UNIVERSITY OF SOUTHAMPTON

Faculty of Natural and Environmental Sciences

School of Chemistry

Towards the Total Synthesis of RP 66453: A Neurotensin Antagonist with a Twist

by

David James Skinner

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ABSTRACT

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

SCHOOL OF CHEMISTRY

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TOWARDS THE TOTAL SYNTHESIS OF RP 66453: A NEUROTENSIN ANTAGONIST WITH A TWIST

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This thesis describes the efforts made towards the total synthesis of RP 66453, a highly strained macrocyclic tetrapeptide. RP 66453 provides an interesting synthetic challenge, not only due to its potential biological activity but also owing to its unusual chemical architecture. The strained bicyclic ring system features a 15-membered macrocycle containing an aryl-aryl bond and a 14-membered *meta,para*-cyclophane

Herein, several strategies towards the model A-B macrocycle of RP 66453 are presented featuring as a key step, a radical induced transannular ring contraction of a benzyl haloaryl ether and a photochemical transannular cyclisation of *cis*-stilbene derivatives. Synthetic efforts towards the B-*O*-C macrocycle are also presented, including copper-mediated and intramolecular S_NAr cyclisation strategies. Finally, research into the union of these two fragments is presented followed by a discussion of a proposed end-game strategy.

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DECLARATION OF AUTHORSHIP

I, David James Skinner

declare that the thesis entitled

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and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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Abbreviations

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Alloc	allyloxycarbonyl
Ar	aryl
atm	standard atmosphere
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bpy	2,2'-bipyridyl
BTEAC	benzyltriethylammonium chloride
Bu	butyl
Cbz	benzyloxycarbonyl
CDI	*N,N'*-carbonyldiimidizole
COSY	correlation spectroscopy
d	days
δ	chemical shift (ppm)
dba	dibenzylideneacetone
DBPO	dibenzoyl peroxide
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one
DEPT	distortionless enhancement by polarisation transfer
DFT	density functional theory
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-*N*,*N*-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DOPA	3,4-dihydroxyphenylalanine
DPPA	diphenyl phosphoryl azide
dppf	1,1'-bis(diphenylphosphino)-ferrocene
D^{t}BPF	1,1'-bis(di-*tert*-butylphosphino)-ferrocene
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
EI	electron impact
ESI$^+$	electrospray ionisation (positive mode)
ESI$^-$	electrospray ionisation (negative mode)
Et	ethyl
et al.	*et alia* (Latin: and others)
eq.	molar equivalent
FDPP	pentafluorophenyl-diphenylphosphinate
Fmoc	9-fluorenylmethyl
FT	Fourier transform
g	gram
Gly	glycine
h	hour
HATU	*N*,*N*,*N*',*N*'-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
Hpg	hydroxyphenylglycine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso

IC_{50}	half maximal inhibitory concentration
Ile	isoleucine
Im	imidazole
Inf.	inflection point (UV)
IR	infra-red
J	coupling constant
JohnPhos	(2-biphenyl)di-*tert*-butylphosphine
k	kilo
L	litre
LRMS	low resolution mass spectrometry
M	molar
m	milli
m	meta
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute
MOM	methoxymethyl
MP	melting point
MRSA	methicillin-resistant *Staphylococcus aureus*
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimde
NIS	*N*-iodosuccinimde
NMM	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	ortho
p	para
PEPPSI-Ipr	[1,3-bis(2,6-diisopropyl-phenyl)-imidazol-2-ylidene](3-chloro-pyridyl)palladium(II) dichloride
Ph	phenyl
Phe	phenylalanine
PMA	phosphomolybdic acid
ppm	parts per million
Pr	propyl
PTC	phase transfer catalysis
py	pyridine
PyBOP	(benzotriazol-1-yloxy)-tripyrrolidinophosphonium hexafluorophosphate
PyBrOP	bromotripyrrolidinophosphonium hexaflurophosphate
quant.	quantitative yield
rac	racemic
R_f	retardation factor
RT	room temperature
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
t	tertiary
tert	tertiary
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (trifyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Trp	tryptophan
Ts	*p*-toluenesulfonyl chloride (tosyl)
TTMSS	tris(trimethylsilyl)silane
TTN	thallium trinitrate
Tyr	tyrosine
UV	ultraviolet
VAZO	1,1-azobis(cyclo-hexanecarbonitrile)
viz.	*videlicet*
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1: Introduction

1.1 Isolation and Assignment

Neurotensin is an endogenous tridecapeptide that was first isolated in 1973 from the extracts of bovine hypothalami,[1] and has since been prepared synthetically using solid phase techniques.[2] Neurotensin has been shown to have physiological effects on both the central and peripheral nervous systems,[3] being closely involved in processes such as dopamine transmission, analgesia, and hypothermia. It is important therefore to have access to both agonists and antagonists of the neurotensin receptor with which to further study its biochemistry and physiology.

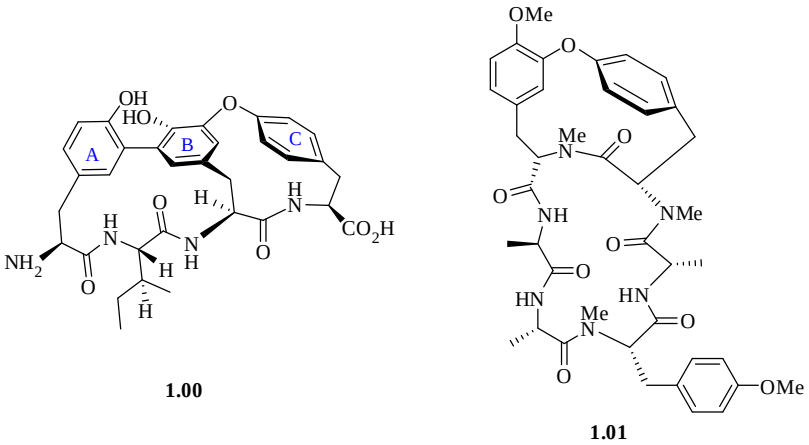
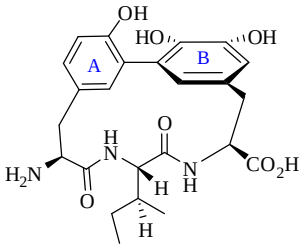


Figure 1.1: RP 66453 **1.00** and RA-VII **1.01**.

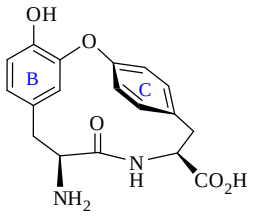
In 1998 RP 66453 **1.00** (Figure **1.1**), a newly identified secondary metabolite from an *Actinomycetes* strain was reported to bind very specifically to the neurotensin receptor from guinea-pig (IC_{50}, 30 μg/mL).[4] The isolation team of Helynck *et al.* were able to show that RP 66453 consisted of a highly strained bicyclic ring system, featuring a 15-membered macrocycle containing an aryl-aryl bond and a 14-membered *meta,para*-cyclophane including a biaryl ether. Interestingly, the peptide sequence of the cycloisodityrosine moiety found within RP 66453 **1.00** is reversed compared to the related RA series (e.g. RA-VII **1.01**).[5-7] The configuration of the biaryl linkage remained unknown for many years until it was revealed in some exquisite studies to be *aR*(*M*),*S*,*S*,*S*,*S*,*S* by the Zhu and Boger research teams.[8-12]

1.2 Nomenclature

To aid with the discussion, macrocycles are referred to by the labels attributed to the constituent arenes of the natural product and the associated linkage. Thus, for RP 66453, the A-B and B-*O*-C macrocycles are as shown in Figure **1.2**.



A-B macrocycle **1.02**



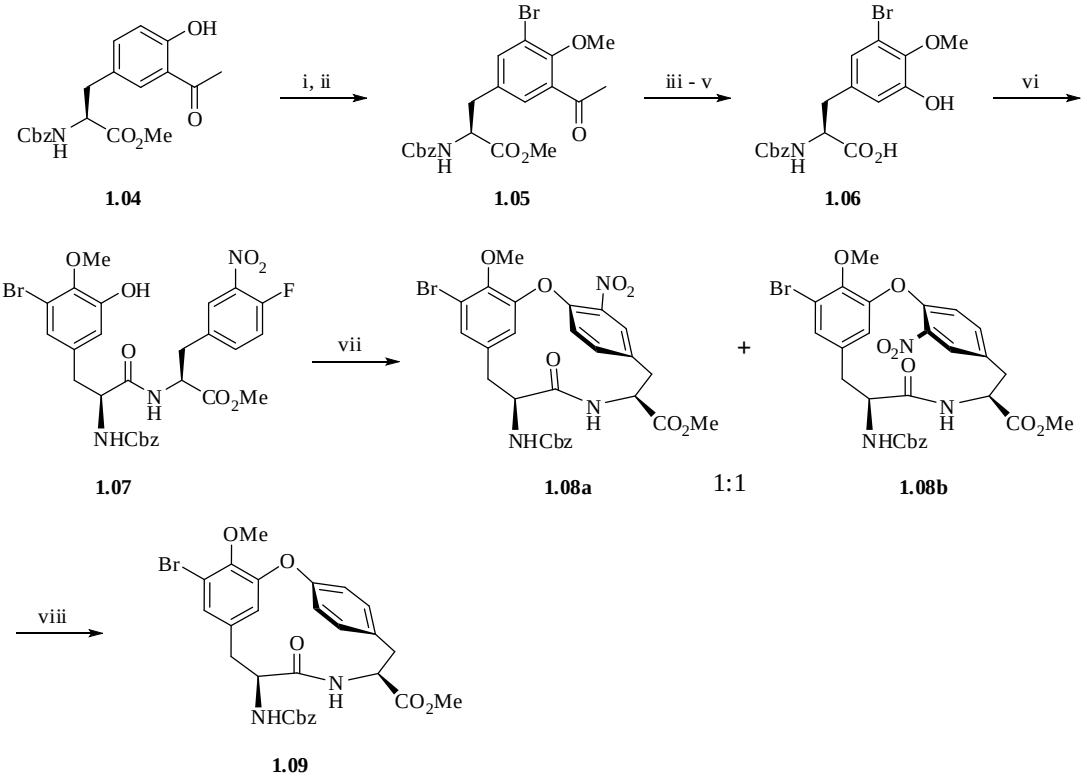
B-*O*-C macrocycle **1.03**

Figure 1.2: Nomenclature used to describe the RP 66453 fragments.

1.3 Previous Syntheses

1.3.1 Contributions from the Boger Group

In 2002 Boger *et al.* published the first synthesis of the 14-membered L,L-cycloisodityrosine subunit of RP 66453 (Scheme **1.1**). Tyrosine derivative **1.04** was readily prepared from L-tyrosine by a Friedel-Crafts acylation reaction, followed by esterification and protection of the free amine.[13] Bromination with NBS proceeded with excellent yield (99%) and regioselectivity, followed by protection of the free phenol as a *O*-methyl ether giving **1.05** in 94% yield.



Reagents & Conditions: i) NBS, MeCN, 18 h, RT, 99%; ii) K_2CO_3, MeI, DMF, 5 h, RT, 94%; iii) CF_3CO_3H, CH_2Cl_2, 2 d, reflux, 61%; iv) HCl, dioxane, 2 h, RT, 88%; v) LiOH, THF/H_2O, 90 min, 0 ^oC, 68%; vi) EDCI, HOAt, L-4-fluoro-3-nitrophenylalanine methyl ester, DMF, 18 h, RT, 85%; vii) K_2CO_3, DMSO, 18 h, RT, 58%; viii) Al-Hg, Et_2O/EtOH/H_2O, 1 h, RT; HBF_4, ^tBuONO, 10 min, 0 ^oC; H_3PO_2, 1 h, RT, 40%.

Scheme 1.1: Synthesis of the B-*O*-C macrocycle by the Boger research team.

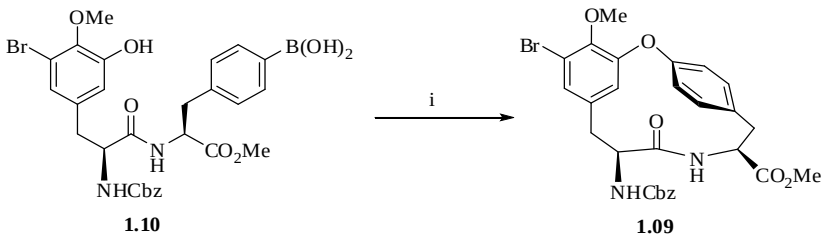
Baeyer-Villiger oxidation mediated by trifluoroperacetic acid followed by hydrolysis of the corresponding acetate and saponification of the methyl ester furnished the free-acid **1.06**. This was then coupled with L-4-fluoro-3-nitrophenylalanine methyl ester to give dipeptide **1.07** in 85% yield. Various conditions for the intramolecular nucleophilic aromatic substitution reaction (0.002 M) were tested, and the key findings are highlighted in Table **1.1**. The best yield resulted from using K_2CO_3 in DMSO. Reactions were slower in DMF, though comparable conversions could be realised using CsF in place of K_2CO_3.

Base	Solvent	Temp. (^{o}C)	Time (h)	Yield (%)
K_2CO_3	DMF	25	18	< 10
K_2CO_3	DMSO	25	18	58
K_2CO_3	DMSO	25	4	34
CsF	DMSO	25	18	51
CsF	DMF	0	6	33
CsF	DMSO	25	4	41

Table 1.1: Reaction conditions for the intramolecular S_NAr.

Macrocyclisation led to a 1:1 mixture of atropisomers **1.08a** and **1.08b** that were not separated. Removal of the nitro group was achieved in three steps by sequential reduction to the corresponding aniline using an aluminium amalgam, diazotisation with fluoroboric acid and *tert*-butyl nitrite and reduction in hypophosphorous acid. This gave **1.09** in 40% yield, with no observable epimerisation occurring during the S_NAr macrocyclisation reaction as confirmed by X-ray crystallography.

The Boger team were also able to show that formation of the B-*O*-C ring could be effected using an Ullmann-type macrocyclisation facilitated by $Cu(OAc)_2$ (Scheme **1.2**).[14] This approach was less satisfactory however, as it gave the desired macrocycle in 9% yield after five days! The majority of the mass balance was accounted for by a mixture of acyclic products derived from either oxidation or reduction of the boronic acid.

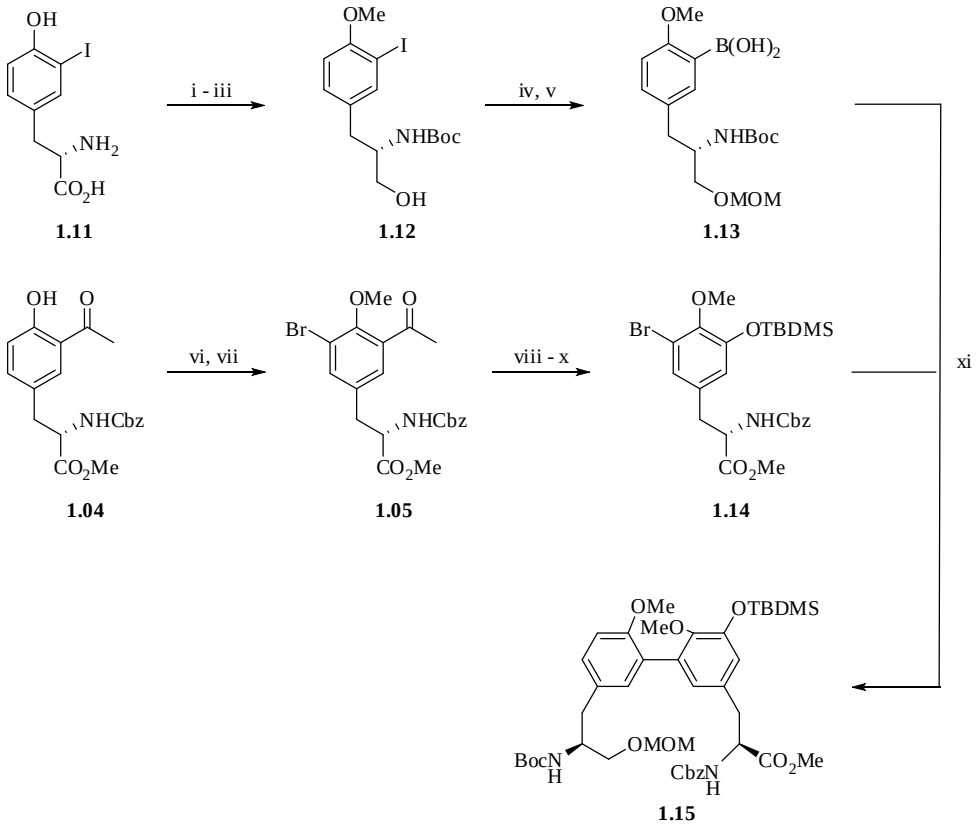


1.10 **1.09**

Reagents & Conditions: i) $Cu(OAc)_2$, py or collidine, CH_2Cl_2, 1 mM, 5 d, RT, 9%.

Scheme 1.2: Alternative route taken to the B-*O*-C macrocycle.

The Boger research group have also described a route to the A-B macrocycle of RP 66453 utilising a macrolactamisation reaction as the key step.[11] The forward synthesis is outlined in Schemes **1.3** and **1.4**.



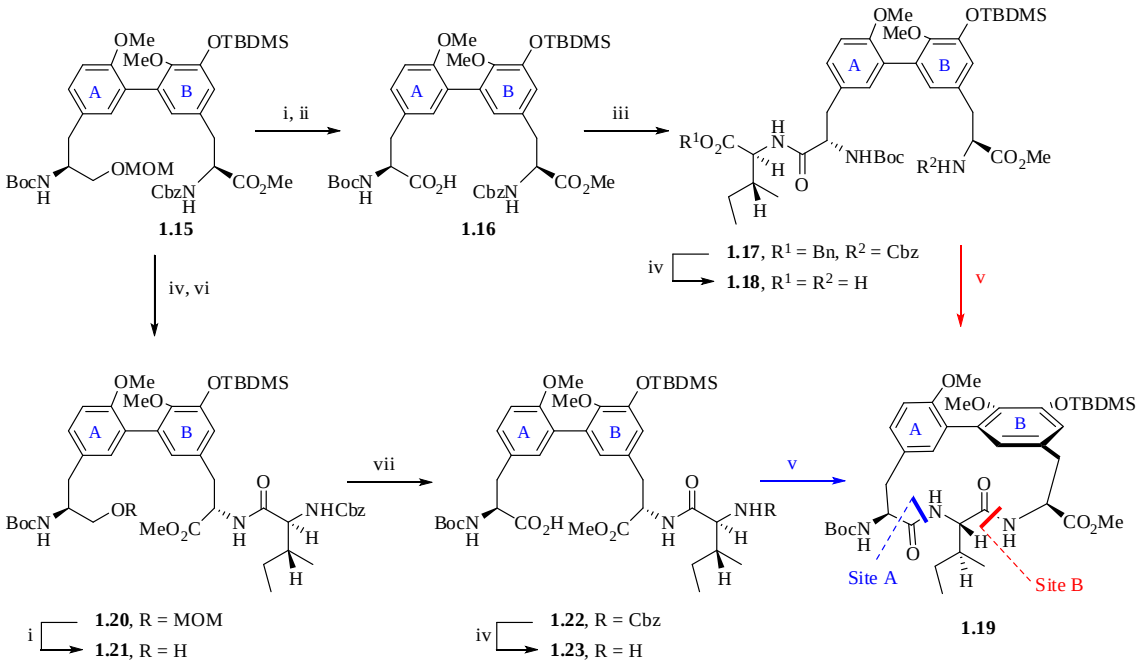
Reagents & Conditions: i) $(Boc)_2O$, $NaHCO_3$, dioxane/H_2O, 18 h, RT, 99%; ii) NaH, MeI, 5% DMF/THF, 3 d, RT, 78%; iii) EtOCOCl, $NaBH_4$, THF/MeOH, 20 min, 0 ^oC, 82%; iv) MOMCl, DIPEA, CH_2Cl_2, 8 h, RT, 92%; v) ^{i}PrMgCl, ^{t}BuLi, $(MeO)_3B$, THF, 1 h, –78 ^oC–RT, 99%; vi) NBS, MeCN, 18 h, RT, 99%; vii) K_2CO_3, MeI, DMF, 5 h, RT, 94%; viii) CF_3CO_3H, CH_2Cl_2, 2 d, reflux, 61%; ix) HCl, 1,4–dioxane, 2 h, RT, 97%; x) TBDMSOTf, lutidine, THF, 4 h, RT, 81%; xi) (*o*-tolyl)$_3$P, $Pd_2(dba)_3$, 1M Na_2CO_3, toluene/MeOH, 15 min, 85 ^oC, 95%.

Scheme 1.3: Forward synthesis of the A-B biaryl precursor for macrolactamisation studies.

Protection of the amine and phenol functionality of 3-iodo-L-tyrosine **1.11** as the ^{t}Bu-carbamate and methyl ether respectively, followed by reduction of the carboxylic acid gave alcohol **1.12**, which was protected as a MOM ether. Deprotonation of the carbamate followed by halogen-lithium exchange gave an aryllithium species that was quenched with trimethyl borate to give boronic acid **1.13** after an acidic work-up. Contemporaneously, regioselective bromination and phenol protection of 3-acetyl-L-

tyrosine derivative **1.04**, gave **1.05**. Baeyer-Villiger oxidation of the aryl ketone followed by hydrolysis of the corresponding acetate and protection of the phenol as a TBDMS ether afforded the aryl halide coupling partner **1.14** in good overall yield. A Suzuki-Miyaura coupling of **1.14** with boronic acid **1.13**, catalysed by $Pd_2(dba)_3$, afforded biaryl **1.15** in good yield (95%).

Two approaches for achieving macrocyclisation were explored (Scheme **1.4**) involving peptide coupling at either end of the isoleucine residue in the peptide backbone (Site A and Site B). After some functional group interconversion and installation of an isoleucine residue (*viz*. **1.15** → **1.18** and **1.15** → **1.23**), the team were able to show that both macrolactamisation strategies were highly effective, giving the A-B macrocycle **1.19** in good yield. Table **1.2** summarises a range of macrocyclisation conditions employed for closure at both the A and B sites.



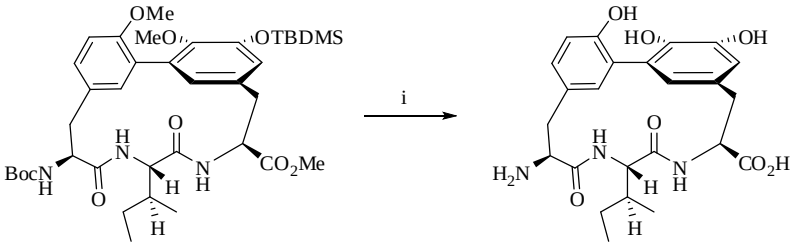
Reagents & Conditions: i) 3 M HCl/EtOAc, 30 min, –10 °C, then $(Boc)_2O$, $NaHCO_3$, THF/H_2O, 69%; ii) cat. CrO_3, H_5IO_6, $MeCN/H_2O$, 1 h, 0 °C, 61%; iii) Ile.*O*Bn tosylate, EDCI, HOAt, $NaHCO_3$, DMF, RT, 90%; iv) 1 atm H_2, Pd/C, MeOH, 15 h, RT, 99%; v) coupling reagent (see table **1.2**); vi) *N*-Cbz.Ile, EDCI, HOAt, DMF, 93%; vii) Jones reagent, acetone, 10 mM, 1 h, 0 °C, 55%.

Scheme 1.4: Synthesis of the fully protected A-B biaryl macrocycle.

Coupling Reagent	Site A	Site B
EDCI, HOAt, $NaHCO_3$	26	53
HATU	29	30
DEPBT	0	14
PyBOP, $NaHCO_3$	-	19
DPPA	0	-
FDPP	64	18

Table 1.2: Reaction conditions and percentage yields for macrolactamisation.

Global deprotection of the resulting macrocycle **1.19** using $AlBr_3$ and EtSH led to the 15-membered A-B macrocycle **1.02** (Scheme **1.5**). Interestingly, the proton NMR spectrum of macrocycle **1.19** contained two complete sets of peaks, whereas by chromatography (TLC, HPLC) only a single species was present. A more advanced NMR study showed that two conformational isomers of **1.19** were present in solution and that these interconverted on the NMR timescale.[15]



1.19 **1.02**

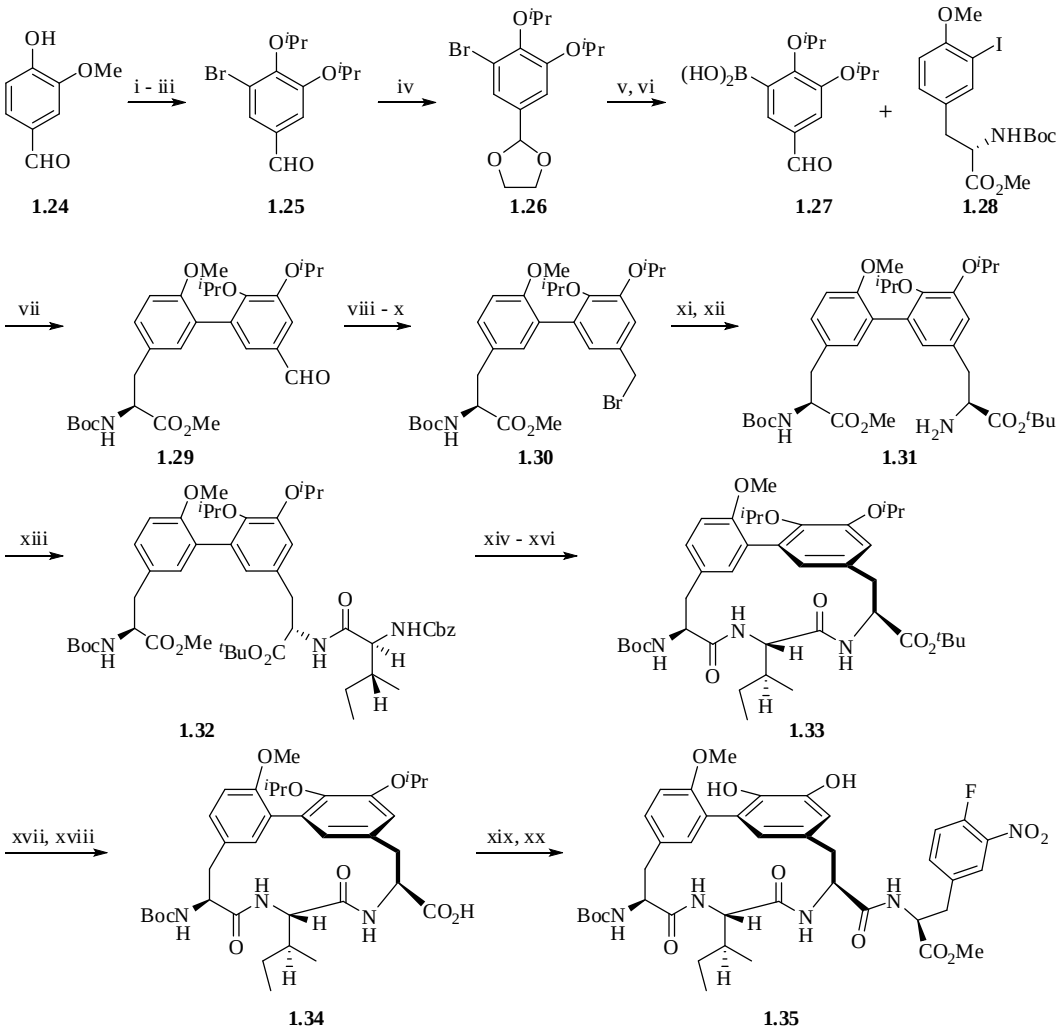
Reagents & Conditions: i) $AlBr_3$, EtSH, yield not given.

Scheme 1.5: Global deprotection of **1.19** affording A-B macrocycle **1.02**.

Whilst methoxy groups *ortho* to a biphenyl linkage do not hinder rotation, the sterically encumbered TBDMS group increases the energy barrier to free rotation. Indeed, upon global deprotection, macrocycle **1.02** only showed one set of signals in its proton NMR spectrum.

1.3.2 Contributions from the Zhu Group

In 2001, Zhu *et al*. reported their first contributions towards the total synthesis of RP 66453. This involved assembly of the tetrapeptide backbone and formation of the A-B macrocycle (Scheme **1.6**).

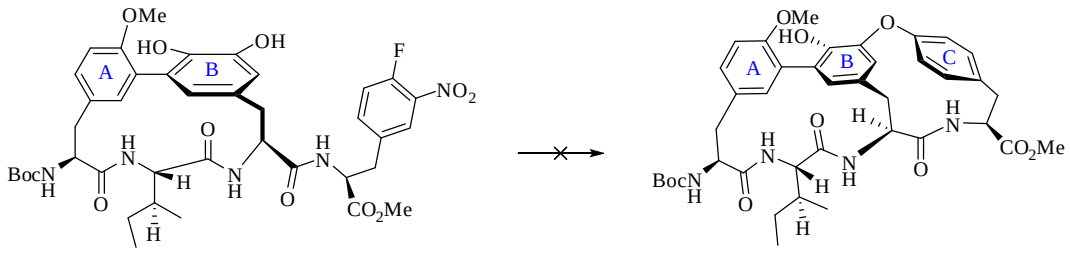


Reagents & Conditions: i) Br_2, acetic acid, 90%; ii) $AlCl_3$, Py, CH_2Cl_2, 98%; iii) K_2CO_3, ^{i}PrBr, DMSO, 83%; iv) ethylene glycol, benzene, *p*-TsOH, Dean-Stark, 91%; v) BuLi, $B(OMe)_3$, THF, –78 ^{o}C; vi) 3N HCl, 67%; vii) $Pd(PPh_3)_4$, aqueous Na_2CO_3, DME, 90 ^{o}C, 85%; viii) $NaBH_4$, MeOH, –78 ^{o}C, 80%; ix) MsCl, Et_3N, CH_2Cl_2; x) LiBr, Me_2CO, 69%; xi) *O*(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide, $CsOH{\cdot}H_2O$, $Ph_2C{=}NCH_2{-}CO_2{}^{t}Bu$; xii) 15% aqueous citric acid, THF, SiO_2, 65%; xiii) EDCI, HOBt, (2*S*,3*S*)-*N*-Cbz isoleucine, 90%; xiv) LiOH, THF/H_2O; xv) EDCI, C_6F_5OH, CH_2Cl_2; xvi) Pd/C, cyclohexene, ^{t}BuOH, DIPEA, 95 ^{o}C, 70%; xvii) TFA; xviii) $(Boc)_2O$, 1,4-dioxane, aqueous $NaHCO_3$, 98%; xix) EDCI, HOBt, L-methyl-4-fluoro-3-nitrophenylalanine, 92 %; xx) BCl_3, CH_2Cl_2, 82 %.

Scheme 1.6: Zhu's initial foray into the preparation of the A-B macrocycle.

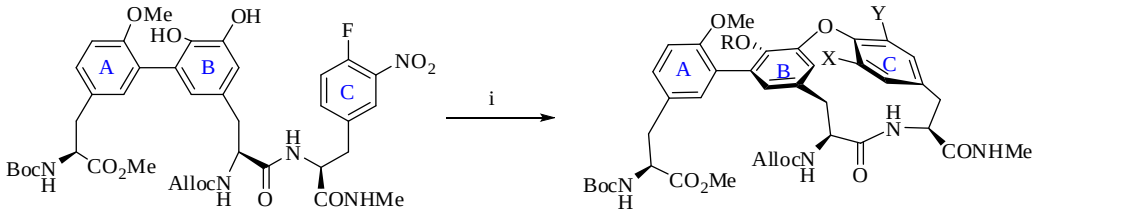
As the absolute configuration of RP 66453 **1.00** was not known, Zhu made the assumption that all asymmetric carbon centres had the *S*-configuration and adopted a convergent approach to allow for modification if required. The first key step was a Suzuki-Miyaura cross-coupling of **1.27** and **1.28** to give biaryl **1.29** in good yield (85%). The aldehyde was converted to the corresponding benzyl bromide **1.30** in three steps. Notably, the ester in **1.29** was particularly susceptible to reduction, even at low temperatures. This was overcome by employing $NaBH_4$ in MeOH rather than THF. Treatment of bromide **1.30** with *N*-(diphenylmethylene)glycine *tert*-butyl ester in the presence of catalytic *O*(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide gave **1.31**, after some protecting group manipulation.

After attachement of an isoleucine residue giving **1.32** and then removal of the protecting groups, Zhu *et al*. were able to close the A-B macrocycle by intramolecular macrolactamisation affording **1.33** in 27% yield. Like Boger, Zhu *et al*. noted that the A-B macrocycle showed two sets of peaks in the proton NMR spectrum. Appendage of L-methyl-4-fluoro-3-nitrophenylalanine afforded tetrapeptide **1.35**, the precursor to the key intramolecular S_NAr reaction. Unfortunately, despite varying the base (NaH, K_2CO_3, K_2CO_3/18-crown-6, CsF, K_2CO_3/$CaCO_3$, DBU), the solvent (THF, DMF, DMSO), and the temperature (0–40 ^oC) only degraded starting material was observed (Scheme **1.7**). The failure was attributed to an unfavourable conformation of **1.35**.[9] It was later noted that ring closure (*viz*. **1.35** → **1.36**) was possible, albeit in low yield, using K_2CO_3 and molecular sieves in THF at 50 ^oC for 4 days.[16] Owing to the low yield of this cyclisation, Zhu and co-workers decided to adopt a different strategy, first closing the B-*O*-C ring then closing the A-B macrocycle (Scheme **1.8**).[9]



Scheme 1.7: Zhu's attempted S_NAr closure of the second macrocycle.

To that end, tri-tyrosine **1.37** was prepared using chemistry as previously described in Scheme **1.6**. In contrast to the cyclisation of **1.35**, the intramolecular S_NAr of **1.37** gave the desired macrocycle as a 3:1 mixture of atropisomers in good yield (60%) (Scheme **1.8**). Importantly, there was no evidence of cyclisation to the highly strained 15-membered *para*,*para*-cyclophane, that would result from nucleophilic addition of the 4-hydroxyl group to the nitro arene. It was noted that **1.38** was unstable towards column chromatography. Consequently, after macrocyclisation was complete (as monitored by TLC), excess iodomethane was added to capture the remaining free phenol. The resulting methyl ethers, **1.39a** and **1.39b** showed much improved stability and thus their preparation gave greater reproducibility.



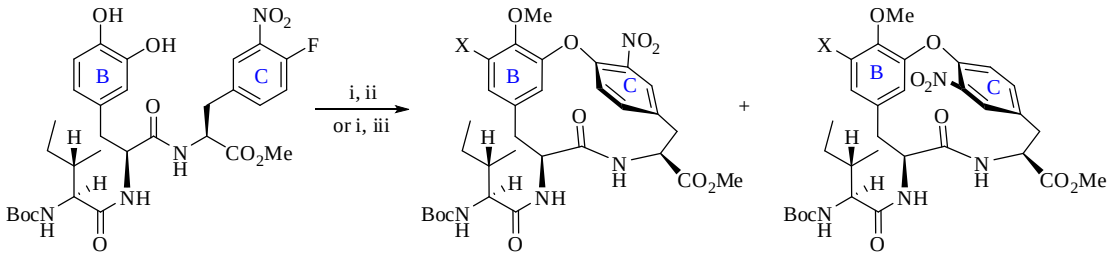
1.37

1.38a, R = Y = H, X = NO_2; **1.38b**, R = X = H, Y = NO_2,
1.39a, R = Me, X = NO_2, Y = H; **1.39b**, R = Me, X = H, Y = NO_2

Reagents & Conditions: i) K_2CO_3, DMF then MeI, 60%.

Scheme 1.8: Zhu's second generation approach to the tetracyclic framework of RP 66453.

This work culminated in 2003 with the publication of the first total synthesis of an atropisomer of RP 66453.[12] Tripeptide **1.40** was prepared in 78% overall yield, starting from commercially available L-DOPA and L-isoleucine. A one-pot S_NAr/iodination/methylation sequence gave **1.41a** and **1.41b** as a 1.3:1 mixture of atropisomers. In a similar vein, **1.42a** and **1.42b** could be obtained from a S_NAr/bromination/methylation sequence in 62% overall yield (Scheme **1.9**). Notably, it proved essential to perform these halogenations before *O*-methylation. Otherwise the halogen was exclusively added *para* to the biaryl linkage.



1.40

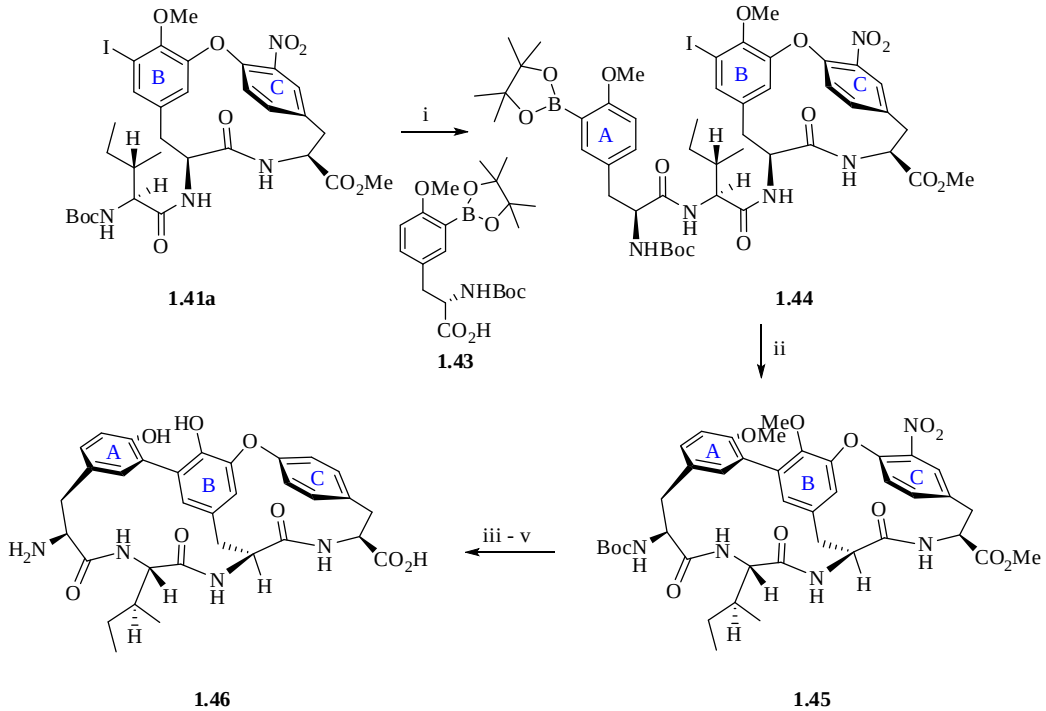
X=I, **1.41a**
X=Br, **1.42a**

X=I, **1.41b**
X=Br, **1.42b**

Reagents & Conditions: i) CsF, DMSO (0.0026 M), 2 h, RT; ii) NIS, DMF, then K_2CO_3, MeI, 48% overall yield of **1.41a** and **1.41b** from **1.40**; iii) NBS, DMF, then MeI, 62% overall yield of **1.42a** and **1.42b** from **1.40**.

Scheme 1.9: Preparation of the B-*O*-C macrocycle.

The lack of atropselectivity in the S_NAr reaction was of little consequence since that stereoelement would be removed later. Zhu *et al*. were able to append in the A ring tyrosine derivative **1.43** using standard peptide bond forming conditions giving tetrapeptide **1.44** (Scheme **1.10**, and similar for bromides **1.42a** and **1.42b**).



1.41a

1.43

1.44

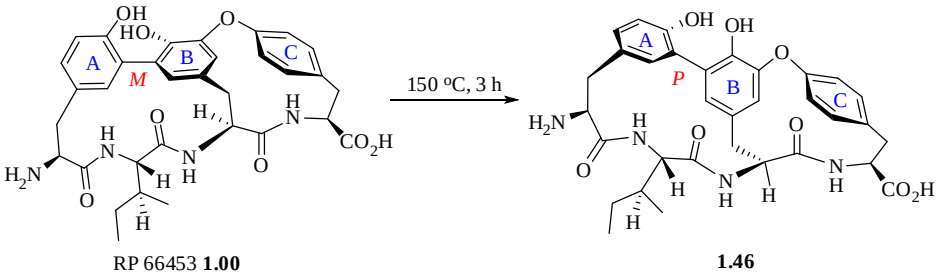
1.46

1.45

Reagents & Conditions: i) 7% HCl in MeCN, RT, aqueous $KHCO_3$ workup, then **1.43**, EDCI, HOBt, Et_3N, DMF, RT, 87%; ii) [$PdCl_2$(dppf)], toluene/H_2O (30:1), K_2CO_3, 90 ^oC, 40%; iii) Pd/C, H_2, MeOH; iv) $NaNO_2$, H_3PO_2, Cu_2O, THF/H_2O (6:1), 42%; v) $AlBr_3$, EtSH, 55%.

Scheme 1.10: End game of Zhu's total synthesis.

The key intramolecular Suzuki-Miyaura coupling was then investigated and it was found that the choice of solvent had a profound impact. Use of a combination of toluene/H_2O (30:1) gave the desired product as a single atropisomer with reproducible yields (~40%), whereas other solvents investigated led to degradation of the starting material. Removal of the nitro group and global deprotection gave the all-*S*-configured bis-macrocycle **1.46**. The spectroscopic data and HRMS of **1.46** were in accordance with its structure, but much of the data differed from that reported for RP 66453 **1.00**, including the optical rotation. Zhu was able to show that on prolonged heating RP 66453 **1.00** gave **1.46**, whereas **1.46** was stable at the same temperature (Scheme **1.11**). This confirmed that the synthetic compound **1.46** was a thermodynamically stable atropisomer of RP 66453.



RP 66453 **1.00** **1.46**

Scheme 1.11: Conversion of RP 66453 to its unnatural atropisomer.

1.4 Related Natural Products

RP 66453 **1.00** belongs to a growing family of macrocyclic peptide natural products, which are often highly strained and typically show promising activities as antibiotics. This natural product 'superfamily' can be subdivided into three smaller classes: those that feature a) a biaryl ether macrocycle, b) a biaryl containing macrocycle, and c) those with both biaryl and biaryl ether macrocycles. This review will mainly focus on the third of these groups since it is to this that RP 66453 belongs.

1.4.1 Natural Products Containing Biaryl Ether Macrocycles

Shown in Figure **1.3** are a selection of macrocyclic peptide natural products containing a biaryl ether linkage, which include K-13 **1.47**,[17-19] piperazinomycin **1.48**,[20-22] RA-VII **1.01**,[5-7, 23, 24] and deoxybouvardin **1.49**.[25-28]

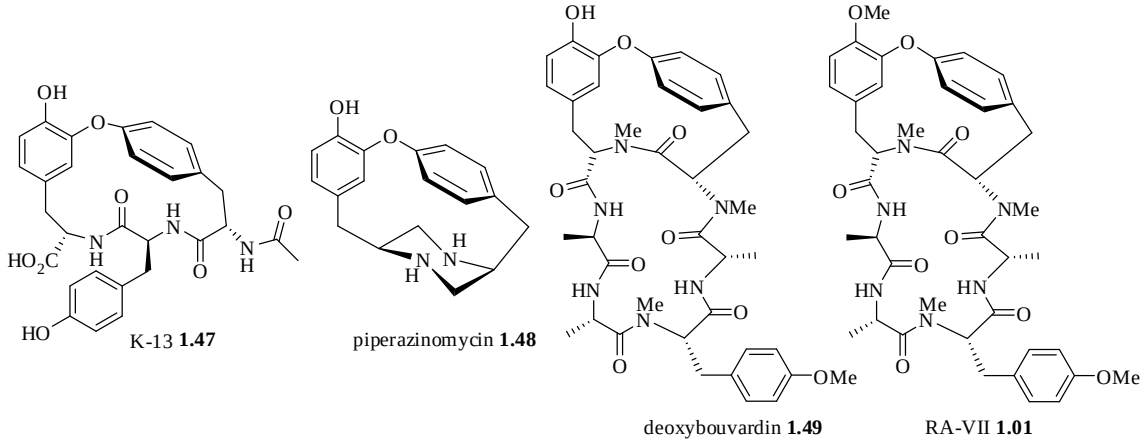


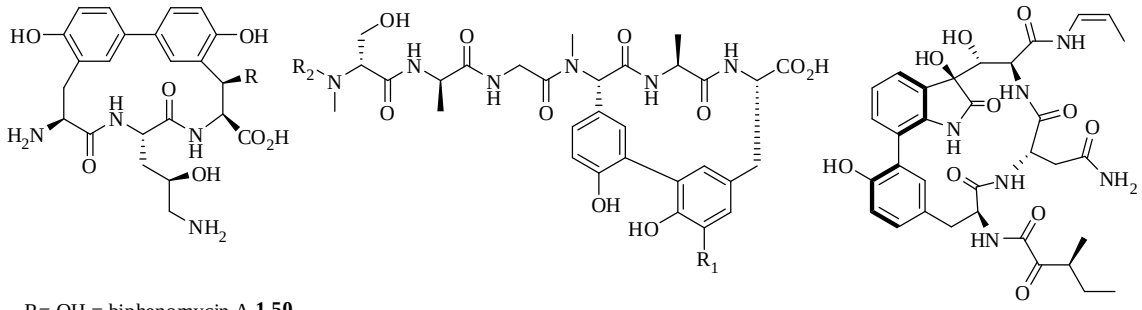
Figure 1.3: Selected natural products containing a biaryl ether macrocycle.

As mentioned in Section 1.1, RP 66453 **1.01** is unique in that the peptide sequence of the cycloisodityrosine is reversed compared to all other natural products in this class. Generally, approaches to the synthesis of such compounds use S_NAr,[29-31] TTN oxidation,[32] or Cu-mediated Ullmann-type chemistry[5, 33-35] to achieve macrocyclisation with biaryl ether formation. For larger ring systems macrocyclisation by classical amide-bond formation is also common, though this has yet to be realised for the highly strained 14-membered system in RP 66453.[6]

1.4.2 Natural Products Containing Biaryl Linked Macrocycles

Shown in Figure **1.4** are a selection of macrocyclic peptide natural products containing an *endo* aryl-aryl linkage including biphenomycins A and B **1.50** and **1.51**,[36-39] the arylomycin core **1.52**,[40-43] and TMC-95 A **1.53**.[44, 45] The biphenomycins are cyclic tripeptides isolated from *Streptomyces filipinensis* and *S. griseorubuginosus*.[36] The absolute configurations of these natural products were established concurrently.[37] In 2005 Zhu and co-workers published a concise asymmetric total synthesis of

biphenomycin B **1.51**, featuring a microwave-promoted Sukuzi-Miyaura reaction as the key macrocyclisation reaction.[46]



R= OH = biphenomycin A **1.50**
R = H = biphenomycin B **1.51**

arylomycin core structure **1.52**

TMC-95 A **1.53**

Figure 1.4: Selected natural products containing an aryl-aryl linkage.

Arylomycins A and B were isolated in 2002 from a *Streptomyces* strain *Tü 6075*, by Jung *et al*.[40, 41] and were shown to display activities against Gram-positive soil-bacteria. Some members of the family were shown to be as active as prescribed antibiotics against *Staphylococcus epidermis*, a Gram-positive human pathogen.[42] In 2010 Zhu completed a total synthesis of peptidase inhibitors A_2 and B_2 using an intramolecular Suzuki-Miyaura reaction to form the aryl-aryl bond.[47]

TMC-95A **1.53** was isolated from the fermentation broth of *Apiospora montagnei* Sacc. TC1093,[44, 48] and was shown to have an IC_{50} = 5.4 nM against ChT-L. In 2002 Danishefsky *et al*. published an elegant total synthesis of TMC-95A, featuring a Suzuki-Miyaura reaction to install the biaryl moiety, a macrolactamisation mediated by HOAt/EDCI and a new rearrangement-hydrolysis of α-silylallylamides to install the (*Z*)-1-propenylamide.[49]

1.4.3 Natural Products Containing both Biaryl and Biaryl Ether Macrocycles

The most complex members of the macrocyclic peptide family contain both biaryl and biaryl ether macrocycles, often with appended sugar moieties. Selected glycopeptide antibiotics are shown in Figure **1.5** and include vancomycin **1.54**, teicoplanin A_2-2 **1.55**, balhimycin **1.56** and ristocetin A (algycon shown) **1.57**.

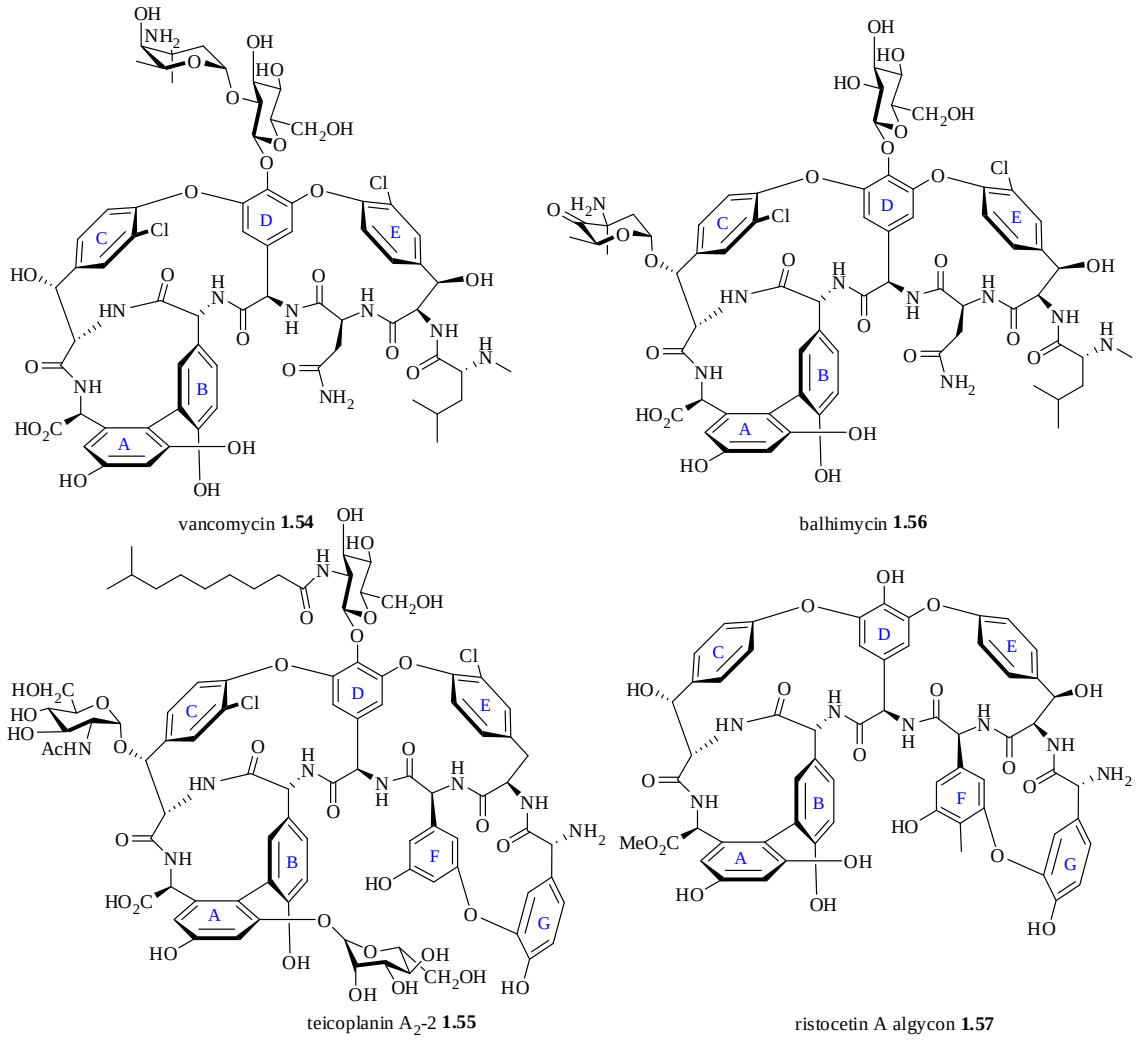


Figure 1.5: Selected glycopeptide antibiotics.

Vancomycin **1.54** was first isolated in 1956 from a fermentation broth of *Streptomyces orientalis* taken from a soil sample in Borneo.[50, 51] It has received much acclaim (along with teicoplanin A_2-2), for its potent activity (MIC = 0.25–10.0 $\mu g mL^{-1}$)[52] against a range of Gram-positive bacteria, including use as a 'last-resort' agent against MRSA. For this reason there has been much interest in vancomycin and teicoplanin A_2-2 from the synthetic chemistry community, including exceptional work from Nicolaou[53] and Boger[54-57] among others. This work has been highlighted in a number of reviews dealing with the syntheses and biological activities of vancomycin[58-61] and is mentioned here for completeness.

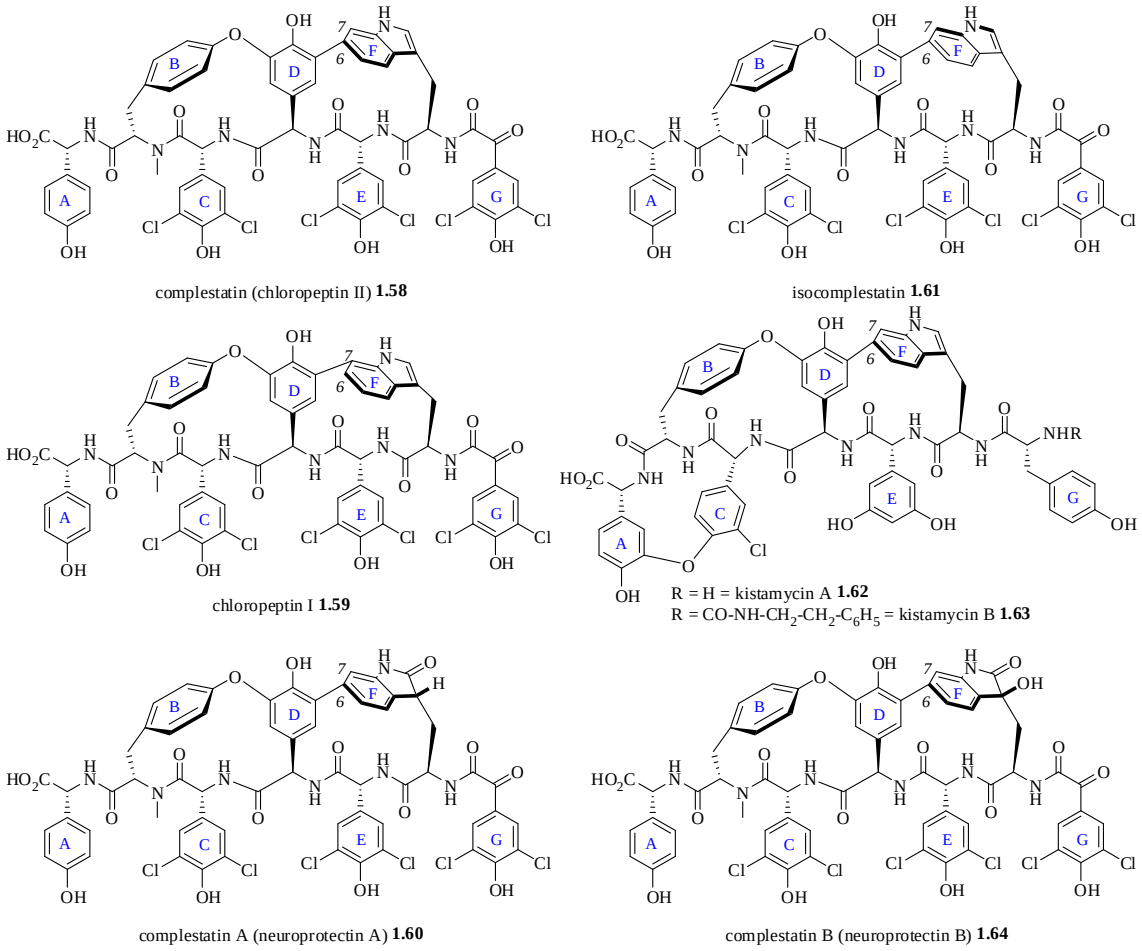
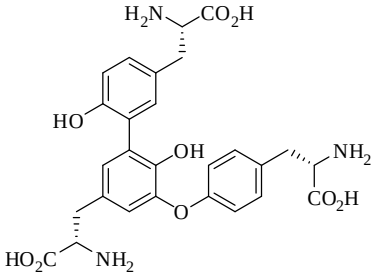


Figure 1.6: Selected tryptophan containing macrocyclic peptides.

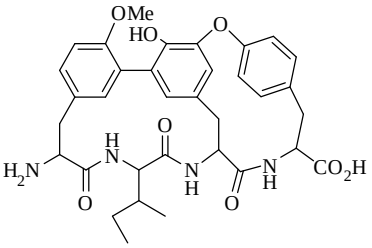
Shown in Figure **1.6** are a series of tryptophan-containing natural products that feature both biaryl and biaryl ether macrocycles. These pose a significant synthetic challenge, due in part to the high degree of strain within their bicyclic ring systems; the racemisation prone aryl-glycine residues and atropselectivity issues associated with the Tyr-Trp bond. The majority of this review will focus on the synthesis and biological activity of these natural products, and in particular, complestatin **1.58**.

At this juncture, mention should be made of pulcherosine **1.65** and cittilin A **1.66** (Figure **1.7**). Pulcherosine, isolated in 1990 by Matsumoto *et al.*[62] is an oxidatively coupled trimer of tyrosine, featuring the same aryl-aryl linkage and biaryl ether moiety as RP 66453 **1.00**. Indeed, it is believed that the biological activity of RP 66453 can be attributed to the pulcherosine core.[63] Cittilin A **1.66** was isolated in 2007 and has the same core structure as RP 66453 but with an additional methyl group. Cittilin B is

thought to have the same structure as RP 66453,[64, 65] though this has yet to be confirmed as its absolute stereochemistry has not yet been established.



pulcherosine **1.65**



cittilin A **1.66**

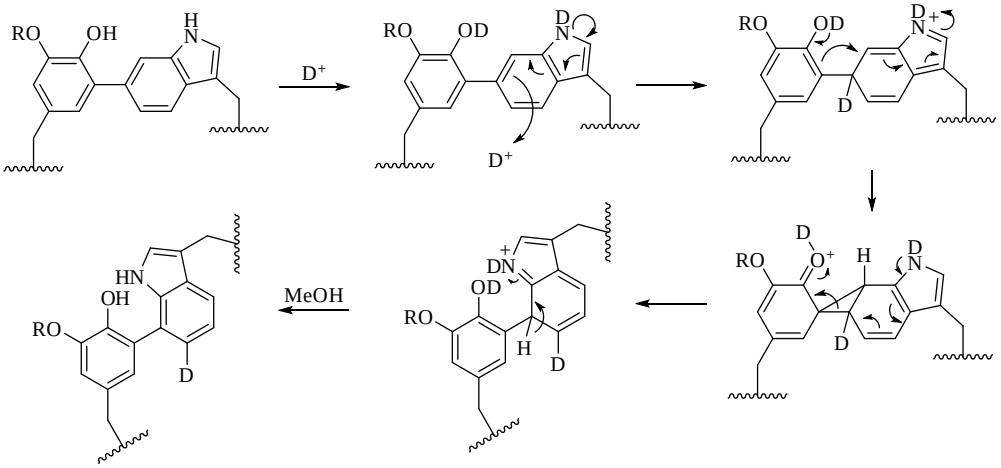
Figure 1.7: Structures of pulcherosine **1.65** and cittilin A **1.66**.

Complestatin (chloropeptin II) and chloropeptin I

Complestatin (**1.58**, chloropeptin II), first extracted from *Streptomyces lavendulae*, was shown to be an inhibitor of the alternate pathway of human complement,[66] although details of its isolation and structure elucidation (connectivity and partial stereochemistry) were not published for a further nine years.[67] Concurrently, the same research team showed that complestatin was a potent inhibitor of hemolysis of sensitised sheep erythrocytes in the classical pathway of the human complement (IC_{50} = 0.7 μgmL^{-1}).[68] Shortly thereafter, was a disclosure showing complestatin to be active against the HIV infection.[69-71]

Chloropeptin I **1.59** a regioisomer of complestatin **1.58**, differing only in C6/C7 connectivity to the Trp residue, was first isolated by Omura *et al*. from *Streptomyces* sp. WK-3419 (along with complestatin). It has been shown that both **1.59** and **1.58** inhibit gp120-CD4 binding with IC_{50} of 1.3 and 2.0 μM respectively.[72-74] The full stereostructure of chloropeptin I was established via high-temperature molecular dynamics, Monte Carlo conformational searching, and NMR studies.[75] Interestingly, the bond transposition between **1.59** and **1.58** does not formally change the ring size. Several years later, Singh *et al*. showed that complestatin **1.58** underwent a facile rearrangement to chloropeptin I **1.59** in the presence of acid, and through an exquisite

deuterium-labelling study, proposed a mechanism for the transformation (Scheme **1.12**).[76]



Scheme 1.12: Proposed mechanism for the acid-catalysed rearrangement.

Singh also went on to elucidate the stereochemistry of complestatin by detailed NMR analysis. However, they noted that the original isolation of these natural products was conducted at pH 2.0 and concluded that chloropeptin I **1.59**, may not be a natural product, but an artefact of isolation. However, this theory was later disproven by the team at Schering, who were able to isolate both natural products independently of each other from two different streptomycete strains.[77] In the years to follow, further disclosures from teams at both Merck and Schering showed additional isolations of the natural products and also several related analogues, including complestatin A **1.60**, complestatin B **1.64**, and the atropisomer of complestatin, isocomplestatin **1.61** (Figure **1.8**).[71, 78, 79]

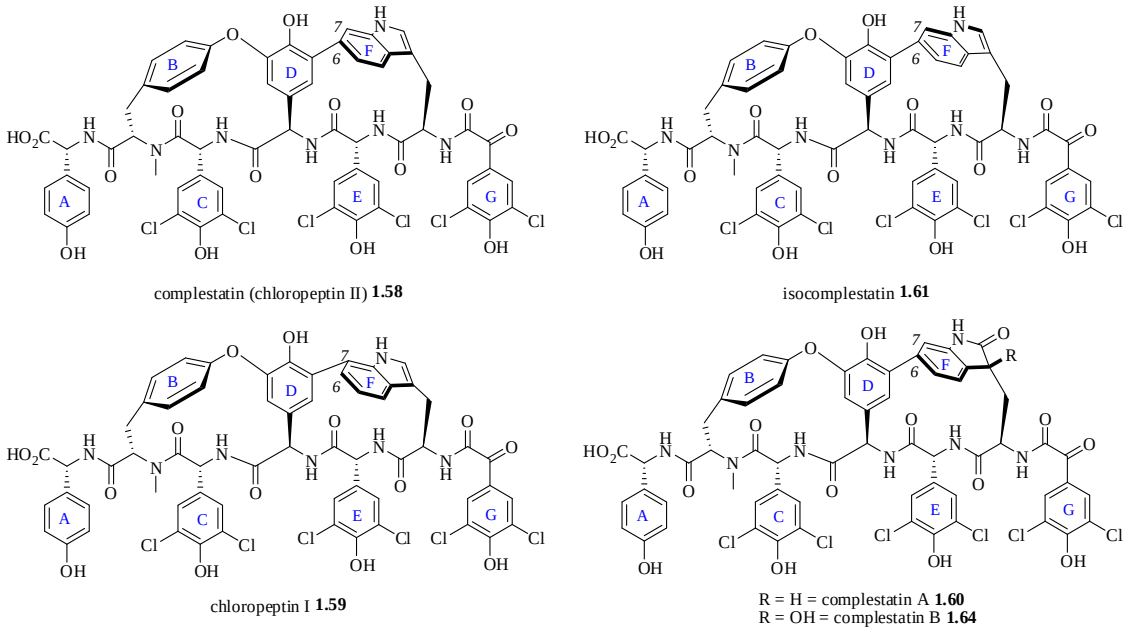
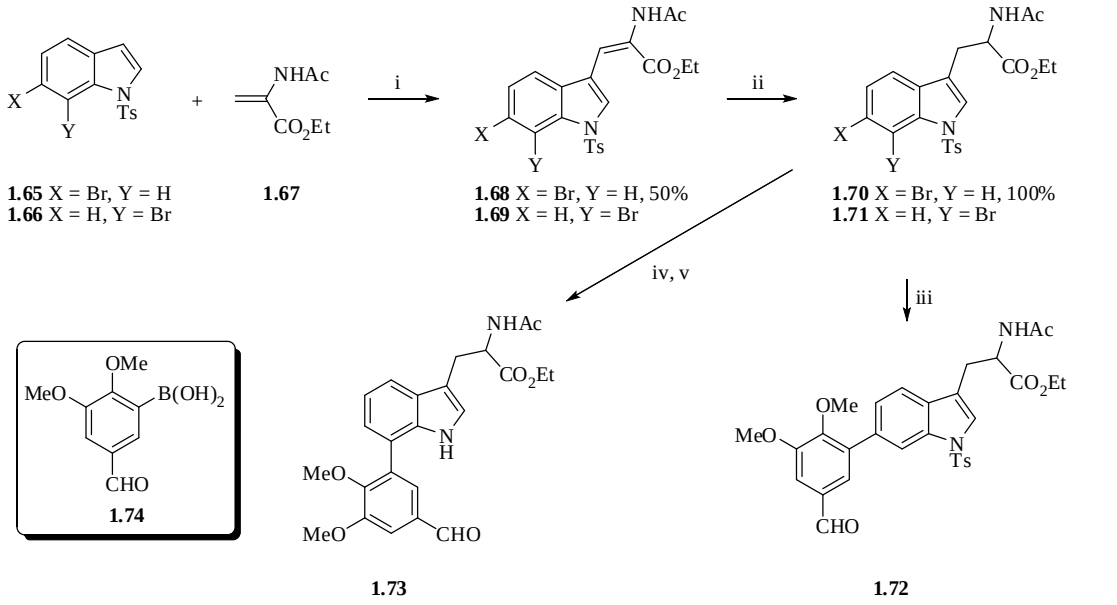


Figure 1.8: Structures of the complestatin family.

The first reported synthetic endeavours towards complestatin **1.58** and chloropeptin **1.59** came in 1997, when Gurjar *et al.* set out to prepare the D-F ring system of both **1.58** and **1.59**, using a Suzuki cross-coupling to form the key biaryl linkage and an intramolecular macrolactamisation (Scheme **1.13**).[80] 6-Bromotryptophan **1.70** was prepared in two steps from 6-bromo-*N*-tosyl indole **1.65** by a Pd-mediated coupling with dehydroserine derivative **1.67**, followed by hydrogenation using Wilkinson's catalyst. The resulting 6-bromotryptophan **1.70** was next elaborated to biaryl **1.72** using a Suzuki cross-coupling reaction with boronic acid **1.74**. The same sequence proved effective for the synthesis of the analogous 7-arylated tryptophan series, although adverse steric interactions imposed by the *N*-tosyl protecting group proved problematic in this case. However, after its removal using sodium naphthalide the desired cross coupling reaction could be realised giving biaryl **1.73** in 30% yield (Scheme **1.13**).



1.65 X = Br, Y = H
1.66 X = H, Y = Br

1.67

1.68 X = Br, Y = H, 50%
1.69 X = H, Y = Br

1.70 X = Br, Y = H, 100%
1.71 X = H, Y = Br

1.74

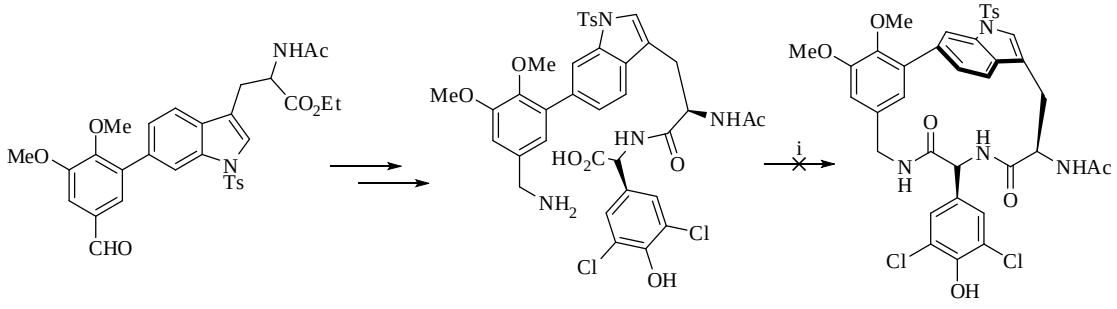
1.73

1.72

Reagents & Conditions: i) $PdCl_2$, NaOAc, HOAc, 6 h, reflux; ii) H_2, $Rh(PPh_3)_3Cl$, CH_2Cl_2/MeOH, 18 h, 60 psi; iii) **1.74**, $Pd(PPh_3)_4$, Na_2CO_3, DME/EtOH, 6 h, reflux, 60%; iv) Na, naphthalene, DME, 5 min, –78 °C; v) **1.74**, $Pd(PPh_3)_4$, Na_2CO_3, DME/EtOH, 6 h, reflux, 30%. Many yields not given.

Scheme 1.13: Preparation of 6- and 7- functionalised tryptophan residues.

An 8-step sequence of standard transformations was next used to convert 6-substituted tryptophan **1.72** into the macrocyclisation precursor **1.75**. Unfortunately, attempts to close the D-F ring using either DCC or DPPA failed (Scheme **1.14**).



1.72

1.75

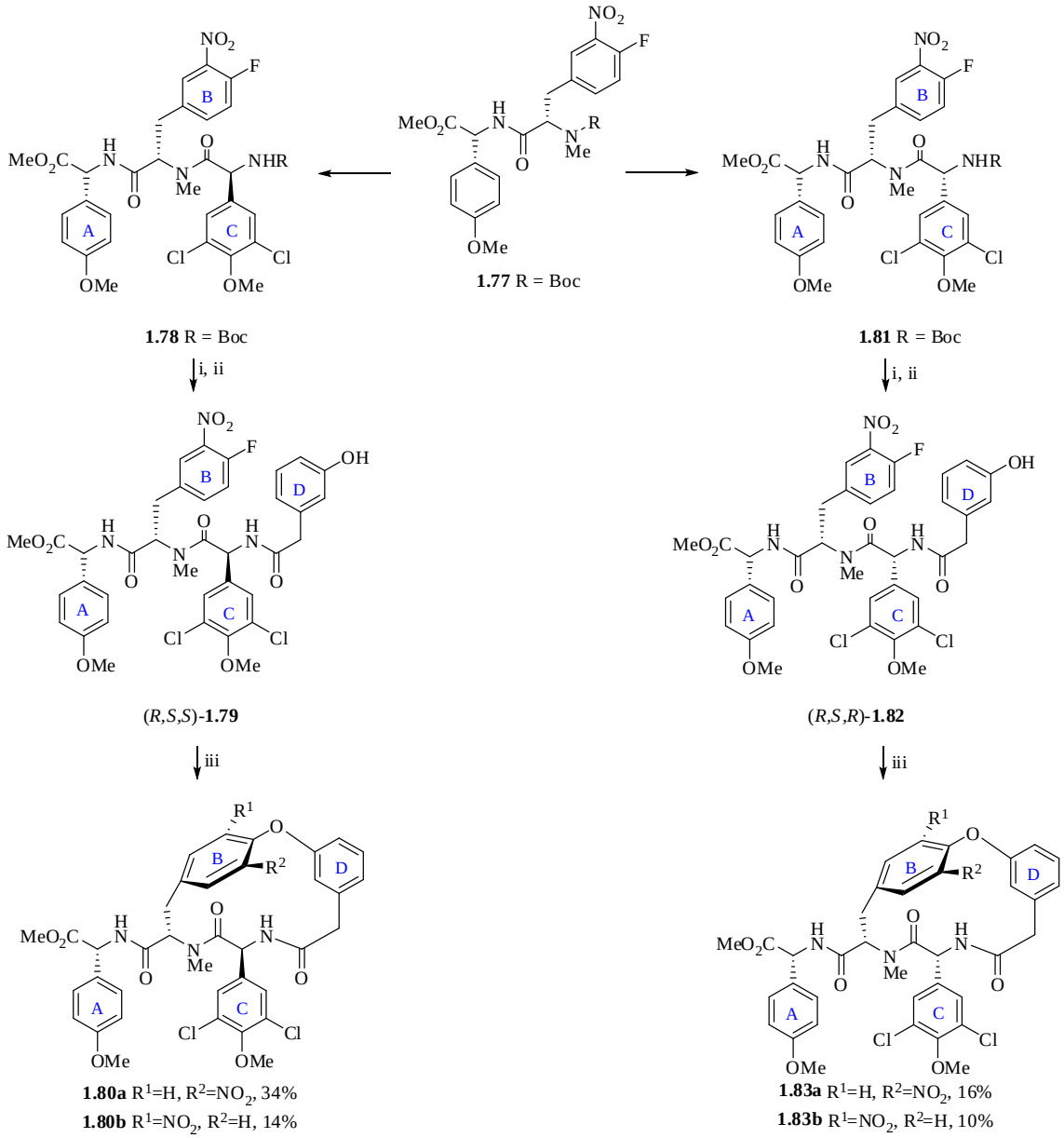
1.76

Reagents & Conditions: i) DCC, HOBt, MeCN or DPPA, Et_3N.

Scheme 1.14: Attempted closure of the D-F model system of complestatin.

The first approach to the B-*O*-D macrocycle of chloropeptin **1.59** and complestatin **1.58** by an intramolecular S_NAr reaction was described by Roussi *et al*. For sake of

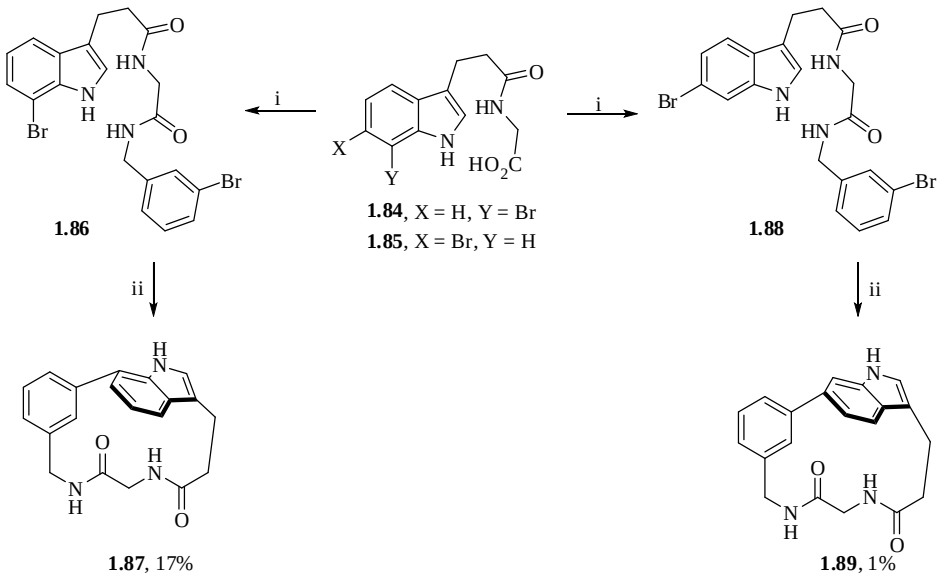
comparison, both the linear *R*,*S*,*S*- **1.79**, and *R*,*S*,*R*- **1.82** diastereomers were prepared using Schöllkolf[81] and Strecker[82] chemistry to assemble the unnatural amino acid residues (Scheme **1.15**).[83] Attempts to effect macrocyclisation of **1.79** and **1.82** using an intramolecular S_NAr reaction led to a complex mixture of products due to epimerisation of the sensitive arylglycine subunits and the formation of atropisomers. Nonetheless, the target products **1.80** and **1.83** were all identified in modest yield (Scheme **1.15**).



Reagents & Conditions: i) PyBrOP, CH_2Cl_2, 0 °C, 65%; ii) *m*-hydroxyphenylacetic acid, HOBt, EDCI CH_2Cl_2, 81%; iii) K_2CO_3, DMF, 40 h.

Scheme 1.15: Preparation of B-*O*-D model macrocycle of chloropeptin and complestatin.

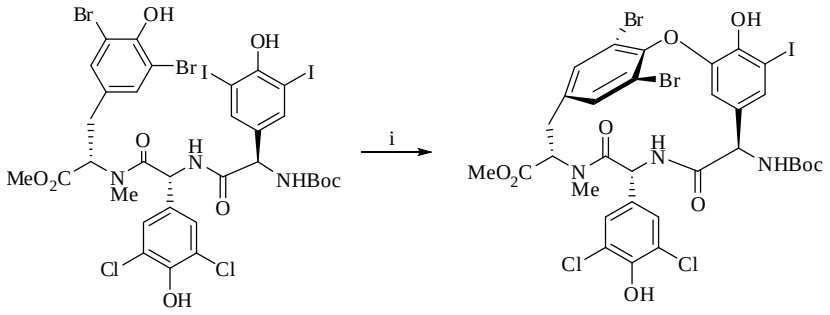
Switching their focus towards the D-F ring of complestatin **1.58**, Roussi *et al*. were able to show that an intramolecular Ni^0 mediated aryl-aryl coupling reaction was effective for macrocyclisation in a model system (Scheme **1.16**).[84, 85] The strategy was also effective for the synthesis of the 17-membered ring **1.87** found in chloropeptin I **1.61**.



Reagents & Conditions: i) 3-bromobenzylamine hydrochloride, HOBt, EDCI, Et_3N, DMF; ii) $Ni(Ph_3P)_2Cl_2$, Zn, Ph_3P, DMF, 0.01 M.

Scheme 1.16: Ni^0 mediated cyclisation of indole derivatives.

An alternative approach to the B-*O*-D ring, *viz*. **1.90** → **1.91**, was described by Kai *et al*. In this case the key biaryl ether linkage was prepared using a biomimetic phenolic oxidation strategy (Scheme **1.17**).[32, 86] Closure of **1.90** to **1.91** required 2 equivalents of TTN in a 4:1 mixture of THF/MeOH. The reaction was equally effective when the Boc protecting group was replaced with Cbz. In both cases the resulting macrocycle existed as two stable rotamers in solution (*cis/trans* about the tertiary amide linkage), with the *N*-methyl derivative favouring the *cis*- isomer.[86]

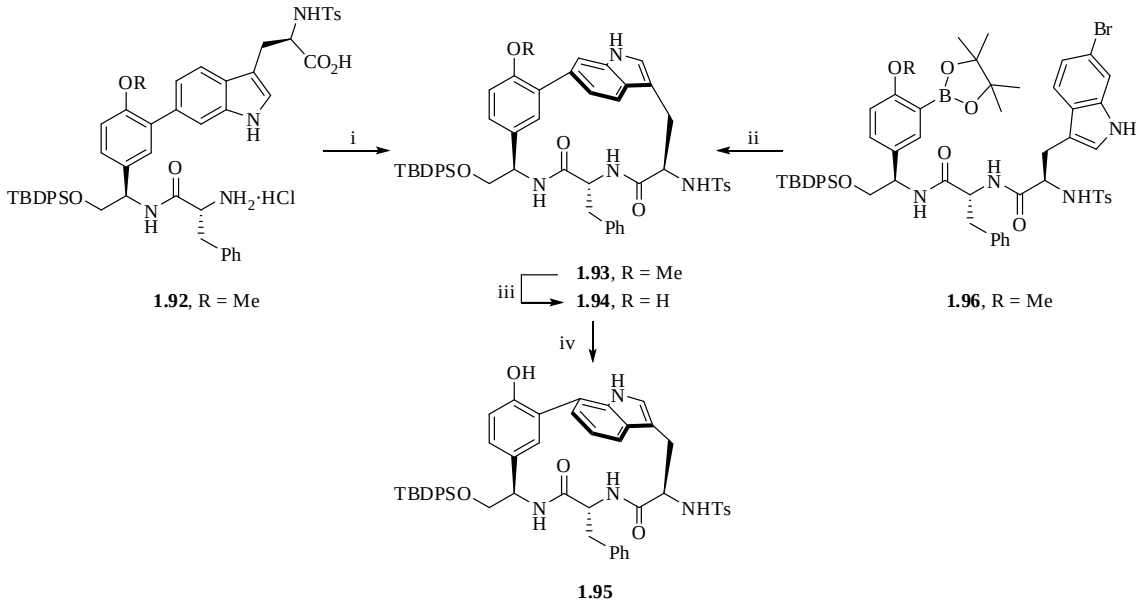


1.90 **1.91**

Reagents & Conditions: i) TTN (2 eq.), THF/MeOH (4:1), 76%.

Scheme 1.17: Optimised conditions of the TTN oxidation.

In 1999 Rich and co-workers were the first to show that closure of the D-F macrocycle was possible by an intramolecular macrolactamisation strategy. They also induced closure using a Suzuki coupling (**1.96 → 1.93**, Scheme **1.18**),[87] complimenting the Ni-mediated closure developed by Roussi.[84]



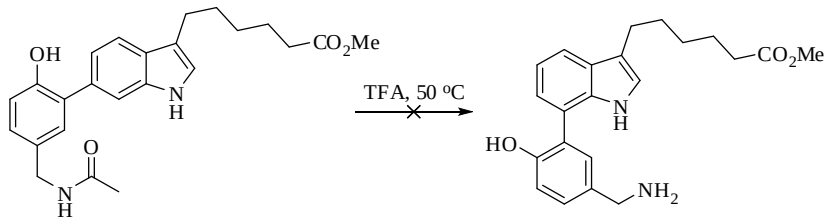
1.92, R = Me **1.93**, R = Me **1.94**, R = H **1.95** **1.96**, R = Me

Reagents & Conditions: i) FDPP, DIPEA, DMF, RT, 43%; ii) $Pd(dppf)Cl_2$, K_2CO_3, DME, 40 °C, 56%; iii) not stated in paper; iv) TFA, 50 °C, quant.

Scheme 1.18: Two ring-closing strategies to the D-F model system of complestatin **1.58**.

