Total synthesis of a cuticular hydrocarbon utilizing bismuth(III) coupling chemistry and towards the total synthesis of vioprolide D

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Leo Hao Liu

School of Chemistry

Table of Contents

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Abstract

***Section One*: Total synthesis of a cuticular hydrocarbon from the cane beetle *Antitrogus parvulus* utilizing bismuth mediated reactions**

This section describes investigations of 1,5-stereocontrol bismuth(III) mediated coupling reactions between allylbromide and aldehydes and successful application of this coupling chemistry in the total synthesis of a cuticular hydrocarbon. The bismuth(III) mediated coupling reaction was investigated using chiral bromide [(*E*,2*R*)-5-bromo-2,4-dimethyl-pent-3-enoxy]methylbenzene **1.79** with benzaldehyde and butyraldehyde; 12:1 diastereoselectivity in favour of forming the 1,5-*anti* product was observed in both model studies. This bismuth(III) coupling chemistry has been successfully applied in the construction of (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21** and (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane **1.22**. ^{13}C NMR spectroscopic comparison of the synthetic diastereomers with the natural product **1.17** revealed that (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21** was consistent with the natural product. Therefore, it was concluded that the natural product **1.17** possesses the same relative stereoconfiguration as (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21**.

***Section Two*: Towards the total synthesis of vioprolide D**

This section describes attempts towards the total synthesis of vioprolide D. Initial disconnection revealed three tripeptide fragments. Fragment one benzyl (2*R*)-2-[[(2*S*)-2-[[(2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-triisopropylsilyloxy-propanoyl]amino]propanoyl]amino]-4-methyl-pentanoate **2.26** was synthesized from commercial amino acid building blocks. Attempts to synthesize fragment two (*S*)-(9H-fluoren-9-yl)methyl 2-(((2*S*,3*R*)-1-(((*S*)-1-(allyloxy)-3-methyl-1-oxobutan-2-yl)(methyl)amino)-3-hydroxy-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate **2.40** were unsuccessful because of a intramolecular cyclization reaction which led to the formation of piperazinedione **2.50**, and this process stopped peptide elongation. Literature search showed that this side reaction could be prevented by changing the allyl ester group in dipeptide (*S*)-allyl 2-((2*S*,3*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)-N-methylbutanamido)-3-methylbutanoate **2.42** to a *tert*-butyl ester group. Synthesis of thiazoline containing fragment three (*E*)-allyl 2-((*R*)-2-((*S*)-1-((2-nitrophenyl)sulfonyl)pyrrolidin-2-yl)-4,5-dihydrothiazole-4-carboxamido)but-2-enoate **2.57** was initially attempted via a cysteine cyclization

reaction with an adjacent amide bond, this approach was unsuccessful due to extensive epimerization observed. In the modified synthetic strategy, thiazoline containing (*E*)-allyl 2-((*R*)-2-((*S*)-1-((*R*)-2-((tert-butoxycarbonyl)amino)-4-methylpentanoyl)pyrrolidin-2-yl)-4,5-dihydrothiazole-4-carboxamido)but-2-enoate **2.73** was successfully constructed as a single diastereomer via dehydration reaction of thioamide with adjacent serine residue using diethylaminosulfur trifluoride. The successful synthesis of tetrapeptide **2.73** would not only lead to the total synthesis of vioprolide D, but also potential access to other vioprolide analogues.

Declaration

No portion of this work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright Statement

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Abbreviations

Ac	Acetyl
Aq	Aqueous
Ar	Aryl
Bn	Benzyl
b.p.	Boiling point
br	Broad
Bu	Butyl
Boc	*tert*-Butyloxycarbonyl
n-BuLi	*n*-Butyl lithium
t-Bu	*tert*-Butyl
t-BuLi	*tert*-Butyl lithium
^{13}C NMR	Carbon nuclear magnetic resonance
Cat.	Catalytic
CI	Chemical ionisation
m-CPBA	*3*-Chloroperbenzoic acid
d	Doublet
dd	Doublet of doublet
dt	Doublet of triplet
δ	Chemical shift
DAST	Diethylaminosulfur tetrafluoride
DCM	Dichloromethane
DIBAl-H	Di-*iso*-butylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMB	3,4-Dimethoxybenzyl
DMDO	Dimethyldioxirane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodonane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	Dimethylsulfide

DMSO	Dimethylsulfoxide
EI	Electron impact ionisation
ES	Electrospray
Et	Ethyl
Ether	Diethyl ether
g	Grams
h	Hour (s)
^{1}H NMR	Proton nuclear magnetic resonance
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HOBt	1-Hydroxybenzotriazole hydrate
Hz	Hertz
IR	Infrared
LDA	Lithium di-*iso*-propylamide
m	Multiplet
M	Molarity
M^{+}	Molecular ion
Me	Methyl
MeLi	Methyllithium
MHz	Megahertz
min	Minute (s)
mg	Milligrams
mmol	Millimoles
mol.	Moles
m.p.	Melting point temperature
Ms	Methanesulfonyl
NMI	1-Neomenthylindenyl
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
OTf	Trifluoromethanesulfonate
P	Protecting group
Ph	Phenyl
ppm	Parts per million

Pr	Propyl
py	Pyridine
q	Quartet
quant.	Quantitative
R	General alkyl group
Rf	Retention factor
rt	Room temperature
s	Singlet
SAR	Structure-activity relationship
SEM	2-(Trimethylsilyl)ethoxymethoxy
t	Triplet
tert	Tertiary
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
TIPS	Tri-isopropylsilyl
TLC	Thin layer chromatography
Ts	*p*-Toluenesulfonyl (tosyl)
X	General leaving group

SECTION ONE

Total synthesis of a cuticular hydrocarbon from the cane beetle *Antitrogus parvulus* utilizing bismuth mediated reactions

Chapter 1 Introduction

1.1 Preface

This section demonstrates the work completed by the author towards the total synthesis of a cuticular hydrocarbon from the cane beetle *Antitrogus parvulus* and the determination of its relative configuration. This project is the extension of work previously carried out on remote acyclic stereocontrol chemistry. In this project, diastereoselective bismuth-mediated reactions between aldehydes and allyl bromides have been investigated and successfully applied in the total synthesis of a natural cuticular hydrocarbon.

The general strategy for the construction of the natural product skeleton involved two fragments which were joined together. Commercially available chiral building blocks were used to initiate the synthetic sequence, in which the newly developed bismuth-mediated reaction will be used to access key intermediates.

The opening chapter is intended to review the chemistry involved in this project and give a brief introduction and background of the cuticular hydrocarbon.

1.2 Remote stereocontrol using functionalized allylmetal reagents

Remote acyclic stereocontrol chemistry has attracted considerable interest in the synthetic chemistry community.[1] This process describes how in an open-chain system, one stereogenic centre influences the introduction of a second stereogenic centre, separated by two or more atoms. The development of this type of chemistry has significantly enhanced synthetic access of chiral compounds bearing more than one stereogenic centres.

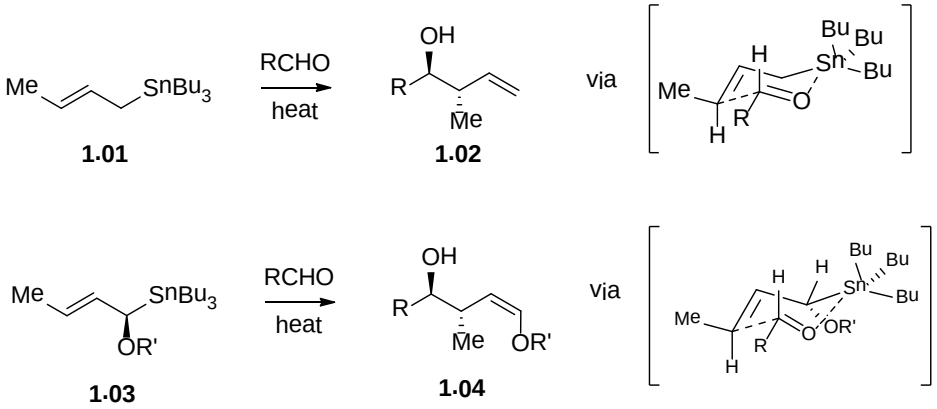
Much work has been done in this area, in the particular reaction of allylstannanes with aldehydes has been showed to give homoallylic alcohols in the presence of a Lewis acid. It was subsequently discovered that tin(IV) halide promoted reactions of 4-, 5-, and 6-substituted allylstannanes with aldehydes proceed with

effective remote stereocontrol.[2] This chemistry has been successfully applied to the total synthesis of several natural products.

Although allylstannanes have demonstrated excellent remote stereocontrol in reactions with aldehydes, they are generally very toxic compounds and can be difficult to handle.[3] More recently, less toxic allylmetal reagents have been studied, such as allylgermanium and allylbismuth compounds, which have also shown a high degree of remote stereocontrol.[4]

1.2.1 Remote stereocontrol using allylstannanes

During early work on the development of an asymmetric version of this reaction, it had been known that allylstannane **1.01** reacts with aldehydes on heating to give the *anti*-homoallylic alcohols **1.02** via a chair-like, six-membered transition state (scheme 1.01).[5] Stannanes **1.03** were found to react with aldehydes with very high stereocontrol in favour of the *anti*-product **1.04**, although high temperatures (>100^{o}C) were required for non-activated aldehydes.[6] These reactions provided very efficient induction of asymmetry from stannane starting materials, but the scope of the reaction was limited to activated aldehydes because of the high temperatures involved.

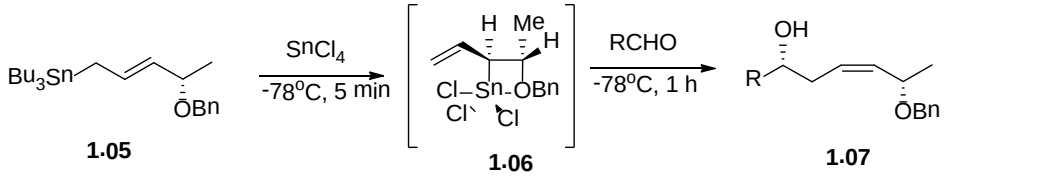


1.01 **1.02** **1.03** **1.04**

Scheme 1.01: Examples of stereocontrol reactions using allylstannanes with aldehyde

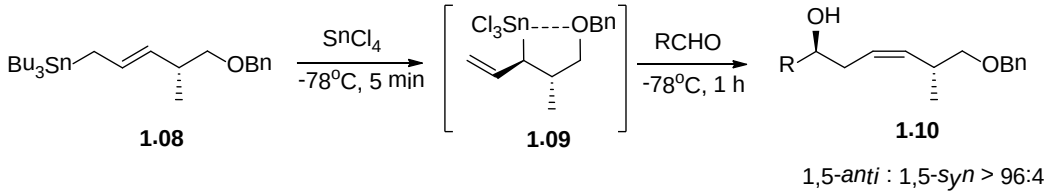
Further study has revealed that the presence of a Lewis acid significantly facilitates the reaction process. It was showed that transmetallation of **1.05** with tin(IV) chloride generated the allytin trichloride **1.06** in less than 5 min at -78^{o}C (scheme 1.02). The intermediate reacted with aldehydes to give coupling product

1.07 with excellent 1,5-*syn*-stereoselectivity.[7] This selectivity was observed for a variety of stannanes and for a broad range of aldehydes.[8]



Scheme 1.02: Allyl stannane reactions with aldehyde

In contrast, transmetallation of stannane **1.08** was stereoselective in favour of the *anti*-allytin trichloride **1.09** (scheme 1.03), which reacted with aldehydes to give the *anti*-product **1.10** with very high 1,5-stereocontrol.[9]



Scheme 1.03: Allyl stannane reactions with aldehyde

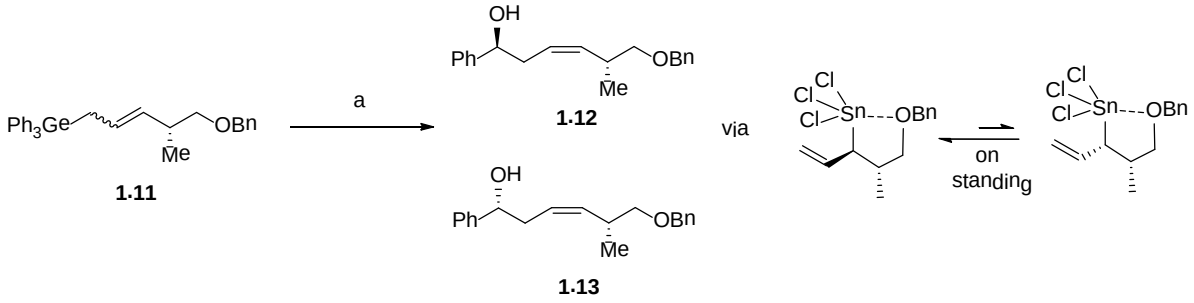
The overall remote stereoselectivity observed in these reactions depends on the stereoselectivity of the initial transmetallation, the configurational stability of the allyltin trihalide intermediates, and the stereoselectivity of the reaction of these intermediates with aldehydes.

1.2.2 Remote stereocontrol using organogermanes

Although allyltin chemistry provides reliable and selective methods for acyclic remote stereocontrol, the inherent toxicity and difficulties in by-product removal associated with organotin reagents are among the limitations regarding its general application.[10] Therefore alternative approaches have been investigated, which essentially avoid the use of the toxic organotin compounds for remote stereocontrol chemistry.

Organogermanium compounds are intermediate between organosilicon and organotin compounds in terms of chemical reactivity, and their reactions with aldehydes mediated by Lewis acids are known although cycloaddition reactions prenominate with 1-substituted allylgermanes.[11]

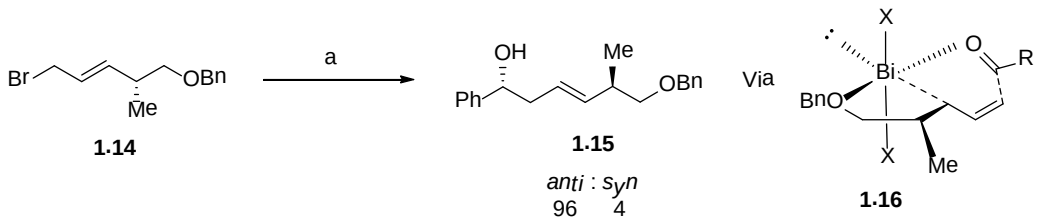
It was reported that organogermane compound **1.11** reacted with benzaldehyde in the presence of tin(IV) chloride to give mixtures of 1,5-*anti*- and *syn*- coupling products **1.12** and **1.13**, with the ratio depending on the time allowed for the transmetallation (scheme 1.04).[12] It was discovered that the length of time for transmetallation was in inversely correlated to the stereoselectivity of the reaction; if the reaction mixture was stirred at -78^{o}C for 45 min before the addition of benzaldehyde, the ratio between coupling products **1.12** and **1.13** was 82:18, whereas if 15 min was allowed for transmetallation, the ratio improved to 94:6.



Scheme 1.04: Reaction of germane compounds with aldehydes in the presence of $SnCl_4$

1.2.3 Remote stereocontrol using organobismuth

It has been reported that reduction of bismuth(III) halides with zinc powder generates bismuth(0), which promotes the reaction of allylic bromides and iodides with aldehydes to give homoallylic alocohols (scheme 1.05).[13] Following the published procedure, the bromide **1.14** and an aldehyde were added to the black suspension generated by the reaction between bismuth(III) and zinc powder in THF, and the mixture was heated under reflux for 2 hours. As a result, a stereoselective reaction in favour of the (3*E*)-1,5-*anti*-homoallylic alcohol **1.15** was obtained.



Reagents and conditions: a) BiI_3, Zn powder, PhCHO, THF, reflux, 2 h, 83%

Scheme 1.05: Bismuth(III) iodide reaction with aldehyde

This reaction provides tin-free 1,5-stereocontrol in good yield with a range of aldehydes. The mechanism of the bismuth mediated reaction has not been elucidated, although it appears that both zinc powder and bismuth(III) iodide are essential for the reaction to proceed.[14] It is also interesting to observe that very different reaction conditions are used for the bismuth(III) mediated reactions than for the tin(IV) halide promoted reactions. One plausible mechanism involves a transition state with coordination of the aldehyde *anti* to the oxygen substituent as shown in **1.16**.[15]

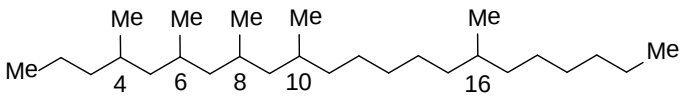
In this project, the bismuth(III) mediated 1,5-diastereoselective coupling reaction of allyl bromide with aldehyde will be further investigated with model studies. Furthermore, the potential application of this bismuth chemistry will be demonstrated in the context of natural product synthesis. The natural product selected for the application of bismuth chemistry is a cuticular hydrocarbon extracted from the cane beetle *Antitrogus parvulus*.

1.3 Discovery and structure of cuticular hydrocarbons

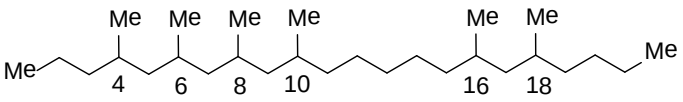
Larvae of melolonthine scarabs (collectively known as canegrubs) are the main pests affecting the productions of sugarcane in Australia by damaging the roots of the plant and the regenerative portion of its underground stem.[16] Nineteen species of endemic canegrubs have been discovered. These species exhibit very diverse life cycles, distribution and behaviour.[17] In order to control the population of these species, current plant protection strategies rely heavily on the use of insecticides,[18] but problems associated with insecticidal breakdown and resistance warrants the needs of developing more environmentally benign

strategies as alternatives. Some success has been achieved with formulations utilizing sex pheromones for controlling herbivorous scarab beetles. Although no pheromones have previously been identified from the Australian canegrubs, other chemically diverse active compounds including phenols and amino acid derivatives have been identified that could be responsible for their behaviour and population growth.[19] In order to develope an understanding of the chemistry of the Australian canegrub complex, studies have been undertaken towards identifying and understanding the chemical substances that govern the biological and behavioural responses of the Australian canegrub family, therefore ultimately controlling their population growth.

Cuticular hydrocarbons were extracted from intact adult female *Antitrogus parvulus* beetles with hexane. As indicated by their fragmentation patterns, two unusual hydrocarbon compounds were revealed by gas chromatography–mass spectrometry (GCMS), in the ratio of 45:38.[20] Separation of the two components in the female extract was carried out by preparative gas chromatography, revealing molecular ions of *m/z* 380.4373 and 394.4536, which corresponded to the formulas $C_{27}H_{56}$ and $C_{28}H_{58}$ respectively.[21] Further analysis showed that these compounds possessed an alternating methyl-branching pattern. High resolution of ^{13}C NMR spectroscopy confirmed the presence of five and six methyl branches in the C27 and C28 hydrocarbons, respectively. ^{13}C NMR shift calculations and the mass spectral fragmentation pattern have indicated the C27 hydrocarbon is an isomer of 4,6,8,10,16-pentamethyldocosane **1.17**, and the C28 hydrocarbon is an isomer of 4,6,8,10,16,18-hexamethyldocosane **1.18** (figure 1.01).



1.17



1.18

Figure 1.01: Extracted cuticular hydrocarbons

Later spectroscopic and synthetic studies have confirmed that hydrocarbons **1.17** and **1.18** feature an unprecedented *anti-anti-anti* stereochemistry in the 4,6,8,10-methyl tetrad, and *syn* configuration between C16- and C18- methyl groups in compound **1.18**. Total synthesis also confirmed the relative stereochemistry of 4,6,8,10,16,18-hexamethyldocosane **1.18** as (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-4,6,8,10,16,18-hexamethyldocosane **1.19**;[22] however, the relative stereochemistry of the C16- methyl group in **1.17** (*S*-**1.21** or *R*-**1.22**) still remains unknown in the current literature (figure 1.02).

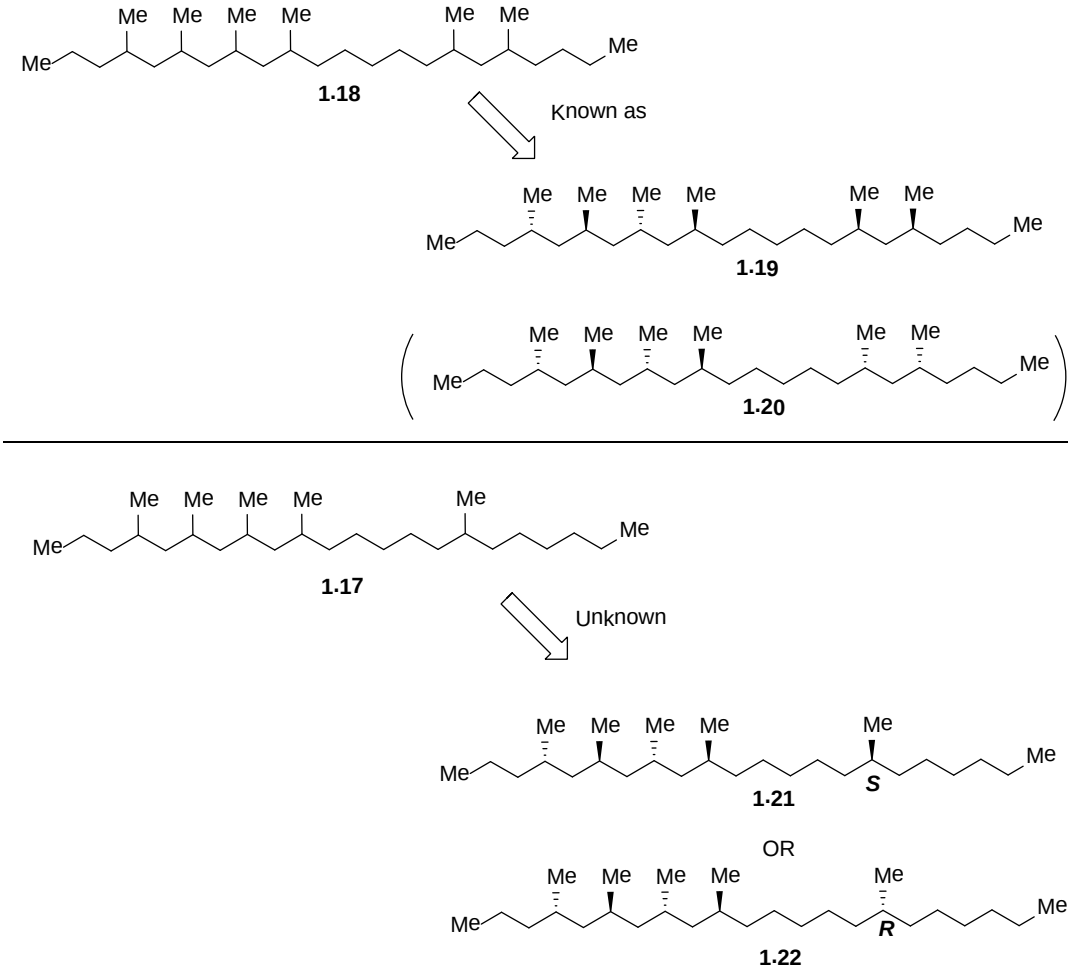


Figure 1.02: Relative stereoconfiguration of cuticular hydrocarbons

The following text is intended to briefly review existing methods in the literature on the chemical synthesis of (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-4,6,8,10,16,18-hexamethyldocosane **1.19** and our proposed strategies towards the construction of both diastereomers of 4,6,8,10,16-pentamethyldocosane **1.17** (compounds **1.21** and **1.22**) utilizing bismuth(III) mediated coupling chemistry.

1.4 Chemical syntheses of cuticular hydrocarbon

Previous total syntheses of cuticular hydrocarbons have been achieved and their relative stereochemistry assigned. The total synthesis of both diastereoisomers of 4,6,8,10,16,18-hexamethyldocosane **1.19** and **1.20** has been reported on several occasions.

1.4.1 Breit's total synthesis of 4,6,8,10,16,18-hexamethyldocosane

The total synthesis of both diastereomers of 4,6,8,10,16,18-hexamethyldocosane **1.19** and **1.20** in their enantiomerically pure forms was achieved by Breit and his coworkers, utilizing copper-mediated and *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB)-directed *syn*-allylic substitution chemistry with Grignard reagents for iterative deoxypropionate synthesis.[23] A copper-catalyzed sp^3-sp^3 cross coupling reaction was demonstrated as a powerful building block for this highly efficient convergent total synthesis.

This synthetic strategy revealed that fragment coupling of the methyl tetrad and the methyl diad by employing a catalytic cross coupling reaction was proposed as an efficient final step of the synthesis to allow the flexible construction of the diastereomers (figure 1.03). The corresponding tetradeoxypropionate building block can be assembled by iterative deoxypropionate synthetic strategy employing enantiomerically pure allylic *o*-DPPB building blocks **1.23** and **1.24** as propionate acetate and propionate units, respectively.[24]

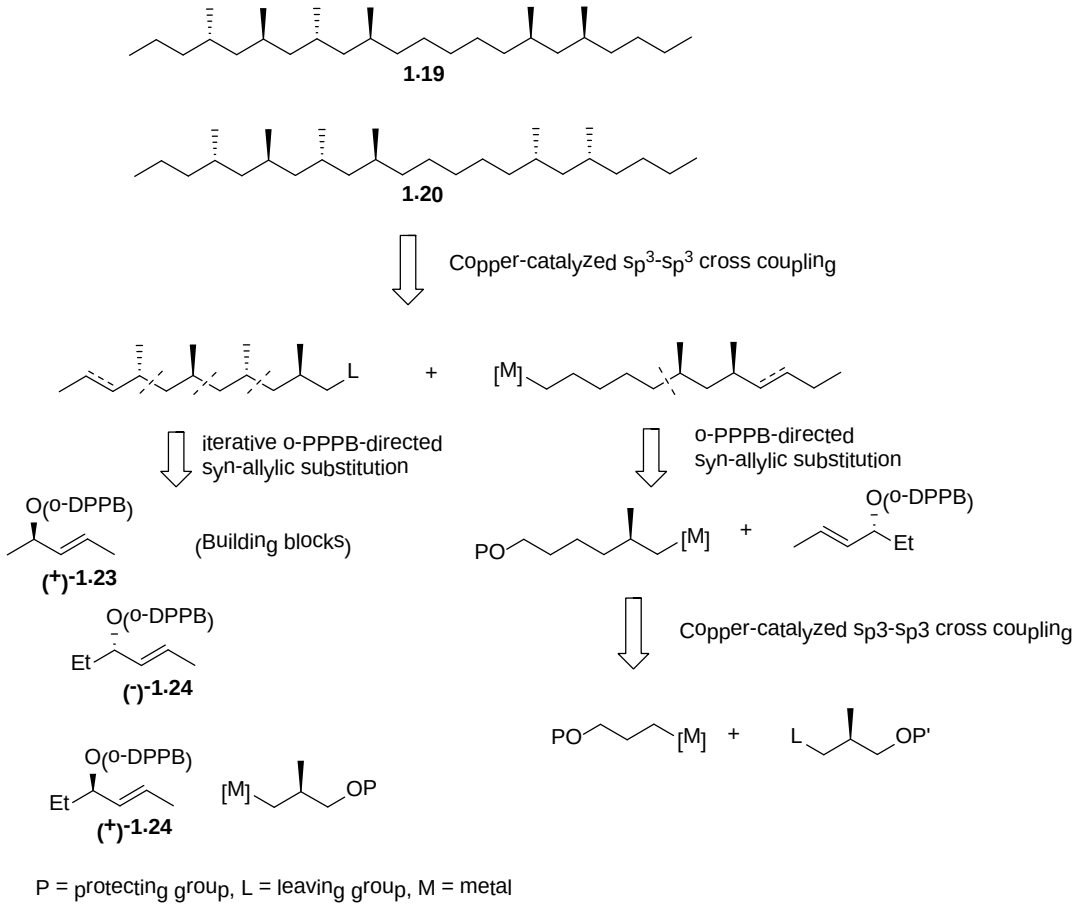
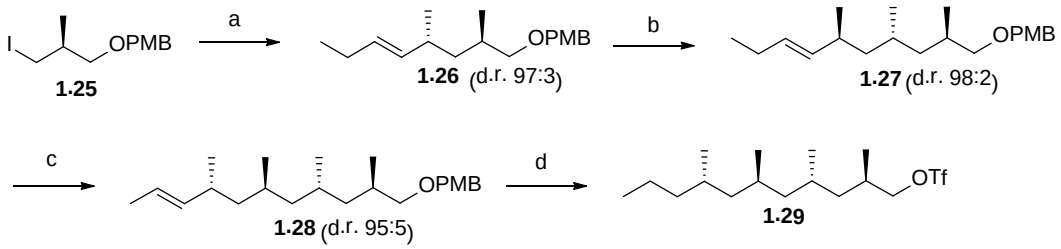


Figure 1.03: Breit synthesis strategy

The synthesis began with construction of the tetrad building block triflate-protected alcohol **1.29** (scheme 1.06). Iodide **1.25** was converted to its corresponding Grignard reagent and subjected to *o*-DPPB ester (*R*)-(+)-**1.24** in the presence of copper bromide-dimethyl sulfide to give the PMB-protected alcohol **1.26** with high degree of 1,3-chirality transfer.[24] Two separate iterations consisting of alkene ozonolysis with reductive workup, conversion to the iodide and directed *syn*-allylic substitution with building blocks (*S*)-(-)-**1.24** and (*R*)-(+)-**1.23** respectively, led to the formation of the methyl tetrad containing intermediate **1.28** with all carbon atoms and stereogenic centres in place. Alkene hydrogenation and reductive cleavage of *para*-methoxybenzyl ether (PMB) group occurred upon heterogenous catalytic hydrogenation to generate key methyl tetrad intermediate triflate **1.29**.

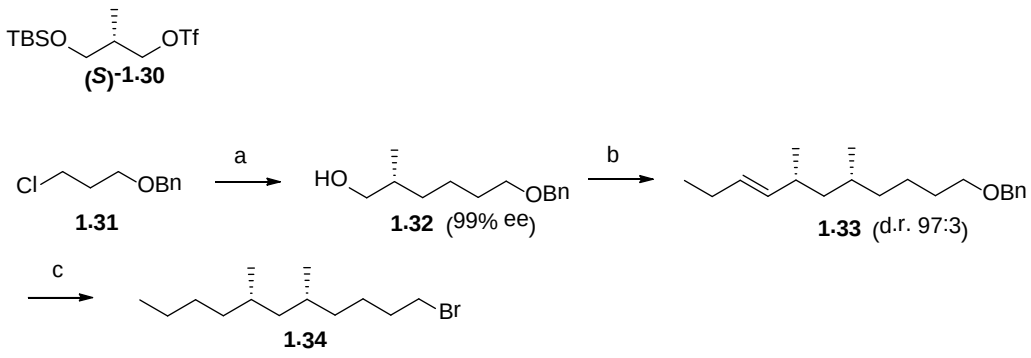


1.25 **1.26** (d.r. 97:3) **1.27** (d.r. 98:2) **1.28** (d.r. 95:5) **1.29**

Reagents and conditions: a) *t*-BuLi, $MgBr_2.Et_2O$ then **(*R*)-(+)-1.24**, $CuBr.SMe_2$, Et_2O, 83%; **b)** (1) *t*-BuLi, $MgBr_2.Et_2O$ then **(*S*)-(-)-1.24**, $CuBr.SMe_2$, Et_2O, 82%; (2) O_3, $NaBH_4$, 95%, (3) Imidazole, Ph_3P, I_2, 92%; **c)** (1) *t*-BuLi, $MgBr_2.Et_2O$ then **(*R*)-(+)-1.23**, $CuBr.SMe_2$, Et_2O, 85%; (2) O_3, $NaBH_4$, 98%; (3) Imidazole, Ph_3P, I_2, 95%; **d)** (1) PtO_2, H_2 (5 bar), then $Pd(OH)_2$, 98%; (2) Tf_2O, NEt_3, DCM, -78°C, 97%.

Scheme 1.06: Synthesis of intermediate **1.29**

Synthesis of bromide building block **1.34** started from chloride **1.31** (scheme 1.07). A cross coupling reaction of chloride **1.31** with triflate **1.30** was achieved by using Li_2CuCl_4 as a catalyst to give primary alcohol **1.32** after removal of the silyl-protecting group.[25] Primary alcohol **1.32**, was converted to its correponding iodide and subjected to *syn*-allylic substitution with building block (*R*)-(+)-**1.24** to give dideoxypropionate **1.33** in excellent yield and diastereoselectivity. Hydrogenation of benzyl-protected alcohol followed by bromination using *N*-bromosuccinimide (NBS) gave the bromide **1.34** in quantitative yield.



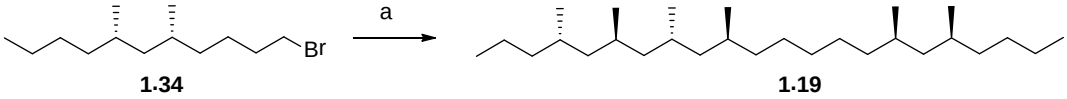
(*S*)-1.30 **1.31** **1.32** (99% ee) **1.33** (d.r. 97:3) **1.34**

Reagents and conditions: a) (1) Mg, THF, 4 mol% Li_2CuCl_4 then **(*S*)-1.30**, (2) 5% HCl in MeOH, 82% 2 steps; **b)** (1) Ph_3P, I_2, Imidazole, DCM, 93%, (2) *t*-BuLi, $MgBr_2.Et_2O$, then **(*R*)-(+)-1.24**, $CuBr.SMe_2$, Et_2O, 85%; **c)** (1) H_2, PtO_2, EtOAc, 12 h, then H_2, 10% Pd/C, 24 h, 96%, (2) Ph_3P, NBS, 97%

Scheme 1.07: Synthesis of bromide intermediate **1.29**

Bromide **1.34** was converted to its corresponding Grignard by magnesium in anhydrous ether. The Grignard formed *in situ* was then coupled with triflate **1.29** in the presence of 4 mol% catalyst Li_2CuCl_4 to afford the final hydrocarbon product 1.19 (scheme 1.08). Excellent yields were obtained for both

diastereomers 4,6,8,10,16,18-hexamethyldocosane **1.19** and **1.20** under these conditions. Purification of the final product was achieved through distillation.



1.34 **1.19**

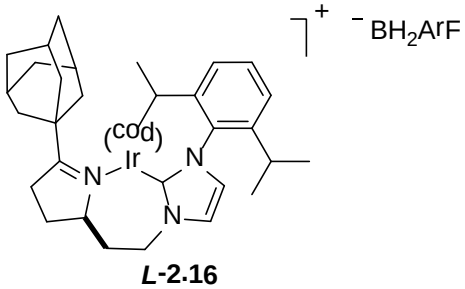
Reagents and conditions: a) Mg, Et_2O, $BrCH_2CH_2Br$ (0.4 equiv.), 4 mol% Li_2CuCl_4, then **1.29**, 93%

Scheme 1.08: Synthesis of hydrocarbon **1.19**

The same methodology was used to synthesize diastereomer **1.20**. ^{13}C NMR spectra of 4,6,8,10,16,18-hexamethyldocosane **1.19** and **1.20** were recorded in the presence of an internal glass-capillary tube containing a solution of the natural product in $CDCl_3$. Comparison of these spectra revealed a perfect match for diastereomer (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-4,6,8,10,16,18-hexamethyldocosane **1.19**.

1.4.2 Burguess' total synthesis of 4,6,8,10,16,18-hexamethyldocosane

Burgess and his coworkers developed a catalyst-controlled diastereoselective hydrogenation methodology for the total synthesis of natural product **1.19**,[26] in which a chiral derivative of the Crabtree catalyst **1.35** was used for achieving high diastereoselectivity (figure 1.04).[27]

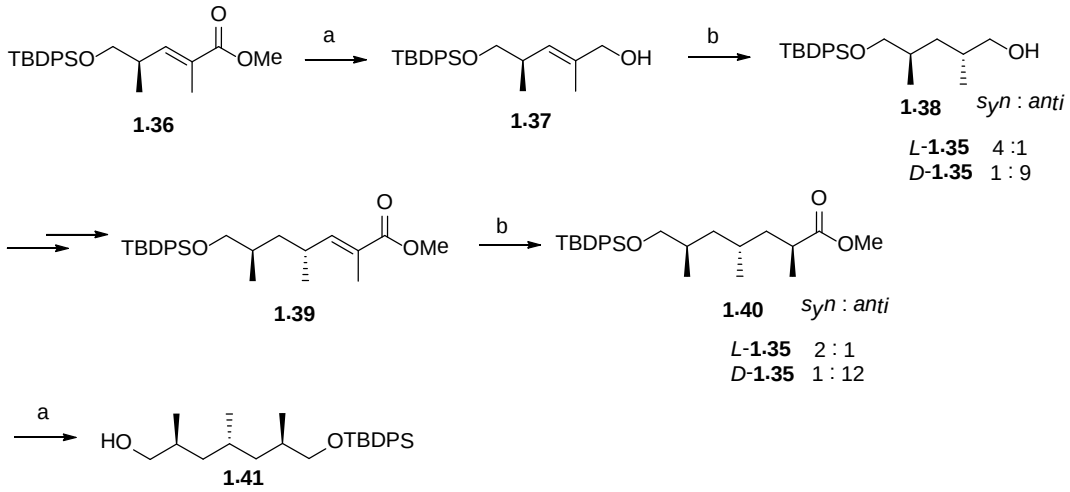


***L*-2.16**

$BArF^-$ = tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate

Figure 1.04: Structure of catalyst

Synthesis started with ester **1.36** which can be easily accessed from commercial materials (scheme 1.09). Ester reduction using DIBAL-H afforded the corresponding primary alcohol, which was then subjected to enantioselective hydrogenation condition using Crabtree catalyst chiral derivative L-**1.35** (L version of the chiral catalyst). It has been found that the catalyst approaches such α,β-unsaturated esters and alcohols from the opposite faces (figure 1.05).[27] Thus, the substrate vector (which implies that the overall stereoselectivity is governed by the substrate) for alcohol **1.37** matched with D-**1.35** (D version of the chiral catalyst), whereas the corresponding ester **1.36** matched with L-**1.35**. It was observed that for the diastereoselective hydrogenation of alkene **1.37**, catalyst D-**1.35** favoured the *anti* product.



Reagents and conditions: a) DIBAL-H, THF, 0°C, 1 h; **b**) 50 atm, cat. (0.2 mol%), DCM, 4 h

Scheme 1.09: Intermediates synthesis

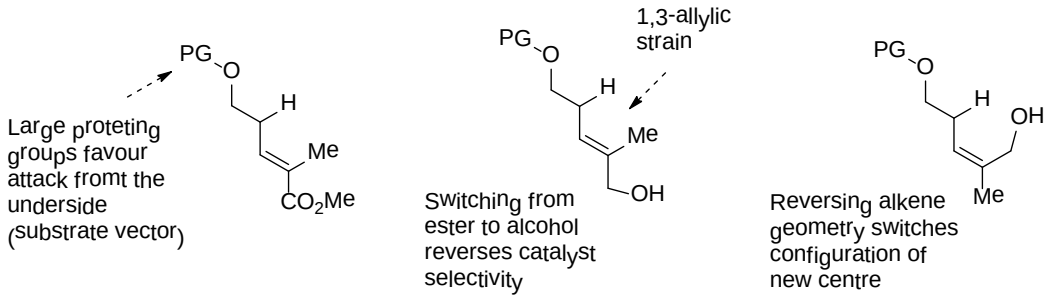
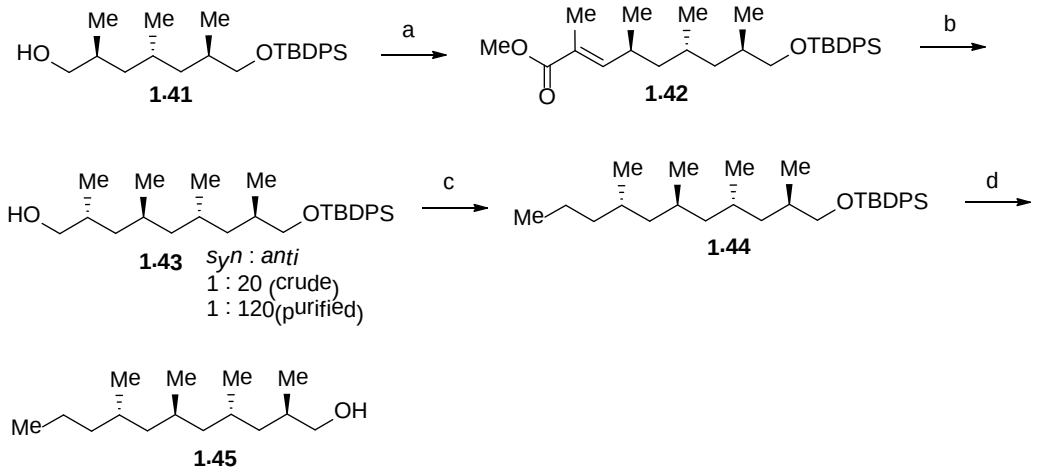


Figure 1.05: Catalyst control mechanism (graph taken from reference 27)

Ester **1.39** was made from alcohol **1.38** through oxidation, Wittig-coupling and DIBAL-H reduction. Hydrogenation of ester **1.36** using D-**1.35** generated the *anti* product **1.40** in excellent diastereoselectivity. Ester **1.40** was subsequently reduced to the corresponding alcohol **1.41** to give the key intermediate for the natural product synthesis.

Another iteration of the oxidation, Wittig-coupling and reduction sequence converted alcohol **1.41** to the ester **1.42** (scheme 1.10). Then, the material was hydrogenated using catalyst L-**1.35**, generating almost exclusively the *anti* hydrogenation product, which was then reduced to its corresponding alcohol **1.43**. The remaining oxidation, Wittig-coupling, heterogeneous hydrogenation and deprotection steps gave the key intermediate alcohol **1.45** with excellent chiral integrity among the tetrad methyl groups.

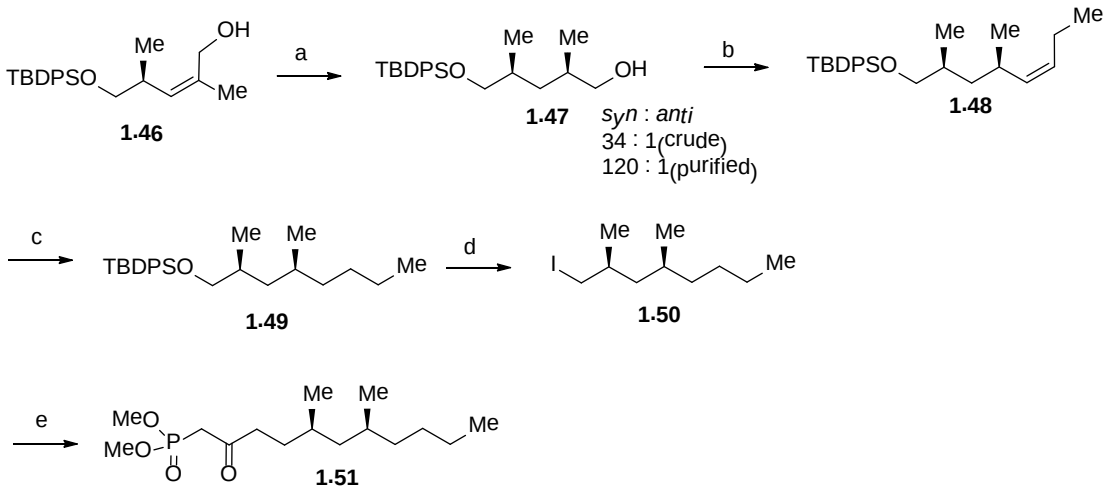


Reagents and conditions: a) (1) TPAP, NMO, DCM, 30 min, (2) $MeC(PPh_3)CO_2Me$, PhMe, 80°C, 12 h, 65%; **b**) (1) 50 atm H_2, 1 mol% **L-1.35**, DCM, 4 h, (2) DIBAL-H, THF, 0°C, 30 min, 80%; **c**) (1) TPAP, NMO, DCM, 30 min, (2) KHMDS, $EtPPh_3Br$, THF, -78°C, 1 h, (3) H_2, Pd/C, MeOH/THF, 7 h, 76%; **d**) TBAF, THF, 1.5 h, 84%

Scheme 1.10: Synthesis of intermediates

Synthesis of the other fragment **1.51** started with hydrogenation of alkene **1.46** using catalyst L-**1.35**; primary alcohol **1.47** was obtained with excellent diastereoselectivity (scheme 1.11). Alcohol **1.47** was subjected to a Swern oxidation followed by Wittig-coupling which gave compound **1.48** in high yield. Hetereogeneous hydrogenation afforded silyl-protected alcohol **1.49** in quantitative yield. Removal of silyl ether and subsequent iodination converted alkene **1.48** to its corresponding iodide **1.50** in high yield. Treatment of iodide

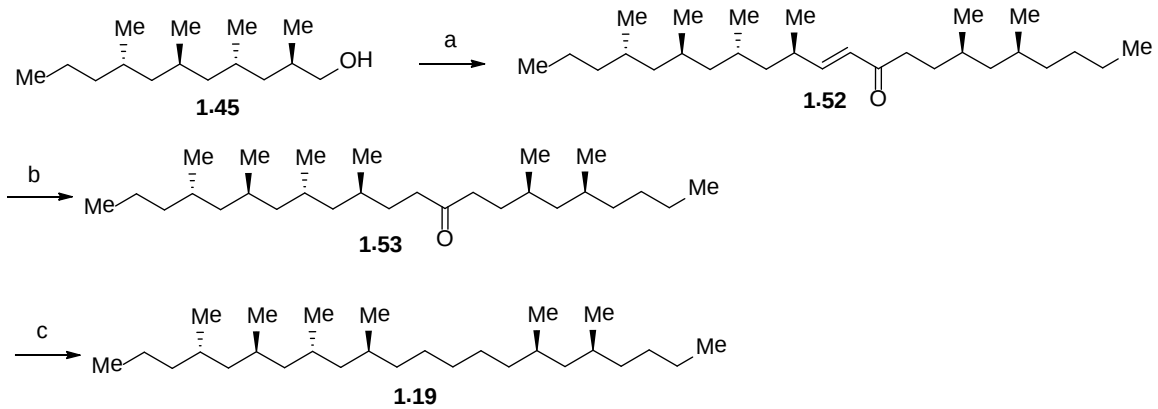
1.50 with a ketophosphonate dianion led to the formation of the key intermediate phosphonate **1.51** which was ready for the coupling reaction.[28]



Reagents and conditions: a) 50 atm H_2, 0.2 mol% **L-1.35**, DCM, 4 h, 93%; **b**) (1) $(COCl)_2$, DMSO, Et_3N, DCM, -78°C, 10 min, (2) KHMDS, $^nPrPPh_3Br$, THF, -78°C, 2 h, 83%; **c**) H_2, Pd/C. MeOH/THF, 7 h, 99%; **d**) (1) TBAF, THF, 2 h, (2) PPh_3, I_2, Imidazole, DCM, 30 min, 86%; **e**) $(MeO)_2POCH_2COMe$, NaH then ^nBuLi, 0°C, 1 h, 79%.

Scheme 1.11: Synthesis of intermediates

Oxidation of alcohol **1.45** followed by Horner-Wadswoth-Emmons coupling afforded ketone **1.52** in good yield (scheme 1.12).[29] Heterogeneous hydrogenation of alkene **1.52** gave intermediate **1.53** in quantitative yield. The ketone intermediate **1.53** was then reduced by a modified Wolff-Kishner reduction method to generate the natural product (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-4,6,8,10,16,18-hexamethyldocosane **1.19** in excellent yield.[30]



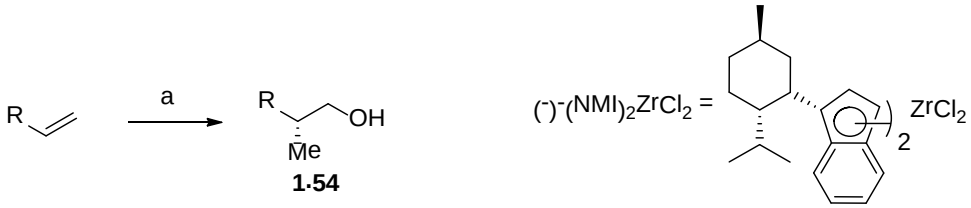
Reagents and conditions: a) (1) TPAP, NMO, DCM, 30 min, (2) $Ba(OH)_2$, phosphonate **1.51**, THF, 15 min, 86%; **b**) H_2, Pd/C, MeOH/THF, 4 h, 99%; **c**) $TsNHNH_2$, $NaBH_3CN$, DMF/sulfolane, 110°C, 2 h, 94%.

Scheme 1.12: Natural product synthesis

1.4.3 Negishi's total synthesis of 4, 6, 8, 10, 16, 18-hexamethyldocosane

Negishi and his coworkers reported an efficient and diastereoselective synthesis of (4*S*,6*R*,8*R*,10*S*,16*R*,18*S*)-4,6,8,10,16,18-hexamethyldocosane **1.19** using zirconium-catalyzed asymmetric carboalumination of alkene (known as ZACA) strategy.[31]

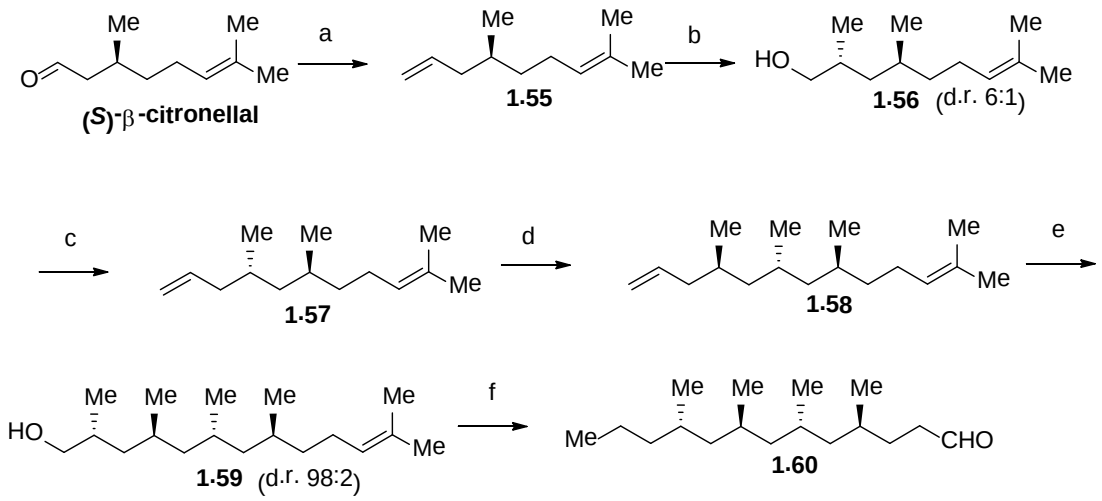
In a ZACA reaction, various monosubstituted alkenes containing hydrocarbon substituents as well as those containing heteroatom substituents reacted with trimethylaluminium (Me_3Al) and catalytic amount of a chiral zirconium catalyst dichlorobis(1-neomenthylindenyl)-zirconium, or $(NMI)_2ZrCl_2$. Oxygen is used as the oxidant in the ZACA reaction in which the alcohol **1.54** is formed in generally high yields with up to 85% enantiomeric excess (scheme 1.13).[32]



Reagents and conditions: a) (1) Me_3Al, 4 mol% $(-)$-$(NMI)_2ZrCl_2$, (2) O_2

Scheme 1.13: A general ZACA reaction

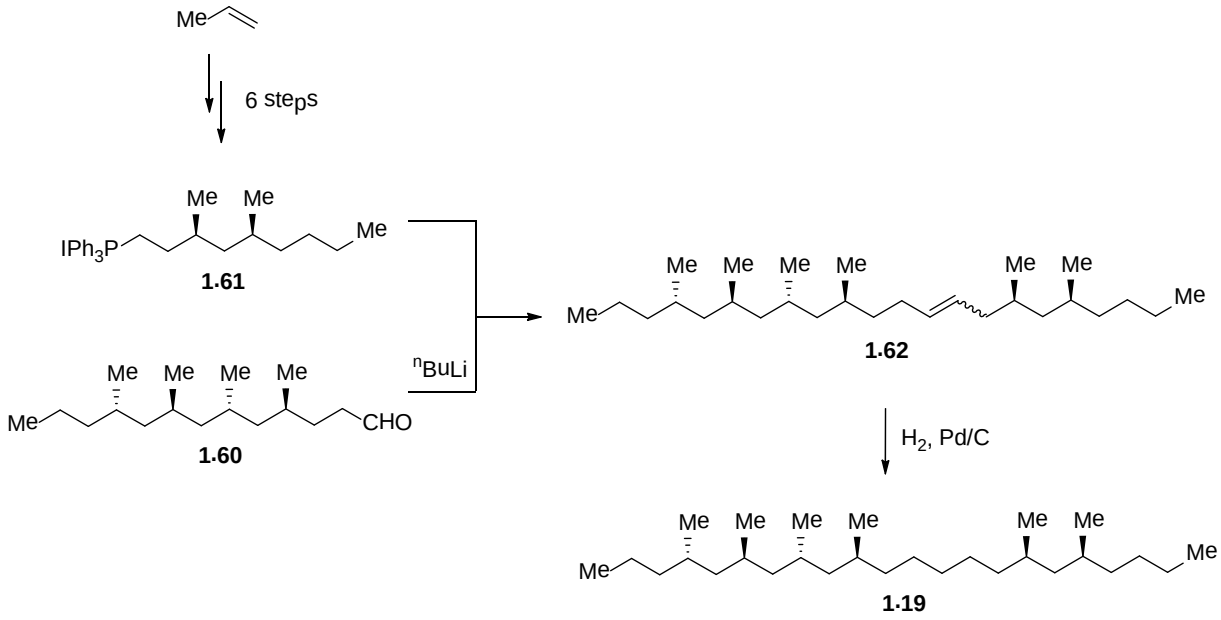
Synthesis began with inexpensive commercially available chiral building block (*S*)-*β*-citronellal (scheme 1.14). Treatment of (*S*)-*β*-citronellal with methylenetriphenylphosphorane led to the formation of terminal alkene **1.55** which was subjected to ZARA oxidation to give primary alcohol **1.56** in quantitative yield with good diastereomeric ratio. Alcohol **1.56** was oxidized to its corresponding aldehyde followed by Wittig coupling to afford terminal alkene **1.57**, which underwent another ZACA oxidation followed by oxidation and Wittig coupling to give terminal alkene **1.58**. A final ZACA oxidation furnished the methyl tetrad intermediate **1.59** with excellent diastereomeric ratio. The hydroxyl group in alcohol **1.59** was converted to the tosylate using tosyl chloride which was then displaced by ethyl cuprate generated in situ before final oxidative cleavage of the double bond to give aldehyde **1.60**.[33]



Reagents and conditions: a) $CH_2=PPh_3$; **b**) (1) Me_3Al (2 equiv.), 4 mol% (-)-$(NMI)_2ZrCl_2$, DCM, 95% (2) O_2; **c**) (1) Ph_3P, I_2, (2) ^tBuLi, -78°C, dry $ZnBr_2$, THF, $CH_2=CHBr$ (3 equiv.), 2 mol% $Pd(PPh_3)_4$ 81%; **d**) (1) Me_3Al, 3 mol% (+)-$(NMI)_2ZrCl_2$, DCM, (2) Evaporation of DCM and Me_3Al, (3) dry $Zn(OTf)_2$ (1 equiv.), DMF, 2 h, 70°C, (4) 3 mol% $Pd(DPEphos)Cl_2$, 6 mol% DIBAL-H, $CH_2=CHBr$ (3 equiv.), DMF, 79%; **e**) (1) Me_3Al (2 equiv.), 4 mol% (+)-$(NMI)_2ZrCl_2$, DCM, (2) O_2, 45%; **f**) (1) TsCl, Et_3N, (2) EtMgBr, 5 mol% Li_2CuCl_4, (3) NMO (3 equiv.), 1 mol% OsO_4, then $NaIO_4$, 89%

Scheme 1.14: Synthesis of intermediates

Another fragment **1.61** was synthesized in six steps starting from propene, with both chiral centres in the methyl diad system introduced by the ZACA route (scheme 1.15).[34] Final assembly of the natural product **1.19** was achieved in 85% yield in two steps via Wittig olefination and catalytic hydrogenation with Pd/C.



Scheme 1.15: Final stage synthesis

In summary, 4,6,8,10,16,18-hexamethyldocosane **1.19** was synthesized in 11% yield in eleven steps in the longest linear sequence from commercially available chiral building block (*S*)-*β*-citronellal. Five of the six stereogenic centres were generated in a catalytic and enantioselective manner using ZACA reaction which was an efficient method of introducing chiral centres onto terminal alkenes.

1.5 Proposed work

Following the discovery and relative structural elucidation of the two novel cuticular hydrocarbons from the cane beetle *Antitrogus parvulus* by Kitching and his coworkers,[35] it is known that 4,6,8,10,16-pentamethyldocosane **1.17** features an unusual *anti-anti-anti*- stereoconfiguration across the 4,6,8,10-methyl tetrad (figure 1.06). However, their attempt of separate synthesis of the two diastereoisomers **1.21** and **1.22** has been unsuccessful, and only a mixture of the two diastereisoomers was obtained.

