was concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (30 mL), then the resultant solution was dried and concentrated *in vacuo*. Purification via trituration from $Et_2O$ and subsequent flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 1:1) gave **197** as a colourless gum (141 mg, 72%, >95:5 dr); $\nu_{max}$ (film) 2934 (C−H), 1686 (C=O); $\delta_H$ (400

MHz, $CDCl_3$) 1.29–1.40 (2H, m, C(4)$H_2$), 1.44 (9H, s, C$Me_3$), 1.49–1.64 (4H, m, C(3)$H_2$, C(5)$H_2$), 1.83–1.96 (2H, m, C(5')$H_2$), 2.09–2.27 (3H, m, C(4')$H_2$, C(1')$H_A$), 2.27–2.38 (1H, m, C(1')$H_B$), 2.68–2.79 (1H, m, C(6)$H_A$), 3.33–3.42 (2H, m, C(6')$H_2$), 3.88–4.02 (1H, m, C(6)$H_B$), 4.15–4.28 (1H, m, C(2)*H*), 5.34–5.47 (2H, m, C(2')*H*, C(3')*H*), 7.49–7.63 (5H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 18.8 (*C*(4)), 25.5 (*C*(5)), 27.6 (*C*(5')), 28.5 (C$Me_3$), 28.7 (*C*(3)), 31.4 (*C*(4')), 32.6 (*C*(6')), 33.1 (*C*(1')), 38.9 (*C*(6)), 58.0 (*C*(2)), 79.0 (*C*$Me_3$), 123.8 (*o-Ph*), 128.7 (*C*(2')), 129.8 (*m-Ph*), 130.1, 130.4 (*C*(3'), *p-Ph*), 133.7 (*i-Ph*), 154.4, 155.1 (*C*(5''), N*C*O); *m/z* ($ESI^+$) 466 ($[M+Na]^+$, 100%); HRMS ($ESI^+$) $C_{23}H_{33}N_5NaO_2S^+$ $[M+Na]^+$ requires 466.2247; found 466.2237.

*Method B*: LiHMDS (0.9 M in PhMe, 0.57 mL, 0.51 mmol) was added dropwise to a stirred solution of **172** (100 mg, 0.44 mmol) and **193** (235 mg, 0.53 mmol) in THF (20 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h, then allowed to warm to rt over 1 h. Satd aq $NH_4Cl$ (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (30 mL), then the resultant solution was dried and concentrated *in vacuo*. Purification via trituration from $Et_2O$ and subsequent flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 1:1) gave **197** as a colourless gum (135 mg, 69%, >95:5 dr).

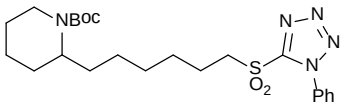
*Method C*: LDA (0.51 M in THF, 1.0 mL, 0.51 mmol) was added dropwise to a stirred solution of **172** (100 mg, 0.44 mmol) and **193** (235 mg, 0.53 mmol) in THF (20 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1 h, then allowed to warm to rt over 1 h. Satd aq $NH_4Cl$ (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (30 mL), then the resultant solution was dried and concentrated *in vacuo*. Purification via trituration from $Et_2O$ and subsequent flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 1:1) gave **197** as a colourless gum (126 mg, 65%, >95:5 dr).

**_N_(1)-*tert*-Butyoxycarbonyl-2-{6'-[_N_(1'')-phenyl-1"_H_-tetrazol-5"-ylsulfanyl]hex-1'-yl}piperidine 198**




$PtO_2$ (21 mg, 92 μmol) was added to a stirred solution of **197** (200 mg, 0.46 mmol) in degassed EtOH (1 mL) at rt in a thick-walled glass vessel. The vessel was sealed, purged with $H_2$ gas, pressurised to 5 bar of $H_2$, and stirred at rt for 4 h. The pressure was then released and the rection mixture was concentrated *in vacuo*. The residue was then dissolved in $Et_2O$, and the resultant solution was filtered through a short plug of Celite® (eluent $Et_2O$), and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 1:1) gave **198** as a colourless gum (175 mg, 89%);[21] $\delta_H$ (400 MHz, $CDCl_3$) 1.15–1.74 (14H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.45 (9H, s, C$Me_3$), 1.78–1.87 (2H, m, C(5')$H_2$), 2.66–2.79 (1H, m, C(6)$H_A$), 3.41 (2H, t, *J* 7.2, C(6')$H_2$), 3.88–4.03 (1H, m, C(6)$H_B$), 4.14–4.23 (1H, m, C(2)*H*), 7.52–7.61 (5H, m, *Ph*).

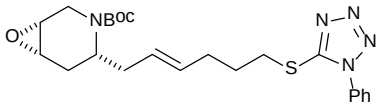
**_N_(1)-*tert*-Butyoxycarbonyl-2-{6'-[_N_(1'')-phenyl-1"_H_-tetrazol-5"-ylsulfonyl]hex-1'-yl}piperidine 199**




*m*-CPBA (214 mg, 71% w/w in $H_2O$, 0.88 mmol) was added portionwise to a stirred solution of **198** (100 mg, 0.22 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C, and the resultant mixture was allowed to warm to rt over 48 h. 10% aq NaOH (5 mL) and 0.5 M aq $Na_2SO_3$ (5 mL) were added sequentially, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo* to give **199** as a white solid (95 mg, 90%);[21] mp 73–75 °C mp {lit.[21] mp 73 °C}; $\delta_H$ (400 MHz, $CDCl_3$) 1.17–1.87 (14H, m, C(3)$H_2$, C(4)$H_2$, C(5)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$),

1.43 (9H, s, C*Me*$_3$), 1.90–2.00 (2H, m, C(5')*H*$_2$), 2.66–2.77 (1H, m, C(6)*H*$_A$), 3.67–3.76 (2H, m, C(6')*H*$_2$), 3.89–4.01 (1H, m, C(6)*H*$_B$), 4.13–4.24 (1H, m, C(2)*H*), 7.56–7.74 (5H, m, *Ph*).

**(2*R*,4*S*,5*R*,2'*E*)-*N*(1)-*tert*-Butoxycarbonyl-2-{6'-[*N*(1'')-phenyl-1"*H*-tetrazol-5"-ylsulfanyl]hex-2'-en-1'-yl}-4,5-epoxypiperidine 192**

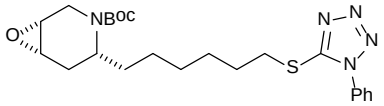



*Method A*: KHMDS (0.5 M in PhMe, 0.64 mL, 0.32 mmol) was added dropwise to a stirred solution of **75** (100 mg, 0.27 mmol) and **193** (142 mg, 0.32 mmol) in THF (20 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1 h, then allowed to warm to rt over 1 h. $H_2O$ (30 mL) was then added, the aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed sequentially with satd aq $NH_4Cl$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification via trituration from $Et_2O$ and subsequent flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 4:1) gave **192** as a colourless oil (47 mg, 38%, >95:5 dr); $[\alpha]_D^{25}$ −12.3 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (film) 2928 (C−H), 1687 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.83–1.95 (2H, m, C(5')*H*$_2$), 2.00–2.10 (2H, m, C(1')*H*$_2$), 2.10–2.17 (2H, m, C(4')*H*$_2$), 2.18–2.29 (1H, m, C(3)*H*$_A$), 2.45–2.58 (1H, m, C(3)*H*$_B$), 3.23–3.33 (2H, m, C(4)*H*, C(5)*H*), 3.33–3.54 (3H, m, C(6)*H*$_A$, C(6')*H*$_2$), 3.99–4.26 (2H, m, C(2)*H*, C(6)*H*$_B$)), 5.32 (1H, app dt, *J* 15.2, 6.8, C(2')*H*), 5.44 (1H, app dt, *J* 15.2, 6.3, C(3')*H*), 7.51–7.63 (5H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 26.3 (C(5')), 28.4 (C*Me*$_3$), 28.7 (C(4')), 31.4 (C(6')), 32.6 (C(3)), 36.3 (C(1')), 50.3, 50.8 (C(4), C(5)), 79.8 (*C*Me$_3$), 123.8 (*o-Ph*), 128.8 (C(2')), 129.8 (*m-Ph*), 130.1 (*p-Ph*), 130.8 (C(3')), 133.7 (*i-Ph*), 154.37, 154.88, (*C*(5"), N*C*O); *m/z* (ESI$^+$) 480 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{31}N_5NaO_3S^+$ [M+Na]$^+$ requires 480.2032; found 480.2040.