Rich found it necessary to use the FDPP coupling reagent to effect the macrolactamisation **1.92 → 1.93**, as the EDCI/HOBt combination failed to yield any of

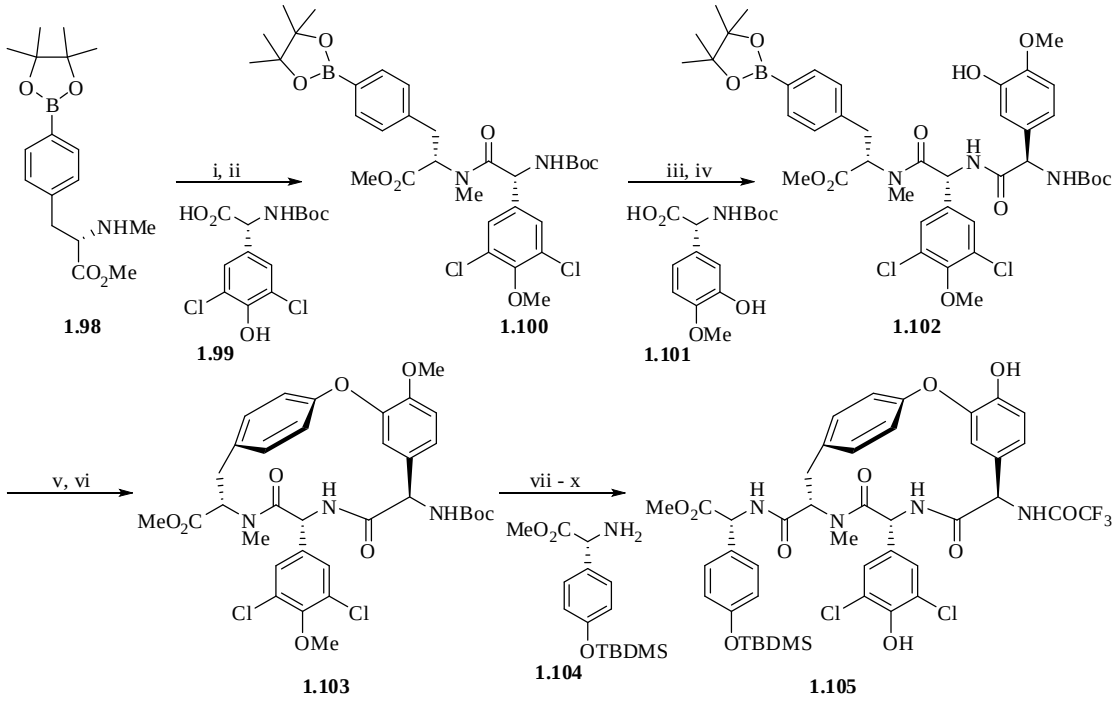
the desired product. By preparation of an epimer of **1.94**, Rich was able to show that both diastereomers undergo the H^+-promoted migration. Curiously, it was shown that the rearrangement was not possible on the simple acyclic precursor **1.96** (Scheme **1.19**), suggesting that ring strain or preorganised orbital overlap are required to drive phenyl migration.



1.96 **1.97**

Scheme 1.19: Attempted rearrangement on acyclic system **1.96**.

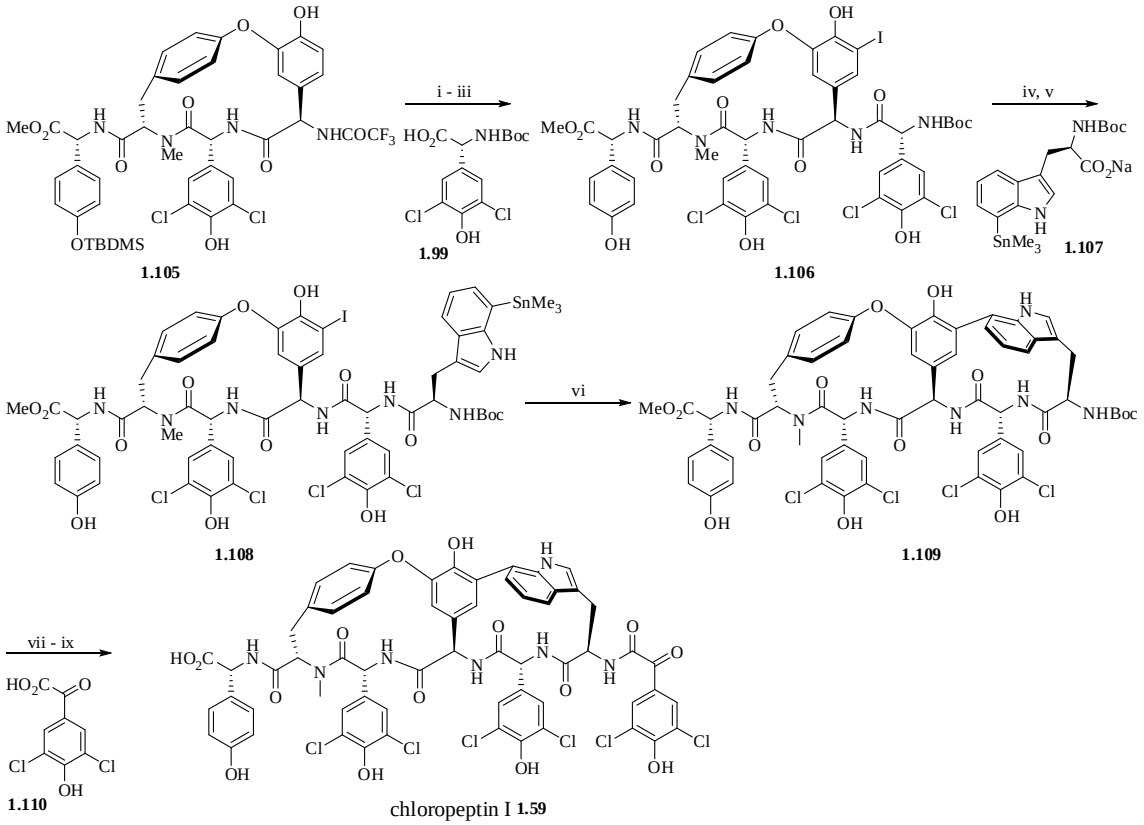
In 2003, Hoveyda *et al*. completed the first total synthesis of chloropeptin I.[88] Central to his strategy were a Cu-mediated biaryl etherification reaction to form the critical B-*O*-D linkage (Scheme **1.20**), and an intramolecular Stille reaction to effect the second macrocyclisation (Scheme **1.21**). Thus, L-tyrosine was first transformed into boronic ester **1.98** then coupled with **1.99** giving dipeptide **1.100** after *O*-methylation with $TMSCHN_2$. Removal of the Boc-protecting group and union with **1.101** using a HOAt/EDCI mediated coupling gave tripeptide **1.102** in 86% overall yield. Hydrolysis of the boronic ester to the corresponding acid set up the key macrocyclisation reaction affording biaryl ether **1.103** in 50% yield.[14] Conversion of the *tert*-butoxycarbamate to the trifluoroacetamide, followed by $AlBr_3$-mediated deprotection of the methyl ester and union with **1.104** furnished tetrapeptide **1.105**. Some noteworthy points from this sequence are a) the periodate mediated hydrolysis to the boronic acid (step v) required high dilution to avoid decomposition; b) the use of 10 equiv. of MeOH in the cyclisation step to improve solubility of the cuprate, or an in situ formation of a dimethyl borate ester; and c) isolation of **1.105** as a single conformational isomer when intermediates to this point had existed as rotameric mixtures.[70, 71]



Reagents & Conditions: i) **1.99**, DEPBT, $NaHCO_3$, THF, 12 h, 0 °C–RT, 74%; ii) $TMSCHN_2$, CH_2Cl_2/MeOH, 1.5 h, RT, >98%; iii) $HCl_{(g)}$, MeOH, 1 h, –78 °C–RT; iv) **1.101**, HOAt, EDCI, $NaHCO_3$, THF/DMF, 12 h, 0 °C–RT, 86% from **1.100**; v) $NaIO_4$, NH_4OAc, acetone/water (0.01 M), 12 h, RT; vi) $Cu(OAc)_2$, Et_3N, 4Å MS, MeOH, CH_2Cl_2 (0.01 M), 5 h, RT, 50% from **1.102**; vii) $HCl_{(g)}$, MeOH, 1.5 h, –78 °C–RT; $NaHCO_3$; viii) TFAA, 2,6-lutidine, CH_2Cl_2, 2 h, 0 °C–RT, 94% for two steps; ix) $AlBr_3$, EtSH, 1.5 h, 0 °C; x) **1.104**, HOAt, EDCI, $NaHCO_3$, THF, 12 h, 0 °C–RT, 80% for two steps.

Scheme 1.20: Hoveyda's route to B-*O*-D fragment of chloropeptin I **1.59**.

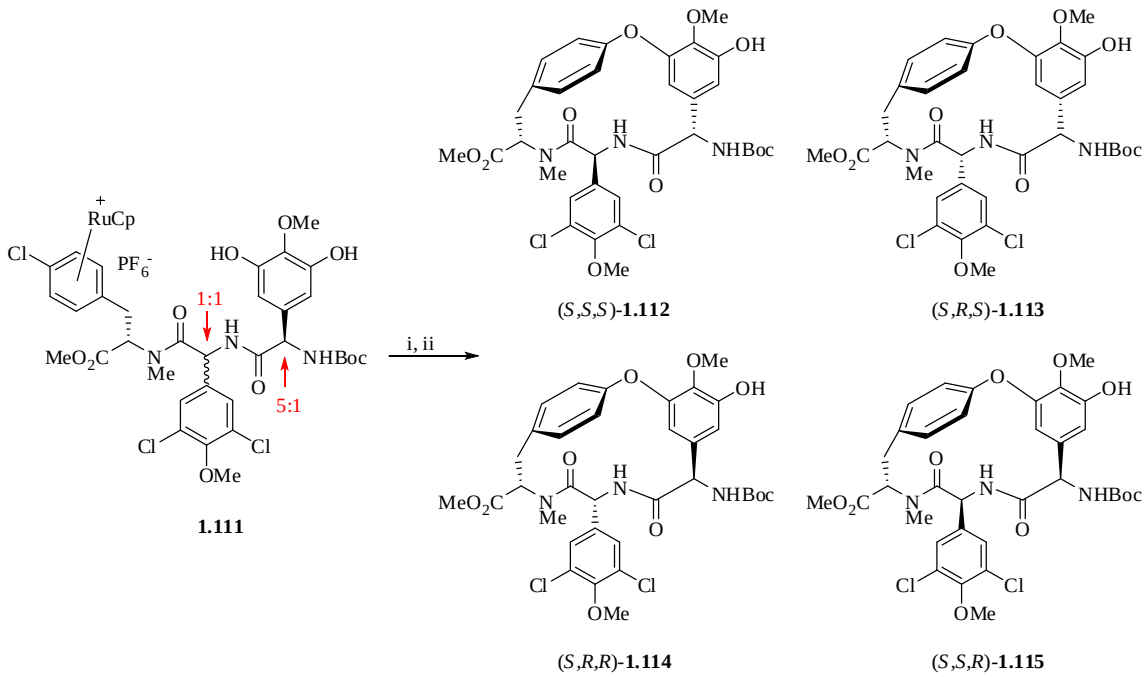
Attentions next focused on appending the D-F fragment and formation of the key Phe-Trp linkage (Scheme **1.21**). Regioselective iodination of **1.105** with NIS, removal of the TFA and TBDMS protecting groups and a HATU coupling with arylglycine **1.99** gave pentapeptide **1.106** in close to 70% overall yield. Cleavage of the terminal Boc protecting group and coupling with the Na salt of **1.107**, gave **1.108**, which was treated with stoichiometric $Pd(P^tBu_3)_2$[89] to give bis-macrocycle **1.109** as a single diastereoisomer. Addition of collidine improved the efficiency of the macrocyclisation step, perhaps due to stabilisation of the active Pd complex. The total synthesis of chloropeptin I **1.59** was completed by removal of the Boc protecting group, coupling the resulting amine with α-ketoacid **1.110** and saponification of the methyl ester.



Reagents & Conditions: i) NIS, MeCN, 1 h, RT, 60%; ii) HCl, MeOH, 4 h, 45 °C; $NaHCO_3$; iii) **1.99**, HATU, collidine, CH_2Cl_2/THF, 3 h, 0 °C–RT, 85% for two steps; iv) HCl, MeOH, 3 h, RT; v) **1.107**, HATU, collidine, CH_2Cl_2/THF, 4 h, 0 °C–RT, vi) $Pd(P^tBu_3)_2$, collidine, CsF, dioxane (2 mM), 5 h, 50 °C, ~40% from **1.106**; vii) HCl, MeOH, 1.5 h, RT; viii) **1.110**, HOAt, EDCI, CH_2Cl_2/DMF, 3 h, 0 °C–RT, 60% for two steps.; ix) LiOH, H_2O/THF, 2 h, 0 °C, 98%.

Scheme 1.21: End-game of Hoveyda's first total synthesis of chloropeptin I **1.59**.

Thus far we have seen several approaches to the biaryl ether fragment, with macrocyclisation induced by classical nucleophilic aromatic substitution, Cu-mediated Ullmann-type coupling and a TTN phenolic oxidation. In 2004 Smith *et al*. showed that this could also be effected using arene-ruthenium chemistry developed by Pearson[90, 91] and Rich[92] (Scheme **1.22**). Preliminary studies had shown that it was necessary to install the ruthenium-arene complex late in the synthesis, as purification of metal-containing intermediates proved difficult.

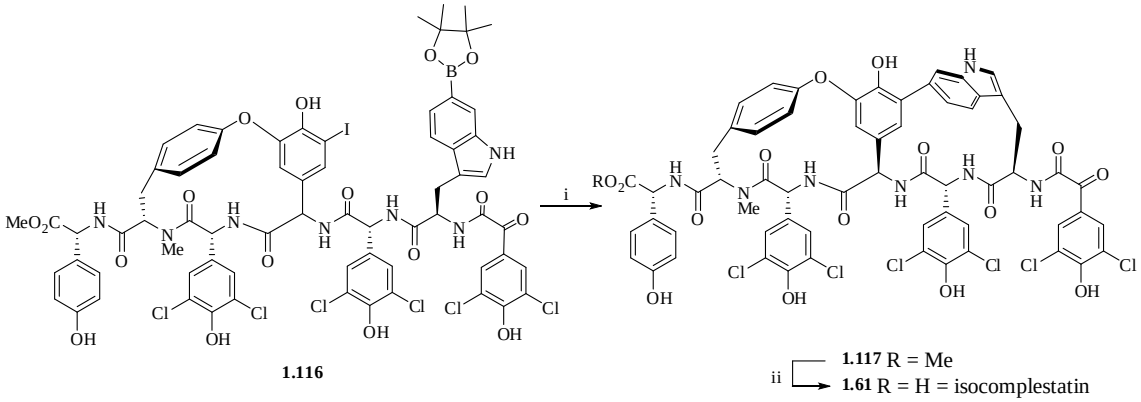


Reagents & Conditions: i) Cs_2CO_3, DMF; ii) hν, MeCN, 60%.

Scheme 1.22: Formation of B-*O*-D macrocycle diastereomers.

The acid-promoted rearrangement of chloropeptin I **1.59** to complestatin **1.58** has been reported to proceed with retention of axial chirality.[76] Thus it was assumed that the biaryl linkage in complestatin **1.58** had the *R*-configuration since it was already known that chloropeptin I had the *R*-configuration. However, when the atropisomer of complestatin, isocomplestatin **1.61** was isolated, it too was reported to have the *R*-configured biaryl despite discrepancies in optical rotation with **1.58**.[71] It was also reported that both complestatin **1.58** and isocomplestatin **1.61**, when exposed to TFA, would rearrange to chloropeptin I **1.59**.[71] This would therefore imply the unusual situation whereby one atropisomer undergoes the 1,2-shift with retention and the other with complete inversion![76] To assign the biaryl configuration of complestatin **1.58** Hoveyda and co-workers set about applying the intramolecular palladium cyclisation to the total synthesis of complestatin **1.58** and its atropisomer, isocomplestatin **1.61** (Scheme **1.23**).[93] On a model system the group were able to isolate the pure *R* and *S* atropisomers of **1.58** and showed that a) the two did not interconvert on heating and b) retention of the biaryl configuration was seen in both cases on rearrangement with acid.[93] When **1.61** was isolated, it became clear that the data did not match those reported for complestatin or isocomplestatin. Detailed NMR analysis of their synthetic

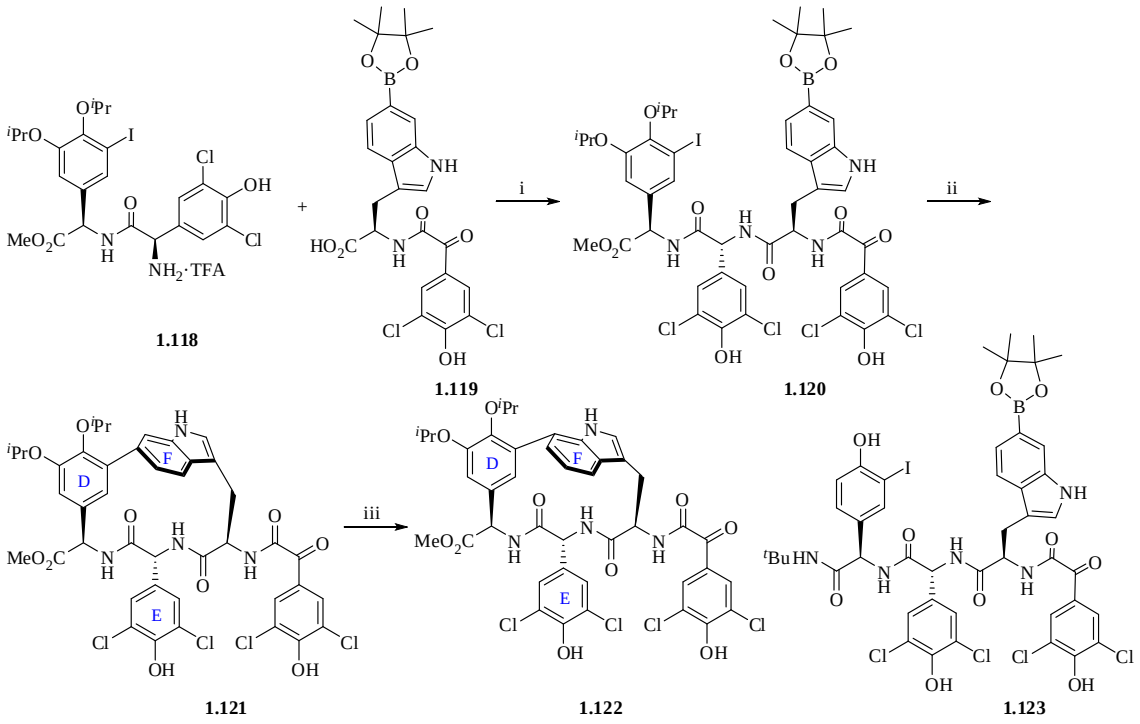
compound and an authentic sample of isocomplestatin led them to conclude that the compound originally isolated as isocomplestatin was incorrectly assigned and was in fact complestatin **1.58**.



Reagents & Conditions: i) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, dioxane/H_2O, 1.5 h, 80 ^oC, 63%; ii) LiOH, H_2O/THF, 2 h, 0 ^oC, >98%.

Scheme 1.23: Key step of Hoveyda's total synthesis of isocomplestatin **1.61**.

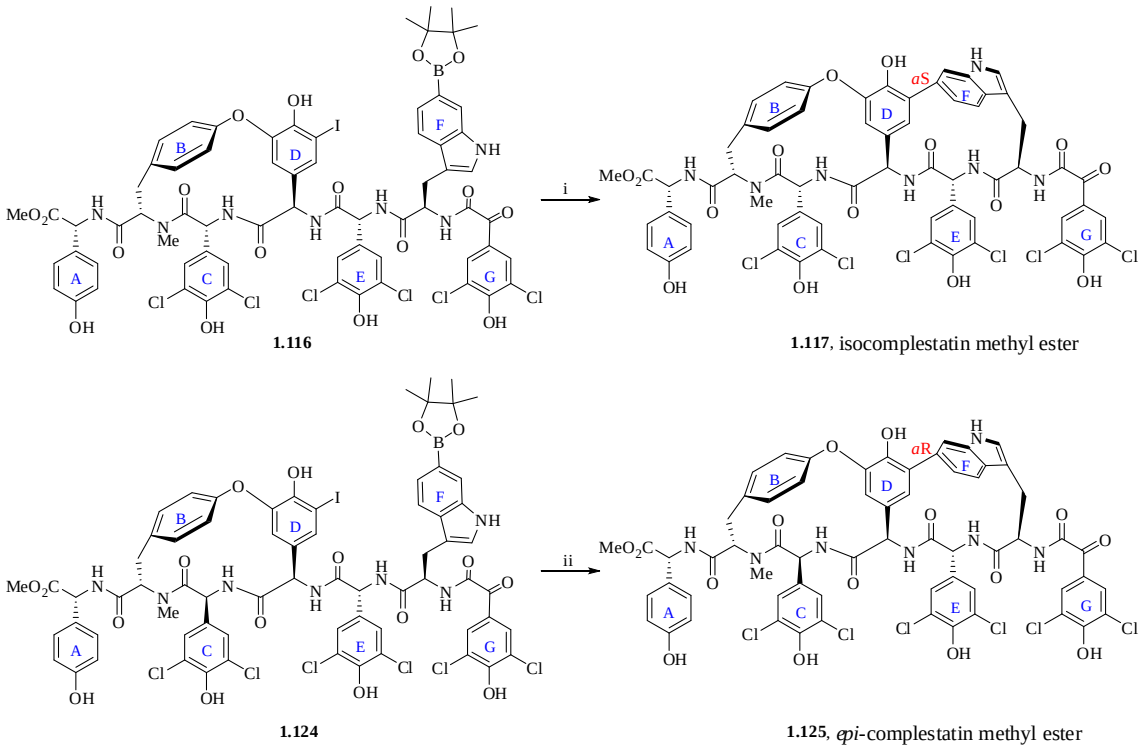
It has been shown by Hoveyda and others[88, 93, 94] that the atropselectivity of macrocyclisation is strongly influenced by other stereochemical features within the molecule. In 2007 Zhu elegantly demonstrated an atropdiastereoselective intramolecular Suzuki-Miyaura coupling for the preparation of the D-F ring system of complestatin **1.58** and chloropeptin I **1.59**.[95] The requisite linear tripeptide **1.120** was prepared in good yield (78%) by coupling of dipeptide **1.118** with tryptophan derivative **1.119**. Macrocyclisation to **1.121** proved difficult, and after much optimisation it was found that 1 equiv. of the Pd source was necessary to avoid sequestration of the catalyst by Lewis basic sites on the substrate. Using 1 eq. of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ with 10 eq. K_2CO_3 and 15:1 dioxane:H_2O as solvent, macrocyclisation of **1.120** to a single atropisomer of **1.121** could be achieved in 66% yield, with the *R*-stereochemistry determined by NOE correlations. Interestingly, when the cyclisation was carried out on **1.123**, a substrate lacking the second hydroxyl on the D ring, a 1:1 ratio of diastereoisomers was formed, showing that atropselectivty is highly substrate dependent. Acid-promoted rearrangement of **1.121** to **1.122** occurred smoothly, showing that free phenols are not a prerequisite for this transformation as previously reported (Scheme **1.24**).[76, 77]



Reagents & Conditions: i) HATU, 2,5-lutidine, CH_2Cl_2/THF, 12 h, 5 °C, 78%; ii) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, dioxane/H_2O, 1 h, 80 °C, 66%; iii) TFA, 30 min, 60 °C, quant.

Scheme 1.24: Zhu's synthesis of the D-F ring system.

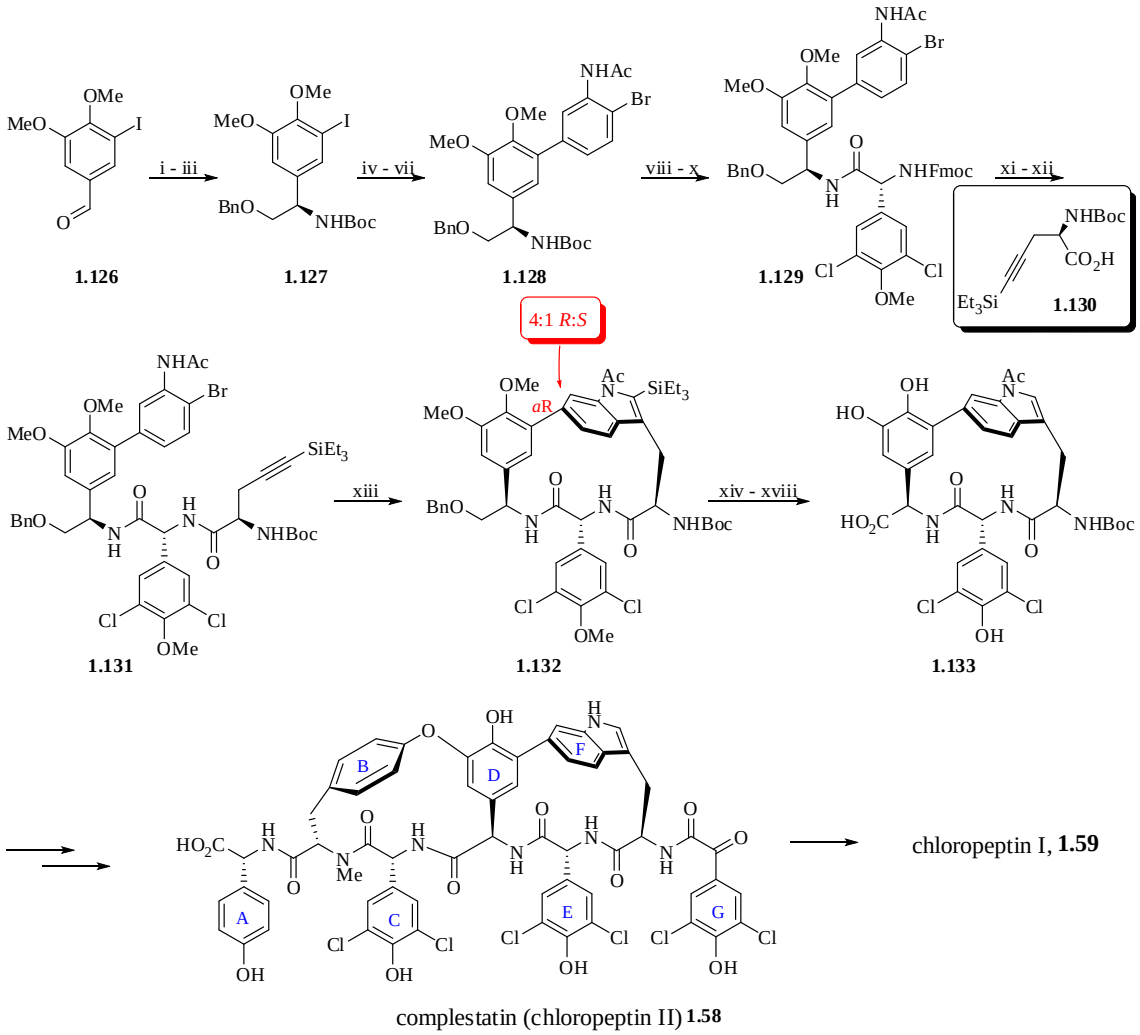
Attempts to extrapolate this work to the total synthesis of complestatin **1.58** led to the formation of isocomplestatin **1.61**.[96] Thus, the intramolecular Suzuki-Miyaura coupling led to the *aS*-atropisomer rather than the *aR*-atropisomer. Zhu *et al*. were able to demonstrate that the stereochemistry of the C ring amino acid had a significant influence on atropselectivity in D-F ring formation. Indeed, by switching the absolute configuration of the C residue, an epimer **1.125** of **1.58** could be formed with complete reversal of axial chirality (Scheme **1.25**).



Reagents & Conditions: i) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, dioxane/H_2O (50:3), 1 h, 90 °C, 66%; ii) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, dioxane/H_2O (50:3), 1 h, 80 °C, 48%.

Scheme 1.25: Zhu's synthesis of the complestatin atropisomer.

The first total synthesis of complestatin **1.58** was realised in 2009[97] when the Boger research team formed the crucial *aR*-stereochemistry using an intramolecular Larock indole synthesis[98, 99] (Scheme **1.26**). Thus, commercially available 3-iodo-4,5-dimethoxybenzaldehyde **1.126** was converted into the corresponding styrene by means of a Wittig olefination. Asymmetric aminohydroxylation with $(DHQD)_2PHAL$,[100] and benzyl protection of the subsequent alcohol afforded **1.127** in excellent yield. Halogen-lithium exchange followed by trapping with trimethyl borate and hydrolysis gave the boronic acid which was used directly in a Suzuki coupling with 2-bromo-5-iodoaniline, to afford biaryl **1.128** after capping with acetic anhydride. Boc deprotection and union with (*R*)-FmocHN-3,5-Cl_2Hpg-OH gave **1.129**. Removal of the Fmoc group and coupling to **1.130** gave the key precursor for a Larock cyclisation **1.131** in good yield (83%).



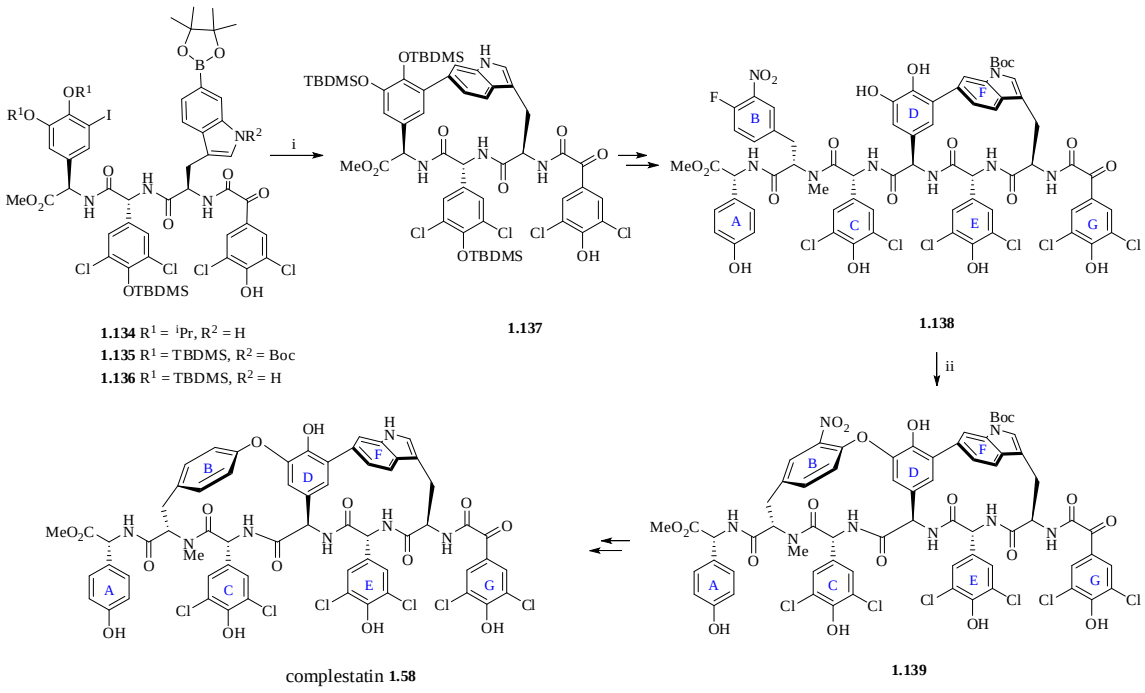
Reagents & Conditions: i) CH_3PPh_3Br, K_2CO_3, 18-crown-6, THF, 25 h, reflux, 99%; ii), $BocNH_2$, ^tBuOCl, $(DHQD)_2PHAL$, $K_2OsO_4{\cdot}2H_2O$, NaOH, ^iPrOH, 1 h, 0 °C–RT, 75%; iii) BnBr, NaH, DMF, 2 h, RT, 92%; iv) ^iPrMgCl, ^nBuLi, THF; v) $B(OMe)_3$, 18 h, –78 °C–RT; vi) $Pd(PPh_3)_4$, 2-bromo-5-iodoaniline, $NaHCO_3$, 28 h, 80 °C, 98%; vii) Ac_2O, CH_2Cl_2, $NaHCO_3$, 1 h, RT, 96%; viii) HCOOH, 4 h, RT; ix) (*R*)-FmocHN-3,5-Cl_2Hpg-OH, HOAt, EDCI, CH_2Cl_2/DMF, 16 h, RT, 98%; x) $TMSCHN_2$, PhH/MeOH, 2 h, RT, 83%; xi) morpholine, MeCN/DMF, 16 h, RT; xii) **1.130**, HOAt, EDCI, DMF, 48 h, 0 °C–RT, 83%; xiii) $Pd(OAc)_2$, D^{t}BPF, Et_3N, MeCN/PhMe 1 h, reflux, 71% pure (*R*)-atropisomer; xiv) $Pd(OH)_2$, H_2, THF, 1 h, RT, 99%; xv) DMP, CH_2Cl_2, 2.5 h, 0 °C–RT; xvi) $NaClO_2$, NaH_2PO_4, ^{t}BuOH, 2-methyl-2-butene, 90 min, 0 °C, 92%; xvii) BBr_3, CH_2Cl_2, 17 h, RT; xviii) $(Boc)_2O$, Et_3N, 5 h, 40 °C, 94%.

Scheme 1.26: Boger's first total synthesis of complestatin **1.58**.

The large triethylsilyl substituent on the alkyne e.g. **1.131**, was found to dictate the cyclisation regiochemistry and allowed the correct atropisomer to be formed in a 4:1 ratio. After some functional group manipulation and coupling in the other unnatural amino acids, the B-*O*-D macrocycle was formed by an S_NAr reaction as previously used

by others.[83, 101] Global deprotection led to the first total synthesis of complestatin **1.58**, which also represents a reversal in cyclisation order compared to the Hoveyda route to chloropeptin.[88] After much optimisation it was found that the acetamide was crucial for successful macrocyclisation to a) deactivate the strained indole towards electrophiles and b) positively influence the atropdiastereoselectivity. The choice of ligand, solvent and base was also important.

A year later Zhu and co-workers published their total synthesis of complestatin.[102] Since the atropselectivity is highly substrate dependent Zhu set about first forming the D-F macrocycle **1.137** using a Sukuzi-Miyaura coupling, before appending the biaryl ether containing macrocycle (Scheme **1.27**).

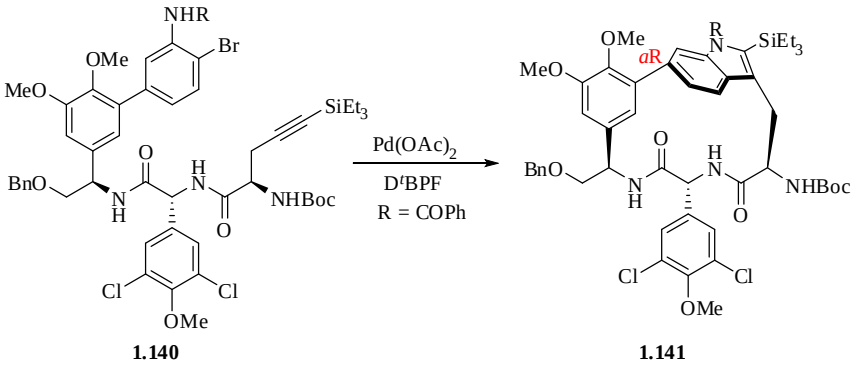


Reagents & Conditions: i) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, K_2CO_3, dioxane/H_2O, 90 °C, 66%; ii) K_2CO_3, DMSO, 4 Å M.S., 20 h, 30 °C, 62%.

Scheme 1.27: Key steps in Zhu's total synthesis of complestatin **1.58**.

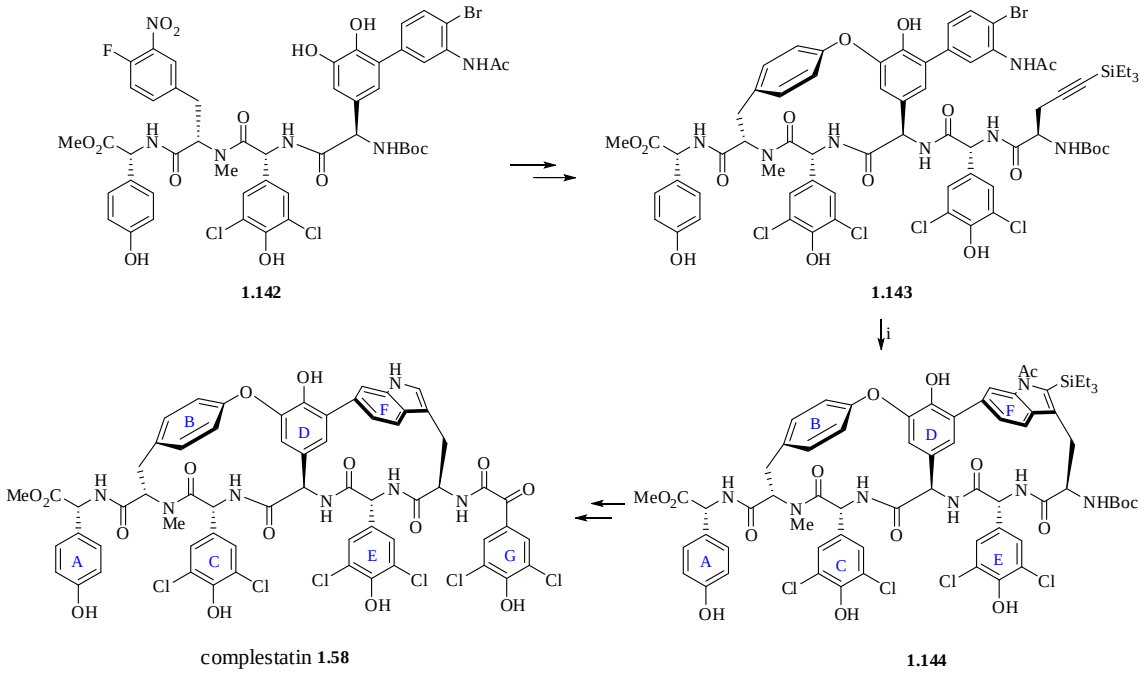
In 2010 Boger published details of a second-generation synthesis of complestatin **1.58** and disclosed further details of the Larock indole macrocyclisation reaction (Scheme **1.28**). Crucial to the success of this reaction was the use of a bulky TES-acetylene as this was shown to dictate the regiochemical course of the reaction.[98, 99] Equally, when

the indole-nitrogen was left unprotected, competitive side-processes would occur. The reactivity of the indole towards electrophiles could be tempered by acylation of the indole-nitrogen. A range of different indole carbamates were trialed and it was found that when R = COPh lower reaction temperatures, higher yields, and improved atropdiastereoselectivity could be achieved. According to simple models, the *N*-acyl substituent lies over the peptide backbone leading to the *S*-atropisomer. Thus, a larger R-group should destabilise the pathway *en route* to isocomplestatin, promoting formation of complestatin **1.58**.



Scheme 1.28: Optimisation of the Larock indole synthesis.

In their second generation synthesis (Scheme **1.29**), Boger *et al*. employed an S_NAr biaryl ring closure to construct the B-*O*-D, then a Larock-indole synthesis to append the second macrocycle. This allowed for a more convergant approach and, more impressively, led to a reversal in atropselectivity compared with the Hoveyda and Zhu approaches.[93, 96]



Reagents & Conditions: i) $Pd(OAc)_2$, D^{t}BPF, Et_3N, MeCN/PhMe, 1.5 h, reflux, 56%.

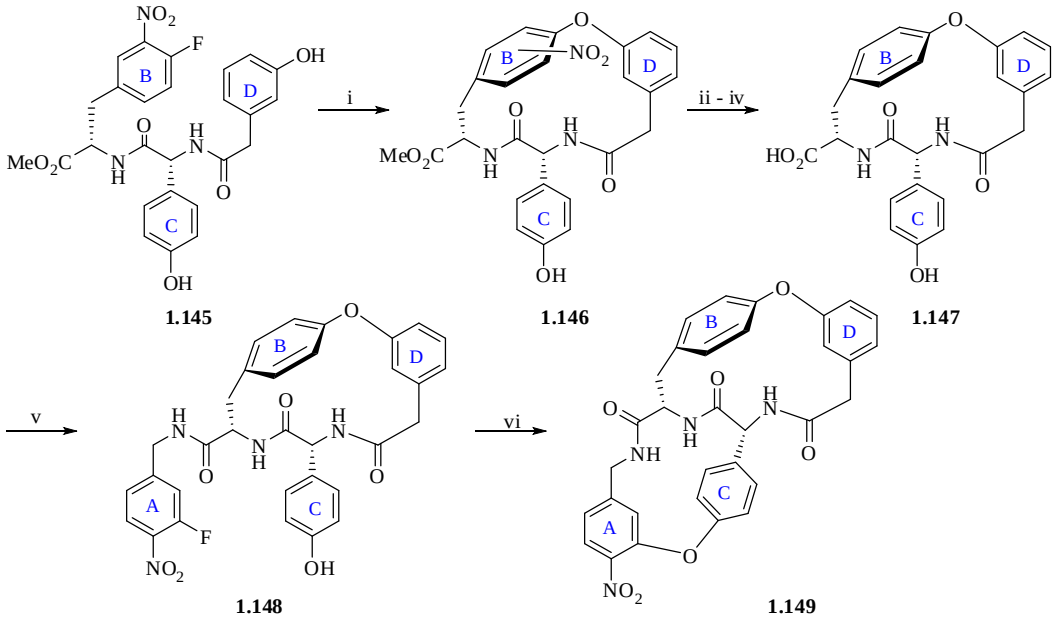
Scheme 1.29: Key steps in Boger's second generation synthesis of complestatin **1.58**.

Kistamicins A and B

Kistamicins A **1.62** and B **1.63** were isolated from *Microtetraspora Parvasaeta* sbsp *Kistanae* by scientists at Bristol-Myers Squibb, and were shown to inhibit type A influenza virus. They also display moderate *in vitro* activity against Gram positive bacteria.[103] The structures of the kistamicins were determined by NMR and degradation experiments,[104] but the configuration of the Trp-Ar axis has yet to be established. In 1997 Roussi *et al*. described work on a model system of the A-*O*-C macrocycle found in kistamicin.[105] Shortly thereafter, the same team also disclosed their synthesis of a bicyclic model of the A-*O*-CB-*O*-D system (Scheme **1.30**).[106]

Tripeptide **1.145** was prepared using several peptide coupling reactions. Cyclisation to **1.146** was realised in 75% yield using $KHCO_3$ in DMF and also led to other diasteromers resulting from epimerisation. The formation of atropisomers was of no consequence as removal of the nitro group by reduction and diazotisation removed this chiral element. Saponification of the terminal methyl ester in **1.146** followed by

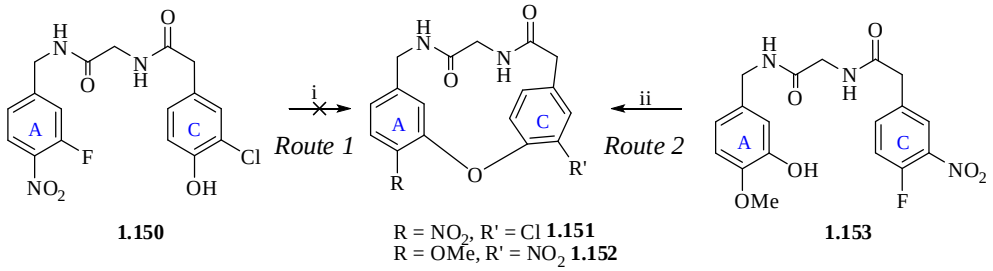
coupling to 3-fluoro-4-nitrobenzylammonium hydrochloride, gave the advanced precursor **1.148**. Cyclisation as before gave bis-macrocycle **1.149** in 80% yield.



Reagents & Conditions: i) $KHCO_3$, DMF, 18-crown-6, 75%; ii) Pd/C, H_2, MeOH, 92%; iii) ^tBuONO, DMF, 40%; iv) LiOH, THF/MeOH/H_2O, 95%; v) 3-fluoro-4-nitrobenzylammonium chloride, EDCI, HOBt, Et_3N, CH_2Cl_2, 87%; vi) $KHCO_3$, DMF, 18-crown-6, 80%.

Scheme 1.30: Roussi's synthesis of a model A-*O*-CB-*O*-D system **1.149**.

In 1999, Roussi and co-workers disclosed further details of the S_NAr A-*O*-C ring-closure approach and a second generation synthesis of the A-*O*-CB-*O*-D bicycle.[101] Shown in Scheme **1.31** is an investigation of the S_NAr macrocyclisation. When using the C ring as the nucleophile and the A ring as the electrophile, *viz.* **1.150** → **1.151**, none of the desired product **1.151** could be identified in the complex product mixture, despite full consumption of the starting material. In sharp contrast, when the A ring was the nucleophilic component and the C ring the electrophile, the desired product **1.152** was afforded in good yield. This dichotomous reactivity was attributed to electronic differences between the two pathways, with route 2 having a more nucleophilic A ring phenol due to the *o*-methoxy group. Consequently, they reasoned that this was better able to overcome the energetic barrier to formation of a highly strained 15-membered macrocycle.

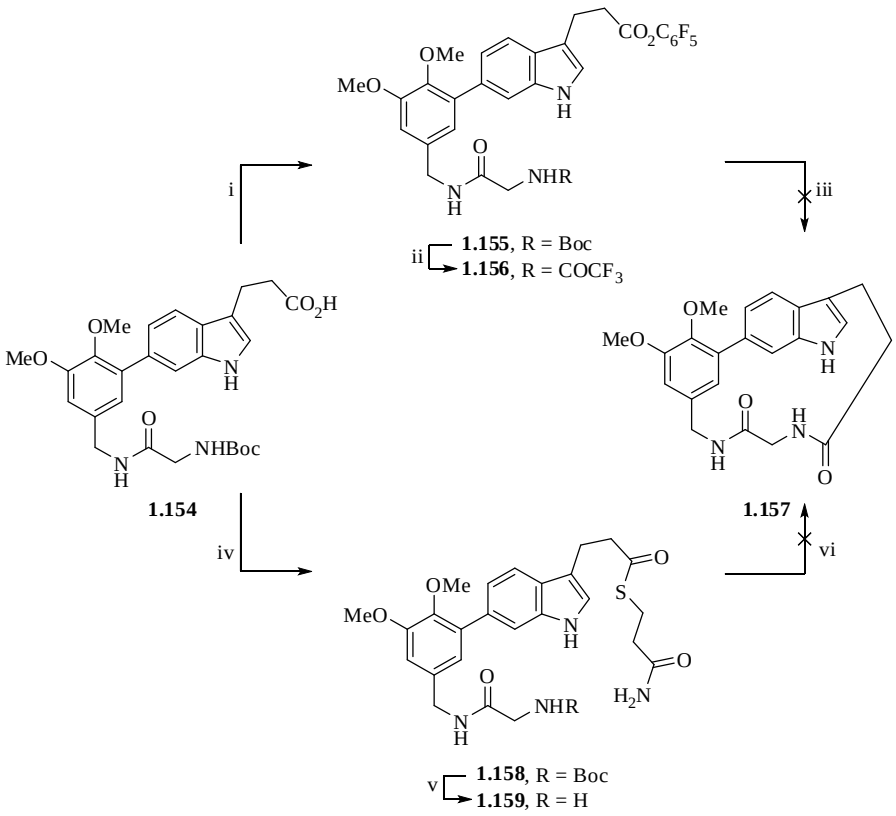


1.150 R = NO_2, R' = Cl **1.151**; R = OMe, R' = NO_2 **1.152**; **1.153**

Reagents & Conditions: i) K_2CO_3, DMF, 18-crown-6, 0%; ii) K_2CO_3, DMF, 18-crown-6, 86%

Scheme 1.31: Study of S_NAr macrocyclisation pathways leading to the A-*O*-C model.

Several attempts were made to realise cyclisation leading to a model of the D-F macrocycle (Scheme **1.32**) including intramolecular lactam formation using a pentafluorophenyl ester (**1.156** → **1.157**) and silver-mediated thio-ester activation strategy (**1.159** → **1.157**). However, neither method yielded any of the desired product, which could only be accessed by means of a Ni-catalysed intramolecular biaryl synthesis akin to that used in their synthesis of the D-F ring of complestatin (Scheme **1.16**).[85]



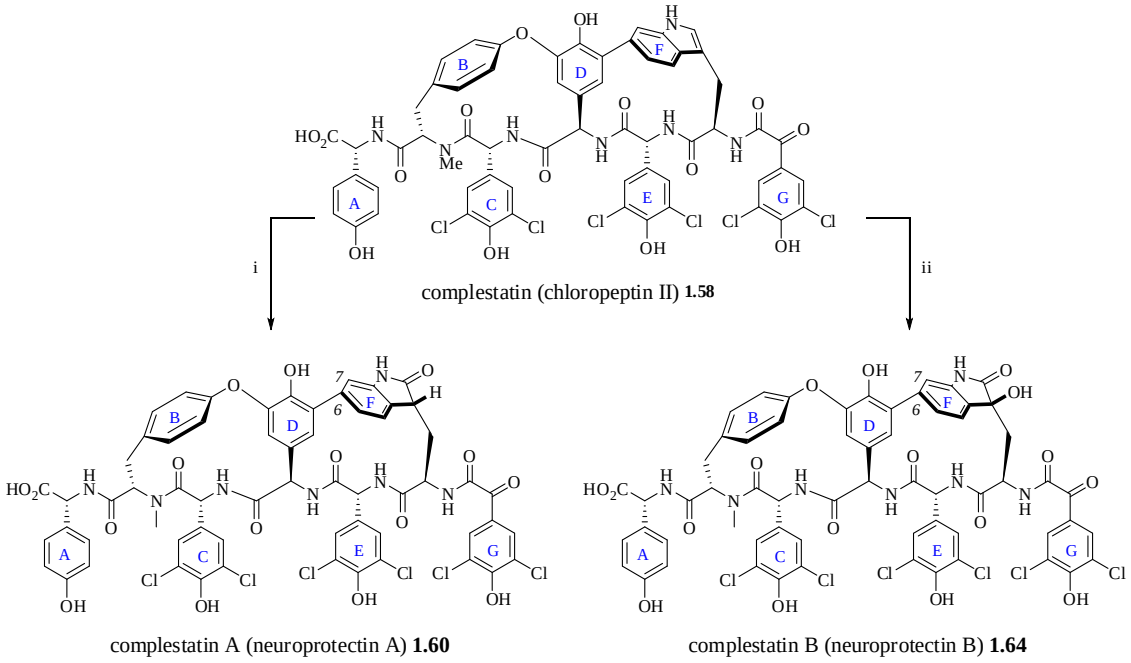
Reagents & Conditions: i) HOC_6F_5, EDCI, DMF; ii) TFA-CH_2Cl_2, thioanisole; iii) dioxane-py (5:1), 90 ^oC; iv) 3-mercaptopropionamide, DPPA, DMF, 86%; v) TFA-CH_2Cl_2; vi) Ag^+, DMSO-buffer, pH=5.5 (1:1)

Scheme 1.32: Attempted closure of the D-F macrocycle **1.157**.

Complestatin A and B (neuroprotectin A and B)

Complestatins A **1.60** and B **1.64** were isolated from *Streptomyces* sp. MA7234 by scientists at Merck, and were shown to inhibit HIV-1 integrase. Though their gross structures were determined, stereochemical configurations were only partly assigned.[71] Independently, **1.60** and **1.64** were isolated from *Streptomyces* sp. Q27107 and disclosed as neuroprotectin A and B respectively. The first total syntheses of both complestatin A and B were achieved by Boger and co-workers in 2011, making use of a single-step oxidation of complestatin **1.58** to give both natural products (Scheme **1.33**).[107] After investigating various oxidation conditions it was found that treatment of **1.58** with HCl in DMSO provided the corresponding oxindole cleanly and in high yield. Remarkably, chloropeptin I **1.59** was not detected during the reaction, which was unexpected given the sensitivity of the complestatin D-F system towards acid.

Complestatin B was realised by chlorination at C3 of the indole followed by tautomerism and hydrolysis.



Reagents & Conditions: i) conc. HCl, DMSO, 72 h, RT, 93%; ii) NCS, THF/H_2O, 0.5 h, RT; then Cs_2CO_3, DMF/H_2O, 1 h, RT, 30%.

Scheme 1.33: Key steps in Boger's total syntheses of complestatins A **1.60** and B **1.64**.

In the aforementioned work we have seen many approaches to the synthesis of members of the RP 66453 family. The biaryl ether containing fragment has been made via TTN phenolic coupling,[86] S_NAr,[83] and Ullmann reactions.[88] The synthesis of the biaryl containing portion has been achieved successfully using a number of Pd-mediated coupling reactions including: Suzuki,[102] Stille[88] and Larock cyclisations.[97] With RP 66453 itself, the Zhu research team has successfully completed the total synthesis of an atropisomer of RP 64453, closing the key biaryl bond by an intramolecular Suzuki reaction.[12]

Chapter 2: Retrosynthetic Analysis and Strategy

As we have seen previously, Zhu and co-workers formed the atropisomer of RP 66453 **1.00** using an intramolecular Suzuki-Miyaura coupling reaction to form the key biaryl linkage (Scheme **1.10**).[12] Furthermore, in an exquisite experiment, they were able to show that the natural product could be converted into the synthetic atropisomer by heating (Scheme **1.11**), thereby proving that natural RP 66453 was not the thermodynamic atropisomer. It is usual for metal-catalysed reactions of this type to give the thermodynamic atropisomer as they are conducted at elevated temperatures and have a late transition-state (Figure **2.1**).

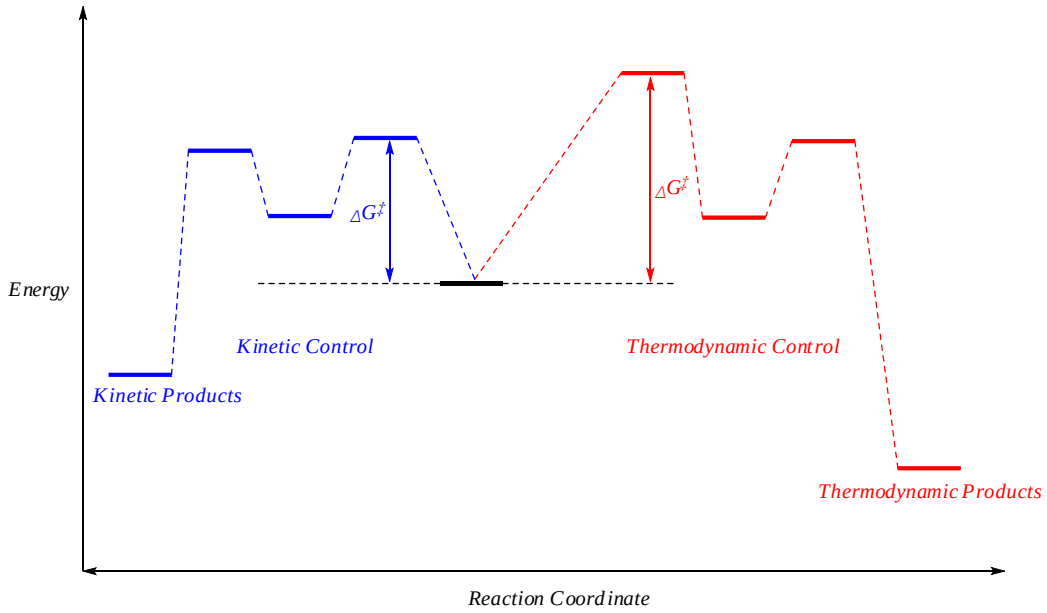
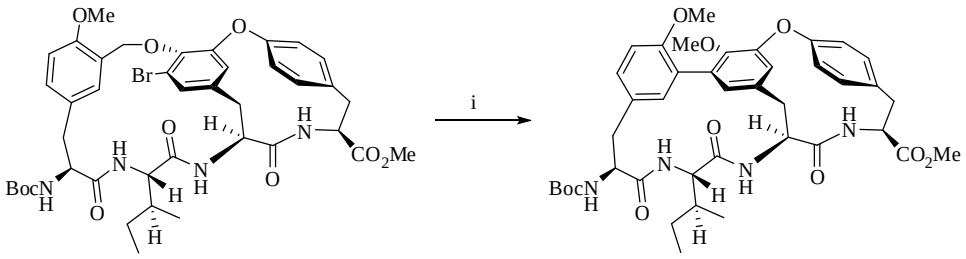


Figure 2.1: Kinectic vs. thermodynamic control.

We believe that the key to securing a total synthesis of RP 66453 **1.00** is to form the crucial biaryl linkage under conditions of kinetic control. As radical cyclisation reactions generally proceed under kinetic control, our plan was to invoke a radical-induced transannular ring contraction to control the atropselectivity and secure the first total synthesis of **1.00** (Scheme **2.1**).



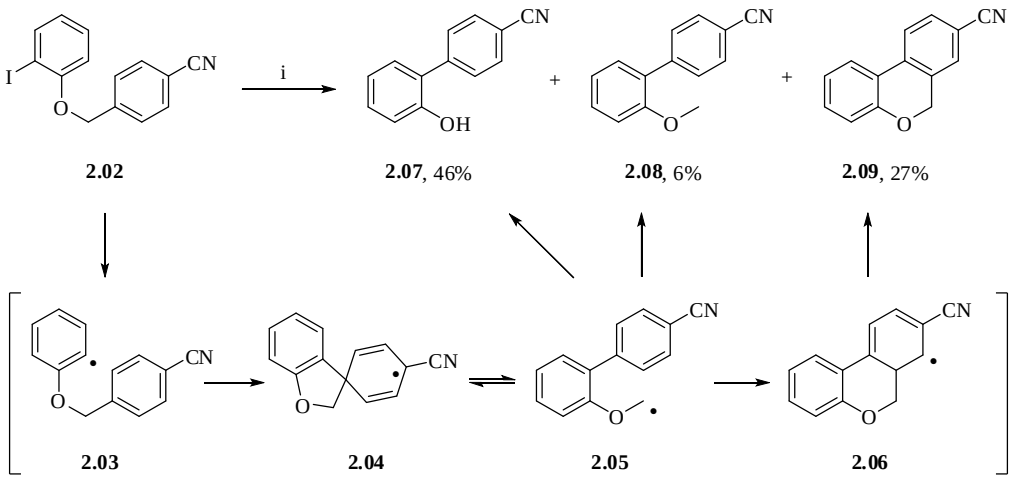
2.00 **2.01**

Reagents & Conditions: i) Bu_3SnH, AIBN, PhMe, 80 ^oC.

Scheme 2.1: Our proposed key step.

2.1 Radical Aryl Migration Reactions for the Synthesis of Biaryls

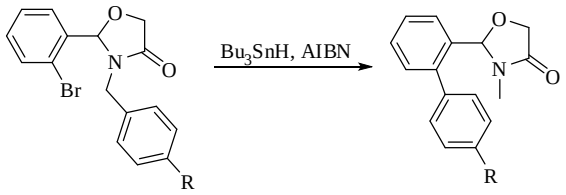
In 2001 Harrowven *et al*. showed that homolysis of benzyl *o*-iodoaryl ethers induced an intramolecular addition of the resulting aryl radical intermediate to an adjacent arene resulting in the formation of biaryls in reasonable yields (Scheme **2.2**).[108] For example, treatment of iodide **2.02** with Bu_3SnH/AIBN gave rise to aryl radical **2.03** which underwent a 5-*exo*-trig cyclisation to spirocyclic intermediate **2.04**. Rearomatisation followed through fragmentation to the methylene radical **2.05**. At this point a number of processes compete: a) H-atom abstraction from Bu_3SnH to afford the methyl ether **2.08** (6%); b) 5-*exo*-trig cyclisation back to **2.04**; c) the more sluggish 6-*exo/endo*-trig cyclisation to **2.06** and hence benzo[*c*]chromene **2.09**; or d) redox processes between **2.05** and a stannane (or dissolved O_2) leading to phenol **2.07**. It was also shown that substituents *ortho* to the benzyl ether enhance regioselectivity and the yield of the desired biaryl.



Reagents & Conditions: i) Bu_3SnH, AIBN, PhMe, 80 ^oC.

Scheme 2.2: Harrowven's synthesis of biaryls from benzyl iodoaryl ethers.

In 1997 Renaud *et al*. showed that a 1,5-aryl migration from carbon to carbon could be used in the formation of biaryls (Scheme **2.3**).[109] A range of aryl bromides **2.10–2.13** were treated with Bu_3SnH/AIBN giving biaryls **2.10'–2.13'** in moderate yield, along with byproducts resulting from reduction of the starting material and from the competing 8-*exo/endo*-trig cyclisation pathway.



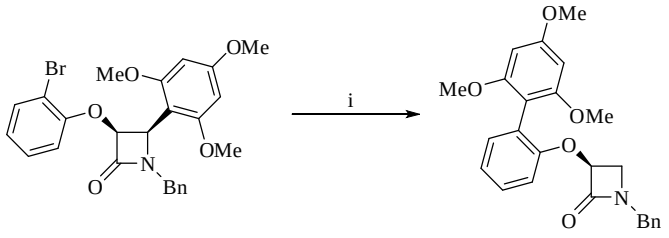
2.10, R = H
2.11, R = CN
2.12, R = CF_3
2.13, R = OMe

2.10', 47%
2.11', 45%
2.12', 46%
2.13', 34%

Scheme 2.3: 1,5-aryl migration in the preparation of biaryls.

Further examples of 1,5-aryl migrations were disclosed by Acaide a year later when it was shown that exposure of bromide **2.14** to standard radical forming conditions gave biaryl **2.15** (Scheme **2.4**).[110] By blocking the *ortho* positions from homolytic attack, competing pathways were largely suppressed allowing high yields of the biaryl

(compared with Scheme **2.3**) to be obtained. The driving force of these reactions (Schemes **2.3** and **2.4**) is the formation of a stabilised amidomethyl radical.

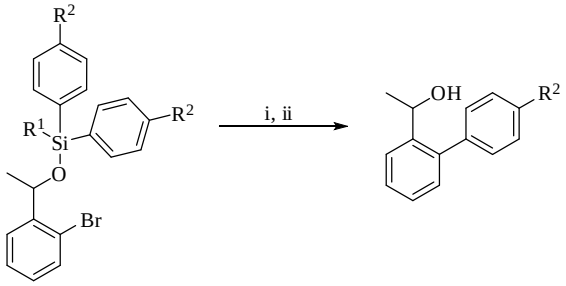


2.14 **2.15**

Reagents & Conditions: i) Bu_3SnH, AIBN, PhMe, 80 ^oC, 80%.

Scheme 2.4: Preparation of biaryls with *o*,*o*-disubstituted substituents.

Heavier atoms too can undergo this 1,5-aryl migration, as shown by Studer and coworkers with a migration from silicon to carbon during the formation of biaryls (Scheme **2.5**).[111] Homolysis of aryl bromide **2.16** under stannous hydride conditions induced cyclisation to the adjacent arene. Fragmentation with ejection of a silyl radical led to the formation of biaryl **2.17** in good yield after desilylation. Studer showed the versatility of the reaction by having various electron donating and withdrawing groups at R^1 and R^2 on the acceptor arene.



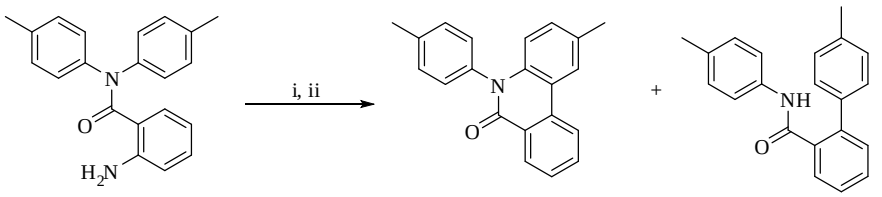
2.16 **2.17**

Reagents & Conditions: i) Bu_3SnH, AIBN, PhMe, 80 ^oC; ii) MeLi, 49–77%.

Scheme 2.5: Biaryl synthesis via 1,5-migration from silicon to carbon.

In 1959 Hey *et al*. disclosed the first example of a 1,4-aryl migration from nitrogen to carbon (Scheme **2.6**).[112] Treatment of aniline **2.18** with sodium nitrite and HCl afforded the corresponding diazonium hydrochloride which, when treated with Cu powder

formed an aryl radical *en route* to the Pschorr product **2.19** (28%) and the 1,4-aryl transfer product **2.20** (58%). The presence of substituent groups had little effect on the outcome of the reaction. However, the product mixture did change when diazonium salt decomposition was induced by thermolysis: In such cases none of the rearrangement product was detected.

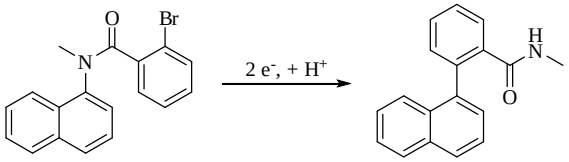


2.18 **2.19**, 28% **2.20**, 58%

Reagents & Conditions: i) $NaNO_2$, $cHCl/H_2O$, then; ii) Cu powder.

Scheme 2.6: Homolytic formation of biaryls from nitrogen.

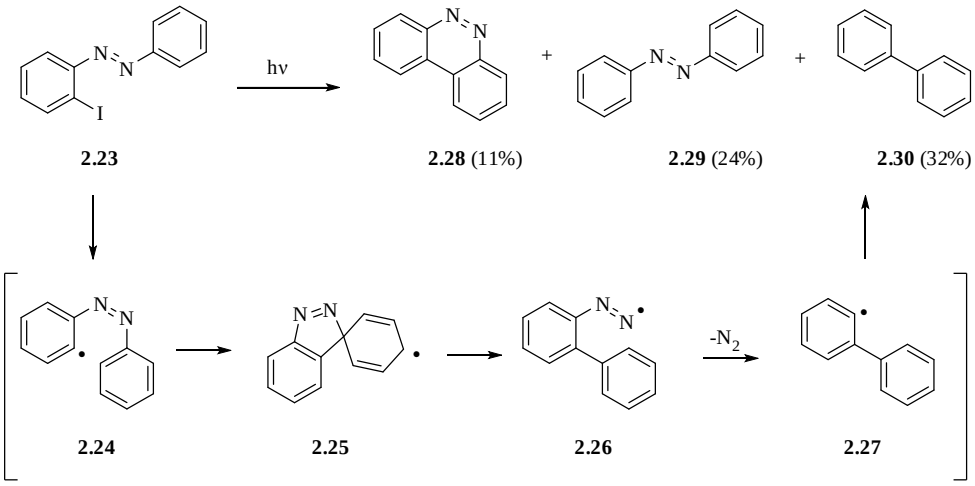
This migration pathway has also been realised by electrochemical mediated radical generation (Scheme **2.7**). Grimshaw *et al*. showed that the electrochemical reduction of aryl bromide **2.21** induced 1,4-phenyl migration leading to biaryl **2.22** in good yield (69%).[113, 114] In this case the driving force for aryl migration is the formation of an *N*-centred amidyl radical.



2.21 **2.22**

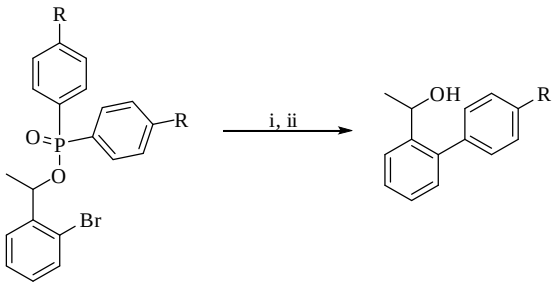
Scheme 2.7: Electrochemical formation of biaryls from nitrogen.

Aryl migrations from nitrogen to carbon have also been mediated photochemically (Scheme **2.8**). Prolonged irradiation of **2.23** led to *trans*/*cis* isomerisation and homolysis of the carbon-iodine bond leading to aryl radical **2.24**. Formation of spirocyclic intermediate **2.25** followed by rearomatisation and loss of nitrogen ultimately leads through to biaryl **2.30**. Other products noted were **2.28** and **2.29** which can be accounted for by 6-*exo*/*endo* cyclisation of **2.24** and reduction of **2.23** respectively.



Scheme 2.8: Photochemical formation of biaryls from diazo-bridged biaryls.

In 2000, Clive *et al*. reported the first example of biaryl synthesis by radical transfer in a phosphinate-tethered system (Scheme **2.9**).[115] Phosphinates **2.31–2.34**, when treated with various alkyl-tin hydrides and AIBN afforded biaryls **2.31'–2.34'** in reasonable yield. Electron-rich, poor and neutral substituents could be tolerated with no significant deviation in yield. Heteroarenes can also be transferred using this methodology.



2.31, R = H
2.32, R = OMe
2.33, R = Me
2.34, R = CO_2Me

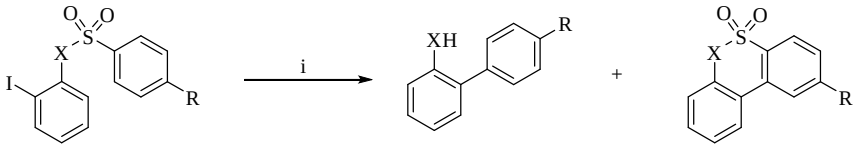
2.31', 64%
2.32', 52%
2.33', 63%
2.34', 54%

Reagents & Conditions: i) R'_3SnH, AIBN, xylene, heat; ii) aqueous KF.

Scheme 2.9: Phosphinate-tethered synthesis of biaryls by 1,5-aryl migration.

Motherwell showed that a series a functionalised biaryls could be prepared by radical-mediated 1,4-aryl migration, this time by using sulfonate and sulfonamide tethered arenes (Scheme **2.10**).[116] This strategy provides another arrow-in-the-quiver of the

synthetic chemist with which to create biaryls. Competing *ortho*-cyclisation was a problem however (**2.35b**–**2.40b**) and in a later disclosure, Motherwell *et al*. showed that by incorporating methyl groups at the *ortho*-positions of the acceptor arene higher yields of the biaryl could be obtained. It was reasoned that the buttressing effect of the *ortho*-methyl groups slows the *ortho*-cyclisation pathway and greatly accelerates the reverse reaction. Overall, this increased the proportion of the reaction pathway proceeding via the spirocyclic intermediate.[117]

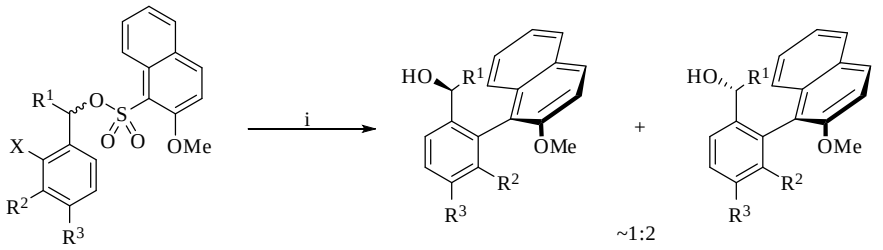


2.35, R = Me, X = NMe	**2.35a**, 34%	**2.35b**, 39%
2.36, R = OMe, X = NMe	**2.36a**, 33%	**2.36b**, 10%
2.37, R = F, X = NMe	**2.37a**, 29%	**2.37b**, 44%
2.38, R = Me, X = O	**2.38a**, -	**2.38b**, 63%
2.39, R = OMe, X = O	**2.39a**, 18%	**2.39b**, 24%
2.40, R = F, X = O	**2.40a**, -	**2.40b**, 50%

Reagents & Conditions: i) Bu_3SnH, AIBN, PhH, reflux.

Scheme 2.10: 1,4-Aryl migration in sulfonates and sulfonamides.

In 2008, Studer and co-workers demonstrated the first example of an atropselective radical aryl migration leading to axially chiral biaryls (Scheme **2.11**).[118] The radical precursors **2.41** were prepared by reaction of the *rac*-secondary benzylic alcohols with the corresponding sulfonyl chlorides. Thus, treatment of a range of racemic secondary sulfonates under standard radical forming conditions led to separable diastereomeric mixtures of biaryl products **2.42a** and **2.42b** with moderate atropselectivity. Although atropselectivity was low, this work provided encouragement for the future development of highly-atropselective routes to axially chiral biaryls by radical aryl migration.



2.41 **2.42a** **2.42b**

Reagents & Conditions: i) Bu_3SnH, VAZO, PhH, 80 ^oC.

Scheme 2.11: Atropselective 1,5-aryl migration.

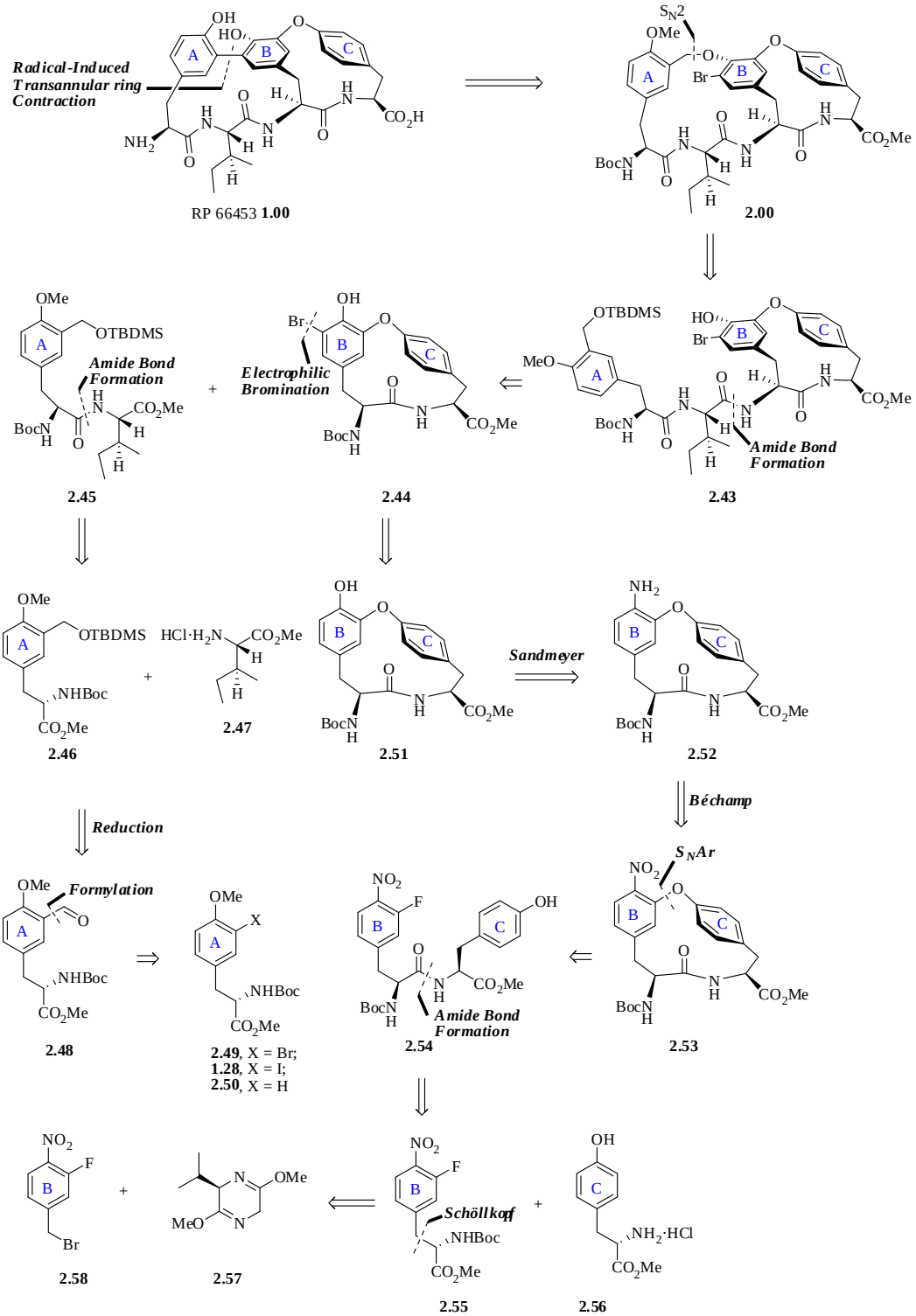
2.2 Our Retrosynthetic Analysis

As discussed previously, we believe that the key to securing the first total synthesis of RP 66453 **1.00** is to form the axially chiral biaryl bond under conditions of kinetic control. This prompted us to investigate the use of a radical-induced transannular ring contraction, as detailed in our retrosynthetic analysis presented in Scheme **2.12**. Disconnection of the biaryl bond in the 15-membered A-B macrocycle of **1.00** leads back to a benzyl ether tethered to an aryl bromide or iodide within an 18-membered macrocycle, **2.00**. Homolysis of the carbon-halogen bond would give an aryl radical which, after a kinetic 5-*exo*-trig cyclisation would give a spirocyclic intermediate of fixed configuration. Fragmentation and rearomatisation would give the corresponding biaryl (*viz.* **2.00** → **1.00**).

It is anticipated that this benzyl ether containing macrocycle **2.00** could arise from an intramolecular Mitsunobu reaction of **2.43**. In turn, this would be prepared by coupling of the two dipeptide fragments **2.44** and **2.45**. For the A-fragment **2.45**, disconnection of the Tyr-Ile bond leads back to isoleucine methyl ester **2.47** and functionalised tyrosine **2.46**. The 3-benzyl alcohol group can be installed by reduction of the corresponding benzaldehyde **2.48** which in turn could be formed by formylation of protected tyrosine **2.49**, **1.28** or **2.50** using, for instance, a Reimer-Tiemann or Vilsmeyer formylation reaction.

Our analysis of the B-*O*-C fragment **2.51** indicated that it could be prepared from phenol **2.54** by an intramolecular S_NAr macrocyclisation reaction. Notably, this is

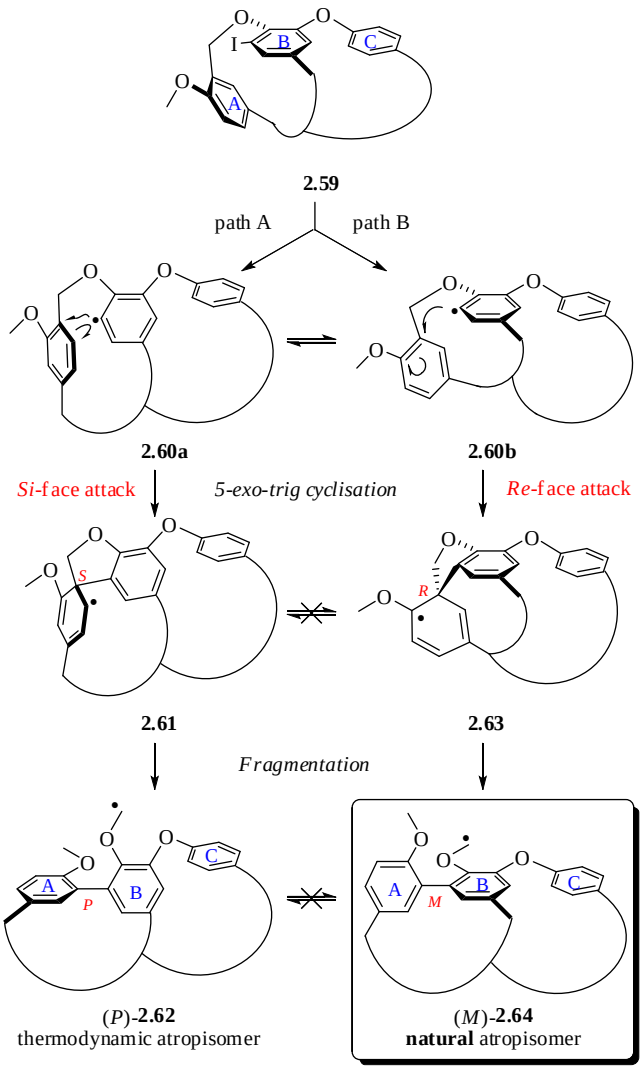
similar to the approach of the Zhu and Boger teams (Schemes **1.1** and **1.9**).[9, 10, 12] However, while they used the B ring as the nucleophile and the C ring as the electrophile, we wish to reverse this strategy. We reasoned that we could make use of the nitro group as a phenol surrogate and that this would be more elegant than simply removing it, as would be the case if placed on the C ring.



Scheme 2.12: Our Initial Retrosynthetic Strategy.

2.3 Stereochemical Rationale

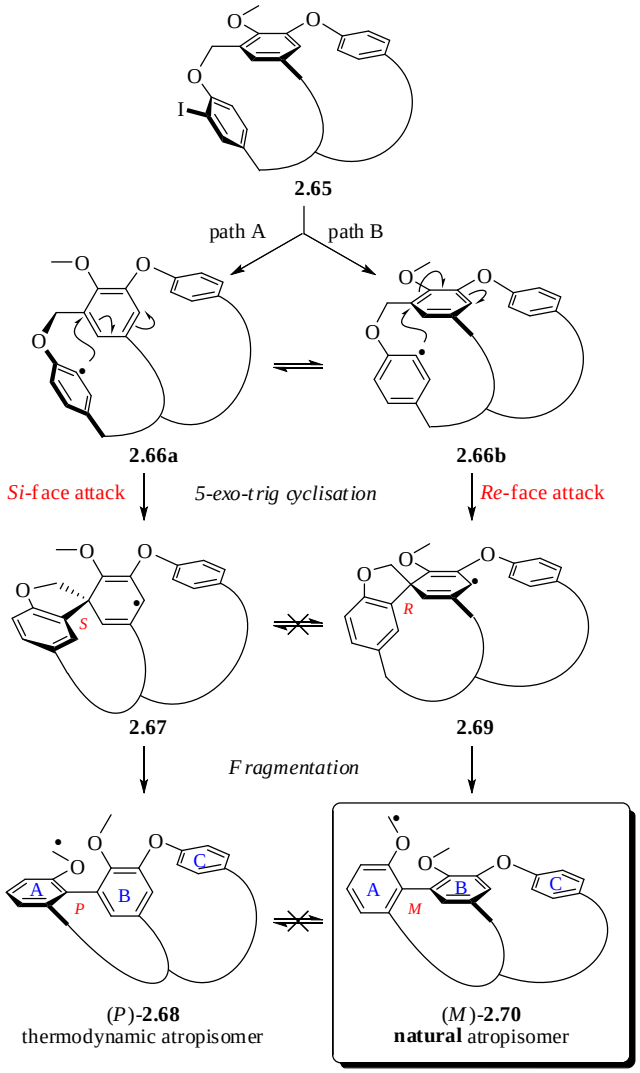
Shown in Scheme **2.13** is our hypothesis of the stereochemical outcome of our crucial radical-induced transannular ring contraction. Homolysis of the carbon-iodine bond in **2.59** gives an aryl radical **2.60** which can add to either the *Si* or *Re* face of arene A (path A or B respectively) via reactive conformers **2.60a** and **2.60b**. At this point a new stereocentre is formed *S*-**2.61** or *R*-**2.63**, which is lost on fragmentation and rearomatisation, when the point-centred chirality is transferred into the chiral axis of the biaryl which must be *P* or *M* configured (**2.62** and **2.64** respectively).



