Asymmetric Syntheses of the Pseudodistomin Alkaloids

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for the degree of Doctor of Philosophy

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2014 until August 2018, 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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Abstract

David Zimmer D Phil. Thesis

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This thesis centres on asymmetric syntheses of the pseudodistomin alkaloids, initially targeting a member of the family that had yet to be subjected to laboratory synthesis, followed by the development and execution of a unified strategy for the synthesis of all of the known pseudodistomin alkaloids as well as non-natural analogues.

Chapter 1 presents a comprehensive and critical review of all literature reports relating to the isolation, structural elucidation and syntheses of the pseudodistomin alkaloids to date, culminating in the realisation of aims for this thesis.

Chapter 2 describes the first total asymmetric synthesis of pseudodistomin E, culminating in confirmation of the assigned absolute configuration and correlation with the ^{1}H and ^{13}C NMR spectroscopic data originally reported for the natural product in the isolation study.

Chapter 3 reviews the first-generation synthesis and details the evaluation of a range of model systems to facilitate the development of a unified strategy for the synthesis of the pseudodistomin alkaloids and non-natural analogues, culminating in an optimised proposed synthetic strategy.

Chapter 4 discusses the development and execution of a general strategy for the asymmetric syntheses of the pseudodistomin alkaloids, culminating in the total asymmetric syntheses of all of the known pseudodistomin alkaloids and a representative non-natural analogue.

C**hapter 5** offers independent assignments of the relative and absolute configurations of the pseudodistomin alkaloids, followed by a comparison of spectroscopic data with literature reports, culminating in correlation with the data provided for the natural materials.

Chapter 6 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2–4.

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Abbreviations

~	Approximately
(+)	Dextrorotatory
(−)	Levorotatory
±	Racemic
°	Degrees
$[\alpha]_D$	Specific rotation
Δ	Difference
δ	NMR chemical shift
η	Hapticity
μ	Micro
σ*	Sigma antibonding orbital
ν_{max}	Infrared absorption maximum
Å	Angstrom
Ac	Acetyl
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmospheres
ATR	Attenuated total reflectance

$B_{AC}2$	Basic, acyl cleavage, bimolecular
BBBPY	4,4'-Di-*tert*-butyl-2,2'-dipyridyl
BBN	9-Borabicylo[3.3.1]nonane
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
^{t}Bu	*tert*-Butyl
Bus	*tert*-Butylsulfonyl
Bz	Benzoyl
c	Crown
c	Concentration
C	Celsius
cat	Catalyst
Cbz	Carboxybenzyl
cm	Centimetres
COSY	Homonuclear correlation spectroscopy
C_p	Cyclopentadienyl
CSO	Camphorsulfoxaziridine
d	Doublet

D	Dextrorotatory relative to (+)-glyceraldehyde
dba	Dibenzylideneacetone
DBT	Dibenzyltriazone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCIMS	Direct chemical ionisation mass spectrometry
DEAD	Diethyl azodicarboxylate
deg	Degrees
DHP	Dihydropyran
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIC	*N*,*N*'-Diisopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMB	2,4-Dimethoxybenzylamine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dp	Diastereomeric purity

DPPA	Diphenylphosphoryl azide
DPPF	1,1'-Ferrocenediyl-bis(diphenylphosphine)
dr	Diastereomeric ratio
DYKAT	Dynamic kinetic asymmetric transformation
ε	Molar absorption coefficient
E	Entgegen
EIMS	Electron ionisation mass spectrometry
eq	Equivalents
equiv	Equivalents
er	Enantiomeric ratio
ESI^+	Positive electrospray ionisation
et al.	*et alia*
Et	Ethyl
EXSY	Exchange spectroscopy
FABMS	Fast atom bombardment mass spectrometry
FT	Fourier transform
g	Grams
h	Hours
hν	Light
HMBC	Heteronuclear multiple bond correlation spectroscopy

HMDS	Bis(trimethylsilyl)amide
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple quantum coherence spectroscopy
HPLC	High performance liquid chromatography
HR	High resolution
HSQC	Heteronuclear single quantum coherence spectroscopy
Hz	Hertz
i	iso
IR	Infrared
J	Coupling constant
L	Litres
LC	Liquid chromatography
lit.	Literature
m	Multiplet
m	Meta
M	Molar
M^+	Molecular Ion
m/*z*	Mass to charge ratio
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl

mg	Milligrams
MHz	Megahertz
min	Minutes
mL	Millilitres
mmol	Millimoles
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry/Molecular sieves
NHP	*N*-hydroxyphthalimide
nm	Nanometres
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o	Ortho
p	Para
P	Unspecified protecting group
PCC	Pyridinium chlorochromate
PFA	Paraformaldehyde
pH	Potential of hydrogen

Ph	Phenyl
phth	Phthalimide
piv	Pivaloyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonic acid
Pr	Propyl
PT	1-Pheny-1*H*-tetrazole
pyr	Pyridine
q	Quartet
quant	Quantitative
quin	Quintet
R	Rectus
R	Unspecified organic group
®	Registered trademark
Ra	Raney
Ref	Reference
rt	Room temperature
s	Singlet
S	Sinister

S_N2	Substitution, nucleophilic, bimolecular
satd	Saturated
SEM	2-(trimethylsilyl)ethoxymethyl ether
t	Tertiary
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TCNHP	Tetrachloro-*N*-hydroxyphthalimide
temp	Temperature
tert	Tertiary
TIPS	Triisopropylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMS	Trimethylsilyl

ToF	Time of flight
Tol	*p*-Methylphenyl
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet
v	Volume
w	Weight
X	Unspecified group
Y	Unspecified group
Z	Zusammen

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Chapter 1

Introduction

1.1 The Pseudodistomin Alkaloids

The pseudodistomin alkaloids were isolated from the Okinawan tunicate *Pseudodistoma kanoko* in 1986[1] and the Palauan tunicate *Pseudodistoma megalarva* in 1997 (Figure 1).[2] Their biological value has been sparsely investigated, however selected members of the family have been reported as being highly cytotoxic against murine leukaemia[1] and lymphoma cells.[3] Their promising biological profile coupled with the numerous challenges relating to structural complexity has led to the pseudodistomin alkaloids being attractive targets for the synthetic community, with multiple syntheses reported to date.

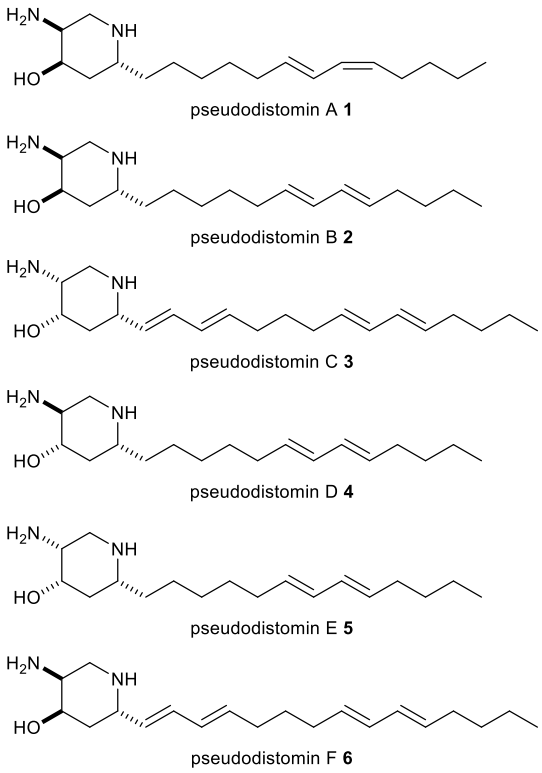


Figure 1 Structures of the pseudodistomin alkaloids.

1.2 Chapter Outline

To facilitate the discussion which follows, this chapter presents a comprehensive and critical review of the isolation, structural elucidation and syntheses of the pseudodistomin alkaloids. For simplicity, the pseudodistomins will be addressed in the following pairs: A/B, C/F and D/E, and within each section the literature reports will be discussed chronologically.

1.2.1 Nomenclature

The descriptors 'head' and 'tail' will be used throughout to refer to any piperidine unit and any segment of the unsaturated carbon chain, respectively. Numbering of the pseudodistomins is illustrated in **7** and **8** (Figure 2).

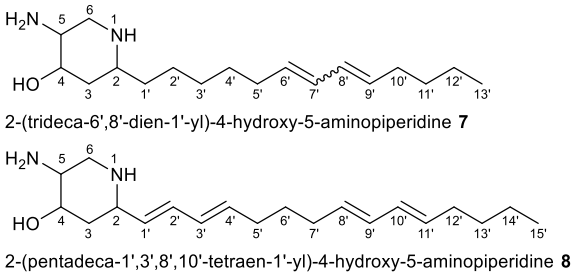


Figure 2 Numbering of the pseudodistomin scaffolds **7** and **8**.

1.3 Pseudodistomin A and Pseudodistomin B

1.3.1 Isolation and Erroneous Structural Assignment

Kobayashi *et al*. isolated pseudodistomin A **1** and pseudodistomin B **2** from the Okinawan tunicate *Pseudodistoma kanoko* in 1986.[1] Extraction with $CHCl_3$ followed by sequential flash column chromatography and reverse-phase HPLC purification gave a ~50:50 mixture of pseudodistomin A **1** and pseudodistomin B **2**. Kobayashi *et al*. assumed that both species shared the same molecular weight *via m/z* analysis [FABMS, *m/z* 295 $(M+H)^+$] of this mixture. Traces (~0.1 mg) of pseudodistomin A **1** and pseudodistomin B **2** were separated by further reverse-phase HPLC, however these were not characterised and were instead supplied for bioassays. It was reported that further purification of the mixture was carried out following

acetylation to circumvent the close retention times, susceptibility to aerial-oxidation and (*E*):(*Z*) isomerisation of the free bases,[4] yielding pure samples of pseudodistomin A acetate **9** and pseudodistomin B acetate **10**, of which the latter was used for structure determination (Figure 3).

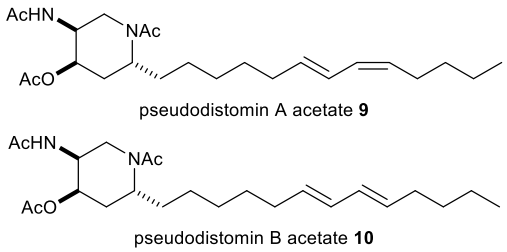


Figure 3 Structures of pseudodistomin A acetate **9** and pseudodistomin B acetate **10**.

Mass spectrometry data [HREIMS, *m/z* 420.2974 $(M)^+$] suggested a molecular formula of $C_{24}H_{40}N_2O_4$, and the increase in molecular weight by 126 versus the parent compound **2** [FABMS, *m/z* 295 $(M+H)^+$], combined with IR bands at 1740 and 1630 cm^{-1} led to Kobayashi *et al*. proposing that pseudodistomin B acetate **10** possessed one *O*-acetyl and two *N*-acetyl groups. NMR spectroscopic (^1H, ^{13}C, COSY and HSQC) and UV analyses (234 nm) were used to propose a trisubstituted piperidine scaffold with acetoxyl and acetamide groups located at C(4) and C(5), respectively. Kobayashi *et al*. deduced that a partially unsaturated hydrocarbon tail was attached to C(2) *via* ^1H and ^{13}C NMR spectroscopic analysis, erroneously assigned as a trideca-3',5'-diene, but offered no explanation for the deduction of position of the olefin functionalities. Due to the overlapping of signals in the ^1H NMR spectra of pseudodistomin B acetate **10**, the allylic methylene ^{13}C NMR signals were instead used to assign the olefin configurations,[5] with δ 32.5 ppm for C(2') and δ 32.2 ppm for C(7') suggesting a (3'*E*)- and (5'*E*)-configuration. Pseudodistomin A acetate **9** was shown to possess the same molecular formula as pseudodistomin B acetate **10** by *m/z* analysis [HREIMS, *m/z* 420.3010 $(M)^+$], and NMR spectroscopic analysis suggested the structure only differed in the olefin geometry of the tail portion. Coupling constants *J* 15 Hz and *J* 11 Hz (erroneously assigned positionally) implied the olefins were of (3'*E*)- and (5'*Z*)-configuration. Hydrogenation of pseudodistomin A acetate **9** and pseudodistomin B acetate **10** afforded an identical product **11**, including the specific

rotation value {$[\alpha]_D^{23}$ +33 (*c* 1.0 in MeOH)}, consistent with the suggested relationship as geometric isomers and also indicating pseudodistomin A **1** and pseudodistomin B **2** share the same absolute configuration. Decoupled ^{1}H NMR spectroscopic coupling constant analysis and nOe experiments on the tetrahydroacetate **11** provided evidence of the relative configuration, with C(2)*H*, C(4)*H* and C(5)*H* occupying equatorial, axial and equatorial sites within **11**, respectively. The absolute configuration within tetrahydroacetate **11** was assigned *via* use of the non-empirical dibenzoate chirality method,[6] which concluded pseudodistomin A **1** and pseudodistomin B **2** possess the (2*R*,4*R*,5*S*)-configuration. Kobayashi *et al*. thus proposed the structure of pseudodistomin A (erroneous) **12** as (2*R*,4*R*,5*S*,3'*E*,5'*Z*)-2-(trideca-3',5'-dien-1'-yl)-4-hydroxy-5-aminopiperidine, and pseudodistomin B (erroneous) **13** as (2*R*,4*R*,5*S*,3'*E*,5'*E*)-2-(trideca-3',5'-dien-1'-yl)-4-hydroxy-5-aminopiperidine and it was also stated that pseudodistomin A **1** and pseudodistomin B **2** were the first piperidine alkaloids to be isolated solely from marine sources (Figure 4).

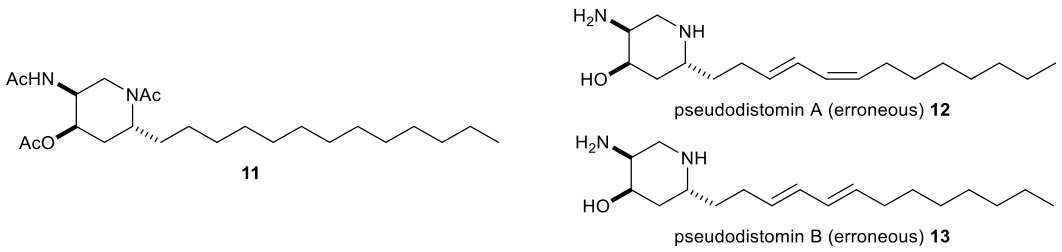
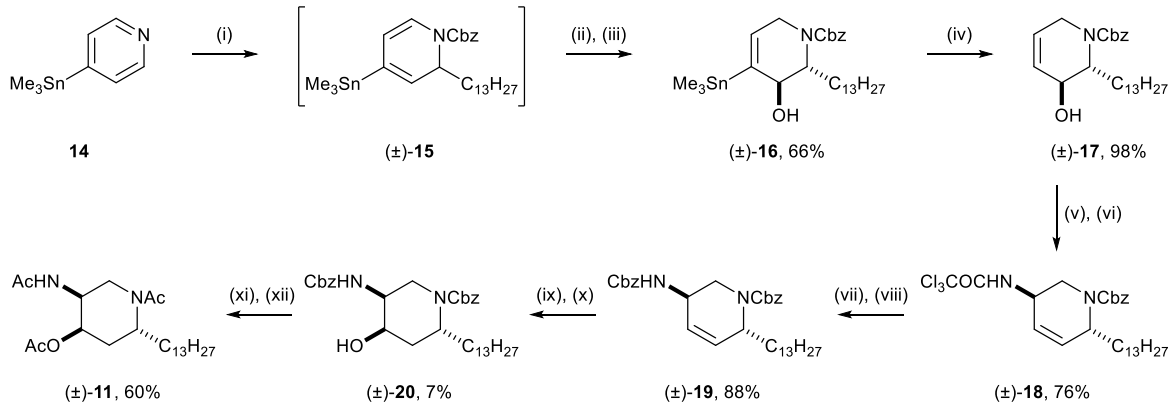


Figure 4 Structures of the tetrahydroacetate derivative **11**, pseudodistomin A **12** (erroneous) and pseudodistomin B **13** (erroneous).

1.3.2 Racemic Syntheses of Tetrahydro Derivatives

In 1992, two reports were published almost simultaneously detailing racemic syntheses of the tetrahydroacetate (±)-**11**. The first, reported by Natsume *et al*.,[7] began with the addition of tridecylmagnesium bromide to 4-trimethylstannylpyridine **14** in the presence of CbzCl to give 1,2-dihydropyridine (±)-**15** in 84% conversion. This intermediate was treated with singlet oxygen and then $NaBH_3CN$ to give, after purification, (±)-**16** in 66% yield (over three steps). The stereochemical outcome was consistent with approach of singlet oxygen from the opposite

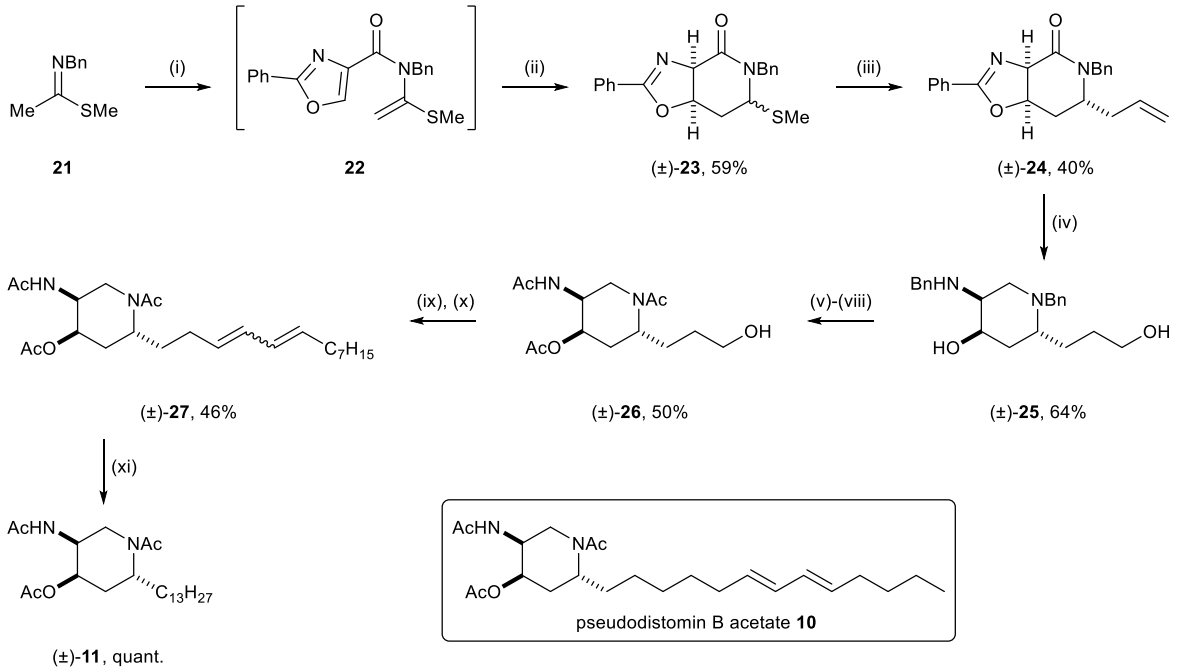
face to that bearing the C(2) substituent. Oxalic acid was used to effect removal of the trimethylstannyl substituent within (±)-**16**, followed by Overman rearrangement[8] of (±)-**17** to effect 1,3-transposition of the hydroxy group for an amino group furnishing (±)-**18**, with retention of relative configuration. Protecting group manipulation gave (±)-**19** in 88% yield, and subsequent hydroboration followed by basic H_2O_2, gave a mixture of stereo- and regioisomers, from which amino alcohol (±)-**20** was obtained in 7% yield. The relative configuration within (±)-**20** was retrospectively assigned *via* elaboration to and data comparison with the known tetrahydroacetate **11**. *N*-Deprotection of (±)-**20** *via* hydrogenolysis and subsequent acetylation furnished tetrahydroacetate (±)-**11** in 60% yield, and 2% total yield over twelve steps (Scheme 1). The ^{1}H and ^{13}C NMR spectroscopic data of (±)-**11** were in good agreement with the data provided by Kobayashi *et al*. in the isolation report,[1] and the authors stated this provided support to the proposed relative configuration assigned to the piperidine head, but offered no insight into the regiochemistry of the tail.



Scheme 1 *Reagents and conditions*: (i) $C_{13}H_{27}MgBr$, CbzCl, −78 °C, THF, 4 h; (ii) O_2, CH_2Cl_2, −65 °C, 30 min; (iii) $NaBH_3CN$, $SnCl_2$, EtOAc, −50 °C, 10 min then 0 °C, 4.5 h; (iv) $(COOH)_2$, THF/H_2O (5:1), 65 °C, 5 h; (v) NaH, THF, 70 °C, 5 min then Cl_3CCN, THF, rt, 1 h; (vi) xylene, 160 °C, 3 h; (vii) NaOH, DME, rt, 14 h; (viii) KHMDS, CbzCl, THF, −70 °C, 1 h; (ix) BH_3·THF, THF, 0 °C, 30 min; (x) H_2O_2, NaOH, rt, 1 h; (xi) H_2 (1 atm), Pd/C, EtOH, rt, 3 h; (xii) Ac_2O, pyridine, rt, 2 h.

The second synthetic report from Naito *et al*.[9] began with reaction of the thioimidate **21** with 2-phenyloxazole-4-carbonyl chloride in the presence of Et_3N to give **22**. Reductive photocyclization of **22** in the presence of $NaBH_4$ gave lactam (±)-**23** in 59% yield, after purification. Irradiation of lactam (±)-**23** in the presence of allyltributyltin gave α-allyllactam (±)-**24** in 40% yield. Treatment of (±)-**24** with BH_3·THF followed by basic H_2O_2, followed by

lactam reduction and oxazoline ring-opening gave (±)-**25** in 64% yield. A four-step protecting group manipulation strategy was employed to furnish the *N*,*N*,*O*-triacetyl protected diaminodiol (±)-**26**, which was subjected to PCC oxidation to give the requisite aldehyde. Subsequent Wittig olefination[10] [with the ylid derived from treatment of (2*E*)-dec-2-en-1-yltriphenylphosphonium bromide[11] with NaH] furnished (±)-**27** as a mixture of olefin isomers in 46% yield. Finally, hydrogenation of the diene functionality within (±)-**27** afforded tetrahydroacetate (±)-**11** in quantitative yield, completing the synthesis in 3% total yield over eleven steps (Scheme 2). The product (±)-**11** was found to be identical by comparison of IR, ^{1}H and ^{13}C NMR spectroscopic data with an authentic sample provided by Kobayashi, offering further support for the assignment of the relative configuration within the piperidine head. Naito *et al*. also attempted separation of the dienes (±)-**27** and succeeded in isolating samples of both (3'*E*,5'*E*)-**27** and (3'*Z*,5'*E*)-**27**. Direct comparison of the ^{1}H and ^{13}C NMR spectra of (3'*E*,5'*E*)-**27** and an authentic sample of pseudodistomin B acetate **10** revealed that the spectra were not superimposable, particularly in the olefinic regions. Thus, Naito *et al*. proposed that the position of the diene moiety within the initially proposed structure of pseudodistomin B **2** deduced by Kobayashi *et al*. should be subjected to revision.



Scheme 2 *Reagents and conditions*: (i) 2-phenyloxazole-4-carbonyl chloride, Et_3N; (ii) hv, $NaBH_4$, MeCN/MeOH (9:1); (iii) hv, allyltributyltin, PhMe/MeCN (7:3), 72 h; (iv) BH_3·THF then H_2O_2, NaOH; (v) TBDMSCl, imidazole; (vi) H_2, $Pd(OH)_2$/C; (vii) Ac_2O, pyridine; (viii) AcOH, THF/H_2O; (ix) PCC, NaOAc; (x) (2*E*)-dec-2-en-1yltriphenylphosphonium bromide, NaH, THF; (xi) H_2, Pd/C.

1.3.3 Structural Revision of Pseudodistomin B

Based on the findings detailed in the report by Naito *et al*.,[9] Kobayashi *et al*. and Naito *et al*. jointly reinvestigated the structure of pseudodistomin B **2** in 1992.[12] Thus, pseudodistomin B acetate **10**, prepared from a natural specimen, was treated with ozone followed by reduction with $NaBH_4$ and acetylation to furnish tetraacetate **28**. The structure of **28** was assigned *via* mass spectrometry data [FABMS, *m/z* 385 $(M+H)^+$] indicating the presence of six carbons in the remaining tail segment, which was not the expected product **29**. These data were indicative of a trideca-6',8'-diene moiety, not the trideca-3',5'-diene moiety as reported initially. Thus, the structure of pseudodistomin B **2** was revised to (2*R*,4*R*,5*S*,6'*E*,8'*E*)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine (Figure 5).

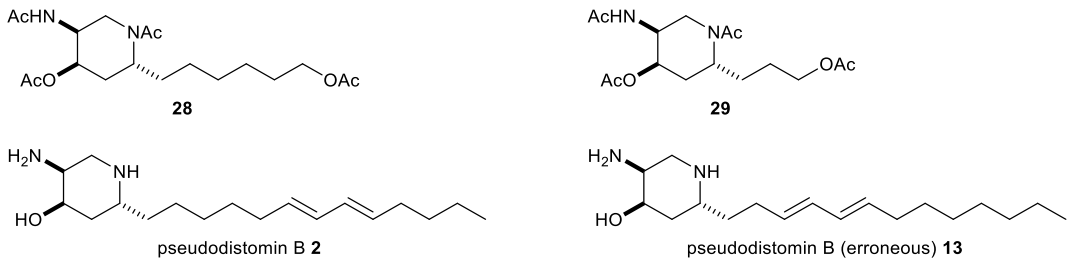
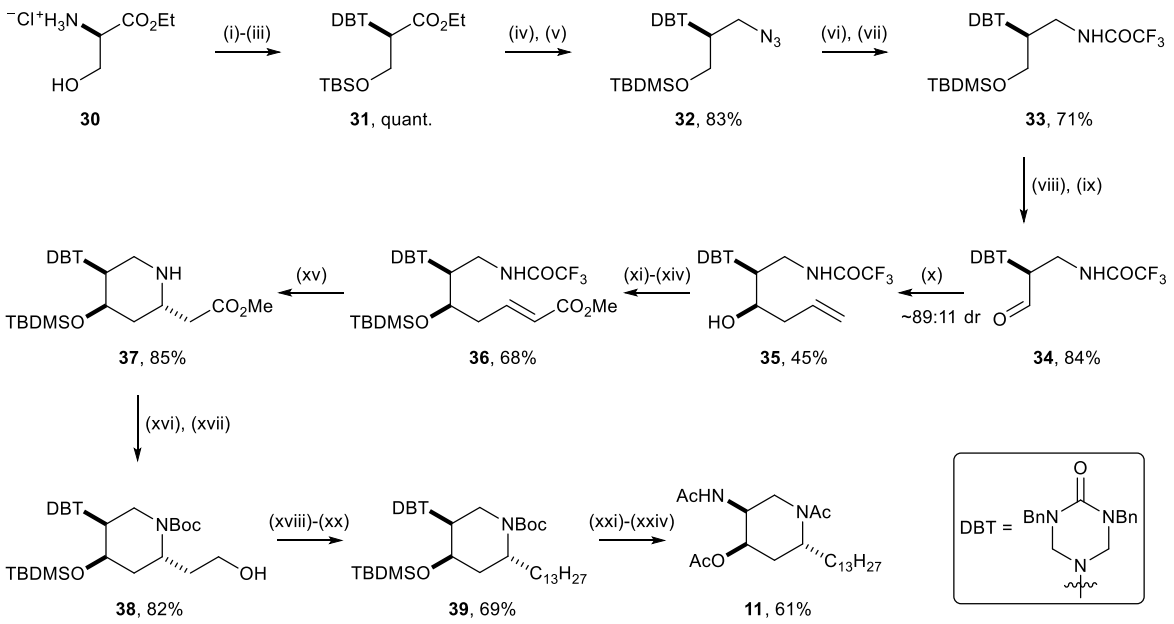


Figure 5 Experiments leading to the revised structure of pseudodistomin B **2**.

1.3.4 Enantiopure Syntheses of Tetrahydro Derivatives

Subsequently, following the structural revision of pseudodistomin B **2**, the first preparation of the enantiopure tetrahydro derivative **11** was completed by Knapp *et al*. in 1993.[13] Ethyl (*R*)-serinate hydrochloride **30** was *O*-silylated and then converted to its dibenzyltriazone derivative **31**. Reduction of the ester functionality within **31** and subsequent Mitsunobu reaction[14] installed the azido moiety within **32**. Hydrogenolytic reduction of **32** followed by *N*-trifluoroacetylation gave **33** in 71% yield. TBAF promoted *O*-deprotection and immediate Swern oxidation[15] of the resultant alcohol gave aldehyde **34** in 84% yield. Lewis-acid promoted addition of allyltrimethylstannane to aldehyde **34** gave an ~89:11 mixture of diastereoisomers, from which **35** was isolated in 45% yield. The configuration within **35** was later confirmed, but was initially assigned based on precedent for the addition[16] and also upon comparison of ^{1}H NMR data of closely related α-amino aldehyde adducts of proven structures.[17] *O*-Silylation of **35**, dihydroxylation of the olefin and oxidative cleavage of the resultant diol gave the corresponding aldehyde; ensuing Wittig olefination[10] then gave α,β-unsaturated ester **36** in 68% yield (over four steps). Methanolic sodium borohydride cleaved the *N*-trifluoroacetate group, triggering an intramolecular Michael reaction from which **37** was isolated in 85% yield as a single diastereoisomer, within which the relative configuration was assigned from ^{1}H NMR ^3J coupling constant analysis. *N*-Protection with Boc_2O followed by ester reduction gave alcohol **38**, which was subjected to sequential Swern oxidation,[15] Wittig olefination[10] (with the ylid derived from deprotonation of the triphenylphonsphonium salt of 1-bromoundecane), and hydrogenation of the resultant olefin to give **39**. The synthesis

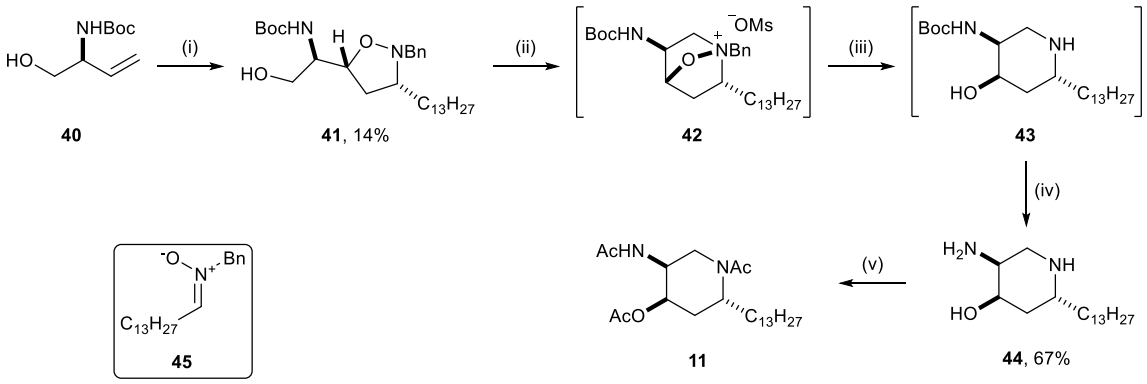
culminated with sequential *O*-deprotection, *N*-Boc removal and unveiling of the primary amino group, followed by global acetylation with Ac_2O to yield tetrahydroacetate **11** in 61% yield, and 4% total yield over twenty-four steps (Scheme 3). ^1H and ^{13}C NMR spectroscopic data were reported to be a close match to those reported by Kobayashi *et al*.,[1] and the specific rotation value of synthetic **11** {$[\alpha]_D$ +36.9 (*c* 0.8 in MeOH)} was in good agreement with the value for the material derived from the natural source {$[\alpha]_D^{23}$ +33 (*c* 1.0 in MeOH)}. This work provides evidence for the assignment of the absolute configuration within the head portion of the natural product, however the position of the diene moiety remained to be confirmed.



Scheme 3 *Reagents and conditions*: (i) DIPEA, DMAP, TBDMSCl, CH_2Cl_2, 0 °C to rt, 3 h; (ii) aq CH_2O, DIPEA, rt, 10 min; (iii) BnNHCONHBn, EtOAc, 80 °C, 1.5 h; (iv) $LiBH_4$, Et_2O, 35 °C, 1 h; (v) PPh_3, DEAD, $Zn(N_3)_2(pyr)_2$, imidazole, PhMe, rt, 20 h; (vi) H_2 (1 atm), Pd/C, EtOH, rt, 16 h; (vii) TFAA, CH_2Cl_2/pyridine (2:1), 0 °C, 30 min; (viii) TBAF, THF, 0 °C to rt, 30 min; (ix) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min then Et_3N, 30 min; (x) $BF_3{\cdot}Et_2O$, allyltributylstannane, CH_2Cl_2, −78 °C, 1 h, then −20 °C, 16 h; (xi) DIPEA, TBDMSOTf, CH_2Cl_2, 0 °C to rt, 1 h; (xii) OsO_4, NMO, acetone/^{t}BuOH/H_2O (2:1:1), rt, 1.5 h; (xiii) $NaIO_4$, THF/H_2O (4:1), rt, 30 min; (xiv) PPh_3CHCO_2Me, PhMe, 70 °C, 1 h; (xv) $NaBH_4$, MeOH, 60 °C, 20 h; (xvi) $(Boc)_2O$, DIPEA, rt, 16 h; (xvii) $LiBH_4$, THF, 70 °C, 2.5 h; (xviii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min then Et_3N, 30 min; (xix) undecylidenetriphenylphosphorane, THF, rt, 16 h; (xx) H_2 (1 atm), Pd/C, EtOAc, rt, 4 h; (xxi) TBAF, THF, −15 °C, 30 min; (xxii) TFA, CH_2Cl_2, 0 °C, 1 h; (xxiii) aq diethanolamine, MeOH, 50 °C, 2 h; (xxiv) Ac_2O, pyridine, DMAP, rt, 16 h.

A second synthesis of tetrahydroacetate **11** was reported by Naito *et al*. in 1994.[18] Their synthesis began with the cycloaddition of **40** [derived from (*S*)-methionine][19] and nitrone **45** (derived from condensation of tetradecanal and *N*-benzylhydroxylamine) to give a separable mixture of adducts, of which **41** was isolated in 14% yield. The configuration within **41** was

assigned later in the synthesis *via* correlation with the known tetrahydroacetate **11**. *O*-Mesylation followed by treatment of intermediate **42** under hydrogenolysis conditions furnished **43**. Finally, *N*-deprotection of **43** with TFA and subsequent global acetylation yielded tetrahydroacetate **11** (Scheme 4). Tetrahydroacetate **11** was reported to be identical with an authentic sample derived from the natural source *via* comparison of IR, ^{1}H and ^{13}C NMR spectroscopic data. The specific rotation value {$[\alpha]_D$ +70.3 (*c* 0.64 in MeOH)} however, was in poor agreement with both the value obtained from derivatization of the natural product by Kobayashi *et al*.[1] {$[\alpha]_D^{23}$ +33 (*c* 1.0 in MeOH)}, and the value quoted by Knapp *et al*.[13] {$[\alpha]_D$ +36.9 (*c* 0.8 in MeOH)} in their report, which Naito *et al*. did not comment on.



Scheme 4 *Reagents and conditions*: (i) **45**, PhMe, 110 °C, 94 h; (ii) MsCl, pyridine, 0 °C; (iii) H_2, Pd/C, MeOH, rt; (iv) TFA, CH_2Cl_2, rt; (v) Ac_2O, pyridine, rt.

1.3.5 Structural Revision of Pseudodistomin A

Given the findings in the structural revision of pseudodistomin B **2**[12] a reinvestigation of the structure of pseudodistomin A **1** was also due. This process was delayed due to the unavailability of a natural specimen. Kobayashi *et al*. therefore re-examined a PhMe extract of their earlier extraction and succeeded in re-isolating pseudodistomin A acetate **9** *via* the procedure previously described.[1] Pseudodistomin A acetate **9** was thus subjected to ozonolysis, $NaBH_4$ reduction and acetylation to yield tetraacetate **28**, and not **29** as would be expected from the initially proposed structure for pseudodistomin A (erroneous) **12**. It was found that **28** was identical with the tetraacetate previously obtained from derivatization of pseudodistomin B

acetate **10** *via* means of TLC, ^{1}H NMR spectroscopic and EIMS analyses. The structure was therefore revised to exhibit a trideca-6',8'-diene, and not a trideca-3',5'-diene as previously suggested. Further NMR spectroscopic analysis of pseudodistomin A acetate **9** indicated C(5') was adjacent to an (*E*)-configured olefin, and C(10') was adjacent to a (*Z*)-configured olefin. Pseudodistomin A **1** must therefore possess a (6'*E*,8'*Z*)-diene in the tail portion, and the structure was revised to (2*R*,4*R*,5*S*,6'*E*,8'Z)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine (Figure 6).

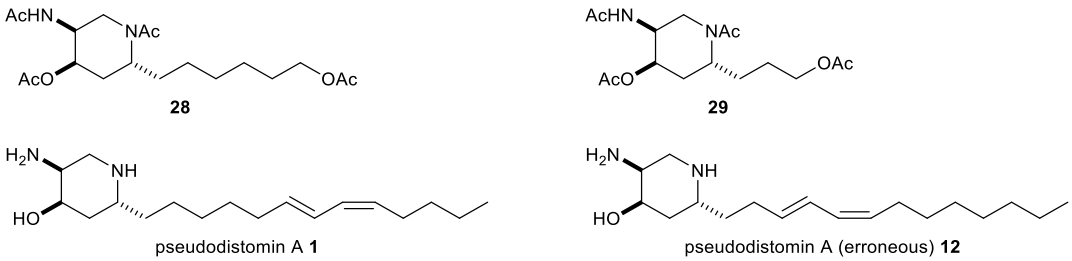
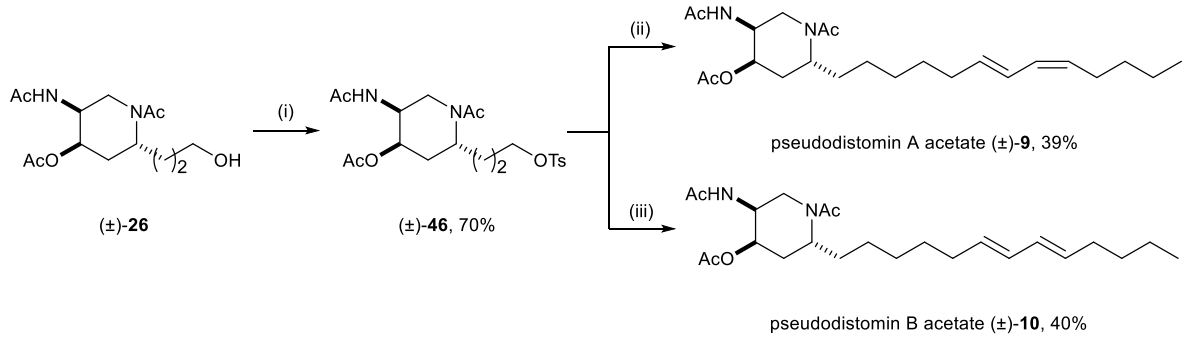


Figure 6 Experiments leading to the revised structure of pseudodistomin A **1**.

1.3.6 Racemic Syntheses of Pseudodistomin A and Pseudodistomin B

With revised structures of pseudodistomin A **1** and pseudodistomin B **2** now established, Naito *et al*. investigated the synthesis of racemic samples of pseudodistomin A acetate (±)-**9** and pseudodistomin B acetate (±)-**10**.[20] The sequence began with known alcohol (±)-**26** [from the synthesis of tetrahydroacetate (±)-**11**][9] which was subjected to tosylation with TsCl in the presence of Et_3N and DMAP to give (±)-**46** in 70% yield. Installation of the tail portions was accomplished *via* S_N2 displacement of the *O*-tosyl functionality with alkyl cuprate reagents, generated *in situ* from reaction of the requisite Grignard reagent (prepared from known alkyl bromides)[21,22] with Li_2CuCl_4. Pseudodistomin A acetate (±)-**9** and pseudodistomin B acetate (±)-**10** were thus isolated in 39% and 40% yield, respectively (Scheme 5). Direct comparison of ^{1}H and ^{13}C NMR spectroscopic data of the synthetic compounds with samples of pseudodistomin A acetate **9** and pseudodistomin B acetate **10** derived from the natural products indicated the compounds were indeed identical, providing confirmation of the gross structure

and relative configuration within the piperidine head portion, as well as the olefinic configuration of the tail portion.



Scheme 5 *Reagents and conditions*: (i) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 20 h; (ii) (3*E*,5*Z*)-decadienylmagnesiumbromide, Li_2CuCl_4, THF, −50 °C, 3 h; (iii) (3*E*,5*E*)-3,5-decadienylmagnesiumbromide, Li_2CuCl_4, THF, −50 °C, 3 h.

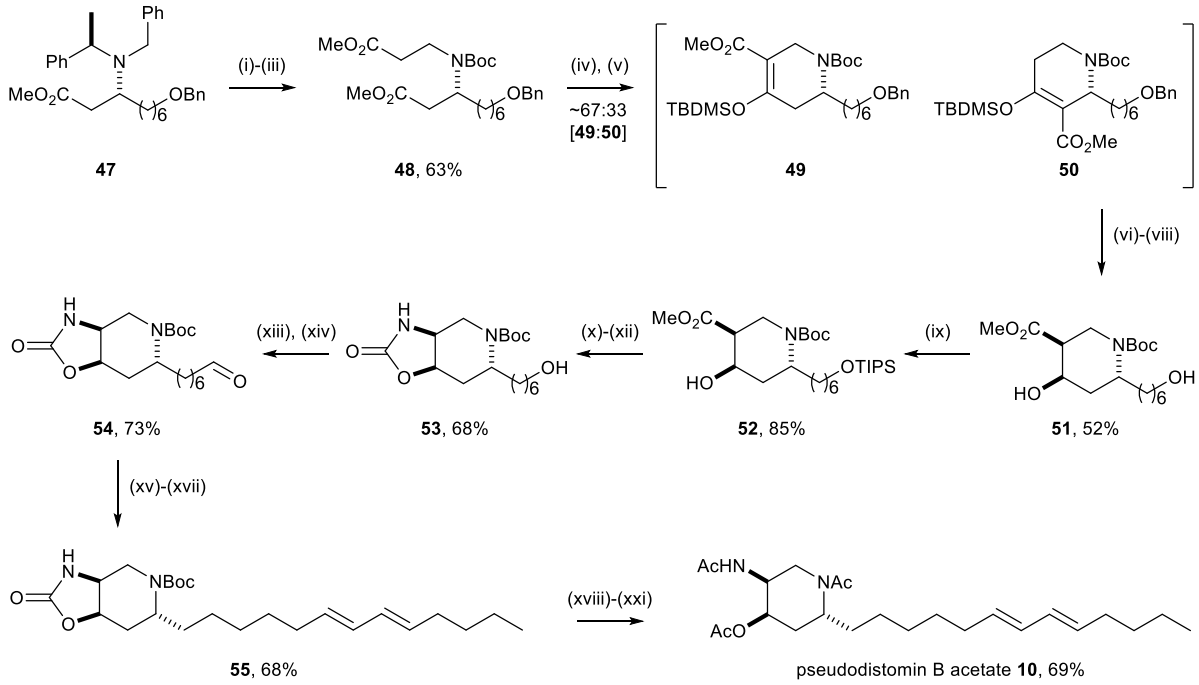
1.3.7 Re-Isolation of Pseudodistomin B

At this point in the timeline, Freyer *et al*. isolated pseudodistomin B **2** from an extract of the ascidian *Pseudodistoma megalarva*, collected in Palau.[2] Freyer *et al*. stated that pseudodistomin B **2** is known, but no evidence is presented that can be compared to data reported by Kobayashi *et al*.[1] The report provided ^{1}H and ^{13}C NMR spectroscopic data (recorded in MeOH-d_4) for the free base, for which no data existed at this point in time for means of comparison. In order to confirm they had indeed isolated pseudodistomin B **2** it can therefore be inferred that Freyer *et al*. either conducted a thorough NMR analysis of their sample of pseudodistomin B **2** [as is detailed for the characterisation of three new pseudodistomins in their report (*vide infra*)], or alternatively carried out derivatization of the sample to the known pseudodistomin B acetate **10** but elected not to reported it. Freyer *et al.* offered the specific rotation value of $[\alpha]_D^{25}$ −13 (*c* 0.87 in MeOH), however this was also incomparable as no value for the free base of pseudodistomin B **2** had been reported at this point.

1.3.8 Enantiopure Syntheses of Pseudodistomin A and Pseudodistomin B

No syntheses of enantiopure pseudodistomin A **1** have been reported. To date the only enantiopure synthesis of pseudodistomin B acetate **10** was completed by Ma *et al*. in 2000.[23] The synthesis began with the β-amino ester **47**, which was prepared in high diastereoselectivity according to Davies' procedure[24] involving conjugate addition of an enantiopure lithium amide reagent to an α,β-unsaturated ester. Hydrogenolysis of the *N*-benzyl groups within **47** followed by Michael addition to methyl acrylate and *N*-protection of the resultant secondary amine with $(Boc)_2O$ gave cyclisation precursor **48** in 63% yield. Dieckmann cyclisation[25] of **48** with subsequent *O*-silylation gave an inseparable ~67:33 mixture of regioisomeric silyl enol ethers, **49** and **50**, respectively. Selective hydrogenolysis of the *O*-Bn moiety within intermediates **49** and **50** was achieved with Pd/C under 30 atm of H_2. Raney Ni catalysed hydrogenation of the resultant mixture with subsequent *O*-desilylation gave **51** in 52% yield, (it was noted that hydrogenation of the olefin within the debenylated derivative of **50** did not occur under the reaction conditions, allowing facile separation of species at this stage). The configuration of the two new stereogenic centres was unambiguously assigned *via* single crystal X-ray diffraction of a derivative. Selective *O*-silylation of the primary alcohol functionality within **51** gave species **52** which was treated sequentially with NaOH, DPPA/Et_3N and TBAF to furnish oxazolidine-2-one **53** in 68% yield (over three steps) *via* means of a Curtis rearrangement.[26] Oxidation of alcohol **53** with DMP followed by tail elongation *via* a Wittig olefination[10] (with the ylid derived from deprotonation of the triphenylarsonium salt of bromoacetalydehyde) gave aldehyde **54** in 73% yield. A three-step Julia olefination[27] protocol using pentylphenylsulfone was used to install the remainder of the tail, affording **55** in 68% yield. The synthesis was completed with full deprotection and global acetylation to give pseudodistomin B acetate **10** in 69% yield, concluding in 6% total yield over twenty-one steps (Scheme 6). It was reported that spectral data for synthetic **10** were the same as those previously reported by Kobayashi *et al.*,[1] with the acknowledgment of some minor olefin isomers observable in the ^1H NMR spectrum in an ~86:14 ratio. Ma *et al.* unfortunately elected to measure the specific rotation of their

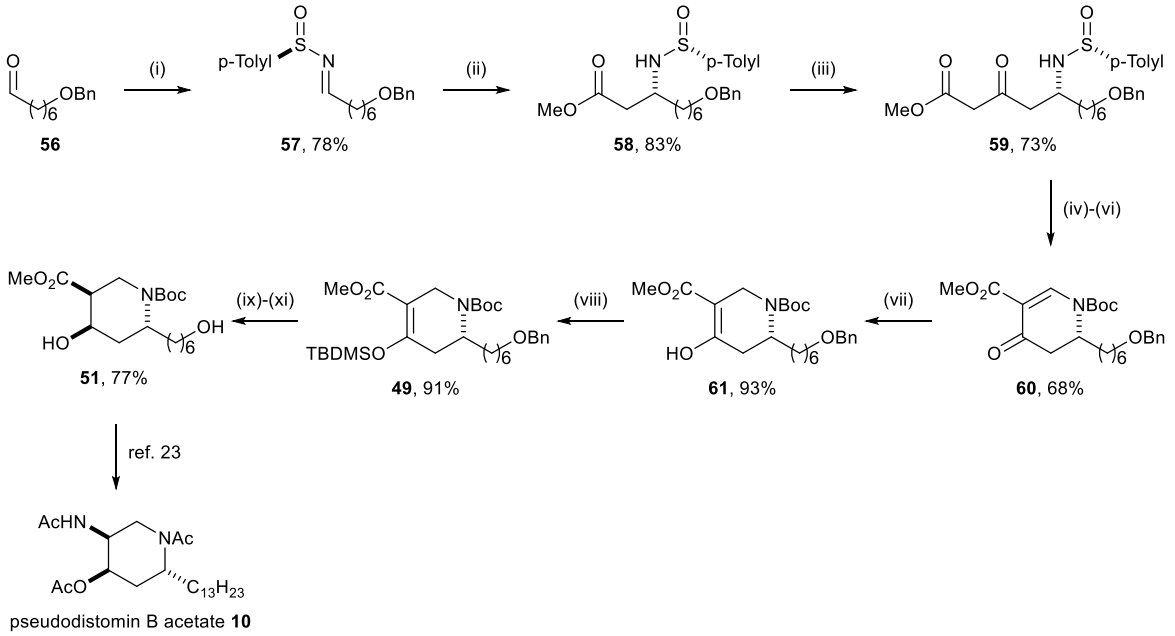
synthetic sample in $CHCl_3$, yielding a value of $[\alpha]_D^{22}$ +35.7 (*c* 1.0 in $CHCl_3$), whereas the acetylated natural specimen was measured in MeOH and gave a value of $[\alpha]_D^{24}$ +35 (*c* 1.0 in MeOH), and so these data cannot be compared and provide no support for the assignment of the absolute configuration of the natural product.



Scheme 6 *Reagents and conditions*: (i) H_2 (1 atm), Pd/C, MeOH, rt, 10 h; (ii) methyl acrylate, MeOH, rt, 48 h; (iii) $(Boc)_2O$, $NaHCO_3$, 1,4-dioxane, 30 °C, 5 h; (iv) Na, MeOH, C_6H_6, rt, 48 h; (v) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt, 24 h; (vi) H_2 (30 atm), Pd/C, EtOAc, 50 °C, 24 h; (vii) H_2 (80 atm), Ra Ni, EtOAc, 80 °C, 24 h; (viii) TsOH, MeOH, rt, 1h; (ix) TIPSCl, DMAP, Et_3N, CH_2Cl_2, rt, 6 h; (x) NaOH, MeOH, rt, 6 h; (xi) DPPA, Et_3N, C_6H_6, 80 °C, 16 h; (xii) TBAF, THF, rt, 6 h; (xiii) DMP, CH_2Cl_2, rt, 2 h; (xiv) $[Ph_3AsCH_2CHO]^+Br^-$, K_2CO_3, H_2O, Et_2O/THF (7:3), rt, 20 h; (xv) $C_5H_{11}SO_2Ph$, BuLi, THF, −78 °C, 3 h; (xvi) BzCl, DMAP, Et_3N, CH_2Cl_2, rt, 3 h; (xvii) Na/Hg, MeOH/EtOAc (2:1), −25 °C, 1 h; (xviii) NaOH, MeOH, 70 °C, 3 h; (xix) Ac_2O, DMAP, Et_3N, rt, 3 h; (xx) HCl, MeOH/EtOAc (1:1), rt, 3 h; (xxi) Ac_2O, DMAP, Et_3N, rt, 2 h.

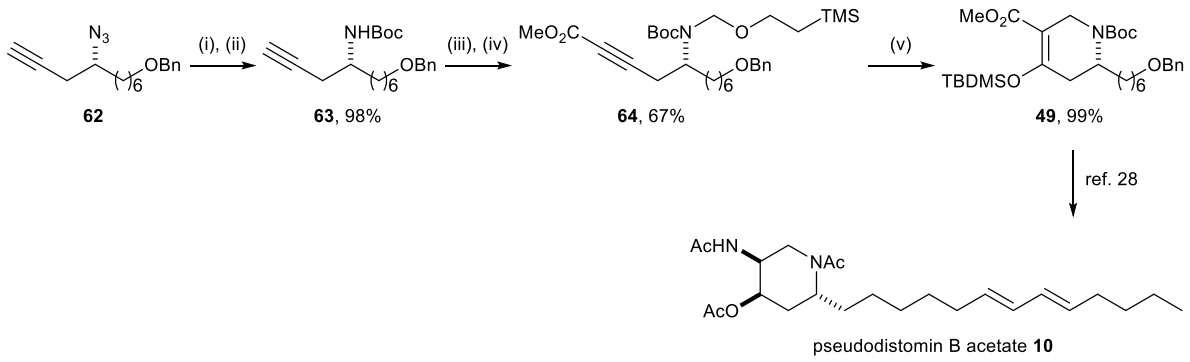
Davis *et al*. reported a formal synthesis of pseudodistomin B acetate **10** in 2005 utilising aldehyde **56** as the starting material.[28] Condensation of (*R*)-*p*-toluenesulfinamide and aldehyde **56** gave imine **57** in 78% yield. Treating imine **57** with an excess of the sodium enolate of methyl acetate facilitated transformation into the 1,3-dicarbonyl **59**. Reaction of **59** with *N*,*N*-dimethylformamide dimethyl acetal, followed by acidic hydrolysis of the intermediate imine, and subsequent *N*-Boc protection afforded cyclised product **60** in 68% yield. Hydrogenation of **60** with Pt/C catalysis gave enol **61** which upon treatment under *O*-silylation conditions gave the key species **49** in 91% yield. Conversion of masked enol **49** to the known diol **51** was achieved *via* sequential *O*-debenzylation, olefin hydrogenation and *O*-desilylation.

This diol was the same as obtained by Ma *et al*. in their report[23] on the basis of ^{1}H NMR spectroscopic analysis and specific rotation values, and thus completed the formal synthesis of pseudodistomin B acetate **10** (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) (*R*)-*p*-toluenesulfinamide, $Ti(OEt)_4$, CH_2Cl_2, rt, 3 h; (ii) NaHMDS, methyl acetate, Et_2O, −78 °C, 1 h; (iii) NaHMDS, methyl acetate, THF, −78 °C, 7 h; (iv) $NMe_2CH(OMe)_2$, PhMe, rt, 5 h; (v) HCl, 1,4-dioxane, rt, 2 h; (vi) $(Boc)_2O$, Et_3N, MeCN, rt, 6 h; (vii) H_2 (1 atm), Pt/C, MeOH, rt, 30 min; (viii) TBDMSCl, DBU, CH_2Cl_2, rt, 30 min; (ix) H_2 (30 atm), Pd/C, EtOAc, 50 °C, 24 h; (x) H_2 (90 atm), Ra Ni, EtOAc, 80 °C, 24 h; (xi) TBAF, THF, 0 °C to rt, 30 min.

The final literature report (to date) mentioning pseudodistomin B **2** was published in 2014,[29] and features a further formal synthesis of pseudodistomin B acetate **10**. Manipulation of azide **62** {derived from (*S*)-2-[6'-(benzyloxy)hex-1'-yl]oxirane}[30] gave *N*-Boc derivative **63** in 98% yield. A two-step procedure converted **63** to **64** in 67% yield, *via* further *N*-derivatization as the SEM ether, and acetylation of the alkyne. Gold catalysed reaction of **64** gave masked enol **49** (Scheme 8). Comparison of the ^{1}H and ^{13}C NMR spectral data along with the specific rotation value for **49** were consistent with those reported by Davis *et al*.[28] in their formal synthesis of pseudodistomin B **10**.



Scheme 8 *Reagents and conditions*: (i) $LiAlH_4$, Et_2O, 0 °C, 2 h; (ii) $(Boc)_2O$, H_2O, 0 °C to rt, 16 h; (iii) PFA, TMSCl, CH_2Cl_2, −15 °C, 10 h then 2-(trimethylsilyl)ethanol, Et_3N; (iv) BuLi, THF, −78 °C, 2 h then $ClCO_2Me$, −78 °C, 3 h; (v) $AgSbF_6$, Au[P(^{t}Bu)$_2$(*o*-biphenyl)]Cl, CH_2Cl_2, −15 °C, 15 min.

1.4 Pseudodistomin C and Pseudodistomin F

1.4.1 Isolation of Pseudodistomin C

In 1995 Kobayashi *et al*. re-examined extracts of *Pseudodistoma kanoko* for the third time.[3] Extraction of the sponge with MeOH/PhMe, followed by sequential flash column chromatography and preparative TLC purification afforded a new compound which was named pseudodistomin C **3**. A fraction from the silica gel column was acetylated, and following reverse-phase HPLC purification, pseudodistomin C acetate **65** was isolated, along with pseudodistomin A acetate **9** and pseudodistomin B acetate **10**. Pseudodistomin C acetate **65** exhibited a specific rotation value of $[\alpha]_D^{22}$ +85 (*c* 1.0 in $CHCl_3$), and *m/z* analysis [HREIMS *m/z* 444.2925 $(M)^+$] indicated a molecular formula of $C_{26}H_{40}N_2O_4$, implying an increase of two carbon atoms and two hydrogen atoms relative to both pseudodistomin A acetate **9** and pseudodistomin B acetate **10**. Analysis of the UV spectrum showed an absorption maximum at 235 nm, with a molar absorption coefficient (ε 37000) of almost twice the magnitude of pseudodistomin A acetate **9** (ε 17000) and pseudodistomin B acetate **10** (ε 18000), which the authors stated was suggestive of the presence of two diene units. NMR spectroscopic analysis was carried out on pseudodistomin C **3** and the corresponding acetate **65** in a range of solvents in order to obtain well resolved spectra with sharp signals. Analysis was therefore carried out in pyridine-d_5 for the natural specimen **3** and MeOH- d_4 for the derived acetate **65**.

Spectral data indicated a similar scaffold as for pseudodistomin A **1** and pseudodistomin B **2**, consisting of a trisubstituted piperidine moiety bearing C(4)-hydroxyl and C(5)-amino functionalities along with an unsaturated hydrocarbon tail portion at C(2). ^{1}H–^{1}H COSY interpretation of pseudodistomin C **3** indicated that one of the two dienes was located at the C(1')–C(4') position. To unambiguously determine the position of the second diene, pseudodistomin C **3** was treated sequentially with O_3, $NaBH_4$ and Ac_2O, from which piperidine **66** and the diacetate of 1,5-pentane diol **67** were detected *via* reverse phase TLC and HPLC analyses (Figure 7). The locations of the diene units were therefore determined to reside at the C(1')–C(4') and C(8')–C(11') positions. Geometries of all olefins were inferred to be (*E*)-configured from a combination of ^{1}H NMR ^{3}J coupling constant analysis ($^{3}J_{1',2'} = {}^{3}J_{3',4'} = 15.4$ Hz) and the ^{13}C NMR chemical shifts of the allylic methylenes [*C*(5'), *C*(7') and *C*(12')], which were all in the range of δ 31.7–32.4 ppm.

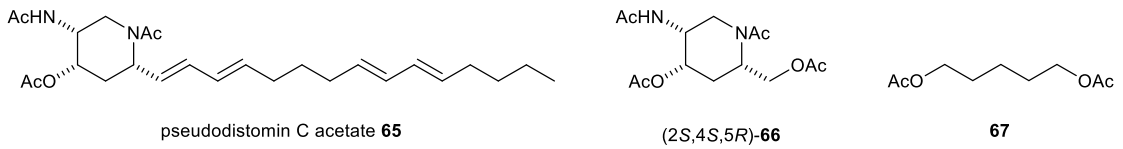
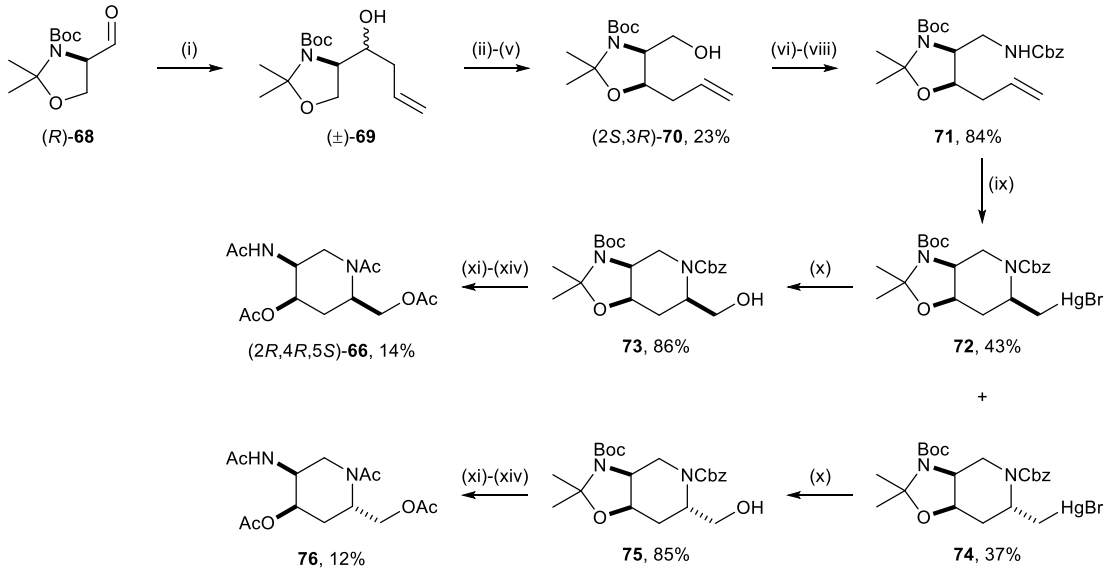


Figure 7 Experiments leading to the structural assignment of pseudodistomin C **3**.

To obtain unambiguous proof of the configuration of the piperidine ring, Kobayashi *et al.* investigated the synthesis of the tetraacetate (2*S*,4*S*,5*R*)-**66**, obtained *via* derivatization of the natural specimen of pseudodistomin C **3**. Thus, a 50:50 mixture of the diastereoisomers of (±)-**69** [obtained by addition of allylmagnesium bromide to Garner's aldehyde (*R*)-**68**][31] was transformed, *via* a four-step procedure, to (2*S*,3*R*)-**70** in 23% yield from (±)-**69**. Manipulation of the alcohol moiety within (2*S*,3*R*)-**70** gave cyclisation precursor **71** in 84% yield (over three steps). Amide mercuration of **71** gave a ~50:50 ratio of diastereomeric piperidine derivatives, from which **72** was isolated in 43% yield, and the epimer **74** was isolated in 37% yield. The configurations within **72** and **74** were assigned *via* ^{1}H NMR nOe spectroscopic analyses of derivatives. Oxidative demercuration of **72** gave alcohol **73**, which was subjected to a four-step protocol to remove the acetonide and *N*-Cbz protecting groups to furnish tetraacetate

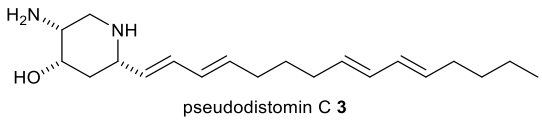
(2*R*,4*R*,5*S*)-**66** in 14% yield. An identical sequence was carried out on the epimer **74**, which gave **76** in 10% yield over five steps (Scheme 9). ^{1}H NMR spectroscopic analysis of (2*R*,4*R*,5*S*)-**66** confirmed it be identical to that of the tetraacetate obtained from derivatization of the natural specimen. However, the sign of its specific rotation $\{[\alpha]_D^{23}$ −19 (*c* 0.28 in MeOH)} was revealed to be opposite to that of the specimen derived from the natural sample $\{[\alpha]_D^{23}$ +16 (*c* 0.1 in MeOH)} indicating that the natural specimen possesses the (2*S*,4*S*,5*R*)-absolute configuration. To confirm this result, Kobayashi *et al*. also prepared the enantiomer (2*S*,4*S*,5*R*)-**66** *via* the above procedures from (*R*)-serine derived Garner's aldehyde[31] (*S*)-**68**. The specific rotation of the product (2*S*,4*S*,5*R*)-**66** $\{[\alpha]_D^{26}$ +20 (*c* 0.35 in MeOH)} was a close match with the value exhibited by the specimen obtained by derivatization of the natural specimen $\{[\alpha]_D^{23}$ +16 (*c* 0.1 in MeOH)}. Furthermore, it was reported that chiral HPLC analysis established both synthetic and naturally derived (2*S*,4*S*,5*R*)-**66** exhibited identical retention times.



Scheme 9 *Reagents and conditions*: (i) allylmagnesium bromide (ii) $TsOH{\cdot}H_2O$, MeOH, rt, 20 h then 45 °C, 3 h; (iii) pivCl, pyridine, rt, 3 h; (iv) $BF_3{\cdot}Et_2O$, 2,2-dimethoxypropane, CH_2Cl_2, 0 °C, 20 min; (v) KOH, MeOH, 40 °C, 20 h; (vi) DIAD, phthalimide, PPh_3, THF, rt, 20 h; (vii) $N_2H_4{\cdot}H_2O$, EtOH, rt, 15 h; (viii) CbzCl, NaOH, THF, rt, 3 h; (ix) $Hg(OTf)_2$, $CHCl_3$, rt, 20 h then satd aq $NaHCO_3$, satd aq NaBr, rt, 3 h; (x) O_2, $NaBH_4$, DMF, rt, 2 h; (xi) TFA, CH_2Cl_2, rt, 20 h; (xii) Ac_2O, pyridine, rt, 2 h; (xiii) H_2 (1 atm), Pd/C, EtOH, rt, 24 h; (xiv) Ac_2O, pyridine, rt, 90 min.

Thus, Kobayashi *et al.* proposed the structure and absolute configuration within pseudodistomin C **3** as (2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(pentadeca-1',3',8',10'-tetraen-1'-yl)-4-hydroxy-5-

aminopiperidine (Figure 8). Following this work, the aforementioned publication by Freyer *et al*.[2] also reported isolating pseudodistomin C **3**. Rather unusually, the report offers no data whatsoever relating to the characterisation of pseudodistomin C **3**, however full data were offered for pseudodistomin B **2** (both of which are known compounds). It is therefore unclear how the congruency of the sample isolated by Freyer *et al*. with that of Kobayashi *et al*. was established.



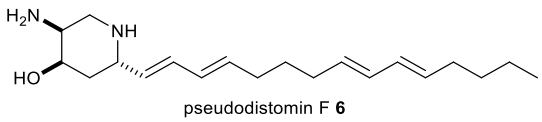
pseudodistomin C **3**

Figure 8 Proposed structure of pseudodistomin C **3**.

1.4.2 Isolation of Pseudodistomin F

The 1997 report saw Freyer *et al*. isolate a total of five pseudodistomins (B **2**, C **3**, D **4**, E **5** & F **6**), three of which were previously unreported (D **4**, E **5** & F **6**), from extraction of Micronesian ascidian *Pseudodistoma megalarva* as part of a high throughput screening to evaluate natural products in a yeast based assay for DNA damaging activity.[2] Mass spectrometry analysis of pseudodistomin F **6** [HRDCIMS, *m/z* 318.2664 $(M)^+$] implied a molecular formula of $C_{20}H_{34}N_2O$ and five degrees of unsaturation, noted as being identical to that of pseudodistomin C **3**. Its IR and UV spectra were also noted as being similar to those exhibited by pseudodistomin C **3**. Freyer *et al*. stated that ^1H and ^{13}C NMR spectroscopic analysis indicated a close match with their sample of pseudodistomin B **2**, suggestive of a piperidine head unit with an unsaturated tail, however with downfield shifts observed for C(2)*H* and *C*(2). Exhaustive NMR spectral analyses (^1H, ^{13}C, COSY, HMBC) established a linear fifteen carbon tail portion, with large ^3J coupling constants ($^3J_{1',2'} = {}^3J_{3',4'} = {}^3J_{8',9'} = {}^3J_{10',11'} =$ 14.4 Hz) indicative of (*E*)-configured olefins. HMBC analysis was used to assign the position of the diene units, with the locations calculated as residing in identical positions to those within pseudodistomin C **3**, namely C(1')–C(4') and C(8')–C(11'). A combination of chemical shift

data, coupling constants and ^{1}H NMR nOe spectroscopic analysis was interpreted to assign the respective positions of the groups borne by the piperidine ring and also the relative configuration therein. Specific rotation data for pseudodistomin F **6** {$[\alpha]_D^{25}$ −13.9 (*c* 0.42 in MeOH)} was observed to be almost identical with that displayed for the sample of pseudodistomin B **2** {$[\alpha]_D^{25}$ −13 (*c* 0.87 in MeOH)} isolated at the same time. Freyer *et al.* suggested that this indicated pseudodistomin B **2** and pseudodistomin F **6** share the same sense of absolute configuration, and thus proposed the structure of pseudodistomin F **6** to be (2*S*,4*R*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(pentadeca-1',3',8',10'-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine (Figure 9).

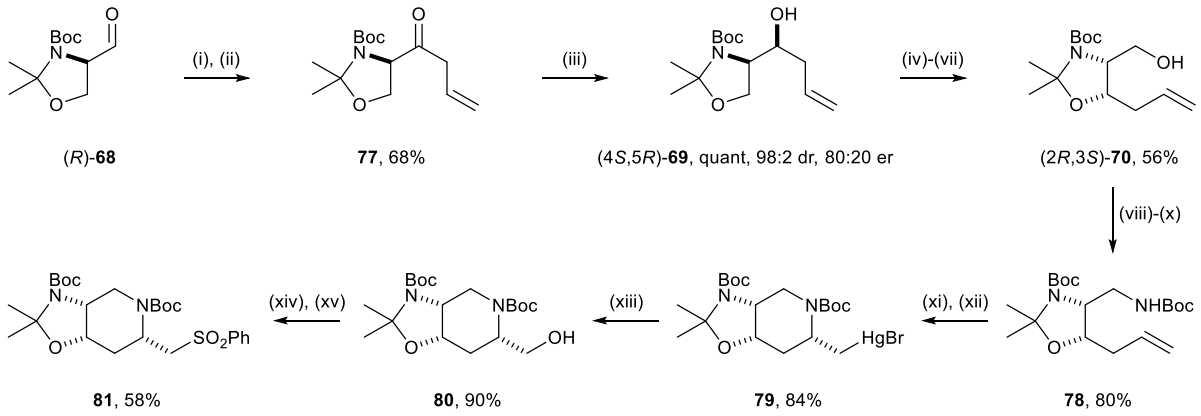


pseudodistomin F **6**

Figure 9 Proposed structure of pseudodistomin F **6**.

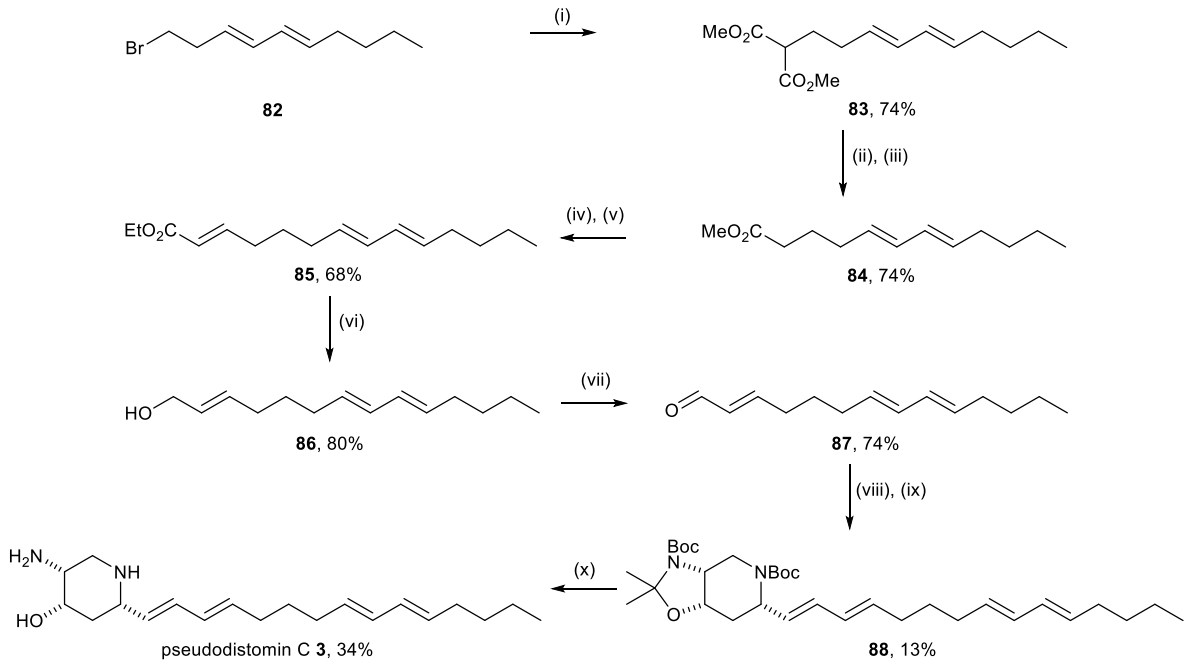
1.4.3 Enantiopure Syntheses of Pseudodistomin C and Pseudodistomin F

The first, and to date only, total synthesis of pseudodistomin C **3** was reported in 1996 by Kobayashi *et al.*,[32] following their isolation report.[3] Their synthesis began with the addition of allylmagnesium bromide to Garner's aldehyde (*R*)-**68**[31] to afford a 50:50 mixture of homoallylic alcohols which were immediately subjected to oxidation with DMP to give ketone **77**. Reduction of ketone **77** with $Zn(BH_4)_2$ furnished alcohol (4*S*,5*R*)-**69** in quantitative yield, 98:2 dr and 80:20 er. This racemization was proposed to occur during the oxidation-reduction process. The synthetic route then emulated their previous work[3] (with the replacement of the *N*-Cbz protecting group with the *N*-Boc protecting group) to furnish alcohol **80** in 34% yield over ten steps. Manipulation of alcohol functionality **80** gave the sulfone **81** in 58% yield over two steps (Scheme 10).



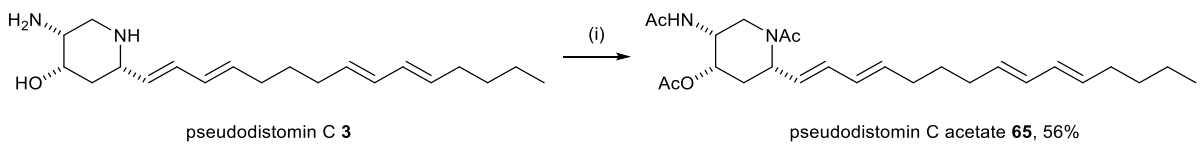
Scheme 10 *Reagents and conditions*: (i) allylmagnesium bromide; (ii) DMP, DMF, rt, 4 h; (iii) $Zn(BH_4)_2$, Et_2O/C_6H_6 (4:1), rt, 15 min; (iv) $TsOH{\cdot}H_2O$, MeOH, rt, 20 h then 45 °C, 3 h; (v) pivCl, pyridine, rt, 3 h; (vi) $BF_3{\cdot}OEt_2$, 2,2-dimethoxypropane, CH_2Cl_2, 0 °C, 20 min; (vii) KOH, MeOH, 40 °C, 20 h; (viii) DIAD, phthalimide, PPh_3, THF, rt, 20 h; (ix) $N_2H_4{\cdot}H_2O$, EtOH, rt, 15 h; (x) $(Boc)_2O$, NaOH, 1,4-dioxane, rt, 1 h; (xi) $Hg(OAc)_2$, $CHCl_3$, rt, 18 h then satd aq $NaHCO_3$, 20 min; (xii) satd aq NaBr, rt, 3 h; (xiii) O_2, $NaBH_4$, DMF, rt, 3 h; (xiv) $(PhS)_2$, n-Bu_3P, pyridine, rt, 4.5 h; (xv) $(PhSe)_2$, H_2O_2, Et_2O/CH_2Cl_2 (17:3), 0 °C, 1 h then rt, 6 h.

Kobayashi *et al*. developed a concise synthesis of the tail segment beginning from the known alkyl bromide **82**.[22] Reaction of the enolate of dimethyl malonate with **82** gave diester **83** which was treated with NaCl in wet DMSO then CH_2N_2 to furnish mono ester **84** in 55% yield (over two steps). Reduction of **84** with DIBAL-H followed by treatment of the resultant aldehyde with ethyl 2-(triphenylphosphranylidene)acetate in a Wittig reaction gave triene **85** in 68% yield. Finally, reduction of ester **85** to alcohol **86**, followed by subsequent PCC promoted oxidation furnished aldehyde **87** in 59% yield (over two steps). In order to couple the head and tail fragments, sulfone **81** was allowed to react sequentially with BuLi and aldehyde **87** in a Julia olefination[27] reaction, to afford **88** in 13% yield. Kobayashi *et al*. noted the newly formed olefin within **88** was of (*E*)-configuration based on ^{1}H NMR coupling constant analysis ($^3J_{1',2'}$ = 14.0 Hz), and HPLC analysis showed "predominantly a single peak". Finally, HCl mediated deprotection of the acetonide moiety and *N*-Boc group unveiled pseudodistomin C **3** in 34% yield and 0.6% total yield over eighteen steps (Scheme 11). It was reported that ^{1}H NMR spectroscopic, EIMS and TLC analyses indicated synthetic pseudodistomin C **3** was identical with the natural specimen although the report unfortunately did not disclose any of the NMR data for pseudodistomin C **3**, and the specific rotation value $\{[\alpha]_D^{24}$ −24 (*c* 0.7 in MeOH)$\}$ was not compared to that of the natural specimen (as Kobayashi *et al*. previously did not report this in their original isolation paper).[3]



Scheme 11 *Reagents and conditions*: (i) Na, MeOH, $(MeO_2C)_2CH_2$, rt, 20 min then 65 °C, 5 min then **82**, 38 °C, 3.5 days; (ii) NaCl, DMSO, 190 °C, 4 h; (iii) CH_2N_2, Et_2O, 0°C, 30 min; (iv) DIBAL-H, PhMe, −78 °C, 1.5 h; (v) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 14 h; (vi) DIBAL-H, CH_2Cl_2, −78 °C, 15 min; (vii) PCC, CH_2Cl_2, rt, 1 h; (viii) BuLi, HMPA, THF, −78 °C, 10 min then **87**, THF, −78 °C, 1.5 h then BzCl, rt, 1 h; (ix) Na/Hg, THF/MeOH (4:1), −20 °C, 3.5 h then Na/Hg, −20 °C, 7.5 h; (x) HCl, EtOAc, rt, 6 h.

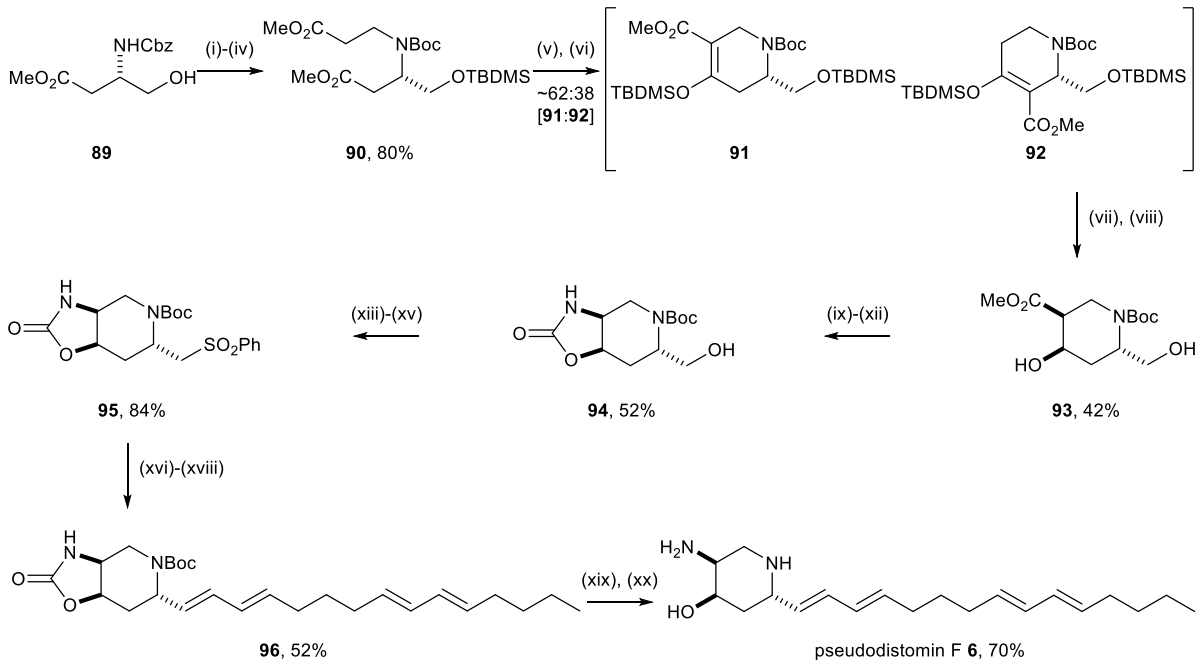
The report also detailed the preparation of the known pseudodistomin C acetate **65**. Thus, pseudodistomin C **3** was treated with Ac_2O in pyridine to give pseudodistomin C acetate **65** in 56% yield (Scheme 12). It was stated that ^{1}H NMR, EIMS, TLC and HPLC examination indicated that the synthetic and naturally derived samples of pseudodistomin C acetate **65** were identical. The specific rotation value of this sample of **65** $\{[\alpha]_D^{23}$ +43 (*c* 0.5 in $CHCl_3)\}$ was compared to the specimen derived from a natural source $\{[\alpha]_D^{22}$ +85 (*c* 0.98 in $CHCl_3)\}$. As the sign was the same in both instances, this synthesis provided confirmation of the absolute configuration within pseudodistomin C **3**. However, the magnitude is significantly different, which was proposed to arise as a function of the sample being 80:20 er.



Scheme 12 *Reagents and conditions*: (i) Ac_2O, pyridine, rt, 1.5 h.

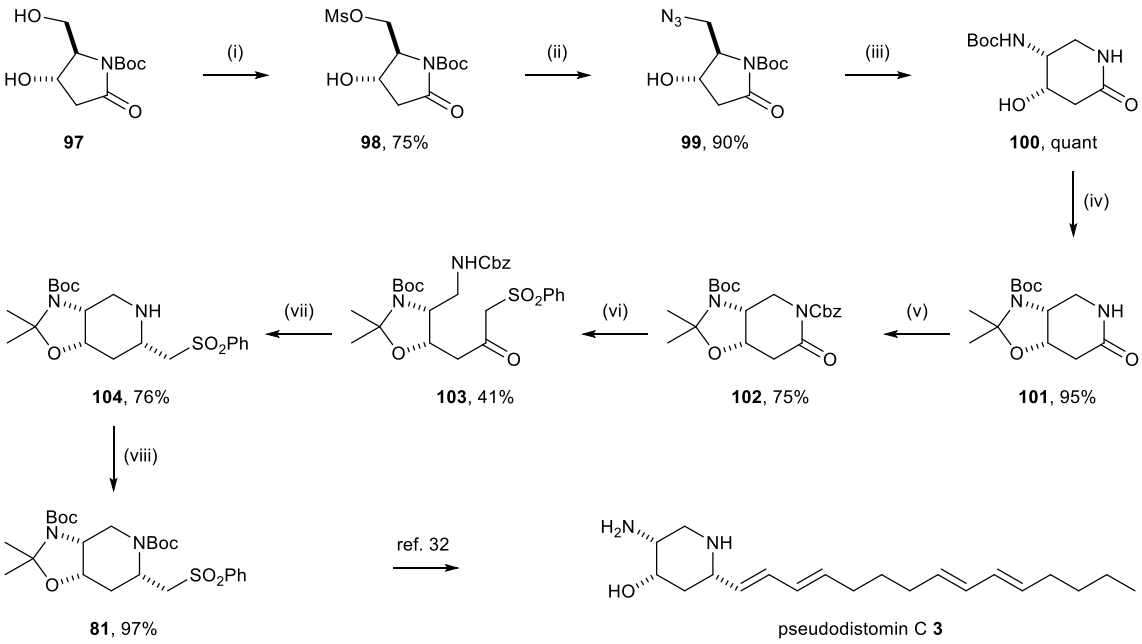
A lone report also exists detailing the asymmetric synthesis of pseudodistomin F **6**, published by Ma *et al*.,[23] using a similar strategy to that used in their synthesis of pseudodistomin B **2**.

(*S*)-Aspartic acid derived alcohol **89** was used to prepare cyclisation precursor **90** *via* sequential *O*-silylation, hydrogenolysis, Michael addition to methyl acrylate and *N*-protection. Dieckmann cyclisation[25] of **90** with subsequent *O*-silylation gave a ~62:38 mixture of **91** and **92**, respectively. As before, olefin hydrogenation and *O*-deprotection furnished, after purification, **93** in 42% yield (over four steps). Construction of oxazolidinone **94** was achieved *via* a four-step protocol in 52% yield, and functionalisation of the resultant alcohol moiety within **94** afforded sulfone **95** in 84% yield. Julia olefination[27] of **95** with the known aldehyde **87**[32] (as used by Kobayashi *et al.*[32] in their synthesis of pseudodistomin C **3**) was used to install the tail, followed by global deprotection to unveil synthetic pseudodistomin F **6** in 5% total yield over twenty steps (Scheme 13). It was reported that a single isomer was observed *via* ^{1}H NMR spectroscopic analysis, indicating a highly stereoselective construction of the C(1')–C(2') olefin moiety. Specific rotation data of this synthetic sample $\{[\alpha]_D^{11}$ −12.6 (*c* 0.2 in MeOH)} was in good agreement with the value reported by Freyer *et al.*[2] for the natural material $\{[\alpha]_D^{25}$ −13.9 (*c* 0.42 in MeOH)}. ^{1}H and ^{13}C NMR spectroscopic data for the synthetic sample of pseudodistomin F **6** were reported as being identical to those recorded for the natural product.



Scheme 13 *Reagents and conditions*: (i) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt, 6 h; (ii) H_2 (1 atm), Pd/C, MeOH, rt, 10 h; (iii) methyl acrylate, rt, 48 h; (iv) $(Boc)_2O$, 1,4-dioxane, 30 °C, 5 h; (v) Na, MeOH, C_6H_6, rt, 48 h; (vi) TBDMSCl, DMAP, Et_3N, CH_2Cl_2, rt, 24 h; (vii) H_2 (80 atm), Ra Ni, EtOAc, 80 °C, 24 h; (viii) TsOH, MeOH, rt, 1h; (ix) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, rt, 6 h; (x) NaOH, MeOH, rt, 6 h; (xi) DPPA, Et_3N, C_6H_6, 80 °C, 16 h; (xii) TBAF, THF, rt, 6 h; (xiii) MsCl, DMAP, Et_3N, CH_2Cl_2, rt, 6 h; (xiv) PhSH, $NaHCO_3$, 1,4-dioxane, rt, 24 h; (xv) *m*CPBA, CH_2Cl_2, rt, 3 h; (xvi) BuLi, DME, −78 °C, 2 h then **87**, DME, −78 °C, 30 min; (xvii) BzCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (xviii) Na/Hg, MeOH/EtOAc (2:1), −25 °C, 1 h; (xix) KOH, MeOH, 70 °C, 3 h; (xx) HCl, MeOH, rt, 30 min.

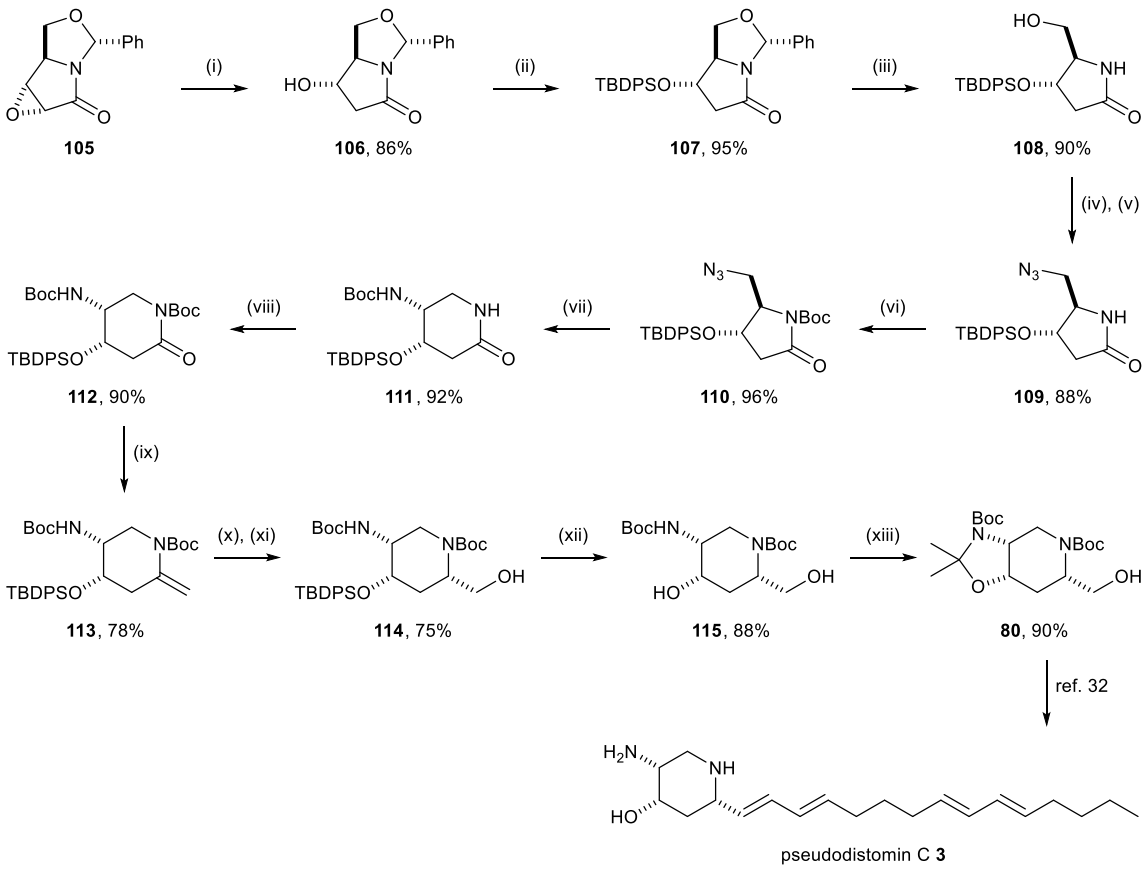
The remaining two reports in this section detail formal syntheses of pseudodistomin C **3**, the first of which was published by Langlois in 2002.[33] Diol **97** [derived from (*S*)-pyroglutaminol][34,35] was subjected to chemoselective *O*-mesylation of the primary hydroxyl group, followed by subsequent displacement with azide to afford **99**. Reduction of the azido functionality within **99** facilitated intramolecular transamidation to furnish piperidone **100** in quantitative yield. Acetonide protection was achieved *via* treatment of **100** with 2,2-dimethoypropane and catalytic acid, to give **101** in 95% yield. *N*-Protection, followed by addition of (benzenesulfonyl)methyllithium gave **103**. Exposure of **103** to a hydrogen atmosphere in the presence of Pearlman's catalyst facilitated *N*-deprotection, cyclisation and subsequent imine reduction to provide sulfone **104**. Finally, *N*-protection with $(Boc)_2O$ gave sulfone **81**, previously reported by Kobayashi *et al.*[32] (Scheme 14). Langlois did not include any data for **81**, the common intermediate in both her and Kobayashi's syntheses, so no comparison could be made.[36]



Scheme 14 *Reagents and conditions*: (i) MsCl, pyridine, −5 °C, 25 min; (ii) NaN_3, DMF, 45 °C, 22 h; (iii) H_2 (1 atm), Pd/C, MeOH, rt, 44 h; (iv) 2,2-dimethoxypropane, TsOH, acetone, rt, 16 h; (v) BuLi, THF, −78 °C, 15 min then CbzCl, −78 °C, 25 min; (vi) $PhSO_2CH_2Li$, THF, −76 °C, 45 min; (vii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 50 h; (viii) $(Boc)_2O$, $NaHCO_3$, THF/H_2O (1:1), rt, 33 h.

The second, and to date final, formal synthesis of pseudodistomin C **3** was completed in 2006 by Tanaka *et al*.[37] In a similar vein to Langlois' work,[33] the known epoxide **105**[38] [derived from (*S*)-pyroglutaminol] was selected as the starting material. Regioselective ring-opening was achieved *via* use of the borane complex $Na[PhSeB(OEt)_3]$, generated *in situ*, to afford hydroxy lactam **106** in 86% yield. *O*-Silylation followed by transfer hydrogenation to remove the benzylidene acetal furnished **108**. *O*-Mesylation of **108** followed by substitution of the mesylate moiety with azide and subsequent *N*-protection gave **110** in 85% yield (over three steps). As before, exposure to a hydrogen atmosphere in the presence of Pd/C facilitated reduction of the azide moiety, cyclisation and reduction of the resultant imine to furnish the piperidine **111** in 92% yield. *N*-Protection of **111** with $(Boc)_2O$ followed by treatment of **112** with Cp_2TiMe_2 afforded *exo*-methylene compound **113** in 78% yield, with no evidence of isomerisation to the *endo*-cyclic species. Hydroboration of the olefinic moiety within **113** with 9-BBN followed by basic H_2O_2, gave **114** as a single diastereoisomer in 75% isolated yield. Finally, following protecting group manipulations, Kobayashi's alcohol **80**[32] was isolated, allowing the synthetic routes to be correlated (Scheme 15). ^1H and ^{13}C NMR spectroscopic data were reported as being

in good agreement with those previously reported, and the specific rotation values were a reasonably good match with $[\alpha]_D^{24}$ −10.8 (*c* 1.3 in $CHCl_3$) and $[\alpha]_D^{24}$ −7.3 (*c* 1.0 in $CHCl_3$) being observed for Tanaka's and Kobayashi's samples of **80**, respectively. Tanaka *et al*. reported the spectral data to be in good agreement with those previously reported, however inspection of the ^{1}H NMR spectroscopic data revealed some discrepancies. The ^{13}C NMR spectroscopic data could not be compared because Kobayashi *et al*. did not include these data in their original report.



Scheme 15 *Reagents and conditions*: (i) $(PhSe)_2$, $NaBH_4$, EtOH, rt, 20 min then AcOH, 0 °C, 5 min then **105**, EtOH, 0 °C, 30 min then O_2, EtOAc, 5 min; (ii) TBDPSCl, imidazole, DMF, rt, 8 h; (iii) $N_2H_4{\cdot}H_2O$, Pd/C, EtOH, 80 °C, 10 h; (iv) MsCl, Et_3N, CH_2Cl_2, rt, 12 h; (v) NaN_3, DMF, 80 °C, 6 h; (vi) $(Boc)_2O$, DMAP, CH_2Cl_2, rt, 8 h; (vii) H_2 (3 atm), Pd/C, MeOH/H_2O (12:1), rt, 48 h; (viii) $(Boc)_2O$, DMAP, CH_2Cl_2, rt, 8 h; (ix) Cp_2TiMe_2, PhMe, 105 °C, 3 h; (x) 9-BBN, THF, rt, 20 h; (xi) H_2O_2, NaOH, rt, 2 h; (xii) TBAF, THF, rt, 6 h; (xiii) 2,2-dimethoxypropane, TsOH, acetone, rt, 12 h.

1.5 Pseudodistomin D and Pseudodistomin E

1.5.1 Isolation of Pseudodistomin D and Pseudodistomin E

The final two pseudodistomins isolated in the 1997 study by Freyer *et al*.[2] were pseudodistomin D **4** and pseudodistomin E **5**. They possessed the same molecular weight [HRDCIMS, *m/z* 294.2662 $(M)^+$ and *m/z* 294.2674 $(M)^+$, respectively], identical to pseudodistomin A **1** and pseudodistomin B **2**, and indicative of a molecular formula of $C_{18}H_{34}N_2O$ with three degrees of unsaturation. ND_3 DCIMS revealed a total of four exchangeable protons, the IR spectra contained a strong hydroxyl absorptions and interpretation of UV spectra suggested the presence of a conjugated diene in each case. Exhaustive NMR spectroscopic analyses were used to determine the gross structures and relative configuration within both pseudodistomin D **4** and pseudodistomin E **5**. ^1H and ^{13}C NMR spectroscopic analyses indicated the presence of four olefinic carbons and protons (accounting for two degrees of unsaturation) and suggesting the final degree of unsaturation was due to the presence of a piperidine ring. COSY and HMQC spectroscopic interpretation revealed an identical substitution pattern of the piperidine ring relative to all other known pseudodistomins. Olefin geometries were determined to be (*E*)-configured in all instances by ^1H NMR ^3J coupling constant ($^3J_{6',7'} = {}^3J_{8',9'} = 14.4$ Hz) analysis and from the chemical shifts of the flanking vicinal carbons (δ 33.3 and 33.5 ppm). The location of the diene units within the tail portions were unambiguously assigned *via* HMBC spectroscopic analysis, showing clear correlations between C(13')H_3 and *C*(12') and *C*(11'), with the resonances at *C*(11') shown to be two bonds removed from the conjugated double bonds. Thus, as seen in pseudodistomin B **2**, an (6'*E*,8'*E*)-configured diene is present. A combination of coupling constant and nOe spectroscopic analyses were used to assign the relative configurations within pseudodistomin D **4** and pseudodistomin E **5**. As with the inference of the absolute configuration within pseudodistomin F **6** from pseudodistomin B **2**, Freyer *et al*. compared the specific rotation value of their sample of pseudodistomin E **5** $\{[\alpha]_D^{25}$ −20.8 (*c* 0.39 in MeOH)$\}$ with that of pseudodistomin C **3** [although it is not clear

whether this refers to their sample, (for which data is not reported) or to Kobayahi's synthetic sample], and concluded they share the same sense of absolute configuration. As pseudodistomin D **4** displays a unique head amongst the pseudodistomins, the aforementioned method could not be applied in this instance, and therefore the absolute configuration was not assigned. Thus, the structures of pseudodistomin D **4** and pseudodistomin E **5** were proposed as (2*RS*,4*SR*,5*SR*,6'*E*,8'*E*)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine and (2*R*,4*S*,5*R*,6'*E*,8'*E*)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine, respectively (Figure 10).

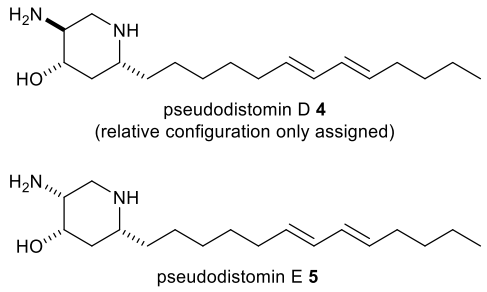
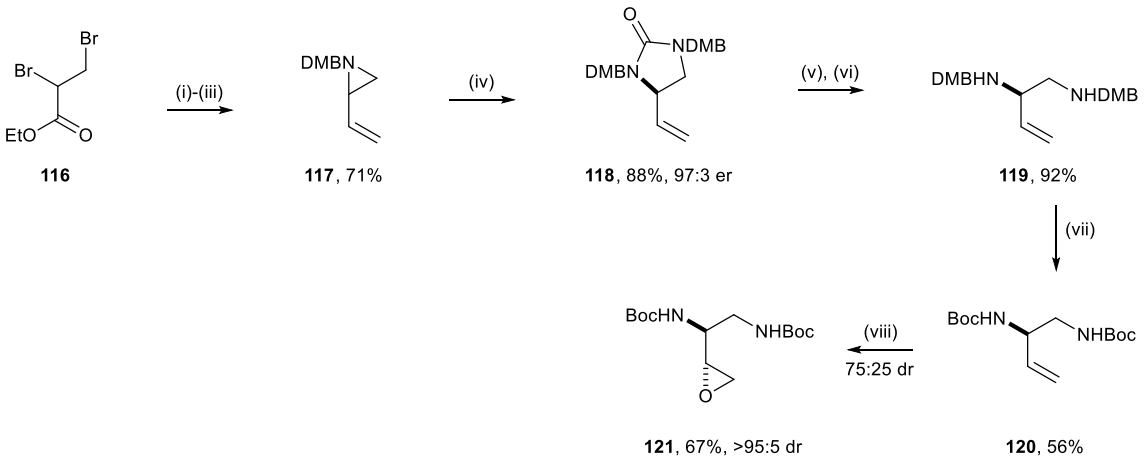


Figure 10 Proposed structures of pseudodistomin D **4** and pseudodistomin E **5**.

1.5.2 Enantiopure Syntheses of Pseudodistomin D and Pseudodistomin E

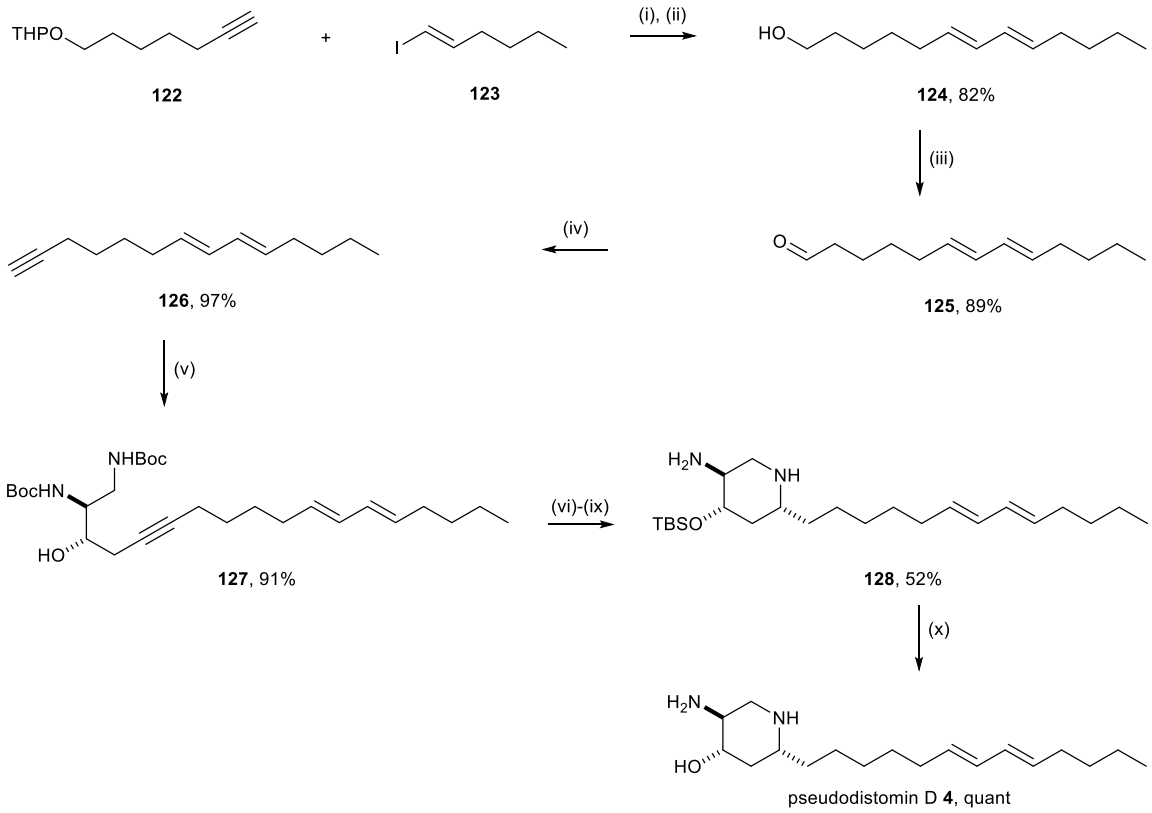
In 2005, Trost *et al*. reported the first synthesis of pseudodistomin D **4** using a dynamic kinetic asymmetric transformation (DYKAT) as the key stereodefining step.[39] Reaction of commercially available ethyl 2,3-dibrompropionate **116** with $DMBNH_2$ formed the aziridine moiety, and subsequent reduction with DIBAL-H and ensuing Wittig olefination[10] of the intermediate aldehyde gave vinylic aziridine **117** in 71% yield (over three steps). DYKAT of DMBNCO and **117** furnished imidazolidinone **118** in 88% yield and 97:3 er. A two-step procedure involving reduction of **118** with $LiAlH_4$ and subsequent hydrolysis gave diamine **119** which was subjected to protecting group manipulation to afford the bis *N*-Boc protected diamine **120** in 56% yield. Directed epoxidation yielded a 75:25 mixture of diastereoisomers, which were readily separable, giving **121** in 67% yield as a single isomer after purification (Scheme 16).



Scheme 16 *Reagents and conditions*: (i) $DMBNH_2$, Et_3N, EtOH, 50 °C, 20 h; (ii) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (iii) $[Ph_3PCH_3]^+Br^-$, KHMDS, THF, −15 °C to rt, 60 min; (iv) $(\eta^3\text{-}C_3H_5PdCl)_2$, (*S*,*S*)-Trost Ligand, CH_2Cl_2, rt, 15 min then AcOH rt, 10 min then **117**, DMBNCO, rt, 18 h; (v) $LiAlH_4$, Et_2O, 35 °C, 6 h; (vi) $NH_2OH{\cdot}HCl$, H_2O, 60 °C, 1 h; (vii) $TsOH{\cdot}H_2O$, PhMe, 110 °C, 7 h then $(Boc)_2O$, Et_3N, MeOH, rt, 45 min then 60 °C, 2.5 h; (viii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 40 °C, 5 h.

