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UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Towards the synthesis of RP 66453

By

Lana Nanson

Thesis for the degree of Doctor of Philosophy

September 2009

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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TOWARDS THE SYNTHESIS OF RP 66453

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This thesis details synthetic studies towards the total synthesis of RP 66453, a natural product isolated from a strain of Actinomycetes bacteria which is shown to bind to the neurotensin antagonist of guinea pigs.

RP 66453 provides an attractive target as its bis-macrocyclic core contains a biaryl axis that displays atropisomerism. The natural atropisomer of RP 66453 is less stable than its diastereoatropisomer. To date there have been no reported syntheses of the natural product, and just one reported synthesis of the unnatural atropisomer.

This thesis describes a new approach towards the synthesis of this challenging natural product. Model studies are described towards the formation of the biaryl macrocyclic ring via a radical induced transannular ring contraction of a halogenated benzyl aryl ether. Also described are model studies towards the formation of the biaryl linkage via phenanthrene formation, accessed in turn from a radical induced transannular ring contraction of a halogenated stilbene. Unfortunately, though short synthetic routes to these macrocyclic precursors were established, we were unable to realize either of the key steps.

Synthesis of the second macrocycle (ether ring) was achieved via an S_NAr ring closure. Coupling of this fragment to an advanced tetrapeptide intermediate was achieved. Further macrocyclisation is needed to advance this material to the natural product.

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Preface

The research described in this thesis was carried out at the University of Southampton under the supervision of Prof. D. C. Harrowven between October 2005 and November 2008. No part of this thesis has previously been submitted for a degree.

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Finally, my eternal thanks go to my family, who have supported my through the whole of my studies, have always believed in me and never once complained even through the toughest of times. I could not have done this without you, thank you.

Abbreviations

Ac	acetate
AIBN	azo- <i>iso</i> -butyronitrile
approx.	approximately
aq.	aqueous
Ar	aryl
Bn	benzyl
Bu	ⁿ butyl
Bz	benzoate
cat.	catalytic
conc.	concentrated
COSY	correlation spectroscopy
d	days
DBPO	dibenzoyl peroxide
DBU	1,8-diazabicyclo[5.4.0]unde-7-ene
DCE	dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	di- <i>iso</i> -butylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
EDC	<i>N</i> -ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide
eq.	equivalents
ES	electrospray
Et	ethyl
ether	diethyl ether
EtOH	ethanol
FT	fourier transform
h	hours
HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole

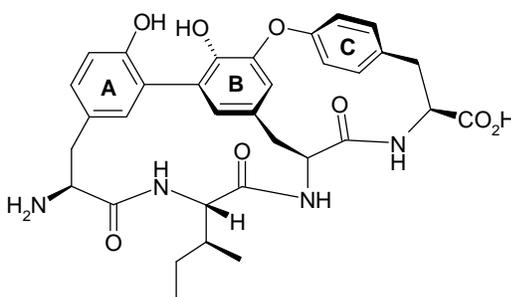
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectroscopy
IR	infra red
lit.	literature
LRMS	low resolution mass spectroscopy
M	molar
<i>m</i>CPBA	meta-chloroperoxybenzoic acid
Me	methyl
min	minutes
m.p.	melting point
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
NEt₃	triethylamine
NMR	nuclear magnetic resonance
obsc.	obscured
Pd	palladium
Ph	phenyl
ppm	parts per million
Pr	propyl
<i>i</i>-Pr	<i>isopropyl</i>
quant.	quantitative
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TTN	thallium trinitrate
UV	ultraviolet
VAZO	1,1'-azobis(cyclohexanecarbonitrile)
vis	visible
X	halide (unless otherwise stated)
Δ	heat

CHAPTER 1 – INTRODUCTION

1.1 RP 66453 – A neurotensin antagonist with a twist

The tridecapeptide neurotensin has received a great deal of attention due to its interesting physiological effects both in the periphery and the central nervous system.^{1,2,3} In order to further understand its complex role within the brain neurotensin antagonists and agonists are needed. During a screening program for compounds that displace neurotensin from its receptor Helynck *et al.* discovered RP 66453, a novel secondary metabolite which bound very specifically to the neurotensin receptor of guinea pigs (IC_{50} , 30 $\mu\text{g/mL}$).⁴

Production of this active compound from *Streptomyces* strain A 9738 yielded 60 mg of the pure metabolite from which the physico-chemical properties were collected. In depth NMR analysis was used to elucidate the gross structure of RP 66453, identifying the four spin systems corresponding to three modified tyrosine moieties and one isoleucine residue. However, the absolute configuration of the five stereogenic carbon centres, as well as the possible atropisomerism of the biaryl axis, remained unknown.



RP 66453 1.1

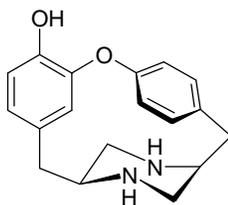
Herein the 15-membered biaryl macrocycle of RP 66453 will also be referred to as the A-B ring, whilst the 14-membered biaryl ether macrocycle will also be referred to as the B-O-C ring.

Hemi-synthetic work on this molecule has led to valuable neurotensin antagonists, envisioned uses of these compounds include treatment for psychosis, Alzheimer's and Parkinson's diseases.⁵

1.2 Related natural products

RP 66453 belongs to a large family of complex macrocyclic peptides, the characteristic features of which can be sub-divided into two groups. Firstly are those natural products which contain a strained 14-membered cyclophane subunit, and this group includes the natural products piperazinomycin, bouvardin, deoxybouvardin and RA-VII.

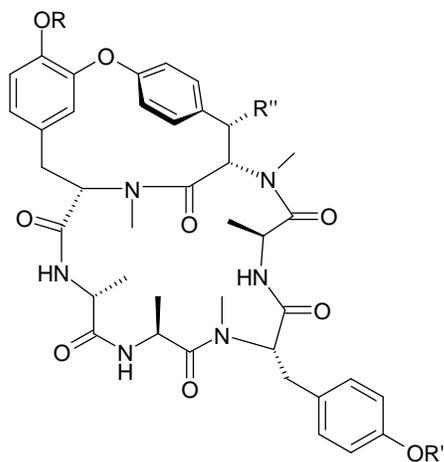
Piperazinomycin **1.2** represents the simplest of the natural products to contain the parent 14-membered para- and metacyclophane diaryl ether subunit.⁶ In this case the macrocycle contains a piperazine ring rather than an amide linkage. Isolated from the cultured broth of *Streptoverticillium olivoreticuli* subsp. *neoenacticus*, piperazinomycin **1.2** displays activity as an antifungal antibiotic, showing inhibitory activity against both fungus and yeasts.⁷



Piperazinomycin **1.2**

RA-VII **1.3**, deoxybouvardin **1.4** and bouvardin **1.5** also include the highly strained 14-membered ring containing a cycloisodityrosine subunit. Although this group of natural products contain an amide linkage, in each case the amide linkage central to the 14-membered ring is reversed with respect to that found in RP 66453. Indeed RP 66453 appears to be unique in its amide orientation within the 14-membered cyclophane ring.

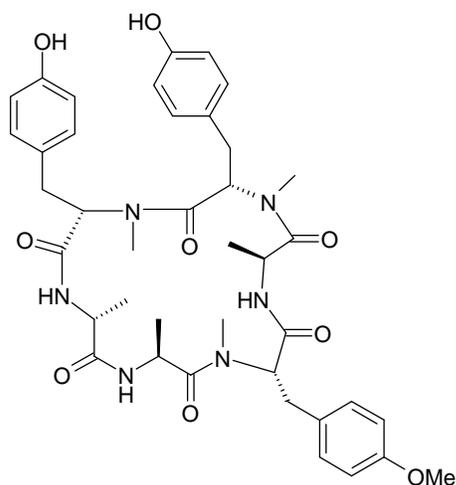
Deoxybouvardin **1.4** and bouvardin **1.5** are found in the stems, leaves and flowers of *Bouvardia ternifolia*, a plant used by ancient Mexican Indians as a general remedy, and still used in Mexico as a treatment for dysentery, hydrophobia and other illnesses.⁸ These two closely related compounds were found to be responsible for the therapeutic effect of the plant, with each also displaying high anti-tumour activity.



RA-VII R = R' = Me, R'' = H **1.3**
 Deoxybouvardin R = R'' = H, R' = Me **1.4**
 Bouvardin R = H, R' = Me, R'' = OH **1.5**

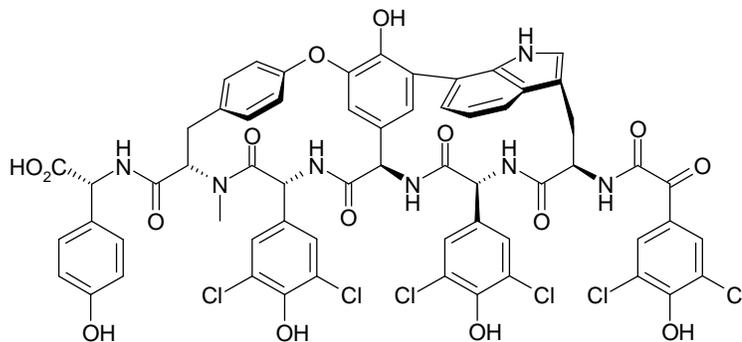
RA-VII **1.3** and its derivatives possess potent cytotoxic activity.⁹ Extensive investigation on the site of action has revealed that they act as protein synthesis inhibitors through binding to eukaryotic 80s ribosomes.¹⁰

These three closely related hexapeptides have a highly unusual structure whereby the central amide bond of the highly-strained 14-membered macrocycle is in the *cis*- conformation. Interestingly the natural products containing this *cis*-amide conformation are more potent than those containing the *trans*-amide.¹¹ The 14-membered cyclophane is crucial to the activity of this group of compounds, since the ring-opened analogue of deoxybouvardin **1.6** was found to lack the activity of the cyclic parent compound.¹²



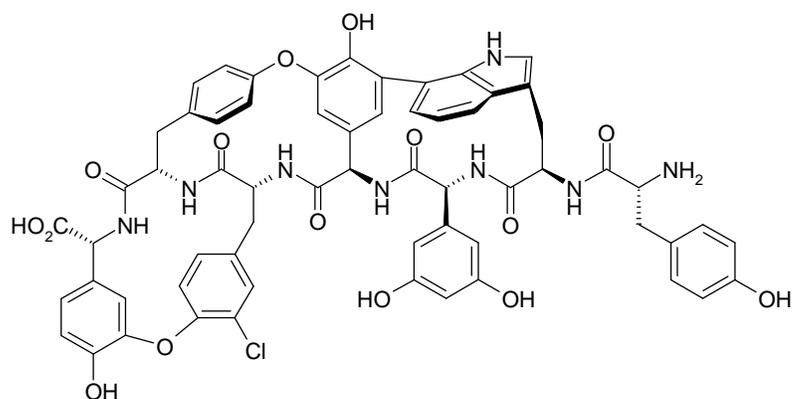
1.6

A second group of related natural products contain both the *endo* aryl-aryl and *endo* aryl-aryl ether bonds. This group includes the natural products chloropeptin **1.7**, kistamicin **1.8** and vancomycin **1.9**. Produced by the soil actinomycete *Streptomyces* sp. WK-3419, chloropeptin **1.7** has been found to possess anti-HIV activity, inhibiting HIV replication in peripheral human lymphocytes.¹³



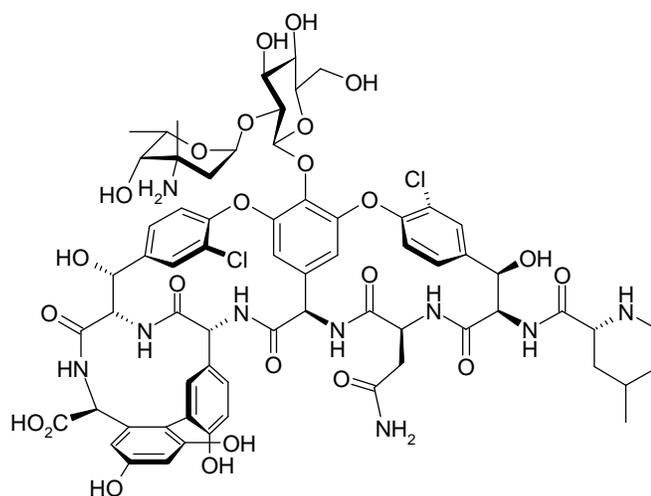
Chloropeptin 1.7

Kistamicin A **1.8**,¹⁴ isolated from the fermented broth of *Microtetraspora parvosata* subsp. *kistnae* subsp. nov., is one of the few natural products found to possess antiviral activity. This antiviral antibiotic has shown inhibitory activity against influenza type A and also moderate antibacterial activity.¹⁵



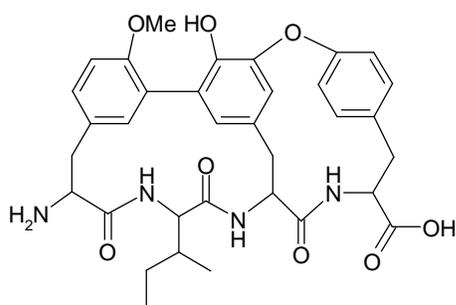
Kistamicin A **1.8**

Vancomycin **1.9** was discovered by Eli Lilly in 1956,¹⁶ and became acclaimed due to its indispensable use against methicillin-resistant *S. aureus* (MRSA). Isolated from the fermented broth of what is now named *Amycolatopsis orientalis*, vancomycin showed extremely potent activity against Gram-positive bacteria. Side-effects were reduced as the purity of the drug was improved, and vancomycin became an invaluable tool against drug-resistant bacteria.¹⁷



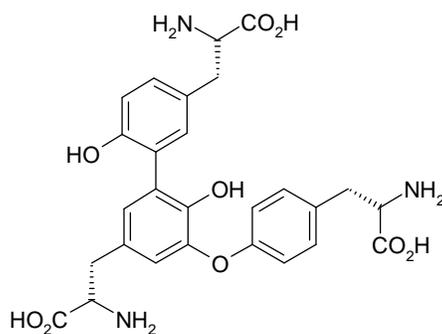
Vancomycin **1.9**

Cittilin A **1.10**, a pancreatic elastase inhibitor¹⁸ isolated from numerous strains of *Myxococcus xanthus*,¹⁹ is the closest natural product to RP 66453. As yet the absolute configuration of cittilin A has not been published. Indeed Helynck *et al.*¹ noted that RP 66453 is thought to be identical to cittilin B, also isolated from *Myxococcus xanthus*.



Cittilin A **1.10**

The acyclic tripeptide pulcherosine **1.11**, found in a wide range of sources including bacteria, plants, yeast and metazoans, is a trimer of tyrosine with both the biaryl and the biaryl ether bonds found in RP 66453.²⁰ It is also found in human phagocytes, and may serve as markers specific for tyrosyl radical-mediated oxidative damage observed in inflammatory conditions.²¹



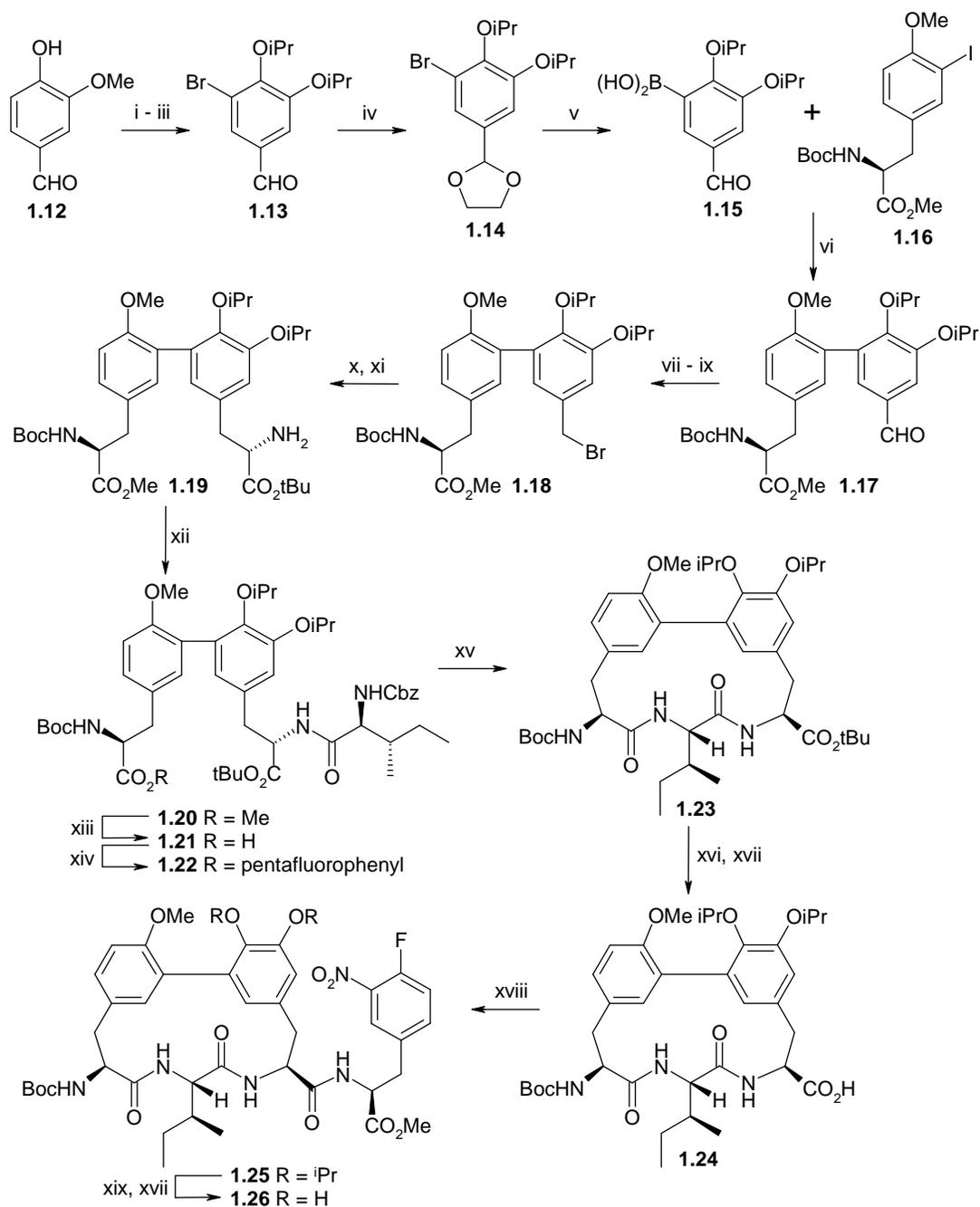
Pulcherosine **1.11**

1.3 Previous synthetic approaches towards RP 66453

i. The Zhu synthesis of the 15-membered A-B ring

In 2001, Zhu *et al.*²² were first to publish work towards the total synthesis of RP 66453. The synthesis relied upon macrolactamization to install the 15-membered biaryl A-B ring system, followed by an intramolecular S_NAr reaction to assemble the biaryl ether B-O-C ring. Tentatively assigning all asymmetric carbon centres as the *S* configuration, a convergent approach was devised to allow easy modification should the assignments be wrong.

In the early stages regioselective bromination of vanillin **1.12** followed by a two-step protecting group exchange and acetal formation gave bromide **1.14** (Scheme 1.1). Protection of the phenol as an isopropyl ether was chosen to facilitate orthogonal deprotection at a late stage of the synthesis under mild conditions. Conversion to the boronic acid **1.15** using lithium-bromide exchange followed by addition of trimethyl borate, facilitated the palladium-catalysed Suzuki cross-coupling to methyl *L-N*-Boc-3-iodo-4-methoxyphenyl alanate **1.16** to give biaryl **1.17**. Reduction of the aldehyde with NaBH₄ was complicated by the ease of reduction of the ester, which yielded the diol as a major byproduct in MeOH at -78 °C. This was overcome by switching the reaction solvent from MeOH to THF, producing the desired benzyl alcohol in 80% yield. Mesylation and Finkelstein bromination then furnished benzyl bromide **1.18**, which was used for the alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester in the presence of *O*-(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (0.1 equiv.).²³ The product, after chemoselective hydrolysis of the imine function, was the orthogonally protected biaryl bisamino acid **1.19**. Standard peptide coupling of **1.19** with (2*S*,3*S*)-*N*-Cbz isoleucine with EDC and HOBt gave the dipeptide **1.20**. The methyl ester was then selectively deprotected and the acid converted into an activated ester **1.23** with pentafluorophenol. Transfer hydrogenation was then used in a one-pot reaction which both hydrolysed the *N*-Cbz protecting group and then induced macrolactamization, affording the 15-membered biaryl macrocycle **1.23** in 70% yield from the dipeptide **1.20**. The use of *tert*-BuOH proved essential to avoid transesterification.



Reagents/Conditions: i) Br₂, acetic acid, 90%; ii) AlCl₃, Py, CH₂Cl₂, 98%; iii) K₂CO₃, *i*PrBr, DMSO, 83%; iv) ethylene glycol, benzene, *p*TsOH, Dean-Stark, 91%; v) a) BuLi, B(OMe)₃, THF, -78 °C; b) 3 N HCl, 67%; vi) Pd(PPh₃)₄, aq. Na₂CO₃, DME, 90 °C, 85%; vii) NaBH₄, THF, -78 °C, 80%; viii) MsCl, Et₃N, CH₂Cl₂; ix) LiBr, Me₂CO, 69%; x) CsOH.H₂O, *O*-(9)-allyl-*N*-(9-anthracenyl-methyl)cinchonidinium bromide, Ph₂C=NCH₂-CO^tBu; xi) 15% aqueous citric acid, THF, SiO₂, 65%; xii) EDC, HOBT, (2*S*,3*S*)-*N*-Cbz isoleucine, 90%; xiii) LiOH, THF-H₂O; xiv) EDC, C₆F₅OH, CH₂Cl₂; xv) Pd/C, cyclohexene, ^tBuOH, Hünig's base, 95 °C, 70%; xvi) TFA; xvii) Boc₂O, dioxane, aqueous NaHCO₃, 98%; xviii) EDC, HOBT, L-methyl 4-fluoro-3-nitrophenylalanate, 92%; xix) BCl₃, 82%.

Scheme 1.1

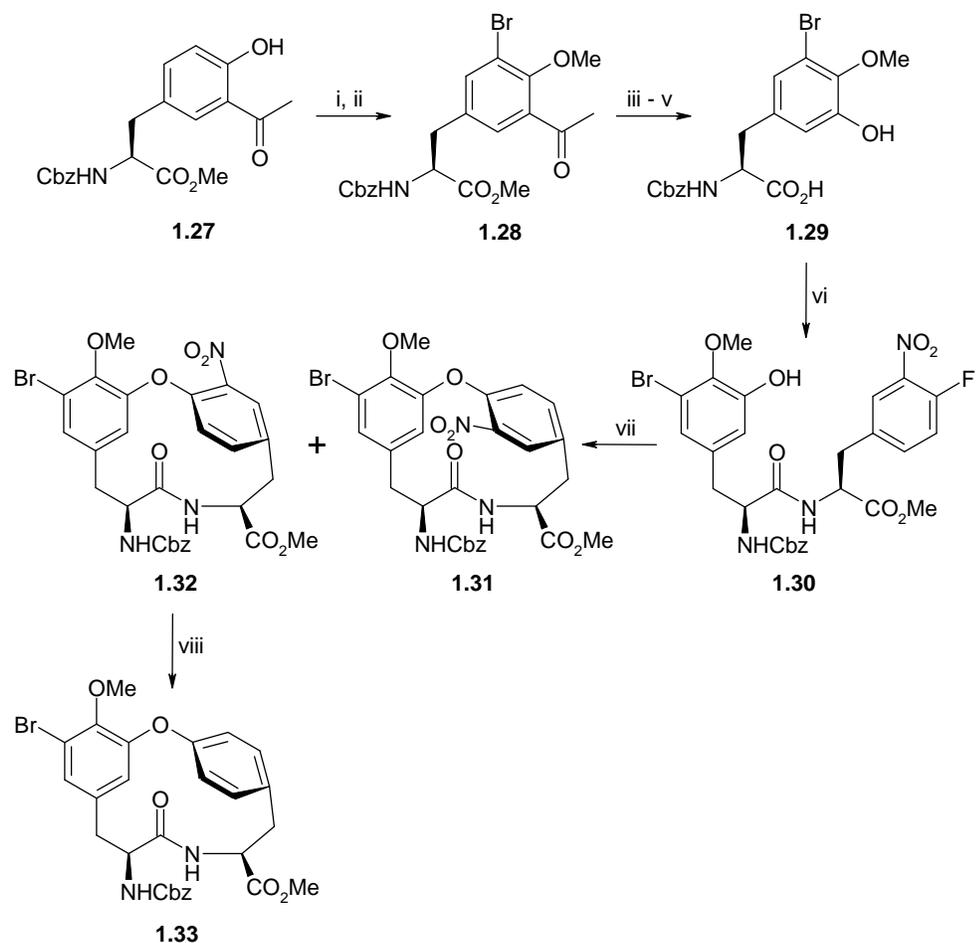
With the 15-membered macrocycle **1.23** in hand, work began on assembling the 14-membered B-O-C ring. Deprotection of the *tert*-butyl ester of **1.23** with TFA also liberated the amine functionality, which was re-protected with Boc₂O. The free acid **1.24** was then coupled to L-methyl 4-fluoro-3-nitrophenylalanate, mediated with EDC and HOBt, providing the tetrapeptide **1.25** in 92% yield. Removal of both isopropyl ether groups with BCl₃ gave catechol **1.26** with which to attempt the S_NAr to close the 14-membered macrocycle. Cyclization was attempted under a wide range of conditions, varying the base (NaH, K₂CO₃, K₂CO₃/crown ether 18-C-6, CsF, K₂CO₃/CaCO₃, DBU), the solvent (THF, DMF, DMSO), and the temperature (0 to 40 °C) but under none of these conditions was the desired bicyclic compound detected. The failure of this final cyclization was tentatively attributed to the unfavourable conformational properties of the precursor **1.26**.

Though unsuccessful in the synthesis of RP 66453, Zhu did achieve the first synthesis of the A-B ring and, possibly more significantly, discovered the difficulty in closing the B-O-C ring *via* nucleophilic aromatic substitution with the A-B ring in place. Zhu therefore planned to reverse the order of the two macrocyclization reactions by constructing the B-O-C ring first and following this by macrolactamization to close the A-B ring and completing the total synthesis.

ii. The Boger synthesis of the 14-membered B-O-C ring

In 2002 Boger *et al.*²⁴ published the first synthesis of the 14-membered L,L-cycloisodityrosine subunit of RP 66453. This strained biaryl-ether ring is notably different from similar rings contained in related natural products such as RA-VII and deoxybouvardin, as the cycloisodityrosine subunit has the orientation of the central amide bond reversed. Nonetheless, using a similar approach to that used in the synthesis of the deoxybouvardin series, Boger planned to close the ring by biaryl ether formation.

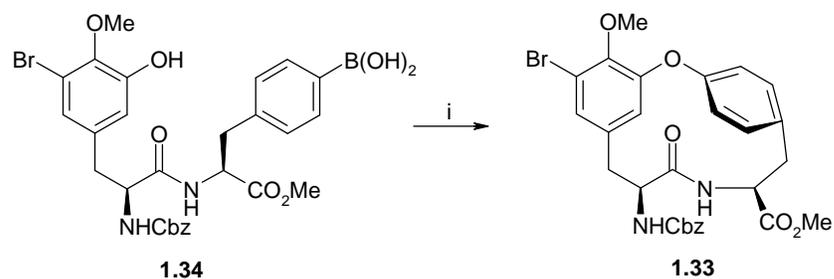
Preparation of the B-O-C ring began with the tyrosine derivative **1.27**, with subsequent bromination and methylation providing **1.28** (Scheme 1.2). Baeyer-Villiger oxidation with trifluoroacetic acid, followed by cleavage of the resulting acetate, and saponification of the methyl ester then gave acid **1.29**. Peptide coupling to L-4-fluoro-3-nitrophenylalanine in the presence of EDCI and HOAt furnished the cyclization precursor **1.30**. The intramolecular aromatic nucleophilic substitution was carried out under a range of conditions, with the best yield resulting from the use of K₂CO₃ in DMSO, leading to a 1:1 mixture of atropisomers **1.31** and **1.32**. This mixture was not separated as removal of the nitro group via reduction to the aniline and subsequent diazotisation and reduction, removed this stereoelement, furnishing the single product **1.33**. X-Ray crystallography confirmed that both chiral centres were conserved as the *S* configuration and that no epimerisation occurred under the conditions of the ring closing reaction.



Reagents/Conditions: i) NBS, CH₃CN, 25 °C, 18 h, 99%; ii) K₂CO₃, MeI, DMF, 25 °C, 5 h, 94%; iii) CF₃CO₃H, CH₂Cl₂, reflux, 2 d, 61%; iv) HCl, dioxane, 25 °C, 2 h, 88%; v) LiOH, THF/H₂O, 0 °C, 90 min, 68%; vi) EDCl, HOAt, L-4-F-3-NO₂-phenylalanine methyl ester, DMF, 25 °C, 18 h, 85%; vii) K₂CO₃, DMSO, 25 °C, 18 h, 58%; viii) Al-Hg, Et₂O/EtOH/H₂O, 25 °C, 1 h; HBF₄, *t*-BuONO, 0 °C, 10 min; H₃PO₂, 25 °C, 1 h, 40%.

Scheme 1.2

An alternative ring closing strategy was also investigated, incorporating a copper(II) acetate promoted closure of boronic acid **1.34** (Scheme 1.3). However, this route led to a low yield of the biaryl ether **1.33** (9%), with the side reactions of oxidation and reduction of the boronic acid competing and producing acyclic phenol byproducts.



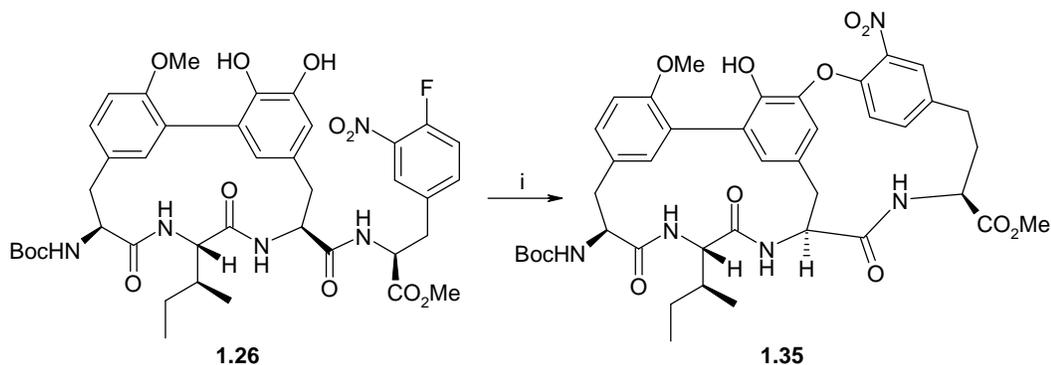
Reagents/Conditions: i) Cu(OAc)₂, pyridine or collidine, 1 mM CH₂Cl₂, 25 °C, 5 d, 9%.

Scheme 1.3

Thus Boger had synthesised the L,L-cycloisodityrosine subunit of RP 66453 in eight steps from the functionalised amino acid **1.27** in an overall yield of 11.5%. This constituted the first synthesis of the biaryl ether ring of RP 66453 with its unique reversed amide orientation, and showed how the key biaryl ether macrocyclization could be achieved using nucleophilic aromatic substitution or a closing of boronic acid **1.34**.

iii. Zhu's studies towards the total synthesis of RP 66453

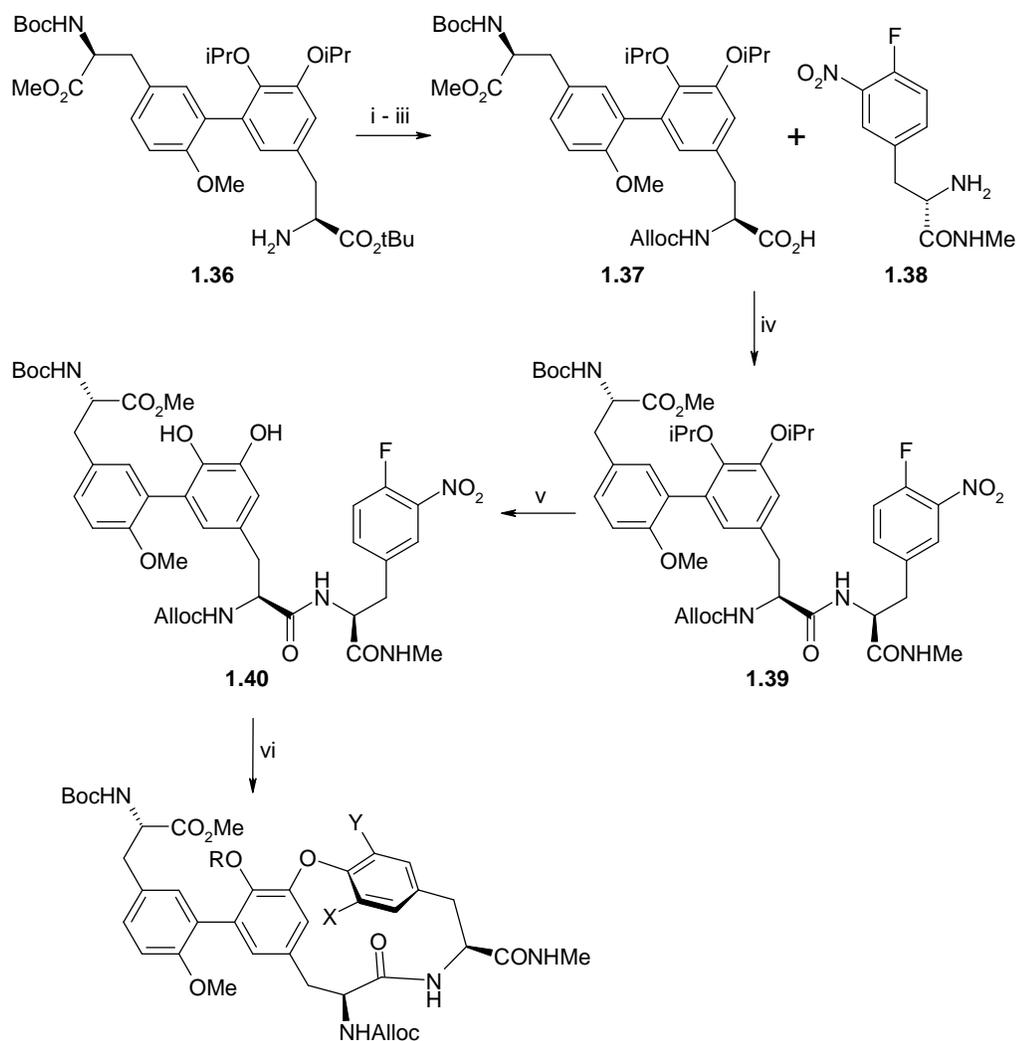
Prompted by Boger's publication of the synthesis of the 14-membered biaryl ether ring of RP 66453, Zhu *et al.*²⁵ published the first synthesis of the bicyclic A-B-O-C ring system. As previously observed, macrocyclization of the B-O-C ring with the A-B ring already in place could not be realized, however Zhu continued to investigate the ring closure of the bicyclic precursor **1.26**. A wide range of reaction conditions were screened, varying the base (K₂CO₃, CsF, DBU, NaH), solvent (DMF, DMSO, MeCN, THF), additives (18-crown ether, molecular sieves) and temperature. The only conditions found to yield the bicyclic product **1.35** were K₂CO₃ in THF at 50 °C in the presence of molecular sieves, but the low yield of around 15% made the overall synthesis unsuitable for the total synthesis of the natural product (Scheme 1.4).



Reagents/Conditions: i) K₂CO₃ (10 equiv.), THF (0.002 M), molecular sieves, 50 °C, 4 d, 15%.

Scheme 1.4

Due to the difficulty of closing the B-O-C ring with the A-B ring in place, Zhu proposed a new strategy in which the B-O-C ring was constructed first, followed by macrocyclization of the biaryl A-B ring. From the known biarylbisamino acid **1.36**, protection of the amine as the *N*-allyloxycarbamate followed by deprotection of the *tert*-butyl ester and reprotection of the Boc group gave the free acid **1.37** (Scheme 1.5). Cleavage of the *tert*-butyl ester while leaving the *N*-*tert*-butyloxycarbamate in place proved difficult, so a two-step procedure involving treatment with acid and restoration of the *N*-Boc functionality was adopted as it provided excellent yields of the required bisamide **1.37**.



1.41a R = Y = H, X = NO₂; **1.41b** R = X = H, Y = NO₂
1.42a R = Me, X = NO₂, Y = H; **1.42b** R = Me, X = H, Y = NO₂

Reagents/Conditions: i) Alloc, K₂CO₃, dioxane-H₂O, RT, 96%; ii) TFA, RT; iii) Boc₂O, aqueous NaHCO₃, dioxane, 91% ; iv) EDC, HOBt, Et₃N, 85%; v) BCl₃, CH₂Cl₂, -78 °C, then Boc₂O, THF, NaHCO₃, RT, 70%; vi) K₂CO₃, DMF then MeI, 60%.

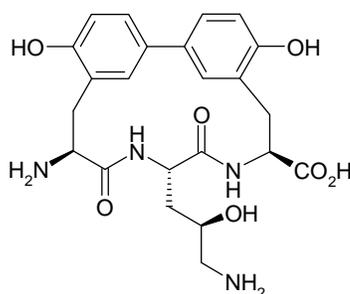
Scheme 1.5

Peptide coupling with methyl amide **1.38** in the presence of EDC, HOBt and NEt₃ gave the tripeptide **1.39** which then revealed catechol **1.40** upon treatment with BCl₃. Unlike cyclization of **1.26**, treatment of **1.40** with K₂CO₃ in DMF (0.002 M) smoothly furnished the 14-membered B-O-C ring as a 3:1 mixture of atropisomers **1.41a** and **1.41b**. Due to the instability of these phenolic products a one-pot cyclization/methylation was employed, reproducibly giving the cycloisodityrosine

1.42a and **1.42b** in greater than 60% yield, thus proving the importance of cyclization of the 14-membered B-O-C ring before closure of the 15-membered A-B ring.

iv. The Boger synthesis of the 15-membered A-B ring

With the stereocentres of RP 66453 still undefined, Boger looked to the biphenomycons, a series of antibiotics also isolated from Streptomycins, which contain a similar ring system. The α -carbons of the three biphenomycin B **1.43** amino acids were each found to possess the *S* configuration. With this precedent the synthesis of the 15-membered (*S,S,S*)-configured A-B ring was undertaken. Boger *et al.*²⁶ also planned to examine the efficiency of macrolactamization at different points of the A-B ring, using an advanced intermediate through which both options could be investigated.

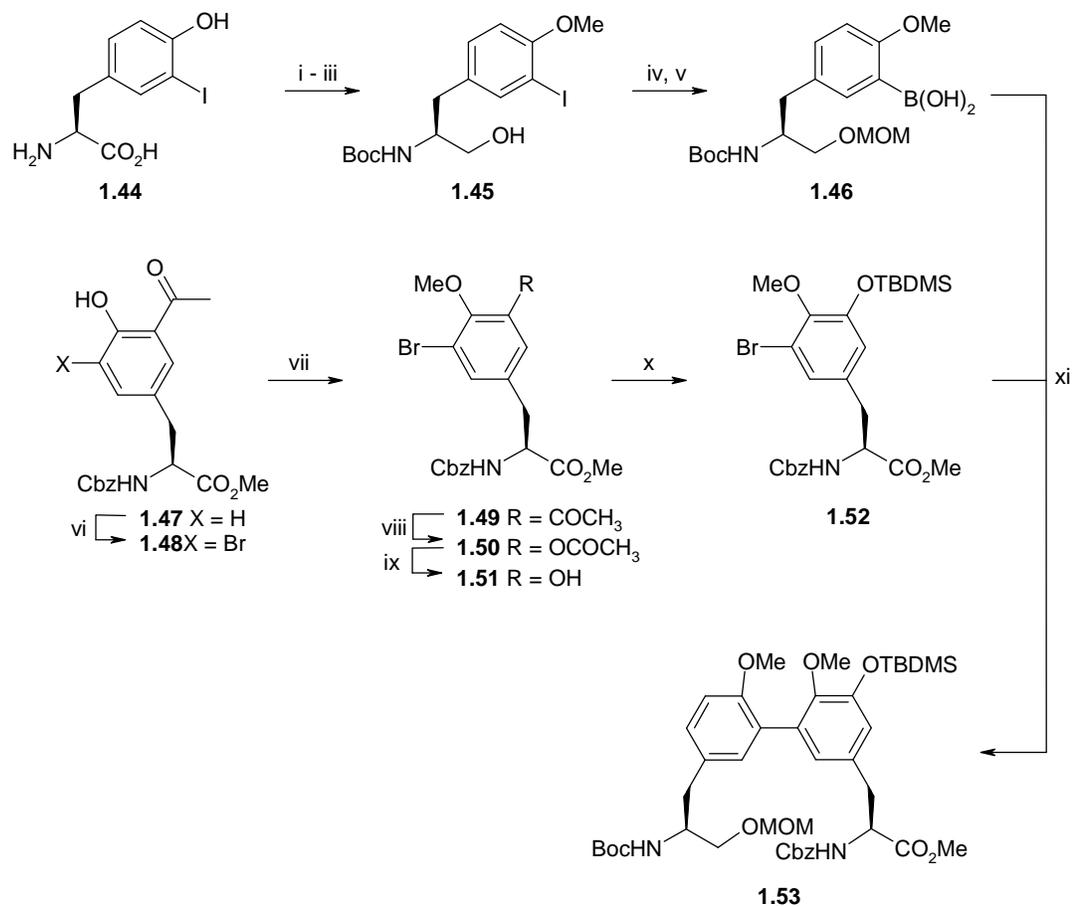


Biphenomycin B **1.43**

Preparation of the A-B ring began with the protection of the amine and phenol groups of 3-iodo-L-tyrosine **1.44** as the *tert*-butyl carbamate and methyl ether respectively (Scheme 1.6). With the free carboxylic acid group preventing conversion of the iodide to the boronic acid, the acid was first reduced to alcohol **1.45** and then masked as a methoxymethyl ether. Sequential deprotonation of the carbamate, magnesium-halogen exchange and treatment with trimethyl borate then gave boronic acid **1.46**.

Synthesis of the bromo-tyrosine derivative **1.52** began with bromination of the known acetylated tyrosine derivative **1.47** using *N*-bromosuccinimide to give peptide **1.48** (Scheme 1.6). Methylation of the phenol followed by Baeyer-Villiger oxidation gave acetate **1.50**, which was then cleaved in the presence of acid to give phenol **1.51**. Protection of the phenol as a TBDMS ether afforded bromo-tyrosine **1.52**. A Suzuki coupling between **1.52** and boronic acid **1.46** using of Pd₂(dba)₃ and (*o*-tolyl)₃P gave

biaryldipeptide **1.53**, the advanced intermediate from which the two different macrolactamization routes could be examined.

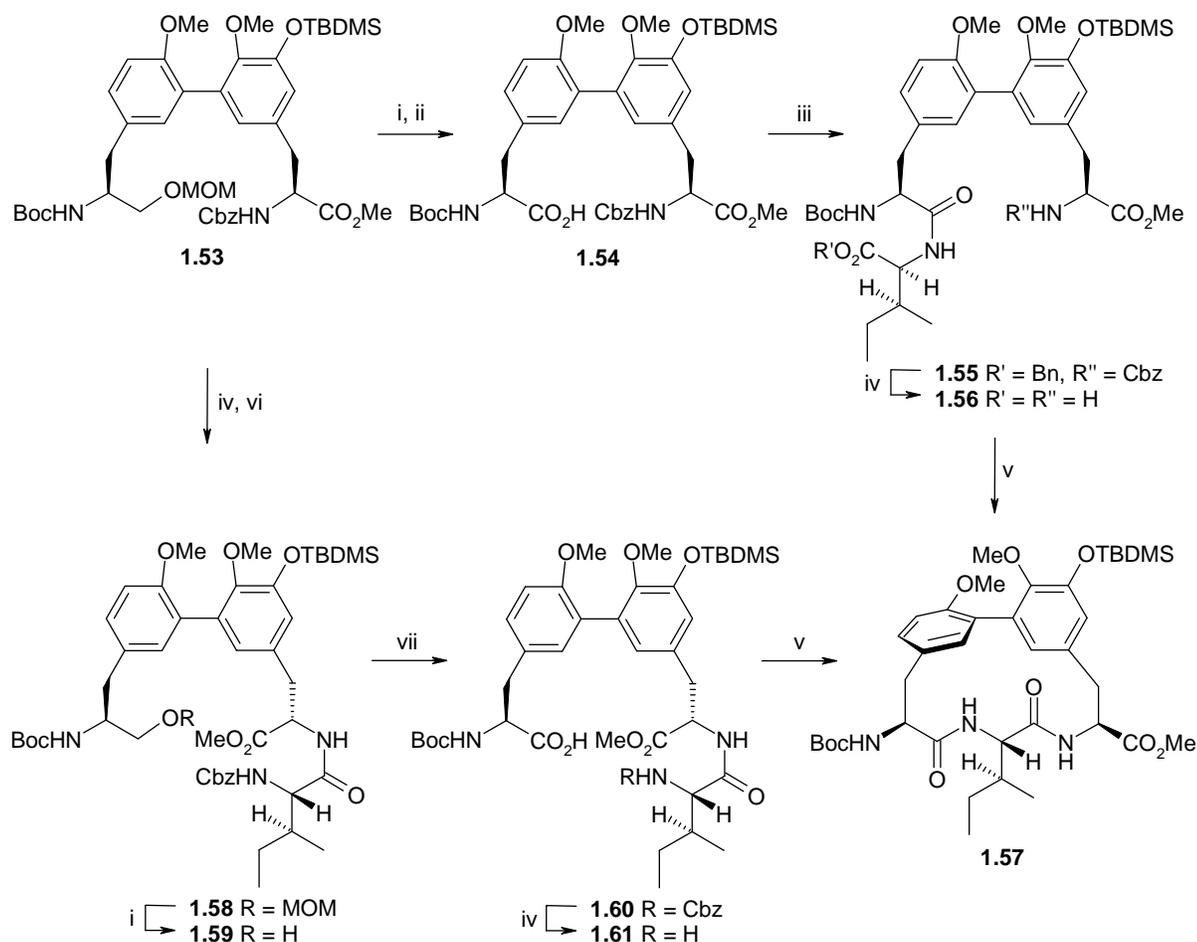


Reagents/Conditions: i) Boc₂O, NaHCO₃, dioxane/H₂O, 25 °C, 18 h, 99%; ii) NaH, MeI, 5% DMF-THF, 25 °C, 3 d, 78%; iii) EtOCOC₂H₅, NaBH₄, THF/MeOH, 0 °C, 20 min, 82%; iv) MOMCl, *i*-Pr₂NEt, CH₂Cl₂, 25 °C, 8 h, 92%; v) *i*-PrMgCl, *t*-BuLi, (MeO)₃B, THF, -78 to 25 °C, 1 h, 99%; vi) NBS, CH₃CN, 25 °C, 18 h, 99%; vii) K₂CO₃, MeI, DMF, 25 °C, 5 h, 94%; viii) CF₃CO₃H, CH₂Cl₂, reflux, 2 d, 61%; ix) HCl, dioxane, 25 °C, 2 h, 97%; x) TBDMSOTf, lutidine, THF, 25 °C, 4 h, 81%; xi) (*o*-tolyl)₃P, Pd₂(dba)₃, 1 M Na₂CO₃, toluene/MeOH, 85 °C, 15 min, 95%.

Scheme 1.6

Cleavage of the MOM ether of **1.53** under acidic conditions also resulted in the cleavage of the Boc protecting group, which was reintroduced before oxidation of the free alcohol to afford the carboxylic acid **1.54** (Scheme 1.7). Coupling of the free acid to L-isoleucine benzyl ester gave the tripeptide **1.55**, hydrogenolysis of both the Cbz and benzyl protecting groups then gave the first macrolactamization precursor **1.56**. Several peptide coupling agents were then assessed, with the best yields resulting from the use of EDCI and HOAt, with NaHCO₃ as the base. Under conditions of high dilution (1 mM) the A-B ring **1.57** was afforded in 53% yield.

In contrast hydrogenolysis of the Cbz protecting group of **1.53** followed by the coupling of the free carboxylic acid to Cbz-protected L-isoleucine afforded the dipeptide **1.58** (Scheme 1.7). Again cleavage of the MOM ether in the presence of acid also removed the Boc protecting group which was reinstated as before. Oxidation of the free alcohol **1.59** with Jones reagent gave the carboxylic acid **1.60**, and hydrogenolysis of the Cbz protected isoleucine moiety afforded the second macrocyclization precursor **1.61**. The same range of peptide coupling reagents were examined, with the best yields in this instance resulting from the use of FDPP as the coupling reagent under conditions of high dilution (1 mM), furnishing the A-B ring **1.57** in 64% yield.



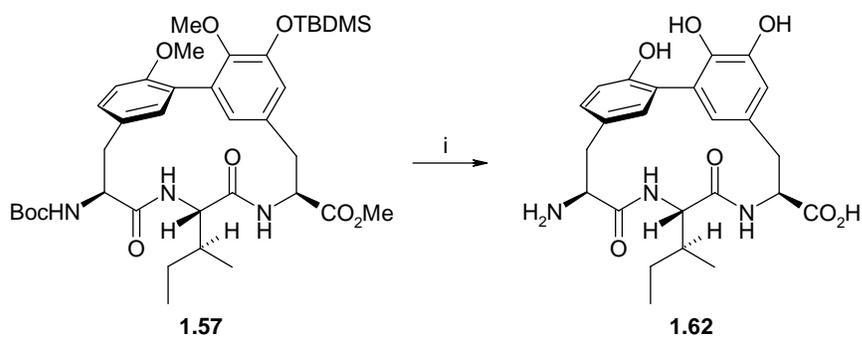
Reagents/Conditions: i) 3 M HCl/EtOAc, -10 °C, 30 min then Boc₂O, NaHCO₃, THF/H₂O, 69%; ii) cat. CrO₃, H₅IO₆, CH₃CN/H₂O, 0 °C, 1 h, 61%; iii) Ile-OBn tosylate, EDCI, HOAt, NaHCO₃ DMF, 25 °C, 90%; iv) 1 atm H₂, Pd/C, MeOH, 25 °C, 15 h, 99%; v) coupling reagent, DMF, 1 mM; vi) Cbz-Ile, EDCI, HOAt, DMF, 93%; vii) Jones reagent, acetone, 10 mM, 0 °C, 1 h, 55%.

Scheme 1.7

Interestingly the proton NMR spectrum of the A-B macrocycle **1.57** showed two sets of peaks for a set of slowly interconverting isomers. Although *ortho*-methoxy groups do not generally hinder rotation about the biaryl axis, in this case Boger reasoned that the *meta*-TBDMS group may be creating a buttressing effect which raises the energy barrier of free rotation, slowing the interconversion to a rate which can be seen on the NMR time-scale.

Global deprotection with AlBr₃ in EtSH provided the 15-membered A-B ring **1.62** which, in contrast to the protected macrocycle **1.57**, shows a single set of peaks

in the proton NMR spectrum (Scheme 1.8). Thus a synthesis of the 15-membered A-B ring **1.62** was achieved, using a highly efficient Suzuki coupling to install the biaryl linkage. Identification of the optimal site of macrolactamization had been established, with the resultant protected macrocycle **1.57** raising some interesting issues in respect of interconverting isomers.

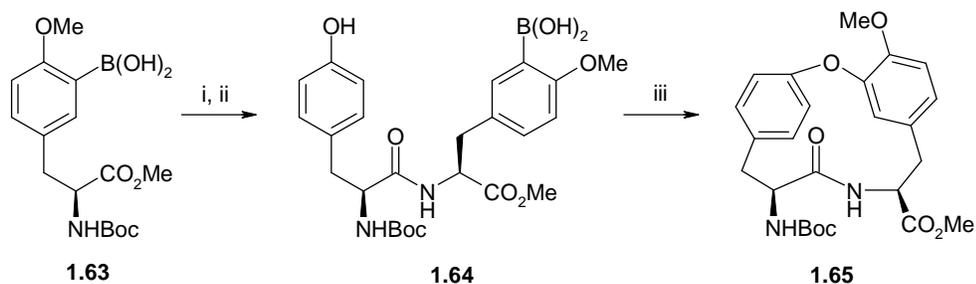


Reagents/Conditions: i) AlBr₃, EtSH.

Scheme 1.8

v. Takeya's copper(II) acetate-DMAP mediated closure of L,L-cycloisodityrosines

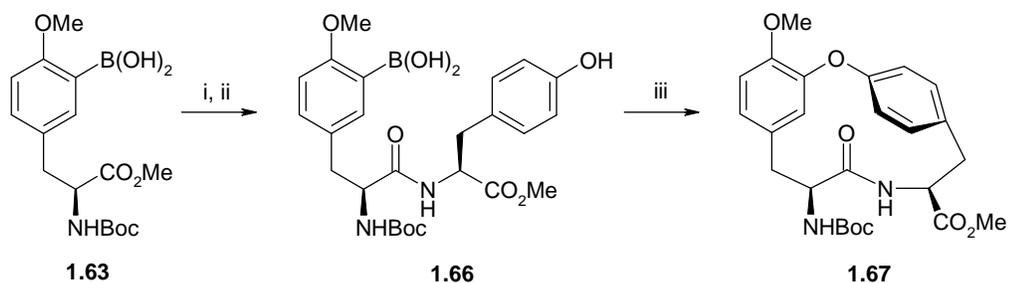
Shortly after Boger's published closure of the B-O-C ring via an intramolecular coupling reaction of an arylboronic acid and a phenol, **1.34**,²⁴ Takeya *et al.*²⁷ disclosed their route towards the cycloisodityrosine rings of RA-VII and RP 66453. Their synthesis began with the peptidic boronic acid **1.63**, synthesised from the commercially available 3-iodo-L-tyrosine over 4 steps in 80% yield (Scheme 1.9). Using the coupling reaction originally developed by Chan,²⁸ Evans²⁹ and Lam,^{30,31} Takeya treated the dipeptide boronic acid **1.64** with copper(II) acetate in the presence of DMAP, effecting the ring closure in 56% yield. Careful selection of the amine used increased the yield of the desired cyclic product and minimised production of the protodeborylated acyclic side-product, a known side reaction when the boronic acid possesses an *ortho*-hetero atom and formed in just 6% yield under these optimised conditions.



Reagents/Conditions: i) 4 M HCl-dioxane, RT; ii) Boc-Tyr, EDC, HOBT, NEt₃, CHCl₃, RT, 83% over two steps; iii) Cu(OAc)₂, DMAP, powdered 4 Å MS, CH₂Cl₂, 0.013 M, 56%.

Scheme 1.9

In the same manner the dipeptide boronic acid **1.66** was also treated with copper(II) acetate in the presence of DMAP, in this instance giving the B-O-C ring of RP 66453 in a moderate yield of 35% (Scheme 1.10). Takeya *et al.* offer no suggestion as to why the reversed orientation of the peptide in this latter example results in such a dramatic reduction in yield.



Reagents/Conditions: i) LiOH, THF-MeOH-H₂O (3:3:1), RT, 90%; ii) Tyr-OMe.HCl, EDC, HOBT, NEt₃, CHCl₃, 85%; iii) Cu(OAc)₂, DMAP, powdered 4 Å MS, CH₂Cl₂, 0.013 M, 35%.

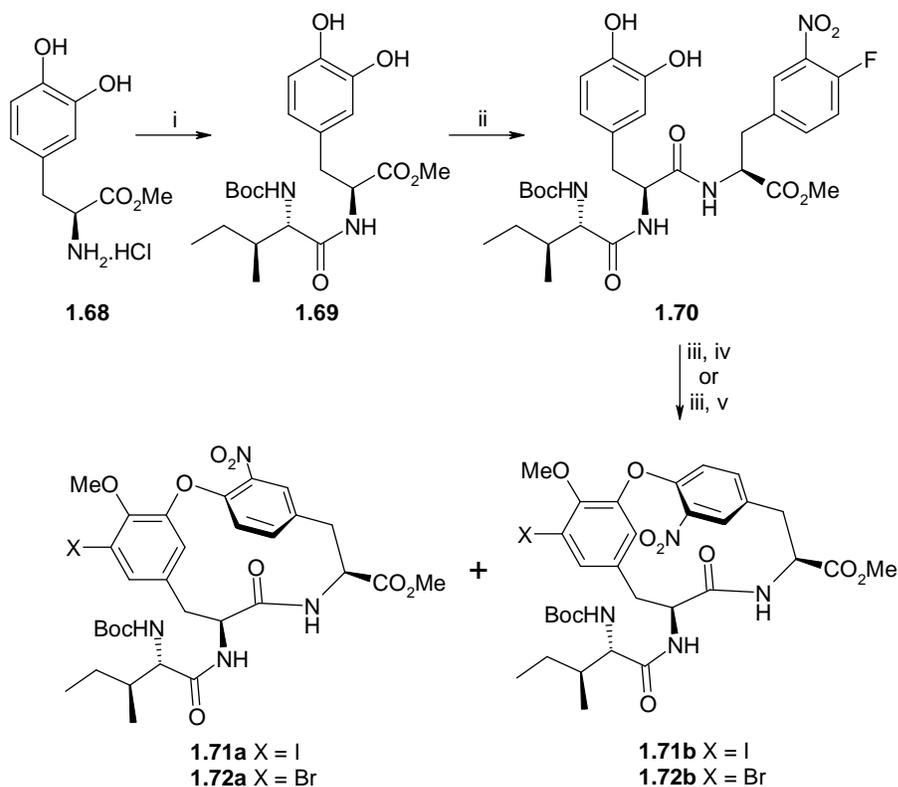
Scheme 1.10

Thus Takeya *et al.* have synthesised the L,L-cycloisodityrosine rings of RA-VII and RP 66453 in 7 steps from the commercially available 3-iodo-L-tyrosine. This constitutes the shortest synthesis of the B-O-C ring of RP 66453, with an overall yield of 21% from 3-iodo-L-tyrosine.

vi. The Zhu total synthesis of an atropdiastereomer of RP 66453

Building upon their previous efforts towards the synthesis of RP 66453, Zhu *et al.*³² began a revised approach to RP 66453. The strategy adopted was to first effect formation of the strained 14-membered B-O-C ring, before closing the biaryl A-B macrocycle with an intramolecular Suzuki-Miyaura reaction. Again, arbitrarily assigning all stereocentres as the *S* configuration, Zhu's convergent approach allowed for easy alteration should any stereocentre need to be changed.