*Method B*: KHMDS (0.5 M in PhMe, 1.06 mL, 0.53 mmol) was added dropwise to a stirred solution of **187** (106 mg, 0.44 mmol) and **193** (235 mg, 0.53 mmol) in THF (25 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1 h, then allowed to warm to rt over 1 h. Satd aq $NH_4Cl$ (1 mL) was then added and the resultant mixture was concentrated *in vacuo*. The residue was dissolved in $CH_2Cl_2$ (50 mL), and the resultant solution was dried

and concentrated *in vacuo*. Purification via trituration from $Et_2O$ and subsequent flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 4:1) gave **192** as a colourless gum (151 mg, 75%, >95:5 dr); $[\alpha]_D^{25}$ −11.6 (*c* 1.0 in $CHCl_3$).

**(2*R*,4*S*,5*R*)-*N*(1)-*tert*-Butoxycarbonyl-2-{6'-[*N*(1'')-phenyl-1''*H*-tetrazol-5''-ylsulfanyl]hex-1'-yl}-4,5-epoxypiperidine 80**

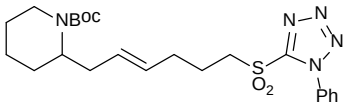



*Method A*: $PtO_2$ (27 mg, 0.12 mmol) was added to a stirred solution of **192** (270 mg, 0.59 mmol) in degassed EtOH (2 mL) at rt in a thick-walled glass vessel. The vessel was sealed, purged with $H_2$ gas, pressurised to 5 bar of $H_2$, and stirred at rt for 4 h. The pressure was then released, and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in $Et_2O$, filtered through a short plug of Celite® (eluent $Et_2O$), and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 1:2) gave **80** as a colourless gum (217 mg, 80%);[21] $[\alpha]_D^{25}$ +2.1 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{25}$ +1.7 (*c* 1.0 in $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 1.07–1.49 (7H, m, C(1')$H_A$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.42 (9H, s, C$Me_3$), 1.77–1.89 (1H, m, C(1')$H_B$), 1.78 (2H, tt, *J* 7.3, 7.3, C(5')$H_2$), 2.00 (1H, app d, *J* 14.9, C(3)$H_A$), 2.06 (1H, ddd, *J* 14.9, 6.6, 1.8, C(3)$H_B$), 3.20–3.29 (2H, m, C(4)*H*, C(5)*H*), 3.32–3.42 (1H, m, C(6)$H_A$), 3.35 (2H, t, *J* 7.3, C(6')$H_2$), 3.95–4.30 (2H, m, C(6)$H_B$, C(2)*H*), 7.50–7.58 (5H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 26.5 (*C*(2')), 28.4 (C$Me_3$), 28.5 (*C*(4')), 28.7 (*C*(5')), 29.0 (*C*(3')), 32.7 (*C*(1')), 33.3 (*C*(6')), 50.3, 50.7 (*C*(4), *C*(5)), 79.7 (*C*$Me_3$), 123.8, 129.7, 130.0, 133.7 (*Ph*), 154.4, 155.0 (*C*(5''), N*C*O);[40] $\delta_H$ (500 MHz, PhMe-$d_8$, 363 K) 1.12–1.47 (7H, m, C(1')$H_A$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.44 (9H, s, C$Me_3$), 1.85 (2H, tt, *J* 7.3, 7.3, C(5')$H_2$), 1.73 (1H, ddd, *J* 15.0, 6.6, 1.9, C(3)$H_A$), 1.78 (1H, app d, *J* 15.0, C(3)$H_B$), 1.85–1.94 (1H, m, C(1')$H_B$), 3.79–3.83 (2H, m, C(4)*H*, C(5)*H*), 3.16 (2H, t, *J* 7.3, C(6')$H_2$), 3.32–3.38 (1H, app d, *J* 15.4, C(6)$H_A$), 3.99–4.09 (2H, m, C(6)$H_B$, C(2)*H*), 7.04–7.11 (3H, m, *m,p-Ph*), 7.28–7.32 (2H, m, *o-Ph*); $\delta_C$ (125 MHz, PhMe-$d_8$, 363 K) 26.8 (*C*(2')), 28.5 (C$Me_3$), 28.8, 28.9 (*C*(5'), *C*(4')), 29.5 (*C*(3')), 33.1 (*C*(1')), 33.7

(*C*(6')), 40.0 (*C*(6)), 48.9 (*C*(2)), 50.0, 50.2 (*C*(4), *C*(5)), 79.2 (*C*Me$_3$), 124.0, 129.4, 129.5, 134.8 (*Ph*), 154.1, 154.9 (*C*(5"), N*C*O).

*Method B*: DEAD (1.04 mL, 6.64 mmol) was added dropwise to a stirred solution of **189** (1.53 g, 5.11 mmol, >99:1 dr), HSPT (1.09 g, 6.13 mmol), and PPh$_3$ (1.61 g, 6.13 mmol) in THF (40 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h. EtOAc (160 mL) was then added and the organic layer was washed sequentially with brine (80 mL) and H$_2$O (80 mL), then dried and concentrated *in vacuo*. Purification via flash chromatography (gradient elution, 0%→60% EtOAc in 30–40 °C petrol) gave **80** as a colourless gum (1.95 g, 83%, >99:1 dr);[21] $[\alpha]_D^{25}$ +2.4 (*c* 1.0 in CHCl$_3$); {lit.[21] $[\alpha]_D^{25}$ +1.7 (*c* 1.0 in CHCl$_3$)}.

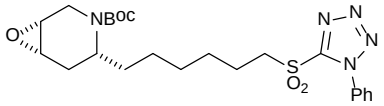
**(*RS*,*E*)-*N*(1)-*tert*-Butoxycarbonyl-2-{6'-[*N*(1'')-phenyl-1''*H*-tetrazol-5''-ylsulfonyl]hex-2'-en-1'-yl}piperidine 200**




