

Synthetic studies towards bistramide D

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**SYNTHETIC STUDIES TOWARDS
BISTRAMIDE D**

BY

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Table of Contents

Abstract	6
Abbreviations	8
Chapter I:	
Introduction to the bistramide family	
Isolation and structural determination	12
Solladie's synthesis of bistramide D	16
Kitching's access to bistramides	17
Wipf's bistramide C analysis	20
Kozmin's approach to bistramide A	27
Crimmins synthesis of bistramide A	30
Panek's access to bistramide A	35
Yadav's synthesis of bistramide A	40
Piva's approach to THP	44
Conclusion	45
Chapter II:	
Synthesis of the THP fragment of bistramide D	
Retrosynthetic analysis	46
Fragment A synthesis	49
Model studies towards the THP fragment	69
Fragment B synthesis	71
Synthesis of the THP	87
Conclusion	93

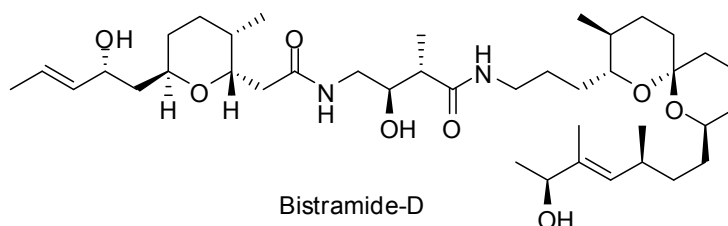
Chapter III:

Synthetic studies to amino acid and spiroketal of bistramide D

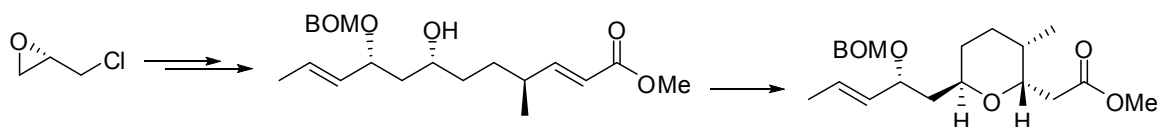
Introduction to amino acid fragment	95
Results and discussion	98
Introduction to spiroketals	120
Results and discussion	123
Conclusion	129
Experimental section	130
References	192

Abstract

Bistramide D is a member of new class of bioactive molecule isolated from the marine ascidian *Lissoclinum bistratum* in New Caledonia. Bistramides (A, B, C, D and K) show a broad spectrum of biological activity which includes antiproliferative, immunomodulatory, neurotoxic, cytotoxic and antiparasitic properties; the recent studies also show that bistramides bind to Actin. Bistramide A was reported to be very potent for the P388/dox, B16, HT29, and NSCLC-N6 cell lines. Bistramide D has similar activity in the NSCLC-N6 cell line but is comparatively less toxic *in vivo*. There has been no total synthesis of bistramide D reported till now to our knowledge. These intriguing biological profiles and challenging molecular architecture of bistramides motivated us to synthesize bistramide D.

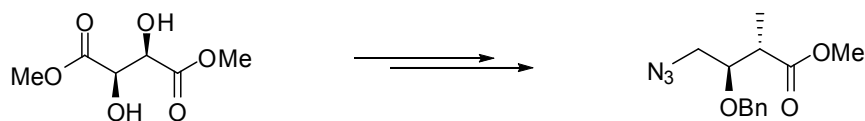


Bistramides incorporate a tetrahydropyran and a spiroketal moiety linked via an amino acid unit. We have successfully synthesised the THP fragment starting from readily available (*S*)-epichlorohydrin. The key steps in the synthesis were the iodolactonisation, selective cross metathesis and an intramolecular Michael addition under kinetic control.

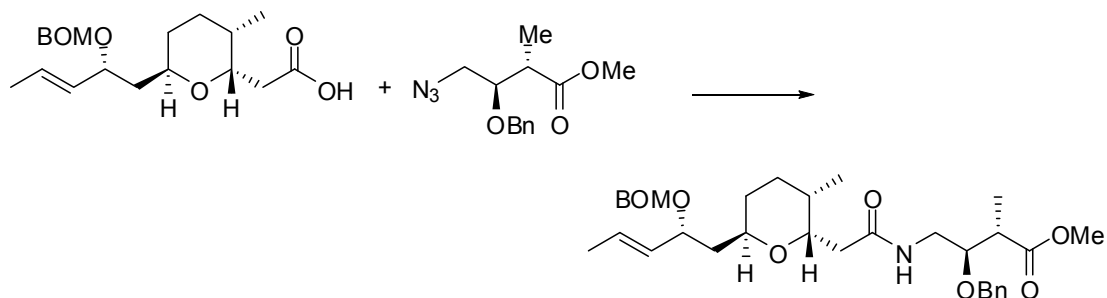


The precursor of the amino acid was synthesised from inexpensive and readily available (+)-dimethyl-L-tartrate by converting to (*R*)-malic acid followed by a

stereoselective methylation, then a regioselective reduction afforded the desired precursor in very good yield and high selectivity.



Modified Staudinger conditions were established to directly couple the azide with THP fragment in an efficient manner without using the protecting/deprotecting strategy.



Our results for the THP part showed that the combination of cross-metathesis and intramolecular Michael addition is a viable pathway to complex tetrahydropyrans, even to produce the less stable isomer, and even in the presence of other alkenes. We have also developed a highly cost effective and efficient synthesis of the amino acid fragment.

Abbreviations:

Ac	Acetyl
AIBN	Azobisisobutyronitrile
ABCN	1,1'-azobiscyclohexane-carbonitrile
Ar	Aryl
App	Apparent
aq	aqueous
Bn	Benzyl
BOC	di- <i>tert</i> -butyl dicarbonate
BOM	Benzyloxymethyl
Bz	Benzoyl
Bu	Butyl
BBN	9-Borabicyclo[3.3.1]nonane
CSA	Camphor sulfonic acid
CBS	Corey-Bakshi-Shibata
CM	Cross metathesis
Cbz	Carbobenzyloxy
DHP	Dihydropyran
DMP	Dess-Martin periodinane
DMAP	4- <i>N,N</i> -Dimethylamino pyridine
DBU	1,8-Diazabicyclo[5.4.0]undecane
DIBAL	Diisobutylaluminium hydride
DMF	<i>N,N</i> -Dimethyl formamide
DCC	1,3-dicyclohexylcarbodiimide
DET	Diethyl tartrate
DMSO	Dimethyl sulfoxide
DDQ	Dichlorodicyanoquinine
DIAD	Diisopropylazodicarboxylate

DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DIPEA	<i>N,N</i> -Diisopropylethylamine
DBTO	Di- <i>n</i> -butyltin oxide
EA	Ethyl acetate
EDC	<i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)-carbodiimide
EDTA	Ethylenediaminetetraacetic acid
ee	enantiomeric excess
eq.	equivalent
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
h	hour
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
IBX	2-Iodoxybenzoic acid
<i>J</i>	coupling constant
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyl amide
m	multiplet
MAO	Methylalumoxane
<i>m</i> CPBA	3-chloroperoxybenzoic acid
Me	Methyl
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide

NMM	<i>N</i> -methyImorpholine
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PPTS	Pyridinium <i>p</i> -toluene sulfonate
PMB	<i>p</i> -methoxybenzyl
ppm	parts per million
PTSA	<i>p</i> -toluensulfonic acid
Pr	Propyl
Pv	Pivaloyl
Py	Pyridine
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
q	quartet
R	undefined alkyl group
RCM	Ring closing metathesis
Red Al	Sodium bis(2-methoxyethoxy)aluminium hydride
ROM	Ring opening metathesis
s	singlet
sat.	saturated
t	triplet
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBAI	Tetra- <i>n</i> -butylammonium iodide

TBDPS	<i>tert</i> -butyldiphenyl silyl
TBS	<i>tert</i> -butyldimethyl silyl
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
<i>tert</i> or <i>t</i>	tertiary
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropyl silyl
TLC	Thin layer Chromatography
TMG	Tetramethyl guanidine
TMS	Trimethyl silyl
TPAP	Tetra- <i>n</i> -propylammonium perruthenate
Ts	Tosyl

Chapter I: Introduction to Bistramides

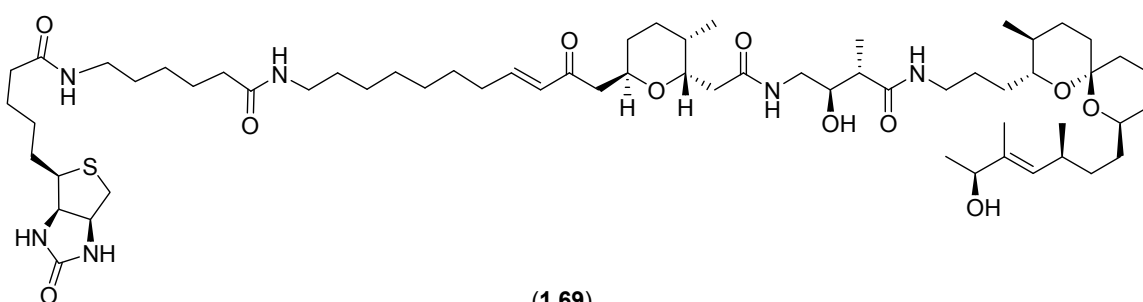
Isolation and biological activities:

Bistramide D is a marine natural product isolated from a marine ascidian *lissoclinum bistratum* slüter, in New Caledonia.¹ Until now, six members of the bistramide family have been discovered, namely bistramides A, B, C, D, K with the recent addition oxobistamide-K.^{2,3} All of these compounds are metabolites showing attractive biological activities, such as antiproliferative, neurotoxic, and immunomodulating properties.^{4,5} Most interestingly, they exhibit cytotoxic properties against a variety of human cancer cells including the human non-small cell lung carcinoma (NSCLC-N6), P388/dox and HL60 cell lines.^{1,6} Considerable efforts have been expended in the mechanistic study of these molecules.^{6,7}

Kozmin *et al.*, studying the biotin conjugates of bistramide A (**1.69**) (Figure 2), showed that Actin is the primary cellular receptor for bistramide A.^{4,8a} This is contrary to the previous suggestion that activation of the protein kinase C, (PKC) δ by bistramide A leads to the antiproliferative effect.⁶ Kozmin suggested that the antiproliferative activity of this molecule arises from binding with the monomeric G-actin. This suggestion was unambiguously proved by a crystal structure of the actin-bistramide A complex.⁴ Though Actin is a globular protein which plays a vital role in the maintenance of cell shape and other important cellular processes, drugs that directly modulate actin have not progressed yet.²⁵⁻²⁷ So, studies “to develop new synthetic analogues as useful probes for studying the actin cytoskeleton and as potential therapeutic leads” are still in progress.⁴ However, the high toxicity of bistramides currently prevents their therapeutic use. Kozmin demonstrated that “the enone moiety of bistramide A is responsible for covalent modification of the protein *in vitro* and in A549 cells, which results in

further increase in the cytotoxicity of the natural product”.^{8b} However, bistramides D and K are less toxic as they hold a hydroxy functionality instead of the enone. Riou showed that only the least toxic bistramides D and K possess antitumor activity against NSCLC-N6 cell lines.⁹ Riou’s study showed that these two substances could be administered as a continuous treatment which would induce terminal differentiation of stem cells at their entry into the cell cycle, thereby causing their destruction.

Bistramide A-Biotin conjugate:



(1.69)
Figure 2

Structural Elucidation:

From the discovery of the bistramides, extensive efforts have been expended on the determination of their structures. Bistramides are structurally complex molecules having 11 to 12 stereo centers, which leads to a huge number of possible stereo isomers. “Assigning the absolute configuration of a complex natural product with multiple stereo centers is not only laborious but also error prone.”¹⁰ However in 1988, the first carbon backbone structure of bistramide A was reported by Gouiffes’s group.¹¹ Later Ireland’s detailed 2D NMR studies allowed an unambiguous structural determination of bistramide A.¹² In 2004, Kozmin’s stereocontrolled synthesis of bistramide A reconfirmed the structural predictions, and also explored the previously unknown C-37 stereochemistry.¹³ Similarly, Wipf and coworkers proposed the structure of bistramide C and

confirmed it by a total synthesis.^{10,14,15} Solladié *et al.* employed a semi synthetic approach to construct bistramide D from bistramide A, which in turn allowed them to determine the absolute and relative configuration of bistramide D through the crystal structure of the product.^{16,17}

Bistramides A, B, C, D have very similar structures consisting of a tetrahydropyran (THP) unit and a spiroketal moiety connected via an amino acid unit (Figure 1). Unlike the others, bistramide K and oxobistramide K do not have a THP ring. The members of the bistramide family are well differentiated by their oxidation level, the difference between bistramide A and C is at the C-39 position; if a hydroxyl group is attached at carbon-39, it is known as bistramide A, if it is a carbonyl group then it is called bistramide C. For bistramide B there is no double bond between C2-C3 while the rest of the family have a double bond in that position. Bistramide D, K and oxobistramide K have a hydroxyl group at the C4 position while rest of the group have a ketone.

Members of bistramide family and their distinguishing features:

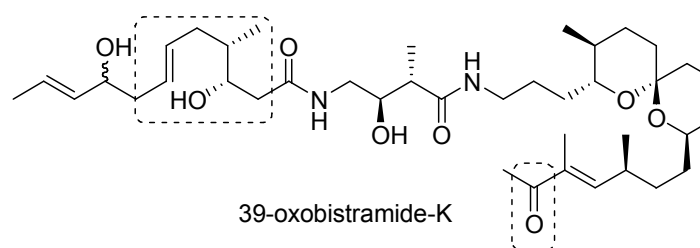
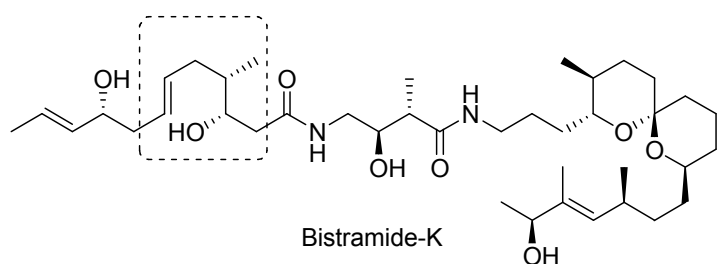
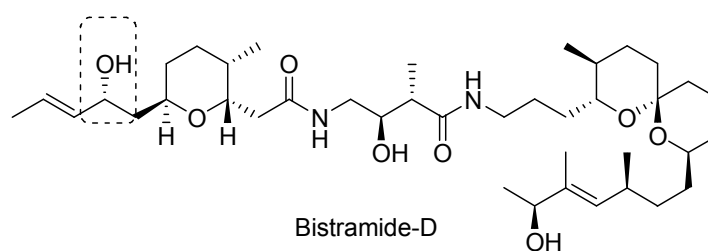
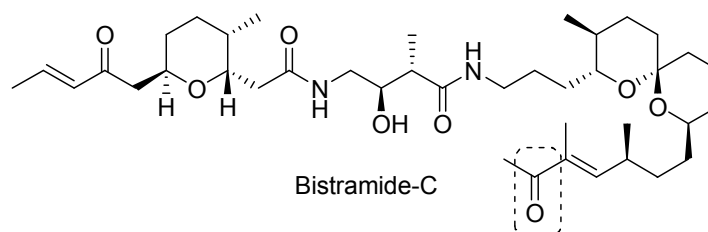
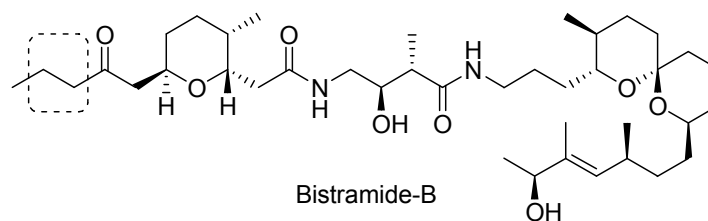
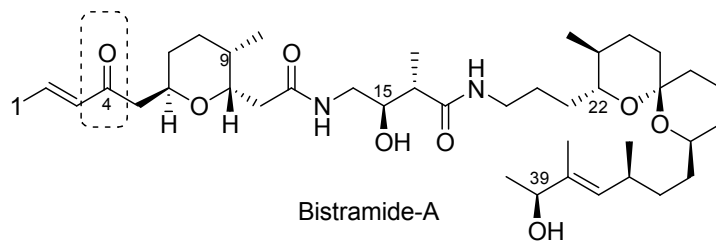


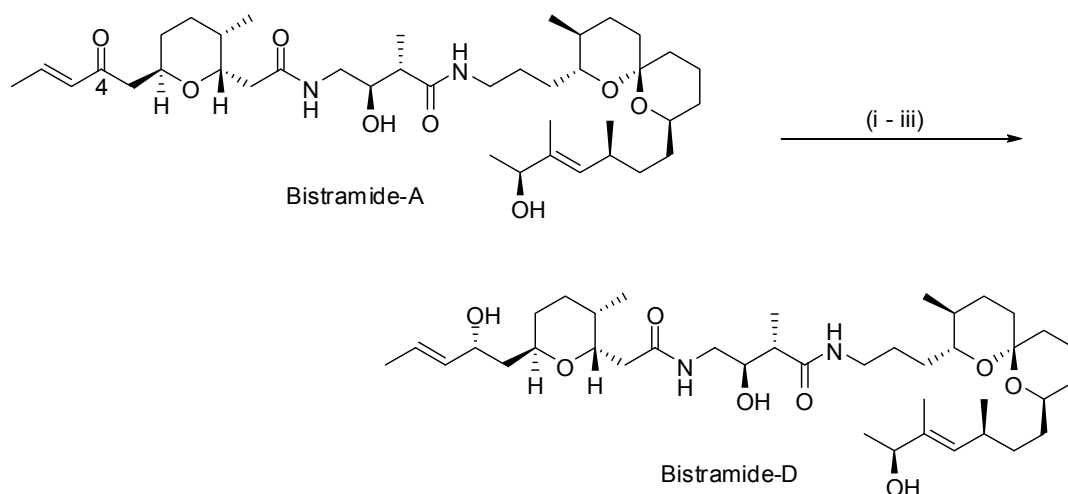
Figure 1

Previous Synthetic Studies of Bistramides:

1. Solladié's semisynthesis of bistramide D:

Solladié *et al.* reported a semi synthesis of bistramide D by stereoselective reduction of bistramide A, which allowed them to partially determine the absolute and relative configurations of bistramide D. ¹⁶ After exploring the conditions with various reducing reagents they found that LiBHET₃ affords, bistramide D in good yield with a high diastereomeric ratio (95:5) (Scheme 1). The Mosher's method was utilised to assign the absolute configuration at carbon-4 of bistramide D, via an esterification of the C-4 hydroxyl group with the two enantiomers of 2-methoxy-2-phenyl-2-trifluoromethyl acetyl chloride (MPTA-Cl). ¹⁸ Detailed NMR studies of the two resulting diastereomers revealed the stereochemistry of the C₄ position as (*R*).

Solladié's stereoselective reduction of bistramide A to bistramide D:

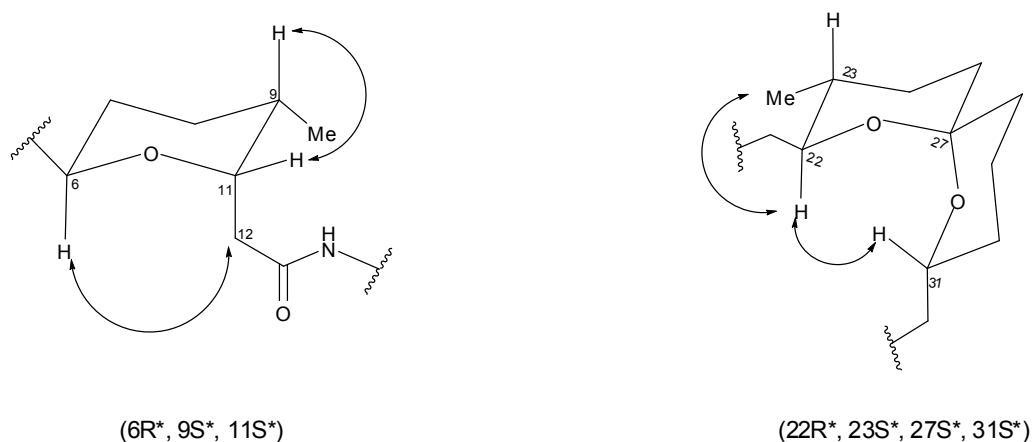


Scheme 1

Reagents and conditions: (i) Ac₂O, pyridine, 96 %; (ii) LiBHET₃, THF, 73 % (95 : 5) mixture; (iii) LAH, 81 %.

Solladié's detailed NMR studies with the diacetylated bistramide A allowed him to assign the relative configurations of the tetrahydropyran and spiroacetal parts as (*6R**, *9S**, *11S**) and (*22R**, *23S**, *27S**, *31S**) respectively. Scheme 2,

below, shows the NOESY interactions of diacetylated bistramide A. ¹⁹ In early 2006, he reported the absolute and relative configuration of bistramide D from a crystalline derivative of bistramide D. ¹⁷



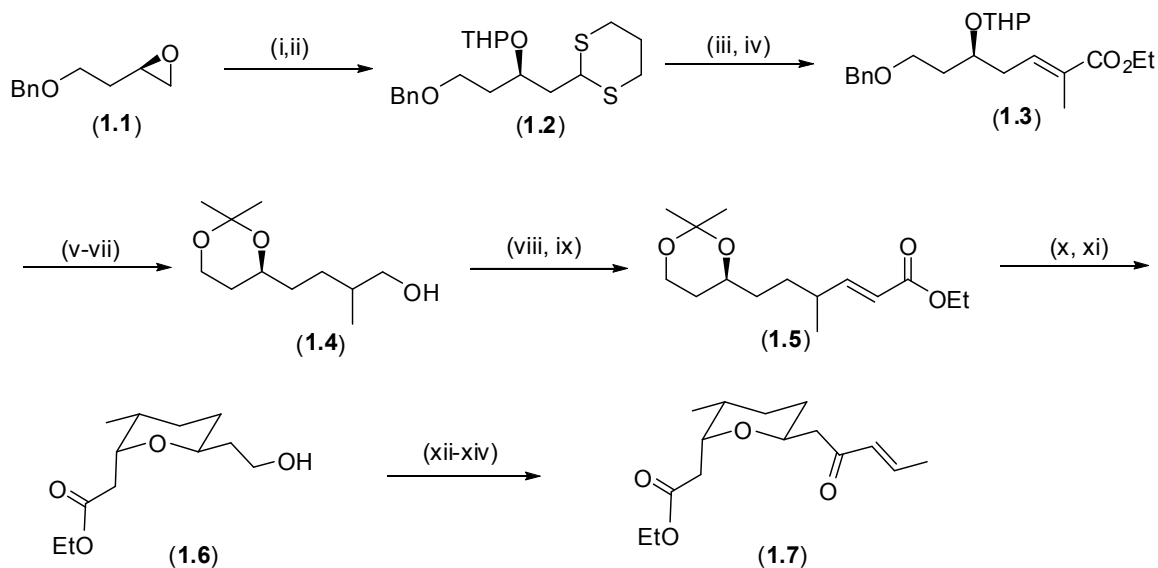
Scheme 2

2. Kitching's substructure synthesis of bistramides:

Followed by Solladié's structural determination of bistramide D, Kitching reported a synthesis of a bistramide substructure. ²⁰ Kitching established the synthesis of the three fragments namely, the THP ring, amino acid and the spiroacetal unit (Scheme 3). His structural assignments revised the previously proposed relative stereochemistry of bistramides.

For the synthesis of the C1-C13 fragment of the bistramides, Kitching used two different methods. In the first method, Kitching started with a known epoxide (**1.1**), which on THP protection followed by Wittig reaction, provided the α , β -unsaturated ester (**1.3**). Compound (**1.3**), on debenzylolation followed by LAH reduction, afforded the alcohol (**1.4**). TPAP oxidation of the alcohol (**1.4**) to aldehyde, which on second Wittig reaction provided the precursor (**1.5**) for cyclisation. The cyclisation reaction was achieved via an Oxymercuration reaction with Hg(II) to afford compound (**1.6**) with the other three possible stereo isomers. ²¹ All of these isomers were separated and their NMR spectra were

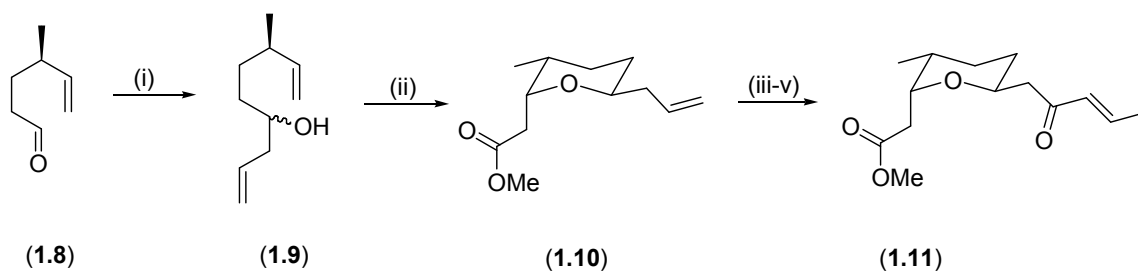
compared with that of bistramide A. The spectrum of the isomer (**1.7**) shown below was the closest match.



Scheme 3

Reagents and conditions: (i) 1,3-Dithiane, BuLi, 70 %; (ii) DHP, PPTS, CH₂Cl₂; (iii) MeI, CaCO₃, 65 %; (iv) Ph₃P=C(CH₃)COOEt; (v) H₂, Pd/C; (vi) DMP, H⁺; (vii) LiAlH₄, 72 %; (viii) TPAP, NMO; (ix) Ph₃P=CHCO₂Et, 80 %; (x) H⁺, MeOH; (xi) Hg(OAc)₂, H⁺, NaBH₄, 55 %; (xii) TPAP, NMO; (xiii) In, allyl bromide; (xiv) TPAP, NMO, Al₂O₃ (neutral), 95 %.

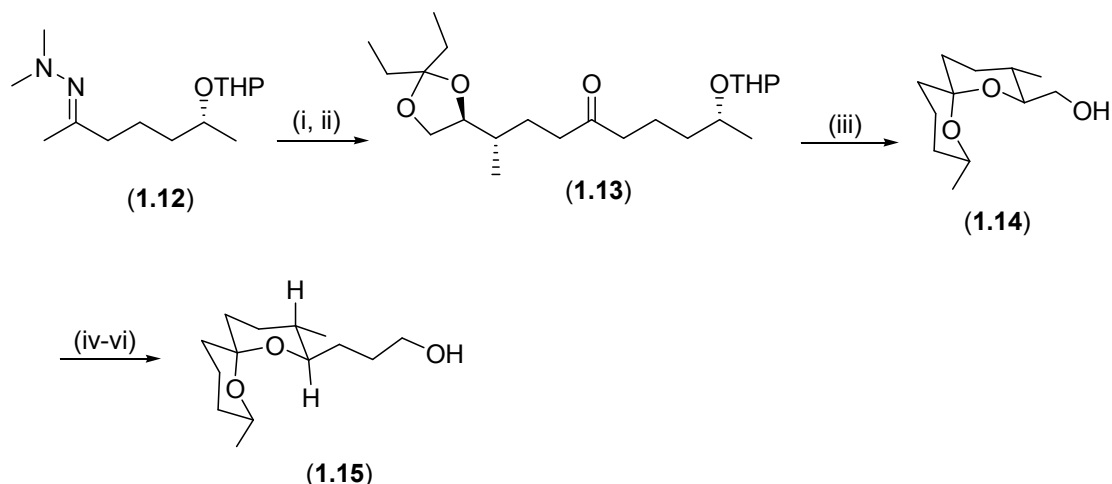
In turn, his second method (Scheme 4), started with the known aldehyde ²² (**1.8**) which on allylation followed by cyclisation with Hg (II) afforded compound (**1.10**) and the other three possible diastereomers as expected. Compound (**1.10**) on ozonolysis, subsequent allylation and Swern oxidation yielded the desired C1-C13 fragment of bistramide A (**1.11**).



Scheme 4

Reagents and conditions: (i) Allyl bromide, Zn, THF-H₂O, 85 % (ii) PdCl₂.2MeCN, CuCl₂, MeOH, CO (1 atm), 81 %; (iii) O₃, CH₂Cl₂, Me₂S, -78 °C; (iv) In, allyl bromide; (v) Swern oxidation-isomerisation, 62 % (3 steps).

The synthesis of spiroketal (**1.15**) was achieved by the chain elongation of hydrazone (**1.12**) followed by an acid mediated cyclisation of the resulting ketone (**1.13**). The spiroketal (**1.14**) on Swern oxidation followed by Wittig olefination and further transformations afforded spiroketal (**1.15**) in 55 % yield over 3 steps.



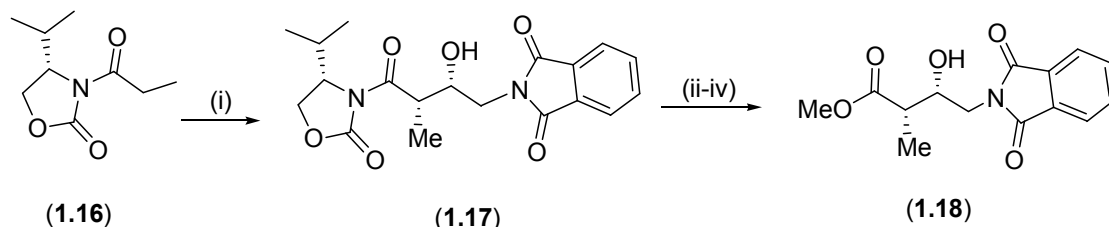
Scheme 5

Reagents and conditions: (i) BuLi, THF, HMPA, 2,2-diethyl-4-(S)-(2-iodo-1-(R)-methylethyl)-[1.3]dioxolane; (ii) SiO₂, 48 % (2 steps); (iii) THF, H₂O, conc. HCl, 59 %; (iv) Swern oxidation, Ph₃P=CHCO₂Et; (v) H₂, Pd/C, 47 % (3 steps); (vi) LiAlH₄, 55 %.

As with the THP fragment, Kitching synthesized the amino acid fragment by two different methods. In method (1) he used an aldol strategy using a boron enolate (^tBu₂BOTf) to obtain a 2.5:1 mixture of *syn* and *anti* aldol products

(1.18). Alternatively in method (2) he used a highly regio-selective Zn-mediated α -methylallylation reaction of aldehyde (1.19) followed by oxidation to obtain the desired amino acid (1.22) in racemic form.

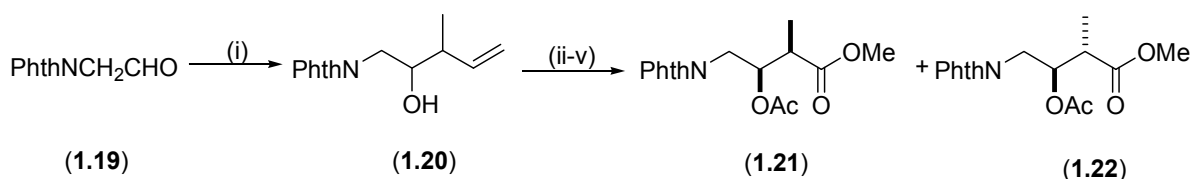
Kitching's synthesis of amino acid fragment method (1):



Scheme 6

Reagents and conditions: (i) $t\text{Pr}_2\text{NEt}$, CH_2Cl_2 , $n\text{Bu}_2\text{BOTf}$, 0°C , PhthNCH₂CHO, 65 %; (ii) NaOMe, MeOH, 75 %; (iii) Ac₂O, pyridine; (iv) NH₂NH₂·xH₂O, EtOH, 50 %.

Kitching's synthesis of amino acid fragment method (2):



Scheme 7

Reagents and conditions: (i) CH₃CH=CHCH₂Cl, Zn, THF-H₂O, NH₄Cl, 87 %; (ii) Ac₂O, Py, 81 %; (iii) KMnO₄/H₂O-C₆H₆, AcOH, TBAI; (iv) CH₂N₂, ether, 52 % (2 steps); (v) HPLC, hexane-EtOAc.

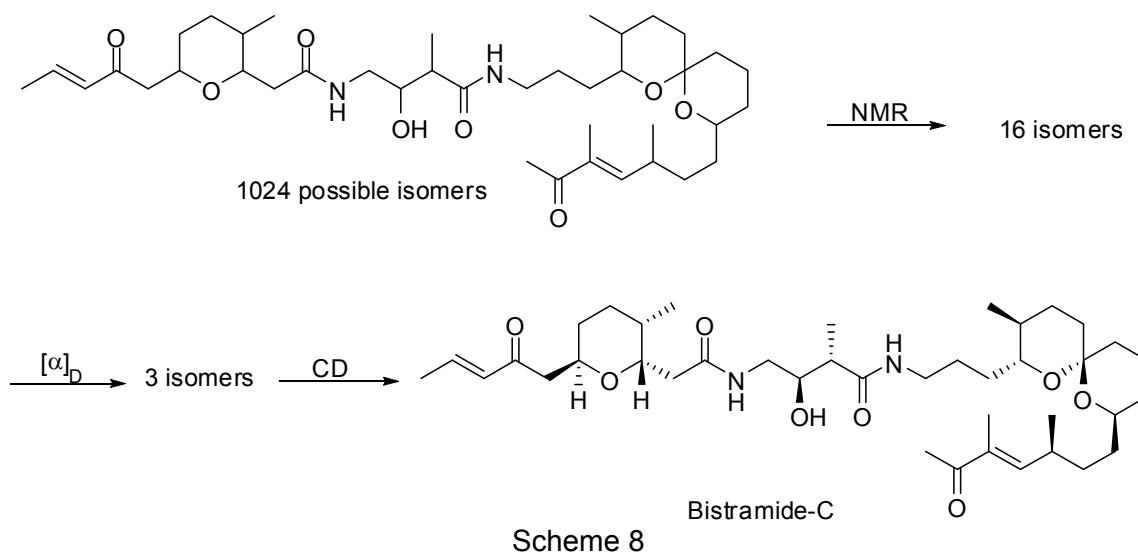
Synthesis of each fragment and comparison with the natural product helped Kitching contribute to the assignment of the relative stereochemistry of bistramide A.

3. Wipf's total synthesis and structural elucidation of bistramide C:

Inspired by the potential biological features of the bistramides, Wipf expended extensive efforts to establish the absolute configuration of bistramide C,¹⁴ which led to the first total synthesis of bistramide C.¹⁵ It was a great challenge to find the absolute stereochemistry as bistramide C contains 10 stereogenic centres

with 1024 possible stereo isomers. However, extensive use of previous NMR investigations¹² and Solladié's synthetic studies helped Wipf to narrow the search to 32 isomers.¹⁶ In spite of the valuable supporting data, the absolute stereostructure of the bistramides still remained elusive. To further simplify the stereochemical puzzle Wipf started a synthesis of one possible isomer of bistramide C (Scheme 8).¹⁴ Elucidation of the structure was finally achieved by a combination of both synthetic and chiroptical tools.¹⁰ (Chiroptical spectroscopy is an advanced tool to determine the optical activity of a chiral compound in which the optical rotation is measured at a fixed wavelength using a spectropolarimeter).

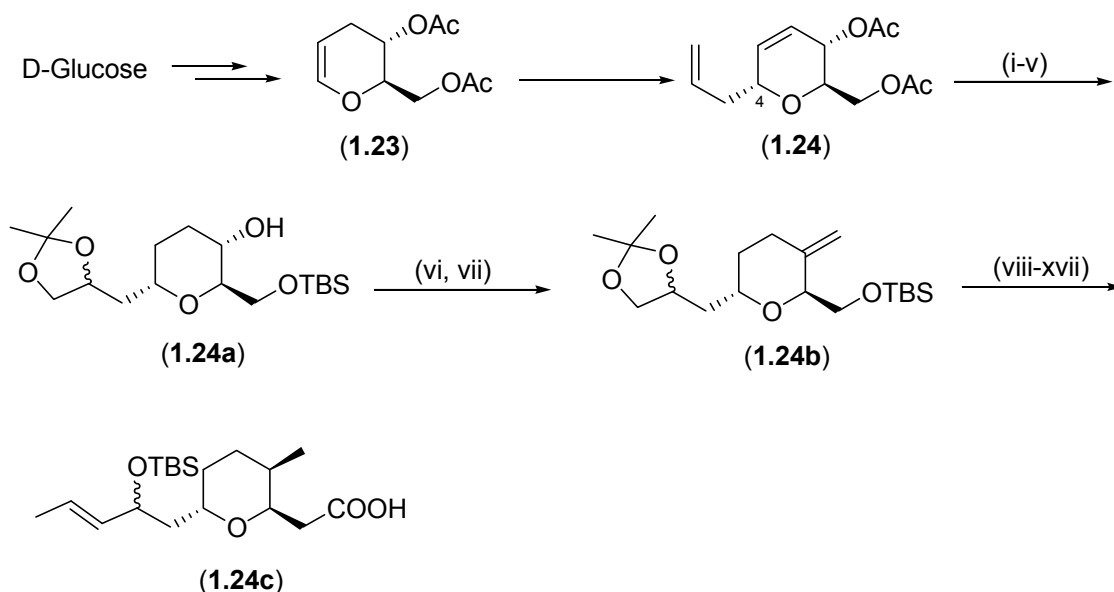
Wipf's structural analysis of bistramide C:



Initially Wipf began the proposed THP synthesis of bistramide C from D-glucose, which following functional group transformations, afforded the dihydropyran (**1.23**) (Scheme 9). The stereochemistry at C-4 was installed by a Lewis acid mediated allylation to obtain the *trans* disubstituted product (**1.24**). Dihydroxylation of (**1.24**) with AD-mix- β and treatment with 2,2-dimethoxypropane gave compound (**1.24a**) in 96 % yield over two steps. Wittig olefination followed by a face selective addition of H₂ and side chain extension

with tris(trimethylthio)methyl lithium afforded the expected C1-C13 fragment (**1.24c**) in 17 steps.

Wipf's synthetic studies towards the THP fragment of bistramide C:



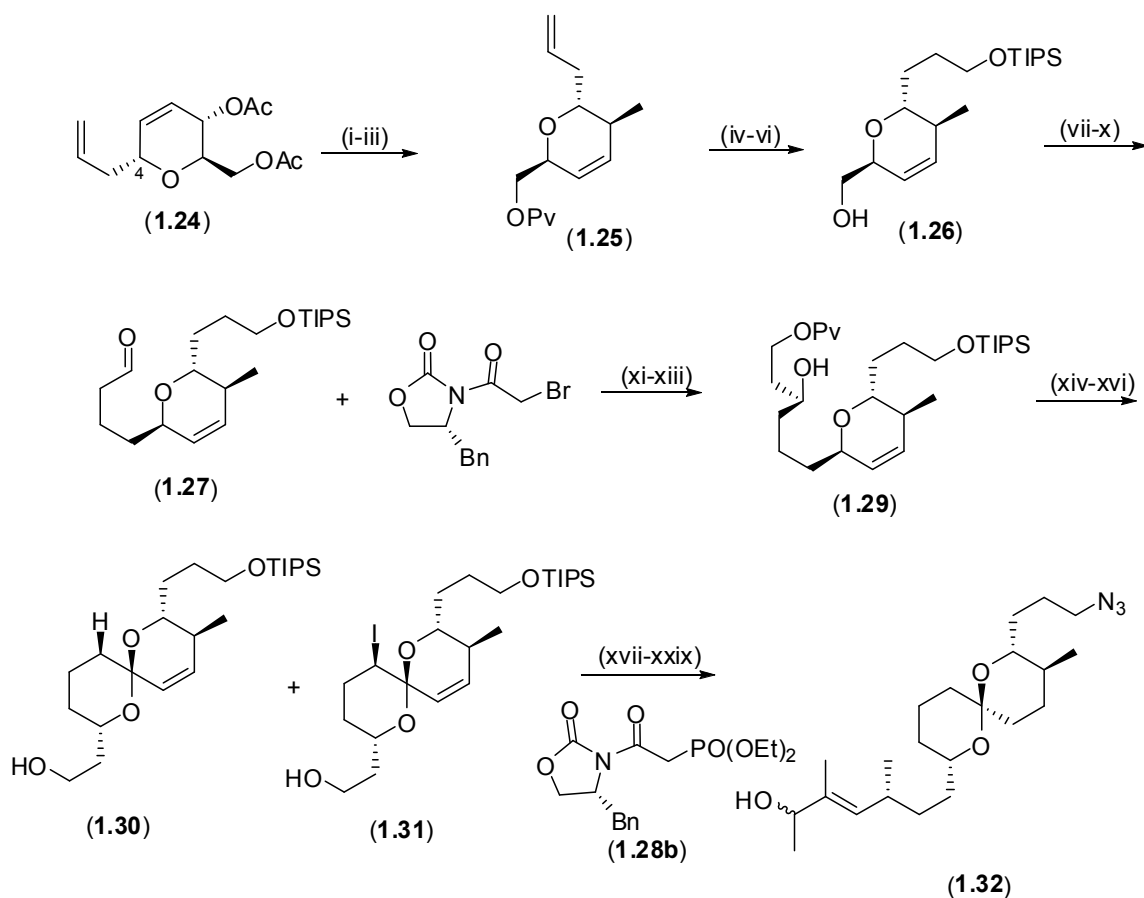
Scheme 9

Reagents and conditions: (i) AD-mix- β ; (ii) $\text{Me}_2\text{C}(\text{OMe})_2$, PPTS, 96 %; (iii) PtO_2 , H_2 , 71 %; (iv) NaOMe , MeOH ; (v) TBSCl , Et_3N , 97 %; (vi) $\text{SO}_3\cdot\text{Py}$, DMSO , Et_3N ; (vii) $\text{Ph}_3\text{P}=\text{CH}_2$, 70 %; (viii) H_2 , PtO_2 ; (ix) TBAF ; (x) Tf_2O , Py ; (xi) $(\text{MeS})_3\text{ClI}$; (xii) $\text{PhI}(\text{OTFA})_2$, $\text{MeOH}-\text{H}_2\text{O}$; (xiii) PPTS, MeOH , 59 %; (xiv) KIO_4 , $\text{Et}_2\text{O}-\text{H}_2\text{O}$, 74 %; (xv) $(E)\text{-CH}_3\text{CH}=\text{CHBr}$, $^t\text{BuLi}$, (xvi) TBSCl , imidazole, 56 %; (xvii) Bu_4NOH , 84 %.

The synthesis of the spiroketal fragment evolved from the previously used intermediate **(1.24)**. Treatment of **(1.24)** with Me_2CuLi displaced the allylic acetate, methanolysis followed by protection of the alcohol afforded **(1.25)** in 58 % yield over 3 steps. Regioselective hydroboration-oxidation of the terminal alkene, a protection and deprotection sequence provided **(1.26)** (Scheme 10). Activation of the alcohol **(1.26)** as a triflate followed by a Grignard reaction with allyl magnesium bromide, a second hydroboration-oxidation, followed by TPAP oxidation afforded aldehyde **(1.27)**. Reformatsky reaction of aldehyde **(1.27)** with Evans alkyl bromide **(1.28)** under Nozaki-Hiyama-Kishi conditions installed

the secondary hydroxyl group with the desired stereochemistry in a 3:1 ratio. Chiral auxiliary removal and introduction of a pivaloyl group allowed separation of the isomers (**1.29**).²³ Compound (**1.29**), on oxidative spirocyclisation with iodobenzene diacetate and iodine under UV irradiation, gave spiroketals (**1.30**) and (**1.31**) in a 3.5:1 ratio. Compound (**1.30**) on further chain elongation afforded the C19-C40 fragment (**1.32**) in 28 steps.

Wipf's synthesis of spiroacetal fragment:



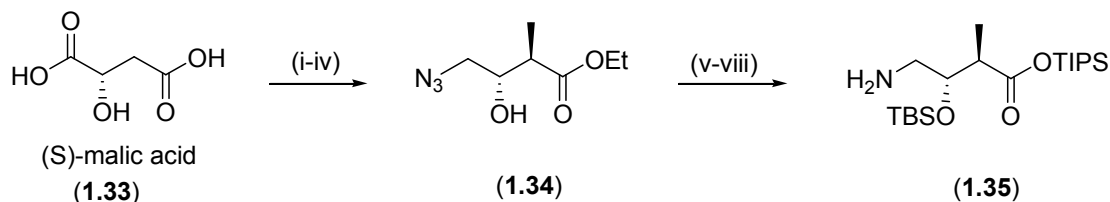
Scheme 10

Reagents and conditions: (i) Me_2CuLi ; (ii) NaOMe , MeOH ; (iii) PvCl , pyridine, 58 % (3 steps); (iv) 9-BBN, H_2O_2 , NaOH ; (v) TIPSCl , DMAP; (vi) LiAlH_4 , 79 % (3 steps); (vii) Tf_2O , pyridine; (viii) allylMgBr $\text{CuBr}\cdot\text{SMe}_2$, 64 % (2 steps); (ix) 9-BBN, H_2O_2 , NaOH ; (x) TPAP, NMO, 65 % (2 steps); (xi) oxazolidinone (**1.28a**), CrCl_2 , NaI , 68 %; (xii) LiBH_4 ; (xiii) PvCl , pyridine, 76 % (2 steps); (xiv) $\text{PhI}(\text{OAc})_2$, I_2 , $h\nu$; (xv) LiAlH_4 , 54 % (2 steps); (xvi) Bu_3SnH , AIBN, 94 %; (xvii) PCC, NaOAc , 82 %; (xviii) Phosphonoester (**1.28b**), *i*-

Pr₂NEt, LiCl, 92 %; (xix) H₂, Pt/C, 63 %; (xx) NaHMDS, MeI, 73 %; (xxi) LiBH₄, 89 %; (xxii) Dess-Martin oxidation, 80 %; (xxiii) Ph₃P=CMeCO₂Et, 66 %; (xxiv) LiAlH₄; (xxv) Dess-Martin oxidation; (xxvi) MeMgBr, 87 % (3 steps); (xxvii) TBAF; (xxviii) MsCl, *i*-Pr₂NEt; (xxix) NaN₃, 74 % (3 steps).

The *anti*-isomer (**1.35**) was synthesised from (*S*)-malic acid (**1.33**) as shown in the (Scheme 11) and this was coupled with the THP fragment (**1.27**) using PyBOP (Scheme 12). The resulting peptide on similar coupling with spiroketal fragment (**1.32**) gave the tentative target structure of bistramide C (**1.36**) (scheme 11). Extensive study of the NMR data and applying Van't Hoff's principle of molar rotation angles to the segments (**1.24c**), (**1.32**) and (**1.35**) allowed deduction of the absolute configuration of bistramide C. ¹⁰

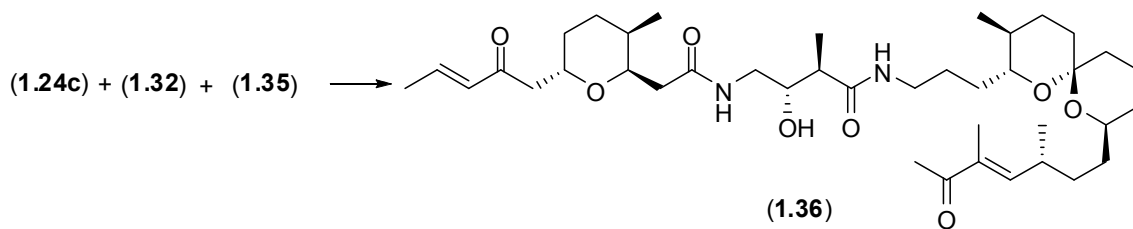
Wipf's aminoacid synthesis:



Scheme 11

Reagents and conditions: (i) EtOH, Conc.HCl, reflux, 92 %; (ii) LDA, MeI, THF, 64 % (6:1); (iii) (a) BH₃.SMe₂, NaBH₄, THF; (b) DBTO, TsCl, Et₃N, CH₂Cl₂, 46 % (2 steps); (vi) NaN₃, DMF, 70 °C, 74 %; (v) TBSCl, imidazole, CH₂Cl₂, 87 % (vi) LiOH, EtOH (vii) TIPSCl, Et₃N, (viii) H₂, Pd/C.

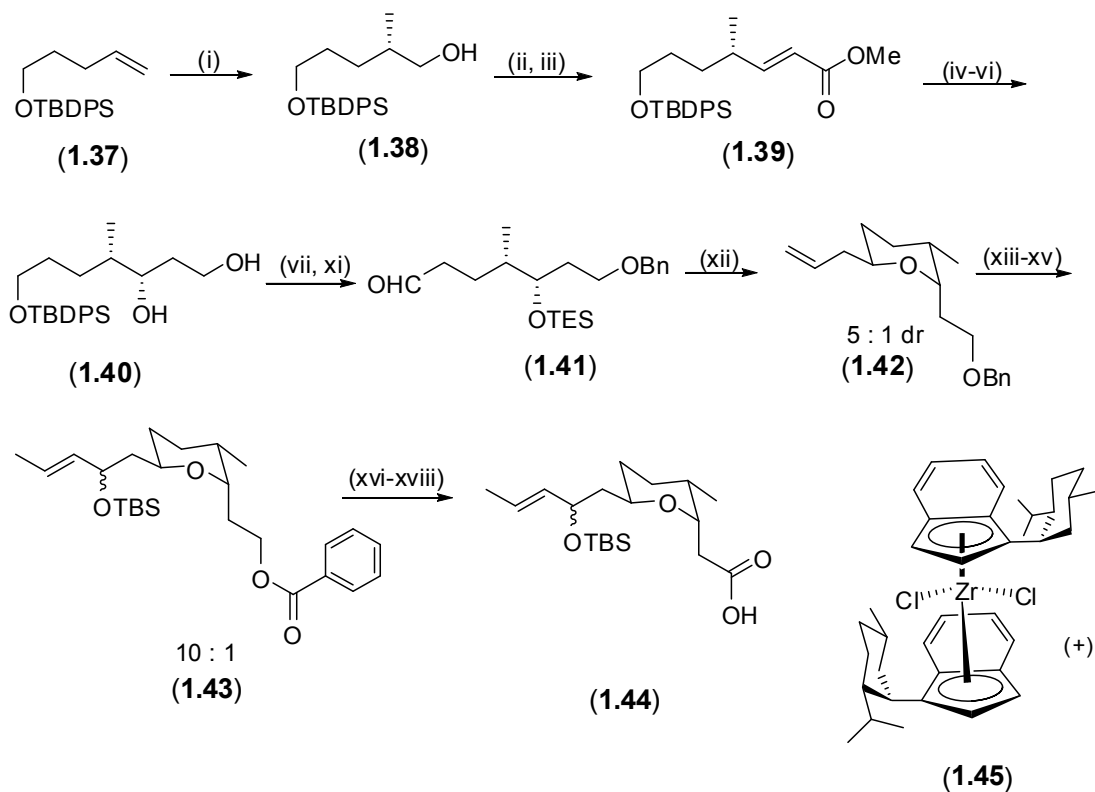
Coupling of THP, amino acid and spiroketal:



Scheme 12

A few years later Wipf reported the total synthesis of bistramide C which reconfirmed his structural assignment.¹⁵ For the synthesis of the C1-C13 fragment (enantiomer of **1.27**) with the correct stereochemistry, he started from 1-pentene-5-ol and the key steps were the asymmetric methylalumination using Erker's chiral zirconocene (**1.45**), Wittig-Horner reaction, Sharpless asymmetric epoxidation followed by allylation provided the THP in 5:1 diastereomeric ratio. Further functional group transformations provided the C1-C13 fragment (**1.44**) of bistramide C.

Wipf's modified approach for THP with corrected stereo chemistry:

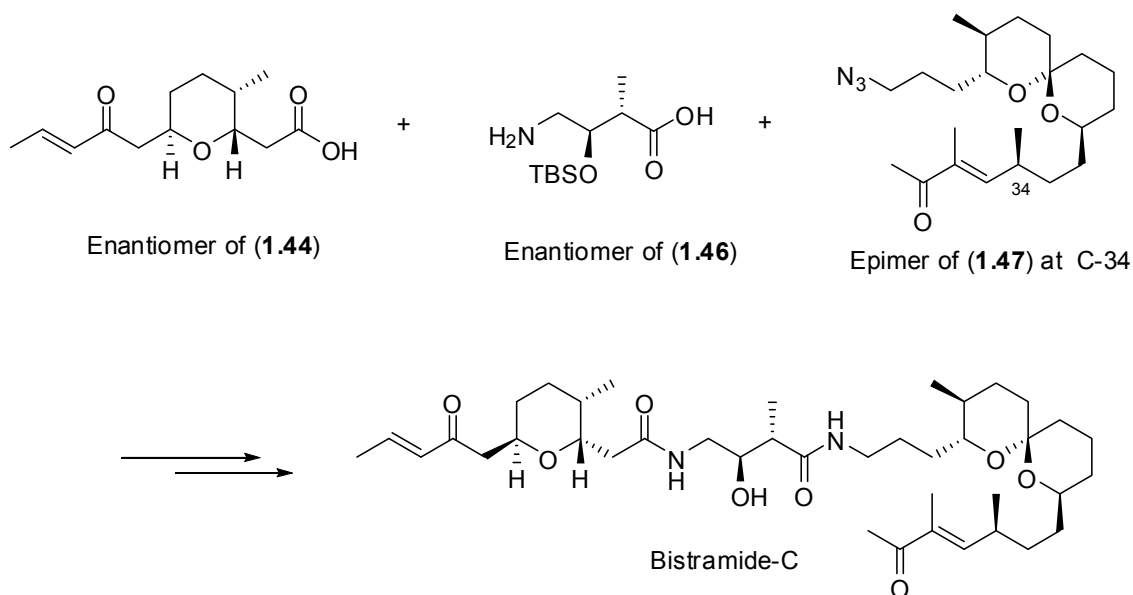


Scheme 13

Reagents and conditions: (i) AlMe_3 , Zr catalyst (**1.45**) 2.8 mol %, MAO, CH_2Cl_2 then O_2 , 78 %; (ii) NaOCl, TEMPO, KBr, NaHCO_3 , Na_2CO_3 , CH_2Cl_2 , 92 %; (iii) trimethyl phosphonoacetate, LiCl, DBU, MeCN, 91 %; (iv) DIBAL-H; (v) TBHP, *D*-(-)DIPT, $\text{Ti}(\text{O-iPr})_4$, CH_2Cl_2 , $-20\text{ }^\circ\text{C}$, 96 %; (vi) Red-Al, quantitative; (vii) NaH, BnBr, TBAI, THF, 87 %; (viii) TBAF, 98 %; (ix) TESOTf, 2,6-lutidine, quantitative; (x) AcOH- H_2O -THF, 79 %; (xi) Dess-Martin periodinane, NaHCO_3 , CH_2Cl_2 , 81 %; (xii) $\text{CH}_2=\text{CHCH}_2\text{TMS}$, BiBr_3 , CH_3CN , 72 %, 5:1 dr; (xiii) O_3/O_2 , methyl pyruvate, CH_2Cl_2 , then PPh_3 , 65 %; (xiv) (*E*) $\text{CH}_3\text{CH}=\text{CHLi}$; (xv) TBSCl, imidazole, 82 %; (xvi) NaOMe, MeOH, 90 %; (xvii) TBAF, 98 %; (ix) TESOTf, 2,6-lutidine, quantitative; (x) AcOH- H_2O -THF, 79 %; (xi) Dess-Martin periodinane, NaHCO_3 , CH_2Cl_2 , 90 %; (xviii) NaClO_2 , NaH_2PO_4 , 2-methyl-2-butene, $t\text{BuOH}$, 67 %.

The spiroketal (**1.47**) was derived from D-glucal and the amino acid (**1.46**) was synthesised from (*R*)-malic acid in a similar way used for the enantiomer synthesis.¹⁴ Finally Wipf achieved the stereoselective synthesis of bistramide C as the stereochemistry and spectroscopic properties of synthetically obtained bistramide C matched those of the natural product (Scheme 14)

Wipf's synthesis of bistramide C with corrected stereochemistry:



Scheme 14

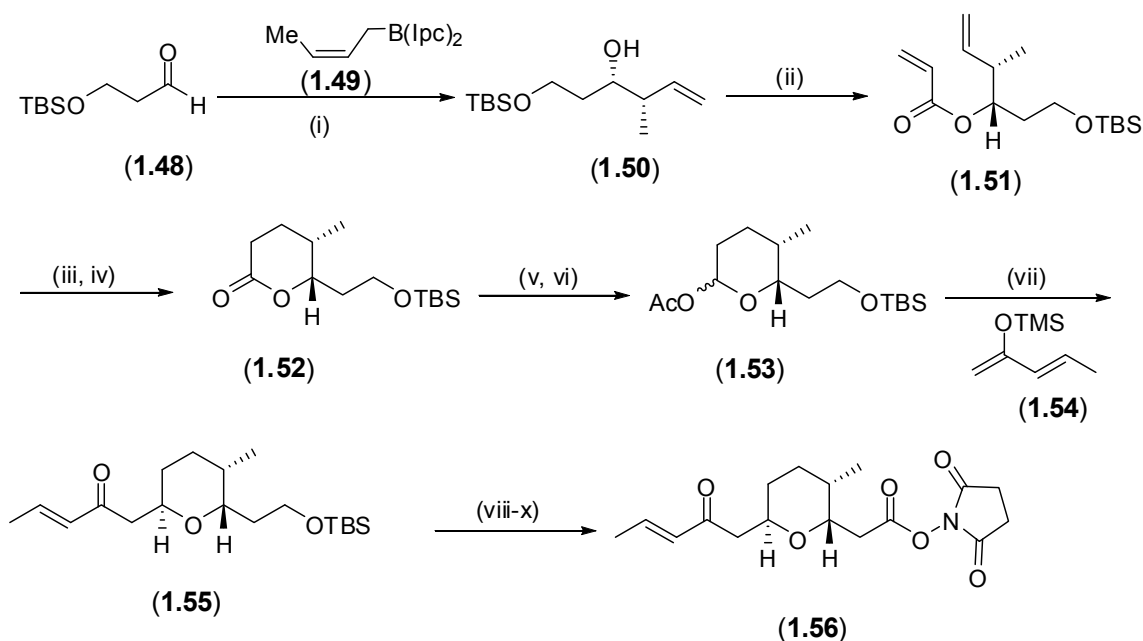
4. Kozmin's synthesis of bistramide A:

The first total synthesis of bistramide A was achieved by Kozmin *et al.* in 2004,¹³ this not only served as an unambiguous support to the earlier structural determinations,^{12,16} but also revealed the previously unknown C-37 stereochemistry. Furthermore, his synthesis supported Wipf's stereochemical assignment of bistramide C.

Kozmin started the C1-C13 fragment (**1.56**) from the aldehyde (**1.48**) which on Brown crotylboration²⁴ afforded (**1.50**) (Scheme 15). The alcohol (**1.50**) on reaction with acryloyl chloride afforded the acylated diene (**1.51**) in 55 % yield. The diene (**1.51**) on ring closing metathesis with the Grubbs II catalyst and

subsequent hydrogenation of the double bond furnished the lactone (**1.52**). DIBAL reduction of the lactone followed by acetylation yielded (**1.53**). ZnCl_2 Promoted C-glycosidation of (**1.53**) with silyl dienol ether (**1.54**), afforded the desired enone (**1.55**) with high diastereoselectivity (92:8). The stereoselectivity was explained by the axial attack of the nucleophile on the oxonium ion intermediate having a pseudo uatorial siloxyethyl substituents and an axial methyl substituent.¹³ Deprotection of the TBS group followed by the oxidation of the resulting alcohol afforded the carboxylic acid which was then activated with *N*-hydroxysuccinimide to afford the THP fragment (**1.56**) of bistramide A.

Kozmin's synthesis of C1-C13 fragment:

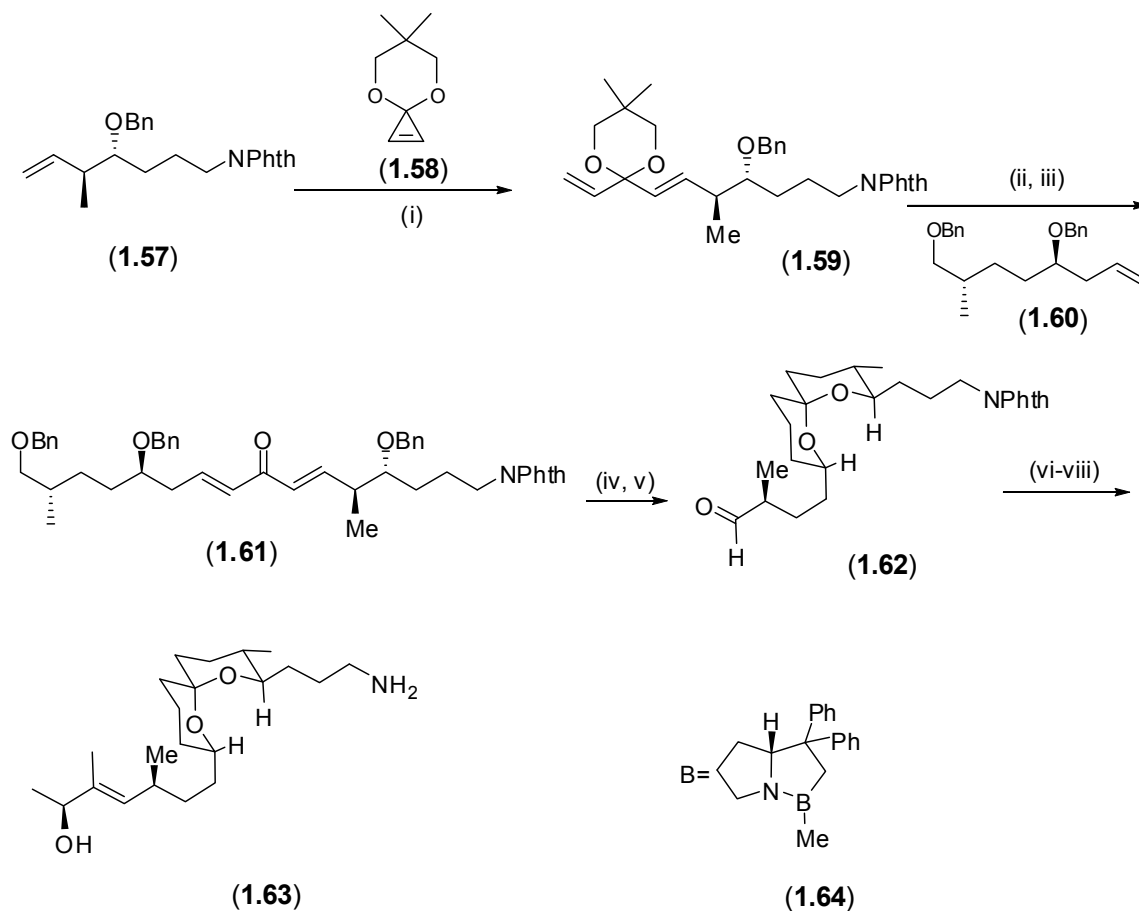


Scheme 15

Reagents and conditions: (i) Borane reagent; H_2O_2 , NaOH, 63 %; (ii) $\text{CH}_2=\text{CHCOCl}$, Et_3N , DMAP, 55 % (2 steps); (iii) Grubbs II, CH_2Cl_2 , reflux; (iv) H_2 , Pd/C, 72 % (2 steps); (v) DIBAL-H, CH_2Cl_2 ; (vi) Ac_2O , pyridine; (vii) ZnCl_2 , alkene (**1.54**), 60 % (3 steps); (viii) HF, CH_3CN ; (ix) H_5IO_6 , CrO_3 (x) DCC, THF, *N*-hydroxy succinimide.

Kozmin devised an impressive method for the synthesis of the spiroketal fragment (**1.63**) (Scheme 16). The synthesis started with a ring opening metathesis (ROM) reaction, a rarely used metathesis reaction in organic synthesis, driven by ring strain, to open the cycloprop-2-enone derivative (**1.58**) with the alkene (**1.57**). Removal of the acetal was achieved with 1M H₂SO₄, and the resulting dienone on cross metathesis with the second partner (**1.60**) afforded the spiroketal precursor (**1.61**) in 68% yield. The precursor (**1.60**) is attractive as it was designed to have a single protecting group (Bn), subsequent deprotection of the all three benzyl groups and removal of the two double bonds could be achieved in one step by catalytic hydrogenation. Thus hydrogenation of (**1.61**) followed by Dess-Martin oxidation afforded the spiroketal (**1.62**) as a single diastereomer. The elongation of the chain was achieved via a Cr-mediated olefination followed by Itsuno-Corey reduction with oxazaborolidine (**1.64**) to afford the spiroketal (**1.63**). The C-37 (*R*) diastereomer was obtained by using the antipode of the oxazaborolidine (**1.64**) reagent.