The tail segment was constructed using a four-step procedure from the alkyne **122** (prepared in two operations from 3-heptyn-1-ol)[40] and known vinyl iodide **123**[41] (prepared from 1-hexyne). Thus, a modified Negishi protocol[42] was used to couple the hydro-zirconated adduct of alkyne **122** with vinyl iodide **123**. THP removal was achieved *via* treatment with $TsOH{\cdot}H_2O$ to reveal alcohol **124** in 82% yield. Swern oxidation[15] afforded aldehyde **125** which was subjected to the Ohira-Bestmann modification[43] of the Seyferth-Gilbert reaction[44,45] to give alkyne **126** in 97% yield. Installation of the tail portion was achieved *via* reaction of the requisite dimethylaluminium reagent derived from alkyne **126** (*vide infra*), to epoxide **121**, thus the carbon skeleton **127** was constructed in 91% yield. A four-step protocol was devised to transform **127** to piperidine **128** involving sequential, *O*-silylation, *N*-deprotection, intramolecular hydroamination of the alkyne moiety and imine reduction to furnish **128** in 52% yield. The final step featured a facile deprotection to yield the first synthetic sample of pseudodistomin D **4** in quantitative yield, and 10% total yield over fourteen steps from **116** (Scheme 17). NMR spectroscopic analysis indicated excellent correlation with the literature data, and the specific rotation value of $[\alpha]_D^{25}$ +6 (*c* 0.2 in MeOH) compared favourably with the value quoted for the natural product by Freyer *et al.*[2] {$[\alpha]_D^{25}$ +5.0 (*c* 0.26 in MeOH)} thus

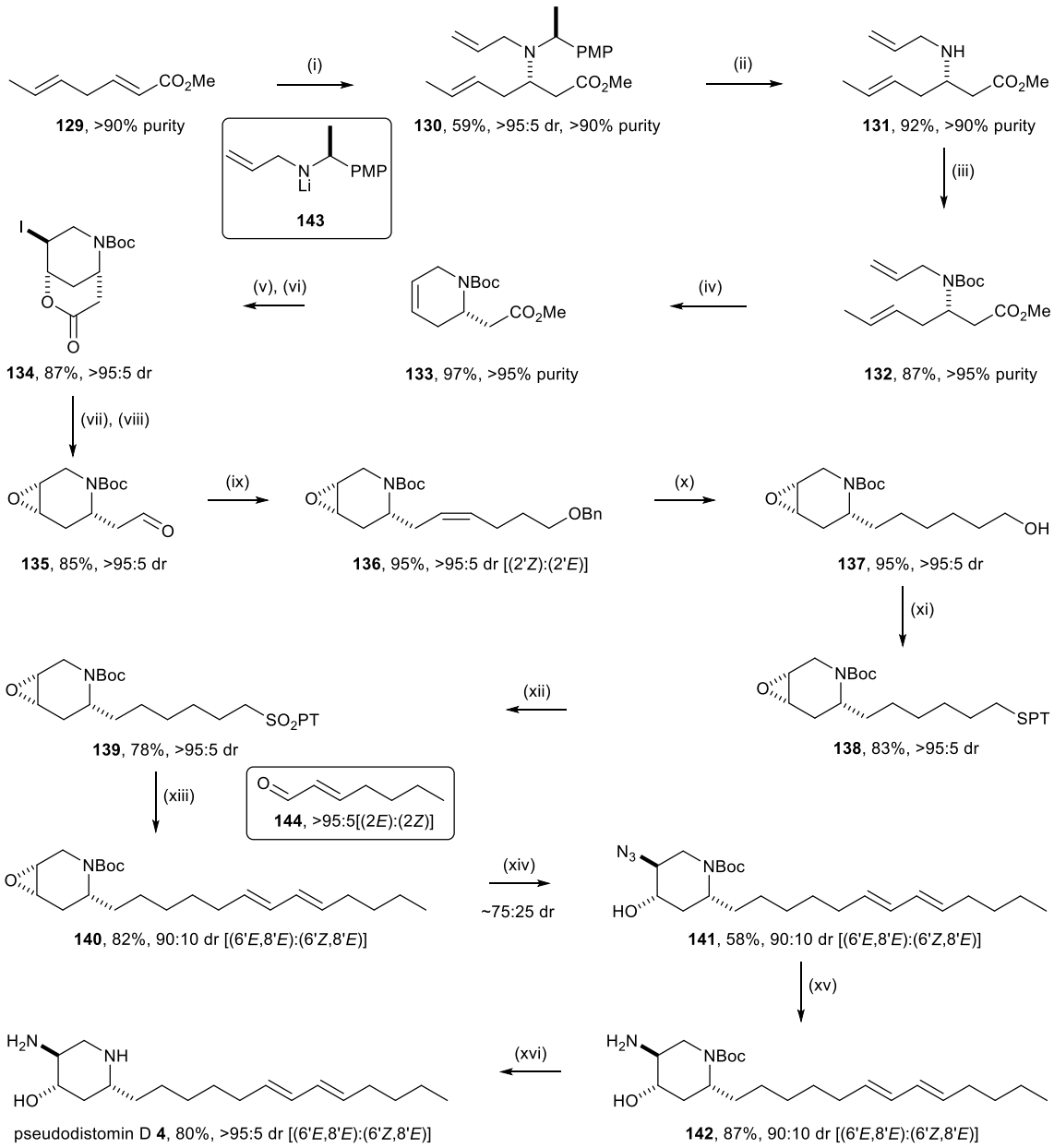
establishing the absolute configuration. This also provided evidence that all pseudodistomins A–F **1**–**6** share the same sense of configuration at the C(2) position.



Scheme 17 *Reagents and conditions*: (i) Cp_2ZrHCl, **122**, THF, rt, 1 h then **123**, $PdCl_2(PhCN)_2$, DPPF, DIBAL-H, THF, rt, 22 h; (ii) $TsOH{\cdot}H_2O$, MeOH, rt, 1.25 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 45 min then Et_3N, −78 °C to rt, 2 h; (iv) Ohira-Bestmann reagent, K_2CO_3, MeOH, 0 °C to rt, 2 h; (v) BuLi, **126**, PhMe, −20 °C, 20 min then 0 °C, 5 min then Me_2AlCl, 0 °C, 1 h then **121**, PhMe, 0 °C, 2.75 h; (vi) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 40 °C, 2 h; (vii) AcOH, MeOH/THF/H_2O (6:2:1), 50 °C, 2 h; (viii) AgOTs, MeCN, 40 °C, 2 h; (ix) $NaBH_3CN$, AcOH, MeOH/THF/H_2O (4:2:1), rt, 18 h; (x) TBAF, THF, rt, 20 h.

To date, only one other synthesis of pseudodistomin D **4** exists, completed by Davies *et al*. in 2012.[46] Conjugate addition of lithium amide reagent **143** to α,β-unsaturated ester **129** gave β-amino ester **130** in 59% yield. Protecting group manipulation of the amino moiety gave *N*-Boc protected β-amino ester **132**, which was subjected to ring-closing metathesis to facilitate construction of tetrahydropyridine **133**. Ester hydrolysis with LiOH followed by regioselective iodocyclisation gave iodolactone **134** in 87% yield (over two steps) as a single diastereoisomer. Reduction of **134** with DIBAL-H gave an iodohydrin intermediate, which was immediately treated with NaOH in order to promote formation of epoxide **135**, which was isolated in 85% yield (over two steps). The tail installation was achieved in a stepwise approach, with an initial portion constructed using a Wittig olefination[10] {with the ylid derived from

$[Ph_3P(CH_2)_4OBn]^+Br^-$ upon treatment with NaHMDS} to give **136** in 95% yield and >95:5 dr [(2'*Z*):(2'*E*)]. Olefin hydrogenation with tandem *O*-Bn hydrogenolysis gave alcohol **137**, which was subjected to Mitsunobu reaction[14] with PTSH, and subsequent oxidation with *m*CPBA to yield sulfone **139**. Julia-Kocieński olefination[47] of **139** with commercially available (2*E*)-hept-2-enal **144** furnished **140** in 90:10 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]. Ring-opening of epoxide **140** with NaN_3 gave a ~75:25 mixture of the regioisomeric azides, from which **141** was isolated in 58% yield. Staudinger reduction[48] of azide **141** afforded aminopiperidine **142**, which was subjected to acidic *N*-deprotection to unveil pseudodistomin D **4** in 7% total yield over sixteen steps (Scheme 18). The spectroscopic properties of **4** were reported as being in excellent agreement with literature values,[2] with $[\alpha]_D^{25}$ +5.6 (*c* 0.3 in MeOH) and $[\alpha]_D^{25}$ +5 (*c* 0.26 in MeOH) recorded for the synthetic and natural samples, respectively.



Scheme 18 *Reagents and conditions*: (i) **143**, 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, 16 h; (v) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), 50 °C, 16 h; (vi) I_2, $NaHCO_3$, MeCN, −20 °C, 2 h then −20 °C to rt, 16 h; (vii) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (viii) aq NaOH, CH_2Cl_2, rt, 1 h; (ix) NaHMDS, $[Ph_3P(CH_2)_4OBn]^+Br^-$, THF, 0 °C to rt, 40 min then **135**, THF, 0 °C to rt, 16 h; (x) H_2 (1 atm), $Pd(OH)_2$/C, EtOAc, rt, 2 h; (xi) PTSH, DEAD, PPh_3, THF, rt, 16 h; (xii) *m*CPBA, CH_2Cl_2, 0 °C to rt, 16 h; (xiii) KHMDS, **144**, THF, −78 °C, 30 min; (xiv) NaN_3, NH_4Cl, DMSO, 80 °C, 16 h; (xv) polymer-supported PPh_3, THF/H_2O (10:1), rt, 24 h; (xvi) HCl, MeOH, 60 °C, 3 h.

Prior to the investigations described herein, no syntheses of pseudodistomin E had been reported.

1.6 Thesis Aim

The initial goal of this thesis was to succeed in the first asymmetric synthesis of pseudodistomin E **5**, *via* modification of the synthetic sequence developed by Davies *et al*. in the synthesis of pseudodistomin D **4**,[46] in order to confirm the structure and absolute configuration of this member of the pseudodistomin family for the first time. Following this, it was proposed that investigations should begin into the development of an efficient synthetic route to access the pseudodistomins A–F. Of all the reported syntheses of the pseudodistomins to date, no group has managed to construct more than two members of the family and in these rare instances[20,23] the compounds shared the same configuration of the head portion and deviated only in the tail portion. Therefore, it was envisaged that a desirable synthetic sequence would involve a common late stage intermediate that would allow facile coupling of any head moiety with any tail portion to ultimately result in the synthesis of pseudodistomins A–F, and also allow construction of a library of unnatural pseudodistomins. Building on the success of the asymmetric synthesis of pseudodistomin D **4**,[46] iodolactone **134** was identified as the potential point of diversification (Figure 11).

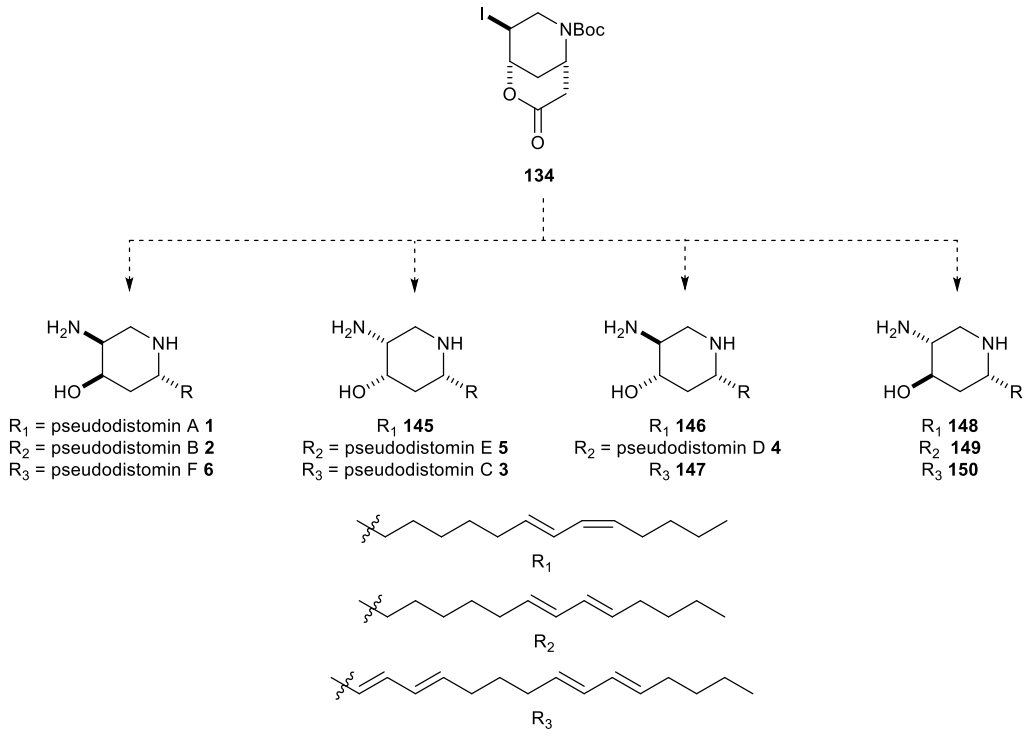


Figure 11 Thesis aim.

1.7 References and Notes

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Chapter 2

Asymmetric Synthesis of Pseudodistomin E

2.1 Chapter Outline

This chapter describes the first total asymmetric synthesis of pseudodistomin E **5**, culminating in confirmation of the assignment of the absolute configuration and correlation with the ^{1}H and ^{13}C NMR spectroscopic data originally reported for the natural product in the isolation study (Figure 12).[1]

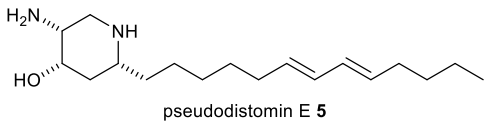
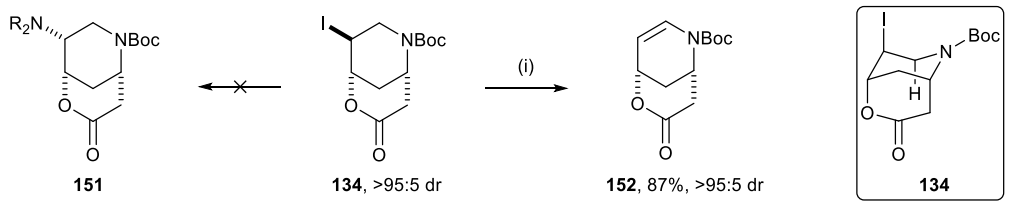


Figure 12 Structure of pseudodistomin E **5**.

2.2 Previous Work

Early investigations towards pseudodistomin E **5** by Davies and Taylor[2] focused on derivatization of iodolactone **134**, as detailed in the synthesis of pseudodistomin D **4**,[3] with the anticipation that this could ultimately be used as a common intermediate in both syntheses. It was initially envisaged that formal substitution of the iodide functionality within **134** *via* an S_N2-type process could be used to install the requisite amino functionality. Intermolecular displacement reactions were hence trialled with a range of nitrogen nucleophiles (LiN_3, NaN_3, PhthNK, $BnNH_2$, Bn_2NH). Unfortunately in all instances the products **151** were not observed, and starting material **134** or *N*-Boc enamine **152** were instead isolated. The formation of **152** is consistent with an E2-type process occurring, presumably rendered facile due to the antiperiplanar relationship between the C(8) iodide functionality, and the axial vicinal C(7) proton. Indeed, treatment of **134** with DBU furnished elimination product **152** in 87% yield and >95:5 dr (Scheme 19).



Scheme 19 *Reagents and conditions*: (i) DBU, CH_2Cl_2, rt, 6 h.

2.3 First Revised Route

Given the successful synthesis of pseudodistomin D **4** by Davies *et al*.[3] it was desirable to use an analogous synthetic pathway where possible to achieve the first asymmetric synthesis of pseudodistomin E **5**. In a revision to the original strategy the key step would involve formal intramolecular substitution of the iodide within **154** by a tethered nitrogen nucleophile. Iodohydrin **153** would be accessible *via* reduction of iodolactone **134**, and subsequent reaction of the hydroxyl functionality within **153** with an isocyanate would furnish intermediate **154**. Assuming **154** adopts a chair conformation, the tethered nitrogen nucleophile could readily access the σ^* orbital of the iodide as it occupies the adjacent axial site resulting in cyclisation to the oxazolidinone **155**. Tail installation in a parallel fashion, and required deprotections would unveil pseudodistomin E **5** (Figure 13).

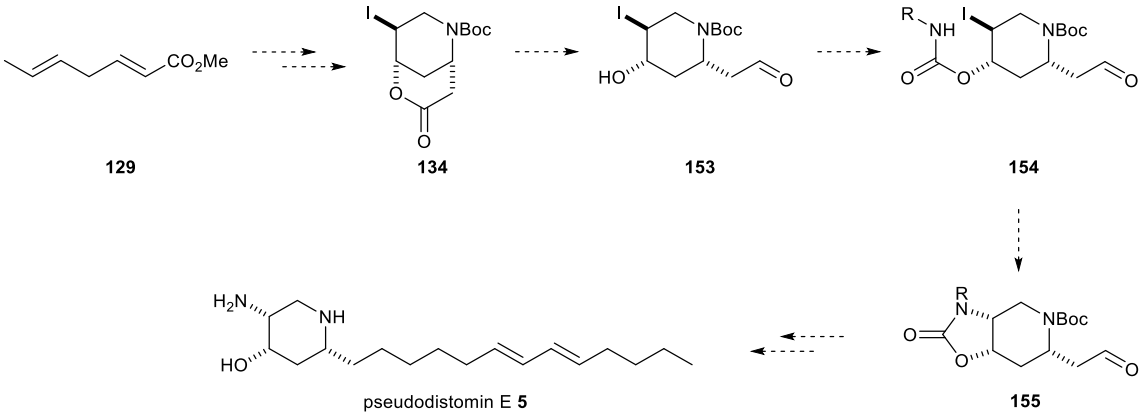
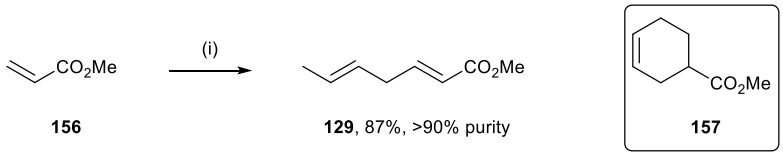


Figure 13 Proposed synthetic route towards pseudodistomin E **5**.

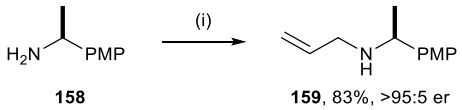
2.3.1 Iodolactone Synthesis

The synthesis of iodolactone **134** on multi-gram scale was initially evaluated. α,β-Unsaturated ester **129** is commercially available,[4] although may also be conveniently prepared on an appreciable scale *via* palladium catalysed coupling of methyl acrylate **156** and butadiene, according to a previously reported procedure.[5] This furnished **129** in 87% isolated yield and >90% purity, with previously characterised impurities including geometric isomers, regioisomers and the Diels-Alder cycloaddition[6] product **157** being present (Scheme 20).[7]



Scheme 20 *Reagents and conditions*: (i) butadiene, $Pd_2(dba)_3 \cdot CHCl_3$, PBu_3, $HBF_4 \cdot Et_2O$, 80 °C, 5 h.

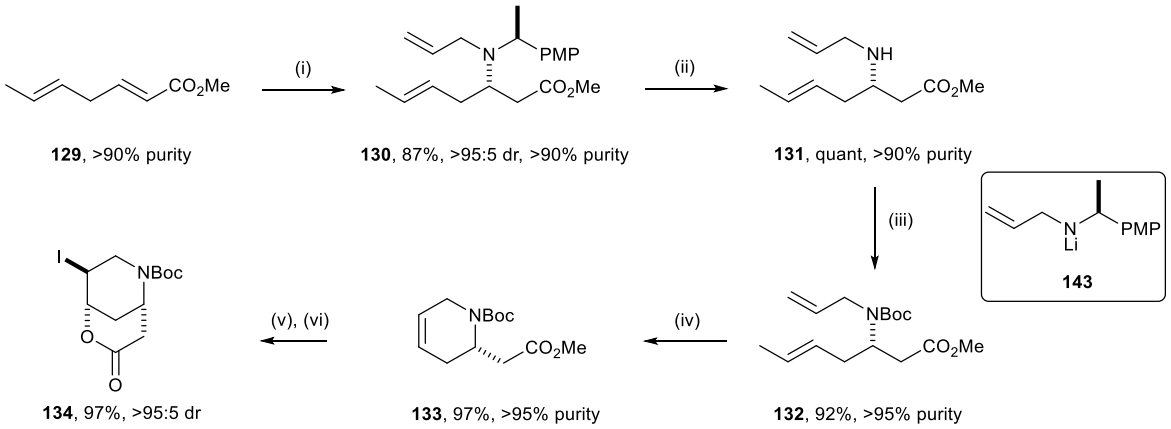
Secondary amine **159** was prepared *via* treatment of enantiopure **158** (>99:1 er) with BuLi, followed by alkylation with allyl bromide to afford **159** in 83% yield and >95:5 er (Scheme 21).



Scheme 21 *Reagents and conditions*: (i) BuLi, THF, 0 °C, 1 h then allyl bromide, THF, 0 °C to rt, 16 h.

Lithium amide reagent **143** was prepared *via* treatment of **159** with BuLi in THF at −78 °C. Conjugate addition of **143** to α,β-unsaturated ester **129** gave β-amino ester **130** in 87% yield, >95:5 dr and >90% purity, installing the first of the three stereogenic centres required for the synthesis of pseudodistomin E **5**. Acid mediated deprotection of the α-methyl-*p*-methoxyphenyl unit within **130** gave secondary amine **131** in quantitative yield and >90% purity. Reprotection of the nitrogen functionality within **131** was achieved *via* treatment with $(Boc)_2O$ under basic conditions.[8] Ring-closing metathesis of diene **132** with Grubbs I catalyst gave tetrahydropyridine **133** in 97% yield and >95% purity. Saponification of **133** followed by subsequent iodolactonization to install the remaining two stereogenic centres gave, after purification, **134** in 97% yield (from **133**) and as a single diastereoisomer (>95:5 dr)

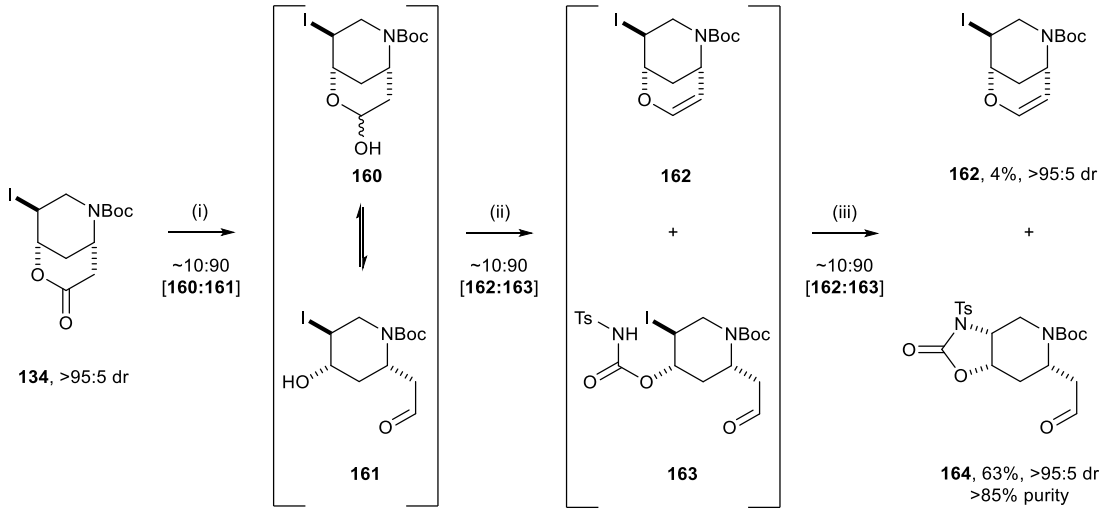
(Scheme 22). The synthesis of iodolactone **134** was thus completed in 75% yield over six steps, a significant increase over the 40% yield previously reported.[3] The relative configuration within iodolactone **134** has been previously unambiguously assigned *via* single-crystal X-ray diffraction analysis.[3]



Scheme 22 *Reagents and conditions*: (i) **143**, 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, 16 h; (v) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), 50 °C, 16 h; (iv) I_2, $NaHCO_3$, MeCN, −20 °C, 2 h then −20 °C to rt, 16 h.

2.3.2 Intramolecular Iodide Displacement

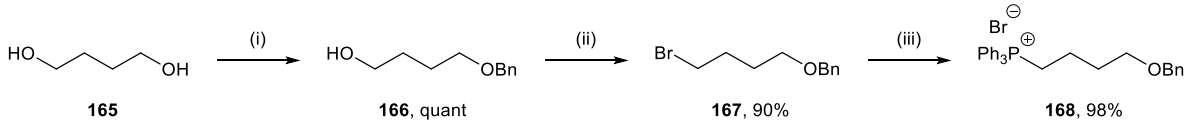
Iodolactone **134** was treated with one equivalent of DIBAL-H at −78 °C which furnished a ~10:90 ratio of lactol **160** and aldehyde **161**, respectively, according to ^{1}H NMR spectroscopic analysis at rt in $CDCl_3$. Treatment of this mixture with TsNCO in THF[9] gave a ~10:90 mixture of vinyl ether **162** and carbamate **163**, respectively, along with $TsNH_2$. Subsequent reaction of this crude mixture with Et_3N in acetone[10] gave a ~10:90 mixture of vinyl ether **162** and oxazolidinone **164**, respectively, along with $TsNH_2$. Purification *via* flash column chromatography gave **162** in 4% yield and >95:5 dr, and **164** in 63% yield (contaminated with $TsNH_2$) and >95:5 dr. The presence of vinyl ether **162** suggested a competing dehydration pathway, consistent with reaction of the hydroxyl functionality within lactol **160** with TsNCO, subsequent fragmentation of the intermediary species would afford vinyl either **162** and *N*-tosylcarbamic acid, of which decarboxylation results in $TsNH_2$ (Scheme 23).



Scheme 23 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ii) TsNCO, THF, 0 °C to rt, 3 h; (ii) Et_3N, acetone, 60 °C, 3 h.

2.3.3 Olefination Post-Oxazolidinone Construction

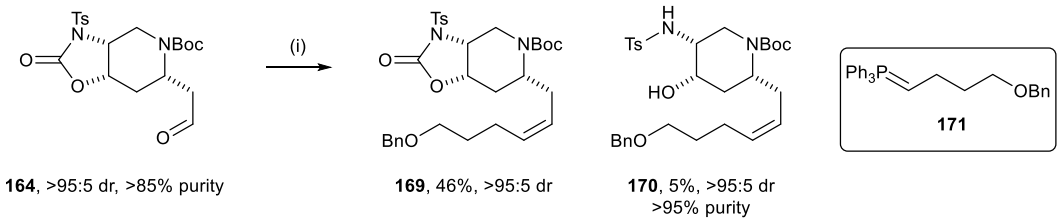
With **164** in hand, it was anticipated that the synthetic route could continue emulating that used in the synthesis of pseudodistomin D **4**,[3] with a Wittig olefination[11] of the aldehyde moiety within **164** to install a portion of the tail unit. Thus, the phosphonium bromide salt **168** was prepared in 88% yield over three steps from 1,4-butanediol **165** *via* sequential monobenzylation, Appel reaction of **166** and substitution of the bromide functionality within **167** with PPh_3 (Scheme 24).



Scheme 24 *Reagents and conditions*: (i) NaH, THF, 0 °C, 30 min then BnBr, THF, 0 °C to rt, 16 h; (ii) PPh_3, CBr_4, CH_2Cl_2, 0 °C to rt, 1 h; (iii) PPh_3, 120 °C, 2 h.

Following the protocol used in the synthesis of pseudodistomin D **4**, treatment of phosphonium bromide salt **168** with NaHMDS generated the requisite ylid **171**, to which aldehyde **164** was added in THF at 0 °C. The reaction generated a complex mixture of products, from which the product distribution could not be quantified, however **169** was isolated in 46% yield and >95:5 dr [(2'*Z*):(2'*E*)], along with **170**, resulting from cleavage of the oxazolidinone, in 5% yield and >95:5 dr [(2'*Z*):(2'*E*)] (Scheme 25). The geometries of the newly constructed olefins were

assigned from the diagnostic values of the ^{1}H NMR ^{3}J coupling constants, with ^{3}J <11 Hz in both instances.



Scheme 25 *Reagents and conditions*: (i) **171**, THF, 0 °C to rt, 16 h.

2.4 Second Revised Route: Head Manipulations

With the inability to isolate **164** free of $TsNH_2$ combined with the subsequent low yield of the olefination reaction, it was hypothesised that an alternative strategy could involve olefination of the aldehyde functionality prior to construction of the oxazolidinone moiety. By treatment of the ~10:90 mixture of lactol **160**, and aldehyde **161**, respectively, with a simple stabilized ylid reagent **174**, it was anticipated that perturbation of the dynamic equilibrium would result in ultimate conversion of the mixture to olefinated iodohydrin **172** which could then be elaborated to oxazolidinone **173** (Figure 14).

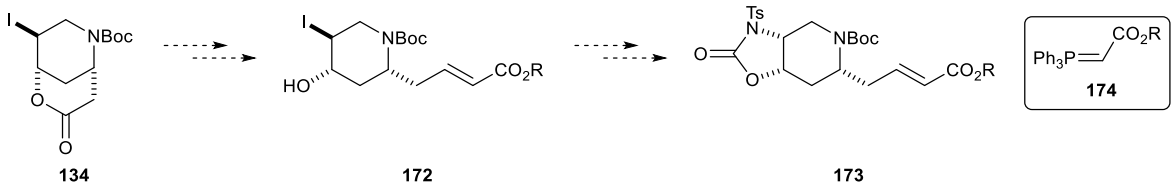
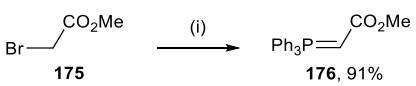


Figure 14 Revised synthetic route.

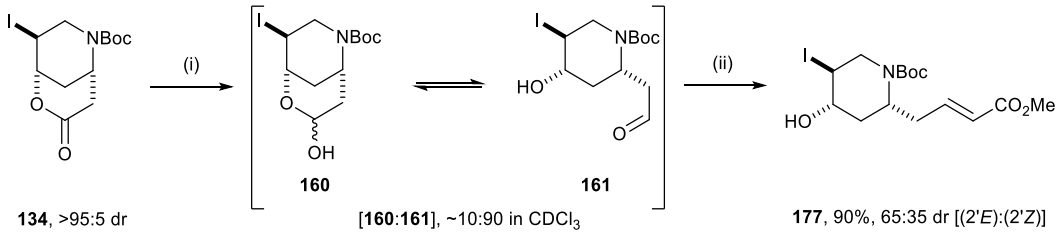
2.4.1 Olefination Pre-Oxazolidinone Construction

Ylid **176** was prepared on multi-gram scale, *via* treatment of **175** with PPh_3 and subsequent deprotonation (Scheme 26).



Scheme 26 *Reagents and conditions*: (i) PPh_3, EtOAc, rt, 16 h then aq NaOH, 0 °C to rt, 5 min.

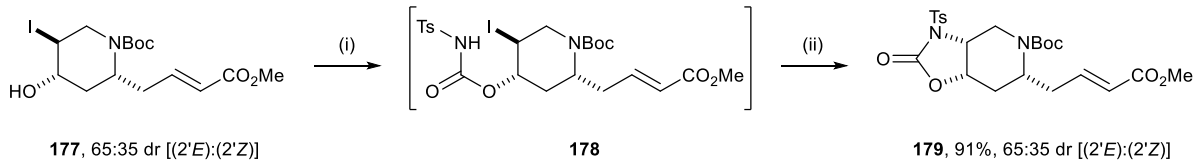
Treatment of iodolactone **134** with DIBAL-H in CH_2Cl_2 at −78 °C produced the ~10:90 mixture of lactol **160** and aldehyde **161**, respectively, which was allowed to react with ylid **176** to give a 65:35 dr mixture of (2'*E*)- and (2'*Z*)-isomers, respectively. After purification, **177** was isolated in 90% yield as a 65:35 dr mixture of (2'*E*)- and (2'*Z*)-isomers, respectively (Scheme 27). Assignment of the olefin geometries were made on the basis of ^{1}H NMR ^3J coupling constant analysis, with ^3J 15.3 Hz for the (2'*E*)-isomer, and ^3J 11.5 Hz for the (2'*Z*)-isomer. The mixture of isomers was not deemed to be an issue as the olefin would be subject to reduction *via* hydrogenation at a later stage, thus converging on a common compound.



Scheme 27 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ii) **176**, CH_2Cl_2, rt, 16 h.

2.4.2 Oxazolidinone Construction

With the success of the new route, attention now turned to the tethering strategy used to deliver the C(5)-amino substituent in an intramolecular fashion. Iodohydrin **177** was treated with TsNCO in THF, followed by exposure to Et_3N in acetone in order to promote closure to oxazolidinone **179**, which was isolated, after purification *via* flash column chromatography, in 91% yield and 65:35 dr [(2'*E*):(2'*Z*)] (Scheme 28).

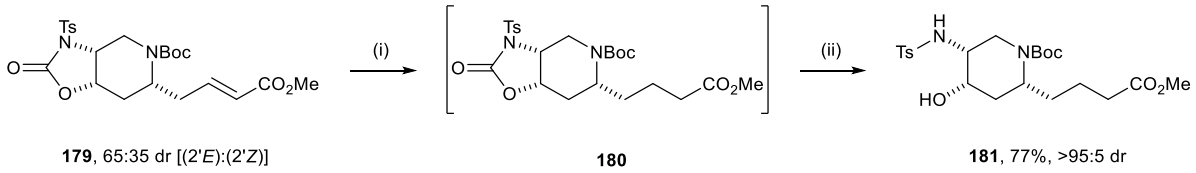


Scheme 28 *Reagents and conditions*: (i) TsNCO, THF, 0 °C to rt, 3 h; (ii) Et_3N, acetone, 60 °C, 3 h.

2.4.3 Proof of Configuration

In order to establish the relative configuration within **179**, it was stirred with Pearlman's catalyst under a hydrogen atmosphere to facilitate reduction of the olefin functionality. The intermediate

180 was then subjected to methanolysis in order to cleave the oxazolidinone moiety. Amino alcohol **181** was isolated in 77% yield as a single diastereoisomer (>95:5 dr), thus confirming the 65:35 dr [(2'*E*):(2'*Z*)] for compounds **177**–**179** conclusively corresponds to a ratio of geometric olefin isomers (Scheme 29).



Scheme 29 *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 6 h; (ii) K_2CO_3, MeOH, rt, 16 h.

The relative configuration within **181** could now be assigned from ^{1}H NMR ^3J coupling constant analysis, assuming a chair conformation in solution in $CDCl_3$. A notable coupling constant observed is ^3J 11.8 Hz between C(6)H_{axial} and C(5)*H*, indicating an ~180° dihedral angle between the protons according to the Karplus curve,[12] implying C(5)*H* occupies an axial site, and thus the C(5)-amino group is equatorial. All other ring based vicinal coupling constants being small in magnitude (^3J <7 Hz) indicates non *trans*-diaxial relationships between vicinal protons. Therefore, C(2)*H* and C(4)*H* must be equatorial, and thus the C(2)-alkyl and C(4)-hydroxy groups are adopting axial positions. This is consistent with 1,2-strain being minimised by placing the C(2)-alkyl substituent axial (Figure 15).[13] Based on this assignment, the relative configurations within **177**–**180** could also be assigned, and confirmation was provided that the formal substitution of the iodide functionality had indeed proceeded with inversion of configuration.

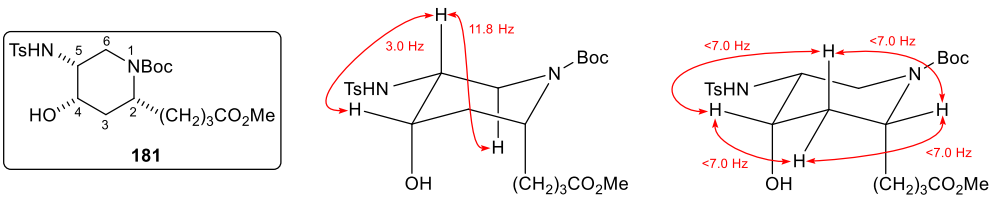
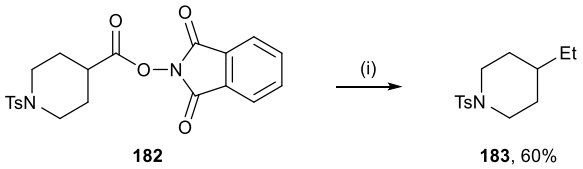


Figure 15 Conformational analysis of **181**.

2.5 Second Revised Route: Tail Installation

With the aforementioned synthetic developments providing an efficient construction of the requisite head configuration, a new approach was required to complete the installation of the tail functionality. Recent work by Baran *et al*. highlighted a novel transformation for Ni catalysed sp^3-sp^3 couplings between redox-active *N*-hydroxyphthalimide esters and alkylzinc reagents.[14] A reported example detailed the treatment of redox-active ester **182** with Et_2Zn under the reaction conditions to furnish the coupling product **183** in 60% yield (Scheme 30).



182 **183**, 60%

Scheme 30 *Reagents and conditions*: (i) $ZnEt_2$, $NiCl_2$·glyme, BBBPY, DMF/THF (1:1), rt, 16 h.

It was proposed that this methodology could be used to couple the appropriate dialkylzinc reagent **187** with the requisite redox-active *N*-hydroxyphthalimide ester **185** resulting in the protected form of pseudodistomin E **186**. Redox-active ester **185** could, in turn, be prepared *via* hydrogenation/hydrogenolysis and manipulation of **184**, of which an efficient synthetic route to the methyl ester derivative **179** had already been developed (Figure 16). It was envisaged that the benzyl ester derivative **184** would be desirable to allow tandem olefin hydrogenation and *O*-Bn hydrogenolysis in a single step, unveiling the carboxylic acid required for subsequent coupling with *N*-hydroxyphthalimide.

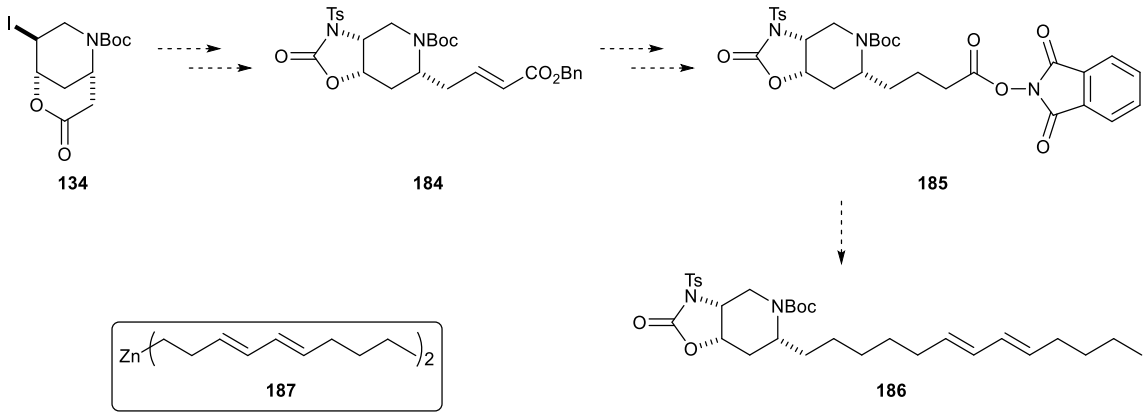
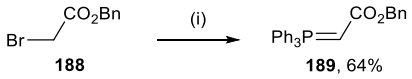


Figure 16 Proposed tail installation.

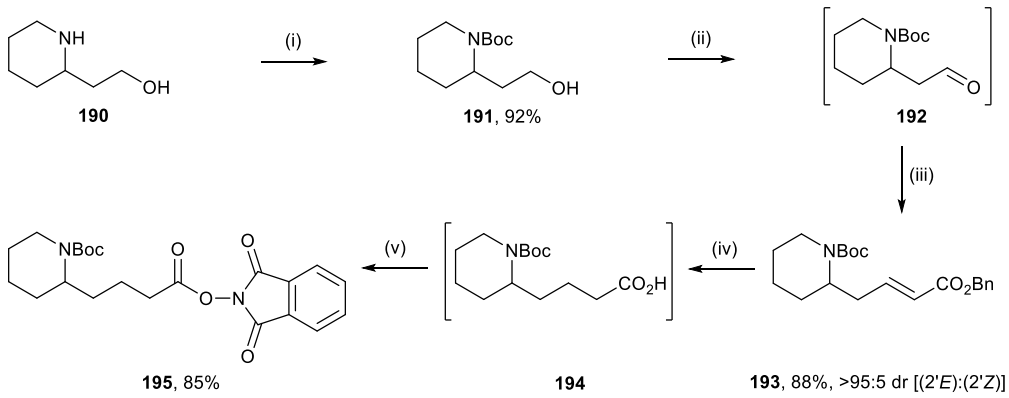
2.5.1 First Model System

In order to validate this choice of synthetic pathway, a simple model system was developed. Firstly, benzyl ester ylid **189** was prepared in 64% yield *via* treatment of **188** with PPh_3 and subsequent deprotonation (Scheme 31).



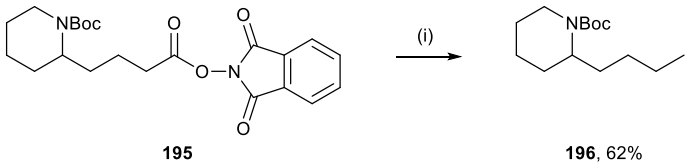
Scheme 31 *Reagents and conditions*: (i) PPh_3, EtOAc, rt, 16 h then aq NaOH, 0 °C to rt, 5 min.

2-Piperidineethanol **190** was protected with $(Boc)_2O$, followed by tandem Swern oxidation[15] and Wittig olefination[11] with ylid **189** to furnish α,β-unsaturated ester **193** in 81% yield (over three steps) and >95:5 dr [(2'*E*):(2'*Z*)]. Tandem hydrogenation and hydrogenolysis of the olefin and *O*-Bn functionalities, respectively, gave carboxylic acid **194**, which was immediately subjected to DIC promoted coupling with *N*-hydroxyphthalimide to provide, after purification *via* flash column chromatography, redox-active ester **195** in 85% yield (Scheme 32).



Scheme 32 *Reagents and conditions*: (i) $(Boc)_2O$, $NaHCO_3$, MeOH, rt, 16 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min then **191**, CH_2Cl_2, −78 °C, 30 min then Et_3N, −78 °C to rt, 20 min; (iii) **189**, CH_2Cl_2, rt, 16 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 6 h; (v) NHP, DIC, DMAP, CH_2Cl_2, rt, 16 h.

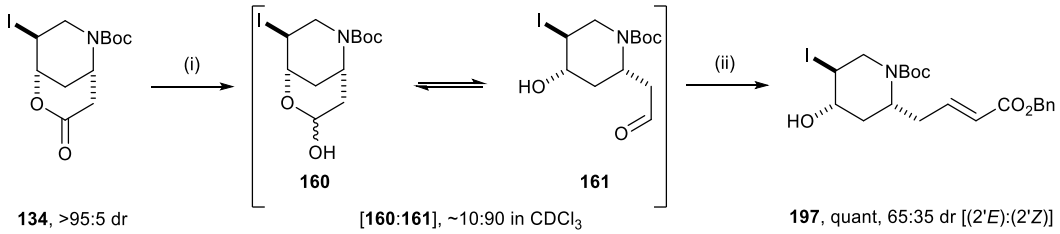
Following the procedure outlined by Baran *et al*.,[14] MeMgCl was added to $ZnCl_2$ to promote transmetallation. The resulting $ZnMe_2$ was added to a premixed solution of redox-active ester **195**, $NiCl_2$·glyme and BBBPY in DMF. This resulted in a complex crude reaction mixture, but after purification the sp^3-sp^3 coupled product **196** was isolated in 62% yield (Scheme 33).



Scheme 33 *Reagents and conditions*: (i) $ZnMe_2$, $NiCl_2$·glyme, BBBPY, DMF/THF (~2:1), rt, 16 h.

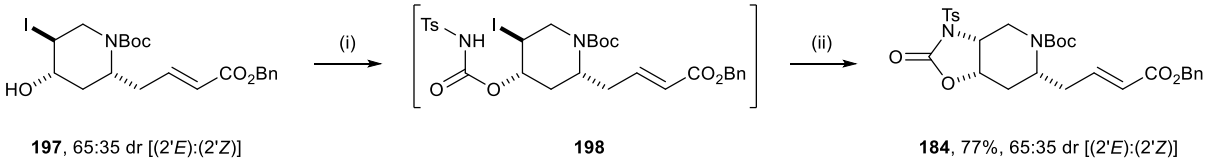
2.5.2 Redox-Active Ester Synthesis

With validation of the proposed route on a simple system, attention turned next to synthesis of the requisite head portion. Thus, iodolactone **134** was reduced under the protocol previously described, then subjected to a Wittig olefination[11] with stabilized benzyl ester ylid **189**, which gave iodohydrin **197** in quantitative yield (over two steps), and 65:35 dr [(2'*E*):(2'Z)] (Scheme 34). Assignment of the olefin geometries were made on the basis of ^1H NMR ^3J coupling constant analysis, with ^3J >15 Hz for the (2'*E*)-isomer, and ^3J <12 Hz for the (2'Z)-isomer.



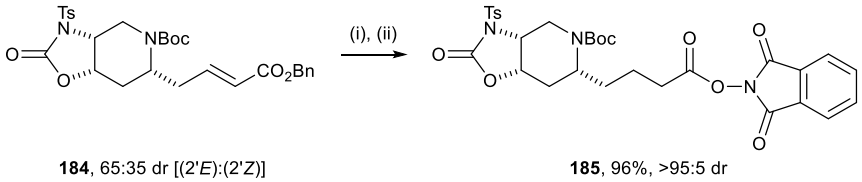
Scheme 34 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ii) **189**, CH_2Cl_2, rt, 16 h.

Oxazolidinone construction was achieved in an analogous fashion, with sequential treatment of iodohydrin **197** with TsNCO in THF, then Et_3N in acetone. After purification *via* flash column chromatography, **184** was isolated in 77% yield and 65:35 dr [(2'*E*):(2'*Z*)] (Scheme 35).



Scheme 35 *Reagents and conditions*: (i) TsNCO, THF, 0 °C to rt, 3 h; (ii) Et_3N, acetone, 60 °C, 3 h.

Tandem hydrogenation/hydrogenolysis of the olefin and *O*-Bn functionalities, respectively, was achieved *via* treatment of oxazolidinone **184** with $Pd(OH)_2/C$ and H_2 (1 atm). The intermediate carboxylic acid was immediately subjected to DIC promoted coupling with *N*-hydroxyphthalimide which gave the redox-active ester **185** in 96% yield (over two steps) as a single diastereoisomer (>95:5 dr), confirming that **197**, **198** and **184** were indeed a mixture of two olefin isomers (Scheme 36).

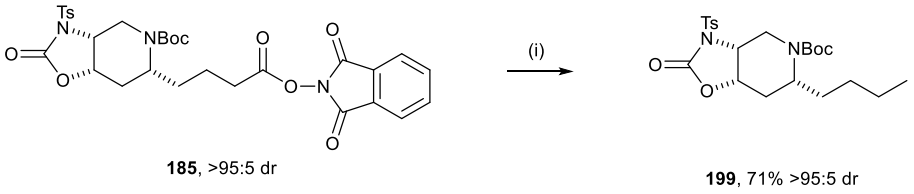


Scheme 36 *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 6 h; (ii) NHP, DIC, DMAP, CH_2Cl_2, rt, 16 h.

2.5.3 Second Model System

Due to the potentially sensitive functionalities within **185**, and to enable direct comparison with the model system **195**, a secondary test reaction was carried out to determine the likely success of the Ni-catalysed coupling on the more complex substrate **185**. Thus, $ZnMe_2$ was once again

prepared, and this time allowed to react with redox-active ester **185** under the conditions outlined by Baran *et al*.[14] The product of decarboxylative coupling **199** was isolated in 71% yield after purification, as a single diastereoisomer (Scheme 37).

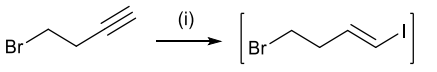


185, >95:5 dr **199**, 71% >95:5 dr

Scheme 37 *Reagents and conditions*: (i) $ZnMe_2$, $NiCl_2$·glyme, BBBPY, DMF/THF (~2:1), rt, 16 h.

2.5.4 First-Generation Tail Synthesis

With the success of the alkyl-alkyl coupling using $ZnMe_2$ as the coupling partner, the focus now turned to the synthesis of the requisite alkylzinc reagent **187** in order to install the remainder of the tail portion and complete the synthesis of pseudodistomin E **5**. Vinyl iodide **201** was prepared *via* DIBAL-H promoted hydroalumination of commercially available bromoalkyne **200** (Scheme 38). The intermediate **201** was not subjected to purification due to stability issues, however it was confirmed to exist as a single diastereoisomer (>95:5 dr [(1'*E*):(1'*Z*)]) according to ^{1}H NMR spectroscopic analysis, with ^3J = 14.5 Hz.

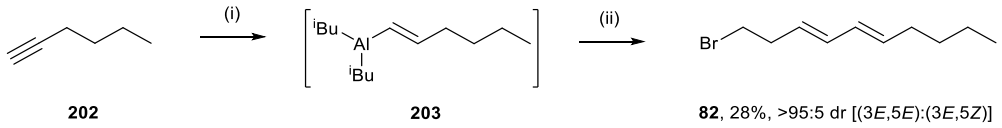


200 **201**, >95:5 dr [(1'*E*):(1'*Z*)]

Scheme 38 *Reagents and conditions*: (i) DIBAL-H, hexanes, 50 °C, 16 h then I_2, THF, −78 °C, 15 min then −78 °C to rt, 45 min.

Simultaneously, 1-hexyne **202** was subjected to an identical hydroalumination reaction. The intermediate vinyl-aluminium species **203** was then allowed to react with the aforementioned vinyl iodide **201** in a $Pd(PPh_3)_4$ catalysed Negishi coupling.[16] After purification, diene **82** was isolated in 28% yield and >95:5 dr [(3*E*,5*E*):(3*E*,5*Z*)] (Scheme 39). It was proposed that the stability and volatility issues of the vinyl iodide intermediate **201** were liable for the low yield.

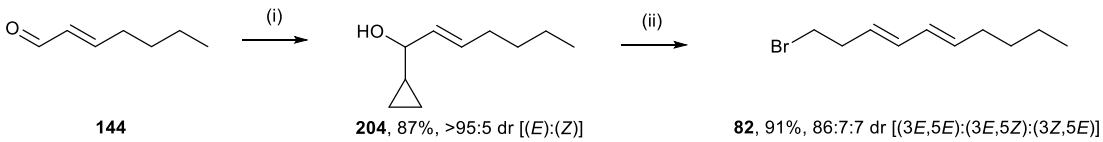
Thus, attention turned to an alternative route for the synthesis of diene **82** in a more efficient manner.



Scheme 39 *Reagents and conditions*: (i) DIBAL-H, hexanes, 50 °C, 16 h; (ii) **201**, $Pd(PPh_3)_4$, $ZnCl_2$, THF, 0 °C to rt, 16 h.

2.5.5 Second-Generation Tail Synthesis

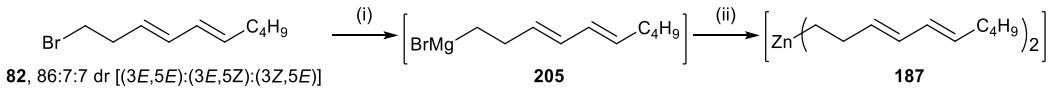
A protocol outlined in the literature was next trialled.[17] Commercially available (2*E*)-2-heptenal **144** was treated with cyclopropylmagnesium bromide to furnish alcohol **204** in 87% yield and >95:5 dr [(2*E*):(2*Z*)]. Elaboration to diene **82** was achieved *via* treatment of alcohol **204** with HBr. The requisite alkyl bromide was thus isolated in 91% yield, albeit in 86:7:7 dr [(3*E*,5*E*):(3*E*,5*Z*):(3*Z*,5*E*)] (Scheme 40). The diastereomeric ratio was assigned *via* utilisation of a combination of ^{1}H NMR ^3J coupling constants and diagnostic ^{13}C NMR shifts: a report by Yoshida *et al.*[18] details investigations into ^{13}C NMR shifts of related conjugated dienic pheromones, reporting common shift deviations between stereoisomers. Comparison of the ^{13}C NMR spectroscopic data for **82** showed agreement with the reported trends, thus allowing full assignment of the ^{13}C NMR spectra, and therefore correlation with the ^{1}H NMR spectra (*via* HSQC analysis) enabled accurate calculation of the ratio of stereoisomers. This spectroscopic method was applied to all dienes synthesised and reported herein.



Scheme 40 *Reagents and conditions*: (i) cyclopropylmagnesium bromide, THF, 0 °C to rt, 16 h; (ii) HBr, 0 °C to rt, 16 h.

With ready access to multi-gram quantities of **82** in 86:7:7 dr [(3*E*,5*E*):(3*E*,5*Z*):(3*Z*,5*E*)], Grignard reagent **205** was prepared following the procedure outlined by Baran *et al.*,[14] *via* treatment of the alkyl bromide **82** with Mg and a small amount of I_2 to aid initiation. Grignard

reagent **205** was subjected to iodometric titration[14] to determine the concentration, before an appropriate amount was added to a stirred solution of $ZnCl_2$ in order to generate the required dialkylzinc reagent **187** (Scheme 41).

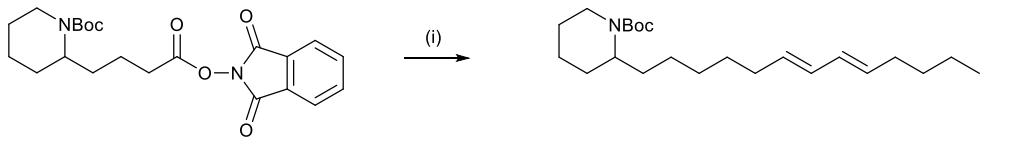


82, 86:7:7 dr [(3*E*,5*E*):(3*E*,5Z):(3*Z*,5*E*)] **205** **187**

Scheme 41 *Reagents and conditions*: (i) Mg, I_2, THF, 70 °C, 1 h; (ii) $ZnCl_2$, THF, 0 °C to rt, 10 min.

2.5.6 Third Model System

Model redox-active ester **195** was allowed to react with alkylzinc species **187** to effect the decarboxylative coupling. Purification of the crude reaction mixture *via* flash column chromatography gave the coupling product **206** in 54% yield and 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)] (Scheme 42).



195 **206**, 54%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'Z):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]

Scheme 42 *Reagents and conditions*: (i) **187**, $NiCl_2$·glyme, BBBPY, DMF/THF (~1:2), rt, 16 h.

Interestingly, the source of the alkylzinc reagent for this experiment was inconsequential, as alkyl bromides prepared *via* either route gave rise to a similar erosion of stereochemical integrity. This was rationalised by the operation of the homoallyl/methylcyclopropyl/cyclobutyl rearrangement of organometallic reagents. The stability of the resultant masked cyclopropyl anion intermediate would be subject to additional stabilisation offered *via* resonance with the adjacent olefin functionality. However, there was no evidence of coupling *via* **207**, **209** or **210** on any occasion (Figure 17).

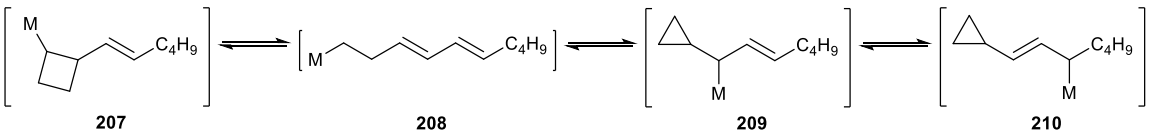
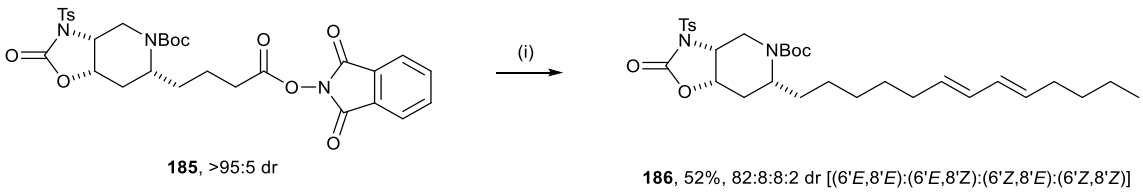


Figure 17 Proposed rearrangement pathway.

2.5.7 Head and Tail Coupling

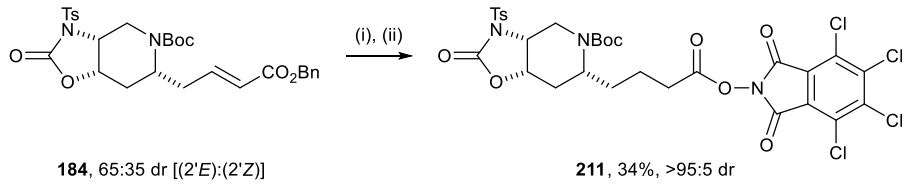
With the three promising model systems in hand, the decarboxylative coupling procedure was applied to the requisite fragments to couple the redox-active ester head fragment **185** with the alkylzinc tail fragment **187**. Coupling product **186** was isolated in 52% yield as an 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)] mixture of olefin isomers (Scheme 43).



Scheme 43 *Reagents and conditions*: (i) **187**, $NiCl_2$·glyme, BBBPY, DMF/THF (~1:1), rt, 16 h.

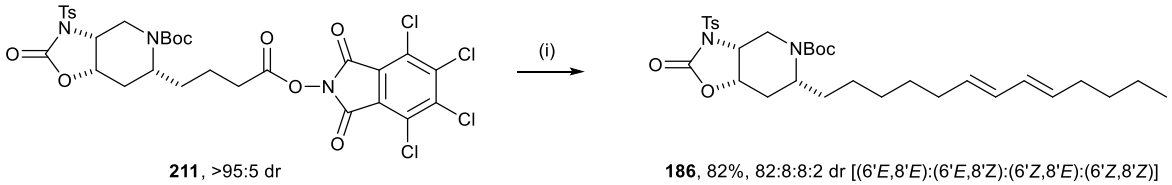
2.5.8 Coupling Optimisation

With the coupling occurring in only a modest yield, a method for optimisation was sought. It was noted by Baran *et al*. that tetrachloro-*N*-hydroxyphthalimide esters underwent the coupling in yields of up to 10% higher than those of *N*-hydroxyphthalimide esters.[14] Therefore, tetrachloro-*N*-hydroxyphthalimide ester **211** was prepared using the same methodology as outlined earlier, to furnish **211** in 34% yield as a single diastereoisomer (>95:5 dr) (Scheme 44).



Scheme 44 *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2$/C, EtOAc, rt, 6 h; (ii) TCNHP, DIC, DMAP, CH_2Cl_2, rt, 16 h.

The Ni-catalysed coupling of redox-active ester **211** and alkylzinc reagent **187** was next completed. The coupled product **186** was obtained in 82% yield and 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)] after purification (Scheme 45). The increased yield observed, from 52% to 82% was encouraging, however the low yielding preparation of the starting material **211** ultimately contributed to lower overall yield (over two steps), thus the original route was favoured.



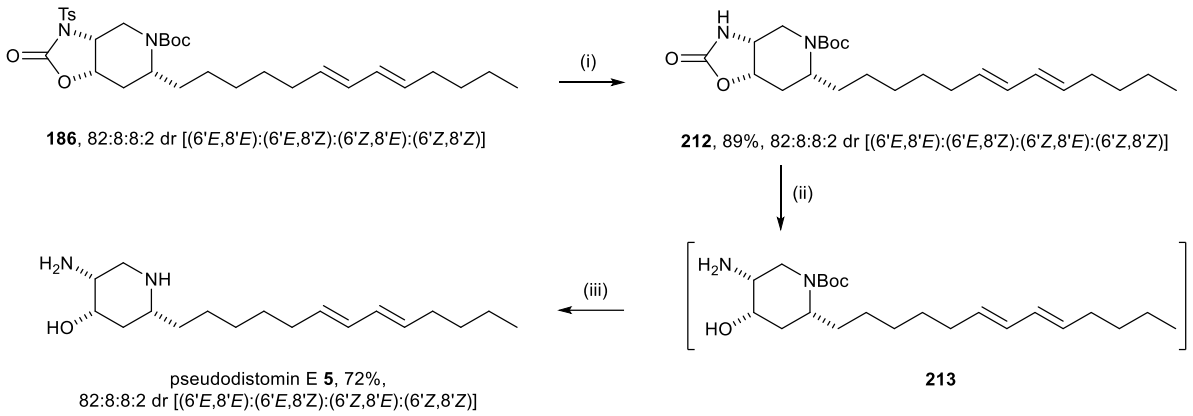
211, >95:5 dr

186, 82%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'Z):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]

Scheme 45 *Reagents and conditions*: (i) **187**, $NiCl_2$·glyme, BBBPY, DMF/THF (~1:1), rt, 16 h.

2.6 Deprotection Steps

Following the successful coupling between the head and tail portions, the scaffold of the target had been ultimately assembled. All that remained was to effect removal of the protecting groups to unveil pseudodistomin E **5**. Deprotection of the *N*-Ts moiety within **186** was effected *via* treatment with sodium naphthalide (generated *in situ* from sodium and naphthalene in DME), which gave **212** in 89% yield and with conservation of diastereomeric purity, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]. This process was believed to be particularly facile due to the adjacent electron withdrawing group in the form of the oxazolidinone.[19] A literature procedure, as carried out in the synthesis of pseudodistomin F **6** by Ma *et al*.,[20] was followed in order to sequentially remove the carbamate and *N*-Boc functionalities. After purification, pseudodistomin E **5** was obtained in 72% yield (over two steps) as an 82:8:8:2 [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)] mixture of olefin isomers (Scheme 46). Separation of the olefin isomers was not possible *via* flash column chromatography, and further methods of separation were not investigated.



186, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'Z):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]

212, 89%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'Z):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]

Scheme 46 *Reagents and conditions*: (i) $Na^{+}[C_{10}H_8]^{-}$, DME, −78 °C, 30 min; (ii) KOH, MeOH, 70°C, 3 h; (iii) HCl, MeOH, 70 °C, 3 h.

2.7 Comparison of NMR and Specific Rotation Data

Upon ^{1}H NMR spectroscopic analysis of the synthetic sample of pseudodistomin E **5**, assuming a chair conformation in solution in MeOH-d_4, the ^{3}J coupling constants provided evidence of the relative configuration around the piperidine ring. The large (^{3}J >11.0 Hz) coupling constants between the C(3)H_{axial} proton and the adjacent C(2)*H* and C(4)*H* indicates an ~180° dihedral angle between the respective protons in both instances, according to the Karplus curve.[12] This is indicative of C(2)*H* and C(4)*H* adopting axial positions, and thus the C(2)-alkyl and C(4)-hydroxy substituents occupying equatorial sites. With the remaining ring based vicinal coupling constants being small in magnitude (^{3}J <7 Hz), this is suggestive of non *trans*-diaxial relationships between vicinal protons. Therefore, C(5)*H* must be equatorial, and thus the C(5)-amino group is axial. This is consistent with 1,3-diaxial interactions and gauche interactions being minimised by placing the larger [(C(2)-alkyl] substituent equatorial (Figure 18).

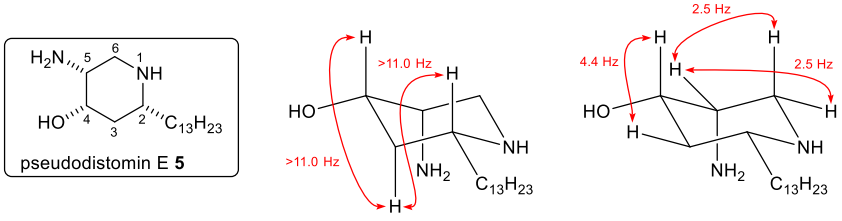


Figure 18 Conformation of pseudodistomin E **5**.

Comparison of the synthetic ^{1}H NMR data with the literature data reported by Freyer *et al*.[1] revealed agreement with $\Delta\delta_H \leq 0.02$ ppm (Figure 19).[21]

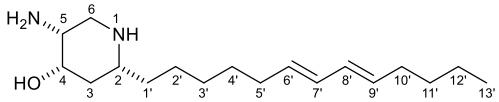
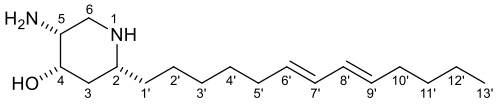
pseudodistomin E **5** 		
	5 Freyer *et al*.[1] (400 MHz, MeOH-d_4)	**5** This work[22] (400 MHz, MeOH-d_4)
C(2)*H*	2.44	2.46 (+0.02)
C(3)H_A C(3)H_B	1.21 1.68	1.22 (+0.01) 1.68 (0.00)
C(4)*H*	3.67	3.67 (0.00)
C(5)*H*	2.90	2.90 (0.00)
C(6)H_A C(6)H_B	2.73 2.98	2.73 (0.00) 2.98 (0.00)
C(1')H_2	1.35	1.36 (+0.01)
C(2')H_2	1.35	1.36 (+0.01)
C(3')H_2	1.35	1.36 (+0.01)
C(4')H_2	1.35	1.36 (+0.01)
C(5')H_2	2.05	2.06 (+0.01)
C(6')*H*	5.52	5.53 (+0.01)
C(7')*H*	5.96	5.98 (+0.02)
C(8')*H*	5.96	5.98 (+0.02)
C(9')*H*	5.52	5.53 (+0.01)
C(10')H_2	2.05	2.06 (+0.01)
C(11')H_2	1.35	1.36 (+0.01)
C(12')H_2	1.35	1.36 (+0.01)
C(13')H_3	0.90	0.91 (+0.01)

Figure 19 ^{1}H NMR data. Values of $\Delta\delta_H$ are given in parentheses relative to the data for the natural product.

^{13}C NMR spectroscopic analysis of the synthetic sample of pseudodistomin E **5** showed agreement ($\Delta\delta_C \leq 0.3$ ppm in general)[23] with the values quoted by Freyer *et al*.[1] for the natural product. However, *C*(4), *C*(6) and *C*(1') exhibited significant deviations of $\Delta\delta_C = 1.3$, 1.1 and 0.5 ppm, respectively. As pseudodistomin E **5** contains two basic functionalities, it was proposed that the spectroscopic data could be liable to significant variance upon exposure to acid. Therefore, TFA was introduced to the synthetic sample of pseudodistomin E **5** in 0.1 equivalent portions. As expected, the spectroscopic data were highly sensitive to the introduction of TFA, with variance observed in both ^{1}H and ^{13}C NMR spectra. Interestingly, it was noted that addition of 0.1 equivalents of TFA to a synthetic sample of pseudodistomin E **5** furnished ^{13}C NMR data that was an excellent match with the literature values ($\Delta\delta_C \leq 0.2$ ppm)[23]

reported for the natural product,[1] although the ^{1}H NMR spectra no longer matched (Figure 20). It was therefore hypothesised that traces of acid were present in the sample of the natural product when the ^{13}C NMR spectrum was recorded (but were absent when the ^{1}H NMR data were collected).

pseudodistomin E **5**



	5 Freyer *et al.*[1] (100 MHz, MeOH-d_4)	**5** This work[21] (100 MHz, MeOH-d_4)	**5**·0.1 TFA This work (100 MHz, MeOH-d_4)	**5**·0.2 TFA This work (100 MHz, MeOH-d_4)	**5**·2.0 TFA This work (100 MHz, MeOH-d_4)
C(2)	56.4	56.5 (+0.1)	56.5 (+0.1)	56.5 (+0.1)	56.1 (−0.3)
C(3)	35.3	35.6 (+0.3)	35.2 (−0.1)	35.0 (−0.3)	33.5 (−1.8)
C(4)	69.7	71.0 (+1.3)	69.6 (−0.1)	68.7 (−1.0)	64.4 (−5.3)
C(5)	51.3	51.4 (+0.1)	51.3 (0.0)	51.3 (0.0)	49.9 (−1.4)
C(6)	49.3	50.4 (+1.1)	49.3 (0.0)	48.6 (−0.7)	43.3 (−6.0)
C(1')	36.9	37.4 (+0.5)	36.8 (−0.1)	36.5 (−0.4)	32.2 (−4.5)
C(2')	26.6	26.9 (+0.3)	26.7 (+0.1)	26.7 (+0.1)	26.2 (−0.4)
C(3')	30.2	30.5 (+0.3)	30.4 (+0.2)	30.3 (+0.1)	29.9 (−0.3)
C(4')	30.4	30.6 (+0.2)	30.6 (+0.2)	30.5 (+0.1)	30.3 (−0.1)
C(5')	33.3	33.5 (+0.2)	33.4 (+0.1)	33.4 (+0.1)	33.5 (+0.2)
C(6')	132.8	133.0 (+0.2)	133.0 (+0.2)	133.0 (+0.2)	132.8 (0.0)
C(7')	132.0	132.1 (+0.1)	132.1 (+0.1)	132.1 (+0.1)	132.2 (+0.2)
C(8')	131.8	132.0 (+0.2)	132.0 (+0.2)	131.9 (+0.1)	131.9 (+0.1)
C(9')	133.1	133.2 (+0.1)	133.2 (+0.1)	133.2 (+0.1)	133.2 (+0.1)
C(10')	33.5	33.7 (+0.2)	33.6 (+0.1)	33.5 (0.0)	33.5 (0.0)
C(11')	32.8	33.0 (+0.2)	33.0 (+0.2)	33.0 (+0.2)	32.9 (+0.1)
C(12')	23.3	23.4 (+0.1)	23.4 (+0.1)	23.4 (+0.1)	23.4 (+0.1)
C(13')	14.3	14.5 (+0.2)	14.4 (+0.1)	14.4 (+0.1)	14.4 (+0.1)

Figure 20 ^{13}C NMR data. Values of $\Delta\delta_C$ are given in parentheses relative to the data for the natural product.

Recording of the specific rotation value for the synthetic sample of pseudodistomin E **5** provided a value of $[\alpha]_D^{25}$ −34.5 (*c* 1.0 in MeOH), highlighting a significant deviation from the value of $[\alpha]_D^{25}$ −20.8 (*c* 0.39 in MeOH) reported by Freyer *et al.*[1] The specific rotation of **5**·0.1 TFA was measured, yielding a value of $[\alpha]_D^{25}$ −22.0 (*c* 0.5 in MeOH), comparing much more favourably with the value recorded for the natural product. This provides further support for the hypothesis that the sample of the natural product was contaminated with traces of acid as this data were collected. On the basis that the sign and magnitude of the specific rotation

values match well, it can thus be concluded that the synthetic and natural products are identical, establishing unambiguously the structure and absolute configuration of the latter.

2.8 Conclusion

In conclusion, pseudodistomin E **5** has been synthesised for the first time, from commercially available methyl (2*E*,5*E*)-hepta-2,5-dieneoate **129** in 19% overall yield, sixteen steps, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)] and >95:5 er.[24] Key steps involved the conjugate addition of a lithium amide reagent to α,β-unsaturated ester **129** to generate the C(2)-stereocenter of the target. Regioselective iodolactonization of a derivative was utilised to install the remaining C(4) and C(5) stereocenters. Use of a tethering strategy to displace the iodide (with inversion of configuration) set the absolute configuration at C(5) required for the synthetic target. The unsaturated hydrocarbon tail was installed using the decarboxylative coupling of a carboxylic acid derivative and an alkylzinc reagent. Global deprotection unveiled the first synthetic sample of pseudodistomin E **5** (Figure 21). Comparison of the ^{1}H NMR spectroscopic data for the synthetic sample with those of the natural product revealed agreement, but differences in the ^{13}C NMR and specific rotation values were observed. Further investigation of these discrepancies resulted in the conclusion that traces of acid were present in the sample derived from the natural source, hence this work provides the only source of correct data for the free base of pseudodistomin E **5**. The structure, relative and absolute configurations have been established conclusively for the first time.

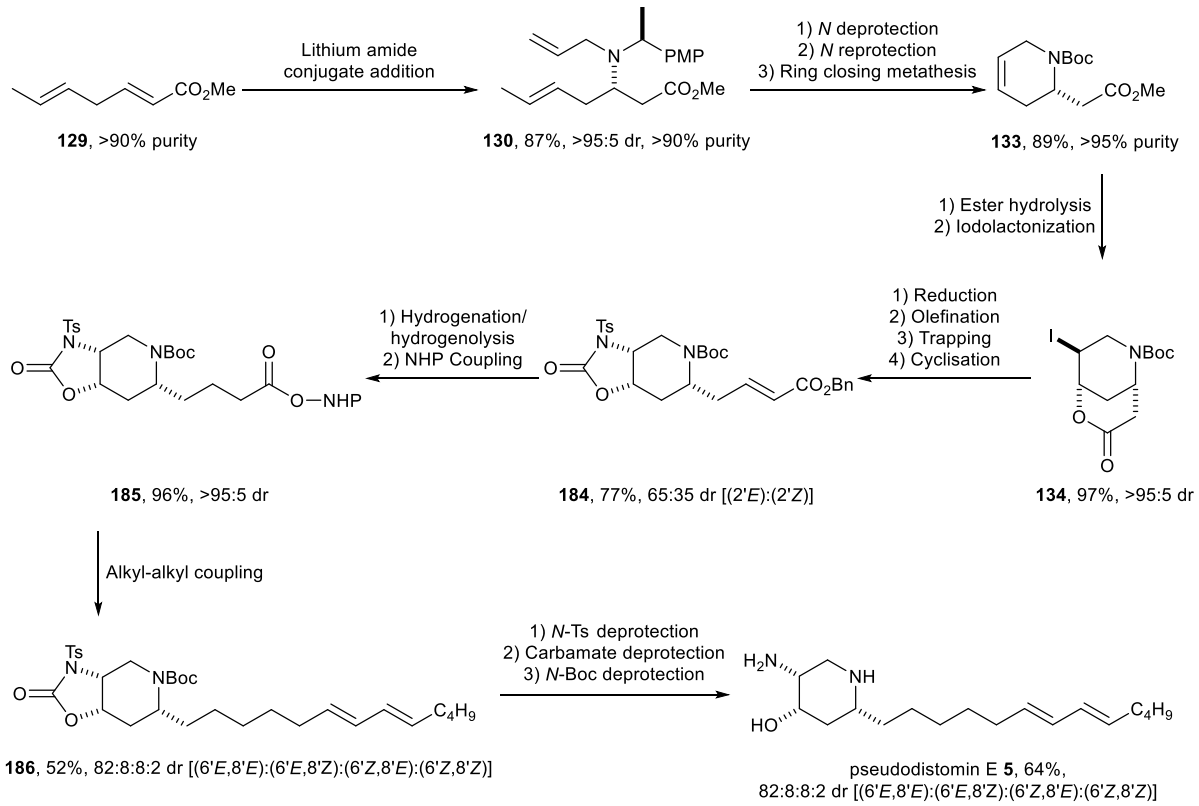


Figure 21 Summary of the asymmetric synthesis of pseudodistomin E **5**.

2.9 References and Notes

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[21] $\Delta\delta_H = |\delta_H\,(\text{natural}) - \delta_H\,(\text{synthetic})|$
[22] Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E.; Zimmer, D. *Org. Lett.* **2017**, *19*, 1638.
[23] $\Delta\delta_C = |\delta_C\,(\text{natural}) - \delta_C\,(\text{synthetic})|$
[24] As the lithium amide reagent used for the conjugate addition reaction was >95:5 er, pseudodistomin E **5** was inferred as being >95:5 er, along with all precursors.

Chapter 3

Towards a Unified Synthesis of Pseudodistomins A–F: Model Systems

3.1 Chapter Outline

This chapter describes the evaluation of a range of model systems to facilitate the development of a general strategy for the synthesis of pseudodistomins A–F **1**–**6** and non-natural analogues (Figure 22).

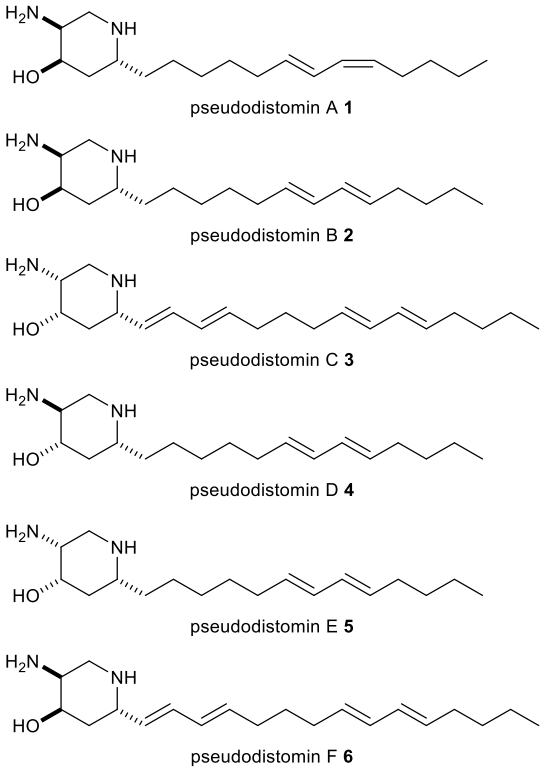


Figure 22 Structures of the pseudodistomin alkaloids.

3.2 Planning of a General Strategy

In order to develop an efficient and general strategy towards the synthesis of pseudodistomins A–F **1**–**6**, progress to date was reviewed. Firstly, the syntheses of pseudodistomin D **4**[1] and pseudodistomin E **5**[2] were assessed for areas of improvement in order to expand their applicability to other family members (Section 3.3). Secondly, effective methods to construct

the isomeric piperidine head units were investigated (Section 3.4). Finally, a general route to couple head and tail segments was sought (Section 3.5).

3.3 A Review of the Asymmetric Syntheses of Pseudodistomin D and Pseudodistomin E

Following the successful syntheses of pseudodistomin D **4**[1] and pseudodistomin E **5**,[2] the synthetic routes were reviewed for areas of improvement prior to investigations into the synthesis of pseudodistomins A–F **1**–**6**. A key potential change was identified involving preparation of the truncated iodolactone **214**. This would unlock the ability to install an olefinic moiety at C(1'), required in pseudodistomin C **3** and pseudodistomin F **6**, *via* an olefination reaction of the aldehyde functionality within **215**, which could in turn be derived from **214** (Figure 23). The two major challenges to be overcome were therefore the construction of the three different isomeric head units, and the coupling of head and tail portions. At this early planning stage, the order in which these challenges would be overcome was not immediately obvious and would be addressed later.

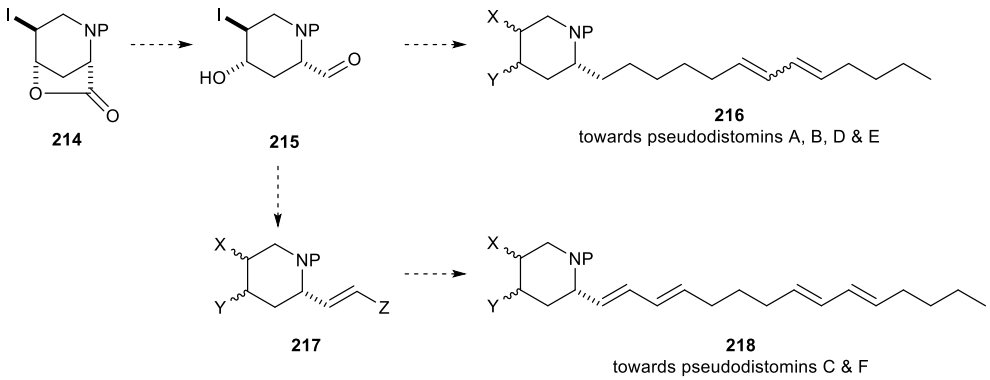


Figure 23 Proposed entry to pseudodistomin scaffolds **216** and **218**.

3.4 A General Route to the Isomeric Head Units

To overcome the challenge of constructing the isomeric head units, it was envisaged that manipulation of functional groups possessed by the iodolactone **214** would allow access to the three required head fragments. An efficient construction of the all-*cis* head unit **222** (present in

pseudodistomin C **3** and pseudodistomin E **5**) was developed in the earlier asymmetric synthesis of pseudodistomin E **5**,[2] and a route to the isomeric head unit **225** (present only in pseudodistomin D **4**) was detailed in the asymmetric synthesis of pseudodistomin D **4**.[1] It was envisaged that these methods could be readily adapted for application in the truncated series. Generation of iodohydrin **219** followed by treatment with TsNCO would furnish **220**, and subsequent exposure to base would promote cyclisation to form oxazolidinone **221**. Elaboration of **221** would unveil pseudodistomin C **3** and pseudodistomin E **5**. Alternatively, treatment of iodohydrin **219** with base would afford epoxide **223**. Regioselective ring-opening with an azide nucleophile would furnish **224**, which could be readily elaborated to **225** *en route* to pseudodistomin D **4**. This left the final head unit **229** (present in pseudodistomins A **1**, B **2** and F **6**) as the only isomer requiring attention. It was proposed that **229** could be accessed *via* manipulation of the aforementioned amino alcohol **225**, derived from iodolactone **214**. It was anticipated that *N*-Boc protection of the amino moiety within **225**, followed by activation of the hydroxyl functionality within **226** would result in cyclisation with inversion of configuration at the C(4) centre to furnish oxazolidinone **228**. Treatment of **228** under basic aqueous conditions would unveil the head unit **229** (Figure 24).

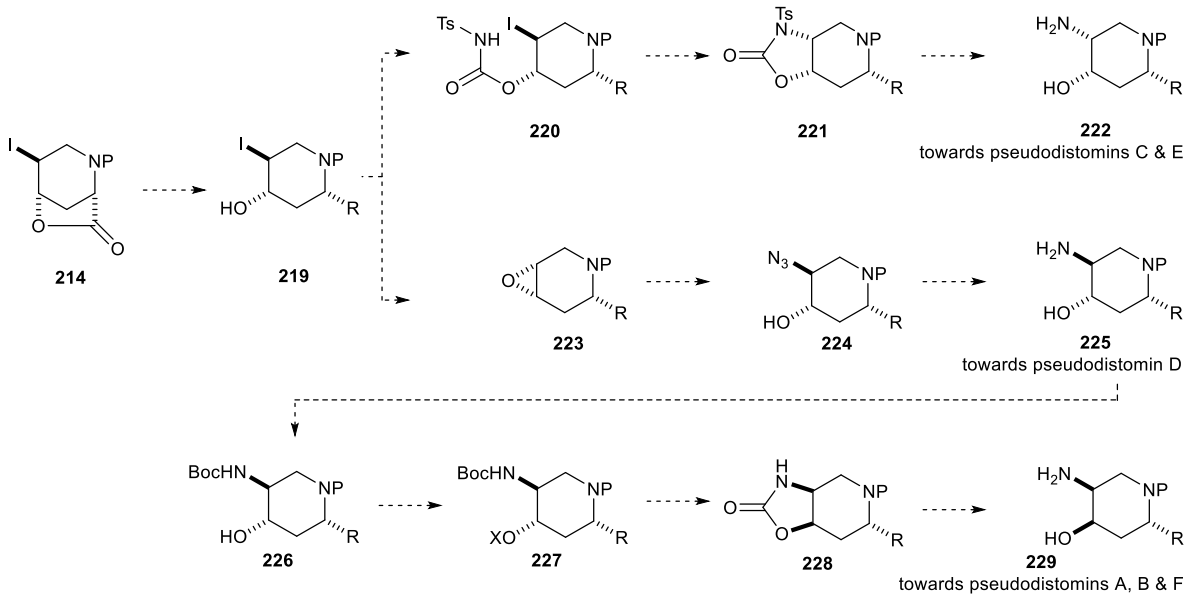
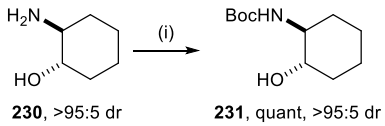


Figure 24 Construction of head units **222**, **225** and **229**.

In order to establish the validity of this approach it was resolved to investigate the process within a number of model systems.

3.4.1 A Model System

Commercially available amino alcohol **230** was selected as an appropriate model to investigate the proposed synthesis of the remaining isomeric head unit and was thus reacted with $(Boc)_2O$ in the presence of Et_3N to furnish **231** in quantitative yield after purification *via* flash column chromatography (Scheme 47).



Scheme 47 *Reagents and conditions*: (i) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 16 h.

In order to activate the hydroxy moiety within **231** and promote cyclisation, two literature protocols for this transformation were assessed.[3,4] Thus, **231** was treated with $SOCl_2$ and after purification the known oxazolidinone **232**[5] was isolated in 74% yield. The second procedure involved treatment of **231** with MsCl in the presence of Et_3N. ^1H NMR spectroscopic analysis of the crude reaction mixture indicated no evidence of cyclisation, and after purification the known mesylate **233**[6] was isolated in 94% yield as a single diastereoisomer (>95:5 dr). Mesylate **233** could, however, be readily cyclised *via* treatment with pyridine at 115 °C, affording **232** in quantitative yield (Scheme 48). These results established proof of principle and suggested that both methods may be applicable to the preparation of the final isomeric head unit.

Scheme 48 *Reagents and conditions*: (i) $SOCl_2$, THF, 0 °C to rt, 16 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h; (iii) pyridine, 115 °C, 16 h.

3.4.2 An Alternative Route

Following subsequent investigations into the syntheses of pseudodistomin C **3** and pseudodistomin E **5** (*vide infra*) it became desirable to access the all-*cis* isomeric head unit **222** from the intermediate epoxide **223**. Protocols to convert epoxides to oxazolidinones are well documented in the literature,[7] and adaptation of existing methods led to the proposition that the epoxide **223** could be treated as a masked halohydrin, and thus regioselective epoxide ring-opening with a halide nucleophile would furnish **234**. The intermediate halohydrin **234** could then readily attack an isocyanate with subsequent exposure to base being expected to facilitate the formation of the protected all-*cis* isomeric head unit **221** (Figure 25).

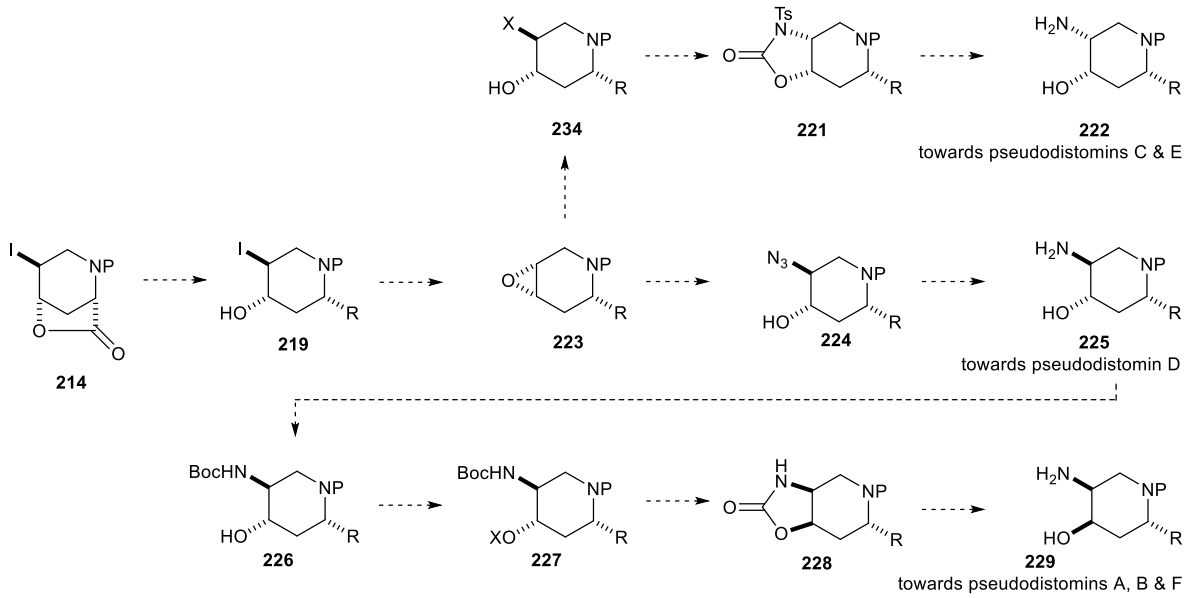
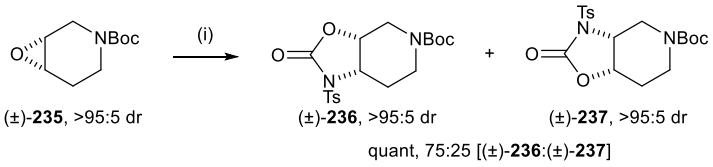


Figure 25 Proposed alternative construction of head units **222**, **225** and **229**.

Thus, commercially available (±)-**235** was selected as a model substrate and was reacted with TsNCO in the presence of TBAI. Following purification *via* flash column chromatography a 75:25 mixture of (±)-**236** and (±)-**237**, respectively, was isolated in quantitative yield (Scheme 49). The structures of **236** and **237** were assigned *via* analysis of diagnostic ^{13}C NMR shifts. The relative configuration could not be determined and was inferred from subsequent derivatization (*vide infra*).



Scheme 49 *Reagents and conditions*: (i) TsNCO, TBAI, PhMe, 100 °C, 16 h.

The distribution of regioisomeric oxazolidinones, (±)-**236** and (±)-**237**, was believed to arise from the inherent preference of (±)-**235** to react *via trans*-diaxial ring-opening at the position best able to stabilise a developing partial positive charge (i.e., the position most distal from the nitrogen). The ratio of regioisomeric oxazolidinones formed in the application of this protocol to a system bearing a C(2)-alkyl substituent would be expected to alter, with the major product arising from the initial attack of the halide at C(5). This behaviour has previously been established in the synthesis of pseudodistomin D **4**,[1] with ring-opening of the C(2)-alkyl substituted epoxide **239** occurring preferentially at C(5). This change in regioselectivity is deemed to arise from the steric preference of the substrate to place the C(2)-alkyl substituent in an axial position to reduce 1,2-strain, and thus *trans*-diaxial ring-opening occurs more readily at C(5) (Figure 26).

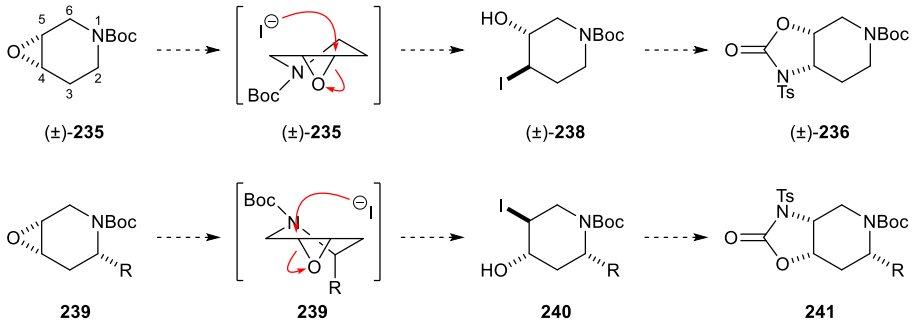
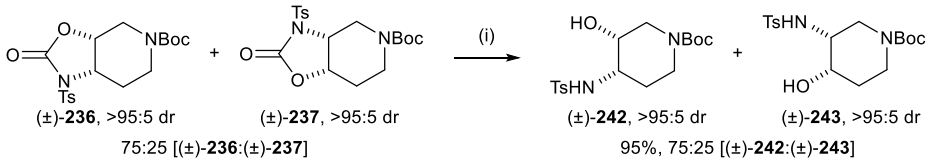


Figure 26 Rationalisation of regioselectivities.

In order to determine the relative configurations within (±)-**236** and (±)-**237**, a sample of the mixture was subjected to hydrolysis. Treatment of the 75:25 mixture of (±)-**236** and (±)-**237**, respectively, with NaOH in MeOH furnished a 75:25 mixture of (±)-**242** and (±)-**243** in 95% yield (Scheme 50).



Scheme 50 *Reagents and conditions*: (i) KOH, MeOH, 70 °C, 6 h.

The relative configuration within (±)-**242** could be assigned from ^{1}H NMR ^{3}J coupling constant analysis, assuming a chair conformation in solution in $CDCl_3$. A notable coupling constant observed is ^{3}J 10.6 Hz between the C(4)*H* and C(3)H_{axial} protons, indicating an ~180° dihedral angle between the protons according to the Karplus curve.[8] This is suggestive of C(4)*H* being axial, and thus the C(4)-amino group occupying an equatorial site. The small (^{3}J 3.5 Hz) coupling constant between C(4)*H* and C(5)*H* is indicative of a non *trans*-diaxial relationship between the protons according to the Karplus curve.[8] Therefore, with C(5)*H* adopting an equatorial site the C(5)-hydroxy functionality must adopt an equatorial position. This is consistent with 1,3-diaxial interactions and gauche interactions being minimised by placing the larger C(4)-amino substituent equatorial (Figure 27). Based on this assignment, the relative configuration within (±)-**236** could also be assigned, and confirmation was provided that the formal substitution of the iodide functionality had indeed proceeded with inversion of configuration.

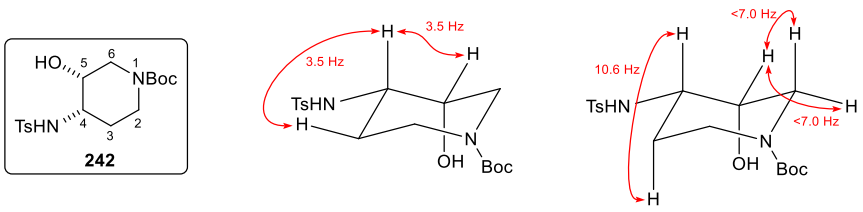


Figure 27 Conformational analysis of **242**.

Upon establishment of successful routes to the three isomeric piperidine head units **222**, **225** and **229**, attention turned to the development of a general method to assemble the carbon backbone of pseudodistomins A–F **1**–**6**.

3.5 Investigations into Head and Tail Couplings

An elegant method was now sought to assemble the backbones of pseudodistomins A–F **1**–**6** *via* a common carbon-carbon bond forming strategy (Figure 28).

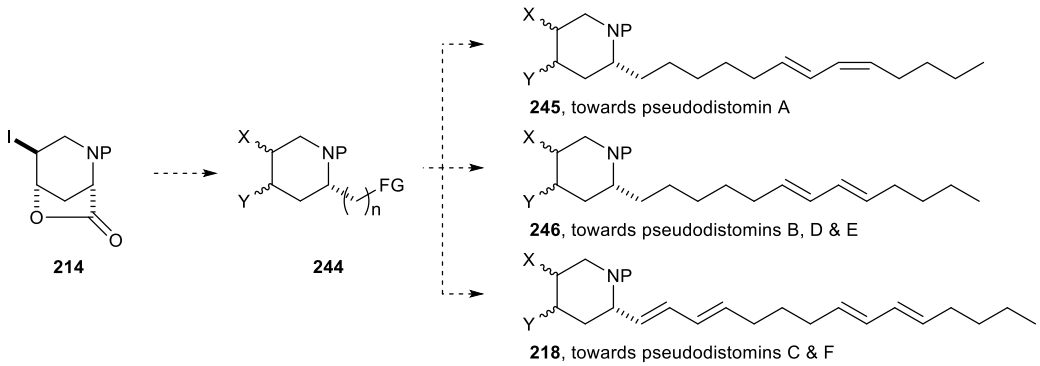


Figure 28 Coupling strategy aims.

3.5.1 Decarboxylative Coupling Strategy

Given the success of the decarboxylative coupling in the asymmetric synthesis of pseudodistomin E **5**,[2] appropriate model systems were designed to test the applicability of the method in order to access pseudodistomins A–F **1**–**6**. Thus, the redox-active esters **247** and **248** were proposed as intermediates in the syntheses of pseudodistomins A **1**, B **2**, D **4** and E **5**, and pseudodistomin C **3** and pseudodistomin F **6**, respectively (Figure 29). The immediate advantage of this system would be that the carbon skeleton of pseudodistomins A–F **1**–**6** could be constructed from importation of the alkyl bromides **249** and **250** to the requisite head fragments. It was anticipated that rearrangement of organometallic derivatives of **249** and **250** would be disfavoured, relative to the truncated alkyl bromide **82** used in the synthesis of pseudodistomin E **5**,[2] thus reducing the risk of erosion of diastereomeric purity in this case.

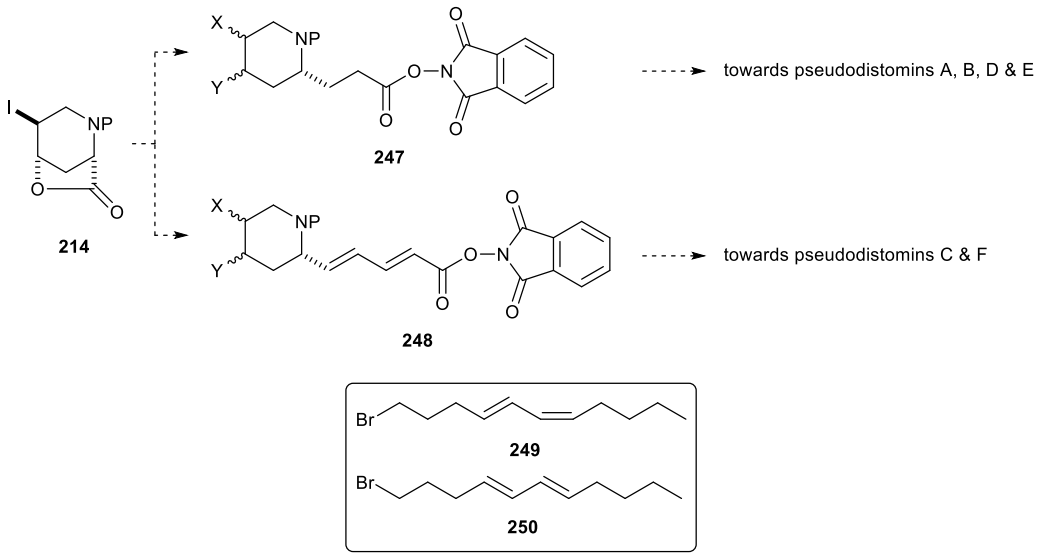


Figure 29 Proposed key intermediates in the decarboxylative coupling route.

Model structures were suggested as the redox-active esters **251** and **252**, derived from 2-piperidneethanol, along with alkyl bromide **250** (Figure 30). Redox-active ester **251** would represent an intermediate in the syntheses of pseudodistomins A **1**, B **2**, D **4** and E **5**, and redox-active ester **252** would represent an intermediate in the synthesis of pseudodistomins C **3** and pseudodistomin F **6**.

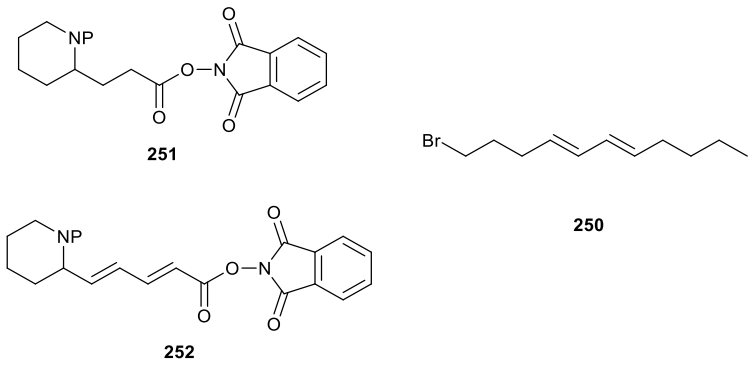
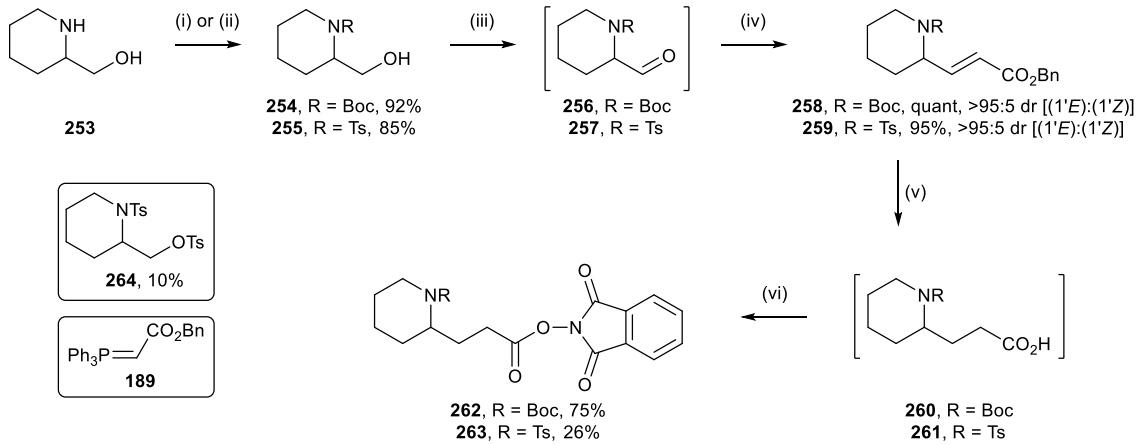


Figure 30 Proposed model compounds in the investigation of the decarboxylative coupling route.

3.5.1.1 Head Construction

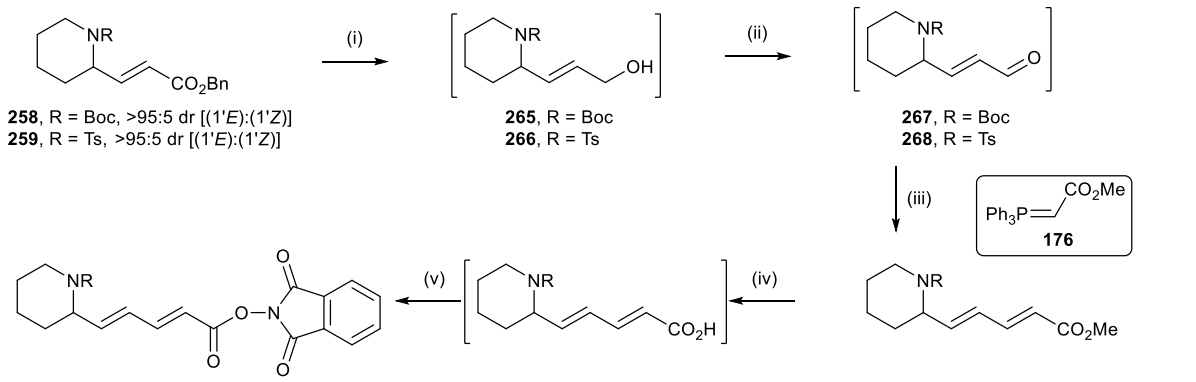
2-Piperidinemethanol **253** was subjected to *N*-protection with $(Boc)_2O$ or TsCl, yielding *tert*-butyl carbamate **254** and the tosylate **255** in 92% and 85% yield, respectively. In the reaction of **253** with TsCl, the di-tosylated species **264** was also isolated in 10% yield. Swern oxidation[9] of **254** and **255** furnished the intermediate aldehydes **256** and **257**, respectively,

which were immediately subjected to Wittig olefination[10] with ylid **189** to afford α,β-unsaturated esters **258** and **259**, in high yields and >95:5 dr [(1'*E*):(1'*Z*)]. Hydrogenation of the olefinic residues and tandem hydrogenolysis of the *O*-Bn moieties within **258** and **259** gave the intermediate acids **260** and **261**, respectively, which were subsequently reacted with DIC, DMAP and NHP to provide the redox-active esters **262** and **263** in 75% and 26% yield, respectively, over two steps (Scheme 51).



Scheme 51 *Reagents and conditions*: (i) $(Boc)_2O$, $NaHCO_3$, MeOH, rt, 16 h; (ii) TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h; (iii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min then **254** or **255**, CH_2Cl_2, 30 min then Et_3N, −78 °C to rt, 20 min; (iv) **189**, CH_2Cl_2, rt, 16 h; (v) H_2 (1 atm), $Pd(OH)_2/C$, EtOAc, rt, 6 h; (vi) NHP, DIC, DMAP, CH_2Cl_2, rt, 16 h.

α,β-Unsaturated esters **258** and **259** were also subjected to DIBAL-H reduction to the corresponding intermediate allylic alcohols **265** and **266**, respectively, which were then re-oxidised under Swern oxidation[9] conditions followed by Wittig olefination[10] with **176**, to yield, after purification, α,β,γ,δ-unsaturated esters **269** and **270**, respectively, in good yield and 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)] in both instances. NaOH promoted $B_{AC}2$ ester hydrolysis of **269** and **270** afforded carboxylic acids **271** and **272**, respectively, which were immediately subjected to DIC promoted coupling with NHP to provide redox-active esters **273** and **274** in 75% and 37% yield, respectively, and 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)] in both instances (Scheme 52).



