Asymmetric synthesis of the Martinella Alkaloids

A thesis submitted in partial fulfilment of the requirement
for the degree of Doctor of Philosophy

by

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The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2009 until April 2013, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Thomas Lorkin

April 2013

Chapter 5: Experimental

Abstract

Thomas J. A. Lorkin D.Phil. Thesis

New College Trinity Term 2013

This thesis is concerned with the application of the conjugate addition of enantiopure lithium amides in the asymmetric syntheses of (−)-martinellic acid.

Chapter 1 introduces the importance of the quinoline motif in a wide variety of natural products and pharmaceuticals. The natural products (–)-martinellic acid and (+)-martinelline are introduced and previous methods for their synthesis are described.

Chapter 2 introduces the conjugate addition reaction of lithium *N*-benzyl-*N*-α-methylbenzylamide as a means of synthesising β-amino esters from α,β-unsaturated esters. Both "tandem" and "stepwise" enolate functionalisation pathways to introduce an α-substituent are discussed, and the products are cyclised to the corresponding quinolin-2-ones. Modification of this strategy allowed the development of a double cyclisation reaction to form the pyrroloquinoline core found within (–)-martinellic acid and (+)-martinelline. Initial attempts at elaborating the tricyclic core to the natural products are described.

Chapter 3 addresses the difficulties encountered in the initial synthetic route by the use of lithium (*R*)-*N*-allyl-*N*-(α-methyl-4-methoxy-benzyl)amide as an alternative enantiopure ammonia equivalent. A key Wittig and intramolecular Michael reaction is used to introduce the remaining stereogenic centre, allowing access to either epimeric series. Full optimisation of the synthetic sequence is described resulting in the synthesis of a simplified triamine core, lacking only the ester functionality required for (–)-martinellic acid and (+)-martinelline.

Chapter 4 presents an asymmetric synthesis of (–)-martinellic acid and the first asymmetric synthesis of 4-*epi*-martinellic acid using the methodology developed in chapter 3, by incorporation of an ester functionality into substrate.

Chapter 5 contains full experimental procedures and characterisation data for all compounds synthesised in Chapters 2, 3 and 4.

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Abbreviations

Å	Angstroms
Ac	Acetyl
AIBN	Azobisisobutyronitrile
app	Apparent
aq	Aqueous
Ar	Aryl
atm	Atmosphere
ATR	Attenuated total reflectance
$[\alpha]_D$	Specific rotation
9-BBN	9-Borabicyclo(3.3.1)nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad
Bu	*n*-Butyl
^{t}Bu	*t*-Butyl
c	Concentration
C	Celsius
CAN	Ceric ammonium nitrate
Cbz	Carboxylbenzyl
cm^{-1}	Wavenumber
conc	Concentrated
CSA	Camphorsulfonic acid
CSO	Camphorsulfonyloxaziridine
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DETA	Diethylenetriamine
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Di(*iso*-butyl)aluminium hydride
DMAP	4-Dimethylaminopyridine
DMBA	1,3-Dimethylbarbituric acid
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereoisomeric ratio
δ_H	Proton (^{1}H) NMR chemical shift
δ_B	Boron (^{11}B) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
δ_F	Fluorine (^{19}F) NMR chemical shift
E	Entgegen
ee	Enantiomeric excess

ε	Extinction coefficient
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FI	Field ionisation
g	Grams
h	Hours
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i	Ipso
i	Iso
IPA	Isopropyl alcohol
J	Joules
J	Coupling constant
k	Rate constant
K	Kelvin
lit.	Literature
L	Unspecified ligand
L	Litres
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilylamide
m	Meta
m	Metres
m	Milli
m	Multiplet
M	Molar
$[M]^+$	Molecular ion
m-CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
min	Minutes
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
m/z	Mass to charge ratio
μ	Micro
n	Normal
NaHMDS	Sodium hexamethyldisilylamide
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
NMP	*N*-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	Ortho
p	Para
Ph	Phenyl
PMP	4-Methoxyphenyl
ppm	Parts per million
Pr	Propyl

^{i}Pr	*i*-Propyl
q	Quartet
quant	Quantitative
quin	Quintet
R	Unspecified organic group
RACE	Radical-addition-cyclisation-elimination
ref.	Reference
rt	Room temperature
s	Singlet
satd	Saturated
t	Tertiary
t	Triplet
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
tert	Tertiary
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroaceticanhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
Tol	Methylphenyl
TPAP	Tetrapropylammonium perruthenate
Troc	Trichloroethyloxycarbonyl
Ts	*p*-Toluenesulphonyl
UV	Ultraviolet
V	Volume
v/v	Volume to volume ratio
ν_{max}	Infra red absorption
w/w	Mass to mass ratio
X	Unspecified substitutent
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Z	Zusammen

Chapter 1: Introduction

1.1. Natural products and pharmaceuticals containing the quinoline motif

The quinoline motif is present in a variety of biologically active molecules, from natural products to antibiotics. The alkaloid quinine **1**, which was isolated from the bark of the South American Chinchona tree, has been used as a treatment for malaria by native people for centuries.[1] More recently, synthetic analogues such as Chloroquine **2**, which have fewer associated side effects, have been developed.[1] A variety of other quinoline derivatives have wide ranging biological activity, for example Yaequinolones J1 and J2 (**4** and **5**), two of a variety of compounds isolated in 2005 from a Japanese sample of *Penicillium*, contain the quinolin-2-one motif and show moderate activity as insecticides.[2,3] The related quinolin-4-one structure is also found in a number of antibiotics, such as Pefloxacin **3**. Tetrahydroquinolines also display a range of biological activity, for instance Oxamniquine **6**, marketed under the tradename Vansil® by Pfizer, is used in the treatment of schistosomiasis (Fig 1).[4]

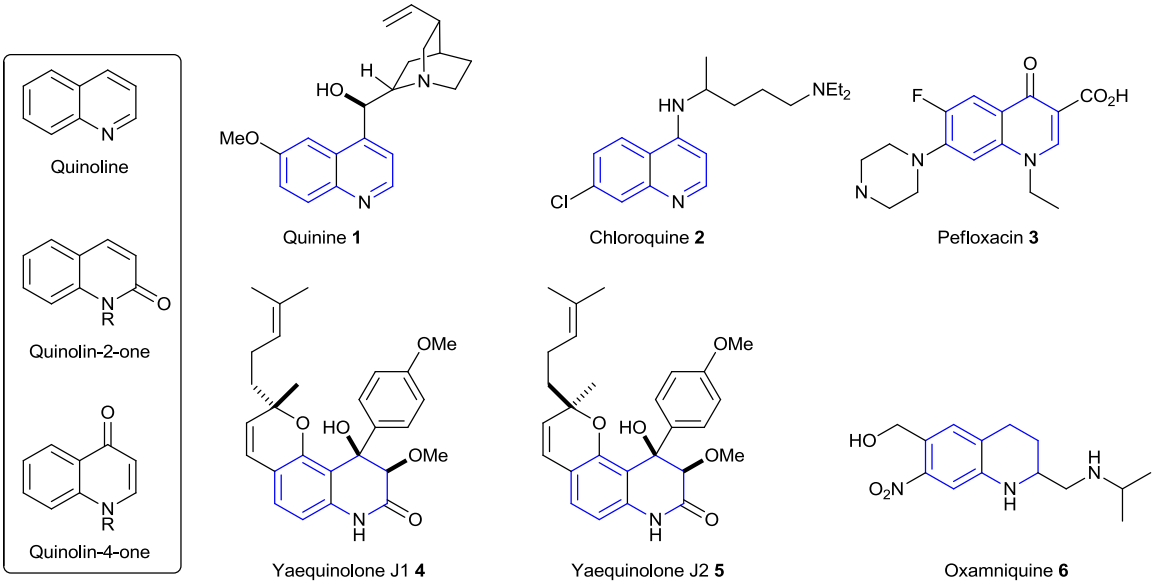


Fig 1. Biologically active quinoline derivatives.

Methods for the synthesis of substituted quinolines include the Skraup,[5] Conrad-Limpach,[6] Doebner-Miller,[7] Combes,[8] Knorr,[9] and Friedländer[10,11] syntheses. Quinolin-2-ones can be obtained from the corresponding 2-chloroquinolines after displacement with hydroxide and subsequent tautomerism,[12] or alternatively from ring enlargement of isatins.[13] The Povarov reaction also allows access to substituted tetrahydroquinolines from the corresponding anilines in one step.[14] Alternatively, tetrahydroquinolines can be obtained from the chemoselective hydrogenation of the corresponding quinoline by a variety of catalysts including metals,[15] or chiral phosphoric acids,[16] allowing access to substituted tetrahydroquinolines in enantiopure form. A subset of quinoline compounds include the highly functionalised pyrroloquinoline alkaloids (–)-martinellic acid **8** and (+)-martinelline **9** (Fig

2).[17] Although the parent compound 1*H*-pyrrolo[3,2-*c*]quinoline **7** has been known for some time,[18] **8** and **9** represent the first and to date only natural products containing this heterocyclic framework.