(NH$_4$)$_6$Mo$_7$O$_{24}$•4H$_2$O (62 mg, 0.05 mmol) was added to a stirred solution of H$_2$O$_2$ (0.39 mL, 30% w/w in H$_2$O, 3.45 mmol) at 0 °C and the resultant mixture was stirred for 10 min, then added dropwise to a stirred solution of **197** (100 mg, 0.23 mmol) in EtOH (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt over 16 h, before satd aq Na$_2$SO$_3$ (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→60% Et$_2$O in 30–40 °C petrol) gave **200** as a colourless gum (96 mg, 70%, >95:5 dr); $\nu_{max}$ (film) 2935 (C–H), 2250 (C=N, N=N), 1682 (C=O), 1596 (C=C); $\delta_H$ (400 MHz, CDCl$_3$) 1.42 (9H, s, C*Me*$_3$), 1.49–1.64 (6H, m, C(3)*H*$_2$, C(4)*H*$_2$, C(5)*H*$_2$), 1.96–2.07 (2H, m, C(5')*H*$_2$), 2.11–2.24 (3H, m, C(1')*H*$_A$, C(4')*H*$_2$), 2.29–2.40 (1H, m, C(1')*H*$_B$), 2.67–2.78 (1H, m, C(6)*H*$_A$), 3.69 (2H, t, *J* 7.8 C(6')*H*$_2$), 3.88–4.01 (1H, m, C(6)*H*$_B$), 4.17–4.28 (1H, m, C(2)*H*), 5.33–5.49 (2H, m, C(2')*H*, C(3')*H*), 7.54–7.72 (5H, m, *Ph*); $\delta_C$ (100 MHz, CDCl$_3$) 18.8 (*C*(4)), 21.7 (*C*(5')), 25.5 (*C*(5)), 27.6 (*C*(3)), 28.5 (C*Me*$_3$), 30.8 (*C*(4')), 33.1 (*C*(1')), 39.0 (*C*(6)), 50.2 (*C*(2)), 55.3 (*C*(6')), 79.1 (*C*Me$_3$),

125.1, 129.3, 129.7, 130.0, 131.4, 133.0 (*C*(2'), *C*(3'), *Ph*), 153.4 (*C*(5"), 155.0 (N*C*O); *m/z* (ESI$^+$) 973 ([2M+Na]$^+$, 100%), 498 ([M+Na]$^+$, 80%), 476 ([M+H]$^+$, 40%); HRMS (ESI$^+$) $C_{23}H_{33}N_5NaO_4S^+$ [M+Na]$^+$ requires 498.2145; found 498.2151.

**(2*R*,4*S*,5*R*)-*N*(1)-*tert*-Butoxycarbonyl-2-{6'-[*N*(1'')-phenyl-1"*H*-tetrazol-5"-ylsulfonyl]hex-1'-yl}-4,5-epoxypiperidine 81**



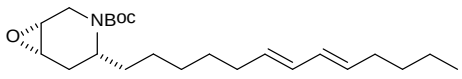

*Method A*: *m*-CPBA (73%, 1.63 g, 6.72 mmol) was added portionwise to a stirred solution of **80** (770 mg, 1.68 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 48 h. 10% aq NaOH (60 mL) and 0.5 M aq $Na_2SO_3$ (60 mL) were then added, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL), and the combined organic extracts were washed with brine (120 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 1:1) gave **81** as a colourless gum (585 mg, 71%);[21] $[\alpha]_D^{25}$ +1.9 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{25}$ +1.7 (*c* +1.0 in $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 1.14–1.61 (8H, m, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.45 (9H, s, C$Me_3$), 1.87–2.14 (4H, m, C(3)$H_2$, C(5')$H_2$), 3.24–3.50 (3H, m, C(4)*H*, C(5)*H*, C(6)$H_A$), 3.69–3.76 (2H, m, C(6')$H_2$), 4.00–4.35 (2H, m, C(2)*H*, C(6)$H_B$), 7.58–7.73 (5H, m, *Ph*); $\delta_H$ (500 MHz, PhMe-$d_8$) 0.90–1.40 (7H, m, C(1')$H_A$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.48 (9H, s, C$Me_3$), 1.63–1.99 (5H, m, C(1')$H_B$, C(3)$H_2$, C(5')$H_2$), 2.73–2.80 (2H, m, C(4)*H*, C(5)*H*), 3.21–3.26 (2H, m, C(6')$H_2$), 3.25–3.44 (1H, m, C(6)$H_A$), 3.83–4.40 (2H, m, C(2)*H*, C(6)$H_B$), 6.97–7.01 (3H, m, *m*,*p*-*Ph*), 7.37–7.41 (2H, m, *o*-*Ph*); $\delta_H$ (500 MHz, PhMe-$d_8$, 363 K) 1.05–1.21 (6H, m, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.32–1.41 (1H, m, C(1')$H_A$), 1.46 (9H, s, C$Me_3$), 1.69–1.81 (4H, m, C(3)$H_2$, C(5')$H_2$), 1.84–1.93 (1H, m, C(1')$H_B$), 2.78–2.85 (2H, m, C(4)*H*, C(5)*H*), 3.29–3.39 (3H, m, C(6)$H_A$, C(6')$H_2$), 3.98–4.10 (2H, m, C(2)*H*, C(6)$H_B$), 7.03–7.11 (3H, m, *m*,*p*-*Ph*), 7.39–7.44 (2H, m, *o*-*Ph*); $\delta_C$ (125 MHz, PhMe-$d_8$) 22.3 (*C*(5')), 26.8 (*C*(2')), 28.3 (*C*(4')), 28.5 (C$Me_3$), 28.5, 28.9 (*C*(3'), *C*(3)), 33.0 (*C*(1')), 40.2 (*C*(6)), 48.8 (*C*(2)), 50.0, 50.3 (*C*(4), *C*(5)), 56.0 (*C*(6')), 79.2 (*C*Me$_3$), 125.2, 129.4, 130.9, 133.7 (*Ph*), 154.1, 154.8 (*C*(5"), N*C*O); $\delta_C$ (125 MHz, PhMe-$d_8$, 363 K) 22.2 (*C*(5')), 26.6

(*C*(2')), 28.2 (*C*(4')), 28.5 (C*Me*$_3$), 28.5, 28.7 (*C*(3'), *C*(5')), 33.0 (*C*(1')), 40.0 (*C*(6)), 48.8 (*C*(2)), 50.0, 50.2 (*C*(4), *C*(5)), 56.4 (*C*(6')), 79.2 (*C*Me$_3$), 125.4, 129.3, 130.8, 134.0 (*Ph*), 154.5, 154.8 (*C*(5''), N*C*O).

*Method B*: *m*-CPBA (71%, 210 mg, 0.88 mmol) was added portionwise to a stirred mixture of **80** (100 mg, 0.22 mmol) in $CH_2Cl_2$ (10 mL) and satd aq $NaHCO_3$ (10 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 48 h. 10% aq NaOH (10 mL) and 0.5 M aq $Na_2SO_3$ (10 mL) were then added, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:0 increased to 1:1) gave **81** as a colourless gum (45 mg, 42%);[21] $[\alpha]_D^{25}$ +2.6 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{25}$ +1.7 (*c* +1.0 in $CHCl_3$)}.

*Method C*: *m*-CPBA (690 mg, 77% w/w in $H_2O$, 3.63 mmol) was added portionwise to a stirred solution of **80** (418 mg, 0.91 mmol, >99:1 dr) in $CH_2Cl_2$ (30 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred for 16 h. Cyclohexene was added dropwise and the reaction mixture was stirred until no evidence of oxidant was indicated by starch-iodide indicator paper. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in EtOAc (30 mL). The resultant solution was washed with satd aq $NaHCO_3$ (30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→50% EtOAc in 30–40 °C petrol) gave **81** as a colourless gum (347 mg, 78%, >99:1 dr);[21] $[\alpha]_D^{20}$ +2.1 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{25}$ +1.7 (*c* +1.0 in $CHCl_3$)}.