Scheme 2.13: Explanation of the stereochemical issues.

As the ring contraction will fix the configuration of the A-B macrocycle we can conclude that the sense of axial chirality will be governed by the point chirality generated upon radical addition. In turn this is governed by the nature of the reactive conformer **2.60a** and **2.60b** as this dictates whether the *Re* or *Si* face of arene A receives the aryl radical intermediate. This brings into play planar chirality elements i.e. whether the peptide backbone is above or below the plane of the B ring.

Should we observe the wrong stereochemical outcome, i.e. opposite to that found in the natural product, we have the option of reversing the donor/acceptor arenes (Scheme **2.14**). It is hoped that reversing the face of attack will put the synthesis back on track. We also have the option of conducting the reaction at low temperature using Et_3B/O_2 as the initiator to help improve atropdiastereoselectivity.

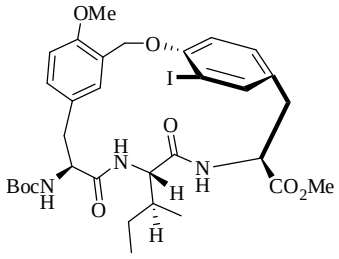


Scheme 2.14: Reversal of donor/acceptor arenes.

Chapter 3: Results & Discussion: A-B Macrocycle

3.1 Initial Route

Guided by our initial retrosynthesis we set about preparing a model system of the A-B macrocycle **3.00** to test the feasibility of our proposed radical-induced transannular ring contraction (Figure **3.1**).

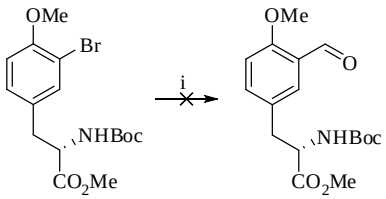


3.00

Figure 3.1: Target for our proposed model system.

3.1.1 Installing a Formyl Equivalent onto Tyrosine

As can be seen from our original retrosynthesis (Scheme **2.12**) we required a benzyl alcohol at the 3-position on tyrosine to form our ether tether, which we reasoned could come from reduction of a formyl group. Previously within our group Nanson had explored this route showing that the Vilsmeier-type formylation of bromide **2.49** failed to give any of the desired product **2.48** (Scheme **3.1**).[119]

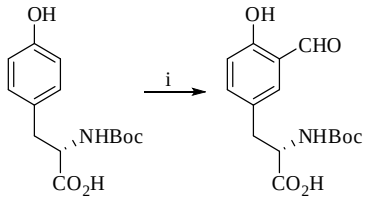


2.49 **2.48**

Reagents & Conditions: i) NaH, ^{n}BuLi, THF then DMF.

Scheme 3.1: Attempted Vilsmeier-type formylation by Nanson.

Nanson also tried a Reimer-Tiemann formylation, shown in the literature to proceed in good yield.[120] However, in our hands this reaction was low yielding and capricious, giving inseparable mixtures of product starting material (Scheme **3.2**).

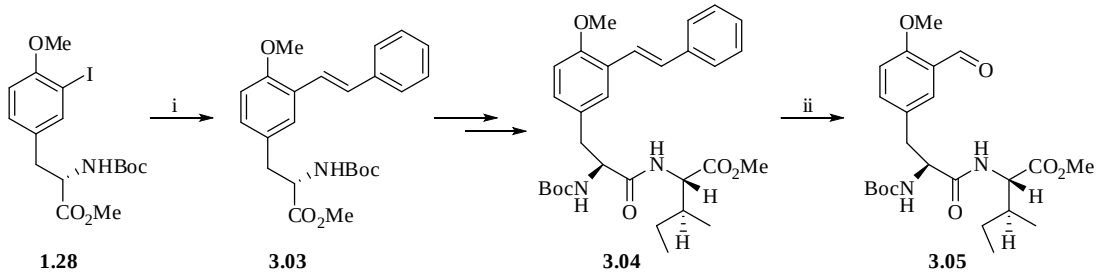


3.01 **3.02**

Reagents & Conditions: i) $CHCl_3$, NaOH, H_2O, 10 h, 61 °C, 10–28%.

Scheme 3.2: Riemer-Tiemann reaction done by Nanson.

Nanson went on to show that the most efficient method for installing the benzyl alcohol was the longer protocol involving a Suzuki reaction onto iodotyrosine **1.28**, followed by ozonolysis and reduction (Scheme **3.3**).

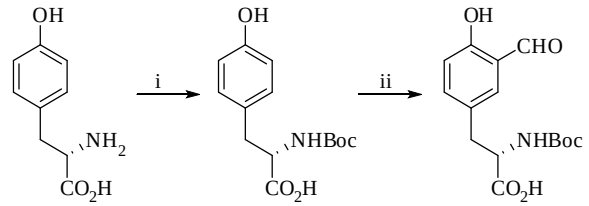


1.28 **3.03** **3.04** **3.05**

Reagents & Conditions: i) *trans*-2-Phenylvinylboronic acid, K_2CO_3, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, DMSO, 18 h, 80 °C, 89%; ii) O_3/O_2, CH_2Cl_2, 30 min, –78 °C then PPh_3 30 min, –78 °C, 83%.

Scheme 3.3: Alternative route to install the formyl group.

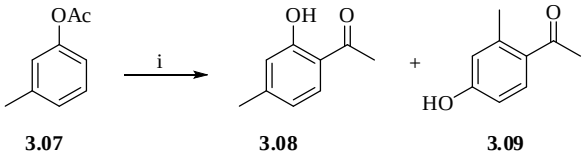
We decided initially to repeat the Reimer-Tiemann protocol to see if we could improve upon the efficiency of the reaction (Scheme **3.4**). The free amine of tyrosine **3.06** was protected as a Boc carbamate in reasonable yield (66%). Treatment of the product **3.01** under the Reimer-Tiemann conditions developed by Jung *et al* proceeded poorly, giving aldehyde **3.02** in 9% yield with the remaining mass balance accounted for by recovered starting material.



Reagents & Conditions: i) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 ^oC–RT, 66%; ii) $CHCl_3$, NaOH, H_2O, 4 h , 61 ^oC, 9%.

Scheme 3.4: Riemer-Tiemann route to 3-formyltyrosine.

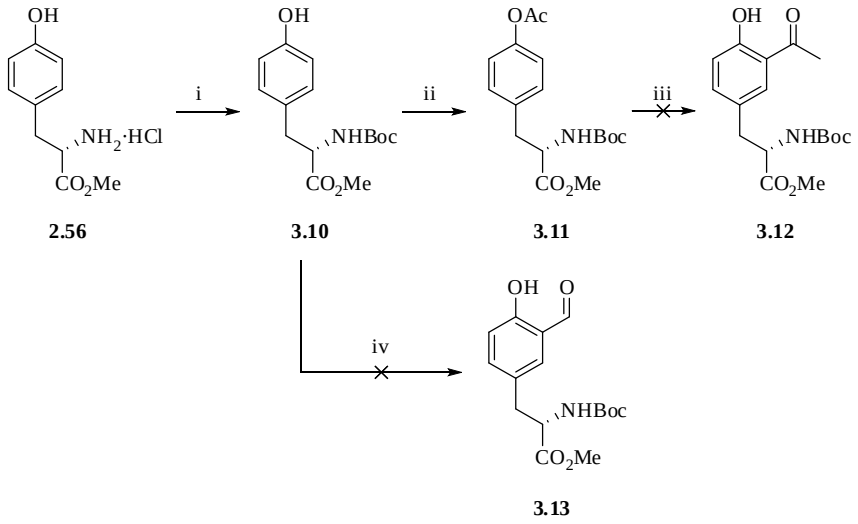
The Fries rearrangement is an important reaction in aromatic chemistry giving rise to acetyl derivatives from acyl esters, typically through activation of a Lewis acid or heating. In 1996 Harrowven *et al*. reported an ambient temperature *ortho*-selective Fries rearrangement mediated by $ZrCl_4$ (Scheme **3.5**).[121]



Reagents & Conditions: i) $AlCl_3$ (2 eq), $PhNO_2$, 66 h, RT, 28% **3.08**, 64% **3.09**;[122] or $AlCl_3$ (2 eq), neat, 15 min, 160 ^oC, 89% **3.08**, 7% **3.09**;[123] or ZrCl (4 eq), CH_2Cl_2, 8 h, RT, 95% **3.08**, <1% **3.09**.

Scheme 3.5: *ortho*-Fries rearrangement of 2'-hydroxy-4'-methylacetophenone.

We sought to use this method as a convenient way to install a 3-acyl substituent which, if successful, could be expanded to the less commonly known Fries-rearrangement of formate esters.[124-126] To that end acetate **3.12** was made in two steps from the commercially available ester in 88% yield (Scheme **3.6**). However, when exposed to the reported Fries-conditions only a complex product mixture was isolated, prompting a switch to another strategy.

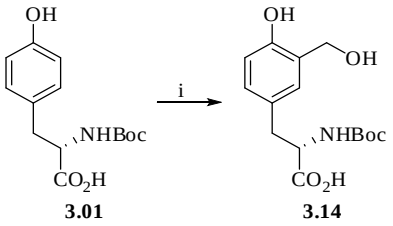


Reagents & Conditions: i) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 °C–RT, 90%; ii) Ac_2O, Et_3N, CH_2Cl_2, 16 h, 0 °C–RT, 98%; iii) $ZrCl_4$, CH_2Cl_2,))); iv) $(CH_2O)_n$ or 1,3,5-trioxane, $SnCl_2$, PhMe.

Scheme 3.6: Attempted 3-functionalisation by Fries rearrangement and direct formylation.

It is known that Lewis acids can facilitate addition of formaldehyde *ortho*- to a phenol.[127-129] We looked to use this methodology to effect the transformation **3.10** → **3.13** by exposing **3.10** to both paraformaldehyde and 1,3,5-trioxane in the presence of $SnCl_2$. However, the reaction did not yield any of the desired product, either returning recovered starting material or giving an unidentified polymeric material through further condensation reactions with the phenol.

In 2010 Huang and co-workers employed a direct hydroxymethylation of tyrosine in their synthesis of the Hirsutellone core.[130] Pleasingly, we were able to repeat this procedure to give the 3-substituted benzyl alcohol **3.14** in good yield from *N*-Boc tyrosine **3.01** (Scheme **3.7**). Drawbacks associated with these formylation conditions were that it was particularly sluggish (5 d) and proved difficult to selectively protect the resulting adduct. We therefore continued to seek a more efficient approach to this key synthetic equivalent.

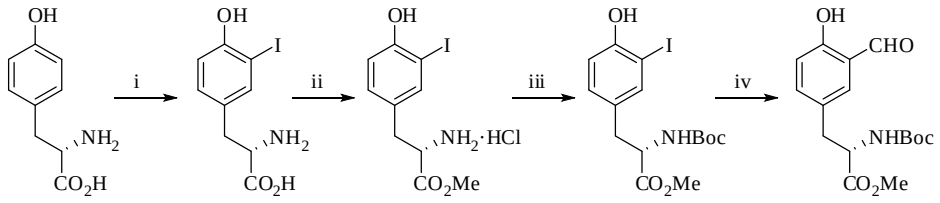


3.01 **3.14**

Reagents & Conditions: i) $Na_2B_4O_7 \cdot 10H_2O$, $(CH_2O)n$, NaOH, H_2O, 5 d, 40 ^oC, 82%.

Scheme 3.7: Borax mediated benzyl alcohol installation.

In 2001 Morera *et al*. showed that 3-formyltyrosine **3.17** could be successfully prepared by means of a Pd-catalysed hydroformylation reaction.[131] To that end we prepared 3-iodotyrosine derivative **3.16** in 3 steps using known procedures (Scheme **3.8**). Tyrosine 3**.06** was iodinated with I_2/KI to give **1.11** in 53% yield. This reaction proved to be rather capricious, due in part to a difficult recrystallisation from H_2O. Instead, it was found that by stirring the crude material in acetone for several hours, higher purities could be achieved. The subsequent methyl ester protection to **3.15** was also capricious as the HCl generated during the reaction often led to protodeiodination. Nonetheless, this route was able to provide multi-gram scale quantities of **3.16** after Boc protection. In our hands the formylation reaction of **3.16** typically gave yields of ~50%, and so offered no significant advantage over Nanson's Suzuki/ozonolysis sequence. Thus at this juncture we moved back to this route.



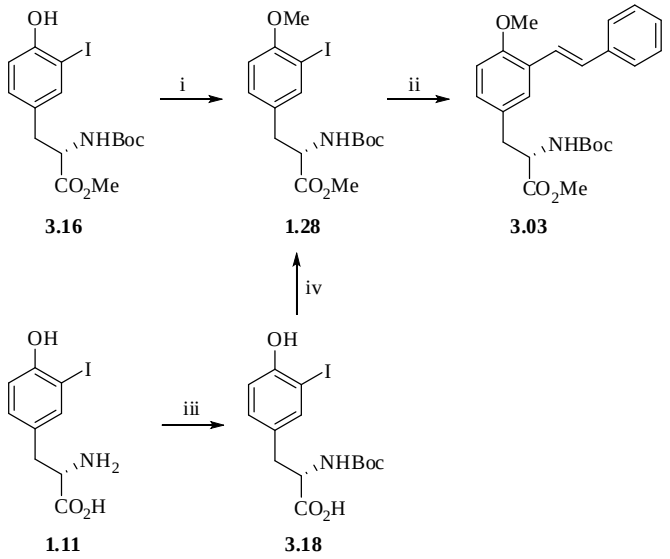
3.06 **1.11** **3.15** **3.16** **3.17**

Reagents & Conditions: i) I_2, 20% KI (w/v H_2O), NH_4OH, 16 h, 0 ^oC–RT, 53%; ii) $SOCl_2$, MeOH, 18 h, 0 ^oC–65^oC–RT, 65%; iii) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 ^oC–RT, 78%; iv) CO, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, Et_3N, Et_3SiH, DMF, 16 h, 80 ^oC, 52%.

Scheme 3.8: 3-Functionalisation of **3.16** by a Pd-catalysed hydroformylation.

Therefore, using the Suzuki reaction described by Nanson,[119] we were able to prepare *trans*-stilbene **3.03** in 76% yield (Scheme **3.9**). Thus, the fully protected tyrosine

derivative **1.28** was made by *O*-methylation of **3.06** under ambient conditions, and could also be prepared by a double methylation of **3.18** through the action of MeI and K_2CO_3 in refluxing acetone, which proceeded without observable epimerisation. The key Suzuki reaction with commercially available *trans*-2-phenylvinylboronic acid gave stilbene **3.03** in 76% yield. Though the boronic acid fragment was costly, Nanson had observed that the corresponding Heck reaction of **1.28** with styrene was far less efficient.

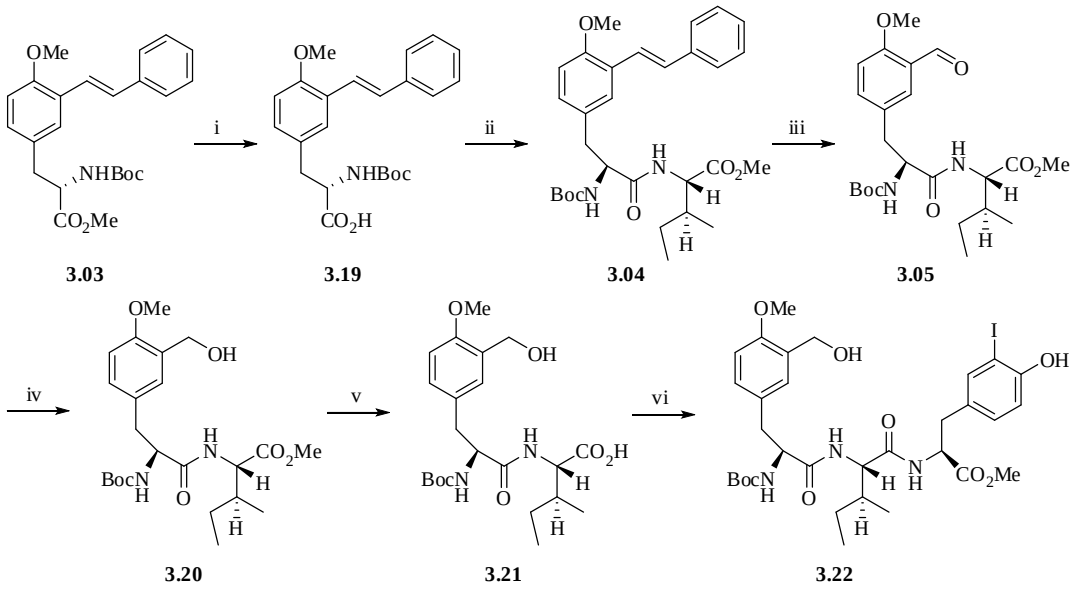


Reagents & Conditions: i) MeI, K_2CO_3, DMF, 16 h, 0 ^oC–RT, 89%; ii) *trans*-2-phenylvinylboronic acid, K_2CO_3, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, DMSO, 16 h, 80 ^oC, 76%; iii) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 ^oC–RT, 98%; iv) MeI, K_2CO_3, acetone, 16 h, 56 ^oC, 82%.

Scheme 3.9: Preparation of ozonolysis precursor.

3.1.2 Towards the Benzyl Ether-Containing Macrocycle

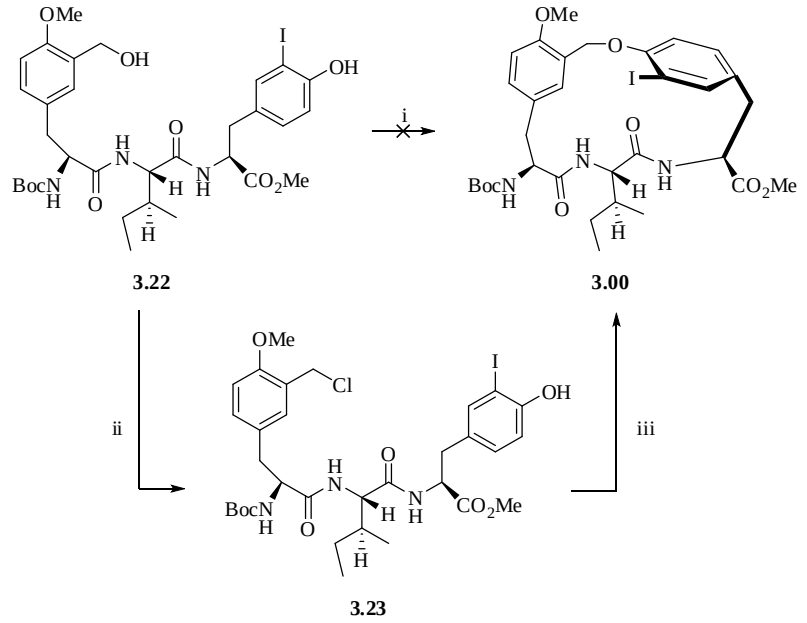
With stilbene **3.03** in hand we set about the synthesis of the A-B macrocycle. Saponification of the methyl ester followed by coupling to an isoleucine residue gave dipeptide **3.04** in good overall yield. The required benzyl alcohol group was installed first by ozonolysis of the olefin to aldehyde **3.05** followed by reduction to the corresponding alcohol **3.20** with $NaBH_4$. Saponification then revealed free acid **3.21** which was coupled to 3-I-Tyr.*O*Me·HCl **3.15** giving tripeptide **3.22** in 62% yield (Scheme **3.10**).



Reagents & Conditions: i) $LiOH{\cdot}H_2O$, THF/H_2O, 3 h, RT, 92%; ii) Ile.*O*Me·HCl, EDCI, HOBt, Et_3N, DMF, 16 h, RT, 73%; iii) O_3/O_2, CH_2Cl_2, 30 min, –78 °C, then PPh_3, 30 min, –78 °C, 76%; iv) $NaBH_4$, MeOH, 4 h, 0 °C–RT, 99%; v) $LiOH{\cdot}H_2O$, THF/H_2O, 3 h, RT, 99%; vi) 3-I-Tyr.*O*Me·HCl **3.15**, EDCI, HOBt, CH_2Cl_2, Et_3N, 24 h, RT, 62%.

Scheme 3.10: Synthesis of acyclic A-B tripeptide.

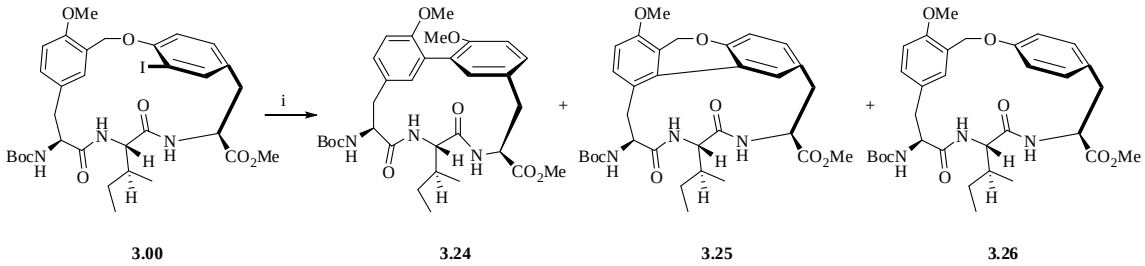
The stage was now set for closure of the A-B macrocycle and the crucial radical-induced transannular ring contraction. It seemed logical to employ an intramolecular Mitsunobu reaction to effect macrocyclisation (*viz.* **3.22** → **3.00**). However, when **3.22** was treated with PPh_3 and DIAD (Scheme **3.11**) a highly complex product mixture resulted. Furthermore, during purification the situation worsened due to decomposition of some of the constituent products. Therefore, benzyl chloride **3.23** was made by action of $SOCl_2$ on benzyl alcohol **3.22**, and pleasing, when treated with potassium carbonate to induce an intramolecular S_N2 reaction, the desired macrocycle **3.00** was given in 30% yield.



Reagents & Conditions: i) PPh_3, DIAD, 16 h, 0 °C–RT; ii) $SOCl_2$, CH_2Cl_2, 3 h, 0 °C, 63%; iii) KI, K_2CO_3, DMF, 18 h, 80 °C, 30%.

Scheme 3.11: Macrocyclisation of A-B tripeptide.

With macrocycle **3.00** in hand the stage was now set for our key radical induced transannular ring contraction (Scheme **3.12**). Unfortunately we could not isolate any of the desired product **3.24** in a pure form and were only ever able to isolate mixtures of what was believed to be benzo[*c*]chromene **3.25**, deiodinated material **3.26** and biaryl **3.24**, with primary evidence for each coming from mass spectrometry.

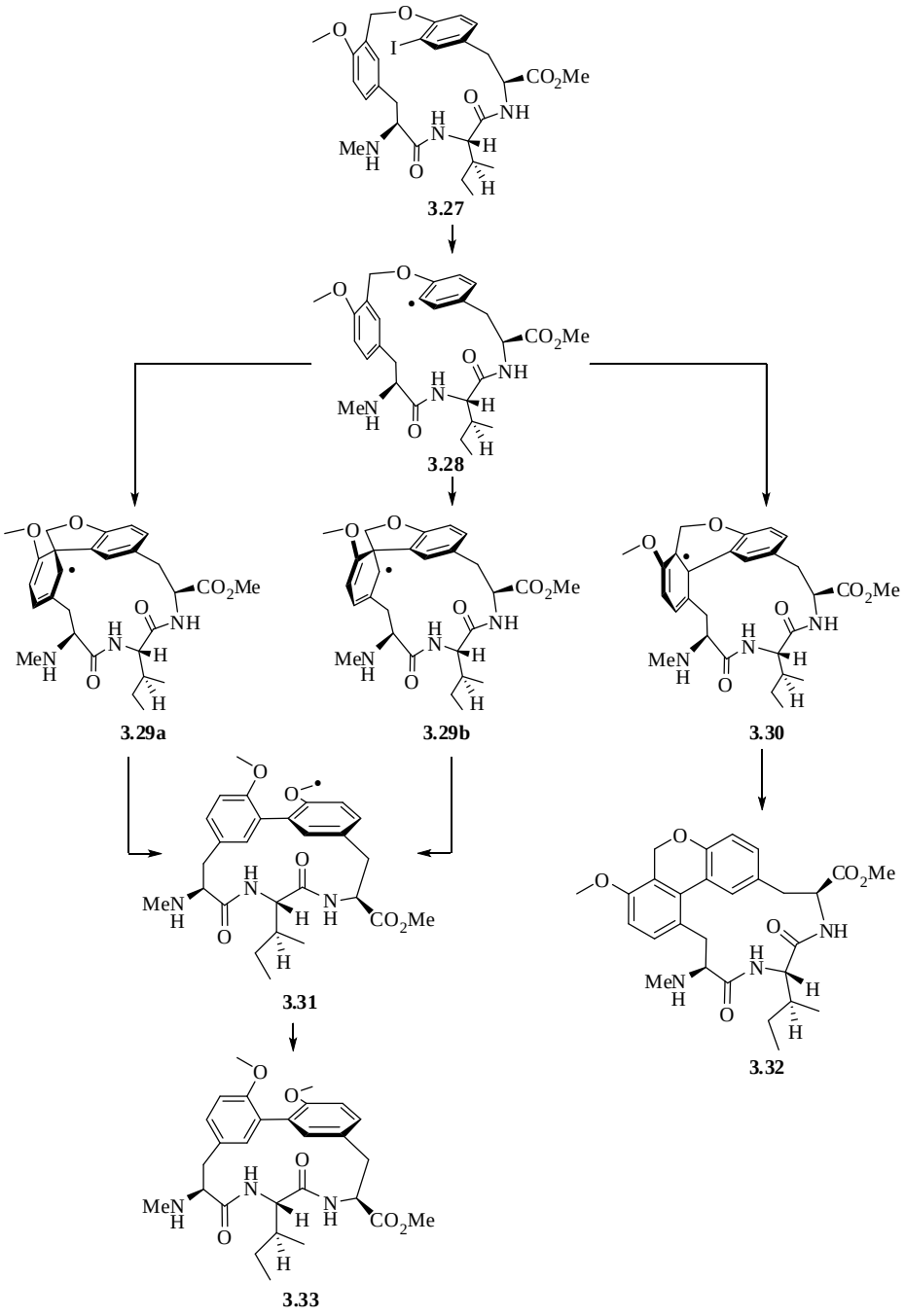


Reagents & Conditions: i) Bu_3SnH, VAZO, PhMe, 16 h, 110 °C.

Scheme 3.12: Radical cyclisation of A-B tripeptide.

3.2 *In Silico* Modeling of the Radical-Induced Transannular Ring Contraction

Frustrated by the inconclusive results from our key ring contraction reaction we decided to use computational chemistry to investigate this process further. Using Spartan 04 we initially constructed a model of the A-B macrocycle (similar to that shown in Figure **3.1**), and postulated reasonable intermediates in the reaction pathway. For each structure, a conformer search was performed using a semi-empirical AM1 method. Once the lowest energy conformer for each structure was obtained we subjected it to higher level DFT calculations using the B3LYP method and the 6-31G* basis set, which are known to be effective for radical species. For compounds containing tin the LACVP* with LACVP pseudopotentials were applied. Radicals were calculated with unrestricted B3LYP and non-radical species with restricted B3LYP and all calculations were carried out *in vacuo*. Once the lowest energy conformers were obtained we were able to calculate the lowest relative electronic energy for each intermediate (including tin and hydrogen radical intermediates) and thus calculate a relative ΔE for the reaction. This was done by the summation of relative energies for intermediates involved in each stage of the reaction pathway and then calculating ΔE ($E_{product} - E_{reactant}$) for each step. Thus, once the ΔE for each step was known we were able to plot the overall relative energy change (Figure **3.2**) and hence show the overall $\Delta E_{reaction}$. This was done for two pathways, those leading through to biaryl **3.33** and those leading to benzo[*c*]chromene **3.32**. By comparing the two relative ΔEs we could get an indication of the likely outcome of the reaction as the values give an insight into the thermodynamics, with electronic energy being a good estimate of the free energy. Since radical cyclisations are fast and typically have low activation energies, no kinetic parameters were investigated in order to save expensive computational time. Thus we were able to provide a qualitative description of the reaction which is depicted in Scheme **3.13**.



Scheme 3.13: Schematic of our calculations.

As we can see from looking at the plot in Figure **3.2**, each reaction pathway is exothermic as the ΔE_{rxn} is negative. The initially formed aryl radical intermediate **3.28** can cyclise to either **3.29a**, **3.29b** or **3.30** and it is shown that the product arising from the 6-*exo*/*endo* pathway **3.30** is of lower energy than either of the 5- *exo*/*endo* pathways. Thus **3.30** collapses to product **3.32**, with the regaining of aromatic stabilisation, driving the reaction. The route to biaryl **3.33** follows a different course, with collapse of

spirocyclic intermediates **3.29a** and **3.29b** leading to a methylene radical **3.31**. Surprisingly this intermediate is higher in energy than either of the spirocycles **3.29a** and **3.29b**, in spite of the gain in aromaticity! The ΔE_{rxn} for biaryl **3.33** is –176 kJ whereas ΔE_{rxn} for benzo[*c*]chromene **3.32** is –334 kJ. This leads us to believe that the major product of the reaction is likely to be the undesired benzo[*c*]chromene **3.32**, resulting from radical cyclisation to the *ortho*-carbon. The propensity for aryl radical intermediates to cyclise to the *ortho*-postion (6-*exo*/*endo* pathway) rather than the *ipso*-position (5-*exo* pathway) is known in macrocyclic systems, as observed by Harrowven *et al*. in the first total synthesis of cavicularin in 2005.[132] This is due to efficient orbital overlap leading through to the *ortho*-cyclised product. Although faster, the 5-*exo*/*endo* pathway is highly strained thus increasing the activation energy.

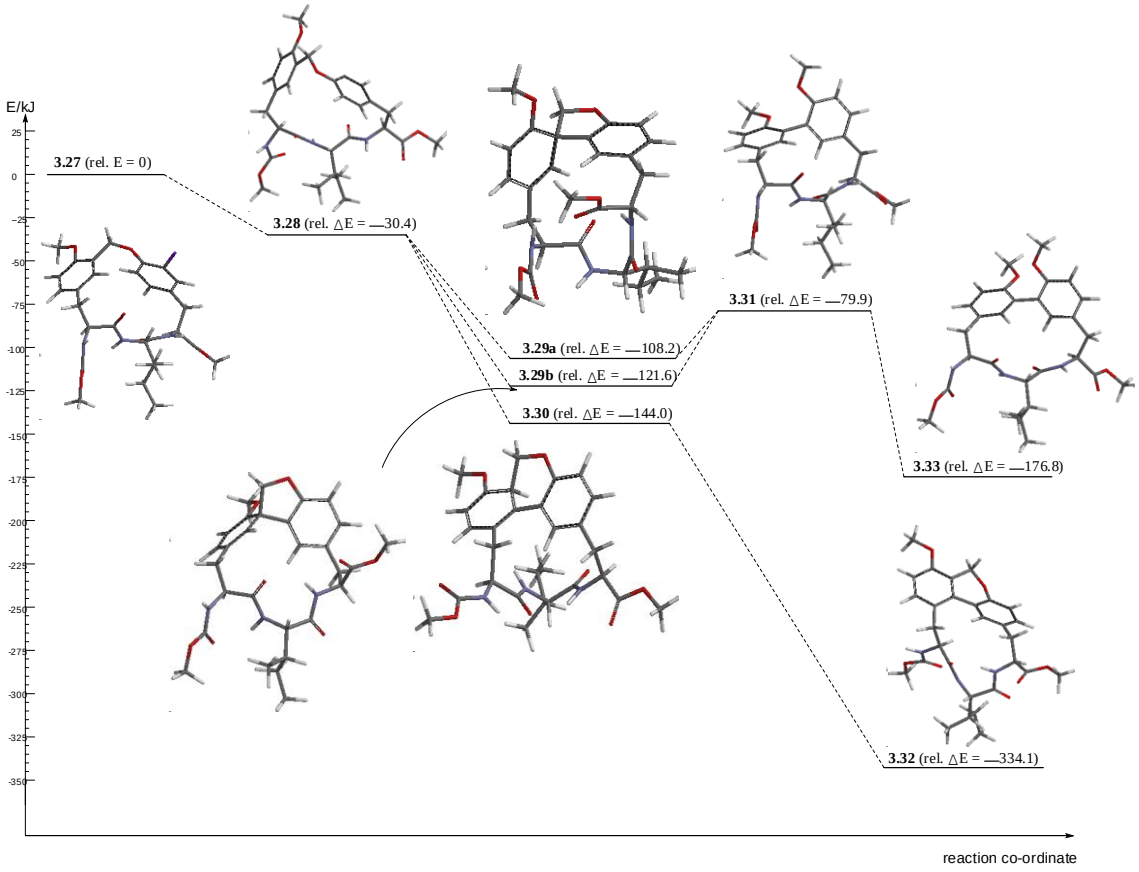
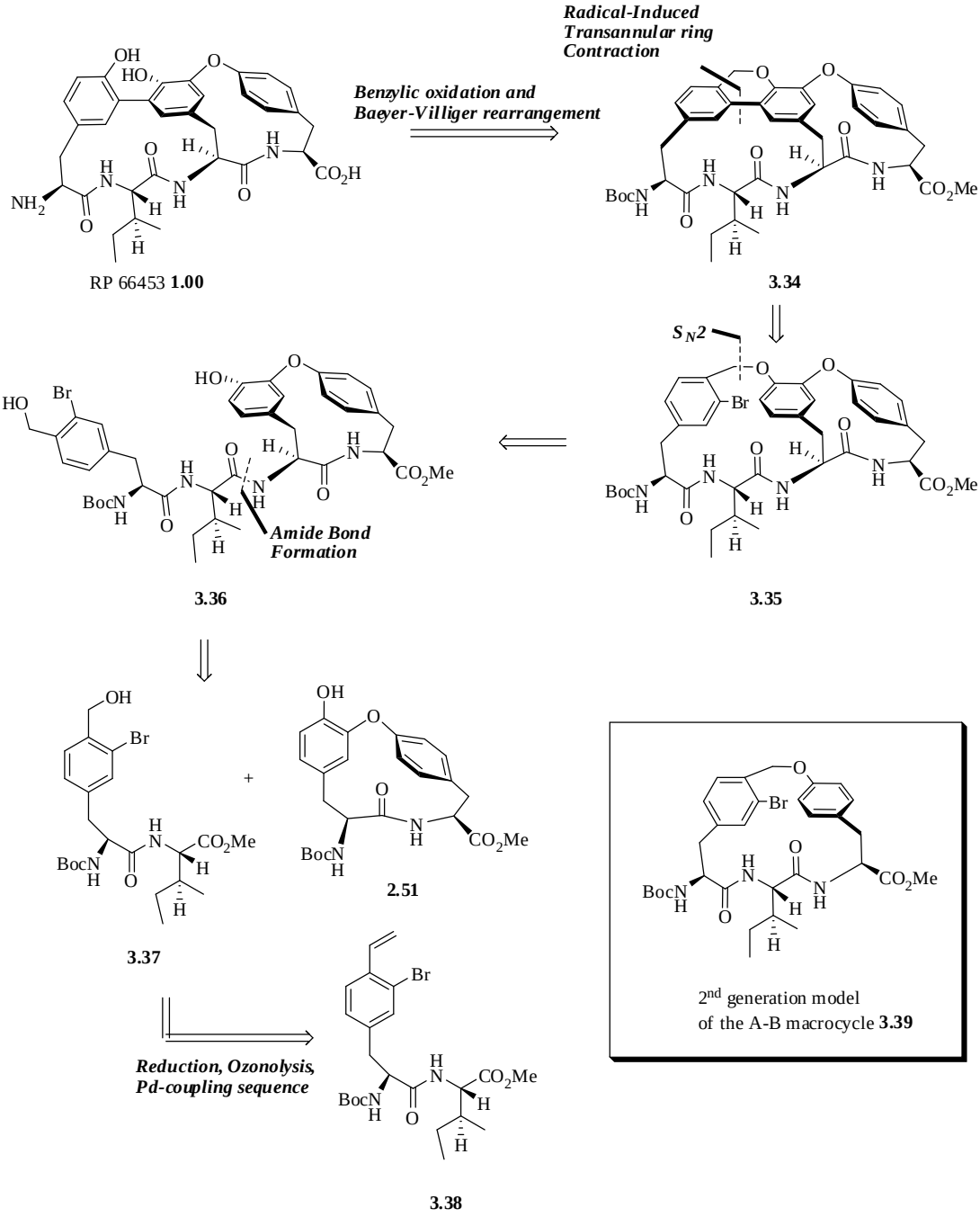


Figure 3.2: Reaction coordinate plot for our transannular ring contraction (transition states not calculated).

3.3 2nd Generation Benzyl Ether-Tethered Macrocycle

Our calculations show that the undesired *ortho*-cyclisation is favoured over our desired *ipso*-cyclisation mode. However, we reasoned that we could make use of this 6-*exo*/*endo* pathway by increasing the macrocyclic cavity thus leading to a benzo[*c*]chromene with the correct size macrocycle for RP 66453 **1.00**. Manipulation of the newly formed ring system would give the desired biaryl and complete the total synthesis. Our new retrosynthesis is outlined in Scheme **3.14**. In a forward sense we intend to form dipeptide **3.37** as before, with the benzyl alcohol arising from ozonolysis of styrene **3.38** followed by reduction. Conversion into a leaving group followed by an intramolecular S_N2 reaction with the B-*O*-C macrocycle will give benzyl ether **3.35**.

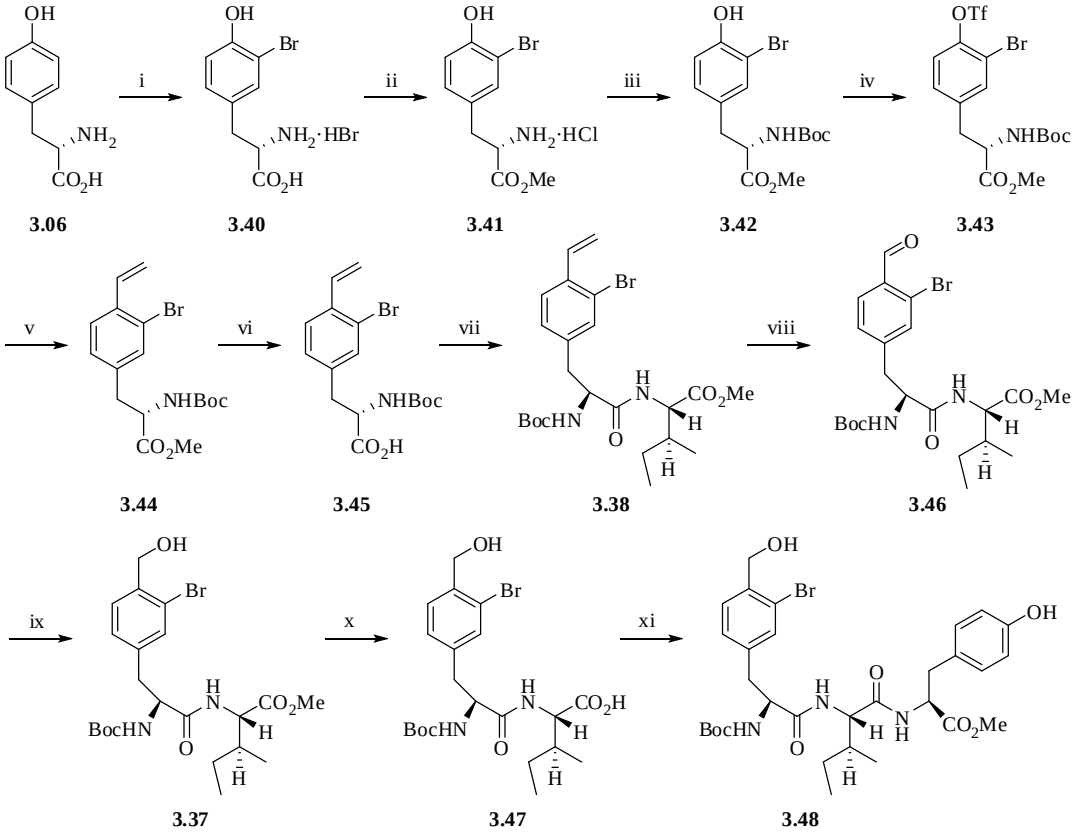
Our new theory suggests that the key radical-induced transannular ring contraction will give benzo[*c*]chromene **3.34**, which has the 15-membered A-B macrocycle required for RP 66453. Installation of the biphenol moiety could result from a benzylic oxidation followed by a Baeyer-Villiger oxidation of the resulting ester, with subsequent hydrolysis. Global deprotection should then give the natural product. The B-*O*-C macrocycle **2.51** will be prepared as proposed previously (Scheme **2.12**).



Scheme 3.14: Summary of our new retrosynthesis.

Following the new strategy as outlined above, we set about the synthesis of macrocycle **3.39**, to test our radical-induced transanunular ring contraction (Scheme **3.15**). 3-Bromotyrosine **3.40** was prepared in excellent yield and regioselectivity by treating tyrosine **3.06** with Br_2 in HBr and glacial acetic acid. This proved more efficient than bromination using $KBrO_3$/KBr which led to small quantities of the dibrominated

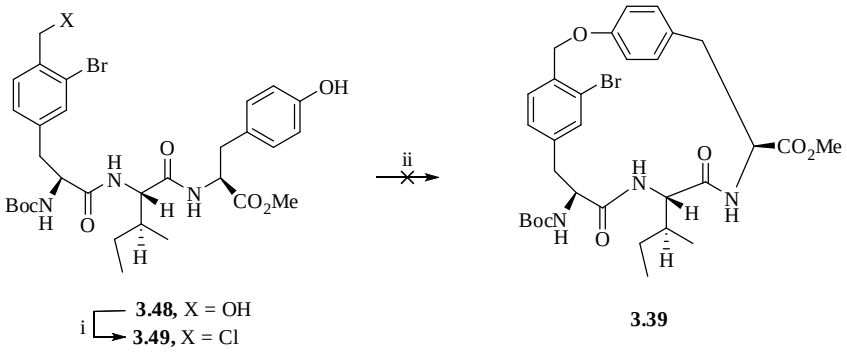
product. Methyl ester formation and then *N*-Boc protection gave **3.42** in 77% yield over two steps. Conversion of this phenol **3.42** into triflate **3.43** proceeded in excellent yield (95%). By contrast, the Stille reaction between **3.43** tributyl(vinyl)stannane to form styrene **3.44** was rather capricious, which was due to the presence of the proximal halide. Indeed, heating the reaction above RT always led to mixtures of products arising from reaction with both the triflate and the bromide. High chemoselectivity could be achieved by the addition of an excess of LiCl and conducting the reaction at room temperature. This was at a cost however, as the reaction seldom went to completion and the triflate starting material and styrene product were difficult to separate! Nonetheless, we were able to achieve this separation and carry on with the synthesis. Saponification of the methyl ester provided free acid **3.45** which was coupled to an isoleucine residue **2.47**, giving dipeptide **3.38** in an acceptable 41% yield. Ozonolysis of the styrene next gave aldehyde **3.46** in good yield (88%), which was reduced to the corresponding benzyl alcohol **3.37** using sodium borohydride. Saponification of the methyl ester gave acid **3.47** which was coupled to tyrosine methyl ester **2.56** to give tripeptide **3.48** in 36% yield over 3 steps.



Reagents & Conditions: i) cHBr/HOAc, Br_2, HOAc, 18 h, RT, 84%; ii) $SOCl_2$, MeOH, 9 h, 0 °C–65 °C, 87%; iii) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 °C–RT, 88%; iv) Tf_2O, py, CH_2Cl_2, 3 h, 0 °C, 95%; v) tributyl(vinyl)stannane, LiCl, Pd(dppf)Cl_2·CH_2Cl_2, DMF, 16 h, RT, 62%; vi) LiOH·H_2O, THF/H_2O, 3 h, RT, 98%; vii) Ile.*O*Me·HCl **2.47**, EDCI, HOBt, DIPEA, DMF, 16 h, RT, 41%; viii) O_3/O_2, CH_2Cl_2, 2 h then PPh_3, –78 °C, 88%; ix) $NaBH_4$, MeOH, 4 h, 0 °C–RT, 97%; x) LiOH·H_2O, THF/H_2O, 16 h, RT, 90%; xi) Tyr.*O*Me·HCl **2.56**, EDCI, HOBt, CH_2Cl_2, Et_3N, 16 h, RT, 41%.

Scheme 3.15: Synthesis of acyclic A-B tripeptide for our new route.

With tripeptide **3.48** now in hand we looked to form macrocycle **3.39** via chloride **3.49**, as before. Thus, benzyl alcohol **3.48** was treated with $SOCl_2$ in MeOH to form the corresponding chloride. Without purification, we treated **3.49** with potassium iodide and potassium carbonate in DMF in order to induce the desired the S_N2 reaction (Scheme **3.16**). Unfortunately, we were unable to identify any of the desired macrocycle **3.39** in the product mixture and isolated only degradation products.



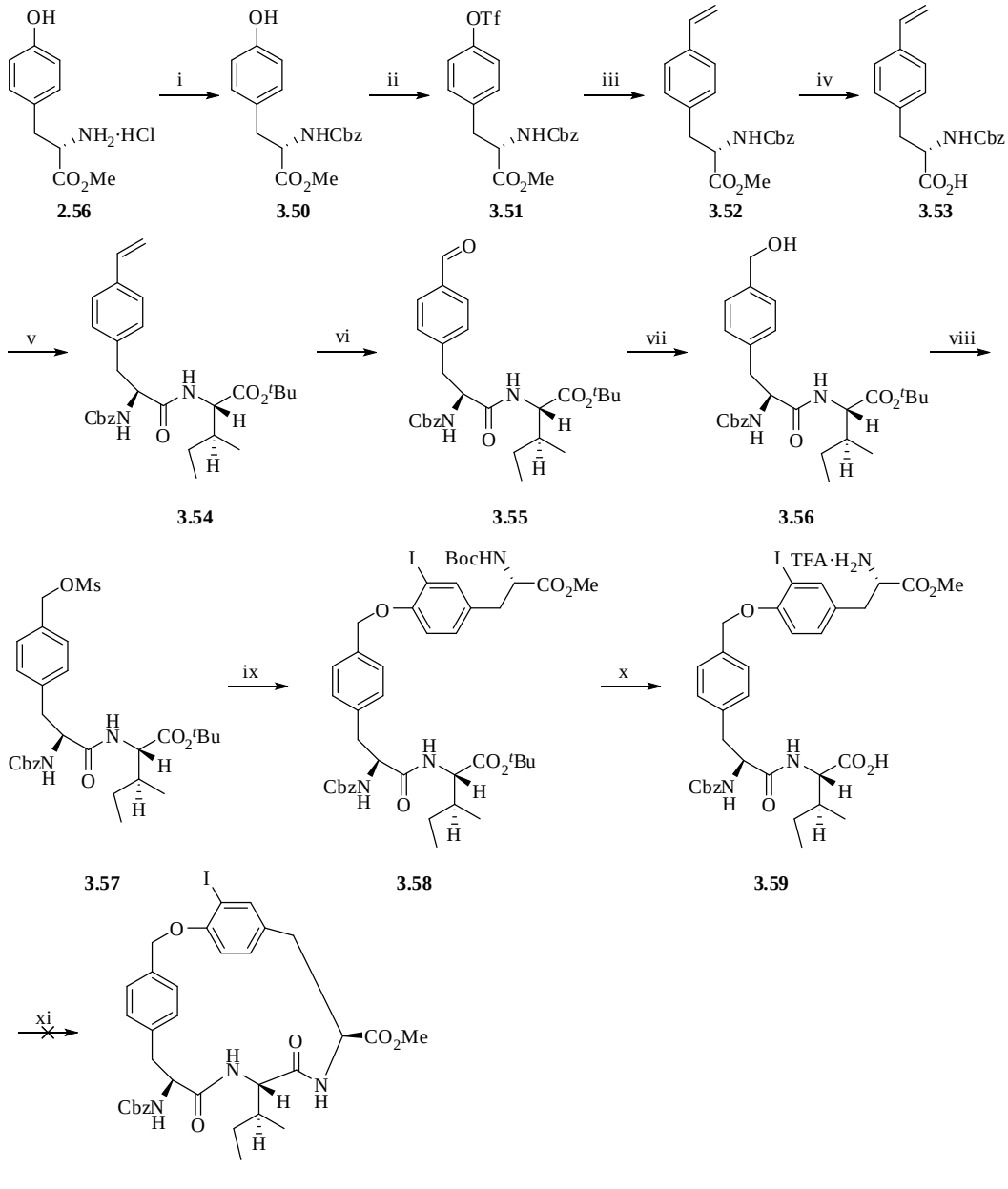
Reagents & Conditions: i) $SOCl_2$, CH_2Cl_2, 3 h, 0 ^oC; ii) KI, K_2CO_3, DMF, 18 h, 80 ^oC.

Scheme 3.16: Macrocyclisation of A-B tripeptide II.

At this juncture we decided to change strategies as the synthesis was being held up by several difficult steps; in particular, the cumbersome Stille reaction was often low-yielding and difficult to separate from the unreacted starting material, and the peptide coupling reactions often proved troublesome. We thought that by reinstating the halide onto the B ring (as in our initial route, Scheme **2.12**) we could heat the Stille reaction, thus driving it to completion, circumventing any chemoselectivity issues. Secondly, we looked to form the benzyl ether bond first and then form the macrocycle by an intramolecular lactamisation reaction.

Our forward synthesis is shown in Scheme **3.17**. We first protected tyrosine methyl ester **2.56** as a *N*-Cbz carbamate, then transformed phenol **3.50** into the corresponding triflate **3.51** in high yield (90%). The key Stille reaction to access styrene **3.52** could now be achieved in a reproducible 64% yield. Saponification of the methyl ester next gave acid **3.53** which was coupled with Ile.*O*^{t}Bu **3.61** (made as outlined in Scheme **3.19**) to give dipeptide **3.54** in 65% yield over two steps. Ozonolysis of the styrene to aldehyde **3.55** (88% yield), reduction to benzyl alcohol **3.56** (93% yield) and conversion into the mesylate **3.57** (quantitative) now set up an S_N2 with functionalised tyrosine derivative **3.16**. This gave tripeptide **3.58** in 67% yield and finally, removal of the acid labile *tert*-butyl ester and carbamate groups with TFA gave the macrocyclisation precursor **3.59** in quantitative yield. A series of small scale intramolecular lactamisation reactions were set up (EDCI/HOAt, PyBOP, HATU and T3P) although the results were inconclusive. On a larger scale however, our preliminary studies for the formation of

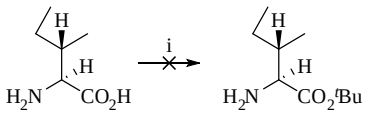
macrocycle were encouraging. Unfortunately though, due to time constraints we had to stop at this juncture, although this strategy is well placed for future endeavors.



Reagents & Conditions: i) CbzCl, Na_2CO_3, acetone/H_2O, 4 h, 0 °C–RT, 86%; ii) Tf_2O, py, CH_2Cl_2, 3 h, 0 °C, 90%; iii) tributyl(vinyl)stannane, LiCl, Pd(dppf)Cl_2·CH_2Cl_2, DMF, 16 h, 80 °C, 64%; iv) LiOH·H_2O, THF/H_2O, 2 h, RT, 87%; v) Ile.*O*^{t}Bu **3.61**, EDCI, HOBt, DIPEA, DMF, 16 h, RT, 87%; vi) O_3/O_2, CH_2Cl_2, 2 h then PPh_3, –78 °C, 84%; vii) $NaBH_4$, MeOH, 4 h, 0 °C–RT, 93%; viii) MsCl, Et_3N, CH_2Cl_2, 3 h, 0 °C, quant. ix) **3.16**, K_2CO_3, DMF, 16 h, RT, 67%; x) TFA/CH_2Cl_2 (4:1), 2 h, RT, quant.; xi) EDCI, HOAt, DIPEA, DMF, 4 d, RT.

Scheme 3.17: Synthesis of acyclic A-B tripeptide for lactamisation strategy.

The isoleucine *tert*-butyl ester **3.61** used in the preceding sequence was prepared as outlined in Scheme **3.19**. Though this appears to be a trivial product to make, it proved rather tricky. We first looked at acid-promoted transesterification reactions using ^{t}BuOAc (Scheme **3.18**).[133] However, in our hands this and several related reactions yielded recovered starting material.



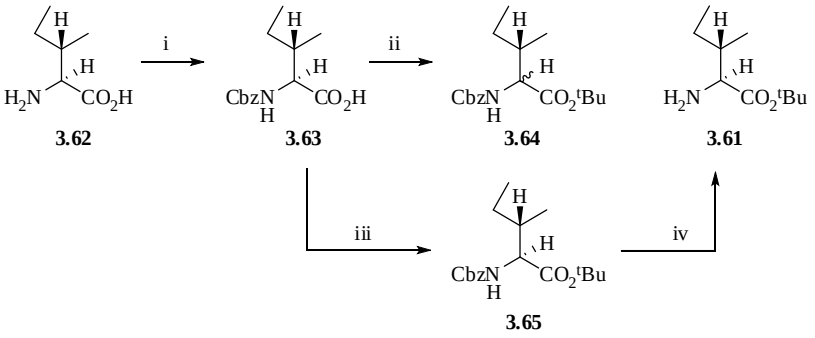
3.62 **3.61**

Reagents & Conditions: i) perchloric acid, ^{t}BuOAc, 16 h, 0 ^{o}C–RT.

Scheme 3.18: Transesterification reaction for the preparation of *tert*-butyl esters.

Thus, a longer 3-step sequence developed by Ramasamy *et al.*[134] was investigated. Protecting the reactive amine as a Cbz carbamate allowed an esterification at the carboxylic acid by a carbodiimide mediated coupling with ^{t}BuOH. However, the NMR spectra of **3.64** showed that the product was formed as a 1:1 mixture of diastereoisomers (Scheme 3.19).

Thankfully, an alternate approach developed by Martinez *et al.*[135] was more successful (Scheme **3.19**). Thus, upon treating **3.63** with ^{t}BuBr, BTEAC and K_2CO_3 in DMF, the desired ester **3.65** was formed in good yield and with excellent diastereomeric integrity. Removal of the Cbz carbamate by hydrogenolysis completed the synthesis of *tert*-butyl ester **3.61** in 3 steps and 38% overall yield. This sequence proved robust and allowed for the preparation of isoleucine *tert*-butyl ester in multi-gram quantities.

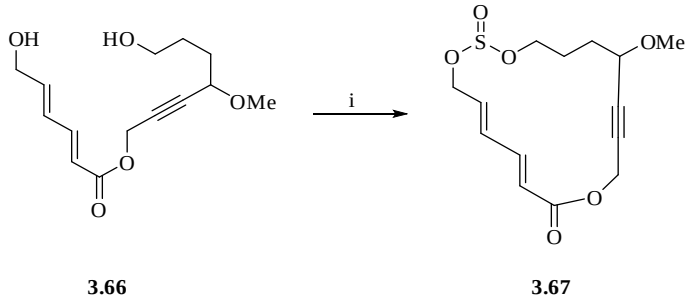


Reagents & Conditions: i) CbzCl, 2M NaOH, Et_2O, 16 h, 0 ^oC–RT, 87%; ii) EDCI, DMAP, ^{t}BuOH, CH_2Cl_2, 6 h, 0 ^oC–RT, 48%; iii) ^{t}BuBr, BTEAC, K_2CO_3, DMF, 16 h, 55 ^oC, 71%; iv) H_2, Pd/C, MeOH, 16 h, RT, 62%.

Scheme 3.19: Preparation of isoleucine *tert*-butyl ester.

3.4 Heteroatom-Tethered Strategy

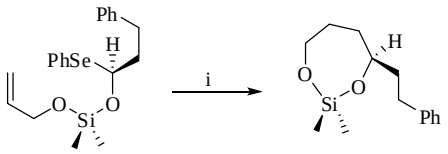
Since our benzyl ether tethered approaches were proving to be disappointing, we sought a new disconnection strategy. It is known that hydroxyl groups can be tethered together with a silicon, sulfur, phosphorus or carbon-centred linker, as exemplified by Clausen *et al*. in 2009, who were able to form the 17-membered macrocyclic sulfite **3.67** by the dropwise addition of $SOCl_2$ to a 10 mM solution of diol **3.66** (Scheme **3.20**).[136]



Reagents & Conditions: i) $SOCl_2$, Et_3N, DMAP, CH_2Cl_2 (10 mM), 24 h, RT, 25%.

Scheme 3.20: Tethered-synthesis of a 17-membered macrocycle.

Myers *et al*. adopted a related strategy with a silicon tether to conjoin two alcohols and prepare protected diol **3.69** by a 7-*endo*-trig radical cyclisation of **3.68**. In this way a key fragment in their synthesis of the tunicamycin antibiotics was assembled (Scheme **3.21**).[137-139]

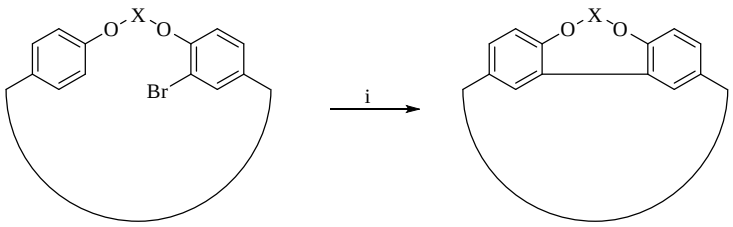


3.68 **3.69**

Reagents & Conditions: i) Bu_3SnH, AIBN, PhMe (3 mM), 60 ^oC, 60–70%.

Scheme 3.21: Myers silicon-tethered radical cyclisation.

We reasoned that a similar tactic might be used to secure the key biaryl linkage in RP 66453, again using a radical-induced transannular ring contraction. In our case we would use a heteroatom tether to join the two phenols then induce an *ortho*-radical cyclisation to form the desired biphenol moiety (Scheme **3.22**).

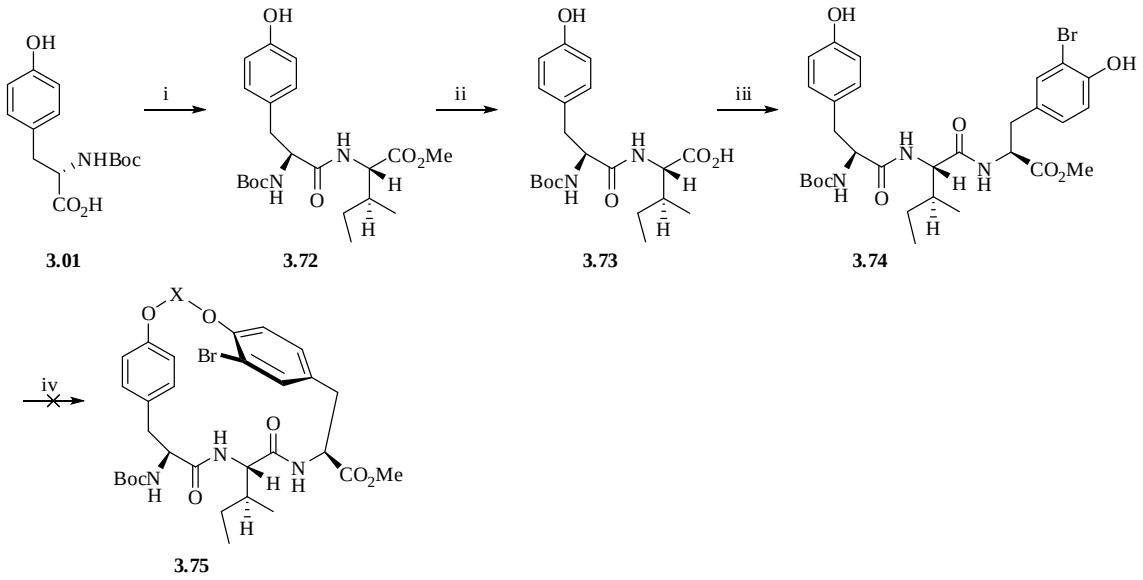


3.70 **3.71**

Reagents & Conditions: i) Bu_3SnH, AIBN, PhMe (high dilution).

Scheme 3.22: Our heteroatom tether approach.

To that end we set about the synthesis of tripeptide **3.74** (Scheme **3.23**). *N*-Boc.tyrosine **3.01** was coupled to isoleucine methyl ester **2.47** to give dipeptide **3.72** in acceptable yield. Saponification revealed free acid **3.73** which was then coupled to amino acid residue **3.41** affording tripeptide **3.74** in reasonable yield (68%). We now faced the critical tethering reaction to form **3.75**. Alas, numerous attempts to effect macrocyclisation failed to deliver any of the desired product, with only recovered starting material identified in most cases (Table **3.1**). When thionyl chloride was used with Et_3N (entries 6 & 7), for example, the reaction gave a waxy residue which we attributed to polymerisation, due to broadened and indistinct peaks in the ^1H NMR spectrum of the crude product mixture.



Reagents & Conditions: i) Ile.*O*Me·HCl **2.47**, EDCI, HOBt, DIPEA, DMF, 16 h, RT, 41%; ii) LiOH·H_2O, THF/H_2O, 1 h, RT, 60%; iii) **3.41**, EDCI, HOBt, DIPEA, DMF, 16 h, RT, 68%; iv) See table **3.1**.

Scheme 3.23: Synthesis of tripeptide and attempted tethered-cyclisation.

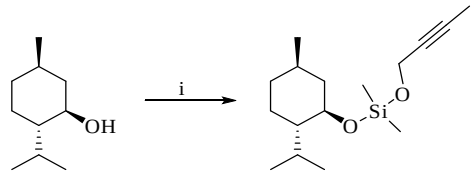
Entry	X	Base (5e q)	Solvent	Temperature	Product
1	^{t}Bu$_2$SiCl$_2$	Et$_3$N	THF	RT/66 ^{o}C	RSM
2	^{t}Bu$_2$SiCl$_2$	Et$_3$N	CH_2Cl_2	RT	RSM
3	^{t}Bu$_2$SiCl$_2$	Im	THF	RT/66 ^{o}C	RSM
4	^{t}Bu$_2$SiCl$_2$	Et$_3$N	THF	RT/66 ^{o}C	RSM
5	Me$_2$SiCl$_2$	Et$_3$N	THF	RT/66 ^{o}C	RSM
6	SOCl$_2$	Et$_3$N	CH_2Cl_2	RT	Polymer
7	SOCl$_2$	Et$_3$N	DCE	RT/80 ^{o}C	Polymer
8	SOCl$_2$	Im	DCE	RT/80 ^{o}C	RSM
9	SOCl$_2$	Im	CH_2Cl_2	RT	RSM
10	SO_2Cl_2	Et$_3$N	CH_2Cl_2	RT	RSM
11	CDI	Et$_3$N	THF	RT/66 ^{o}C	RSM

.

Table 3.1: Conditions examined to achieve a tethered-macrocyclisation.

As the intramolecular tethering approach was giving only negative results we thought it might be better to form the two silyl ether linkages first, and then perform an

intramolecular peptide coupling to close the macrocycle. In 2003 Malacria *et al*. showed that unsymmetrical silaketals could be efficiently prepared by the sequential reaction of an alcohol with a dialkylchlorosilane, followed by conversion of the Si-H bond to a Si-Br bond with NBS, allowing coupling to a second alcohol through nucleophilic displacement (Scheme **3.24**).[140] By using this method a range of unsymmetrical silaketals could be formed, with a variety of alcohols, including phenols, allyl and propargyl alcohols.

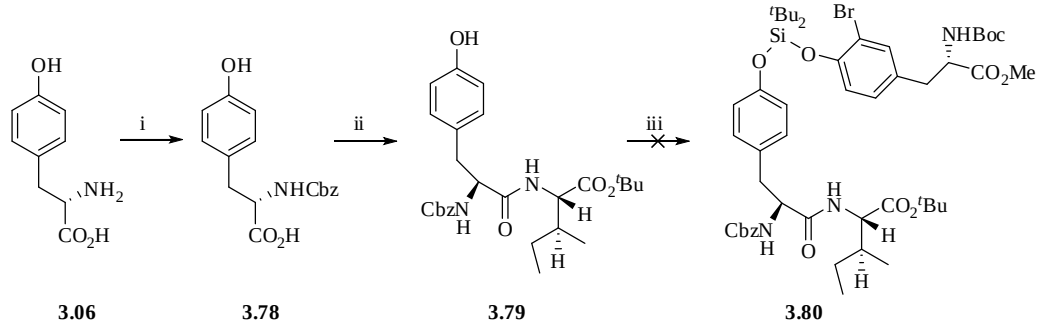


3.76 **3.77**

Reagents & Conditions: i) $ClSiMe_2H$, Et_3N, DMAP, CH_2Cl_2, then; NBS, then; 3-butyn-1-ol, Et_3N, DMAP.

Scheme 3.24: Exemplar unsymmetrical silaketal formation by Malacria *et al*.

We decided to examine this strategy for the synthesis of bis-phenol **3.80**, recognising that the use of two phenols may prove troublesome as these are relatively good leaving groups. Our synthetic route is shown in Scheme **3.25**. Following the silylation reaction by TLC it appeared that the initial silyation of **3.79** was successful as was the subsequent bromination step. However, problems occurred during the second etherification step when the TLC appeared to show decomposition. Furthermore, all that was isolated on purification was the dipeptide starting material **3.79**, indicating the labile nature of silyl tethered phenols.



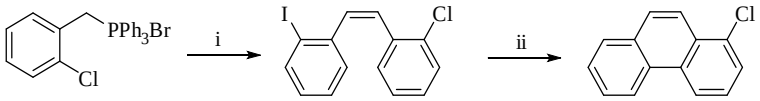
3.06 **3.78** **3.79** **3.80**

Reagents & Conditions: i) CbzCl, 2M NaOH, 16 h, 0 ^oC–RT, 50%; ii) Ile.*O*^{t}Bu **3.61**, PyBOP, DIPEA, DMF, 16 h, 0 ^oC–RT, 59%; iii) $^tBu_2SiClH$, Et_3N, CH_2Cl_2, then NBS, then **3.42**.

Scheme 3.25: Attempted synthesis of tripeptide.

3.5 Phenanthrene Tether & Photocyclisation Strategy

In 2006 Harrowven *et al*. reported an efficient strategy for the synthesis of phenanthrenes, helicenes and azahelicenes.[141] The strategy made use of the co-operative *ortho* effect to achieve a highly *Z*-selective Wittig reaction to give stilbene **3.82**. Homolysis of the carbon-iodine bond then gave an aryl radical which underwent a 6-*exo*/*endo*-trig cyclisation to the proximal arene to afford phenanthrene **3.83** in high yield (90%) (Scheme **3.26**). The methodology could be extended to highly substituted arenes as well as bis-stilbenes, leading to helicenes.

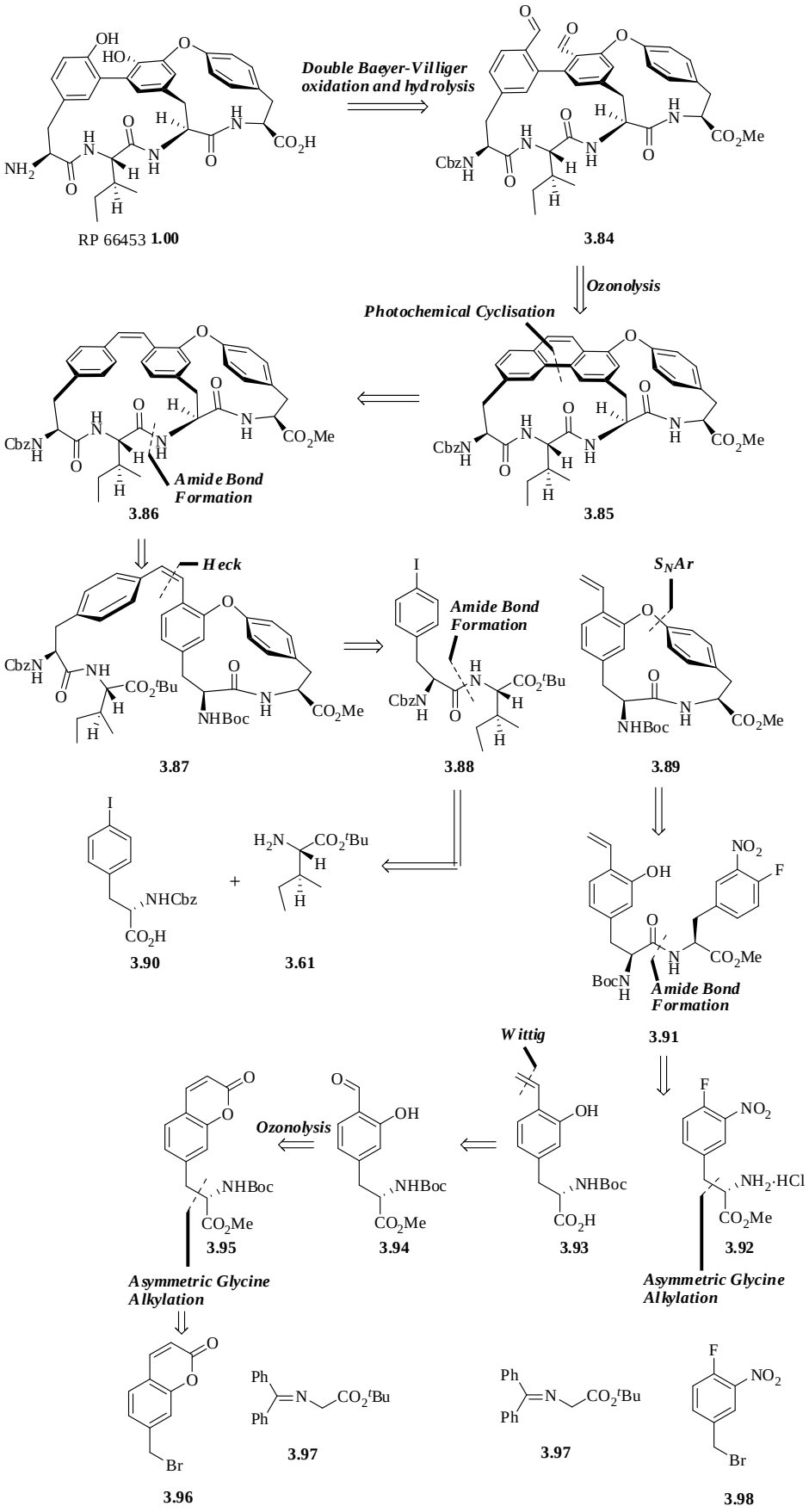


3.81 **3.82** **3.83**

Reagents & Conditions: i) KOtBu, THF, 0 ^{o}C then, 2-iodobenzaldehyde, RT, d.r .~9:1, 92%; ii) Bu_3SnH (2.4 eq), AIBN (0.4 eq), PhMe, 90 ^{o}C, 90%.

Scheme 3.26: Cooperative *ortho* effected Wittig reaction and radical cyclisation.

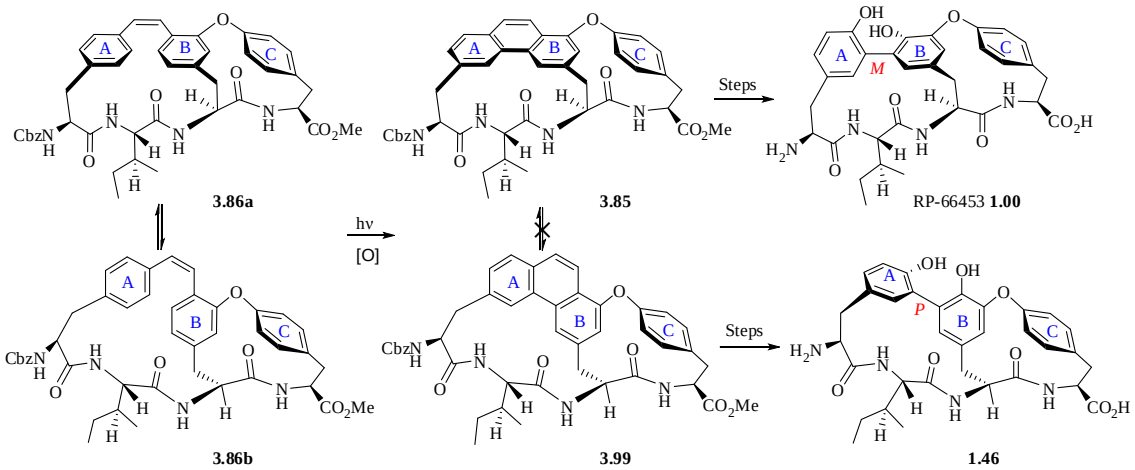
Whilst work on the benzyl ether-tethered systems was ongoing we contemporaneously investigated using the aforementioned methodology to construct the crucial biaryl linkage via a phenanthrene, believing that it could serve as a surrogate for the biphenol. However, work from elsewhere within our group had shown that the radical-induced transannular ring contraction strategy towards the phenanthrene was proving difficult and that a photochemical closure of a stilbene held better prospects. The retrosynthesis for this new approach is shown in Scheme **3.27**.



Scheme 3.27: Retrosynthesis for the stilbene tether.

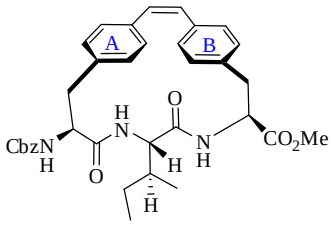
We reasoned that a Heck reaction could be used to install the requisite stilbene **3.87**. This would of course provide the *trans*-stilbene, but was of little consequence as the photochemical isomerisation to *cis*-stilbenes is well known. For ease of synthetic preparation we reasoned that the olefin component should be on B-*O*-C ring **3.89** and the iodide on the A ring fragment **3.88**. The B-*O*-C ring would be prepared by a phase transfer catalysis reaction to form coumarin amino acid **3.95**, which could be converted into the required styrene by ozonolysis to **3.94** and a Wittig methylenation reaction. Coupling to amino acid **3.92** followed by an intramolecular S_NAr macrocyclisation reaction would complete the B-*O*-C macrocycle (this will be discussed in greater detail in Chapter 4). The iodinated A fragment **3.88** would be assembled using classical methods and coupled to **3.89** by a Heck reaction which, after isomerisation, should give *cis*-stilbene **3.87**. The *tert*-butyl ester and carbamate functions would be removed to facilitate intramolecular peptide coupling to the bis-macrocycle **3.86**. Photochemical phenanthrene synthesis to **3.85** would then set up an end-game strategy involving ozonolysis, to bis-aldehyde **3.84** and a double Baeyer-Villiger oxidation with hydrolysis. Global deprotection should then provide RP 66453 **1.00**.

The stereochemical rationale for this new approach is shown in Scheme **3.28**. Macrocyclic stilbene **3.86** would exhibit rotomers with differing planar chirality (*e.g.* **3.86a** and **3.86b**). These should freely interconvert at RT and notably each has a different face of arene B encumbered by the encapsulating peptide backbone. Upon irradiation the newly formed phenanthrenes **3.85** and **3.99** would not be free to interconvert at RT, each differentiated by planar chirality in arene B. Since the biaryl bond is also formed in this operation we can see that the two stereoelements are interdependent. **3.85** and **3.99** are two isolable diastereomers, the ratio of which relflects the proportion of reactive conformers **3.86a** and **3.86b**. As before, cleavage of the C9-C10 bond in **3.85** would lead to an (*M*)-configured biaryl linkage while cleavage of the C9-C10 bond in **3.99** would lead to a (*P*)-configured biaryl linkage, neither of which is free to equilibrate at room temperature.



Scheme 3.28: Stereochemical explanation for phenanthrene route.

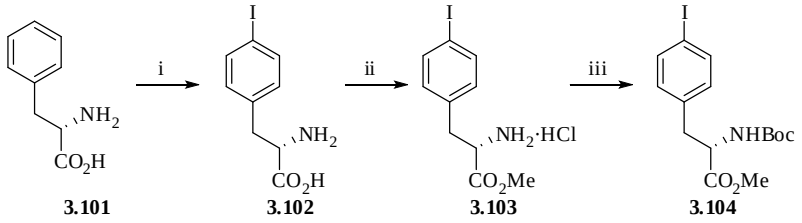
To test the feasibility of the approach we decided to form a model of the A-B macrocycle **3.100** (Figure **3.3**). If successful it should be easy to swap the B ring tyrosine residue for the B-*O*-C macrocycle of the real system and thus press on with the total synthesis.



3.100

Figure 3.3: Model system for our phenanthrene approach.

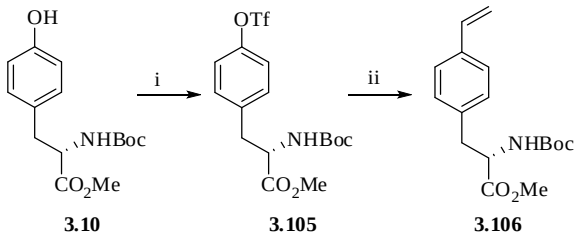
To explore the viability of the approach we first examined the Heck reaction (Figure **3.5**). To that end iodide **3.104** was made in 3 steps from phenylalanine **3.101** by regioselective iodination to **3.102** followed by protection of the carboxylic acid as methyl ester **3.103** and the amine as its Boc-carbamate **3.104** (Scheme **3.29**).



Reagents & Conditions: i) I_2, $NaIO_3 \cdot H_2O$, $NaIO_4$, cH_2SO_4, HOAc, 24 h, 70 °C, quant.; ii) $SOCl_2$, MeOH, 16 h, 0 °C–64 °C–RT, 72%; iii) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 °C–RT, 82%.

Scheme 3.29: Preparation of the iodide precursor.

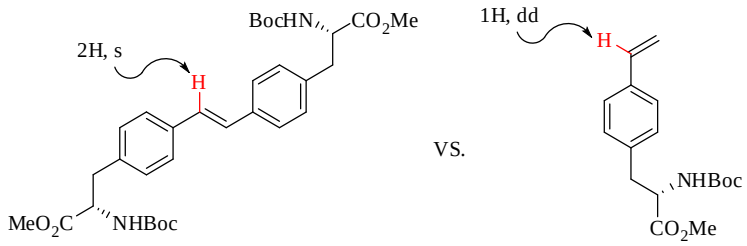
Styrene fragment **3.106** was made in 2 steps from protected tyrosine **3.10** by first converting the phenol into the corresponding triflate **3.105**, and then a Stille reaction with tributyl(vinyl)stannane (Scheme **3.30**).



Reagents & Conditions: i) Tf_2O, py, CH_2Cl_2, 3 h, 0 °C, 93%; ii) tri(butyl)vinylstannane, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, LiCl, DMF, 16 h, 80 °C, 86%.

Scheme 3.30: Preparation of the styrene precursor.

With iodide **3.104** and styrene **3.106** in hand we looked at optimising their union using a Heck reaction. Initially we looked at the influence of catalyst and ligand on the reaction. An array of small scale reactions were conducted at 80 °C, with the product mixtures analysed by ^1H NMR. Integrations of the styrene protons in the starting material and the stilbene protons in the product (Figure **3.4**) were compared to give an indication to the progress of the reaction. The overlaid NMR traces are shown in Figure **3.5**.



3.107 **3.106**

Figure **3.4**: Indicating protons and their respective multiplicities.

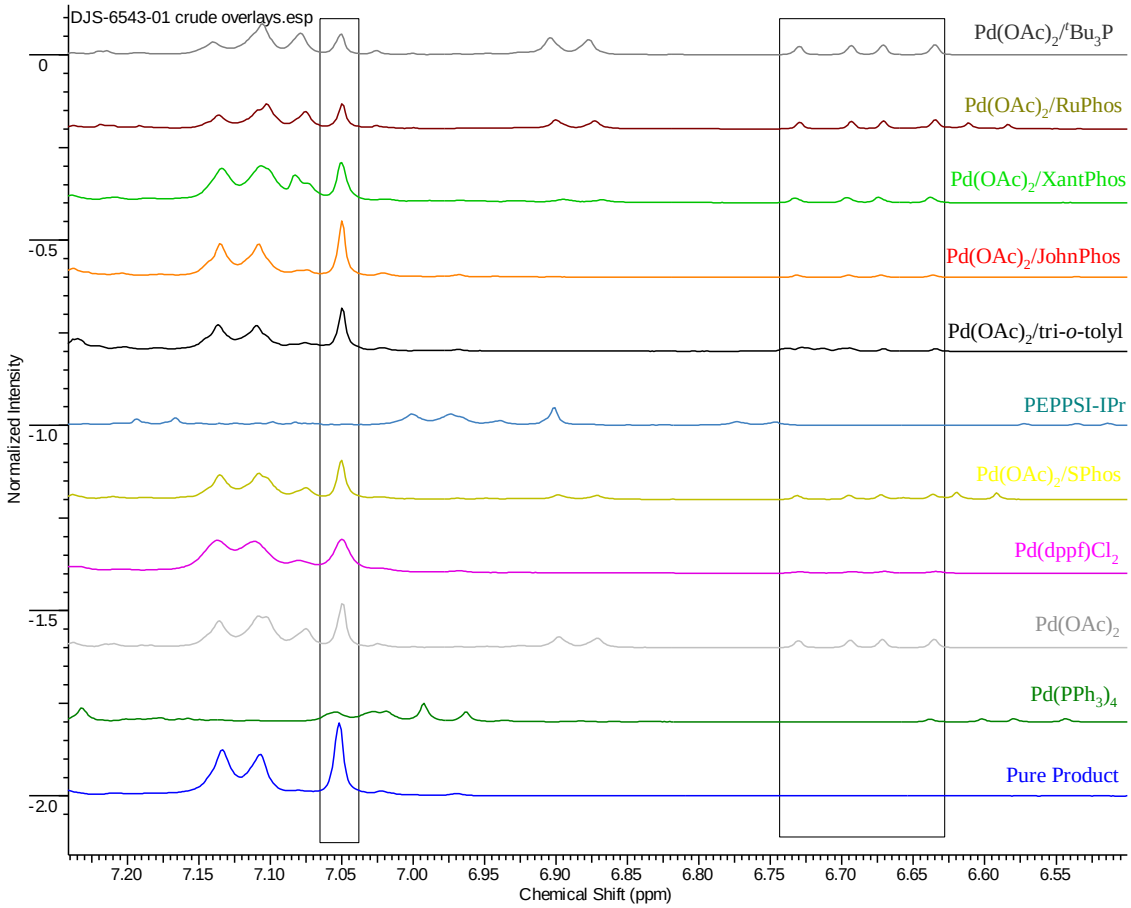


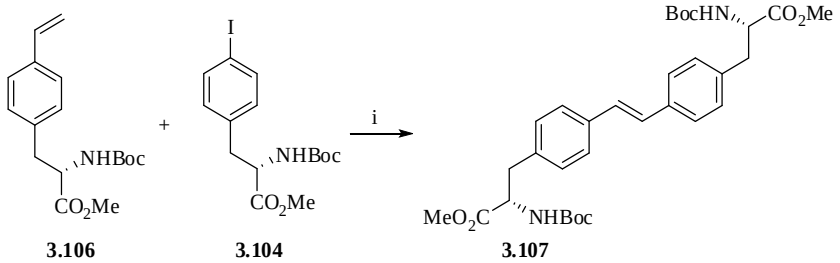
Figure **3.5**: Study of catalyst and ligand effect on the Heck reaction.