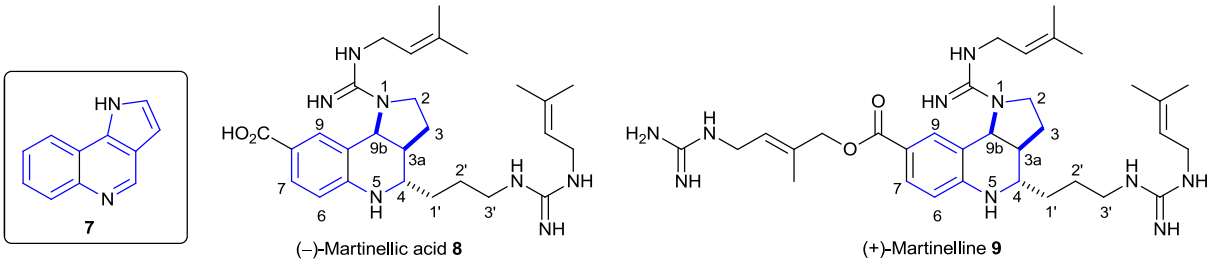


Fig 2. (–)-Martinellic acid **8** and (+)-Martinelline **9** with the numbering system used throughout this thesis.[19]

1.2. Isolation of the *Martinella* alkaloids

(–)-Martinellic acid **8** and (+)-martinelline **9**, were isolated by Witherup *et al.* in 1994 from the roots of the species *Martinella iquitoensis*,[17,20] a plant cultivated by South American tribes as a cure for eye ailments and first documented in 1791 by Anderson.[21,22] The ground root extracts are said to immediately treat inflammation of the eye and will eventually cure conjunctivitis, a condition often caused by bacterial infection. The biological activity of **8** and **9** were assessed by Merck, and it was noted that (+)-martinelline **9** showed a much higher inhibitory aptitude for bradykinin receptors compared to (–)-martinellic acid **8**,[23] and increased antimicrobial properties.[17] Given the greater efficacy of (+)-martinelline **9**, the chemists at Merck further suggested that (+)-martinelline **9** is likely the active component in this natural remedy, with (–)-martinellic acid **8** perhaps arising as a by-product from hydrolysis during the isolation process. The tricyclic framework of these compounds has spurred research into the medicinal use of these structures, resulting in the publication of a patent by Merck in 1994.[24]

1.2.1. Structural elucidation

The structure of (+)-Martinelline **9**, isolated after HPLC purification as the TFA salt, was determined by a series of NMR experiments.[17] ^{19}F NMR spectroscopic analysis indicated that 2.8 equivalents of TFA were present per molecule of **9**, which is consistent with the presence of 3 basic sites. ^{13}C NMR spectroscopic analysis indicated the presence of 33 distinct carbon environments: 10 quaternary, 3 aromatic *C*H, 3 *C*H$_2$, 6 heteroatom *C*H$_2$X, 3 aliphatic *C*H, 3 olefinic *C*H and 5 *Me*. From the combined results of COSY, HMBC and nOe experiments, it was determined that a [3,2-*c*]-pyrroloquinoline core was present. The stereochemistry at the pyrroloquinoline juncture was determined to be *cis* by the characteristic ^{1}H ^{3}J coupling constants ($^{3}J_{3a,9b}$ = 6.8 Hz), as an alternative *trans* juncture would be expected to show a larger ^{3}J coupling constant. The relative 3a,4-*anti* configuration was assigned on the basis of a strong nOe between the C(9b)*H* and C(1')*H* protons, which is consistent with both lying on the same face of the molecule. Further support came from the

$^{3}J_{3a,4}$ value of < 2Hz; it was assumed that the C(3a)*H* and C(4)*H* atoms sit in a pseudo-equatorial position and thus the dihedral angle between them is small. The structure of (–)-martinellic acid **8** was assigned by an analogous series of NMR experiments. The assigned structures and relative configuration within both (–)-martinellic acid **8** and (+)-martinelline **9** have subsequently been confirmed by total synthesis. To date there has been one total asymmetric synthesis of (+)-martinelline **9**,[19] and three total asymmetric syntheses of (–)-martinellic acid **8**.[19,25,26] Although the spectroscopic data of the synthetic samples have been found to be in agreement with those of the isolated material, there are discrepancies in the magnitude of the specific rotation values in all cases. For the natural sample of (–)-martinellic acid **8** a specific rotation of $[\alpha]_D$ –8.5 (*c* 0.01 in MeOH) was reported, whereas all synthetic samples have exhibited much larger values, for which a number of suggestions to account for these discrepancies have arisen (*vide infra*).

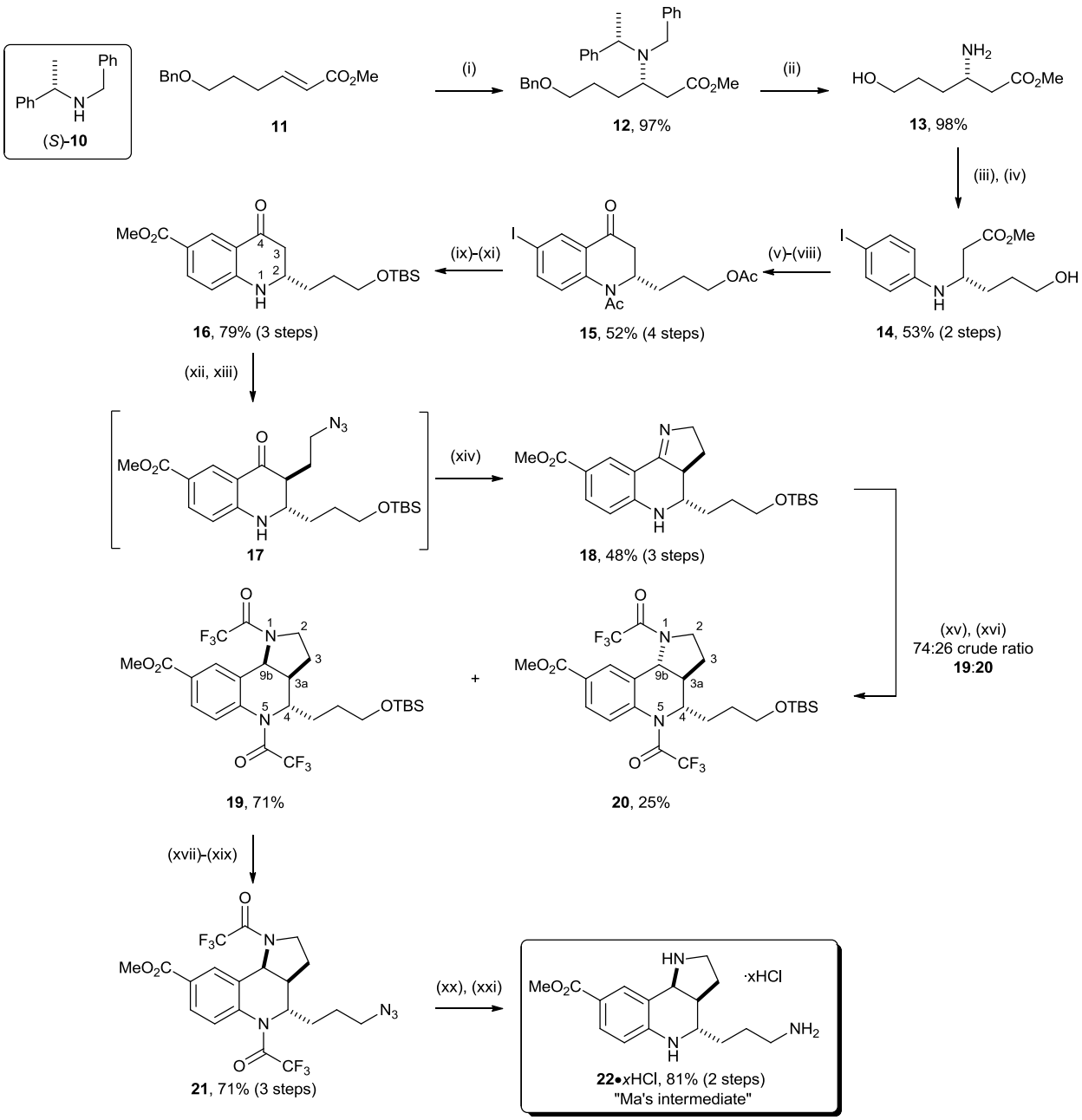
1.3. Previous syntheses of the *Martinella* alkaloids

Due to the unique structure and interesting biological activity of (–)-martinellic acid **8** and (+)-martinelline **9**, several different methods have been devised for the synthesis of the tricyclic framework present within these natural products. This has resulted in several formal and total syntheses of **8** and **9**, which have been reviewed.[27,28] The following sections will give a comprehensive overview of the methods which have been developed for their asymmetric synthesis, in approximately chronological order.

1.3.1. Ma approach: First total synthesis of (–)-martinellic acid

The first total synthesis of (–)-martinellic acid **8** was reported in 2001 by Ma *et al*.[25] Conjugate addition of the lithium amide derived from (*S*)-**10** to α,β-unsaturated ester **11** (derived from 1,4-butanediol), using the methodology developed by Davies *et al.*,[29,30] gave β-amino ester **12** in 97% yield and >99:1 dr.[31] Hydrogenolysis of the *N*- and *O*-protecting groups within **12** gave β-amino ester **13** in 98% yield. Coupling of **13** with 1,4-diiodobenzene in a CuI mediated Ullmann reaction followed by re-esterification gave **14** in 53% yield over two steps from **13**. A four step sequence of (i) global acetylation, (ii) hydrolysis of both ester moieties, (iii) acetate protection of the alcohol and (iv) a key $AlCl_3$–mediated intramolecular Friedel-Crafts acylation reaction gave dihydroquinolin-4-one **15** in 52% yield over four steps from **14**. Methoxycarbonylation of **15** catalysed by $Pd(OAc)_2$, *N*- and *O*-acetate hydrolysis and *O*-silyl protection of the corresponding alcohol gave intermediate **16** in 79% yield over three steps from **15**. The stereochemistry at the C(2) position was used to direct the stereoselective formation of the pyrrolidine ring. Thus, **16** was treated with LiHMDS to give the corresponding enolate, which was alkylated on the least hindered face, *anti* to the C(2) substituent,