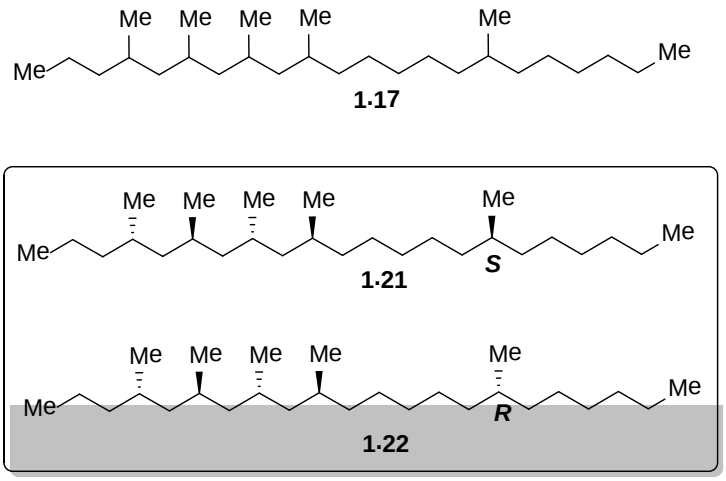


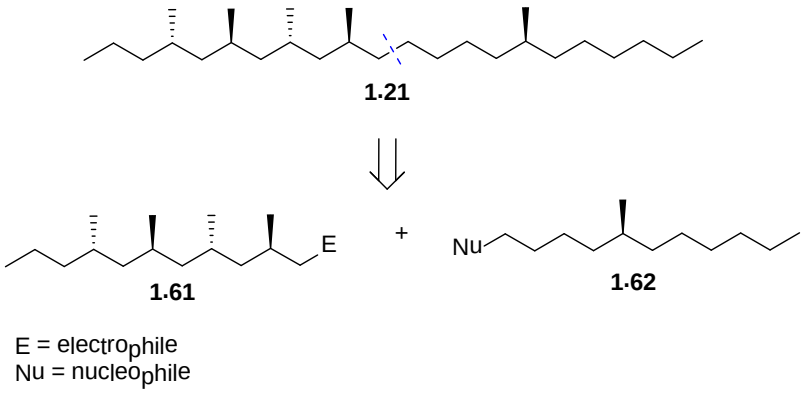
Figure 1.06: Structure of diastereomers

Currently the relative stereoconfiguration of 4,6,8,10,16-pentamethyldocosane **1.17** has not yet been determined because the configuration of the remote methyl group on C16 is not known (whether *S* or *R*). This project is intended to demonstrate our attempts in the total synthesis of both diastereoisomers of (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21** and (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane **1.22**, while applying bismuth(III) mediated coupling chemistry as a key step in the construction of the

skeleton of the hydrocarbon molecule. After having accessed the two diastereoisomers separately, comparison of spectroscopic data of the two diastereoisomers against that of the natural product **1.17** would then reveal the natural product's true relative stereochemical configuration.

1.5.1 Retrosynthetic analysis of the cuticular hydrocarbon 1.21

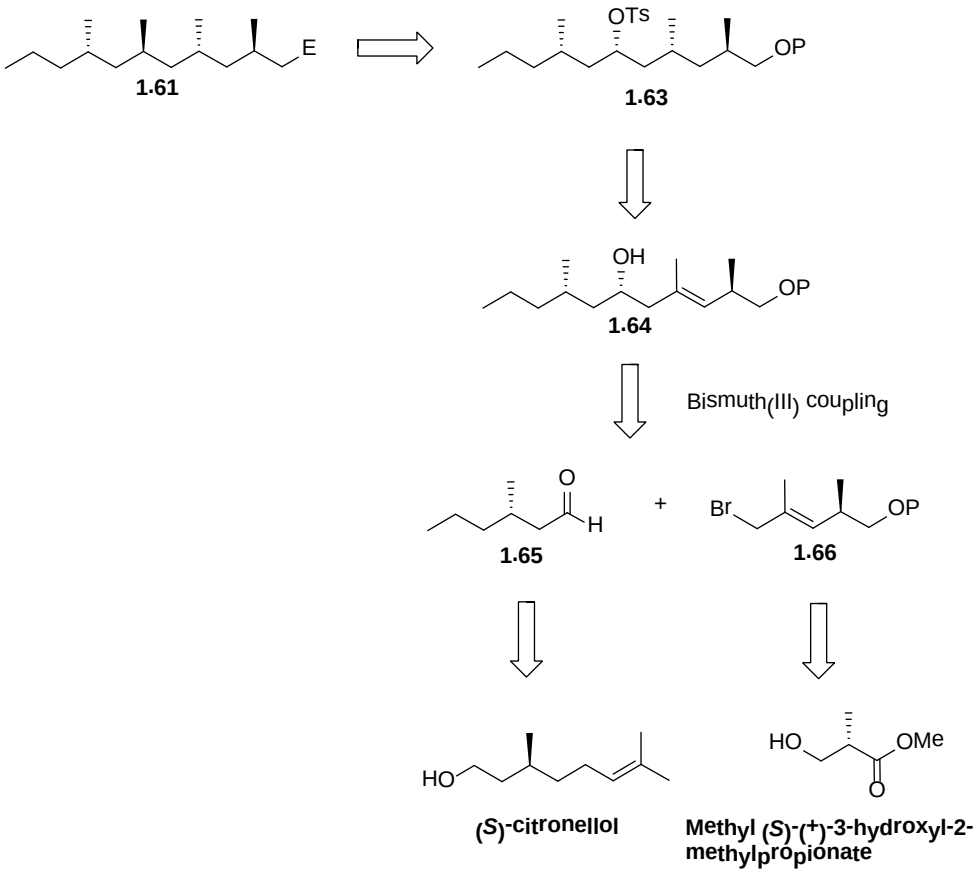
Our chosen strategy involved the division of the hydrocarbon **1.21** into two fragments: a electrophile containing the *anti-anti-anti*- 4,6,8,10-methyl tetrad unit and a nucleophile containing the remote methyl group (scheme 1.16). The final step of the total synthesis would be the coupling of the two components followed by appropriate deprotections, enabling synthetic access to the hydrocarbon.



Scheme 1.16: Retrosynthetic analysis

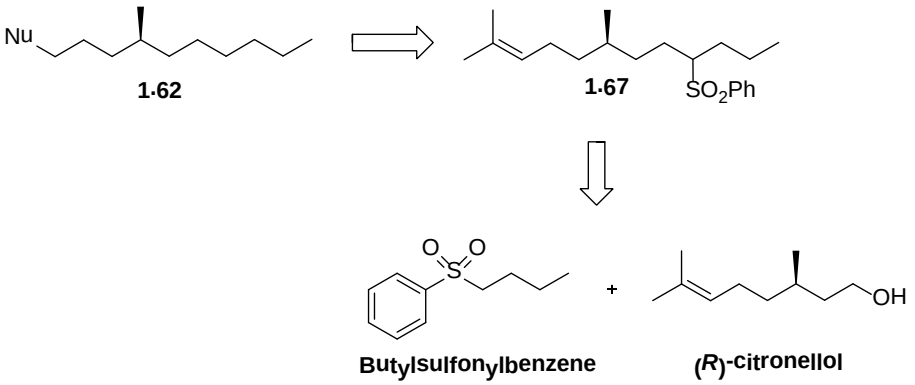
The *anti-anti-anti*- 4,6,8,10-methyl tetrad electrophile **1.61** could be accessed from the tosylate containing protected alcohol **1.63** (scheme 1.17). The tosylate group would be synthesized from alcohol **1.64** with tosyl chloride, and one of the chiral methyl group adjacent to the tosylate group in **1.63** could be derived from a diastereoselective hydrogenation reaction. Further disconnection revealed the alkene containing mono-protected diol **1.64** as a key intermediate. Disconnection of mono-protected diol **1.64** showed that it could be accessed by a bismuth(III) coupling reaction using chiral aldehyde **1.65** and chiral bromide **1.66**. The chiral aldehyde **1.65** could be synthesized from commercially available (*S*)-citronellol

and chiral bromide **1.66** could be made from methyl (*S*)-(+)-3-hydroxyl-2-methylpropionate, which was also commercially available.



Scheme 1.17: Retrosynthetic analysis of electrophile **1.61**

Synthetic access to the second fragment **1.62** containing the remote methyl group would be more straightforward. Nucleophile **1.62** can be made from alkene containing sulfone **1.67** via desulfonation followed by ozonlysis. Further disconnection of sulfone **1.67** revealed butylsulfonylbenzene and (*R*)-citronellol, both of which were commercially available (scheme 1.18).



Scheme 1.18: Retrosynthetic analysis of nucleophile **1.62**

In the proposed synthetic strategy, hydrocarbon **1.21** was broken down into two smaller fragments. Two of the five stereogenic centres in the molecule would be made from achiral functionalities while the remaining three would come from commercial chiral building blocks. Bismuth(III) mediated coupling chemistry would be used in the synthetic sequence to construct a key intermediate. Total synthesis of the second diastereoisomer **1.22** would be attempted using the same approach.

Experimental observations and results will be discussed in detail in the following chapter.

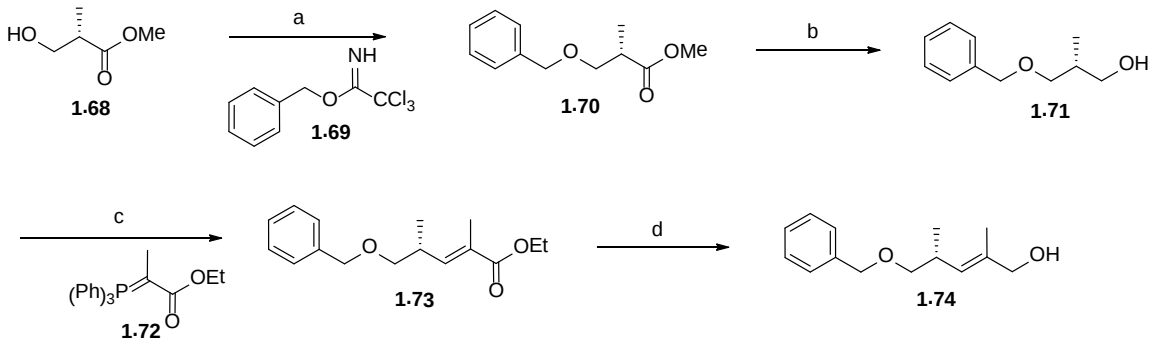
Chapter 2 Results and Discussion

2.1 Synthesis of chiral alcohol 1.74

Chiral alcohol **1.74** was identified as a key early stage intermediate in the overall synthetic strategy (scheme 1.19). Not only did it provide one of the chiral centres present in the natural product, but it was also the precursor to the allylbromide intermediate with which the bismuth (III) coupling reaction was to be investigated. It was expected that this chiral alcohol could be synthesized from the commercially available chiral building block methyl (*S*)-(+)-3-hydroxy-2-methylpropionate **1.68** in a few steps.

Acid-mediated benzylation reaction with benzyl trichloroacetimidate **1.69** worked well, delivering the benzyl-protected alcohol **1.70** in good yield. DIBAL-H reduction of ester **1.70** gave the primary alcohol **1.71** in high yield. Initial attempts at Swern oxidation immediately followed by Wittig coupling reaction with (carbethoxyethylidene)triphenylphosphorane **1.72** met with extensive racemization of the chiral methyl group observed in ester **1.73**. With the Swern oxidation giving poor chiral integrity, attention turned to the use of Dess-Martin oxidation. Dess-Martin oxidation using three equivalents of Dess-Martin periodinane buffered with $NaHCO_3$ successfully minimized the racemization problem. During the attempt to minimize racemization, it was found that a small amount of base present in the commercial bottle of stabilized phosphorane may have been the problem of the aldehyde racemization. Therefore it appeared necessary that the phosphorane needed to be washed with deionized water and dried overnight prior to use. Three equivalents of Wittig coupling phosphorane had to be used in order to achieve reasonable yield of coupling product. The desired *E*-geometry in alkene **1.73** was isolated exclusively. This experimental observation was confirmed by NOE study; irradiating the allylic proton revealed zero enhancements of the protons of methyl group on the double bond. Slow Wittig coupling reaction was seen as the thermodynamic *E*-alkene product was formed. DIBAL-H reduction of ester **1.73** in DCM proceeded cleanly to give the early stage key intermediate **1.74** in high yield. Chiral alcohol **1.74** contained the

first chiral centre be introduced sequentially in the natural product synthesis, therefore at this stage it was important to fully investigate its chiral integrity by measuring the degree of racemization by preparing Mosher's ester derivatives.

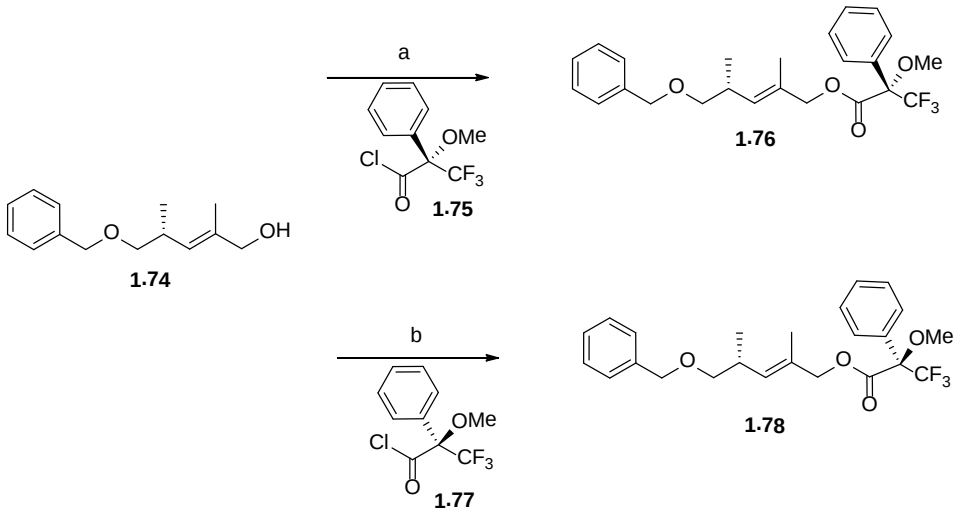


Reagents and conditions: **a**) add **1.69** in DCM, then triflic acid, DCM, RT, 16 h, 90%; **b**) DIBAL-H, DCM, -78°C - RT, 16 h, 82%; **c**) DMP, $NaHCO_3$, RT, 30 min, after work-up and isolation of crude aldehyde then add **1.72** in DCM, RT, 24 h, 68%; d) DIBAL-H, DCM, -78°C - RT, 16 h, 85%.

Scheme 1.19: Synthesis of chiral alcohol **1.74**

2.1.1 Measurement of degree of racemization of chiral alcohol 1.74

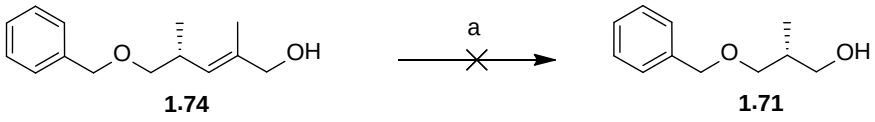
The degree of racemisation was measured by preparing Mosher's ester derivatives from alcohol **1.74** by reacting it with Mosher's acid chloride (scheme 1.20). Both reactions delivered Mosher's ester **1.76** and ester **1.78** in quantitative yield. By comparing protons in the CH_2 group adjacent to the ester group, ^1H NMR analysis of Mosher's ester **1.76** showed approximately 88% chiral integrity with the corresponding optical rotation of alcohol **1.74** of -11.7°. It was expected that chiral integrity was proportional to the optical rotation. In later synthesis, the optical rotation of alcohol **1.74** was optimized to -15.4°, hence it was believed that less than 10% of racemization took place in this batch, which was also later confirmed by a Mosher's ester derivatization study. ^{13}C NMR spectroscopy should also reveal minor discrepancies between the two, however, the ^{13}C NMR spectra of the two diastereoisomers **1.76** and **1.78** were indistinguishable in this case.



Reagents and conditions: a) Et_3N, DMAP, DCM, 16 h, 90%; **b**) Et_3N, DMAP, DCM, 16 h, 91%

Scheme 1.20: Mosher's ester derivatization

The degree of racemization was also investigated by the ozonolysis method (scheme 1.21). Reductive ozonlysis cleavage of double bond in alcohol **1.74** would, in principle, give back the starting material alcohol **1.71**. Therefore measuring the optical rotation of the product isolated from ozonolysis reaction and comparing it against the starting alcohol **1.71** would give indication as to whether racemization had taken place. Alcohol **1.74** was dissolved in MeOH and subjected to reductive ozonolysis condition at -78^{o}C. However this approach was deemed unsuccessful amid the appearance of a very messy reaction profile. ^{1}H NMR analysis of the crude material from the reaction showed oxidation may have occurred at the benzylic position. In light of these experimental observations, no further investigation regarding ozonolysis was carried out.



Reagents and conditions: a) O_3, MeOH, -78^{o}C then $NaBH_4$, RT, 16 h.

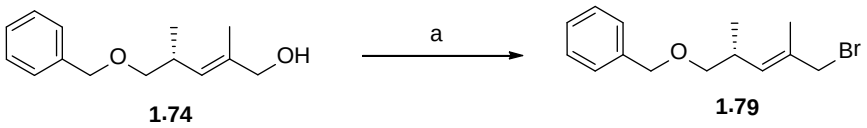
Scheme 1.21: Reductive ozonolysis of alcohol **1.74**

2.2 Study of bismuth (III) mediated coupling reaction

The bismuth(III) mediated coupling chemistry was complementary to the work on remote acyclic stereocontrol using allylstannanes and related studies using allylgermanes.[36] It was shown that the organometallic reagent generated *in situ* from allyl bromide, using low valency bismuth species generated from bismuth(III) iodide and zinc powder,[37] reacted with aldehydes to form secondary alcohols with acceptable 1,5-stereocontrol.[38,39]

The bismuth(III) mediated coupling reaction was seen as critical to the overall success of our natural product synthesis. Therefore it was decided to investigate this reaction in more detail with two model studies involving the use of two simple aldehydes: benzaldehyde and butanal, each representing aromatic and aliphatic aldehydes, respectively.

Treatment of alcohol **1.74** with triphenylphosphine and tetrabromomethane in DCM led to the formation of its corresponding bromide **1.79** in quantitative yield (scheme 1.22). The allylbromide **1.79** was then used to investigate bismuth(III) coupling chemistry in the the models studies.



1.74 **1.79**

Reagents and conditions: a) Ph_3P, CBr_4, DCM, RT, 2 h, 89%

Scheme 1.22: Preparation of allylbromide **1.79**

2.2.1 Allylbromide coupling with benzaldehyde

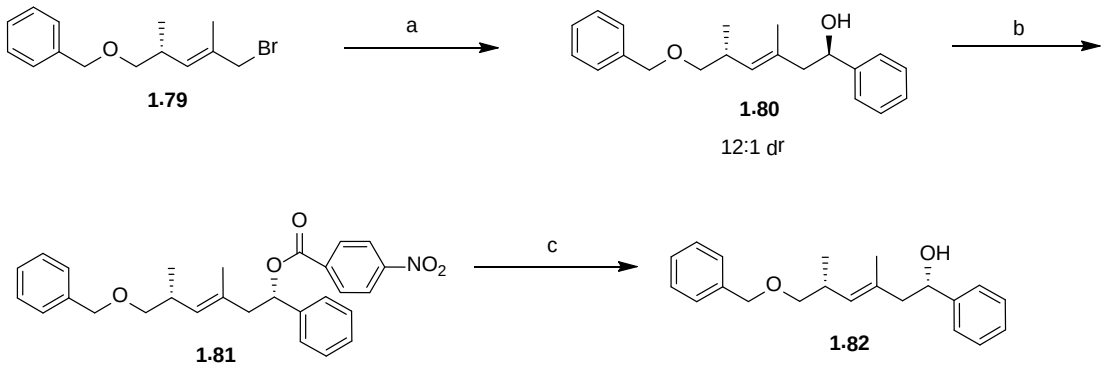
The diastereoselectivity of bismuth(III) mediated coupling reaction between aldehydes and allylbromide **1.79** was first studied using benzylaldehyde. It was found that optimal yields of the bismuth coupling product were obtained when using 3 equivalents of bismuth(III) iodide and 5 equivalents of zinc powder in THF at reflux for 2 hours. In order for this reaction to proceed, it was found that it was essential to stir bismuth(III) iodide with zinc in THF at ambient temperature for 1 hour, during which time a black precipitate was observed,

before bromide and benzaldehyde were added to the reaction, and the resulting mixture was heated at reflux for 2 hours. These reaction conditions led to the formation of the coupling product **1.80** in 60% yield after purification by flash chromatography (scheme 1.23).

According to ^{1}H NMR analysis, the 1,5-*anti* product **1.80** from the bismuth (III) coupling reaction with benzaldehyde was obtained in 12:1 diastereomeric ratio. Inverting the secondary hydroxyl group in the coupling product **1.80** should lead to the formation of the 1,5-*syn* product, which in principle should represent the minor component isolated from the bismuth(III) coupling reaction, verifying the diastereoselectivity. Inversion of secondary hydroxyl group could be achieved by a S_N2 reaction. Treatment of secondary alcohol **1.80** with *p*-nitrobenzoic acid, triphenylphosphine and diisopropyl azodicarboxylate furnished the corresponding ester **1.81** in good yield. Subsequent hydrolysis of benzoic ester **1.81** with lithium hydroxide at 60^{o}C gave the inverted secondary alcohol **1.78** in high yield.

^{1}H NMR analysis of the inverted secondary alcohol **1.82** fully supported our previous experimental observation, that this 1,5-*syn* secondary alcohol appeared to be the minor component isolated from the bismuth(III) coupling reaction. Therefore it was concluded that a diastereomeric ratio of 12:1 was achieved for the bismuth (III) coupling reaction of bromide **1.79** with benzaldehyde.

The *E*-geometry of the double bond in the coupling product **1.80** was confirmed by NOE experiments, in which irradiating the alkene proton showed no enhancement of the methyl group on the double bond. This result showed that the double bond configuration was retained during the course of the coupling process.



Reagents and conditions: a) BiI_3, Zn powder, then benzaldehyde, THF, reflux 2 h, 60%; **b**) *p*-nitrobenzoic acid, PPh_3, DIAD, THF, rt, 90%; **c**) LiOH, DCM/MeOH (1:1) 60°C, 2 h, 92%.

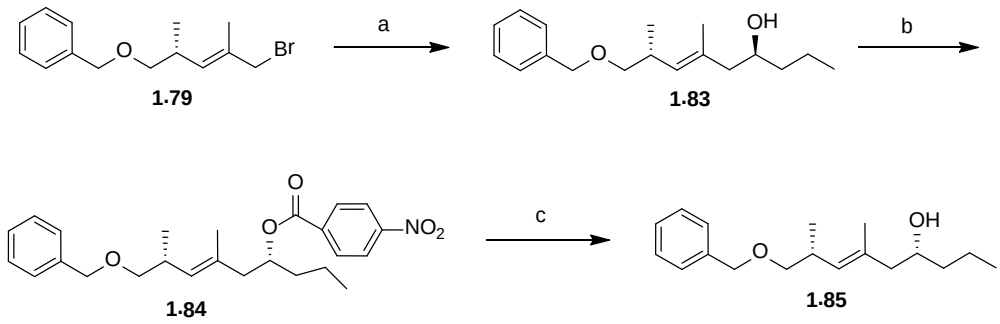
Scheme 1.23: Model study with benzaldehyde

2.2.2 Allyl bromide coupling with butyraldehyde

Having achieved a diastereoselectivity of 12:1 for the coupling reaction of allylbromide **1.79** with benzaldehyde, it was decided that another model study with an aliphatic aldehyde should be investigated in order to further determine the scope and limitation of the bismuth (III) coupling chemistry and see whether the same diastereoselectivity can be reproduced in a different system. Butyraldehyde was chosen for this model study (scheme 1.24).

A bismuth(III) coupling reaction with butyaldehyde was carried out with 3 equivalents of bismuth(III) iodide and 5 equivalents of zinc powder, in this case the 1,5-*anti* coupling product **1.83** was obtained in 56% yield. ^{1}H NMR analysis of the isolated product revealed 8% of a minor component, which presumably was the 1,5-*syn* coupling product **1.85**. These experimental results were subsequently verified by inverting the secondary hydroxyl group in coupling product **1.83**. Mitsunobu inversion reaction with *p*-nitrobenzoic acid led to the formation of ester **1.84** in good yield. Hydrolysis of ester **1.84** gave the 1,5-*syn* product **1.85** in quantitative yield. ^{1}H NMR analysis of the 1,5-*syn* secondary alcohol **1.85** has validated our previous assumption, that this material was the minor component derived from the bismuth(III) coupling reaction with butyladehyde.

According to the experimental outcome of the two model studies involving two simple aromatic and aliphatic aldehydes, it was concluded that the bismuth(III) coupling reaction using allylbromide **1.79** was successful in delivering the desired 1,5-*anti* product in good yield with high degree of diastereoselectivity.



Reagents and conditions: a) BiI_3, Zn powder, then butyraldehyde, THF, reflux 2 h, 56%; **b**) *p*-nitrobenzoic acid, PPh_3, DIAD, THF, rt, 87%; **c**) LiOH, MeOH.DCM (1:1), 60°C 2 h, 95%.

Scheme 1.24: Model study with butyraldehyde

2.2.3 Determination of 1,5-*anti* stereoconfiguration

In order to determine the 1,5-*anti* geometry of the secondary hydroxyl group in the bismuth (III) coupling product **1.80** relative to the chiral methyl group (figure 1.29), *O*-methylmandelate ester derivatives were prepared.

In 1983, Trost and his co-workers developed a method of using *O*-methylmandelate esters to determine the absolute configuration of chiral alcohols.[40] This investigation was achieved by preparing (*S*)- and (*R*)- mandelic esters with chiral alcohols and comparing their ^{1}H NMR spectra for small but noticeable upfield movement changes in chemical shift.

In Trost's model (figure 1.07), the substituent which eclipses the phenyl ring in such an extended Newman projection is then always slightly more upfield, presumably as a result of the shielding it experiences by the phenyl ring. In model **1**, this group is R', and in the chiral alcohol which corresponds to model **2**, this group is R. Thus, group R' in model **1** should show its proton shift upfield from the corresponding signal and in **2** the reverse should be true for group R.[40]

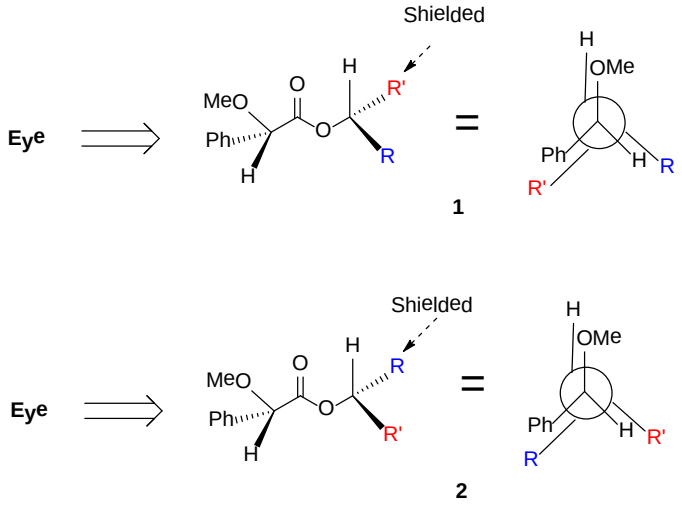
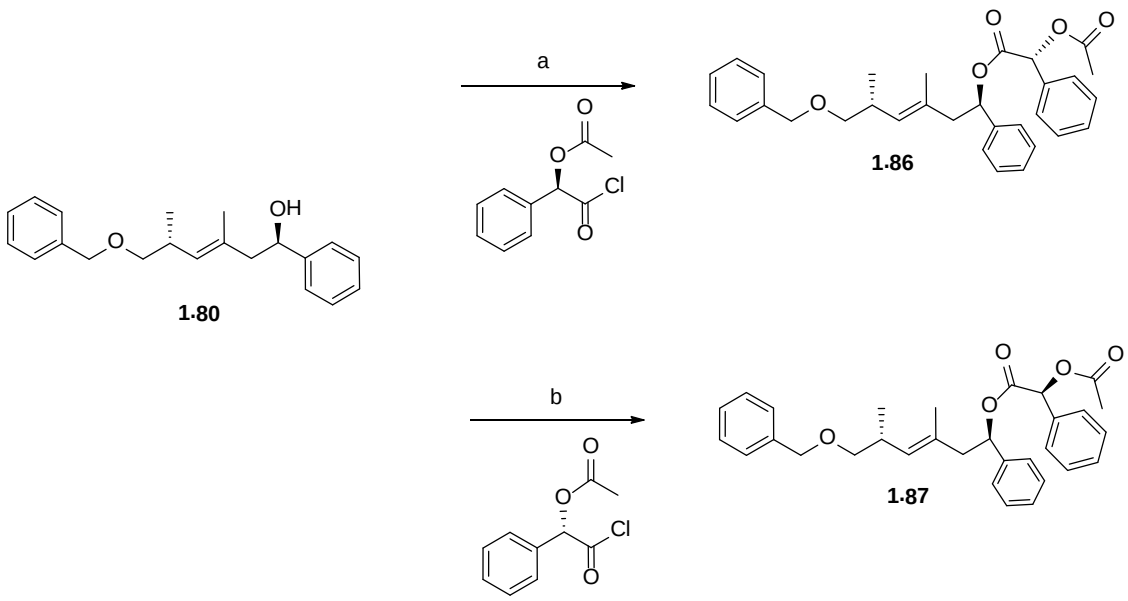


Figure 1.07: Trost model: mechanism of shielding effect (taken from reference 40)

In light of Trost's model theory, treatment of secondary alcohol **1.80** with (*R*)- and (*S*)- acetylmandelyl chloride with pyridine and DMAP led to the formation of their corresponding (*R*)- and (*S*)- mandelic esters in quantitative yield (scheme 1.25). ^{1}H NMR analysis revealed a small upfield chemical shift in ester **1.87** comparing to its diastereoisomer **1.86**. These results were consistent with the Trost model, therefore, it was concluded that during the bismuth(III) coupling reaction, the chiral methyl group in the allylbromide starting material has led to the formation of the secondary alcohol with 1,5-*anti* stereoconfiguration.



Reagents and conditions: a) (*R*)-acetylmandelyl chloride, pyridine, DMAP, DCM, 0^{o}C - rt, 93%, **b**) (*S*)-acetylmandelyl chloride, pyridine, DMAP, DCM, 0^{o}C - rt, 92%

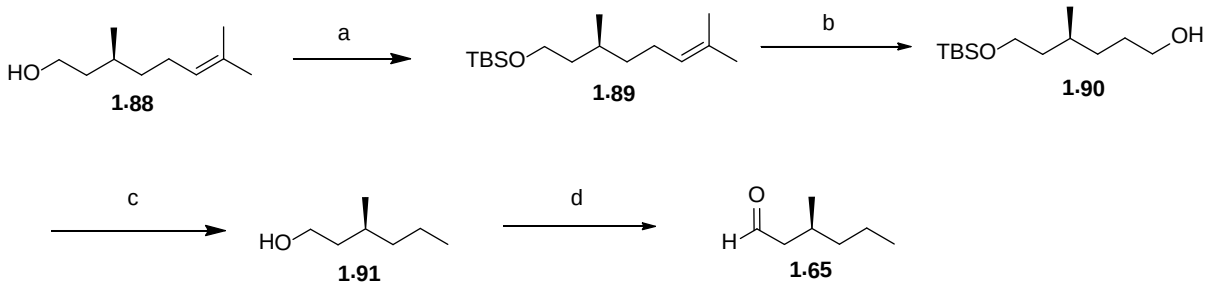
Scheme 1.25: Formation of (*S*)- and (*R*)- mandelic esters

2.3 Bismuth coupling reaction with chiral aldehyde

Having investigated the bismuth(III) coupling reaction with model studies of benzaldehyde and butyraldehyde and obtained satisfactory diastereoselectivity outcome, it was decided to move forward and apply the bismuth(III) coupling chemistry in the real system with the chiral aldehyde **1.65**.

2.3.1 Synthesis of chiral aldehyde 1.65

Chiral aldehyde **1.65** was synthesized in four standard steps starting from commercially available building block (*S*)-citronellal **1.88** (scheme 1.26). The primary hydroxyl group in (*S*)-citronellal **1.88** was protected by a *tert*-butyldimethyl silyl (TBS) group in quantitative yield. Treatment of alkene **1.89** under ozonolysis conditions, followed by $NaBH_4$ reduction, generated the mono-protected diol **1.90** in good yield. The conversion of mono-protected diol **1.90** to primary alcohol **1.91** was achieved in four telescoped steps, during which chromatographic purification was only carried out after the final hydrogenation reaction. The primary hydroxyl group in alcohol **1.90** was converted to its corresponding iodide by standard iodination conditions using imidazole, triphenylphosphine and iodine. The iodine subsequently underwent an elimination reaction facilitated by potassium *tert*-butoxide to generate its corresponding terminal alkene. Deprotection of the TBS group was achieved by HCl in dioxane. Final hydrogenation of the terminal alkene gave the desired primary alcohol **1.91**; the overall yield over the four steps was 64%. Alcohol **1.91** was oxidized to aldehhyde **1.65** by Dess-Martin oxidation.

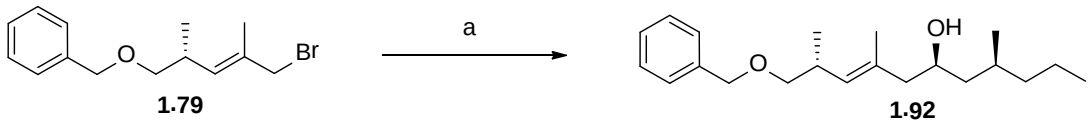


Reagents and conditions: a) Imidazole, TBSCl, THF, rt, 3 h, 98%; **b**) O_3, DCM/MeOH (1:1), -78°C, then $NaBH_4$, -78°C - rt, 89%; **c**) 1. Imidazole, PPh_3, I_2; 2. KO^{t}Bu, THF; 3. HCl in dioxane; 4. H_2, Pd/C, MeOH, 64% over 4 steps; **d**) Dess-Martion periodinane, DCM

Scheme 1.26: Synthesis of chiral aldehyde **1.65**

2.3.2 Bismuth(III) coupling reaction with chiral aldehyde 1.65

A bismuth(III) coupling reaction was successfully carried out using bromide **1.79** with chiral aldehyde **1.65**, delivering the desired 1,5-*anti* coupling product in 60% yield (scheme 1.27). Three equivalents of bismuth(III) iodide was stirred with 5 equivalents of zinc powder at room temperature in THF for 1 hour. When a black precipitate had formed, a solution of bromide **1.79** and aldehyde **1.65** in THF was then added to the bismuth-zinc reaction mixture. The resulting mixture was stirred at reflux for an additional 2 hours. According to the preceding model investigation, the reaction yield appeared to increase proportionally to the amount of bismuth(III) iodide used in the reaction, however, when more than 3 equivalents of bismuth(III) iodide were used, only a marginal increase in yield was observed. Therefore it was concluded that 3 equivalents of bismuth(III) iodide was optimal for this coupling reaction to deliver the best possible yield.

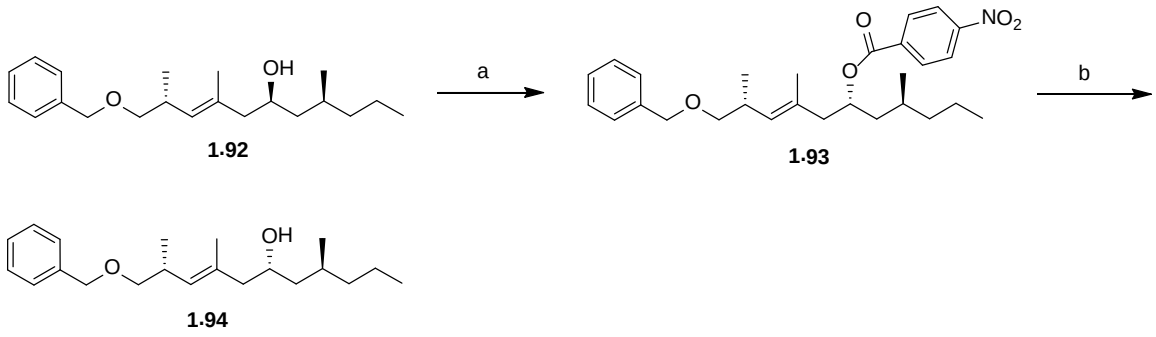


Reagents and conditions: a) BiI_3, Zn powder, then aldehyde **1.65**, THF, reflux 2 h, 60%.

Scheme 1.27: Bismuth(III) coupling with chiral aldehyde **1.65**

2.3.3 Investigation of diastereoselectivity of bismuth(III) coupling reaction

Having successfully carried out the bismuth(III) coupling reaction with the chiral aldehyde **1.65**, it was important at this stage to verify and compare the diastereoselectivity of this reaction with that from our previous model studies (scheme 1.28). Treatment of secondary alcohol **1.92** with *p*-nitrobenzoic acid under Mitsunobu reaction condition led to the formation of the corresponding ester **1.93**, which was immediately subject to hydrolysis using sodium hydroxide to give the secondary alcohol **1.94** with inversion of stereoconfiguration at the secondary hydroxyl group. Comparison of ^{1}H NMR revealed that 1,5-*syn* product **1.94** matched the minor component present in 1,5-*anti* product **1.93** from bismuth(III) coupling reaction, and the minor component accounted for less than 10%. Therefore it was concluded that the bismuth (III) coupling reaction with chiral aldehyde **1.65** was diastereoselective in delivering the 1,5-*anti* coupling product, and these results were consistent with our preceding model investigations.



Reagents and conditions: a) *p*-nitrobenzoic acid, PPh_3, DIAD, THF, rt, 89%; **b**) 2N NaOH, MeOH/DCM (1:1), 50°C, 2 h, 90%.

Scheme 1.28: Investigation of diastereoselectivity

2.4 Synthesis of key intermediate

Application of bismuth(III) coupling chemistry using chiral bromide **1.79** and chiral aldehyde **1.65** to successfully achieved 1,5-*anti* diastereoselective coupling product **1.94**, which was a partial skeleton of the natural product target. The

planned synthetic sequence leading up to the synthesis of the natural product continued from this point.

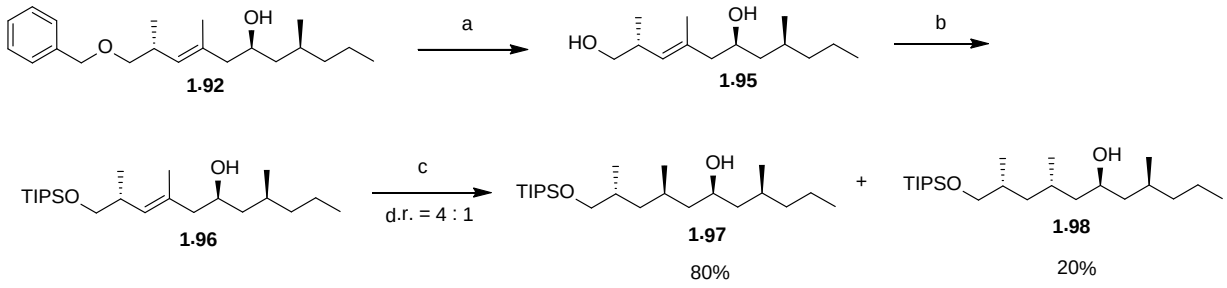
2.4.1 Diastereoselective hydrogenation

Debenzylation of secondary alcohol **1.92** was achieved in 70% yield by dissolving lithium metal in THF solution of naphthalene to give the diol **1.95** (scheme 1.29). Treatment of diol **1.95** with triisopropylsilyl chloride (TIPSCl) and imidazole selectively protected the primary alcohol in the presence of the secondary hydroxyl group to give mono-protected diol **1.96**. This mono silyl protection reaction appeared to take more than 24 hours to complete at ambient temperature, and excess TIPSCl and imidazole were required for reaction to reach completion.

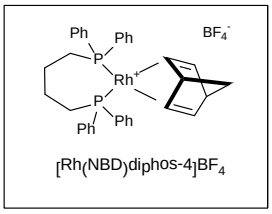
The next objective in the synthetic sequence was to introduce another stereogenic centre by diastereoselective hydrogenation reaction using an achiral catalyst. In 1984, Evans and his co-workers developed an efficient method for diastereoselective hydrogenation of linear homoallylic alcohols using a rhodium catalyst [Rh(NBD)diphos-4]BF_4.[41] The stereoconfiguration of the substituent on the double bond is controlled by the configuration of the homoallylic hydroxyl group. High pressure and high catalyst loading were reported to be essential for achieving high diastereoselectivity.

Diastereoselective hydrogenation of homoallylic alcohol **1.96** was carried out in anhydrous DCM at ambient temperature in a hydrogenation bomb at 950 psi for 5 hours. Several initial attempts failed to achieve any selectivity in favour of forming the desired hydrogenation product **1.97** over the wrong hydrogenation product **1.98**. Different catalyst loading and various pressures were tried but no diastereoselectivity was observed. However, after another attempt with a fresh batch of catalyst, the desired hydrogenation product **1.97** was achieved from the reaction with a diastereoselective ratio of 4:1. After a few more attempts using fresh catalyst at different pressures with different catalyst loading, 4:1 diastereomeric ratio was the best result obtained at 950 psi. In light of these experimental results, it was found that the selectivity of the hydrogenation

reaction generally decreased as the pressure decreased, therefore high pressure appeared to be essential for achieving high diastereoselectivity. In terms of catalyst loading, the initial 17.5 mol% catalyst loading reported in the literature was optimized to 5 mol %, delivering the best diastereomeric ratio of 4:1. Therefore, it was concluded that good quality of rhodium catalyst and high pressure were essential for achieving high diastereoselectivity.



Reagents and conditions: a) Li, naphthalene, THF, -25°C - rt, 70%; **b**) TIPSCl, imidazole, THF, rt, 81%, **c**) H_2, 5 mol % $[Rh(NBD)diphos\text{-}4]BF_4$, DCM, 950 psi, rt, 5 h, 75%.

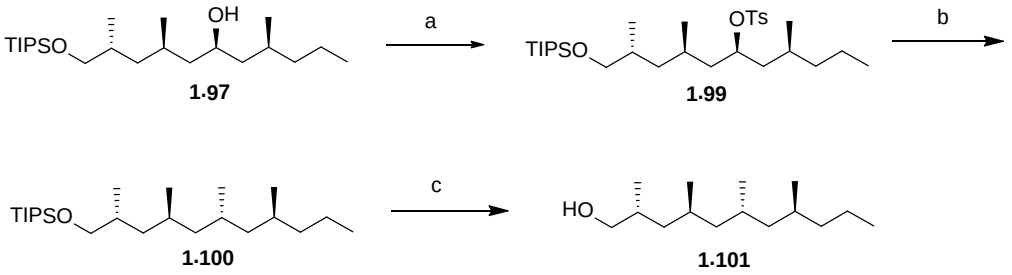


Scheme 1.29: Diastereoselective hydrogenation

2.4.2 Synthesis of key intermediate 1.101 via cuprate S_N2 displacement reaction

Having successfully introduced another stereogenic centre with the diastereoselective hydrogenation reaction, the next objective in the planned synthetic sequence was to displace the secondary hydroxyl group in alcohol **1.97** with a methyl group, in order to achieve the 2,4,6,8-methyl tetrad skeleton.

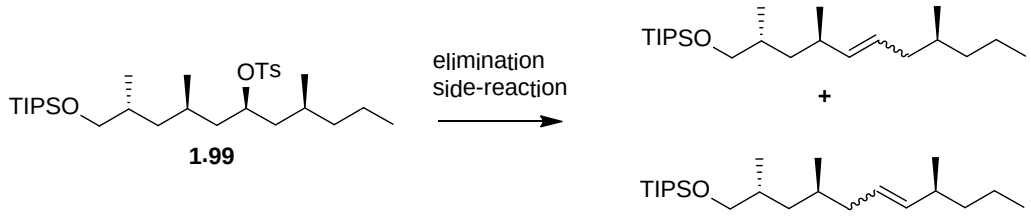
Secondary alcohol **1.97** was converted to its corresponding tosylate by tosyl chloride in the presence of DMAP in good yield (scheme 1.30). This tosylate intermediate **1.99** was set up ready for S_N2 displacement reaction using methyl cuprate. The S_N2 displacement reaction of tosylate **1.99** was initially attempted by forming the methyl cuprate *in situ* using copper(I) cyanide with methyl lithium solution in THF. No reaction took place, however, and upon increasing temperature from -78°C to -20°C, extensive elimination reaction was observed and no methyl displacement product was isolated (scheme 1.31).



Reagents and conditions: a) TsCl, DMAP, DCM, rt, 16 h, 93%; **b**) CuI, MeLi-LiI complex, Et_2O, 0°C - rt, 16 h, 21%; **c**) 4 M HCl in dioxane, THF, rt, 2 h, 91%.

Scheme 1.30: Synthesis of key intermediate **1.101**

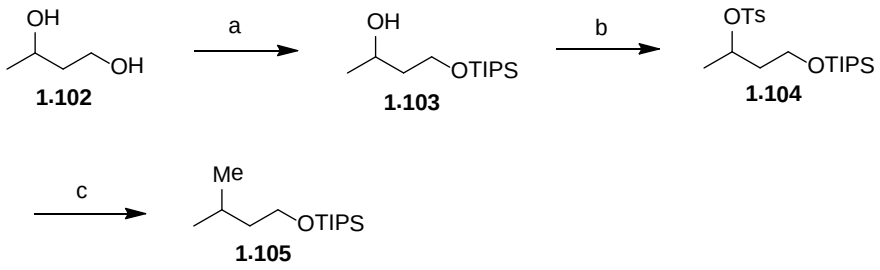
Extensive literature research was carried out to find the optimal conditions for generating methyl cuprate. According to the report by Lipshutz and his co-workers on spectroscopic studies of copper(I) iodide derived organocuprates,[42] it has been reported that the presence of lithium iodide (LiI) may be essential for the formation and stabilization of methyl cuprate (Me_2CuLi), and in the absence of LiI the concentration ratio between methyl lithium and Me_2CuLi substantially increases. In light of this report, another reaction was attempted using copper(I) iodide with 1 molar THF solution of methyl lithium – lithium iodide complex. This time, despite the fact that the elimination products were still observed as the major products of the reaction, S_N2 displacement product **1.100** was isolated in 21% yield. Several other attempts were made with various reaction temperatures, length of reaction and different amount of copper(I) iodide and methyl lithium – lithium iodide complex; however the best yield obtained for the desired product formation was only 21%.



Scheme 1.31: Elimination side-reactions

Model studies concerning methyl cuprate displacement of simple secondary tosylate group were investigated (scheme 1.32). Tosylate **1.104** was prepared from diol **1.102** followed by mono silyl protection to form mono-protected silyl ether **1.103**. S_N2 displacement reaction using methyl cuprate was attempted on

this model tosylate, and quantitative displacement product **1.105** was obtained. Therefore it was concluded that the exceptionally low yield in the S_N2 methyl cuprate displacement reaction of tosylate **1.99** to form 2,4,6,8-methyl tetrad **1.100** was substrate specific, presumably because of the adjacent methyl groups that make the nucleophilic attack less accessible while promoting the elimination side-reactions to take place.



Reagents and conditions: a) TIPSCl, imidazole, THF, rt, 16 h, 65%; **b**) TsCl, DMAP, DCM, 16 h, 82%; **c**) CuI, 1 M MeLi-LiI complex THF solution, Et_2O, 0°C - rt, 91%.

Scheme 1.32: Methyl cuprate reaction model study

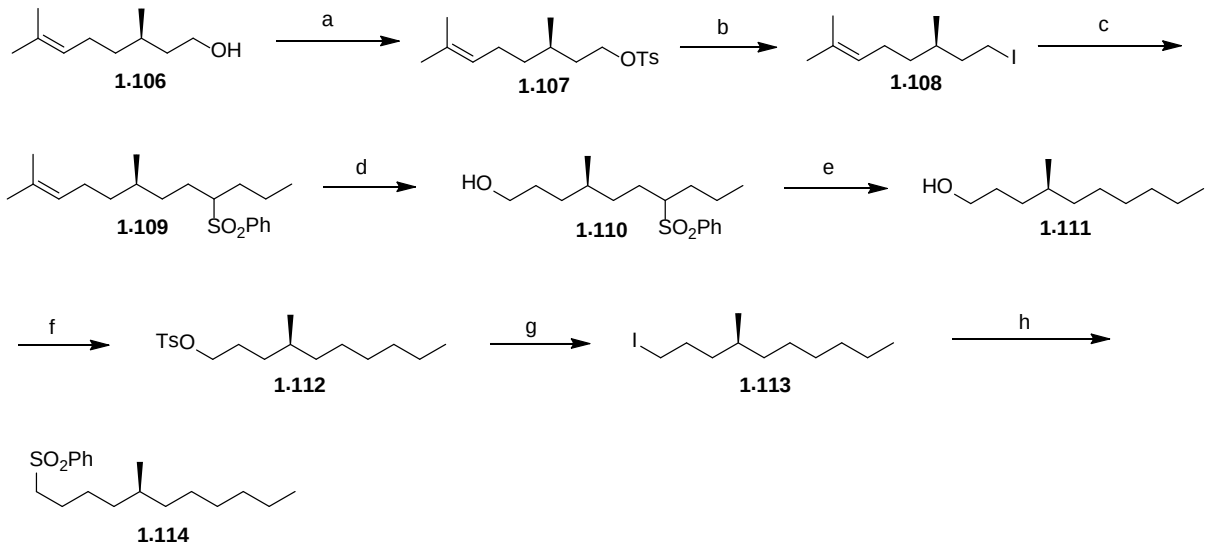
Having successfully constructed the 2,4,6,8-*anti-anti-anti*- methyl tetrad skeleton **1.100**, the TIPS group was removed by 4 M HCl in dioxane to give the key intermediate primary alcohol **1.101** in high yield (scheme 1.30).

2.5 Synthesis of the second fragment 1.114

Following the successful synthesis of the 2,4,6,8-*anti-anti-anti*- methyl tetrad containing intermediate **1.101**, the next objective was to construct the right hand side of the hydrocarbon natural product. Retrosynthetic analysis showed that the sulfone intermediate **1.114** bearing one methyl stereogenic centre could be easily accessed from commercial chiral building block (*R*)-citronellal **1.106**.

(*R*)-citronellal **1.106** was converted to the tosylate **1.107** by tosyl chloride with 4-dimethylamino pyridine (DMAP) in quantitative yield. Treatment of tosylate **1.107** with sodium iodide in acetone at reflux afforded the corresponding iodide **1.108** (scheme 1.33). Linear carbon chain extension was achieved by coupling iodide **1.108** with *n*-butylphenyl sulfone to afford sulfone **1.109** as a mixture two diastereomers. Subsequent reductive ozonolysis cleanly cleaved the double bond in the sulfone **1.109** and led to the formation of primary alcohol **1.110** in good

yield. The sulfone group was subsequently removed by a dissolving metal reaction using sodium amalgam in MeOH to generate alcohol **1.111**. Primary alcohol **1.111** was then converted to its corresponding iodide **1.113** via the tosylate intermediate **1.112** in quantitative yield. Finally iodide **1.113** was coupled with methylphenyl sulfone to afford the right hand side intermediate **1.114**, which was ready to couple with the left hand side intermediate **1.101** to form the hydrocarbon skeleton.



Reagents and conditions: a) TsCl, DMAP, DCM, rt, 16 h, 96%; **b**) NaI, acetione, reflux, 16 h, 90%; **c**) *n*-butylphenyl sulfone, DMPU, *n*-BuLi, THF, -40°C, then **1·108**, rt, 16 h, 95%; **d**) O_3, DCM/MeOH (1:1), -78°C, then $NaBH_4$, rt, 16 h, 85%; **e**) Na/Hg, MeOH, rt, 16 h, 73%; **f**) TsCl, DMAP, DCM, rt, 16 h, 99%; **g**) NaI, acetione, reflux, 16 h, 90%; **h**) $PhSO_2Me$, DMPU, *n*-BuLi, THF, -40°C, then **1·113**, rt, 16 h, 73%.

Scheme 1.33: Synthesis of second fragment **1.114**

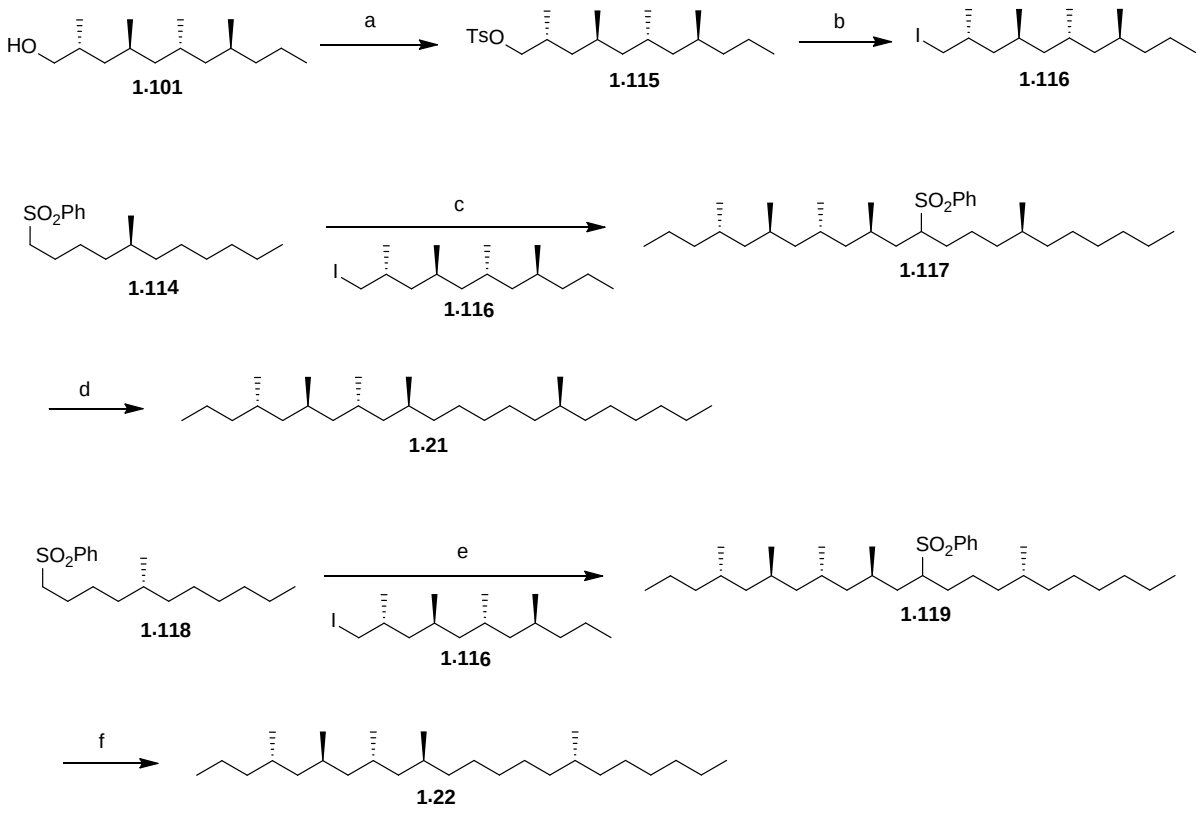
2.6 Final synthesis to form hydrocarbon natural product

With both sulfone **1.114** and 2,4,6,8-*anti-anti-anti*- methyl tetrad containing alcohol **1.101** in hand, it was possible to synthesize the two diastereomeric hydrocarbon natural products **1.21** and **1.22**.

Alcohol **1.101** was converted to its corresponding iodide **1.116** via tosylate intermediate **1.115** in high yield (scheme 1.34). Coupling of sulfone **1.114** with iodide **1.116** using *n*-BuLi at -40°C afforded the coupling product **1.117** as a mixture of two diastereoisomers in modest yield. The lower isolated yield for this sulfone coupling reaction with iodide was probably due to steric hindrance. Finally, desulfonation of **1.117** with sodium amalgam in methanol followed by

flash chromatography using 100% pentane afforded the hydrocarbon (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21** in good yield.

Sulfone intermediate **1.118**, which was the enantiomer of sulfone **1.114**, was synthesized by analogy following the same reaction sequence as the preparation for sulfone **1.114**, except the starting building block used in this case was (*S*)-citronellal. Coupling of the sulfone intermediate **1.118** with iodide **1.116** led to the formation of coupling product **1.119** as a mixture of two diastereoisomers. Upon desulfonation using sodium amalgam in methanol (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane **1.22** was isolated in good yield.

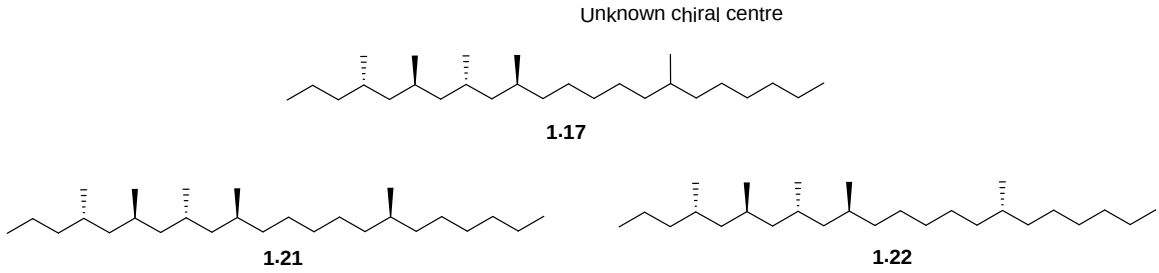


Reagents and conditions: a) TsCl, DMAP, DCM, rt, 16 h, 85%; **b**) NaI, acetone, reflux, 16 h, 90%, **c**) *n*-BuLi, DMPU, THF, -40°C, then **1·116**, rt, 16 h, 45%; **d**) Na/Hg, MeOH, 6 h, 83%; **e**) *n*-BuLi, DMPU, THF, -40°C, then **1·116**, rt, 16 h, 34%; **f**) Na/Hg, MeOH, 6 h, 85%.

Scheme 1.34: Final synthesis to form the hydrocarbon natural product

2.7 Determination of relative stereochemistry of cuticular hydrocarbon natural product by ^{13}C NMR spectroscopy comparison

The next object was to compare the ^{1}H and ^{13}C NMR of the synthetic diastereomers **1.21** and **1.22** with spectroscopic data of the real natural hydrocarbon natural product **1.17** to determine its relative stereochemistry (scheme 1.35).



Scheme 1.35: Structures of natural product and synthetic diastereomers

^{1}H NMR spectra of synthetic diastereomers **1.21** and **1.22** were compared but this method has been proven ineffective because of extensive proton overlapping between the two. Therefore it was necessary to compare their ^{13}C NMR spectra.

^{13}C NMR spectra of (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21** and (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane **1.22** were compared with the ^{13}C NMR spectra of the natural product **1.17** (figure 1.08).[43] The below spectra looked almost identical to each other. More precise analysis was therefore warranted to determine the relative stereochemistry of the natural product. In this case the ^{13}C chemical peaks were measured to four decimal places in order to reveal small but noticeable discrepancies.