Entry	Catalyst	Ligand	Base	Solvent	Conversion
1	$Pd(PPh_3)_4$	–	Et_3N	DMF	25%
2	$Pd(OAc)_2$	–	Et_3N	DMF	68%
3	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$	–	Et_3N	DMF	89%
4	$Pd(OAc)_2$	SPhos	Et_3N	DMF	81%
5	PEPPSI-IPr	–	Et_3N	DMF	–
6	$Pd(OAc)_2$	(*o*-tolyl)$_3$P	Et_3N	DMF	92%
7	$Pd(OAc)_2$	JohnPhos	Et_3N	DMF	93%
8	$Pd(OAc)_2$	XantPhos	Et_3N	DMF	75%
9	$Pd(OAc)_2$	RuPhos	Et_3N	DMF	50%
10	$Pd(OAc)_2$	(^{t}Bu)$_3$P	Et_3N	DMF	25%

Catalyst loadings were at 10mol%, ligand (20mol%), base (4.3 eq) at 0.1 M, for 16 h at 80 ^oC.

Table **3.2**: Results from the Heck catalyst screen.

From the data obtained from this catalyst screen we could see that the best conversion was achieved when JohnPhos was used as the ligand (93%), although (*o*-tolyl)$_3$P provided a comparable result (92%). Omitted from the table are some preliminary experiments conducted in 1,4-dioxane with $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ and $Pd(OAc)_2$/SPhos. These proved inferior in every case with the conversions at least 50% lower than the respective reaction in DMF. With our optimal catalyst combination in hand we applied the same reaction conditions in a scaled-up reaction and were able to isolate, after work up and purification, *trans*-stilbene **3.107** in 79% yield (Scheme **3.31**).

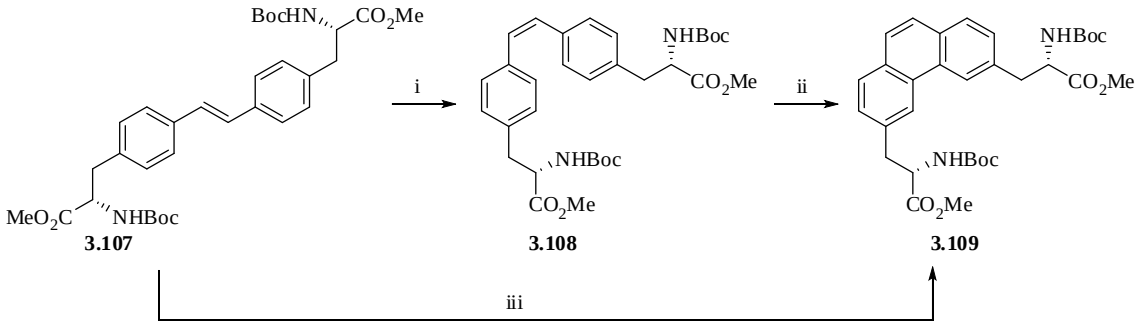


3.106 **3.104** **3.107**

Reagents & Conditions: i) $Pd(OAc)_2$, JohnPhos, Et_3N, DMF, 16 h, 80 ^oC, 79%.

Scheme 3.31: Optimum Heck reaction.

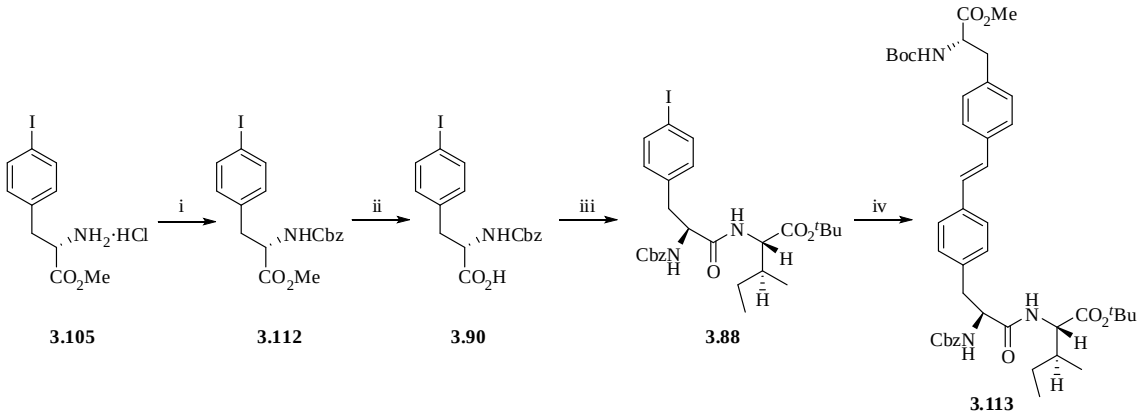
Although **3.107** lacked the orthogonality needed to advance it to the macrocyclic system, it did provide an opportunity to investigate our key photochemical steps using *prior art* developed within our laboratories.[142, 143] Thus, **3.107** was irradiated under continuous flow by a 9 W Philips broad-spectrum light source on a Vapourtec R4/R2+ flow device. Much to our delight, *cis*-stilbene **3.108** was isolated in excellent yield (99%) which could be further irradiated, this time in the presence of an oxidant (I_2), to give phenanthrene **3.109** in 75% yield (Scheme **3.32**). We were also able to show that *trans*-stilbene **3.107** leads directly to phenanthrene **3.109** when the reaction was conduced in the presence of I_2.



Reagents & Conditions: i) hν, (9 W lamp λ 280–370 nm), continuous flow, MeCN, 5 h, RT, 99%; ii) hν, (9 W lamp λ 280–370 nm), continuous flow, I_2, MeCN, 5 h, RT, 74%; iii) hν, (9 W lamp λ 280–370 nm), continuous flow, I_2, MeCN, 5 h, RT, 71%.

Scheme 3.32: Photochemistry on model system.

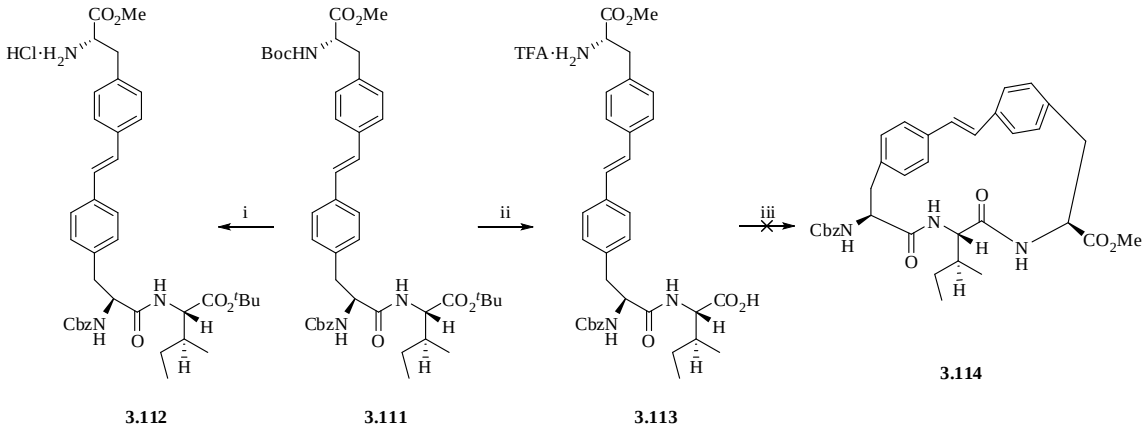
We next sought to construct a system leading to macrocycle **3.100**. Therefore, iodide **3.103** was first protected as a Cbz carbamate, giving **3.110**, before saponification of the methyl ester to acid **3.90** and coupling with Ile.*O*^{t}Bu giving dipeptide **3.88** in 74% yield. The synthesis of *trans*-stilbene **3.111** was completed using the Heck conditions developed on our model system to provide stilbene **3.111** in 62% (Scheme **3.33**).



Reagents & Conditions: i) CbzCl, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 ^oC–RT, 74%; ii) $LiOH \cdot H_2O$, THF/H_2O, 3 h, RT, 94%; iii) **3.61**, EDCI, HOBt, DIPEA, DMF, 16 h, RT, 74%; iv) **3.106**, $Pd(OAc)_2$, JohnPhos, Et_3N, DMF, 16 h, 80 ^oC, 62%.

Scheme 3.33: Heck reaction on real system.

Curosity led us to ask the question: Can we form macrocycle **3.114** containing the *E*-olefin? To that end we looked at concomitant removal of both acid labile protecting groups – the *tert*-butyl ester and *tert*-butyl carbamate. Initially, **3.111** was treated with 4M HCl in 1,4-dioxane (Scheme **3.34**). After 2 h, we could isolate the mono-deprotected adduct **3.112** exclusively. Monitoring the reaction by ^1H NMR we could follow the slow removal of the second *tert*-butyl group, although the reaction would never go to completion. Pleasingly however, the double deprotection sequence could be effected by reaction of **3.111** with TFA/CH_2Cl_2 (4:1) in 2 h. However, attempts to close the macrocycle proved futile. Using a number of different peptide coupling systems (EDCI/HOAt, PyBOP, HATU and T3P*) only RSM was isolated.

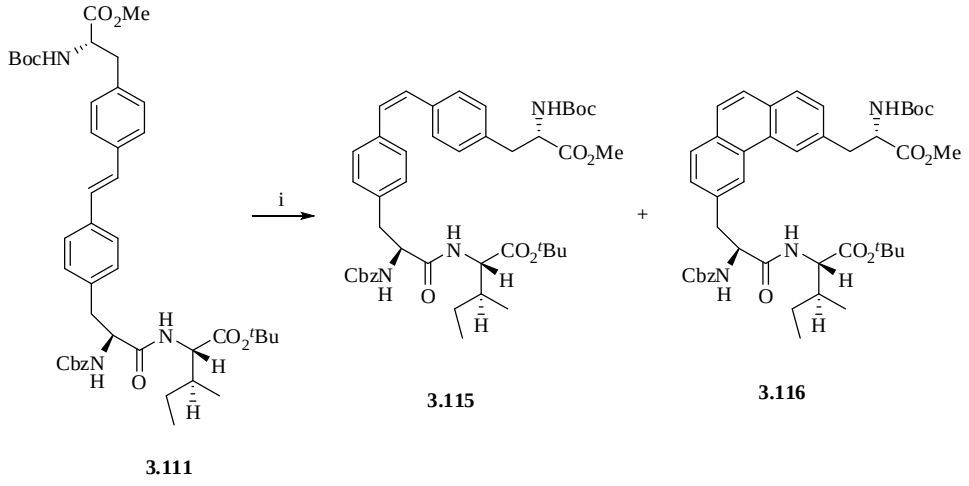


3.112 **3.111** **3.113** **3.114**

Reagents & Conditions: i) 4M HCl in 1,4-dioxane, 2 h, RT, 100%; ii) TFA/CH_2Cl_2, 2 h, RT, 100%; iii) Peptide coupling reagent (see text), DIPEA, DMF, 4 d, RT.

Scheme 3.34: Double deprotection and attempted cyclisation sequence.

Since we could not close the macrocycle containing the *E*-olefin we looked at isomerisation of the double bond to the Z-isomer prior to closure. This would provide a more favourable conformation with which to form the macrocycle. However, owing to mechanical problems with the flow apparatus, an air leak provided sufficient oxygen to transform some of *cis*-stilbene **3.115** into the phenanthrene **3.116** (Scheme **3.35**) which were given as an inseparable mixture.

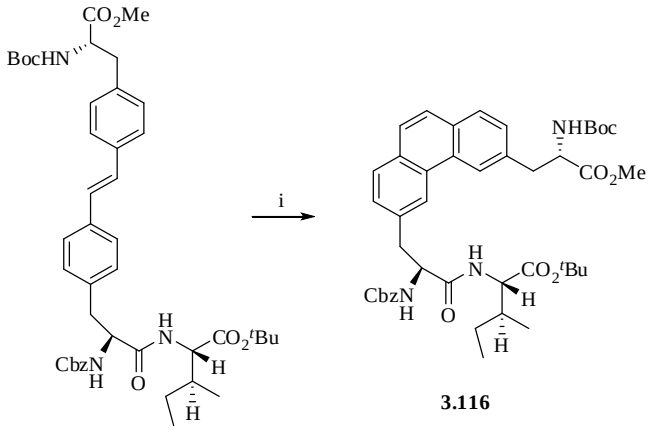


3.111 **3.115** **3.116**

Reagents & Conditions: i) hν, (9 W lamp λ 280–370 nm), continuous flow, MeCN, 5 h, RT.

Scheme 3.35: Attempted photochemical isomerisation.

Undeterred, we then set about forming macrocycle **3.117** with the phenanthrene already in place. Thus, by repeating the experiment shown in Scheme **3.35**, this time in the presence of I_2, we were able to exclusively obtain phenanthrene **3.116** (Scheme **3.36**) in near quantitative yield.



Reagents & Conditions: i) hν, (9 W lamp λ. 280–370 nm), continuous flow, I_2, MeCN, 5 h, RT, 99%.

Scheme 3.36: Photochemical isomerisation and cyclisation.

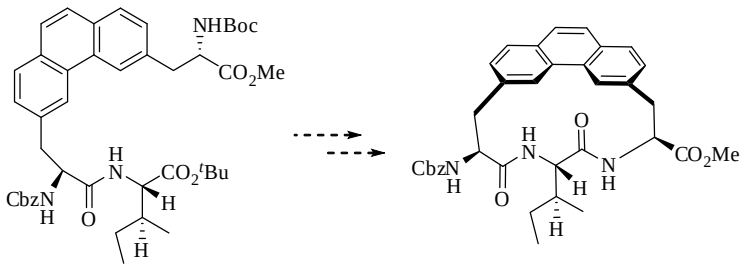
With **3.116** in hand, time was unfortunately against us and we had to suspend our efforts, in order to prepared this thesis!

3.6 Concluding Remarks and Further Work

Our initial strategy to form macrocycle **3.00** (Scheme **3.12**) using a benzyl haloaryl ether and a radical-induced transannular ring contraction was bitter-sweet. We were able to form the macrocycle successfully, but attempts to form the crucial biaryl bond by our radical methodology proved ineffective. Attempts to close the expanded macrocycle **3.39** by an intramolecular S_N2 reaction led to decomposition of the tripeptide precursor. Thus, we considered a new strategy in which the macrocycle is closed by an intramolecular amide bond formation. This work remains in its infancy but initial experiments have shown promise. Macrocyclisation by a heteroatom tethered strategy also proved ineffective, giving only recovered starting material. Using the *cis*-stilbene tether proved more promising however. Initially a Heck reaction was developed to

allow union of two appropriately functionalised tyrosine residues. The resulting *trans*-stilbene **3.107** was then shown to photoisomerise into the corresponding *cis*-stilbene **3.108** and cyclise into phenanthrene **3.109**. Applying this to the real system we have phenanthrene **3.116** in hand and this is awaiting further synthetic development.

All that remains is to first complete the synthesis of the model A-B macrocycle **3.117**, by achieving our intramolecular peptide coupling strategy (Scheme **3.37**).



3.116 **3.117**

Scheme **3.37**: Completion of A-B model system.

For further work towards the completion of the total synthesis please see Section **4.3**.

Chapter 4: Results & Discussion: B-*O*-C Macrocycle

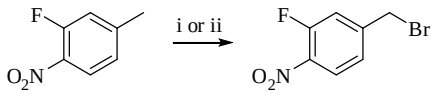
As discussed in Section **2.2**, we intended to form the B-*O*-C macrocycle by an intramolecular S_NAr reaction of **2.54**. By using the C ring phenol as a nucleophile we hoped to use the residual nitro group as a surrogate for the requisite B ring phenol, rather than simply removing it by reduction, providing greater atom economy (Scheme **2.12**).

4.1 Approaches to the B-*O*-C Macrocycle: Initial Route

4.1.1 Formation of unnatural amino acid **2.55** using Schöllkopf's auxiliary

Non-proteinogenic α-amino acids are important targets owing to their extensive biochemical, pharmaceutical and herbicidal activities.[144] This has led to the development of asymmetric methodologies aimed at their synthesis, typically involving alkylation of a heterocyclic chiral auxiliary with an appended homochiral residue to control the diastereoselective addition of the incoming electrophile. Such methodologies include Seebach's imidazolidinone,[145] Oppolzer's chiral sultam,[146] Evan's oxazolidinone,[147] and Schöllkopf's bis-lactim.[81] We intend to prepare unnatural amino acid **2.55** using the Schöllkopf method as previous work within our group had centred around this.[119]

The electrophilic component for Schöllkopf's amino acid synthesis, benzyl bromide **2.58**, was prepared in one step from 3-fluoro-4-nitrotoluene **4.00** (Scheme **4.1**). Thermal-induced radical bromination provided **2.58** in only 12% isolated yield, with the remaining mass balance accounted for by an inseparable mixture of starting material and product. However, this could be improved to 48% by photolysis of **4.00** in the presence of NBS. Notably, if the reaction was warmed above RT or treated for longer than 3.5 h, then significant quantities of the corresponding dibrominated product were formed as monitored by ^{1}H NMR spectroscopy.

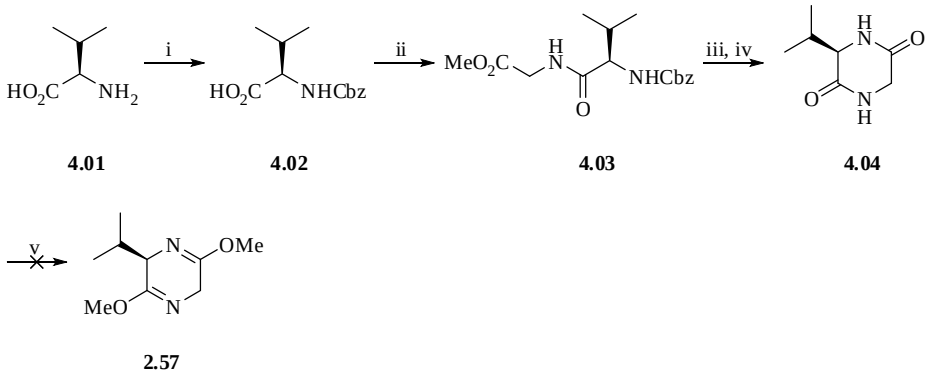


4.00 **2.58**

Reagents & Conditions: i) NBS, DBPO, 1,2-DCE, 24 h, 84 ^{o}C, 12%; ii) NBS, hν, 1,2-DCE, 3.5 h, RT, 48%.

Scheme 4.1: Preparation of 3-fluoro-4-nitrobenzyl bromide.

Outlined in Scheme **4.2** is our progress towards the bis-lactim ether auxillary **2.57**. In order to achieve the desired stereochemical outcome, the opposite enantiomer of that desired must be used so as to direct addition of the incoming electrophile to the opposite face of the bis-lactim, setting the correct stereochemistry in the product. Thus, for a required L-amino acid, the corresponding D-valine must be used to create the bis-lactim. To that end, dipeptide **4.03** was prepared from D-valine in two steps in reasonable overall yield. Removal of the Cbz protecting group by hydrogenolysis proceeded in quantitative yield prior to cyclisation to **4.04**. This was only affected in 26% yield with large quantities of a gelatinous polymer also isolated. When **4.04** was treated with trimethyloxonium tetrafluoroborate we failed to isolate any of the desired bis-lactim auxiliary **2.57**. It is known that diketopiperazine **4.04** is a potent gelling agent for most common organic solvents and that it is extremely hygroscopic and prone to cleave back to its constituent amino acids on reaction with water.[148] Furthermore, commercially available $[Me_3O]^+BF_4^-$ was found to be inferior to the freshly prepared reagent but its synthesis is tricky. Therefore, at this juncture we sought an alternate strategy to the B-*O*-C ring, as the Schöllkopf route to unnatural amino acid **2.55** was proving expensive and laborious.

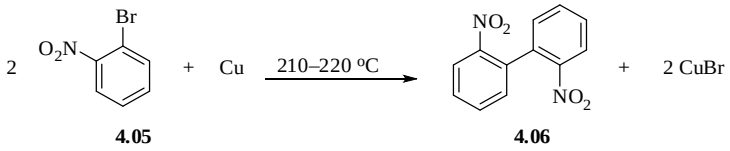


Reagents & Conditions: i) CbzCl, NaOH/Et_2O, 16 h, 0 ^oC–RT, 83%; ii) Gly.*O*Me·HCl, ^{i}BuOCOCl, NMM, THF/DMF, 16 h, –5 ^oC–RT, 94%; iii) H_2, Pd/C, CH_2Cl_2/MeOH, 5 d, RT, quant; iv) PhMe, 24 h, 111 ^oC, 26%; v) $[Me_3O]^+BF_4^-$, CH_2Cl_2.

Scheme 4.2: Preparation of the Schöllkopf diketopiperazine and attempted *O*-methylation.

4.1.2 Ullmann Chemistry for the Preparation of the B-*O*-C Ring

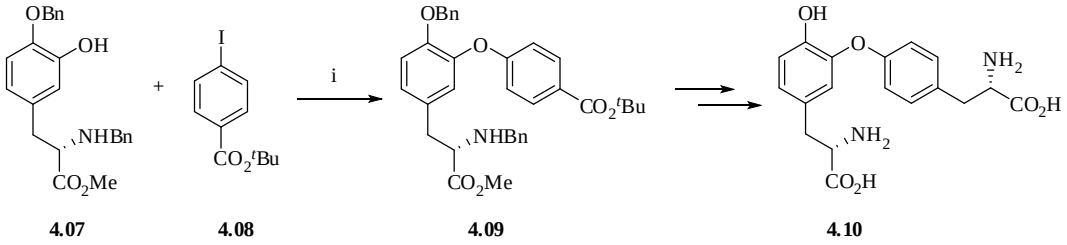
In 1901 Fritz Ullmann observed that when *o*-bromonitrobenzene **4.05** was heated with Cu powder, 2,2'-bis(nitrobenzene) **4.06** was isolated (Scheme **4.3**).[149] This methodology was extended independently by Ullmann and Goldberg for the synthesis of biarylethers[150] and biarylamines[151] respectively, and later by Hurtley, who noted that bromoarenes are readily substituted by sodium salts of 1,3-dicarbonyl compounds in the presence of copper-bronze or copper-acetate.[152]



Scheme 4.3: Birth of the Ullmann reaction.

The intermolecular C-O Ullmann-type reaction featuring amino acid residues has been used by Boger *et al*. in their synthesis of L,L–isodityrosine **4.10** (Scheme **4.4**).[153] Protected L-DOPA **4.07** was treated with 1.4 eq of $CuBr·SMe_2$ and NaH in the presence of iodide **4.08** to afford biaryl ether **4.09** in 46% yield. Boger and co-workers also employed an analogous reaction in their synthesis of K-13[19] and OF4949-III.[154] Several

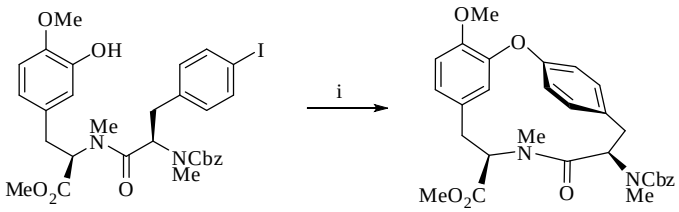
years later Ma *et al*. formed isodityrosine using this strategy, coupling two amino acids together, mediated by CuI and *N*,*N*-dimethylglycine.[155]



Reagents & Conditions: i) $CuBr{\cdot}SMe_2$ (1.4 eq), NaH (1.0 eq), $PhNO_2$, 8 h, 130 °C, 46%.

Scheme 4.4: Formation of biaryl ether in the total synthesis of isodityrosine.

In 1991, the approach was extended to an intramolecular variant in the total synthesis of deoxybouvardin **1.49** and RA-VII **1.01** (Scheme **4.5**).[5] When treated with 10 eq of $CuBr{\cdot}SMe_2$ in the presence of collidine, dipeptide **4.11** underwent cyclisation to biaryl ether **4.12** in 28% yield. The lower yields for the intramolecular reaction could be attributed to the extra energetic barrier needed to overcome macrocyclisation.



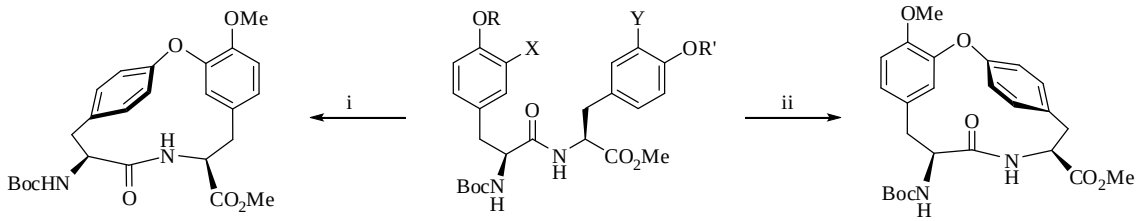
Reagents & Conditions: i) $CuBr{\cdot}SMe_2$ (10.0 eq), NaH (2.0 eq), collidine, 8 h, 130 °C, 28%.

Scheme 4.5: Intramolecular Ullmann type reaction in Boger's synthesis of RA VII and deoxybouvardin.

Boger *et al*. showed that it was possible to extend this methodology to the synthesis of the B-*O*-C macrocycle found in RP 66453 **1.00** (Scheme **1.2**).[10] In this case the team obtained only a 9% yield using a Cu^{II} promoted closure between an aryl boronic acid and a phenol, opposed to the Cu^{I}/aryl halide systems shown above for the RA series. Interestingly, the RP 66453 system contains an amide orientation with a peptide backbone that is reversed compared with these related natural products. Thus, it may be

that macrocyclisation of the B-*O*-C system of RP 66453 is more demanding than that found in **1.49** and **1.01**.

In 2003, Takeya and co-workers disclosed optimised conditions for the closure of the cycloisodityrosine found in RP 66453 (Scheme **4.6**).[35] Using what is effectively the B ring as the nucleophile (**4.14** → **4.15**), macrocycle **4.15** was formed in a satisfactory 55% yield. However, when the B ring was used as the electrophile (*viz*. **4.13** → **4.16**), the corresponding biaryl ether was formed in only 35%. Again, this suggests that one macrocyclisation strategy can more readily adopt a reactive conformation than the alternate. This was further optimised by Kumar *et al*. seven years later, who found that by using the analogous Pd-mediated ring-closure, *viz*. **4.14** → **4.15**, could be realised in yields of up to 90%.[156]

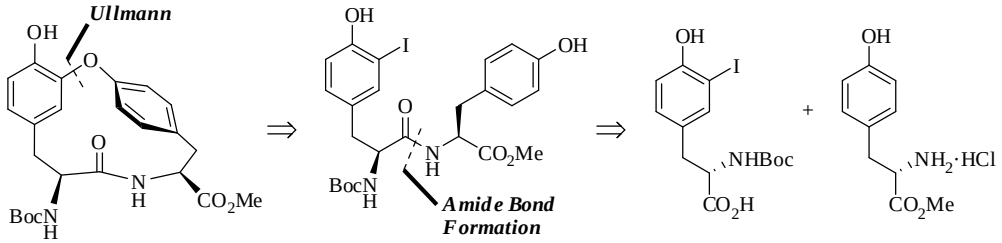


4.15 **4.13**, R = Me, X = $B(OH)_2$, Y = R' = H
4.14, R = X = H, Y = $B(OH)_2$, R' = Me **4.16**

Reagents & Conditions: i) $Cu(OAc)_2$, DMAP, powdered 4 Å MS, CH_2Cl_2 (6.3 mM), 48 h, RT, 55%; ii) $Cu(OAc)_2$, DMAP, powdered 4 Å MS, CH_2Cl_2 (130 mM), 48 h, RT, 35%.

Scheme 4.6: Intramolecular Ullmann-type reaction used by Takeya.

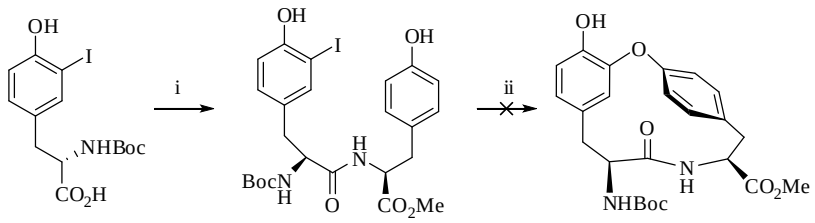
To that end our new retrosynthesis of the B-*O*-C ring is highlighted in Scheme **4.7**. Scission of the biaryl ether bond in **2.51** reveals acyclic dipeptide **4.17**, which can be disconnected back to two tyrosine fragments: iodotyrosine **3.18**, and tyrosine methyl ester **2.56**. This new retrosynthesis offers significant advantages to that shown in Scheme **2.12**: a) it is shortened to only four steps; b) chirality is introduced from the chiral pool; c) there is no need to remove the nitro group, which could have been problematic in the presence of benzyl ethers and d) it avoids the use of 3-fluoro-4-nitrobenzyl bromide, a potent lachrymator.



2.51 **4.17** **3.18** **2.56**

Scheme 4.7: 2nd generation retrosynthesis of the B-*O*-C macrocycle.

In a forward sense, dipeptide **4.17** was prepared in 88% yield by coupling Tyr.*O*Me·HCl **2.56** to **3.18** (Scheme **4.8**). In the first instance, the crucial Ullmann-type macrocyclisation of **4.17** was tried with $[Cu(bpy)_2]BF_4$ as described by Li *et al.*[157] Unfortunately none of the desired product **2.51** was formed, with only decomposition observed. We attributed this failure to the presence of the free phenol group *ortho*- to the iodide as this may sequester the active copper species.



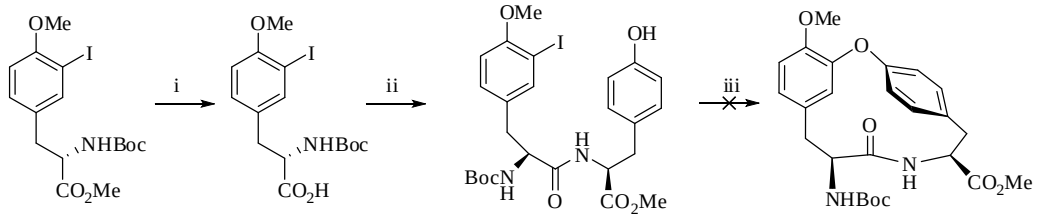
3.18 **4.17** **2.51**

Reagents & Conditions: i) Tyr.*O*Me·HCl, PyBOP, DIPEA, DMF, 16 h, 0 °C–RT, 88%; ii) $[Cu(bpy)_2]BF_4$, K_3PO_4, DMF, 18 h, 90 °C.

Scheme 4.8: Preparation of the B-*O*-C ring by Ullmann type chemistry.

Therefore, we set about making the methyl ether analogue in the first instance as, if successful, we could consider an appropriate protecting group strategy to advance our synthesis. To that end, protected iodotyrosine **1.28** was prepared in three steps as shown in Scheme **3.9**. Saponification of the methyl ester proceeded smoothly and gave acid **4.18** in 84% yield. Coupling with Tyr.*O*Me·HCl then gave dipeptide **4.19** in 68% (Scheme **4.9**). Various conditions were trialed for the crucial intramolecular Ullmann-type coupling as summarised in Table **4.1**. Unfortunately none gave access to the desired macrocycle. The catalyst system developed by Li gave a complex mixture of

RSM and deiodinated material that was inseparable (entry 1). Prolonged reaction times at the same temperature (entry 2) gave rise to a more complex mixture of decomposed products with loss of the ^{t}Bu carbamate and methyl groups being indicated by ^{1}H NMR. No reaction was observed with the CuI/*N*,*N*-dimethylglycine system developed by Ma *et al*.[158] (entry 3) or $Cu(PPh_3)_3Br$ (entry 4), with both returning starting material after 16 h. Switching tact to a Cu^{II} system (entry 5) also returned starting material as did the analogous Pd-catalysed reaction (entry 6). In this case no evidence for oxidative addition into the labile C-I bond was observed.



Reagents & Conditions: i) $LiOH{\cdot}H_2O$, THF/H_2O, 3 h, RT, 84%; ii) Tyr.*O*Me·HCl, EDCI, HOBt, Et_3N, DMF, 16 h, RT, 68%; iii) see Table **4.1**.

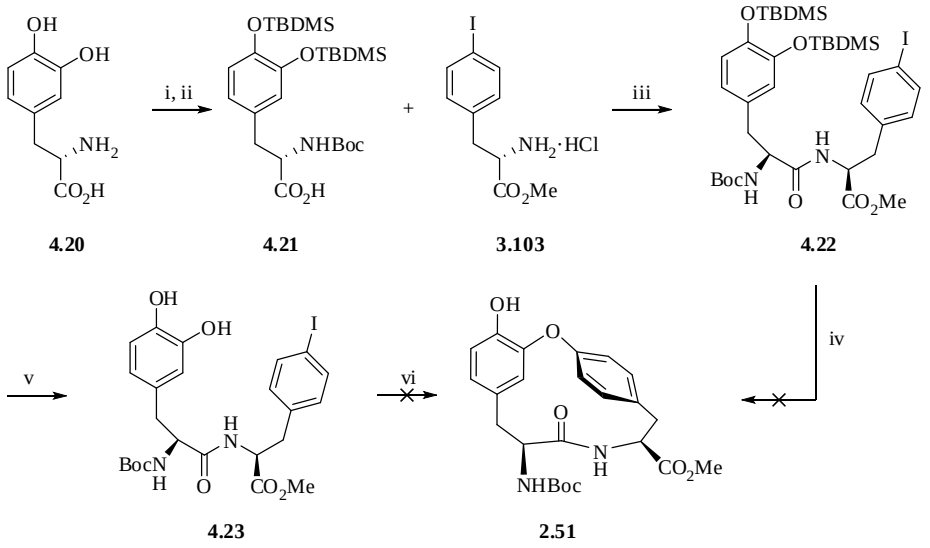
Scheme 4.9: Preparation of B-*O*-C ring by Ullmann type chemistry.

Entry	Complex	Base	Solvent	Time (temp)
1	$[Cu(bpy)_2]BF_4^-$	K_3PO_4	DMF	16 h (80 ^{o}C)
2	$[Cu(bpy)_2]BF_4^-$	K_3PO_4	DMF	4 d (80 ^{o}C)
3	$CuI/Me_2NCH_2CO_2H$	Cs_2CO_3	dioxane	16 h (80 ^{o}C)
4	$Cu(PPh_3)_3Br$	Cs_2CO_3	NMP	16 h (100 ^{o}C)
5	$Cu(OAc)_2$	DMAP	dioxane	16 h (80 ^{o}C)
6	$Pd(OAc)_2$	DMAP	DMF	16 h (80 ^{o}C)

Table 4.1: Conditions examined to achieve the intramolecular Ullmann reaction, **4.19** → **4.16**.

We next turned our focus towards an alternate strategy of using the B ring as the nucleophilic component (Scheme **4.10**). Protection of the catechol moiety of L-DOPA as a bis-silyl ether, followed by Boc protection of the free amine gave **4.21** in reasonable overall yield. Coupling to iodotyrosine **3.103** then gave dipeptide **4.22** in 65%. Using the CuI/*N*,*N*-dimethylglycine system with bis-silyl ether **4.22** led to a

mixture of RSM and mono-silylated starting material. Treatment of **4.22** with TBAF gave catechol **4.23** which, when exposed to the same conditions as before again gave only RSM.



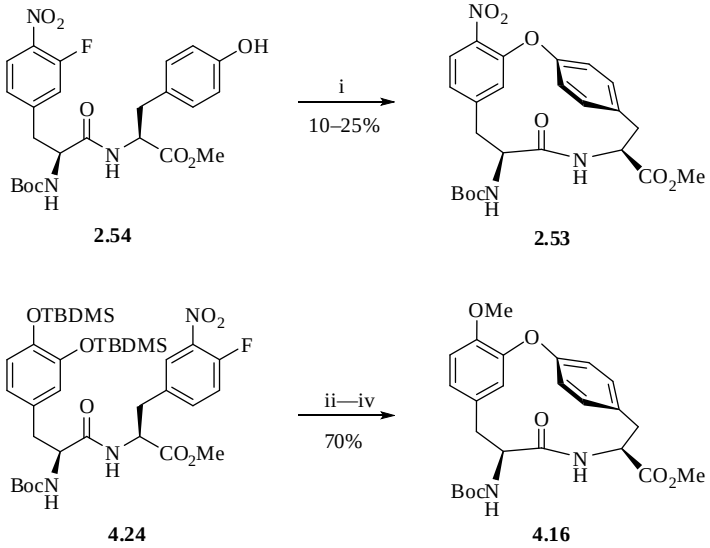
Reagents & Conditions: i) TBDMSCl, DBU, MeCN, 2 d, 0 ^{o}C–RT; ii) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, RT, 57% over two steps; iii) EDCI, HOBt, Et_3N, CH_2Cl_2, 16 h, RT, 65%; iv) CuI/*N*,*N*-dimethylglycine, Cs_2CO_3, 1,4-dioxane, 16 h, 90 ^{o}C; v) TBAF (1M in THF), THF, 4 h, RT, 77%; vi) CuI/*N*,*N*-dimethylglycine, Cs_2CO_3, 1,4-dioxane, 16 h, 90 ^{o}C.

Scheme 4.10: Preparation of B-*O*-C ring using B ring as nucleophile.

Having examined a number of conditions to effect closure of the B-*O*-C macrocycle, including the use of the C ring as both the nucleophile and the electrophile, we decided that a change of strategy maybe prudent at this juncture. As discussed previously, we were concerned that the reverse-amide sequence in our peptide precursor may be a root cause of our problems with respect to cyclisation. In particular, the mechanism of the Ullmann reaction may not allow for the formation of smaller, strained macrocycles where there is a need to pay a severe energetic penalty as evidenced by the need to drive aromatic rings out of planarity.[15] With success using the S_NAr methodology reported in the literature, and from previous studies in our group we decided to change tactic and move back to the S_NAr strategy. We also decided to create the requiste unnatural amino acid **3.92** by an organocatalysed Schiff-base alkylation rather than using the cumbersome Schöllkopf methodology.

4.1.3 Phase Transfer Catalysis for the Formation of Unnatural Amino Acid

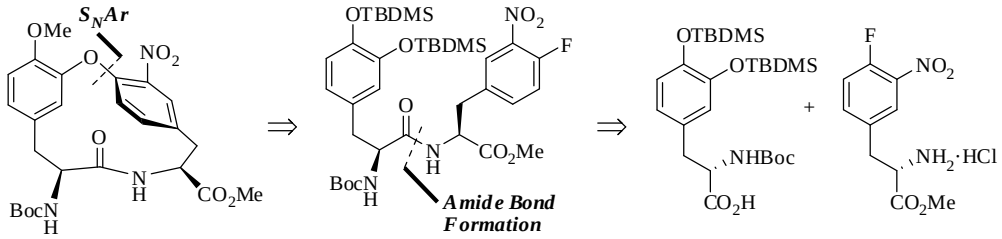
Using the pioneering work by the Zhu[9, 12] and Boger[10] teams and also within our group,[159] Scott Twiddy was able to show that closure of the B-*O*-C ring by our original strategy, (using the C ring as the nucleophilic component) consistently gave low yields. Whereas when the B ring was the nucleophile (Boger[10] and Zhu[12] approaches) yields of 70% were readily achievable (Scheme **4.11**).[159]



Reagents & Conditions: i) NaH, THF (26.0 mM), 16 h, RT, 10–25%; ii) CsF, DMSO (26 mM), 6 h, RT, then, MeI, 16 h, RT, 70%; iii) Fe, NH_4Cl, MeOH; iv) $NaNO_2$, H_3PO_4, Cu_2O.

Scheme 4.11: Comparison of the two S_NAr strategies.

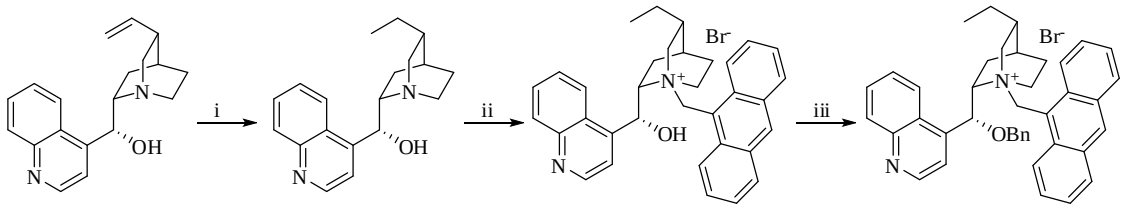
Thus, Scheme **4.12** shows our 3rd generation retrosynthesis of the B-*O*-C macrocycle. Zhu had previously shown that it is possible to achieve regioselective *ortho*-halogenation (Scheme **1.9**), which would provide us with a way of installing the halide we needed for our radical-induced ring contraction strategy. Scission of the biaryl ether bond leads back to acyclic dipeptide **4.24** which in turn can be made by union of amino acids **4.21** and **3.92**. The unnatural **3.92** would be prepared by an organocatalysed asymmetric alkylation of glycine.



4.25 **4.24** **4.21** **3.92**

Scheme 4.12: 3rd generation retrosynthesis of the B-*O*-C macrocycle.

In 1989 O'Donnell demonstrated the first examples of asymmetric alkylation of glycine imines for the synthesis of chiral α-amino acids using phase transfer catalysis.[160] Since then this work has been extensively developed by Lygo,[161-165] Corey[166] and others. The method employs a cinchonidine derived catalyst **4.29**, whose synthesis, is detailed in Scheme **4.13**. Thus, commercially available cinchonidine **4.26** was hydrogenated to afford the dihydro analogue **4.27** in good yield. We noted that it was crucial to monitor this reaction closely by ^{1}H NMR, as if left too long significant by-products were observed, presumably resulting from hydrogenation of the quinoline. *N*-alkylation of **4.27** with 9-(bromomethyl)anthracene **4.31** gave quaternary ammonium salt **4.28** in high yield (92%). *O*-alkylation with benzyl bromide then gave the desired catalyst **4.29** in 77% yield.

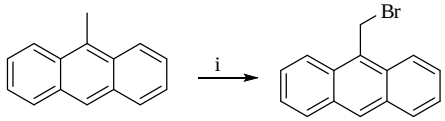


4.26 **4.27** **4.28** **4.29**

Reagents & Conditions: i) H_2, Pd/C, MeOH, 16 h, RT, 99%; ii) **4.31**, PhMe, 2 d, RT, 92%; iii) BnBr, 50% w/w $KOH_{(aq)}$, CH_2Cl_2, 4 h, RT, 77%.

Scheme 4.13: Preparation of phase-transfer catalyst.

Scheme **4.14** shows the one-step quantitative conversion of 9-methylanthracene into 9-(bromomethyl)anthracene **4.31**. It should be noted that in our hands, purification of **4.31** by column chromatography led to severe degradation, despite reports in the literature saying otherwise.[167] It could be conveniently purified however by dissolving the crude material in hexane and filtering off the precipitated succinimide.

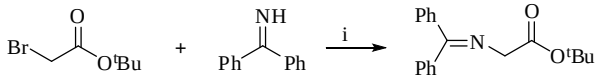


4.30 **4.31**

Reagents & Conditions: i) NBS, CCl_4, 16 h, 76 ^oC, 100%.

Scheme 4.14: Preparation of 9-(bromomethyl)anthracene.

The literature synthesis of protected glycine **3.97** is shown in Scheme **4.15** and was easily accomplished in one step by the alkylation of benzophenone imine **4.33** with *tert*-butyl bromoacetate **4.32**. This reaction could be performed on a large scale and the product recrystallised to high purity.

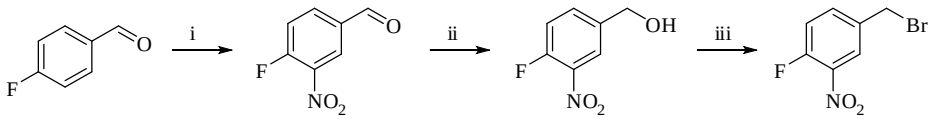


4.32 **4.33** **3.97**

Reagents & Conditions: i) DIPEA, MeCN, 16 h, 82 ^oC, 71%.

Scheme 4.15: Preparation of protected gylcine.

The electrophilic component of the PTC reaction, benzyl bromide **3.98**, was prepared in three steps from readily available 4-fluorobenzaldehyde **4.34** (Scheme **4.16**). Nitration using standard conditions gave 3-nitro-4-fluorobenzaldehyde **4.35** in excellent yield and regioselectivity. Reduction of the aldehyde with $NaBH_4$ smoothly furnished the corresponding benzyl alcohol **4.36** in high yield (99%). Finally, conversion of **4.36** to benzyl bromide **3.98** was achieved in 89% yield by reaction with PBr_3.



4.34 **4.35** **4.36** **3.98**

Reagents & Conditions: i) HNO_3, H_2SO_4, 3 h, 0 ^oC–RT, 99%; ii) $NaBH_4$, MeOH, 1 h, 0 ^oC, 99%; iii) PBr_3, PhMe, 5 h, 0 ^oC–RT, 89%.

Scheme 4.16: Preparation of 4-fluoro-3-nitrobenzyl bromide.

The stage was now set for the synthesis of the unnatural amino acid **3.92** and hence the B-*O*-C macrocycle (Scheme **4.17**). Asymmetric alkylation of benzophenone imine **3.97** with benzyl bromide **3.98**, mediated by catalyst **4.29**, gave amino acid **4.37** in good yield (63%) and and good *e.r.* 86:14 (Figure **4.1**).

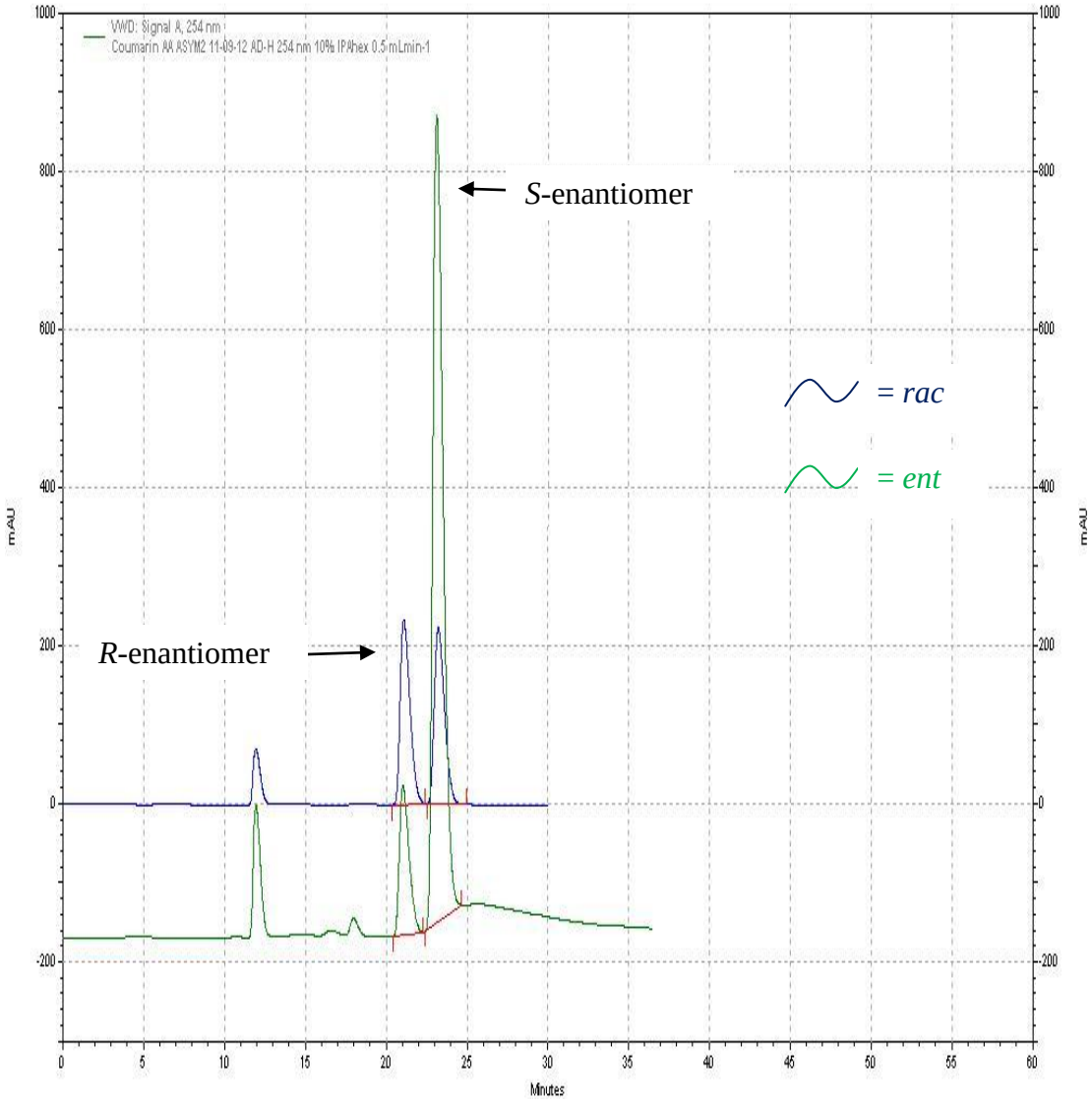
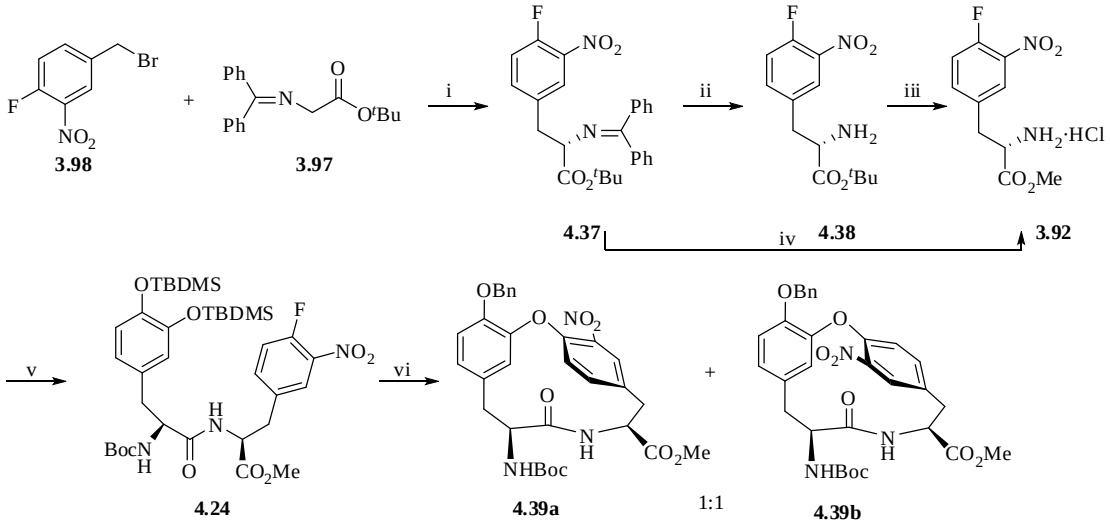


Figure 4.1: Chiral HPLC trace for amino acid **4.37** synthesis. HPLC performed using an AD-H column at 254 nm in 10% ^{i}PrOH/hexane at 0.5 mL.min^{-1}.

Several protecting group manipulations then followed. We found that a two-step protocol to methyl ester **3.92** was more efficient than the direct approach involving exposure of **4.37** to $SOCl_2$/MeOH. Thus, removal of the benzophenone imine protecting group by reaction with 15% citric acid gave amine **4.38** in good yield (75%) with

subsequent methanolysis giving **3.92** in quantitative yield. The isolation of ^{t}Bu ester **4.38** in the two-step route gives us orthogonality of protecting groups should we need it later. Union of methyl ester **3.92** with protected L-DOPA **4.21** occurred in low yield (34%), although it did provide us with enough material to examine the key macrocyclisation step. Thus, using the conditions developed by Zhu,[12, 159] dipeptide **4.24**, was exposed to CsF in DMSO at high dilution and pleasingly gave a 1:1 mixture of the macrocyclic atropisomers **4.39a** and **4.39b** in 64% yield. The phenoxide anion was trapped *in situ* by addition of benzyl bromide, providing a useful model of the more advanced benzyl ether as outlined in Chapter **3**. The formation of atropisomers was of no consequence as this stereoelement was to be removed by reduction. Consequently, the mixture was not separated.



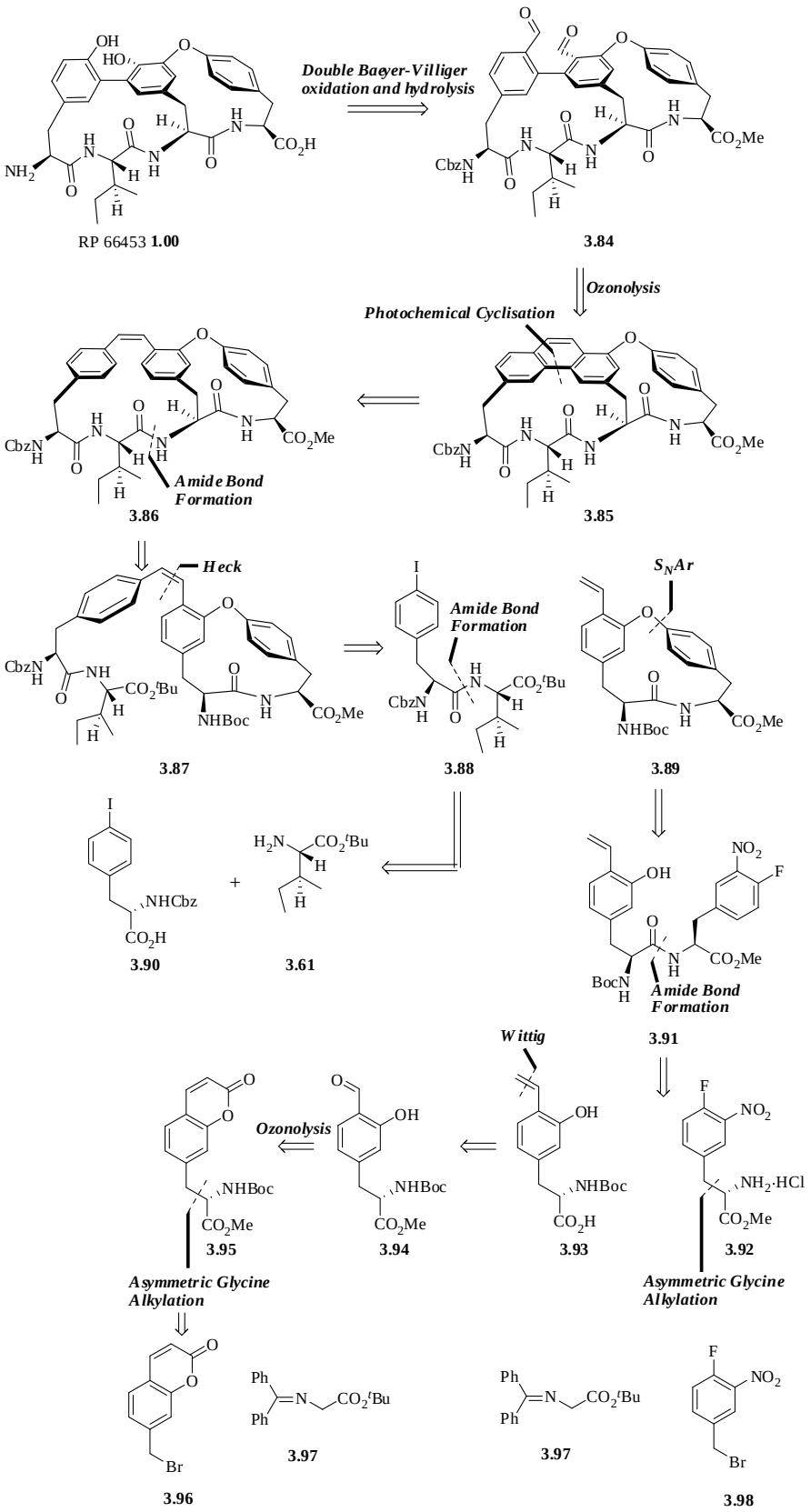
Reagents & Conditions: i) **4.29**, 50% w/w $KOH_{(aq)}$, PhMe, 4 d, –20 ^{o}C–RT, 63%; ii) 15% citric acid solution, THF, 16 h, RT, 75%; iii) $SOCl_2$, MeOH, 16 h, 0–65 ^{o}C, 100%; iv) $SOCl_2$, MeOH; v) **4.21**, HOBt, EDCI, DIPEA, DMF, 16 h, RT, 34%; vi) CsF, DMSO, 17 mM, 6 h, RT, then BnBr, 12 h, RT, 64%.

Scheme 4.17: Preparation of B-*O*-C macrocycle by a S_NAr reaction.

4.2 Phenanthrene Tether

As we have seen in Section **3.5**, we also sought to form the A-B macrocycle via a phenanthrene, which could in turn be derived from a *cis*-stilbene. We therefore required a new handle on the B-*O*-C ring to facilitate our intermolecular Heck reaction between

the B-*O*-C and A fragements. This section of our retrosynthesis (Scheme **3.27**) is shown again below.



Scheme 3.27: Retrosynthesis of the A-B and B-*O*-C macrocycle via phenanthrene **3.85**.

In a forward sense (Scheme **4.18**) amino acid **4.42** was prepared first, by bromination of 7-methylcoumarin using NBS and VAZO giving benzyl bromide **3.96** in 70% yield. Then, using the PTC reaction as before, alkylation with benzophenone imine **3.97** gave amino acid derivative **4.40** in 65% yield and good *e.r.* 85:15 (Figure **4.2**).

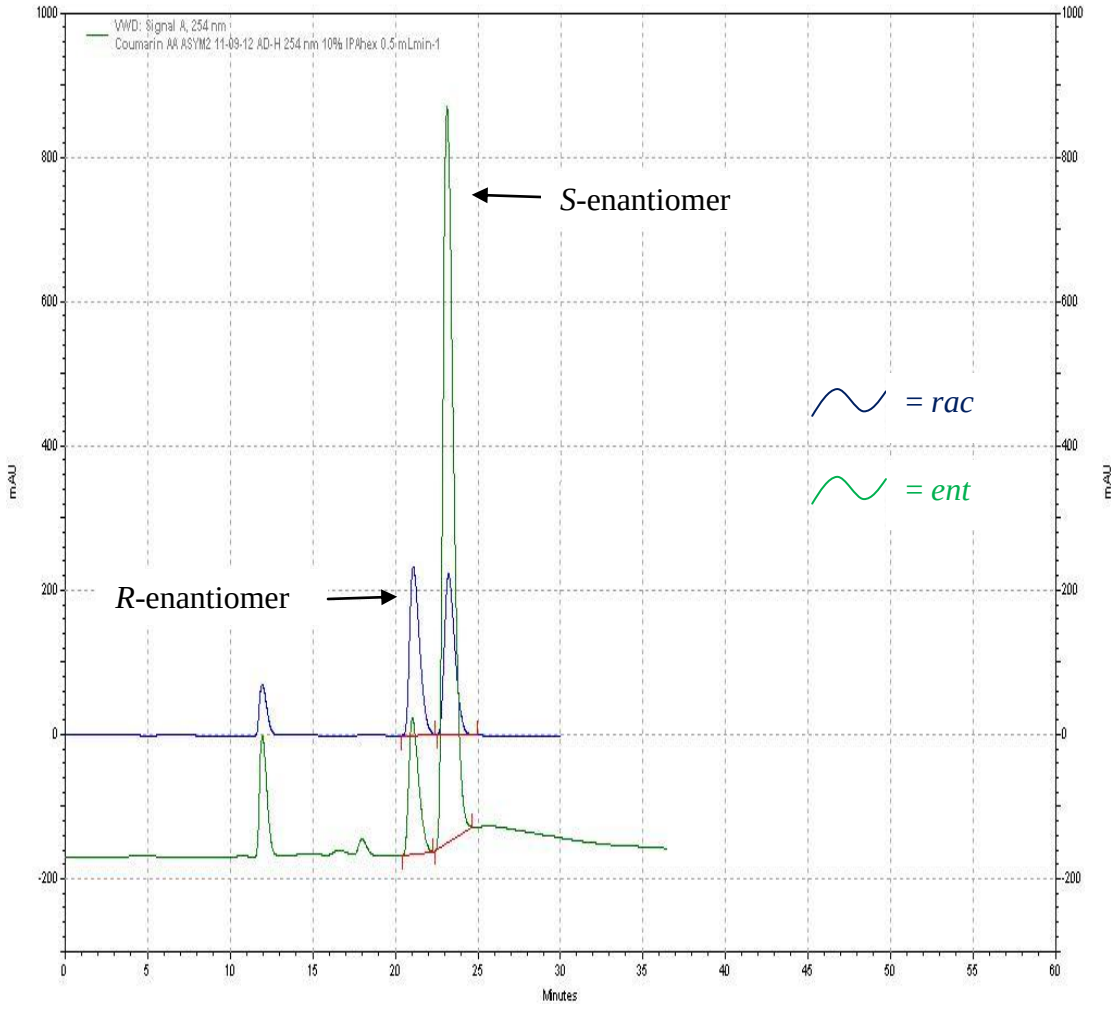
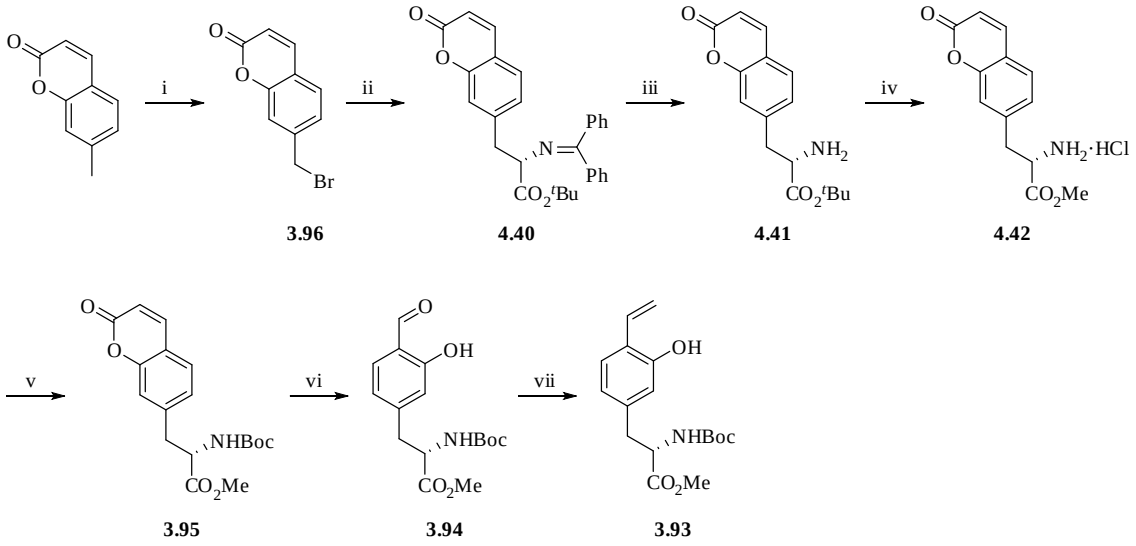


Figure 4.2: Chiral HPLC trace for amino acid **4.40** synthesis. HPLC performed using an AD-H column at 254 nm in 10% ^{i}PrOH/hexane at 0.5 mL.min^{-1}.

This PTC reaction proved to be particularly problematic. The benzyl bromide starting material was sparingly soluble in toluene, the usual solvent for this type of reaction. Consequently a large excess of CH_2Cl_2 had to be used to solublise all the components of the reaction mixture. Furthermore, when cooled to 0 ^{o}C, the starting materials began to precipitate from solution. We also believe that the use of the 50% KOH led to the

saponification of the coumarin. Nevertheless, we could still bring through sufficient quantities of **4.40** to test the viability of this as a route to styrene **3.93**. Hence, amino acid **4.40** was treated with citric acid to liberate free amine **4.41**. Transesterification with $SOCl_2$/MeOH and Boc protection then gave **3.95** in 67% over 3 steps. Ozonolysis of the coumarin next gave aldehyde **3.94** in 57% isolated yield, observing that significant decomposition of this material occurred on loading it to silica for purification. Finally, a Wittig reaction afforded the desired styrene **3.93** in excellent yield. Unfortunately, due to time constraints, chemistry on this route was stopped at this juncture.



Reagents & Conditions: i) NBS, VAZO, MeCN, 16 h, 80 °C, 70%; ii) **3.97**, **4.29**, 50% w/w $KOH_{(aq)}$, CH_2Cl_2, 3 d, RT, 65%; iii) 15% citric acid solution, THF, 16 h, RT, 99%; iv) $SOCl_2$, MeOH, 16 h, 0–64 °C, 95%; v) $(Boc)_2O$, Et_3N, 1,4-dioxane/H_2O, 16 h, 0 °C–RT, 71%; vi) O_3/O_2, PPh_3, CH_2Cl_2, 16 h, –60 °C, 57%; vii) $MePPh_3Br$, KO^{t}Bu, THF, 1 h, 0 °C, 99%.

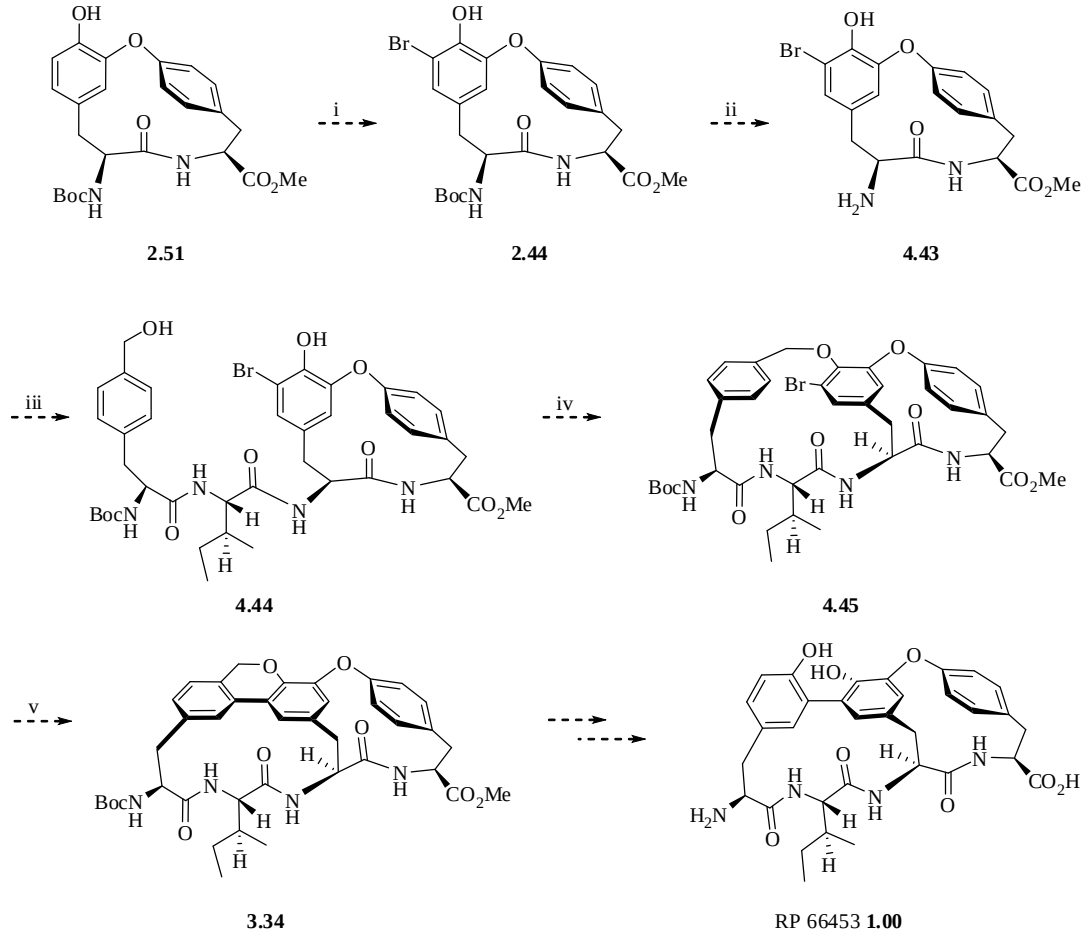
Scheme 4.18: Preparation of styrene **3.93**.

4.3 Concluding Remarks and Further Work

The synthesis of unnatural amino acid **2.55** was initially carried out using Schollkopf's bis-lactim methodology. However, this proved costly and highly problematic in our hands, due to a long, expensive, and low yielding synthesis of auxiliary **2.57**. As a consequence, we changed to a shorter sequence in which we planned to use an intramolecular Ullmann-type reaction as the key step. Unfortunately, this approach had

to be abandoned when it failed to deliver any of the highly strained 14-membered macrocycle. Thus we reverted back to an S_NAr strategy for preparing macrocycle **2.51**, this time using the asymmetric phase transfer reaction to form the requiste unnatural amino acid **3.92**, by alkylation of a glycine derivative. We went on to form the B-*O*-C macrocycle as a mixture of atropisomers **4.39a** and **4.39b** trapping the free phenol with benzyl bromide.

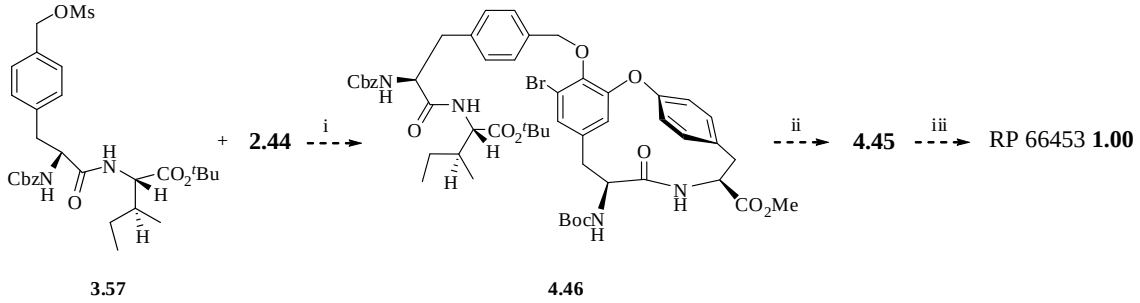
This leaves us well placed to advance the synthesis further. We need to effect the union of dipeptides **4.43** and **3.27**, and formation of the key benzyl ether bond to give bis-macrocycle **4.45**. A radical induced transannular ring contraction to benzo[*c*]chromene **3.34** followed by benzylic and Baeyer-Villiger oxidation reactions and global deprotection provides a plausible route to RP 66453 (Scheme **4.19**).



Reagents & Conditions: i) Br_2; ii) TFA; iii) **3.47**, EDCI, HOBt; iv) $SOCl_2$ then K_2CO_3, KI; v) Bu_3SnH, VAZO.

Scheme 4.19: Proposed forward synthesis for the end-game of our total synthesis.

Alternatively, we have the option of trapping the phenoxide anion of **2.44** with **3.57**, and closing the macrocycle by an intramolecular lactamisation (Scheme **4.20**). The radical sequence would be the same as that shown above.

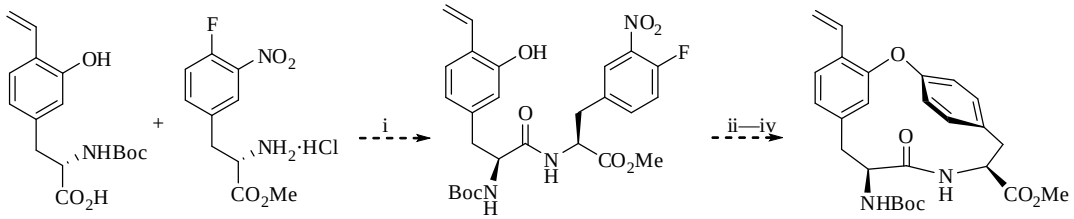


3.57 **4.46**

Reagents & Conditions: i) K_2CO_3, KI; ii) H^+, then EDCI, HOAt; iii) Bu_3SnH, VAZO

Scheme 4.20: Alternative strategy for our benzyl ether tethered end-game.

For the phenanthrene tethered approach, styrene **3.93** is in hand, through an unoptimised 7 step sequence as shown in Scheme **4.18**. Therefore, to complete the total synthesis of the B-*O*-C macrocycle we first need to append in unnatural amino acid **3.92**, then perform the S_NAr macrocyclisation reaction and remove the nitro group (Scheme **4.21**).



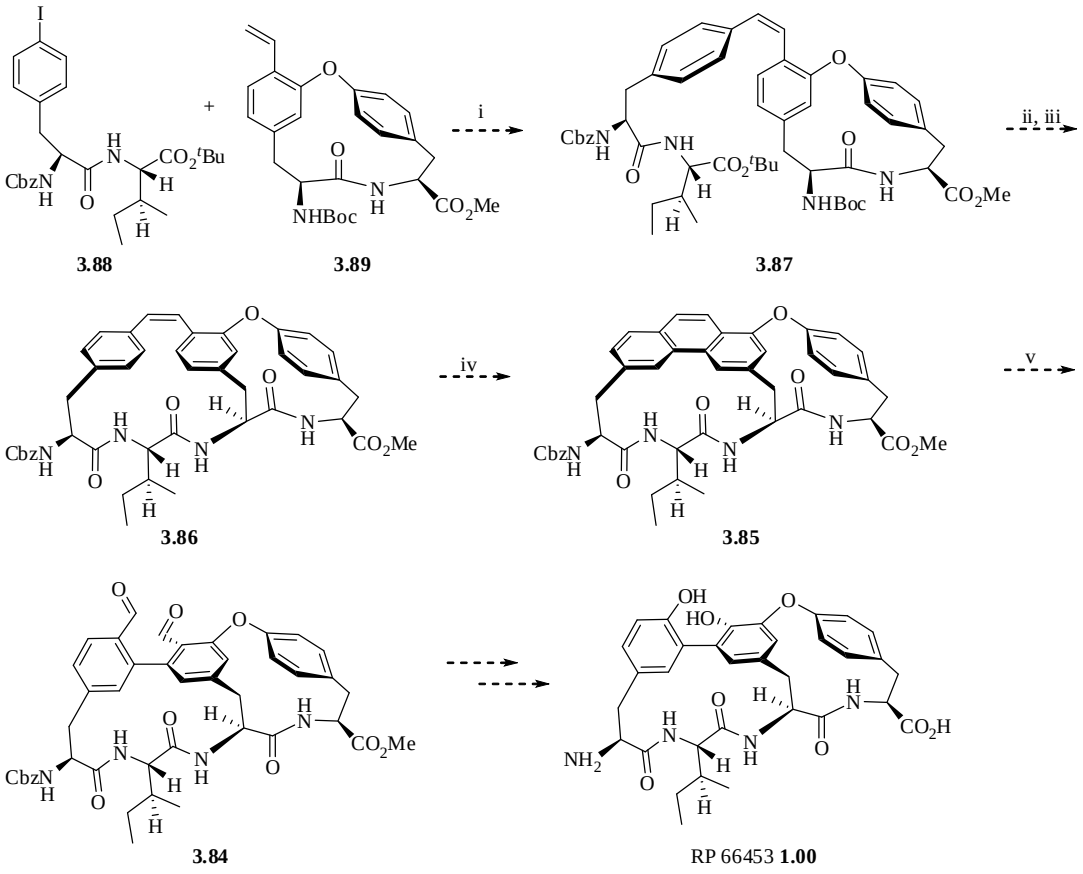
4.47 **3.92** **3.91** **3.89**

Reagents & Conditions: i) EDCI, HOBt; ii) CsF, DMSO; iii) Fe, NH_4Cl, MeOH; iv) $NaNO_2$, H_3PO_4, Cu_2O.

Scheme 4.21: Alternative strategy for our benzyl ether tethered end-game.

This can then be linked to the A fragment by a Heck reaction (e.g. **3.89** → **3.87**), prior to closure of the macrocycle by an intramolecular amide bond formation **3.87** → **3.86** (Scheme **4.22**). The phenanthrene could be formed using the photochemical strategy detailed in Section **3.5**. Ozonolysis of the C9–C10 phenanthrene bond, a double Baeyer-

Villiger reaction on the resulting dialdehyde and global deprotection should then provide RP 66453 **1.00**.



Reagents & Conditions: i) $Pd(OAc)_2$, JohnPhos; ii) TFA; iii) EDCI, HOBt; iv) hv; v) O_3.

Scheme 4.22: Proposed forward synthesis for the end-game of our total synthesis.

Chapter 5: Experimental

5.1 General Experimental

Melting Points: Melting points were recorded on Barnstead Electrothermal 9100 apparatus and are uncorrected.

NMR Spectra: Proton (^{1}H) and carbon (^{13}C) spectra were recorded on a Bruker AV300 (300/75 MHz) or Bruker DPX400 (400/100 MHz) spectrometer at 298 K unless otherwise stated. Chemical shifts are quoted in parts per million downfield of tetramethylsilane with residual solvent as the internal standard. Fluorine (^{19}F) spectra were recorded on a Bruker AV300 (282 MHz) or Bruker DPX400 (376 MHz) spectrometer and were referenced externally to $CFCl_3$ Assignments were made on the basis of chemical shifts, coupling constants, DEPT-135, COSY, HMQC, HMBC and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), sext. (sextet), sept. (septet), oct. (octet), app. (apparent) and br. (broad). Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.1 Hz.

Infrared Spectra: Infrared spectra were recorded neat as an oil film or solid compression on a Nicolet 380 FT-IR. Absorption maxima (ν_{max}) are described as s (strong), m (medium), w (weak) and br (broad) and are quoted in wavenumbers (cm^{-1}).

Mass Spectra: ESI mass spectra were recorded using a Waters ZMD single quadrupole mass spectrometer with a 2700 autosampler and a 600 pump with MeCN as the eluent. EI were measured on a thermoquest trace single quadrupole GC-MS at 70 eV. High resolution mass spectra were recorded on either a Bruker Apex III FT-ICR mass spectrometer equipped with a 4.7 T actively shielded superconducting magnet and Apollo ESI ion source or a Bruker maXis ESI-ToF coupled to a Dionex Ultimate 3000 HPLC and Apollo ESI ion source. Recorded by Dr John Langley, Ms. Julie Herniman or Miss Christianne Wicking.

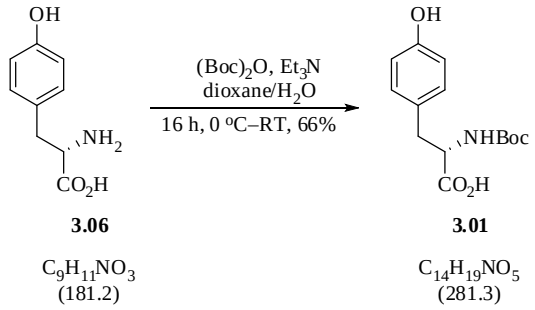
Chromatography Techniques: Thin layer chromatography was performed on Merck DC-Alufolien 60 F_{254} 0.2 mm precoated plates. Product spots were visualised by, most commonly, 5% potassium permanganate in 5% aqueous NaOH solution and 10% PMA in EtOH solution as appropriate. Flash column chromatography was carried out on silica gel (200–400 mesh) with the solvent system used as given in parentheses. Analytical chiral HPLC was performed on an Agilent Technologies 1120 Compact LC system using normal phase Daicel AD-H column with 254 nm detection, eluted with 1% IPA/hexane at 0.5 $mL.min^{-1}$. Preparative HPLC was carried out using Biorad Bio-Sil D 90–10 columns (250 x 22 mm at 15–20 $mL.min^{-1}$ and 250 x 10 mm at 5 $mL.min^{-1}$.

Optical Rotation: Optical rotations were recorded on an Optical Activity Polaar 2001 polarimeter at 589 nm.

Solvents and Reagents: Commercially available reagents were purchased and used without further purification. Solvents were used as purchased unless stated as dry. In which case, THF and 1,4-dioxane were freshly distilled and dried over sodium and benzophenone, toluene and acetonitrile were freshly distilled over sodium and CH_2Cl_2 was distilled and dried over CaH_2 immediately prior to use.