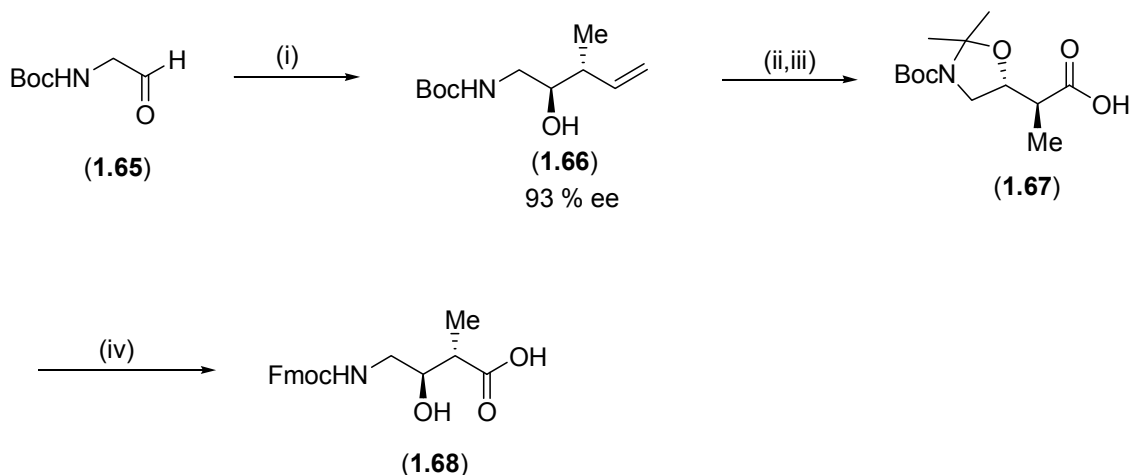
Kozmin's synthesis of spiroacetal fragment:



Scheme 16

Reagents and conditions: (i) cyclopropene acetal (**1.58**), Grubbs II, C_6H_6 , $60\text{ }^\circ\text{C}$; (ii) 1M H_2SO_4 , MeCN, 63 % (2 steps); (iii) Grubbs II, alkene (**1.60**), 68 %; (iv) H_2 (80 psi), $Pd(OH)_2/C$; (v) Dess-Martin oxidation, 53 % (2 steps); (vi) $CrCl_2$, THF, CH_3COCH_2Br ; (vii) (**1.64**) catechol borane, toluene; (viii) $MeNH_2$, MeOH, $65\text{ }^\circ\text{C}$, 40 % (3 steps).

For the synthesis of amino acid fragment (**1.68**), Kozmin *et al.* utilised the Brown crotylboration²⁴ once again, this time to get the *anti* product (**1.66**). Their amino acid synthesis started from the Boc protected amino aldehyde (**1.65**), which on crotylboration with (+)-(Ipc)₂BOMe, provided (**1.66**) in 93 % ee. The alkene (**1.66**), on subsequent protection and oxidation afforded (**1.67**). Compound (**1.67**) on acid hydrolysis followed by protection as the Fmoc derivative provided compound (**1.68**).

Kozmin's synthesis of amino acid fragment:

Reagents and conditions: (i) borane reagent, NaOH, H₂O₂, 93% ee; (ii) (Me)₂C(OMe)₂; TsOH, acetone; (iii) NaIO₄, RuCl₃; (iv) 3N HCl, EtOAc; (v) FmocOSu, Na₂CO₃, Dioxane-H₂O.

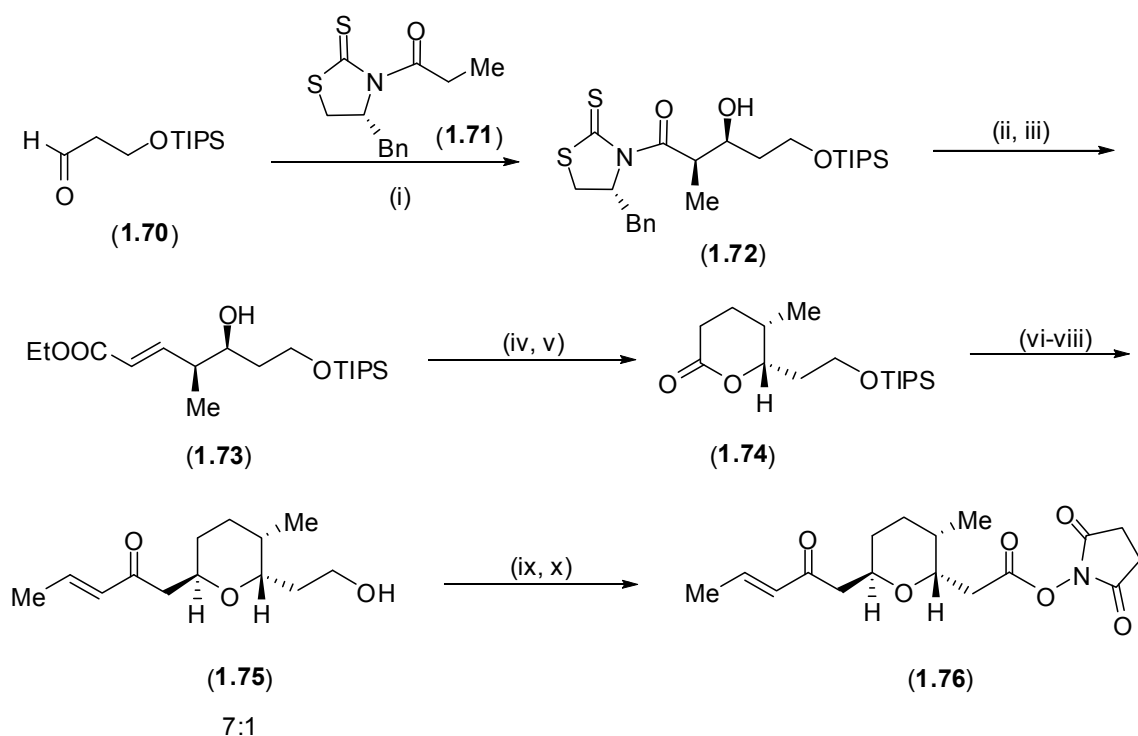
The highlight of the Kozmin synthesis is the use of a novel strategy for the spiroketal synthesis which was achieved via ring opening and cross metathesis reactions. The right choice of protecting groups allowed them to minimise the number of steps.

5. Crimmins Synthesis of Bistramide A:

At the end of 2005, Crimmins reported an enantioselective synthesis of bistramide A,²⁸ which was the second stereoselective synthesis reported for this molecule. Crimmins started the THP fragment synthesis from a known aldehyde (1.70)²⁹ which on aldol reaction with the N-propionyl thiazolidinethione enolate (1.71) (Scheme 18), afforded the *syn* product (1.72) with excellent diastereoselectivity (98:2). Reductive cleavage of the chiral auxiliary followed by Wittig reaction gave the corresponding α,β -unsaturated ester (1.73) in 78 % yield in two steps. Hydrogenation of the resulting ketone, lactonisation followed by reductive acylation gave compound (1.74), which is similar to the Kozmin's

intermediate **(1.52)**.¹³ The stereochemistry was installed by treating the acetate **(1.74)** with 2-trimethylsilyloxy-1,3-pentadiene³⁰ to obtain **(1.75)** in 9:1 diastereomeric ratio. After deprotection of the TIPS ether, similar to Kozmin, Crimmins also used the chromium catalysed oxidation of the primary alcohol to the acid followed by esterification with *N*-hydroxysuccinimide to afford the THP fragment **(1.56)** over 10 steps.

Crimmin's synthesis of the THP fragment of bistramide A:

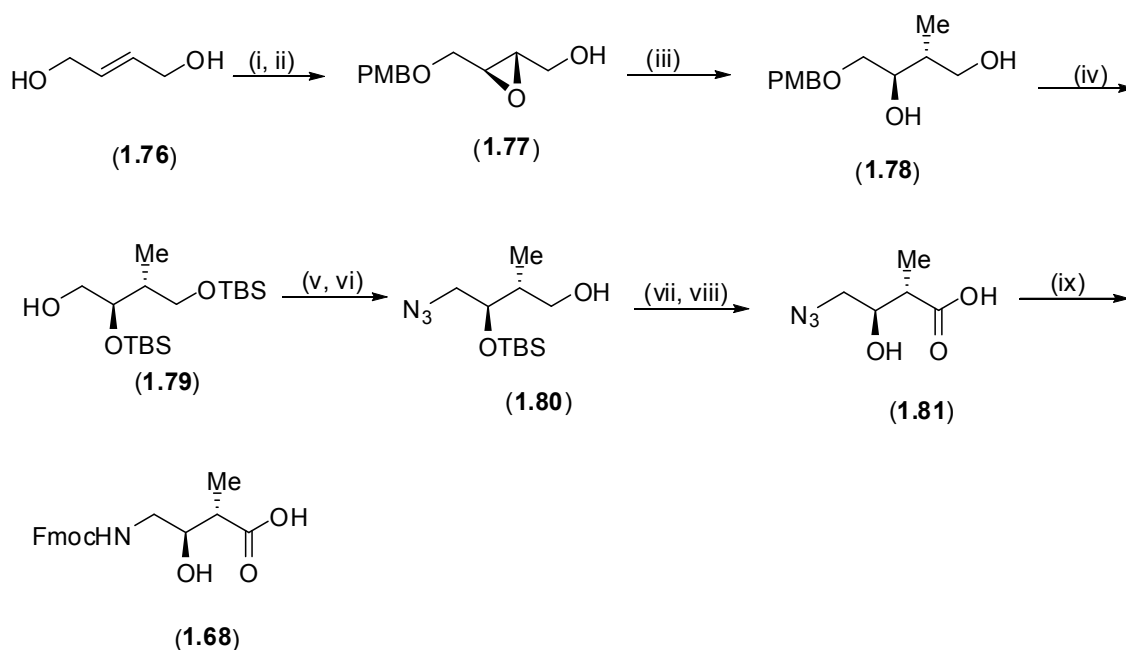


Scheme 18

Reagents and conditions: (i) TiCl_4 , NMP, (-)-sparteine, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, chiral auxiliary **(1.71)**, 87 %; (ii) *i*- Bu_2AlH , THF, $-78\text{ }^\circ\text{C}$; (iii) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, CH_2Cl_2 , 78 % (2 steps); (iv) H_2 , Raney Ni, EtOH; (v) PPTS, CH_2Cl_2 , $40\text{ }^\circ\text{C}$, 81 % (2 steps); (vi) *i*- Bu_2AlH , pyridine, DMAP, Ac_2O , CH_2Cl_2 , -78 to $-20\text{ }^\circ\text{C}$, 96 %; (vii) Et_3N , TMSOTf, 3-penten-2-one, CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to $-78\text{ }^\circ\text{C}$, acetate, 87 %, 9:1 dr; (viii) H_2SiF_6 , CH_3CN , $0\text{ }^\circ\text{C}$, 75 %; (ix) $\text{H}_5\text{IO}_6/\text{CrO}_3$, CH_3CN , 77 %; (x) *N*-hydroxysuccinimide, EDC.HCl, CH_2Cl_2 , 100 %.

Crimmins started his amino acid synthesis with the commercially available diol (**1.76**) which on PMB protection followed by Sharpless asymmetric epoxidation afforded the epoxide (**1.77**) in high yield (Scheme 19). Methylation with lithium dimethylcuprate, yielded the 1,3-diol (**1.78**) in a 6:1 ratio with its regioisomeric 1,2-diol. The undesired diol was removed by treatment with NaIO_4 . TBS protection of both free hydroxyls of (**1.78**) followed by removal of the PMB ether provided alcohol (**1.79**) in 95 % yield over two steps. The free primary alcohol was displaced by azide via a Mitsunobu reaction, subsequent deprotection of the primary TBS ether provided (**1.80**). One pot TEMPO oxidation of the alcohol to carboxylic acid followed by deprotection of the TBS ether yielded (**1.81**). Hydrogenation of the azide provided the primary amine which on *in situ* Fmoc protection afforded the amino acid fragment (**1.68**).

Crimmins synthesis of amino acid fragment:

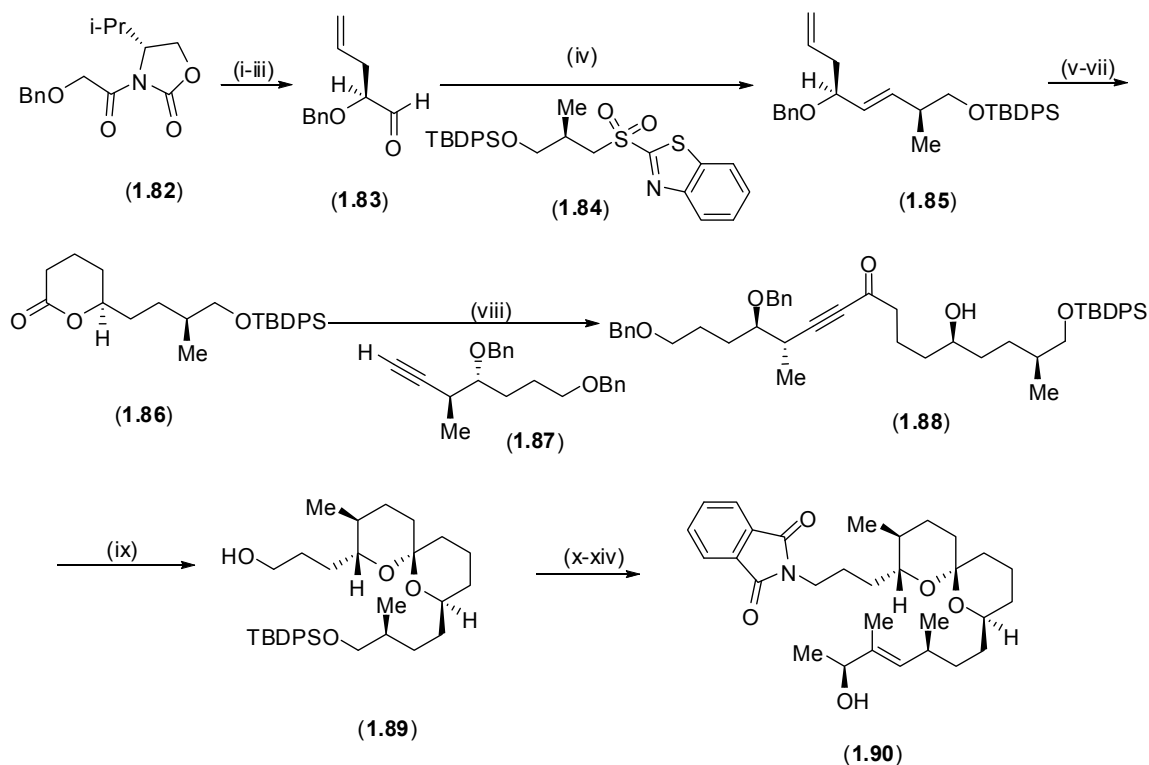


Scheme 19

Reagents and conditions: (i) NaH , *p*-methoxybenzylchloride, DMF, 71 %; (ii) L-(+)-DET, $\text{Ti}(\text{O}i\text{Pr})_4$, $t\text{BuOOH}$, CH_2Cl_2 , 4 Å sieves, $-20\text{ }^\circ\text{C}$, 95 %, 98 % ee; (iii) (a) Me_2CuLi , Et_2O , $-50\text{ }^\circ\text{C}$ to $-25\text{ }^\circ\text{C}$, 6:1 of 1,3- to 1,2-diol; NaIO_4 , H_2O , 71 %; (b) TBSOTf, 2,6-lutidine,

CH₂Cl₂, 0 °C, 97 %; (iv) DDQ, pH 7 buffer, CH₂Cl₂, 0 °C, 98 %; (v) DEAD, PPh₃, (PhO)₂PON₃, THF, 0 °C, 90 %; (vi) CSA, MeOH, CH₂Cl₂, 0 °C, 85 %; (vii) NaClO₂, TEMPO, CH₃CN, 35 °C, 95 %; (viii) HF/pyridine, THF, 70 %; (ix) H₂, Pd/C, Fmoc-OSu, THF, 70 %.

The spiroacetal fragment synthesis began with a stereoselective allylation of the enolate (**1.82**), derived from an Evans chiral oxazolidinone to give the allylated acyl oxazolidinone in 98:2 diastereomeric ratio (Scheme 20). Chiral auxiliary removal followed by Swern oxidation of the resulting alcohol afforded the aldehyde (**1.83**). Aldehyde (**1.83**) upon modified Julia reaction with sulfone (**1.84**) yielded the diene (**1.85**) as a 60:40 mixture of *E*:*Z* isomers. The terminal alkene (**1.85**) on cross metathesis with methyl acrylate resulted in the unsaturated methyl ester, which on hydrogenation followed by acid treatment gave the desired lactone (**1.86**) in 70% yield. Addition of the lactone (**1.86**) to the lithium acetylide of alkyne (**1.87**) afforded the spiroketal precursor (**1.88**) which on hydrogenation afforded the trihydroxy ketone which concomitantly cyclised to give the desired spiroketal (**1.89**) as a single stereoisomer in 83% yield. The side chain of (**1.89**) was extended to obtain the spiroketal fragment (**1.90**) in five steps, including Mitsunobu reaction, deprotection of the silyl ether, Dess-Martin oxidation followed by Horner-Wadsworth-Emmons olefination and then Corey's stereoselective reduction of the C-39 carbonyl group.

Crimmins synthesis of spiroacetal fragment:

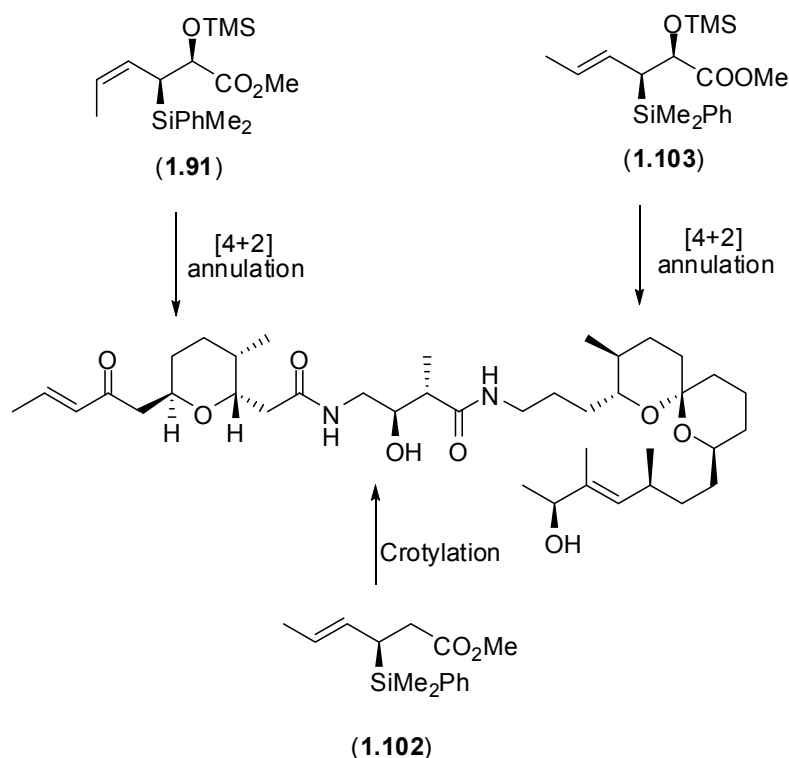
Reagents and conditions: (i) NaHMDS, allyl iodide, THF, PhMe, -78 to -45 °C, 81 %; (ii) LiBH_4 , MeOH, Et_2O , 98 %; (iii) Et_3N , DMSO, $(\text{COCl})_2$, CH_2Cl_2 , -78 to 25 °C, 98 %; (iv) LiHMDS , THF, sulfone (N), then aldehyde, -78 to -20 °C, 87 %; (v) Grubbs II, methyl acrylate, CH_2Cl_2 , 40 °C, 87 %; (vi) H_2 , Pd/C, EtOAc; (vii) *p*-TSA, benzene, 80 °C, 70% (2 steps); (viii) alkyne, $^n\text{BuLi}$, -78 °C, then lactone; (ix) H_2 , Pd/C, MeOH, EtOAc, 83 % (2 steps); (x) PPh_3 , DEAD, phthalimide, THF, 0 °C; (xi) HF/pyridine, THF, 84 % (2 steps); (xii) Dess-Martin periodinane, CH_2Cl_2 , pyridine, 92 %; (xiii) $\text{Ba}(\text{OH})_2$, THF, $\text{MeCOCH}(\text{Me})\text{P}(\text{O})(\text{OEt})_2$, 58 %; (xiv) (*R*)-CBS, catecholborane, toluene, -78 °C, 65 %, $>98:2$ dr.

Similar to Kozmin, Crimmins also coupled the three fragments namely THP (F), amino acid (K) and the spiroketal (S) using a PyBOP mediated condensation to afford bistramide A. In summary, Crimmins achieved the total synthesis of bistramide A in 18 (longest) linear steps, the key steps are the aldol, Sharpless asymmetric epoxidation and the modified Julia reaction.

6. Panek's bistramide A synthesis:

Developing novel methodologies and applying them to synthesise natural products and biologically active compounds are well known in organic synthesis. Similarly, bistramide A was synthesised³¹ by Panek in 2006, by an application of his [4+2] annulation protocol.³² Initially Panek developed the [4+2] annulation strategy mainly for the synthesis of dihydropyrans, later it was utilised for the synthesis of number of natural products including bistramide A. The best part of his bistramide A synthesis, was the construction of 8 out of 11 stereogenic centers exclusively from three different organosilanes (Scheme 21).

Organosilanes approach to bistramide A:

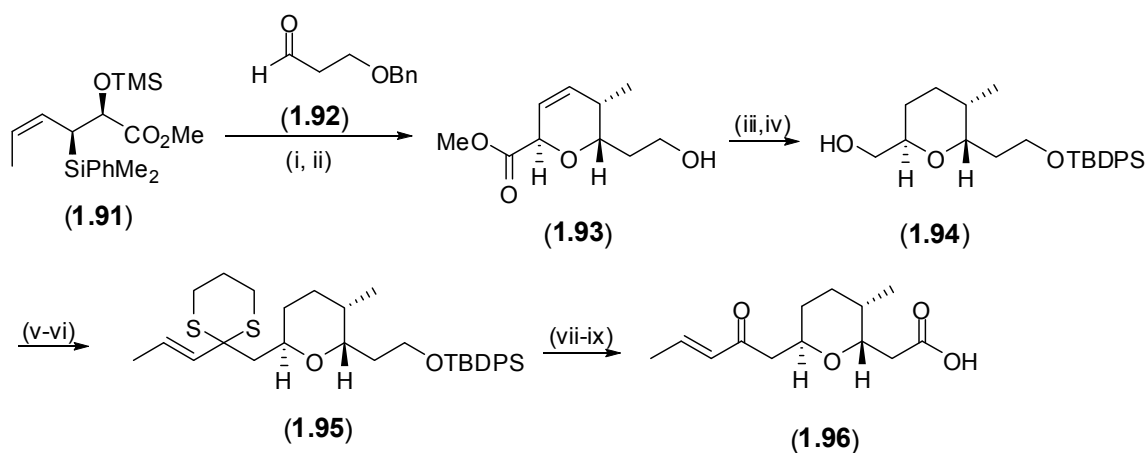


Scheme 21

The synthesis of the THP fragment began with (Z)-crotylsilane **(1.91)** which on annulation with aldehyde **(1.92)** gave the desired dihydropyran **(1.93)** in a 12:1 diastereomeric ratio (Scheme 22). The stereochemistry of the cyclisation was controlled by the silicon bearing carbon.³² Hydrogenation of **(1.93)** using

Adam's catalyst resulted in the reduction of the double bond as well as the deprotection of the benzyl ether. The alcohol was protected as its TBDPS ether; LiBH_4 reduction of the methyl ester afforded compound (**1.94**) in 74 % yield over 3 steps. The primary alcohol obtained from the methyl ester was converted into the corresponding iodide which on displacement with the lithium anion of 2-propenyl-dithiane afforded compound (**1.95**). Deprotection of the TBDPS ether was achieved by treatment with HF. Similar to Kozmin¹³ and Crimmins,²⁸ Panek also used the chromium catalysed oxidation of alcohol to obtain the acid (**1.96**).

Panek's synthesis of the THP fragment of bistramide A:



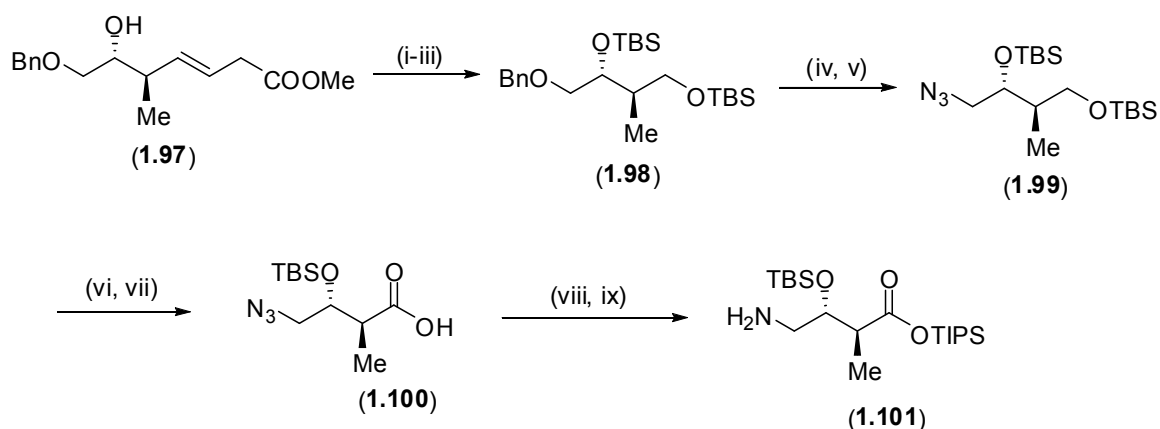
Scheme 22

Reagents and conditions: (i) TMSOTf, CH_2Cl_2 , $-50\text{ }^\circ\text{C}$, 61 % dr 12:1; (ii) H_2 , PtO_2 , MeOH; (iii) TBDPSCI, Et_3N , CH_2Cl_2 ; (iv) LiBH_4 , Et_2O , 74 % (3 steps); (v) $(\text{CH}_3\text{O})_3\text{P}^+\text{CH}_3\text{I}^-$; (vi) 2-propenyl-dithiane, $n\text{BuLi}$, HMPA, THF, 86 % (2 steps); (vii) Dess-Martin; (viii) HF, CH_3CN , 69 % (2 steps); (ix) CrO_3 , H_5IO_4 , $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 85 %.

For the amino acid synthesis, Panek started with a known homoallylic alcohol (**1.97**) (Scheme 23), as the enantiomer was prepared by his group as part of their Callipeltoside synthesis.³³ TBS protection of the secondary alcohol (**1.97**) followed by ozonolysis and concomitant reduction of the resulting aldehyde provided the primary alcohol, which on protection as its TBS ether gave (**1.98**).

Debenzylation of the alcohol was achieved by hydrogenation, the free alcohol was then displaced by azide under Mitsunobu conditions to afford (**1.99**). The selective deprotection of the TBS group followed by oxidation to acid (**1.100**) were achieved in the similar way to Crimmins.²⁸ Acid (**1.100**) on esterification with TIPSCI followed by the reduction of azide afforded the C14-C18 fragment (**1.101**) of bistramide A.

Panek's synthesis of amino acid fragment:

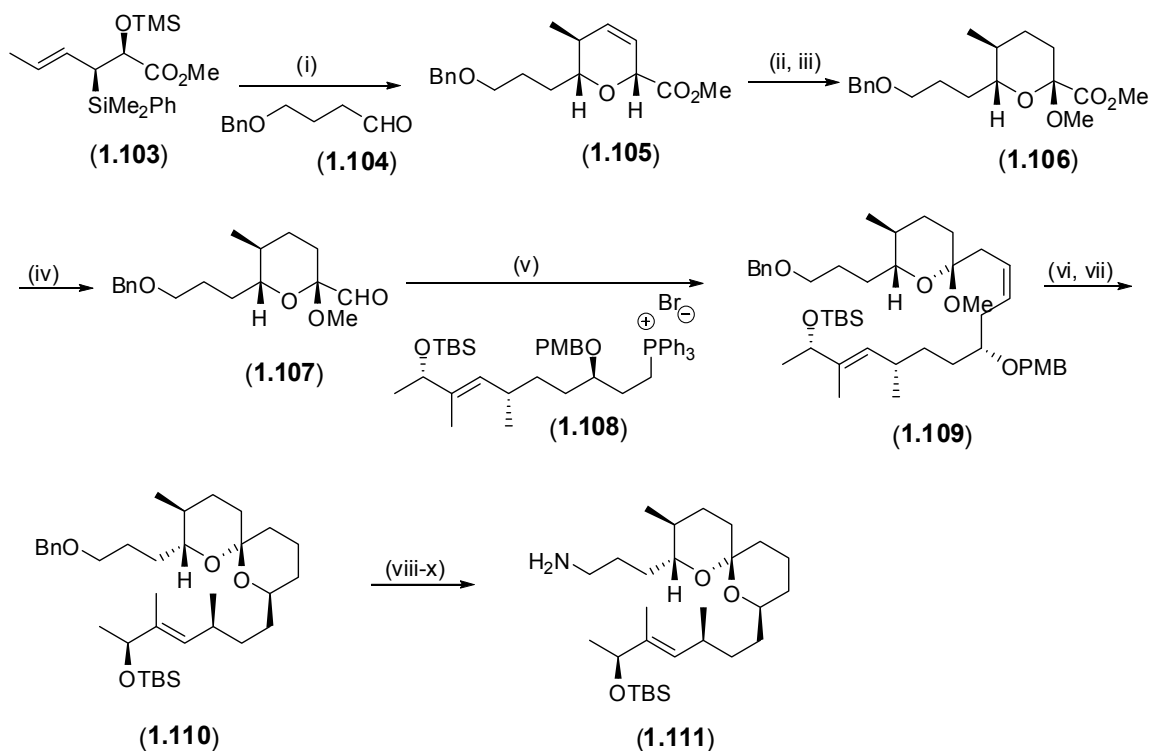


Reagents and conditions: (i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 99 %; (ii) O₃, MeOH, pyridine, NaBH₄, 92 %; (iii) TBSCl, imidazole, DMF, 99 %; (iv) H₂, Pd/C, EtOAc, 84 %; (v) PPh₃, DIAD, THF, (C₆H₅O)₂P(O)N₃, 93 %; (vi) CSA, MeOH, CH₂Cl₂, 90 %; (vii) NaOCl, NaClO₂, TEMPO; (viii) TIPSCI, CH₂Cl₂, Et₃N, 76 % (2 steps); (ix) H₂, Pd/C, THF.

Panek used the second [4+2] annulation strategy for the spiroketal fragment (**1.111**) synthesis (Scheme 23). The synthesis started with [4+2] annulations of *syn*-(*E*)-crotylsilane reagent (**1.103**) with the aldehyde (**1.104**) providing the desired dihydropyran (**1.105**) as a single diastereomer in excellent yield. Isomerisation of the double bond followed by treatment with CSA in methanol afforded methyl glycoside (**1.106**). The aldehyde (**1.107**) was derived from the ester (**1.106**) via a DIBAL reduction. The second key step in Panek's strategy was the olefination of the aldehyde (**1.107**) with phosphonium salt (**1.108**) which

afforded a single olefin isomer (**1.109**) in 86 % yield. Regioselective hydrogenation of the double bond at C28-C29 was achieved using Wilkinson's catalyst, removal of PMB ether using DDQ in pyridine resulted in spiroacetal formation (**1.110**). Deprotection of the benzylated alcohol was achieved by Birch reduction, the alcohol on displacement with azide followed by treatment with Me₃P afforded the spiroacetal fragment (**1.111**).

Panek's synthesis of spiroacetal fragment:



Scheme 24

Reagents and conditions: (i) TMSOTf, CH₂Cl₂, BnO(CH₂)₃CHO, -50 °C, 97 %; (ii) ⁿBu₄NOH, THF, 96 %; (iii) CSA, MeOH, 81 %; (iv) DIBAL-H, Et₂O, 94 %; (v) ⁿBuLi, THF, 0 °C, 86 %; (vi) H₂, (Ph₃P)₃RhCl, benzene, 75 %; (vii) DDQ, pyridine, CH₂Cl₂, 76 %; (viii) Na, NH₃(l), THF, 91 %; (ix) PPh₃, DIAD, (PhO)₂P(O)N₃, THF, 86 %; (x) PMe₃, THF/H₂O.

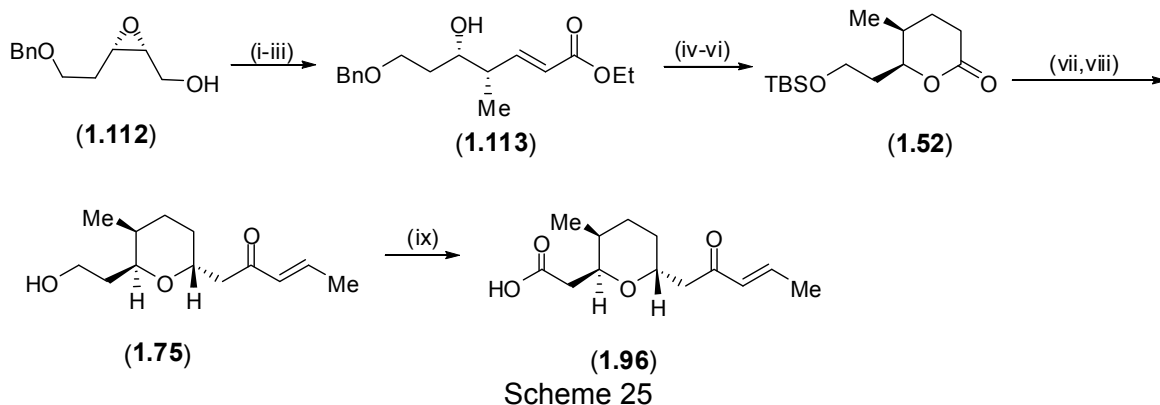
Similar to the previous syntheses, Panek also used the PyBop mediated coupling of the three fragments (**1.96**), (**1.101**) and (**1.111**) to obtain bistramide

A. The highlight of the synthesis is the extensive use of enantioenriched silanes to control the stereochemistry. Recently Panek *et al.* illustrated the synthesis of 35 isomers of bistramide A, by extensive use of their organosilane methodology.²⁵

7. Yadav's synthesis of bistramide A:

The latest total synthesis of bistramide A was reported by Yadav in 2007.³⁴ He depicted a slightly different approach to synthesise the spiroketal fragment by using a TosMIC derivative (tosylmethyl isocyanide) (**1.119**).³⁵ TosMIC is considered to be the most versatile synthon of the methyl isocyanide family, the chemistry of which was extensively explored by Van Leusen.³⁶ An attractive feature of this chemical is due to the 3 functional groups namely the isocyano group which undergoes facile α -addition reactions, an acidic α -carbon atom which can be dialkylated and hydrolysed to give a ketone thus acting as a carbonyl umpolung synthetic equivalent, and a sulfonyl group which serves as a good leaving group as well as helping to increase the acidity of the α -carbon.³⁷ Yadav started his THP synthesis from a known *cis* epoxy alcohol (**1.112**)³⁸ (Scheme 25) which was converted into γ,δ -epoxy acrylate using conventional procedures. On subsequent methylation using Miyashita's protocol³⁹ the *syn* product (**1.113**) was obtained with high stereo and regio selectivity. Treatment of (**1.113**) with Raney-nickel resulted in the concomitant deprotection of the benzyl ether and the removal of double bond. Yadav *et al.* utilised a similar strategy to Crimmins²⁸ to construct the pyran ring (**1.75**) while the side chain was extended by a method similar to Kozmin's approach.¹³

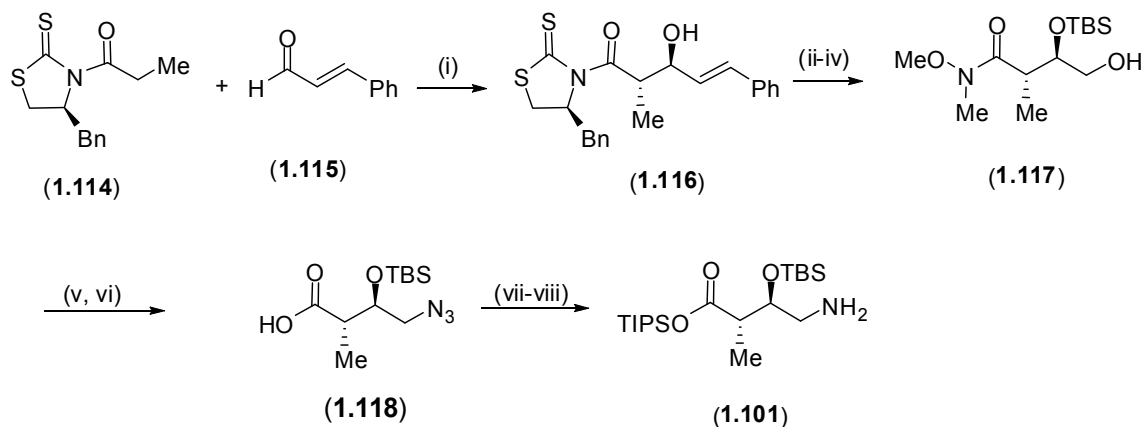
Yadav's synthesis of THP fragment of bistramide A.



Reagents and conditions: (i) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 (ii) $\text{Ph}_3\text{PCHCO}_2\text{Et}$, benzene, 92 % (2 steps); (iii) Me_3Al , CH_2Cl_2 , H_2O , 92 %; (iv) Raney Ni, H_2 , EtOH ; (v) PPTS, CH_2Cl_2 , 78 % (2 steps); (vi) TBSCl, imidazole, CH_2Cl_2 , 93 %; (vii) DIBAL-H, CH_2Cl_2 , pyridine, DMAP, Ac_2O , 78 %; (viii) TMSOTf, Et_3N , CH_2Cl_2 , 3-penten-2-one, 62 %; (ix) $\text{H}_5\text{IO}_6/\text{CrO}_3$, CH_3CN .

Yadav utilized the aldol reaction to fix the stereochemistry in the construction of amino acid fragment (**1.101**) (Scheme 26). Aldehyde (**1.115**) on treatment with Evans enolate (**1.114**) afforded the *anti* aldol adduct (**1.116**) in 90 % de. The aldol (**1.116**) was then converted to the Weinreb amide; TBS protection of the alcohol followed by an ozonolysis of the double bond with reductive workup provided the primary alcohol (**1.117**). Mitsunobu displacement of the alcohol to the corresponding azide and deprotection/protection sequence resulted in TIPS ester (**1.118**). Hydrogenation of the azide (**1.118**) afforded the desired amino acid fragment (**1.101**).

Yadav's synthesis of amino acid fragment of bistramide A.

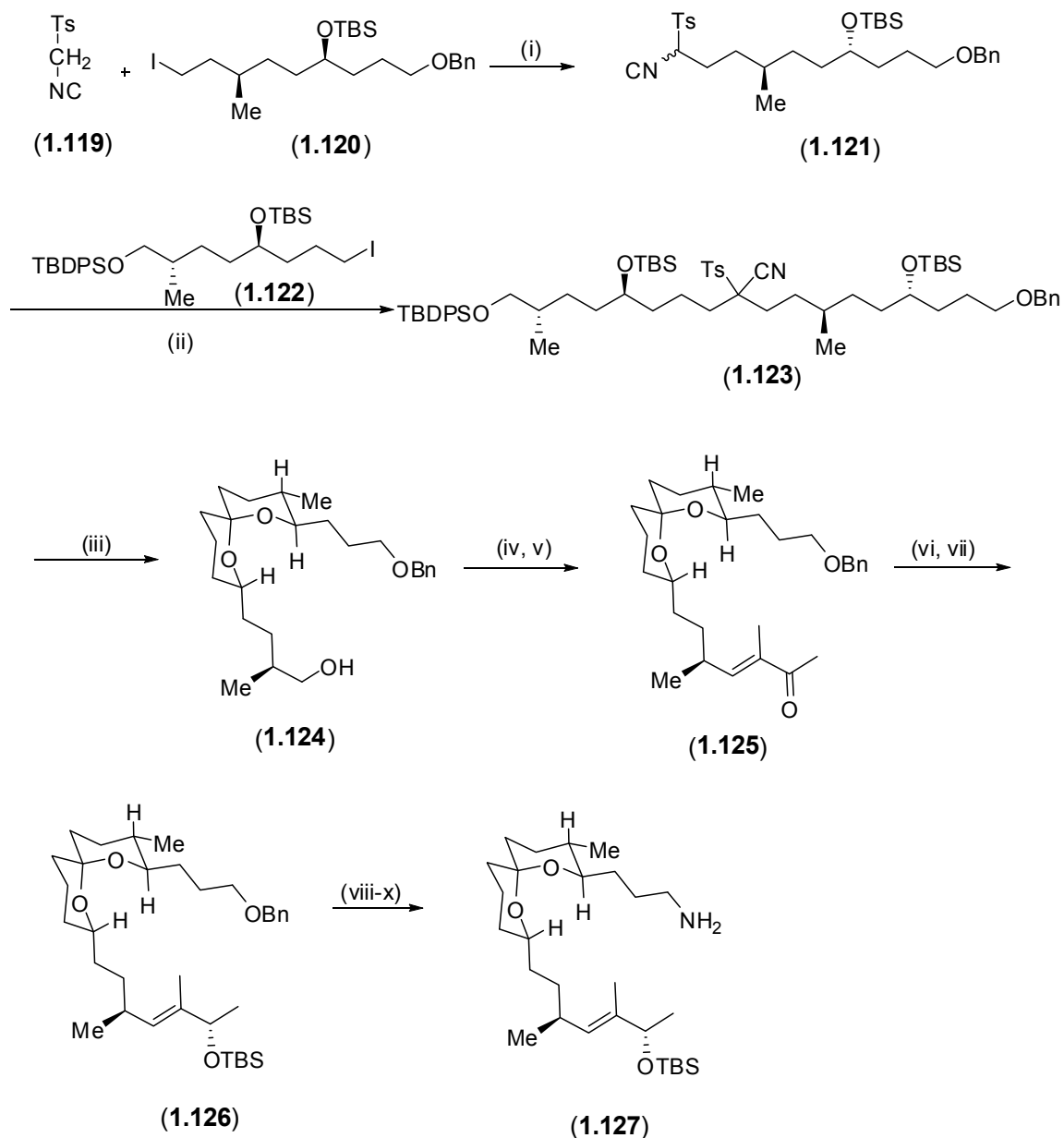


Scheme 26

Reagents and conditions: (i) $\text{MgBr}_2 \cdot \text{OEt}_2$, Et_3N , TMSCl , EtOAc ; (ii) $\text{MeO}(\text{H})\text{NMe} \cdot \text{HCl}$, Imidazole, CH_2Cl_2 , 84 %; (iii) TBSOTf , 2,6-lutidine, CH_2Cl_2 , 95 %; (iv) O_3 , CH_2Cl_2 , PPh_3 , MeOH , NaBH_4 , 75 %; (v) PPh_3 , $(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{O})\text{N}_3$, DIAD , THF , 80 %; (vi) KO^tBu , THF , H_2O (vii) TIPSOTf , CH_2Cl_2 , Et_3N , 72 %, (2 steps); (viii) H_2 , Pd/C , THF .

Yadav started the synthesis of spiroketal fragment **(1.127)** (Scheme 27) by alkylating TosMIC **(1.119)** with the alkyl iodide **(1.120)** to obtain **(1.121)**. Compound **(1.121)** on second alkylation with **(1.122)** yielded the dialkylated TosMIC **(1.123)** which on treatment with aq. HF afforded the desired spiroketal **(1.124)** in 85 % yield.³⁵ Swern oxidation of the primary alcohol yielded the corresponding aldehyde, which on Horner-Wadsworth-Emmons olefination, provided **(1.125)**. The stereoselective reduction of the ketone was achieved using a CBS reagent to obtain **(1.126)** which on subsequent conversions afforded the spiroacetal fragment **(1.127)**.

Yadav's synthesis of spiroketal fragment of bistramide A:



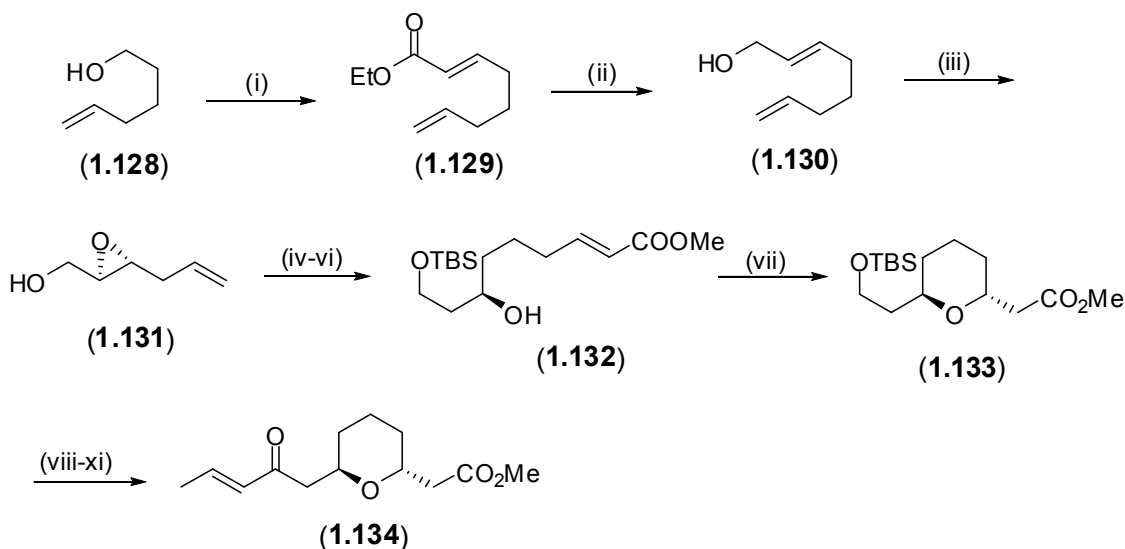
Scheme 27

Reagents and conditions: (i) n BuLi, HMPA, THF, -78 °C to rt, 90%; (ii) n BuLi, HMPA, THF, compound (1.122), -78 °C to rt, 83 %; (iii) aq. HF, MeOH, THF (1:1:1), 85 %; (iv) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -78 °C; (v) $\text{MeCOCH}(\text{Me})\text{P}(\text{O})(\text{OEt})_2$, $\text{Ba}(\text{OH})_2$, THF, 63 %, (2 steps); (vi) (*R*)-CBS, catecholborane, toluene, 93 %; (vii) TBSOTf, 2,6-lutidine, CH_2Cl_2 , 91 %; (viii) Na, $\text{NH}_3(l)$, THF, 89 %; (ix) PPh_3 , $(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{O})\text{N}_3$, DIAD, THF, 85 %; (x) PMe_3 , THF/ H_2O .

The highlight of Yadav's bistramide synthesis is the use of TosMIC intermediate to obtain the spiroketal. The advantage of using TosMIC over the dithiane is due to the presence of the sulphonyl group which not only enhances the acidity of the α -carbon but also acts as sulphinyl leaving group.

8. Piva's synthetic approach to bistramide A's THP fragment:

After our report on the synthesis of normethyl THP of bistramide D, Piva reported a similar approach for the synthesis of the THP of bistramide A, using Sharpless asymmetric epoxidation, a cross metathesis and an intramolecular Michael addition.⁴⁰⁻⁴² Piva's synthesis started from 1-hexenol (**1.128**), which on Swern oxidation and Wittig olefination provided the α,β -unsaturated ester (**1.129**) in 88 % yield. DIBAL reduction of the ester followed by Sharpless asymmetric epoxidation provided the epoxide (**1.131**) in high yield. Reduction of the epoxide followed by the selective protection of the primary alcohol and cross metathesis with methyl acrylate afforded the α,β -unsaturated ester (**1.132**) with a 97:3 *E/Z* ratio. Michael addition of the ester (**1.132**) under Banwell's conditions afforded the tetrahydropyran (**1.133**) as a 1.5:1 mixture of *trans* and *cis* isomers.⁴³ The side chain was then elaborated in a further four steps to give (**1.134**).

Piva's approach to normethyl THP of bistramide A:

Scheme 28

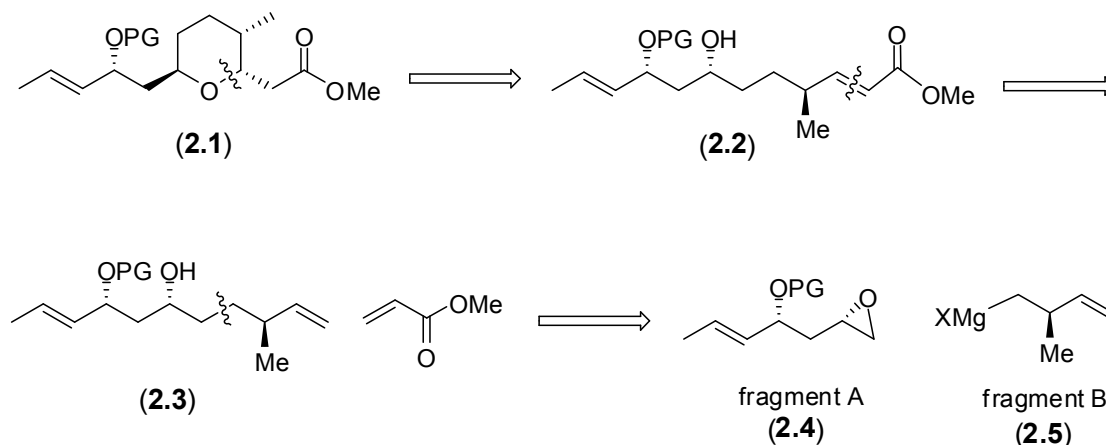
Reagents and conditions: (i) DMSO, (COCl)₂, CH₂Cl₂, -78 °C; 15 min then -78 °C to 0 °C, Ph₃P=CHCO₂Me, rt, 88 %; (ii) DIBAL-H, toluene, 85 %, (iii) (-)-D-DET, Ti(Oi-Pr)₄, ^tBuOOH, CH₂Cl₂, -20 °C, 81 % (iv) Red-Al, THF, 0 °C, 94 %; (v) TBSCl, imidazole, DMF, 0 °C, 78 %; (vi) methyl acrylate, Grubbs II, CH₂Cl₂, reflux, 99 %, *E/Z*=97:3, (vii) NaH, THF, -78 °C to rt, 90 %, *trans/cis*=1.5:1; (viii) TBAF, THF, 79 %; (ix) Dess-Martin periodinane, CH₂Cl₂; (x) allyl bromide, zinc, THF (xi) DMSO, (COCl)₂, CH₂Cl₂, -78 °C, 40 % (3 steps).

Conclusion:

In summary, bistramides are very attractive targets due to their important biological activities. Inspired by the biological activities and molecular architecture of bistramides, we are interested in the synthesis of bistramide D; not only because of its lower toxicity compared with the other congeners, but also that there has been no total synthesis of bistramides D reported to our knowledge.

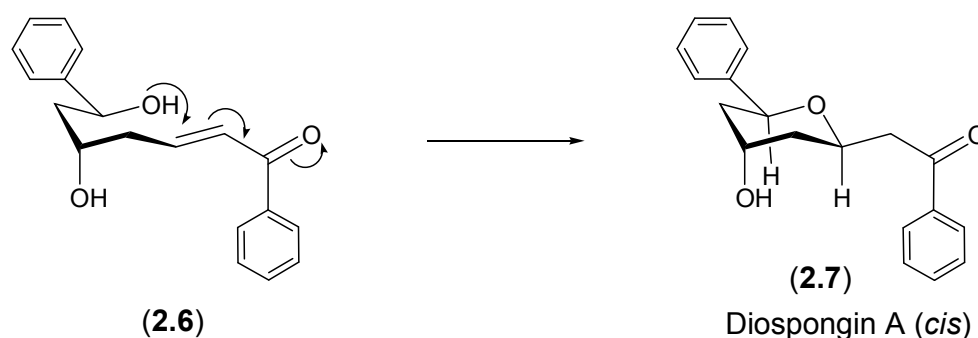
Chapter II: Synthesis of THP unit of bistramide D

Retrosynthetic approach to THP Fragment:



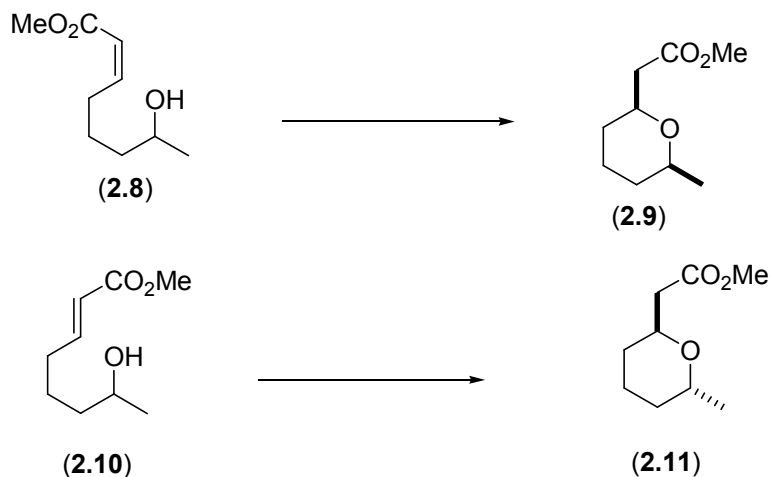
Scheme 29

Our retrosynthetic analysis starts with disconnection of the C-O bond in the tetrahydropyran ring (2.1), for which we planned to utilise an intramolecular Michael addition as it is a facile method for constructing heterocyclic rings and has recently been used for the synthesis of Diospongins A (2.7) in our group.⁴⁴ In the Diospongins synthesis an alcohol (2.6) undergoes nucleophilic addition to an enone moiety (Scheme 30). The product, the *cis* and therefore bis-equatorial isomer, is clearly the more stable of the two possible epimers, and it appears likely that the reaction is under thermodynamic control. On the other hand, Banwell has shown that the corresponding reaction of an alcohol under careful conditions can yield the product of kinetic control, the *trans* isomer, the one we required for bistramide D synthesis.⁴³



Scheme 30

Banwell showed that the stereoselectivity of the Michael addition is influenced by the geometry of the carbon-carbon double bond, while the (*Z*)-acrylate (**2.8**) proceeded to give the 2,6-*cis* tetrahydropyran (**2.9**), and the (*E*)-acrylate (**2.10**) provided the 2,6-*trans* tetrahydropyran (**2.11**) as the main product (scheme 31).



Scheme 31

Reagents and conditions: NaH, THF, - 78 °C to rt.

For the synthesis of the α,β -unsaturated ester (**2.2**), we planned to use a regioselective cross metathesis of the terminal alkene (**2.3**) with methyl acrylate. In recent years, olefin cross metathesis (CM) has emerged as a powerful and convenient synthetic technique in organic chemistry.⁴⁵ The prominence is due to the availability of catalysts with varied activities, such as (**2.12**), (**2.13**) and (**2.14**) (Figure 3) and these catalysts have expanded the variety of functional groups compatible with CM and have demonstrated the ability to prepare highly substituted olefins by CM.^{46,47}

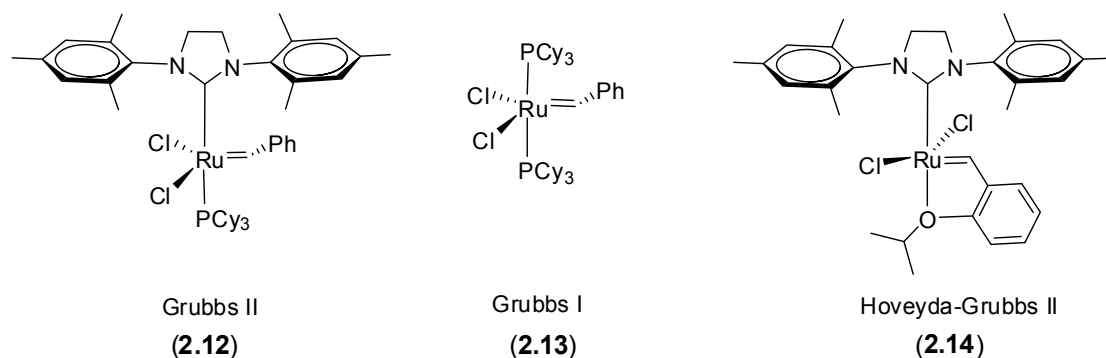
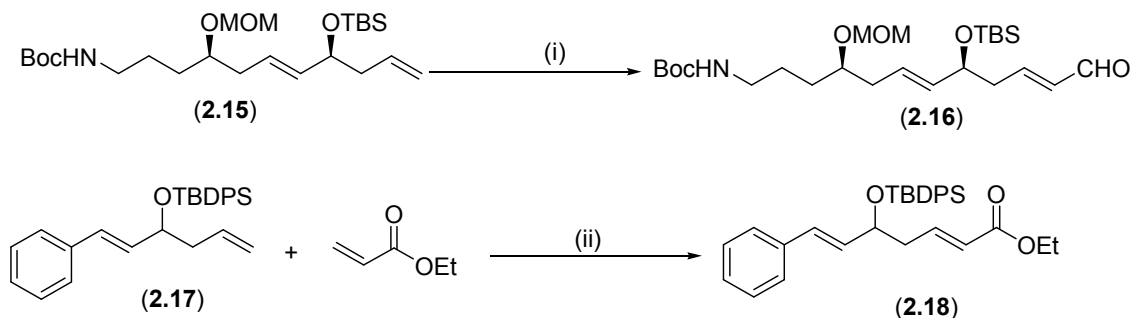


Figure 3

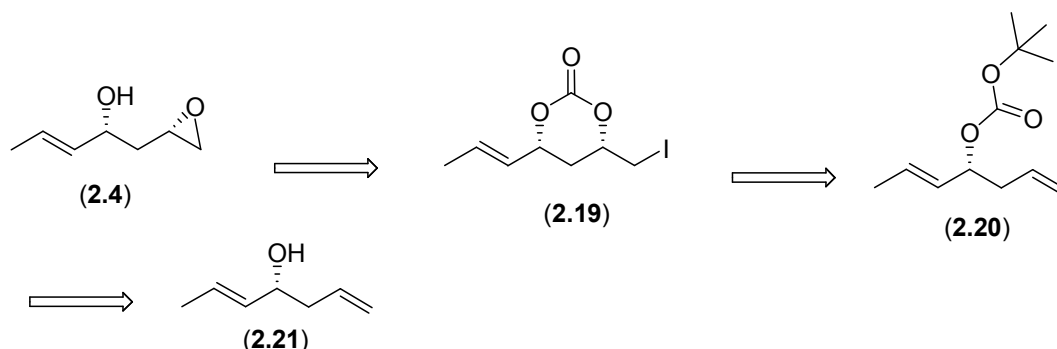
For the synthesis of the C1-C14 fragment of tetrafibracin, Cossy used an iterative sequence of chemoselective CM reactions (Scheme 32).^{48,49} Alkene (2.15), on treatment with excess acrolein (3 eq.) in the presence of 5 mol% of catalyst (2.14) exclusively afforded the aldehyde (2.16). Cossy explained that the observed selectivity is due to the presence of the bulky *tert*butyldimethylsilyl protecting group. This steric effect in the chemoselective CM reaction has been extensively studied.⁵⁰ We also hoped to achieve our regioselective CM by making use of this concept.



Scheme 32

Reagents and conditions: (i) Hoveyda-Grubbs II (5 mol %), Acrolein, CH₂Cl₂; (ii) Hoveyda-Grubbs II (5 mol %), CH₂Cl₂, 40 °C.

It was planned that the CM precursor (2.3) would be obtained from the epoxide ring opening of fragment A (2.4) by the Grignard reagent of fragment B (2.5).

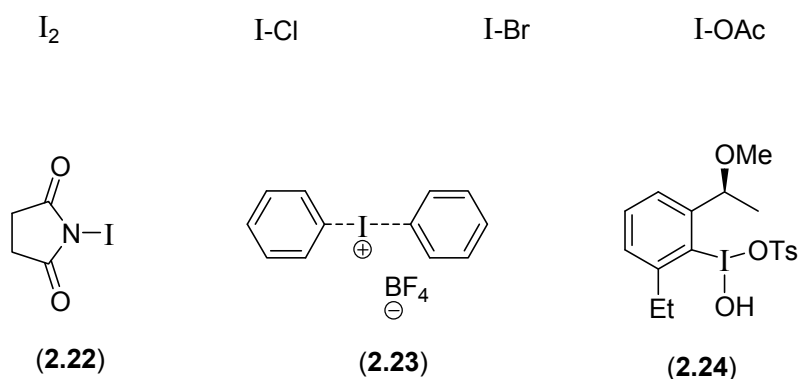
Synthesis of fragment A (2.4):**Retrosynthetic approach to Fragment A:**

Scheme 33

The synthesis of epoxide (2.4) could be achieved by a hydrolysis of the iodo carbonate (2.19). 1,3-Asymmetric induction of the homoallylic alcohol (2.21) was planned to be achieved via an iodocyclisation reaction, a convenient method to obtain a *syn* 1,3 diol, also used for the Diospongin A synthesis in our laboratory.

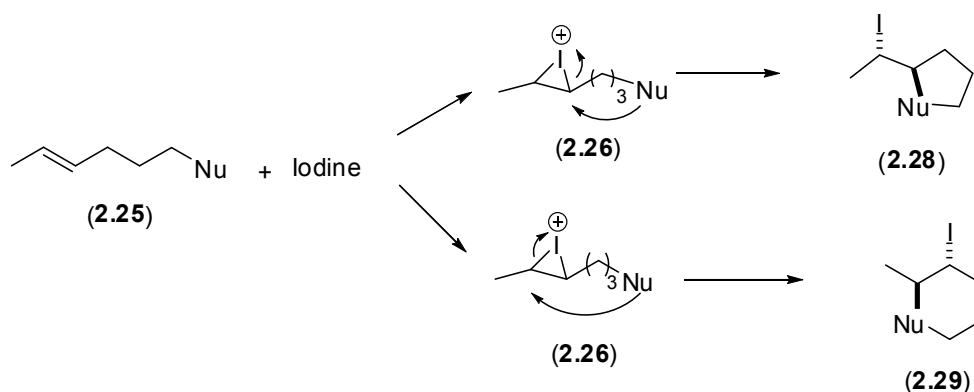
⁴⁴ The iodocyclisation reaction is well known for functionalizing double bonds in a regio and stereoselective manner. ⁵¹ Cardillo ⁵² and Bartlett ⁵³ studied in detail the applicability of this reaction towards primary, secondary, and tertiary allylic and homoallylic alcohols. The functionalisation of the double bond is highly regioselective; while allylic alcohols give five-membered rings, homoallylic alcohols give six membered rings.