258, R = Boc, >95:5 dr [(1′*E*):(1′*Z*)]
259, R = Ts, >95:5 dr [(1′*E*):(1′*Z*)]

265, R = Boc
266, R = Ts

267, R = Boc
268, R = Ts

269, R = Boc, 80%, 90:10 dr [(1′*E*,3′*E*):(1′*Z*,3′*E*)]
270, R = Ts, 86%, 90:10 dr [(1′*E*,3′*E*):(1′*Z*,3′*E*)]

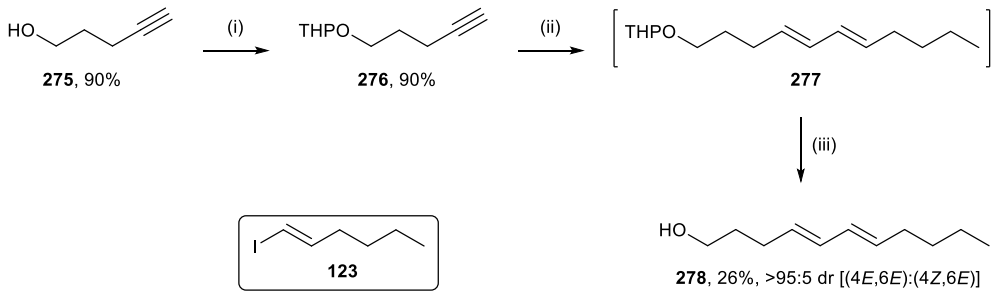
271, R = Boc
272, R = Ts

273, R = Boc, 75%, 90:10 dr [(1′*E*,3′*E*):(1′*Z*,3′*E*)]
274, R = Ts, 37%, 90:10 dr [(1′*E*,3′*E*):(1′*Z*,3′*E*)]

Scheme 52 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min then **265** or **266**, CH_2Cl_2, 30 min then Et_3N, −78 °C to rt, 20 min; (iii) **176**, CH_2Cl_2, rt, 16 h; (iv) NaOH, THF, 70 °C, 8 h; (v) NHP, DIC, DMAP, CH_2Cl_2, rt, 16 h.

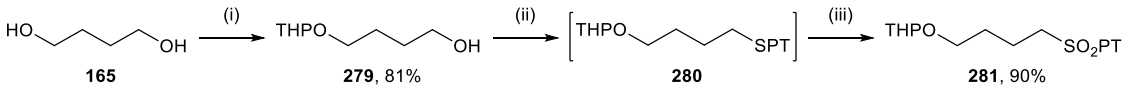
3.5.1.2 Tail Construction

Commercially available alkyne **275** was subjected to THP protection to afford **276** in 90% yield. A modified Negishi protocol, outlined by Trost *et al.*[11] in their synthesis of pseudodistomin D **4**, was used to couple the hydro-zirconated adduct of alkyne **276** with the known vinyl iodide **123**,[12] which is commercially available (although expensive) and can also be readily prepared from 1-hexyne **202**. The intermediate diene **277** was immediately treated with $TsOH·H_2O$ to effect *O*-deprotection unveiling alcohol **278** in 26% yield as a single diastereoisomer {>95:5 dr [(4*E*,6*E*):(4*Z*,6*E*)]} (Scheme 53). The low yielding sequence was deemed to be a function of the instability and volatility of the intermediate vinyl iodide **123**. Attempted repetition of the coupling returned starting material in all instances, even with fresh reagents and catalysts, suggesting an alternative route for the preparation of **278** should be investigated.



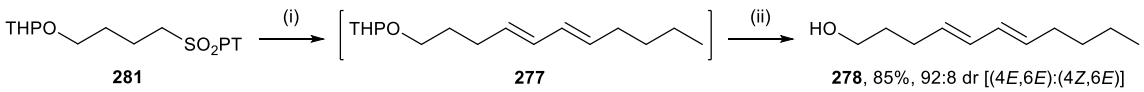
Scheme 53 *Reagents and conditions*: (i) DHP, PPTS, CH_2Cl_2, 0 °C to rt, 16 h; (ii) **276**, Cp_2ZrHCl, THF, rt, 1 h then DIBAL-H, $PdCl_2(PhCN)_2$, DPPF, **123**, THF, rt, 16 h; (iii) $TsOH{\cdot}H_2O$, MeOH, rt, 2 h.

1,4-Butanediol **165** was subjected to mono-THP protection to afford **279** in 81% yield. DIAD promoted Mitsunobu reaction[13] of alcohol **279** with PTSH and PPh_3 gave the intermediate sulfide **280** which was oxidised to the corresponding sulfone **281** in 90% yield over two steps (Scheme 54).



Scheme 54 *Reagents and conditions*: (i) DHP, PPTS, CH_2Cl_2, 0°C to rt, 16 h; (ii) DIAD, PPh_3, PTSH, THF, rt, 30 min; (iii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 0 °C to rt, 16 h.

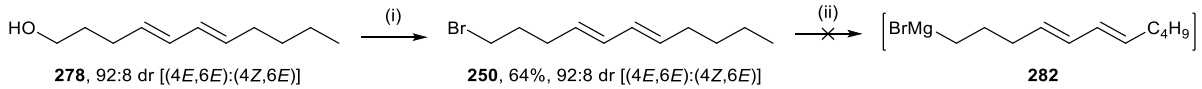
A comprehensive screen of solvents (THF and DME), concentrations (0.5 M to 0.05 M), temperatures (−100 °C to −55 °C), additives (18c6) and bases (LiHMDS, NaHMDS, KHMDS) was undertaken to determine the optimal conditions for the Julia-Kocieński olefination[14] of **281** with (2*E*)-2-heptenal **144**. Optimised conditions led to reaction of sulfone **281** with (2*E*)-2-heptenal **144** in DME at −55 °C to provide the intermediate diene **277**, which upon acid mediated deprotection gave alcohol **278** in 85% yield and 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)] (Scheme 55).



Scheme 55 *Reagents and conditions*: (i) NaHMDS, **144**, DME, −55 °C, 30 min; (ii) $TsOH{\cdot}H_2O$, MeOH, rt, 2 h.

With ready access to multi-gram quantities of alcohol **278** a method was sought to prepare the Grignard reagent **282**. Thus, Appel reaction[15] of **278** with PPh_3 and CBr_4 gave bromodiene **250** in 64% yield without compromising the diastereomeric integrity (i.e. 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)])

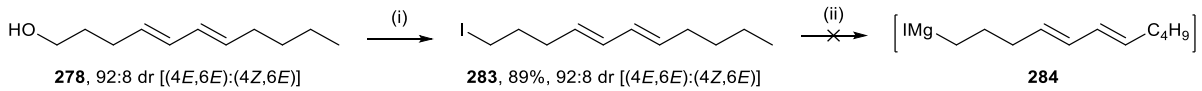
of the sample. However, all subsequent attempts at forming Grignard reagent **282** failed (Scheme 56).



278, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)] **250**, 64%, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)] **282**

Scheme 56 *Reagents and conditions*: (i) PPh_3, CBr_4, CH_2Cl_2, −30 °C, 30 min then **278**, imidazole, CH_2Cl_2, −30 °C to rt, 3 h; (ii) Mg, I_2, THF, 70 °C, 1 h.

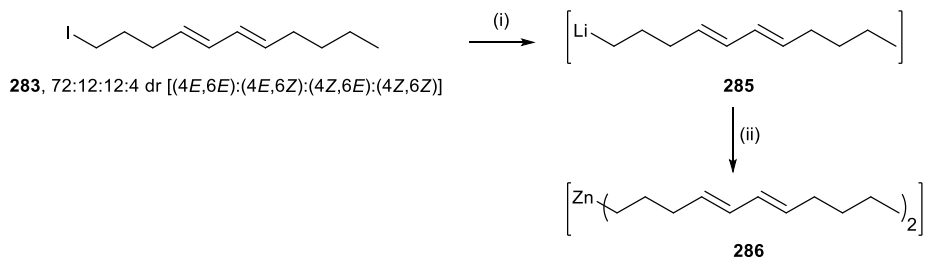
In an effort to aid the ease of Grignard formation, iododiene **283** was prepared (*via* an analogous Appel reaction[15] of **278** with PPh_3 and I_2) in 89% yield and 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)]. Again, all attempts at forming Grignard reagent **284** failed (Scheme 57). It was noted that **283** underwent isomerisation when stored neat at room temperature, with a 72:12:12:4 dr [(4*E*,6*E*):(4*E*,6*Z*):(4*Z*,6*E*):(4*Z*,6*E*)] sample being observed after twelve days.



278, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)] **283**, 89%, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)] **284**

Scheme 57 *Reagents and conditions*: (i) imidazole, PPh_3, **278**, CH_2Cl_2, 0 °C, 5 min then I_2, 0 °C, 1 h then 0 °C to rt, 1 h; (ii) Mg, I_2, THF, 70 °C, 1 h.

An in-depth screen of solvents (THF and Et_2O), temperatures (−100 °C to −20 °C) and order of additions was conducted to determine the optimal conditions for formation of alkyllithium **285**. Thus, under optimal conditions, iododiene **283** was treated with ^{t}BuLi in Et_2O at −78 °C to promote lithium-halogen exchange, and formation of **285**. Alkyllithium **285** was titrated following a procedure outlined by Knochel *et al.*[16] to determine the concentration before the addition of the requisite amount of $ZnCl_2$ which is known[17] to promote transmetallation to dialkylzinc **286** (Scheme 58).

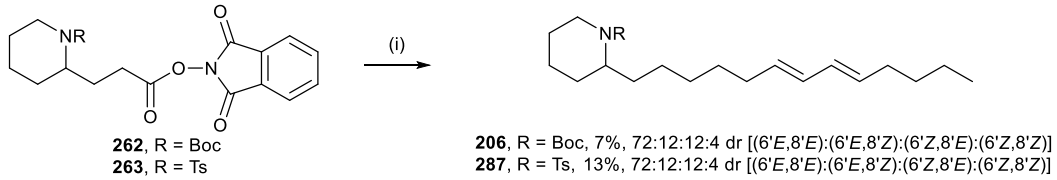


283, 72:12:12:4 dr [(4*E*,6*E*):(4*E*,6*Z*):(4*Z*,6*E*):(4*Z*,6*Z*)] **285** **286**

Scheme 58 *Reagents and conditions*: (i) ^{t}BuLi, Et_2O, −78 °C, 5 min; (ii) $ZnCl_2$, THF, −78 °C to rt, 15 min.

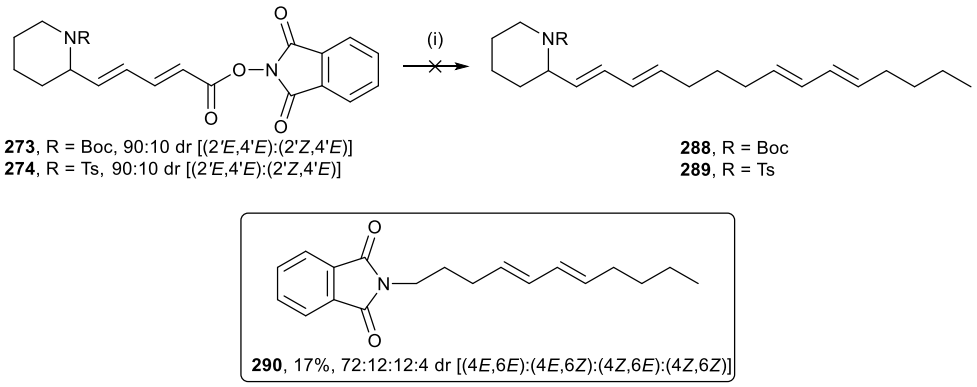
3.5.1.3 Head and Tail Coupling

The model systems representative of pseudodistomins A **1**, B **2**, D **4** and E **5** were trialled first. Following the protocol outlined by Baran *et al*.[18] dialkylzinc **286** was allowed to react with redox-active esters **262** and **263** under the reported conditions. Both resulted in complex crude reaction mixtures from which the products **206** and **287** were isolated in only 7% and 13% yield, respectively (Scheme 59).



Scheme 59 *Reagents and conditions*: (i) **286**, $NiCl_2$·glyme, BBBPY, DMF, rt, 16 h.

Following these results, the model systems representative of pseudodistomin C **3** and pseudodistomin F **6** were next trialled. In the reaction of redox-active esters **273** and **274** with dialkylzinc reagent **286** the products **288** and **289**, respectively, were not isolated. However, **290** was isolated in 17% yield and 72:12:12:4 dr [(4*E*,6*E*):(4*E*,6*Z*):(4*Z*,6*E*):(4*Z*,6*E*)] from the reaction of **273** (Scheme 60).



Scheme 60 *Reagents and conditions*: (i) **286**, $NiCl_2$·glyme, BBBPY, DMF, rt, 16 h.

3.5.1.4 Method Conclusion

A possible rationale for the low yielding coupling reactions in the model system representative of pseudodistomins A **1**, B **2**, D **4** and E **5** could be an unfavourable response from the reaction

to the introduction of Et_2O (required for generation of the organolithium reagent **285**), whereas the conditions outlined by Baran *et al*. report a THF/DMF mixture to be the optimal reaction solvent. A plausible explanation for the failure of the coupling in the model system representative of pseudodistomin C **3** and pseudodistomin F **6** may include reaction of the intermediate radical **291** or the vinyl nickel species **292** *via* an unknown pathway (Figure 31). In contrast to the successful Ni catalysed decarboxylative coupling carried out in the synthesis of pseudodistomin E **5**,[2] these models provided poor yields or failure. Thus, it was concluded that an alternative strategy should be devised.

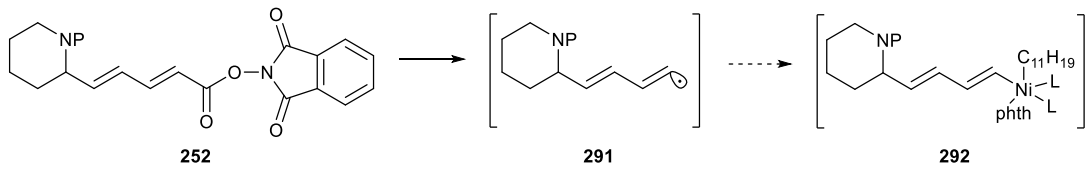


Figure 31 Potential rationale for the failure of the decarboxylative coupling.

3.5.2 Cuprate Displacement Strategy

Given the success of a copper mediated S_N2 reaction in early work by Naito *et al.*[19] in their syntheses of pseudodistomin A acetate **9** and pseudodistomin B acetate **10**, a similar approach was evaluated. Keeping with the strategy of using alkyl halide derived organometallic reagents as coupling partners, **293** was proposed as an intermediate in the synthesis of pseudodistomins A **1**, B **2**, D **4** and E **5**, and **294** in the synthesis of pseudodistomin C **3** and pseudodistomin F **6**. Reaction of these head portions, **293** and **294**, with the organocuprate reagent derived from **295**, **296** or **297** would allow construction of the carbon skeleton of pseudodistomins A–F **1**–**6** (Figure 32).

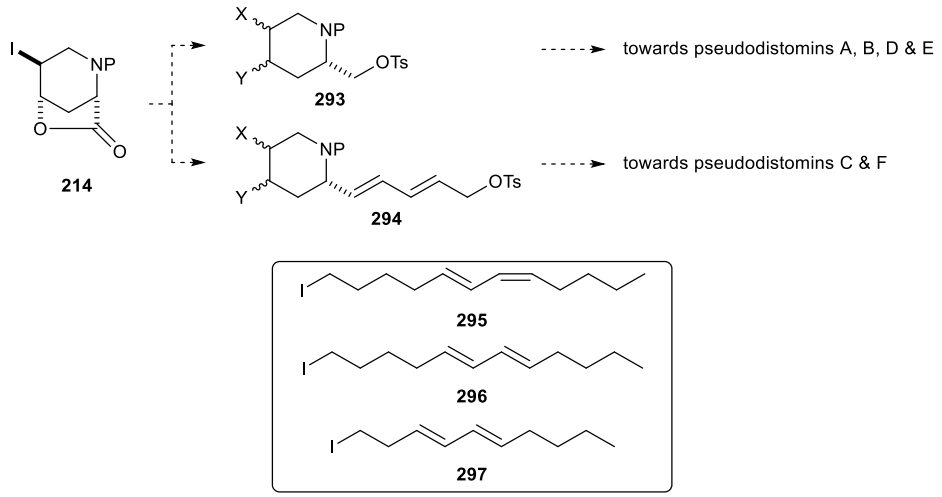


Figure 32 Proposed key intermediates in the cuprate displacement coupling route.

Tosylates **298** and **299** were proposed as model structures, representative of intermediates in the syntheses of pseudodistomins A **1**, B **2**, D **4** and E **5**, and pseudodistomin C **3** and pseudodistomin F **6**, respectively. These could be coupled with the organocuprate reagent derived from commercially available iodooctane **300** (Figure 33).

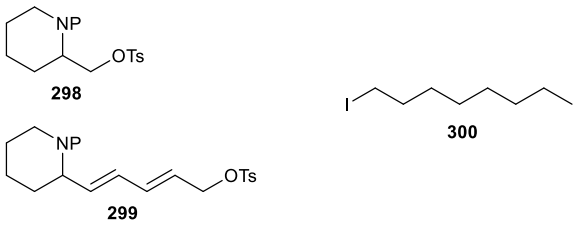
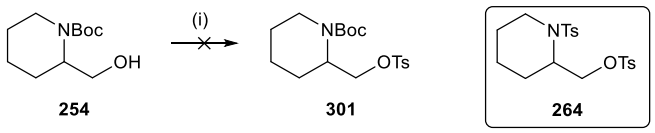


Figure 33 Proposed model compounds in the investigation of the cuprate displacement route.

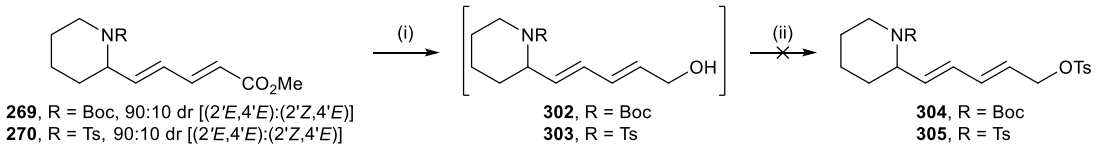
3.5.2.1 Head Construction

Attempted *O*-tosylation of **254** with TsCl in the presence of Et_3N gave a complex mixture that was not amenable to purification *via* flash column chromatography. The aforementioned di-tosylated species **264** had already been procured as a side-product in the *N*-tosylation of 2-piperidineethanol (Scheme 61).



Scheme 61 *Reagents and conditions*: (i) TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h.

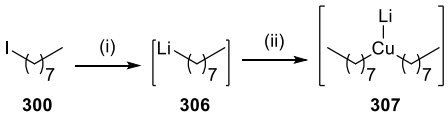
To access the dienyl head fragments **304** and **305** the esters **269** and **270** were treated with DIBAL-H to effect reduction to the intermediate allylic alcohols **302** and **303**, respectively. Attempted tosylation of **302** and **303** gave, in both instances, complex mixtures of products from which **304** and **305**, respectively, were not isolated (Scheme 62).



Scheme 62 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ii) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h.

3.5.2.2 Tail Construction

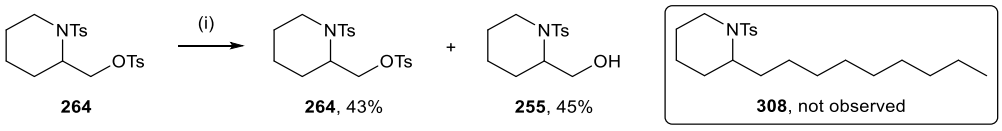
Iodooctane **300** was treated with ^{t}BuLi in Et_2O to effect lithium-halogen exchange and afford organolithium species **306**. The intermediate organolithium **306** was added to a suspension of CuI in Et_2O at −35 °C which is known[20] to promote transmetallation to the organocopper species **307** (Scheme 63).



Scheme 63 *Reagents and conditions*: (i) ^{t}BuLi, Et_2O, −78 °C, 10 min; (ii) CuI, Et_2O, −35 °C, 1 h.

3.5.2.3 Head and Tail Coupling

Treatment of **264** with organocopper reagent **307** gave, after purification, returned starting material **264** in 43% yield, and **255**, the product of *O*-deprotection, in 45% yield (Scheme 64).



Scheme 64 *Reagents and conditions*: (i) **307**, Et_2O, −35 °C, 2 h.

3.5.2.4 Method Conclusion

Given the difficulties encountered in the preparation of representative model systems, it was decided that this route was not to be applied to the real systems. A potential explanation for the failure in preparation of head fragments **301**, **304** and **305** could include *N*-participation in the intramolecular displacement of the tosylate moiety, either directly in the model system representative of pseudodistomins A **1**, B **2**, D **4** and E **5**, or *via* interaction with the olefinic moieties borne by the model system representative of pseudodistomin C **3** and pseudodistomin F **6**.

3.5.3 Suzuki Coupling Strategy

The third proposed strategy subjected to investigation was the palladium-catalysed Suzuki coupling.[21] Reaction of vinyl iodide **309** with boronic acids **311** and **312** would allow construction of the scaffold of pseudodistomins A **1**, B **2**, D **4** and E **5**. Coupling of vinyl iodide **310** with the boronic acid **313** would allow entry to the scaffold of pseudodistomin C **3** and pseudodistomin F **6** (Figure 34).

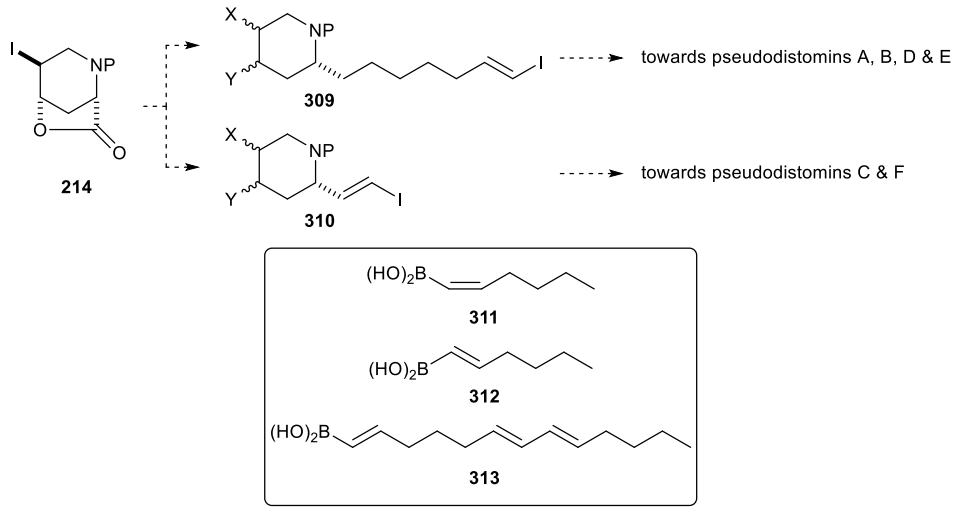


Figure 34 Proposed key intermediates in the Suzuki coupling route.

Model structures were suggested as vinyl iodide **314** and the boronic acid **312**. This would allow evaluation of the validity of the Suzuki coupling[21] in the construction of a diene, and also require investigation into the synthesis of boronic acid derivatives (Figure 35).

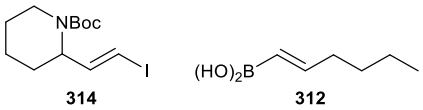
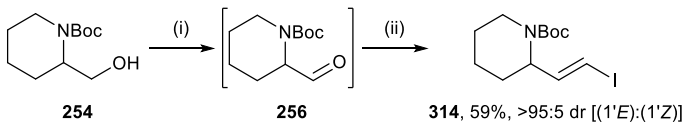


Figure 35 Proposed model compounds in the investigation of the Suzuki coupling route.

3.5.3.1 Head Construction

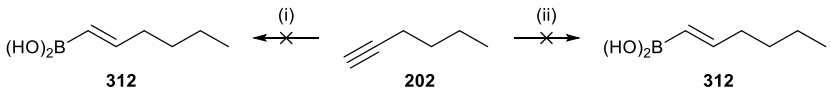
Alcohol **254** was subjected to Swern oxidation[9] to generate the intermediate aldehyde **256**. Conversion of aldehyde **256** to the vinyl iodide **314** was achieved *via* use of the Takai olefination,[22] yielding **314** in 59% yield as a single geometric isomer (>95:5 dr [(1'*E*):(1'*Z*)]) (Scheme 65).



Scheme 65 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min then **254**, CH_2Cl_2, 30 min then Et_3N, −78 °C to rt, 30 min; (ii) $CrCl_2$, CHI_3, THF, 30 min, rt.

3.5.3.2 Tail Construction

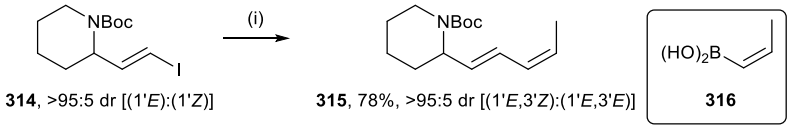
1-Hexyne **202** was treated sequentially with Me_2SBHBr_2 and NaOH, under literature conditions,[23] in order to effect a hydroboration reaction followed by displacement of the *B*-bromides. Similarly, 1-hexyne **202** was treated sequentially with catechcolborane and H_2O under previously reported conditions[24] to effect an identical reaction sequence. Both reactions produced complex mixtures of products from which boronic acid **312** was not isolated (Scheme 66).



Scheme 66 *Reagents and conditions*: (i) Me_2SBHBr_2, CH_2Cl_2, 0 °C to rt, 16 h then aq NaOH, Et_2O, 0 °C to rt, 1 h; (ii) catechcolborane, THF, 0 °C to rt 1 h then 50 °C, 16 h then H_2O, 0 °C to rt, 2 h.

3.5.3.3 Head and Tail Coupling

Despite setbacks in the synthesis of boronic acid **312**, the Suzuki coupling[21] of **314** was instead trialled with commercially available (1*Z*)-1-propen-1-ylboronic acid **316**. The coupling was accomplished with $Pd(PPh_3)_4$ catalysis, in the presence of aq KOH as the base. The diene **315** was isolated in 78% yield as a single geometric isomer (>95:5 dr [(1'*E*,3'*Z*):(1'*E*,3'*Z*)]) after purification (Scheme 67).



Scheme 67 *Reagents and conditions*: (i) $Pd(PPh_3)_4$, **316**, aq KOH, THF, 50 °C, 16 h.

3.5.3.4 Method Conclusion

Given the moderate yield for the preparation of the vinyl iodide **314**, the difficulty encountered in the synthesis of boronic acid **312**, and likely issues in the construction of more complex boronic acids, attention was turned elsewhere.

3.5.4 Julia-Kocieński Olefination Strategy

A further proposed strategy for the construction of the carbon backbone of the pseudodistomins was the Julia-Kocieński olefination.[14] This transformation could be accomplished in two directions *via* interconversion of the requisite functional groups borne by the head and tail portions. Under the guidance of previous work by Kobayashi *et al.*[25] and Ma *et al.*[26] it was proposed that if the sulfone moiety resided on the head portion, as in **317**, this could be coupled

with aldehydes **318** or **87**, to allow construction of the carbon scaffold of pseudodistomins A **1**, B **2**, D **4** and E **5** and pseudodistomin C **3** and pseudodistomin F **6**, respectively. Alternatively, aldehyde **319** could be reacted with sulfone **320** to furnish an intermediate that could be readily elaborated to pseudodistomins A **1**, B **2**, D **4** and E **5**. Reaction of aldehyde **319** with the more complex sulfone **321** would allow entry into the synthesis of pseudodistomin C **3** and pseudodistomin F **6** (Figure 35).

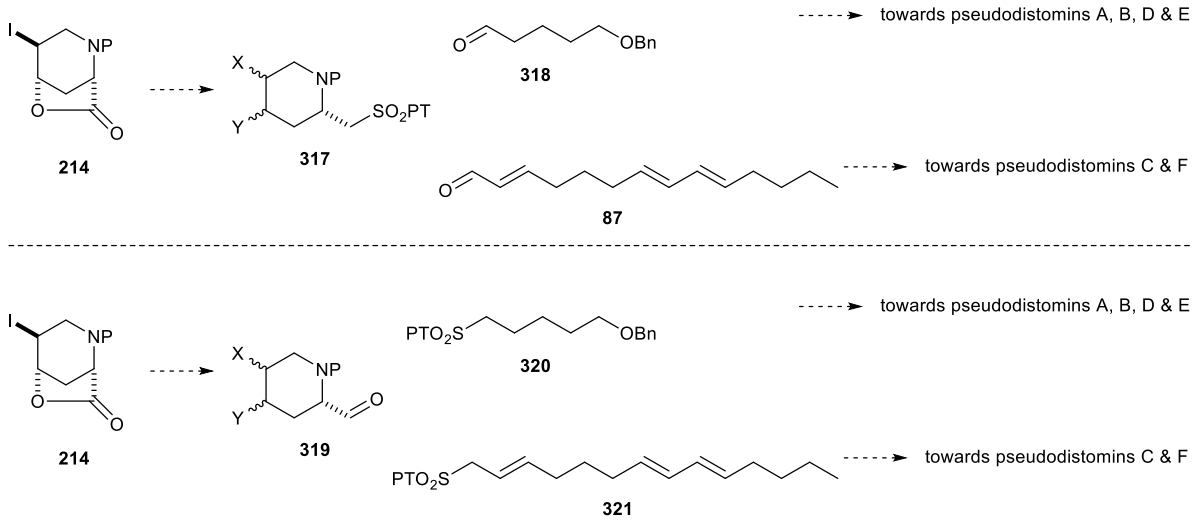


Figure 35 Proposed key intermediates in the Julia-Kocieński olefination route.

Two strategies for the model coupling were proposed. Firstly, structures were suggested as sulfone **322**, and the aldehydes **318** and **87**. Olefination utilising **322** and aldehyde **318** would allow entry into the scaffolds of pseudodistomins A **1**, B **2**, D **4** and E **5**. Olefination using **322** and aldehyde **87** allows construction of the scaffold of pseudodistomins C **3** and pseudodistomin F **6**. Alternatively, the aldehyde **256** could be coupled with sulfones **320** and **321**, to allow entry into the carbon scaffolds of pseudodistomins A **1**, B **2**, D **4** and E **5**, and pseudodistomin C **3** and pseudodistomin F **6**, respectively (Figure 36).

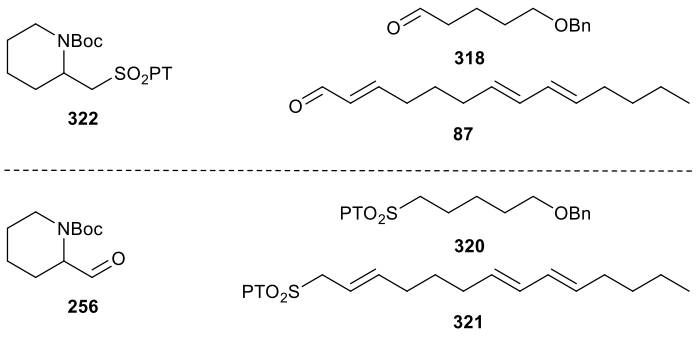
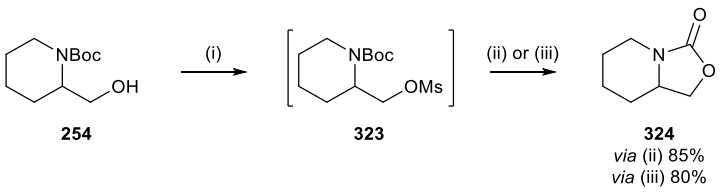


Figure 36 Proposed model compounds in the investigation of the Julia-Kocieński route.

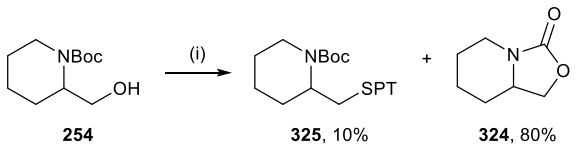
3.5.4.1 Head Construction

To target the sulfone **322**, alcohol **254** was reacted under conditions outlined by Ma *et al*.[26] on a similar substrate. Alcohol **254** was treated with MsCl and Et_3N in CH_2Cl_2 to promote *O*-mesylation and provide intermediate **323**. Mesylate **323** was then treated with PTSH and $NaHCO_3$ in 1,4-dioxane at rt to effect displacement, however, after purification, **324** was isolated in 85% yield over two steps. Alternatively, the intermediate mesylate **323** was treated with PTSH and K_2CO_3 in acetone at 60 °C, yielding **324** in 80% yield over two steps (Scheme 68).



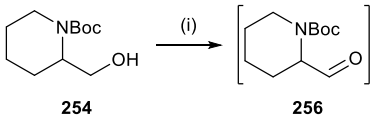
Scheme 68 *Reagents and conditions*: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 4 h; (ii) PTSH, $NaHCO_3$, 1,4-dioxane, rt, 36 h; (iii) PTSH, K_2CO_3, acetone, 60 °C, 16 h.

An alternative Mitsunobu strategy[13] was next trialled. Thus, **254** was treated with DIAD, PTSH and PPh_3. Following purification, sulfide **325** was isolated in 10% yield, and **324** was isolated in 80% yield (Scheme 69). Following these results, it was elected to abandon this sub-route, and focus efforts on the head portion bearing the aldehyde functionality which had been previously prepared successfully.



Scheme 69 *Reagents and conditions*: (i) DIAD, PTSH, PPh_3, THF, 0 °C to rt, 30 min.

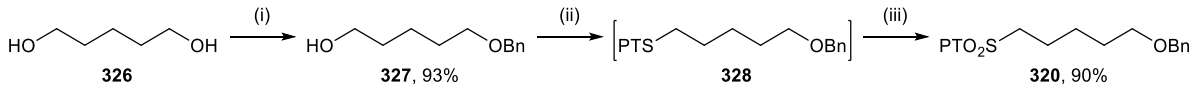
However, as outlined earlier, aldehyde **256** could be readily prepared *via* Swern oxidation[9] of alcohol **254** (Scheme 70).



Scheme 70 *Reagents and conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min then **254**, CH_2Cl_2, 20 min then Et_3N, −78 °C to rt, 30 min.

3.5.4.2 Tail Construction

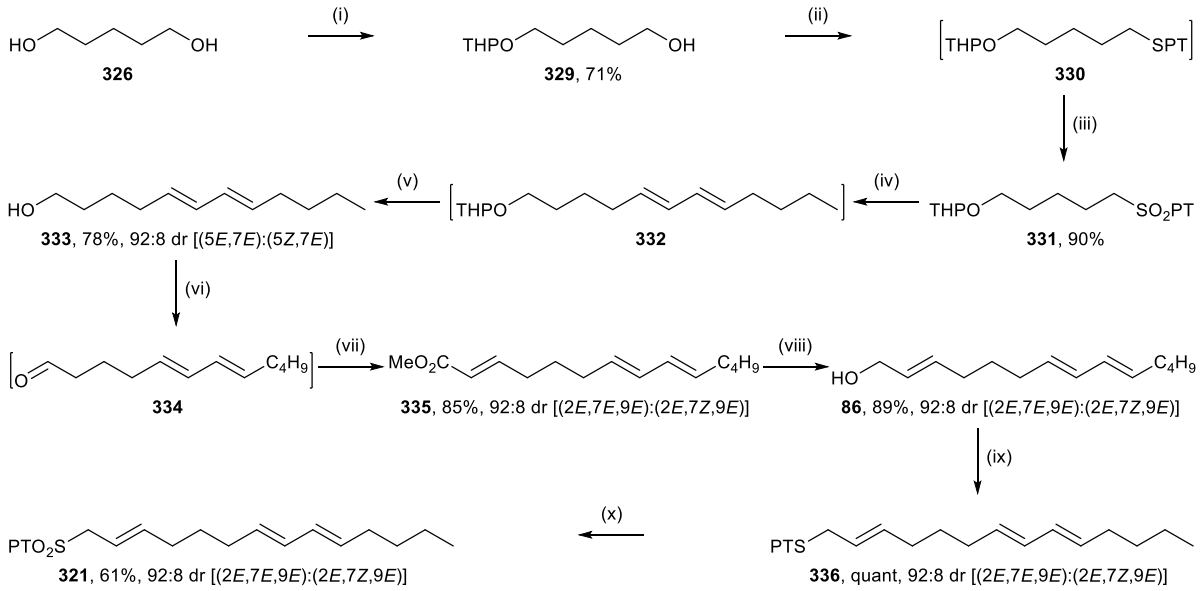
1,5-Pentane diol **326** was subjected to mono-benzylation to afford **327** in 93% yield. A two-step Mitsunobu reaction[13] and then oxidation protocol was used to furnish sulfone **320** in 90% yield over two steps (Scheme 71).



Scheme 71 *Reagents and conditions*: (i) NaH, THF, 0 °C, 30 min then BnBr, THF, 0 °C to rt, 16 h; (ii) DIAD, PTSH, PPh_3, THF, 0 °C to rt, 30 min; (iii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH/THF (1:1), 0 °C to rt, 16 h.

1,5-Pentane diol **326** was also subjected to mono *O*-protection as the THP ether **329** in 71% yield. As before, a stepwise Mitsunobu reaction[13] and then oxidation procedure gave sulfone **331** in 90% isolated yield over two steps. Julia-Kocieński olefination[14] of **331** with (2*E*)-2-heptenal **144** under the conditions optimised previously (*vide supra*) with subsequent $TsOH{\cdot}H_2O$ mediated *O*-THP deprotection gave dienic alcohol **333** in 78% yield and 92:8 dr [(5*E*,7*E*):(5*Z*,7*E*)]. Swern oxidation[9] of **333** followed by Wittig olefination[10] with **176** gave, after purification, α,β-unsaturated ester **335** in 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)], suggestive of a highly stereoselective olefination reaction. DIBAL-H reduction of ester **335**, followed by

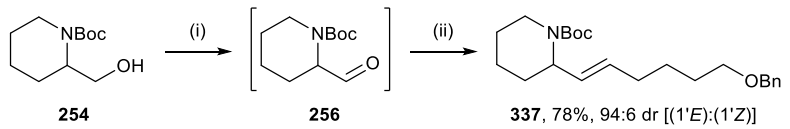
Mitsunobu reaction[13] and oxidation furnished sulfone **321** in 54% yield (over three steps) and 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)] (Scheme 72).



Scheme 72 *Reagents and conditions*: (i) DHP, PPTS, CH_2Cl_2, 0 °C to rt, 16 h; (ii) DIAD, PTSH, PPh_3, THF, 0 °C, 30 min; (iii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 0 °C to rt, 16 h; (iv) NaHMDS, **144**, DME, −55 °C, 30 min; (v) $TsOH{\cdot}H_2O$, MeOH, rt, 2 h; (vi) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 10 min then **333**, CH_2Cl_2, 30 min then Et_3N, −78 °C to rt, 20 min; (vii) **176**, CH_2Cl_2, rt, 16 h; (viii) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ix) DIAD, PTSH, PPh_3, THF, 0 °C to rt, 30 min; (x) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH/THF (1:1 mL), 0 °C to rt, 16 h.

3.5.4.3 Head and Tail Coupling

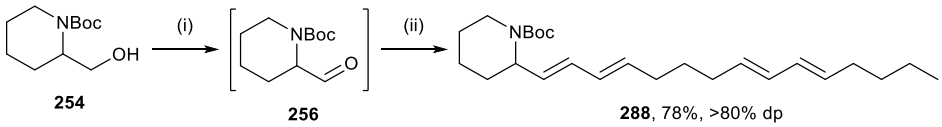
With the requisite components in hand, aldehyde **256** was subjected to Julia-Kocieński olefination[14] with sulfone **320** under an alternative protocol outlined in the literature,[27] to address the predicted stability issues of exposing **256** to stoichiometric amounts of strong base. Thus, sulfone **320** was treated with KHMDS in THF at −78 °C and was allowed to stir for 1 h. Addition of **256** at −78 °C followed by warming to room temperature overnight gave, after purification *via* flash column chromatography, **337** in 78% yield and 94:6 dr [(1'*E*):(1'*Z*)] (Scheme 73). The mixture of isomers was not deemed to be an issue as when applied to the synthesis of pseudodistomins A **1**, B **2**, D **4** and E **5** the olefin would be subject to reduction *via* hydrogenation at a later stage, thus converging on a common compound.



254 **256** **337**, 78%, 94:6 dr [(1'*E*):(1'*Z*)]

Scheme 73 *Reagents and conditions*: (i) DMP, CH_2Cl_2, rt, 1 h; (ii) KHMDS, **320**, THF, −78 °C, 1 h then **256**, THF, −78 °C to rt, 16 h.

Reaction of aldehyde **256** with the more complex sulfone **321** was completed next, under the guidance of a procedure outlined in the literature,[28] with the introduction of 18c6 in order to enhance (*E*):(*Z*) stereoselectivity. Thus, **288** (representative of pseudodistomin C **3** and pseudodistomin F **6**) was obtained in 78% yield and >80% diastereomeric purity (Scheme 74). ^{1}H and ^{13}C NMR spectroscopic analysis provided complex olefinic regions from which a conclusive ratio of geometric isomers could not be determined. It was elected to instead quote diastereomeric purity for tetraenes, where diastereomeric purity can be defined as the percentage of major diastereoisomer present in the sample. This was calculated *via* analysis of quantitative ^{13}C NMR spectroscopic data, with the value quoted being the relative integral of the major geometric isomer versus the combined integrals of all other isomers (of unknown configuration). This method was applied to all tetraenes reported herein.



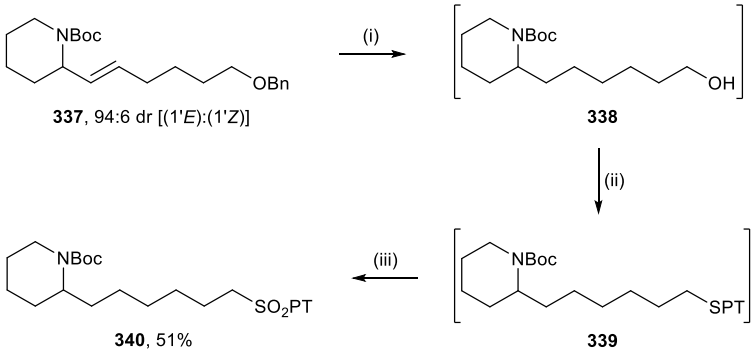
254 **256** **288**, 78%, >80% dp

Scheme 74 *Reagents and conditions*: (i) DMP, CH_2Cl_2, rt, 1 h; (ii) KHMDS, **321**, 18c6, THF, −78 °C, 1 h then **256**, THF, −78 °C to rt, 16 h.

3.5.4.4 Second Head and Tail Coupling

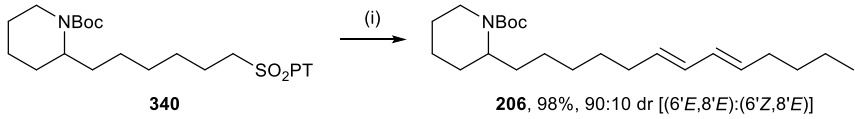
For completeness, the remainder of the tail portions were to be installed in an analogous fashion to that reported in the synthesis of pseudodistomin D **4** by Davies *et al.*,[1] with a second Julia-Kocieński olefination[14] as the key step. Thus, **337** was exposed to a hydrogen atmosphere in the presence of Pearlman's catalyst to effect tandem hydrogenation of the olefin moiety and hydrogenolysis of the *O*-Bn functionality. The intermediate alcohol **338** was immediately

subjected to a Mitsunobu reaction[13] with PTSH followed by oxidation to afford sulfone **340** in 51% yield over three steps (Scheme 75).



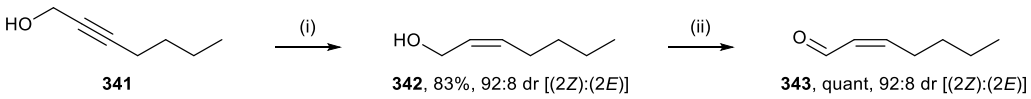
Scheme 75 *Reagents and conditions*: (i) H_2 (1 atm), $Pd(OH)_2$, EtOAc, 2 h; (ii) DIAD, PPh_3, PTSH, THF, 0 °C to rt, 30 min; (iii) *m*CPBA, CH_2Cl_2, 0 °C to rt, 1 h.

Following the protocol outlined by Davies *et al.*,[1] KHMDS was added to a mixture of **340** and commercially available (2*E*)-2-heptenal **144**. Following purification, **206** (representative of pseudodistomins B **2**, D **4** and E **5**) was isolated in 98% yield and 90:10 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)] (Scheme 76).



Scheme 76 *Reagents and conditions*: (i) KHMDS, **144**, THF, −78 °C, 30 min.

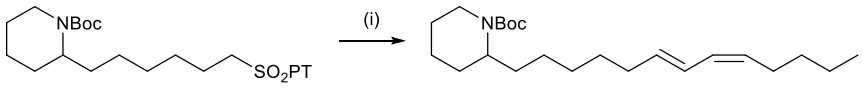
To access the carbon scaffold of pseudodistomin A **1**, (2*Z*)-2-heptenal **343** was the required coupling partner in the Julia-Kocieński olefination.[14] A facile two step synthesis was devised using commercially available 2-heptyn-1-ol **341** as the starting material. Mono-reduction of the alkyne was achieved *via* hydrogenation in the presence of Lindlar catalyst to afford **342** in 83% yield and 92:8 dr [(2'*Z*):(2'*E*)]. Oxidation of the alcohol moiety within **342** was accomplished *via* treatment with DMP in CH_2Cl_2. Following purification *via* flash column chromatography, (2*Z*)-2-heptenal **343** was isolated in quantitative yield and 92:8 dr [(2'*Z*):(2'*E*)] (Scheme 77).



341 **342**, 83%, 92:8 dr [(2*Z*):(2*E*)] **343**, quant, 92:8 dr [(2*Z*):(2*E*)]

Scheme 77 *Reagents and conditions*: (i) H_2 (1 atm), Lindlar cat, quinoline, EtOAc, rt, 2 h; (ii) DMP, CH_2Cl_2, rt, 1 h.

Sulfone **340** was readily elaborated to **344** (representative of pseudodistomin A **1**) in 71% yield and 93:7 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)] (Scheme 78).



340 **344**, 71%, 93:7 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]

Scheme 78 *Reagents and conditions*: (i) KHMDS, **343**, THF, −78 °C, 30 min.

3.5.4.5 Method Conclusion

Given the success of both olefination reactions, and literature precedence for installing the remainder of the tail in the first instance,[1] it was concluded that the Julia-Kocieński olefination[14] would be used as the method to couple head and tail fragments in the synthesis of pseudodistomins A–F **1**–**6**.

3.6 Conclusion

In conclusion, this chapter has described the foundations of a general strategy for the synthesis of pseudodistomins A–F **1**–**6**. Firstly, the truncated iodolactone **214** has been selected as a key intermediate in the synthesis of pseudodistomins A–F **1**–**6**. Secondly, a range of routes to the isomeric piperidine head units, **229**, **222** and **225** have been devised. Finally, following extensive investigations, the Julia-Kocieński olefination[14] strategy has proved to be the most efficacious in the coupling of head and tail fragments (Figure 36).

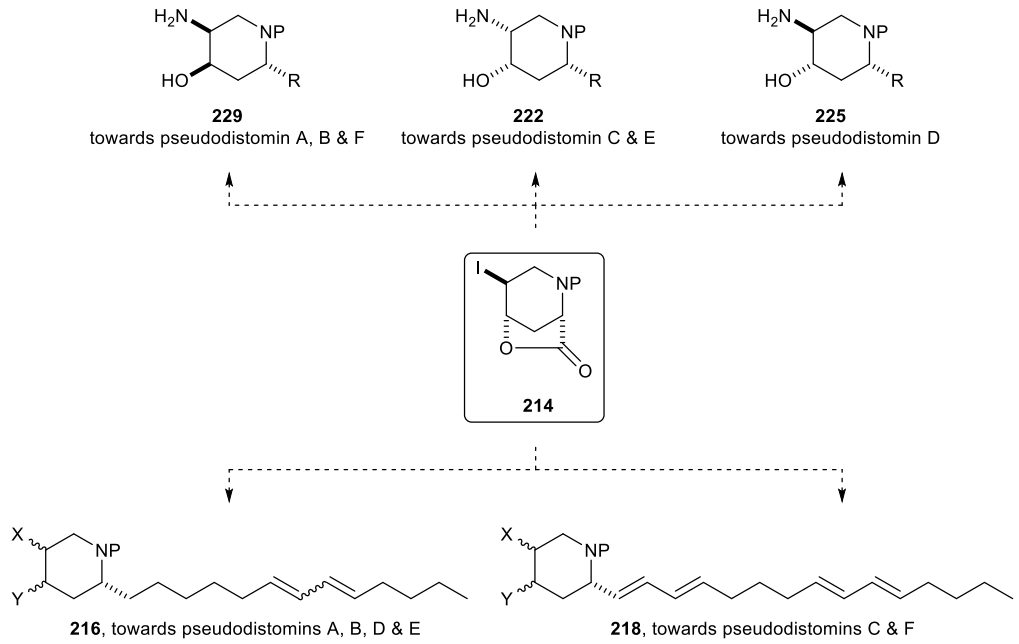


Figure 36 Chapter conclusions.

3.7 References and Notes

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Chapter 4

A Unified Synthesis of Pseudodistomins A–F

4.1 Chapter Outline

This chapter describes the development and execution of a general strategy for the asymmetric synthesis of pseudodistomins A–F **1**–**6** (Figure 37).

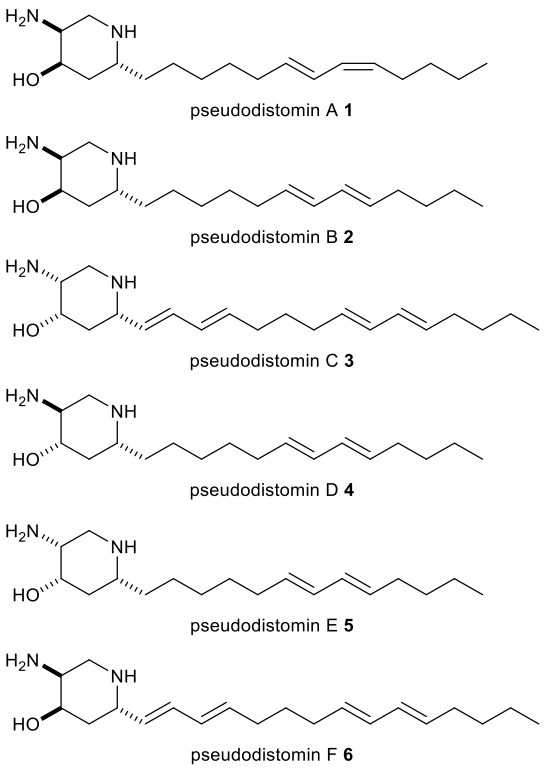


Figure 37 Structures of the pseudodistomin alkaloids.

4.2 Planning of a General Strategy

Extensive investigations of representative model systems concluded that the truncated iodolactone **214** could potentially be used as a key intermediate in the synthesis of pseudodistomins A–F **1**–**6**. It was anticipated that **214** could be elaborated to the two piperidine head fragments **345** and **346**. Julia-Kocieński olefination[1] of oxazolidinone aldehyde **345** and sulfone **320** would provide an intermediate *en route* to pseudodistomin E **5**. Alternatively, Julia-Kocieński olefination[1] of oxazolidinone aldehyde **345** with sulfone **321** would furnish an

intermediate for elaboration to pseudodistomin C **3**. Considering the epoxide containing head fragment **346**, Julia-Kocieński olefination[1] of **346** with sulfone **320** would provide an intermediate *en route* to pseudodistomins A **1**, B **2** and D **4**. Alternatively, Julia-Kocieński olefination[1] of **346** with sulfone **321** would furnish an intermediate for elaboration to pseudodistomin F **6** (Figure 38). Initial attention was thus directed towards an efficient synthesis of truncated iodolactone **214** (Section 4.3). Following this, derivatization of iodolactone **214** to provide key fragment **345** and subsequent Julia-Kocieński olefinations[1] are discussed (Section 4.4). Construction of **346** from **214** and ensuing Julia-Kocieński olefinations[1] are discussed (Section 4.5). Finally, manipulations of the head portions are reported, culminating in the asymmetric synthesis of pseudodistomins A–F **1–6** (Section 4.6).

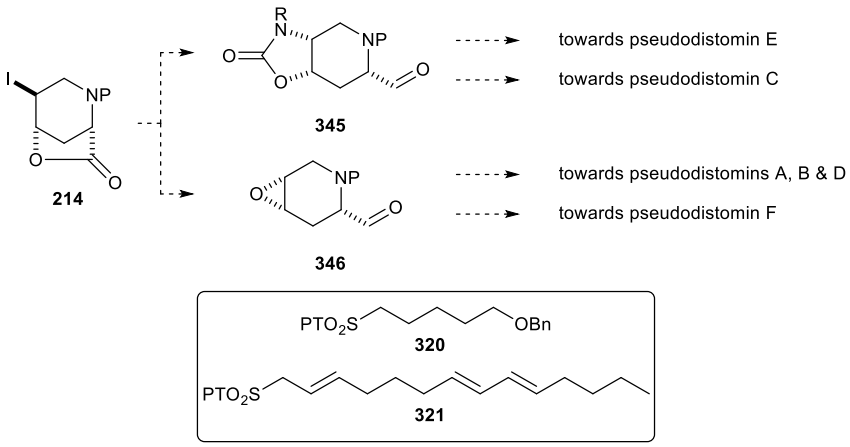


Figure 38 Proposed strategy for the synthesis of pseudodistomins A–F **1**–**6**.

4.3 Truncated Iodolactone Synthesis

Given the *N*-Boc protected iodolactone **349** had been previously reported by Riera *et al*.,[2] it was decided to attempt its construction as a priority. The literature report detailed an inefficient and only moderately yielding preparation of intermediate **348** in 96:4 er from **347**, which was then elaborated to iodolactone **349**. It was anticipated that simple changes to the synthetic route resembling work outlined in the synthesis of pseudodistomin E **5**[3] (*vide supra*) would allow also access to intermediate **348** from **129**, and the synthesis could be completed *via* protocols outlined in the original report by Riera *et al*. (Figure 39).[2]

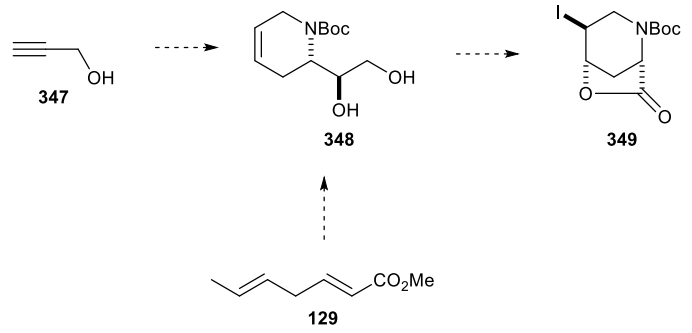
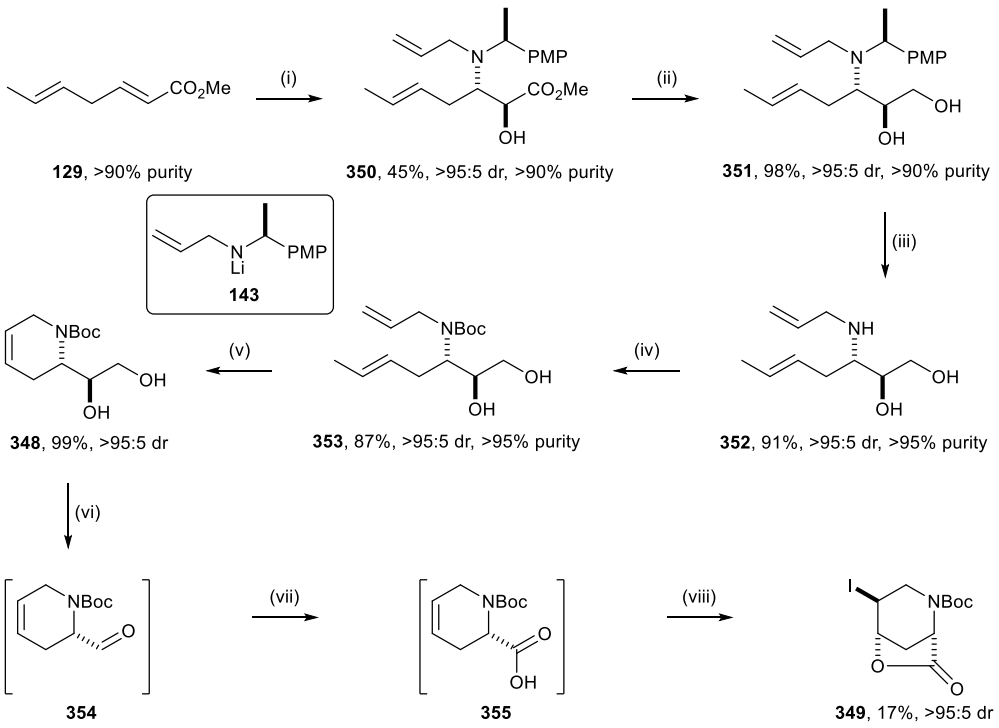


Figure 39 Literature and proposed syntheses of iodolactone **349**.

4.3.1 First-Generation Synthesis

α,β,-Unsaturated ester **129** was treated with lithium amide reagent **143** in THF at −78 °C before the addition of (+)-CSO. After purification, α-hydroxy β-amino ester **350** was obtained in 45% yield as a single diastereoisomer (>95:5 dr) in >90% purity. The stereochemical outcome of this reaction was assigned by analogy to the well-documented result of this aminohydroxylation reaction.[4] Despite several attempts at optimisation, involving changes in reaction concentration and stoichiometry, this result could not be improved upon. Reduction of the ester functionality within **350** was achieved *via* treatment with $LiAlH_4$ to afford the diol **351** in 98% yield. *N*-Deprotection was accomplished *via* acid mediated cleavage of the PMP moiety, to unveil secondary amine **352** in 91% yield as a single diastereoisomer (>95:5 dr). *N*-Protection of **352** as the *tert*-butyl carbamate followed by Grubbs I catalysed ring-closing metathesis gave the known tetrahydropyridine **348**[2] in 99% yield. Following procedures outlined by Riera *et al*.[2] the diol moiety within **348** was subjected to oxidative cleavage to furnish the intermediate aldehyde **354** which was further oxidised *via* Pinnick oxidation[5] to the carboxylic acid **355**. Iodocyclisation of **355** was achieved *via* treatment with I_2, KI and $NaHCO_3$, affording **349** with quantitative conversion, but only 17% isolated yield after column chromatography over three steps from **348** (Scheme 79). ^{1}H NMR spectroscopic analysis of the crude iodolactonization reaction mixture indicated full conversion of **355** to iodolactone **349**, and the mass return was adequate. Upon exposure to flash column chromatography **349** appeared to decompose to an unknown mixture of products and was thus responsible for the poor yield.



Scheme 79 *Reagents and conditions*: (i) **143**, THF, 2 h, −78 °C h then (+)-CSO, −78 °C to rt, 16 h; (ii) $LiAlH_4$, THF, −78 °C to rt, 16 h; (iii) TFA, CH_2Cl_2, rt, 16 h; (iv) $(Boc)_2O$, $NaHCO_3$, MeOH, rt, 16 h; (v) Grubbs I, CH_2Cl_2, rt, 16 h; (vi) $NaIO_4$, H_2O/THF (3:1), rt, 2 h; (vii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH/THF (2:1), rt, 16 h; (viii) I_2, KI, $NaHCO_3$, H_2O/CH_2Cl_2 (2:1), rt, 48 h.

Spectroscopic data for **349** were in agreement with the sample prepared by Riera *et al.*,[2] however the literature report unfortunately omitted any specific rotation data so a comparison could not be made. The relative configuration within **349** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 40). A Flack *x* parameter[6] of −0.003(9) for the crystal structure of **349** was also consistent with its assigned absolute (1*S*,4*S*,5*S*)-configuration.

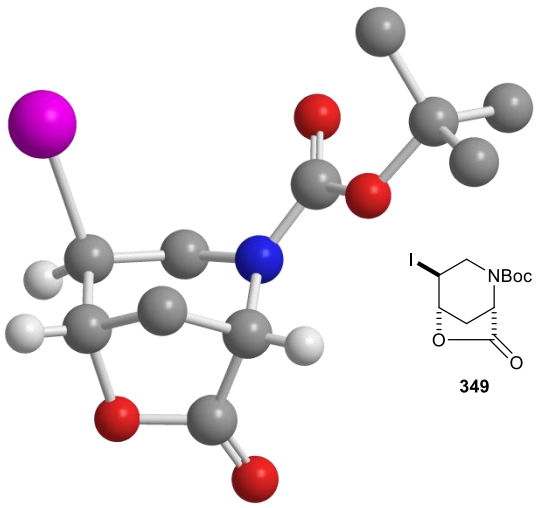
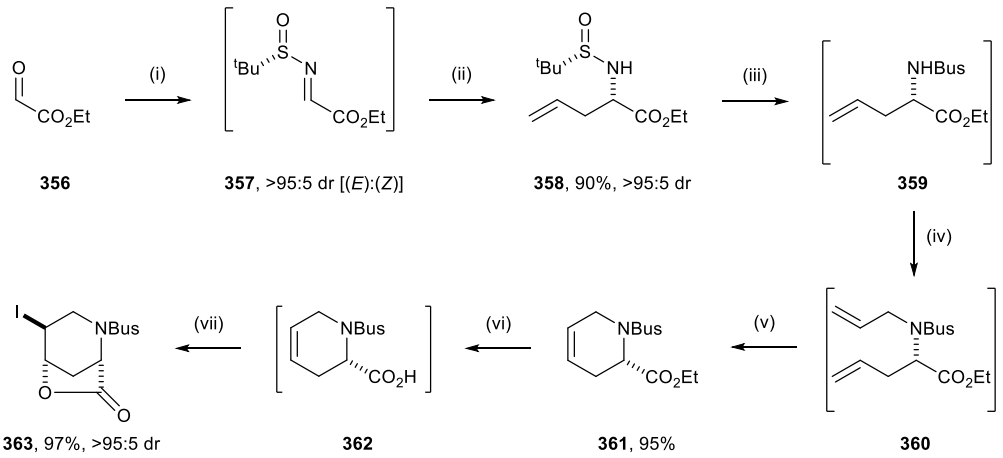


Figure 40 X-ray crystal structure of **349** (selected H atoms are omitted for clarity).

4.3.2 Second-Generation Synthesis

Given the low yielding and multistep first-generation synthesis, an alternative route to iodolactone **349** was devised, featuring ethyl glyoxalate **356** as the starting material. Condensation of **356** and (*S*)-*tert*-butylsulfinamide gave *N*-sulfinyl imine **357** which was treated as an intermediate. According to a previously reported procedure,[7] **357** was stirred with indium powder and allyl bromide in sat aq NaBr to afford the known[7] compound **358** in 90% yield and >95:5 dr. The absolute configuration within **358** has previously been established *via* elaboration to the known D-allylglycine.[7] A three step procedure was next developed involving oxidation of **358** with *m*CPBA, subsequent *N*-allylation and Grubbs I promoted ring-closing metathesis to furnish tetrahydropyridine **361** in 95% yield over three steps. Ester hydrolysis was accomplished with $LiOH{\cdot}H_2O$ to give the intermediate carboxylic acid **362**, which was reacted under iodolactonization conditions to afford *N*-Bus protected iodolactone **363** in 97% yield (over two steps) and >95:5 dr (Scheme 80).



Scheme 80 *Reagents and conditions*: (i) 50 °C, 5 min then (*S*)-*tert*-butylsulfinamide, 4Å MS, CH_2Cl_2, rt, 48 h; (ii) In, allyl bromide, sat aq NaBr, rt, 16 h; (iii) *m*CPBA, CH_2Cl_2, 0 °C to rt, 1 h; (iv) Cs_2CO_3, allyl bromide, DMF, 0 °C to rt, 2 h; (v) Grubbs I, CH_2Cl_2, rt, 16 h; (vi) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), rt, 48 h; (vii) I_2, $NaHCO_3$, MeCN, −20 °C, 2 h then −20 °C to rt, 16 h.

The relative configuration within **363** was confirmed *via* single crystal X-ray diffraction analysis (Figure 41). A Flack *x* parameter[6] of +0.005(7) for the crystal structure of **363** was also consistent with its assigned absolute (1*S*,4*S*,5*S*)-configuration, confirming that the

indium-mediated allyl addition to **357** had proceeded with the stereochemical outcome reported previously.[7]

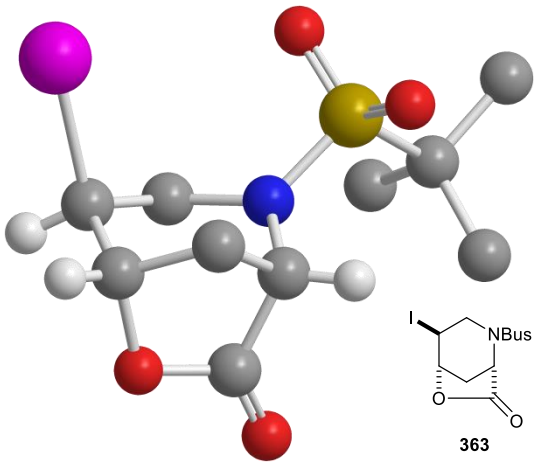
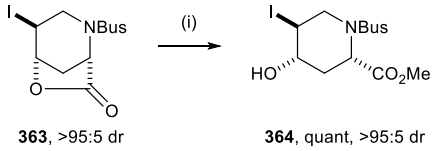


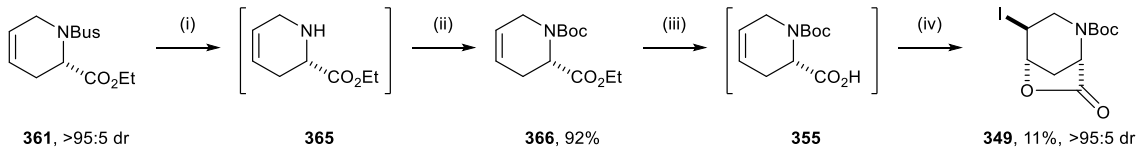
Figure 41 X-ray crystal structure of **363** (selected H atoms are omitted for clarity).

Iodolactone **363** was treated with TFA in MeOH in accordance with the protocol of Riera *et al.*[8] furnishing **364** in quantitative yield as a single diastereoisomer (>95:5 dr) after purification (Scheme 81).



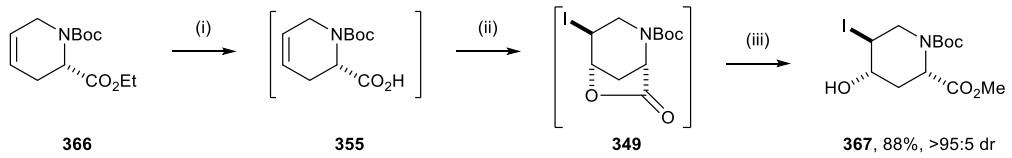
Scheme 81 *Reagents and conditions*: (i) TFA, MeOH, rt, 16 h.

With an efficient route to the *N*-Bus protected iodolactone **363** in hand, a simple route was devised to access the *N*-Boc protected iodolactone **349** also, in order to evaluate both protecting groups as the synthesis advanced. Thus, ester **361** was treated with TfOH to effect *N*-deprotection, the resultant secondary amine **365** was treated as an intermediate and allowed to react with $(Boc)_2O$ to effect *N*-Boc protection. After purification, the product **366** was isolated in 92% yield. **366** was subjected to the ester hydrolysis/iodolactonization procedure to give *N*-Boc substituted iodolactone **349** in 11% yield over two steps, and >95:5 dr (Scheme 82). Again, the low yielding final sequence was deemed to be a function of the instability of **349** upon purification *via* flash column chromatography.



Scheme 82 *Reagents and conditions*: (i) TfOH, anisole, CH_2Cl_2, 0 °C rt, 1 h; (ii) $(Boc)_2O$, Et_3N, MeOH, rt, 16 h; (iii) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), rt, 48 h; (iv) I_2, KI, $NaHCO_3$, H_2O/CH_2Cl_2 (2:1), rt, 48 h.

A method to avoid the degradation of **349** upon purification was sought, hence *N*-Boc protected iodolactone **349** was treated with TFA in MeOH in an analogous fashion to the protocol used on *N*-Bus protected iodolactone **363**. Thus, **366** was subjected to a three-step protocol, involving ester hydrolysis, iodolactonization and finally acid mediated ring-opening to furnish iodohydrin **367** in 88% yield over three steps (Scheme 83). The spectroscopic data for **367** were in agreement with those previously reported in the literature.[2] Iodohydrin **367** could thus be prepared in 69% yield over ten steps, with only four purifications, a significant improvement upon the 31% yield over nine steps and five purifications offered by the route of Riera *et al*.[8]



Scheme 83 *Reagents and conditions*: (i) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), rt, 48 h; (ii) I_2, KI, $NaHCO_3$, H_2O/CH_2Cl_2 (2:1), rt, 48 h; (iii) TFA, MeOH, rt, 16 h.

The relative configuration within **367** was confirmed unambiguously *via* single crystal X-ray diffraction analysis (Figure 42). A Flack *x* parameter[6] of −0.029(13) for the crystal structure of **367** was also consistent with its assigned absolute (2*S*,4*S*,5*S*)-configuration.

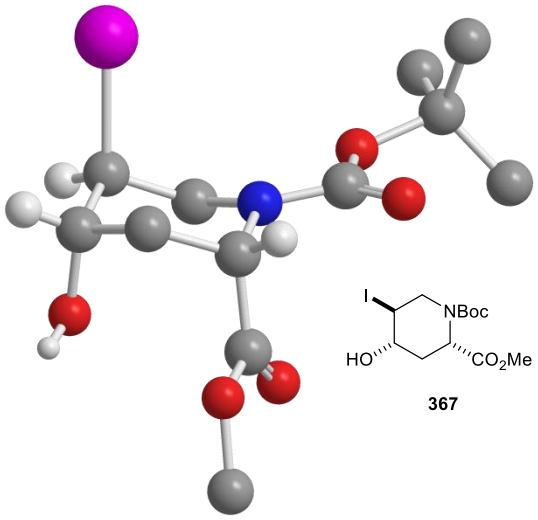


Figure 42 X-ray crystal structure of **367** (selected H atoms are omitted for clarity).

4.3.3 Section Conclusion

The second-generation synthesis offered efficient and scalable access to the iodolactones **363** and **349**. Derivatization of iodolactones, **363** and **349**, (to avoid purification issues in the latter case) furnished the key iodohydrins **364** and **367**, in 83% yield over seven steps with only three points of purification, and 69% yield over ten steps with only four points of purification, respectively (Figure 43). These results offered the ability to assess different *N*-protecting groups as the synthesis advanced.

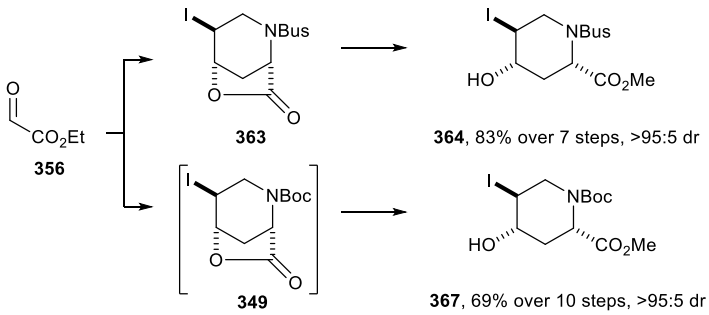


Figure 43 Summary of investigations into synthesis of iodolactones **363** and **349**.

4.4 Oxazolidinone Head Fragment Investigations

With iodohydrins **364** and **367** in hand, attention now turned to construction of the oxazolidinone within **369** in an analogous fashion to that developed for the synthesis of

pseudodistomin E **5**.[3] Manipulation of **368** would furnish **369**, a key intermediate on the synthetic route towards pseudodistomin C **3** and pseudodistomin E **5** (Figure 44).

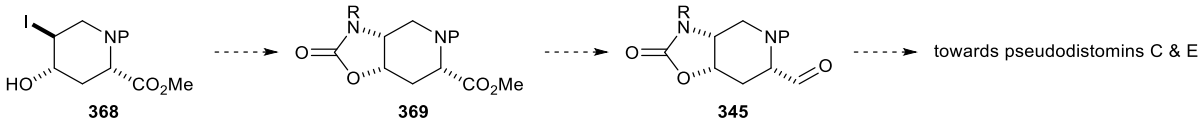
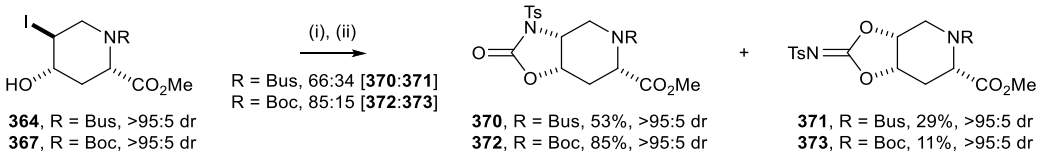


Figure 44 Proposed construction and elaboration of the oxazolidinone head fragment **345**.

4.4.1 Oxazolidinone Construction

N-Bus and *N*-Boc iodohydrins, **364** and **367**, were subjected to the previously reported procedures[3] to effect oxazolidinone formation with intramolecular iodide displacement. ^{1}H NMR spectroscopic analysis of the crude reaction mixture derived from **364** indicated a 66:34 mixture of **370** and **371** had been formed. Following purification, **370** was isolated in 53% yield, and **371** was isolated in 29% yield, respectively, as single diastereoisomers (>95:5 dr) in each case. ^{1}H NMR spectroscopic analysis of the crude reaction mixture derived from **367** indicated a 85:15 mixture of **372** and **373** had been formed. Purification gave **372** in 85% yield, and **373** in 11% yield, respectively, as single diastereoisomers (>95:5 dr) in each case (Scheme 84). The structures of **370**–**373** were assigned *via* a combination of IR data [~1790 cm^{-1} and ~1640 cm^{-1} for the carbonyl resonance of the *N*,*O*-carbonyl and *O*,*O*-(*N*-tosylamino) moieties, respectively] and diagnostic ^{13}C NMR peaks [~151 ppm and ~159 ppm for the carbonyl resonance of the *N*,*O*-carbonyl and *O*,*O*-(*N*-tosylamino) moieties, respectively]. Interestingly, no *O*,*O*-(*N*-tosylamino) species were isolated in the analogous reaction reported in the asymmetric synthesis of pseudodistomin E **5**.[3] Due to the greater success of the *N*-Boc system in the oxazolidinone formation protocol, it was decided to continue further investigations in this series only.



364, R = Bus, >95:5 dr
367, R = Boc, >95:5 dr

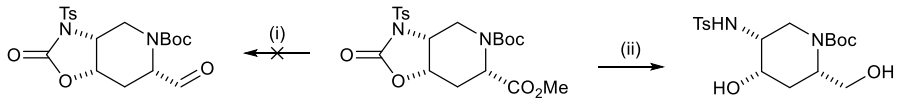
370, R = Bus, 53%, >95:5 dr
372, R = Boc, 85%, >95:5 dr

371, R = Bus, 29%, >95:5 dr
373, R = Boc, 11%, >95:5 dr

Scheme 84 *Reagents and conditions*: (i) TsNCO, THF, 0 °C to rt, 3 h; (ii) Et_3N, acetone, 60 °C, 3 h.

4.4.2 Ester Manipulations

Reduction of the ester functionality within **372** to aldehyde **373** (required for the Julia-Kocieński olefination)[1] with DIBAL-H was next attempted. ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated a complex mixture of products had been produced, with no aldehydic protons observed. Oxazolidinone **372** was instead treated with $LiAlH_4$, with the anticipation that given the reducing ability of $LiAlH_4$ reduction of the ester moiety within **372** to the alcohol would occur. However, the reaction gave a complex mixture of products, from which **374** was isolated in 17% yield and >95:5 dr (Scheme 85).



373

372, >95:5 dr

374, 17%, >95:5 dr

Scheme 85 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ii) $LiAlH_4$, THF, −78 °C to −40 °C, 4 h.

The relative configuration within **374** was confirmed unambiguously *via* single crystal X-ray diffraction analysis (Figure 45). A Flack *x* parameter[6] of −0.008(17) for the crystal structure of **374** was also consistent with its assigned absolute (2*S*,4*S*,5*S*)-configuration. This offered confirmation that intramolecular iodide substitution had occurred with inversion of configuration at C(5), validating the assignment of the absolute configuration within **372** and **373**.

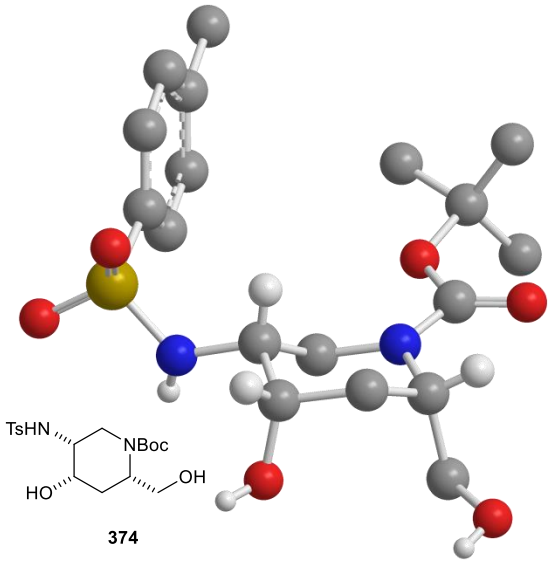
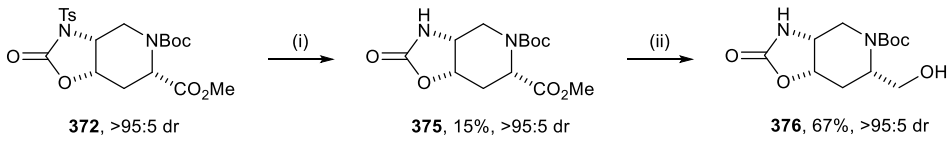


Figure 45 X-ray crystal structure of **374** (selected H atoms are omitted for clarity).

4.4.3 An Alternative Strategy

Attempts were made to reduce the susceptibility of the oxazolidinone moiety to reduction, with the anticipation that following *N*-Ts deprotection removal of the acidic *N*-H proton would offer *in situ* protection against further reaction of the oxazolidinone functionality. A detosylation reaction was carried out with sodium naphthalide (generated *in situ* from treatment of naphthalene with Na). The ^{1}H NMR spectrum of the crude reaction mixture was complex and thus uninterpretable. Problems were also encountered with purification, and **375** was isolated in only 15% yield. Treatment of **375** with $LiAlH_4$ effected reduction of the ester moiety and **376** was isolated in 67% yield as a single diastereoisomer (>95:5 dr) (Scheme 86).

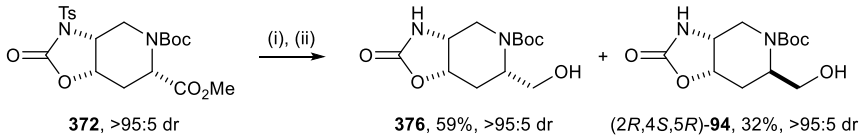


372, >95:5 dr **375**, 15%, >95:5 dr **376**, 67%, >95:5 dr

Scheme 86 *Reagents and conditions*: (i) $Na^{+}[C_{10}H_8]^{-}$, DME, −78 °C, 30 min; (ii) $LiAlH_4$, THF, −40 °C, 1.5 h.

With a promising, albeit low-yielding, route to **376** established, reaction telescoping was applied. Thus, **372** was treated with sodium naphthalide, and the residue was allowed to react with $LiAlH_4$ to give **376** in 59% yield (over two steps), and the known[9] epimer (2*R*,4*S*,5*R*)-**94** in 32% yield over two steps (Scheme 87). These results were indicative of an epimerisation

occurring at C(2). Due to the uninterpretable nature of ^{1}H NMR spectrum for both the crude reaction mixtures, the origin of the epimerisation could not be conclusively established.

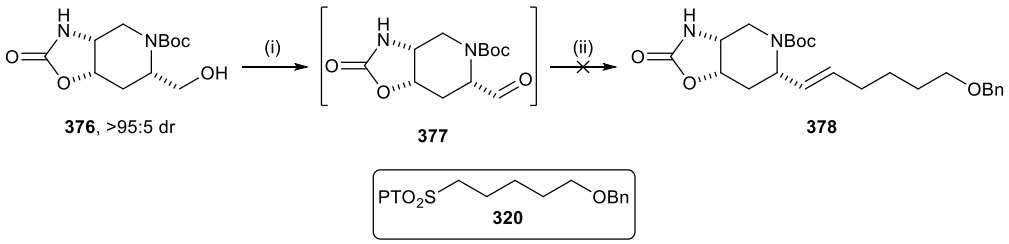


372, >95:5 dr **376**, 59%, >95:5 dr (2*R*,4*S*,5*R*)-**94**, 32%, >95:5 dr

Scheme 87 *Reagents and conditions*: (i) $Na^{+}[C_{10}H_8]^{-}$, DME, −78 °C, 30 min; (ii) $LiAlH_4$, THF, −78 °C to −40 °C, 4 h.

4.4.4 Julia-Kocieński Olefination

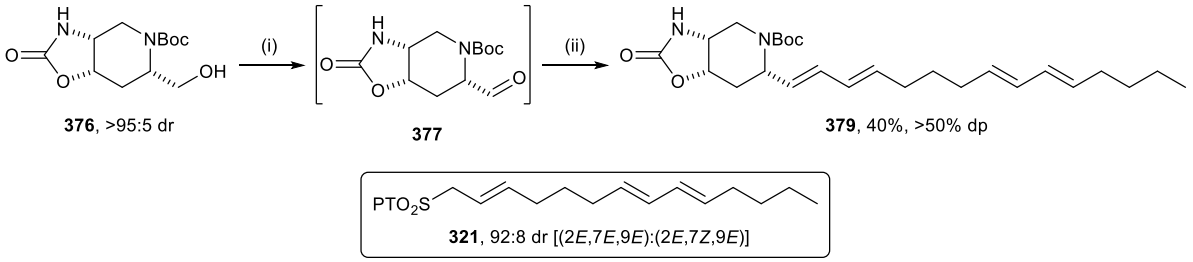
With alcohol **376** in hand, Julia-Kocieński olefinations[1] could now be attempted. Firstly, alcohol **376** was readily oxidised with DMP to furnish the key head fragment **377**. Sulfone **320** was reacted with aldehyde **377** to effect the Julia-Kocieński olefination[1] to construct an intermediate in the synthesis of pseudodistomin E **5**. ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated the reaction had generated a complex mixture of products, from which **378** could not be isolated upon attempted purification (Scheme 88).



376, >95:5 dr **377** **378** **320**

Scheme 88 *Reagents and conditions*: (i) DMP, CH_2Cl_2, rt, 1 h; (ii) **320**, KHMDS, THF, −78°C, 1 h then **377**, THF, −78 °C to rt, 16 h.

An analogous protocol was employed to effect olefination of aldehyde **377** with sulfone **321**. ^{1}H and ^{13}C NMR spectroscopic analysis of the crude reaction mixture indicated the newly formed olefin was produced in ~60:40 dr [(1'*E*):(1'*Z*)]. Following purification *via* flash column chromatography, the isomers were found not to be separable, and tetraene **379** (an intermediate for the proposed synthesis of pseudodistomin C **3**) was isolated in 40% yield and >50% dp (Scheme 89).



Scheme 89 *Reagents and conditions*: (i) DMP, CH_2Cl_2, rt, 1 h; (ii) **321**, KHMDS, 18c6, THF, −78°C, 1 h then **377**, THF, −78 °C to rt, 16 h.

4.4.5 Section Conclusion

At this point the synthetic advances were assessed, with three areas being raised as problematic. Firstly, the yield for the preparation of alcohol **376** from iodohydrin **367** was deemed to be prohibitively low (50% yield over two steps). Secondly, the Julia-Kocieński olefinations[1] resulted in poor or no success. Finally, the stereoselectivity of the Julia-Kocieński olefination[1] with the complex sulfone **321** was non-satisfactory. Thus, the synthetic route operating *via* the oxazolidinone head fragment was abandoned, and after evaluation of a further model system (*vide supra*) efforts were instead focused on the derivatization of the epoxide head fragment as a common intermediate in the syntheses of pseudodistomins A–F **1**–**6**.

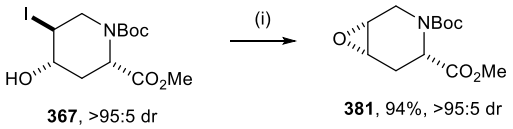
4.5 Epoxide Head Fragment Investigations

It was anticipated that the epoxide head **346** could be readily prepared from iodohydrin **368**, *via* sequential epoxide formation, and reduction/oxidation protocols (Figure 46).

Figure 46 Proposed construction and elaboration of the epoxide head fragment **346**.

4.5.1 Epoxide Construction

Iodohydrin **367** was treated with DBU in CH_2Cl_2 to effect epoxide formation, and after purification, **381** was isolated in 95% yield and >95:5 dr (Scheme 90).

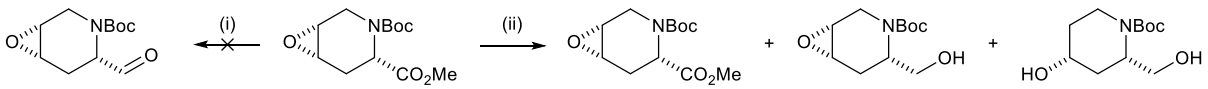


367, >95:5 dr **381**, 94%, >95:5 dr

Scheme 90 *Reagents and conditions*: (i) DBU, CH_2Cl_2, rt, 3 h.

4.5.2 Ester Manipulations

Firstly, controlled reduction of ester **381** to aldehyde **382** with DIBAL-H was trialled. ^{1}H NMR spectroscopic analysis of the crude reaction mixture was indicative of a complex mixture of products, with only trace amounts of aldehyde **382** present. It was therefore proposed that reduction of **381** to alcohol **383** (followed by a re-oxidation protocol) should be trialled. Thus, in a similar vein to investigations in the oxazolidinone series, **381** was cautiously treated with $LiAlH_4$ at −78 °C with warming to −40 °C to effect reduction to alcohol **383**. Following purification *via* flash column chromatography, unreacted **381** was isolated in 9% yield, epoxy-alcohol **383** was isolated in 71% yield, and the product of over-reduction **384** was isolated in 17% yield (Scheme 91). It was found *via* TLC reaction monitoring that the reaction was highly temperature sensitive, with little reaction progress at −78 °C, and significant over-reduction to **384** occurring at −20 °C.



382 **381**, >95:5 dr **381**, 9%, >95:5 dr **383**, 71%, >95:5 dr **384**, 17%, >95:5 dr

Scheme 91 *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h; (ii) $LiAlH_4$, THF, −78 °C to −40 °C, 4 h, rt.

4.5.3 Julia-Kocieński Olefinations

With the key epoxy-alcohol fragment **383** in hand, attention turned to the construction of the complete carbon backbones *via* the previously optimised Julia-Kocieński olefination[1] strategy. Oxidation of **383** to the intermediate aldehyde **382** with subsequent olefination with the aforementioned short or long sulfones, **320** or **321** respectively would furnish intermediates for the syntheses of pseudodistomins A **1**, B **2**, D **4** and E **5**, and for pseudodistomin C **3** and pseudodistomin F **6**, respectively (Figure 47).

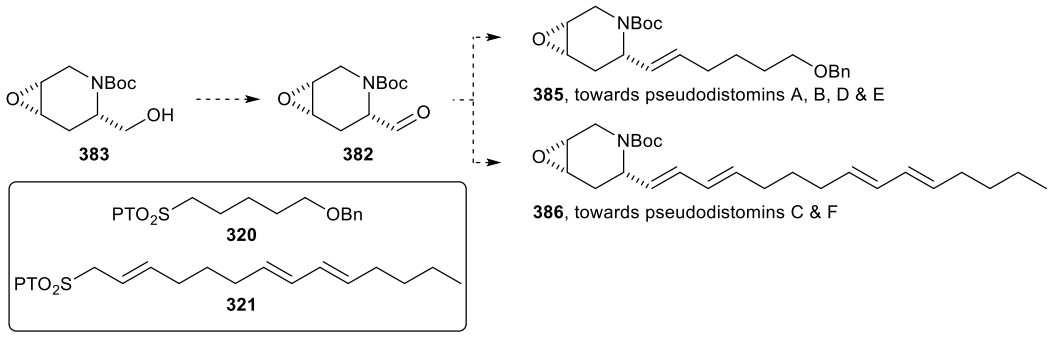
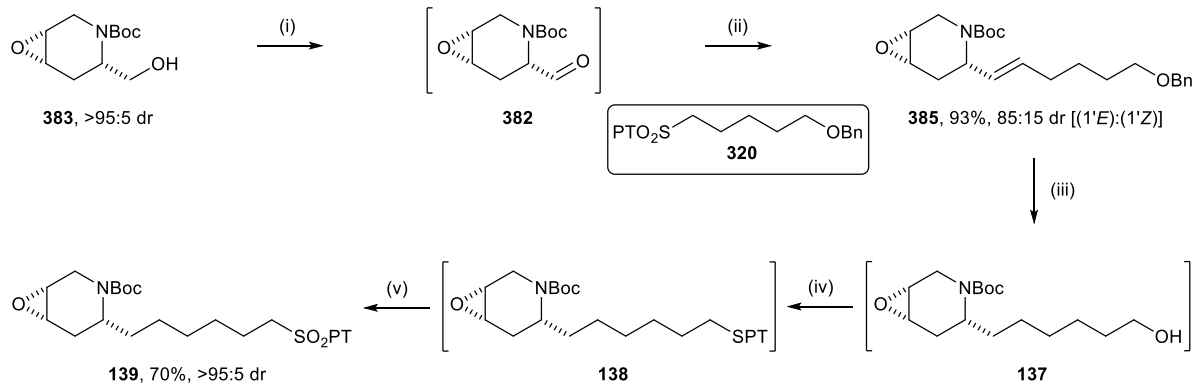


Figure 47 Proposed Julia-Kocieński olefination strategy to access pseudodistomins A–F **1**–**6**.

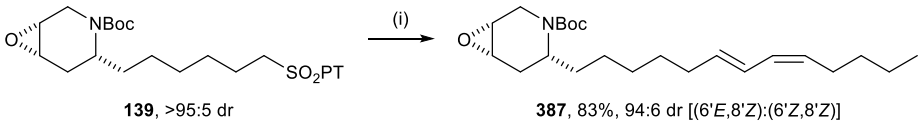
4.5.4 Towards Pseudodistomins A, B, D and E

DMP promoted oxidation of **383** furnished aldehyde **382** which was used immediately without purification. Reaction of the anion of **320** (prepared *via* treatment of **320** with KHMDS in THF) with aldehyde **382**, gave, after purification, **385** in 93% yield and 85:15 dr [(1'*E*):(1'*Z*)]. The mixture of olefin isomers was not deemed to be an issue as the **385** would next be subject to reduction *via* hydrogenation, thus converging on a common compound. Olefin **385** was next subjected to a three-step protocol involving tandem hydrogenation/hydrogenolysis, Mitsunobu reaction[10] of the alcohol moiety within **137** and finally oxidation of sulfur with *m*CPBA. Sulfone **139** was isolated in 70% yield and >95:5 dr after purification *via* flash column chromatography thus conclusively confirming the 85:15 dr [(1'*E*):(1'*Z*)] for **385** corresponds to a ratio of geometric olefin isomers (Scheme 92).



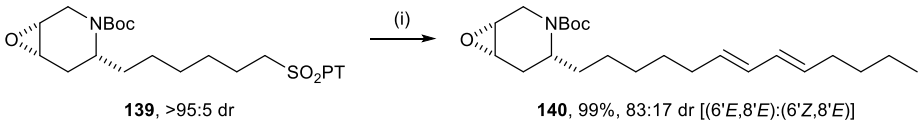
Scheme 92 *Reagents and conditions*: (i) DMP, CH_2Cl_2, rt, 1 h; (ii) **320**, KHMDS, THF, −78°C, 1 h then **382**, THF, −78 °C to rt, 16 h; (iii) H_2 (1 atm), $Pd(OH)_2$, EtOAc, rt, 2 h; (iv) DIAD, PPh_3, PTSH, THF, 0 °C to rt, 30 min; (v) *m*CPBA, CH_2Cl_2, 0 °C to rt, 16 h.

To construct the carbon backbone of pseudodistomin A **1**, KHMDS was added to a mixture of **139** and (*Z*)-2-heptenal **343** {92:8 dr [(2*Z*):(2*E*)]} in THF at −78 °C. Diene **387** was obtained following purification in 83% yield and 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)] (Scheme 93).



Scheme 93 *Reagents and conditions*: (i) **343**, KHMDS, THF, −78 °C, 30 min.

An analogous strategy was used to install the remainder of the carbon backbone required in pseudodistomins B **2**, D **4** and E **5**. Using a comparable protocol, with commercially available (2*E*)-2-heptenal **144** {>95:5 dr [(2*E*):(2*Z*)]} as the coupling partner gave diene **140** in 99% yield and 83:17 dr [(6'*E*,8'Z):(6'Z,8'Z)] (Scheme 94).

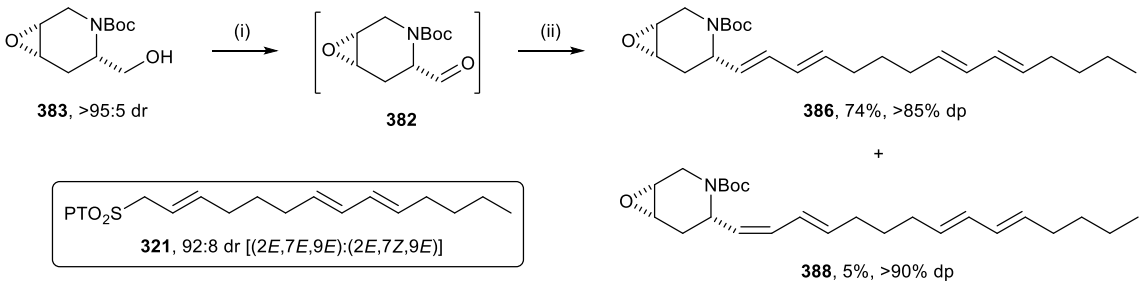


Scheme 94 *Reagents and conditions*: (i) **144**, KHMDS, THF, −78 °C, 30 min.

4.5.5 Towards Pseudodistomins C and F

The remaining coupling to be tested involved reaction of aldehyde **382** with sulfone **321** in order to assemble the carbon backbone of pseudodistomin C **3** and pseudodistomin F **6**. Thus, aldehyde **382** was reacted with sulfone **321** in the presence of 18c6.[11] ^{1}H and ^{13}C NMR

spectroscopic analysis of the crude reaction mixture indicated the newly formed olefin was formed in ~80:20 dr [(1'*E*):(1'*Z*)]. Following purification *via* flash column chromatography, the isomers were found to be partially separable, and the tetraene **386** was isolated in 74% yield and >85% dp. Also obtained was the C(1') geometric isomer **388** in 5% yield and >90% dp (Scheme 95).



Scheme 95 *Reagents and conditions*: (i) DMP, CH_2Cl_2, rt, 1 h; (ii) **321**, KHMDS, 18c6, THF, −78°C, 1 h then **382**, THF, −78 °C to rt, 16 h.

4.5.6 Section Conclusion

At this point, the recent synthetic advances were reviewed. Notably, epoxy-alcohol **383** could be constructed in fewer steps and higher yields than the analogous oxazolidinone-alcohol **376**. Additionally, the Julia-Kocieński olefinations[1] in the epoxy series were all successful, with higher stereoselectivity and partially separable geometric isomers in the epoxy-tetraene being considerable advantages. Thus, it was decided to focus efforts on construction of pseudodistomins A–F **1**–**6** from the epoxy series.

4.6 End Game

With efficient routes to construct the carbon backbones of pseudodistomins A–F **1**–**6**, the final challenges involved manipulation of the epoxide functionality within **389** to unveil pseudodistomins A–F **1**–**6**. It was anticipated that the all-*cis* head, found in pseudodistomin E **5** and pseudodistomin C **3**, could be accessed *via* treatment of the epoxide as the masked halohydrin **390** based on prior investigations (*vide supra*). Treatment of **389** with a

halide nucleophile would afford halohydrin **390**, which could be reacted in an analogous fashion to that developed on the model system (±)-**235** in order to construct the oxazolidinone within **392**. Removal of all protecting groups would unveil the all-*cis* head featured in pseudodistomin C **3** and pseudodistomin E **5**. To access the head unit present in pseudodistomin D **4**, epoxide **389** would be subjected to regioselective ring-opening with azide as outlined in the asymmetric synthesis of pseudodistomin D **4**.[12] Reduction of the azide moiety within **393** would unveil the required primary amine, and *N*-Boc deprotection would unveil the *trans* head unit, featured in pseudodistomin D **4**. Finally, the remaining *cis*-head unit, found in pseudodistomins A **1**, B **2** and F **6**, could be accessed *via* further derivatization of azide **393**. Staudinger reduction[13] of **393** with subsequent primary amine protection would afford **394**. Activation of the alcohol within **394** would allow an intramolecular displacement to occur, with inversion of configuration at C(4). Global deprotection would unveil the final isomeric head unit, featured in pseudodistomins A **1**, B **2** and F **6** (Figure 48).

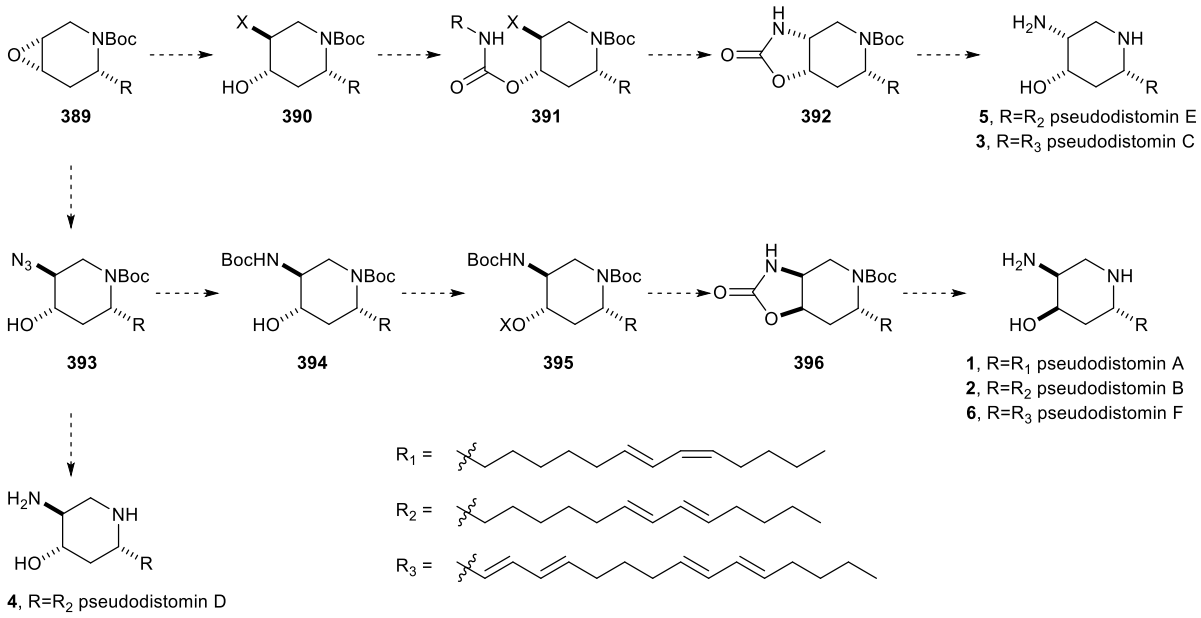
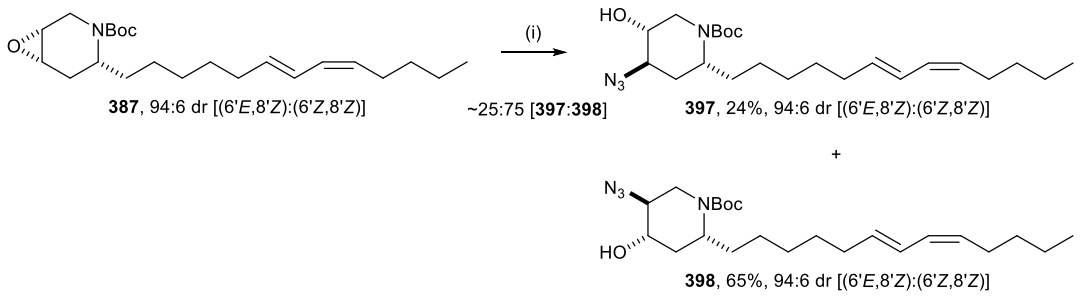


Figure 48 End game strategy to access pseudodistomins A–F **1**–**6**.

4.6.1 Asymmetric Synthesis of Pseudodistomin A

Epoxide **387** was treated with NaN_3 in DMSO at 80 °C to effect ring-opening. ^{1}H NMR spectroscopic analysis of the crude reaction mixture indicated a ~25:75 mixture of the regioisomeric products, **397** and **398**, respectively, had been generated. Following purification *via* flash column chromatography, **397** was isolated in 24% yield, and **398** was isolated in 65% yield, both in 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)] (Scheme 96).



Scheme 96 *Reagents and conditions*: (i) NaN_3, NH_4Cl, DMSO, 80 °C, 16 h.

NMR spectroscopic analyses (^{1}H, ^{13}C, COSY and HSQC techniques) were used to determine the structures of **397** and **398**, with diagnostic ^{13}C shifts observed for centres bearing azido (~62 ppm) or hydroxy (~69 ppm) moieties in each instance. The relative configurations within **397** and **398** could now be assigned from ^{1}H NMR ^3J coupling constant analyses, assuming chair conformations in solution in $CDCl_3$. Regarding **397**, notable coupling constants of ^3J 11.5 Hz between C(3)H_{axial} and C(4)*H*, and ^3J 11.9 Hz between C(6)H_{axial} and C(5)*H* were observed, indicating an ~180° dihedral angles between the respective protons in both instances according to the Karplus curve.[14] This implies C(4)*H* and C(5)*H* occupy axial sites, and thus, the C(4)-azido and C(5)-hydroxy functionalities within **397** must be adopting equatorial positions. The coupling constant of ^3J <7.0 Hz between C(3)H_{axial} and C(2)*H* is indicative of C(2)*H* adopting an equatorial site and thus the C(2)-alkyl group adopting an axial site. Regarding **398**, ^3J <7.0 Hz was observed between C(6)H_{axial} and C(5)*H* and between C(3)H_{axial} and C(4)*H*, indicating non *trans*-diaxial relationships between the respective protons in both instances according to the Karplus curve.[14] This is indicative of C(5)*H* and C(4)*H* adopting equatorial sites in both instances, and thus the C(4)-hydroxy and C(5)-azido substituents

residing on axial sites. Additionally, ^{3}J <7.0 Hz was observed between C(3)H_{axial} and C(2)*H*, indicative of C(2)*H* adopting an equatorial site, and thus the C(2)-alkyl group resides on an axial site. These conformations are consistent with 1,2-strain being minimised by placing the C(2)-alkyl substituent axial to avoid steric interactions with the *N*-Boc protecting group (Figure 49).