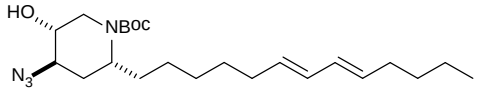
**(2*R*,4*S*,5*R*,*E*,*E*)-*N*(1)-*tert*-Butoxycarbonyl-2-(trideca-6',8'-dien-1'-yl)-4,5-epoxypiperidine 83**



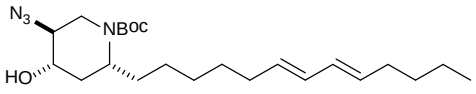

KHMDS (0.5 M in PhMe, 0.94 mL, 0.47 mmol) was added dropwise to a stirred solution of **81** (190 mg, 0.39 mmol, >99:1 dr) and **82** (57 μL, 0.43 mmol) in THF (15 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 15 min. $H_2O$ (30 mL) was then added, the

aqueous layer was extracted with $Et_2O$ (3 × 30 mL), and the combined organic extracts were washed sequentially with satd aq $NH_4Cl$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 0%→20% EtOAc in 30–40 °C petrol) gave **83** as a colourless oil (137 mg, 77%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]);[21] $[\alpha]_D^{25}$ +4.0 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{25}$ +2.2 (*c* 1.0 in $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(13')$H_3$), 1.11–1.93 (14H, m, C(3)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.46 (9H, s, C$Me_3$), 1.99–2.15 (4H, m, C(5')$H_2$, C(10')$H_2$), 3.23–3.34 (2H, m, C(4)*H*, C(5)*H*), 3.35–3.49 (1H, m, C(6)$H_A$), 3.97–4.36 (2H, m, C(6)$H_B$, C(2)*H*), 5.50–5.61 (2H, m, C(6')*H*, C(9')*H*), 5.93–6.04 (2H, m, C(7')*H*, C(8')*H*); $\delta_H$ (500 MHz, PhMe-$d_8$, 363 K) 0.84 (3H, t, *J* 7.1, C(13')$H_3$), 1.11–1.87 (14H, m, C(3)$H_2$, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.40 (9H, s, C$Me_3$), 1.96–2.04 (4H, m, C(5')$H_2$, C(10')$H_2$), 2.86–2.91 (2H, m, C(4)*H*, C(5)*H*), 3.33 (1H, app d, *J* 15.4, C(6)$H_A$), 3.93–4.08 (2H, m, C(6)$H_B$, C(2)*H*), 5.45–5.52 (2H, m, C(6')*H*, C(9')*H*), 5.92–6.00 (2H, m, C(7')*H*, C(8')*H*); $\delta_C$ (125 MHz, PhMe-$d_8$, 363 K) 13.7 (*C*(13')), 22.3 (*C*(12')), 26.9 (*C*(2')), 28.2 (*C*(3)), 28.5 (C$Me_3$), 29.1, 29.7, 31.9, 32.3, 32.6, 33.1 (*C*(1'), *C*(3'), *C*(4'), *C*(5'), *C*(10'), *C*(11')), 39.7 (*C*(6)), 48.9 (*C*(2)), 50.1, 50.3 (*C*(4), *C*(5)), 79.4 (*C*$Me_3$), 130.4, 130.8, (*C*(7'), *C*(8')), 132.8, 133.3 (*C*(6'), *C*(9')), 155.0 (N*C*O). Data for (6'*Z*,8'*E*)-isomer: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.27 (1H, dt, *J* 10.6, 7.3, C(6')*H*), 5.64 (1H, dt, *J* 15.0, 7.1, C(9')*H*), 6.28 (1H, ddd, *J* 15.0, 11.1, 1.1, C(8')*H*); $\delta_H$ (500 MHz, PhMe-$d_8$, 363 K) [selected peaks] 5.24 (1H, dt, *J* 10.4, 7.9, C(6')*H*), 5.57 (1H, dt, *J* 14.5, 7.1, C(9')*H*), 6.30 (1H, ddd, *J* 14.5, 11.0, 0.9, C(8')*H*); $\delta_C$ (100 MHz, $CDCl_3$) [selected peaks] 27.6, 29.7, 125.5, 128.7, 129.8, 134.7; $\delta_C$ (125 MHz, PhMe-$d_8$, 363 K) [selected peaks] 26.9, 27.9, 29.2, 30.0, 126.2, 129.2, 129.8, 134.4.

**(*R*,*R*,*R*,*E*,*E*)-*N*(1)-*tert*-Butoxycarbonyl-2-(trideca-6',8'-dien-1'-yl)-4-azido-5-hydroxypiperidine 203 and (2*R*,4*S*,5*S*,*E*,*E*)-*N*(1)-*tert*-butoxycarbonyl-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-azidopiperidine 84**




**203**

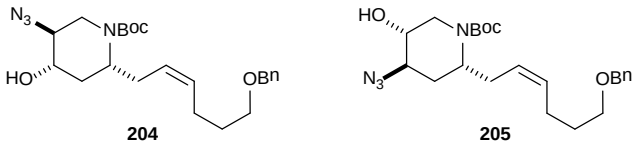



**84**

$NH_4Cl$ (775 mg, 14.5 mmol) and $NaN_3$ (944 mg, 14.5 mmol) were added to a stirred solution of **83** (913 mg, 2.42 mmol, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]) in DMSO (10 mL) at rt and the resultant mixture was stirred at 80 °C for 16 h. The reaction mixture was then cooled to rt, and $H_2O$ (30 mL) was added. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with $H_2O$ (2 × 20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 15%→35% $Et_2O$ in 30–40 °C petrol) gave **203** as a colourless gum (185 mg, 20%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]); $[\alpha]_D^{25}$ +14.1 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3427 (O–H), 2928 (C–H), 2103 ($N_3$), 1694 (C=C), 1669 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0, C(13')$H_3$), 1.19–1.43 (11H, m, C(1')$H_A$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.44 (9H, s, C$Me_3$), 1.52–1.70 (2H, m, C(3)$H_A$, C(1')$H_B$), 1.81–1.91 (1H, m, C(3)$H_B$), 2.00–2.08 (4H, m, C(5')$H_2$, C(10')$H_2$), 2.60–2.71 (1H, m, C(6)$H_A$), 3.39–3.54 (2H, m, C(4)*H*, C(5)*H*), 4.09–4.36 (2H, m, C(2)*H*, C(6)$H_B$), 5.48–5.60 (2H, m, C(6')*H*, C(9')*H*), 5.92–6.03 (2H, m, C(7')*H*, C(8')*H*); $\delta_C$ (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 21.2 (*C*(12')), 26.2 (*C*(2')), 28.3 (C$Me_3$), 28.8, 29.3, 29.6, 31.5, 32.2, 32.5, 32.5, (*C*(3), *C*(1'), *C*(3'), *C*(4'), *C*(5'), *C*(10'), *C*(11')), 43.2 (*C*(6)), 50.4 (*C*(2)), 61.5 (*C*(4)), 71.1 (*C*(5)), 80.3 (*C*$Me_3$), 130.2 (*C*(8')), 130.6 (*C*(7')), 131.9 (*C*(9')), 132.6 (*C*(6')), 154.7 (N*C*O); *m/z* ($ESI^+$) 864 ($[2M+Na]^+$, 100%), 443 ($[M+Na]^+$, 80%); HRMS ($ESI^+$) $C_{23}H_{40}N_4NaO_3^+$ ($[M+Na]^+$) requires 443.2993; found 443.2986. Data for (6'*Z*,8'*E*)-isomer: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.27 (1H, dt, *J* 10.9, 7.6, C(6')*H*), 5.65 (1H, dt, *J* 15.1, 6.8, C(9')*H*), 6.27 (1H, ddd, *J* 15.1, 10.9, 1.0, C(8')*H*); $\delta_C$ (100 MHz, $CDCl_3$) [selected peaks] 125.5, 128.8, 129.6, 134.8. Further elution gave **84** as a colourless gum (598 mg, 59%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]);[21] $[\alpha]_D^{25}$ +6.2 (*c* 1.0 in $CHCl_3$); {lit.[21] $[\alpha]_D^{25}$ +6.3 (*c* 0.5 in $CHCl_3$)}; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (3H, m, *J* 7.1, C(13')$H_3$), 1.22–1.92 (14H, m, C(3)$H_2$, C(1')$H_2$,