A number of iodine electrophiles are available for iodocyclisation reactions; however elemental iodine is the most commonly used electrophile for the iodocyclisation reactions. Iodine monochloride, and iodine monobromide have been used for specific cases to achieve higher reactivity than iodine (Scheme 34). *N*-Iodosuccinimide (2.22), iodonium acetate and bispyridine iodonium tetrafluoroborate (2.23) and other chiral iodonium variants have also been synthesised and used in appropriate reactions. ⁵⁴



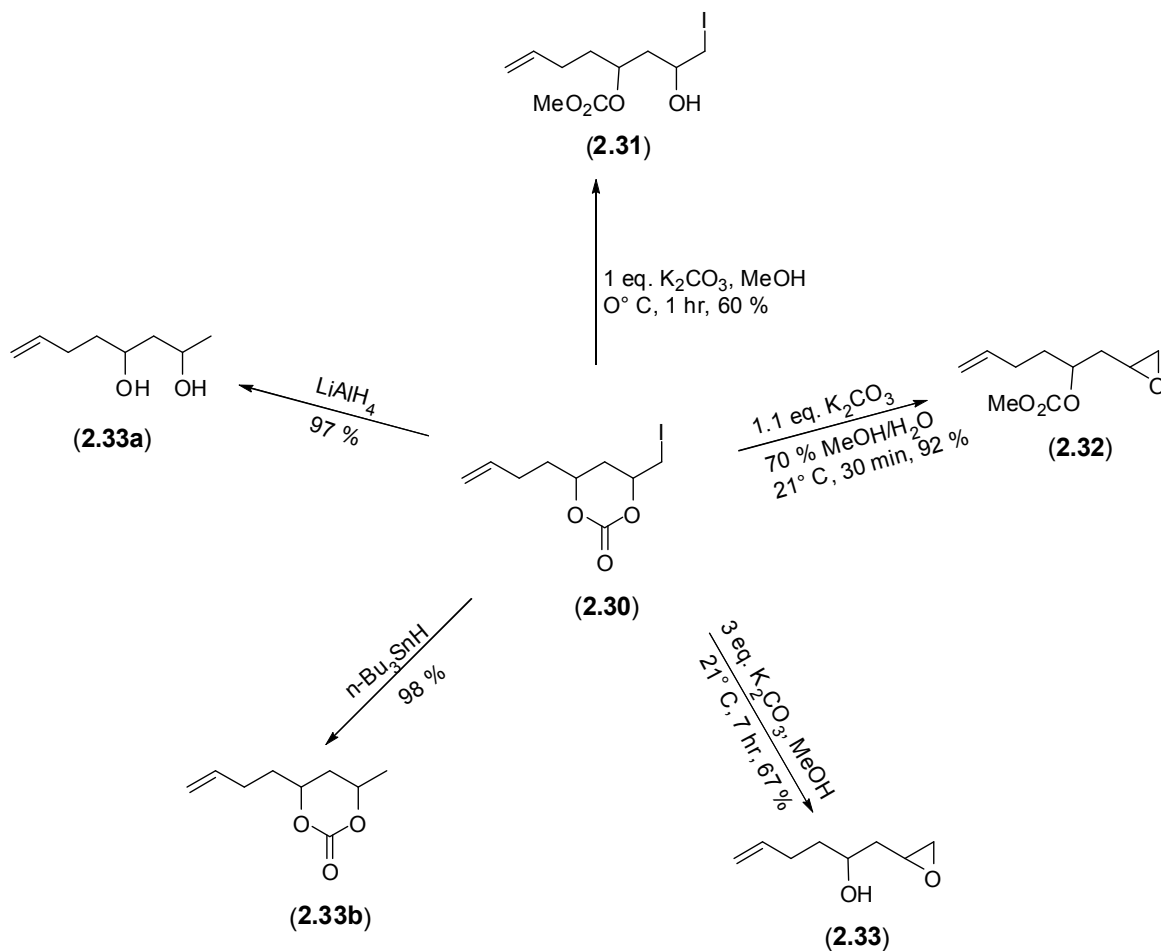
Scheme 34

The general reaction mechanism starts with the addition of the iodine to the alkene (2.25), to form an active iodonium intermediate (2.26) which is then attacked by the nucleophile (Scheme 35). The stereo and regiochemistry of the product mostly depends upon the structure of the starting material.⁵⁴



Scheme 35

The iodo carbonates are versatile with regard to their hydrolytic reactions. Bartlett showed that, depending on the vigour of alkaline methanolysis, iodo carbonate (2.30) can be converted to iodohydrin methyl carbonate (2.31), epoxy methyl carbonate (2.32), epoxy alcohol (2.33) or the diol (2.33a) in good to excellent yields (scheme 36).⁵³ These interesting features impressed us to opt for iodocyclisation to obtain the 1, 3 asymmetric induction.

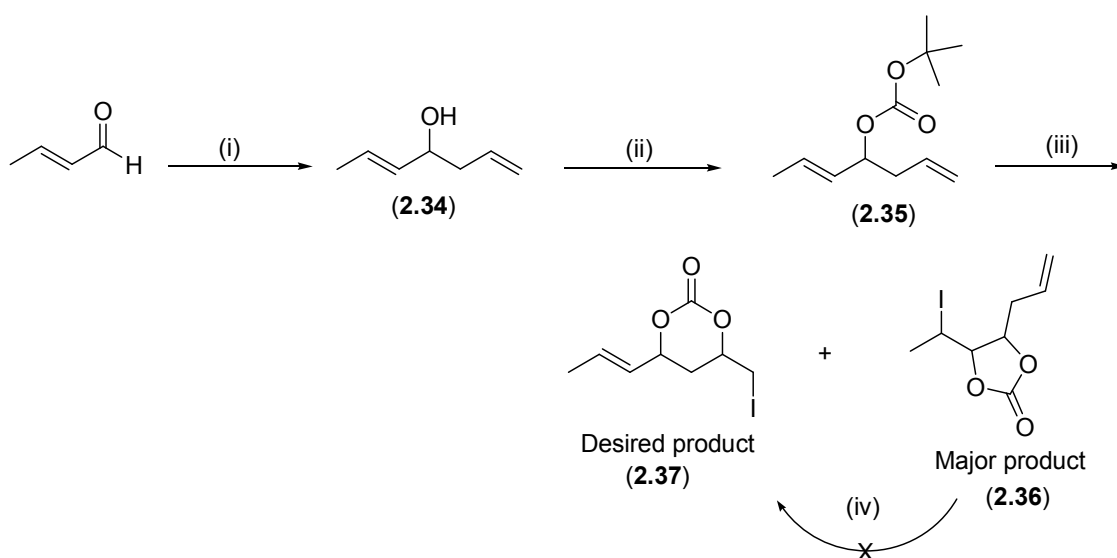
Iodolactone transformations: ⁵³

Scheme 36

Results and discussion:

Before proceeding to the iodocyclisation of the chiral alcohol, a model study was carried out to determine the cyclisation selectivity of the homoallylic double bond over the allylic double bond (scheme 37). The iodo cyclisation precursor (**2.35**) was synthesised from crotonaldehyde, which on reaction with allyl bromide under modified Luche conditions afforded the desired alcohol (**2.34**) in good yield.⁵⁵ The alcohol (**2.34**) was then treated with di-*tert*-butyl dicarbonate under standard conditions to obtain the iodocyclisation precursor (**2.35**) in 95 % yield. The iodocyclisation of alkene (**2.35**) with elemental iodine under Bartlett's conditions provided a mixture of two diastereomers. However careful ¹H NMR analysis of the crude reaction mixture revealed that the reaction yielded mainly

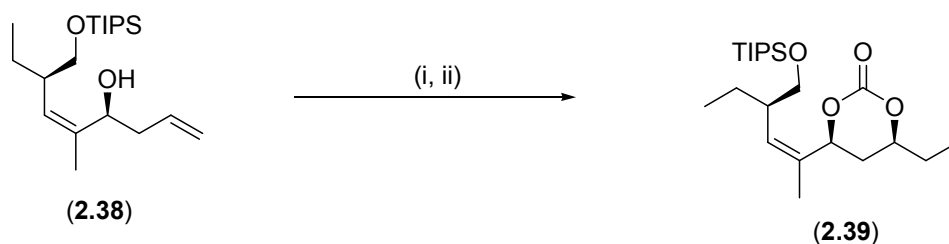
the five membered lactone (**2.36**), by cyclisation onto the allylic double bonds. The desired six membered cyclic carbonate (**2.37**) was formed as a minor product. This result was not surprising as five membered ring formation is faster than the six membered ring formation and also the disubstituted alkene is more reactive.⁵⁶ Iodocyclisation is a reversible reaction, so equilibration of the five membered cyclic carbonate (**2.36**) to the desired six membered cyclic carbonate (**2.37**) was attempted using NaI. To our disappointment no change was observed in the reaction, however, even after a prolonged period of time.



Scheme 37

Reagents and conditions: (i) Allyl bromide, Zn, aq. NH_4Cl , THF, 56 %; (ii) $(\text{Boc})_2\text{O}$, DMAP, CH_3CN , imidazole, EtOH, 95 %; (iii) I_2 , CH_3CN , $-40\text{ }^\circ\text{C}$, DMF; (iv) NaI, CH_3CN .

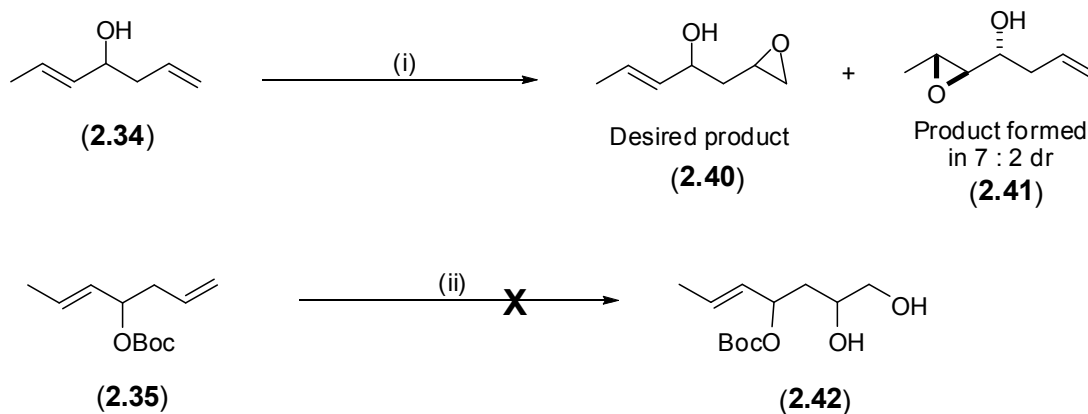
N-iodosuccinamide was used as an alternative iodine electrophile to improve the selectivity of the cyclisation as Taylor reported that NIS selectively lactonised the homo allylic bond in the presence of an allylic bond (Scheme 38).⁵⁷ However our trials with NIS resulted in a complex mixture of products.



Scheme 38

Reagents and conditions: (i) Boc-ON, 91 %; (ii) NIS, CH₃CN, 92 %.

As Iodocyclisation turned to be very selective towards the allylic double bond we moved our focus to try other alternatives to get the selective functionalisation of the homo allylic double bond. Epoxidation was our next reaction. Recently a remarkable number of stereoselective epoxidations been achieved for various allylic and homoallylic alkenes but we were unaware of any experiments to compare the two. As our first trial we opted for Mihelich's and Sharpless's vanadium catalysed epoxidation (Scheme 39), using VO(acac)₂ with *tert*-butyl hydroperoxide in anhydrous dichloromethane.⁵⁸ ¹H NMR results showed that, epoxidation is highly selective for the allylic bond (**2.41**) forming a ratio of 7:2 diastereomers and no epoxide formation at the homo allylic bond (**2.40**) was observed. This once again confirmed the strong preference for the allylic double bond over the homo allylic bond. Moving on from epoxidation, we also explored the selectivity of dihydroxylation of the homoallylic bond over the allylic bond. Tsuji's osmium tetroxide catalysed vicinal hydroxylation was carried out (Scheme 39).⁵⁹ Despite the literature precedent, the reaction was not selective; giving a number of components by TLC and no attempt was taken to purify the reaction mixture.

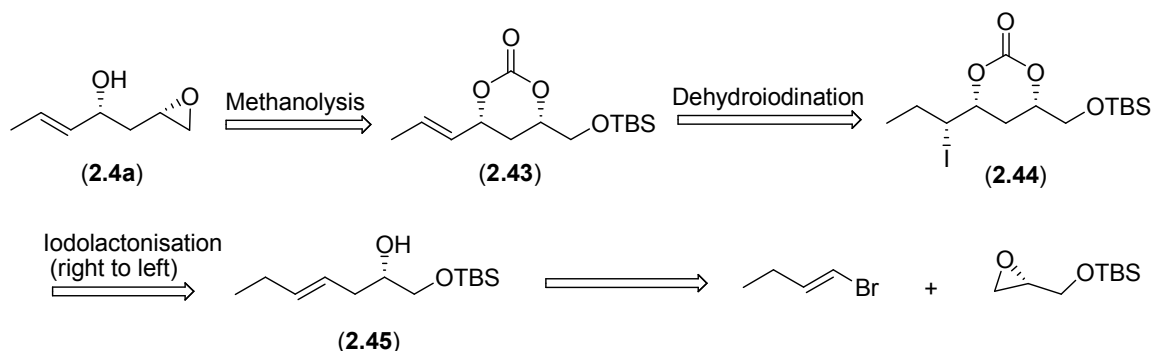


Scheme 39

Reagents and conditions: (i) VO(acac)₂, Na₂HPO₄, ^tBuOOH, CH₂Cl₂; (ii) K₂OsO₄·2H₂O, K₃FeCN₆, K₂CO₃, ^tBuOH, H₂O, no product.

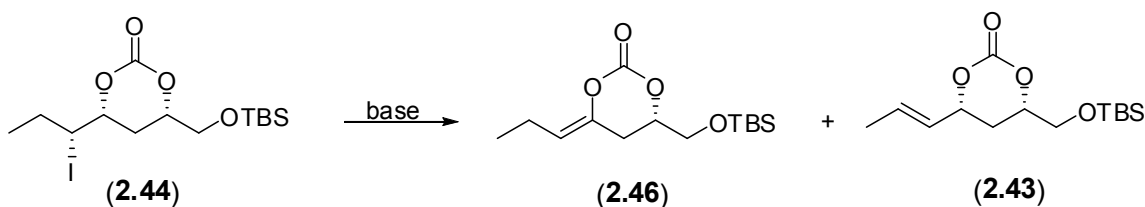
New Retrosynthetic Approach to Fragment A:

Since our approach for selective functionalisation of homo allylic double bond in presence of highly reactive allylic double bond did not proceed, we therefore turned to the “right-to-left” option, constructing the required homoallylic alcohol (2.45) first and introducing the allylic double bond later as shown in retrosynthesis. (Scheme 40)



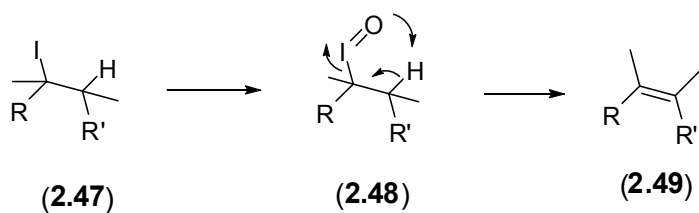
Scheme 40

The new retrosynthesis starts from the methanolysis of cyclic carbonate (2.43) to obtain the hydroxy epoxide (2.4a). The dehydroiodination reaction of (2.44) was planned to be achieved using Reich’s iodoso elimination procedure, since the normal base induced elimination may lead to the unwanted alkene (2.46) formation (Scheme 41).⁶⁰



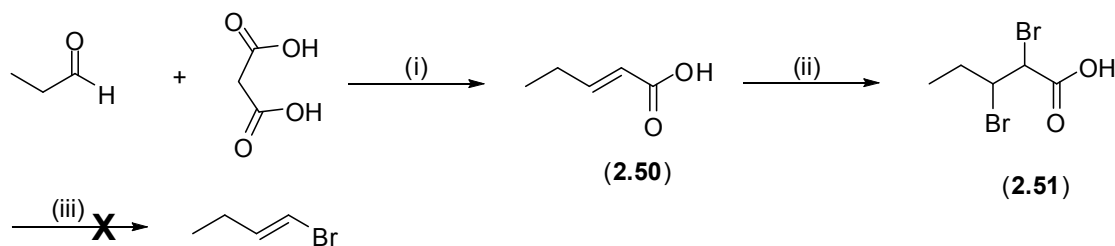
Scheme 41

Reich's iodoso elimination is a rare kind of elimination process where the alkyl iodide has been oxidised (2.47) to an iodoso intermediate (2.48) (Scheme 42). Similar to sulfoxide and selenoxide eliminations, the iodoso intermediate also undergoes a *syn* elimination to afford the desired olefin (2.49). The iodocarbonate (2.44) can be prepared from Bartlett's Iodocyclisation of the hydroxyl heptene (2.45), which was planned to be prepared from the appropriate butene organometallics and the TBS protected (racemic) epichlorohydrin.⁶⁰



Scheme 42

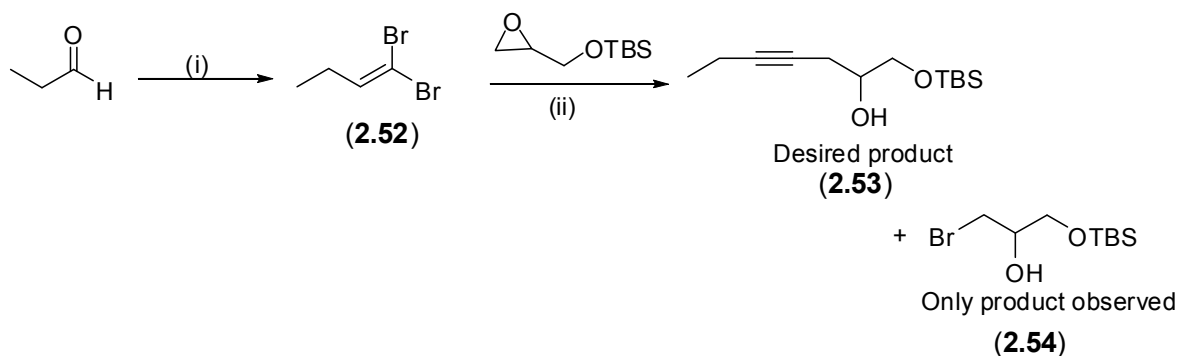
Michelot's procedure was used for the synthesis of 1-butenylbromide.^{61,62} Knoevenagal condensation, following Doebner's modification, of propanaldehyde with malonic acid in the presence of pyridine afforded *trans*-2-pentenoic acid (2.50) in excellent yield, which on treatment with bromine in dichloromethane provided the corresponding α,β -dibromo acid (2.51) in high yield.⁶³ However, attempts for debromination and decarboxylation to obtain the desired butenyl bromide were not successful despite several attempts.



Scheme 43

Reagents and conditions: (i) pyridine, reflux, 97 %; (ii) Br₂, CH₂Cl₂, 0 °C to RT, 95 %; (iii) NaHCO₃, DMF, no product.

Since this route did not give satisfactory results, Corey and Fuchs's method was used to synthesise the dibromobutene (**2.52**), as a source of lithio butyne for the epoxide ring opening reaction.⁶⁴ Treatment of propanal with carbon tetrabromide and triphenyl phosphine afforded the desired dibromobutene (**2.52**) in moderate yield (Scheme 44). However the lithiobutene generated from the dibromobutene (**2.52**) did not undergo the nucleophilic ring opening of the epoxide even in the presence of a Lewis acid, BF₃.Et₂O, instead, the bromohydrin (**2.54**) was obtained as the sole product.

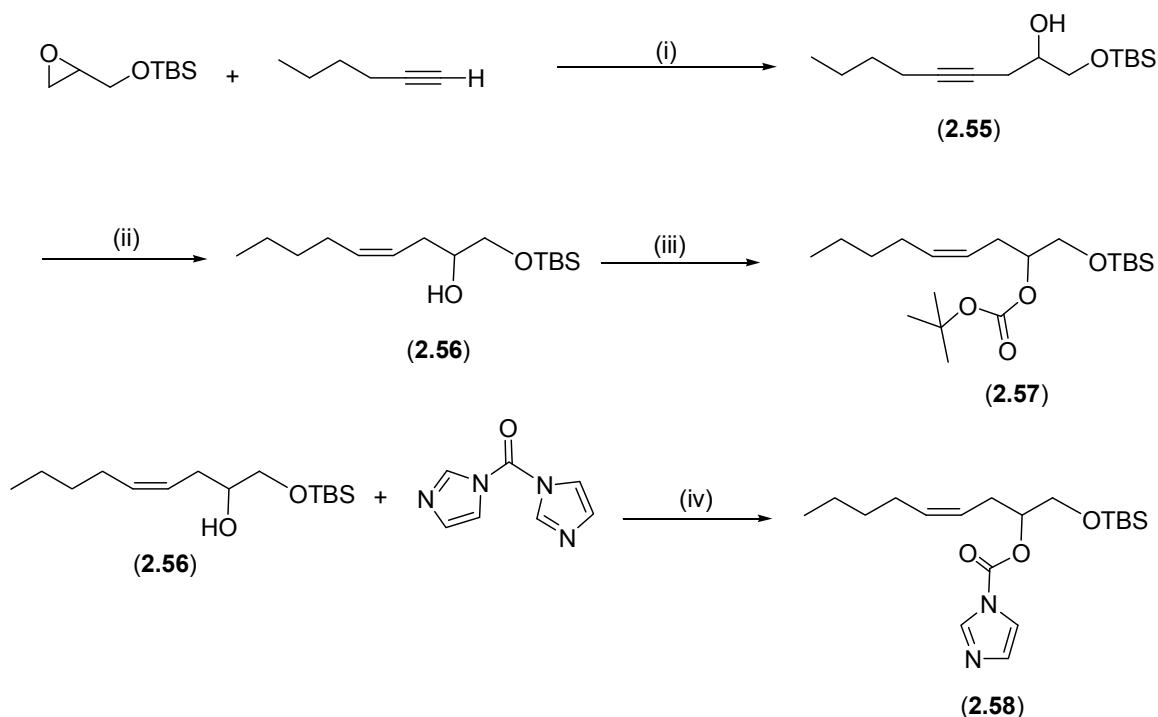


Scheme 44

Reagents and conditions: (i) CBr₄, PPh₃, Zn, CH₂Cl₂, 40 %; (ii) 2 eq. ⁿBuLi, BF₃.Et₂O, THF, -78 °C.

After encountering difficulties in generating appropriate butene organometallics, we chose lithio-butyne, as our next alternative. While waiting for the arrival of 1-

butyne gas, model studies were carried out with 1-hexyne, as it is a liquid and more convenient to work with. Epoxide ring opening with lithiohexyne worked well in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in THF at -78°C to afford the desired product (**2.55**) in 98 % yield (Scheme 45).^{65,66} However trials to introduce *tert*-butoxycarbonyl (Boc) group on alcohol (**2.55**) under standard conditions were not successful. The *in situ* generation of Boc group using carbonyldiimidazole and *tert*-butyl alcohol resulted in the formation of acyl imidazole derivative (**2.58**) as the only isolated product, which we presume to be derived from the direct attack of the alcohol on the carbonyldiimidazole without participation of the $^t\text{BuOH}$.⁶⁷

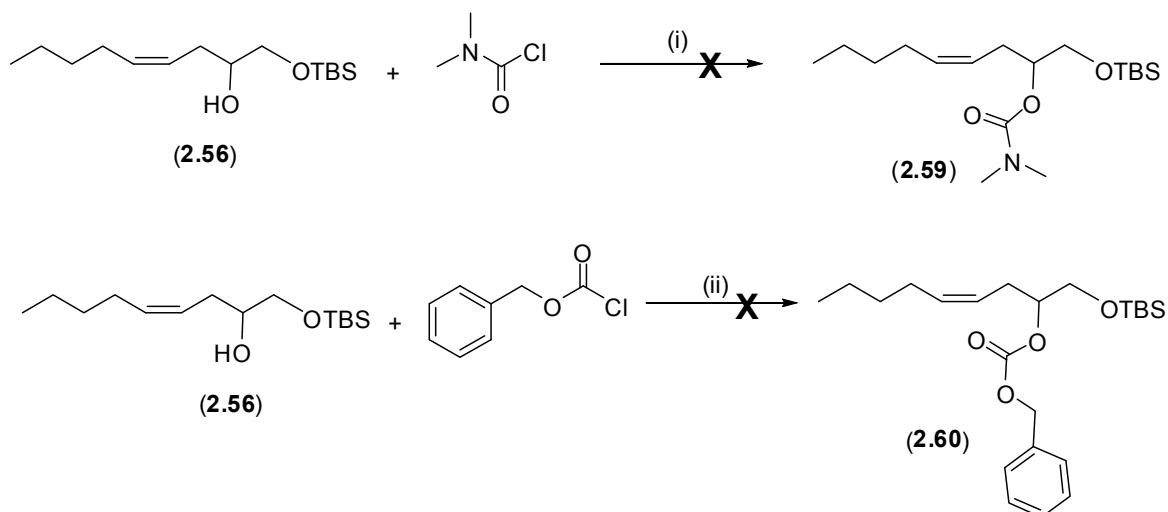


Scheme 45

Reagents and conditions: (i) $^n\text{BuLi}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF, -78°C , 98 %; (ii) H_2 , Pd (Pb, poisoned), pyridine, THF, 99 %; (iii) Boc_2O , DMAP, CH_3CN , no product; (iv) $^t\text{BuOH}$, DMAP, THF.

Since the attempts to introduce the Boc group were unsuccessful, carbonylation was carried out with dimethylcarbonyl chloride under standard conditions (Scheme 46). Disappointingly there was no product formation and the starting

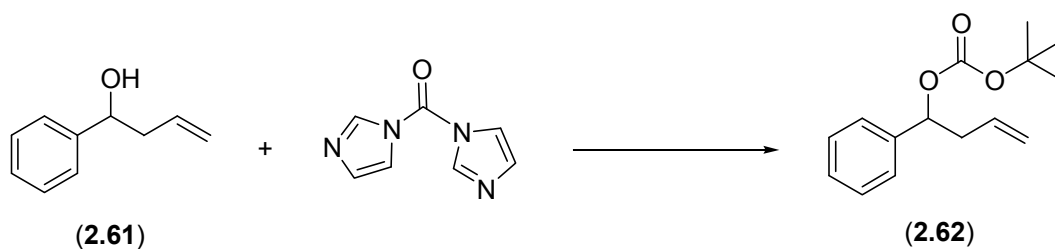
material was recovered. Our last trial was the reaction with carbobenzyloxy chloride (Cbz-Cl) to obtain the Cbz precursor (**2.60**) for the iodocyclisation. To our frustration that reaction also did not result in the product (**2.60**) formation, even under forcing conditions.



Scheme 46

Reagents and conditions: (i) Et_3N , CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to RT, no product; (ii)(a) Et_3N , CH_2Cl_2 , $0\text{ }^\circ\text{C}$ to RT, no product; (b) Et_3N , toluene, reflux, no product; (c) Et_3N , DMAP, toluene, reflux, no product.

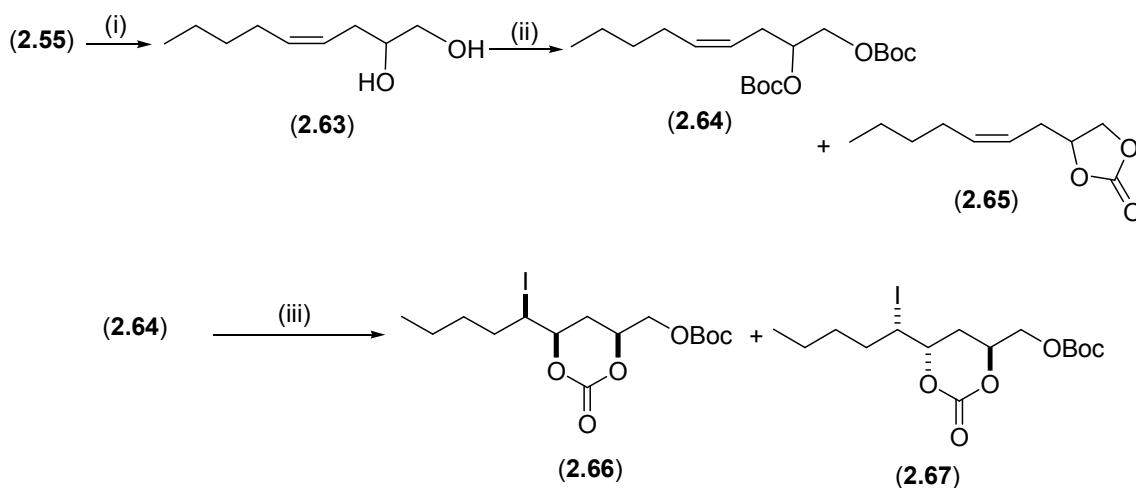
From the above experimental results we presumed that this reluctance of the alcohol (**2.56**) may be due to the steric hindrance of the bulky TBS group, which is prohibiting the neighbouring oxygen, from reacting with a comparatively large Boc group. To confirm the steric effect, Boc substitution was carried out with the less hindered alcohol (**2.61**) under the identical conditions used for the alcohol (**2.56**). Unsurprisingly, the model alcohol (**2.61**) afforded the Boc substituted product (**2.62**) in 90 % yield.



Scheme 47

Reagents and conditions: ^tBuOH, DMAP, THF, 90 %.

At one time during the hydrogenation of the alkyne (**2.55**) under Lindlar's conditions, the diol (**2.63**) was obtained unexpectedly, which was the desired *cis* alkene, but without the protecting (TBS) group. We planned to utilise this diol (**2.63**) to make the Boc derivative (**2.64**) and then to try an iodocyclisation reaction to check the selectivity. The reaction of diol (**2.63**) with Boc₂O under standard conditions afforded the desired product (**2.64**) in moderate yield but the reaction also yielded an equal amount of the five membered cyclic carbonate (**2.65**) as side product. Surprisingly there was not even a trace amount of mono Boc substituted product was observed. Iodocyclisation was carried out with the diBoc derivate (**2.64**), using iodine under Bartlett conditions.⁶⁸ The reaction proceeded smoothly in good yield but with moderate selectivity affording (3:1) mixture of the desired *syn* product (**2.66**) and the corresponding *anti* isomer (**2.67**).

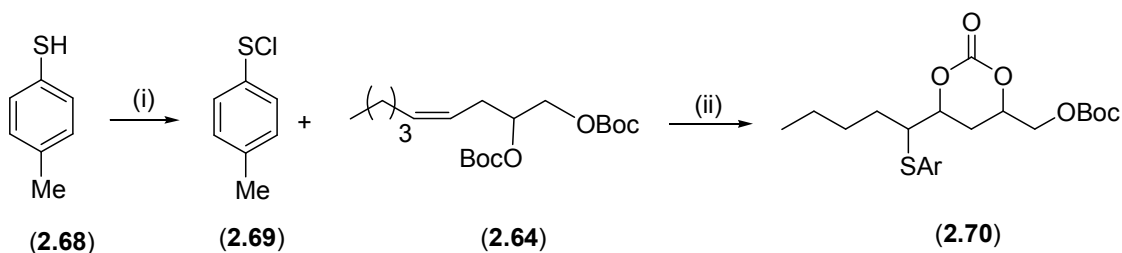


3 : 1

Scheme 48

Reagents and conditions: (i) (a) H₂, Pd (Pb, poisoned), pyridine, THF, 64 % (b) PPTS, MeOH, 98 %; (ii) Boc₂O, DMAP, THF 0 °C to RT, 21%; (iii) I₂, CH₃CN, 0 °C to RT, 80 % (3 : 1).

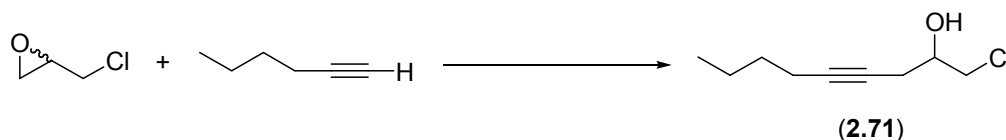
A simultaneous approach for the cyclisation reaction was carried out using aryl sulfenylchloride (**2.69**) as other alternative for the halogen electrophiles.⁶⁹ The aryl sulfenylchloride (**2.69**) was synthesised from arylthiol (**2.68**), by reacting with *N*-chlorosuccinimide in dichloromethane (Scheme 49). Reaction of the alkene (**2.64**) with arylsulfenyl chloride in dichloromethane at -78 °C resulted in the formation of more than 3 components in TLC. The crude ¹H NMR analysis showed, the disappearance of the double bond protons at 5.6 and 5.3 ppm and appearance of the new protons in the aryl region 7.1 and 7.3 ppm, however, peaks consistent with the formation of the desired product (**2.70**) were observed. We suspect this result may be due to the too high reactivity of ArSCl which is undergoing the unwanted side reactions.⁷⁰



Scheme 49

Reagents and conditions: (i) NCS, CH₂Cl₂, 0 °C; (ii) CH₂Cl₂, -78 °C, no product.

The above experiments clearly showed that the bulky TBS and Boc groups at the terminal positions are not suitable for the synthesis of fragment-A (**2.4**), so we modified our synthetic approach by using epichlorohydrin instead of the TBS protected epoxy propane (Scheme 50). Considering that the chlorine atom is relatively small, it would not cause any problem during the Boc substitution and also it can be easily transformed when required. The model study was continued with 1-hexyne and racemic epichlorohydrin as it is cheap and obtaining it in its optically pure form is also easy via a kinetic resolution using Jacobsen's strategy.⁷¹

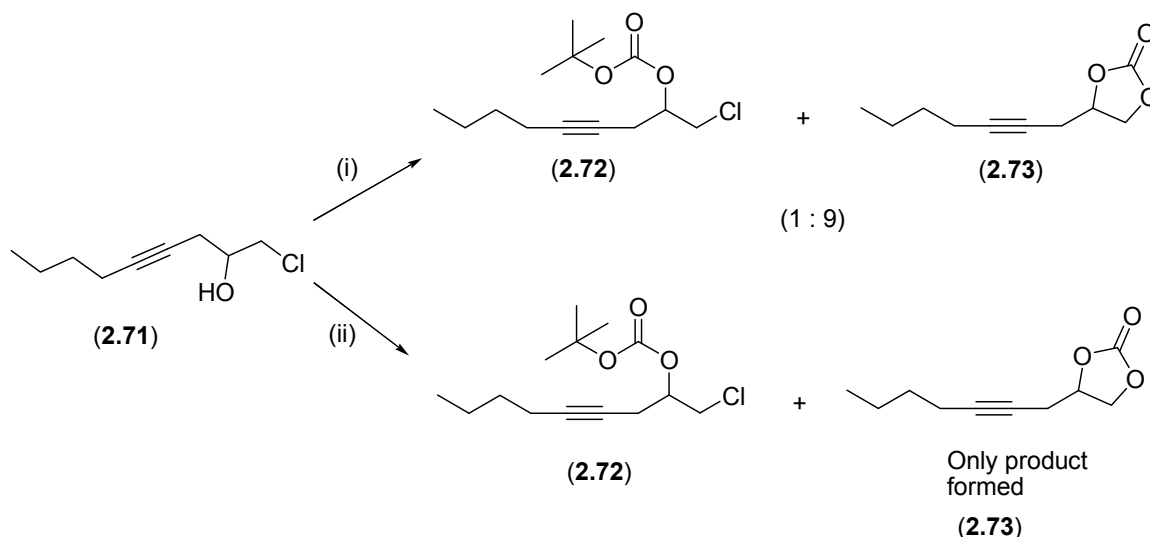


Scheme 50

Reagents and conditions: ⁿBuLi, BF₃.Et₂O, THF, -78 °C, 88 %.

Ring opening of epichlorohydrin with lithiohexyne proceeded well under the same conditions used for the TBS protected epoxide, yielding the chlorohydrin (**2.71**) in 88% yield (Scheme 51). Attempts to introduce the Boc group on the secondary alcohol (**2.71**) under standard conditions resulted in the formation of large amount of the cyclic carbonate (**2.73**) and only a small amount of the

desired product (**2.72**) in (~9:1) ratio. This may be because of the nucleophilic oxygen next to the *tert*-butyl group is displacing the chlorine atom; it's not surprising, as chloride is expected to be a good leaving group.⁷² In order to prevent the formation of the cyclic carbonate (**2.73**), Boc substitution was carried out under mild conditions using carbonyldiimidazole in *t*BuOH. To our disappointment, under this condition the reaction yielded the cyclic carbonate (**2.73**) as the sole product. However, subsequent optimisation reactions (Table 1) showed that the use of 1.5 eq. of Boc₂O with 0.4 eq. of DMAP at low temperature affords the desired product (**2.72**) in 84 % yield without any formation of the cyclic carbonate.



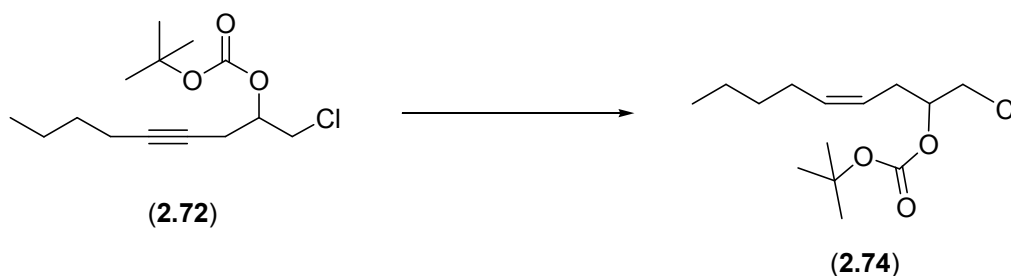
Reagents and conditions: (i) Boc₂O, DMAP, CH₃CN, RT, (1:9) ratio; (ii) carbonyl diimidazole, *t*BuOH, DMAP, THF.

Table 1: Optimisation conditions for the Boc substitution.

Boc ₂ O (eq.)	DMAP (eq.)	Solvent	Temperature	Yield/ratio (2.72):(2.73)
2.5	2.0	CH ₃ CN	RT	1:9
2.0	1.0	CH ₃ CN	RT	1:2
2.0	0.5	CH ₃ CN	RT	1:1 ^a
2.0	0.6	CH ₃ CN	0 °C	8:1
1.5	0.4	THF	-40 °C	78 % ^{a,b}
1.5	0.6	THF	-40 °C to 0 °C	8:2 ^a
1.5	0.4	THF	-40 °C to 0°C	84 %^b

a: some starting material was recovered, b:(**2.72**) is the only product and no cyclic carbonate formation was observed

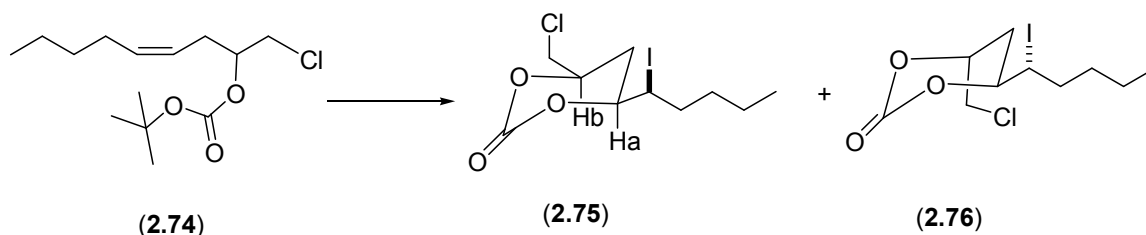
After identifying suitable conditions for the Boc substitution reaction, semi-hydrogenation of the alkyne was carried out using Lindlar's catalyst, which afforded the *cis* alkene (**2.74**) in quantitative yield. However, the yield of the hydrogenation was capricious, older bottles of catalyst resulting in no product formation, even with a high loading of catalyst and extended reaction time. Due to this unpredictability of Lindlar's catalyst, Brown's nickel boride was used.⁷³ Brown's P2-Nickel was very efficient for the hydrogenation of alkyne (**2.72**) affording the desired alkene (**2.74**) in quantitative yield. In addition, the synthesis of the nickel boride is also very simple from readily available starting materials.



Scheme 52

Reagents and conditions: (a) H₂, Lindlar's catalyst, pyridine, THF, 0-99 %; (b) H₂, P2-Nickel, EtOH, 99 %.

Iodocyclisation of the alkene was carried out using Bartlett and Cardillo's conditions.^{74,68} Our initial trials of the iodocyclisation under standard conditions did not give satisfactory selectivity. So, optimisation of the reaction using various halogen sources, solvents and temperatures were carried out (Table 2). To our delight, the treatment of alkene (2.74) with iodine in acetonitrile at -10 °C affords the desired *syn* cyclic carbonate (2.75) in moderate yield with good selectivity (4:1). The stereochemistry was clearly identifiable by ¹H NMR via the coupling constants (*J*) of the two axial protons H_a and H_b. The signal for H_a appeared at 4.37 ppm as (ddd, *J* = 3.1, 3.1, 11.7 Hz), but H_b appeared as a multiplet at 4.66-4.74 ppm. To simplify the multiplicity pattern, a homo nuclear decoupling experiment was carried out by irradiating the CH₂Cl protons, and the *J*_{ax-ax} was found to be 11.6 Hz. It may be noted that these iodocarbonates (2.75), (2.76) are light sensitive, and decomposable at room temperature, so need to be stored at low temperature and in the dark.



Scheme 53

Table 2: Optimisation conditions for the iodocyclisation.

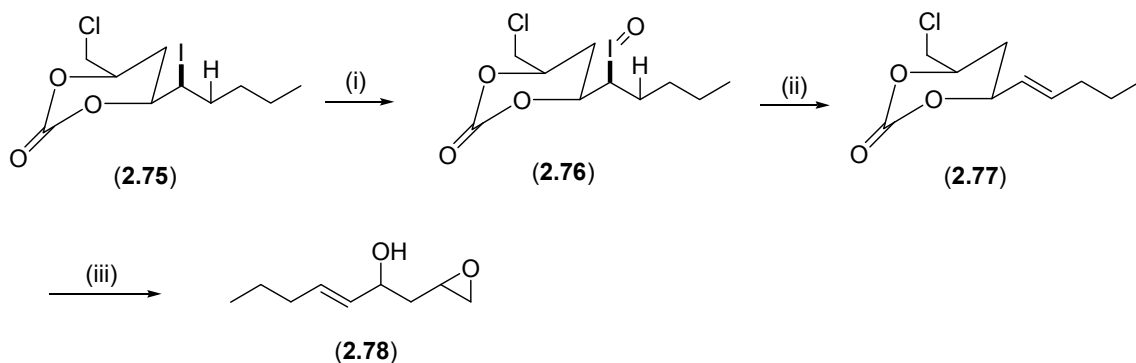
Reagent (additive)	Solvent	Temperature	Ratio (2.75):(2.76) Yield (%)
Iodine	Acetonitrile	-40 °C	50 (1.3:1)
Iodine	Acetonitrile	RT	15 (4:1) ^a
Iodine	THF	-10 °C	52 (3:1)
Iodine (NaHCO ₃)	Ether	0 °C to RT	54 (3:1)
Iodine	Acetonitrile	0 °C	48 (4:1)
Iodine	THF	RT	0
Iodine (NaH ₂ PO ₄)	Acetonitrile	RT	0
NBS	Acetonitrile	-78 °C	0 ^c
NBS	Acetonitrile	-20 °C	0 ^c
NBS	Acetonitrile	RT	0 ^c
NIS ^b	Acetonitrile	-20 °C	0 ^c
Iodine	Acetonitrile	-10 °C	67 (4:1)

(a) Product decomposed at room temperature over prolonged time; (b) synthesised from NCS; (c) only starting material recovered.

Reich's strategy was used for the dehydroiodination of the iodo carbonate (**2.75**).

⁶⁰ Our initial attempt for dehydroiodination with 1.5 eq. of *m*CPBA in presence of satd. aq. NaHCO₃ solution in dichloromethane at room temperature did not proceed well. The crude ¹H NMR spectrum showed, a large amount of starting material and the presence of the desired alkene (**2.77**), clearly identifiable at 5.87 ppm as a double triplet and a double doublet at 5.48 ppm. To achieve complete conversion, the reaction mixture was stirred for a longer time (48 h). Frustratingly, it resulted in the formation of number of impurities and the reaction did not go to completion as the crude ¹H NMR spectrum was still showing the presence of starting material (**2.75**). However, our attempts to purify the crude

reaction mixture by flash column chromatography also failed as there is no difference in the R_f values of the starting material (**2.75**) and product (**2.77**). Since increasing the reaction time gave many impurities, the amount of oxidant was increased from 1.5 to 2.2 eq. and the reaction was repeated at lower temperature (-30 °C). To our surprise, under the above conditions the desired alkene (**2.77**) was obtained in high yield without any purification, other than extraction, as the ^1H NMR of the crude reaction mixture was very clean and no epoxide formation was observed at the newly formed alkene. As anticipated methanolysis of the cyclic carbonate was efficient giving the epoxide (**2.78**) in 82 % yield, showing that the choice of chloride was justified.⁵³

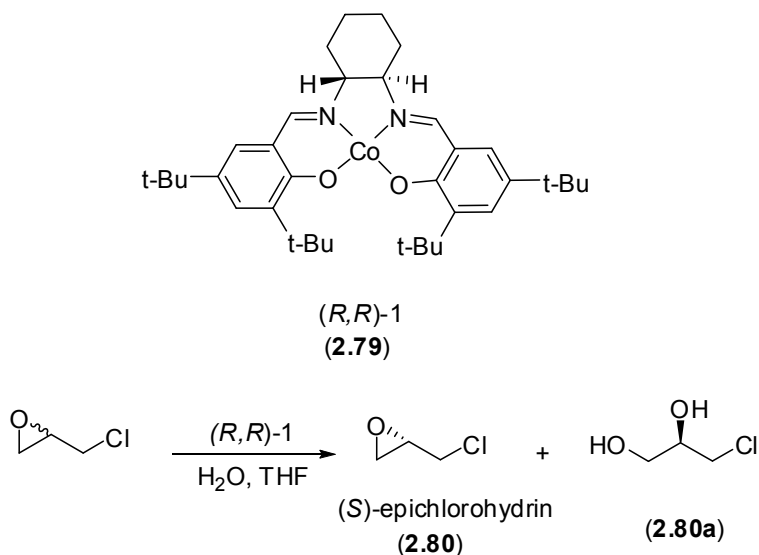


Scheme 54

Reagents and conditions: (i) (a) *m*CPBA (1.5 eq.), satd. aq. NaHCO_3 , CH_2Cl_2 , RT; (b) *m*CPBA (2.2 eq.), NaHCO_3 , CH_2Cl_2 , -30 °C to RT, 95 % (iii) MeOH, K_2CO_3 , 0 °C to RT, 82 %.

After demonstrating the synthesis of fragment-A with the model (racemic epichlorohydrin and 1-hexyne), the synthesis of fragment A (**2.4**) was started with 1-butyne and (*S*)-epichlorohydrin (**2.80**) (Scheme 56). To obtain optically pure (*S*)-epichlorohydrin, we adopted Jacobsen's hydrolytic kinetic resolution (HKR).⁷⁵ The racemic epichlorohydrin on treatment with the (*R,R*)-Jacobsen's catalyst (**2.79**) and water in THF afforded optically pure epichlorohydrin (**2.80**) (Scheme 55) in 41% yield. HKR is an efficient way to synthesise optically pure

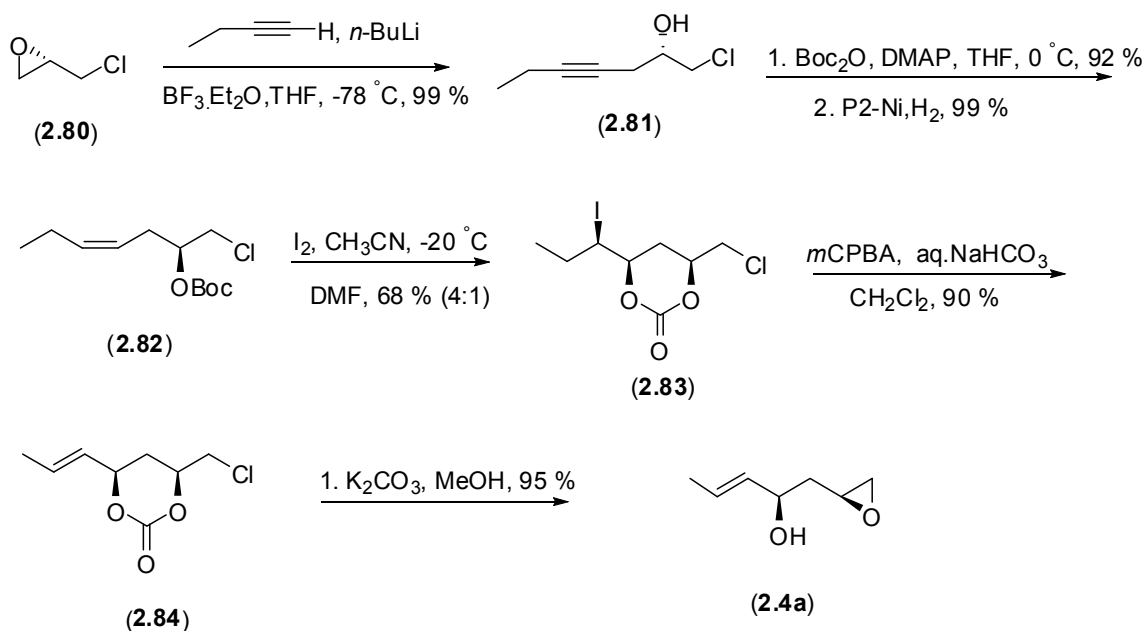
epichlorohydrin as the catalyst loading is low (5 mol %), use of water as the nucleophile makes the process more environmentally acceptable; and, notably, the separation of the product from the diol by-product (**2.80a**) was easy via a simple distillation. 1-Butyne is commercially available, but, it is difficult to handle and measure this chemical as it is a gas. The reaction was carried out by filling an evacuated round bottom flask with 1-butyne gas and calculating the amount of gas from the volume of the flask using the ideal gas law. Epoxide (**2.80**) ring opening was carried out by cooling the flask to $-78\text{ }^{\circ}\text{C}$ and following the same procedure used for 1-hexyne, affording the alcohol (**2.81**) in quantitative yield, which was taken for the next step without further purification.



Scheme 55

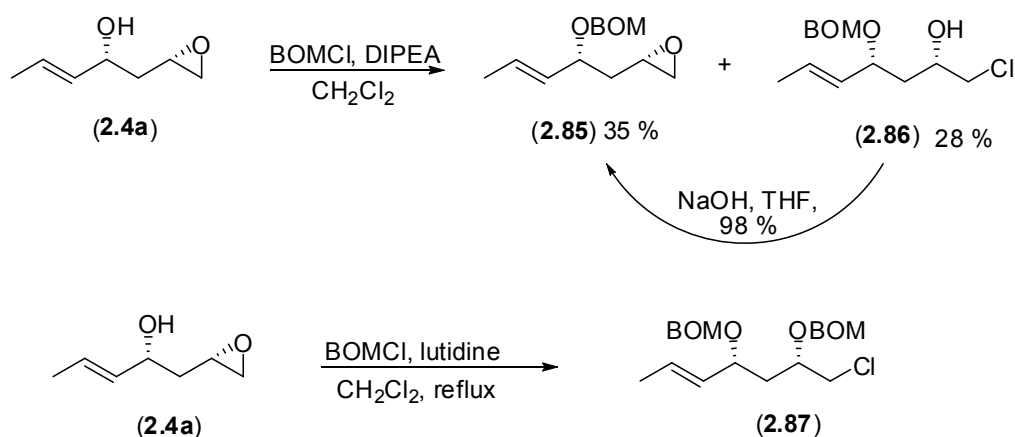
The rest of our synthesis including Boc substitution, hydrogenation, iodocyclisation, dehydroiodination and methanolysis worked well, as in the model (Scheme 56). Before proceeding to the epoxide ring opening reaction with the Grignard of fragment-B (**2.5**) we needed to protect the secondary alcohol (**2.4a**). The TBS group was our first choice to protect the alcohol as it is a versatile silyl protective group and can be easily introduced and removed. But our trials for TBS protection of the alcohol (**2.4a**) under standard conditions did

not give any of the desired product and the starting material was recovered.⁷⁶ We assumed that this may be due to the steric hindrance of the large TBS group.



Scheme 56

The next choice of our protecting group was the BOM group as it is less bulky than TBS, but equivalently versatile. Our initial attempts to protect the alcohol with BOMCl and DIPEA under Stork's conditions, 1.2 eq. of BOMCl and 1.2 eq. of DIPEA in dichloromethane, gave a (1 : 1) mixture of desired product (2.85) and the BOM protected chlorohydrin (2.86) (Scheme 57).⁷⁷ We assume that the BOM protected chlorohydrin (2.86) was arrived at from the chloride attack on the epoxide during the reaction.

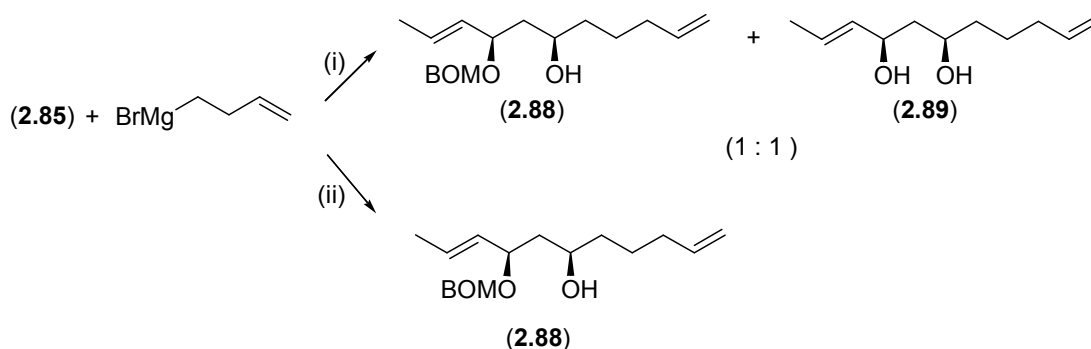


Scheme 57

To stop the epoxide ring opening by the chloride ion, the protection was carried out at lower temperature, but the reaction was very slow, showing very little of the desired product. When we used lutidine instead of DIPEA at RT there was no reaction. However, at elevated temperatures, the diprotected alcohol (**2.87**) was obtained as the sole product. Since our attempts to obtain the protected epoxide always yielded some amount of the BOM protected chlorohydrin (**2.86**), we simply re-converted the protected chlorohydrin (**2.86**) to the epoxide (**2.85**) by treatment with NaOH in THF.

Model studies towards the THP fragment (**2.189**):

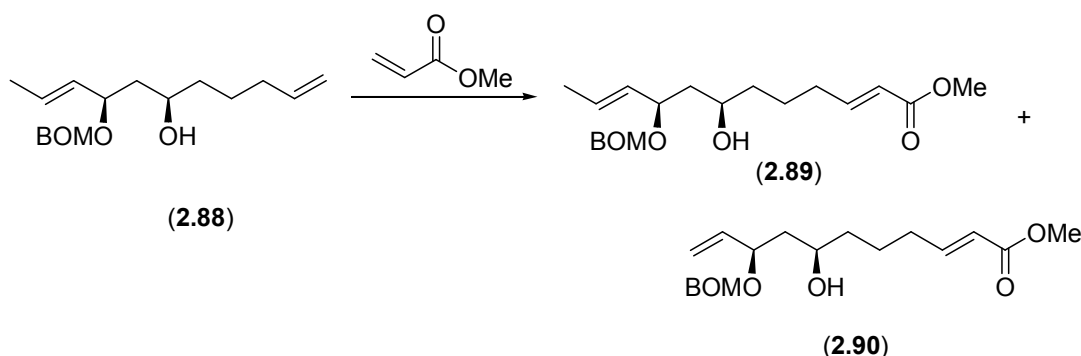
Model studies were carried out with the Grignard reagent of commercially available 4-bromo butene and fragment (A) (**2.85**) (Scheme 58). The ring opening of the epoxide (**2.85**) with the Grignard reagent obtained from 4-bromo butene proceeded smoothly provided THF was used as solvent. In ether or ether-THF mixtures, products resulting from attack on the BOM group (**2.89**) by the Lewis acidic magnesium were also isolated along with the desired product (**2.88**) in equal amounts.⁴⁰



Scheme 58

Reagents and conditions: (i) CuI, Et₂O, THF, 1:1 mixture of (2.88) and (2.89); (ii) Mg, CuI, THF, 70 %.

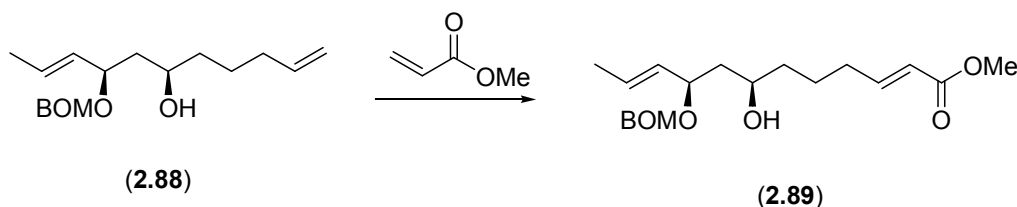
With the diene (2.88) in hand we proceeded to the next step which is the cross metathesis reaction with the methyl acrylate using Grubbs II (2.12) catalyst (5 mol %) in dichloromethane at room temperature (Scheme 59).⁴⁵ Our initial trials of cross-metathesis with methyl acrylate resulted in the formation of an inseparable mixture of two compounds. However, the products were identified, as the desired methyl ester (2.89) and its corresponding desmethyl compound (2.90), by extensive analysis of NMR data. It was apparent that cross-metathesis with the acrylate had occurred exclusively at the terminal alkene, but some cross-metathesis of the internal alkene had occurred with the ethylene by-product of the first cross-metathesis, giving rise to desmethyl compound (2.90).⁴⁰



Scheme 59

Reagents and conditions: Grubbs II (5 mol %), CH₂Cl₂, 0 °C to rt.

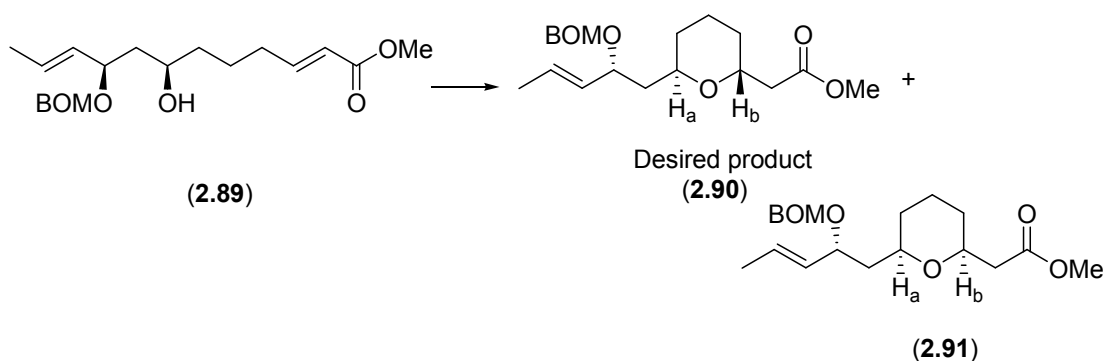
The above problem was easily solved by simply passing a stream of nitrogen through the reaction mixture to sweep away the ethylene as soon as generated. With this trivial modification the cross metathesis proceeded well to yield the desired product (**2.89**) in 76 % yield (Scheme 60).



Scheme 60

Reagents and conditions: Grubbs II (5 mol %), CH_2Cl_2 , N_2 flow, 0 °C to rt, 76 %.

Finally, we turned to do the critical intramolecular Michael addition (Scheme 61). Following Banwell's procedure we treated the ester (**2.89**) with sodium hydride in THF at -78 °C, the reaction was completed in few minutes at -78 °C, giving a separable mixture of isomers in favour of the desired one (**2.90**) with a similar ratio reported to that by Banwell for a simpler substrate.⁴³ Comparison of the ^1H NMR data, particularly the chemical shifts of the ring protons α to the oxygen, with the data reported by Banwell for his simple THPs (**2.9** and **2.11**) and the data for the natural product allowed us to assign the stereochemistry (Table 3).



Scheme 61

Reagents and conditions: (a) NaH, THF, -78 °C, 87 % (7:3); (b) KO^tBu , THF, -78 °C, 98 % (8.5:1.5).

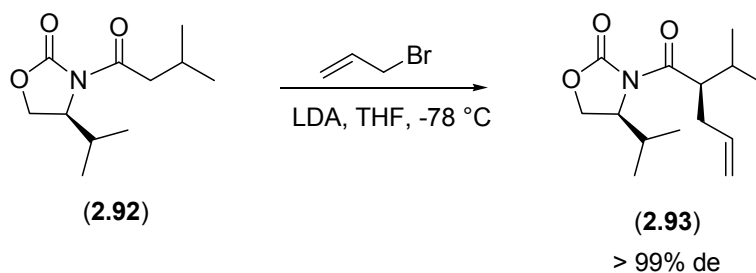
The cyclisation reaction was optimised to improve the selectivity of the desired *trans* isomer, and found, use of THF solution of potassium-*tert*-butoxide at -78 °C affords the desired isomer (**2.90**) in (8.5:1.5) ratio with excellent yield (Scheme 61).¹⁸⁹ The enhanced selectivity and yield is due to the solubility of potassium-*tert*-butoxide in THF, allowing the reaction to occur at a lower temperature, compared with the insoluble base NaH.

Table 3: ¹H NMR chemical shifts (ppm) of the THP protons Ha and Hb.