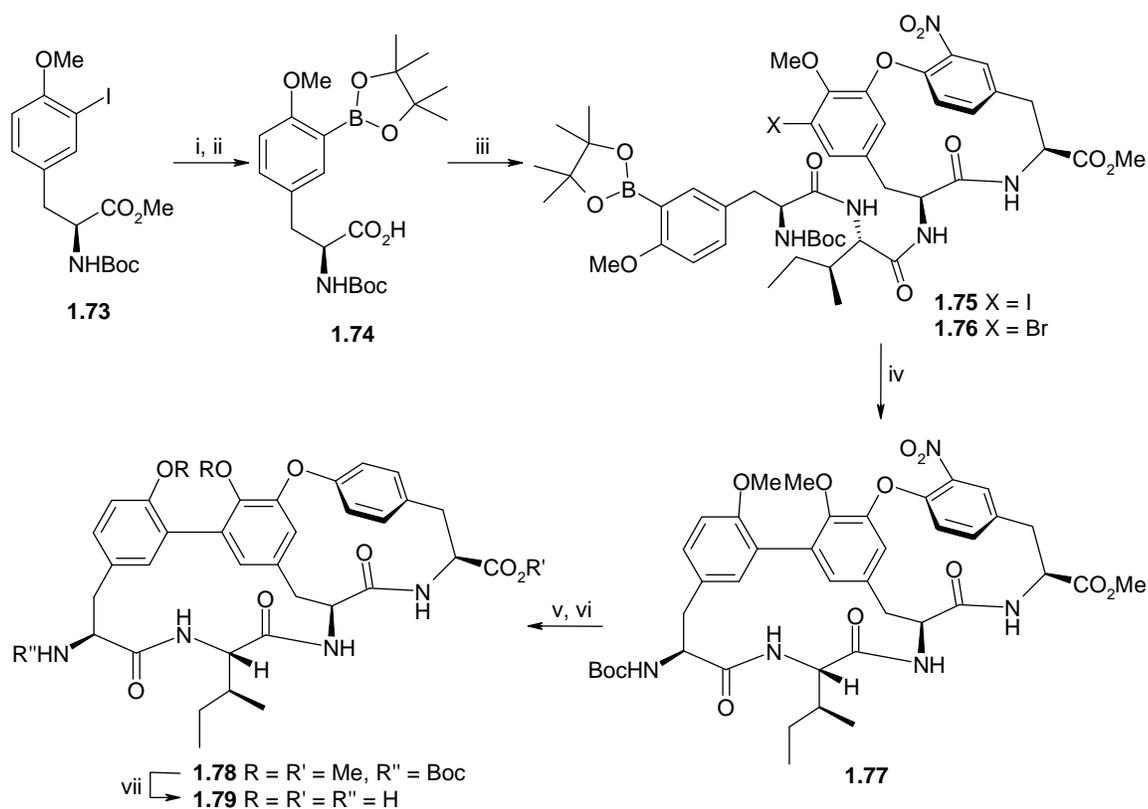
The synthesis began with the peptide coupling of (*S*)-dopa methyl ester **1.68** and (*S,S*)-*N*-Boc L-isoleucine, to afford the dipeptide **1.69** (Scheme 1.11). Saponification of the methyl ester then facilitated further coupling to the hydrochloride salt of (*S*)-methyl 4-fluoro-3-nitrophenylalanate to give the tripeptide **1.70**. Intramolecular nucleophilic aromatic substitution using CsF in DMSO (0.0026 M) selectively formed the 14-membered B-O-C ring in good yield. Treatment with either *N*-iodosuccinimide or *N*-bromosuccinimide, followed by methylation in a one-pot procedure, afforded the separable atropisomers **1.71a** and **1.71b**, or **1.72a** and **1.72b** respectively. It was found necessary to effect halogenation prior to methylation to achieve the correct regiochemistry. If reversed halogenation occurred in the position *para* to the biaryl ether linkage.



Reagents/Conditions: i) (*S,S*)-*N*-Boc isoleucine, EDC, HOBt, Et₃N, CH₂Cl₂, RT, 94%; ii) LiOH, THF/H₂O, RT, then (*S*)-methyl 4-fluoro-3-nitrophenylalanate.HCl, EDC, HOBt, Et₃N, DMF, RT, 77%; iii) CsF, DMSO (0.0026 M), RT, 2 h; iv) NIS, DMF, then K₂CO₃, MeI, 48% overall yield of **1.71a** and **1.71b** from **1.70**; v) NBS, DMF then MeI, 62% overall yield of **1.72a** and **1.72b** from **1.70**.

Scheme 1.11

Although later steps destroy the atropisomerism, the synthesis was continued with the atropisomerically pure compounds **1.71a** and **1.72a**. Removal of the Boc protecting group facilitated coupling to arylboronate **1.74** (prepared in two steps from (*S*)-3-iodotyrosine **1.73**) to afford the tetrapeptides **1.75** and **1.76** (Scheme 1.12). Intramolecular Suzuki-Miyaura coupling of iodide **1.75** reproducibly furnished the bicyclic A-B-O-C rings **1.77** as a single atropstereoisomer in around 40% yield when heated to 90 °C in toluene/H₂O in the presence of K₂CO₃ and [PdCl₂(dppf)]. However the same reaction with bromide **1.76** was found to proceed in much lower yields of around 5%. The choice of solvent was significant as when conducted in DMF, DMSO, toluene or MeOH a complex product mixture was given. Removal of the nitro group then gave protected bicycle **1.78** which was globally deprotected to afford the all-*S*-configured A-B-O-C bicyclic compound **1.79**.

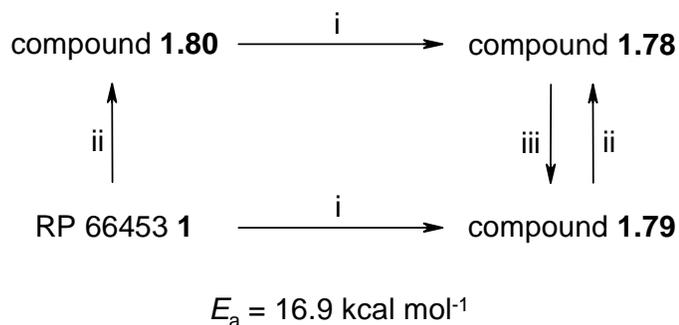


Reagents/Conditions: i) [PdCl₂(dppf)], bis(pinacolato)diboron, KOAc, DMSO, 80%; ii) LiOH, THF/H₂O (1:1), RT, quantitative; iii) **1.71a**, 7% HCl in MeCN, RT, aqueous KHCO₃ workup, then **1.74**, EDC, HOBT, Et₃N, DMF, RT, 87%; iv) [PdCl₂(dppf)], toluene/H₂O (30:1), K₂CO₃, 90 °C, 40%; v) Pd/C, H₂, MeOH; vi) NaNO₂, H₃PO₂, Cu₂O, THF/H₂O (6:1), 42%; vii) AlBr₃, EtSH, 55%.

Scheme 1.12

Although the spectroscopic data recorded on this product was in accord with the structure of bicycle **1.79** (¹H NMR, COSY, M/S) they did not match those reported for RP 66453 **1**. The optical rotation was also found to differ (**1.79**: +208 (c=1, MeOH); RP 66453 **1**: -181 (c=1, MeOH)). Further investigation showed that RP 66453 and **1.79** varied only in their axial chirality, with RP 66453 containing the all-*S*-configured amino acid backbone of **1.79**. This was exemplified by taking a solution of RP 66453 in DMSO and heating it to 150 °C (Scheme 1.13). After 3 h, complete conversion of RP 66453 to **1.79** was observed with no apparent decomposition. However when **1.79** was subjected to the same conditions it was found to be stable, indicating that **1.79** is the thermodynamically more stable atropisomer. Comparably when RP 66453 was protected to give **1.80**, treatment under analogous conditions

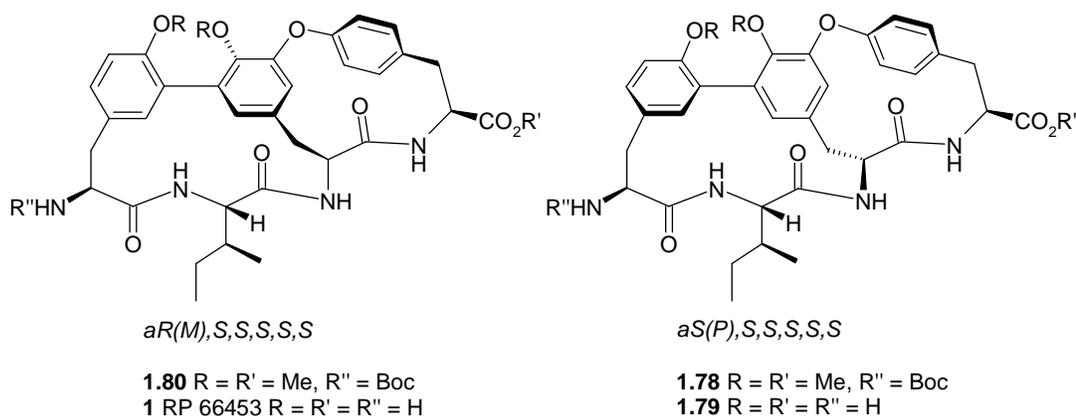
resulted in the complete conversion to **1.78**. Examination of the spectroscopic data of RP 66453 **1** and **1.80**, and also **1.78** and **1.80**, showed that there was no major conformational alteration occurring with the protection of any peripheral functional group. Axial chirality was also shown to be unaffected during the deprotection of **1.78** to **1.79**, with the activation energy (E_a) of isomerization calculated to be 16.9 kcal mol⁻¹.



Reagents/Conditions: i) DMSO, 150 °C, 3 h, quantitative; ii) Boc₂O, MeOH, Et₃N, then CsF, DMF, MeI, 50 °C, 80%; iii) AlBr₃, EtSH, CH₂Cl₂, 55%.

Scheme 1.13

The ¹H NMR spectra of RP 66453 **1** and **1.79** both show a single set of peaks, therefore implying that both exist as single stable conformers at ambient temperature. NOE studies deduced the axial chirality of **1.80**, and therefore the axial chirality of RP 66453 **1**, as the *aR* (*M*) configuration. Although there were no correlations to prove the axial chirality of **1.78**, as the previous experiments showed that **1.78** is an atropisomer of **1.80**, the configuration *aS* (*P*) was assigned.



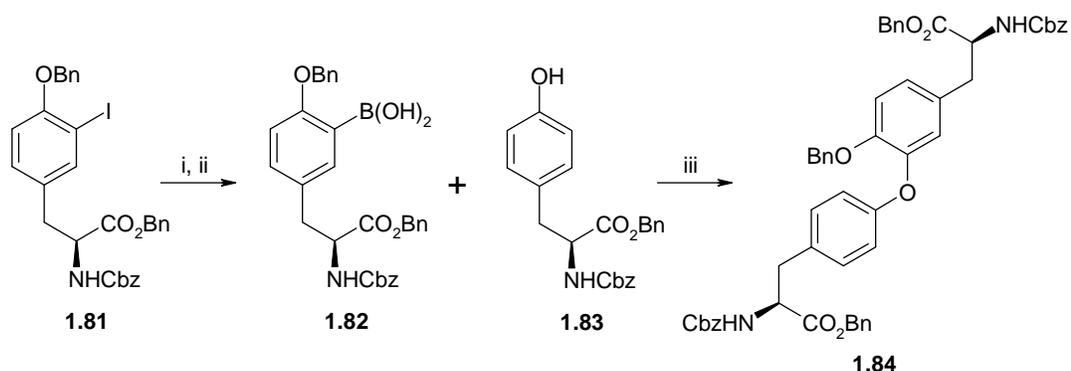
In conclusion, Zhu *et al.* completed the first total synthesis of the all *S*-configured diastereoisomer of RP 66453 **1.79**. In completing the total synthesis of atropdiastereomer **1.79**, they were able to determine the absolute configuration of RP 66453 **1** to be (*aR,S,S,S,S,S*) and showed that RP 66453 was the thermodynamically less stable atropisomer of synthetic **1.79**.

1.4 Previous synthetic approaches towards related natural products.

i. Hutton's synthesis of pulcherosine

In 2005, Hutton *et al.* published the first synthesis of pulcherosine **1.11**, an acyclic tripeptide incorporating both the biaryl and biaryl ether linkages of RP 66453.³³ Hutton envisaged that the biaryl bond could be installed with a Suzuki coupling of iodotyrosine and tyrosine boronic acid derivatives, whilst the biaryl ether could be formed by a copper(II) catalysed coupling of a tyrosine boronic acid and the tyrosine phenolic group.

The synthesis of pulcherosine began with the formation of the biaryl ether, a copper(II) acetate catalysed coupling of boronic acid **1.82** with the protected tyrosine derivative **1.83** gave the biaryl ether dipeptide **1.84** in a poor yield of 33% (Scheme 1.14). The product of protodeborylation of the boronic acid **1.82** was isolated in 15% yield, once again demonstrating the complications involved with copper(II) catalysed couplings of phenols and boronic acids which possess an *ortho* heteroatom.

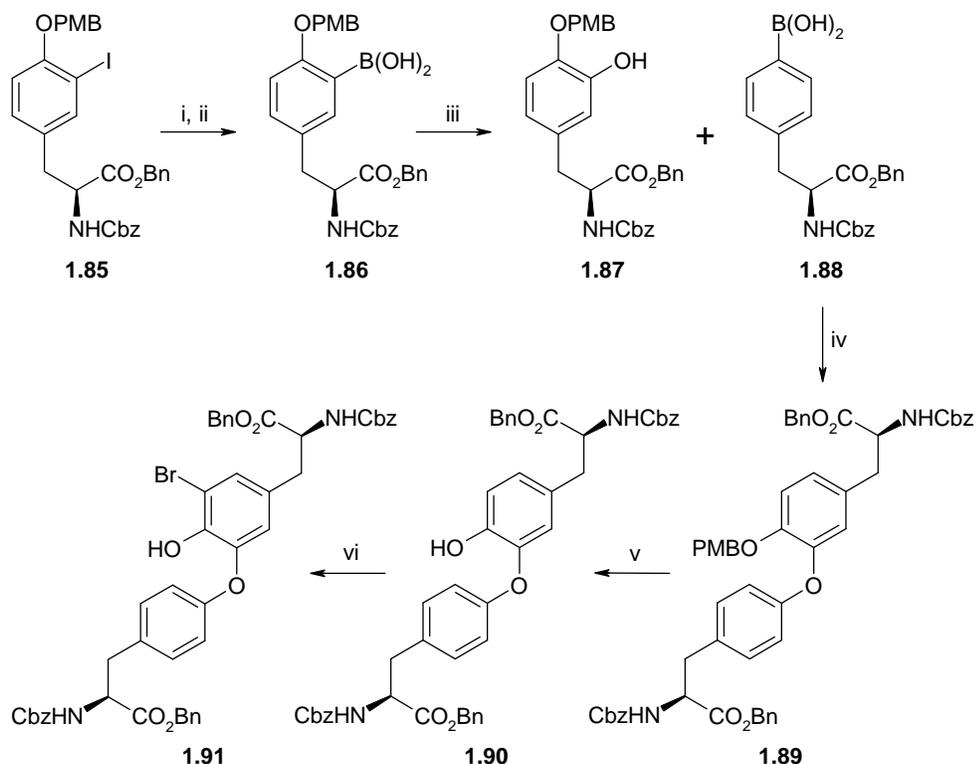


Reagents/Conditions: i) [PdCl₂(dppf)], bis(pinacolato)diboron, KOAc, DMSO, 80 °C; ii) EtOAc/H₂O, 92% over two steps; iii) Cu(OAc)₂, DMAP, 4Å MS, 33%.

Scheme 1.14

In an effort to overcome this side-reaction the phenol and boronic acid groups were switched, thereby removing the *ortho* heteroatom from the boronic acid. A similar coupling was previously reported by Jung and Lazarova.²⁶ The phenolic protecting group was also changed from the benzyl protecting group used previously

to a *p*-methoxybenzyl protecting group, therefore allowing selective deprotection at a later stage of the synthesis.



Reagents/Conditions: i) $[\text{PdCl}_2(\text{dppf})]$, bis(pinacolato)diboron, KOAc, DMSO, 80 °C; ii) EtOAc/ H_2O , 89% over two steps; iii) H_2O_2 , MeOH, 81%; iv) $\text{Cu}(\text{OAc})_2$, pyridine, 4 Å MS, 80%; v) DDQ, 78%; vi) NBS, 70%.

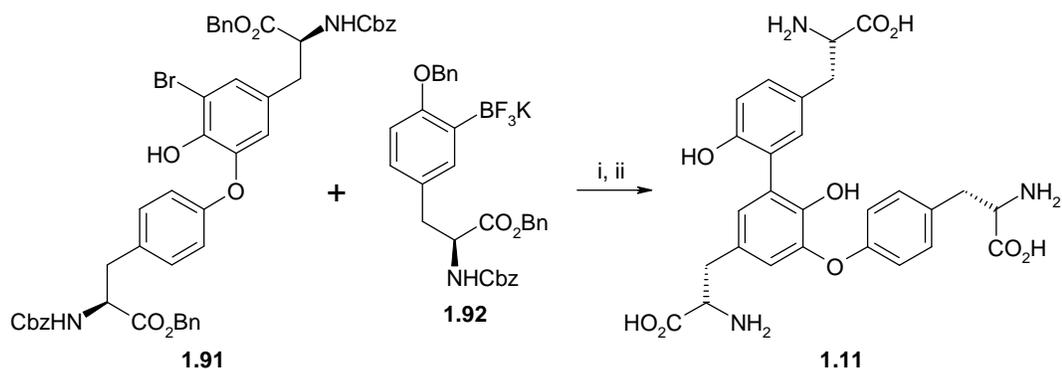
Scheme 1.15

Treatment of the fully protected iodotyrosine derivative **1.85** with bis(pinacolato)diboron, followed by immediate hydrolysis, afforded boronic acid **1.86** in 89% yield over two steps (Scheme 1.15). Subsequent treatment with one equivalent of hydrogen peroxide smoothly furnished the protected dopa derivative **1.87** in 81% yield. Coupling with the phenylalanine-4-boronic acid derivative **1.88**, synthesised from 4-iodo-L-phenylalanine in 63% yield over 4 steps, was then facilitated with copper(II) acetate in the presence of pyridine and 4 Å molecular sieves. On this occasion, in the absence of an *ortho* heteroatom to the boronic acid, the copper(II) catalysed coupling proved much more efficient, with the desired biaryl ether **1.89** formed in 80% yield. Selective removal of the phenolic protecting group was then required as 3,4-*O,O*-dialkyl protected dopa derivatives are known to halogenate

selectively at the 6-position, whereas the greater directing ability of the unprotected 4-phenolic group ensures selective halogenation at the desired 5-position. Removal of the PMB protecting group was achieved in the presence of DDQ, furnishing the phenol **1.90** in 78% yield.

With the biaryl ether **1.90** in hand, selective iodination of the 5-position was then investigated. All efforts to achieve this using iodine and silver(I) salts were unsuccessful. There appears to be no simple explanation for this lack of success when regioselective iodination of closely related tyrosine derivatives appears facile. In contrast, bromination of **1.90** with 1.5 equivalents of *N*-bromosuccinimide smoothly afforded aryl bromide **1.91** in 70% yield.

Suzuki coupling of aryl bromide **1.91** with the trifluoroborate salt **1.92**, quantitatively prepared by treatment of the bis(pinacolato)diboronate with potassium hydrogen fluoride according to the procedure of Vedejs *et al.*,³⁴ was then investigated (Scheme 1.16). In the presence of K_2CO_3 and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ in aqueous THF, the coupled product was isolated in just 7% yield, with unreacted starting material and protodeborated side-products isolated in 67% and 26% yield respectively. However employing conditions developed by Molander *et al.*,^{35,36} with 6 equivalents of NEt_3 and an *i*-PrOH/ H_2O solvent mixture, the yield was raised to 32%. Global deprotection was then achieved through hydrogenolysis to afford pulcherosine **1.11**.



Reagents/Conditions: i) $[PdCl_2(dppf)]$, NEt_3 , *i*-PrOH: H_2O (2:1), Δ , 48 h, 32%; ii) H_2 , Pd/C, THF:MeOH: H_2O (5:5:1), quant.

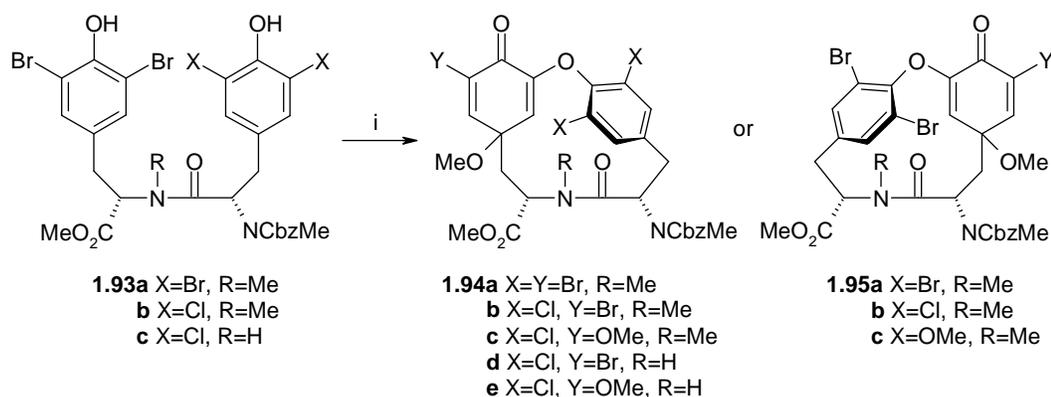
Scheme 1.16

Thus Hutton *et al.* have achieved the first synthesis of the tripeptide pulcherosine **1.11**, the acyclic trimer of tyrosine found within RP 66453. Interestingly, their synthesis highlighted a problem with the iodination of the mono-protected dopa derivative **1.90**, although bromination was successful.

ii. Synthesis of the reversed amide B-O-C ring of RA-VII, bouvardin, deoxybouvardin and related products

Several approaches to the 14-membered isodityrosine ring with a reversed amide link with respect to that of RP 66453, as found in bouvardin, deoxybouvardin and the RA-VII series, have been described. As with the B-O-C ring of RP 66453, nucleophilic aromatic substitution provides a popular and successful entry to the strained 14-membered ring. A wide variety of other methods have also been described to achieve the synthesis of this challenging product.

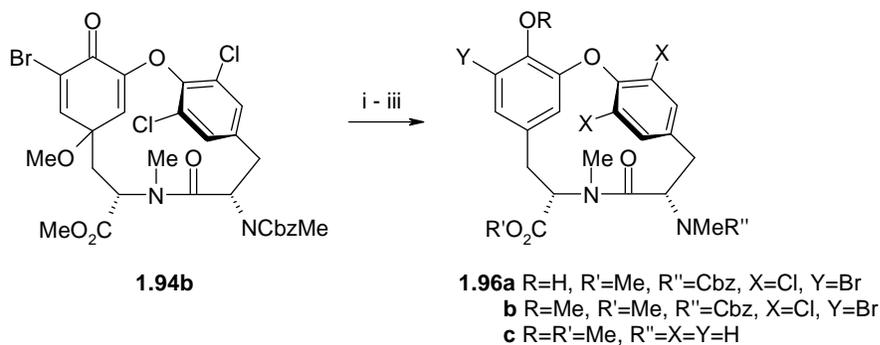
The first published attempt to close the reversed amide cyclophane ring appeared eleven years before the discovery of RP 66453. In their synthesis of deoxybouvardin and RA-VII, Inaba *et al.* relied upon an intramolecular oxidative coupling of two phenolic tyrosine derivatives to induce macrocyclization.³⁷ Utilizing a procedure of Yamamura *et al.*,³⁸ they treated tetra-bromo dityrosine derivative **1.93a** with thallium trinitrate in methanol (Scheme 1.17). Unfortunately under these conditions the unwanted products **1.95a** and **1.95c** were formed in 33% and 49% yields respectively, with none of the desired macrocycle **1.94a** detected. Modelling suggested that the phenolic oxygen of the ‘left’ tyrosine derivative can more easily attack the *ortho*-carbon of the ‘right’ tyrosine, as attack is impeded by the steric clash with the methoxycarbonyl group. Interestingly, when the bromine was substituted for chlorine the ring closing proceeded in the opposite manner, yielding the desired macrocycles **1.94b** and **1.94c** in 5% and 14% yields respectively, with no contamination by **1.95b**. This trend was confirmed as treatment of **1.93c** with TTN proceeded to furnish the 14-membered rings **1.94d** and **1.94e** in 9% and 16% yields respectively.



Reagents/Conditions: i) 3 eq. TTN, MeOH, RT.

Scheme 1.17

Treatment of macrocycle **1.94b** with zinc in 90% acetic acid at room temperature resulted in the rearomatization to **1.96a**, which was immediately methylated with diazomethane to yield biaryl ether **1.96b** (Scheme 1.18). Hydrogenolysis with Pd-C in methanol in the presence of potassium acetate then effected the simultaneous amine deprotection and dehalogenation, affording isodityrosine **1.96c** in 43% yield from **1.94b**. Inaba then advanced this cyclophane ring to both deoxybouvardin and RA-VII.

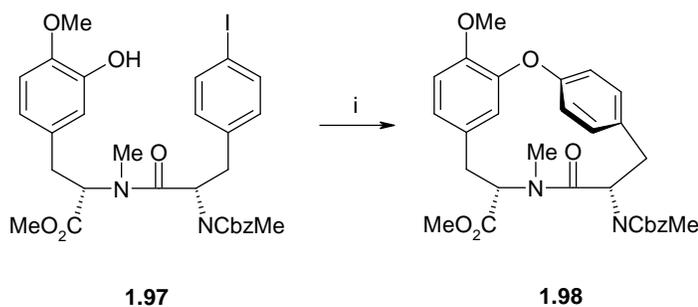


Reagents/Conditions: i) Zn, 90% acetic acid, RT; ii) CH₂N₂, Et₂O/MeOH; iii) 5% Pd-C, MeOH, KOAc, 43% yield from **1.94b**.

Scheme 1.18

Boger *et al.* subsequently reported an alternative approach using an intramolecular Ullmann reaction to form the biaryl ether linkage.³⁹ Optimum

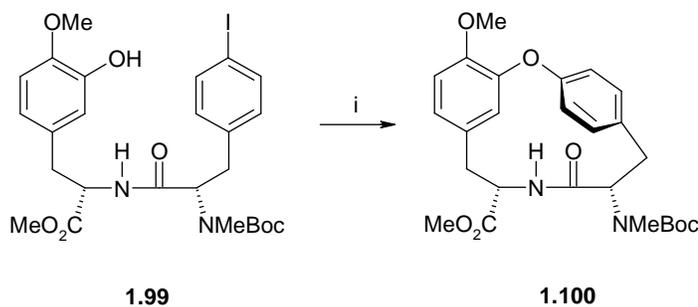
conditions to effect the ring closure involved treatment of **1.97** with CuBr-SMe₂ under conditions of high dilution (0.004 M in pyridine) (Scheme 1.19). Racemisation was suppressed by addition of collidine or dioxane. This intermediate was then used to complete syntheses of both deoxybouvardin and RA-VII.



Reagents/Conditions: i) 2 eq. NaH, 10 eq. CuBr-SMe₂, collidine, 130 °C, 8 h, 30%.

Scheme 1.19

Following the success of the intramolecular Ullmann reaction, Boger *et al.* utilized this methodology in a number of later syntheses. In 2001 Boger's synthesis of *N*²⁹-desmethyl-RA-VII relied on the formation of the 14-membered ring using an intramolecular Ullmann reaction (Scheme 1.20).⁴⁰ Again, the optimised coupling conditions were used, affording the cyclophane ring **1.100** in 36% yield.

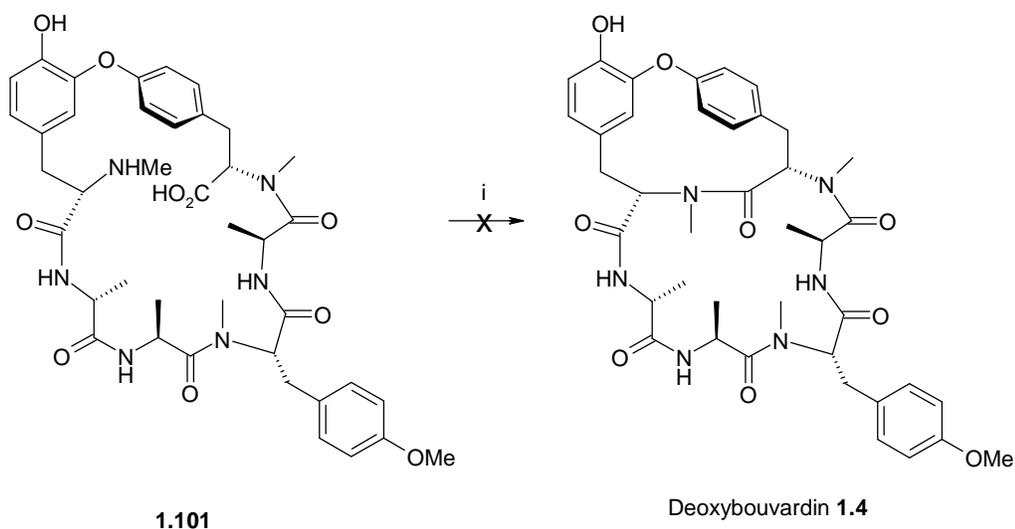


Reagents/Conditions: i) 2 eq. CH₃Cu, collidine, 130 °C, 9 h, 36%.

Scheme 1.20

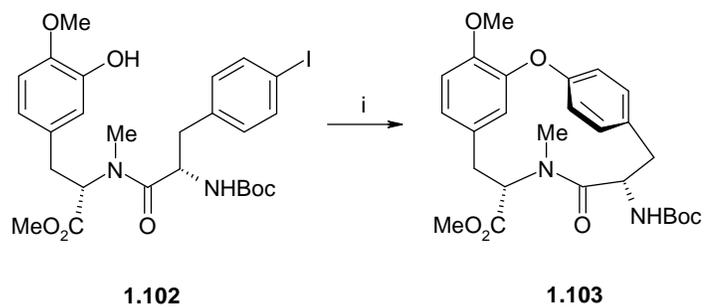
Boger's later attempts to close the 14-membered ring of deoxybouvardin via an intramolecular amide coupling proved unsuccessful (Scheme 1.21).⁴¹ With macrolactamization proving challenging, Boger returned to the intramolecular

Ullmann coupling strategy of **1.97**, **1.97**, **1.102** (Scheme 1.22)⁴² and **1.104** (Scheme 1.23).⁴³



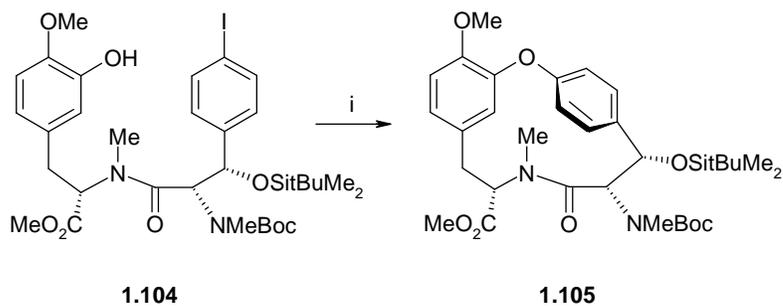
Reagents/Conditions: i) 1.5 eq. DPPA, 5 eq. NaHCO₃, DMF, 0 °C, 72 h.

Scheme 1.21



Reagents/Conditions: i) 2 eq. NaH, 10 eq. CuBr-SMe₂, collidine, 130 °C, 10 h, 34%.

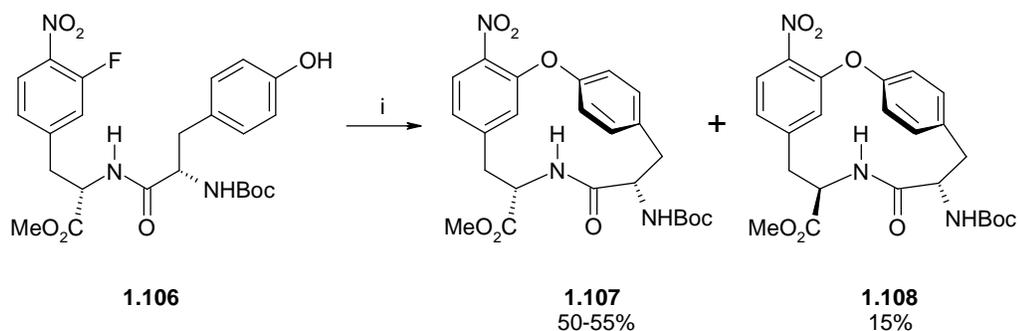
Scheme 1.22



Reagents/Conditions: i) 1.1 eq. NaH, 10 eq. CuBr-SMe₂, 2,6-lutidine, 130 °C, 9 h, 37%.

Scheme 1.23

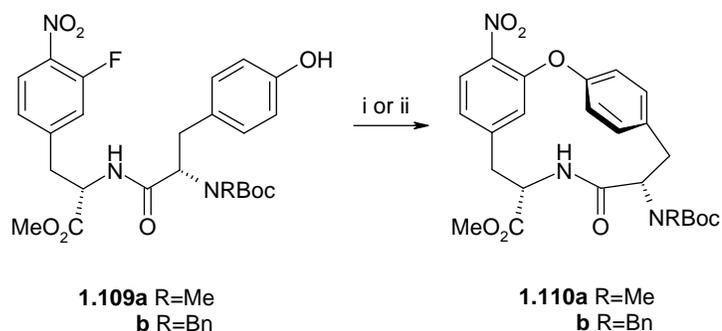
Boger *et al.* were also first to report the use of an intramolecular nucleophilic aromatic substitution to achieve macrocyclization. Cyclization of dipeptide **1.106** was promoted in the presence of NaH in THF, affording the desired 14-membered macrocycle **1.107** in 50-55% yield (Scheme 1.24).⁴⁴ Unfortunately epimerisation was observed adjacent to the ester centre, to **1.108**, and this proved to be an intractable problem under the conditions investigated. The use of K₂CO₃ in DMF was also investigated, but this resulted in a lower yield of the desired macrocycle and increased epimerisation. Reduction to the aniline with hydrogen in the presence of Pd-C, followed by diazotisation with HBF₄ and *t*-BuONO and conversion to the phenol with Cu(NO₃)₂-Cu₂O, afforded the cycloisodityrosine in 47% yield from **1.107**.



Reagents/Conditions: i) 3.3 eq. NaH, THF, 0-25 °C.

Scheme 1.24

In-depth studies on the intramolecular aromatic substitution reaction to close the cycloisodityrosine ring established optimal conditions to maximise the yield of the desired *S,S*-macrocyclic product whilst minimising the epimerisation of the centre adjacent to the ester functionality (Scheme 1.25).⁴⁵ The reaction conditions required careful control as extended reaction times or excess NaH led to increasing amounts of the undesired epimerised macrocycle. Interestingly, performing the reaction under the seemingly mild conditions of K₂CO₃ in DMF gave predominantly the undesired epimerised product **1.108**. Again reduction of the nitro group and conversion to the phenol afforded the cycloisodityrosine ring. Cyclization of the benzyl protected amine **1.109b** afforded marginally improved yields of the macrocycle with no detected epimerisation using NaH as the mediator.

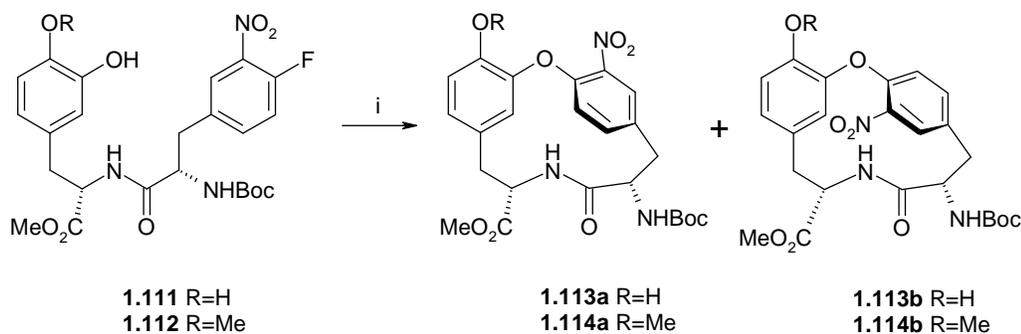


Reagents/Conditions: i) 2.2 eq. NaH, THF, 0-25 °C, 2-6 h, **1.110a** in 50-61% yield; ii) 2.2 eq. NaH, 20:1 THF:DMF, 0-25 °C, 4.5 h, **1.110b** in 63% yield.

Scheme 1.25

Subsequently, Zhu *et al.* published their observations on macrocyclization of dipeptide **1.109a**.⁴⁶ Like Boger, it was observed that treatment with K_2CO_3 in DMF induced epimerisation while treatment with LiH in THF, Na_2CO_3 in DMF and CsF in DMF all failed to induce the desired cyclization, with the latter providing the epimerised product after extending reaction times to 15 days. Treatment under the more basic conditions of KH in THF resulted in a 1:1 mixture of the desired and epimerised macrocycles, whilst the optimum conditions were found to be NaH in THF which gave in their hands the cyclophane ring in 54% yield, with 19% yield of the epimerised side-product.

Zhu *et al.* then published an intramolecular nucleophilic aromatic substitution in which the nucleophilic phenolic group and the electrophilic fluorine partner were reversed (Scheme 1.26).⁴⁷ Use of the L-dopa derivative with a 4-fluoro-3-nitrophenylalanine moiety was expected to bring several advantages. Firstly it would allow the use of commercially available L-dopa which does not require selective protection of one phenolic group. Secondly 4-fluoro-3-nitrophenylalanine becomes the electrophilic partner, with the effect of minimising epimerisation seen when using 3-fluoro-4-nitrophenylalanine. Finally, later steps would require the removal of the nitro group rather than its conversion to a phenol group, which is generally more reliable on larger scale reactions.

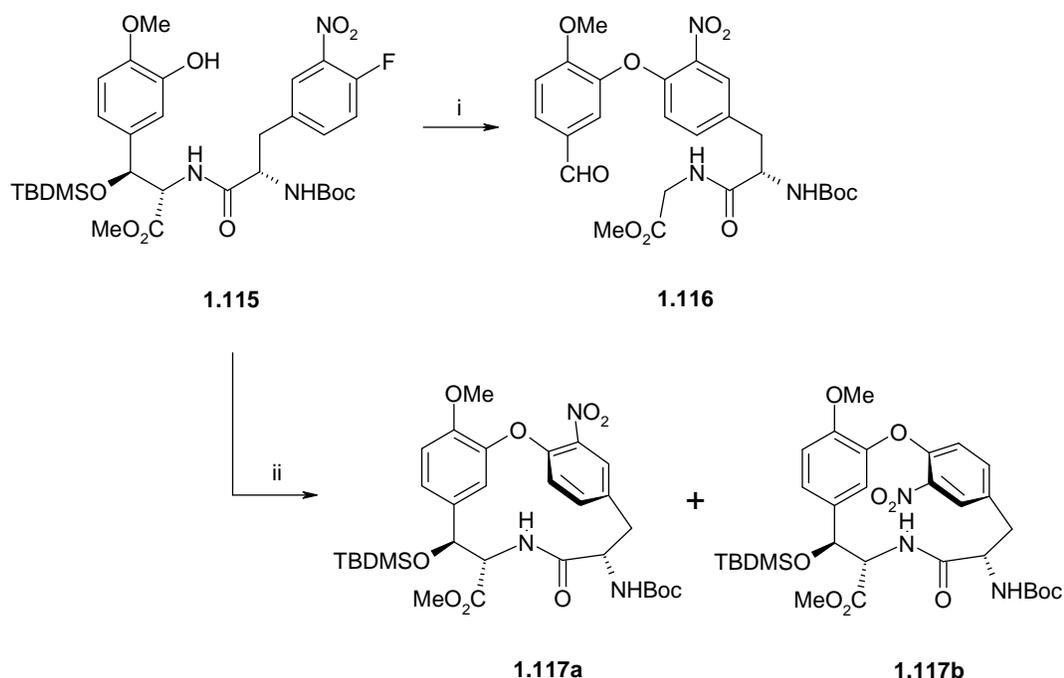


Reagents/Conditions: i) K_2CO_3 , DMSO, 0.002 M, RT, 55-65% of **1.113a** and **1.113b**, 75% of **1.114a** and **1.114b**.

Scheme 1.26

Optimal conditions for cyclization required polar aprotic solvents. Though no reaction was observed with THF, in DMSO it proceeded smoothly to furnish diastereomers **1.113a** and **1.113b** in good yield (Scheme 1.26). Due to the instability of the cyclophane rings towards flash chromatography, a one-pot cyclization and methylation of the phenolic group was developed. Finally reduction of the nitro group to an aniline group, followed by diazotization and reduction afforded the 14-membered cycloisodityrosine ring. Most importantly this route demonstrates the advantage of the use of 4-fluoro-3-nitrophenylalanine over 3-fluoro-4-nitrophenylalanine, as epimerisation is more facile for the latter. Zhu *et al.* have also shown that cyclization of the pre-protected dipeptide **1.112** is more efficient still, affording a mixture of cyclophanes **1.114a** and **1.114b** in a combined yield of 75%.⁴⁸

Greck *et al.* have recently reported their use of the method in the synthesis of bouvardin and RA-V.⁴⁹ Notably, their route required an additional protected hydroxyl group next to the ester moiety, **1.115** (Scheme 1.27). However, when this substrate was exposed to standard cyclization conditions cleavage of the TBDMS protecting group was observed followed by a retro-Aldol reaction, yielding the acyclic aldehyde **1.116** in 45% yield. Using the conditions established by Boger *et al.*,⁵⁰ and with the addition of $CaCO_3$ to scavenge the fluoride, the nucleophilic aromatic substitution reaction was successfully realised affording a mixture of the two atropisomers **1.117a** and **1.117b** in 10% yield.



Reagents/Conditions: i) 4 eq. K_2CO_3 , 3Å MS, DMSO, 0.01 M, RT, 1 h, 45%; ii) $CaCO_3$, DMSO, 0.002 M, RT, 10% of **1.117a** and **1.117b**.

Scheme 1.27

In conclusion, closure of the 14-membered cyclophane ring poses a tough synthetic challenge, highlighted by the frequent use of the degradation of RA-VII as a source of the macrocycle.^{51, 52, 53, 54} Inaba's intramolecular oxidative coupling was the first published route towards the cycloisodityrosine ring. Yields were poor and the starting materials required numerous and low yielding steps, however the strained 14-membered ring was synthesised and used in total syntheses of both deoxybouvardin and RA-VII. In comparison, the intramolecular Ullmann reaction shows considerable advantages for closure of the 14-membered ring. Though yields are generally modest the method allows the use of readily available amino acids, rather than dibromo- or dichlorophenols which require lengthy syntheses. Finally, intramolecular nucleophilic aromatic substitution offers further advantages including the use of commercially available amino acid starting materials, including L-dopa, and vastly reduced racemisation, making the synthesis of the macrocycle both robust and reliable.

CHAPTER 2 – RESEARCH AND DISCUSSION

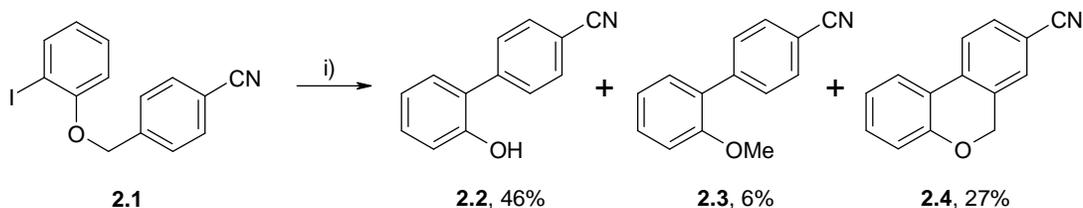
2.1 Background

At the outset of this program, six papers had been published describing routes towards RP 66453. Of these six routes two had succeeded in closing both macrocyclic rings, with just one route providing enough material to continue with the synthesis. With the stereocentres of the natural product still ambiguous, Zhu's total synthesis of an atropisomer of RP 66453 defined not only the chirality of all five stereocentres but also the atropisomerism of the biaryl axis, establishing the absolute configuration as (*M,S,S,S,S,S*). Central to Zhu's strategy was the closure of the A-B ring using a palladium catalysed Suzuki cross-coupling reaction to form the aryl-aryl bond, however in doing so Zhu set the atropisomerism as the thermodynamically more stable product, eventually yielding the atropisomer of RP 66453 with the (*P,S,S,S,S,S*) configuration. With this in mind we reasoned that a synthesis of RP 66453 could be achieved if the biaryl linkage were formed under conditions of kinetic control.

Previous work within the Harrowven group demonstrated a cascade reaction which resulted in the synthesis of biaryls from benzyl iodoaryl ethers.⁵⁵ We envisaged the application of this method, the addition of an aryl radical intermediate to an arene, to establish the biaryl linkage. Crucially, radical cyclization reactions of this type are known to be under kinetic control, and as a consequence the stereochemical outcome will be determined by the trajectory followed by the radical donor as it adds to the acceptor arene, rather than the product stability.

2.2 Radical formation of biaryls from benzyl iodoaryl ethers

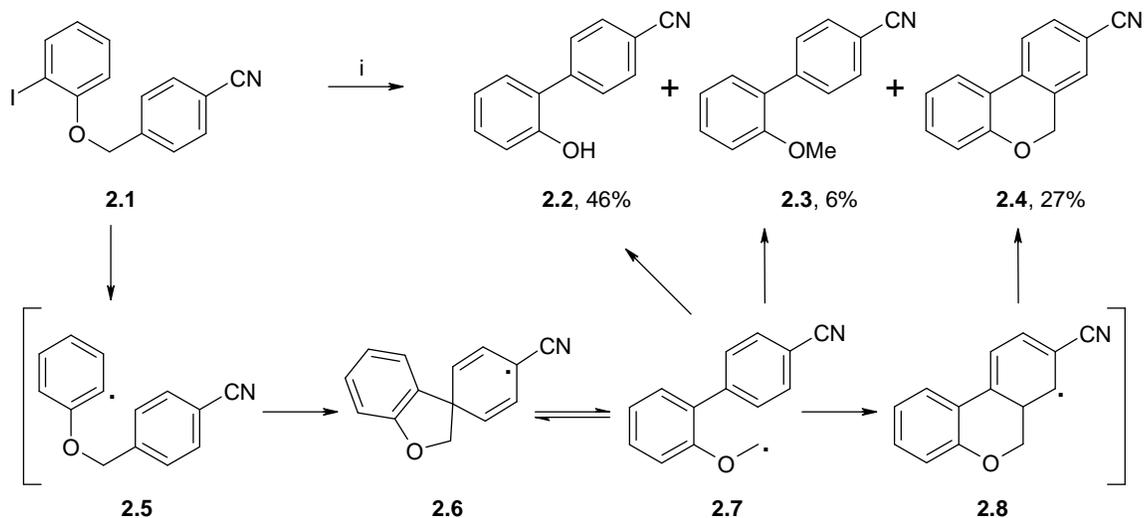
Inspiration for the key step came from work previously carried out within the Harrowven group, whereby treatment of benzyl ether **2.1** with tributyltin hydride under standard radical forming conditions led to the formation of biaryls **2.2** and **2.3**, and chromene **2.4** (Scheme 2.1).⁵⁵



Reagents/Conditions: i) Bu_3SnH , AIBN, PhMe, 80 °C.

Scheme 2.1

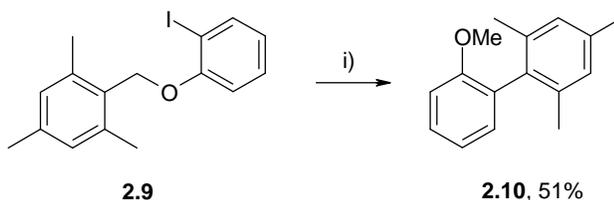
The reaction is presumed to proceed by homolysis of the carbon iodine bond leading to radical intermediate **2.5** (Scheme 2.2). 5-*exo*-Trig cyclization, with *ipso*-attack leads to spirocycle **2.6**. Fragmentation to **2.7** facilitates rearomatization, and from this intermediate several pathways are possible. Hydrogen atom abstraction from the tributyltin hydride yields the methyl ether **2.3**, whilst a less obvious process, possibly involving a redox reaction of **2.7** and a stannane, or trapping with molecular oxygen, leads through to the phenol **2.2**. Addition of the radical onto the arene in a 5-*exo*-trig cyclization results in reformation of the spirocycle **2.6**, whereas the slower 6-*endo/exo*-trig leads to formation of benzo[*c*]chromene **2.8**.



Reagents/Conditions: i) Bu₃SnH, AIBN, PhMe, 80 °C.

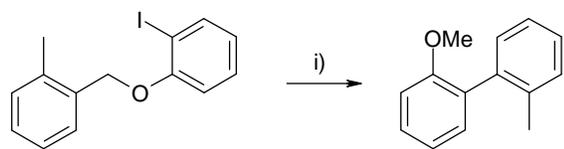
Scheme 2.2

Several examples of the reaction have been accomplished, and from these some general trends have emerged.⁵⁵ For electron deficient arenes the phenol is the major product. When the 6-*endo*-trig cyclization pathway is blocked by the presence of *ortho*-methyl substituents as in 2,4,6-trimethylbenzyl ether **2.9**, the methyl ether **2.10** is the sole product (Scheme 2.3). Indeed when only one *ortho*-methyl substituent is present as in the *o*-tolyl ether **2.11**, the methyl ether product **2.12** is still the major product, indicating that the intermediate methylene radical akin to **2.7** first abstracts a hydrogen atom from the proximal methyl group to give a tolyl radical which then abstracts a hydrogen atom from tributyltin hydride (Scheme 2.4). This method can also be extended to include a tandem variant whereby a cascade sequence is applied to diiodide **2.13**, furnishing terphenyl **2.14** in 67% yield (Scheme 2.5).



Reagents/Conditions: i) Bu₃SnH, AIBN, PhMe, 80 °C.

Scheme 2.3

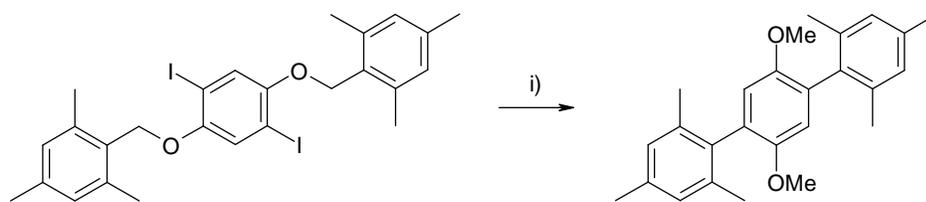


2.11

2.12, 47%

Reagents/Conditions: i) Bu_3SnH , AIBN, PhMe, 80 °C.

Scheme 2.4



2.13

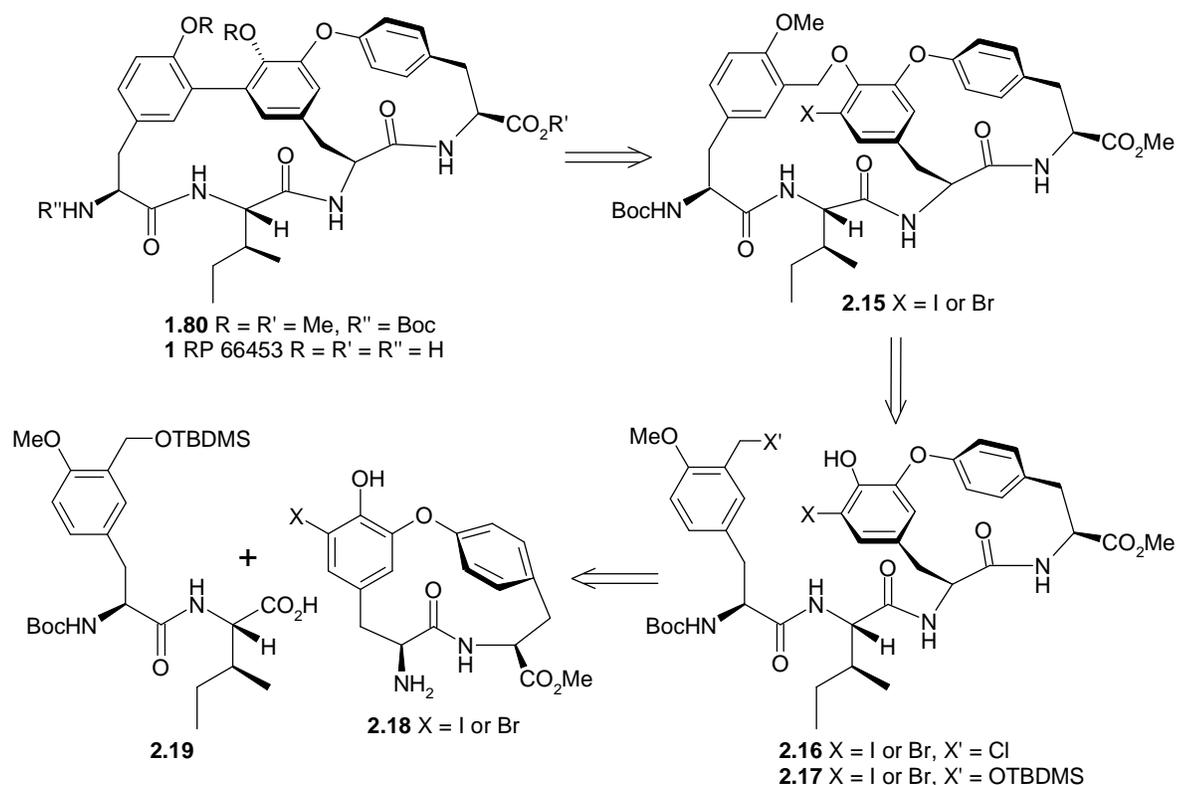
2.14, 67%

Reagents/Conditions: i) Bu_3SnH , AIBN, PhMe, 80 °C.

Scheme 2.5

2.3 Our retrosynthesis of RP 66453

In a retrosynthetic sense, formation of the aryl-aryl bond would result from a radical induced transannular ring contraction of the halogenated macrocycle **2.15** (Scheme 2.3). Formation of benzyl aryl ether **2.15** results from a S_N2 nucleophilic substitution of the benzyl chloride **2.16**, which in turn is the product of a peptide coupling between TBDMS protected benzyl alcohol **2.19** and the halogenated B-O-C ring **2.18**.



Scheme 2.3

The calculated energy minimum for the radical transannular ring contraction precursor (Figure 1, hydrogen atoms omitted for clarity), suggests that the desired *Re* face addition to the arene will be favoured. If the wrong atropisomer is formed, then the radical acceptor and donor arenes can be switched, thereby providing an alternative strategy for the synthesis of the natural atropisomer of RP 66453 (Scheme 2.4).