5.2 Experimental Procedures for Chapter 3

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-hydroxyphenyl)propanoic acid **3.01**



3.06 **3.01**

$C_9H_{11}NO_3$ (181.2) $C_{14}H_{19}NO_5$ (281.3)

To a solution of L-tyrosine **3.06** (20.0 g, 110 mmol) in 1,4-dioxane/water (1:1, 400 mL) at 0 °C was added $(Boc)_2O$ (24.0 g, 110 mmol) dropwise, followed by the dropwise addition of Et_3N (23.1 mL, 165 mmol). The reaction mixture was warmed to RT and after 16 h was concentrated under reduced pressure giving a crude off-white solid that was taken up in EtOAc (400 mL) and washed sequentially with 2M HCl (250 mL) and brine (250 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the title compound **3.01** (20.4 g, 72.7 mmol, 66%) as a white solid that was used without further purification. These data are in accordance with those reported in the literature.[168]

M.P. 136–139 °C (Et_2O/MeOH). Lit. 136–138 °C (EtOAc/petroleum ether).[169]

FT-IR (ν_{max}, neat) 3329 br. m, 2974 m, 2921 w, 2500 br. w, 1715 m, 1682 s, 1617 m, 1515 s, 1413 m, 1386 m, 1244 m, 1162 s, 1049 m, 833 m, 771 m, 530 w cm^{-1}.

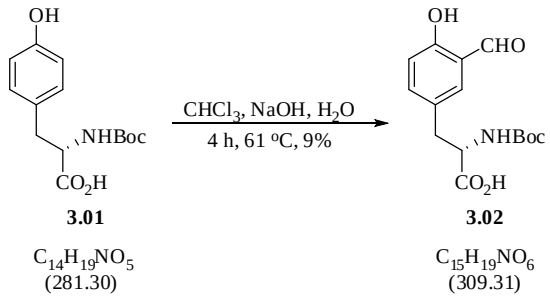
^{1}H NMR (300 MHz, *d*$_4$-MeOD) δ_H ppm 7.04 (d, *J*=8.4 Hz, 2H, Ar*H*), 6.70 (d, *J*=8.4 Hz, 2H, Ar*H*), 4.28 (app. dd, *J*=8.4, 5.1 Hz 1H, NC*H*CO), 4.19 (br. s, 1H, N*H*), 3.04 (dd, *J*=13.9, 5.1 Hz, 1H, C*H*H), 2.81 (dd, *J*=13.9, 8.8 Hz, 1H, CH*H*), 1.39 (s, 9H, C(CH_3)$_3$), 1.35 (br. s, 1H, O*H*).

^{13}C NMR (75 MHz, d_4-MeOD) δ_C ppm 175.6 (*C*), 157.9 (*C*), 157.4 (*C*), 131.5 (2 x *C*H), 129.4 (*C*), 116.3 (2 x *C*H), 80.7 (*C*), 56.7 (*C*H), 38.1 (*C*H_2), 28.8 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^-$) 280 ([M–H]$^-$, 2%), 207 (100%).

$[\alpha]_D^{26}$ + 27.3 (c = 0.45, CH_2Cl_2).

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(3-formyl-4-hydroxyphenyl)propanoic acid **3.02**



3.01 $C_{14}H_{19}NO_5$ (281.30)

3.02 $C_{15}H_{19}NO_6$ (309.31)

To a suspension of arene **3.01** (2.00 g, 7.12 mmol) in $CHCl_3$ (30 mL) and H_2O (257 µL) was added powdered NaOH (1.71 g, 42.7 mmol) and the reaction mixture heated at 61 ^{o}C. After 4 h the reaction mixture was cooled to RT and concentrated under reduced pressure. The crude residue was partioned between H_2O (100 mL) and EtOAc (50 mL) and the aqueous phase washed with EtOAc (50 mL) then acidifed to pH 2 with 2M HCl (30 mL). The products were extracted with EtOAc (3 x 50 mL) and the combined organic phases washed with brine (70 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (5% MeOH/$CHCl_3$ + 1% HOAc) to give the title compound **3.02** (210 mg, 679 µmol, 9%) as a pale brown oil. These data are in accordance with those reported in the literature.[120]

FT-IR (ν_{max}, neat) br. w 3333, 2978 m, 2929 m, 2864 w, 2745 w, 1692 s, 1653 s, 1482 m, 1368 m, 1279 m, 1210 m, 1155 s, 1053 m, 767 m, 732 s, 669 m cm^{-1}.

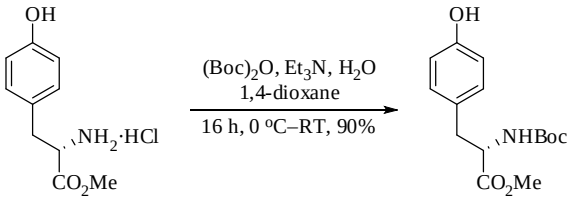
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 10.90 (s, 1H, O*H*), 10.01 (br. s, 1H, CO_2*H*), 9.84 (s, 1H, C*H*), 7.43–7.32 (m, 2H, 2 x Ar*H*), 6.93 (d, *J*=8.6 Hz, 1H, Ar*H*), 5.10 (d, *J*=7.1 Hz, 1H, N*H*), 4.66–4.56 (br. m, 1H, NC*H*CO), 3.28–3.14 (m, 1H, C*H*H), 3.04 (dd, *J*=13.4, 5.8 Hz, 1H, CH*H*), 1.41 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 196.5 (*C*H), 177.4 (*C*), 160.6 (*C*), 155.3 (*C*), 138.1 (*C*H), 134.2 (*C*H), 127.6 (*C*), 120.4 (*C*), 117.8 (*C*H), 80.5 (*C*), 54.3 (*C*H), 36.9 (CH_2), 28.2 ((CH_3)$_3$).

LRMS (m/z, ESI$^-$) 308 ($[M–H]^-$, 100%).

$[\alpha]_D^{29}$ + 83.6 (c = 0.55, MeOH).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-hydroxyphenyl)propanoate **3.10**



2.56
$C_{10}H_{14}ClNO_3$
(231.7)

3.10
$C_{15}H_{21}NO_5$
(295.3)

To a solution of hydrochloride salt **2.56** (8.59 g, 37.1 mmol) in 1,4-dioxane/water (1:1, 150 mL) at 0 ^{o}C was added Et_3N (5.18 mL, 37.1 mmol) followed by the dropwise addition of $(Boc)_2O$ (8.10 g, 37.1 mmol) and a second charge of Et_3N (5.18 mL, 37.1 mmol). The reaction mixture was warmed to RT and after 16 h was quenched with 2M HCl (100 mL). The aqueous phase was extracted with EtOAc (4 x 50 mL), and the combined organic phases were washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (30% EtOAc/petroleum ether) to give the title compound **3.10** (9.84 g, 33.3 mmol, 90%) as a white solid. These data are in accordance with those reported in the literature.[170]

M.P. 101–104 °C (EtOAc/petroleum ether), Lit. 100–102 °C.[171]

FT-IR (ν_{max}, neat) 3358 br. m, 3007 w, 2974 m, 2953 w, 2925 w, 2242 w, 1736 m, 1685 s, 1605 m, 1513 s, 1440 m, 1365 m, 1219 s, 1159 s, 1056 m, 1910 m, 816 m, 729 s, 649 m cm^{-1}.

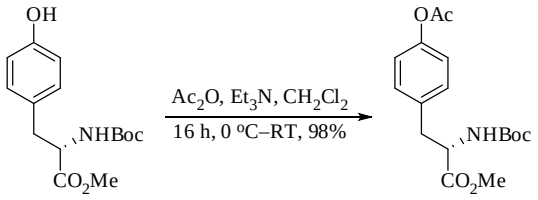
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 6.96 (d, *J*=7.9 Hz, 2H, Ar*H*), 6.73 (d, *J*=7.9 Hz, 2H, Ar*H*), 6.43 (br. s, 1H, O*H*), 5.05 (d, *J*=8.1 Hz, 1H, N*H*), 4.59–4.51 (br. m, 1H, NC*H*CO), 3.71 (s, 3H, CH_3), 3.03 (dd, *J*=14.2, 5.6 Hz, 1H, C*H*H), 2.96 (dd, *J*=14.2, 6.1 Hz, 1H, CH*H*), 1.42 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.7 (*C*), 155.3 (*C*), 155.2 (*C*), 130.3 (2 x *C*H), 127.3 (*C*), 115.6 (2 x *C*H), 80.2 (*C*), 54.6 (*C*H), 52.2 (*C*H_3), 37.5 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 413 ([2M–2Boc+Na]$^+$, 100%), 359 ([M+Na+MeCN]$^+$, 21%), 318 ([M+Na]$^+$, 2%).

$[\alpha]_D^{26}$ + 47.3 (c = 0.43, CH_2Cl_2).

Methyl (*S*)-3-(4-acetoxyphenyl)-2-(*tert*-butoxycarbonylamino)propanoate **3.11**



3.10 $C_{15}H_{21}NO_5$ (295.3)

3.11 $C_{17}H_{23}NO_6$ (337.4)

To a solution of phenol **3.10** (1.00 g, 3.39 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (946 µL, 6.78 mmol) followed by Ac_2O (354 µL, 3.73 mmol) dropwise over 5 min. The reaction mixture was warmed to RT and after 16 h, 1M HCl (30 mL) was

added. The organic phase was separated, washed with sat. $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a colourless oil. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compound **3.11** (1.12 g, 3.32 mmol, 98%) as a white crystalline solid.

M.P. 84–86 ^{o}C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3463 w, 3374 m, 2998 w, 2982 m, 2929 w, 1746 s, 1710 s, 1505 s, 1437 m, 1366 m, 1192 s, 1163 s, 1057 m, 1016 m, 914 m, 849 m, 771 w, 534 w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.13 (d, *J*=8.3 Hz, 2H, Ar*H*), 7.01 (d, *J*=8.3 Hz, 2H, Ar*H*), 5.02 (d, *J*=7.6 Hz, 1H, N*H*), 4.57 (app. q, *J*=6.2 Hz, 1H, NC*H*CO), 3.70 (s, 3H, CH_3), 3.10 (dd, *J*=14.1, 6.1 Hz, 1H, CH*H*), 3.03 (dd, *J*=14.1, 6.6 Hz, 1H, C*H*H), 2.27 (s, 3H, CH_3), 1.41 (s, 9H, C(CH_3)$_3$).

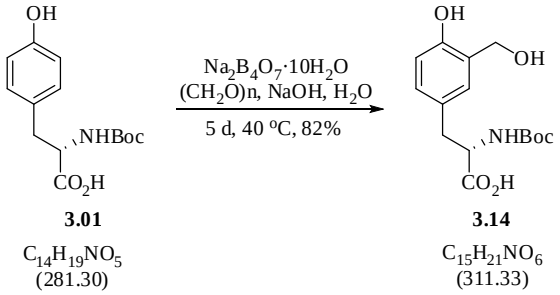
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.1 (*C*), 169.3 (*C*), 155.0 (*C*), 149.6 (*C*), 133.6 (*C*), 130.1 (2 x *C*H), 121.5 (2 x *C*H), 79.8 (*C*), 54.3 (*C*H), 52.2 (*C*H$_3$), 37.6 (*C*H$_2$), 28.2 ((*C*H$_3$)$_3$), 21.0 (*C*H$_3$).

LRMS (m/z, ESI$^+$) 360 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{17}H_{23}INO_6$ [M+Na]$^+$ requires 360.1423; found: 360.1418.

$[\alpha]_D^{27}$ + 43.2 (c = 0.87, CH_2Cl_2).

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-hydroxy-3-(hydroxymethyl)phenyl)propanoic acid **3.14**



3.01 $C_{14}H_{19}NO_5$ (281.30)

3.14 $C_{15}H_{21}NO_6$ (311.33)

Prepared according to the method of Liu *et al.*[130]

To a solution of *N*-Boc.Tyr **3.01** (5.00 g, 17.8 mmol) in 1M NaOH (35.6 mL) was added a solution of borax (13.6 g, 35.6 mmol) in H_2O (45 mL). After 30 min, 37% formaldehyde solution (5.5 mL, 71.2 mmol) was added. The solution was heated at 40 ^oC for 5 d then cooled to RT and 2M HCl (50 mL) added. The aqueous phase was separated, and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (150 mL), dried ($MgSO_4$,) filtered, and concentrated under reduced pressure affording a crude residue. Purification by flash column chromatography (1:1 EtOAc/petroleum ether + 1% HOAc–EtOAc + 1% HOAc) to give the title compound (4.54 g, 14.6 mmol, 82%) **3.14** as a pale yellow solid. These data are in accordance with those reported in the literature.[130]

M.P. 134–138 ^oC (MeOH), Lit. not given.[130]

FT-IR (ν_{max}, neat) 2930 br. s, 1688 s, 1502 s, 1433 m, 1365 m, 1247 m, 1162 s, 1052 m, 1008 m, 836 m, 560 w, 475 m cm^{-1}.

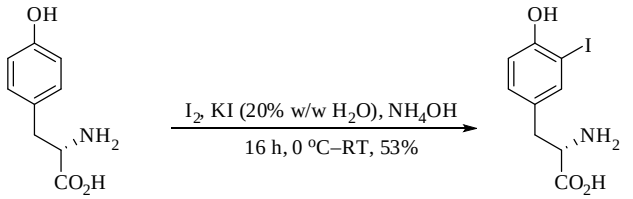
^{1}H NMR (400 MHz, d_6-DMSO) δ_H ppm 9.14 (br. s, 1H, CO_2H), 7.16 (br. s, 1H, Ar*H*), 6.95 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.90 (br. dd, *J*=8.1, 1.5 Hz, 1H, Ar*H*), 6.65 (br. d, *J*=8.1, Hz, 1H, N*H*), 4.45 (s, 2H, CH_2), 4.07–3.96 (m, 1H, NC*H*CO), 3.44 (br. s, 2H, O*H*), 2.89 (dd, *J*=13.6, 4.5 Hz, 1H, C*H*H), 2.72 (dd, *J*=13.6, 9.6 Hz, 1H, CH*H*), 1.34 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, d_6-DMSO) δ_C ppm 173.8 (*C*), 155.5 (*C*), 152.7 (*C*), 128.2 (*C*), 128.0 (*C*H), 127.9 (*C*H), 114.3 (*C*H), 78.1 (*C*), 58.4 (*C*H_2), 55.7 (*C*H), 36.0 (*C*H_2), 28.2 ((*C*H_3)$_3$). *NB: One quaternary resonance not observed.*

LRMS (m/z, ESI$^-$) 310 ([M–H]$^-$, 100%).

$[\alpha]_D^{27}$ + 13.8 (c = 0.626, MeOH).

(*S*)-2-Amino-3-(4-hydroxy-3-iodophenyl)propanoic acid **1.11**



3.06
$C_9H_{11}NO_3$
(181.19)

1.11
$C_9H_{10}INO_3$
(307.08)

Prepared according to the method of Joulie *et al*.[172]

L-tyrosine **3.06** (15.0 g, 82.8 mmol) was dissolved in sat. NH_4OH (345 mL) and stirred vigorously. After complete dissolution a solution of I_2 (21.0 g, 82.8 mmol) in 20% $KI_{(aq)}$ (w/w, 168 mL) was added dropwise over 45 min at 0 °C. The mixture was warmed to RT and after 16 h was concentrated under reduced pressure affording a brown solid which was stirred in acetone (500 mL) for 30 min. The beige precipitate was collected by filtration, and dried under reduced pressure to give the title compound **1.11** (13.5 g, 44.0 mmol, 53%) as a beige solid that was used without further purification. These data are in accordance with those reported in the literature.[172]

M.P. dec. > 200 °C. Lit. 205–209 °C (solvent not given).[173]

FT-IR (ν_{max}, neat) 3323 br. m, 2835 br. m, 2692 m, 2573 m, 1585 s, 1504 m, 1412 s, 1354 s, 1326 s, 1270 m, 1227 m, 1029 m, 830 m, 743 m, 536 s cm^{-1}.

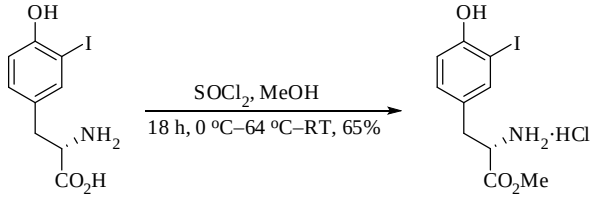
^{1}H NMR (300 MHz, *d*-TFA) δ_H ppm 7.69 (br. s, 1H Ar*H*), 7.30–6.93 (m, 2H 2 x Ar*H*), 4.72–4.50 (m, 1H, NC*H*CO), 3.52 (br. d, *J*=13.9 Hz, 1H, C*H*H), 3.30 (br.dd, *J*=14.6, 8.1 Hz, 1H, CH*H*).

^{13}C NMR (75 MHz, *d*-TFA) δ_C ppm 172.1 (*C*), 156.5 (*C*), 141.6 (*C*H), 132.7 (*C*H), 128.6 (*C*), 117.8 (*C*H), 86.4 (*C*), 57.1 (*C*H), 35.8 (*C*H_2).

LRMS (m/z, ESI$^+$) 615 ($[2M+H]^+$, 2%), 349 ($[M+H+MeCN]^+$, 100%), 308 ($[M+H]^+$, 26%)

$[\alpha]_D^{27}$ –5.6 (c = 0.68, H_2O).

Methyl (*S*)-2-ammonium-3-(4-hydroxy-3-iodophenyl)propanoate hydrochloride **3.15**



1.11
$C_9H_{10}INO_3$
(307.08)

3.15
$C_{10}H_{13}ClINO_3$
(357.57)

Prepared according to the method of Kita *et al*.[174]

Thionyl chloride (21.4 mL, 293 mmol) was added dropwise over 15 min to MeOH (500 mL) at 0 °C with rapid stirring. Acid **1.11** (30.0 g, 97.7 mmol) was added portionwise and then the reaction mixture heated at 64 °C for 4 h and RT for 14 h. The reaction mixture was concentrated under reduced pressure affording a crude beige-coloured solid. The solid was stirred in acetone (400 mL) for 3 h to remove soluble byproducts then collected by filtration and dried under reduced pressure to give the title compound **3.15** (22.6 g, 63.3 mmol, 65%) as a beige solid. These data are in accordance with those reported in the literature.[174]

M.P. dec. > 220 °C (MeOH/Et_2O), Lit. 194–197 °C (MeOH/Et_2O).[175]

FT-IR (ν_{max}, neat) 3105 br. m, 2958 w, 1405 m, 1254 br. m, 1212 m, 1118 s, 1061 m, 1009 m, 759 s, 617 s, 571 m, 555 m cm^{-1}.

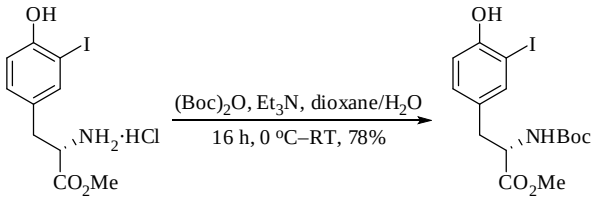
^{1}H NMR (300 MHz, D_2O) δ_H ppm 7.57 (d, *J*=2.2 Hz, 1H, Ar*H*), 7.08 (dd, *J*=8.1, 2.2 Hz, 1H, Ar*H*), 6.87 (d, *J*=8.1 Hz, 1H, Ar*H*), 4.31 (app. dd, *J*=7.3, 6.2 Hz, 1H, NC*H*CO), 3.79 (s, 3H, CH_3), 3.15 (dd, *J*=14.6, 5.9 Hz, 1H, C*H*H), 3.06 (dd, *J*=14.6, 7.3 Hz, 1H, CH*H*).

^{13}C NMR (75 MHz, D_2O) δ_C ppm 169.9 (*C*), 154.8 (*C*), 139.9 (*C*H), 130.8 (*C*H), 127.4 (*C*), 115.4 (*C*H), 83.9 (*C*), 54.0 (*C*H), 53.6 (*C*H_3), 34.0 (*C*H_2).

LRMS (m/z, ESI$^+$) 354 ([M–HCl+H+MeOH]$^+$, 10%), 326 (100%).

$[\alpha]_D^{27}$ + 9.7 (c = 1.1, MeOH).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-hydroxy-3-iodophenyl)propanoate **3.16**



3.15
$C_{10}H_{13}ClINO_3$
(357.6)

3.16
$C_{15}H_{20}INO_5$
(421.2)

To a solution of hydrochloride salt **3.15** (10.6 g, 29.6 mmol) in 1,4-dioxane/water (1:1 v/v, 150 mL) at 0 ^{o}C was added Et_3N (4.13 mL, 29.6 mmol) followed by the dropwise addition of $(Boc)_2O$ (6.46 g, 29.6 mmol) over 5 min and a second charge of Et_3N (4.13 mL, 29.6 mmol). The reaction mixture was warmed to RT and after 16 h was concentrated under reduced pressure. The crude oil was dissolved in EtOAc (250 mL) and washed sequentially with 10% citric acid solution (2 x 100 mL) and brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a brown/orange oil. Purification by flash column chromatography (20–40%

EtOAc/petroleum ether) to give the title compound **3.16** (9.81 g, 23.3 mmol, 78%) as a colourless oil that crystallised on standing to an off-white solid. These data are in accordance with those reported in the literature.[176]

M.P. 96–102 ^{o}C (EtOAc/petroleum ether), Lit. 110–112 ^{o}C.[177]

FT-IR (ν_{max}, neat) 3358 br. m, 3007 w, 2974 m, 2929 w, 2868 w, 1684 s, 1605 w, 1503 m, 1433 m, 1364 m, 1286 m, 1216 m, 1161 s, 1049 m, 730 s, 657 w cm^{-1}.

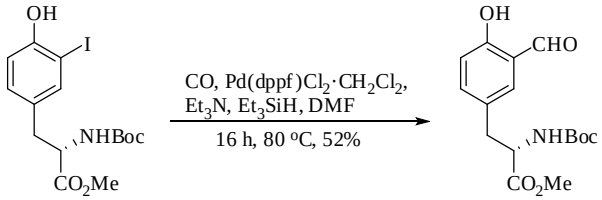
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.43 (br. s, 1H, Ar*H*), 6.97 (dd, *J*=8.3, 1.8 Hz, 1H, Ar*H*), 6.86 (d, *J*=8.6 Hz, 1H, Ar*H*), 6.53 (br. s, 1H, O*H*), 5.08 (d, *J*=7.6 Hz 1H, N*H*), 4.55–4.45 (br. m, 1H, NC*H*CO), 3.72 (s, 3H, CH_3), 3.01 (dd, *J*=14.1, 5.6 Hz, 1H, C*H*H), 2.92 (dd, *J*=14.1, 6.1 Hz, 1H, CH*H*), 1.45 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.2 (*C*), 156.5 (*C*), 154.4 (*C*), 139.2 (*C*H), 130.7 (*C*H), 129.8 (*C*), 115.9 (*C*H), 85.0 (*C*), 80.1 (*C*), 54.5 (*C*H), 52.2 (*C*H$_3$), 36.9 (*C*H$_2$), 28.2 ((*C*H$_3$)$_3$).

LRMS (m/z, ESI^{+}) 485 ([M+Na+MeCN]$^{+}$, 74%), 363 ([M–Boc+H+MeCN]$^{+}$, 100%)$^{+}$.

$[\alpha]_D^{27}$ + 49.3 (c = 0.3, CH_2Cl_2).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(3-formyl-4-hydroxyphenyl) propanoate **3.17**



3.16 $C_{15}H_{20}INO_5$ (421.2)

3.17 $C_{16}H_{21}NO_6$ (323.34)

To a solution of iodide **3.16** (500 mg, 1.19 mmol) in DMF (10 mL) was added Et_3N (414 µL, 2.97 mmol), and Et_3SiH (379 µL, 2.38 mmol). The reaction mixture was degassed under argon for 30 min by immersion in a sonicator bath prior to the addition of $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (48 mg, 59.0 mmol). The reaction mixture was stirred at 80 °C under an atmosphere of CO for 16 h then cooled to RT, diluted with H_2O (300 mL) and the products extracted with EtOAc (4 x 75 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a brown oil. Purification by flash column chromatography (0–20% EtOAc/petroleum ether) to give the title compound **3.17** (202 mg, 620 µmol, 52%) as a white solid. These data are in accordance with those reported in the literature.[131]

M.P. 70–72 °C (EtOAc/petroleum ether), Lit. 85–86 °C (CH_2Cl_2/hexane).[131]

FT-IR (ν_{max}, neat) 3362 br. m, 2970 m, 2929 w, 2855 w, 2745 w, 1742 m, 1707 s, 1654 s, 1485 s, 1364 m, 1279 s, 1245 s, 1159 s, 1057 m, 1019 m, 770 m, 736 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 10.89 (s, 1H, O*H*), 9.85 (s, 1H, C*H*), 7.32 (d, *J*=2.0 Hz, 1H, Ar*H*), 7.29 (dd, *J*=8.3, 2.0 Hz, 1H, Ar*H*), 6.92 (d, *J*=8.3 Hz, 1H, Ar*H*), 5.07 (d, *J*=6.6 Hz 1H, N*H*), 4.61–4.52 (br. m, 1H, NC*H*CO), 3.72 (s, 3H, CH_3), 3.13 (dd,

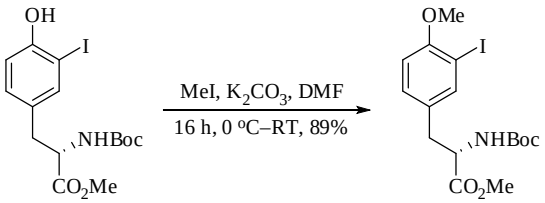
J=14.1, 5.6 Hz, 1H, C*H*H), 3.00 (dd, *J*=14.1, 6.1 Hz, 1H, CH*H*), 1.40 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 196.3 (*C*H), 172.0 (*C*), 160.6 (*C*), 154.9 (*C*), 137.9 (*C*H), 134.0 (*C*H), 127.7 (*C*), 120.4 (*C*), 117.8 (*C*H), 80.1 (*C*), 54.3 (*C*H), 52.3 (*C*H_3), 37.3 (*C*H_2), 28.2 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 387 ([M+Na+MeCN]$^+$, 100%).

$[\alpha]_D^{27}$ + 44.0 (c = 0.7, CH_2Cl_2).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(3-iodo-4-methoxyphenyl)propanoate **1.28**



3.16
$C_{15}H_{20}INO_5$
(421.2)

1.28
$C_{16}H_{22}INO_5$
(435.3)

Prepared according to the method of Zhu *et al.*[178]

To a solution of phenol **3.16** (23.6 g, 56.0 mmol) in DMF (300 mL) at 0 ^oC was added K_2CO_3 (7.70 g, 56.0 mmol) and iodomethane (3.48 mL, 56.0 mmol). The reaction mixture was warmed to RT and after 16 h was quenched with H_2O (3 L). The products were extracted with EtOAc (6 x 500 mL), and the combined organic phases were washed with brine (4 x 500 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude bronze oil. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compound **1.28** (21.8 g, 50.1 mmol, 89%) as a colourless oil. These data are in accordance with those reported in the literature.[178]

FT-IR (ν_{max}, neat) 3374 br. m, 2998 w, 2974 m, 2945 m, 2843 w, 2238 w, 2165 w, 1748 s, 1709 s, 1597 m, 1491 s, 1437 m, 1364 s, 1278 s, 1253 s, 1163 s, 1049 m, 1012 m, 808 m, 730 m cm^{-1}.

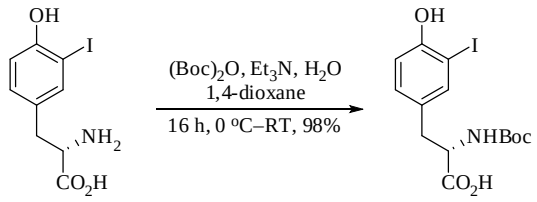
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.53 (app. br. s, 1H, Ar*H*), 7.07 (d, *J*=8.2 Hz, 1H, Ar*H*), 6.75 (dd, *J*=8.2, 1.3 Hz, 1H, Ar*H*), 5.00 (d, *J*=7.1 Hz, 1H, N*H*), 4.52 (br. dt, *J*=7.1, 6.1 Hz, 1H, NC*H*CO), 3.86 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.04 (dd, *J*=13.8, 5.1 Hz, 1H, C*H*H), 2.95 (dd, *J*=13.8, 5.1 Hz, 1H, CH*H*), 1.43 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.1 (*C*), 157.2 (*C*), 155.0 (*C*), 140.3 (*C*H), 130.3 (*C*H), 130.2 (*C*), 110.9 (*C*H), 85.9 (*C*), 80.0 (*C*), 56.4 (*C*H_3), 54.5 (*C*H), 52.3 (*C*H_3), 36.9 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 544 (58%), 499 ([M+Na+MeCN]$^+$, 100%), 488 (44%), 413 (31%), 411 (29%), 377 (33%).

$[\alpha]_D^{25.5}$ +36.3 (c = 0.5, CH_2Cl_2).

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-hydroxy-3-iodophenyl)propanoic acid **3.18**



1.11 $C_9H_{10}INO_3$ (307.08)

3.18 $C_{14}H_{18}INO_5$ (407.20)

Prepared according to the method of Zhu *et al*.[47]

To a solution of amine **1.11** (5.00 g, 16.3 mmol) in 1,4-dioxane/water (1:1 v/v, 80 mL) at 0 °C was added Et_3N (2.27 mL, 16.3 mmol) followed by the dropwise addition of $(Boc)_2O$ (3.56 g, 16.3 mmol). The reaction mixture was warmed to RT and after 16 h

was concentrated under reduced pressure. The crude was partioned between EtOAc (200 mL) and a 10% citric acid solution (w/w, 200 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.18** (6.52 g, 16.0 mmol, 98%) as a pale yellow foamy solid, that was used without further purification These data are in accordance with those reported in the literature.[47]

M.P. 89–94 ^{o}C (EtOAc/petroleum ether), Lit. 88–90 ^{o}C (no solvent given).[177]

FT-IR (ν_{max}, neat) 3182 br. m, 2966 m, 2929 m, 1680 s, 1502 s, 1411 m, 1366 m, 1219 m, 1155 s, 1054 m, 1035 m, 819 m, 540 m, 496 m cm^{-1}.

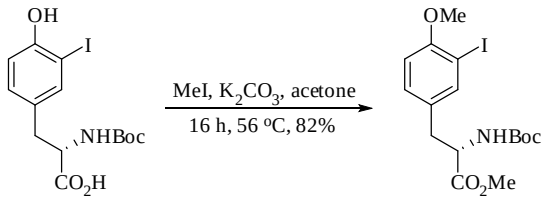
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.49 (br. s, 1H, Ar*H*), 7.05 (dd, *J*=8.1, 1.5 Hz, 1H, Ar*H*), 6.88 (d, *J*=8.1 Hz, 1H, Ar*H*), 5.03 (d, *J*=7.1 Hz, 1H, N*H*), 4.53 (app. d, *J*=6.1 Hz, 1H, NC*H*CO), 4.36 (br. s, 2H, CO_2H+O*H*), 3.16–3.05 (m, 1H, C*H*H), 2.97 (dd, *J*=13.6, 5.5 Hz, 1H, CH*H*), 1.44 (br. s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 175.0 (*C*), 154.1 (*C*), 139.0 (*C*H), 131.0 (*C*H), 130.0 (*C*), 115.1 (*C*H), 85.4 (*C*), 80.6 (*C*), 54.4 (*C*H), 31.1 (CH_2), 28.3 ((CH_3)$_3$). *N.B. One quaternary resonance not observed*.

LRMS (m/z, ESI$^-$) 406 ([M–H]$^-$, 60%), 332 (100%).

$[\alpha]_D^{23}$ + 10.9 (c = 0.40, MeOH).

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(3-iodo-4-methoxyphenyl)propanoate **1.28**



3.18
$C_{14}H_{18}INO_5$
(407.20)

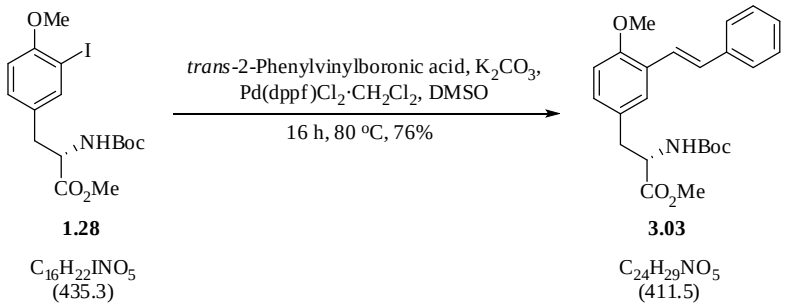
1.28
$C_{16}H_{22}INO_5$
(435.3)

Prepared according to the method of Zhu *et al*.[47]

A solution of phenol **3.18** (3.02 g, 7.42 mmol), K_2CO_3 (3.08 g, 22.3 mmol) and iodomethane (2.30 mL, 37.1 mmol) in acetone (30 mL) was heated at 56 ^oC for 16 h then concentrated under reduced pressure. The crude material was dissolved in EtOAc (50 mL) and washed with H_2O (2 x 50 mL). The combined aqueous phases were extracted with EtOAc (2 x 50 mL). Then, the combined organic phases were washed sequentially with sat. $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (15% EtOAc/petroleum ether) to give the title compound **1.28** (2.64 g, 6.06 mmol, 82%) as a colourless oil. These data are in accordance with those reported in the literature.[47]

Data as previously reported.

Methyl (*S*,*E*)-2-(*tert*-butoxycarbonylamino)-3-(4-methoxy-3-styrylphenyl)-propanoate **3.03**



1.28

$C_{16}H_{22}INO_5$
(435.3)

3.03

$C_{24}H_{29}NO_5$
(411.5)

To a solution of iodide **1.28** (1.13 g, 2.60 mmol) in DMSO (10 mL) was added *trans*-2-phenylvinylboronic acid (462 mg, 3.12 mmol) and K_2CO_3 (1.44 g, 10.4 mmol). This was degassed under argon by immersion in a sonicator bath for 30 min. then, Pd(dppf)Cl_2·CH_2Cl_2 (66.0 mg, 78 µmol) was added. The reaction mixture was heated at 80 °C and after 16 h H_2O (500 mL) and EtOAc (100 mL) were added. The aqueous phase was separated and extracted with EtOAc (4 x 100 mL), then the combined organic phases were washed with brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude brown oil. Purification by flash column chromatography (15% EtOAc/petroleum ether) to give the title compound **3.03** (820 mg, 1.99 mmol, 76%) as a white solid. These data are in accordance with those reported in the literature.[119]

M.P. 119–121 °C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3463 w, 3362 br. w, 2998 m, 2978 m, 2941 m, 2835 m, 1740 m, 1708 s, 1597 m, 1495 s, 1433 m, 1352 m, 1244 s, 1161 s, 1021 m, 936 m, 729 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.43 (d, *J*=7.1 Hz, 2H, Ar*H*), 7.34 (d, *J*=16.4 Hz, 1H, ArC*H*=CHAr), 7.26–7.21 (m, 3H, Ar*H*), 7.17– 7.12 (m, 1H, Ar*H*), 6.98 (d, *J*=16.4 Hz, 1H, ArCH=C*H*Ar), 6.89 (dd, *J*=8.2, 1.8 Hz, 1H, Ar*H*), 6.72 (d, *J*=8.2 Hz, 1H, Ar*H*), 4.91 (d, *J*=7.6 Hz 1H, N*H*), 4.48 (app. q, *J*=6.6 Hz, 1H,

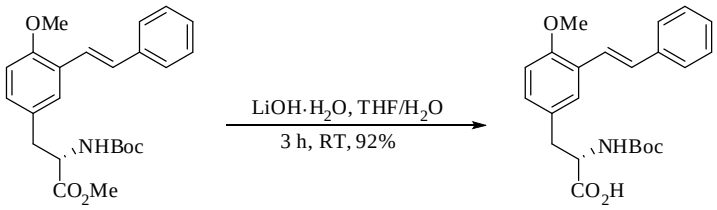
NC*H*CO), 3.77 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.01 (dd, *J*=12.9, 5.6 Hz, 1H, C*H*H), 2.92 (dd, *J*=12.9, 6.1 Hz, 1H, CH*H*), 1.33 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.4 (*C*), 156.0 (*C*), 155.1 (*C*), 137.8 (*C*), 129.3 (CH), 129.2 (*C*H), 128.6 (2 x *C*H), 128.0 (*C*), 127.4 (*C*H), 127.3 (*C*H), 126.5 (2 x *C*H), 126.4 (*C*), 123.3 (*C*H), 111.1 (*C*H), 79.9 (*C*), 55.6 (*C*H), 54.6 (*C*H_3), 52.3 (*C*H_3), 37.6 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 475 ([M+Na+MeCN]$^+$, 23%), 219 (100%).

$[\alpha]_D^{28}$ + 22 (c = 0.05, CH_2Cl_2).

(*S*,*E*)-2-(*tert*-Butoxycarbonylamino)-3-(4-methoxy-3-styrylphenyl)propanoic acid **3.19**



3.03 $C_{24}H_{29}NO_5$ (411.5)

3.19 $C_{23}H_{27}NO_5$ (397.46)

To a solution of ester **3.03** (19.8 g, 48.0 mmol) in THF/H_2O (1:1, 500 mL) was added LiOH·H_2O (6.04 g, 144 mmol). The reaction mixture was stirred at RT and after 3 h was extracted with EtOAc (200 mL). The aqueous phase was acidified to pH 4 with 2M HCl (150 mL) and the products extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.19** (17.5 g, 44.0 mmol, 92%)as an off-white solid that was used without further purification.
These data are in accordance with those reported in the literature.[119]

M.P. 165–167 ^{o}C (Et_2O/MeOH), Lit. not given.

FT-IR (ν_{max}, neat) 3419 w, 3305 br. w, 2978 m, 2919 m, 2835 m, 2349 w, 1711 s, 1496 s, 1397 m, 1367 m, 1246 s, 1161 s, 1028 m, 908 m, 816 w, 730 s, 694 m cm^{-1}.

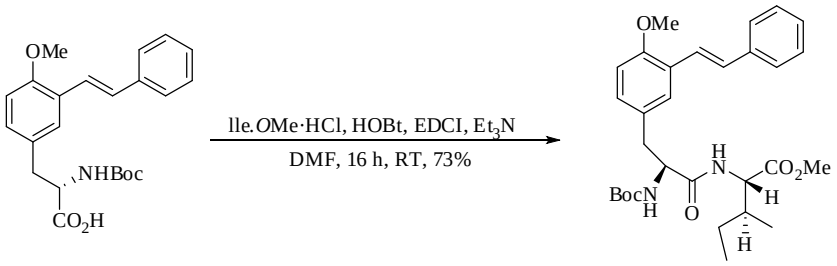
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.54 (d, *J*=7.1 Hz, 2H, Ar*H*), 7.44 (d, *J*=16.2 Hz, 1H, ArC*H*=CHAr), 7.39 (br. s, 1H, Ar*H*), 7.35 (t, *J*=7.6 Hz, 2H, Ar*H*), 7.27–7.22 (m, 1H, Ar*H*), 7.09 (d, *J*=16.2 Hz, 1H, ArCH=C*H*Ar), 7.04 (d, *J*=8.6 Hz, 1H, Ar*H*), 6.82 (d, *J*=8.6 Hz, 1H, Ar*H*), 6.16 (br. s, 1H, CO_2H), 4.99 (d, *J*=6.6 Hz, 1H, N*H*), 4.66–4.54 (br. m, 1H, NC*H*CO), 3.86 (s, 3H, CH_3), 3.15 (dd, *J*=14.2, 5.1 Hz, 1H, C*H*H), 3.03 (dd, *J*=14.2, 7.1 Hz, 1H, CH*H*), 1.43 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 176.1 (*C*), 156.1 (*C*), 155.4 (*C*), 137.9 (*C*), 129.3 (*C*H), 128.6 (2 x *C*H), 127.8 (*C*), 127.4 (*C*H), 127.3 (*C*H), 126.6 (2 x *C*H), 126.5 (*C*), 123.2 (*C*H), 111.2 (*C*H), 80.3 (*C*), 55.6 (*C*H_3), 54.5 (*C*H), 37.0 (*C*H_2), 28.3 ((*C*H_3)$_3$). *NB: 1 x CH resonance not observed.*

LRMS (m/z, ESI$^-$) 396 ([M–H]$^-$, 100%).

$[\alpha]_D^{27}$ + 8.65 (c = 1.0, CH_2Cl_2).

Methyl (*E*,2*S*,3*S*)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-methoxy-3-styrylphenyl)-propanamido)-3-methylpentanoate **3.04**



3.19

$C_{23}H_{27}NO_5$
(397.46)

3.04

$C_{30}H_{40}N_2O_6$
(524.65)

To a solution of carboxylic acid **3.19** (698 mg, 1.76 mmol) in DMF (20 mL) was added EDCI (261 µL, 2.46 mmol), HOBt (332 mg, 2.46 mmol), Ile.*O*Me·HCl (447 mg, 2.46 mmol) and Et_3N (7.37 µL, 5.28 mmol). After 16 h the reaction mixture was diluted in H_2O (500 mL) and extracted with EtOAc (4 x 100 mL). The combined organic phases were washed sequentially with 0.5M HCl (200 mL), sat. $NaHCO_3$ (200 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude oil. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compound **3.04** (678 mg, 1.29 mmol, 73%) as a white solid. These data are in accordance with those reported in the literature.[119]

M.P. 143–146 ^oC (EtOAc/petroleum ether), Lit. reported an oil.

FT-IR (ν_{max}, neat) 3317 br. m, 3056 w, 2966 m, 2929 m, 2872 w, 1740 s, 1657 s, 1499 s, 1458 m, 1360 m, 1245 s, 1168 s, 1025 m, 967 w, 730 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.54 (d, *J*=7.6 Hz, 2H, Ar*H*), 7.43 (d, *J*=16.4 Hz, 1H, CH=C*H*), 7.43 (d, *J*=1.5 Hz, 1H, Ar*H*), 7.35 (app. t, *J*=7.6 Hz, 2H, Ar*H*), 7.25 (t, *J*=7.6 Hz, 1H, Ar*H*), 7.11 (d, *J*=16.4 Hz, 1H, C*H*=CH), 7.11 (obs. dd, *J*=8.6, 1.5 Hz, 1H, Ar*H*), 6.84 (d, *J*=8.6 Hz, 1H, Ar*H*), 6.40 (d, *J*=8.1 Hz, 1H, N*H*), 5.09 (br.s, 1H, N*H*), 4.52 (dd, *J*=8.6, 5.1 Hz, 1H, NC*H*CO), 4.35 (app.

d, *J*=6.6 Hz, 1H, NC*H*CO), 3.87 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.10 (dd, *J*=13.6, 6.6 Hz, 1H, C*H*H), 3.02 (d, *J*=13.6, 7.1 Hz, 1H, CH*H*), 1.88–1.77 (m, 1H, C*H*CH_2CH_3), 1.44 (s, 9H, C(CH_3)$_3$), 1.42–1.31 (m, 1H, CH*H*CH_3), 1.16–1.03 (m, 1H, C*H*HCH_3), 0.87 (t, *J*=7.3 Hz, 3H, CH_3), 0.83 (d, *J*=7.1 Hz, 3H, CH_3).

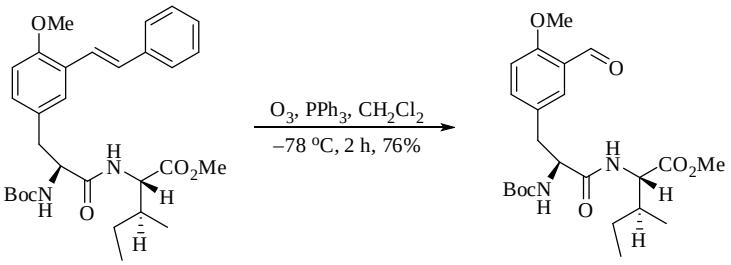
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.7 (*C*), 170.9 (*C*), 155.9 (*C*), 155.4 (*C*), 137.8 (*C*), 129.4 (*C*H), 129.3 (*C*H), 128.6 (2 x *C*H), 127.4 (*C*H), 127.2 (*C*H), 126.5 (2 x *C*H), 123.1 (*C*H), 111.2 (*C*H), 80.2 (*C*), 56.5 (*C*H), 55.9 (*C*H), 55.6 (*C*H_3), 52.01 (*C*H_3), 37.9 (*C*H), 37.4 (*C*H_2), 28.2 ((*C*H_3)$_3$), 25.1 (*C*H_2), 15.2 (*C*H_3), 11.5 (*C*H_3). *N.B. Two quaternary resonances not observed.*

LRMS (m/z, ESI$^+$) 1071 ([2M+Na]$^+$, 6%), 547 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{30}H_{40}N_2O_6$ [M+Na]$^+$ requires 547.2784; found: 547.2790.

$[\alpha]_D^{25}$ +5.0 (c = 0.1, CH_2Cl_2).

Methyl (2*S*,3*S*)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(3-formyl-4-methoxyphenyl)-propanamido)-3-methylpentanoate **3.05**



3.04
$C_{30}H_{40}N_2O_6$
(524.65)

3.05
$C_{23}H_{34}N_2O_7$
(450.53)

Ozone (1–4% in O_2) was bubbled through a solution of styrene **3.04** (678 mg, 1.29 mmol) in CH_2Cl_2 (25 mL) at –78 ^{o}C until a blue colour was observed (*ca.* 30 min).

Oxygen was then bubbled through until the blue colour had disappeared. PPh_3 (677 mg, 2.58 mmol) was added. After 30 min the reaction mixture tested negative for the presence of any peroxides, so was warmed to RT and concentrated under reduced pressure affording a yellow oil. Purification by flash column chromatography (20–40% EtOAc/petroleum ether) to give the title compound **3.05** (441 mg, 980 μmol, 76%) as a pale yellow oil. These data are in accordance with those reported in the literature.[119]

FT-IR (ν_{max}, neat) 3313 br. m, 2962 m, 2925 m, 2872 w, 2761 w, 1740 s, 1679 s, 1658 s, 1613 m, 1495 s, 1458 m, 1364 m, 1252 s, 1160 s, 1021 s, 914 m, 735 m, 649 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 10.42 (s, 1H, C*H*O), 7.63 (d, *J*=2.1 Hz, 1H, Ar*H*), 7.43 (dd, *J*=8.6, 2.1 Hz, 1H, Ar*H*), 6.93 (d, *J*=8.6 Hz, 1H, Ar*H*), 6.46 (d, *J*=7.6 Hz, 1H, N*H*), 5.04 (br. s, 1H, N*H*), 4.52 (dd, *J*=8.3, 4.8 Hz, 1H, NC*H*CO), 4.31 (q, *J*=6.6 Hz, 1H, NC*H*CO), 3.91 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.09 (dd, *J*=14.2, 6.6 Hz, 1H, C*H*H), 2.99 (d, *J*=14.2, 7.1 Hz, 1H, CH*H*), 1.90–1.80 (m, 1H, C*H*CH_2CH_3), 1.41 (s, 9H, C(CH_3)$_3$), 1.40–1.32 (m, 1H, CH*H*CH_3), 1.18–1.06 (m, 1H, C*H*HCH_3), 0.89 (t, *J*=7.3 Hz, 3H, CH_3), 0.85 (d, *J*=7.1 Hz, 3H, CH_3).

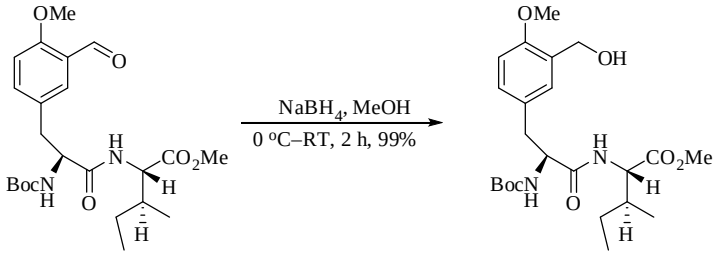
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 189.5 (*C*H), 171.8 (*C*), 170.6 (*C*), 160.8 (*C*), 155.4 (*C*), 136.8 (*C*H), 129.2 (*C*), 128.9 (*C*H), 124.6 (*C*), 112.1 (*C*H), 80.3 (*C*), 56.5 (*C*H), 55.7 (*C*H_3), 52.1 (*C*H_3), 37.9 (*C*H), 36.9 (*C*H_2), 28.2 ((*C*H_3)$_3$), 25.1 (*C*H_2), 14.8 (*C*H), 15.2 (*C*H_3), 11.5 (*C*H_3).

LRMS (m/z, ESI$^+$) 473 ($[M+Na]^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{23}H_{34}N_2O_7$ $[M+Na]^+$ requires 473.2264; found: 473.2258.

$[\alpha]_D^{25}$ +8.0 (c = 0.05, CH_2Cl_2).

Methyl (2*S*,3*S*)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(3-(hydroxymethyl)-4-methoxyphenyl)propanamido)-3-methylpentanoate **3.20**



3.05 $C_{23}H_{34}N_2O_7$ (450.53)

3.20 $C_{23}H_{36}N_2O_7$ (452.54)

To a solution of aldehyde **3.05** (384 mg, 852 µmol) in MeOH (10 mL) at 0 °C was added $NaBH_4$ (38.6 mg, 1.02 mmol). After 2 h the reaction mixture was warmed to RT and after a further 2 h was quenched with H_2O (30 mL) and extracted with EtOAc (3 x 150 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.20** (381 mg, 843 µmol, 99%) as a colourless oil that was used without further purification. These data are in accordance with those reported in the literature.[119]

FT-IR (ν_{max}, neat) 3309 br. m, 2966 m, 2925 m, 2876 w, 2761 w, 1738 m, 1660 s, 1502 s, 1461 m, 1366 m, 1250 s, 1170 s, 1042 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.16–7.13 (m, 2H, 2 x Ar*H*), 6.82 (d, *J*=9.1 Hz, 1H, Ar*H*), 6.29 (d, *J*=8.1 Hz, 1H, N*H*), 5.04 (br. s, 1H, N*H*), 4.65 (br. s, 2H, CH_2), 4.49 (dd, *J*=8.3, 5.3 Hz, 1H, NC*H*CO), 4.30 (app. d, *J*=6.1 Hz, 1H, NC*H*CO), 3.85 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.09–2.93 (m, 2H, CH_2), 2.49 (br. s, 1H, O*H*), 1.88–1.76 (m, 1H, C*H*CH_2CH_3), 1.44 (s, 9H, C(CH_3)$_3$), 1.41–1.30 (m, 1H, CH*H*CH_3), 1.16–1.02 (m, 1H, C*H*HCH_3), 0.88 (t, *J*=7.3 Hz, 3H, CH_3), 0.83 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.9 (*C*), 170.9 (*C*), 156.4 (*C*), 155.3 (*C*), 129.7 (*C*H), 129.6 (*C*H), 129.4 (*C*), 128.6 (*C*), 110.4 (*C*H),

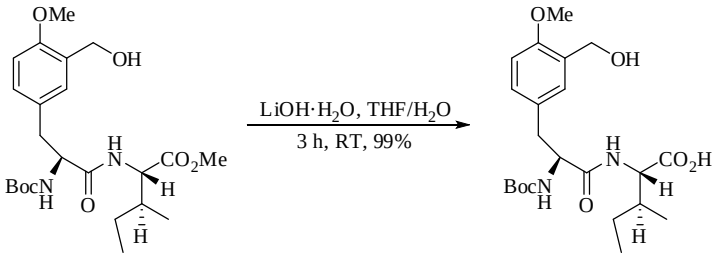
80.2 (*C*), 61.7 (*C*H_2), 56.5 (*C*H), 55.4 (*C*H_3), 52.1 (*C*H_3), 37.8 (*C*H), 37.4 (*C*H_2), 28.3 ((*C*H_3)$_3$), 25.1 (*C*H_2), 19.6 (*C*H), 15.3 (*C*H_3), 11.5 (*C*H_3).

LRMS (m/z, ESI$^+$) 475 ($[M+Na]^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{23}H_{36}N_2O_7$ $[M+Na]^+$ requires 475.2420; found: 475.2416.

$[\alpha]_D^{25}$ +31 (c = 0.05, CH_2Cl_2).

(2*S*,3*S*)-2-((*S*)-2-(*tert*-Butoxycarbonylamino)-3-(3-(hydroxymethyl)-4-methoxyphenyl)-propanamido)-3-methylpentanoic acid **3.21**



3.20

$C_{23}H_{36}N_2O_7$
(452.54)

3.21

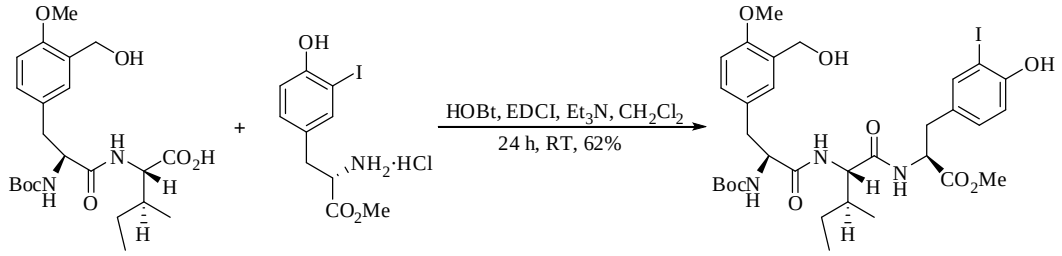
$C_{22}H_{34}N_2O_7$
(438.51)

To a solution of ester **3.20** (242 mg, 535 µmol) in THF/water (1:1, 10 mL) was added LiOH·H_2O (67.6 mg, 1.61 mmol). The reaction mixture was stirred at RT for 3 h then 2M HCl (20 mL) was added. The aqueous phase was separated and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.21** (232 mg, 530 µmol, 99%) as a white foamy solid that was used without further purification. These data are in accordance with those reported in the literature.[119]

FT-IR (ν_{max}, neat) 3309 br. m, 2962 m, 2929 m, 2872 w, 2843 w, 2365 w, 1658 s, 1502 s, 1458 m, 1360 m, 1249 s, 1165 s, 1041 m, 906 m, 732 s cm^{-1}.

^{1}H NMR	(400 MHz, $CDCl_3$) δ_H ppm 7.16 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.07 (br. s, 1H, Ar*H*), 6.80 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.35 (d, *J*=8.1 Hz, 1H, N*H*), 5.47 (d, *J*=6.6 Hz, 1H, N*H*), 5.10–4.97 (m, 2H, CO_2H + O*H*), 4.73 (d, *J*=12.3 Hz, 1H, C*H*H), 4.54 (d, *J*=12.3 Hz, 1H, CH*H*), 4.45 (app. t, *J*=7.1 Hz, 1H, NC*H*CO), 4.33 (br. s, 1H, NC*H*CO), 3.81 (s, 3H, CH_3), 2.99 (dd, *J*=13.6, 5.6 Hz, 1H, C*H*H), 2.94–2.85 (m, 1H, CH*H*), 1.87–1.73 (m, 1H, $CHCH_2CH_3$), 1.42 (s, 9H, $C(CH_3)_3$), 1.41–1.36 (m, 1H, $CHHCH_3$), 1.19–1.05 (m, 1H, $CHHCH_3$), 0.95–0.88 (m, 6H, 2 x CH_3).
^{13}C NMR	(100 MHz, $CDCl_3$) δ_C ppm 173.7 (*C*), 171.2 (*C*), 156.5 (*C*), 155.4 (*C*), 130.2 (*C*H), 129.9 (*C*H), 128.5 (*C*), 128.2 (*C*), 110.5 (*C*H), 80.1 (*C*), 61.5 (CH_2), 56.7 (*C*H), 56.3 (*C*H), 55.4 (CH_3), 38.3 (CH_2), 37.3 (*C*H), 28.3 ($(CH_3)_3$), 24.8 (CH_2), 15.2 (CH_3), 11.3 (CH_3).
LRMS (m/z, ESI$^-$)	437 ($[M–H]^-$, 100%).
HRMS (m/z, ESI$^-$)	calcd for $C_{22}H_{34}N_2O_7$ $[M+Na]^+$ requires 461.2264; found: 461.2256.
$[\alpha]_D^{25}$	–14.2 (c = 0.18, CH_2Cl_2).

Methyl (6*S*,9*S*,12*S*)-9-*sec*-butyl-12-(4-hydroxy-3-iodobenzyl)-6-(3-(hydroxymethyl)-4-methoxybenzyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **3.22**



3.21 $C_{22}H_{34}N_2O_7$ (438.51)

3.15 $C_{10}H_{13}ClINO_3$ (357.57)

3.22 $C_{32}H_{44}IN_3O_9$ (741.61)

To a solution of carboxylic acid **3.21** (654 mg, 1.49 mmol) in CH_2Cl_2 (40 mL) was added EDCI (324 mg, 2.09 mmol), HOBt (282 mg, 2.09 mmol), hydrochloride salt **3.15** (747 mg, 2.09 mmol) and Et_3N (582 µL, 4.17 mmol). After 24 h the reaction mixture was quenched by addition of 10% citric acid solution (40 mL). The products were extracted with CH_2Cl_2 (4 x 20 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (5% MeOH/CH_2Cl_2) to give the title compound **3.22** (684 mg, 922 µmol, 62%) as a colourless glass.

M.P. 151–153 ^oC (MeOH/CH_2Cl_2).

FT-IR (ν_{max}, neat) 3268 br. m, 2966 m, 2921 m, 2872 w, 2241 w, 1736 m, 1640 s, 1502 s, 1438 m, 1366 m, 1249 s, 1168 s, 1037 m, 908 m, 730 s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm (rotamer ratio ~ 1:1) 7.42 (br. dd, *J*=6.6, 1.8 Hz, 1H, Ar*H*), 7.15–6.55 (m, 7H, 5 x Ar*H* + 2 x N*H*), 5.30 (d, *J*=7.7 Hz, 0.5 x 1H, N*H*), 5.15 (d, *J*=7.3 Hz, 0.5 x 1 H, N*H*), 4.87–4.73 (br. m, 1H, NC*H*CO), 4.68 (d, *J*=13.5 Hz, 1H, C*H*H), 4.62 (d, *J*=13.5 Hz, 1H, CH*H*), 4.49–4.19 (br. m, 2H, 2 x NC*H*CO), 4.37–4.28 (br. m, 1H, NC*H*CO), 3.80 (s, 0.5 x 3H, CH_3), 3.78 (s, 0.5 x 3H, CH_3), 3.71 (s, 3H, CH_3), 3.12–2.84 (m,

4H, 2 x CH_2), 2.09 (br. s, 1H, O*H*), 1.85–1.69 (m, 1H, C*H*CH$_2$CH$_3$), 1.42 (s, 0.5 x 9H, C(CH_3)$_3$), 1.41–1.37 (m, 1H, C*H*HCH$_3$), 1.39 (s, 0.5 x 9H, C(CH_3)$_3$), 1.05–0.90 (m, 1H, CH*H*CH$_3$), 0.83 (d, *J*=6.6 Hz, 0.5 x 3H, CH_3), 0.81 (t, *J*=6.6 Hz, 3H, CH_3), 0.61 (d, *J*=6.6 Hz, 0.5 x 3H, CH_3).

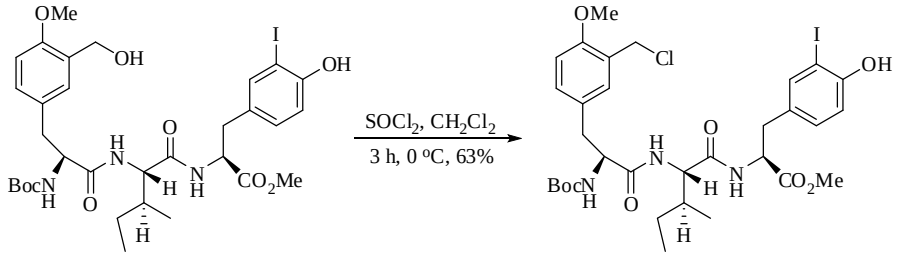
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.4 (*C*), 170.6 (*C*), 156.4 (*C*), 156.1 (*C*), 154.6 (*C*), 139.2 (*C*H), 139.1 (*C*), 130.8 (*C*H), 129.6 (*C*H), 129.4 (*C*), 129.3 (*C*H), 128.4 (*C*), 115.1 (*C*H), 110.4 (*C*H), 84.9 (*C*), 79.5 (*C*), 61.3 (*C*H$_2$), 57.8 (*C*H), 56.5 (*C*H), 55.3 (*C*H$_3$), 53.2 (*C*H), 52.4 (*C*H$_3$), 36.8 (*C*H), 36.5 (*C*H$_2$), 36.3 (*C*H$_2$), 28.3 ((*C*H$_3$)$_3$), 24.6 (*C*H$_2$), 15.2 (*C*H$_3$), 11.1 (*C*H$_3$). *NB: One quaternary resonance not observed.*

LRMS (m/z, ESI$^+$) 764 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{32}H_{44}IN_3O_9$ [M+Na]$^+$ requires 764.2020; found: 764.2014.

$[\alpha]_D^{23}$ +1.4 (c = 0.26, MeOH).

Methyl (6*S*,9*S*,12*S*)-9-*sec*-butyl-6-(3-(chloromethyl)-4-methoxybenzyl)-12-(4-hydroxy-3-iodobenzyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **3.23**



3.22

$C_{32}H_{44}IN_3O_9$
(741.61)

3.23

$C_{32}H_{43}ClIN_3O_8$
(760.06)

To a solution of tripeptide **3.22** (500 mg, 674 μmol) in dry CH_2Cl_2 (50 mL) at 0 ^oC was added $SOCl_2$ (51.6 μL, 708 μmol). After 3 h the reaction mixture was quenched with H_2O (50 mL). The products were extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (0–2% MeOH/CH_2Cl_2) to give the title compound **3.23** (321 mg, 423 μmol, 63%) as a pale yellow solid.

M.P. 142–145 ^oC (MeOH/CH_2Cl_2).

FT-IR (ν_{max}, neat) 3288 br. m, 2966 m, 2929 m, 2876 w, 1644 s, 1503 s, 1440 m, 1366 m, 1256 s, 1219 m, 1165 s, 1033 m, 910 m, 732 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm (rotamer ratio ~ 1:1) 7.43 (br. dd, *J*=4.8, 1.8 Hz, 1H, Ar*H*), 7.22–7.08 (br. m, 2H, Ar*H*), 7.06–6.94 (br. m, 1H, Ar*H*), 6.90–6.77 (br. m, 2H, Ar*H*), 6.64–6.25 (br. m, 2H, N*H*), 5.09 (br. d, *J*=6.0 Hz, 0.5 x 1H, N*H*), 4.99 (br. d, *J*=7.5 Hz, 0.5 x 1H, N*H*), 4.86–4.74 (br. m, 1H, NC*H*CO), 4.63 (d, *J*=13.6 Hz, 1H, C*H*H), 4.58 (d, *J*=13.6 Hz, 1H, CH*H*), 4.49–4.22 (br. m, 2H, 2 x NC*H*CO), 3.84 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.12–2.86 (m, 4H, 2 x CH_2), 1.88–1.73 (br. m, 2H, O*H*+C*H*CH_2CH_3), 1.42 (s, 0.5 x 9H, C(CH_3)$_3$), 1.41–1.38 (m, 1H, C*H*HCH_3), 1.40 (s, 0.5 x 9H, C(CH_3)$_3$), 1.09–0.92 (m, 1H, CH*H*CH_3), 0.85 (d, *J*=6.5 Hz, 0.5 x 3H, CH_3), 0.84 (t, *J*=6.5 Hz, 3H, CH_3), 0.64 (d, *J*=6.5 Hz, 0.5 x 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.4 (*C*), 170.2 (*C*), 156.4 (*C*), 155.5 (*C*), 154.4 (*C*), 139.0 (*C*H), 138.9 (*C*), 131.5 (*C*H), 130.9 (*C*H), 130.7 (*C*H), 128.5 (*C*), 126.0 (*C*), 115.2 (*C*H), 110.1 (*C*H), 85.3 (*C*), 79.8 (*C*), 57.9 (*C*H), 56.4 (*C*H), 55.6 (*C*H_3), 53.2 (*C*H), 52.4 (*C*H_3), 41.4 (*C*H_2), 36.8 (*C*H), 36.6 (*C*H_2), 36.5 (*C*H_2), 28.2

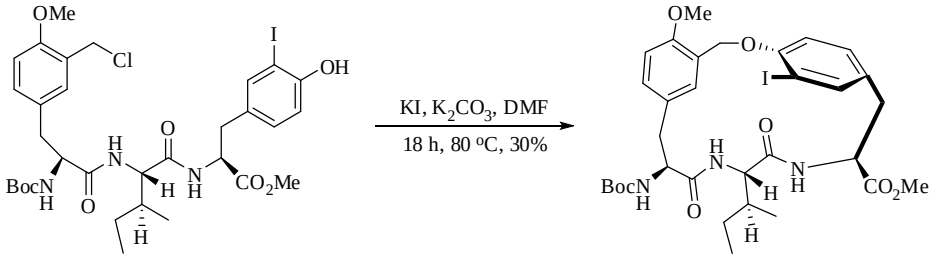
((CH_3)$_3$), 26.2 (CH_2), 15.3 (CH_3), 11.3 (CH_3). *NB: One quaternary resonance not observed.*

LRMS (m/z, ESI$^+$) 782 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{32}H_{43}ClIN_3O_8$ [M+Na]$^+$ requires 782.1681; found: 782.1676.

$[\alpha]_D^{23}$ +1.8 (c = 0.25, MeOH).

(10*S*,13*S*,12*S*)-20-Iodo-10-*tert*-butoxycarbonylamino-13-((*S*)-*sec*-butyl)-5-methoxy-11,14-dioxo-2-oxa-12,15-diaza-tricyclo[16.2.2.1]^{4,8}]tricosa-1(21)4,6,8(23),18(22),19-hexane-16-carboxylic acid (*S*)-methyl ester **3.00**



3.23
$C_{32}H_{44}IN_3O_9$
(741.61)

3.00
$C_{32}H_{42}IN_3O_8$
(723.59)

To a solution of tripeptide **3.23** (85.0 mg, 112 µmol) in DMF (22 mL) was added K_2CO_3 (21.7 mg, 157 µmol) and KI (3.65 mg, 22.0 µmol) and the reaction mixture heated at 80 ^oC. After 18 h the reaction mixture was cooled to RT, concentrated under reduced pressure to *ca.* 5 mL, then partitioned between H_2O (100 mL) and EtOAc (30 mL). The aqueous phase was extracted with EtOAc (4 x 30 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (0–2% MeOH/CH_2Cl_2). Further purification by preparative HPLC (2.5% MeOH/CH_2Cl_2) to give the title compound **3.00** (24.0 mg, 33.2 µmol, 30%) as a colourless oil.

FT-IR (ν_{max}, neat) 3329 br. m, 3031 w, 2941 m, 2839 w, 1709 s, 1490 s, 1438 m, 1348 m, 1277 m, 1251 s, 1210 s, 1048 s, 1017 m, 906 m, 731 s, 697 m, 579 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm (rotamer ratio ~ 1:1) 7.51 (br. s, 1H, Ar*H*), 7.38 (br. s, 1H, Ar*H*), 7.14 (br. app. d, *J*=8.0 Hz, 1H, Ar*H*), 7.06–6.92 (br. m, 0.5 x 3H, Ar*H*), 6.85–6.69 (br. m, 5H, 0.5 x 3 x Ar*H* + 2 x N*H*), 6.58 (br. d, *J*=8.0 Hz, 1H, N*H*), 5.55 (d, *J*=14.0 Hz, 1H, CH*H*), 5.15 (d, *J*=14.0 Hz, 1H, C*H*H), 4.75 (dd, *J*=9.0, 4.5 Hz, 1H, NC*H*CO), 4.58 (d, *J*=3.0 Hz, 1H, NC*H*CO), 4.48 (t, *J*=5.3 Hz, 1H, NC*H*CO), 4.22 (d, *J*=9.0 Hz, 2H, NC*H*CO), 4.11 (d, *J*=5.0 Hz, 1H, NC*H*CO), 3.91 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.41–2.98 (m, 4H, 2xCH_2), 2.77–2.55 (m, 4H, 2xCH_2), 1.90–1.81 (br. m, 1H, C*H*CH_2CH_3), 1.75–1.67 (br. m, 1H, C*H*CH_2CH_3), 1.47 (s, 18H, 2xC(CH_3)$_3$), 1.40–1.35 (m, 2H, 2x C*H*HCH_3), 1.23–1.03 (m, 2H, CH*H*CH_3), 0.96–0.80 (m, 12H, 4xCH_3).

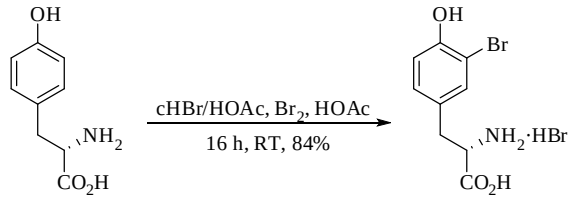
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.0 (*C*), 171.7 (*C*), 170.7 (*C*), 170.4 (*C*), 156.3 (*C*), 155.7 (*C*), 155.2 (*C*), 140.4 (*C*H), 140.2 (*C*H), 131.4 (*C*H), 130.8 (*C*H), 130.6 (*C*H), 130.1 (*C*H), 129.7 (*C*H), 129.3 (*C*H), 124.5 (*C*), 114.7 (*C*H), 114.5 (*C*H), 110.9 (*C*H), 110.7 (*C*H), 87.6 (*C*), 81.5 (*C*), 80.8 (*C*), 65.9 (*C*H_2), 65.6 (*C*H_2), 57.6 (*C*H), 55.8 (*C*H_3), 53.5 (*C*H), 52.8 (*C*H_3), 52.5 (*C*H_3), 37.2 (*C*H), 36.7 (*C*H_2), 35.7 (*C*H_2), 34.5 (*C*H), 28.8 ((*C*H_3)$_3$), 28.7 ((*C*H_3)$_3$), 26.9 (*C*H_2), 24.8 (*C*H_2), 15.5 (*C*H_3), 14.2 (*C*H_3), 12.2 (*C*H_3), 11.9 (*C*H_3). *NB: One quaternary resonance not observed*.

LRMS (m/z, ESI$^+$) 746 ($[M+Na]^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{32}H_{42}IN_3O_8$ $[M+Na]^+$ requires 746.1914; found: 746.1907.

$[\alpha]_D^{27}$ +16.4 (c = 0.61, MeOH).

(*S*)-2-Amino-3-(3-bromo-4-hydroxyphenyl)propanoic acid hydrobromide **3.40**



3.06 **3.40**

$C_9H_{11}NO_3$ (181.19) $C_9H_{11}Br_2NO_3$ (341.00)

Prepared according to the method of Giralt *et al.*[179]

HBr in glacial acetic acid (33% w/v, 45 mL) was added dropwise to rapidly stirred suspension of L-tyrosine (15.0 g, 82.7 mmol) in glacial acetic acid (40 mL), followed by the dropwise addition of bromine (4.57 mL, 89.3 mmol) in glacial acetic acid (40 mL) over ca. 3 h. After 16 h the resulting precipitate was collected by filtration, washed with ice-cold Et_2O (100 mL) and dried under reduced pressure to give the title compound **3.40** (23.7 g, 69.5 mmol, 84%) as a white solid that was used without further purification. These data are in accordance with those reported in the literature.[179]

M.P. dec. > 215 ^oC, Lit. dec. > 210 ^oC.[179]

FT-IR (ν_{max}, neat) 3031 br. s, 2927 br. s, 1722 s, 1494 m, 1419 m, 1383 m, 1345 m, 1199 s, 1111 s, 1084 m, 810 m cm^{-1}

^{1}H NMR (400 MHz, d_6-DMSO) δ_H ppm 13.27 (br. s, CO_2H), 10.16 (br. s, 1H, O*H*), 8.34–8.11 (m, 3H, 3 x N*H*), 7.37 (s, 1H, Ar*H*), 7.06 (d, *J*=7.7 Hz, 1H, Ar*H*), 6.92 (d, *J*=7.7 Hz, 1H, Ar*H*), 4.14 (app. t, *J*=5.8 Hz, 1H, NC*H*CO), 3.07–2.94 (m, 2H, CH_2).

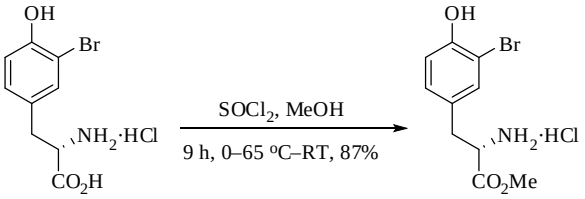
NB. Sample contaminated with residual HOAc.

^{13}C NMR (100 MHz, d_6-DMSO) δ_C ppm 170.3 (*C*), 153.3 (*C*), 133.7 (*C*H), 129.8 (*C*H), 126.7 (*C*), 116.4 (*C*H), 109.3 (*C*), 53.2 (*C*H), 34.4 (*C*H_2).

LRMS (m/z, ESI$^+$) 303 ([M{^{81}Br}+H-HBr]$^+$ 100%), 301 ([M{^{79}Br}+H-HBr]$^+$ 96%).

$[\alpha]_D^{26}$ +0.54 (c = 0.92, MeOH).

Methyl (*S*)-2-amino-3-(3-bromo-4-hydroxyphenyl)propanoate hydrochloride **3.41**



3.40
$C_9H_{11}BrClNO_3$
(296.5)

3.41
$C_{10}H_{13}BrClNO_3$
(310.6)

Prepared according to the method of Jung *et al.*[180]

$SOCl_2$ (5.64 mL, 68.0 mmol) was added dropwise to rapidly stirred dry MeOH (250 mL) at 0 °C, followed by portionwise addition carboxylic acid **3.40** (14.4 g, 48.6 mmol). After complete addition the reaction mixture was heated at 65 °C for 3 h, cooled to RT and concentrated under reduced pressure after a further 6 h affording a crude yellow solid. Purification by recrystalisation (Et_2O/MeOH) to give the title compound **3.41** (15.8 g, 42.3 mmol, 87%) as a beige solid. These data are in accordance with those reported in the literature.[180]

M.P. 100–103 °C (Et_2O/MeOH), Lit. Decomposed above 185 °C.[180]

FT-IR (ν_{max}, neat) 2923 br. s, 2360 m, 1737 s, 1607 m, 1502 s, 1439 m, 1421 m, 1348 m, 1236 s, 1045 s, 823 s cm^{-1}

^{1}H NMR (300 MHz, d_4-MeOD) δ_H ppm 7.39 (d, *J*=2.2 Hz, 1H, Ar*H*), 7.07 (dd, *J*=8.2, 2.2 Hz, 1H, Ar*H*), 6.90 (d, *J*=8.2 Hz, 1H, Ar*H*), 4.27

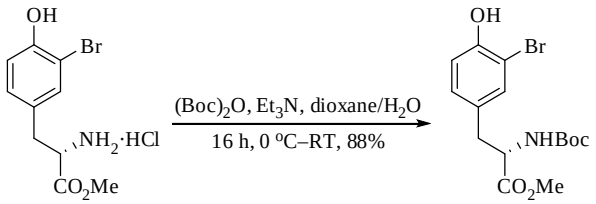
(dd, *J*=7.3, 6.2 Hz, 1H, NC*H*CO), 3.81 (s, 3H, CH_3) 3.17 (dd, *J*=14.5, 6.0 Hz, 1H, C*H*H), 3.08 (dd, *J*=14.5, 7.3 Hz, 1H, CH*H*).

^{13}C NMR (75 MHz, d_4-MeOD) δ_C ppm 170.4 (*C*), 155.4 (*C*), 135.1 (*C*H), 130.8 (*C*H), 127.6 (*C*), 117.8 (*C*H), 111.4 (*C*), 55.3 (*C*H), 53.7 (*C*H_3), 36.3 (*C*H_2).

LRMS (m/z, ESI$^+$) 549 ([2M-HCl+H]$^+$, 28%), 317 ([M–HCl+2H+MeCN]$^+$, 33%), 257 (100%).

$[\alpha]_D^{26}$ +2.2 (c = 0.81, MeOH).

Methyl (*S*)-3-(3-bromo-4-hydroxyphenyl)-2-(*tert*-butoxycarbonylamino) propanoate **3.42**



3.41 $C_{10}H_{13}BrClNO_3$ (310.6)

3.42 $C_{15}H_{20}BrNO_5$ (374.2)

To a solution of hydrochloride salt **3.41** (14.2 g, 45.7 mmol) in 1,4-dioxane/water (1:1, 400 mL) at 0 ^{o}C was added Et_3N (6.38 mL, 45.7 mmol) then $(Boc)_2O$ (10.5 g, 48.0 mmol) dropwise over 15 min, and a second charge of Et_3N (6.38 mL, 45.7 mmol). The reaction mixture was warmed to RT and after 16 h was concentrated under reduced pressure. The crude material was dissolved in EtOAc (300 mL) and washed sequentially with 2M HCl (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude oil. Purification by flash column chromatography (25% EtOAc/petroleum ether) to give the title compound **3.42** (15.0 g, 40.0 mmol, 88%) as a colourless oil. These data are in accordance with those reported in the literature.[181]

FT-IR (ν_{max}, neat) 3350 br. m, 2974 m, 2949 w, 2933 w, 2859 w, 2361 w, 2332 w, 1732 m, 1687 s, 1601 m, 1507 s, 1437 m, 1366 s, 1282 m, 1218 s, 1164 s, 1053 m, 1033 m cm^{-1}.

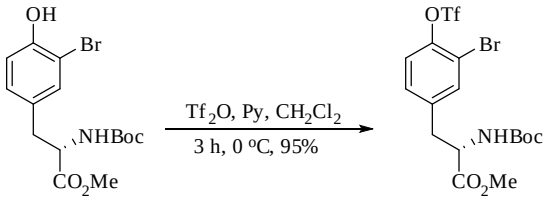
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.24 (br. s, 1H, Ar*H*), 6.98 (br. d, *J*=8.6 Hz, 1H, Ar*H*), 6.93 (br. d, *J*=8.6 Hz, 1H, Ar*H*), 5.59 (br. s, 1H, O*H*), 5.01 (d, *J*=7.1 Hz, 1H, N*H*), 4.58–4.50 (br. m, 1H, NC*H*CO), 3.73 (s, 3H, CH_3), 3.06 (dd, *J*=14.1, 5.6 Hz, 1H, C*H*H), 2.96 (dd, *J*=13.6, 5.6 Hz, 1H, CH*H*), 1.44 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.1 (*C*), 155.0 (*C*), 151.4 (*C*), 132.7 (*C*H), 130.0 (*C*H), 129.7 (*C*), 116.1 (*C*H) 110.1 (*C*), 80.1 (*C*), 54.4 (*C*H), 52.3 (*C*H_3), 37.2 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 439 ([M+Na{^{81}Br}]$^+$, 13%), 437 ([M+Na{^{79}Br}]$^+$, 13%), 317 ([M-Boc+H+MeCN{^{81}Br}]$^+$, 13%), 315 ([M-Boc+H+MeCN {^{79}Br}]$^+$, 152 (100%).

$[\alpha]_D^{26}$ + 8.95 (c = 0.5, CH_2Cl_2).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(3-bromo-4-trifluoromethanesulfonyloxy-phenyl)propanoate **3.43**



3.42 $C_{15}H_{20}BrNO_5$ (374.2)

3.43 $C_{16}H_{19}BrF_3NO_7S$ (506.3)

To a solution of phenol **3.42** (13.3 g, 35.5 mmol) in CH_2Cl_2 (250 mL) and pyridine (8.61 mL, 107 mmol) at 0 °C was added Tf_2O (6.27 mL, 37.3 mmol) dropwise over

20 min. After 3 h the reaction mixture was quenched with H_2O (250 mL). The organic phase was washed sequentially with sat. $NaHCO_3$ (250 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (1% MeOH/CH_2Cl_2) to give the title compound **3.43** (17.2 g, 33.9 mmol, 95%) as a white solid. These data are in accordance with those reported in the literature.[119]

M.P. 74–75 ^oC (CH_2Cl_2), Lit. 61–63 ^oC.[119]

FT-IR (ν_{max}, neat) 3354 br. w, 2978 w, 2921 w, 2357 w, 1744 m, 1703 m, 1478 m, 1421 m, 1348 m, 1209 s, 1166 s, 1135 s, 1037 m, 894 m, 726 m, 608 m, 510 m cm^{-1}.

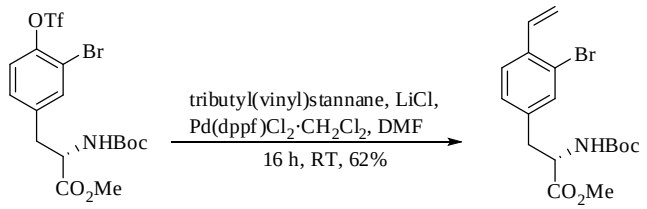
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.48 (br. s, 1H, Ar*H*), 7.28 (d, *J*=8.6 Hz, 1H, Ar*H*), 7.18 (dd, *J*=8.6, 2.2 Hz, 1H, Ar*H*), 5.08 (d, *J*=7.1 Hz, 1H, N*H*), 4.67–4.52 (br. m, 1H, NC*H*CO), 3.74 (s, 3H, CH_3), 3.18 (dd, *J*=13.6, 5.6 Hz, 1H, C*H*H), 3.01 (dd, *J*=13.6, 6.6 Hz, 1H, CH*H*), 1.42 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.6 (*C*), 154.9 (*C*), 145.9 (*C*), 138.5 (*C*), 135.1 (*C*H), 129.9 (*C*H), 122.6 (*C*H), 118.6 (q, *J*=320 Hz, *C*F_3) 115.7 (*C*), 80.3 (*C*), 54.1 (*C*H), 52.5 (*C*H_3), 37.6 (*C*H_2), 28.2 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 530 ([M+Na{^{81}Br}]$^+$, 100%), 528 ([M+Na{^{79}Br}]$^+$, 88%), 489 (25%), 288 (20%).

$[\alpha]_D^{27}$ + 81.1 (c = 0.23, CH_2Cl_2).