Protons	<i>trans</i> isomer (2.90)	<i>trans</i> THP (2.11) (Banwell)	bistramide D	<i>cis</i> isomer (2.91)	<i>cis</i> THP (2.9) (Banwell)
H _a	3.84	3.88	3.87	3.37	3.44
H _b	4.19	4.25	4.22	3.72	3.75

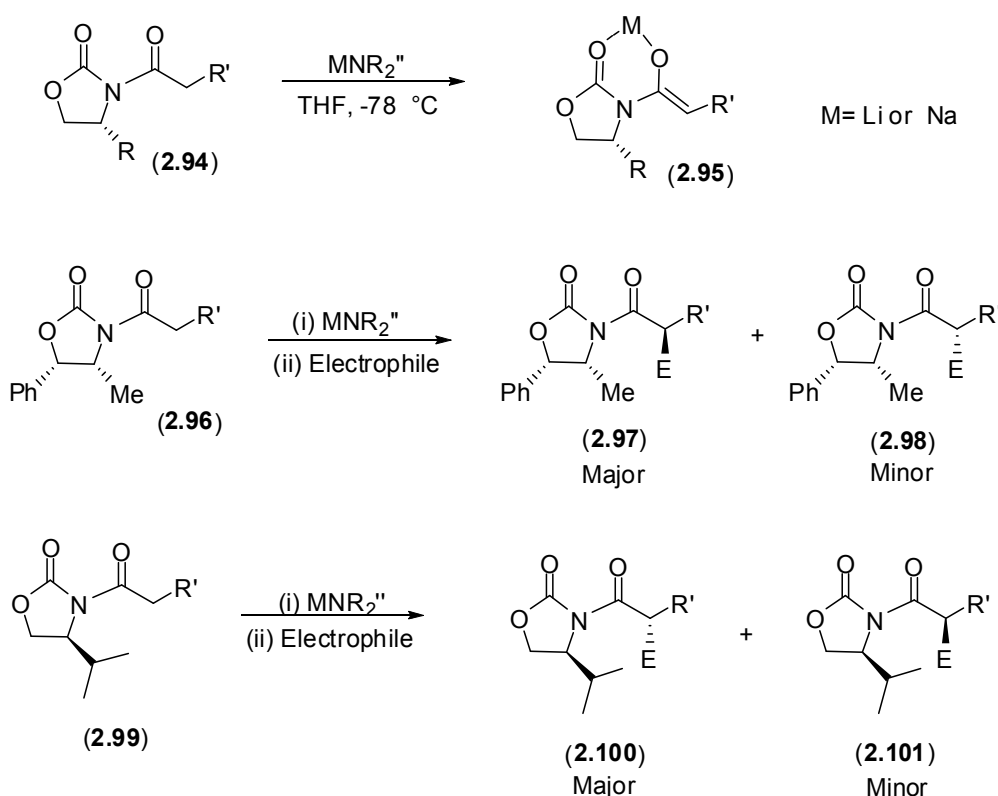
Synthesis of fragment-B:

The major challenge in asymmetric synthesis is to find good methodology for stereoselective bond construction. Though a number of impressive methods are available for the asymmetric synthesis including asymmetric catalysis, biocatalysis; the use of chiral auxiliary is still remains an attractive, reliable and predictable method for many enantioselective transformations.⁷⁸ Since the pioneering work of Meyers and others remarkable improvements in the asymmetric induction using chiral auxiliaries have been developed.⁷⁹ For the stereoselective alkylation of fragment-B (**2.5**) we opted to employ the Evans chiral oxazolidinone.⁸⁰ Though there are several protocols available for stereoselective alkylation including Oppolzer's camphor sultam,⁸¹ we preferred Evans chiral oxazolidinone due to its high levels of selectivity (Scheme 62) and the easy synthesis of the chiral auxiliary from readily available amino acids.⁷⁸



Scheme 62

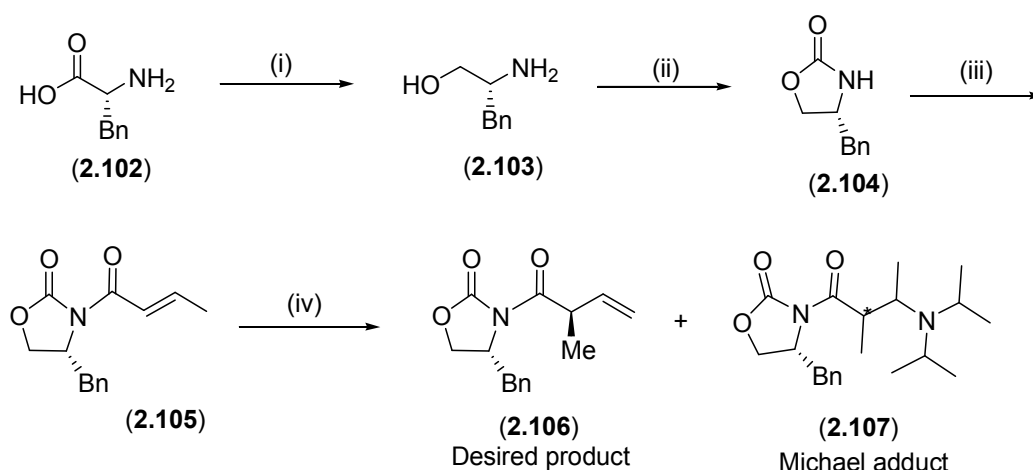
Evans suggested that the observed stereoselectivity of the chiral oxazolidinone is due to the complementary levels of diastereofacial selectivity by the chelated enolates structure ($Z > 100:1$) as well as the structure of electrophile, i.e., larger alkyl halides give higher stereocontrol than their sterically less demanding counterparts (BnBr vs. MeI) (Scheme 63).⁸²



Scheme 63

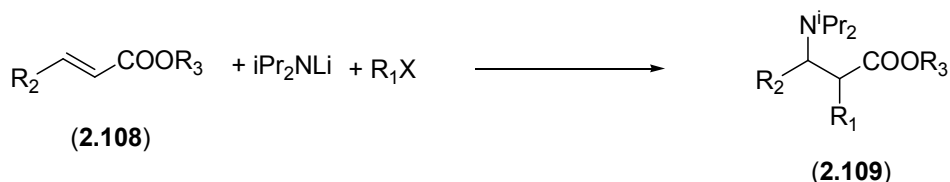
The synthesis of the chiral oxazolidinone **(2.88)** was achieved by starting with D-phenylalanine **(2.102)**, an inexpensive and readily available starting material with the desired stereocenter (Scheme 64). The amino acid reduction was achieved using *in situ* generation of borane from sodium borohydride and borontrifluoride-

diethyletherate complex. The borane reduction is exceptionally convenient giving the alcohol (**2.103**) in an excellent yield (95 %) with no perceptible racemisation.⁸³ Heating the amino alcohol (**2.103**) with diethyl carbonate in the presence of anhydrous potassium carbonate at 135 °C provided the desired oxazolidinone (**2.104**) in 93 % yield. Deprotonation of the oxazolidinone (**2.104**) with ⁿbutyl lithium in THF at -78 °C followed by treatment with crotonyl chloride afforded the desired crotonyl oxazolidinone (**2.105**) in 98 % yield. But, to our surprise, our attempts to methylate the crotonyl oxazolidinone (**2.105**) with LDA and MeI in THF at -78 °C provided the Michael adduct (**2.107**) as the sole product and as a single diastereomer, although our studies to explore the stereochemistry of the new chiral centre was unsuccessful. Though LDA is commonly known as a non-nucleophilic base, and, is used for many deprotonation reactions, a few examples of its nucleophilic addition to α,β-unsaturated systems are also known (Scheme 65).^{84,85}



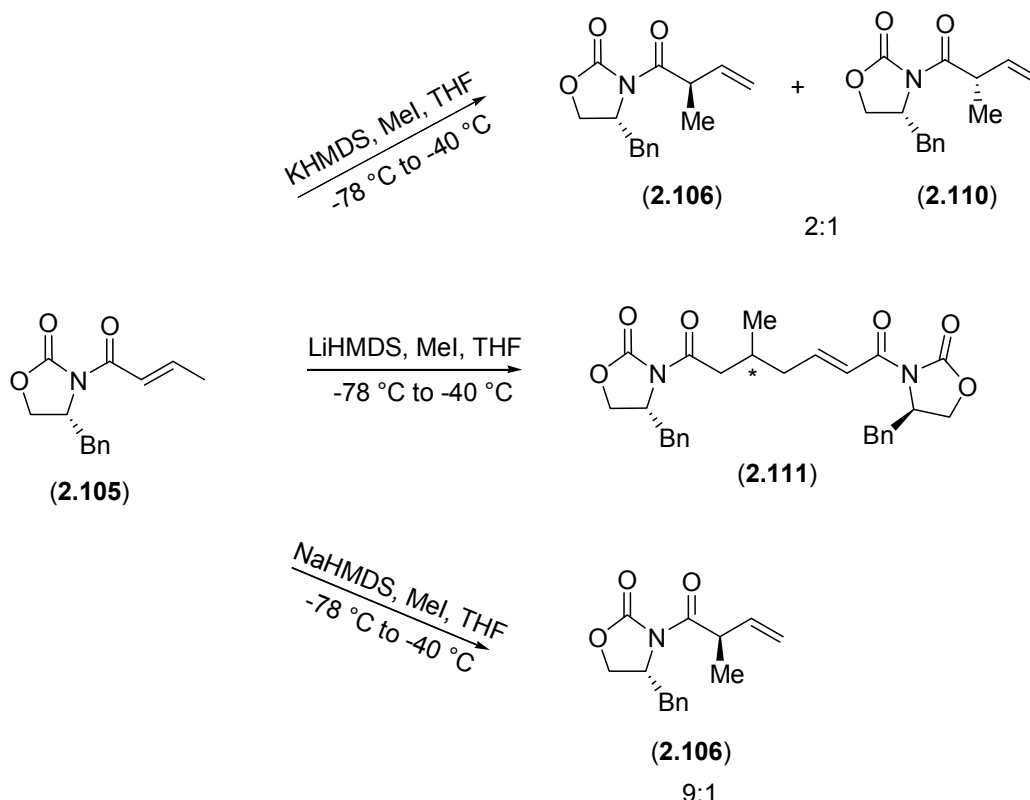
Scheme 64

Reagents and conditions: (i) NaBH₄, BF₃·Et₂O, THF, 0 °C to RT, 95 %; (ii) diethyl carbonate, K₂CO₃, 135 °C, 93 %; (iii) ⁿBuLi, Crotonyl chloride, THF, -78 °C, 98 %; (iv) LDA, MeI, THF, -78 °C.



Scheme 65

After trying several methods for the stereoselective methylation, finally, it was found that use of KHMDS affords the methylated product **(2.106)** and its separable diastereomer **(2.110)** in good yield but with moderate selectivity, (2:1) ratio (Scheme 66). Trials with LiHMDS resulted in unexpected results, giving the dimer **(2.111)** of the starting material as a single diastereomer, but the reaction was capricious as the product formation was not consistent over several repetitions. However methylation with NaHMDS was found to be more efficient giving 9:1 selectivity with moderate yield.



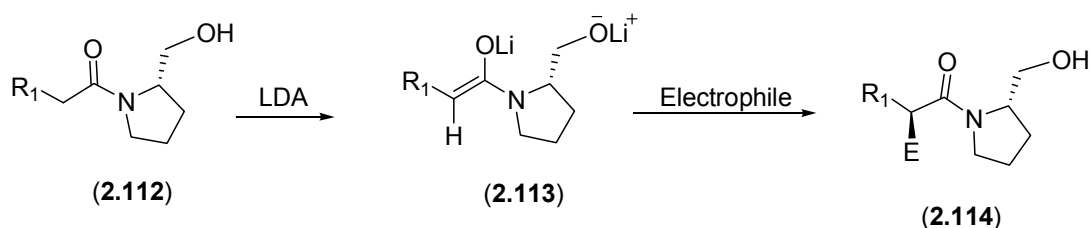
Scheme 66

The difference in the stereoselectivity of Li, Na and K may be explained by the cation size. The Li atom being small, the chelation is strong, resulting in the

powerful activation of the crotonyl moiety to Michael addition. However, potassium is larger and the chelation is not efficiently taking place which leads to the low selectivity on alkylation. Sodium being if the correct size forms tight chelation without high Lewis acidity and directs the electrophile efficiently.

Unsuccessful approaches to fragment B:

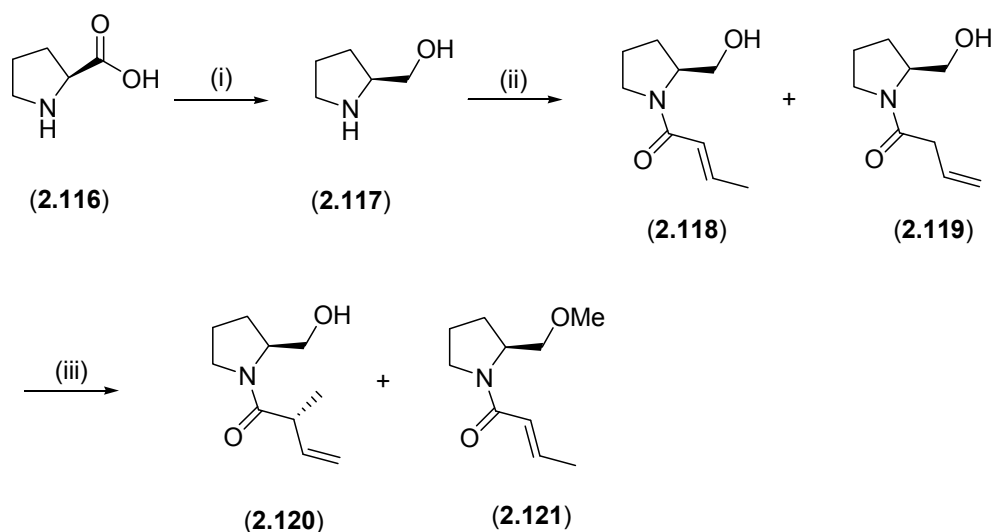
As our trials for methylation of the α,β -unsaturated system (**2.105**) with LDA did not afford the desired methylated product, we moved on to use the Evans proline derived chiral auxiliary (**2.112**) as it has been used in a number of diastereotopic alkylation reactions.⁸⁶ Evans suggested that the stereoselectivity arises from the hydroxyl moiety of the prolinol which directs the alkylation process (Scheme 67).



Scheme 67

The synthesis of chiral auxiliary was started from L-proline (**2.116**), which on reduction with borane afforded the desired prolinol (**2.117**) in 52 % yield. Crotylation of the prolinol (**2.117**) with triethyl amine afforded the isomerised terminal alkene (**2.119**) as the sole product. This is due to formation of a vinyl ketene by elimination of HCl from crotonyl chloride, followed by α -protonation of the enolate that subsequently formed. This small problem was solved by employing a weak base, sodium carbonate, and the reaction worked well, affording the desired alkene (**2.118**) in 98 % yield. Once we had the chiral amide in hand, we moved forward to the stereoselective methylation with LDA and MeI in the presence of DMPU, a less toxic alternative to HMPA, but unexpectedly it provided the O-methylated compound (**2.121**). Initially it was thought that this

may be due to moisture in the DMPU as we used the commercial grade. However the reaction with distilled DMPU and without DMPU, did not afford the desired product (**2.120**), only recovery of starting material.



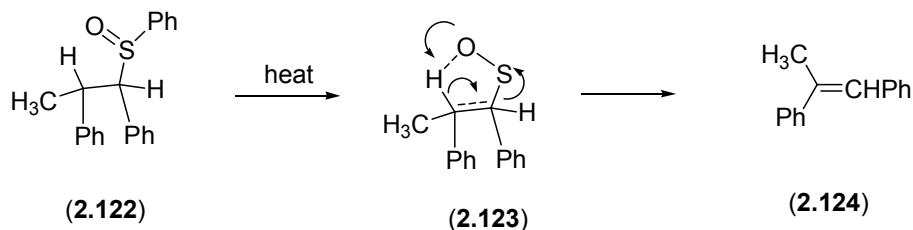
Scheme 68

Reagents and conditions: (i) NaBH₄, BF₃·Et₂O, THF, 0 °C to RT, 52 %; (ii) (a) Et₃N, crotonyl chloride, only (**2.120**) (b) 10% aq. Na₂CO₃, crotonyl chloride, 98 %; (iii) (a) LDA, MeI, DMPU, THF, -78 °C, only (**2.121**); (b) LDA, MeI, THF, -78 °C, no product.

Our strategy for making fragment-B from the crotonyl oxazolidinone using LDA was frustrating as it was giving the Michael adduct (**2.107**) as the sole product and our attempts to perform the methylation using prolinol chemistry also did not proceed well. On careful consideration of these results, we concluded that the problem arose from the presence of the double bond. Hence we modified the strategy to introduce the alkene group later in the synthesis to avoid the unwanted side reactions during methylation.

There is an enormous number of protocols available for the synthesis of alkenes; such as Cope elimination,⁸⁷ Wittig, Horner Wadsworth Emmons (HWE),⁸⁸ Peterson olefination,⁸⁹ twofold extrusion (of carbon dioxide or thio compounds),

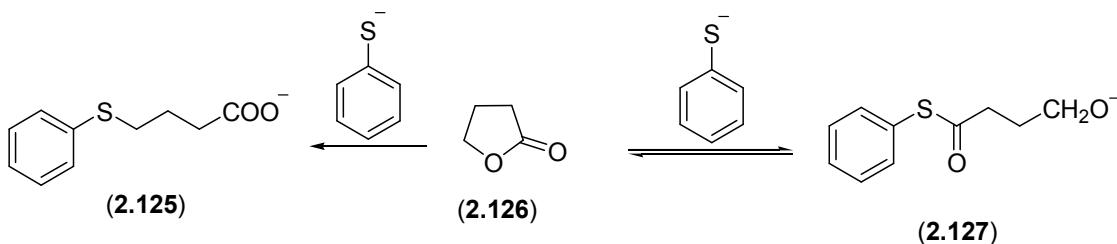
⁹⁰ sulphone elimination reactions ⁹¹ and the sulfoxide ⁹² elimination⁹³ reactions. We intended to obtain the alkene using sulfoxide chemistry, as sulfoxides are easily prepared from readily available starting materials and convenient procedures are available to obtain an alkene either by a base induced β -elimination or a simple pyrolysis. ⁹⁴ Kingsbury showed that the elimination of sulfoxides proceeded by a concerted *syn* elimination (Scheme 69). ⁹⁵



Scheme 69

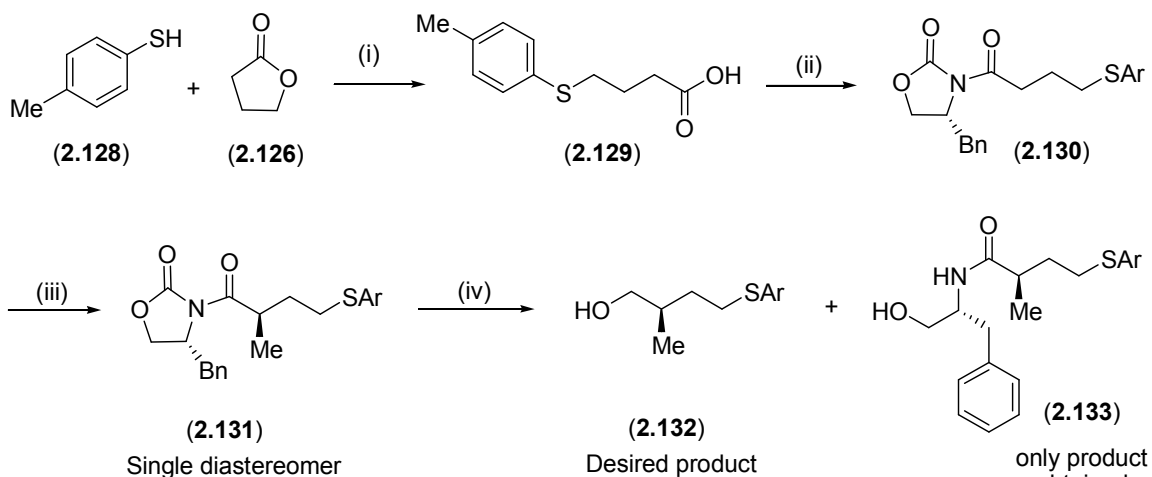
For the new strategy we started with Evans chiral oxazolidinone (**2.104**), but instead of coupling with crotonyl chloride, it was coupled with the acid chloride of the thio acid (**2.129**); by considering that the chiral auxiliary would direct the stereoselective methylation and the desired double bond could be generated via a dehydrosulfenation reaction.

The synthesis was started with thiocresol (**2.128**) which on reaction with γ -butyrolactone (**2.126**) using a modification of Reppe's method afforded the arylthio butanoic acid (**2.129**) in 98 % yield. ⁹⁶ This reaction is interesting as it appears to cleave the alkyl oxygen bond instead of usually anticipated acyl-oxygen bond. Traynelis explained that the selectivity for the alkyl oxygen fission involves a rapid but reversible ring opening by acyl-oxygen fission in competition with an irreversible alkyl-oxygen fission which gives the sodium salt of carboxylate (**2.127**) (Scheme 70). ⁹⁶



Scheme 70

The acid chloride of the thioacid (**2.129**) was reacted with oxazolidinone to give the precursor (**2.130**) for methylation (Scheme 71). To our delight, methylation of the compound (**2.130**) with LDA in THF at $-78\text{ }^{\circ}\text{C}$ afforded the methylated compound (**2.131**) as a single diastereomer in 91 % yield. Our initial trial for chiral auxiliary removal with lithium aluminium hydride did not give the desired alcohol (**2.132**), instead giving a reduced compound, which we tentatively assigned as (**2.133**).

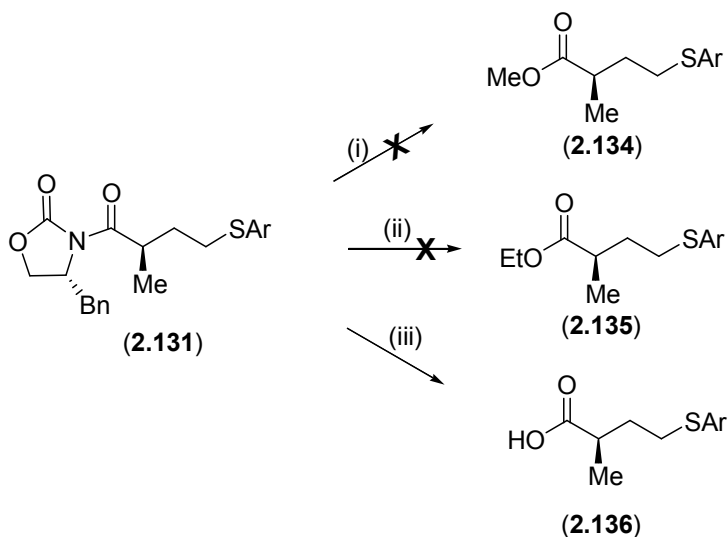


Scheme 71

Reagents and conditions: (i) NaOEt, 98 %; (ii) (a) oxalyl chloride, CH_2Cl_2 , DMF; (b) Oxazolidinone (**2.104**), $n\text{BuLi}$, THF, $-78\text{ }^{\circ}\text{C}$, 84 %; (iii) LDA, MeI, THF, $78\text{ }^{\circ}\text{C}$, 91 %; (iv) LiAlH_4 , THF, $5\text{ }^{\circ}\text{C}$, no product.

As an alternative for chiral auxiliary removal, Kanomata's method was used to convert the chiral amide to the corresponding ester (**2.135**) with sodium ethoxide

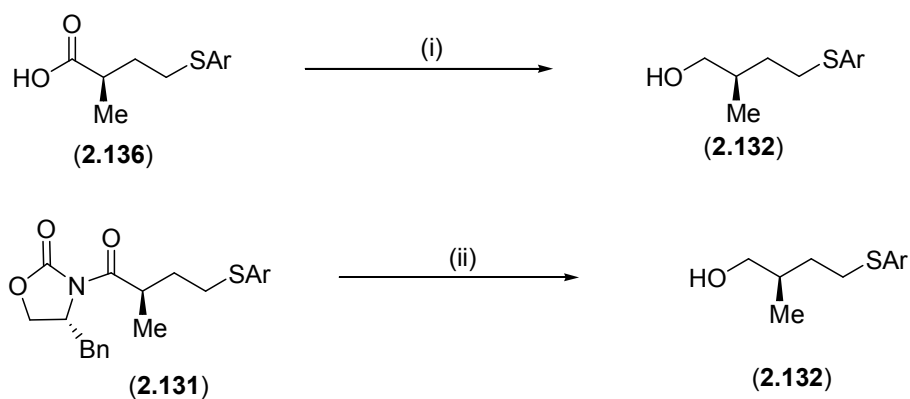
and diethyl carbonate, frustratingly this also did not result in product formation (Scheme 72).⁹⁷ However, hydrolysing the chiral amide (**2.131**) with hydrogen peroxide and lithium hydroxide in THF afforded the carboxylic acid (**2.136**) in 65% yield, notable no oxidation at sulphur was observed.⁹⁸



Scheme 72

Reagents and conditions: (i) NaOMe, CH₂Cl₂, no product; (ii) NaOEt, Diethyl carbonate, CH₂Cl₂, no product was observed; (iii) H₂O₂, LiOH, THF, H₂O, 65 %.

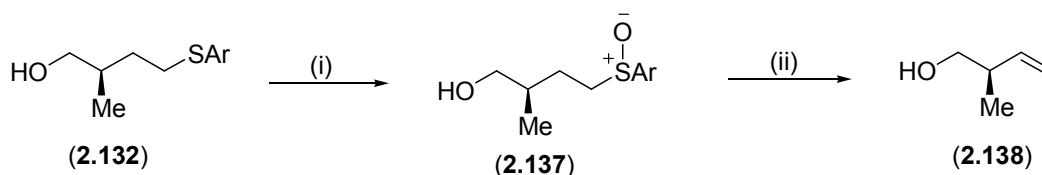
The reduction of the acid (**2.136**) to an alcohol (**2.132**) worked well with sodium borohydride or with LAH giving good to excellent yields (Scheme 73). Later, it was found that the direct reduction of the chiral amide (**2.131**) to the alcohol (**2.132**) can be achieved with LAH, this contrary result may be explained due to the different batches of LAH, as the old batch seemed to be partially decomposed therefore it could not complete the reduction.



Scheme 73

Reagents and conditions: (i) (a) NaBH_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, THF, $0\text{ }^\circ\text{C}$ to RT, 83 %; (b) LiAlH_4 , THF, $0\text{ }^\circ\text{C}$ to RT, 99 % (ii) LiAlH_4 , Et_2O , $0\text{ }^\circ\text{C}$ to RT, 98 %.

After having the alcohol **(2.132)** in hand, oxidation was carried out using sodium metaperiodate to obtain the sulfoxide **(2.137)** (Scheme 74) but, the reaction resulted in a mixture of the desired product with some other impurities by ^1H NMR. The use of *m*CPBA in dichloromethane at low temperature afforded the desired sulfoxide **(2.137)** in quantitative yield.⁹⁹ Despite the good yield and high stereoselectivity on the methylation with thio compound **(2.130)**, several difficulties were faced during the sulfoxide elimination. The various conditions used for the elimination are tabulated (Table 4). Neat pyrolysis of the sulfoxide **(2.137)** at $60\text{ }^\circ\text{C}$ did not give any product **(2.138)** except the starting material. Regrettably, at elevated temperatures the starting material decomposed **(2.137)**. Heating the sulfoxide in dichloromethane at reflux for longer times did not provide anything other than the starting material. Elimination under thermal conditions in the presence of mild bases, including NaHCO_3 , K_2CO_3 and CaCO_3 was also tried. To our disappointment none of the above conditions gave the desired product.



Scheme 74

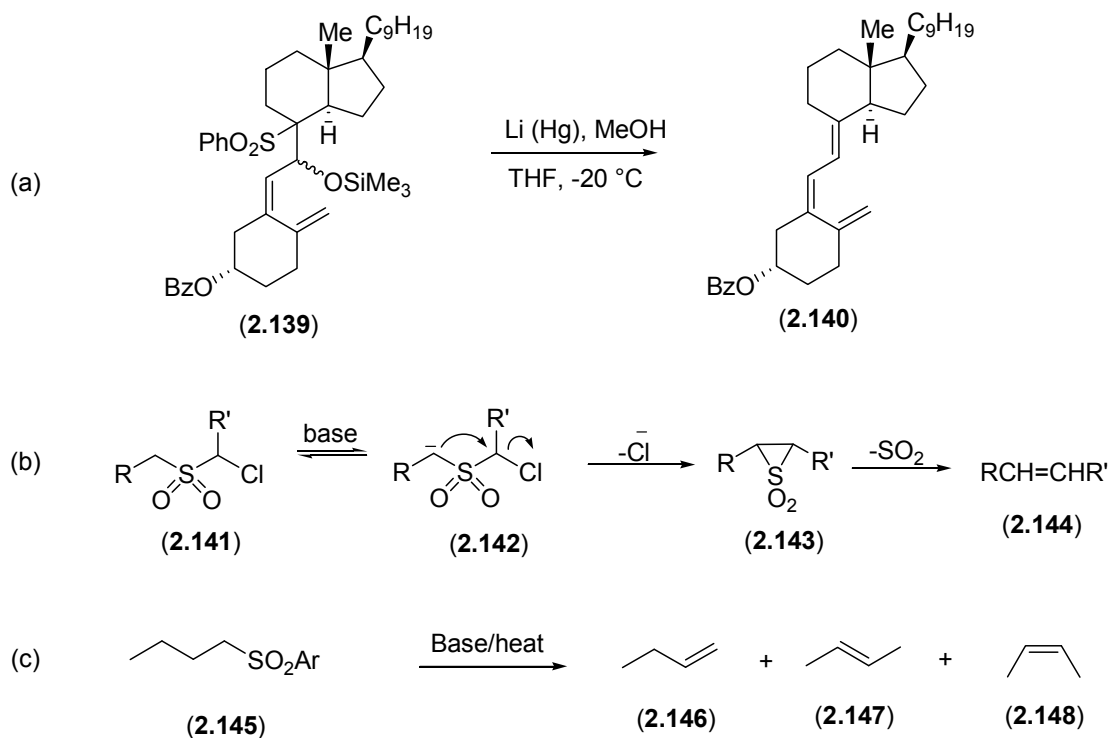
Reagents and conditions: (i) (a) NaIO_4 , MeOH, no product; (b) m-CPBA, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 99 %; (ii) conditions are tabulated.

Table 4: Reactions conditions for the sulfoxide elimination.

Solvent	Base	Temperature	Time	Result
CH_2Cl_2	-	Reflux	48 h	No reaction ^a
CH_2Cl_2	NaHCO_3	Reflux	16 h	No reaction ^a
Toluene	K_2CO_3	$110\text{ }^\circ\text{C}^{\text{b}}$	36 h	No product ^c
Toluene	CaCO_3	Reflux	30 h	No product ^c
Neat	NaHCO_3	$160\text{ }^\circ\text{C}$	3 h	No product ^c

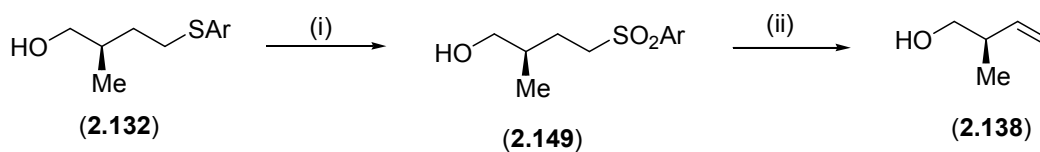
a: only starting material recovered, b: reaction carried out in sealed tube, c: material decomposed.

Since the sulfoxide (**2.137**) was reluctant to undergo elimination reaction, even under forcing conditions, we chose sulfone elimination as our next option. Not only is the synthesis of sulphone (**2.140**) easy from the thioalcohol precursor (**2.132**) but also, the sulfone elimination is well known in the literature.¹⁰⁰ Until now, three types of sulfone elimination reactions are known, namely (i) the Julia olefination (Scheme 75a) where the β -hydroxy sulphones reductively eliminated by sodium or lithium amalgam to give the desired alkene.¹⁰¹ (ii) Ramberg-Backlund reaction (Scheme 75b) which is a rearrangement of sulphone compounds with α -substituted leaving group to give rise to alkenes in a regioselective manner.¹⁰² (iii) The third and common type of sulfone elimination is base induced (Scheme 75c).¹⁰³



Scheme 75

The oxidation of the sulfide **(2.145)** using *m*CPBA at 0 °C in dichloromethane was efficient giving sulfone **(2.149)** in quantitative yield (Scheme 76). To our disappointment there was no elimination reaction when the sulfone was treated with potassium *tert*-butoxide, despite literature precedent.¹⁰³

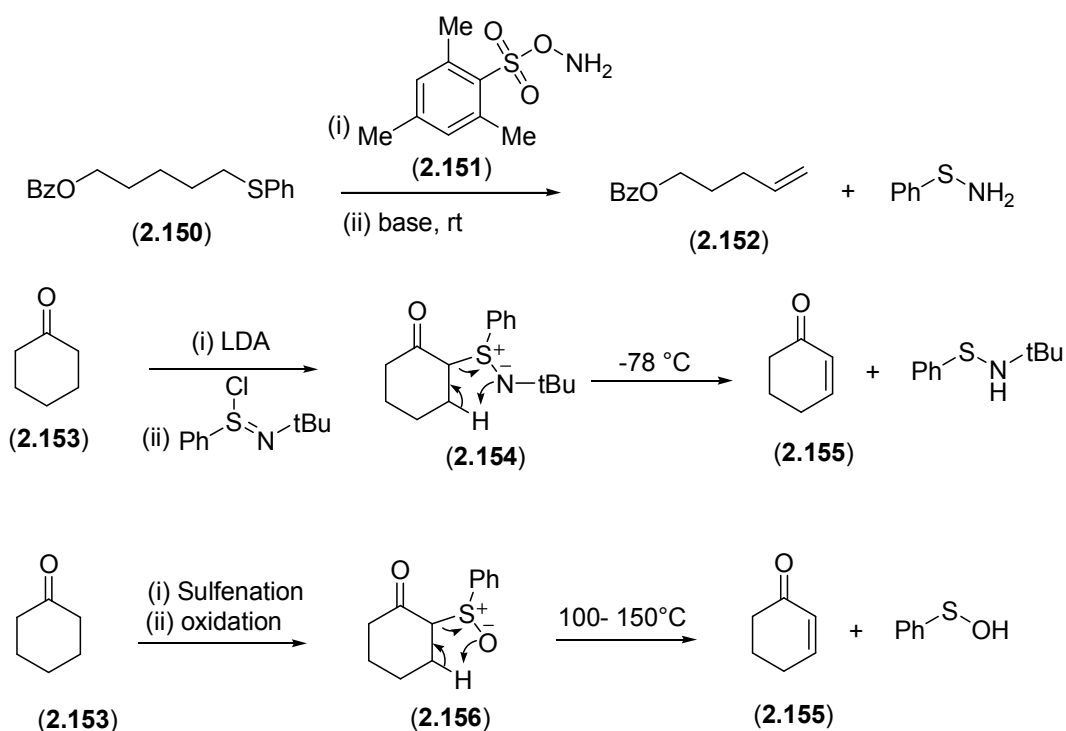


Scheme 76

Reagents and conditions: (i) *m*CPBA, 0 °C, CH₂Cl₂, 99 %; (ii)(a) KO^tBu, DMSO, no product; (b) KO^tBu, THF, no product.

As our anticipated elimination reactions with sulfoxide and sulfone did not work under standard conditions, we looked for alternatives in the literature; Matsuo and Ishibashi reported that mesitylene sulfonylhydroxylamine (MSH) **(2.151)**, is

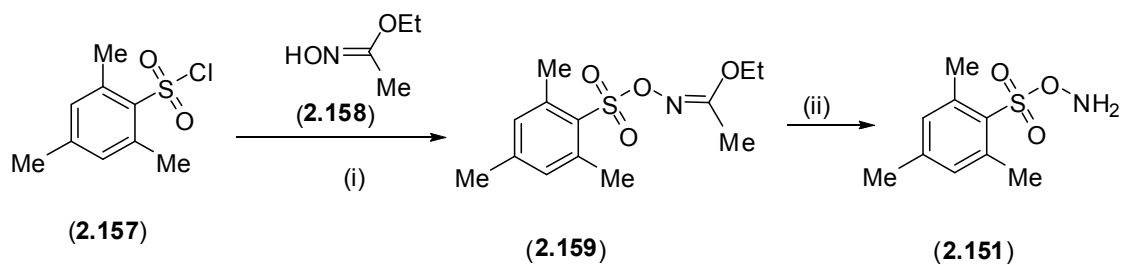
capable of inducing the elimination of aryl sulphides under mild conditions (Scheme 77).¹⁰⁴ Matsuo showed that the sulfilimines (**2.154**) undergo elimination at very low temperatures ($-78\text{ }^{\circ}\text{C}$) compared with their sulfoxide analogs (**2.156**) which need higher temperatures ($100\text{-}150\text{ }^{\circ}\text{C}$). Matsuo suggested that, the difference in the reactivity between sulfilimine (**2.154**) and sulfoxide (**2.156**) was due to the enhanced basicity of the nitrogen compared to the oxygen atom.



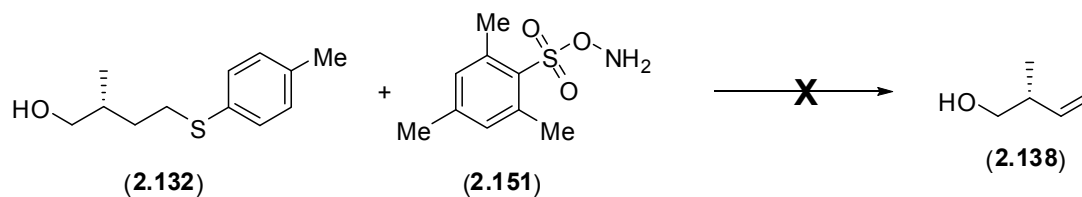
Scheme 77

We were really encouraged by Matsuo's mild elimination procedure, since we knew from the previous experiments that, the sulfoxide (**2.137**) is not that stable under harsh conditions. For the synthesis of MSH we used Tamura's¹⁰⁵ procedure, treatment of mesitylenesulfonyl chloride (**2.157**) with ethyl *N*-hydroxyacetimidate (**2.158**) in the presence of triethylamine in DMF (3.7 M) at $0\text{ }^{\circ}\text{C}$ afforded the desired product (**2.159**) in quantitative yield. MSH (**2.151**) was obtained from ethyl *O*-arylsulfonylhydroxamate, (**2.159**) by treating with 70% perchloric acid. Having the MSH (**2.151**) in hand, one pot elimination reaction

with aryl sulphide (2.132) was carried out (Scheme 78). To our disappointment the olefination reaction was unsuccessful under these conditions.



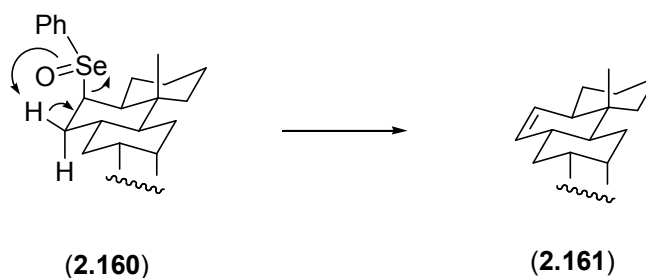
Reagents and conditions: (i) Et₃N, DMF (3.7 M), 99 % (ii) HClO₄, Dioxane, 95 %.



Scheme 78

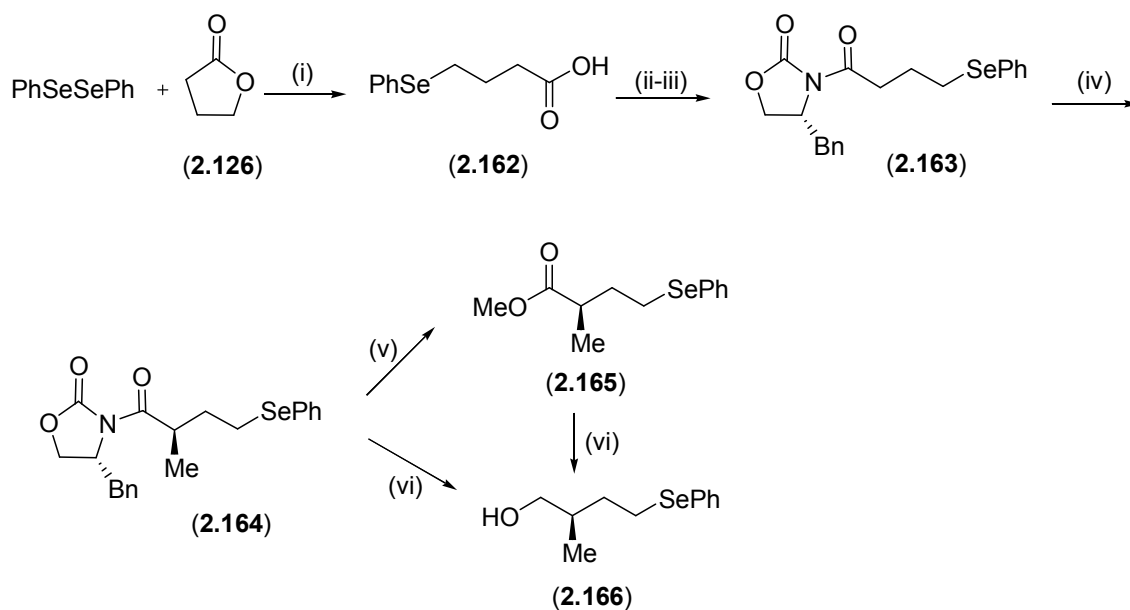
Reagents and conditions: K₂CO₃, CH₂Cl₂, no product observed.

All our attempts to synthesise fragment B from sulphide, sulfoxide and sulfone analogs turned out to be unsuccessful. We then attempted our final trial with selenoxide chemistry, despite the toxicity of selenoxides; their instability makes them important as they are more easily decomposed into olefins.¹⁰⁶ Moreover the β-elimination of selenoxides are known to be more efficient than their sulfoxide analogs; due to the greater polarization in the Se-O bond and longer Se-C, Se-O bond lengths.¹⁰⁷ Similar to the sulfoxide, the nature of the selenoxide elimination has been shown to be *syn* (Scheme 79).¹⁰⁸



Scheme 79

The selenoxide analog (**2.164**) was synthesised from diphenyldiselenide using a similar procedure to the sulfoxide derivative (Scheme 80). Butyrolactone (**2.126**) ring opening with diphenyl diselenide in presence of sodium borohydride in DMF under nitrogen was efficient, giving a quantitative yield of phenylselenenylbutanoic acid (**2.162**).¹⁰⁹ Coupling of the acid (**2.162**) with oxazolidinone (**2.104**) proceeded in a similar way to the sulfide analog affording the desired amide (**2.163**) in 99 % yield. Methylation of (**2.163**) with LDA and MeI in THF solvent afforded the desired product (**2.164**), as a single diastereomer in 82 % yield. Chiral auxiliary removal was achieved either by converting the amide into the corresponding methyl ester (**2.165**) and then reduction with LAH or the direct reduction of the chiral amide to desired alcohol (**2.166**).

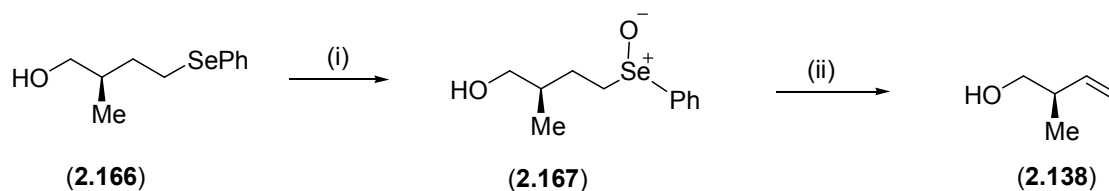


Scheme 80

Reagents and conditions: (i) NaBH_4 , DMF, 99 %; (ii) Oxalyl chloride, CH_2Cl_2 ; (iii) Oxazolidinone (**2.104**), $n\text{BuLi}$, THF, $-78\text{ }^\circ\text{C}$, 98 %; (iv) LDA, MeI, THF, $-78\text{ }^\circ\text{C}$ to $-40\text{ }^\circ\text{C}$, 82 %; (v) LiOMe, MeOH, 62 %; (vi) LAH, THF, $0\text{ }^\circ\text{C}$ to rt, 99 %.

Ozonolysis of selenide (**2.166**) in dichloroethane at $-20\text{ }^\circ\text{C}$ afforded the selenoxide (**2.167**) in good yield, and it was surprisingly stable at room

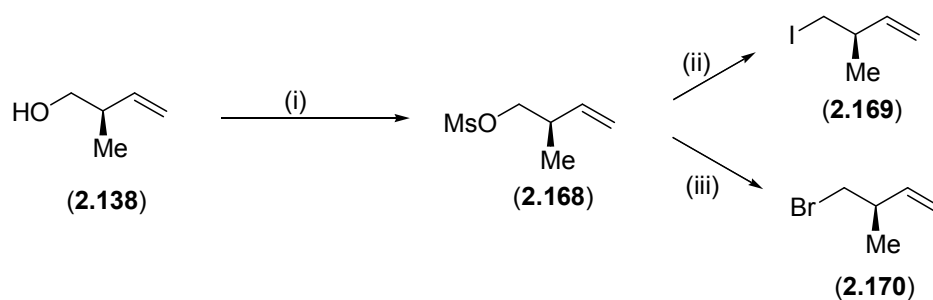
temperature (Scheme 81).¹¹⁰ To our delight, the pyrolysis of selenoxide in refluxing dichloroethane resulted in the formation of desired product (**2.138**), the data matched with the literature.¹¹¹



Scheme 81

Reagents and conditions: (i) O_3 , dichloroethane, $-20\text{ }^\circ\text{C}$, 99 % (ii) dichloroethane, reflux.

After having the alcohol (**2.138**) in hand, we moved on to convert it to the corresponding iodide (**2.169**) using iodine, triphenyl phosphine and imidazole under standard conditions. Disappointingly the reaction was unsuccessful despite several trials, only starting material was recovered. Finkelstein reaction was opted as the next approach, by converting the alcohol into the mesylate (**2.168**) then displacing it with halide. Treatment of the alcohol (**2.138**) with methanesulfonyl chloride in presence of triethyl amine in dichloromethane at $0\text{ }^\circ\text{C}$ afforded the mesylate (**2.168**) in 99 % yield (Scheme 82). To our disappointment there was no reaction when the mesylate was heated with sodium iodide in acetone, even at elevated temperatures and extended reaction times, the starting material was recovered. Since the displacement reaction with NaI was unsuccessful, LiBr was used as a next alternative and the solvent was changed from acetone to THF. Since the pentenyl bromide (**2.170**) has low boiling point, complete removal of acetone from the reaction mixture would be difficult and the remaining acetone would cause problems for the subsequent Grignard reaction, so THF was chosen.

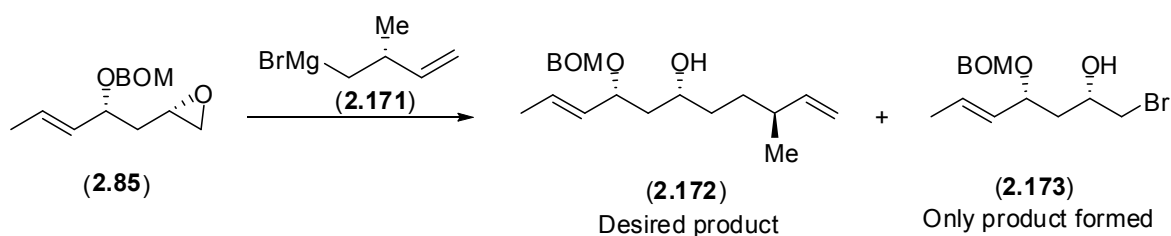


Scheme 82

Reagents and conditions: (i) MsCl, Et₃N, CH₂Cl₂, 63 % (ii) NaI, acetone, reflux, no product; (iii) LiBr, THF, 99 %.

Synthesis of the THP ring:

After solving all the problems in the synthesis of precursor of fragment-B (**2.170**), we proceeded to the next step, which is the epoxide ring opening reaction of fragment A (**2.85**) with the Grignard reagent of fragment B (**2.171**) (Scheme 83). Despite several attempts, the Grignard reaction under standard conditions resulted, only in the formation of the bromo compound (**2.173**) as the sole product and small amount of starting material (**2.85**) being recovered.

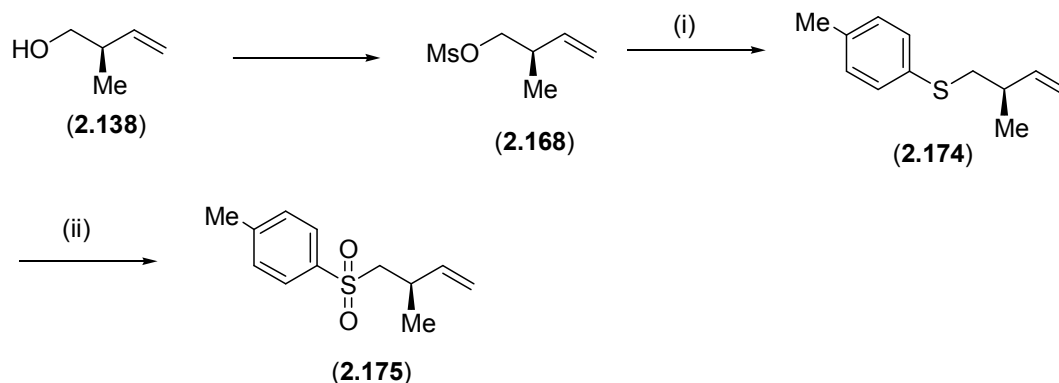


Scheme 83

Reagents and conditions: CuI, THF, -40 °C to 0 °C, no product.

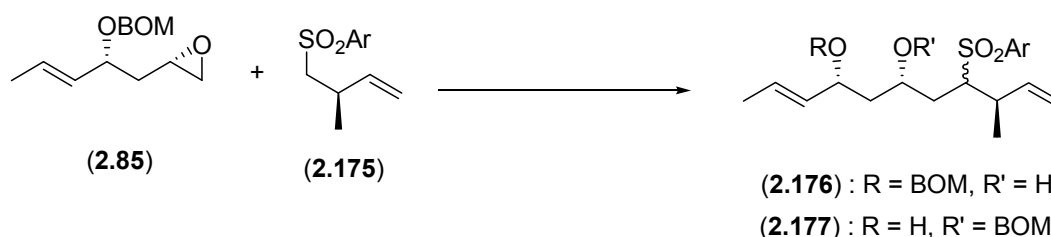
Since the Grignard reaction with fragment B (**2.171**) did not work, despite several attempts, the approach was modified by using the sulfone (**2.175**) instead of the proposed bromide (**2.170**) (Scheme 84). The sulfone (**2.175**) was synthesised from the corresponding sulphide (**2.174**) by oxidation, the use of H₂O₂ and a

molybdenum catalyst ensures no alkene oxidation. The sulphide (**2.174**) was obtained from the alcohol (**2.138**).



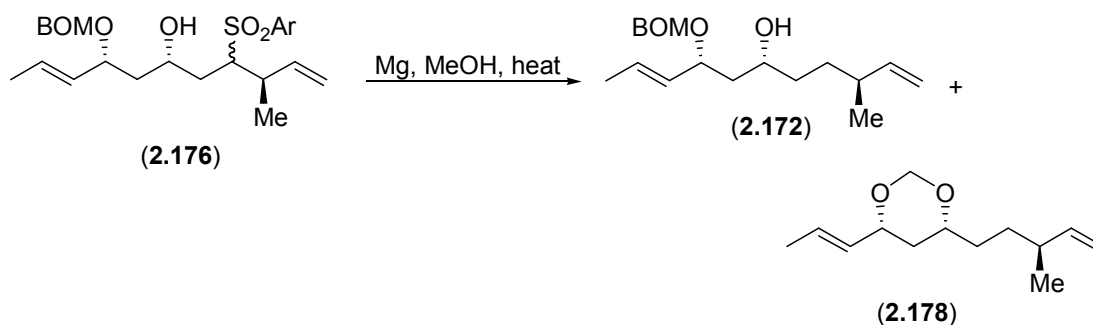
Reagents and conditions: (i) ArSH, NaH, THF, DMF, 70 °C; (ii) $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$, H_2O_2 , EtOH, 88 % (2 steps).

The epoxide ring opening reaction of fragment A (**2.185**) with the lithio derivative of the sulfone (**2.175**) in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, resulted in a complex mixture of products (Scheme 85).¹¹² However, detailed NMR studies showed that the reaction afforded the desired product (**2.176**) and its BOM migrated isomer (**2.177**). This migration of the BOM group may be explained by the Lewis acidity of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, which makes the BOM group more labile. However, in the absence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, no reaction was observed. Nevertheless, the desired product (**2.177**) was obtained in good yield, without the migration of BOM group by simply reducing the amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ from 2.5 eq. to 1.1 eq. and quenching the reaction, soon after completion at -78 °C with a Lewis base, Et_3N .



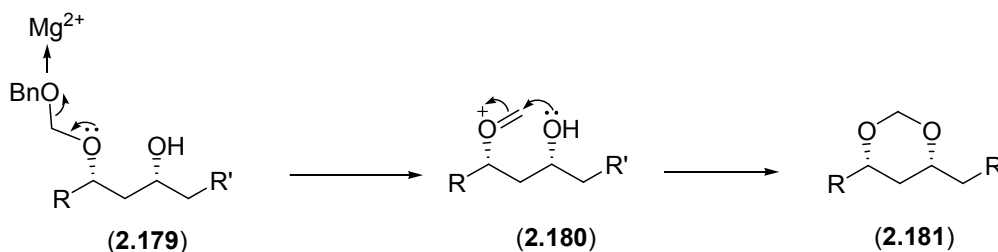
Reagents and conditions: (a) $n\text{BuLi}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.5 eq.), THF, $-78\text{ }^\circ\text{C}$, aq. NaHCO_3 ; (b) $n\text{BuLi}$, THF, $-78\text{ }^\circ\text{C}$, no product; (c) $n\text{BuLi}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.1 eq.), THF, $-78\text{ }^\circ\text{C}$, Et_3N , 85 %.

The next step was the reductive desulfonation for which we adopted Carpino's method using Mg, which is a substitute for the conventional sodium amalgam.¹¹³ Mg was preferred due to the absence of toxicity compared to mercury, its ready availability, and ease of handling. To our disappointment, the desulfonation reaction under Carpino's conditions resulted in the formation of a 1:1 mixture of the desired product (**2.172**) and the methylene acetal (**2.178**) (Scheme 86). We suspected that the formation of the methylene acetal arises due to the Lewis acidic Mg^{2+} , which forms during the desulfonation reaction and activates the BOM group to acetal formation (Scheme 87).



Scheme 86

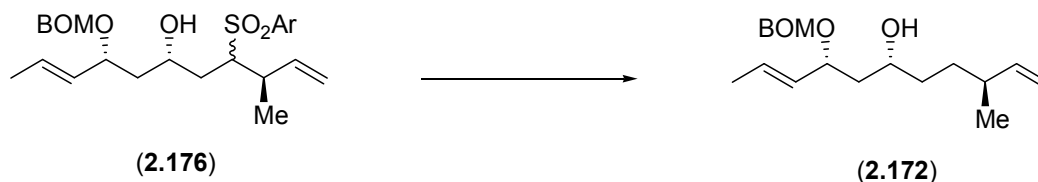
Proposed mechanism for the methylene acetal formation:



Scheme 87

To solve this problem, calcium was used instead of magnesium, due to its lower Lewis acidity. However, no reaction was observed with calcium, only the starting material was recovered. So, the approach was modified by using magnesium

but with a complexing agent, to sequester the Mg^{2+} ions in the reaction mixture. Though our initial trials with EDTA, a well known complexing agent, did not work; the reaction in the presence of TMEDA, worked well to afford the desired product (**2.172**) in 79 % yield without the formation of the methylene acetal (**2.178**) (Scheme 88). Though this reaction is rapid under sonication (~ 30 min), the yield was superior under thermal conditions.

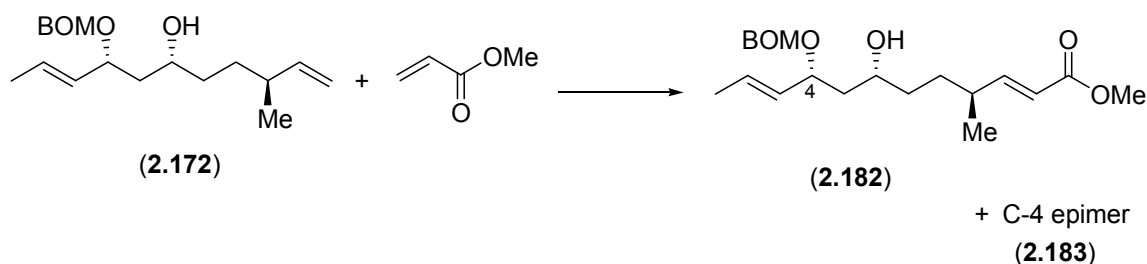


Scheme 88

Reagents and conditions: (a) Ca, MeOH, 55 °C, no product; (b) Mg, EDTA, MeOH, 55 °C, no product; (c) Mg, TMEDA, MeOH, 55 °C, 79 %. (d) Mg, TMEDA, MeOH, sonication, 57 %.

The next step is the cross metathesis of the terminal alkene (**2.172**) with methyl acrylate, which we expected to work in a similar way to the model (**2.88**), but, the reaction was comparatively slow, completing only after 8 h, unlike the model (**2.88**), which completed in 3 h. This may be due to the steric hindrance of the methyl group next to the terminal alkene. Regrettably, continuing the reaction for longer times resulted in the formation of inseparable mixture of the desired product (**2.182**) and an isomer (Table 5); detailed NMR studies clearly showed that the isomer is not from *cis/trans* isomerisation and must therefore be a C-4 epimer (Scheme 89). We suspect that this epimerisation is due to the Ru-H species, which are known catalyst degradation products formed during metathesis reactions with ruthenium catalysts.¹¹⁴ We presume that the epimerisation at C-4 arose from the Ru-H catalysed alkene isomerisation reaction as shown in the mechanism (Scheme 90). Grubbs reported that these

isomerisation reactions can be stopped by using 1,4-benzoquinone as additive to oxidise the Ru-H species. However, our trials with 1,4-benzoquinone did not suppress the epimerisation. It was observed that the epimerisation took place only when the reaction continued for longer time, as the build up of the Ru-H is gradual. The reaction was stopped after 3 h and the desired product (**2.182**) was obtained without any epimerisation; however, some starting material recovered as the reaction was stopped before completion.

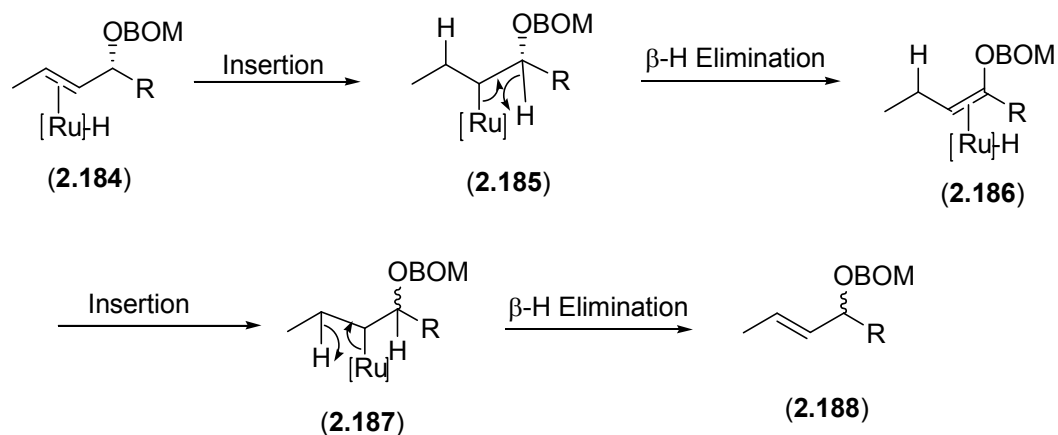


Scheme 89

Table 5: Cross metathesis results:

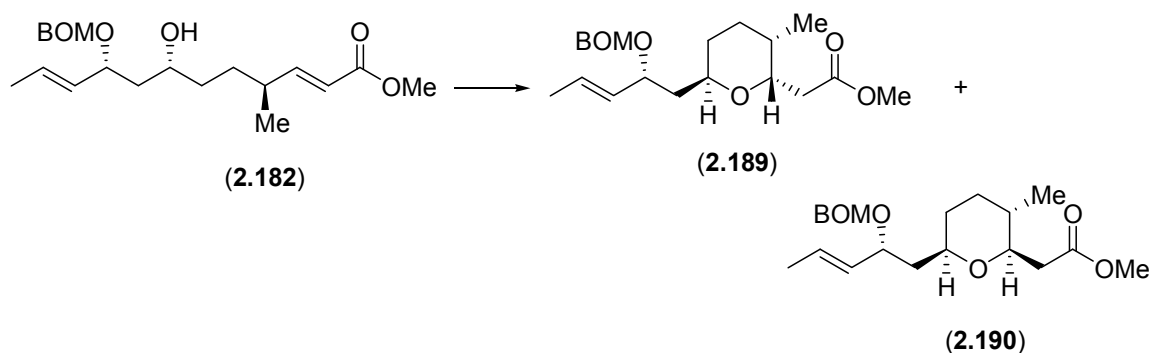
Catalyst	Yield ^a (%)	Ratio (2.182):(2.183)
Grubbs II	81	7 : 1
Hoveyda-Grubbs II	76	8 : 2
Hoveyda-Grubbs II ^c	60	8 : 2
Hoveyda-Grubbs II	71 ^b	Only (2.182)

a: all reactions were carried out in dichloromethane at 0 °C to RT with nitrogen flow; b: reaction stopped in 3 h and 23 % of starting material was recovered, c: reaction was carried out with 1,4- benzoquinone.



Scheme 90

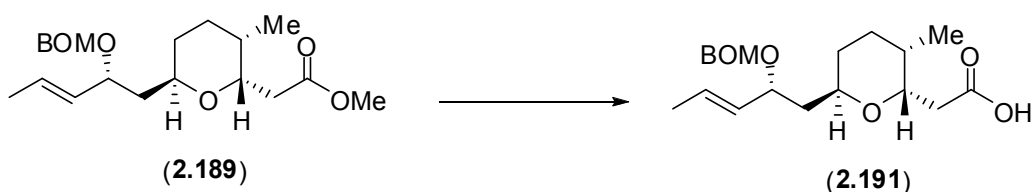
After having the CM product (**2.182**), the intramolecular Michael addition was carried out using the same conditions optimised with the model, afforded the desired *trans* THP (**2.189**) in 9:1 ratio, a similar selectivity to the model (Scheme 91). The stereochemistry was determined by comparing with natural product and as well as with Banwell's THPs (**2.9** and **2.11**).^{43,1}



Scheme 91

Reagents and conditions: KOtBu^\dagger , THF, -78°C , 92 %, (9:1).

It is notable that the ratio of isomers is slightly improved compared to the model system (**2.89** to **2.90** and **2.91**). The additional methyl group appears to further destabilize the transition state leading to the minor isomer (**2.190**). The methyl ester (**2.189**) was then hydrolysed to the corresponding carboxylic acid (**2.191**) using lithium hydroxide (Scheme 92).



(Scheme 92)

Reagents and conditions: LiOH, MeOH, H₂O, THF (1:1:1), 98 %.

Conclusion:

In summary, the synthesis of the THP fragment of bistramide D was achieved efficiently starting from readily available epichlorohydrin. Kinetic resolution of the racemic epichlorohydrin, 1,3 asymmetric induction using iodocyclisation, regioselective cross metathesis and stereoselective intramolecular Michael addition under kinetic condition to achieve the thermodynamically less stable *trans* isomer are the highlights of the synthesis. The synthesis of the THP fragment was achieved with a total of 11 steps (longest linear) with an overall yield of 14 %. Our research continues in the suppression of C-4 epimerisation during cross metathesis.

Chapter III: Synthetic Approach to Amino acid and Spiroketal Units of Bistramide D

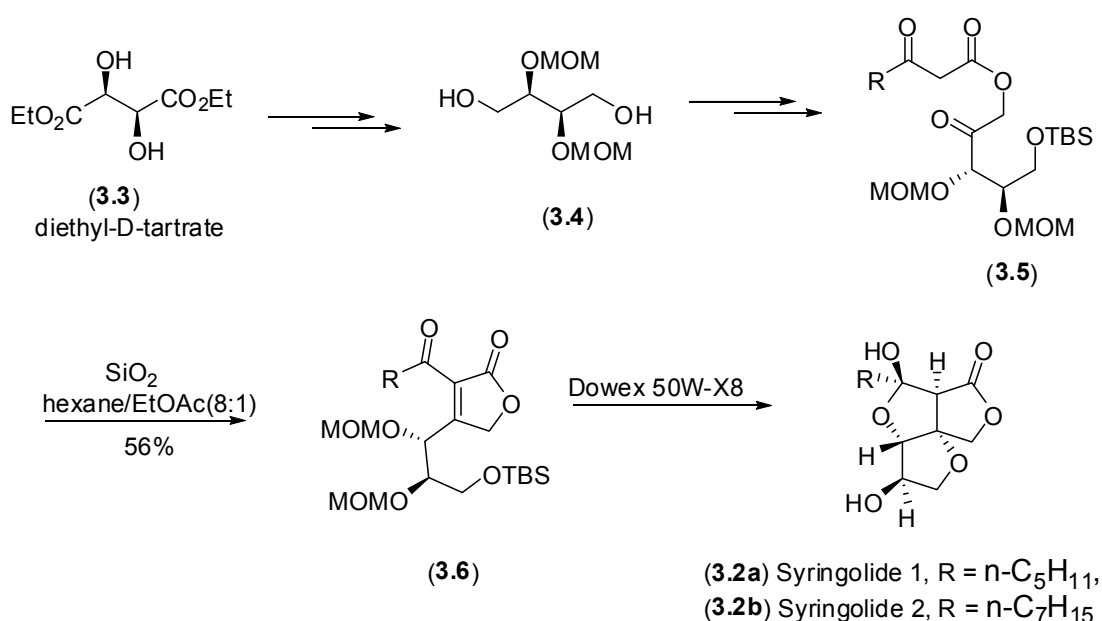
Introduction:

“Efficient and cost-effective syntheses of natural products are often important synthetic challenges in organic synthesis. For convenient and economic reasons, it is ideal if such syntheses can be achieved by selective manipulation of readily available and inexpensive starting materials.”¹¹⁵ Tartaric acid (**3.1**), is one such chiral resource, both enantiomers of which are readily available. In early years, tartaric acid (**3.1**) played an important role in the development of stereochemistry, as the term “enantiomerism” was introduced when Louis Pasteur (1848), achieved the first resolution of racemic tartrate from the tartar deposits in barrels of maturing wine.^{116a} Hannesian has referred to the use of readily available natural chiral starting materials in synthesis as the “Chiron approach”.^{116b} Unlike many other natural chiral sources such as amino acids and sugars, which are available only as one of the two enantiomeric forms, tartaric acid (**3.1**) is available in both enantiomeric forms. Over the years there have been an impressive number of communications dealing with the use of tartaric acid and its derivatives in stereoselective organic synthesis. Among the other contributors, Seebach *et al.*¹¹⁷ and Gawronski *et al.*¹¹⁸ employed tartrates extensively as chiral auxiliaries, resolving agents and starting materials for various reactions. To highlight the synthetic utility of tartaric acid (**3.1**), enantiomeric syntheses of two natural products Syringolide (**3.2a** and **3.2b**) (Scheme 93) and Lentiginosine (**3.8**) (Scheme 94) are shown.

Synthesis of Syringolides: Syringolide 1 and 2 (**3.2a** and **2b**) are compounds produced by *Pseudomonas syringae* pv. *tomato* and function as specific molecular signals which cause hypersensitive responses. Kuwahara synthesised

Syringolides 1 (**3.2a**) and 2 (**3.2b**) from diethyl D-tartrate.¹¹⁹ Starting from a known diol (**3.4**),¹²⁰ mono protection with TBSCl followed by Swern oxidation and further functional group transformations afforded the β -keto ester (**3.5**). The lactone (**3.6**) was obtained from the β -keto ester (**3.5**) via a Knoevenagel condensation. The final cyclisation was achieved by treating the lactone (**3.6**) with Dowex-50-X8/Amberlyst in dry methanol followed by treatment with p-TsOH in acetone/water mixture to provide Syringolides 1 (**3.2a**) and 2 (**3.2b**).