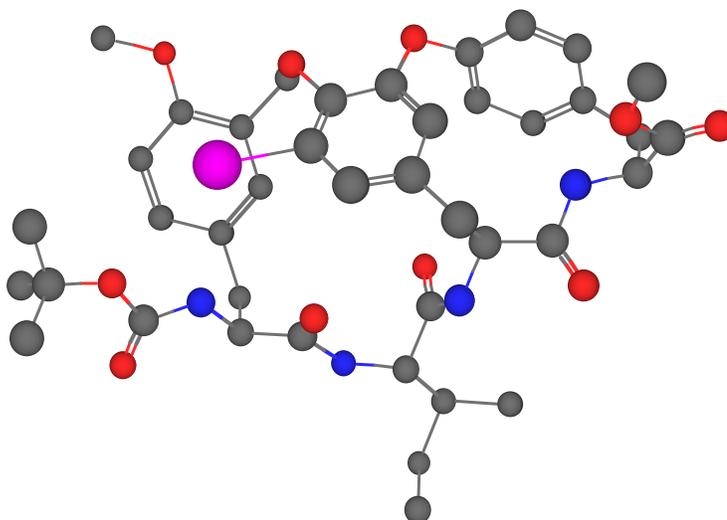
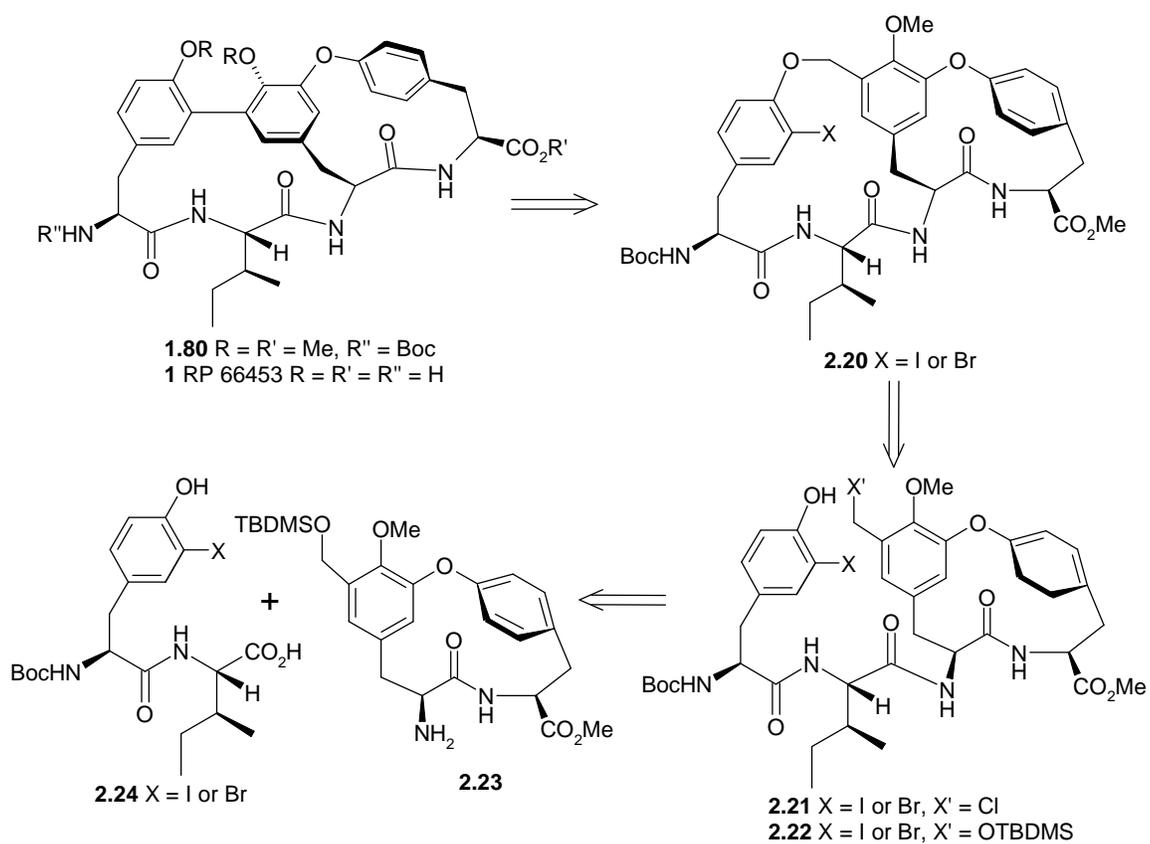


Figure 1.

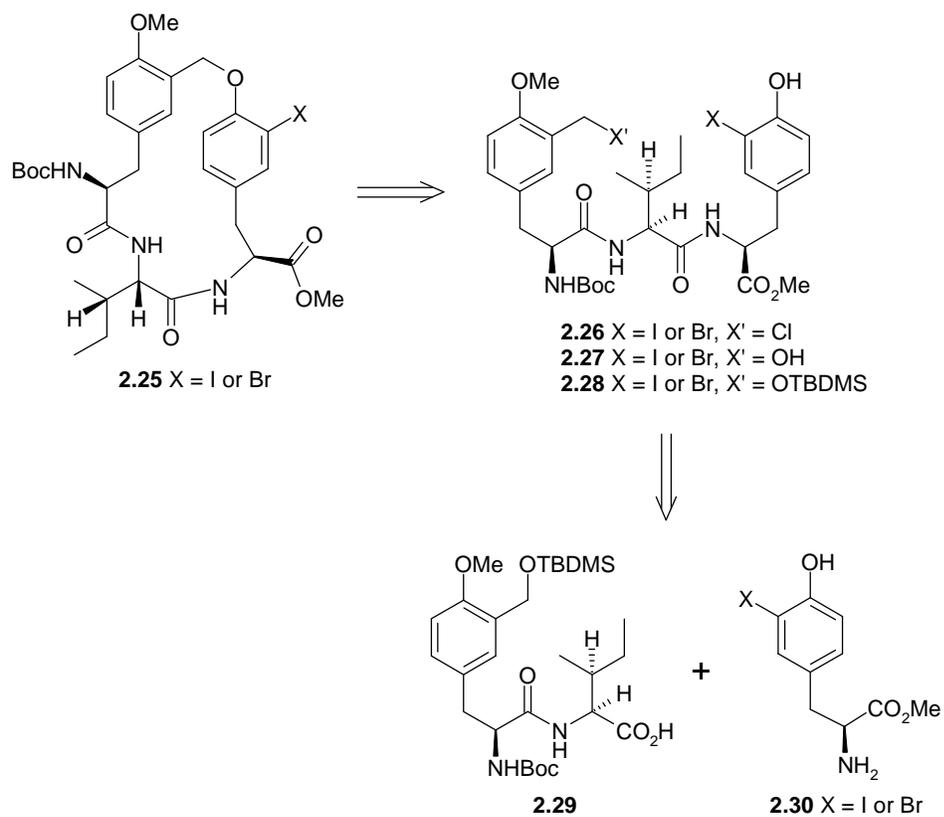


Scheme 2.4

In order to verify the viability of our proposed route, model studies were carried out.

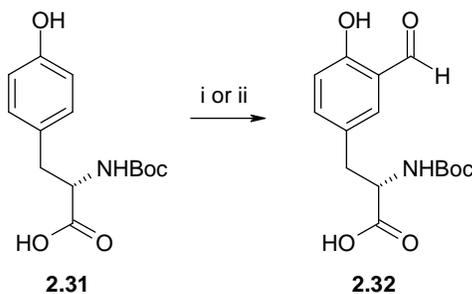
2.4 Modelling the formation of the biaryl linkage

Our proposed route relies on a radical induced transannular ring contraction, and in order to test the viability of this route to form our vital biaryl linkage we chose to carry out tests upon a simplified system **2.25**. Synthesis of the model system requires macrocyclization of benzyl chloride **2.26** which in turn can be accessed from the benzyl alcohol **2.27** (Scheme 2.5). Protection of the benzyl alcohol as TBDMS ether **2.29** is required to permit coupling to the halogenated tyrosine methyl ester **2.30**.



Scheme 2.5

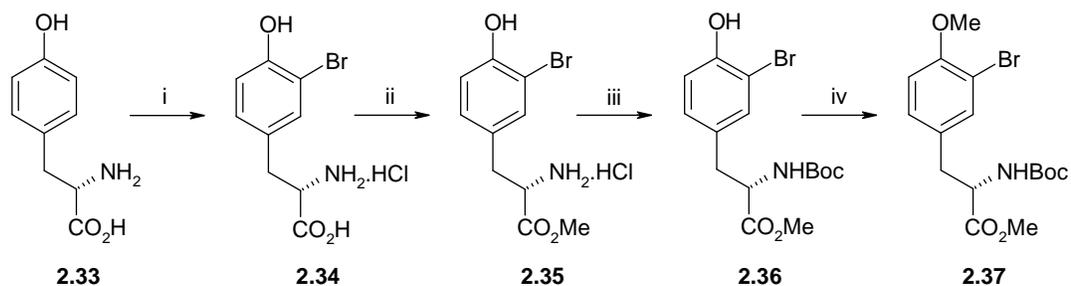
Synthesis of the protected benzyl alcohol **2.29** began with the formylation of Boc-protected L-tyrosine **2.31** using Reimer-Tiemann conditions (Scheme 2.6).⁵⁶ Though successful, this route was low yielding and capricious, prompting us to find an alternative route to install the aldehyde. Direct formylation with SnCl₄ and paraformaldehyde was investigated, but failed to yield any of the desired product **2.32**.



Reagents/Conditions: i) NaOH, CHCl₃, H₂O, 10-28%; ii) SnCl₄, Bu₃N, paraformaldehyde, toluene, 0%.

Scheme 2.6

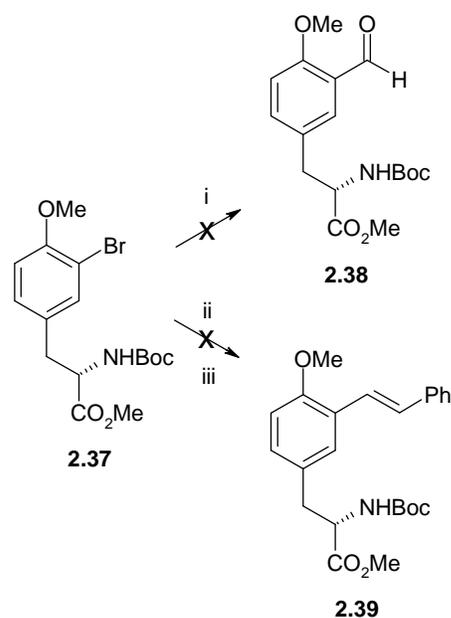
As direct formylation proved troublesome, an alternative strategy was devised involving the protected bromo-L-tyrosine derivative **2.37** (Scheme 2.7). With the halide installed at the 3-position, we envisioned the use of this functionality to provide a handle for further manipulation at this position. Thus bromination of L-tyrosine **2.33** and global protection yielded **2.37** in four steps in 51% overall yield.



Reagents/Conditions: i) KBrO₃, KBr, 0.5 N HCl; ii) SOCl₂, MeOH, 68% over two steps; iii) (Boc)₂O, NEt₃, dioxane/H₂O, 81%; iv) MeI, K₂CO₃, DMF, 92%.

Scheme 2.7

Subsequent halogen-lithium exchange, followed by the addition of DMF failed to install the aldehyde at the 3-position (Scheme 2.8). A range of conditions were investigated in an attempt to induce a Heck coupling with styrene. A variety of catalysts ($\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$), ligands (DPPP, PPh_3) and solvents (DMF, MeCN) were utilized, however in each case only starting material was recovered. Similarly a range of conditions were examined for the Suzuki coupling of the bromo-L-tyrosine derivative **2.37** and *trans*-phenylvinylboronic acid, varying the catalyst (PdCl_2 , $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$), base (K_3PO_4 , Na_2CO_3 , K_2CO_3) and solvent (DMF, THF), however all attempts failed to yield the desired stilbene **2.39**.

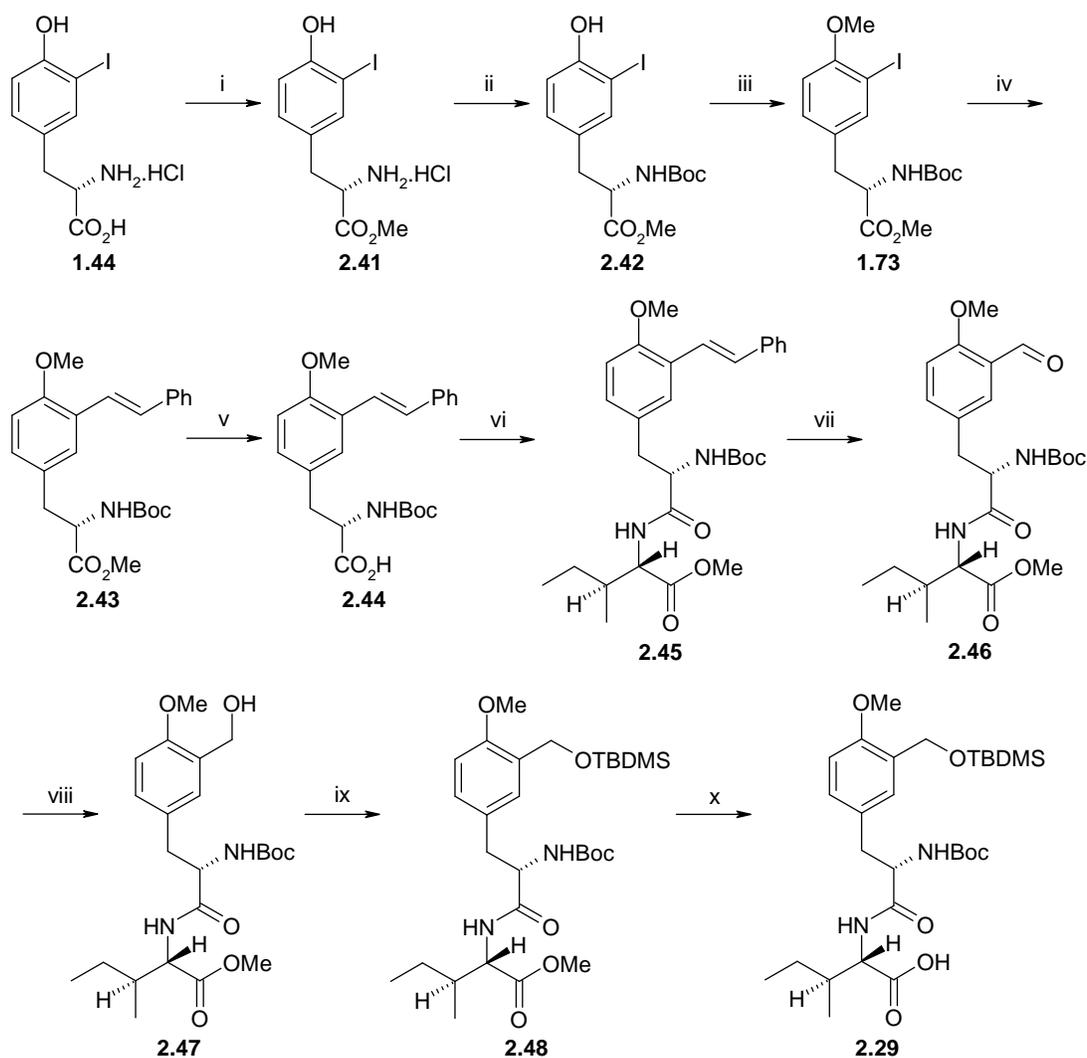


Reagents/Conditions: i) NaH, *n*BuLi, THF then DMF; ii) styrene, Pd catalyst, NEt_3 , solvent; iii) *trans*-phenylvinylboronic acid, Pd catalyst, PPh_3 , base, solvent.

Scheme 2.8

With the 3-bromo-L-tyrosine **2.37** failing to promote the required functionalisation, we considered whether the problem lay with the reactivity of the halide. With this in mind we reasoned that conversion to the iodo-derivative should enhance the reactivity of the 3-position, facilitating manipulation of this position. Pleasingly conversion to the 3-iodo-derivatives did prove adequately reactive to facilitate reaction at the 3-position.

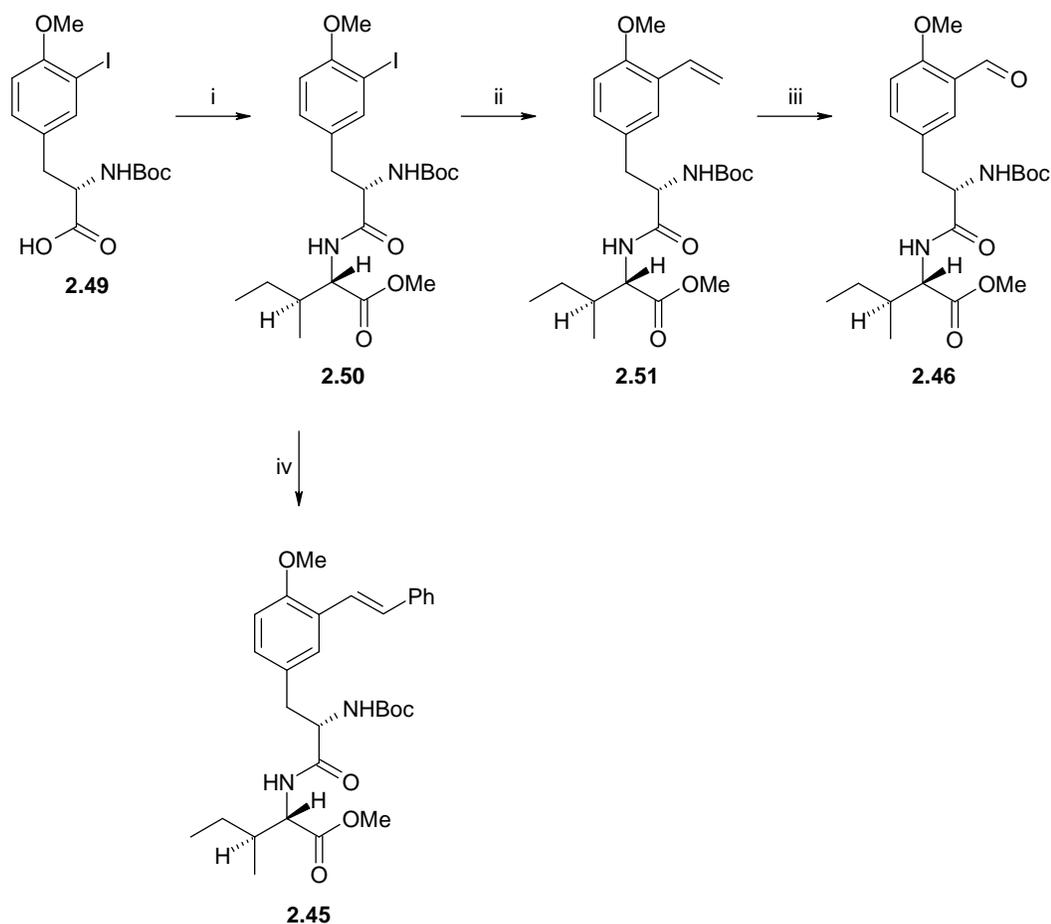
Thus commercially available 3-iodo-L-tyrosine **1.44** was transformed into the fully protected derivative **1.73** in three steps and 60% overall yield (Scheme 2.9). Suzuki coupling to *trans*-phenylvinylboronic acid then proceeded smoothly, furnishing the stilbene **2.43** in 89% yield. Saponification of the methyl ester then allowed coupling to L-isoleucine methyl ester to give the dipeptide **2.45**. Ozonolysis next revealed aldehyde **2.46**, which was converted to the benzyl alcohol **2.47** by the action of NaBH₄ in 99% yield. Protection of the benzyl alcohol with TBDMSCl and saponification of the methyl ester then furnished the dipeptide fragment **2.29**.



Reagents/Conditions: i) SOCl₂, MeOH, Δ, 71%; ii) Boc₂O, NEt₃, dioxane/H₂O, 0 °C-RT, 84%; iii) MeI, K₂CO₃, DMF, RT, 100%; iv) *trans*-phenylvinylboronic acid, K₂CO₃, Pd(dppf)Cl₂.CH₂Cl₂, DMSO, 80 °C, 89%; v) LiOH.H₂O, THF/H₂O, RT, 100%; vi) L-isoleucine methyl ester, EDC, HOBT, NEt₃, DCM, RT, 94%; vii) O₃, PPh₃, DCM, -78 °C, 83%; viii) NaBH₄, MeOH, 0 °C, 99%; ix) TBDMSCl, DMAP, NEt₃, DCM, RT, 89%; x) LiOH.H₂O, THF/H₂O, RT, 99%.

Scheme 2.9

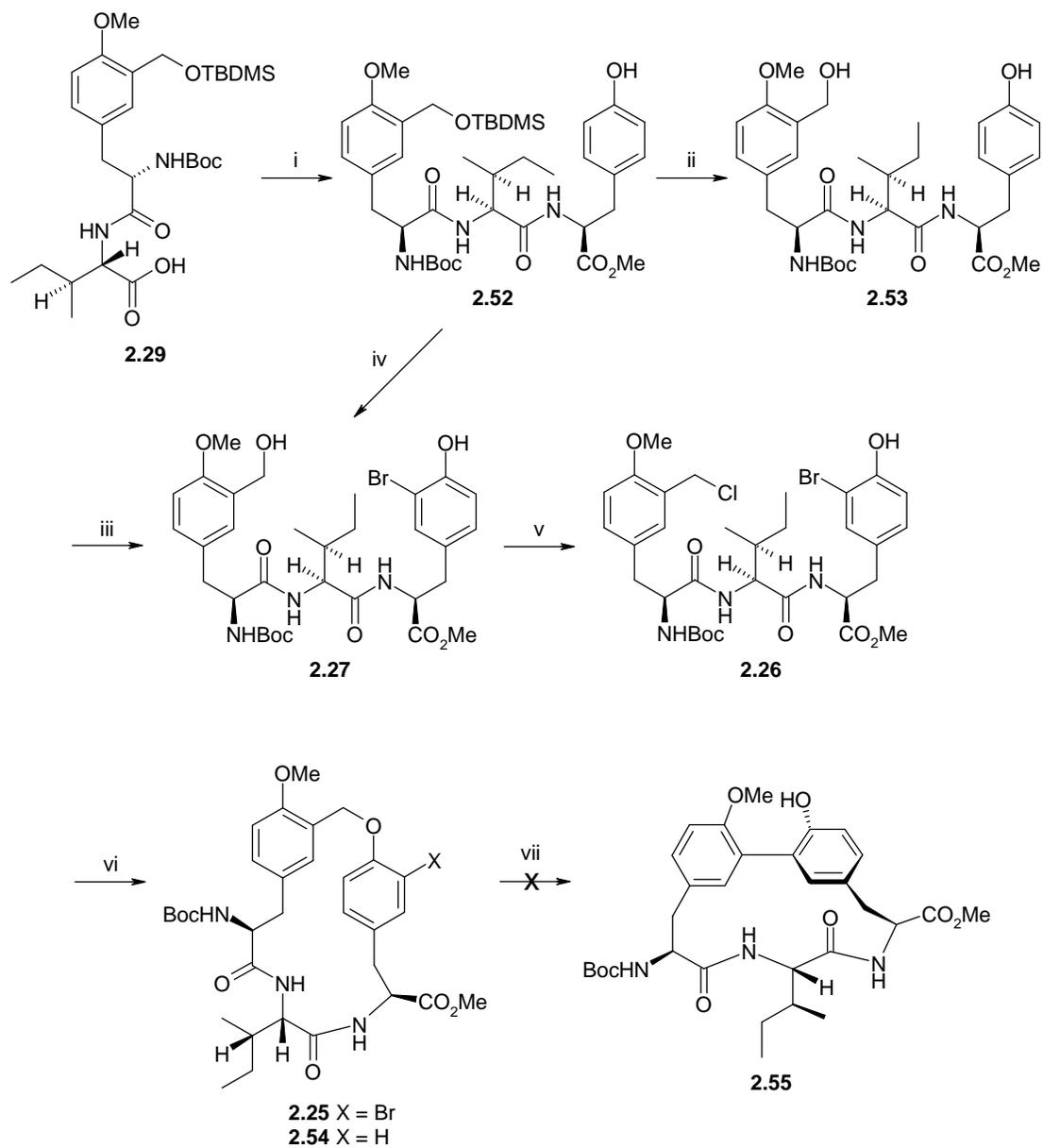
Alternatively, coupling of the iodo-tyrosine derivative **2.49** with L-isoleucine methyl ester provided dipeptide **2.50** (Scheme 2.10). Suzuki coupling of iodide **2.50** with *trans*-phenylvinylboronic acid did yield the desired stilbene **2.45**, but yields were greatly reduced to that achieved previously. Likewise, the Stille coupling of **2.50** with tributylvinyltin furnished styrene **2.51**, but yields were much poorer than the previous Suzuki cross-coupling reaction. Ozonolysis of this styrene was comparable to that of the stilbene, affording the aldehyde **2.46** in 83% yield.



Reagents/Conditions: i) L-isoleucine methyl ester, EDC, HOBt, NEt₃, DCM, RT, 86%; ii) tributylvinyltin, Pd(dppf)Cl₂.CH₂Cl₂, DMF, RT, 37%; iii) O₃, PPh₃, DCM, -78 °C, 83%; iv) *trans*-phenylvinylboronic acid, K₂CO₃, Pd(dppf)Cl₂.CH₂Cl₂, DMSO, 80 °C, 29%.

Scheme 2.10

Coupling of the TBDMS protected benzyl alcohol **2.29** with L-tyrosine methyl ester was promoted with EDC and HOBT, furnishing the tripeptide **2.52** in 70% yield (Scheme 2.11). Deprotection of the TBDMS protecting group with TBAF next furnished benzyl alcohol **2.53** in excellent yield (94%), as did the subsequent bromination with NBS to the brominated benzyl alcohol **2.27** (82%). Alternatively direct bromination and deprotection could be achieved in one-pot by simply treating the TBDMS protected alcohol with NBS. However, this gave a yield of 74%, making the two-step synthesis more efficient. Conversion of benzyl alcohol **2.27** to benzyl chloride **2.26** was achieved with thionyl chloride in 93% yield. S_N2 displacement of the benzyl chloride was then promoted by treatment with potassium carbonate and potassium iodide at 50 °C, closing the ring and furnishing the precursor for our radical induced transannular ring contraction **2.25**. Unfortunately, treatment of **2.25** under standard radical forming conditions failed to yield any of the biaryl product **2.55**. Indeed the only product isolated was that of the direct halide reduction, **2.54**, though this was in insufficient quantity to allow full characterisation. A lack of material prevented further attempts at the reaction and it was decided to focus our attention on an alternative strategy to form the biaryl linkage.

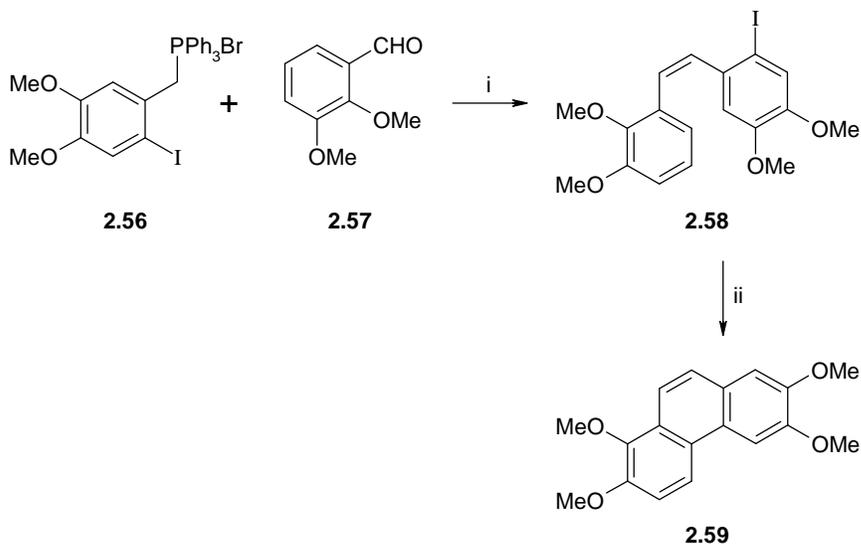


Reagents/Conditions: i) L-Tyrosine methyl ester, EDC, HOBT, NEt₃, DCM, RT, 70%; ii) TBAF, THF, RT, 94%; iii) NBS, DMF, RT, 82%; iv) NBS, DMF, RT, 74%; v) SOCl₂, DCM, 0 °C, 93%; vi) K₂CO₃, KI, DMF, 80 °C, 58%; vii) Bu₃SnH, VAZO, PhMe, 110 °C, 0%.

Scheme 2.11

2.5 Formation of biaryls from phenanthrenes

The formation of biaryl bonds using radical intermediates can also be realised using halogenated *cis*-stilbenes.^{57, 58, 59} Previous work within the Harrowven group has shown that phenanthrene **2.59** can be formed in high yield from stilbene **2.58** using a radical cyclization methodology (Scheme 2.12).⁶⁰ This method has many advantages over the classical oxidative photocyclization of bis(stilbene)s which often suffer from complex product mixtures arising from poor regiochemical control and competitive side reactions.⁶¹ The formation of the *cis*-stilbene is controlled during the Wittig reaction by utilizing cooperative *ortho*-effects.⁶²

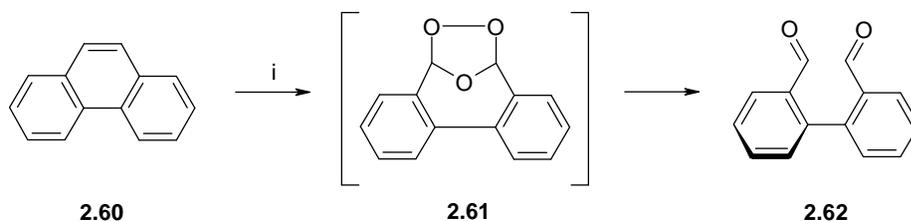


Reagents/Conditions: i) KO^tBu, THF, 0 °C, 99%, *Z/E* ~ 90:1; ii) Bu₃SnH, AIBN, PhMe, 90 °C, 74%.

Scheme 2.12

It should then be possible to selectively ozonolyze the C9-C10 phenanthrene bond, Clar's rules state that the central ring of phenanthrenes is the least aromatic of the three, therefore making it susceptible to chemical manipulation. Indeed many previous papers have been published on the ozonolysis of phenanthrenes. In 1905 Harries *et al.* reported the first ozonolysis of phenanthrene, although the ozonide was identified by elemental analysis they were unable to identify the decomposition products of this explosive intermediate.⁶³ However in 1955 Schmitt *et al.* isolated not only the ozonide but also the decomposition products, confirming the attack of ozone

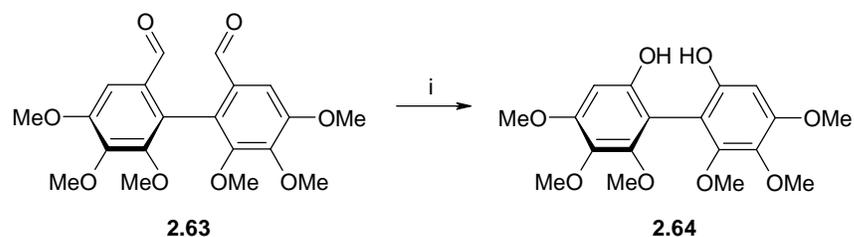
at the central double bond of the phenanthrene resulting in the formation of a bis-aldehyde.⁶⁴ Shortly after Bailey *et al.* published the first investigations into the course and mechanism of the reaction, demonstrating that treatment of phenanthrene **2.60** with ozone results in the formation of the dialdehyde **2.62** via a mono-ozonide intermediate **2.61** (Scheme 2.13).⁶⁵



Reagents/Conditions: i) O₃, MeOH, -20 °C – 0 °C then NaI, AcOH, 84%.

Scheme 2.13

Finally a double Baeyer-Villiger oxidation can be envisioned to convert the bis-aldehyde into a biphenol.^{66, 67} First utilized by Huang *et al.* in the synthesis of 6-phenyl- and 8-phenyl tetrahydro-isoquinolines from boldine,⁶⁸ the reaction is exemplified by the oxidation of bis-aldehyde **2.63** into biphenol **2.64** as published by Meyers *et al.* (Scheme 2.14).⁶⁹

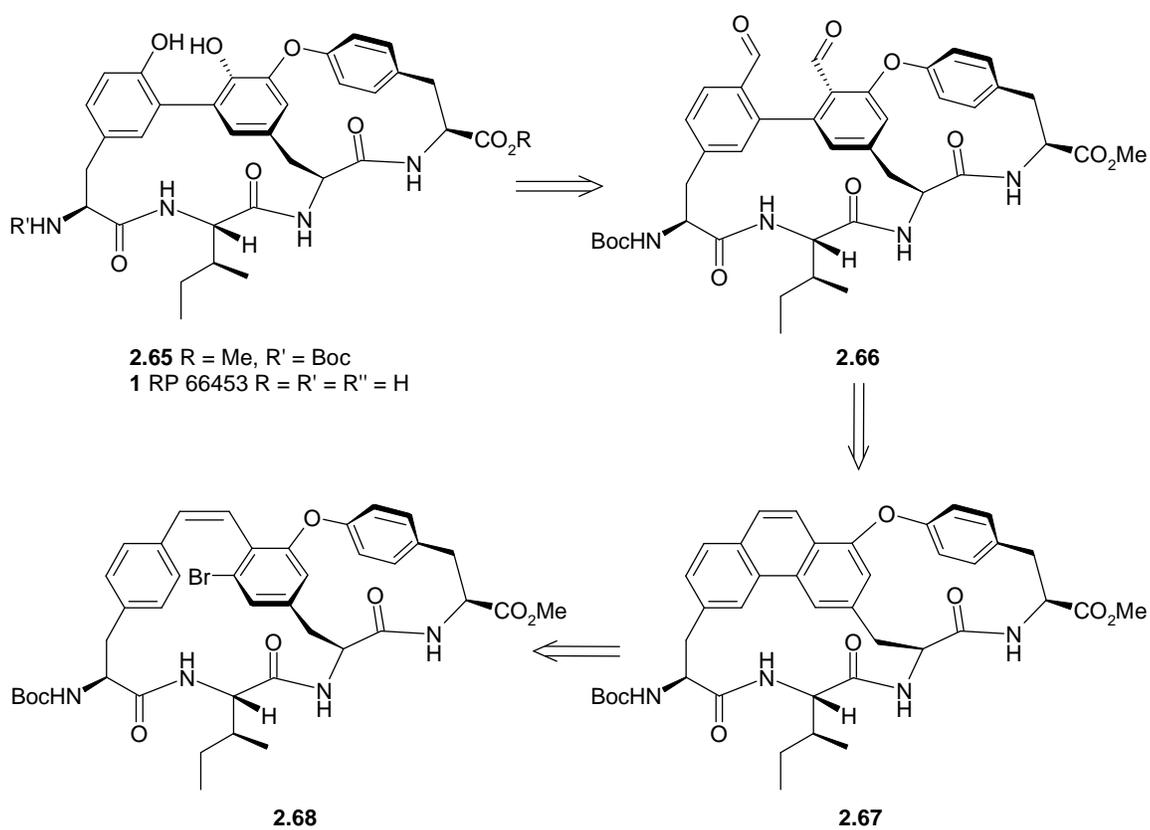


Reagents/Conditions: i) *m*CPBA, NaHCO₃, DCM, 83%.

Scheme 2.14

2.6 The A-B ring – formation of the phenanthrene

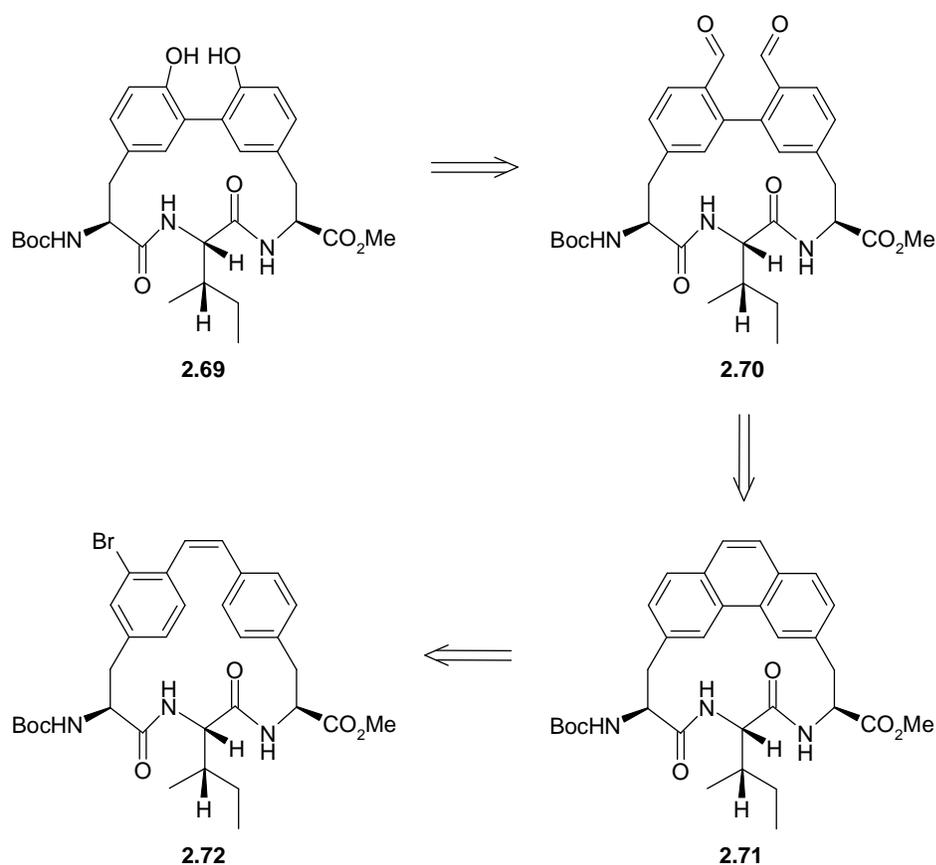
Our alternative strategy for the formation of the biaryl linkage centres upon the formation and subsequent cleavage of phenanthrene **2.67** (Scheme 2.15). Our plan was to prepare *cis*-stilbene **2.68** and treat it under standard radical forming conditions to form phenanthrene **2.67**. Ozonolysis should then induce cleavage of the central carbon-carbon double bond, leading through to the bis-aldehyde **2.66**. From this intermediate a double Baeyer-Villiger oxidation and saponification of the resultant formate esters should furnish the required *bis*-phenol **2.65**.



Scheme 2.15

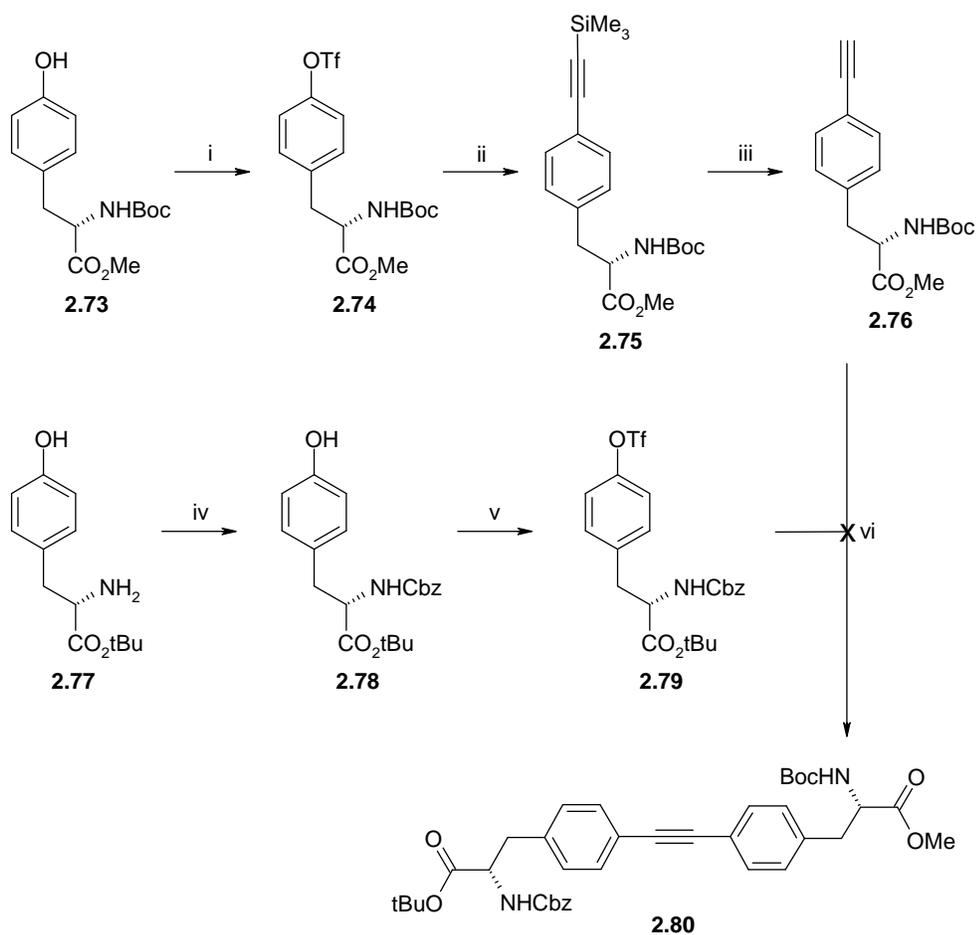
2.7 Formation of a model phenanthrene system

Key to our proposed route is the formation of a biaryl linkage through radical induced transannular ring contraction to form a phenanthrene. To demonstrate the viability of this approach we decided carry out tests upon a simplified system **2.69** which mirrors the biaryl A-B ring of RP 66453 (Scheme 2.16). Synthesis of the *bis*-phenol **2.69** requires the double Baeyer-Villiger oxidation of *bis*-aldehyde **2.70**, which in turn is accessed by ozonolysis of phenanthrene **2.71**, formed by a radical-induced transannular ring contraction of stilbene **2.72**.



Scheme 2.16

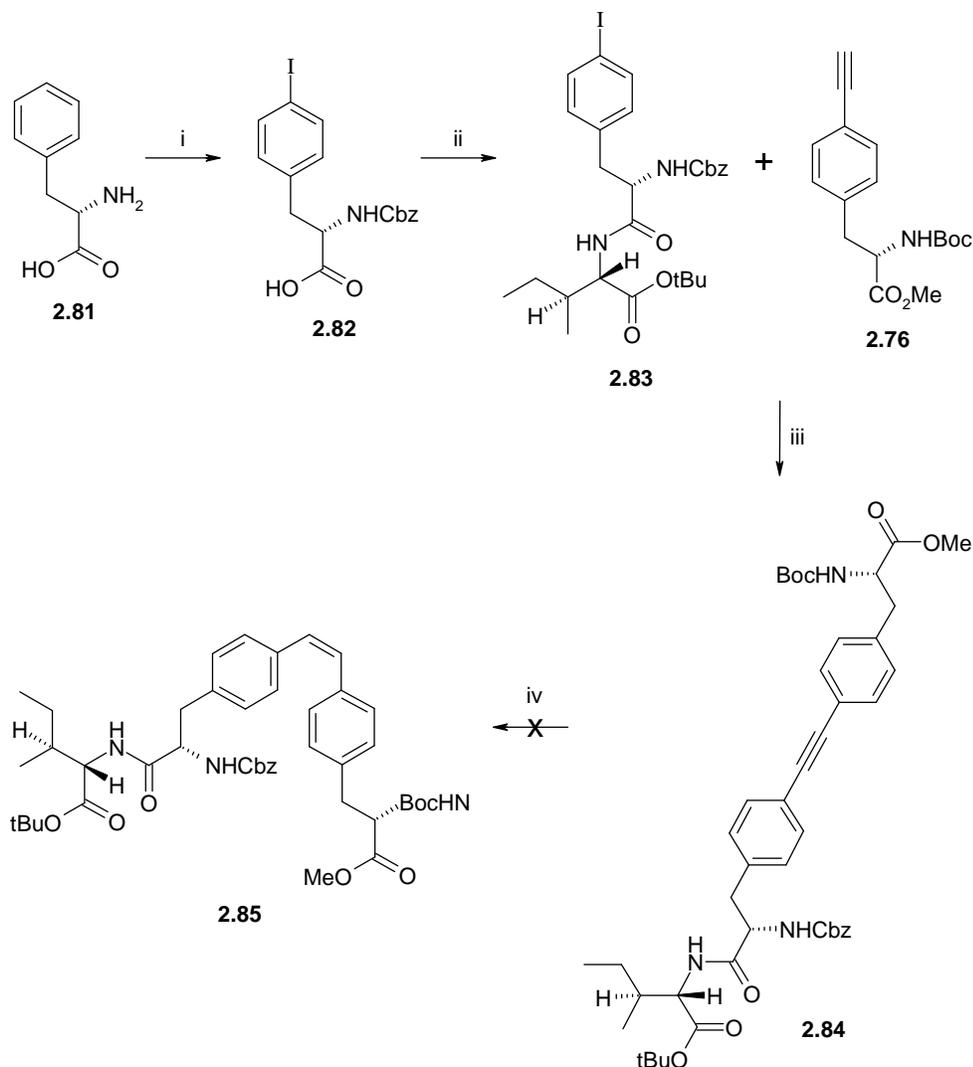
Our first approach to the synthesis of the *cis*-stilbene precursor began with the coupling of triflate **2.74** with trimethylsilylacetylene (Scheme 2.17). Removal of the TMS group from the resulting arylacetylene then provided **2.76** in quantitative yield. Concomitantly, Cbz protection of L-tyrosine *tert*-butyl ester **2.77** gave tyrosine derivative **2.78** which was then converted to triflate **2.79** in an excellent yield of 99%. Alas, attempts to induce a Sonogashira coupling between triflate **2.79** and phenylacetylene **2.76** returned only recovered starting materials.



Reagents/Conditions: i) $\text{ Tf}_2\text{O}$, pyridine, DCM, 93%; ii) trimethylsilylacetylene, LiCl, $\text{ Pd}(\text{PPh}_3)_2\text{Cl}_2$, NEt_3 , DMF, 68%; iii) AgNO_3 , acetone/ $\text{ H}_2\text{O}$, 100%; iv) CbzCl, $\text{ Na}_2\text{CO}_3$, ether/ $\text{ H}_2\text{O}$, 91%; v) $\text{ Tf}_2\text{O}$, pyridine, DCM, 99%; vi) $\text{ Pd}(\text{PPh}_3)_2\text{Cl}_2$ or $\text{ Pd}(\text{OAc})_2$ or $\text{ Pd}(\text{PPh}_3)_4$, LiCl, NEt_3 , CuCl, DMF.

Scheme 2.17

This disappointing result led us to conclude that the low reactivity of the aryl triflate was responsible for failure of the Sonogashira coupling. We further reasoned that the corresponding iodide would display increased reactivity and might therefore promote the desired coupling reaction. Thus iodination of phenylalanine **2.81** and Cbz protection of the free amine gave **2.82**, which was then coupled to L-isoleucine *tert*-butyl ester to yield the dipeptide **2.83** (Scheme 2.18). Pleasingly, Sonogashira coupling of iodide **2.83** to phenylacetylene **2.76** successfully furnished the disubstituted acetylene **2.84**, which we planned to reduce to the *cis*-alkene **2.85**. A range of conditions were investigated to effect the reduction. H₂ and Lindlar's catalyst were ineffective as the reaction was slow, required extended reaction times and gave a myriad of over-reduced products that could not be isolated in a pure state. Other classic conditions were investigated, including diimide reduction and transfer hydrogenation. These, even under extended reaction times and elevated temperatures, failed to reduce the alkyne. The use of zinc dust and a zinc/copper/silver amalgam also proved ineffective, whilst the use of Ti(OⁱPr)₄ led to degradation of the starting material.



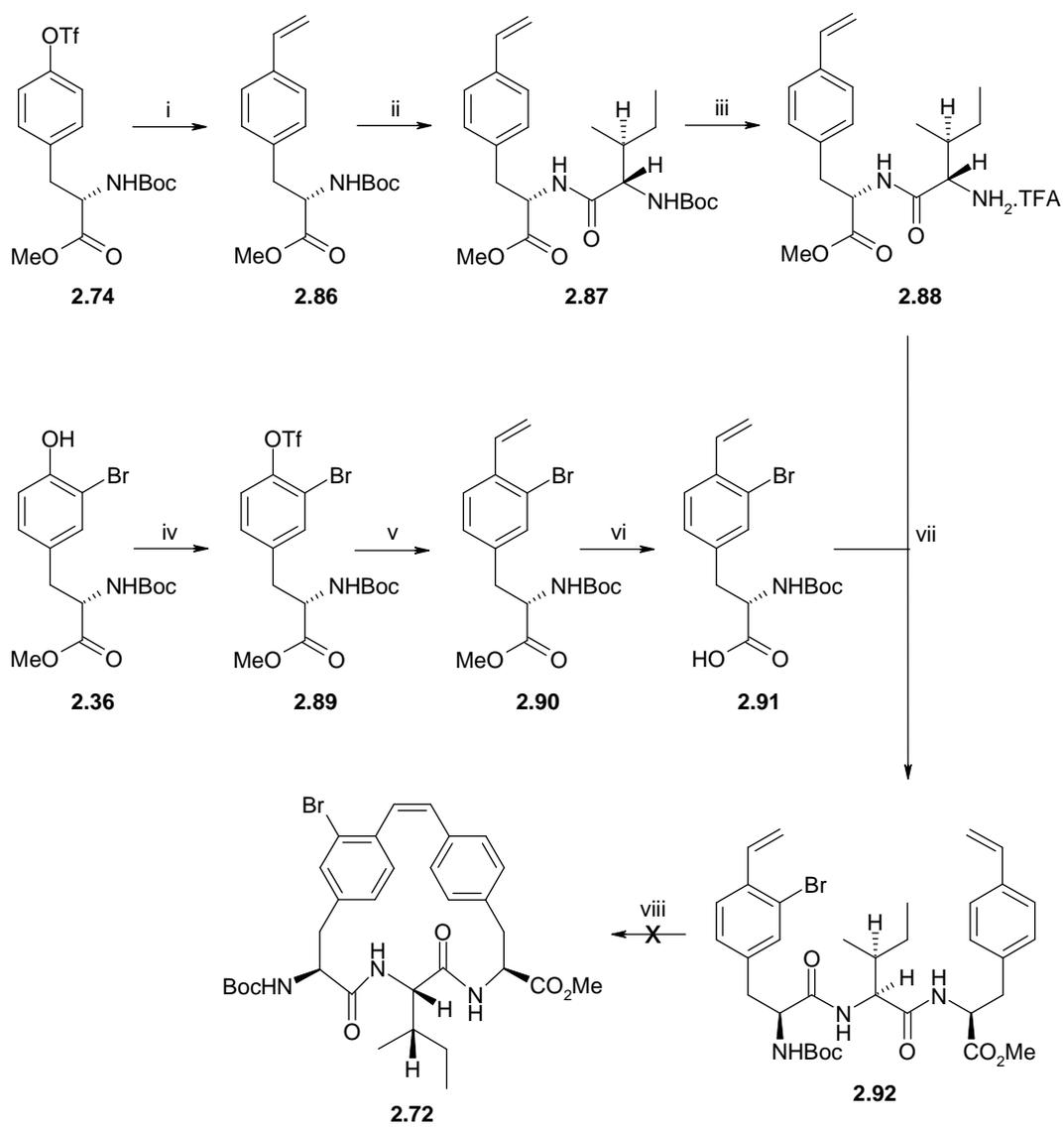
Reagents/Conditions: i) I₂, AcOH, conc. H₂SO₄, NaIO₃ then CbzCl, NaOH, H₂O/ether, RT, 43%; ii) L-isoleucine tBu ester, EDC, HOBT, NEt₃, DCM, RT, 74%; iii) Pd(PPh₃)₂Cl₂, CuI, NEt₃, RT, 35%; iv) Lindlar's catalyst or Pd on BaSO₄, quinoline, EtOH or EtOAc or MeOH, or tosyl hydrazine, NaOAc, THF/H₂O or formic acid, Pd/C, NEt₃ or Zn/Cu/Ag amalgam or Zn dust, 1,2-dibromoethane, EtOH or Ti(OⁱPr)₄, ⁿBuLi, THF or NaBH₄, HSCH₂CH₂SH, FeCl₂EtOH.

Scheme 2.18

With the partial reduction of the alkyne to the *cis*-alkene proving unfeasible, we began to consider other methods of forming the *cis*-alkene. Ring closing metathesis provides a route to form the alkene and close the macrocycle simultaneously, and so with this in mind we began the synthesis of the model system **2.92**.

Treatment of triflate **2.74** with tributylvinyltin gave styrene **2.86**. Deprotection of the amine with TFA and peptide coupling with Boc-protected L-isoleucine furnished dipeptide **2.87** (Scheme 2.19). The second coupling partner was also prepared from L-tyrosine in this case. Conversion of the 3-bromo-L-tyrosine derivative **2.36** to triflate **2.89** facilitated a Stille coupling with tributylvinyltin to yield styrene **2.90**. Pleasingly, at room temperature the coupling occurred exclusively through the triflate, with no product resulting from Stille coupling with the bromide. Temperature was a critical factor in determining the course of the reaction as when heated to 80 °C coupling through the bromide became the primary pathway.

Saponification of methyl ester **2.90** gave the free acid **2.91** which was coupled to amine **2.88** under standard peptide coupling conditions to yield the tripeptide **2.92**, the precursor for our key ring closing metathesis reaction. Treatment of this dialkene with Grubb's second generation catalyst was attempted in DCM and toluene, but returned only starting material, with no evidence of any cross metathesis having occurred.



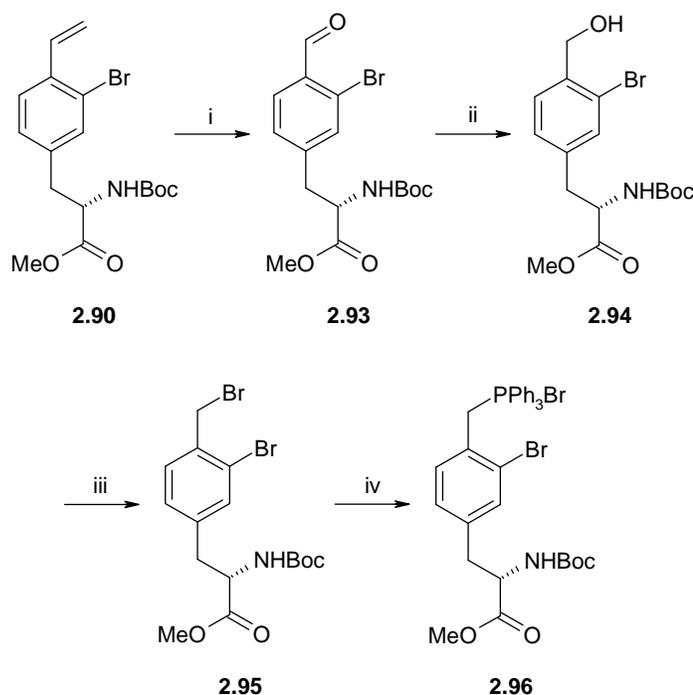
Reagents/Conditions: i) tributylvinyltin, Pd(dppf)Cl₂.CH₂Cl₂, DMF, 80 °C, 70%; ii) TFA, DCM then Boc L-isoleucine, EDC, HOBt, NEt₃, DCM, RT, 76%; iii) TFA, DCM, RT, quant.; iv) Tf₂O, pyridine, DCM, 0 °C, 96%; v) tributylvinyltin, Pd(dppf)Cl₂.CH₂Cl₂, DMF, RT, 81%; vi) LiOH.H₂O, THF/H₂O, RT, 96%; vii) EDC, HOBt, NEt₃, DCM, RT, 75%; viii) Grubbs (II) catalyst, toluene or DCM, Δ.

Scheme 2.19

Disheartened by our unsuccessful attempts to form stilbene **2.72** by ring closing metathesis we decided to focus on a more classical method of forming the stilbene. Previous work within the Gilheany and Harrowven groups has shown that Wittig reactions display cooperative *ortho*-effects leading to *cis*-alkenes.^{62,70} Our system is a reasonable candidate with which to benefit from the effect as it has one,

(rather than the optional two) halides or ether groups on the *ortho*-carbon centres of the ylide or aryl aldehyde to affect the *cis*-selectivity.

Synthesis of the Wittig salt began from bromo-styrene **2.90** (Scheme 2.20). Ozonolysis of the alkene provided aldehyde **2.93** which was then reduced to benzyl alcohol **2.94**. Conversion of the benzyl alcohol to the benzyl bromide **2.95** at first proved challenging. Treatment with PBr_3 led to degradation of the starting material, whilst treatment with bromine or *N*-bromosuccinimide led to oxidation of the benzyl alcohol, reforming aldehyde **2.93**. Eventually conditions were discovered that effected the transformation involving treatment of benzyl alcohol **2.94** with *N*-bromosuccinimide in the presence of triphenylphosphine which furnished benzyl bromide **2.95** in 80% yield. This was then converted to the Wittig salt **2.96** in quantitative yield.



Reagents/Conditions: i) O_3 , PPh_3 , DCM , -78°C , 84%; ii) NaBH_4 , MeOH , 0°C , 90%; iii) NBS , PPh_3 , THF , RT , 80%; iv) PPh_3 , toluene , 90°C , 100%.