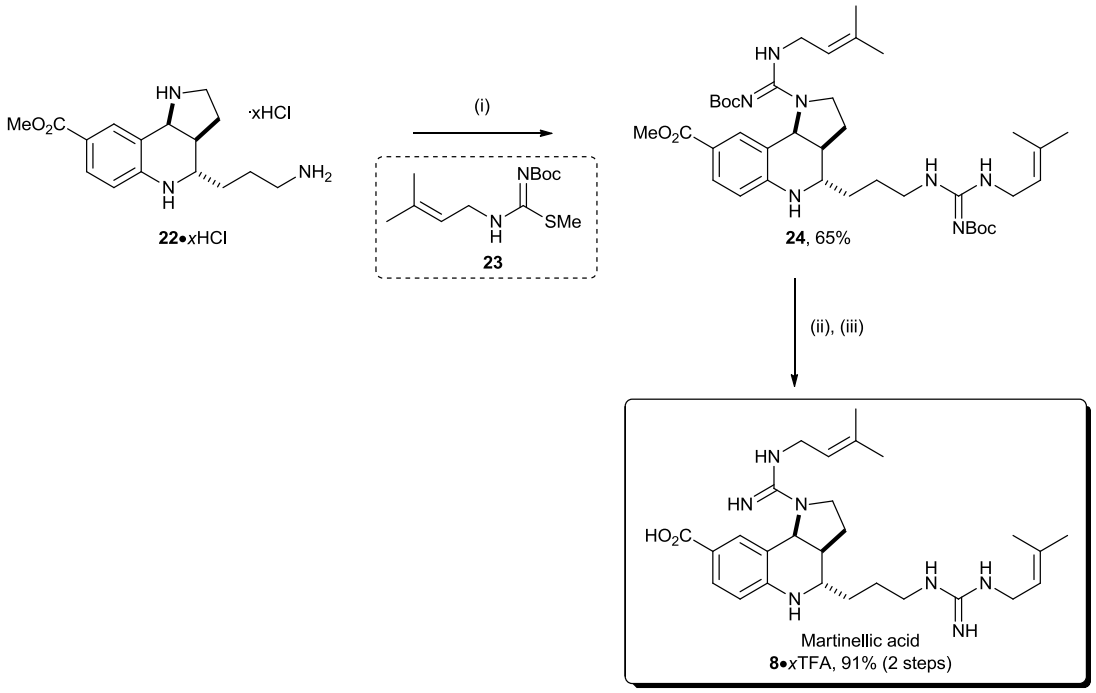
with $BrCH_2CH_2OTf$ and immediately converted into azide **17**. Staudinger reduction of **17** was followed by intramolecular condensation of the resultant primary amine onto the ketone moiety to give imine **18** in 48% yield over three steps. Reduction of the imine with $NaBH_4$ and subsequent protection of both amine moieties with TFAA gave a 74:26 ratio of the epimers **19** and **20**, which were isolated in 71 and 25% yield, respectively. With the stereochemistry of the tricyclic core in place, elaboration of **19** to (–)-martinellic acid was accomplished in 8 further steps. The *O*-TBS group within **19** was removed with TFA; the resultant alcohol was activated as the mesylate and treated with NaN_3 to give azide **21** in 71% yield (from **19**). Staudinger reduction of azide **21** followed by methanolysis led to cleavage of the trifluoroacetate groups and isolation of key triamine **22** as the HCl salt in 81% yield (Scheme 1).[32] The synthesis of key triamine **22**·*x*HCl proceeded in 2.1% yield in 24 linear steps from 1,4-butanediol. As martinellic acid **8** is readily derived from triamine **22**·*x*HCl after guanylation and ester hydrolysis, many subsequent syntheses (formal and total) converge on **22**·*x*HCl, and so **22**·*x*HCl has been termed "Ma's intermediate" in the literature.



Scheme 1. *Reagents and Conditions*: (i) (*S*)-**10**, BuLi, THF, –78 °C, 2 h; (ii) Pd/C (5% w/w), EtOH/HCl/H_2O, H_2 (5 atm), 50 °C, 6 h; (iii) 1,4-diiodobenzene (1.2 equiv), K_2CO_3 (3 equiv), CuI (0.1 equiv), DMF, 100 °C, 48 h; (iv) $SOCl_2$, MeOH, rt, 16 h; (v) Ac_2O, 80 °C, 2 h; (vi) H_2O, 1,4-dioxane, 50 °C, 30 min; (vii) DMF, $(COCl)_2$, CH_2Cl_2, rt, 1 h; (viii) $AlCl_3$, CH_2Cl_2, rt, 12 h; (ix) $Pd(OAc)_2$ (0.05 equiv), dppp (0.05 equiv), MeOH, Et_3N, DMF, CO (1 atm), 80 °C, 12 h; (x) methanolic HCl, rt, 16 h; (xi) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, rt, 6 h; (xii) LiHMDS (2.0 equiv), $BrCH_2CH_2OTf$ (2.0 equiv), THF, –40 °C, 1 h; (xiii) NaN_3 (2.0 equiv), DMF, rt, 10 h; (xiv) PPh_3, H_2O, THF, rt, 14 h; (xv) $NaBH_4$, MeOH –40 °C to rt, 1 h; (xvi) TFAA, Et_3N, DMAP, CH_2Cl_2, rt, 2 h; (xvii) THF/TFA (5:1), rt, 16 h; (xviii) MsCl (1.2 equiv), Et_3N (1.4 equiv), CH_2Cl_2, rt, 1 h; (xix) NaN_3 (2.3 equiv), DMF, rt, 10 h; (xx) PPh_3 (3.0 equiv), THF/H_2O (20:1), rt, 14 h; (xxi) methanolic HCl, rt, 16 h.

(–)-Martinellic acid **8** can be derived from **22**·*x*HCl through bis-guanylation and subsequent ester hydrolysis. However, the guanylation of **22**·*x*HCl proved challenging, and decomposition occurred when **22**·*x*HCl was exposed to high reaction temperatures.[33] Ultimately, mild guanylation conditions were developed by Ma *et al*. which used $AgNO_3$ as a promoter for the coupling of amine **22**·*x*HCl with *N*-Boc isothiourea **23**.[33] Under these conditions both primary and secondary amines reacted, with the hindered and conjugated aniline unaffected, to give **24** in 65% isolated yield. Hydrolysis and subsequent removal of the *N*-Boc groups gave (–)-martinellic acid **8**·*x*TFA in 91% yield from **24** (Scheme 2). Ma *et al.* therefore completed the synthesis of (–)-martinellic acid **8** in 1.3% overall

yield in 27 linear steps. Although the ^{1}H and ^{13}C NMR spectroscopic data were in agreement with the natural sample isolated by the Merck chemists, the specific rotation of the synthetic material {$[\alpha]_D^{20}$ –122.7 (*c* 0.31 in MeOH)} was substantially different from that of the natural sample {lit.[34] for the natural material $[\alpha]_D$ –8.5 (*c* 0.01 in MeOH)}. It was postulated by Ma that this discrepancy could be due to the weak sample used by the Merck chemists when recording the specific rotation.[25] An alternative suggestion proposed by Ma is that both (–)-martinellic acid **8** and (+)-martinelline **9** derived from the natural source may be scalemic, an idea which has been supported by other groups (*vide infra*), although no other data has been reported in support of this hypothesis.



Scheme 2. *Reagents and Conditions*: (i) **23** (5 equiv), Et_3N (12 equiv), $AgNO_3$ (7 equiv), MeCN/MeOH, rt, 16 h; (ii) NaOH, MeOH/H_2O, reflux, 10 h; (iii) TFA, anisole, CH_2Cl_2, rt, 16 h, then reverse phase HPLC.

1.3.2. Azomethine ylid cycloaddition routes to martinellic acid

An intramolecular 1,3-dipolar cycloaddition of an azomethine ylide can be used to generate both heterocyclic rings of the pyrroloquinoline core in one step, allowing high diastereocontrol over the C(3a) and C(9b) stereocentres (Fig 3). Numerous groups have utilised this approach and some of the most successful applications are described below.[35]

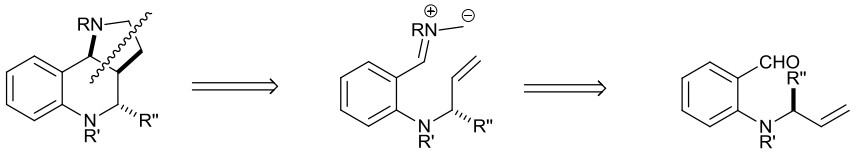
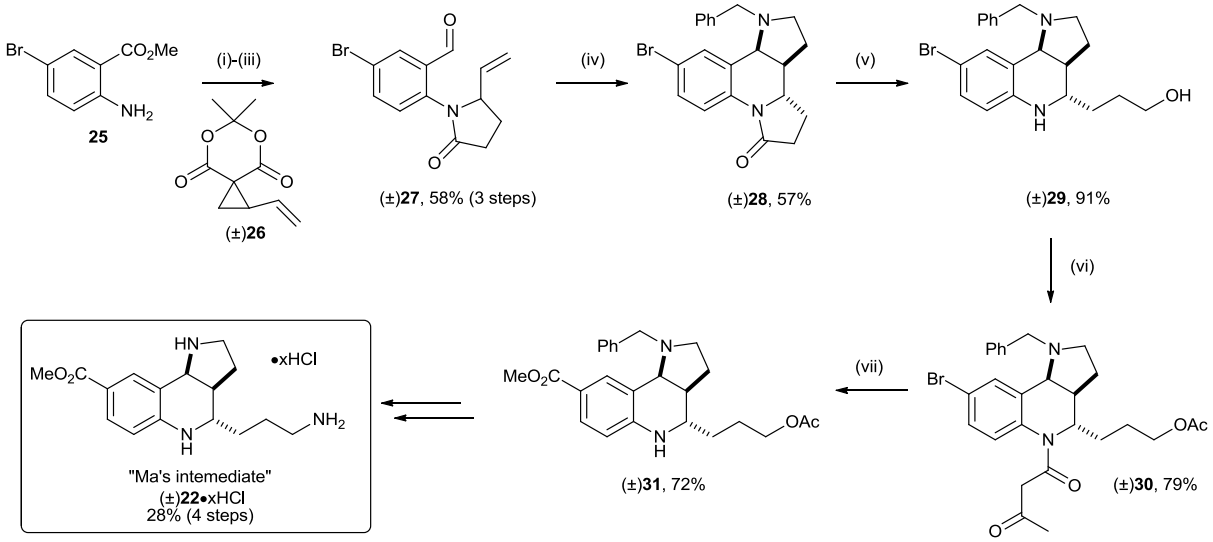


Fig 3. Cycloaddition disconnection of the martinelline skeleton.