Synthesis of Syringolide 1 and 2:



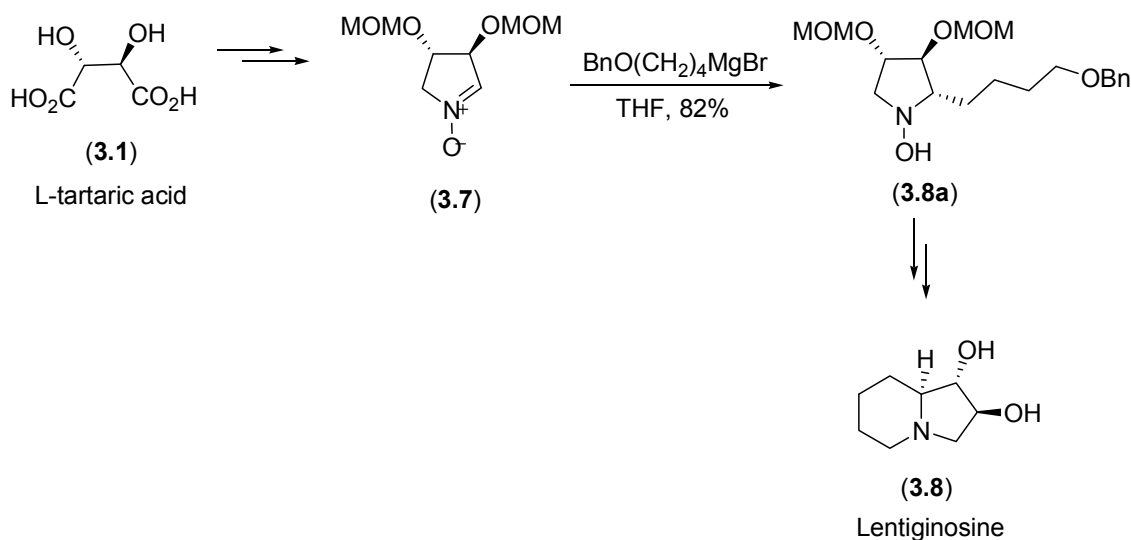
Scheme 93

Synthesis of Lentiginosine (3.3): The biosynthetic origin of Lentiginosine (**3.3**) is related to other polyhydroxylated indolizidine metabolites, and, like swainsonine and castanospermine it also has interesting biological activities which include glycosidase inhibitory and anti-HIV activities. Giovannini synthesised Lentiginosine (**3.3**) starting from L-(+)-tartaric acid (**3.1**) (Scheme 94).¹²¹ Protection of the two hydroxyl groups with MOM followed by condensation provided the nitron intermediate (**3.7**), which on reaction with 4-

benzyloxybutylmagnesium bromide afforded the pyrrolidine ring (**3.8a**).

Lentiginosine (**3.3**) was then obtained from the pyrrolidine (**3.8**) in four steps.

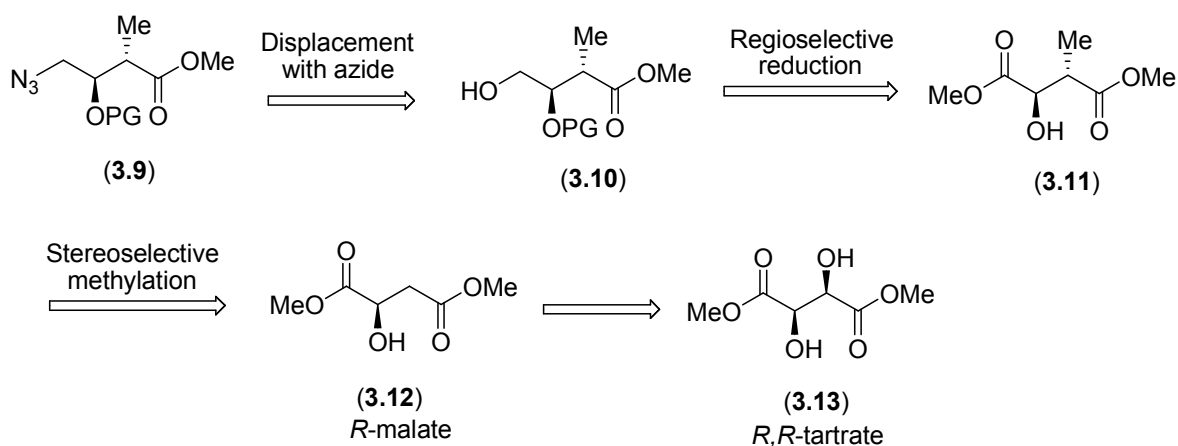
Synthesis of Lentiginosine:



Scheme 94

Retrosynthesis of amino acid fragment:

The essential challenges in our approach to the synthesis of the amino acid fragment are the stereoselective methylation and the regioselective reduction of the diester, the retrosynthetic approach is shown in the (Scheme 95). Our target is to prepare the amino acid precursor azide (**3.9**). Similar to Wipf, we intended to start with malic acid, but with the (*R*) isomer, while the natural one is (*S*). Though naturally available (*S*)-malic acid is cheap and readily available, its unnatural isomer, (*R*)-malic acid is very expensive. Hence we decided make the unnatural malic acid from tartaric acid, as both enantiomers of tartaric acid are commercially available. By choosing L-(+)-tartaric acid (**3.1**) as starting material, one of the chiral centers is already available, through which we planned to induce the other chiral center via a stereoselective methylation.¹²² Notably it is a dicarboxylic ester, so one end of the amino acid fragment is also fixed and suitable functional group transformation of the other end should lead to the precursor to the amino acid (**3.9**).

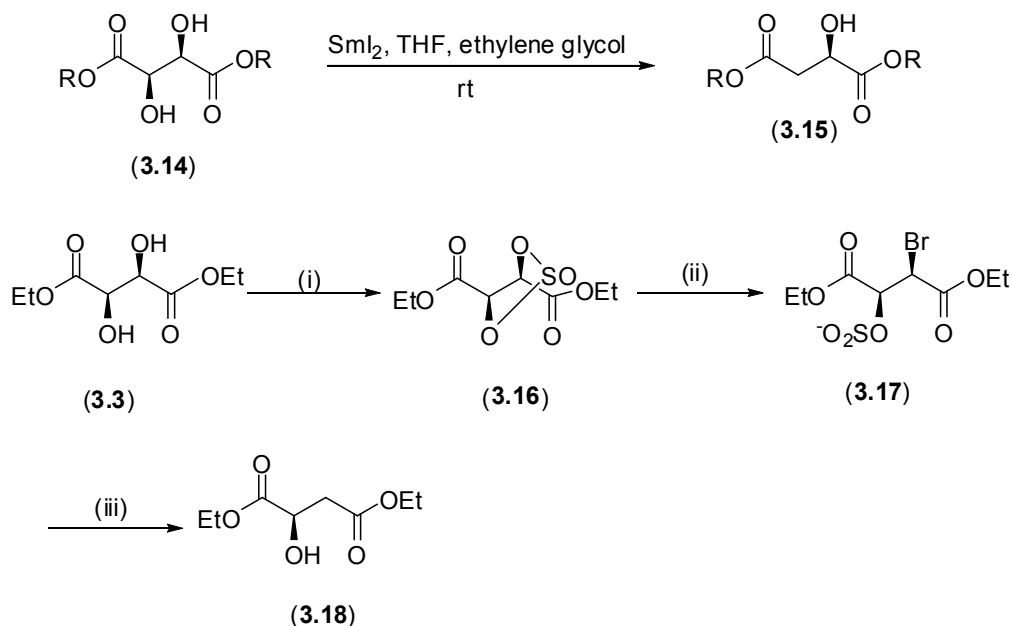


Scheme 95

Results and discussion:

Procedures are available for the conversion of (*R,R*)-tartrate to (*R*)-malate (Scheme 96).¹²³ Inanaga demonstrated a reductive elimination of the α -hydroxyl group of (*R,R*)-tartrate to (*R*)-malate using SmI_2 -THF-ethylene glycol system.¹²⁴ Though this is an impressive one step procedure to obtain (*R*)-malate from (*R,R*)-tartaric acid, samarium is too expensive and air sensitive. However, Gao's one pot procedure of converting (*R,R*)-tartrate to (*R*)-malate via a cyclic sulfite intermediate was chosen, as the reagents are readily available.¹²⁵ Our synthesis started from (*R,R*)-diethyl tartrate (**3.3**), which on one pot reaction with thionyl chloride, LiBr and treatment with zinc provided the desired (*R*)-malate (**3.18**). However, the yield of the reaction was very low, 40 %, and regrettably our attempts to improve the yield were unsuccessful.

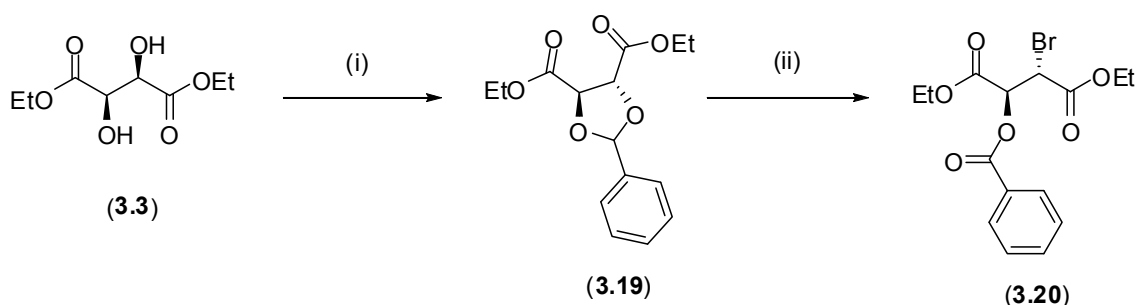
Methods for converting tartrates to malates:



Scheme 96

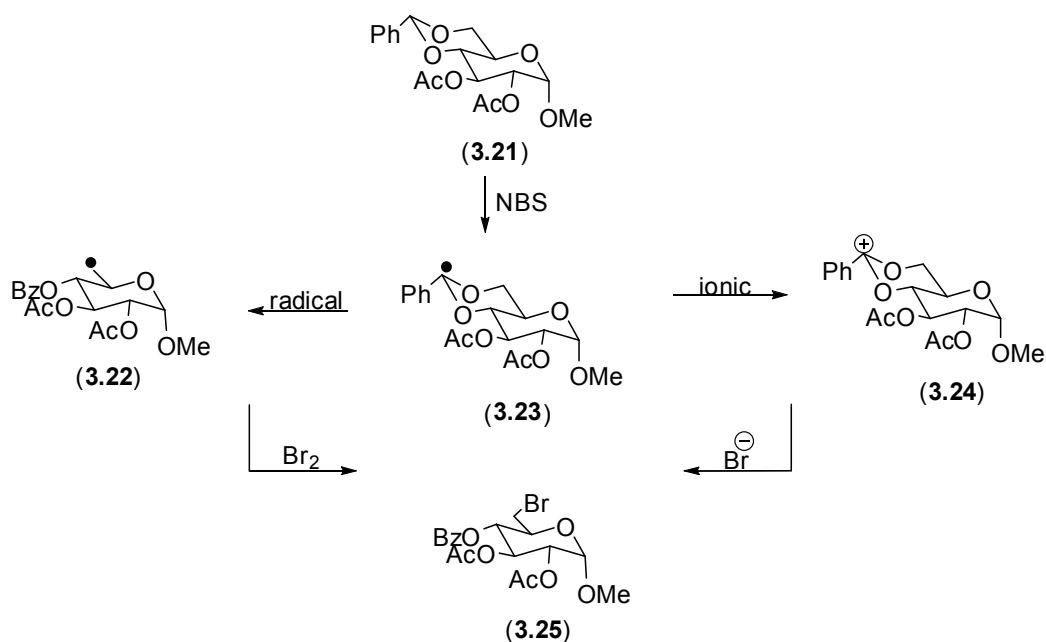
Reagents and conditions: (i) SOCl_2 , CH_2Cl_2 , $50\text{ }^\circ\text{C}$ (ii) LiBr , 0 to $50\text{ }^\circ\text{C}$ (iii) Zn , water, $50\text{ }^\circ\text{C}$, 40% .

Since the cyclic sulfite chemistry did not provide satisfactory results, a conventional procedure was adopted. Condensing diethyl tartrate (**3.3**) with benzaldehyde afforded the corresponding benzylidene derivative (**3.19**) in 98% yield (Scheme 97).¹²⁶ For bromination of the benzylidene derivative (**3.19**), the Hanessian reaction was used, which is a NBS mediated regioselective bromination reaction of benzylidene acetals.¹²⁷ Two different plausible mechanisms are available for this reaction (Scheme 98), under Hanessian conditions, which favor the ionic fragmentation; no product (**3.20**) formation was observed.^{127,128} Hence, Hullar conditions, free radical pathway, were employed by repeating the reaction with the free radical initiator ABCN. However no progress in the reaction was observed, and only starting material was recovered.



Scheme 97

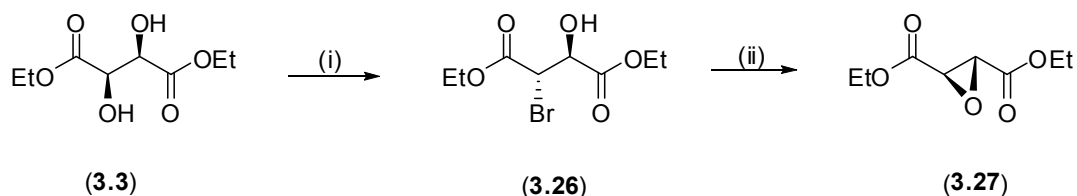
Radical and ionic pathways for benzylidene fragmentation:



Scheme 98

Reagents and conditions: (i) PhCHO, PTSA, Toluene, 98 %; (ii)(a) NBS, Toluene, no product; (b) NBS, ABCN, CCl₄, no product.

As this route did not give the expected bromotartrate (3.20), we used Mori's procedure.¹³⁰ Brominating diethyl tartrate (3.3) with HBr/AcOH mixture afforded the desired bromohydrin (3.26) in 96 % yield (Scheme 99). Our next step was the removal of bromine and then stereoselective methylation, to achieve the better selectivity in the methylation, the bromohydrin was converted to epoxide (3.27). Ring closure of the bromohydrin (3.26) was achieved using DBU in diethyl ether in 89 % yield.

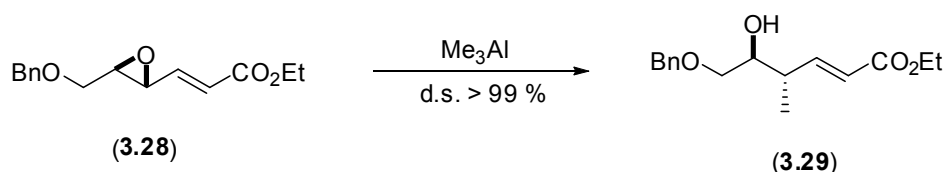


Scheme 99

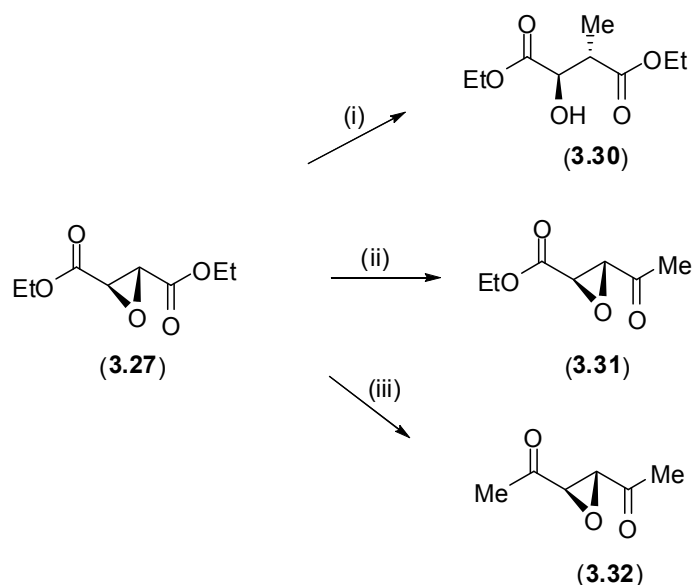
Reagents and conditions: (ii)(a) HBr/AcOH; (b) AcCl, EtOH, 96 % (two steps); (ii) DBU, Et₂O, 89 %.

For methylation reaction, epoxide ring opening with dimethylcopperlithium was tried under standard conditions (Scheme 101).¹³¹ There was no reaction as the starting material was recovered after the reaction. However, use of methyl magnesium bromide resulted in the formation of the mono methylated ketone (3.37) instead of the expected epoxide ring opening. Still showed that trimethyl aluminium selectively reacts with the epoxide (3.28) to give the methylated product (3.29), keeping the ester group intact (Scheme 100).¹³² Following the literature precedent, the epoxide (3.27) was treated with trimethyl aluminium in dichloromethane at -30 °C, disappointingly the reaction afforded the methyl ketone (3.32) as the sole product.³⁹

Still example for regio, stereoselective methylation with Me₃Al:



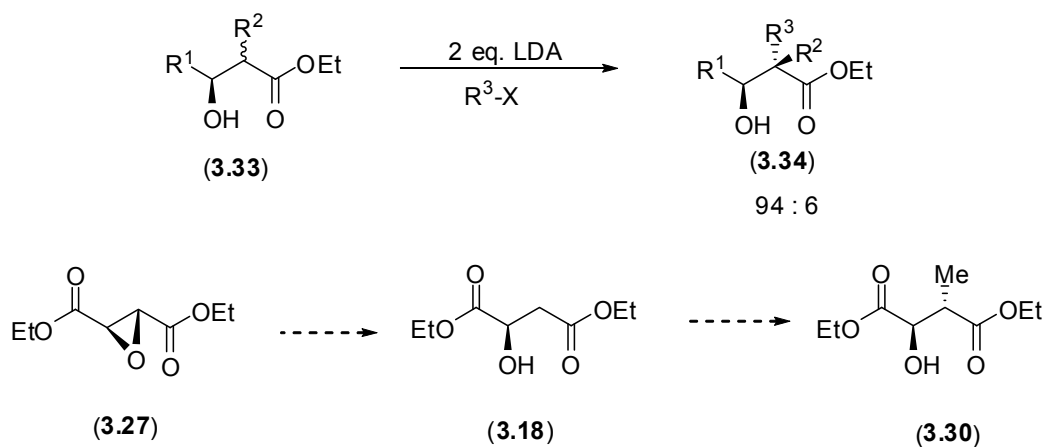
Scheme 100



Scheme 101

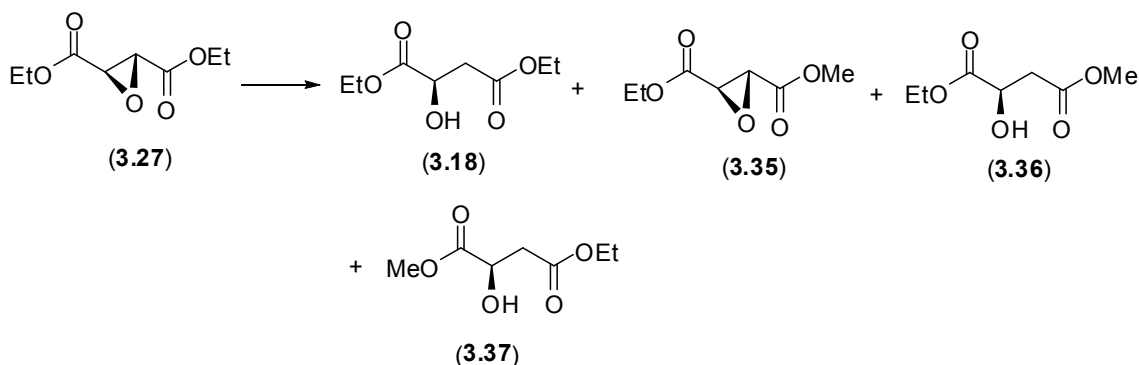
Reagents and conditions: (i) CuI , MeLi , Et_2O , -70°C , no product; (ii) MeMgCl , CuCN , THF , -78°C ; (iii) Me_3Al , CH_2Cl_2 , RT .

As our attempts towards the methylation of the epoxide were unsuccessful we changed our scheme by reducing the epoxide **(3.27)** to alcohol **(3.18)**, as a number of literature procedures are available for the α -alkylation of β -hydroxy esters using dianion chemistry (Scheme 102).¹²² The first stereoselective alkylation of β -hydroxy esters using the dianion chemistry was achieved by Frater in 1979 and in recent years, modified procedures with better selectivity and yield have become available.^{133,134}



Scheme 102

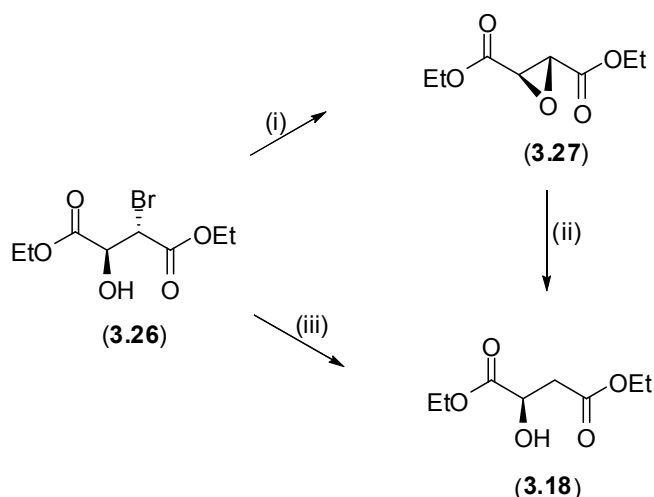
For the reduction of the epoxide (**3.27**), palladium catalysed hydrogenation in MeOH was used. In 8 h the reaction showed (^1H NMR) the presence of the desired product (**3.18**) and the starting material (**3.27**) in a 8:2 ratio. So the hydrogenation was continued for overnight, to our surprise the reaction afforded four different compounds with some starting material being left unreacted. Detailed NMR studies revealed that the compounds formed are the desired product (**3.18**), transesterified (methyl) epoxide (**3.35**) and transesterified alcohols (**3.36**) and (**3.37**) (Scheme 103). The unexpected transesterification during hydrogenation might be due to the relatively small amount of acid present in Pd/C, (the acid catalysed transesterification). This simple problem was solved just by switching the solvent from methanol to ethanol to obtain the desired product (**3.18**) in quantitative yield.



Scheme 103

Reagents and conditions: (a) H_2 , Pd/C, MeOH; (b) H_2 , Pd/C, EtOH, quantitative.

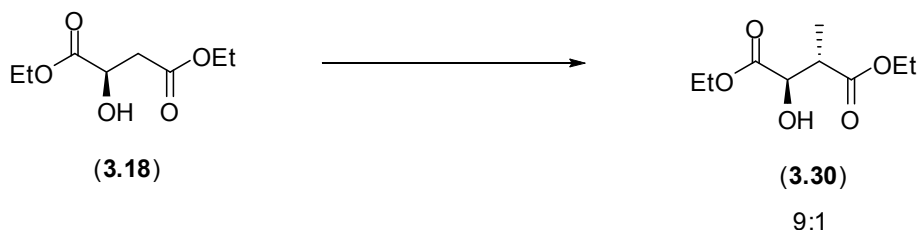
The (*R*)-malate (**3.18**) can also be prepared from the bromohydrin (**3.26**) via zinc reduction (Scheme 104).



Scheme 104

Reagents and Conditions: (i) DBU, Et₂O, 89 %; (ii) Pd/C (5 mol %), H₂ (balloon), MeOH, 20 h, 99 %; (iii) Zn, acetone, water, 50 °C/sonication, 99 %.

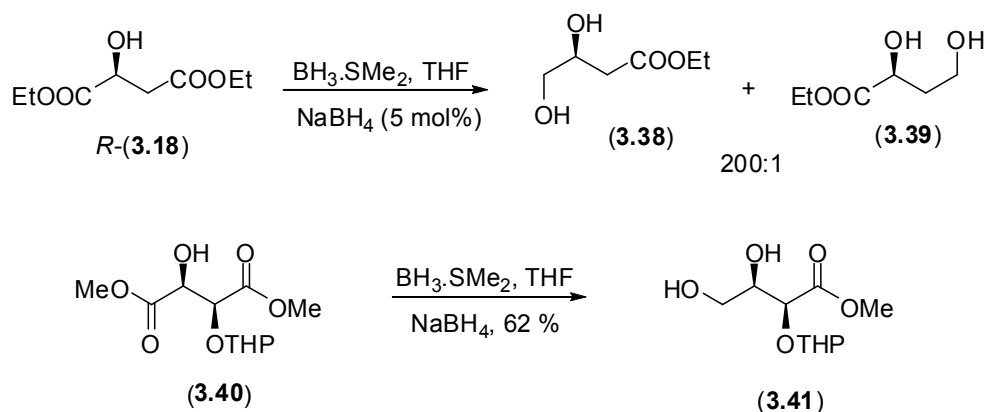
Methylation was promising with MeI and LDA at -78 °C to afford the methylated malate (**3.30**) in 78 % yield as a 9:1 mixture of diastereomers (Scheme 105). The product was clearly identifiable by ¹H NMR, showing the presence of the methyl group as a doublet at 1.30 ppm, the diastereomeric ratio was obtained by integrating methyl proton peaks. Comparison of the data with the literature confirmed that the desired stereochemistry was obtained.^{14,135} However at this point the isomers were not separable by column chromatography, but further functional group modifications in subsequent steps allowed separation to be achieved.



Scheme 105

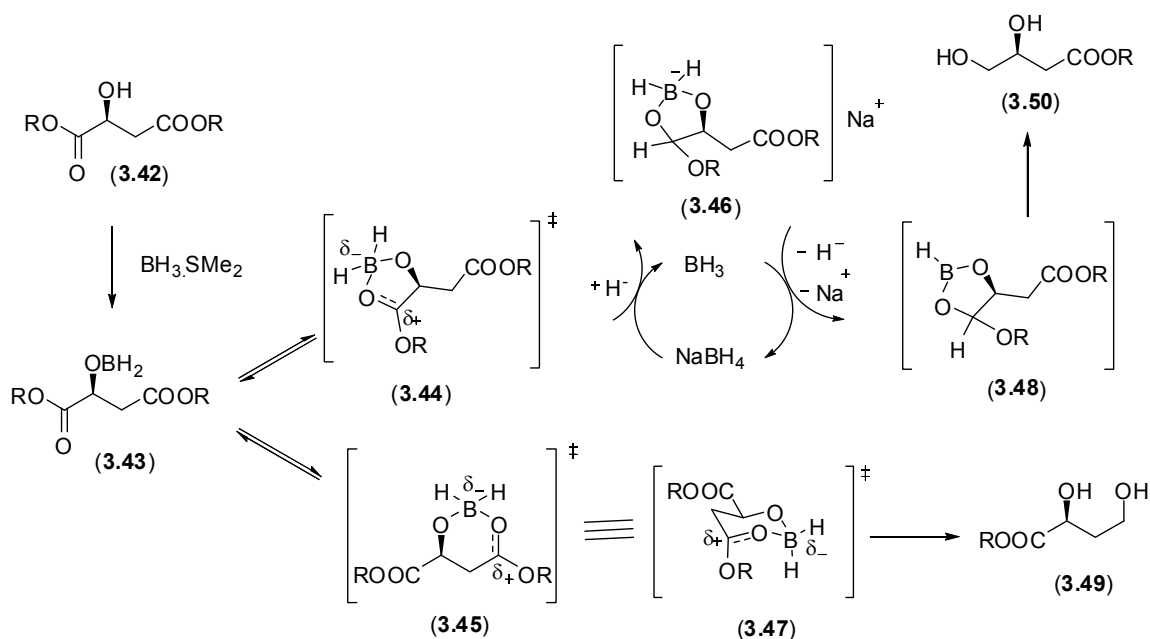
Reagents and condition: LDA, MeI, THF, -78 to -5 °C, 78 %, (9:1).

The next step was the regioselective reduction of the diester. Saito,^{136,137} and Keck¹³⁸ have demonstrated very efficient protocols for the regioselective reduction of the diester. Saito reported that the Borane-dimethyl sulfide complex with a catalytic amount of sodium borohydride is capable of reducing the diester group selectively at the carbonyl which is α to the hydroxyl group (Scheme 106).



Saito and Moriwake suggested the regio selectivity arises from the activation energy difference between the two possible transition states, namely the five (3.44) and six (3.45) membered ring systems (Scheme 107).¹³⁷ Neighbouring group participation would be most favoured for five membered ring systems (3.44) than the six membered systems. Saito also added the concept of bond length for the selectivity, the shorter boron-oxygen (3.45) bond length, causes the severe 1,3 diaxial interaction between the ester alkoxy group and the hydrogen on the boron atom making the six membered transition state (3.45) less favourable.

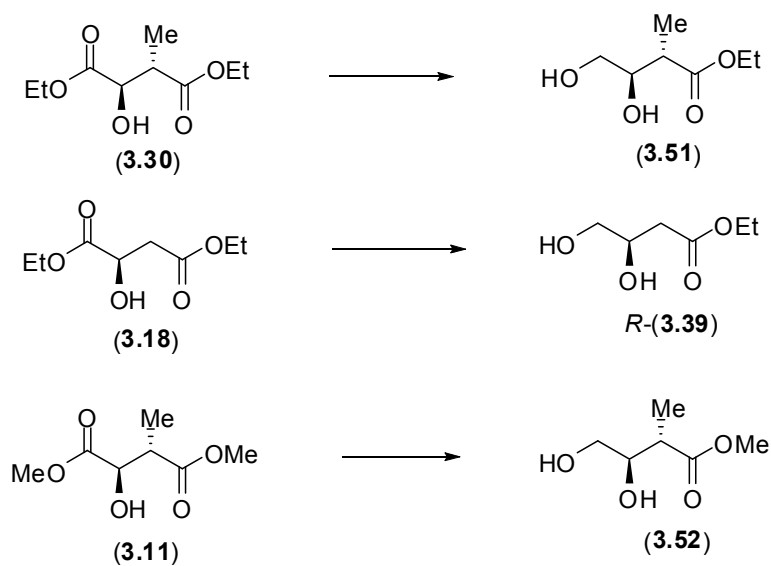
Saito's proposed mechanism for the regioselective reduction.



Scheme 107

We chose to apply Saito's reaction conditions for the reduction of methylated diethyl (*R*)-malate (**3.30**), but to our disappointment the reaction gave a complex mixture of products and large amount of starting material (**3.30**) being recovered (Scheme 108). Initially it was thought that it may be due to the presence of methyl group which was hindering the reduction, so the reduction was tried with diethyl malate (**3.18**), however there was no progress in the reduction. The reduction was also tried with dimethyl ester (**3.11**) to see any improvement in the reduction, but all our trials were unsuccessful under these conditions.

Trials for the methylation with diethyl malate.

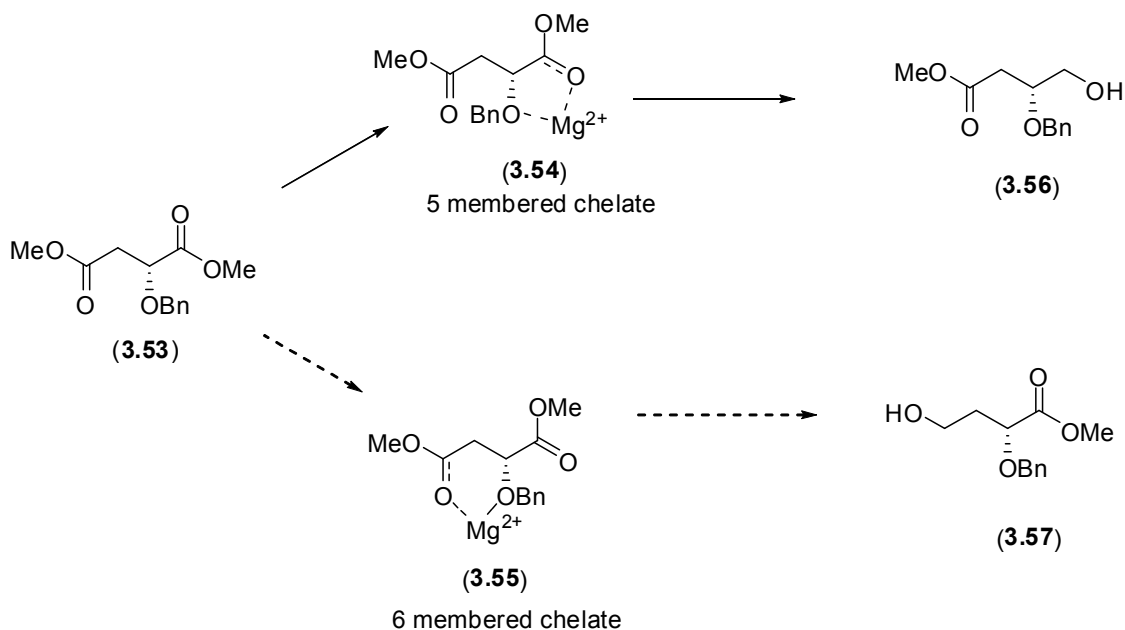


Scheme 108

Reagents and conditions: $\text{BH}_3 \cdot \text{SMe}_2$, NaBH_4 , THF, no product.

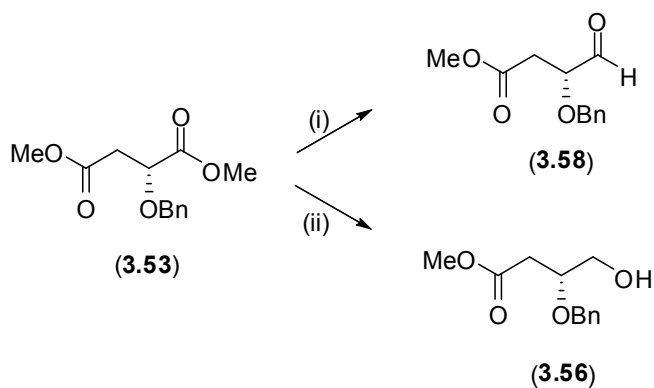
Since our attempts for the regioselective reduction with borane did not work, we moved on to use Keck's protocol, which is a chelation controlled reduction with $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ (Scheme 109).¹³⁸ Similar to Saito, Keck also suggested that the regioselective reduction of the ester α to the hydroxyl group is due to the marked preference of five membered bidentate complex **(3.54)** over the six membered ring **(3.55)**.

Keck's regioselective reduction:



Scheme 109

Depending upon the need, Keck's protocol can be used to prepare either the aldehyde (**3.58**) or the alcohol (**3.56**) by controlling the number of eq. of DIBAL-H and the reaction temperature (Scheme 110).

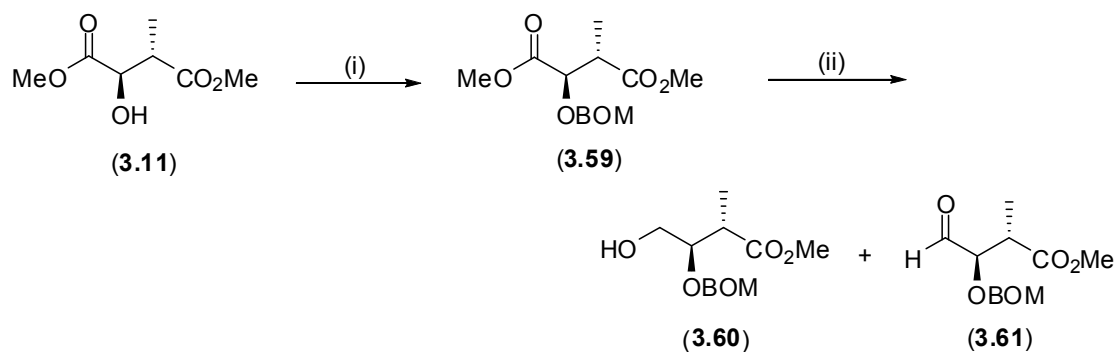


Scheme 110

Reagents and conditions : (i) $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, DIBALH (1 eq.), CH_2Cl_2 , -95°C ; (ii) $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, DIBALH (2 eq.), CH_2Cl_2 , -40°C .

Since the Keck strategy required the hydroxyl group to be protected, our first choice for the protection of hydroxyl group was the BOM group, since the hydroxyl group of the THP fragment (**2.191**) had already been protected with the BOM group. Hence it would be logical to use the same protecting group for

subsequent simultaneous deprotection. BOM protection of dimethyl malate (**3.11**) was achieved using BOMCl in presence of DIPEA in dichloromethane in 76 % yield (Scheme 111). The protected product (**3.59**) was clearly identifiable by ^1H NMR, doublets at 4.46 and 4.71 ppm and the disappearance of the OH stretch at 3487 cm^{-1} in the IR spectrum were observed. With the protected alcohol (**3.59**) in hand, we moved on to try the regioselective reduction, by following Keck's procedure exactly. However, our trials for the regioselective reduction only afforded 20 % of the desired product (**3.60**) with 29 % of the aldehyde (**3.61**) and large amount of starting material being recovered.

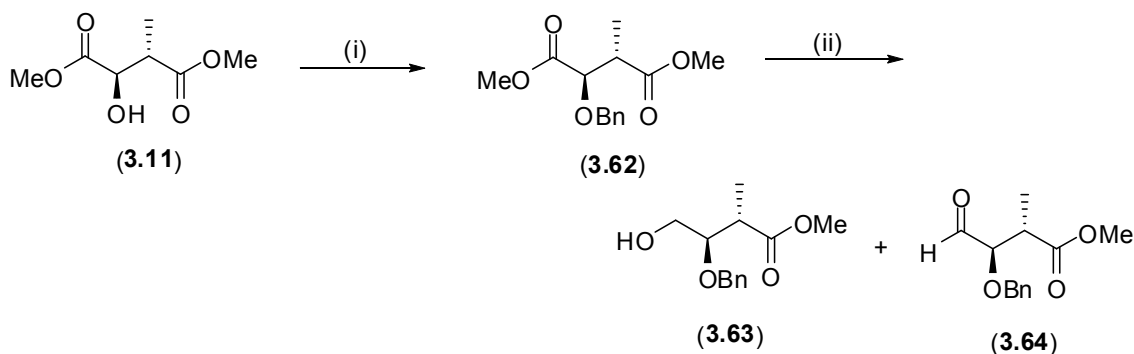


Scheme 111

Reagents and conditions: (i) BOMCl, DIPEA, CH_2Cl_2 , 76%; (ii) $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, DIBALH, CH_2Cl_2 , $-40\text{ }^\circ\text{C}$, 20 %.

Since the BOM group was not giving satisfactory results, we changed the protecting group to benzyl, the one Keck used for a similar diester (Scheme 112). Our initial trail for benzylation with benzyl trichloroacetimidate using Bundle's procedure did not proceed at all.¹³⁹ However benzylation using benzyl chloride in the presence of silver oxide in ethyl acetate afforded the desired product (**3.62**) in 98 % yield. On the other hand this reaction was highly dependent on the purity of Ag_2O ; since the yield of the reaction varied with different batches. Use of Dudley's reagent, 2-Benzyloxy-1-methylpyridinium

triflate, provided the benzylated product in 96 % yield and the yield was consistent over several repetitions.¹⁴⁰ Having the benzylated product (**3.62**) in hand, we moved on to the reduction under the same conditions reported by Keck, to our surprise, the desired alcohol (**3.63**) was obtained in 82 % yield with a small amount of the aldehyde (**3.64**) (9 %) as side product. The product was clearly identifiable by ¹H NMR, showing one singlet at 3.69 ppm for the mono methyl ester and two new double double doublets at 3.73 and 3.78 ppm. This characteristic multiplicity pattern showed that the regioselective reduction was successful. Comparison of literature data with further conversions allowed us to confirm that the above characterisation was precise.¹³⁵



Scheme 112

Reagents and conditions: (i) (a) benzyl trichloroacetimidate, CF₃COOH, hexane, CH₂Cl₂, no product; (b) BnCl, Ag₂O, ethyl acetate, 98 %; (c) BnOPT, MgO, dichloroethane, 80 °C, 96 %; (ii) MgBr₂·Et₂O, DIBALH, CH₂Cl₂, -40 °C, 82 %.

Our next goal was to obtain the azide (**3.67**) from the alcohol (**3.63**) (Scheme 113). Mitsunobu conditions were chosen, as it is an one pot procedure compared with the conventional two step procedure, where the alcohol needs to be activated and then displaced with azide. Recently Rollin introduced a zinc azide mediated Mitsunobu reaction, which is considered to be an expedient one pot method for the synthesis of azides from alcohols.¹⁴¹ The desired azide

(**3.67**) was synthesised by using Rollin's zinc azide/bispyridine complex (**3.65**) (Figure 4) with PPh_3 in toluene in the presence of DIAD in 62 % yield. The advantage of using Rollin's complex (**3.65**) is its non hygroscopic nature, and there is no need to use an external H^+ source, as Zn^{2+} serves as a Lewis acid. Though the reaction was simple the yield was not high and was not consistent over several repetitions. The conventional 2 step procedure was, therefore, adopted.

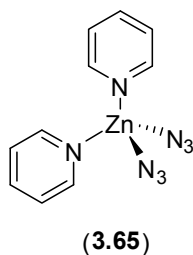
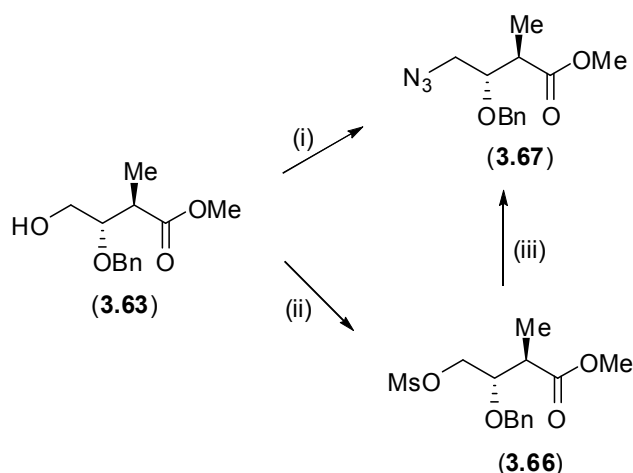


Figure 4: zinc azide/bispyridine complex

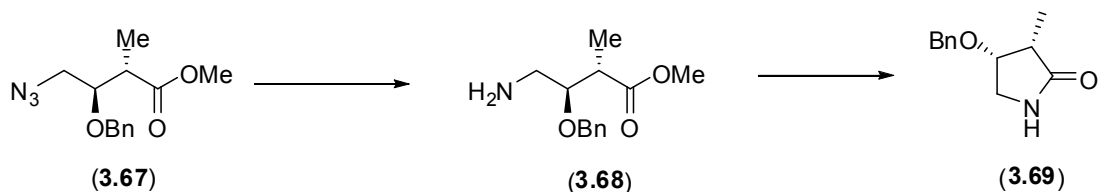
Mesylation was achieved in quantitative yield by treating the alcohol with MsCl and triethylamine in dichloromethane. The product (**3.66**) was clearly identifiable by the loss of the hydroxyl stretch at 3434 cm^{-1} in the IR and a characteristic peak in the ^1H NMR at 2.98 ppm as a singlet. Displacement of mesylate with azide was achieved by heating the mesylate (**3.66**) with NaN_3 in DMF, identifiable most evidently by the characteristic IR band at 2102 cm^{-1} . From our observations, the azide (**3.67**) formation using the conventional procedure was more easily purified and better yielding (93 %, two steps) compared with the Mitsunobu reaction by using the zinc azide/bispyridine complex.



Scheme 113

Reagents and Conditions: (i) $\text{Zn}(\text{N}_3)_2\text{Py}_2$, DIAD, PPh_3 , Toluene, 62 %; (ii) MsCl , Et_3N , CH_2Cl_2 , 99 %; (iii) NaN_3 , DMF, 60 °C, 93 %.

It was anticipated that the reduction of azide (3.67) to amine (3.68) would be troublesome as the formation of amine (3.68) might lead to cyclisation to form a pyrrolidinone derivative (3.69) (Scheme 114).

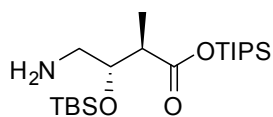


Scheme 114

In order to prevent this unwanted cyclisation Wipf, Panek and Yadav protected the carboxylic end with a bulky TIPS group; Kozmin and Crimmins protected the amine end by Fmoc group (Scheme 115) In order to avoid the protection and deprotection steps, it was planned to couple the azide (3.67) directly to the carboxylic acid end of the THP fragment (2.191) via a modified Staudinger reaction (Scheme 116).¹⁴²

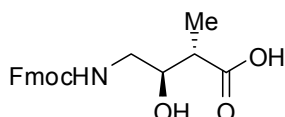
Common intermediates in the synthesis of bistramides:

Wipf, Panek and Yadav



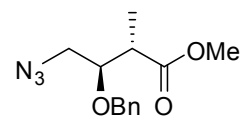
(1.35)

Kozmin and Crimmins



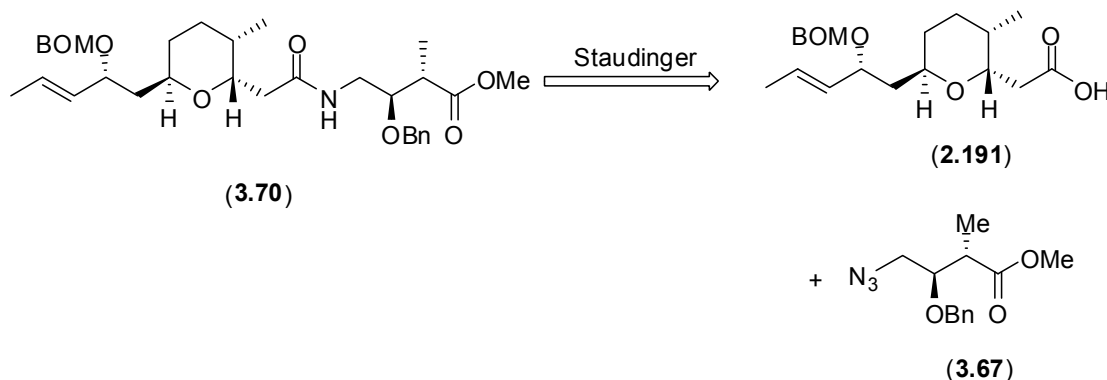
(1.68)

Our proposed precursor



(3.67)

Scheme 115

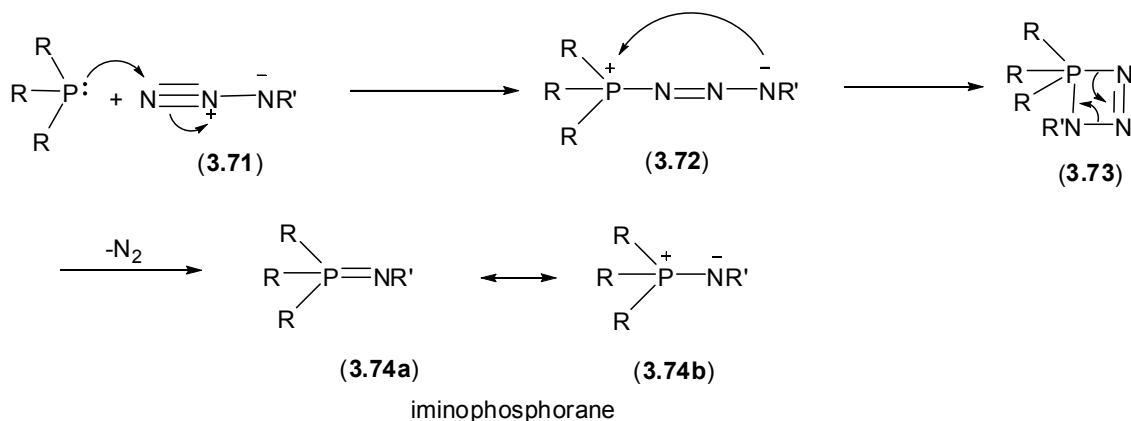


Scheme 116

Staudinger coupling of THP and Amino acid:

The Staudinger reaction, introduced by Hermann Staudinger in 1919, in which an azide (**3.71**) reacts with triarylphosphine to form an iminophosphorane (**3.74**), under mild conditions in good yield.^{143,144} Iminophosphoranes are often used for the reduction of azides to amines as it is a mild procedure for reduction. Due to the highly nucleophilic nitrogen atom in iminophosphoranes (**3.74**), they are able to react with many electrophiles, which has allowed them to find many applications in organic synthesis including alkylation, cyclisation, substitution, aza-Wittig reaction¹⁴⁵ and Staudinger ligation.¹⁴⁶ In the last few decades, a detailed mechanism for the formation of iminophosphoranes has been revealed (Scheme 117).^{143,147} The mechanism involves a four membered heterocyclic ring that extrudes N₂ via an apparent retro-cycloaddition.

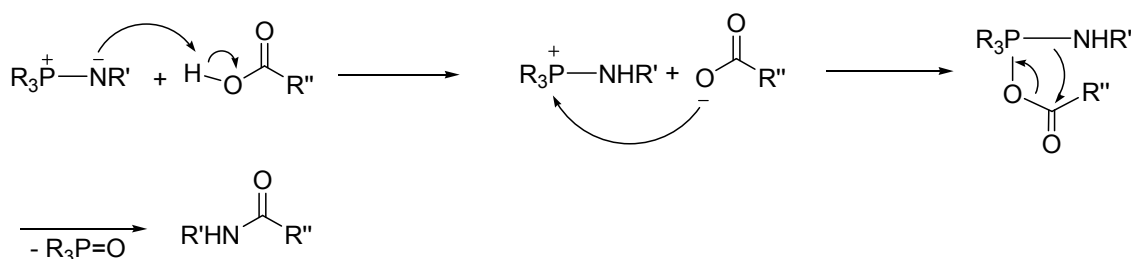
Mechanism for the formation of iminophosphorane.



Scheme 117

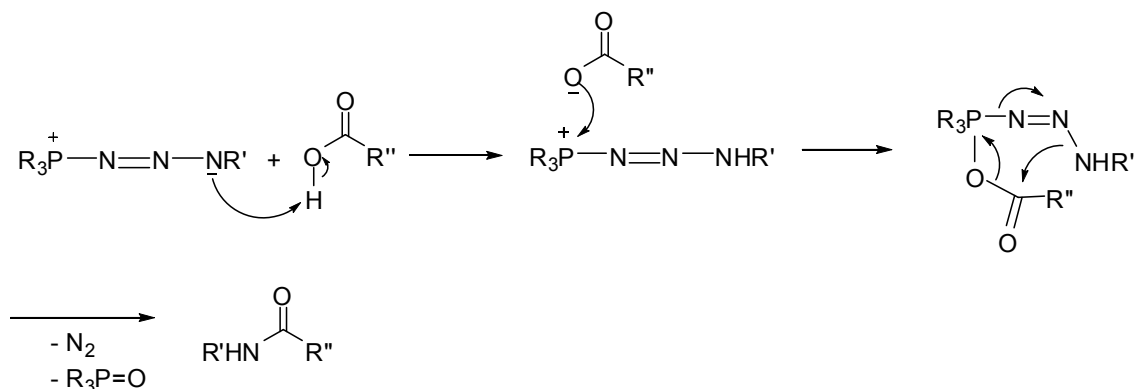
In 1984 Vilarasa showed that the iminophosphoranes can react with carboxylic acids to obtain amides.¹⁴² Recently, Inazu postulated two different mechanisms for the amide formation (Scheme 118) depending upon the order of addition of the reagents and the reaction temperature.¹⁴⁸ At higher temperatures, the trialkyl/aryl phosphine/phosphite reacts with the azide to form the iminophosphorane, which undergoes further rearrangement with the carboxylic acid to form the amide bond. At lower temperatures, the carboxylic acid is involved in the initial stage of the mechanism, before the iminophosphorane forms (Scheme 119).

Mechanism of amide formation at high temperature:



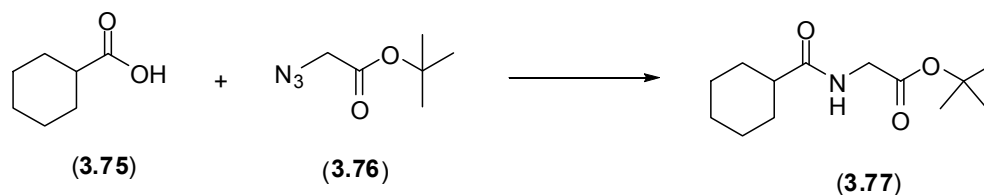
Scheme 118

Mechanism of amide formation at low temperature:



Scheme 119

Before starting the Staudinger coupling with the THP fragment (**2.191**) and azide (**3.67**), a model study with cyclohexanecarboxylic acid (**3.75**) and the tert-butyl 2-azidoacetate (**3.76**) was carried out to establish suitable conditions for the amide bond formation (Scheme 120).



Scheme 120

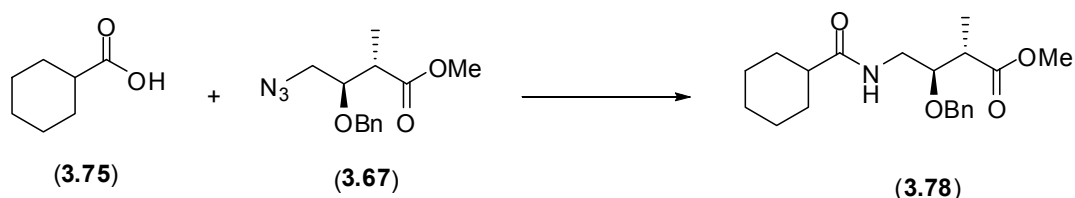
The various conditions tried for the Staudinger coupling are shown in table 6. The use of standard Staudinger conditions with PPh_3 in acetonitrile did not work with the model system. This implies that the reaction requires a more reactive phosphine; therefore Bu_3P was used instead of PPh_3 , due to its higher reactivity. After trying various phosphines and solvent systems it was found that Bu_3P in dichloromethane at reflux gave the coupled product (**3.77**) in 80 % yield.

Table 6: Optimisation conditions for the model Staudinger coupling.

Reagent	Solvent	Temperature	Yield of (3.77) (%)
Ph ₃ P	CH ₃ CN	RT	0 ^a
Bu ₃ P	CH ₂ Cl ₂	-65 °C	30 ^b
Ph ₃ P	Toluene	70 °C	25 ^b
Bu ₃ P	CH ₂ Cl ₂	RT	50 ^b
Bu ₃ P	Toluene	70 °C	50 ^b
Ph ₃ P	CH ₂ Cl ₂	RT	0 ^a
D	CH ₂ Cl ₂	RT	0 ^a
Bu₃P	CH₂Cl₂	reflux	80

a: carboxylic acid (3.75) was recovered; b: yields were calculated from ¹H NMR by comparing the ratio of product and starting material, D=trifuryl phosphine.

After optimising the conditions, a reaction with the model acid (3.75) and the real azide (3.67) was carried out (Scheme 121). As expected, the reaction worked well under identical conditions to give the desired product (3.78) in 69 % yield, the lower yield may be due to bulkier azide (3.67).

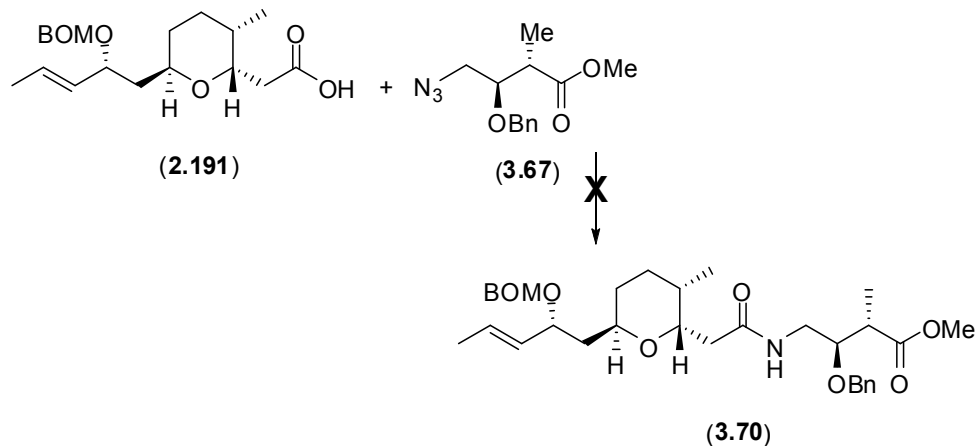


Scheme 121

Reagents and conditions: Bu₃P, CH₂Cl₂, reflux, 69 %.

Employing the same conditions, coupling of the THP fragment (2.191) with the azide (3.67) was carried out. To our disappointment, under these conditions, the coupling did not give the desired product (3.70) and none of the starting materials were recovered. It was clear that the azide (3.67) reacts with the phosphine to give the iminophosphorane as evolution of nitrogen gas bubbles

could be seen as soon as the Bu_3P was added. Suspecting that the intermediates might be thermally unstable, the reaction was tried at room temperature. Disappointingly there was no reaction but it was possible to recover the starting material (**2.191**).

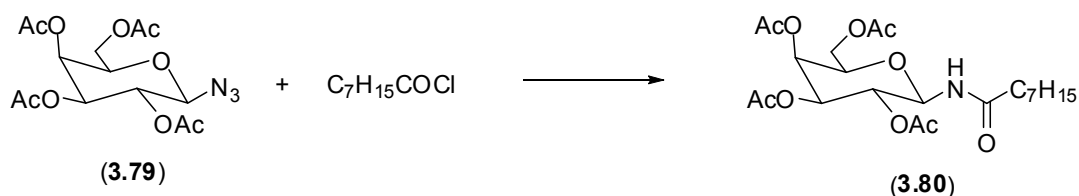


Scheme 122

Reagents and conditions: (a) Bu_3P , CH_2Cl_2 , reflux, no product; (b) Bu_3P , CH_2Cl_2 , rt, no reaction.

Modified Staudinger procedures where the carboxylic acid is activated just before the coupling are known. Paul used acid chlorides to couple with the azide **(3.79)** and found that the reaction is efficient giving impressive yields and requiring less time compared with the reaction with carboxylic acid (Scheme 123).¹⁴⁹

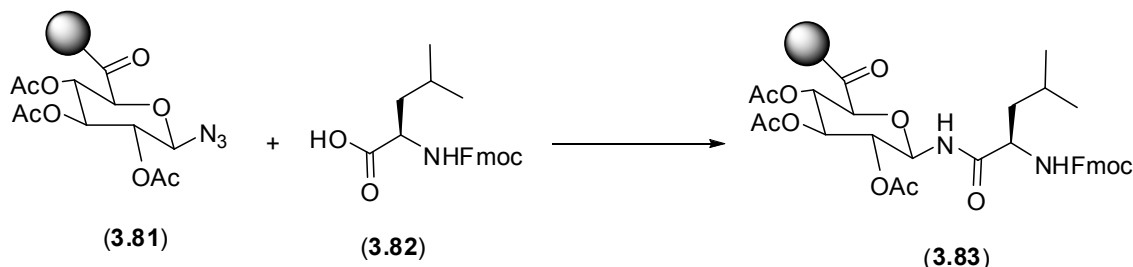
Staudinger reaction with an acid chloride:



Scheme 123

Reagents and conditions: PPh_3 , CH_2Cl_2 , rt, 90 %.

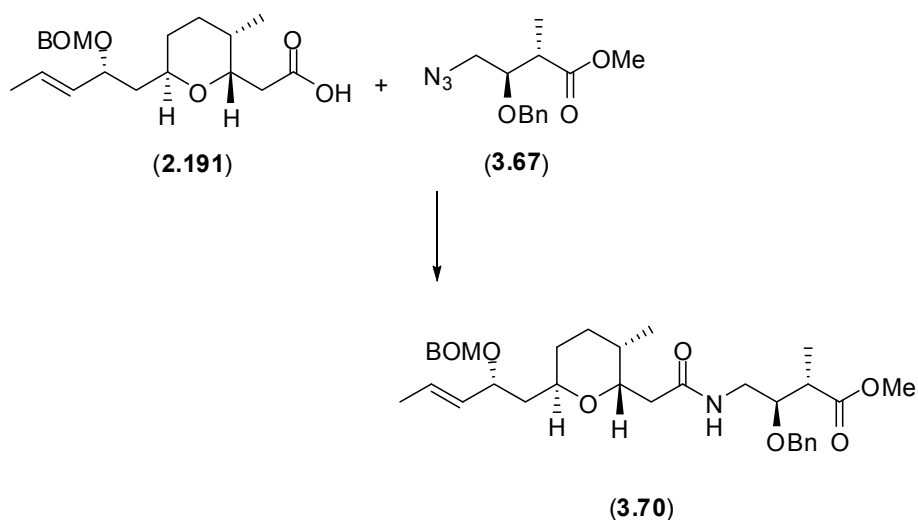
Later, Malkinson extended the modified Staudinger reaction by activating the carboxylic acid (**3.82**) using *N,N*-diisopropylcarbodiimide (DIC) and 1-hydroxy benzotriazole (HOBt). The coupling was achieved at low temperature in high yield (Scheme 124).¹⁵⁰



Scheme 124

Reagents and conditions: DIC, HOBt, PBU₃, THF, 0 °C.

Impressed by these conditions, we activated the carboxylic acid part of the THP fragment (**2.191**) using PyBOP, a phosphonium type coupling reagent, and then reacted it with the azide (**3.67**) in presence of Bu₃P at -78 °C (Scheme 125). To our regret there was no reaction at that low temperature but when the temperature was raised to -20 °C there was the formation of new component observed by TLC. The stirring was continued until all the starting material had disappeared, and, after a simple purification, the desired amide (**3.70**) was obtained in 71 % yield. The product was clearly identifiable by ¹H NMR, a broad triplet at 6.79 ppm showing the presence of the amide proton (NH) and comparing the NMR data with the natural product.¹



Scheme 125

Reagents and conditions: PyBOP, NMM, CH_2Cl_2 , PBU_3 , $-78\text{ }^\circ\text{C}$ to $-20\text{ }^\circ\text{C}$, 71 %.

In summary, we were able to achieve the synthesis of the amino acid precursor (3.67) from a cheap and replenishable source, (*R,R*)-tartaric acid (3.1), via a stereoselective methylation and regioselective reduction. Coupling the azide (3.67) directly to the acid (2.191) saves the protection and deprotection steps. Using the Staudinger reaction for the coupling of THP fragment (2.191) and azide (3.67) to obtain the C1-C18 fragment of bistramide D is new for bistramide family, as all other groups coupled these fragments using the conventional acid-amine peptide bond formation.

Synthetic approaches to the Spiroketal Fragment

Introduction:

Spiroketals are bicyclic ethers in which two rings are fused together by a single atom, called *spiro* atom. Spiroketals are well known due to their presence in numerous natural products ranging from insect pheromones to antibiotics and are famous for their attractive biological properties.¹⁵¹

Generally, the spiroketals have a structure in which the two oxygen atom are axial to each other, though it is often expected that substituents in a ring tends to prefer equatorial position over the axial position to avoid destabilising steric repulsions. However, in tetrahydropyrans and other related compounds substituents, (especially the electronegative groups) prefers the axial position; this is due to the anomeric effect.¹⁵²

The anomeric effect is the tendency of an electronegative substituent on a THP ring to take an axial rather than equatorial position despite the unfavourable steric interactions. There are number of explanations available for the anomeric effect including the molecular orbitals and dipole moment. However the most accepted explanation comes from molecular orbital theory. The stability of the axial substituents can be explained by the strong interactions between the lone pair of the oxygen in the ring and the antibonding σ^* orbital of the C-O bond (Scheme 126), which is possible only when the substituent is in the axial position.¹⁵³

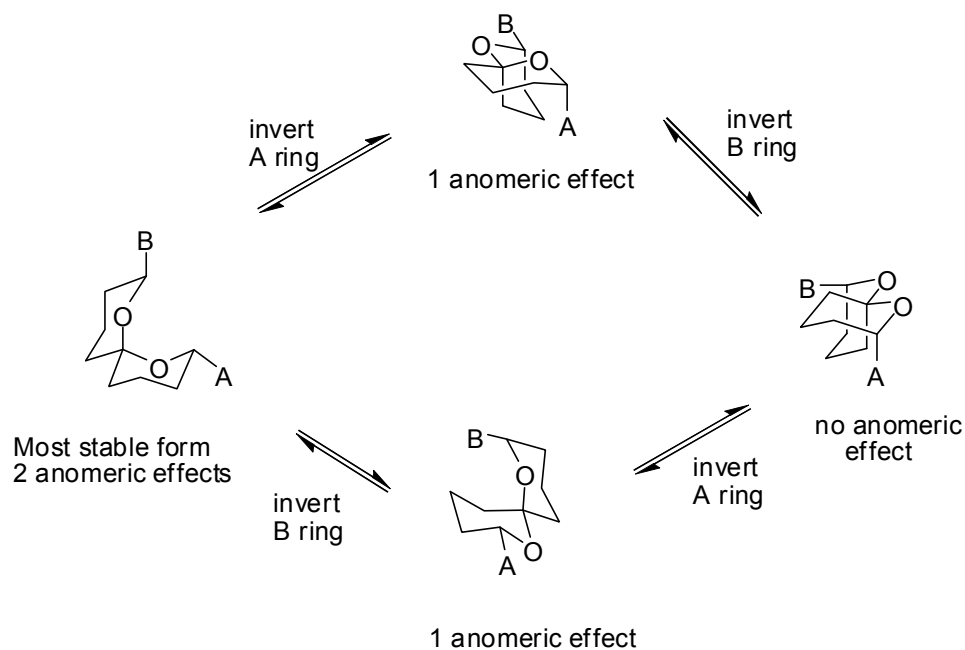
Orbital interactions in axial, equatorial substituents:



Scheme 126

Deslongchamps has provided a detailed conformational studies of [6,6]-spiroketals using 1,7-dioxaspiro[5.5]undecane (Scheme 127) as a model.¹⁵⁴ He explained that four chair conformers of [6,6] spiroketals are possible and they are interconvertible with each other by inversion of each ring. The most stable conformer is the one wherein anomeric interactions are maximised and the unfavourable steric interactions between the substituents are minimised.¹⁵³

Four conformers of 2,8-disubstituted [6,6] spiroketal:

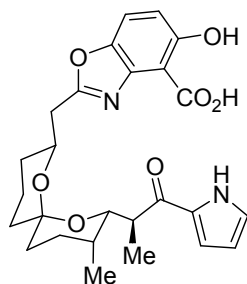


Scheme 127

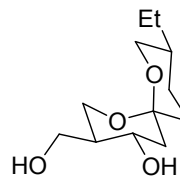
Most of the naturally available spiroketals, including the bistramides, possess the bisaxial form, where the C-O bond of one ring is axial to the C-O of the other ring

(Scheme 128). Therefore the stereochemistry of the spiro carbon will be under thermodynamic control.