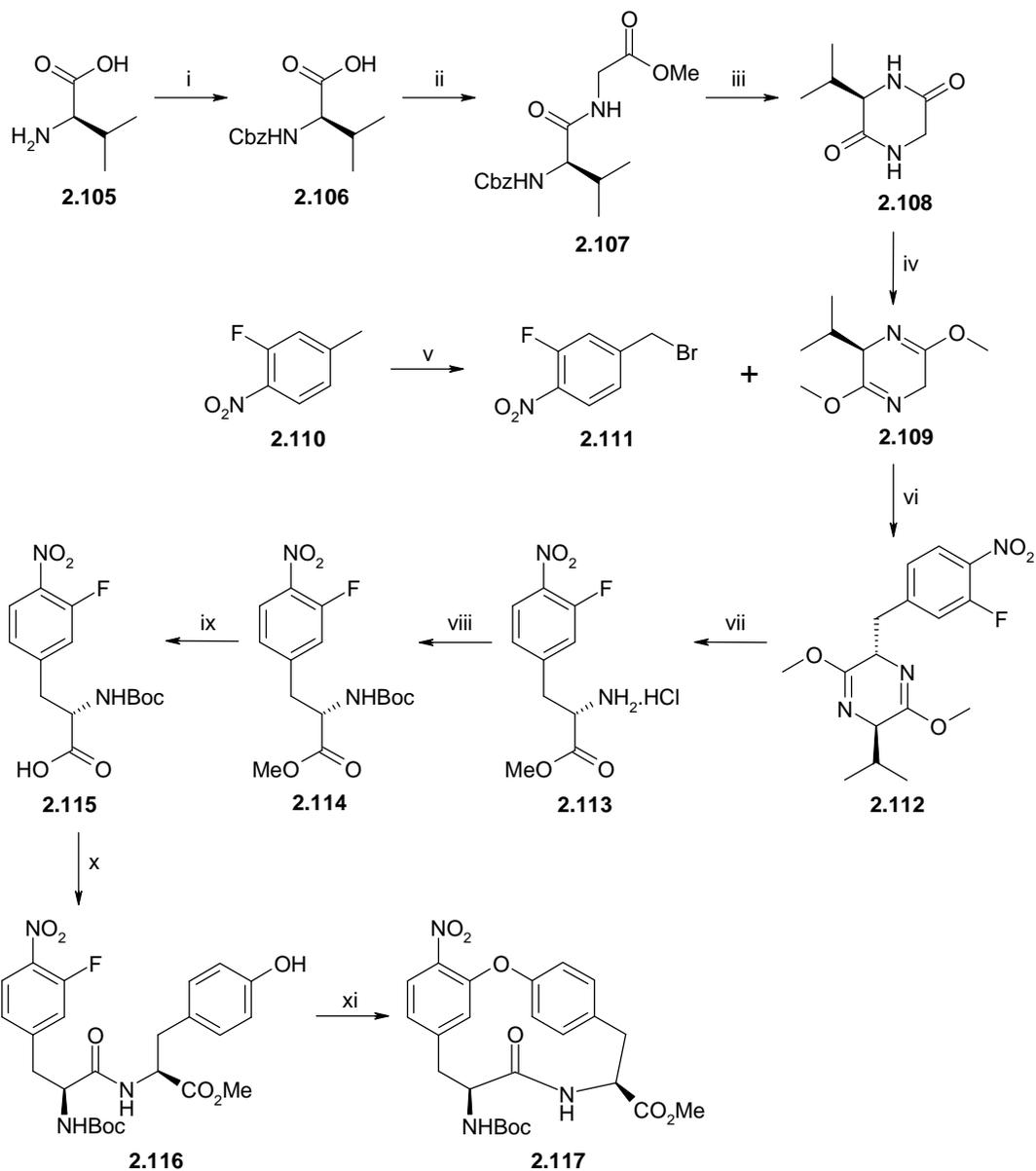
Scheme 2.20

Meanwhile synthesis of the aldehyde fragment was underway. Stille coupling of triflate **2.97** gave styrene **2.98** which was then hydrolysed to the free acid **2.99**

(Scheme 2.21). Peptide coupling to L-isoleucine *tert*-butyl ester furnished the dipeptide **2.100** which, following ozonolysis, afforded the aldehyde **2.101**. The Wittig reaction between aldehyde **2.101** and Wittig salt **2.96** was attempted under a variety of reaction conditions, using alternative bases (potassium *tert*-butoxide, sodium methoxide) and solvents (THF, DCM). The only conditions that successfully yielded the stilbene **2.102** used a combination of potassium carbonate and 18-crown-6 in DCM. Unfortunately the *cis*- and *trans*-alkenes **2.102** and **2.103** were formed in a 1:1 ratio. It should be possible to improve this selectivity by adding a sacrificial halide *ortho* to the aldehyde in **2.101**, or using the 3,5-dibromo Wittig salt. Using this Wittig salt, or alternatively employing the brominated aldehyde, would not affect the later steps as the additional halide would be removed in the key radical transannular ring closing step. Disappointingly, treatment of the *cis*-stilbene **2.102** under standard radical forming conditions failed to yield the phenanthrene **2.104** (Scheme 2.22), leading instead to degradation of the starting material.

2.8 Synthesis of the B-O-C ring

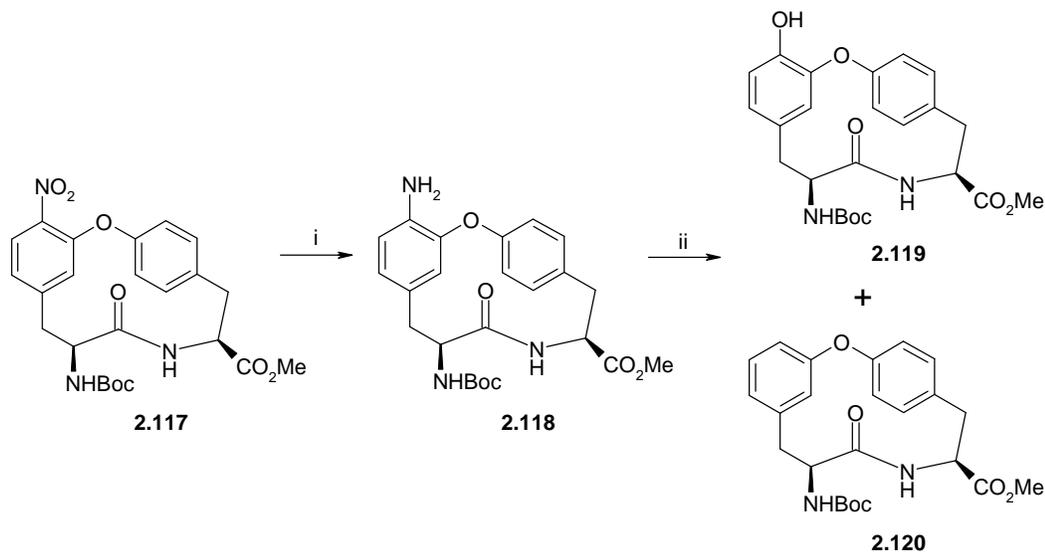
Construction of the B-O-C ring requires the synthesis of unnatural amino acid **2.113**. Previous syntheses of this amino acid have been achieved by two routes. The first was developed by Zhu *et al.*, with alkylation of Schollkopf's bislactim ether with 3-fluoro-4-nitrobenzyl bromide providing the enantiomerically pure product.⁷¹ Alternatively the synthesis could be achieved by enzymatic hydrolysis of a racemic mixture of (*R,S*)-*N*-trifluoroacetyl 3-fluoro-4-nitro phenylalanine methyl ester. The use of Subtilisin is shown to selectively catalyse the hydrolysis of the (*S*)-enantiomer whilst leaving the unreacted (*R*)-enantiomer, thereby allowing easy separation of the two enantiomers.⁷² This route is particularly useful when both enantiomers are required, but is extremely wasteful when a single enantiomer is necessary. For this reason we chose the former route to access the (*S*)-unnatural amino acid. The correct stereochemistry is installed with the use of Schollkopf's bislactim ether **2.109**, coupled with 3-fluoro-4-nitrobenzyl bromide **2.111** *via* organocuprate formation (Scheme 2.23). It was found that careful control of the reaction temperature is essential to reproducibly achieve the coupling in high yields. Acid catalysed hydrolysis of the masked amino acid **2.112** then reveals the unnatural amino acid methyl ester **2.113**, which was converted to Boc-protected free acid **2.115** in two steps by simple protecting group manipulation. Coupling with L-tyrosine methyl ester under standard peptide coupling conditions then afforded dipeptide **2.116**. Finally, nucleophilic aromatic substitution promoted with sodium hydride at high dilution furnished the desired 14-membered macrocycle **2.117**.



Reagents/Conditions: i) CbzCl, 2 M NaOH, ether, RT, 93%; ii) glycine methyl ester, isobutyl chloroformate, *N*-methylmorpholine, THF, DMF, -5 °C - RT, 89%; iii) H₂, Pd/C, DCM/MeOH then toluene, Δ, 80%; iv) [Me₃O]⁺BF₄⁻, DCM, RT, 77%; v) NBS, DBPO, DCE, Δ, 70%; vi) CuCN, ^tBuLi, THF, -78 °C, 59%; vii) 0.25 N HCl, RT, 97%; viii) Boc₂O, NEt₃, dioxane/H₂O, 0 °C - RT, 98%; ix) LiOH.H₂O, THF/H₂O, RT, quant.; x) L-tyrosine methyl ester, EDC, HOBT, NEt₃, DMF, RT, 80%; xi) NaH, DMF, 0 °C - RT, 57%.

Scheme 2.23

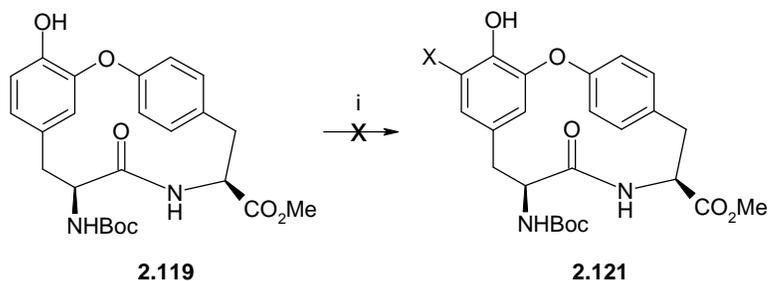
Despite the disappointing cyclization yield the synthesis was continued with the reduction of the nitro functionality, using H₂ and Pd/C to aniline **2.118** which was obtained in 78% yield (Scheme 2.24). Conversion to the phenol **2.119** was then accomplished in a two step sequence, with diazotization followed by hydrolysis of the resultant diazonium salt, yielding the phenol **2.119** and the reduced by-product **2.120**.



Reagents/Conditions: i) H₂, Pd/C, MeOH, RT, 78%; ii) HBF₄, ^tBuONO, Cu₂O, Cu(NO₃)₂·2.5H₂O, THF, 0 °C - RT, 66% **2.119**, 21% **2.120**.

Scheme 2.24

Attempts to halogenate the phenol **2.119** appeared successful when monitored by TLC, however upon work-up and purification the product was found to degrade, and no pure product was obtained (Scheme 2.25). This instability of the halogenated macrocycle, which has previously been noted by Zhu *et al.*, prompted us to attempt a one-pot halogenation / S_N2 coupling sequence to the A fragment.



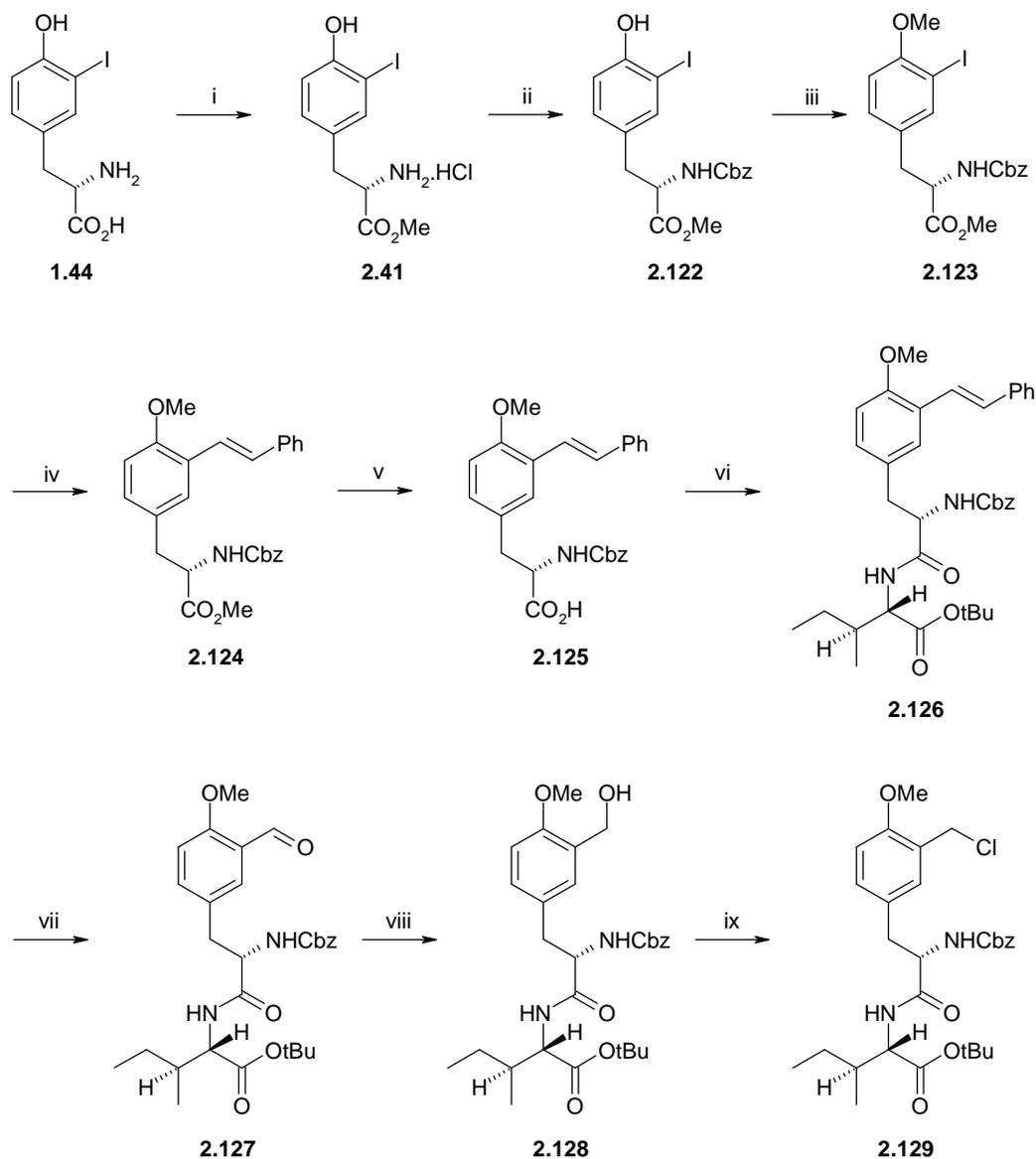
Reagents/Conditions: i) NBS, DMF or NIS, DMF.

Scheme 2.25

Coupling of the A fragment at this stage requires orthogonal protection of its amine and that in the B-O-C ring so that selective deprotection can be realised for macrolactamization at a later stage. With this in mind we chose to prepare *N*-Cbz / *tert*-butyl ester **2.129**, which would allow simultaneous deprotection of the *tert*-butyl ester and Boc-protecting groups in the presence of TFA.

2.9 Synthesis of the A fragment

From 3-iodo-L-tyrosine **1.44** the fully protected iodo-tyrosine derivative **2.123** was obtained in 57% yield over three steps (Scheme 2.26). Suzuki coupling to *trans*-phenylvinylboronic acid proceeded smoothly, providing the desired stilbene **2.124** in 84% yield. Saponification of the methyl ester followed by coupling to L-isoleucine *tert*-butyl ester gave dipeptide **2.126**. Ozonolysis of the stilbene revealed the aldehyde **2.127** which was then reduced to benzyl alcohol **2.128** and converted to benzyl chloride **2.129**.

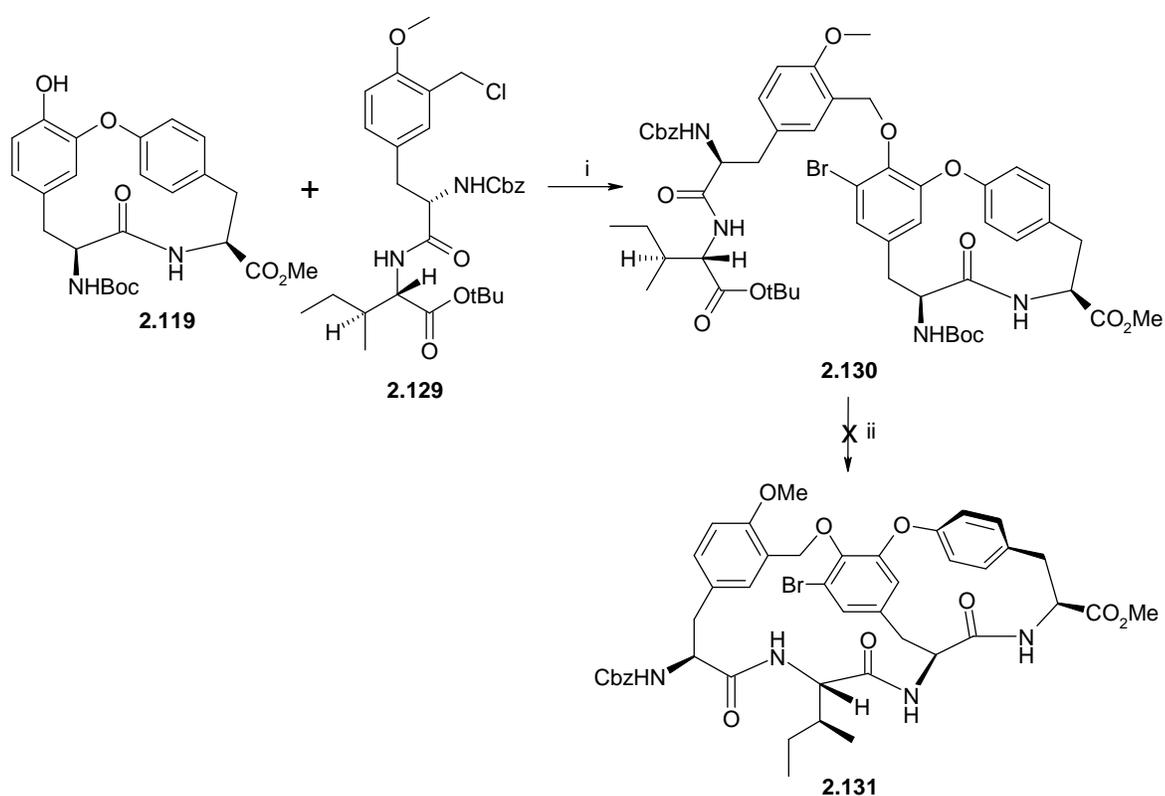


Reagents/Conditions: i) SOCl_2 , MeOH, 71%; ii) CbzCl, Na_2CO_3 , H_2O , 0 °C, 91%; iii) MeI, K_2CO_3 , DMF, 0 °C - RT, 88%; iv) *trans*-phenylvinylboronic acid, K_2CO_3 , $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$, DMSO, 80 °C, 84%; v) $\text{LiOH} \cdot \text{H}_2\text{O}$, THF/ H_2O , RT; vi) L-isoleucine ^tBu ester, EDC, HOBT, NEt_3 , DCM, RT, 90% over two steps; vii) O_3 , PPh_3 , DCM, -78 °C, 83%; viii) NaBH_4 , MeOH, 0 °C, 90%; ix) SOCl_2 , DCM, 0 °C, 99%.

Scheme 2.26

2.10 Coupling of the B-O-C ring and A fragment

Pleasingly the one-pot bromination / S_N2 coupling of the B-O-C ring **2.119** and A fragment **2.129** proceeded smoothly, furnishing the advanced intermediate **2.130** (Scheme 2.27). Unfortunately the following macrolactamization could not be realised. Despite the double deprotection appearing to be successful by TLC, treatment of the resulting crude material with HATU or EDC and HOBT with NEt_3 failed to yield the desired product, instead resulting in degradation of the starting material.

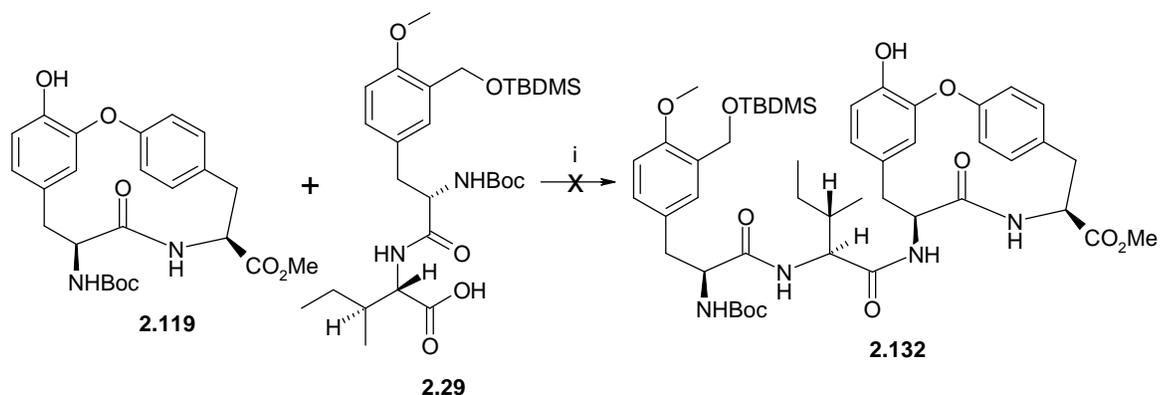


Reagents/Conditions: i) **2.119**, NBS, DMF then **2.129**, K_2CO_3 , KI, DMF, 50 °C, 74%; ii) TFA, DCM then HATU, DMF or EDC, HOBT, NEt_3 , DMF.

Scheme 2.27

With the macrolactamization proving difficult, we instead reverted to our previous plan of coupling the B-O-C ring **2.119** to the A fragment **2.29** and closing the A-B ring with the S_N2 displacement of the benzyl chloride with the phenol of the B-O-C ring. Thus, deprotection of the B-O-C ring **2.119** was followed by peptide coupling

with the dipeptide free acid **2.29**. Alas we were again unable to affect the coupling, obtaining only a complex mixture of unidentified products (Scheme 2.28).



Reagents/Conditions: i) TFA, DCM then **2.29**, EDC, HOBT, NEt₃, DCM.

Scheme 2.28

2.11 Conclusion and further work

With a route to the B-O-C ring **2.119** in hand, and routes to the orthogonally protected A fragments **2.29** and **2.129** established, prospects for the synthesis of RP 66453 in the near future appear promising. Work continues within the Harrowven group towards the synthesis of this challenging natural product. Current research into the biaryl ether transannular ring contraction route is aimed at exploring both different reaction conditions and the possibility of switching the aryl radical acceptor and donor groups. Likewise further research into the formation of the biaryl linkage via phenanthrene formation continues. *Cis*-selectivity of the Wittig reaction may be improved by using an *ortho*-halogenated aldehyde as a coupling partner for the phosphonium salt. Alternatively incorporation of halogens at both the 3- and 5-positions may favour formation of the *cis*-stilbene, and also improve the yield of the radical transannular ring contraction.

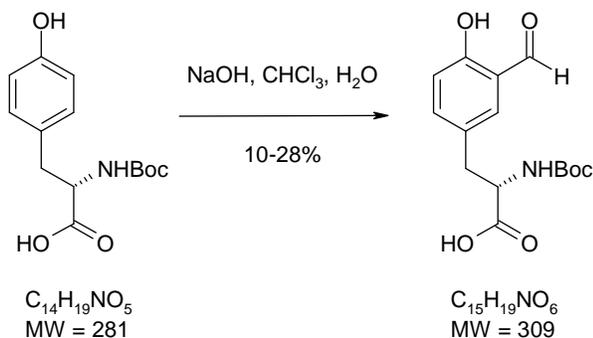
CHAPTER 3 – EXPERIMENTAL

3.1 – General remarks

All air and/or moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame-dried glassware. Diethyl ether and THF were distilled from sodium, with benzophenone as an internal indicator, immediately before use. Toluene was distilled from sodium. Chloroform and dichloromethane were distilled from calcium hydride immediately prior to use. Where appropriate all other solvents and reagents were purified according to standard methods.⁷³ Reactions were monitored by TLC using aluminium-backed sheets coated with silica gel 60 containing a fluorescent indicator active at 254 nm; the chromatograms were visualised under UV light (254 nm) and by staining with, most commonly, 10% aqueous KMnO_4 or 20% phosphomolybdic acid in ethanol. Where flash chromatography was undertaken, Apollo silica gel (0.040-0.063 mm, 230-400 mesh) was used, slurry packed and run at low pressure. Infrared (IR) spectroscopy was performed using a BioRad FT-IR Goldengate spectrometer. Positions of absorption maxima are quoted in cm^{-1} . Letters after give an indication of the relative strength of the peak (w = weak, m = moderate, s = strong, br. = broad). ^1H and ^{13}C spectroscopy was performed on a Bruker Avance 300 or Bruker DPX 400 spectrometer at operating frequencies indicated in the text. Chemical shifts (δ_{H} , δ_{C}) are reported in parts per million relative to residual CHCl_3 ($\delta_{\text{H}} = 7.27$ ppm, $\delta_{\text{C}} = 77.2$ ppm). Coupling constants are reported as observed and are uncorrected. Multiplicities are reported using the following notations: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, app. = apparent, br. = broad, obs. = obscured. Electrospray (ES) mass spectroscopy was performed on a Waters ZMD spectrometer. High resolution ESMS was performed on a Bruker Apex III spectrometer. Mass spectroscopic data are reported as values in atomic mass units with peak intensities reported relative to the base peak (100%). Melting points were carried out using a Griffin melting point apparatus and are uncorrected. Optical rotations were measured on a PolAAr 2001 polarimeter operating at a wavelength of 589 nm with an external temperature of 24 °C.

3.2 – Synthetic procedures

(S)-2-tert-Butoxycarbonylamino-3-(3-formyl-4-hydroxy-phenyl)-propanoic acid **2.32**



Prepared following the procedure of Schmidt *et al.*⁷⁴

To a suspension of *N*-tert-butoxycarbonyl-L-tyrosine **2.31** (563 mg, 2 mmol) in CHCl₃ (9 mL) and H₂O (0.07 mL) was added NaOH (480 mg, 12 mmol). The reaction was stirred vigorously and heated at reflux for 6 h. Additional NaOH (120 mg, 3 mmol) was added after 90 min and then again after 3 h, water (20 mL) and ethyl acetate (20 mL) were added and the aqueous adjusted to pH 1 with 2 M HCl. The aqueous phase was extracted with ethyl acetate (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 7% MeOH/CHCl₃, 1% acetic acid) afforded the product **2.32** as a yellow oil (169 mg, 0.55 mmol, 28%).

Yields were found to vary between 10–28%.

FT-IR (v/cm⁻¹) 2980 (br), 2287 (w), 2080 (w), 1712 (s), 1656 (s), 1510 (w), 1487 (w), 1394 (w), 1368 (w), 1265 (m), 1156 (w), 1056 (w).

¹H NMR δ_H (300 MHz, CDCl₃): 10.55 (1H, br. s, **OH**), 9.85 (1 H, s, **CHO**), 7.38 (1 H, s, **ArH**), 7.37 (1 H, d, *J* = 8.8 Hz, **ArH**), 6.94 (1 H, d, *J* = 8.4 Hz, **ArH**), 5.07 (1 H, d, *J* = 6.6 Hz, **NH**), 4.50 (1 H, m, **CH**), 3.20 (1 H, m, **CHH**), 3.03 (1 H, m, **CHH**), 1.41, (9 H, s, 3 x **CH₃**).

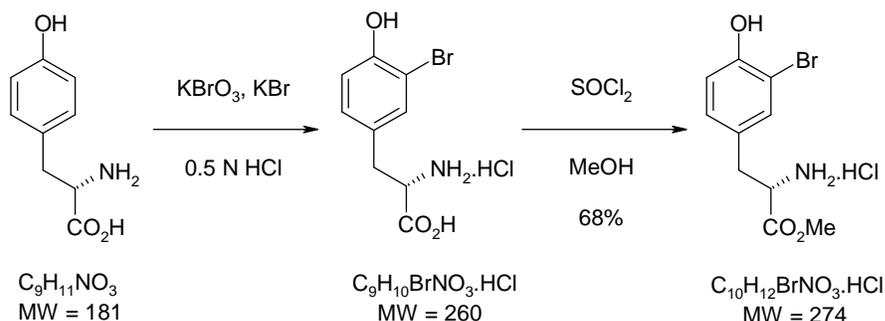
^{13}C NMR δ_{C} (75 MHz, CDCl_3): 196.6 (CCHO), 177.4 (C), 160.8 (C), 155.4 (C), 138.2 (CH), 134.4 (CH), 127.7 (C), 120.6 (C), 118.0 (CH), 80.6 (C), 54.4 (CH), 37.1 (CH_2), 28.4 (3 x CH_3).

LRMS m/z (ES^-) 308 ($[\text{M}-\text{H}]^-$, 18), 617 ($[\text{2M}-\text{H}]^-$, 100%).

$[\alpha]_{\text{D}}$ + 31.3 (c = 0.5, CHCl_3).

The data are consistent with the literature.⁵⁶

(S)-2-Amino-3-(4-hydroxy-3-bromo-phenyl)-propionic acid methyl ester **2.35**



Prepared following the procedure of Jung *et al.*⁷⁵

To a stirred solution of L-tyrosine **2.33** (500 mg, 2.76 mmol) in 0.5 N HCl (28 mL) was added KBr (548 mg, 4.60 mmol) and $KBrO_3$ (154 mg, 0.92 mmol) in H_2O (100 mL). The reaction was stirred at RT for 17 h then concentrated *in vacuo* to afford the crude product **2.34** as a pale yellow solid. To a solution of $SOCl_2$ (0.24 mL, 3.31 mmol) in MeOH (10 mL) at $-5\ ^\circ C$ was added the crude 3-bromo-L-tyrosine hydrochloride **2.34**. The reaction was heated at reflux for 30 min, then cooled and stirred at RT for a further 2 h. Concentration *in vacuo* and recrystallisation from MeOH/diethyl ether afforded **2.35** as a pale beige solid (592 mg, 1.91 mmol, 68%).

m.p. 66–69 $^\circ C$

FT-IR (v/cm^{-1}) 3346 (br), 2970 (m), 2925 (m), 2864 (w), 1682 (s), 1496 (m), 1393 (m), 1367 (m), 1249 (m), 1155 (s), 1046 (m), 1025 (m), 817 (w).

1H NMR δ_H (400 MHz, MeOD): 7.39 (1 H, d, $J=2.0$ Hz, ArH), 7.07 (1 H, dd, $J=8.5, 2.5$ Hz, ArH), 6.90 (1 H, d, $J=8.5$ Hz, ArH), 4.28 (1 H, app. t, $J=6.8$ Hz, CH), 3.81 (3 H, s, CH_3), 3.17 (1 H, dd, $J=14.6, 6.0$ Hz, CHH), 3.09 (1 H, dd, $J=14.6, 7.0$ Hz, CHH).

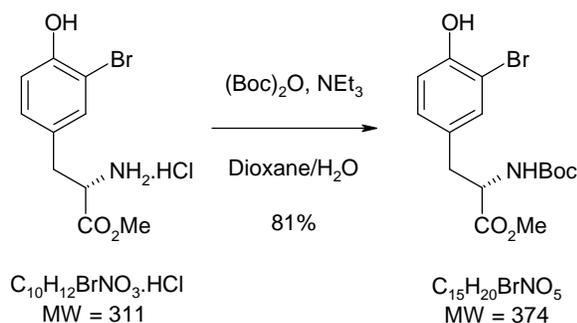
^{13}C NMR δ_C (100 MHz, MeOD): 170.5 (C), 155.4 (C), 135.2 (CH), 130.8 (CH), 127.7 (C), 117.9 (CH), 111.3 (C), 55.4 (CH_3), 53.7 (CH), 36.2 (CH_2).

LRMS m/z (ES+) 296 ([M (^{79}Br)+Na] $^+$, 95), 298 ([M (^{81}Br)+Na] $^+$, 100).

$[\alpha]_{\text{D}}$ + 64.3 (c = 0.7, MeOH).

The data are consistent with the literature.⁷⁵

tert-Butoxycarbonylamino-3-bromo-L-tyrosine methyl ester 2.36



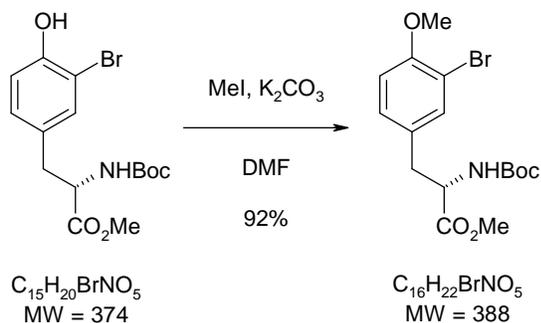
To a stirred solution of (*S*)-2-amino-3-(4-hydroxy-3-bromo-phenyl)-propionic acid methyl ester **2.35** (2.0 g, 6.43 mmol) and NEt_3 (1.8 mL, 12.86 mmol) in 1,4-dioxane: H_2O (10 mL:10 mL) at 0 °C was added $(\text{Boc})_2\text{O}$ (1.5 g, 7.07 mmol). The reaction was stirred at 0 °C for 1 h and then warmed to RT and stirred for a further 4 h. The reaction was concentrated *in vacuo* and the residue diluted with H_2O (25 mL) and ethyl acetate (25 mL). The aqueous phase was acidified to pH 1 with 2 M HCl and extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined and washed with brine (50 mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , 1% MeOH/DCM) afforded **2.36** as a pale yellow foam (1.95 g, 5.21 mmol, 81%).

FT-IR (v/cm^{-1}) 3262 (br), 2983 (w), 2937 (w), 1759 (s), 1687 (s), 1504 (s), 1423 (w), 1364 (m), 1295 (w), 1215 (s), 1147 (s), 1071 (m), 1026 (w), 824 (m).

^1H NMR δ_{H} (300 MHz, CDCl_3): 7.24 (1 H, d, $J=1.5$ Hz, ArH), 6.98 (1 H, dd, $J=8.4, 1.8$ Hz, ArH), 6.93 (1 H, d, $J=8.1$ Hz, ArH), 5.59 (1 H, br. s, OH), 5.01 (1 H, br. d, $J=6.2$ Hz, NH), 4.53 (1 H, br. app. q, $J=6.2$ Hz, CHNH), 3.73 (3 H, s, OCH_3), 3.06 (1 H, dd, $J=14.3, 6.2$ Hz, CHH), 2.95 (1 H, dd, $J=13.9, 5.9$ Hz, CHH), 1.43 (9 H, s, 3 x CH_3).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 172.1 (C), 155.0 (C), 151.4 (C), 132.6 (CH), 130.0 (CH), 129.6 (C), 116.1 (CH), 110.1 (C), 80.1 (C), 54.4 (CH), 52.3 (CH_3), 37.2 (CH_2), 28.3 (3 x CH_3).
LRMS	m/z (ES+) 396 ($[\text{M} (^{79}\text{Br})+\text{Na}]^+$, 93), 398 ($[\text{M} (^{81}\text{Br})+\text{Na}]^+$, 100), 769 ($[\text{2M} (^{79}\text{Br}, ^{79}\text{Br})+\text{Na}]^+$, 18), 771 ($[\text{2M} (^{79}\text{Br}, ^{81}\text{Br})+\text{Na}]^+$, 32), 773 ($[\text{2M} (^{81}\text{Br}, ^{81}\text{Br})+\text{Na}]^+$, 20).
HRMS	m/z (ES+) Found $[\text{M} (^{79}\text{Br})+\text{Na}]^+$ 396.0420. Required 396.0417.
$[\alpha]_{\text{D}}$	+ 58.7 (c = 1.0, CHCl_3).

(S)-3-(3-Bromo-4-methoxy-phenyl)-2-tert-butoxycarbonylamino propionic acid methyl ester **2.37**



To a stirred solution of *tert*-butoxycarbonylamino-3-bromo-L-tyrosine methyl ester **2.36** (1.24 g, 3.32 mmol) and K₂CO₃ (459 mg, 3.32 mmol) in DMF (40 mL) at 0 °C was added MeI (0.21 mL, 3.32 mmol). The reaction was stirred at 0 °C for 1 h, allowed to warm to RT and stirred for a further 5 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (4 x 50 mL). The organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL) then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 20% ethyl acetate/petroleum ether) afforded **2.37** as a colourless oil (1.19 g, 3.05 mmol, 92%).

FT-IR (v/cm⁻¹) 3367 (w), 3015 (w), 3974 (m), 2925 (w), 2360, 1742 (m), 1705 (s), 1497 (s), 1439 (w), 1365 (m), 1256 (m), 1159 (s), 1055 (s), 1019 (s), 751 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.31 (1 H, d, *J*=1.8 Hz, ArH), 7.04 (1 H, dd, *J*=8.4, 2.2 Hz, ArH), 6.83 (1 H, d, *J*=8.4 Hz, ArH), 4.99 (1 H, br. d, *J*=7.0 Hz, NH), 4.53 (1 H, m, CHNH), 3.88 (3 H, s, OCH₃), 3.73 (3 H, s, CO₂CH₃), 3.06 (1 H, dd, *J*=13.5, 5.5 Hz, CHH), 2.96 (1 H, dd, *J*=13.2, 5.5 Hz, CHH), 1.43 (9 H, s, 3 x CH₃).

¹³C NMR δ_C (75 MHz, CDCl₃): 171.8 (C), 171.4 (C), 154.7 (C), 133.2 (CH), 129.4 (C), 129.0 (CH), 111.7 (CH), 111.3 (CBr), 79.8

(C), 60.3 (CH₃), 54.2 (CH), 52.0 (CH₃), 36.9 (CH₂), 28.0 (3 x CH₃).

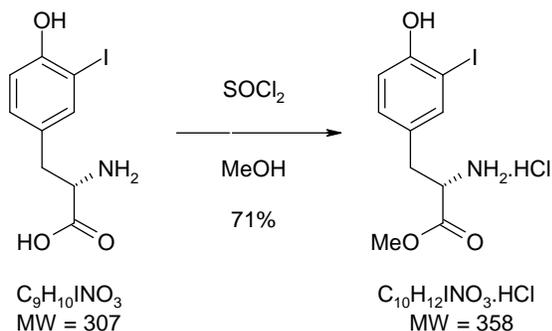
LRMS m/z (ES+) 410 ([M (⁷⁹Br)+Na]⁺, 92), 412 ([M (⁸¹Br)+Na]⁺, 100), 797 ([2M (⁷⁹Br, ⁷⁹Br)+Na]⁺, 17), 799 ([2M (⁷⁹Br, ⁸¹Br)+Na]⁺, 31), 800 ([2M (⁸¹Br, ⁸¹Br)+Na]⁺, 18).

HRMS m/z (ES+) Found [M (⁷⁹Br)+Na]⁺ 410.0574. Required 410.0574.

[α]_D + 29.6 (c = 2.0, CHCl₃).

The data are consistent with the literature.⁷⁶

(S)-2-Amino-3-(4-hydroxy-3-iodo-phenyl)-propionic acid methyl ester **2.41**



Prepared following the procedure of White *et al.*⁷⁷

To a stirred solution of SOCl_2 (1.43 mL, 19.5 mmol) in MeOH (65 mL) at 0 °C was added 3-iodo-L-tyrosine **1.44** (5.00 g, 16.3 mmol). The reaction was heated at reflux for 30 min then cooled and stirred at RT for 16 h. Concentration *in vacuo* and recrystallisation from MeOH/diethyl ether afforded **2.41** as a beige solid (4.15 g, 11.6 mmol, 71%).

m.p. 174–176 °C

FT-IR (v/cm^{-1}) 3207 (m), 2946 (br. m), 2882 (s), 2627 (m), 2586 (m), 1743 (s), 1515 (s), 1505 (s), 1416 (m), 1284 (m), 1247 (m), 1216 (m), 820 (w).

^1H NMR δ_{H} (400MHz, CDCl_3): 7.51 (1 H, d, $J=2.5$ Hz, ArH), 7.04 (1 H, dd, $J=8.3, 2.3$ Hz, ArH), 6.81 (1 H, d, $J=8.0$ Hz, ArH), 4.09 (1 H, app. t, $J=6.3$ Hz, CH), 3.78 (3 H, s, CH_3), 3.10 (2 H, app. dd, $J=6.3, 2.8$ Hz, CHH and CHH).

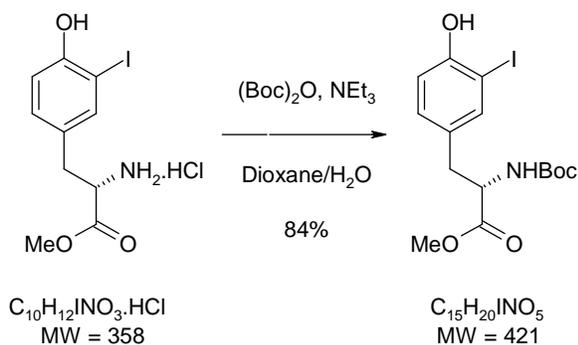
^{13}C NMR δ_{C} (100 MHz, CDCl_3): 169.5 (C), 156.9 (C), 140.2 (CH), 131.0 (CH), 126.7 (C), 115.7 (CH), 84.9 (CI), 54.5 (CH), 53.4 (CH_3), 35.3 (CH_2).

LRMS m/z (ES^+) 322 ($[\text{M}+\text{H}]^+$, 100), 344 ($[\text{M}+\text{Na}]^+$, 35).

$[\alpha]_D$ + 16.3 (c = 0.4, CHCl₃).

The data are consistent with the literature.⁷⁷

(S)-2-tert-Butoxycarbonylamino-3-(3-iodo-4-hydroxy-phenyl)-propionic acid methyl ester **2.42**



Prepared following the procedure of White *et al.*⁷⁷

To a solution of (S)-2-amino-3-(4-hydroxy-3-iodo-phenyl)-propionic acid methyl ester **2.41** (5.00 g, 14.0 mmol) and NEt₃ (3.90 mL, 28.0 mmol) in 1,4-dioxane:water (45 mL:45 mL) at 0 °C was added (Boc)₂O (3.36 g, 15.4 mmol). The reaction was stirred at 0 °C for 1 h, allowed to warm to RT and stirred for a further 16 h. The reaction was concentrated *in vacuo* and the residues dissolved in water (25 mL) and ethyl acetate (25 mL). The aqueous phase was acidified to pH 1 with 2 M HCl and extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.42** as a white foam (4.93 g, 11.7 mmol, 84%).

FT-IR (v/cm⁻¹) 3331 (m), 1715 (m), 1685 (s), 1394 (m), 1290 (m), 1253 (w), 1149 (m), 1125 (m), 1051 (w), 1002 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.43 (1 H, d, *J*=1.5 Hz, ArH), 6.99 (1 H, dd, *J*=8.1, 1.8 Hz, ArH), 6.85 (1 H, d, *J*=8.1 Hz, ArH), 5.04 (1 H, br. d, *J*=6.6 Hz, NH), 4.51 (1 H, m, CHNH), 3.73 (3 H, s, OCH₃), 3.03 (1 H, dd, *J*=13.9, 5.9 Hz, CHH), 2.92 (1 H, dd, *J*=13.5, 5.5 Hz, CHH), 1.43 (9 H, s, 3 x CH₃).

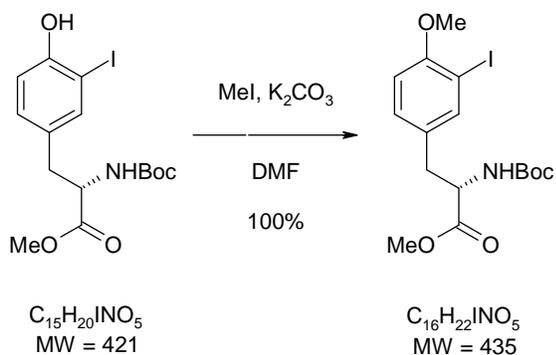
¹³C NMR δ_C (75 MHz, CDCl₃): 172.1 (C), 155.1 (C), 154.2 (C), 139.0 (CH), 130.9 (CH), 129.9 (C), 115.0 (CH), 85.2 (CI), 80.2 (C), 54.5 (CH), 52.3 (CH₃), 37.0 (CH₂), 28.3 (3 x CH₃).

LRMS m/z (ES+) 422 ([M+H]⁺, 38), 843 ([2M+H]⁺, 72), 865 ([2M+Na]⁺, 100).

[α]_D + 60.4 (c = 0.5, CHCl₃).

The data are consistent with the literature.⁷⁷

(S)-2-tert-Butoxycarbonylamino-3-(3-iodo-4-methoxy-phenyl)-propionic acid methyl ester **1.73**



Prepared following the procedure of Moon *et al.*⁷⁸

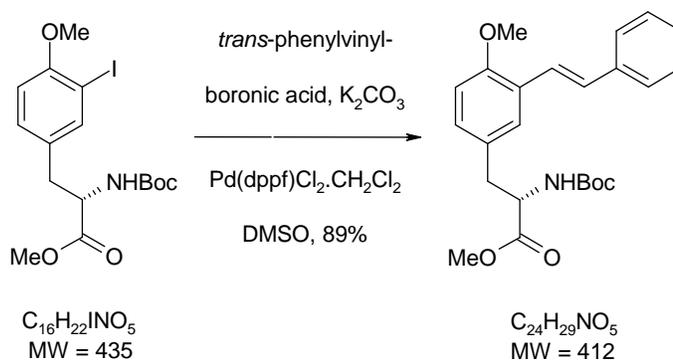
To a stirred solution of (*S*)-2-tert-butoxycarbonylamino-3-(3-iodo-4-hydroxy-phenyl)-propionic acid methyl ester **2.42** (1.00 g, 2.37 mmol) and K_2CO_3 (328 mg, 2.37 mmol) in DMF (30 mL) at 0 °C was added MeI (0.15 mL, 2.37 mmol). The reaction was stirred at 0 °C for 1 h, allowed to warm to RT and stirred for a further 5 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (4 x 50 mL). The organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL) then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 20% ethyl acetate/petroleum ether) afforded **1.73** as a colourless oil (1.03 g, 2.37 mmol, 100%).

FT-IR (v/cm^{-1}) 3382 (w), 2985 (w), 1741 (m), 1708 (s), 1489 (s), 1433 (w), 1365 (m), 1278 (m), 1251 (s), 1213 (m), 1159 (s), 1048 (m), 1016 (m), 908 (w), 729 (m).

1H NMR δ_H (400 MHz, $CDCl_3$): 7.53 (1 H, br. s, ArH), 7.07 (1 H, dd, $J=8.3, 2.1$ Hz, ArH), 6.74 (1 H, d, $J=8.4$ Hz, ArH), 5.00 (1 H, br. d, $J=6.7$ Hz, NH), 4.52 (1 H, m, CHNH), 3.85 (3 H, s, OCH_3), 3.73 (3 H, s, CO_2CH_3), 3.04 (1 H, dd, $J=13.8, 5.5$ Hz, CHH), 2.94 (1 H, dd, $J=13.4, 5.4$ Hz, CHH), 1.43 (9 H, s, 3 x CH_3).

^{13}C NMR	δ_{C} (100 MHz, CDCl_3): 172.1 (C), 157.2 (C), 154.9 (C), 140.2 (CH), 130.2 (CH), 110.8 (CH and C), 85.9 (C), 80.0 (C), 56.3 (CH_3), 54.4 (CH), 52.2 (CH_3), 36.9 (CH_2), 28.3 (3 x CH_3).
LRMS	m/z (ES+) 436 ($[\text{M}+\text{H}]^+$, 48), 458 ($[\text{M}+\text{Na}]^+$, 39), 871 ($[\text{2M}+\text{H}]^+$, 73), 893 ($[\text{2M}+\text{Na}]^+$, 100).
$[\alpha]_{\text{D}}$	+ 51.3 (c = 0.5, CHCl_3).

(S)-2-tert-Butoxycarbonylamino-3-[4-methoxy-3-((E)-styryl)-phenyl]-propionic acid methyl ester **2.43**



To a stirred solution of (S)-2-tert-butoxycarbonylamino-3-(3-iodo-4-methoxyphenyl)-propionic acid methyl ester **1.73** (1.34 g, 3.07 mmol), *trans*-phenylvinylboronic acid (0.50 g, 3.38 mmol) and K_2CO_3 (1.70 g, 12.29 mmol) in DMSO (36 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (75 mg, 0.09 mmol). The reaction was heated to 80 °C for 18 h, and then quenched with water (40 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL), the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL) then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 20% ethyl acetate/petroleum ether) afforded **2.43** as a white solid (1.13 g, 2.74 mmol, 89%).

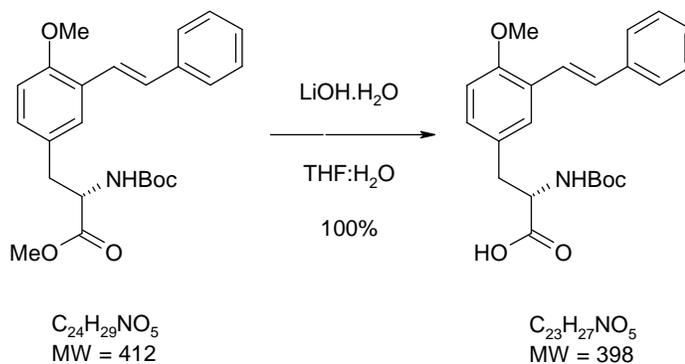
FT-IR (v/cm^{-1}) 3376 (w), 2979 (w), 2944 (w), 1752 (m), 1682 (s), 1512 (s), 1497 (s), 1439 (w), 1363 (m), 1248 (m), 1218 (m), 1157 (s), 1024 (m), 755 (w).

1H NMR δ_H (300 MHz, $CDCl_3$): 7.54 (2 H, app. dd, $J=8.4, 1.1$ Hz, 2 x ArH), 7.45 (1 H, d, $J=16.8$ Hz, CH=CH), 7.40–7.31 (3 H, m, 3 x ArH), 7.25 (1 H, app. tt, $J=7.3, 1.1$ Hz, ArH), 7.10 (1 H, d, $J=16.5$ Hz, CH=CH), 7.01 (1 H, dd, $J=8.4, 2.2$ Hz, ArH), 6.84 (1 H, d, $J=8.4$ Hz, ArH), 5.02 (1 H, m, NH), 4.59 (1 H, m, CHNH), 3.88 (3 H, s, OCH_3), 3.74 (3 H, s, CO_2CH_3), 3.11 (1 H, dd, $J=13.9, 5.9$ Hz, CHH), 3.07–2.94 (1 H, m, CHH), 1.44 (9 H, s, 3 x CH_3).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 172.4 (C), 156.1 (br., 2 x C), 137.9 (C), 129.3 (2 x CH and CH=CH), 128.6 (CH), 128.1 (C), 127.4 (CH), 127.3 (CH), 126.5 (2 x CH and C), 123.4 (CH=CH), 111.1 (CH), 79.9 (C), 55.6 (OCH_3), 54.6 (CH), 52.1 (CO_2CH_3), 37.7 (CH_2), 28.3 (3 x CH_3).
LRMS	m/z (ES+) 434 ($[\text{M}+\text{Na}]^+$, 54), 846 ($[\text{2M}+\text{Na}]^+$, 100).
HRMS	m/z (ES+) Found $[\text{M}+\text{Na}]^+$ 434.1939. Required 434.1938.
$[\alpha]_{\text{D}}$	+ 52.2 (c = 1.9, CHCl_3).

(S)-2-tert-Butoxycarbonylamino-3-[4-methoxy-3-((E)-styryl)-phenyl]-propionic acid

2.44



To a stirred solution of (S)-2-tert-butoxycarbonylamino-3-[4-methoxy-3-((E)-styryl)-phenyl]-propionic acid methyl ester **2.43** (1.12 g, 2.72 mmol) in THF:H₂O (150 mL:150 mL) was added LiOH.H₂O (286 mg, 6.81 mmol). The reaction was stirred at RT for 16 h and quenched with sat. NH₄Cl (100 mL). The aqueous phase was extracted with ethyl acetate (4 x 50 mL), the organic extracts combined and dried (MgSO₄). Concentration *in vacuo* afforded **2.44** as a beige solid (1.08 g, 2.72 mmol, 100%).

FT-IR (v/cm⁻¹) 3341 (w), 3312 (w), 2973 (w), 2938 (w), 1683 (m), 1657 (m), 1497 (m), 1392 (m), 1366 (m), 1245 (s), 1159 (s), 1118 (w), 1026 (m), 966 (m).

¹H NMR δ_H (300 MHz, MeOD): 7.55–7.36 (4 H, m, 3 x ArH and CH=CH), 7.31 (2 H, app. t, *J*=7.3 Hz, 2 x ArH), 7.24–7.01 (3 H, m, 2 x ArH and CH=CH), 6.85 (1 H, br. s, ArH), 4.38 (1 H, br. s, CHNH), 3.84 (3 H, s, OCH₃), 3.15 (1 H, br. s, CHHAr), 2.93 (1 H, br. s, CHHAr), 1.38 (9 H, s, 3 x CH₃).

¹³C NMR δ_C (100 MHz, CDCl₃): 157.4 (C), 139.6 (C), 131.5 (C), 131.0 (CH), 129.9 (CH), 129.8 (2 x CH), 128.5 (2 x CH), 127.6 (2 x

CH), 127.3 (C), 124.6 (CH), 112.2 (CH), 80.4 (C), 56.3 (OCH₃), 49.4 (CH), 38.9 (CH₂), 28.9 (3 x CH₃).

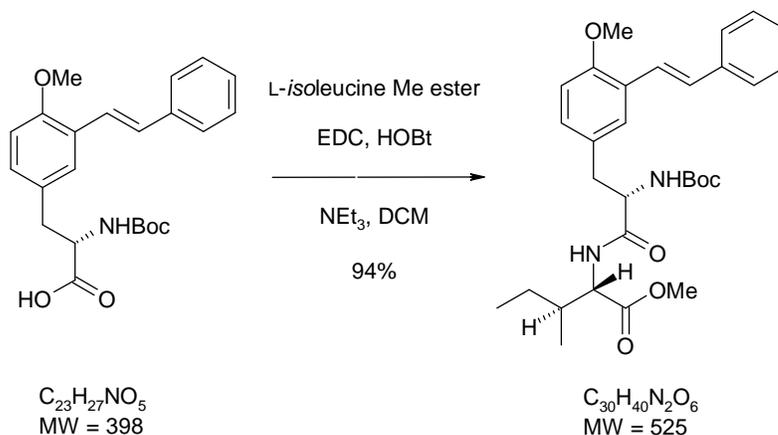
Cannot see two (C).

LRMS m/z (ES+) 420 ([M+Na]⁺, 100), 818 ([2M+H]⁺, 32).

HRMS m/z (ES+) Found [M+Na]⁺ 420.1785. Required 420.1781.

[α]_D + 6.2 (c = 1.0, MeOH).

(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxy-3-(*E*)-styryl-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.45**



To a stirred solution of (*S*)-2-*tert*-butoxycarbonylamino-3-[4-methoxy-3-(*E*)-styryl-phenyl]-propionic acid **2.44** (1.30 g, 3.28 mmol) in DCM (35 mL) was added L-isoleucine methyl ester (0.54 g, 2.98 mmol), EDC (0.58 mL, 3.28 mmol), HOBT (0.44 g, 3.28 mmol) and NEt₃ (0.83 mL, 5.96 mmol). The reaction was stirred at RT for 20 h and then quenched with sat. NH₄Cl (80 mL). The aqueous phase was extracted with ethyl acetate (4 x 50 mL), the organic extracts were combined, washed with brine (50 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 1% MeOH/DCM) afforded **2.45** as a white solid (1.46 g, 2.79 mmol, 94%).

FT-IR (v/cm⁻¹) 3341 (w), 3300 (w), 2961 (w), 1734 (m), 1685 (w), 1655 (s), 1515 (s), 1248 (s), 1162 (m), 1024 (m), 964 (w).

¹H NMR δ_H (300 MHz, CDCl₃): 7.56 (2 H, app. d, *J*=7.3 Hz, 2 x ArH), 7.45 (2 H, m, ArH and CH=CH), 7.38 (2 H, app. t, *J*=7.5 Hz, 2 x ArH), 7.31–7.22 (1 H, m, ArH), 7.19–7.07 (2 H, m, ArH and CH=CH), 6.86 (1 H, d, *J*=8.4 Hz, ArH), 6.40 (1 H, br. d, *J*=8.1 Hz, NH), 5.09 (1 H, br. s, NH), 4.55 (1 H, dd, *J*=8.4, 4.8 Hz, CHNH), 4.37 (1 H, br. app. q, *J*=7.0 Hz, CHNH), 3.90 (3 H, s, OCH₃), 3.68 (3 H, s, CO₂CH₃), 3.12 (1 H, dd, *J*=13.9, 6.6 Hz,

CHH), 3.04 (1 H, dd, $J=13.9, 7.0$ Hz, **CHH**), 1.93–1.77 (1 H, m, **CH(CH₃)CH₂CH₃**), 1.47 (9 H, s, 3 x **CH₃**), 1.44–1.32 (1 H, m, **CHHCH₃**), 1.21–1.04 (1 H, m, **CHHCH₃**), 0.90 (3 H, t, $J=7.3$ Hz, **CH₂CH₃**), 0.86 (3 H, d, $J=6.6$ Hz, **CHCH₃**).