C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.48 (9H, s, C$Me_3$), 2.01–2.10 (4H, m, C(5')$H_2$, C(10')$H_2$), 3.42 (1H, dd, *J* 14.6, 2.7, C(6)$H_A$), 3.51 (1H, app q, *J* 2.9, C(5)*H*), 3.89 (1H, app quintet, 3.7, C(4)*H*), 4.06 (1H, dd, *J* 14.6, 2.2, C(6)$H_B$), 4.14 (1H, app dtd, *J* 9.0, 6.1, 3.0, C(2)*H*), 5.51–5.61 (2H, m, C(6')*H*, C(9')*H*), 5.94–6.04 (2H, m, C(7')*H*, C(8')*H*). Data for (6'*Z*,8'*E*)-isomer: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.29 (1H, dt, *J* 11.0, 7.3, C(6')*H*), 5.66 (1H, dt, *J* 15.1, 7.1, C(9')*H*), 5.94 (1H, app t, *J* 11.0, C(7')*H*), 6.28 (1H, app ddq, *J* 15.1, 11.0, 1.3, C(8')*H*).

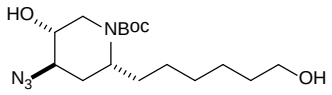
**(2*R*,4*S*,5*S*,*Z*)-*N*(1)-*tert*-Butoxycarbonyl-2-(6'-(benzyloxy)hex-2'-en-1'-yl)-4-hydroxy-5-azidopiperidine 204 and (*R*,*R*,*R*,*Z*)-*N*(1)-*tert*-butoxycarbonyl-2-(6'-(benzyloxy)hex-2'-en-1'-yl)-4-azido-5-hydroxypiperidine 205**



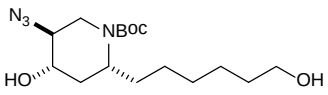

$NH_4Cl$ (110 mg, 2.05 mmol) and $NaN_3$ (107 mg, 1.64 mmol) were added to a stirred solution of **188** (160 mg, 0.41 mmol, >99:1 dr) in DMSO (5.0 mL) at rt and the resultant mixture was stirred at 80 °C for 16 h. The reaction mixture was then cooled to rt and $H_2O$ (10 mL) was added. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with $H_2O$ (2 × 30 mL) and brine (2 × 30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 10%→80% $Et_2O$ in 30–40 °C petrol) gave a 73:27 mixture of **204** and **205** as a colourless oil (159 mg, 90% combined yield). Data for **204**: $\delta_H$ (400 MHz, $CDCl_3$) 1.47 (9H, s, C$Me_3$), 1.53–1.66 (2H, m, C(3)$H_A$, C(5')$H_A$), 1.70–1.81 (1H, m, C(5')$H_B$), 1.88 (1H, ddd, *J* 14.7, 6.8, 3.3, C(3)$H_B$), 2.00–2.10 (1H, m, C(4')$H_A$), 2.27 (1H, dt, *J* 13.6, 5.8, C(1')$H_A$), 2.32–2.43 (1H, m, C(4')$H_B$), 2.78 (1H, dt, *J* 13.6, 8.8, C(1')$H_B$), 3.39–3.46 (2H, m, C(5)*H*, C(6)$H_A$), 3.47 (1H, ddd, *J* 9.6, 6.6, 5.3, C(6')$H_A$), 3.55 (1H, ddd, *J* 9.6, 6.8, 5.1, C(6')$H_B$), 3.71 (1H, app q, *J* 3.3, C(4)*H*), 4.05 (1H, app d, *J*, 13.9, C(6)$H_B$), 4.10–4.17 (1H, m, C(2)*H*), 4.51 (2H, s, OC$H_2$Ph), 5.27–5.53 (2H, m, C(2')*H*, C(3')*H*), 7.27–7.38 (5H, m, *Ph*); $\delta_C$ (100 MHz, $CDCl_3$) 23.8 (*C*(4')), 28.4 (C$Me_3$), 29.1, 29.5, 30.8 (*C*(3), *C*(1'), *C*(5')), 37.7 (*C*(6)), 49.1 (*C*(2)), 60.2

(*C*(5)), 66.6 (*C*(4)), 69.4 (*C*(6')), 72.9 (O*C*$H_2$Ph), 80.0 (*C*$Me_3$), 127.1 (*C*(2'), 127.8, 127.8, 128.4 (*o,m,p-Ph*), 131.2 (*C*(3')), 138.1 (*i-Ph*), 154.9 (N*C*O). Data for **205**: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 1.45 (9H, s, C*Me*$_3$), 2.62–2.76 (1H, m, C(6)$H_A$), 3.38–3.57 (4H, m, C(4)*H*, C(5)*H*, C(6')$H_2$), 4.10–4.43 (2H, m, C(2)*H*, C(6)$H_B$).

**(*R,R,R*)-*N*(1)-*tert*-Butoxycarbonyl-2-(6'-hydroxyhex-1'-yl)-4-azido-5-hydroxypiperidine 207 and (2*R*,4*S*,5*S*)-*N*(1)-*tert*-butoxycarbonyl-2-(6'-hydroxyhex-1'-yl)-4-hydroxy-5-azidopiperidine 206**




**207**

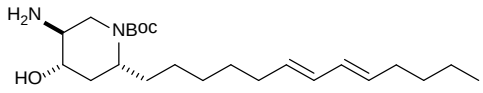



**206**

$NH_4Cl$ (99 mg, 1.85 mmol) and $NaN_3$ (96 mg, 1.48 mmol) were added to a stirred solution of **189** (110 mg, 0.37 mmol, >99:1 dr) in DMSO (4.5 mL) at rt and the resultant mixture was stirred at 80 °C for 16 h. The reaction mixture was then cooled to rt, and $H_2O$ (10 mL) was added. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with $H_2O$ (2 × 30 mL) and brine (2 × 30 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 10%→60% $Et_2O$ in 30–40 °C petrol) gave **207** as a colourless gum (44 mg, 35%, >99:1 dr); $[\alpha]_D^{25}$ −10.9 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3392 (O–H), 2974, 2931, 2859 (C–H), 2103 ($N_3$), 1667 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.23–1.39 (6H, m, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.44 (9H, s, C*Me*$_3$), 1.51–1.71 (4H, m, C(3)$H_A$, C(1')$H_A$, C(5')$H_2$), 1.83–2.00 (2H, m, C(3)$H_B$, C(1')$H_B$), 2.60–2.73 (1H, m, C(6)$H_A$), 3.37–3.56 (2H, m, C(4)*H*, C(5)*H*), 3.63 (2H, t, *J* 6.6, C(6')$H_2$), 4.06–4.40 (2H, m, C(2)*H*, C(6)$H_B$); $\delta_C$ (100 MHz, $CDCl_3$) 25.6 (*C*(4')), 26.2 (*C*(2')), 28.4 (C*Me*$_3$), 29.0 (*C*(3')), 32.6 (*C*(5')), 61.4 (*C*(4)), 62.7 (*C*(6')), 71.1 (*C*(5)), 80.3 (*C*$Me_3$), 154.6 (N*C*O);[41] *m/z* (ESI$^+$) 707 ([2M+Na]$^+$, 40%), 365 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{30}N_4NaO_4^+$ ([M+Na]$^+$) requires 365.2159; found 365.2164. Further elution gave **206** as a colourless gum (82 mg, 65%, >99:1 dr); $[\alpha]_D^{25}$ +22.1 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3392 (O–H), 2975, 2930, 2858 (C–H), 2107 ($N_3$), 1663 (C=O); $\delta_H$ (400 MHz, $CDCl_3$) 1.21–1.39 (6H, m, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$), 1.46 (9H, s, C*Me*$_3$), 1.50–1.62 (4H, m, C(3)$H_A$,