Methyl (S)-3-(3-bromo-4-vinylphenyl)-2-(*tert*-butoxycarbonylamino)propanoate **3.44**



3.43
$C_{16}H_{19}BrF_3NO_7S$
(506.3)

3.44
$C_{17}H_{22}BrNO_4$
(384.3)

To a solution of triflate **3.43** (15.0 g, 29.6 mmol) in DMF (250 mL) was added tributyl(vinyl)stannane (9.09 mL, 31.1 mmol) and LiCl (6.27 g, 148 mmol). This was degassed under argon by immersion in a sonicated bath for *ca.* 30 min then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.2 g, 1.48 mmol) was added. After 16 h the reaction mixture was concentrated under reduced pressure to ~50 mL and H_2O (500 mL) was added. The aqueous phase was extracted with EtOAc (5 x 100 mL) and the combined organic phases were washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (10% w/w K_2CO_3/silica,[182] 20% EtOAc/petroleum ether) to give the title compound **3.44** (7.02 g, 18.3 mmol, 62%) as a colourless oil. These data are in accordance with those reported in the literature.[119]

FT-IR (ν_{max}, neat) 3358 br. m, 2970 m, 2925 m, 1740 s, 1699 s, 1605 w, 1503 s, 1421 m, 1356 m, 1162 s, 1057 m, 1012 m cm^{-1}.

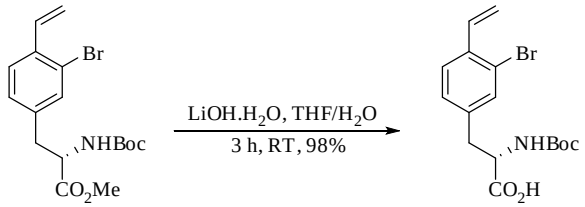
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.48 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.33 (s, 1H, Ar*H*), 7.06 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.00 (dd, *J*=17.2, 10.6 Hz, 1H, ArC*H*=CH_2), 5.68 (d, *J*=17.2 Hz, 1H, ArCH=C*H*H), 5.35 (d, *J*=10.6 Hz, 1H, ArCH=CH*H*), 5.01 (d, *J*=6.6 Hz 1H, N*H*), 4.62–4.53 (br. m, 1H, NC*H*CO), 3.74 (s, 3H, CH_3), 3.11 (dd, *J*=13.3, 5.6 Hz, 1H, C*H*H), 3.00 (dd, *J*=13.3, 5.6 Hz, 1H, CH*H*), 1.44 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.9 (*C*), 154.9 (*C*), 137.5 (*C*), 136.1 (*C*), 135.4 (*C*H), 133.6 (*C*H), 128.5 (*C*H), 126.7 (*C*H), 123.5 (*C*) 116.5 (*C*H_2), 80.1 (*C*), 54.2 (*C*H), 52.3 (*C*H_3), 37.6 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 449 ([M+Na{^{81}Br}]$^+$, 100%), 447 ([M+Na{^{79}Br}]$^+$, 94%).

$[\alpha]_D^{26}$ + 36.5 (c = 0.2, CH_2Cl_2).

(*S*)-3-(3-Bromo-4-vinylphenyl)-2-(*tert*-butoxycarbonylamino)propanoic acid **3.45**



3.44 $C_{17}H_{22}BrNO_4$ (384.3)

3.45 $C_{16}H_{20}BrNO_4$ (370.2)

To a solution of ester **3.44** (310 mg, 807 µmol) in THF/water (1:1 v/v, 8 mL) was added $LiOH{\cdot}H_2O$ (102 mg, 2.42 mmol). After 3 h at RT 2M HCl (5 mL) was added. The aqueous phase was separated and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.45** (292 mg, 789 µmol, 98%) as a colourless oil that was used without further purification.

FT-IR (ν_{max}, neat) 3423 w, 3313 m, 3092 m, 2974 m, 2925 m, 2594 br. w, 1709 s, 1499 m, 1395 s, 1367 m, 1249 m, 1159 s, 1053 m, 909 s, 732 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.49 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.39 (br. s, 1H, CO_2*H*), 7.38 (app. br. s, 1H, Ar*H*), 7.12 (br. d, *J*=8.1 Hz, 1H, Ar*H*), 7.02 (dd, *J*=17.4, 11.1 Hz, 1H, C*H*), 5.68 (d, *J*=17.4 Hz, 1H, CH*H*), 5.35 (d, *J*=11.1 Hz, 1H, C*H*H), 5.03 (d, *J*=7.1 Hz,

1H, N*H*), 4.60 (br. app. d, *J*=5.6 Hz, 1H, NC*H*CO), 3.25–3.11 (m, 1H, CH*H*), 3.03 (dd, *J*=13.6, 5.6 Hz, 1H, C*H*H), 1.44 (s, 9H, C(CH_3)$_3$).

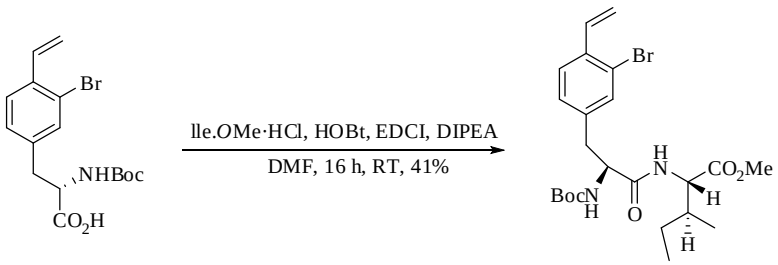
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 175.7 (*C*), 155.3 (*C*), 137.3 (*C*), 136.2 (*C*), 135.4 (*C*H), 133.7 (*C*H), 128.5 (*C*H), 126.8 (*C*H), 123.5 (*C*), 116.6 (*C*H_2), 80.5 (*C*), 54.1 (*C*H), 37.0 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^-$) 370 ([M–H{^{81}Br}]$^-$, 20%), 368 ([M–H{^{79}Br}]$^-$, 21%), 296 (100%).

HRMS (m/z, ESI$^-$) calcd for $C_{16}H_{20}BrNO_4$ [M–H{^{81}Br}]$^-$ requires 370.0482; found: 370.0479. [M–Na{^{79}Br}]$^-$ requires 368.0503; found: 368.0505.

$[\alpha]_D^{27}$ +18.5 (c = 0.68, CH_2Cl_2).

Methyl (2*S*,3*S*)-2-((*S*)-3-(3-bromo-4-vinylphenyl)-2-(*tert*-butoxycarbonylamino) propanamido)-3-methylpentanoate **3.38**



3.45
$C_{16}H_{20}BrNO_4$
(370.2)

3.38
$C_{23}H_{33}BrN_2O_5$
(497.4)

To a solution of carboxylic acid **3.45** (6.22 g, 16.8 mmol) in DMF (160 mL) was added EDCI (2.50 mL, 23.5 mmol), HOBt (3.17 g, 23.5 mmol), Ile.*O*Me·HCl (4.27 g, 23.5 mmol) and DIPEA (8.18 mL, 47.0 mmol). After 16 h the reaction mixture was concentrated under reduced pressure to *ca.* 50 mL, then diluted in H_2O (500 mL), and extracted with EtOAc (5 x 100 mL). The combined organic phases were washed sequentially with 0.5M HCl (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and

concentrated under reduced pressure affording a crude oil. Purification by flash column chromatography (25–50% EtOAc/petroleum ether) to give the title compound **3.38** (3.40 g, 6.84 mmol, 41%) as a white crystalline solid.

M.P. 108–111 ^{o}C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3305 br. m, 2966 m, 2925 m, 2872 w, 2246 w, 1744 m, 1652 s, 1524 s, 1360 m, 1245 m, 1165 s, 1017 m, 906 s, 731 m, 645 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.47 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.40 (d, *J*=1.0 Hz, 1H, Ar*H*), 7.14 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.01 (dd, *J*=17.5, 11.1 Hz, 1H, ArC*H*=CH_2), 6.46 (d, *J*=8.6 Hz, 1H, N*H*), 5.67 (d, *J*=17.5 Hz, 1H, ArCH=C*H*H), 5.34 (d, *J*=11.1 Hz, 1H, ArCH=CH*H*), 5.07 (br. d, *J*=5.6 Hz, 1H, N*H*), 4.51 (dd, *J*=8.1, 5.1 Hz, 1H, NC*H*CO), 4.37–4.28 (br. m, 1H, NC*H*CO), 3.70 (s, 3H, CH_3), 3.03 (d, *J*=6.6 Hz, 2H, CH_2), 1.90–1.78 (m, 2H, CH_2), 1.43 (s, 9H, C(CH_3)$_3$), 1.18–1.06 (m, 1H, C*H*CH_2CH_3), 0.89 (t, *J*=7.3 Hz, 3H, CH_3), 0.85 (d, *J*=7.0 Hz, 3H, CH_3).

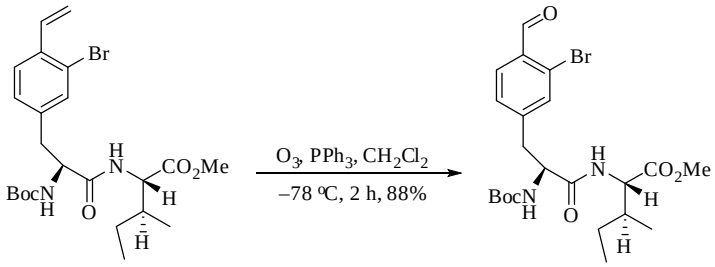
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.1 (*C*), 170.5 (*C*), 155.3 (*C*), 138.0 (*C*), 136.1 (*C*), 135.3 (*C*H), 133.6 (*C*H), 128.5 (*C*H), 126.8 (*C*H), 123.6 (*C*), 116.4 (*C*H_2), 80.4 (*C*), 56.6 (*C*H), 55.4 (*C*H), 52.1 (*C*H_3), 37.9 (*C*H), 37.2 (*C*H_2), 28.2 ((*C*H_3)$_3$), 25.1 (*C*H_2), 15.3 (*C*H_3), 11.5 (*C*H_3).

LRMS (m/z, ESI^{+}) 562([M+Na+MeCN{^{81}Br}]$^{+}$,44%), 560 ([M+Na+MeCN{^{79}Br}]$^{+}$, 38%), 521 ([M+Na{^{81}Br}]$^{+}$, 100%), 519 ([M+Na{^{79}Br}]$^{+}$, 95%), 499 ([M+H{^{81}Br}]$^{+}$, 66%), 497 ([M+H{^{79}Br}]$^{+}$, 65%).

HRMS (m/z, ESI^{+}) calcd for $C_{23}H_{33}BrN_2O_5$ [M+K{^{81}Br}]$^{+}$ requires 537.1189; found: 537.1168. [M+K{^{79}Br}]$^{+}$ requires 535.1210; found: 535.1188.

$[\alpha]_D^{26}$ 11.5 (c = 0.1, CH_2Cl_2).

Methyl (2*S*,3*S*)-2-((*S*)-3-(3-bromo-4-formylphenyl)-2-(*tert* butoxycarbonylamino)-propanamido)-3-methylpentanoate **3.46**



3.38
$C_{23}H_{33}BrN_2O_5$
(497.4)

3.46
$C_{22}H_{31}BrN_2O_6$
(499.4)

Ozone (1–4% in O_2) was bubbled through a solution of styrene **3.38** (3.40 g, 6.84 mmol) in CH_2Cl_2 (100 mL) at –78 ^oC until a blue colour was observed *ca.* 30 min. Oxygen was then bubbled through until the blue colour had disappeared to remove any excess ozone. PPh_3 (3.59 g, 13.7 mmol) was added and after 30 min the reaction mixture was tested for the presence of any peroxides. The reaction mixture was warmed to RT and concentrated under reduced pressure affording a crude golden oil. Purification by flash column chromatography (17.5% EtOAc/petroleum ether) to give the title compound **3.46** (3.00 g, 6.01 mmol, 88%) as a pale-yellow oil.

FT-IR (ν_{max}, neat) 3313 br. m, 2962 m, 2929 w, 2872 w, 2749 w, 1740 m, 1686 s, 1653 s, 1597 m, 1525 s, 1387 m, 1366 m, 1256 m, 1205 m, 1164 s, 1021 m, 910 m, 730 s, cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 10.31 (s, 1H, C*H*O), 7.83 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.51 (d, *J*=1.3 Hz, 1H, Ar*H*), 7.29 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.51 (d, *J*=8.1 Hz, 1H, N*H*), 5.12 (d, *J*=7.6 Hz, 1H, N*H*), 4.52 (dd, *J*=8.3, 4.8 Hz, 1H, NC*H*CO), 4.38 (app. q, *J*=6.9 Hz, 1H, NC*H*CO), 3.71 (s, 3H, CH_3), 3.16 (dd, *J*=13.7, 6.8 Hz, 1H, C*H*H), 3.07 (dd, *J*=13.7, 7.1 Hz, 1H, CH*H*), 1.93–1.81 (m, 1H, C*H*CH_2CH_3), 1.75 (br. s, 1H, C*H*HCH_3) 1.42

(s, 9H, C(CH_3)$_3$), 1.20–1.07 (m, 1H, CH*H*CH_3), 0.90 (t, *J*=7.1 Hz, 3H, CH_3), 0.87 (d, *J*=7.1 Hz, 3H, CH_3).

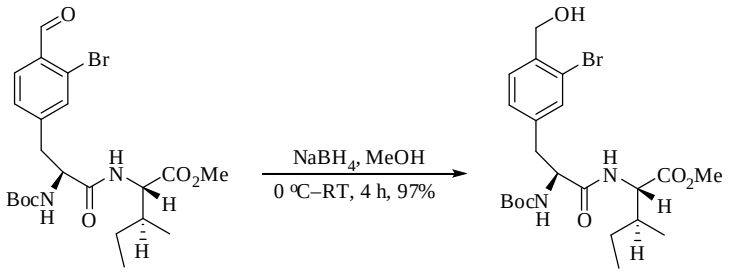
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 191.4 (*C*HO), 171.8 (*C*), 170.2 (*C*), 155.3 (*C*), 145.4 (*C*), 134.6 (*C*H), 131.3 (*C*), 129.9 (*C*H), 129.0 (*C*H), 127.2 (*C*), 80.6 (*C*), 56.6 (*C*H), 55.2 (*C*H), 52.2 (*C*H_3), 37.9 (*C*H), 37.7 (*C*H_2), 28.2 ((*C*H_3)$_3$), 25.0 (*C*H_2), 15.3 (*C*H_3), 11.5 (*C*H_3).

LRMS (m/z, ESI$^+$) 564([M+Na+MeCN{^{81}Br}]$^+$,88%), 562 ([M+Na+MeCN{^{79}Br}]$^+$, 72%), 523 ([M+Na{^{81}Br}]$^+$, 54%), 521 ([M+Na{^{79}Br}]$^+$, 94%), 501 ([M+H{^{81}Br}]$^+$, 15%), 499 ([M+H{^{79}Br}]$^+$, 16%).

HRMS (m/z, ESI$^+$) calcd for $C_{22}H_{31}BrN_2O_6$ [M+Na{^{79}Br}]$^+$ requires 521.1263; found: 521.1258.

$[\alpha]_D^{26.5}$ 8.5 (c = 0.467, CH_2Cl_2).

Methyl (2*S*,3*S*)-2-((*S*)-3-(3-bromo-4-(hydroxymethyl)phenyl)-2-(*tert*-butoxycarbonyl-amino)propanamido)-3-methylpentanoate **3.37**



3.46
$C_{22}H_{31}BrN_2O_6$
(499.4)

3.37
$C_{22}H_{33}BrN_2O_6$
(501.4)

To a solution of aldehyde **3.46** (1.28 g, 2.56 mmol) in MeOH (30 mL) at 0 ^{o}C was added $NaBH_4$ (116 mg, 3.07 mmol). After 2 h the reaction mixture was warmed to RT and after a further 2 h was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$),

filtered, and concentrated under reduced pressure to give the title compound **3.37** (1.25 g, 2.49 mmol, 97%) as a white foamy/solid that was used without further purification.

M.P. 63–67 ^{o}C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3309 br. m, 2966 m, 2921 m, 2868 w, 2246 w, 1744 m, 1656 s, 1525 s, 1366 m, 1250 m, 1206 m, 1164 s, 1029 m, 909 m, 730 s, 647 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.39 (d, *J*=7.8 Hz, 1H Ar*H*), 7.38 (d, *J*=2.0 Hz, 1H, Ar*H*), 7.17 (dd, *J*=7.8, 2.0 Hz, 1H, Ar*H*), 6.48 (d, *J*=8.6 Hz, 1H, N*H*), 5.12 (d, *J*=7.6 Hz, 1H, N*H*), 4.70 (s, 2H, CH_2), 4.51 (dd, *J*=8.6, 5.1 Hz, 1H, NC*H*CO), 4.36–4.29 (br. m, 1H, NC*H*CO), 3.71 (s, 3H, CH_3), 3.03 (app. d, *J*=6.6 Hz, 2H, CH_2), 2.50 (br. s, 1H, O*H*), 1.89–1.78 (m, 2H, CH_2CH$_3$), 1.42 (s, 9H, C(CH_3)$_3$), 1.18–1.06 (m, 1H, C*H*CH$_2$CH$_3$), 0.89 (t, *J*=7.1 Hz, 3H, CH_3), 0.84 (d, *J*=7.1 Hz, 3H, CH_3).

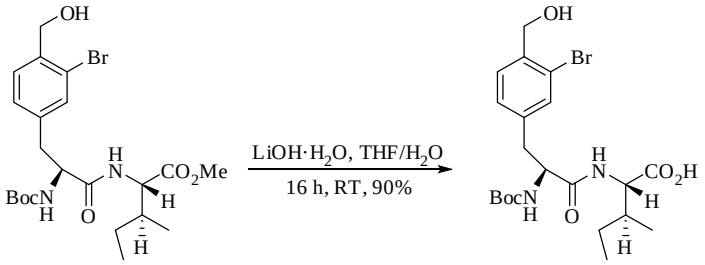
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.8 (*C*), 170.6 (*C*), 155.3 (*C*), 138.4 (*C*), 137.9 (*C*), 133.3 (*C*H), 129.0 (*C*H), 128.5 (*C*H), 122.6 (*C*), 80.4 (*C*), 64.6 (*C*H$_2$), 56.5 (*C*H), 55.6 (*C*H), 52.1 (*C*H$_3$), 37.9 (*C*H), 37.2 (*C*H$_2$), 28.2 ((*C*H$_3$)$_3$), 25.0 (*C*H$_2$), 15.3 (*C*H$_3$), 11.5 (*C*H$_3$).

LRMS (m/z, ESI^{+}) 525 ([M+Na{^{81}Br}]$^{+}$, 100%), 523 ([M+Na{^{79}Br}]$^{+}$, 95%), 503 ([M+H{^{81}Br}]$^{+}$, 40%), 519 ([M+H{^{79}Br}]$^{+}$, 40%).

HRMS (m/z, ESI^{+}) calcd for $C_{22}H_{33}BrN_2O_6$ [M+H{^{81}Br}]$^{+}$ requires 503.1580; found: 503.1577. [M+H{^{79}Br}]$^{+}$ requires 501.1600; found: 501.1604.

$[\alpha]_D^{26}$ +2.45 (c = 0.367, CH_2Cl_2).

(2*S*,3*S*)-2-((*S*)-3-(3-bromo-4-(hydroxymethyl)phenyl)-2-(*tert*-butoxycarbonyl-amino)propanamido)-3-methylpentanoic acid **3.47**



3.37 $C_{22}H_{33}BrN_2O_6$ (501.4)

3.47 $C_{21}H_{31}BrN_2O_6$ (487.4)

To a solution of ester **3.37** (558 mg, 1.11 mmol) in THF/H_2O (1:1, 12 mL) was added LiOH·H_2O (140 mg, 3.33 mmol). After 16 h the reaction mixture was diluted in 2M NaOH (20 mL) and washed with EtOAc (2 x 10 mL). The aqueous phase was acidified to pH 2 with 2M HCl (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give the title compound **3.47** (489 mg, 1.00 mmol, 90%) as a white foamy solid that was used without further purification.

M.P. 71–76 ^{o}C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3309 br. m, 2967 m, 2932 m, 2872 w, 1657 s, 1524 s, 1454 w, 1391 m, 1367 m, 1250 m, 1208 w, 1164 s, 1049 w, 908 m, 732 s, 648 w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.38 (d, *J*=1.7 Hz, 1H, Ar*H*), 7.34 (br. d, *J*=7.7 Hz, 1H, Ar*H*), 7.13 (br. dd, *J*=7.7, 1.7 Hz, 1H, Ar*H*), 6.60 (d, *J*=7.1 Hz, 1H, N*H*), 5.46 (d, *J*=7.6 Hz, 1H, N*H*), 4.69 (s, 2H, CH_2), 4.47 (dd, *J*=7.6, 5.1 Hz, 1H, NC*H*CO), 4.38 (td, *J*=7.6, 6.6 Hz, 1H, NC*H*CO), 3.01 (dd, *J*=13.3, 6.6 Hz, 1H, C*H*H), 2.94 (dd, *J*=13.3, 8.6 Hz, 1H, CH*H*), 1.90–1.80 (m, 2H, CH_2CH$_3$), 1.42 (s, 9H, C(CH_3)$_3$), 1.22–1.09 (m, 1H, C*H*CH$_2$CH$_3$), 0.93–0.85 (m, 6H, 2 x CH_3).

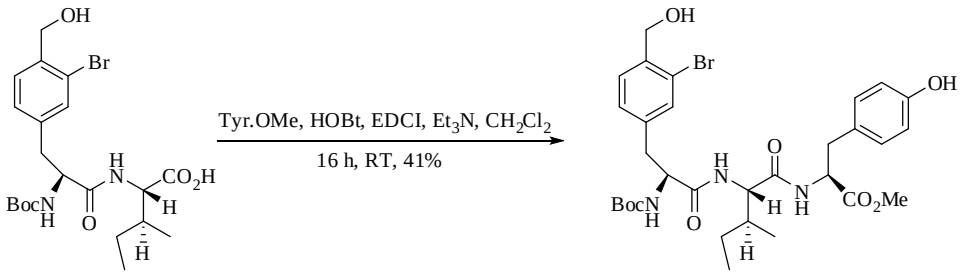
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 174.0 (*C*), 170.9 (*C*), 155.6 (*C*), 138.0 (*C*), 137.9 (*C*), 133.2 (*C*H), 129.4 (*C*H), 128.5 (*C*H), 122.9 (*C*), 80.5 (*C*), 64.5 (CH_2), 56.6 (*C*H), 55.9 (*C*H), 38.0 (*C*H), 37.8 (CH_2), 28.3 ((CH_3)$_3$), 24.9 (CH_2), 15.2 (CH_3), 11.5 (CH_3).

LRMS (m/z, ESI$^-$) 487 ([M–H{^{81}Br}]$^-$, 100%), 485 ([M–H{^{79}Br}]$^-$, 90%).

HRMS (m/z, ESI$^-$) calcd for $C_{21}H_{31}BrN_2O_6$ [M–H+Na{^{81}Br}]$^-$ requires 511.1243; found: 511.1249. [M–H+Na{^{79}Br}]$^-$ requires 509.1263; found: 509.1268.

$[\alpha]_D^{26.5}$ +6.9 (c = 0.8, CH_2Cl_2).

Methyl (6*S*,9*S*,12*S*)-6-(3-bromo-4-(hydroxymethyl)benzyl)-9-*sec*-butyl-12-(4-hydroxybenzyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **3.48**



3.47

$C_{21}H_{31}BrN_2O_6$
(487.38)

3.48

$C_{31}H_{42}BrN_3O_8$
(664.58)

To a solution of carboxylic acid **3.47** (250 mg, 513 µmol) in CH_2Cl_2 (15 mL) was added EDCI (65.4 µL, 616 µmol), HOBt (83.2 mg, 616 µmol), Tyr.*O*Me (120 mg, 616 µmol) and Et_3N (86.0 µL, 616 µmol). After 16 h the reaction mixture was quenched by addition of 1M HCl (40 mL). The products were extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (0–5% MeOH/CH_2Cl_2) to give the title compound **3.48** (138 mg, 208 µmol, 41%) as a white solid.

M.P. 158–162 ^{o}C (MeOH/CH_2Cl_2).

FT-IR (ν_{max}, neat) 3305 br. m, 2974 m, 2925 m, 2876 w, 1734 m, 1679 m, 1656 s, 1540 s, 1519 s, 1366 m, 1296 m, 1254 m, 1191 s, 1161 s, 1043 m, 1008 m, 853 w, 732 m, 648 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.48 (br. s, 1H, O*H*), 7.25–6.99 (m, 3H, Ar*H*), 6.90–6.76 (br. m, 1H, N*H*), 6.60 (d, *J*=8.4 Hz, 1H, 2H, Ar*H*), 6.42–6.31 (br. m, 1H, N*H*), 6.36 (d, *J*=8.4 Hz, 1H, 2H, Ar*H*), 5.92–5.70 (br. m, 1H, N*H*), 4.28 (d, *J*=6.6 Hz, 1H, NC*H*CO), 4.24 (s, 2H, CH_2), 4.12–3.85 (br. m, 2H, NC*H*CO), 3.30 (s, 3H, CH_3), 2.67–2.44 (m, 4H, 2xCH_2), 1.53–1.36 (m, 1H, C*H*CH_2CH_3), 1.10–0.91 (m, 1H, C*H*HCH_3), 0.97 (s, 9H, C(CH_3)$_3$), 0.83–0.68 (m, 1H, CH*H*CH_3), 0.52 (d, *J*=6.6 Hz, 0.5 x 3H, CH_3), 0.50 (t, *J*=6.6 Hz, 3H, CH_3), 0.33 (d, *J*=6.6 Hz, 0.5 x 3H, CH_3).

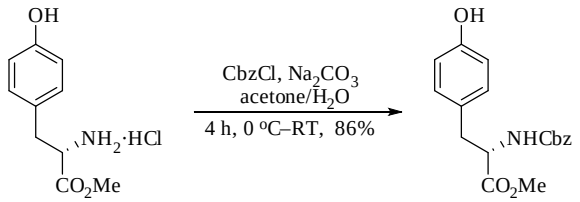
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.0 (*C*), 170.2 (*C*), 155.4 (*C*), 154.5 (*C*), 154.3 (*C*), 137.4 (*C*), 132.1 (*C*H), 129.2 (2 x *C*H), 127.6 (*C*H), 127.3 (*C*H), 125.8 (*C*), 120.7 (*C*), 114.6 (2 x *C*H), 92.3 (*C*), 78.5 (*C*), 62.5 (*C*H_2), 56.5 (*C*H), 54.7 (*C*H), 52.9 (*C*H_3), 51.0 (*C*H), 36.4 (*C*H), 36.1 (*C*H_2), 35.8 (*C*H_2), 27.4 ((*C*H_3)$_3$), 26.7 (*C*H_2), 14.4 (*C*H_3), 10.3 (*C*H_3).

LRMS (m/z, ESI^{+}) 688 ([M+Na{^{81}Br}]$^{+}$, 100%), 686 ([M+Na{^{79}Br}]$^{+}$, 87%).

HRMS (m/z, ESI^{+}) calcd for $C_{31}H_{42}BrN_3O_8$ [M+H{^{79}Br}]$^{+}$ requires 686.2053; found: 686.2047.

$[\alpha]_D^{24}$ +6.4 (c = 0.18, MeOH).

(*S*)-Methyl 2-(benzyloxycarbonylamino)-3-(4-hydroxyphenyl)propanoate **3.50**



2.56
$C_{10}H_{14}ClNO_3$
(231.68)

3.50
$C_{18}H_{19}NO_5$
(329.35)

To a solution of hydrochloride salt **2.56** (10.0 g, 43.2 mmol) in acetone/water (1:1, 180 mL) at 0 °C was added Na_2CO_3 (4.58 g, 43.2 mmol) followed by CbzCl (6.78 mL, 47.5 mmol) dropwise over 10 min. The reaction mixture was warmed to RT and after 4 h was diluted with EtOAc (200 mL). The organic phase was separated and washed sequentially with H_2O (200 mL) and brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (10–30% EtOAc/petroleum ether) to give the title compound **3.50** (12.3 g, 37.2 mmol, 86%) as a white solid. These data are in accordance with those reported in the literature.[183]

M.P. 93–96 °C (EtOAc/petroleum ether). Lit. 93–94 °C (no solvent given).[184]

FT-IR (ν_{max}, neat) 3346 br. m, 3064 w, 3023 w, 2949 w, 1693 s, 1613 m, 1605 m, 1513 s, 1441 m, 1347 m, 1215 s, 1175 w, 1056 m, 1024 m, 906 m, 824 m, 732 m, 697 m cm^{-1}.

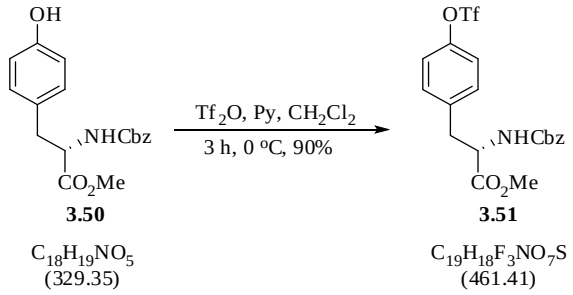
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.41–7.28 (m, 5H, Ar*H*), 6.94 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.70 (d, *J*=8.1 Hz, 2H, Ar*H*), 5.99 (s, 1H, O*H*), 5.31 (d, *J*=8.1 Hz, 1H, N*H*), 5.15–5.05 (m, 2H, CH_2), 4.69–4.57 (m, 1H, NC*H*CO), 3.73 (s, 3H, CH_3), 3.07 (dd, *J*=14.2, 5.6 Hz, 1H, C*H*H), 2.99 (dd, *J*=14.2, 6.6 Hz, 1H, CH*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.2 (*C*), 155.8 (*C*), 155.1 (*C*), 136.0 (*C*), 130.3 (2 x *C*H), 128.5 (2 x *C*H), 128.2 (2 x *C*H), 128.0 (*C*H), 127.2 (*C*), 115.5 (2 x *C*H), 67.1 (*C*H_2), 54.9 (*C*H), 52.4 (*C*H_3), 37.4 (*C*H_2).

LRMS (m/z, ESI$^+$) 681 ($[2M+Na]^+$, 27%), 352 ($[M+Na]^+$, 8%)$^+$, 229 (100%).

$[\alpha]_D^{27}$ + 40.5 (c = 0.7, CH_2Cl_2).

(*S*)-Methyl 2-(benzyloxycarbonylamino)-3-(4-(trifluoromethylsulfonyloxy)-phenyl)propanoate **3.51**



3.50 $C_{18}H_{19}NO_5$ (329.35)

3.51 $C_{19}H_{18}F_3NO_7S$ (461.41)

To a solution of phenol **3.50** (13.2 g, 39.9 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added pyridine (9.68 mL, 119.7 mmol) then Tf_2O (7.01 mL, 41.9 mmol) dropwise over 10 min. After 3 h H_2O (200 mL) was added, the organic phase separated and was washed sequentially with sat. $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (1% MeOH/CH_2Cl_2) to give the title compound **3.51** (16.7 g, 36.1 mmol, 90%) as a white solid. These data are in accordance with those reported in the literature.[185]

M.P. 72–74 °C (Et_2O/MeOH), Lit. 72–74 °C (no solvent given).[185]

FT-IR (ν_{max}, neat) 3333 br. m, 3068 w, 3035 w, 2953 w, 1718 m, 1501 m, 1420 m, 1343 m, 1208 s, 1137 s, 1053 m, 1008 m, 888 s, 739 m, 694 m, 608 m cm^{-1}.

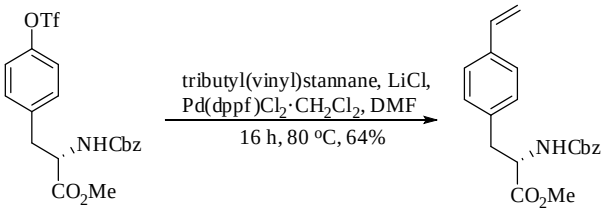
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.41–7.30 (m, 5H, Ar*H*), 7.18 (app. br. s, 4H, Ar*H*), 5.28 (d, *J*=7.1 Hz, 1H, N*H*), 5.12 (d, *J*=12.1 Hz, 1H, CH*H*), 5.08 (d, *J*=12.1 Hz, 1H, C*H*H), 4.74–4.62 (m, 1H, NC*H*CO), 3.72 (s, 3H, CH_3), 3.20 (dd, *J*=14.2, 5.6 Hz, 1H, C*H*H), 3.09 (dd, *J*=14.2, 6.6 Hz, 1H, CH*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.5 (*C*), 155.5 (*C*), 148.6 (*C*), 136.6 (*C*), 136.1 (*C*), 131.1 (2 x *C*H), 128.6 (2 x *C*H), 128.3 (*C*H), 128.2 (2 x *C*H), 121.4 (2 x *C*H), 118.7 (q, *J*=320 Hz, *C*F_3), 67.1 (*C*H_2), 54.6 (*C*H), 52.5 (*C*H_3), 37.7 (*C*H_2).

LRMS (m/z, ESI$^+$) 484 ($[M+Na]^+$, 10%), 457 (100%).

$[\alpha]_D^{27}$ +32.8 (c = 0.95, CH_2Cl_2).

Methyl (*S*)-2-(benzyloxycarbonylamino)-3-(4-vinylphenyl)propanoate **3.52**



3.51 $C_{19}H_{18}F_3NO_7S$ (461.41)

3.52 $C_{20}H_{21}NO_4$ (339.38)

Prepared according to the method of Shibuya *et al.*[185]

To a solution of triflate **3.51** (10.0 g, 21.7 mmol) in DMF (62 mL) was added tributyl(vinyl)stannane (6.98 mL, 23.9 mmol) and LiCl (1.29 g, 30.4 mmol). This was degassed under argon by immersion in a sonication bath for *ca.* 30 min then Pd(dppf)Cl_2·CH_2Cl_2 (882 mg, 1.08 mmol) was added. The reaction mixture was heated at 80 ^{o}C for 16 h then cooled to RT, diluted with H_2O (1 L) and extracted with EtOAc (5 x 300 mL). The combined organic phases were washed with H_2O (2 x 300 mL) and brine (2 x 300 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (10% w/w

K_2CO_3/silica,[182] 0–15% EtOAc/petroleum ether) to give the title compound **3.52** (4.67 g, 13.8 mmol, 64%) as a white solid. These data are in accordance with those reported in the literature.[185]

M.P. 46–48 ^oC (EtOAc/petroleum ether), Lit. not given

FT-IR (ν_{max}, neat) 3338 br. m, 3088 w, 3035 m, 2945 m, 1702 s, 1510 s, 1438 m, 1347 m, 1253 m, 1209 s, 1055 s, 1025 m, 991 m, 909 m, 738 m, 697 m cm^{-1}.

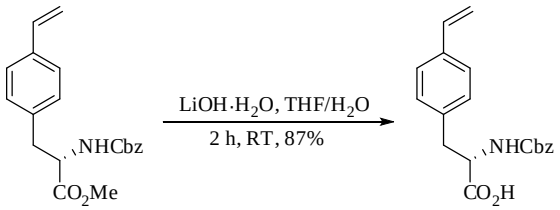
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.41–7.34 (m, 5H, Ar*H*), 7.33 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.08 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.70 (dd, *J*=17.7, 11.1 Hz, 1H, ArC*H*=CH_2), 5.74 (d, *J*=17.7 Hz, 1H, ArCH=C*H*H), 5.31 (d, *J*=7.6 Hz, 1H, N*H*), 5.25 (d, *J*=11.1 Hz, 1H, ArCH=CH*H*), 5.14 (d, *J*=12.6 Hz, 1H, C*H*H), 5.08 (d, *J*=12.6 Hz 1H, CH*H*), 4.73–4.64 (br. m, 1H, NC*H*CO), 3.74 (s, 3H, CH_3), 3.16 (dd, *J*=13.8, 5.6 Hz, 1H, C*H*H), 3.08 (dd, *J*=13.3, 6.6 Hz, 1H, CH*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.9 (*C*), 155.6 (*C*), 136.4 (*C*), 136.3 (*C*H), 136.2 (*C*), 135.2 (*C*), 129.4 (2 x *C*H), 128.4 (2 x *C*H), 128.1 (2 x *C*H), 127.9 (*C*H), 126.3 (2 x *C*H), 113.7 (*C*H_2), 54.7 (*C*H), 52.2 (*C*H_3), 37.8 (*C*H_2).

LRMS (m/z, ESI$^+$) 701 ($[2M+Na]^+$, 44%), 403 ($[M+Na+MeCN]^+$, 76%), 362 ($[M+Na]^+$, 100%).

$[\alpha]_D^{26}$ + 48.6 (c = 0.4, CH_2Cl_2).

(*S*)-2-(Benzyloxycarbonylamino)-3-(4-vinylphenyl)propanoic acid **3.53**



3.52 $C_{20}H_{21}NO_4$ (339.38)

3.53 $C_{19}H_{19}NO_4$ (325.36)

To a solution of ester **3.52** (4.67 g, 13.8 mmol) in THF/H_2O (1:1 v/v, 70.0 mL) was added LiOH·H_2O (1.74 g, 41.4 mmol). After 2 h, 2M HCl (20 mL) was added. The aqueous phase was separated and extracted with EtOAc (3 x 150 mL). The combined organic phases were then washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.53** (4.92 g, 16.1 mmol, 87%) as a white solid that was used without further purification. These data are in accordance with those reported in the literature.[119]

M.P. 112–114 ^oC (EtOAc/petroleum ether), Lit. reported an oil.[119]

FT-IR (ν_{max}, neat) 3407 br. w, 3317 br. m, 3084 br. w, 3031 br. m, 2953 br. m, 1701 s, 1511 s, 1454 m, 1408 m, 1344 m, 1215 s, 1057 m, 908 m, 735 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.41–7.28 (m, 7H, Ar*H*), 7.12 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.69 (dd, *J*=17.7, 11.1 Hz, 1H, ArC*H*=CH_2), 6.66 (br. s, 1H, CO_2*H*), 5.73 (d, *J*=17.7 Hz, 1H, ArCH=C*H*H), 5.24 (d, *J*=11.1 Hz, 1H, ArCH=CH*H*), 5.23 (br. s, 1H, N*H*), 5.12 (d, *J*=12.1 Hz, 1H, C*H*H), 5.07 (d, *J*=12.1 Hz, 1H, CH*H*), 4.76–4.65 (m, 1H, NC*H*CO), 3.21 (dd, *J*=14.2, 5.1 Hz, 1H, CH*H*), 3.10 (dd, *J*=14.2, 6.8 Hz, 1H, C*H*H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 175.9 (*C*), 155.9 (*C*), 136.6 (*C*), 136.4 (*C*H), 136.0 (*C*), 135.0 (*C*), 129.5 (2 x *C*H), 128.5 (2 x *C*H),

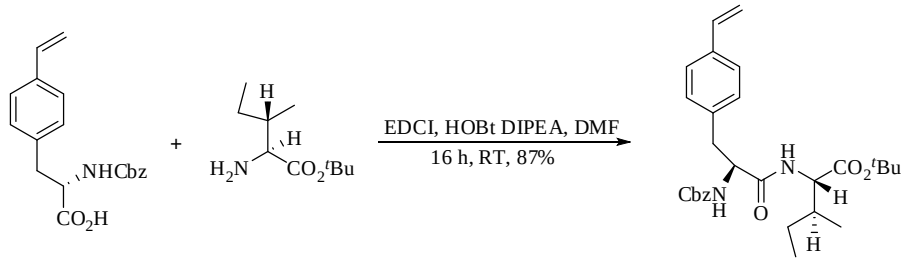
128.2 (2 x *C*H), 128.0 (*C*H), 126.5 (2 x *C*H), 113.8 (*C*H_2), 67.2 (*C*H_2), 54.5 (*C*H), 37.0 (*C*H_2).

LRMS (m/z, ESI⁻) 324 ([M–Na]⁻, 88%), 216 (100%).

HRMS (m/z, ESI⁻) calcd for $C_{19}H_{19}NO_4$ [M–H]⁻ requires 324.1236; found: 324.1239.

$[\alpha]_D^{26}$ –12.3 (c = 1.11, acetone).

tert-Butyl (2*S*,3*S*)-2-((*S*)-2-(benzyloxycarbonylamino)-3-(4-vinylphenyl)propanamido)-3-methylpentanoate **3.54**



3.53 $C_{19}H_{19}NO_4$ (325.36)

3.61 $C_{10}H_{21}NO_2$ (187.3)

3.54 $C_{29}H_{38}N_2O_5$ (494.62)

To a solution of carboxylic acid **3.53** (3.00 g, 9.22 mmol) in DMF (40 mL) was added EDCI (2.28 mL, 12.9 mmol), HOBt (1.74 g, 12.9 mmol), amine **3.61** (2.42 g, 12.9 mmol) and DIPEA (4.49 mL, 25.8 mmol). After 16 h H_2O (600 mL) was added, and the products extracted with EtOAc (4 x 150 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure affording a brown oil. Purification by flash column chromatography (10–25% EtOAc/petroleum ether) to give the title compound **3.54** (3.99 g, 8.07 mmol, 87%) as a colourless oil. These data are in accordance with those reported in the literature.[119]

FT-IR (ν_{max}, neat) 3309 br. m, 3080 w, 3060 w, 2958 m, 2925 m, 2872 w, 1732 s, 1695 s, 1657 s, 1539 s, 1364 m, 1262 m, 1139 m, 1049 w cm^{-1}.

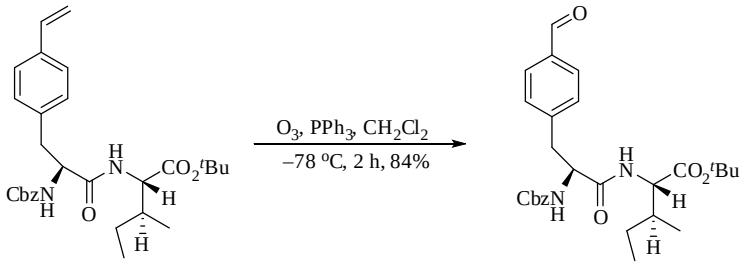
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.39–7.33 (m, 5H, Ar*H*), 7.31 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.15 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.68 (dd, *J*=17.7, 10.6 Hz, 1H, ArC*H*=CH_2), 6.30 (d, *J*=7.6 Hz, 1H, N*H*), 5.71 (d, *J*=17.7 Hz, 1H, ArCH=C*H*H), 5.30 (br. d, *J*=7.6 Hz, 1H, N*H*), 5.22 (d, *J*=11.6 Hz, 1H, ArCH=CH*H*), 5.10 (d, *J*=12.4 Hz, 1H, CH*H*), 5.09 (d, *J*=12.4 Hz, 1H, C*H*H), 4.48–4.41 (br. m, 1H, NC*H*CO), 4.39 (dd, *J*=8.6, 4.5 Hz, 1H, NC*H*CO), 3.12–3.03 (m, 2H, CH_2), 1.87–1.76 (m, 1H, C*H*CH_2CH_3), 1.45 (s, 9H, C(CH_3)$_3$), 1.42–1.34 (m, 1H, CH*H*CH_3), 1.16–1.04 (m, 1H, C*H*HCH_3), 0.90 (t, *J*=7.6 Hz, 3H, CH_3), 0.85 (d, *J*=7.0 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 170.2 (*C*), 170.1 (*C*), 155.8 (*C*), 136.4 (*C*H), 136.2 (*C*), 135.8 (*C*), 129.5 (2 x *C*H), 128.5 (2 x *C*H), 128.2 (*C*H), 128.0 (2 x *C*H), 127.7 (*C*), 126.5 (2 x *C*H), 113.6 (*C*H_2), 82.1 (*C*), 67.0 (*C*H_2), 56.8 (*C*H), 56.1 (*C*H), 38.1 (*C*H), 29.7 (*C*H_2), 28.0 ((*C*H_3)$_3$), 25.4 (*C*H_2), 15.2 (*C*H_3), 11.7 (*C*H_3).

LRMS (m/z, ESI$^+$) 517 ($[M+Na]^+$, 100%).

$[\alpha]_D^{26}$ +19.0 (c = 0.55, CH_2Cl_2).

tert-Butyl (2*S*,3*S*)-2-((*S*)-2-(benzyloxycarbonylamino)-3-(4-formylphenyl)-propanamido)-3-methylpentanoate **3.55**



3.54
$C_{29}H_{38}N_2O_5$
(494.62)

3.55
$C_{28}H_{36}N_2O_6$
(496.59)

Ozone (1–4% in O_2) was bubbled through a solution of styrene **3.54** (3.98 g, 8.05 mmol) in CH_2Cl_2 (115 mL) at –78 °C until a blue colour was observed (*ca.* 30 min). Oxygen was then bubbled through the solution until the blue colour had disappeared. PPh_3 (4.22 g, 16.1 mmol) was added and after 30 min the reaction mixture was tested for the presence of any peroxides. The reaction mixture was warmed to RT and concentrated under reduced pressure affording a golden oil. Purification by flash column chromatography (17.5% EtOAc/petroleum ether) to give the title compound **3.55** (3.35 g, 6.75 mmol, 84%) as a white solid. These data are in accordance with those reported in the literature.[119]

M.P. 111–112 °C (EtOAc/petroleum ether), Lit. not given.[119]

FT-IR (ν_{max}, neat) 3305 br. m, 3060 w, 2966 m, 2929 m, 2876 w, 2729 w, 1732 s, 1699 s, 1656 s, 1605 m, 1536 s, 1364 m, 1255 s, 1145 s, 1045 m, 730 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 9.96 (s, 1H, C*H*), 7.77 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.39–7.28 (m, 7H, Ar*H*), 6.36 (br. s, 1H, N*H*), 5.43 (br. s, 1H, N*H*), 5.09 (s, 2H, CH_2), 4.50 (d, *J*=6.6 Hz, 1H, NC*H*CO), 4.39 (dd, *J*=8.6, 4.5 Hz, 1H, NC*H*CO), 3.20 (dd, *J*=13.6, 7.1 Hz, 1H, C*H*H), 3.13 (dd, *J*=13.6, 6.6 Hz, 1H, CH*H*), 1.87–1.71 (br. m, 1H, C*H*CH_2CH_3), 1.44 (s, 9H, C(CH_3)$_3$), 1.42–

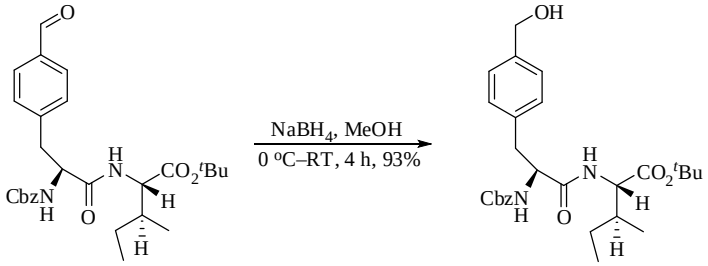
1.34 (m, 1H, CH*H*CH_3), 1.19–1.06 (m, 1H, C*H*HCH_3), 0.90 (t, *J*=7.6 Hz, 3H, CH_3), 0.83 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 191.8 (*C*H), 170.3 (*C*), 169.8 (*C*), 155.8 (*C*), 143.5 (*C*), 136.1 (*C*), 135.3 (*C*), 130.6 (2 x *C*H), 130.0 (2 x *C*H), 128.6 (2 x *C*H), 128.3 (*C*H), 128.0 (2 x *C*H), 82.3 (*C*), 67.1 (CH_2), 56.8 (*C*H), 55.8 (*C*H), 38.6 (CH_2), 38.1 (*C*H), 28.0 ((CH_3)$_3$), 25.3 (CH_2), 15.2 (CH_3), 11.7 (CH_3).

LRMS (m/z, ESI$^+$) 1015 ($[2M+Na]^+$, 100%), 519 ($[M+Na]^+$, 100%).

$[\alpha]_D^{28}$ +16.0 (c = 0.71, CH_2Cl_2).

<u>*tert*-Butyl (2*S*,3*S*)-2-((*S*)-2-(benzyloxycarbonylamino)-3-(4-(hydroxymethyl)-phenyl)propanamido)-3-methylpentanoate **3.56**</u>



3.55
$C_{28}H_{36}N_2O_6$
(496.59)

3.56
$C_{28}H_{38}N_2O_6$
(498.61)

A solution of aldehyde **3.55** (3.33 g, 6.71 mmol) in MeOH (84 mL) was cooled to 0 ^oC and then $NaBH_4$ (304 mg, 8.05 mmol) was added carefully ensuring the temperature remained at 0 ^oC. The reaction mixture was stirred at this temperature for 2 h before warming to RT for a further 2 h. H_2O (150 mL) added and the products extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.56** (3.35 g, 6.75 mmol, 93%) as a white foamy solid, used without further purification.

M.P. 123–125 ^{o}C (MeOH).

FT-IR (ν_{max}, neat) 3305 br. m, 2966 m, 2929 m, 2876 w, 1707 s, 1657 s, 1514 m, 1454 m, 1367 m, 1252 m, 1143 s, 1044 m, 909 m, 730 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.31–7.21 (m, 5H, Ar*H*), 7.18 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.08 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.30 (d, *J*=8.1 Hz, 1H, N*H*), 5.33 (d, *J*=8.1 Hz, 1H, N*H*), 5.03 (d, *J*=12.3 Hz, 1H, C*H*H), 4.99 (d, *J*=12.3 Hz, 1H, CH*H*), 4.55 (s, 2H, CH_2), 4.40–4.35 (m, 1H, NC*H*CO), 4.33 (dd, *J*=8.1, 4.6 Hz, 1H, NC*H*CO), 3.02–2.96 (m, 2H, CH_2), 1.88 (br. s, 1H, O*H*), 1.77–1.68 (m, 1H, C*H*CH_2CH_3), 1.38 (s, 9H, C(CH_3)$_3$), 1.34–1.25 (m, 1H, CH*H*CH_3), 1.10–0.97 (m, 1H, C*H*HCH_3), 0.82 (t, *J*=7.1 Hz, 3H, CH_3), 0.74 (d, *J*=7.1 Hz, 3H, CH_3).

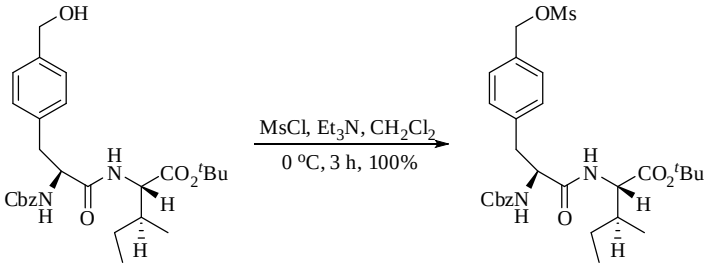
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 170.3 (*C*), 170.3 (*C*), 155.8 (*C*), 139.6 (*C*), 136.2 (*C*), 135.6 (*C*), 129.5 (2 x *C*H), 128.5 (2 x *C*H), 128.2 (*C*H), 127.9 (2 x *C*H), 127.4 (*C*H), 128.0 (2 x *C*H), 82.1 (*C*), 66.9 (*C*H_2), 65.0 (*C*H_2), 56.8 (2 x *C*H), 56.1 (*C*H), 38.1 (*C*H_2), 28.0 ((*C*H_3)$_3$), 25.3 (*C*H_2), 15.2 (*C*H_3), 11.7 (*C*H_3).

LRMS (m/z, ESI^{+}) 1019 ([2M+Na]$^{+}$, 100%), 521 ([M+Na]$^{+}$, 100%).

HRMS (m/z, ESI^{+}) calcd for $C_{28}H_{38}N_2O_6$ [M+Na]$^{+}$ requires 521.2628; found: 521.2630.

$[\alpha]_D^{28.5}$ +11.8 (c = 0.67, CH_2Cl_2).

tert-Butyl (2*S*,3*S*)-2-((*S*)-2-(benzyloxycarbonylamino)-3-(4-((methylsulfonyloxy)-methyl)-phenyl)propanamido)-3-methylpentanoate **3.57**



3.56
$C_{28}H_{38}N_2O_6$
(498.61)

3.57
$C_{29}H_{40}N_2O_8S$
(576.70)

To a solution of alcohol **3.56** (500 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Et_3N (307 µL, 2.20 mmol) followed by the dropwise addition of MsCl (92.9 µL, 1.20 mmol) over 3 min. After 3 h sat. $NaHCO_3$ (20 mL) was added and the products extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.57** (576 g, 1.00 mmol, 100%) as a pale yellow oil that was used without further purification.

FT-IR (ν_{max}, neat) 3301 br. m, 2962 m, 2929 m, 2872 w, 1723 s, 1657 s, 1535 s, 1349 s, 1253 s, 1221 s, 1170 s, 1042 m, 918 m, 735 m, 526 m cm^{-1}.

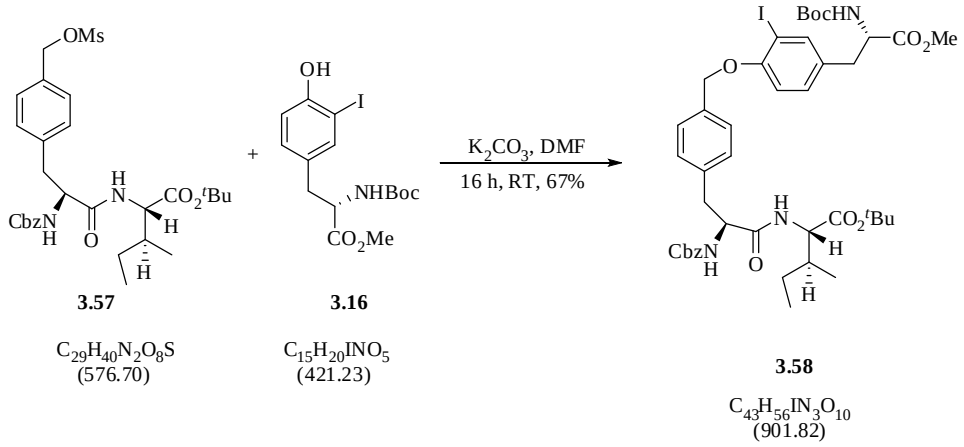
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.35–7.28 (br. m, 7H, Ar*H*), 7.22 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.42 (d, *J*=8.1 Hz, 1H, N*H*), 5.40 (d, *J*=7.6 Hz, 1H, N*H*), 5.18 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 4.43–4.38 (m, 1H, NC*H*CO), 4.33 (dd, *J*=8.1, 4.6 Hz, 1H, NC*H*CO), 3.17–3.02 (m, 4H, 2 x CH_2), 2.88 (s, 3H, CH_3), 1.88–1.77 (m, 1H, C*H*CH_2CH_3), 1.46 (s, 9H, C(CH_3)$_3$), 1.43–1.35 (m, 1H, CH*H*CH_3), 1.19–1.05 (m, 1H, C*H*HCH_3), 0.90 (t, *J*=7.3 Hz, 3H, CH_3), 0.83 (d, *J*=6.6 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 170.3 (*C*), 170.0 (*C*), 155.8 (*C*), 139.6 (*C*), 137.8 (*C*), 136.1 (*C*), 132.4 (*C*H), 129.9 (2 x *C*H), 129.1 (2 x *C*H), 128.5 (2 x *C*H), 127.9 (2 x *C*H), 82.1 (*C*), 71.2 (*C*H_2), 67.0 (*C*H_2), 56.8 (*C*H), 56.1 (*C*H), 52.6 (*C*H_2), 38.3 (*C*H), 28.0 ((*C*H_3)$_3$), 25.2 (*C*H_2), 15.2 (*C*H_3), 11.6 (*C*H_3), 8.0 (*C*H_3).

HRMS (m/z, ESI$^+$) calcd for $C_{29}H_{40}N_2O_8S$ $[M+Na]^+$ requires 599.2403; found: 521.2398.

$[\alpha]_D^{28.5}$ +8.5 (c = 0.88, CH_2Cl_2).

<u>*tert*-Butyl (2*S*,3*S*)-2-((*S*)-2-(benzyloxycarbonylamino)-3-(4-((4-((*S*)-2-(*tert*-butoxycarbonylamino)-3-methoxy-3-oxopropyl)-2-iodophenoxy)-methyl)-phenyl)propanamido)-3-methylpentanoate **3.58**</u>



To a solution of mesylate **3.57** (480 mg, 840 µmol) in DMF (10 mL) was added iodide **3.16** (421 mg, 1.00 mmol) and K_2CO_3 (290 mg, 2.10 mmol). After 16 h H_2O (200 mL) was added and the products extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (30% EtOAc/petroleum ether) to give the title compound **3.58** (510 mg, 565 µmol, 67%) as a white foamy solid.

M.P. 54–57 ^oC (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3423 br. w, 3317 w, 2970 w, 2929 w, 2876 w, 1707 s, 1662 s, 1489 s, 1366 s, 1249 s, 1157 s, 1047 s, 1018 m, 907 s, 727 s, 696 m, 646 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.56 (br. s, 1H, Ar*H*), 7.37 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.35–7.28 (m, 5H, Ar*H*), 7.20 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.03 (dd, *J*=8.1, 1.8 Hz, 1H, Ar*H*), 6.75 (d, *J*=8.2 Hz, 1H, Ar*H*), 6.54 (d, *J*=6.1 Hz, 1H, N*H*), 5.46 (br. d, *J*=6.6 Hz, 1H, N*H*), 5.08 (s, 2H, CH_2), 5.04 (s, 2H, CH_2), 5.03 (br. s, 1H, N*H*), 4.56–4.45 (m, 2H, 2 x NC*H*CO), 4.42 (dd, *J*=8.3, 4.8 Hz, 1H, NC*H*CO), 3.72 (s, 3H, CH_3), 3.16–3.07 (m, 2H, CH_2), 3.03 (dd, *J*=14.1, 5.3 Hz, 1H, C*H*H), 2.93 (dd, *J*=14.1, 5.6 Hz, 1H, CH*H*), 1.88–1.76 (m, 1H, C*H*CH_2CH_3), 1.45 (s, 9H, C(CH_3)$_3$), 1.43 (s, 9H, C(CH_3)$_3$), 1.44–1.39 (m, 1H, C*H*HCH_3), 1.18–1.06 (m, 1H, CH*H*CH_3), 0.90 (t, *J*=7.2 Hz, 3H, CH_3), 0.83 (d, *J*=7.2 Hz, 3H, CH_3).

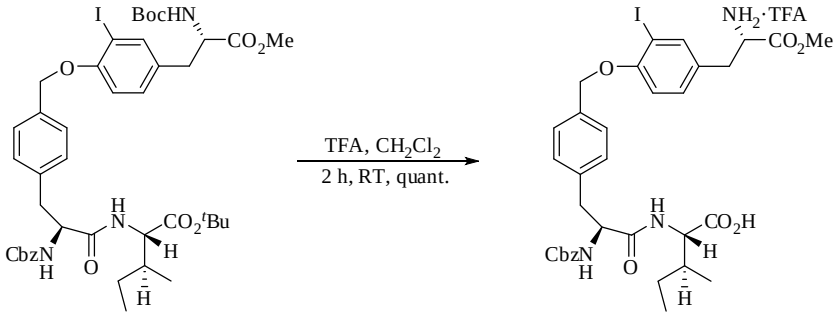
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.1 (*C*), 170.4 (*C*), 156.3 (*C*), 155.9 (*C*), 154.9 (*C*), 154.4 (*C*), 140.2 (*C*H), 136.1 (*C*), 135.9 (*C*), 135.1 (*C*), 130.6 (*C*), 130.1 (*C*H), 129.5 (2 x *C*H), 128.4 (2 x *C*H), 128.1 (*C*H), 128.0 (2 x *C*H), 127.1 (*C*H), 114.9 (*C*H), 112.5 (*C*H), 86.6 (*C*), 82.0 (*C*), 79.9 (*C*), 70.6 (*C*H_2), 67.0 (*C*H_2), 56.8 (*C*H), 55.9 (*C*H), 54.4 (*C*H), 52.2 (*C*H_3), 38.0 (*C*H), 37.9 (*C*H_2), 36.9 (*C*H_2), 28.2 ((*C*H_3)$_3$), 28.0 ((*C*H_3)$_3$), 25.3 (*C*H_2), 15.2 (*C*H_3), 11.6 (*C*H_3).

LRMS (m/z, ESI^{+}) 924 ([M+Na] $^{+}$, 100%).

HRMS (m/z, ESI^{+}) calcd for $C_{43}H_{56}IN_3O_{10}$ $[M+Na]^+$ requires 924.2908; found: 924.2887.

$[\alpha]_D^{27}$ + 33.5 (c = 0.47, CH_2Cl_2).

(2*S*,3*S*)-2-((*S*)-3-(4-((4-((*S*)-2-Ammonium-3-methoxy-3-oxopropyl)-2-iodophenoxy)-methyl)phenyl)-2-(benzyloxycarbonylamino)propanamido)-3-methylpentanoic acid trifluoroacetate **3.59**



3.58

$C_{43}H_{56}IN_3O_{10}$
(901.82)

3.59

$C_{36}H_{41}F_3IN_3O_{10}$
(859.62)

To a solution of peptide **3.58** (100 mg, 110 μmol) in CH_2Cl_2 (1 mL) was added with TFA (4 mL). After 2 h the reaction mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (10 mL) and concentrated under reduced pressure (x3) to effect azeotropic removal of residual TFA to give the title compound **3.59** (95 mg, 110 μmol, 100%) as a colourless oil.

FT-IR (ν_{max}, neat) 2961 br. m, 2872 w, 1745 m, 1668 s, 1516 m, 1442 m, 1199 s, 1141 s, 1045 w, 800 w cm^{-1}.

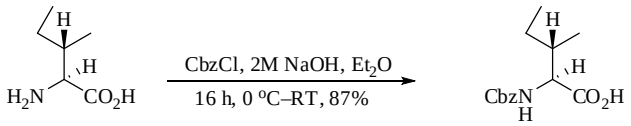
^{1}H NMR (400 MHz, d_4-MeOH) δ_H ppm 7.69 (br. s, 1H, Ar*H*), 7.59 (br. s, 1H, Ar*H*), 7.39 (br. d, *J*=7.6 Hz, 2H, Ar*H*), 7.33–7.22 (m, 5H, Ar*H*), 7.11–7.03 (m, 2H, Ar*H*), 6.95 (d, *J*=8.6 Hz, 1H, Ar*H*), 5.11 (br. s, 2H, CH_2), 4.99 (s, 2H, CH_2), 4.54–4.45 (br. m, 1H, NC*H*CO), 4.42–4.35 (br. m, 1H, NC*H*CO), 4.29–4.20 (br. m, 1H, NC*H*CO), 3.79 (br. s, 3H, CH_3), 3.21–3.00 (m, 4H, 2 X CH_2), 1.95–1.83 (br. m, 1H, C*H*CH_2CH_3), 1.58–1.44 (m, 1H, C*H*HCH$_3$), 1.31–1.16 (m, 1H, CH*H*CH$_3$), 1.00–0.86 (m, 6H, 2 x CH_3).

^{13}C NMR (100 MHz, d_4-MeOH) δ_C ppm 174.6 (*C*), 170.5 (*C*), 158.6 (*C*), 158.0 (*C*), 141.3 (*C*H), 138.4 (*C*), 136.5 (*C*), 131.8 (*C*H), 131.7 (*C*H), 130.6 (2 x *C*H), 129.7 (*C*), 129.6 (*C*H), 129.5 (*C*H), 129.1 (*C*H), 128.4 (*C*H), 127.9 (*C*), 125.7 (*C*), 117.0 (*C*H), 116.3 (2 x *C*H), 87.8 (*C*), 71.8 (CH_2), 67.7 (CH_2), 58.3 (*C*H), 57.6 (*C*H), 55.7 (*C*H), 55.4 (CH_3), 38.8 (CH_2), 38.6 (*C*H), 36.8 (CH_2), 36.1 (CH_2), 16.1 (CH_3), 12.0 (CH_3).

HRMS (m/z, ESI$^+$) calcd for $C_{34}H_{40}IN_3O_8$ $[M+H]^+$ requires 746.1938; found: 746.1925.

$[\alpha]_D^{29}$ + 0.5 (c = 0.2, MeOH).

(2*S*,3*S*)-2-(Benzyloxycarbonylamino)-3-methylpentanoic acid **3.63**



3.62 $C_6H_{13}NO_2$ (131.17)

3.63 $C_{14}H_{19}NO_4$ (265.30)

To a solution of L-isoleucine **3.62** (25.0 g, 191 mmol) in a mixture of 2M NaOH (500 mL) and Et_2O (100 mL) at 0 °C was added CbzCl (43.7 mL, 306 mmol) dropwise over 15 min. The reaction mixture was warmed to RT and after 16 h the phases were separated. The aqueous phase was acidified to pH 2 with 2M HCl (~400 mL) then extracted with EtOAc (4 x 100 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the title compound **3.63** (44.1 g, 166 mmol, 87%) as a colourless oil that was used without further purification. These data are in accordance with those reported in the literature.[186]

FT-IR (ν_{max}, neat) 3313 br. m, 2966 m, 2925 w, 2876 w, 1700 s, 1517 s, 1454 m, 1413 m, 1334 m, 1213 s, 1091 m, 1041 m, 910 w, 735 s cm^{-1}.

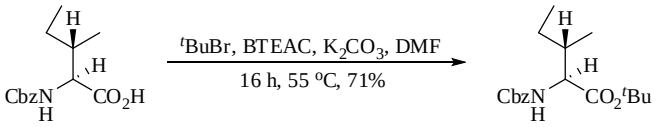
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.69 (br. s, 1H, CO_2H), 7.45–7.28 (m, 5H, Ar*H*), 5.32 (d, *J*=8.8 Hz, 1H, N*H*), 5.13 (s, 2H, CH_2), 4.40 (dd, *J*=8.8, 4.6 Hz, 1H, NC*H*CO), 2.03–1.87 (m, 1H, C*H*), 1.56–1.41 (m, 1H, C*H*H), 1.30–1.14 (m, 1H, CH*H*), 0.98 (t, *J*=7.1 Hz, 3H, CH_3), 0.94 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 176.8 (*C*), 156.4 (*C*), 136.1 (*C*), 128.5 (2 x *C*H), 128.2 (*C*H), 128.1 (*C*H), 127.0 (*C*H), 67.2 (CH_2), 58.8 (*C*H), 37.8 (CH_2), 24.8 (*C*H), 15.4 (CH_3), 11.6 (CH_3).

LRMS (m/z, ESI$^-$) 264 ([M–H]$^-$, 4%), 249 (100%).

$[\alpha]_D^{28}$ + 8.1 (c = 0.9, CH_2Cl_2).

<u>*tert*-Butyl (2*S*,3*S*)-2-(benzyloxycarbonylamino)-3-methylpentanoate **3.65**</u>



3.63 $C_{14}H_{19}NO_4$ (265.31)

3.65 $C_{18}H_{27}NO_4$ (321.41)

Prepared according to the method of Martinez *et al.*[135]

To a solution of acid **3.63** (500 mg, 1.88 mmol) in DMF (15 mL) was added BTEAC (428 mg, 1.88 mmol), K_2CO_3 (6.76 g, 48.9 mmol) and ^{t}BuBr (10.1 mL, 90.2 mmol). The reaction mixture was heated at 55 ^{o}C for 16 h then cooled to RT, diluted with H_2O (200 mL) and extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (0–10% EtOAc/petroleum ether) to give the title compound **3.65** (431 mg, 1.34 mmol, 71%) as a colourless oil. These data are in accordance with those reported in the literature.[187]

FT-IR (ν_{max}, neat) 3440 w, 3342 br. m, 2966 m, 2933 m, 2876 w, 1714 s, 1510 br. m, 1458 m, 1367 m, 1219 br. m, 1154 s, 1037 m, 730 m, 694 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.39–7.31 (m, 5H, C*H*), 5.31 (d, *J*=8.6 Hz, 1H, N*H*), 5.12 (s, 2H, CH_2), 4.24 (dd, *J*=8.6, 4.5 Hz, 1H, NC*H*CO), 1.91–1.82 (m, 1H, C*H*H), 1.47 (s, 9H, (CH_3)$_3$), 1.45–1.40 (m, 1H, CH*H*), 1.25–1.12 (m, 1H, C*H*), 0.94 (t, *J*=7.3 Hz, 3H, CH_3), 0.94 (d, *J*=6.8 Hz, 3H, CH_3).

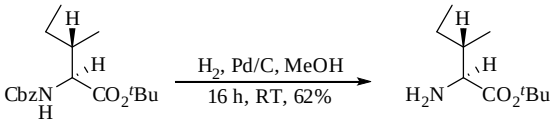
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.0 (*C*), 156.0 (*C*), 136.4 (*C*), 128.5 (2 x *C*H), 128.1 (2 x *C*H), 81.9 (*C*), 66.9 (*C*H_2), 58.4 (*C*H), 38.3 (*C*H), 28.0 (*C*H_3)$_3$), 25.1 (*C*H_2), 15.3 (*C*H_3), 11.7 (*C*H_3). *NB: One CH resonance not observed.*

LRMS (m/z, ESI$^+$) 665 ([2M+Na]$^+$, 8%), 385 ([M+Na+MeCN]$^+$, 88%), 344 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{18}H_{27}NO_4$ [M+Na]$^+$ requires 344.1838; found: 344.1835.

$[\alpha]_D^{27}$ + 13.4 (c = 0.683, CH_2Cl_2).

<u>*tert*-Butyl (2*S*,3*S*)-2-amino-3-methylpentanoate **3.61**</u>



3.65 $C_{18}H_{27}NO_4$ (321.41)

3.61 $C_{10}H_{21}NO_2$ (187.28)

To a solution of carbamate **3.65** (344 mg, 1.07 mmol) in MeOH (10 mL) was added 10% Pd/C (34 mg). The reaction mixture was stirred under an atmosphere of hydrogen for 16 h then filtered through Celite®. The layer cake was washed with MeOH (10 mL)

and the filtrate concentrated under reduced pressure to give the title compound **3.61** (125 mg, 667 µmol, 62%) as a pale yellow oil, that was used without further purification. These data are in accordance with those reported in the literature.[188]

FT-IR (ν_{max}, neat) 2967 br. s, 2933 br. m, 2877 m, 1732 s, 1589 br. w, 1519 br. w, 1368 m, 1244 m, 1157 s, 845 m cm^{-1}.

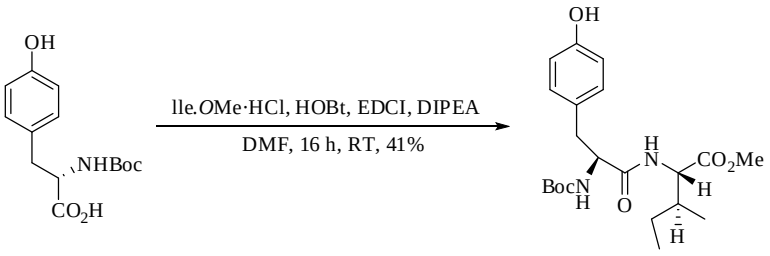
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 5.31 (br. s, 2H, N*H*$_2$), 3.59–3.52 br. m, 1H, NC*H*CO), 1.95 (br. s, 1H, C*H*), 1.50–1.47 (m, 1H, CH*H*), 1.48 (s, 1H, (C*H*$_3$)$_3$), 1.39–1.27 (m, 1H, C*H*H), 1.02 (d, *J*=7.1 Hz, 3H, C*H*$_3$), 0.95 (d, *J*=7.6 Hz, 3H, C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 170.6 (*C*), 82.5 (*C*), 58.4 (*C*H), 37.9 (*C*H), 28.0 (*C*H$_3$)$_3$), 25.3 (*C*H$_2$), 15.3 (*C*H$_3$), 11.7 (*C*H$_3$).

LRMS (m/z, ESI$^+$) 188 ($[M+H]^+$, 100%).

$[\alpha]_D^{27}$ + 16.7 (c = 1.18, CH_2Cl_2).

Methyl (2*S*,3*S*)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-hydroxyphenyl)-propanamido)-3-methylpentanoate **3.72**



3.01
$C_{14}H_{19}NO_5$
(281.3)

3.72
$C_{21}H_{32}N_2O_6$
(408.5)

To a solution of carboxylic acid **3.01** (10.0 g, 35.5 mmol) in DMF (50 mL) was added EDCI (5.28 mL, 49.7 mmol), HOBt (6.72 g, 49.7 mmol), Ile.*O*Me·HCl (9.02 g, 49.7 mmol) and DIPEA (17.3 mL, 99.4 mmol). After 16 h the reaction mixture was diluted in H_2O (500 mL), and the products extracted with EtOAc (5 x 100 mL). The

combined organic phases were washed sequentially with 1M HCl (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude golden oil. Purification by flash column chromatography (50% EtOAc/petroleum ether) to give the title compound **3.72** (5.96 g, 14.6 mmol, 41%) as a white foamy solid. These data are in accordance with those reported in the literature.[189]

M.P. 73–76 ^{o}C (EtOAc/petroleum ether), Lit. not given.

FT-IR (ν_{max}, neat) 3317 br. m, 2962 m, 2929 m, 2872 w, 1657 s, 1514 s, 1366 m, 1247 m, 1165 s, 732 m cm^{-1}.

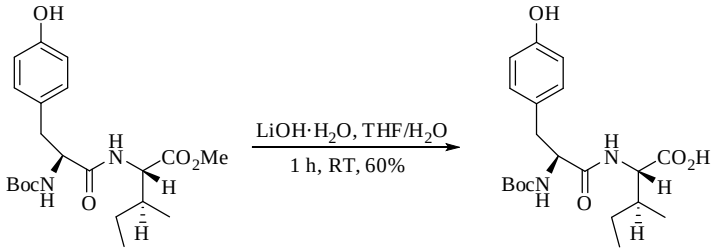
^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm 7.03 (d, *J*=8.4 Hz, 2H, Ar*H*), 6.74 (d, *J*=8.4 Hz, 2H, Ar*H*), 6.45 (d, *J*=8.4 Hz, 1H, N*H*), 6.40 (br. s, 1H, O*H*), 5.17–5.05 (m, 1H, N*H*), 4.50 (dd, *J*=8.2, 5.3 Hz, 1H, NC*H*CO), 4.34–4.22 (br. m, 1H, NC*H*CO), 3.69 (s, 3H, CH_3), 2.98 (d, *J*=6.6 Hz, 2H, CH_2), 1.89–1.76 (m, 2H, CH_2CH$_3$), 1.43 (s, 9H, C(CH_3)$_3$), 1.20–1.03 (m, 1H, C*H*CH$_2$CH$_3$), 0.89 (t, *J*=7.3 Hz, 3H, CH_3), 0.83 (d, *J*=7.0 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C ppm 171.8 (*C*), 171.3 (*C*), 155.6 (*C*), 155.1 (*C*), 130.4 (2 x *C*H), 128.0 (*C*), 115.6 (2 x *C*H), 80.4 (*C*), 56.6 (*C*H), 55.9 (*C*H), 52.1 (*C*H$_3$), 37.9 (*C*H), 37.3 (*C*H$_2$), 28.3 ((*C*H$_3$)$_3$), 25.1 (*C*H$_2$), 15.3 (*C*H$_3$), 11.5 (*C*H$_3$).

LRMS (m/z, ESI^{+}) 839 ([2M+Na]$^{+}$, 10%), 472 ([M+Na+MeCN]$^{+}$, 20%), 431 ([M+Na]$^{+}$, 100%), 372 ([M-Boc+Na+MeCN]$^{+}$, 15%), 309 ((M-Boc+H)$^{+}$, 26%).

$[\alpha]_D^{25}$ –4.25 (c = 0.2, CH_2Cl_2).

(2*S*,3*S*)-2-((*S*)-2-(*tert*-Butoxycarbonylamino)-3-(4-hydroxyphenyl)propanamido)-3-methylpentanoic acid **3.73**



3.72

$C_{21}H_{32}N_2O_6$
(408.5)

3.73

$C_{20}H_{30}N_2O_6$
(394.5)

To a solution of ester **3.72** (5.64 g, 13.8 mmol) in THF/water (1:1, 150 mL) was added $LiOH{\cdot}H_2O$ (1.74 g, 41.4 mmol). The reaction mixture was stirred at RT and after 1 h was quenched with 2M HCl (100 mL). The aqueous phase was extracted with EtOAc (3 x 75 mL), and the combined organic phases were washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.73** (3.29 g, 8.34 mmol, 60%) as a white foamy solid that was used without further purification. These data are in accordance with those reported in the literature.[189]

M.P. 75–78 °C (Et_2O/MeOH), Lit. 79–83 °C (no solvent given).[189]

FT-IR (ν_{max}, neat) 3313 br. m, 2970 m, 2929 m, 2872 m, 1716 s, 1659 s, 1516 s, 1368 m, 1247 m, 1166 m cm^{-1}.

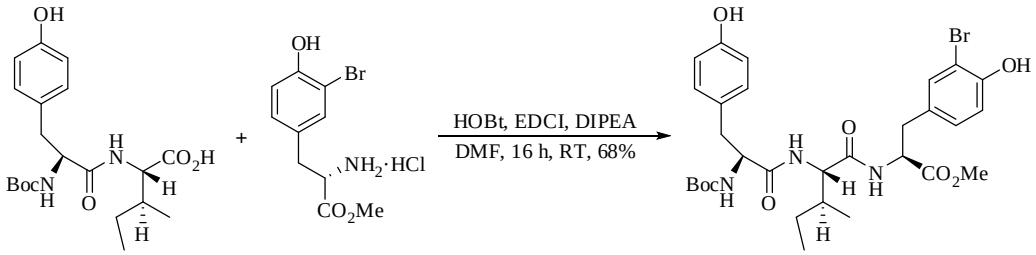
^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm 6.98 (d, *J*=8.2 Hz, 2H, Ar*H*), 6.71 (d, *J*=8.2 Hz, 2H, Ar*H*), 6.64–6.52 (m, 1H, N*H*), 5.44 (br. d, *J*=6.6 Hz, 1H, N*H*), 4.50–4.42 (br. m, 1H, NC*H*CO), 4.40–4.30 (br. m, 1H, NC*H*CO), 2.98–2.90 (m, 2H, CH_2), 1.90–1.79 (m, 1H, C*H*CH_2CH_3), 1.43 (s, 9H, C(CH_3)$_3$), 1.27–1.08 (m, 2H, CH_2), 0.94–0.84 (m, 6H, 2x CH_3). *NB: OH and CO_2H not observed.*

^{13}C NMR (75 MHz, $CDCl_3$) δ_C ppm 175.6 (*C*), 172.0 (*C*), 155.8 (*C*), 155.2 (*C*), 130.2 (2 x *C*H), 127.5 (*C*), 115.6 (2 x *C*H), 80.7 (*C*), 56.8 (*C*H), 56.2 (*C*H), 37.7 (*C*H), 37.4 (CH_2), 28.3 ((CH_3)$_3$), 24.9 (CH_2), 15.2 (CH_3), 11.4 (CH_3).

LRMS (m/z, ESI$^-$) 393 ([M–H]$^-$, 100%), 249 (71%), 142 (31%).

$[\alpha]_D^{25.5}$ + 3.29 (c = 0.17, CH_2Cl_2).

Methyl (6*S*,9*S*,12*S*)-methyl 12-(3-bromo-4-hydroxybenzyl)-9-sec-butyl-6-(4-hydroxy-benzyl)-2,2-dimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate **3.74**



3.73 $C_{20}H_{30}N_2O_6$ (394.46)

3.41 $C_{10}H_{13}BrClNO_3$ (310.57)

3.74 $C_{30}H_{40}BrN_3O_8$ (650.56)

To a solution of carboxylic acid **3.73** (3.26 g, 8.26 mmol) in DMF (82 mL) was added EDCI (1.23 mL, 11.6 mmol), HOBt (1.57 g, 11.6 mmol), hydrochloride salt **3.41** (3.60 g, 11.6 mmol) and DIPEA (4.02 mL, 23.1 mmol). After 16 h the reaction mixture was diluted with H_2O (400 mL) and the products extracted with EtOAc (4 x 150 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (50% EtOAc/petroleum ether–EtOAc) to give the title compound **3.74** (3.66 g, 5.62 mmol, 68%) as an off-white solid.

M.P. 108–112 ^oC (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 2965 br. s, 1645 s, 1511 s, 1440 m, 1366 m, 1222 m, 1161 m, 1046 w, 827 w cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm (rotamer ratio~1:1) 7.35–7.18 (br. m, 2H, O*H*+Ar*H*), 7.03–6.90 (m, 4H, Ar*H*), 6.89–6.79 (m, 2H, Ar*H*+N*H*), 6.75–6.65 (m, 2H, Ar*H*+N*H*), 5.23 (d, *J*=7.6 Hz, 1H, N*H*), 4.87–4.74 (m, 1H, NC*H*CO), 4.47–4.24 (m, 2H, 2xNC*H*CO), 3.70 (s, 0.5 x 3H, CH_3), 3.69 (s, 0.5 x 3H, CH_3), 3.17–2.82 (m, 4H, 2 x CH_2), 2.23 (br. s, 1H, O*H*), 1.86–1.74 (m, 1H, C*H*CH_2CH_3), 1.41 (s, 0.5 x 9H, C(CH_3)$_3$), 1.40 (s, 0.5 x 9H, C(CH_3)$_3$), 1.40–1.39 (m, 1H, C*H*HCH_3), 1.10–0.96 (m, 1H, CH*H*CH_3), 0.84 (d, *J*=7.1 Hz, 0.5 x 3H, CH_3), 0.79 (t, *J*=7.1 Hz, 3H, CH_3), 0.64 (d, *J*=7.1 Hz, 0.5 x 3H, CH_3).

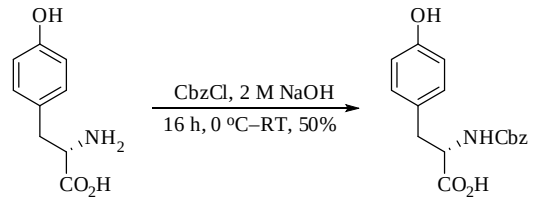
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.2 (*C*), 171.5 (*C*), 155.7 (*C*), 155.3 (*C*), 155.2 (*C*), 151.9 (*C*), 132.9 (*C*H), 130.3 (2 x *C*H), 129.7 (*C*H), 129.3 (*C*), 127.4 (*C*), 116.4 (*C*H), 115.7 (2 x *C*H), 110.0 (*C*), 80.6 (*C*), 57.9 (*C*H), 56.7 (*C*H), 53.4 (*C*H_3), 52.4 (*C*H), 36.9 (*C*H_2), 36.7 (*C*H_2), 36.6 (*C*H), 28.2 ((*C*H_3)$_3$), 26.0 (*C*H_2), 15.2 (*C*H_3), 11.6 (*C*H_3).