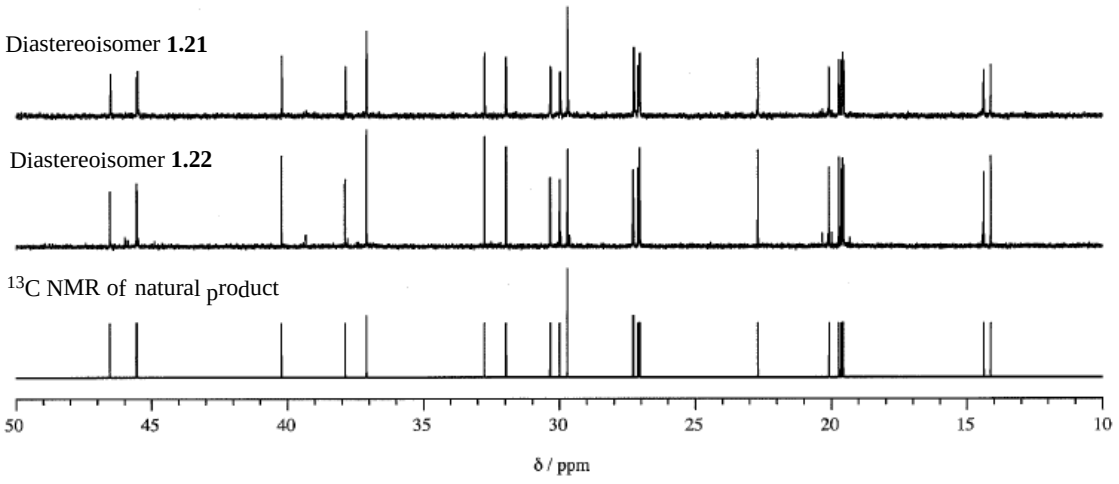


Figure 1.08: ^{13}C NMR comparison

Having prepared the two synthetic diastereoisomers **1.21** and **1.22**, it remained to establish which diastereoisomer corresponded to the natural product. Unfortunately, no sample of the natual product was available and its optical rotation was unknown, and so it was necessary to compare the ^{13}C NMR data of the two epimers **1.21** and **1.22** with the data available for the natual product. NMR samples were parepared in deuterated chloroform at concentration of 3 mg per mL. NMR data were obtained at 298 K. As the ^{13}C NMR spectra similar of the two epimers were very similar, a quantitative comparison was used. The original data were measured at high field (17.6 T) and reported to 1 ppb precision, so spectra measured at 9.4 T were processed with Gaussian weighting and extensive zero filling to allow detaied comparison.

The ^{13}C NMR chemical shifts of each diastereomers and that of the natural product are tabulated below (figure 1.09).

Natural product assignment	Compound **1.21**	Compound **1.22**	Natural product **1.17**
C7	46.5428	46.5191	46.538
C9	45.566	45.5533	45.561
C5	45.5496	45.5296	45.545
C3	40.2229	40.2101	40.218
C11	37.8848	37.8702	37.879
C15	37.1003	37.0966	37.093
C17	37.0948	37.0884	37.089
C16(CH)	32.7567	32.7439	32.751
C20	31.9639	31.9603	31.957
C13	30.3457	30.3311	30.339
C10(CH)	30.0012	29.9757	29.996
C4(CH)	29.7169	29.6951	29.712

C19	29.6987	29.6951	29.712
C6(CH)	27.3003	27.2689	27.295
C8(CH)	27.2933	27.2629	27.291
C14	27.1128	27.1037	27.106
C12	27.0672	27.0599	27.06
C18	27.0508	27.0472	27.044
C21	22.699	22.699	22.694
C2	20.0803	20.0766	20.074
Me-16	19.7286	19.7176	19.724
Me4/6/8/10	19.6502	19.6338	19.646
Me4/6/8/10	19.5882	19.5773	19.585
Me4/6/8/10	19.5682	19.5518	19.564
Me4/6/8/10	19.5518	19.5354	19.549
C1	14.3854	14.389	14.38
C22	14.1212	14.1266	14.116

Figure 1.09: ^{13}C NMR chemical shifts

In order to present the chemical shift differences between the ^{13}C NMR spectra of the synthetic compounds **1.21** and **1.22** and the natural product, scattered graphs were plotted with chemical shift differences shown in the y-axis and ^{13}C NMR chemical shifts shown in the x-axis. This method measured the deviation range of differences in the ^{13}C NMR chemical shifts between the natural product and the synthetic diastereomers. The objective was to analyze the scattered graphs in order to determine which diastereomer matched the relative stereoconfiguration of the natural product, i.e. the less scattered the graph would represent a better structural match.

Except for one out-of-range data point, the scattered graph showing chemical shift differences between the natural product **1.17** and the synthetic diastereomer

(4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21** revealed a near-perfect match (figure 1.10), i.e. compound **1.21** has represented a very good structural match to the natural product. The comparison of natural product **1.17** with the other synthetic diastereomer (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane **1.22** showed a much more dispersed picture amid a much wider deviation range (figure 1.11), therefore it was concluded that compound **1.22** was a poor structural match to the natural product.

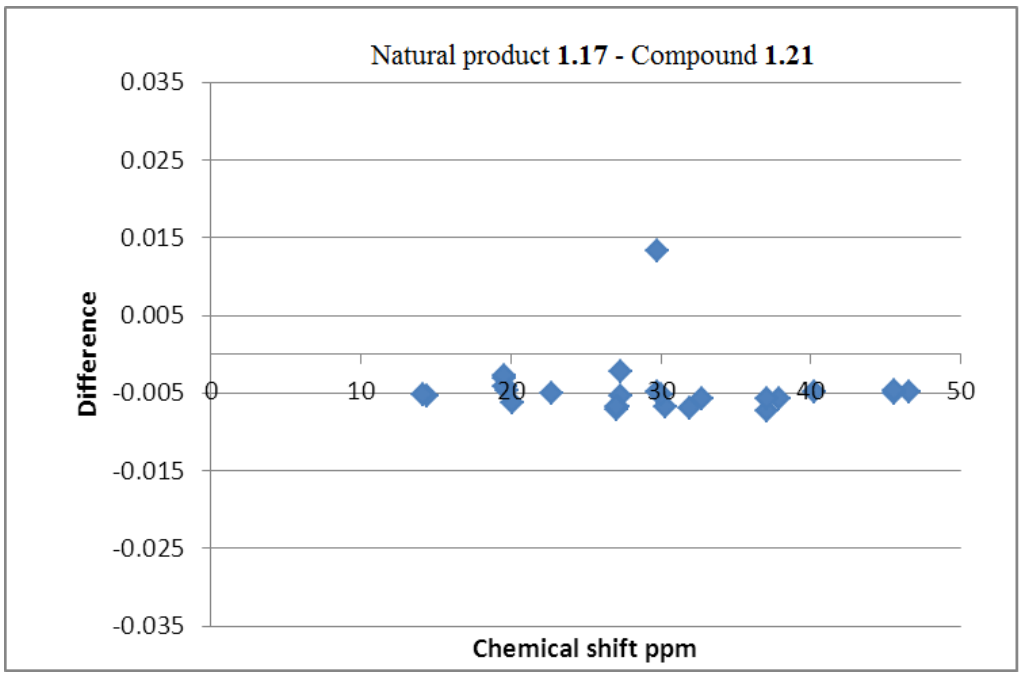


Figure 1.10: Comparison of natural product with compound **1.21**

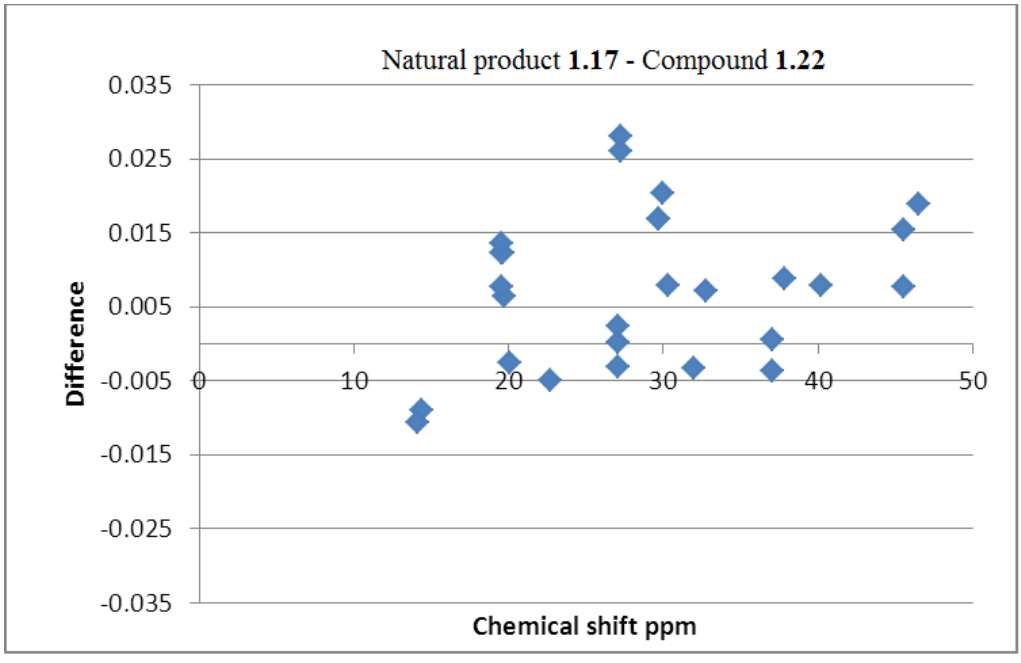


Figure 1.11: Comparison of natural product with compound **1.22**

2.8 Conclusion

In this project, investigation of the diastereoselectivity of bismuth(III) coupling chemistry was accomplished by a model study using two simple aromatic and aliphatic aldehydes.[44] The outcome of this model investigation was successfully applied in the total synthesis of a cuticular hydrocarbon natural product. In order to determine the relative stereochemistry of the natural product **1.17**, both diastereoisomers (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21** and (4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane **1.22** were synthesized. ^{13}C NMR chemical shift comparison revealed that the synthetic compound **1.21** represented a near-perfect match with the natural product, therefore it was concluded that the natural product **1.17** has the same relative stereochemical configuration as the synthetic compound (4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane **1.21**.[45]

SECTION TWO

Towards the Total Synthesis of Vioprolide D

Chapter 1 Introduction

1.1 Preface

This section demonstrates the work completed by the author towards preliminary studies of the total synthesis of vioprolide D in the family of vioprolides, which are newly discovered antifungal and cytotoxic peptolides from *Cystobacter violaceus*.

Two strategies towards the construction of vioprolide D have been investigated. The first of these involved breaking down the macrocyclic molecule into three equal-sized fragments, each containing three amino acid residues. The synthesis of each fragment will be described in the relevant chapters of the text.

Based on the results from this initial strategy, a modified strategy was proposed and investigated. The second strategy involved disconnection of the molecule into two fully assembled fragments in which the more challenging part of the syntheses was the construction, without epimerization, of a tetrapeptide intermediate containing both dehydrobutyrine and thiazoline functionalities. Successful access to this key intermediate would not only lead to the total synthesis of vioprolide D, but also open doors of opportunity to synthesize a range of other analogues of the macrocylic peptides.

The opening chapter is intended to review the biological background and medicinal importance of the vioprolides family, followed by review of general approaches used in peptide synthesis. The intrinsic synthetic challenges involved in the project will also be discussed in this chapter.

1.2 Introduction to depsipeptides

A depsipeptide is a peptide in which one or more amide bonds are replaced by ester bonds.[46] Depsipeptides have often been used in research to probe the importance of hydrogen bond networks in protein folding kinetics and thermodynamics.

Naturally occurring depsipeptides are usually cyclic and they are common metabolic products from microorganisms. Depsipeptides have also emerged as an important source of biologically active peptides and promising lead structures for the research and discovery of novel drugs candidates.[47] This class of natural products has been disvcovered in many organisms, such as bacteria, fungi, and marine organisms. It is very well known that cyclic depsipeptides and their derivatives exhibit a diverse spectrum of biological activities, including insecticidal, antimicrobial, antiviral, antitumor, and anti-inflammatory activities. They have shown the most promising therapeutic potential as anticancer and particularly antimicrobial agents. However, difficulties in accessing large quantities of this class of natural products and their synthetic analogues significantly reduced the scope of cyclic depsipeptides exploitation as lead compounds for development of new potential drug molecules.

Vioprolides A – D (figure 2.01) belong to this class of compounds.

1.3 Discovery and biological background of vioprolides family

In a screening of myxobacteria for antifungal metabolites the *Cystobacter violaceus* strain, Cb vi35, was selected for its activity against *Pythium debaryanum*. After fermentation in the presence of the adsorber resin XAD-1180, analytical HPLC showed that the product isolated by preparative TLC consisted of four related components, later called vioprolides A – D (figure 2.01).[48]

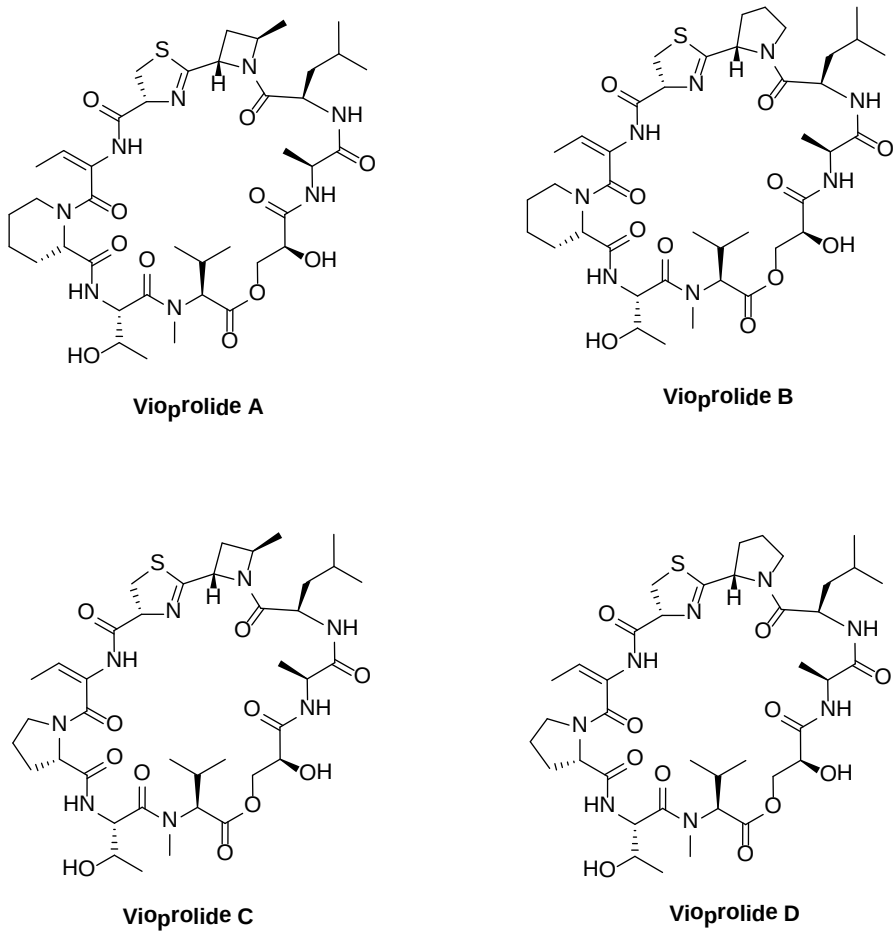


Figure 2.01: Structures of vioprolides A – D

Vioprolides A – D are toxic to mammalian cells and show a broad spectrum of antifungal activity.[49] Interestedly, Vioprolide D is the most active compound against a variety of fungi and yeasts, but the least toxic against mammalian cells (LD_{50} = 200 ng/mL) and the brine shrimp *Artemia salina* (LD_{50} > 20 µg/mL). In contrast, Vioprolides A – C show a lower antifungal activity but a significantly higher toxicity against mammalian cells (LD_{50} = 2 – 30 ng/mL) and *Artemia salina* (LD_{50} = 2 – 20 µg/mL).

Found in various bacteria, like Myxobacteria, secondary metabolites such as vioprolides have been described as having biological activity.[50] Cyclic peptides, in particular vioprolides, can be in the use for the treatment and prevention of various diseases, disorders and other conditions.[51] In particular, they are useful in enhancing and/or supporting interferon type I, treatment and prevention of diseases. Furthermore it has been demonstrated that these compounds have anti-viral activity, e.g. inhibiting replication of the virus or to protect subjects from

viral infection. In addition, it has been shown these compounds have anti-proliferative activity, thus, they are useful in treating disorders like cancer and tumours (figure 2.02).

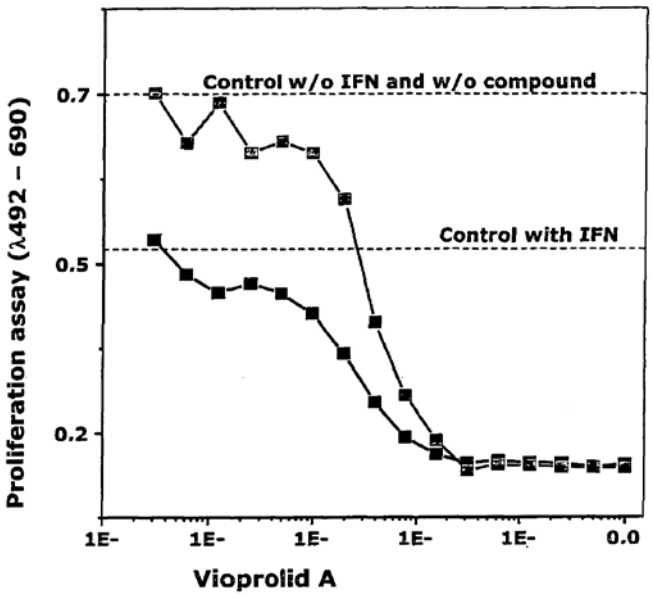


Figure 2.02: Dose response curve for the cyclic peptide vioprolide A when combined with Interferon alpha tested in the system (Graph taken from reference 51)

Vioprolides A - D consisting of eight amino acid residues and a glyceric acid unit were determined by spectroscopic methods and total hydrolysis. The absolute configurations of the building blocks were established by GC analysis on chiral stationary phases, and comparison with authentic reference compounds. Authentic samples of the four stereoisomers of 4-methylazetidinecarboxylate (Maz) were synthesized and their absolute configuration was determined by X-ray structural analysis.[52] It has been found that the (2*S*,4*R*) configuration found for Maz corresponds to the L configuration of proline, which occupies its position in vioprolides B and D. Common building blocks of the vioprolides A – D are L-Ala, L-Cys, D-Leu, L-Thr, L-MeVal, (*E*)-dehydrobutyrine (*E*-Dhb), and L-glyceric acid. Two variable positions were occupied by L-Pro or L-homo-Pro and L-Pro or trans-(2*S*,4*R*)-4-methylazetidinecarboxylic acid [(2*S*,4*R*)-Maz]. Two conformational isomers were detected for each of the vioprolides A – D in $CDCl_3$ in a ratio of 3:2 (2D – ^{1}H NOESY).[48] However, despite their interesting biological activity and molecular complexity, no previous total synthesis of vioprolides has been reported in the literature.

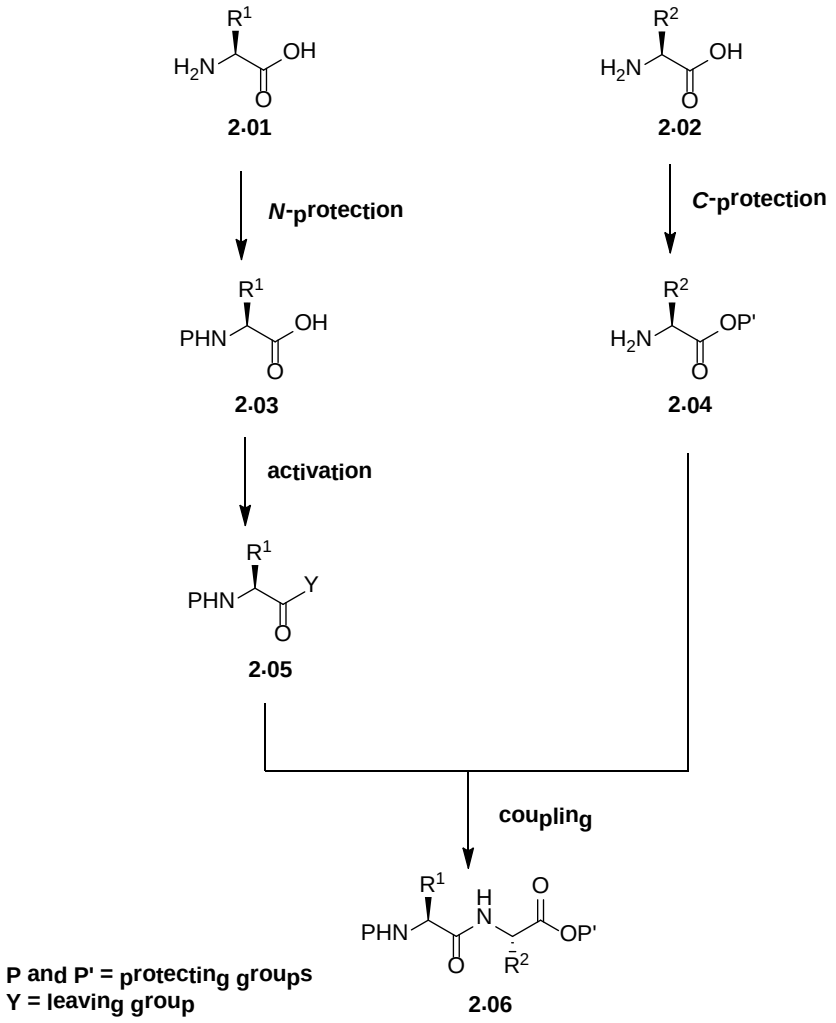
1.4 General approaches to peptide synthesis

1.4.1 Peptide bond formation

The initial goal in peptide synthesis is the formation of an amide linkage between two amino acid residues (e.g. **2.01** and **2.02**) (scheme 2.01). Two amino acids will combine to form a salt at room temperature, and if heated at elevated temperatures, they can lose a water molecule and form a peptide (amide) bond. However, such harsh conditions (that require heating) are not considered suitable when starting materials are enantiomerically pure and preservation of chiral integrity is necessary. Since each individual amino acid is a bifunctional molecule with two reaction sites of an amino *N*-terminal and a carboxylic *C*-terminal, reaction between two different amino acids can, in principle, lead to the formation of four different dimers, as well as trimers and tetramers, etc. Therefore, in order to achieve a single dipeptide product, the functional groups which do not participate in the coupling process, must be protected by suitable protecting groups.

The ideal protecting group should be installed and removed under mild reaction conditions, and also should be chemically inert to coupling conditions. The amino group is usually protected as a carbamate functionality and although a wide variety of carbamate derivatives are available, *tert*-butyl (boc), benzyl (Cbz) and fluorenylmethyl (Fmoc) groups are the most widely used protecting groups in peptide coupling chemistry. The carboxylic acid group is normally protected as its *tert*-butyl (boc), benzyl (Bn), or allyl ester (All). The protected amino acids **2.03** and **2.04** can undergo a peptide coupling reaction to generate dipeptide molecule **2.06** with a much reduced risk of side product formation. During the course of the reaction, the *C*-terminal protected amino acid **2.04** acts as the nucleophilic component, and the *N*-terminal protected amino acid **2.03** is the electrophilic component. In order for peptide bond formation between **2.03** and **2.04** to proceed under mild conditions, “activation” is required at the carboxyl group in **2.03**. By definition, any electronegative atom or group that acts as a

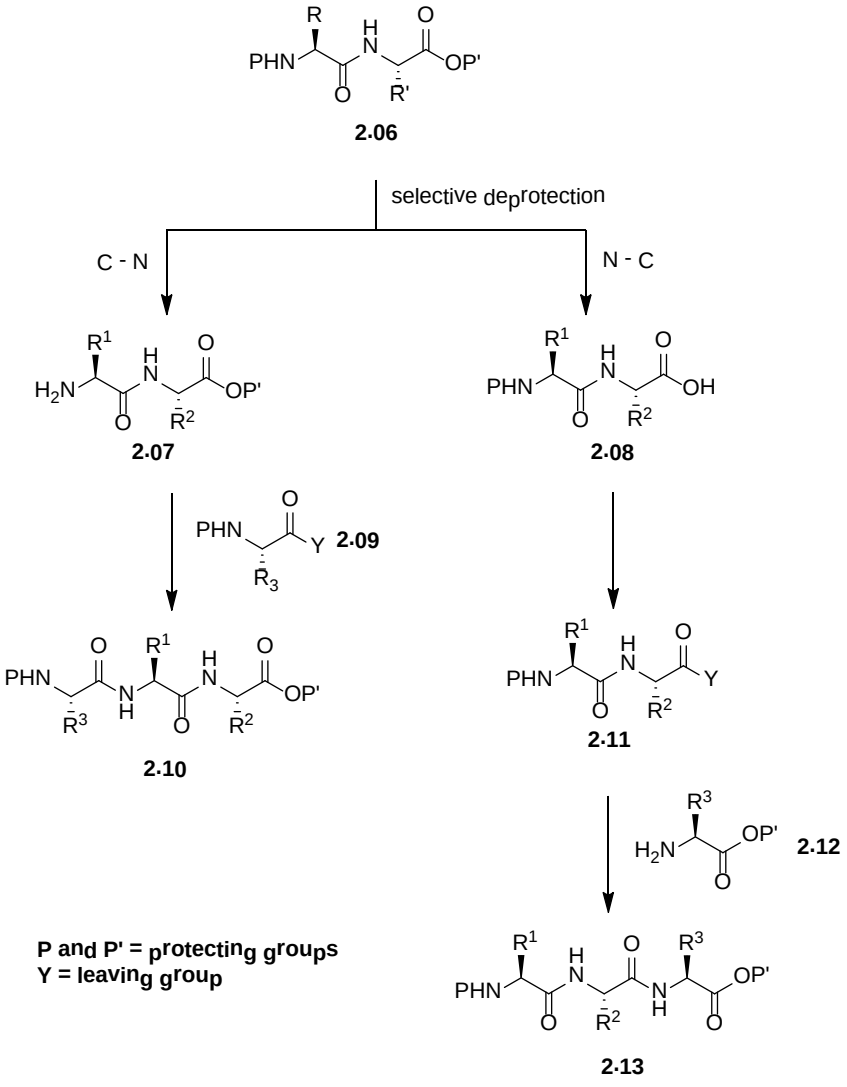
good leaving group can be considered as an activating group in **2.05**. Typical leaving groups include acyl azides,[53] anhydrides,[54] and various activated esters.[55] The carboxyl group can be activated in a separated step or generated *in situ* during the course of the coupling reaction in the presence of the amino component. In the presence of the activated carboxyl group, coupling between the two residues can proceed to give a protected dipeptide unit **2.06**. The peptide chain can be extended by iteration of this process.



Scheme 2.01: Peptide bond formation

1.4.2 Process of chain elongation in peptide synthesis

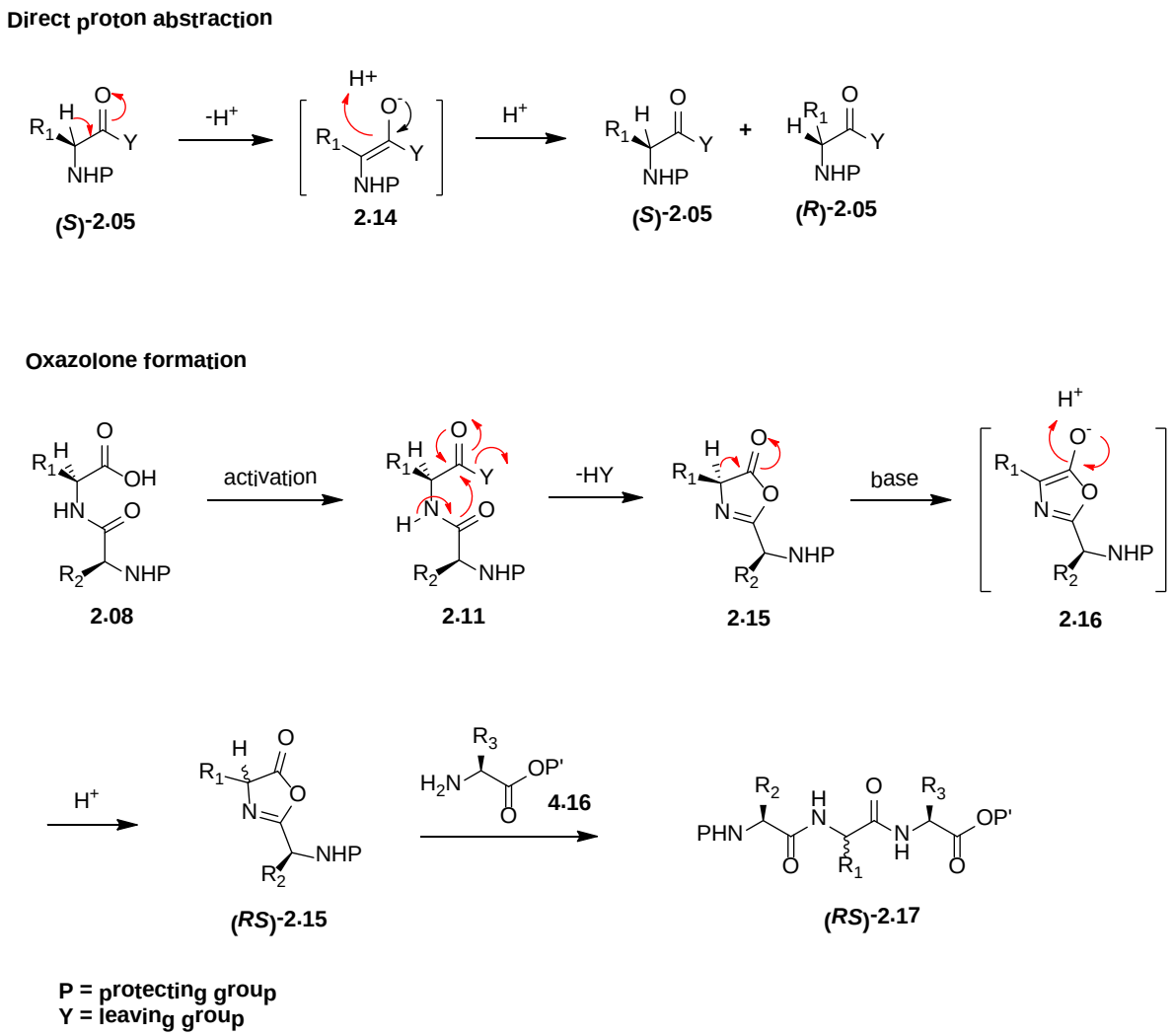
Two general strategies of peptide chain elongation process are known: the *N*-*C* and the *C*-*N* strategies.[56] The *C*-*N* strategy requires deprotection of the *N*-terminal (i.e**. 2.06** to **2.07**) and coupling with a carboxyl-end activated amino acid **2.09** while the *N*-terminal is protected. The *N*-*C* strategy requires deprotection (i.e. **2.06** to **2.08**) and activation (i.e. **2.08** to **2.11**) of the carboxyl group in the dipeptide and coupling with a *C*-protected amino acid **2.12**. Although nature utilizes the *N*-*C* strategy for peptide assembly, the *C*-*N* strategy is generally preferred in laboratory peptide synthesis because of the reduced tendency towards racemisation (scheme 2.02).



Scheme 2.02: Peptide chain elongation process

1.4.3 Side reactions in peptide synthesis

The formation of highly reactive intermediates in the carboxyl group activation process can lead to undesired side reactions, resulting in racemization of amino acid residues during peptide coupling steps. Direct proton abstraction and the formation of oxazolones upon activation (scheme 2.03) are the two mechanisms proposed to explain the racemization process.[57,58]



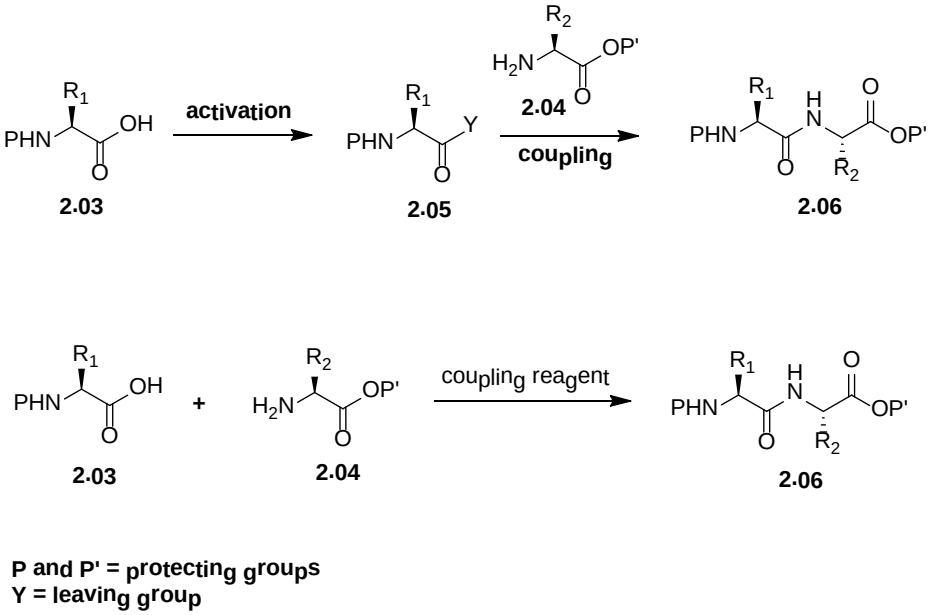
Scheme 2.03: Proposed mechanism for peptide racemization process

As the presence of an electron withdrawing group in the activated intermediate (*S*)-**2.05** increases the acidity of the α-proton, if excess base is present, proton abstraction will generate an enolate **2.14**, which can then be reprotonated from either face resulting the formation of undesired stereoisomers in 1:1 ratio.

Racemization via oxazolone formation has been studies by Kemp and co-workers.[59] It involves the conversion of activated intermediate **2.11** into oxazolone compound **2.15**, which can be readily deprotonated in the presence of base to form the intermediate **2.16**.[60,61,62] This intermediate can then be reprotonated from either face to produce a mixture of diastereomeric oxazolones (*RS*)-**2.15**, which will lead to racemization of amino acid residue, as in (*RS*)-**2.17**. One of the reasons for the preference of the *C-N* chain elongation strategy over the *N-C* strategy in peptide synthesis is the high tendency in the latter strategy to form the diastereomeric oxazolone intermediates.

1.4.4 Peptide coupling approaches and coupling reagents

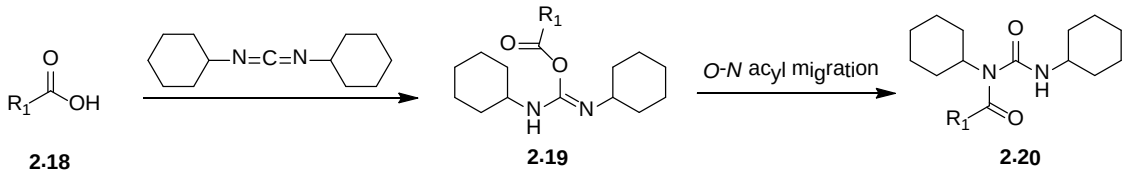
Extensive research has been conducted to develop efficient methods and reagents for peptide coupling. In general, peptide coupling approaches can be classified into two categories: those that involve activation of the carboxyl group in a separate step, in the absence of the amino acid component, and those where activation of the carboxyl group is done *in situ* in the presence of the amino component (scheme 2.04).



Scheme 2.04: two categories of general peptide coupling approaches

Utilization of acid chlorides to form amide linkages in simple molecules was historically one of the first known coupling procedures in the synthesis of peptides. However, the harsh conditions typically used to prepare acid chloride derivatives (e.g. $SOCl_2$, $POCl_3$) are considered inappropriate for sensitive compounds. When used in the synthesis of peptides, acid chlorides undergo a variety of side reactions. As an alternative to acyl chloride, the method using acyl azide, introduced by Curtius in the beginning of twentieth century, is still used in the synthesis of peptides.[63] It has been shown that acyl azides are slow to racemize during coupling steps and have been used to suppress other side reactions.[64] Alternatively, acyl azides can be prepared *in situ* by reacting *C*-terminus protected amino acid with diphenylphosphoryl azide (DPPA.[65,66]

Amide coupling reactions using coupling reagents begin with the *in situ* formation of reactive intermediates. One of the most popular coupling reagents in peptide chemistry is *N*,*N*'-dicyclohexylcarbodiimide (DCC).[67] Despite the possibility of side reactions associated with the use of DCC in peptide coupling reactions, which are racemization and *O*-*N* acyl migration (scheme 2.05) due to the over-activation of the carboxyl group, this is reagent is widely used in peptide synthesis. However, the by-product *N*,*N*'-dicyclohexylurea, derived from the use of DCC during coupling step, cannot be easily removed from the reaction mixture. This practical inconvenience has led to the search for other carbodiimide derivatives that can produce easily removable by-products. Water soluble carbodiimide 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC-HCl) was later developed as a more efficient coupling reagent. In the case of EDC-HCl, the urea by-product is water soluble and can be easily removed by aqueous work up.

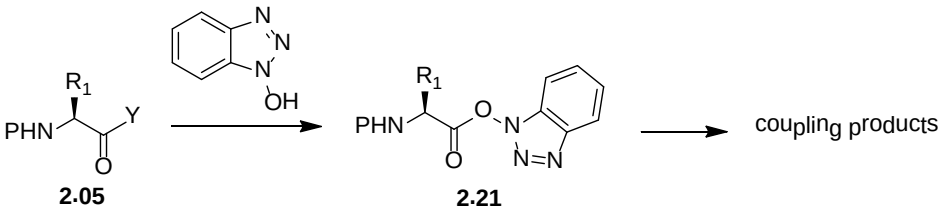


2.18 **2.19** **2.20**

Scheme 2.05: DCC used in amide coupling

The problem associated with over-activation of the carboxyl group in amide coupling approaches can be mitigated by using additives such as 1-

hydroxybenzotriazole (HOBt)[68] and *N*-hydroxysuccinimide (HONSu).[69] The effectiveness of coupling additives has been interpreted as a reduction in reactivity of the carboxyl group by the formation of HOBt or HONSu esters, which favour peptide coupling reactions over side reactions (scheme 2.06). Additionally Carpino and his co-workers[70] reported that 1-hydroxyl-7-azabenzotriazole (HOAt) appears to be a more efficient coupling additive that offers the additional advantage of being a visual indicator for the end point of the coupling reaction.



Scheme 2.06: Use of HOBt as an additive for peptide coupling reaction

The evolution of coupling additives is for them to become a part of the coupling reagent for the purpose of more efficient coupling reactions. Many HOBt based phosphorus coupling reagents were developed, such as (Benzotriazol-1-yloxy) - tris(dimethylamino)phosphonium hexafluorophosphate (BOP).[71,72]

In the class of carbodiimide-based coupling reagents, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU)[73] and *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU)[74,75,76] are very efficient coupling reagents which produce very low levels of racemization with significantly reduced coupling reaction length.

1.4.5 Solid-phase peptide synthesis

Solid-phase peptide synthesis (SPPS), pioneered by Merrifield in 1959,[77] resulted in a revolutionary shift in the concept of peptide synthesis. The general approach is that peptides are bound to an insoluble support and then any unreacted reagents left at the end of synthesis can be removed by a simple wash procedure, which significantly decreases the time required for carrying out chemical

synthesis. It has now become the method of choice for creating large peptides and proteins in a synthetic manner. SPPS is a very versatile method which allows the synthesis of natural peptides which are difficult to express in bacteria, the incorporation of unnatural amino acids, peptide/proteins backbone modification, and the synthesis of D-proteins, which consist of D-amino acids.

Insoluble but porous small solid beads are treated with functional units (“linkers”) on which peptide chains can be built. The peptide will remain attached to the bead by a covalent bond until it is cleaved by a chemical reagent, in which case strong acids are generally used such as anhydrous hydrogen fluoride or trifluoroacetic acid (TFA). This process allows the peptide to be immobilized on the solid-phase and can be retained during filtration processes, in which excess reagents and by-products in the liquid phase can be removed.

The general principle of SPPS is the repeated iteration of peptide coupling, wash, deprotection and wash process. The *N*-terminus of a solid-phase attached peptide is first coupled to a single *N*-protected amino acid. This *N*-protected amino acid is then deprotected to form a new *N*-terminus to which a further amino acid can be attached (figure 2.03). Reagents are generally used in excess; this allows the reactions to proceed to completion in minimal time and results in faster synthesis of peptides with high purity. Peptide couplings proceed in a *C*-*N* direction.

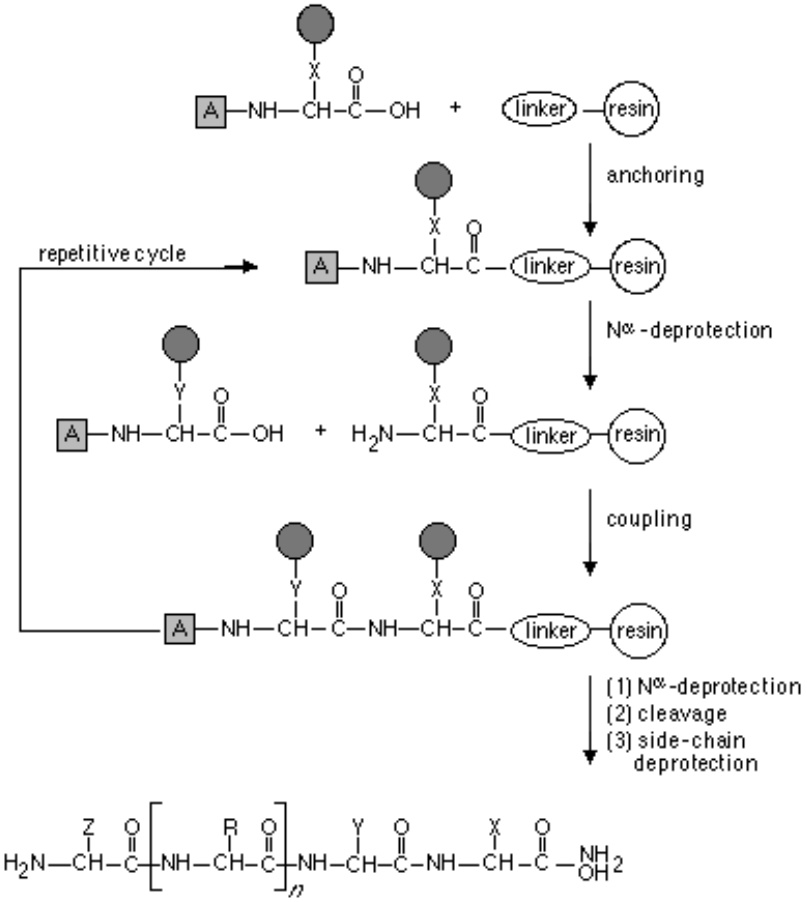


Figure 2.07: Solid-phase peptide synthesis (graph taken from reference 77)

The overwhelmingly important consideration in SPPS is to generate extremely high yields in each step. For example, if each coupling step were to have a yield of 99%, a 26-amino acid peptide would be synthesized in 77% overall yield assuming a 100% yield in each deprotection; if each step were to have a 95% yield, the overall synthetic yield of the 26-amino acid peptide would decrease to 25%. Therefore a large excess of each amino acid unit would be needed and coupling amino acids together is optimized by a series of well-characterized reagents.

There are two most commonly used protecting groups in SPPS, those are the 9-fluorenylmethoxy carbonyl (Fmoc) group and the di-*tert*-butyl dicarbonate (Boc) group. The *N*-terminus of amino acid monomers is protected by either of these two groups and coupled with a deprotected amino acid chain. Automated synthesizers are available for both techniques.

SPPS is limited by yields, and generally peptides and proteins in the range of 70 amino acids are considered the limits of synthetic accessibility. Longer peptides can be accessed by using native chemical ligation to couple two peptides together with quantitative yield.

SPPS has been significantly optimized since its introduction.[78] The resins have been optimized and the linkers between the *C*-terminal amino acid and polystyrene resin have improved attachment and cleavage for delivering quantitative yields.[79]

1.5 Synthetic approaches of thiazoline derivatives

One of the intrinsic challenges in the total synthesis of vioprolide D is the incorporation of the thiazoline unit without loss of chiral integrity.

Thiazoline is a heterocyclic compound containing both sulphur and nitrogen in its ring. Although thiazoline itself as a monomer is rarely encountered, its derivatives often exhibit biological activities.[80]

The thiazoline ring system is an important building block in pharmaceutical agents and occurs as a modified peptide residue in a variety of biologically active natural products.[81] Especially, thiazoline rings are characteristic structural segments of marine cyclopeptide alkaloids such as lissoclinamides,[82] patellins,[83] bistratamides [84] and many others (figure 2.04).[85]

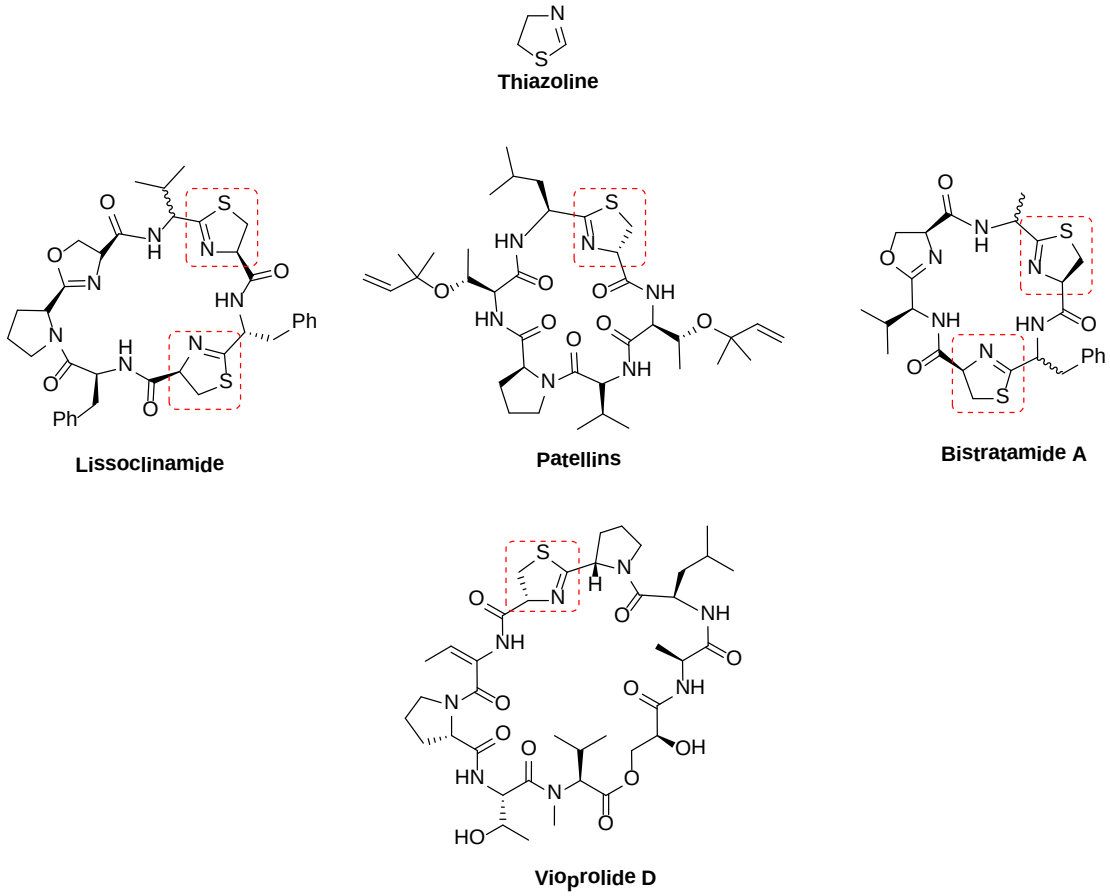
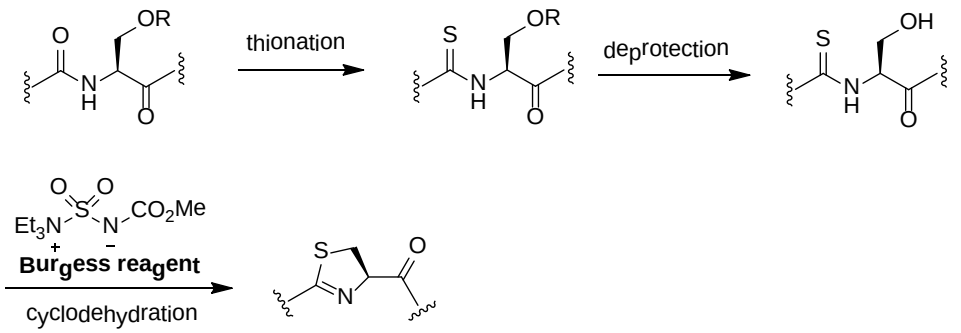


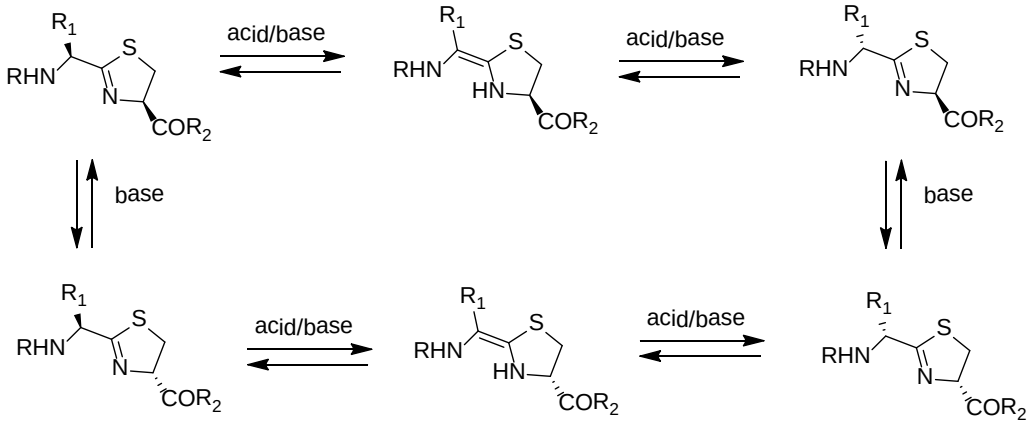
Figure 2.04: Natural products containing thiazoline ring system

Studies towards the total synthesis of these thiazoline containing compounds and investigations of their biological activities have prompted interest in synthetic attempts at stereodefined thiazoline containing peptides.[86] Most chemical synthesis of thiazoline rings employ serine residues, where the serine side chain is transformed into an electrophile that is attacked by the thioamide group of the proceeding residue.[87] This dehydration reaction is facilitated by the use of methyl *N*-(triethylammoniumsulfonyl) carbamate, more commonly known as Burgess' reagent (scheme 2.07).[88] Burgess' reagent is a mild and selective dehydrating reagent often used in converting secondary and tertiary alcohols, with an adjacent proton, into alkenes. In this case, it converts thioamides into thiazolines in high stereochemical purity.[87]



Scheme 2.07: Conversion of serines to thiazolines using Burgess' reagent

Although thiazolines can be prepared in high yield and high diastereomeric purity by cyclodehydration of *β*-hydroxy thioamides, the real difficulty is actually maintaining the stereo integrity of thiazoline containing peptides, as they are very prone to epimerization in the presence of mild acid or base as illustrated below (scheme 2.08).[89]

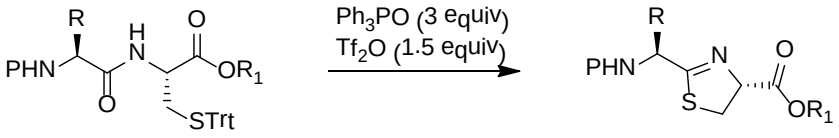


Scheme 2.08: Thiazoline epimerization

The substructure of thiazoline confers conformational rigidity and serves as a recognition site for DNA, RNA, and protein binding.[90] Thiazolines are biosynthesized from peptides by nucleophilic attack of the cysteine thiol group on the amide carbonyl group of the neighbouring residue, followed by dehydration.[91]

In contrast to traditional synthesis of thiazolines from *β*-hydroxy thioamides, it has been reported that facile and efficient biomimetic synthesis of thiazolines can be achieved by using *N*-acylated cysteine substrates with hexaphenyloxodiphosphonium trifluoromethanesulfonate.[92] The reaction

proceeds in high yield with retention of configuration at the C4- and C2-exomethine carbon atoms of the thiazoline. (scheme 2.09)



Scheme 2.09: Biomimetic synthesis of thiazolines

This chemical transformation utilizes the phosphorus reagent hexaphenyloxodiphosphonium trifluoromethanesulfonate to convert a fully protected *N*-acyl cysteine residue to the corresponding thiazoline via *in situ* deprotection, amide bond activation and dehydrocyclization processes.

Extensive investigations have been carried out with various substituents to study the scope and limitations of this reaction. In general, it has been found that triphenylphosphine oxide with triflic anhydride yields an *O*-bridged bis-phosphonium salt (figure 2.05), which is the sole active species for this tandem dehydrocyclization reaction, irrespective of the stoichiometry of triphenylphosphine oxide and triflic anhydride used. This reaction generally leads to optically pure products in moderate to high yield. And it is also possible to utilize catalytic amounts of triphenylphosphine oxide in preparation of thiazoine without a significant decrease in yield or stereoselectivity.[93]

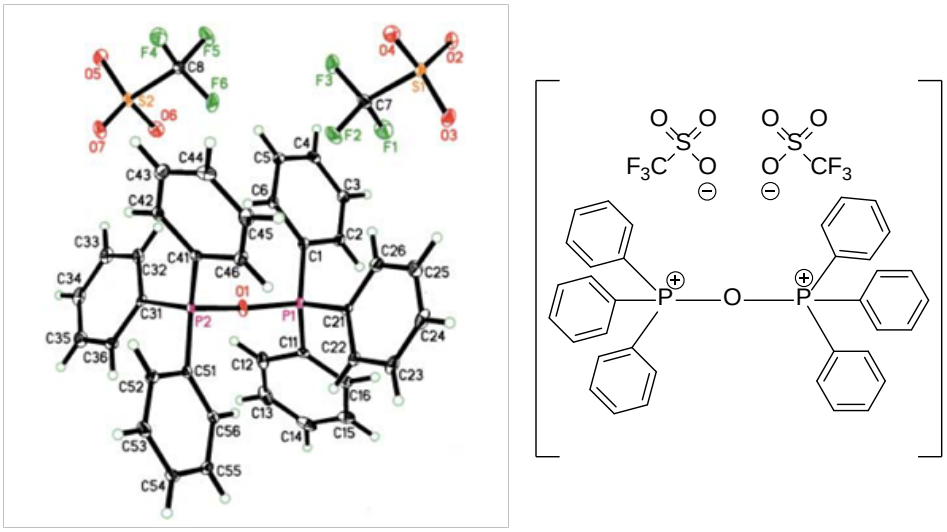
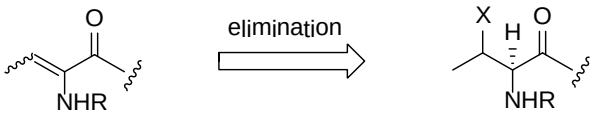


Figure 2.05: X-ray crystal structure of the O-bridged phosphonium salt

1.6 Synthesis of (*E*)-α,β-dehydropeptides

α,β-Dehydroamino acids are an important class of amino acid derivatives as synthetic intermediates of naturally occurring peptides[93] having various intriguing biological activities[94]. They have also been used as precursors for the synthesis of unnatural amino acids[95] and building blocks to control conformation of peptides[96].

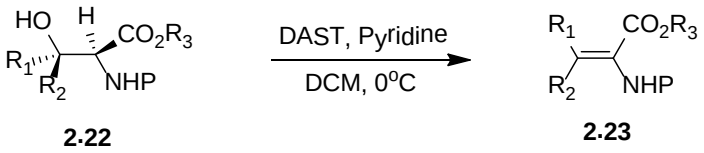
One of the most common approaches in the synthesis of α,β-dehydroamino acids is *via* the β-elimination reaction of the β-hydroxy amino acids[94], e.g. serine and threonine derivatives, containing various leaving groups derived from the hydroxyl groups (scheme 2.10).



Scheme 2.10: Strategy in the synthesis of α,β-dehydroamino acids

Being able to stereoselectively control the formation of *E* or *Z* isomer during the formation of α,β-dehydroamino acids can be particularly challenging. The dehydration reaction of *N*-benzyloxycarbonylthreonine has been investigated using various dehydrating agents, and the thermodynamically more stable (*Z*)-2-benzyloxycarbonylaminocrotonate is usually produced as the sole product[97]. Selective preparation of the *E*-isomer has been attempted by using a combination of Ph_3P/DEAD combination (*E*/*Z* 1:1),[98] diisopropyl carbodiimide (DIPC)/CuCl (*E*/*Z* 3:2),[99] and PCl_5/DBU (*E*/*Z* 85:15),[100] but the stereoselectivity of these methods has not been satisfactory.

In 1983, Shanzer and Somekh[101] reported the stereospecific preparation of (*Z*)- and (*E*)- α,β-dehydroamino acid derivatives from threonine and *allo*-threonine derivatives, respectively, using (dimethylamino)sulphur trifluoride (DAST) as a dehydrating agent in a E2 elimination process (figure 2.06).



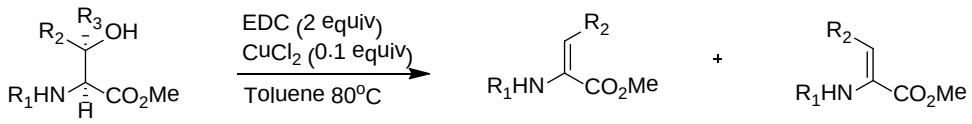
2.22 **2.23**

R_1	R_2	R_3	P	**2.23** (% yield)	Stereochemistry
H	CH_3	CH_2Ph	Cbz	90	*Z*
CH_3	H	CH_2Ph	Cbz	90	*E*
H	CH_3	Et	Boc	70	*Z*
CH_3	H	Et	Boc	65	*E*

Figure 2.06: Dehydration of threonine derivatives with DAST

Under Shanzer and Somekh conditions[101], threonine derivatives produced the *Z* product in 90% and 70% yield, respectively. The use of *allo*-threonine derivatives generated the *E* product with yields of 90% and 65%, respectively. No *E*/*Z* isomerization was observed, which may suggest a concerted pathway for the elimination process. However, this method is not very practical because they use the expensive *allo*-threonine as starting material.