1.3.2.1. Snider approach: Total synthesis of (±)-martinellic acid

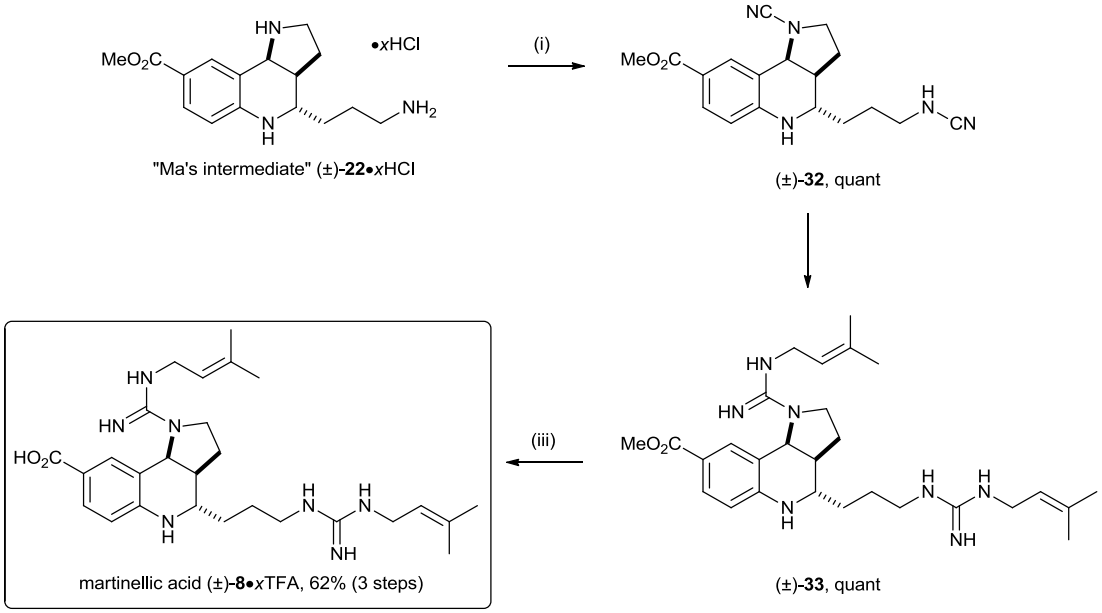
Snider *et al*. were the first to utilise this cycloaddition approach in a total synthesis of (±)-martinellic acid **8**.[32] Treatment of methyl 5-bromo-2-aminobenzoate **25** with $LiAlH_4$ gave the corresponding alcohol, which was treated with vinyl cyclopropane **26** followed by oxidation with MnO_2 to give

aldehyde **27** in 58% yield over three steps. Treatment of aldehyde **27** with *N*-benzylglycine, followed by *in situ* decarboxylation to give the corresponding azomethine ylide and ensuing intramolecular cycloaddition gave **28** in 57% yield. Ring-opening of **28** was achieved by treatment with $LiBH_4$ to give alcohol **29** in 91% yield. In order to activate the aryl bromide towards oxidative addition during the subsequent palladium-catalysed methoxycarbonylation, it was necessary to deactivate the aromatic ring by the addition of an electron withdrawing group on the aniline nitrogen atom. An acetyl group was initially favoured as *O*-acetylation was also necessary in subsequent steps. However, although mild acetylation conditions were successful in acetylation of the alcohol within **29**, the quinoline nitrogen was unreactive. Under more forcing conditions using AcCl (10 equiv), acetoacetamide **30** was isolated in 79% yield. The ester functionality was introduced by a palladium-catalysed methoxycarbonylation reaction using a $Pd(OAc)_2/PPh_3$/NaOAc catalyst system, which proceeded with *in situ* deprotection of the acetoacetamide to give **31** in 72% isolated yield. Further functional group manipulations gave "Ma's intermediate" (±)-**22**·*x*HCl in 28% yield over four steps from **31**. Thus the synthesis of (±)-**22**·*x*HCl proceeded in 4.7% yield over 11 steps from **25** (Scheme 3).



Scheme 3. *Reagents and Conditions*: (i) **25**, $LiAlH_4$, THF, –78 °C to rt, 5 h; (ii) **26**, PhMe, reflux, 16 h; (iii) MnO_2, CH_2Cl_2, rt, 16 h; (iv) *N*-benzylglycine, PhMe, reflux, 15 h; (v) $LiBH_4$ portionwise, MeOH, THF, reflux, 8 days; (vi) AcCl (10 equiv), CH_2Cl_2, rt, 3 h; (vii) $Pd(OAc)_2$ (0.02 equiv), PPh_3 (0.08 equiv), NaOAc (5 equiv), MeOH, CO (60 psi), 120 °C, 3 days.

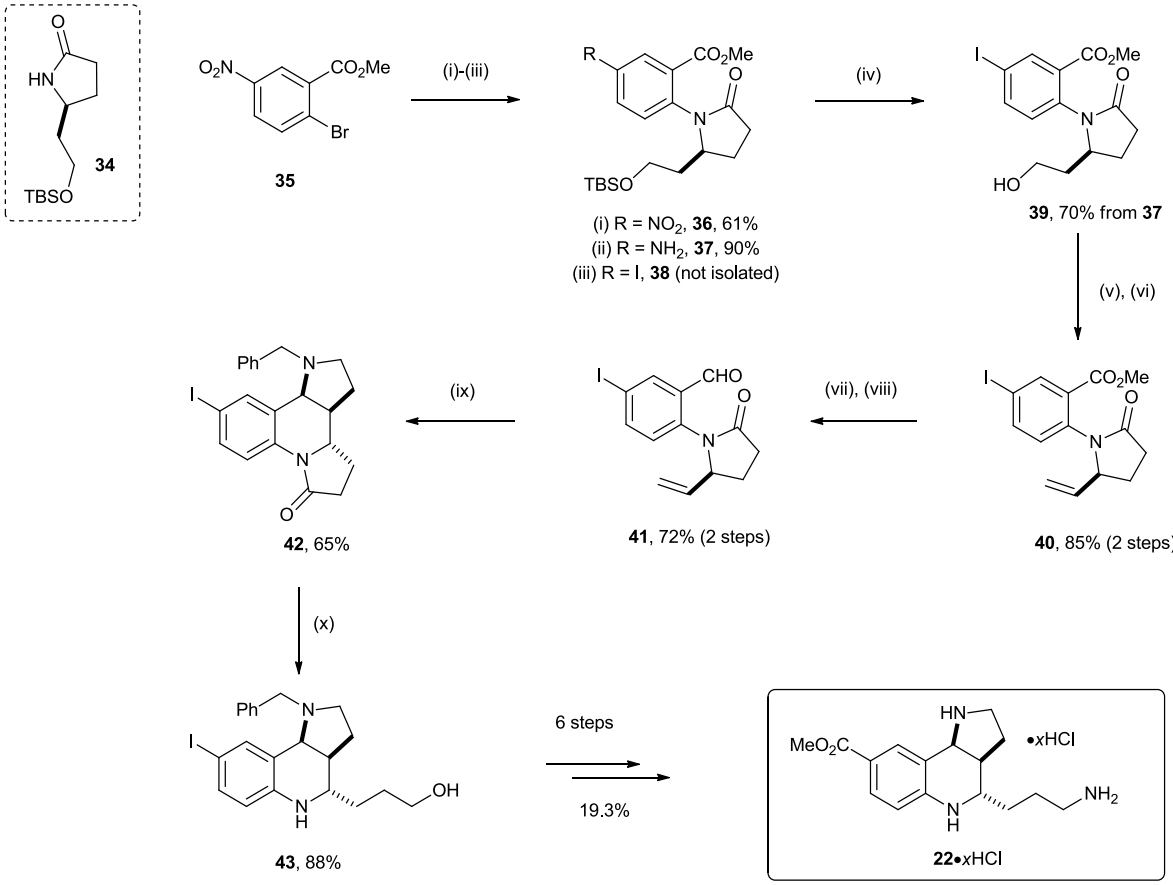
Snider *et al* reported an alternative method for the introduction of the guanidine moieties. Treatment of triamine (±)-**22**·*x*HCl with BrCN and $NaHCO_3$ gave the bis-cyanamide **32** in quantitative yield. Treatment of **32** with prenylamine gave **33**, which was hydrolysed with NaOH to give (±)-martinellic acid **8** in 62% yield over three steps (Scheme 4). Thus, the synthesis of (±)-martinellic acid proceeded in 2.9% yield over 14 steps from methyl 5-bromo-2-aminobenzoate **25**.



Scheme 4. *Reagents and Conditions*: (i) BrCN, $NaHCO_3$, MeOH, 0 °C, 1 h; (ii) prenylamine, HFIP, 120 °C, 32 h; (iii) NaOH, MeOH, reflux, 14 h, then HPLC.

1.3.2.2. Lovely approach: Asymmetric synthesis of "Ma's intermediate"

The chemistry discussed in the previous section is readily amenable to the asymmetric synthesis of (–)-martinellic acid **8**, by preparing enantiopure precursors to the cycloaddition reaction. Following a synthesis conceptually similar to that of Snider above, Lovely and Badarinarayana coupled enantiopure lactam **34** (derived in five steps and 34% yield from pyroglutamate) with aryl bromide **35** using a Pd_2dba_3/Xantphos/Cs_2CO_3 catalyst system, to give **36** in 61% isolated yield.[36,37] Reduction of the nitro group with Pd/C and H_2 gave aniline **37** in 90% yield, which was diazotized with *n*-$C_5H_{11}ONO$ and trapped with iodide (from CH_2I_2) to give **38**.[38] Desilylation with TBAF gave **39** in 70% overall yield over two steps. Conversion of the alcohol to the selenide, oxidation with H_2O_2 and elimination of the resultant selenoxide gave **40** in 85% yield over two steps. Conversion of **40** to aldehyde **41** was achieved in a two step sequence involving reduction of the ester with $LiBH_4$ in MeOH at 0 °C, followed by oxidation with MnO_2 giving **41** in 72% overall yield from **40**. Condensation of **41** with *N*-benzyl glycine in PhH at reflux and ensuing 1,3-dipolar cycloaddition gave 65% isolated yield of the desired tetracyclic product **42**. Chemoselective ring-opening of **42** was achieved with $LiBH_4$ to give alcohol **43** in 88% yield (13.8% over ten steps from lactam **34**). Ma's intermediate (–)-**22**·*x*HCl was prepared in six steps and 19.3% yield from **43**, employing an analogous route to that of Snider. Thus, the synthesis of (–)-**22**·*x*HCl was completed in 21 steps and 0.9% yield (Scheme 5).