C(1')$H_A$, C(5')$H_2$), 1.87 (1H, ddt, *J* 14.4, 9.0, 6.6, C(1')$H_B$), 2.00 (1H, ddd, *J* 14.7, 6.4, 3.5, C(3)$H_B$), 2.03 (1H, br s, O*H*), 2.90 (1H, br s, O*H*), 3.40 (1H, dd, *J* 14.7, 2.6, C(6)$H_A$), 3.50 (1H, ddd, *J* 3.1, 2.6, 2.5, C(5)*H*), 3.61 (2H, t, *J* 6.6, C(6')$H_2$), 3.85 (1H, app td, *J* 3.5, 3.1, C(4)*H*), 4.03 (1H, dd, *J* 14.7, 2.5, C(6)$H_B$), 4.14 (1H, dddd, *J* 9.0, 6.4, 6.1, 3.0, C(2)*H*); $\delta_C$ (100 MHz, $CDCl_3$) 25.6 (*C*(2')), 26.5 (*C*(4')), 28.4 (C*Me*$_3$), 29.7 (*C*(3')), 30.9 (*C*(1')), 32.5, 32.6 (*C*(3), *C*(5')), 37.7 (*C*(6)), 59.5 (*C*(2)), 60.9 (*C*(5)), 62.8 (*C*(6')), 69.5 (*C*(4)), 80.0 (*C*Me$_3$), 155.2 (N*C*O); *m/z* (ESI$^+$) 707 ([2M+Na]$^+$, 100%), 365 ([M+Na]$^+$, 90%); HRMS (ESI$^+$) $C_{16}H_{30}N_4NaO_4^+$ ([M+Na]$^+$) requires 365.2159; found 365.2154.

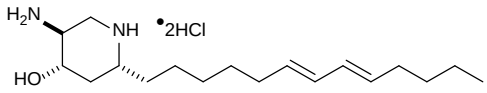
**(2*R*,4*S*,5*S*,*E*,*E*)-*N*(1)-*tert*-Butoxycarbonyl-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine 208**




Polymer-supported $PPh_3$ (356 mg, 100–200 mesh, 1.6 mmol/g loading, 0.57 mmol) was added to a stirred solution of **84** (78 mg, 0.19 mmol, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]) in THF (3 mL) and $H_2O$ (0.3 mL) and the resultant mixture was stirred for 16 h at rt. The reaction mixture was then filtered and the resin was washed with MeOH (15 mL) and $CH_2Cl_2$ (15 mL), and the combined organic washings were concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/2.0 M $NH_3$ in MeOH, 20:1) gave **208** as a white solid (60 mg, 80%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]); mp 83–85 °C; $[\alpha]_D^{25}$ −13.3 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3353, 3293 (O–H, N–H), 2957, 2925, 2855 (C–H), 1685 (C=O, C=C); $\delta_H$ (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.1, C(13')$H_3$), 1.19–1.39 (10H, m, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.44 (9H, s, C*Me*$_3$), 1.46–1.56 (2H, m, C(3)$H_A$, C(1')$H_A$), 1.80–1.91 (1H, m, C(1')$H_B$), 1.97–2.07 (5H, m, C(3)$H_B$, C(5')$H_2$, C(10')$H_2$), 2.10–2.35 (2H, m, N$H_2$), 2.78–2.83 (1H, m, C(5)*H*), 3.35–3.42 (1H, m, C(6)$H_A$), 3.61–3.68 (2H, m, C(4)*H*, C(6)$H_B$), 3.95–4.02 (1H, m, C(2)*H*), 5.49–5.58 (2H, m, C(6')*H*, C(9')*H*), 5.91–6.01 (2H, m, C(7')*H*, C(8')*H*); $\delta_C$ (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.2 (*C*(12')), 26.5 (*C*(2')), 28.4 (C*Me*$_3$), 29.0, 29.4 (*C*(3'), *C*(4')), 31.5, 31.5 (*C*(3), *C*(11')), 32.3, 32.5 (*C*(5'), *C*(10')), 33.1 (*C*(1')), 42.3 (*C*(6)), 50.8 (*C*(2)), 52.8 (*C*(5)), 70.8 (*C*(4)), 79.6 (*C*Me$_3$), 130.2 (*C*(8')), (*C*(7')), 132.2

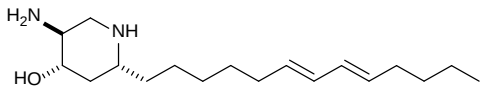
(*C*(9')), 132.4 (*C*(6')), 155.9 (N*C*O); *m/z* (ESI$^+$) 812 ([2M+Na]$^+$, 75%), 790 ([2M+H]$^+$, 95%), 417 ([M+Na]$^+$, 70%), 395 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{43}N_2O_3^+$ ([M+H]$^+$) requires 395.3268; found 395.3262. Data for (6'*Z*,8'*E*)-isomer: $\delta_H$ (400 MHz, $CDCl_3$) [selected peaks] 5.27 (1H, dt, *J* 10.7, 7.5, C(6')*H*), 5.64 (1H, dt, *J* 14.8, 7.3, C(9')*H*), 5.92 (1H, app t, *J* 10.7, C(7')*H*), 6.27 (1H, ddd, *J* 14.8, 10.7, 1.3, C(8')*H*); $\delta_C$ (100 MHz, $CDCl_3$) [selected peaks] 22.2, 26.6, 27.6, 28.4, 29.1, 29.7, 125.5, 128.6, 129.8, 134.7.

**(2*R*,4*S*,5*S*,*E*,*E*)-2-(Trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine dihydrochloride 4•2HCl**




A stirred solution of **208** (200 mg, 0.51 mmol, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]) in methanolic HCl (1.25 M, 5 mL) was heated at 60 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purifiction via recrystallisation from MeOH gave **4**•2HCl as a white solid (148 mg, 79%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]); mp 168–170 °C (MeOH); $[\alpha]_D^{25}$ +9.5 (*c* 1.0 in $CHCl_3$); $\nu_{max}$ (ATR) 3360 (O–H), 3000, 2922, 2857 (C–H); $\delta_H$ (400 MHz, MeOH-$d_4$) 0.91 (3H, t, *J* 6.8, C(13')$H_3$), 1.27–1.52 (10H, m, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 1.58–1.73 (2H, m, C(3)$H_A$, C(1')$H_A$), 1.73–1.84 (1H, m, C(1')$H_B$), 2.01–2.13 (4H, m, C(5')$H_2$, C(10')$H_2$), 2.30–2.39 (1H, m, C(3)$H_B$), 3.16–3.28 (1H, m, C(6)$H_A$), 3.34–3.45 (2H, m, C(2)*H*, C(5)*H*), 3.62–3.70 (1H, m, C(6)$H_B$), 3.83–4.93 (1H, m, C(4)*H*), 5.49–5.60 (2H, m, C(6')*H*, C(9')*H*), 5.93–6.03 (2H, m, C(7')*H*, C(8')*H*); $\delta_C$ (100 MHz, MeOH-$d_4$) 13.3 (*C*(13')), 22.3 (*C*(12')), 25.1 (*C*(2')), 28.8, 29.2 (*C*(3'), *C*(4')), 31.8, 32.3, 32.4, 32.9 (*C*(1'), *C*(5'), *C*(10'), *C*(11')), 36.2 (*C*(3)), 43.7 (*C*(6)), 51.3 (*C*(5)), 56.2 (*C*(2)), 67.1 (*C*(4)), 130.8 (*C*(8')), 131.1 (*C*(7')), 131.6 (*C*(6')), 132.2 (*C*(9')). Data for (6'*Z*,8'*E*)-isomer: $\delta_H$ (400 MHz, MeOH-$d_4$) [selected peaks] 5.28 (1H, dt, *J* 10.4, 7.6, C(6')*H*), 5.64 (1H, dt, *J* 14.7, 6.8, C(9')*H*), 6.32 (1H, app dd, *J* 14.7, 11.5, C(8')*H*); $\delta_C$ (100 MHz, MeOH-$d_4$) [selected peaks] 27.5, 28.9, 29.5, 125.9, 129.2, 130.9, 134.6.