In search for a more practical strategy for the synthesis of (*E*)- α,β-dehydroamino acid derivatives, Sai and his co-workders have reported highly stereoselective syntheses of (*E*)- α,β-dehydroamino acids and (*E*)- α,β-dehydropeptides in good yield and stereospecificity using a 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)/$CuCl_2$ combination (figure 2.07).[102]



2.24 **(*E*)-2.25** **(*Z*)-2.25**

R_1	R_2	R_3	Time	**2.25** (% yield)	*E* / *Z*
Cbz	Me	H	0.5 h	97	98 / 2
Cbz	H	Me	0.5 h	99	<1 / 99
Cbz	Me	H	24 h	82	90 / 10
Cbz	Me	H	2 h	77	67 / 33
Boc-Ala	Me	H	0.5 h	95	98 / 2
Boc-Ala	Me	H	2 h	62	67 / 33

Figure 2.07: Preparation of α,β-dehydroamino acid derivatives using EDC and $CuCl_2$

Treatment of *N*-benzyloxycarbonylthreonine methyl ester **2.24** with EDC and catalytic amount of $CuCl_2$ in toluene at 80^{o}C for 0.5 hours afforded methyl (*E*)-2-benzyloxycarbonylaminocrotonate (*E*)-**2.25** stereoselectively in good yield. On the other hand, the *allo*-threonine version of the starting material afforded (*Z*)-**2.25** under the same condition. This investigation also showed that longer reaction time led to a decreased stereoselectivity, which may suggest that isomerization of the *E*-isomer into the *Z*-isomer takes place probably due to the basic nature of EDC. Additionally, it has also been reported that the dehydration reaction of threonine derivative **2.24** with EDC hydrochloride salt (EDC-HCl) instead of EDC resulted in a mixture of *E*,*Z*-isomers. These results revealed that in the case of EDC-HCl, the thermodynamically more stable *Z*-isomer was obtained preferentially and the dehydrating ability of EDC-HCl was weak compared with EDC.

In summary, Sai and his co-workers have managed to develop a highly stereoselective method for the synthesis of α,β-dehydroamino acids and α,β-dehydropeptides using EDC and $CuCl_2$. And their results showed that it is an easy, reliable and high-yielding method for accessing a wide range of amino acids and peptides which may otherwise be difficult to synthesize. As there is a (*E*)-α,β-dehydroamino group present in the target molecule vioprolide D, the

EDC/$CuCl_2$ method would be our first approach to address this synthetic challenge.

1.7 Strategic synthetic approach

In our preliminary study, vioprolide D was disconnected into three equal-sized fragments (figure 2.08). Each fragment contains the appropriate protecting groups. Final macrocyclization takes place by incorporating fragment one and fragment two onto fragment three, followed by intramolecular lactonization to complete the total synthesis.

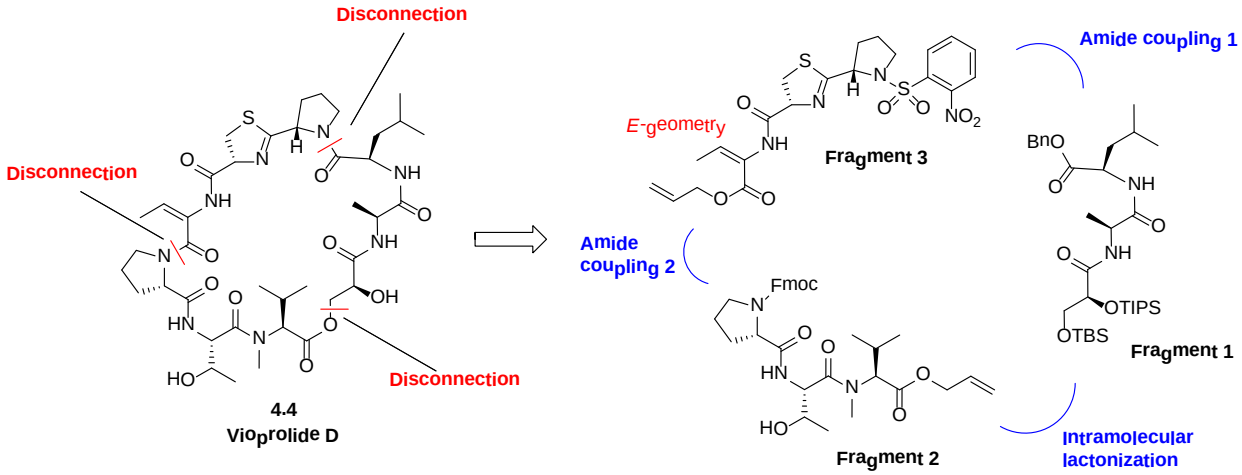
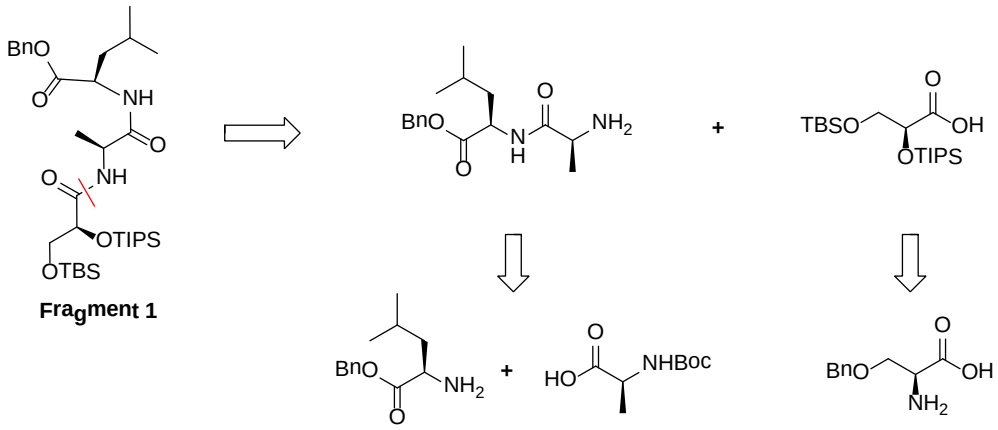


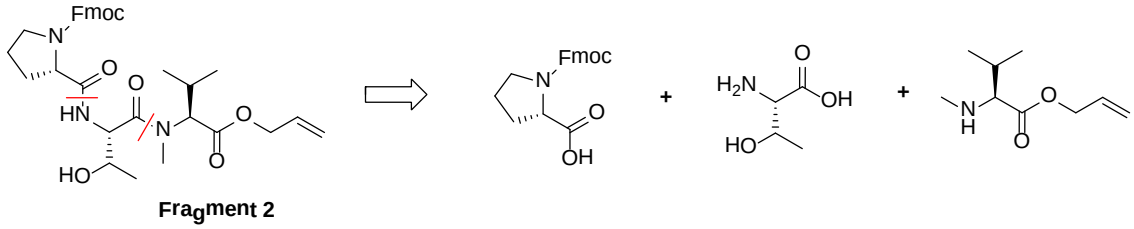
Figure 2.08: Vioprolide D disconnection

Fragment one consists of two amino acid units D-leucine and L-alanine and a dihydroxyl unit. The *C*-terminus is protected by benzyl group. Fragment one can be disconnected to give two smaller intermediates: a dipeptide molecule and a dihydroxycarboxylic acid which can be coupled under standard amide coupling conditions. The dipeptide unit can be made from benzyl-protected D-leucine and boc-protected L-alanine. The dihydroxyl intermediate can be accessed from benzyl-protected L-serine (scheme 2.11).



Scheme 2.11: Disconnection of fragment one

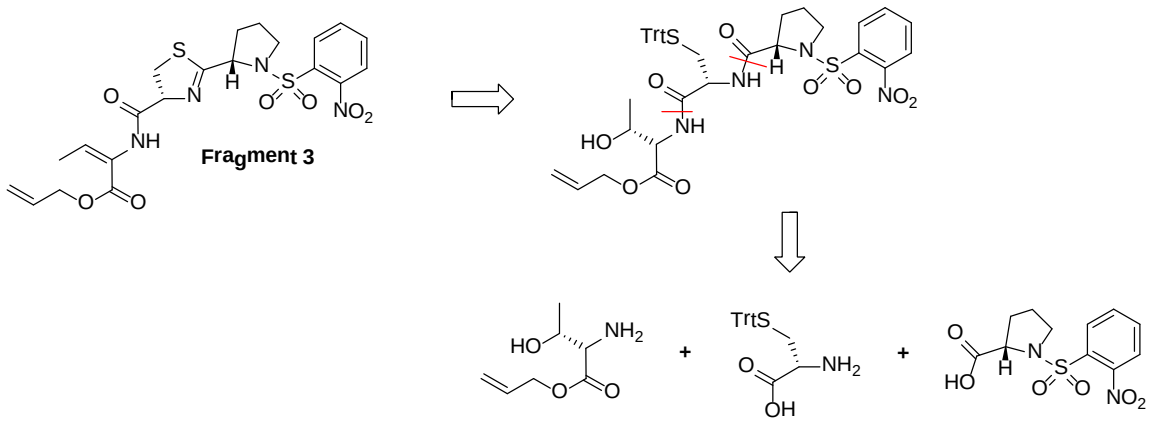
Fragment two is a linear tripeptide consisting of L-proline, L-threonine and L-valine amino acid residues (scheme 2.12). There is an additional methyl group on the amide bond between the L-threonine and L-valine residues. The *C*-terminus of fragment two is masked as an allyl ester and Fmoc group is used to protect the *N*-terminus.



Scheme 2.12: Disconnection of fragment two

Fragment three is the most challenging fragment of the three. It consists of an *E*-geometry dehydrobutyrine unit, a thiazoline ring and an L-proline amino acid residue (scheme 2.13). Although the dehydrobutyl group would originate from L-threonine amino acid residue, a dehydration reaction must be performed using specially tailored conditions because the more thermodynamically favoured product is the *Z*-geometry isomer. The thiazoline ring can be generated from a trityl-protected cysteine amino acid residue. An additional challenge arises from handling the thiazoline ring because it is well documented that thiazoline containing peptides are prone to epimerization under both mild acid and mild base conditions.[103] If the thiazoline ring was to be generated after forming the

dehydrobutyl unit, the reaction conditions used to form thiazoline must be able to tolerate the presence of the double bond. In order to avoid the formation of rotamers the *N*-terminus is protected with a 4-nitrophenylsulfonyl (nosyl or Ns) group, and the *C*-terminus is protected as its corresponding allyl ester.



Scheme 2.13: Disconnection of fragment three

In the proposed synthetic strategy, the macrocycle was broken down into three small linear fragments. Synthesis of each fragment will be investigated, and all amide coupling reactions will be carried out using conventional wet chemistry.

Experimental observations and results will be discussed in detail in the following chapter.

Chapter 2 Results and Discussion

2.1 Preparation of fragment one

As discussed in the previous chapter, vioprolide D was disconnected into three small equally-sized fragments among which fragment one **2.26** was identified as one of the key intermediates to access vioprolide D. Fragment one **2.26** comprised of a tripeptide unit in which the terminal di-hydroxyl groups were protected with *tert*-butyl-dimethyl silyl (TBS) group and triisopropyl silyl (TIPS) group, respectively (figure 2.09). The *C*-terminus of the tripeptide was protected by a benzyl group.

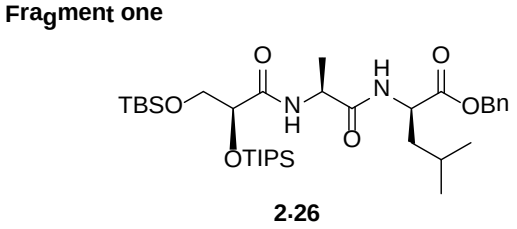
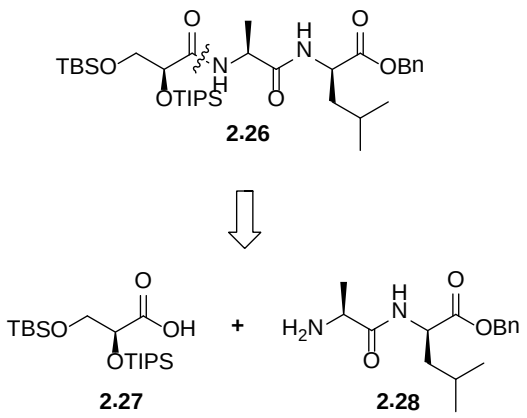


Figure 2.09: Structure of fragment one

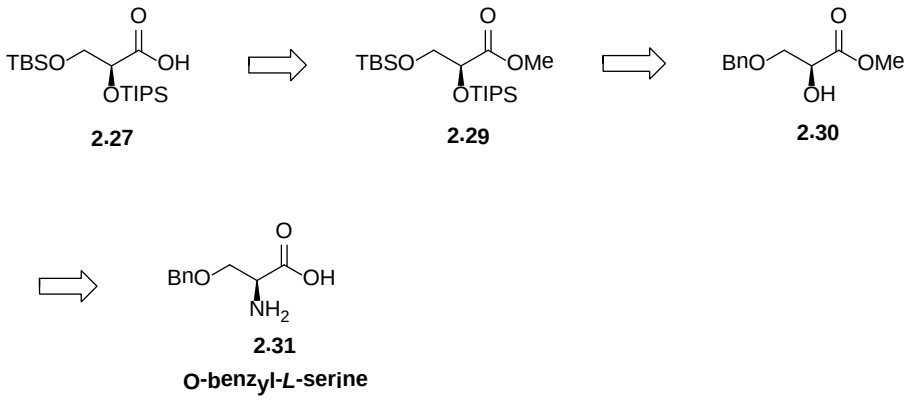
2.1.1 Retrosynthetic analysis of fragment one

Fragment one **2.26** can be disconnected into two units; a protected dihydroxy-carboxylic acid **2.27** and a dipeptide species **2.28**. The coupling of the two substrates can be achieved by standard amide coupling conditions (scheme 2.14).



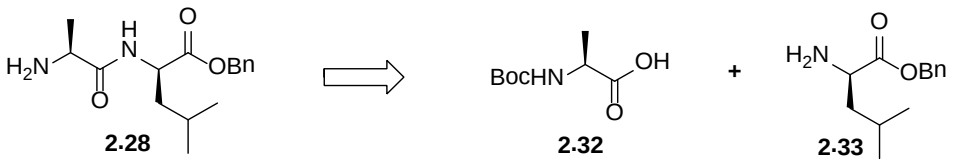
Scheme 2.14: Disconnection of fragment one **2.26**

A literature search revealed that both substrates **2.27** and **2.28** can be synthesized from simple amino acid building blocks. Carboxylic acid **2.27** would originate from its corresponding methyl ester **2.29**. The TBS and TIPS protecting groups can be introduced selectively in the desired order from the intermediate methyl 3-(benzyloxy)-2-hydroxypropanoate **2.30**. This intermediate can be easily accessed from commercially available building block *O*-benzyl-L-serine **2.31**, and a S_N2 double inversion reaction would convert benzyl-protected L-serine **2.31** to compound **2.30** with retention of configuration (scheme 2.15).



Scheme 2.15: Disconnection of carboxylic acid **2.27**

Dipeptide **2.28** can be accessed by standard amide coupling of boc-protected L-alanine **2.28** and *O*-benzyl-D-leucine **2.33**; both amino acid monomers are commercially available (scheme 2.16).



Scheme: 2.16: Disconnection of dipeptide **2.28**

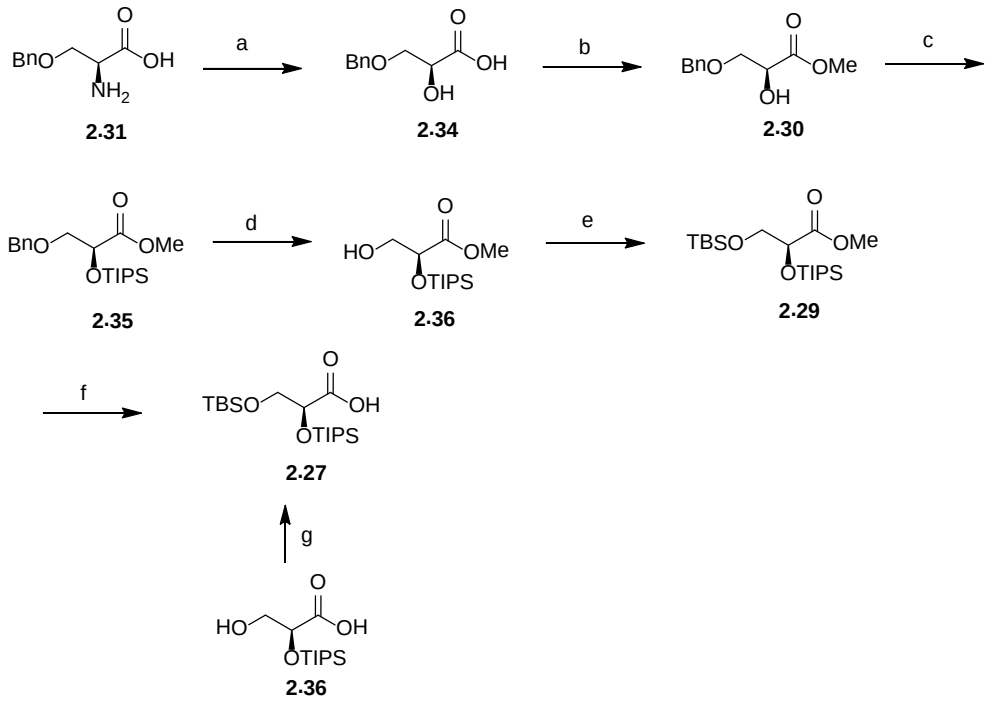
2.1.2 Synthesis of silyl-protected dihydroxyl carboxylic acid 2.27

Synthesis of silyl-protected dihydroxyl carboxylic acid **2.27** started with commercially available building block *O*-benzyl-L-serine **2.31** (scheme 2.17). *O*-benzyl-L-serine **2.31** was converted to hydroxyl carboxylic acid **2.34** by a S_N2 double inversion reaction. This reaction undergoes double S_N2 inversion of configuration *via* a diazonium intermediate. Slow addition of sodium nitrite *via* a syringe pump was required and the pH of the solvent was kept constant using a buffer solution at pH 3. This reaction delivered a modest 50% conversion according to ^{1}H NMR analysis of the crude material. The crude material from this reaction was taken to the next step without further purification.

Addition of trimethyl orthoformate to the hydroxyl carboxylic acid **2.34** led to the formation of methyl ester **2.30**. It was necessary to convert carboxylic acid **2.34** to its methyl ester **2.30** because carboxylic acid **2.34** only had limited solubility in organic solvent. The secondary hydroxyl group was subsequently protected by TIPS group using triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) in the presence of 2,6-lutidine to give compound **2.35** in quantitative yield. The benzyl group was then removed under hydrogenation conditions to generate the primary alcohol **2.36**. Treatment of the primary alcohol with *tert*-butyldimethylsilyl chloride (TBSCl) afforded the protected dihydroxyl ester **2.29** in good yield.

The first attempt of hydrolysing ester **2.29** to generate carboxylic acid **2.27**, using 10 equivalents of lithium hydroxide at room temperature for 16 hours, did not go to completion. This reaction was observed to reach completion at reflux in a mixture of THF and water (10:1 by volume) after 5 hours, however, only 25% of the desired hydrolysed product **2.27** was isolated as extensive loss of TBS group was observed. Therefore, it was decided that TBS group had to be re-introduced

back to the alcohol **2.36** using TBSCl with imidazole. The reason for the less reactive hydrolysis was probably because of the steric hindrance caused by the neighbouring TIPS group.

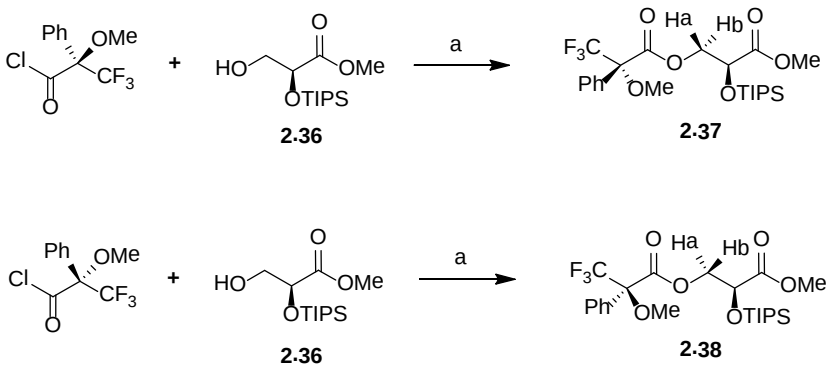


Reagents and conditons: **a**) $NaNO_2$, TFA, H_2O, 0°C 3 h; **b**) $(MeO)_3CH$, HCl in MeOH, MeOH, rt, 16 h, 35% over two steps; **c**) TIPSOTf, 2,6-lutidine, DCM, rt, 4 h, 97%; **d**) Pd/C, H_2, MeOH, rt, 16 h, 81%; **e**) TBSCl, imidazole, DCM, rt, 16 h, 95%; **f**) LiOH, H_2O/THF, reflux 16 h, 25%; **g**) TBSCl, imidazole, DCM, rt, 16 h, 95%.

Scheme 2.17: Synthesis of substrate **2.27**

2.1.3 Preparation of Mosher's ester derivatives

The next objective was to investigate the chiral integrity of the S_N2 double inversion reaction. Mosher's ester derivatives were prepared by treatment of primary alcohol **2.36** with Mosher's acetyl chloride, triethylamine and DMAP in DCM (scheme 2.18). Mosher's ester derivatives **2.37** and **2.38** were produced in quantitative yield.



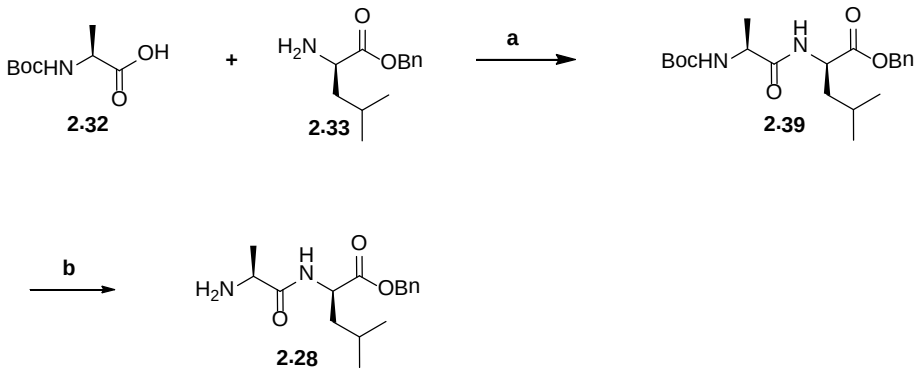
Reagents and conditions: 1) Et_3N, DMAP, DCM, rt, 16 h, 86%

Scheme 2.18: Synthesis of Mosher's ester derivatives

Protons H_a and H_b in Mosher's esters **2.37** and **2.38** revealed an explicit doublet of doublet peak pattern due to coupling of the germinal proton and the proton on the adjacent carbon. ^{1}H NMR analysis showed there was no visible sign of racemization of the stereogenic centre in compound **2.36**. Hence it was concluded that the S_N2 double inversion reaction converting *O*-benzyl-L-serine **2.31** to hydroxyl carboxylic acid **2.34** proceeded with high retention of configuration.

2.1.4 Preparation of dipeptide intermediate 2.28

The next object was to prepare the dipeptide intermediate **2.28**. Treatment of *N*-boc protected L-alanine **2.32** and *O*-benzyl-D-leucine **2.33** under standard amide coupling condition led to the formation of protected dipeptide **2.39** in quantitative yield (scheme 2.19). The boc group was subsequently removed by TFA to give the dipeptide **2.28**. Having accessed both carboxylic acid intermediate **2.27** and amine dipeptide **2.28**, it was ready for the final amide coupling step to proceed.

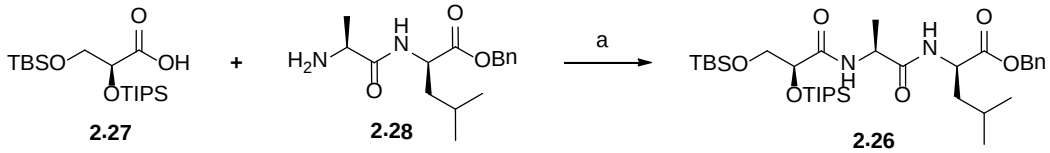


Reagents and conditions: **a**) EDCI, HOBt, Et_3N, DCM, rt, 16 h, 98%; **b**) TFA, DCM, rt, 16 h, 97%.

Scheme 2.19: Preparation of dipeptide **2.28**

2.1.5 Synthesis of fragment one 2.26

Amide coupling of carboxylic acid **2.27** with amine **2.28** successfully afforded the tripeptide molecule **2.26** in a modest 58% yield (scheme 2.20). This modest yield may be due to steric hindrance caused by the neighbouring TIPS group adjacent to the carboxylic acid. This tripeptide intermediate **2.26** was the first fragment towards the total synthesis of natural product vioprolide D.



Reagents and conditions: **a**) EDCI, HOBt, Et_3N, DCM, rt, 16 h, 58%

Scheme 2.20: Synthesis of fragment one **2.26**

2.2 Preparation of fragment two 2.40

Fragment two **2.40** represented the second fragment that would be used in the assembly of vioprolide D. This fragment was a tripeptide molecule that comprised of three amino acid residues: L-proline, L-threonine and *N*-methylated L-valine (figure 2.10). The *N*-terminus of this tripeptide was protected by a Fmoc group which could be easily removed under basic conditions, and the *C*-terminus

was protected as the allyl ester which could be deprotected by a mild base with a palladium catalyst.

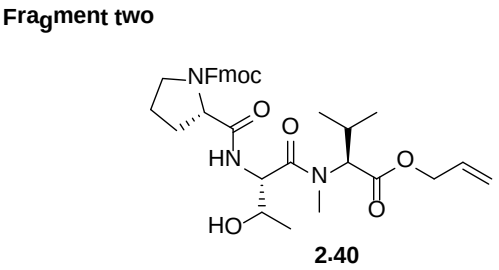
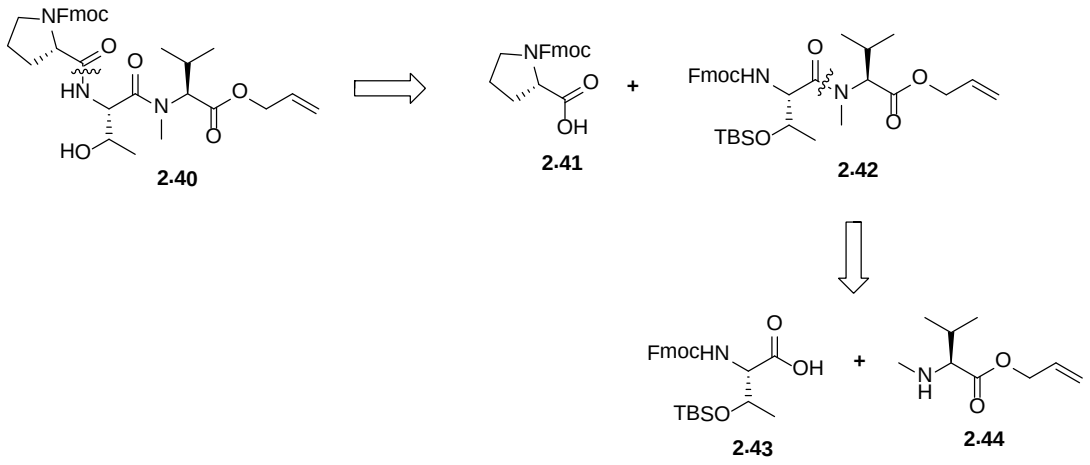


Figure 2.10: Structure of fragment two **2.40**

2.2.1 Retrosynthetic analysis of fragment two 2.40

Simple disconnection of fragment two **2.40** revealed three amino acids: L-proline, L-threonine and *N*-methylated L-valine. Since the chemical synthesis of a peptide goes from the *C*-terminus to the *N*-terminus in order to avoid the risk of epimerization, dipeptide intermediate **2.42** had to be prepared prior to the final peptide coupling with Fmoc-protected L-proline **2.41**. Further disconnection showed that dipeptide intermediate **2.42** could be prepared from two monomers: TBS-protected L-threonine **2.43** and *N*-methylated *C*-allyl-protected L-valine **2.44** (scheme 2.21).

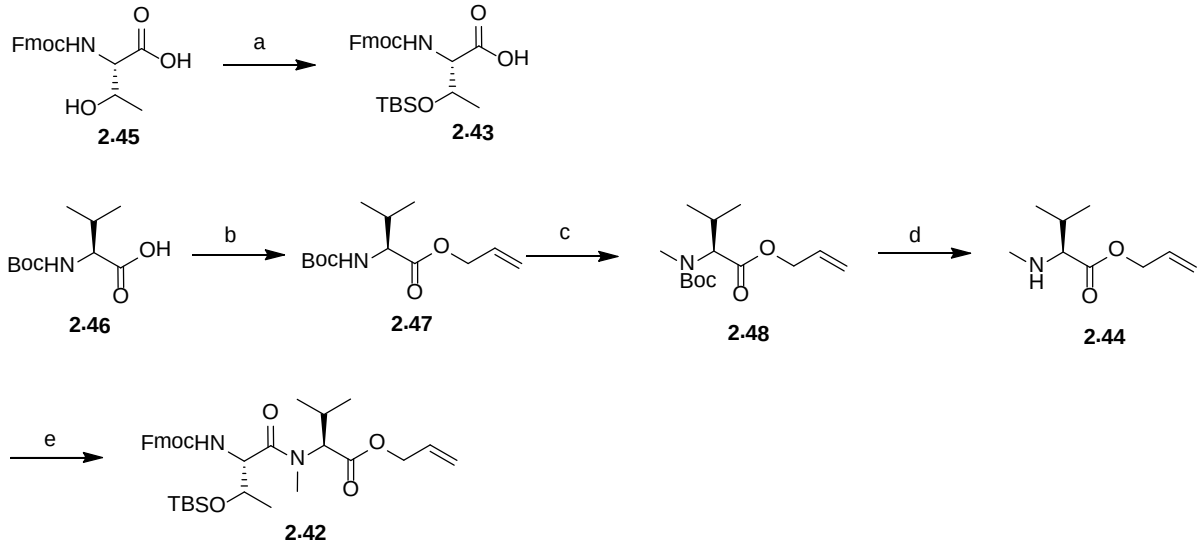


Scheme 2.21: Retrosynthetic analysis of fragment two **2.40**

2.2.2 Synthesis of dipeptide 2.42

Synthesis of dipeptide **2.42** began with the introduction of a TBS protecting group onto the *N*-Fmoc-protected L-threonine amino acid **2.45** (scheme 2.22). Two equivalents of TBSCl were used in this reaction because the reaction of the free carboxylic acid group with TBSCl was faster than that of the secondary alcohol. Upon completion of the reaction, the carboxyl-silyl bond was cleaved *in situ* upon aqueous workup. After purification by flash chromatography the silyl ester 2.43 was isolated in 65% yield.

Treatment of boc-protected L-valine **2.46** with allyl bromide in the presence of potassium carbonate afforded the corresponding allyl ester **2.47**. Treatment of the ester **2.47** with an excess of sodium hydride and methyl iodide led to the formation of *N*-methylated boc-valine **2.48**. Without chromatographic purification, the boc protecting group on the allyl ester **2.47** was then removed by TFA to generate the secondary amine **2.44** in 55% yield over two steps. Amide coupling of secondary amine **2.44** with protected L-threonine **2.43** using HATU as the amide coupling agent with HOBt gave the corresponding dipeptide **2.42** in good yield.

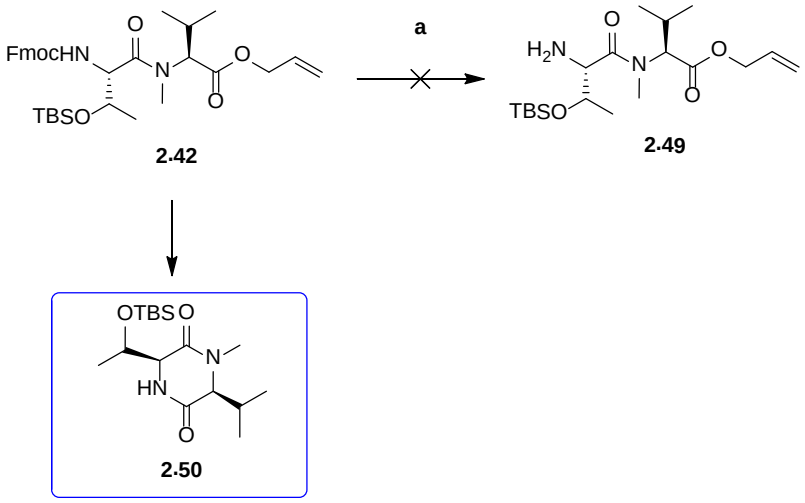


Reagents and conditions: **a**) TBSCl, imidazole, THF, rt, 16 h, 65%; **b**) Allyl bromide, K_2CO_3, DMSO, 16 h, 98%; **c**) NaH, MeI, THF, 0^oC - rt, 16 h; **d**) TFA, DCM, rt, 2 h, 55% over two steps; **e**) HATU, HOBt, DIPEA, then **2.43**, DMF, rt, 16 h, 72%.

Scheme 2.22: Synthesis of dipeptide **2.42**

2.2.3 Attempts to synthesize fragment two 2.40

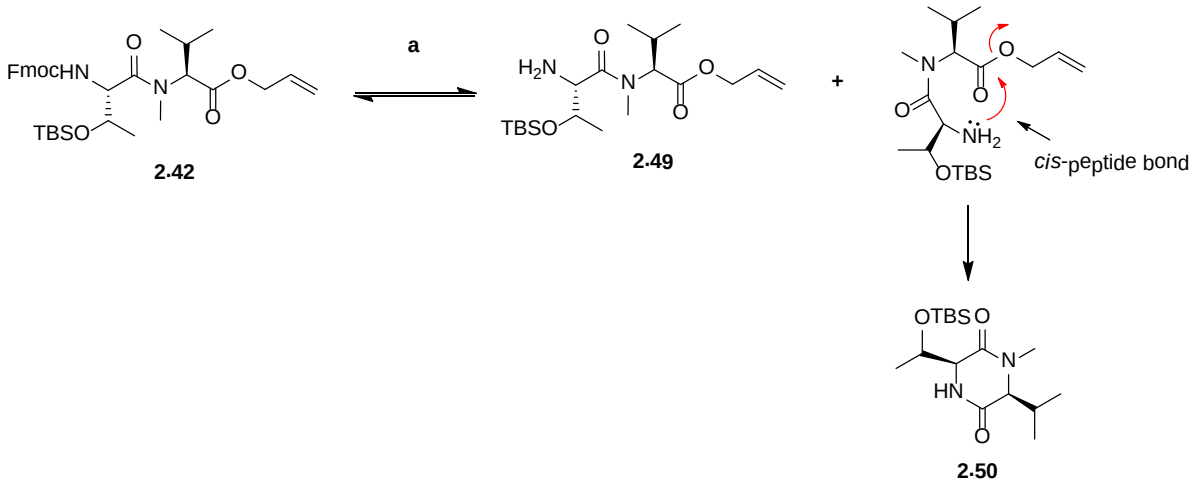
Dipeptide **2.42** was treated with piperidine in DMF, however, this reaction failed to generate the desired free amine product **2.49** and upon flash chromatography an unknown species was isolated in quantitative yield. ^{1}H NMR analysis of this unknown species revealed the disappearance of both Fmoc group and allyl ester groups. This unknown species was later discovered to be a cyclic piperazinedione derivative **2.50** (scheme 2.23).



Reagents and conditons: **a**) piperidine, DMF, rt, 16 h.

Scheme 2.23: Deprotection of Fmoc group led to side reaction

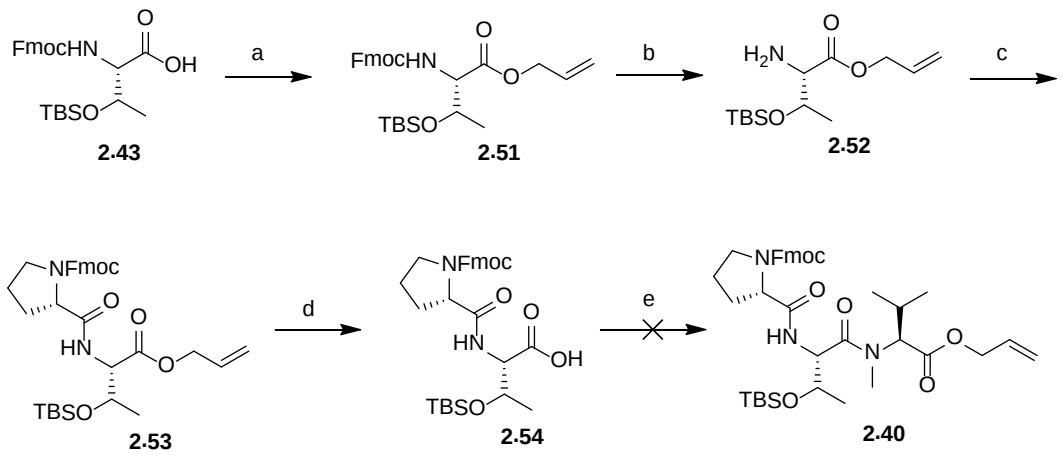
A plausible mechanism of the side reaction is *via* an intramolecular condensation reaction initiated by attack of the amine on the ester moiety. Such self-condensation reactions are usually facilitated by a *cis*-amide bond present in the dipeptide, and the spatial conformation of *N*-methylated dipeptide **2.49** may have just resembled the correct conformation which favours this intramolecular cyclization reaction to take place (scheme 2.24).



Reagents and conditons: **a**) piperidine, DMF, rt, 16 h.

Scheme 2.24: Plausible mechanism of side reaction

Having failed to extend the peptide chain at the dipeptide **2.49** step, alternative approaches were then investigated, one of which was to reverse the order of reactions in order to avoid the intrinsically unstable dipeptide **2.49** (scheme 2.25). The synthetic sequence started from Fmoc-protected L-threonine **2.43**, the *C*-terminus of which was subsequently treated with allyl bromide to afford allyl ester **2.51** in quantitative yield. Subsequent removal of the Fmoc group using piperidine in DMF gave free amine **2.52**. Amide coupling of free amine **2.52** with Fmoc-L-proline led to the formation of dipeptide **2.53** in good yield. Conversion of allyl ester **2.53** to the corresponding carboxylic acid **2.54** was achieved using *N*-methylaniline with a catalytic amount of tetrakistriphenylphosphine palladium in THF. However, the final amide coupling of carboxylic acid **5.27** with amine **5.17** using standard HATU peptide coupling condition was unsuccessful. The reaction was observed to have a very messy reaction profile and upon chromatographic purifiation no desired product was isolated. The unsuccessful coupling reaction was not surprising because in *N* to *C* peptide coupling reactions, the adjacent carbonyl group is likely to attack the activated carboxylic acid group in an intramolecular fashion, resulting in peptide epimerization (as reviewed in the previous chapter), and in this case the side reaction had led to the formation of other side products.



Reagents and conditions: **1**) allyl bromide, $NaHCO_3$, DMSO, rt, 16 h, 82%; **2**) piperidine, DMF, rt, 2 h, 91%; **3**) HATU, HOBt, DIPEA, then Fmoc-Pro-OH, DMF, rt, 16 h, 85%; **4**) N-methylaniline, $Pd(PPh_3)_4$, THF, rt, 16 h, 70%; **5**) HATU, HOBt, DIPEA, then **2.44**, DMF, rt, 16 h.

Scheme 2.25: Alternative approach to synthesize fragment two **2.40**

2.2.4 Piperazinedione formation literature

An extensive literature search was carried out and it was shown that piperazinediones are formed readily from dipeptide derivatives, including esters and amides,[104,105] especially when these are not *N*-protected, and particularly those containing *N*-methylated amino acid residues or proline.[106,107,108,109] This reaction proceeds through self-condensation to dipeptide esters, and kinetic data showed that all the dipeptide ester cyclizations completed very effectively with saponification, within the pH range 7.3 – 8.5.[110]

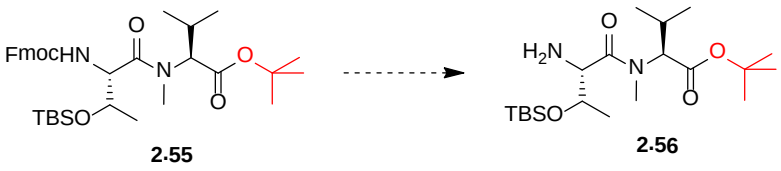
The cyclization of dipeptide esters to piperazinediones is interesting as the peptide bond must be in the *cis*-form so that the terminal amino group and ester carbonyl can interact to form the six-membered ring which then contains two *cis*-bonds. The planar protonated peptide bond in open-chain peptides exists almost exclusively in the *trans*-conformation with a barrier to rotation of *ca*. 20 kcal mol-1.[111] However with *N*-methylated peptide bonds, the *cis*-conformation is relatively less unfavourable and NMR studies have shown that equilibrium occurs in aqueous solution between *cis*- and *trans*-forms in peptides of *N*-methylalanine.[112]

Although the formation of piperazinediones is a known problem with *N*-methylated amino acids, it can be prevented by switching to *tert*-butyl ester derivatives as illustrated by Wenger[113] and McDermott.[114]

2.2.5 Future work on the synthesis of fragment two 2.40

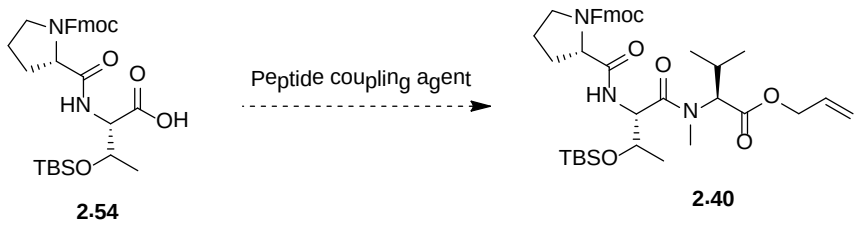
Due to project needs and priorities, it was decided that the preparation of fragment two **2.40** would be investigated at a later time.

Several attempts could be investigated in order to avoid the formation of piperazinedione from the dipeptide self-condensation reaction. First, it has been shown in the literature that a *tert*-butyl ester could effectively suppress the side reaction, so one alternative approach would be to synthesize *tert*-butyl ester **2.55** and subsequent removal of Fmoc group should result in the formation of the free amine **2.56** from which point the peptide chain extension process could continue (scheme 2.26).



Scheme 2.26: Alternative approach using *tert*-butyl ester

An alternative approach would be to screen a number of different peptide coupling agents to optimize the amide coupling reaction of carboxylic acid **2.54** with amine **2.44** to generate fragment two **2.40** (scheme 2.27).



Scheme 2.27: Alternative approach by screening coupling agents

2.3 Preparation of fragment three 2.57

Having had access to fragment one and potential access to fragment two, the next objective was to prepare fragment three, which was the final fragment for the total assembly of the natural product vioprolide D.

Fragment three **2.57** was a protected tripeptide system consisting of a (*E*)-dehydrobutyrine unit, a thiazoline ring and a L-proline unit (figure 2.11). The *C*-terminus was protected as its allyl ester. The *N*-terminus was protected by a 2-nitrophenylsulfonyl (nosyl) group in order to minimize the formation of rotamers, because it was observed that for Boc-protected peptides, the ^{1}H NMR spectra were complicated by the presence of rotamers.

Fragment three **2.57** was the most challenging fragment to synthesize because of its inherent structural complexity. There were two unnatural amino acid units (dehydrobutyrine and thiazoline) incorporated in the tripeptide system and peptides containing thiazolines were well known for their instability towards epimerization.[115]

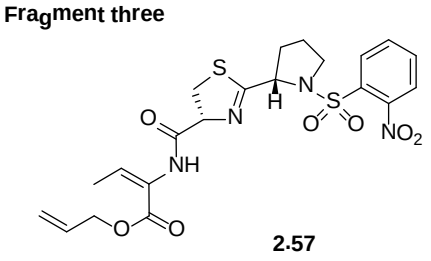


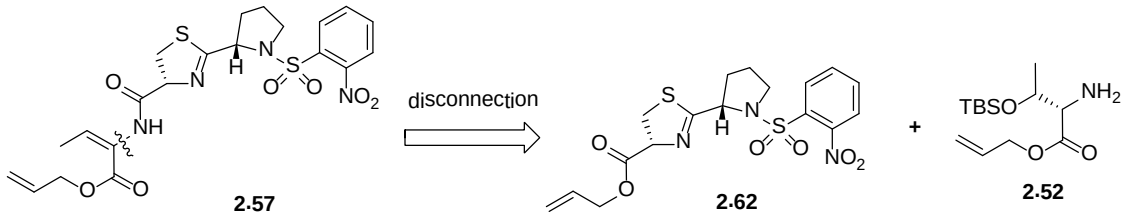
Figure 2.11: Structure of fragment three **2.57**

Procedures were available from the literature for the dehydration of threonine-containing peptides to generate both (*E*)- and (*Z*)-dehydrobutyrine units.[116,117] As discussed in the previous chapter that there were two general strategies synthesizing thiazoline containing peptides; thiazolines could be accessed by the dehydration of thioamides with a neighbouring serine residue[118] or via cyclization of a protected-cysteine residue with an adjacent amide bond.[119] The latter approach was chosen for the initial investigation.

2.3.1 Initial investigation of preparing thiazoline containing peptide

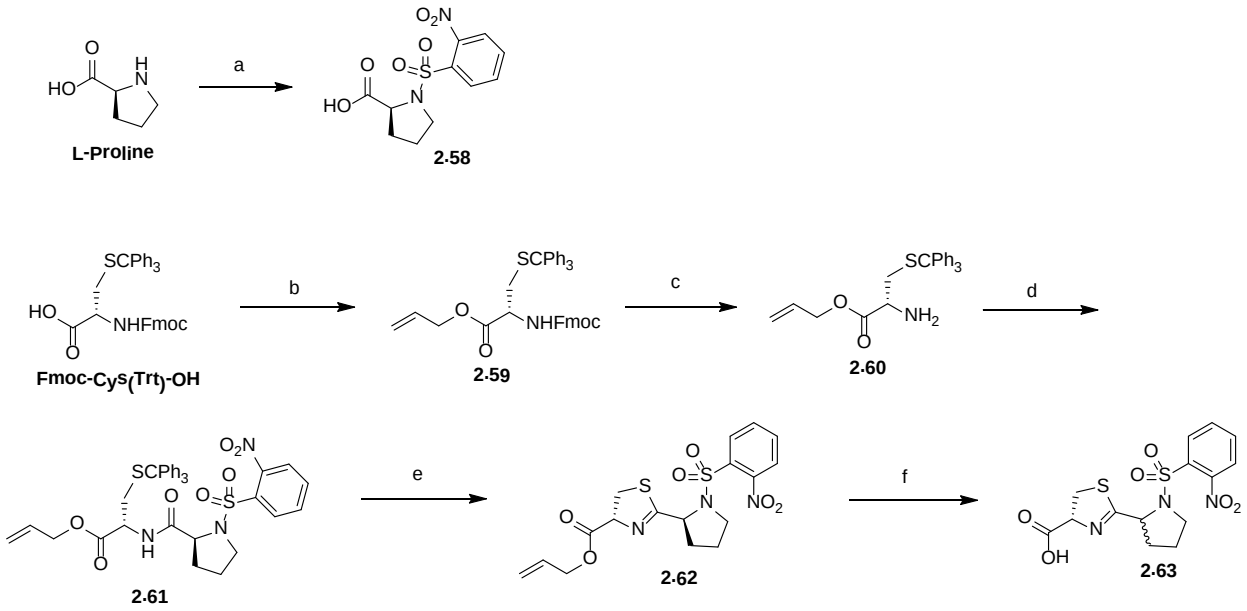
Since the formation of thiazoline unit and the preservation of the the stereogenic centres involved in the peptide synthesis were both critical to the overall success of this project, it was decided that the synthesis of dipeptide **2.62** would be initially investigated.

Disconnection revealed that fragment three **2.57** could be accessed from the thiazoline containing dipeptide **2.62** and TBS-protected threonine **2.52** by an amide coupling reaction (scheme 2.28). Subsequent dehydration of threonine would afford the (*E*)-dehydrobutyrine residue.



Scheme 2.28: Disconnection of fragment three

The synthetic sequence started with commercially available building blocks (scheme 2.29). L-proline was protected by nosyl group using 2-nitrobenzenesulfonyl chloride to give the *N*-nosyl-protected L-proline **2.58** in goold yield. Trityl-*N*-Fmoc-protected L-cysteine was converted to its corresponding allyl ester **2.59** using allyl bromide. Treatment of allyl ester **2.59** with piperidine in DMF cleanly cleaved the Fmoc group and gave the primary amine **2.60** in quantitative yield. Amide coupling of amine **2.60** with protected L-proline **2.58** was achieved by HATU with HOBt in DMF, delivering dipeptide **2.61** in high yield and only one diastereoisomer was observed and isolated upon flash chromatography purification. Treatment of dipeptide **2.61** with a mixture of triflic anhydride and triphenylphosphine oxide in dichloromethane at 0^{o}C afforded the formation of thiazline system **2.62** in good yield and as a single diastereoisomer according to ^{1}H and ^{13}C NMR analysis. However during attempts to convert the thiazoline containing allyl ester **2.62** to its corresponding carboxylic acid **2.63**, extensive epimerization of the proline was observed and carboxylic acid **2.63** was obtained as a mixture of epimers.

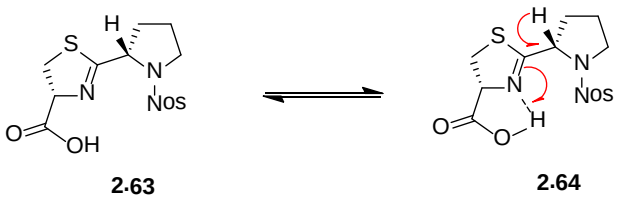


Reagents and conditions: **a**) 2-nitrobenzenesulfonyl chloride, $NaHCO_3$, H_2O, rt, 16 h, 85%; **b**) Allyl bromide, $NaHCO_3$, DMSO, rt, 16 h, 83%; **c**) Piperidine, DMF, rt, 2 h, 94%; **d**) Carboxylic acid **2·58**, HATU, HOBt, DIPEA, then **2·60**, DMF, rt, 16 h, 77%; **e**) Tf_2O, Ph_3PO, 0°C for 10 min then **2·61**, rt, 2 h, 80%; **f**) $Pd(Ph_3P)_4$, *N*-methylaniline, THF, rt, 3 h, 95%.

Scheme 2.29: Initial investigation into preparing thiazoline containing peptide

In the case of **2.63** the rapid epimerization could be facilitated by the hydrogen-bonding between the carboxylic acid and the nitrogen of the thiazoline in a five-membered transition state (scheme 2.30).

In light of experimental observations that rapid epimerization has occurred during the step from allyl ester **2.62** to thiazoline containing carboxylic acid **2.63**, peptide chain extension could not, therefore, continue from this point. According to the literature, the epimerization of chiral thiazoline derivatives would occur rapidly in both mild acid and basic conditions, hence it was decided that an alternative route would have to be investigated, and the thiazoline unit had to be introduced as late as possible in order to minimize epimerization.

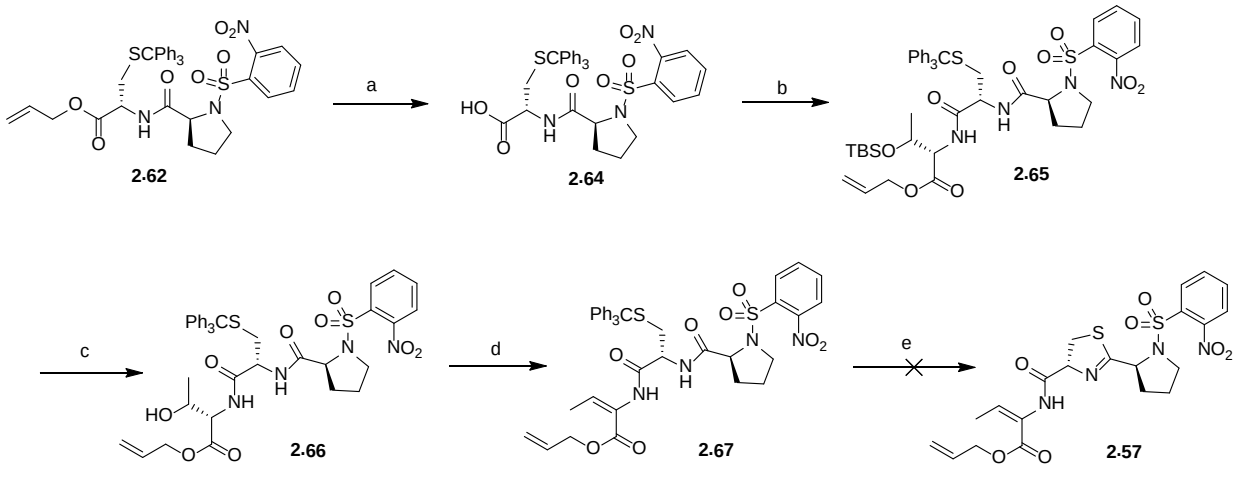


Scheme 2.30: Plausible mechanism for thiazoline epimerization

2.3.2 Alternative approach to fragment three 2.57

Having successfully synthesized dipeptide **2.62** as a single diastereoisomer, it was decided to extend the peptide at this point and introduce the next amino acid residue.

Treatment of *N*-methylaniline with tetrakis(triphenylphosphine)palladium in THF led to deallylation and gave carboxylic acid **2.64** in good yield (scheme 2.31). Amide coupling of carboxylic acid **2.64** with *O*-TBS-protected L-threonine **2.52** using HATU and HOBt afforded the corresponding tripeptide **2.65** in good yield. Slow desilylation of **2.65** using triethylamine trihydrofluoride gave the deprotected secondary alcohol **2.66** ready for the dehydration to form the corresponding dehydrobutyrine unit. Treatment of threonine containing tripeptide **2.66** with EDC and copper (II) chloride in toluene at 80^{o}C led to the formation of (*E*)-dehydrobutyrine **2.67** in good yield and only one diasteroisomer was observed and isolated upon flash chromatography. The *E* geometry of the double bond of **2.67** was assigned at this stage was by analogy with the literature.[117] Unfortunately subsequent attempts of cyclization to generate the thiazoline unit using triflic anhydride and triphenylphosphine oxide were unsuccessful, a very messy reaction profile was observed and no desired thiazoline containing tripeptide **2.57** was isolated.

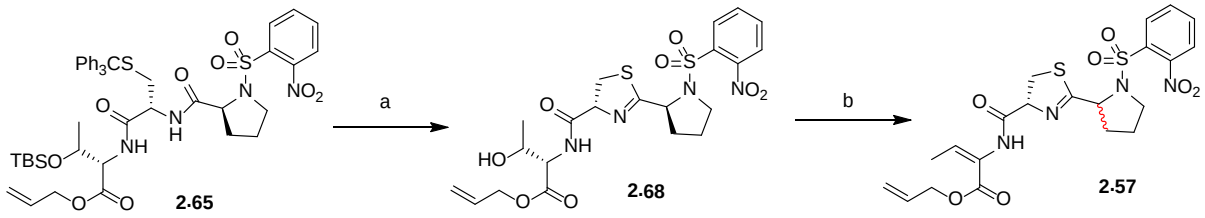


Reagents and conditions: a) *N*-methylaniline, $Pd(Ph_3P)_4$, THF, rt, 3 h, 95%; **b**) Carboxylic acid **2.64**, HATU, HOBt, DIPEA, then TBS-protected threonine **2.52**, DMF, rt, 16 h, 67%; **c**) Et_3N-3HF, THF, rt, 48 h, 62%; **d**) EDC, $CuCl_2$, toluene, 80^{o}C, 30 min, 62%, **e**) Tf_2O, Ph_3PO, DCM, 0^{o}C, 10 min, then **2.67**, rt, 2 h.

Scheme 2.31: Alternative approach to fragment three

It has appeared that the double bond of the dehydrobutyrine **2.67** was incompatible with the thiazoline formation reaction conditions in which triflic anhydride and triphenylphosphine oxide were used. This experimental observation suggested that cyclization from the cysteine containing peptide to form thiazoline may not be accomplished in the presence of a dehydrobutyrine unit. Therefore the immediate alternative approach to overcome this problem was to reverse the order of reactions that the synthesis of thiazoline was carried out prior to the double bond formation (scheme 2.32).

Treatment of tripeptide **2.65** with triflic anhydride and triphenylphosphine oxide successfully afforded thiazoline **2.68** with deprotected L-threonine unit in good yield. No sign of epimerization was observed at this stage, however, the product **2.68** was heavily contaminated with triphenylphosphine oxide and purification was particularly difficult. Dehydration of the thiazoline containing tripeptide **2.68** with EDC and copper (II) iodide in toluene at 80^{o}C for 30 min successfully led to the formation of fragment three **2.57**, however, again extensive epimerization was observed and it was believed that rapid epimerization was due to the basic reaction conditions used in this dehydration step.



Reagents and conditions: a) Tf_2O, Ph_3PO, DCM, 0^{o}C, 10 min, then **2.65**, rt, 2 h, 68%; **b**) EDC, $CuCl_2$, toluene, 80^{o}C, 30 min.