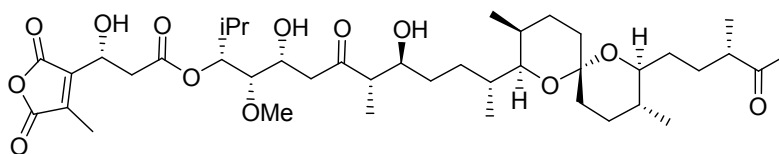
Naturally occurring bisaxial [6,6] spiroketals:



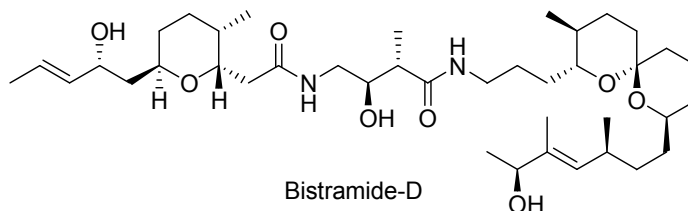
Routiennocin
(CP-61, 405)



Taloromycin B



Tautomycin

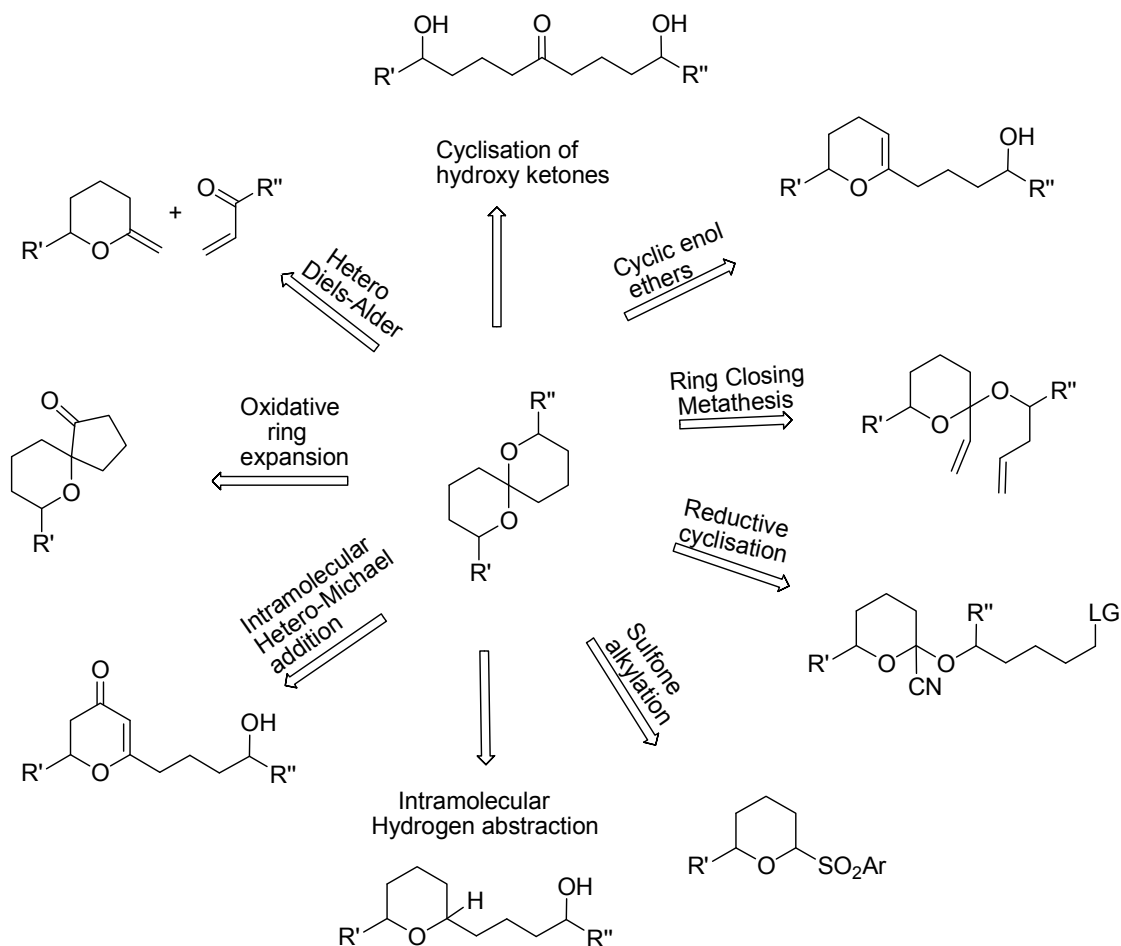


Bistramide-D

Scheme 128

Synthetic approach to spiroketal:

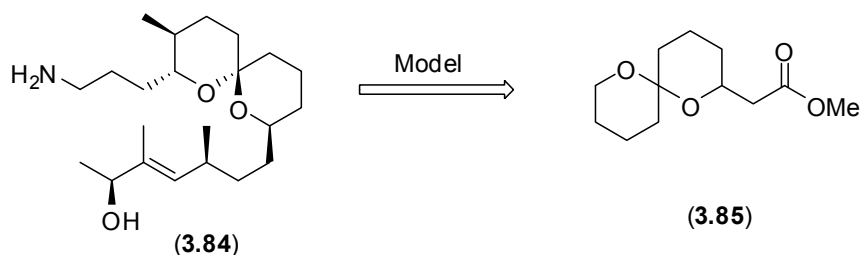
There are number of synthetic approaches to spiroketals available in the literature, and a selection of them are shown below (Scheme 129).^{155,156}



Results and discussion:

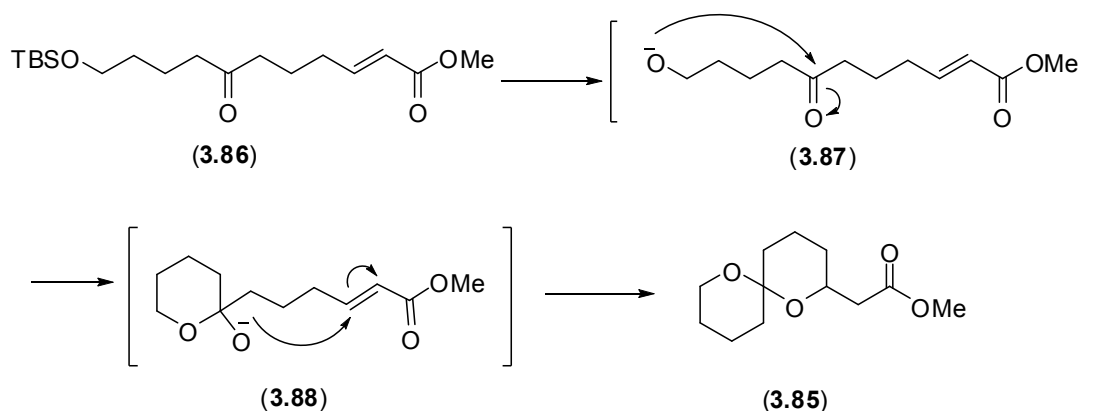
Though various approaches are available for the construction of spiroketals, we were interested in using an intramolecular Michael addition, related to the cyclisation for the left end (THP) of bistramide D. So far, few people have used the Michael strategy for the synthesis of spiroketals, Kishi was the first one to report the intramolecular Michael addition for a spiroketal synthesis.^{157,158} To prepare for the synthesis of spiroketal fragment (**3.84**), a model study with a much simpler version (**3.85**) was attempted (Scheme 130). Our strategy is to construct the spiroketal in one pot from the protected alcohol (**3.86**) via a tandem deprotection and cyclisation process, with installation of the Michael acceptor by cross-metathesis (Scheme 131).

Michael strategy with the model spiroketal system.



Scheme 130

Tandem deprotection and cyclisation:

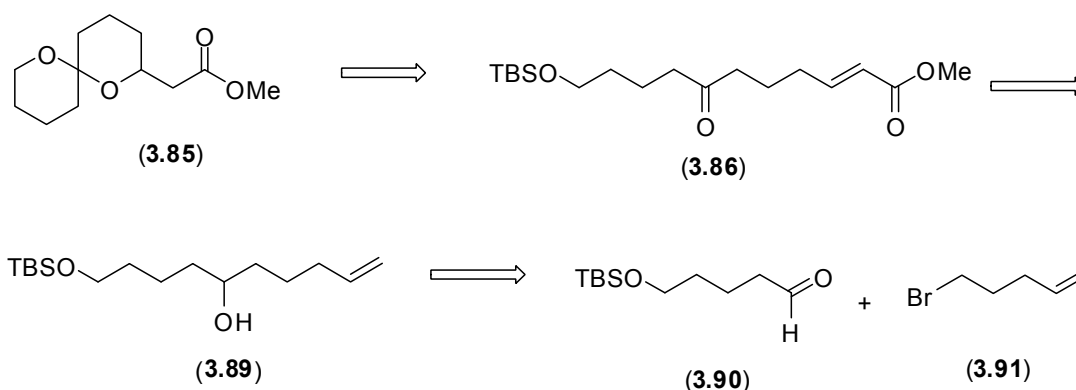


Scheme 131

The retrosynthesis is shown in Scheme 132 below. We chose a TBS protecting group, as it is a versatile protecting group and can be removed under a wide range of conditions, both acidic and basic, anticipating that the deprotecting reagent will also promote the proposed cyclisation reaction in one pot.

Retrosynthetic approach to model spiroketal:

The ketone (3.86) on tandem deprotection, cyclisation followed by Michael addition will provide the spiroketal (3.85). The ketone (3.86) can be prepared by a cross metathesis of the alkene (3.89) with methyl acrylate. The alkene can be arrived at from the TBS protected pentanal (3.90) and the bromide (3.91) via a Grignard reaction.



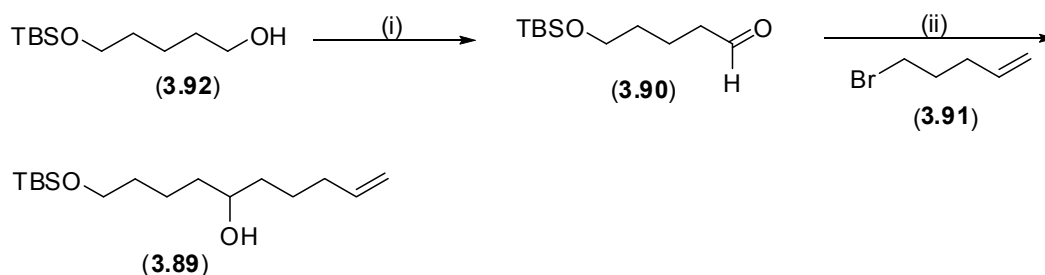
Scheme 132

For the model cyclisation we started with 1,5-pentanediol, the mono protection of the symmetric diol was achieved by the procedure of Nicolaou.¹⁵⁹ Reacting 1 eq. of TBSCl and 5 equivalents of the diol in the presence of imidazole in THF afforded the desired mono protected alcohol **(3.92)** in 89 % yield. This method is efficient; as there was no diprotection observed and the excess diol was easily removed by washing with water. The next step was oxidising the alcohol to aldehyde **(3.90)**. Although a number of protocols available for this transformation, including Swern oxidation,¹⁶⁰ oxidation with PDC¹⁶¹ (Pyridinium dichromate), PCC¹⁶² (Pyridinium chlorochromate) and using hypervalent iodine compounds such as *o*-iodoxybenzoic acid¹⁶³ ((IBX) and the Dess-Martin periodinane¹⁶⁴ (DMP). Each of the above method has their own advantages and disadvantages.¹⁶⁵ We chose to use Tetra-*n*-propylammonium perruthenate (TPAP), which is a catalytic alternative to the above oxidants.¹⁶⁶

The alcohol **(3.92)** on treatment with 5 mol % of TPAP and the co-oxidant NMM (*N*-methyl morpholine) in dichloromethane afforded the desired aldehyde **(3.90)** in high yield. However, the reaction was not reliable as the yield varied with different batches (Scheme 133). The next trial for the oxidation was using IBX, as it is very efficient for the oxidation of alcohols and easy to use, can be readily

prepared from 2-iodobenzoic acid. Though IBX can only be used with very polar solvents such as DMSO, we adopted this method. The conversion of the alcohol (**3.92**) to aldehyde (**3.90**) was high yielding (90 %).

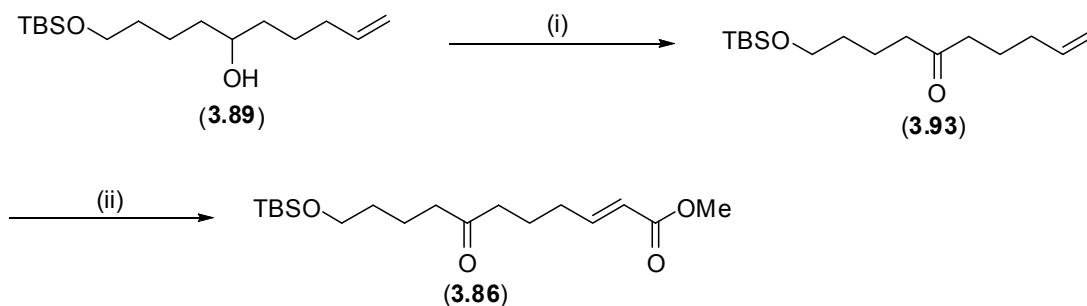
Grignard reaction of the aldehyde (**3.90**) with 5-bromopentene (**3.91**) was accomplished using the established procedure, afforded the alcohol (**3.89**) in 88 % yield. The product was clearly identifiable by ^1H NMR, the terminal alkene was observed as two doublets at 4.95 and 5.01 ppm and a multiplet around 5.74-5.87.



Scheme 133

Reagents and conditions: (i) (a) TPAP, NMO, CH_2Cl_2 , 24-88 %; (b) IBX, DMSO, 90 %; (ii) 5-bromopentene, Mg, THF, 88 %.

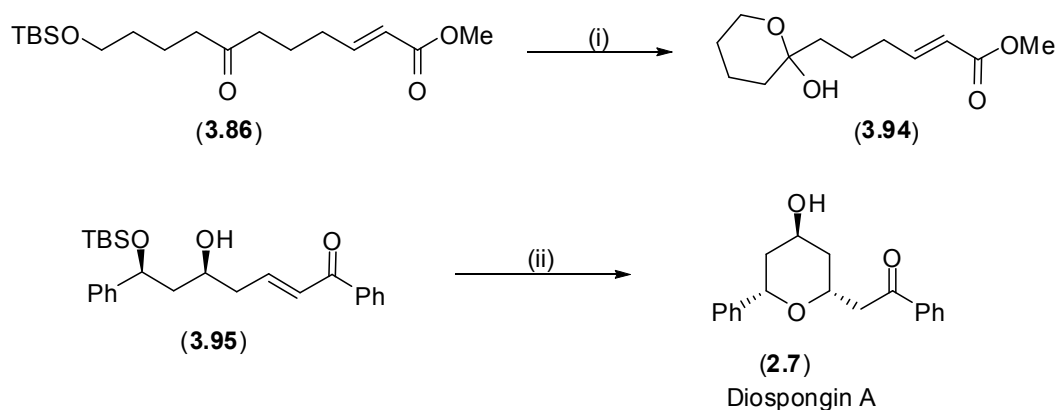
Oxidation of the secondary alcohol (**3.89**) was also achieved using IBX in DMSO affording the desired ketone (**3.93**) in 63 % yield, the lower yield was due to carrying over impurities from the previous 3 steps, as no purification has been carried out before this step (Scheme 134). Cross metathesis was achieved with Grubbs II catalyst (2 mol %) with methyl acrylate in dichloromethane. Methyl acrylate proved to be a good partner for this metathesis providing the desired product (**3.86**) in 94 % yield. The product was clearly obtained, from analysis of its ^1H and ^{13}C NMR spectra.



Scheme 134

Reagents and conditions: (i) IBX, DMSO, 63 %; (ii) methyl acrylate, Grubbs II (2 mol %), CH_2Cl_2 , 94 %.

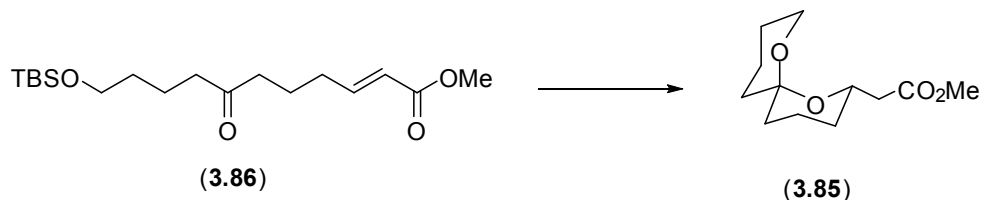
With the ester in hand (**3.86**), we were ready to test whether our proposed tandem deprotection and intramolecular Michael addition for the spiroketal would be possible or not. A methanolic solution of the TBS protected alcohol (**3.86**) was treated with amberlyst 15,¹⁶⁷ a polymer supported sulfonic acid. The advantage of using this reagent instead of a conventional acid is its simple workup procedure, as it can be removed just by filtration. As there was no reaction at room temperature, the mixture was heated at 70 °C for 8 h. TLC showed complete disappearance of starting material and formation of a new polar spot. Inspection of the NMR spectrum revealed that we had obtained the monocyclic product, hemi acetal (**3.94**). The product is clearly identifiable by a characteristic peak at 98.4 ppm in ^{13}C NMR and the presence of double bond protons at 6.92 and 5.83 ppm as double triplets and a singlet for the methyl ester at 3.70 ppm as well as the disappearance of TBS group at -0.04 and 0.89 ppm. It was surprising that not even a small amount of the spiroketal (**3.85**) was observed. In parallel studies in these laboratories, it has been found that this method is very effective for addition to enones, but not to α,β -unsaturated esters (Scheme 134).⁴⁴



Scheme 135

Reagents and conditions: (i) Amberlyst 15, MeOH, 70 °C; (ii) Amberlyst 15, MeOH, 83 %.

Since the reaction using amberlyst 15 did not give the desired product, sodium methoxide was used.¹⁵⁸ As there was no reaction at room temperature, the reaction mixture was heated at reflux for 8 h. A complex mixture was obtained by TLC and no attempt was taken to purify the reaction mixture. Finally, TBAF in THF at room temperature was used, to our delight the spiroketal (**3.85**) was obtained in 85 % yield as an 8:1 ratio, in favour of the thermodynamically stable bisaxial isomer (**3.85**), the one we aimed for, and an unknown isomer. The product is clearly identifiable by a characteristic peak for the acetal carbon at 96.1 ppm in ¹³C NMR and the disappearance of the alkenic protons in ¹H NMR. The relative stereochemistry was determined by comparing the ¹H NMR data with literature (Scheme 136).¹⁶⁸



Scheme 136

Reagents and conditions: (a) NaOMe, THF, reflux, no product; (b) TBAF, THF, 0 °C to rt, 85 %, (8:1) ratio of the desired isomer.

TBAF is extensively used for the deprotection of silyl protection groups, since its a good source of organic soluble fluoride ions.^{169,170} Nevertheless, TBAF has also used as a mild base in number of organic reactions including alkylation, halogenations, elimination, Michael addition and intramolecular cyclisation reactions.¹⁷¹⁻¹⁷³

Conclusion:

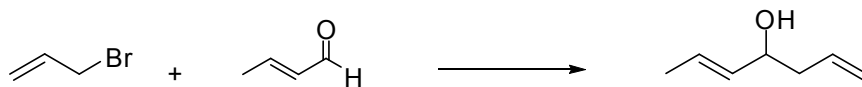
In summary, the synthesis of the C1-C18 fragment of bistramide D was achieved via a modified Staudinger reaction of coupling the carboxylic acid of the THP fragment directly with the azide, which avoided the protection/deprotection steps. The amino acid fragment was synthesised by starting from an inexpensive and readily available chiral source, L-tartaric acid which on diastereoselective methylation and regioselective reduction provided the desired azide. The THP fragment was obtained starting from epichlorohydrin, asymmetric induction via iodolactonisation, regioselective crossmetathesis, intramolecular Michael addition under kinetic conditions to achieve the thermodynamically less stable *trans* isomer are the highlights of the synthesis. The model cyclisation of spiroketal was achieved in one pot via a tandem deprotection and cyclisation strategy via Michael addition using TBAF. The model spirocyclisation gives a real insight to obtain the spiroketal fragment (**3.84**). Our research continues to achieve the total synthesis of Bistramide D.

EXPERIMENTAL SECTION

General Methods

When required, reactions were carried out under an inert atmosphere of nitrogen in oven dried glassware. Tetrahydrofuran was distilled from sodium-benzophenone; dichloromethane and acetonitrile were dried by distillation from CaH_2 immediately prior to use. Methanol was distilled from activated magnesium. All other solvents and reagents were used as received, or purified if required, using standard methods.¹ ^1H NMR and ^{13}C NMR (500 and 125 MHz respectively) were recorded in CDCl_3 solutions using a Bruker AV500. ^1H -NMR and ^{13}C -NMR (400 and 100 MHz respectively) were recorded in CDCl_3 solutions using a Jeol ECA 400, or on a Jeol ECA 400SL, or on a Bruker AV400. ^1H -NMR and ^{13}C -NMR (300 and 75 MHz respectively) were recorded in CDCl_3 solutions using a Bruker AV300. Chemical shifts are reported in δ units using CDCl_3 as an internal standard (δ 7.26 ppm ^1H , δ 77.00 ppm ^{13}C). Coupling constants J were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), br (broad), m (multiplet) and app (apparent). Infrared spectra were recorded on a Bruker Alpha-E FT-IR, either neat or as nujol mulls. Melting points were obtained using a OptiMelt MPA100. Mass spectra were obtained on a Finnigan LCQ DECA XP MAX with ESI mode. High resolution mass spectra were obtained using a Waters Q-Tof premier also with ESI mode. Specific rotation, $[\alpha]_D$, were recorded on a Jasco P-1030 polarimeter. Enantiomeric excess were determined with chiral HPLC

analysis, performed on a Shimadzu HPLC and Daicel chemical industries Chiralcel OD-H column, eluting with IPA/hexane.



Synthesis of (*E*)-hepta-1,5-dien-4-ol (2.34): Allyl bromide (0.52 ml, 6.00 mmol) and zinc dust (0.39 g, 6.00 mmol) were added to a solution of crotonaldehyde (0.41 ml, 5.00 mmol) in a mixture of satd. aq. NH_4Cl (5 ml) and THF (1 ml). The mixture was stirred for 60 minutes at room temperature then filtered through a celite pad, washing with diethyl ether (10 ml). THF was evaporated *in vacuo*, the residue was extracted with diethyl ether (2 x 20 ml) and the combined organic layers were washed with brine, and dried over anhydrous MgSO_4 . The solvent was evaporated and the residue was purified by distillation under reduced pressure (45 °C at 5 mmHg) to give the title compound as a colourless oil (0.31 g, 56 %).

^1H NMR (300 MHz, CDCl_3) δ 1.70 (d, 3H, $J = 6.4$ Hz), 2.20-2.37 (m, 2H), 4.08-4.14 (m, 1H), 5.12 (dd, 2H, $J = 6.0, 16.7$ Hz), 5.51 (ddq, 1H, $J = 14.9, 6.7, 1.3$ Hz), 5.64-5.88 (m, 2H).

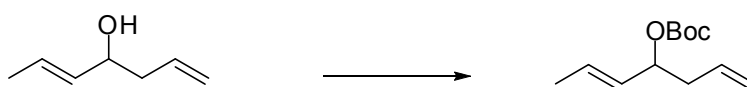
^{13}C NMR (75 MHz, CDCl_3): 17.6, 42.0, 71.8, 118.0, 127.0, 133.3, 134.4.

m/z : 113.74 ($\text{M}+\text{H}$) $^+$, 112.8 (M) $^+$.

HRMS calculated for $\text{C}_7\text{H}_{12}\text{ONa}$ ($\text{M}+\text{Na}$) $^+$: 135.0786; found: 135.0790.

IR: 2962, 2920, 2870, 1261, 1025, 965 cm^{-1} .

The data are consistent with that of the literature.¹⁷⁴



Synthesis of (*E*)-tert-butyl hepta-1,5-dien-4-yl carbonate (2.35): Di-*tert*-butyldicarbonate (4.1 g, 18.75 mmol) and DMAP (0.61 g, 5.00 mmol) were

added sequentially to a solution of alcohol (**2.34**) (1.42 g, 12.50 mmol) in CH₃CN (40 ml), with external cooling. The reaction mixture was warmed up to room temperature and stirred for 5 h. CH₃CN was evaporated under reduced pressure and the residue was taken up in EtOH (25ml), to this solution imidazole (4.3g, 63.75 mmol) was added, and the mixture was stirred for 15 minutes at room temperature. The mixture was diluted with dichloromethane (30 ml) the combined organic layers were then washed with 5% aq. HCl (3 x 5 ml) and then with water and brine, dried over anhydrous MgSO₄. Evaporation of the solvents *in vacuo* afforded the title compound as a colourless oil (2.5 g, 95 %).

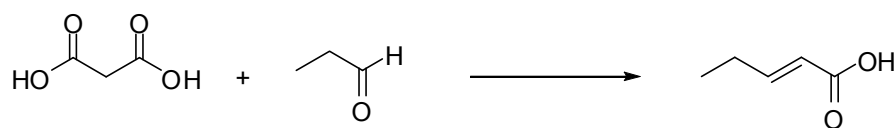
¹H NMR (400 MHz, CDCl₃) δ 1.47 (s, 9H), 1.69 (d, 3H, *J* = 6.4 Hz), 2.35-2.41 (m, 2H), 3.45-3.47 (m, 1H), 4.98-5.10 (m, 2H), 5.41-5.50 (m, 1H), 5.61-5.85 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): 17.7, 27.8, 39.1, 78.0, 81.8, 117.8, 128.7, 129.8, 133.3, 152.9.

m/z: 236 (M+Na)⁺, 190, 189.

HRMS calculated for C₁₂H₂₀O₃Na (M+Na)⁺: 235.1310 found: 235.1311.

IR: 3081, 1737, 1248, 1160, 965 cm⁻¹.

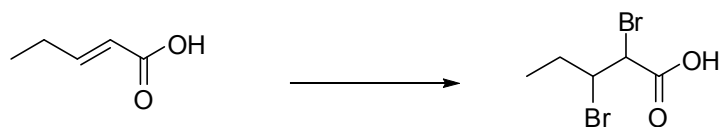


Synthesis of (E)-pent-2-enoic acid (2.50): Pyridine (1.3 ml, 16.04 mmol) was placed in a 3 neck flask equipped with a condenser and solid addition funnel containing malonic acid (1.2 g, 12.34 mmol). Malonic acid was added portionwise to the flask, followed by dropwise addition of propanal (1 ml, 13.88 mmol). The reaction mixture was heated at reflux until carbon dioxide evolution ceased, then poured into an icebath and quenched with conc. H₂SO₄. The mixture was extracted with dichloromethane (3 x 40 ml), the combined organic

layers were washed with water and brine, dried over anhydrous MgSO_4 . Evaporation of the solvent *in vacuo* yielded the title compound as a colourless oil (1.20 g, 97 %).

^1H NMR (300 MHz, CDCl_3) δ 1.08 (t, 3H, $J = 7.5$ Hz), 2.20-2.30 (m, 2H), 5.83 (d, 1H, $J = 15.5$ Hz), 7.10 (dt, 1H, $J = 15.5, 6.4$ Hz), 8.63 (broad d, 1H, $J = 4.2$ Hz).

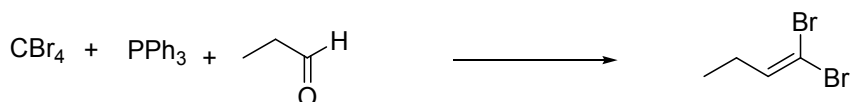
Data are consistent with that of literature.¹⁷⁵



Synthesis of 2,3-dibromopentanoic acid (2.51): A solution of bromine (0.18 ml, 3.41 mmol) in dichloromethane (2 ml) was slowly added to a solution of acid (**2.50**) (0.33 g, 3.25 mmol) in dichloromethane (7 ml) at 0 °C. The reaction mixture was stirred for 1 hr at 0 °C and then warmed to room temperature and stirred for 5 h. The mixture was poured into cold aq. NaHCO_3 solution (10%) and extracted with dichloromethane (2 x 25 ml). The combined organic layers were washed with water and brine. The solvent was evaporated *in vacuo* to afford the dibromo compound (**2.51**) as a colourless oil (0.8 g, 95 %).

^1H NMR (300 MHz, CDCl_3) δ 1.10 (t, 3H, $J = 7.3$ Hz), 1.82-1.97 (m, 1H), 2.23-2.36 (m, 1H), 4.33-4.40 (m, 2H), 10.78 (broad s, 1H).

Data are consistent with that of literature.¹⁷⁵

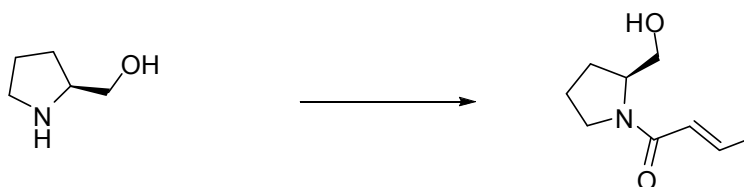


Synthesis of 1,1-dibromobut-1-ene (2.52): Carbon tetrabromide (9.22 g, 27.76 mmol), triphenyl phosphine (7.3 g, 27.76 mmol) and zinc dust (1.83 g, 27.76 mmol) were stirred in dry dichloromethane (40 ml) at 0 °C under nitrogen for 24

h. Propanaldehyde (1 ml, 13.88 mmol) was added dropwise and the mixture was stirred for a further 2 h at 0 °C, then warmed up to room temperature. The solvents were removed under reduced pressure, the residue was extracted with hexane (4 X 20 ml) and filtered. Hexane was evaporated *in vacuo* to give the title compound as a pale yellow oil (1.19 g, 40 %).

¹H NMR (300 MHz, CDCl₃) δ 1.03 (t, 3H, *J* = 7.6 Hz), 2.06-2.16 (m, 2H), 6.39 (t, 1H, *J* = 7.2 Hz).

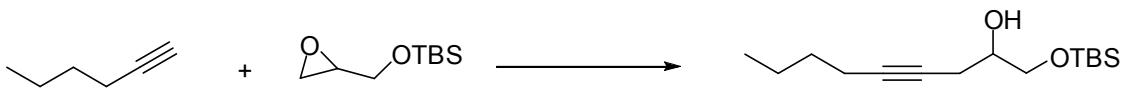
Data are consistent with that of literature.¹⁷⁶



Synthesis of (S,E)-1-(2-(hydroxymethyl)pyrrolidin-1-yl)but-2-en-1-one (2.118):¹⁷⁷ Crotonyl chloride (0.1 ml, 0.99 mmol) was added to a solution of L-prolinol (**2.117**) (0.1 g, 0.99 mmol) in THF (5 ml) and aq. Na₂CO₃ (10 % soln., 2 ml). The mixture was stirred for 1 h. THF was evaporated under reduced pressure; the residue was extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with water and brine then dried over anhydrous Na₂SO₄. Removal of solvent under reduced pressure afforded the title compound as a pale yellow oil (0.16 g, 98 %).

¹H NMR (300 MHz, CDCl₃) δ 1.56-1.68 (m, 2H), 1.83-2.09 (m, 5H), 3.57-3.69 (m, 4H), 4.26-4.33 (m, 1H), 5.28 (dd, 1H, *J* = 2.5, 7.6 Hz), 6.14 (dq, 1H, *J* = 15.0, 1.6 Hz), 6.97 (dq, 1H, *J* = 13.9, 7.0 Hz).

HRMS calculated for C₉H₁₆NO₂ (M+H)⁺: 170.1181; found: 170.1187.



Synthesis of 1-(*tert*-butyldimethylsilyloxy)non-4-yn-2-ol (2.55): n BuLi (1.6M in hexane, 1.25 ml, 2.00 mmol) was added dropwise at -78 °C to a solution of 1-hexyne (0.23 ml, 2.00 mmol) in THF (3 ml) under nitrogen. The mixture was stirred at -78 °C for another 30 minutes then a solution of the epoxide (94 mg, 0.50 mmol) in THF (1 ml) followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ¹⁷⁸ (0.32 ml 2.50 mmol) was added. The reaction mixture was stirred for 30 min at -78 °C then quenched with satd. aq. NH_4Cl solution. The mixture was extracted with ethyl acetate (2 x 20 ml), and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 . Solvent was evaporated under reduced pressure to afford the title compound as a colourless oil (132 mg, 98 %).

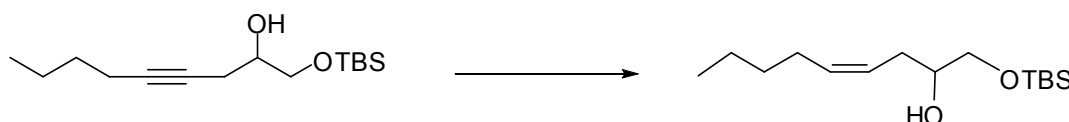
^1H NMR (300 MHz, CDCl_3) δ 0.08 (s, 6H), 0.86-0.96 (m, 12H), 1.35-1.50 (m, 4H), 2.13-2.18 (m, 2H), 2.35-2.41 (m, 2H), 2.43 (d, 1H, $J = 5.0$ Hz), 3.59 (dd, 1H, $J = 6.0, 9.8$ Hz), 3.70 (dd, 1H, $J = 4.4, 9.9$ Hz), 3.68-3.75 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3): 86.0, 75.6, 70.5, 65.7, 31.0, 29.7, 25.9, 23.4, 22.0, 18.4, 13.6, -5.4.

m/z : 272 ($\text{M}+\text{H}$)⁺, 271 (M)⁺.

HRMS calculated for $\text{C}_{15}\text{H}_{31}\text{O}_2\text{Si}$ ($\text{M}+\text{H}$)⁺: 271.2093; found: 271.2093.

IR : 3485, 2931, 1255, 1118 cm^{-1} .



Synthesis of (*Z*)-1-(*tert*-butyldimethylsilyloxy)non-4-en-2-ol (2.56): A solution of the alkyne (2.55) (100mg, 0.37 mmol) in THF (2 ml) containing Lindlar's

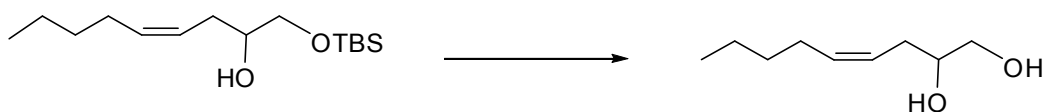
catalyst (5 mg, 5% by Wt.) and a drop of pyridine was stirred under hydrogen (balloon) for 6 h. The reaction mixture was filtered and the filtrate was evaporated to give the title compound as a colourless oil (100 mg, 99 %), which was used in the next step without purification.

^1H NMR (300 MHz, CDCl_3) δ 0.07 (s, 6H), 0.86-0.96 (m, 12H), 1.29-1.35 (m, 4H), 2.04 (dd, 2H, $J = 7.0, 13.1$ Hz), 2.30-2.21 (m, 2H), 2.40 (s, 1H), 3.44 (dd, 1H, $J = 7.1, 9.9$ Hz), 3.64 (dd, 1H, $J = 3.6, 9.1$ Hz), 3.65-3.71 (m, 1H), 5.35-5.55 (m, 2H).

m/z: 297 ($\text{M}+\text{Na}$) $^+$, 273 (M) $^+$, 247, 219.

HRMS calculated for $\text{C}_{15}\text{H}_{33}\text{O}_2\text{Si}$ ($\text{M}+\text{H}$) $^+$: 273.2250; found: 273.2255

IR: 2956, 1253, 1164, 1102 cm^{-1} .



Synthesis of (Z)-non-4-ene-1,2-diol (2.63): Pyridinium *p*-toluenesulfonate (49 mg, 0.193 mmol) was added to a solution of TBS protected alcohol (**2.56**) (520 mg, 1.93 mmol) in methanol (10 ml). The reaction mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure; the residue was diluted with ethyl acetate (50 ml) and washed with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4 . Solvent was evaporated under reduced pressure to give the title compound as a colourless oil (299 mg, 98 %).

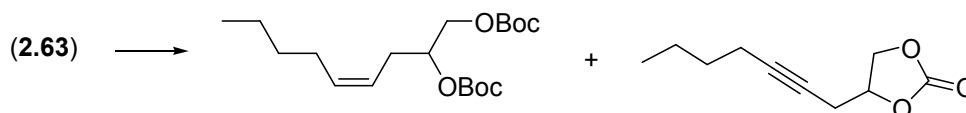
^1H NMR (400 MHz, CDCl_3) 0.90 (t, 3H, $J = 7.1$ Hz), 1.33-1.50 (m, 4H), 2.16 (tt, 2H, $J = 2.2, 6.9$ Hz), 2.41 (dt, 2H, $J = 5.7, 2.3$ Hz), 3.58 (dd, 1H, $J = 6.4, 11.2$ Hz), 3.73 (dd, 1H, $J = 3.5, 11.3$ Hz), 3.80-3.85 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3): 13.6, 18.4, 22.0, 23.9, 31.0, 65.7, 70.4, 75.2, 83.6.

m/z: 181 ($\text{M}+\text{Na}$) $^+$, 156.9 (M) $^+$, 149, 107.

HRMS calculated for $\text{C}_9\text{H}_{17}\text{O}_2$ ($\text{M}+\text{H}$): 157.1229; found: 157.1224

IR: 3358, 2929, 1080, 1034 cm^{-1} .



Synthesis of (Z)-tert-butyl non-4-ene-1,2-diyl dicarbonate (2.64): DMAP

(0.39 g, 3.21 mmol) and Boc_2O (0.92 ml, 4.01 mmol) were added to a solution of diol (2.63) (0.25 g, 1.60 mmol) in acetonitrile (10 ml). The reaction mixture was stirred for 5 h at room temperature. The solvent was evaporated under reduced pressure, the residue was diluted with dichloromethane (40 ml), washed with water. The organic layer was separated and the aqueous layer was extracted dichloromethane (2 x 10 ml). The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4 . The solvent was evaporated and the residue was purified by flash column chromatography (hexane: ethyl acetate = 90:10) on silica gel (8 g) to give the title compound (0.12 g, 21%) and the cyclic carbonate (2.65) as by-product (0.07 g, 24 %)

^1H NMR (300 MHz, CDCl_3) δ 0.89 (t, 3H, $J = 6.9$ Hz), 1.27-1.34 (m, 4H), 1.47 (s, 9H), 1.48 (s, 9H), 2.03 (dd, 2H, $J = 7.0, 13.4$ Hz), 2.40 (broad t, 2H, $J = 6.9$ Hz), 4.04 (dd, 1H, $J = 6.8, 11.7$ Hz), 4.21 (dd, 1H, $J = 3.5, 11.7$ Hz), 4.83-4.90 (m, 1H), 5.33 (dt, 1H, $J = 10.8, 7.5$ Hz), 5.53 (dt, 1H, $J = 10.8, 7.4$ Hz).

^{13}C NMR (75 MHz, CDCl_3): 13.9, 22.3, 27.0, 27.7, 27.7, 28.7, 31.7, 66.8, 74.0, 82.2, 82.3, 122.5, 133.9, 153.0, 153.3.

m/z: 361($\text{M}+\text{H}$) $^+$, 360(M) $^+$.

HRMS calculated for $\text{C}_{19}\text{H}_{35}\text{O}_6$ ($\text{M}+\text{H}$): 359.2434; found: 359.2433.

IR: 2932, 1740, 1248, 1157, 1095 cm^{-1} .

Data for 4-(hept-2-ynyl)-1,3-dioxolan-2-one (2.65):

^1H NMR (300 MHz, CDCl_3) δ 0.90 (t, 3H, $J = 7.3$ Hz), 1.31-1.50 (m, 4H), 2.14 (tt, 2H, $J = 7.0, 2.3$ Hz), 2.67-2.63 (m, 2H), 4.35 (dd, 1H, $J = 8.6, 6.1$ Hz), 4.54 (broad t, 1H, $J = 8.0$ Hz), 4.74-4.82 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): 13.5, 18.2, 21.8, 24.2, 30.6, 68.3, 71.2, 74.1, 84.8, 154.7.

m/z : 205 ($\text{M}+\text{Na}$) $^+$, 183 ($\text{M}+\text{H}$) $^+$, 153, 107.

HRMS calculated for $\text{C}_{10}\text{H}_{15}\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 183.1021; found: 183.1021.

IR: 2933, 1789, 1163, 1077 cm^{-1} .



Synthesis of 1-chloronon-4-yn-2-ol (2.71): $n\text{BuLi}$ (1.6M in hexane, 2.7 ml, 4.30 mmol) was added dropwise at -78 $^{\circ}\text{C}$ to a solution of 1-hexyne (0.55 ml, 4.73 mmol) in THF (8 ml) under nitrogen. The mixture was stirred for 10 minutes at -78 $^{\circ}\text{C}$, then $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.6 ml, 4.73 mmol) followed by a THF solution (2 ml) of epichlorohydrin (0.17 ml, 2.15 mmol) were added dropwise. The mixture was stirred for 30 min at -78 $^{\circ}\text{C}$, and then quenched with satd. aq. NH_4Cl solution. The mixture was extracted with ethyl acetate (3 x 25 ml). The combined organic layers were washed with water and brine, and dried over anhydrous MgSO_4 . The solvents were removed under reduced pressure and the residue was purified by flash chromatography (hexane: ethyl acetate = 92:8) on silica gel (6 g) to give the title compound as a colourless oil (0.31g, 88 %).

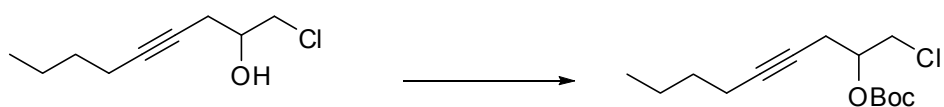
^1H NMR (400 MHz, CDCl_3) δ 0.91 (t, 3H, J = 6.8 Hz), 1.34-1.51 (m, 4H), 2.16 (tt, 2H, J = 2.5, 6.9 Hz), 2.34 (s, 1H), 2.46-2.58 (m, 2H), 3.62 (dd, 1H, J = 6.1, 11.1 Hz), 3.71 (dd, 1H, J = 4.5, 11.1 Hz), 3.91-3.96 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): 13.4, 18.2, 21.8, 24.5, 30.8, 48.2, 69.9, 74.3, 83.6.

m/z : 198 ($\text{M}+\text{Na}$) $^+$, 174 (M) $^+$, 155.

HRMS calculated for $\text{C}_9\text{H}_{16}\text{O}^{35}\text{Cl}$ ($\text{M}+\text{H}$) $^+$: 175.0890 found: 175.0896.

IR: 2924, 1249, 907, 732 cm^{-1} .



Synthesis of *tert*-butyl 1-chloronon-4-yn-2-yl carbonate (2.72): DMAP (15 mg, 0.12 mmol) was added to a solution of alcohol (2.71) (50 mg, 0.31 mmol) in THF (1.6 ml) at -40 $^\circ\text{C}$ followed by dropwise addition of a solution of Boc_2O (0.1 ml, 0.46 mmol) in acetonitrile (1 ml). The reaction mixture was stirred overnight at 0 $^\circ\text{C}$, and the solvent was evaporated under reduced pressure. The residue was diluted with dichloromethane (20 ml), and then the organic layer was washed with water and brine and dried over anhydrous Na_2SO_4 . The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (hexane: ethyl acetate = 95:5) on silica gel (2 g) to give the title compound (68 mg, 84 %).

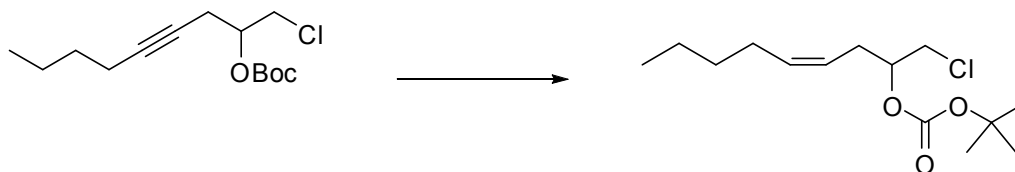
^1H NMR (300 MHz, CDCl_3) δ 0.90 (t, 3H, J = 7.1 Hz), 1.32-1.46 (m, 4H), 1.50 (s, 9H), 2.14 (tt, 2H, J = 2.3, 6.9 Hz), 2.61 (dt, 2H, J = 6.3, 2.3 Hz), 3.73 (dd, 1H, J = 5.5, 11.7 Hz), 3.81 (dd, 1H, J = 4.5, 11.7 Hz), 4.84-4.92 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): 13.6, 18.4, 21.9, 22.0, 27.7, 30.9, 44.5, 73.6, 74.2, 82.9, 83.5, 152.6.

m/z : 297 ($\text{M}+\text{Na}$) $^+$, 275 (M) $^+$, 223, 195.

HRMS calculated for $C_{14}H_{24}O_3^{35}Cl$ (M+H)⁺: 275.1424 found: 275.1414.

IR: 2933, 1789, 1163, 1077 cm^{-1} .



Synthesis of (Z)-tert-butyl 1-chloronon-4-en-2-yl carbonate (2.74): The title compound (100 mg, 99 %), was obtained from the previous compound (2.72) by the method described for (2.56) to give a colourless oil, which was used in the next step without purification.

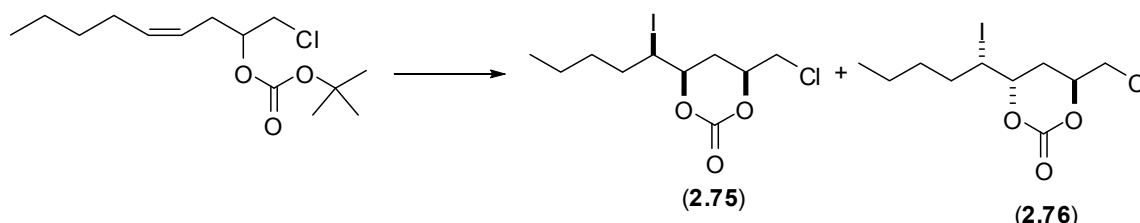
¹H NMR (400 MHz, CDCl₃) δ 0.87 (t, 3H, *J* = 7.0 Hz), 1.29-1.32 (m, 4H), 1.46 (s, 9H), 2.01 (dd, 2H, *J* = 6.9, 13.9 Hz), 2.39-2.51 (m, 2H), 3.55 (dd, 1H, *J* = 5.7, 11.6 Hz), 3.61 (dd, 1H, *J* = 4.6, 11.7 Hz), 4.77-4.82 (m, 1H), 5.27-5.35 (m, 1H), 5.49-5.58 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): 13.9, 22.2, 27.0, 27.6, 29.4, 31.6, 44.8, 75.4, 82.3, 122.2, 134.2, 152.7.

m/z: 301 (M+Na)⁺, 279 (M(³⁷Cl))⁺, 277 (M(³⁵Cl))⁺, 264, 222.

HRMS calculated for $C_{14}H_{26}O_3^{35}Cl$ (M+H)⁺: 277.1570 found: 277.1570.

IR: 2930, 1742, 1278, 1255, 1098, 836, 793 cm^{-1} .



Synthesis of (4*S*^{*},6*R*^{*})-4-(chloromethyl)-6-((*R*^{*})-1-iodopentyl)-1,3-dioxan-2-one (2.75): The literature⁵³ procedure was modified as follows: iodine (300 mg, 1.18 mmol) was added to a solution of alkene (2.74) (100 mg, 0.38 mmol) in

acetonitrile (10 ml) at -40 °C under nitrogen. The reaction mixture was warmed to -10 °C and stirred overnight. DMF (30 μ l, 1.18 mmol) was added to the mixture and stirring was continued for one hour. The reaction mixture was diluted with ethyl acetate (30 ml), washed with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with aq. Na₂S₂O₃, aq. NaHCO₃ solution and then brine. They were dried over anhydrous MgSO₄, and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane: ethyl acetate = 85:15) on silica gel (4 g) to give the title compound as a pale yellow oil (71 mg, 54 %) and the trans isomer (**2.76**) as minor product (13 mg, 12 %)

¹H NMR (300 MHz, CDCl₃) δ 0.93 (t, 3H, *J* = 6.9 Hz), 1.28-1.45 (m, 2H), 1.47-1.67 (m, 2H), 1.77-1.94 (m, 2H), 2.04-2.16 (m, 1H), 2.49 (ddd, 1H, *J* = 3.1, 3.1, 14.1 Hz), 3.66 (dd, 1H, *J* = 6.4, 11.7 Hz), 3.75 (dd, 1H, *J* = 4.3, 11.8 Hz), 4.14 (dt, 1H, *J* = 9.8, 4.2 Hz), 4.37 (ddd, 1H, *J* = 3.1, 3.1, 11.7 Hz), 4.66-4.74 (m, 1H).

¹³C NMR (75 MHz, CDCl₃): 13.9, 21.8, 29.1, 31.7, 34.4, 34.5, 44.6, 77.2, 80.3, 147.5.

m/z: 361(M+Na)⁺, 347.0 (M+H)⁺, 328, 319.

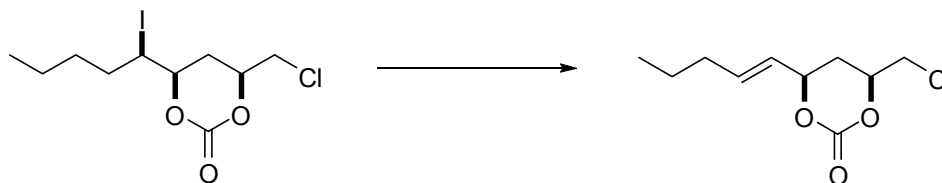
HRMS calculated for C₁₀H₁₇IO₃³⁵Cl (M+H)⁺: 346.9911 found: 346.9914.

IR: 1725, 1258, 1072, 852, 750 cm⁻¹.

Data for (4S*,6S*)-4-(chloromethyl)-6-((S*)-1-iodopentyl)-1,3-dioxan-2-one (2.76):

¹H NMR (300 MHz, CDCl₃) δ 0.93 (t, 3H, *J* = 7.3 Hz), 1.27-1.46 (m, 2H), 1.50-1.67 (m, 2H), 1.76-2.02 (m, 2H), 2.29-2.50 (m, 2H), 3.67 (dd, 1H, *J* = 7.9, 11.7 Hz), 3.80 (dd, 1H, *J* = 4.6, 11.7 Hz), 4.13 (dt, 1H, *J* = 10.2, 3.9 Hz), 4.35 (dt, 1H, *J* = 9.9, 3.8 Hz), 4.75-4.83 (m, 1H).

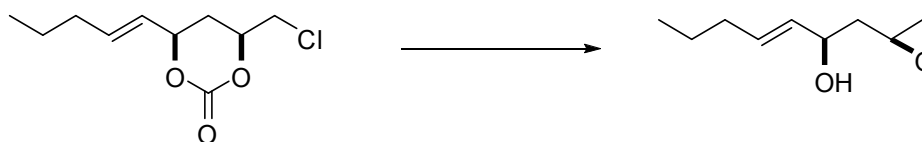
^{13}C NMR (75 MHz, CDCl_3): 13.9, 21.8, 27.5, 31.7, 35.0, 35.4, 43.6, 75.2, 77.4, 147.8.



Synthesis of (*E*)-4-(4*S,6*R**)-4-(chloromethyl)-6-(*R**)-(pent-1-enyl)-1,3-dioxan-**

2-one (2.77): The literature procedure⁶⁸ was modified as follows: *m*CPBA (180 mg, 0.57 mmol) and NaHCO_3 (109 mg, 1.30 mmol) was added to a solution of iodo carbonate (**2.75**) (70 mg, 0.26 mmol) in dichloromethane (4 ml) at $-30\text{ }^\circ\text{C}$. The reaction mixture was slowly warmed up to room temperature and stirred for 6 h. The reaction mixture was diluted with dichloromethane (20 ml), the organic layer was washed with aq. NaHSO_3 and aq. NaHCO_3 solution, and dried over anhydrous MgSO_4 . The solvent was removed under reduced and the crude was used in the next step without purification.

^1H NMR (300 MHz, CDCl_3) δ 0.90 (t, 3H, $J = 7.4$ Hz), 1.29-1.47 (m, 2H), 1.87-2.11 (m, 3H), 2.27 (ddd, 1H, $J = 3.2, 3.2, 14.2$ Hz), 3.57-3.74 (m, 2H), 4.64-4.72 (m, 1H), 4.88 (ddd, 1H, $J = 2.7, 7.0, 7.0$ Hz), 5.48 (ddt, 1H, $J = 15.4, 7.1, 1.4$ Hz), 5.87 (dt, 1H, $J = 15.0, 6.8$ Hz).

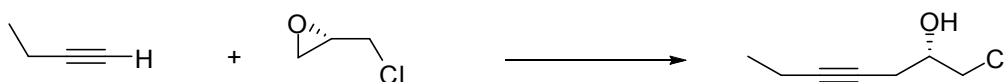


Synthesis of (*R,*E**)-1-((*S**)-oxiran-2-yl)hept-3-en-2-ol (2.78):** The literature

procedure⁵³ was modified as follows: Potassium carbonate (108 mg, 0.78 mmol) was added to a solution of cyclic carbonate (**2.77**) (50 mg, 0.26 mmol) in methanol (2 ml). The reaction mixture was stirred for 2 h at room temperature. Methanol was evaporated *in vacuo* and the residue was extracted with diethyl

ether (5 ml x 2), the combined organic layers were washed with water and brine solution, dried over anhydrous Na₂SO₄. The solvent was removed *in vacuo*, the residue was purified by flash column chromatography (hexane: ethyl acetate = 80:20) on silica gel (1.5 g) to give the title compound as a colourless oil (27 mg, 82 %).

¹H NMR (300 MHz, CDCl₃) δ 0.90 (t, 3H, *J* = 7.3 Hz), 1.34-1.46 (m, 2H), 1.67 (dt, 1H, *J* = 14.3, 7.2 Hz), 1.83 (dt, 1H, *J* = 14.1, 4.7 Hz), 1.93 (broad s, 1H), 2.01 (dd, 2H, *J* = 7.2, 14.2 Hz), 2.52 (dd, 1H, *J* = 2.7, 4.9 Hz), 2.77 (dd, 1H, *J* = 4.6, 4.6 Hz), 3.01-3.06 (m, 1H), 4.29-4.36 (m, 1H), 5.51 (ddt, 1H, *J* = 15.4, 7.1, 1.5 Hz), 5.71 (dt, 1H, *J* = 15.4, 6.7 Hz).



Synthesis of (S)-1-chlorohept-4-yn-2-ol (2.81): The title compound (98 %) was obtained from the previous compound (2.80) by the method described for (2.55) to give colourless oil.

¹H NMR (400 MHz, CDCl₃) δ 1.08 (t, 3H, *J* = 7.5 Hz), 2.13 (qt, 2H, *J* = 7.5, 2.3 Hz), 2.52-2.40 (m, 2H), 2.66 (br. s, 1H), 3.57 (dd, 1H, *J* = 6.0, 11.1 Hz), 3.66 (dd, 1H, *J* = 4.5, 11.1 Hz), 3.92-3.86 (m, 1H).

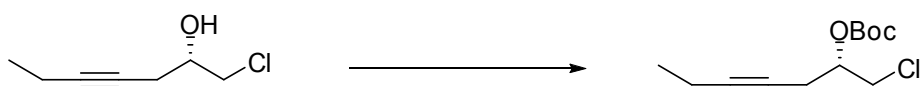
¹³C NMR (100 MHz, CDCl₃): δ 12.3, 13.9, 24.5, 48.2, 69.9, 73.8, 85.0.

m/z: 147 (M), 129, 125, 107.

HRMS calculated for C₇H₁₂O³⁵Cl (M+H)⁺: 147.0577 found: 147.0581.

IR: 3487, 1438, 1200, 1007 cm⁻¹.

[α]_D²² = +10.2 (CHCl₃, *c* = 1.5).



Synthesis of (S)-tert-butyl 1-chlorohept-4-yn-2-yl carbonate (2.82a): The title compound (92 %) was obtained from the previous compound (**2.81**) by the method described for (**2.72**) to give a colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 1.11 (t, 3H, $J = 7.6$ Hz), 1.49 (s, 9H), 2.15 (qt, 2H, $J = 7.5, 2.4$ Hz), 2.61 (dt, 2H, $J = 6.4, 2.4$ Hz), 3.73 (dd, 1H, $J = 5.5, 11.7$ Hz), 3.81 (dd, 1H, $J = 4.5, 11.7$ Hz), 4.85-4.91 (m, 1H).

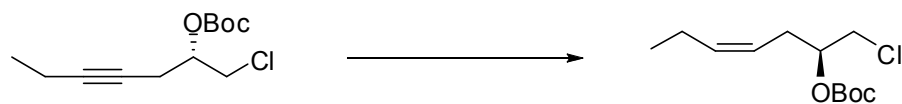
^{13}C NMR (100 MHz, CDCl_3): δ 12.3, 14.0, 22.0, 27.7, 44.4, 72.1, 74.1, 82.9, 84.8, 152.6.

m/z : 247 (M) $^+$, 191, 128, 91.

HRMS calculated for $\text{C}_{12}\text{H}_{20}\text{O}_3^{35}\text{Cl}$ ($\text{M}+\text{H}$) $^+$: 247.1101 found: 247.1101.

IR: 1818, 1743, 1433, 1277, 1157, 789 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +12.0$ (CHCl_3 , $c = 1.0$).



Synthesis of (S,Z)-tert-butyl 1-chlorohept-4-en-2-yl carbonate (2.82):

A solution of NaBH_4 (190 mg, 5.00 mmol) in ethanol (4.8 ml) and water (0.3 ml) were added dropwise to a stirred suspension of nickel acetate (1.24 g, 5.00 mmol) in a mixture of ethanol (47.5 ml) and water (2.5) cautiously. The mixture was stirred until gas evolution ceased (~ 30 minutes). A solution of alkyne (**2.82a**) (10.17 g, 41.32 mmol) in EtOH (5 ml) was then added to the mixture; the flask was placed under hydrogen (balloon). The mixture was stirred for 2 h then filtered through a sandwich of silica gel/celite. The solvent was removed under reduced pressure to give the title compound as a colourless oil (10.2 g, 99 %).

^1H NMR (400 MHz, CDCl_3) δ 0.91 (t, 3H, J = 7.5 Hz), 1.42 (s, 9H), 1.98-2.05 (m, 2H), 2.36-2.47 ((m, 2H), 3.52 (dd, 1H, J = 5.7, 11.7 Hz), 3.59 (dd, 1H, J = 4.6, 11.7 Hz), 4.73-4.79 (m, 1H), 5.24 (dt, 1H, J = 10.1, 7.4 Hz), 5.49 (dt, 1H, J = 10.6, 7.6 Hz).

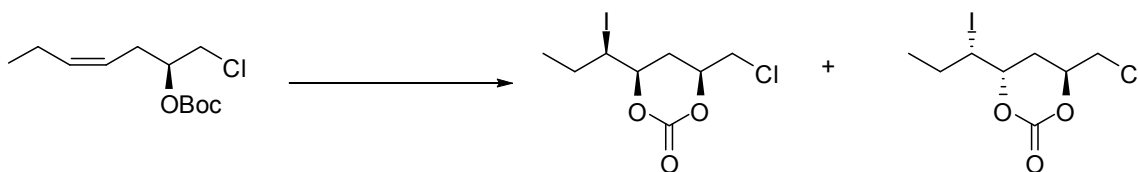
^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 20.5, 27.5, 29.2, 44.7, 75.3, 82.1, 121.6, 135.7, 152.7.

m/z : 271 ($\text{M}+\text{Na}$) $^+$, 249 (M) $^+$, 214, 196.

HRMS calculated for $\text{C}_{12}\text{H}_{22}\text{O}_3^{35}\text{Cl}$ ($\text{M}+\text{H}$) $^+$: 249.1257; found: 249.1262.

IR: 2969, 1737, 1368, 1156, 1007, 836 cm^{-1} .

$[\alpha]_D^{22} = +15.0$ (CHCl_3 , c = 1.0).



Synthesis of (4S,6R)-4-(chloromethyl)-6-((R)-1-iodopropyl)-1,3-dioxan-2-one

(2.83): The title compound (540 mg, 68 %) and the *anti* isomer (141 mg, 17 %) were obtained as a pale yellow oils from the previous compound (**2.82**) by the method described for (**2.75**). The isomers were separated by a flash column chromatography (hexane: ethyl acetate = 80:20, *cis*; 75:25, *trans*) on silica gel (15 g).

^1H NMR (400 MHz, CDCl_3) δ 1.06 (t, 3H, J = 7.3 Hz), 1.85-1.95 (m, 2H), 2.09 (ddd, 1H, J = 11.4, 11.4, 13.8 Hz), 2.42 (ddd, 1H, J = 3.2, 3.2, 14.2 Hz), 3.68 (dd, 1H, J = 4.6, 11.9 Hz), 3.72 (dd, 1H, J = 5.5, 11.9 Hz), 4.06 (ddd, 1H, J = 3.2, 5.5, 11.9 Hz), 4.34 (ddd, 1H, J = 3.2, 3.2, 11.9 Hz), 4.70-4.76 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 28.4, 29.2, 37.2, 44.7, 76.4, 79.9, 147.7.

m/z : 341 ($\text{M}+\text{Na}$) $^+$, 319 (M) $^+$, 260, 223.

HRMS calculated for $\text{C}_8\text{H}_{13}\text{O}_3^{35}\text{ClI}$ ($\text{M}+\text{H}$) $^+$: 318.9598; found: 318.9608.

IR: 2970, 1746, 1264, 1051, 1010, 790, 737 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +18.0$ (CHCl_3 , $c = 0.5$).

Data for (4*S*,6*S*)-4-(chloromethyl)-6-((*S*)-1-iodopropyl)-1,3-dioxan-2-one

(2.83a):

^1H NMR (500 MHz, CDCl_3) δ 1.10 (t, 3H, $J = 7.2$ Hz), 1.85-2.00 (m, 2H), 2.34 (ddd, 1H, $J = 6.1, 10.0, 16.0$ Hz), 2.47 (ddd, 1H, $J = 4.1, 4.1, 14.5$ Hz), 3.68 (dd, 1H, $J = 8.0, 11.7$ Hz), 3.80 (dd, 1H, $J = 4.5, 11.7$ Hz), 4.07 (ddd, 1H, $J = 3.8, 3.8, 9.8$ Hz), 4.37 (ddd, 1H, $J = 4.0, 4.0, 10.0$ Hz), 4.77-4.82 (m, 1H).