LRMS (m/z, ESI$^+$) 674 ([M+Na{^{81}Br}]$^+$, 100%), 672 ([M+Na{^{79}Br}]$^+$, 87%).

HRMS (m/z, ESI$^+$) calcd for $C_{30}H_{40}BrN_3O_8$ [M+Na{^{81}Br}]$^+$ requires 674.1876; found: 674.1871. [M+Na{^{79}Br}]$^+$ requires 672.1896; found: 672.1884.

$[\alpha]_D^{26}$ –6.7 (c = 0.9, MeOH).

(*S*)-2-(Benzyloxycarbonylamino)-3-(4-hydroxyphenyl)propanoic acid **3.78**



3.06 $C_9H_{11}NO_3$ (181.2)

3.78 $C_{17}H_{17}NO_5$ (315.3)

To a solution of L-tyrosine **3.06** (10.0 g, 55.2 mmol) in 2M NaOH (500 mL) at 0 °C was added CbzCl (8.66 mL, 60.7 mmol) dropwise over 15 min. The reaction mixture was warmed to RT and after 16 h was extracted with EtOAc (3 x 100 mL). The aqueous phase was acidified to pH 1 with 6M HCl (150 mL) and then extracted with EtOAc (4 x 100 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.78** (8.70 g, 27.6 mmol, 50%) as a colourless oil that became an off-white solid on standing, used without further purification. These data are in accordance with those reported in the literature.[190]

M.P. 88–92 °C (Et_2O/MeOH), Lit. 92–94 °C (solvent not given).[191]

FT-IR (ν_{max}, neat) 3323 br. m, 3027 m, 2949 w, 1693 s, 1613 m, 1514 s, 1447 m, 1344 m, 1219 s, 1105 w, 1056 s, 829 m, 752 s, 542 w cm^{-1}.

^{1}H NMR (300 MHz, *d*$_4$-MeOD) δ_H ppm 7.36–7.22 (m, 5H, Ar*H*), 7.03 (d, *J*=8.4 Hz, 2H, Ar*H*), 6.69 (d, *J*=8.4 Hz, 2H, Ar*H*), 5.06 (d, *J*=12.8 Hz, 1H, C*H*H), 4.97 (d, *J*=12.8 Hz, 1H, CH*H*), 4.37 (dd, *J*=9.1, 5.1 Hz 1H, NC*H*CO), 3.09 (dd, *J*=13.9, 4.8 Hz, 1H, C*H*H), 2.83 (dd, *J*=13.9, 9.2 Hz, 1H, CH*H*).

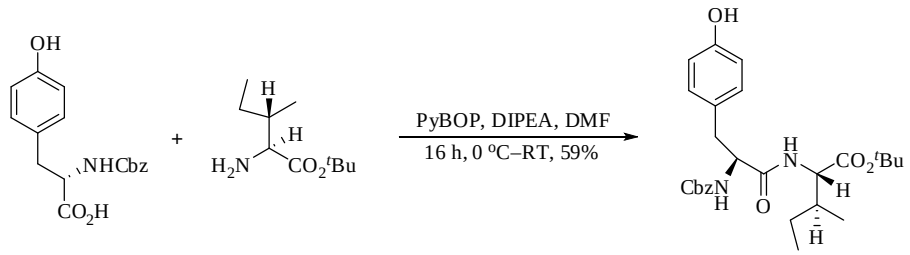
^{13}C NMR (75 MHz, *d*$_4$-MeOD) δ_C ppm 175.4 (*C*), 158.5 (*C*), 157.4 (*C*), 138.4 (*C*), 131.4 (2 x *C*H), 129.6 (2 x *C*H), 129.3 (*C*), 129.0

(*C*H), 128.7 (2 x *C*H), 116.3 (2 x *C*H), 67.6 (*C*H_2), 57.1 (*C*H), 38.1 (*C*H_2).

LRMS (m/z, ESI⁻) 314 ([M–H]⁻, 29%), 206 (100%).

$[\alpha]_D^{28}$ + 1.61 (c = 1.24, MeOH).

tert-Butyl (2*S*,3*S*)-2-((*S*)-3-(4-hydroxyphenyl)-2-(2-oxo-2-phenylethylideneamino)-propanamido)-3-methylpentanoate **3.79**



3.78 $C_{17}H_{15}NO_4$ (297.3)

3.61 $C_{10}H_{21}NO_2$ (187.3)

3.79 $C_{27}H_{34}N_2O_5$ (466.6)

To a solution of carboxylic acid **3.78** (2.47 g, 8.31 mmol) in DMF (50 mL) was added PyBOP (6.50 g, 12.5 mmol) and DIPEA (4.34 mL, 24.9 mmol). After cooling to 0 °C Ile.*O*^{t}Bu **3.61** (1.87 g, 9.97 mmol) was added and the reaction mixture warmed to RT. After 16 h H_2O (500 mL) was added, and the products extracted with EtOAc (4 x 100 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a golden oil. Purification by flash column chromatography (40% EtOAc/petroleum ether) to give the title compound **3.79** (2.29 g, 4.91 mmol, 59%) as a white foamy solid. These data are in accordance with those reported in the literature.[184]

M.P. 67–72 °C (EtOAc/petroleum ether), Lit. 99–101 °C.[184]

FT-IR (ν_{max}, neat) 3317 br. m, 2970 m, 2929 m, 2884 w, 2246 w, 2189 w, 1707 s, 1656 s, 1515 s, 1450 m, 1360 m, 1249 s, 1146 s, 1049 m, 906 m, 837 m, 732 m, 694 m cm^{-1}.

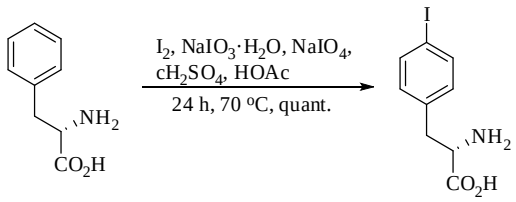
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.37–7.28 (m, 5H, Ar*H*), 6.99 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.70 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.51 (br. s, 1H, O*H*), 6.47 (br. s, 1H, N*H*), 5.43 (d, *J*=7.1 Hz, 1H, N*H*), 5.09 (s, 2H, CH_2), 4.40 (app. dd, *J*=8.1, 4.5 Hz, 2H, NC*H*CO), 3.05–2.94 (m, 2H, CH_2), 1.87–1.76 (m, 1H, C*H*HCH$_3$), 1.46 (s, 9H, C(CH_3)$_3$), 1.43–1.35 (m, 1H, CH*H*CH$_3$), 1.13 (app. sept, *J*=7.3 Hz, 1H, C*H*CH$_2$CH$_3$), 0.90 (t, *J*=7.3 Hz, 3H, CH_3), 0.83 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 170.8 (*C*), 170.4 (*C*), 156.0 (*C*), 155.2 (*C*), 136.1 (*C*), 130.4 (2 x *C*H), 128.5 (2 x *C*H), 128.2 (*C*H), 128.0 (2 x *C*H), 115.6 (2 x *C*H), 82.2 (*C*), 67.1 (*C*H$_2$), 56.9 (*C*H), 56.3 (*C*H), 38.1 (*C*H), 37.6 (*C*H$_2$), 28.0 ((*C*H$_3$)$_3$), 25.3 (*C*H$_2$), 15.2 (*C*H$_3$), 11.6 (*C*H$_3$).

LRMS (m/z, ESI$^+$) 507 ([M+Na]$^+$, 100%).

$[\alpha]_D^{28}$ +12.5 (c = 0.1, CH_2Cl_2).

(*S*)-2-Amino-3-(4-iodophenyl)propanoic acid **3.102**



3.101 $C_9H_{11}NO_2$ (165.19)

3.102 $C_9H_{10}INO_2$ (291.09)

To a solution of L-phenylalanine **3.101** (8.52 g, 51.6 mmol) in HOAc (47 mL) and cH_2SO_4 (6.2 mL) was added I_2 (5.24 g, 20.6 mmol) and $NaIO_3 \cdot H_2O$ (2.23 g, 10.3 mmol). The reaction mixture was heated at 70 ^{o}C and after 24 h was cooled to RT and $NaIO_4$ (400 mg, 1.87 mmol) added. After stirring for a further 30 min, the reaction mixture was concentrated under reduced pressure. The crude mixture was taken up into

H_2O (80 mL) and washed sequentially with Et_2O (40 mL) and CH_2Cl_2 (40 mL). The aqueous phase was taken to pH 5 by careful addition of cNaOH. The white precipitate was collected by filtration, and dried under reduced pressure to give the title compound **3.102** (15.0 g, 51.6 mmol, 100%) as an off-white solid. These data are in accordance with those reported in the literature.[192]

M.P. dec. > 215 ^oC (H_2O), Lit. 260–263 ^oC (H_2O/EtOH).[193]

FT-IR (ν_{max}, neat) 3007 br. m, 2929 m, 2590 w, 2108 w, 1583 s, 1521 m, 1482 m, 1397 m, 1315 m, 1134 s, 1008 m, 853 m, 804 m, 635 m, 618 s, 514 m cm^{-1}.

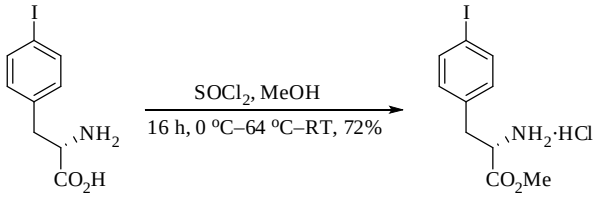
^{1}H NMR (300 MHz, *d*-TFA) δ_H ppm 11.52 (br. s, 1H, CO_2H), 7.68 (d, *J*=6.8 Hz, 2H, Ar*H*), 6.97 (d, *J*=6.8 Hz, 2H, Ar*H*), 4.68–4.59 (m, 1H, NC*H*CO), 3.58–3.42 (m, 1H, C*H*H), 3.34–3.19 (m, 1H, CH*H*).

^{13}C NMR (75 MHz, *d*-TFA) δ_C ppm 175.0 (*C*), 141.6 (2 x *C*H), 133.5 (*C*), 132.9 (2 x *C*H), 96.2 (*C*), 57.6 (*C*H), 37.4 (*C*H_2).

LRMS (m/z, ESI$^+$) 333 ($[M+H+MeCN]^+$, 100%)$^+$.

$[\alpha]_D^{28}$ –9.42 (c = 0.6, HOAc).

Methyl (*S*)-2-amino-3-(4-iodophenyl)propanoate hydrochloride **3.103**



3.102
$C_9H_{10}INO_2$
(291.1)

3.103
$C_{10}H_{13}ClINO_2$
(341.6)

Thionyl chloride (16.1 mL, 222 mmol) was added dropwise to rapidly stirred MeOH (100 mL) at 0 °C over 15 min. After complete addition, acid **3.102** (10.8 g, 37.1 mmol) was added in one portion. The reaction mixture was heated at 64 °C for 3 h. then cooled to RT and concentrated under reduced pressure after 13 h affording a crude beige-coloured solid. Purification by recrystalisation (MeOH/Et_2O) to give the title compound **3.103** (9.08 g, 26.6 mmol, 72%) as a white solid. These data are in accordance with those reported in the literature.[194]

M.P. 196–199 °C (MeOH/Et_2O).

FT-IR (ν_{max}, neat) 3382 br. m, 2949 br. m, 2929 br. m, 2494 br. s, 2226 w, 2067 m, 1743 s, 1580 w, 1485 m, 1442 m, 1401 w, 1246 m, 1118 m, 971 s, 808 m, 480 br. m cm^{-1}.

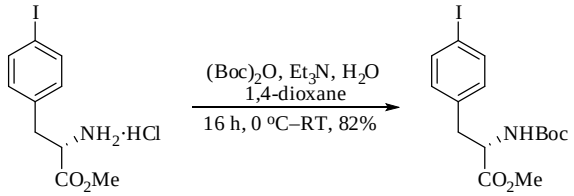
^{1}H NMR (300 MHz, *d*$_4$-MeOD) δ_H ppm 7.73 (d, *J*=8.4 Hz, 2H, Ar*H*), 7.06 (d, *J*=8.4 Hz, 2H, Ar*H*), 4.33 (app. dd, *J*=6.9, 6.2 Hz, 1H, NC*H*CO), 3.81 (s, 3H, CH_3), 3.23 (dd, *J*=14.3, 6.2 Hz, 1H, C*H*H), 3.14 (dd, *J*=14.3, 6.9 Hz, 1H, CH*H*).

^{13}C NMR (75 MHz, *d*$_4$-MeOD) δ_C ppm 170.4 (*C*), 139.4 (2 x *C*H), 135.3 (*C*), 132.6 (2 x *C*H), 94.3 (*C*), 54.9 (*C*H), 53.7 (*C*H_3), 37.0 (*C*H_2).

LRMS (m/z, ESI$^+$) 306 ($[M–HCl+H]^+$, 2%), 154 (100%).

$[\alpha]_D^{25}$ + 8.36 (c = 0.67, MeOH).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-iodophenyl)propanoate **3.104**



3.103

$C_{10}H_{13}ClINO_2$
(341.57)

3.104

$C_{15}H_{20}INO_4$
(405.23)

To a solution of hydrochloride salt **3.103** (500 mg, 1.46 mmol) in 1,4-dioxane/water (1:1, 20 mL) at 0 °C was added $(Boc)_2O$ (382 mg, 1.75 mmol) and Et_3N (408 µL, 2.92 mmol). The reaction mixture was warmed to RT and after 16 h was concentrated under reduced pressure giving a crude solid that was taken up in EtOAc (30 mL) and washed sequentially with sat. NH_4Cl (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compound **3.104** (481 mg, 1.19 mmol, 82%) as a white solid. These data are in accordance with those reported in the literature.[195]

M.P. 68–73 °C (EtOAc/petroleum ether), Lit. 79–80 °C.[195]

FT-IR (ν_{max}, neat) 3464 w, 3362 br. m, 2974 m, 2917 m, 2847 w, 1742 s, 1709 s, 1495 m, 1486 s, 1433 m, 1364 m, 1249 m, 1214 m, 1163 s, 1058 m, 1007 m, 816 w, 800 w cm^{-1}.

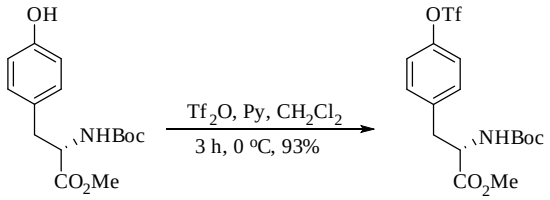
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.62 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.88 (d, *J*=8.1 Hz, 2H, Ar*H*), 4.98 (d, *J*=7.1 Hz, 1H, N*H*), 4.57 (app. br. q, *J*=6.5 Hz, 1H, NC*H*CO), 3.72 (s, 3H, CH_3), 3.08 (dd, *J*=13.8, 5.6 Hz, 1H, C*H*H), 2.98 (dd, *J*=13.8, 6.1 Hz, 1H, CH*H*), 1.42 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.0 (*C*), 154.9 (*C*), 137.6 (2 x *C*H), 135.7 (*C*), 131.3 (2 x *C*H), 92.5 (*C*), 80.1 (*C*), 54.2 (*C*H), 52.3 (*C*H_3), 37.9 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 469 ([M+Na+MeCN]$^+$, 46%)$^+$, 457 (100%).

$[\alpha]_D^{29}$ + 66.2 (c = 0.5, CH_2Cl_2).

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-3-(4-(trifluoromethylsulfonyloxy)-phenyl)-propanoate **3.105**



3.10 $C_{15}H_{21}NO_5$ (295.33)

3.105 $C_{16}H_{20}F_3NO_7S$ (427.39)

To a solution of phenol **3.10** (5.00 g, 16.9 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added pyridine (4.10 mL, 50.7 mmol) followed by Tf_2O (2.98 mL, 17.7 mmol) dropwise over 10 min. After 3 h H_2O (100 mL) was added. The organic phase was separated then washed sequentially with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a yellow oil. Purification by flash column chromatography (1% MeOH/CH_2Cl_2) to give the title compound **3.105** (6.71 g, 15.7 mmol, 93%) as a white solid. These data are in accordance with those reported in the literature.[196]

M.P. 54–58 °C (MeOH/CH_2Cl_2), Lit. 48–49 °C.[197]

FT-IR (ν_{max}, neat) 3440 w, 3358 br. w, 2974 w, 1744 m, 1708 m, 1501 m, 1421 m, 1360 m, 1248 m, 1207 s, 1164 s, 1135 s, 1053 m, 1017 m, 885 s, 732 m, 607 m cm^{-1}.

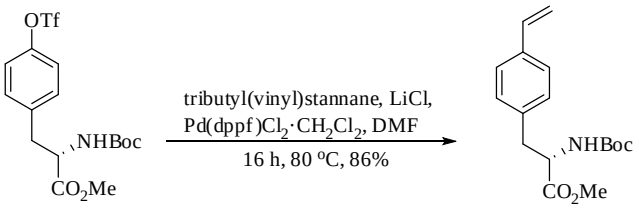
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.22 (d, *J*=8.6 Hz, 2H, Ar*H*), 7.18 (d, *J*=8.6 Hz, 2H, Ar*H*), 5.13 (d, *J*=6.6 Hz, 1H, N*H*), 4.57 (br. m, *J*=5.6 Hz, 1H, NC*H*CO), 3.68 (s, 3H, CH_3), 3.15 (dd, *J*=13.2, 5.1 Hz, 1H, C*H*H), 3.01 (dd, *J*=13.2, 6.3 Hz, 1H, CH*H*,) 1.37 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.7 (*C*), 154.9 (*C*), 148.5 (*C*), 136.9 (*C*), 131.0 (2 x *C*H), 121.2 (2 x *C*H), 118.7 (q, *J*=320 Hz, *C*F_3) 79.9 (*C*), 54.2 (*C*H), 52.2 (*C*H_3), 37.7 (*C*H_2), 28.1 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 450 ($[M+Na]^+$, 100%).

$[\alpha]_D^{26}$ + 27.4 (c = 1.17, CH_2Cl_2).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-vinylphenyl)propanoate **3.106**



3.105
$C_{16}H_{20}F_3NO_7S$
(427.39)

3.106
$C_{17}H_{23}NO_4$
(305.37)

To a solution of triflate **3.105** (8.00 g, 18.7 mmol) in DMF (53.4 mL) was added tributyl(vinyl)stannane (6.02 mL, 20.6 mmol) and LiCl (1.11 g, 26.2 mmol). The solution was degassed under argon by immersion in a sonication bath for 30 min then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (764 mg, 935 μmol) was added. The reaction mixture was heated at 80 ^{o}C for 16 h then cooled to RT, diluted with H_2O (500 mL) and extracted with EtOAc (4 x 200 mL). The combined organic phases were washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (10% w/w K_2CO_3/silica,[182] 0–10% EtOAc/petroleum ether) to give the title compound **3.106** (4.92 g, 16.1 mmol,

86%) as a white solid. These data are in accordance with those reported in the literature.[198]

M.P. 47–50 ^{o}C (EtOAc/petroleum ether), Lit. reported a colourless oil.

FT-IR (ν_{max}, neat) 3436 br. w, 3362 br. m, 2998 w, 2974 m, 2949 w, 2925 w, 1748 s, 1710 s, 1506 m, 1429 m, 1364 m, 1245 m, 1163 s, 1061 m, 980 m, 824 m cm^{-1}.

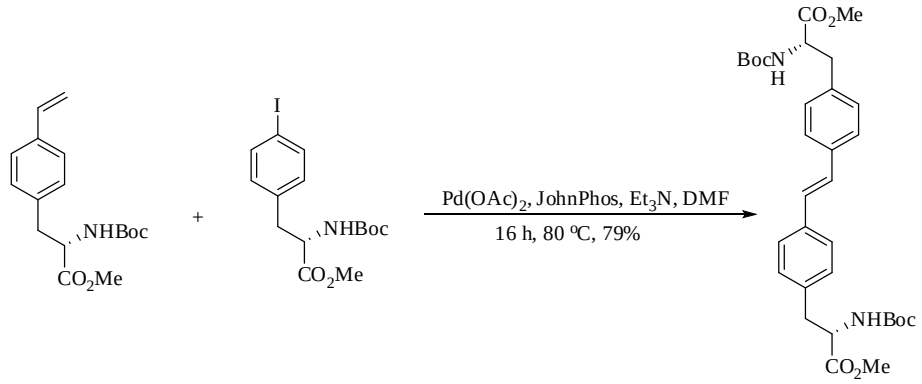
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.34 (d, *J*=7.8 Hz, 2H, Ar*H*), 7.09 (d, *J*=7.8 Hz, 2H, Ar*H*), 6.69 (dd, *J*=17.5, 10.8 Hz, 1H, ArC*H*=CH_2), 5.73 (d, *J*=17.5 Hz, 1H, ArCH=C*H*H), 5.23 (d, *J*=10.8 Hz, 1H, ArCH=CH*H*), 4.98 (d, *J*=6.6 Hz 1H, N*H*), 4.59 (app. br. q, *J*=6.6 Hz, 1H, NC*H*CO), 3.72 (s, 3H, CH_3), 3.11 (dd, *J*=13.8, 5.6 Hz, 1H, CH*H*), 3.04 (dd, *J*=13.8, 6.1 Hz, 1H, C*H*H), 1.42 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.3 (*C*), 155.1 (*C*), 136.4 (*C*H), 135.6 (*C*), 129.4 (2 x *C*H), 126.4 (2 x *C*H), 113.7 (*C*H_2), 79.9 (*C*), 54.4 (*C*H), 52.2 (*C*H_3), 38.0 (*C*H_2), 28.3 ((*C*H_3)$_3$). *NB. One quaternary resonance not observed.*

LRMS (m/z, ESI^{+}) 633 ([2M+Na]$^{+}$, 2%), 369 ([M+Na+MeCN]$^{+}$, 100%), 369 ([M+Na]$^{+}$, 36%),

$[\alpha]_D^{28}$ + 49 (c = 0.98, CH_2Cl_2).

Dimethyl (2*S*,2'*S*)-3,3'-(4,4'-((*E*)-ethene-1,2-diyl)bis(4,1-phenylene))bis(2-(*tert*-butoxycarbonylamino)propanoate) **3.107**



3.106 $C_{17}H_{23}NO_4$ (305.37)

3.104 $C_{15}H_{20}INO_4$ (405.23)

3.107 $C_{32}H_{42}N_2O_8$ (582.68)

A solution of styrene **3.106** (1.00 g, 3.27 mmol), iodide **3.104** (1.32 g, 3.27 mmol) and Et_3N (1.97 mL, 14.1 mmol) in DMF (30 mL) was degassed for *ca.* 30 min under argon by immersion in a sonication bath prior to the addition of $Pd(OAc)_2$ (73.4 mg, 377 µmol) and JohnPhos (195 mg, 654 µmol). The reaction mixture was heated at 80 ^oC for 16 h then cooled to RT, diluted with H_2O (500 mL) and extracted with EtOAc (5 x 150 mL). The combined organic phases were washed with brine (400 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (5–20% EtOAc/petroleum ether) to give the title compound **3.107** (1.51 mg, 2.59 mmol, 79%) as a white foamy solid.

M.P. 57–62 ^oC (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3436 w, 3366 br. m, 2978 m, 2949 w, 2929 w, 1741 s, 1707 s, 1503 s, 1356 s, 1249 m, 1215 m, 1163 s, 1057 m, 1012 m, 732 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.43 (d, *J*=8.1 Hz, 4H, Ar*H*), 7.12 (d, *J*=8.1 Hz, 4H, Ar*H*), 7.05 (s, 2H, C*H*), 5.01 (d, *J*=7.6 Hz, 2H, N*H*), 4.60 (br. q, *J*=6.6 Hz, 2H, NC*H*CO), 3.73 (s, 6H, CH_3), 3.13

(dd, *J*=13.6, 6.1 Hz, 2H, C*H*H), 3.06 (dd, *J*=14.2, 6.1 Hz, 2H, CH*H*), 1.43 (s, 18H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.3 (2 x *C*), 155.0 (2 x *C*), 136.1 (2 x *C*), 135.5 (2 x *C*), 129.6 (4 x *C*H), 128.1 (2 x *C*H), 126.6 (4 x *C*H), 79.9 (2 x *C*), 54.4 (2 x *C*H), 52.2 (2 x *C*H_3), 38.1 (2 x *C*H_2), 28.3 (2 x (*C*H_3)$_3$).

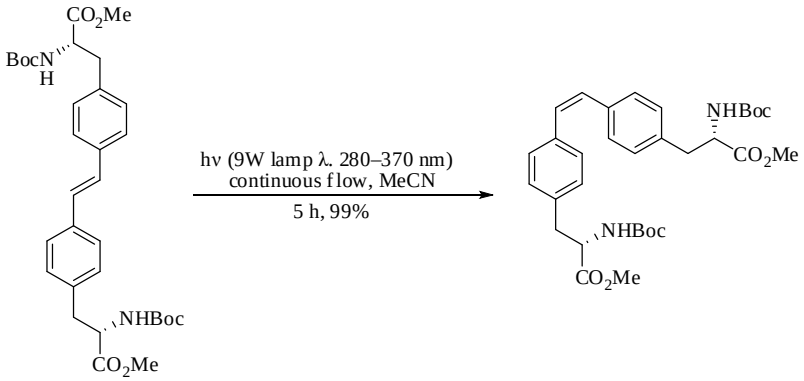
LRMS (m/z, ESI$^+$) 1187 ([2M+Na]$^+$, 7%), 605 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{32}H_{42}N_2O_8$ [M+Na]$^+$ requires 605.2839; found: 605.2834.

UV (MeCN) λ_{max} (ε), 328 inf (21802); 314.3 (34011); 301.7 (33720) nm.

$[\alpha]_D^{28}$ + 67.5 (c = 0.595, CH_2Cl_2).

(2*S*,2'*S*)-Dimethyl 3,3'-(4,4'-((*Z*)-ethene-1,2-diyl)bis(4,1-phenylene))bis(2-(*tert*-butoxycarbonylamino)propanoate) **3.108**



3.107
$C_{32}H_{42}N_2O_8$
(582.68)

3.108
$C_{32}H_{42}N_2O_8$
(582.68)

A solution of stilbene **3.107** (100 mg, 172 μmol) in degassed acetonitrile (17.2 mL) was irradiated under continuous flow by a 9 W Philips broad-spectrum light source (PL-S

9W/12/2P, 280–370 nm) for a residence time of 5 h controlled by a Vapourtec R4/R2+ flow device. The reaction mixture was concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (10–30% EtOAc/petroleum ether) to give the title compound **3.108** as a pale yellow oil (99.6 mg, 171 μmol, 99%).

FT-IR (ν_{max}, neat) 3432 w, 3358 br. m, 2974 m, 2925 w, 2246 w, 1742 s, 1708 s, 1503 m, 1437 m, 1365 m, 1249 m, 1164 s, 1061 m, 1008 m, 730 m cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm 8.40 (br. s, 1H, C*H*), 7.83 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.69 (br. s, 1H, C*H*), 7.39 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.17 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.99 (d, *J*=7.7 Hz, 2H, Ar*H*), 5.12–4.95 (m, 2H, N*H*), 4.79–4.67 (br. m, 1H, NC*H*CO), 4.65–4.50 (br. m, 1H, NC*H*CO), 3.74 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.41–3.30 (m, 2H, CH_2), 3.11–2.96 (m, 2H, CH_2), 1.41 (s, 18H, 2 x C(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C ppm 172 4 (*C*), 172.3 (*C*), 155.1 (2 x *C*), 134.9 (*C*), 134.4 (*C*), 131.1 (*C*), 129.9 (*C*), 129.8 (*C*H), 129.6 (*C*H), 129.1 (2 x *C*H), 128.9 (2 x *C*H), 128.8 (*C*H), 127.8 (*C*H), 126.4 (*C*H), 123.0 (*C*H), 80.0 (*C*), 79.9 (*C*), 54.7 (*C*H), 54.3 (*C*H), 52.3 (*C*H_3), 52.2 (*C*H_3), 38.9 (*C*H_2), 38.1 (*C*H_2), 28.2 ((2 x *C*H_3)$_3$).

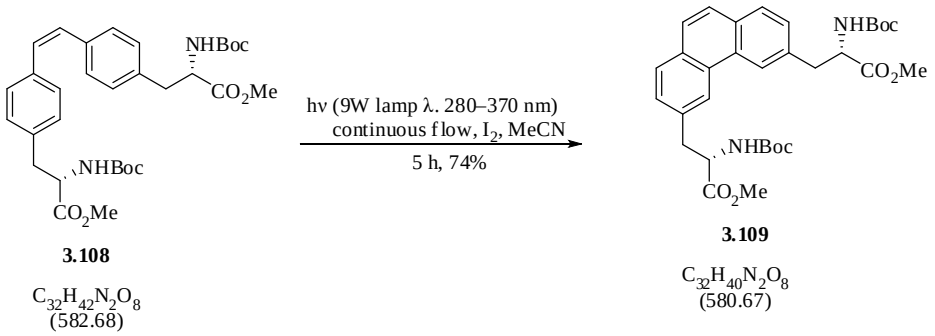
LRMS (m/z, ESI$^+$) 641 ($[M+NH_4+MeCN]^+$, 31%), 605 ($[M+Na]^+$, 15%), 242 (100%).

HRMS (m/z, ESI$^+$) calcd for $C_{32}H_{42}N_2O_8$ $[M+Na]^+$ requires 605.2839; found: 605.2831.

UV (MeCN) λ_{max} (ε), 299 (6950); 288 inf (6950); 279 inf (7950); 255 (20000), 227 (13200) nm.

$[\alpha]_D^{29}$ + 49.6 (c = 0.455, CH_2Cl_2).

Dimethyl (2*S*,2'*S*)-3,3'-(phenanthrene-3,6-diyl)bis(2-(*tert*-butoxycarbonylamino)-propanoate) **3.109**



3.108

$C_{32}H_{42}N_2O_8$
(582.68)

3.109

$C_{32}H_{40}N_2O_8$
(580.67)

A solution of stilbene **3.108** (100 mg, 172 µmol) and I_2 (one crystal) in degassed acetonitrile (17.2 mL) was irradiated under continuous flow by a 9 W Philips broad-spectrum light source (PL-S 9W/12/2P, 280–370 nm) for a residence time of 5 h controlled by a Vapourtec R4/R2+ flow device. The reaction mixture was concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (10–30% EtOAc/petroleum ether) to give the title compound **3.109** (73.7 mg, 127 µmol, 74%) as a pale orange oil.

FT-IR (ν_{max}, neat) 3436 w, 3362 m, 2974 m, 2921 m, 2847 w, 1743 s, 1710 s, 1609 w, 1504 m, 1437 m, 1365 m, 1221 m, 1165 s, 1061 m, 1021 m, 849 m, 726 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.41 (br. s, 2H, 2 x C*H*), 7.83 (d, *J*=8.1 Hz, 2H, 2 x Ar*H*), 7.69 (br. s, 2H, 2 x C*H*), 7.40 (d, *J*=8.1 Hz, 2H, 2 x Ar*H*), 5.06 (br. s, 2H, 2 x N*H*), 5.73 (br. s, 2H, 2 x NC*H*CO), 3.74 (s, 6H, 2 x CH_3), 3.42–3.31 (m, 4H, 2 x CH_2), 1.41 (br. s, 18H, 2 x C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.4 (2 x *C*), 155.1 (2 x *C*), 134.4 (2 x *C*), 131.2 (2 x *C*), 130.0 (2 x *C*), 128.9 (2 x *C*H), 127.9 (2 x

*C*H), 126.4 (2 x *C*H), 123.1 (2 x *C*H), 79.9 (2 x *C*), 54.7 (2 x *C*H), 52.3 (2 x CH_3), 38.9 (2 x CH_2), 28.3 ((2 x CH_3)$_3$).

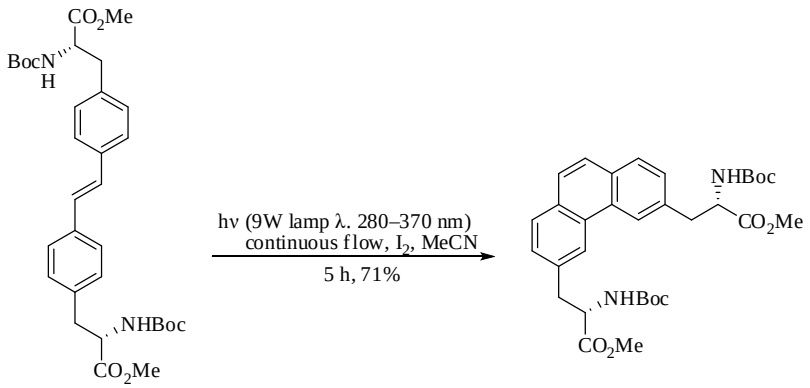
LRMS (m/z, ESI$^+$) 603 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{32}H_{40}N_2O_8$ [M+Na]$^+$ requires 603.2682; found: 603.2677.

UV (MeCN) λ_{max} (ε), 299 (10900); 256 (50300); 225 (22100) nm.

$[\alpha]_D^{27}$ + 42.4 (c = 0.35, CH_2Cl_2).

Dimethyl (2*S*,2'*S*)-3,3'-(phenanthrene-3,6-diyl)bis(2-(*tert*-butoxycarbonylamino)-propanoate) **3.109**

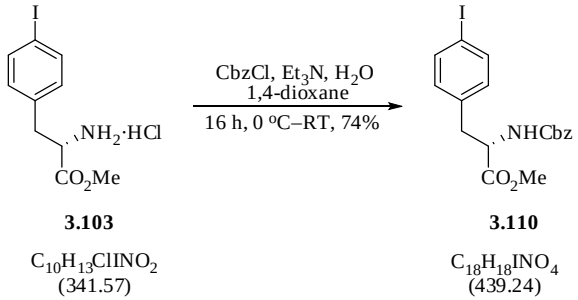


3.107
$C_{32}H_{42}N_2O_8$
(582.68)

3.109
$C_{32}H_{40}N_2O_8$
(580.67)

A solution of stilbene **3.107** (100 mg, 172 µmol) and I_2 (one crystal) in degassed acetonitrile (17.2 mL) was irradiated under continuous flow by a 9 W Philips broad-spectrum light source (PL-S 9W/12/2P, 280–370 nm) for a residence time of 5 h controlled by a Vapourtec R4/R2+ flow device. The reaction mixture was concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (10–30% EtOAc/petroleum ether) to give the title compound **3.109** (70.8 mg, 122 µmol, 71%) as a pale orange oil.
Data matches those reported previously.

Methyl (*S*)-2-(benzyloxycarbonylamino)-3-(4-iodophenyl)propanoate **3.110**



3.103

$C_{10}H_{13}ClINO_2$
(341.57)

3.110

$C_{18}H_{18}INO_4$
(439.24)

To a solution of hydrochloride salt **3.103** (31.0 g, 90.8 mmol) in 1,4-dioxane/water (1:1, 400 mL) at 0 °C was added Et_3N (13.9 mL, 99.9 mmol) followed by CbzCl (14.3 mL, 99.9 mmol) and Et_3N (13.9 mL, 99.9 mmol). The reaction mixture was warmed to RT and after 16 h was concentrated to ~100 mL, and EtOAc (300 mL) added. The organic phase was washed sequentially with 2M HCl (200 mL), sat. $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compound **3.110** (29.6 g, 67.4 mmol, 74%) as a white solid. These data are in accordance with those reported in the literature.[192]

M.P. 110–111 °C (EtOAc/petroleum ether), Lit. (not given).[192]

FT-IR (ν_{max}, neat) 3325 br. m, 3060 w, 3027 w, 2949 m, 1702 s, 1517 s, 1485 m, 1438 m, 1346 m, 1252 m, 1210 s, 1056 s, 1007 m, 743 m, 696 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.59 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.41–7.30 (m, 5H, Ar*H*), 6.84 (d, *J*=8.1 Hz, 2H, Ar*H*), 5.25 (d, *J*=7.6 Hz, 1H, N*H*), 5.13 (d, *J*=12.1 Hz, 1H, CH*H*), 5.06 (d, *J*=12.1 Hz, 1H, C*H*H), 4.70–4.59 (m, 1H, NC*H*CO), 3.73 (s, 3H, CH_3), 3.11 (dd, *J*=13.8, 5.6 Hz, 1H, C*H*H), 3.01 (dd, *J*=13.8, 6.1 Hz, 1H, CH*H*).

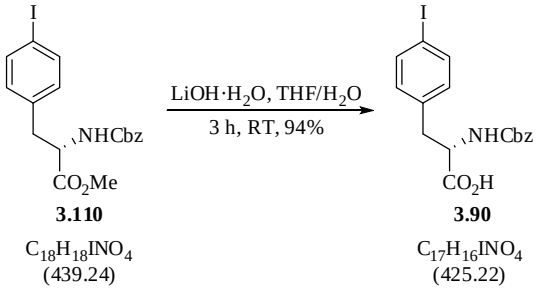
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.6 (*C*), 155.5 (*C*), 137.6 (2 x *C*H), 136.1 (*C*), 135.4 (*C*), 131.2 (2 x *C*H), 128.5 (2 x *C*H), 128.2 (*C*H), 128.1 (2 x *C*H), 92.6 (*C*), 67.0 (*C*H_2), 54.6 (*C*H), 52.4 (*C*H_3), 37.8 (*C*H_2).

LRMS (m/z, ESI$^+$) 469 ([2M+Na]$^+$, 100%), 503 ([M+Na+MeCN]$^+$, 50%), 462 ([M+Na]$^+$, 35%).

HRMS (m/z, ESI$^+$) calcd for $C_{18}H_{18}INO_4$ [M+Na]$^+$ requires 462.0178; found: 462.0181.

$[\alpha]_D^{27}$ + 40.8 (c = 1.27, CH_2Cl_2).

(*S*)-2-(Benzyloxycarbonylamino)-3-(4-iodophenyl)propanoic acid **3.90**



To a solution of ester **3.110** (8.59 g, 37.1 mmol) in THF/water (1:1 v/v, 130 mL) was added $LiOH·H_2O$ (3.26 g, 77.7 mmol). After 3 h the reaction mixture was concentrated under reduced pressure and the crude residue partitioned between EtOAc (200 mL) and 2M NaOH (200 mL). The aqueous phase was washed with EtOAc (200 mL) and then acidified to pH 2 by slow addition of 2M HCl (350 mL). The products were extracted with EtOAc (3 x 200 mL) then the combined organic phases were washed with brine (300 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **3.90** (10.4 g, 24.3 mmol, 94%) as a white solid, that was used without further purification. These data are in accordance with those reported in the literature.[63]

M.P. 151–154 ^oC (EtOAc), Lit. 161–162 ^oC (MeOH).[199]

FT-IR (ν_{max}, neat) 3309 m, 3064 br. m, 2929 w, 2357 m, 2332 m, 1696 s, 1530 s, 1325 m, 1259 m, 1222 s, 1058 s, 1006 m, 882 m, 826 w, 810 m, 736 s, 667 s, 550 m cm^{-1}.

^{1}H NMR (400 MHz, d_6-acetone) δ_H ppm 7.64 (d, *J*=8.4, Hz, 2H, Ar*H*), 7.39–7.25 (m, 5H, Ar*H*), 7.12 (d, *J*=8.4, Hz, 2H, Ar*H*), 6.55 (d, *J*=8.1 Hz, 1H, N*H*), 5.07 (d, *J*=12.8 Hz, 1H, CH*H*), 5.01 (d, *J*=12.8 Hz, 1H, C*H*H), 4.50 (app. q, *J*=8.6 Hz, 1H, NC*H*CO), 3.22 (dd, *J*=13.5, 4.5 Hz, 1H, C*H*H), 2.99 (dd, *J*=13.5, 9.3 Hz, 1H, CH*H*).

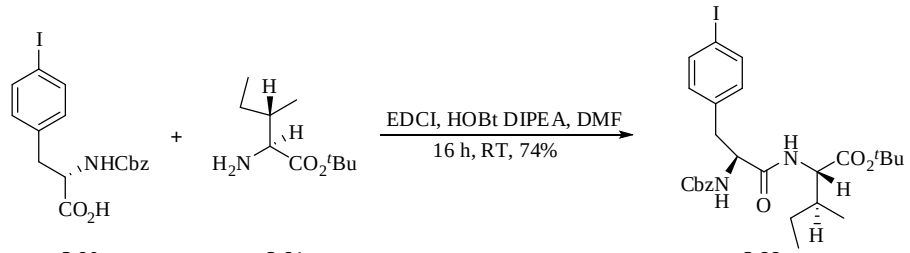
^{13}C NMR (100 MHz, d_6-acetone) δ_C ppm 173.2 (*C*), 156.9 (*C*), 138.5 (*C*), 138.3 (2 x *C*H), 138.2 (*C*H), 132.6 (2 x *C*H), 131.2 (*C*), 129.3 (2 x *C*H), 128.7 (*C*H), 128.6 (*C*H), 93.4 (*C*), 66.8 (CH_2), 55.9 (*C*H), 37.7 (CH_2).

LRMS (m/z, ESI$^-$) 424 ($[M–H]^-$, 37%), 316 (100%).

HRMS (m/z, ESI$^+$) calcd for $C_{17}H_{16}INO_4$ $[M+Na]^+$ requires 448.0022; found: 448.0024.

$[\alpha]_D^{26}$ –13.3 (c = 0.75, acetone).

tert-Butyl (2*S*,3*S*)-2-((*S*)-2-(benzyloxycarbonylamino)-3-(4-iodophenyl)-propanamido)-3-methylpentanoate **3.88**



3.90 $C_{17}H_{16}INO_4$ (425.22)

3.61 $C_{10}H_{21}NO_2$ (187.3)

3.88 $C_{27}H_{35}IN_2O_5$ (594.48)

To a solution of carboxylic acid **3.90** (500 mg, 1.18 mmol) in DMF (15 mL) was added EDCI (292 µL, 1.65 mmol), HOBt (223 mg, 1.65 mmol), Ile.*O*^{t}Bu **3.61** (3.09 mg, 1.65 mmol) and DIPEA (575 µL, 3.30 mmol). After 16 h H_2O (400 mL) was added, and the products extracted with EtOAc (4 x 100 mL). The combined organic phases were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to affording a golden oil. Purification by flash column chromatography (0–10% EtOAc/petroleum ether) to give the title compound **3.88** (519 mg, 873 µmol, 74%) as a white foamy solid. These data are in accordance with those reported in the literature.[119]

M.P. 50–52 ^{o}C (EtOAc/petroleum ether), Lit. reported an oil.[119]

FT-IR (ν_{max}, neat) 3301 br. m, 2966 m, 2929 m, 2872 w, 1732 m, 1703 m, 1655 s, 1537 s, 1364 m, 1254 m, 1143 m, 1057 w, 733 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.58 (d, *J*=8.1 Hz, 2H, Ar*H*) 7.40–7.29 (m, 5H, Ar*H*), 6.93 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.36 (d, *J*=7.6 Hz, 1H, N*H*), 5.36 (d, *J*=7.1 Hz, 1H, N*H*), 5.10 (s, 2H, CH_2), 4.47–4.41 (m, 1H, NC*H*CO), 4.39 (dd, *J*=8.1, 4.5 Hz, 1H, NC*H*CO), 3.08–2.96 (m, 2H, CH_2), 1.88–1.77 (m, 1H, C*H*CH$_2$CH$_3$), 1.46 (s, 9H, C(CH_3)$_3$), 1.43–1.34 (m, 1H, CH*H*CH$_3$), 1.18–1.05 (m, 1H, C*H*HCH$_3$), 0.91 (t, *J*=7.3 Hz, 3H, CH_3), 0.83 (d, *J*=6.6 Hz, 3H, CH_3).

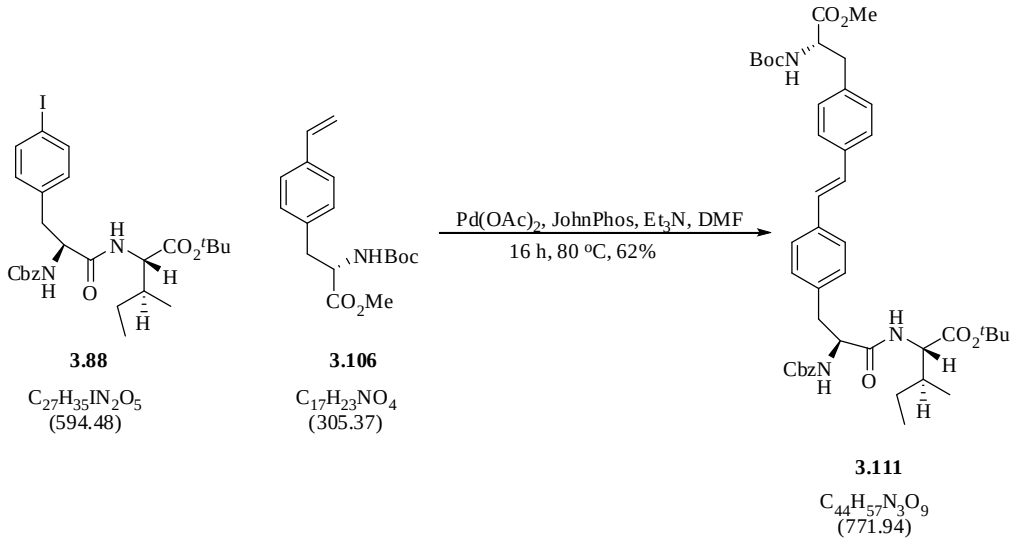
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 170.3 (*C*), 169.9 (*C*), 155.8 (*C*), 137.7 (2 x *C*H), 136.1 (*C*), 135.9 (*C*), 131.4 (2 x *C*H), 128.5 (2 x *C*H), 128.2 (*C*H), 128.0 (2 x *C*H), 92.5 (*C*), 82.2 (*C*), 67.1 (*C*H_2), 56.8 (*C*H), 55.9 (*C*H), 38.1 (*C*H), 37.9 (*C*H_2), 28.0 ((*C*H_3)$_3$), 25.3 (*C*H_2), 15.2 (*C*H_3), 11.7 (*C*H_3).

LRMS (m/z, ESI$^+$) 617 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{27}H_{35}IN_2O_5$ [M+Na]$^+$ requires 617.1488; found: 617.1483.

$[\alpha]_D^{25}$ +15.2 (c = 0.75, CH_2Cl_2).

<u>*tert*-Butyl (2*S*,3*S*)-*tert*-butyl 2-((*S*)-2-(benzyloxycarbonylamino)-3-(4-(4-((*S*)-2-(*tert*-butoxy-carbonylamino)-3-methoxy-3-oxopropyl)styryl)phenyl)-propanamido)-3-methyl-pentanoate **3.111**</u>



A solution of styrene **3.106** (1.05 g, 3.45 mmol), iodide **3.88** (2.05 g, 3.45 mmol) and Et_3N (2.06 mL, 14.8 mmol) in DMF (34 mL) was degassed under argon for *ca.* 30 min by immersion in a sonication bath prior to the addition of $Pd(OAc)_2$ (77.4 mg, 345 µmol) and JohnPhos (206 mg, 690 µmol). The reaction mixture was heated at 80 °C for 16 h then cooled to RT, diluted with H_2O (600 mL) and extracted with EtOAc (4 x

150 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (0–20% EtOAc/petroleum ether) to give the title compound **3.111** (1.65 g, 2.14 mmol, 62%) as a white foamy solid.

M.P. 63–66 ^{o}C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3427 w, 3333 br. m, 3023 w, 2966 m, 2925 m, 2876 w, 1710 s, 1661 s, 1514 s, 1450 m, 1366 s, 1251 s, 1161 s, 1053 m, 906 m, 732 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.43 (d, *J*=8.6 Hz, 2H, Ar*H*), 7.41 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.37–7.31 (m, 5H, Ar*H*), 7.18 (d, *J*=8.6 Hz, 2H, Ar*H*), 7.12 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.03 (s, 2H, 2 x C*H*), 6.31 (d, *J*=8.1 Hz, 1H, N*H*), 5.33 (br. d, *J*=6.1 Hz, 1H, N*H*), 5.13 (d, *J*=12.5 Hz, 1H, CH*H*), 5.09 (d, *J*=12.5 Hz, 1H, C*H*H), 5.00 (br. d, *J*=7.6 Hz, 1H, N*H*), 4.60 (br. app. q, *J*=5.8 Hz, 1H, NC*H*CO), 4.48–4.42 (m, 1H, NC*H*CO), 4.39 (dd, *J*=8.1, 4.6 Hz, 1H, NC*H*CO), 3.74 (s, 3H, CH_3), 3.19–3.01 (m, 4H, CH_2), 1.86–1.78 (m, 1H, C*H*CH_2CH_3), 1.44 (s, 9H, C(CH_3)$_3$), 1.44–1.41 (m, 1H, C*H*HCH_3), 1.43 (s, 9H, C(CH_3)$_3$), 1.17–1.04 (m, 1H, CH*H*CH_3), 0.91 (t, *J*=7.3 Hz, 3H, CH_3), 0.82 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.3 (*C*), 170.2 (*C*), 170.1 (*C*), 155.8 (*C*), 155.0 (*C*), 136.1 (*C*), 135.6 (*C*), 135.4 (*C*), 129.7 (2 x *C*H), 129.6 (2 x *C*H), 128.5 (2 x *C*H), 128.2 (2 x *C*H), 128.1 (*C*H), 128.0 (2 x *C*H), 127.2 (*C*), 126.8 (2 x *C*H), 126.6 (2 x *C*H), 82.2 (*C*), 79.9 (*C*), 67.1 (*C*H_2), 56.8 (2 x *C*H), 56.1 (*C*H), 54.4 (*C*H), 52.2 (*C*H_3), 38.1 (*C*H_2), 29.7 (*C*H_2), 28.3 ((*C*H_3)$_3$), 28.0 ((*C*H_3)$_3$), 25.4 (*C*H_2), 15.2 (*C*H_3), 11.7 (*C*H_3). *NB. One quaternary resonance not observed.*

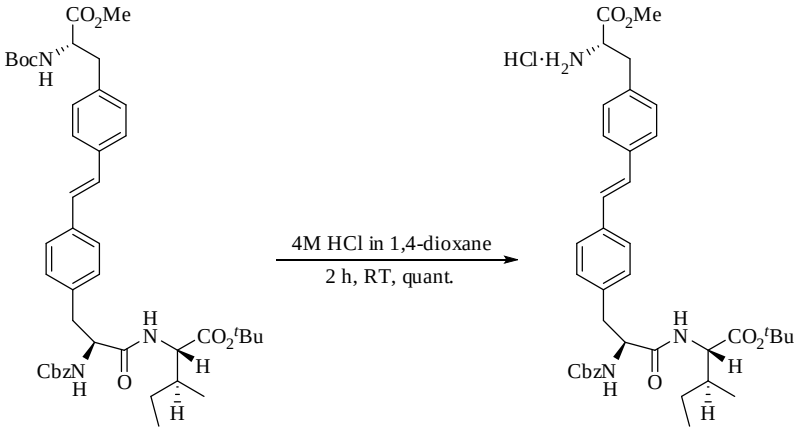
LRMS (m/z, ESI$^+$) 794 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{44}H_{57}N_3O_9$ [M+Na]$^+$ requires 794.3993; found: 794.3987.

UV (MeCN) λ_{max} (ε), 329.4 inf (18400); 316 (32300); 303 (31500), 289.5 inf (26900) nm.

$[\alpha]_D^{25}$ + 48.8 (c = 0.5, $CHCl_3$).

tert-Butyl (2*S*,3*S*)-2-((*S*)-3-(4-(4-((*S*)-2-amino-3-methoxy-3-oxopropyl)styryl)-phenyl)-2-(benzyloxycarbonylammonium)propanamido)-3-methylpentanoate hydrochloride **3.112**



A solution of styrene **3.111** (100 mg, 129 µmol) in 4M HCl in 1,4-dioxane (4 mL, 440 µmol) was stirred at RT for 2 h. After this time the reaction mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (10 mL) and concentrated under reduced pressure (x3) to effect the azeotropic removal of residual HCl/1,4–dioxane, to give the title compound **3.112** (84.0 mg, 129 µmol, quant.) as a white foamy solid.

FT-IR (ν_{max}, neat) 3321 br. w, 3027 w, 2963 br. m, 2931 m, 2878 m, 2484 br. w, 1734 s, 1701 s, 1516 s, 1451 s, 1367 m, 1248 s, 1145 s, 1045 m, 959 w, 735 w, 694 m cm^{-1}.

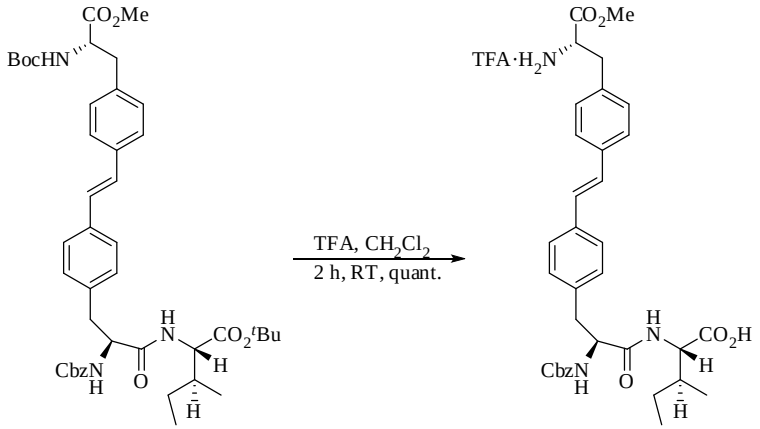
^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ_H ppm 7.56 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.44 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.32–7.21 (m, 10H, Ar*H*+2 x C*H*), 7.16–7.12 (br. m, 1H, Ar*H*), 5.01 (br. s, 2H, N*H*), 4.50 (dd, *J*=9.6, 5.1 Hz, 1H, NC*H*CO), 4.42–4.24 (m, 2H, NC*H*CO), 3.82 (s, 2H, CH_2), 3.65 (s, 3H, CH_3), 3.28–3.09 (m, 4H, CH_2), 1.55–1.47 (m, 1H, C*H*CH_2CH_3), 1.45 (s, 9H, C(CH_3)$_3$), 1.31–1.17 (m, 2H, CH_2CH_3), 0.97–0.84 (m, 6H, 2 x CH_3). *NB: 3 x NH not observed.*

^{13}C NMR (100 MHz, *d*$_4$-MeOH) δ_C ppm 174.0 (*C*), 172.0 (*C*), 170.6 (*C*), 158.3 (*C*), 138.8 (*C*), 138.3 (*C*), 137.3 (*C*), 134.5 (*C*), 131.0 (2 x *C*H), 130.9 (2 x *C*H), 130.2 (*C*H), 129.6 (2 x *C*H), 129.0 (2 x *C*H), 128.8 (2 x *C*H), 128.3 (2 x *C*H), 127.8 (2 x *C*H), 83.1 (*C*), 68.3 (*C*H_2), 58.9 (*C*H), 57.7 (*C*H), 55.3 (*C*H), 53.8 (*C*H_3), 38.9 (*C*H), 37.3 (2 x *C*H_2), 28.5 ((*C*H_3)$_3$), 26.5 (*C*H_2), 16.0 (*C*H_3), 11.9 (*C*H_3). *NB: 1 x quaternary resonance not observed.*

HRMS (m/z, ESI$^+$) calcd for $C_{39}H_{49}N_3O_7$ $[M+Na]^+$ requires 694.3468; found: 694.3463.

$[\alpha]_D^{24}$ + 2.5 (c = 0.2, MeOH).

(2*S*,3*S*)-2-((*S*)-3-(4-(4-((*S*)-2-Ammonium-3-methoxy-3-oxopropyl)styryl)phenyl)-2-(benzyloxycarbonylamino)propanamido)-3-methylpentanoic acid trifluoroacetate **3.113**



3.111
$C_{44}H_{57}N_3O_9$
(771.94)

3.113
$C_{37}H_{42}F_3N_3O_9$
(729.74)

To a solution of styrene **3.111** (94.0 mg, 122 μmol) in CH_2Cl_2 (1 mL) was added TFA (4 mL, 53.8 mmol) at RT for 2 h. After this time the reaction mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (10 mL) and concentrated under reduced (x3) to effect the azeotropic removal of residual TFA, to give the title compound **3.113** (89.0 mg, 122 μmol, quant.) as a pale yellow oil.

FT-IR (ν_{max}, neat) 3399 br. w, 2963 m, 2643 br. w, 1660 s, 1517 m, 1452 m, 1246 m, 1199 s, 1139 s, 1049 w, 963 w, 837 m, 722 m cm^{-1}.

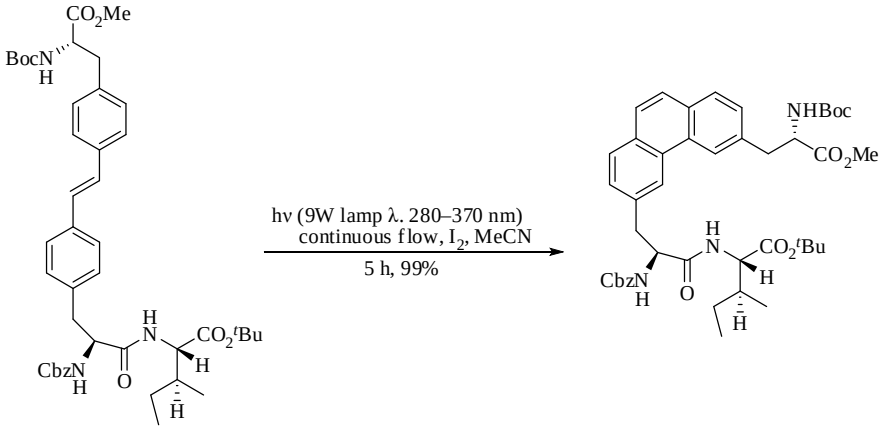
^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ_H ppm 7.55 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.44 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.31–7.21 (m, 9H, Ar*H*), 7.16–7.12 (br. m, 2H, C*H*), 4.94 (s, 2H, CH_2), 4.50 (dd, *J*=9.6, 5.1 Hz, 1H, NC*H*CO), 4.40 (d, *J*=5.1 Hz, 1H, NC*H*CO), 4.32 (t, *J*=6.8 Hz, 1H, NC*H*CO), 3.81 (s, 3H, CH_3), 3.26 (dd, *J*=14.6, 6.1 Hz, 1H, C*H*H), 3.22–3.11 (m, 3H, CH*H*+CH_2), 1.95–1.85 (br. s, 2H, N*H*), 1.55–1.45 (m, 2H, C*H*CH*H*CH$_3$), 1.26–1.23 (m, 1H, C*H*HCH$_3$), 0.96–0.87 (m, 6H, 2 x CH_3). *NB: 3 x NH not observed.*

^{13}C NMR (100 MHz, d_4-MeOH) δ_C ppm 174.6 (*C*), 174.2 (*C*), 170.6 (*C*), 161.1 (*C*), 158.4 (*C*), 138.8 (*C*), 138.3 (*C*), 137.2 (*C*), 134.5 (*C*), 130.9 (2 x *C*H), 130.1 (2 x *C*H), 129.6 (2 x *C*H), 128.9 (2 x *C*H), 128.7 (2 x *C*H), 128.4 (*C*H), 128.3 (2 x *C*H), 127.8 (2 x *C*H), 67.7 (CH_2), 58.3 (*C*H), 57.7 (*C*H), 55.3 (*C*H), 53.8 (CH_3), 38.9 (*C*H), 38.7 (CH_2), 37.3 (CH_2), 26.2 (CH_2), 16.0 (CH_3), 11.9 (CH_3).

HRMS (m/z, ESI$^+$) calcd for $C_{35}H_{41}N_3O_7$ $[M+H]^+$ requires 616.3023; found: 616.3037.

$[\alpha]_D^{24}$ + 6.4 (c = 0.4, MeOH).

tert-Butyl (2*S*,3*S*)-2-((*S*)-2-(benzyloxycarbonylamino)-3-(6-((*S*)-2-(*tert*-butoxycarbonyl-amino)-3-methoxy-3-oxopropyl)phenanthren-3-yl)propanamido)-3-methyl-pentanoate **3.116**



A solution of stilbene **3.111** (170 mg, 220 µmol) and I_2 (one crystal) in degassed acetonitrile (34 mL) was irradiated under continuous flow by a 9 W Philips broad-spectrum light source (PL-S 9W/12/2P, 280–370 nm) for a residence time of 5 h using a Vapourtec R4/R2+ flow device. The reaction mixture was concentrated under reduced pressure affording a crude orange oil. Purification by flash column chromatography

(10–30% EtOAc/petroleum ether) to give the title compound **3.116** (168 mg, 219 μmol, 99%) as a pale yellow oil.

FT-IR (ν_{max}, neat) 3325 br. m, 2966 m, 2925 m, 2872 w, 1708 s, 1659 s, 1512 s, 1453 m, 1366 m, 1249 m, 1156 s, 1046 m, 1025 m, 909 m, 847 m, 730 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.48 (br. s, 1H, Ar*H*), 8.41 (br. s, 1H, Ar*H*), 7.84–7.76 (m, 2H, Ar*H*), 7.67 (br. s, 2H, Ar*H*), 7.46 (d, *J*=7.6 Hz, 1H, Ar*H*), 7.39 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.28–7.21 (m, 5H, Ar*H*), 6.44 (d, *J*=6.1 Hz, 1H, N*H*), 5.49 (br. s, 1H, N*H*), 5.14–5.08 (m, 1H, N*H*), 5.07 (br. d, *J*=11.6 Hz, 1H, C*H*H), 5.04 (br. d, *J*=11.6 Hz, 1H, CH*H*), 4.78–4.68 (m, 1H, NC*H*CO), 4.62 (br. app. s, 1H, NC*H*CO), 4.40 (dd, *J*=8.1, 4.6 Hz, 1H, NC*H*CO), 3.73 (s, 3H, CH_3), 3.43–3.28 (m, 4H, CH_2), 1.86–1.78 (m, 2H, CH_2CH$_3$), 1.40 (s, 9H, C(CH_3)$_3$), 1.33 (s, 9H, C(CH_3)$_3$), 1.12–0.99 (m, 1H, C*H*CH$_2$CH$_3$), 0.84 (t, *J*=7.3 Hz, 3H, CH_3), 0.76 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.4 (*C*), 170.4 (*C*), 170.2 (*C*), 155.9 (*C*), 155.1 (*C*), 136.1 (*C*), 134.7 (*C*), 134.4 (*C*), 131.1 (*C*), 130.1 (*C*), 130.0 (*C*), 129.1 (*C*H), 129.0 (*C*H), 128.7 (2 x *C*H), 128.4 (2 x *C*H), 128.0 (*C*H), 127.9 (2 x *C*H), 127.8 (*C*H), 126.4 (2 x *C*H), 123.3 (*C*H), 81.9 (*C*), 79.9 (*C*), 67.0 (*C*H$_2$), 56.8 (*C*H), 56.4 (*C*H), 54.6 (*C*H), 52.2 (*C*H$_3$), 39.0 (*C*H$_2$), 38.8 (*C*H$_2$), 38.0 (*C*H), 28.3 ((*C*H$_3$)$_3$), 27.9 ((*C*H$_3$)$_3$), 25.3 (*C*H$_2$), 15.1 (*C*H$_3$), 11.6 (*C*H$_3$). *NB. One quaternary resonance not observed.*

LRMS (m/z, ESI$^+$) 792 ([M+Na]$^+$, 100%).

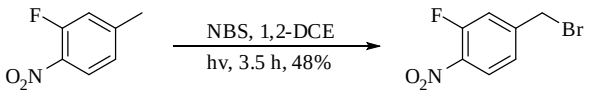
HRMS (m/z, ESI$^+$) calcd for $C_{44}H_{55}N_3O_9$ [M+Na]$^+$ requires 792.3836; found: 792.3815.

UV (MeCN) λ_{max} (ε), 282 (9519); 226 (21899) nm.

$[\alpha]_D^{29}$ + 64.0 (c = 0.1, CH_2Cl_2).

5.3 Experimental Procedures for Chapter 4

4-(Bromomethyl)-2-fluoro-1-nitrobenzene **2.58**



4.00
$C_7H_6FNO_2$
(155.1)

2.58
$C_7H_5BrFNO_2$
(234.0)

To a solution of arene **4.00** (10.0 g, 64.5 mmol) in 1,2-DCE (120 mL) was added NBS (16.1 g, 90.3 mmol). The suspension was irradiated with UV light for 3.5 h at which point the reaction was stopped due to formation of a dibrominated product as (indicated by NMR). The reaction mixture was washed with sat. sodium thiosulfate solution (100 mL), and the aqueous phase was re-extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a yellow oil. Cooling at –5 ^oC gave a yellow precipitate that was purified by recrystalisation (MeOH) to give the title compound **2.58** (7.25 g, 30.9 mmol, 48%) as a yellow crystalline solid. These data are in accordance with those reported in the literature.[106]

M.P. 46–49 ^oC (MeOH), Lit. 46–49 ^oC (no solvent given).[200]

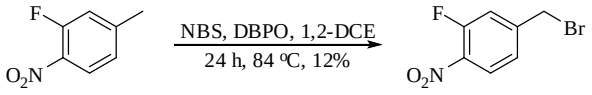
FT-IR (ν_{max}, neat) 3109 w, 3088 w, 3039 m, 2974 w, 2859 w, 1604 s, 1537 m, 1342 s, 1311 m, 1278 m, 1221 m, 1086 m, 959 m, 841 m, 693 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.05 (app. t, *J*=8.1 Hz, 1H, Ar*H*), 7.37–7.30 (m, 2H, 2 x Ar*H*), 4.47 (s, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 155.4 (d, J_{CF}=265 Hz, *C*F), 146.2 (d, J_{CF}=7.3 Hz, *C*), 136.9 (*C*), 126.6 (d, J_{CF}=2.9 Hz, *C*H), 124.9 (d, J_{CF}=2.9 Hz, *C*H), 118.9 (d, J_{CF}=22.0 Hz, *C*H), 29.9 (CH_2).

LRMS (EI) 235 ({^{81}Br}$M^{+\bullet}$, 7%), 233 ({^{79}Br}$M^{+\bullet}$, 6%), 154 (100%).

4-(Bromomethyl)-2-fluoro-1-nitrobenzene **2.58**

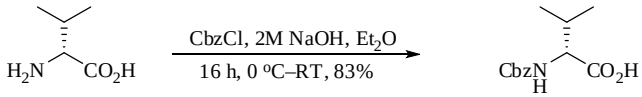


4.00
$C_7H_6FNO_2$
(155.1)

2.58
$C_7H_5BrFNO_2$
(234.0)

To a solution of arene **4.00** (5.00 g, 32.2 mmol) in 1,2-DCE (25 mL) was added NBS (5.73 g, 32.2 mmol) and DBPO (779 mg, 3.22 mmol). The reaction mixture was heated at 84 ^{o}C for 24 h then concentrated under reduced pressure. The crude residue was dissolved in Et_2O (50 mL) and the precipitated succinimide was removed by filtration. The filtrate was concentrated under reduced pressure affording a brown oil. Purification by flash column chromatography (0–10% EtOAc/petroleum ether) to give the title compound **2.58** (930 mg, 3.97 mmol, 12%) as a yellow oil. These data match those previously reported and are in accordance with those reported in the literature.[106]

(*R*)-2-(Benzyloxycarbonylamino)-3-methylbutanoic acid **4.02**



4.01
$C_5H_{11}NO_2$
(117.15)

4.02
$C_{13}H_{17}NO_4$
(251.28)

To a solution of D-valine **4.01** (25.0 g, 210 mmol) in a mixture of 2M NaOH (500 mL) and Et_2O (110 mL) at 0 ^{o}C was added CbzCl (48.7 mL, 340 mmol) dropwise over 15 min. The reaction mixture was warmed to RT and after 16 h the phases were separated and the aqueous phase acidified to pH 2 with 2M HCl (~450 mL) then

extracted with EtOAc (4 x 300 mL). The combined organic phases were washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **4.02** (43.8 g, 174 mmol, 83%) as a colourless oil, that was used without further purification. These data are in accordance with those reported in the literature.[186]

FT-IR (ν_{max}, neat) 3321 br. m, 3060 w, 3035 w, 2962 m, 2929 w, 2872 w, 1698 s, 1518 s, 1454 m, 1339 m, 1213 s, 1094 m, 1025 m, 734 s cm^{-1}.

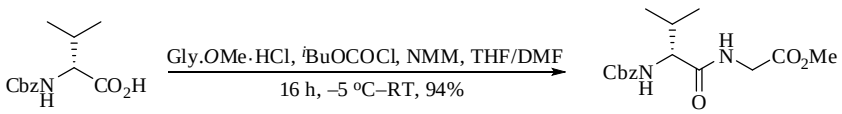
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.67 (br. s, 1H, CO_2H), 7.41–7.30 (m, 5H, Ar*H*), 5.33 (d, *J*=8.8 Hz, 1H, N*H*), 5.20–5.11 (m, 2H, CH_2), 4.37 (dd, *J*=8.8, 4.6 Hz, 1H, NC*H*CO), 2.30–2.17 (m, 1H, C*H*), 1.02 (d, *J*=7.1 Hz, 3H, CH_3), 0.94 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 176.8 (*C*), 156.4 (*C*), 136.1 (*C*), 128.5 (2 x *C*H), 128.2 (*C*H), 128.1 (*C*H), 127.1 (*C*H), 67.2 (*C*H_2), 58.8 (*C*H), 31.0 (*C*H), 18.9 (*C*H_3), 17.3 (*C*H_3).

LRMS (m/z, ESI$^-$) 250 ([M–H]$^-$, 8%), 142 (100%).

$[\alpha]_D^{26}$ + 10 (c = 0.3, CH_2Cl_2).

Methyl (*R*)-2-(2-(benzyloxycarbonylamino)-3-methylbutanamido)acetate **4.03**



4.02 $C_{13}H_{17}NO_4$ (251.28)

4.03 $C_{16}H_{22}N_2O_5$ (322.35)

Prepared according to the method of Gani *et al.*[201]

To a solution of carboxylic acid **4.02** (45.7 g, 182 mmol) in THF (400 mL) at –5 °C was firstly added NMM (20.0 mL, 182 mmol) dropwise over 15 min, then ^{i}BuOCOCl

(23.5 mL, 182 mmol) dropwise over 15 mins causing a white precipitate to form. After 10 min a suspension of Gly.*O*Me.HCl (22.9 g, 182 mmol) in DMF (65 mL) was added along with a second charge of NMM (20.0 mL, 182 mmol). The reaction mixture was warmed to RT and after 16 h the white precipitate formed was collected by filtration. Purification by recystallisation (CH_2Cl_2/Et_2O) to give the title compound **4.03** (53.5 g, 166 mmol, 94%) as a white solid. These data are in accordance with those reported in the literature.[201]

M.P. 161–163 ^oC (CH_2Cl_2/Et_2O), Lit. 139–140 ^oC (CH_2Cl_2/petroleum ether).[201]

FT-IR (ν_{max}, neat) 3287 s, 3101 w, 3027 w, 2958 m, 2868 w, 1751 s, 1687 s, 1652 s, 1537 s, 1388 m, 1292 m, 1245 s, 1209 s, 1135 m, 1038 m, 972 m, 906 m, 744 m, 698 s cm^{-1}.

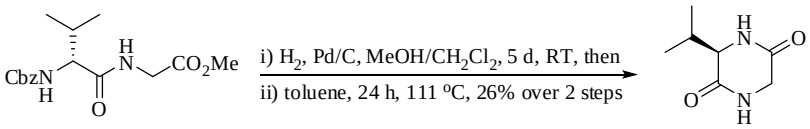
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.39–7.29 (m, 5H, Ar*H*), 6.63 (br. s, 1H, N*H*), 5.45 (br. d, *J*=8.6 Hz, 1H, N*H*), 5.13 (d, *J*=12.4 Hz, 1H, C*H*H), 5.09 (d, *J*=12.4 Hz, 1H, CH*H*), 4.12–4.03 (m, 2H, NC*H*HCO+NC*H*), 3.99 (dd, *J*=18.2, 6.6 Hz, 1H, NCH*H*CO), 3.75 (s, 3H, CH_3), 2.16 (app. oct, *J*=6.8 Hz, 1H, C*H*), 0.99 (d, *J*=7.1 Hz, 3H, CH_3), 0.95 (d, *J*=7.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.6 (*C*), 170.0 (*C*), 156.4 (*C*), 136.2 (*C*), 128.5 (2 x *C*H), 128.2 (*C*H), 128.0 (2 x *C*H), 67.1 (*C*H_2), 60.3 (*C*H), 52.3 (*C*H_3), 41.0 (*C*H_2), 30.9 (*C*H), 19.1 (*C*H_3), 17.7 (*C*H_3).

LRMS (m/z, ESI$^+$) 667 ($[2M+Na]^+$, 8%), 345 ($[M+Na]^+$, 100%).

$[\alpha]_D^{25}$ + 3.7 (c = 0.22, CH_2Cl_2).

(*R*)-3-Isopropylpiperazine-2,5-dione **4.04**



4.03
$C_{16}H_{22}N_2O_5$
(322.35)

4.04
$C_7H_{12}N_2O_2$
(156.18)

Prepared according to the method of Gani *et al.*[201]

A solution of dipeptide **4.03** (53.0 g, 164 mmol) in MeOH (75 mL) and CH_2Cl_2 (450 mL) containing 10% Pd/C (4.90 g) was stirred under an atmosphere of $H_{2(g)}$ for 5 d, then filtered through Celite®. The residue on Celite® was washed with CH_2Cl_2 (500 mL). The filtrate was concentrated under reduced pressure to give a glassy opaque solid (30.8 g, 164 mmol, 100%) that was used directly in the next step.

The product was suspended in toluene (500 mL), heated at reflux for 24 h, then cooled to RT. The precipitate was collected by filtration and washed with ether (200 mL). Purification by recrystalisation (H_2O) and then dried by azeotroping with $CHCl_3$ to give the title compound **4.04** (6.38 g, 41.0 mmol, 26%) as a white solid. These data are in accordance with those reported in the literature.[201]

M.P. dec. > 240 °C (H_2O), Lit. 257–259 °C (H_2O).[201]

FT-IR (ν_{max}, neat) 3186 m, 3047 m, 2958 m, 2921 w, 2880 w, 2361 m, 2336 m, 1666 s, 1453 s, 1343 m, 1326 m, 1098 m, 855 s, 833 s, 808 s, 445 s cm^{-1}.

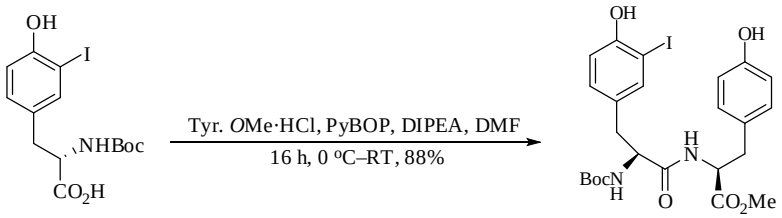
^{1}H NMR (400 MHz, *d*$_4$-MeOD) δ_H ppm 4.00 (br. dd, *J*=18.4, 1.0 Hz, 1H, NC*H*HCO), 3.83 (br. dd, *J*=18.4, 1.0 Hz, 1H, NCH*H*CO), 3.74 (d, *J*=4.00 Hz, 1H, NC*H*CO), 2.25 (sextd, *J*=7.1, 4.0 Hz, 1H, C*H*), 1.04 (d, *J*=7.1 Hz, 3H, CH_3), 0.97 (d, *J*=6.6 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, *d*$_4$-MeOD) δ_C ppm 170.4 (*C*), 170.0 (*C*), 61.8 (*C*H), 45.4 (*C*H_2), 34.5 (*C*H), 19.2 (*C*H_3), 17.4 (*C*H_3).

LRMS (m/z, ESI$^+$) 189 ([M+H+MeOH]$^+$, 100%).

$[\alpha]_D^{25}$ + 27.8 (c = 0.91, H_2O).

Methyl (*S*)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-hydroxy-3-iodophenyl)-propanamido)-3-(4-hydroxyphenyl)propanoate **4.17**



3.18
$C_{15}H_{20}INO_5$
(421.2)

4.17
$C_{25}H_{31}IN_2O_7$
(598.4)

To a solution of carboxylic acid **3.18** (4.00 g, 9.82 mmol) in DMF (30 mL) was added PyBOP (7.64 mL, 14.7 mmol), and DIPEA (5.14 mL, 29.5 mmol). After cooling to 0 ^oC, hydrochloride salt (2.73 g, 11.8 mmol) was added and the reaction mixture warmed to RT. After 16 h H_2O (300 mL) and EtOAc (100 mL) were added. The aqueous phase was separated and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed sequentially with sat. NH_4Cl (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a pale yellow solid. Purification by flash column chromatography (45% EtOAc/petroleum ether) to give the title compound **4.17** (5.06 g, 8.66 mmol, 88%) as a white solid.

M.P. 99–104 ^oC (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3309 br. m, 2970 w, 2933 m, 2851 w, 2357 w, 2165 m, 1659 s, 1514 s, 1440 m, 1416 w, 1367 m, 1274 m, 1222 s, 1166 s, 732 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.48 (d, *J*=2.0 Hz, 1H, Ar*H*), 7.01 (br. s, 1H, O*H*), 6.85–6.79 (m, 2H, 2 x Ar*H*), 6.84 (br. d, *J*=8.6 Hz, 2H, Ar*H*), 6.80 (s, 1H, Ar*H*), 6.69 (d, *J*=8.6 Hz, 2H, 2 x Ar*H*),

6.29 (br. d, *J*=6.6 Hz, 1H, N*H*), 5.92 (br. s, 1H, O*H*), 5.11 (br. d, *J*=7.1 Hz, 1H, N*H*), 4.76 (app. br. q, *J*=6.1 Hz, 1H, NC*H*CO), 4.25 (br. s, 1H, NC*H*CO), 3.71 (s, 3H, CH_3), 3.01 (dd, *J*=14.1, 5.6 Hz, 1H, C*H*H), 2.96 (dd, *J*=14.1, 5.6 Hz, 1H, CH*H*), 2.93–2.84 (m, 2H, CH_2), 1.44 (s, 9H, C(CH_3)$_3$).

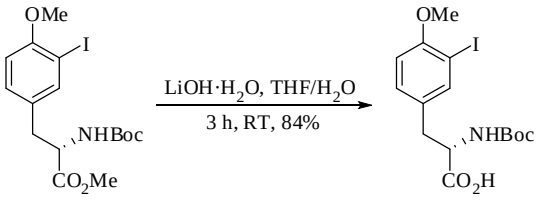
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.5 (*C*), 170.7 (*C*), 155.4 (*C*), 155.1 (*C*), 154.1 (*C*), 139.0 (*C*H), 131.0 (*C*H), 130.3 (2 x *C*H), 127.1 (*C*), 121.9 (*C*), 115.6 (2 x *C*H), 115.1 (*C*H), 97.7 (*C*), 85.4 (*C*), 55.8 (*C*H), 53.4 (*C*H), 52.5 (*C*H_3), 37.1 (2 x *C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 1191 ([2M+Na]$^+$, 24%), 648 ([M+Na+MeCN]$^+$, 41%), 607 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{24}H_{29}IN_2O_7$ [M+Na]$^+$ requires 607.0917; found: 607.0918.

$[\alpha]_D^{26.5}$ +11.1 (c = 0.35, CH_2Cl_2).

(*S*)-2-(*tert*-Butoxycarbonylamino)-3-(3-iodo-4-methoxyphenyl)propanoic acid **4.18**



1.28
$C_{16}H_{22}INO_5$
(435.25)

4.18
$C_{15}H_{20}INO_5$
(421.23)

To a solution of ester **1.28** (1.17 g, 269 mmol) in THF/H_2O (1:1, 10 mL) was added LiOH·H_2O (339 mg, 8.07 mmol). After 3 h 2M HCl (10 mL) was added. The aqueous phase was separated then extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **4.18** (956 mg, 2.27 mmol, 84%) as a

white foamy solid, that was used without further purification. These data are in accordance with those reported in the literature.[11]

M.P. 61–64 ^{o}C (EtOAc/petroleum ether), Lit. not given.

FT-IR (ν_{max}, neat) 3317 br. m, 2974 m, 2933 m, 2835 w, 2369 w, 1711 s, 1601 m, 1490 s, 1397 s, 1364 m, 1253 s, 1159 s, 1050 m, 1012 m, 910 m, 816 w, 731 m cm^{-1}.

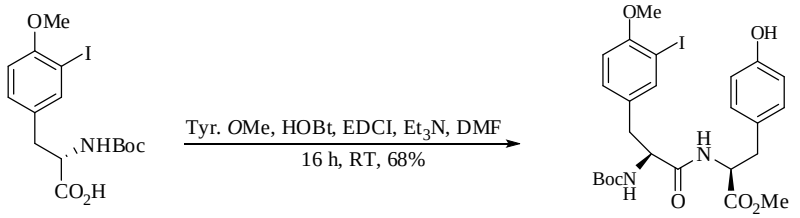
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.62 (br. s, 1H, Ar*H*), 7.14 (dd, *J*=8.1, 2.0 Hz, 1H, Ar*H*), 7.10 (br. s, 1H, CO_2H), 6.76 (d, *J*=8.1 Hz, 1H, Ar*H*), 5.00 (br. d, *J*=7.6 Hz, 1H, N*H*), 4.55 (br. app. q, *J*=6.6 Hz, 1H, NC*H*CO), 3.86 (s, 3H, CH_3), 3.17–3.06 (m, 1H, C*H*H), 2.98 (dd, *J*=13.9, 5.8 Hz, 1H, CH*H*), 1.44 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 175.5 (*C*), 157.2 (*C*), 155.3 (*C*), 140.3 (*C*H), 130.4 (*C*H), 130.1 (*C*), 110.9 (*C*H), 85.9 (*C*), 80.4 (*C*), 56.4 (*C*H$_3$), 54.3 (*C*H), 36.4 (*C*H$_2$), 28.3 ((*C*H$_3$)$_3$).