Scheme 5. *Reagents and Conditions*: (i) Pd_2dba_3, Xantphos, Cs_2CO_3, dioxane; (ii) Pd/C, H_2, EtOH; (iii) $^nC_5H_{11}ONO$, CH_2I_2; (iv) TBAF, THF; (v) *o*-$NO_2C_6H_4SeCN$, PBu_3, THF; (vi) H_2O_2; (vii) $LiBH_4$, MeOH, 0 °C; (viii) MnO_2, CH_2Cl_2; (ix) *N*-benzyl glycine, PhH, Et_3N, reflux; (x) $LiBH_4$, MeOH, reflux, 16 h.

1.3.3. Hetero Diels-Alder approach to the tricyclic martinelline framework

An intramolecular imino Diels-Alder reaction between a 2-azadiene and a dieneophile, known as the Povarov reaction, has been used by several groups to construct the pyrroloquinoline core (Fig 4).[39] In the first step a 2-azadiene is formed by condensation of an aniline with the requisite aldehyde. The second step involves trapping of the 2-azadiene with a dieneophile through a cycloaddition.

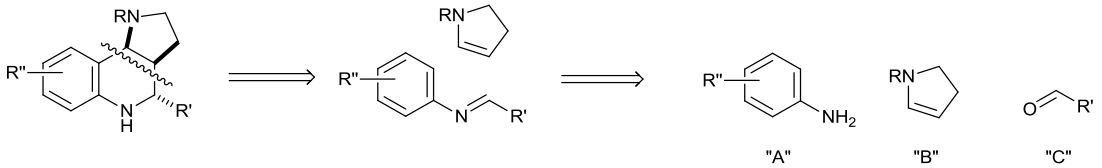
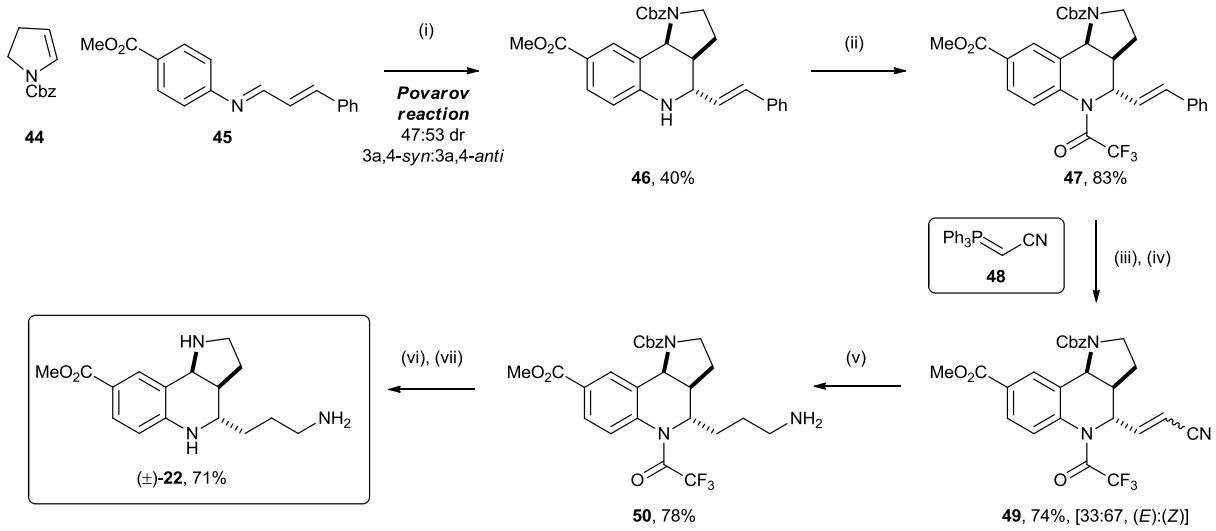


Fig 4. Povarov approach to the martinelline core.

1.3.3.1. Stevenson approach: "*ABC*" cycloaddition

For example, Stevenson *et al*. utilised the cycloaddition of 2-azadiene **45** with 2-pyrroline **44** under $InCl_3$ catalysis to give a 47:53 mixture of 3a,4-*syn* and 3a,4-*anti* adducts, respectively, with *anti* adduct **46** isolated in 40% yield after purification.[40] The conversion of **46** to (±)-**22** was completed in a six step sequence. *N*-Trifluoroacetyl protection of **46** gave **47** in 83% yield. Ozonolysis to the corresponding aldehyde followed by Wittig reaction with phosphorane **48** gave **49** in 74% yield as a 33:67 mixture of [(*E*):(*Z*)] isomers, respectively. Hydrogenation of **49** gave amine **50** in 78% yield. Finally, *N*(5)-deprotection was achieved by treatment with methanolic ammonia, followed by

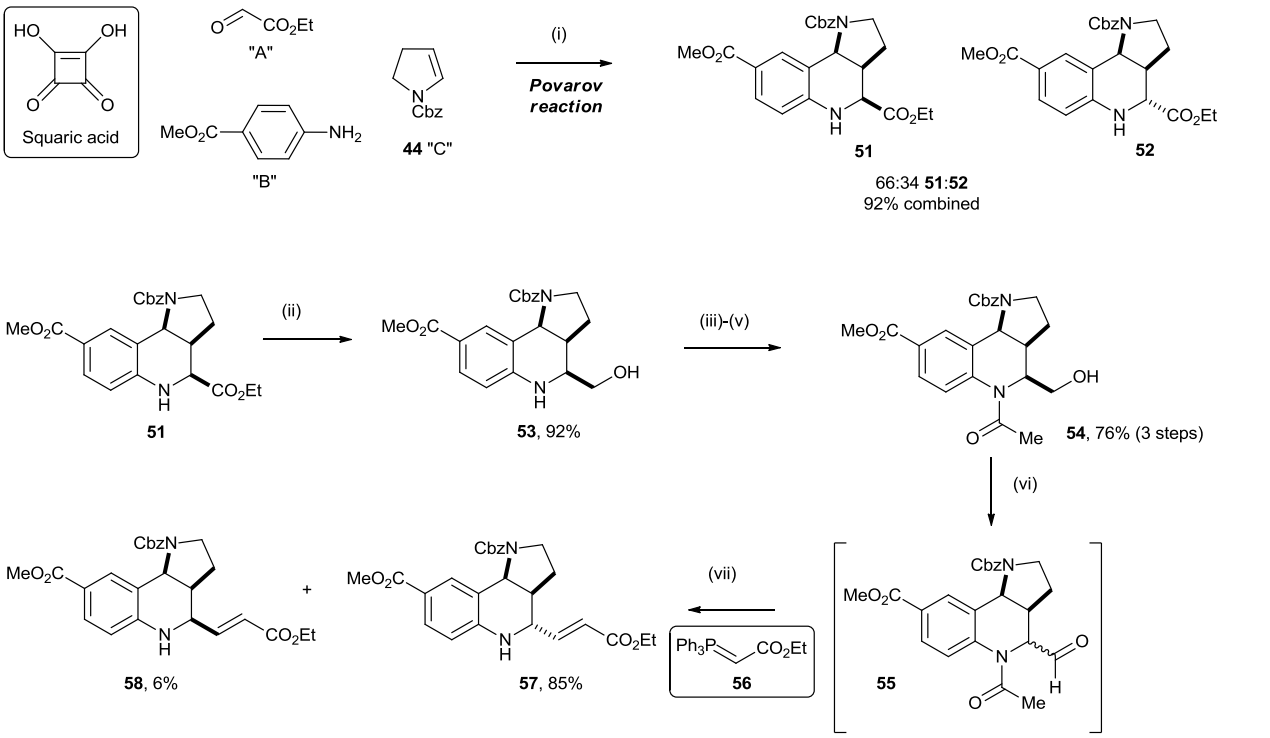
hydrogenolysis with Pearlman's catalyst which was reported to give triamine (±)-**22** in 71% yield over two steps, although other groups have indicated that the free base of **22** is unstable with respect to polymerisation (Scheme 6).[41]



Scheme 6. (i) $InCl_3$ (0.12 equiv), CH_3CN, 25 °C, 12 h; (ii) $(CF_3CO)_2O$, DMAP, PhMe reflux, 30 h; (iii) CH_2Cl_2, O_3, –78 °C then Me_2S; (iv) **48**; (v) PtO_2, EtOH, $CHCl_3$, 70 °C, 45 psi, 144 h; (vi) MeOH, NH_3, 25 °C, 24 h; (vii) $Pd(OH)_2$, CH_3OH, 60 °C, 45 psi, 24 h.