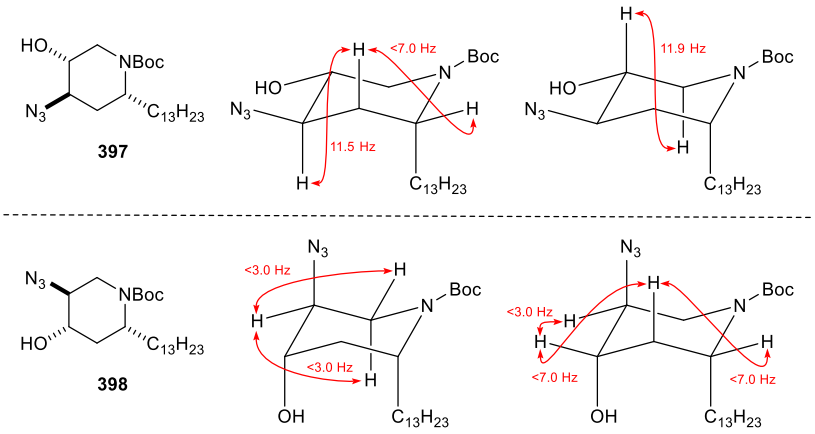
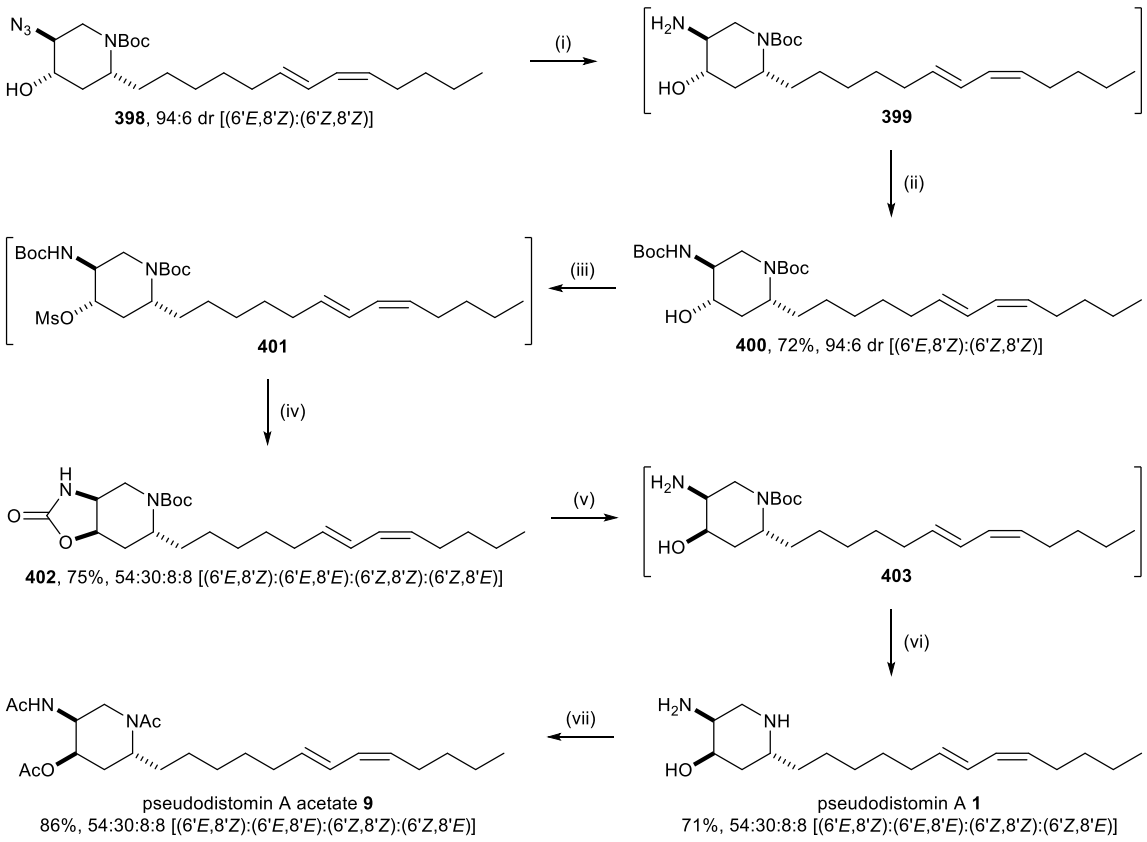


Figure 49 Conformational analysis of **397** and **398**.

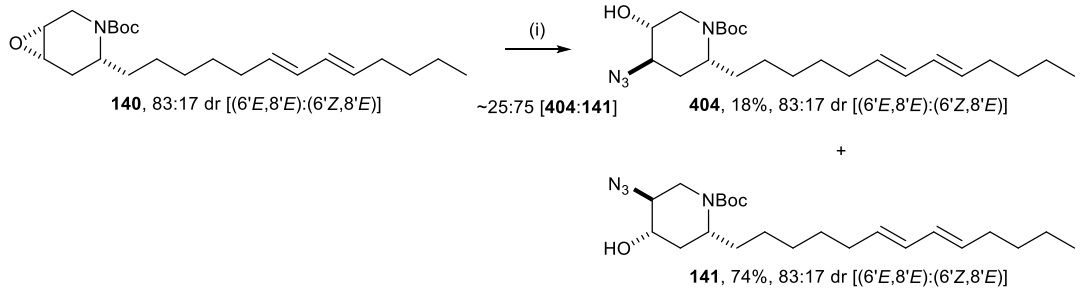
The azide moiety within **398** was subjected to Staudinger reduction[13] affording the intermediate amino-alcohol **399** which was immediately treated with $(Boc)_2O$ and Et_3N to effect *N*-protection, furnishing **400** in 72% yield and 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]. Following the higher yielding of the two developed protocols for oxazolidinone construction (*vide supra*), the alcohol moiety within **400** was activated and the resultant mesylate **401** was stirred in pyridine at 115 °C for 16 h. Following purification, oxazolidinone **402** was isolated in 75% yield and 54:30:8:8 dr [(6'*E*,8'*Z*):(6'*E*,8'*E*):(6'*Z*,8'*Z*):(6'*Z*,8'*E*)], indicative of an olefinic isomerisation occurring within the two-step sequence. The configuration of **402** was retrospectively assigned *via* inference following conformational analysis of pseudodistomin A **1**. The deprotection strategy outlined in the earlier synthesis of pseudodistomin E **5**[3] was employed to effect unveiling of pseudodistomin A **1** in 71% yield with conservation of diastereomeric integrity, i.e. 54:30:8:8 dr [(6'*E*,8'*Z*):(6'*E*,8'*E*):(6'*Z*,8'*Z*):(6'*Z*,8'*E*)]. Pseudodistomin A **1** was elaborated to the known pseudodistomin A acetate **9**[15] *via* treatment with Ac_2O in pyridine, furnishing **9** in 86% yield and 54:30:8:8 dr [(6'*E*,8'*Z*):(6'*E*,8'*E*):(6'*Z*,8'*Z*):(6'*Z*,8'*E*)] (Scheme 97).



Scheme 97 *Reagents and conditions*: (i) polymer-supported PPh_3, THF/H_2O (10:1), 70 °C, 16 h; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 16 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h; (iv) pyridine, 115 °C, 16 h; (v) KOH, MeOH, 70 °C, 6 h; (vi) HCl, MeOH, 70 °C, 3 h; (vii) Ac_2O, pyridine, rt, 1.5 h.

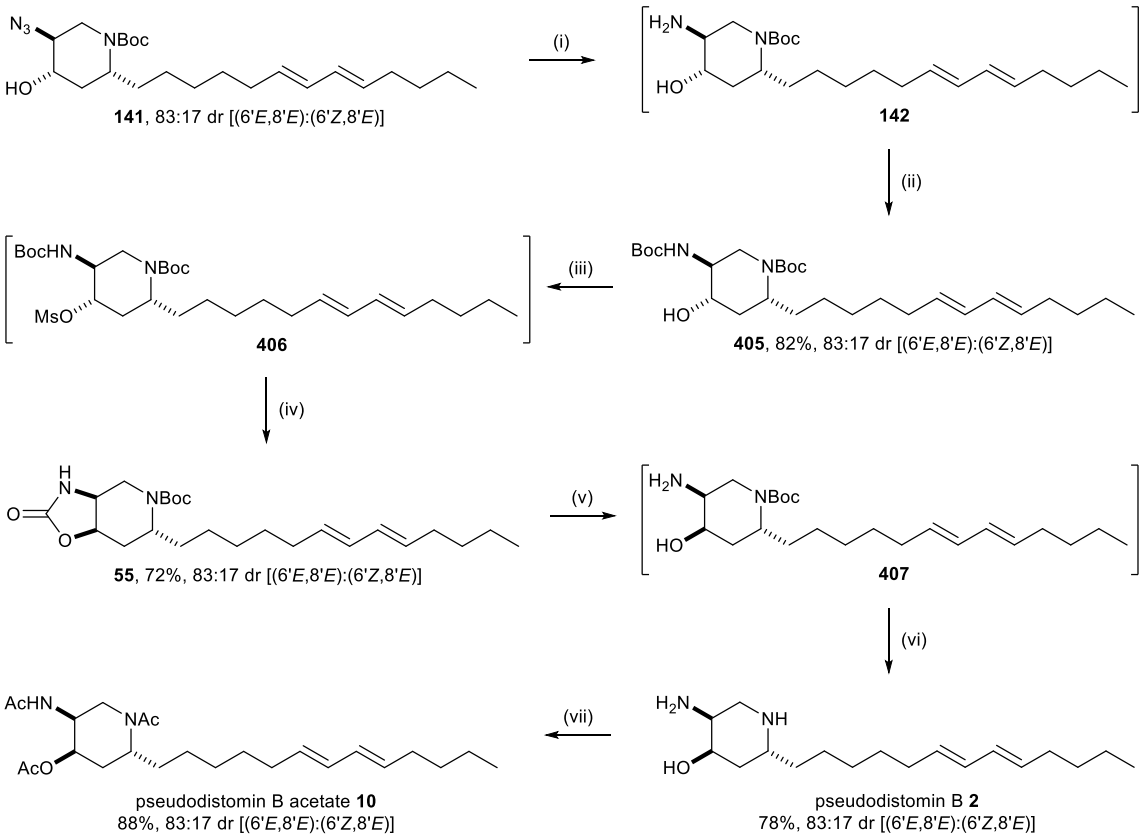
4.6.2 Asymmetric Synthesis of Pseudodistomin B

Following an analogous route outlined in the asymmetric syntheses of pseudodistomin D **4**[12] and pseudodistomin A **1**, epoxide **140** was reacted with NaN_3 to furnish the known[12] compounds **404** in 18% yield, and **141** in 74% yield, with both samples exhibiting conservation of diastereomeric integrity {83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]} during the transformation (Scheme 98).



Scheme 98 *Reagents and conditions*: (i) NaN_3, NH_4Cl, DMSO, 80 °C, 16 h.

An analogous reaction sequence was applied to **141** as outlined in the synthesis of pseudodistomin A **1**. Thus **141**, was converted to the known[16] pseudodistomin B **2** in 46% yield over six steps, and pseudodistomin B acetate **10** in 41% yield over seven steps, with both samples exhibiting 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)] indicating conservation of stereochemical integrity in this case (Scheme 99). Identical conditions were applied in the syntheses of pseudodistomin A **1** and pseudodistomin B **2**, however olefinic isomerisation was only observed in the synthesis of pseudodistomin A **1** during the two-step oxazolidinone formation.

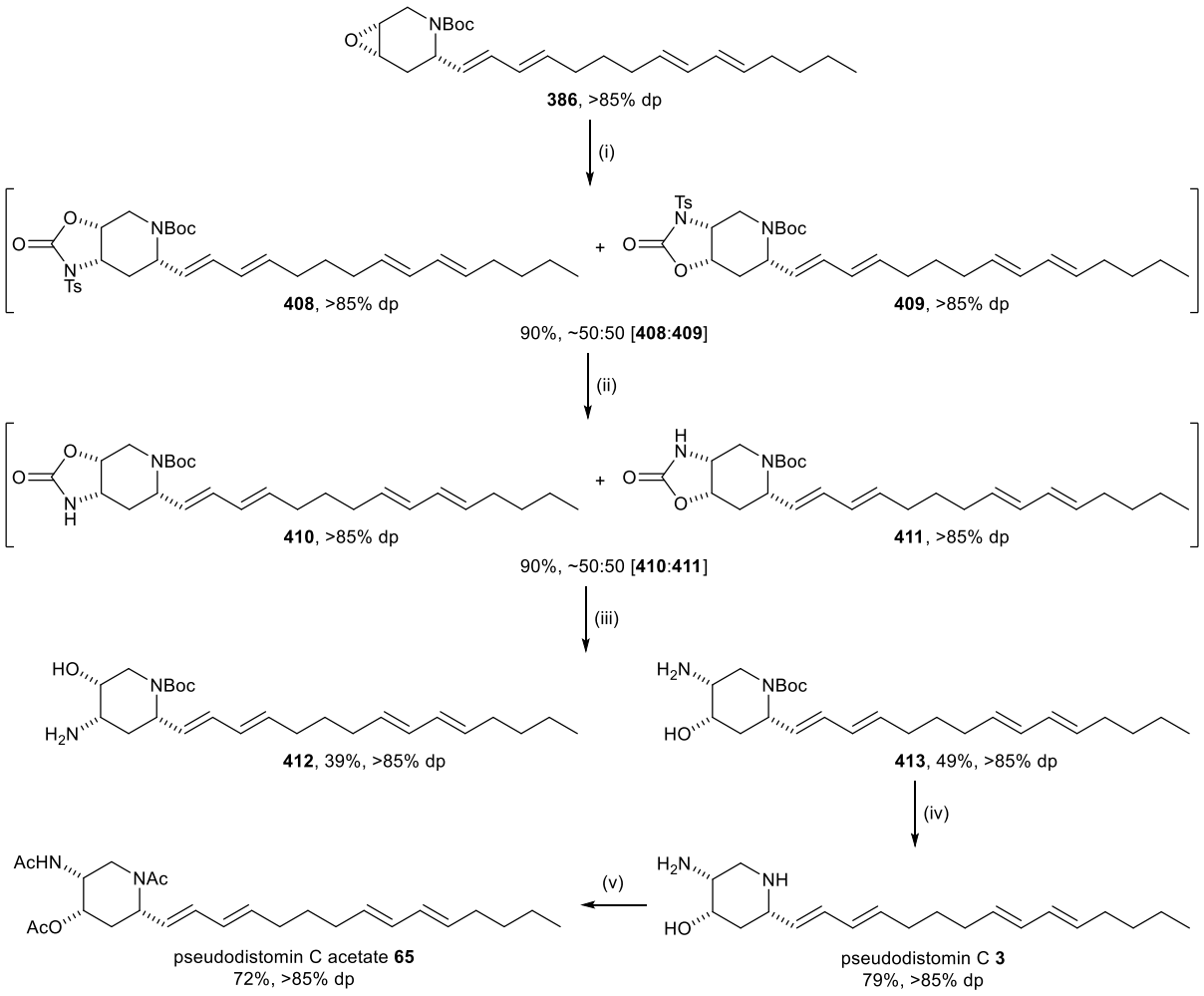


Scheme 99 *Reagents and conditions*: (i) polymer-supported PPh_3, THF/H_2O (10:1), 70 °C, 16 h; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 16 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h; (iv) pyridine, 115 °C, 16 h; (v) KOH, MeOH, 70 °C, 6 h; (vi) HCl, MeOH, 70 °C, 3 h; (vii) Ac_2O, pyridine, rt, 1.5 h.

4.6.3 Asymmetric Synthesis of Pseudodistomin C

Epoxide **386** was treated with TBAI in the presence of TsNCO[17] to afford an inseparable ~50:50 mixture of the regioisomeric oxazolidinones **408** and **409** in 90% yield. The mixture was treated with sodium naphthalide to effect destosylation, furnishing an inseparable ~50:50 mixture of **410** and **411** in 90% yield. Oxazolidinone cleavage was achieved *via*

treatment of the mixture of **410** and **411** with aqueous base to give **412** in 39% yield, and **413** in 49% yield, both in >85% dp. Amino-alcohol **413** was allowed to react with methanolic HCl to effect *N*-deprotection, unveiling pseudodistomin C **3** in 79% yield and >85% dp indicative of conservation of stereochemical integrity. Pseudodistomin C **3** was elaborated to pseudodistomin C acetate **65** in 72% yield and >85% dp (Scheme 100). Configurations of **408**–**413** were retrospectively assigned *via* inference following conformational analysis of pseudodistomin C **3**.

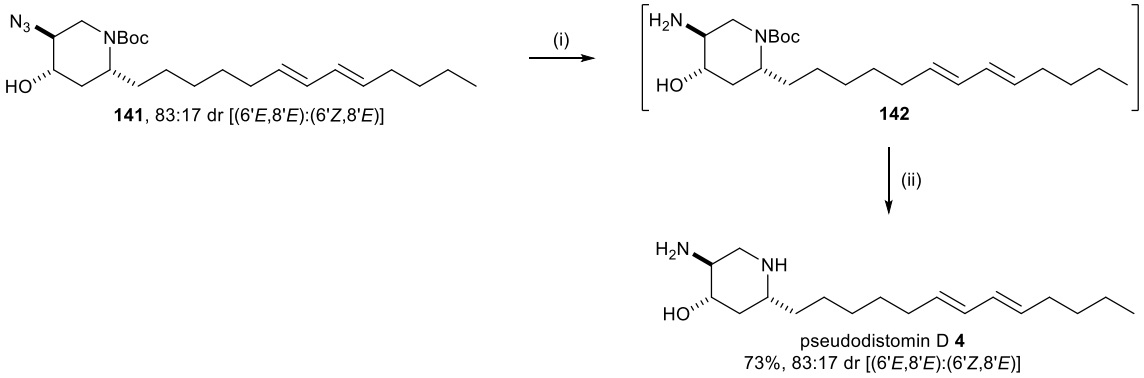


Scheme 100 *Reagents and conditions*: (i) TsNCO, TBAI, PhMe, 100 °C, 16 h; (ii) $Na^+[C_{10}H_8]^-$, THF, −78 °C, 30 min; (iii) KOH, MeOH, 70°C, 6 h; (iv) HCl, MeOH, 70 °C, 3 h; (v) Ac_2O, pyridine, rt, 1.5 h.

4.6.4 Asymmetric Synthesis of Pseudodistomin D

In a telescoped approach to work previously described,[12] azido-alcohol **141** was subjected to Staudinger reduction[13] to give the intermediate amino-alcohol **142**, which was immediately

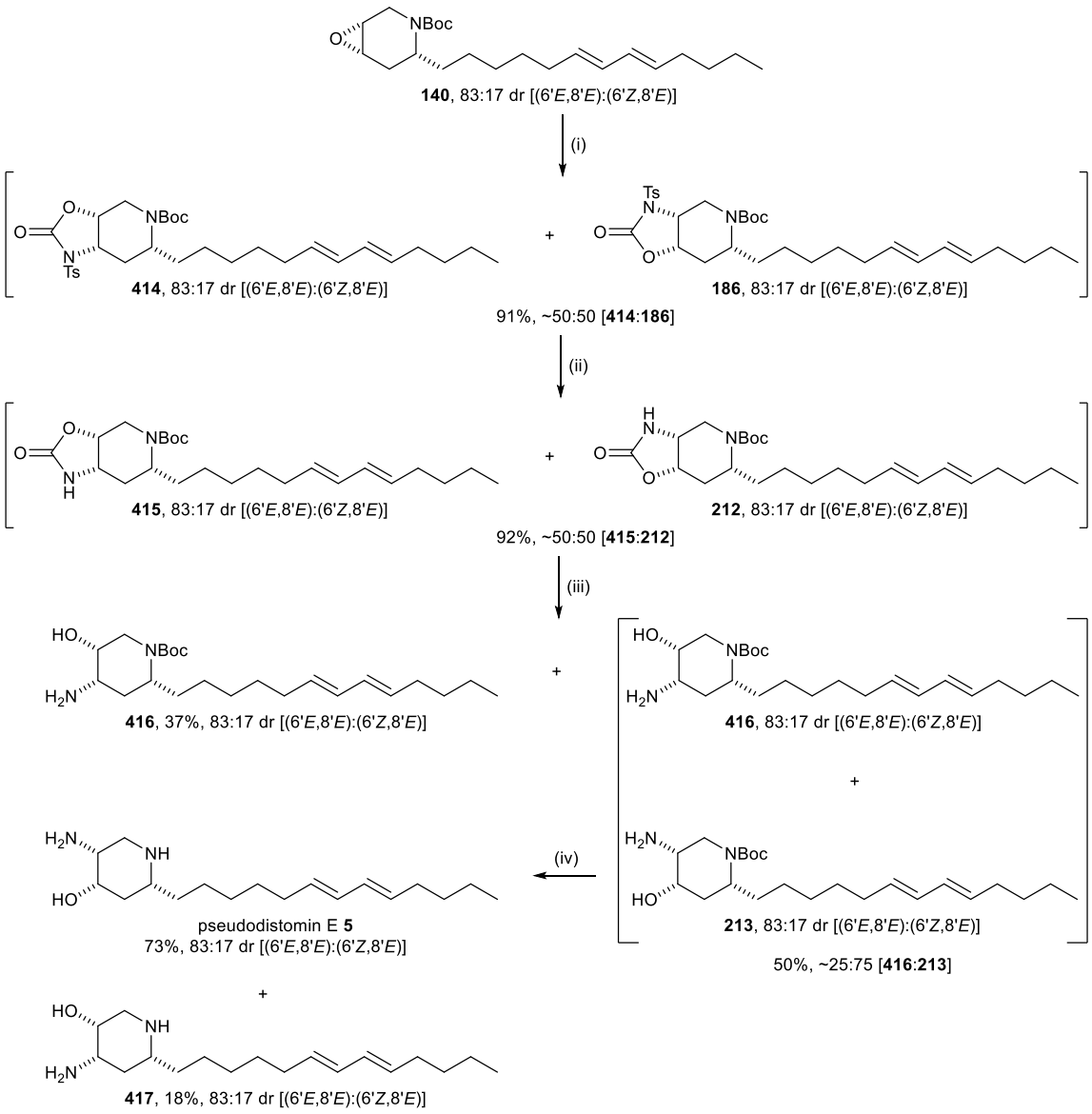
exposed to methanolic HCl, to afford, after purification, pseudodistomin D **4** in 73% yield and 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)] (Scheme 101).



Scheme 101 *Reagents and conditions*: (i) polymer-supported PPh_3, THF/H_2O (10:1), 70 °C, 16 h; (ii) HCl, MeOH, 70 °C, 3 h.

4.6.5 Asymmetric Synthesis of Pseudodistomin E

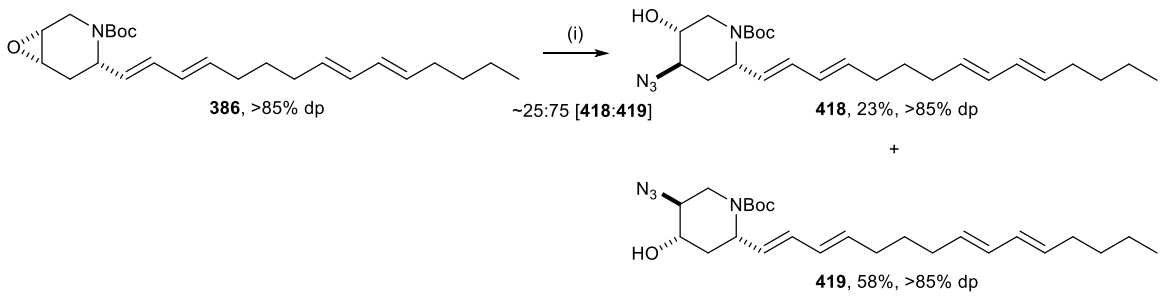
Utilising an analogous series of transformations as described in the synthesis of pseudodistomin C **3**, epoxide **140** was readily converted to pseudodistomin E **5** in 31% yield and 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)] (Scheme 102). The configurations of **414**–**416** were retrospectively assigned *via* comparison of data for pseudodistomin E **5** with previously reported data,[3] and the expected stereochemical outcomes for the S_N2 type processes occurring in the construction of the oxazolidinone moiety.



Scheme 102 *Reagents and conditions*: (i) TsNCO, TBAI, PhMe, 100 °C, 16 h; (ii) $Na^+[C_{10}H_8]^-$, THF, −78 °C, 30 min; (iii) KOH, MeOH, 70°C, 6 h; (iv) HCl, MeOH, 70 °C, 3 h.

4.6.6 Asymmetric Synthesis of Pseudodistomin F

The aforementioned ring-opening protocol was applied to **386**, affording the regioisomeric azido-alcohols **418** and **419** in 23% and 58% yield, respectively, both in >85% dp (Scheme 103).



Scheme 103 *Reagents and conditions*: (i) NaN_3, NH_4Cl, DMSO, 80 °C, 16 h.

NMR spectroscopic analyses (^{1}H, ^{13}C, COSY and HSQC techniques) were used to determine the structures of **418** and **419**, with diagnostic ^{13}C shifts observed for centres bearing azido (~61 ppm) or hydroxy (~ 69 ppm) moieties in each instance. The relative configurations within **418** and **419** could now be assigned from ^{1}H NMR ^3J coupling constant analyses, assuming chair conformations in solution in $CDCl_3$. Regarding **418**, notable coupling constants of ^3J 12.7 Hz between C(3)H_{axial} and C(4)*H*, and ^3J 10.3 Hz between C(6)H_{axial} and C(5)*H* were observed, indicating an ~180° dihedral angles between the respective protons in both instances according to the Karplus curve.[14] This is indicative of C(4)*H* and C(5)*H* residing on axial sites, and thus the C(4)-azido and C(5)-hydroxy groups must be adopting equatorial sites. The coupling constant of ^3J 5.7 Hz between C(3)H_{axial} and C(2)*H* is indicative of C(2)*H* adopting an equatorial site, and thus the C(2)-alkyl group adopting an axial site. Regarding **419**, ^3J <3.0 Hz was observed between C(6)H_{axial} and C(5)*H*, and ^3J <7.0 Hz was between C(3)H_{axial} and C(4)*H*, indicating non *trans*-diaxial relationships between the respective protons in both instances according to the Karplus curve.[14] This is suggestive of C(4)*H* and C(5)*H* occupying equatorial sites, and thus the C(4)-hydroxy and C(5)-azido groups must be adopting axial sites. Additionally, ^3J <7.0 Hz was observed between C(3)H_{axial} and C(2)*H*, indicative of C(2)*H* adopting an equatorial site, and thus the C(2)-alkyl group adopting an axial site. These conformations are consistent with 1,2-strain being minimised by placing the C(2)-alkyl substituent axial to avoid steric interactions with the *N*-Boc protecting group (Figure 50).

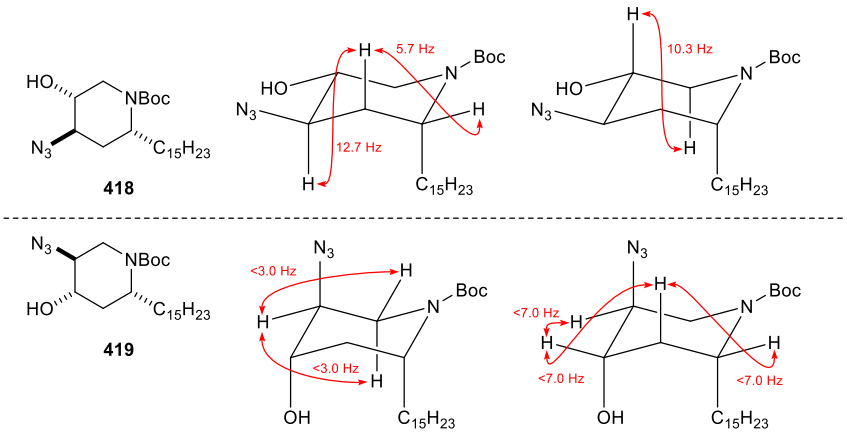
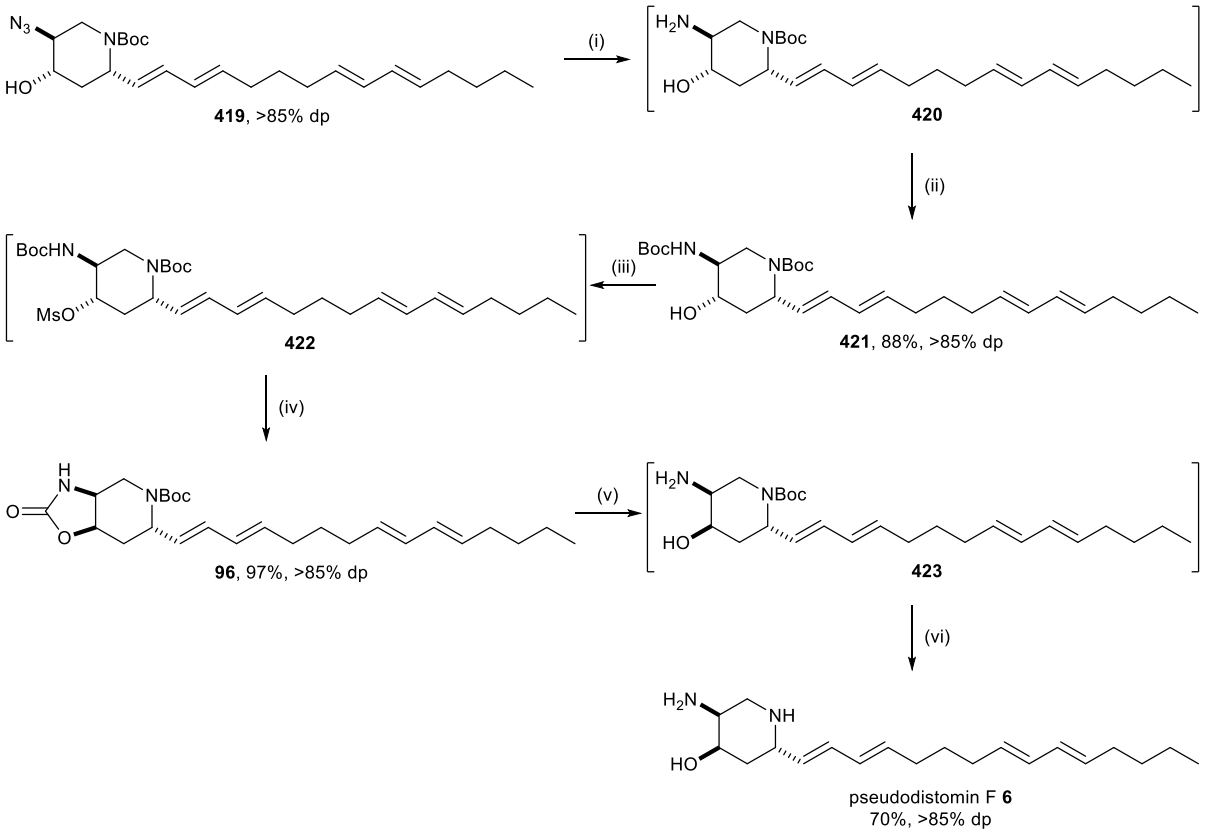


Figure 50 Conformational analysis of **418** and **419**.

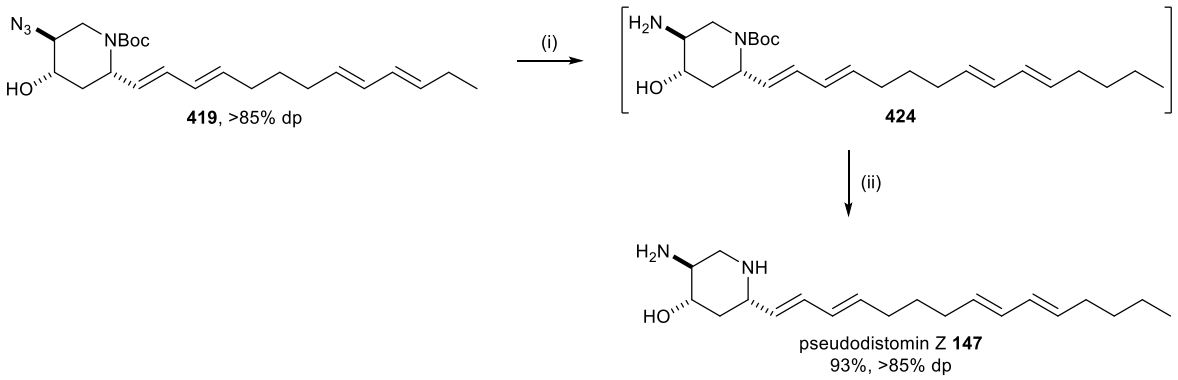
Azido-alcohol **419** was exposed to the successful reaction sequences demonstrated in the synthesis of pseudodistomin A **1** and pseudodistomin B **2** to afford pseudodistomin F **6** in 60% yield and >85% dp over six steps (Scheme 104).



Scheme 104 *Reagents and conditions*: (i) polymer-supported PPh_3, THF/H_2O (10:1), 70 °C, 16 h; (ii) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 16 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 16 h; (iv) pyridine, 115 °C, 16 h; (v) KOH, MeOH, 70 °C, 6 h; (vi) HCl, MeOH, 70 °C, 3 h.

4.6.7 Asymmetric Synthesis of Pseudodistomin Z

In order to demonstrate the applicability of the developed methodology in the construction of non-natural pseudodistomin analogues, **419** was subjected to the two-step reaction sequence outlined in the synthesis of pseudodistomin D **4**, to afford a new pseudodistomin **147** (herein named as pseudodistomin Z **147**) in 93% yield and >85% dp (Scheme 105).



Scheme 105 *Reagents and conditions*: (i) polymer-supported PPh_3, THF/H_2O (10:1), 70 °C, 16 h; (ii) HCl, MeOH, 70 °C, 3 h.

4.7 Conclusion

In conclusion, a range of routes to construct the iodolactone **214** have been assessed. A new route was designed and executed to construct *N*-Boc iodohydrin **367** in higher yield and with fewer modes of purification than existing methods.[8] Evaluation of the oxazolidinone containing series of compounds revealed that preparation and subsequent derivatizations were low yielding and offered disappointing stereoselectivities. Efforts were focused in the epoxide series, with comprehensive investigations allowing the construction of the pseudodistomin carbon backbones, represented in **386**, **387** and **140** (Figure 51).

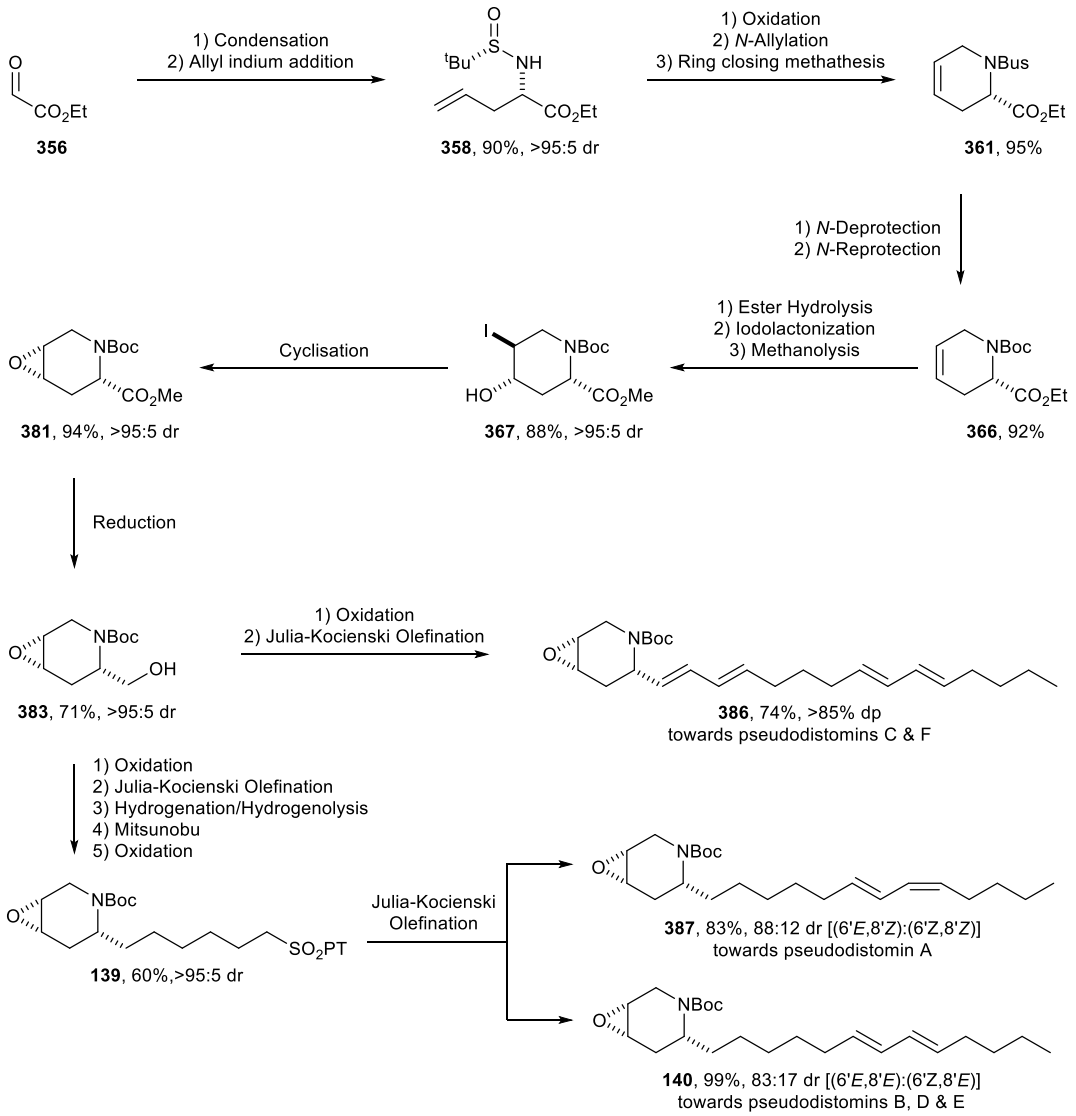


Figure 51 Summary of the preparation of key fragments **386**, **387**, and **140**.

The key fragments, **387**, **140** and **386** were elaborated to pseudodistomins A–F **1–6** *via* manipulation of the epoxide moieties. Pseudodistomins A–F **1–6** were constructed in between eighteen and twenty-five steps, >95:5 er[18] and in overall yields of 6–16%, with the average yield per transformation being 90%. A representative non-natural analogue **147** was also prepared to demonstrate the ready applicability of the methods reported to the construction of a library of pseudodistomins (Figure 52).

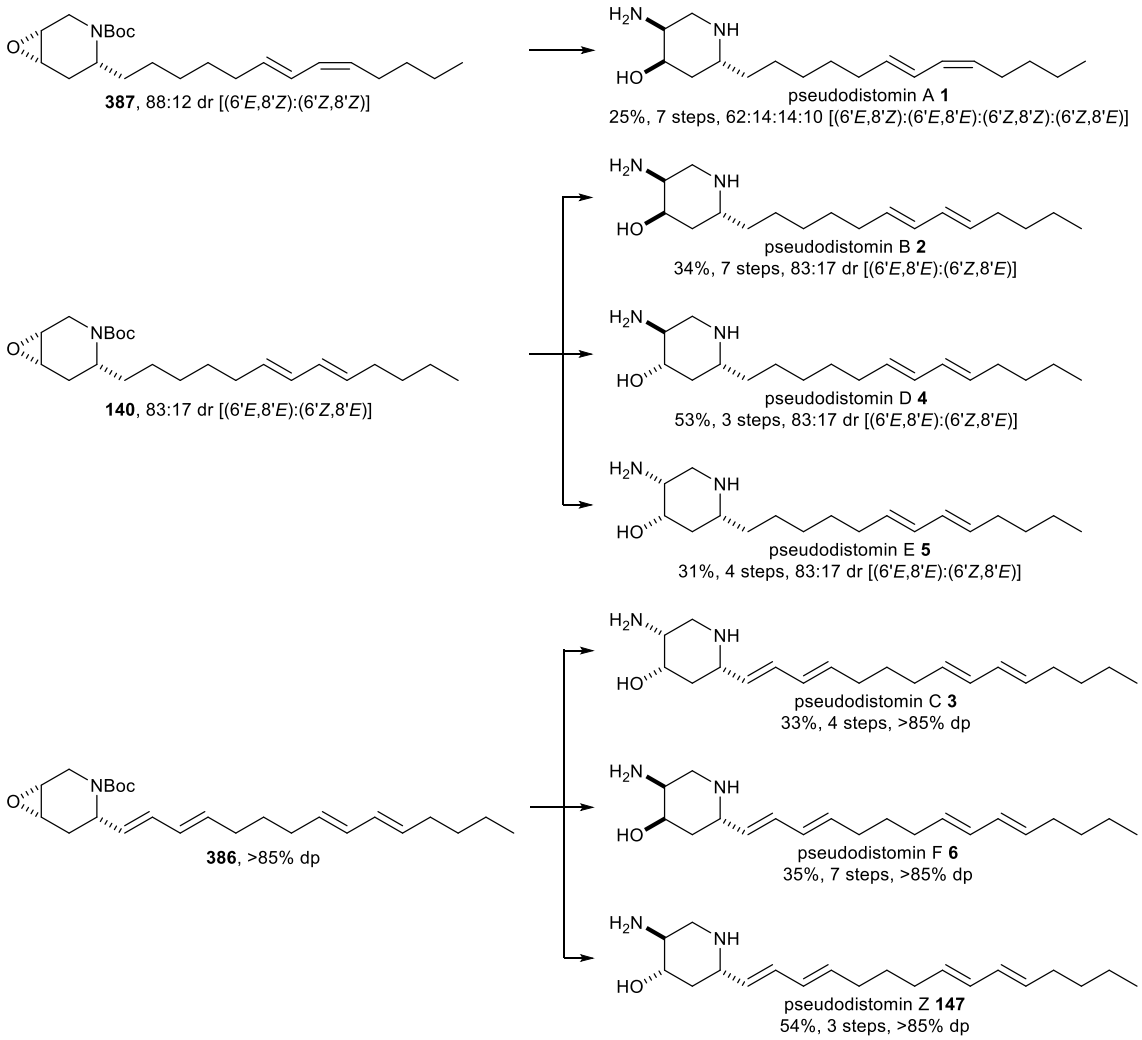


Figure 52 Asymmetric synthesis of pseudodistomins A–F **1**–**6** and pseudodistomin Z **147**.

Full conformational analysis of pseudodistomins A–F **1**–**6** and comparison with literature data is reported in the following chapter.

4.8 References and Notes

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[17] Speranza, G. P.; Peppel, W. J. *J. Org. Chem.* **1958**, *23*, 1922.
[18] The enantiomeric purity of **4** was confirmed as >95:5 er by ^{1}H NMR spectroscopic analyses in the presence of (*S*)-*O*-acetylmandelic acid and (*RS*)-*O*-acetylmandelic acid; see: Parker, D. *Chem. Rev*. **1991**, *91*, 1441. This value is consistent with conservation of the er obtained in the indium-mediated allyl addition to **357**. As all compounds *en route* are derivatives of **357** (>95:5 er), and conservation of er has been demonstrated in **4**, the er of all compounds derived from **357** can be assumed to be >95:5 er.

Chapter 5

Data Analysis of Pseudodistomins A–F

5.1 Chapter Outline

This chapter presents independent assignment of relative configurations for pseudodistomins A–F **1**–**6** and Z **147**, followed by specific rotation and spectroscopic data comparison with all other previous reports (Figure 53).

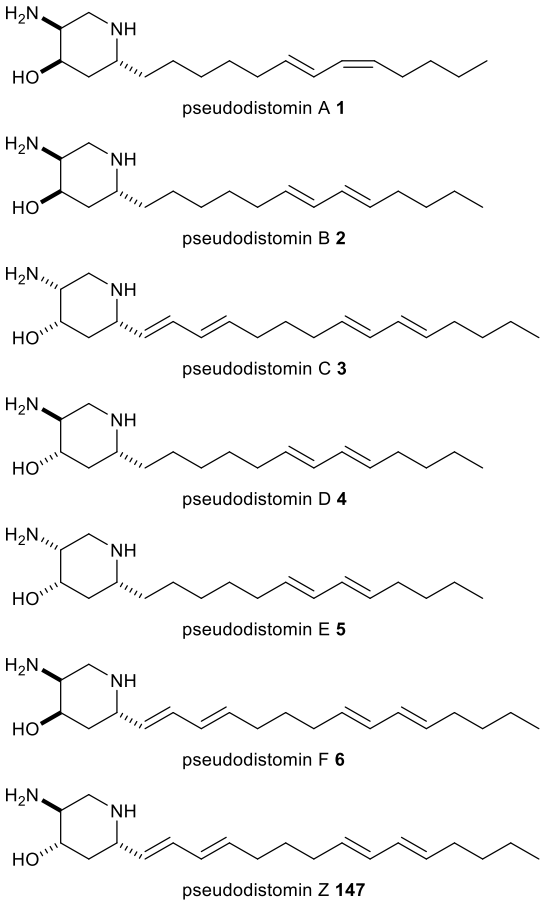


Figure 53 Structures of pseudodistomins A–F **1**–**6** and Z **147**.

5.2 Model Systems for NMR Acid Titrations

Given experience gained during analysis of the spectroscopic data of pseudodistomin E **5** (*vide supra*),[1] it was anticipated that data exhibited by all of the pseudodistomin alkaloids may be extremely sensitive to the presence of small amounts of ammonium ion formation, resulting

from the presence of acidic contaminants. Thus, prior to conducting NMR spectroscopic analyses on pseudodistomins A–F **1**–**6** and Z **147**, investigations were undertaken to evaluate the behaviour of a simple representative model system, $BnNH_2$, when exposed to acid. TFA was selected as the acidic dopant as full dissociation would be expected (pK_a 3.5 in DMSO),[2] and the minimum of additional resonances would be introduced in the ^1H and ^{13}C NMR spectra. Samples of $BnNH_2$ were prepared in MeOH-d_4 and C_5D_5N, the two solvents that the NMR spectra of pseudodistomins B–F **2**–**6** have been recorded in previously.[3,4,5] ^1H and ^{13}C NMR spectra were collected on both samples, followed by the subsequent acquisition of data following the addition of 0.1, 0.5 and 1.0 equivalents of TFA. ^{13}C NMR spectroscopic analysis was found to be more efficacious in quantifying the effects of acidic contaminants, relative to ^1H NMR spectroscopic analysis due to the appearance of resonances as single peaks. Thus, in each subsequent instance the ^{13}C NMR data were analysed first, followed by the ^1H NMR data.

5.2.1 Methanol Studies

Upon the introduction of TFA to $BnNH_2$ in MeOH-d_4, an upfield shift for the benzylic carbon resonance was observed in the ^{13}C NMR spectra (Figure 54). The approximately linear response is likely evidence for the stoichiometric transfer of the proton from TFA to $BnNH_2$, with the observed peak positions thus being the average between those for the resonances associated with $BnNH_2$ and $BnNH_3^+$, weighted by their populations.

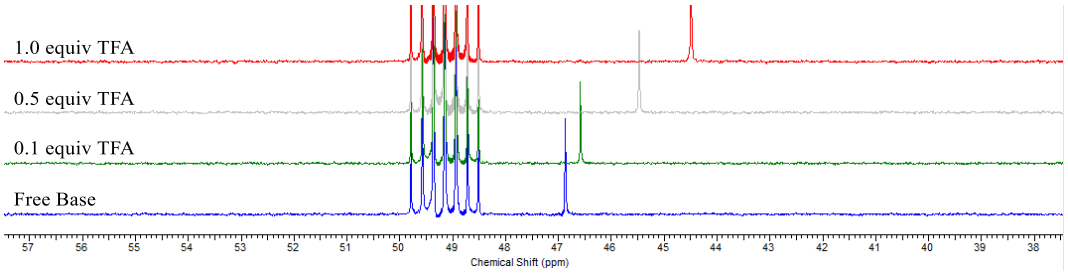


Figure 54 ^{13}C NMR data for TFA additions to $BnNH_2$ in MeOH-d_4.

A similar phenomenon, but in the opposite manner, was observed in the ^1H NMR spectra, with the resonance associated with the benzylic protons exhibiting a downfield shift with increasing amounts of TFA (Figure 55).

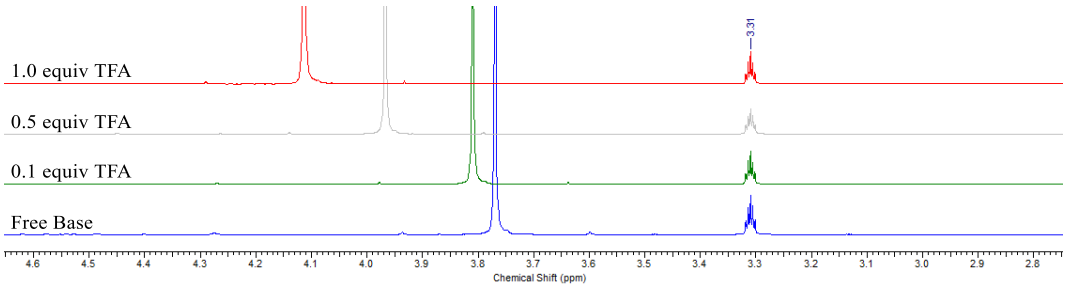


Figure 55 ^{1}H NMR data for TFA additions to $BnNH_2$ in MeOH-d_4.

5.2.2 Pyridine Studies

An analogous study was carried out on $BnNH_2$ in C_5D_5N. An approximately linear upfield shift was again observed for the benzylic carbon resonance in the ^{13}C NMR spectra (Figure 56). This is once more suggestive of stoichiometric transfer of the proton from TFA to $BnNH_2$. Given that the proton appears to reside solely on $BnNH_2$ it can be presumed that the difference in basicities between C_5D_5N ($C_5H_6N^+$, pK_a 3.4 in DMSO)[2] and $BnNH_2$ ($BnNH_3^+$, pK_a 10.2 in DMSO)[6] outweighs the excess of C_5D_5N relative to $BnNH_2$ present in the sample.

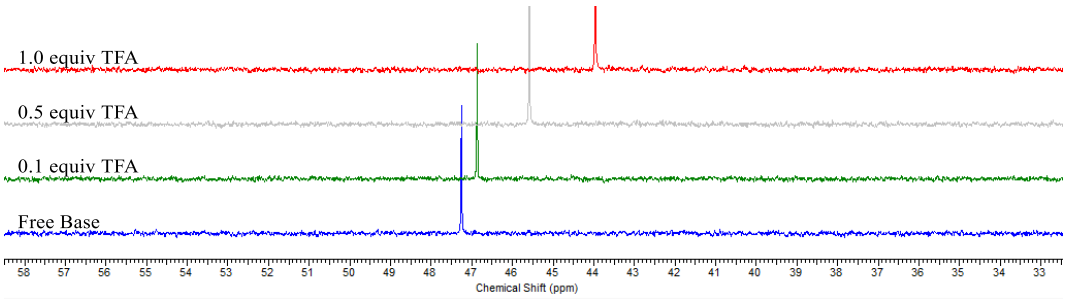


Figure 56 ^{13}C NMR data for TFA additions to $BnNH_2$ in C_5D_5N.

Upon ^{1}H NMR spectroscopic analyses in C_5D_5N, an approximately linear response was observed in the form of a downfield shift for the benzylic resonance (Figure 57).

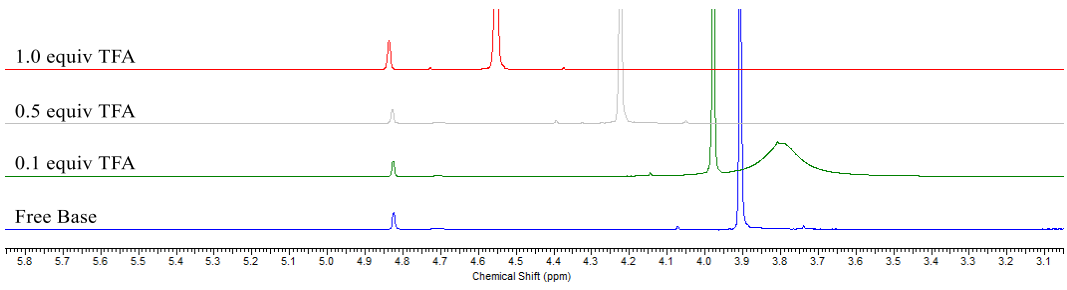


Figure 57 ^{1}H NMR data for TFA additions to $BnNH_2$ in C_5D_5N.

5.2.3 Section Conclusion

These studies clearly demonstrate large deviations in chemical shift for both ^{1}H and ^{13}C NMR spectroscopic analyses of amines upon the presence of even small amounts (5–10 mol%) of the corresponding ammonium species which arise due to the introduction of acidic dopants. It was hypothesised that the observed peak positions would be representative of the average peak positions for the resonances associated with a free base and the relevant ammonium ion, weighted by their populations. This technique could be used as a judge of the amount of ammonium ion present in a sample, however not as a judge of the percentage of acidic contaminant, which may be expected to deviate with contaminants of differing acidic strength. It is therefore of utmost importance that samples are purified prior to conducting such analyses to ensure the free base is present. It was therefore decided to subject all of the final pseudodistomin alkaloid products to basification *via* an aqueous work-up (i.e., aq KOH/$CHCl_3$ extraction) prior to acquisition of specific rotation and NMR spectroscopic data.

5.3 Data Analysis of Pseudodistomins A–F

The relative configurations within pseudodistomins A–F **1**–**6** and Z **147** were determined *via* ^{3}J coupling constant analyses of the samples in MeOH-d_4, assuming chair conformations in solution. On occasion, several resonances in the ^{1}H NMR spectra were poorly resolved, however approximate coupling constant magnitudes could be discerned from the width of relevant multiplets. The Karplus curve[7] was invoked when determining the relationship between vicinal protons. All relative configurations were found to be consistent with 1,3-diaxial interactions and gauche interactions being minimised by placing the larger [(C(2)-alkyl] substituent equatorial. Given the assigned absolute configurations of the synthetic samples in this study are secure, based upon the outcome of the indium-mediated allyl addition to **357**, and the Flack x parameters for the crystal structures of **349** and **367**, which satisfy the criteria for the reliable assignment of absolute configuration of a species known to be enantiopure, it can thus be concluded that the synthetic materials and natural products are identical in each case,

confirming or corroborating the assigned configurations of the natural products. Pseudodistomins A, B and C **1**, **2** and **3**, were elaborated to their respective triacetate derivatives, **9**, **10** and **65**, respectively, in order to enable a full comparison of spectroscopic and specific rotation data. Whilst the triacetates may offer effectively non-basic derivatives of the pseudodistomins (reducing the likelihood of inadvertently acquiring data on a partially acidified sample) the triacetate derivatives, **9**, **10** and **65** exhibit poorly resolved rotameric NMR spectra which were not amenable to ^{3}J coupling constant analysis,[8] this derivatization technique was not applied to pseudodistomins D, E, F and Z **4**, **5**, **6** and **147**. For ^{1}H NMR analyses the midpoint of multiplets are quoted. The lock frequencies for the residual solvent peaks in the ^{1}H NMR spectra were defined as 7.27 ppm, 3.31 ppm and 8.74 ppm for $CDCl_3$, MeOH-d_4 and C_5D_5N, respectively. The lock frequencies for the ^{13}C NMR spectra were defined as 77.00 ppm, 49.15 ppm and 150.35 ppm for $CDCl_3$, MeOH-d_4 and C_5D_5N, respectively.

5.3.1 Pseudodistomin A

Both C(3)H_{axial} and C(3)$H_{equatorial}$ display small (<3.5 Hz) ^{3}J coupling constants to C(4)*H* suggestive of non *trans*-diaxial relationships between the respective protons in both instances. This is indicative of C(4)*H* occupying an equatorial site, and thus the C(4)-hydroxy substituent adopting an axial site. Furthermore, C(3)H_{axial} shares a coupling constant of ^{3}J >11.0 Hz with C(2)*H*, indicative of a *trans*-diaxial relationship between the protons, and suggestive of the C(2)-alkyl group adopting an equatorial site. Finally, C(6)H_{axial} displays a coupling constant of ^{3}J >9.0 Hz to C(5)*H*, indicative of a *trans*-diaxial relationship between the protons, and implying the C(5)-amino group resides on an equatorial site (Figure 58).

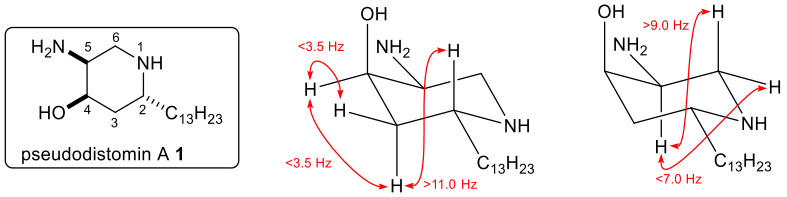
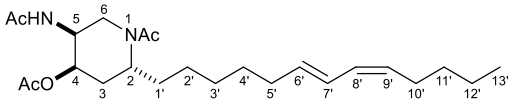


Figure 58 Conformational analysis of pseudodistomin A **1**.

As no data have been reported for the sample of pseudodistomin A **1** isolated from the natural source, a comparison of data had to be conducted on pseudodistomin A acetate **9** derived from the natural product. The value of the specific rotation for the synthetic sample of pseudodistomin A acetate **9** {$[\alpha]_D^{25}$ +48.0 (*c* 1.0 in MeOH)} was compared with the value provided by Kobayashi *et al*.[3] for the sample derived from the natural material {$[\alpha]_D^{24}$ +36 (*c* 1.0 in MeOH)} with the identical sign of the specific rotations allowing corroboration of the assigned absolute configuration. Upon NMR spectroscopic analysis of pseudodistomin A acetate **9**, poorly resolved spectra with a ~67:33 mixture of rotamers was observed. The lock frequency used in the ^{13}C NMR of pseudodistomin A acetate **9** by Kobayashi *et al*.[3] was 76.9 ppm, thus a +0.1 ppm correction was applied to Kobayashi's data prior to assessment. Comparison of the synthetic ^{13}C NMR data with the literature data reported by Kobayashi *et al*.[3] revealed agreement with $\Delta\delta_C \leq 0.2$ ppm (Figure 59).[9]

pseudodistomin A acetate **9**

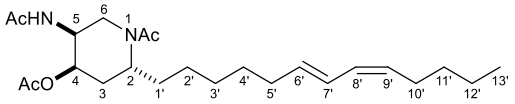


	9 Kobayashi *et al.*[3,10,11] (100 MHz, $CDCl_3$)	**9** This work (125 MHz, $CDCl_3$)
C(2)	47.6	47.5 (−0.1)
C(2)*	-----†	54.0
C(3)	28.3	28.3 (0.0)
C(4)	67.0	66.9 (+0.1)
C(5)	46.9	47.1 (+0.2)
C(5)*	-----†	46.2
C(6)	43.9	43.7 (−0.2)
C(6)*	-----†	39.3
C(1')	30.2	30.1 (−0.0)
C(2')	26.2	26.1 (−0.0)
C(3')	28.9	28.9 (0.0)
C(4')	29.2	29.2 (0.0)
C(5')	32.7	32.7 (0.0)
C(6')	134.1	134.2 (+0.1)
C(7')	125.9	125.8 (−0.1)
C(8')	128.5	128.5 (0.0)
C(9')	130.2	130.2 (0.0)
C(10')	27.2	27.4 (+0.2)
C(11')	31.9	31.9 (0.0)
C(12')	22.3	22.3 (0.0)
C(13')	13.9	14.0 (+0.1)
C(O)*Me*	21.0	21.0 (0.0)
C(O)*Me*	21.7	21.8 (+0.1)
C(O)*Me*	23.3	23.3 (0.0)
C(O)Me	170.1	170.0 (−0.1)
C(O)Me	170.2	170.2 (0.0)
C(O)Me	170.5	170.6 (+0.1)

Figure 59 ^{13}C NMR data for pseudodistomin A acetate **9**. Values of $\Delta\delta_C$ are given in parentheses relative to the data for material derived from the natural product. Signals for the minor rotamer are indicated by an asterix (*). † These data are not quoted for the material derived from the natural product.

Comparison of the synthetic ^1H NMR data with the literature data reported by Kobayashi *et al.*[3] revealed agreement with $\Delta\delta_H \leq 0.04$ ppm (Figure 60).[12]

pseudodistomin A acetate **9**



	9 Kobayashi *et al.*[3,13] (400 MHz, $CDCl_3$)	**9** This work (500 MHz, $CDCl_3$)
C(2)*H*	4.93	4.93 (0.00)
C(2)*H**	4.00	4.00 (0.00)
C(3)H_2	1.75	1.77 (+0.02)
C(4)*H*	5.15	5.15 (0.00)
C(5)*H*	4.31	4.35 (+0.04)
C(5)*H**	4.51	4.50 (−0.01)
C(6)H_A	3.27	3.29 (+0.02)
C(6)H_B	3.97	3.95 (−0.02)
C(6)H_A*	2.91	2.92 (+0.01)
C(6)H_B*	4.61	4.62 (+0.01)
C(1')H_2	1.60	1.60 (0.00)
C(2')H_2	1.32	1.30 (−0.02)
C(3')H_2	1.32	1.30 (−0.02)
C(4')H_2	1.32	1.30 (−0.02)
C(5')H_2	2.07	2.08 (+0.01)
C(6')*H*	5.65	5.63 (−0.02)
C(7')*H*	6.29	6.29 (0.00)
C(8')*H*	5.93	5.94 (+0.01)
C(9')*H*	5.30	5.31 (+0.01)
C(10')H_2	2.15	2.16 (+0.01)
C(11')H_2	1.32	1.30 (−0.02)
C(12')H_2	1.32	1.30 (−0.02)
C(13')H_3	0.89	0.91 (+0.02)
C(O)*Me*	2.00	2.03 (+0.03)
C(O)*Me*	2.04	2.04 (0.00)
C(O)*Me*	2.06	2.05 (−0.01)

Figure 60 ^{1}H NMR data for pseudodistomin A acetate **9**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for material derived from the natural product. Signals for the minor rotamer are indicated by an asterix (*).

5.3.2 Pseudodistomin B

The ^{1}H NMR spectra of pseudodistomin B **2** was similar to pseudodistomin A **1** when considering the piperidine head. Both C(3)H_{axial} and C(3)$H_{equatorial}$ display small (<3.5 Hz) ^3J coupling constants to C(4)*H* suggestive of non *trans*-diaxial relationships between the respective protons in both instances. This is indicative of C(4)*H* occupying an equatorial site, and thus the C(4)-hydroxy substituent adopting an axial site. Furthermore, C(3)H_{axial} also shares a coupling constant of ^3J >11.0 Hz with C(2)*H*, implying a *trans*-diaxial relationship between

the protons, and inferring the C(2)-alkyl group resides on an equatorial site. Finally, C(6)H_{axial} displays a large (>9.0 Hz) ^{3}J coupling constant to C(5)*H*, suggestive of a *trans*-diaxial relationship between the protons, and implying the C(5)-amino group adopts an equatorial site (Figure 61). This analysis proposes the same relative configuration within the piperidine heads of pseudodistomin A **1** and pseudodistomin B **2**, which is to be expected. The value of the specific rotation for the synthetic sample of pseudodistomin B **2** {$[\alpha]_D^{25}$ −21.7 (*c* 1.0 in MeOH)} was compared with the value provided by Freyer *et al.*[5] for the natural material {$[\alpha]_D^{24}$ −13 (*c* 0.87 in MeOH)}, with the identical sign of the specific rotations allowing corroboration of the assigned absolute configurations.[14] The value of the specific rotation for the synthetic sample of pseudodistomin B acetate **10** {$[\alpha]_D^{25}$ +49.7 (*c* 1.0 in MeOH)} was compared with the value provided by Kobayashi *et al.*[3] for the sample derived from the natural material {$[\alpha]_D^{24}$ +35 (*c* 1.0 in MeOH)}, with the identical sign of the specific rotations adding further support to the corroboration of the assigned absolute configurations.

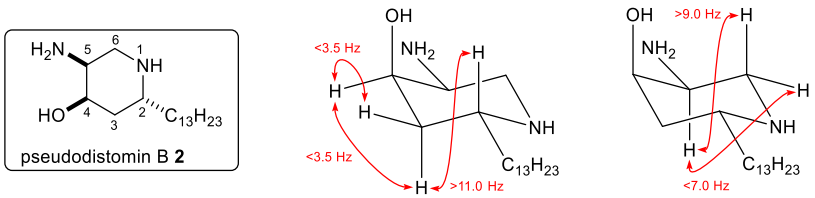


Figure 61 Conformational analysis of pseudodistomin B **2**.

Initial ^{13}C NMR spectroscopic analysis of pseudodistomin B **2** revealed a likely referencing discrepancy in the data provided by Freyer *et al.*,[5] with a systematic −0.2 ppm deviation observed in resonances most removed from the basic sites, and by extension likely all resonances. Thus, Freyer's data[5] were corrected prior to comparison.[15] ^{13}C NMR spectroscopic analysis of pseudodistomin B **2** showed agreement ($\Delta\delta_C \leq 0.3$ ppm in general)[9] with the corrected values quoted by Freyer *et al.*[5] for the natural product. However, *C*(4) and *C*(6), exhibited deviations of $\Delta\delta_C = 0.4$ and 0.6 ppm, respectively. TFA was thus introduced to the synthetic sample of pseudodistomin B **2** in 0.05 equivalent increments with variance of resonances observed (Figure 62).

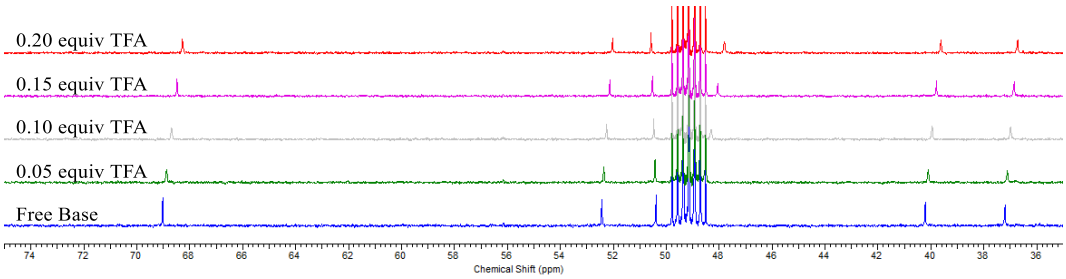


Figure 62 ^{13}C NMR data for TFA additions to pseudodistomin B **2**.

Corrected ^{13}C NMR data for the sample obtained by Freyer *et al.*[5] now showed agreement ($\Delta\delta_C \leq 0.1$ ppm)[9] with **2**·0.15 TFA (Figure 63). These studies are suggestive of Freyer's sample likely being pseudodistomin B **2**·*x*HA where *x*~0.15.

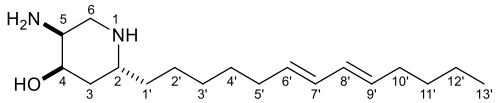
pseudodistomin B **2** 			
	2 Freyer *et al.*[5,15] (100 MHz, MeOH-d_4)	**2** This work (125 MHz, MeOH-d_4)	**2**·0.15 TFA This work (100 MHz, MeOH-d_4)
C(2)	50.5	50.4 (−0.1)	50.5 (0.0)
C(3)	39.9	40.2 (+0.3)	39.8 (−0.1)
C(4)	68.6	69.0 (+0.4)	68.5 (−0.1)
C(5)	52.2	52.4 (+0.2)	52.1 (−0.1)
C(6)	48.1	48.7 (+0.6)	48.1 (0.0)
C(1')	36.9	37.2 (+0.3)	36.9 (0.0)
C(2')	26.9	27.1 (+0.2)	27.0 (+0.1)
C(3')	30.4	30.5 (+0.1)	30.4 (0.0)
C(4')	30.6	30.6 (0.0)	30.6 (0.0)
C(5')	33.4	33.5 (+0.1)	33.4 (0.0)
C(6')	133.0	133.0 (0.0)	133.0 (0.0)
C(7')	132.1	132.1 (0.0)	132.1 (0.0)
C(8')	132.0	132.0 (0.0)	132.0 (0.0)
C(9')	133.2	133.2 (0.0)	133.2 (0.0)
C(10')	33.6	33.7 (+0.1)	33.7 (+0.1)
C(11')	33.0	33.0 (0.0)	33.0 (0.0)
C(12')	23.4	23.4 (0.0)	23.4 (0.0)
C(13')	14.4	14.4 (0.0)	14.4 (0.0)

Figure 63 ^{13}C NMR data for pseudodistomin B **2**. Values of $\Delta\delta_C$ are given in parentheses relative to the data for the natural product.

^{1}H NMR spectroscopic analysis of pseudodistomin B **2** showed agreement ($\Delta\delta_H \leq 0.03$ ppm in general)[12] with the values quoted by Freyer *et al.*[5] for the natural product. However, C(2)*H*, C(3)H_A, and C(5)*H* exhibited deviations of $\Delta\delta_H$ = 0.06, 0.05 and 0.05 ppm, respectively. Thus, ^{1}H NMR spectroscopic data were acquired on the TFA doped samples of **2** (Figure 64).

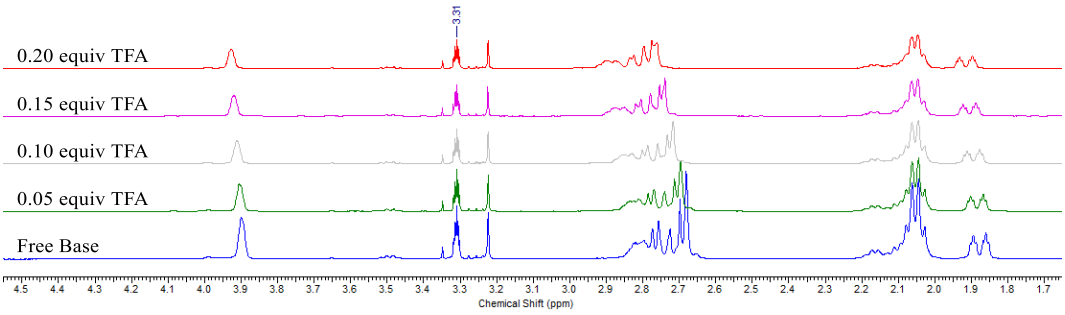
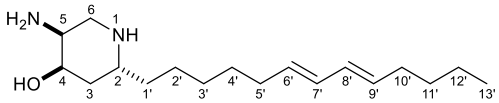


Figure 64 ^{1}H NMR data for TFA additions to pseudodistomin B **2**.

When ^{1}H NMR spectroscopic data were collected on **2**·0.15 TFA the data showed agreement once more ($\Delta\delta_H \leq 0.03$ ppm in general)[12] with the values quoted by Freyer *et al.*[5] for the natural product. The resonance associated with C(3)H_A continued to exhibit a deviation of $\Delta\delta_H$ = 0.05 ppm, however C(2)*H* and C(5)*H* now offered no deviation (Figure 65). This adds support to the hypothesis that Freyer's sample likely being pseudodistomin B **2**·xHA where x~0.15.

pseudodistomin B **2**

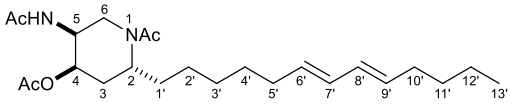


	2 Freyer *et al.*[5] (400 MHz, MeOH-d_4)	**2** This work (500 MHz, MeOH-d_4)	**2**·0.15 TFA This work (400 MHz, MeOH-d_4)
C(2)*H*	2.87	2.81 (−0.06)	2.87 (0.00)
C(3)H_A	1.30	1.35 (+0.05)	1.35 (+0.05)
C(3)H_B	1.90	1.88 (−0.02)	1.91 (+0.01)
C(4)*H*	3.91	3.90 (−0.01)	3.92 (+0.01)
C(5)*H*	2.74	2.69 (−0.05)	2.74 (0.00)
C(6)H_A	2.72	2.69 (−0.03)	2.74 (+0.02)
C(6)H_B	2.78	2.75 (−0.03)	2.81 (+0.03)
C(1')H_2	1.35	1.35 (0.00)	1.35 (0.00)
C(2')H_2	1.35	1.35 (0.00)	1.35 (0.00)
C(3')H_2	1.35	1.35 (0.00)	1.35 (0.00)
C(4')H_2	1.35	1.35 (0.00)	1.35 (0.00)
C(5')H_2	2.04	2.06 (+0.02)	2.06 (+0.02)
C(6')*H*	5.53	5.53 (0.00)	5.53 (0.00)
C(7')*H*	5.96	5.97 (+0.01)	5.97 (+0.01)
C(8')*H*	5.96	5.97 (+0.01)	5.97 (+0.01)
C(9')*H*	5.53	5.53 (0.00)	5.53 (0.00)
C(10')H_2	2.04	2.06 (+0.02)	2.06 (+0.02)
C(11')H_2	1.35	1.35 (0.00)	1.35 (0.00)
C(12')H_2	1.35	1.35 (0.00)	1.35 (0.00)
C(13')H_3	0.90	0.91 (+0.01)	0.91 (+0.01)

Figure 65 ^{1}H NMR data for pseudodistomin B **2**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for the natural product.

In order to correlate the sample of pseudodistomin B **2** obtained by Freyer *et al*.[5] and pseudodistomin B acetate **10** attained by Kobayashi *et al*.[3] for the first time, pseudodistomin B acetate **10** was prepared from pseudodistomin B **2**. Upon NMR spectroscopic analysis of pseudodistomin B acetate **10**, poorly resolved spectra with a ~67:33 mixture of rotamers was observed. The lock frequency used in the ^{13}C NMR of pseudodistomin A acetate **9** by Kobayashi *et al*.[3] was 76.9 ppm, thus a +0.1 ppm correction was applied to Kobayashi's data prior to assessment. Comparison of the synthetic ^{13}C NMR data with the literature data reported by Kobayashi *et al*.[3] revealed agreement with $\Delta\delta_C \leq 0.2$ ppm (Figure 66).[9]

pseudodistomin B acetate **10**

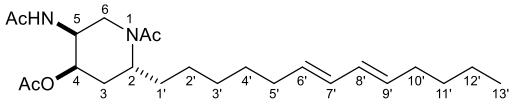


	10 Kobayashi *et al.*[3,10,11] (400 MHz, $CDCl_3$)	**10** This work (500 MHz, $CDCl_3$)
C(2)	47.7	47.6 (−0.1)
C(2)*	-----†	53.9
C(3)	28.3	28.2 (−0.1)
C(4)	67.0	66.9 (−0.1)
C(5)	47.0	46.8 (−0.2)
C(5)*	-----†	46.1
C(6)	44.0	43.9 (−0.1)
C(6)*	-----†	39.3
C(1')	30.2	30.1 (−0.1)
C(2')	26.2	26.1 (−0.1)
C(3')	29.0	28.8 (−0.2)
C(4')	29.3	29.2 (−0.1)
C(5')	32.3	32.2 (−0.1)
C(6')	132.0	131.9 (−0.1)
C(7')	130.7	130.5 (−0.2)
C(8')	130.3	130.2 (+0.1)
C(9')	132.7	132.6 (−0.1)
C(10')	32.6	32.4 (−0.2)
C(11')	31.6	31.5 (−0.1)
C(12')	22.3	22.1 (−0.2)
C(13')	14.0	13.9 (−0.1)
C(O)*Me*	21.1	21.0 (−0.1)
C(O)*Me*	21.9	21.8 (−0.1)
C(O)*Me*	23.3	23.2 (−0.1)
C(O)Me	170.1	170.1 (0.0)
C(O)Me	170.3	170.1 (−0.2)
C(O)Me	170.8	170.7 (−0.1)

Figure 66 ^{13}C NMR data for pseudodistomin B acetate **10**. Values of $\Delta\delta_C$ are given in parentheses relative to the data for material derived from the natural product. Signals for the minor rotamer are indicated by an asterix (*). † These data are not quoted for the material derived from the natural product.

Comparison of the synthetic ^1H NMR data with the literature data reported by Kobayashi *et al.*[3] revealed agreement ($\Delta\delta_H \leq 0.04$ ppm in general)[12] observed in most instances, however the C(3)H_2 and C(1')H_B multiplets exhibit deviations of 0.06 ppm and 0.09 ppm, respectively (Figure 67).

pseudodistomin B acetate **10**



	10 Kobayashi *et al.*[3,13] (400 MHz, $CDCl_3$)	**10** This work (500 MHz, $CDCl_3$)
C(2)*H*	4.92	4.89 (−0.03)
C(2)*H**	3.97	4.00 (+0.03)
C(3)H_2	1.74	1.80 (+0.06)
C(4)*H*	5.11	5.13 (+0.02)
C(5)*H*	4.34	4.38 (+0.04)
C(5)*H**	4.47	4.51 (+0.04)
C(6)H_A	3.26	3.29 (+0.03)
C(6)H_B	3.87	3.90 (+0.03)
C(6)H_A*	2.88	2.91 (+0.03)
C(6)H_B*	4.58	4.61 (+0.03)
C(1')H_A	1.55	1.52 (−0.03)
C(1)H_B	1.55	1.64 (+0.09)
C(2')H_2	1.30	1.28 (−0.02)
C(3')H_2	1.30	1.28 (−0.02)
C(4')H_2	1.30	1.28 (−0.02)
C(5')H_2	2.03	2.03 (0.00)
C(6')*H*	5.52	5.54 (+0.02)
C(7')*H*	5.95	5.95 (0.00)
C(8')*H*	5.95	5.95 (0.00)
C(9')*H*	5.54	5.54 (0.00)
C(10')H_2	2.03	2.03 (0.00)
C(11')H_2	1.30	1.28 (−0.02)
C(12')H_2	1.30	1.28 (−0.02)
C(13')H_3	0.86	0.89 (+0.03)
C(O)*Me*	2.00	2.03 (+0.03)
C(O)*Me*	2.00	2.03 (+0.03)
C(O)*Me*	2.01	2.04 (+0.03)

Figure 67 ^{1}H NMR data for pseudodistomin B acetate **10**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for material derived from the natural product. Signals for the minor rotamer are indicated by an asterix (*).

5.3.3 Pseudodistomin C

The large (^3J 11.5 Hz) coupling constant between C(3)H_{axial} and C(4)*H* indicates a ~180° dihedral angle between the protons. This is implicit of C(4)*H* occupying an axial site, and thus the C(4)-hydroxy group adopting an equatorial site. With the depicted ring based vicinal coupling constants being small in magnitude (^3J <5.0 Hz), non *trans*-diaxial relationships between the respective protons are suggested. Therefore, C(2)*H* and C(5)*H* must adopt axial and equatorial sites, respectively, and thus the C(2)-alkyl and C(5)-amino groups

reside on equatorial and axial sites, respectively (Figure 68). The value of the specific rotation for the synthetic sample of pseudodistomin C **3** {$[\alpha]_D^{25}$ −43.7 (*c* 1.0 in MeOH)} was compared with the value provided by Kobayashi *et al.*[16] for their synthetic material {$[\alpha]_D^{24}$ −24 (*c* 0.7 in MeOH)}, (although it should be noted that this sample corresponds to material of 80:20 er),[17] with the identical sign of the specific rotations allowing corroboration of the assigned absolute configurations.[18] The value of the specific rotation for the synthetic sample of pseudodistomin C acetate **65** {$[\alpha]_D^{25}$ +62.3 (*c* 1.0 in $CHCl_3$)} was compared with the value provided by Kobayashi *et al.*[3] for the sample derived from the natural material {$[\alpha]_D^{22}$ +85 (*c* 1.0 in $CHCl_3$)}, with the identical sign of the specific rotations adding further support to the corroboration of the assigned absolute configurations.

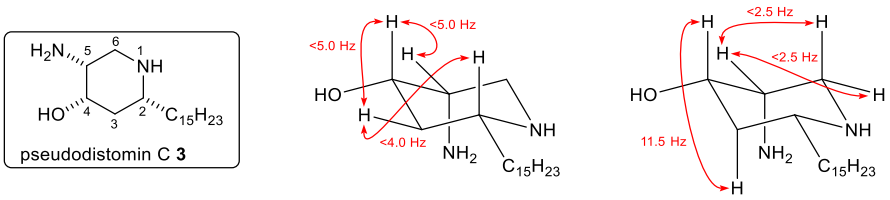


Figure 68 Conformational analysis of pseudodistomin C **3**.

As Kobayashi *et al.*[4] only offered NMR data in C_5D_5N for pseudodistomin C **3**, data for the synthetic sample of pseudodistomin C **3** were collected in C_5D_5N in addition to MeOH-d_4. Initial ^{13}C NMR spectroscopic analysis of pseudodistomin C **3** revealed a likely referencing discrepancy in the data provided by Kobayashi *et al.*,[4] with a systematic −0.5 ppm deviation observed in resonances most removed from the basic sites, and by extension likely all resonances. Thus, Kobayashi's data[4] were corrected prior to comparison.[19] ^{13}C NMR spectroscopic analysis of pseudodistomin C **3** showed poor agreement, with significant deviations across all sites of up to $\Delta\delta_C$ = 4.8 ppm being noted, other than for carbons in the tail portion from *C*(5')–*C*(15'). TFA was thus introduced to the synthetic sample of pseudodistomin C **3** in 0.05 equivalent increments with variance of resonances observed (Figures 69 & 70).

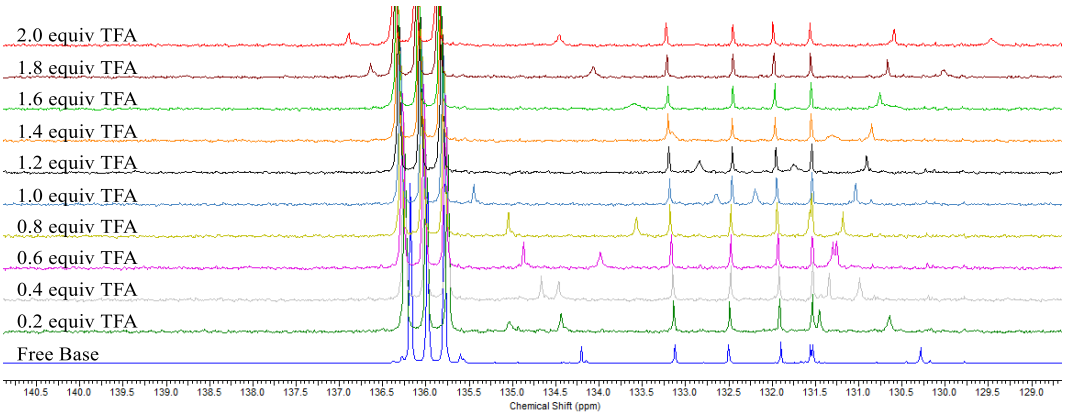


Figure 69 ^{13}C NMR data for TFA additions to pseudodistomin C **3** (δ_C 129–140 ppm).

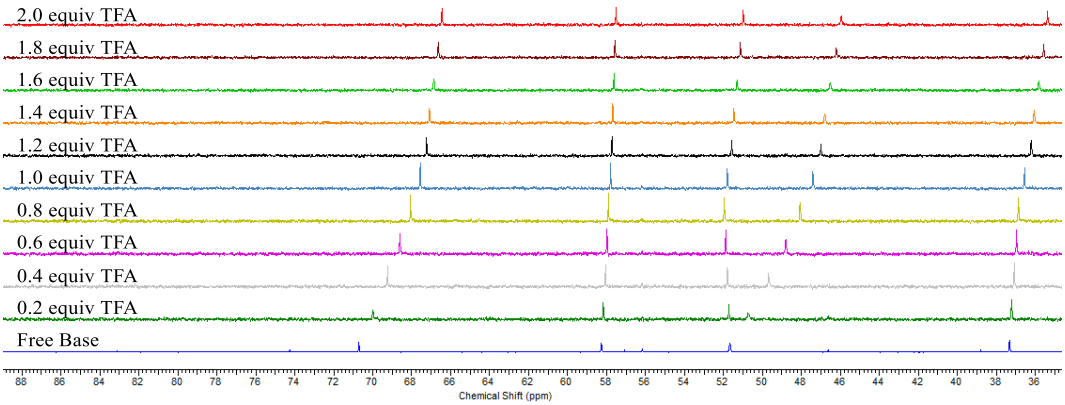
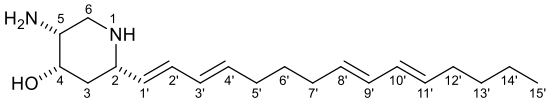


Figure 70 ^{13}C NMR data for TFA additions to pseudodistomin C **3** (δ_C 36–88 ppm).

Corrected ^{13}C NMR data for the sample obtained by Kobayashi *et al*.[4] now showed agreement ($\Delta\delta_C \leq 0.2$ ppm in general)[9] with **3**·1.0 TFA, including all the piperidine ring resonances. However, *C*(1'), *C*(2') and *C*(4'), exhibited deviations of $\Delta\delta_C = 0.5$, 2.9 and 0.7 ppm, respectively (Figure 71). Whilst the size and magnitude of these deviations could be influenced with the addition of further TFA, a simultaneous match for all carbon resonances could not be achieved. This could potentially be explained differential interactions of pseudodistomin C **3** with TFA and the unknown acidic contaminant in Kobayashi's sample. These studies are suggestive of Kobayashi's sample likely being pseudodistomin C **3**·*x*HA where *x*~1.

pseudodistomin C **3**



	3 Kobayashi *et al.*[4,20,19] (100 MHz, C_5D_5N)	**3** This work (125 MHz, C_5D_5N)	**3**·1.0 TFA This work (100 MHz, C_5D_5N)	**3**·2.0 TFA This work (100 MHz, C_5D_5N)
C(2)	57.9	58.3 (+0.4)	57.8 (−0.1)	57.5 (−0.4)
C(3)	36.5	37.3 (+0.8)	36.6 (+0.1)	35.4 (−1.1)
C(4)	67.8	70.7 (+2.9)	67.6 (−0.2)	66.5 (−1.3)
C(5)	52.0	51.7 (−0.3)	51.8 (−0.2)	51.0 (−1.0)
C(6)	47.5	51.7 (+4.2)	47.4 (−0.1)	46.0 (−1.5)
C(1')	133.1	135.6 (+2.5)	132.6 (−0.5)	129.5 (−3.6)
C(2')	135.1	130.3 (−4.8)	132.2 (−2.9)	134.5 (−0.6)
C(3')	131.1	131.6 (+0.5)	131.0 (−0.1)	130.6 (−0.5)
C(4')	136.2	134.2 (−2.0)	135.5 (−0.7)	136.9 (+0.7)
C(5')	32.9	33.0 (+0.1)	33.0 (+0.1)	33.0 (+0.1)
C(6')	29.7	29.8 (+0.1)	29.7 (0.0)	29.6 (−0.1)
C(7')	32.8	32.8 (0.0)	32.8 (0.0)	32.8 (0.0)
C(8')	132.5	132.5 (0.0)	132.5 (0.0)	132.5 (0.0)
C(9')	131.9	131.9 (0.0)	132.0 (+0.1)	132.0 (+0.1)
C(10')	131.5	131.5 (0.0)	131.5 (0.0)	131.6 (+0.1)
C(11')	133.1	133.1 (0.0)	133.2 (+0.1)	133.2 (+0.1)
C(12')	32.8[21]	32.8 (0.0)	32.8 (0.0)	32.8 (0.0)
C(13')	32.2	32.2 (0.0)	32.3 (+0.1)	32.3 (+0.1)
C(14')	22.7	22.9 (+0.2)	22.9 (+0.2)	22.9 (+0.2)
C(15')	14.5	14.5 (0.0)	14.5 (0.0)	14.6 (+0.1)

Figure 71 ^{13}C NMR data for pseudodistomin C **3**. Values of $\Delta\delta_C$ are given in parentheses relative to the data for the natural product.

^{1}H NMR spectroscopic analysis of pseudodistomin C **3** showed agreement ($\Delta\delta_H \leq 0.12$ ppm) for resonances associated with protons in the tail portion from *C*(1')–*C*(15'), however significant deviations across resonances associated with protons borne by the piperidine head of up to $\Delta\delta_H = 0.74$ ppm. Thus, ^{1}H NMR spectroscopic data were acquired on the TFA doped samples of **3** (Figure 72).

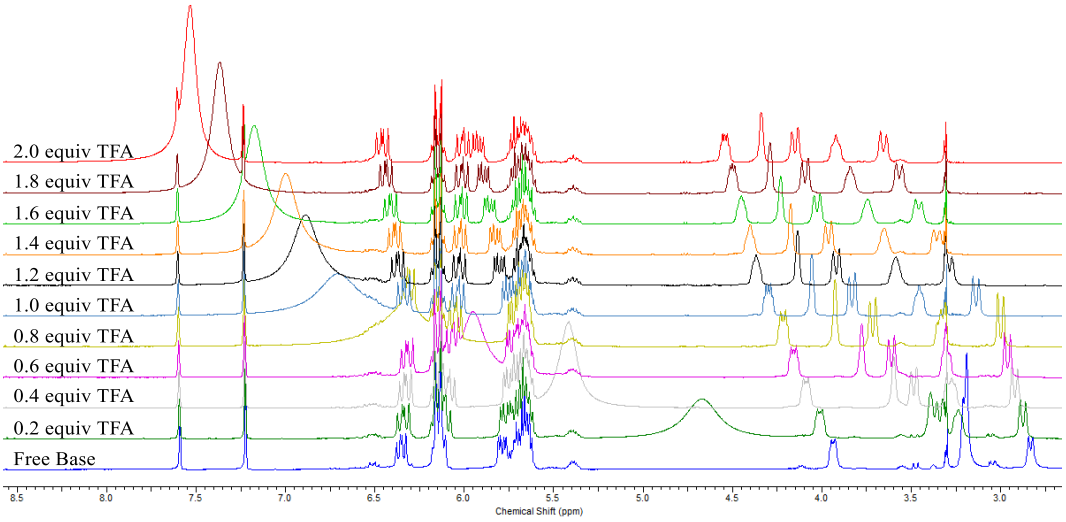
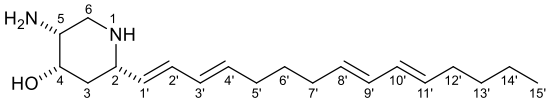


Figure 72 ^{1}H NMR data for TFA additions to pseudodistomin C **3**.

When ^{1}H NMR spectroscopic data were collected on **3**·1.0 TFA the data showed agreement once more ($\Delta\delta_H \leq 0.10$ ppm)[12] with the values quoted by Kobayashi *et al.*[4] for the natural product (Figure 73). This adds support to the hypothesis that Kobayashi's sample likely being pseudodistomin C **3**·xHA where x~1.

pseudodistomin C **3**



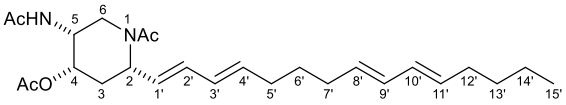
	3 Kobayashi *et al.*[4] (400 MHz, C_5D_5N)	**3** This work (500 MHz, C_5D_5N)	**3**·1.0 TFA This work (400 MHz, C_5D_5N)	**3**·2.0 TFA This work (400 MHz, C_5D_5N)
C(2)*H*	3.40	3.19 (−0.21)	3.46 (+0.06)	3.92 (+0.52)
C(3)H_A	2.12	1.82 (−0.30)	2.19 (+0.07)	2.36 (+0.24)
C(3)H_B	2.12	1.97 (−0.15)	2.19 (+0.07)	2.36 (+0.24)
C(4)*H*	4.28	3.94 (−0.32)	4.30 (+0.02)	4.54 (+0.26)
C(5)*H*	4.03	3.19 (−0.84)	4.06 (+0.03)	4.34 (+0.31)
C(6)H_A	3.11	2.83 (−0.28)	3.14 (+0.03)	3.66 (+0.55)
C(6)H_B	3.93	3.19 (−0.74)	3.83 (−0.10)	4.15 (+0.22)
C(1')*H*	5.83	5.79 (−0.04)	5.76 (−0.07)	5.92 (+0.09)
C(2')*H*	6.32	6.35 (+0.03)	6.34 (+0.02)	6.46 (+0.14)
C(3')*H*	6.00	6.14 (+0.14)	6.03 (+0.03)	6.01 (+0.01)
C(4')*H*	5.63	5.68 (+0.05)	5.67 (+0.04)	5.68 (+0.05)
C(5')H_2	2.01	2.07 (+0.06)	2.07 (+0.06)	2.06 (+0.05)
C(6')H_2	1.35	1.47 (+0.12)	1.45 (+0.10)	1.43 (+0.08)
C(7')H_2	2.01	2.07 (+0.06)	2.07 (+0.06)	2.06 (+0.05)
C(8')*H*	5.63	5.68 (+0.05)	5.67 (+0.04)	5.68 (+0.05)
C(9')*H*	6.11	6.14 (+0.03)	6.15 (+0.04)	6.15 (+0.04)
C(10')*H*	6.11	6.14 (+0.03)	6.15 (+0.04)	6.15 (+0.04)
C(11')*H*	5.63	5.68 (+0.05)	5.67 (+0.04)	5.68 (+0.05)
C(12')H_2	2.01	2.07 (+0.06)	2.07 (+0.06)	2.06 (+0.05)
C(13')H_2	1.35	1.29 (−0.06)	1.30 (−0.05)	1.31 (−0.04)
C(14')H_2	1.35	1.29 (−0.06)	1.30 (−0.05)	1.31 (−0.04)
C(15)H_3	0.80	0.84 (+0.04)	0.85 (+0.05)	0.85 (+0.05)

Figure 73 ^{1}H NMR data for pseudodistomin C **3**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for the natural product.

As pseudodistomin C acetate **65** had been prepared in order to correlate the specific rotation value of the synthetic material in this study with material isolated from the natural source, pseudodistomin C acetate **65** was also subjected to NMR spectroscopic analysis. This resulted in poorly resolved spectra with a ~50:50 mixture of rotamers observed.[22] Comparison of ^{13}C NMR data of pseudodistomin C acetate **65** with the data provide by Kobayashi *et al.*,[4] revealed a likely referencing discrepancy, with a systematic −0.2 ppm deviation observed in resonances most removed from the basic sites, and by extension likely all resonances. Thus, Kobayashi's data[4] were corrected prior to comparison.[15] Comparison of the synthetic ^{13}C NMR data with the corrected literature data revealed agreement ($\Delta\delta_C \leq 0.2$ ppm)[9] with the quoted values. However, due to the presence of rotamers, numerous additional resonances were present

in the sample which Kobayashi *et al*. did not report. Furthermore, Kobayashi *et al*. also did not report resonances for *C*(2), which were likely masked by the MeOH-d_4 resonance, and those of the three acetate methyl groups. Finally, whilst agreement existed when comparing the absolute values, the assignments did not. Hence, for simplicity, a comparison of only the corrected absolute values presented by Kobayashi *et al*. with (selected) peaks from the synthetic sample prepared in this study is presented (Figure 74).

pseudodistomin C acetate **65**



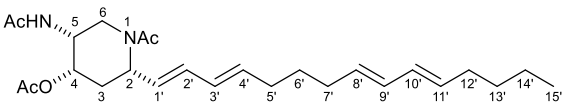
65 Kobayashi *et al*.[4,20,15] (100 MHz, MeOH-d_4)	**65** This work (125 MHz, MeOH-d_4)
14.4	14.4 (0.0)
23.5	23.4 (+0.1)
30.4	30.4 (0.0)
33.1	33.0 (−0.1)
33.2	33.2 (0.0)
33.3	33.2 (−0.1)
33.5	33.5 (0.0)
37.4	37.3 (−0.1)
42.6	42.6 (0.0)
49.4	49.4 (0.0)
70.4	70.5 (+0.1)
131.0	131.0 (0.0)
131.2	131.2 (0.0)
131.3	131.3 (0.0)
131.4	131.6 (+0.2)
132.0	131.9 (−0.1)
132.4	132.4 (0.0)
132.6	132.6 (0.0)
133.4	133.4 (0.0)
172.2	172.2 (0.0)
173.1	173.1 (0.0)
173.4	173.4 (0.0)

Figure 74 ^{13}C NMR data for pseudodistomin C acetate **65**. Values of $\Delta\delta_C$ are given in parentheses relative to the data for material derived from the natural product.

Initial ^{1}H NMR spectroscopic analysis of pseudodistomin C acetate **65** revealed a likely referencing discrepancy in the data provided by Kobayashi *et al*.,[4] with a systematic +0.04 ppm deviation observed in resonances most removed from the basic sites, and by extension likely all resonances. Thus, Kobayashi's data[4] were corrected prior to comparison.[23] Comparison of

the synthetic ^{1}H NMR data with the corrected literature data revealed agreement ($\Delta\delta_H \leq 0.05$ ppm)[9] with the quoted values. However, again, due to the presence of rotamers, numerous additional resonances were present in the sample, which Kobayashi *et al*. did not report.[22] Finally, whilst agreement existed when comparing the absolute values, the assignments did not. Hence, for simplicity, a comparison of only the corrected absolute values presented by Kobayashi *et al*. with (selected) peaks from the synthetic sample prepared in this study is presented (Figure 75).

pseudodistomin C acetate **65**



65 Kobayashi *et al*.[4,20,23] (400 MHz, MeOH-d_4)	**65** This work (500 MHz, MeOH-d_4)
0.91	0.91 (0.00)
1.51†	1.47 (−0.04)
2.11†	2.07 (−0.04)
2.93	2.93 (0.00)
3.97	4.01 (+0.04)
4.45	4.44 (−0.01)
4.65	4.66 (+0.01)
5.07	5.08 (+0.01)
5.55	5.54 (−0.01)
5.64	5.68 (+0.04)
5.96	5.98 (+0.02)
6.08	6.07 (−0.01)

Figure 75 ^{1}H NMR data for pseudodistomin C acetate **65**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for material derived from the natural product. † Values were estimated from the ^{1}H NMR spectra.

5.3.4 Pseudodistomin D

Large (^{3}J >9.0 Hz) coupling constants were observed between the C(2)*H* and C(3)H_{axial}, C(3)H_{axial} and C(4)*H*, C(4)*H* and C(5)*H*, and C(5)*H* and C(6)H_{axial}, indicative of ~180° dihedral angles between the respective protons in each instance. Therefore, C(2)*H*, C(4)*H* and C(5)*H* must occupy axial sites, and thus the C(2)-alkyl, C(4)-hydroxy and C(5)-amino moieties adopt equatorial sites (Figure 76). The value of the specific rotation for the synthetic sample of pseudodistomin D **4** {$[\alpha]_D^{25}$ −1.1 (*c* 1.0 in MeOH)} was of opposite sign when compared to the

values provided by Freyer *et al.*[5] for the natural material {$[\alpha]_D^{25}$ +5 (*c* 0.26 in MeOH)} and the previously reported synthetic samples offered by Trost *et al.* {$[\alpha]_D^{25}$ +6 (*c* 0.2 in MeOH)[24] and Davies *et al.* $[\alpha]_D^{25}$ +5.6 (*c* 0.3 in MeOH)}.[25] The specific rotation was re-recorded following introduction of TFA, with **4**·0.05 TFA exhibiting a value of $[\alpha]_D^{25}$ +5.4 (*c* 1.0 in MeOH), with the identical sign of the specific rotations now allowing corroboration of the assigned absolute configurations.

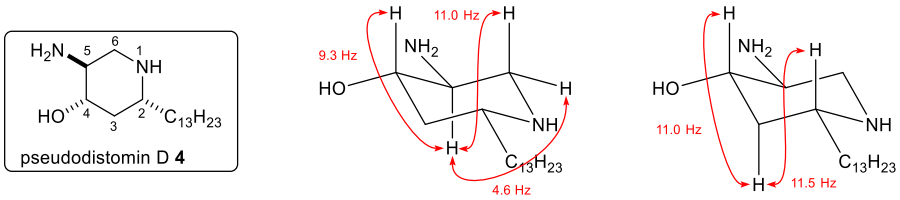


Figure 76 Conformational analysis of pseudodistomin D **4**.

^{13}C NMR spectroscopic analysis of pseudodistomin D **4** showed agreement ($\Delta\delta_C \leq 0.2$ ppm in general)[9] with the values quoted in the isolation report.[5] However, *C*(4) exhibited a deviation of $\Delta\delta_C = 0.5$ ppm, and discrepancies were also observed when compared with the data offered in the previously reported syntheses of Trost *et al.*[24] and Davies *et al.*[25] TFA was thus introduced to the synthetic sample of pseudodistomin D **4** in 0.05 equivalent increments with variance of resonances observed (Figure 77).

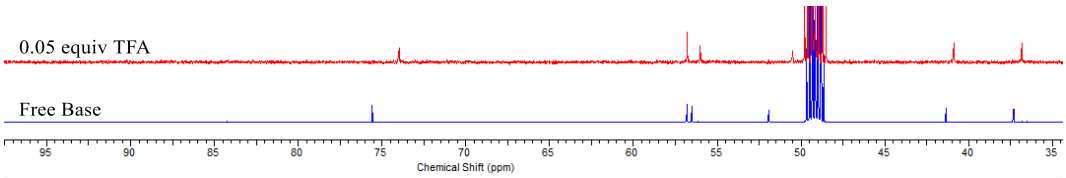
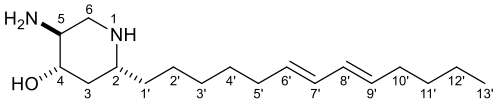


Figure 77 ^{13}C NMR data for TFA additions to pseudodistomin D **4**.

^{13}C NMR data for the sample obtained by Freyer *et al.*[5] and the synthetic samples isolated by Trost *et al.*[24] and Davies *et al.*[25] now largely resided between the data provided here for pseudodistomin D **4** and **4**·0.05 TFA (Figure 78). These studies are suggestive of all previously reported samples likely being pseudodistomin D **4**·*x*HA where $0<x\leq0.05$.

pseudodistomin D **4**



	4 Freyer *et al.*[5] (100 MHz, MeOH-d_4)	**4** Trost *et al.*[24] (125 MHz, MeOH-d_4)	**4** Davies *et al.*[25] (125 MHz, MeOH-d_4)	**4** This work (125 MHz, MeOH-d_4)	**4**·0.05 TFA This work (100 MHz, MeOH-d_4)
C(2)	56.7	56.8 (+0.1)	56.7 (0.0)	56.8 (+0.1)	56.8 (+0.1)
C(3)	41.2	41.2 (0.0)	41.2 (0.0)	41.4 (+0.2)	40.9 (−0.3)
C(4)	75.5	75.0 (−0.5)	75.3 (−0.2)	76.0 (+0.5)	74.0 (−1.5)
C(5)	56.4	56.3 (−0.1)	56.3 (−0.1)	56.5 (+0.1)	56.0 (−0.4)
C(6)	51.9	51.4 (−0.5)	51.6 (−0.3)	51.9 (0.0)	50.5 (−1.4)
C(1')	37.2	37.2 (0.0)	37.1 (−0.1)	37.3 (+0.1)	36.8 (−0.4)
C(2')	26.9	27.0 (+0.1)	26.9 (0.0)	27.1 (+0.2)	26.9 (0.0)
C(3')	30.3	30.4 (+0.1)	30.2 (−0.1)	30.5 (+0.2)	30.4 (+0.1)
C(4')	30.5	30.6 (+0.1)	30.5 (0.0)	30.6 (+0.1)	30.6 (+0.1)
C(5')	33.3	33.5 (+0.2)	33.3 (0.0)	33.5 (+0.2)	33.4 (+0.1)
C(6')	132.9	133.0 (+0.1)	132.9 (0.0)	133.0 (+0.1)	133.0 (+0.1)
C(7')	132.0	132.1 (+0.1)	132.0 (0.0)	132.1 (+0.1)	132.1 (+0.1)
C(8')	131.8	132.0 (+0.2)	131.9 (+0.1)	132.0 (+0.2)	132.0 (+0.2)
C(9')	133.1	133.2 (+0.1)	133.1 (0.0)	133.2 (+0.1)	133.2 (+0.1)
C(10')	33.5	33.6 (+0.1)	33.5 (0.0)	33.7 (+0.2)	33.6 (+0.1)
C(11')	32.8	33.0 (+0.2)	32.7 (−0.1)	33.0 (+0.2)	33.0 (+0.2)
C(12')	23.3	23.4 (+0.1)	23.3 (0.0)	23.4 (+0.1)	23.4 (+0.1)
C(13')	14.3	14.4 (+0.1)	14.3 (0.0)	14.4 (+0.1)	14.4 (+0.1)

Figure 78 ^{13}C NMR data for pseudodistomin D **4**. Values of $\Delta\delta_C$ are given in parentheses relative to the data for the natural product.

^{1}H NMR spectroscopic analysis of pseudodistomin D **4** showed agreement ($\Delta\delta_H \leq 0.02$ ppm)[12] with the values quoted in the isolation report.[5] Given the earlier findings, it was proposed that agreement with the synthetic samples[24,25] could be improved upon the introduction of a small amount of acid to the sample, thus, ^{1}H NMR spectroscopic data were acquired on the TFA doped sample of **4** (Figure 79).

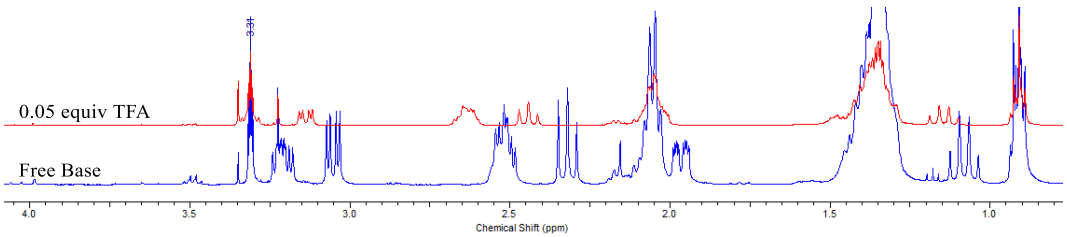
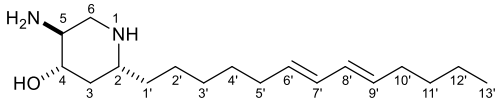


Figure 79 ^{1}H NMR data for TFA additions to pseudodistomin D **4**.