**(2*R*,4*S*,5*S*,*E*,*E*)-2-(Trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine [pseudodistomin D] 4**




*Method A*: *Step 1*: $PPh_3$ (29 mg, 0.11 mmol) was added to a stirred solution of **84** (31 mg, 74 μmol) in THF (5 mL) and the resultant mixture was stirred at rt for 16 h. $H_2O$ (0.5 mL) was added and the reaction was stirred at 50 °C for 16 h, then concentrated *in vacuo* to give **208** (28 mg).

*Step 2*: 3.0 M aq HCl (2.5 mL) was added to a stirred solution of **208** (28 mg) in MeOH (6 mL) and the resultant mixture was heated at 50 °C for 3 h, then allowed to cool to rt. The reaction mixture was then passed through a Biotage Isolute® SCX-2 amine scavenging column and washed with MeOH (10 mL) and $CH_2Cl_2$ (10 mL), before being eluted with 2.0 M $NH_3$ in MeOH (10 mL) and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 9:1) gave **4** as a white gum (11 mg, 51% over 2 steps, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]);[42] $[\alpha]_D^{25}$ +5.2 (*c* 0.3 in MeOH); {lit.[42] $[\alpha]_D^{25}$ +5.0 (*c* 0.26 in MeOH-$d_4$)}; $\nu_{max}$ (ATR) 3283 (O–H), 3014, 2956, 2925, 2854 (C–H), 1583 (C=C), 1464, 985; $\delta_H$ (500 MHz, MeOH-$d_4$) 0.93 (3H, t, *J* 7.1, C(13')$H_3$), 1.12 (1H, ddd, *J* 12.2, 11.7, 11.7, C(3)$H_A$), 1.28–1.52 (12H, m, C(1')$H_2$, C(2')$H_2$, C(3')$H_2$, C(4')$H_2$, C(11')$H_2$, C(12')$H_2$), 2.00 (1H, ddd, *J* 12.2, 4.6, 2.4, C(3)$H_B$), 2.04–2.11 (4H, m, C(5)$H_2$, C(10)$H_2$), 2.37 (1H, dd, *J* 12.0, 11.2, C(6)$H_A$), 2.52–2.61 (2H, m, C(2)*H*, C(5)*H*), 3.09 (1H, dd, *J* 12.0, 4.6, C(6)$H_B$), 3.23–3.29 (1H, m, C(4)*H*), 5.51–5.59 (2H, m, C(6')*H*, C(9')*H*), 5.96–6.04 (2H, m, C(7')*H*, C(8')*H*); $\delta_C$ (125 MHz, MeOH-$d_4$) 14.3 (*C*(13')), 23.3 (*C*(12')), 26.9 (*C*(2')), 30.3 (*C*(3')), 30.5 (*C*(4')), 32.9 (*C*(11')), 33.3 (*C*(5')), 33.5 (*C*(10')), 37.1 (*C*(1')), 41.1 (*C*(3)), 51.4 (*C*(6)), 56.3 (*C*(5)), 56.7 (*C*(2)), 75.1 (*C*(4)), 131.8 (*C*(8')), 132.0 (*C*(7')), 132.9 (*C*(6')), 133.1 (*C*(9')); *m/z* ($ESI^+$) 295 ($[M+H]^+$, 100%); HRMS ($ESI^+$) $C_{18}H_{35}N_2O^+$ $[M+H]^+$ requires 295.2744; found 295.2740. Data for (6'*Z*,8'*E*)-isomer: $\delta_H$ (400 MHz, MeOH-$d_4$) [selected peaks] 5.29 (1H, dt, *J* 10.5, 8.0, C(6')*H*), 5.65 (1H, dt, *J* 15.1, 6.9, C(9')*H*), 6.33 (1H, ddd, *J* 15.1, 11.0, 1.3, C(8')*H*); $\delta_C$ (100 MHz, MeOH-$d_4$) [selected peaks] 28.5, 28.8, 30.1, 30.7, 33.6, 127.0, 130.1, 130.4, 135.5.

*Method B*: A sample of **4**•2HCl (30 mg, 82 μmol, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]) was suspended in 2 M aq KOH (3 mL), and the resultant suspension was extracted with $CHCl_3$/$^{i}$PrOH (v:v, 3:1, 6 × 6 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated in *vacuo* to give **4** as a white gum (22 mg, 92%, 90:10 dr [(*E*,*E*):(6'*Z*,8'*E*)]);[42] $[\alpha]_D^{25}$ +5.6 (*c* 0.3 in MeOH); {lit.[42] $[\alpha]_D^{25}$ +5.0 (*c* 0.26 in MeOH-$d_4$)}.

**6.6 References and notes**

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[4] The ee of amine (*S*)-**71** was determined from 400 MHz $^{1}$H NMR spectroscopic analysis in the presence of chiral solvating agent (*S*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample.

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[7] Due to the similarity of the $^{1}$H and $^{13}$C NMR spectra of **65** and **103**, no data for **103** could be reported due to extensive peak overlap.

[8] An accurate ratio for **65**, **103**, **104** and **105** could not be determined due to the complexity of the $^{1}$H NMR spectrum of the crude reaction mixture, and the similarity of the $^{1}$H NMR spectra for these compounds.

[9] Due to the similarity of the $^{1}$H and $^{13}$C NMR spectra of **72** and **108**, no data for **108** could be reported due to extensive peak overlap.

[10] An accurate ratio for **72**, **108**, **109** and **110** could not be determined due to the complexity of the $^{1}$H NMR spectrum of the crude reaction mixture, and the similarity of the $^{1}$H NMR spectra for these compounds.

[11] A ratio for **73**, **111**, **112** and **113** could not be determined due to the rotameric nature of these compounds at rt, and the resultant complexity of the $^{1}$H NMR spectrum of the crude reaction mixture.

[12] A ratio for **74** and **106** could not be determined due to the rotameric nature of these compounds at rt, and the resultant complexity of the $^{1}$H NMR spectrum of the crude reaction mixture.

[13] Chemical shifts in italics represent doubled peaks due to the rotameric nature of the compound, which was confirmed by EXSY NMR spectroscopy.

[14] EXSY NMR spectroscopic analysis confirmed that doubled peaks were caused by distinct rotamers.

[15] A ratio for **66** and **115** could not be determined due to the rotameric nature of these compounds at rt, and the resultant complexity of the $^{1}$H NMR spectrum of the crude reaction mixture.

[16] This compound was previously reported as "a viscous yellow oil", see: Taylor, R. J. *Part II Thesis*, University of Oxford, **2006**.

[17] Incomplete mass return was observed due to the volatility of **87**.

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[26] $^{1}$H NMR resonances in the region between $\delta_H$ 5.20–6.40 ppm suggested the presence of other geometric isomers, as well as other unknown olefinic products.

[27] This reaction proved to be irreproducible and so sufficient material for full characterisation could not be obtained.

[28] * Denotes a single diastereoisomer, however, the relative configuration remains undefined.