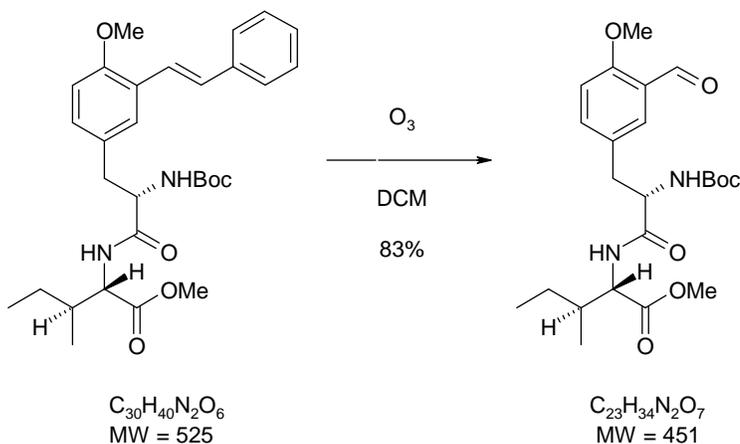
¹³C NMR δ_C (75 MHz, CDCl₃): 171.7 (C), 171.0 (C), 156.1 (C), 155.3 (C), 137.9 (C), 129.4 (CH), 128.6 (2 x CH), 128.5 (C), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.6 (C), 126.5 (2 x CH), 123.2 (CH), 111.3 (CH), 80.2 (C), 56.6 (2 x CH), 55.6 (ArOCH₃), 51.9 (CO₂CH₃), 38.0 (CH), 37.4 (CH₂), 28.3 (3 x CH₃), 25.1 (CH₂), 15.3 (CH₃), 11.5 (CH₃).

LRMS m/z (ES+) 526 ([M+H]⁺, 100), 547 ([M+Na]⁺, 47), 1050 ([2M+H]⁺, 24), 1073 ([2M+Na]⁺, 13).

HRMS m/z (ES+) Found [M+Na]⁺ 547.2788. Required 547.2779.

[α]_D + 13.1 (c = 1.5, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(3-formyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.46**



A stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-(4-methoxy-3-(*E*)-styryl-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.45** (653 mg, 1.09 mmol) and sudan red (10 mg) in DCM (100 mL) was cooled to -78 °C and O₃ (1–4% in O₂) bubbled through until the red colour disappeared. O₂ was then bubbled through the reaction for 20 min before PPh₃ (571 mg, 2.18 mmol) was added. The reaction was stirred at -78 °C for 20 min and then allowed to warm to RT. Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.46** as a yellow oil (472 mg, 0.90 mmol, 83%).

FT-IR (v/cm⁻¹) 3308 (m), 3013 (w), 2968 (m), 2865 (w), 1740 (w), 1655 (s), 1496 (s), 1366 (m), 1252 (s), 1216 (m), 1161 (s), 1023 (m), 751 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 10.43 (1 H, s, ArCHO), 7.63 (1 H, d, *J*=2.2 Hz, ArH), 7.43 (1 H, dd, *J*=8.8, 2.2 Hz, ArH), 6.93 (1 H, d, *J*=8.4 Hz, ArH), 6.44 (1 H, br. d, *J*=8.4 Hz, NH), 5.03 (1 H, m, NH), 4.52 (1 H, br. app. dd, *J*=8.6, 4.9 Hz, CHNH), 4.31 (1 H, br. app. dd, *J*=13.9, 7.3 Hz, CHNH), 3.92 (3 H, s, OCH₃), 3.71 (3 H, s, CO₂CH₃), 3.09 (1 H, dd, *J*=14.3, 6.6 Hz, CHH), 2.99 (1 H, dd, *J*=13.9, 7.0 Hz, CHH), 1.93–1.78 (1 H, m,

CH(CH₃)CH₂CH₃, 1.42 (9 H, s, 3 x **CH₃**), 1.39–1.30 (1 H, m, **CHHCH₃**), 1.22–1.02 (1 H, m, **CHHCH₃**), 0.89 (3 H, t, *J*=7.3 Hz, **CH₂CH₃**), 0.85 (3 H, d, *J*=7.0 Hz, **CHCH₃**).

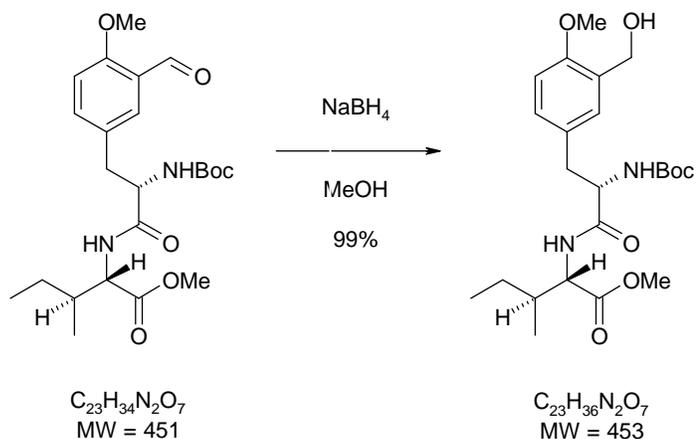
¹³C NMR δ_C (75 MHz, CDCl₃): 189.5 (**CHO**), 171.8 (**C**), 170.6 (**C**), 160.8 (**C**), 155.7 (**C**), 136.8 (**CH**), 129.2 (**CH**), 128.9 (**C**), 124.6 (**C**), 112.0 (**CH**), 79.3 (**C**), 56.5 (**OCH₃**), 55.7 (**CHNH**), 55.7 (**CHNH**), 52.1 (**CO₂CH₃**), 37.9 (**CH**), 37.0 (**CH₂**), 28.2 (3 x **CH₃**), 25.1 (**CH₂**), 15.3 (**CH₃**), 11.5 (**CH₃**).

LRMS m/z (ES+) 473 ([**M+Na**]⁺, 100), 924 ([**2M+Na**]⁺, 22).

HRMS m/z (ES+) Found [**M+Na**]⁺ 473.2263. Required 473.2258.

[α]_D + 38.9 (c = 0.7, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.47**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-(3-formyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.46** (259 mg, 0.57 mmol) in MeOH (10 mL) at 0 °C was added NaBH₄ (26 mg, 0.69 mmol). The reaction was stirred at 0 °C for 2 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), then the organic extracts were combined, washed with brine (10 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 60% ethyl acetate/petroleum ether) afforded **2.47** as a yellow oil (255 mg, 0.56 mmol, 99%).

FT-IR (v/cm⁻¹) 3308 (br), 2968 (m), 2877 (w), 1738 (m), 1659 (s), 1500 (s), 1366 (m), 1247 (s), 1165 (s), 1020 (s), 734 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.18–7.08 (2 H, m, 2 x ArH), 6.81 (1 H, d, *J*=8.8 Hz, ArH), 6.29 (1 H, br. d, *J*=8.4 Hz, NH), 5.10 (1 H, br., NH), 4.65 (2 H, br. d, *J*=3.7 Hz, ArCH₂OH), 4.49 (1 H, app. dd, *J*=8.2, 4.9 Hz, CHNH), 4.29 (1 H, br. app. q, *J*=7.0 Hz, CHNH), 3.85 (3 H, s, OCH₃), 3.70 (3 H, s, CO₂CH₃), 3.05 (1 H, dd, *J*=13.9, 6.2 Hz, CHH), 2.97 (1 H, dd, *J*=13.9, 7.3 Hz, CHH), 2.51 (1 H, br., OH), 1.82 (1 H, m, CH(CH₃)CH₂CH₃), 1.43 (9 H, s, 3 x CH₃), 1.40–1.30 (1 H, m, CHHCH₃), 1.18–1.00 (1 H, m,

CHHCH₃), 0.88 (3 H, t, $J=7.3$ Hz, CH₂CH₃), 0.83 (3 H, d, $J=6.6$ Hz, CHCH₃).

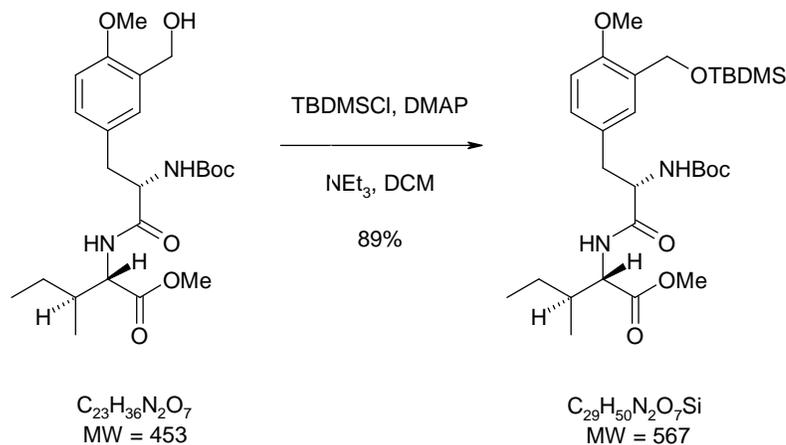
¹³C NMR δ_c (75 MHz, CDCl₃): 171.9 (C), 170.9 (C), 156.4 (C), 155.7 (C), 129.7 (CH), 129.5 (CH), 129.3 (C), 128.5 (C), 110.4 (CH), 80.0 (C), 61.7 (CH₂), 56.5 (OCH₃), 56.0 (CHNH), 55.4 (CHNH), 52.1 (CO₂CH₃), 37.8 (CH), 37.4 (CH₂), 28.3 (3 x CH₃), 25.1 (CH₂), 15.3 (CH₃), 11.5 (CH₃).

LRMS m/z (ES+) 475 ([M+Na]⁺, 100), 927 ([2M+Na]⁺, 7).

HRMS m/z (ES+) Found [M+Na]⁺ 475.2409. Required 475.2415.

[α]_D + 13.3 (c = 0.5, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-[3-(*tert*-butyl-dimethyl-silynyloxymethyl)-4-methoxy-phenyl]-propionylamino]-3-methyl-pentanoic acid methyl ester **2.48**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.47** (230 mg, 0.51 mmol) in DCM (12 mL) was added TBDMSCl (154 mg, 1.02 mmol), DMAP (62 mg, 0.51 mmol) and NEt₃ (0.14 mL, 1.02 mmol). The reaction was stirred at RT for 16 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic extracts combined, washed with brine (10 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 50% ethyl acetate/petroleum ether) afforded **2.48** as a colourless oil (256 mg, 0.45 mmol, 89%).

FT-IR (v/cm⁻¹) 3324 (w), 2957 (m), 2930 (m), 2856 (w), 1741 (m), 1662 (s), 1500 (s), 1366 (m), 1249 (s), 1168 (s), 1081 (s), 1029 (m), 836 (s), 775 (s), 733 (w).

¹H NMR δ_H (300 MHz, CDCl₃): 7.29 (1 H, obs. d, ArH), 7.07 (1 H, br. d, *J*=8.4 Hz, ArH), 6.75 (1 H, d, *J*=8.4 Hz, ArH), 6.44 (1 H, br. d, *J*=7.3 Hz, NH), 4.97 (1 H, br. s, NH), 4.72 (2 H, s, ArCH₂O), 4.51 (1 H, app. dd, *J*=8.4, 4.8 Hz, CHNH), 4.30 (1 H, br. app. q, *J*=7.3 Hz, CHNH), 3.80 (3 H, s, OCH₃), 3.69 (3 H, s, CO₂CH₃),

3.03 (2 H, br. d, $J=6.2$ Hz, CH_2CH), 1.93–1.75 (1 H, m, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$), 1.42 (9 H, s, 3 x CH_3), 1.40–1.28 (1 H, m, CHHCH_3), 1.18–1.03 (1 H, m, CHHCH_3), 0.96 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.89 (3 H, t, $J=7.3$ Hz, CH_2CH_3), 0.83 (3 H, d, $J=7.0$ Hz, CHCH_3), 0.12 (6 H, s, $\text{Si}(\text{CH}_3)_2$).

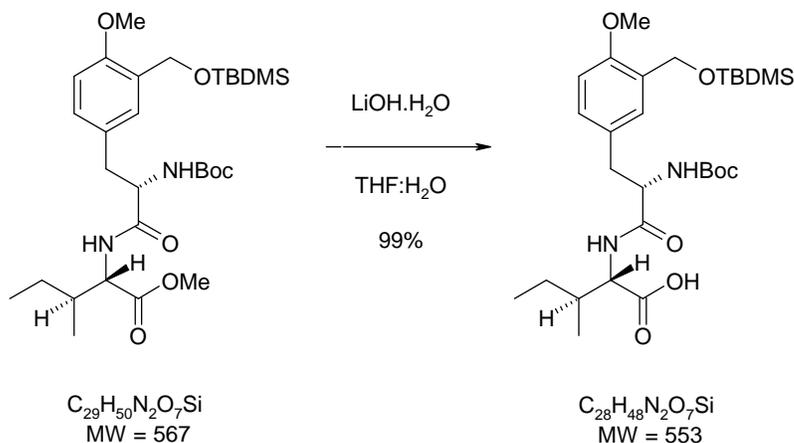
^{13}C NMR δ_{C} (75 MHz, CDCl_3): 171.7 (C), 171.1 (C), 155.4 (C), 155.1 (C), 129.9 (2 x C), 128.2 (CH), 127.9 (CH), 109.8 (CH), 80.1 (C), 60.1 (CH_2), 56.4 (CH_3), 55.9 (CH), 55.1 (CH), 51.9 (CH_3), 37.9 (CH), 37.2 (CH_2), 28.2 (3 x CH_3), 26.0 (3 x CH_3), 25.1 (CH_2), 18.4 (C), 15.2 (CH_3), 11.5 (CH_3), -5.3 (2 x CH_3).

LRMS m/z (ES+) 590 ($[\text{M}+\text{Na}]^+$, 100), 1156 ($[\text{2M}+\text{Na}]^+$, 2).

HRMS m/z (ES+) Found $[\text{M}+\text{Na}]^+$ 589.3272. Required 589.3279.

$[\alpha]_{\text{D}}$ + 74.7 ($c = 1.2$, CHCl_3).

(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-[3-(*tert*-butyl-dimethyl-silynyloxymethyl)-4-methoxy-phenyl]-propionylamino]-3-methyl-pentanoic acid **2.29**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-[3-(*tert*-butyl-dimethyl-silynyloxymethyl)-4-methoxy-phenyl]-propionylamino]-3-methyl-pentanoic acid methyl ester **2.48** (335 mg, 0.59 mmol) in THF:H₂O (12 mL:12 mL) was added LiOH.H₂O (62 mg, 1.48 mmol). The reaction was stirred at RT for 18 h then quenched with sat. NH₄Cl (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), then the organic extracts were combined, washed with brine (10 mL) and dried (MgSO₄). Concentration *in vacuo* afforded **2.29** as a colourless oil (322 mg, 0.58 mmol, 99%).

FT-IR (v/cm⁻¹) 3324 (br), 2963 (m), 2930 (m), 1660 (s), 1502 (s), 1463 (w), 1369 (w), 1249 (s), 1164 (s), 1037 (m), 856 (w), 835 (w), 753 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.20 (1 H, br. s, ArH), 7.10 (1 H, br. d, *J*=8.4 Hz, ArH), 6.75 (1 H, d, *J*=8.4 Hz, ArH), 6.39 (1 H, br. d, *J*=8.1 Hz, NH), 5.27 (1 H, br., NH), 4.78 (1 H, d, *J*=13.5 Hz, OCHH), 4.65 (1 H, d, *J*=13.2 Hz, OCHH), 4.47 (1 H, br. app. dd, *J*=7.7, 6.2 Hz, CHNH), 4.33 (1 H, br. app. q, *J*=6.2 Hz, CHNH), 3.78 (3 H, s, OCH₃), 3.09–2.90 (2 H, m, CH₂CH), 1.90–1.76 (1 H, m, CH(CH₃)CH₂CH₃), 1.53–1.43 (1 H, m,

CHHCH₃), 1.41 (9 H, s, 3 x CH₃), 1.22–1.04 (1 H, m, CHHCH₃), 0.97 (9 H, s, OSiC(CH₃)₃), 0.94 (3 H, d, *J*=6.5 Hz, CHCH₃), 0.87 (3 H, t, *J*=6.2 Hz, CH₂CH₃), 0.15 (3 H, s, OSiCH₃), 0.14 (6 H, s, OSi(CH₃)₂).

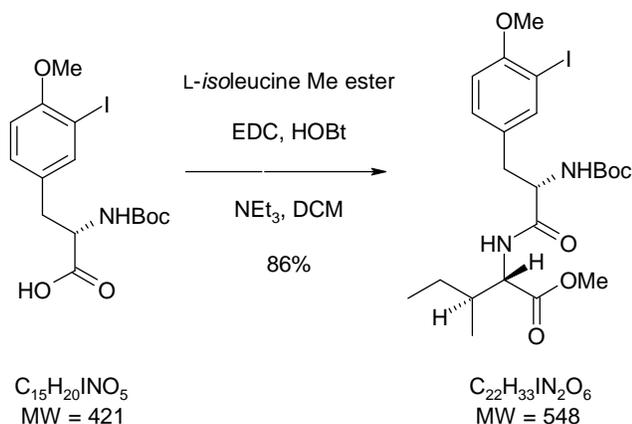
¹³C NMR δ_C (75 MHz, CDCl₃): 171.4 (2 x C), 155.6 (C), 155.5 (C), 128.8 (2 x CH), 128.1 (C), 128.0 (C), 110.1 (CH), 79.7 (C), 60.8 (CH₂), 56.8 (CH), 56.1 (CH), 55.1 (OCH₃), 37.9 (CH₂), 37.3 (CH), 28.2 (3 x CH₃), 26.0 (3 x CH₃), 25.0 (CH₂), 18.5 (C), 15.2 (CH₃), 11.4 (CH₃), -5.3 (2 x CH₃).

LRMS ^{m/z} (ES⁻) 552 ([M-H]⁻, 100).

HRMS ^{m/z} (ES⁺) Found [M+Na]⁺ 575.3117. Required 575.3123.

[α]_D + 5.7 (c = 1.4, CHCl₃).

(2*S*, 3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(3-iodo-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.50**



To a solution of (*S*)-2-*tert*-butoxycarbonylamino-3-(3-iodo-4-methoxy-phenyl)-propionic acid **2.49** (4.14 g, 9.83 mmol) in DCM (85 mL) was added L-isoleucine methyl ester (1.39 g, 7.65 mmol), EDC (1.34 mL, 7.65 mmol), HOBT (1.03 g, 7.65 mmol) and NEt₃ (3.20 mL, 22.95 mmol). The reaction was stirred at RT for 12 h then quenched with sat. NH₄Cl (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL), the organic extracts were combined, washed with brine (100 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.50** as a white solid (3.61 g, 6.58 mmol, 86%).

m.p 123–125 °C

FT-IR (v/cm⁻¹) 3327 (m), 3298 (m), 2962 (w), 2933 (w), 1733 (s), 1683 (m), 1657 (s), 1524 (s), 1491 (m), 1253 (s), 1163 (m), 1046 (m), 1021 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.61 (1 H, d, *J*=1.8 Hz, ArH), 7.16 (1 H, dd, *J*=8.4, 1.8 Hz, ArH), 6.74 (1 H, d, *J*=8.4 Hz, ArH), 6.40 (1 H, br. d, *J*=8.4 Hz, NH), 5.03 (1 H, m, NH), 4.51 (1 H, app. dd, *J*=8.6, 4.9 Hz, CHNH), 4.28 (1 H, br. app. q, *J*=7.7 Hz, CHNH),

3.86 (3 H, s, OCH₃), 3.71 (3 H, s, CO₂CH₃), 3.10–2.86 (2 H, m, CH₂CH), 1.92–1.77 (1 H, m, CH(CH₃)CH₂CH₃), 1.43 (9 H, s, 3 x CH₃), 1.40–1.29 (1 H, m, CHHCH₃), 1.20–1.02 (1 H, m, CHHCH₃), 0.90 (3 H, t, *J*=7.3 Hz, CH₂CH₃), 0.84 (3 H, d, *J*=7.0 Hz, CHCH₃).

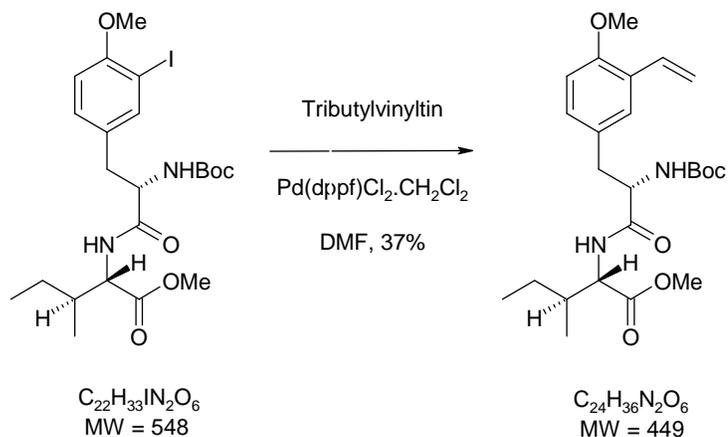
¹³C NMR δ_C (75 MHz, CDCl₃): 171.7 (C), 170.6 (C), 157.1 (C), 155.3 (C), 140.1 (CH), 130.7 (C), 130.3 (CH), 110.9 (CH), 86.0 (C), 80.3 (C), 56.5 (CHNH), 56.3 (OCH₃), 55.8 (CHNH), 52.1 (OCH₃), 37.9 (CH), 36.6 (CH₂), 28.2 (3 x CH₃), 25.1 (CH₂), 15.3 (CH₃), 11.5 (CH₃).

LRMS *m/z* (ES+) 571 ([M+Na]⁺, 100), 1120 ([2M+Na]⁺, 12).

HRMS *m/z* (ES+) Found [M+Na]⁺ 571.1278. Required 571.1276.

[α]_D + 52.3 (c = 2.0, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxy-3-vinyl-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.51**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-(3-iodo-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.50** (1.47 g, 2.36 mmol) and tributylvinyltin (0.76 mL, 2.59 mmol) in DMF (50 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (96 mg, 0.12 mmol). The reaction was stirred at RT for 16 h then quenched with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (10% w/w K₂CO₃ in SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.51** as a yellow oil (387 mg, 0.86 mmol, 37%).

FT-IR (v/cm⁻¹) 3304 (m), 2964 (m), 1743 (w), 1654 (s), 1522 (m), 1495 (m), 1366 (w), 1250 (s), 1203 (w), 1167 (s), 1023 (w).

¹H NMR δ_H (300 MHz, CDCl₃): 7.28 (1 H, d, *J*=2.2 Hz, ArH), 7.08 (1 H, dd, *J*=8.2, 2.0 Hz, ArH), 6.99 (1 H, dd, *J*=17.9, 11.3 Hz, ArCH=CH₂), 6.80 (1 H, d, *J*=8.4 Hz, ArH), 6.38 (1 H, br. d, *J*=8.4 Hz, NH), 5.72 (1 H, dd, *J*=17.9, 1.5 Hz, ArCH=CHH), 5.25 (1 H, dd, *J*=11.2, 1.3 Hz, ArCH=CHH), 5.04 (1 H, m, NH), 4.50 (1 H, dd, *J*=8.4, 5.1 Hz, CHNH), 4.31 (1 H, br. app. q, *J*=7.0 Hz, CHNH), 3.83 (3 H, s, ArOCH₃), 3.68 (3 H, s,

CO₂CH₃), 3.13–2.91 (2 H, m, CH₂), 1.88–1.76 (1 H, m, CH(CH₃)CH₂CH₃), 1.43 (9 H, s, 3 x CH₃), 1.39–1.29 (1 H, m, CHHCH₃), 1.18–1.01 (1 H, m, CHHCH₃), 0.88 (3 H, t, *J*=7.3 Hz, CH₂CH₃), 0.82 (3 H, d, *J*=7.0 Hz, CHCH₃).

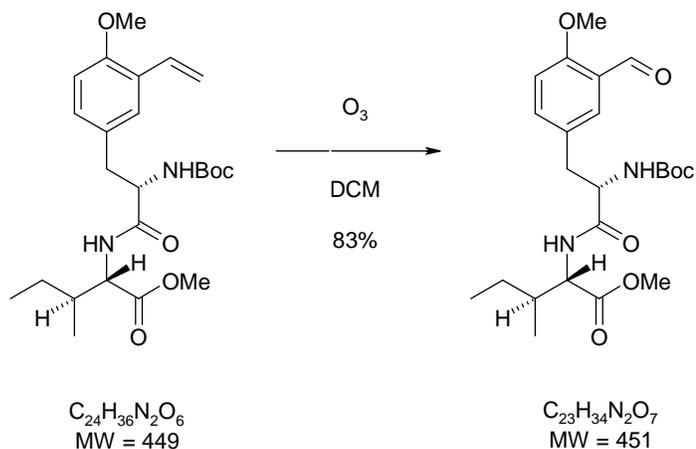
¹³C NMR δ_C (75 MHz, CDCl₃): 171.7 (C), 170.9 (C), 155.8 (C), 155.3 (C), 131.3 (CH), 129.5 (CH), 128.4 (C), 127.4 (CH), 126.8 (C), 114.7 (CH₂), 111.1 (CH), 80.2 (C), 56.5 (OCH₃), 55.9 (CHNH), 55.5 (CHNH), 52.0 (CO₂CH₃), 37.9 (CH), 37.2 (CH₂), 28.2 (3 x CH₃), 25.1 (CH₂), 15.2 (CH₃), 11.5 (CH₃).

LRMS ^{m/z} (ES+) 471 ([M+Na]⁺, 100), 920 ([2M+Na]⁺, 10).

HRMS ^{m/z} (ES+) Found [M+Na]⁺ 471.2467. Required 471.2466.

[α]_D + 14.1 (c = 1.4, CHCl₃).

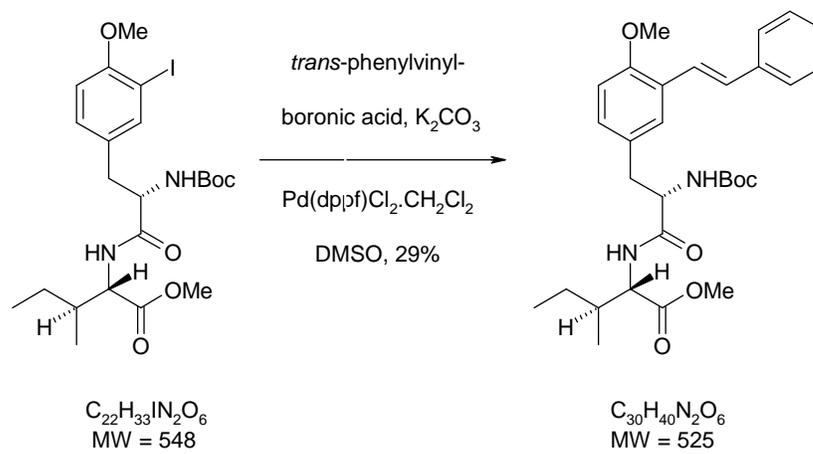
(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(3-formyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.46**



A stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-(4-methoxy-3-vinyl-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.51** (370 mg, 0.83 mmol) and sudan red (10 mg) in DCM (100 mL) was cooled to -78 °C and O₃ (1–4% in O₂) bubbled through until the red colour disappeared. O₂ was then bubbled through for 20 min before PPh₃ (433 mg, 1.65 mmol) was added. The reaction was stirred at -78 °C for 20 min then allowed to warm to RT. Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.46** as a yellow oil (309 mg, 0.69 mmol, 83%).

The data matches that previously reported.

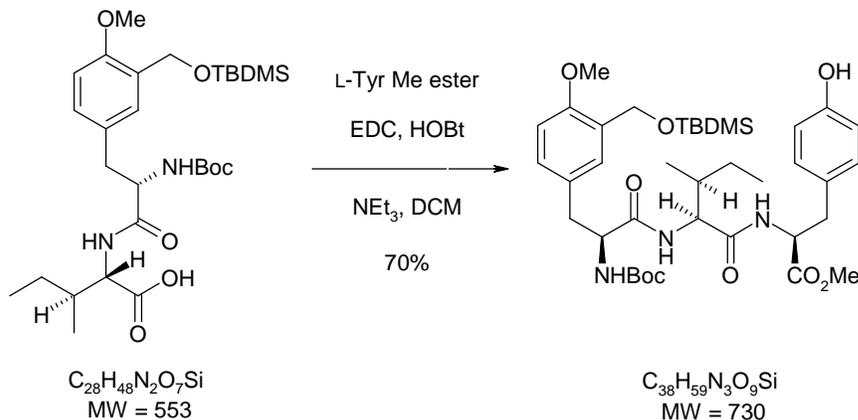
(2*S*,3*S*)-2-[(*S*)-2-*tert*-Butoxycarbonylamino-3-(4-methoxy-3-styryl-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.45**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-(3-iodo-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid methyl ester **2.50** (2.36 g, 3.78 mmol), *trans*-phenylvinylboronic acid (615 mg, 4.16 mmol) and K₂CO₃ (2.09 g, 15.1 mmol) in DMSO (45 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (124 mg, 0.15 mmol). The reaction was heated at 80 °C for 16 h, allowed to cool then quenched with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL), the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.45** as a yellow oil (653 mg, 1.09 mmol, 29%).

Data matches that previously reported.

(S)-2-(2-((S)-2-tert-Butoxycarbonylamino-3-[3-(tert-butyl-dimethyl-silynyloxymethyl)-4-methoxy-phenyl]-propionylamino)-3-methyl-pentanoylamino)-3-(4-hydroxy-phenyl)-propionic acid methyl ester **2.52**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-[3-(*tert*-butyl-dimethyl-silynyloxymethyl)-4-methoxy-phenyl]-propionylamino]-3-methyl-pentanoic acid **2.29** (223 mg, 0.40 mmol) in DCM (5 mL) was added L-tyrosine methyl ester (187 mg, 0.81 mmol), EDC (0.14 mL, 0.81 mmol), HOBT (109 mg, 0.81 mmol) and NEt₃ (0.17 mL, 1.21 mmol). The reaction was stirred at RT for 12 h then quenched with sat. NH₄Cl (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic extracts combined, washed with brine (10 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 2% MeOH/DCM) afforded **2.52** as a white foam (204 mg, 0.28 mmol, 70%).

FT-IR (v/cm⁻¹) 3289 (br.), 2952 (m), 2926 (m), 2854 (w), 1748 (w), 1684 (w), 1647 (s), 1516 (s), 1507 (m), 1452 (w), 1361 (w), 1251 (m), 1172 (m), 1081 (w), 837 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.02 (1 H, dd, *J*=8.4, 1.8 Hz, ArH), 6.93 (2 H, d, *J*=8.4 Hz, 2 x ArH), 6.78 - 6.66 (3 H, m, 3 x ArH), 6.58 (1 H, d, *J*=8.1 Hz, ArH), 6.45 (1H, m, NH), 5.07 (1H, m, NH), 4.92 (1 H, d, *J*=7.7 Hz, NH), 4.81 (1 H, br. app. q, *J*=7.1 Hz, CHNH), 4.73 (2 H, br. s, OCH₂), 4.42 (1H, m, OH), 4.35 -

4.20 (2 H, m, 2 x CHNH), 3.77 (3 H, s, OCH₃), 3.71 (3 H, s, CO₂CH₃), 3.12 - 2.89 (4 H, m, 2 x CH₂CH), 1.92 - 1.71 (1 H, m, CH(CH₃)CH₂CH₃), 1.41 (9 H, s, 3 x CH₃), 1.36 - 1.23 (1 H, m, CHHCH₃), 1.10 - 0.99 (1 H, m, CHHCH₃), 0.96 (9 H, s, OSi(CH₃)₃), 0.86 - 0.75 (6 H, m, CHCH₃ and CH₂CH₃), 0.12 (6 H, s, OSi(CH₃)₂).

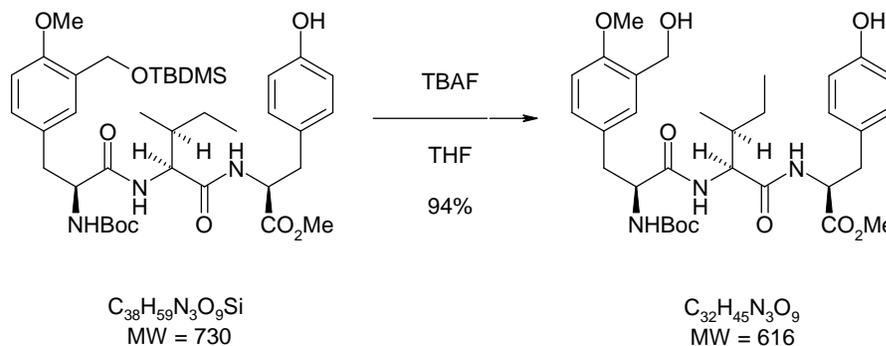
¹³C NMR δ_C (75 MHz, CDCl₃): 172.0 (C), 171.7 (C), 170.4 (C), 155.7 (C), 155.5 (C), 155.2 (C), 130.3 (2 x CH), 129.7 (C), 128.4 (CH), 128.1 (CH), 128.0 (C), 126.8 (C), 115.7 (2 x CH), 110.0 (CH), 80.6 (C), 60.2 (CH₂), 60.2 (CH), 57.8 (CHNH), 55.2 (OCH₃), 53.1 (CHNH), 52.3 (CO₂CH₃), 37.0 (br. s, 2 x CH₂), 36.8 (CH), 28.2 (3 x CH₃), 26.0 (3 x CH₃), 24.5 (CH₂), 18.5 (C), 15.2 (CH₃), 11.3 (CH₃), -5.3 (2 x CH₃).

LRMS ^{m/z} (ES+) 752 ([M+Na]⁺, 100).

HRMS ^{m/z} (ES+) Found [M+Na]⁺ 752.3907. Required 752.3913.

[α]_D + 36.7 (c = 0.3, CHCl₃).

(S)-2-([2S,3S]-2-[(S)-2-*tert*-Butoxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoylamino]-3-(4-hydroxy-phenyl)-propionic acid methyl ester **2.53**



To a stirred solution of (*S*)-2-(2-((*S*)-2-*tert*-butoxycarbonylamino-3-[3-(*tert*-butyl-dimethyl-silyloxymethyl)-4-methoxy-phenyl]-propionylamino)-3-methyl-pentanoylamino)-3-(4-hydroxy-phenyl)-propionic acid methyl ester **2.52** (56 mg, 0.08 mmol) in THF (5 mL) at 0 °C was added TBAF (1 M in THF, 0.08 mL, 0.08 mmol). The reaction was stirred at RT for 3 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic extracts combined, washed with brine (10 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 5% MeOH/DCM) afforded **2.53** as a beige oil (44 mg, 0.07 mmol, 94%).

FT-IR (v/cm⁻¹) 3308 (w), 2962 (w), 2926 (m), 2850 (w), 1740 (w), 1692 (m), 1638 (s), 1501 (m), 1477 (w), 1456 (w), 1439 (m), 1366 (w), 1247 (s), 1167 (s), 1043 (m).

¹H NMR δ_H (300 MHz, MeOD): 7.18 (1 H, s, ArH), 7.05 (1 H, d, *J*=8.4 Hz, ArH), 6.98 (2 H, d, *J*=7.0 Hz, 2 x ArH), 6.76 (1 H, d, *J*=8.1 Hz, ArH), 6.70 (2 H, d, *J*=6.6 Hz, 2 x ArH), 4.59 (3 H, br. s, CHNH and CH₂OH), 4.36 - 4.23 (1 H, m, CHNH), 4.20 (1 H, br. app. d, *J*=7.7 Hz, CHNH), 3.77 (3 H, s OCH₃), 3.65 (3 H, s, CO₂CH₃), 3.13 - 2.83 (3 H, m, CHH and CHH and CHH), 2.76 (1 H, dd, *J*=12.4, 10.2 Hz, CHH), 1.84 - 1.66 (1 H, m,

CH(CH₃)CH₂CH₃, 1.36 (10 H, br. s, 3 x **CH₃** and **CHHCH₃**), 1.18 - 0.98 (1 H, m, **CHHCH₃**), 0.95 - 0.63 (6 H, m, **CHCH₃** and **CH₂CH₃**).

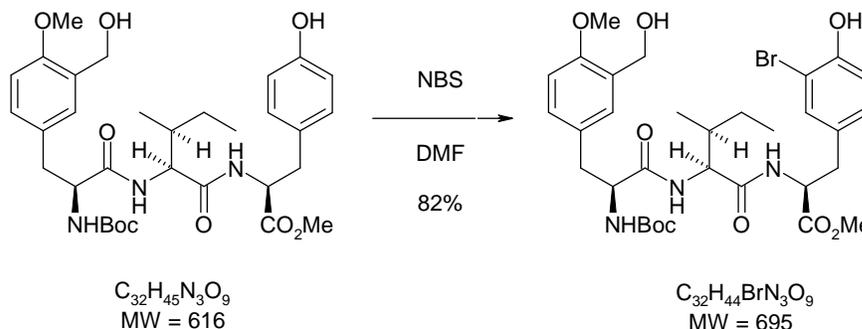
¹³C NMR δ_C (100 MHz, MeOD): 173.7 (**C**), 173.1 (**C**), 172.7 (**C**), 157.0 (**C**), 156.9 (br. 2 x **C**), 131.1 (2 x **CH**), 130.1 (**CH**), 130.0 (**CH**), 129.8 (**C**), 128.0 (**C**), 122.2 (**C**), 116.2 (2 x **CH**), 111.0 (**CH**), 80.7 (**C**), 60.6 (**CH₂**), 58.5 (**CHNH**), 57.1 (**CHNH**), 55.8 (**OCH₃**), 55.1 (**CHNH**), 52.6 (**OCH₃**), 38.0 (**CH**), 37.5 (**CH₂**), 37.4 (**CH₂**), 28.7 (3 x **CH₃**), 25.4 (**CH₂**), 15.7 (**CH₃**), 11.4 (**CH₃**).

LRMS m/z (ES+) 638 ([**M+Na**]⁺, 100).

HRMS m/z (ES+) Found [**M+Na**]⁺ 638.3046. Required 638.3048.

[α]_D + 17.8 (c = 0.4, MeOH).

(S)-3-(3-Bromo-4-hydroxyphenyl)-2-[(2S,3S)-2-[(S)-2-*tert*-butoxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoylamino]-propionic acid methyl ester **2.27**



To a stirred solution of (S)-2-{2S,3S}-2-[(S)-2-*tert*-butoxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoylamino]-3-(4-hydroxy-phenyl)-propionic acid methyl ester **2.53** (45 mg, 0.07 mmol) in DMF (1 mL) was added NBS (14 mg, 0.08 mmol). The reaction was stirred at RT for 16 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the organic extracts were combined and washed with water (5 x 5 mL) and brine (5 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 2% MeOH/DCM) afforded **2.27** as a colourless oil (42 mg, 0.06 mmol, 82%).

FT-IR (v/cm⁻¹) 3305 (w), 2962 (w), 2929 (w), 1740 (m), 1692 (m), 1638 (s), 1532 (w), 1477 (m), 1441 (m), 1413 (m), 1245 (m), 1175 (m), 1150 (m), 1043 (m).

¹H NMR δ_H (400 MHz, MeOD): 7.34 (1H, s, ArH), 7.29 (1H, s, ArH), 7.23 (1 H, s, ArH), 7.08 (1 H, d, *J*=8.0 Hz, ArH), 7.00 (1 H, d, *J*=8.0 Hz, ArH), 6.85 (1H, br. d, *J*=8.6 Hz, NH), 6.83 - 6.76 (2 H, m, ArH and NH), 6.64 (1H, br. d, *J*=8.4 Hz, NH), 4.59 (3 H, br. s, CH₂OH and CHNH), 4.36 - 4.17 (2 H, m, 2 x CHNH), 3.78 (3 H, s, OCH₃), 3.67 (3 H, s, OCH₃), 3.07 - 2.95 (2 H, m, CHH and CHH), 2.92 - 2.82 (1 H, m, CHH), 2.80 - 2.67 (1 H,

m, CHH), 1.85 - 1.70 (1 H, m, CH), 1.56 - 1.43 (1 H, m, CHHCH₃), 1.37 (9 H, s, 3 x CH₃), 1.20 - 1.05 (1 H, m, CHHCH₃), 0.95 - 0.83 (6 H, m, 2 x CH₃).

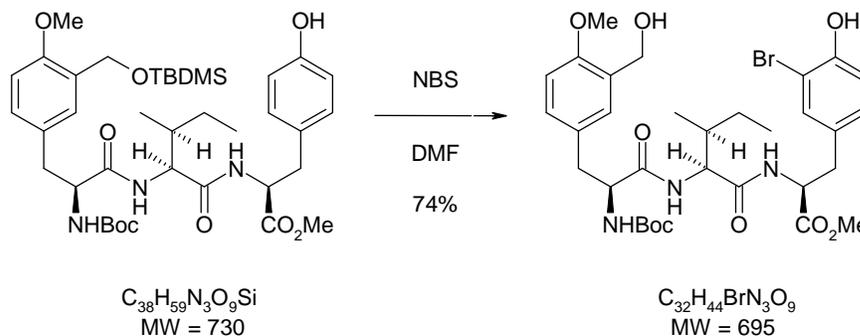
¹³C NMR δ_C (100 MHz, MeOD): 174.3 (C), 173.5 (C), 173.2 (C), 157.8 (C), 157.4 (C), 154.4 (C), 134.8 (CH), 134.2 (CH), 132.3 (C), 130.6 (CH), 130.5 (CH), 130.4 (C), 130.4 (C), 117.4 (CH), 111.4 (CH), 110.8 (C), 80.8 (C), 60.7 (CH₂), 59.0 (CH), 57.6 (CH), 56.0 (OCH₃), 55.4 (CH), 52.8 (OCH₃), 38.6 (CH), 38.3 (CH₂), 37.3 (CH₂), 28.8 (3 x CH₃), 25.8 (CH₂), 15.8 (CH₃), 11.5 (CH₃).

LRMS m/z (ES+) 716 ([M (⁷⁹Br)+Na]⁺, 100), 718 ([M (⁸¹Br)+Na]⁺, 93).

HRMS m/z (ES+) Found [M (⁷⁹Br)+Na]⁺ 716.2140. Required 716.2153.

$[\alpha]_D$ + 21.5 (c = 2.0, MeOH).

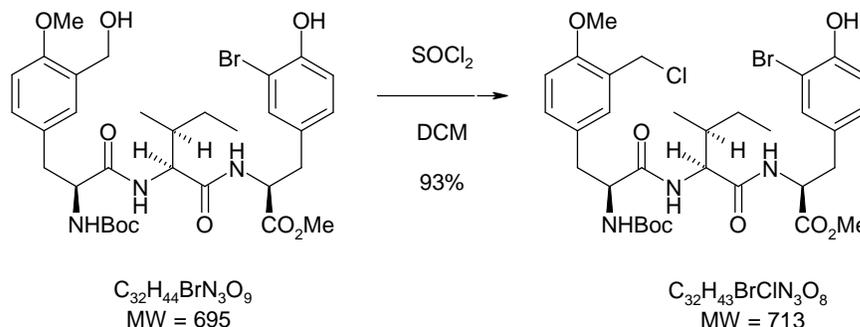
(S)-3-(3-Bromo-4-hydroxyphenyl)-2-[(2S,3S)-2-[(S)-2-*tert*-butoxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoylamino]-propionic acid methyl ester **2.27**



To a stirred solution of (S)-2-(2-[(S)-2-*tert*-butoxycarbonylamino-3-[3-(*tert*-butyl-dimethyl-silyloxymethyl)-4-methoxy-phenyl]-propionylamino]-3-methyl-pentanoylamino)-3-(4-hydroxy-phenyl)-propionic acid methyl ester **2.52** (54 mg, 0.07 mmol) in DMF (1 mL) was added NBS (15 mg, 0.08 mmol). The reaction was stirred at RT for 16 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the organic extracts were combined, washed with water (5 x 5 mL) and brine (5 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 2% MeOH/DCM) afforded **2.27** as a colourless oil (38 mg, 0.06 mmol, 74%).

Data matches that previously reported.

(S)-3-(3-Bromo-4-hydroxyphenyl)-2-[(2S,3S)-2-[(S)-2-*tert*-butoxycarbonylamino-3-(3-chloromethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoylamino]-propionic acid methyl ester **2.26**



To a stirred solution of (S)-3-(3-bromo-4-hydroxyphenyl)-2-[(2S,3S)-2-[(S)-2-*tert*-butoxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoylamino]-propionic acid methyl ester **2.27** (38 mg, 0.06 mmol) in DCM (5 mL) at 0 °C was added SOCl₂ (7 mg, 0.06 mmol). The reaction was stirred at 0 °C for 3 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), the organic extracts combined, washed with brine (5 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 2% MeOH/DCM) afforded **2.26** as a colourless oil (36 mg, 0.05 mmol, 93%).

FT-IR (v/cm⁻¹) 3293 (br.), 2965 (w), 2931 (w), 1743 (w), 1638 (s), 1504 (m), 1439 (m), 1367 (w), 1293 (w), 1258 (m), 1218 (m), 1164 (m), 1029 (m), 754 (s).

¹H NMR δ_H (400 MHz, MeOD): 7.23 (1 H, d, *J*=2.0 Hz, ArH), 7.16 (1 H, d, *J*=2.0 Hz, ArH), 7.09 (1 H, dd, *J*=8.5, 2.0 Hz, ArH), 6.91 (1 H, dd, *J*=8.0, 1.5 Hz, ArH), 6.82 - 6.72 (2 H, m, 2 x ArH), 4.61 (1 H, t, *J*=6.5 Hz, CHNH), 4.57 (2 H, s, CH₂Cl), 4.28 - 4.20 (1 H, m, CHNH), 4.15 (1 H, br. app. d, *J*=8.0 Hz, CHNH), 3.79 (3 H, s, OCH₃), 3.65 (3 H, s, CO₂CH₃), 3.07 - 2.95 (1 H, m, CHH), 2.97 (1 H, dd, *J*=13.6, 6.0 Hz, CHH), 2.87 (1 H, dd, *J*=14.1, 7.5

Hz, **CHH**), 2.82 - 2.72 (1 H, m, **CHH**), 1.80 - 1.68 (1 H, m, **CH(CH₃)CH₂CH₃**), 1.34 (10 H, br. s, 3 x **CH₃** and **CHHCH₃**), 1.11 - 0.97 (1 H, m, **CHHCH₃**), 0.89 - 0.71 (6 H, m, 2 x **CH₃**).

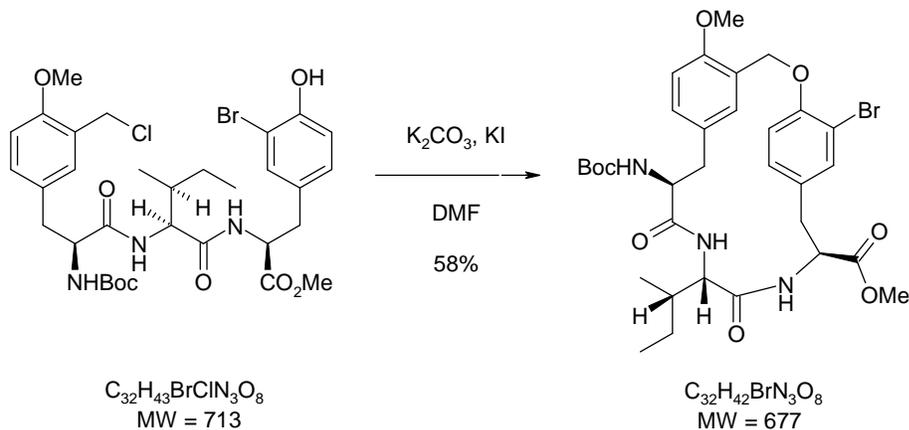
¹³C NMR δ_C (100 MHz, MeOD): 172.8 (C), 172.4 (C), 172.1 (C), 156.9 (C), 156.6 (C), 153.3 (C), 134.0 (CH), 132.0 (CH), 131.3 (CH), 129.8 (CH), 129.5 (C), 129.3 (C), 126.3 (C), 116.7 (CH), 111.5 (CH), 110.2 (CBr), 80.7 (C), 58.2 (CHNH), 56.9 (CHNH), 56.0 (OCH₃), 54.3 (CHNH), 52.6 (OCH₃), 41.9 (CH₂Cl), 37.5 (CH), 37.4 (CH₂), 36.9 (CH₂), 28.5 (3 x CH₃), 25.1 (CH₂), 15.5 (CH₃), 11.3 (CH₃).

LRMS m/z (ES+) 734 ([M (³⁵Cl, ⁷⁹Br)+Na]⁺, 88), 736 ([M (³⁵Cl, ⁸¹Br and ³⁷Cl, ⁷⁹Br)+Na]⁺, 100), 738 ([M (³⁷Cl, ⁸¹Br)+Na]⁺, 40).

HRMS m/z (ES+) Found [M (³⁵Cl, ⁷⁹Br)+Na]⁺ 734.1825. Required 734.1820.

[α]_D + 39.6 (c = 1.0, MeOH).

(10*S*,13*S*)-20-Bromo-10-*tert*-butoxycarbonylamino-13-((*S*)-*sec*-butyl)-5-methoxy-11,14-dioxo-2-oxa-12,15-diaza-tricyclo[16.2.2.1^{4,8}]tricoso-1(21)4,6,8(23),18(22),19-hexaene-16-carboxylic acid (*S*)-methyl ester **2.25**



A stirred solution of (*S*)-3-(3-bromo-4-hydroxyphenyl)-2-[(2*S*,3*S*)-2-[(*S*)-2-*tert*-butoxycarbonylamino-3-(3-chloromethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoylamino]-propionic acid methyl ester **2.26** (37 mg, 0.05 mmol), K_2CO_3 (10 mg, 0.07 mmol) and KI (2 mg, 0.01 mmol) in DMF (8 mL) was heated at 80 °C for 16 h. The reaction was quenched with water (10 mL) and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with water (5 x 10 mL) and brine (5 mL), then dried (MgSO_4). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 2% MeOH/DCM) afforded **2.25** as a colourless oil (20 mg, 0.03 mmol, 58%).

FT-IR (v/cm^{-1}) 2962 (m), 2932 (m), 2869 (w), 2475 (w), 2389 (w), 1742 (m), 1671 (s), 1492 (s), 1437 (m), 1408 (m), 1366 (w), 1290 (w), 1252 (m), 1163 (m), 1051 (w), 1029 (m), 731 (m).

¹H NMR δ_{H} (300 MHz, MeOD): 7.32 (1 H, d, $J=1.8$ Hz, ArH), 7.11 (1 H, dd, $J=8.4, 1.8$ Hz, ArH), 6.93 (1 H, s, ArH), 6.87 (1 H, dd, $J=8.4, 1.8$ Hz, ArH), 6.79 (1 H, d, $J=8.4$ Hz, ArH), 6.60 (1 H, d, $J=8.4$ Hz, ArH), 5.37 (1 H, d, $J=14.6$ Hz, ArCHHOAr), 5.15 (1 H, d, $J=14.6$ Hz, ArCHHOAr), 4.64 (1 H, dd, $J=11.9, 3.8$ Hz,

CHNH), 4.16 (1 H, app. br. d, $J=10.8$ Hz, CHNH), 4.00 (1 H, app. br. d, $J=6.6$ Hz, CHNH), 3.83 (3 H, s, OCH₃), 3.71 (3 H, s, CO₂CH₃), 3.22 - 2.99 (2 H, m, CHH and CHH), 2.70 - 2.55 (2 H, m, CHH and CHH), 1.74 - 1.61 (1 H, m, CH(CH₃)CHCH₃), 1.42 (9 H, s, 3 x CH₃), 1.36 - 1.29 (1 H, m, CHHCH₃), 1.08 - 0.93 (1 H, m, CHHCH₃), 0.86 - 0.74 (6 H, m, 2 x CH₃).

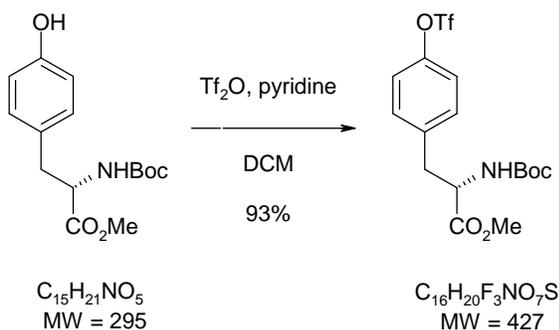
¹³C NMR δ_C (75 MHz, MeOD): 172.5 (C), 171.7 (C), 171.5 (C), 156.6 (C), 156.4 (C), 153.2 (C), 134.5 (CH and C), 130.6 (CH), 129.5 (CH and C), 129.0 (CH), 124.6 (C), 115.1 (CH), 112.6 (C), 111.1 (CH), 80.7 (C), 65.8 (ArCH₂OAr), 57.4 (CHNH), 55.9 (OCH₃), 55.7 (CHNH), 53.1 (CHNH), 52.8 (CO₂CH₃), 38.7 (CH), 36.6 (2 x CH₂), 28.7 (3 x CH₃), 24.6 (CH₂), 15.5 (CH₃), 11.4 (CH₃).

LRMS m/z (ES+) 698 ([M (⁷⁹Br)+Na]⁺, 91), 700 ([M (⁸¹Br)+Na]⁺, 100).

HRMS m/z (ES+) Found [M (⁷⁹Br)+Na]⁺ 698.2063. Required 698.2047.

[α]_D + 31.2 (c = 0.5, MeOH).

(S)-2-tert-Butoxycarbonyl-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid methyl ester **2.74**



Prepared following the procedure of Tilley *et al.*⁷⁹

A stirred solution of (S)-2-tert-butoxycarbonylamino-3-(4-hydroxyphenyl)-propionic acid methyl ester **2.73** (2.00 g, 6.77 mmol) and pyridine (1.64 mL, 20.32 mmol) in DCM (40 mL) was cooled to 0 °C and Tf_2O (1.20 mL, 7.11 mmol) was added dropwise. The reaction was stirred at 0 °C for 3 h then quenched with water (50 mL). The aqueous phase was separated and the organic phase washed with sat. $NaHCO_3$ (50 mL) and brine (50 mL), then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 1% MeOH/DCM) afforded **2.74** as a white solid (2.70 g, 6.31 mmol, 93%).

m.p 45–48 °C

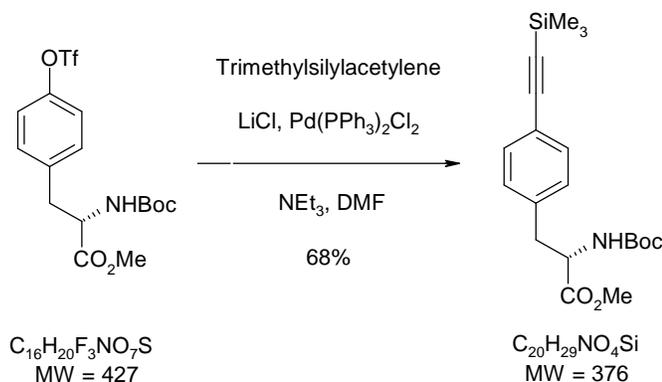
FT-IR (v/cm^{-1}) 3376 (m), 2979 (w), 2952 (m), 1733 (s), 1689 (s), 1516 (s), 1502 (m), 1426 (s), 1368 (w), 1302 (w), 1248 (m), 1217 (s), 1196 (s), 1171 (s), 1140 (s), 1129 (s), 1049 (m), 993 (m), 895 (s), 843 (m).

1H NMR δ_H (300 MHz, $CDCl_3$): 7.22 (4 H, s, 4 x ArH), 5.03 (1 H, br. d, $J=7.3$ Hz, NH), 4.60 (1 H, br. app. q, $J=6.6$ Hz, CHNH), 3.72 (3 H, s, CO_2CH_3), 3.18 (1 H, dd, $J=13.9, 5.9$ Hz, CHH), 3.04 (1 H, dd, $J=13.9, 6.2$ Hz, CHH), 1.41 (9 H, s, 3 x CH_3).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 171.8 (C), 154.9 (C), 148.6 (COTf), 136.9 (C), 131.1 (2 x CH), 121.3 (2 x CH), 118.7 (q, $J=322$ Hz, CF_3), 80.2 (C), 54.2 (CHNH), 52.3 (CH_3), 37.9 (CH_2), 28.2 (3 x CH_3).
LRMS	m/z (ES+) 450 ($[\text{M}+\text{Na}]^+$, 100), 877 ($[\text{2M}+\text{Na}]^+$, 12).
HRMS	m/z (ES+) Found $[\text{M}+\text{Na}]^+$ 450.0802. Required 450.0805.
$[\alpha]_{\text{D}}$	+ 34.4 (c = 0.9, CHCl_3).

The data are consistent with the literature.⁷⁹

(S)-2-tert-Butoxycarbonylamino-3-(4-trimethylsilyl-ethynyl-phenyl)-propionic acid methyl ester **2.75**



A stirred solution of (S)-2-tert-butoxycarbonyl-3-(4-trifluoromethanesulfonyloxyphenyl)-propionic acid methyl ester **2.74** (250 mg, 0.58 mmol), trimethylsilylacetylene (0.12 mL, 0.88 mmol), LiCl (248 mg, 5.85 mmol), Pd(PPh₃)₂Cl₂ (41 mg, 0.06 mmol) and NEt₃ (0.82 mL, 5.85 mmol) in DMF (5 mL) was heated at 80 °C for 16 h. The reaction was quenched with water (10 mL) and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with water (5 x 10 mL) and brine (10 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 10% ethyl acetate/petroleum ether) afforded **2.75** as a yellow oil (149 mg, 0.40 mmol, 68%).