Data for the synthetic samples isolated by Trost *et al.*[24] and Davies *et al.*[25] now largely resided between the data provided here for pseudodistomin D **4** and **4**·0.05 TFA (Figure 80). This adds

support to the hypothesis that the synthetic samples[24,25] likely exist as pseudodistomin D **4**·xHA where $0<x\leq0.05$.

pseudodistomin D **4**



	4 Freyer *et al.*[5] (400 MHz, MeOH-d_4)	**4** Trost *et al.*[24] (500 MHz, MeOH-d_4)	**4** Davies *et al.*[25] (500 MHz, MeOH-d_4)	**4** This work (500 MHz, MeOH-d_4)	**4**·0.05 TFA This work (400 MHz, MeOH-d_4)
C(2)*H*	2.50	2.55 (+0.05)	2.57 (+0.07)	2.52 (+0.02)	2.64 (+0.14)
C(3)H_A	1.07	1.09 (+0.02)	1.12 (+0.05)	1.08 (+0.01)	1.14 (+0.07)
C(3)H_B	1.96	1.98 (+0.02)	2.00 (+0.04)	1.96 (0.00)	2.06 (+0.10)
C(4)*H*	3.20	3.24 (+0.04)	3.26 (+0.06)	3.21 (+0.01)	3.32 (+0.12)
C(5)*H*	2.50	2.55 (+0.05)	2.57 (+0.07)	2.52 (+0.02)	2.64 (+0.14)
C(6)H_A	2.31	2.35 (+0.04)	2.37 (+0.06)	2.32 (+0.01)	2.46 (+0.15)
C(6)H_B	3.04	3.07 (+0.03)	3.09 (+0.05)	3.05 (+0.01)	3.14 (+0.10)
C(1')H_2	1.35	1.37 (+0.02)	1.35 (0.00)	1.37 (+0.02)	1.37 (+0.02)
C(2')H_2	1.35	1.37 (+0.02)	1.35 (0.00)	1.37 (+0.02)	1.37 (+0.02)
C(3')H_2	1.35	1.37 (+0.02)	1.35 (0.00)	1.37 (+0.02)	1.37 (+0.02)
C(4')H_2	1.35	1.37 (+0.02)	1.35 (0.00)	1.37 (+0.02)	1.37 (+0.02)
C(5')H_2	2.04	2.05 (+0.01)	2.08 (+0.04)	2.05 (+0.01)	2.06 (+0.02)
C(6')*H*	5.53	5.52 (−0.01)	5.55 (+0.02)	5.53 (0.00)	5.53 (0.00)
C(7')*H*	5.96	5.97 (+0.01)	6.00 (+0.04)	5.98 (+0.02)	5.98 (+0.02)
C(8')*H*	5.96	5.97 (+0.01)	6.00 (+0.04)	5.98 (+0.02)	5.98 (+0.02)
C(9')*H*	5.53	5.52 (−0.01)	5.55 (+0.02)	5.53 (0.00)	5.53 (0.00)
C(10')H_2	2.04	2.05 (+0.01)	2.08 (+0.04)	2.05 (+0.01)	2.06 (+0.02)
C(11')H_2	1.35	1.37 (+0.02)	1.35 (0.00)	1.37 (+0.02)	1.37 (+0.02)
C(12')H_2	1.35	1.37 (+0.02)	1.35 (0.00)	1.37 (+0.02)	1.37 (+0.02)
C(13')H_3	0.90	0.90 (0.00)	0.93 (+0.03)	0.91 (+0.01)	0.91 (+0.01)

Figure 80 ^{1}H NMR data for pseudodistomin D **4**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for the natural product.

5.3.5 Pseudodistomin E

The relative configuration of pseudodistomin E **5** was assigned following spectroscopic data comparison with the sample prepared previously.[1] The value of the specific rotation for this synthetic sample of pseudodistomin E **5** {$[\alpha]_D^{25}$ −33.1 (*c* 1.0 in MeOH)} was in agreement with the previously reported value {$[\alpha]_D^{25}$ −34.5 (*c* 1.0 in MeOH)}, which was correlated with the specific rotation value of the natural sample.[1] ^{13}C NMR spectroscopic analysis of

pseudodistomin E **5** showed agreement ($\Delta\delta_C \leq 0.1$ ppm)[9] with the values previously reported, which have previously been correlated with those of the natural sample (Figure 81).[1]

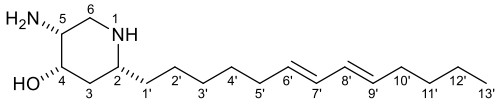
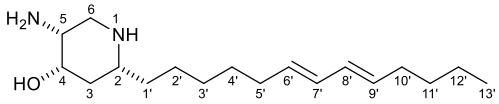
pseudodistomin E **5** 		
	5 Davies *et al.*[1] (100 MHz, MeOH-d_4)	**5** This work (125 MHz, MeOH-d_4)
C(2)	56.5	56.5 (0.0)
C(3)	35.6	35.6 (0.0)
C(4)	71.0	71.0 (0.0)
C(5)	51.4	51.4 (0.0)
C(6)	50.4	50.4 (0.0)
C(1')	37.4	37.4 (0.0)
C(2')	26.9	26.9 (0.0)
C(3')	30.5	30.5 (0.0)
C(4')	30.6	30.6 (0.0)
C(5')	33.5	33.5 (0.0)
C(6')	133.0	133.0 (0.0)
C(7')	132.0	132.1 (+0.1)
C(8')	132.0	132.0 (0.0)
C(9')	133.2	133.2 (0.0)
C(10')	33.7	33.7 (0.0)
C(11')	33.0	33.0 (0.0)
C(12')	23.4	23.4 (0.0)
C(13')	14.5	14.5 (0.0)

Figure 81 ^{13}C NMR data for pseudodistomin E **5**. Values of $\Delta\delta_C$ are given in parentheses relative to the earlier synthesis.

^{1}H NMR spectroscopic analysis of this synthetic sample of pseudodistomin E **5** showed agreement ($\Delta\delta_H \leq 0.04$ ppm)[12] with the values exhibited by the synthetic sample from the first-generation synthesis, and the material obtained by Freyer *et al.*[5] in their isolation report (Figure 82).

pseudodistomin E **5**



	5 Freyer *et al.*[5] (400 MHz, MeOH-d_4)	**5** Davies *et al.*[1] (400 MHz, MeOH-d_4)	**5** This work (500 MHz, MeOH-d_4)
C(2)*H*	2.44	2.46 (+0.02)	2.45 (+0.01)
C(3)H_A C(3)H_B	1.21 1.68	1.22 (+0.01) 1.68 (0.00)	1.22 (+0.01) 1.68 (0.00)
C(4)*H*	3.67	3.67 (0.00)	3.67 (0.00)
C(5)*H*	2.90	2.90 (0.00)	2.89 (−0.01)
C(6)H_A C(6)H_B	2.73 2.98	2.73 (0.00) 2.98 (0.00)	2.73 (0.00) 2.98 (0.00)
C(1')H_2	1.35	1.36 (+0.01)	1.39 (+0.04)
C(2')H_2	1.35	1.36 (+0.01)	1.39 (+0.04)
C(3')H_2	1.35	1.36 (+0.01)	1.39 (+0.04)
C(4')H_2	1.35	1.36 (+0.01)	1.39 (+0.04)
C(5')H_2	2.05	2.06 (+0.01)	2.06 (+0.01)
C(6')*H*	5.52	5.53 (+0.01)	5.53 (+0.01)
C(7')*H*	5.96	5.98 (+0.02)	5.98 (+0.02)
C(8')*H*	5.96	5.98 (+0.02)	5.98 (+0.02)
C(9')*H*	5.52	5.53 (+0.01)	5.53 (+0.01)
C(10')H_2	2.05	2.06 (+0.01)	2.06 (+0.01)
C(11')H_2	1.35	1.36 (+0.01)	1.39 (+0.04)
C(12')H_2	1.35	1.36 (+0.01)	1.39 (+0.04)
C(13')H_3	0.90	0.91 (+0.01)	0.91 (+0.01)

Figure 82 ^{1}H NMR data for pseudodistomin E **5**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for the natural product.

5.3.6 Pseudodistomin F

Firstly, C(6)H_{axial} displays a large (<10.3 Hz) ^3J coupling constant to C(5)*H*, indicative of a *trans*-diaxial relationship between the protons, and implying C(5)*H* occupies an axial site, and thus the C(5)-amino substituent adopts an equatorial site. Furthermore, C(4)*H* exhibits a coupling constant of ^3J 2.5 Hz to C(3)H_{axial}, implying a non *trans*-diaxial relationship between the protons, suggestive of C(4)*H* occupying an equatorial site, and thus the C(4)-hydroxy moiety occupying an axial site. Finally, C(3)H_{axial} shares a large (11.8 Hz) ^3J coupling constant with C(2)*H*, inferring a *trans*-diaxial relationship between the protons is present and implying C(2)*H* adopts an axial site, and thus the C(2)-alkyl group is on an equatorial site (Figure 83). The value of the specific rotation for the synthetic sample of pseudodistomin F **6**

{$[\alpha]_D^{25}$ −5.7 (*c* 0.4 in MeOH)} was compared with the value provided by Freyer *et al.*[5] for the sample derived from the natural material {$[\alpha]_D^{24}$ −13.9 (*c* 0.42 in MeOH)} and the previously reported synthetic sample offered by Ma *et al.* {$[\alpha]_D^{11}$ −12.6 (*c* 0.2 in MeOH)}.[26] The specific rotation was re-recorded following introduction of TFA, with **6**·0.05 TFA exhibiting a value of $[\alpha]_D^{25}$ −14.0 (*c* 0.4 in MeOH), with the identical sign of the specific rotations allowing corroboration of the assigned absolute configurations.

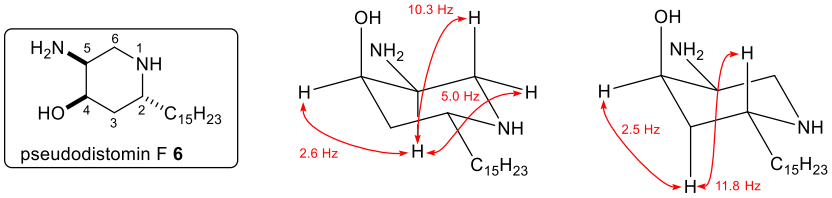


Figure 83 Conformational analysis of pseudodistomin F **6**.

Initial ^{13}C NMR spectroscopic analysis of pseudodistomin F **6** revealed a likely referencing discrepancy in the data provided by Freyer *et al.*,[5] with a systematic −0.2 ppm deviation observed in resonances most removed from the basic sites, and by extension likely all resonances. Thus, Freyer's data[5] were corrected prior to comparison. ^{13}C NMR spectroscopic analysis of pseudodistomin F **6** showed agreement ($\Delta\delta_C \leq 0.3$ ppm in general)[9] with the corrected values.[15,5,27] However, resonances associated with *C*(3), *C*(4), *C*(6) and *C*(1'), exhibited deviations of up to $\Delta\delta_C = 0.7$ ppm. TFA was thus introduced to the synthetic sample of pseudodistomin F **6** in 0.05 equivalent increments with variance of resonances observed (Figure 84).

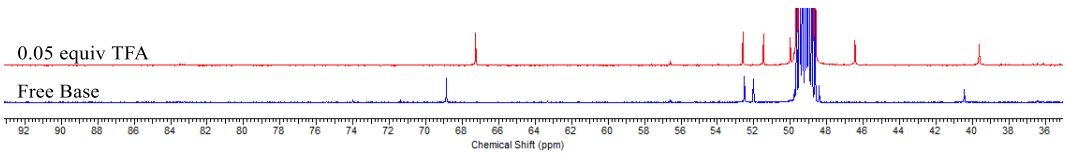
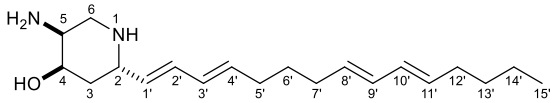


Figure 84 ^{13}C NMR data for TFA additions to pseudodistomin F **6**.

Corrected ^{13}C NMR data for the sample obtained by Freyer *et al.*[5] now now largely resided between the data provided here for pseudodistomin F **6** and **6**·0.05 TFA (Figure 85). No comparison could be made with the synthetic sample reported by Ma *et al.*[26] as no ^{13}C NMR

data were provided. These studies are suggestive of Freyer's sample likely being pseudodistomin F **6**·*x*HA where $0<x\leq0.05$.

pseudodistomin F **6**

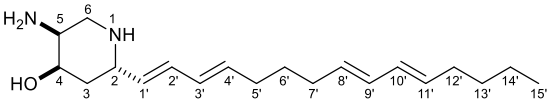


	6 Freyer *et al.*[5,15] (100 MHz, MeOH-d_4)	**6** This work (125 MHz, MeOH-d_4)	**6**·0.05 TFA This work (125 MHz, MeOH-d_4)
C(2)	52.5	52.5 (0.0)	52.6 (+0.1)
C(3)	40.1	40.5 (+0.4)	39.6 (−0.5)
C(4)	68.3	68.9 (+0.6)	67.3 (−1.0)
C(5)	51.8	52.0 (+0.2)	51.5 (−0.3)
C(6)	47.7	48.4 (+0.7)	46.5 (−1.2)
C(1')	133.4	133.9 (+0.5)	133.4 (0.0)
C(2')	132.6	132.4 (−0.2)	132.6 (0.0)
C(3')	131.6	131.7 (+0.1)	131.4 (−0.2)
C(4')	135.7	135.4 (−0.3)	136.3 (+0.6)
C(5')	33.4	33.5 (+0.1)	33.5 (+0.1)
C(6')	30.4	30.4 (0.0)	30.4 (0.0)
C(7')	33.2	33.2 (0.0)	33.2 (0.0)
C(8')	132.6	132.7 (+0.1)	132.4 (−0.2)
C(9')	132.4	132.2 (−0.2)	132.1 (−0.3)
C(10')	131.9	131.9 (0.0)	131.9 (0.0)
C(11')	133.2	133.3 (+0.1)	133.4 (+0.2)
C(12')	33.2	33.2 (0.0)	33.2 (0.0)
C(13')	33.0	33.0 (0.0)	33.0 (0.0)
C(14')	23.4	23.4 (0.0)	23.4 (0.0)
C(15')	14.4	14.4 (0.0)	14.4 (0.0)

Figure 85 ^{13}C NMR data for pseudodistomin F **6**. Values of $\Delta\delta_C$ are given in parentheses relative to the data for the natural product.

When ^{1}H NMR spectroscopic data were collected on **6** the data showed agreement ($\Delta\delta_H \leq 0.06$ ppm)[12] with the values quoted by Freyer *et al.*[5] and the synthetic sample prepared by Ma *et al.*[26] The agreement of selected olefinic resonances could be improved when the isolated material was compared to **6**·0.05 TFA, however at the expense of resonances associated with the piperidine head (Figure 86). This adds support to the hypothesis that Freyer's sample likely being pseudodistomin F **6**·*x*HA where $0<x\leq0.05$.

pseudodistomin F **6**



	6 Freyer *et al.*[5] (400 MHz, MeOH-d_4)	**6** Ma *et al.*[26,20,28] (300 MHz, MeOH-d_4)	**6** This work (500 MHz, MeOH-d_4)	**6**·0.05 TFA This work (500 MHz, MeOH-d_4)
C(2)*H*	3.45	3.45 (0.00)	3.46 (+0.01)	3.57 (+0.12)
C(3)H_A	1.50	1.48 (−0.02)	1.50 (0.00)	1.58 (+0.08)
C(3)H_B	1.84	1.85 (+0.01)	1.85 (+0.01)	1.90 (+0.06)
C(4)*H*	3.91	3.95 (+0.04)	3.92 (+0.01)	3.99 (+0.08)
C(5)*H*	2.69	2.73 (+0.04)	2.69 (0.00)	2.89 (+0.20)
C(6)H_A	2.73	2.73 (0.0)	2.74 (+0.01)	2.89 (+0.16)
C(6)H_B	2.77	2.73 (−0.04)	2.78 (+0.01)	2.89 (+0.12)
C(1')*H*	5.55	5.55 (0.00)	5.52 (−0.03)	5.52 (−0.03)
C(2')*H*	6.17	6.17 (0.00)	6.16 (−0.01)	6.22 (+0.05)
C(3')*H*	6.05	6.05 (0.00)	5.99 (−0.06)	6.03 (−0.02)
C(4')*H*	5.67	5.67 (0.00)	5.66 (−0.01)	5.71 (+0.04)
C(5')H_2	2.08	2.06 (−0.02)	2.07 (−0.01)	2.06 (−0.02)
C(6')H_2	1.47	1.48 (+0.01)	1.46 (−0.01)	1.46 (−0.01)
C(7')H_2	2.05	2.06 (+0.01)	2.07 (+0.02)	2.06 (+0.01)
C(8')*H*	5.55	5.55 (0.00)	5.52 (−0.03)	5.52 (−0.03)
C(9')*H*	6.00	6.00 (0.00)	5.99 (−0.01)	5.98 (−0.02)
C(10')*H*	6.00	6.00 (0.00)	5.99 (−0.01)	5.98 (−0.02)
C(11')*H*	5.55	5.55 (0.00)	5.52 (−0.03)	5.52 (−0.03)
C(12')H_2	2.05	2.06 (+0.01)	2.07 (+0.02)	2.06 (+0.01)
C(13')H_2	1.36	1.36 (0.00)	1.34 (−0.02)	1.35 (−0.01)
C(14')H_2	1.36	1.36 (0.00)	1.34 (−0.02)	1.35 (−0.01)
C(15)H_3	0.90	0.92 (+0.02)	0.91 (+0.01)	0.91 (+0.01)

Figure 86 ^{1}H NMR data for pseudodistomin F **6**. Values of $\Delta\delta_H$ are given in parentheses relative to the data for the natural product.

5.3.7 Pseudodistomin Z

C(6)H_{axial} displays a large (11.0 Hz) ^3J coupling constant to C(5)*H*, which also displays ^3J 9.5 Hz to C(4)*H* indicative of a *trans*-diaxial relationships between the respective protons in both instances. This implies C(4)*H* and C(5)*H* adopt axial sites, and thus the C(4)-hydroxy group and the C(5)-amino group occupy equatorial sites. Finally, C(3)H_{axial} shares a large (>11.0 Hz) ^3J coupling constant with C(2)*H*, indicative of a *trans*-diaxial relationship between the protons, and implying the C(2)-alkyl group resides on an equatorial site (Figure 87).

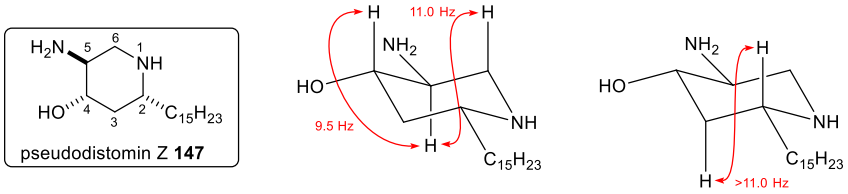


Figure 87 Conformational analysis of pseudodistomin Z **147**.

5.4 Conclusion

In conclusion, this study provides for the first time a complete set of ^{1}H and ^{13}C NMR data in a uniform solvent (MeOH-d_4) and specific rotation data in a uniform solvent (MeOH) for pseudodistomins A–F **1**–**6**. The relative configuration within each member has been independently established *via* ^{3}J coupling constant analysis, whilst the absolute configurations have been established *via* inference from the indium mediated allyl addition to **357** and the Flack *x* parameters of **349** and **367**. Data for each pseudodistomin has been correlated with literature reports (as the relevant acetate or *via* TFA titration), hence allowing the corroboration of the absolute configuration in each instance with previous reports. This study therefore provides the only consistent and correct set of data for the pseudodistomin alkaloids as the free bases.

5.5 References and Notes

[1] Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E.; Zimmer, D. *Org. Lett.* **2017**, *19*, 1638.
[2] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
[3] Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem.* **1987**, *52*, 450.
[4] Kobayashi, J.; Naitoh, K.; Doi, Y.; Deki, K.; Ishibashi, M. *J. Org. Chem.* **1995**, *60*, 6941.
[5] Freyer, A. J.; Patil, A, D.; Killmer, L.; Troupe, N.; Mentzer, M.; Carte, B.; Faucette, L.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 986.
[6] Crampton, M. R.; Robotham, I. A. *J. Chem. Res.* **1997**, 22.
[7] Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.
[8] The samples were not subjected to variable temperature NMR experiments, (which may be expected to induce coalescence of rotamers), as the free bases could be readily subjected to ^{3}J coupling constant analyses, and thus the triacetates were only required for comparison of NMR and specific rotation data.
[9] $\Delta\delta_C = |\delta_C\,(\text{natural}) - \delta_C\,(\text{synthetic})|$
[10] Following data reassignment.
[11] Following correction for a systematic −0.1 ppm deviation.
[12] $\Delta\delta_H = |\delta_H\,(\text{natural}) - \delta_H\,(\text{synthetic})|$
[13] Following data reassignment.
[14] The specific rotation of pseudodistomin B **2** was re-recorded following introduction of TFA, with **2**·0.2 TFA exhibiting a value of $[\alpha]_D^{25}$ −20.5 (*c* 1.0 in MeOH).
[15] Following correction for a systematic −0.2 ppm deviation.
[16] Doi, Y.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573.

[17] Kobayashi's value could hypothetically be extrapolated to enantiopure material (24/0.6 = 40), to yield a corrected value of $[\alpha]_D^{24}$ −40 (*c* 0.7 in MeOH), which could be compared with the synthetic sample of pseudodistomin C **3** isolated in this study.
[18] The specific rotation of pseudodistomin C **3** was re-recorded following introduction of TFA, with **3**·2.0 TFA exhibiting a value of $[\alpha]_D^{25}$ −7.8 (*c* 1.0 in MeOH).
[19] Following correction for a systematic −0.5 ppm deviation.
[20] Following assignment.
[21] Kobayashi associates this resonance with one position only, whereas it is likely a coincident peak for two resonances. Hence it is included twice in this data set.
[22] EXSY NMR analysis was conducted on the sample of pseudodistomin C acetate **65**, unambiguously establishing the presence of two major rotameric species.
[23] Following correction for a systematic +0.04 ppm deviation.
[24] Trost, B. M.; Fandrick, D. R. *Org. Lett*. **2005**, *7*, 823.
[25] Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Taylor, R. J.; Thomson, A. D.; Thomson, J. E. *Org. Lett.* **2012**, *14*, 1672.
[26] Ma, D.; Sun, H. *J. Org. Chem.* **2000**, *65*, 6009.
[27] ^{13}C NMR data were not disclosed in the report by Ma *et al*. (see ref 26).
[28] An additional resonance was erroneously quoted in the data set (see ref 26) which has been excluded here.

Chapter 6

Experimental

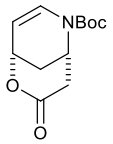
6.1 General Experimental

Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame-dried and cooled under vacuum before use. Solvents were dried according to the procedure outlined by Grubbs *et al*.[1] Water was purified by an Elix® UV-10 system. Allyl bromide and (2*E*)-2-heptenal were distilled from $MgSO_4$. BuLi was purchased from Sigma-Aldrich (as a 2.50 M solution in hexanes) and was titrated against diphenylacetic acid before use. MeMgCl was purchased from Sigma-Aldrich (as a 3.00 M solution in THF) and was titrated against I_2 before use. All other reagents were used as supplied. Organic layers were dried over $MgSO_4$ unless otherwise stated. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm) and 1% $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica. For biphasic eluents, the aqueous phase was removed prior to flash column chromatography. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer on a diamond ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance. The lock frequencies for the residual solvent peaks in the ^{1}H NMR spectra were defined as 7.27 ppm, 3.31 ppm and 8.74 ppm for $CDCl_3$, MeOH-d_4 and C_5D_5N, respectively. The lock frequencies for the ^{13}C NMR spectra were defined as 77.00 ppm, 49.15 ppm and 150.35 ppm for $CDCl_3$, MeOH-d_4 and C_5D_5N, respectively. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Owing to the rotameric nature of some

compounds, several resonances in the rt ^{13}C NMR spectra were doubled and/or broadened. In the latter instance, such resonances appeared at very low intensity; their chemical shift values are reported to the nearest integer (shown in italics and asterisked). Low-resolution mass spectra were recorded on either a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

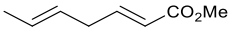
6.2 Experimental Data for Chapter 2

(1*S*,5*S*)-*N*(6)-(*tert*-Butoxycarbonyl)-2-oxa-6-azabicyclo[3.3.1]non-7-en-3-one 152



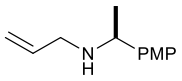
DBU (81 μL, 0.54 mmol) was added dropwise *via* syringe to a stirred solution of **134** (100 mg, 0.27 mmol, >95:5 dr) in CH_2Cl_2 (1 mL) at rt, and the resultant solution was stirred at rt for 6 h. H_2O (1 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organics were washed with brine (4 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 5:1) gave **152** as a white solid (57 mg, 87%, >95:5 dr); mp 111–113 °C; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −303 (*c* 1.0 in $CHCl_3$); ν_{max} 1716, 1692, 1640; δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 2.02–2.05 (1H, m, C(9)*H*$_A$), 2.30–2.33 (1H, m, C(9)*H*$_B$), 2.58–2.63 (1H, m, C(4)*H*$_A$), 2.79–2.85 (1H, m, C(4)*H*$_B$), 4.65–4.87 (2H, m, C(1)*H*, C(5)*H*), 5.18–5.33 (1H, m, C(8)*H*), 6.92–7.09 (1H, m, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 26.8 (*C*(9)), 28.0 (C*Me*$_3$), 36.3, 36.4 (*C*(4)), 43.3, 44.6 (*C*(5)), 68.1 (*C*(1)), 82.3 (*C*Me$_3$), 103.3, 103.9 (*C*(8)), 127.8, 128.0 (*C*(7)), 150.9, *151** (N(6)*C*O), 170.1, 170.4 (*C*(3)); *m/z* (EI^+) 239 ($[M]^+$, 100%); HRMS (EI^+) $C_{12}H_{17}NO_4^+$ ($[M]^+$) requires 239.1152; found 239.1159.

(2*E*,5*E*)-Methyl hepta-2,5-dienoate 129



Butadiene (2.78 mL, 32.0 mmol) was added dropwise *via* syringe to a stirred solution of **156** (2.88 mL, 32.0 mL), $Pd_2(dba)_3{\cdot}CHCl_3$ (66 mg, 64 μmol), $HBF_4{\cdot}Et_2O$ (35 μL, 0.26 mmol) and PBu_3 (32 μL, 0.13 mmol) in a thick-walled vessel at –78 °C. The resultant solution was heated at 80 °C for 5 h behind a blast shield, then cooled to –78 °C before the vessel was opened and allowed to warm to rt over 10 min. The resultant solution was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 50:1) gave **129** as a colourless oil (3.90 g, 87%, >90% purity);[2] δ_H (400 MHz, $CDCl_3$) 1.68 (3H, dd, *J* 6.1, 1.5, C(7)*H*$_3$), 2.88 (2H, td, *J* 6.5, 1.5, C(4)*H*$_2$), 3.73 (3H, s, O*Me*), 5.38–5.57 (2H, m, C(5)*H*, C(6)*H*), 5.83 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 6.97 (1H, dt, *J* 15.7, 6.5, C(3)*H*).

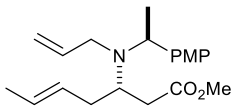
(α*S*)-*N*-Allyl-*N*-(α-methyl-*p*-methoxybenzyl)amine 159



BuLi (2.30 M in hexanes, 80.2 mL, 184 mmol) was added dropwise *via* syringe to a stirred solution of **158** (26.6 g, 176 mmol, >99:1 er) in THF (290 mL) at 0 °C and the resultant solution was stirred at 0 °C for 1 h. A solution of allyl bromide (15.2 mL, 176 mmol) in THF (20 mL) at 0 °C was added dropwise *via* cannula and the resultant solution was allowed to warm to rt over 16h, then quenched with satd aq NH_4Cl (40 mL) and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (300 mL) and H_2O (300 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). Aq NaOH (2.00 M, 200 mL) was added to the aqueous layer, and the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo* to give **159** as a colourless oil (27.9 g, 83%, >95:5 er);[3,4] $[\alpha]_D^{25}$ −59.5 (*c* 1.0 in $CHCl_3$); {lit.[3] for enantiomer

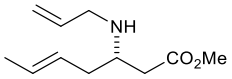
$[\alpha]_D^{20}$ +66 (*c* 1.7 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.6, C(α)*Me*), 3.10 (2H, ddd, *J* 6.2, 1.6, 1.3, C(1)H_2), 3.77 (1H, q, *J* 6.6, C(α)*H*), 3.81 (3H, s, O*Me*), 5.07 (1H, dt, *J* 10.4, 1.3, C(3)H_A), 5.13 (1H, dt, *J* 17.0, 1.6, C(3)H_B), 5.89 (1H, ddt, *J* 17.0, 10.4, 6.2, C(2)*H*), 6.88 (2H, d, *J* 8.7, *Ar*), 7.24 (2H, d, *J* 8.7, *Ar*).

Methyl (3*S*,5*E*,*αS*)-3-[*N*-allyl-*N*-(*α*-methyl-*p*-methoxybenzyl)amino]hept-5-enoate 130



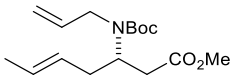
BuLi (2.30 M in hexanes, 10.7 mL, 24.6 mmol) was added dropwise *via* syringe to a stirred solution of **159** (4.86 g, 25.4 mmol, >95:5 er) in THF (20 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. A solution of **129** (2.22 g, 15.9 mmol, >90% purity) in THF (20 mL) at −78 °C was added dropwise *via* syringe and the resultant solution was stirred at −78 °C for 2 h, then quenched with satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were washed sequentially with satd aq $NaHCO_3$ (45 mL) and brine (45 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 15:1) gave **130** as a colourless oil (4.56 g, 87%, >95:5 dr, >90% purity);[5] $[\alpha]_D^{25}$ +2.8 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{20}$ +13.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.65 (3H, d, *J* 5.3, C(7)H_3), 1.92–1.99 (1H, m, C(4)H_A), 2.19–2.29 (3H, m, C(2)H_2, C(4)H_B), 3.00 (1H, app ddt, *J* 15.1, 6.1, 1.5, C(1')H_A), 3.20 (1H, app ddt, *J* 15.1, 6.1, 1.5, C(1')H_B), 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*), 5.01–5.06 (1H, m, C(3')H_A), 5.10–5.16 (1H, m, C(3')H_B), 5.34–5.47 (2H, m, C(5)*H*, C(6)*H*), 5.77–5.87 (1H, m, C(2')*H*), 6.83 (2H, d, *J* 8.6, *Ar*), 7.22 (2H, d, *J* 8.6, *Ar*).

Methyl (3*S*,5*E*)-3-(*N*-allylamino)hept-5-enoate 131



Et_3SiH (11.8 mL, 109 mmol) was added dropwise *via* syringe to a stirred solution of **130** (22.5 g, 67.9 mmol, >95:5 dr, >90% purity) in HCO_2H (300 mL) and the resultant solution was heated at 90 °C for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (65 mL) and satd aq $NaHCO_3$ (65 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 65 mL). The combined organics were washed with brine (195 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O/35% aq NH_4OH,[6] 50:50:1) gave **131** as a pale yellow oil (13.4 g, quant, >90% purity);[5] $[\alpha]_D^{25}$ +5.1 (*c* 0.5 in $CHCl_3$); {lit.[5] $[\alpha]_D^{20}$ +5.5 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.49 (1H, br s, N*H*), 1.69 (3H, d, *J* 6.4, C(7)H_3), 2.16–2.21 (2H, m, C(4)H_2), 2.43 (2H, d, *J* 6.4, C(2)H_2), 3.02–3.08 (1H, m, C(3)*H*), 3.26–3.28 (2H, m, C(1')H_2), 3.69 (3H, s, O*Me*), 5.06–5.11 (1H, m, C(3')H_A), 5.14–5.22 (1H, m, C(3')H_B), 5.35–5.43 (1H, m, C(5)*H*), 5.49–5.56 (1H, m, C(6)*H*), 5.89 (1H, ddt, *J* 17.1, 10.3, 6.0, C(2')*H*).

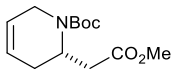
Methyl (3*S*,5*E*)-3-[*N*-allyl-*N*-(*tert*-butoxycarbonyl)amino]hept-5-enoate 132



$NaHCO_3$ (12.8 g, 152 mmol) and Boc_2O (18.3 g, 83.6 mmol) were added sequentially to a solution of **131** (15.0 g, 76.1 mmol, >90% purity) in MeOH (800 mL) and the resultant suspension was sonicated at rt for 16 h, then filtered through Celite® and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (70 mL) and H_2O (70 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 70 mL). The combined organics were washed with satd aq $NaHCO_3$ (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 3:1) gave **132** as a colourless oil (20.9 g, 92%, >95% purity);[5] $[\alpha]_D^{25}$ +13.9 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{20}$ +16.0 (*c* 1.0 in $CHCl_3$)}; δ_H

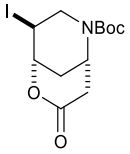
(400 MHz, $CDCl_3$) 1.44–1.48 (9H, m, C*Me*$_3$), 1.64 (3H, dd, *J* 6.4, 0.7, C(7)*H*$_3$), 2.18–2.27 (1H, m, C(4)*H*$_A$), 2.28–2.39 (1H, m, C(4)*H*$_B$), 2.52 (1H, dd, *J* 15.2, 5.9, C(2)*H*$_A$), 2.67 (1H, dd, *J*, 15.2, 8.3, C(2)*H*$_B$), 3.66 (3H, s, O*Me*), 3.67–4.26 (3H, m, C(3)*H*, C(1')*H*$_2$), 5.05–5.18 (2H, m, C(3')*H*$_2$), 5.29–5.36 (1H, m, C(5)*H*), 5.43–5.52 (1H, m, C(6)*H*), 5.74–5.86 (1H, m, C(2')*H*).

Methyl (2*S*)-2-[*N*(1')-(*tert*-butoxycarbonyl)-1',2',3',6'-tetrahydropyridin-2'-yl]ethanoate 133



Grubbs I catalyst (930 mg, 1.13 mmol) was added to a stirred solution of **132** (6.70 g, 22.5 mmol, >95% purity) in degassed CH_2Cl_2 (950 mL) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo* (to a volume of ~200 mL). $P(CH_2OH)_3$ (14.0 g, 113 mmol), Et_3N (6.27 mL, 45.1 mmol) and excess silica were added sequentially and the resultant suspension was stirred at rt for 16 h, then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:1) gave **133** as a pale brown oil (5.59 g, 97%, >95% purity);[5] $[\alpha]_D^{25}$ −24.5 (*c* 1.0 in $CHCl_3$); {lit.[7,5] $[\alpha]_D^{20}$ −29.4 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 1.92–2.04 (1H, m, C(3')*H*$_A$), 2.41–2.56 (3H, C(2)*H*$_2$, C(3')*H*$_B$), 3.47–3.65 (1H, m, C(6')*H*$_A$), 3.66 (3H, s, O*Me*), 4.07–4.33 (1H, m, C(6')*H*$_B$), 4.71–4.91 (1H, m, C(2')*H*), 5.60–5.77 (2H, m, C(4')*H*, C(5')*H*).

(1*S*,5*S*,8*S*)-*N*(6)-(*tert*-Butoxycarbonyl)-8-iodo-2-oxa-6-azabicyclo[3.3.1]nonan-3-one 134

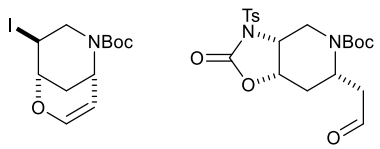


Step 1. A solution of $LiOH·H_2O$ (5.73 g, 136 mmol) in H_2O (350 mL) was added dropwise *via* cannula to a stirred solution of **133** (5.80 g, 22.7 mmol, >95% purity) in THF (650 mL) at rt and the resultant solution was heated at 50 °C for 16 h. The resultant solution was allowed to

cool to rt, then acidified to pH 4 with aq $KHSO_4$ (2.00 M) and extracted with $CHCl_3$ (3 × 500 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*.

Step 2. $NaHCO_3$ (5.73 g, 68.2 mmol) and I_2 (17.3 g, 68.2 mmol) were added sequentially to a stirred solution of the residue from the previous step in MeCN (115 mL) at −20 °C and the resultant solution was stirred at −20 °C for 2 h, then stirred at rt for 16 h. Et_2O (100 mL) and satd aq $Na_2S_2O_3$ (100 mL) were added sequentially and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organics were washed sequentially with H_2O (300 mL) and brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:1) gave **134** as a white solid (8.09 g, 97%, >95:5 dr);[5] mp 87–89 °C;[8] $[\alpha]_D^{25}$ −19.8 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{20}$ −26.3 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 1.89–1.96 (1H, m, C(9)*H*$_A$), 2.58–2.66 (1H, m, C(4)*H*$_A$), 2.80–2.93 (2H, m, C(4)*H*$_B$, C(9)*H*$_B$), 3.30–3.49 (1H, m, C(7)*H*$_A$), 4.23–4.30 (1H, m, C(7)*H*$_B$), 4.36–4.45 (1H, m, C(8)*H*), 4.59–4.85 (1H, m, C(5)*H*), 4.85–4.90 (1H, m, C(1)*H*).

(1*S*,5*S*,8*S*)-*N*(6)-(*tert*-Butoxycarbonyl)-8-iodo-2-oxa-6-azabicyclo[3.3.1]non-3-ene 162 and (2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(2′-oxoethyl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 164



162 **164**

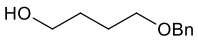
Step 1. DIBAL-H (1.00 M in PhMe, 0.61 mL, 0.61 mmol) was added dropwise *via* syringe to a stirred solution of **134** (225 mg, 0.61 mmol, >95:5 dr) in CH_2Cl_2 (5 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1.5 h. Satd aq Rochelle salt (5 mL) was added and the resultant mixture was stirred at −78 °C for 5 min, then stirred at rt for 1 h. The aqueous layer

was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organics were dried and concentrated *in vacuo* to give a ~10:90 mixture of **160** and **161**, respectively.

Step 2. TsNCO (89 μL, 0.58 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in THF (2 mL) at 0 °C and the resultant solution was stirred at rt for 3 h, then concentrated *in vacuo* to give a ~10:90 mixture of **162** and **163**, respectively.

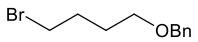
Step 3. Et_3N (85 μL, 0.61 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in acetone (2 mL) at rt and the resultant solution was heated at 60 °C for 3 h, then allowed to cool to rt and concentrated *in vacuo* to give a ~10:90 mixture of **162** and **164**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **162** as a colourless oil (9 mg, 4%, >95:5 dr); $[\alpha]_D^{25}$ −82.5 (*c* 1.0 in $CHCl_3$); ν_{max} 1691, 1637; δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.72–1.79 (1H, m, C(9)H_A), 2.74–2.80 (1H, m, C(9)H_B), 3.40–3.58 (1H, m, C(7)H_A), 4.12–4.26 (1H, m, C(7)H_B), 4.33–4.42 (1H, m, C(8)*H*), 4.52–4.58 (1H, m, C(1)*H*), 4.73–4.79 (1H, m, C(5)*H*), 4.82–4.90 (1H, m, C(4)*H*), 6.60 (1H, d, *J* 5.6, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 24.9 (*C*(9)), 28.2 (*C*(8)), 28.4 (C*Me*$_3$), 40.2, *42** (*C*(5)), *45**, 45.9 (*C*(7)), 72.8 (*C*(1)), 80.3 (*C*Me$_3$), 99.8 (*C*(4)), 147.2 (*C*(3)), *154** (N*C*(1)O); *m/z* (ESI$^+$) 374 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{18}INNaO_3^+$ ([M+Na]$^+$) requires 374.0224; found 374.0223. Further elution gave **164** as a pale yellow oil (186 mg, 63%, >95:5 dr, >85% purity); ν_{max} 1715, 1689, 1367, 1163; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 1.88 (1H, app dt, *J* 14.2, 9.0, C(3)H_A), 2.26–2.34 (1H, m, C(3)H_B), 2.44 (3H, s, Ar*Me*), 2.70 (1H, ddd, *J* 17.4, 6.9, 1.0, C(1′)H_A), 2.77 (1H, ddd, *J* 17.4, 5.4, 1.7 C(1′)H_B), 3.05–3.25 (1H, C(6)H_A), 4.31–4.44 (2H, m, C(2)*H*, C(5)*H*), 4.45–4.58 (1H, m, C(6)H_B), 4.62 (1H, app td, *J* 9.0, 5.1, C(4)*H*), 7.35 (2H, d, *J* 8.0, *Ar*), 7.92 (2H, d, *J* 8.0, *Ar*), 9.70 (1H, s, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*Me*), 28.2 (C*Me*$_3$), *30** (*C*(3)), *40**, *41** (*C*(6)), 44.8 (*C*(2)), *48** (*C*(1′)), 53.9 (*C*(5)), 71.7 (*C*(4)), 81.4 (*C*Me$_3$), 128.4, 129.9, 134.1, 145.9 (*Ar*), 151.5 (TsN*C*O), 154.1 (N(1)*C*O), 199.3 (*C*(2′)); *m/z* (ESI$^+$) 461 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{26}N_2NaO_7S^+$ ([M+Na]$^+$) requires 461.1353; found 461.1346.

4-(Benzyloxy)butan-1-ol 166



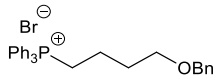
A solution of **165** (40.0 mL, 452 mmol) in THF (80 mL) was added dropwise *via* cannula to a stirred solution of NaH (60% in mineral oil, 4.33 g, 108 mmol) in THF (150 mL) at 0 °C and the resultant solution was stirred at 0 °C for 30 min. A solution of BnBr (10.7 mL, 90.3 mmol) in THF (20 mL) was added dropwise *via* cannula and the resultant solution was allowed to warm to rt over 16 h, then quenched with satd aq NH_4Cl (50 mL). EtOAc (300 mL) and H_2O (300 mL) were added and the aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:1) gave **166** as a colourless oil (16.3 g, quant);[9] δ_H (400 MHz, $CDCl_3$) 1.65–1.77 (4H, m, C(2)H_2, C(3)H_2), 2.28 (1H, br s, O*H*), 3.53 (2H, t, *J* 5.7, C(4)H_2), 3.66 (2H, app q, *J* 5.5, C(1)H_2), 4.53 (2H, s, OCH_2Ph), 7.28–7.38 (5H, m, *Ph*).

1-Bromo-4-(benzyloxy)butane 167



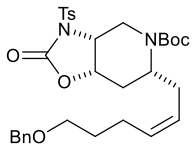
PPh_3 (10.4 g, 39.7 mmol) and CBr_4 (6.38 g, 19.3 mmol) were added sequentially to a stirred solution of **166** (2.00 g, 12.0 mmol) in CH_2Cl_2 (230 mL) at 0 °C and the resultant solution was allowed to warm to rt over 1 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 9:1) gave **167** as a colourless oil (2.44 g, 90%);[10] δ_H (400 MHz, $CDCl_3$) 1.78 (2H, app quin, *J* 6.8, C(3)H_2), 1.99 (2H, app quin, *J* 7.1, C(2)H_2), 3.45 (2H, t, *J* 6.7, C(4)H_2), 3.52 (2H, t, *J* 6.2, C(1)H_2), 4.51 (2H, s, OCH_2Ph), 7.28–7.38 (5H, m, *Ph*).

[4-(Benzyloxy)butyl]triphenylphosphonium bromide 168

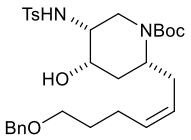


PPh_3 (2.16 g, 8.23 mmol) was added to a stirred solution of **167** (2.00 g, 8.23 mmol) and the resultant solution was heated at 120 °C for 2 h, then allowed to cool to rt. Purification *via* recrystallization from CH_2Cl_2 gave **168** as a white solid (4.08 g, 98%);[11] mp 150–152 °C;[8] δ_H (400 MHz, $CDCl_3$) 1.80 (2H, app dq, *J* 15.6, 7.9, C(2)H_2), 2.05 (2H, app q, *J* 6.4, C(3)H_2), 3.64 (2H, t, *J* 5.6, C(4)H_2), 3.88–3.95 (2H, m, C(1)H_2), 4.48 (2H, s, OCH_2Ph), 7.09–7.95 (20H, m, *Ph*).

(2*R*,4*S*,5*R*,2'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[6′-(benzyloxy)hex-2′-en-1′-yl]-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 169 and (2*R*,4*S*,5*R*,2'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(6′-(benzyloxy)hex-2′-en-1′-yl)-4-hydroxy-5-(*N*-tosylamino)piperidine 170



169

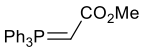


170

NaHMDS (1.00 M in THF, 1.00 mL, 1.00 mmol) was added dropwise *via* syringe to a stirred solution of **168** (502 mg, 1.00 mmol) in THF (1 mL) at 0 °C and resultant solution was stirred at rt for 40 min, then re-cooled to 0 °C. A solution of **164** (175 mg, 0.37 mmol, >95:5 dr, ~85% purity) in THF (2 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 16 h, then quenched with satd aq NH_4Cl (5 mL). Et_2O (10 mL) and H_2O (5 mL) were added and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organics were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **169** as a colourless oil (101 mg, 46%, >95:5 dr [(2'*Z*):(2'*E*)]); $[\alpha]_D^{25}$ −28.8 (*c* 1.0 in $CHCl_3$); ν_{max} 1693, 1597, 1368, 1171; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, CMe_3), 1.60 (2H, app quin, *J* 6.9, C(5')H_2),

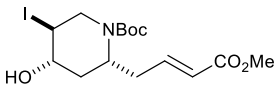
1.71 (1H, app dt, *J* 14.1, 10.2, C(3)H_A), 2.03–2.09 (3H, m, C(3)H_B, C(4')H_2), 2.22–2.33 (2H, m, C(1')H_2), 2.38 (3H, s, Ar*Me*), 2.90–3.04 (1H, m, C(6)H_A), 3.40 (2H, t, *J* 6.4, C(6')H_2), 3.76–3.96 (1H, m, C(2)*H*), 4.22–4.36 (1H, m, C(5)*H*), 4.43 (2H, app s, OCH_2Ph), 4.45–4.76 (2H, m, C(4)*H*, C(6)H_B), 5.23–5.30 (1H, m, C(2')*H*), 5.46 (1H, dt, *J* 11.0, 7.4, C(3')*H*), 7.22–7.30 (7H, m, *Ar*, *Ph*), 7.88 (2H, d, *J* 6.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*Me*), 23.9 (*C*(4')), 28.2 (C*Me*$_3$), 29.4 (*C*(5')), *30** (*C*(3)), *31** (*C*(1')), *41**, *42** (*C*(6)), *49**, *50** (*C*(2)), 53.9 (*C*(5)), 69.4 (*C*(6')), 72.2 (*C*(4)), 72.8 (O*C*H_2Ph), 80.6 (*C*Me$_3$), 124.0 (*C*(2')), 127.4, 127.5, 128.2, 128.4, 129.8 (*Ar*, *Ph*), 132.9 (*C*(3')), 134.1, 138.4, 145.8 (*Ar*, *Ph*), *152** (TsN*C*O), *154** (N(1)*C*O); *m/z* (ESI^+) 607 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{31}H_{40}N_2NaO_7S^+$ ($[M+Na]^+$) requires 607.2448; found 607.2447. Further elution gave **170** as a colourless oil (10 mg, 5%, >95:5 dr [(2'*Z*):(2'*E*)], ~95% purity); $[\alpha]_D^{25}$ +0.5 (*c* 0.25 in $CHCl_3$); ν_{max} 3274, 1689, 1599, 1365, 1160; δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.47–1.56 (2H, m, C(3)H_A, C(5')H_A), 1.69–1.84 (2H, m, C(3)H_B, C(5')H_B), 1.91–2.07 (2H, m, C(1')H_A, C(4')H_A), 2.39 (3H, s, Ar*Me*), 2.42–2.55 (1H, m, C(4')H_B), 2.83–2.95 (2H, m, C(6)H_A, C(1')H_B), 3.16–3.23 (1H, m, C(5)*H*), 3.33 (1H, br s, O*H*), 3.46 (1H, ddd, *J* 9.8, 6.9, 3.9, C(6')H_A), 3.59 (1H, ddd, *J* 9.8, 7.3, 3.9, C(6')H_B), 3.64 (1H, m, C(4)*H*), 3.75 (1H, dd, *J* 13.1, 4.3, C(6)H_B), 4.01 (1H, app dt, *J* 10.3, 5.5, C(2)*H*), 4.44 (2H, d, *J* 11.6, OC$H_A$$H_B$Ph), 4.48 (2H, d, *J* 11.6, OC$H_A$$H_B$Ph), 4.92 (1H, d, *J* 8.8, N*H*), 5.26–5.41 (2H, m, C(2')*H*, C(3')*H*), 7.26–7.42 (7H, m, *Ar*, *Ph*), 7.73 (2H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*Me*), 23.7 (*C*(4')), 28.3 (C*Me*$_3$), 29.4 (*C*(5')), 30.7 (*C*(1')), 32.2 (*C*(3)), *38** (*C*(6)), *47** (*C*(2)), 52.2 (*C*(5)), 66.1 (*C*(4)), 69.4 (*C*(6')), 73.0 (O*C*H_2Ph), 79.8 (*C*Me$_3$), 126.8 (*Ar*, *Ph*), 127.5 (*C*(2')), 128.1, 128.2, 128.5, 129.7 (*Ar*, *Ph*), 131.1 (*C*(3')), 138.5, 143.3 (*Ar*, *Ph*), 154.5 (N*C*(1)O); *m/z* (ESI^+) 581 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{30}H_{42}N_2NaO_6S^+$ ($[M+Na]^+$) requires 581.2656; found 581.2659.

Methyl 2-(triphenylphosphranylidene)acetate 176



175 (23.7 mL, 250 mmol) was added dropwise *via* syringe to a stirred solution of PPh_3 (65.6 g, 250 mmol) in EtOAc (500 mL) at rt. After 16 h the precipitate was collected by vacuum filtration and was washed with Et_2O (400 mL). The solid residue was dissolved in CH_2Cl_2 (800 mL), the resultant solution was cooled to 0 °C, and aq NaOH (2.00 M, 500 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to a total volume of 100 mL. The resultant mixture was stirred at rt for 16 h, then filtered to give **176** as a white solid (76.1 g, 91%);[12] mp 164–167 °C; {lit.[13] mp 162–163 °C}; δ_H (400 MHz, $CDCl_3$) 2.85–2.97 (1H, br s, PC*H*), 3.45–3.62 (3H, br s, O*Me*), 7.43–7.71 (15H, m, *Ph*).

(2*R*,4*S*,5*S*,2'*E*)- and (2*R*,4*S*,5*S*,2'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(4′-methoxy-4′-oxobut-2′-en-1′-yl)-4-hydroxy-5-iodopiperidine 177

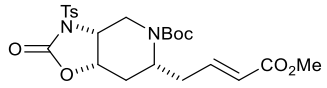


Step 1. DIBAL-H (1.00 M in PhMe, 4.20 mL, 4.20 mmol) was added dropwise *via* syringe to a stirred solution of **134** (1.54 g, 4.20 mmol, >95:5 dr) in CH_2Cl_2 (35 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1.5 h. Satd aq Rochelle salt (35 mL) was added and the resultant mixture was stirred at −78 °C for 5 min, then stirred at rt for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL) and the combined organics were dried and concentrated *in vacuo* to give a ~10:90 mixture of **160** and **161**, respectively.

Step 2. **176** (1.54 g, 4.62 mmol) was added to a stirred solution of the residue from the previous in CH_2Cl_2 (20 mL) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **177** as a colourless oil (1.60 g, 90%, 65:35 dr [(2'*E*):(2'*Z*)]); ν_{max} 3437,

1723, 1694, 1662; *m/z* (ESI$^+$) 426 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{25}INO_5^+$ ([M+H]$^+$) requires 426.0772; found 426.0770. Data for (*E*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.62–1.68 (1H, m, C(3)*H*$_A$), 2.44–2.52 (1H, m, C(3)*H*$_B$), 2.53–2.58 (1H, m, C(1′)*H*$_A$), 2.79–2.87 (1H, m, C(1′)*H*$_B$), 3.48–3.54 (2H, m, C(6)*H*$_A$, O*H*), 3.68 (3H, s, O*Me*), 4.00–4.06 (1H, m, C(6)*H*$_B$), 4.18–4.23 (2H, m, C(4)*H*, C(5)*H*), 4.29–4.35 (1H, m, C(2)*H*), 5.80–5.85 (1H, m, C(3′)*H*), 6.87 (1H, dt, *J* 15.3, 7.6, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 29.0 (*C*(3)), 30.6 (*C*(5)), 36.0 (*C*(1′)), 41.3 (*C*(6)), 48.4 (*C*(2)), 51.4 (O*Me*), 70.1 (*C*(4)), 80.3 (*C*Me$_3$), 122.8 (*C*(3′)), 146.4 (*C*(2′)), 154.7 (N*C*(1)O), 166.8 (*C*(4′)). Data for (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 1.62–1.68 (1H, m, C(3)*H*$_A$), 2.44–2.52 (1H, m, C(3)*H*$_B$), 3.02–3.15 (2H, m, C(1′)*H*$_2$), 3.60 (1H, dd, *J* 15.2, 2.2, C(6)*H*$_A$), 3.68 (3H, s, O*Me*), 3.75 (1H, d, *J* 2.2, O*H*), 4.00–4.06 (1H, m, C(6)*H*$_B$), 4.18–4.23 (2H, m, C(4)*H*, C(5)*H*), 4.29–4.35 (1H, m, C(2)*H*), 5.80–5.85 (1H, m, C(3′)*H*), 6.21 (1H, dt, *J* 11.5, 7.9, C(2′)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 28.9 (*C*(3)), 30.7 (*C*(5)), 33.1 (*C*(1′)), 41.2 (*C*(6)), 48.2 (*C*(2)), 51.3 (O*Me*), 70.0 (*C*(4)), 80.2 (*C*Me$_3$), 120.7 (*C*(3′)), 147.1 (*C*(2′)), 154.8 (N*C*(1)O), 167.2 (*C*(4′)).

(2*R*,4*S*,5*R*,2'*E*)- and (2*R*,4*S*,5*R*,2'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(4′-methoxy-4′-oxobut-2′-en-1′-yl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 179

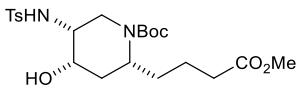


Step 1. TsNCO (1.38 mL, 9.05 mmol) was added dropwise *via* syringe to a stirred solution of **177** (4.05 g, 9.53 mmol, 65:35 dr [(2'*E*):(2'*Z*)]) in THF (60 mL) at 0 °C and the resultant solution was stirred at rt for 3 h, then concentrated *in vacuo*.

Step 2. Et_3N (1.23 mL, 8.84 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in acetone (100 mL) at rt and the resultant solution was heated at 60 °C for 3 h, then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 5:1) gave **179** as a white solid (4.28 g, 91%, 65:35 dr [(2'*E*):(2'*Z*)]). Data for mixture: mp 68–70 °C; ν_{max} 1719, 1690,

1597, 1329, 1159; *m/z* (ESI$^+$) 517 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}N_2NaO_8S^+$ ([M+Na]$^+$) requires 517.1615; found 517.1611. Data for (*E*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 1.75–1.83 (1H, m, C(3)*H*$_A$), 2.11–2.18 (1H, m, C(3)*H*$_B$), 2.43 (3H, s, Ar*Me*), 2.48–2.60 (2H, m, C(1′)*H*$_2$), 2.87–3.08 (1H, m, C(6)*H*$_A$), 3.69 (3H, s, O*Me*), 3.97–4.15 (1H, m, C(2)*H*), 4.29–4.42 (1H, m, C(5)*H*), 4.50–4.62 (1H, m, C(4)*H*), 4.66–4.79 (1H, m, C(6)*H*$_B$), 5.81–5.86 (1H, m, C(3′)*H*), 6.80 (1H, dt, *J* 15.4, 7.6, C(2′)*H*), 7.34 (2H, d, *J* 8.1, *Ar*), 7.90 (2H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*Me*), 28.1 (C*Me*$_3$), 30.1 (*C*(3)), *36** (*C*(1′)), *40**, *41** (*C*(6)), *49** (*C*(2)), 51.4 (O*Me*), 53.7 (*C*(5)), 71.9 (*C*(4)), 81.0 (*C*Me$_3$), 124.0 (*C*(3′)), 128.3, 129.8, 134.1 (*Ar*), 143.2 (*C*(2′)), *146** (*Ar*), 151.5 (TsN*C*O), 154.0 (N(1)*C*O), 166.2 (*C*(4′)). Data for (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 1.75–1.83 (1H, m, C(3)*H*$_A$), 2.11–2.18 (1H, m, C(3)*H*$_B$), 2.43 (3H, s, Ar*Me*), 2.87–3.08 (3H, m, C(6)*H*$_A$, C(1′)*H*$_2$), 3.65 (3H, s, O*Me*), 3.97–4.15 (1H, m, C(2)*H*), 4.29–4.42 (1H, m, C(5)*H*), 4.50–4.62 (2H, m, C(4)*H*, C(6)*H*$_B$), 5.81–5.86 (1H, m, C(3′)*H*), 6.07–6.21 (1H, m, C(2′)*H*), 7.34 (2H, d, *J* 8.1, *Ar*), 7.90 (2H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*Me*), 28.1 (C*Me*$_3$), 30.1 (*C*(3)), 32.7 (*C*(1′)), *40**, *41** (*C*(6)), *49** (*C*(2)), 51.0 (O*Me*), 53.7 (*C*(5)), 72.0 (*C*(4)), 80.8 (*C*Me$_3$), *122** (*C*(3′)), 128.3, 129.8, 134.1 (*Ar*), *144** (*C*(2′)), 145.8 (*Ar*), 151.5 (TsN*C*O), 154.2 (N(1)*C*O), 166.2 (*C*(4′)).

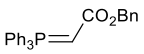
(2*R*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(4′-methoxy-4′-oxobut-1′-yl)-4-hydroxy-5-(*N*-tosylamino)piperidine 181



Step 1. Pd(OH)$_2$/C (146 mg, 50% w/w of **179**) was added to a stirred solution of **179** (292 mg, 0.59 mmol, 65:35 dr [(2′*E*):(2′*Z*)]) in degassed EtOAc (5 mL) at rt and the resultant suspension was stirred at rt for 6 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. K_2CO_3 (815 mg, 5.90 mmol) was added to a stirred solution of the residue from the previous step in MeOH (10 mL) at rt and the resultant suspension was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between EtOAc (1 mL) and H_2O (1 mL) and the aqueous layer was extracted with EtOAc (2 × 1 mL). The combined organics were washed with brine (3 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **181** as a colourless oil (214 mg, 77%, >95:5 dr); $[\alpha]_D^{25}$ +15.7 (*c* 1.0 in $CHCl_3$); ν_{max} 3493, 3285, 1735, 1686, 1328, 1155; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 1.50–1.67 (3H, m, C(1′)*H*$_A$, C(2′)*H*$_2$), 1.75 (1H, ddd, *J* 14.7, 6.8, 3.0, C(3)*H*$_A$), 1.79–1.84 (1H, m, C(1′)*H*$_B$), 1.84 (1H, ddd, *J* 14.7, 3.0, 1.7, C(3)*H*$_B$), 2.15–2.19 (1H, m, O*H*), 2.32 (2H, t, *J* 7.2, C(3′)*H*$_2$), 2.44 (3H, s, Ar*Me*), 2.86 (1H, dd, *J* 12.7, 11.8, C(6)*H*$_A$), 3.26 (1H, dddd, *J* 11.8, 8.2, 4.9, 3.0, C(5)*H*), 3.66 (3H, s, O*Me*), 3.78 (1H, dd, *J* 12.7, 4.9, C(6)*H*$_B$), 3.97 (1H, app t, *J* 3.0, C(4)*H*), 4.10 (1H, app q, *J* 6.8, C(2)*H*), 5.03 (1H, d, *J* 8.2, N*H*), 7.32 (2H, d, *J* 8.2, *Ar*), 7.79 (2H, d, *J* 8.2, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*Me*), 22.0 (*C*(2′)), 28.3 (C*Me*$_3$), 31.7 (*C*(1′)), 33.5 (*C*(3′)), 33.8 (*C*(3)), *38** (*C*(6)), *48** (*C*(2)), 51.6 (O*Me*), 52.5 (*C*(5)), 66.8 (*C*(4)), 79.9 (*C*Me$_3$), 126.8, 129.8, 138.0, 143.5 (*Ar*), 154.5 (N*C*(1)O), 174.3 (*C*(4′)); *m/z* (ESI$^+$) 493 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{34}N_2NaO_7S^+$ ([M+Na]$^+$) requires 493.1979; found 493.1973.

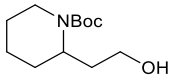
Benzyl 2-(triphenylphosphranylidene)acetate 189



188 (35.0 mL, 222 mmol) was added dropwise *via* syringe to a stirred solution of PPh_3 (58.1 g, 222 mmol) in EtOAc (500 mL) at rt. After 16 h the precipitate was collected by vacuum filtration and was washed with Et_2O (300 mL). The solid residue was dissolved in CH_2Cl_2 (800 mL), the resultant solution was cooled to 0 °C, and aq NaOH (2.00 M, 444 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to a total volume of 100 mL. The resultant mixture was

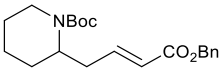
stirred at rt for 16 h, then filtered to give **189** as a white solid (58.2 g, 64%);[14] mp 121–123 °C; {lit.[14] mp 115–120 °C}; δ_H (400 MHz, $CDCl_3$) 2.76–3.15 (1H, br s, PC*H*), 4.85–5.15 (2H, br s, OCH_2Ph), 7.14–7.83 (20H, m, *Ph*).

(2*RS*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(2'-hydroxyeth-1'-yl)piperidine 191



$NaHCO_3$ (13.0 g, 155 mmol) and Boc_2O (18.6 g, 85.1 mmol) were added sequentially to a solution of **190** (10.0 g, 77.4 mmol) in MeOH (800 mL) and the resultant suspension was sonicated at rt for 16 h, then filtered through Celite® and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (70 mL) and H_2O (70 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 70 mL). The combined organics were washed with satd aq $NaHCO_3$ (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:3) gave **191** as a colourless oil (16.3 g, 92%);[15] δ_H (400 MHz, $CDCl_3$) 1.33–1.41 (1H, m, C(5)H_A), 1.44 (9H, s, CMe_3), 1.46–1.62 (5H, m, C(3)H_A, C(4)H_2, C(5)H_B, C(1')H_A), 1.65–1.76 (1H, m, C(3)H_B), 1.92 (1H, app t, *J* 13.0, C(1')H_B), 2.66 (1H, app td, *J* 13.1, 2.7, C(6)H_A), 3.25–3.44 (1H, m, C(2')H_A), 3.53–3.62 (1H, m, C(2')H_B), 3.70–4.03 (2H, m, C(6)H_B, O*H*), 4.34–4.47 (1H, m, C(2)*H*).

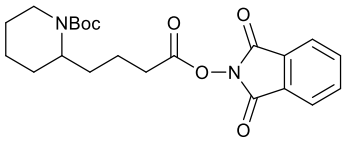
(2*RS*,2'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(4'-benzyloxy-4'-oxobut-2'-en-1'-yl)piperidine 193



DMSO (6.19 mL, 87.2 mmol) was added dropwise *via* syringe to a stirred solution of $(COCl)_2$ (3.69 mL, 43.6 mmol) in CH_2Cl_2 (55 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of **191** (5.00 g, 21.8 mmol) in CH_2Cl_2 (55 mL) was added

dropwise *via* cannula at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (18.1 mL, 131 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 20 min, then **189** (9.85 g, 24.0 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 7:1) gave **193** as a colourless oil (6.90 g, 88%, >95:5 dr [(2'*E*):(2'*Z*)]); ν_{max} 1719, 1686, 1656; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, CMe_3), 1.49–1.68 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.31–2.37 (1H, m, C(1')H_A), 2.55–2.63 (1H, m, C(1')H_B), 2.74 (1H, app td, *J* 13.1, 2.6, C(6)H_A), 4.01 (1H, app d, *J* 11.7, C(6)H_B), 4.32–4.47 (1H, m, C(2)*H*), 5.16 (2H, s, OCH_2Ph), 5.90 (1H, dt, *J* 15.6, 1.3, C(3')*H*), 6.95 (1H, dt, *J* 15.6, 7.6, C(2')*H*), 7.30–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8, 25.3, 28.3 (*C*(3), *C*(4), *C*(5)), 28.3 (CMe_3), 33.0 (*C*(1')), *39** (*C*(6)), *50** (*C*(2)), 66.1 (OCH_2Ph), 79.5 (*C*Me_3), 122.8 (*C*(3')), 128.1, 128.3, 128.5, 136.0 (*Ph*), 146.4 (*C*(2')), 154.8 (N*C*(1)O), 166.0 (*C*(4')); *m/z* (ESI$^+$) 382 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{29}NNaO_4^+$ ([M+Na]$^+$) requires 382.1989; found 382.1986.

(2*RS*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[4'-(phthalimidooxy)-4'-oxobut-1'yl]piperidine 195

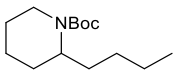


Step 1. $Pd(OH)_2/C$ (1.00 g, 50% w/w of **193**) was added to a stirred solution of **193** (2.00 g, 5.56 mmol, >95:5 dr [(2'*E*):(2'*Z*)]) in degassed EtOAc (55 mL) at rt and the resultant suspension was stirred at rt for 6 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. DIC (0.86 mL, 5.56 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, NHP (907 mg, 5.56 mmol) and DMAP (68 mg, 0.56 mmol) in CH_2Cl_2 (55 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in*

vacuo. Purification *via* flash column chromatography (eluent CH_2Cl_2/Et_2O, 30:1) gave **195** as a colourless oil (1.97 g, 85%); ν_{max} 1815, 1788, 1742, 1680; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, C*Me*$_3$), 1.49–1.67 (7H, m, C(3)*H*$_2$, C(4)*H*$_2$, C(5)*H*$_2$, C(1')*H*$_A$), 1.69–1.80 (2H, m, C(2')*H*$_2$), 1.87–1.96 (1H, m, C(1')*H*$_B$), 2.66–2.79 (3H, m, C(6)*H*$_A$, C(3')*H*$_2$), 3.93–4.04 (1H, m, C(6)*H*$_B$), 4.22–4.34 (1H, m, C(2)*H*), 7.76–7.81 (2H, m, *Ar*), 7.86–7.90 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.0, 21.5, 25.5 (*C*(3), *C*(4), *C*(5)), 28.4 (C*Me*$_3$), 28.4 (*C*(2')), 28.7 (*C*(1')), 30.7 (*C*(3')), *39** (*C*(6)), *50** (*C*(2)), 79.2 (*C*Me$_3$), 123.9, 128.9, 134.7 (*Ar*), 155.0 (N*C*(1)O), 161.9 (Ar*C*O), 169.4 (*C*(4')); *m/z* (ESI$^+$) 439 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{28}N_2NaO_6^+$ ([M+Na]$^+$) requires 439.1840; found 439.1835.

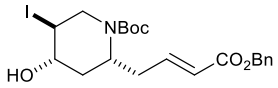
(2*RS*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(but-1'-yl)piperidine 196



Step 1. MeMgCl (3.00 M in THF, 0.72 mL, 2.16 mmol) was added dropwise *via* syringe to a stirred solution of $ZnCl_2$ (0.50 M in THF, 2.16 mL, 1.08 mmol) at 0 °C. The resultant solution was allowed to warm to rt over 10 min.

Step 2. A solution of $NiCl_2$·glyme (24 mg, 0.11 mmol) and BBBPY (59 mg, 0.22 mmol) in DMF (6 mL) was added dropwise *via* syringe to **195** (226 mg, 0.54 mmol) and the resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (3 mL). Et_2O (2 mL) and H_2O (2 mL) were added and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave **196** as a colourless oil (81 mg, 62%);[16] δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2, C(4')*H*$_3$), 1.14–1.72 (12H, m, C(3)*H*$_2$, C(4)*H*$_2$, C(5)*H*$_2$, C(1')*H*$_2$, C(2')*H*$_2$, C(3')*H*$_2$), 1.46 (9H, s, C*Me*$_3$), 2.75 (1H, app td, *J* 11.5, 2.5, C(6)*H*$_A$), 3.97 (1H, app d, *J* 11.5, C(6)*H*$_B$), 4.14–4.24 (1H, m, C(2)*H*).

(2*R*,4*S*,5*S*,2'*E*)- and (2*R*,4*S*,5*S*,2'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[4′-(benzyloxy)-4′-oxobut-2′-en-1′-yl]-4-hydroxy-5-iodopiperidine 197

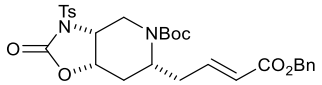


Step 1. DIBAL-H (1.00 M in PhMe, 3.73 mL, 3.73 mmol) was added dropwise *via* syringe to a stirred solution of **134** (1.37 g, 3.73 mmol, >95:5 dr) in CH_2Cl_2 (30 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1.5 h. Satd aq Rochelle salt (30 mL) was added and the resultant mixture was stirred at −78 °C for 5 min, then stirred at rt for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organics were dried and concentrated *in vacuo* to give a ~10:90 mixture of **160** and **161**, respectively.

Step 2. **189** (1.69 g, 4.62 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (20 mL) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **197** as a colourless oil (1.87 g, quant, 65:35 dr [(2'*E*):(2'*Z*)]). Data for mixture: ν_{max} 3429, 1718, 1691, 1663; *m/z* (ESI^+) 502 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{29}INO_5^+$ ($[M+H]^+$) requires 502.1085; found 502.1076. Data for (*E*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 1.62–1.67 (1H, m, C(3)*H*$_A$), 2.47–2.54 (1H, m, C(3)*H*$_B$), 2.59 (1H, app dtd, *J* 14.2, 7.2, 1.2, C(1′)*H*$_A$), 2.78–2.86 (1H, m, C(1′)*H*$_B$), 3.15 (1H, br s, O*H*), 3.55 (1H, dd, *J* 15.3, 2.6, C(6)*H*$_A$), 4.02–4.09 (1H, m, C(6)*H*$_B$), 4.15–4.25 (2H, m, C(4)*H*, C(5)*H*), 4.32–4.38 (1H, m, C(2)*H*), 5.16 (2H, s, OC*H*$_2$Ph), 5.91 (1H, dt, *J* 15.7, 1.2, C(3′)*H*), 6.94 (1H, dt, *J* 15.7, 7.2, C(2′)*H*), 7.30–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 29.1 (*C*(3)), 30.6 (*C*(5)), 35.9, 36.1 (*C*(1′)), 42.7, 43.4 (*C*(6)), 48.3 (*C*(2)), 66.0 (OC*H*$_2$Ph), 70.2 (*C*(4)), 80.2 (*C*Me$_3$), 122.9 (*C*(3′)), 128.1, 128.2, 128.4, 135.9 (*Ph*), 146.7 (*C*(2′)), 154.6 (N*C*(1)O), 166.4 (*C*(4′)). Data for (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 1.62–1.67 (1H, m, C(3)*H*$_A$), 2.42 (1H, br s, O*H*), 2.47–2.54 (1H, m, C(3)*H*$_B$), 3.01 (1H, app dtd, *J* 14.4, 7.2, 1.6, C(1′)*H*$_A$), 3.17–3.23 (1H, m, C(1′)*H*$_B$), 3.61 (1H, dd, *J* 15.2, 2.0, C(6)*H*$_A$), 4.02–4.09 (1H, m, C(6)*H*$_B$), 4.15–4.25 (2H, m, C(4)*H*, C(5)*H*), 4.32–4.38 (1H, m, C(2)*H*), 5.17 (2H, s, OC*H*$_2$Ph),

5.92 (1H, dt, *J* 11.6, 1.6, C(3′)*H*), 6.27 (1H, ddd, *J* 11.6, 8.7, 7.2, C(2′)*H*), 7.30–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 29.0 (*C*(3)), 30.7 (*C*(5)), 33.2 (*C*(1′)), 41.2, 41.3 (*C*(6)), 48.2 (*C*(2)), 66.0 (O*C*H$_2$Ph), 70.0 (*C*(4)), 80.1 (*C*Me$_3$), 120.8 (*C*(3′)), 128.1, 128.2, 128.5, 135.7 (*Ph*), 147.5 (*C*(2′)), 154.7 (N*C*(1)O), 166.1 (*C*(4′)).

(2*R*,4*S*,5*R*,2'*E*)- and (2*R*,4*S*,5*R*,2'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[4′-(benzyloxy)-4′-oxobut-2′-en-1′-yl]-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 184

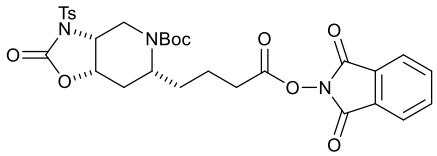


Step 1. TsNCO (1.62 mL, 10.6 mmol) was added dropwise *via* syringe to a stirred solution of **197** (5.59 g, 11.2 mmol, 65:35 dr [(2'*E*):(2'*Z*)]) in THF (90 mL) at 0 °C and the resultant solution was stirred at rt for 3 h, then concentrated *in vacuo*.

Step 2. Et_3N (1.55 mL, 11.2 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in acetone (75 mL) at rt and the resultant solution was heated at 60 °C for 3 h, then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 5:1) gave **184** as a colourless oil (4.90 g, 77%, 65:35 dr [(2'*E*):(2'*Z*)]). Data for mixture: ν_{max} 1718, 1692, 1597, 1367, 1169; *m/z* (ESI$^+$) 571 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{35}N_2O_8S^+$ ([M+H]$^+$) requires 571.2109; found 571.2103. Data for (*E*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.13–2.20 (1H, m, C(3)*H*$_A$), 1.72–1.86 (1H, m, C(3)*H*$_B$), 2.40–2.61 (2H, m, C(1′)*H*$_2$), 2.45 (3H, s, Ar*Me*), 2.94–3.10 (1H, m, C(6)*H*$_A$), 3.99–4.17 (1H, m, C(2)*H*), 4.29–4.46 (1H, m, C(5)*H*), 4.52–4.85 (2H, m, C(4)*H*, C(6)*H*$_B$), 5.17 (2H, app s, OC*H*$_2$Ph), 5.89–5.95 (1H, m, C(3′)*H*), 6.87 (1H, dt, *J* 15.4, 7.0, C(2′)*H*), 7.30–7.37 (7H, m, *Ar*, *Ph*), 7.94 (2H, d, *J* 6.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (Ar*Me*), 28.2 (C*Me*$_3$), 30.3 (*C*(3)), *36**, *37** (*C*(1′)), *40**, *41** (*C*(6)), *48**, *49** (*C*(2)), 53.8 (*C*(5)), 66.0 (O*C*H$_2$Ph), 72.0 (*C*(4)), 81.0 (*C*Me$_3$), 124.2 (*C*(3′)), 128.2, 128.3, 128.4, 128.5, 128.6, 129.9, 134.2, 135.7 (*Ar*, *Ph*), 143.7 (*C*(2′)), 151.5 (TsN*C*O), 154.3 (N(1)*C*O), 165.6 (*C*(4′)). Data for (*Z*)-isomer: δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.13–2.20 (1H, m,

C(3)H_A), 1.72 –1.86 (1H, m, C(3)H_B), 2.45 (3H, s, Ar*Me*), 2.94–3.10 (3H, m, C(1′)H_2, C(6)H_A), 3.99–4.17 (1H, m, C(2)*H*), 4.29–4.46 (1H, m, C(5)*H*), 4.52–4.85 (2H, m, C(4)*H*, C(6)H_B), 5.13 (1H, d, *J* 12.2, OC$H_A$$H_B$Ph), 5.17 (1H, d, *J* 12.2, OCH$_A$$H_B$Ph), 5.89–5.95 (1H, m, C(3′)*H*), 6.11–6.26 (1H, m, C(2′)*H*), 7.30–7.37 (7H, m, *Ar*, *Ph*), 7.94 (2H, d, *J* 6.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (Ar*Me*), 28.2 (C*Me*$_3$), 30.3 (*C*(3)), 32.9 (*C*(1′)), *40**, *41** (*C*(6)), *48**, *49** (*C*(2)), 53.8 (*C*(5)), 66.2 (O*C*H$_2$Ph), 72.0 (*C*(4)), 81.2 (*C*Me$_3$), *122** (*C*(3′)), 128.2, 128.3, 128.4, 128.5, 128.6, 129.9, 134.2, 135.7 (*Ar*, *Ph*), 145.9 (*C*(2′)), 151.5 (TsN*C*O), 154.1 (N(1)*C*O), 165.6 (*C*(4′)).

(2*R*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[4'-(phthalimidooxy)-4'-oxobut-1'yl]-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 185

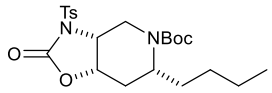


Step 1. Pd(OH)$_2$/C (550 mg, 50% w/w of **184**) was added to a stirred solution of **184** (1.10 g, 1.93 mmol, 65:35 dr [(2'*E*):(2'*Z*)]) in degassed EtOAc (19 mL) at rt and the resultant suspension was stirred at rt for 6 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. DIC (0.30 mL, 1.93 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, NHP (315 mg, 1.93 mmol) and DMAP (24 mg, 0.19 mmol) in CH_2Cl_2 (19 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/Et_2O, 20:1) gave **185** as a white solid (1.16 g, 96%, >95:5 dr); mp 85–87 °C; $[\alpha]_D^{25}$ −14.1 (*c* 1.0 in $CHCl_3$); ν_{max} 1744, 1692, 1367, 1173; δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 1.58–1.66 (1H, m, C(1′)H_A), 1.72–1.87 (4H, m, C(3)H_A, C(1′)H_B, C(2′)H_2), 2.16–2.28 (1H, m, C(3)H_B), 2.43 (3H, s, Ar*Me*), 2.67–2.72 (2H, m, C(3′)H_2), 2.93–3.08 (1H, m, C(6)H_A), 3.95–4.13 (1H, m, C(2)*H*), 4.31–4.47 (1H, m, C(5)*H*), 4.52–4.79 (1H, m, C(6)H_B), 4.58 (1H, app td, *J* 8.4, 5.0, C(4)*H*), 7.35 (2H, d,

J 8.1, *Ar*), 7.77–7.81 (2H, m, *Ar*), 7.85–7.89 (2H, m, *Ar*), 7.91–7.97 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.9 (*C*(2′)), 21.7 (Ar*Me*), 28.2 (C*Me*$_3$), 30.2 (*C*(3)), 30.5 (*C*(3′)), 32.6 (*C*(1′)), 39.7, 40.8 (*C*(6)), 48.1, 48.9 (*C*(2)), 53.8 (*C*(5)), 72.3 (*C*(4)), 81.0 (*C*Me$_3$), 123.9, 128.4, 128.8, 129.9, 134.3, 134.8, 145.8 (*Ar*), 151.6 (TsN*C*O), 154.4 (N*C*(1)O), 161.8 (Ar*C*O), 169.1 (*C*(4′)).[17]

(2*R*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(but-1'-yl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 199

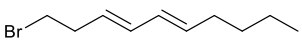


Step 1. MeMgCl (3.00 M in THF, 0.38 mL, 1.14 mmol) was added dropwise *via* syringe to a stirred solution of $ZnCl_2$ (0.50 M in THF, 1.14 mL, 0.57 mmol) at 0 °C. The resultant solution was allowed to warm to rt over 10 min.

Step 2. A solution of $NiCl_2$·glyme (13 mg, 59 μmol) and BBBPY (31 mg, 0.11 mmol) in DMF (3 mL) was added dropwise *via* syringe to **185** (178 mg, 0.29 mmol, >95:5 dr) and the resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (2 mL). Et_2O (1 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **199** as a colourless oil (91 mg, 71%, >95:5 dr); $[\alpha]_D^{25}$ −26.6 (*c* 1.0 in $CHCl_3$); ν_{max} 1786, 1693, 1597, 1367, 1173; δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.2, C(4')*H*$_3$), 1.40–1.46 (1H, m, C(1')*H*$_A$), 1.17–1.34 (4H, m, C(2')*H*, C(3')*H*$_2$), 1.47 (9H, s, C*Me*$_3$), 1.60–1.69 (1H, m, C(1')*H*$_B$), 1.78 (1H, app dt, *J* 14.4, 8.8, C(3)*H*$_A$), 2.10–2.22 (1H, m, C(3)*H*$_B$), 2.45 (3H, s, Ar*Me*), 2.89–3.07 (1H, m, C(6)*H*$_A$), 3.84–4.05 (1H, m, C(2)*H*), 4.28–4.44 (1H, m, C(5)*H*), 4.53–4.79 (2H, m, C(4)*H*, C(6)*H*$_B$), 7.35 (2H, d, *J* 7.8, *Ar*), 7.94 (2H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(4')), 21.6 (Ar*Me*), 22.3 (*C*(3')), 27.6 (*C*(2')), 28.3 (C*Me*$_3$), *30** (*C*(3)), *33** (*C*(1')), *40** (*C*(6)), *48** (*C*(2)), 54.0 (*C*(5)), 72.5 (*C*(4)), 80.5 (*C*Me$_3$), 128.4, 129.8, 134.3, 145.8 (*Ar*), 151.7

(TsN*C*O), 154.4 (N*C*(1)O); *m/z* (ESI$^+$) 475 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{32}N_2NaO_6S^+$ ([M+Na]$^+$) requires 475.1873; found 475.1868.

(3*E*,5*E*)-1-Bromodeca-3,5-diene 82



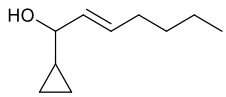
Method A. HBr (48% aq, 15 mL) was added dropwise *via* syringe to stirred **204** (5.50 g, 35.6 mmol, >95:5 dr [(2*E*):(2*Z*)]) at 0 °C and the resultant solution was stirred at rt for 16 h. Hexane (35 mL) and H_2O (35 mL) were added and the aqueous layer was extracted with hexane (2 × 35 mL). The combined organics were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether, neat) gave **82** as a colourless oil (7.03 g, 91%, 86:7:7 dr [(3*E*,5*E*):(3*E*,5*Z*):(3*Z*,5*E*)]).[18] Data for mixture: ν_{max} 1656.[17] Data for 82: δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(10)H_3), 1.30–1.44 (4H, m, C(8)H_2, C(9)H_2), 2.08 (2H, app q, *J* 6.8, C(7)H_2), 2.63 (2H, app q, *J* 7.0, C(2)H_2), 3.39 (2H, t, *J* 7.1, C(1)H_2), 5.53 (1H, dt, *J* 14.5, 7.2, C(3)*H*), 5.66 (1H, dt, *J* 14.5, 7.2, C(6)*H*), 5.99–6.14 (2H, m, C(4)*H*, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(10)), 22.2 (*C*(9)), 31.4 (*C*(8)), 32.3 (*C*(1)), 32.4 (*C*(7)), 36.0 (*C*(2)), 127.5 (*C*(3)), 129.6 (*C*(5)), 133.3 (*C*(4)), 134.6 (*C*(6)).[19]

Method B. Step 1. **200** (3.20 mL, 34.1 mmol) was added dropwise *via* syringe to stirred DIBAL-H (1.00 M in hexanes, 34.1 mL, 34.1 mmol) at 0 °C and the resultant solution was heated at 50 °C for 16 h, then cooled to −78 °C. A solution of I_2 (10.4 g, 40.9 mmol) in THF (22 mL) was added dropwise *via* cannula 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 added dropwise *via* cannula to a stirred mixture of pentane (100 mL) and aq HCl (2.00 M, 100 mL) at 0 °C and the resultant mixture was stirred for 5 min at 0 °C. The aqueous layer was extracted with pentane (2 × 100 mL) and the combined organics were washed sequentially with satd aq $NaHCO_3$ (300

mL), $Na_2S_2O_3$ (300 mL) and brine (300 mL), then dried and concentrated *in vacuo* to give **201** in >95:5 dr [(1*E*):(1*Z*)].

Step 2. **202** (3.92 mL, 34.1 mmol) was added dropwise *via* syringe to stirred DIBAL-H (1.00 M in hexanes, 34.1 mL, 34.1 mmol) at 0 °C and the resultant solution was heated at 50 °C for 16 h, then cooled to 0 °C. A solution of $ZnCl_2$ (5.34 g, 39.2 mmol), $Pd(PPh_3)_4$ (118 mg, 0.10 mmol) and the residue from the previous step in THF (8 mL) was added dropwise *via* syringe and the resultant solution was stirred allowed to warm to rt over 16 h. The reaction solution was added dropwise *via* cannula to a stirred mixture of pentane (100 mL) and aq HCl (2.00 M, 100 mL) at 0 °C and the resultant mixture was stirred for 5 min at 0 °C. The aqueous layer was extracted with pentane (2 × 100 mL) and the combined organics were washed sequentially with satd aq $NaHCO_3$ (300 mL) and brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether, neat) gave **82** as a colourless oil (2.05 g, 28%, >95:5 dr [(3*E*,5*E*):(3*E*,5*Z*)]).

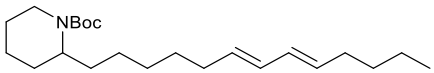
(1*RS*,2*E*)-1-Cyclopropylhept-2-en-1-ol 204



Cyclopropylmagnesium bromide (0.26 M in THF, 18.0 mL, 4.68 mmol) was added dropwise *via* syringe to a stirred solution of **144** (0.31 mL, 2.34 mmol, >95:5 dr [(2*E*):(2*Z*)]) in THF (5 mL) at 0 °C. The resultant solution was allowed to warm to rt over 16 h, then quenched with satd aq NH_4Cl (2 mL). Et_2O (2 mL) and H_2O (2 mL) were added and the aqueous layer was extracted with Et_2O (2 × 4 mL). The combined organics were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 3:1) gave **204** as a pale yellow oil (313 mg, 87%, >95:5 dr [(2*E*):(2*Z*)]);[18] ν_{max} 3353, 1673;[20] δ_H (400 MHz, $CDCl_3$) 0.20–0.26 (1H, m, C(2')H_A), 0.31–0.37 (1H, m, C(3')H_A), 0.47–0.58 (2H, m, C(2')H_B, C(3')H_B), 0.90 (3H, t, *J* 7.1, C(7)H_3), 0.95–1.03

(1H, m, C(1')*H*), 1.28–1.41 (4H, m, C(5)H_2, C(6)H_2), 1.65 (1H, br s, O*H*), 2.05 (2H, app q, *J* 6.8, C(4)H_2), 3.45 (1H, app t, *J* 7.4, C(1)*H*), 5.55 (1H, dd, *J* 15.4, 7.4, C(2)*H*), 5.67 (1H, dtd, *J* 15.4, 6.6, 0.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 2.0, 3.0 (*C*(2'), *C*(3')), 13.9 (*C*(7)), 17.6 (*C*(1')), 22.2 (*C*(6)), 31.3 (*C*(5)), 31.9 (*C*(4)), 77.1 (*C*(1)), 131.2 (*C*(2)), 132.1 (*C*(3));[19] *m/z* (EI^+) 154 ($[M]^+$, 100%); HRMS (EI^+) $C_{10}H_{18}O^+$ ($[M]^+$) requires 154.1352; found 154.1350.[21]

(2*RS*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)piperidine 206



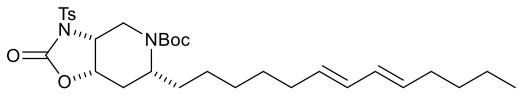
Step 1. A small portion (~1 mL) of a solution of **82** (600 mg, 2.76 mmol, 86:7:7 dr [(3*E*,5*E*):(3*E*,5*Z*):(3*Z*,5*E*)]) in THF (6 mL) was added to Mg turnings (101 mg, 4.14 mmol) and I_2 (8 mg, 32 μmol) at rt. The resultant suspension was heated with a heat gun until the dark brown colour disappeared. The remaining solution was added and the resultant suspension was heated at 70 °C for 1 h, then allowed to cool to rt and then further cooled to 0 °C. The concentration of the resultant dec-3,5-dien-1-ylmagnesium bromide solution was determined *via* iodometric titration.[22]

Step 2. A solution of 1-deca-3,5-dienylmagnesium bromide (0.23 M in THF, 5.57 mL, 1.28 mmol) was added dropwise *via* syringe to a stirred solution of $ZnCl_2$ (0.50 M in THF, 1.28 mL, 0.64 mmol) at 0 °C. The resultant solution was allowed to warm to rt over 10 min.

Step 3. A solution of $NiCl_2$·glyme (14 mg, 64 μmol) and BBBPY (34 mg, 0.13 mmol) in DMF (3 mL) was added dropwise *via* syringe to **195** (133 mg, 0.32 mmol) and the resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (2 mL). Et_2O (1 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 30:1) gave **206** as a colourless oil (63 mg, 54%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]); ν_{max} 1689; δ_H

(400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9, C(13')H_3), 1.17–1.72 (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), 1.45 (9H, s, CMe_3), 1.99–2.09 (4H, m, C(5')H_2, C(10')H_2), 2.73 (1H, app d, *J* 12.2, C(6)H_A), 3.96 (1H, app d, *J* 12.2, C(6)H_B), 4.12–4.23 (1H, m, C(2)*H*), 5.49–5.61 (2H, m, C(6')*H*, C(9')*H*), 5.91–6.07 (2H, m, C(7')*H*, C(8')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 19.0, 22.2, 25.6, 26.2, (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 28.5 (CMe_3) 29.1, 29.4, 29.6, 29.6, 31.5 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 32.2, 32.5 (*C*(5'), *C*(10')), *39** (*C*(6)), *50** (*C*(2)), 78.9 (*C*Me_3), 130.3, 130.4 (*C*(7'), *C*(8')), 132.1, 132.4 (*C*(6'), *C*(9')), 155.1 (N*C*(1)O); *m/z* (ESI^+) 386 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{41}NNaO_2^+$ ($[M+Na]^+$) requires 386.3030; found 386.3026.

(2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 186



Method A. *Step 1*. A small portion (~1 mL) of a solution of **82** (2.50 g, 11.5 mmol, 86:7:7 dr [(3*E*,5*E*):(3*E*,5*Z*):(3*Z*,5*E*)]) in THF (12 mL) was added to Mg turnings (420 mg, 17.3 mmol) and I_2 (30 mg, 0.12 mmol) at rt. The resultant suspension was heated with a heat gun until the dark brown colour disappeared. The remaining solution was added and the resultant suspension was heated at 70 °C for 1 h, then allowed to cool to rt and then further cooled to 0 °C. The concentration of the resultant dec-3,5-dien-1-ylmagnesium bromide solution was determined *via* iodometric titration.[22]

Step 2. A solution of 1-deca-3,5-dienylmagnesium bromide (0.48 M in THF, 5.00 mL, 2.40 mmol) was added dropwise *via* syringe to a stirred solution of $ZnCl_2$ (0.50 M in THF, 2.40 mL, 1.20 mmol) at 0 °C. The resultant solution was allowed to warm to rt over 10 min.

Step 3. A solution of $NiCl_2$·glyme (26 mg, 0.12 mmol) and BBBPY (64 mg, 0.24 mmol) in DMF (6 mL) was added dropwise *via* syringe to **211** (459 mg, 0.60 mmol, >95:5 dr) and the

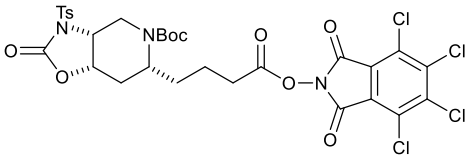
resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (5 mL). Et_2O (1 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 10:1) gave **186** as a colourless oil (281 mg, 82%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]); $[\alpha]_D^{25}$ −26.6 (*c* 0.5 in $CHCl_3$); ν_{max} 1692, 1597, 1366, 1170; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.1, C(13)H_3), 1.18–1.38 (10H, m, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.41–1.52 (10H, m, C(1')H_A, CMe_3), 1.58–1.67 (1H, m, C(1')H_B), 1.75 (1H, app dt, *J* 14.4, 8.5, C(3)H_A), 1.98–2.17 (5H, m, C(3)H_B, C(5')H_2, C(10')H_2), 2.43 (3H, s, Ar*Me*), 2.86–3.04 (1H, m, C(6)H_A), 3.82–4.02 (1H, m, C(2)*H*), 4.27–4.42 (1H, m, C(5)*H*), 4.52–4.76 (1H, m, C(6)H_B), 4.54 (1H, app td, *J* 8.5, 5.0, C(4)*H*), 5.47–5.52 (2H, m, C(6')*H*, C(9')*H*), 5.89–6.00 (2H, m, C(7')*H*, C(8')*H*), 7.34 (2H, d, *J* 7.8, *Ar*), 7.92 (2H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.8 (*C*(13')), 21.6 (Ar*Me*), 22.1, 25.2 (*C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 28.2 (CMe_3), 28.7, 29.1 (*C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), *30** (*C*(3)), 31.4 (*C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 32.1, 32.3 (*C*(5')), *C*(10')), 33.4 (*C*(1')), 39.8, 40.9 (*C*(6)), 48.6, 49.2 (*C*(2)), 53.9 (*C*(5)), 72.4 (*C*(4)), 80.4 (*C*Me_3), 128.3, 129.8 (*Ar*), 130.1, 130.4 (*C*(7')), *C*(8')), 131.7, 132.4 (*C*(6')), *C*(9')), 134.2, 145.7 (*Ar*), 151.6 (TsN*C*O), 154.4 (N(1)*C*O); *m/z* (ESI^+) 597 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{31}H_{46}N_2NaO_6S^+$ ($[M+Na]^+$) requires 597.2969; found 597.2961.

Method B. *Step 1*. A small portion (~1 mL) of a solution of **82** (2.47 g, 11.4 mmol, 86:7:7 dr [(3*E*,5*E*):(3*E*,5*Z*):(3*Z*,5*E*)]) in THF (11 mL) was added to Mg turnings (415 mg, 17.1 mmol) and I_2 (29 mg, 0.11 mmol) at rt. The resultant suspension was heated with a heat gun until the dark brown colour disappeared. The remaining solution was added and the resultant suspension was heated at 70 °C for 1 h, then allowed to cool to rt and then further cooled to 0 °C. The concentration of the resultant dec-3,5-dien-1-ylmagnesium bromide solution was determined *via* iodometric titration.[22]

Step 2. A solution of 1-deca-3,5-dienylmagnesium bromide (0.52 M in THF, 4.62 mL, 2.40 mmol) was added dropwise *via* syringe to a stirred solution of $ZnCl_2$ (0.50 M in THF, 2.40 mL, 1.20 mmol) at 0 °C. The resultant solution was allowed to warm to rt over 10 min.

Step 3. A solution of $NiCl_2$·glyme (26 mg, 0.12 mmol) and BBBPY (64 mg, 0.24 mmol) in DMF (6 mL) was added dropwise *via* syringe to **185** (375 mg, 0.60 mmol, >95:5 dr) and the resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (5 mL). Et_2O (1 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 10:1) gave **186** as a colourless oil (179 mg, 52%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]).

(2*R*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[4'-(tetrachlorophthalimidooxy)-4'-oxobut-1'yl]-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 211

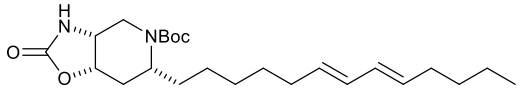


Step 1. $Pd(OH)_2/C$ (2.93 g, 50% w/w of **184**) was added to a stirred solution of **184** (5.85 g, 10.2 mmol, 65:35 dr [(2'*E*):(2'*Z*)]) in degassed EtOAc (102 mL) at rt and the resultant suspension was stirred at rt for 6 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. DIC (1.58 mL, 10.2 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, TCNHP (3.07 g, 10.2 mmol) and DMAP (125 mg, 1.02 mmol) in CH_2Cl_2 (102 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/Et_2O, 50:1) gave **211** as a white solid (2.65 g, 34%, >95:5 dr); mp 108–110 °C; $[\alpha]_D^{25}$ −1.6 (*c* 1.0 in $CHCl_3$); ν_{max} 1818,

1788, 1749, 1692, 1368, 1172; δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.58–1.68 (1H, m, C(2')H_A), 1.69–1.88 (4H, m, C(3)H_A, C(1')H_2, C(2')H_B), 2.14–2.30 (1H, m, C(3)H_B), 2.45 (3H, s, Ar*Me*), 2.64–2.77 (2H, m, C(3')H_2), 2.90–3.10 (1H, m, C(6)H_A), 3.95–4.14 (1H, m, C(2)*H*), 4.29–4.47 (1H, m, C(5)*H*), 4.52–4.80 (1H, m, C(6)H_B), 4.58 (1H, app td, *J* 8.4, 5.0, C(4)*H*), 7.37 (2H, d, *J* 8.1, *Ar*), 7.89–7.99 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.8 (*C*(1')), 21.7 (Ar*Me*), 28.3 (C*Me*$_3$), 30.3 (*C*(3)), 30.4 (*C*(3')), *32** (*C*(2')), *40**, *41** (*C*(6)), *48**, *49** (*C*(2)), 53.8 (*C*(5)), 72.2 (*C*(4)), *81** (*C*Me$_3$), 124.6, 128.4, 129.9, 130.4, 134.2, 141.0, 145.9 (*Ar*), 151.6 (TsN*C*O), 154.4 (N*C*(1)O), 157.4 (Ar*C*O), 168.7 (*C*(4')).[17]

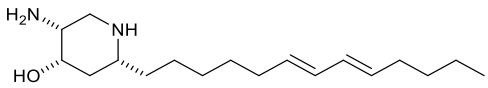
(2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 212



Na (36 mg, 1.58 mmol) was added to a stirred solution of naphthalene (243 mg, 1.90 mmol) in DME (2 mL) at rt. The resultant solution was stirred at rt for 16 h, then cooled to −78 °C. A solution of **186** (91 mg, 0.16 mmol, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]) in DME (1 mL) at −78 °C was added dropwise *via* syringe and the resultant solution was stirred for 30 min at −78 °C, then quenched with EtOH (2 mL). CH_2Cl_2 (2 mL) and satd aq $NaHCO_3$ (2 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organics were washed sequentially with H_2O (6 mL) and brine (6 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 5:1) gave **212** as a colourless oil (59 mg, 89%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]); $[\alpha]_D^{25}$ −31.8 (*c* 0.5 in $CHCl_3$); ν_{max} 1692, 1589; δ_H (400 MHz, $CDCl_3$)[23] 0.88 (3H, m, C(13')H_3), 1.25–1.39 (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*$_3$), 1.46–1.54 (1H, m, C(1')H_A), 1.64–1.73 (1H, m, C(1')H_B), 1.76–1.84 (1H, m, C(3)H_A), 2.01–2.22 (5H, m, C(3)H_B, C(5')H_2, C(10')H_2), 2.78–2.93 (1H, m, C(6)H_A), 3.79–4.00 (2H, m, C(2)*H*, C(5)*H*), 4.03–4.32 (1H, m, C(6)H_B),

4.66 (1H, app dd, *J* 13.7, 8.1, C(4)*H*), 5.50–5.59 (2H, m, C(6')*H*, C(9')*H*), 5.91–6.02 (2H, m, C(7')*H*, C(8')*H*), 6.13 (0.6H, br s, N*H*), 6.45 (0.4H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.2, 25.3 (*C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 28.3 (C*Me*$_3$), 28.9, 29.3 (*C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), *30** (*C*(3)), 31.5 (*C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 32.1, 32.4 (*C*(5'), *C*(10')), *34** (*C*(1')), 40.5, 41.7 (*C*(6)), *49**, *50** (*C*(2), *C*(5)), 74.0 (*C*(4)), 80.3 (*C*Me$_3$), 130.2, 130.5 (*C*(7'), *C*(8')), 131.9, 132.5 (*C*(6'), *C*(9')), 154.8 (N(1)*C*O), 159.2 (HN*C*O); *m/z* (ESI^+) 443 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{24}H_{40}N_2NaO_4^+$ ($[M+Na]^+$) requires 443.2880; found 443.2878.

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

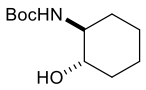


Step 1. KOH (30% aq, 3.0 mL) was added dropwise *via* syringe to a stirred solution of **212** (59 mg, 0.14 mmol, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]) in MeOH (3 mL) at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. *Step 2*. HCl (1.25 M in MeOH, 2 mL) was added dropwise *via* syringe to the residue from the previous step at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 3 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc/MeOH/35% aq NH_4OH,[6] 40:4:1) gave **5** as a colourless oil (30 mg, 72%, 82:8:8:2 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*,8'*Z*)]);[24] $[\alpha]_D^{25}$ −34.5 (*c* 1.0 in MeOH); $[\alpha]_D^{25}$ −9.2 (*c* 1.0 in 1.25 M methanolic HCl); {lit.[24] $[\alpha]_D^{25}$ −20.8 (*c* 0.39 MeOH)}; ν_{max} 3283, 3016, 2924, 2854, 1575, 1457, 986; δ_H (400 MHz, MeOH-*d*$_4$) 0.91 (3H, t, *J* 7.1, C(13)*H*$_3$),

1.22 (1H, app q, *J* 12.0, C(3)H_A), 1.29–1.42 (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), 1.68 (1H, ddd, *J* 12.3, 4.4, 2.7, C(3)H_B), 2.03–2.08 (4H, m, C(5')H_2, C(10')H_2), 2.43–2.48 (1H, m, C(2)*H*), 2.73 (1H, dd, *J* 13.3, 2.5, C(6)H_A), 2.90 (1H, m, C(5)*H*), 2.98 (1H, dd, *J* 13.3, 2.5, C(6)H_B), 3.67 (1H, app dt, *J* 11.4, 4.2, C(4)*H*), 5.49–5.57 (2H, m, C(6')*H*, C(9')*H*), 5.95–6.01 (2H, m, C(7')*H*, C(8')*H*); δ_C (100 MHz, MeOH-d_4) 14.5 (*C*(13'), 23.4 (*C*(12')), 26.9 (*C*(2')), 30.5, 30.6 (*C*(3'), *C*(4')), 33.0 (*C*(11')), 33.5, 33.7 (*C*(5'), *C*(10')), 35.6 (*C*(3)), 37.4 (*C*(1')), 50.4 (*C*(6)), 51.4 (*C*(5)), 56.5 (*C*(2)), 71.0 (*C*(4)), 132.0, 132.1 (*C*(7'), *C*(8')), 133.0, 133.2 (*C*(6'), *C*(9')); *m/z* (ESI$^+$) 295 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{35}N_2O^+$ ([M+H]$^+$) requires 295.2744; found 295.2744. Data for **5**·0.1 TFA: $[\alpha]_D^{25}$ −22.0 (*c* 0.5 in MeOH).

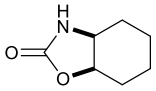
6.3 Experimental Data for Chapter 3

(1*S*,2*S*)-1-Hydroxy-2-[*N*-(*tert*-butoxycarbonyl)amino]cyclohexane 231



Boc_2O (9.50 g, 43.4 mmol) and Et_3N (6.02 mL, 43.4 mmol) were added sequentially to a stirred solution of **230** (5.00 g, 43.4 mmol, >95:5 dr) in CH_2Cl_2 (220 mL) at rt and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **231** as a white solid (9.35 g, quant, >95:5 dr);[25] mp 106–108 °C; {lit.[25] mp 108–110 °C}; $[\alpha]_D^{25}$ +27.9 (*c* 1.0 in MeOH); {lit.[25] $[\alpha]_D^{25}$ +23.6 (*c* 0.5 in MeOH)}; δ_H (400 MHz, $CDCl_3$) 1.07–1.34 (4H, m, C(3)H_A, C(4)H_A, C(5)H_A, C(6)H_A), 1.43 (9H, s, CMe_3), 1.63–1.73 (2H, m, C(4)H_B, C(5)H_B), 1.91–2.05 (2H, m, C(3)H_B, C(6)H_B), 3.23–3.2 (2H, m, C(2)*H*, C(1)*H*), 3.38 (1H, br s, O*H*), 4.69 (1H, d, *J* 4.4, N*H*).

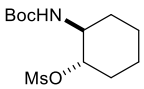
(1*R*,2*S*)-1-Hydroxy-2-amino-*N*,*O*-carbonyl-cyclohexane 232



Method A. Pyridine (2 mL) was added dropwise *via* syringe to **233** (595 g, 2.03 mmol, >95:5 dr) and the resultant solution was heated at 115 °C for 16 h then cooled to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **232** as a white solid (286 mg, quant, >95:5 dr);[26] mp 92–94 °C; {lit.[26] for enantiomer mp 92–93 °C}; $[\alpha]_D^{25}$ +28.3 (*c* 1.0 in $CHCl_3$); {lit.[26] for enantiomer $[\alpha]_D^{25}$ −28.8 (*c* 1.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.20–1.32 (1H, m, C(4)H_A), 1.36–1.64 (4H, m, C(3)H_A, C(4)H_B, C(5)H_2), 1.67–1.85 (2H, m, C(3)H_B, C(6)H_A), 1.89–2.00 (1H, m, C(6)H_B), 3.72 (1H, q, *J* 5.8, C(2)*H*), 4.52–4.59 (1H, m, C(1)*H*), 6.38 (1H, br s, N*H*).

Method B. $SOCl_2$ (0.12 mL, 1.71 mmol) was added dropwise *via* syringe to a stirred solution of **231** (307 mg, 1.43 mmol, >95:5 dr) in THF (7 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **232** as a white solid (148 mg, 74%, >95:5 dr).