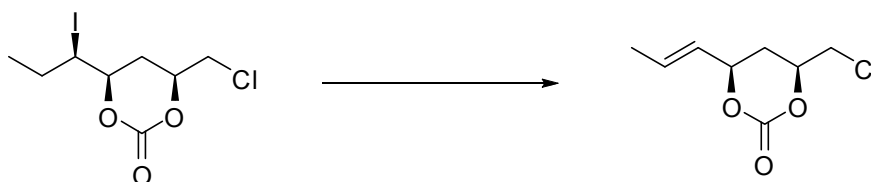
^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 27.4, 28.8, 37.6, 43.6, 76.7, 77.3, 147.8.

m/z : 341 ($\text{M}+\text{Na}$) $^+$, 319 (M) $^+$, 260, 223.

HRMS calculated for $\text{C}_8\text{H}_{13}\text{O}_3^{35}\text{ClI}$ ($\text{M}+\text{H}$) $^+$: 318.9598 found: 318.9602.

IR: 1746, 1264, 1051, 1010, 790, 737 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = -10.0$ (CHCl_3 , $c = 0.5$).



Synthesis of (4*S*,6*R*)-4-(chloromethyl)-6-((*E*)-prop-1-enyl)-1,3-dioxan-2-one

(2.84): The title compound (90 %) was obtained as a colourless oil from the previous compound **(2.83)** by the method described for **(2.77)**.

^1H NMR (400 MHz, CDCl_3) δ 1.75 (d, 3H, $J = 6.5$ Hz), 1.93 (ddd, 1H, $J = 5.9, 5.9, 11.7$ Hz), 2.26 (ddd, 1H, $J = 3.0, 3.0, 14.3$ Hz), 3.64 (dd, 1H, $J = 6.1, 11.7$ Hz), 3.71 (dd, 1H, $J = 4.2, 11.7$ Hz), 4.65-4.71(m, 1H), 4.87 (ddd, 1H, $J = 2.8, 7.3, 11.0$ Hz), 5.51 (ddq, 1H, $J = 15.1, 7.3, 1.8$ Hz), 5.90 (dq, 1H, $J = 15.1, 6.4, 0.9$ Hz).

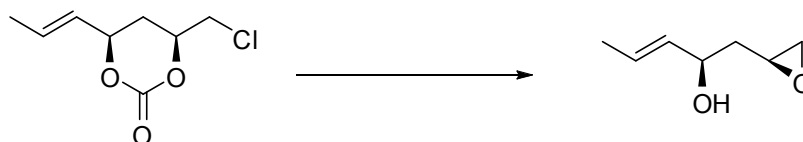
^{13}C NMR (100 MHz, CDCl_3): δ 17.6, 30.9, 44.8, 76.8, 78.8, 127.0, 132.1, 148.1.

m/z: 213 (M+Na)⁺, 193 (M(³⁷Cl))⁺, 191 (M(³⁵Cl))⁺, 129.

HRMS calculated for C₈H₁₁O₃³⁵ClNa (M+Na)⁺: 213.0294 found: 213.0297.

IR: 2968, 1745, 1397, 1195, 760 cm⁻¹.

[α]_D²² = -26.0 (CHCl₃, c = 1.0).



Synthesis of (R,E)-1-((S)-oxiran-2-yl) pent-3-en-2-ol (2.4a): The title compound (95 %) was obtained as a colourless oil from the previous compound (2.84) by the method described for (2.78).

¹H NMR (400 MHz, CDCl₃) δ 1.59 (d, 3H, J = 7.3 Hz), 1.70-1.74 (m, 2H), 2.43 (dd, 1H, J = 2.8, 4.6 Hz), 2.68 (dd, 1H, J = 4.1, 4.7 Hz), 2.92-2.97 (m, 1H), 3.43 (d, 1H, J = 5.5 Hz), 4.17-4.22 (m, 1H), 5.44 (dd, 1H, J = 7.3, 15.1 Hz), 5.64 (dq, 1H, J = 14.2, 6.9 Hz).

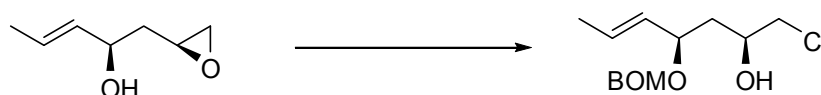
¹³C NMR (100 MHz, CDCl₃): δ 17.5, 39.8, 46.7, 49.8, 70.8, 127.1, 133.1.

m/z: 141 (M+Na)⁺, 129 (M+H)⁺.

HRMS calculated for C₇H₁₃O₂ (M+H)⁺: 129.0916, found: 129.0917

IR: 3395, 2920, 1510, 1031, 967 cm⁻¹.

[α]_D²² = +7.0 (CH₂Cl₂, c = 0.8).



Synthesis of (2S,4R,E)-4-(benzyloxymethoxy)-1-chlorohept-5-en-2-ol (2.86):

DIPEA (2.2 ml, 12.60 mmol) and BOMCl (1.8 ml, 12.60 mmol) were added sequentially to a solution of alcohol (2.4a) (1.1 g, 8.40 mmol) in dichloromethane (150 ml) at -40 °C. The mixture was warmed to room temperature and stirred for

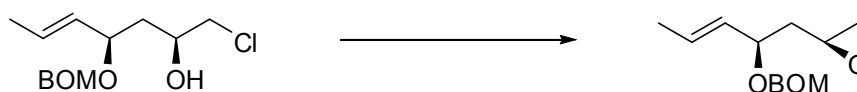
14 h. The reaction mixture was quenched with aq. NH_4Cl solution and extracted with dichloromethane (2 x 50 ml). The combined organic layers were washed with water and brine and dried over anhydrous MgSO_4 . The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane: ethyl acetate = 94:6) on silica gel (20 g) to give the epoxide (**2.85**) (228 mg, 11%) and the title compound (**2.86**) (hexane: ethyl acetate = 90:10) as a colourless oil (1.63 g, 68 %).

^1H NMR (400 MHz, CDCl_3) δ 1.71 (dd, 3H, $J = 1.4, 6.9$ Hz), 1.78-1.88 (m, 2H), 3.38 (d, 1H, $J = 3.2$ Hz), 3.53 (dd, 1H, $J = 5.5, 11.0$ Hz), 3.57 (dd, 1H, $J = 5.0, 11.0$ Hz), 3.96-4.02 (m, 1H), 4.31(dt, 1H, $J = 5.5, 8.3$ Hz), 4.53 (d, 1H, $J = 11.8$ Hz), 4.66 (d, 1H, $J = 6.9$ Hz), 4.70 (d, 1H, $J = 11.3$ Hz), 4.83 (d, 1H, $J = 6.9$ Hz), 5.31 (ddq, 1H, $J = 15.4, 8.5, 1.5$ Hz), 5.74 (dq, 1H, $J = 15.3, 6.5$ Hz), 7.27-7.37 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): δ 17.7, 39.7, 49.4, 69.8, 70.3, 76.1, 91.0, 127.8, 127.9, 128.4, 129.8, 130.8, 137.6.

m/z: 309 ($\text{M}+\text{Na}$) $^+$, 284 (M) $^+$, 225, 198.

HRMS calculated for $\text{C}_{15}\text{H}_{22}\text{O}_3^{35}\text{Cl}$ ($\text{M}+\text{H}$) $^+$: 285.1257, found: 285.1263



Synthesis of (S)-2-((R,E)-2-(benzyloxymethoxy)pent-3-enyl)oxirane (**2.85**):

The title compound (98 %) was obtained as a colourless oil from the previous compound (**2.86**) by following a literature procedure.¹⁷⁹

^1H NMR (400 MHz, CDCl_3) δ 1.73 (d, 3H, $J = 6.6$ Hz), 1.76-1.89 (m, 2H), 2.49 (dd, 1H, $J = 2.7, 4.8$ Hz), 2.74 (dd, 1H, $J = 4.8, 4.8$ Hz), 2.97-3.04 (m, 1H), 4.25-4.30 (m, 1H), 4.55 (d, 1H, $J = 11.8$ Hz), 4.70 (d, 1H, $J = 6.9$ Hz), 4.71 (d, 1H, $J =$

11.5 Hz), 4.83 (d, 1H, $J = 6.9$ Hz), 5.38 (dd, 1H, $J = 8.4, 15.3$ Hz), 5.75 (dq, 1H, $J = 15.2, 6.4$ Hz), 7.27-7.36 (m, 5H).

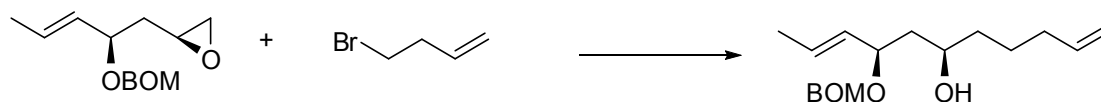
^{13}C NMR (100 MHz, CDCl_3): 17.6, 38.7, 46.6, 49.4, 69.3, 74.7, 91.1, 127.5, 127.7, 128.3, 130.0, 130.1, 137.9.

m/z : 271 ($\text{M}+\text{Na}$), 219, 153.

HRMS calculated for $\text{C}_{15}\text{H}_{20}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 271.1310, found: 271.1306

IR: 2942, 1453, 1025, 968 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +85.0$ (CHCl_3 , $C = 1$).



Synthesis of (6R, 8R, E)-8-(benzyloxymethoxy)undeca-1,9-dien-6-ol (2.88):

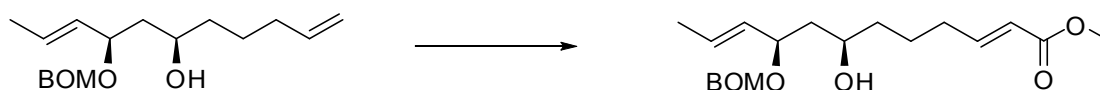
CuCN (15 mg, 0.17 mmol) was added to a solution of epoxide (**2.85**) (0.42 g, 1.70 mmol) in THF (5 ml). The reaction mixture was cooled to -40 $^{\circ}\text{C}$, and but-3-enylmagnesium bromide (2.50 mmol) was added dropwise. The reaction mixture was stirred for 1 h by slowly warming to -20 $^{\circ}\text{C}$, quenched with aq. satd. NH_4Cl solution. The mixture was extracted with diethyl ether (10 ml x 3); the combined organic layers were washed with water, brine and dried over anhydrous MgSO_4 to provide the title compound as a colourless oil (0.36 g, 70 %).

^1H NMR (300 MHz, CDCl_3) δ 1.41-1.78 (m, 9H), 2.07 (dd, 2H, $J = 6.4, 12.9$ Hz), 3.20 (br d, 1H, $J = 1.9$ Hz), 3.78-3.83 (m, 1H), 4.31 (dt, 1H, $J = 8.9, 4.9$ Hz), 4.53 (d, 1H, $J = 11.7$ Hz), 4.67 (d, 1H, $J = 7.0$ Hz), 4.72 (d, 1H, $J = 11.7$ Hz), 4.83 (d, 1H, $J = 7.0$ Hz), 4.95 (d, 1H, $J = 10.2$ Hz), 5.01 (d, 1H, $J = 17.3$ Hz), 5.29 (ddq, 1H, $J = 15.3, 8.7, 1.5$ Hz), 5.70 (dq, 1H, $J = 14.9, 6.4$ Hz), 5.76-5.86 (m, 1H), 7.27-7.36 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): 17.6, 24.7, 33.7, 37.0, 42.6, 69.7, 70.8, 77.3, 90.9, 114.5, 127.7, 127.9, 128.4, 130.2, 130.3, 137.6, 138.7.

m/z : 327 ($\text{M}+\text{Na}$) $^+$.

HRMS calculated for $\text{C}_{19}\text{H}_{20}\text{O}_3$ ($\text{M}+\text{H}$) $^+$: 305.2117, found: 305.2114.



Synthesis of (2*E*, 7*R*, 9*R*, 10*E*)-methyl 9-(benzyloxymethoxy)-7-hydroxy

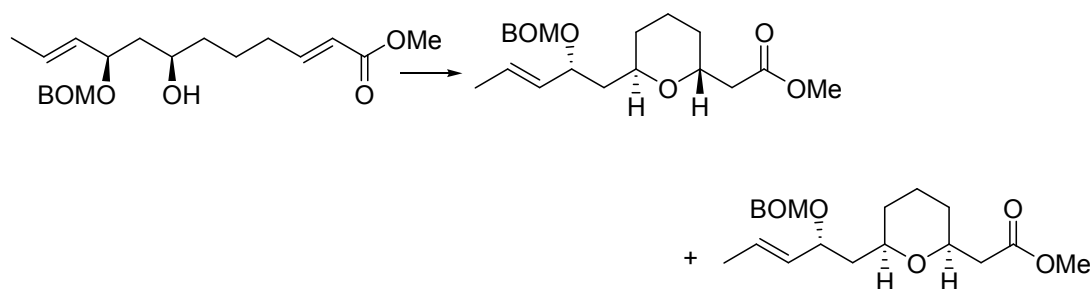
dodeca-2,10-dienoate (2.89): ⁴⁰ Methyl acrylate (26 μl , 0.29 mmol) was added to a solution of diene (2.88) (44 mg, 0.15 mmol) in dichloromethane (5 ml). Grubbs II catalyst (3 mg, 0.02 mmol) was added to the reaction mixture with continuous nitrogen flow. The reaction mixture was stirred for 3 h at room temperature with continuous nitrogen bubbling. The solvent was evaporated under reduced pressure, the residue was purified by column chromatography (hexane: ethyl acetate = 82:18) on silica gel (1.5 g) to give the title compound as a colourless oil (76 %, 40 mg).

^1H NMR (400 MHz, CDCl_3) δ 1.40-1.76 (m, 9H), 2.22 (dd, 2H, $J = 7.0, 13.6$ Hz), 3.25 (d, 1H, $J = 1.8$ Hz), 3.72 (s, 3H), 3.76-3.82 (m, 1H), 4.30 (dt, 1H, $J = 8.9, 4.2$ Hz), 4.52 (d, 1H, $J = 11.9$ Hz), 4.67 (d, 1H, $J = 7.0$ Hz), 4.70 (d, 1H, $J = 11.7$ Hz), 4.83 (d, 1H, $J = 6.8$ Hz), 5.28 (ddq, 1H, $J = 15.3, 8.5, 1.7$ Hz), 5.70 (dq, 1H, $J = 15.1, 6.5$ Hz), 5.83 (dt, 1H, $J = 15.7, 1.6$ Hz), 5.97 (dt, 1H, $J = 15.5, 6.9$ Hz), 7.27-7.36 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): 17.6, 23.9, 32.1, 36.9, 42.6, 51.4, 69.8, 70.7, 77.4, 90.9, 121.1, 127.8, 127.9, 128.4, 130.2, 130.3, 137.6, 149.3, 167.1.

m/z : 385 ($\text{M}+\text{Na}$) $^+$, 337, 157.

HRMS calculated for $\text{C}_{21}\text{H}_{31}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 363.2171, found: 363.2165.



Synthesis of methyl 2-((2R,6R)-6-((R,E)-2-(benzyloxymethoxy)pent-3-enyl) tetrahydro-2H-pyran-2-yl)acetate-*trans* isomer (2.90) (Major):

A solution of the ester (**2.89**) (20 mg, 0.06 mmol) in THF (0.5 ml) was added dropwise to a solution of potassium *tert*-butoxide (6 mg, 0.06 mmol) in THF (1 ml) under nitrogen at -78 °C. The mixture was stirred for 20 minutes at -78 °C, then quenched with aq. satd. NH₄Cl solution. The mixture was extracted with diethyl ether (10 ml x 2). The combined organic layers were washed with water, brine and then dried over anhydrous MgSO₄. The solvents were removed *in vacuo*. The residue was purified by flash column chromatography (hexane: ethyl acetate = 93:7) on silica gel (1 g) to give the *cis* isomer (**2.91**) (3 mg, 15 %) and the title compound (hexane: ethyl acetate = 90:10) as a colourless oil (16 mg, 76 %).

¹H NMR (500 MHz, CDCl₃) δ 1.39-1.31 (m, 2H), 1.47 (ddd, 1H, *J* = 13.6, 8.8, 4.9 Hz), 1.68-1.57 (m, 4H), 1.71 (dd, 3H, *J* = 6.5, 1.3 Hz), 2.14 (ddd, 1H, *J* = 13.8, 8.8, 5.0 Hz), 2.44 (dd, 1H, *J* = 14.8, 5.7 Hz), 2.56 (dd, 1H, *J* = 14.8, 8.2 Hz), 3.66 (s, 3H), 3.84 (m, 1H), 4.22-4.12 (m, 2H), 4.54 (d, 1H, *J* = 11.8 Hz), 4.68 (d, 1H, *J* = 7.0 Hz), 4.68 (d, 1H, *J* = 11.7 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 5.27 (ddq, 1H, *J* = 15.3, 8.5, 1.3 Hz), 5.67 (dq, 1H, *J* = 15.3, 6.5 Hz), 7.37-7.28 (m, 5H).

¹³C NMR (75 MHz, CDCl₃) δ 171.8, 138.2, 130.7, 130.0, 128.3, 127.9, 127.5, 91.6, 74.5, 69.4, 68.4, 67.6, 51.6, 39.5, 38.4, 30.0, 29.5, 18.4, 17.7.

m/z: 241 (M-BOM)⁺, 157, 125.

HRMS calculated for C₁₃H₂₁O₄ (M-BOM)⁺: 241.1434; found 241.1434.

IR: 2930, 1736, 1380, 1097, 1024 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +42.6$ (MeOH, $c = 0.6$).

Data for methyl 2-((2*S*,6*R*)-6-((*R*,*E*)-2-(benzyloxymethoxy)pent-3-enyl) tetrahydro-2*H*-pyran-2-yl)acetate-*cis* isomer (2.91):

^1H NMR (500 MHz, CDCl_3) δ 1.27-1.19 (m, 2H), 1.50 (ddd, 1H, $J = 13.5, 8.9, 4.7$ Hz), 1.62-1.55 (m, 3H), 1.72 (dd, 3H, $J = 6.5, 1.5$ Hz), 1.83-1.80 (m, 1H), 1.88 (ddd, 1H, $J = 13.6, 8.8, 5.2$ Hz), 2.38 (dd, 1H, $J = 14.8, 5.2$ Hz), 2.53 (dd, 1H, $J = 14.9, 8.3$ Hz), 3.34-3.40 (m, 1H), 3.69 (s, 3H), 3.74-3.69 (m, 1H), 4.23-4.19 (m, 1H), 4.50 (d, 1H, $J = 11.8$ Hz), 4.65 (d, 1H, $J = 6.6$ Hz), 4.66 (d, 1H, $J = 11.9$ Hz), 4.79 (d, 1H, $J = 6.9$ Hz), 5.26 (ddq, 1H, $J = 15.4, 8.6, 1.4$ Hz), 5.65 (dq, 1H, $J = 15.3, 6.6$ Hz), 7.35-7.27 (m, 5H).

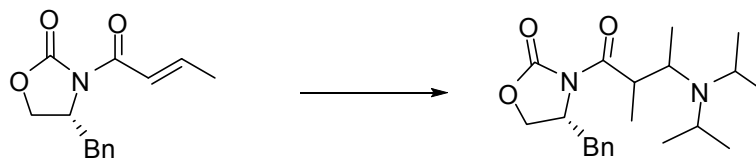
^{13}C NMR (100 MHz, CDCl_3) δ 172.0, 138.1, 130.7, 130.0, 128.3, 127.9, 127.5, 91.4, 74.6, 74.4, 74.2, 69.3, 51.5, 42.0, 41.6, 31.2, 31.2, 23.4, 17.8.

m/z : 241 (M-BOM) $^+$, 157, 125.

HRMS calculated for $\text{C}_{13}\text{H}_{21}\text{O}_4$ (M-BOM) $^+$: 241.1434; found 241.1434.

IR: 2935, 1736, 1380, 1097, 1026 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = 6.7$ (CHCl_3 , $c = 0.5$).



Synthesis of (4*R*)-4-benzyl-3-(3-(diisopropylamino)-2-ethylbutanoyl)oxazolidin-2-one (2.107): Lithium diisopropylamide (LDA) was generated by reacting diisopropylamine (90 μl , 0.61 mmol) in THF (4 ml) with $n\text{BuLi}$ (1.6M in

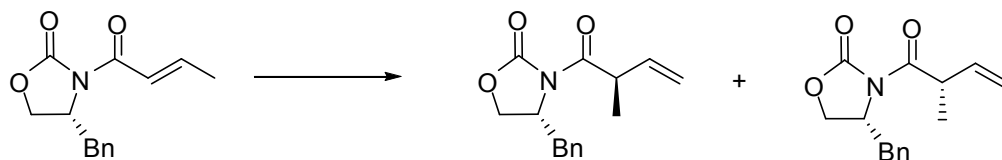
hexane, 0.36 ml, 0.57 mmol) under nitrogen at $-78\text{ }^{\circ}\text{C}$ for 30 minutes. A solution of oxazolidinone (**2.105**) (100 mg, 0.41 mmol) in THF (2 ml) was added dropwise at $-78\text{ }^{\circ}\text{C}$ to the LDA solution, the mixture was stirred for 30 min, then iodomethane (0.13 ml, 2.04 mmol) was added dropwise and the temperature was slowly warmed to $-40\text{ }^{\circ}\text{C}$. The mixture was stirred for 4 h, and then quenched with satd. aq. NH_4Cl solution. The reaction mixture was warmed to room temperature; the solvents were evaporated under reduced pressure and the residue was extracted with ethyl acetate (20 ml x 2). The combined organic layers were washed with water, aq. NaHCO_3 solution and brine, dried over anhydrous Na_2SO_4 . The residue was purified by flash column chromatography (hexane: ethyl acetate = 95:5) on silica gel (3 g) to give the title compound as a colourless oil (103 mg, 70 %).

^1H NMR (400 MHz, CDCl_3): δ 1.06 (d, 6H, $J = 4.6\text{ Hz}$), 1.07 (d, 6H, $J = 4.6\text{ Hz}$), 1.12 (d, 3H, $J = 6.5\text{ Hz}$), 1.23 (d, 3H, $J = 6.8\text{ Hz}$), 2.65 (dd, 1H, $J = 10.5, 13.1\text{ Hz}$), 3.13-3.25 (m, 3H), 3.44(dd, 1H, $J = 3.2, 13.1\text{ Hz}$), 3.94-4.02 (m, 1H), 4.13-4.20 (m, 2H), 4.68-4.74 (m, 1H), 7.26-7.38 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): 17.0, 18.9, 22.1, 37.9, 42.2, 44.7, 52.3, 55.4, 65.8, 127.3, 128.9, 129.4, 135.3, 153.2, 178.2.

m/z : 384 ($\text{M}+\text{Na}$)⁺, 362 ($\text{M}+\text{H}$)⁺.

HRMS calculated for $\text{C}_{21}\text{H}_{33}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}$)⁺: 361.2491 found: 361.2485.



Synthesis of (*R*)-4-benzyl-3-((*R*)-2-methylbut-3-enoyl)oxazolidin-2-one

(2.106) :¹⁸⁰

NaHMDS (1M solution in THF, 0.45 ml, 0.45 mmol) was added dropwise to a solution of chiral imide (**2.105**) (100 mg, 0.41 mmol) in THF (5 ml) under nitrogen at -78 °C. The mixture was stirred for 1 h at -78 °C, and a solution of MeI (0.13 ml, 2.04 mmol) in THF (1 ml) was added. The mixture was warmed to -40 °C and stirred for 2 h. The reaction mixture was quenched by addition of water (0.5 ml). The mixture was extracted with ethyl acetate and the organic layer was washed with water and brine and dried over anhydrous Na₂SO₄. The solvents were removed under reduced pressure and the residue was purified by column chromatography (hexane: ethyl acetate = 95:5) on silica gel (3 g) to give the minor isomer (**2.110**) (8 mg, 7 %) and the title compound (hexane: ethyl acetate = 92:8) as a colourless oil (67 mg, 63 %).

¹H NMR (400 MHz, CDCl₃) δ 1.35 (d, 3H, *J* = 6.9 Hz), 2.77 (dd, 1H, *J* = 9.6, 13.4 Hz), 3.29 (dd, 1H, *J* = 3.1, 13.4 Hz), 4.15-4.22 (m, 2H), 4.41-4.50 (m, 1H), 4.62-4.68 (m, 1H), 5.13 (d, 1H, *J* = 10.2 Hz), 5.20 (d, 1H, *J* = 17.2 Hz), 5.98 (ddd, 1H, *J* = 8.0, 10.3, 17.7 Hz), 7.20-7.35 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): 17.2, 37.9, 41.7, 55.5, 66.1, 116.6, 127.3, 128.9, 129.4, 135.2, 136.9, 152.9, 174.8.

HRMS calculated for C₁₅H₁₈NO₃ (M+H)⁺: 260.1287; found 260.1288.

[α]_D²² = - 88.0 (CHCl₃, c = 0.5).

IR: 1782, 1719, 1459, 1212, 1109 cm⁻¹.

Data for (R)-4-benzyl-3-((S)-2-methylbut-3-enoyl) oxazolidin-2-one**(2.110):** ¹⁸⁰

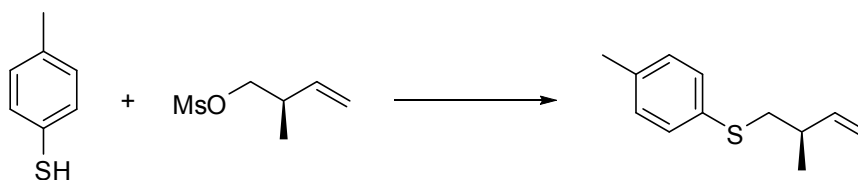
¹H NMR (400 MHz, CDCl₃) δ 1.32 (d, 3H, *J* = 6.8 Hz), 2.75 (dd, 1H, *J* = 9.6, 13.4 Hz), 3.26 (dd, 1H, *J* = 2.9, 13.2 Hz), 4.14-4.23 (m, 2H), 4.45-4.53 (m, 1H), 4.65-4.72 (m, 1H), 5.19 (d, 1H, *J* = 10.3 Hz), 5.26 (d, 1H, *J* = 17.6 Hz), 6.02 (ddd, 1H, *J* = 7.6, 10.2, 17.6 Hz), 7.19-7.35 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): 16.7, 37.7, 41.5, 55.2, 66.0, 116.7, 127.3, 128.9, 129.5, 135.2, 136.9, 153.0, 174.6.

[α]_D²² = -26.0 (CHCl₃, *c* = 0.5)

HRMS calculated for C₁₅H₁₈NO₃ (M+H)⁺: 260.1287; found 260.1286.

IR: 1782, 1719, 1459, 1212, 1109 cm⁻¹.



Synthesis of (R)-(2-methylbut-3-enyl)(p-tolyl)sulfane (2.174): NaH (0.18 g, 4.57 mmol) was added to a solution of *p*-thiocresol (**2.128**) (0.5 g, 4.02 mmol) in a mixture of dry DMF (2 ml) and THF (2 ml) at room temperature. The mixture was stirred for 5 minutes then a solution of mesylate (**2.168**) (0.3 g, 1.83 mmol) in THF (2 ml) was added dropwise via a cannula. The mixture was heated to 70 °C for 12 h, then quenched with aq. NaOH solution (5 ml), extracted with diethyl ether (3 x 30 ml). The combined organic layers were washed with water and brine and dried over anhydrous MgSO₄. The solvents were removed under reduced pressure to give the title compound as a colourless oil (0.35 g, 86 %) which was used in next step without purification.

^1H NMR (400 MHz, CDCl_3) δ 1.12 (d, 3H, $J = 6.9$ Hz) 2.31 (s, 3H), 2.37-2.43 (m, 1H), 2.80 (dd, 1H, $J = 7.3, 12.8$ Hz), 2.92 (dd, 1H, $J = 6.8, 12.8$ Hz), 5.02 (ddd, 2H, $J = 1.4, 1.8, 10.6$ Hz), 5.79 (ddd, 1H, $J = 7.3, 10.6, 17.9$ Hz), 7.09 (d, 2H, $J = 8.2$ Hz), 7.25 (d, 2H, $J = 8.2$ Hz).

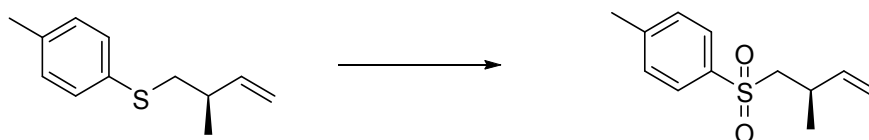
^{13}C NMR (100 MHz, CDCl_3): 19.3, 21.0, 37.2, 41.1, 114.0, 129.6, 129.9, 133.1, 135.9, 142.4.

m/z : 215 ($\text{M}+\text{Na}$) $^+$, 193 ($\text{M}+\text{H}$) $^+$, 173.

HRMS calculated for $\text{C}_{12}\text{H}_{17}\text{S}$ ($\text{M}+\text{H}$) $^+$: 193.1051 found: 193.1048.

IR: 3076, 2962, 1091, 799 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +14$ (CHCl_3 , $c=0.5$).



Synthesis of (*R*)-1-methyl-4-(2-methylbut-3-enylsulfonyl) benzene (2.175):

Ammonium heptamolybdate 181 (1.54 g, 1.25 mmol) was added to a solution of hydrogen peroxide (30% in water, 2.5 ml, 24.79 mmol) at 0 °C, the mixture was stirred for 10 minutes, then 1 ml of the mixture was added to a solution of sulphide (**2.174**) (0.1 g, 0.52 mmol) in ethanol (5 ml) at 0 °C. The mixture was stirred for 4 h at 0 °C, then diluted with ethyl acetate (25 ml). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 . Solvents were evaporated *in vacuo*, the residue was purified by column chromatography (hexane: ethyl acetate = 95: 5) on silica gel (3 g) to give the title compound as a colourless oil (0.12 g, 98 %).

^1H NMR (400 MHz, CDCl_3) δ 1.16 (d, 3H, $J = 6.9$ Hz), 2.44 (s, 3H), 2.71-2.82 (m, 1H), 3.00 (dd, 1H, $J = 7.3, 14.2$ Hz), 3.13 (dd, 1H, $J = 5.9, 14.2$ Hz), 4.94-5.01

(m, 2H), 5.71 (ddd, 1H, $J = 7.3, 11.4, 17.5$ Hz), 7.34 (d, 2H, $J = 7.2$ Hz), 7.77 (d, 2H, $J = 8.2$ Hz).

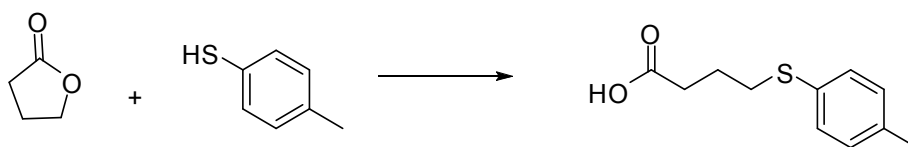
^{13}C NMR (100 MHz, CDCl_3): 19.9, 21.6, 32.7, 62.0, 114.5, 128.0, 129.8, 137.0, 140.7, 144.5.

m/z : 247 ($\text{M}+\text{Na}$)⁺, 225 ($\text{M}+\text{H}$)⁺.

HRMS calculated for $\text{C}_{12}\text{H}_{17}\text{O}_2\text{S}$ ($\text{M}+\text{H}$)⁺: 225.0949 found: 225.0942.

IR: 3066, 1313, 1288, 1145, 766 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +4.1$ (CHCl_3 , $c=1.05$).



Synthesis of 4-(*p*-tolylthio)butanoic acid (2.129): ⁹⁶ Thio cresol (2.128) (2.89 g, 23.34 mmol) was added portionwise to a solution of sodium ethoxide (1.59 g, 23.34 mmol) in ethanol (10 ml) under nitrogen. The mixture was stirred for 20 minutes then γ -butyrolactone (2 ml, 24.52 mmol) was added in one portion. The mixture was heated at reflux for 4 h. Ethanol was removed under reduced pressure; the residue was dissolved in water and filtered through a silica plug. The filtrate was acidified with dil.HCl to obtain a precipitate which was separated from the filtrate by careful filtration, and then dried under reduced pressure to afford the title compound as a colourless solid (4.8 g, 98 %).

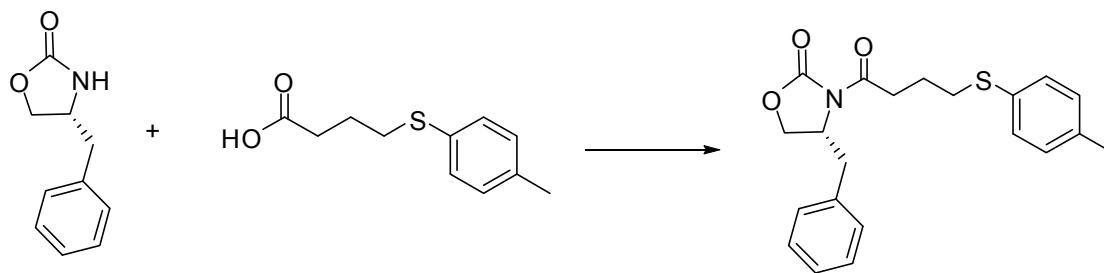
^1H NMR (300 MHz, CDCl_3) δ 1.86-1.96 (m, 2H), 2.31 (s, 3H), 2.50 (t, 2H, $J = 7.2$ Hz), 2.92 (t, 2H, $J = 7.1$ Hz), 7.10 (d, 2H, $J = 7.9$ Hz), 7.25 (d, 2H, $J = 7.9$ Hz).

^{13}C NMR (75 MHz, CDCl_3): 20.0, 23.2, 29.9, 32.7, 128.7, 129.3, 131.0, 135.4, 206.1.

m/z : 211, 208.

HRMS calculated for $\text{C}_{11}\text{H}_{15}\text{O}_2\text{S}$ ($\text{M}+\text{H}$)⁺: 211.0793 found: 211.0793.

IR: 2914, 1698, 1453, 1248, 1198 cm^{-1} .



Synthesis of (R)-4-benzyl-3-(4-(p-tolylthio) butanoyl) oxazolidin-2-one

(2.130): Oxalyl chloride (88 μl , 1.02 mmol) was added dropwise to a solution of acid **(2.129)** (142 mg, 0.68 mmol) in dichloromethane (3 ml), with external cooling, followed by a drop of DMF. The mixture was stirred for 30 minutes at room temperature; the volatiles were evaporated under reduced pressure. $n\text{BuLi}$ (1.6M in hexane, 0.36 ml, 0.57 mmol) was added dropwise to a flask containing a solution of the oxazolidinone (100 mg, 0.57 mmol) in THF (3 ml) at $-78\text{ }^{\circ}\text{C}$. The acid chloride was redissolved in THF (2 ml), transferred to the mixture dropwise and the mixture was stirred for 2 h at $-78\text{ }^{\circ}\text{C}$. It was quenched with satd. aq. NH_4Cl solution, warmed to room temperature. The solvents were removed under reduced pressure; the residue was extracted with dichloromethane (15 ml x 3). The combined organic layers were washed with 2M aq. NaOH solution, water and then with brine solution. Dichloromethane was evaporated and the residue was purified by flash column chromatography (hexane: ethyl acetate = 92:8) on silica gel (3 g) to give the title compound as a colourless oil (175 mg, 84 %).

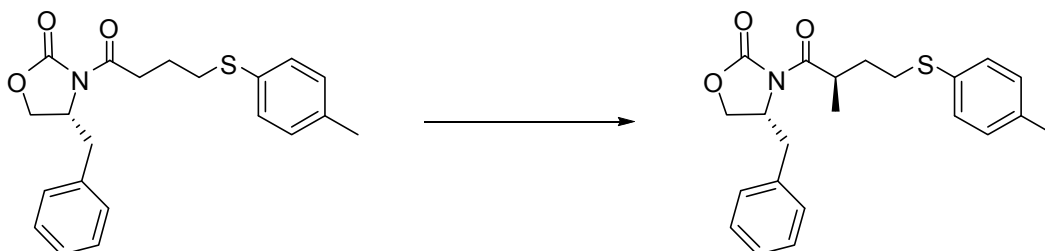
^1H NMR (400 MHz, CDCl_3) δ 1.97-2.04 (m, 2H), 2.32 (s, 3H), 2.75 (dd, 1H, $J = 9.6, 13.3$ Hz), 2.98 (t, 2H, $J = 7.1$ Hz), 3.08 (dt, 2H, $J = 7.2, 4.7$ Hz), 3.28 (dd, 1H, $J = 3.3, 13.4$ Hz), 4.15-4.22 (m, 2H), 4.65 (ddd, 1H, $J = 3.3, 6.9, 13.0$ Hz), 7.11 (d, 2H, $J = 7.9$ Hz), 7.20 (d, 2H, $J = 7.6$ Hz), 7.28-7.35 (m, 5H).

IR: 2973, 1776, 1690, 1387, 1211, 1104 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = -46.6$ (CH_2Cl_2 , $c = 1$).

m/z: 392 (M+Na)⁺, 279, 223.

HRMS calculated for C₂₁H₂₄NO₃S (M+H)⁺: 370.1477 found: 370.1477.



Synthesis of (*R*)-4-benzyl-3-((*R*)-2-methyl-4-(*p*-tolylthio)butanoyl)oxazolidin-

2-one (2.131): The literature procedure ¹²² was modified as follows, Lithium diisopropylamide (LDA) was generated by reacting diisopropylamine (0.1 ml, 0.71 mmol) in THF (3 ml) with ^tBuLi (1.6M in hexane, 0.41 ml, 0.65 mmol) under nitrogen at -78 °C for 30 minutes. A solution of oxazolidinone (**2.130**) (200 mg, 0.54 mmol) in THF (2 ml) was added dropwise at -78 °C to the LDA solution, the mixture was stirred for 30 min, then iodomethane (0.17 ml, 2.71 mmol) was added dropwise and the mixture was slowly warmed to -40 °C. The mixture was stirred overnight, and then quenched with satd. aq. NH₄Cl solution. The reaction mixture was warmed to room temperature; the solvents were evaporated under reduced pressure and the residue was extracted with ethyl acetate (30 ml x 2). The combined organic layers were washed with water, aq. NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄. The residue was purified by flash column chromatography (hexane: ethyl acetate = 95:5) on silica gel (4 g) to give the title compound as a colourless oil (191 mg, 91 %).

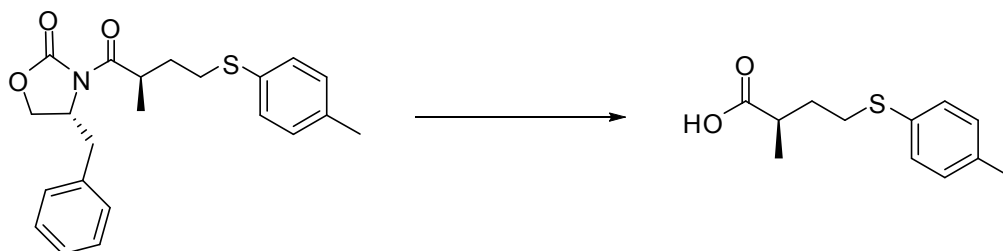
¹H NMR (400 MHz, CDCl₃) δ 1.25 (d, 3H, *J* = 6.9 Hz) 1.68-1.79 (m, 1H), 2.08-2.21 (m, 1H), 2.32 (s, 3H), 2.78 (dd, 1H, *J* = 9.5, 13.4 Hz), 2.82-3.02 (m, 2H), 3.26 (dd, 1H, *J* = 3.3, 13.3 Hz), 3.82-3.96 (m, 1H), 4.17 (d, 2H, *J* = 5.1 Hz), 4.57-4.71 (m, 1H), 7.05-7.38 (m, 9H).

^{13}C NMR (75 MHz, CDCl_3): 17.7, 21.0, 32.0, 32.8, 37.0, 37.9, 55.3, 66.1, 127.4, 129.0, 129.5, 129.7, 130.1, 132.3, 135.2, 136.2, 152.9, 176.3.

m/z : 384.9 ($\text{M}+\text{H}$) $^+$.

HRMS calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 384.1633 found: 384.1629.

$[\alpha]_{\text{D}}^{22} = -70.4$ (CHCl_3 , $C = 0.7$).



Synthesis of (*R*)-2-methyl-4-(*p*-tolylthio)butanoic acid (2.136): The literature procedure⁹⁸ was modified as follows: H_2O_2 solution (30% in water, 38 μl , 0.42 mmol) and LiOH (7 mg, 0.17 mmol) were added in sequence to a solution of imide (**2.131**) (40 mg, 0.10 mmol) in a mixture of THF (4 ml) and water (1 ml) with external cooling. The mixture was stirred for 3 h, and then quenched with aq. Na_2SO_3 solution. The reaction mixture was washed with dichloromethane (5 ml x 2). The aqueous layer was cooled to 0 $^\circ\text{C}$, acidified with dil. HCl to pH1 and extracted with ethyl acetate (10 ml x 3). The combined organic layers were washed with water and brine solution. Evaporation of the solvent afforded the title compound as a colourless oil (15 mg, 65 %).

^1H NMR (400 MHz, CDCl_3) δ 1.19 (d, 3H, $J = 7.0$ Hz) 1.70-1.79 (m, 1H), 1.98-2.04 (m, 1H), 2.31 (s, 3H), 2.60-2.68 (m, 1H), 2.81-2.92 (m, 2H), 7.09 (d, 2H, $J = 8.0$ Hz), 7.25 (d, 2H, $J = 8.1$ Hz), 10.60 (broad s, 1H).

^{13}C NMR (100 MHz, CDCl_3): 16.8, 21.0, 32.0, 32.7, 38.3, 129.8, 130.2, 132.2, 136.3, 182.5.



Synthesis of (R)-2-methyl-4-(p-tolylthio)butan-1-ol (2.132): LiAlH₄ (285 mg, 7.50 mmol) was added portionwise to a solution of acid (2.136) (280 mg, 1.25 mmol) in THF (10 ml) under nitrogen at 0 °C. The mixture was stirred for 1 h with slow warming to room temperature, and then quenched with 5% aq. NaHCO₃ and aq. NaOH solutions; the mixture was stirred for 5 minutes, and then filtered through celite. The filtrate was extracted with ethyl acetate (20 ml x 3), the combined organic layers were washed with water and brine. The residue was used in the next step without purification.

¹H NMR (400 MHz, CDCl₃) δ 0.94 (d, 3H, *J* = 6.6 Hz) 1.42-1.50 (m, 1H), 1.73-1.84 (m, 2H), 1.86 (broad s, 1H), 2.32 (s, 3H), 2.88-2.98 (m, 2H), 3.42-3.50 (m, 2H), 7.09 (d, 2H, *J* = 7.8 Hz), 7.25 (d, 2H, *J* = 7.9 Hz).

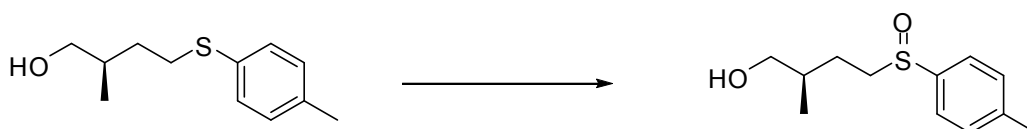
¹³C NMR (100 MHz, CDCl₃): 16.4, 21.0, 32.1, 32.7, 35.0, 67.7, 129.7, 129.9, 132.7, 136.0.

m/z: 211 (M+H)⁺, 193, 178.

HRMS calculated for C₁₂H₁₈OS (M+H)⁺: 211.1157 found: 211. 1150.

IR: 3370, 2952, 1091, 804, 701 cm⁻¹.

[α]_D²² = +27.2 (CH₂Cl₂, *c* = 0.8).



Synthesis of (2R)-2-methyl-4-(p-tolylsulfinyl)butan-1-ol (2.137):⁹⁹ *mCPBA* (70 mg, 0.20 mmol) was added to a solution of the sulfide (2.132) (40 mg, 0.19 mmol) in dichloromethane (4 ml) at -78 °C. The solution was slowly warmed to 0

°C, and stirred for 10 minutes. The reaction mixture was diluted with dichloromethane (20 ml), washed with aq. NaHCO₃ and then dried with anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure to get the title compound as a colourless oil (42 mg, 99%), which was used in the the next step without purification.

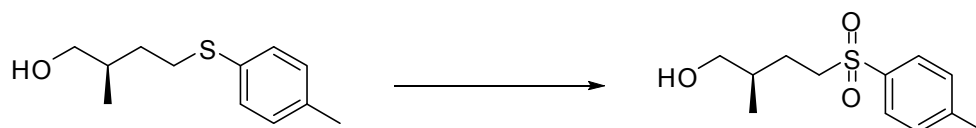
¹H NMR (400 MHz, CDCl₃) δ 0.88-0.92 (m, 3H), 1.41-1.79 (m, 3H), 2.34 (s, 3H), 2.74-2.81(m, 2H), 3.32-3.40 (m, 2H), 7.21-7.45 (m, 4H).

¹³C NMR (100 MHz, CDCl₃), 1:1 mixture of diastereomers: 16.45, 16.54, 21.4, 25.5, 25.6, 34.95, 35.0, 54.58, 54.63, 67.07, 67.12, 124.15, 124.19, 130.0, 140.1, 141.6.

m/z: 249 (M+Na), 227 (M+H)⁺, 203.

HRMS calculated for C₁₂H₁₉O₂S (M+H)⁺: 227.1106 found: 227.1112

IR: 3399, 1288, 1144, 1038 cm⁻¹.



Synthesis of (R)-2-methyl-4-tosylbutan-1-ol (2.149): *m*CPBA (360 mg, 1.04 mmol) was added to a solution of sulphide (**2.132**) (109mg, 0.52 mmol) in dichloromethane (5 ml) with external cooling. The mixture was stirred for 2 h at room temperature, then poured into a beaker containing 50 ml of diethyl ether and 20 ml of aqueous sodium sulphite solution. The organic layer was separated and washed twice with satd. aq. NaHCO₃ solution. Solvents were removed under reduced pressure to afford the title compound as a colourless solid (122 mg, 99 %).

¹H NMR (400 MHz, CDCl₃) δ 0.87 (d, 3H, *J* = 6.7 Hz), 1.53-1.55 (m, 1H), 1.62-1.68 (m, 1H), 1.74-1.89 (m, 1H), 2.03 (broad s, 1H), 2.44 (s, 3H), 3.07-3.20 (m,

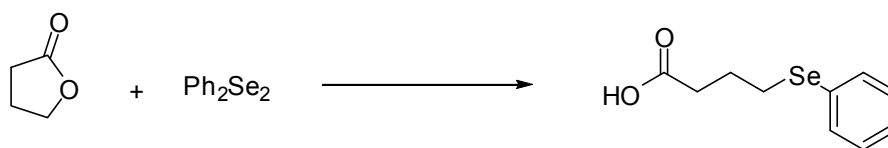
2H), 3.41 (dd, 1H, $J = 5.6, 10.7$ Hz), 3.48 (dd, 1H, $J = 6.4, 10.7$ Hz), 7.35 (d, 2H, $J = 8.0$ Hz), 7.77 (d, 2H, $J = 8.2$ Hz).

^{13}C NMR (100 MHz, CDCl_3): 16.3, 21.6, 26.1, 34.5, 54.3, 67.2, 128.1, 129.9, 133.6, 144.8.

m/z : 265 ($\text{M}+\text{Na}$) $^+$, 243 ($\text{M}+\text{H}$) $^+$, 225

HRMS calculated for $\text{C}_{12}\text{H}_{19}\text{O}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 243.1055 found: 243.1049

IR: 3507, 1284, 1140, 1039 cm^{-1} .



Synthesis of 4-(phenylselenenyl)butanoic acid (2.162): ¹⁰⁹ Diphenyl diselenide (312 mg, 1.0 mmol) was dissolved in dry DMF (5 ml), which had been deoxygenated by bubbling nitrogen over 20 min. Sodium borohydride (86 mg, 2.25 mmol) was added to the solution and the reaction was heated to 100 °C. γ -Butyrolactone (0.14 ml, 1.85 mmol) was then added and the temperature was further increased to 120 °C and stirring was continued for 2 h. The mixture was cooled to room temperature and diluted with diethyl ether (50 ml). The organic layers were washed with water and brine and dried over anhydrous MgSO_4 . The solvent was removed *in vacuo* to afford the title compound (242 mg, 99 %) as yellow solid.

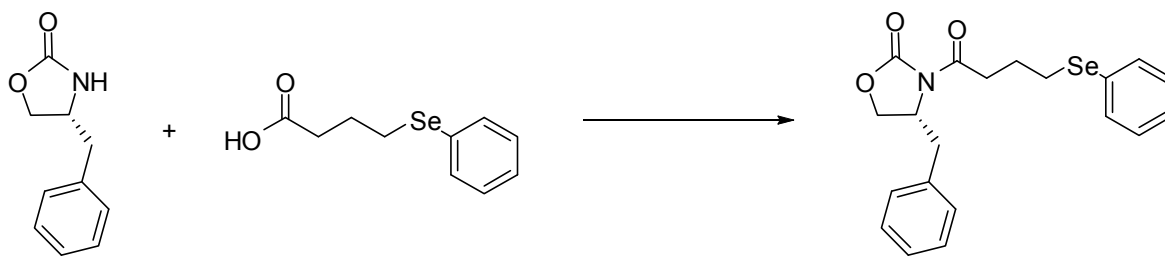
^1H NMR (400 MHz, CDCl_3) δ 1.96-2.04 (m, 2H), 2.50 (t, 2H, $J = 7.3$ Hz), 2.94 (t, 2H, $J = 7.3$ Hz), 7.20–7.28 (m, 3H), 7.47-7.50 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3): 24.9, 26.8, 33.6, 127.0, 129.1, 129.6, 132.8, 179.2.

m/z : 268 ($\text{M}+\text{Na}$) $^+$, 246 ($\text{M}+\text{H}$) $^+$.

HRMS calculated for $\text{C}_{10}\text{H}_{13}\text{O}_2\text{Se}$ ($\text{M}+\text{H}$) $^+$: 245.0081 found: 245.0082.

IR: 3058, 1688, 1180, 728 cm^{-1} .



Synthesis of (R)-4-benzyl-3-(4-(phenylselanyl)butanoyl)oxazolidin-2-one

(2.163): The title compound (328 mg, 98 %) was obtained from the previous compound (**2.162**) by the method described for (**2.130**) to give a colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 1.97-2.02 (m, 2H), 2.67 (dd, 1H, $J = 9.6, 13.3$ Hz), 2.93 (t, 2H, $J = 7.2$ Hz), 3.01 (dt, 2H, $J = 1.2, 7.1$ Hz), 3.19 (dd, 1H, $J = 3.2, 13.4$ Hz), 4.03-4.14 (m, 2H), 4.56 (ddd, 1H, $J = 3.6, 6.9, 13.2$ Hz), 7.11-7.28 (m, 8H), 7.43-7.46 (m, 2H).

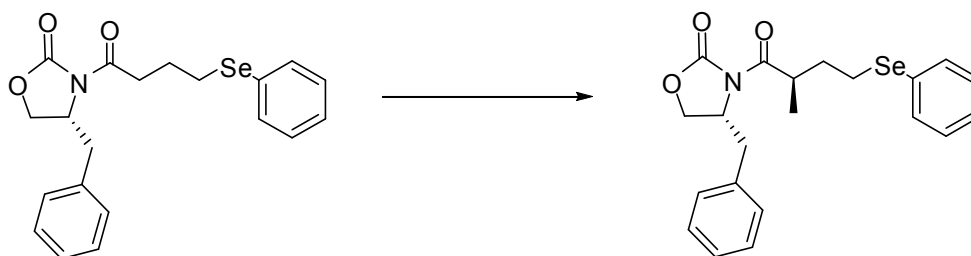
^{13}C NMR (75 MHz, CDCl_3): 24.7, 27.0, 35.3, 37.9, 55.1, 66.2, 126.9, 127.4, 129.0, 129.1, 129.4, 130.0, 132.8, 135.2, 153.4, 172.4.

m/z : 426 ($\text{M}+\text{Na}$) $^+$, 404 ($\text{M}+\text{H}$) $^+$, 306, 210, 178.

HRMS calculated for $\text{C}_{20}\text{H}_{21}\text{NO}_3\text{Se}$ ($\text{M}+\text{H}$) $^+$: 403.0681 found: 403.0660

IR: 1778, 1695, 1386, 1212, 737 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = -45.2$ (CHCl_3 , $c = 0.7$).



Synthesis of (R)-4-benzyl-3-((R)-2-methyl-4-(phenylselanyl) butanoyl)

oxazolidin-2-one (2.164): The title compound (203 mg, 82 %) was obtained from the previous compound (**2.163**) by the method described for (**2.131**) to give a colourless oil.

^1H NMR (300 MHz, CDCl_3) δ 1.23 (d, 3H, $J = 6.9$ Hz) 1.75-1.86 (m, 1H), 2.16-2.28 (m, 1H), 2.76 (dd, 1H, $J = 9.4, 13.3$ Hz), 2.85-3.01 (m, 2H), 3.23 (dd, 1H, $J = 3.3, 13.4$ Hz), 3.79-3.90 (m, 1H), 4.15 (d, 2H, $J = 5.2$ Hz), 4.61(ddd, 1H, $J = 3.4, 5.1, 14.5$ Hz), 7.18-7.36 (m, 8H), 7.48-7.51 (m, 2H).

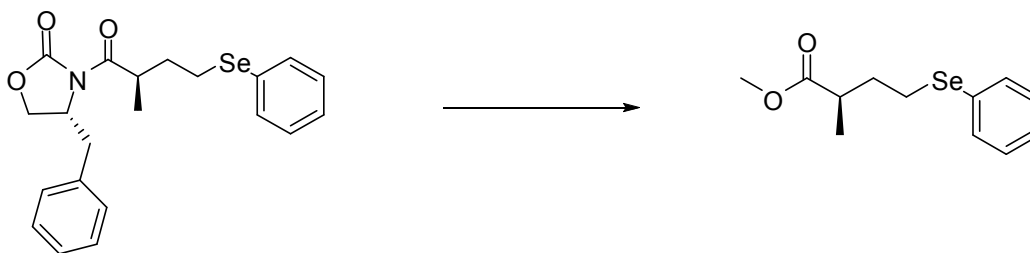
^{13}C NMR (100 MHz, CDCl_3): 17.5, 25.1, 33.7, 37.8, 38.0, 55.1, 66.0, 126.7, 127.3, 128.9, 129.0, 129.4, 130.1, 132.5, 135.2, 152.8, 176.1.

m/z : 418($\text{M}+\text{H}$) $^+$, 372, 308, 260, 178.

HRMS calculated for $\text{C}_{21}\text{H}_{23}\text{NO}_3\text{Se}$ ($\text{M}+\text{H}$) $^+$: 417.0838 found: 417.0857

IR: 1777, 1697, 1383, 1102, 912 cm^{-1} .

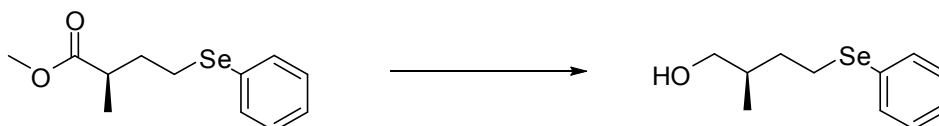
$[\alpha]_{\text{D}}^{22} = -49.8$ (CHCl_3 , $c = 1.1$).



Synthesis of (*R*)-methyl 2-methyl-4-(phenylselanyl)butanoate (2.165): The literature ⁹⁷ procedure was modified as follows: A solution of LiOMe (30 mg, 0.78 mmol) in methanol (1 ml) was added dropwise to a solution of imide (**2.164**) (100mg, 0.26 mmol) in methanol (1 ml) at -40 °C. The mixture was stirred for 2 h then warmed to -5 °C, stirred for another 20 minutes then quenched with aq. satd. NH_4Cl solution. The reaction mixture was extracted with ethyl acetate (10 ml x 3), the combined organic layers were washed with water and brine. The solvents were removed *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 90:10) on silica gel (1 g) to give the title compound as a colourless oil (38 mg, 62%)

^1H NMR (400 MHz, CDCl_3) δ 1.16 (d, 3H, $J = 7.0$ Hz), 1.73-1.84 (m, 1H), 2.02-2.14 (m, 1H), 2.57-2.68 (m, 1H), 2.82-2.96 (m, 2H), 3.66 (s, 3H), 7.23-7.30 (m, 2H), 7.47-7.53 (m, 2H).

m/z : 272 ($\text{M}+1$)⁺, 115.



Synthesis of (R)-2-methyl-4-(phenylselanyl) butan-1-ol (2.166): The title compound (31 mg, 99 %) was obtained from the previous compound (**2.165**) by the method described for (**2.132**) to give a colourless oil.

^1H NMR (400 MHz, CDCl_3) δ 0.93 (d, 3H, $J = 6.7$ Hz) 1.50-1.59 (m, 1H), 1.71-1.88 (m, 2H), 1.99 (broad s, 1H), 2.91 (ddd, 1H, $J = 6.5, 9.5, 15.9$ Hz), 3.00 (ddd, 1H, $J = 5.7, 9.5, 15.1$ Hz), 3.45 (ddd, 2H, $J = 5.9, 10.8, 16.9$ Hz), 7.20-7.31 (m, 3H), 7.47-7.50 (m, 2H).

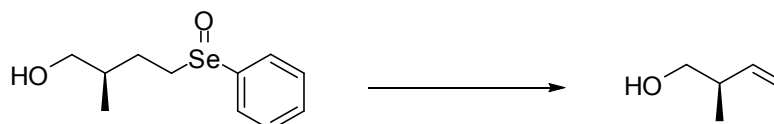
^{13}C NMR (100 MHz, CDCl_3): 16.1, 25.4, 33.5, 35.8, 67.5, 126.6, 128.9, 130.3, 132.7.

m/z : 266 ($\text{M}+\text{Na}$)⁺, 244 ($\text{M}+\text{H}$)⁺, 210, 178.

HRMS calculated for $\text{C}_{11}\text{H}_{16}\text{O}^{78}\text{SeNa}$ ($\text{M}+\text{Na}$)⁺: 265.0272 found: 265.0268.

IR: 3426, 2929, 1242, 1023, 736 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +31.1$ (CH_2Cl_2 , $c = 0.4$).



Synthesis of (R)-2-methylbut-3-en-1-ol (2.138): An aq. 30% solution of Hydrogen peroxide¹⁸² (0.66 ml, 8.23 mmol) was added to a solution of selenide (**2.166**) (200 mg, 0.82 mmol) and pyridine (0.15 ml, 1.65 mmol) in dichloroethane

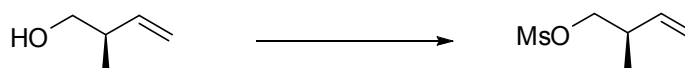
(2 ml). The reaction mixture was stirred for 15 minutes then transferred to a refluxing mixture of dichloroethane (3 ml) and pyridine (0.15 ml, 1.65 mmol). The reaction mixture immediately turned to yellow and was heated for 15 min. The solvents were evaporated carefully under reduced pressure. The crude product was used in the next step without further purification.

^1H NMR (500 MHz, CDCl_3) δ 1.02 (d, 3H, $J = 6.8$ Hz), 2.34-2.42 (m, 1H), 3.43 (ddd, 1H, $J = 4.7, 7.5, 10.5$ Hz), 3.53 (ddd, 1H, $J = 5.4, 7.1, 10.3$ Hz), 5.12 (m, 2H), 5.71 (ddd, 1H, $J = 7.6, 10.4, 17.6$ Hz).

$[\alpha]_{\text{D}}^{22} = +30.0$ ($c=0.8$, CH_2Cl_2)

IR: 2926, 1457, 1035.

All data are consistent with literature.^{111,183}



Synthesis of (*R*)-2-methylbut-3-enyl methanesulfonate (2.168): Et_3N (0.72 ml, 5.16 mmol) and MsCl (0.4 ml, 5.16 mmol) were added in sequence to a solution of the crude alcohol (**2.138**) (0.25 g, 2.88 mmol) in dichloromethane (7 ml) with external cooling. The mixture was stirred for 1 h at room temperature, quenched with aq. satd. NH_4Cl (1 ml) solution. The reaction mixture was extracted with dichloromethane (20 ml x 2); the combined organic layers were then washed with aq. NaHCO_3 solution, water and brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane: ethyl acetate = 90:10) on silica gel (7 g) to give the title compound as a colourless oil (300 mg, 63 %).

^1H NMR (300 MHz, CDCl_3) δ 1.10 (d, 3H, $J = 6.7$ Hz) 2.55-2.69 (m, 1H), 3.00 (s, 3H), 4.05 (dd, 1H, $J = 6.6, 9.6$ Hz), 4.12 (dd, 1H, $J = 6.6, 9.7$ Hz), 5.12 (dd, 1H,

$J = 1.2, 10.4$ Hz), 5.15 (dd, 1H, $J = 1.3, 17.3$ Hz), 5.74 (ddd, 1H, $J = 7.0, 10.4, 17.4$ Hz).

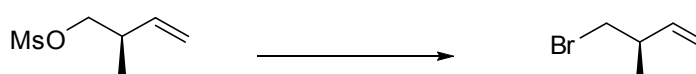
^{13}C NMR (75 MHz, CDCl_3): 16.0, 37.2, 37.4, 73.3, 116.3, 138.4

m/z : 187 ($\text{M}+\text{Na}$) $^+$, 165 ($\text{M}+\text{H}$) $^+$, 117, 102.

HRMS calculated for $\text{C}_6\text{H}_{13}\text{O}_3\text{S}$ ($\text{M}+\text{H}$) $^+$: 165.0585 found: 165.0581

IR: 3085, 1350, 1171, 957 cm^{-1} .

$[\alpha]_D^{22} = +5.0$ (CHCl_3 , $c=0.6$).

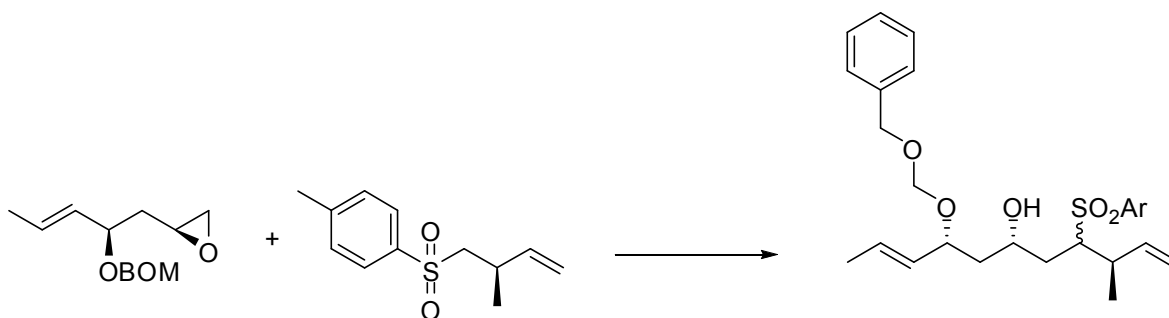


Synthesis of (R)-4-bromo-3-methylbut-1-ene (2.170): LiBr (60 mg, 0.69 mmol) was added to a solution of mesylate (**2.168**) (75 mg, 0.48 mmol) in THF (2 ml). The mixture was heated at reflux overnight, then cooled to room temperature and filtered through celite. The solvent was evaporated *in vacuo* to provide the title compound as a colourless oil (68 mg, 99 %), which was used in the next step without further purification.

^1H NMR (300 MHz, CDCl_3) δ 1.14 (d, 3H, $J = 6.7$ Hz) 2.49-2.62 (m, 1H), 3.31 (dd, 1H, $J = 6.6, 9.8$ Hz), 3.38 (dd, 1H, $J = 6.0, 9.8$ Hz), 5.10 (dd, 1H, $J = 1.2, 10.4$ Hz), 5.08 (dd, 1H, $J = 1.3, 17.3$ Hz), 5.76 (ddd, 1H, $J = 7.0, 10.4, 17.3$ Hz).

m/z : 151 ($\text{M}+\text{H}$) $^+$, 147, 127.

HRMS calculated for $\text{C}_5\text{H}_{10}^{81}\text{Br}$ ($\text{M}+\text{H}$): 150.9945 found: 150.9950.