[29] A sample of **157** derived from 2-(piperidin-2'-yl)ethanol **122** was kindly supplied by Dr P. M. Roberts.

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[34] Peaks corresponding to *C*(2), *C*(6), *C*(1') were not visible in the $^{13}$C NMR spectrum of this compound due to line broadening.

[35] A peak corresponding to *C*(1') was not visible in the $^{13}$C NMR spectrum of this compound due to line broadening.

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[37] A peak corresponding to *C*(2) was not visible in the $^{13}$C NMR spectrum of this compound due to line broadening.

[38] Peaks corresponding to *C*(3) and *C*(1') were not visible in the $^{13}$C NMR spectrum of this compound due to line broadening.

[39] Peaks corresponding to *C*(2), *C*(3), *C*(6) and *C*(1') were not visible in the $^{13}$C NMR spectrum of this compound due to line broadening.

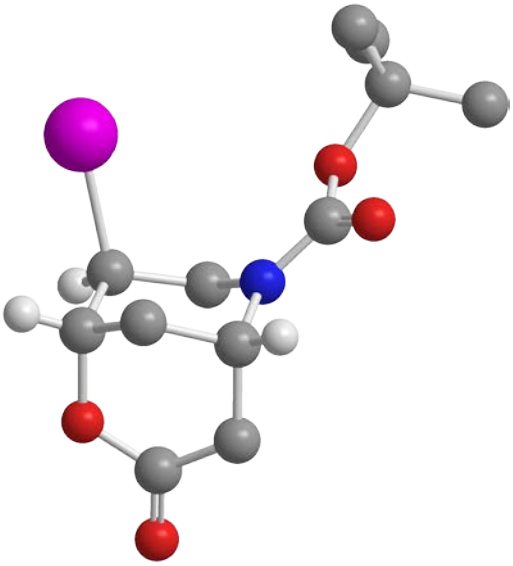
[40] Peaks corresponding to *C*(2), *C*(3) and *C*(6) were not visible in the $^{13}$C NMR spectrum of this compound due to line broadening.

[41] Peaks corresponding to *C*(2), *C*(3), *C*(6), and *C*(1') were not visible in the $^{13}$C NMR spectrum of this compound due to line broadening.

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# Appendix I: X-Ray crystal structure data for (2*S*,4*S*,5*S*)-67

**(Some H atoms omitted for clarity)**



**X-ray crystal structure determination for 67**

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

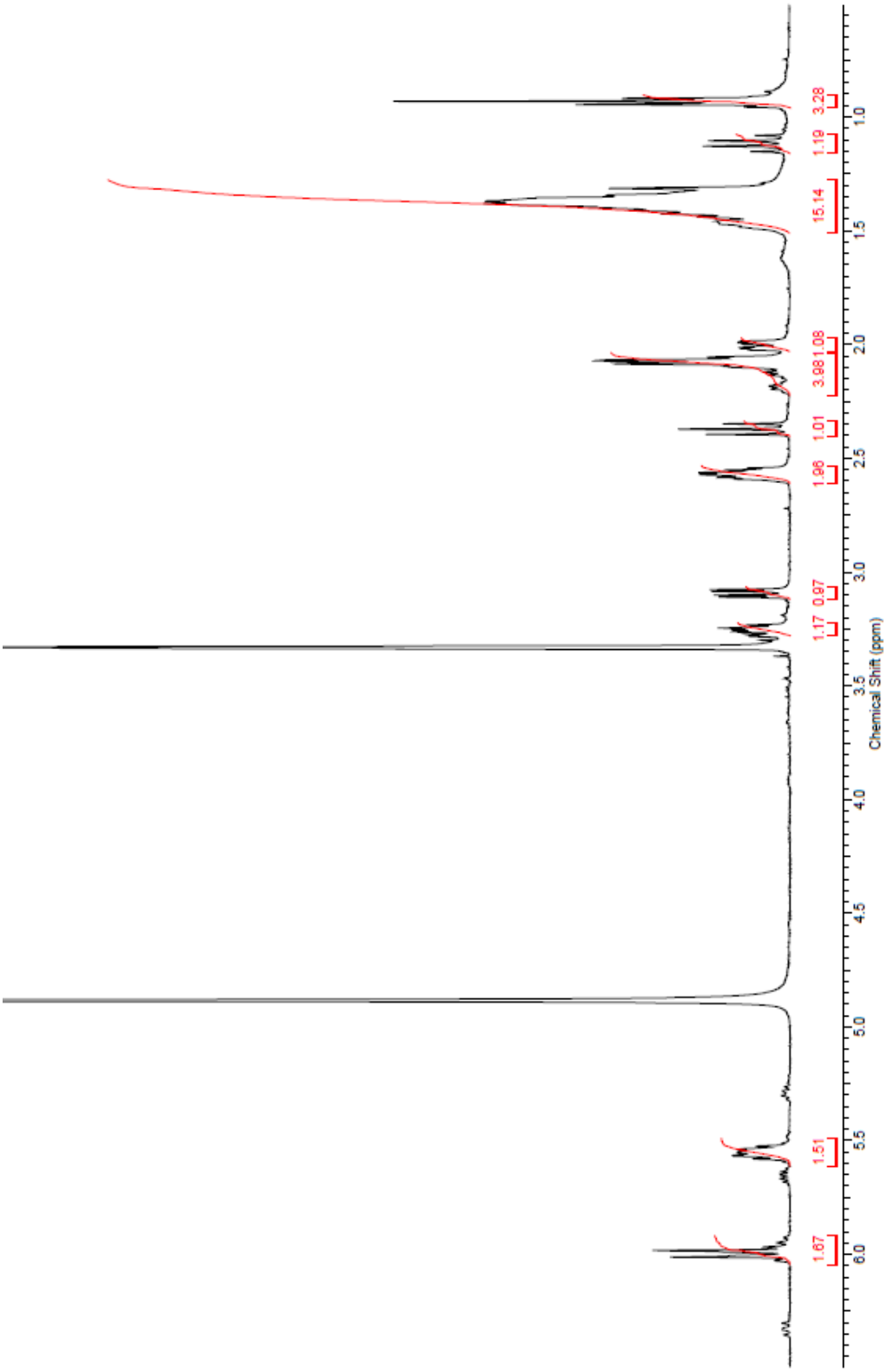
X-ray crystal structure data for **67** [$C_{12}H_{18}INO_4$]: $M$ = 367.18, monoclinic, space group $P\,2_1$, $a$ = 6.2929(3) Å, $b$ = 8.6827(4) Å, $c$ = 13.7341(6) Å, $\beta$ = 92.4948(19)º, $V$ = 749.71(6) Å$^3$, $Z$ = 2, $\mu$ = 2.14 mm$^{-1}$, colourless plate, crystal dimensions = 0.08 × 0.11 × 0.17 mm$^3$. A total of 3084 unique reflections were measured for $5 < \theta < 27$ and 3084 reflections were used in the refinement. The final parameters were $wR_2$ = 0.072 and $R_1$ = 0.045 [$I$>–3.0$\sigma$($I$)], Flack enantiopole = –0.01(2).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, UK.

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**(2*R*,4*S*,5*S*,*E*,*E*)-2-(trideca-6′,8′-dienyl)-4-hydroxy-5-aminopiperidine [Pseudodistomin D] 4 (500 MHz $^{1}H$, MeOD-$d_4$)**



**(2*R*,4*S*,5*S*,*E*,*E*)-2-(trideca-6′,8′-dienyl)-4-hydroxy-5-aminopiperidine [Pseudodistomin D] 4 (125 MHz $^{13}$C, MeOD-$d_4$)**