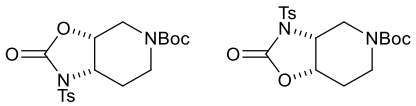
(1*S*,2*S*)-1-Mesyloxy-2-[*N*-(*tert*-butoxycarbonyl)amino]cyclohexane 233



Et_3N (1.29 mL, 9.29 mmol) was added dropwise *via* syringe to a stirred solution of **231** (500 mg, 2.32 mmol, >95:5 dr) and MsCl (0.36 mL, 4.64 mmol) in CH_2Cl_2 (11 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **233** as a white solid (642 mg, 94%, >95:5 dr);[27] mp 127–129 °C; {lit.[27] mp 121 °C}; $[\alpha]_D^{25}$ +13.4 (*c* 1.0 in CH_2Cl_2); {lit.[27] $[\alpha]_D^{25}$ +13.3 (*c* 1.5 in CH_2Cl_2)}; δ_H (400 MHz, $CDCl_3$) 1.20–1.34 (3H, m, C(3)H_A, C(4)H_A, C(5)H_A), 1.38 (9H, s,

C*Me*$_3$), 1.53–1.66 (2H, m, C(4)*H*$_B$, C(6)*H*$_A$), 1.68–1.77 (1H, m, C(5)*H*$_B$), 1.95–2.06 (1H, m, C(3)*H*$_B$), 2.09–2.17 (1H, m, C(6)*H*$_B$), 2.98 (3H, s, *Me*), 3.45–3.60 (1H, m, C(2)*H*), 4.33–4.43 (1H, m, C(1)*H*), 4.86 (1H, d, *J* 8.6, N*H*).

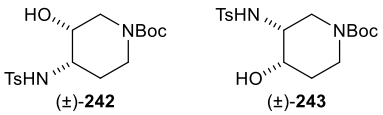
(4*RS*,5*SR*)-*N*(1)-(*tert*-Butoxycarbonyl)-4-(*N*-tosylamino)-5-hydroxy-*N*,*O*-carbonylpiperidine (±)-236 and (4*RS*,5*SR*)-*N*(1)-(*tert*-Butoxycarbonyl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine (±)-237



(±)-**236** (±)-**237**

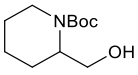
TBAI (558 mg, 1.51 mmol) was added to a stirred solution of (±)-**235** (300 mg, 1.51 mmol, >95:5 dr) and TsNCO (0.35 mL, 2.26 mmol) in PhMe (7.5 mL) at rt and the resultant mixture was heated at 100 °C for 16 h then cooled to rt. EtOAc (7 mL) and H_2O (7 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 7 mL). The combined organics were washed with brine (21 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave a 75:25 mixture of (±)-**236** and (±)-**237**, respectively, as a white solid (597 mg, quant). Data for mixture: ν_{max} 1782, 1678, 1365, 1162; *m/z* (ESI$^+$) 419 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{24}N_2NaO_6S^+$ ([M+Na]$^+$) requires 419.1247; found 419.1240. Data for (±)-**236**: δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 1.89–2.18 (2H, m, C(3)*H*$_2$), 2.43 (3H, s, Ar*Me*), 3.04–3.31 (1H, m, C(2)*H*$_A$), 3.26 (1H, dd, *J* 15.3, 2.3, C(6)*H*$_A$), 3.38–3.57 (1H, m, C(2)*H*$_B$), 4.11 (1H, app d, *J* 15.3, C(6)*H*$_B$), 4.59–4.87 (2H, m, C(4)*H*, C(5)*H*), 7.34 (2H, d, *J* 8.4, *Ar*), 7.92 (2H, d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*Me*), 25.9 (*C*(3)), 28.2 (C*Me*$_3$), *38** (*C*(2)), *40**, *42** (*C*(6)), *54** (*C*(4)), 72.6 (*C*(5)), 80.5 (*C*Me$_3$), 128.2, 129.5, 134.7, 145.7 (*Ar*), 151.5 (TsN*C*O), *155** (N(1)*C*O). Data for (±)-**237**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.86 (1H, dd, *J* 14.5, 4.8, C(6)*H*$_B$); δ_C (100 MHz, $CDCl_3$) [selected peaks] *37** (*C*(2)), *55** (*C*(5)), 71.9 (*C*(4)), 129.7 (*Ar*).

(4*RS*,5*SR*)-*N*(1)-(*tert*-Butoxycarbonyl)-4-(*N*-tosylamino)-5-hydroxypiperidine (±)-242 and (4*RS*,5*SR*)-*N*(1)-(*tert*-Butoxycarbonyl)-4-hydroxy-5-(*N*-tosylamino)piperidine (±)-243



KOH (30% aq, 2 mL) was added dropwise *via* syringe to a stirred solution of a 75:25 mixture of (±)-**236** and (±)-**237**, respectively, (100 mg, 0.25 mmol) in MeOH (2 mL) at rt and the resultant solution was heated at 70 °C for 6 h, then allowed to cool to rt. CH_2Cl_2 (4 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 4 mL). The combined organic extracts were washed with brine (12 mL), then dried (over Na_2SO_4) and concentrated *in vacuo* to give a 75:25 mixture of (±)-**242** and (±)-**243**, respectively, as a pale yellow oil (89 mg, 95%). Data for mixture: ν_{max} 3455, 3274, 1672, 1366, 1159; *m/z* (ESI^+) 393 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{26}N_2NaO_5S^+$ ($[M+Na]^+$) requires 393.1455; found 393.1449. Data for (±)-**242**: δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 1.54–1.76 (2H, m, C(3)*H*$_2$), 2.38 (3H, s, Ar*Me*), 2.74 (1H, app t, *J* 11.5, C(2)*H*$_A$), 2.88 (1H, app d, *J* 13.4, C(6)*H*$_A$), 3.25 (1H, app dt, *J* 10.6, 3.5, C(4)*H*), 3.64–3.69 (1H, m, C(5)*H*), 3.78–3.87 (1H, m, C(2)*H*$_B$), 3.92 (1H, app d, *J* 12.2, C(6)*H*$_B$), 7.24 (2H, d, *J* 8.1, *Ar*), 7.74 (2H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.4 (Ar*Me*), 27.2 (*C*(3)), 28.3 (C*Me*$_3$), *42** (*C*(2)), *48** (*C*(6)), 53.7 (*C*(4)), 66.7 (*C*(5)), 80.0 (*C*Me$_3$), 126.8, 129.6, 138.4, 143.1 (*Ar*), 155.6 (N(1)*C*O). Data for (±)-**243**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.36 (9H, s, C*Me*$_3$), 2.37 (3H, s, Ar*Me*), 3.04 (1H, app dd, *J* 12.2, 10.0, C(2)*H*$_A$), 3.13–3.21 (1H, m, C(5)*H*), 3.78–3.87 (2H, m, C(4)*H*, C(6)*H*$_B$); δ_C (100 MHz, $CDCl_3$) [selected peaks] 53.1 (*C*(5)), 66.8 (*C*(4)), 79.7 (*C*Me$_3$), 126.9, 138.3, 142.9 (*Ar*), 154.7 (N(1)*C*O).

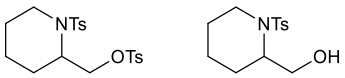
(2*RS*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)piperidine 254



$NaHCO_3$ (14.6 g, 174 mmol) and Boc_2O (20.8 g, 95.5 mmol) were added sequentially to a solution of **253** (10.0 g, 86.8 mmol) in MeOH (600 mL) and the resultant suspension was

sonicated at rt for 16 h, then filtered through Celite® and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (80 mL) and H_2O (80 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The combined organics were washed with satd aq $NaHCO_3$ (250 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:3) gave **254** as a white solid (17.2 g, 92%);[28] mp 74–76 °C; {lit.[28] mp 75–77 °C}; δ_H (400 MHz, $CDCl_3$) 1.38–1.45 (2H, m, C(4)H_A, C(5)H_A), 1.45 (9H, s, CMe_3), 1.55–1.70 (4H, m, C(3)H_2, C(4)H_B, C(5)H_B), 2.19 (1H, br s, O*H*), 2.86 (1H, app t, *J* 11.4, C(6)H_A), 3.60 (1H, app dt, *J* 11.1, 5.7, C(1')H_A), 3.78–3.84 (1H, m, C(1')H_B), 3.93 (1H, app d, *J* 13.6, C(6)H_B), 4.25–4.33 (1H, m, C(2)*H*).

(2*RS*)-*N*(1)-Tosyl-2-(tosyloxymethyl)piperidine 264 and (2*RS*)-*N*(1)-Tosyl-2-(hydroxymethyl)piperidine 255



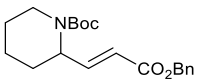
264 **255**

Method A. TsCl (5.77 g, 30.2 mmol) was added to a stirred solution of **253** (3.00 g, 27.5 mmol) and Et_3N (6.90 mL, 49.5 mmol) in CH_2Cl_2 (140 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. H_2O (140 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were washed sequentially with aq HCl (1.00 M, 200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:2) gave **264** as a colourless oil (1.10 g, 10%);[29] δ_H (400 MHz, $CDCl_3$) 1.17–1.54 (5H, m, C(3)H_A, C(4)H_2, C(5)H_2), 1.65–1.73 (1H, m, C(3)H_B), 2.41 (3H, s, Ar*Me*), 2.45 (3H, s, Ar*Me*), 2.81 (1H, app td, *J* 13.0, 2.7, C(6)H_A), 3.66–3.73 (1H, m, C(6)H_B), 3.99–4.10 (2H, m, C(1')H_2), 4.20–4.28 (1H, m, C(2)*H*), 7.26 (2H, d, *J* 8.3, Ar), 7.34 (2H, d, *J* 8.3, Ar), 7.66 (2H, d, *J* 8.3, Ar), 7.73 (2H, d, *J* 8.3, Ar). Further elution gave **255** as a colourless oil (5.96 g, 85%);[29] δ_H (400 MHz, $CDCl_3$) 1.15–1.61 (6H, m, C(3)H_2, C(4)H_2, C(5)H_2), 2.18 (1H, br s, O*H*), 2.41 (3H, s,

Ar*Me*), 3.04–3.12 (1H, m, C(6)H_A), 3.55 (1H, dd, *J* 11.2, 5.7, C(1')H_A), 3.75–3.86 (2H, m, C(6)H_B, C(1')H_B), 3.97–4.04 (1H, m, C(2)*H*), 7.28 (2H, d, *J* 8.1, *Ar*), 7.73 (2H, d, *J* 8.1, *Ar*).

Method B. ^{t}BuLi (1.70 M in pentane, 7.33 mL, 12.5 mmol) was added dropwise *via* syringe to a stirred solution of **307** (1.02 mL, 5.67 mmol) in Et_2O (11 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. The solution was transferred *via* syringe to a stirred solution of CuI (540 mg, 2.83 mmol) in Et_2O (6 mL) at −35 °C and the resultant solution was stirred at −35 °C for 1 h. A solution of **264** (262 mg, 0.71 mmol) in Et_2O (7 mL) was added dropwise *via* syringe and the resultant solution was stirred at −35 °C for 2 h. Satd aq NH_4Cl (24 mL) was added and the aqueous layer was extracted with Et_2O (2 × 24 mL). The combined organics were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:1) gave **263** as a colourless oil (113 mg, 43%). Further elution gave **255** as a colourless oil (75 mg, 45%).

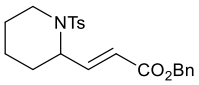
(2*RS*,1'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[3'-(benzyloxy)-3'-oxoprop-1'-en-1'-yl]piperidine 258



DMSO (14.9 mL, 210 mmol) was added dropwise *via* syringe to a stirred solution of $(COCl)_2$ (8.88 mL, 105 mmol) in CH_2Cl_2 (125 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of **254** (11.3 g, 52.5 mmol) in CH_2Cl_2 (125 mL) was added dropwise *via* cannula at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (43.9 mL, 315 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 20 min, then **189** (23.7 g, 57.8 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (250 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 9:1) gave **258** as a colourless oil (18.1 g, quant, >95:5 dr [(1'*E*):(1'*Z*)]); ν_{max} 1720, 1689, 1653; δ_H (400 MHz, $CDCl_3$) 1.38–1.44 (2H, m, C(4)H_A, C(5)H_A), 1.49 (9H, s, CMe_3), 1.58–1.67 (2H, m, C(4)H_B, C(5)H_B), 1.70–1.83

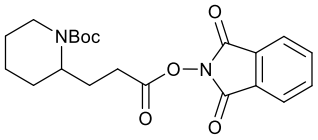
(2H, m, C(3)H_2), 2.81 (1H, app td, *J* 12.8, 2.6, C(6)H_A), 3.99 (1H, app d, *J* 12.5, C(6)H_B), 4.92–5.01 (1H, m, C(2)*H*), 5.19 (2H, s, OCH_2Ph), 5.87 (1H, dd, *J* 16.0, 2.2, C(2')*H*), 6.93 (1H, dd, *J* 16.0, 4.0, C(1')*H*), 7.32–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9 (*C*(4)), 25.3 (*C*(5)), 28.4 (C*Me*$_3$), 28.9 (*C*(3)), *40** (*C*(6)), *51** (*C*(2)), 66.3 (O*C*H$_2$Ph), 79.9 (*C*Me$_3$), 121.7 (*C*(2')), 128.2, 128.3, 128.5, 135.9 (*Ph*), 148.3 (*C*(1')), 155.0 (N(1)*C*O); *m/z* (ESI$^+$) 346 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}NO_4^+$ ([M+H]$^+$) requires 346.2013; found 346.2012.

(2*RS*,1'*E*)-*N*(1)-Tosyl-2-[3'-(benzyloxy)-3'-oxoprop-1'-en-1'-yl]piperidine 259



DMSO (5.20 mL, 72.8 mmol) was added dropwise *via* syringe to a stirred solution of $(COCl)_2$ (3.10 mL, 36.4 mmol) in CH_2Cl_2 (45 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of **255** (4.90 g, 18.2 mmol) in CH_2Cl_2 (45 mL) was added dropwise *via* cannula at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (15.1 mL, 109 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 20 min, then **189** (8.20 g, 20.0 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **259** as a white solid (6.92 g, 95%, >95:5 dr [(1'*E*):(1'*Z*)]); mp 70–72 °C; ν_{max} 1717, 1654, 1321, 1155; δ_H (400 MHz, $CDCl_3$) 1.34–1.45 (2H, m, C(4)H_A, C(5)H_A), 1.51–1.59 (2H, m, C(4)H_B, C(5)H_B), 1.64–1.75 (2H, m, C(3)H_2), 2.38 (3H, s, Ar*Me*), 2.95–3.01 (1H, m, C(6)H_A), 3.69–3.76 (1H, m, C(6)H_B), 4.72–4.77 (1H, m, C(2)*H*), 5.16 (2H, s, OCH_2Ph), 5.94 (1H, dd, *J* 15.8, 1.8, C(2')*H*), 6.81 (1H, dd, *J* 15.8, 5.3, C(1')*H*), 7.24 (2H, d, *J* 8.2, *Ar*), 7.32–7.41 (5H, m, *Ph*), 7.67 (2H, d, *J* 8.2, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.3 (*C*(4)), 21.4 (Ar*Me*), 24.6 (*C*(5)), 29.5 (*C*(3)), 41.8 (*C*(6)), 53.9 (*C*(2)), 66.3 (OCH_2Ph), 122.9 (*C*(2')), 127.1, 128.2, 128.2, 128.5, 129.6, 135.8, 137.2, 143.3 (*Ar*, *Ph*), 146.1 (*C*(1')), 165.6 (*C*(3')); *m/z* (ESI$^+$) 400 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{26}NO_4S^+$ ([M+H]$^+$) requires 400.1577; found 400.1573.

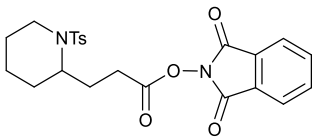
(2*RS*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[3'-(phthalimidooxy)-3'-oxoprop-1'yl]piperidine 262



Step 1. $Pd(OH)_2/C$ (3.54 g, 50% w/w of **258**) was added to a stirred solution of **258** (7.08 g, 20.5 mmol, >95:5 dr [(1'*E*):(1'*Z*)]) in degassed EtOAc (50 mL) at rt and the resultant suspension was stirred at rt for 6 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. DIC (3.16 mL, 20.5 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, NHP (3.34 g, 20.5 mmol) and DMAP (251 mg, 2.05 mmol) in CH_2Cl_2 (70 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/Et_2O, 30:1) gave **262** as a white solid (6.20 g, 75%); mp 100–102 °C; ν_{max} 1816, 1788, 1743, 1682; δ_H (400 MHz, $CDCl_3$) 1.37–1.45 (1H, m, C(5)H_A), 1.48 (9H, s, CMe_3), 1.54–1.73 (5H, m, C(3)H_2, C(4)H_2, C(5)H_B), 1.80–1.88 (1H, m, C(1')H_A), 2.20–2.30 (1H, m, C(1')H_B), 2.57–2.73 (2H, m, C(2')H_2), 2.73–2.83 (1H, m, C(6)H_A), 3.95–4.11 (1H, m, C(6)H_B), 4.27–4.41 (1H, m, C(2)*H*), 7.80 (2H, dd, *J* 5.5, 3.1, *Ar*), 7.89 (2H, dd, *J* 5.5, 3.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.0 (*C*(4)), 25.0 (*C*(1')), 25.4 (*C*(5)), 28.2 (*C*(2')), 28.4 (CMe_3), *29** (*C*(3)), *39** (*C*(6)), *50** (*C*(2)), 79.6 (*C*Me_3), 123.9, 128.9, 134.7 (*Ar*), 155.0 (N(1)*C*O), 161.9 (Ar*C*O), 169.5 (*C*(3')); *m/z* (ESI^+) 403 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{27}N_2O_6^+$ ($[M+H]^+$) requires 403.1864; found 403.1860.

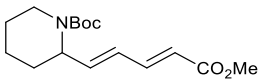
(2*RS*)-*N*(1)-Tosyl-2-[3'-(phthalimidooxy)-3'-oxoprop-1'yl]piperidine 263



Step 1. $Pd(OH)_2/C$ (1.75 g, 50% w/w of **259**) was added to a stirred solution of **259** (3.50 g, 8.76 mmol, >95:5 dr [(1'*E*):(1'*Z*)]) in degassed EtOAc (50 mL) at rt and the resultant suspension was stirred at rt for 6 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. DIC (1.35 mL, 8.76 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, NHP (1.43 g, 8.76 mmol) and DMAP (107 mg, 0.88 mmol) in CH_2Cl_2 (60 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/Et_2O, 50:1) gave **263** as a white solid (1.04 g, 26%); mp 144–146 °C; ν_{max} 1815, 1787, 1741, 1319, 1155; δ_H (400 MHz, $CDCl_3$) 1.08–1.20 (1H, m, C(5)H_A), 1.35–1.54 (5H, m, C(3)H_2, C(4)H_2, C(5)H_B), 1.77–1.86 (1H, m, C(1')H_A), 2.17–2.29 (1H, m, C(1')H_B), 2.43 (3H, s, Ar*Me*), 2.69–2.84 (2H, m, C(2')H_2), 3.00–3.08 (1H, m, C(6)H_A), 3.86 (1H, app dd, *J* 14.4, 3.7, C(6)H_B), 4.11 (1H, dt, *J* 10.0, 4.7, C(2)*H*), 7.31 (2H, d, *J* 8.2, *Ar*), 7.75 (2H, d, *J* 8.2, *Ar*), 7.78–7.81 (2H, m, *Ar*), 7.88–7.90 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.4 (*C*(4)), 21.5 (Ar*Me*), 23.9 (*C*(5)), 24.9 (*C*(1')), 27.6 (*C*(3)), 28.3 (*C*(2')), 40.6 (*C*(6)), 52.2 (*C*(2)), 123.9, 126.9, 129.9, 129.8, 134.7, 138.6, 143.1 (*Ar*), 161.8 (Ar*C*O), 169.5 (*C*(3')); *m/z* (ESI$^+$) 457 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{25}N_2O_6S^+$ ([M+H]$^+$) requires 457.1428; found 457.1427.

(2*RS*,1'*E*,3'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(5'-methoxy-5'-oxopent-1',3'-dien-1'-yl)piperidine 269

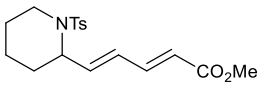


Step 1. DIBAL-H (1.00 M in CH_2Cl_2, 26.4 mL, 26.4 mmol) was added dropwise *via* syringe to a stirred solution of **258** (3.23 g, 12.0 mmol, >95:5 dr [(1'*E*):(1'*Z*)]) in CH_2Cl_2 (80 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1.5 h. Satd aq Rochelle salt (30 mL) was added and the resultant mixture was stirred at −78 °C for 5 min, then stirred at rt for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organics were dried and concentrated *in vacuo*.

Step 2. DMSO (3.41 mL, 48.0 mmol) was added dropwise *via* syringe to a stirred solution of $(COCl)_2$ (2.03 mL, 24.0 mmol) in CH_2Cl_2 (30 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of the residue from the previous step in CH_2Cl_2 (30 mL) was added dropwise *via* cannula at −78 °C and the resultant mixture was stirred at −78 °C

for 30 min. Et_3N (10.0 mL, 72.0 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 20 min, then **176** (4.41 g, 13.2 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (60 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 7:1) gave **269** as a white solid (2.21 g, 80%, 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)]); mp 64–66 °C; ν_{max} 1720, 1687, 1643, 1616; δ_H (400 MHz, $CDCl_3$) 1.33–1.40 (2H, m, C(4)H_A, C(5)H_A), 1.41 (9H, s, CMe_3), 1.53–1.63 (2H, m, C(4)H_A, C(5)H_B), 1.66–1.76 (2H, m, C(3)H_2), 2.70–2.80 (1H, m, C(6)H_A), 3.70 (3H, s, O*Me*), 3.93 (1H, app d, *J* 12.4, C(6)H_B), 4.83–4.91 (1H, m, C(2)*H*), 5.80 (1H, d, *J* 15.4, C(4')*H*), 5.99–6.15 (2H, m, C(1')*H*, C(2')*H*), 7.25 (1H, dd, *J* 15.4, 10.0, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 19.8 (*C*(4)), 25.4 (*C*(5)), 28.5 (CMe_3), 29.2 (*C*(3)), *40** (*C*(6)), 51.6 (O*Me*), *52** (*C*(2)), 79.7 (*C*Me_3), 120.4 (*C*(4')), 128.8 (*C*(2')), 142.4 (*C*(1')), 144.3 (*C*(3')), 155.3 (N(1)*C*O), 167.5 (*C*(5')); *m/z* (ESI^+) 318 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{25}NNaO_4^+$ ($[M+Na]^+$) requires 318.1676; found 318.1673.

(2*RS*,1'*E*,3'*E*)-*N*(1)-Tosyl-2-(5'-methoxy-5'-oxopent-1',3'-dien-1'-yl)piperidine 270

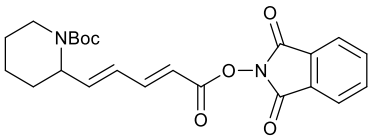


Step 1. DIBAL-H (1.00 M in CH_2Cl_2, 26.4 mL, 26.4 mmol) was added dropwise *via* syringe to a stirred solution of **259** (3.88 g, 12.0 mmol, >95:5 dr [(1'*E*):(1'*Z*)]) in CH_2Cl_2 (80 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1.5 h. Satd aq Rochelle salt (30 mL) was added and the resultant mixture was stirred at −78 °C for 5 min, then stirred at rt for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organics were dried and concentrated *in vacuo*.

Step 2. DMSO (3.41 mL, 48.0 mmol) was added dropwise *via* syringe to a stirred solution of $(COCl)_2$ (2.03 mL, 24.0 mmol) in CH_2Cl_2 (30 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of the residue from the previous step in CH_2Cl_2 (30 mL) was added dropwise *via* cannula at −78 °C and the resultant mixture was stirred at −78 °C

for 30 min. Et_3N (10.0 mL, 72.0 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 20 min, then **176** (4.41 g, 13.2 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (60 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 5:1) gave **270** as a white solid (2.92 g, 86%, 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)]); mp 84–86 °C ; ν_{max} 1715, 1644, 1616, 1319, 1155; δ_H (400 MHz, $CDCl_3$) 1.38–1.47 (2H, m, C(4)H_A, C(5)H_A), 1.52–1.60 (2H, m, C(4)H_B, C(5)H_B), 1.68–1.73 (2H, m, C(3)H_2), 2.42 (3H, s, Ar*Me*), 2.95 (1H, app td, *J* 12.7, 2.7, C(6)H_A), 3.69–3.75 (1H, m, C(6)H_B), 3.75 (3H, s, O*Me*), 4.67–4.72 (1H, m, C(2)*H*), 5.81 (1H, dd, *J* 15.4, 0.6, C(4')*H*), 5.92 (1H, dd, *J* 15.4, 5.6, C(1')*H*), 6.18 (1H, ddd, *J* 15.4, 11.0, 0.6, *C*(2')*H*), 7.13 (1H, dd, *J* 15.4, 11.0, C(3')*H*), 7.27 (2H, d, *J* 8.3, *Ar*), 7.66 (2H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.3 (*C*(4)), 21.5 (Ar*Me*), 24.8 (*C*(5)), 30.0 (*C*(3)), 41.9 (*C*(6)), 51.6 (O*Me*), 54.5 (*C*(2)), 121.1 (*C*(4')), 127.3, 129.6 (*Ar*), 130.0 (*C*(2')), 137.4 (*Ar*), 139.8 (*C*(1')), 143.2 (*Ar*), 143.6 (*C*(3')), 167.3 (*C*(5')); *m/z* (ESI^+) 350 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{24}NO_4S^+$ ($[M+H]^+$) requires 350.1421; found 350.1416.

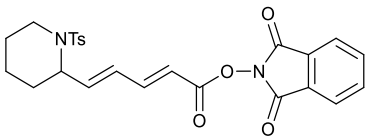
(2*RS*,1'*E*,3'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[5'-(phthalimidooxy)-5'-oxopent-1',3'-dien-1'-yl]piperidine 273



Step 1. Aq NaOH (1.50 M, 35.0 mL, 52.5 mmol) was added dropwise *via* cannula to a stirred solution of **269** (2.22 g, 7.50 mmol, 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)]) in THF (50 mL) at rt and the resultant mixture was heated at 70 °C for 8 h then cooled to rt. Satd aq $NaHCO_3$ (100 mL) was added and the aqueous layer was extracted with Et_2O (2 × 100 mL). The aqueous layer was cooled to 0 °C then acidified to pH 1 with aq HCl (3.00 M). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) then dried and concentrated *in vacuo*.

Step 2. DIC (1.15 mL, 7.50 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, NHP (1.22 g, 7.50 mmol) and DMAP (92 mg, 0.75 mmol) in CH_2Cl_2 (50 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/Et_2O, 30:1) gave **273** as a pale yellow oil (2.41 g, 75%, 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)]); ν_{max} 1745, 1729, 1685, 1639, 1613; δ_H (400 MHz, $CDCl_3$) 1.38–1.45 (2H, m, C(4)H_A, C(5)H_B), 1.47 (9H, s, CMe_3), 1.59–1.82 (4H, m, C(3)H_2, C(4)H_B, C(5)H_B), 2.76–2.82 (1H, m, C(6)H_A), 3.97–4.05 (1H, m, C(6)H_B), 4.92–5.00 (1H, m, C(2)*H*), 6.06–6.10 (1H, m, C(4')*H*), 6.24–6.26 (2H, m, C(1')*H*, C(2')*H*), 7.53–7.60 (1H, m, C(3')*H*), 7.80 (2H, dd, *J* 5.6, 2.9, *Ar*), 7.90 (2H, dd, *J* 5.6, 2.9, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.8 (*C*(4)), 25.3 (*C*(5)), 28.4 (CMe_3), 29.0 (*C*(3)), *40** (*C*(6)), *52** (*C*(2)), 79.9 (*C*Me_3), 114.1 (*C*(4')), 123.9 (*Ar*), 128.4 (*C*(2')), 128.9, 134.7 (*Ar*), 146.2 (*C*(1')), 149.1 (*C*(3')), 155.1 (N(1)*C*O), 162.1 (Ar*C*O), 162.9 (*C*(5')); *m/z* (ESI^+) 449 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{26}N_2NaO_6^+$ ($[M+Na]^+$) requires 449.1683; found 449.1683.

(2*RS*,1'*E*,3'*E*)-*N*(1)-Tosyl-2-[5'-(phthalimidooxy)-5'-oxopent-1',3'-dien-1'-yl]piperidine 274

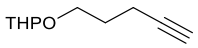


Step 1. Aq NaOH (1.50 M, 7.80 mL, 11.7 mmol) was added dropwise *via* cannula to a stirred solution of **270** (583 mg, 1.67 mmol, 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)]) in THF (12 mL) at rt and the resultant mixture was heated at 70 °C for 8 h then cooled to rt. Satd aq $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with Et_2O (2 × 20 mL). The aqueous layer was cooled to 0 °C then acidified to pH 1 with aq HCl (3.00 M). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) then dried and concentrated *in vacuo*.

Step 2. DIC (0.26 mL, 1.67 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, NHP (272 mg, 1.67 mmol) and DMAP (20 mg, 0.17 mmol) in CH_2Cl_2 (11 mL) at rt. The resultant solution was stirred at rt for 16 h, then concentrated *in*

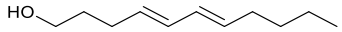
vacuo. Purification *via* flash column chromatography (eluent CH_2Cl_2/Et_2O, 50:1) gave **274** as a white solid (300 mg, 37%, 90:10 dr [(1'*E*,3'*E*):(1'*E*,3'*Z*)]); mp 74–76 °C; ν_{max} 1764, 1743, 1640, 1612, 1326, 1155; δ_H (400 MHz, $CDCl_3$) 1.35–1.53 (2H, m, C(4)H_A, C(5)H_A), 1.57–1.67 (2H, m, C(4)H_B, C(5)H_B), 1.72–1.77 (2H, m, C(3)H_2), 2.44 (3H, s, Ar*Me*), 2.97 (1H, app td, *J* 12.2, 2.5, C(6)H_A), 3.72–3.79 (1H, m, C(6)H_B), 4.71–4.76 (1H, m, C(2)*H*), 6.02 (1H, d, *J* 15.4, C(4')*H*), 6.08 (1H, dd, *J* 15.4, 5.6, C(1')*H*), 6.26 (1H, dd, *J* 15.4, 11.0, C(2')*H*), 7.31 (1H, d, *J* 8.2, *Ar*), 7.38 (1H, dd, *J* 15.4, 10.9, C(3')*H*), 7.67 (2H, d, *J* 8.2, *Ar*), 7.81 (2H, dd, *J* 5.5, 3.1, *Ar*), 7.91 (2H, dd, *J* 5.5, 3.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.4 (*C*(4)), 21.5 (Ar*Me*), 24.8 (*C*(5)), 30.0 (*C*(3)), 42.0 (*C*(6)), 54.5 (*C*(2)), 115.0 (*C*(4')), 124.0 (*Ar*), 127.3 (*Ar*), 129.0 (*C*(2')), 129.6, 129.7, 134.7, 137.3 (*Ar*), 143.5 (*C*(1')), 148.5 (*C*(3')), 162.0 (Ar*C*O), 162.7 (*C*(5')); *m/z* (ESI^+) 503 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{25}H_{24}N_2NaO_6S^+$ ($[M+Na]^+$) requires 503.1247; found 503.1250.

(2'*RS*)-5-(Tetrahydro-2*H*-pyran-2'-yloxy)pent-1-yne 276



DHP (2.94 mL, 32.2 mmol) and PPTS (1.01 g, 4.03 mmol) were added sequentially to a stirred solution of **275** (2.50 mL, 26.9 mmol) in CH_2Cl_2 (50 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. $NaHCO_3$ (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were washed with brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 6:1) gave **276** as a colourless oil (4.06 g, 90%);[30] δ_H (400 MHz, $CDCl_3$) 1.48–1.86 (8H, m, C(4)H_2, C(3')H_2, C(4')H_2, C(5')H_2), 1.95 (1H, t, *J* 2.7, C(1)*H*), 2.30–2.35 (2H, m, C(3)H_2), 3.46–3.54 (2H, m, C(5)H_A, C(6')H_A), 3.81–3.90 (2H, m, C(5)H_B, C(6')H_B), 4.59–4.62 (1H, m, C(2')*H*).

(4*E*,6*E*)-1-Hydroxyundeca-4,6-diene 278



Method A. Step 1. NaHMDS (1.00 M in THF, 72.0 mL, 72.0 mmol) was added dropwise *via* syringe to a stirred solution of **281** (13.2 g, 36.0 mmol) and **144** (5.17 mL, 39.6 mmol, >95:5 dr [(2*E*):(2*Z*)]) in DME (500 mL) at −55 °C and the resultant solution was stirred at −55 °C for 30 min. H_2O (500 mL) was added and the aqueous layer was extracted with Et_2O (3 × 500 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*. The residue was filtered through a silica plug (eluent 30–40 °C petroleum ether/Et_2O, 10:1) and concentrated *in vacuo*.

Step 2. $TsOH·H_2O$ (301 mg, 1.58 mmol) was added to a stirred solution of the residue from the previous step in MeOH (100 mL) at rt and the resultant solution was stirred at rt for 2 h. Et_3N (0.44 mL, 3.17 mmol) was added dropwise *via* syringe added and the resultant solution was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 2:1) gave **278** as a colourless oil (5.13 g, 85%, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)]);[31] δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, C(11)H_3), 1.29–1.42 (4H, m, C(9)H_2, C(10)H_2), 1.65–1.72 (2H, m, C(2)H_2), 2.08 (2H, app q, *J* 7.0, C(8)H_2), 2.18 (2H, app q, *J* 7.4, C(3)H_2), 3.68 (2H, t, *J* 6.5, C(1)H_2), 5.55–5.64 (2H, m, C(4)*H*, C(7)*H*), 5.98–6.10 (2H, m, C(5)*H*, C(6)*H*).

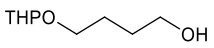
Method B. Step 1. **202** (4.00 mL, 34.8 mmol) was added dropwise *via* syringe to stirred DIBAL-H (1.00 M in hexanes, 34.8 mL, 34.8 mmol) at 0 °C and the resultant solution was heated at 50 °C for 16 h, then cooled to −78 °C. A solution of I_2 (10.6 g, 41.8 mmol) in THF (20 mL) was added dropwise *via* cannula 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 added dropwise *via* cannula to a stirred mixture of pentane (100 mL) and aq HCl (2.00 M, 100 mL) at 0 °C and the resultant mixture was stirred for 5 min at 0 °C. The aqueous layer was extracted with pentane (2 × 100 mL) and the combined organics were washed sequentially with satd aq $NaHCO_3$ (300

mL), $Na_2S_2O_3$ (300 mL) and brine (300 mL), then dried and concentrated *in vacuo* to give **123** in >95:5 dr [(1*E*):(1*Z*)].

Step 2. Cp_2ZrHCl (4.14 g, 16.0 mmol) was added to a stirred solution of **276** (2.67 g, 15.9 mmol) in THF (80 mL) at rt and the resultant solution was stirred at rt for 1 h whilst shielded from light. In a separate flask, DIBAL-H (1.00 M in hexanes, 0.95 mL, 0.95 mmol) was added dropwise *via* syringe to a stirred solution of $PdCl_2(PhCN)_2$ (184 mg, 0.48 mmol) and DPPF (527 mg, 0.95 mmol) in THF (10 mL) at rt and the resultant solution was stirred at rt for 15 min. A solution of the residue from the previous step in THF (10 mL) was added dropwise *via* cannula at rt and the resultant solution was stirred at rt for 5 min. The second solution was added dropwise *via* syringe to the first solution at rt and the resultant solution was stirred at rt for 16 h whilst shielded from light. Pentane (100 mL) was added and the resultant suspension was filtered through neutral alumina (eluent pentane) and concentrated *in vacuo*. Et_2O (100 mL) was added and the resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*.

Step 3. $TsOH·H_2O$ (116 mg, 0.61 mmol) was added to a stirred solution of the residue from the previous step in MeOH (40 mL) at rt and the resultant solution was stirred at rt for 2 h. Et_3N (0.17 mL, 1.22 mmol) was added dropwise *via* syringe and the resultant solution was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 2:1) gave **278** as a colourless oil (702 mg, 26%, >95:5 dr [(4*E*,6*E*):(4*Z*,6*E*)]).

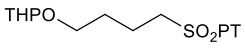
(2'*RS*)-4-(Tetrahydro-2*H*-pyran-2'-yloxy)butan-1-ol 279



DHP (9.14 mL, 100 mmol) and PPTS (1.26 g, 5.00 mmol) were added sequentially to a stirred solution of **165** (17.7 mL, 200 mmol) in CH_2Cl_2 (300 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. $NaHCO_3$ (300 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). The combined organics were washed with brine (900 mL),

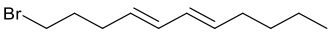
then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:2) gave **279** as a colourless oil (14.1 g, 81%);[32] δ_H (400 MHz, $CDCl_3$) 1.50–1.87 (10H, m, C(3)H_2, C(2)H_2, C(3')H_2, C(4')H_2, C(5')H_2), 2.23 (1H, br s, O*H*), 3.43–3.48 (1H, m, C(4)H_A), 3.50–3.56 (1H, m, C(6')H_A), 3.65–3.72 (2H, m, C(1)H_2), 3.80–3.91 (2H, m, C(4)H_B, C(6')H_B), 4.59–4.64 (1H, m, C(2')*H*).

(2'*RS*)-1-(Tetrahydro-2*H*-pyran-2'-yloxy)-4-[(1''-phenyl-1*H*-tetrazol-5''-yl)sulfonyl]butane 281



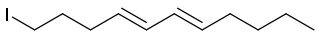
Step 1. DIAD (9.86 mL, 50.1 mmol) was added dropwise *via* syringe to a stirred solution of **279** (5.82 g, 33.4 mmol), PPh_3 (13.1 g, 50.1 mmol) and PTSH (8.93 g, 50.1 mmol) in THF (170 mL) at rt and the resultant solution was stirred at rt for 30 min and then concentrated *in vacuo*. *Step 2*. A solution of the residue from the previous step in EtOH (350 mL) was added dropwise *via* cannula to a stirred solution of $(NH_4)_2Mo_7O_{24}{\cdot}4H_2O$ (6.03 g, 4.88 mmol) in aq H_2O_2 (30% v/v, 41.5 mL, 366 mmol) at 0 °C and the resultant solution was stirred allowed to warm to rt over 16 h. EtOAc (300 mL) and Na_2SO_3 (300 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 3:1) gave **281** as a colourless oil (11.0 g, 90%);[33] δ_H (400 MHz, $CDCl_3$) 1.47–1.61 (4H, m, C(3')H_A, C(4')H_A, C(5')H_2), 1.67–1.74 (1H, m, C(3')H_B), 1.75–1.83 (3H, m, C(2)H_2, C(4')H_B), 2.08 (2H, app quin, C(3)H_2), 3.40–3.46 (1H, m, C(1)H_A), 3.47–3.53 (1H, m, C(6')H_A), 3.77–3.86 (4H, m, C(1)H_B, C(4)H_2, C(6')H_B), 4.55–4.58 (1H, m, C(2')*H*), 7.56–7.71 (5H, m, *Ph*).

(4*E*,6*E*)-1-Bromoundeca-4,6-diene 250



A solution of PPh_3 (1.98 g, 7.55 mmol) in CH_2Cl_2 (7 mL) was added dropwise *via* syringe to a stirred solution of CBr_4 (1.25 g, 3.77 mmol) in CH_2Cl_2 (4 mL) at −30 °C and the resultant solution was stirred at −30 °C for 30 min. A solution of **278** (635 mg, 3.77 mmol, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)]) and imidazole (514 mg, 7.55 mmol) in CH_2Cl_2 (4 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 3 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether) gave **250** as a colourless oil (558 mg, 64%, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)]); ν_{max} 1656; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, C(11)H_3), 1.27–1.41 (4H, m, C(9)H_2, C(10)H_2), 1.95 (2H, app quin, *J* 6.9, C(2)H_2), 2.07 (2H, app q, *J* 6.8, C(8)H_2), 2.23 (2H, app q, *J* 7.3, C(3)H_2), 3.43 (2H, t, *J* 6.7, C(1)H_2), 5.51 (1H, dt, *J* 14.3, 7.0, C(4)*H*), 5.61 (1H, dt, *J* 14.3, 7.0, C(7)*H*), 5.97–6.10 (2H, m, C(5)*H*, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(11)), 22.2 (*C*(10)), 30.8 (*C*(3)), 31.5 (*C*(9)), 32.3 32.3 (*C*(2)), (*C*(8)), 33.3 (*C*(1)), 129.4 (*C*(4)), 129.9 (*C*(6)), 131.9 (*C*(5)), 133.4 (*C*(7)).[17]

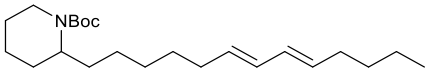
(4*E*,6*E*)-1-Iodoundeca-4,6-diene 283



Imidazole (6.07 g, 89.1 mmol) and PPh_3 (11.7 g, 44.6 mmol) were added sequentially to a stirred solution of **278** (5.00 g, 29.7 mmol, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)]) in CH_2Cl_2 (130 mL) at rt and the resultant solution was stirred for 5 min then cooled to 0 °C. I_2 (11.3 g, 44.6 mmol) was added and the resultant solution was stirred at 0 °C for 1 h then allowed to warm to rt over 1 h whilst shielded from light. Satd aq $NaHCO_3$ (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organics were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether) gave **283** as a colourless oil (7.35 g, 89%, 92:8 dr [(4*E*,6*E*):(4*Z*,6*E*)]); ν_{max} 1656; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(11)H_3), 1.28–1.41 (4H, m, C(9)H_2, C(10)H_2), 1.91 (2H, app quin, *J* 7.0, C(2)H_2), 2.07 (2H, app q, *J* 7.0, C(8)H_2),

2.18 (2H, app q, *J* 7.1, C(3)H_2), 3.19 (2H, t, *J* 7.0, C(1)H_2), 5.49 (1H, dt, *J* 14.6, 7.1, C(4)*H*), 5.61 (1H, dt, *J* 14.6, 6.9, C(7)*H*), 5.96–6.10 (2H, m, C(5)*H*, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 6.5 (*C*(1)), 13.9 (*C*(11)), 22.2 (*C*(10)), 31.5 (*C*(9)), 32.2 (*C*(8)), 32.9 (*C*(2)), 33.1 (*C*(3)), 129.2 (*C*(4)), 129.9 (*C*(6)), 131.9 (*C*(5)), 133.4 (*C*(7)).[17]

(2*RS*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)piperidine 206



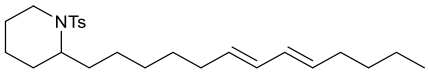
Method A. KHMDS (1.00 M in THF, 0.25 mL, 0.25 mmol) was added dropwise *via* syringe to a stirred solution of **340** (60 mg, 0.13 mmol) and **144** (33 μL, 0.25 mmol, >95:5 dr [(2*E*):(2*Z*)]) in THF (1.3 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. EtOAc (3 mL) and H_2O (3 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organics were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 9:1) gave **206** as a colourless oil (45 mg, 98%, 90:10 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]).[34]

Method B. *Step 1*. ^{t}BuLi (1.70 M in pentane, 23.5 mL, 39.9 mmol) was added dropwise *via* syringe to a stirred solution of **283** (5.05 g, 18.2 mmol, 72:12:12:4 dr [(4*E*,6*E*):(4*E*,6*Z*):(4*Z*,6*E*):(4*Z*,6*Z*)]) in Et_2O (18 mL) at −78 °C and the resultant solution was stirred at −78 °C for 5 min. $ZnCl_2$ (1.00 M in THF, 9.08 mL, 9.08 mmol) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 15 min. The concentration of the resultant di(undec-4,6-dien-1-yl)zinc solution was determined *via* iodometric titration.[35]

Step 2. A solution of $NiCl_2$·glyme (22 mg, 0.10 mmol) and BBBPY (54 mg, 0.20 mmol) in DMF (5 mL) was added dropwise *via* syringe to **262** (201 mg, 0.50 mmol) and the resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (2 mL). Et_2O (1 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1)

gave **206** as a colourless oil (13 mg, 7%, 72:12:12:4 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*:8'*Z*)]).[34]

(2*RS*,6'*E*,8'*E*)-*N*(1)-Tosyl-2-(trideca-6',8'-dien-1'-yl)piperidine 287

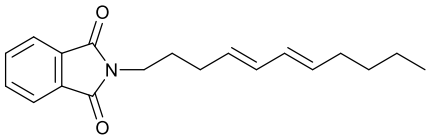


Step 1. ^{t}BuLi (1.70 M in pentane, 23.5 mL, 39.9 mmol) was added dropwise *via* syringe to a stirred solution of **283** (5.05 g, 18.2 mmol, 72:12:12:4 dr [(4*E*,6*E*):(4*E*,6*Z*):(4*Z*,6*E*):(4*Z*,6*Z*)]) in Et_2O (18 mL) at −78 °C and the resultant solution was stirred at −78 °C for 5 min. $ZnCl_2$ (1.00 M in THF, 9.08 mL, 9.08 mmol) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 15 min. The concentration of the resultant di(undec-4,6-dien-1-yl)zinc solution was determined *via* iodometric titration.[35]

Step 2. A solution of $NiCl_2$·glyme (22 mg, 0.10 mmol) and BBBPY (54 mg, 0.20 mmol) in DMF (5 mL) was added dropwise *via* syringe to **263** (228 mg, 0.50 mmol) and the resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (2 mL). Et_2O (1 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1) gave **287** as a colourless oil (28 mg, 13%, 72:12:12:4 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*:8'*Z*)]); ν_{max} 1716, 1598, 1323, 1154; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(13)H_3), 1.18–1.63 (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), 2.00–2.09 (4H, m, C(5')H_2, C(10')H_2), 2.42 (3H, s, Ar*Me*), 2.97 (1H, app td, *J* 14.1, 2.7, C(6)H_A), 3.76 (1H, app dd, *J* 14.1, 3.8, C(6)H_B), 3.96–4.03 (1H, m, C(2)*H*), 5.51–5.61 (2H, m, C(6')*H*, C(9')*H*), 5.92–6.04 (2H, m, C(7')*H*, C(8')*H*), 7.27 (2H, d, *J* 8.0, *Ar*), 7.72 (2H, d, *J* 8.0, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 18.4 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 21.5 (Ar*Me*), 22.2, 24.5, 26.3, 27.4, 28.9, 29.2, 29.3, 31.6 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 32.3,

32.5 (*C*(5'), *C*(10')), 40.6 (*C*(6)), 52.9 (*C*(2)), 126.9, 129.5 (*Ar*), 130.3, 130.4 (*C*(7'), *C*(8')), 132.2, 132.5 (*C*(6'), *C*(9')), 139.0, 142.7 (*Ar*); *m/z* (ESI^+) 418 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{40}NO_2S^+$ ($[M+H]^+$) requires 418.2774; found 418.2765.

1-Phthalimidoundeca-4,6-diene 290

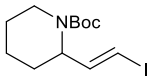


Step 1. ^{t}BuLi (1.70 M in pentane, 23.5 mL, 39.9 mmol) was added dropwise *via* syringe to a stirred solution of **283** (5.05 g, 18.2 mmol, 72:12:12:4 dr [(4*E*,6*E*):(4*E*,6*Z*):(4*Z*,6*E*):(4*Z*,6*Z*)]) in Et_2O (18 mL) at −78 °C and the resultant solution was stirred at −78 °C for 5 min. $ZnCl_2$ (1.00 M in THF, 9.08 mL, 9.08 mmol) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 15 min. The concentration of the resultant di(undec-4,6-dien-1-yl)zinc solution was determined *via* iodometric titration.[35]

Step 2. A solution of $NiCl_2$·glyme (22 mg, 0.10 mmol) and BBBPY (54 mg, 0.20 mmol) in DMF (5 mL) was added dropwise *via* syringe to **273** (213 mg, 0.50 mmol) and the resultant solution was stirred at rt for 10 min. The dialkylzinc reagent solution was added dropwise *via* syringe, and the resultant solution was stirred at rt for 16 h, then quenched with half satd aq NH_4Cl (2 mL). Et_2O (1 mL) and H_2O (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1) gave **290** as a colourless oil (25 mg, 17%, 72:12:12:4 dr [(6'*E*,8'*E*):(6'*E*,8'*Z*):(6'*Z*,8'*E*):(6'*Z*:8'*Z*)]); ν_{max} 1772, 1713, 1616; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(11)H_3), 1.26–1.38 (4H, m, C(9)H_2, C(10)H_2), 1.78 (2H, app quin, *J* 7.3, C(2)H_2), 2.03 (2H, app q, *J* 6.8, C(8)H_2), 2.13 (2H, app q, *J* 7.3, C(3)H_2), 3.70 (2H, t, *J* 7.3, C(1)H_2), 5.51–5.60 (2H, m, C(4)*H*, C(7)*H*), 5.91–6.06 (2H, m, C(5)*H*, C(6)*H*), 7.71 (2H, dd, *J* 5.4, 2.9, *Ar*), 7.84 (2H, dd, *J* 5.4, 2.9, *Ar*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(11)), 22.2 (*C*(10)), 28.1 (*C*(2)), 29.9 (*C*(3)), 31.5 (*C*(9)), 32.2 (*C*(8)), 37.6 (*C*(1)), 123.2, 130.0, 130.2, 131.3, 132.1, 133.1,

133.8 (*C*(4), *C*(5), *C*(6), *C*(7), *Ar*), 168.4 (Ar*C*O); *m/z* (ESI$^+$) 298 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}NO_2^+$ ([M+H]$^+$) requires 298.1802; found 298.1805.

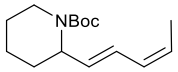
(2*RS*,1'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(2'-iodo-ethen-1'-yl)piperidine 314



Step 1. DMSO (0.85 mL, 12.0 mmol) was added dropwise *via* syringe to a stirred solution of $(COCl)_2$ (0.51 mL, 6.00 mmol) in CH_2Cl_2 (4 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of **254** (646 mg, 3.00 mmol) in CH_2Cl_2 (4 mL) was added dropwise *via* cannula at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (2.50 mL, 18.0 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 30 min. H_2O (8 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL), then dried and concentrated *in vacuo*.

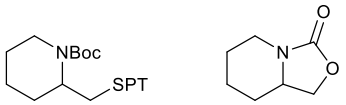
Step 2. A solution of CHI_3 (2.36 g, 6.00 mmol) and the residue from the previous step in THF (18 mL) was added dropwise *via* syringe to a stirred solution of $CrCl_2$ in THF (9 mL) at rt and the resultant suspension was stirred at rt for 30 min. $CHCl_3$ (30 mL) and H_2O (30 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave **314** as a pale yellow oil (626 mg, 59%, >95:5 dr [(1'*E*):(1'*Z*)]); ν_{max} 1687, 1600; δ_H (400 MHz, $CDCl_3$) 1.32–1.49 (2H, m, C(4)H_A, C(5)H_A), 1.43 (9H, s, CMe_3), 1.57–1.75 (4H, m, C(3)H_2, C(4)H_B, C(5)H_B), 2.77 (1H, app t, *J* 12.8, C(6)H_A), 3.94 (1H, app d, *J* 13.4, C(6)H_B), 4.70–4.78 (1H, m, C(2)*H*), 6.12 (1H, ddd, *J* 14.6, 2.0, 0.7, C(2')*H*), 6.52 (1H, dd, *J* 14.6, 5.2, C(1')*H*); δ_C (100 MHz, $CDCl_3$) 19.5 (*C*(4)), 25.2 (*C*(5)), 28.4 (CMe_3), 28.7 (*C*(3)), 39.9 (*C*(6)), 54.8 (*C*(2)), 77.2 (*C*(2')), 79.7 (*C*Me$_3$), 144.5 (*C*(1')), 154.9 (N(1)*C*O); *m/z* (ESI$^+$) 360 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{20}INNaO_2^+$ ([M+Na]$^+$) requires 360.0431; found 360.0431.

(2*RS*,1'*E*,2'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pent-1',3'-dien-1'-yl)piperidine 315



$Pd(PPh_3)_4$ (17 mg, 15 μmol) was added to a stirred solution of **314** (100 mg, 0.30 mmol, >95:5 dr [(1'*E*):(1'*Z*)]) in degassed THF (4 mL) at rt and the resultant solution was stirred at rt for 5 min. A solution of **316** (51 mg, 0.59 mmol, >95:5 dr [(1*Z*):(1*E*)]) in aq KOH (2.00 M, 1 mL) was added dropwise *via* syringe and the resultant solution was heated to 50 °C for 16 h. The resultant solution was allowed to cool to rt, then $CHCl_3$ (10 mL) and brine (10 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 20:1) gave **315** as a colourless oil (50 mg, 78%, >95:5 dr [(1'*E*,3*Z*):(1'*E*,3'*E*)]); ν_{max} 1691; δ_H (400 MHz, $CDCl_3$) 1.38–1.43 (1H, m, C(5)H_A), 1.45 (9H, s, CMe_3), 1.47–1.71 (5H, m, C(3)H_2, C(4)H_2, C(5)H_B), 1.72 (3H, d, *J* 6.8, C(5')H_3), 2.83 (1H, app td, *J* 12.9, 2.6, C(6)H_A), 3.94 (1H, app d, *J* 13.4, C(6)H_B), 4.81–4.87 (1H, m, C(2)*H*), 5.46 (1H, dt, *J* 11.1, 6.8, C(4')*H*), 5.62 (1H, dd, *J* 15.4, 4.9, C(1')*H*), 5.99 (1H,app t, *J* 11.1, C(3')*H*), 6.34 (1H, dd, *J* 15.4, 11.1, C(2')*H*); δ_C (100 MHz, $CDCl_3$) 13.3 (*C*(5')), 19.6 (*C*(4)), 25.5 (*C*(5)), 28.4 (C*Me*$_3$), 29.4 (*C*(3)), 39.7 (*C*(6)), 52.0 (*C*(2)), 79.2 (*C*Me$_3$), 125.6 (*C*(4')), 126.1 (*C*(2')), 128.9 (*C*(3')), 131.7 (*C*(1')), 155.3 (N(1)*C*O); *m/z* (ESI$^+$) 274 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 274.1778; found 274.1778.

(2*RS*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[(1'-phenyl-1*H*-tetrazol-5'-yl)thiomethyl]piperidine 325 and (8a*RS*)-Hexahydro-3*H*-oxazolo[3,4-a]pyridin-3-one 324



325 **324**

Method A. DIAD (0.68 mL, 3.48 mmol) was added dropwise *via* syringe to a stirred solution **254** (500 mg, 2.32 mmol), PPh_3 (913 mg, 3.48 mmol) and PTSH (621 mg, 3.48 mmol) in THF (12 mL) at 0 °C and the resultant solution was allowed to warm to rt over 30 min. Et_2O (12 mL)

and H_2O (25 mL) were added, and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organics were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:3) gave **325** as a colourless oil (87 mg, 10%); ν_{max} 1683; δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.35–1.77 (6H, m, C(3)*H*$_2$, C(4)*H*$_2$, C(5)*H*$_2$), 2.73–2.85 (1H, m, C(6)*H*$_A$), 3.58 (1H, dd, *J* 13.0, 4.2, C(1')*H*$_A$), 3.73 (1H, app t, *J* 11.1, C(1')*H*$_B$), 4.07–4.12 (1H, m, C(6)*H*$_B$), 4.67–4.75 (1H, m, C(2)*H*), 7.43–7.59 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (*C*(4)), 25.1, 27.9 (*C*(3), *C*(5)), 28.2 (C*Me*$_3$), 33.5 (*C*(1')), *39*[*] (*C*(6)), 48.9 (*C*(2)), 80.1 (*C*Me$_3$), 123.4, 129.0, 129.6, 133.4 (*Ph*), 154.1 (*Ar*), 155.0 (N(1)*C*O); *m/z* (ESI^+) 398 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{25}N_5NaO_2S^+$ ($[M+Na]^+$) requires 398.1621; found 398.1619. Further elution gave **324** as a colourless oil (262 mg, 80%);[36] δ_H (400 MHz, $CDCl_3$) 1.22–1.45 (3H, m, C(6)*H*$_A$, C(7)*H*$_A$, C(8)*H*$_A$), 1.58–1.68 (1H, m, C(6)*H*$_B$), 1.75–1.90 (2H, m, C(8)*H*$_B$, C(7)*H*$_B$), 2.74–2.81 (1H, m, C(5)*H*$_A$), 3.58–3.65 (1H, m, C(8a)*H*), 3.78–3.85 (2H, m, C(5)*H*$_B$, C(1)*H*$_A$), 4.32–4.38 (1H, m, C(1)*H*$_B$).

Method B. *Step 1*. Et_3N (1.03 mL, 7.43 mmol) was added dropwise *via* syringe to a stirred solution of **254** (400 mg, 1.86 mmol) and MsCl (0.29 mL, 3.72 mmol) in CH_2Cl_2 (9 mL) at 0 °C and the resultant solution was allowed to warm to rt over 4 h. H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried and concentrated *in vacuo*.

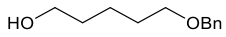
Step 2. PTSH (497 mg, 2.79 mmol) and $NaHCO_3$ (234 mg, 2.79 mmol) were added to a stirred solution of the residue from the previous step in 1,4-dioxane (12 mL) at rt and the resultant suspension was stirred at rt for 36 h. The resultant solution was filtered through a silica plug (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:3) gave **324** as a colourless oil (223 mg, 85%).

Method C. *Step 1*. Et_3N (1.03 mL, 7.43 mmol) was added dropwise *via* syringe to a stirred solution of **254** (400 mg, 1.86 mmol) and MsCl (0.29 mL, 3.72 mmol) in CH_2Cl_2 (9 mL) at 0 °C and the resultant solution was allowed to warm to rt over 4 h. H_2O (10 mL) was added and

the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried and concentrated *in vacuo*.

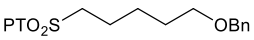
Step 2. PTSH (497 mg, 2.79 mmol) and K_2CO_3 (2.57 g, 18.6 mmol) were added to a stirred solution of the residue from the previous step in acetone (9 mL) at rt and the resultant suspension was heated at 60 °C for 16 h, then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:3) gave **324** as a colourless oil (210 mg, 80%).

5-(Benzyloxy)pentan-1-ol 327



A solution of **326** (26.3 mL, 250 mmol) in THF (45 mL) was added dropwise *via* cannula to a stirred solution of NaH (2.40 g, 60 mmol) in THF (85 mL) at 0 °C and the resultant solution was stirred at 0 °C for 30 min. A solution of BnBr (5.94 mL, 50 mmol) in THF (15 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 16 h. EtOAc (100 mL) and NH_4Cl (210 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organics were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:2) gave **327** as a colourless oil (9.00 g, 93%);[37] δ_H (400 MHz, $CDCl_3$) 1.42–1.50 (2H, m, C(4)H_2), 1.56–1.70 (4H, m, C(2)H_2, C(3)H_2), 3.49 (2H, t, *J* 6.5, C(5)H_2), 3.65 (2H, t, *J* 6.2, C(1)H_2), 4.51 (2H, s, OCH_2Ph), 7.26–7.39 (5H, m, *Ph*).

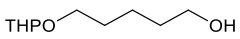
1-(Benzyloxy)-5-[(1'-phenyl-1*H*-tetrazol-5'-yl)sulfonyl]pentane 320



Step 1. DIAD (1.52 mL, 7.72 mmol) was added dropwise *via* syringe to a stirred solution of **327** (1.00 g, 5.15 mmol), PPh_3 (2.02 g, 7.72 mmol) and PTSH (1.38 g, 7.72 mmol) in THF (25 mL) at 0 °C and the resultant solution was allowed to warm to rt over 30 min. EtOAc (25 mL)

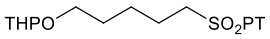
and H_2O (25 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The combined organics were washed with brine (75 mL), then dried and concentrated *in vacuo*. *Step 2*. A solution of $(NH_4)_6Mo_7O_{24}·4H_2O$ (1.27 g, 1.03 mmol) in aq H_2O_2 (30% v/v, 10.6 mL, 104 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in EtOH/THF (1:1, 50 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. EtOAc (50 mL) and Na_2SO_3 (50 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organics were washed with brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **320** as a white solid (1.79 g, 90%); mp 48–50 °C; ν_{max} 1339, 1150; δ_H (400 MHz, $CDCl_3$) 1.57–1.72 (4H, m, C(3)H_2, C(2)H_2), 1.95–2.03 (2H, m, C(4)H_2), 3.49 (2H, t, *J* 6.0, C(1)H_2), 3.72–3.76 (2H, m, C(5)H_2), 4.51 (2H, s, OCH_2Ph), 7.27–7.38 (5H, m, *Ph*), 7.57–7.66 (3H, m, *Ph*), 7.67–7.72 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.8 (*C*(4)), 24.9 (*C*(3)), 29.0 (*C*(2)), 55.9 (*C*(5)), 69.4 (*C*(1)), 72.9 (O*C*H_2Ph), 125.0, 127.5, 127.6, 128.3, 129.6, 131.4, 133.0, 138.3, 153.4 (*Ar*, *Ph*); *m/z* (ESI^+) 409 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{22}N_4NaO_3S^+$ ($[M+Na]^+$) requires 409.1305; found 409.1303.

(2'*RS*)-5-(Tetrahydro-2*H*-pyran-2'-yloxy)pentan-1-ol 329



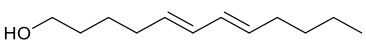
DHP (13.7 mL, 150 mmol) and PPTS (1.88 g, 7.50 mmol) were added sequentially to a stirred solution of **326** (31.6 mL, 300 mmol) in CH_2Cl_2 (450 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. $NaHCO_3$ (450 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 450 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:2) gave **329** as a colourless oil (20.1 g, 71%);[38] δ_H (400 MHz, $CDCl_3$) 1.42–1.87 (12H, m, C(4)H_2, C(3)H_2, C(2)H_2, C(3')H_2, C(4')H_2, C(5')H_2), 3.41 (1H, dt, *J* 9.7, 6.4, C(5)H_A), 3.48–3.53 (1H, m, C(6')H_A), 3.66 (2H, t, *J* 6.5, C(1)H_2), 3.76 (1H, dt, *J* 9.7, 6.7, C(5)H_B), 3.85–3.90 (1H, m, C(6')H_B), 4.57–4.59 (1H, m, C(2')*H*).

(2'*RS*)-1-(Tetrahydro-2*H*-pyran-2'-yloxy)-5-[(1''-phenyl-1*H*-tetrazol-5''-yl)sulfonyl]pentane 331



DIAD (1.56 mL, 7.97 mmol) was added dropwise *via* syringe to a stirred solution of **329** (1.00 g, 5.31 mmol), PPh_3 (2.09 g, 7.97 mmol) and PTSH (1.42 g, 7.97 mmol) in THF (20 mL) at 0 °C and the resultant solution was allowed to warm to rt over 30 min. EtOH (25 mL) was added and the resultant solution cooled to 0 °C. A solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (1.31 g, 1.06 mmol) in aq H_2O_2 (30% v/v, 10.8 mL, 106 mmol) was added dropwise *via* syringe at 0 °C and the resultant solution was allowed to warm to rt over 16 h. EtOAc (100 mL) and Na_2SO_3 (100 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organics were washed with brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 3:1) gave **331** as a colourless oil (1.82 g, 90%); ν_{max} 1339, 1150; δ_H (400 MHz, $CDCl_3$) 1.48–1.85 (10H, m, C(2)H_2, C(3)H_2, C(3')H_2, C(4')H_2, C(5')H_2), 1.94–2.02 (2H, m, C(4)H_2), 3.38 (1H, dt, *J* 9.7, 5.9, C(6')H_A), 3.45–3.51 (1H, m, C(1)H_A), 3.72–3.77 (3H, m, C(5)H_2, C(6')H_B), 3.79–3.85 (1H, m, C(1)H_B), 4.55 (1H, m, C(2')*H*), 7.55–7.69 (5H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.5 (*C*(2), *C*(3), *C*(3'), *C*(4'), *C*(5')), 21.8 (*C*(4)), 25.0, 25.3, 28.9, 30.6 (*C*(2), *C*(3), *C*(3'), *C*(4'), *C*(5')), 55.8 (*C*(5)), 62.3 (*C*(1)), 66.7 (*C*(6')), 98.8 (*C*(2')), 125.0, 129.6, 131.3, 132.9, 153.3 (*Ar*, *Ph*); *m/z* (ESI^+) 403 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{24}N_4NaO_4S^+$ ($[M+Na]^+$) requires 403.1410; found 403.1407.

(5*E*,7*E*)-1-Hydroxydodeca-5,7-diene 333

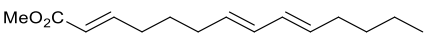


Step 1. NaHMDS (1.00 M in THF, 14.7 mL, 14.7 mmol) was added dropwise *via* syringe to a stirred solution of **331** (2.80 g, 7.36 mmol) and **144** (1.06 mL, 8.09 mmol, >95:5 dr [(2*E*):(2*Z*)]) in DME (150 mL) at −55 °C and the resultant solution was stirred at −55 °C for 30 min. H_2O (150 mL) was added and the aqueous layer was extracted with Et_2O (3 × 200 mL). The

combined organics were washed with brine (600 mL), then dried and concentrated *in vacuo*. The residue was filtered through a silica plug (eluent 30–40 °C petroleum ether/Et_2O, 10:1) and concentrated *in vacuo*.

Step 2. $TsOH·H_2O$ (70 mg, 0.37 mmol) was added to a stirred solution of the residue from the previous step in MeOH (25 mL) at rt and the resultant solution was stirred at rt for 2 h. Et_3N (75 μL, 0.74 mmol) was added dropwise *via* syringe and the resultant solution was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:1) gave **333** as a colourless oil (1.05 g, 78%, 92:8 dr [(5*E*,7*E*):(5*Z*,7*E*)]); ν_{max} 3327, 1624; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(12)H_3), 1.26–1.39 (4H, m, C(10)H_2, C(11)H_2), 1.40–1.49 (2H, m, C(3)H_2), 1.52–1.61 (2H, m, C(2)H_2), 2.02–2.11 (4H, m, C(4)H_2, C(9)H_2), 3.63 (2H, t, *J* 6.5, C(1)H_2), 5.49–5.60 (2H, m, C(5)*H*, C(8)*H*), 5.94–6.04 (2H, m, C(6)*H*, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(12)), 22.4 (*C*(11)), 25.6 (*C*(3)), 31.7, 32.3, 32.4, 32.4 (*C*(2), *C*(4), *C*(9), *C*(10)), 62.9 (*C*(1)), 130.3, 130.9 (*C*(5), *C*(8)), 131.8, 132.9 (*C*(6), *C*(7)); *m/z* (ESI^+) 183 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{12}H_{23}O^+$ ($[M+H]^+$) requires 183.1743; found 183.1746.

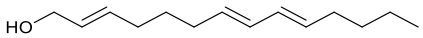
Methyl (2*E*,7*E*,9*E*)-tetradeca-2,7,9-trienoate 335



DMSO (3.74 mL, 52.7 mmol) was added dropwise *via* syringe to a stirred solution of $(COCl)_2$ (2.23 mL, 26.3 mmol) in CH_2Cl_2 (35 mL) at −78 °C and the resultant solution was stirred at −78 °C for 10 min. A solution of **333** (2.40 g, 13.2 mmol, 92:8 dr [(5*E*,7*E*):(5*Z*,7*E*)]) in CH_2Cl_2 (35 mL) was added dropwise *via* cannula at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (11.0 mL, 79.0 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 20 min, then **176** (4.85 g, 14.5 mmol) was added and the resultant mixture was stirred at rt for 16 h. H_2O (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 30:1) gave **335** as a

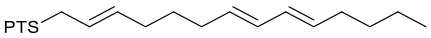
colourless oil (2.63 g, 85%, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]); ν_{max} 1725, 1657; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(14)H_3), 1.25–1.39 (4H, m, C(12)H_2, C(13)H_2), 1.53 (2H, app quin, C(5)H_2), 2.01–2.10 (4H, m, C(6)H_2, C(11)H_2), 2.16–2.22 (2H, m, C(4)H_2), 3.71 (3H, s, O*Me*), 5.47–5.60 (2H, m, C(7)*H*, C(10)*H*), 5.81 (1H, d, *J* 15.6, C(2)*H*), 5.94–6.03 (2H, m, C(8)*H*, C(9)*H*), 6.95 (1H, dt, *J* 15.6, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(14)), 22.4 (*C*(13)), 27.8 (*C*(5)), 31.6 (*C*(12)), 31.7 (*C*(4)), 32.0, 32.4 (*C*(6), *C*(11)), 51.5 (O*Me*), 121.2 (*C*(2)), 130.2, 131.0, 131.4, 133.1 (*C*(7), *C*(8), *C*(9), *C*(10)), 149.2 (*C*(3)), 167.7 (*C*(1)); *m/z* (ESI^+) 259 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{24}NaO_2^+$ ($[M+Na]^+$) requires 259.1669; found 259.1670.

(2*E*,7*E*,9*E*)-Tetradeca-2,7,9-trien-1-ol 86



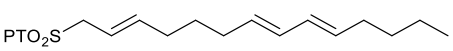
DIBAL-H (1.00 M in CH_2Cl_2, 40.9 mL, 40.9 mmol) was added dropwise *via* syringe to a stirred solution of **335** (4.40 g, 18.6 mmol, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]) in CH_2Cl_2 (125 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1.5 h. Satd aq Rochelle salt (100 mL) was added and the resultant mixture was stirred at −78 °C for 5 min, then stirred at rt for 1 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 4:1) gave **86** as a colourless oil (3.45 g, 89%, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]); ν_{max} 3306, 1670; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, C(14)H_3), 1.25–1.43 (4H, m, C(12)H_2, C(13)H_2), 1.48 (2H, app quin, *J* 7.5, C(5)H_2), 2.03–2.10 (6H, m, C(4)H_2, C(6)H_2, C(11)H_2), 4.09 (2H, d, *J* 4.9, C(1)H_2), 5.50–5.73 (4H, m, C(2)*H*, C(3)*H*, C(7)*H*, C(10)*H*), 5.95–6.05 (2H, m, C(8)*H*, C(9)*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(14)), 22.2 (*C*(13)), 28.8 (*C*(5)), 31.5 (*C*(12)), 31.6, 32.0, 32.2 (*C*(4), *C*(6), *C*(11)), 63.8 (*C*(1)), 129.2, 131.6, 132.7, 133.0 (*C*(2), *C*(3), *C*(7), *C*(10)), 130.2, 130.8 (*C*(8), *C*(9)); *m/z* (ESI^+) 209 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{25}O^+$ ($[M+H]^+$) requires 209.1900; found 209.1901.

(2*E*,7*E*,9*E*)-1-[(1'-Phenyl-1*H*-tetrazol-5'-yl)thio]tetradeca-2,7,9-triene 336



DIAD (3.10 mL, 15.8 mmol) was added dropwise *via* syringe to a stirred solution **86** (2.20 g, 10.6 mmol, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]), PPh_3 (4.14 g, 15.8 mmol) and PTSH (2.82 g, 15.8 mmol) in THF (50 mL) at 0 °C and the resultant solution was allowed to warm to rt over 30 min. Et_2O (200 mL) and H_2O (200 mL) were added, and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organics were washed with brine (600 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 4:1) gave **336** as a colourless oil (3.89 g, quant, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]); ν_{max} 1663, 1597; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(14)H_3), 1.25–1.38 (4H, m, C(12)H_2, C(13)H_2), 1.43 (2H, app quin, *J* 7.4, C(5)H_2), 1.98–2.07 (6H, m, C(4)H_2, C(6)H_2, C(11)H_2), 3.99 (2H, dd, *J* 7.3, 0.7, C(1)H_2), 5.46–5.65 (3H, m, C(2)*H*, C(7)*H*, C(10)*H*), 5.80 (1H, dt, *J* 15.2, 6.9, C(3)*H*), 5.91–6.02 (2H, m, C(8)*H*, C(9)*H*), 7.50–7.59 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(14)), 22.2 (*C*(13)), 28.5 (*C*(5)), 31.5, 31.6, 31.8, 32.2 (*C*(4), *C*(6), *C*(11), *C*(12)), 35.6 (*C*(1)), 123.0 (*C*(2)), 123.8, 129.7, 130.0 (*Ph*), 130.1, 130.8 (*C*(8), *C*(9)), 131.3, 132.7 (*C*(7), *C*(10)), 133.6 (*Ph*), 136.8 (*C*(3)), 153.9 (*Ar*); *m/z* (ESI^+) 391 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{28}N_4NaS^+$ ($[M+Na]^+$) requires 391.1927; found 391.1931.

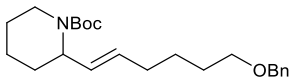
(2*E*,7*E*,9*E*)-1-[(1'-Phenyl-1*H*-tetrazol-5'-yl)sulfonyl]tetradeca-2,7,9-triene 321



A solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (2.68 g, 2.17 mmol) in aq H_2O_2 (30% v/v, 22.0 mL, 217 mmol) was added dropwise *via* syringe to a stirred solution of **336** (4.00 g, 10.9 mmol, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. EtOAc (200 mL) and Na_2SO_3 (200 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organics were washed with brine (600 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C

petroleum ether/Et_2O, 5:1) gave **321** as a pale yellow oil (2.65 g, 61%, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]); ν_{max} 1596, 1344, 1152; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0, C(14)H_3), 1.21–1.46 (6H, m, C(5)H_2, C(12)H_2, C(13)H_2), 1.96–2.10 (6H, m, C(4)H_2, C(6)H_2, C(11)H_2), 4.36 (2H, d, *J* 7.4, C(1)H_2), 5.42–5.60 (3H, m, C(2)*H*, C(7)*H*, C(10)*H*), 5.89–6.01 (3H, m, C(3)*H*, C(8)*H*, C(9)*H*), 7.55–7.65 (5H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*(14)), 22.3 (*C*(13)), 28.2, 31.6 (*C*(5), *C*(12)), 31.8, 32.1, 32.3 (*C*(4), *C*(6), *C*(11)), 59.9 (*C*(1)), 113.2 (*C*(2)), 125.3, 129.7 (*Ar*), 130.2, 131.0, 131.3, 131.5, 133.0, 133.1 (*C*(7), *C*(8), *C*(9), *C*(10), *Ar*), 144.9 (*C*(3)), 153.2 (*Ar*); *m/z* (ESI^+) 401 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{29}N_4O_2S^+$ ($[M+H]^+$) requires 401.2006; found 401.2018.

(2*RS*,1'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[6'-(benzyloxy)hex-1'-en-1'-yl]piperidine 337

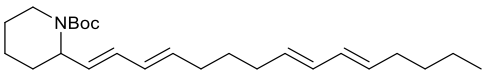


Step 1. DMP (219 mg, 0.52 mmol) was added to a stirred solution of **254** (101 mg, 0.47 mmol) in CH_2Cl_2 (3 mL) at rt and the resultant solution was stirred at rt for 1 h. $NaHCO_3$ (131 mg, 1.56 mmol) was added and the resultant suspension was stirred at rt for 5 min. The resultant mixture was then filtered through a silica plug (eluent Et_2O) and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*.

Step 2. KHMDS (1.00 M in THF, 0.52 mL, 0.52 mmol) was added dropwise *via* syringe to a stirred solution of **320** (235 mg, 0.61 mmol) in THF (3 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1 h. A solution of the residue from the previous step in THF (1.5 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 16 h. EtOAc (4 mL) and H_2O (4 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 4 mL). The combined organics were washed with brine (12 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 5:1) gave **337** as a colourless oil (136 mg, 78%, 94:6 dr [(1'*E*):(1'*Z*)]); ν_{max} 1688; δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 1.47–1.70 (10H, m, C(3)H_2, C(4)H_2,

C(5)H_2, C(4')H_2, C(5')H_2), 2.06 (2H, app q, *J* 6.8, C(3')H_2), 2.82 (1H, app td, *J* 12.9, 2.8, C(6)H_A), 3.47 (2H, t, *J* 6.5, C(6')H_2), 3.92 (1H, app d, *J* 13.2, C(6)H_B), 4.50 (2H, s, OCH_2Ph), 4.71–4.77 (1H, m, C(2)*H*), 5.36–5.50 (2H, m, C(1')*H*, C(2')*H*), 7.24–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.4, 25.5, 25.9 (*C*(3), *C*(4), *C*(5), *C*(4'), *C*(5')), 28.4 (CMe_3), 29.1, 29.3 (*C*(3), *C*(4), *C*(5), *C*(3'), *C*(5')), 32.1 (*C*(3')), 39.6 (*C*(6)), 51.8 (*C*(2)), 70.1 (*C*(6')), 72.8 (OCH_2Ph), 79.0 (CMe_3), 127.4, 127.5, 128.2 (*Ph*), 128.4 (*C*(2')), 131.4 (*C*(1')), 138.6 (*Ph*), 155.3 (N(1)*C*O); *m/z* (ESI^+) 396 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{35}NNaO_3^+$ ($[M+Na]^+$) requires 396.2509; found 396.2503.

(2*RS*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',8',10'-tetraen-1'-yl)piperidine 288

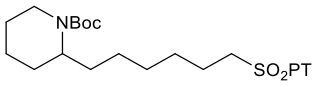


Step 1. DMP (648 mg, 1.53 mmol) was added to a stirred solution of **254** (299 mg, 1.39 mmol) in CH_2Cl_2 (7 mL) at rt and the resultant solution was stirred at rt for 1 h. $NaHCO_3$ (386 mg, 4.59 mmol) was added and the resultant suspension was stirred at rt for 5 min. The resultant mixture was then filtered through a silica plug (eluent Et_2O) and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*.

Step 2. KHMDS (1.00 M in THF, 1.53 mL, 1.53 mmol) was added dropwise *via* syringe to a stirred solution of **321** (698 mg, 1.81 mmol, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]) and 18c6 (404 mg, 1.53 mmol) in THF (9 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1 h. A solution of the residue from the previous step in THF (4.5 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 16 h. EtOAc (15 mL) and H_2O (15 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organics were washed with brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 9:1) gave **288** as a pale yellow oil (420 mg, 78%, >80% dp); ν_{max} 1693; δ_H (400 MHz, $CDCl_3$) 0.89

(3H, t, *J* 7.1, C(15)H_3), 1.27–1.77 (12H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(6')H_2, C(13')H_2, C(14')H_2), 1.46 (9H, s, CMe_3), 2.01–2.13 (6H, m, C(5')H_2, C(7')H_2, C(12')H_2), 2.82 (1H, app td, *J* 13.0, 2.7, C(6)H_A), 3.94 (1H, app d, *J* 13.0, C(6)H_B), 4.78–4.85 (1H, m, C(2)*H*), 5.47–5.68 (4H, m, C(1')*H*, C(4')*H*, C(8')*H*, C(11')*H*), 5.90–6.08 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 19.6, 22.2, 25.5 (*C*(3), *C*(4), *C*(5), *C*(6'), *C*(13'), *C*(14')), 28.4 (CMe_3), 28.9, 29.3, 31.5 (*C*(3), *C*(4), *C*(5), *C*(6'), *C*(13'), *C*(14')), 32.0, 32.0, 32.2 (*C*(5'), *C*(7'), *C*(12')), 39.7 (*C*(6)), 51.8 (*C*(2)), 79.2 (*C*Me_3), 129.8, 130.0, 130.2, 130.7, 131.3, 131.7, 132.6, 133.8 (*C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(8'), *C*(9'), *C*(10'), *C*(11')), 155.3 (N(1)*C*O); *m/z* (ESI^+) 410 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{24}H_{41}NNaO_2^+$ ($[M+Na]^+$) requires 410.3030; found 410.3030.

(2*RS*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-{6'-[(1''-phenyl-1*H*-tetrazol-5''-yl)sulfonyl]hex-1'-yl}piperidine 340



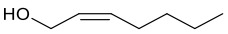
Step 1. $Pd(OH)_2/C$ (40 mg, 20% w/w of **337**) was added to a stirred solution of **337** (200 mg, 0.54 mmol, 94:6 dr [(1'*E*):(1'*Z*)]) in degassed EtOAc (6 mL) at rt and the resultant suspension was stirred at rt for 2 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. DIAD (0.16 mL, 0.81 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, PPh_3 (212 mg, 0.81 mmol) and PTSH (144 mg, 0.81 mmol) in THF (3 mL) at 0 °C and the resultant solution was allowed to warm to rt over 30 min. Et_2O (3 mL) and H_2O (3 mL) were added, and the aqueous layer was extracted with Et_2O (2 × 3 mL). The combined organics were washed with brine (10 mL), then dried and concentrated *in vacuo*. The residue was filtered through a silica plug (eluent 30–40 °C petroleum ether/EtOAc, 7:1) and concentrated *in vacuo*.

Step 3. *m*CPBA (75%, 497 mg, 2.16 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (18 mL) at 0 °C and the resultant solution was allowed to warm to

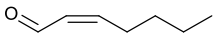
rt over 1 h, then cooled to 0 ° C. Satd aq Na_2SO_3 (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 6:1) gave **340** as a colourless oil (130 mg, 51%); ν_{max} 1681, 1341, 1151; δ_H (400 MHz, $CDCl_3$) 1.17–1.70 (14H, m, C(3)H_2, C(4)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, CMe_3), 1.92 (2H, app quin, *J* 7.3, C(5)H_2), 2.70 (1H, app t, *J* 13.0, C(6)H_A), 3.70 (2H, t, *J* 7.8, C(6')H_2), 3.93 (1H, app d, *J* 11.7, C(6)H_B), 4.12–4.22 (1H, m, C(2)*H*), 7.54–7.68 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.9 (*C*(3), *C*(4), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(5')), 21.8 (*C*(5)), 25.5, 25.8, 28.0, 28.4 (*C*(3), *C*(4), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(5')), 28.4 (C*Me*$_3$), 28.7, 29.4 (*C*(3), *C*(4), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(5')), *39*[*] (*C*(6)), *50*[*] (*C*(2)), 55.9 (*C*(6')), 78.9 (*C*Me$_3$), 125.0, 129.6, 131.3, 133.0 (*Ph*), 153.4 (*Ar*), 155.0 (N(1)*C*O); *m/z* (ESI$^+$) 500 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{35}N_5NaO_4S^+$ ([M+Na]$^+$) requires 500.2302; found 500.2299.

(2*Z*)-2-Hepten-1-ol 342



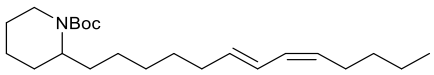
Lindlar catalyst (66 mg, 15% w/w of **341**) was added to a stirred solution of **341** (0.50 mL, 3.92 mmol) and quinoline (81 µL, 20% w/w of **341**) in degassed EtOAc (33 mL) at rt and the resultant suspension was stirred at rt for 2 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 2:1) gave **342** as a colourless oil (373 mg, 83%, 92:8 dr [(2*Z*):(2*E*)]);[39,40] ν_{max} 3313, 1656; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(7)H_3), 1.27–1.39 (4H, m, C(5)H_2, C(6)H_2), 1.49 (1H, br s, O*H*), 2.08 (2H, app q, *J* 6.6, C(4)H_2), 4.19 (2H, d, *J* 6.1, C(1)H_2), 5.50–5.62 (2H, m, C(2)*H*, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(7)), 22.2 (*C*(6)), 27.1 (*C*(4)), 31.7 (*C*(5)), 58.5 (*C*(1)), 128.3 (*C*(2)), 133.1 (*C*(3)).[17]

(2*Z*)-2-Heptenal 343



DMP (1.39 g, 3.27 mmol) was added to a stirred solution of **342** (340 mg, 2.98 mmol, 92:8 dr [(2*Z*):(2*E*)]) in CH_2Cl_2 (15 mL) at rt and the resultant solution was stirred at rt for 1 h. $NaHCO_3$ (824 mg, 9.81 mmol) was added and the resultant suspension was stirred at rt for 5 min. The resultant mixture was then filtered through a silica plug (eluent Et_2O) and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 2:1) gave **343** as a pale yellow oil (334 mg, quant, 92:8 dr [(2*Z*):(2*E*)]);[41] δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.1, C(7)H_3), 1.32–1.41 (2H, m, C(6)H_2), 1.45–1.52 (2H, m, C(5)H_2), 2.60 (2H, app qd, *J* 7.9, 1.7, C(4)H_2), 5.91–5.97 (1H, m, C(2)*H*), 6.62 (1H, dt, *J* 11.1, 7.9, C(3)*H*), 10.06 (1H, d, *J* 8.1, C(1)*H*).

(2*RS*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)piperidine 344

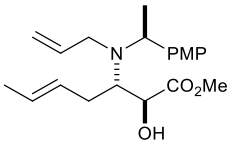


KHMDS (1.00 M in THF, 0.25 mL, 0.25 mmol) was added dropwise *via* syringe to a stirred solution of **340** (60 mg, 0.13 mmol) and **343** (33 µL, 0.25 mmol, 92:8 dr [(2*Z*):(2*E*)]) in THF (1.3 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. EtOAc (3 mL) and H_2O (3 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organics were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 9:1) gave **344** as a colourless oil (32 mg, 71%, 92:8 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]); ν_{max} 1689; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, C(13')H_3), 1.20–1.71 (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, CMe_3), 2.10 (2H, app q, *J* 7.0, C(5')H_2), 2.17 (2H, app q, *J* 7.0, C(10')H_2), 2.74 (1H, app t, *J* 13.9, C(6)H_A), 3.97 (1H, app d, *J* 12.2, C(6)H_B), 4.16–4.23 (1H, m, C(2)*H*), 5.31 (1H, dt, *J* 10.8, 7.6, C(9')*H*), 5.65 (1H, dt, *J* 15.0, 7.2, C(6')*H*), 5.94 (1H, app t, *J* 10.8, C(8')*H*), 6.30 (1H, ddd, *J* 15.0, 10.8, 1.0, C(7')*H*);

δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 19.0, 22.3, 25.7, 26.2 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 27.4 (*C*(10')), 28.5 (C*Me*$_3$), 28.5, 29.1, 29.4, 29.6, 31.9 (*C*(3), *C*(4), *C*(5), *C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(11'), *C*(12')), 32.8 (*C*(5')), *39*[*] (*C*(6)), *50*[*] (*C*(2)), 78.9 (*C*Me$_3$), 125.7 (*C*(7')), 128.6 (*C*(8')), 130.1 (*C*(9')), 134.5 (*C*(6')), 155.2 (N(1)*C*O); *m/z* (ESI^+) 386 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{41}NNaO_2^+$ ($[M+Na]^+$) requires 386.3030; found 386.3031.

6.4 Experimental Data for Chapter 4

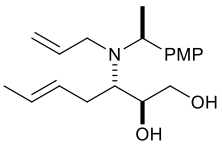
Methyl (2*S*,3*S*,5*E*,α*S*)-2-hydroxy-3-[*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]hept-5-enoate 350



BuLi (2.30 M in hexanes, 11.0 mL, 25.3 mmol) was added dropwise *via* syringe to a stirred solution of **159** (5.00 g, 26.1 mmol, >95:5 er) in THF (20 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. A solution of **129** (2.29 g, 16.3 mmol, >90% purity) in THF (20 mL) at −78 °C was added dropwise *via* syringe and the resultant solution was stirred at −78 °C for 2 h. (+)-CSO (6.37 g, 27.8 mmol) was added and the resultant mixture was allowed to warm to rt over 16 h, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were washed sequentially with satd aq $NaHCO_3$ (45 mL) and brine (45 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 2:1) gave **350** as a pale yellow oil (2.55 g, 45%, >95:5 dr, >90% purity); $[\alpha]_D^{25}$ +22.6 (*c* 1.0 in $CHCl_3$); ν_{max} 3505, 1731, 1610; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.65 (3H, dd, *J* 6.4, 1.0, C(7)*H*$_3$), 2.21–2.30 (2H, m, C(4)*H*$_2$), 2.88 (1H, d, *J* 6.8, O*H*), 3.06–3.16 (2H, m, C(3)*H*, C(1')*H*$_A$), 3.30–3.35 (1H, m, C(1)*H*$_B$), 3.69 (3H, s, CO_2*Me*), 3.80 (3H, s, ArO*Me*), 3.95–4.00 (1H, m, C(2)*H*), 4.05 (1H, q, *J* 6.8, C(α)*H*), 5.11–5.14 (1H, m, C(3')*H*$_A$), 5.17–5.22 (1H, m, C(3')*H*$_B$), 5.34–5.42 (1H, m, C(5)*H*), 5.46–5.55 (1H, m, C(6)*H*), 5.88 (1H, dddd, *J* 17.4, 10.0, 7.3, 5.1, C(2')*H*), 6.87 (2H, d,

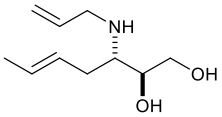
J 8.7, *Ar*), 7.27 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 18.0 (*C*(7)), 31.0 (*C*(4)), 50.0 (*C*(1')), 51.9 (CO_2*Me*), 55.1 (ArO*Me*), 56.8 (*C*(α)), 60.1 (*C*(3)), 71.2 (*C*(2)), 113.6 (*Ar*), 116.2 (*C*(3')), 127.6 (*C*(6)), 128.1 (*C*(5)), 128.8, 136.1 (*Ar*), 138.8 (*C*(2')), 158.4 (*Ar*), 174.5 (*C*(1)); *m/z* (ESI^+) 348 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{30}NO_4^+$ ($[M+H]^+$) requires 348.2169; found 348.2167.

(2*S*,3*S*,5*E*,α*S*)-3-[*N*-Allyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]hept-5-en-1,2-diol 351



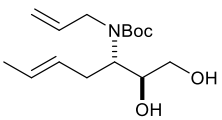
$LiAlH_4$ (2.40 M in THF, 8.15 mL, 19.6 mmol) was added dropwise *via* syringe to a stirred solution of **350** (3.40 g, 9.78 mmol, >95:5 dr, >90% purity) in THF (35 mL) at −78 °C and the resultant solution was allowed to warm to rt over 16 h, then cooled to −78 °C. Aq NaOH (2.00 M, 9.80 mL, 19.6 mmol) was added dropwise *via* syringe and the resultant mixture was allowed to warm to rt over 2 h. The resultant mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:3) gave **351** as a pale yellow oil (3.06 g, 98%, >95:5 dr, >90% purity); $[\alpha]_D^{25}$ +14.1 (*c* 1.0 in $CHCl_3$); ν_{max} 3395, 1611; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.67 (3H, d, *J* 4.6, C(7)H_3), 2.18–2.39 (2H, m, C(4)H_2), 2.84 (1H, ddd, *J* 8.9, 7.0, 3.9, C(3)*H*), 3.18–3.31 (2H, m, C(1')H_2), 3.39–3.42 (2H, m, C(1)H_2), 3.51–3.56 (1H, m, C(2)*H*), 3.81 (3H, s, O*Me*), 4.03 (1H, q, *J* 6.8, C(α)*H*), 5.15–5.23 (2H, m, C(3')H_2), 5.45–5.59 (2H, m, C(5)*H*, C(6)*H*), 5.82–5.93 (1H, m, C(2')*H*), 6.88 (2H, d, *J* 8.6, *Ar*), 7.24 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 14.5 (C(α)*Me*), 18.0 (*C*(7)), 32.7 (*C*(4)), 50.7 (*C*(1')), 55.2 (O*Me*), 57.1 (*C*(α)), 58.6 (*C*(3)), 64.7 (*C*(1)), 73.0 (*C*(2)), 113.7 (*Ar*), 117.2 (*C*(3')), 127.1 (*C*(6)), 128.9 (*Ar*), 129.3 (*C*(5)), 135.8 (*Ar*), 137.6 (*C*(2')), 158.6 (*Ar*); *m/z* (ESI^+) 320 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{30}NO_3^+$ ($[M+H]^+$) requires 320.2220; found 320.2215.

(2*S*,3*S*,5*E*)-3-(*N*-Allylamino)hept-5-en-1,2-diol 352



TFA (10.0 mL, 131 mmol) was added dropwise *via* syringe to a stirred solution of **351** (3.20 g, 10.0 mmol, >95:5 dr, >90% purity) in CH_2Cl_2 (10 mL) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo*. The residue was partitioned between $CHCl_3$/^{i}PrOH (3:1, 15 mL) and satd aq $NaHCO_3$ (15 mL), and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 15 mL). The combined organics were washed with brine (45 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 100:10:1) gave **352** as a pale yellow oil (1.69 g, 91%, >95:5 dr, >95% purity); $[\alpha]_D^{25}$ +43.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3333, 1643; δ_H (400 MHz, $CDCl_3$) 1.67 (3H, d, *J* 6.4, C(7)H_3), 2.16–2.19 (2H, m, C(4)H_2), 2.71–2.75 (1H, m, C(3)*H*), 2.92 (3H, br s, 2 × O*H*, N*H*), 3.22–3.32 (2H, m, C(1')H_2), 3.60–3.66 (2H, m, C(1)H_2), 3.70–3.78 (1H, m, C(2)*H*), 5.07–5.11 (1H, m, C(3')H_A), 5.13–5.17 (1H, m, C(3')H_B), 5.32–5.39 (1H, m, C(5)*H*), 5.49–5.57 (1H, m, C(6)*H*), 5.83 (1H, app ddt, *J* 16.8, 10.6, 5.9, C(2')*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (*C*(7)), 33.3 (*C*(4)), 50.6 (*C*(1')), 60.0 (*C*(3)), 64.7 (*C*(1)), 71.1 (*C*(2)), 116.3 (*C*(3')), 126.8 (*C*(5)), 129.0 (*C*(6)), 136.3 (*C*(2')); *m/z* (ESI$^+$) 186 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{20}NO_2^+$ ([M+H]$^+$) requires 186.1489; found 186.1491.

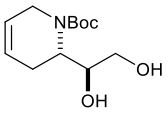
(2*S*,3*S*,5*E*)-3-[*N*-Allyl-*N*-(*tert*-butoxycarbonyl)amino]hept-5-en-1,2-diol 353



$NaHCO_3$ (1.45 g, 17.3 mmol) and Boc_2O (2.07 g, 9.50 mmol) were added sequentially to a solution of **352** (1.60 g, 8.63 mmol, >95:5 dr, >95% purity) in MeOH (50 mL) and the resultant suspension was sonicated at rt for 16 h, then filtered and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$/^{i}PrOH (3:1, 30 mL) and satd aq $NaHCO_3$ (30 mL), and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, 2 × 30 mL). The combined organics were

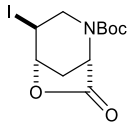
washed with brine (90 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:1) gave **353** as a colourless oil (2.14 g, 87%, >95:5 dr, >95% purity); $[\alpha]_D^{25}$ −14.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3408, 1691, 1665; δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 1.63 (3H, dd, *J* 6.2, 0.9, C(7)*H*$_3$), 2.33–2.41 (1H, m, C(4)*H*$_A$), 2.48–2.57 (1H, m, C(4)*H*$_B$), 3.25–3.37 (1H, br s, O*H*), 3.47–3.83 (6H, m, C(1)*H*$_2$, C(2)*H*, C(3)*H*, C(1')*H*$_2$), 5.07–5.14 (2H, m, C(3')*H*$_2$), 5.29–5.37 (1H, m, C(5)*H*), 5.43–5.52 (1H, m, C(6)*H*), 5.72 (1H, app ddt, *J* 17.0, 10.4, 6.1, C(2')*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (*C*(7)), 28.3 (C*Me*$_3$), 30.7 (*C*(4)), *49** (*C*(1')), *59** (*C*(3)), 63.4 (*C*(1)), 73.6 (*C*(2)), 80.6 (*C*Me$_3$), 116.9 (*C*(3')), 127.4 (*C*(6)), 127.6 (*C*(5)), 135.0 (*C*(2')), 157.2 (N*C*O); *m/z* (ESI^+) 308 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{27}NNaO_4^+$ ($[M+Na]^+$) requires 308.1832; found 308.1830.

(2*S*,1'*S*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(1',2'-dihydroxyeth-1'-yl)-1,2,3,6-tetrahydropyridine 348



Grubbs I catalyst (536 mg, 0.65 mmol) was added to a stirred solution of **353** (3.10 g, 10.9 mmol, >95:5 dr, >95% purity) in degassed CH_2Cl_2 (1.00 L) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo* (to a volume of ~200 mL). $P(CH_2OH)_3$ (8.05 g, 65.0 mmol), Et_3N (3.60 mL, 26.0 mmol) and excess silica were added sequentially and the resultant suspension was stirred at rt for 16 h, then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:2) gave **348** as a white solid (2.62 g, 99%, >95:5 dr);[42] mp 91–93 °C; {lit.[42] mp 92–93 °C}; $[\alpha]_D^{25}$ +37.8 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.27–2.38 (1H, m, C(3)*H*$_A$), 2.52–2.66 (1H, m, C(3)*H*$_B$), 3.36–3.69 (4H, m, C(6)*H*$_A$, C(1')*H*, C(2')*H*$_2$), 4.07–4.19 (2H, m, C(2)*H*), C(6)*H*$_B$), 5.57–5.84 (1H, m, C(4)*H*), 5.74–5.84 (1H, m, C(5)*H*).

(1*S*,4*S*,5*S*)-*N*(2)-(*tert*-Butoxycarbonyl)-4-iodo-6-oxa-2-azabicyclo[3.2.1]octan-7-one 349



Method A. *Step 1*. $NaIO_4$ (3.43 g, 16.0 mmol) was added to a stirred solution of **348** (2.60 g, 10.7 mmol, >95:5 dr) in H_2O/THF (3:1, 32 mL) at rt and the resultant mixture was stirred at rt for 2 h. EtOAc (30 mL) and H_2O (10 mL) were added and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organics were washed with brine (90 mL), then dried and concentrated *in vacuo*.

Step 2. 2-methyl-2-butene (6.80 mL, 64.1 mmol), NaH_2PO_4 (1.67 g, 13.9 mmol) and aq $NaClO_2$ (2.00 M, 6.95 mL, 13.9 mmol) were added sequentially to a stirred solution of the residue from the previous step in ^{t}BuOH/THF (2:1, 75 mL) at rt and the resultant mixture was stirred at rt for 16 h. EtOAc (100 mL) and aq $NaHSO_3$ (5% w/v, 100 mL) were added and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organics were washed with brine (300 mL), then dried and concentrated *in vacuo*.

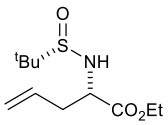
Step 3. $NaHCO_3$ (1.79 g, 21.4 mmol), I_2 (8.14 g, 32.1 mmol) and KI (10.7 g, 64.1 mmol) were added sequentially to a stirred solution of the residue from the previous step in H_2O/CH_2Cl_2 (2:1, 150 mL) at rt and the resultant mixture was stirred at rt for 48 h. The resultant mixture was cooled to −78 °C and satd aq $Na_2S_2O_3$ (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were washed with brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **349** as a white solid (655 mg, 17%, >95:5 dr);[42] mp 120–122 °C; {lit.[42] mp 88–89 °C}; $[\alpha]_D^{25}$ −104 (*c* 1.0 in $CHCl_3$);[43] δ_H (400 MHz, $CDCl_3$) 2.25–2.32 (1H, m, C(8)H_A), 2.94 (1H, d, *J* 12.7, C(8)H_B), 3.70–3.86 (1H, m, C(3)H_A), 4.19–4.46 (2H, m, C(4)*H*, C(3)H_B), 4.62–4.85 (1H, m, C(1)*H*), 4.97 (1H, app t, *J* 4.8, C(5)*H*).

Method B. *Step A*. A solution of $LiOH{\cdot}H_2O$ (1.09 g, 25.9 mmol) in H_2O (65 mL) was added dropwise *via* cannula to a stirred solution of **366** (2.20 g, 8.62 mmol) in THF (250 mL) at rt and the resultant solution was stirred at rt for 48 h. The resultant solution was cooled to 0 °C, then

acidified to pH 4 with aq $KHSO_4$ (2.00 M) and extracted with $CHCl_3$ (3 × 300 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*.

Step 2. $NaHCO_3$ (1.45 g, 17.2 mmol), I_2 (6.57 g, 25.9 mmol) and KI (8.58 g, 51.7 mmol) were added sequentially to a stirred solution of the residue from the previous step in H_2O/CH_2Cl_2 (2:1, 120 mL) at rt and the resultant mixture was stirred at rt for 48 h. The resultant mixture was cooled to −78 °C and satd aq $Na_2S_2O_3$ (40 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organics were washed with brine (120 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **349** as a white solid (325 mg, 11%, >95:5 dr).

Ethyl (2*S*,*S*$_S$)-2-[(*tert*-butylsulfinyl)amino]pent-4-enoate 358

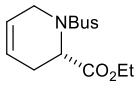


Step 1. A stirred solution of **356** (50% w/v in toluene, 8.63 mL, 43.6 mmol) was heated at 50 °C for 5 min, then allowed to cool to rt. 4Å MS (27 g) and a solution of (*S*)-*tert*-butylsulfinamide (5.28 g, 43.6 mmol) in CH_2Cl_2 (120 mL) were added sequentially and the resultant suspension was stirred at rt for 48 h. The resultant solution was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. Allyl bromide (15.1 mL, 174 mmol) was added dropwise *via* syringe to a stirred suspension of indium powder (20.0 g, 174 mmol) and the residue from the previous step in satd aq NaBr (440 mL) at rt and the resultant mixture was stirred at rt for 16 h, then cooled to 0 °C. EtOAc (500 mL) and satd aq $NaHCO_3$ (100 mL) were added and the aqueous layer was extracted with EtOAc (2 × 500 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 2:1) gave **358** as a pale yellow oil (9.71 g, 90%, >95:5 dr);[44] $[\alpha]_D^{25}$ +91.1 (*c* 1.0 in $CHCl_3$); {lit.[44] $[\alpha]_D^{30}$ +77 (c 1.96 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.28 (3H, t, *J* 7.2, OCH_2*Me*), 2.44–2.57 (2H, m, C(3)*H*$_2$), 4.02 (1H, q, *J* 6.0.

C(2)*H*), 4.12 (1H, d, *J* 6.4, N*H*), 4.21 (2H, q, *J* 7.2, OCH_2Me), 5.06–5.14 (2H, m, C(5)H_2), 5.66–5.77 (1H, m, C(4)*H*).

Ethyl (2'*S*)-[*N*(1')-(*tert*-butylsulfonyl)-1',2',3',6'-tetrahydropyridin-2'-yl]methanoate 361



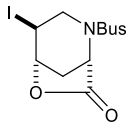
Step 1. *m*CPBA (73%, 13.6 g, 57.6 mmol) was added to a stirred solution of **358** (9.50 g, 38.4 mmol, >95:5 dr) in CH_2Cl_2 (400 mL) at 0 °C and the resultant solution was allowed to warm to rt over 1 h, then cooled to 0 ° C. Satd aq Na_2SO_3 (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*.

Step 2. Cs_2CO_3 (15.0 g, 46.1 mmol) and allyl bromide (6.60 mL, 76.8 mmol) were added sequentially to a stirred solution of the residue from the previous step in DMF (40 mL) at 0 °C and the resultant solution was allowed to warm to rt over 2 h, then cooled to 0 °C. Satd aq NH_4Cl (40 mL) and H_2O (100 mL) were added and the aqueous later was extracted with EtOAc (3 × 100 mL). The combined organics were washed with brine (300 mL), then dried and concentrated *in vacuo*.

Step 3. Grubbs I catalyst (1.58 g, 1.92 mmol) was added to a stirred solution of the residue from the previous step in degassed CH_2Cl_2 (1.50 L) at rt and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo* (to a volume of ~200 mL). $P(CH_2OH)_3$ (23.8 g, 192 mmol), Et_3N (10.6 mL, 76.8 mmol) and excess silica were added sequentially and the resultant suspension was stirred at rt for 16 h, then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave **361** as a pale yellow oil (10.0 g, 95%); $[\alpha]_D^{25}$ −10.9 (*c* 1.0 in $CHCl_3$); ν_{max} 1737, 1318, 1135; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1, OCH_2*Me*), 1.38 (9H, s, C*Me*$_3$), 2.59–2.64 (2H, m, C(3')H_2), 3.94–4.15 (2H, m, C(6')H_2), 4.20 (2H, q, *J* 7.1, OCH_2Me), 4.57–4.74 (1H, m, C(2')*H*), 5.62–5.69 (1H, m, C(5')*H*), 5.73–5.80 (1H, m, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (OCH_2*Me*),

24.2 (C*Me*$_3$), 27.8 (*C*(3')), 44.0 (*C*(6')), 54.5 (*C*(2')), 61.4 (O*C*H$_2$Me), 61.7 (*C*Me$_3$), 122.5 (*C*(4')), 124.2 (*C*(5')), 170.1 (*C*(1)); *m/z* (ESI$^+$) 298 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{21}NNaO_4S^+$ ([M+Na]$^+$) requires 298.1083; found 298.1083.