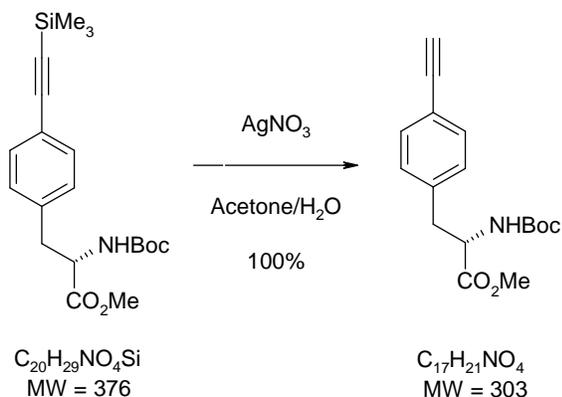
FT-IR (v/cm⁻¹) 3376 (w), 2958 (m), 2158 (m), 1744 (s), 1713 (s), 1504 (m), 1437 (w), 1366 (m), 1249 (m), 1216 (m), 1162 (s), 1058 (w), 1019 (w), 862 (s), 840 (s), 755 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.40 (2 H, d, *J*=8.1 Hz, 2 x ArH), 7.06 (2 H, d, *J*=8.1 Hz, 2 x ArH), 4.96 (1 H, br. d, *J*=7.7 Hz, NH), 4.57 (1 H, m, CHNH), 3.70 (3 H, s, CO₂CH₃), 3.11 (1 H, dd, *J*=13.9, 5.9 Hz, CHH), 3.02 (1 H, dd, *J*=13.9, 6.2 Hz, CHH), 1.42 (9 H, s, 3 x CH₃), 0.25 (9 H, s, Si(CH₃)₃).

^{13}C NMR	δ_{C} (100 MHz, CDCl_3): 172.10 (C), 155.00 (C), 136.62 (C), 132.11 (2 x CH), 129.18 (2 x CH), 121.85 (C), 104.80 (C \equiv C), 94.33 (C \equiv C), 80.03 (C), 54.27 (CH), 52.24 (CH ₃), 38.28 (CH ₂), 28.29 (3 x CH ₃), -0.05 (3 x CH ₃).
LRMS	m/z (ES+) 398 ([M+Na] ⁺ , 100), 774 ([2M+Na] ⁺ , 70).
HRMS	m/z (ES+) Found [M+Na] ⁺ 398.1759. Required 398.1758.
$[\alpha]_{\text{D}}$	+ 35.5 (c = 0.2, CHCl_3).

(S)-2-tert-Butoxycarbonylamino-3-(4-ethynyl-phenyl)-propionic acid methyl ester

2.76



To a stirred solution of (*S*)-2-*tert*-butoxycarbonylamino-3-(4-trimethylsilyl-ethynyl-phenyl)-propionic acid methyl ester **2.75** (21 mg, 0.046 mmol) in acetone (1 mL) was added water (1 drop) and AgNO₃ (1 mg, 0.005 mmol). The reaction was stirred in the dark for 16 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL), the organic extracts were combined, washed with brine (5 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 10% ethyl acetate/petroleum ether) afforded **2.76** as a colourless oil (18 mg, 0.046 mmol, 100%).

FT-IR (v/cm⁻¹) 3281 (w), 2970 (w), 2380 (m), 1743 (s), 1716 (s), 1507 (m), 1437 (w), 1366 (m), 1217 (m), 1166 (m), 1058 (w), 1020 (w).

¹H NMR δ_H (300 MHz, CDCl₃): 7.42 (2 H, d, *J*=8.1 Hz, 2 x ArH), 7.09 (2 H, d, *J*=8.1 Hz, 2 x ArH), 4.99 (1 H, br. d, *J*=7.3 Hz, NH), 4.58 (1 H, br. app. q, *J*=7.7 Hz, CHNH), 3.71 (3 H, s, CO₂CH₃), 3.13 (1 H, dd, *J*=13.9, 5.9 Hz, CHH), 3.07 (1 H, s, C≡CH), 3.03 (1 H, dd, *J*=13.9, 7.7 Hz, CHH), 1.42 (9 H, s, 3 x CH₃).

¹³C NMR δ_C (75 MHz, CDCl₃): 172.0 (C), 155.0 (C), 137.0 (C), 132.2 (2 x CH), 129.3 (2 x CH), 120.8 (C-C≡C), 83.3 (C≡CH), 80.0 (C), 77.3 (C≡CH), 54.2 (CH), 52.3 (CO₂CH₃), 38.3 (CH₂), 28.2 (3 x CH₃).

LRMS m/z (ES+) 326 ($[M+Na]^+$, 100), 630 ($[2M+Na]^+$, 32).

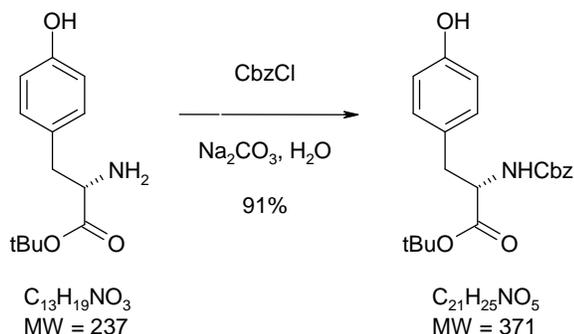
HRMS m/z (ES+) Found $[M+Na]^+$ 326.1362. Required 326.1363.

$[\alpha]_D$ + 18.6 (c = 0.5, $CHCl_3$).

The data are consistent with the literature.⁸⁰

(S)-2-Benzoyloxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester

2.78



Prepared following the procedure of Moody *et al.*⁸¹

To a stirred solution of (S)-2-amino-3-(4-hydroxy-phenyl)-propionic acid tert-butyl ester **2.77** (1.40 g, 5.91 mmol) in water (30 mL) and ether (25 mL) was added Na₂CO₃ (1.88 g, 17.72 mmol) and CbzCl (0.84 mL, 5.91 mmol). The reaction was stirred for 16 h then the aqueous phase was separated and adjusted to pH 2 with conc. HCl. The aqueous phase was extracted with ethyl acetate (4 x 50 mL), the organic extracts were combined then washed with brine (50 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 1% MeOH/DCM) afforded the product as a colourless oil **2.78** (2.00 g, 5.38 mmol, 91%).

FT-IR (v/cm⁻¹) 3417 (br.), 3342 (br.), 3020 (w), 2975 (w), 2926 (w), 1697 (s), 1615 (w), 1514 (s), 1455 (w), 1368 (w), 1216 (s), 1151 (s), 104 (w), 1056 (m), 843 (m), 749 (s), 696 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.41 - 7.28 (5 H, m, 5 x ArH), 6.99 (2 H, d, *J*=8.1 Hz, 2 x ArH), 6.71 (2 H, d, *J*=8.1 Hz, 2 x ArH), 5.88 (1 H, s, OH), 5.29 (1 H, d, *J*=6.6 Hz, NH), 5.13 (1 H, d, *J*=12.5 Hz, OCHH), 5.08 (1 H, d, *J*=12.3 Hz, OCHH), 4.50 (1 H, app. q, *J*=8.1 Hz, CHNH), 3.00 (2 H, app. t, *J*=5.1 Hz, CH₂), 1.43 (9 H, s, 3 x CH₃).

¹³C NMR δ_C (75 MHz, CDCl₃): 170.8 (C), 155.8 (C), 155.0 (C), 136.2 (C), 130.5 (2 x CH), 128.5 (2 x CH), 128.1 (CH), 128.0 (2 x

CH), 127.6 (C), 115.3 (2 x CH), 82.4 (C), 67.0 (OCH₂), 55.4 (CH), 37.6 (CH₂), 27.9 (3 x CH₃).

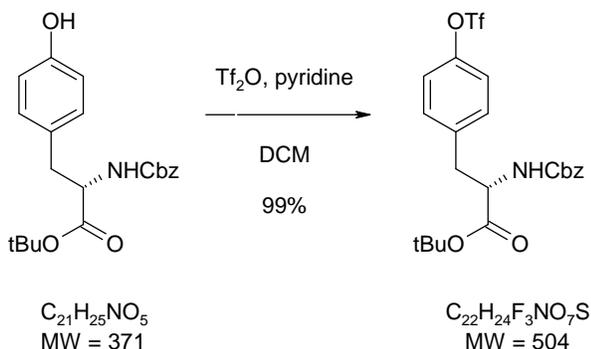
LRMS m/z (ES+) 394 ([M+Na]⁺, 100), 766 ([2M+Na]⁺, 64).

HRMS m/z (ES+) Found [M+Na]⁺ 394.1627. Required 394.1625.

[α]_D + 42.6 (c = 0.5, CHCl₃).

The data are consistent with the literature.⁸¹

(S)-2-Benzoyloxycarbonylamino-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid *tert*-butyl ester **2.79**



A stirred solution of (*S*)-2-benzoyloxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid *tert*-butyl ester **2.78** (0.92 g, 2.49 mmol) and pyridine (0.60 mL, 7.46 mmol) in DCM (20 mL) was cooled to 0 °C and Tf₂O (0.44 mL, 2.61 mmol) added dropwise. The reaction was stirred at 0 °C for 90 min then quenched with water (30 mL). The aqueous phase was separated then the organic phase was washed with sat. NaHCO₃ (30 mL) and brine (30 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 0.5% MeOH/DCM) afforded **2.79** as a white solid (1.24 g, 2.46 mmol, 99%).

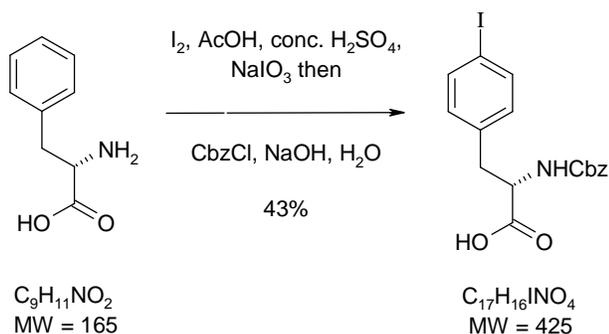
m.p 43–44 °C

FT-IR (v/cm⁻¹) 3334 (w), 2975 (w), 2930 (w), 1716 (s), 1500 (m), 1420 (m), 1369 (w), 1249 (w), 1206 (s), 1135 (s), 1055 (m), 1018 (w), 885 (s), 844 (w).

¹H NMR δ_H (300 MHz, CDCl₃): 7.42 - 7.30 (5 H, m, 5 x ArH), 7.25 (2 H, d, *J*=8.8 Hz, 2 x ArH), 7.17 (2 H, d, *J*=8.8 Hz, 2 x ArH), 5.36 (1 H, br. d, *J*=7.7 Hz, NH), 5.14 (1 H, d, *J*=12.2 Hz, OCHH), 5.08 (1 H, d, *J*=12.3 Hz, OCHH), 4.54 (1 H, app. q, *J*=6.2 Hz, CHNH), 3.11 (2 H, d, *J*=5.9 Hz, CH₂), 1.39 (9 H, s, 3 x CH₃).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 170.0 (C), 155.4 (C), 148.5 (C), 137.0 (C), 136.2 (C), 131.2 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 128.1 (2 x CH), 121.2 (2 x CH), 118.7 (q, $J=322$ Hz, CF_3), 82.8 (C), 67.0 (OCH_2), 55.0 (CHNH), 37.9 (CH_2), 27.8 (3 x CH_3).
LRMS	m/z (ES+) 526 ($[\text{M}+\text{Na}]^+$, 100), 1030 ($[\text{2M}+\text{Na}]^+$, 9).
HRMS	m/z (ES+) Found $[\text{M}+\text{Na}]^+$ 526.1120. Required 526.1118.
$[\alpha]_{\text{D}}$	+ 56.8 (c = 2.4, CHCl_3).

(S)-2-Benzoyloxycarbonylamino-3-(4-iodo-phenyl)-propionic acid **2.82**



To a stirred solution of L-phenylalanine (10.0 g, 60.6 mmol) in AcOH (55 mL) and conc. H_2SO_4 (135 mL) was added I_2 (6.2 g, 24.3 mmol) and $NaIO_3$ (2.5 g, 12.9 mmol). The reaction was heated to 70 °C for 16 h, before additional $NaIO_3$ (0.5 g, 2.5 mmol) was added. The reaction was stirred for a further 8 h at 70 °C then the solvent was removed *in vacuo*. The residue was then diluted with water (100 mL), and the aqueous phase was washed with ether (50 mL) and DCM (50 mL). The aqueous phase was then neutralised with 2M NaOH to precipitate the crude product which was collected by filtration and washed with water (50 mL) and ethanol (50 mL). Recrystallisation from AcOH afforded 4-iodo-L-phenylalanine as a yellow solid. To a stirred solution of 4-iodo-L-phenylalanine (2.3 g, 7.9 mmol) in water (40 mL) and ether (30 mL) was added Na_2CO_3 (2.5 g, 23.7 mmol) and CbzCl (1.1 mL, 7.9 mmol). The reaction was stirred for 18 h then the aqueous phase was separated and adjusted to pH 2 with 2M HCl. The aqueous phase was extracted with ethyl acetate (4 x 50 mL), the organic extracts were combined then washed with brine (50 mL) and dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 2% MeOH/DCM) afforded the product as a pale yellow oil **2.82** (1.4 g, 3.4 mmol, 43%).

FT-IR (v/cm^{-1}) 3311 (m), 3093 (br.), 1715 (m), 1696 (s), 1530 (m), 1481 (w), 1399 (w), 1325 (m), 1259 (m), 1221 (s), 1058 (m), 1005 (w).

1H NMR δ_H (400 MHz, MeOD): 7.53 (2 H, d, $J=8.0$ Hz, 2 x ArH), 7.36 - 7.15 (5 H, m, 5 x ArH), 6.90 (2 H, d, $J=8.0$ Hz, 2 x ArH), 5.06 (1 H, d, $J=11.5$ Hz, CHH), 4.99 (1 H, d, $J=12.0$ Hz, CHH), 4.50

- 4.37 (1 H, obs. m, CHNH), 3.12 (1 H, dd, $J=13.8, 5.3$ Hz, CHH), 2.92 (1 H, dd, $J=14.1, 7.5$ Hz, CHH).

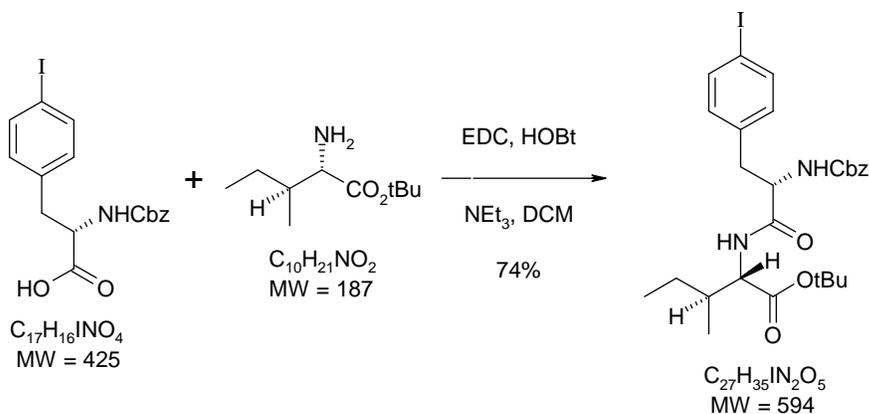
^{13}C NMR δ_{C} (100 MHz, MeOD): 173.9 (C), 157.0 (C), 138.0 (2 x CH), 137.0 (C), 136.9 (C), 131.9 (2 x CH), 129.0 (2 x CH), 128.6 (CH), 128.4 (2 x CH), 92.7 (CI), 67.3 (CH₂), 55.3 (CH), 37.8 (CH₂).

LRMS m/z (ES+) 448 ([M+Na]⁺, 100).

HRMS m/z (ES+) Found [M+Na]⁺ 448.0012. Required 448.0016.

$[\alpha]_{\text{D}}$ + 12.4 (c = 0.5, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-Benzyloxycarbonylamino-3-(4-iodo-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.83**



To a stirred solution of (*S*)-2-benzyloxycarbonylamino-3-(4-iodo-phenyl)-propionic acid **2.82** (6.36 g, 15.0 mmol) in DCM (50 mL) was added L-isoleucine *tert*-butyl ester (2.00 g, 10.7 mmol), EDC (2.63 mL, 15.0 mmol), HOBt (2.02 g, 15.0 mmol) and NEt₃ (4.48 mL, 32.1 mmol). The reaction was stirred at RT for 16 h then quenched with sat. NH₄Cl (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) then the organic extracts were combined, washed with brine (50 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 50% ethyl acetate/petroleum ether) afforded **2.83** as a colourless oil (4.68 g, 7.88 mmol, 74%).

FT-IR (v/cm⁻¹) 3425 (w), 3308 (m), 2967 (m), 2933 (m), 2873 (w), 1729 (m), 1708 (s), 1661 (s), 1538 (m), 1452 (m), 1389 (m), 1257 (m), 1231 (m), 1143 (m), 1058 (m), 1005 (m), 735 (m), 695 (m).

¹H NMR δ_H (400 MHz, CDCl₃): 7.49 (2 H, d, *J*=8.0 Hz, 2 x ArH), 7.34 - 7.16 (5 H, m, 5 x ArH), 6.84 (2 H, d, *J*=8.0 Hz, 2 x ArH), 6.36 (1 H, d, *J*=7.5 Hz, NH), 5.37 (1 H, br. d, *J*=8.5 Hz, NH), 5.02 (2 H, br. s, CH₂), 4.44 - 4.35 (1 H, m, CH), 4.33 (1 H, app. q, *J*=4.5 Hz, CH), 3.03 - 2.83 (2 H, m, CH₂), 1.74 (1 H, m, CH), 1.43 - 1.36 (9 H, m, 3 x CH₃), 1.36 - 1.25 (1 H, m, CHH), 1.12 -

0.95 (1 H, m, CHH), 0.83 (3 H, t, $J=7.5$ Hz, CH₃), 0.76 (3 H, d, $J=7.0$ Hz, CH₃).

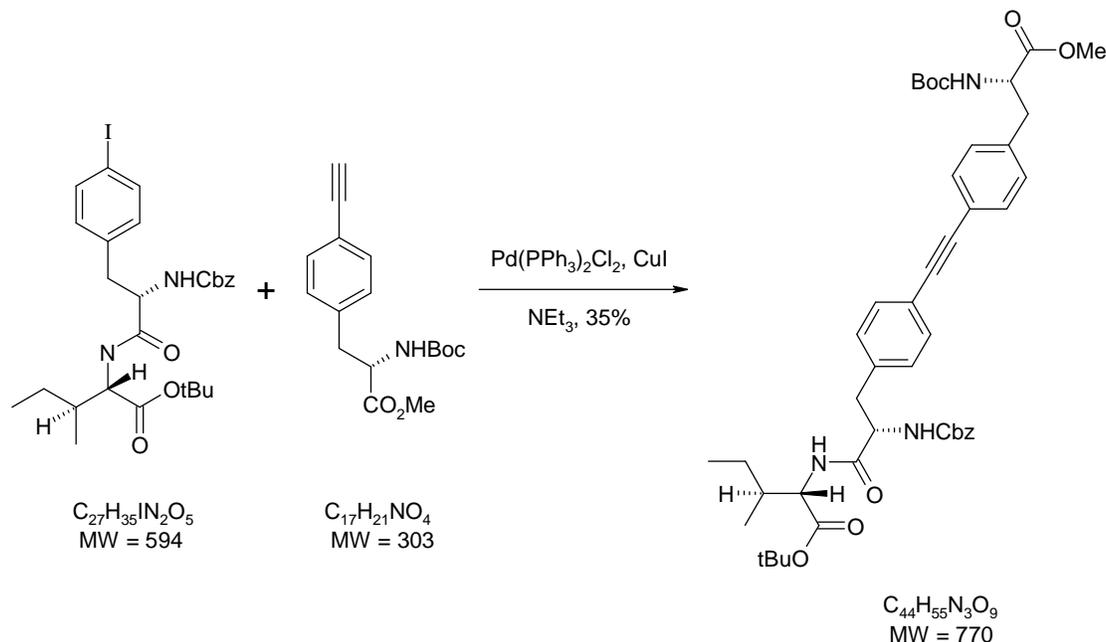
¹³C NMR δ_C (100 MHz, CDCl₃): 170.3 (C), 170.0 (C), 155.8 (C), 137.6 (2 x CH), 136.1 (C), 131.3 (2 x CH), 128.6 (C), 128.5 (2 x CH), 128.4 (CH), 128.3 (2 x CH), 92.4 (CI), 82.1 (C), 67.3 (CH₂), 56.8 (CH), 55.8 (CH), 38.0 (CH), 37.9 (CH₂), 28.0 (3 x CH₃), 25.3 (CH₂), 15.2 (CH₃), 11.7 (CH₃).

LRMS m/z (ES+) 617 ([M+Na]⁺, 100).

HRMS m/z (ES+) Found [M+Na]⁺ 617.1497. Required 617.1483.

[α]_D + 17.2 (c = 1.2, CHCl₃).

(2*S*,3*S*)-2-((*S*)-2-Benzyloxycarbonylamino-3-{4-[4-((*S*)-2-*tert*-butoxycarbonylamino-2-methoxycarbonyl-ethyl)-phenylethynyl]-phenyl}-propionylamino)-3-methyl-pentanoic acid *tert*-butyl ester **2.84**

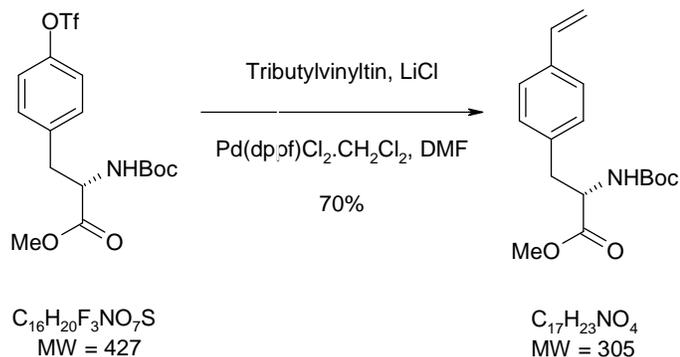


To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-benzyloxycarbonylamino-3-(4-iodo-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.83** (471 mg, 0.79 mmol), (*S*)-2-*tert*-butoxycarbonylamino-3-(4-ethynyl-phenyl)-propionic acid methyl ester **2.76** (200 mg, 0.66 mmol) and CuI (3 mg, 0.01 mmol) in NEt₃ (10 mL) was added Pd(PPh₃)₂Cl₂ (5 mg, 0.007 mmol). The reaction was stirred at RT for 16 h then diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, washed with water (3 x 50 mL) and brine (50 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 20-30% ethyl acetate/petroleum ether) afforded **2.84** as a beige solid (180 mg, 0.23 mmol, 35%).

FT-IR (v/cm⁻¹) 3346 (w), 2978 (m), 1713 (vs), 1516 (m), 1366 (m), 1250 (m), 1217 (m), 1155 (s), 1056 (m), 1020 (m), 751 (s).

¹H NMR	<p>δ_{H} (300 MHz, CDCl₃): 7.45 (2 H, d, $J=8.4$ Hz, 2 x ArH), 7.41 (2 H, d, $J=8.4$ Hz, 2 x ArH), 7.38 - 7.29 (5 H, m, 5 x ArH), 7.17 (2 H, d, $J=8.1$ Hz, 2 x ArH), 7.12 (2 H, d, $J=8.1$ Hz, 2 x ArH), 6.35 (1 H, d, $J=8.1$ Hz, NH), 5.39 (1 H, d, $J=7.7$ Hz, NH), 5.10 (2 H, br. s, OCH₂), 5.02 (1 H, d, $J=7.7$ Hz, NH), 4.60 (1 H, m, CHNH), 4.47 (1 H, br. app. q, $J=7.0$ Hz, CHNH), 4.39 (1 H, m, CHNH), 3.72 (3 H, s, CO₂CH₃), 3.23 - 2.97 (4 H, m, 2 x CHH), 1.88 - 1.76 (1 H, m, CH(CH₃)CH₂CH₃), 1.46 (9 H, s, 3 x CH₃), 1.43 (9 H, s, 3 x CH₃), 1.39 - 1.33 (1 H, m, CHHCH₃), 1.19 - 1.03 (1 H, m, CHHCH₃), 0.91 (3 H, t, $J=7.3$ Hz, CH₂CH₃), 0.83 (3 H, d, $J=7.0$ Hz, CHCH₃).</p>
¹³C NMR	<p>δ_{C} (75 MHz, CDCl₃): 172.1 (C), 170.2 (C), 170.0 (C), 155.8 (C), 155.0 (C), 136.6 (C), 136.3 (C), 136.1 (C), 131.8 (2 x CH), 131.7 (2 x CH), 129.4 (2 x CH), 129.3 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 128.0 (2 x CH), 122.0 (2 x C-C≡C), 89.3 (C≡C), 89.2 (C≡C), 82.2 (C(CH₃)₃), 80.0 (C(CH₃)₃), 67.0 (OCH₂), 56.8 (CHNH), 56.0 (CHNH), 54.3 (CHNH), 52.3 (CO₂CH₃), 38.3 (2 x CH₂CH), 38.1 (CH(CH₃)CH₂CH₃), 28.3 (3 x CH₃), 28.0 (3 x CH₃), 25.3 (CH₂CH₃), 15.2 (CHCH₃), 11.7 (CH₂CH₃).</p>
LRMS	m/z (ES+) 793 ([M+Na] ⁺ , 100).
HRMS	m/z (ES+) Found [M+Na] ⁺ 792.3840. Required 792.3831.
[α]_D	+ 26.8 (c = 1.0, CHCl ₃).

(S)-2-tert-Butoxycarbonylamino-3-(4-vinyl-phenyl)-propionic acid methyl ester 2.86



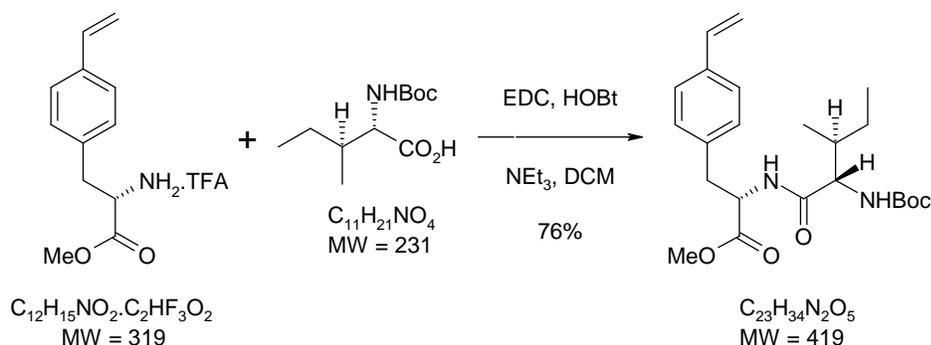
To a stirred solution of (S)-2-tert-butoxycarbonylamino-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid methyl ester **2.74** (674 mg, 1.58 mmol), tributylvinyltin (0.46 mL, 1.58 mmol) and LiCl (201 mg, 4.73 mmol) in DMF (35 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (64 mg, 0.08 mmol). The reaction was heated at 80 °C for 15 h the quenched with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (10% w/w K₂CO₃ in SiO₂, 10% ethyl acetate/petroleum ether) afforded **2.86** as a colourless oil (338 mg, 1.11 mmol, 70%).

FT-IR (v/cm⁻¹) 3353 (w), 3009 (w), 2977 (m), 2926 (w), 1740 (m), 1701 (s), 1509 (m), 1366 (m), 1216 (m), 1163 (s), 1055 (w), 1019 (w), 753 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.34 (2 H, d, *J*=8.0 Hz, 2 x ArH), 7.09 (2 H, d, *J*=8.0 Hz, 2 x ArH), 6.69 (1 H, dd, *J*=17.6, 11.0 Hz, ArCHCH₂), 5.72 (1 H, d, *J*=17.6 Hz, ArCHCHH), 5.22 (1 H, d, *J*=11.5 Hz, ArCHCHH), 4.99 (1 H, br. d, *J*=4.5 Hz, NH), 4.58 (1 H, br. app. d, *J*=5.5 Hz, CHNH), 3.72 (3 H, s, CO₂CH₃), 3.11 (1 H, dd, *J*=13.6, 5.5 Hz, CHH), 3.04 (1 H, m, CHH), 1.42 (9 H, s, 3 x CH₃).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 172.2 (C), 155.0 (C), 136.4 (C and CH), 135.6 (C), 129.4 (2 x CH), 126.3 (2 x CH), 113.6 (C=CH ₂), 79.9 (C), 54.3 (CHNH), 52.2 (CO ₂ CH ₃), 38.0 (CH ₂), 28.3 (3 x CH ₃).
LRMS	m/z (ES+) 328 ([M+Na] ⁺ , 100), 634 ([2M+Na] ⁺ , 87).
HRMS	m/z (ES+) Found [M+Na] ⁺ 328.1521. Required 328.1519.
$[\alpha]_{\text{D}}$	+ 35.5 (c = 0.4, CHCl_3).

(S)-2-((2S,3S)-2-tert-Butoxycarbonylamino-3-methyl-pentanoylamino)-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.87**



To a stirred solution of (S)-2-amino-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.86** (354 mg, 1.11 mmol) in DCM (12 mL) was added Boc-L-isoleucine (358 mg, 1.55 mmol), EDC (0.27 mL, 1.55 mmol), HOBt (210 mg, 1.55 mmol) and NEt₃ (0.31 mL, 2.22 mmol). The reaction was stirred at RT for 16 h then quenched with sat. NH₄Cl (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), the organic extracts were combined then washed with brine (10 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 2% MeOH/DCM) afforded **2.87** as a white foam (351 mg, 0.84 mmol, 76%).

FT-IR (v/cm⁻¹) 3310 (m), 2966 (m), 1745 (m), 1686 (s), 1655 (s), 1522 (m), 1367 (w), 1247 (w), 1213 (w), 1171 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.33 (2 H, d, *J*=8.1 Hz, 2 x ArH), 7.08 (2 H, d, *J*=8.1 Hz, 2 x ArH), 6.68 (1 H, dd, *J*=17.7, 10.8 Hz, ArCH=CH₂), 6.47 (1 H, d, *J*=7.7 Hz, NH), 5.72 (1 H, d, *J*=17.6 Hz, ArCH=CHH), 5.23 (1 H, d, *J*=11.0 Hz, ArCH=CHH), 5.10 (1 H, d, *J*=8.4 Hz, NH), 4.88 (1 H, app. q, *J*=6.2 Hz, CHNH), 3.95 (1 H, app. t, *J*=7.5 Hz, CHNH), 3.73 (3 H, s, CO₂CH₃), 3.16 (1 H, dd, *J*=14.3, 6.2 Hz, CHH), 3.08 (1 H, dd, *J*=13.9, 6.6 Hz, CHH), 1.89 - 1.76 (1 H, m, CH(CH₃)CH₂CH₃), 1.44 (9 H, s, 3 x CH₃), 1.42 - 1.35 (1 H, m, CHHCH₃), 1.15 - 1.02 (1 H, m,

CHHCH₃), 0.96 (3 H, t, $J=7.0$ Hz, CH₂CH₃), 0.89 (3 H, d, $J=6.6$ Hz, CHCH₃).

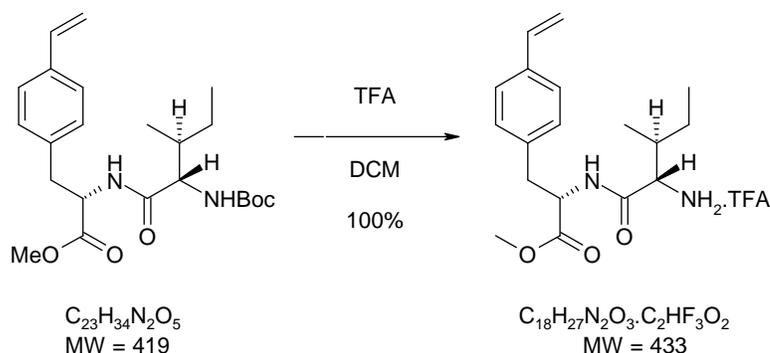
¹³C NMR δ_C (75 MHz, CDCl₃): 172.0 (C), 171.4 (C), 155.9 (C), 136.5 (C), 136.3 (CH=CH₂), 135.1 (C), 129.4 (2 x CH), 126.4 (2 x CH), 113.7 (CH=CH₂), 80.3 (C), 59.3 (CHNH), 53.2 (CHNH), 52.4 (OCH₃), 37.6 (CH₂), 36.9 (CH), 28.2 (3 x CH₃), 24.6 (CH₂), 15.4 (CH₃), 11.2 (CH₃).

LRMS m/z (ES+) 441 ([M+Na]⁺, 100), 860 ([2M+Na]⁺, 15).

HRMS m/z (ES+) Found [M+Na]⁺ 441.2357. Required 441.2360.

[α]_D + 27.2 (c = 0.8, CHCl₃).

(S)-2-((2S,3S)-2,3-Dimethyl-pentanoylamino)-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.88**



To a stirred solution of (S)-2-((2S,3S)-2-*tert*-butoxycarbonylamino-3-methyl-pentanoylamino)-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.87** (325 mg, 0.78 mmol) in DCM (4 mL) was added TFA (1 mL). The reaction was stirred at RT for 4 h then concentrated *in vacuo* to afford **2.88** as a white foam (336 mg, 0.78 mmol, 100%).

FT-IR (ν/cm^{-1}) 3351 (m), 2963 (m), 2910 (m), 1738 (s), 1615 (s), 1525 (m), 1439 (w), 1347 (w), 1205 (w), 1219 (w), 1177 (s), 751 (w).

^1H NMR δ_{H} (400 MHz, MeOD): 7.35 (2 H, d, $J=8.0$ Hz, 2 x ArH), 7.19 (2 H, d, $J=8.0$ Hz, 2 x ArH), 6.69 (1 H, dd, $J=17.6, 11.0$ Hz, CH=CH₂), 5.72 (1 H, d, $J=18.1$ Hz, CH=CHH), 5.18 (1 H, d, $J=10.5$ Hz, CHCHH), 4.73 (1 H, dd, $J=8.5, 6.0$ Hz, CHNH), 3.75 (1 H, d, $J=5.0$ Hz, CHNH₂), 3.68 (3 H, s, OCH₃), 3.23 - 3.13 (1 H, m, CHH), 3.11 - 2.98 (1 H, m, CHH), 1.61 - 1.49 (1 H, m, CH), 1.44 - 1.32 (1 H, m, CHHCH₃), 1.24 - 1.13 (1 H, m, CHHCH₃), 1.05 - 1.00 (3 H, s, CH₃), 0.95 (3 H, t, $J=7.3$ Hz, CH₃).

^{13}C NMR δ_{C} (75 MHz, CDCl₃): 172.9 (C), 169.8 (C), 139.5 (C), 138.8 (C), 137.8 (CH=CH₂), 130.4 (2 x CH), 127.4 (2 x CH), 113.9

(CH=CH₂), 58.9 (CHNH), 55.5 (CHNH), 52.8 (OCH₃), 38.1 (CH₂), 37.2 (CH), 25.6 (CH₂), 15.1 (CH₃), 11.8 (CH₃).

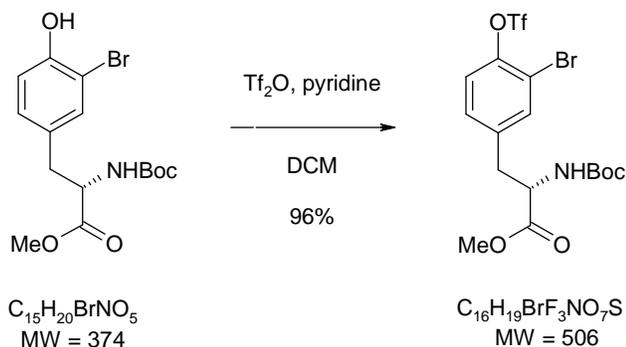
LRMS

^{m/z} (ES+) 319 ([M+Na]⁺, 100), 433 ([M+TFA]⁺, 41).

[α]_D

+ 18.6 (c = 0.2, CHCl₃).

(S)-3-(3-Bromo-4-trifluoromethanesulfonyloxy-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.89**



A stirred solution of (S)-3-(3-bromo-4-hydroxy-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.36** (2.49 g, 6.67 mmol) and pyridine (1.62 mL, 20.00 mmol) in DCM (40 mL) was cooled to 0 °C and Tf₂O (1.22 mL, 7.00 mmol) added dropwise. The reaction was stirred at 0 °C for 3 h then quenched with water (50 mL). The aqueous phase was separated and the organic phase washed with sat. NaHCO₃ (50 mL) and brine (50 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 1% MeOH/DCM) afforded **2.89** as a pale yellow solid (3.23 mg, 6.38 mmol, 96%).

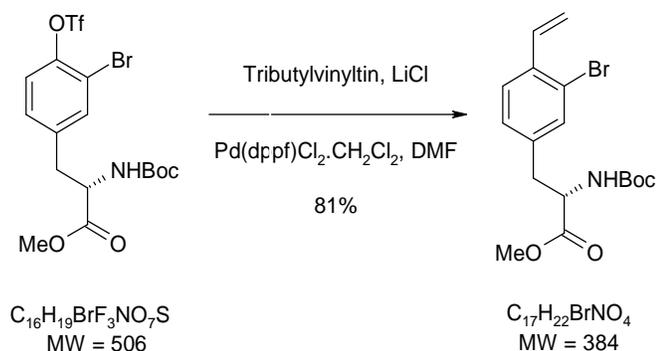
m.p 61–63 °C

FT-IR (v/cm⁻¹) 3361 (w), 2975 (w), 1743 (m), 1712 (m), 1502 (w), 1482 (w), 1425 (m), 1366 (m), 1208 (s), 1166 (s), 1136 (s), 1041 (w), 884 (m), 757 (w), 617 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.48 (1 H, d, *J*=1.5 Hz, ArH), 7.28 (1 H, m, *J*=7.3 Hz, ArH), 7.18 (1 H, dd, *J*=8.8, 2.2 Hz, ArH), 5.07 (1 H, d, *J*=7.3 Hz, NH), 4.59 (1 H, app. q, *J*=6.6 Hz, CHNH), 3.74 (3 H, s, CO₂CH₃), 3.18 (1 H, dd, *J*=13.5, 5.9 Hz, CHH), 3.01 (1 H, dd, *J*=13.9, 6.6 Hz, CHH), 1.43 (9 H, s, 3 x CH₃).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 171.6 (C), 146.0 (C), 138.5 (C), 135.1 (CH), 129.9 (CH), 122.7 (CH), 120.7 (C), 118.6 (q, $J=321$ Hz, CF_3), 115.8 (CBr), 80.4 (C), 54.1 (CH), 52.5 (CH_3), 37.6 (CH_2), 28.2 (3 x CH_3).
LRMS	m/z (ES+) 528 ($[\text{M} (^{79}\text{Br})+\text{Na}]^+$, 94), 530 ($[\text{M} (^{81}\text{Br})+\text{Na}]^+$, 100).
HRMS	m/z (ES+) Found $[\text{M} (^{79}\text{Br})+\text{Na}]^+$ 527.9917. Required 527.9910.
$[\alpha]_{\text{D}}$	+ 49.5 (c = 0.8, CHCl_3).

(S)-3-(3-Bromo-4-vinyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.90**



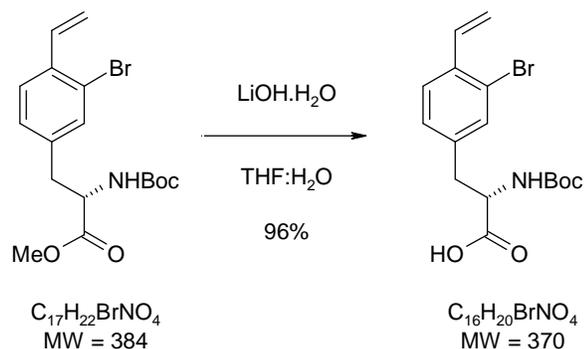
To a stirred solution of (S)-3-(3-bromo-4-trifluoromethanesulfonyloxy-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.89** (2.25 g, 4.45 mmol), tributylvinyltin (1.30 mL, 4.45 mmol) and LiCl (0.94 g, 22.24 mmol) in DMF (45 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (0.18 g, 0.22 mmol). The reaction was stirred at RT for 16 h then quenched with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL), the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (10% w/w K₂CO₃ in SiO₂, 10% ethyl acetate/petroleum ether) afforded **2.90** as a colourless oil (1.39 g, 3.62 mmol, 81%).

FT-IR (v/cm⁻¹) 3353 (w), 2971 (w), 1742 (s), 1712 (s), 1501 (m), 1485 (m), 1426 (m), 1366 (m), 1249 (m), 1212 (s), 1162 (s), 1139 (s), 1056 (m), 1043 (m), 1018 (m), 888 (m), 756 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.48 (1 H, d, *J*=8.1 Hz, ArH), 7.33 (1 H, s, ArH), 7.06 (1 H, d, *J*=7.3 Hz, ArH), 7.01 (1 H, dd, *J*=17.6, 11.0 Hz, ArCH=CH₂), 5.68 (1 H, d, *J*=17.6 Hz, ArCH=CHH), 5.34 (1 H, d, *J*=11.0 Hz, ArCH=CHH), 5.03 (1 H, d, *J*=7.3 Hz, NH), 4.57 (1 H, app. q, *J*=7.0 Hz, CHNH), 3.74 (3 H, s, CO₂CH₃), 3.11 (1 H, dd, *J*=13.5, 5.5 Hz, CHH), 2.99 (1 H, dd, *J*=13.5, 5.9 Hz, CHH), 1.43 (9 H, s, 3 x CH₃).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 171.9 (C), 154.9 (C), 137.4 (C), 136.1 (C), 135.3 (CH), 133.6 (CH), 128.4 (CH), 126.7 (CH), 123.5 (C), 116.5 (CH_2), 80.1 (C), 54.2 (CH), 52.3 (CH_3), 37.6 (CH_2), 28.2 (3 x CH_3).
LRMS	m/z (ES+) 406 ($[\text{M} (^{79}\text{Br})+\text{Na}]^+$, 96), 408 ($[\text{M} (^{81}\text{Br})+\text{Na}]^+$, 100).
HRMS	m/z (ES+) Found $[\text{M} (^{79}\text{Br})+\text{Na}]^+$ 406.0627. Required 406.0624.
$[\alpha]_{\text{D}}$	+ 36.8 (c = 1.0, CHCl_3).

(S)-3-(3-Bromo-4-vinyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid **2.91**



To a stirred solution of 2(*S*)-3-(3-bromo-4-vinyl-phenyl)-2-*tert*-butoxycarbonylamino-propionic acid methyl ester **2.90** (95 mg, 0.25 mmol) in THF:H₂O (5 mL:5 mL) was added LiOH.H₂O (26 mg, 0.62 mmol). The reaction was stirred at RT for 16 h then quenched with sat. NH₄Cl (10 mL). The aqueous phase was extracted with ethyl acetate (4 x 10 mL) and the organic extracts combined, then dried (MgSO₄). Concentration *in vacuo* afforded **2.91** as a yellow foam (89 mg, 0.24 mmol, 96%).

FT-IR (v/cm⁻¹) 3421 (w), 3342 (w), 2978 (w), 2933 (w), 1964 (s), 1506 (m), 1394 (m), 1368 (m), 1249 (m), 1216 (m), 1162 (s), 1047 (w), 1027 (w), 755 (m).

¹H NMR δ_H (300 MHz, MeOD): 7.53 (1 H, d, *J*=8.1 Hz, ArH), 7.45 (1 H, s, ArH), 7.20 (1 H, d, *J*=8.1 Hz, ArH), 7.00 (1 H, dd, *J*=17.6, 11.0 Hz, CH=CH₂), 5.71 (1 H, d, *J*=17.6 Hz, CH=CHH), 5.31 (1 H, d, *J*=11.0 Hz, CH=CHH), 4.34 (1 H, dd, *J*=9.1, 4.8 Hz, CHNH), 3.15 (1 H, dd, *J*=13.9, 4.8 Hz, CHH), 2.86 (1 H, dd, *J*=13.7, 9.3 Hz, CHH), 1.38 (9 H, s, 3 x CH₃).

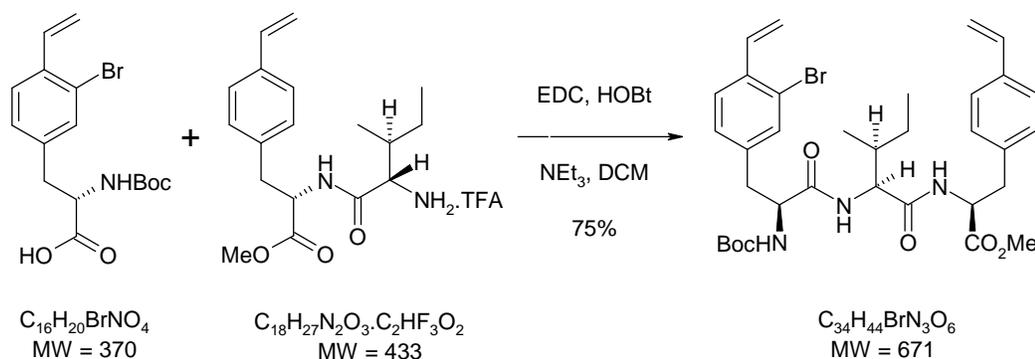
¹³C NMR δ_C (75 MHz, MeOD): 175.0 (C), 157.8 (C), 140.6 (C), 137.0 (C), 136.6 (CH), 134.8 (CH), 129.9 (CH), 127.7 (CH), 124.2 (C), 116.9 (CH₂), 80.7 (C), 56.0 (CH), 38.1 (CH₂), 28.8 (3 x CH₃).

LRMS m/z (ES+) 392 ([M (^{79}Br)+Na] $^+$, 57), 394 ([M (^{81}Br)+Na] $^+$, 58), 761 ([2M (^{79}Br , ^{79}Br)+Na] $^+$, 47), 763 ([2M (^{79}Br , ^{81}Br)+Na] $^+$, 100), 765 ([M (^{81}Br , ^{81}Br)+Na] $^+$, 45).

HRMS m/z (ES+) Found [M+Na] $^+$ 392.0463. Required 392.0468.

$[\alpha]_D$ + 11.8 (c = 1.0, MeOH).

(S)-2-[2-[(S)-3-(3-Bromo-4-vinyl-phenyl)-2-*tert*-butoxycarbonylamino]-acetylamino]-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.92**



To a stirred solution of (*S*)-3-(3-bromo-4-vinyl-phenyl)-2-*tert*-butoxycarbonylamino-propionic acid **2.91** (89 mg, 0.24 mmol) in DCM (5 mL) was added (*S*)-2-((2*S*,3*S*)-2,3-dimethyl-pentanoylamino)-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.88** (92 mg, 0.29 mmol), EDC (0.05 mL, 0.29 mmol), HOBT (39 mg, 0.29 mmol) and NEt₃ (0.13 mL, 0.96 mmol). The reaction was stirred at RT for 14 h then quenched with sat. NH₄Cl (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic extracts combined, washed with brine (10 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 1% MeOH/DCM) afforded **2.92** as a white foam (331 mg, 0.79 mmol, 75%).

FT-IR (v/cm⁻¹) 3274 (w), 3016 (m), 2970 (m), 1739 (s), 1643 (m), 1521 (w), 1440 (w), 1366 (s), 1228 (s), 1217 (s), 1168 (w), 909 (w), 753 (s).

¹H NMR δ_H (400 MHz, CDCl₃): 7.46 (1 H, d, *J*=8.0 Hz, ArH), 7.40 (1 H, d, *J*=2.0 Hz, ArH), 7.34 (2 H, d, *J*=8.0 Hz, 2 x ArH), 7.09 - 7.15 (2 H, m, ArH and NH), 7.07 (2 H, d, *J*=8.0 Hz, 2 x ArH), 7.00 (1 H, dd, *J*=17.6, 11.0 Hz, CH=CHH), 6.67 (1 H, dd, *J*=17.6, 11.0 Hz, CH=CHH), 6.34 (1H, d, *J*=7.5 Hz, NH), 5.72 (1 H, d, *J*=17.6 Hz, CH=CHH), 5.66 (1 H, d, *J*=17.6 Hz, CH=CHH), 5.33 (1 H, d, *J*=11.5 Hz, CH=CHH), 5.22 (1 H, d,

$J=11.0$ Hz, CH=CHH), 5.01 (1 H, br. d, $J=8.0$ Hz, NH), 4.84 (1 H, app. q, $J=6.5$ Hz, CHNH), 4.33 (1 H, m, CHNH), 4.26 (1 H, app. dd, $J=8.0, 6.5$ Hz, CHNH), 3.72 (3 H, s, CH₃), 3.19 - 2.94 (4 H, m, 2 x CHH), 1.90 - 1.74 (1 H, m, CH), 1.41 (9 H, s, 3 x CH₃), 1.38 - 1.31 (1 H, m, CHH), 1.15 - 0.96 (1 H, m, CHH), 0.71 - 0.95 (6 H, m, 2 x CH₃).

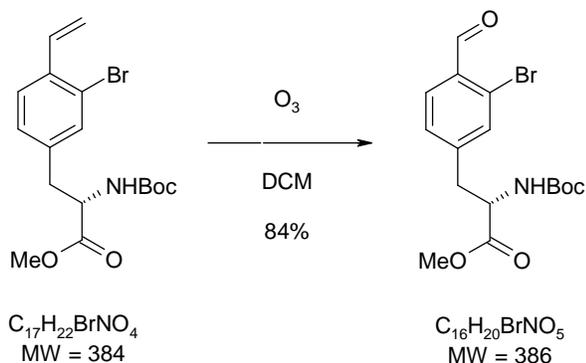
¹³C NMR δ_C (100 MHz, CDCl₃): 171.6 (C), 170.8 (C), 170.3 (C), 155.4 (C), 138.1 (C), 136.5 (C), 136.3 (CH=CH₂), 136.0 (C), 135.3 (CH=CH₂), 135.2 (C), 133.6 (CH), 129.4 (2 x CH), 128.5 (CH), 126.8 (CH), 126.5 (2 x CH), 123.6 (CBr), 116.5 (CH=CH₂), 113.8 (CH=CH₂), 80.5 (C), 57.8 (CH), 55.4 (CH), 53.1 (CH₃), 52.3 (CH), 37.7 (CH₂), 37.6 (CH₂), 37.3 (CH), 28.2 (3 x CH₃), 24.7 (CH₂), 15.2 (CH₃), 11.3 (CH₃).

LRMS m/z (ES+) 692 ([M (⁷⁹Br)+Na]⁺, 89), 694 ([M (⁸¹Br)+Na]⁺, 100).

HRMS m/z (ES+) Found [M+Na]⁺ 692.2321. Required 692.2306.

[α]_D + 37.5 (c = 2.0, CHCl₃).

(S)-3-(3-Bromo-4-formyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.93**



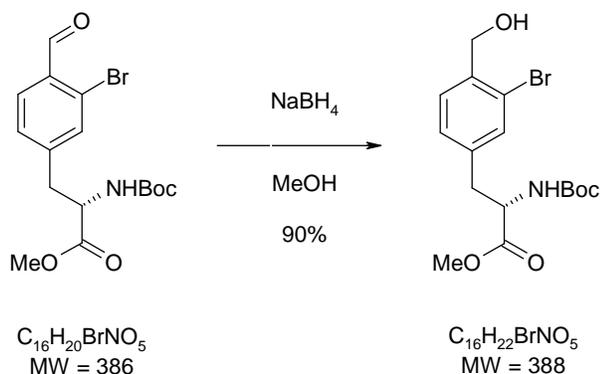
A stirred solution of (S)-3-(3-bromo-4-vinyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.90** (3.06 g, 7.98 mmol) and sudan red (10 mg) in DCM (100 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and O_3 (1–4% in O_2) bubbled through until the red colour disappeared. O_2 was then bubbled through for 20 min before PPh_3 (4.19 g, 15.96 mmol) was added. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min then allowed to warm to RT. Concentration *in vacuo* and purification by column chromatography (SiO_2 , 20% ethyl acetate/petroleum ether) afforded **2.93** as a pale orange foam (2.60 g, 6.74 mmol, 84%).

FT-IR (v/cm^{-1}) 3367 (w), 2977 (w), 1742 (s), 1694 (s), 1598 (w), 1507 (m), 1366 (m), 1250 (m), 1216 (m), 1163 (m), 1041 (m), 756 (w).

^1H NMR δ_{H} (300 MHz, CDCl_3): 10.31 (1 H, s, ArCHO), 7.84 (1 H, d, $J=8.1$ Hz, ArH), 7.44 (1 H, s, ArH), 7.21 (1 H, d, $J=8.1$ Hz, ArH), 5.09 (1 H, d, $J=7.3$ Hz, NH), 4.60 (1 H, app. q, $J=5.9$ Hz, CHNH), 3.74 (3 H, s, CO_2CH_3), 3.21 (1 H, dd, $J=13.5, 5.5$ Hz, CHH), 3.05 (1 H, dd, $J=13.5, 6.2$ Hz, CHH), 1.42 (9 H, s, 3 x CH_3).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 191.4 (CHO), 171.5 (C), 154.8 (C), 144.9 (C), 134.6 (CH), 132.3 (C), 129.8 (CH), 128.9 (CH), 127.0 (C), 80.3 (C), 54.0 (CH), 52.5 (CH_3), 38.1 (CH_2), 28.2 (3 x CH_3).
LRMS	m/z (ES+) 408 ($[\text{M}(^{79}\text{Br})+\text{Na}]^+$, 60), 410 ($[\text{M}(^{81}\text{Br})+\text{Na}]^+$, 60).
HRMS	m/z (ES+) Found $[\text{M}(^{79}\text{Br})+\text{Na}]^+$ 408.0417. Required 408.0417.
$[\alpha]_{\text{D}}$	+ 30.8 (c = 0.2, CHCl_3).

(S)-3-(3-Bromo-4-hydroxymethyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.94**



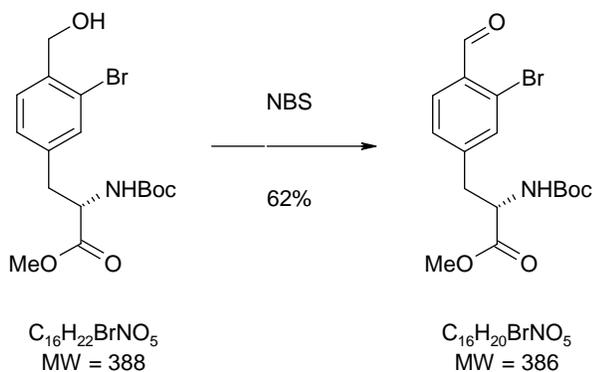
To a stirred solution of (S)-3-(3-bromo-4-formyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.93** (378 mg, 0.98 mmol) in MeOH (18 mL) at 0 °C was added NaBH₄ (44 mg, 1.18 mmol). The reaction was stirred at 0 °C for 3 h then quenched with water (20 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL), the organic extracts were combined, washed with brine (20 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 40% ethyl acetate/petroleum ether) afforded **2.94** as a yellow oil (342 mg, 0.88 mmol, 90%).

FT-IR (v/cm⁻¹) 3367 (br), 2977 (m), 1740 (s), 1693 (s), 1507 (m), 1438 (m), 1366 (m), 1217 (m), 1165 (s), 1062 (m), 1032 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.40 (1 H, d, *J*=7.7 Hz, ArH), 7.32 (1 H, s, ArH), 7.09 (1 H, dd, *J*=7.7, 1.1 Hz, ArH), 5.04 (1 H, d, *J*=7.3 Hz, NH), 4.70 (2 H, s, ArCH₂OH), 4.55 (1 H, app. q, *J*=6.2 Hz, CHNH), 3.73 (3 H, s, CO₂CH₃), 3.11 (1 H, dd, *J*=13.9, 5.9 Hz, CHH), 3.00 (1 H, dd, *J*=13.5, 5.9 Hz, CHH), 2.29 (1 H, br. s, OH), 1.42 (9 H, s, 3 x CH₃).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 171.9 (C), 155.0 (C), 138.5 (C), 137.4 (C), 133.3 (CH), 128.8 (CH), 128.5 (CH), 122.4 (C), 80.1 (C), 64.6 (CH_2), 54.2 (CH), 52.3 (CH_3), 37.5 (CH_2), 28.2 (3 x CH_3).
LRMS	m/z (ES+) 410 ($[\text{M} (^{79}\text{Br})+\text{Na}]^+$, 100), 412 ($[\text{M} (^{81}\text{Br})+\text{Na}]^+$, 92).
HRMS	m/z (ES+) Found $[\text{M} (^{79}\text{Br})+\text{Na}]^+$ 410.0567. Required 410.0571.
$[\alpha]_{\text{D}}$	+ 11.8 (c = 0.8, CHCl_3).