Synthesis of (3*R*, 6*S*, 8*R*, *E*)-8-(benzyloxymethoxy)-3-methyl-4-tosylundeca-

1,9-dien-6-ol (2.176): ^tBuLi (1.6 M in hexane, 0.17 ml, 0.27 mmol) was added dropwise to a solution of sulfone (**2.175**) (60 mg, 0.27 mmol) in THF (1.5 ml) at -78 °C. The mixture was stirred at -78 °C for 30 minutes then BF₃·Et₂O (35 μl, 0.27 mmol) and a solution of the epoxide (**2.85**) (55 mg, 0.22 mmol) in THF (1 ml) were added. The reaction mixture was stirred for 2 h at -78 °C, then quenched with triethyl amine (80 μl, 0.58 mmol) and warmed to room temperature. The mixture was diluted with diethyl ether (20 ml), the organic layers were washed with water, aq. NaHCO₃ and finally with brine. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane: ethyl acetate = 88:12) on silica gel (2 g) to give the title compound as a colourless oil (88 mg, 85 %).

¹H NMR (400 MHz, CDCl₃) δ 1.05 (d, 3H, *J* = 9.3 Hz, major), 1.21(d, 3H, *J* = 9.3 Hz, minor), 1.53-1.71 (m, 7H, major and minor), 1.76-2.07 (m, 2H, major and minor), 2.41 (s, 3H, major), 2.44 (s, 3H, minor), 2.72-2.78 (m, 1H, major), 2.92-2.99 (m, 1H, minor), 3.75-3.95(m, 1H, major and minor), 4.18-4.26 (m, 1H, major and minor), 4.47 (d, 1H, *J* = 11.2 Hz, major and minor), 4.62 (d, 1H, *J* = 6.2 Hz, major and minor), 4.65 (d, 1H, *J* = 12.5 Hz, major and minor), 4.77 (d, 1H, *J* = 6.2 Hz, major), 4.79 (d, 1H, *J* = 6.8 Hz, minor), 5.00 (d, 1H, *J* = 18.5 Hz, major), 5.09 (d, 1H, *J* = 10.6 Hz, minor), 5.19-5.26 (m, 1H, minor and major), 5.63-5.71 (m, 1H, major and minor), 5.85 (ddd, 1H, *J* = 6.1, 10.4, 16.2 Hz,

minor), 6.01 (ddd, 1H, $J = 6.1, 10.6, 16.3$ Hz, major), 7.30-7.37(m, 7H, major and minor), 7.79 (d, 2H, $J = 9.5$ Hz, major and minor).

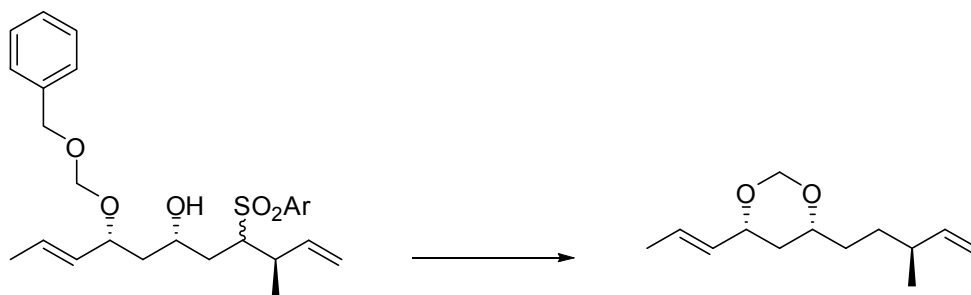
^{13}C NMR (100 MHz, CDCl_3 , major isomer): 17.6, 21.5, 32.5, 35.8, 42.9, 64.8, 68.4, 69.6, 76.6, 90.8, 114.8, 115.9, 127.8, 127.9, 128.4, 128.6, 129.9, 130.0, 130.4, 136.0, 137.5, 140.8, 144.4.

^{13}C NMR (100 MHz, CDCl_3 , minor isomer): 17.7, 21.5, 32.0, 35.3, 42.8, 64.8, 67.5, 69.5, 76.6, 90.9, 114.8, 115.9, 127.7, 127.9, 128.4, 128.5, 129.7, 129.9, 130.5, 135.6, 137.7, 140.8, 144.4.

m/z: 495 ($\text{M}+\text{Na}$) $^+$, 473 ($\text{M}+\text{H}$) $^+$, 365, 335, 317.

HRMS calculated for $\text{C}_{27}\text{H}_{37}\text{O}_5\text{S}$ ($\text{M}+\text{H}$) $^+$: 473.2358 found: 473.2362.

IR: 3513, 3031, 1454, 1298, 1143, 1085, 1025 cm^{-1} .



Synthesis of (4*R*,6*R*)-4-((*S*)-3-methylpent-4-enyl)-6-((*E*)-prop-1-enyl)-1,3-

dioxane (2.178): The literature procedure ¹¹³ was modified as follows: Activated magnesium (11 mg, 0.04 mmol) was added to a solution of sulfone (**2.176**) (70 mg, 0.15 mmol) in methanol (5 ml). The mixture was heated at 55 °C for 1 h, after all the magnesium granules had dissolved, additional Mg (11 mg, 0.04 mmol) was added and the mixture was continuously stirred at 55 °C for 5 h. The methanol was removed under reduced pressure, the residue was diluted with ethyl acetate (50 ml), washed with water and brine. The organic layer was dried over anhydrous MgSO_4 , the solvent was evaporated *in vacuo* and the residue

was purified by column chromatography (hexane: ethyl acetate = 95: 5) on silica gel (2 g) to give the title compound as a colourless oil (22 mg, 69 %).

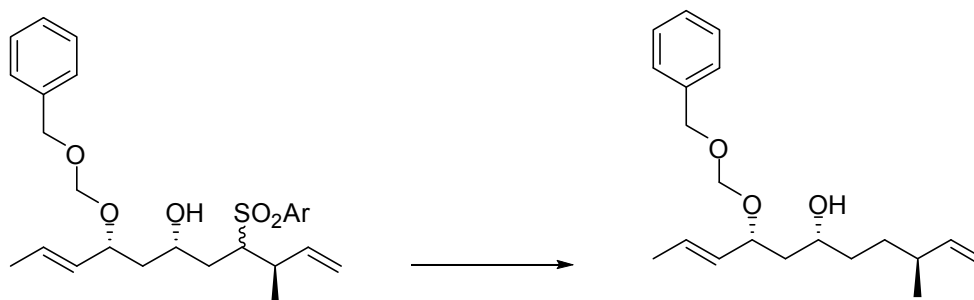
^1H NMR (400 MHz, CDCl_3) δ 0.99 (d, 3H, J = 6.8 Hz), 1.29-1.62 (m, 6H), 1.71(dd, 3H, J = 0.9, 7.3 Hz), 2.08-2.15 (m, 1H), 3.52-3.57 (m, 1H), 4.01(ddd, 1H, J = 2.8, 6.6, 9.6 Hz), 4.73 (d, 1H, J = 6.5 Hz), 4.93 (dd, 2H, J = 11.0, 16.9 Hz), 5.09 (d, 1H, J = 6.0 Hz), 5.50 (ddq, 1H, J = 15.4, 6.2, 1.4 Hz), 5.67 (ddd, 1H, J = 7.8, 10.1, 17.9 Hz), 5.74 (dq, 1H, J = 15.6, 6.9 Hz).

^{13}C NMR (100 MHz, CDCl_3): 17.8, 20.2, 31.6, 33.5, 37.7, 37.8, 76.4, 77.2, 93.4, 112.9, 127.9, 130.9, 144.3.

m/z : 211 ($\text{M}+\text{H}$) $^+$, 181, 163.

HRMS calculated for $\text{C}_{13}\text{H}_{23}\text{O}_2$ ($\text{M}+\text{H}$) $^+$: 211.1698 found: 211.1704.

$[\alpha]_{\text{D}}^{22} = +16.2$ (CH_2Cl_2 , $c = 0.8$).



Synthesis of (3*S*,6*R*,8*R*,*E*)-8-(benzyloxymethoxy)-3-methylundeca-1,9-dien-

6-ol (2.172): Activated magnesium (53 mg, 2.20 mmol) was added to a solution of sulfone (**2.176**) (260 mg, 0.55 mmol), TMEDA (1.7 ml, 11.02 mmol) in methanol (7 ml). The mixture was heated at 55 °C for 2 h, after all the magnesium granules had dissolved, additional Mg (72 mg, 2.98 mmol) and TMEDA (2.5 ml, 16.21 mmol) were added and the mixture was continuously stirred at 55 °C for 6 h. The methanol was removed under reduced pressure, the residue was diluted with ethyl acetate (50 ml), washed with water, dil.HCl and

brine then dried over anhydrous MgSO_4 . The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (hexane: ethyl acetate = 92: 8) on silica gel (7 g) to give the title compound as a colourless oil (120 mg, 95 %).

^1H NMR (400 MHz, CDCl_3) δ 1.00 (d, 3H, $J = 6.8$ Hz), 1.21-1.76 (m, 6H), 1.71 (dd, 3H, $J = 1.8, 6.4$ Hz), 2.09-2.17 (m, 1H), 3.22 (br. s, 1H), 3.78-3.80 (m, 1H), 4.30 (dt, 1H, $J = 4.6, 9.2$ Hz), 4.52 (d, 1H, $J = 11.9$ Hz), 4.67 (d, 1H, $J = 6.9$ Hz), 4.72 (d, 1H, $J = 11.9$ Hz), 4.83 (d, 1H, $J = 6.9$ Hz), 4.90-4.98 (m, 2H), 5.28 (ddq, 1H, $J = 15.6, 8.7, 1.8$ Hz), 5.64-5.74 (m, 2H), 7.27-7.34 (m, 5H).

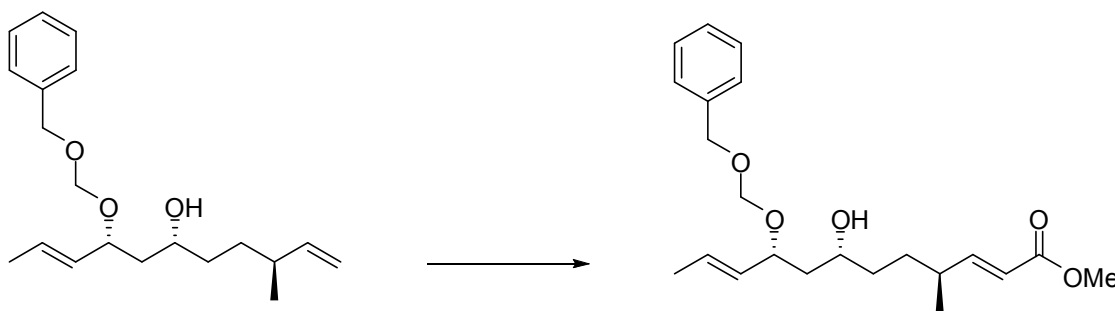
^{13}C NMR (100 MHz, CDCl_3): 17.6, 20.3, 32.2, 35.2, 37.8, 42.6, 69.7, 71.1, 77.4, 90.9, 112.7, 127.7, 127.9, 128.4, 130.2, 130.4, 137.7, 144.5.

m/z : 341 ($\text{M}+\text{Na}$) $^+$.

HRMS calculated for $\text{C}_{20}\text{H}_{30}\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 341.2093 found: 341.2096.

IR: 3504, 2938, 1165, 1098, 1025 cm^{-1}

$[\alpha]_D^{22} = +81.3$ (CHCl_3 , $c=1.1$).



Synthesis of (2*E*,4*S*,7*R*,9*R*,10*E*)-methyl 9-(benzyloxymethoxy)-7-hydroxy-4-methyl dodeca-2,10-dienoate (2.182): Hoveyda-Grubbs II catalyst (2.14) (4 mg, 0.005 mmol) was added to a solution of diene (2.172) (30 mg, 0.09 mmol) and methyl acrylate (17 μl , 0.19 mmol) in dichloromethane (2 ml). The system was maintained under a continuous nitrogen flow while stirring for 3 h at room

temperature. The TLC showing 3:1 of product and starting material and the reaction was stopped at this point, to prevent the unwanted epimerisation. Solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane: ethyl acetate = 85: 15) on silica gel (1 g) to give the title compound as a colourless oil (29 mg, 81 %, calculated according to the starting material recovered).

^1H NMR (400 MHz, CDCl_3) δ 1.05 (d, 3H, J = 6.7 Hz), 1.39-1.78 (m, 6H), 1.70 (dd, 3H, J = 1.6, 6.6 Hz), 2.27-2.34 (m, 1H), 3.26 (br. s, 1H), 3.72 (s, 3H), 3.74-3.78 (m, 1H), 4.29(dt, 1H, J = 4.4, 9.0 Hz), 4.52 (d, 1H, J = 11.2 Hz), 4.67 (d, 1H, J = 7.0 Hz), 4.71 (d, 1H, J = 11.1 Hz), 4.83 (d, 1H, J = 7.0 Hz), 5.21-5.31 (m, 1H), 5.69 (dq, 1H, J = 15.6, 6.5 Hz), 5.78 (d, 1H, J = 15.1 Hz), 6.86 (dd, 1H, J = 15.1, 8.0 Hz), 7.27-7.37 (m, 5H).

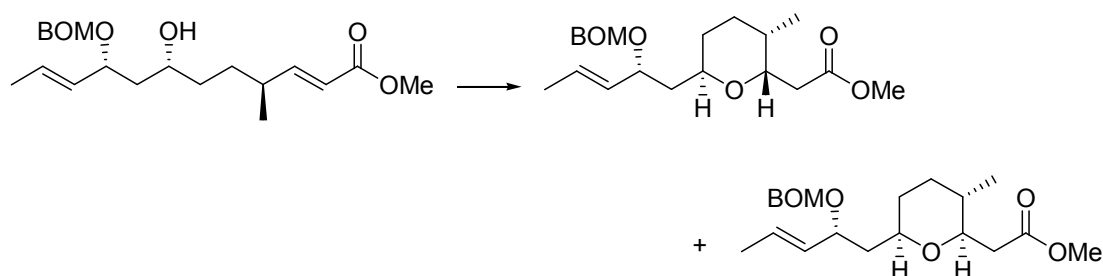
^{13}C NMR (100 MHz, CDCl_3): 17.6, 19.5, 31.6, 35.0, 36.5, 42.6, 51.4, 69.7, 70.9, 77.4, 90.9, 119.5, 127.8, 127.9, 128.4, 130.2, 130.4, 137.6, 154.6, 167.2.

m/z : 399.16 ($\text{M}+\text{Na}$) $^+$.

HRMS calculated for $\text{C}_{22}\text{H}_{33}\text{O}_5$ ($\text{M}+\text{H}$) $^+$: 377.2328 found: 377.2326.

IR: 2924, 1720, 1272, 1169, 1098, 1025 cm^{-1}

$[\alpha]_D^{22} = +109.2$ (CHCl_3 , $c = 0.9$).



Synthesis of methyl 2-((2S,3S,6R)-6-((R,E)-2-(benzyloxymethoxy) pent-3-enyl)-3-methyltetrahydro-2H-pyran-2-yl)acetate (2.189): The title compound (46 mg, 83 %, major) and the *cis* isomer (5 mg, 9%) were obtained from the

previous compound (**2.182**) by the method described for (**2.90**). The isomers were separated by column chromatography (hexane: ethyl acetate = 94: 6 for *cis* (**2.190**) and 93: 7 for *trans* isomer (**2.189**) on silica gel (2 g).

^1H NMR (400 MHz, CDCl_3) δ 0.82 (d, 3H, $J = 7.0$ Hz), 1.24-1.32 (m, 2H), 1.49 (ddd, 1H, $J = 4.4, 8.3, 13.3$ Hz), 1.61-1.70 (m, 2H), 1.71 (dd, 3H, $J = 0.9, 6.2$ Hz), 1.86-1.98 (m, 2H), 2.35 (dd, 1H, $J = 4.4, 14.7$ Hz), 2.63 (dd, 1H, $J = 9.7, 14.9$ Hz), 3.62-3.72 (m, 1H), 3.66 (s, 3H), 4.09-4.17 (m, 1H), 4.29-4.33 (m, 1H), 4.52 (d, 1H, $J = 11.8$ Hz), 4.66 (d, 1H, $J = 6.5$ Hz), 4.67 (d, 1H, $J = 11.6$ Hz), 4.78 (d, 1H, $J = 6.5$ Hz), 5.20-5.31 (m, 1H), 5.66 (dq, 1H, $J = 12.6, 6.1$ Hz), 7.28-7.35 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): 16.3, 17.8, 26.6, 30.1, 32.7, 33.2, 41.1, 51.7, 66.7, 69.3, 73.2, 74.2, 91.4, 127.5, 127.9, 128.3, 129.8, 130.8, 138.1, 172.4.

m/z: 400 (M+Na), 239, 221, 171.

HRMS calculated for $\text{C}_{22}\text{H}_{32}\text{O}_5\text{Na}$ (M+Na) $^+$: 399.2147 found: 399.2141.

IR: 2956, 1739, 1437, 1073, 1021 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +46.2$ (CHCl_3 , $c = 0.13$).

Data for Methyl 2-((2*R*,3*S*,6*R*)-6-((*R*,*E*)-2-(benzyloxymethoxy)pent-3-enyl)-3-methyltetrahydro-2*H*-pyran-2-yl)acetate (2.190**):** ^1H NMR (400 MHz, CDCl_3) δ 0.82 (d, 3H, $J = 6.5$ Hz), 1.14-1.25 (m, 1H), 1.29-1.40 (m, 2H), 1.45-1.59 (m, 2H), 1.73 (dd, 3H, $J = 1.3, 6.3$ Hz), 1.66-1.79 (m, 1H), 1.83-1.92 (m, 1H), 2.36 (dd, 1H, $J = 10.0, 14.6$ Hz), 2.61 (dd, 1H, $J = 3.1, 14.4$ Hz), 3.28-3.41 (m, 2H), 3.62 (s, 3H), 4.19 (dt, 1H, $J = 5.2, 8.8$ Hz), 4.53 (d, 1H, $J = 9.4$ Hz), 4.65 (d, 1H, $J = 7.1$ Hz), 4.67 (d, 1H, $J = 10.2$ Hz), 4.78 (d, 1H, $J = 6.9$ Hz), 5.25 (dd, 1H, $J = 10.0, 17.3$ Hz), 5.66 (dq, 1H, $J = 15.1, 6.4$ Hz), 7.27-7.35 (m, 5H).

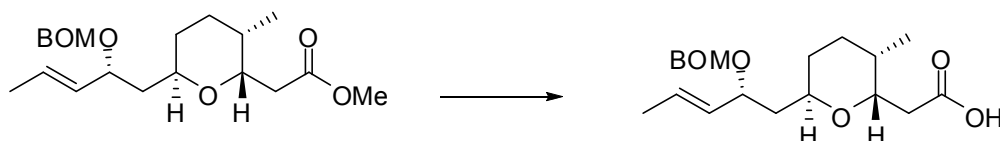
^{13}C NMR (100 MHz, CDCl_3): 17.6, 17.8, 32.0, 32.7, 35.4, 39.4, 41.8, 51.6, 69.3, 74.2, 74.4, 80.3, 91.3, 127.5, 127.9, 128.3, 130.1, 130.6, 138.2, 172.6.

m/z: 400 ($\text{M}+\text{Na}$) $^+$, 239, 221, 171.

HRMS calculated for $\text{C}_{22}\text{H}_{32}\text{O}_5\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 399.2147 found: 399.2143.

IR: 2956, 1739, 1437, 1073, 1021 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +9.6$ (CHCl_3 , $c = 0.5$).



Synthesis of 2-(2S,3S,6R)-6-(R,E)-2-(benzyloxy-methoxy)pent-3-enyl)-3-methyl tetrahydro-2H-pyran-2-yl)acetic acid (2.191): LiOH (17 mg, 0.40 mmol) was added to a solution of ester (**2.189**) (50 mg, 0.13 mmol) in a (1:1:1) mixture of THF (0.5 ml), water (0.5 ml) and methanol (0.5 ml). The mixture was stirred for 6 h at room temperature, and then acidified to pH 2 with dil.HCl. The mixture was extracted with ethyl acetate (10 ml x 2), the combined organic layers were washed with water and brine and dried over anhydrous MgSO_4 . The solvents were removed *in vacuo* to obtain the title compound as a colourless oil (48 mg, 99 %), which was used in the next step without purification.

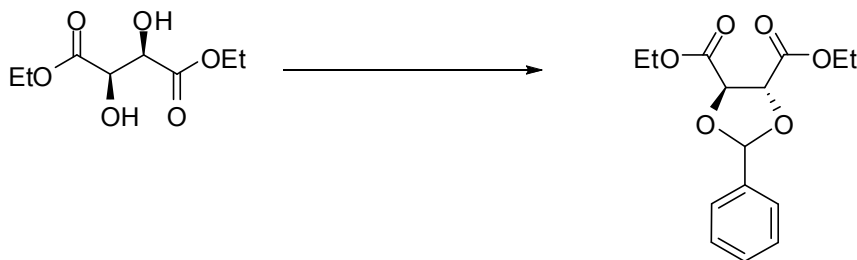
^1H NMR (400 MHz, CDCl_3) δ 0.84 (d, 3H, $J = 6.9$ Hz), 1.19-1.36 (m, 3H), 1.52 (ddd, 1H, $J = 4.9, 7.7, 13.6$ Hz), 1.62-1.76 (m, 1H), 1.70 (d, 3H, $J = 6.5$ Hz), 1.87-2.01 (m, 2H), 2.36 (dd, 1H, $J = 3.9, 15.5$ Hz), 2.65 (dd, 1H, $J = 10.3, 15.3$ Hz), 3.66-3.76 (m, 1H), 4.14 (dt, 1H, $J = 14.0, 7.6$ Hz), 4.26-4.32 (m, 1H), 4.53 (d, 1H, $J = 11.9$ Hz), 4.66 (d, 1H, $J = 7.0$ Hz), 4.67 (d, 1H, $J = 11.5$ Hz), 4.78 (d, 1H, $J = 6.9$ Hz), 5.20-5.30 (m, 1H), 5.68 (dq, 1H, $J = 15.2, 6.1$ Hz), 7.27-7.35 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): 16.0, 17.8, 26.3, 29.7, 30.9, 32.7, 40.7, 67.5, 69.4, 72.8, 74.4, 91.4, 127.6, 127.9, 128.4, 130.4, 130.6, 138.0, 174.0.

m/z : 363 (M)⁺, 279, 210.

IR: 2922, 1711, 1025, 969 734 cm^{-1} .

HRMS calculated for $\text{C}_{21}\text{H}_{31}\text{O}_5$ ($\text{M}+\text{H}$)⁺: 363.2171 found: 363.2177.



Synthesis of (4*R*,5*R*)-diethyl 2-phenyl-1,3-dioxolane-4,5-dicarboxylate

(3.19): A procedure reported in the literature ¹⁸⁴ was modified as follows: Benzaldehyde (4.93 ml, 48.54 mmol) and few crystals of *p*-TsOH were sequentially added to a solution of diethyl tartrate (**3.18**) (4 g, 19.42 mmol) in toluene (25 ml). The mixture was heated at reflux for 12 h with a Dean-Stark trap to remove water. The mixture was cooled to room temperature, diluted with diethyl ether (50 ml), washed with aq. NaHCO_3 solution and brine. The organic layer was dried over anhydrous MgSO_4 , the solvents were removed under reduced pressure to afford the title compound as a pale yellow solid (5.7 g, 99 %), which was used in the next step without purification.

^1H NMR (300 MHz, CDCl_3) δ 1.31 (t, 3H, $J = 7.1$ Hz), 1.35 (t, 3H, $J = 7.1$ Hz), 4.28 (q, 2H, $J = 7.1$ Hz), 4.33 (q, 2H, $J = 7.1$ Hz), 4.83 (d, 1H, $J = 4.0$ Hz), 4.95 (d, 1H, $J = 4.0$ Hz), 6.16(s, 1H), 7.39-7.59 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 14.1, 62.0, 62.0, 77.3, 77.6, 106.7, 127.2, 128.3, 129.9, 135.5, 169.0, 169.6.

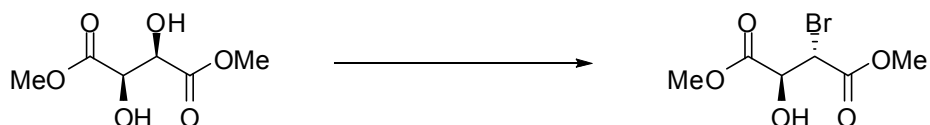
m/z : 317 ($\text{M}+\text{Na}$)⁺, 295 (M)⁺, 260, 242.

HRMS calculated for $C_{15}H_{19}O_6$ ($M+H$)⁺: 295.1182 found: 295.1187.

IR: 2985, 1739, 1643, 1460, 1372, 1217, 1026 cm^{-1}

$[\alpha]_D^{22} = -31.5$ (CH_2Cl_2 , $c = 1$).

All data are consistent with that of literature.¹²⁶



Synthesis of (2S, 3S)-dimethyl 2-bromo-3-hydroxysuccinate (3.26a): A

solution of HBr (45 % in acetic acid, 42.1 ml, 337.08 mmol) was added dropwise to L-dimethyl tartrate (**3.13**) (15 g, 84.30 mmol) with external cooling. The mixture was slowly warmed to room temperature and stirring was continued for 12 h, and then poured onto crushed ice. The mixture was extracted with diethyl ether (3 x 200 ml), the organic layers were washed with water, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, the residue was diluted with methanol (200 ml) and acetyl chloride (3 ml, 42.14 mmol) was added. The mixture was heated at reflux for 4 h, and then cooled to room temperature. The methanol was removed under reduced pressure. The residue was passed through a silica gel column (40:60 Ethyl acetate/Hexane) to give the title compound as a colourless oil (16.3 g, 80%).

1H NMR (400 MHz, $CDCl_3$) δ 3.53 (d, 1H, $J = 11.6$ Hz), 3.81 (s, 3H), 3.82 (s, 3H), 4.66 (dd, 1H, $J = 4.5, 7.5$ Hz), 4.70 (d, 1H, $J = 4.5$ Hz).

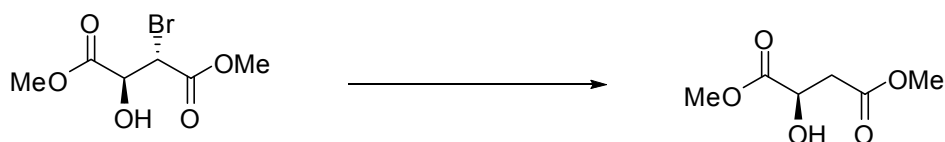
m/z : 263 ($M+Na$)⁺, 241 (M)⁺, 205, 173.

HRMS calculated for $C_9H_{10}O_5^{81}Br$ ($M+H$)⁺: 278.9695 found: 278.9691.

IR: 3474, 2945, 1301, 1022, 736, 698 cm^{-1} .

$[\alpha]_D^{22} = -23.5$ (MeOH, $c = 0.9$).

All data are consistent with that of literature.¹³⁰



Synthesis of (R)-dimethyl 2-hydroxysuccinate (3.12): Activated zinc (81 mg, 1.25 mmol) and water (2 drops) were added to a solution of bromide (**3.26a**) (100 mg, 0.42 mmol) in acetone (2 ml). The mixture was heated to 50 °C for 1 h, then it was filtered through a celite pad. The filtrate was dried over anhydrous Na₂SO₄. The acetone was removed under reduced pressure to give the title compound as a colourless oil (68 mg, 99 %), which was used in the next step without purification.

¹H NMR (400 MHz, CDCl₃) δ 2.76 (dd, 1H, *J* = 5.0, 16.9 Hz), 2.84 (dd, 1H, *J* = 4.6, 17.0 Hz), 3.36 (br s, 1H), 3.67 (s, 3H), 3.77 (s, 3H), 4.48 (dd, 1H, *J* = 4.6, 4.6 Hz).

¹³C NMR (100 MHz, CDCl₃) δ 38.3, 51.9, 52.7, 67.1, 170.9, 173.7.

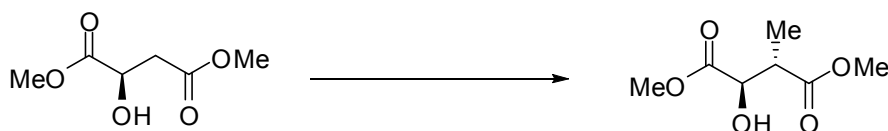
m/z : 163 (M+H)⁺, 131.

HRMS calculated for C₆H₁₁O₅ (M+H)⁺: 163.0606 found: 163.0608.

IR: 1728, 1438, 1165, 1043 cm⁻¹.

[α]_D²² = +8.8 (CH₂Cl₂, *c* = 2.2).

Data are consistent with that of literature.¹⁸⁵



Synthesis of (2R, 3S)-dimethyl 2-hydroxy-3-methylsuccinate (3.11) : Lithium diisopropylamide (LDA) was generated by reacting diisopropylamine (2.2 ml, 16.67 mmol) in THF (20 ml) with ⁿBuLi (1.6M in hexane, 10.4 ml, 16.67 mmol) under nitrogen at -78 °C over 30 minutes. A solution of (R)-dimethyl malate (**3.12**) (1 g, 6.17 mmol) in THF (5 ml) was added dropwise to LDA at -78 °C, the

mixture was stirred for 30 min at -30 °C, then cooled to -78 °C once again. Iodomethane (1.9 ml, 30.86 mmol) was added dropwise to the mixture and it was slowly warmed to -10 °C. The mixture was stirred for 2 h, and then quenched with a solution of acetic acid (1.4 ml, 24.69 mmol) in diethyl ether (10 ml) at -40 °C. The reaction mixture was warmed to room temperature, and diluted with dichloromethane (80 ml). The solution was washed with water and aq. NaHCO₃, and dried over anhydrous Na₂SO₄. The solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane: ethyl acetate = 85:5) on silica gel (20 g) to give the title compound as a colourless oil (0.85 g, 78 %).

¹H NMR (300 MHz, CDCl₃) δ 1.30 (d, 3H, *J* = 7.3 Hz), 3.04 (dq, 1H, *J* = 3.6, 7.3 Hz), 3.14 (d, 1H, *J* = 6.6 Hz), 3.69 (s, 3H), 3.80 (s, 3H), 4.27 (dd, 1H, *J* = 3.7, 6.6 Hz).

¹³C NMR (100 MHz, CDCl₃) δ 13.0, 43.1, 52.0, 52.7, 72.4, 173.4, 173.6.

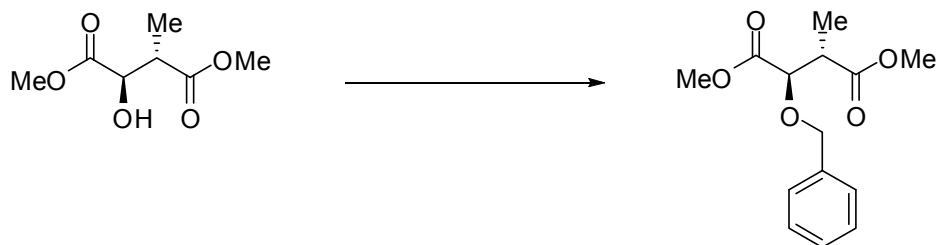
m/z: 177 (M+H), 145.

HRMS calculated for C₇H₁₃O₅ (M+H)⁺: 177.0763 found: 177.0766.

IR: 3487, 1731, 1438, 1205, 1141 cm⁻¹.

[α]_D²² = +6.3 (MeOH, c = 1.2).

Data are consistent with literature.¹³³



Synthesis of (2*R*, 3*S*)-dimethyl 2-(benzyloxy)-3-methylsuccinate (3.62): Bn-
OPT (380 mg, 1.14 mmol) and MgO (46 mg, 1.14 mmol) were added to a

solution of alcohol (**3.11**) (100 mg, 0.57 mmol) in dichloroethane (1 ml). The mixture was heated at 80 °C for 20 h, cooled to room temperature and then filtered through celite washing with dichloromethane. The solvents were removed *in vacuo*, and the residue was purified by flash column chromatography (hexane: ethyl acetate = 90:10) on silica gel (3 g) to give the title compound as a colourless oil (147 mg, 96 %).

^1H NMR (300 MHz, CDCl_3) δ 1.10 (d, 3H, $J = 7.2$ Hz), 2.94-3.04 (m, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 4.16 (d, 1H, $J = 7.0$ Hz) 4.46 (d, 1H, $J = 11.7$ Hz), 4.71 (d, 1H, $J = 11.7$ Hz), 7.24-7.35 (m, 5H).

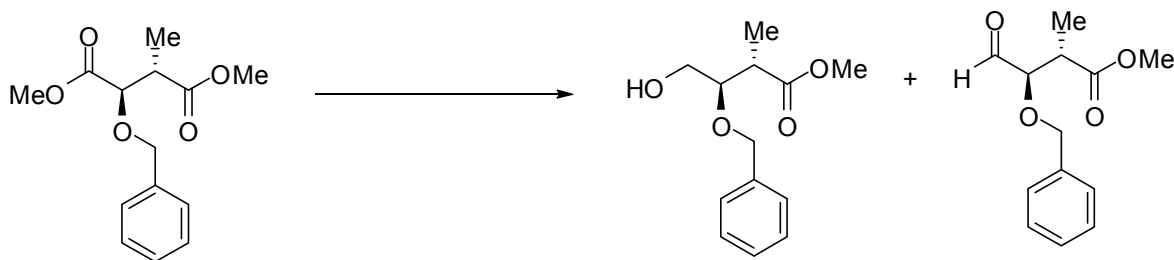
^{13}C NMR (75 MHz, CDCl_3) δ 12.7, 42.7, 51.8, 51.9, 72.9, 79.7, 127.8, 128.0, 128.2, 137.0, 171.2, 173.2.

$m/z = 289$ ($\text{M} + \text{Na}$) $^+$, 267 (M) $^+$.

HRMS calculated for $\text{C}_{14}\text{H}_{19}\text{O}_5$ ($\text{M} + \text{H}$) $^+$: 267.1232 found: 267.1231.

IR: 2952, 1734, 1454, 1266, 1166, 1001 cm^{-1} .

$[\alpha]_{\text{D}}^{22} = +73.8$ (MeOH, $c = 1.0$).



Synthesis of (2S, 3R)-methyl 3-(benzyloxy)-4-hydroxy-2-methyl butanoate

(3.63): $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ [prepared by heating dibromoethane (20 μl , 0.25 mmol) and Mg (6 mg, 0.25 mmol) in diethyl ether (4 ml)] was added to a solution of diester (**3.62**) (50 mg, 0.19 mmol) in dichloromethane (3 ml) at 0 °C. The mixture was stirred for 1 h at room temperature, and then cooled to -40 °C. DIBAL-H (1M in cyclohexane, 0.5 ml, 0.47 mmol) was added slowly over 2 h using a syringe pump. The mixture was stirred for 8 h at -40 °C. Methanol (4 ml) was

added dropwise, followed by an aqueous solution of Rochelle's salt (2 ml). The mixture was warmed to room temperature, filtered through celite and extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed with water and brine and dried over anhydrous MgSO₄. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (hexane: ethyl acetate = 78:22) on silica gel (2 g) to give the title compound as a colourless oil (35 mg, 82 %) and the aldehyde (**3.64**) (4 mg, 9%).

¹H NMR (400 MHz, CDCl₃) δ 1.17 (d, 3H, *J* = 7.1 Hz), 1.86 (dd, 1H, *J* = 4.9, 7.4 Hz), 2.88-2.94 (m, 1H), 3.60 (ddd, 1H, *J* = 3.9, 7.4, 11.6 Hz), 3.69 (s, 3H), 3.73 (ddd, 1H, *J* = 3.9, 3.9, 7.9 Hz), 3.78 (ddd, 1H, *J* = 3.9, 7.8, 11.8 Hz), 4.56 (d, 1H, *J* = 11.4 Hz) 4.60 (d, 1H, *J* = 11.7 Hz), 7.28-7.35 (m, 5H).

¹³C NMR (75 MHz, CDCl₃) δ 12.9, 41.1, 51.6, 60.7, 72.4, 81.2, 127.7, 127.8, 128.3, 137.9, 175.3.

m/z: 240 (M+H)⁺, 219.

HRMS calculated for C₁₃H₁₉O₄ (M+H)⁺: 239.1283 found: 239.1285.

IR: 3434, 2949, 1731, 1454, 1060, 1027 cm⁻¹

[α]_D²² = +46.6 (MeOH, *c* = 0.8).

Data for (2*S*, 3*R*)-methyl 3-(benzyloxy)-2-methyl-4-oxobutanoate (3.64**):** ¹⁸⁶

¹H NMR (400 MHz, CDCl₃) δ 1.21 (d, 3H, *J* = 7.2 Hz), 2.97-3.00 (m, 1H), 3.70 (s, 3H), 3.85 (d, 1H, *J* = 5.0 Hz), 4.61 (d, 1H, *J* = 11.9 Hz) 4.71 (d, 1H, *J* = 11.8 Hz), 7.32-7.36 (m, 5H), 9.69 (br s, 1H)

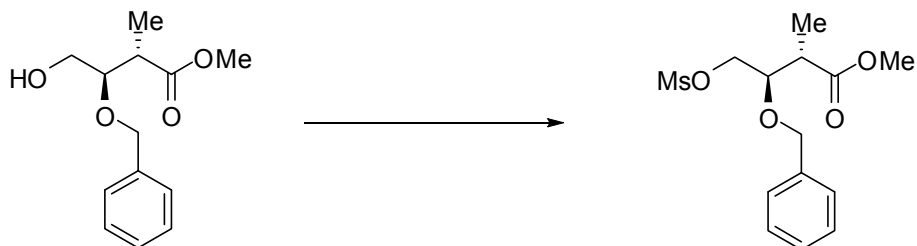
¹³C NMR (75 MHz, CDCl₃) δ 12.7, 41.6, 52.0, 73.4, 84.2, 128.0, 128.1, 128.5, 136.7, 172.9, 202.6.

m/z: 259 (M+Na)⁺, 237 (M+H)⁺, 219.

HRMS calculated for C₁₃H₁₆O₄Na (M+Na)⁺: 259.0946 found: 259.0940.

IR: 2923, 1720, 1687, 1031, 807 cm⁻¹.

$[\alpha]_D^{22} = +9.5$ (CH₂Cl₂, c = 0.9).



Synthesis of (2S, 3R)-methyl 3-(benzyloxy)-2-methyl-4-(methylsulfonyloxy)butanoate (3.66):

The title compound (94 %) was obtained as a colourless oil from the previous compound (**3.63**) by the method described for (**2.168**).

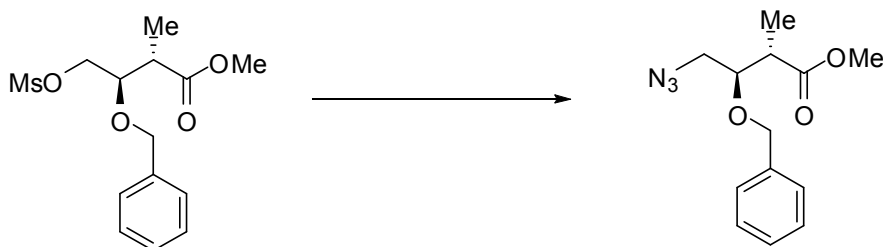
¹H NMR (300 MHz, CDCl₃) δ 1.19 (d, 3H, *J* = 6.8 Hz), 2.82-2.89 (m, 1H), 2.98 (s, 3H), 3.69 (s, 3H), 3.90 (ddd, 1H, *J* = 2.7, 4.1, 7.3 Hz), 4.25 (dd, 1H, *J* = 4.6, 11.0 Hz), 4.49 (dd, 1H, *J* = 3.2, 11.4 Hz), 4.56 (d, 1H, *J* = 11.5 Hz), 4.66 (d, 1H, *J* = 11.0 Hz), 7.27-7.36 (m, 5H).

¹³C NMR (75 MHz, CDCl₃) δ 12.9, 37.6, 41.5, 51.9, 68.2, 72.9, 78.5, 127.7, 127.9, 128.4, 137.3, 174.2.

m/z = 339 (M+Na)⁺, 317 (M)⁺, 239, 227, 131.

HRMS calculated for C₁₄H₂₁O₆S (M+H)⁺: 317.1059 found: 317.1058.

$[\alpha]_D^{22} = +36.9$ (MeOH, c = 1.2).



Synthesis of (2S, 3R)-methyl 4-azido-3-(benzyloxy)-2-methylbutanoate (3.67):

Sodium azide (21 mg, 0.33 mmol) was added to a solution of mesylate (**3.66**) (52 mg, 0.17 mmol) in DMF (1.5 ml). The mixture was heated at 60 °C for

8 h. The mixture was diluted with ethyl acetate (20 ml), the organic layers were washed with water (2 x 5 ml) and brine, and dried over anhydrous MgSO₄. The solvents were removed *in vacuo* and the residue (42 mg, 93 %) was used in the next step without purification.

¹H NMR (300 MHz, CDCl₃) δ 1.14 (d, 3H, *J* = 7.2 Hz), 2.85-2.92 (m, 1H), 3.30 (dd, 1H, *J* = 5.7, 13.2 Hz), 3.44 (dd, 1H, *J* = 3.2, 13.2 Hz), 3.67 (s, 3H), 3.83 (ddd, 1H, *J* = 3.2, 5.7, 8.8 Hz), 4.57 (d, 1H, *J* = 11.2 Hz), 4.66 (d, 1H, *J* = 11.2 Hz), 7.29-7.35 (m, 5H).

¹³C NMR (100 MHz, CDCl₃) δ 12.7, 42.0, 51.2, 51.9, 72.9, 79.9, 127.8, 127.9, 128.4, 137.6, 174.6.

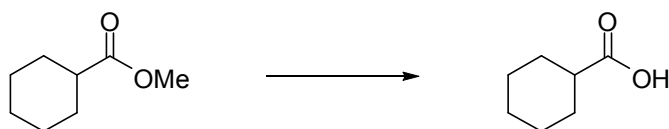
m/z: 286 (M+Na)⁺, 263 (M+H)⁺, 236.

HRMS calculated for C₁₃H₁₈ N₃O₃ (M+H)⁺: 264.1348 found: 264.1350.

IR: 3458, 2102, 1732, 1643, 1265, 1172 cm⁻¹

[α]_D²² = + 33.8 (CH₂Cl₂, *c* = 0.6).

All data are consistent with that of literature.¹³⁵



Synthesis of cyclohexanecarboxylic acid (3.75): The title compound (0.72 g, 99 %) was obtained as a colourless solid from the corresponding methyl ester by the method described for (2.191).

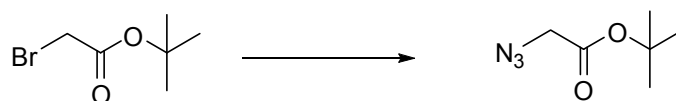
¹H NMR (400 MHz, CDCl₃): 1.19-1.34 (m, 3H), 1.40-1.50 (m, 2H), 1.62-1.66 (m, 1H), 1.74-1.78 (m, 2H), 1.91-1.96 (m, 2H), 2.33 (tt, 1H, *J* = 3.7, 11.5 Hz), 10.96 (br s, 1H).

¹³C NMR (100 MHz, CDCl₃): 25.3, 25.7, 28.8, 42.9, 182.7.

m/z: 151 (M+Na)⁺, 129 (M+H)⁺.

HRMS calculated for $C_7H_{13}O_2$ (M+H)⁺: 129.0916 found: 129.0917.

IR: 3042, 1697, 1256, 1212, 894 cm^{-1} .



Synthesis of tert-butyl 2-azidoacetate (3.76): Sodium azide (1.34 g, 20.51 mmol) was added to a solution of tert-butyl-bromoacetate (2 g, 10.26 mmol) in DMF (34 ml). The mixture was heated at 80 °C for 2 h, cooled to room temperature and diluted with diethyl ether and hexane (1:1 mixture, 100 ml). The combined organic layers were washed with dilute HCl and water and dried over anhydrous Na_2SO_4 . The solvents were removed *in vacuo* to give the title compound as a pale yellow oil (1.6 g, 99 %) which was used in the next step without purification.

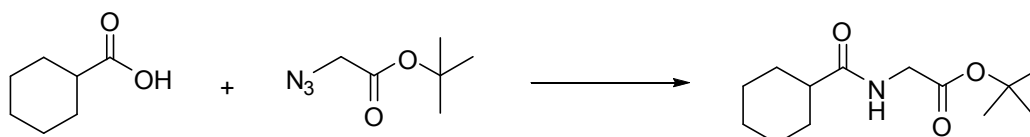
¹H NMR (500 MHz, $CDCl_3$): 3.74 (s, 2H), 1.50 (s, 9H).

¹³C NMR (125 MHz, $CDCl_3$): 28.0, 50.9, 83.0, 167.4.

m/z: 180 (M+Na)⁺, 158 (M+H)⁺, 130.

HRMS calculated for $C_6H_{12}N_3O_2$ (M+H)⁺: 158.0930 found: 158.0930.

IR: 2983, 2103, 1737, 1223, 1148 cm^{-1} .



Synthesis of tert-butyl 2-(cyclohexanecarboxamido)acetate (3.77): A literature procedure¹⁸⁷ was modified as follows: tri-*n*-butylphosphine (10 % soln. in hexane, 1.5 ml, 0.51 mmol) was added to a solution of azide (3.76) (61 mg, 0.39 mmol) in dichloromethane (4 ml). The mixture was stirred until gas (N_2) evolution ceased, then cyclohexanecarboxylic acid (3.75) (50 mg, 0.39 mmol) in

dichloromethane (1 ml) was added. The mixture was heated at reflux for 8 h. The solvents were removed *in vacuo* and the residue was purified by flash column chromatography (hexane: ethyl acetate = 80:20) on silica gel (1 g) to give the title compound as a colourless oil (75 mg, 80 %).

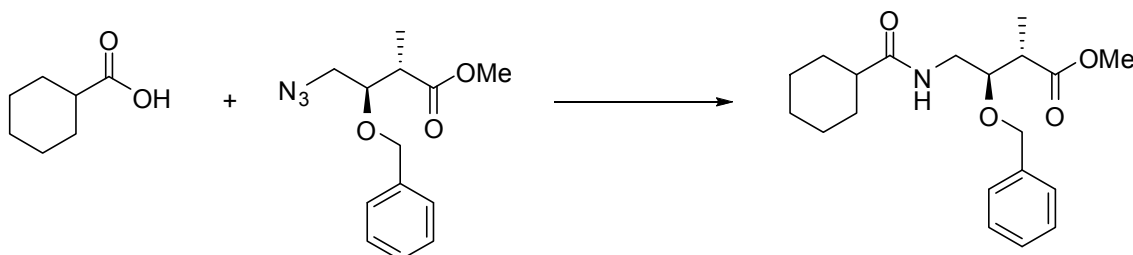
^1H NMR (500 MHz, CDCl_3) δ 1.20-1.30 (m, 3H), 1.40-1.47 (m, 10H), 1.67-1.71 (m, 2H), 1.77-1.81 (m, 2H), 1.87-1.90 (m, 2H), 2.11-2.16 (m, 1H), 3.92 (t, 2H, $J = 4.9$ Hz), 5.96 (br s, 1H).

^{13}C NMR (100 MHz, CDCl_3): 25.6, 25.7, 28.0, 29.5, 41.9, 42.2, 82.3, 169.4, 176.1.

m/z : 264 ($\text{M}+\text{Na}$) $^+$, 242 ($\text{M}+\text{H}$) $^+$, 186.

HRMS calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 242.1756 found: 242.1756.

IR: 1704, 1644, 1538, 1156, 844 cm^{-1} .

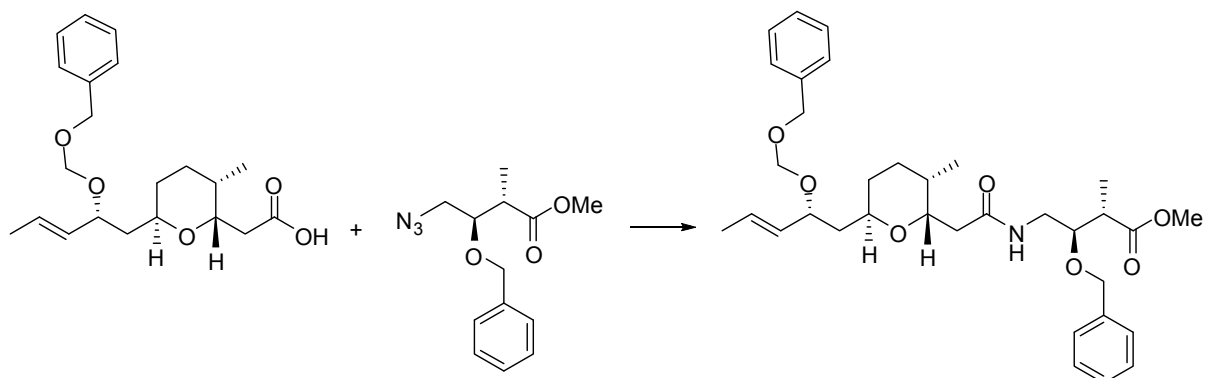


Synthesis of (2S,3R)-methyl 3-(benzyloxy)-4-(cyclohexanecarboxamido)-2-methylbutanoate (3.78): The title compound (22 mg, 69 %) was obtained as a colourless oil from cyclohexanecarboxylic acid and the corresponding azide (3.67) by the method described for (3.75).

^1H NMR (400 MHz, CDCl_3) δ 1.16 (d, 3H, $J = 7.4$ Hz), 1.22-1.39 (m, 6H), 1.55-1.68 (m, 2H), 1.71-1.81 (m, 2H), 1.96 (tt, 1H, $J = 3.2, 15.1$ Hz), 2.67-2.74 (m, 1H), 3.38 (ddd, 1H, $J = 3.8, 3.8, 14.2$ Hz), 3.50 (ddd, 1H, $J = 5.0, 6.9, 14.2$ Hz), 3.69(s, 3H), 3.73-3.79 (m, 1H), 4.52 (d, 1H, $J = 11.4$ Hz), 4.57 (d, 1H, $J = 11.5$ Hz), 5.64 (br s, 1H), 7.29-7.36 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): 14.2, 22.7, 25.8, 29.8, 38.6, 42.3, 45.6, 51.9, 72.6, 79.9, 128.0, 128.1, 128.6, 138.1, 175.1, 176.5.

m/z: 370 ($\text{M}+\text{Na}$) $^+$, 348 ($\text{M}+\text{H}$) $^+$.



Synthesis of (2S,3R)-methyl 3-(benzyloxy)-4-(2-((2S,3S,6R)-6-((R,E)-2-(benzyloxymethoxy)pent-3-enyl)-3-methyltetrahydro-2H-pyran-2-yl)

acetamido)-2-methylbutanoate (3.70): The literature procedure ¹⁵⁰ was modified as follows: PyBOP (12 mg, 0.02 mmol) and NMM (5 μl , 0.04 mmol) were added to a solution of acid (**2.191**) (8 mg, 0.02 mmol) in dichloromethane (1 ml) at 0 $^{\circ}\text{C}$. The mixture was stirred for 30 minutes, then added to a solution of azide (**3.67**) (10 mg, 0.04 mmol) and tributylphosphine (10% solution in hexane, 0.2 ml, 0.07 mmol) in dichloromethane (1 ml) under nitrogen at -78 $^{\circ}\text{C}$. The above mixture was warmed to -20 $^{\circ}\text{C}$ and stirred for 4 h. The reaction mixture was diluted with ethyl acetate; the organic layers were washed with water, aq. NaHCO_3 solution and brine, dried over anhydrous Na_2SO_4 . The solvents were removed *in vacuo*. The residue was purified by column chromatography on silica gel (0.5 g) (hexane: ethyl acetate = 80:20) to obtain the title compound as a colourless oil (9 mg, 71 %).

^1H NMR (400 MHz, CDCl_3): δ 0.83 (d, 3H, $J = 7.3$ Hz), 1.15 (d, 3H, $J = 7.4$ Hz), 1.40-1.48 (m, 2H), 1.49-1.65 (m, 2H), 1.67 (dd, 3H, $J = 1.4, 6.5$ Hz), 1.73-1.81 (m, 1H), 1.90-1.97 (m, 2H), 2.16 (dd, 1H, $J = 2.7, 16.0$ Hz), 2.56 (dd, 1H, $J =$

10.5, 15.6 Hz), 2.70-2.78 (m, 1H), 3.43-3.55 (m, 2H), 3.66 (s, 3H), 3.74-3.78 (m, 2H), 4.04-4.10 (m, 1H), 4.11-4.15 (m, 1H), 4.48 (d, 1H, $J = 11.9$ Hz), 4.52 (d, 1H, $J = 11.4$ Hz), 4.58 (d, 1H, $J = 11.4$ Hz), 4.61 (d, 1H, $J = 6.9$ Hz), 4.66 (d, 1H, $J = 11.0$ Hz), 4.74 (d, 1H, $J = 11.9$ Hz), 5.23 (ddq, 1H, $J = 15.1, 8.2, 1.8$ Hz), 5.61 (dq, 1H, $J = 15.6, 6.9$ Hz), 6.79 (br t, 1H, $J = 3.9$ Hz), 7.27-7.35 (m, 10H).

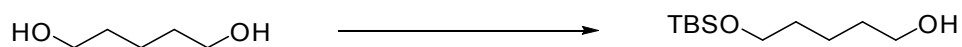
^{13}C NMR (100 MHz, CDCl_3): 13.2, 13.6, 17.7, 26.4, 29.7, 32.9, 33.9, 38.7, 40.7, 42.1, 51.7, 66.8, 69.5, 72.4, 73.1, 74.1, 79.7, 91.5, 127.6, 127.7, 127.8, 127.9, 128.3, 128.4, 129.5, 131.0, 138.0, 171.8, 175.1.

m/z : 581.98 ($\text{M}+\text{H}$) $^+$.

HRMS calculated for $\text{C}_{34}\text{H}_{48}\text{NO}_7$ ($\text{M}+\text{H}$) $^+$: 582.3431 found: 582.3430.

IR: 2953, 1737, 1638, 1280, 1095, 1040 cm^{-1} .

$[\alpha]_{\text{D}} = +72.3$ (CHCl_3 , $c = 0.2$).



Synthesis of 5-(*tert*-butyldimethylsilyloxy) pentan-1-ol (3.92): A solution of TBSCl (2.89 g, 19.20 mmol) in THF (10 ml) was added dropwise to a stirred solution of 1,5-pentanediol (10 g, 96.00 mmol) in THF (10 ml) under nitrogen at 0 °C. The reaction mixture was stirred for 3 h at room temperature then quenched by addition of satd. aq. NH_4Cl and subsequently extracted with diethyl ether (5 x 100 ml). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 . Solvents were removed under reduced pressure to give the title compound as colourless oil (3.7 g, 89%) which was used in next step without purification.

^1H NMR (300 MHz, CDCl_3) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.35-1.44 (m, 2H), 1.50-1.63 (m, 4H), 3.61 (t, 2H, $J = 6.5$ Hz), 3.65 (t, 2H, $J = 6.5$ Hz).

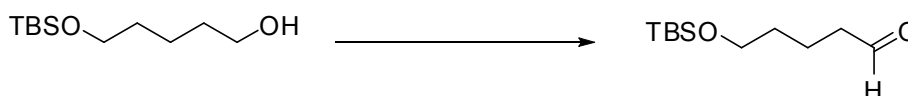
^{13}C NMR (75 MHz, CDCl_3): -5.3, 18.4, 22.0, 26.0, 32.4, 32.5, 62.9, 63.1

m/z: 219 (M+H)⁺, 193.

HRMS calculated for C₁₁H₂₇O₂Si (M+H)⁺: 219.1780 found: 219.1780.

IR: 3401, 1253, 1096, 832, 773 cm⁻¹.

All data are consistent with that of literature.¹⁸⁸



Synthesis of 5-(*tert*-butyldimethylsilyloxy)pentanal (3.90): IBX (1.67 g, 5.96 mmol) was dissolved in DMSO (9 ml), and the mixture was stirred until a clear solution was obtained (~ 10 min). Alcohol (**3.92**) (1 g, 4.58 mmol) in DMSO (2 ml) was added to the mixture and stirred for 3 h. The mixture was diluted with ethyl acetate (50 ml) and the organic layers were washed with water (3 x 10 ml), aq. NaHCO₃ solution and brine, and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (15:85 Ethyl acetate/Hexane) to give the title compound as a colourless oil (0.89 g, 90 %).

¹H NMR (300 MHz, CDCl₃) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.50-1.61 (m, 2H), 1.63-1.75 (m, 2H), 2.38 (t, 1H, *J* = 7.5 Hz), 2.45 (dt, 1H, *J* = 1.7, 7.1 Hz), 3.62 (t, 2H, *J* = 6.2 Hz), 9.76 (br t, 1H, *J* = 1.7 Hz).

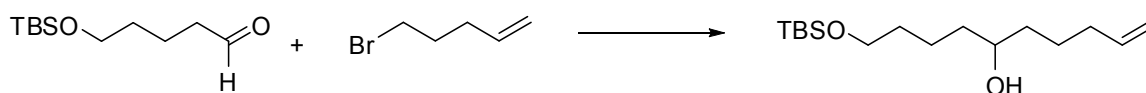
¹³C NMR (75 MHz, CDCl₃): -5.4, 18.6, 21.2, 25.9, 32.1, 43.6, 62.6, 202.8.

m/z: 240 (M+Na)⁺, 217 (M+H)⁺, 195.

HRMS calculated for C₁₁H₂₅O₂Si (M+H)⁺: 217.1624 found: 217.1624.

IR: 1734, 1254, 1200, 835 cm⁻¹.

All data are consistent with that of literature.¹⁸⁸



Synthesis of 1-(*tert*-butyldimethylsilyloxy)dec-9-en-5-ol (3.89): A small amount of iodine crystals (~2 mg) were added to magnesium (67 mg, 2.77 mmol) in dry THF (4 ml) under nitrogen. The mixture was heated at reflux for 10 min. 5-Bromo-1-pentene (**3.91**) (0.25 ml, 2.08 mmol) was added dropwise and the mixture was heated at reflux for 30 minutes. The Grignard reagent was added dropwise (via a cannula) to a solution of aldehyde (**3.90**) (300 mg, 1.39 mmol) in THF (5 ml) at 0 °C. The mixture was stirred for 2 h at room temperature then quenched with satd. aq. NH₄Cl solution. The mixture was extracted with diethyl ether (3 x 20 ml), the combined organic layers were washed with water, brine and dried over anhydrous MgSO₄. The solvents were removed *in vacuo*. The residue was purified by a silica gel column (5:95 Ethyl acetate/Hexane) to give the title compound as colourless oil (348 mg, 88 %).

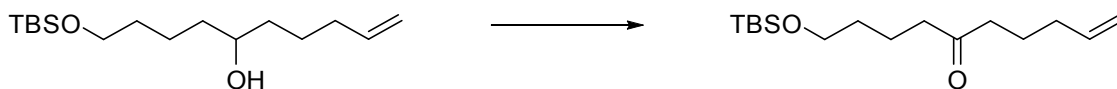
¹H NMR (300 MHz, CDCl₃) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.37-1.64 (m, 10H), 2.07 (dt, 2H, *J* = 5.2, 5.2 Hz), 3.58-3.64 (m, 1H), 3.61 (t, 2H, *J* = 6.2 Hz), 4.95 (dd, 1H, *J* = 1.5, 10.2 Hz), 5.01 (dd, 1H, *J* = 1.7, 17.2 Hz), 5.74-5.87 (m, 1H).

¹³C NMR (75 MHz, CDCl₃): -5.3, 18.4, 21.9, 24.9, 26.0, 32.7, 33.7, 36.8, 37.2, 63.1, 71.7, 114.6, 138.7.

m/z: 287 (M+H)⁺.

HRMS calculated for C₁₆H₂₅O₂Si (M+H)⁺: 287.1624 found: 287.1621.

IR: 2930, 1253, 1097, 833 cm⁻¹.



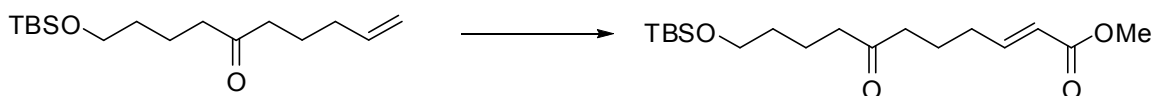
Synthesis of 1-(*tert*-butyldimethylsilyloxy)dec-9-en-5-one (3.93): The title compound (310 mg, 63 %) was obtained as a colourless oil from the alcohol (3.89) by the method described for (3.90).

^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.47-1.54 (m, 2H), 1.59-1.70 (m, 4H), 2.03 (dt, 2H, $J = 5.6, 5.6$ Hz), 2.38-2.43 (m, 4H), 3.60 (t, 2H, $J = 5.1$ Hz), 4.97 (dd, 1H, $J = 1.5, 10.8$ Hz), 5.01 (dd, 1H, $J = 2.0, 18.0$ Hz), 5.72-5.80 (m, 1H).

m/z : 307 ($\text{M}+\text{Na}$) $^+$, 285 ($\text{M}+\text{H}$) $^+$, 233, 193.

HRMS calculated for $\text{C}_{16}\text{H}_{33}\text{O}_2\text{Si}$ ($\text{M}+\text{H}$) $^+$: 285.2250 found: 285.2246.

IR: 2928, 1712, 1254, 1099, 908 cm^{-1} .



Synthesis of (*E*)-methyl 11-(*tert*-butyldimethylsilyloxy)-7-oxoundec-2-enoate (3.86): The title compound (260 mg, 94 %) was obtained as colourless oil from the alkene (3.93) by the method described for (2.89).

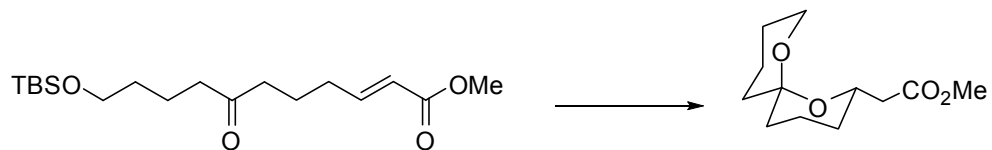
^1H NMR (400 MHz, CDCl_3) δ -0.04 (s, 6H), 0.89 (s, 9H), 1.45-1.65 (m, 4H), 1.69-1.79 (m, 2H), 2.21 (dt, 2H, $J = 5.9, 5.9$ Hz), 2.41 (t, 2H, $J = 7.6$ Hz), 2.42 (t, 2H, $J = 7.3$ Hz), 3.60 (t, 2H, $J = 6.3$ Hz), 3.73 (s, 3H), 5.83 (dt, 1H, $J = 1.4, 15.6$ Hz), 6.92 (dt, 1H, $J = 7.1, 15.6$ Hz).

^{13}C NMR (125 MHz, CDCl_3): -5.3, 20.3, 21.9, 26.0, 30.0, 31.4, 32.2, 41.6, 42.7, 51.5, 62.8, 121.6, 148.5, 167.1, 210.3.

m/z : 367 ($\text{M}+\text{Na}$) $^+$, 343 ($\text{M}+\text{H}$) $^+$, 229, 211.

HRMS calculated for $\text{C}_{18}\text{H}_{35}\text{O}_4\text{Si}$ ($\text{M}+\text{H}$) $^+$: 343.2305 found: 343.2303.

IR: 1721, 1658, 1461, 1255, 1099, 731 cm^{-1} .



Synthesis of methyl 2-((2S*,6S*)-1,7-dioxaspiro[5.5]undecan-2-yl)acetate

(3.85): TBAF (1M soln. in THF, 0.1 ml, 0.10 mmol) was added dropwise to a solution of ester **(3.86)** (35 mg, 0.10 mmol) in THF (3 ml) at 0 °C. The mixture was stirred for 48 h at room temperature and quenched by addition of satd. aq. NH_4Cl solution. The mixture was extracted with diethyl ether (2 x 20 ml), washed with water, brine and dried over anhydrous Na_2SO_4 . The solvents were removed *in vacuo*, the residue was purified by flash column chromatography (hexane: ethyl acetate = 80:20) using silica gel (1 g) to obtain the title compound as a colourless oil (20 mg, 85 %) as an inseparable (8:1) mixture with a minor unknown isomer.

^1H NMR (500 MHz, CDCl_3) δ 1.07-1.92 (m, 12H), 1.99 (dd, 1H, $J = 8.6, 14.5$ Hz), 2.42 (dd, 1H, $J = 4.6, 14.6$ Hz), 3.58-3.61 (m, 1H), 3.65-3.68 (m, 1H), 3.65 (s, 3H), 3.97-4.04 (m, 1H).

m/z : 241 ($\text{M}+\text{Na}$) $^+$, 229 ($\text{M}+\text{H}$) $^+$.

HRMS calculated for $\text{C}_{12}\text{H}_{21}\text{O}_4$ ($\text{M}+\text{H}$) $^+$: 229.1440 found: 229.1441.

IR: 1704, 1361, 1223, 1090 cm^{-1} .

Data are consistent with the literature.¹⁶⁸

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