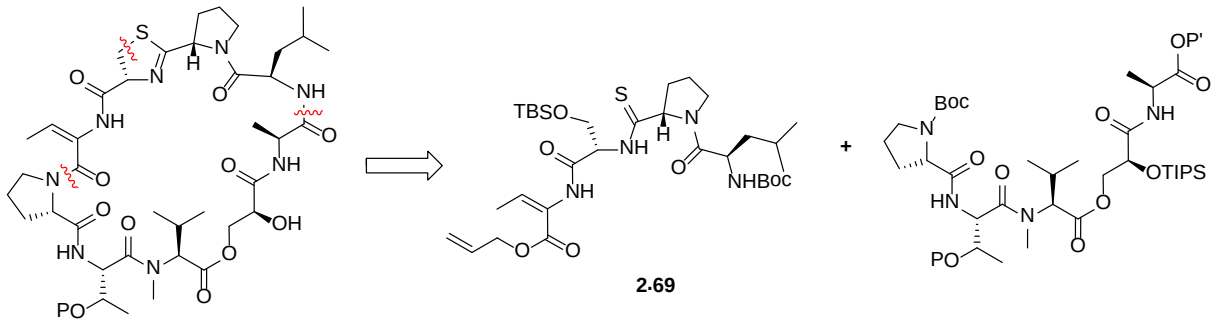
Scheme 2.32: Alternative approach to fragment three

In summary, our initial investigation into the preparation of fragment three has demonstrated that the dehydrobutyrine and thiazoline units can be synthesized separately. It has also showed that the L-proline adjacent to the thiazoline was very prone to epimization which suggested that the thiazoline would have to be introduced as late as possible in the synthesis in order to avoid epimerization of the neighbouring amino acid residue. Furthermore, it revealed that the strategy of the dehydration of the threonine containing peptide **2.66** followed by thiazoline formation was unsuccessful due to incompatibility of the double bond of

hydrobutyrine during the reaction. In light of these experimental results, it was concluded that the formation of thiazoline containing tripeptide **2.57** may not be achieved via cysteine derived peptides, therefore attempts at an alternative thiazoline formation method were investigated.

2.3.3 Modified synthetic strategy

As discussed in the previous chapter, thiazolines can also be accessed from thioamide containing peptides where the serine residue is converted to an electrophile and attacked by the neighbouring thioamide to form the thiazoline ring.[87] Therefore a modified synthetic strategy was proposed that vioprolide D was disconnected to two fragments: thioamide containing pentapeptide **2.69** and protected peptide **2.70** (scheme 2.33).



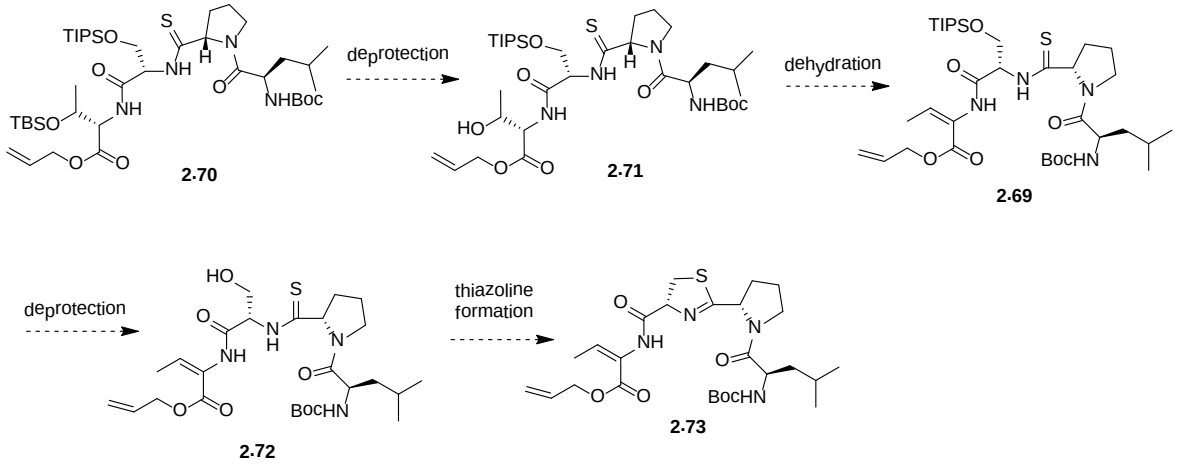
Scheme 2.33: Modified synthetic strategy

According to our previous investigation into the preparation of fragment one **2.26** and fragment two **2.40**, the preparation of protected peptide **2.70** should be relatively straightforward.

The key challenges involved in this modified synthetic strategy were the formation of thioamide containing peptide **2.69** followed by selective deprotection of secondary TBS-protected threonine residue in the presence of a primary TIPS-protected serine residue, followed by dehydration, removal of the TIPS group and final intramolecular cyclization to form thiazoline ring **2.73** as a

single diastereoisomer from thioamide and its neighbouring serine residue (scheme 2.34).

If the modified synthetic studies were successful and thiazoline containing pentapeptide **2.73** could be formed as a single diastereoisomer, then it would have been proven that pentapeptide amide **2.69** could be used as the precursor for accessing not only vioprolide D, but potentially other vioprolide family analogues as well.



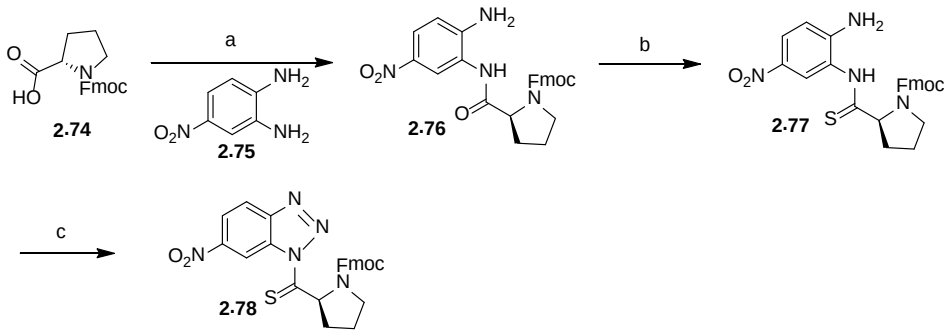
Scheme 2.34: Proposed modified synthetic sequence

2.3.3.1 Preparation of thioamide acylating agent

Preparation of thioamides usually begins with preparing thioacylation agents. In this case L-proline derived thioacylating agent **2.78** was prepared according to literature conditions.[120]

Treatment of Fmoc-protected L-proline with *N*-methylmorpholine, isobutyl chloroformate and 4-nitro-1,3-phenylenediamine led to the formation of amide **2.76** in good yield (scheme 2.35). Thioamide **2.77** was made in high yield by reacting amide **2.76** with phosphorus pentasulfide. This was a very smelly reaction and it was carried out inside fume cupboard and all glassware associated with this reaction was decontaminated by bleach. The structure of thioamide **2.77** was confirmed by ^{13}C NMR spectroscopy which showed a characteristic signal for the thioamide carbon at lower field that was absent in the starting material.

Intramolecular diazonium cyclization of **2.76**, using nitrous acid generated *in situ* with sodium nitrite in acetic acid gave benzotriazole **2.78** in quantitative yield. Benzotriazole **2.78** was used as the thioacylating agent in the subsequent peptide synthesis.



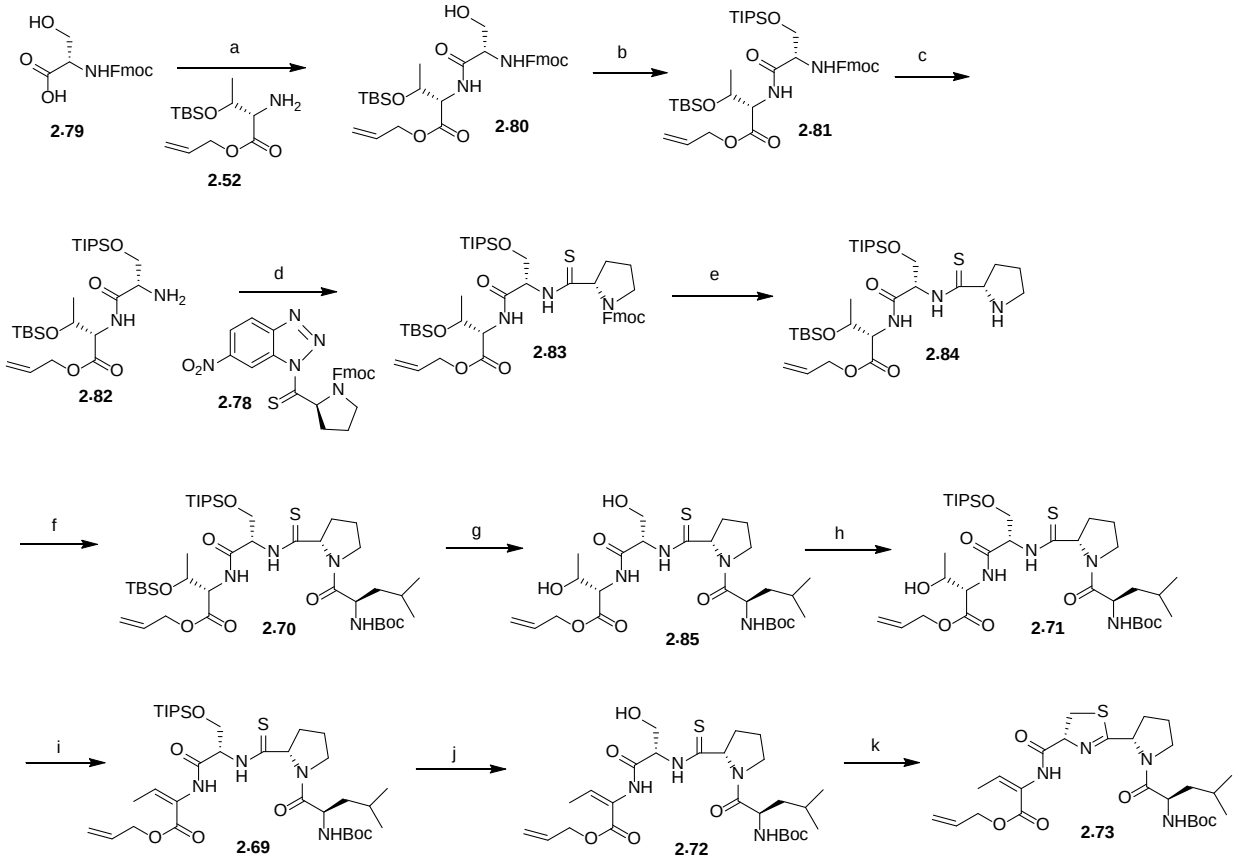
Reagents and conditions: a) NMM, ^{i}BuOCOCl, THF, -20^{o}C, then **2.75**, rt, 16 h, 72%; **b**) P_4S_{10}, $NaHCO_3$, THF, 1 h, then add **2.76**, 0^{o}C - rt, 3 h, 89%; **c**) $NaNO_2$, AcOH with 5% H_2O, 0^{o}C, 30 min, 99%.

Scheme 2.35: Preparation of thioacylating agent

2.3.3.2 Preparation of thiazoline containing tetrapeptide 2.73

Synthesis of the thiazoline containing tetrapeptide **2.73** began with Fmoc-protected serine **2.79** (scheme 2.36). Amide coupling of Fmoc-protected serine **2.79** with the allyl ester of *O*-TBS protected threonine **2.52** gave the corresponding dipeptide **2.80** in quantitative yield. The free hydroxyl group on the serine residue in the dipeptide **2.80** was subsequently protected by a TIPS group to form the bis-silylated dipeptide **2.81**. Removal of the Fmoc group using piperidine gave the free amine **2.82** in good yield. Treatment of free amine **2.82** with thioacylating agent **2.78** in THF afforded the tripeptide thioamide **2.83**, which was then converted to its corresponding amine **2.84** with piperidine in DMF. Peptide chain extension of tripeptide **2.84** with boc-protected D-leucine was achieved under standard peptide coupling conditions to give bis-silylated tetrapeptide **2.70**. Selective deprotection of the *O*-TBS protected threonine residue proved difficult in the presence of the primary TIPS group, so both silyl protecting groups were removed using tetrabutylammonium fluoride to give the corresponding diol **2.85**. Selective silyl protection of the serine residue was achieved by using an excess of triisopropylsilyl chloride with imidazole to give

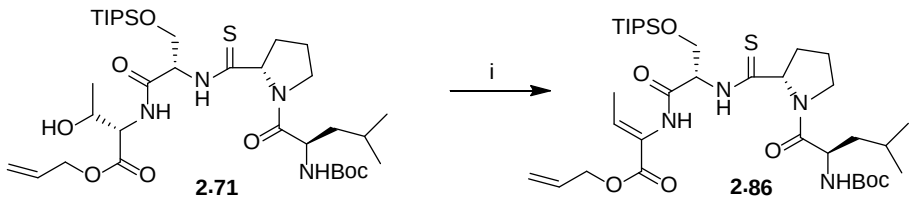
the mono silyl-protected tetrapeptide **2.71**. Treatment of the mono silyl-protected tetrapeptide **2.71** with EDC and copper (II) chloride, which was known to be selective for the formation of (*E*)-dehydrobutyrines,[117] successfully generated the desired dehydrobutyrine containing tetrapeptide **2.69** in modest yield. Subsequent deprotection of triisopropylsilyl ether **2.69** using tetrabutylammonium fluoride delivered the corresponding alcohol **2.72**, which was the precursor for the final thiazoline formation reaction. Treatment of the thioamide containing tetrapeptide with diethylaminosulfur trifluoride (DAST) in DCM at -15^{o}C successfully generated the desired thiazoline **2.73** in 75% yield, and this product was observed on TLC and later isolated by flash chromatography as a single diastereoisomer. Initial ^{1}H NMR study showed that thiazoline containing tetrapeptide **2.73** was isolated as a 2:1 mixture of two rotamers, which was confirmed by Various Temperature NMR studies with temperature ranging between 30^{o}C to 117^{o}C.



Reagents and conditions: **a**) HATU, HOBt, DIPEA, DMF, then protected threonine **2·52**, rt, 16 h, 97%; **b**) TIPSOTf, 2,6-lutidine, DCM, rt, 16 h, 56%; **c**) Piperidine, DMF, rt, 2 h, 89%; **d**) Thioacylating agent **2.78**, THF, rt, 6 h, 60%; **e**) Piperidine, DMF, rt, 2 h, 66%; **f**) HATU, HOBt, DIPEA, DMF, then add **boc-D-Leu-OH**, rt, 16 h, 85%; **g**) TBAF, THF, rt, 16 h, 45%; **h**) TIPSCl, imidazole, THF, rt, 24 h, 68%; **i**) EDC, $CuCl_2$, toluene, 80°C, 30 min, 65%; **j**) TBAF, THF, 16 h, rt, 68%; **k**) DAST, DCM, -15°C, 1 h, 75%.

Scheme 2.36: Preparation of thiazoline containing tetrapeptide **2.73**

It is worth noting that DAST is an extremely reactive substance, the cyclization reaction to form thiazoline **2.73** must be carried out at relatively low temperature for a short period of time. It was observed that prolonged exposure of thiazoline **2.73** to DAST resulted in product degradation, even at a low temperature. In order to confirm the (*E*)-geometry of the double bond formed during the dehydration reaction from secondary alcohol **2.71** to dehydrobutyrine tetrapeptide **2.69**, alcohol **2.71** was treated with DAST with pyridine at 0°C which is the reaction condition known to be selective for generating (*Z*)-dehydrobutyrines (scheme 2.37).[121] After chromatography dehydrobutyrine **2.86** with (*Z*)-double bond was isolated in 31% yield. It has been observed that this was a slow reaction which may suggest that the (*E*)-double bond isomer was the kinetic product, whereas the thermodynamic product was the (*Z*)-isomer.



Reagents and conditions: a) DAST, pyridine, DCM, 0°C, 2 h, 31%.

Scheme 2.37: Preparation of (*Z*)-dehydrobutyrine

2.4 Conclusions and future work

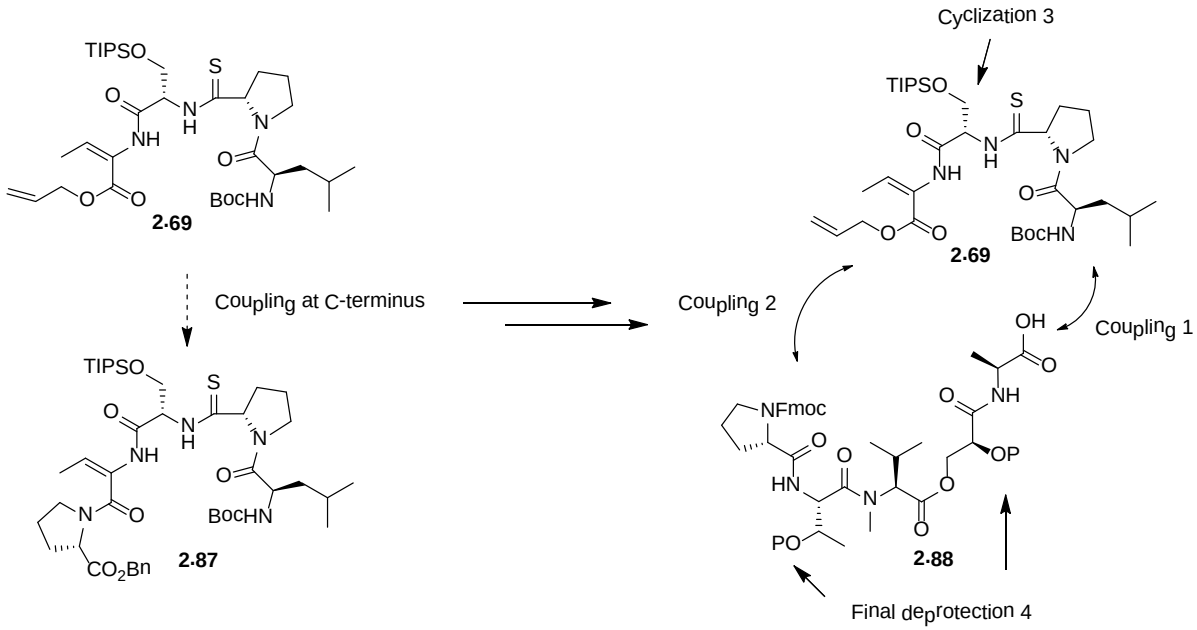
In this project, towards the total synthesis of macrocylic depsipeptide vioprolide D, initial disconnection revealed that three tripeptide fragments were the key components in the overall synthesis of the natural product. Preparation of fragment one **2.26** was accomplished from commercially available amino acid building blocks.

During the attempts to synthesize fragment two **2.40**, an intramolecular cyclization reaction, upon removal of Fmoc group in dipeptide **2.42**, was found to be a major side reaction which stopped the peptide chain extension. The problem was due to the presence of the *N*-methyl group in the dipeptide structure that prevented hydrogen-bonding and changed the dipeptide's conformation from *trans*- to *cis*-peptide bond. The resulting change in the overall structural conformation therefore facilitated the side reaction. After extensive literature search, it was believed that by changing the allyl ester in dipeptide **2.42** to a *t*-butyl ester should suppress the side reaction from taking place.

Numerous attempts were made to synthesize fragment three **2.57** as a single diastereoisomer *via* cysteine containing peptides. Thiazoline and dehydrobutyrine units were achieved separately, however it was found that the thiazoline system could not be made in the presence of the dehydrobutyrine because of the incompatibility of the double bond with the reaction conditions. Furthermore it was found that the L-proline residue adjacent to thiazoline was extremely prone to epimerization so that thiazoline ring must be introduced as late as possible.

In the modified synthetic strategy, the thiazoline containing tetrapeptide **2.73** was synthesized as a single diastereoisomer from the cyclization of the thioamide with an adjacent serine amino acid residue. These results have demonstrated that thiazoline and dehydrobutyrine can co-exist within one peptide molecule as a single diastereoisomer and this has opened the scope for not only the synthesis of vioprolide D, but also potentially other vioprolide family analogues bearing similar amino acid residues.

In terms of future work, it is necessary to investigate that thioamide containing tetrapeptide **2.69** can undergo amide coupling at the *C*-terminus to give pentapeptide **2.87** (scheme 2.38). If this reaction was successful, it would have demonstrated that tetrapeptide **2.69** would be able to couple with peptide **2.88** at both the *N*- and *C*- terminals to form the macrocycle of vioprolide D. Once the macrocycle was formed, removal of the TIPS group on the serine residue, followed by dehydration with DAST, would give the desired thiazoline unit, and subsequent alcohol deprotection would lead to the natural product of vioprolide D.



Scheme 2.38: Future work

Experimental Section

General information

All reactions were carried out under an atmosphere of dry nitrogen unless otherwise stated. Temperatures quoted are for the external heating / cooling source and are given in degrees Celsius (^{o}C).

Low resolution mass spectra were recorded on a Micromass Trio 200 spectrometer. High resolution mass spectra were recorded on a Kratos Concept IS spectrometer. Modes of ionisation were electron impact (EI), chemical ionisation (CI) using ammonia or electrospray in positive mode (ES+).

Infrared spectra were recorded on a Genesis FTIR as evaporated films on sodium chloride plates and are quoted in cm^{-1}.

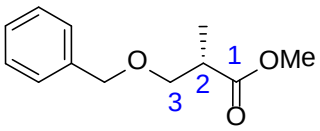
Nuclear magnetic resonance (NMR) spectra were recorded using deuterated chloroform as solvent unless otherwise stated. Proton NMR spectra (^{1}H NMR) were recorded on Bruker (500 MHz), Varian Unity 500 (500 MHz), Varian INOVA 400 (400 MHz) or Varian INOVA Unity 300 (300 MHz) spectrometers. Residual non-deuterated solvent was used as internal standard. Chemical shifts (δ H) are quoted in parts per million (ppm) downfield from tetramethyl silane (TMS). Signal splitting patterns are described as singlet (s), doublet (d),doublet of doublet (dd), doublet of triplet (dt), triplet (t), quartet (q), doublet of quartet (dq), quintet (qn), broad singlet (br. s), broad double (br d), broad multiplet (br m) or multiplet (m). Coupling constants (*J*) are quoted in Hz. Carbon NMR spectra (^{13}C NMR) were recorded on a Varian INOVA unity 300 spectrometer at 75 MHz, again with residual non-deuterated solvent as the internal standard. Chemical shifts (δ C) are quoted in ppm downfield from TMS.

Flash column chromatography was carried out using silica gel 60H (40 – 60 nm, 230 – 300 mesh) from Merck. Thin layer chromatography (TLC) was carried out using glass plates coated with Merck HF 254 / 366 silica gel. Detection was by ultraviolet absorption or by treatment with potassium permanganate or anisaldehyde solutions followed by heating.

‘Light petroleum’ refers to the fraction of petroleum ether that boils between 40^{o}C and 60^{o}C at atmospheric pressure and was distilled prior to use. ‘Ether’ refers to diethyl ether, which was used without further purification. Tetrahydrofuran was dried over sodium / benzophenone and distilled under a nitrogen atmosphere prior to use. Dichloromethane was dried over calcium hydride and distilled under an atmosphere of nitrogen prior to use. Methanol was dried and distilled from calcium hydride before storing over 4Å molecular sieves. Ethanol was dried and distilled from calcium hydride before storing over 4Å molecular sieves. Benzene, toluene, and hexane were dried and stored over sodium wire. All other reagents and solvents were used as purchased unless otherwise stated.

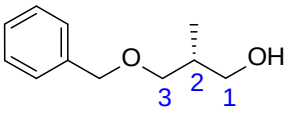
Experimental for compounds in section one

Methyl (2*S*)-3-benzyloxy-2-methyl-propanoate[122] (1.70)



At room temperature, benzyl 2,2,2-trichloroacetimidate (4.21 mL, 22.7 mmol) and methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (2 mL, 18.1 mmol) were dissolved in DCM/cyclohexane (24 mL / 40 mL). To this reaction mixture was slowly added triflic acid (160 ul, 1.8 mmol). The resulting reaction mixture was allowed to stir at room temperature for 16 h. Solid was filtered, the residue was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the title compound **1.70** (3.7 g, 98%) as a colourless oil, R_f 0.4 (4:1 petrol-ether); $[\alpha]_D^{20}$ +12 (c 1.6 in $CHCl_3$); [literature value: $[\alpha]_D^{20}$ +11.6 (c 1.0 in $CHCl_3$)]; (Found $[M+Na]^+$, 231.0998; $C_{12}H_{16}O_3Na$, requires *M*, 231.0992) ν_{max} 2951, 2860, 1736, 1497, 1454, 1435, 1364, 1247, 1199, 1176, 1092, 1029, 993, 906, 838, 737 and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.18 (3 H, d, *J* 6.9, 2-CH_3), 2.80 (1 H, m, 2-H), 3.48 (1 H, dd, *J* 9.1 and 6.0, 3-H_a), 3.67 (1 H, dd, *J* 9.1 and 7.3, 3-H_b), 3.71 (3 H, s, OCH_3), 4.53 (2 H, s, O*C*H_2Ph), 7.33 (5 H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 14.00, 40.20, 51.75, 71.98, 73.12, 127.59, 127.61, 128.37, 138.18 and 175.32; *m*/*z* (ES+) 231 ($[M+23]^+$, 100%).

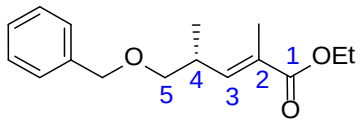
(2*R*)-3-Benzyloxy-2-methyl-propan-1-ol[128] (1.71)



DIBAL-H (1 M in hexane, 12.3 mL, 12.3 mmol) was added dropwise to a solution of ester (853 mg, 4.1 mmol) in DCM (25 mL) at -78 ^oC. The resulting solution was stirred at -78 ^oC for 1 h and then cold bath was removed and

reaction was allowed to warm gradually to room temperature. After stirring at room temperature for 1 h, the reaction was cooled to 0 ^{o}C and to this reaction was slowly added saturated aqueous potassium tartrate (15 mL). Diethyl ether (30 mL) was added, the mixture was stirred at RT for 2 h. The two phases were separated and organic phase was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (1:1) gave the *title compound* **1.71** (608 mg, 82%) as a colourless oil, R_f 0.3 (1:1 petrol-ether); $[\alpha]_D^{20}$ +14.9 (c 0.4 in $CHCl_3$); (Found $[M+Na]^+$, 203.1049; $C_{11}H_{16}O_2Na$, requires *M*, 203.1043); ν_{max} 3370, 2862, 1496, 1454, 1363, 1206, 1092, 1029, 735, 697 and 610 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.82 (3 H, d, *J* 6.9, 2-CH_3), 2.01 (1 H, m, 2-H), 3.36 (1 H, dd, *J* 9.1 and 8.2, 3-H_a), 3.55 (1 H, dd, *J* 6.0 and 4.4, 3-H_b), 3.55 (2 H, m, 1-H_2), 4.45 (2 H, s, OC*H*$_2$Ph), 7.26 (5 H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 13.5, 35.6, 68.0, 73.4, 75.5, 127.6, 127.8, 128.5 and 138.1; *m/z* (ES+) 203 ($[M+23]^+$, 100%).

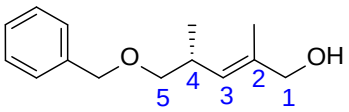
Ethyl (*E*,4*R*)-5-benzyloxy-2,4-dimethyl-pent-2-enoate[129] (1.73)



To a solution of alcohol **1.71** (100 mg, 0.55 mmol) in DCM (10mL) was added $NaHCO_3$ (238 mg, 2.8 mmol) and DMP (468 mg, 1.1 mmol) at room temperature. The reaction was stirred at room temperature for 30 min. To the reaction was added with saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL). The resulting mixture was extracted with DCM, the combined organic layer was subsequently washed with brine, dried over $MgSO_4$ and concentrated to yield the aldehyde. The aldehyde was dissolved in DCM (10 mL) and to this solution was added phosphorane **1.72** (598 mg, 1.65 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.73** (104 mg, 71%) as a colourless oil, R_f 0.5 (9:1 petrol-EtOAc); $[\alpha]_D^{20}$ -6.7 (c 0.2 in $CHCl_3$); (Found

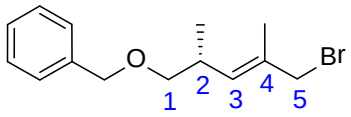
[M+Na]$^+$, 285.1468; $C_{16}H_{22}O_3Na$, requires *M*, 285.1461) ν_{max} 2979, 2360, 1707, 1652, 1497, 1454, 1367, 1234, 1146, 1084, 1029, 906, 864, 748 and 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.97 (3 H, d, *J* 6.6, 4-CH_3), 1.23 (3 H, t, *J* 7.1, OCH_2CH_3), 1.79 (3 H, s, 2-CH_3), 2.78 (1 H, m, 4-H), 3.26 (2 H, d, *J* 6.8, 5-H_2), 4.12 (2 H, q, *J* 7.1, OCH_2CH_3), 4.44 (2 H, s, OCH_2Ph), 6.52 (1 H, m, 3-H), 7.26 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 12.7, 14.4, 16.7, 34.0, 60.6, 73.1, 74.3, 127.6 (2), 128.2, 128.4, 138.4, 144.3 and 168.3; *m*/*z* (ES+) 285 ([M+23]$^+$, 100%).

(*E*,4*R*)-5-Benzyloxy-2,4-dimethyl-pent-2-en-1-ol[129] **(1.74)**



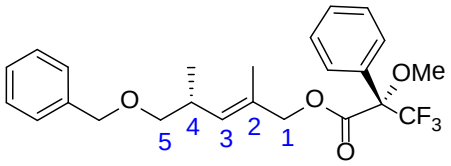
H-DIBAL (1 M in hexane, 1.1 mL, 1.1 mmol) was added dropwise to a solution of ester (82 mg, 0.31 mmol) in DCM (3 mL) at -78 ^oC. The resulting solution was stirred at -78 ^oC for 1 h and then cold bath removed and reaction was allowed to warm gradually to room temperature. After stirring at room temperature for 1 h, the reaction was cooled to 0 ^oC and quenched by careful addition of saturated aqueous potassium tartrate (5 mL). Diethyl ether (10 mL) was added, the mixture was stirred at room temperature for 2 h. The two phases were separated and organic phase was extracted with ether and washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (1:1) gave the *title compound* **1.74** (66 mg, 97%) as a colourless oil, R_f 0.5 (1:1 petrol-ether); $[\alpha]_D^{20}$ -14.3 (c 0.2 in $CHCl_3$); (Found [M+Na]$^+$, 243.1356; $C_{14}H_{20}O_2Na$, requires *M*, 243.1356) ν_{max} 3367, 2856, 1496, 1453, 1365, 1205, 1071, 1008, 854, 809, 735 and 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.92 (3 H, d, *J* 6.8, 4-CH_3), 1.26 (1 H, q, *J* 6.3, OH), 1.60 (3 H, s, 2-CH_3), 2.69 (1 H, m, 4-H), 3.19 (1 H, dd, *J* 9.1 and 6.6, 5-H_a), 3.24 (1 H, dd, *J* 9.1 and 7.1, 5-H_b), 3.88 (2 H, s, 1-H_2), 4.41 (2 H, s, OCH_2Ph), 5.15 (1 H, m, 3-H), 7.24 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.0, 17.7, 32.7, 68.8, 73.0, 75.2, 127.5, 127.6, 128.4, 128.8, 135.4 and 138.6; *m*/*z* (ES+) 243 ([M+23]$^+$, 100%).

[(*E*,2*R*)-5-Bromo-2,4-dimethyl-pent-3-enoxy]methylbenzene (1.79)



Triphenylphosphine (196 mg, 0.75 mmol) was added at room temperature to a solution of alcohol **1.74** (100 mg, 0.45 mmol) and carbon tetrabromide (196 mg, 0.59 mmol) in DCM (3 mL). The reaction mixture was then stirred at room temperature for 2 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (9:1) gave *the title compound* **1.79** (121 mg, 94%) as a colourless oil. R_f 0.7 (9:1 petrol-ether); (Found $[M\text{-}Br]^+$, 203.1425; $C_{14}H_{19}O_1$, requires *M*, 203.1430); $[\alpha]_D^{20}$ -10.0 (c 0.4 in $CHCl_3$); ν_{max} 2959, 2854, 1496, 1453, 1362, 1201, 1092, 1028, 811, 735, 642 and 613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.93 (3 H, d, *J* 6.6, 2-CH_3), 1.72 (3 H, s, 4-CH_3), 2.62 (1 H, m, 2-H), 3.23 (1 H, dd, *J* 6.8 and 4.1, 1-H_a), 3.26 (1 H, dd, *J* 6.8 and 4.1, 1-H_b), 3.90 (2 H, s, 5-H_2), 4.44 (2 H, s, OC*H*$_2$Ph), 5.38 (1 H, d, *J* 9.1, 3-H), 7.26 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.9, 17.1, 33.5, 41.6, 73.0, 74.7, 127.5 (2), 128.4, 132.5, 134.0 and 138.6; *m*/*z* (EI) 203 ($[M\text{-}79]^+$, 5%).

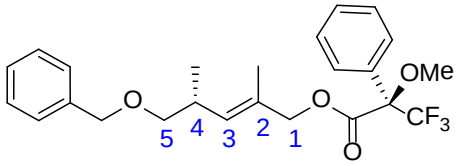
[(*E*,4*R*)-5-Benzyloxy-2,4-dimethyl-pent-2-enyl] (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (1.76)



To a solution of alcohol **1.74** (10 mg, 0.045 mmol) in DCM (0.5 mL) was added NEt_3 (14 mg, 0.14 mmol), (*R*)-MTPA-Cl (13 mg, 0.05 mmol) and DMAP (17 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 16 h. Reaction mixture was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (80:20) gave the *title compound* **1.76** (19 mg, 97%) as a colourless oil. R_f 0.5 (80:20 petrol-ether). δ_H (300 MHz, $CDCl_3$) 0.91 (3 H, d, *J* 6.8, 4-Me), 2.65 (1 H, m, 4-H), 3.21 (2 H, m, 5-H_2), 3.47 (3 H, s, OCH_3), 4.42 (3 H, s, OC*H*$_2$Ph), 4.63 (2 H, m, 1-H_2), 5.29 (1

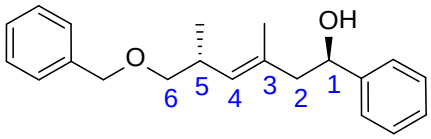
H, d, *J* 9.2, 3-H) and 7.19-7.44 (10 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.3, 17.3, 33.0, 55.5, 71.9, 73.0, 74.8, 87.4, 92.0, 127.3, 127.5, 128.4, 128.4 128.9, 129.5, 129.6, 132.4, 134.2, 138.5 and 166.4.

[(*E*,4*R*)-5-Benzyloxy-2,4-dimethyl-pent-2-enyl] (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (1.78)



To a solution of alcohol **1.74** (10 mg, 0.045 mmol) in DCM (0.5 mL) was added NEt_3 (14 mg, 0.14 mmol), (*R*)-MTPA-Cl (13 mg, 0.05 mmol) and DMAP (17 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 16 h. Reaction mixture was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (80:20) gave the *title compound* **1.78** (18 mg, 93%) as a colourless oil. R_f 0.5 (80:20 petrol-ether). δ_H (300 MHz, $CDCl_3$) 0.91 (3 H, d, *J* 6.9, 4-CH_3), 2.66 (1 H, m, 4-H), 3.21 (2 H, m, 5-H_2), 3.47 (3 H, s, OCH_3), 4.42 (3 H, s, O*C*H_2Ph), 4.63 (2 H, m, 1-H_2), 5.29 (1 H, d, *J* 9.1, 3-H) and 7.19-7.45 (10 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.27, 17.30, 33.03, 55.50, 71.94, 73.02, 74.82, 81.0, 98.2, 127.4, 127.5, 127.6, 128.4 (2), 129.5, 129.6, 133.3, 134.2, 138.6 and 166.4.

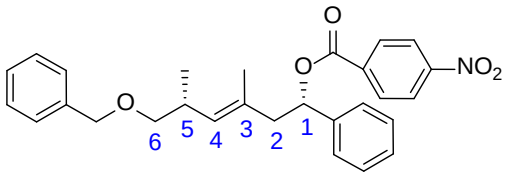
(*E*,1*R*,5*R*)-6-Benzyloxy-3,5-dimethyl-1-phenyl-hex-3-en-1-ol (1.80)



Zinc powder (39 mg, 0.6 mmol) was suspended in a solution of bismuth iodide (312 mg, 0.53 mmol) in THF (3 mL) and the mixture was stirred vigorously at room temperature for 1 h, during which time the orange/grey suspension turned black. A solution of bromide (100 mg, 0.35 mmol) and benzaldehyde (38 mg, 0.35 mmol) in THF (2 mL) was added and the resulting mixture was stirred

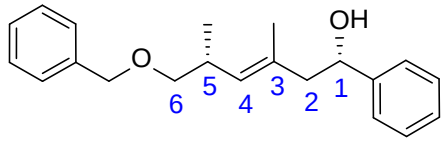
under reflux for 2 h. Reaction mixture was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **1.80** (51 mg, 47%) as a colourless oil. R_f 0.3 (70:30 petrol-ether). δ_H (400 MHz, $CDCl_3$) 0.87 (3 H, d, *J* 6.6, 5-Me), 1.66 (3 H, s, 3-Me), 1.82 (1 H, br s, OH), 2.22 (1 H, dd, *J* 9.8 and 13.1, 6-H_a), 2.34 (1 H, dd, *J* 3.5 and 12.9, 6-H_b), 2.71 (1 H, m, 5-H), 3.18 (1 H, dd, *J* 7.6 and 8.8, 2-H_a), 3.25 (1 H, dd, *J* 6.3 and 8.8, 2-H_b), 4.45 (2 H, dd, *J* 12.4 and 20.7, OCH_2Ph), 4.64 (1 H, dd, *J* 3.8 and 9.8, 1-H), 5.03 (1 H, d, *J* 9.6, 4-H) and 7.17-7.32 (10 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 16.4, 17.2, 33.20, 50.80, 70.7, 73.0, 75.2, 125.8, 127.3, 127.6, 127.7 (2), 128.32, 128.39, 132.88, 138.46 and 144.12.

[(*E*,1*S*,5*R*)-6-Benzyloxy-3,5-dimethyl-1-phenyl-hex-3-enyl] 4-nitrobenzoate (1.81)



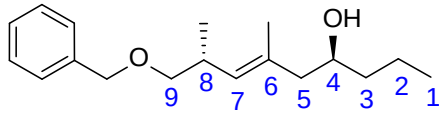
To a solution of alcohol **1.80** (104 mg, 0.34 mmol) in THF (3 mL) was added 4-nitrobenzoic acid (73 mg, 0.44 mmol) followed by Ph_3P (176 mg, 0.68 mmol) and DIAD (136 mg, 0.68 mmol). Reaction was stirred at room temperature for 16 h. Reaction mixture was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **1.81** (123 mg, 80%) as a colourless oil. R_f 0.6 (70:30 petrol-ether). δ_H (400 MHz, $CDCl_3$) 0.68 (3 H, d, *J* 6.8, 5-CH_3), 1.65 (3 H, s, 3- CH_3), 2.46 (1 H, dd, *J* 4.5 and 13.4, 2-H_a), 2.57 (1 H, m, 5-H), 2.68 (1 H, dd, *J* 9.3 and 13.1, 2-H_b), 3.08 (2 H, m, 6-H_2), 4.37 (2 H, s, OCH_2Ph), 4.97 (1 H, d, *J* 9.1, 4-H), 6.10 (1 H, m, 1-H), 7.19-7.35 (10 H, m, Ar-H) and 8.08-8.20 (4 H, m, Ar-H).

(*E*,1*S*,5*R*)-6-Benzyloxy-3,5-dimethyl-1-phenyl-hex-3-en-1-ol (1.82)



To a solution of ester **1.81** (96 mg, 0.21 mmol) in THF (1.5 mL) was LiOH (25 mg, 1.05 mmol) in H_2O (0.5 mL). Reaction mixture was stirred at 60^oC for 1 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **1.82** (123 mg, 80%) as a colourless oil. R_f 0.3 (70:30 petrol-ether). δ_H (400 MHz, $CDCl_3$) 1.04 (3 H, d, *J* 6.8, 5-CH_3), 1.72 (3 H, s, 3- CH_3), 2.36 (1 H, dd, *J* 8.6 and 13.4, 2-H_a), 2.46 (1 H, dd, *J* 4.3 and 13.4, 2-H_b), 2.78 (1 H, m, 5-H), 3.29 (2 H, m, 1-H_2), 4.53 (2 H, s, OC*H*$_2$Ph), 4.79 (1 H, m, 1-H), 5.15 (1 H, d, *J* 9.1, 4-H) and 7.26-7.39 (10 H, m, Ar-H).

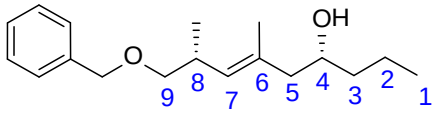
(*E*,4*S*,8*R*)-9-Benzyloxy-6,8-dimethyl-non-6-en-4-ol (1.83)



Zinc powder (46 mg, 0.69 mmol) was suspended in a solution of bismuth iodide (360 mg, 0.61 mmol) in THF (4 mL) and the mixture was stirred vigorously at room temperature for 1 h, during which time the orange/grey suspension turned black. A solution of bromide (115 mg, 0.41 mmol) and butyraldehyde (29 mg, 0.41 mmol) in THF (2 mL) was added and the resulting mixture was stirred under reflux for 2 h. Reaction mixture was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **1.83** (50 mg, 45%) as a colourless oil. R_f 0.4 (70:30 petrol-ether). δ_H (400 MHz, $CDCl_3$) 0.88 (6 H, m, 8- CH_3 and 1-H_3), 1.38 (4 H, m, 3-H_2 and 2-H_2), 1.60 (3 H, ms, 6-CH_3), 1.68 (1 H, br s, OH), 1.90 (1 H, dd, *J* 9.8 and 12.9, 5-H_a), 2.12 (1 H, dd, *J* 2.8 and 12.9, 5-H_b), 2.68 (1 H, m, 8-H), 3.15 (1 H, dd, *J* 8.8 and 6.6, 1-H_a), 3.22 (1 H, t, *J* 6.6 and 8.8, 1-H_b), 3.56 (1 H, m, 4-H), 4.41 (1 H, d, *J* 12.0 and 30.9, OC*H*$_a$Ph), 4.44 (1 H, d, *J* 12.3, OC*H*$_b$Ph), 4.98 (1 H, d, *J*

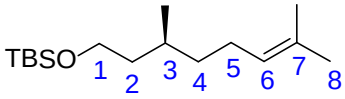
9.1, 7-H) and 7.25 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.2, 16.4, 17.3, 19.0, 33.1, 39.1, 48.2, 67.7, 73.0, 75.2, 127.5, 127.6, 128.4, 132.0, 132.6 and 138.5.

(*E*,4*R*,8*R*)-9-Benzyloxy-6,8-dimethyl-non-6-en-4-ol (1.85)



To a solution of ester **1.84** (75 mg, 0.18 mmol) in THF (1.5 mL) was LiOH (21 mg, 0.88 mmol) in H_2O (0.5 mL). Reaction mixture was stirred at 60 ^oC for 1 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **1.85** (38 mg, 80%) as a colourless oil. R_f 0.4 (70:30 petrol-ether). δ_H (500 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 6.9, 9-H_3), 0.98 (6 H, d, *J* 6.6, 8-Me), 1.35-1.49 (4 H, m, 3-H_2 and 2-H_2), 1.66 (3 H, s, 6-Me), 1.82 (1 H, br s, OH), 1.97 (1 H, dd, *J* 9.5 and 13.2, 5-H_a), 2.19 (1 H, dd, *J* 3.2 and 13.2, 5-H_b), 2.73 (1 H, m, 8-H), 3.28 (2 H, m, 9-H_2), 3.66 (1 H, m, 4-H), 4.50 (2 H, s, OCH_2Ph), 5.07 (1 H, d, *J* 9.1, 7-H) and 7.31 (5 H, m, Ar-H); δ_C (125MHz, $CDCl_3$) 14.18, 16.53, 18.01, 18.98, 33.15, 39.17, 47.99, 68.18, 72.96, 75.20, 127.53, 127.62, 128.35, 131.77, 132.73 and 138.63.

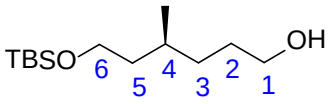
***tert*-Butyl-[(3*S*)-3,7-dimethyloct-6-enoxy]-dimethyl-silane[123] (1.89)**



To a solution of (*S*)-citronellol **1.88** (1.0 g, 6.4 mmol) in THF (25 mL) was added imidazole (479 mg, 7.0 mmol), the mixture was stirred at RT for 10 min before adding *tert*-butyldimethylsilyl chloride (1.06 g, 7.0 mmol). The reaction mixture was stirred at room temperature overnight for 16 h. Reaction was diluted with diethylether (25 mL) and partitioned between ether (20 mL) and aqueous saturated $NaHCO_3$, organic layer was washed with brine (20 mL), dried over Na_2SO_4. Reaction was concentrated under reduced pressure. Column

chromatography of the residue eluting with petrol (100%) gave the title compound **1.89** (1.7 g, 98%) as a colourless oil, R_f 0.3 (100% petrol); $[\alpha]_D^{20}$ -1.7 (c 0.2 in $CHCl_3$); [Literature value: $[\alpha]_D^{20}$ -4.5 (neat)]; (Found $[M\text{-}C_4H_9]^+$, 213.1675; $C_{12}H_{25}O_1Si$, requires *M*, 231.1669); ν_{max} 2955, 2928, 2857, 1463, 1378, 1361, 1254, 1095, 988, 897, 833, 773 and 662 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 (6 H, s, $Si(CH_3)_2$), 0.82 (3 H, d, *J* 7, 3-CH_3), 0.85 (9 H, s, $SiC(CH_3)_3$), 1.07-1.15 (2 H, m, 4-H_2), 1.24-1.32 (2 H, m, 5-H_2), 1.51 (1 H, m, 3-H), 1.55 and 1.63 (each 3 H, s, 8-H_3 or 7-CH_3), 1.85-1.99 (2 H, m, 2-H_2), 3.60 (2 H, m, 1-H_2) and 5.04 (1 H, t, *J* 6.9, 6-H); δ_C (125MHz, $CDCl_3$) -5.2, 17.7, 18.4, 19.7, 25.5, 25.8, 26.0, 29.1, 37.2, 40.0, 61.5, 124.9 and 131.1; *m/z* (EI) 213 $([M\text{-}57]^+$, 100%).

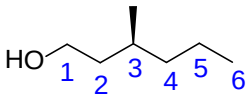
(4*S*)-6-[*tert*-Butyl(dimethyl)silyl]oxy-4-methyl-hexan-1-ol[130] (1.90)



In a 3-neck flask alkene **1.88** (1.3 g, 4.8 mmol) was dissolved in 1:1 DCM/MeOH (30 mL) and reaction was cooled to -78 ^oC. Ozone from an ozone generator was bubbled through the stirred solution for approximately 2 h until solution turned blue, which indicated ozone was saturated. Ozone generator was turned off leaving O_2 keep bubbling through the stirred solution at -78^oC until the blue color disappeared. N_2 inlet was then switched over and O_2 cylinder was turned off. Solid sodium borohydride (910 mg, 24 mmol) then was added at -78 ^oC and cold bath was removed and reaction was stirred at room temperature for 3 h. Reaction solvent was evaporated and the residue was partitioned between aqueous saturated $NaHCO_3$ (20 mL) and diethylether (30 mL), organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.90** (1.7 g, 98%) as a colourless oil, R_f 0.5 (1:1 petrol-ether); $[\alpha]_D^{20}$ +1.2 (c 0.2 in $CHCl_3$); (Found $[M]^+$, 247.2090; $C_{13}H_{31}O_2Si$, requires *M*, 247.2088) ν_{max} 3324, 2929, 2857, 1463, 1388, 1361, 1254, 1094, 1006, 939, 897, 833, 773 and 662 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (6 H, s, $Si(CH_3)_2$), 0.84 (9 H, s, $SiC(CH_3)_3$), 0.86 (3 H, d, *J* 7.0, 4-CH_3), 1.14 (1 H, m,

4-H), 1.30 (2 H, m, 3-H_2), 1.53 (4 H, m, 2-H_2 and 5-H_2) and 3.59 (4 H, m, 1-H_2, 6-H_2); δ_C (100 MHz, $CDCl_3$) -5.3, 18.4, 19.7, 26.0, 29.3, 30.2, 33.0, 39.8, 61.4 and 63.4. m/z (ES+) 269 ($[M+23]^+$, 100%); 247 ($[M+1]^+$, 60%).

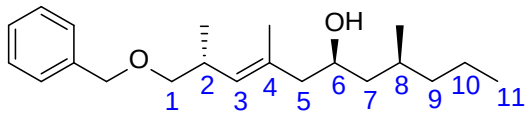
(3*S*)-3-Methylhexan-1-ol[124] (1.91)



Iodine (4.21 g, 16.6 mmol) was added portionwise to a stirred solution of triphenylphosphine (4.33 g, 16.6 mmol), imidazole (1.73 g, 25.4 mmol) and alcohol **1.90** (3.14 g, 12.7 mmol) in DCM (70 mL). The orange mixture was stirred at room temperature for 2 h. To this reaction was added aqueous Na_2SO_3 (30 mL). Then diethylether (50 mL) was added and reaction was partitioned between water and ether. Organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to yield the corresponding iodide a colourless crude oil. Without further purification, iodide (3.0g, 8.4 mmol) was dissolved in THF (40 mL). To this solution was added potassium *tert*-butoxide (2.9 g, 25 mmol) and reaction stirred at room temperature for 16 h. Reaction was partitioned between water (70 mL) and ether. Organic layer was dried washed with brine (50 mL), dried over Na_2SO_4 and concentrated to yield a colourless crude oil. Without further purification, this crude material was dissolved in THF (30 mL). To this solution was added 4M HCl in dioxane (2.2 mL, 9.0 mmol) and reaction was stirred at room temperature for 3 h. Reaction was neutralized using $NaHCO_3$ and partitioned between aqueous $NaHCO_3$ (50 mL) and diethylether. Organic layer was washed with brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (1:1) gave the interim alkene as a colourless oil. The alkene was then dissolved in THF (20 mL), to this solution was added Pd-C (150 mg, 10% by weight). Reaction mixture was stirred under H_2 atmosphere at room temperature for 16 h. Catalyst was filtered and solvent was removed under reduced pressure to give the title compound **1.91** (1.88 g, 60%

overall yield) as a colourless oil. R_f 0.5 (1:1 petrol-ether); $[\alpha]_D^{20}$ -1.1 (c 0.2 in $CHCl_3$); [literature value: $[\alpha]_D^{20}$ -0.94 (c 0.91 in $CHCl_3$)]; (Found $[M\text{-}H_2O]^+$, 98.1087; C_7H_{14}, requires *M*, 98.1090) ν_{max} 3323, 2955, 2926, 2871, 1458, 1378, 1120, 1054, 1008, 960, 836 and 738 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.78 (3 H, t, *J* 7.0, 6-H_3), 0.80 (3 H, d, *J* 6.8, 3-CH_3), 1.03 (1 H, m, 3-H), 1.16-1.31 (4 H, m, 4-H_2 and 5-H_2), 1.50 (2 H, m, 2-H_2) and 3.59 (2 H, m, 1-H_2); δ_C (125 MHz, $CDCl_3$) 14.4, 19.6, 20.0, 29.2, 39.4, 40.0 and 61.3; *m*/*z* (GCMS) 98 ($[M\text{-}18]^+$, 10%).

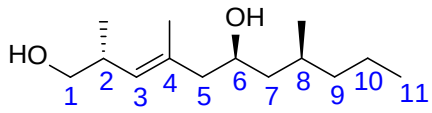
(*E*,2*R*,6*S*,8*S*)-1-Benzyloxy-2,4,8-trimethyl-undec-3-en-6-ol (1.92)



To a solution of alcohol **1.91** (63 mg, 0.54mmol) in DCM (5 mL) was added $NaHCO_3$ (212 mg, 2.5 mmol) and Dess-Martin Periodinane (261 mg, 0.62 mmol), the reaction mixture was stirred at room temperature for 30 min. To the reaction was added saturated aqueous $NaHCO_3$ (4 mL) and $Na_2S_2O_3$ (4 mL), and the mixture was extracted with DCM (2 x 10 mL). The combined organic layer was subsequently washed with brine (15 mL), dried over Na_2SO_4 and concentrated to yield aldehyde **1.65**. Zinc powder (80 mg, 1.22 mmol) was suspended in a solution of bismuth(III) iodide (637 mg, 1.08 mmol) in THF (4 mL) and the mixture was stirred vigorously at room temperature for 1 h, during which time the orange/grey suspension turned black. Bromide **1.79** (102 mg, 0.36 mmol) and a solution of aldehyde **1.65** in THF (2 mL) were then added to the bismuth suspension and the reaction mixture was stirred under reflux for 2 h before cooling down to room temperature. Reaction mixture was concentrated to give a black slurry. Column chromatography eluting with petrol-ether (7:3) gave the *title compound* **1.92** (67 mg, 60%) as a colourless oil, R_f 0.5 (7:3 petrol-ether); $[\alpha]_D^{20}$ -6.7 (c 0.2 in $CHCl_3$); (Found $[M+Na]^+$, 341.2453; $C_{21}H_{34}O_2Na$, requires *M*, 341.2452); ν_{max} 3436, 2956, 2926, 2870, 1454, 1378, 1273, 1205, 1089, 1028, 901, 832 and 735 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82 (6 H, m, 8-CH_3 and 11-H_3), 0.88 (3 H, d, *J* 7.0, 2-CH_3), 1.09 (1 H, m, 7-H_a), 1.19-1.29 (5 H, m,

8-H, 9-H_2 and 10-H_2), 1.41 (1 H, m, 7-H_b), 1.60 (3H, s, 4-CH_3), 1.86 (1 H, dd, *J* 12.8 and 10.0, 5H_a), 2.11 (1 H, dd, *J* 12.8 and 7.2, 5-H_b), 2.69 (1 H, m, 2-H), 3.15 (1 H, dd, *J* 9.1 and 7.8, 1-H_a), 3.23 (1 H, dd, *J* 9.1 and 7.3, 1-H_b), 3.63 (1 H, m, 6-H), 4.40 (1 H, d, *J* 12.1, OCH_aPh), 4.43 (1 H, d, *J* 12.1, OCH_bPh), 4.97 (1 H, d, *J* 8.9, 3-H) and 7.25 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.5, 16.5, 17.4, 20.0, 20.3, 29.5, 33.2, 39.1, 44.6, 48.5, 66.0, 73.0, 75.3, 127.5, 127.6, 128.4, 132.1, 132.6 and 138.5; *m*/*z* (ES+) 341 ($[M+23]^+$, 100%).

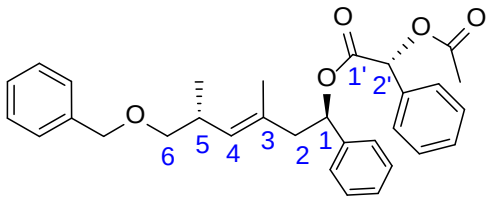
(*E*,2*R*,6*S*,8*S*)-2,4,8-Trimethylundec-3-ene-1,6-diol (1.95)



To a solution of naphthalene (290 mg, 2.3 mmol) in THF (3 mL) was added lithium metal (12 mg, 1.7 mmol) in small pieces. The reaction mixture was stirred at room temperature until lithium was completely dissolved and reaction turned into a dark green solution. The resulting mixture dark green solution of lithium naphthalenide was then cooled to -25^oC, followed by the dropwise addition of benzyl ether **1.92** (90 mg, 0.28 mmol) in THF (2 mL). The resulting mixture was stirred at -25^oC for 2 h. Saturated aqueous NH_4Cl (5 mL) and water (5 mL) was added and the solution was extracted with ether. Organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated by reduced pressure. Column chromatography eluting with petrol-ether (20:80) gave the *title compound* (50 mg, 78%) as a colourless gum, R_f 0.3 (3:7 petrol-ether); $[\alpha]_D^{20}$ +26.7 (c 0.4 in $CHCl_3$); (Found $[M+Na]^+$, 251.1983; $C_{14}H_{28}O_2Na$, requires *M*, 251.1982) ν_{max} 3309, 2954, 2925, 2870, 1455, 1378, 1072, 1031, 893, 831, 739 and 610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.81-0.88 (9 H, m, 2-CH_3, 8-CH_3 and 11-H_3), 1.01 (1 H, m, 7-H_a), 1.21 (1 H, m, 7-H_b), 1.28-1.31 (4 H, m, 9-H_2 and 10-H_2), 1.55 (1 H, m, 8-H), 1.57 (3 H, s, 4-CH_3), 1.90 (1 H, dd, *J* 12.8 and 10.0, 5-H_a), 2.09 (1 H, dd, *J* 12.7 and 3.3, 5-H_b), 2.56-2.64 (1 H, m, 2-H), 3.23 (1 H, dd, *J* 9.8 and 8.6, 1-H_a), 3.47 (1 H, dd, *J* 9.8 and 6.2, 1-H_b), 3.68-3.75 (1 H, m, 6-H) and 4.91 (1 H, d, *J* 9.0, 3-H); δ_C (100 MHz, $CDCl_3$) 14.4, 16.6, 16.7,

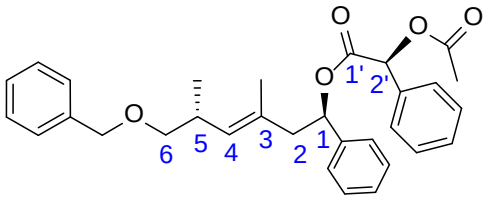
20.0, 20.3, 29.5, 35.4, 39.1, 45.0, 48.5, 66.4, 67.8, 131.2 and 134.2; *m*/*z* (ES+) 251 ([M+23]$^+$, 100%).

[(*E*,1*R*,5*R*)-6-Benzyloxy-3,5-dimethyl-1-phenyl-hex-3-enyl] (2*R*)-2-acetoxy-2-phenyl-acetate (1.86)



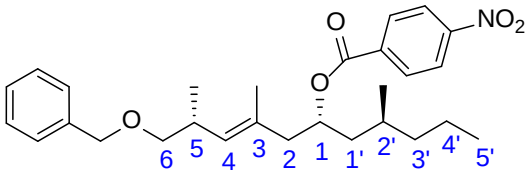
To a solution of alcohol **1.80** (23 mg, 0.074 mmol) in DCM (0.5 mL) was added pyridine (74 mg, 0.89 mmol) and DMAP (1 mg, 0.007 mmol) before cooling to 0^{o}C. A solution of acetylmandelyl chloride (47 mg, 0.22 mmol) in DCM (0.5 mL) was added dropwise before warming to room temperature and reaction was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **1.86** (30 mg, 83%) as a colourless oil. R_f 0.4 (70:30 petrol-ether). δ_H (400 MHz, $CDCl_3$) 0.73 (3 H, d, *J* 6.6, 5-CH_3), 1.36 (3 H, s, OCOCH_3), 2.08 (3 H, s, 3-CH_3), 2.22 (1 H, dd, *J* 5.8 and 13.9, 2-H_a), 2.37-2.48 (2 H, m, 2-H_b and 5-H), 2.92 (1 H, dd, *J* 7.6 and 9.1, 1-H_a), 3.00 (1 H, dd, *J* 6.1 and 9.1, 1-H_b), 4.36 (2 H, d, *J* 4.8, OCH_2Ph), 4.67 (1 H, d, *J* 7.8, 4-H), 5.75 (1 H, m, 1-H), 5.90 (1 H, s, 2'-H) and 7.19-7.39 (15 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 16.4, 17.5, 20.1, 32.9, 46.4, 72.9, 74.5, 75.0, 76.5, 126.3, 127.5 (2), 127.7 (2), 127.9, 128.3, 128.8 (2), 129.2, 130.5, 131.6, 133.9, 138.7, 168.1 and 170.1.