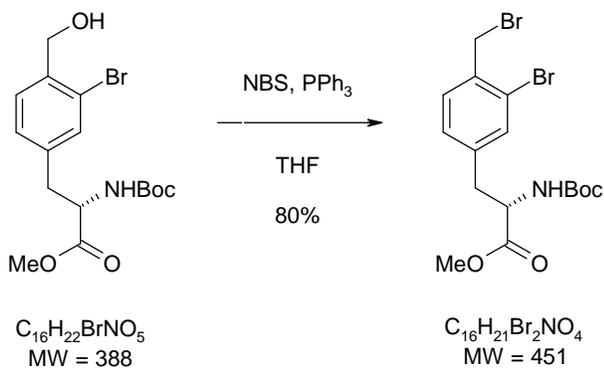
(S)-3-(3-Bromo-4-formyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.93**



To a stirred solution of (S)-3-(3-bromo-4-hydroxymethyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.94** (250 mg, 0.64 mmol) in THF (20 mL) was added NBS (114 mg, 0.64 mmol). The reaction was stirred at RT for 8 h then SiO₂ added and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 40% ethyl acetate/petroleum ether) afforded **2.93** as yellow foam (153 mg, 0.40 mmol, 62%).

The data matches that previously reported.

(S)-3-(3-Bromo-4-hydroxymethyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.95**



To a stirred solution of (S)-3-(3-bromo-4-hydroxymethyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.94** (303 mg, 0.78 mmol) in THF (15 mL) was added NBS (417 mg, 2.34 mmol) and PPh₃ (615 mg, 2.34 mmol). The reaction was stirred at RT for 3 h then SiO₂ added and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.95** as white solid (281 mg, 0.62 mmol, 80%).

m.p 98–100 °C

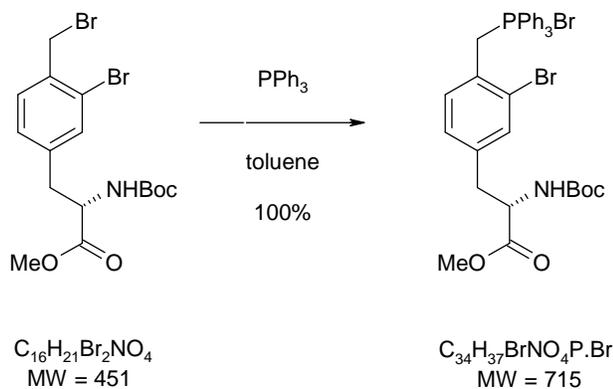
FT-IR (v/cm⁻¹) 3353 (w), 2979 (w), 2949 (w), 1741 (m), 1699 (s), 1507 (m), 1436 (w), 1365 (m), 1215 (m), 1160 (s), 1043 (m), 618 (m).

¹H NMR δ_H (400 MHz, CDCl₃): 7.39 (1 H, d, *J*=8.0 Hz, ArH), 7.37 (1 H, s, ArH), 7.08 (1 H, d, *J*=7.5 Hz, ArH), 5.03 (1 H, d, *J*=7.0 Hz, NH), 4.58 (3 H, br. s, ArCH₂Br and CHNH), 3.74 (3 H, s, CO₂CH₃), 3.13 (1 H, dd, *J*=13.6, 5.5 Hz, CHHCH), 2.99 (1 H, dd, *J*=13.6, 6.0 Hz, CHHCH), 1.43 (9 H, s, 3 x CH₃).

¹³C NMR δ_C (100 MHz, CDCl₃): 171.8 (C), 154.9 (C), 138.8 (C), 135.6 (C), 134.1 (CH), 131.2 (CH), 128.9 (CH), 124.4 (C), 80.2 (C), 54.2 (CH), 52.4 (CH₃), 37.7 (CH₂), 33.0 (CH₂), 28.3 (3 x CH₃).

LRMS	m/z (ES+) 472 ([M (^{79}Br , ^{79}Br)+Na] $^+$, 53), 474 ([M (^{79}Br , ^{81}Br)+Na] $^+$, 100), 476 ([M (^{81}Br , ^{81}Br)+Na] $^+$, 57).
HRMS	m/z (ES+) Found [M (^{79}Br , ^{79}Br)+Na] $^+$ 471.9734. Required 471.9730.
$[\alpha]_D$	- 66.0 (c = 0.2, CHCl ₃).

(S)-3-{3-Bromo-4-[(triphenyl-lambda⁵-phosphanyl)-methyl]-phenyl}-2-tert-butoxycarbonylamino-propionic acid methyl ester bromide **2.96**



A stirred solution of (S)-3-(3-bromo-4-bromomethyl-phenyl)-2-tert-butoxycarbonylamino-propionic acid methyl ester **2.95** (284 mg, 0.63 mmol) and PPh₃ (181 mg, 0.69 mmol) in toluene (8 mL) was heated at 90 °C for 16 h. The reaction was cooled to RT and the resultant precipitate collected by filtration and washed with petroleum ether to afford **2.96** as white solid (448 mg, 0.63 mmol, 100%).

m.p >250 °C

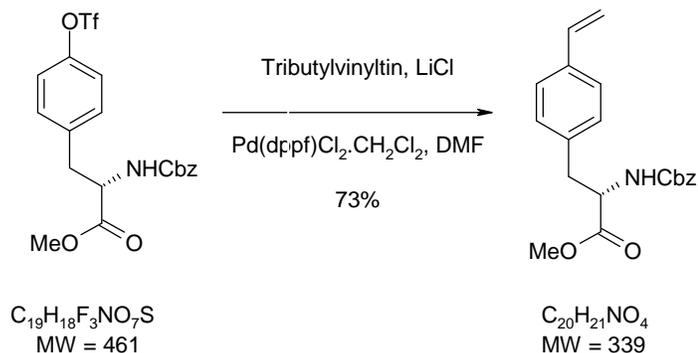
FT-IR (v/cm⁻¹) 2971 (w), 2843 (w), 1741 (m), 1699 (s), 1520 (w), 1489 (w), 1437 (m), 1365 (w), 1251 (w), 1162 (s), 1110 (m), 922 (s), 722 (s), 689 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.83 - 7.74 (3 H, m, 3 x ArH), 7.71 - 7.60 (9 H, m, 12 x ArH), 7.49 (1 H, dd, *J*=8.1, 2.6 Hz, ArH), 7.22 (1 H, d, *J*=7.3 Hz, ArH), 7.18 - 7.12 (3 H, m, 3 x ArH), 6.93 (1 H, d, *J*=8.1 Hz, ArH), 5.70 (1 H, t, *J*=14.6 Hz, ArCHHP), 5.51 (1 H, dd, *J*=15.4, 14.3 Hz, ArCHHP), 5.02 (1 H, d, *J*=8.1 Hz, NH), 4.47 (1 H, dd, *J*=12.4, 6.2 Hz, CHNH), 3.67 (3 H, s, CO₂CH₃), 3.04 (1 H, dd, *J*=13.5, 5.1 Hz, CHH), 2.91 (1 H, dd, *J*=13.5, 6.2 Hz, CHH), 1.38 (9 H, s, 3 x CH₃).

NMR contaminated with traces of PPh₃.

¹³C NMR	δ_C (75 MHz, CDCl ₃): 171.6 (C), 154.9 (C), 139.2 (C), 135.2 (3 x CH), 134.4 (d, $J=10$ Hz, 6 x CH), 133.6 (CH), 133.1 (CH), 130.3 (d, $J=12$ Hz, 6 x CH), 128.2 (CH), 127.2 (CBr), 125.3 (C), 117.4 (d, $J=86$ Hz, 3 x C), 80.1 (C), 54.5 (CH), 52.4 (CH ₃), 37.7 (CH ₂), 30.7 (d, $J=50$ Hz, CH ₂), 28.3 (3 x CH ₃).
LRMS	m/z (ES+) 632 ([M (⁷⁹ Br)+Na] ⁺ , 100), 634 ([M (⁸¹ Br)+Na] ⁺ , 91).
HRMS	m/z (ES+) Found [M (⁷⁹ Br)+Na] ⁺ 632.1555. Required 632.1560.
[α]_D	+ 4.2 (c = 3.1, CHCl ₃).

(S)-2-Benzyloxycarbonylamino-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.98**



Prepared following the procedure of Yokomatsu *et al.*⁸²

To a stirred solution of (S)-2-benzyloxycarbonylamino-3-(4-trifluoromethanesulfonyloxy-phenyl)-propionic acid methyl ester **2.97** (1.84 g, 3.98 mmol), tributylvinyltin (1.28 mL, 4.38 mmol) and LiCl (0.84 g, 19.90 mmol) in DMF (80 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (162 mg, 0.20 mmol). The reaction was stirred at RT for 16 h then quenched with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the organic extracts were combined then washed with water (5 x 50 mL) and brine (50 mL) and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (10% w/w K₂CO₃ in SiO₂, 10% ethyl acetate/petroleum ether) afforded **2.98** as a colourless oil (0.99 g, 2.91 mmol, 73%).

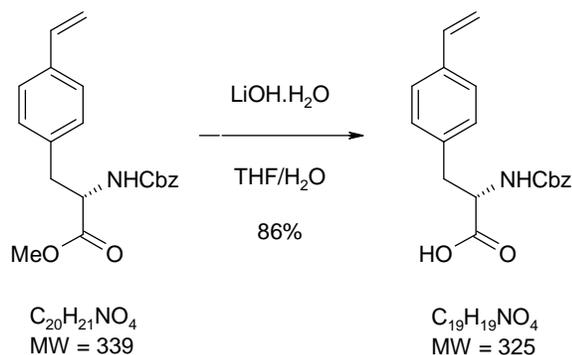
FT-IR (v/cm⁻¹) 3338 (m), 3036 (w), 2952 (m), 1718 (vs), 1511 (s), 1437 (w), 1349 (w), 1252 (m), 1211 (s), 1056 (m), 1027 (w), 909 (w), 739 (w), 697 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.42 - 7.28 (7 H, m, 7 x ArH), 7.06 (2 H, d, *J*=8.4 Hz, 2 x ArH), 6.69 (1 H, dd, *J*=17.6, 11.0 Hz, ArCH=CH₂), 5.73 (1 H, d, *J*=17.6 Hz, ArCH=CHH), 5.24 (2 H, d, *J*=11.0 Hz, ArCH=CHH and NH), 5.11 (2 H, br. s, OCH₂), 4.67 (1 H, app. q, *J*=5.9 Hz, CHNH), 3.73 (3 H, s, CO₂CH₃), 3.15 (1 H, dd, *J*=13.9, 5.9 Hz, CHH), 3.07 (1 H, dd, *J*=13.9, 6.2 Hz, CHH).

^{13}C NMR	δ_{C} (75 MHz, CDCl_3): 171.9 (C), 155.6 (C), 136.4 (C), 136.3 (CH=CH ₂), 136.2 (C), 135.2 (C), 129.4 (2 x CH), 128.5 (2 x CH), 128.1 (CH), 128.0 (2 x CH), 126.4 (2 x CH), 113.7 (CH=CH ₂), 66.9 (OCH ₂), 54.7 (CH), 52.3 (CH ₃), 37.9 (CH ₂).
LRMS	m/z (ES+) 362 ([M+Na] ⁺ , 100), 701 ([2M+Na] ⁺ , 27).
HRMS	m/z (ES+) Found [M+Na] ⁺ 362.1368. Required 362.1363.
$[\alpha]_{\text{D}}$	+ 20.8 (c = 0.8, CHCl_3).

The data are consistent with the literature.⁸²

(S)-2-Benzyloxycarbonylamino-3-(4-vinyl-phenyl)-propionic acid **2.99**



A stirred solution of (S)-2-benzyloxycarbonylamino-3-(4-vinyl-phenyl)-propionic acid methyl ester **2.98** (419 mg, 1.24 mmol) and LiOH.H₂O (130 mg, 3.09 mmol) in THF (23 mL) and water (23 mL) was stirred at RT for 16 h. The reaction was quenched with sat. NH₄Cl (50 mL) and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL) then dried (MgSO₄). Concentration *in vacuo* afforded **2.99** as a colourless oil (360 mg, 1.07 mmol, 86%).

FT-IR (v/cm⁻¹) 3414 (w), 3319 (w), 3085 (br), 3033 (w), 2955 (w), 1717 (vs), 1512 (s), 1408 (w), 1346 (w), 1215 (m), 1058 (m), 909 (w), 839 (w), 739 (w), 697 (m).

¹H NMR δ_{H} (300 MHz, MeOD): 7.39 - 7.24 (7 H, m, 7 x ArH), 7.18 (2 H, d, *J*=8.4 Hz, 2 x ArH), 6.70 (1 H, dd, *J*=17.6, 11.0 Hz, ArCH=CH₂), 5.73 (1 H, d, *J*=17.6 Hz, ArCH=CHH), 5.19 (1 H, d, *J*=11.0 Hz, ArCH=CHH), 5.06 (1 H, d, *J*=12.4 Hz, OCHHAr), 4.99 (1 H, d, *J*=12.4 Hz, OCHHAr), 4.43 (1 H, app. q, *J*=4.9 Hz, CHNH), 3.19 (1 H, dd, *J*=13.9, 5.1 Hz, ArCHHCH), 2.91 (1 H, dd, *J*=13.9, 9.5 Hz, ArCHHCH).

¹³C NMR δ_{C} (75 MHz, MeOD): 175.2 (C), 158.5 (C), 138.4 (2 x C), 138.1 (CH), 137.7 (C), 130.6 (2 x CH), 129.6 (2 x CH), 129.0 (CH),

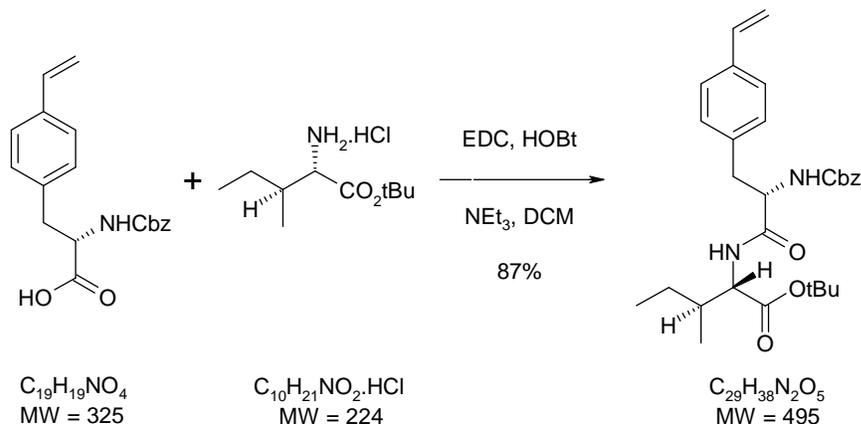
128.8 (2 x CH), 127.4 (2 x CH), 113.9 (CH₂), 67.6 (CH₂), 56.8 (CH), 38.5 (CH₂).

LRMS m/z (ES+) 348 ([M+Na]⁺, 100), 674 ([2M+Na]⁺, 11).

HRMS m/z (ES+) Found [M+Na]⁺ 348.1209. Required 348.1206.

[α]_D + 12.1 (c = 0.8, MeOH).

(2*S*,3*S*)-2-[(*S*)-2-Benzyloxycarbonylamino-3-(4-vinyl-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.100**



To a stirred solution of (*S*)-2-benzyloxycarbonylamino-3-(4-vinyl-phenyl)-propionic acid **2.99** (360 mg, 1.07 mmol) in DCM (10 mL) was added L-isoleucine *tert*-butyl ester (220 mg, 1.18 mmol), EDC (0.21 mL, 1.18 mmol), HOBt (159 mg, 1.18 mmol) and NEt₃ (0.45 mL, 3.20 mmol). The reaction was stirred at RT for 12 h then quenched with sat. NH₄Cl (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), the organic extracts were combined and washed with brine (10 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 1% MeOH/DCM) afforded **2.100** as a white foam (461 mg, 0.93 mmol, 87%).

FT-IR (v/cm⁻¹) 3307 (m), 2967 (m), 2933 (m), 1729 (m), 1654 (s), 1537 (m), 1512 (m), 1252 (m), 1217 (m), 1140 (s), 1046 (w), 905 (w), 846 (w), 752 (s), 696 (m).

¹H NMR δ_H (400 MHz, CDCl₃): 7.39 - 7.29 (7 H, m, 7 x ArH), 7.15 (2 H, d, *J*=8.0 Hz, 2 x ArH), 6.68 (1 H, dd, *J*=17.8, 10.8 Hz, CH=CHH), 6.29 (1 H, br. d, *J*=8.0 Hz, NH), 5.71 (1 H, d, *J*=17.6 Hz, CH=CHH), 5.29 (1 H, br. d, *J*=7.0 Hz, NH), 5.23 (1 H, d, *J*=10.5 Hz, CH=CHH), 5.12 (1 H, d, *J*=12.5 Hz, CHH), 5.09 (1 H, d, *J*=12.5 Hz, CHH), 4.49 - 4.41 (1 H, m, CH), 4.39 (1 H, dd, *J*=8.0, 4.5 Hz, CH), 3.16 - 3.01 (2 H, m, CHH), 1.88 -

1.75 (1 H, m, **CH**), 1.45 (9 H, s, 3 x **CH**₃), 1.42 - 1.33 (1 H, m, **CHH**), 1.19 - 1.04 (1 H, m, **CHH**), 0.91 (3 H, t, $J=7.5$ Hz, **CH**₂**CH**₃), 0.82 (3 H, d, $J=7.0$ Hz, **CHCH**₃).

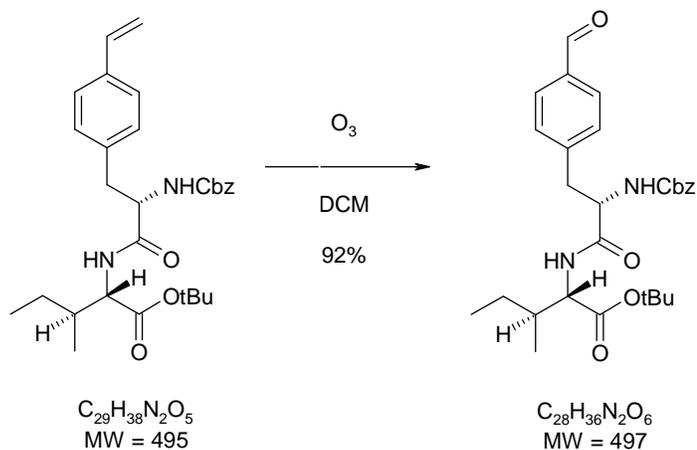
¹³C NMR δ_C (100 MHz, CDCl₃): 169.9 (**C**), 169.8 (**C**), 155.5 (**C**), 138.1 (**C**), 136.1 (**CH=CH**₂), 135.9 (**C**), 135.5 (**C**), 129.2 (2 x **CH**), 128.2 (2 x **CH**), 127.9 (**CH**), 127.7 (2 x **CH**), 126.2 (2 x **CH**), 113.3 (**CH=CH**₂), 81.8 (**C**), 66.7 (**CH**₂), 56.5 (**CH**), 55.8 (**CH**), 38.0 (**CH**₂), 37.8 (**CH**), 27.7 (3 x **CH**₃), 25.0 (**CH**₂), 14.8 (**CH**₃), 11.4 (**CH**₃).

LRMS m/z (ES+) 517 ([**M+Na**]⁺, 100), 1012 ([**2M+Na**]⁺, 88).

HRMS m/z (ES+) Found [**M+Na**]⁺ 517.2666. Required 517.2673.

[α]_D + 8.0 (c = 1.0, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-Benzyloxycarbonylamino-3-(4-formyl-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.101**



A stirred solution of (2*S*,3*S*)-2-[(*S*)-2-benzyloxycarbonylamino-3-(4-vinyl-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.100** (413 mg, 0.82 mmol) and sudan red (10 mg) in DCM (100 mL) was cooled to -78 °C and O₃ (1–4% in O₂) bubbled through until the red colour disappeared. O₂ was then bubbled through for 20 min before PPh₃ (428 mg, 1.63 mmol) was added. The reaction was stirred at -78 °C for 20 min then allowed to warm to RT. Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.101** as a yellow foam (383 mg, 0.75 mmol, 92%).

FT-IR (v/cm⁻¹) 3307 (m), 2968 (m), 2933 (m), 1729 (m), 1698 (s), 1655 (s), 1534 (m), 1455 (w), 1367 (w), 1254 (m), 1215 (m), 1141 (s), 1045 (w), 752 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 9.95 (1 H, s, CHO), 7.76 (2 H, d, *J*=8.1 Hz, 2 x ArH), 7.39 - 7.28 (7 H, m, 7 x ArH), 6.45 (1 H, d, *J*=8.1 Hz, NH), 5.49 (1 H, d, *J*=8.1 Hz, NH), 5.08 (2 H, s, OCH₂Ar), 4.53 (1 H, app. q, *J*=6.2 Hz, CHNH), 4.40 (1 H, app. dd, *J*=8.2, 4.6 Hz, CHNH), 3.20 (1 H, dd, *J*=13.5, 6.6 Hz, CHH), 3.11 (1 H, dd, *J*=13.5, 7.0 Hz, CHH), 1.89 - 1.74 (1 H, m, CH(CH₃)CH₂CH₃), 1.44 (9 H, s, 3 x CH₃), 1.41 - 1.30 (1 H,

m, CHHCH₃), 1.20 - 1.02 (1 H, m, CHHCH₃), 0.89 (3 H, t, J=7.3 Hz, CH₂CH₃), 0.82 (3 H, d, J=7.0 Hz, CHCH₃).

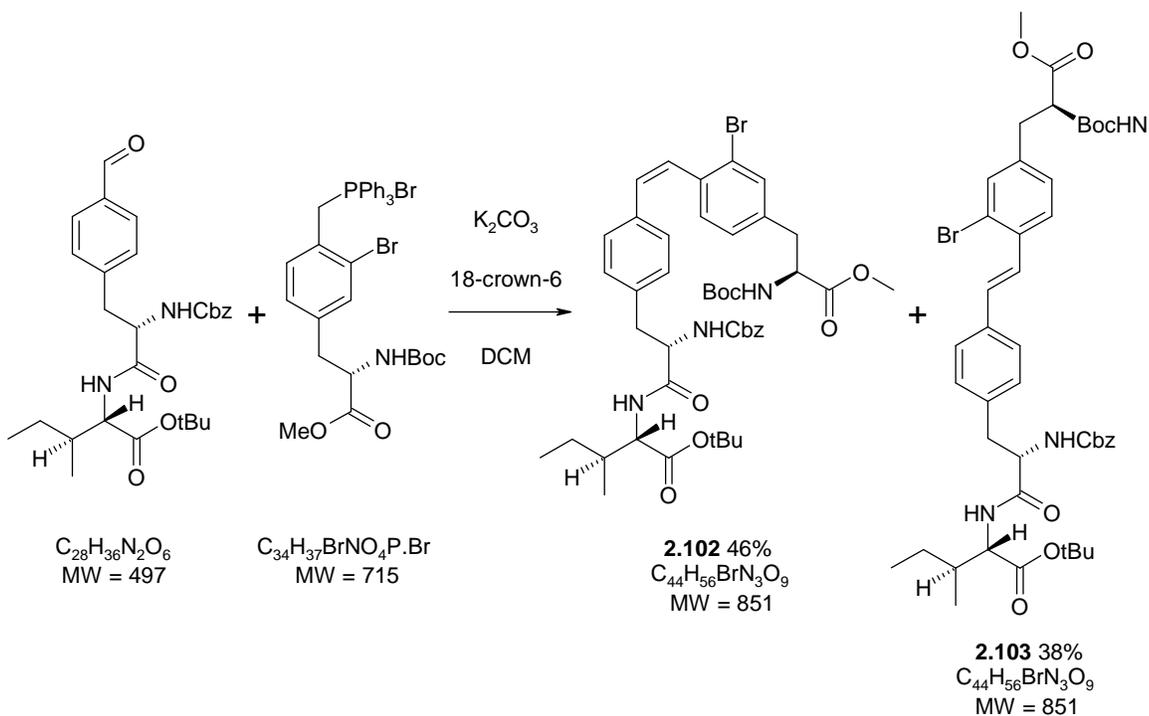
¹³C NMR δ_C (75 MHz, CDCl₃): 191.8 (CHO), 170.3 (C), 169.8 (C), 155.8 (C), 143.6 (C), 136.0 (C), 135.2 (C), 130.0 (2 x CH), 139.9 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 128.0 (2 x CH), 82.2 (C), 67.1 (OCH₂), 56.8 (CHNH), 55.7 (CHNH), 38.6 (CH₂), 38.1 (CH), 28.0 (3 x CH₃), 25.3 (CH₂), 15.2 (CH₃), 11.7 (CH₃).

LRMS m/z (ES+) 519 ([M+Na]⁺, 100), 1015 ([2M+Na]⁺, 10).

HRMS m/z (ES+) Found [M+Na]⁺, 519.2457. Required 519.2466.

[α]_D + 69.5 (c = 0.7, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-Benzyloxycarbonylamino-3-[4-((*Z*)-2-{2-bromo-4-[2-*tert*-butoxycarbonylamino-2-((*S*)-methoxycarbonyl)-ethyl]-phenyl}-vinyl)-phenyl]-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.102** and (2*S*,3*S*)-2-[(*S*)-2-benzyloxycarbonylamino-3-[4-((*E*)-2-{2-bromo-4-[2-*tert*-butoxycarbonylamino-2-((*S*)-methoxycarbonyl)-ethyl]-phenyl}-vinyl)-phenyl]-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.103**



To a stirred solution of (*S*)-3-{3-bromo-4-[(triphenyl- λ^5 -phosphanyl)-methyl]-phenyl}-2-*tert*-butoxycarbonylamino-propionic acid methyl ester bromide **2.96** (357 mg, 0.50 mmol) in DCM (5 mL) was added 18-crown-6 (10 mg). After 20 min at RT (2*S*,3*S*)-2-[(*S*)-2-benzyloxycarbonylamino-3-(4-formyl-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.101** (132 mg, 0.26 mmol) was added, followed after 18 h by SiO₂ (2 g). Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded firstly *cis*-**2.102** as a yellow oil (102 mg, 0.12 mmol, 46%) then *trans*-**2.103** as a yellow oil (89 mg, 0.10 mmol, 38%).

Cis-1.102:

FT-IR (v/cm⁻¹) 3015 (w), 2974 (w), 1712 (m), 1500(m), 1368 (w), 1215 (m), 1160 (m), 1046 (w), 746 (s), 667 (m).

¹H NMR δ_{H} (400 MHz, CDCl₃): 7.39 (1 H, s, ArH), 7.37 - 7.29 (5 H, m, 5 x ArH), 7.11 (1 H, d, $J=8.0$ Hz, ArH), 7.02 (4 H, dd, $J=12.5, 7.0$ Hz, 4 x ArH), 6.86 (1 H, d, $J=7.5$ Hz, ArH), 6.61 (1 H, d, $J=12.0$ Hz, CH=CH), 6.55 (1 H, d, $J=12.0$ Hz, CH=CH), 6.34 (1 H, d, $J=6.0$ Hz, NH), 5.32 (1 H, br. s, NH), 5.15 - 5.00 (3 H, m, OCH₂ and NH), 4.56 (1 H, br. d, $J=5.5$ Hz, CHNH), 4.46 - 4.31 (2 H, m, 2 x CHNH), 3.71 (3 H, s, OCH₃), 3.15 - 2.91 (4 H, m, 2 x CHH), 1.87 - 1.76 (1 H, m, CH(CH₃)CH₂CH₃), 1.44 (9 H, s, 23 x CH₃), 1.44 (9 H, s, 3 x CH₃), 1.40 - 1.33 (1 H, m, CHHCH₃), 1.19 - 1.04 (1 H, m, CHHCH₃), 0.90 (3 H, t, $J=7.3$ Hz, CH₂CH₃), 0.81 (3 H, d, $J=6.0$ Hz, CHCH₃).

¹³C NMR δ_{C} (100 MHz, CDCl₃): 171.9 (C), 170.2 (C), 170.2 (C), 155.8 (C), 154.9 (C), 137.1 (C), 136.5 (C), 136.1 (C), 135.5 (C), 135.0 (C), 133.4 (CH), 130.9 (CH), 130.7 (CH), 129.2 (2 x CH), 129.1 (2 x CH), 129.0 (CH), 128.5 (2 x CH), 128.1 (CH), 128.0 (CH), 128.0 (2 x CH), 123.8 (CBr), 82.1 (C), 80.1 (C), 67.0 (OCH₂), 56.8 (CHNH), 56.0 (CHNH), 54.3 (CHNH), 52.3 (OCH₃), 38.1 (CH), 37.7 (br. s, 2 x CH₂), 28.3 (3 x CH₃), 28.0 (3 x CH₃), 25.3 (CH₂), 15.2 (CH₃), 11.7 (CH₃).

LRMS m/z (ES+) 873 ([M (⁷⁹Br)+Na]⁺, 93), 875 ([M (⁸¹Br)+Na]⁺, 100).

HRMS m/z (ES+) Found [M (⁷⁹Br)+Na]⁺ 872.3080. Required 872.3092.

[α]_D + 17.5 (c = 0.4, CHCl₃).

Trans-1.103:

FT-IR (v/cm^{-1}) 3015 (w), 2974 (w), 1712 (m), 1500(m), 1368 (w), 1215 (m), 1160 (m), 1046 (w), 746 (s), 667 (m).

^1H NMR δ_{H} (400 MHz, CDCl_3): 7.57 (1 H, d, $J=8.0$ Hz, ArH), 7.43 (2 H, d, $J=8.0$ Hz, 2 x ArH), 7.41 - 7.29 (7 H, m, 6 x ArH and CH=CH), 7.19 (2 H, d, $J=7.5$ Hz, 2 x ArH), 7.09 (1 H, d, $J=8.0$ Hz, ArH), 6.97 (1 H, d, $J=16.1$ Hz, CH=CH), 6.37 (1 H, d, $J=8.0$ Hz, NH), 5.38 (1 H, d, $J=7.0$ Hz, NH), 5.09 - 5.01 (3 H, m, OCH_2 and NH), 4.59 (1 H, br. d, $J=6.5$ Hz, CHNH), 4.47 (1 H, br. d, $J=7.0$ Hz, CHNH), 4.40 (1 H, dd, $J=8.5, 4.5$ Hz, CHNH), 3.75 (3 H, s, OCH_3), 3.17 - 3.06 (3 H, m, CHH and CHH), 3.01 (1 H, dd, $J=13.6, 7.0$ Hz, CHH), 1.88 - 1.76 (1 H, m, CH(CH₃)CH₂CH₃), 1.45 (18 H, s, 2 x (3 x CH₃)), 1.40 - 1.34 (1 H, m, CHHCH₃), 1.19 - 1.06 (1 H, m, CHHCH₃), 0.91 (3 H, t, $J=7.3$ Hz, CH₂CH₃), 0.83 (3 H, d, $J=6.5$ Hz, CHCH₃).

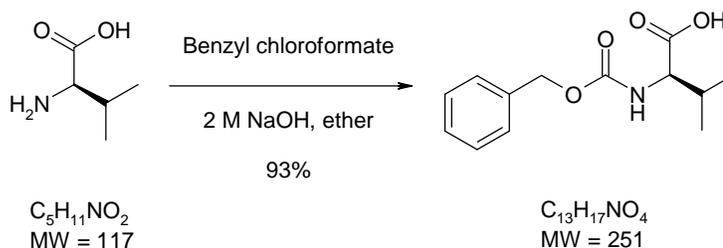
^{13}C NMR δ_{C} (100 MHz, CDCl_3): 172.0 (C), 170.2 (C), 170.1 (C), 155.8 (C), 155.0 (C), 137.2 (C), 136.2 (2 x C), 135.8 (2 x C), 133.8 (CH), 130.8 (C), 129.7 (2 x CH), 128.5 (3 x CH), 128.2 (CH), 128.0 (2 x CH), 127.1 (2 x CH), 126.8 (CH), 126.5 (CH), 124.0 (CBr), 82.1 (C), 80.1 (C), 67.0 (CH₂), 56.8 (CHNH), 56.1 (CHNH), 54.3 (CHNH), 52.3 (OCH₃), 38.2 (CH₂), 38.1 (CH), 37.6 (CH₂), 28.3 (3 x CH₃), 28.0 (3 x CH₃), 25.4 (CH₂), 15.2 (CH₃), 11.7 (CH₃).

LRMS m/z (ES+) 873 ([M (^{79}Br)+Na]⁺, 93), 875 ([M (^{81}Br)+Na]⁺, 100).

HRMS m/z (ES+) Found [M (^{79}Br)+Na]⁺ 872.3080. Required 872.3092.

$[\alpha]_{\text{D}}$ + 37.7 (c = 0.6, CHCl_3).

(R)-2-Benzoyloxycarbonylamino-3-methyl-butyrlic acid **2.106**



Prepared following the procedure of Aitken *et al.*⁸³

To a stirred solution of D-Valine **2.105** (6.0 g, 50 mmol) in 2 M NaOH (117 mL) and ether (26 mL) at 0 °C was added benzyl chloroformate (11.7 mL, 80 mmol). The reaction was warmed to RT after 17 h, the aqueous phase was separated, adjusted to pH 2 with conc. HCl and extracted with ethyl acetate (4 x 50 mL). The organic extracts were combined, washed with brine (50 mL), then dried ($MgSO_4$). Concentration *in vacuo* afforded the product **2.106** as a colourless oil (11.7 g, 46 mmol, 93%).

FT-IR (ν/cm^{-1}) 3325 (br), 2965 (w), 2388 (br), 2282 (br), 2112 (br), 1698 (s), 1519 (m), 1455 (w), 1414 (w), 1303 (w), 1213 (m), 1025 (m), 911 (w), 735 (m), 696 (m).

1H NMR δ_H (300 MHz, $CDCl_3$): 7.45 - 7.29 (5 H, m, 5 x ArH), 5.27 (1 H, d, $J=8.8$ Hz, NH), 5.14 (2 H, s, CH_2), 4.36 (1 H, dd, $J=8.8, 4.4$ Hz, $CHCO_2H$), 2.33 - 2.16 (1 H, m, $CH(CH_3)_2$), 1.02 (3 H, d, $J=6.6$ Hz, CH_3), 0.95 (3 H, d, $J=7.0$ Hz, CH_3).

^{13}C NMR δ_C (75 MHz, $CDCl_3$): 176.6 (C), 156.4 (C), 136.1 (C), 128.5 (2 x CH), 128.2 (CH), 128.1 (2 x CH), 67.2 (CH_2), 58.9 (CHNH), 31.0 ($CH(CH_3)_2$), 19.0 (CH_3), 17.3 (CH_3).

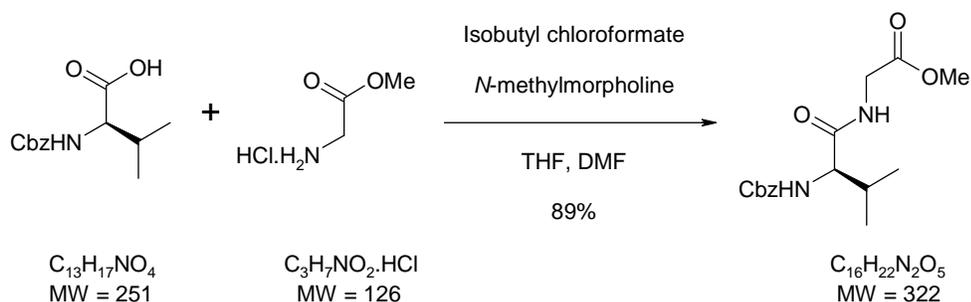
LRMS m/z (ES+) 274 ($[M+Na]^+$, 100), 525 ($[2M+Na]^+$, 28).

$[\alpha]_D$ + 13.7 ($c = 2.6$, $CHCl_3$).

The data are consistent with the literature.⁸³

((R)-2-Benzyloxycarbonylamino-3-methyl-butyrylamino)-acetic acid methyl ester

2.107



Prepared following the procedure of Rose *et al.*⁸⁴

To a stirred solution of (*R*)-2-benzyloxycarbonylamino-3-methyl-butyric acid **2.106** (44.4 g, 0.18 mol) in THF (400 mL) at $-5\text{ }^{\circ}\text{C}$ was added *N*-methylmorpholine (19.5 mL, 0.18 mol) and isobutyl chloroformate (22.9 mL, 0.18 mol). After 10 min a solution of glycine methyl ester (22.2 g, 0.18 mol) in DMF (65 mL) was added followed by further *N*-methylmorpholine (19.5 mL, 0.18 mol). The reaction was warmed to RT and after 20 h was quenched with water (100 mL) and concentrated *in vacuo* to approx. 150 mL. The resultant precipitate was collected by filtration and recrystallised from DCM/diethyl ether to afford **2.107** as a white solid (50.6 g, 0.16 mol, 89%).

m.p. 162–163 $^{\circ}\text{C}$

FT-IR (v/cm^{-1}) 3287 (s), 2954 (w), 2349 (w), 1750 (m), 1687 (m), 1652 (m), 1537 (s), 1208 (s), 1038 (s), 745 (m), 697 (s).

^1H NMR δ_{H} (300 MHz, CDCl_3): 7.40 - 7.31 (5 H, m, 5 x ArH), 6.62 (1 H, br. s, NH), 5.45 (1 H, d, $J=8.4$ Hz, NH), 5.11 (2 H, d, $J=2.6$ Hz, CH_2Ar), 4.16 - 3.93 (3 H, m, CH_2NH and CHNH), 3.75 (3 H, s, OCH_3), 2.24 - 2.08 (1 H, m, $\text{CH}(\text{CH}_3)_2$), 0.99 (3 H, d, $J=6.6$ Hz, CH_3), 0.95 (3 H, d, $J=7.0$ Hz, CH_3).

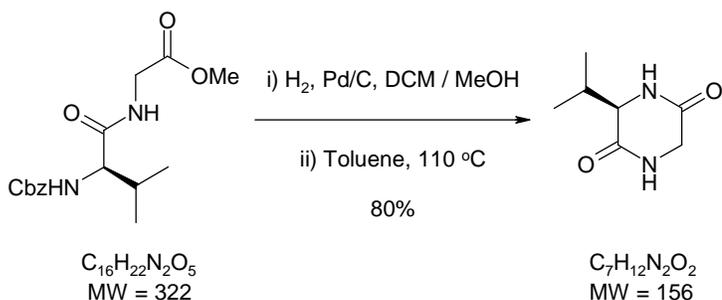
^{13}C NMR δ_{C} (75 MHz, CDCl_3): 171.6 (C), 170.1 (C), 156.4 (C), 136.2 (C), 128.5 (2 x CH), 128.2 (CH), 128.0 (2 x CH), 67.1 (CH_2Ar), 60.3 (CHNH), 52.3 (OCH_3), 41.1 (CH_2NH), 31.0 ($\text{CH}(\text{CH}_3)_2$), 19.1 (CH_3), 17.7 (CH_3).

LRMS m/z (ES+) 345 ($[\text{M}+\text{Na}]^+$, 100), 667 ($[\text{2M}+\text{Na}]^+$, 30).

$[\alpha]_{\text{D}}$ + 46.8 ($c = 2.0$, CHCl_3).

The data are consistent with the literature.⁸⁴

(R)-3-Isopropyl-piperazine-2,5-dione **2.108**



Prepared following the procedure of Rose *et al.*⁸⁴

To a stirred solution of ((R)-2-benzyloxycarbonylamino-3-methyl-butylamino)-acetic acid methyl ester **2.107** (4.42 g, 13.7 mmol) in MeOH (24 mL) and DCM (72 mL) was added 5% Pd/C (400 mg). The reaction was stirred under an atmosphere of H_2 for 4 d, then filtered through celite and concentrated *in vacuo*. The residue was dissolved in toluene (70 mL) and heated at reflux for 20 h. The reaction was cooled to 0 °C and the resulting precipitate was collected by filtration, then washed with diethyl ether and recrystallised from water to afford **2.108** as a white solid (1.70 g, 10.9 mmol, 80%).

m.p. 215–217 °C

FT-IR (ν/cm^{-1}) 3193 (w), 3050 (w), 2963 (w), 2918 (w), 2875 (w), 1663 (s), 1453 (s), 1344 (m), 1327 (m), 1101 (w), 852 (m), 833 (m), 807 (m).

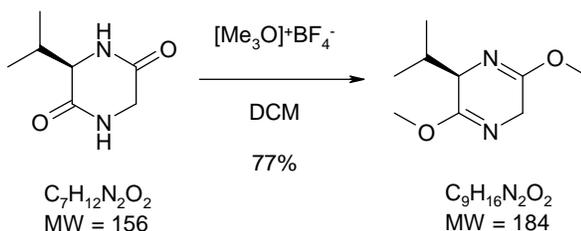
1H NMR δ_H (300 MHz, DMSO): 8.16 (1 H, br. s, NH), 7.98 (1 H, br. s, NH), 3.81 (1 H, d, $J=17.9$ Hz, CHH), 3.62 (1 H, dd, $J=17.6, 2.9$ Hz, CHH), 3.52 (1 H, app. t, $J=3.3$ Hz, CHNH), 2.11 (1 H, dsep, $J=6.9, 4.1$ Hz, $CH(CH_3)_2$), 0.92 (3 H, d, $J=7.3$ Hz, CH_3), 0.85 (3 H, d, $J=7.0$ Hz, CH_3).

^{13}C NMR δ_{C} (75 MHz, DMSO): 167.2 (C), 166.0 (C), 59.8 (CHNH), 44.1 (CH₂NH), 32.2 (CH(CH₃)₂), 18.5 (CH₃), 17.0 (CH₃).

$[\alpha]_{\text{D}}$ + 7.5 (c = 1.7, CHCl₃).

The data are consistent with the literature.⁸⁴

(R)-3-Isopropyl-2,5-dimethoxy-3,6-dihydropyrazine **2.109**



Prepared following the procedure of Davies *et al.*⁸⁵

To a stirred suspension of (*R*)-3-isopropyl-piperazine-2,5-dione **2.108** (3.71 g, 23.8 mmol) in DCM (150 mL) was added trimethyloxonium tetrafluoroborate (10.56 g, 71.4 mmol). The reaction was stirred at RT for 5 d and further trimethyloxonium tetrafluoroborate (2.20 g, 15.0 mmol) was added. The reaction was stirred at RT for 10 d then quenched with a sat. NaHCO_3 (100 mL). The aqueous phase was extracted with DCM (4 x 100 mL) then the organic phases were combined and dried (MgSO_4). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 2% MeOH/DCM) afforded **2.109** as a pale yellow oil (3.37 g, 18.3 mmol, 77%).

FT-IR (v/cm^{-1}) 2958 (m), 2938 (m), 2864 (m), 2844 (m), 2360 (s), 2341 (s), 1696 (s), 1454 (m), 1437 (m), 1234 (s), 1195 (m), 1102 (m), 1009 (m), 758 (m).

^1H NMR δ_{H} (300 MHz, CDCl_3): 4.03 - 3.96 (3 H, m, CH_2 and CHN), 3.71 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 2.22 (1 H, d, $J=6.7$, 3.2 Hz, $\text{CH}(\text{CH}_3)_2$), 1.03 (3 H, d, $J=7.0$ Hz, CH_3), 0.75 (3 H, d, $J=7.0$ Hz, CH_3).

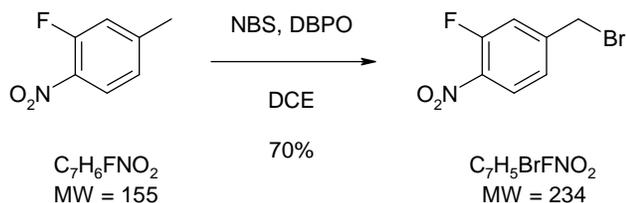
^{13}C NMR δ_{C} (75 MHz, CDCl_3): 165.0 (C), 162.4 (C), 61.2 (CH), 53.1 (CH₃), 52.6 (CH₃), 46.7 (CH₂), 32.6 (CH(CH₃)₂), 19.1 (CH₃), 17.1 (CH₃).

LRMS m/z (ES+) 185 ($[\text{M}+\text{H}]^+$, 100).

$[\alpha]_{\text{D}}$ + 24.9 ($c = 2.0$, CHCl_3).

The data are consistent with the literature.⁸⁵

3-Fluoro-4-nitro-benzylbromide 2.111



Prepared following the procedure of Zhu *et al.*⁸⁶

A stirred solution of 3-fluoro-4-nitrotoluene **2.110** (4.03 g, 26.0 mmol), DBPO (0.63 g, 2.6 mmol) and *N*-bromosuccinimide (4.63 g, 26.0 mmol) in 1,2-dichloroethane (25 mL) was heated at reflux for 17 h, then allowed to cool to RT and stirred for a further 3 d. Concentration *in vacuo* and purification by column chromatography (SiO₂, 5-10% ethyl acetate/petroleum ether), then recrystallisation from ethanol afforded **2.111** as pale yellow crystals (4.28 g, 18.3 mmol, 70%).

m.p. 32–34 °C

FT-IR (v/cm⁻¹) 3113 (m), 3089 (m), 3040 (m), 2856 (w), 2108 (w), 1601 (s), 1527 (s), 1486 (m), 1429 (m), 1342 (s), 1317 (m), 1280 (m), 1209 (m), 964 (m), 839 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 8.06 (1 H, dd, *J*=8.6, 7.9 Hz, CH), 7.39 - 7.29 (2 H, m, 2 x CH), 4.47 (2 H, s, CH₂Br).

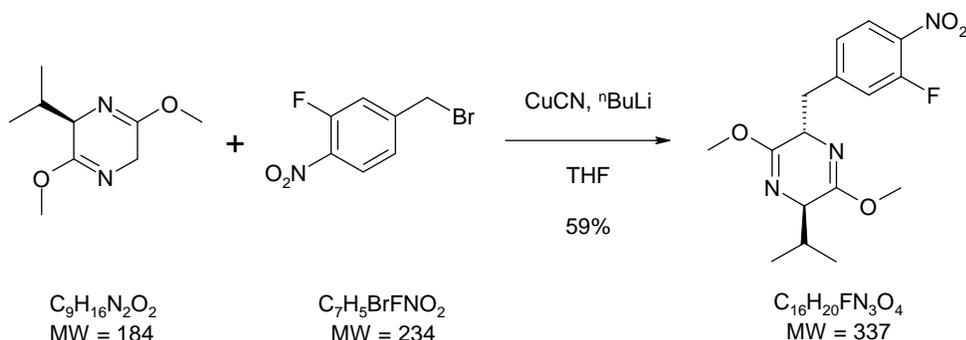
¹³C NMR δ_C (75 MHz, CDCl₃): 155.4 (d, *J*=266.5 Hz, CF), 146.2 (d, *J*=7.7 Hz, C), 136.7 (CNO₂), 126.6 (d, *J*=2.2 Hz, CH), 124.9 (d, *J*=3.3 Hz, CH), 118.9 (d, *J*=21.0 Hz, CH), 30.0 (CH₂Br).

LRMS ^{m/z} (ES+) 234 ([M+H]⁺, 100).

The data are consistent with the literature.⁸⁶

(2*S*-5*R*)-2-(3'-Fluoro-4'-nitrobenzyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine

2.112



Prepared following the procedure of Beugelmans *et al.*⁸⁷

To a stirred solution of (*R*)-3-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine **2.109** (417 mg, 2.26 mmol) in THF (6 mL) at $-78\text{ }^\circ\text{C}$ was added $^n\text{BuLi}$ (1.0 mL, 2.26 mmol). The reaction was stirred at $-78\text{ }^\circ\text{C}$ for 10 min, then allowed to warm to $0\text{ }^\circ\text{C}$ and added dropwise to a solution of CuCN (203 mg, 2.26 mmol) in THF (25 mL) at $-78\text{ }^\circ\text{C}$. After 30 min a solution of 3-fluoro-4-nitrobenzyl bromide **2.111** (530 mg, 2.26 mmol) in THF (3 mL) was added dropwise, followed after 1 h by a saturated solution of $\text{NH}_4\text{Cl}:\text{NH}_4\text{OH}$ (9 mL:1 mL). On warming to RT the aqueous phase was extracted with ethyl acetate (4 x 50 mL). The organic extracts were combined, washed with water (50 mL), then dried (MgSO_4). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 0-10% ethyl acetate/petroleum ether) afforded firstly **2.112** as a yellow oil (445 mg, 1.32 mmol, 59%), then recovered 3-fluoro-4-nitrobenzyl bromide (154 mg, 0.66 mmol, 29%).

FT-IR (v/cm^{-1}) 2962 (m), 2942 (m), 2876 (w), 2835 (w), 2360 (s), 2341 (s), 2088 (w), 1693 (s), 1601 (s), 1525 (s), 1435 (m), 1346 (s), 1238 (s), 1015 (m).

^1H NMR δ_{H} (300 MHz, CDCl_3): 7.94 (1 H, app. t, $J=8.2$ Hz, ArH), 7.16 - 7.03 (2 H, m, 2 x ArH), 4.31 (1 H, dd, $J=5.9$, 4.2 Hz, CH), 3.73 (3 H, s, OCH_3), 3.67 (3 H, s, OCH_3), 3.63 (1 H, app. t, $J=3.7$ Hz, CHCH(CH_3)₂), 3.22 (1 H, dd, $J=13.2$, 4.4 Hz, CHH), 3.12 (1 H, dd, $J=13.2$, 6.2 Hz, CHH), 2.15 (1 H, dsep, $J=6.9$,

3.4 Hz, $\text{CH}(\text{CH}_3)_2$), 0.98 (3 H, d, $J=7.0$ Hz, CH_3), 0.65 (3 H, d, $J=7.0$ Hz, CH_3).

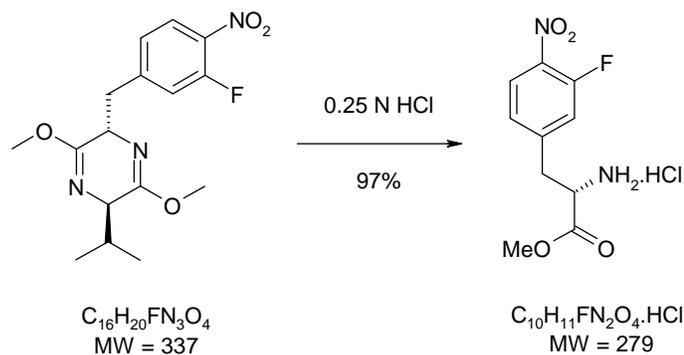
^{13}C NMR δ_{C} (75 MHz, CDCl_3): 164.4 (C), 161.6 (C), 155.0 (d, $J=264.3$ Hz, CF), 147.8 (d, $J=8.8$ Hz, C), 137.9 (CNO_2), 125.9 (d, $J=3.3$ Hz, CH), 125.4 (d, $J=2.2$ Hz, CH), 119.6 (d, $J=21.0$ Hz, CH), 60.8 ($\text{CHCH}(\text{CH}_3)_2$), 55.8 (CHCH_2Ar), 52.4 (OCH_3), 52.4 (OCH_3), 39.7 (CH_2Ar), 31.8 ($\text{CH}(\text{CH}_3)_2$), 18.9 ($\text{CH}(\text{CH}_3)\text{CH}_3$), 16.5 ($\text{CH}(\text{CH}_3)\text{CH}_3$).

LRMS m/z (ES+) 338 ($[\text{M}+\text{H}]^+$, 100%).

$[\alpha]_{\text{D}}$ + 18.6 (c = 1.0, CHCl_3).

The data are consistent with the literature.⁸⁷

3-Fluoro-4-nitro-L-phenylalanine methyl ester **2.113**



Prepared following the procedure of Beugelmans *et al.*⁸⁷

A solution of (2*S*-5*R*)-2-(3'-fluoro-4'-nitrobenzyl)-5-isopropyl-3,6-dimethoxy-2,5-**2.112** (741 mg, 2.20 mmol) in 0.25 *N* HCl (18 mL) was stirred at RT for 30 h. Ether (10 mL) was added and the aqueous phase separated and concentrated *in vacuo*. The residue was dissolved in water (10 mL), treated with sat. NaHCO₃ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The organic phases were then combined, washed with water (20 mL) and brine (20 mL), and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 0–5% MeOH/CHCl₃) afforded **2.113** as a yellow oil (515 mg, 2.13 mmol, 97%).

FT-IR (v/cm⁻¹) 3354 (m), 2950 (m), 2909 (m), 2844 (w), 2353 (m), 2337 (m), 1739 (s), 1614 (s), 1578 (m), 1525 (m), 1493 (s), 1430 (w), 1347 (s), 1271 (m), 1202 (s), 1177 (m), 1067 (w), 753 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 8.01 (1 H, dd, *J*=8.4 Hz, ArH), 7.25 - 7.11 (2 H, m, 2 x ArH), 3.82 - 3.69 (4 H, m, CO₂CH₃ and CHNH₂), 3.14 (1 H, dd, *J*=13.7, 5.3 Hz, CHH), 2.93 (1 H, dd, *J*=13.9, 7.7 Hz, CHH), 1.54 (2 H, br. s, NH₂).

¹³C NMR δ_C (75 MHz, CDCl₃): 174.7 (C), 155.4 (d, *J*=265 Hz, CF), 147.2 (d, *J*=9 Hz, CNO₂), 136.1 (C), 126.1 (d, *J*=2 Hz, CH), 125.4 (d, *J*=3 Hz, CH), 119.1 (d, *J*=21 Hz, CH), 55.2 (CH), 52.3 (CH₃), 40.5 (CH₂).

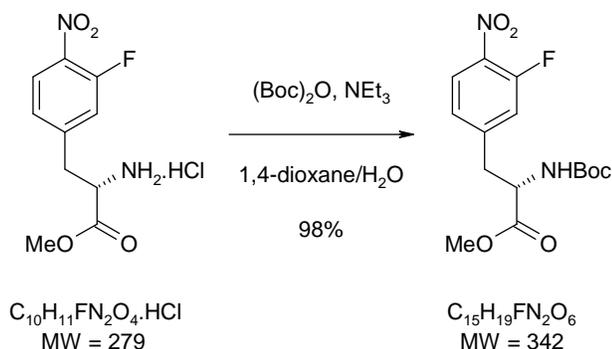
LRMS m/z (ES+) 280 ($[2M+H]^+$, 100).

$[\alpha]_D$ + 11.4 (c = 0.5, $CHCl_3$).

The data are consistent with the literature.⁸⁷

2-tert-Butoxycarbonylamino-3-(3-fluoro-4-nitro-phenyl)-propionic acid methyl ester

2.114



To a stirred solution of 3-fluoro-4-nitro-L-phenylalanine methyl ester **2.113** (177 mg, 0.73 mmol) and NEt_3 (0.15 mL, 1.09 mmol) in 1,4-dioxane:water (2 mL:2 mL) at 0 °C was added $(Boc)_2O$ (175 mg, 0.80 mmol). The reaction was stirred at 0 °C for 50 min then allowed to warm to RT. After 15 h the reaction was concentrated *in vacuo* and the residues partitioned between water (5 mL) and ethyl acetate (5 mL). The aqueous phase was acidified to pH 1 with 2 M HCl, then extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine (5 mL) then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 5% MeOH/ $CHCl_3$) afforded **2.114** as a yellow oil (244 mg, 0.71 mmol, 98%).

FT-IR (ν/cm^{-1}) 3363 (m), 2974 (m), 2929 (w), 2864 (w), 2357 (m), 2333 (m), 1742 (m), 1709 (s), 1603 (m), 1525 (s), 1347 (s), 1159 (s), 1058 (m), 1017 (m), 841 (w), 751 (m).

1H NMR δ_H (300 MHz, $CDCl_3$): 8.01 (1 H, app. t, $J=8.1$ Hz, ArH), 7.20 - 7.01 (2 H, m, 2 x ArCH), 5.11 (1 H, br. d, $J=4.8$ Hz, NH), 4.62 (1 H, br. app. d, $J=5.5$ Hz, CHNH), 3.76 (3 H, s, CO_2CH_3), 3.26 (1 H, dd, $J=13.5, 5.5$ Hz, CHH), 3.08 (1 H, dd, $J=13.9, 6.6$ Hz, CHH), 1.43 (9 H, s, 3 x CH_3).

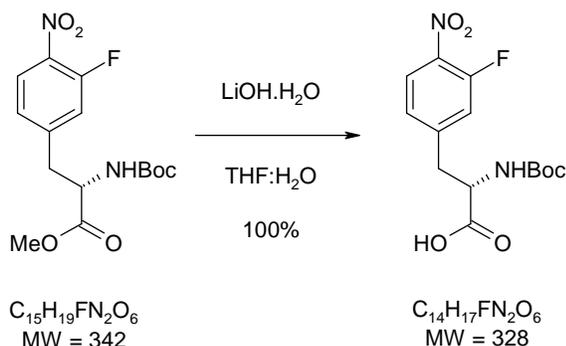
^{13}C NMR δ_C (75 MHz, $CDCl_3$): 171.4 (C), 158.8 (d, $J=258$ Hz, CF), 154.9 (C), 146.0 (C), 131.5 (CNO_2), 126.3 (CH), 125.6 (CH),

119.4 (d, $J = 19.8$ Hz, CH), 81.0 (C), 53.9 (CH), 52.8 (CH₃),
38.4 (CH₂), 28.4 (3 x CH₃).

LRMS m/z (ES+) 365 ([M+Na]⁺, 100).

[α]_D + 32.4 (c = 1.5, CHCl₃).