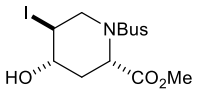
(1*S*,4*S*,5*S*)-*N*(2)-(*tert*-Butylsulfonyl)-4-iodo-6-oxa-2-azabicyclo[3.2.1]octan-7-one 363



Step 1. A solution of LiOH·H$_2$O (2.29 g, 54.5 mmol) in H$_2$O (135 mL) was added dropwise *via* cannula to a stirred solution of **361** (5.00 g, 18.2 mmol) in THF (520 mL) at rt and the resultant solution was stirred at rt for 48 h. The resultant solution was cooled to 0 °C, then acidified to pH 4 with with aq KHSO$_4$ (2.00 M) and extracted with CHCl$_3$ (3 × 600 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*.

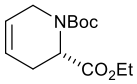
Step 2. NaHCO$_3$ (4.58 g, 54.5 mmol) and I$_2$ (13.8 g, 54.5 mmol) were added sequentially to a stirred solution of the residue from the previous step in MeCN (90 mL) at −20 °C and the resultant solution was stirred at −20 °C for 2 h, then stirred at rt for 16 h. Et$_2$O (100 mL) and satd aq Na$_2$S$_2$O$_3$ (100 mL) were added sequentially and the aqueous layer was extracted with Et$_2$O (2 × 100 mL). The combined organics were washed sequentially with H$_2$O (300 mL) and brine (300 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **363** as a white solid (6.57 g, 97%, >95:5 dr); mp 174–176 °C; $[\alpha]_D^{25}$ −60.5 (*c* 1.0 in CHCl$_3$); ν_{max} 1791, 1322, 1129; δ_H (400 MHz, CDCl$_3$) 1.41 (9H, s, C*Me*$_3$), 2.28–2.33 (1H, m, C(8)*H*$_A$), 3.07 (1H, app dd, *J* 13.2, 5.2, C(8)*H*$_B$), 3.86 (1H, dd, *J* 15.6, 4.2, C(3)*H*$_A$), 3.96–4.13 (1H, m, C(3)*H*$_B$), 4.39–4.44 (2H, m, C(1)*H*, C(4)*H*), 4.98 (1H, app t, *J* 4.8, C(5)*H*); δ_C (100 MHz, CDCl$_3$) 19.1 (*C*(4)), 24.3 (C*Me*$_3$), 34.9 (*C*(8)), 50.8 (*C*(3)), 56.3 (*C*(1)), 62.3 (*C*Me$_3$), *80** (*C*(5)), 171.4 (*C*(7)); *m/z* (ESI$^+$) 396 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{16}INNaO_4S^+$ ([M+Na]$^+$) requires 395.9737; found 395.9736.

(2*S*,4*S*,5*S*)-*N*(1)-(*tert*-Butylsulfonyl)-2-(methoxycarbonyl)-4-hydroxy-5-iodopiperidine 364



TFA (0.10 mL, 1.34 mmol) was added dropwise *via* syringe to a stirred solution of **363** (250 mg, 0.67 mmol, >95:5 dr) in MeOH (3.5 mL) at rt and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **364** as a colourless oil (287 mg, quant, >95:5 dr); $[\alpha]_D^{25}$ +30.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3488, 1745, 1315, 1127; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 2.34 (1H, app d, *J* 14.4, C(3)*H*$_A$), 2.69–2.82 (2H, m, C(3)*H*$_B$, O*H*), 3.60–3.73 (1H, m, C(6)*H*$_A$), 3.74 (3H, s, O*Me*), 4.15 (1H, dd, *J* 15.3, 2.6, C(6)*H*$_B$), 4.23–4.28 (1H, m, C(4)*H*), 4.28–4.45 (2H, m, C(2)*H*, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 24.2 (C*Me*$_3$), 28.2 (*C*(5)), 29.7 (*C*(3)), *47** (*C*(6)), 52.3 (O*Me*), *54** (*C*(2)), 62.5 (*C*Me$_3$), 68.7 (*C*(4)), 172.6 (*C*(1')); *m/z* (ESI^+) 428 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{11}H_{20}INNaO_5^+$ ($[M+Na]^+$) requires 427.9999; found 427.9998.

Ethyl (2'*S*)-[*N*(1')-(*tert*-butoxycarbonyl)-1',2',3',6'-tetrahydropyridin-2'-yl]methanoate 366

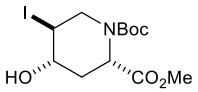


Step 1. A solution of TfOH (5.60 mL, 63.2 mmol) in CH_2Cl_2 (300 mL) was added dropwise *via* cannula to a stirred solution of **361** (2.90 g, 10.5 mmol) and anisole (22.9 mL, 211 mmol) in CH_2Cl_2 (300 mL) at 0 °C and the resultant solution was allowed to warm to rt over 1 h. Aq NaOH (10% w/v, 200 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 400 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*.

Step 2. Boc_2O (3.45 g, 15.8 mmol) and Et_3N (2.19 mL, 15.8 mmol) were added sequentially to a stirred solution of the residue from the previous step in MeOH (100 mL) at rt and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent 30–40 °C petroleum ether/Et_2O, 5:1) gave **366** as a pale yellow oil (2.47 g, 92%); $[\alpha]_D^{25}$ −5.1 (*c* 1.0 in $CHCl_3$); ν_{max} 1739, 1699; δ_H (400 MHz, $CDCl_3$)[23] 1.22 (3H, t, *J* 7.1, OCH_2*Me*), 1.44 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 2.41–2.52 (1H, m, C(3')H_A), 2.57–2.69 (1H, m, C(3')H_B), 3.67–3.84 (1H, m, C(6')H_A), 3.99–4.19 (3H, m, C(6')H_B, OCH_2Me), 4.83 (1H, d, *J* 6.5, C(2')*H*), 5.01 (1H, d, *J* 6.5, C(2')*H*), 5.58–5.76 (2H, m, C(4')*H*, C(5')*H*); δ_C (100 MHz, $CDCl_3$) 14.3, 14.3 (OCH_2*Me*), 26.7, 26.7 (*C*(3')), 28.5, 28.5 (C*Me*$_3$), 41.7, 42.4 (*C*(6')), 51.2, 52.6 (*C*(2')), 61.2, 61.3 (O*C*H_2Me), 80.3 (*C*Me$_3$), 122.0, 122.4 (*C*(4')), 124.2, 124.5 (*C*(5')), 155.3, 156.0 (N(1)*C*O), 171.8, 172.0 (*C*(1)); *m/z* (ESI^+) 278 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{21}NNaO_4^+$ ($[M+Na]^+$) requires 278.1363; found 278.1363.

(2*S*,4*S*,5*S*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-4-hydroxy-5-iodopiperidine 367



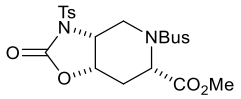
Step 1. A solution of $LiOH \cdot H_2O$ (1.09 g, 25.9 mmol) in H_2O (65 mL) was added dropwise *via* cannula to a stirred solution of **366** (2.20 g, 8.62 mmol) in THF (250 mL) at rt and the resultant solution was stirred at rt for 48 h. The resultant solution was cooled to 0 °C, then acidified to pH 4 with with aq $KHSO_4$ (2.00 M) and extracted with $CHCl_3$ (3 × 300 mL). The combined organics were washed with brine (1.00 L), then dried and concentrated *in vacuo*.

Step 2. $NaHCO_3$ (1.45 g, 17.2 mmol), I_2 (6.57 g, 25.9 mmol) and KI (8.58 g, 51.7 mmol) were added sequentially to a stirred solution of the residue from the previous step in H_2O/CH_2Cl_2 (2:1, 120 mL) at rt and the resultant mixture was stirred at rt for 48 h. The resultant mixture was cooled to −78 °C and satd aq $Na_2S_2O_3$ (40 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The combined organics were washed with brine (120 mL), then dried and concentrated *in vacuo*.

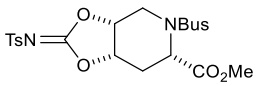
Step 3. TFA (1.32 mL, 17.2 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in MeOH (43 mL) at rt and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent

30–40 °C petroleum ether/acetone, 4:1) gave **367** as a white solid (2.92 g, 88%, >95:5 dr);[45] mp 175–177 °C; {lit.[45] mp 170–173 °C}; $[\alpha]_D^{25}$ −6.8 (*c* 0.5 in $CHCl_3$); {lit.[45] $[\alpha]_D$ −16.6 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 2.32 (1H, ddd, *J* 14.7, 4.5, 2.1, C(3)H_A), 2.56 (1H, br s, O*H*), 2.71 (1H, app dd, *J* 14.7, 6.6, C(3)H_B), 3.59–3.74 (1H, m, C(6)H_A), 3.75 (3H, s, O*Me*), 4.08 (1H, app d, *J* 14.4, C(6)H_B), 4.16–4.26 (2H, m, C(4)*H*, C(5)*H*), 4.64–5.05 (1H, m, C(2)*H*).

(2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butylsulfonyl)-2-(methoxycarbonyl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 370 and (2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butylsulfonyl)-2-(methoxycarbonyl)-4,5-dihydroxy-*O*,*O*-(*N*-tosylimino)piperidine 371



370



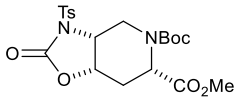
371

Step 1. TsNCO (53 µL, 0.35 mmol) was added dropwise *via* syringe to a stirred solution of **364** (140 mg, 0.35 mmol, >95:5 dr) in THF (2.5 mL) at 0 °C and the resultant solution was stirred at rt for 3 h, then concentrated *in vacuo*.

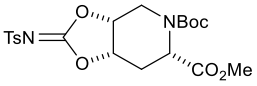
Step 2. Et_3N (72 µL, 0.52 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in acetone (2.5 mL) at rt and the resultant solution was heated at 60 °C for 3 h, then allowed to cool to rt and concentrated *in vacuo* to give a 66:34 mixture of **370** and **371**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **370** as a white solid (87 mg, 53%, >95:5 dr); mp 65–67 °C; $[\alpha]_D^{25}$ −29.1 (*c* 1.0 in $CHCl_3$); ν_{max} 1789, 1746, 1318, 1170; δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 2.36 (1H, ddd, *J* 15.5, 7.5, 3.9, C(3)H_A), 2.45 (3H, s, Ar*Me*), 2.65 (1H, app dt, *J* 15.5, 3.6, C(3)H_B), 3.42 (1H, dd, *J* 14.4, 10.1, C(6)H_A), 3.75 (3H, s, O*Me*), 4.23 (1H, dd, *J* 14.4, 6.8, C(6)H_B), 4.53 (1H, app dt, *J* 10.1, 6.8, C(5)*H*), 4.57–4.65 (2H, m, C(2)*H*, C(4)*H*), 7.36 (2H, d, *J* 8.3, *Ar*), 7.93 (2H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.7 (Ar*Me*), 24.0 (C*Me*$_3$), 28.8 (*C*(3)), 44.3 (*C*(6)), 52.1 (*C*(2)), 52.9 (O*Me*), 53.7 (*C*(5)), 62.3 (*C*(4)), 71.9 (*C*Me$_3$), 128.3, 129.9, 134.6, 146.0 (*Ar*), 151.0 (TsN*C*O), 170.0 (*C*(1')); *m/z* (ESI$^+$) 497 ([M+Na]$^+$, 100%); HRMS (ESI$^+$)

$C_{19}H_{26}N_2NaO_8S_2^+$ ([M+Na]$^+$) requires 497.1023; found 497.1028. Further elution gave **371** as a white solid (48 mg, 29%, >95:5 dr); mp 75–77 °C; $[\alpha]_D^{25}$ −1.4 (*c* 1.0 in $CHCl_3$); ν_{max} 1744, 1646, 1320, 1165; δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, C*Me*$_3$), 2.41 (3H, s, Ar*Me*), 2.42–2.48 (1H, m, C(3)H_A), 2.94 (1H, app d, *J* 15.8, C(3)H_B), 3.21–3.40 (1H, m, C(6)H_A), 3.86 (3H, s, O*Me*), 4.00–4.08 (1H, m, C(6)H_B), 4.63 (1H, app d, *J* 6.8, C(2)*H*), 4.92–4.97 (2H, m, C(4)*H*, C(5)*H*), 7.29 (2H, d, *J* 8.1, *Ar*), 7.82 (2H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*Me*), 24.0 (C*Me*$_3$), 28.4 (*C*(3)), 42.5 (*C*(6)), 52.0 (*C*(2)), 53.3 (O*Me*), 62.5 (*C*Me$_3$), *73**, *74** (*C*(4), *C*(5)), 127.1, 129.3, 138.1, 143.5 (*Ar*), 158.7 (*C*NTs), 169.4 (*C*(1')); *m/z* (ESI$^+$) 497 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{26}N_2NaO_8S_2^+$ ([M+Na]$^+$) requires 497.1023; found 497.1024.

(2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 372 and (2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-4,5-dihydroxy-*O*,*O*-(*N*-tosylimino)piperidine 373



372



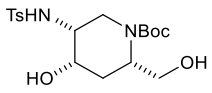
373

Step 1. TsNCO (54 µL, 0.36 mmol) was added dropwise *via* syringe to a stirred solution of **367** (137 mg, 0.36 mmol, >95:5 dr) in THF (2.5 mL) at 0 °C and the resultant solution was stirred at rt for 3 h, then concentrated *in vacuo*.

Step 2. Et_3N (74 µL, 0.53 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in acetone (2.5 mL) at rt and the resultant solution was heated at 60 °C for 3 h, then allowed to cool to rt and concentrated *in vacuo* to give a 85:15 mixture of **372** and **373**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **372** as a white solid (137 mg, 85%, >95:5 dr); mp 78–80 °C; $[\alpha]_D^{25}$ +1.9 (*c* 1.0 in $CHCl_3$); ν_{max} 1788, 1740, 1701, 1323, 1172; δ_H (400 MHz, $CDCl_3$) [major rotamer] 1.37 (9H, s, C*Me*$_3$), 2.27 (1H, ddd, *J* 15.2, 6.6, 3.7, C(3)H_A), 2.35–2.42 (1H, m, C(3)H_B), 2.42 (3H, s, Ar*Me*), 3.41 (3H, s, O*Me*), 3.69 (1H, app d, *J* 14.9, C(6)H_A), 4.27 (1H, dd, *J* 14.9, 4.4, C(6)H_B), 4.33 (1H, app t, *J* 5.9, C(2)*H*), 4.73–4.77 (1H, m, C(5)*H*), 4.81–4.86

(1H, m, C(4)*H*), 7.32 (2H, d, *J* 7.9, *Ar*), 8.00 (2H, d, *J* 7.9, *Ar*); δ_H (400 MHz, $CDCl_3$) [minor rotamer] 1.50 (9H, s, C*Me*$_3$), 2.27 (1H, ddd, *J* 15.2, 6.6, 3.7, C(3)H_A), 2.35–2.42 (1H, m, C(3)H_B), 2.45 (3H, s, Ar*Me*), 3.59 (3H, s, O*Me*), 3.82 (1H, dd, *J* 14.2, 6.8, C(6)H_A), 4.04 (1H, app d, *J* 14.2, C(6)H_B), 4.48 (1H, app t, *J* 6.0, C(2)*H*), 4.55–4.60 (1H, m, C(5)*H*), 4.73–4.77 (1H, m, C(4)*H*), 7.36 (2H, d, *J* 8.1, *Ar*), 7.94 (2H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$) [major rotamer] 21.6 (Ar*Me*), 28.0 (C*Me*$_3$), 28.4 (*C*(3)), 39.6 (*C*(6)), 51.8 (*C*(2)), 52.3 (O*Me*), 54.5 (*C*(5)), 69.8 (*C*(4)), 81.1 (*C*Me$_3$), 128.9, 129.5, 134.5, 145.3 (*Ar*), 151.3 (NTs*C*O), 154.2 (N(1)*C*O), 171.9 (*C*(1')); δ_C (100 MHz, $CDCl_3$) [minor rotamer] 21.7 (Ar*Me*), 28.2 (C*Me*$_3$), 28.4 (*C*(3)), 41.4 (*C*(6)), 50.7 (*C*(2)), 52.5 (O*Me*), 54.4 (*C*(5)), 70.6 (*C*(4)), 81.6 (*C*Me$_3$), 128.4, 129.7, 134.5, 145.8 (*Ar*), 151.2 (NTs*C*O), 154.7 (N(1)*C*O), 171.4 (*C*(1')); *m/z* (ESI^+) 477 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}N_2NaO_8S^+$ ($[M+Na]^+$) requires 477.1302; found 477.1295. Further elution gave **373** as a colourless oil (18 mg, 11%, >95:5 dr); $[\alpha]_D^{25}$ +17.6 (*c* 1.0 in $CHCl_3$); ν_{max} 1746, 1703, 1636, 1318, 1164; δ_H (400 MHz, $CDCl_3$)[23] 1.39 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 2.31–2.39 (1H, m, C(3)H_A), 2.41 (3H, s, Ar*Me*), 2.47–2.61 (1H, m, C(3)H_B), 3.68–4.02 (5H, m, C(6)H_2, O*Me*), 4.32–4.54 (1H, m, C(2)*H*), 5.02–5.17 (2H, m, C(4)*H*, C(5)*H*), 7.28 (2H, d, *J* 7.8, *Ar*), 7.85 (2H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*Me*), 28.1 (*C*(3)), 28.2 (C*Me*$_3$), *39**, *40** (*C*(6)), *50**, *51** (*C*(2)), *53** (O*Me*), *74**, *75** (*C*(4), *C*(5)), 81.7 (*C*Me$_3$), 127.1, 129.3, 138.3, 147.1 (*Ar*), 154.1 (N(1)*C*O), 158.6 (*C*NTs), 171.4 (*C*(1')); *m/z* (ESI^+) 477 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{26}N_2NaO_8S^+$ ($[M+Na]^+$) requires 477.1302; found 477.1301.

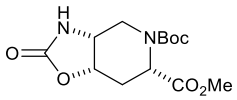
(2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-4-hydroxy-5-(*N*-tosylamino)piperidine 374



$LiAlH_4$ (2.00 M in THF, 1.19 mL, 2.38 mmol) was added dropwise *via* syringe to a stirred solution of **372** (1.08 g, 2.38 mmol, >95:5 dr) in THF (12 mL) at −78 °C and the resultant

solution was stirred at −40 °C for 4 h. H_2O (5 mL) was added and the resultant mixture was allowed to warm to rt over 1 h. The resultant mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 2:1) gave **374** as a white solid (158 mg, 17%, >95:5 dr); mp 203–205 °C; $[\alpha]_D^{25}$ +2.5 (*c* 1.0 in MeOH); ν_{max} 3510, 3283, 1667, 1328, 1159; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.90 (1H, ddd, *J* 15.1, 7.8, 3.4, C(3)*H*$_A$), 1.99 (1H, ddd, *J* 15.1, 7.7, 3.4, C(3)*H*$_B$), 2.43 (3H, s, Ar*Me*), 3.30 (1H, app t, *J* 12.3, C(6)*H*$_A$), 3.20–3.27 (1H, m, C(5)*H*), 3.69 (1H, dd, *J* 11.0, 4.0, C(1')*H*$_A$), 3.73–3.78 (1H, m, C(4)*H*), 3.87 (2H, app dd, *J* 11.0, 3.4, C(6)*H*$_B$, C(1')*H*$_B$), 4.13–4.23 (1H, m, C(2)*H*), 4.43 (1H, br s, O*H*), 5.35 (1H, d, *J* 8.6, N*H*), 7.31 (2H, d, *J* 8.3, *Ar*), 7.79 (2H, d, *J* 8.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*Me*), 28.3 (C*Me*$_3$), 33.0 (*C*(3)), *40** (*C*(6)), *49** (*C*(2)), 52.3 (*C*(5)), 64.7 (*C*(4)), 65.5 (*C*(1')), 80.5 (*C*Me$_3$), 126.9, 129.8, 138.2, 143.5 (*Ar*), 154.8 (N(1)*C*O); *m/z* (ESI^+) 423 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{28}N_2NaO_6S^+$ ($[M+Na]^+$) requires 423.1560; found 423.1562.

(2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 375

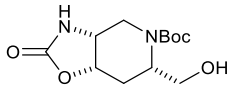


Step 1. Na (51 mg, 2.20 mmol) was added to a stirred solution of naphthalene (338 mg, 2.64 mmol) in DME (6 mL) at rt. The resultant solution was stirred at rt for 16 h, then cooled to −78 °C.

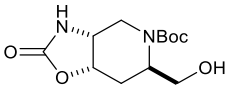
Step 2. The solution from the previous step was added dropwise *via* syringe to a stirred solution of **372** (200 mg, 0.44 mmol, >95:5 dr) in DME (3 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min, then quenched with EtOH (1 mL). The resultant solution was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organics were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **375** as a colourless oil (20 mg, 15%, >95:5 dr); $[\alpha]_D^{25}$ −16.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3320, 1749, 1696; δ_H (400 MHz, $CDCl_3$)[23] 1.40 (9H, s, C*Me*$_3$), 1.45 (9H, s, C*Me*$_3$), 2.30–2.38 (2H, m, C(3)*H*$_2$), 3.40 (1H, dd, *J* 14.0, 8.2, C(6)*H*$_A$), 3.57 (1H, dd, *J* 14.0, 6.7, C(6)*H*$_A$), 3.73–3.79 (1H, m, C(6)*H*$_B$), 3.75 (3H, s, O*Me*), 3.88 (1H, dd, *J* 14.0, 5.4, C(6)*H*$_B$), 4.01–4.08 (1H, m, C(5)*H*), 4.09–4.17 (1H, m, C(5)*H*), 4.31–4.43 (1H, t, *J* 7.3, C(2)*H*), 4.74–4.86 (1H, m, C(4)*H*), 6.07 (1H, br s, N*H*), 6.37 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 28.1, 28.2 (C*Me*$_3$), 28.7 (*C*(3)), 41.0, 42.4 (*C*(6)), 50.1, 50.2 (*C*(5)), 51.3, 52.4 (*C*(2)), 52.5 (O*Me*), 71.6, 72.2 (*C*(4)), 81.3 (*C*Me$_3$), 154.6, 154.6 (N(1)*C*O), 158.2, 158.8 (HN*C*O), 171.5, 172.1 (*C*(1')); *m/z* (ESI$^+$) 323 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{20}N_2NaO_6^+$ ([M+Na]$^+$) requires 323.1214; found 323.1213.

(2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 376 and (2*R*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine (2*R*,4*S*,5*R*)-94



376



(2*R*,4*S*,5*R*)-**94**

Method A. $LiAlH_4$ (2.00 M in THF, 0.24 mL, 0.48 mmol) was added dropwise *via* syringe to a stirred solution **375** (145 mg, 0.48 mmol, >95:5 dr) in THF (5 mL) at −40 °C and the resultant solution was stirred at −40 °C for 1.5 h. H_2O (1 mL) was added and the resultant mixture was allowed to warm to rt over 1 h. The resultant mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:2) gave **376** as a white solid (88 mg, 67%, >95:5 dr); mp 95–97 °C; $[\alpha]_D^{25}$ −95.3 (*c* 1.0 in MeOH); ν_{max} 3294, 1747, 1671; δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.89–2.22 (2H, m, C(3)*H*$_2$), 2.93–3.11 (1H, m, C(6)*H*$_A$), 3.23–4.28 (6H, m, C(2)*H*, C(5)*H*, C(6)*H*$_B$, C(1')*H*$_2$, O*H*), 4.73 (1H, app q, *J* 8.3, C(4)*H*), 6.72 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) *27** (*C*(3)), 28.3 (C*Me*$_3$), *42**, *43** (*C*(6)), *50** (*C*(5)), *52** (*C*(2)), *64**, *65**

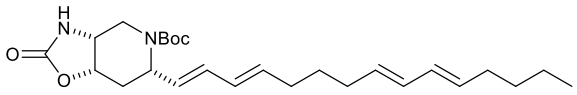
(*C*(1')), *73** (*C*(4)), *81** (*C*Me$_3$), *155** (N(1)*C*O), 159.4 (HN*C*O); *m/z* (ESI$^+$) 295 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{20}N_2NaO_5^+$ ([M+Na]$^+$) requires 295.1264; found 295.1265.

Method B. *Step 1*. Na (253 mg, 11.0 mmol) was added to a stirred solution of naphthalene (1.69 g, 13.2 mmol) in DME (30 mL) at rt. The resultant solution was stirred at rt for 16 h, then cooled to −78 °C.

Step 2. The solution from the previous step was added dropwise *via* cannula to a stirred solution of **372** (1.00 g, 2.20 mmol, >95:5 dr) in DME (15 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min, then quenched with EtOH (2 mL). The resultant solution was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (15 mL) and H_2O (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were washed with brine (45 mL), then dried and concentrated *in vacuo*.

Step 3. $LiAlH_4$ (2.00 M in THF, 1.10 mL, 2.20 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step in THF (22 mL) at −78 °C and the resultant solution was stirred at −40 °C for 4 h. H_2O (1 mL) was added and the resultant mixture was allowed to warm to rt over 1 h. The resultant mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:2) gave **376** as a white solid (353 mg, 59%, >95:5 dr). Further elution gave (2*R*,4*S*,5*R*)-**94** as a white solid (192 mg, 32%, >95:5 dr);[46] mp 89–91 °C;[8] $[\alpha]_D^{25}$ +78.7 (*c* 1.0 in MeOH); {lit.[46] for enantiomer $[\alpha]_D^{21}$ –111.4 (*c* 0.92 in MeOH)}; δ_H (400 MHz, $CDCl_3$)[23] 1.45 (9H, s, C*Me*$_3$), 1.99 (1H, app d, *J* 13.2, C(3)*H*$_A$), 2.05 (1H, app d, *J* 15.1, C(3)*H*$_A$), 2.14 (1H, app d, *J* 13.9, C(3)*H*$_B$), 2.25 (1H, app d, *J* 12.3, C(3)*H*$_B$), 2.59 (1H, br s, O*H*), 3.05 (1H, app d, *J* 14.3, C(6)*H*$_A$), 3.11 (1H, app d, *J* 15.1, C(6)*H*$_A$), 3.50–3.65 (1H, m, C(1')*H*$_A$), 3.71–3.90 (1H, m, C(1')*H*$_B$), 3.96 (1H, app d, *J* 8.8, C(5)*H*), 4.00–4.28 (1H, m, C(2)*H*), 4.06 (1H, app d, *J* 14.0, C(6)*H*$_B$), 4.97 (1H, app d, *J* 9.0, C(4)*H*), 5.66 (1H, br s, N*H*), 5.94 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) *26**, *26** (*C*(3)), 28.3 (C*Me*$_3$), *42**, *42** (*C*(6)), *50** (*C*(2)), *51**, *51** (*C*(5)), *64**, *66** (*C*(1')), 72.9 (*C*(4)), 81.1 (*C*Me$_3$), *156**, *156** (N(1)*C*O), 158.6 (HN*C*O).[19]

(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',8',10'-tetraen-1'-yl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 379

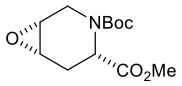


Step 1. DMP (481 mg, 1.13 mmol) was added to a stirred solution of **376** (280 mg, 1.03 mmol, >95:5 dr) in CH_2Cl_2 (5 mL) at rt and the resultant solution was stirred at rt for 1 h. $NaHCO_3$ (285 mg, 3.39 mmol) was added and the resultant suspension was stirred at rt for 5 min. The resultant mixture was then filtered through a silica plug (eluent Et_2O) and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*.

Step 2. KHMDS (1.00 M in THF, 1.55 mL, 1.55 mmol) was added dropwise *via* syringe to a stirred solution of **321** (660 mg, 1.65 mmol, 92:8 dr [(2*E*,7*E*,9*E*):(2*E*,7*Z*,9*E*)]) and 18c6 (409 mg, 1.55 mmol) in THF (7 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1 h. A solution of the residue from the previous step in THF (3.5 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 16 h. EtOAc (10 mL) and H_2O (10 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organics were washed with brine (30 mL), then dried and concentrated *in vacuo* to give a ~60:40 mixture of (1'*E*,3'*E*,8'*E*,10'*E*) and (1'Z,3'*E*,8'*E*,10'*E*)-isomers, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **379** as a colourless oil (184 mg, 40%, >50% dp); $[\alpha]_D^{25}$ +11.1 (*c* 1.0 in $CHCl_3$); ν_{max} 1761, 1693; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')*H*$_3$), 1.24–1.52 (6H, m, C(6')*H*$_2$, C(13')*H*$_2$, C(14')*H*$_2$), 1.42 (9H, s, C*Me*$_3$), 1.91–2.23 (8H, m, C(3)*H*$_2$, C(5')*H*$_2$, C(7')*H*$_2$, C(12')*H*$_2$), 3.09 (1H, dd, *J* 13.7, 9.8, C(6)*H*$_A$), 3.91–4.06 (1H, m, C(5)*H*), 4.06–4.23 (1H, m, C(6)*H*$_B$), 4.71–4.80 (2H, m, C(2)*H*, C(4)*H*), 5.47–5.76 (4H, m, C(1')*H*, C(4')*H*, C(8')*H*, C(11')*H*), 5.91–6.11 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 22.2 (*C*(14')), 28.4 (C*Me*$_3$), 28.9, 31.5, 32.1, 32.2, 32.2, 32.3 (*C*(3), *C*(5'), *C*(6'), *C*(7'), *C*(12'), *C*(13')), *41** (*C*(6)), *47** (*C*(2)), 49.8 (*C*(5)), 73.5 (*C*(4)), 80.6 (*C*Me$_3$), 130.1, 130.7, 130.8, 131.1 (*C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.5, 131.6, 132.7, 135.2 (*C*(1'), *C*(4'), *C*(8'), *C*(11')), 154.5

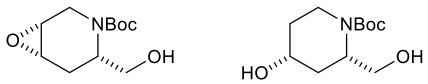
(N(1)*C*O), 158.9 (HN*C*O); *m/z* (ESI$^+$) 467 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{40}N_2NaO_4^+$ ([M+Na]$^+$) requires 467.2880; found 467.2878.

(2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-4,5-epoxypiperidine 381



DBU (61 µL, 0.41 mmol) was added dropwise *via* syringe to a stirred solution of **367** (130 mg, 0.34 mmol, >95:5 dr) in CH_2Cl_2 (2.5 mL) at rt, and the resultant solution was stirred at rt for 3 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave **381** as a colourless oil (82 mg, 94%, >95:5 dr); $[\alpha]_D^{25}$ −2.2 (*c* 1.0 in $CHCl_3$); ν_{max} 1745, 1698; δ_H (400 MHz, $CDCl_3$)[23] 1.38 (9H, s, C*Me*$_3$), 1.44 (9H, s, C*Me*$_3$), 2.14–2.25 (1H, m, C(3)*H*$_A$), 2.76–2.86 (1H, m, C(3)*H*$_A$), 3.17–3.28 (2H, m, C(4)*H*, C(5)*H*), 3.64–3.76 (4H, m, C(6)*H*$_A$, O*Me*), 3.84–3.93 (1H, m, C(6)*H*$_B$), 4.47–4.72 (1H, m, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 27.3, 27.5 (*C*(3)), 28.1, 28.2 (C*Me*$_3$), 39.6, 40.1 (*C*(6)), 48.8 (*C*(2)), 49.6, 49.6, 49.8, 49.9 (*C*(4), *C*(5)), 50.1 (*C*(2)), 52.1 (O*Me*), 80.4, 80.5 (*C*Me$_3$), 154.7, 155.4 (N(1)*C*O), 171.7, 171.8 (*C*(1')); *m/z* (ESI$^+$) 280 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{19}NNaO_5^+$ ([M+Na]$^+$) requires 280.1155; found 280.1155.

(2*S*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-4,5-epoxypiperidine 383 and (2*S*,4*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(hydroxymethyl)-4-hydroxypiperidine 384

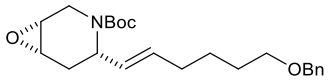


383 **384**

$LiAlH_4$ (2.00 M in THF, 3.89 mL, 7.77 mmol) was added dropwise *via* syringe to a stirred solution of **381** (2.00 g, 7.77 mmol, >95:5 dr) in THF (40 mL) at −78 °C and the resultant solution was stirred at −40 °C for 4 h. H_2O (5 mL) was added and the resultant mixture was allowed to warm to rt over 1 h. The resultant mixture was then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–

40 °C petroleum ether/acetone, 3:1) gave **381** as a colourless oil (181 mg, 9%, >95:5 dr). Further elution gave **383** as a white solid (1.27 g, 71%, >95:5 dr);[47] mp 45–47 °C;[8] $[\alpha]_D^{25}$ +2.8 (*c* 1.0 in $CHCl_3$);[43] ν_{max} 3445, 1687, 1682;[20] δ_H (400 MHz, $CDCl_3$) 1.44 (9H, s, C*Me*$_3$), 2.09–2.26 (2H, m, C(3)*H*$_2$), 2.95–3.38 (2H, m, C(4)*H*, C(5)*H*), 3.48–4.20 (5H, m, C(2)*H*, C(6)*H*$_2$, C(1')*H*$_2$); δ_C (100 MHz, $CDCl_3$) *26** (*C*(3)), 28.3 (C*Me*$_3$), *39**, *41** (*C*(6)), 50.2, 50.4, 50.4, (*C*(2), *C*(4), *C*(5)), *64** (*C*(1')), 80.4 (*C*Me$_3$), 156.0 (N(1)*C*O);[19] *m/z* (ESI$^+$) 252 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{19}NNaO_4^+$ ([M+Na]$^+$) requires 252.1206; found 252.1206.[48] Further elution gave **384** as a pale yellow oil (305 mg, 17%, >95:5 dr); $[\alpha]_D^{25}$ −39.1 (*c* 1.0 in $CHCl_3$); ν_{max} 3586, 1664; δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.60–1.69 (2H, m, C(5)*H*$_2$), 1.81 (1H, app d, *J* 14.4, C(3)*H*$_A$), 1.92 (1H, ddd, *J* 14.4, 7.2, 3.2, C(3)*H*$_B$), 3.27–3.38 (1H, m, C(6)*H*$_A$), 3.64–3.73 (1H, m, C(1')*H*$_A$), 3.78–3.86 (2H, m, C(6)*H*$_B$, C(1')*H*$_B$), 4.03–4.09 (1H, m, C(4)*H*), 4.12–4.19 (1H, m, C(2)*H*), 4.47 (1H, br s, O*H*), 4.52 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 28.4 (C*Me*$_3$), 31.9 (*C*(5)), 33.3 (*C*(3)), *36** (*C*(6)), 50.6 (*C*(2)), 62.6 (*C*(4)), 65.0 (*C*(1')), 79.8 (*C*Me$_3$), 155.4 (N(1)*C*O); *m/z* (ESI$^+$) 254 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{11}H_{21}NNaO_4^+$ ([M+Na]$^+$) requires 254.1363; found 254.1361.

(2*S*,4*S*,5*R*,1'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-[6'-(benzyloxy)hex-1'-en-1'-yl]-4,5-epoxypiperidine 385

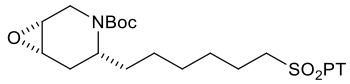


Step 1. DMP (407 mg, 0.96 mmol) was added to a stirred solution of **383** (200 mg, 0.87 mmol, >95:5 dr) in CH_2Cl_2 (4.5 mL) at rt and the resultant solution was stirred at rt for 1 h. $NaHCO_3$ (242 mg, 2.88 mmol) was added and the resultant suspension was stirred at rt for 5 min. The resultant mixture was then filtered through a silica plug (eluent Et_2O) and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*.

Step 2. KHMDS (1.00 M in THF, 1.31 mL, 1.31 mmol) was added dropwise *via* syringe to a stirred solution of **320** (539 mg, 1.40 mmol) in THF (6 mL) at −78 °C and the resultant solution

was stirred at −78 °C for 1 h. A solution of the residue from the previous step in THF (3 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 16 h. EtOAc (10 mL) and H_2O (10 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organics were washed with brine (30 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 9:1) gave **385** as a colourless oil (314 mg, 93%, 85:15 dr [(1'*E*):(1'*Z*)]); $[\alpha]_D^{25}$ +2.0 (*c* 1.0 in $CHCl_3$); ν_{max} 1691; δ_H (400 MHz, $CDCl_3$) 1.39–1.47 (2H, m, C(4')H_2), 1.45 (9H, s, CMe_3), 1.57–1.64 (2H, m, C(5')H_2), 2.11–2.14 (2H, m, C(3')H_2), 2.15–2.20 (2H, m, C(3)H_2), 3.26–3.29 (2H, m, C(4)*H*, C(5)*H*), 3.45 (2H, t, *J* 6.5, C(6')H_2), 3.56 (1H, app d, *J* 15.3, C(6)H_A), 4.02 (1H, dd, *J* 15.3, 2.7, C(6)H_B), 4.49 (2H, app s, OCH_2Ph), 4.53–4.62 (1H, m, C(2)*H*), 5.42 (1H, dt, *J* 15.4, 7.3, C(2')*H*), 5.67 (1H, dd, *J* 15.4, 7.6, C(1')*H*), 7.24–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.7 (*C*(4')), 28.3 (CMe_3), 29.1 (*C*(5')), 29.5 (*C*(3)), 31.8 (*C*(3')), *39** (*C*(6)), *50** (*C*(2)), 50.0, 50.3 (*C*(4), *C*(5)), 70.1 (*C*(6')), 72.7 (O*C*H_2Ph), 79.7 (*C*Me_3), 127.3, 127.5, 128.2 (*Ph*), 130.2 (*C*(1')), 131.4 (*C*(2')), 138.6 (*Ph*), 154.8 (N(1)*C*O); *m/z* (ESI^+) 410 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{33}NNaO_4^+$ ($[M+Na]^+$) requires 410.2302; found 410.2315.

(2*R*,4*S*,5*R*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-{6'-[(1''-phenyl-1*H*-tetrazol-5''-yl)sulfonyl}hex-1'-yl]-4,5-epoxypiperidine 139



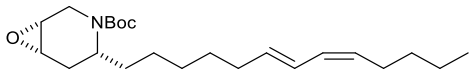
Step 1. $Pd(OH)_2/C$ (155 mg, 20% w/w of **385**) was added to a stirred solution of **385** (775 mg, 2.00 mmol, 85:15 dr [(1'*E*):(1'*Z*)]) in degassed EtOAc (24 mL) at rt and the resultant suspension was stirred at rt for 2 h under H_2 (1 atm), then filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*.

Step 2. DIAD (0.59 mL, 3.01 mmol) was added dropwise *via* syringe to a stirred solution of the residue from the previous step, PPh_3 (790 mg, 3.01 mmol) and PTSH (536 mg, 3.01 mmol) in THF (17 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. Et_2O (20

mL) and H_2O (20 mL) were added, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organics were washed with brine (60 mL), then dried and concentrated *in vacuo*. The residue was filtered through a silica plug (eluent 30–40 °C petroleum ether/Et_2O, 2:1) and concentrated *in vacuo*.

Step 3. *m*CPBA (75%, 1.84 g, 8.00 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (65 mL) at 0 °C and the resultant solution was allowed to warm to rt over 1 h, then cooled to 0 ° C. Satd aq Na_2SO_3 (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organics were washed with brine (100 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 2:3) gave **139** as a colourless oil (692 mg, 70%, >95:5 dr);[5] $[\alpha]_D^{25}$ +1.6 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{25}$ +1.9 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.11–1.53 (8H, m, C(1')H_2, C(2')H_2, C(3')H_2, C(4')H_2), 1.45 (9H, s, CMe_3), 1.89–1.97 (2H, m, C(5')H_2), 2.00–2.13 (2H, m, C(3)H_2), 3.23–3.31 (2H, m, C(4)*H*, C(5)*H*), 3.33–3.48 (1H, m, C(6)H_A), 3.69–3.73 (2H, m, C(6')H_2), 3.98–4.35 (2H, m, C(2)*H*, C(6)H_B), 7.57–7.71 (5H, m, *Ph*).

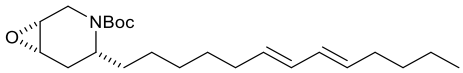
(2*R*,4*S*,5*R*,6'*E*,8'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4,5-epoxypiperidine 387



KHMDS (1.00 M in THF, 1.38 mL, 1.38 mmol) was added dropwise *via* syringe to a stirred solution of **139** (340 mg, 0.69 mmol, >95:5 dr) and **343** (0.18 mL, 1.38 mmol, 92:8 dr [(2*Z*):(2*E*)]) in THF (7 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. EtOAc (7 mL) and H_2O (7 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 7 mL). The combined organics were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 4:1) gave **387** as a colourless oil (218 mg, 83%, 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]); $[\alpha]_D^{25}$ +2.4 (*c* 1.0 in $CHCl_3$); ν_{max} 1691; δ_H (400 MHz, $CDCl_3$) 0.90 (3H,

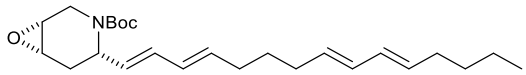
t, *J* 7.1, C(13')H_3), 1.12–1.42 (11H, m, C(1')H_A, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.44 (9H, s, CMe_3), 1.77–1.92 (1H, m, C(1')H_B), 2.04–2.11 (4H, m, C(3)H_2, C(5')H_2), 2.12–2.18 (2H, m, C(10')H_2), 3.21–3.25 (1H, m, C(4)*H*), 3.25–3.30 (1H, m, C(5)*H*), 3.39 (1H, app d, *J* 14.9, C(6)H_A), 4.00–4.30 (2H, m, C(2)*H*, C(6)H_B), 5.29 (1H, dt, *J* 10.9, 7.6, C(9')*H*), 5.62 (1H, dt, *J* 15.2, 7.1, C(6')*H*), 5.92 (1H, app t, *J* 10.9, C(8')*H*), 6.27 (1H, dd, *J* 15.2, 10.9, C(7')*H*); δ_C (100 MHz, $CDCl_3$) 13.4 (*C*(13')), 22.3 (*C*(12')), 26.6 (*C*(11')), 27.3 (*C*(10')), *28** (*C*(3)), 28.4 (CMe_3), 28.9, 29.4, 31.9, 32.7 (*C*(2'), *C*(3'), *C*(4'), *C*(5')), 32.8 (*C*(1')), *39** (*C*(6)), *48** (*C*(2)), 50.3 (*C*(5)), 50.7 (*C*(4)), 79.6 (*C*Me_3), 125.7 (*C*(7')), 128.5 (*C*(8')), 130.0 (*C*(9')), 134.4 (*C*(6')), 155.0 (N(1)*C*O); *m/z* (ESI$^+$) 400 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{39}NNaO_3^+$ ([M+Na]$^+$) requires 400.2822; found 400.2819.

(2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4,5-epoxypiperidine 140

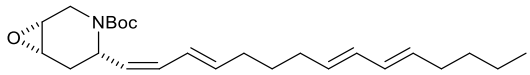


KHMDS (1.00 M in THF, 0.45 mL, 0.45 mmol) was added dropwise *via* syringe to a stirred solution of **139** (110 mg, 0.12 mmol, >95:5 dr) and **144** (58 µL, 0.45 mmol,>95:5 dr [(2*E*):(2*Z*)]) in THF (2.5 mL) at −78 °C and the resultant solution was stirred at −78 °C for 30 min. EtOAc (3 mL) and H_2O (3 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organics were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 4:1) gave **140** as a colourless oil (84 mg, 99%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]);[5] $[\alpha]_D^{25}$ +2.0 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{25}$ +4.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')H_3), 1.11–1.40 (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), 1.45 (9H, s, CMe_3), 1.78–1.93 (1H, m, C(1')H_B), 2.00–2.10 (6H, m, C(3)H_2, C(5')H_2, C(10')H_2), 3.22–3.25 (1H, m, C(4)*H*), 3.26–3.30 (1H, m, C(5)*H*), 3.40 (1H, app d, *J* 14.9, C(6)H_A), 4.01–4.31 (2H, m, C(2)*H*, C(6)H_B), 5.50–5.59 (2H, m, C(7')*H*, C(8')*H*), 5.93–6.02 (2H, m, C(6')*H*, C(9')*H*).

(*2S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',8',10'-tetraen-1'-yl)-4,5-epoxypiperidine 386 and (*2S*,4*S*,5*R*,1'*Z*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',8',10'-tetraen-1'-yl)-4,5-epoxypiperidine 388



386



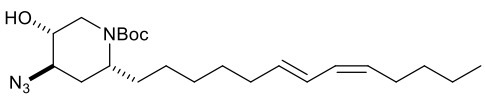
388

Step 1. DMP (407 mg, 0.96 mmol) was added to a stirred solution of **383** (200 mg, 0.87 mmol, >95:5 dr) in CH_2Cl_2 (4.5 mL) at rt and the resultant solution was stirred at rt for 1 h. $NaHCO_3$ (242 mg, 2.88 mmol) was added and the resultant suspension was stirred at rt for 5 min. The resultant mixture was then filtered through a silica plug (eluent Et_2O) and concentrated *in vacuo*. Et_2O (10 mL) was added and the resultant suspension was filtered through Celite® (eluent Et_2O) and concentrated *in vacuo*.

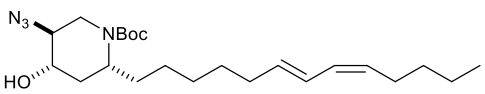
Step 2. KHMDS (1.00 M in THF, 1.31 mL, 1.31 mmol) was added dropwise *via* syringe to a stirred solution of **321** (561 mg, 1.40 mmol, 92:8 dr [(2'*E*,7'*E*,9'*E*):(2'*E*,7'*Z*,9'*E*)]) and 18c6 (268 mg, 1.31 mmol) in THF (6 mL) at −78 °C and the resultant solution was stirred at −78 °C for 1 h. A solution of the residue from the previous step in THF (3 mL) was added dropwise *via* syringe and the resultant solution was allowed to warm to rt over 16 h. EtOAc (10 mL) and H_2O (10 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organics were washed with brine (30 mL), then dried and concentrated *in vacuo* to give a ~80:20 mixture of (1'*E*,3'*E*,8'*E*,10'*E*) and (1'Z,3'*E*,8'*E*,10'*E*)-isomers, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 5:2) gave **386** as a colourless oil (259 mg, 74%, >85% dp); $[\alpha]_D^{25}$ +89.9 (*c* 0.5 in $CHCl_3$); ν_{max} 1692; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(15')H_3), 1.26–1.41 (4H, m, C(13')H_2, C(14')H_2), 1.44–1.51 (2H, m, C(6')H_2), 1.46 (9H, s, CMe_3), 2.04–2.16 (7H, m, C(3)H_A, C(5')H_2, C(7')H_2, C(12')H_2), 2.25 (1H, ddd, *J* 15.2, 6.6, 1.5, C(3)H_B), 3.29–3.35 (2H, m, C(4)*H*, C(5)*H*), 3.56 (1H, app d, *J* 15.7, C(6)H_A), 4.13 (1H, dd, *J* 15.7, 4.4, C(6)H_B), 5.02–5.10 (1H, m, C(2)*H*), 5.51–5.72 (4H, m, C(1')*H*, C(4')*H*, C(8')*H*, C(11')*H*), 5.92 (1H, app t, *J* 11.3, C(3')*H*), 5.96–6.04 (2H, m, C(9')*H*, C(10')*H*), 6.32 (1H, dd, *J* 14.5, 11.3, C(2')*H*); δ_C (100 MHz, $CDCl_3$)

13.9 (*C*(15')), 22.2 (*C*(14')), 28.4 (C*Me*$_3$), 29.0 (*C*(6')), 30.0 (*C*(3)), 31.5 (*C*(13')), 32.1, 32.2, 32.4 (*C*(5'), *C*(7'), *C*(12')), *39** (*C*(6)), *45** (*C*(2)), 50.3, 50.6 (*C*(4), *C*(5)), 80.0 (*C*Me$_3$), 125.5 (*C*(2')), 128.7 (*C*(1')), 129.2 (*C*(3')), 130.2, 130.8 (*C*(9'), *C*(10')), 131.6, 132.6 (*C*(8'), *C*(11')), 136.2 (*C*(4')), 154.4 (N(1)*C*O); *m/z* (ESI$^+$) 424 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{39}NNaO_3^+$ ([M+Na]$^+$) requires 424.2822; found 424.2822. Further elution gave **388** as a colourless oil (18 mg, 5%, >90% dp); $[\alpha]_D^{25}$ −3.4 (*c* 1.0 in $CHCl_3$); ν_{max} 1693; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')*H*$_3$), 1.27–1.39 (4H, m, C(13')*H*$_2$, C(14')*H*$_2$), 1.41–1.50 (2H, m, C(6')*H*$_2$), 1.45 (9H, s, C*Me*$_3$), 2.01–2.12 (6H, m, C(5')*H*$_2$, C(7')*H*$_2$, C(12')*H*$_2$), 2.14–2.27 (2H, m, C(3)*H*$_2$), 3.26–3.31 (2H, m, C(4)*H*, C(5)*H*), 3.57 (1H, app d, *J* 15.3, C(6)*H*$_A$), 4.04 (1H, dd, *J* 15.3, 3.1 C(6)*H*$_B$), 4.57–4.72 (1H, m, C(2)*H*), 5.50–5.64 (3H, m, C(4')*H*, C(8')*H*, C(11')*H*), 5.74–5.80 (1H, m, C(1')*H*), 5.93–6.03 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 22.2 (*C*(14')), 28.4 (C*Me*$_3$), 28.9 (*C*(6')), 29.5 (*C*(3)), 31.5 (*C*(13')), 32.0, 32.0, 32.2 (*C*(5'), *C*(7'), *C*(12')), *40** (*C*(6)), *50** (*C*(2)), 50.0, 50.3 (*C*(4), *C*(5)), 79.9 (*C*Me$_3$), 130.0, 130.2, 130.7, 131.0 (*C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.2 (*C*(1')), 131.7, 132.5, 134.2 (*C*(4'), *C*(8'), *C*(11')), 154.8 (N(1)*C*O); *m/z* (ESI$^+$) 424 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{39}NNaO_3^+$ ([M+Na]$^+$) requires 424.2822; found 424.2822.

(2*R*,4*R*,5*R*,6'*E*,8'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-azido-5-hydroxypiperidine 397 and (2*R*,4*S*,5*S*,6'*E*,8'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-azidopiperidine 398



397

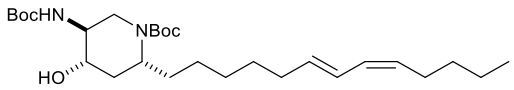


398

NH_4Cl (176 mg, 3.29 mmol) and NaN_3 (214 mg, 3.29 mmol) were added sequentially to a stirred solution of **387** (207 mg, 0.55 mmol, 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]) in DMSO (2.2 mL) at rt and the resultant solution was heated at 80 °C for 16 h, then allowed to cool to rt. H_2O (2 mL) was added and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organics were washed with H_2O (3 × 2 mL) and brine (6 mL), then dried and concentrated *in vacuo* to

give a ~25:75 mixture of **397** and **398**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 4:1) gave **397** as a colourless oil (55 mg, 24%, 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]); $[\alpha]_D^{25}$ −10.6 (*c* 1.0 in $CHCl_3$); ν_{max} 3427, 2104, 1695, 1671; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, C(13')H_3), 1.23–1.42 (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), 1.45 (9H, s, CMe_3), 1.57–1.68 (2H, m, C(3)H_A, C(1')H_B), 1.89 (1H, app d, *J* 11.5, C(3)H_B), 2.07–2.12 (2H, app q, *J* 7.0, C(5')H_2), 2.14–2.19 (2H, m, C(10')H_2), 2.67 (1H, app t, *J* 11.9, C(6)H_A), 2.97 (1H, br s, O*H*), 3.39–3.54 (2H, m, C(4)*H*, C(5)*H*), 4.12–4.38 (2H, m, C(2)*H*, C(6)H_B), 5.31 (1H, dt, *J* 10.9, 7.6, C(9')*H*), 5.64 (1H, dt, *J* 15.2, 6.9, C(6')*H*), 5.94 (1H, app t, *J* 10.9, C(8')*H*), 6.26–6.33 (1H, m, C(7')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.3 (*C*(12')), 26.1 (*C*(2')), 27.4 (*C*(10')), 28.3 (CMe_3), 28.8, 29.3 (*C*(3'), *C*(4')), 30.1 (*C*(1')), 31.9 (*C*(11')), 32.7, 32.7 (*C*(3), *C*(5')), *43** (*C*(6)), *50** (*C*(2)), *62** (*C*(4)), 71.1 (*C*(5)), 80.2 (*C*Me_3), 125.8 (*C*(7')), 128.5 (*C*(8')), 130.2 (*C*(9')), 134.2 (*C*(6')), 154.6 (N(1)*C*O); *m/z* (ESI^+) 443 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{40}N_4NaO_3^+$ ($[M+Na]^+$) requires 443.2993; found 443.2990. Further elution gave **398** as a colourless oil (150 mg, 65%, 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]); $[\alpha]_D^{25}$ +21.4 (*c* 1.0 in $CHCl_3$); ν_{max} 3427, 2108, 1695, 1664; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.1, C(13')H_3), 1.26–1.41 (10H, m, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.48 (9H, s, CMe_3), 1.53–1.59 (2H, m, C(3)H_A, C(1')H_A), 1.83–1.93 (1H, m, C(1')H_B), 2.01–2.06 (1H, m, C(3)H_B), 2.06–2.12 (2H, m, C(5')H_2), 2.14–2.19 (2H, m, C(10')H_2), 3.42 (1H, dd, *J* 14.6, 2.6, C(6)H_A), 3.50 (1H, app d, *J* 2.9, C(5)*H*), 3.88 (1H, app d, *J* 3.7, C(4)*H*), 4.06 (1H, dd, *J* 14.6, 2.0, C(6)H_B), 4.13 (1H, app dtd, *J* 9.0, 6.2, 3.4, C(2)*H*), 5.31 (1H, dt, *J* 10.9, 7.6, C(9')*H*), 5.64 (1H, dt, *J* 15.2, 7.1, C(6')*H*), 5.94 (1H, app t, *J* 10.9, C(8')*H*), 6.26–6.33 (1H, m, C(7')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.3 (*C*(12')), 26.6 (*C*(2')), 27.4 (*C*(10')), 28.4 (CMe_3), 29.0, 29.4 (*C*(3'), *C*(4')), 31.3 (*C*(3)), 31.9 (*C*(11')), 32.8, 32.9 (*C*(5'), *C*(1')), 37.9 (*C*(6)), 49.7 (*C*(2)), 61.1 (*C*(5)), 67.7 (*C*(4)), 80.0 (*C*Me_3), 125.7 (*C*(7')), 128.5 (*C*(8')), 130.1 (*C*(9')), 134.4 (*C*(6')), 155.1 (N(1)*C*O); *m/z* (ESI^+) 443 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{40}N_4NaO_3^+$ ($[M+Na]^+$) requires 443.2993; found 443.2989.

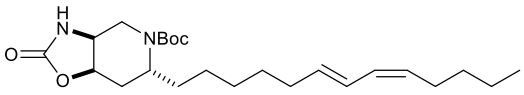
(2*R*,4*S*,5*S*,6'*E*,8'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-[*N*-(*tert*-butoxycarbonyl)amino]piperidine 400



Step 1. Polymer-supported PPh_3 (100–200 mesh, 321 mg, 0.96 mmol) was added to a stirred solution of **398** (135 mg, 0.32 mmol, 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]) in THF/H_2O (10:1, 4.6 mL) at rt and the resultant suspension was heated at 70 °C for 16 h, then allowed to cool to rt. The resultant suspension was filtered through through Celite® (eluent CH_2Cl_2/MeOH, 1:1) and concentrated *in vacuo*.

Step 2. Boc_2O (77 mg, 0.35 mmol) and Et_3N (49 μL, 0.35 mmol) were added sequentially to a stirred solution of the residue from the previous step in CH_2Cl_2 (1.6 mL) at rt and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **400** as a colourless oil (114 mg, 72%, 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]); $[\alpha]_D^{25}$ −25.4 (*c* 1.0 in $CHCl_3$); ν_{max} 3445, 3364, 1692; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0, C(13')H_3), 1.25–1.58 (12H, m, C(3)H_A, C(1')H_A, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.43 (9H, s, CMe_3), 1.47 (9H, s, CMe_3), 1.72–1.81 (1H, m, C(1')H_B), 1.94 (1H, ddd, *J* 14.3, 6.5, 3.4, C(3)H_B), 2.07 (2H, app q, *J* 7.0, C(5')H_2), 2.15 (2H, app q, *J* 7.0, C(10')H_2), 3.33 (1H, dd, *J* 14.7, 3.7, C(6)H_A), 3.44 (1H, br s, O*H*), 3.50–3.56 (1H, m, C(5)*H*), 3.76–3.81 (2H, m, C(4)*H*, C(6)H_B), 3.98–4.06 (1H, m, C(2)*H*), 5.13 (1H, d, *J* 3.7, N*H*), 5.29 (1H, dt, *J* 10.8, 7.6, C(9')*H*), 5.63 (1H, dt, *J* 15.0, 7.0, C(6')*H*), 5.92 (1H, app t, *J* 10.8, C(8')*H*), 6.28 (1H, ddd, *J* 15.0, 10.8, 1.0, C(7')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.3 (*C*(12')), 26.2 (*C*(2')), 27.3 (*C*(10')), 28.3 (CMe_3), 28.4 (CMe_3), 29.0, 29.4 (*C*(3'), *C*(4')), 31.4 (*C*(3)), 31.9 (*C*(11')), 32.8 (*C*(5')), 33.1 (*C*(1')), 39.2 (*C*(6)), 50.7 (*C*(2)), 53.8 (*C*(5)), 70.0 (*C*(4)), 79.9 (*C*Me_3), 80.0 (*C*Me_3), 125.7 (*C*(7')), 128.5 (*C*(8')), 130.1 (*C*(9')), 134.4 (*C*(6')), 155.9, 156.4 (N(1)*C*O, NH*C*O); *m/z* (ESI^+) 517 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{28}H_{50}N_2NaO_5^+$ ($[M+Na]^+$) requires 517.3612; found 517.3608.

(2*R*,4*R*,5*S*,6'*E*,8'*Z*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 402

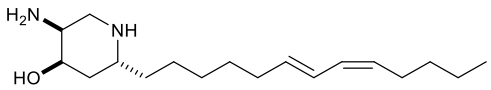


Step 1. Et_3N (0.12 mL, 0.81 mmol) was added dropwise *via* syringe to a stirred solution of **400** (100 mg, 0.20 mmol, 94:6 dr [(6'*E*,8'*Z*):(6'*Z*,8'*Z*)]) and MsCl (31 µL, 0.40 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. H_2O (1 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*.

Step 2. Pyridine (0.2 mL) was added dropwise *via* syringe to the residue from the previous step and the resultant solution was heated at 115 °C for 16 h then cooled to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **402** as a colourless oil (64 mg, 75%, 54:30:8:8 dr [(6'*E*,8'*Z*):(6'*E*,8'*E*):(6'*Z*,8'*Z*):(6'*Z*,8'*E*)]): $[\alpha]_D^{25}$ −56.4 (*c* 1.0 in $CHCl_3$); ν_{max} 3297, 1749, 1686; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0, C(13')H_3), 1.25–1.66 (13H, m, C(3)H_A, C(1')H_2, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.45 (9H, s, CMe_3), 1.99–2.19 (4H, m, C(5')H_2, C(10')H_2), 2.27 (1H, app d, *J* 14.7, C(3)H_B), 2.88 (1H, app d, *J* 13.9, C(6)H_A), 3.93 (1H, app d, *J* 9.3, C(5)*H*), 3.98–4.11 (2H, m, C(2)*H*, C(6)H_B), 4.89 (1H, app d, *J* 8.8, C(4)*H*), 5.30 (1H, dt, *J* 10.9, 7.6, C(9')*H*), 5.63 (1H, dt, *J* 14.8, 7.2, C(6')*H*), 5.74 (1H, br s, N*H*), 5.94 (1H, app t, *J* 10.9, C(8')*H*), 6.29 (1H, dd, *J* 14.8, 10.9, C(7')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.3 (*C*(12')), 25.0 (*C*(2')), 27.3 (*C*(10')), 28.3 (CMe_3), *29**, 29.3 (*C*(3'), *C*(4')), *30** (*C*(3)), 31.8 (*C*(11')), 32.7 (*C*(5')), *35** (*C*(1')), *40** (*C*(6)), *48** (*C*(2)), 51.4 (*C*(5)), 72.9 (*C*(4)), *80** (*C*Me_3), 125.8 (*C*(7')), 128.5 (*C*(8')), 130.2 (*C*(9')), 134.2 (*C*(6')), *156** (N(1)*C*O), *159** (HN*C*O); *m/z* (ESI^+) 443 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{24}H_{40}N_2NaO_4^+$ ($[M+Na]^+$) requires 443.2880; found 443.2879.

(2*R*,4*R*,5*S*,6′*E*,8′*Z*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine

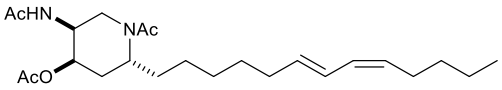
[Pseudodistomin A] 1



Step 1. KOH (30% aq, 2.0 mL) was added dropwise *via* syringe to a stirred solution of **402** (30 mg, 71 μmol, 54:30:8:8 dr [(6′*E*,8′*Z*):(6′*E*,8′*E*):(6′*Z*,8′*Z*):(6′*Z*,8′*E*)]) in MeOH (2 mL) at rt and the resultant solution was heated at 70 °C for 6 h, then allowed to cool to rt. CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. *Step 2*. HCl (1.25 M in MeOH, 3 mL) was added dropwise *via* syringe to the residue from the previous step at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 3 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 3:1:0.1) gave a fraction which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **1** as a white gum (15 mg, 71%, 54:30:8:8 dr [(6′*E*,8′*Z*):(6′*E*,8′*E*):(6′*Z*,8′*Z*):(6′*Z*,8′*E*)]);[49] $[\alpha]_D^{25}$ −20.7 (*c* 1.0 in MeOH); ν_{max} 3259, 3108, 2925, 2855, 1570, 1464, 985; δ_H (500 MHz, MeOH-d_4) 0.92 (3H, t, *J* 7.1, C(13′)H_3), 1.27–1.43 (13H, m, C(3)H_A, C(1′)H_2, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(11′)H_2, C(12′)H_2), 1.88 (1H, app dt, *J* 13.9, 3.0, C(3)H_B), 2.05 (2H, app q, *J* 7.0, C(5′)H_2), 2.16 (2H, app q, *J* 7.0, C(10′)H_2), 2.65–2.71 (2H, m, C(6)H_A, C(5)*H*), 2.74–2.76 (1H, m, C(6)H_B), 2.78–2.82 (1H, m, C(2)*H*), 3.88–3.90 (1H, m, C(4)*H*), 5.27 (1H, dt, *J* 10.8, 7.8, C(9′)*H*), 5.63 (1H, dt, *J* 14.9, 7.3, C(6′)*H*), 5.92 (1H, app t, *J* 10.8, C(8′)*H*), 6.31 (1H, ddd, *J* 14.9, 10.8, 0.9, C(7′)*H*); δ_C (125 MHz, MeOH-d_4) 14.5 (*C*(13′)), 23.4 (*C*(12′)), 27.1 (*C*(2′)), 28.4 (*C*(10′)), 30.5 (*C*(3′)), 30.6 (*C*(4′)), 33.3 (*C*(11′)), 33.9 (*C*(5′)), 37.3 (*C*(1′)), 40.3 (*C*(3)), 48.8 (*C*(6)),[50] 50.4 (*C*(2)), 52.5 (*C*(5)), 69.1 (*C*(4)), 127.2 (*C*(7′)),

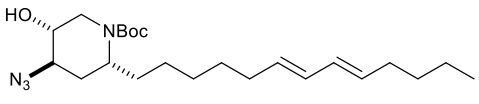
130.1 (*C*(8')), 130.7 (*C*(9')), 135.4 (*C*(6')); *m/z* (ESI$^+$) 295 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{35}N_2O^+$ ([M+H]$^+$) requires 295.2744; found 295.2743.

(2*R*,4*R*,5*S*,6′*E*,8′*Z*)-*N*,*N*,*O*-Triacetyl-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin A acetate] 9

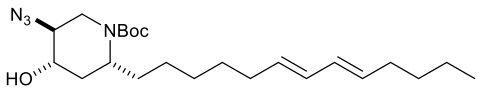


Ac_2O (0.5 mL) was added to a stirred solution of **1** (9 mg, 31 μmol, 54:30:8:8 dr [(6'*E*,8'*Z*):(6'*E*,8'*E*):(6'*Z*,8'*Z*):(6'*Z*,8'*E*)]) in pyridine (1.0 mL) at rt and the resultant solution was stirred at rt for 1.5 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 30:1) gave **9** as a colourless oil (11 mg, 86%, 54:30:8:8 dr [(6'*E*,8'*Z*):(6'*E*,8'*E*):(6'*Z*,8'*Z*):(6'*Z*,8'*E*)]);[49] $[\alpha]_D^{25}$ +48.0 (*c* 1.0 in MeOH); {lit.[49] $[\alpha]_D^{24}$ +36 (*c* 1.0 in MeOH)}; ν_{max} 3298, 1741, 1631, 1544, 1431, 1370, 1241, 1043, 988; δ_H (500 MHz, $CDCl_3$) [major rotamer] 0.91 (3H, t, *J* 7.0, C(13')H_3), 1.17–1.43 (10H, m, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.47–1.72 (2H, m, C(1')H_2), 1.74–1.80 (2H, m, C(3)H_2), 2.03 (3H, s, C(O)*Me*), 2.04 (3H, s, C(O)*Me*), 2.04–2.11 (2H, m, C(5')H_2), 2.05 (3H, s, C(O)*Me*), 2.14–2.18 (2H, m, C(10')H_2), 3.29 (1H, app d, *J* 14.4, C(6)H_A), 3.95 (1H, app d, *J* 14.4, C(6)H_B), 4.32–4.37 (1H, m, C(5)*H*), 4.89–4.96 (1H, m, C(2)*H*), 5.11–5.18 (1H, m, C(4)*H*), 5.31 (1H, dt, *J* 10.8, 7.6, C(9')*H*), 5.63 (1H, dt, *J* 14.7, 7.2, C(6')*H*), 5.94 (1H, app t, *J* 10.8, C(8')*H*), 6.29 (1H, dd, *J* 14.7, 10.8, C(7')*H*); δ_H (500 MHz, $CDCl_3$) [minor rotamer, selected peaks] 2.92 (1H, app d, *J* 14.0, C(6)H_A), 3.97–4.03 (1H, m, C(2)*H*), 4.47–4.53 (1H, m, C(5)*H*), 4.62 (1H, app d, *J* 12.9, C(6)H_B); δ_C (125 MHz, $CDCl_3$) [major rotamer] 14.0 (*C*(13')), 21.0 (C(O)*Me*), 21.8 (C(O)*Me*), 22.3 (*C*(12')), 23.3 (C(O)*Me*), 26.1 (*C*(2')), 27.4 (*C*(10')), 28.3 (*C*(3)), 28.9 (*C*(3')), 29.2 (*C*(4')), 30.1 (*C*(1')), 31.9 (*C*(11')), 32.7 (*C*(5')), 43.7 (*C*(6)), 47.1 (*C*(5)), 47.5 (*C*(2)), 66.9 (*C*(4)), 125.8 (*C*(7')), 128.5 (*C*(8')), 130.2 (*C*(9')), 134.2 (*C*(6')), 170.0 (*C*(O)Me), 170.2 (*C*(O)Me), 170.6 (*C*(O)Me); δ_C (125 MHz, $CDCl_3$) [minor rotamer, selected peaks] 39.3 (*C*(6)), 46.2 (*C*(5)), 54.0 (*C*(2)); *m/z* (ESI$^+$) 421 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{41}N_2O_4^+$ ([M+H]$^+$) requires 421.3061; found 421.3057.

(2*R*,4*R*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-azido-5-hydroxypiperidine 404 and (2*R*,4*S*,5*S*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-azidopiperidine 141



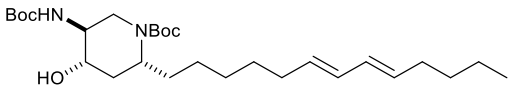
404



141

NH_4Cl (68 mg, 1.27 mmol) and NaN_3 (83 mg, 1.27 mmol) were added sequentially to a stirred solution of **140** (80 mg, 0.21 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) in DMSO (0.8 mL) at rt and the resultant solution was heated at 80 °C for 16 h, then allowed to cool to rt. H_2O (1 mL) was added and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organics were washed with H_2O (3 × 1 mL) and brine (3 mL), then dried and concentrated *in vacuo* to give a ~25:75 mixture of **404** and **141**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 4:1) gave **404** as a colourless oil (16 mg, 18%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]);[5] $[\alpha]_D^{25}$ −13.7 (*c* 1.0 in $CHCl_3$); {lit.[7,5] $[\alpha]_D^{25}$ −14.1 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(13')H_3), 1.22–1.42 (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), 1.46 (9H, s, CMe_3), 1.58–1.70 (2H, m, C(3')H_A, C(1')H_B), 1.91 (1H, app dd, *J* 13.7, 2.9, C(3)H_B), 2.02–2.11 (4H, m, C(5')H_2, C(10')H_2), 2.42 (1H, br s, O*H*), 2.67 (1H, app t, *J* 11.5, C(6)H_A), 3.41–3.54 (2H, m, C(4)*H*, C(5)*H*), 4.12–4.39 (2H, m, C(2)*H*, C(6)H_B), 5.51–5.61 (2H, m, C(6')*H*, C(9')*H*), 5.96–6.03 (2H, m, C(7')*H*, C(8')*H*). Further elution gave **141** as a colourless oil (66 mg, 74%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]);[5] $[\alpha]_D^{25}$ +21.4 (*c* 1.0 in $CHCl_3$); {lit.[5] $[\alpha]_D^{25}$ +6.3 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.1, C(13')H_3), 1.26–1.39 (10H, m, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.48 (9H, s, CMe_3), 1.53–1.59 (2H, m, C(3)H_A, C(1')H_A), 1.83–1.92 (2H, m, C(3)H_B, C(1')H_B), 2.02–2.08 (4H, m, C(5')H_2, C(10')H_2), 3.42 (1H, dd, *J* 14.4, 2.9, C(6)H_A), 3.49 (1H, app q, *J* 2.9, C(5)*H*), 3.88 (1H, app q, *J* 3.9, C(4)*H*), 4.06 (1H, dd, *J* 14.4, 1.0, C(6)H_B), 4.10–4.16 (1H, m, C(2)*H*), 5.51–5.60 (2H, m, C(6')*H*, C(9')*H*), 5.94–6.03 (2H, m, C(7')*H*, C(8')*H*).

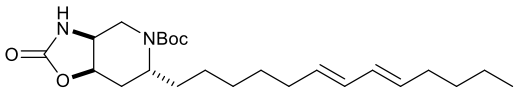
(2*R*,4*S*,5*S*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-[*N*-(*tert*-butoxycarbonyl)amino]piperidine 405



Step 1. Polymer-supported PPh_3 (100–200 mesh, 310 mg, 0.93 mmol) was added to a stirred solution of **141** (130 mg, 0.31 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) in THF/H_2O (10:1, 4.4 mL) at rt and the resultant suspension was heated at 70 °C for 16 h, then allowed to cool to rt. The resultant suspension was filtered through through Celite® (eluent CH_2Cl_2/MeOH, 1:1) and concentrated *in vacuo*.

Step 2. Boc_2O (74 mg, 0.34 mmol) and Et_3N (47 μL, 0.34 mmol) were added sequentially to a stirred solution of the residue from the previous step in CH_2Cl_2 (1.6 mL) at rt and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **405** as a colourless oil (125 mg, 82%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]); $[\alpha]_D^{25}$ −26.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3346, 3364, 1692; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(13')*H*$_3$), 1.25–1.55 (12H, m, C(3)*H*$_A$, C(1')*H*$_A$, C(2')*H*$_2$, C(3')*H*$_2$, C(4')*H*$_2$, C(11')*H*$_2$, C(12')*H*$_2$), 1.43 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 1.71–1.81 (1H, m, C(1')*H*$_B$), 1.94 (1H, ddd, *J* 14.1, 5.8, 3.5, C(3)*H*$_B$), 2.00–2.07 (4H, m, C(5')*H*$_2$, C(10')*H*$_2$), 3.33 (1H, dd, *J* 14.4, 3.7, C(6)*H*$_A$), 3.43 (1H, br s, O*H*), 3.50–3.56 (1H, m, C(5)*H*), 3.78–3.81 (2H, m, C(4)*H*, C(6)*H*$_B$), 4.02 (1H, app t, *J* 5.8, C(2)*H*), 5.14 (1H, d, *J* 3.4, N*H*), 5.50–5.59 (2H, m, C(6')*H*, C(9')*H*), 5.94–6.01 (2H, m, C(7')*H*, C(8')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.2 (*C*(12')), 26.2 (*C*(2')), 28.3 (C*Me*$_3$), 28.4 (C*Me*$_3$), 29.0, 29.4 (*C*(3'), *C*(4')), 31.4 (*C*(3)), 31.5, 32.2, 32.5 (*C*(5'), *C*(10'), *C*(11')), 33.2 (*C*(1')), 39.2 (*C*(6)), *51** (*C*(2)), *54** (*C*(5)), *70** (*C*(4)), 79.9 (*C*Me$_3$), 80.0 (*C*Me$_3$), 130.3, 130.4 (*C*(7'), *C*(8')), 132.1, 132.4 (*C*(6'), *C*(9')), 155.9, 156.4 (N(1)*C*O, NH*C*O); *m/z* (ESI$^+$) 517 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{50}N_2NaO_5^+$ ([M+Na]$^+$) requires 517.3612; found 517.3612.

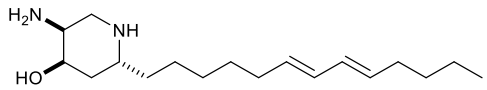
(2*R*,4*R*,5*S*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-amino-*N*,*O*-carbonyl-piperidine 55



Step 1. Et_3N (0.11 mL, 0.81 mmol) was added dropwise *via* syringe to a stirred solution of **405** (100 mg, 0.20 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) and MsCl (31 μL, 0.40 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. H_2O (1 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*.

Step 2. Pyridine (0.2 mL) was added dropwise *via* syringe to the residue from the previous step and the resultant solution was heated at 115 °C for 16 h then cooled to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **55** as a colourless oil (61 mg, 72%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]);[46] $[\alpha]_D^{25}$ −49.2 (*c* 1.0 in $CHCl_3$); {lit.[46] $[\alpha]_D^{25}$ −47.6 (*c* 0.82 MeOH)}; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(13')H_3), 1.26–1.40 (10H, m, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.45 (9H, s, CMe_3), 1.46–1.53 (2H, m, C(3)H_A, C(1')H_A), 1.57–1.66 (1H, m, C(1')H_B), 2.02–2.09 (4H, m, C(5')H_2, C(10')H_2), 2.27 (1H, app d, *J* 14.7, C(3)H_B), 2.88 (1H, app d, *J* 14.2, C(6)H_A), 3.93 (1H, app d, *J* 9.0, C(5)*H*), 3.99–4.10 (2H, m, C(2)*H*, C(6)H_B), 4.89 (1H, app dt, *J* 9.0, 2.9, C(4)*H*), 5.50–5.60 (2H, m, C(6')*H*, C(9')*H*), 5.68 (1H, br s, N*H*), 5.95–6.03 (2H, m, C(7')*H*, C(8')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.2 (*C*(12')), 25.0 (*C*(2')), 28.4 (CMe_3), 29.0 (*C*(3')), 29.3 (*C*(4')), *30** (*C*(3)), 31.5 (*C*(11')), 32.2, 32.4 (*C*(5'), *C*(10')), *35** (*C*(1')), *40** (*C*(6)), *48** (*C*(2)), 51.4 (*C*(5)), 72.9 (*C*(4)), *80** (*C*Me_3), 130.2, 130.6 (*C*(7'), *C*(8')), 131.9, 132.5 (*C*(6')), *C*(9')), *156** (N(1)*C*O), *159** (HN*C*O).[19]

(2*R*,4*R*,5*S*,6′*E*,8′*E*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin B] 2

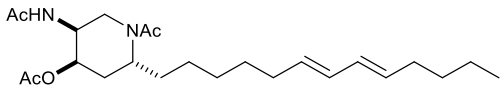


Step 1. KOH (30% aq, 2.0 mL) was added dropwise *via* syringe to a stirred solution of **55** (31 mg, 74 μmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) in MeOH (2 mL) at rt and the resultant solution was heated at 70 °C for 6 h, then allowed to cool to rt. CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*.

Step 2. HCl (1.25 M in MeOH, 3 mL) was added dropwise *via* syringe to the residue from the previous step at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 3 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 5:1:0.1) gave a fraction which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **2** as a white gum (17 mg, 78%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]);[49,24] $[\alpha]_D^{25}$ −21.7 (*c* 1.0 in MeOH); {lit.[24] $[\alpha]_D^{25}$ −13 (*c* 0.87 MeOH)}; ν_{max} 3254, 3015, 2923, 2852, 1573, 1464, 985; δ_H (500 MHz, MeOH-d_4) 0.91 (3H, t, *J* 7.1, C(13')H_3), 1.27–1.43 (13H, m, C(3)H_A, C(1')H_2, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.88 (1H, app dt, *J* 13.8, 3.0, C(3)H_B), 2.03–2.08 (4H, m, C(5')H_2, C(10')H_2), 2.65–2.72 (2H, m, C(5)*H*, C(6)H_A), 2.73–2.77 (1H, m, C(6)H_B), 2.78–2.84 (1H, m, C(2)*H*), 3.88–3.91 (1H, m, C(4)*H*), 5.50–5.56 (2H, m, C(6')*H*, C(9')*H*), 5.94–6.00 (2H, m, C(7')*H*, C(8')*H*); δ_C (125 MHz, MeOH-d_4) 14.4 (*C*(13')), 23.4 (*C*(12')), 27.1 (*C*(2')), 30.5 (*C*(3')), 30.6 (*C*(4')), 33.0 (*C*(11')), 33.5 (*C*(5')), 33.7 (*C*(10')), 37.2 (*C*(1')), 40.2 (*C*(3)), 48.7 (*C*(6)), 50.4 (*C*(2)), 52.4 (*C*(5)), 69.0 (*C*(4)), 132.0 (*C*(8')), 132.1 (*C*(7')), 133.0 (*C*(6')), 133.2 (*C*(9')); *m/z*

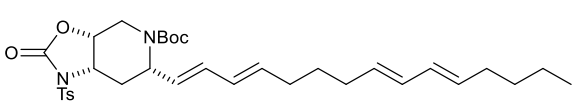
(ESI$^+$) 295 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{35}N_2O^+$ ([M+H]$^+$) requires 295.2744; found 295.2743. Data for **2**·0.2 TFA: $[\alpha]_D^{25}$ −20.5 (*c* 1.0 in MeOH).

(2*R*,4*R*,5*S*,6′*E*,8′*E*)-*N*,*N*,*O*-Triacetyl-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin B acetate] 10

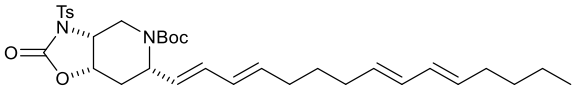


Ac_2O (0.5 mL) was added to a stirred solution of **2** (16 mg, 54 μmol, 83:17 dr [(6′*E*,8′*E*):(6′*Z*,8′*E*)]) in pyridine (1.0 mL) at rt and the resultant solution was stirred at rt for 1.5 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 30:1) gave **10** as a colourless oil (20 mg, 88%, 83:17 dr [(6′*E*,8′*E*):(6′*Z*,8′*E*)]);[49] $[\alpha]_D^{25}$ +49.7 (*c* 1.0 in MeOH); {lit.[49] $[\alpha]_D^{24}$ +35 (*c* 1.0 in MeOH)}; ν_{max} 3303, 1742, 1632, 1541, 1430, 1369, 1239, 1043, 988; δ_H (500 MHz, MeOH-d_4) [major rotamer] 0.89 (3H, t, *J* 6.7, C(13′)H_3), 1.15–1.40 (10H, m, C(2′)H_2, C(3′)H_2, C(4′)H_2, C(11′)H_2, C(12′)H_2), 1.47–1.57 (1H, m, C(1′)H_A), 1.59–1.68 (1H, m, C(1′)H_B), 1.72–1.87 (2H, m, C(3)H_2), 1.98–2.07 (4H, m, C(5′)H_2, C(10′)H_2), 2.03 (3H, s, C(O)*Me*), 2.03 (3H, s, C(O)*Me*), 2.04 (3H, s, C(O)*Me*), 3.29 (1H, app d, *J* 14.7, C(6)H_A), 3.85–3.95 (1H, m, C(6)H_B), 4.35–4.41 (1H, m, C(5)*H*), 4.85–4.92 (1H, m, C(2)*H*), 5.10–5.15 (1H, m, C(4)*H*), 5.48–5.60 (2H, m, C(6′)*H*, C(9′)*H*), 5.91–5.99 (2H, m, C(7′)*H*, C(8′)*H*), 6.38 (1H, br s, N*H*); δ_H (500 MHz, MeOH-d_4) [minor rotamer, selected peaks] 2.91 (1H, app d, *J* 14.0, C(6)H_A), 3.96–4.03 (1H, m, C(2)*H*), 4.48–4.53 (1H, m, C(5)*H*), 4.61 (1H, app d, *J* 14.3, C(6)H_B); δ_C (125 MHz, MeOH-d_4) [major rotamer] 13.9 (*C*(13′)), 21.0 (C(O)*Me*), 21.8 (C(O)*Me*), 22.1 (*C*(12′)), 23.2 (C(O)*Me*), 26.1 (*C*(2′)), 28.2 (*C*(3)), 28.8 (*C*(3′)), 29.2 (*C*(4′)), 30.1 (*C*(1′)), 31.5 (*C*(11′)), 32.2 (*C*(5′)), 32.4 (*C*(10′)), 43.9 (*C*(6)), 46.8 (*C*(5)), 47.6 (*C*(2)), 66.9 (*C*(4)), 130.2 (*C*(8′)), 130.5 (*C*(7′)), 131.9 (*C*(6′)), 132.6 (*C*(9′)), 170.1 (*C*(O)Me), 170.1 (*C*(O)Me), 170.7 (*C*(O)Me); δ_C (125 MHz, MeOH-d_4) [minor rotamer, selected peaks] 39.3 (*C*(6)), 46.1 (*C*(5)), 53.9 (*C*(2)); *m/z* (ESI$^+$) 421 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{41}N_2O_4^+$ ([M+H]$^+$) requires 421.3061; found 421.3051.

(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-(*N*-tosylamino)-5-hydroxy-*N*,*O*-carbonyl-piperidine 408 and (2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonyl-piperidine 409



408

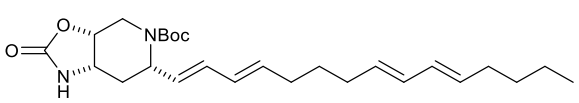


409

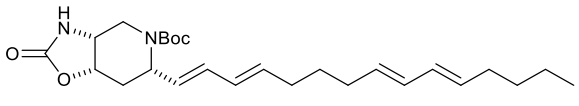
TBAI (120 mg, 0.32 mmol) was added to a stirred solution of **386** (130 mg, 0.32 mmol, >85% dp) and TsNCO (74 µL, 0.49 mmol) in PhMe (1.6 mL) at rt and the resultant mixture was heated at 100 °C for 16 h then cooled to rt. EtOAc (2 mL) and H_2O (2 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 2 mL). The combined organics were washed with brine (6 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave a ~50:50 mixture of **408** and **409**, respectively, as a pale yellow oil (175 mg, 90%, >85% dp). Data for mixture: ν_{max} 1785, 1692, 1597, 1366, 1171; δ_H (400 MHz, $CDCl_3$)[51] 0.89 (6H, t, *J* 7.1, C(15')*H*$_3$×2), 1.26–1.38 (8H, m, C(13')*H*$_2$×2, C(14')*H*$_2$×2), 1.43 (9H, s, C*Me*$_3$), 1.44–1.51 (4H, m, C(6')*H*$_2$×2), 1.46 (9H, s, C*Me*$_3$), 1.81 (1H, app dt, *J* 13.8, 9.0, C(3)*H*$_A$), 1.94 (1H, app dt, *J* 14.3, 9.0, C(3)*H*$_A$), 2.02–2.12 (12H, m, C(5')*H*$_2$×2, C(7')*H*$_2$×2, C(12')*H*$_2$×2), 2.13–2.15 (1H, m, C(3)*H*$_B$), 2.45 (6H, s, Ar*Me*×2), 2.56 (1H, app dt, *J* 13.9, 5.4, C(3)*H*$_B$), 3.11 (1H, dd, *J* 14.2, 9.3, C(6)*H*$_A$), 3.20 (1H, dd, *J* 13.6, 9.4, C(6)*H*$_A$), 4.29–4.51 (3H, m, C(2)*H*×2, C(6)*H*$_B$), 4.47 (2H, ddd, *J* 11.3, 8.7, 4.6, C(4)*H*, C(5)*H*), 4.51–4.60 (1H, m, C(6)*H*$_B$), 4.63 (1H, app td, *J* 8.7, 4.9, C(5)*H*), 4.70 (1H, app td, *J* 9.1, 8.8, C(4)*H*), 5.37 (1H, dd, *J* 14.9, 6.1, C(1')*H*), 5.45 (1H, dd, *J* 12.0, 6.1, C(1')*H*), 5.50–5.70 (6H, m, C(4')*H*×2, C(8')*H*×2, C(11')*H*×2), 5.90–6.09 (8H, m, C(2')*H*×2, C(3')*H*×2, C(9')*H*×2, C(10')*H*×2), 7.36 (4H, d, *J* 8.1, *Ar*×2), 7.94 (2H, d, *J* 8.1, *Ar*), 7.95 (2H, d, *J* 8.1, *Ar*); δ_C (100 MHz, $CDCl_3$)[51] 13.9 (*C*(15')×2), 21.6 (Ar*Me*×2), 22.2 (*C*(14')×2), 28.2 (C*Me*$_3$), 28.3 (C*Me*$_3$), 28.8, 28.8 (*C*(6')×2), 31.2 (*C*(3)), 31.5 (*C*(3)), 31.9 (*C*(13')×2), 32.0, 32.0, 32.2 (*C*(5')×2, C(7')×2, *C*(12')×2), *40*[*] (*C*(6)), *41*[*] (*C*(6)), *52*[*] (*C*(2)×2), 54.2, 54.2 (*C*(4), *C*(5)), 70.5 (*C*(5)), 71.9 (*C*(4)), 80.8, 80.8 (*C*Me$_3$×2), 128.2, 128.3 (*C*(1')×2), 128.5, 128.4 (*Ar*×2), 129.2,

129.2 (*C*(2')×2, *C*(3')×2, *C*(9')×2, *C*(10')×2), 129.8, 129.8 (*Ar*×2), 130.2, 130.2, 130.8, 130.8 (*C*(2')×2, *C*(3')×2, *C*(9')×2, *C*(10')×2), 131.0, 131.0 (*C*(2')×2, *C*(3')×2, *C*(9')×2, *C*(10')×2), 131.5, 131.5 (*C*(8')×2, *C*(11')×2), 132.6, 132.6 (*C*(8')×2, *C*(11')×2), 134.4, 134.9 (*Ar*×2), 135.4, 135.4 (*C*(4')×2), 145.7, 145.7 (*Ar*×2), 151.1, 151.6 (TsN*C*O), *155*[*] (N(1)*C*O×2); *m/z* (ESI$^+$) 621 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{46}N_2NaO_6S^+$ ([M+Na]$^+$) requires 621.2969; found 621.6966.

(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-amino-5-hydroxy-*N*,*O*-carbonylpiperidine 410 and (2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 411



410

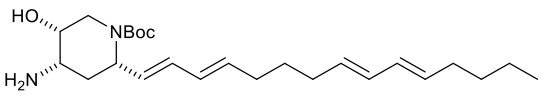


411

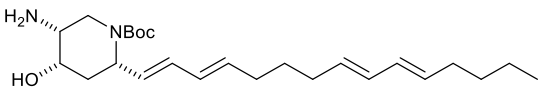
Na (33 mg, 1.42 mmol) was added to a stirred solution of naphthalene (219 mg, 1.71 mmol) in THF (4 mL) at rt. The resultant solution was stirred at rt for 16 h, then cooled to −78 °C. A solution of a ~50:50 mixture of **408** and **409** (170 mg, 0.28 mmol, >85% dp) in THF (2 mL) at −78 °C was added dropwise *via* syringe and the resultant solution was stirred for 30 min at −78 °C, then quenched with EtOH (2 mL). CH_2Cl_2 (2 mL) and satd aq $NaHCO_3$ (2 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organics were washed sequentially with H_2O (6 mL) and brine (6 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 4:1) gave a ~50:50 mixture of **410** and **411**, respectively, as a pale yellow oil (113 mg, 90%, >85% dp). Data for mixture: ν_{max} 3291, 1758, 1694; δ_H (400 MHz, $CDCl_3$)[51] 0.89 (6H, m, C(15')H_3×2), 1.25–1.38 (8H, m, C(13')H_2×2, C(14')H_2×2), 1.43 (18H, s, CMe_3×2), 1.44–1.51 (4H, m, C(6')H_2×2), 1.71 (1H, app dt, *J* 12.5, 12.0, C(3)H_A), 1.95 (1H, app dt, *J* 13.9, 10.0, C(3)H_A), 2.03–2.10 (13H, C(3)H_B, C(5')H_2×2, C(7')H_2×2, C(12')H_2×2), 2.15–2.23 (1H, m, C(3)H_B), 3.00 (1H, dd, *J* 13.4, 10.0, C(6)H_A), 3.12 (1H, dd, *J* 13.9, 9.5, C(6)H_A), 3.87 (1H, td,

J 10.8, 4.7, C(4)*H*), 3.94–4.04 (1H, m, C(5)*H*), 4.07–4.21 (1H, m, C(6)H_B), 4.23–4.47 (3H, m, C(2)*H*×2, C(6)H_B), 4.70–4.78 (2H, m, C(4)*H*, C(5)*H*), 5.44–5.60 (6H, m, C(1')*H*×2, C(8')*H*×2, C(11')*H*×2), 5.62–5.65 (2H, m, C(4')*H*×2), 5.91–6.10 (8H, m, C(2')*H*×2, C(3')*H*×2, C(9')*H*×2, C(10')*H*×2), 6.42 (2H, br s, N*H*×2); δ_C (100 MHz, $CDCl_3$)[51] 13.9 (*C*(15')×2), 22.2 (*C*(14')×2), 28.3 (C*Me*$_3$×2), 28.8 (*C*(6')×2), 31.5 (*C*(3), *C*(13')×2), 31.9, 32.0 (*C*(5')×2, *C*(7')×2, *C*(12')×2), 32.2 (*C*(3)), *40** (*C*(6)), *41** (*C*(6)), 49.4 (*C*(4)), 49.9 (*C*(5)), *52** (*C*(2)×2), 72.3 (*C*(5)), 73.5 (*C*(4)), 80.5 (*C*Me$_3$×2), 129.0, 129.1 (*C*(1')×2, *C*(8')×2, *C*(11')×2), 130.2, 130.7, 130.7, 131.1 (*C*(2')×2, *C*(3')×2, *C*(9')×2, *C*(10')×2), 131.5, 132.6 (*C*(1')×2, *C*(8')×2, *C*(11')×2), 135.1, 135.1 (*C*(4')×2), *155** (N(1)*C*O×2), *159** (HN*C*O×2); *m/z* (ESI$^+$) 467 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{40}N_2NaO_4^+$ ([M+Na]$^+$) requires 467.2880; found 467.2871.

(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-amino-5-hydroxypiperidine 412 and (2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine 413



412

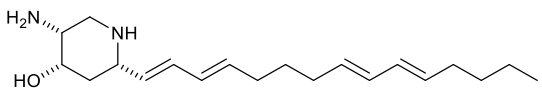


413

KOH (30% aq, 2.0 mL) was added dropwise *via* syringe to a stirred solution of of a ~50:50 mixture of **410** and **411** (80 mg, 0.18 mmol, >85% dp) in MeOH (2 mL) at rt and the resultant solution was heated at 70 °C for 6 h, then allowed to cool to rt. CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/MeOH/35% aq NH_4OH,[6] 30:1:0.1) gave **412** as a white gum (29 mg, 39%, >85% dp); $[\alpha]_D^{25}$ −16.6 (*c* 1.0 in $CHCl_3$); ν_{max} 3361, 3310, 1693, 1589; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')*H*$_3$), 1.25–1.45 (6H, m, C(6')*H*$_2$, C(13')*H*$_2$, C(14')*H*$_2$), 1.46 (9H, s, C*Me*$_3$), 1.89–2.19 (8H, m, C(3)*H*$_2$, C(5')*H*$_2$, C(7')*H*$_2$, C(12')*H*$_2$), 2.78 (1H, app t, *J* 11.9, C(6)H_A), 3.07–3.17 (1H, m, C(4)*H*), 3.55–3.65 (1H, m, C(5)*H*), 4.02 (1H, dd, *J* 13.1, 4.8, C(6)H_B), 4.73–4.78 (1H, m, C(2)*H*), 5.51–5.68 (4H, m, C(1')*H*, C(4')*H*, C(8')*H*,

C(11')*H*), 5.92–6.06 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 22.2 (*C*(14')), 28.4 (C*Me*$_3$), 28.9, 31.5, 32.0, 32.0, 32.2 (*C*(5'), *C*(6'), *C*(7'), *C*(12'), *C*(13')), *36** (*C*(3)), 40.7 (*C*(6)), *49** (*C*(4)), 49.6 (*C*(2)), *66** (*C*(5)), 80.0 (*C*Me$_3$), 129.4, 129.7, 130.2, 130.3, 130.8 (*C*(1'), *C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.6, 132.7 (*C*(8'), *C*(11')), 134.7 (*C*(4')), 155.1 (N(1)*C*O); *m/z* (ESI^+) 419 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{43}N_2O_3^+$ ($[M+H]^+$) requires 419.3268; found 419.3258. Further elution gave **413** as a white gum (37 mg, 49%, >85% dp); $[\alpha]_D^{25}$ −4.6 (*c* 1.0 in $CHCl_3$); ν_{max} 3354, 3286, 1671, 1588; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')*H*$_3$), 1.26–1.50 (6H, m, C(6')*H*$_2$, C(13')*H*$_2$, C(14')*H*$_2$), 1.46 (9H, s, C*Me*$_3$), 1.82–2.18 (8H, m, C(3)*H*$_2$, C(5')*H*$_2$, C(7')*H*$_2$, C(12')*H*$_2$), 2.78–2.95 (2H, m, C(5)*H*, C(6)*H*$_A$), 3.81 (1H, app d, *J* 6.6, C(6)*H*$_B$), 3.86–3.93 (1H, m, C(4)*H*), 4.70 (1H, app t, *J* 5.6, C(2)*H*), 5.50–5.65 (3H, m, C(4')*H*, C(8')*H*, C(11')*H*), 5.84 (1H, dd, *J* 14.1, 6.0, C(1')*H*), 5.94–6.05 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 22.0 (*C*(14')), 28.4 (C*Me*$_3$), 28.9, 31.5, 32.0, 32.0, 32.2 (*C*(5'), *C*(6'), *C*(7'), *C*(12'), *C*(13')), 35.0 (*C*(3)), *41** (*C*(6)), 50.0 (*C*(2)), *50** (*C*(5)), 67.7 (*C*(4)), 79.8 (*C*Me$_3$), 129.9, 130.2, 130.2, 130.7, 130.9 (*C*(1'), *C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.7, 132.6 (*C*(8'), *C*(11')), 134.2 (*C*(4')), 154.9 (N(1)*C*O); *m/z* (ESI^+) 419 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{43}N_2O_3^+$ ($[M+H]^+$) requires 419.3268; found 419.3252.

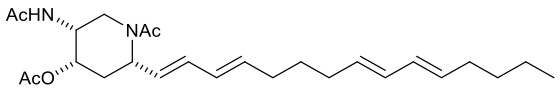
(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C] 3



HCl (1.25 M in MeOH, 3 mL) was added dropwise *via* syringe to **413** (30 mg, 72 μmol, >85% dp) at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 3 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 8:1:0.1) gave a fraction

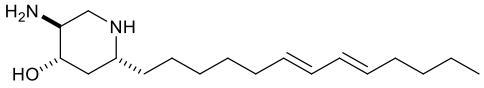
which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **3** as a white gum (17 mg, 79%, >85% dp);[52] $[\alpha]_D^{25}$ −43.7 (*c* 1.0 in MeOH); {lit.[53] $[\alpha]_D^{24}$ −24 (*c* 0.7 MeOH)};[54] ν_{max} 3275, 3016, 2926, 2858, 1573, 1457, 987; δ_H (500 MHz, MeOH-*d*$_4$) 0.91 (3H, t, *J* 7.1, C(15')*H*$_3$), 1.29–1.43 (5H, m, C(3)*H*$_A$, C(13')*H*$_2$, C(14')*H*$_2$), 1.47 (2H, app quin, *J* 7.5, C(6')*H*$_2$), 1.68 (1H, app dt, *J* 12.3, 3.7, C(3)*H*$_B$), 2.04–2.11 (6H, m, C(5')*H*$_2$, C(7')*H*$_2$, C(12')*H*$_2$), 2.78 (1H, dd, *J* 13.2, 1.9, C(6)*H*$_A$), 2.89 (1H, app d, *J* 1.9, C(5)*H*), 3.00 (1H, dd, *J* 13.2, 2.2, C(6)*H*$_B$), 3.10 (1H, app t, *J* 8.3, C(2)*H*), 3.72 (1H, app dt, *J* 11.5, 3.7, C(4)*H*), 5.51–5.57 (3H, m, C(1')*H*, C(8')*H*, C(11')*H*), 5.67 (1H, dt, *J* 15.0, 7.1, C(4')*H*), 5.95–6.05 (3H, m, C(3')*H*, C(9')*H*, C(10')*H*), 6.18 (1H, dd, *J* 15.3, 10.4, C(2')*H*); δ_C (125 MHz, MeOH-*d*$_4$) 14.4 (*C*(15')), 23.4 (*C*(14')), 30.4 (*C*(6')), 33.0 (*C*(13')), 33.2, 33.2 (*C*(7'), *C*(12')), 33.5 (*C*(5')), 35.8 (*C*(3)), 50.1 (*C*(6)), 51.0 (*C*(5)), 58.2 (*C*(2)), 70.7 (*C*(4)), 131.7 (*C*(3')), 131.9 (*C*(10')), 132.0 (*C*(9')), 132.4 (*C*(2')), 132.7 (*C*(8')), 133.3 (*C*(11')), 133.6 (*C*(1')), 135.6 (*C*(4')); δ_H (500 MHz, C_5D_5N) 0.84 (3H, t, *J* 7.1, C(15')*H*$_3$), 1.22–1.35 (4H, m, C(13')*H*$_2$, C(14')*H*$_2$), 1.47 (2H, app quin, *J* 7.3, C(6')*H*$_2$), 1.82 (1H, app q, *J* 11.5, C(3)*H*$_A$), 1.97 (1H, app d, *J* 10.7, C(3)*H*$_B$), 2.03–2.10 (6H, m, C(5')*H*$_2$, C(7')*H*$_2$, C(12')*H*$_2$), 2.83 (1H, app d, *J* 10.9, C(6)*H*$_A$), 3.14–3.24 (3H, m, C(2)*H*, C(5)*H*, C(6)*H*$_B$), 3.93–3.95 (1H, m, C(4)*H*), 5.61–5.75 (3H, m, C(4')*H*, C(8')*H*, C(11')*H*), 5.79 (1H, dd, *J* 15.3, 6.1, *C*(1')*H*), 6.10–6.18 (3H, m, C(3')*H*, C(9')*H*, C(10')*H*), 6.35 (1H, dd, *J* 15.3, 10.5, C(2')*H*); δ_C (125 MHz, C_5D_5N) 14.5 (*C*(15')), 22.9 (*C*(14')), 29.8 (*C*(6')), 32.2 (*C*(13')), 32.8 (*C*(12')), 32.8 (*C*(7')), 33.0 (*C*(5')), 37.3 (*C*(3)), 51.7 (*C*(5)), 51.7 (*C*(6)), 58.3 (*C*(2)), 70.7 (*C*(4)), 130.3 (*C*(2')), 131.5 (*C*(10')), 131.6 (*C*(3')), 131.9 (*C*(9')), 132.5 (*C*(8')), 133.1 (*C*(11')), 134.2 (*C*(4')), 135.6 (*C*(1')); *m/z* (ESI^+) 319 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{35}N_2O^+$ ($[M+H]^+$) requires 319.2744; found 319.2743. Data for **3**·2.0 TFA: $[\alpha]_D^{25}$ −7.8 (*c* 1.0 in MeOH).

(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*,*N*,*O*-Triacetyl-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C acetate] 65



Ac_2O (0.5 mL) was added to a stirred solution of **3** (10 mg, 31 μmol, >85% dp) in pyridine (1.0 mL) at rt and the resultant solution was stirred at rt for 1.5 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 25:1) gave **65** as a colourless oil (10 mg, 72%, >85% dp);[52] $[\alpha]_D^{25}$ +62.3 (*c* 1.0 in $CHCl_3$); {lit.[52] $[\alpha]_D^{22}$ +85 (*c* 0.98 in $CHCl_3$)}; ν_{max} 3288, 1741, 1635, 1542, 1428, 1373, 1236, 1040, 989; δ_H (500 MHz, MeOH-d_4)[23] 0.91 (3H, t, *J* 7.1, C(15')H_3), 1.29–2.19 (23H, m, C(3)H_2, C(5')H_2, C(6')H_2, C(7')H_2, C(12')H_2, C(13')H_2, C(14')H_2, C(O)*Me*×3), 2.93 (1H, app t, *J* 12.1, C(6)H_A), 3.40 (1H, app t, *J* 11.6, C(6)H_A), 3.75 (1H, app d, *J* 11.6, C(6)H_B), 3.94 (1H, app d, *J* 10.2, C(5)*H*), 4.01 (1H, app d, *J* 8.5, C(5)*H*), 4.44 (1H, app d, *J* 8.8, C(6)H_B), 4.63–4.68 (1H, m, C(2)*H*), 5.06–5.10 (1H, m, C(4)*H*), 5.28–5.32 (1H, m, C(2)*H*), 5.50–6.11 (6H, m, 6 of C(1')*H*, C(2')*H*, C(3')*H*, C(4')*H*, C(8')*H*, C(10')*H*, C(11')*H*, C(12')*H*);[55] δ_C (125 MHz, MeOH-d_4) 14.4 (*C*(15')), 21.4, 21.4, 21.5, 21.8 (C(O)*Me*×3), 30.4, 33.0, 33.2, 33.2, 33.5, 33.5, 34.4, 37.3 (*C*(3), *C*(5'), *C*(6'), *C*(7'), *C*(12'), *C*(13'), *C*(14')), 37.4, 42.6 (*C*(6)), 48.5 (*C*(5)), 48.9 (*C*(2)),[50] 49.6 (*C*(5)), 54.1 (*C*(2)), 70.3, 70.4 (*C*(4)), 131.0, 131.2, 131.3, 131.6, 131.9, 132.4, 132.6, 133.4, 135.6, 136.2 (*C*(1'), *C*(2'), *C*(3'), *C*(4'), *C*(8'), *C*(9'), *C*(10'), *C*(11')), 172.2, 172.4, 173.0, 173.2, 173.4 (*C*(O)Me×3); *m/z* (ESI^+) 467 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{26}H_{40}N_2NaO_4^+$ ($[M+Na]^+$) requires 467.2880; found 467.2878.

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

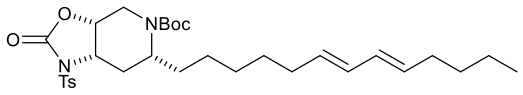


Step 1. Polymer-supported PPh_3 (100–200 mesh, 131 mg, 0.39 mmol) was added to a stirred solution of **141** (55 mg, 0.13 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) in THF/H_2O (10:1, 1.9 mL)

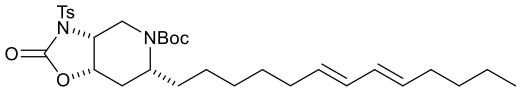
at rt and the resultant suspension was heated at 70 °C for 16 h, then allowed to cool to rt. The resultant suspension was filtered through through Celite® (eluent CH_2Cl_2/MeOH, 1:1) and concentrated *in vacuo*.