[(*E*,1*R*,5*R*)-6-Benzyloxy-3,5-dimethyl-1-phenyl-hex-3-enyl] (2*S*)-2-acetoxy-2-phenyl-acetate (1.87)



To a solution of alcohol **1.80** (23 mg, 0.074 mmol) in DCM (0.5 mL) was added pyridine (74 mg, 0.89 mmol) and DMAP (1 mg, 0.007 mmol) before cooling to 0^{o}C. A solution of acetylmandelyl chloride (47 mg, 0.22 mmol) in DCM (0.5 mL) was added dropwise before warming to room temperature and reaction was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **1.87** (32 mg, 89%) as a colourless oil. R_f 0.4 (70:30 petrol-ether). δ_H (400 MHz, $CDCl_3$) 0.68 (3 H, d, *J* 6.6, 5-CH_3), 1.35 (3 H, s, $OCOCH_3$), 2.09 (3 H, s, 3-CH_3), 2.22 (1 H, dd, *J* 6.8 and 13.6, 2-H_a), 2.36-2.48 (2 H, m, 2-H_b and 5-H), 2.96 (1 H, dd, *J* 7.6 and 9.1, 6-H_a), 3.04 (1 H, dd, *J* 6.1 and 9.1, 6-H_b), 4.35 (2 H, d, *J* 12.4, OCH_aPh), 4.40 (2 H, d, *J* 12.9, OCH_bPh), 4.65 (1 H, d, *J* 9.1, 4-H), 5.74 (1 H, t, *J* 6.8, 1-H), 5.90 (1 H, s, 2'-H) and 7.17-7.38 (15 H, m, Ar-H).

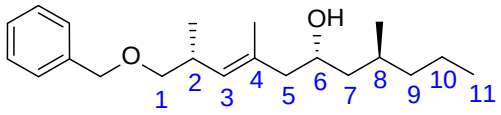
[(*E*,1*R*,5*R*)-6-Benzyloxy-3,5-dimethyl-1-[(2*S*)-2-methylpentyl]hex-3-enyl] 4-nitrobenzoate (1.93)



To a THF suspension of alcohol **1.87** (40 mg, 0.13 mmol), 4-nitrobenzoic acid (32 mg, 0.19 mmol) and Ph_3P (66 mg, 0.25 mmol) was added DIAD (51 mg, 0.25 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated and column chromatography of the residue eluting with petrol-ether (90:10) gave the *title compound* **1.93** (41 mg, 70%) as a colourless oil, R_f 0.8 (4:1 petrol-ether); δ_H (400 MHz, $CDCl_3$) 0.60 (3 H, d, *J* 6.8, 2'-CH_3), 0.79 (3 H, t, *J* 7.3, 5'-H_3), 0.84 (3 H, d, *J* 6.6, 5-CH_3), 1.00-1.33 (6 H, m, 1'-H_2, 3'-H_2 and 4'-H_2), 1.64 (3 H, s, 3- CH_3), 1.70 (1 H, m, 2'-H),

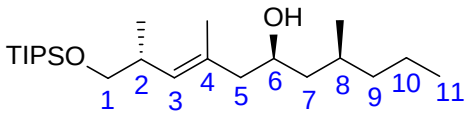
2.22 (2 H, m, 2-H_2), 2.56 (1 H, m, 2-H), 3.14 (2 H, m, 6-H_2), 4.39 (2 H, s, OCH_2Ph), 4.91 (1 H, d, *J* 9.3, 4-H), 5.34 (1 H, m, 1-H), 7.23 (5 H, m, Ar-H), 8.10 (2 H, d, *J* 8.6, Ar-H) and 8.19 (2 H, d, *J* 9.1, Ar-H).

(*E*,2*R*,6*R*,8*S*)-1-Benzyloxy-2,4,8-trimethyl-undec-3-en-6-ol (1.94)



Ester **1.93** (41 mg, 0.09 mmol) dissolved in THF (1.5 mL). To this reaction mixture was added 2N NaOH solution(1 mL), reaction was stirred at 50 ^oC for 1 h. Reaction was concentrated and column chromatography of the residue eluting with petrol-ether (80:20) gave the *title compound* **1.94** (41 mg, 70%) as a colourless oil, R_f 0.5 (7:3 petrol-ether); δ_H (400 MHz, $CDCl_3$) 0.80-0.84 (6 H, m, 8-CH_3 and 11-H_3), 0.92 (3 H, d, *J* 6.6, 2- CH_3), 1.03-1.30 (6 H, m, 7-H_2, 9-H_2 and 10-H_2), 1.39 (1 H, m, 8-H), 1.61 (3 H, s, 4- CH_3), 1.94 (1 H, dd, *J* 9.1 and 13.6, 5-H_a), 2.08 (1 H, dd, *J* 4.3 and 13.4, 5-H_b), 2.68 (1 H, m, 2-H), 3.23 (2 H, m, 1-H_2), 3.70 (1 H, m, 6-H), 4.44 (2 H, s, OC*H*$_2$Ph), 5.02 (1 H, d, *J* 9.1, 3-H) and 7.26 (5 H, m, Ar-H). δ_C (125 MHz, $CDCl_3$) 14.38, 16.58, 18.03, 19.31, 20.05, 29.08, 33.15, 40.18, 44.56, 48.78, 66.08, 72.96, 75.20, 127.50, 127.53, 128.36, 131.81, 132.72 and 138.64.

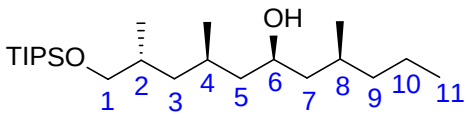
(*E*,2*R*,6*S*,8*S*)-2,4,8-Trimethyl-1-triisopropylsilyloxy-undec-3-en-6-ol (1.96)



Imidazole (75 mg, 1.1 mmol) was added to a solution of diol **1.95** (50 mg, 0.22 mmol) in THF (4 mL), after 10 min triisopropylsilyl chloride (51 mg, 0.24 mmol) was added at 0 ^oC. Reaction was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue

eluting with petrol-ether (4:1) gave the *title compound* **1.96** (80 mg, 94%) as a colourless oil, R_f 0.7 (4:1 petrol-ether); $[\alpha]_D^{20}$ +9.6 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 385.3503; $C_{23}H_{49}O_2Si$, requires *M*, 385.3496); ν_{max} 2926, 2865, 1461, 1381, 1248, 1089, 1065, 1013, 995, 918, 881, 785, 680 and 658 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.83 (6 H, m, 8-CH_3 and 11-H_3), 0.87 (3 H, d, J 7, 2-CH_3), 0.98 (21 H, m, OSi^iPr_3), 1.15 (1 H, m, 7-H_a), 1.22 (1 H, m, 7-H_b), 1.25-1.34 (4 H, m, 9-H_2 and 10-H_2), 1.54 (1 H, m, 8-H), 1.61 (3 H, s, 4-CH_3), 1.86 (1 H, dd, *J* 12.8 and 9.8, 5-H_a), 2.10 (1 H, dd, *J* 12.8 and 3.2, 5-H_b), 2.54 (1 H, m, 2-H), 3.37 (1 H, dd, *J* 6.9 and 9.2, 1-H_a), 3.42 (1 H, dd, *J* 6.9 and 9.2, 1-H_b), 3.61-3.66 (1 H, m, 6-H) and 4.96 (1 H, d, *J* 9.1, 3-H); δ_C (100 MHz, $CDCl_3$) 12.0, 14.4, 16.6, 17.1, 18.0, 20.0, 20.2, 29.5, 35.8, 39.1, 44.4, 48.5, 66.0, 68.4, 132.1 and 132.4; *m/z* (ES+) 407 ($[M+23]^+$, 100%).

(2*R*,4*R*,6*S*,8*S*)-2,4,8-Trimethyl-1-triisopropylsilyloxy-undecan-6-ol (1.97)

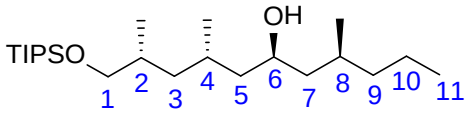


To a boiling tube with stirrer bar was placed alkene **1.96** (80 mg, 0.21 mmol) followed by [Rh(NBD)Diphos-4]BF_4 catalyst (7.5 mg, 0.01 mmol) and DCM (3 mL). The tube was put inside a steel screw cap high pressure bomb. The pressure gauge block was attached and the bomb was flushed three times with hydrogen and then filled to 950 psi of hydrogen. Reaction was left at room temperature under 950 psi pressures for 5 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the following:

Diastereoisomer one: the *title compound* **1.97** (61 mg, 70%) as a colourless oil, R_f 0.45 (4:1 petrol-ether); $[\alpha]_D^{20}$ +7.8 (c 0.2 in $CHCl_3$); (Found $[M+Na]^+$, 409.3486; $C_{23}H_{50}O_2SiNa$, requires *M*, 409.3473); ν_{max} 3325, 2922, 2864, 1461, 1379, 1245, 1100, 1067, 1012, 995, 918, 881, 784, 679 and 658 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.81-0.84 (12 H, m, 2-CH_3, 4-CH_3, 8-CH_3 and 11-H_3), 0.99 (21 H,

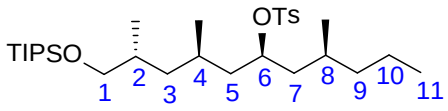
m, OSi^{i}Pr$_3$), 1.09 (2 H, m, 3-H$_2$), 1.15-1.33 (8 H, m, 5-H$_2$, 7-H$_2$, 9-H$_2$ and 10-H$_2$), 1.53 (1 H, m, 8-H), 1.61-1.70 (2 H, m, 2-H and 4-H), 3.38 (1 H, dd, *J* 9.8 and 6.1, 1-H$_a$), 3.43 (1 H, dd, *J* 9.8 and 6.1, 1-H$_b$) and 3.73 (1 H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 12.0, 14.4, 16.4, 18.1, 19.2, 20.0, 20.4, 26.8, 29.3, 33.5, 38.9, 40.4, 45.8, 46.6, 67.9 and 69.4; *m*/*z* (ES+) 409 ([M+23]$^+$, 100%).

(2*R*,4*S*,6*S*,8*S*)-2,4,8-Trimethyl-1-triisopropylsilyloxy-undecan-6-ol (1.98)



Diastereoisomer two: the *title compound* **1.98** (15 mg, 16%) as a colorless oil, R$_f$ 0.5 (4:1 petrol-ether); ν_{max} 3351, 2955, 2926, 2867, 1462, 1380, 1248, 1099, 1067, 1213, 882, 787, 680 and 658 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.81-0.86 (12 H, m, 2-CH_3, 4- CH_3, 8- CH_3 and 11-H$_3$), 0.99 (21 H, m, OSi^{i}Pr$_3$), 1.04-1.33 (10 H, m, 3-H$_2$, 5-H$_2$, 7-H$_2$ and 10-H$_2$), 1.50 (1 H, m, 8-H), 1.62-1.72 (2 H, m, 2-H and 4-H), 3.36 (1 H, dd, *J* 6.6 and 9.5, 1-H$_a$), 3.47 (1 H, dd, *J* 5.7 and 9.5, 1-H$_b$) and 3.73 (1 H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 12.0, 14.4, 17.5, 18.1, 19.2 20.0, 20.2, 26.6, 29.4, 33.4, 39.1, 42.0, 45.0, 46.3, 67.7 and 68.8; *m*/*z* (ES+) 409 ([M+23]$^+$, 100%).

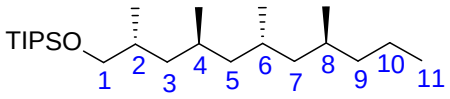
(2*R*,4*R*,6*S*,8*S*)-2,4,8-Trimethyl-1-(triisopropylsilyloxy)undecan-6-yl-4-methyl benzenesulfonate (1.99)



Tosyl chloride (205 mg, 1.1 mmol) and 4-(dimethylamino)pyridine (202 mg, 1.65 mmol) were added to a stirred solution of alcohol **1.97** (143 mg, 0.37 mmol) in DCM (4 mL) at room temperature and the reaction was stirred at room

temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.99** (185 mg, 93%) as a colourless oil, R_f 0.8 (4:1 petrol-ether); $[\alpha]_D^{20}$ +3.2 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 541.3741; $C_{30}H_{57}O_4SSi$, requires *M*, 541.3741); ν_{max} 2954, 2863, 1598, 1462, 1362, 1305, 1245, 1186, 1175, 1096, 1067, 1012, 920, 880, 813, 760, 679 and 662 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.72-0.77 (12 H, m, 2-CH_3, 4-CH_3, 8-CH_3 and 11-H_3), 0.98 (21 H, m, OSi^iPr_3), 1.04-1.21 (5 H, m, 8-H, 9-H_2 and 10-H_2), 1.27-1.49 (7 H, m, 3-H_2, 4-H, 5-H_2 and 7-H_2), 1.55-1.61 (1 H, m, 2-H), 2.37 (3 H, s, Ar-CH_3), 3.37 (2 H, d, *J* 6.0, 1-H_2), 4.64 (1 H, m, 6-H), 7.25 (2 H, d, *J* 7.9, Ar-H) and 7.72 (2 H, d, *J* 7.8, Ar-H); δ_C (100 MHz, $CDCl_3$) 11.0, 13.2, 15.2, 17.1, 18.5, 18.8, 20.6, 25.6, 27.9, 32.3, 37.7, 38.5, 39.5, 41.3, 42.3, 68.2, 80.7, 126.7, 128.6, 133.9 and 143.3; *m/z* (ES+) 563 ($[M+23]^+$, 100%).

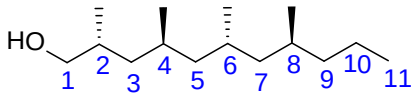
Triisopropyl((2*R*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethylundecyloxy)silane (1.100)



Copper(I) iodide (224 mg, 1.18 mmol) was placed in a round bottom flask. The flask was evacuated and then purged with nitrogen with sequence repeated three times. THF (2 mL) was injected, followed by cooling to 0 ^oC where methyllithium lithium iodide complex (1.6 M, 1.3 mL, 2.13 mmol) was added dropwise to produce a clear solution of Me_2CuLi. Then the tosylate **1.99** (64 mg, 0.12 mmol) in THF (1 mL) was injected and reaction continued at 0 ^oC for 1 h and gradually warm up to room temperature and continued for 16 h. Aqueous NH_4Cl solution (10 mL) was added. Reaction was filtered through a pad of celite and partitioned between water and ether. Organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated using reduced pressure. Column chromatography of the residue eluting with petrol (100%) gave the *title compound* **1.100** (10 mg, 21%) as a colourless oil. R_f 0.7 (100% petrol); $[\alpha]_D^{20}$ +14.7 (c 0.2 in $CHCl_3$); (Found $[M-C_3H_7]^+$, 341.3229; $C_{21}H_{45}O_1Si$, requires *M*,

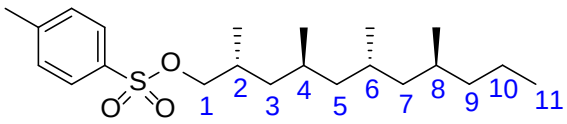
341.3234); ν_{max} 2954, 2921, 2864, 1461, 1378, 1245, 1098, 1067, 1012, 994, 918, 881, 783, 679 and 657 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.72-0.82 (15 H, m, 2-CH_3, 4-CH_3, 6-CH_3, 8-CH_3 and 11-H_3), 0.99 (21 H, m, OSi^iPr_3), 0.95-1.28 (8 H, m, 6-H, 7-H_2, 8-H, 9-H_2 and 10-H_2), 1.39-1.45 (4 H, m, 4-H), 1.48-1.54 (4 H, m, 3-H_2 and 5-H_2), 1.60-1.67 (1 H, m, 2-H), 3.35 (1 H, dd, *J* 6.2 and 9.3, 1-H_a) and 3.45 (1H, dd, *J* 6.2 and 9.3, 1-H_b); δ_C (100 MHz, $CDCl_3$) 11.0, 13.4, 15.8, 17.1, 18.5, 18.5, 18.6, 19.1, 26.2, 26.3, 28.7, 32.5, 39.2, 40.4, 44.5, 45.6 and 68.2; *m*/*z* (EI) 341 ($[M-43]^+$, 100%).

(2*R*,4*S*,6*R*,8*S*)-2,4,6,8-Tetramethylundecan-1-ol[125] (1.101)



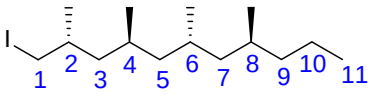
TIPS protected alcohol **1.100** (75 mg, 0.19 mmol) was dissolved in THF (2 mL), to this reaction mixture was added HCl in dioxane (4 M, 0.24 mL, 0.96 mmol) at room temperature, reaction was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (7:3) gave the title compound **1.101** (40 mg, 91%) as a colourless oil. R_f 0.5 (60:40 petrol-ether); $[\alpha]_D^{20}$ +30.0 (c 0.2 in $CHCl_3$); [literature value: $[\alpha]_D^{20}$ +23.1 (c 1.0 in $CHCl_3$)]; (Found $[M-H_2O]^+$, 210.2342; $C_{15}H_{30}$, requires *M*, 210.2342); ν_{max} 3223, 2954, 2910, 2868, 2841, 1456, 1377, 1034, 985, 808, 738 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.72 (15 H, m, 2-CH_3, 4-CH_3, 6-CH_3, 8-CH_3 and 11-H_3), 0.89-1.28 (10 H, m, 5-H_2, 6-H, 7-H_2, 8-H, 9-H_2 and 10-H2), 1.41 (1 H, m, 4-H), 1.48-1.56 (2 H, m, 3-H_2), 1.66 (1 H, m, 2-H), 3.35 (1 H, m, 1-H_a) and 3.40 (1 H, m, 1-H_b); δ_C (125 MHz, $CDCl_3$) 14.4, 16.8, 19.5, 19.5, 19.6, 20.1, 27.3, 27.3, 29.7, 33.5, 40.3, 41.5, 45.6, 46.6 and 69.2; *m*/*z* (EI) 210 ($[M-13]^+$, 50%), 136 ($[M-92]^+$, 100%).

(2*R*,4*S*,6*R*,8*S*)-2,4,6,8-tetramethylundecyl 4-methylbenzenesulfonate (1.115)



Tosyl chloride **1.101** (25 mg, 0.13 mmol) and DMAP (19 mg, 0.15 mmol) were added to a stirred solution of alcohol (20 mg, 0.088 mmol) in DCM (2 mL) at room temperature and the mixture was allowed to stir at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.115** (28 mg, 85%) as a colorless oil. R_f 0.7 (80:20 petrol-ether); $[\alpha]_D^{20}$ +9.5 (c 0.2 in $CHCl_3$); (Found $[M+Na]^+$, 405.2433; $C_{22}H_{38}O_3Na$, requires *M*, 405.2434) ν_{max} 2956, 2915, 2870, 1596, 1458, 1360, 1307, 1292, 1188, 1174, 1098, 962, 831, 812, 791, 665 and 654 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.66-0.79 (12 H, m, 2-CH_3, 4-CH_3, 6-CH_3 and 8-CH_3), 0.80 (3 H, t, *J* 7.3, 11-H_3), 0.86-1.45 (13 H, m, 3-H_2, 4-H, 5-H_2, 6-H, 7-H_2, 8-H, 9-H_2 and 10-H_2), 1.78 (1 H, m, 2-H), 2.38 (3 H, s, Ar-CH_3), 3.72 (1 H, dd, *J* 6.8 and 9.3, 1-H_a), 3.77 (1 H, dd, *J* 5.8 and 9.3 1-H_b), 7.25 (2 H, d, *J* 7.8, Ar-H) and 7.72 (2 H, d, *J* 8.3, Ar-H); δ_C (125MHz, $CDCl_3$) 14.4, 16.4, 19.2, 19.4, 19.6, 20.1, 21.7, 27.0, 27.2, 29.7, 30.4, 39.3, 40.8, 45.5, 46.1, 75.8, 127.9, 129.8, 133.2 and 144.6; *m/z* (ES+) 405 ($[M+23]^+$, 100%).

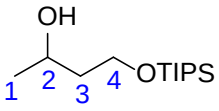
(2*R*,4*S*,6*R*,8*S*)-1-iodo-2,4,6,8-tetramethylundecane (1.116)



Sodium iodide (22 mg, 0.15 mmol) was added to a solution of tosylate **1.115** (28 mg, 0.07 mmol) in acetone (2 mL). The mixture was stirred under reflux for 16 h. The reaction mixture was partitioned between hexane and water. The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol (100%) gave the *title compound* **1.116** (21 mg, 90%) as a colourless oil. R_f 0.8 (100% petrol); $[\alpha]_D^{20}$ +12.0 (c 0.2 in $CHCl_3$); (Found M^+, 338.1462; $C_{15}H_{31}I$, requires *M*, 338.1465); ν_{max} 2955, 2911, 2869, 2841, 1457, 1378, 1193, 912, 816

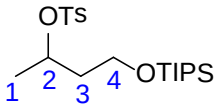
and 739 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.72-0.89 (15 H, m, 2-CH_3, 4-CH_3, 6-CH_3, 8-CH_3 and 11-H_3), 0.92-1.28 (11 H, m, 4-H, 5-H_2, 6-H, 7-H_2, 8-H, 9-H_2 and 10-H_2), 1.41 (2 H, m, 2-H), 1.49 (2 H, m, 3-H_2), 3.07 (1 H, dd, *J* 3.2 and 9.5, 1-H_a) and 3.15 (1 H, dd, *J* 4.7 and 9.5, 1-H_b); δ_C (125 MHz, $CDCl_3$) 14.4, 18.8, 19.5, 19.5, 19.6, 20.1, 20.4, 27.2, 27.5, 29.7, 32.3, 40.2, 44.8, 45.5 and 46.0; *m/z* (GCMS) 338 (M^+, 5%).

4-(Triisopropylsilyloxy)butan-2-ol[131] (1.103)



Imidazole (378 mg, 5.6 mmol) was added to a solution of diol **1.102** (100 mg, 1.1 mmol) in THF, after 10 min TIPSCl (256 mg, 1.3 mmol) was added to the reaction at 0 ^oC. Reaction was stirred at room temperature for 16 h. Reaction was concentrated and purified by flash chromatography eluting with petrol-ether (80:20) gave the *title compound* **1.103** (177 mg, 65%) as a colourless oil, R_f 0.3 (80:20 petrol-ether); δ_H (300 MHz, $CDCl_3$) 1.01 (21 H, m, OSi^iPr_3), 1.13 (3 H, d, *J* 6.2, 1-H_3), 1.63 (2 H, m, 3-H_2) and 3.81-3.99 (3 H, m, 2-H and 4-H_2).

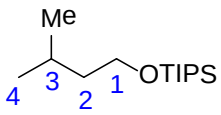
4-(Triisopropylsilyloxy)butan-2-yl 4-methylbenzenesulfonate (1.104)



Tosyl chloride (164 mg, 0.86 mmol) and DMAP (132 mg, 1.08 mmol) were added to a stirred solution of alcohol **1.103** (177 mg, 0.72 mmol) in DCM (10 mL) at room temperature and the mixture was allowed to stir at RT overnight. Reaction was stirred at room temperature for 16 h. Reaction was concentrated and purified by flash chromatography eluting with petrol-ether (80:20) gave the *title compound* **1.104** (328 mg, 82%) as a colourless oil, R_f 0.5 (80:20 petrol-

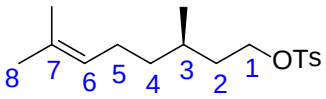
ether); δ_H (400 MHz, $CDCl_3$) 0.93 (21 H, m, OSi^iPr_3), 1.26 (3 H, d, *J* 6.2, 1-H_3), 1.62 (1 H, m, 3-H_a), 1.81 (1 H, m, 3-H_b), 3.51 (2 H, m, 4-H_2), 4.72 (1 H, m, 2-H), 7.24 (2 H, d, *J* 7.9, Ar-H) and 7.74 (2 H, d, *J* 7.9, Ar-H).

Isopentyloxytriisopropylsilane[132] (1.105)



A suspension of CuI (224 mg, 2.5 mmol) in ether (8 mL) was cooled to 0^{o}C. methyllithium – lithium iodide complex in THF (1.6 M, 2.8 mL, 4.5 mmol) was added dropwise . Tosylate **1.104** (100 mg, 0.25 mmol) in DCM (2 mL) was then added dropwise, and reaction mixture stirred at 0 ^{o}C for 3 h and gradually warm up to room temperature and stirred for 16 h. To the reaction was then added aqueous NH_4Cl (10 mL) at 0 ^{o}C and kept stirring for 1 h. Reaction was filtered through a pad of celite and partitioned between water and ether. Organic layer was washed with brine, dried over Na_2SO_4 concentrated under reduced pressure. The residue was then purified by flash chromatography eluting with petrol (100%) gave the *title compound* **1.105** (52 mg, 91%) as a colourless oil, R_f 0.8 (100% petrol); δ_H (300 MHz, $CDCl_3$) 0.84 (6 H, d, *J* 6.6, 4-H_3 and 3-CH_3), 0.99 (21 H, m, OSi^iPr_3), 1.37 (2 H, q, *J* 6.8, 2-H_2), 1.65 (1 H, m, 3-H) and 3.63 (2 H, t, *J* 6.9, 1-H_2).

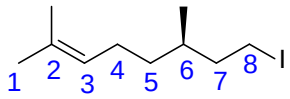
(*R*)-3,7-Dimethyloct-6-enyl 4-methylbenzenesulfonate[133] (1.107)



Tosyl chloride (1.83 g, 9.6 mmol) and 4-dimethylamino pyridine (1.4 g, 11.5 mmol) were added to a stirred solution of alcohol **1.106** (1.0 g, 6.4 mmol) in DCM (25 mL) at room temperature and the mixture was allowed to stir at room

temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.107** (1.92 g, 96%) as a colourless oil. R_f 0.7 (70:30 petrol-ether); $[\alpha]_D^{20}$ +1.3 (c 0.3 in $CHCl_3$); $[\alpha]_D^{20}$ +2.68 (*c* 1.0 in EtOH)]; (Found $[M+Na]^+$, 333.1494; $C_{17}H_{26}O_3NaS$, requires *M*, 333.1495); ν_{max} 2961, 2913, 1597, 1453, 1356, 1306, 1290, 1187, 1173, 1096, 1019, 940, 887, 813, 761, 705, 689 and 662 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.75 (3 H, d, *J* 6.6, 3-CH_3), 1.04 (1 H, m, 4-H_a), 1.17 (1 H, m, 4-H_b), 1.39 (1 H, m, 5-H_a), 1.45 (1 H, m, 5-H_b), 1.50 (3 H, s, 7-CH_3 or 8-H_3), 1.59 (1 H, m, 3-H), 1.60 (3 H, s, 7-CH_3 or 8-H_3), 1.75-1.93 (2 H, m, 2-H_2), 2.38 (3 H, s, Ar-CH_3), 4.00 (2 H, m, 1-H_2), 4.95 (1 H, m, 6-H), 7.28 (2 H, d, *J* 8.6, Ar-H) and 7.72 (2 H, d, *J* 8.1, Ar-H); δ_C (100 MHz, $CDCl_3$) 17.7, 19.1, 21.7, 25.3, 25.8, 28.9, 35.7, 36.7, 69.1, 124.3, 127.9, 128.9, 131.5, 133.2 and 144.7; *m/z* (ES+) 333 ($[M+23]^+$, 100%).

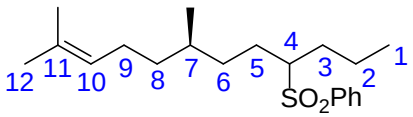
(*R*)-8-Iodo-2,6-dimethyloct-2-ene[126] (1.108)



Sodium iodide (1.83 g, 12.2 mmol) was added to a solution of tosylate **1.107** (1.90 g, 6.1 mmol) in acetone (15 mL). The mixture was stirred under reflux for 16 h. The reaction mixture was concentrated and partitioned between hexane (30 mL) and aqueous Na_2SO_3 (15 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol (100%) gave the title compound **1.108** (1.44 g, 90%) as a colourless oil. R_f 0.8 (100% petrol); $[\alpha]_D^{20}$ -5.2 (c 1.0 in $CHCl_3$); [literature value: $[\alpha]_D^{20}$ -14.34 (neat)]; (Found M^+, 266.0533; $C_{10}H_{19}I$, requires *M*, 266.0526); ν_{max} 2961, 2912, 2851, 1449, 1377, 1218, 1178, 1120, 984, 826 and 733 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.82 (3 H, d, *J* 6.6, 6-CH_3), 1.11 (1 H, m, 5-H_a), 1.27 (1 H, m, 5-H_b), 1.49 (1 H, m, 4-H_a), 1.54 (3 H, s, 2-CH_3 or 1-H_3), 1.59 (1 H, m, 4-H_b), 1.62 (3 H, s, 2-CH_3 or 1-H_3), 1.83 (1 H, m, 6-H), 1.93 (2 H, m, 7-H_2), 3.11 (1 H, m, 8-H_a), 3.19 (1 H, m, 8-H_b) and

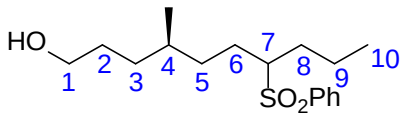
5.02 (1 H, m, 3-H); δ_C (100 MHz, $CDCl_3$) 5.3, 17.7, 18.7, 25.4, 25.8, 33.6, 36.4, 40.9, 124.5 and 131.5; *m/z* (GCMS) 266 (M^+, 5%).

[(7*R*)-7,11-Dimethyldodec-10-en-4-ylsulfonyl]benzene (1.109)



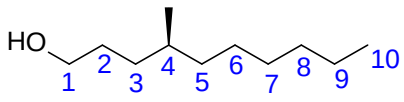
T o a stirred solution of n-butylphenyl sulfone (776 mg, 3.91 mmol) in dry THF (14 mL) and DMPU (2 mL) was slowly added *n*-BuLi (2.94 mL, 1.6 M in hexane, 4.70 mmol) at -40 ^oC under nitrogen atmosphere. The mixture was stirred for 30 min. Then a solution of iodide **1.108** (1.25 g, 4.7 mmol) in THF (4 mL) was added to the reaction mixture. Reaction was let gradually warm up to room temperature and stirred for 16 h. To the reaction was added saturated aqueous NH_4Cl solution (10 mL) and partitioned between water (10 mL) and ether (20 mL). Organic layer was dried over washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.109** (1.23 g, 95%) as a colourless oil, this is a 50:50 mixture of two diasteroisomers. R_f 0.4 (4:1 petrol-ether); $[\alpha]_D^{20}$ -1.7 (c 1.6 in $CHCl_3$); (Found $[M+H]^+$, 337.2194; $C_{20}H_{33}O_2S$, requires *M*, 337.2196); ν_{max} 2959, 2926, 2871, 1446, 1377, 1302, 1143, 1083, 1024, 998, 756, 725, 690 and 621 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.73 (1.5 H, d, *J* 6.3, 7-CH_3), 0.74 (1.5 H, d, *J* 6.6, 7-CH_3), 0.81 (3 H, t, *J* 7.3, 1-H_3), 0.98-1.54 (9 H, m, 2-H_2, 6-H_2, 7-H, 8-H_2 and 9-H_2), 1.51 (3 H, s, 11-CH_3 or 12-H_3), 1.61 (3 H, s, 11-CH_3 or 12-H_3), 1.70-1.93 (4 H, m, 3-H_2 and 5-H_2), 2.80 (1 H, m, 4-H), 4.98 (1 H, m, 10-H), 7.49 (2 H, t, *J* 7.8, Ar-H), 7.58 (1 H, t, *J* 7.3, Ar-H) and 7.82 (2 H, d, *J* 7.5, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.0 (2), 17.7, 19.2, 19.4, 20.1, 25.4 (2), 25.7, 25.8, 29.9, 30.0, 32.5, 33.7, 34.0, 36.6, 36.9, 124.6 (2), 128.8, 129.1, 131.3 (2), 133.5 and 138.3; *m/z* (ES+) 359 ($[M+23]^+$, 100%).

(4*R*)-4-Methyl-7-(phenylsulfonyl)decan-1-ol (1.110)



In a 3-neck flask alkene **1.109** (460 mg, 1.37 mmol) was dissolved in DCM/MeOH (1:1, 20 mL) and reaction was cooled to -78 ^{o}C. Ozone from an ozone generator was bubbled through the stirred solution solution turned blue, which indicated ozone is saturated in DCM. Ozone generator was turned off leaving O_2 keep bubbling through the stirred solution at -78 ^{o}C until reaction became clear. $NaBH_4$ (250 mg, 6.61 mmol) was added and reaction was allowed to warm to room temperature and stirred for 16 h. Reaction mixture was extracted between diethylether (20 mL) and brine (20 mL), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (1:4) gave the *title compound* **1.110** (364 mg, 85%) as a colourless oil, this is a 50:50 mixture of two diastereoisomers. R_f 0.4 (4:1 petrol-ether); $[\alpha]_D^{20}$ -2.9 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 313.1833; $C_{17}H_{29}O_3S$, requires *M*, 313.1832) ν_{max} 3395, 2933, 2871, 1447, 1380, 1287, 1141, 1084, 758, 727, 691 and 622 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.75 (1.5 H, d, *J* 6.9, 4-CH_3), 0.78 (1.5 H, d, *J* 5.0, 4-CH_3), 0.80 (3 H, t, *J* 7.6, 10-H_3), 1.02-1.58 (11 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 8-H_2 and 9-H_2), 1.71-1.83 (2 H, m, 2-H_2), 2.81 (1 H, m, 7-H), 3.54 (2 H, t, *J* 6.6, 1-H_2), 7.50 (2 H, m, Ar-H), 7.59 (1 H, m, Ar-H) and 7.82 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$, mixture of two diastereoisomers) 14.0 (2), 15.3, 19.3, 19.5, 20.1, 25.4, 29.9, 30.0 (2), 30.1 (2), 32.5 (2), 32.7 (2), 33.8, 33.9, 63.3, 64.6, 64.7, 65.9, 128.8, 129.1, 133.5 and 138.2; *m*/*z* (ES+) 335 ($[M+23]^+$, 100%).

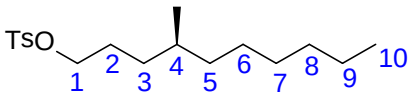
(*S*)-4-Methyldecan-1-ol (1.111)



To a stirred solution of sulfone **1.110** (360 mg, 1.15 mmol) in dry methanol (30 mL), 10% sodium amalgam (10.0 g, 34.6 mmol) was added. After being stirred

at room temperature for 16 h, the solution was transferred to another and concentrated under reduced pressure. The residue was partitioned between saturated aqueous NH_4Cl (40 mL) and ether (40 mL). Organic layer was washed with brine (20 mL) dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.111** (143 mg, 73%) as a colourless oil. R_f 0.6 (1:1 petrol-ether); $[\alpha]_D^{20}$ -3.9 (c 0.3 in $CHCl_3$); [literature value: $[\alpha]_D^{20}$ -1.1 (*c* 5.33 in $CHCl_3$)]; (Found $[M\text{-}H_20]^+$, 154.1723; $C_{11}H_{22}$, requires *M*, 154.1716) ν_{max} 3314, 2924, 2855, 1459, 1378, 1057, 898 and 723 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.80 (3 H, d, *J* 6.6, 4-CH_3), 0.81 (3 H, t, *J* 6.6, 10-H_3), 1.01-1.31 (11 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 7-H_2, 8-H_2 and 9-H_2), 1.41-1.59 (2 H, m, 3-H_2) and 3.59 (2 H, t, *J* 6.8, 1-H_2); δ_C (100 MHz, $CDCl_3$) 14.2, 19.7, 22.7, 27.0, 29.7, 30.4, 32.0, 32.7, 33.0, 37.0 and 63.5; *m/z* (EI) 154 ($[M\text{-}18]^+$, 5%).

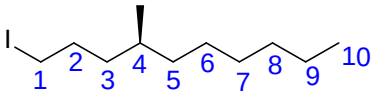
(*S*)-4-Methyldecyl benzenesulfonate (1.112)



Tosyl chloride (166 mg, 0.87 mmol) and DMAP (127 mg, 1.04 mmol) were added to a stirred solution of alcohol **1.111** (100 mg, 0.58 mmol) in DCM (8 mL) at room temperature and the mixture was allowed to stir at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.112** (187 mg, 99%) as a colourless oil. R_f 0.7 (7:3 petrol-ether); $[\alpha]_D^{20}$ +3.1 (c 0.4 in $CHCl_3$); (Found $[M+Na]^+$, 349.1812; $C_{18}H_{30}O_3NaS$, requires *M*, 349.1808) ν_{max} 2954, 2922, 2853, 1598, 1465, 1358, 1306, 1290, 1187, 1174, 1096, 1019, 961, 914, 812, 790, 732 and 661 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.73 (3 H, d, *J* 6.6, 4-CH_3), 0.81 (3 H, t, *J* 7.0, 10-H_3), 0.97-1.27 (13 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 7-H_2, 8-H_2 and 9-H_2), 1.51-1.65 (2 H, m, 2-H_2), 2.38 (3 H, s, Ar-CH_3), 3.94 (2 H, t, *J* 6.6, 1-H_2), 7.28 (2 H, m, Ar-H) and 7.72 (2 H, m,

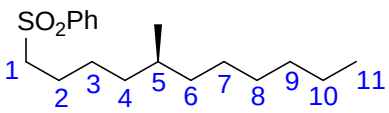
Ar-H); δ_C (100 MHz, $CDCl_3$) 14.2, 17.5, 19.5, 21.7, 22.7, 26.5, 26.9, 29.6, 32.3, 33.6, 36.8, 71.2, 127.9, 129.8, 133.3 and 144.7; *m/z* (ES+) 349 ($[M+23]^+$, 70%).

(*S*)-1-Iodo-4-methyldecane (1.113)



Sodium iodide (1.06 g, 7.04 mmol) was added to a solution of tosylate **1.112** (1.15 g, 3.52 mmol) in acetone (15 mL). The mixture was stirred under reflux for 2 h. The reaction mixture was concentrated and partitioned between hexane (30 mL) and aqueous sodium sulphite solution (15 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the *title compound* **1.113** (891 mg, 90%) as a colourless oil. R_f 0.8 (100% petrol); $[\alpha]_D^{20}$ +2.6 (c 0.2 in $CHCl_3$); (Found $[M]^+$, 282.0837; $C_{11}H_{23}I$, requires *M*, 282.0839) ν_{max} 2955, 2922, 2853, 1460, 1378, 1234, 1173, 926 and 724 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.79 (3 H, d, *J* 6.6, 4-CH_3), 0.81 (3 H, t, *J* 6.6, 10-H_3), 1.01-1.36 (13 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 7-H_2, 8-H_2 and 9-H_2), 1.77 (2 H, m, 2-H_2) and 3.10 (2 H, dt, *J* 2.5 and 7.1, 1-H_2); δ_C (100 MHz, $CDCl_3$) 7.7, 14.2, 19.7, 22.7, 27.0, 29.7, 31.3, 32.0, 32.1, 36.9 and 37.9; *m/z* (GCMS) 282 (M^+, 5%).

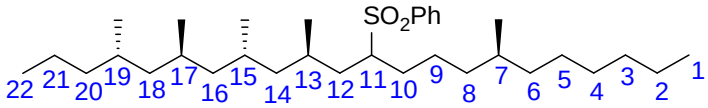
(*S*)-((5-Methylundecyl)sulfonyl)benzene (1.114)



To a stirred solution of methylphenylsulfone (50 mg, 0.32 mmol) in dry THF (3 mL) and DMPU (1 mL) was slowly added n-BuLi (240 µL, 1.6 M in hexane, 0.38 mmol) at -40 ^oC under nitrogen atmosphere. The mixture was stirred for 30 min. Then a solution of iodide **1.113** (108 mg, 0.38 mmol) in THF (1 mL) was

added to the reaction mixture. Reaction was let warm up to room temperature and stirred for 16 h. To the reaction was added saturated aqueous NH_4Cl (5 mL) and partitioned between water (2 mL) and ether (10 mL). Organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.114** (72 mg, 73%) as a colorless oil. R_f 0.5 (60:40 petrol-ether); $[\alpha]_D^{20}$ -6.4 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 311.2032; $C_{18}H_{31}O_2S$, requires *M*, 311.2040) ν_{max} 2923, 2854, 1463, 1446, 1404, 1377, 1305, 1144, 1086, 1024, 998, 794, 745, 727 and 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.73 (3 H, d, *J* 6.6, 5-CH_3), 0.81 (3 H, t, *J* 7.0, 11-H_3), 0.94-1.32 (15 H, m, 3-H_2, 4-H_2, 5-H, 6-H_2, 7-H_2, 8-H_2, 9-H_2 and 10-H_2), 1.62 (2 H, m, 2-H_2), 3.02 (2 H, t, *J* 8.1, 1-H_2), 7.51 (2 H, m, Ar-H), 7.59 (1 H, m, Ar-H) and 7.84 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$, a mixture of two diastereoisomers) 14.1, 19.6, 22.7, 23.0, 25.8, 27.0, 29.7, 31.9, 32.5, 36.4, 36.9, 56.4, 128.1, 129.3, 133.6 and 139.3; *m/z* (ES+) 333 ($[M+23]^+$, 100%).

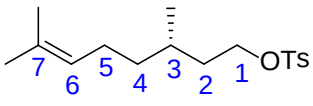
[(7*S*,13*R*,15*S*,17*R*,19*S*)-7,13,15,17,19-Pentamethyldocosan-11-ylsulfonyl]benzene (1.117)



To a stirred solution of sulfone **1.114** (13 mg, 0.044 mmol) in dry THF (0.5 mL) and DMPU (0.5 mL) was slowly added n-BuLi (33 µL, 1.6 M in hexane, 0.053 mmol) at -40 ^oC under nitrogen atmosphere. The mixture was stirred for 30 min. Then a solution of iodide **1.116** (18 mg, 0.053 mmol) in THF (0.5 mL) was added to the reaction mixture. Reaction was let gradually warm up to room temperature for 16 h. To the reaction was added saturated aqueous NH_4Cl (3 mL) and partitioned between water (2 mL) and ether (5 mL). Organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1) gave the *title compound* **1.117** (10 mg, 45%) as a colourless oil, this was a 50:50

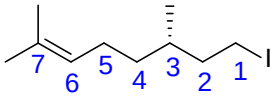
mixture of two diastereoisomers. R_f 0.6 (4:1 petrol-ether); $[\alpha]_D^{20}$ -3.7 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 521.4380; $C_{33}H_{61}O_2S$, requires *M*, 521.4387) ν_{max} 2955, 2923, 2870, 1462, 1379, 1303, 1145, 1086, 1025, 802, 764, 727 and 691 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.64-0.84 (21 H, m, 1-H_3, 7-CH_3, 13-CH_3, 15-CH_3, 17-CH_3, 19-CH_3 and 22-H_3), 0.86-1.80 (33 H, br m, 2-H_2, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H, 8-H_2, 9-H_2, 10-H_2, 12-H_2, 13-H, 14-H_2, 15-H, 16-H_2, 17-H, 18-H_2, 19-H, 20-H_2 and 21-H_2), 2.91 (1 H, m, 11-H), 7.49 (2 H, t, *J* 7.5, Ar-H), 7.57 (1 H, t, *J* 6.9, Ar-H), 7.81 (2 H, d, *J* 7.9, Ar-H); δ_C (100 MHz, $CDCl_3$, a mixture of two diastereoisomers) 14.1, 14.4, 19.0, 19.4, 19.5, 19.6 (2), 20.1, 22.7, 24.2, 27.0, 27.2, 27.3, 27.9, 28.1, 29.0, 29.7 (2), 32.0, 32.5, 36.2, 36.9, 37.0, 40.2, 40.3, 45.8, 46.3, 62.7, 128.9, 128.9, 129.1, 133.5 and 138.3; *m*/*z* (ES+) 543 ($[M+23]^+$, 100%).

(*S*)-3,7-Dimethyloct-6-enyl 4-methylbenzenesulfonate



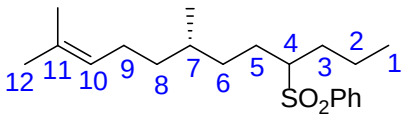
This compound was prepared in accordance to the procedure described in the preparation of compound **1.107**. R_f 0.7 (70:30 petrol-ether); $[\alpha]_D^{20}$ -1.1 (c 0.3 in $CHCl_3$); (Found $[M+Na]^+$, 333.1494; $C_{17}H_{26}O_3NaS$, requires *M*, 333.1495); ν_{max} 2961, 2913, 1597, 1453, 1356, 1306, 1290, 1187, 1173, 1096, 1019, 940, 887, 813, 761, 705, 689 and 662 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.76 (3 H, d, *J* 6.7, 3-CH_3), 1.02 (1 H, m, 4-H_a), 1.15 (1 H, m, 4-H_b), 1.36 (1 H, m, 5-H_a), 1.43 (1 H, m, 5-H_b), 1.49 (3 H, s, 7-CH_3 or 8-H_3), 1.55 (1 H, m, 3-H), 1.59 (3 H, s, 7-CH_3 or 8-H_3), 1.72-1.90 (2 H, m, 2-H_2), 2.37 (3 H, s, Ar-CH_3), 3.97 (2 H, m, 1-H_2), 4.94 (1 H, m, 6-H), 7.26 (2 H, d, *J* 8.6, Ar-H) and 7.70 (2 H, d, *J* 8.1, Ar-H); δ_C (100 MHz, $CDCl_3$) 17.9, 19.3, 21.8, 25.6, 26.1, 29.2, 35.9, 36.8, 69.5, 124.4, 128.0, 129.1, 131.7, 133.4 and 144.8; *m*/*z* (ES+) 333 ($[M+23]^+$, 100%).

(*S*)-8-Iodo-2,6-dimethyloct-2-ene



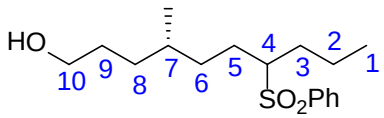
This compound was prepared in accordance to the procedure described in the preparation of compound **1.108**. R_f 0.8 (100% petrol); $[\alpha]_D^{20}$ +7.6 (c 0.6 in $CHCl_3$); (Found M^+, 266.0534; $C_{10}H_{19}I$, requires *M*, 266.0526); ν_{max} 2961, 2912, 2851, 1449, 1377, 1218, 1178, 1120, 984, 826 and 733 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.84 (3 H, d, *J* 6.7, 3-CH_3), 1.13 (1 H, m, 4-H_a), 1.29 (1 H, m, 4-H_b), 1.51 (1 H, m, 5-H_a), 1.57 (3 H, s, 7-CH_3 or 8-H_3), 1.61 (1 H, m, 5-H_b), 1.63 (3 H, s, 7-CH_3 or 8-H_3), 1.84 (1 H, m, 3-H), 1.88-1.99 (2 H, m, 2-H_2), 3.14 (1 H, m, 1-H_a), 3.21 (1 H, m, 1-H_b) and 5.04 (1 H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 5.5, 17.9, 18.9, 25.5, 26.0, 33.8, 36.5, 41.2, 124.58 and 131.6; *m/z* (GCMS) 266 (M^+, 5%).

[(7*S*)-7,11-Dimethyldodec-10-en-4-ylsulfonyl]benzene



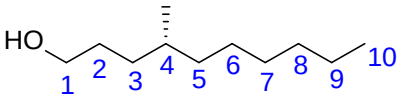
This compound was prepared in accordance to the procedure described in the preparation of compound **1.109**. R_f 0.4 (4:1 petrol-ether); $[\alpha]_D^{20}$ +3.0 (c 1.6 in $CHCl_3$); (Found $[M+Na]^+$, 359.2025; $C_{20}H_{33}O_2NaS$, requires *M*, 359.2016); ν_{max} 3063, 2958, 2927, 2871, 1446, 1378, 1303, 1144, 1084, 1024, 999, 757, 726, 691 and 624 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.76 (3 H, d, *J* 6.7, 7-CH_3), 0.82 (3 H, t, *J* 7.3, 1-H_3), 1.00-1.55 (9 H, m, 2-H_2, 6-H_2, 7-H, 8-H_2 and 9-H_2), 1.52 (3 H, s, 11-CH_3 or 12-H_3), 1.64 (3 H, s, 11-CH_3 or 12-H_3), 1.72-1.95 (4 H, m, 3-H_2 and 5-H_2), 2.81 (1 H, m, 4-H), 5.01 (1 H, m, 10-H), 7.51 (2 H, t, *J* 7.8, Ar-H), 7.60 (1 H, t, *J* 7.3, Ar-H) and 7.85 (2 H, d, *J* 7.5, Ar-H); δ_C (125 MHz, $CDCl_3$, this was a 50:50 mixture of two diastereoisomers) 14.0, 14.1, 17.7, 19.2, 19.4, 20.1, 25.4 (2), 25.7, 25.9, 29.9, 30.0, 32.4, 33.7, 34.0, 36.6, 36.9, 124.6 (2), 128.8, 129.2, 131.3 (2), 133.5 and 138.3; *m/z* (ES+) 359 ($[M+23]^+$, 100%).

(4*S*)-4-Methyl-7-(phenylsulfonyl)decan-1-ol



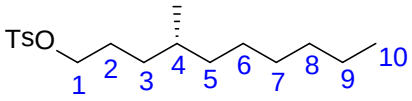
This compound was prepared in accordance to the procedure described in the preparation of compound **1.110**. R_f 0.4 (4:1 petrol-ether); $[\alpha]_D^{20}$ +4.7 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 313.1831; $C_{17}H_{29}O_3S$, requires *M*, 313.1832) ν_{max} 3490, 2933, 2871, 1725, 1586, 1447, 1380, 1287, 1141, 1084, 1024, 999, 900, 758, 726, 691 and 622 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.78 (3 H, d, *J* 6.8, 4-CH_3), 0.81 (3 H, t, *J* 7.6, 10-H_3), 1.04-1.61 (11 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 8-H_2 and 9-H_2), 1.72-1.84 (2 H, m, 2-H_2), 2.82 (1 H, m, 7-H), 3.56 (2 H, t, *J* 6.6, 1-H_2), 7.49 (2 H, m, Ar-H), 7.61 (1 H, m, Ar-H) and 7.82 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$, this was a 50:50 mixture of two diastereoisomers) 14.0 (2), 15.3, 19.2, 19.4, 20.1, 25.4, 29.2, 30.0 (2), 30.1 (2), 32.5 (2), 32.7 (2), 33.8, 33.9, 63.2, 64.6, 64.6, 65.9, 128.8, 129.1, 133.5 and 138.2; *m/z* (ES+) 335 ($[M+23]^+$, 100%).

(*R*)-4-Methyldecan-1-ol



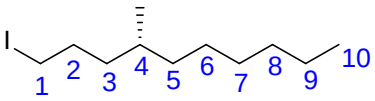
This compound was prepared in accordance to the procedure described in the preparation of compound **1.111**. R_f 0.6 (1:1 petrol-ether); $[\alpha]_D^{20}$ +4.7 (c 0.3 in $CHCl_3$); (Found $[M-H_2O]^+$, 154.1714; $C_{11}H_{22}$, requires *M*, 154.1716) ν_{max} 3325, 2955, 2924, 2855, 1710, 1459, 1378, 1057, 898 and 724 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.80 (3 H, d, *J* 6.6, 4-CH_3), 0.81 (3 H, t, *J* 6.6, 10-H_3), 1.02-1.32 (11 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 7-H_2, 8-H_2 and 9-H_2), 1.43-1.60 (2 H, m, 3-H_2) and 3.60 (2 H, t, *J* 6.8, 1-H_2); δ_C (100 MHz, $CDCl_3$) 14.2, 19.7, 22.6, 27.1, 29.8, 30.4, 32.1, 32.6, 33.1, 37.0 and 63.5; *m/z* (EI) 154 ($[M-18]^+$, 5%).

(*R*)-4-Methyldecyl 4-methylbenzenesulfonate



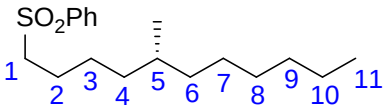
This compound was prepared in accordance to the procedure described in the preparation of compound **1.112**. R_f 0.7 (7:3 petrol-ether); $[\alpha]_D^{20}$ -3.8 (c 0.4 in $CHCl_3$); (Found $[M+Na]^+$, 349.1810; $C_{18}H_{30}O_3NaS$, requires *M*, 349.1808); ν_{max} 2956, 2924, 2855, 2359, 1735, 1599, 1496, 1465, 1362, 1307, 1189, 1176, 1098, 1021, 964, 917, 814, 791, 734, 706, 690 and 663 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.74 (3 H, d, *J* 6.6, 4-CH_3), 0.83 (3 H, t, *J* 7.0, 10-H_3), 0.98-1.30 (13 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 7-H_2, 8-H_2 and 9-H_2), 1.52-1.66 (2 H, m, 2-H_2), 2.39 (3 H, s, Ar-CH_3), 3.95 (2 H, t, *J* 6.6, 1-H_2), 7.28 (2 H, m, Ar-H) and 7.73 (2 H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) 14.3, 17.5, 19.4, 21.9, 22.8, 26.5, 29.5, 32.0, 32.4, 33.6, 36.8, 71.3, 127.9, 129.9, 133.4 and 144.7; *m*/*z* (ES+) 349 ($[M+23]^+$, 70%).

(*R*)-1-iodo-4-methyldecane



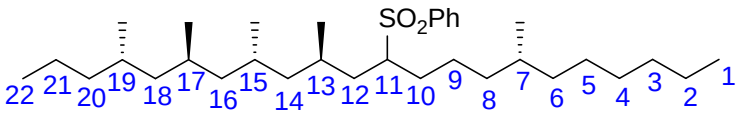
This compound was prepared in accordance to the procedure described in the preparation of compound **1.113**. R_f 0.8 (100% petrol); $[\alpha]_D^{20}$ -1.7 (c 0.2 in $CHCl_3$); (Found M^+, 282.0835; $C_{11}H_{23}I$, requires *M*, 282.0839) ν_{max} 2954, 2921, 2852, 2359, 2341, 1458, 1377, 1233, 1173, 723 and 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$)) 0.79 (3 H, d, *J* 6.6, 4-CH_3), 0.81 (3 H, t, *J* 6.6, 10-H_3), 1.02-1.36 (13 H, m, 3-H_2, 4-H, 5-H_2, 6-H_2, 7-H_2, 8-H_2 and 9-H_2), 1.78 (2 H, m, 2-H_2) and 3.11 (2 H, m, 1-H_2); δ_C (100 MHz, $CDCl_3$) 7.8, 14.2, 19.6, 22.6, 27.1, 29.8, 31.4, 32.1, 32.2, 36.9 and 38.0; *m*/*z* (GCMS) 282 (M^+, 5%).

(*R*)-((5-Methylundecyl)sulfonyl)benzene (1.118)



This compound was prepared in accordance to the procedure described in the preparation of compound **1.114**. R_f 0.5 (60:40 petrol-ether); $[\alpha]_D^{20}$ +5.2 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 311.2034; $C_{18}H_{31}O_2S$, requires *M*, 311.2040) ν_{max} 2922, 2984, 1586, 1465, 1447, 1404, 1378, 1318, 1305, 1145, 1071, 1024, 999, 794, 746, 727 and 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.75 (3 H, d, *J* 6.6, 5-CH_3), 0.82 (3 H, t, *J* 7.0, 11-H_3), 0.96-1.33 (15 H, m, 3-H_2, 4-H_2, 5-H, 6-H_2, 7-H_2, 8-H_2, 9-H_2 and 10-H_2), 1.63 (2 H, m, 2-H_2), 3.03 (2 H, t, *J* 8.1, 1-H_2), 7.51 (2 H, m, Ar-H), 7.60 (1 H, m, Ar-H) and 7.85 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.2, 19.7, 22.7, 23.1, 25.9, 27.1, 29.7, 32.0, 32.5, 36.5, 36.9, 56.4, 128.2, 129.4, 133.8 and 139.4; *m/z* (ES+) 333 ($[M+23]^+$, 100%).

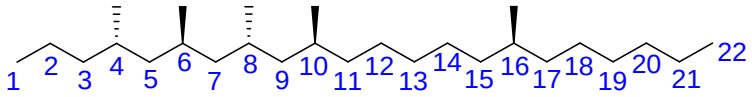
[(7*R*,13*R*,15*S*,17*R*,19*S*)-7,13,15,17,19-pentamethyldocosan-11-ylsulfonyl]benzene (1.119)



To a stirred solution of sulfone **1.118** (20 mg, 0.07 mmol) in dry THF (0.8 mL) and DMPU (0.8 mL) was slowly added n-BuLi (50 µL, 1.6 M in hexane, 0.08 mmol) at -40 ^oC under nitrogen atmosphere. The mixture was stirred for 30 min. Then a solution of iodide **1.113** (27 mg, 0.8 mmol) in THF (0.8 mL) was added to the reaction mixture. Reaction was let warm up to room temperature and stirred for 16 h. To the reaction was added saturated aqueous NH_4Cl (5 mL) and partitioned between water (3 mL) and ether (8 mL). Organic layer was dried over washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (4:1)

gave the *title compound* **1.119** (11 mg, 34%) as a colourless oil, this was a 50:50 mixture of two diastereoisomers. R_f 0.6 (4:1 petrol-ether); $[\alpha]_D^{20}$ +4.0 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 521.4371; $C_{33}H_{61}O_2S$, requires *M*, 521.4387) ν_{max} 2955, 2923, 2870, 1462, 1379, 1303, 1145, 1086, 1025, 802, 764, 727 and 691 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.63-0.83 (21 H, m, 1-H_3, 7-CH_3, 13-CH_3, 15-CH_3, 17-CH_3, 19-CH_3 and 22-H_3), 0.87-1.80 (33 H, m, 2-H_2, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H, 8-H_2, 9-H_2, 10-H_2, 12-H_2, 13-H, 14-H_2, 15-H, 16-H_2, 17-H, 18-H_2, 19-H, 20-H_2 and 21-H_2), 2.91 (1 H, br m, 11-H), 7.49 (2 H, t, *J* 7.5, Ar-H), 7.58 (1 H, m, Ar-H), 7.82 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$, a mixture of two diastereoisomers) 14.1, 14.4, 19.0, 19.2, 19.6 (2), 19.7, 20.1, 20.7, 24.2, 27.0, 27.2, 27.9, 28.2, 29.7 (2), 31.9, 32.5, 36.9 (2), 37.0, 40.2, 40.3, 45.6, 45.9, 46.3, 46.7, 62.7, 128.9 (2), 129.1, 133.4 and 138.3; *m/z* (ES+) 543 ($[M+23]^+$, 100%).