1.3.3.2. Ma approach: "*ABC*" cycloaddition route to (±)-martinelline

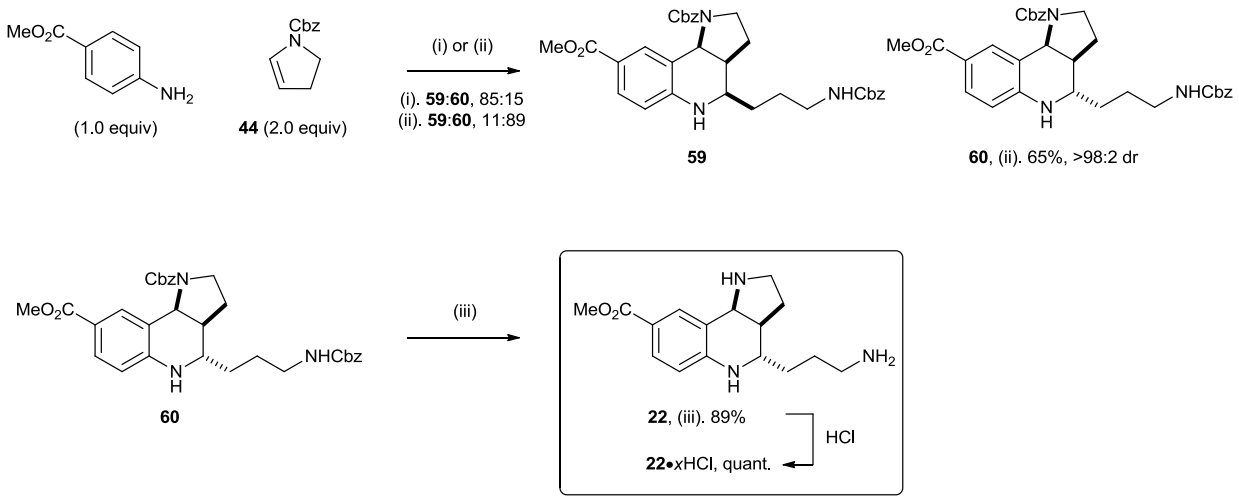
A similar approach to that of Stevenson was used by Ma *et al*. in a synthesis of (±)-martinelline **9**, in which ethyl glyoxalate was utilised as the aldehyde component in a Povarov reaction.[42] Under optimised conditions, treatment of methyl 4-aminobenzoate with ethyl glyoxalate (1.0 equiv) and 2-pyrroline **44** (1.0 equiv) in the presence of squaric acid (0.05 equiv) in MeCN at rt gave a 66:34 mixture of *syn*-**51** and *anti*-**52**, respectively, which were isolated in 92% combined yield. Reduction of the aliphatic ester within a diastereoisomerically pure sample of **51** was achieved with $NaBH_4$/LiCl in 92% yield to give alcohol **53**. The aniline within **53** was selectively acetylated in a three step sequence comprising: (i) *O*-silylation of **53** with TBSCl, (ii) acetylation of the aniline with Ac_2O at 100 °C and (iii) *O*-silyl deprotection with TsOH/MeOH to give **54** in 76% overall yield. Swern oxidation of **54** gave aldehyde **55** as a mixture of C(4)-epimers, indicating epimerisation had occurred *in situ*. Treatment of aldehyde **55** with phosphorane **56** gave a mixture of **57** and **58**,[43] which were isolated in 85 and 6% yield over two steps, respectively. The major product **57** was subsequently converted by Ma *et al.* into (±)-martinelline **9** in ten steps and 28% yield (Scheme 7).



Scheme 7. *Reagents and Conditions*: (i) **44** (1.0 equiv), methyl 4-aminobenzoate (1.0 equiv), ethyl glyoxalate (1.0 equiv), MeCN, rt, 40 min then squaric acid (0.05 equiv), rt, 2 h; (ii) $NaBH_4$, LiCl, MeOH/THF, rt; (iii) TBSCl, Et_3N; (iv) Ac_2O, 100 °C; (v) TsOH/MeOH; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (vii) $Ph_3PCH{=}CO_2Et$.

1.3.4. Batey approach: "*ABB*" cycloaddition approach to (±)-martinellic acid

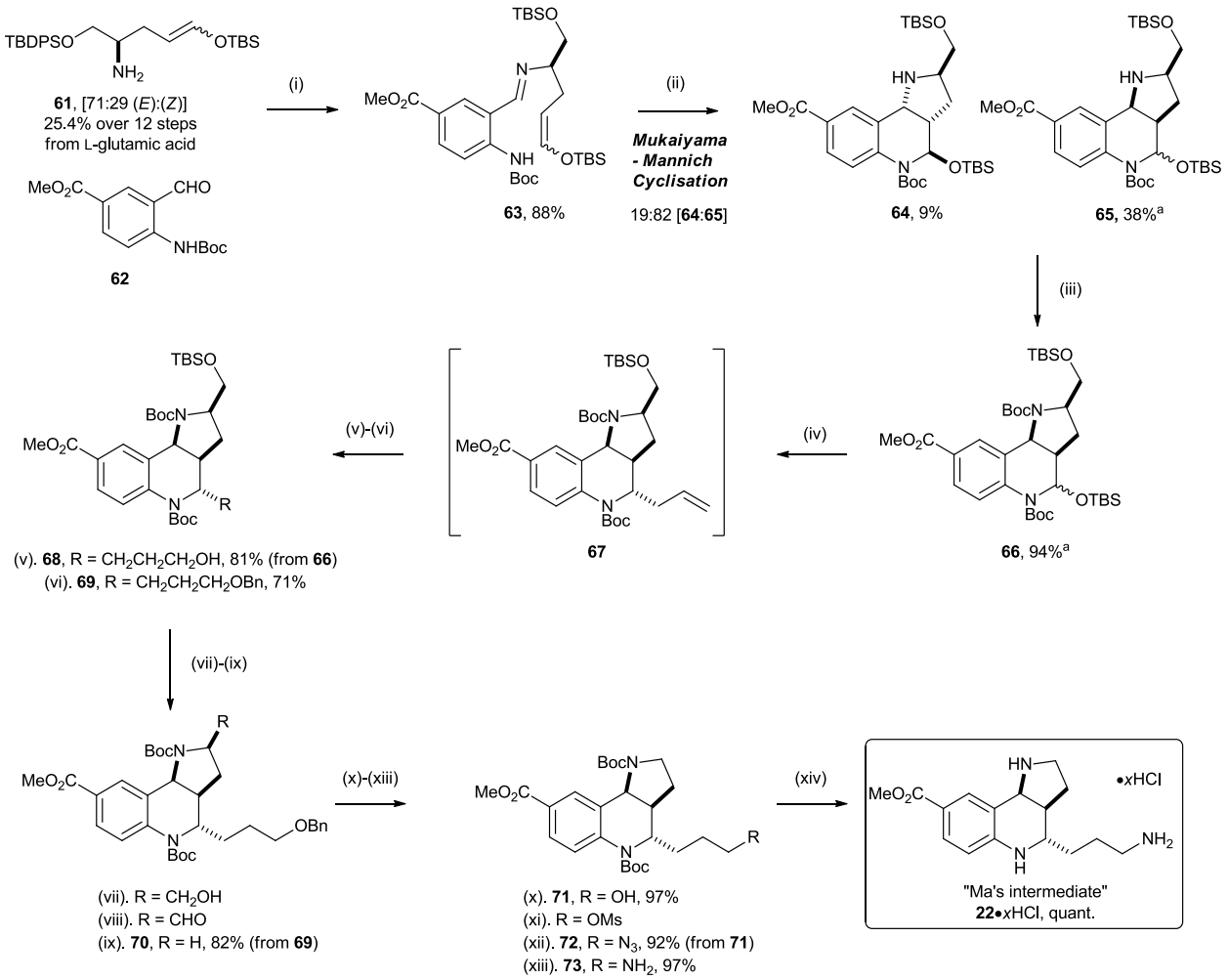
It was noted by Batey *et al*. that the coupling of methyl 4-aminobenzoate with two equivalents of an *N*-protected-2-pyrroline, with one equivalent acting as the aldehyde component and another as the dieneophile, would lead to the tricyclic martinelline core directly, after condensation and Povarov reaction.[41,44] Initial studies using $Dy(OTf)_3$ as the catalyst, gave an 85:15 mixture of 3a,4-*syn*-**59** and 3a,4-*anti*-**60**, respectively, in 92% combined yield.[41] It was found that the product ratio of **59** to **60** was highly dependent on the nature of the acid catalyst and the solvent. Under optimised conditions [CSA (0.05 equiv) in dry THF] a switchover in the diastereoselectivity was obtained to give an 11:89 ratio of **59** and **60**, respectively, with **60** isolated in 65% yield and >98:2 dr after purification. Deprotection of the *N*-Cbz protecting groups within **60** with $Pd(OH)_2$/C in MeOH/AcOH followed by cation exchange chromatography gave (±)-**22** in 89% yield, which was converted into (±)-**22**·*x*HCl "Ma's intermediate" by treatment with HCl. The synthesis of (±)-**22**·*x*HCl therefore proceeded in 58% yield over two steps. Batey *et al*. subsequently converted **22**·*x*HCl into (±)-martinellic acid **8** in a further seven steps in 21.1% overall yield. Ultimately, the synthesis of (±)-martinellic acid **8** proceeded in 12.2% overall yield in nine steps from 4-methyl-aminobenzoate (Scheme 8).[45] Recent studies by Jacobsen and Dagousset have shown that high enantioselectivity can be imparted on the Povarov reaction by using a chiral phosphoric acid catalyst, although the products of these reactions have not been elaborated to (–)-martinellic acid **8** or (+)-martinelline **9**.[46,47]



Scheme 8. *Reagents and Conditions*: (i) $Dy(OTf)_3$ (0.2 equiv), MeCN, 4 °C, 16 h; (ii) CSA (0.05 equiv), THF, rt, 48 h; (iii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH/AcOH (10:1), 5 h, then cation exchange chromatography.

1.3.5. Iwabuchi approach: Total synthesis of (–)-martinellic acid and (+)-martinelline

The second total enantiospecific synthesis of (–)-martinellic acid **8**, and the only total asymmetric synthesis of (+)-martinelline **9** to date were reported by Iwabuchi *et al*., in which a $BF_3{\cdot}OEt_2$ promoted Mukaiyama-Mannich reaction of imino silyl enol ether **63** was used as the key stereodefining step. Aldehyde **62** was prepared *via* an eight step sequence (in 48% overall yield), from 3-methyl-4-nitro benzoic acid.[19] Silyl enol ether **61** was prepared in 12 steps from L-glutamic acid in 25% yield [71:29 dr, (*E*):(*Z*)]. Condensation of silyl enol ether **61** [71:29 dr, (*E*):(*Z*)] and aldehyde **62** gave imino silyl enol ether **63** in 88% yield [71:29 dr, (*E*):(*Z*)]. Treatment of imino silyl enol ether **63** [71:29 dr, (*E*):(*Z*)] with $BF_3{\cdot}OEt_2$ promoted the Mukaiyama-Mannich cyclisation, with the diastereoisomers **65** and **64** isolated in 38 and 9% yield, respectively. *N*-Boc protection of **65** proceeded to give **66** in 94% yield.[48] The 3a,4-*anti* stereochemistry was introduced through a Hosomi-Sakurai allylation using allyltributyltin and $BF_3{\cdot}OEt_2$ to give **67**, which was hydrated with 9-BBN and H_2O_2 to give alcohol **68** in 81% yield over two steps. *O*-Benzylation proceeded in 71% yield to give **69**. The silyloxymethylene substituent was removed in a three step sequence: (i) desilylation with TBAF, (ii) oxidation with MnO_2 and (iii) a Tsuji-Wilkinson reaction using $Rh(PPh_3)_3Cl$ gave **70** in 82% yield (three steps). Hydrogenolysis of the *O*-benzyl group gave alcohol **71** in 97% yield, which was converted to the corresponding mesylate, and was displaced with NaN_3 to give azide **72** in 92% yield (two steps). Hydrogenation with Lindlar's catalyst gave amine **73** in 97% yield. Global deprotection with methanolic HCl gave **22**·*x*HCl in quantitative yield (Scheme 9). The conversion of the 71:39 [(*E*):(*Z*)] mixture of imines **63** to **22**·*x*HCl therefore proceeded in 14.9% yield over 13 steps. Overall, "Ma's intermediate" was synthesised in 26 linear steps from L-glutamic acid in 1.3% yield.