LRMS (m/z, ESI$^-$) 420 ([M–H]$^-$, 100%).

$[\alpha]_D^{27}$ +18.6 (c = 0.567, CH_2Cl_2).

Methyl (*S*)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-2-(3-iodo-4-methoxyphenyl)-acetamido)-3-(4-hydroxyphenyl)propanoate **4.19**



4.18
$C_{15}H_{20}INO_5$
(421.2)

4.19
$C_{25}H_{31}IN_2O_7$
(598.4)

To a solution of carboxylic acid **4.18** (5.77 g, 13.7 mmol) in DMF (100 mL) was added EDCI (1.13 mL, 10.6 mmol), and HOBt (1.43 g, 10.6 mmol). To this was added a solution of Tyr.*O*Me (3.17 g, 13.7 mmol) and Et_3N (1.90 mL, 13.7 mmol) in DMF (50 mL), followed by a second charge of Et_3N (1.90 mL, 13.7 mmol). After 16 h the reaction mixture was concentrated under reduced pressure to *ca.* 10 mL, diluted with H_2O (500 mL), and extracted with EtOAc (4 x 100 mL). The combined organic phases were washed sequentially with sat. NH_4Cl (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording an orange oil. Purification by flash column chromatography (10–50% EtOAc/petroleum ether) to give the title compound **4.19** (5.60 g, 9.36 mmol, 68%) as a white solid.

M.P. 143–146 ^oC (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3309 br. m, 2978 m, 2921 m, 2851 m, 1740 m, 1659 s, 1609 m, 1515 s, 1494 s, 1433 m, 1367 m, 1252 s, 1168 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.59 (d, *J*=2.1 Hz, 1H, Ar*H*), 7.12 (dd, *J*=8.1, 2.1 Hz, 1H, Ar*H*), 6.85 (d, *J*=8.6 Hz, 2H, Ar*H*), 6.73 (d, *J*=8.6 Hz, 2H, Ar*H*), 6.69 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.31 (d, *J*=7.6 Hz, 1H, N*H*), 5.68 (br. s, 1H, O*H*), 5.07–5.00 (br. m, 1H, N*H*), 4.76 (app. q, *J*=6.1 Hz, 1H, NC*H*CO), 4.33–4.21 (br. m, 1H, NC*H*CO), 3.85 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.02 (dd,

J=14.2, 5.6 Hz, 1H, C*H*H), 3.02 (dd, *J*=14.2, 5.6 Hz, 1H, CH*H*), 2.95–2.87 (m, 2H, CH_2), 1.43 (s, 9H, C(CH_3)$_3$).

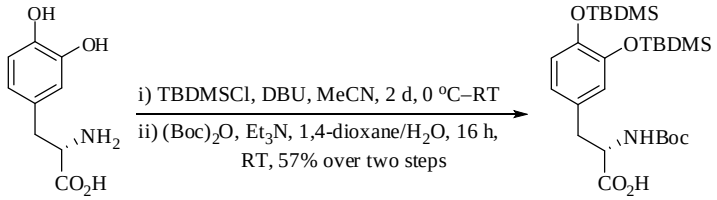
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.4 (*C*), 170.6 (*C*), 155.4 (*C*), 155.0 (*C*), 140.1 (*C*H), 130.6 (*C*H), 130.5 (*C*), 130.4 (2 x *C*H), 127.3 (*C*), 115.5 (2 x *C*H), 110.9 (*C*H), 86.9 (*C*), 80.4 (*C*), 56.4 (*C*H), 53.4 (*C*H), 52.4 (2 x *C*H_3), 37.1 (*C*H_2), 36.9 (*C*H_2), 28.3 ((*C*H_3)$_3$). *NB. One quaternary resonance not observed.*

LRMS (m/z, ESI$^+$) 662 ([M+Na+MeCN]$^+$, 44%), 621 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{25}H_{31}IN_2NaO_7$ [M+Na]$^+$ requires 621.1074; found: 621.1068.

$[\alpha]_D^{27}$ +21 (c = 0.2, CH_2Cl_2).

((*S*)-3-(3,4-bis(*tert*-Butyldimethylsilyloxy)phenyl)-2-(*tert*-butoxycarbonylamino)-propanoic acid **4.21**



4.20
$C_9H_{11}NO_4$
(197.2)

4.21
$C_{26}H_{47}NO_6Si_2$
(525.8)

Prepared according to the method of Sever *et al.*[202]

To a solution of TBDMSCl (18.3 g, 122 mmol) in dry MeCN (70 mL) was added L-DOPA **4.20** (8.00 g, 40.6 mmol) and the thick slurry mixed vigorously using an overhead-stirrer. The reaction mixture was cooled to 0 °C prior to the dropwise addition of DBU (18.2 mL, 122 mmol) over 10 min. The reaction mixture was warmed to RT and after 2 d was concentrated under reduced pressure to give the crude bis-protected catechol (17.3 g, 40.6 mmol, 100%) as a beige solid.

To a solution of this solid (17.3 g, 40.6 mmol) in 1,4-dioxane/water (1:1, 300 mL) was added $(Boc)_2O$ (9.31 g, 42.6 mmol) portionwise followed by Et_3N (5.99 mL, 42.6 mmol). After 16 h the reaction mixture was concentrated under reduced pressure. The crude residue was dissolved in EtOAc (250 mL), washed with 1M HCl (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a brown oil. Purification by flash column chromatography (10% MeOH/CH_2Cl_2) to give the title compound **4.21** (12.2 g, 23.2 mmol, 57%) as a brown foamy oil. These data are in accordance with those reported in the literature.[202]

FT-IR (ν_{max}, neat) 2955 m, 2931 m, 2858 m, 1718 s, 1510 s, 1296 m, 1254 m, 1164 m, 908 m, 838 s, 781 m cm^{-1}.

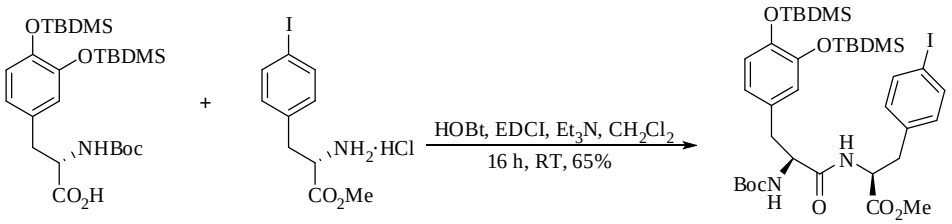
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 6.76 (d, *J*=7.8 Hz, 1H, Ar*H*), 6.67 (d, *J*=2.2 Hz, 1H, Ar*H*), 6.63 (dd, *J*=7.8, 2.2 Hz, 1H, Ar*H*), 4.90 (br. d, *J*=7.1 Hz, 1H, N*H*), 4.57–4.50 (br. m, 1H, NC*H*CO), 3.09–3.02 (m, 1H, C*H*H), 3.01–2.94 (m, 1H, CH*H*), 1.43 (s, 9H, C(CH_3)$_3$), 0.99 (s, 9H, C(CH_3)$_3$), 0.98 (s, 9H, C(CH_3)$_3$), 0.20 (s, 6H, Si(CH_3)$_2$), 0.19 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 176.2 (*C*), 155.4 (*C*), 146.8 (*C*), 146.0 (*C*), 128.7 (*C*), 122.3 (*C*H), 122.2 (*C*H), 121.1 (*C*H), 80.4 (*C*), 54.2 (*C*H), 36.9 (*C*H_2), 28.3 ((*C*H_3)$_3$), 25.7 (2 x (*C*H_3)$_3$), 18.4 (2 x Si*C*(CH$_3$)$_3$), –4.1 (2 x (*C*H_3)$_2$).

LRMS (m/z, ESI$^-$) 524 ([M–H]$^-$, 41%), 450 (40%), 249 (100%).

$[\alpha]_D^{26.5}$ +6.2 (c = 0.33, CH_2Cl_2).

Methyl (*S*)-2-((*S*)-3-(3,4-bis(*tert*-butyldimethylsilyloxy)phenyl)-2-(*tert*-butoxy-carbonylamino)propanamido)-3-(4-iodophenyl)propanoate **4.22**



4.21 $C_{26}H_{47}NO_6Si_2$ (525.8)

3.103 $C_{10}H_{13}ClINO_2$ (341.6)

4.22 $C_{36}H_{57}IN_2O_7Si_2$ (812.9)

To a solution of carboxylic acid **4.21** (4.00 g, 7.61 mmol) in CH_2Cl_2 (200 mL) was added EDCI (1.13 mL, 10.6 mmol), HOBt (1.43 g, 10.6 mmol), hydrochloride salt **3.103** (3.62 g, 10.6 mmol) and Et_3N (2.97 mL, 21.3 mmol). After 16 h the reaction mixture was quenched with 1M HCl (200 mL). The organic phase was washed sequentially with sat. $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. purification by flash column chromatography (0–40% MTBE/hexane) to give the title compound **4.22** (3.99 g, 4.91 mmol, 65%) as a white solid.

M.P. 62–66 ^oC (Et_2O/petroleum ether).

FT-IR (ν_{max}, neat) 3317 br. w, 2958 m, 2925 m, 2855 m, 2357 w, 1748 m, 1658 m, 1508 s, 1254 m, 1160 m, 906 s, 837 s, 780 m, 730.3 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.57 (d, *J*=8.4 Hz, 2H, Ar*H*), 6.77 (d, *J*=8.4 Hz, 2H, Ar*H*), 6.74 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.66 (d, *J*=2.1 Hz, 1H, Ar*H*), 6.63 (dd, *J*=8.1, 2.1 Hz, 1H, Ar*H*), 6.46 (br. d, *J*=7.1 Hz, 1H, N*H*), 4.84 (br. s, 1H, N*H*), 4.77 (app. dt, *J*=7.1, 6.1 Hz, 1H, NC*H*CO), 4.32–4.19 (br. m, 1H, NC*H*CO), 3.68 (s, 3H, CH_3), 3.09–2.85 (m, 4H, 2 x CH_2), 1.41 (s, 9H, C(CH_3)$_3$), 0.99 (s, 9H, C(CH_3)$_3$), 0.98 (s, 9H, C(CH_3)$_3$), 0.20 (s, 3H, Si(CH_3)), 0.19 (s, 3H, Si(CH_3)), 0.18 (s, 6H, Si(CH_3)$_2$).

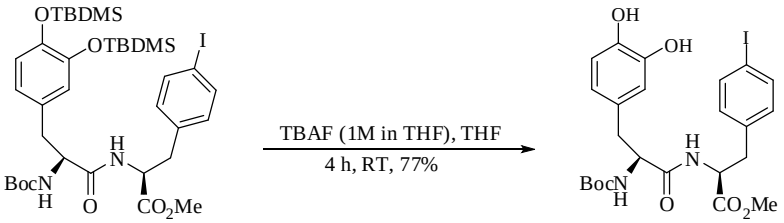
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.1 (*C*), 171.0 (*C*), 155.3 (*C*), 146.9 (*C*), 146.0 (*C*), 137.6 (2 x *C*H), 135.4 (*C*), 131.3 (2 x *C*H), 129.3 (*C*), 122.3 (*C*H), 122.1 (*C*H), 121.2 (*C*H), 92.6 (*C*), 80.3 (*C*), 55.7 (*C*H), 53.1 (*C*H), 52.3 (CH_3), 37.5 (CH_2), 37.1 (CH_2), 28.3 ((CH_3)$_3$), 25.9 (2 x (CH_3)$_3$), 18.4 (2 x Si*C*(CH_3)$_3$), -3.99 (CH_3), –4.1 (CH_3), –4.1 (CH_3), –4.1 (CH_3).

LRMS (m/z, ESI$^+$) 835 ($[M+Na]^+$, 100%), 813 (65%), 757 (62%), 713 ($[M\text{-}Boc+H]^+$, 64%).

HRMS (m/z, ESI$^+$) calcd for $C_{36}H_{57}IN_2O_7Si_2$ $[M+Na]^+$ requires 835.2647; found: 835.2641

$[\alpha]_D^{25}$ –11.9 (c = 1.57, CH_2Cl_2).

Methyl (*S*)-2-((*S*)-2-(*tert*-butoxycarbonylamino)-3-(3,4-dihydroxyphenyl)-propanamido)-3-(4-iodophenyl)propanoate **4.23**



4.22
$C_{36}H_{57}IN_2O_7Si_2$
(812.9)

4.23
$C_{24}H_{29}IN_2O_7$
(584.4)

To a solution of bis-silyl ether **4.22** (2.75 g, 3.38 mmol) in dry THF (20 mL) was added TBAF (1M in THF, 7.1 mL, 7.1 mmol). After 4 h the reaction mixture was quenched with H_2O (50 mL), and the products extracted with EtOAc (3 x 30 mL). The organic phases were combined, washed sequentially with 1M HCl (40 mL), H_2O (40 mL) and brine (40 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a crude brown oil. Purification by flash column chromatography (40% EtOAc/petroleum ether) to give the title compound **4.23** (1.51 g, 2.60 mmol, 77%) as an off-white solid.

M.P. 158–161 ^{o}C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3333 br. m, 2974 m, 2925 m, 2843 m, 2238 w, 1732 m, 1661 s, 1601 w, 1518 s, 1433 m, 1366 s, 1282 s, 1254 s, 1164 s, 1111 m, 1008 m, 906 m, 804 m, 732 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.56 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.84–6.71 (m, 1H, Ar*H*), 6.76 (d, *J*=8.1 Hz, 2H, Ar*H*), 6.70 (br. s, 1H, N*H*), 6.61–6.52 (m, 2H, Ar*H*), 6.24–5.95 (br.s, 1H, N*H*), 5.11 (br. d, *J*=5.6 Hz, 1H, N*H*), 4.74 (br. s, 1H, NC*H*CO), 4.28 (m, 1H, NC*H*CO), 3.67 (s, 3H, CH_3), 3.06–2.82 (m, 4H, 2 x CH_2), 1.42 (s, 9H, C(CH_3)$_3$), 1.26 (s, 2H, 2 x O*H*).

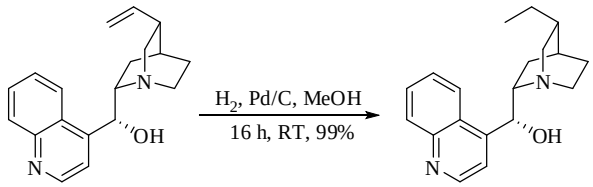
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.5 (*C*), 171.2 (*C*), 155.4 (*C*), 144.0 (*C*), 143.4 (*C*), 137.6 (2 x *C*H), 135.2 (*C*), 131.2 (2 x *C*H), 128.3 (*C*), 121.5 (*C*H), 116.1 (*C*H), 115.3 (*C*H), 92.7 (*C*), 80.8 (*C*), 56.0 (*C*H), 53.2 (*C*H), 52.5 (*C*H$_3$), 37.7 (*C*H$_2$), 37.4 (*C*H$_2$), 28.3 ((*C*H$_3$)$_3$).

LRMS (m/z, ESI$^+$) 648 ([M+Na+MeCN]$^+$, 32%), 607 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{24}H_{29}IN_2O_7$ [M+Na]$^+$ requires 607.0917; found: 607.0912.

$[\alpha]_D^{26.5}$ +10.4 (c = 0.5, CH_2Cl_2).

(1*R*)-(8-Ethylquinuclidin-2-yl)(quinolin-4-yl)methanol **4.27**



4.26
$C_{19}H_{22}N_2O$
(294.39)

4.27
$C_{19}H_{24}N_2O$
(296.41)

Cinchonidine **4.26** (10.0 g, 34.0 mmol) and Pd/C (2.00 g, 3.4 mmol) in MeOH (400 mL) were mixture stirred under an atmosphere of hydrogen. After 16 h the reaction mixture was filtered through Celite® and the layer cake washed with MeOH (500 mL). The filtrate was concentrated under reduced pressure affording an off-white solid that was stirred in hexane (300 mL) for 3 h. The precipitate was collected by filtration to give the title compound **4.27** (9.95 g, 33.6 mmol, 99%) as a white solid. These data are in accordance with those reported in the literature.[203]

M.P. dec. > 210 ^{o}C (MeOH/hexane) , Lit. 231 ^{o}C (no solvent given).[204]

FT-IR (ν_{max}, neat) 3072 w, 3035 w, 2941 m, 2922 m, 2855 m, 2700 br. m, 1580 m, 1507 w, 1442 m, 1327 m, 1108 m, 1029 m, 882 m, 824 m, 755 s cm^{-1}.

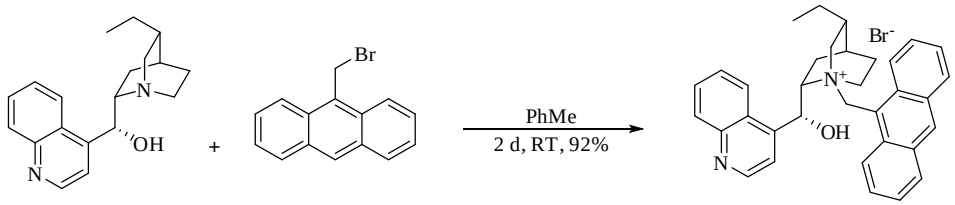
^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ_H ppm 8.82 (d, *J*=4.6 Hz, 1H, Ar*H*), 8.23 (d, *J*=8.3 Hz, 1H, Ar*H*), 8.06 (d, *J*=8.3 Hz, 1H, Ar*H*), 7.77 (ddd, *J*=8.3, 7.0, 1.3 Hz, 1H, Ar*H*), 7.72 (d, *J*=4.6 Hz, 1H, Ar*H*), 7.66 (ddd, *J*=8.3, 7.0, 1.3 Hz, 1H, Ar*H*), 5.64 (d, *J*=4.0 Hz, 1H, C*H*), 3.61 (dddd, *J*=13.1, 10.6, 5.1, 2.5 Hz, 1H, C*H*H), 3.15–3.02 (m, 2H, C*H*+CH*H*), 2.65 (ddd, *J*=14.6, 11.1, 5.10 Hz, 1H, CH*H*), 2.36 (ddd, *J*=13.6, 5.1, 2.5 Hz, 1H, C*H*H), 1.90–1.81 (m, 2H, C*H*$_2$), 1.79 (br. sext, *J*=3.0 Hz, 1H, C*H*), 1.55–1.40 (m, 3H, C*H*+C*H*$_2$), 1.25 (app. quind, *J*=7.6, 1.8 Hz, 2H, C*H*$_2$), 0.82 t, *J*=7.6 Hz, 3H, C*H*$_3$).

^{13}C NMR (100 MHz, d_4-MeOH) δ_C ppm 152.5 (*C*), 151.1 (*C*H), 149.0 (*C*), 130.8 (*C*H), 130.2 (*C*H), 128.3 (*C*H), 127.3 (*C*), 124.7 (*C*H), 120.1 (*C*H), 72.5 (*C*H), 61.8 (*C*H), 59.5 (CH_2), 44.2 (CH_2), 38.7 (*C*H), 28.9 (CH_2), 28.7 (CH_2), 26.9 (*C*H), 22.1 (CH_2), 12.4 (CH_3).

LRMS (m/z, ESI$^+$) 299 (100%), 297 ($[M+H]^+$, 50%).

$[\alpha]_D^{28}$ –124.8 (c = 0.51, MeOH).

1-(Anthracen-9-ylmethyl)-8-ethyl-2-((*R*)-hydroxy(quinolin-4-yl)-methyl)-1-azoniabicyclo[2.2.2]octane bromide **4.28**



4.27 $C_{19}H_{24}N_2O$ (296.41) + **4.31** $C_{15}H_{11}Br$ (271.15) → **4.28** $C_{34}H_{35}BrN_2O$ (567.56)

Prepared according to the method of Corey *et al.*[205]

Amine **4.27** (3.40 g, 11.5 mmol) was dissolved in dry PhMe (80 mL) and benzyl bromide **4.31** (3.19 g, 11.5 mmol) was added. After 2 d in the dark at RT, the precipitate was collected by filtration and washed with cold hexane (50 mL) to give the title compound **4.28** (6.02 g, 10.6 mmol, 92%) as a pale yellow solid.

M.P. dec. > 176 ^{o}C (hexane), Lit. dec. > 180 ^{o}C.[205]

FT-IR (ν_{max}, neat) 3166 br. m, 3080 w, 3056 w, 2953 m, 2872 w, 2202 m, 1715 w, 1585 w, 1499 m, 1446 m, 1319 w, 1229 w, 1155 m, 1049 m, 907 s, 722 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.94–8.87 (br. m, 1H, Ar*H*), 8.83 (d, *J*=4.6 Hz, 1H, Ar*H*), 8.81–8.74 (br. m, 2H, Ar*H*), 8.03 (d,

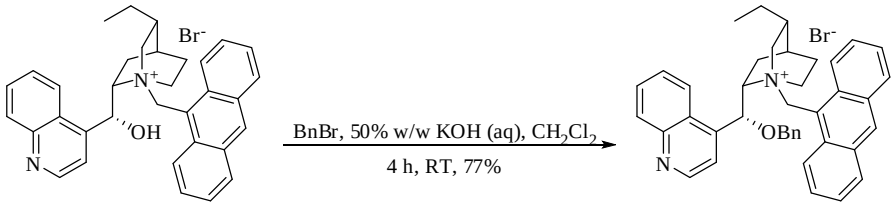
J=4.6 Hz, 1H, Ar*H*), 7.99 (br. app. s, 1H, Ar*H*), 7.67 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.63–7.56 (m, 2H, Ar*H*), 7.52 (t, *J*=7.6 Hz, 1H, Ar*H*), 7.30–7.20 (m, 3H, Ar*H*), 7.19–7.14 (m, 2H, Ar*H*), 7.04 (br. app. s, 1H, C*H*), 6.57 (d, *J*=13.3 Hz, 1H, C*H*H), 6.37 (d, *J*=13.3 Hz, 1H, CH*H*), 4.82 (td, *J*=9.6, 3.5 Hz, 1H, C*H*H), 4.65 (br. q, *J*=9.1 Hz, 1H, C*H*), 3.82 (d, *J*=12.6 Hz, 1H, CH*H*), 2.62 (app. t, *J*=11.4 Hz, 1H, CH*H*), 2.33–2.26 (br. m, 1H, C*H*H), 1.86–1.74 (br. m, 1H, C*H*), 1.64 (br. s, 1H, C*H*), 1.31–1.15 (m, 3H, CH_2+C*H*H), 1.11–0.94 (m, 3H, CH_2+CH*H*), 0.56 (t, *J*=7.6 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 149.4 (*C*H), 147.2 (*C*), 145.3 (*C*), 133.1 (*C*), 132.4 (*C*), 131.2 (*C*H), 130.2 (*C*), 129.3 (*C*H), 128.9 (*C*H), 128.7 (*C*H), 128.4 (*C*H), 128.2 (*C*H), 127.7 (*C*H), 127.2 (*C*H), 125.9 (*C*H), 125.7 (*C*H), 124.8 (*C*H), 124.7 (*C*H), 124.1 (*C*H), 124.0 (*C*), 120.2 (*C*H), 117.7 (*C*), 66.9 (*C*H), 66.7 (*C*H), 63.7 (*C*H_2), 54.8 (*C*H_2), 50.6 (*C*H_2), 37.1 (*C*H), 26.4 (*C*H_2), 26.1 (*C*H_2), 23.2 (*C*H), 23.0 (*C*H_2), 11.4 (*C*H_3). *NB: One quaternary resonance not observed*.

LRMS (m/z, ESI$^+$) 487 ([M]$^+$, 100%).

$[\alpha]_D^{29}$ –22.1 (c = 0.71, MeOH).

1-(Anthracen-9-ylmethyl)-2-((*R*)-benzyloxy(quinolin-4-yl)methyl)-8-ethyl-1-azoniabicyclo[2.2.2]octane bromide **4.29**



4.28
$C_{34}H_{35}BrN_2O$
(567.56)

4.29
$C_{41}H_{41}BrN_2O$
(657.68)

Prepared according to the method of Lygo *et al.*[206]

To a solution of alcohol **4.28** (6.02 g, 10.6 mmol) in CH_2Cl_2 (50 mL) was added benzyl bromide (4.57 mL, 38.2 mmol) and 50% $KOH_{(aq.)}$ (w/w, 7 mL) and the reaction mixture stirred vigorously. After 4 h the reaction mixture was diluted with H_2O (50 mL) and the phases separated. The organic phase was washed with a solution of 1M NaBr (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the title compound **4.29** (5.38 g, 8.18 mmol, 77%) as a yellow solid. These data are in accordance with those reported in the literature.[206]

M.P. dec. > 150 °C (hexane), Lit. 137–138 °C.[206]

FT-IR (ν_{max}, neat) 3382 br. w, 3060 w, 3031 w, 2958 m, 2929 m, 2872 w, 2189 m, 1670 m, 1597 m, 1450 m, 1356 w, 907 s, 721 s, 640 s cm^{-1}.

^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ_H ppm 9.08 (d, *J*=4.5 Hz, 1H, Ar*H*), 8.86 (s, 1H, Ar*H*), 8.68 (d, *J*=9.1 Hz, 1H, Ar*H*), 8.60 (s, 1H, Ar*H*), 8.26–8.18 (m, 3H, Ar*H*), 8.12–8.06 (m, 2H, Ar*H*), 8.00–7.92 (m, 2H, Ar*H*), 7.82–7.77 (m, 1H, Ar*H*), 7.73–7.69 (m, 2H, Ar*H*), 7.66–7.48 (m, 5H, Ar*H*), 7.40–7.34 (m, 1H, Ar*H*), 7.05 (br. s, 1H, C*H*), 6.26 (d, *J*=13.9 Hz, 1H, C*H*H), 5.18 (d, *J*=13.9 Hz, 1H, CH*H*), 4.99 (q, *J*=11.1 Hz, 2H, C*H*$_2$), 4.56 (br. s, 1H, C*H*), 4.48–4.35 (br. m, 2H, C*H*+CH*H*), 3.47 (ddd, *J*=12.4, 5.8, 3.0 Hz, 1H,

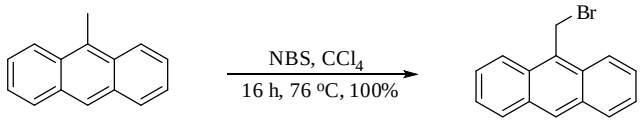
C*H*H), 3.11 (t, *J*=11.4 Hz, 1H, CH*H*), 2.83–2.73 (m, 1H, C*H*H), 2.54 (dd, *J*=12.4, 7.3 Hz, 1H, C*H*H), 2.18–2.07 (m, 1H, CH*H*), 1.94 (dq, *J*=5.4, 2.9 Hz, 1H, C*H*), 1.66–1.45 (m, 2H, CH_2), 1.29–1.18 (m, 2H, CH_2), 0.65 (t, *J*=7.3 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, d_4-MeOH) δ_C ppm 151.3 (*C*H), 149.6 (*C*), 143.1 (*C*), 138.3 (*C*), 134.9 (*C*), 134.6 (*C*), 134.0 (*C*H), 133.2 (*C*), 133.1 (*C*), 131.7 (*C*H), 131.4 (*C*H), 131.3 (*C*H), 130.9 (*C*H), 130.5 (2 x *C*H), 130.0 (2 x *C*H), 129.6 (*C*H), 129.4 (2 x *C*H), 129.3 (*C*H), 126.8 (2 x *C*H), 126.4 (2 x *C*H), 125.5 (*C*H), 124.9 (*C*H), 118.9 (*C*), 72.8 (*C*H), 70.4 (*C*H_2), 65.4 (*C*H_2), 57.7 (*C*H_2), 54.4 (*C*H_2), 39.8 (*C*H), 37.5 (*C*H), 27.4 (*C*H_2), 26.9 (*C*H_2), 25.3 (*C*H), 23.2 (*C*H_2), 11.6 (*C*H_3). *NB: One quaternary resonance not observed*.

LRMS (m/z, ESI$^+$) 577 ([M]$^+$, 14%), 477 (100%).

$[\alpha]_D^{27}$ –133 (c = 0.94, CH_2Cl_2).

9-(Bromomethyl)anthracene **4.31**



4.30

$C_{15}H_{12}$
(192.26)

4.31

$C_{15}H_{11}Br$
(271.15)

To a solution of 9-methylanthracene **4.30** (5.00 g, 26.0 mmol) in CCl_4 (400 mL) was added NBS (4.63 g, 26.0 mmol). The reaction mixture was stirred at 76 °C and after 16 h was cooled to RT and concentrated under reduced pressure affording a dark yellow solid. This was taken up into CH_2Cl_2 (10 mL) and hexane (~100 mL) added. The precipitated succinimide was removed by filtration and the filtrate concentrated under reduced pressure to give the title compound **4.31** (7.05 g, 26.0 mmol, 100%) as a yellow crystalline solid. These data are in accordance with those reported in the literature [207]

M.P. 145–148 °C (CH_2Cl_2), Lit. 147–148 °C (no solvent given).[208]

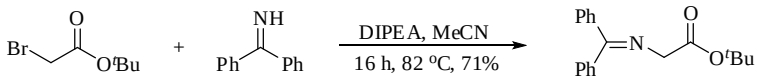
FT-IR (ν_{max}, neat) 3064 w, 3023 w, 2357 m, 2159 s, 2031 s, 2016 s, 1972 m, 1699 m, 1665 m, 1593 m, 1460 m, 1321 m, 1302 m, 1168 w, 935 w, 886 w, 754 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.52 (s, 1H, Ar*H*), 8.32 (d, *J*=8.6 Hz, 2H, Ar*H*), 8.06 (d, *J*=8.6 Hz, 2H, Ar*H*), 7.70–7.62 (m, 2H, Ar*H*), 7.55–7.48 (m, 2H, Ar*H*), 5.57 (s, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 131.6 (*C*), 129.7 (*C*), 129.3 (2 x *C*H), 129.2 (*C*H), 127.9 (*C*), 126.8 (2 x *C*H), 125.4 (2 x *C*H), 123.5 (2 x *C*H), 26.9 (*C*H_2).

LRMS (EI) 272 ($M^{+\bullet}${^{81}Br}, 2%), 270 ($M^{+\bullet}${^{79}Br}, 32%), 207 (100%).

tert-Butyl 2-(diphenylmethyleneamino)acetate **3.97**



4.32 $C_6H_{11}BrO_2$ (195.05)

4.33 $C_{13}H_{11}N$ (181.23)

3.97 $C_{19}H_{21}NO_2$ (295.38)

Prepared according to the method of Maier *et al*.[209]

To a stirred solution of ^{t}butyl 2-bromoacetate **4.32** (22.7 mL, 154 mmol), in MeCN (160 mL) was added benzophenone imine **4.33** (27.1 mL, 161.7 mmol) and DIPEA (26.8 mL, 154 mmol). The reaction mixture was heated at 82 °C for 16 h then cooled to RT and concentrated under reduced pressure to a yellow solid that was taken up into Et_2O (400 mL). The organic phase was washed sequentially with H_2O (3 x 200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a yellow solid. Purification by recrystalisation (Et_2O) to give the title compound **3.97** (32.1 g, 109 mmol, 71%) as a white crystalline solid. These data are in accordance with those reported in the literature.[209]

M.P. 112–114 °C (Et_2O), Lit. 111–112 °C.[210]

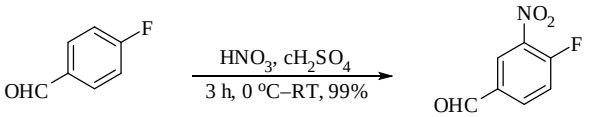
FT-IR (ν_{max}, neat) 3056 w, 2974 m, 2933 w, 2876 w, 1736 s, 1658 m, 1621 m, 1442 m, 1392 w, 1282 m, 1148 s, 1025 w, 849 m, 697 s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm 7.71–7.63 (m, 2H, Ar*H*), 7.51–7.29 (m, 6H, Ar*H*), 7.24–7.14 (m, 2H, Ar*H*), 4.13 (s, 2H, CH_2), 1.47 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ_C ppm 171.5 (*C*), 169.8 (*C*), 139.3 (*C*), 136.1 (*C*), 130.3 (2 x *C*H), 128.7 (2 x *C*H), 128.6 (2 x *C*H), 128.0 (2 x *C*H), 127.7 (2 x *C*H), 81.0 (*C*), 56.3 (*C*H_2), 28.1 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 296 ([M+Na]$^+$, 100%).

4-Fluoro-3-nitrobenzaldehyde **4.35**



4.34
C_7H_5FO
(124.11)

4.35
$C_7H_4FNO_3$
(169.11)

Prepared according to the method of Zhu *et al*.[211]

To a solution of nitric acid (70%, 13.4 mL, 302 mmol) in conc. H_2SO_4 (91.0 mL, 1.70 mol) at 0 °C was added dropwise 4-fluoro-nitrobenzaldehyde **4.34** (20.3 mL, 189 mmol). The reaction mixture was warmed to RT and after 3 h was poured onto cold H_2O (200 mL). The products were extracted with Et_2O (4 x 100 mL), then the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a yellow solid. Purification by flash column chromatography (20% Et_2O/petroleum ether) to give the title compound **4.35** (31.8 g, 188 mmol, 99%) as a pale yellow crystalline solid. These data are in accordance with those reported in the literature.[211]

M.P. 41–44 °C (EtOAc/petroleum ether), Lit. 46.5 °C (Et_2O).[212]

FT-IR (ν_{max}, neat) 3096 w, 3056 w, 2847 w, 2741 w, 1701 s, 1612 s, 1539 s, 1491 m, 1421 m, 1349 s, 1256 m, 1204 m, 1078 m, 921 m, 827 m, 710 w, 608 m cm^{-1}.

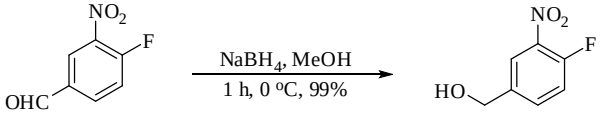
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 10.05 (s, 1H, C*H*O), 8.60 (dd, *J*=7.1, 2.2 Hz, 1H, Ar*H*), 8.21 (ddd, *J*=8.6, 4.4, 2.2 Hz, 1H, Ar*H*), 7.51 (dd, *J*=10.1, 8.6 Hz, 1H, Ar*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 188.1 (*C*H), 158.9 (d, J_{CF}=275 Hz, *C*F), 138.0 (*C*), 135.5 (d, J_{CF}=10.2 Hz, *C*H), 132.9 (d, J_{CF}=4.4 Hz, *C*), 127.9 (*C*H), 119.8 (d, J_{CF}=20.5 Hz, *C*H).

^{19}F NMR (376 MHz, $CDCl_3$) δ_F ppm -107.6 (ddd, *J*=10.1, 7.0, 4.3 Hz, C*F*).

LRMS (EI) 169 ($M^{+\bullet}$) 90%, 168 $(M\text{-}H)^+$ 60%, 93 (100%).

(4-Fluoro-3-nitrophenyl)methanol **4.36**



4.35
$C_7H_4FNO_3$
(169.11)

4.36
$C_7H_6FNO_3$
(171.13)

Prepared according to the method of Zhu *et al*.[211]

To a solution of aldehyde **4.35** (30.5 g, 180 mmol) in dry MeOH (300 mL) at 0 °C was added $NaBH_4$ (7.15 g, 189 mmol). After 1 h a saturated solution of NH_4Cl (200 mL) was added dropwise at over 15 min. The aqueous phase was extracted with EtOAc (4 x 200 mL), then the combined organic phases were washed with brine (400 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a dark brown oil. Purification by flash column chromatography (20–40% Et_2O/petroleum ether) to give

the title compound **4.36** (30.7 g, 179 mmol, 99%) as a pale yellow solid. These data are in accordance with those reported in the literature.[211]

M.P. 44–47 ^{o}C (Et_2O), Lit. 42–44 ^{o}C (benzene/hexane).[213]

FT-IR (ν_{max}, neat) 3358 br. m, 3072 w, 2933 w, 2876 w, 2357 w, 1621 m, 1593 s, 1531 s, 1499 m, 1344 s, 1247 m, 1037 m, 921 m, 818 m cm^{-1}.

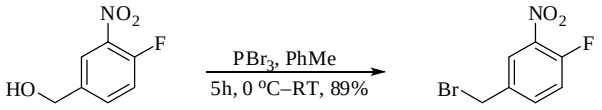
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.98 (dd, *J*=7.1, 2.4 Hz, 1H, Ar*H*), 7.56 (ddd, *J*=8.6, 4.3, 2.4 Hz, 1H, Ar*H*), 7.20 (dd, *J*=10.6, 8.6 Hz, 1H, Ar*H*), 4.68 (s, 2H, CH_2), 2.17 (br. s, 1H, O*H*).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 154.7 (d, J_{CF}=265 Hz, *C*F), 137.9 (d, J_{CF}=10.2 Hz, *C*), 137.1 (*C*), 133.5 (d, J_{CF}=8.8 Hz, *C*H), 123.9 (d, J_{CF}=2.93 Hz, *C*H), 118.4 (d, J_{CF}=22.0 Hz, *C*H), 63.2 (*C*H_2).

^{19}F NMR (376 MHz, $CDCl_3$) δ_F ppm –119.7 (dddt, *J*=10.6, 7.1, 4.1, 0.9 Hz, CF,).

LRMS (EI) 171 ($M^{+\bullet}$) 50%, 95 (100%).

4-(Bromomethyl)-1-fluoro-2-nitrobenzene **3.98**



4.36 $C_7H_6FNO_3$ (171.13)

3.98 $C_7H_5BrFNO_2$ (234.02)

To a solution of benzyl alcohol **4.36** (500 mg, 2.92 mmol) in dry toluene (12 mL) at 0 ^{o}C was added PBr_3 (274 µL, 2.92 mmol) over 5 min. The reaction mixture was warmed to RT and after 5 h a saturated solution of NH_4Cl (30 mL) was added. The aqueous phase was extracted with EtOAc (3 x 20 mL), and the combined organic phases were

washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a dark brown oil. Purification by trituration from cold hexane to give the title compound **3.98** (610 mg, 2.60 mmol, 89%) as a pale brown solid. These data are in accordance with those reported in the literature.[211]

M.P. 56–59 ^oC (Et_2O/MeOH), Lit. 59 ^oC (heptane/EtOAc).[211]

FT-IR (ν_{max}, neat) 3064 w, 2872 w, 1621 m, 1533 s, 1486 m, 1349 s, 1307 w, 1254 m, 1229 m, 1135 m, 1086 m, 902 m, 829 m, 624 m cm^{-1}.

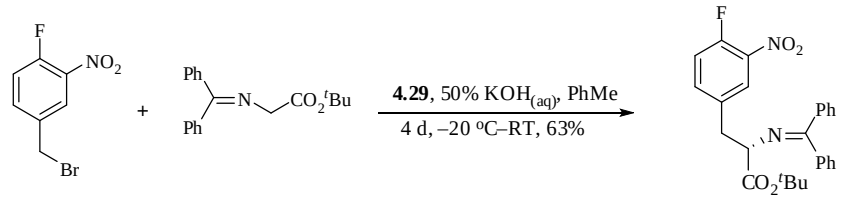
^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.08 (dd, *J*=6.8, 2.4 Hz, 1H, Ar*H*), 7.66 (ddd, *J*=8.6, 4.0, 2.4 Hz, 1H, Ar*H*), 7.27 (dd, *J*=10.6, 8.6 Hz, 1H, Ar*H*), 4.47 (s, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 155.1 (d, *J*=266 Hz, *C*F), 135.9 (d, *J*=8.8 Hz, *C*H), 134.9 (d, *J*=4.4 Hz, *C*), 126.5 (*C*H), 119.0 (d, *J*=20.5 Hz, *C*H), 30.2 (*C*H_2). *NB: One quaternary resonance not observed.*

^{19}F NMR (376 MHz, $CDCl_3$) δ_F ppm –117.4 (ddd, *J*=10.7, 6.8, 4.1 Hz, 1F, *F*), –109.1 (ddd, *J*=10.1, 7.2, 4.3 Hz, C*F*).

LRMS (EI) 235 ({^{81}Br}$M^{+\bullet}$) 3%, 233 ({^{79}Br}$M^{+\bullet}$) 3%, 154 (100%).

tert-Butyl (*S*)-2-(diphenylmethyleneamino)-3-(4-fluoro-3-nitrophenyl)propanoate **4.37**



3.98 $C_7H_5BrFNO_2$ (234.02)

3.97 $C_{19}H_{21}NO_2$ (295.37)

4.37 $C_{26}H_{25}FN_2O_4$ (448.48)

To a solution of imine **3.97** (500 mg, 1.69 mmol) in toluene (11 mL) was added **4.29** (111 mg, 169 µmol). The reaction mixture was cooled to –20 °C and 50% $KOH_{(aq)}$ (1.00 mL) was added dropwise over 10 min with vigorous stirring. After 30 min benzyl bromide **3.98** (5.15 mg, 2.20 mmol) in toluene (2.00 mL) was added dropwise over 5 min. The reaction mixture was warmed to RT and after 4 d was partitioned between Et_2O (100 mL) and H_2O (150 mL). The aqueous phase was extracted with Et_2O (3 x 25 mL) then the combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording an orange oil. Purification by flash column chromatography (0–25% Et_2O /petroleum ether) to give the title compound **4.37** (620 mg, 1.38 mmol, 63%) as a pale yellow oil. These data are in accordance with those reported in the literature.[214] Chiral HPLC performed using an AD-H column at 254 nm in 10% ^{i}PrOH/hexane at 0.5 mL.min^{-1}.

FT-IR (ν_{max}, neat) 3056 br. w, 2970 br. m, 2917 br. m, 2847 br. w, 2153 m, 1730 m, 1537 m, 1350 m, 1278 m, 1151 s, 701 s cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm 7.78 (dd, *J*=7.1, 2.0 Hz, 1H, Ar*H*), 7.60 (br. d, *J*=7.7 Hz, 2H, Ar*H*), 7.48 – 7.30 (m, 7H, Ar*H*), 7.14 (dd, *J*=10.6, 8.4 1H, Ar*H*), 6.84–6.76 (m, 2H, Ar*H*), 4.19 (app. t, *J*=6.4 Hz 1H, NC*H*CO), 3.30–3.23 (m, 2H, CH_2), 1.46 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.2 (*C*), 169.9 (*C*), 154.2 (d, J_{CF}=263 Hz, *C*F), 138.9 (*C*), 137.0 (d, J_{CF}=7.3 Hz, *C*H), 136.0

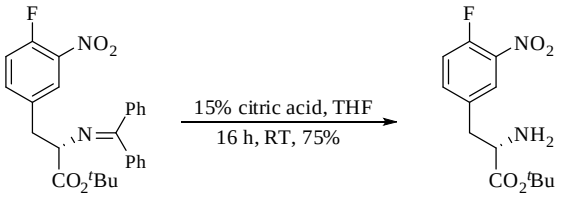
(*C*), 135.6 (*C*), 135.5 (*C*), 130.6 (2 x *C*H), 128.8 (2 x *C*H), 128.4 (2 x *C*H), 128.1 (2 x *C*H), 127.4 (2 x *C*H), 126.9 (d, J_{CF}=2.9 Hz, *C*H), 117.8 (d, J_{CF}=20.5 Hz, *C*H), 81.8 (*C*), 66.7 (*C*H), 38.4 (*C*H_2), 28.0 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 919 ([2M+Na]$^+$, 14%), 471 ([M+Na]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{26}H_{25}FN_2O_4$ [M+Na]$^+$ requires 471.1696; found: 471.1691.

$[\alpha]_D^{26}$ –148 (c = 1.46, CH_2Cl_2).

<u>*tert*-Butyl (*S*)-2-amino-3-(4-fluoro-3-nitrophenyl)propanoate **4.38**</u>



4.37
$C_{26}H_{25}FN_2O_4$
(448.48)

4.38
$C_{13}H_{17}FN_2O_4$
(284.28)

To a solution of imine **4.37** (6.97 g, 15.5 mmol) in THF (80 mL) was added 15% citric acid solution (60 mL) dropwise over 10 min. After 16 h the reaction mixture was partitioned between Et_2O (100 mL) and 1M HCl (100 mL). The organic phase was extracted with 1M HCl (2 x 50 mL) and the combined aqueous phases basified to pH 9 by the careful addition of K_2CO_3 (50 g). The products were extracted with EtOAc (4 x 200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **4.38** (3.31 g, 11.6 mmol, 75%) as a yellow oil that was used without further purification. These data are in accordance with those reported in the literature.[215]

FT-IR (ν_{max}, neat) 3378 w, 2978 m, 2929 m, 1723 s, 1625 m, 1535 s, 1349 s, 1248 m, 1151 s, 1086 w, 841 m, 743 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.95 (dd, *J*=7.1, 2.1 Hz, 1H, Ar*H*), 7.53 (ddd, *J*=8.6, 4.0, 2.1 Hz, 1H, Ar*H*), 7.22 (dd, *J*=10.6, 8.3 Hz, 1H, Ar*H*), 3.61 dd, *J*=13.8, 5.6 Hz, 1H, NC*H*CO), 3.06 (dd, *J*=13.8, 5.6 Hz, 1H, CH*H*), 2.91 (dd, *J*=13.8, 7.1 Hz, 1H, C*H*H), 1.67 (br. s, 2H, NH_2), 1.44 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 173.6 (*C*), 154.4 (d, J_{CF}=263 Hz, *C*), 137.0 (d, J_{CF}=7.3 Hz, *C*), 136.6 (d, J_{CF}=8.8 Hz, *C*H), 134.9 (d, J_{CF}=4.4 Hz, *C*), 126.6 (d, J_{CF}=2.9 Hz, *C*H), 118.2 (d, J_{CF}=20.5 Hz, *C*H), 81.9 (*C*), 55.8 (*C*H), 39.8 (*C*H_2), 27.9 ((*C*H_3)$_3$).

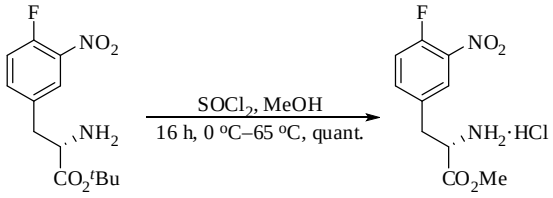
^{19}F NMR (376 MHz, $CDCl_3$) δ_F ppm –120.7 (ddd, *J*=10.8, 6.9, 4.4 Hz, *F*).

LRMS (m/z, ESI$^+$) 571 (100%), 348 ([M+Na+MeCN]$^+$, 44%).

HRMS (m/z, ESI$^+$) calcd for $C_{13}H_{17}FN_2O_4$ [M+Na]$^+$ requires 307.1070; found: 307.1068.

$[\alpha]_D^{26}$ –82.3 (c = 0.81, acetone).

Methyl (*S*)-2-ammonium-3-(4-fluoro-3-nitrophenyl)propanoate chloride **3.92**



4.38 $C_{13}H_{17}FN_2O_4$ (284.28)

3.92 $C_{10}H_{12}ClFN_2O_4$ (278.66)

Thionyl chloride (1.17 mL, 16.1 mmol) was added dropwise over 2 min to dry MeOH (50 mL) at 0 °C with rapid stirring. Ester **4.38** (3.28 g, 11.5 mmol) was added and the reaction mixture was heated at 64 °C for 16 h then cooled to RT and concentrated under

reduced pressure to give the title compound **3.92** (2.78 g, 11.5 mmol, 100%) as a yellow foamy solid that was used without further purification. These data are in accordance with those reported in the literature.[106]

FT-IR (ν_{max}, neat) br. w, 2970, 2844 br. s, 2729 br. w, 2622 br. m, 1744 s, 1533 s, 1513 s, 1349 s, 1242 s, 1214 s, 1150 m, 1129 m, 1056 m, 843 m, 739 m, 510 m cm^{-1}.

^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ_H ppm 8.08 (dd, *J*=6.8, 2.4 Hz, 1H, Ar*H*), 7.69 (ddd, *J*=8.6, 4.2, 2.4 Hz, 1H, Ar*H*), 7.45 (dd, *J*=11.0, 8.6 Hz, 1H, Ar*H*), 4.44 (app. t, *J*=6.8 Hz, 1H, NC*H*CO), 3.39 (dd, *J*=14.6, 7.1 Hz, 1H, CH*H*), 3.34 (dd, *J*=14.6, 6.1 Hz, 1H, C*H*H).

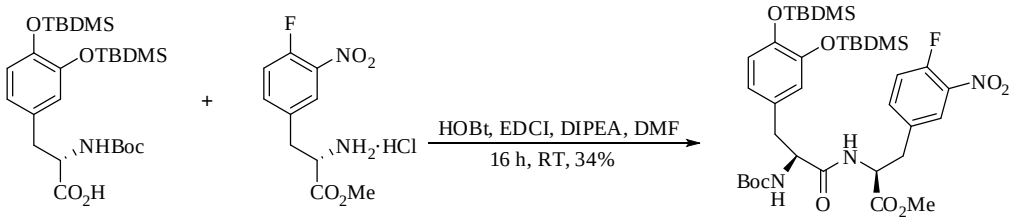
^{13}C NMR (100 MHz, *d*$_4$-MeOH) δ_C ppm 170.1 (*C*), 156.4 (d, J_{CF}=156 Hz, *C*), 138.9 (*C*), 138.3 (d, J_{CF}=8.8 Hz, *C*H), 133.3 (d, J_{CF}=4.4 Hz, *C*), 128.3 (d, J_{CF}=2.9 Hz, *C*H), 120.2 (d, J_{CF}=21.9 Hz, *C*H), 54.9 (*C*H), 53.9 (*C*H_3), 36.1 (*C*H_2).

^{19}F NMR (376 MHz, *d*$_4$-MeOH) δ_F ppm –121.5 (ddd, *J*=11.0, 6.9, 4.2 Hz, C*F*).

LRMS (m/z, ESI$^+$) 284 ($[M+Na+MeCN]^+$, 100%), 243 ($[M+Na]^+$, 18%).

$[\alpha]_D^{27}$ +1.35 (c = 0.81, MeOH).

Methyl (*S*)-2-((*S*)-3-(3,4-bis(*tert*-butyldimethylsilyloxy)phenyl)-2-(*tert*-butoxy-carbonylamino)propanamido)-3-(4-fluoro-3-nitrophenyl)propanoate **4.24**



4.21 $C_{26}H_{47}NO_6Si_2$ (525.8)

3.92 $C_{10}H_{12}ClFN_2O_4$ (278.66)

4.24 $C_{36}H_{56}FN_3O_9Si_2$ (749.36)

To a solution of carboxylic acid **4.21** (7.30 g, 13.9 mmol) in DMF (200 mL) was added EDCI (2.46 mL, 13.9 mmol), HOBt (1.88 g, 13.9 mmol), hydrochloride salt **3.92** (2.78 g, 9.97 mmol) and DIPEA (27.9 mL, 4.86 mmol). After 16 h the reaction mixture was diluted with H_2O (600 mL) and the products extracted with EtOAc (4 x 150 mL). The combined organic phases were washed with brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a brown oil. Purification by flash column chromatography (10–20% EtOAc/petroleum ether) to give the title compound **4.24** (2.57 g, 3.42 mmol, 34%) as a pale yellow solid. These data are in accordance with those reported in the literature.[159]

M.P. 49–55 ^oC (EtOAc/petroleum ether), Lit. 66–69 ^oC (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3309 br. m, 2949 m, 2929 m, 2851 m, 1744 m, 1659 m, 1537 s, 1508 s, 1350 m, 1292 s, 1251 s, 1165 s, 1127 m, 908 m, 838 s, 781 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.78 (dd, *J*=7.1, 2.0 Hz, 1H, Ar*H*), 7.35 (ddd, *J*=8.4, 4.2, 2.0 Hz, 1H, Ar*H*), 7.18 (dd, *J*=10.4, 8.4 Hz, 1H, Ar*H*), 6.75 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.66 (d, *J*=2.0 Hz, 1H, Ar*H*), 6.63 (dd, *J*=8.1, 2.0 Hz, 1H, Ar*H*), 6.60 (br. s, 1H, N*H*), 4.84 (br. s, 1H, N*H*), 4.79 (app. br. q, *J*=6.0 Hz, 1H, NC*H*CO), 4.22 (app. br. q, *J*=7.1 Hz, 1H, NC*H*CO), 3.73 (s, 3H, CH_3), 3.23

(dd, *J*=14.0, 5.6 Hz, 1H, C*H*H), 3.10 (dd, *J*=14.0, 5.6 Hz, 1H, CH*H*), 2.97 (dd, *J*=14.2, 6.6 Hz, 1H, C*H*H), 2.87 (dd, *J*=14.2, 7.6 Hz, 1H, CH*H*), 1.40 (s, 9H, C(CH_3)$_3$), 0.98 (s, 9H, C(CH_3)$_3$), 0.98 (s, 9H, C(CH_3)$_3$), 0.19 (s, 3H, Si(CH_3)), 0.19 (s, 3H, Si(CH_3)), 0.18 (s, 6H, Si(CH_3)$_2$).

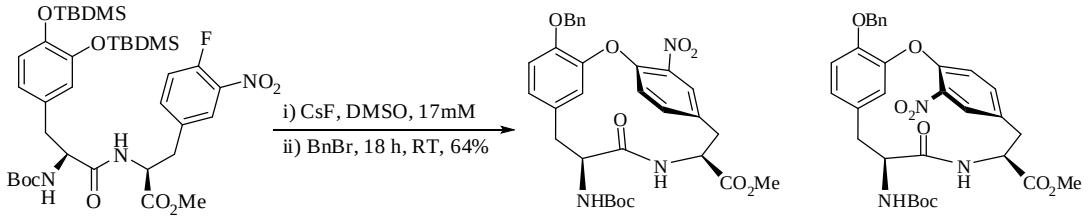
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.4 (*C*), 170.7 (*C*), 155.2 (d, J_{CF}=152 Hz, *C*), 146.9 (*C*), 146.0 (*C*), 137.1 (d, J_{CF}=7.0 Hz, *C*H), 136.9 (*C*H), 133.2 (*C*), 129.1 (*C*), 126.6 (*C*H), 122.0 (d, J_{CF}=13.2 Hz, *C*H), 121.2 (*C*H), 118.5 (d, J_{CF}=20.5 Hz, *C*H), 80.5 (*C*), 55.9 (*C*H), 53.0 (*C*H), 52.7 (*C*H_3), 36.9 (2 x *C*H_2), 28.2 ((*C*H_3)$_3$), 25.9 (2 x (*C*H_3)$_3$), 18.4 (2 x Si*C*(CH_3)$_3$), –4.1 (*C*H_3), –4.1 (*C*H_3), –4.2 (2 x *C*H_3). *NB: One quaternary resonance not observed*.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F ppm –120.5 (br. s, C*F*).

LRMS (m/z, ESI$^+$) 772 ([M+Na]$^+$, 100%).

$[\alpha]_D^{26}$ +9.9 (c = 1.07, CH_2Cl_2).

4-Benzyloxy-9-*tert*-butoxycarbonylamino-16-nitro-10-oxo-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 **4.39a** with 4-Benzyloxy-9-*tert*-butoxycarbonylamino-17-nitro-10-oxo-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 **4.39b**



4.24
$C_{36}H_{56}FN_3O_9Si_2$
(749.36)

4.39a
$C_{31}H_{33}N_3O_9$
(591.61)

4.39b
$C_{31}H_{33}N_3O_9$
(591.61)

To a solution of dipeptide **4.24** (500 mg, 667 µmol) in DMSO (400 mL) was added CsF (503 mg, 3.33 mmol) and after 6 h, BnBr (318 µL, 2.67 µmol). The reaction mixture was stirred for a further 12 h and then diluted with H_2O (500 mL). 1M HCl (200 mL) was added and the products extracted with EtOAc (5 x 200 mL). The combined organic phases were washed with H_2O (5 x 300 mL) and brine (500 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compounds **4.39a** and **4.39b** (251 mg, 424 µmol, 64%) as a yellow oil as a 1:1 mixture of atropisomers.

FT-IR (ν_{max}, neat) 3391.2 w, 3346 br. m, 3035 w, 2982 m, 2921 m, 2876 w, 1732 s, 1703 s, 1670 s, 1528 s, 1350 m, 1258 m, 1230 s, 1160 s, 1120 m, 1025 m, 902 m, 731 s, 694 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 8.10 (d, *J*=2.0 Hz, 1H, Ar*H*), 7.66 (dd, *J*=8.3, 2.3 Hz, 1H, Ar*H*), 7.60 (d, *J*=2.0 Hz, 1H, Ar*H*), 7.56–7.49 (m, 5H, Ar*H*), 7.45 (s, 1H, Ar*H*), 7.44–7.37 (m, 5H, Ar*H*), 7.36–7.30 (m, 3H, Ar*H*), 7.25 (br. s, 1H, N*H*), 7.02 (br. s, 1H, N*H*), 6.96 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.81 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.79 (d, *J*=8.6 Hz, 1H, Ar*H*), 6.59 (br. app. d, 2H, 2xN*H*),

5.26–5.19 (m, 4H, 2xC*H*$_2$), 5.17 (d, *J*=2.0 Hz, 1H, Ar*H*), 5.13 (s, 1H, Ar*H*), 5.12–4.99 (m, 3H, 3xNC*H*CO), 4.66 (br. app. d, *J*=2.0 Hz, 1H, NC*H*CO), 3.83 (s, 3H, C*H*$_3$), 3.82 (s, 3H, C*H*$_3$), 3.65–3.53 (m, 4H, 2xC*H*$_2$), 2.79–2.65 (m, 2H, C*H*$_2$), 2.59–2.46 (m, 2H, C*H*$_2$), 1.50–1.41 (s, 18H, 2xC(C*H*$_3$)$_3$),

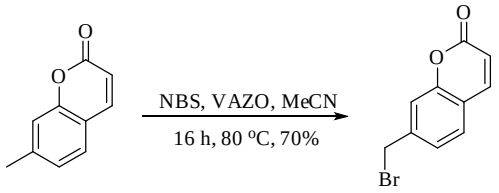
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.8 (*C*), 171.3 (*C*), 171.2 (*C*), 171.1 (*C*), 152.8 (*C*), 152.4 (*C*), 152.1 (*C*), 151.2 (*C*), 148.0 (*C*), 147.1 (*C*), 146.7 (*C*), 145.5 (*C*), 145.2 (*C*), 144.8 (*C*), 137.8 (*C*H), 136.9 (*C*), 136.8 (*C*), 135.4 (*C*), 135.2 (*C*), 134.5 (*C*H), 129.1 (*C*H), 128.9 (*C*), 128.6 (2x*C*H), 128.0 (*C*H), 127.9 (2x*C*H), 127.8 (*C*H), 127.6 (2x*C*H), 127.4 (2x*C*H), 125.3 (*C*H), 124.9 (*C*H), 117.7 (*C*H), 117.6 (*C*H), 116.9 (*C*H), 116.4 (*C*H), 116.1 (*C*H), 115.1 (*C*H), 80.4 (*C*), 80.1 (*C*), 72.1 (*C*H_2), 71.4 (*C*H_2), 52.9 (*C*H), 52.8 (*C*H), 52.6 (*C*H_3), 52.5 (*C*H_3), 38.3 (2 x *C*H_2), 32.6 (2 x *C*H_2), 28.2 ((*C*H_3)$_3$), 28.1 ((*C*H_3)$_3$), *NB: One quaternary and one aromatic CH resonance not observed*.

LRMS (m/z, ESI$^+$) 614 ($[M+Na]^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{31}H_{33}N_3O_9$ $[M+Na]^+$ requires 614.2114; found: 614.2107.

$[\alpha]_D^{29}$ +4.0 (c = 0.05, CH_2Cl_2).

7-(Bromomethyl)-2*H*-chromen-2-one **3.96**



3.96

$C_{10}H_8O_2$ (160.17)

$C_{10}H_7BrO_2$ (239.06)

Prepared according to the method of Carotti *et al.*[216]

To a solution of 7-methylcoumarin (10.0 g, 62.4 mmol) in MeCN (250 mL) at was added NBS (13.3 g, 74.9 mmol) and VAZO (1.52 g, 6.24 mmol). The reaction mixture was heated at 80 °C for 16 h, cooled to RT and concentrated under reduced pressure. Purification by recrystalisation (acetone) to give the title compound **3.96** (10.2 g, 42.8 mmol, 70%) as a white crystalline solid. These data are in accordance with those reported in the literature.[216]

M.P. 177–179 °C (acetone), Lit. 172–176 °C (ethanol).[217]

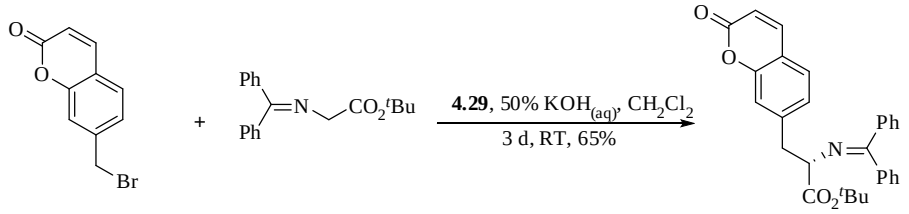
FT-IR (ν_{max}, neat) 3035 br. m, 2917 m, 2847 w, 261 w, 1709 s, 1616 s, 1533 m, 1394 m, 1215 m, 1190 m, 1130 m, 1098 s, 840 s, 755 m, 650 m, 538 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.69 (d, *J*=9.6 Hz, 1H, C*H*), 7.47 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.35 (br. s, 1H, Ar*H*), 7.31 (dd, *J*=8.1, 1.5 Hz, 1H, Ar*H*), 6.43 (d, *J*=9.6 Hz, 1H, C*H*), 4.52 (s, 2H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 160.3 (*C*), 154.0 (*C*), 142.8 (*C*H), 142.0 (*C*), 128.3 (*C*H), 125.1 (*C*H), 118.7 (*C*), 117.2 (*C*H), 117.1 (*C*H), 31.8 (*C*H_2).

LRMS (m/z, ESI$^+$) 369 (100%), 303 ([M+Na+MeCN]$^+$, 6%), 262 ([M+Na]$^+$, 2%).

tert-Butyl (*S*)-2-(diphenylmethyleneamino)-3-(2-oxo-*2H*-chromen-7-yl)propanoate **4.40**



3.96 $C_{10}H_7BrO_2$ (239.06)

3.97 $C_{19}H_{21}NO_2$ (295.37)

4.40 $C_{29}H_{27}NO_4$ (453.53)

To a solution of imine **3.97** (10.0 g, 33.9 mmol), coumarin **3.96** (10.5 g, 44.0 mmol) and catalyst **4.29** (2.23 g, 3.39 mmol) in CH_2Cl_2 (100 mL) was added 50% $KOH_{(aq)}$ (10 mL) dropwise over 10 min whilst stirring vigoursly. After 3 d H_2O (200 mL) was added then the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phases washed with brine (3 x 200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (0–20% Et_2O /petroleum ether) to give the title compound **4.40** (1.93 g, 4.26 mmol, 65%) as a yellow foamy solid. Chiral HPLC performed using an AD-H column at 254 nm in 10% ^{i}PrOH/hexane at 0.5 mL.min^{-1}.

FT-IR (ν_{max}, neat) 3056 w, 2978 m, 2925 m, 2872 w, 1729 s, 1619 s, 1445 m, 1367 m, 1286 m, 1226 m, 1148 s, 890 m, 844 m, 755 m, 731 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.65 (d, *J*=9.6 Hz, 1H, C*H*), 7.60–7.58 (br. m, 1H, Ar*H*), 7.58–7.56 (br. m, 1H, Ar*H*), 7.38 (br. app. s, 1H, Ar*H*), 7.38–7.36 (br. m, 1H, Ar*H*), 7.35–7.28 (br. m, 5H, Ar*H*), 7.05 (br. app. s, 2H, Ar*H*), 6.75 (d, *J*=7.1 Hz, 2H, Ar*H*), 6.37 (d, *J*=9.6 Hz, 1H, C*H*), 4.20 (dd, *J*=8.7, 4.7 Hz, 1H, NC*H*CO), 3.32 (dd, *J*=13.1, 4.7 Hz, 1H, CH*H*), 3.25 (dd, *J*=13.1, 8.7 Hz, 1H, C*H*H), 1.45 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 170.8 (*C*), 170.2 (*C*), 160.9 (*C*), 153.9 (*C*), 143.6 (*C*), 143.2 (*C*H), 139.2 (*C*), 136.1 (*C*), 130.4 (*C*H),

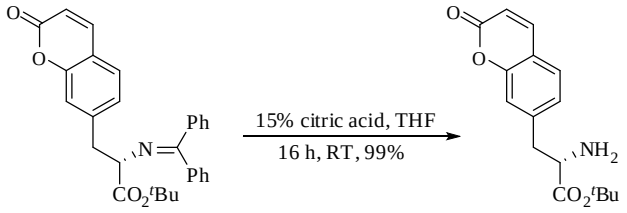
128.7 (2 x *C*H), 128.6 (*C*H), 128.2 (2 x *C*H), 128.0 (2 x *C*H), 127.5 (*C*H), 126.3 (*C*H), 117.8 (2 x *C*H), 117.0 (*C*), 115.9 (*C*H), 81.6 (*C*), 67.2 (*C*H), 39.6 (CH_2), 28.3 ((CH_3)$_3$).

LRMS (m/z, ESI$^+$) 929 ([2M+Na]$^+$, 33%), 517 ([M+Na+MeCN]$^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{29}H_{27}NO_4$ [M+H]$^+$ requires 454.2018; found: 454.2016.

$[\alpha]_D^{31}$ –92.5 (c = 0.6, CH_2Cl_2).

<u>*tert*-Butyl (*S*)-2-amino-3-(2-oxo-*2H*-chromen-7-yl)propanoate **4.41**</u>



4.40
$C_{29}H_{27}NO_4$
(453.53)

4.41
$C_{16}H_{19}NO_4$
(289.32)

To a solution of imine **4.40** (1.49 g, 3.28 mmol) in THF (20 mL) was added 15% citric acid solution (15 mL) dropwise over 5 min. After 16 h the reaction mixture was partitioned between Et_2O (50 mL) and 1M HCl (50 mL). The organic phase was washed with 1M HCl (2 x 50 mL) and the combined aqueous phases were basified to pH 9 by the careful addition of K_2CO_3 (17 g, 123 mmol) then extracted with EtOAc (4 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the title compound **4.41** (940 mg, 3.25 mmol, 99%) as a light brown oil that was used without further purification.

FT-IR (ν_{max}, neat) 3382 w, 2974 m, 2925 m, 1722 s, 1619 s, 1364 m, 1221 m, 1150 s, 890 w, 843 s, 751 m cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H ppm 7.68 (d, *J*=9.5 Hz, 1H, C*H*), 7.42 (d, *J*=7.8 Hz, 1H, Ar*H*), 7.21 (br. app. s, 1H, Ar*H*), 7.17 (dd, *J*=7.8, 1.3 Hz, 1H, Ar*H*), 6.38 (d, *J*=9.5 Hz, 1H, C*H*), 3.65 (app. t, *J*=6.6 Hz, 1H, NC*H*CO), 3.12 (dd, *J*=13.5, 5.5 Hz, 1H, CH*H*), 2.93 (dd, *J*=13.5, 7.5 Hz, 1H, C*H*H), 1.72 (br. s, 2H, NH_2), 1.44 (s, 9H, C(CH_3)$_3$).

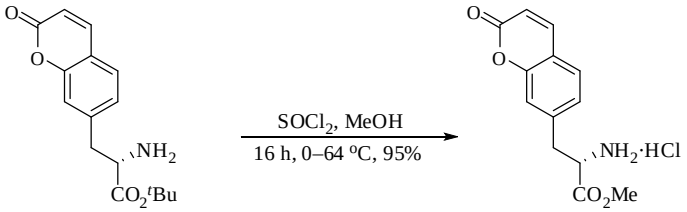
^{13}C NMR (75 MHz, $CDCl_3$) δ_C ppm 173.8 (*C*), 160.8 (*C*), 154.0 (*C*), 143.2 (*C*H), 142.7 (*C*), 128.2 (*C*), 127.7 (*C*H), 125.8 (*C*H), 117.5 (*C*H), 116.1 (*C*H), 81.6 (*C*), 56.0 (*C*H), 40.9 (*C*H_2), 28.0 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 353 ([M+Na+MeCN]$^+$, 36%), 275 (100%).

HRMS (m/z, ESI$^+$) calcd for $C_{16}H_{19}NO_4$ [M+Na]$^+$ requires 312.1212; found: 312.1209.

$[\alpha]_D^{29}$ +5.7 (c = 0.365, CH_2Cl_2).

Methyl (*S*)-2-ammonium-3-(2-oxo-*2H*-chromen-7-yl)propanoate chloride **4.42**



4.41
$C_{16}H_{19}NO_4$
289.33

4.42
$C_{13}H_{14}ClNO_4$
283.71

$SOCl_2$ (868 µL, 11.9 mmol) was added dropwise to dry MeOH (20 mL) at 0 °C, followed amine **4.41** (860 mg, 2.97 mmol) added portionwise over 3 min. The reaction mixture was heated at 64 °C for 16 h, cooled to RT and concentrated under reduced pressure to give the title compound **4.42** (760 mg, 2.68 mmol, 95%) as a yellow foamy solid that was used without further purification.

FT-IR (ν_{max}, neat) 3399 br. w, 2843 br. m, 2614 br. w, 1729 s, 1693 s, 1619 s, 1554 w, 1504 m, 1425 m, 1230 s, 1136 s, 1104 m, 891 m, 839 m, 756 m, 704 m, 617 m cm^{-1}.

^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ_H ppm 7.97 (d, *J*=9.6 Hz, 1H, C*H*), 7.66 (d, *J*=7.6 Hz, 1H, Ar*H*), 7.31 (app. s, 1H, Ar*H*), 7.28 (dd, *J*=7.9, 1.8 Hz, 1H, Ar*H*), 6.44 (d, *J*=9.6 Hz, 1H, C*H*), 4.45 (app. t, *J*=6.8 Hz, 1H, NC*H*CO), 3.83 (s, 3H, CH_3), 3.41 (dd, *J*=14.5, 6.6 Hz, 1H, CH*H*), 3.32 (dd, *J*=15.5, 7.1 Hz, 1H, C*H*H).

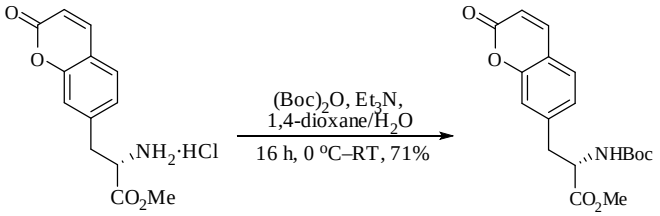
^{13}C NMR (100 MHz, *d*$_4$-MeOH) δ_C ppm 170.3 (*C*), 162.6 (*C*), 155.6 (*C*), 145.4 (*C*H), 140.4 (*C*), 130.3 (*C*H), 127.1 (*C*H), 120.1 (*C*), 118.6 (*C*H), 117.4 (*C*H), 54.9 (*C*H), 53.9 (*C*H_3), 37.3 (*C*H_2).

LRMS (m/z, ESI$^+$) 289 ($[M+H+MeCN]^+$, 100%), 248 ($[M+H]^+$, 29%).

HRMS (m/z, ESI$^+$) calcd for $C_{13}H_{13}NO_4$ $[M+H]^+$ requires 248.0923; found: 248.0917.

$[\alpha]_D^{29}$ +5.4 (c = 0.6, MeOH).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(2-oxo-*2H*-chromen-7-yl)propanoate **3.95**



4.42 $C_{13}H_{14}ClNO_4$ (283.71)

3.95 $C_{18}H_{21}NO_6$ (347.36)

To a solution of hydrochloride salt **4.42** (720 mg, 2.54 mmol) in 1,4-dioxane/water (1:1, 30 mL) at 0 °C was added Et_3N (389 µL, 2.79 mmol) followed by the dropwise addition of $(Boc)_2O$ (578 mg, 3.05 mmol) and a second charge of Et_3N (389 µL, 2.79 mmol).

The reaction mixture was warmed to RT and after 16 h 2M HCl (30 mL) was added and the products extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a crude brown oil. Purification by flash column chromatography (20–40% EtOAc/petroleum ether) to give the title compound **3.95** (625 mg, 1.60 mmol, 71%) as a white solid.

M.P. 95–97 ^{o}C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3346 w, 2974 w, 1699 s, 1619 s, 1507 m, 1364 m, 1215 m, 1161 s, 1134 m, 1102 m, 1012 m, 914 m, 841 m, 730 s cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.67 (d, *J*=9.3 Hz, 1H, C*H*), 7.41 (d, *J*=8.1 Hz, 1H, Ar*H*), 7.10 (app. s, 1H, Ar*H*), 7.07 (dd, *J*=8.1, 1.5 Hz, 1H, Ar*H*), 6.39 (d, *J*=9.3 Hz, 1H, C*H*), 5.08 (br. d, *J*=7.1 Hz, 1H, N*H*), 4.62 (app. q, *J*=6.6 Hz, 1H, NC*H*CO), 3.74 (s, 3H, CH_3), 3.24 (dd, *J*=13.5, 5.6 Hz, 1H, CH*H*), 3.11 (dd, *J*=13.5, 5.8 Hz, 1H, C*H*H). 1.41 (s, 9H, C(CH_3)$_3$).

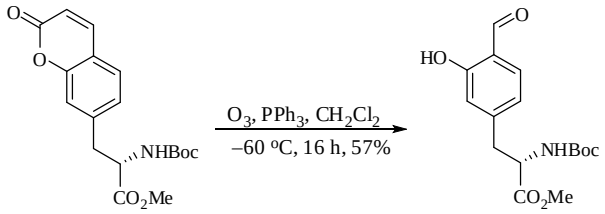
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 171.7 (*C*), 160.7 (*C*), 154.9 (*C*), 153.9 (*C*), 143.1 (*C*H), 141.1 (*C*), 127.8 (*C*H), 125.6 (*C*H), 117.7 (*C*), 117.5 (*C*H), 116.3 (*C*H), 80.2 (*C*), 54.2 (*C*H), 52.4 (*C*H_3), 38.4 (*C*H_2), 28.2 ((*C*H_3)$_3$),

LRMS (m/z, ESI^{+}) 717 ([2M+Na]$^{+}$, 29%), 411 ([M+Na+MeCN]$^{+}$, 100%).

HRMS (m/z, ESI^{+}) calcd for $C_{18}H_{21}NO_6$ [M+Na]$^{+}$ requires 370.1267; found: 370.1261.

$[\alpha]_D^{27}$ +54.6 (c = 0.94, CH_2Cl_2).

Methyl(*S*)-2-(*tert*-butoxycarbonylamino)-3-(4-formyl-3-hydroxyphenyl)propanoate **3.94**



3.95

$C_{18}H_{21}NO_6$
(347.36)

3.94

$C_{16}H_{21}NO_6$
(323.34)

Ozone (1–4% in O_2) was bubbled through a solution of courmarin **3.95** (818 mg, 2.35 mmol) in CH_2Cl_2 (21 mL) at –60 °C until a blue colour was observed (*ca.* 30 min). Oxygen was then bubbled through the solution until the blue colour had disappeared to remove any excess ozone. PPh_3 (1.23 g, 4.70 mmol) was added and after 30 min the reaction mixture was tested for the presence of any peroxides. The reaction mixture was warmed to RT overnight and concentrated under reduced pressure affording brown oil. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compound **3.94** (320 mg, 990 µmol, 57%) as a white solid.

M.P. 86–88 °C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3362 br. m, 2978 m, 2929 w, 2843 w, 2749 w, 1744 s, 1711 s, 1657 s, 1629 s, 1507 m, 1365 m, 1283 m, 1206 m, 1164 s, 1053 m, 1107 m, 722 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 11.02 (s, 1H, O*H*), 9.86 (s, 1H, C*H*O), 7.49 (d, *J*=8.0 Hz, 1H, Ar*H*), 6.82 (dd, *J*=8.0, 1.3 Hz, 1H, Ar*H*), 6.77 (app. br. s, 1H, Ar*H*), 5.04 (br. d, *J*=7.1 Hz, 1H, N*H*), 4.62 (app. q, *J*=6.6 Hz, 1H, NC*H*CO), 3.75 (s, 3H, CH_3), 3.17 (dd, *J*=13.3, 5.6 Hz, 1H, CH*H*), 3.04 (dd, *J*=13.3, 6.1 Hz, 1H, C*H*H). 1.43 (s, 9H, C(CH_3)$_3$).

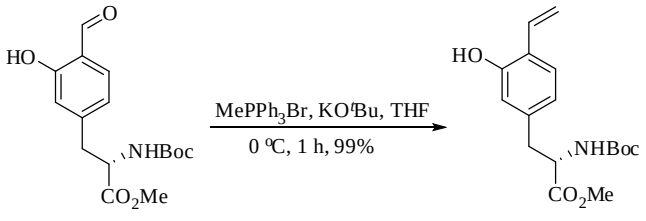
^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 195.9 (*C*H), 171.8 (*C*), 161.6 (*C*), 154.9 (*C*), 146.6 (*C*), 133.8 (*C*H), 121.0 (*C*), 119.6 (*C*), 118.4

(*C*H), 80.2 (*C*), 54.0 (*C*H), 52.4 (*C*H_3), 38.8 (*C*H_2), 28.3 ((*C*H_3)$_3$). *NB. One aromatic CH resonance not observed.*

HRMS (m/z, ESI$^+$) calcd for $C_{16}H_{21}NO_6$ $[M+Na]^+$ requires 346.1267; found: 346.1266.

$[\alpha]_D^{23}$ +37.6 (c = 0.42, CH_2Cl_2).

Methyl (*S*)-2-(*tert*-butoxycarbonylamino)-3-(3-hydroxy-4-vinylphenyl)propanoate **3.93**



3.94
$C_{16}H_{21}NO_6$
(323.34)

3.93
$C_{17}H_{23}NO_5$
(321.37)

To a solution of $MePPh_3Br$ (1.33 g, 3.71 mmol) in THF (20 mL) at 0 °C was added KO^{t}Bu (416 mg, 3.71 mmol). After 30 min aldehyde **3.94** (300 mg, 928 µmol) in THF (10 mL) was added dropwise over 5 min. After a further 30 min 1M HCl (40 mL) was added and the products extracted with Et_2O (3 x 30 mL). The combined organic phases were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording the crude material. Purification by flash column chromatography (20% EtOAc/petroleum ether) to give the title compound **3.93** (295 mg, 918 µmol, 99%) as a white solid.

M.P. 117–119 °C (EtOAc/petroleum ether).

FT-IR (ν_{max}, neat) 3358 br. m, 2974 m, 2949 w, 2929 w, 1686 s, 1502 s, 1430 m, 1221 m, 1158 s, 1057 m, 1017 m, 908 s, 729 s, 641 m, 538 m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H ppm 7.32 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.95 (dd, *J*=17.7, 11.1 Hz, 1H, C*H*), 6.70 (s, 1H, O*H*), 6.67–6.61 m, 2H, Ar*H*), 5.72 (dd, *J*=17.7, 1.5 Hz, 1H, CH*H*), 5.27 (dd, *J*=11.1, 1.5 Hz, 1H, C*H*H), 5.08 (d, *J*=8.1 Hz, 1H, N*H*), 4.56 (app. q, *J*=6.6 Hz, 1H, NC*H*CO), 3.70 (s, 3H, CH_3), 3.03 (dd, *J*=13.6, 8.1 Hz, 1H, CH*H*), 2.95 (dd, *J*=14.2, 6.6 Hz, 1H, C*H*H). 1.42 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C ppm 172.6 (*C*), 155.4 (*C*), 153.6 (*C*), 136.7 (*C*), 131.4 (*C*H), 128.7 (*C*), 127.1 (*C*H), 121.3 (*C*H), 116.6 (*C*H), 114.6 (*C*H_2), 80.3 (*C*), 54.3 (*C*H), 52.3 (*C*H_3), 37.9 (*C*H_2), 28.3 ((*C*H_3)$_3$).

LRMS (m/z, ESI$^+$) 665 ($[2M+Na]^+$, 33%), 385 ($[M+Na+MeCN]^+$, 100%).

HRMS (m/z, ESI$^+$) calcd for $C_{17}H_{23}NO_5$ $[M+Na]^+$ requires 344.1474; found: 344.1472.

$[\alpha]_D^{29}$ +35.8 (c = 0.25, CH_2Cl_2).

5.4 Details for *in Silico* Modelling

The energy values obtained for our modeling study (Figure **3.2**) are shown in the the following table. Also included is the procedure for calculating ΔE, involving all intermediates from the reaction pathway. Finally the relative energy values are given (as plotted in Figure **3.2**).

Intermediate	E/kJmol^{-1}	Σ	Rel. E/kJ
3.27	–4999633.39	**3.27** + Me_3SnH + $Me_3Sn^{\bullet}$ –5647598.089	0
3.28	–4969521.93	**3.28** + Me_3SnH + Me_3SnI –5647628.24	–5647628.24 – –5647598.089 = –30.371
3.29a	–4969599.76	**3.29a** + Me_3SnH + Me_3SnI –5647706.29	–5647706.29 – –5647598.089 = –108.201
3.29b	–4969613.17	**3.29b** + Me_3SnH + Me_3SnI –5647719.7	–5647719.7 – –5647598.089 = –121.611
3.30	–4969635.6	**3.30** + Me_3SnH + Me_3SnI –5647742.13	–5647742.13 – –5647598.089 = –144.041
3.31	–4969571.41	**3.31** + Me_3SnH + Me_3SnI –5647677.94	–5647677.94 – –5647598.089 = –79.851
3.32	–4971315.69	**3.32** + Me_3SnI + $Me_3Sn^{\bullet}$ –5647774.875	–5647774.875 – –5647598.089 = –176.786
3.33	–4968178.27	(**3.33** + Me_3SnH)– (**3.30** + $Me_3Sn)^{\bullet}$ –5292984.292 – –5292794.277 = –190.015	–190.015 + –144.041 = –334.056
Me_3SnH	–324806.022		
Me_3SnI	–353300.508		
$Me_3Sn^{\bullet}$	–323158.677		
$H^{\bullet}$	–1313.46711		
$I^{\bullet}$	–29836.1384		

Chapter 6: References

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