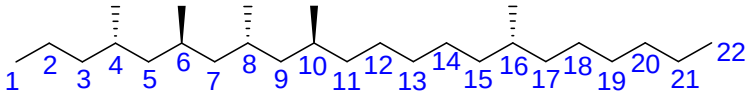
(4*S*,6*R*,8*R*,10*S*,16*S*)-4,6,8,10,16-pentamethyldocosane (1.21)



To a stirred solution of sulfone **1.117** (9 mg, 0.017 mmol) in MeOH (2 mL) was added 20% sodium amalgam (85 mg, 0.518 mmol) at room temperature. Reaction was stirred at room temperature for 6 h. Reaction was then concentrated under reduced pressure, aqueous NH_4Cl solution (4 mL) was added and reaction was partitioned between aqueous NH_4Cl solution (6 mL) and hexane (6 mL). Organic layer was dried over washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with two column volumes of hexane (100%) gave the *title compound* **1.21** (5 mg, 83%) as a colorless oil. R_f 1.0 (100% petrol); $[\alpha]_D^{20}$ +23.3 (c 1.2 in $CHCl_3$); ν_{max} 2956, 2923, 2854, 1463, 1378, 1260, 1094, 1018, 799, 725, 664 and 622 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.72-0.82 (21 H, m, 7 x CH_3), 0.89-1.07 (10 H, m), 1.13-1.30 (20 H, m), 1.41 (2 H, m) and 1.49 (3 H, m); δ_C (100 MHz, $CDCl_3$) 14.1212, 14.3854, 19.5518, 19.5682, 19.5882, 19.6502, 19.7286, 20.0803, 22.6990, 27.0508, 27.0672, 27.1128, 27.2933, 29.3003, 29.6987,

29.7169, 30.0012, 30.3457, 31.9639, 32.7567, 37.0948, 37.1003, 37.8848, 40.2229, 45.5496, 45.5660 and 46.5428.

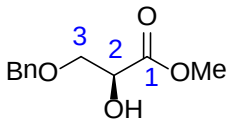
(4*S*,6*R*,8*R*,10*S*,16*R*)-4,6,8,10,16-pentamethyldocosane (1.22)



To a stirred solution of sulfone **1.119** (11 mg, 0.021 mmol) in MeOH (2 mL) was added 20% sodium amalgam (104 mg, 0.641 mmol) at room temperature. Reaction was stirred at room temperature for 6 h. Reaction was then concentrated under reduced pressure, aqueous NH_4Cl solution (4 mL) was added and reaction was partitioned between aqueous NH_4Cl solution (6 mL) and hexane (6 mL). Organic layer was dried over washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with two column volumes of hexane (100%) gave the *title compound* **1.22** (6 mg, 85%) as a colorless oil. R_f 1.0 (100% petrol); $[\alpha]_D^{20}$ -4.8 (c 1.1 in $CHCl_3$); ν_{max} 2957, 2924, 2854, 1464, 1378, 1260, 1094, 1018, 799, 725 and 664 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.72-0.83 (21 H, m, 7 x CH_3), 0.89-1.06 (10 H, m), 1.11-1.30 (20 H, m), 1.41 (2 H, m) and 1.49 (3 H, m); δ_C (100 MHz, $CDCl_3$) 14.1266, 14.3890, 19.5354, 19.5518, 19.5773, 19.6338, 19.7176, 20.0766, 22.6990, 27.0472, 27.0599, 27.1037, 27.2629, 27.2689, 29.6951, 29.6951, 29.9757, 30.3311, 31.9603, 32.7439, 37.0884, 37.0966, 37.8702, 40.2101, 45.8296, 45.5533 and 46.5191.

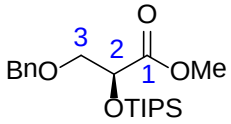
Experimental for compounds in section two

Methyl (2*S*)-3-benzyloxy-2-hydroxy-propanoate[127] (2.30)



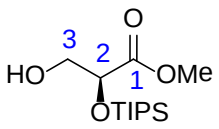
A mixture of carboxylic acid **2.34** (500 mg, 2.55 mmol), MeOH (5 mL) and methanolic HCl (1 M, 1.02 mL, 1.02 mmol) was stirred at room temperature for 1.5 h. Trimethyl orthoformate (541 mg, 5.1 mmol) was added and the mixture was stirred at room temperature for 16 h. The solution was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (3:7) gave the title compound **2.30** as a colourless oil (153 mg, 28%). R_f 0.4 (30:70 petrol-ether). $[\alpha]_D^{20}$ +6.0 (c 0.2 in $CHCl_3$); [Literature value: $[\alpha]_D^{20}$ +11.7 (c 5.04 in $CHCl_3$)]; (Found $[M+Na]^+$, 233.0780; $C_{11}H_{14}O_4Na$, requires *M*, 233.0785) ν_{max} 3471, 3031, 2951, 2864, 1738, 1496, 1453, 1361, 1233, 1101, 1027, 974, 918, 737, and 698 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.07 (1 H, d, *J* 6.9, OH), 3.79 (2 H, d, *J* 3.1, 3-H_2), 3.82 (3 H, s, OCH_3), 4.36 (1 H, m, 2-H), 4.57 (1 H, dd, *J* 12.3, OCH_aPh), 4.64 (1 H, dd, *J* 12.3, OCH_bPh) and 7.33 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 52.6, 70.9, 71.3, 73.5, 127.7, 127.8, 128.4, 137.7 and 173.1; *m*/*z* (ES+) 233 ($[M+23]^+$, 100%).

Methyl (2*S*)-3-benzyloxy-2-triisopropylsilyloxy-propanoate (2.35)



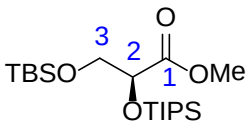
A solution of alcohol **2.30** (150 mg, 0.71 mmol) in DCM (5 mL) was stirred at 0 ^{o}C. 2,6-Lutidine (535 mg, 4.99 mmol) and TIPSOTf (1.09 g, 3.57 mmol) were added. The reaction mixture was stirred at room temperature for 3.5 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (90:10) gave the *title compound* **2.35** (253 mg, 97%) as a colourless oil. Rf 0.5 (9:1 petrol-ether). $[\alpha]_D^{20}$ -2.1 (c 0.2 in $CHCl_3$); (Found $[M+Na]^+$, 389.2112; $C_{20}H_{34}O_4NaSi$, requires *M*, 389.2119) ν_{max} 3030, 2943, 2891, 2865, 1759, 1496, 1463, 1454, 1384, 1364, 1278, 1256, 1201, 1146, 1117, 997, 919, 882, 833, 734, 696, and 610 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90 (21 H, m, OSi^iPr_3), 3.55 (2 H, d, *J* 5.3, 3-H_2), 3.58 (3 H, s, OCH_3), 4.35 (1 H, t, *J* 5.1, 2-H), 4.36 (1 H, dd, *J* 7.3 and 12.4, O*CH*$_a$Ph), 4.44 (1 H, dd, *J* 7.3 and 12.4, O*CH*$_b$Ph) and 7.15 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 12.2, 17.8, 51.9, 72.6, 72.7, 73.5, 127.6, 127.7, 128.3, 138.0 and 172.4; *m*/*z* (ES+) 384 $[M+18]^+$, 100%); 389 $[M+23]^+$, 30%).

Methyl (2*S*)-3-hydroxy-2-triisopropylsilyloxy-propanoate (2.36)



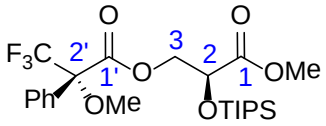
To a stirred solution of benzoester **2.35** (250 mg, 0.68 mmol) in MeOH (4 mL) was added Pd/C (25 mg, 10% by weight). The reaction mixture was stirred at room temperature under H_2 atmosphere for 16 h. Catalyst was filtered. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting petrol-ether (70:30) gave the *title compound* **2.36** (153 mg, 81%) as a colourless oil. R_f 0.5 (60:40 petrol-ether). $[\alpha]_D^{20}$ -28.8 (c 0.3 in $CHCl_3$); (Found $[M+Na]^+$, 299.1649; $C_{13}H_{28}O_4NaSi$, requires *M*, 299.1650) ν_{max} 3471, 2943, 2866, 1742, 1463, 1385, 1274, 1199, 1138, 1060, 1015, 996, 948, 882, 838, 744, 681, and 658 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.86-0.97 (21 H, m, OSi^iPr_3), 1.98 (1 H, dd, *J* 6.0 and 7.3, OH), 3.55 (3 H, s, OCH_3), 3.63 (2 H, m, 3-H_2) and 4.23 (1 H, t, *J* 4.2, 2-H); δ_C (100 MHz, $CDCl_3$) 12.2, 17.9, 52.0, 65.5, 72.9 and 172.4; *m*/*z* (ES+) 299 ($[M+23]^+$, 100%).

Methyl (2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-triisopropylsilyloxy-propanoate (2.29)



To a solution of alcohol **2.36** (120 mg, 0.43 mmol) in DCM (3 mL) was added imidazole (106 mg, 1.3 mmol) followed by TBSCl (79 mg, 0.52 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting petrol-ether (95:5) gave the *title compound* **2.29** (160 mg, 95%) as a colourless oil. R_f 0.7 (95:5 petrol-ether). $[\alpha]_D^{20}$ -2.4 (c 0.3 in $CHCl_3$); (Found $[M+Na]^+$, 413.2506; $C_{19}H_{42}O_4NaSi_2$, requires *M*, 413.2514) ν_{max} 2946, 2867, 1760, 1464, 1436, 1388, 1362, 1255, 1122, 1005, 939, 883, 833, 777, 728, 681, and 664 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 (6 H, s, 2 x $OSiCH_3$), 0.83 (9 H, s, OSi^tBu), 1.01 (21 H, m, OSi^iPr_3), 3.68 (3 H, s, OCH_3), 3.75 (2 H, d, *J* 6.0, 3-H_2) and 4.34 (1 H, t, *J* 5.9, 2-H); δ_C (100 MHz, $CDCl_3$) -5.5, 12.2, 17.9, 18.3, 25.8, 51.6, 66.1, 73.9 and 172.8; *m/z* (ES+) 413 ($[M+23]^+$, 100%).

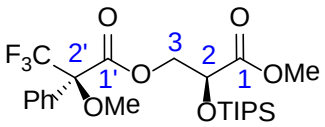
[(2*S*)-3-Methoxy-3-oxo-2-triisopropylsilyloxy-propyl] (2*S*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (2.37)



To a solution of alcohol **2.36** (10 mg, 0.036 mmol) in DCM (0.5 mL) was added triethylamine (11 mg, 0.11 mmol), (*R*)-MTPA-Cl (10.1 mg, 0.04 mmol) and DMAP (14 mg, 0.11 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (9:1) gave *the title compound* **2.37** (15 mg, 85 %) as a colourless oil. R_f 0.5 (90:10 petrol-ether). $[\alpha]_D^{20}$ -46.0 (c 0.2 in $CHCl_3$); (Found $[M+Na]^+$, 515.2048; $C_{23}H_{35}O_6$,$NaSiF_3$

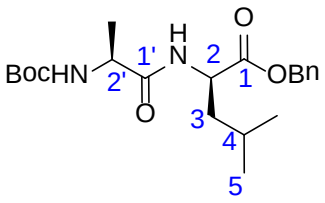
requires *M*, 515.2048) ν_{max} 2947, 2894, 2868, 1754, 1464, 1452, 1385, 1268, 1241, 1156, 1125, 1081, 1019, 998, 919, 882, 835, 765, 719, 683, and 661 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.95-1.07 (21 H, m, OSi^iPr_3), 3.49 (3 H, m, 2'-OCH_3), 3.57 (3 H, s, 1-OCH_3), 4.37 (1 H, dd, *J* 3.5 and 11.1, 3-H_a), 4.52 (1 H, t, *J* 4.3, 2-H), 4.63 (1 H, dd, *J* 4.3 and 10.9, 3-H_b), 7.32 (3 H, m, Ar-H) and 7.47 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 12.1, 17.8, 52.1, 55.6, 68.0, 70.4, 84.8, 127.4, 128.4, 129.6, 132.0, 166.3 and 171.0; *m/z* (ES+) 515 ($[M+23]^+$, 100%), 510 ($[M+18]^+$, 50%).

[(2*S*)-3-Methoxy-3-oxo-2-triisopropylsilyloxy-propyl] (2*R*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate (2.38)



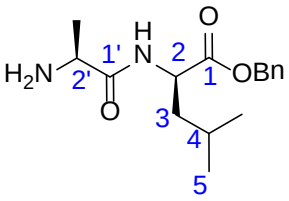
To a solution of alcohol **2.36** (10 mg, 0.036 mmol) in DCM (0.5 mL) was added triethylamine (11 mg, 0.11 mmol), (*S*)-MTPA-Cl (10.1 mg, 0.04 mmol) and DMAP (14 mg, 0.11 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (9:1) gave *the title compound* **2.38** (14 mg, 79 %) as a colourless oil. R_f 0.5 (90:10 petrol-ether). $[\alpha]_D^{20}$ +34.6 (c 0.2 in $CHCl_3$); (Found $[M+Na]^+$, 493.2229; $C_{23}H_{36}O_6SiF_3$, requires *M*, 493.2228) ν_{max} 2947, 2894, 2868, 1753, 1464, 1452, 1385, 1348, 1270, 1241, 1166, 1123, 1081, 1020, 999, 919, 882, 834, 718, 683, and 659 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.94-1.04 (21 H, m, OSi^iPr_3), 3.45 (3 H, m, 2'-OCH_3), 3.60 (3 H, s, 1-OCH_3), 4.43 (1 H, dd, *J* 6.6 and 9.8, 2-H), 4.52 (2 H, m, 3-H_2), 7.32 (3 H, m, Ar-H) and 7.44 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 12.1, 17.7, 52.1, 55.5, 67.9, 70.6, 84.8, 127.5, 128.4, 129.6, 131.9, 166.4 and 171.1; *m/z* (ES+) 510 ($[M+18]^+$, 100%), 515 ($[M+23]^+$, 50%).

Benzyl (2*R*)-2-{[(2*S*)-2-(*tert*-butoxycarbonylamino)propanoyl]amino}-4-methyl-pentanoate (2.39)



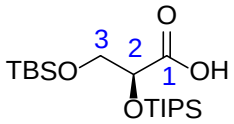
D-leucine benzyl ester **2.33** (400 mg, 1.02 mmol), EDC (234 mg, 1.22 mmol), HOBt (138 mg, 1.02 mmol) and triethylamine (170 µL, 1.02 mmol) were dissolved in DCM (20 mL) until in solution. Boc-protected alanine **2.32** (193 mg, 1.02 mmol) was added and the mixture was stirred at room temperature for 16 h. The mixture was diluted with DCM and washed with brine (20 mL) three times. Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (30:70) gave the *title compound* **2.39** (394 mg, 98%) as a white solid. R_f 0.5 (30:70 petrol-ether). $[\alpha]_D^{20}$ -2.4 (c 0.2 in $CHCl_3$); m.p. = 92 - 93°C; (Found $[M+Na]^+$, 415.2207; $C_{23}H_{32}N_2O_5Na$, requires *M*, 415.2204); ν_{max} 3328, 3306, 3062, 2971, 2934, 2875, 2360, 2341, 1735, 1684, 1651, 1547, 1524, 1501, 1452, 1389, 1364, 1327, 1281, 1239, 1163, 1124, 1067, 1050, 1023, 931, 856, 763, 728, and 676 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.84 (3 H, d, *J* 4.3, 4-CH_3 or 5-H_3), 0.85 (3 H, d, *J* 4.0, 4-CH_3 or 5-H_3), 1.29 (3 H, d, *J* 7.1, 2'-CH_3), 1.38 (9 H, s, $OC(CH_3)_3$), 1.48 (1 H, m, 4-H), 1.57 (2 H, m, 3-H_2), 4.12 (1 H, br s, 2-H), 4.58 (1 H, m, 2'-H), 4.81 (1 H, br s, NH), 5.06 (1 H, d, *J* 12.4, OCH_aPh), 5.11 (1 H, d, *J* 12.1, OCH_bPh), 6.49 (1 H, br s, NH) and 7.29 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 18.0, 21.9, 22.9, 24.8, 28.3, 41.4, 50.1, 50.8, 67.1, 128.3, 128.4, 128.6, 135.4, 172.4 (2) and 172.7; *m/z* (ES+) 415 ($[M+23]^+$, 100%).

Benzyl (2*R*)-2-[[(2*S*)-2-aminopropanoyl]amino]-4-methyl-pentanoate (2.28)



Boc-protected dipeptide **2.39** (385 mg, 0.98 mmol) was dissolved in DCM (10 mL). To this mixture was added TFA (1.12 g, 9.8 mmol) and reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated and partitioned between saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL). Aqueous layer was extracted twice with EtOAc (10 mL x 2). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with DCM-MeOH-NH_3 (90:10:1) gave the *title compound* **2.28** (277 mg, 97%) as a colourless gum. R_f 0.6 (60:40 ether-solution A) $[\alpha]_D^{20}$ -2.4 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 293.1873; $C_{16}H_{25}N_2O_3$, requires *M*, 293.1860); ν_{max} 3302, 3035, 2958, 2872, 1739, 1657, 1514, 1455, 1369, 1335, 1272, 1190, 1151, 1081, 955, 909, 855, 739 and 697 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.86 (6 H, d, *J* 6.0, 4-CH_3 and 5-H_3), 1.27 (3 H, d, *J* 6.9, 2'-CH_3), 1.50-1.63 (5 H, m, 3-H_2, 4-H and NH_2), 3.48 (1 H, br s, 2-H), 4.57 (1 H, m, 2'-H), 5.06 (1 H, d, *J* 12.3, OCH_aPh), 5.12 (1 H, d, *J* 12.3, OCH_bPh), 7.25-7.31 (5 H, m, Ar-H) and 7.57 (1 H, br s, NH); δ_C (100 MHz, $CDCl_3$) 21.5, 21.9, 22.9, 25.0, 41.3, 50.5, 50.6, 67.0, 128.3, 128.4, 128.6, 135.5, 172.9 and 175.4; *m*/*z* (ES+) 293 ($[M+1]^+$, 100%).

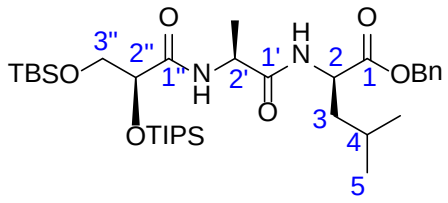
(2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-triisopropylsilyloxy-propanoic acid (2.27)



Ester **2.29** (182 mg, 0.47 mmol) was dissolved in THF (5 mL). To the mixture was added LiOH (112 mg, 4.7 mmol) in H_2O (1 mL). The resulting mixture was stirred under reflux for 16 h. Reaction was cooled and concentrated under reduced pressure. The residue was dissolved in water (10 mL) and was then acidified (pH = 3) with AcOH. The aqueous solution was then extracted with Et_2O (20 mL). Organic layer was washed with brine (20 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (80:20) gave the *title compound* **2.27** (45 mg,

25%) as a colorless oil. R_f 0.5 (80:20 petrol-ether). $[\alpha]_D^{20}$ +1.1 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 377.2544; $C_{18}H_{41}O_4Si_2$, requires *M*, 377.2538); ν_{max} 3051, 2943, 2893, 2868, 1713, 1464, 1386, 1285, 1248, 1130, 1106, 1016, 921, 882, 837, 782, 731 and 682 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.06 (3 H, s, $SiCH_3$), 0.07 (3 H, s, $SiCH_3$), 0.84 (9 H, s, $OSiC(CH_3)_3$), 0.99 (21 H, m, OSi^iPr_3), 1.46 (1 H, m, COOH), 3.80 (1 H, dd, *J* 3.5 and 10.4, 3-H_a), 3.90 (1 H, dd, *J* 4.1 and 10.4, 3-H_b) and 4.19 (1 H, t, *J* 4.1, 2-H); δ_C (100 MHz, $CDCl_3$) -5.3, -4.7, -3.6, 11.9, 17.9, 25.7, 65.7, 74.1 and 171.8; *m*/*z* (ES-) 375 ($[M-1]^-$, 100%).

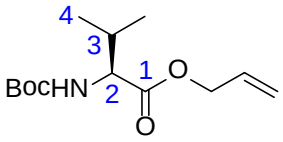
Benzyl (2*R*)-2-[[(2*S*)-2-[[(2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-triisopropylsilyloxy-propanoyl]amino]propanoyl]amino]-4-methyl-pentanoate (2.26)



Amine **2.28** (31 mg, 0.11 mmol) was dissolved in DCM/MeOH (1.5 mL/0.5 mL). To this solution was added carboxylic acid (40 mg, 0.11 mmol), EDC (21 mg, 0.13 mmol), HOBt (15 mg, 0.11 mmol) and triethylamine (15 µL, 0.11 mmol). The mixture was stirred at room temperature for 16 h. The mixture was diluted with DCM and washed with brine (15 mL). Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (50:50) gave the *title compound* **2.26** (10 mg, 14%) as a colourless gum. R_f 0.2 (60:40 petrol-ether). $[\alpha]_D^{20}$ -24.5 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 651.4238; $C_{34}H_{63}N_2O_6Si_2$, requires *M*, 651.4220); ν_{max} 3405, 3299, 2929, 2867, 1745, 1693, 1652, 1520, 1463, 1386, 1260, 1142, 1106, 1036, 939, 882, 838, 803, 783, 737 and 682 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.00 (3 H, s, $SiCH_3$), 0.01 (3 H, s, $SiCH_3$), 0.83 (6 H, d, *J* 6.3, 4-CH_3 and 5-H_3), 0.85 (9 H, s, $OSiC(CH_3)_3$), 0.99 (21 H, m, OSi^iPr_3), 1.30 (3 H, d, *J* 7.3, 2'-CH_3), 1.49-1.59 (3 H, m, 3-H_2 and 4-H), 3.82 (1 H, dd, *J* 2.2 and 10.1, 3''-H_a), 3.91 (1 H, dd, *J* 4.1 and 10.4, 3''-H_b), 4.12 (1 H, m, 2''-H), 4.40 (1 H, q, *J* 7.3, 2'-H), 4.56 (1 H, dt, *J* 5.0 and 8.5, 2-H), 5.06 (2 H, s, OCH_2Ph), 6.56 (1 H, d, *J* 7.9,

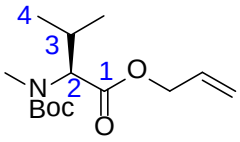
NH), 7.00 (1 H, d, *J* 7.9, NH) and 7.27 (5 H, m, Ar-H); δC (100 MHz, $CDCl_3$) -6.4, -5.8, 0.0, 10.9, 16.9, 20.9, 21.8, 23.8, 24.7, 28.7, 29.3, 40.4, 47.3, 49.8, 65.3, 65.9, 74.3, 127.2, 127.3, 127.5, 134.4, 170.5, 171.3 and 171.3; *m*/*z* (ES+) 651 ($[M+1]^+$, 100%).

Allyl (2*S*)-2-(*tert*-butoxycarbonylamino)-3-methyl-butanoate[135] (2.47)



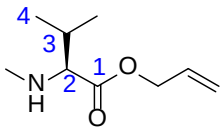
Boc-protected L-valine **2.46** (500 mg, 2.3 mmol) was dissolved in DMSO (10 mL). To this solution was added allyl bromide (423 mg, 3.5 mmol) and K_2CO_3 (802 mg, 5.8 mmol). The reaction mixture was stirred at room temperature for 16 h. Reaction mixture was partitioned between aqueous $NaHCO_3$ (15 mL) and ether (30 mL). The organic layer was extracted with ether (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (80:20) gave the *title compound* **2.47** (580 mg, 98%) as a colourless oil. R_f 0.4 (80:20 petrol-ether). $[\alpha]_D^{20}$ +3.5 (c 0.2 in $CHCl_3$); (Found $[M+Na]^+$, 280.1519; $C_{13}H_{23}NO_4$, requires *M*, 280.1520); ν_{max} 3375, 2968, 2935, 1711, 1650, 1501, 1456, 1391, 1366, 1310, 1244, 1155, 1090, 989, 931, 868, 779 and 673 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.83 (3 H, d, *J* 6.8, 3-CH_3 or 4-H_3), 0.90 (3 H, d, *J* 6.8, 3-CH_3 or 4-H_3), 1.38 (9 H, s, $OC(CH_3)_3$), 2.09 (1 H, m, 3-H), 4.19 (1 H, dd, *J* 5.0 and 9.3, 2-H), 4.51-4.62 (2 H, m, OCH_2CHCH_2), 4.94-4.96 (1 H, m, NH), 5.19 (1 H, d, *J* 10.3, OCH_2CHCH_a), 5.27 (1 H, d, *J* 15.6, OCH_2CHCH_b) and 5.80-5.89 (1 H, m, OCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) 17.6, 19.0, 28.3, 31.3, 58.6, 65.7, 79.8, 118.8, 131.7, 155.7 and 172.1; *m*/*z* (ES+) 280 ($[M+23]^+$, 100%).

Allyl (2*S*)-2-[*tert*-butoxycarbonyl(methyl)amino]-3-methyl-butanoate (2.48)



N-boc-*O*-allyl-protected L-valine **2.47** (1.0 g, 4.6 mmol) was THF (20 mL). To this solution was added sodium hydride 60% in mineral oil (553 mg, 13.6 mmol) at 0 ^{o}C. After 30 min, methyl iodide was added. The reaction mixture was stirred at room temperature for 16 h. Reaction mixture was partitioned between saturated aqueous NH_4Cl (30 mL) and EtOAc (30 mL). The organic layer was extracted with EtOAc (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (80:20) gave the *title compound* **2.48** (672 mg, 55%) as a colourless oil, this was a mixture of two rotamers. R_f 0.4 (20:80 ether-petrol). $[\alpha]_D^{20}$ -57.5 (c 1.2 in $CHCl_3$);-(Found $[M+Na]^+$, 294.1678; $C_{14}H_{25}NO_4$, requires *M*, 294.1676); ν_{max} 2969, 1739, 1695, 1446, 1391, 1367, 1311, 1257, 1143, 991, 932, 878 and 772 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 50:50 mixture of two rotamers) 0.83 (1.5 H, d, *J* 6.6, 3-CH_3 or 4-H_3), 0.84 (1.5 H, d, *J* 6.6, 3-CH_3 or 4-H_3), 0.91 (1.5 H, d, *J* 6.6, 3-CH_3 or 4-H_3), 0.92 (1.5 H, d, *J* 6.6, 3-CH_3 or 4-H_3), 1.39 (9 H, s, $C(CH_3)_3$), 2.13 (1 H, m, 3-H), 2.75 (1.5 H, s, NCH_3), 2.79 (1.5 H, s, NCH_3), 4.06 (0.5 H, d, *J* 10.6, 2-H), 4.41 (0.5 H, d, *J* 10.6, 2-H), 4.55 (2 H, d, *J* 5.3, OCH_2CHCH_2), 5.20 (2 H, m, OCH_2CHCH_2) and 5.84 (1 H, m, OCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) 17.56, 19.01, 27.80, 28.37, 30.9, 51.34, 65.15, 65.69, 118.81, 131.74, 155.68 and 172.17 *m*/*z* (ES+) 294 ($[M+23]^+$, 100%).

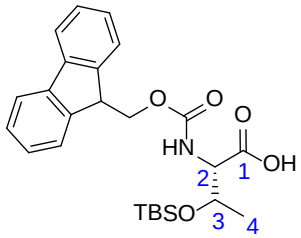
Allyl (2*S*)-3-methyl-2-(methylamino)butanoate (2.44)



Boc-protected amine **2.48** (367 mg, 1.4 mmol) was dissolved in DCM (10 mL). To this mixture was added TFA (1.54 g, 13.5 mmol) and reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated and basified by $NaHCO_3$. Reaction was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and EtOAc (20 mL). Aqueous layer was extracted twice with EtOAc (10 mL x 2). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with DCM-MeOH-NH_3 (90:10:1) gave the *title compound* **2.44** (90 mg, 38%) as a colourless gum. R_f 0.7

(90:10:1 DCM-MeOH-NH_3). $[\alpha]_D^{20}$ -8.5 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 172.1328; $C_9H_{18}NO_2$, requires *M*, 172.1333); ν_{max} 3089, 2965, 2801, 1731, 1455, 1368, 1273, 1174, 1062, 987, 932, 885, and 776 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.88 (3 H, d, *J* 1.8, 3-CH_3 or 4-H_3), 0.90 (3 H, d, *J* 1.8, 3-CH_3 or 4-H_3), 1.38 (1 H, br s, NH), 1.86 (1 H, m, 3-H), 2.30 (3 H, s, NCH_3), 2.87 (1 H, d, *J* 6.1, 2-H), 4.58 (2 H, m, O*C*H_2CHCH_2), 5.19 (1 H, dq, *J* 1.3 and 10.3, OCH_2CHCH_a), 5.28 (1 H, dq, *J* 1.3 and 10.3, OCH_2CHCH_b) and 5.88 (1 H, m, OCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) 18.7, 19.3, 31.6, 35.4, 65.1, 69.4, 118.7, 132.2 and 174.7 *m*/*z* (ES+) 172 ($[M+1]^+$, 100%).

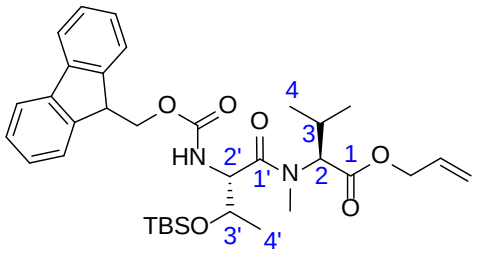
(2*S*)-3-[*tert*-Butyl(dimethyl)silyl]oxy-2-(9H-fluoren-9-ylmethoxycarbonylamino) butanoic acid[134] (2.43)



Fmoc-protecting threonine **2.45** (100 mg, 0.28 mmol) was dissolved in THF (4 mL). To the reaction mixture was added TBSCl (168 mg, 1.1 mmol) followed by imidazole (114 mg, 1.7 mmol). The reaction was stirred at room temperature for 16 h. Reaction was partitioned between saturated aqueous NH_4Cl (10 mL) and ether (10 mL) and stirred for 30 min. Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with ether-petrol (50:50) gave the *title compound* **2.43** (50 mg, 40%) as a colourless foam. R_f 0.5 (50:50 ether-petrol). $[\alpha]_D^{20}$ +12.0 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 456.2198; $C_{25}H_{34}NO_5Si$, requires *M*, 456.2201); ν_{max} 3442, 3067, 2954, 2930, 2887, 2857, 1723, 1513, 1450, 1351, 1310, 1252, 1210, 1103, 1080, 975, 939, 836, 810, 778, 758, 739, 675 and 620 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (3 H, s, $OSiCH_3$), 0.01 (3 H, s, $OSiCH_3$), 0.77 (9 H, s, $OSiC(CH_3)_3$), 1.04 (3 H, d, *J* 6.3, 4-H_3), 4.08 (1 H, t, *J* 6.0, 2-H), 4.16 (1 H, m, 3-H), 4.22-4.31 (3 H, m, fluorenyl-CH_2 and fluorenyl-*H*), 5.47 (1 H, d, *J* 6.0, NH), 7.15 (2 H, t, *J* 7.3, Ar-H), 7.24 (2 H, t, *J* 7.8, Ar-H), 7.44 (2 H, m, Ar-H)

and 7.61 (2 H, d, *J* 7.6, Ar-H); δ_C (100 MHz, $CDCl_3$) -5.22, -4.66, 17.87, 25.64, 47.14, 58.77, 65.88, 67.30, 68.28, 120.05, 125.13, 127.10, 127.79, 141.33, 141.36, 143.61 and 143.82; *m*/*z* (ES+) 456 ($[M+1]^+$, 100%).

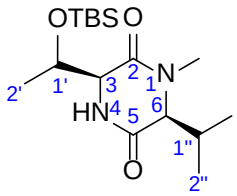
Allyl (2*S*)-2-[[(2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-(9H-fluoren-9-ylmethoxycarbonylamino)butanoyl]-methyl-amino]-3-methyl-butanoate (2.42)



A solution of carboxylic acid **2.43** (45 mg, 0.1 mmol) in DCM (1 mL) was treated with HATU (53 mg, 0.14 mmol) and HOBt (7 mg, 0.05mmol). Amine **2.44** (17 mg, 0.1 mmol) in DMF (1 mL) was added followed by DIPEA (51 mg, 0.4 mmol). Reaction reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with ether-petrol (70:30) gave the *title compound* **2.42** (25 mg, 42%) as a colorless gum. R_f 0.6 (50:50 ether-petrol). $[\alpha]_D^{20}$ -46.7 (c 0.2 in $CHCl_3$); (Found $[M+H]^+$, 609.3350; $C_{34}H_{49}N_2O_6Si$, requires *M*, 609.3355); ν_{max} 3302, 3067, 2957, 2930, 2856, 1722, 1634, 1472, 1450, 1413, 1362, 1294, 1251, 1333, 1189, 1136, 1088, 1034, 988, 937, 833, 777, 758, 739, 668 and 622 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (6 H, 2 x $OSiCH_3$), 0.81 (3 H, d, *J* 6.6, 3-CH_3 or 4-H_3), 0.83 (9 H, s, $OSiC(CH_3)_3$), 0.96 (3 H, d, *J* 6.6, 3-CH_3 or 4-H_3), 1.12 (3 H, d, *J* 6.3, 4'-H_3), 2.19 (1 H, m, 3-H), 3.06 (3 H, s, NCH_3), 4.01 (1 H, m, fluorenyl-*H*), 4.16 (1 H, m, 2'-H), 4.28 (2 H, m, fluorenyl-C*H*$_2$), 4.55 (3 H, m, OC*H*$_2$CHCH$_2$ and 3'-H), 4.89 (1 H, d, *J* 10.4, 2-H), 5.18 (1 H, d, *J* 10.4, OCH_2CHCH_a), 5.26 (1 H, d, *J* 17.0, OCH_2CHCH_b), 5.58 (1 H, d, *J* 8.5, NH), 5.83 (1 H, m, OCH_2CHCH_2), 7.25 (2 H, m, Ar-H), 7.33 (2 H, m, Ar-H), 7.54 (2 H, m, Ar-H) and 7.70 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) -4.89, -4.59, 17.99, 18.86, 19.79, 20.42, 25.78, 27.37, 31.79, 47.12, 56.53, 61.79, 65.61, 67.11, 69.53,

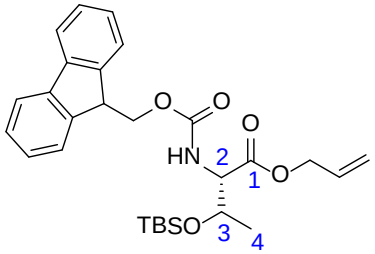
119.09, 119.98, 125.19, 125.29, 127.06, 127.71, 131.64, 141.31, 143.79, 143.99, 156.14, 170.52 and 171.23; *m*/*z* (ES+) 631 ($[M+23]^+$, 100%); 609 ($[M+1]^+$, 70%).

(3*S*,6*S*)-3-[1-[*tert*-Butyl(dimethyl)silyl]oxyethyl]-6-isopropyl-1-methyl-piperazine-2,5-dione (2.50)



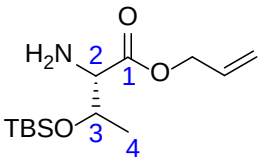
Fmoc-protected amine **2.42** (25 mg, 0.04 mmol) was dissolved DMF (2 mL). To the reaction mixture was added piperidine (4 mg, 0.05 mmol). Reaction was stirred at room temperature for 16 h. Reaction was partitioned between ether (20 mL) and water (20 mL). Organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with ether-petrol (50:50) gave the *title compound* **2.50** (12 mg, 89%) as a colourless gum. R_f 0.5 (50:50 ether-petrol). $[\alpha]_D^{20}$ -24.1 (c 0.2 in $CHCl_3$); ν_{max} 3734, 3629, 2930, 2361, 2341, 1682, 1458, 1259, 1092, 1024, 973, 836, 802, 778 and 669 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (3 H, s, $OSiCH_3$), 0.03 (3 H, s, $OSiCH_3$), 0.82 (9 H, s, $OSiC(CH_3)_3$), 0.98 (3 H, d, *J* 7.1, 2''-H_3), 1.09 (3 H, d, *J* 6.8, 1''-CH_3), 1.28 (3 H, d, *J* 6.1, 2'- H_3), 2.16 (1 H, m, 1''-H), 2.93 (3 H, s, N-CH_3), 3.60 (1 H, d, *J* 5.3, 6-H), 3.70 (1 H, dd, *J* 3.0 and 7.3, 3-H), 4.20 (1 H, m, 1'-H) and 6.09 (1 H, br s, NH); δ_C (100 MHz, $CDCl_3$) -4.60, -4.40, 18.04, 18.53, 20.26, 21.36, 25.83, 32.58, 35.33, 61.74, 68.03, 70.81, 164.20 and 166.26; *m*/*z* (ES+) 329 ($[M+1]^+$, 100%).

Allyl (2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-(9H-fluoren-9-ylmethoxycarbonylamino) butanoate (2.51)



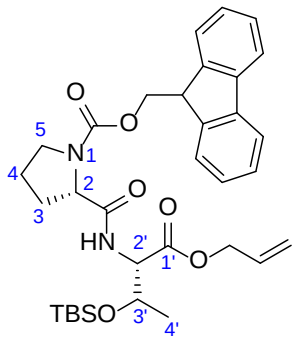
Carboxylic acid **2.43** (280 mg, 0.61 mmol) was dissolved in DMSO (15 mL). To the reaction mixture was added allyl bromide (89 mg, 0.74 mmol) followed by $NaHCO_3$ (103 mg, 1.23 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was partitioned between water (20 mL) and Et_2O (30 mL). Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (80:20) gave the *title compound* 2.51(249 mg, 82%) as a colourless oil. R_f 0.3 (80:20 petrol-ether). $[\alpha]_D^{20}$ -4.8 (c 1.1 in $CHCl_3$); (Found $[M+H]^+$, 496.2526; $C_{28}H_{38}NO_5Si$, requires *M*, 496.2514); ν_{max} 3445, 2951, 2929, 2855, 1728, 1505, 1472, 1463, 1450, 1378, 1361, 1311, 1251, 1199, 1129, 1100, 1078, 1033, 986, 937, 837, 827, 810, 777, 758, 740, 664 and 621 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.06 (3 H, s, $OSiCH_3$), 0.00 (3 H, s, $OSiCH_3$), 0.81 (9 H, s, $OSiC(CH_3)_3$), 1.16 (3 H, d, *J* 6.3, Thr-Me), 4.25 (3 H, m, fluorenyl-*H*, 2-H and 3-H), 4.38 (2 H, m, fluorenyl-CH_2), 4.52 (1 H, dd, *J* 5.8 and 13.1, OCH_aCHCH_2), 4.59 (1 H, dd, *J* 5.8 and 13.1, OCH_bCHCH_2), 5.18 (1 H, dd, *J* 1.5 and 10.3, OCH_2CHCH_a), 5.27 (1 H, dd, *J* 1.5 and 17.2, OCH_2CHCH_b), 5.44 (1 H, d, *J* 10.1, NH), 5.84 (1 H, m, OCH_2CHCH_2), 7.24 (2 H, t, *J* 7.6, Ar-H), 7.33 (2 H, t, *J* 7.6, Ar-H), 7.55 (2 H, t, *J* 7.8, Ar-H) and 7.70 (2 H, d, *J* 6.8, Ar-H); δ_C (100 MHz, $CDCl_3$) -5.20, -4.28, 17.91, 20.95, 25.70, 47.17, 59.97, 66.18, 67.28, 68.87, 119.08, 120.00, 125.19, 125.29, 127.08, 127.73, 131.53, 141.32, 143.78, 144.05, 156.73 and 170.60; *m*/*z* (ES+) 496 ($[M+1]^+$, 100%).

Allyl (2*S*)-2-amino-3-[*tert*-butyl(dimethyl)silyl]oxy-butanoate (2.52)



Fmoc-protected amine **2.51** (249 mg, 0.50 mmol) was dissolved in THF (15 mL). To this solution was added piperidine (64 mg, 0.75 mmol). The reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduce pressure. Column chromatography of the residue eluting with DCM-MeOH-NH_3 (95:5:0.5) gave the *title compound* **2.52** (125 mg, 91%) as a colorless oil. R_f 0.7 (90:10 DCM-MeOH-NH_3). $[\alpha]_D^{20}$ -14.5 (c 2.2 in $CHCl_3$); (Found $[M+Na]^+$, 296.1645; $C_{13}H_{27}N_1O_3$, requires *M*, 296.1653); ν_{max} 2954, 2929, 2886, 2856, 1741, 1649, 1596, 1473, 1463, 1374, 1361, 1251, 1154, 1075, 1039, 986, 966, 932, 883, 836, 807, 774, 738 and 667 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (3 H, s, $OSiCH_3$), 0.06 (3 H, s, $OSiCH_3$), 0.86 (9 H, s, $OSiC(CH_3)_3$), 1.27 (3 H, d, *J* 6.3, 4-H_3), 3.32 (1 H, d, *J* 6.3, 3-H), 4.34 (1 H, m, 2-H), 4.56 (1 H, dd, *J* 5.8 and 13.1, OCH_aCHCH_2), 4.66 (1 H, dd, *J* 5.8 and 13.1, OCH_bCHCH_2), 5.27 (1 H, m, OCH_2CHCH_a), 5.35 (1 H, m, OCH_2CHCH_b) and 5.95 (1 H, m, OCH_2CHCH_2); δ_C (100 MHz, $CDCl_3$) -5.17, -4.25, 17.92, 20.97, 25.70, 60.83, 65.75, 69.53, 118.84, 131.90 and 174.25 *m/z* (ES+) 274 ($[M+1]^+$, 100%).

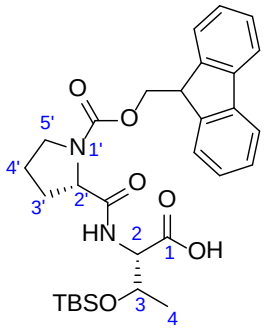
9H-fluoren-9-ylmethyl (2*S*)-2-[[(1*S*)-1-allyloxycarbonyl-2-[*tert*-butyl(dimethyl)silyl]oxy-propyl]carbamoyl]pyrrolidine-1-carboxylate (2.53)



A solution of Fmoc-protected L-proline (62 mg, 0.18 mmol) in DMF (2 mL) was treated with HATU (97 mg, 0.26 mmol) and HOBt (12 mg, 0.09mmol). Amine **2.52** (50 mg, 0.18 mmol) in DMF (2 mL) was added followed by DIPEA (95 mg, 0.73 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with ether-petrol (80:20) gave the *title compound* **2.53** (92 mg, 85%) as a colorless gum. R_f 0.5 (80:20 ether-petrol). $[\alpha]_D^{20}$ -28.0 (c 1.0 in $CHCl_3$); (Found

$[M+H]^+$, 593.3039; $C_{33}H_{45}N_2O_6$, requires *M*, 593.3042); ν_{max} 3330, 3066, 2930, 2853, 2348, 1746, 1682, 1514, 1471, 1451, 1414, 1354, 1311, 1252, 1187, 1150, 1120, 1093, 1031, 1061, 985, 961, 937, 837, 809, 776, 758 and 739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.05 (3 H, s, $OSiCH_3$), 0.00 (3 H, s, $OSiCH_3$), 0.82 (9 H, s, $OSiC(CH_3)_3$), 1.12 (3 H, d, *J* 6.1, 4'-H_3), 1.96-2.33 (4 H, m, 4-H_2 and 3-H_2), 3.48-3.65 (2 H, m, 5-H_2), 4.25 (1 H, m, 2-H), 4.38 (2 H, m, 2'-H and 3'-H), 4.45 (3 H, m, fluorenyl-*H* and fluorenyl-CH_2), 4.55 (2 H, m, OCH_2CHCH_2), 5.22 (2 H, m, OCH_2CHCH_2), 5.71 (1 H, m, NH), 5.88 (1 H, m, OCH_2CHCH_2), 7.30 (2 H, m, Ar-H), 7.39 (2 H, m, Ar-H), 7.57 (2 H, m, Ar-H) and 7.75 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) -5.28, -4.35, 17.81, 25.63, 28.92, 30.32, 42.54, 47.18, 57.47, 57.94, 60.62, 66.13, 68.29, 68.81, 120.01, 123.04, 125.14, 126.46, 127.10, 127.74, 131.62, 132.55, 138.27, 141.33, 169.03, 173.43 and 176.75; *m/z* (ES+) 627 ($[M+1]^+$, 100%).

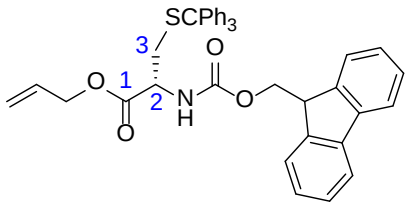
(2*S*)-3-[*tert*-Butyl(dimethyl)silyl]oxy-2-[[(2*S*)-1-(9H-fluoren-9-ylmethoxycarbonyl) pyrrolidine-2-carbonyl]amino]butanoic acid (2.54)



Allyl ester **2.53** (92 mg, 0.16 mmol) and palladium tetrakis(triphenylphosphine) (10 mg, 0.008 mmol) were dissolved in THF (4 mL). To this reaction mixture was added *N*-methylaniline (33 mg, 0.32 mmol). Reaction was stirred at room temperature for 3 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with ether-petrol-acetic acid (80:20:1) gave the *title compound* **2.54** (60 mg, 70%) as a white foam. R_f 0.3 (80:20:1 ether-petrol-acetic acid). $[\alpha]_D^{20}$ -26.6 (c 1.0 in $CHCl_3$); (Found $[M+H]^+$, 553.2722; $C_{30}H_{41}N_2O_6$, requires *M*, 553.2729); ν_{max} 2952, 2855, 1711, 1686, 1527, 1451, 1412, 1353, 1252, 1195, 1149, 1120, 1093, 1032, 995, 937, 837, 810, 777, 758, 739, 375 and 621 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (3 H, s, $OSiCH_3$),

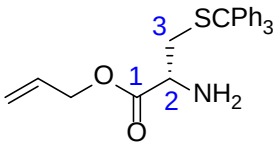
0.02 (3 H, s, $OSiCH_3$), 0.77 (9 H, s, $OSiC(CH_3)_3$), 1.04 (3 H, m, 4-H_3), 1.82-2.13 (4 H, m, 4'-H_2 and 3'-H_2), 3.42-3.50 (2 H, m, 5'-H_2), 4.15 (1 H, m, 2'-H), 4.28-4.40 (5 H, m, fluorenyl-*H*, fluorenyl-CH_2, 2-H and 3-H), 7.22 (2 H, m, Ar-H), 7.29 (2 H, m, Ar-H), 7.50 (2 H, m, Ar-H) and 7.67 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) -5.25, -4.67, 14.46, 14.89, 18.72, 19.86, 25.60, 29.74, 30.33, 46.12, 47.16, 66.81, 67.94, 114.78, 120.16, 125.09, 127.09, 127.47, 127.76, 141.32, 148.51, 159.70 and 171.26; *m*/*z* (ES+) 551 ($[M-1]^-$, 100%).

Allyl (2*R*)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-tritylsulfanyl-propanoate[137] (2.59)



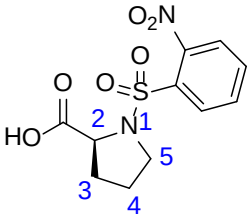
Fmoc-Cys(Trt)-OH (1.0 g, 1.71 mmol) was dissolved in DMSO (20 mL). To the reaction mixture was added allyl bromide (148 mg, 2.05 mmol) followed by $NaHCO_3$ (287 mg, 3.14 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was partitioned between water (20 mL) and Et_2O (30 mL). Organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (50:50) gave the *title compound* **2.59** (890 mg, 83%) as a white solid. R_f 0.5 (50:50 petrol-ether). $[\alpha]_D^{20}$ +22.2 (c 1.8 in $CHCl_3$); m.p. = 59 - 61°C; ν_{max} 3326, 3056, 2946, 1720, 1594, 1491, 1445, 1333, 1249, 1183, 1034, 987, 934, 851, 739, 699 and 620 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.69 (2 H, dt, *J* 6.6 and 12.6, 3-H_2), 4.26 (1 H, t, *J* 6.9, 2-H), 4.39 (3 H, m, fluorenyl-*H* and fluorenyl-CH_2), 4.65 (2 H, m, OCH_2CHCH_2), 5.28 (2 H, d, *J* 11.4, OCH_2CHCH_2), 5.33 (1 H, d, *J* 17.0, NH), 5.90 (1 H, m, OCH_2CHCH_2), 7.22-7.35 (11 H, m, Ar-H), 7.41-7.43 (8 H, m, Ar-H), 7.64 (2 H, m, Ar-H) and 7.80 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 34.07, 47.09, 52.96, 66.31, 67.04, 67.17, 118.85, 120.00, 125.19, 126.94, 127.12, 127.76, 128.06, 128.69, 129.52, 131.41, 141.29, 143.74, 143.89, 144.25, 155.60 and 170.24; *m*/*z* (ES+) 648 ($[M+23]^+$, 30%).

Allyl (2*R*)-2-amino-3-tritylsulfanyl-propanoate (2.60)



Fmoc-protected amine **2.59** (890 mg, 1.42 mmol) was dissolved DMF (15 mL). To the reaction mixture was added piperidine (242 mg, 2.85 mmol). Reaction was stirred at room temperature for 16 h. Reaction was partitioned between water (20 mL) and ether (20 mL). Organic layer was concentrated under reduced pressure. Column chromatography of the residue eluting with DCM-MeOH-NH_3 (95:5:0.5) gave the *title compound* **2.60** (540 mg, 94%) as a colourless oil. R_f 0.5 (95:5:0.5 DCM-MeOH-NH_3). $[\alpha]_D^{20}$ +42.0 (c 2.0 in $CHCl_3$); (Found $[M+H]^+$, 404.1678; $C_{25}H_{26}NO_2S$, requires *M*, 404.1679); ν_{max} 3380, 3056, 3029, 2934, 1735, 1594, 1488, 1444, 1318, 1242, 1172, 1083, 1033, 990, 928, 844, 741, 698, 675 and 618 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.47 (2 H, ddd, *J* 4.7, 12.4 and 17.3, 3-H_2), 3.15 (1 H, dd, *J* 4.9 and 7.9, 2-H), 4.49 (2 H, d, *J* 7.2, OCH_2CHCH_2), 5.17 (2 H, m, OCH_2CHCH_2), 5.79 (1 H, m, OCH_2CHCH_2), 7..21 (10 H, m, Ar-H) and 7.36 (5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 15.30, 36.94, 53.92, 65.88, 118.49, 126.80, 127.98, 129.60, 131.75, 144.55 and 173.47; *m*/*z* (ES+) 807 ($[2M+1]^+$, 100%).

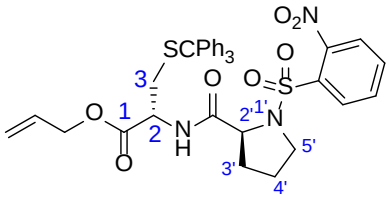
(2*S*)-1-(2-nitrophenyl)sulfonylpyrrolidine-2-carboxylic acid[136] (2.58)



To a solution of L-proline (500 mg, 4.34 mmol) in H_2O (20 mL) was added 2-nitrobenzenesulfonyl chloride (1.44 g, 6.51 mmol) followed by $NaHCO_3$ (730 mg, 8.69 mmol). Reaction was stirred at room temperature for 16 h. Reaction was concentrated and acidified using 2 N aqueous HCl and partitioned between H_2O (20 mL) and ether (30 mL). Organic layer was concentrated under reduced pressure. Column chromatography of the residue eluting with 100% ether with 1%

formic acid gave the *title compound* **2.58** (1.1 g, 85%) as a colourless oil. R_f 0.5 (100% ether with 1% formic acid). $[\alpha]_D^{20}$ -74.5 (c 2.9 in $CHCl_3$); (Found $[M-H]^-$, 299.0340; $C_{11}H_{11}N_2O_6$, requires *M*, 299.0343); ν_{max} 3101, 2981, 2946, 1714, 1542, 1370, 1347, 1159, 1081, 1018, 917, 852, 777, 729 and 653 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.05 (2 H, m, 4-H_2), 2.21 (1 H, m, 3-H_a), 2.34 (1 H, m, 3-H_b), 3.55 (1 H, m, 5-H_a), 3.69 (1 H, m, 5-H_b), 4.65 (1 H, dd, *J* 3.0 and 8.6, 2-H), 7.67 (1 H, m, Ar-H), 7.74 (2 H, m, Ar-H) and 8.12 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 24.51, 30.97, 48.50, 60.71, 124.18, 131.15, 131.74, 132.55, 133.76, 148.11 and 177.17; *m/z* (ES-) 299 ($[M-1]^-$, 100%).

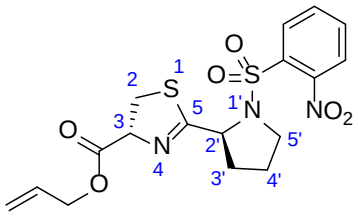
Allyl (2*R*)-2-[[(2*S*)-1-(2-nitrophenyl)sulfonylpyrrolidine-2-carbonyl]amino]-3-tritylsulfanyl-propanoate (2.61)



A solution of carboxylic acid **2.58** (75 mg, 0.25 mmol) in DMF (2.0 mL) was treated with HATU (132 mg, 0.35 mmol) and HOBt (14 mg, 0.10 mmol). Amine **2.60** (100 mg, 0.25 mmol) in DMF (2.0 mL) was added followed by DIPEA (128 mg, 0.99 mmol). Reaction reaction mixture was stirred at room temperature for 16 h. Reaction was partitioned between aqueous NH_4Cl (5 mL) and ether (10 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with ether (100%) gave the *title compound* **2.61** (132 mg, 77%) as a white foam. R_f 0.5 (100% ether). $[\alpha]_D^{20}$ -100.0 (c 1.8 in $CHCl_3$); (Found $[M+Na]^+$, 708.1808; $C_{36}H_{35}N_3O_7S_2Na$, requires *M*, 708.1809); ν_{max} 3373, 3055, 3021, 2949, 1741, 1677, 1514, 1509, 1489, 1443, 1343, 1160, 1125, 1080, 984, 926, 851, 741, 699 and 653 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.90 (2 H, m, 4'-H_2), 2.40 (1 H, m, 3'-H_a), 2.17 (1 H, m, 3'-H_b), 2.49 (1 H, m, 3-H_2), 3.59 (2 H, m, 5'-H_2), 4.23 (1 H, m, 2-H), 4.38 (1 H, dd, *J* 2.3 and 8.3, 2'-H), 4.45 (2 H, m, O*C*H_2CHCH$_2$), 5.18 (2 H, m, OCH$_2$CHC*H*$_2$), 5.75 (1 H, m, OCH$_2$C*H*CH$_2$), 6.93 (1 H, d, *J* 7.8, NH), 7.13-7.30 (15 H, m, Ar-H), 7.56 (3 H, m, Ar-H) and 8.00 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 24.33, 31.37, 33.58, 49.30, 51.46, 62.32, 66.18, 66.73, 118.75,

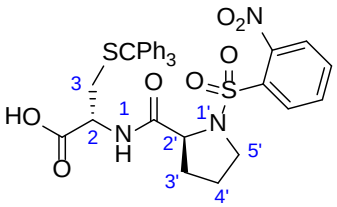
124.71, 126.92, 128.06, 129.47, 131.41, 131.49, 131.56, 132.01, 132.69, 134.09, 144.15, 169.23, and 170.77; *m*/*z* (ES+) 708 ([M+23]$^+$, 100%).

Allyl (4*R*)-2-[(2*S*)-1-(2-nitrophenyl)sulfonylpyrrolidin-2-yl]-4,5-dihydrothiazole-4-carboxylate (2.62)



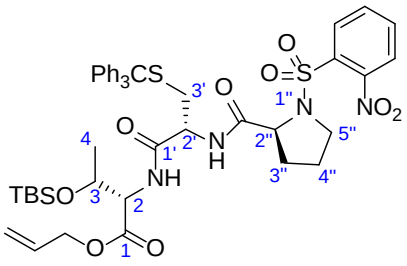
Triflic anhydride (80 mg, 0.28 mmol) was added slowly to a solution of triphenylphosphine oxide (158 mg, 0.57 mmol) in dry DCM (2 mL) at 0 ^{o}C. The reaction mixture was stirred for 10 min at 0 ^{o}C. Then to the reaction mixture was added protected cysteine depeptide **2.61** (130 mg, 0.19 mmol). The reaction was monitored by TLC. After 2 h, reaction was quenched with 10% aqueous $NaHCO_3$ (5 mL). The aqueous layer was extracted with DCM, and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with ether (100%) gave the *title compound* **2.62** as a colourless oil (65 mg, 80%) which gradually turned yellow on standing at RT. R_f 0.3 (100% ether). $[\alpha]_D^{20}$ +53.3 (c 0.9 in $CHCl_3$); (Found $[M+H]^+$, 426.0788; $C_{17}H_{20}N_3O_6S_2$, requires *M*, 426.0789); ν_{max} 3095, 2980, 2950, 2882, 1739, 1617, 1541, 1439, 1353, 1163, 1126, 1078, 994, 939, 852, 778, 742, 729 and 654 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.82-2.22 (4 H, m, 3'-H_2 and 4'-H_2), 3.35 (2 H, m, 2-H_2), 3.60 (2 H, m, 5'-H_2), 4.65 (2 H, dt, *J* 1.3 and 5.8, OCH_2CHCH$_2$), 4.91 (1 H, m, 2'-H), 4.97 (1 H, dt, *J* 1.3 and 9.1, 3-H), 5.23 (1 H, m, OCH$_2$CHCH_a), 5.32 (1 H, m, OCH$_2$CHCH_b), 5.90 (1 H, m, OCH$_2$C*H*CH$_2$), 7.60 (3 H, m, Ar-H) and 8.01 (1 H, m, Ar-H); *m*/*z* (ES+) 426 ([M+1]$^+$, 100%).