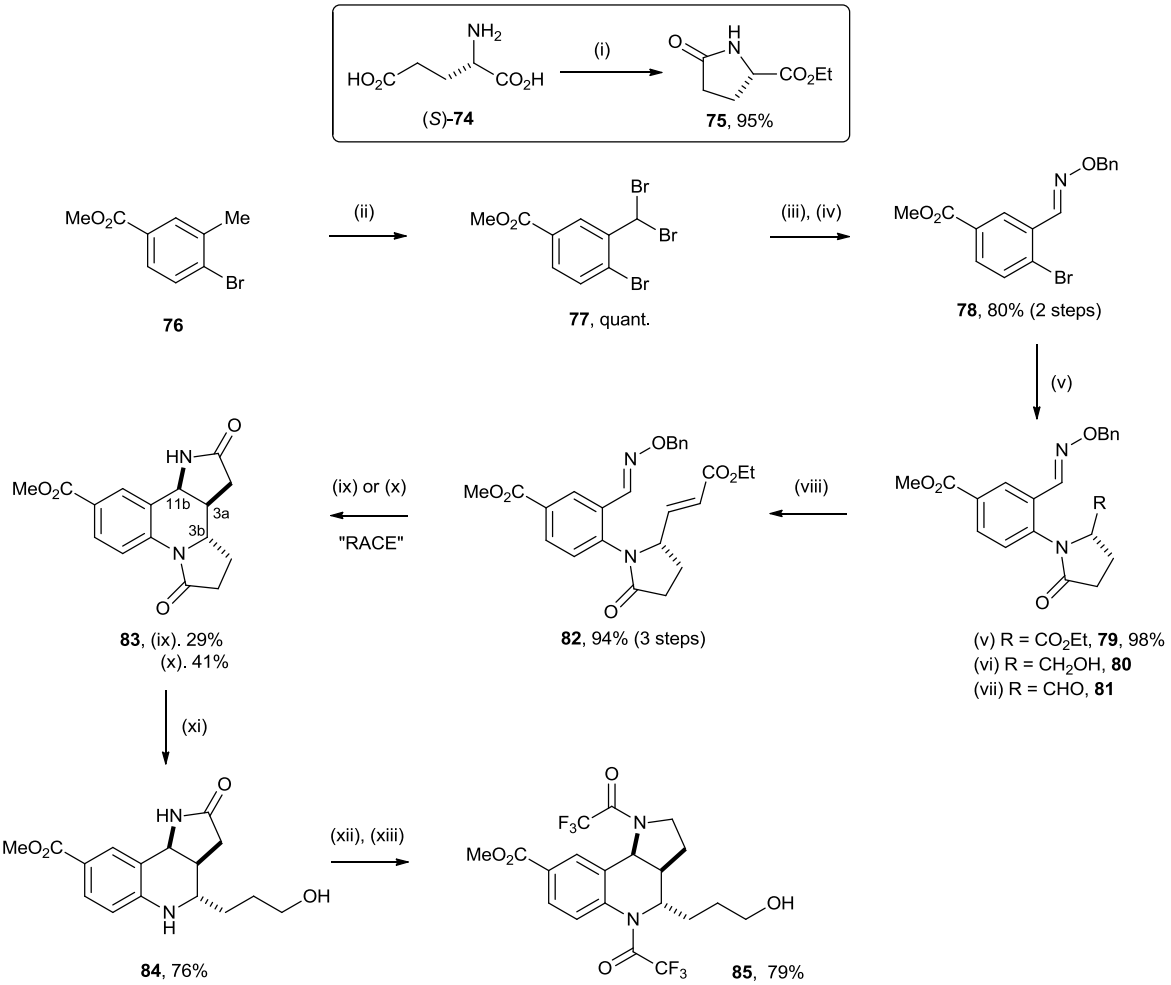
Scheme 9. *Reagents and Conditions*: (i) 4 Å MS, $LiBF_4$, C_6H_6, reflux, 6 h; (ii) 4 Å MS, $BF_3{\cdot}OEt_2$, –40 °C to 0 °C, 3 h; (iii) **65**, Boc_2O, NaHMDS, 0 °C to rt, 1.5 h; (iv) allyltributylstannane, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –40 °C to –5 °C, 1 h; (v) TBAF, THF; (v) 9-BBN, THF, 0 °C, 3 h, then H_2O_2, NaOH, 30 min; (vi) NaH, BnBr, THF; (vii) TBAF, THF, 5 h; (viii) 4Å MS, NMO, TPAP, rt; (ix) $RhCl(PPh_3)_3$, xylene, reflux, 30 min; (x) Pd/C, MeOH, H_2 (1 bar), 10 h; (xi) MsCl, Et_3N, DMAP, CH_2Cl_2, 40 min; (xii) NaN_3, DMF, 50 °C; (xiii) Lindlar's catalyst, MeOH, H_2 (1 bar); (xiv) HCl/MeOH, rt, 12 h. [a] The configuration at C(4) was undetermined.

Iwabuchi *et al*. converted **22**·*x*HCl to (–)-martinellic acid **8** using the procedure reported by Ma *et al.*,[25] in 34% yield over three steps. Thus the synthesis of (–)-martinellic acid **8** was completed in 29 linear steps and 0.4% overall yield. Iwabuchi *et al*. converted **22**·*x*HCl to martinelline **9** using the procedure reported by Batey, in four steps and 29% yield.[44] Thus the total asymmetric synthesis of martinelline **9** was completed in 0.4% yield over 30 steps. It was noted that the specific rotation of the synthetic sample of martinelline **9** $\{[\alpha]_D^{28} -108$ (*c* 0.11 in MeOH)$\}$ was substantially different from the natural sample $\{[\alpha]_D +9.4$ (*c* 0.02 in MeOH)$\}$. Iwabuchi *et al.* suggested that this result may demonstrate that the natural sample was "nearly racemic". Iwabuchi *et al*. also converted the minor product from the Mukaiyama-Aldol reaction **64** to the antipodes (+)-martinellic acid **8** and (+)-martinelline **9** by an analogous series of steps.

1.3.6. Naito approach: Radical Addition-Cyclization-Elimination (RACE) route and third total asymmetric synthesis of (–)-martinellic acid

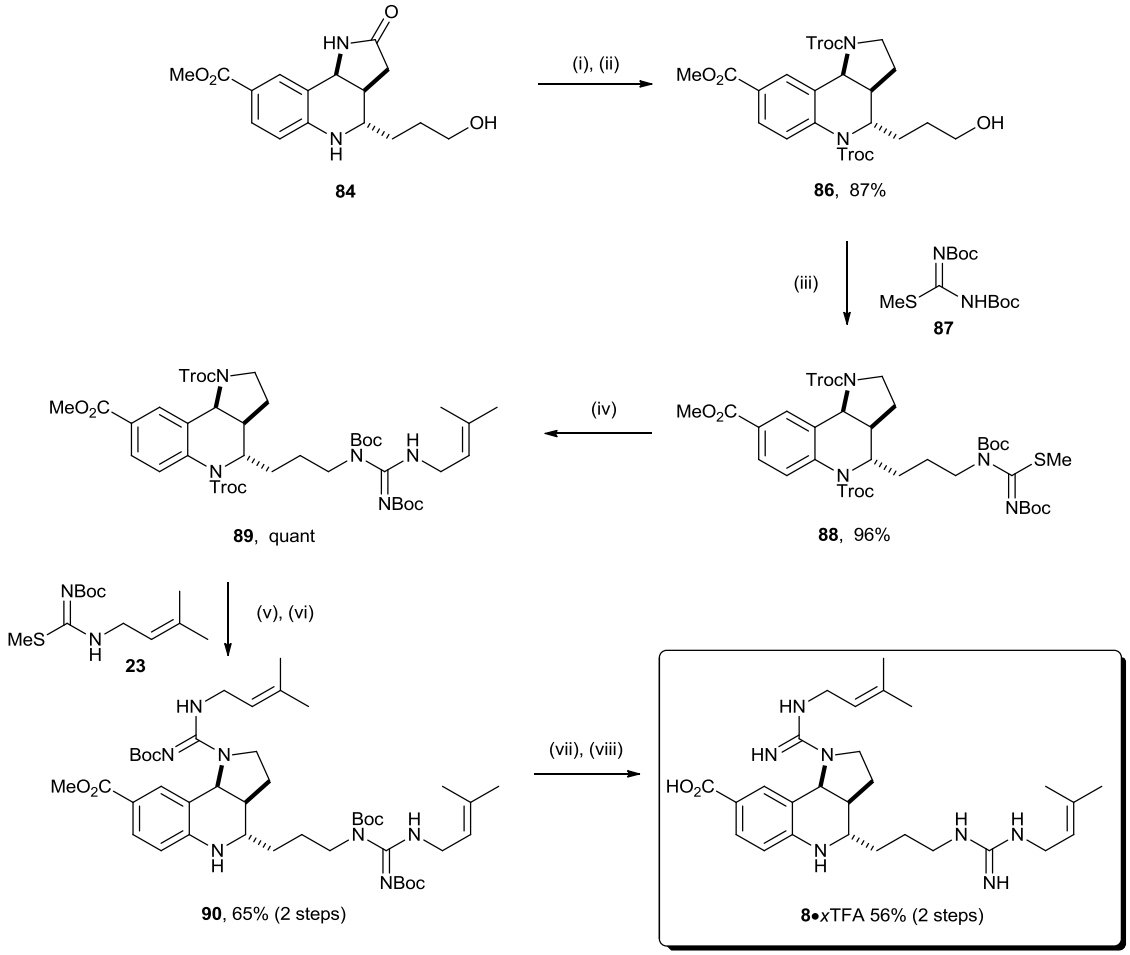
A different approach to the tricyclic core found within **8** and **9** was developed by Naito *et al*.,[49] culminating in the third reported total asymmetric synthesis of (–)-martinellic acid **8**.[26,50] The