(S)-2-tert-Butoxycarbonylamino-3-(3-fluoro-4-nitro-phenyl)-propionic acid **2.115**



Prepared following the procedure of Zhu *et al.*⁷²

To a stirred solution of 2-tert-butoxycarbonylamino-3-(3-fluoro-4-nitro-phenyl)-propionic acid methyl ester **2.114** (577 mg, 1.69 mmol) in THF:H₂O (75 mL:75 mL) was added LiOH.H₂O (177 mg, 4.22 mmol). After 15 h the reaction was quenched with sat. NH₄Cl (100 mL). The aqueous phase was extracted with ethyl acetate (4 x 50 mL) and the organic extracts combined and dried (MgSO₄). Concentration *in vacuo* afforded **2.115** as a yellow foam (554 mg, 1.69 mmol, 100%).

FT-IR (v/cm⁻¹) 3420 (w), 2978 (w), 2925 (w), 2864 (w), 2360 (s), 2341 (s), 1705 (s), 1602 (m), 1525 (s), 1347 (s), 1158 (s), 749 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 9.00 (1H, br, OH), 8.01 (1 H, dd, *J*=8.1 Hz, ArH), 7.24 - 7.00 (2 H, m, 2 x ArH), 5.15 (1 H, br. s, NH), 4.73 - 4.31 (1 H, m, CHNH), 3.44 - 3.19 (1 H, m, ArCHH), 3.19 - 2.98 (1 H, m, ArCHH), 1.41 (9 H, s, 3 x CH₃).

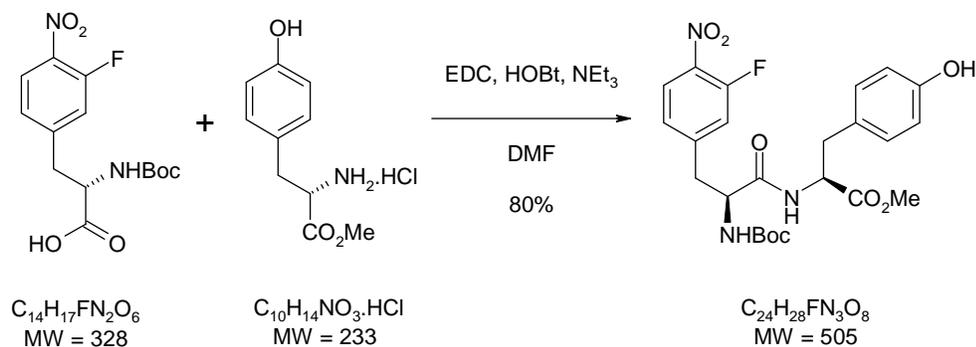
¹³C NMR δ_C (75 MHz, CDCl₃): 157.3 (C), 155.3 (d, *J*=265 Hz, CF), 145.9 (C), 136.4 (CNO₂), 126.3 (CH), 125.8 (CH), 119.4 (d, *J*=19.8 Hz, CH), 81.2 (C), 39.0 (CH), 37.9 (CH₂), 28.3 (CH₃). Cannot see one C.

LRMS *m/z* (ES⁺) 309 ([M-F]⁺, 100).

[α]_D + 14.9 (c = 0.5, CHCl₃).

The data are consistent with the literature.⁷²

(9S,12S)-2-[2-*tert*-Butoxycarbonylamino-3-(3-fluoro-4-nitro phenyl)-propionylamino]-3-(4-hydroxy-phenyl)-propionic acid methyl ester **2.116**



Prepared following the procedure of Zhu *et al.*⁷²

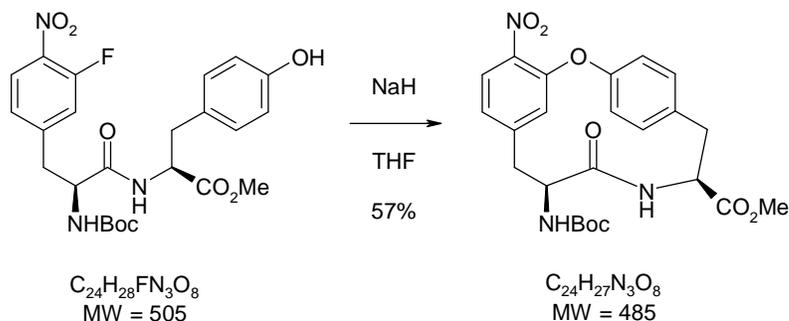
To a stirred solution of 2-*tert*-butoxycarbonylamino-3-(3-fluoro-4-nitrophenyl)-propionic acid **2.115** (1.42 g, 4.33 mmol) in DMF (70 mL) was added L-tyrosine methyl ester hydrochloride (1.10 g, 4.76 mmol), EDC (0.84 mL, 4.76 mmol), HOBt (0.64 g, 4.76 mmol) and NEt₃ (2.12 mL, 15.16 mmol). The reaction was stirred at RT for 16 h then quenched with sat. NH₄Cl (50 mL). The aqueous phase was extracted with ethyl acetate (4 x 50 mL) then the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL), and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 2% MeOH/DCM) afforded **2.116** as a yellow oil (1.75 g, 3.46 mmol, 80%).

FT-IR (v/cm⁻¹) 3314 (br), 3011 (w), 2958 (w), 2921 (w), 2848 (w), 2360 (s), 2342 (s), 1683 (s), 1603 (m), 1517 (s), 1348 (s), 1249 (m), 1219 (m), 1163 (s).

¹H NMR δ_H (300 MHz, MeOD): 7.97 (1 H, app. t, *J*=8.1 Hz, ArH), 7.26 - 7.13 (2 H, m, 2 x ArH), 6.98 (2 H, d, *J*=8.4 Hz, 2 x ArH), 6.70 (2 H, d, *J*=8.4 Hz, 2 x ArH), 4.62 (1 H, dd, *J*=7.3, 6.2 Hz, CHNH), 4.35 (1 H, dd, *J*=7.9, 6.4 Hz, CHNH), 3.66 (3 H, s, OCH₃), 3.13 (1 H, dd, *J*=13.7, 5.7 Hz, CHH), 3.02 (1 H, dd, *J*=13.5, 5.5 Hz, CHH), 2.96 - 2.80 (2 H, m, 2 x CHH), 1.36 (9 H, s, 3 x CH₃).

^{13}C NMR	δ_{C} (100 MHz, MeOD): 172.6 (C), 171.6 (C), 156.5 (C), 156.6 (d, $J=14$ Hz, C), 156.3 (C), 155.8 (d, $J=263$ Hz, CF), 147.5 (d, $J=9$ Hz, C), 136.4 (d, $J=7$ Hz, CH), 130.7 (2 x CH), 127.3 (C), 126.3 (d, $J=21$ Hz, CH), 119.7 (d, $J=20$ Hz, CH), 115.9 (2 x CH), 80.9 (C), 55.1 (CH), 54.4 (CH), 52.7 (CH ₃), 38.6 (CH ₂), 37.3 (CH ₂), 28.5 (3 x CH ₃).
LRMS	m/z (ES+) 528 ([M+Na] ⁺ , 100).
HRMS	m/z (ES+) Found [M+Na] ⁺ 528.1744. Required 528.1753.
$[\alpha]_{\text{D}}$	+ 31.2 (c = 2.4, MeOH).

(9*S*,12*S*)-9-*tert*-Butoxycarbonylamino-4-nitro-10-oxo-2-oxa-11-aza-tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12-carboxylic acid methyl ester **2.117**



Prepared following the procedure of Boger *et al.*⁸⁸

A solution of 2-[2-*tert*-butoxycarbonylamino-3-(3-fluoro-4-nitrophenyl)-propionylamino]-3-(4-hydroxyphenyl)-propionic acid methyl ester **2.116** (94 mg, 0.19 mmol) in THF (1.3 mL) was added dropwise to a suspension of NaH (16.4 mg, 0.41 mmol) in THF (45 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h then warmed to RT. After 2.5 h water (3 mL) was added. The aqueous phase was extracted with ethyl acetate (4 x 20 mL), then the organic extracts were combined, washed with water (10 mL) and brine (15 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 0-5% MeOH/DCM) afforded **2.117** as a yellow oil (53 mg, 0.11 mmol, 57%).

FT-IR (v/cm⁻¹) 3015 (w), 2360 (s), 2341 (s), 1736 (m), 1699 (m), 1667 (m), 1520 (m), 1506 (m), 1348 (m), 1215 (s), 1160 (m), 745 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.89 (1 H, d, *J*=8.4 Hz, ArH), 7.51 (1 H, dd, *J*=8.4, 1.8 Hz, ArH), 7.25 (1 H, dd, *J*=8.4, 2.6 Hz, ArH), 7.16 (1 H, dd, *J*=8.4, 2.2 Hz, ArH), 6.90 (1 H, dd, *J*=8.2, 2.4 Hz, ArH), 6.74 (2 H, m, ArH and NH), 5.10 - 4.98 (2 H, m, ArH and NH), 4.51 (1 H, app. dd, *J*=8.1, 7.0 Hz, CHNH), 3.99 (1 H, br. d, *J*=9.1 Hz, CHNH), 3.82 (3 H, s, OCH₃), 3.71 - 3.54 (2 H,

m, **CHH** and **CHH**), 2.80 - 2.59 (2 H, m, **CHH** and **CHH**), 1.45 (9 H, s, 3 x **CH₃**).

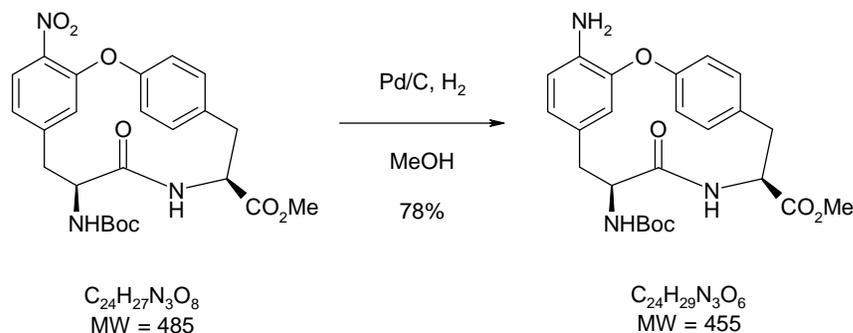
¹³C NMR δ_C (75 MHz, CDCl₃): 171.4 (C), 170.4 (C), 156.6 (C), 156.5 (2 x C), 143.5 (C), 137.0 (C), 135.3 (C), 133.6 (CH), 130.9 (CH), 126.0 (CH), 125.0 (CH), 123.2 (CH), 122.4 (CH), 118.2 (CH), 81.5 (C), 53.0 (CH₃ and CH), 52.7 (CH), 38.5 (CH₂), 33.6 (CH₂), 28.2 (3 x CH₃).

LRMS m/z (ES+) 508 ([M+Na]⁺, 100), 994 ([2M+Na]⁺, 17).

HRMS m/z (ES+) Found [M+Na]⁺ 508.1690. Required 508.1690.

[α]_D + 12.1 (c = 1.6, CHCl₃).

(9*S*,12*S*)-4-Amino-9-*tert*-butoxycarbonylamino-10-oxo-2-oxa-11-aza-tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12-carboxylic acid methyl ester **2.118**



Prepared following the procedure of Boger *et al.*⁸⁸

To a stirred solution of (9*S*,12*S*)-9-*tert*-butoxycarbonylamino-4-nitro-10-oxo-2-oxa-11-aza-tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12-carboxylic acid methyl ester **2.117** (43 mg, 0.089 mmol) in MeOH (5 mL) was added Pd/C (18 mg). The reaction was stirred under an atmosphere of H₂ for 1 h then filtered through celite and concentrated *in vacuo*. Purification by column chromatography (SiO₂, 50% ethyl acetate/petroleum ether) afforded **2.118** as a yellow oil (31 mg, 0.069 mmol, 78%).

FT-IR (v/cm⁻¹) 3338 (w), 2975 (w), 2922 (w), 1737 (m), 1695 (s), 1588 (w), 1519 (s), 1505 (s), 1347 (s), 1224 (m), 1194 (m), 1171 (s), 845 (w), 834 (w), 753 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.43 (1 H, dd, *J*=8.2, 2.0 Hz, ArH), 7.21 (1 H, dd, *J*=8.4, 2.6 Hz, ArH), 7.08 (1 H, dd, *J*=8.1, 1.8 Hz, ArH), 6.85 (1 H, dd, *J*=8.2, 2.4 Hz, ArH), 6.61 (1 H, d, *J*=7.7 Hz, ArH), 6.57 - 6.50 (1 H, m, NH), 6.46 (1 H, dd, *J*=7.9, 0.9 Hz, ArH), 5.01 (1 H, ddd, *J*=12.1, 10.4, 4.9 Hz, CHNH), 4.72 (1 H, s, ArH), 4.38 (1 H, t, *J*=7.7 Hz, CHNH), 4.17 - 4.01 (1 H, m, NH), 3.92 (2H, br. s, NH₂), 3.79 (3 H, s, OCH₃), 3.64 - 3.50 (2

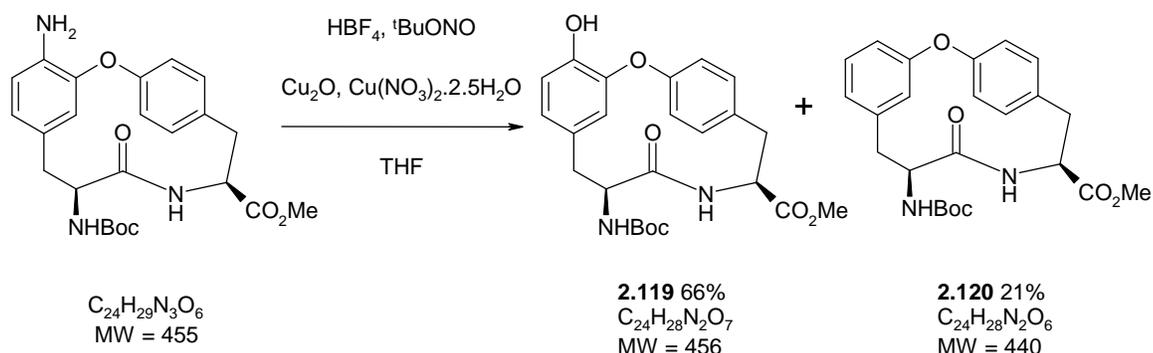
H, m, **CHH** and **CHH**), 2.65 (1 H, app. t, $J=13.0$ Hz, **CHH**), 2.50 (1 H, dd, $J=15.4, 7.0$ Hz, **CHH**), 1.45 (9 H, s, 3 x **CH₃**).

¹³C NMR δ_C (75 MHz, CDCl₃): 171.7 (**C**), 171.3 (**C**), 158.1 (**C**), 151.5 (**C**), 134.2 (2 x **C**), 133.9 (**C**), 133.3 (**CH**), 129.8 (**CH** and **C**), 125.5 (**CH**), 123.7 (**CH**), 123.4 (**CH**), 115.8 (**CH**), 115.5 (**CH**), 80.9 (**C**), 53.1 (**CH₃**), 52.5 (2 x **CH**), 38.3 (**CH₂**), 32.9 (**CH₂**), 28.2 (3 x **CH₃**).

LRMS m/z (ES+) 478 ([**M+Na**]⁺, 100), 934 ([**2M+Na**]⁺, 12).

[α]_D + 27.9 (c = 2.0, CHCl₃).

(9S,12S)-9-tert-Butoxycarbonylamino-4-hydroxy-10-oxo-2-oxa-11-aza-tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12-carboxylic acid methyl ester **2.119** and (9S,12S)-9-tert-butoxycarbonylamino-10-oxo-2-oxa-11-aza-tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12-carboxylic acid methyl ester **2.120**



Prepared following the procedure of Boger *et al.*⁸⁸

To a stirred solution of (9S,12S)-4-amino-9-tert-butoxycarbonylamino-10-oxo-2-oxa-11-aza-tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12-carboxylic acid methyl ester **2.118** (29 mg, 0.063 mmol) in THF (1.5 mL) at 0 °C was added HBF₄ (23 mg, 0.13 mmol). The reaction was stirred at 0 °C for 30 min, then allowed to warm to RT and stirred for a further 1 h. The reaction was cooled to 0 °C and tBuONO (16 mg, 0.13 mmol) in THF (0.5 mL) was added. The reaction was stirred at 0 °C for 1 h and then concentrated *in vacuo* at 0 °C. The residue was treated with a solution of Cu(NO₃)₂·2.5H₂O (1.52 g, 6.28 mmol) and Cu₂O (45 mg, 0.31 mmol) in water (14 mL) at 0 °C, then allowed to warm to RT and stirred for 1 h. The reaction was filtered through celite, then washed with water (30 mL) and DCM (30 mL). The aqueous phase was extracted with DCM (3 x 10 mL). The organic extracts were combined, washed with sat. NH₄Cl (30 mL) and brine (30 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 40% ethyl acetate/petroleum ether) afforded firstly **2.119** as a yellow oil (19 mg, 0.042 mmol, 66%) then the reduced side product **2.120** as a colourless oil (6 mg, 0.013 mmol, 21%).

Phenol-1,119:

FT-IR (v/cm⁻¹)	3417 (w), 3351 (m), 3017 (w), 2926 (m), 2843 (w), 1736 (m), 1705 (m), 1667 (m), 1504 (s), 1436 (m), 1367 (m), 1211 (m), 1159 (s), 1022 (m), 750 (s).
¹H NMR	δ_{H} (300 MHz, CDCl ₃): 7.45 (1 H, dd, $J=8.3, 1.8$ Hz, ArH), 7.21 (1 H, dd, $J=8.5, 2.5$ Hz, ArH), 7.09 (1 H, d, $J=7.0$ Hz, ArH), 6.84 (1 H, dd, $J=8.5, 2.5$ Hz, ArH), 6.81 (1 H, d, $J=8.0$ Hz, ArH), 6.57 (1 H, br. s, NH), 6.53 (1 H, dd, $J=8.3, 1.3$ Hz, ArH), 5.85 (1 H, br. s, NH), 5.02 (1 H, ddd, $J=12.0, 10.5, 5.0$ Hz, CHNH), 4.82 (1 H, s, ArH), 4.41 (1 H, app. t, $J=7.5$ Hz, CHNH), 4.01 (1 H, d, $J=8.5$ Hz, OH), 3.80 (3 H, s, OCH ₃), 3.65 - 3.50 (2 H, m, CHH and CHH), 2.66 (1 H, app. t, $J=13.1$ Hz, CHH), 2.53 (1 H, dd, $J=15.6, 6.5$ Hz, CHH), 1.45 (9 H, s, 3 x CH ₃).
¹³C NMR	δ_{C} (75 MHz, CDCl ₃): 171.6 (C), 171.2 (C), 157.8 (C), 155.9 (C), 150.7 (C), 143.5 (C), 134.7 (C), 133.5 (CH), 129.9 (CH), 127.4 (C), 125.5 (CH), 124.0 (CH), 123.2 (CH), 115.9 (CH), 115.6 (CH), 81.0 (C), 53.1 (CH ₃), 52.6 (2 x CH), 38.2 (CH ₂), 33.1 (CH ₂), 28.2 (3 x CH ₃).
LRMS	m/z (ES+) 479 ([M+Na] ⁺ , 100), 936 ([2M+Na] ⁺ , 18).
HRMS	m/z (ES+) Found [M+Na] ⁺ 479.1787. Required 479.1789.
$[\alpha]_{\text{D}}$	+ 20.3 (c = 0.4, CHCl ₃).

Reduced-**1.120**:

FT-IR (v/cm^{-1}) 2975 (m), 2930 (w), 2359 (w), 1735 (s), 1683 (m), 1506 (m), 1372 (m), 1235 (s), 1161 (m), 1044 (s).

^1H NMR δ_{H} (400 MHz, CDCl_3): 7.45 (1 H, dd, $J=8.5, 2.0$ Hz, ArH), 7.23 - 7.14 (2 H, m, 2 x ArH), 7.11 (1 H, dd, $J=8.3, 1.8$ Hz, ArH), 7.03 (1 H, dd, $J=8.5, 2.5$ Hz, ArH), 6.87 (1 H, dd, $J=8.5, 2.5$ Hz, ArH), 6.64 (1 H, d, $J=7.0$ Hz, ArH), 6.60 - 6.50 (1 H, m, NH), 5.02 (1 H, ddd, $J=12.0, 10.5, 5.0$ Hz, CH), 4.83 (1H, s, ArH), 4.45 (1 H, app. br. t, $J=7.0, 7.0$ Hz, NH), 4.16 - 4.00 (1 H, m, CH), 3.80 (3 H, s, CH_3), 3.58 (1 H, dd, $J=13.3, 5.3$ Hz, CHH), 2.73 - 2.57 (3 H, m, 2 x CHH and CHH), 1.45 (9 H, s, 3 x CH_3).

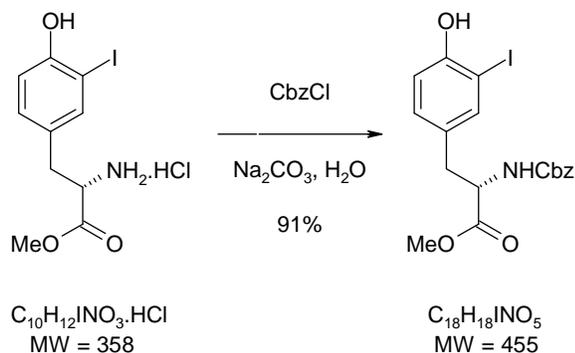
^{13}C NMR δ_{C} (100 MHz, CDCl_3): 171.7 (C), 171.0 (C), 163.6 (C), 157.8 (C), 155.9 (C), 136.9 (C), 134.3 (C), 133.3 (CH), 130.2 (CH), 129.7 (CH), 125.5 (CH), 123.3 (CH), 115.1 (2 x CH), 114.9 (CH), 81.0 (C), 53.1 (CH_3), 52.6 (CH), 52.4 (CH), 38.3 (CH_2), 33.5 (CH_2), 28.2 (3 x CH_3).

LRMS m/z (ES+) 463 ($[\text{M}+\text{Na}]^+$, 100), 904 ($[\text{2M}+\text{Na}]^+$, 99).

HRMS m/z (ES+) Found $[\text{M}+\text{Na}]^+$ 463.1835. Required 463.1840.

$[\alpha]_{\text{D}}$ + 8.6 ($c = 1.0, \text{CHCl}_3$).

(S)-2-Benzoyloxycarbonylamino-3-(3-iodo-4-hydroxy-phenyl)-propionic acid methyl ester **2.122**



Prepared following the procedure of Ortar *et al.*⁸⁹

To a stirred solution of 2-amino-3-(3-iodo-4-hydroxy-phenyl)-propionic acid methyl ester **2.41** (6.30 g, 19.6 mmol) and Na_2CO_3 (6.24 g, 58.9 mmol) in water (100 mL) and ether (80 mL) at 0 °C was added $CbzCl$ (2.80 mL, 19.6 mmol). The reaction was stirred at 0 °C for 3 h, then allowed to warm to RT. After 12 h the aqueous phase was separated, adjusted to pH 2 with conc. HCl, then extracted with ethyl acetate (4 x 50 mL). The organic extracts were combined and washed with brine (50 mL), then dried ($MgSO_4$). Concentration *in vacuo* afforded the product **2.122** as a colourless oil (8.12 g, 17.8 mmol, 91%).

FT-IR (v/cm^{-1}) 3334 (br), 3024 (w), 2949 (w), 1694 (s), 1505 (m), 1437 (w), 1345 (m), 1254 (m), 1212 (s), 1178 (m), 1057 (m), 1018 (m), 748 (s), 696 (m).

1H NMR δ_H (300 MHz, $CDCl_3$): 7.44 (2 H, br. s, 2 x ArH), 7.42 - 7.28 (6 H, m, 6 x ArH), 5.82 (1 H, br. s, OH), 5.38 (1 H, br. d, $J=8.1$ Hz, NH), 5.15 (1 H, d, $J=12.4$ Hz, OCHHAr), 5.09 (1 H, d, $J=12.4$ Hz, OCHH), 4.59 (1 H, app. q, $J=6.2$ Hz, CHNH), 3.74 (3 H, s, OCH_3), 3.14 - 2.81 (2 H, m, CHCHH).

^{13}C NMR δ_C (75 MHz, $CDCl_3$): 171.5 (C), 155.5 (C), 152.8 (C), 139.8 (CH), 136.0 (C), 131.8 (C), 130.3 (CH), 128.5 (2 x CH), 128.2

(CH), 128.0 (2 x CH), 115.5 (CH), 82.3 (Cl), 67.1 (OCH₂),
54.8 (CH), 52.4 (OCH₃), 36.3 (CH₂CH).

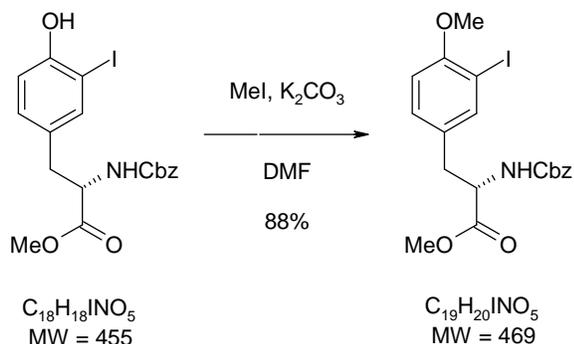
LRMS m/z (ES+) 478 ([M+H]⁺, 100), 933 ([2M+Na]⁺, 22).

HRMS m/z (ES+) Found [M+Na]⁺ 478.0125. Required 478.0122.

[α]_D + 54.7 (c = 1.0, CHCl₃).

The data are consistent with the literature.⁸⁹

(S)-2-Benzoyloxycarbonylamino-3-(3-iodo-4-methoxy-phenyl)-propionic acid methyl ester **2.123**



Prepared following the procedure of Hunter *et al.*⁹⁰

To a stirred solution of (S)-2-benzoyloxycarbonylamino-3-(3-iodo-4-hydroxy-phenyl)-propionic acid methyl ester **2.122** (2.41 g, 5.31 mmol) and K_2CO_3 (0.73 g, 5.31 mmol) in DMF (50 mL) at 0 °C was added MeI (0.33 mL, 5.31 mmol). The reaction was stirred at 0 °C for 3 h, then allowed to warm to RT. After 5 h water (30 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 50 mL), the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL), then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 1% MeOH/DCM) afforded **2.123** as a colourless oil (2.20 g, 4.69 mmol, 88%).

FT-IR (v/cm^{-1}) 3009 (w), 2979 (w), 2926 (w), 1712 (s), 1490 (m), 1253 (m), 1151 (m), 1049 (m), 1019 (w), 748 (s).

1H NMR δ_H (400 MHz, $CDCl_3$): 7.53 (1 H, d, $J=2.0$ Hz, ArH), 7.41 - 7.29 (5 H, m, 5 x ArH), 7.05 (1 H, dd, $J=8.5, 2.0$ Hz, ArH), 6.72 (1 H, d, $J=8.5$ Hz, ArH), 5.29 - 5.18 (1 H, m, NH), 5.14 (1 H, d, $J=12.0$ Hz, CHH), 5.09 (1 H, d, $J=12.0$ Hz, CHH), 4.62 (1 H, dd, $J=13.1, 6.0$ Hz, CH), 3.86 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 3.06 (1 H, d, $J=13.6, 5.5$ Hz, CHH), 2.99 (1 H, d, $J=14.1, 6.0$ Hz, CHH).

^{13}C NMR δ_C (100 MHz, $CDCl_3$): 171.7 (C), 157.3 (C), 155.5 (C), 140.2 (CH), 136.2 (C), 130.3 (CH), 129.8 (C), 128.6 (2 x CH), 128.2

(CH), 128.1 (2 x CH), 110.8 (CH), 86.0 (Cl), 67.0 (CH₂), 56.3 (CH₃), 54.8 (CH), 52.4 (CH₃), 36.9 (CH₂).

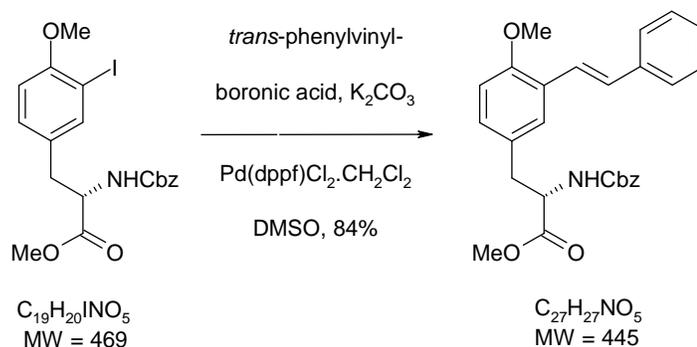
LRMS m/z (ES+) 492 ([M+H]⁺, 100), 961 ([2M+Na]⁺, 51).

HRMS m/z (ES+) Found [M+Na]⁺ 492.0280. Required 492.0278.

[α]_D + 7.2 (c = 1.4, CHCl₃).

The data are consistent with the literature.⁹⁰

(S)-2-Benzoyloxycarbonylamino-3-[4-methoxy-3-((E)-styryl)-phenyl]-propionic acid methyl ester **2.124**



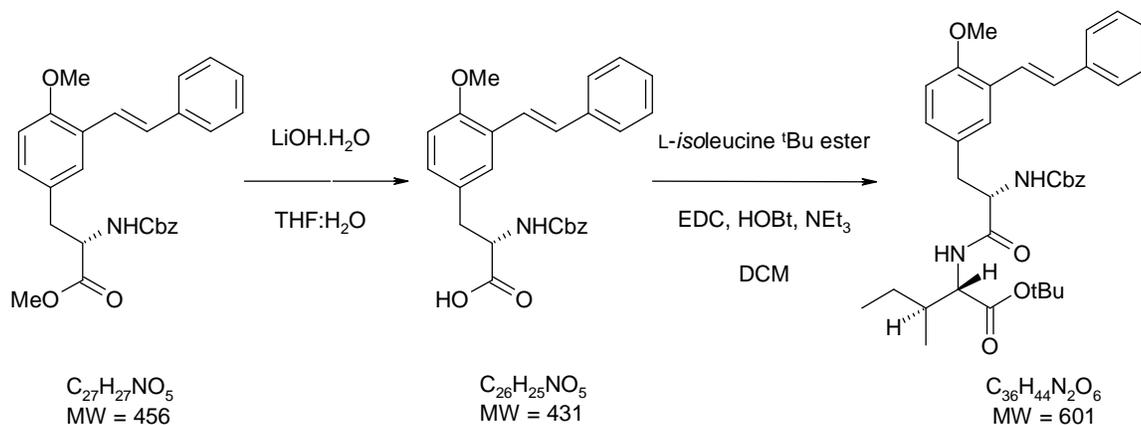
To a stirred solution of (*S*)-2-benzoyloxycarbonylamino-3-(3-iodo-4-methoxy-phenyl)-propionic acid methyl ester **2.123** (2.20 g, 4.69 mmol), *trans*-phenylvinyl boronic acid (0.76 g, 5.15 mmol) and K₂CO₃ (2.59 g, 18.74 mmol) in DMSO (55 mL) was added Pd(dppf)Cl₂·CH₂Cl₂ (153 mg, 0.19 mmol). The reaction was heated at 80 °C for 16 h then cooled to RT and quenched with water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the organic extracts were combined, washed with water (5 x 50 mL) and brine (50 mL), then dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 30% ethyl acetate/petroleum ether) afforded **2.124** as a beige solid (1.75 g, 3.93 mmol, 84%).

FT-IR (v/cm⁻¹) 3323 (w), 3299 (w), 3028 (w), 1949 (m), 1735 (s), 1689 (s), 1532 (m), 1463 (m), 1433 (m), 1258 (s), 1214 (m), 1050 (m), 996 (m), 959 (m), 740 (m), 691 (s).

¹H NMR δ_H (400 MHz, CDCl₃): 7.56 - 7.40 (4 H, m, 4 x ArH), 7.39 - 7.19 (9 H, m, 7 x ArH and CH=CH and CH=CH), 7.11 - 6.98 (2 H, m, 2 x ArH), 5.29 (1 H, br. app. t, *J*=6.3, 6.3 Hz, NH), 5.11 (1 H, br. d, *J*=12.5 Hz, CHH), 5.06 (1 H, br. d, *J*=12.0 Hz, CHH), 4.74 - 4.58 (1 H, m, CH), 3.75 (3 H, s, CH₃), 3.72 (3 H, s, CH₃), 3.18 - 2.90 (2 H, m, CH₂).

^{13}C NMR	<p>δ_{C} (100 MHz, CDCl_3): 172.0 (C), 156.4 (C), 154.9 (C), 140.5 (C), 138.9 (C), 131.7 (CH), 131.3 (C), 130.2 (CH), 128.7 (2 x CH), 128.5 (2 x CH), 128.2 (CH), 128.0 (2 x CH), 127.8 (CH), 127.6 (CH), 126.7 (CH), 126.6 (2 x CH), 126.3 (C), 122.8 (CH), 67.1 (CH_2), 62.0 (CH), 54.9 (CH_3), 52.4 (CH_3), 38.0 (CH_2).</p> <p>NMR shows a mixture of rotomers, the major rotomer is reported.</p>
LRMS	m/z (ES+) 468 ($[\text{M}+\text{Na}]^+$, 100), 914 ($[\text{2M}+\text{Na}]^+$, 44).
HRMS	m/z (ES+) Found $[\text{M}+\text{Na}]^+$ 468.1774. Required 468.1781.
$[\alpha]_{\text{D}}$	+ 12.8 (c = 1.7, CHCl_3).

(2*S*,3*S*)-2-{2-Benzyloxycarbonylamino-3-[4-methoxy-3-((*E*)-styryl)-phenyl]-propionylamino}-3-methyl-pentanoic acid *tert*-butyl ester **2.126**

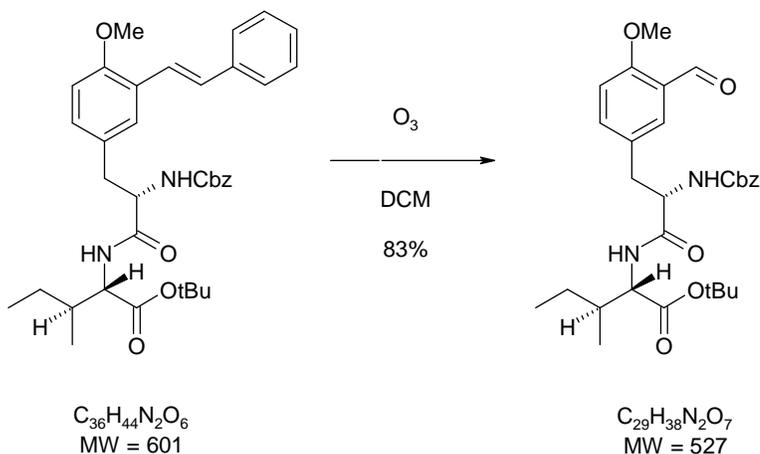


To a stirred solution of (*S*)-2-benzyloxycarbonylamino-3-[4-methoxy-3-((*E*)-styryl)-phenyl]-propionic acid methyl ester **2.124** (679 mg, 1.52 mmol) in $THF:H_2O$ (40 mL:40 mL) was added $LiOH \cdot H_2O$ (160 mg, 3.81 mmol). After 16 h sat. NH_4Cl (50 mL) was added. The aqueous phase was extracted with ethyl acetate (4 x 20 mL) and the organic extracts were combined and dried ($MgSO_4$). Concentration *in vacuo* afforded the crude **2.125** as a beige solid (622 mg, 1.44 mmol). To a stirred solution of crude (*S*)-2-benzyloxycarbonylamino-3-[4-methoxy-3-((*E*)-styryl)-phenyl]-propionic acid **2.125** (1.69 g, 3.93 mmol) in DCM (60 mL) was added L-isoleucine *tert*-butyl ester (0.81 g, 4.32 mmol), EDC (0.76 mL, 4.32 mmol), $HOBT$ (0.58 g, 4.32 mmol) and NEt_3 (2.74 mL, 19.65 mmol). The reaction was stirred at RT for 16 h then quenched with sat. NH_4Cl (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the organic extracts were combined, washed with brine (50 mL), then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 30% ethyl acetate/petroleum ether) afforded **2.126** as a colourless oil (2.24 g, 3.73 mmol, 90% over two steps).

FT-IR (ν/cm^{-1}) 3306 (m), 2965 (w), 2935 (w), 1731 (m), 1655 (s), 1538 (m), 1499 (m), 1456 (w), 1367 (w), 1246 (s), 1144 (m), 1028 (m), 755 (m), 694 (w).

¹H NMR	<p>δ_{H} (300 MHz, CDCl₃): 7.53 (2 H, d, $J=7.0$ Hz, 2 x ArH), 7.47 - 7.41 (2 H, m, 2 x ArH), 7.38 (1 H, d, $J=4.8$ Hz, ArH), 7.36 - 7.29 (7 H, m, 6 x ArH and CH=CH), 7.09 (1 H, d, $J=16.5$ Hz, CH=CH), 7.08 (1 H, m, ArH), 6.81 (1 H, d, $J=8.4$ Hz, ArH), 6.36 (1 H, d, $J=8.1$ Hz, NH), 5.35 (1 H, d, $J=6.2$ Hz, NH), 5.12 (2 H, s, OCH₂Ar), 4.46 (1 H, app. q, $J=5.9$ Hz, CHNH), 4.41 (1 H, dd, $J=8.1, 4.4$ Hz, CHNH), 3.86 (3 H, s, OCH₃), 3.13 (1 H, dd, $J=13.5, 6.2$ Hz, CHH), 3.03 (1 H, dd, $J=13.9, 7.0$ Hz, CHH), 1.89 - 1.74 (1 H, m, CH(CH₃)CH₂CH₃), 1.43 (9 H, s, 3 x CH₃), 1.40 - 1.31 (1 H, m, CHHCH₃), 1.17 - 1.00 (1 H, m, CHHCH₃), 0.89 (3 H, t, $J=7.0$ Hz, CH₂CH₃), 0.80 (3 H, d, $J=6.6$ Hz, CHCH₃).</p>
¹³C NMR	<p>δ_{C} (75 MHz, CDCl₃): 170.3 (C), 170.2 (C), 156.0 (C), 155.9 (C), 137.8 (C), 136.1 (C), 129.4 (CH and C), 128.5 (3 x CH), 128.1 (2 x CH), 128.0 (3 x CH), 127.3 (2 x CH and C), 126.6 (2 x CH), 123.1 (CH), 111.2 (CH), 82.1 (C), 67.0 (CH₂), 56.8 (CH), 56.3 (CH), 55.5 (CH₃), 38.1 (CH₂), 37.7 (CH), 28.0 (3 x CH₃), 25.4 (CH₂), 15.1 (CH₃), 11.7 (CH₃).</p>
LRMS	<p>m/z (ES+) 624 ([M+H]⁺, 100).</p>
HRMS	<p>m/z (ES+) Found [M+Na]⁺ 623.3078. Required 623.3092.</p>
$[\alpha]_{\text{D}}$	<p>+ 24.5 (c = 2.0, CHCl₃).</p>

(2*S*,3*S*)-2-[(*S*)-2-*tert*-Benzyloxycarbonylamino-3-(3-formyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.127**



A stirred solution of (2*S*,3*S*)-2-{2-benzyloxycarbonylamino-3-[4-methoxy-3-((*E*)-styryl)-phenyl]-propionylamino}-3-methyl-pentanoic acid *tert*-butyl ester **2.126** (1.74 g, 2.90 mmol) and sudan red (10 mg) in DCM (100 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and O_3 (1–4% in O_2) was bubbled through until the red colour disappeared. O_2 was then bubbled through for 20 min before PPh_3 (1.52 g, 5.79 mmol) was added. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min and then allowed to warm to RT. Concentration *in vacuo* and purification by column chromatography (SiO_2 , 30% ethyl acetate/petroleum ether) afforded **2.127** as a yellow oil (1.22 g, 2.32 mmol, 83%).

FT-IR (v/cm^{-1}) 3306 (m), 3009 (w), 2968 (m), 2926 (w), 2869 (w), 1728 (m), 1681 (s), 1655 (s), 1611 (w), 1534 (m), 1496 (s), 1456 (w), 1393 (w), 1368 (w), 1287 (w), 1252 (s), 1218 (m), 1141 (s), 1026 (m), 751 (s).

^1H NMR δ_{H} (300 MHz, CDCl_3): 10.39 (1 H, s, CHO), 7.63 (1 H, d, $J=2.2$ Hz, ArH), 7.43 - 7.28 (6 H, m, 6 x ArH), 6.87 (1 H, d, $J=8.4$ Hz, ArH), 6.50 (1 H, d, $J=7.3$ Hz, NH), 5.46 (1 H, d, $J=8.4$ Hz, NH), 5.07 (2 H, s, OCH_2), 4.51 - 4.44 (1 H, m, CHNH), 4.41 (1 H, dd, $J=8.4, 4.4$ Hz, CHNH), 3.88 (3 H, s, OCH_3), 3.09 (1 H,

dd, $J=14.3, 6.6$ Hz, CHH), 3.00 (1 H, dd, $J=13.5, 6.6$ Hz, CHH), 1.93 - 1.71 (1 H, m, CH(CH₃)CH₂CH₃), 1.44 (9 H, s, 3 x CH₃), 1.41 - 1.31 (1 H, m, CHHCH₃), 1.20 - 1.03 (1 H, m, CHHCH₃), 0.90 (3 H, t, $J=7.3$ Hz, CH₂CH₃), 0.82 (3 H, d, $J=7.0$ Hz, CHCH₃).

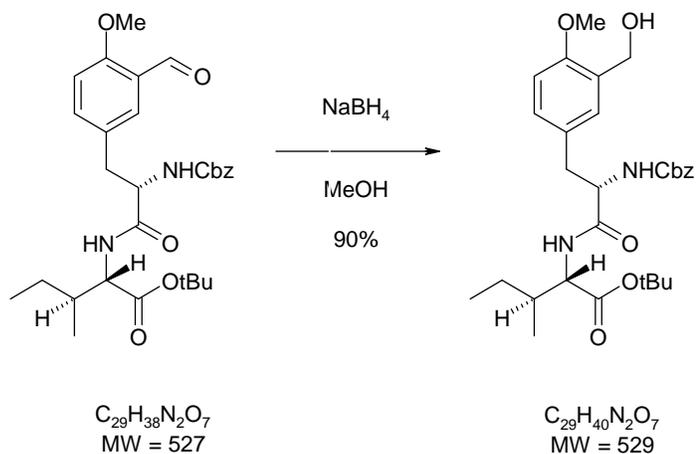
¹³C NMR δ_C (75 MHz, CDCl₃): 189.4 (CHO), 170.3 (C), 170.1 (C), 160.8 (C), 155.8 (C), 136.7 (CH), 136.1 (C), 129.3 (CH), 128.7 (C), 128.4 (2 x CH), 128.1 (CH), 128.0 (2 x CH), 124.6 (CCHO), 112.0 (CH), 82.1 (C), 67.0 (OCH₂), 56.8 (CHNH), 55.9 (CHNH), 55.6 (OCH₃), 38.1 (CH(CH₃)CH₂CH₃), 37.4 (CH₂), 28.0 (3 x CH₃), 25.3 (CH₂CH₃), 15.2 (CHCH₃), 11.7 (CH₂CH₃).

LRMS m/z (ES+) 549 ([M + Na]⁺, 100), 1076 ([2M + Na]⁺, 54).

HRMS m/z (ES+) Found [M+Na]⁺ 549.2581. Required 549.2571.

[α]_D + 18.8 (c = 0.5, CHCl₃).

(2*S*,3*S*)-2-[(*S*)-2-Benzoyloxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.128**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-*tert*-benzyloxycarbonylamino-3-(3-formyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.127** (275 mg, 0.52 mmol) in MeOH (9 mL) at 0 °C was added NaBH₄ (24 mg, 0.63 mmol). The reaction was stirred at 0 °C for 2 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), then the organic extracts were combined, washed with brine (10 mL), and dried (MgSO₄). Concentration *in vacuo* and purification by column chromatography (SiO₂, 50% ethyl acetate/petroleum ether) afforded **2.128** as a yellow oil (246 mg, 0.47 mmol, 90%).

FT-IR (v/cm⁻¹) 3305 (br), 2968, (m), 2934 (w), 2876 (w), 1728 (s), 1655 (s), 1540 (m), 1501 (s), 1456 (w), 1368 (w), 1249 (s), 1143 (s), 1041 (m), 753 (m).

¹H NMR δ_H (300 MHz, CDCl₃): 7.37 - 7.28 (5 H, m, 5 x ArH), 7.14 (1 H, s, ArH), 7.11 (1 H, d, *J*=9.5 Hz, ArH), 6.77 (1 H, d, *J*=8.1 Hz, ArH), 6.31 (1 H, d, *J*=8.4 Hz, NH), 5.45 (1 H, d, *J*=7.0 Hz, NH), 5.09 (2 H, s, OCH₂), 4.62 (2 H, s, CH₂OH), 4.47 - 4.41 (1 H, m, CHNH), 4.38 (1 H, dd, *J*=8.2, 4.6 Hz, CHNH), 3.82 (3 H, s, OCH₃), 3.14 - 2.92 (2 H, m, CHH), 2.56 (1 H, br. s, OH), 1.87 - 1.73 (1 H, m, CH(CH₃)CH₂CH₃), 1.45 (9 H, s, 3 x CH₃),

1.41 - 1.30 (1 H, m, CHHCH₃), 1.18 - 1.01 (1 H, m, CHHCH₃), 0.89 (3 H, t, *J*=7.3 Hz, CH₂CH₃), 0.81 (3 H, d, *J*=7.0 Hz, CHCH₃).

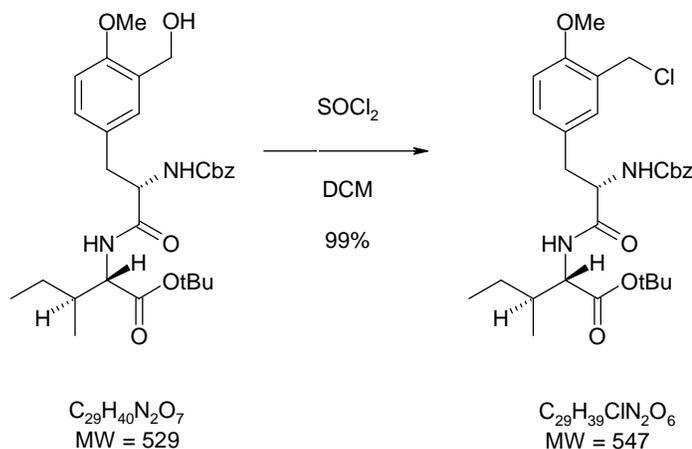
¹³C NMR δ_C (75 MHz, CDCl₃): 170.4 (2 x C), 156.3 (C), 155.8 (C), 136.2 (C), 129.6 (CH), 129.5 (CH), 129.4 (C), 128.5 (2 x CH), 128.2 (C), 128.1 (CH), 128.0 (2 x CH), 110.3 (CH), 82.1 (C), 66.9 (OCH₂Ar), 61.6 (CH₂OH), 56.8 (CHNH), 56.3 (CHNH), 55.3 (OCH₃), 38.0 (CH(CH₃)CH₂CH₃), 37.7 (CH₂), 28.0 (3 x CH₃), 25.3 (CH₂CH₃), 15.2 (CHCH₃), 11.7 (CH₂CH₃).

LRMS ^{m/z} (ES+) 552 ([M + Na]⁺, 100), 1080 ([2M + Na]⁺, 51).

HRMS ^{m/z} (ES+) Found [M+Na]⁺ 551.2728. Required 551.2728.

[α]_D + 20.2 (c = 0.5, CHCl₃).

(2*S*,3*S*)-2-[2-Benzyloxycarbonylamino-3-(3-chloromethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.129**



To a stirred solution of (2*S*,3*S*)-2-[(*S*)-2-benzyloxycarbonylamino-3-(3-hydroxymethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.128** (245 mg, 0.46 mmol) in DCM (5 mL) at 0 °C was added SOCl₂ (55 mg, 0.46 mmol). The reaction was stirred at 0 °C for 2 h then quenched with water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), and the organic extracts were combined, washed with brine (10 mL), then dried (MgSO₄). Concentration *in vacuo* afforded **2.129** as a yellow oil (249 mg, 0.46 mmol, 99%).

FT-IR (ν/cm⁻¹) 3293 (w), 2967 (m), 2922 (w), 1733 (m), 1700 (m), 1653 (s), 1540 (m), 1503 (m), 1456 (w), 1367 (w), 1257 (s), 1217 (m), 1140 (s), 1028 (m), 751 (s).

¹H NMR δ_H (300 MHz, CDCl₃): 7.37 - 7.29 (5 H, m, 5 x ArH), 7.18 (1 H, d, *J*=1.8 Hz, ArH), 7.12 (1 H, dd, *J*=8.4, 1.8 Hz, ArH), 6.78 (1 H, d, *J*=8.4 Hz, ArH), 6.39 (1 H, d, *J*=8.1 Hz, NH), 5.38 (1 H, d, *J*=7.0 Hz, NH), 5.10 (2 H, s, CH₂Ar), 4.58 (2 H, s, CH₂Cl), 4.49 - 4.41 (1 H, m, CHNH), 4.40 (1 H, dd, *J*=8.4, 4.4 Hz, CHNH), 3.84 (3 H, s, OCH₃), 3.03 (2 H, d, *J*=6.2 Hz, CHH), 1.93 - 1.72 (1 H, m, CH(CH₃)CH₂CH₃), 1.44 (9 H, s, 3 x CH₃), 1.41 - 1.30 (1 H, m, CHHCH₃), 1.21 - 1.02 (1 H, m, CHHCH₃).

0.90 (3 H, t, $J=7.3$ Hz, CH_2CH_3), 0.82 (3 H, d, $J=7.0$ Hz, CHCH_3).

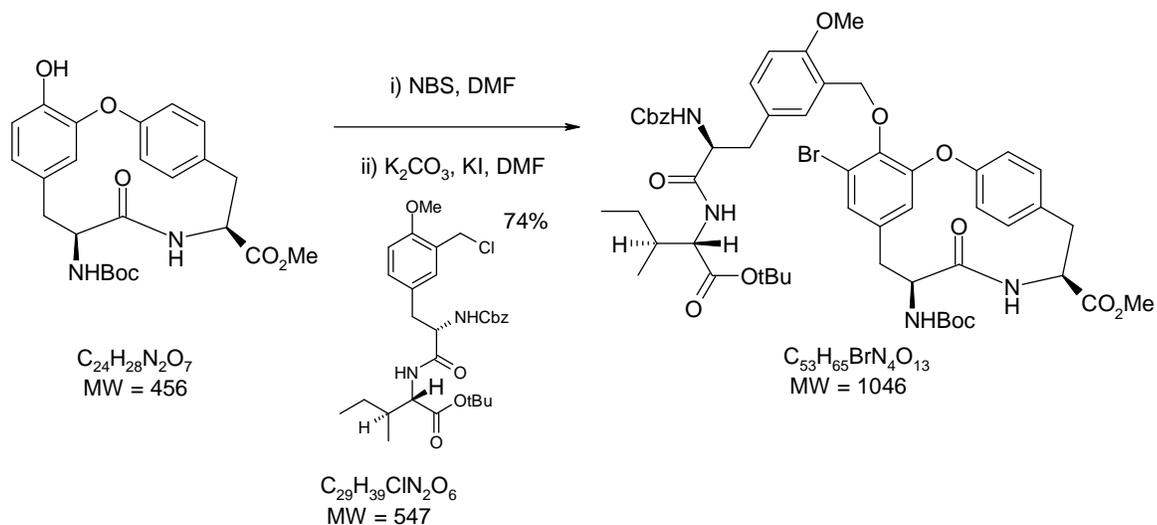
^{13}C NMR δ_{C} (75 MHz, CDCl_3): 170.2 (2 x C), 156.3 (C), 155.8 (C), 136.2 (C), 131.5 (CH), 130.8 (CH), 128.5 (2 x CH), 128.3 (C), 128.1 (CH), 128.0 (2 x CH), 125.9 (C), 110.9 (CH), 82.1 (C), 67.0 (OCH_2), 56.8 (CHNH), 56.1 (CHNH), 55.5 (OCH_3), 41.3 (CH_2Cl), 38.0 (CH), 37.4 (CH_2), 28.0 (3 x CH_3), 25.3 (CH_2CH_3), 15.2 (CHCH_3), 11.7 (CH_2CH_3).

LRMS m/z (ES+) 569 ($[\text{M} + \text{Na}]^+$, 100), 1116 ($[\text{2M} + \text{Na}]^+$, 38).

HRMS m/z (ES+) Found $[\text{M} + \text{Na}]^+$ 569.2389. Required 569.2389.

$[\alpha]_{\text{D}}$ + 25.1 ($c = 1.2$, CHCl_3).

2-Methoxy-5-(2-benzyloxycarbonylamino-3-oxo-4-aza-5-carbo-*tert*-butoxy-6-methyl-octanyl)-benzyl 9-*tert*-butoxycarbonylamino-10-oxo-2-oxa-11-aza-12-carbomethoxy--tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-4-yl ether **2.130**



To a stirred solution of (9*S*,12*S*)-9-*tert*-butoxycarbonylamino-4-hydroxy-10-oxo-2-oxa-11-aza-tricyclo[12.2.2.1^{3,7}]nonadeca-1(17),3,5,7(19),14(18),15-hexaene-12-carboxylic acid methyl ester **2.119** (20 mg, 0.04 mmol) in DMF (1 mL) was added NBS (9 mg, 0.05 mmol). The reaction was stirred at RT for 16 h then (2*S*,3*S*)-2-[2-benzyloxycarbonylamino-3-(3-chloromethyl-4-methoxy-phenyl)-propionylamino]-3-methyl-pentanoic acid *tert*-butyl ester **2.129** (48 mg, 0.09 mmol), K_2CO_3 (9 mg, 0.07 mmol) and KI (2 mg, 0.01 mmol) were added. The reaction was heated at 50 °C for 16 h then quenched with water (2 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL), and the organic extracts were combined, washed with brine (10 mL), then dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (SiO_2 , 40% ethyl acetate/petroleum ether) afforded **2.130** as a yellow oil (34 mg, 0.03 mmol, 74%).

FT-IR (ν/cm^{-1}) 3015 (m), 2970 (m), 1737 (s), 1504 (m), 1456 (w), 1366 (m), 1228 (m), 1217 (m), 1169 (m), 1028 (w).

¹H NMR δ_{H} (300 MHz, CDCl₃): 7.41 (1 H, d, $J=8.4$ Hz, ArH), 7.38 - 7.30 (6 H, m, 6 x ArH), 7.13 (1 H, d, $J=7.3$ Hz, ArH), 7.08 (2 H, dd, $J=8.2, 2.4$ Hz, 2 x ArH), 6.86 - 6.69 (3 H, m, 3 x ArH), 6.59 (1 H, br. s, NH), 6.50 (1 H, d, $J=8.4$ Hz, NH), 5.38 (1 H, d, $J=5.1$ Hz, ArH), 5.32 (1 H, d, $J=11.7$ Hz, ArCHHO), 5.22 (1 H, d, $J=11.7$ Hz, ArCHHO), 5.15 - 5.07 (2 H, m, ArCHHO), 5.06 - 4.91 (1 H, m, NH), 4.47 - 4.35 (3 H, m, 2 x CHNH and NH), 4.27 (1 H, d, $J=6.6$ Hz, CHNH), 4.12 (1 H, d, $J=6.2$ Hz, CHNH), 3.81 (6 H, s, 2 x OCH₃), 3.65 - 3.42 (2 H, m, CHH), 3.17 - 2.99 (2 H, m, CHH), 2.67 - 2.44 (2 H, m, CHH), 1.89 - 1.72 (1 H, m, CH(CH₃)₃), 1.46 (9 H, s, 3 x CH₃), 1.44 (9 H, s, 3 x CH₃), 1.38 - 1.28 (1 H, m, CHHCH₃), 1.19 - 1.01 (1 H, m, CHHCH₃), 0.89 (3 H, t, $J=7.3$ Hz, CH₂CH₃), 0.82 (3 H, d, $J=6.6$ Hz, CHCH₃).

¹³C NMR δ_{C} (75 MHz, CDCl₃): 171.5 (C), 170.9 (C), 170.4 (C), 170.3 (C), 157.6 (C), 157.1 (C), 156.5 (C), 155.8 (C), 143.4 (2 x C), 136.2 (C), 134.5 (C), 133.4 (CH), 132.1 (C), 130.9 (CH), 130.1 (2 x CH and C), 128.5 (2 x CH), 128.1 (2 x CH), 127.1 (CH), 125.6 (C), 125.2 (CH), 123.0 (2 x CH), 118.1 (CH and CBr), 110.4 (CH), 81.9 (2 x C), 70.1 (CH₂), 67.0 (CH₂), 56.8 (OCH₃), 55.5 (2 x CHNH), 53.1 (2 x CHNH), 52.6 (OCH₃), 38.4 (2 x CH₂), 38.1 (CH), 37.4 (CH₂), 28.2 (3 x CH₃), 28.0 (3 x CH₃), 25.3 (CH₂), 15.2 (CH₃), 11.7 (CH₃).

LRMS m/z (ES+) 1068 ([M (⁷⁹Br)+Na]⁺, 80), 1070 ([M (⁸¹Br)+Na]⁺, 100).

$[\alpha]_{\text{D}}$ + 64.6 (c = 0.5, CHCl₃).

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