(2*R*)-2-[[(2*S*)-1-(2-Nitrophenyl)sulfonylpyrrolidine-2-carbonyl]amino]-3-tritylsulfanyl-propanoic acid (2.64)



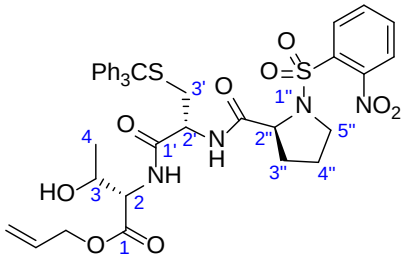
Allyl ester **2.62** (231 mg, 0.34 mmol) and palladium tetrakis(triphenylphosphine) (39 mg, 0.03 mmol) were dissolved in THF (4 mL). To this reaction mixture was added *N*-methylaniline (72 mg, 0.67 mmol). The reaction was stirred at room temperature for 3 h. The reaction was concentrated under reduced pressure. To the residue was added ether/petrol mixture (50 mL, ether-petrol 1:3), the resulting solid was washed thoroughly with petrol to give the *title compound* **2.64** (208 mg, 95%) as a yellow foam. $[\alpha]_D^{20}$ -134.3 (c 2.8 in $CHCl_3$); m.p. = 96 ^oC; (Found $[M-H]^-$, 644.1532; $C_{33}H_{30}N_3O_7S_2$, requires *M*, 644.1530); ν_{max} 3360, 3088, 3065, 3033, 2892, 1730, 1634, 1593, 1541, 1489, 1440, 1366, 1301, 1161, 1124, 1067, 1033, 1000, 851, 741, 677 and 653 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.00 (3 H, m, 4'-H_2 and OH), 2.23 (2 H, m, 3'-H_2), 2.59 (2 H, m, 3-H_2), 3.71 (2 H, m, 5'-H_2), 4.11 (1 H, dt, *J* 4.8 and 7.3, 2-H), 4.48 (1 H, dd, *J* 2.5 and 8.6, 2'-H), 7.10 (1 H, d, *J* 7.6, NH), 7.23-7.41 (15 H, m, Ar-H), 7.59 (3 H, m, Ar-H) and 8.07 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 20.70, 24.25, 31.70, 32.89, 51.43, 62.08, 66.96, 127.03, 128.16, 128.70, 129.45, 131.25, 132.32, 134.68, 135.74, 143.99, 148.12, 171.58, and 176.76; *m/z* (ES-) 644 ($[M-1]^-$, 100%); 680 ($[M+35]^-$, 50%).

Allyl (2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-[[(2*R*)-2-[[(2*S*)-1-(2-nitrophenyl)sulfonylpyrrolidine-2-carbonyl]amino]-3-tritylsulfanyl-propanoyl]amino]butanoate (2.65)



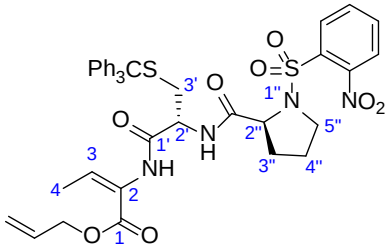
A solution of carboxylic acid **2.64** (20 mg, 0.03 mmol) in DMF (1.0 mL) was treated with HATU (17 mg, 0.04 mmol) and HOBt (2 mg, 0.01 mmol). Amine (9 mg, 0.03 mmol) was added followed by DIPEA (16 mg, 0.12 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was partitioned between aqueous NH_4Cl (3 mL) and ether (6 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (20:80) gave the *title compound* **2.65** (18 mg, 67%) as a white foam. R_f 0.3 (20:80 petrol-ether). $[\alpha]_D^{20}$ -36.7 (c 1.2 in $CHCl_3$); m.p. = 77 ^oC; (Found $[M+H]^+$, 901.3336; $C_{46}H_{57}N_4O_9SiS_2$, requires *M*, 901.3331); ν_{max} 2950, 2929, 2855, 1740, 1670, 1543, 1509, 1492, 1443, 1362, 1316, 1251, 1192, 1161, 1126, 1087, 986, 936, 837, 776, 742, 699 and 653 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.06 (3 H, s, $OSiCH_3$), 0.00 (3 H, s, $OSiCH_3$), 0.80 (9 H, s, $OSi(CH_3)_3$) 1.03 (3 H, d, *J* 6.3, 4-H_3), 1.89 (2 H, m, 4''-H_2), 2.01-2.20 (2 H, m, 3''-H_2), 2.59 (2 H, m, 3'-H_2), 3.57 (2 H, m, 5''-H_2), 3.82 (1 H, dt, *J* 5.6 and 8.3, 2'-H), 4.35 (3 H, m, 2-H, 2''-H and 3-H), 4.51 (2 H, ddt, *J* 1.3, 5.8 and 10.9, OCH_2CHCH_2), 5.16 (1 H, m, OCH_2CHCH_a), 5.25 (1 H, m, OCH_2CHCH_b), 5.80 (1 H, m, OCH_2CHCH_2), 6.47 (1 H, d, *J* 9.6, NH), 6.78 (1 H, d, *J* 7.6, NH), 7.17-7.40 (15 H, m, Ar-H), 7.59 (3 H, m, Ar-H) and 8.03 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) -5.21, -4.34, 17.89, 20.65, 24.40, 25.68, 31.27, 33.45, 49.38, 52.38, 58.07, 62.26, 66.07, 67.08, 68.71, 119.01, 124.60, 126.88, 128.11, 129.57, 131.18, 131.55, 131.58, 131.74, 134.08, 144.32, 148.41, 169.74, 169.76 and 170.74; *m/z* (ES+) 923 ($[M+23]^+$, 100%).

Allyl (2*S*)-3-hydroxy-2-[[(2*R*)-2-[[(2*S*)-1-(2-nitrophenyl)sulfonylpyrrolidine-2-carbonyl]amino]-3-tritylsulfanyl-propanoyl]amino]butanoate (2.66)



To a solution of silyl-protected alcohol **2.65** (85mg, 0.09 mmol) in THF (4 mL) was added triethylamine trishydrofluoride (152 mg, 0.94 mmol). Reaction mixture was stirred at room temperature for 48 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with ether-methanol (95:5) gave *the title compound* **2.66** (46 mg, 62%) as a white solid. R_f 0.5 (95:5 ether-methanol). $[\alpha]_D^{20}$ -70.0 (c 1.6 in $CHCl_3$); m.p. = 95 ^oC; (Found $[M+H]^+$, 787.2458; $C_{40}H_{43}N_4O_9S_2$, requires *M*, 787.2466); ν_{max} 3371, 2973, 2942, 1735, 1662, 1542, 1517, 1442, 1371, 1348, 1275, 1190, 1162, 1126, 1080, 1068, 991, 930, 851, 772, 741, 699 and 637 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.05 (3 H, d, *J* 6.6, 4-H_3), 1.83 (2 H, m, 4''-H_2), 2.04 (2 H, m, 3''-H_2), 2.53 (1 H, dd, *J* 4.7 and 12.9, 3'-H_a), 2.63 (1 H, dd, *J* 8.8 and 12.9, 3'-H_b), 3.53 (2 H, m, 5''-H_2), 3.97 (1 H, dt, *J* 5.0 and 8.5, 2'-H), 4.15 (1 H, m, 3-H), 4.24 (1 H, dd, *J* 3.2 and 8.5, 2''-H), 4.37 (1 H, dd, *J* 3.2 and 9.1, 2-H), 4.53 (2 H, d, *J* 5.7, OC*H*$_2$CHCH$_2$), 5.12 (1 H, d, *J* 10.4, OCH$_2$CHC*H*$_a$), 5.22 (1 H, d, *J* 17.0, OCH$_2$CHC*H*$_b$), 5.78 (1 H, m, OCH$_2$C*H*CH$_2$), 6.66 (1 H, d, *J* 9.1, NH), 6.80 (1 H, d, *J* 8.2, NH), 7.12-7.32 (15 H, m, Ar-H), 7.53-7.65 (3 H, m, Ar-H) and 7.97 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 20.01, 24.46, 30.33, 31.48, 33.13, 52.58, 57.70, 62.35, 66.10, 67.08, 68.38, 118.81, 124.56, 126.96, 128.14, 129.52, 130.00, 131.53, 131.76, 132.01, 134.58, 144.26, 148.49, 169.71, 169.93 and 171.00; *m/z* (ES+) 809 ($[M+23]^+$, 100%).

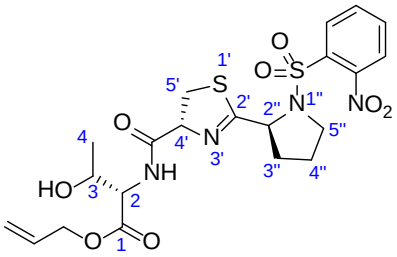
Allyl (*E*)-2-[[(2*R*)-2-[[(2*S*)-1-(2-nitrophenyl)sulfonylpyrrolidine-2-carbonyl]amino]-3-tritylsulfanyl-propanoyl]amino]but-2-enoate (2.67)



A solution of secondary alcohol **2.66** (45 mg, 0.06 mmol), EDC (18 mg, 0.11 mmol) and $CuCl_2$ (1 mg, 0.01 mmol) in anhydrous toluene (2 mL) was stirred at 80 ^oC under N_2 for 30 min. The reaction was quenched with H_2O and the mixture was extracted with EtOAc (5 mL). Combined organic layer was dried

over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with 100% ether gave the *title compound* **2.67** (46 mg, 62%) as white foam. R_f 0.3 (100% ether). $[\alpha]_D^{20}$ -87.6 (c 1.0 in $CHCl_3$); m.p. = 92 ^oC; (Found $[M+Na]^+$, 791.2183; $C_{40}H_{40}N_4O_8S_2Na$, requires *M*, 791.2180); ν_{max} 3360, 3334, 2953, 2937, 1668, 1593, 1542, 1442, 1345, 1254, 1160, 1125, 1079, 997, 926, 851, 773, 742, 699 and 653 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.87 (2 H, m, 4''-H_2), 1.99 (3 H, d, *J* 7.6, 4-H_3), 2.12 (2 H, m, 3''-H_2), 2.51 (2 H, m, 3'-H_2), 3.57 (2 H, t, *J* 6.8, 5''-H_2), 3.84 (1 H, q, *J* 7.8, 2'-H), 4.30 (1 H, dd, *J* 3.0 and 8.3, 2''-H), 4.63 (2 H, d, *J* 6.1, OCH_2CHCH_2), 5.20 (1 H, m, OCH_2CHCH_a), 5.28 (1 H, m, OCH_2CHCH_b), 5.88 (1 H, m, OCH_2CHCH_2), 6.80 (1 H, q, *J* 7.8, 3-H), 6.83 (1 H, d, *J* 8.3, NH), 7.13-7.34 (15 H, m, Ar-H), 7.53 (3 H, m, Ar-H), 7.73 (1 H, br s, NH), and 7.93 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.30, 24.39, 31.58, 32.83, 49.67, 52.94, 62.12, 66.10, 67.09, 119.02, 124.65, 125.50, 126.94, 128.12, 129.10, 129.52, 130.78, 131.34, 131.71, 131.83, 134.46, 144.24, 148.19, 163.40, 167.65 and 171.12; *m/z* (ES+) 791 ($[M+23]^+$, 100%).

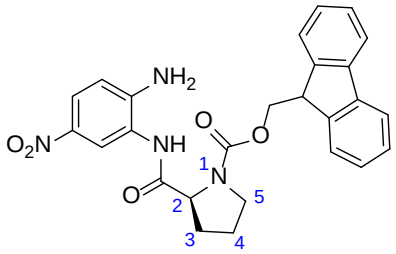
Allyl (2*S*)-3-hydroxy-2-[[(4*R*)-2-[(2*S*)-1-(2-nitrophenyl)sulfonylpyrrolidin-2-yl]-4,5-dihydrothiazole-4-carbonyl]amino]butanoate (2.68)



Triflic anhydride (94 mg, 0.33 mmol) was added slowly to a solution of triphenylphosphine oxide (186 mg, 0.67 mmol) in dry DCM (2 mL) at 0 ^oC. The reaction mixture was stirred for 10 min at 0 ^oC. Then to the reaction mixture was added cysteine depeptide **2.65** (200 mg, 0.22 mmol) in DCM (2 mL). Reaction was stirred at room temperature for 2 h. The progress of reaction was monitored by TLC. Reaction was quenched with 10% aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (15 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with ether-methanol (97:3) gave *the title compound* **2.68** (79 mg, 68%) as

white foam. R_f 0.4 (97:3 ether-methanol). (Found $[M+Cl]^-$, 561.0884; $C_{21}H_{26}N_4O_8S_2$, requires *M*, 561.0886); ν_{max} 3397, 3271, 3056, 3022, 2977, 1744, 1677, 1619, 1574, 1542, 1511, 1484, 1436, 1371, 1310, 1269, 1181, 1117, 1070, 996, 925, 852, 752, 718 and 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.11 (3 H, d, *J* 6.56, 4-H_3), 1.86 (1H, m, 3''-H_a), 2.05 (2 H, m, 4''-H_2), 2.18 (1 H, m, 3''-H_b), 2.59 (1 H, d, *J* 8.07, NH), 3.45 (2 H, m, 5'-H_2), 3.62 (2 H, m, 5''-H_2), 4.24 (1 H, m, 3-H), 4.59 (3 H, m, OC*H*2CHCH_2 and 2-H), 4.83 (1 H, m, 2''-H), 5.02 (1 H, dd, *J* 5.8 and 10.3, 4'-H), 5.20 (2 H, m, OCH_2CHCH_2), 5.83 (1 H, m, OCH_2CHCH_2), 7.64 (3 H, m, Ar-H) and 7.96 (1 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 19.92, 24.82, 30.34, 32.63, 36.35, 49.48, 57.69, 61.55, 66.07, 68.49, 118.66, 124.21, 131.36, 131.65, 131.82, 133.09, 134.09, 148.42, 170.12, 171.37 and 178.44; *m*/*z* (ES+) 507 ($[M+35]^-$, 100%).

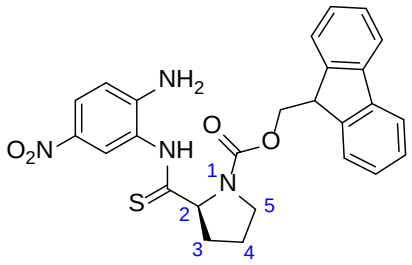
9H-Fluoren-9-ylmethyl (2*S*)-2-[(2-amino-5-nitro-phenyl)carbamoyl]pyrrolidine-1-carboxylate (2.76)



N-methylmorpholine (600 mg, 5.93 mmol) was added to a solution of Fmoc-protected L-proline **2.74** (1.0 g, 2.96 mmol) in THF (25 mL) at -20 ^oC, followed by dropwise addition of isobutyl chloroformate (405 mg, 2.96 mmol). The mixture was stirred for 10 min, 4-nitro-1,3-phenylenediamine **2.75** (454 mg, 2.96 mmol) was added, and the resulting slurry was stirred at room temperature for 16 h. The precipitate was filtered off and the filtrate was concentrated. The residue was dissolved in EtOAc (100 mL), and the solution washed successively with aqueous $NaHCO_3$, and brine then dried and evaporated to dryness. Crystallization of the residue from EtOAc/hexane (1:5) afforded the *title compound* **2.76** (1.0 g, 72%) as yellow solid. R_f 0.3 (80:20 petrol-ether). $[\alpha]_D^{20}$ -72.0 (c 2.0 in $CHCl_3$); m.p. = 216 ^oC; (Found $[M+H]^+$, 473.1813; $C_{26}H_{25}N_4O_5$, requires *M*, 473.1820); ν_{max} 3433, 3351, 3235, 2980, 1725, 1676, 1648, 1591,

1514, 1491, 1423, 1330, 1255, 1159, 1127, 1093, 1042, 990, 896, 757, and 643 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.99-2.17 (3 H, m, 3-H_a and 4-H_2), 2.49 (1 H, m, 3-H_b), 3.54 (2 H, m, 5-H_2), 4.28 (1 H, t, *J* 6.8, fluorenyl-*H*), 4.44 (1 H, m, 2-H), 4.52 (2 H, d, *J* 6.3, fluorenyl-C*H*$_2$), 4.74 (2 H, br s, NH_2), 6.70 (1 H, d, *J* 9.1, Ar-H), 7.31 (2 H, m, Ar-H), 7.42 (2 H, m, Ar-H), 7.60 (2 H, m, Ar-H), 7.80 (2 H, d, *J* 7.6, Ar-H), 7.99 (1 H, dd, *J* 6.3 and 8.8, Ar-H), 8.20 (1 H, br s, NH) and 8.30 (1 H, br s, Ar-H); δ_C (100 MHz, $CDCl_3$) 14.22, 21.09, 47.22, 60.44, 61.05, 68.03, 114.64, 120.15, 121.36, 122.63, 123.81, 124.90, 127.23, 127.97, 141.35, 143.38, 143.63, 147.31, 171.22 and 193.61; *m*/*z* (ES+) 495 ($[M+23]^+$, 100%).

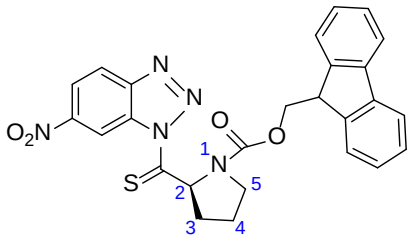
9H-Fluoren-9-ylmethyl (2*S*)-2-[(2-amino-5-nitro-phenyl)carbamothioyl]pyrrolidine-1-carboxylate (2.77)



Under a flow of nitrogen, P_4S_{10} (470 mg, 1.06 mmol) was mixture with Na_2CO_3 (112 mg, 1.06 mmol) in THF (25 mL). The mixture was stirred for 1 h and then cooled to 0 ^oC. To this clear solution was added anilide **2.76** (1.0 g, 2.12 mmol), and the reaction mixture was stirred at 0 ^oC for 30 min and at room temperature for 2.5 h. Solvent was removed under reduced pressure. The residue was taken up in 2:1 EtOAc/hexane (60 mL) and washed with 5% aqueous $NaHCO_3$ (30 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-EtOAc (50:50) gave the *title compound* **2.77** (915 mg, 89%) as yellow foam. R_f 0.5 (50:50 petrol-EtOAc). $[\alpha]_D^{20}$ -77.3 (c 2.0 in $CHCl_3$); (Found $[M-H]^-$, 487.1448; $C_{26}H_{23}N_4O_4S$, requires *M*, 487.1445); ν_{max} 3441, 3346, 3231, 2980, 2900, 1731, 1682, 1633, 1603, 1516, 1493, 1478, 1415, 1372, 1312, 1239, 1132, 1091, 1042, 987, 938, 826, 758, 739, 690, and 641 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.05 (2 H, br m, 4-H_2), 2.35 (2 H, br m, 3-H_2), 3.49 (2 H, m, 5-H_2), 4.17 (1 H, m,

fluorenyl-*H*), 4.44 (2 H, br m, fluorenyl-CH_2), 4.66 (1 H, br m, 2-H), 4.85 (2 H, br s, NH_2), 6.64 (1 H, d, *J* 8.8, Ar-H), 7.22 (2 H, m, Ar-H), 7.32 (2 H, m, Ar-H), 7.51 (2 H, d, *J* 7.6, Ar-H), 7.71 (2 H, d, *J* 7.8, Ar-H), 8.00 (2 H, m, Ar-H) and 8.77 (1 H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.22, 21.10, 47.30, 60.44, 67.85, 68.58, 120.16, 124.87, 124.91, 125.37, 125.76, 127.14, 127.25, 127.95, 141.37, 141.45, 143.38, 143.63, 171.22 and 203.12; *m*/*z* (ES-) 487 ([M-1]$^-$, 100%).

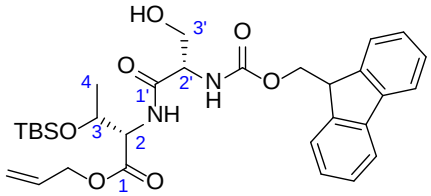
9H-fluoren-9-ylmethyl (2*S*)-2-(6-nitrobenzotriazole-1-carbothioyl)pyrrolidine-1-carboxylate (2.78)



Sodium nitrite (194 mg, 2.81 mmol) was added in one portion to a stirred solution of the thioanilide **2.77** (915 mg, 1.87 mmol) in glacial acetic acid (15 mL, diluted with 5% water) at 0^{o}C. The resulting mixture was stirred at 0 ^{o}C for 30 min and the ice water (100 mL) was added and the resulting suspension was washed with cold EtOAc (100 mL). The precipate was filtered to give the *title compound* **2.78** (457 mg, 99%) as an orange solid. This was a 50:50 mixture two rotamers. $[\alpha]_D^{20}$ -22.2 (c 2.0 in $CHCl_3$); m.p. = 175 ^{o}C; (Found $[M+Na]^+$, 522.1207; $C_{26}H_{21}N_5O_4SNa$, requires *M*, 522.1207); ν_{max} 2959, 1690, 1533, 1467, 1438, 1420, 1377, 1361, 1332, 1254, 1199, 1163, 1129, 1053, 983, 953, 886, 833, 794, 769, 742, 730, 681, and 609 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 50:50 mixture of two rotamers) 1.91 (2 H, m, 4-H_2), 2.20 (1 H, m, 3-H_a), 2.47 (0.5 H, m, 3-H_b), 2.71 (0.5 H, m, 3-H_b), 3.42 (0.5 H, m, 2-H), 3.73 (2 H, m, 5-H_2), 3.99 (0.5 H, m, 2-H), 4.61 (0.5 H, m, fluorenyl-*H*), 4.78 (0.5 H, dd, *J* 4.0 and 10.9, fluorenyl-*H*), 5.66 (0.5 H, m, Ar-H), 6.27 (0.5 H, m, Ar-H), 6.84 (1 H, m, 5-H_2), 7.02 (1 H, m, 5-H_2), 7.13 (2 H, m, Ar-H), 7.34-7.49 (4 H, m, Ar-H), 7.69 (0.5 H, m, Ar-H), 7.82 (0.5 H, m, Ar-H), 8.37 (1 H, m, Ar-H), 8.53 (1 H, m, Ar-H), 9.54 (0.5 H, m, Ar-H) and 9.73 (0.5 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$, a mixture of two rotamers) 22.57, 23.83, 33.57, 34.07, 47.15, 47.33, 62.86, 62.90, 65.29, 67.25,

67.52, 68.19, 113.00, 113.41, 119.15, 119.27, 120.06, 121.17, 121.40, 122.06, 122.12, 123.92, 124.08, 125.09, 125.26, 126.86, 127.22, 127.78, 131.98, 140.94, 141.40, 143.58, 143.64, 144.09, 148.74, 149.44, 153.85, 154.66, 206.07 and 206.99; *m*/*z* (ES+) 522 ($[M+23]^+$, 100%).

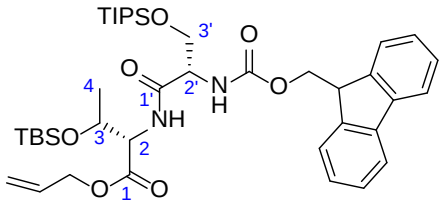
Allyl (2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-[[(2*S*)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-hydroxy-propanoyl]amino]butanoate (2.80)



A solution of Fmoc-protected L-serine **2.79** (360 mg, 1.10 mmol) in DMF (10 mL) was treated with HATU (586 mg, 1.54 mmol) and HOBt (60 mg, 0.44 mmol). Amine (300 mg, 1.10 mmol) in DMF (5 mL) was added followed by DIPEA (568 mg, 4.39 mmol). Reaction mixture was stirred at room temperature for 16 h. The reaction was partitioned between aqueous NH_4Cl (40 mL) and ether (60 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (20:80) gave the *title compound* **2.80** (620 mg, 97%) as a pale yellow oil. R_f 0.3 (20:80 petrol-ether). $[\alpha]_D^{20}$ -7.4 (c 2.0 in $CHCl_3$); (Found $[M+H]^+$, 583.2837; $C_{31}H_{43}N_2O_7Si$, requires *M*, 583.2835); ν_{max} 3406, 3338, 2931, 2883, 2857, 1731, 1668, 1518, 1500, 1251, 1202, 1148, 1092, 1023, 969, 937, 838, 777, 759, 740 and 651 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.00 (3 H, s, $OSiCH_3$), 0.06 (3 H, s, $OSiCH_3$), 0.86 (9 H, s, $OSiC(CH_3)_3$), 1.23 (3 H, d, *J* 6.3, 4-H_3), 3.34 (1 H, m, 3-H_a), 3.70 (1 H, m, 3-H_b), 4.06 (1 H, m, OH), 4.24 (1 H, m, 3-H), 4.41 (3 H, m, fluorenyl-*H* and fluorenyl-CH_2), 4.52 (2 H, m, 2-H and 2'-H), 4.60 (1 H, m, OCH_aCHCH_2), 4.68 (1 H, m, OCH_bCHCH_a), 5.34 (2 H, m, OCH_2CHCH_2), 5.80 (1 H, m, OCH_2CHCH_2), 5.93 (1 H, s, NH), 6.85 (1 H, m, NH), 7.33 (2 H, t, *J* 7.3, Ar-H), 7.42 (2 H, t, *J* 7.6, Ar-H), 7.61 (2 H, d, *J* 7.1, Ar-H), and 7.79 (2 H, d, *J* 7.6, Ar-H),; δ_C (100 MHz, $CDCl_3$-5.36, -4.29, 17.80, 21.26, 25.57, 47.11, 55.47,

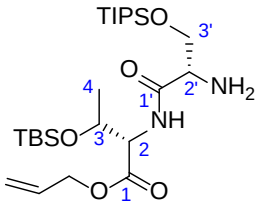
58.68, 63.44, 66.74, 67.30, 68.13, 119.64, 120.02, 125.16, 127.11, 127.76, 131.15, 141.33, 169.84 and 173.44; *m/z* (ES+) 605 ($[M+23]^+$, 100%).

Allyl (2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-[[(2*S*)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-triisopropylsilyloxy-propanoyl]amino]butanoate (2.81)



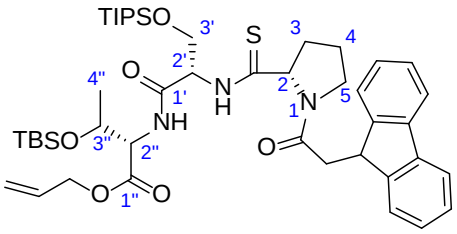
To a solution of alcohol **2.80** (796 mg, 1.37 mmol) in DCM (20 mL) was added TIPSOTf (628 mg, 2.05 mmol) and followed by 2,6-lutidine (293 mg, 2.73 mmol) at room temperature. The reaction mixture was stirred at room temperauture for 16 h. The reaction was concentrated and column chromatography of the residue eluting with petrol-ether (70:30) gave the *title compound* **2.81** (564 mg, 56%) as a colourless gum. R_f 0.3 (70:30 petrol-ether). $[\alpha]_D^{20}$ -18.7 (c 2.0 in $CHCl_3$); (Found $[M+H]^+$, 739.4170; $C_{40}H_{63}N_2O_7Si_2$, requires *M*, 739.4168); ν_{max} 3432, 3345, 3065, 2943, 2891, 2865, 1731, 1681, 1593, 1579, 1504, 1463, 1541, 1376, 1310, 1251, 1223, 1199, 1094, 996, 882, 836, 773, 739, 680 and 660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.05 (3 H, s, $OSiCH_3$), 0.00 (3 H, s, $OSiCH_3$), 0.80 (9 H, s, $OSiC(CH_3)_3$), 1.05 (21 H, m, OSi^iPr_3), 1.15 (3 H, d, *J* 6.3, 4-H_3), 3.83 (2 H, dd, *J* 5.6 and 9.6, 3'-H_2), 4.21 (2 H, m, fluorenyl-CH_2), 4.29 – 4.43 (4 H, m, 2-H, 2'H, fluorenyl-*H* and 3-H), 4.58 (2 H, m, OCH_2CHCH_2), 5.24 (2 H, m, OCH_2CHCH_2), 5.69 (1 H, m, OCH_2CHCH_2), 5.87 (1 H, m, NH), 7.09 (1 H, m, NH), 7.27 (2 H, t, *J* 7.3, Ar-H), 7.37 (2 H, t, *J* 7.1, Ar-H), 7.55 (2 H, m, Ar-H) and 7.74 (2 H, d, *J* 7.6, Ar-H); δ_C (125MHz, DMSO, 117°C) 11.82, 12.54, 17.73, 17.87, 17.94, 17.98, 18.01, 18.05, 24.53, 25.68, 25.94, 47.07, 58.05, 66.11, 120.02, 120.18, 125.18, 127.09, 127.76, 131.53, 136.58, 141.29 and 157.67; *m/z* (ES+) 761 ($[M+23]^+$, 100%).

Allyl (2*S*)-2-[[(2*S*)-2-amino-3-triisopropylsilyloxy-propanoyl]amino]-3-[*tert*-butyl(dimethyl)silyl]oxy-butanoate (2.82)



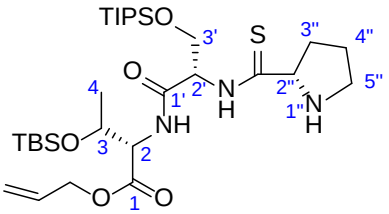
Fmoc-protected amine **2.81** (564 mg, 0.74 mmol) was dissolved DMF (10 mL). To the reaction mixture was added piperidine (130 mg, 1.53 mmol). The reaction was stirred at room temperature for 16 h. Reaction was partitioned between H_2O (20 mL) and EtOAc (20 mL). Organic layer was concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (20:80) gave the *title compound* **2.82** (340 mg, 89%) as a colourless gum. This was a 50:50 mixture of two rotamers. R_f 0.5 (20:80 petrol-ether). $[\alpha]_D^{20}$ +26.6 (c 2.0 in $CHCl_3$); (Found $[M+H]^+$, 517.3488; $C_{25}H_{53}N_2O_5Si_2$, requires *M*, 517.3488); ν_{max} 3376, 2937, 2865, 1748, 1677, 1506, 1463, 1447, 1378, 1313, 1252, 1190, 1153, 1096, 1015, 935, 882, 837, 777, 757, 738 and 679 cm^{-1}; δ_H (500 MHz, $CDCl_3$, 50:50 mixture of two rotamers) 0.00 (1.5 H, s, $OSiCH_3$), 0.05 (1.5 H, s, $OSiCH_3$), 0.06 (1.5 H, s, $OSiCH_3$), 0.08 (1.5 H, s, $OSiCH_3$), 0.87 (4.5 H, s, $OSiC(CH_3)_3$), 0.90 (4.5 H, s, $OSiC(CH_3)_3$), 1.06 (21 H, m, OSi^iPr_3), 1.15 (1.5 H, d, *J* 6.3, 4-H_3), 1.21 (1.5 H, d, *J* 6.6, 4-H_3), 1.71 (2 H, br s, NH_2), 3.56 (1 H, m, 3-H), 3.92 (1 H, m, 3'-H_a), 3.98 (1 H, dt, *J* 6.0 and 9.5, 3'-H_b), 4.54 (2 H, m, 2-H and 2'-H), 4.66 (2 H, m, OCH_2CHCH_2), 5.25 (1 H, m, OCH_2CHCH_a), 5.34 (1 H, m, OCH_2CHCH_b), 5.92 (1 H, m, OCH_2CHCH_2) and 8.23 (1 H, m, NH); δ_C (100 MHz, $CDCl_3$, 50:50 mixture of two rotamers) -5.43, -5.39, -5.26, -4.30, 11.88, 12.62, 14.34, 15.53, 17.83, 20.94, 21.19, 29.07, 56.79, 56.95, 57.01, 57.67, 57.76, 65.27, 65.48, 65.93, 66.00, 68.78, 69.21, 118.76, 131.66, 170.43 and 173.40; *m*/*z* (ES+) 517 ($[M+1]^+$, 100%).

9H-Fluoren-9-ylmethyl (2*S*)-2-[[(1*S*)-2-[[(1*S*)-1-allyloxycarbonyl-2-[*tert*-butyl(dimethyl)silyl]oxy-propyl]amino]-2-oxo-1-(triisopropylsilyloxymethyl)ethyl]carbamothioyl]pyrrolidine-1-carboxylate (2.83)



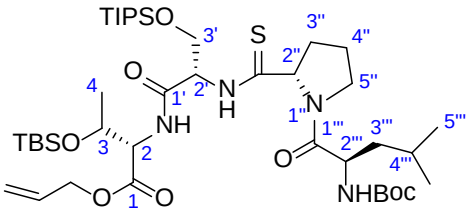
To a cool solution of thioacylating reagent **2.78** (340 mg, 0.66 mmol) in THF (6 mL) was added dropwise a solution of amine **2.82** (340 mg, 0.66 mmol) over 5 min. Reaction was stirred at room temperature for 6 h. Reaction was concentrated and column chromatography of the residue eluting with petrol-ether (50:50) gave the *title compound* **2.83** (375 mg, 60%) as a colourless gum, this was a mixture of two diastereoisomers. R_f 0.5 (50:50 petrol-ether). $[\alpha]_D^{20}$ +31.1 (c 1.2 in $CHCl_3$); (Found $[M-H]^-$, 850.4313; $C_{45}H_{68}N_3O_7Si_2S$, requires *M*, 850.4322); ν_{max} 3346, 3064, 2937, 2864, 1749, 1710, 1681, 1511, 1449, 1407, 1346, 1253, 1192, 1096, 991, 936, 882, 837, 776, 755, 738, 682 and 621 cm^{-1}; δ_H (400 MHz, $CDCl_3$, mixture of two diastereoisomers) 0.02 (3 H, s, $OSiCH_3$), 0.04 (3 H, s, $OSiCH_3$), 0.86 (9 H, s, $OSiC(CH_3)_3$), 1.00 – 1.24 (24 H, m, OSi^iPr_3 and 4''-H_3), 1.73 (1 H, m, 4-H_a), 1.94 (1 H, m, 4-H_b), 2.42 (1 H, m, 3-H_a), 2.61 (1 H, m, 3-H_b), 3.64 (2 H, m, 5-H_2), 3.93 (2 H, m, 3'-H_2), 4.12 (4 H, m, fluorenyl-*H*, fluorenyl-CH_2 and 3'-H), 4.49 – 4.70 (4 H, m, OCH_2CHCH_2, 2''-H and 2'-H), 4.84 (1 H, m, 2-H), 5.08 (1 H, m, NH), 5.26 (1 H, m, OCH_2CHCH_a), 5.34 (1 H, m, OCH_2CHCH_b), 5.92 (1 H , m, OCH_2CHCH_2), 6.98 (1 H, m, NH), 7.34 (2 H, m, Ar-H), 7.41 (2 H, m, Ar-H), 7.61 (2 H, m, Ar-H) and 7.77 (2 H, m, Ar-H); δ_C (100 MHz, $CDCl_3$, mixture of two diastereoisomers) -5.17, -4.42, 11.80, 12.45, 17.74, 17.99, 18.05, 25.73, 26.21, 44.78, 47.19, 54.95, 63.03, 66.05, 68.01, 68.76, 119.67, 119.99, 125.20, 125.48, 126.73, 127.06, 127.10, 127.73, 140.99, 141.28, 169.26, 203.59 and 204.92; *m/z* (ES-) 850 ($[M-1]^-$, 100%).

Allyl (2*S*)-3-[*tert*-butyl(dimethyl)silyl]oxy-2-[[(2*S*)-2-[[(2*S*)-pyrrolidine-2-carbothioyl]amino]-3-triisopropylsilyloxy-propanoyl]amino]butanoate (2.84)



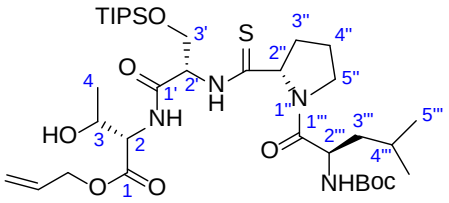
Fmoc-protected amine **2.83** (375 mg, 0.44 mmol) was dissolved DMF (10 mL). To the reaction mixture was added piperidine (75 mg, 0.88 mmol). The reaction was stirred at room temperature for 16 h. Reaction was partitioned between water (20 mL) and ether (20 mL). Organic layer was concentrated under reduced pressure. Column chromatography of the residue eluting with 100% ether gave the *title compound* **2.84** (184 mg, 66%) as a colourless gum. R_f 0.2 (100% ether). $[\alpha]_D^{20}$ -44.0 (c 1.2 in $CHCl_3$); (Found $[M+H]^+$, 630.3789; $C_{31}H_{59}N_4O_2Si_2SNa$, requires *M*, 630.3790); ν_{max} 3203, 2941, 2865, 1738, 1682, 1504, 1462, 1378, 1361, 1274, 1252, 1194, 1096, 993, 962, 921, 882, 836, 809, 776, 740, 681 and 660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.06 (3 H, s, $OSiCH_3$), 0.00 (3 H, s, $OSiCH_3$), 0.80 (9 H, s, $OSiC(CH_3)_3$), 1.02 (21 H, m, OSi^iPr_3), 1.11 (3 H, d, *J* 6.3, 4-H_3), 1.65 (4 H, m, 3''-H_2 and 4''-H_2), 1.97 (1 H, m, 5''-H_a), 2.37 (1 H, m, 5''-H_b), 2.93 (1 H, m, 3'-H_a), 3.02 (1 H, m, 3'-H_b), 3.87 (1 H, dd, *J* 5.0 and 9.8, 2-H), 4.22 (1 H, dd, *J* 5.4 and 9.2, 2'-H), 4.34 (1 H, m, 3-H), 4.41 (1 H, dt, *J* 1.9 and 6.3, 2''-H), 4.52 (1 H, m, NH), 4.58 (2 H, m, OCH_2CHCH_2), 5.11 (1 H, m, NH), 5.21 (1 H, m, OCH_2CHCH_a), 5.29 (1 H, m, OCH_2CHCH_b), 5.87 (1 H, m, OCH_2CHCH_2) and 6.83 (1 H, d, *J* 9.1, NH); δ_C (100 MHz, $CDCl_3$) -4.35, -5.22, 11.80, 12.54, 17.87, 17.95, 18.10, 20.79, 25.71, 26.06, 34.61, 47.50, 58.04, 59.01, 62.46, 68.30, 68.88, 119.02, 131.58, 169.27, 169.80 and 206.72; *m/z* (ES+) 652 ($[M+23]^+$, 100%).

Allyl (2*S*)-2-[[(2*S*)-2-[[(2*S*)-1-[(2*R*)-2-(*tert*-butoxycarbonylamino)-4-methyl-pentanoyl]pyrrolidine-2-carbothioyl]amino]-3-triisopropylsilyloxy-propanoyl]amino]-3-[*tert*-butyl(dimethyl)silyl]oxy-butanoate (2.70)



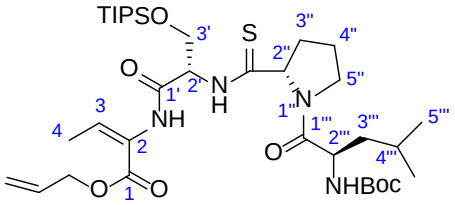
A solution of boc-protected D-leucine (68 mg, 0.29 mmol) in DMF (2.5 mL) was treated with HATU (156 mg, 0.41 mmol) and HOBt (17 mg, 0.12 mmol). Amine **2.84** (184 mg, 0.29 mmol) in DMF (2.5 mL) was added followed by DIPEA (151 mg, 1.17 mmol). The reaction mixture was stirred at room temperature for 16 h. Reaction was partitioned between aqueous NH_4Cl (20 mL) and ether (30 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (30:70) gave the *title compound* **2.70** (207 mg, 85%) as a colourless gum. R_f 0.6 (30:70 petrol-ether). $[\alpha]_D^{20}$ -20.0 (c 1.2 in $CHCl_3$); (Found $[M+H]^+$, 843.5149; $C_{41}H_{79}N_4O_8Si_2S$, requires *M*, 843.5152); ν_{max} 3314, 2944, 2866, 1681, 1626, 1514, 1062, 1391, 1365, 1307, 1252, 1163, 1097, 990, 934, 881, 836, 776, 682 and 661 cm^{-1}; δ_H (400 MHz, $CDCl_3$) -0.05 (3 H, s, $OSiCH_3$), 0.00 (3 H, s, $OSiCH_3$), 0.80 (9 H, s, $OSiC(CH_3)_3$), 0.89 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 0.93 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 1.03 (21 H, m, OSi^iPr_3), 1.11 (3 H, d, *J* 6.6, 4-H_3), 1.37 (4 H, m, 4''-H_2 and 3'''-H_2), 1.53 (9 H, s, $CO_2C(CH_3)_3$), 1.65 (1 H, m, 4'''-H), 1.92 (1 H, m, 5''-H_a), 2.12 (2 H, m, 3''-H_2), 2.44 (1 H, m, 5''-H_b), 3.50 (1 H, m, 3-H), 3.77 (1 H, m, 3'-H_a), 3.91 (1 H, m, 3'-H_b), 4.27 (1 H, m, 2'''-H), 4.39 (1 H, m, 2'-H), 4.48 – 4.62 (3 H, m, OCH_2CHCH_2 and 2-H), 4.83 (1 H, m, 2''-H), 5.07 (1 H, m, NH), 5.18 (1 H, m, OCH_2CHCH_a), 5.28 (1 H, m, OCH_2CHCH_b), 5.86 (1 H, m, OCH_2CHCH_2), 7.13 (1 H, m, NH) and 8.84 (1 H, m, NH); δ_C (100 MHz, $CDCl_3$) -5.57, -5.13, -4.62, 11.62, 12.11, 17.66, 17.78, 19.88, 19.96, 21.63, 22.92, 24.14, 25.61, 25.71, 28.22, 46.93, 50.89, 58.03, 60.03, 62.45, 65.03, 67.20, 68.48, 68.61, 78.39, 117.93, 132.09, 155.18, 168.41, 169.08 and 204.42; *m/z* (ES+) 865 ($[M+23]^+$, 100%).

Allyl (2*S*)-2-[[(2*S*)-2-[[(2*S*)-1-[(2*R*)-2-(*tert*-butoxycarbonylamino)-4-methyl-pentanoyl]pyrrolidine-2-carbothioyl]amino]-3-triisopropylsilyloxy-propanoyl]amino]-3-hydroxy-butanoate (2.71)



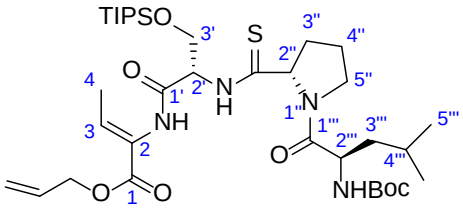
To a solution of TBS-protected alcohol (207 mg, 0.25 mmol) in THF (5 mL) was added TBAF (1 M, 300 uL, 0.3 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with ether-methanol (95:5) gave the protected diol **2.85** (64 mg, 45%) as a white gum. This diol **2.85** (64 mg, 0.11 mmol) was dissolved in THF (4 mL). To the reaction mixture was added imidazole (46 mg, 0.68 mmol) followed by TIPSCl (108 mg, 0.56 mmol), the reaction was stirred at room temperature for 48 h. Reaction was partitioned between water (10 mL) and ether (15 mL). Organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (30:70) gave the *title compound* **2.71** (54 mg, 68%) as a colorless gum. R_f 0.3 (30:70 petrol-ether). $[\alpha]_D^{20}$ -15.6 (c 2.0 in $CHCl_3$); (Found $[M+H]^+$, 729.4286; $C_{35}H_{65}N_4O_8SiS$, requires *M*, 729.4287); ν_{max} 3307, 2944, 1743, 1677, 1632, 1515, 1451, 1390, 1366, 1251, 1163, 1104, 1014, 991, 920, 882, 785, 733, 682 and 659 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, d, *J* 4.8, 4'''-CH_3 or 5'''-H_3), 0.91 (3 H, d, *J* 4.8, 4'''-CH_3 or 5'''-H_3), 0.98 (21 H, m, OSi^{i}Pr$_3$), 1.12 (3 H, d, *J* 6.1, 4-H_3), 1.36 (2 H, m, 4''-H_3), 1.51 (9 H, s, $CO_2C(CH_3)_3$), 1.57 (1 H, m, 4'''-H), 1.95 (2 H, m, 3'''-H_2), 2.30 (1 H, m, 3''-H_a), 2.39 (1 H, m, 3''-H_b), 3.54 (1 H, m, 3-H), 3.92 (1 H, m, 3'-H_a), 4.17 (3 H, 5''-H_2 and 2'''-H), 4.27 (1 H, m, 3'-H_b), 4.47 (1 H, m, 2'-H), 4.57 (2 H, m, OC*H*$_2$CHCH$_2$), 4.94 (1 H, dd, *J* 4.3 and 8.6, 2-H), 5.03 (1 H, m, 2''-H), 5.15 (1 H, m, OCH$_2$CHC*H*$_a$), 5.27 (1 H, m, OCH$_2$CHC*H*$_b$), 5.42 (1 H, br m, NH), 5.86 (1 H, m, OCH$_2$C*H*CH$_2$), 7.16 (1 H, d, *J* 7.1, NH) and 8.28 (1 H, d, *J* 8.3, NH); δ_C (100 MHz, $CDCl_3$) 11.78, 17.91, 19.91, 21.93, 23.35, 23.79, 24.22, 24.66, 28.33, 31.03, 33.11, 51.12, 54.40, 62.21, 65.90, 67.69, 68.14, 69.63, 80.62, 118.49, 131.92, 148.98, 168.01, 168.46, 169.88 and 202.59; *m*/*z* (ES+) 751 ($[M+23]^+$, 100%).

Allyl (*E*)-2-[[(2*S*)-2-[[(2*S*)-1-[(2*R*)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]pyrrolidine-2-carbothioyl]amino]-3-triisopropylsilyloxy-propanoyl]amino]but-2-enoate (2.69)



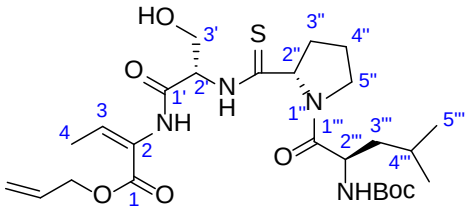
A solution of secondary alcohol **2.71** (40 mg, 0.05 mmol), EDC (17 mg, 0.11 mmol) and $CuCl_2$ (1 mg, 0.01 mmol) in anhydrous toluene (2 mL) was stirred at 80^{o}C under nitrogen for 30 min. The reaction was quenched with water and the mixture was extracted with EtOAc (5 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with 100% ether gave the *title compound* **2.69** (23 mg, 65%) as a colourless gum. R_f 0.6 (30:70 petrol-ether). $[\alpha]_D^{20}$ -37.5 (c 2.0 in $CHCl_3$); (Found $[M+H]^+$, 711.4189; $C_{35}H_{63}N_4O_7SiS$, requires *M*, 711.4182); ν_{max} 3294, 2943, 2867, 1682, 1645, 1507, 1447, 1386, 1366, 1251, 1163, 1106, 1066, 1046, 1014, 994, 920, 881, 851, 778, 735, 681 and 659 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 0.91 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 0.99 (21 H, s, $OSiC(CH_3)_3$), 1.33 (9 H, s, $CO_2C(CH_3)_3$), 1.36 (2 H, m, 3'''-H_2), 1.64 (1 H, m, 4'''-H), 1.92 (1 H, m, 4''-H_a), 1.98 (3 H, d, *J* 7.6, 4-H_3), 2.04 (1 H, m, 4''-H_b), 2.22 (1 H, m, 3''-H_a), 2.34 (1 H, m, 3''-H_b), 3.51 (2 H, m, 5''-H_2), 3.81 (1 H, m, 3'-H_a), 3.96 (1 H, m, 3'-H_b), 4.21 (1 H, m, 2'''-H), 4.34 (1 H, m, 2'-H), 4.63 (2 H, m, OCH_2CHCH_2), 4.85 (1 H, m, 2''-H), 5.08 (1 H, m, NH), 5.18 (1 H, m, OCH_2CHCH_a), 5.28 (1 H, m, OCH_2CHCH_b), 5.9 (1 H, m, OCH_2CHCH_2), 6.68 (1 H, m, 3-H), 8.13 (1 H, m, NH) and 8.62 (1 H, br d, *J* 7.3, NH); δ_C (100 MHz, $CDCl_3$) 11.79, 14.17, 17.91, 21.93, 23.42, 24.36, 24.64, 28.32, 30.33, 32.37, 41.37, 47.71, 50.85, 62.26, 65.89, 79.99, 82.65, 103.73, 118.55, 126.11, 129.12, 131.96, 148.99, 155.72, 163.59 and 203.33; *m/z* (ES+) 733 ($[M+23]^+$, 100%).

Allyl (*Z*)-2-[[(2*S*)-2-[[(2*S*)-1-[(2*R*)-2-(tert-butoxycarbonylamino)-4-methyl-pentanoyl]pyrrolidine-2-carbothioyl]amino]-3-triisopropylsilyloxy-propanoyl]amino]but-2-enoate (2.85)



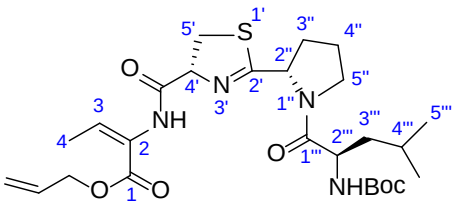
Diethylaminosulfuer trifuoride (7 mg, 0.04 mmol) was added dropwise over 1 min to a stirred solution of alcohol **2.71** (20 mg, 0.027 mmol) and pyridine (8 mg, 0.11 mmol) at 0 ^{o}C. The reaction was stirred at 0 ^{o}C for 2 h then quenched with saturated aqueous NaHCO3. Combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with petrol-ether (30:70) gave the *title compound* **2.85** (6 mg, 31%) as a colourless gum. R_f 0.5 (30:70 petrol-ether). $[\alpha]_D^{20}$ -11.4 (c 2.0 in $CHCl_3$); (Found $[M+H]^+$, 711.4183; $C_{35}H_{63}N_4O_7SiS$, requires *M*, 711.4184); ν_{max} 3323, 2943, 2867, 1686, 1641, 1509, 1450, 1366, 1250, 1163, 1068, 1046, 1015, 994, 921, 882, 757, 682 and 659 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.86 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 0.88 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 0.99 (21 H, s, $OSiC(CH_3)_3$), 1.36 (12 H, s, $CO_2C(CH_3)_3$, 3'''-H_2 and 4'''-H), 1.72 (3 H, d, *J* 7.1, 4-H_3), 1.95 (2 H, m, 4''-H_2), 2.26 (2 H, m, 3''-H_2), 3.55 (2 H, m, 5''-H_2), 3.85 (2 H, m, 3'-H_2), 4.28 (1 H, m, 2'''-H), 4.39 (1 H, m, 2'-H), 4.59 (2 H, m, OCH_2CHCH_2), 4.85 (1 H, m, 2''-H), 5.17 (1 H, m, OCH_2CHCH_a), 5.25 (1 H, m, OCH_2CHCH_b), 5.84 (1 H, m, OCH_2CHCH_2), 6.79 (1 H, m, 3-H), 7.45 (1 H, br d, *J* 8.6, NH), 7.97 (1 H, s, NH) and 8.48 (1 H, m, NH); δ_C (100 MHz, $CDCl_3$) 11.75, 14.59, 17.91, 21.97, 23.41, 23.47, 24.56, 28.36, 30.33, 32.67, 41.90, 47.77, 50.88, 62.08, 65.75, 69.05, 79.08, 118.89, 126.24, 131.50, 132.14, 135.54, 155.60, 163.71, 166.84 and 203.37; *m/z* (ES+) 733 ($[M+23]^+$, 100%).

Allyl (*E*)-2-[[(2*S*)-2-[[(2*S*)-1-[(2*R*)-2-(*tert*-butoxycarbonylamino)-4-methyl-pentanoyl]pyrrolidine-2-carbothioyl]amino]-3-hydroxy-propanoyl]amino]but-2-enoate (2.72)



To a solution of TIPS-protected alcohol **2.69** (23 mg, 0.032 mmol) in THF (1 mL) was added TBAF (1 M, 49 µL, 0.049 mmol). Reaction was stirred at room temperature for 16 h. The reaction was concentrated under reduced pressure. Column chromatography of the residue eluting with 100% ether gave the *title compound* **2.72** (11 mg, 62%) as a white foam. R_f 0.3 (100% ether). $[\alpha]_D^{20}$ -24.1 (c 2.0 in $CHCl_3$); (Found $[M+Na]^+$, 577.2672; $C_{26}H_{42}N_4O_7NaS$, requires *M*, 577.2667); ν_{max} 3059, 2942, 2867, 1730, 1681, 1633, 1540, 1515, 1438, 1366, 1251, 1160, 1121, 999, 882, 851, 742 and 696 cm^{-1}; δ_H (400 MHz, $CHCl_3$) 0.80 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 0.81 (3 H, d, *J* 6.6, 4'''-CH_3 or 5'''-H_3), 1.25 (9 H, s, $CO_2C(CH_3)_3$), 1.27 (2 H, m, 3'''-H_2), 1.55 (1 H, m, 4'''-H), 1.90 (3 H, d, *J* 7.5, 4-H_3), 1.92 (2 H, m, 4''-H_2), 2.16 (1 H, m, 3''-H_a), 2.30 (1 H, m, 3''-H_b), 2.96 (1 H, br s, OH), 3.42 (1 H, m, 5''-H_a), 3.76 (2 H, m, 3'-H_2), 4.00 (1 H, m, 5''-H_b), 4.24 (1 H, m, 2'''-H), 4.55 (2 H, m, OC*H*$_2$CHCH$_2$), 4.77 (1 H, m, 2'-H), 4.92 (1 H, m, 2''-H), 5.03 (1 H, br m, NH), 5.10 (1 H, m, OCH_2CHCH_a), 5.21 (1 H, m, OCH_2CHCH_b), 5.80 (1 H, m, OCH_2CHCH_2), 6.52 (1 H, m, 3-H), 8.20 (1 H, br s, NH) and 8.71 (1 H, br d, *J* 7.4, NH); δ_C (100 MHz, $CDCl_3$) 12.29, 14.22, 21.76, 23.37, 28.34, 30.33, 34.25, 40.84, 47.80, 50.90, 59.88, 65.90, 66.05, 68.02, 80.50, 118.78, 125.56, 128.48, 130.88, 131.83, 132.08, 132.17, 168.00 and 203.60; *m*/*z* (ES+) 577 ($[M+23]^+$, 100%).

Allyl (*E*)-2-[[(4*R*)-2-[(2*S*)-1-[(2*R*)-2-(*tert*-butoxycarbonylamino)-4-methyl-pentanoyl]pyrrolidin-2-yl]-4,5-dihydrothiazole-4-carbonyl]amino]but-2-enoate (2.73)



Diethylaminosulfuer trifuoride (10 mg, 0.06 mmol) was added dropwise over 1 min to a stirred solution of tetrapeptide **2.72** (11 mg, 0.02 mmol) at -15 ^{o}C. The soltuion was stirred at -15 ^{o}C for 1 h, then to the reaction mixture was added saturated aqueous $NaHCO_3$ and the reaction was allowed to warm up to room temperature. DCM (5 mL) and water (5 mL) were added and the mixture was extracted with DCM (10 mL). Combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography of the residue eluting with 100% ether gave the *title compound* **2.73** (8 mg, 75%) as a colourless gum, this was a 2:1 mixture of two rotamers. R_f 0.5 (100% ether). $[\alpha]_D^{20}$ -15.6 (c 2.0 in $CHCl_3$); (Found [M-H]$^-$, 535.2596; $C_{26}H_{39}N_4O_6S$, requires *M*, 535.2595); ν_{max} 3321, 2955, 2932, 2871, 1702, 1682, 1643, 1510, 1425, 1366, 1343, 1250, 1162, 1015, 988, 932, 854, 780 and 639 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 2:1 mixture of two rotamers) 0.74 (1 H, d, *J* 6.6, 4’’’-CH_3 or 5’’’-H_3), 0.80 (1 H, d, *J* 6.6, 4’’’-CH_3 or 5’’’-H_3), 0.87 (2 H, d, *J* 6.6, 4’’’-CH_3 or 5’’’-H_3), 0.91 (2 H, d, *J* 6.6, 4’’’-CH_3 or 5’’’-H_3), 1.35 (9 H, s, $CO_2C(CH_3)_3$), 1.41 (2 H, dd, *J* 4.8 and 9.3, 2’’’-H_2), 1.64 (1 H, m, 4’’’-H), 1.94 (2 H, m, 4’’-H_2), 2.03 (3 H, d, *J* 7.6, 5-H_3), 2.12 (2 H, m, 3’’-H_2), 3.51 (2 H, m, 5’-H_2), 3.63 (0.67 H, m, 5’’-H_2), 3.88 (1.34 H, m, 5’’-H_2), 4.19 (0.33 H, dt, *J* 4.8 and 9.6, 2’’’-H), 4.44 (0.67 H, dt, *J* 4.8 and 9.6, 2’’’-H), 4.67 (2 H, m, OC*H*$_2$CHCH$_2$), 4.84 (1 H, m, NH), 5.00 (0.33 H, m, 2’’-H), 5.03 (2 H, m, 4’-H), 5.19 (1 H, m, OCH$_2$CHC*H*$_a$), 5.23 (0.67 H, m, 2’’-H), 5.30 (1 H, m, OCH$_2$CHC*H*$_b$), 5.90 (1 H, m, OCH$_2$C*H*CH$_2$), 6.96 (0.67 H, q, *J* 7.8, 4-H), 7.13 (0.33 H, q, *J* 7.8, 4-H) and 8.62 (1 H, br s, NH); δ_C (100 MHz, DMSO, 117 ^{o}C) 13.26, 21.66, 22.03, 22.87, 24.23, 28.19, 31.17, 34.99, 46.32, 50.89, 59.04, 64.98, 74.89, 78.39, 78.90, 117.88, 126.90, 127.20, 132.40, 155.12, 155.97, 156.20, 163.11 and 171.23; *m*/*z* (ES+) 559 ([M+23]$^+$, 100%).

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