Step 2. HCl (1.25 M in MeOH, 2 mL) was added dropwise *via* syringe to the residue from the previous step at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 2 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 4:1:0.1) gave a fraction which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **4** as a white gum (28 mg, 73%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)], >95:5 er);[24,56] $[\alpha]_D^{25}$ −1.1 (*c* 1.0 in MeOH); {lit.[24] $[\alpha]_D^{25}$ +5.0 (*c* 0.26 MeOH)}; {lit.[57] $[\alpha]_D^{25}$ +6.0 (*c* 0.2 MeOH)}; {lit.[5] $[\alpha]_D^{25}$ +5.6 (*c* 0.42 MeOH)}; ν_{max} 3285, 3015, 2956, 2854, 1577, 1464, 985; δ_H (500 MHz, MeOH-d_4) 0.91 (3H, t, *J* 7.1, C(13')H_3), 1.08 (1H, app dd, *J* 12.5, 11.5, C(3)H_A), 1.29–1.45 (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), 1.96 (1H, ddd, *J* 12.5, 4.6, 2.4, C(3)H_B), 2.03–2.07 (4H, m, C(5')H_2, C(10')H_2), 2.32 (1H, dd, *J* 12.0, 11.0, C(6)H_A), 2.49–2.54 (2H, m, C(2)*H*, C(5)*H*), 3.05 (1H, dd, *J* 12.0, 4.6, C(6)H_B), 3.21 (1H, ddd, *J* 11.0, 9.3, 4.6, C(4)*H*), 5.50–5.56 (2H, m, C(6')*H*, C(9')*H*), 5.94–6.01 (2H, m, C(7')*H*, C(8')*H*); δ_C (125 MHz, MeOH-d_4) 14.4 (*C*(13')), 23.4 (*C*(12')), 27.1 (*C*(2')), 30.5 (*C*(3')), 30.6 (*C*(4')), 33.0 (*C*(11')), 33.5 (*C*(5')), 33.7 (*C*(10')), 37.3 (*C*(1')), 41.4 (*C*(3)), 51.9 (*C*(6)), 56.5 (*C*(5)), 56.8 (*C*(2)), 76.0 (*C*(4)), 132.0 (*C*(8')), 132.1 (*C*(7')), 133.0 (*C*(6')), 133.2 (*C*(9')); *m/z* (ESI$^+$) 295 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{35}N_2O^+$ ([M+H]$^+$) requires 295.2744; found 295.2743. Data for **4**·0.05 TFA: $[\alpha]_D^{25}$ +5.4 (*c* 1.0 in MeOH).

(2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 414 and (2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-(*N*-tosylamino)-*N*,*O*-carbonylpiperidine 186



414

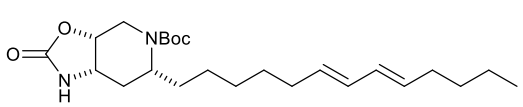


186

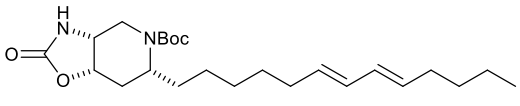
TBAI (196 mg, 0.53 mmol) was added to a stirred solution of **140** (200 mg, 0.53 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) and TsNCO (0.12 mL, 0.79 mmol) in PhMe (2.5 mL) at rt and the resultant mixture was heated at 100 °C for 16 h then cooled to rt. EtOAc (3 mL) and H_2O (3 mL) were added, and the aqueous layer was extracted with EtOAc (2 × 3 mL). The combined organics were washed with brine (15 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 5:1) gave a ~50:50 mixture of **414** and **186**, respectively, as a pale yellow oil (277 mg, 91%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]). Data for mixture: ν_{max} 1785, 1691, 1597, 1366, 1171; δ_H (400 MHz, $CDCl_3$)[51] 0.86 (6H, t, *J* 7.1, C(13')H_3×2), 1.20–1.39 (20H, m, C(2')H_2×2, C(3')H_2×2, C(4')H_2×2, C(11')H_2×2, C(12')H_2×2), 1.42 (9H, s, CMe_3), 1.45 (9H, s, CMe_3), 1.46–1.66 (5H, m, C(3)H_A, C(1')H_2×2), 1.70–1.78 (1H, m, C(3)H_A), 1.98–2.15 (9H, m, C(3)H_B, C(5')H_2×2, C(10')H_2×2), 2.41 (6H, s, Ar*Me*×2), 2.50–2.58 (1H, m, C(3)H_B), 2.87–3.03 (2H, m, C(6)H_A×2), 3.78–4.01 (2H, m, C(2)*H*×2), 4.33–4.39 (3H, m, C(4)*H*, C(5)*H*, C(6)H_B), 4.51–4.56 (1H, m, C(5)*H*), 4.59–4.74 (2H, m, C(4)*H*, C(6)H_B), 5.47–5.57 (4H, m, C(6')*H*×2, C(9')*H*×2), 5.92–6.01 (4H, m, C(7')*H*×2, C(8')*H*×2), 7.33 (4H, m, *Ar*×2), 7.91 (4H, m, *Ar*×2); δ_C (100 MHz, $CDCl_3$)[51] 13.8 (*C*(13')×2), 21.5 (Ar*Me*×2), 22.0, 22.1 (*C*(14')×2), 24.9, 25.2 (*C*(2')×2), 28.2 (CMe_3×2), 28.6, 28.8, 29.1 (*C*(3')×2, *C*(4')×2), *30**, 30.6 (*C*(3)×2), 31.3 (*C*(11')×2), 32.1, 32.2 (*C*(5')×2, *C*(10')×2), 33.3, 34.3 (*C*(1')×2), *39** (*C*(6)), *40**, *41** (*C*(6)), *49**, *49** (*C*(2)), *50** (*C*(2)), 53.8 (*C*(5)), 54.7 (*C*(4)), 70.3 (*C*(5)), 72.4 (*C*(4)), 80.3, 80.4 (*C*Me_3), 128.2, 128.3, 129.7, 129.7 (*Ar*×2), 130.1, 130.4 (*C*(7')×2, *C*(8')×2), 131.7, 132.3 (*C*(6')×2, *C*(9')×2), 134.4, 134.8 (*Ar*×2),

145.6 (*Ar*×2), 151.1, 151.5 (HN*C*O×2), *154** (N(1)*C*O×2); *m/z* (ESI$^+$) 597 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{46}N_2NaO_6S^+$ ([M+Na]$^+$) requires 597.2969; found 597.2970.

(2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4-amino-5-hydroxy-*N*,*O*-carbonylpiperidine 415 and (2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 212



415

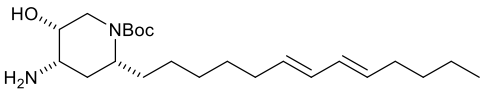


212

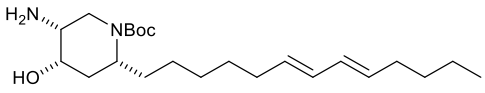
Na (52 mg, 2.26 mmol) was added to a stirred solution of naphthalene (347 mg, 2.71 mmol) in THF (6 mL) at rt. The resultant solution was stirred at rt for 16 h, then cooled to −78 °C. A solution of a ~50:50 mixture of **414** and **186** (260 mg, 0.45 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) in THF (3 mL) at −78 °C was added dropwise *via* syringe and the resultant solution was stirred for 30 min at −78 °C, then quenched with EtOH (2 mL). CH_2Cl_2 (2 mL) and satd aq $NaHCO_3$ (2 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organics were washed sequentially with H_2O (6 mL) and brine (6 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 5:1) gave a ~50:50 mixture of **415** and **212**, respectively, as a pale yellow oil (175 mg, 92%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]). Data for mixture: ν_{max} 3284, 1754, 1691; δ_H (400 MHz, $CDCl_3$) 0.88 (6H, t, *J* 7.1, C(13')H_3×2), 1.25–1.40 (20H, m, C(2')H_2×2, C(3')H_2×2, C(4')H_2×2, C(11')H_2×2, C(12')H_2×2), 1.44 (18H, s, CMe_3×2), 1.45–1.74 (5H, m, C(3)H_A, C(1')H_2×2), 1.80 (1H, app dt, *J* 14.0, 9.5, C(3)H_A), 2.01–2.10 (9H, m, C(3)H_B, C(5')H_2×2, C(10')H_2×2), 2.12–2.20 (1H, m, C(3)H_B), 2.78–2.91 (1H, m, C(6)H_A), 2.91–3.04 (1H, m, C(6)H_A), 3.66–4.01 (4H, m, C(2)*H*×2, C(4)*H*, C(5)*H*), 4.03–4.50 (2H, m, C(6)H_B×2), 4.63–4.76 (2H, m, C(4)*H*, C(5)*H*), 5.49–5.69 (4H, m, C(6')*H*×2, C(9')*H*×2), 5.91–6.01 (4H, m, C(7')*H*×2, C(8')*H*×2), 6.53 (2H, br s, N*H*×2);[51] δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')×2), 22.2 (*C*(12')×2), 25.1, 25.3 (*C*(2')×2), 28.3 (CMe_3×2), 28.9, 28.9, 29.3 (*C*(3')×2, *C*(4')×2), *30** (*C*(3)),

31.5 (*C*(11')×2), *32** (*C*(3)), 32.2, 32.4 (*C*(5')×2, *C*(10')×2), *34** (*C*(1')×2), *39**, *41**, *41** (*C*(6)×2), 49.7, *50** (*C*(2)×2, *C*(4), *C*(5)), 72.2 (*C*(5)), 74.0 (*C*(4)), 80.3, 80.3 (*C*Me$_3$×2), 130.2, 130.5 (*C*(7')×2, *C*(8')×2), 131.9, 132.5 (*C*(6')×2, *C*(10')×2), *155** (N(1)*C*O×2), *159** (HN*C*O×2);[51] *m/z* (ESI$^+$) 443 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{40}N_2NaO_4^+$ ([M+Na]$^+$) requires 443.2880; found 443.2879

(2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4-amino-5-hydroxypiperidine 416 and (2*R*,4*S*,5*R*,6'*E*,8'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine 213



416

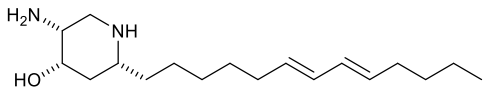


213

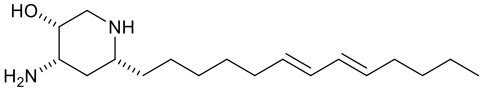
KOH (30% aq, 2.0 mL) was added dropwise *via* syringe to a stirred solution of a ~50:50 mixture of **415** and **212** (170 mg, 0.40 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) in MeOH (2 mL) at rt and the resultant solution was heated at 70 °C for 6 h, then allowed to cool to rt. CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent Et_2O/MeOH/35% aq NH_4OH,[6] 25:1:0.1) gave **416** as a colourless oil (59 mg, 37%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]); $[\alpha]_D^{25}$ −15.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3367, 3290, 1692, 1559; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(13')H_3), 1.24–1.39 (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, CMe_3), 1.45–1.53 (1H, m, C(1')H_A), 1.58–1.64 (1H, m, C(3)H_A), 1.70–1.81 (2H, m, C(3)H_B, C(1')H_B), 2.00–2.06 (4H, m, C(5')H_2, C(10')H_2), 2.85 (1H, dd, *J* 13.4, 10.0, C(6)H_A), 3.07–3.13 (1H, m, C(4)*H*), 3.67 (1H, app dt, *J* 9.2, 4.8, C(5)*H*), 3.97–4.01 (2H, m, C(2)*H*, C(6)H_B), 5.50–5.58 (2H, m, C(6')*H*, C(9')*H*), 5.93–6.01 (2H, m, C(7')*H*, C(8')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.2 (*C*(12')), 26.6 (*C*(2')), 28.4 (CMe_3), 29.0, 29.3 (*C*(3'), *C*(4')), 31.5 (*C*(11')), 32.2, 32.5 (*C*(5'), *C*(10')), 33.7, 33.8 (*C*(3), *C*(1')), 41.2 (*C*(6)), 48.5 (*C*(4)), 50.6 (*C*(2)), 66.8 (*C*(5)), 79.5 (*C*Me$_3$), 130.2, 130.4 (*C*(7'), *C*(8')), 132.0, 132.4 (*C*(6'), *C*(9')), 155.1 (N(1)*C*O); *m/z* (ESI$^+$) 395

([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{43}N_2O_3^+$ ([M+H]$^+$) requires 395.3268; found 395.3264. Further elution gave a ~25:75 mixture of **416** and **213** as a colourless oil (80 mg, 50%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]). Data for mixture: ν_{max} 3361, 3294, 1689, 1578; *m/z* (ESI$^+$) 395 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{43}N_2O_3^+$ ([M+H]$^+$) requires 395.3268; found 395.3262. Data for 213: δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.1, C(13')H_3), 1.21–1.38 (10H, m, C(2')H_2, C(3')H_2, C(4')H_2, C(11')H_2, C(12')H_2), 1.43 (9H, s, CMe_3), 1.50–1.59 (1H, m, C(1')H_A), 1.67–1.74 (1H, m, C(3)H_A), 1.83–1.92 (2H, m, C(3)H_B, C(1')H_B), 1.99–2.06 (4H, m, C(5')H_2, C(10')H_2), 2.79–2.80 (2H, m, C(5)*H*, C(6)H_A), 3.75–3.84 (2H, m, C(4)*H*, C(6)H_B), 4.04–4.10 (1H, m, C(2)*H*), 5.49–5.57 (2H, m, C(6')*H*, C(9')*H*), 5.92–6.00 (2H, m, C(7')*H*, C(8')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(13')), 22.2 (*C*(12')), 26.8 (*C*(2')), 28.4 (CMe_3), 29.0, 29.4 (*C*(3'), *C*(4')), 31.5 (*C*(11')), 32.2, 32.5 (*C*(5'), *C*(10')), 32.7 (*C*(1')), *34** (*C*(3)), *40** (*C*(6)), 49.1 (*C*(2)), 50.2 (*C*(5)), 67.3 (*C*(4)), 79.4 (*C*Me_3), 130.3, 130.3 (*C*(7'), *C*(8')), 132.2, 132.3 (*C*(6'), *C*(9')), 155.0 (N(1)*C*O).

(2*R*,4*S*,5*R*,6'*E*,8'*E*)-2-(Trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin E] 5 and (2*R*,4*S*,5*R*,6'*E*,8'*E*)-2-(Trideca-6',8'-dien-1'-yl)-4-amino-5-hydroxypiperidine 417



5

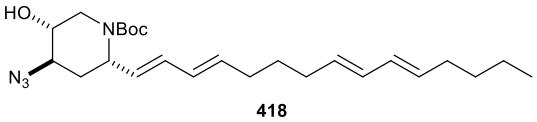


416

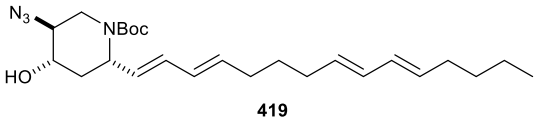
HCl (1.25 M in MeOH, 3 mL) was added dropwise *via* syringe to a ~25:75 mixture of **416** and **213** (75 mg, 0.40 mmol, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]) at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 3 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 8:1:0.1) gave a fraction which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted

with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **5** as a white gum (41 mg, 73%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]);[24] $[\alpha]_D^{25}$ −33.1 (*c* 1.0 in MeOH); {lit.[58] $[\alpha]_D^{25}$ −34.5 (*c* 1.0 in MeOH)}; ν_{max} 3292, 3015, 2924, 2854, 1577, 1458, 985; δ_H (500 MHz, MeOH-d_4) 0.91 (3H, t, *J* 7.1, C(13')H_3), 1.22 (1H, app q, *J* 12.0, C(3)H_A), 1.29–1.48 (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), 1.68 (1H, app d, *J* 12.2, C(3)H_B), 2.04–2.08 (4H, m, C(5')H_2, C(10')H_2), 2.43–2.46 (1H, m, C(2)*H*), 2.73 (1H, dd, *J* 13.2, 1.7, C(6)H_A), 2.87–2.90 (1H, m, C(5)*H*), 2.98 (1H, dd, *J* 13.2, 1.9, C(6)H_B), 3.67 (1H, ddd, *J* 11.8, 4.3, 4.1, C(4)*H*), 5.50–5.56 (2H, m, C(6')*H*, C(9')*H*), 5.95–6.01 (2H, m, C(7')*H*, C(8')*H*); δ_C (125 MHz, MeOH-d_4) 14.5 (*C*(13')), 23.4 (*C*(12')), 26.9 (*C*(2')), 30.5 (*C*(3')), 30.6 (*C*(4')), 33.0 (*C*(11')), 33.5 (*C*(5')), 33.7 (*C*(10')), 35.6 (*C*(3)), 37.4 (*C*(1')), 50.4 (*C*(6)), 51.4 (*C*(5)), 56.5 (*C*(2)), 71.0 (*C*(4)), 132.0 (*C*(8')), 132.1 (*C*(7')), 133.0 (*C*(6')), 133.2 (*C*(9')); *m/z* (ESI$^+$) 295 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{35}N_2O^+$ ([M+H]$^+$) requires 295.2744; found 295.2746. Further elution gave a fraction which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **417** as a white gum (10 mg, 18%, 83:17 dr [(6'*E*,8'*E*):(6'*Z*,8'*E*)]); $[\alpha]_D^{25}$ −41.1 (*c* 1.0 in MeOH); ν_{max} 3288, 3015, 2924, 2854, 1572, 1463, 985; δ_H (400 MHz, MeOH-d_4) 0.91 (3H, t, *J* 7.1, C(13')H_3), 1.17 (1H, app q, *J* 12.1, C(3)H_A), 1.29–1.50 (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), 1.65 (1H, app dt, *J* 12.6, 3.2, C(3)H_B), 2.03–2.08 (4H, m, C(5')H_2, C(10')H_2), 2.42–2.50 (1H, m, C(2)*H*), 2.68 (2H, m, C(4)*H*, C(6)H_A), 3.01 (1H, dd, *J* 13.7, 2.7, C(6)H_B), 3.60–3.63 (1H, m, C(5)*H*), 5.50–5.57 (2H, m, C(6')*H*, C(9')*H*), 5.94–6.01 (2H, m, C(7')*H*, C(8')*H*); δ_C (100 MHz, MeOH-d_4) 14.4 (*C*(3')), 23.4 (*C*(12')), 26.9 (*C*(2')), 30.5 (*C*(3')), 30.6 (*C*(4')), 33.0 (*C*(11')), 33.5 (*C*(5')), 33.7 (*C*(10')), 37.0 (*C*(3)), 37.6 (*C*(1')), 52.5 (*C*(4)), 52.5 (*C*(6)), 56.7 (*C*(2)), 68.8 (*C*(5)), 132.0 (*C*(8')), 132.1 (*C*(7')), 133.0 (*C*(6')), 133.2 (*C*(9')); *m/z* (ESI$^+$) 295 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{35}N_2O^+$ ([M+H]$^+$) requires 295.2744; found 295.2743.

(2*S*,4*R*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-azido-5-hydroxypiperidine 418 and (2*S*,4*S*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-azidopiperidine 419



418

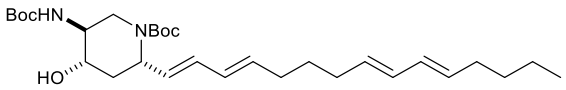


419

NH_4Cl (148 mg, 2.76 mmol) and NaN_3 (179 mg, 2.76 mmol) were added sequentially to a stirred solution of **386** (185 mg, >85% dp) in DMSO (1.8 mL) at rt and the resultant solution was heated at 80 °C for 16 h, then allowed to cool to rt. H_2O (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organics were washed with H_2O (3 × 15 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give a ~25:75 mixture of **418** and **419**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 4:1) gave **418** as a colourless oil (48 mg, 23%, >85% dp); $[\alpha]_D^{25}$ +0.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3420, 2105, 1697, 1672; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')H_3), 1.28–1.39 (4H, m, C(13')H_2, C(14')H_2), 1.46 (9H, s, CMe_3), 1.47–1.53 (2H, m, C(6')H_2), 1.70 (1H, app td, *J* 12.7, 5.7, C(3)H_A), 2.04–2.12 (7H, m, C(3)H_B, C(5')H_2, C(7')H_2, C(12')H_2), 2.76 (1H, dd, *J* 13.0, 10.3, C(6)H_A), 2.82 (1H, br s, O*H*), 3.43–3.52 (2H, m, C(4)*H*, C(5)*H*), 4.17 (1H, app d, *J* 12.0, C(6)H_B), 4.87–4.99 (1H, m, C(2)*H*), 5.42–5.49 (1H, m, C(1')*H*), 5.51–5.74 (3H, m, C(4')*H*, C(8')*H*, C(11')*H*), 5.96–6.08 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 22.2 (*C*(14')), 28.3 (CMe_3), 28.8 (*C*(6')), 31.5 (*C*(13')), 32.0, 32.0, 32.2 (*C*(5'), *C*(7'), *C*(12')), *33** (*C*(3)), *44** (*C*(6)), *51** (*C*(2)), 61.7 (*C*(4)), 71.1 (*C*(5)), 80.5 (*C*Me_3), 127.4 (*C*(1')), 129.3, 130.2, 130.8 (*C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.5 (*C*(4'), *C*(8'), *C*(11')), 132.3 (*C*(2'), *C*(3'), *C*(9'), *C*(10')), 132.7, 135.4 (*C*(4'), *C*(8'), *C*(11')), 154.6 (N(1)*C*O); *m/z* (ESI^+) 467 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{25}H_{40}N_4NaO_3^+$ ($[M+Na]^+$) requires 467.2993; found 467.2991. Further elution gave **419** as a colourless oil (118 mg, 58%, >85% dp); $[\alpha]_D^{25}$ +7.9 (*c* 1.0 in $CHCl_3$); ν_{max} 3440, 2109, 1696, 1667; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')H_3), 1.27–1.40 (4H, m, C(13')H_2, C(14')H_2), 1.43–1.50 (2H, m, C(6')H_2), 1.48 (9H, s, CMe_3), 1.75 (1H, app d, *J* 14.7, C(3)H_A), 2.03–2.10 (6H, m, C(5')H_2, C(7')H_2, C(12')H_2),

2.12–2.20 (1H, m, C(3)H_B), 2.27 (1H, br s, O*H*), 3.47 (1H, dd, *J* 14.7, 2.4, C(6)H_A), 3.55 (1H, app d, *J* 2.7, C(5)*H*), 3.86–3.91 (1H, m, C(4)*H*), 4.06 (1H, app d, *J* 14.7, C(6)H_B), 4.75–4.81 (1H, m, C(2)*H*), 5.50–5.70 (3H, m, C(4')*H*, C(8')*H*, C(11')*H*), 5.73–5.80 (1H, m, C(1')*H*), 5.96–6.08 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 22.2 (*C*(14')), 28.3 (C*Me*$_3$), 28.8 (*C*(6')), 31.5 (*C*(13')), 31.9 (*C*(3)), 32.0, 32.0, 32.2 (*C*(5'), *C*(7'), *C*(12')), 38.0 (*C*(6)), 50.1 (*C*(2)), 60.1 (*C*(5)), 67.1 (*C*(4)), 80.4 (*C*Me$_3$), 129.5 (*C*(2'), *C*(3'), *C*(9'), *C*(10')), 130.0 (*C*(1')), 130.2, 130.7, 130.7 (*C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.6, 132.6, 134.9 (*C*(4'), *C*(8'), *C*(11')), 155.0 (N(1)*C*O); *m/z* (ESI$^+$) 467 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{40}N_4NaO_3^+$ ([M+Na]$^+$) requires 467.2993; found 467.2991.

(2*S*,4*S*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-[*N*-(*tert*-butoxycarbonyl)amino]piperidine 421

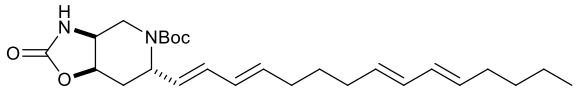


Step 1. Polymer-supported PPh_3 (100–200 mesh, 72 mg, 0.22 mmol) was added to a stirred solution of **419** (32 mg, 72 μmol, >85% dp) in THF/H_2O (10:1, 1 mL) at rt and the resultant suspension was heated at 70 °C for 16 h, then allowed to cool to rt. The resultant suspension was filtered through through Celite® (eluent CH_2Cl_2/MeOH, 1:1) and concentrated *in vacuo*.

Step 2. Boc_2O (17 mg, 79 μmol) and Et_3N (11 μL, 79 μmol) were added sequentially to a stirred solution of the residue from the previous step in CH_2Cl_2 (1 mL) at rt and the resultant solution was stirred at rt for 16 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave **421** as a colourless oil (33 mg, 88%, >85% dp); $[\alpha]_D^{25}$ −24.2 (*c* 1.0 in $CHCl_3$); ν_{max} 3447, 1695; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.1, C(15')H_3), 1.25–1.39 (6H, m, C(6')H_2, C(13')H_2, C(14')H_2), 1.43 (9H, s, C*Me*$_3$), 1.46 (9H, s, C*Me*$_3$), 1.70 (1H, app dt, *J* 14.4, 5.1, C(3)H_A), 2.02–2.09 (7H, m, C(3)H_B, C(5')H_2, C(7')H_2, C(12')H_2), 3.18 (1H, br s, O*H*), 3.41 (1H, dd, *J* 14.4, 3.4, C(6)H_A), 3.55–3.62 (1H, m, C(5)*H*), 3.80 (1H, app d, *J* 14.4, C(6)H_B), 3.86–3.91 (1H, m, C(4)*H*), 4.61 (1H, app d, *J* 4.6, C(2)*H*), 5.03 (1H, d, *J* 6.1, N*H*), 5.49–5.66 (3H, m, C(4')*H*, C(8')*H*, C(11')*H*), 5.75 (1H, dd, *J*

14.4, 6.1, C(1')*H*), 5.95–6.06 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (*C*(15')), 22.2 (*C*(14')), 28.3, 28.4 (C*Me*$_3$, C*Me*$_3$), 28.9, 31.5, 32.0, 32.0, 32.0, 32.2 (*C*(3), *C*(5'), *C*(6'), *C*(7'), *C*(12'), *C*(13')), 39.6 (*C*(6)), 51.6 (*C*(2)), 52.5 (*C*(5)), 68.8 (*C*(4)), 79.9, 80.3 (*C*Me$_3$, *C*Me$_3$), 129.8, 129.9, 130.2, 130.6, 130.7 (*C*(1'), *C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.6, 132.6, 134.5 (*C*(4'), *C*(8'), *C*(11')), 155.8, 156.1 (N(1)*C*O, NH*C*O); *m/z* (ESI$^+$) 541 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{50}N_2NaO_5^+$ ([M+Na]$^+$) requires 541.3612; found 541.3610.

(2*S*,4*R*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*(1)-(*tert*-Butoxycarbonyl)-2-(pentadeca-1',3',8',10'-tetraen-1'-yl)-4-hydroxy-5-amino-*N*,*O*-carbonylpiperidine 96

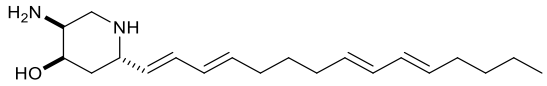


Step 1. Et_3N (75 µL, 0.54 mmol) was added dropwise *via* syringe to a stirred solution of **421** (70 mg, 0.14 mmol, >85% dp) and MsCl (21 µL, 0.27 mmol) in CH_2Cl_2 (1 mL) at 0 °C and the resultant solution was allowed to warm to rt over 16 h. H_2O (1 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organics were dried and concentrated *in vacuo*.

Step 2. Pyridine (0.5 mL) was added dropwise *via* syringe to the residue from the previous step and the resultant solution was heated at 115 °C for 16 h then cooled to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 3:1) gave **96** as a colourless oil (58 mg, 97%, >85% dp):[46] $[\alpha]_D^{25}$ −19.4 (*c* 1.0 in $CHCl_3$); {lit.[46] $[\alpha]_D^{11}$ +10.1 (*c* 1.5 in $CHCl_3$)};[59] ν_{max} 3295, 1747, 1687;[20] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.1, C(15')*H*$_3$), 1.26–1.51 (6H, m, C(6')*H*$_2$, C(13')*H*$_2$, C(14')*H*$_2$), 1.43 (9H, s, C*Me*$_3$), 1.68 (1H, app t, *J* 13.3, C(3)H_A), 2.03–2.11 (6H, m, C(5')*H*$_2$, C(7')*H*$_2$, C(12')*H*$_2$), 2.26 (1H, app dt, *J* 15.0, 4.5, C(3)H_B), 2.99 (1H, app d, *J* 15.2, C(6)H_A), 3.96 (1H, app d, *J* 9.0, C(5)*H*), 4.04 (1H, app d, *J* 13.2, C(6)H_B), 4.47–4.57 (1H, m, C(2)*H*), 4.91 (1H, app d, *J* 9.0, C(4)*H*), 5.45 (1H, dd, *J* 14.3, 6.2, C(1')*H*), 5.50–5.60 (2H, m, C(8')*H*, C(11')*H*), 5.66 (1H, dt, *J* 14.2, 6.9, C(4')*H*), 5.96–6.10 (4H, m, C(2')*H*, C(3')*H*, C(9')*H*, C(10')*H*); δ_C (100 MHz, $CDCl_3$)

13.9 (*C*(15')), 22.2 (*C*(14')), 28.3 (C*Me*$_3$), 28.9 (*C*(6')), *30** (*C*(3)), 31.5 (*C*(13')), 32.0, 32.0, 32.2 (*C*(5'), *C*(7'), *C*(12')), *41** (*C*(6)), *50** (*C*(2)), 51.2 (*C*(5)), 72.6 (*C*(4)), 80.6 (*C*Me$_3$), 129.5 (*C*(1')), 129.6, 130.2, 130.6, 130.8 (*C*(2'), *C*(3'), *C*(9'), *C*(10')), 131.6, 132.7 (*C*(8'), *C*(11')), 135.0 (*C*(4')), 156.0 (N(1)*C*O), 158.6 (HN*C*O).[19]

(2*S*,4*R*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin F] 6

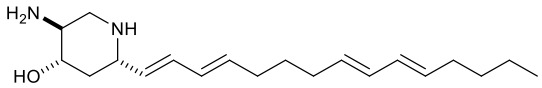


Step 1. KOH (30% aq, 2.0 mL) was added dropwise *via* syringe to a stirred solution of **96** (20 mg, 45 μmol, >85% dp) in MeOH (2 mL) at rt and the resultant solution was heated at 70 °C for 6 h, then allowed to cool to rt. CH_2Cl_2 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*.

Step 2. HCl (1.25 M in MeOH, 3 mL) was added dropwise *via* syringe to the residue from the previous step at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 3 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 5:1:0.1) gave a fraction which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **6** as a white gum (10 mg, 70%, >85% dp);[24] $[\alpha]_D^{25}$ −5.7 (*c* 0.4 in MeOH); {lit.[24] $[\alpha]_D^{25}$ −13.9 (*c* 0.42 MeOH)}; {lit.[46] $[\alpha]_D^{11}$ −12.6 (*c* 0.2 MeOH)}; ν_{max} 3285, 3016, 2925, 2856, 1576, 1457, 987; δ_H (500 MHz, MeOH-d_4) 0.91 (3H, t, *J* 7.1, C(15')H_3), 1.29–1.39 (4H, m, C(13')H_2, C(14')H_2), 1.46 (2H, app quin, *J* 7.3, C(6')H_2), 1.50 (1H, ddd, *J* 13.9, 11.8, 2.5, C(3)H_A), 1.85 (1H, app dt, *J* 13.9, 3.3, C(3)H_B), 2.03–2.10 (6H,

m, C(5')H_2, C(7')H_2, C(12')H_2), 2.69 (1H, ddd, *J* 10.3, 5.0, 2.6, C(5)*H*), 2.74 (1H, dd, *J* 11.3, 10.3, C(6)H_A), 2.78 (1H, dd, *J* 11.3, 5.0, C(6)H_B), 3.43–3.48 (1H, m, C(2)*H*), 3.91–3.93 (1H, m, C(4)*H*), 5.47–5.57 (3H, m, C(1')*H*, C(8')*H*, C(11')*H*), 5.66 (1H, dt, *J* 15.1, 6.9, C(4')*H*), 5.95–6.03 (3H, m, C(3')*H*, C(9')*H*, C(10')*H*), 6.16 (1H, dd, *J* 15.3, 10.4, C(2')*H*); δ_C (125 MHz, MeOH-d_4) 14.4 (*C*(15')), 23.4 (*C*(14')), 30.4 (*C*(6')), 33.0 (*C*(13')), 33.2, 33.2 (*C*(7'), *C*(12')), 33.5 (*C*(5')), 40.5 (*C*(3)), 48.4 (*C*(6)), 52.0 (*C*(5)), 52.5 (*C*(2)), 68.9 (*C*(4)), 131.7 (*C*(3')), 131.9 (*C*(10')), 132.2 (*C*(9')), 132.4 (*C*(2')), 132.7 (*C*(8')), 133.3 (*C*(11')), 133.9 (*C*(1')), 135.4 (*C*(4')); *m/z* (ESI$^+$) 319 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{35}N_2O^+$ ([M+H]$^+$) requires 319.2744; found 319.2743. Data for **6**·0.05 TFA: $[\alpha]_D^{25}$ −14.0 (*c* 0.4 in MeOH).

(2*S*,4*S*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin Z] 147



Step 1. Polymer-supported PPh_3 (100–200 mesh, 135 mg, 0.41 mmol) was added to a stirred solution of **419** (60 mg, 0.14 mmol, >85% dp) in THF/H_2O (10:1, 2 mL) at rt and the resultant suspension was heated at 70 °C for 16 h, then allowed to cool to rt. The resultant suspension was filtered through through Celite® (eluent CH_2Cl_2/MeOH, 1:1) and concentrated *in vacuo*.

Step 2. HCl (1.25 M in MeOH, 3 mL) was added dropwise *via* syringe to the residue from the previous step at rt and the resultant solution was heated at 70 °C for 3 h, then allowed to cool to rt. $CHCl_3$/^{i}PrOH (v/v 3:1, 3 mL) and aq KOH (2.00 M, 3 mL) were added and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (v/v 3:1, 3 × 3 mL). The combined organics were washed with brine (10 mL), then dried (over Na_2SO_4) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH,[6] 5:1:0.1) gave a fraction which was concentrated *in vacuo*. $CHCl_3$ (1 mL) and aq KOH (2.00 M, 1 mL) were added and the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL). The combined organics were dried (over Na_2SO_4) and concentrated *in vacuo* to give **147** as a white gum (40 mg, 93%, >85% dp); $[\alpha]_D^{25}$ −0.7 (*c* 1.0 in MeOH); ν_{max} 3281, 3016, 2956, 2855, 1594, 1457, 986; δ_H (500 MHz,

MeOH-d_4) 0.91 (3H, t, *J* 7.1, C(15')H_3), 1.26–1.38 (5H, m, C(3)H_A, C(13')H_2, C(14')H_2), 1.47 (2H, app quin, *J* 7.4, C(6')H_2), 1.97 (1H, ddd, *J* 12.6, 4.6, 2.6, C(3)H_B), 2.03–2.11 (6H, m, C(5')H_2, C(7')H_2, C(12')H_2), 2.41 (1H, dd, *J* 12.0, 11.0, C(6)H_A), 2.58 (1H, ddd, *J* 11.0, 9.5, 4.5, C(5)*H*), 3.10 (1H, dd, *J* 12.0, 4.5, C(6)H_B), 3.18–3.21 (1H, m, C(2)*H*), 3.28–3.33 (1H, m, C(4)*H*), 5.50–5.57 (3H, m, C(1')*H*, C(8')*H*, C(11')*H*), 5.69 (1H, dt, *J* 15.1, 7.0, C(4')*H*), 5.95–6.04 (3H, m, C(3')*H*, C(9')*H*, C(10')*H*), 6.18 (1H, dd, *J* 15.3, 10.4, C(2')*H*); δ_C (125 MHz, MeOH-d_4) 14.4 (*C*(15')), 23.4 (*C*(14')), 30.4 (*C*(6')), 33.0 (*C*(13')), 33.2, 33.2 (*C*(7'), *C*(12')), 33.5 (*C*(5')), 41.5 (*C*(3)), 51.2 (*C*(6)), 56.0 (*C*(5)), 58.5 (*C*(2)), 74.7 (*C*(4)), 131.5 (*C*(3')), 131.9 (*C*(10')), 132.4, 132.4 (*C*(8'), *C*(9')), 132.6 (*C*(2')), 133.0 (*C*(11')), 133.3 (*C*(1')), 135.8 (*C*(4')); *m/z* (ESI$^+$) 319 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{35}N_2O^+$ ([M+H]$^+$) requires 319.2744; found 319.2744.

6.5 References and notes

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[7] The specific rotation value for this compound was erroneously given positive value in the original report; see (ref 5).
[8] A melting point was not disclosed in the literature report.
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[54] The specific rotation corresponds to a sample with 80:20 er.
[55] The olefinic region under-integrated by approximately two protons. A similar phenomenon was noted upon analysis of the spectra provided by Kobayashi *et al*. for their synthetic sample. The sample in this study was subjected to NMR analysis at −40 °C in an attempt to encourage sharpening of broad peaks and enable observation of the remaining olefinic protons, however the sample found to still be highly rotameric at −40 °C. Following this, a pure shift NMR experiment was conducted in attempt to reduce the number of signals present, however the resultant spectra remained highly rotameric, and thus no conclusions could be made.
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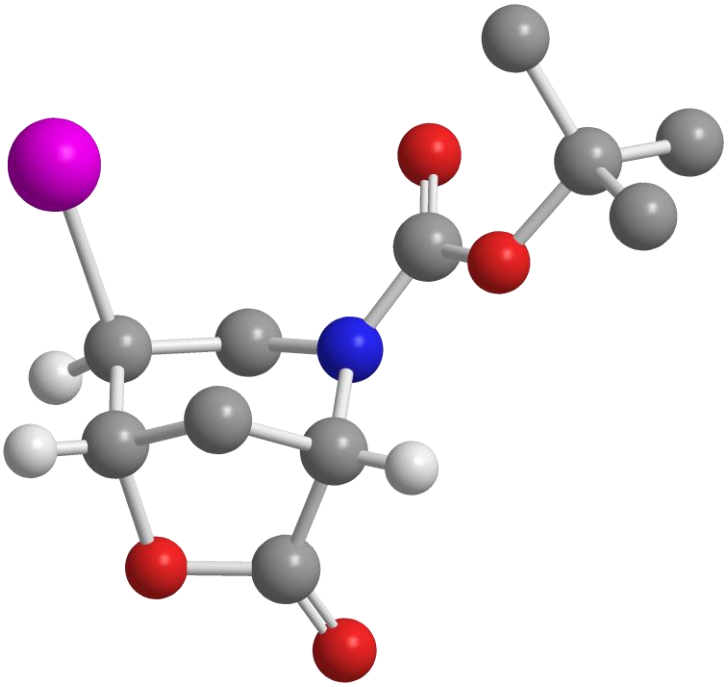
[59] The ^{1}H NMR spectroscopic data for **96** were in agreement with literature values, however both the sign and magnitude of the specific rotation value for the synthetic sample of **96** in this study did not match the literature value and the origin of this discrepancy is unknown. Despite this disparity, the assignment of the configuration of **96** was secured following elaboration to pseudodistomin F **6**.

Appendix 1:X-Ray Crystal Structure Data

X-Ray crystal structure data for (1*S*,4*S*,5*S*)-349

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 349

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-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 **349** [$C_{11}H_{16}INO_4$]: M = 353.16, orthrohombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.43857(8) Å, b = 10.79679(18) Å, c = 20.0560(3) Å, V = 1394.21(4) Å^3, Z = 4, μ = 18.100 mm^{-1}, colourless block, crystal dimensions = 0.24 × 0.25 × 0.31 mm^3. A total of 2875 unique reflections were measured for 4 < θ < 76 and 2425 reflections were used in the refinement. The final parameters were wR_2 = 0.104 and R_1 = 0.041 [I>–3.0σ(I)], with Flack enantiopole = –0.003(9).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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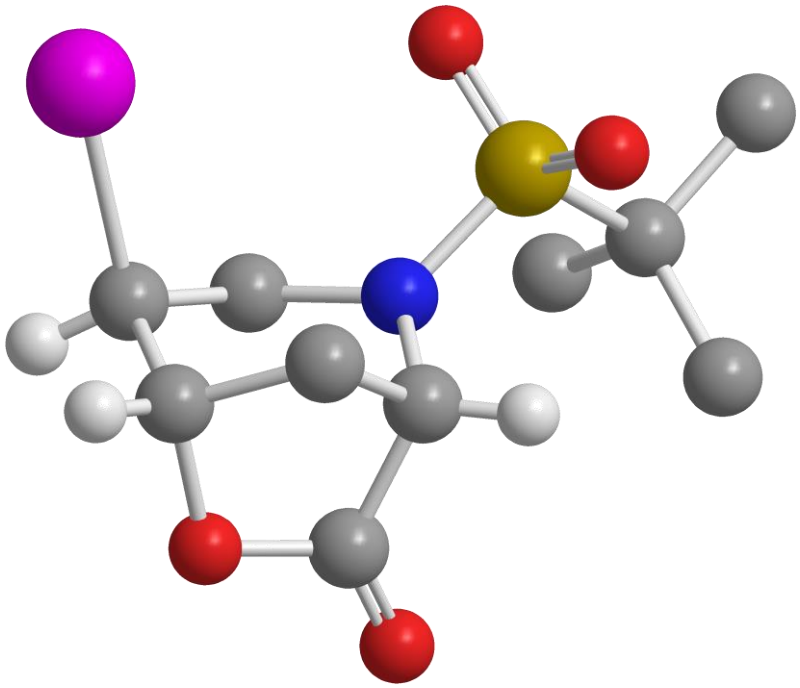
1 Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

2 Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,4*S*,5*S*)-363

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 363

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-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.[3]

X-ray crystal structure data for **363** [$C_{10}H_{16}INO_4S$]: M = 373.21, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.63589(19) Å, b = 10.13619(16) Å, c = 20.6103(4) Å, V = 1386.31(5) Å^3, Z = 4, μ = 19.611 mm^{-1}, colourless block, crystal dimensions = 0.13 × 0.14 × 0.30 mm^3. A total of 2628 unique reflections were measured for 4 < θ < 77 and 2616 reflections were used in the refinement. The final parameters were wR_2 = 0.080 and R_1 = 0.030 [I>–3.0σ(I)], with Flack enantiopole = 0.005(7).[4] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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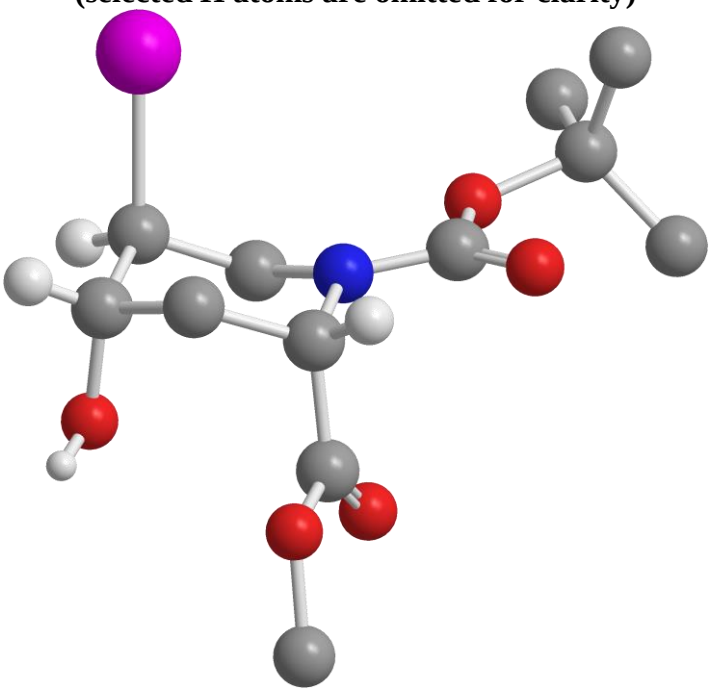
3 Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

4 Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (2*S*,4*S*,5*S*)-367

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 367

Data were collected using an Oxford Diffraction SuperNova 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.[5]

X-ray crystal structure data for **367** [$C_{12}H_{20}INO_5$]: M = 385.20, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.4793(3) Å, b = 11.9670(4) Å, c = 12.1098(4) Å, V = 1518.62(8) Å^3, Z = 4, μ = 0.2.124 mm^{-1}, colourless block, crystal dimensions = 0.20 × 0.21 × 0.21 mm^3. A total of 4038 unique reflections were measured for 3 < θ < 30 and 3650 reflections were used in the refinement. The final parameters were wR_2 = 0.036 and R_1 = 0.021 [I>–3.0σ(I)], with Flack enantiopole = –0.029(13).[6] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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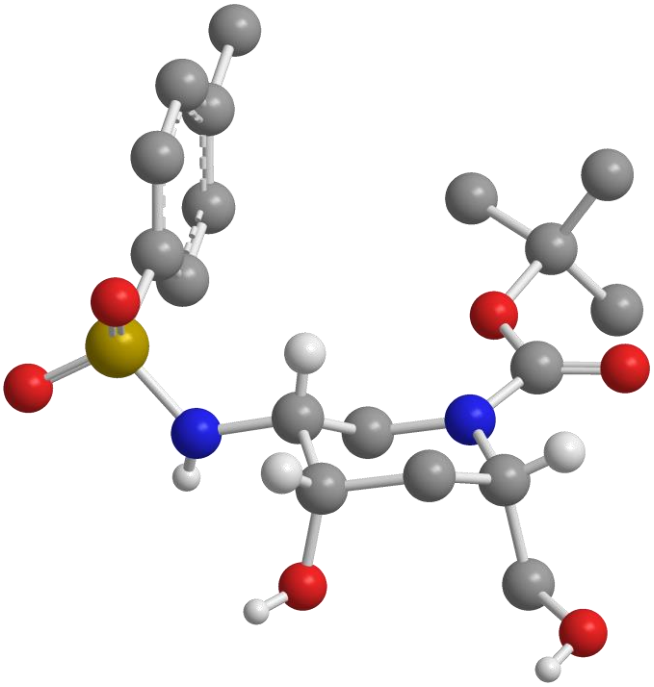
5 Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

6 Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (2*S*,4*S*,5*R*)-374

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 374

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-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.[7]

X-ray crystal structure data for **374** [$C_{18}H_{28}N_2O_6S$]: M = 400.50, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.5687(2) Å, b = 10.8079(2) Å, c = 19.6354(5) Å, V = 2030.65(9) Å^3, Z = 4, μ = 1.792 mm^{-1}, colourless prism, crystal dimensions = 0.02 × 0.04 × 0.17 mm^3. A total of 3806 unique reflections were measured for 5 < θ < 76 and 3609 reflections were used in the refinement. The final parameters were wR_2 = 0.077 and R_1 = 0.034 [I>–3.0σ(I)], with Flack enantiopole = –0.008(17).[8] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

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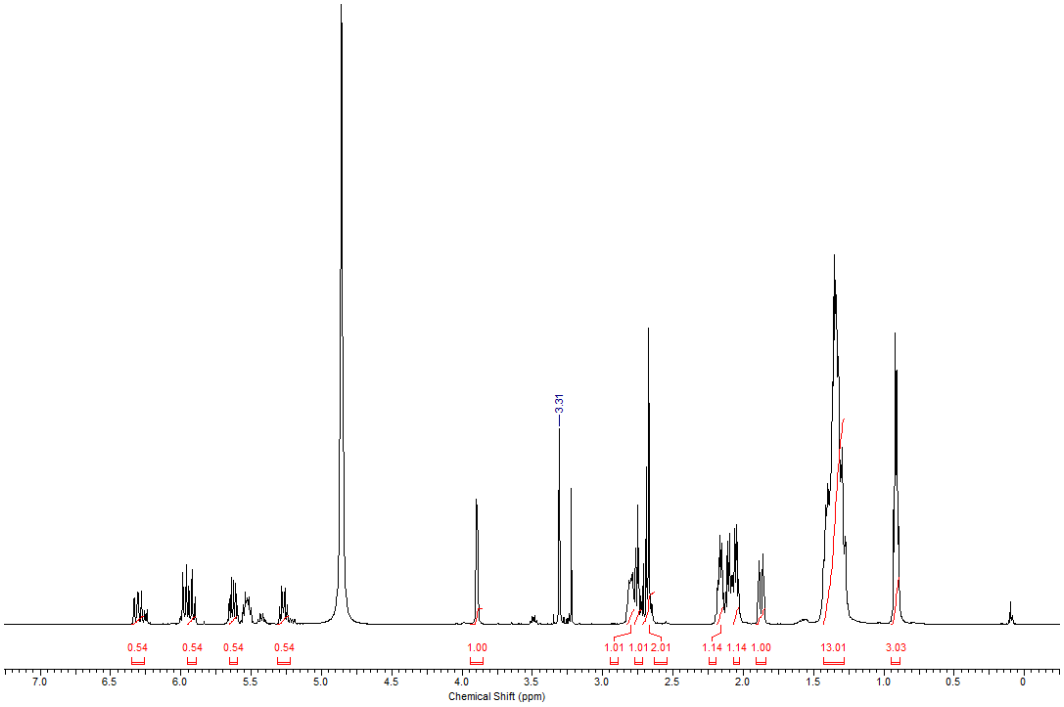
7 Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

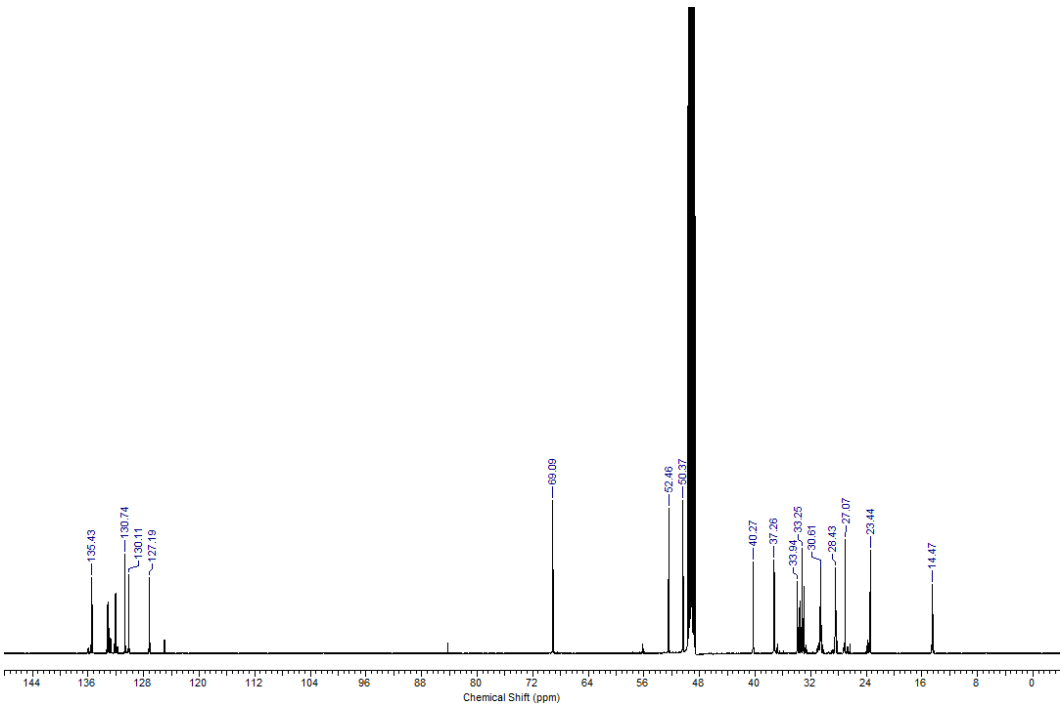
8 Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

Appendix 2: NMR Data

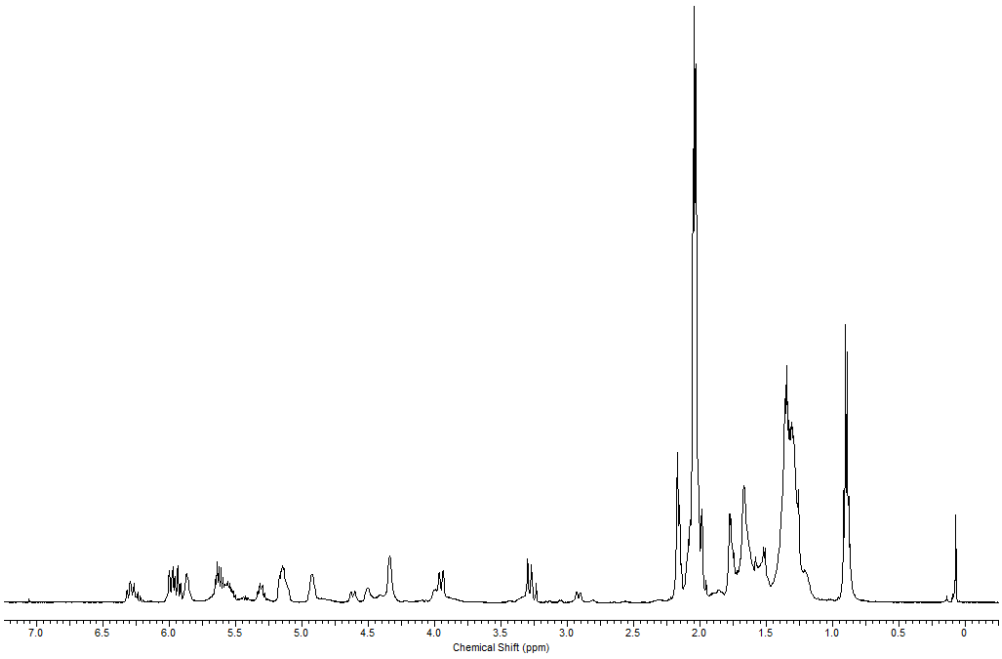
(2*R*,4*R*,5*S*,6′*E*,8′*Z*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin A] 1, 54:30:8:8 dr (500 MHz, ^{1}H, MeOH-d_4)



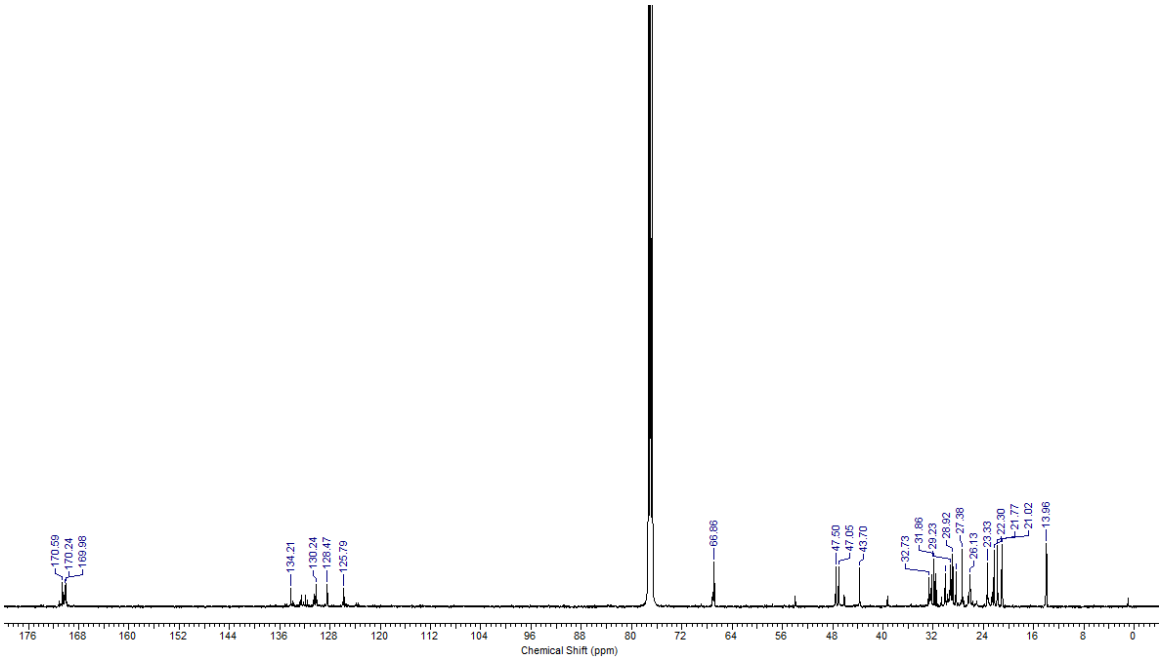
(2*R*,4*R*,5*S*,6′*E*,8′*Z*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin A] 1, 54:30:8:8 dr (125 MHz, ^{13}C, MeOH-d_4)



(2*R*,4*R*,5*S*,6′*E*,8′*Z*)-*N*,*N*,*O*-Triacetyl-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin A acetate] 9, 54:30:8:8 dr (500 MHz, ^{1}H, $CDCl_3$)[9]

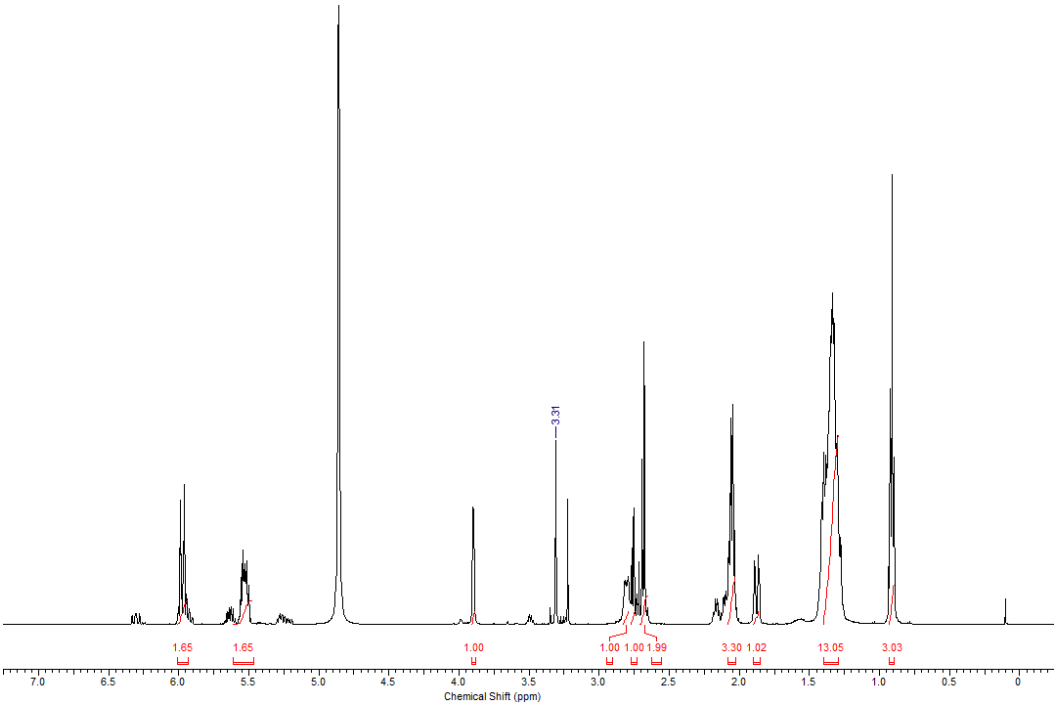


(2*R*,4*R*,5*S*,6′*E*,8′*Z*)-*N*,*N*,*O*-Triacetyl-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin A acetate] 9, 54:30:8:8 dr (125 MHz, ^{13}C, $CDCl_3$)[10]

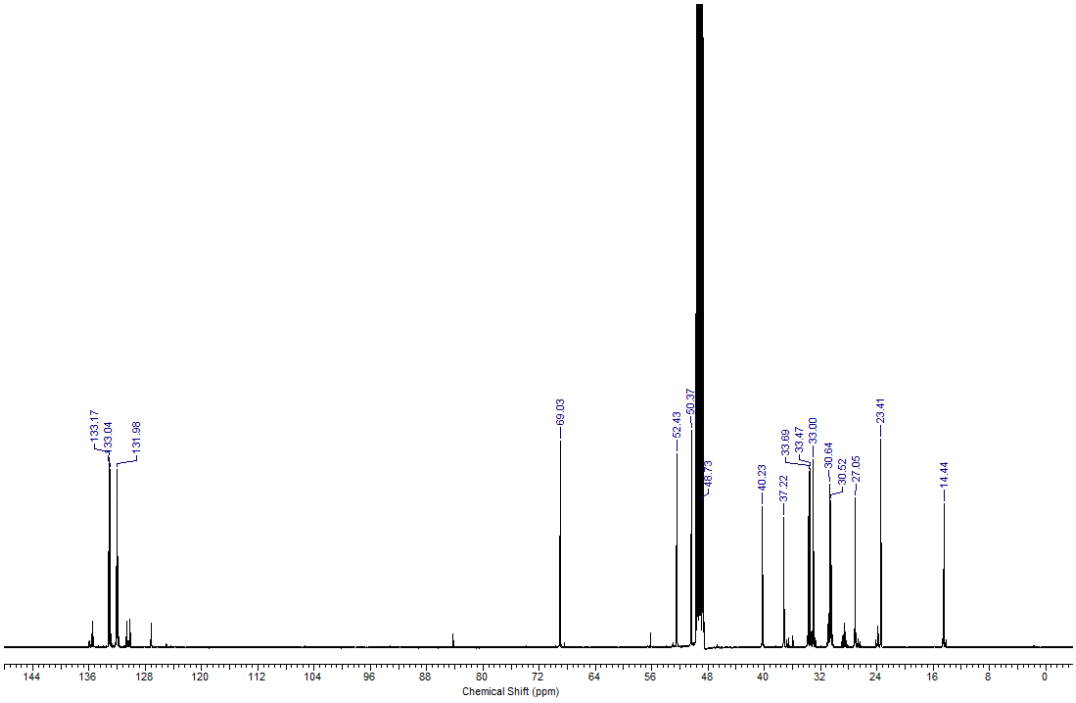


[9] Due to the rotameric nature of the spectrum, integrations were not applied.
[10] Only the resonances for the major rotamer are highlighted.

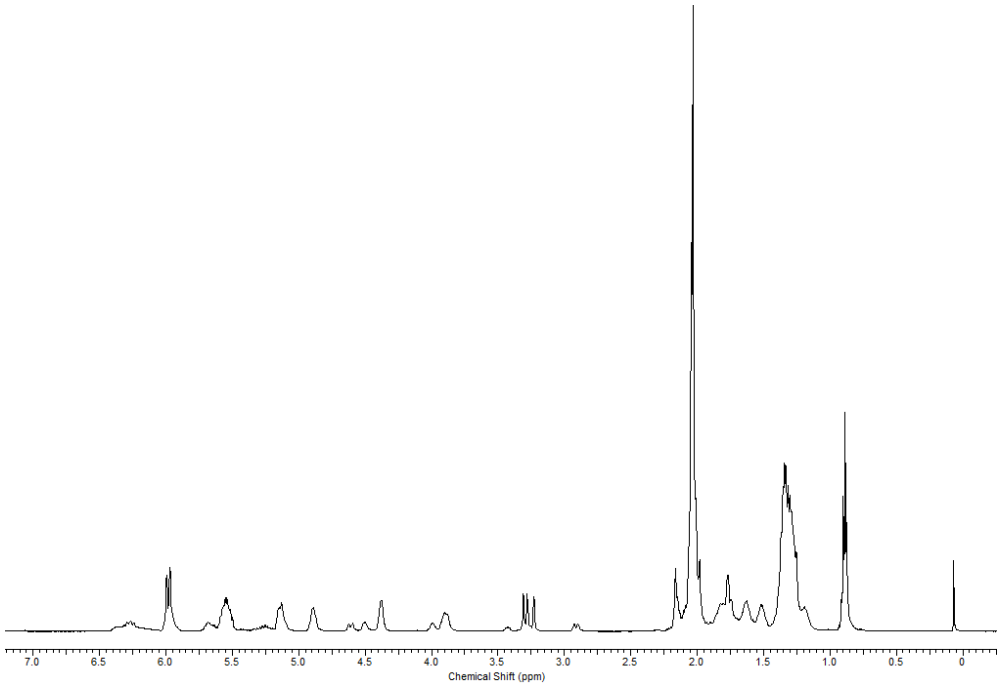
(2*R*,4*R*,5*S*,6′*E*,8′*E*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin B] 2, 83:17 dr (500 MHz, ^{1}H, MeOH-d_4)



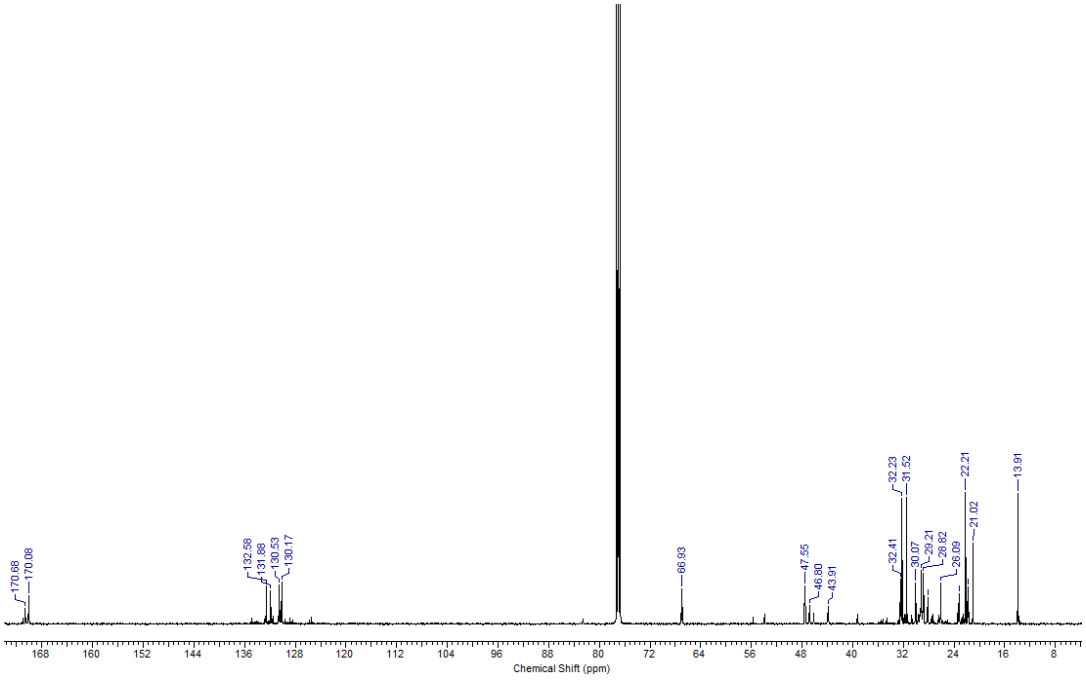
(2*R*,4*R*,5*S*,6′*E*,8′*E*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin B] 2, 83:17 dr (125 MHz, ^{13}C, MeOH-d_4)



(2*R*,4*R*,5*S*,6′*E*,8′*E*)-*N*,*N*,*O*-Triacetyl-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin B acetate] 10, 83:17 dr (500 MHz, ^{1}H, $CDCl_3$)[11]



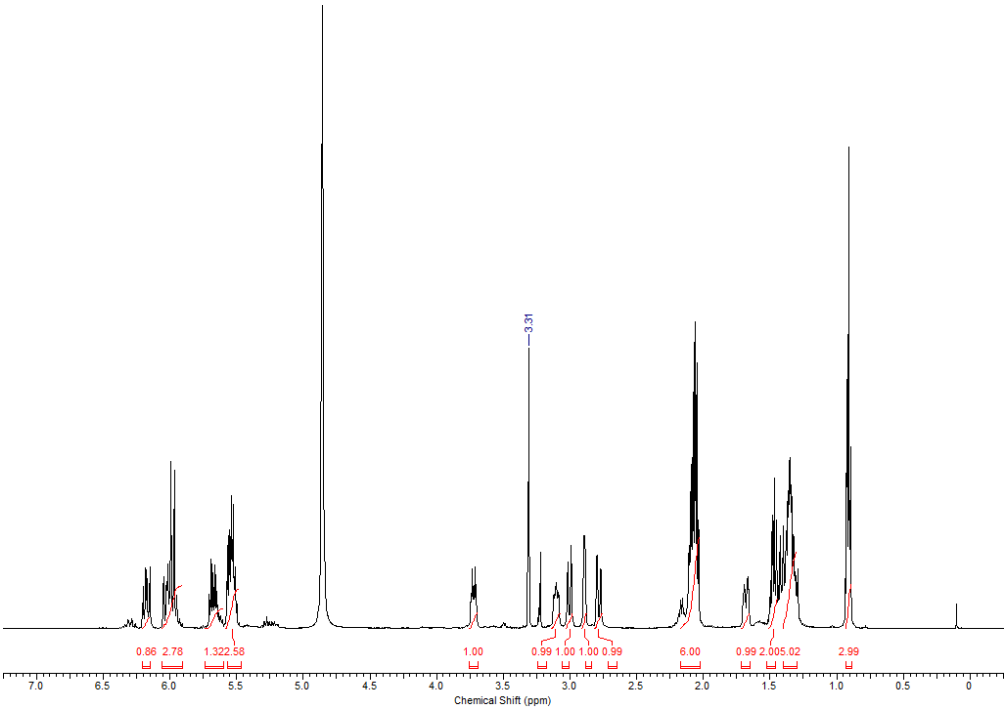
(2*R*,4*R*,5*S*,6′*E*,8′*E*)-*N*,*N*,*O*-Triacetyl-2-(trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin B acetate] 10, 83:17 dr (125 MHz, ^{13}C, $CDCl_3$)[12]



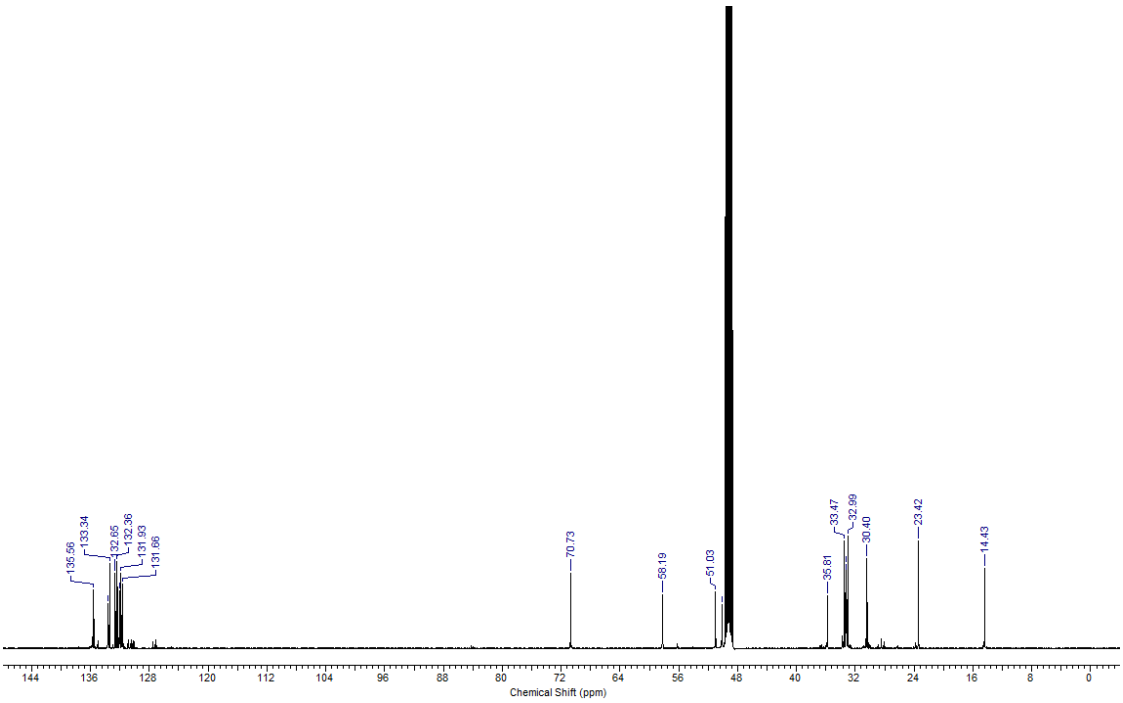
[11] Due to the rotameric nature of the spectrum, integrations were not applied.

[12] Only the resonances for the major rotamer are highlighted.

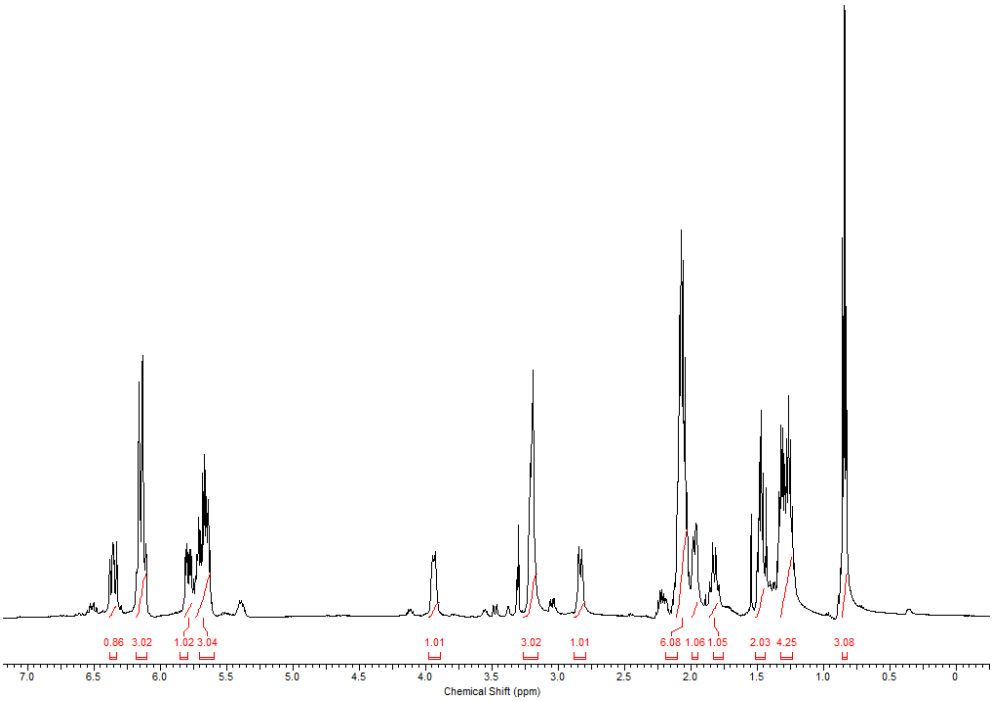
(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C] 3, >85% dp (500 MHz, ^{1}H, MeOH-d_4)



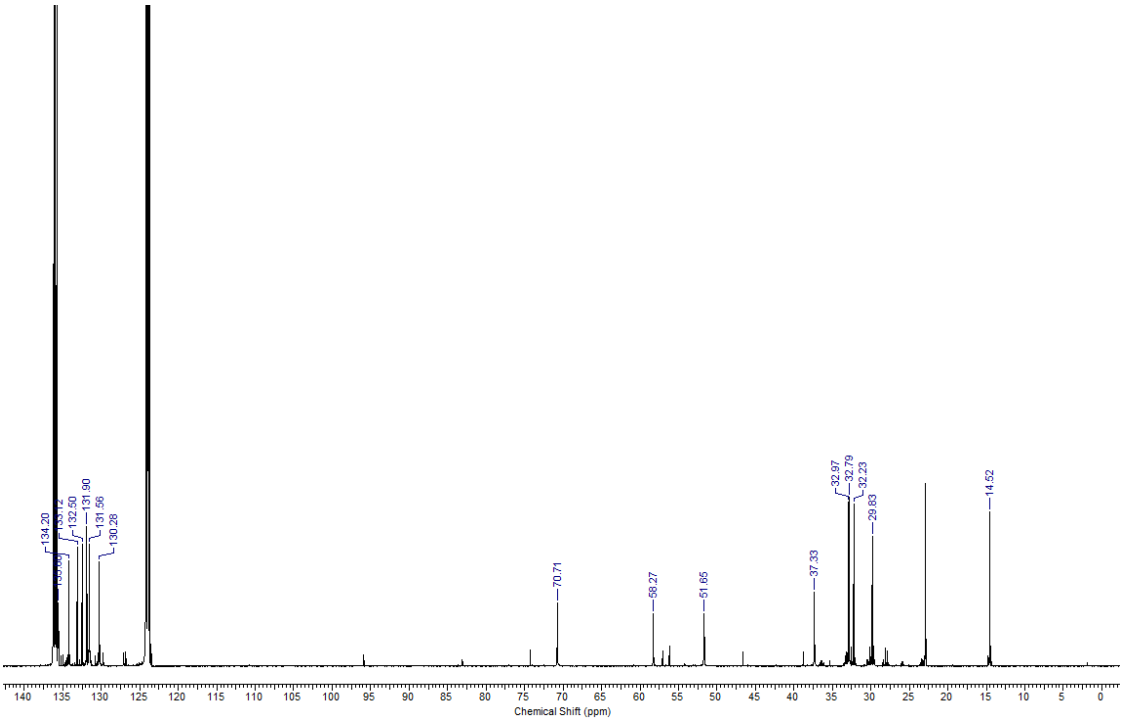
(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C] 3, >85% dp (125 MHz, ^{13}C, MeOH-d_4)



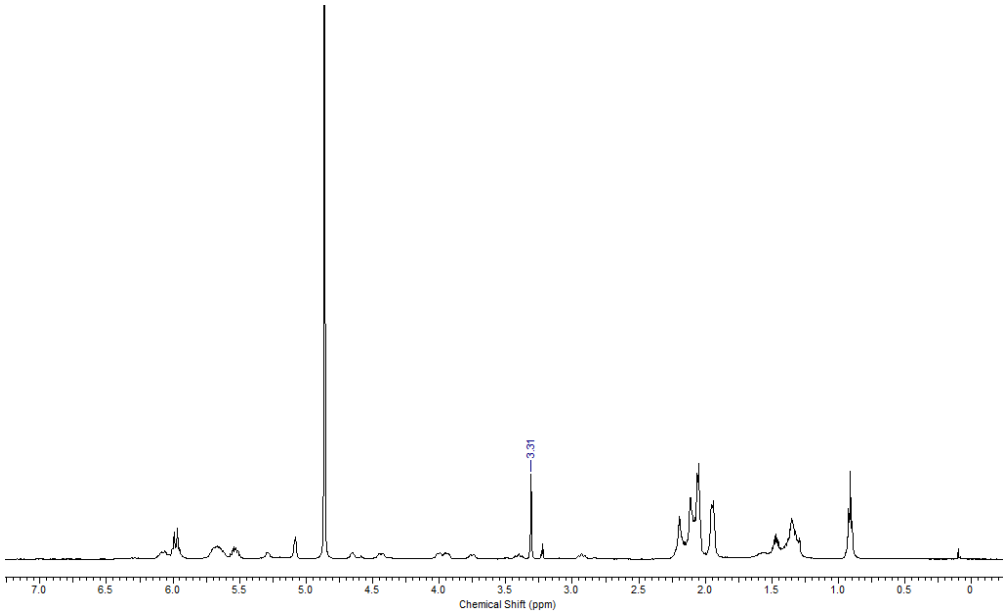
(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C] 3, >85% dp (500 MHz, ^{1}H, C_5D_5N)



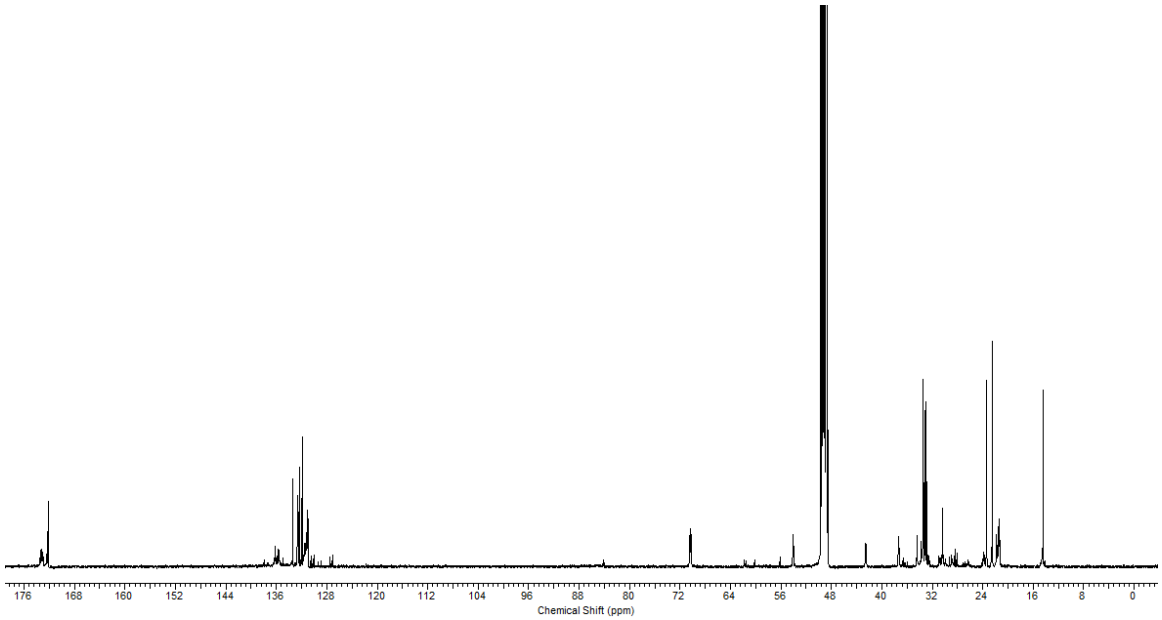
(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C] 3, >85% dp (125 MHz, ^{13}C, C_5D_5N)



(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*,*N*,*O*-Triacetyl-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C acetate] 65, >85% dp (500 MHz, ^{1}H, MeOH-d_4)[13]



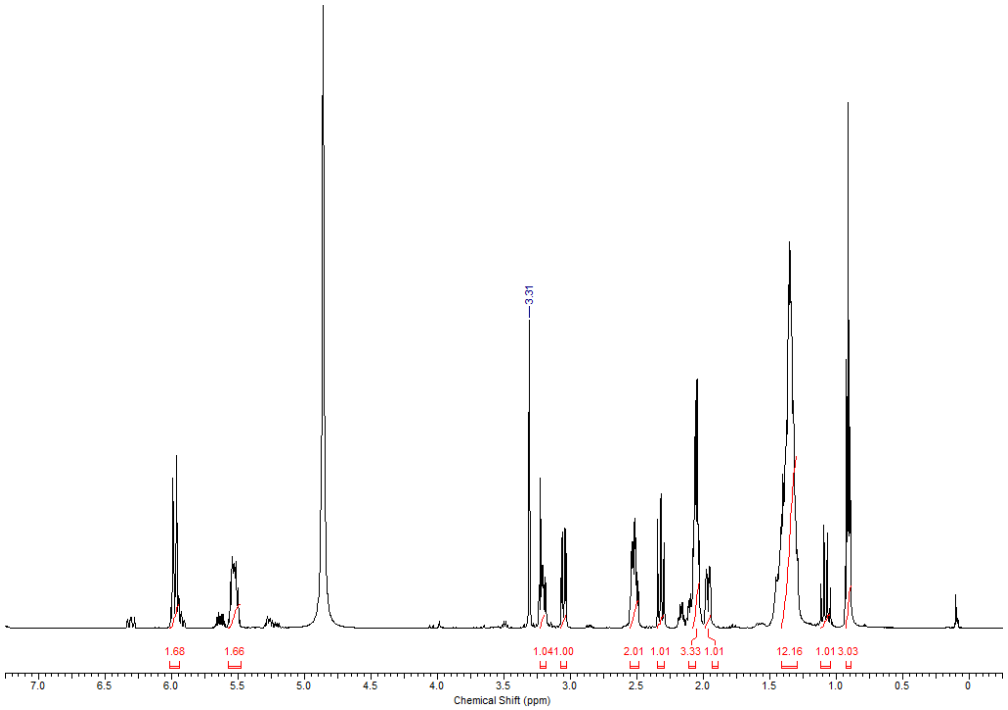
(2*S*,4*S*,5*R*,1'*E*,3'*E*,8'*E*,10'*E*)-*N*,*N*,*O*-Triacetyl-2-(pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin C acetate] 65, >85% dp (125 MHz, ^{13}C, MeOH-d_4)[14]



[13] Due to the rotameric nature of the spectrum, integrations were not applied.
[14] Due to the rotameric nature of the spectrum, resonances were not highlighted.

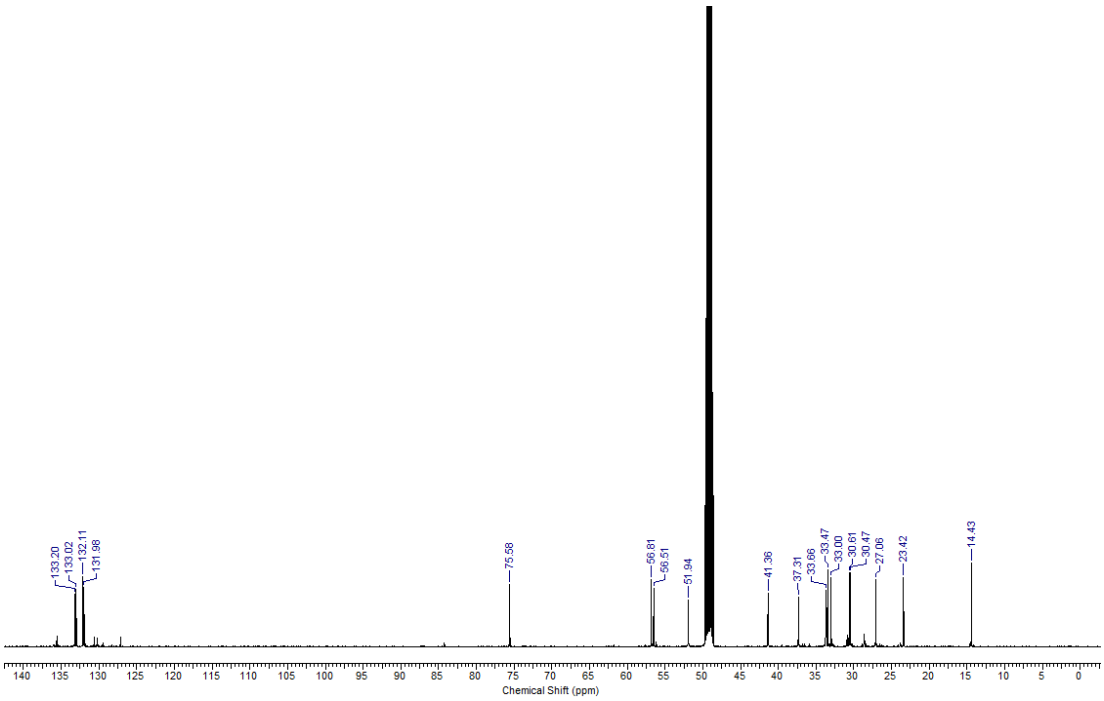
(2*R*,4*S*,5*S*,6'*E*,8'*E*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine

[Pseudodistomin D] 4, 83:17 dr (500 MHz, ^{1}H, MeOH-d_4)



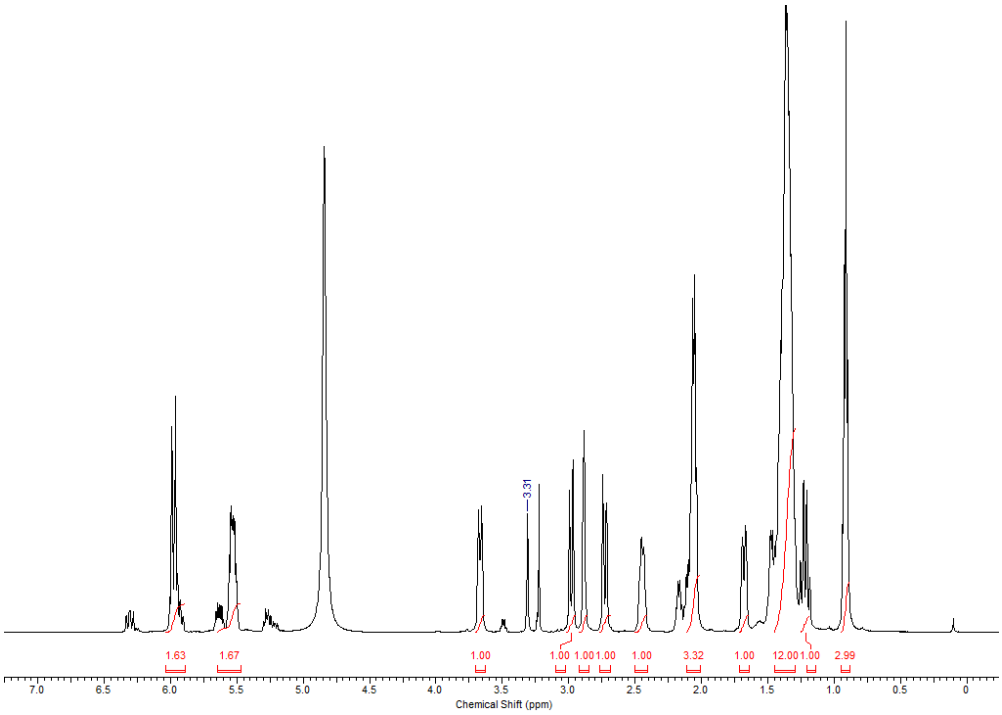
(2*R*,4*S*,5*S*,6'*E*,8'*E*)-2-(Trideca-6′,8′-dien-1′-yl)-4-hydroxy-5-aminopiperidine

[Pseudodistomin D] 4, 83:17 dr (125 MHz, ^{13}C, MeOH-d_4)



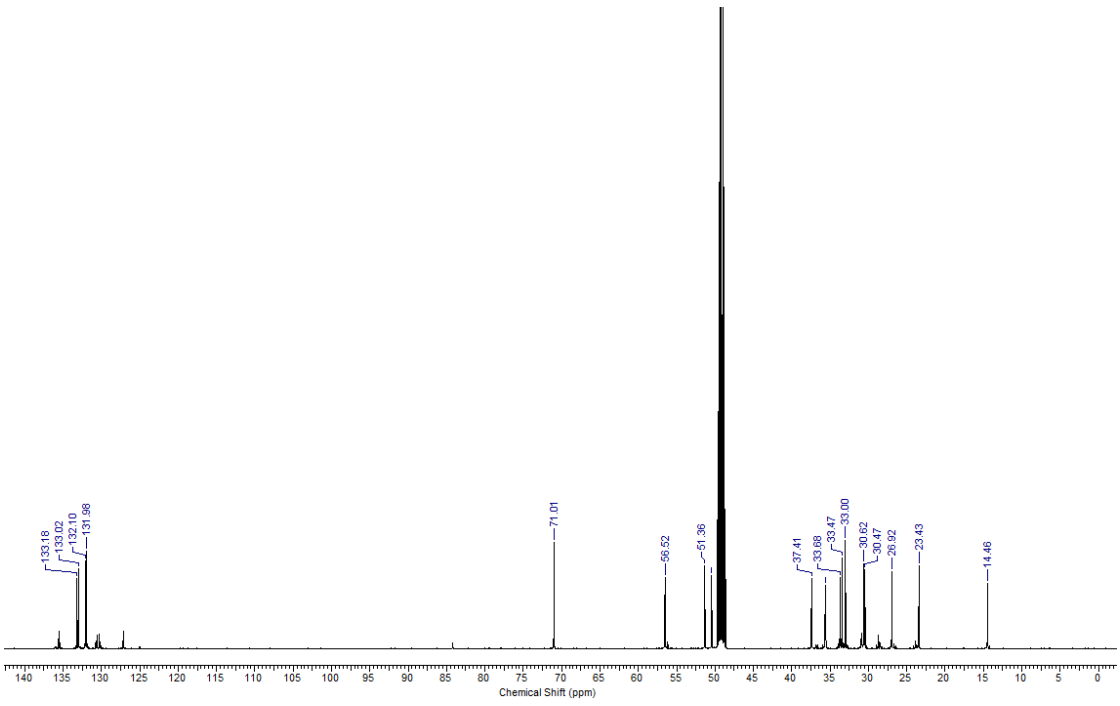
(2*R*,4*S*,5*R*,6'*E*,8'*E*)-2-(Trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine

[Pseudodistomin E] 5, 83:17 dr (500 MHz, ^{1}H, MeOH-*d*$_4$)

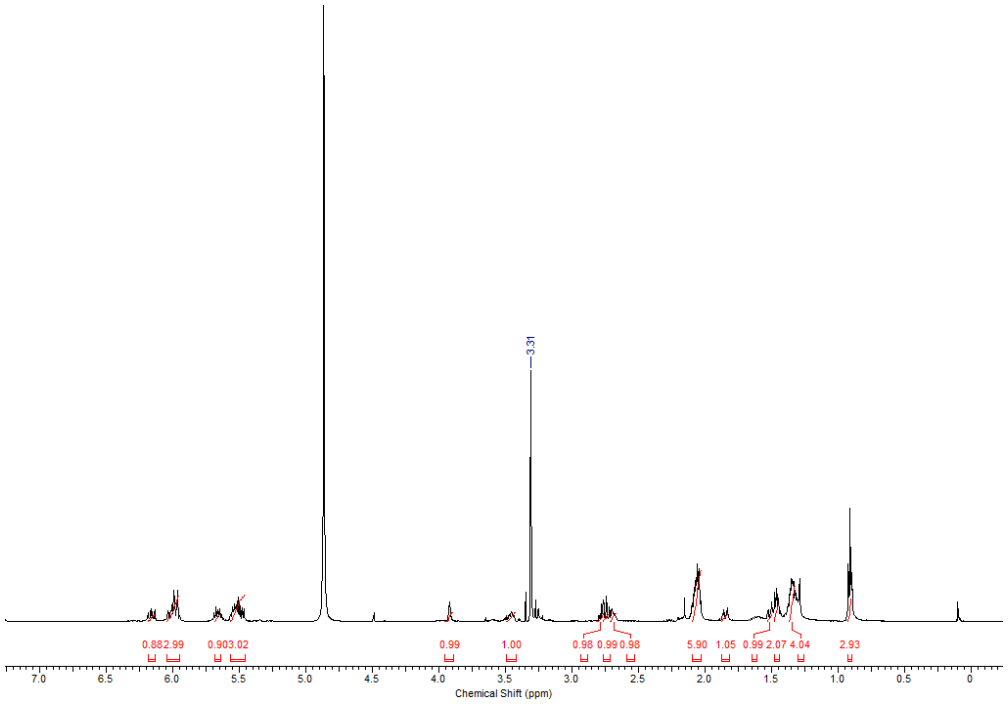


(2*R*,4*S*,5*R*,6'*E*,8'*E*)-2-(Trideca-6',8'-dien-1'-yl)-4-hydroxy-5-aminopiperidine

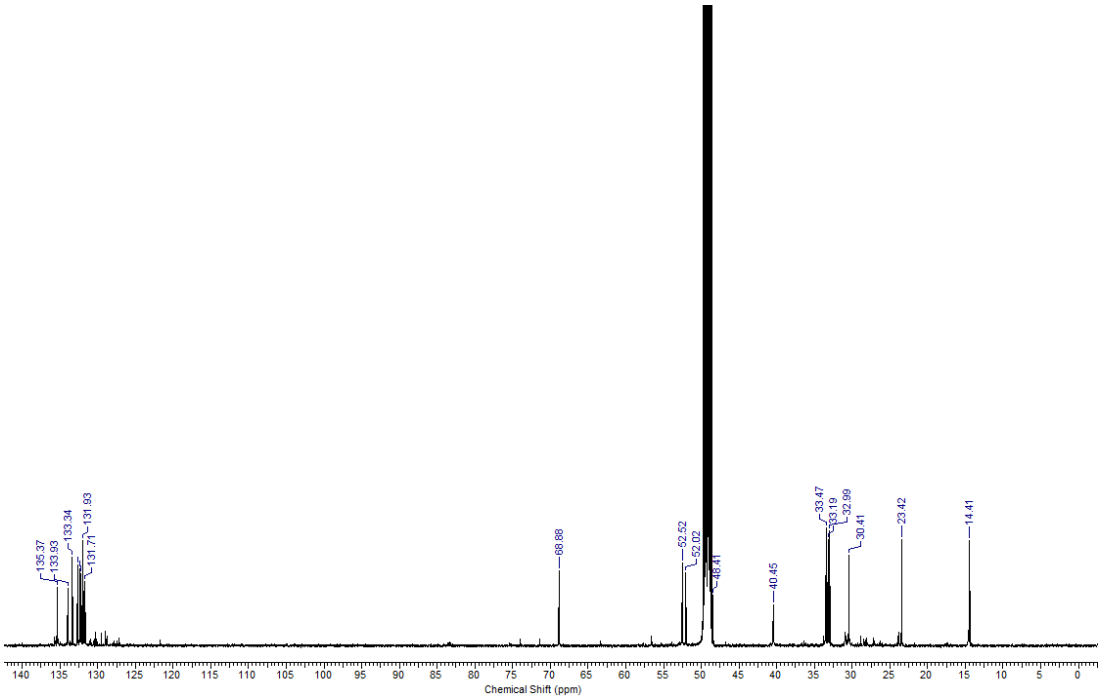
[Pseudodistomin E] 5, 83:17 dr (125 MHz, ^{13}C, MeOH-*d*$_4$)



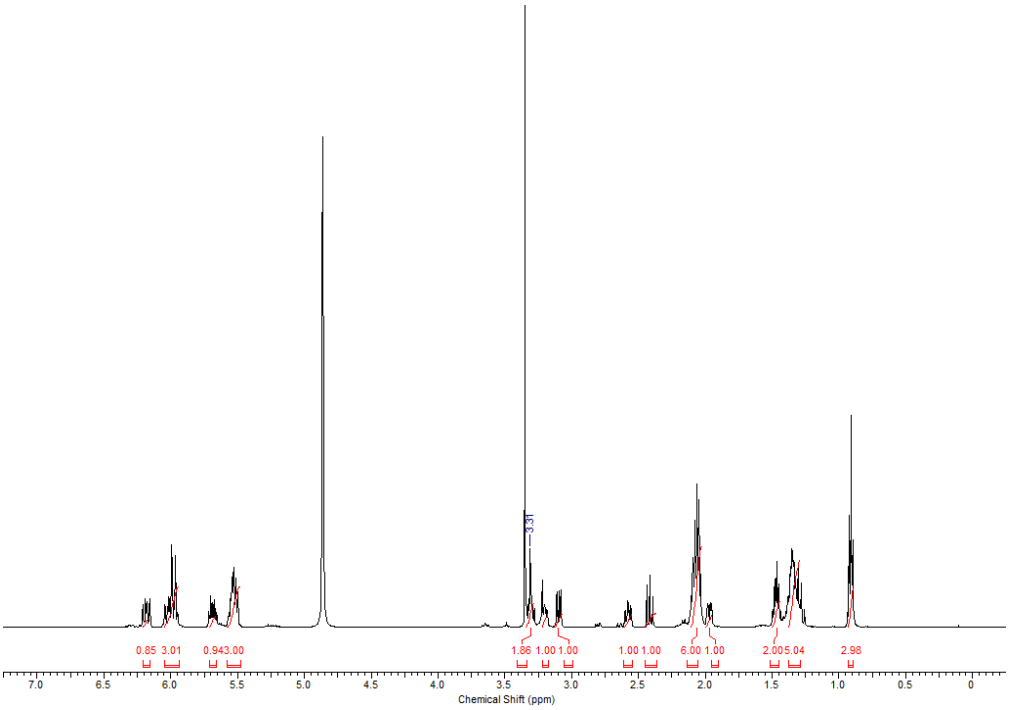
(2*S*,4*R*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin F] 6, >85% dp (500 MHz, ^{1}H, MeOH-*d*$_4$)



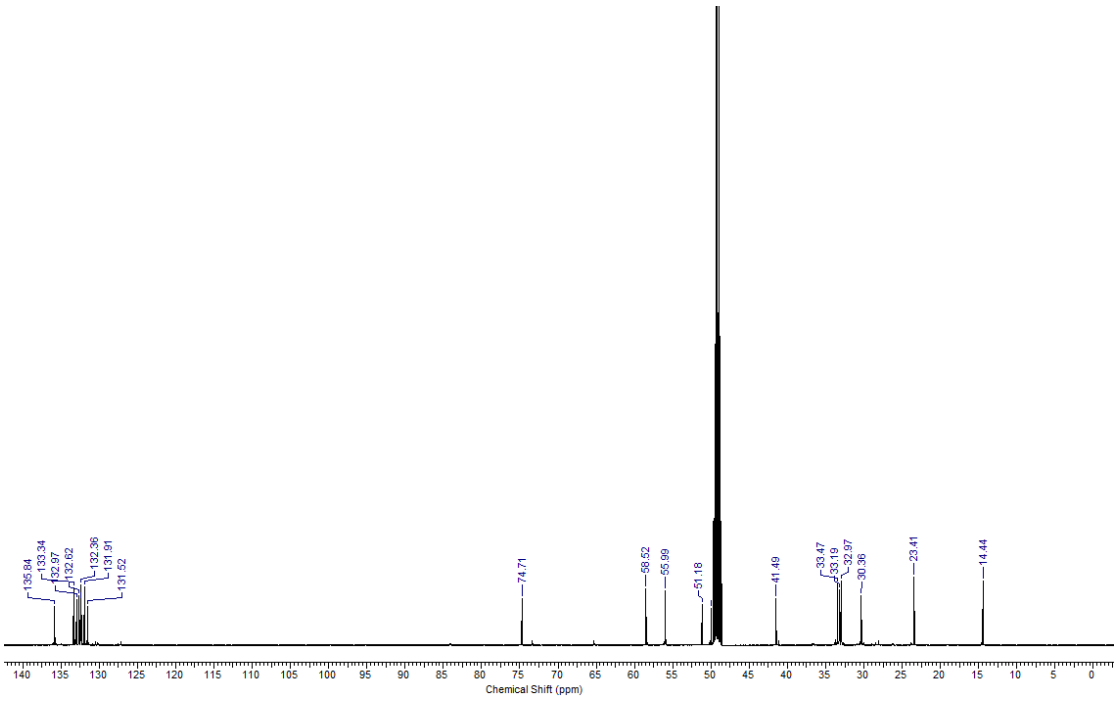
(2*S*,4*R*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin F] 6, >85% dp (125 MHz, ^{13}C, MeOH-*d*$_4$)



(2*S*,4*S*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin Z] 147, >85% dp (500 MHz, ^{1}H, MeOH-*d*$_4$)

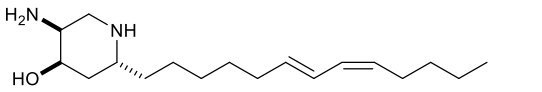


(2*S*,4*S*,5*S*,1'*E*,3'*E*,8'*E*,10'*E*)-2-(Pentadeca-1',3',6′,8′-tetraen-1'-yl)-4-hydroxy-5-aminopiperidine [Pseudodistomin Z] 147, >85% dp (125 MHz, ^{13}C, MeOH-*d*$_4$)

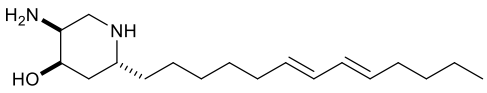


	1	**2**	**3**	**4**	**5**	**6**	**147**
C(2)	50.4	50.4	58.2	56.8	56.5	52.5	58.5
C(3)	40.3	40.2	35.8	41.4	35.6	40.5	41.5
C(4)	69.1	69.0	70.7	76.0	71.0	68.9	74.7
C(5)	52.5	52.4	51.0	56.5	51.4	52.0	56.0
C(6)	48.8	48.7	50.1	51.9	50.4	48.4	51.2
C(1')	37.3	37.2	133.6	37.3	37.4	133.9	133.3
C(2')	27.1	27.1	132.4	27.1	26.9	132.4	132.4
C(3')	30.5	30.5	131.7	30.5	30.5	131.7	131.5
C(4')	30.6	30.6	135.6	30.6	30.6	135.4	135.8
C(5')	33.9	33.5	33.5	33.5	33.5	33.5	33.5
C(6')	135.4	133.0	30.4	133.0	133.0	30.4	30.4
C(7')	127.2	132.1	33.2	132.1	132.1	33.2	33.2
C(8')	130.1	132.0	132.7	132.0	132.0	132.7	132.6
C(9')	130.7	133.2	132.0	133.2	133.2	132.2	132.4
C(10')	28.4	33.7	131.9	33.7	33.7	131.9	131.9
C(11')	33.3	33.0	133.3	33.0	33.0	133.3	133.0
C(12')	23.4	23.4	33.2	23.4	23.4	33.2	33.2
C(13')	14.5	14.4	33.0	14.4	14.5	33.0	33.0
C(14')			23.4			23.4	23.4
C(15')			14.4			14.4	14.4

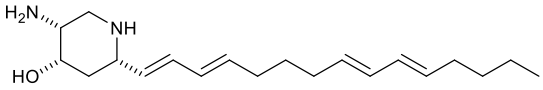
^{13}C NMR data comparison for pseudodistomins A–F **1**–**6** and Z **147**.



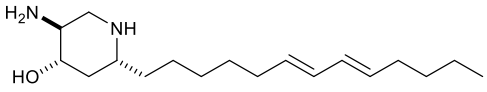
pseudodistomin A **1**



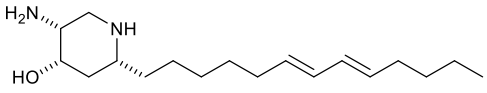
pseudodistomin B **2**



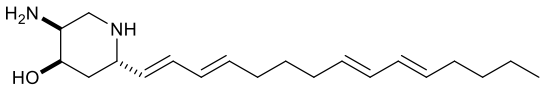
pseudodistomin C **3**



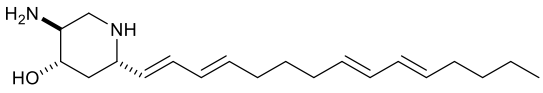
pseudodistomin D **4**



pseudodistomin E **5**



pseudodistomin F **6**



pseudodistomin Z **147**