chirality was derived from L-glutamic acid **74**, which was cyclized and esterified with $SOCl_2$/EtOH to give pyrrolidinone **75** in 95% yield. Oxime **78** was derived in three steps from commercially available **76**: bromination of **76** with NBS and AIBN in CCl_4 at reflux gave tribromide **77** in quantitative yield. Hydrolysis with MeOH/H_2O in the presence of $AgNO_3$ gave the corresponding aldehyde, which was condensed with *O*-benzyl hydroxylamine·HCl to give oxime **78** in 80% yield over 2 steps. Buchwald Hartwig coupling of oxime **78** with pyrrolidinone **75** gave **79** in 98% yield. Reduction of the ester functionality within **79** with $NaBH_4$ gave the corresponding alcohol **80**, which was oxidised to the corresponding aldehyde **81** with DMSO/TFAA, followed by Wittig olefination to give **82** in 82% yield over three steps. A key RACE reaction with Bu_3SnH and AIBN resulted in a mixture of tetracyclic products varying in their configuration at the 3a, and 11b stereocentres, with the major diastereoisomer being (3a*R*,3b*S*,11b*S*)-**83**, which was isolated in 29% yield.[51] It was found that improved selectivity was obtained by using SmI_2 as the reducing agent, with the desired tetracycle **83** being obtained in 41% yield after purification. The reaction is proposed to proceed through (i) addition of a stannyl radical (or electron transfer in the case of SmI_2) to the nitrogen end of the oxime ether in **82**, (ii) radical cyclisation to form the quinoline ring, (iii) pyrrolidinone ring formation and finally N–O bond cleavage. Chemoselective reductive ring-opening of the *N*-aryl-pyrrolidinone within **83** was achieved with $LiBH_4$ with MeOH in THF to give amino alcohol **84** in 76% yield.[49] Reduction of the primary amide within **84** with BH_3·THF, followed by global acetylation with TFAA gave alcohol **85** in 79% yield.[25] Thus the synthesis of alcohol **85** proceeded in 18% yield over 11 steps from bromide **76**. In comparison, Ma *et al.* prepared alcohol **85** in ~3.7% yield over 20 steps,[52] and therefore this constitutes a higher yielding formal synthesis of **22**·*x*HCl (Scheme 10).



Scheme 10. *Reagents and Conditions*: (i) $SOCl_2$, EtOH, reflux; (ii) NBS, AIBN, CCl_4, reflux, quant.; (iii) $AgNO_3$, H_2O, MeOH, reflux; (iv) $BnONH_2$·HCl, NaOAc, MeOH, CH_2Cl_2, rt; (v) **75**, Pd_2dba_3, Xantphos, Cs_2CO_3, 1,4-dioxane, 100 °C; (vi) $NaBH_4$, MeOH, rt, 40 min; (vii) TFAA, DMSO, Et_3N, CH_2Cl_2, –65 °C to rt; (viii) **56**, THF, rt; (ix) AIBN, $SnBu_3H$, AIBN, PhH, reflux, 4.5 h; (x) SmI_2, THF, ^tBuOH, 0 °C, 3 h; (xi) $LiBH_4$, MeOH, THF, reflux; (xii) BH_3·THF, THF, reflux; (xiii) TFAA, Et_3N, DMAP, CH_2Cl_2, rt, 79%.

Naito *et al.* used a different strategy to convert lactam **84** into (–)-martinellic acid **8** from those previously reported, and ultimately found that the best yields were obtained starting with bis-*N*-Troc derivative **86**, which was derived in two steps from lactam **84** in 87% yield. Mitsunobu reaction of alcohol **86** with **87** gave isothiourea **88** in 96% yield. Treatment of **88** with prenylamine allowed attachment of the prenyl group to the C(3') end to give **89** in quantitative yield. *N*-Troc deprotection with Zn, followed by coupling of isothiourea **23** mediated by $HgCl_2$ gave tris-*N*-Boc compound **90** in 65% yield over two steps. Finally, ester hydrolysis and global *N*-Boc deprotection gave (–)-martinellic acid **8** in 56% yield over two steps (Scheme 11). Thus the synthesis of (–)-martinellic acid **8** was completed in 17 steps and 7.0% yield.

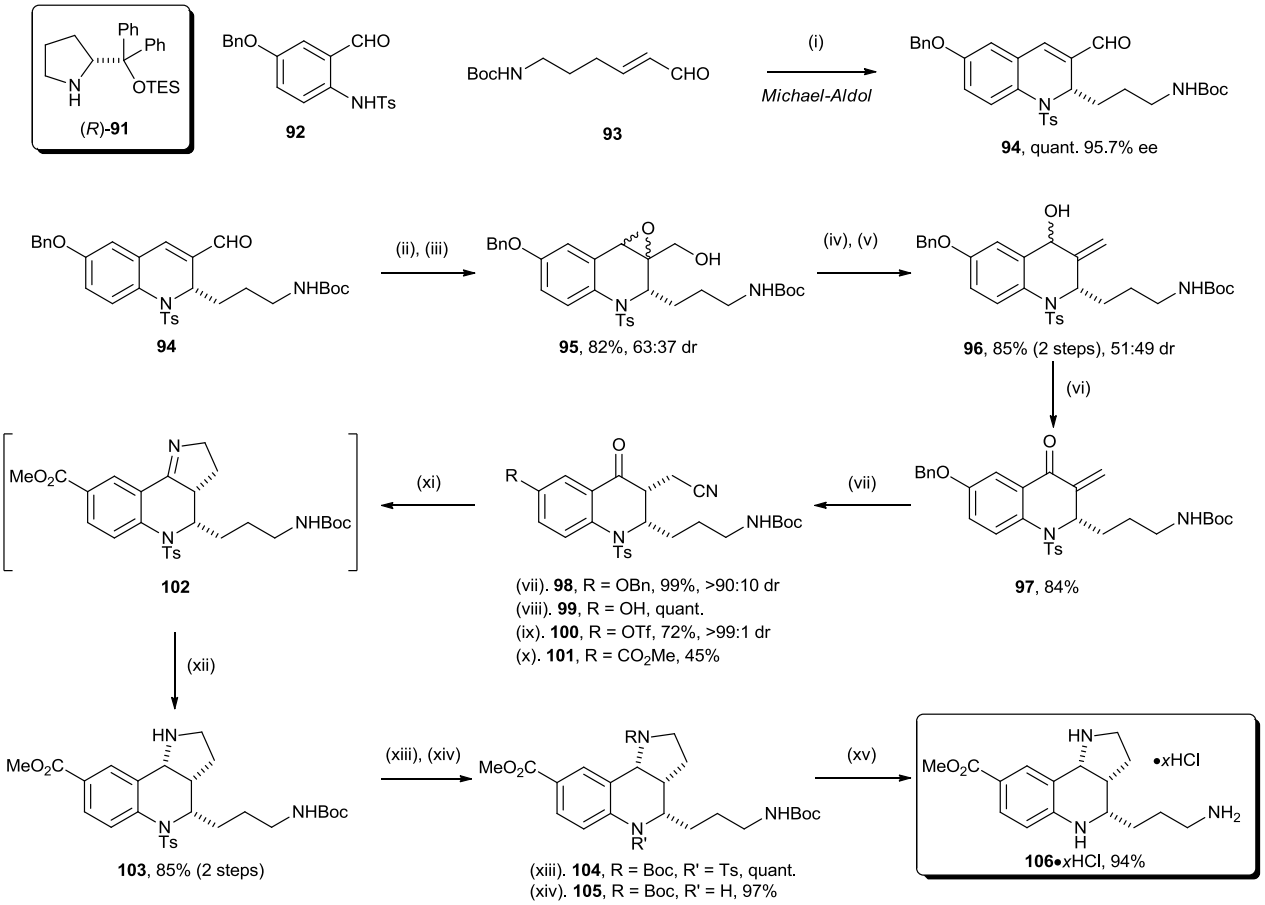


Scheme 11. *Reagents and Conditions*: (i) BH_3·THF, THF, reflux, 90 min; (ii) TrocCl, Et_3N, DMAP, CH_2Cl_2, then K_2CO_3 (1.5 equiv), MeOH/H_2O, rt, 16 h; (iii) **87** (3.0 equiv), Ph_3P, DIAD, THF, rt, 1 h; (iv) prenylamine (10 equiv), THF, rt, 5 h; (v) Zn, NH_4Cl, THF, rt, 6 h; (vi) **23** (1.2 equiv), Et_3N, $HgCl_2$, DMF, rt, 2 h; (vii) MeOH/H_2O, NaOH, reflux, 14 h; (viii) TFA, CH_2Cl_2, rt, 16 h.

1.3.7. Hamada approach: Asymmetric Michael-Aldol reaction cascade route to both C(4)-epimers

An alternative synthetic route to the tricyclic core reported by Hamada *et al*. relied on an enantioselective Michael-Aldol reaction sequence between aniline **92** and α,β-unsaturated aldehyde **93** with proline derived catalyst (*R*)-**91** to generate dihydroquinoline derivative **94** in 95.7% ee in quantitative yield.[53,54] Reduction of the aldehyde within **94** under Luche conditions gave the corresponding allylic alcohol in quantitative yield, which was epoxidised with *m*-CPBA to give a 63:37 ratio of diastereoisomeric epoxides **95** (of unknown configuration) in 82% combined yield. Conversion of the alcohol within **95** to an iodide and reduction with Zn in AcOH gave the corresponding isomeric allylic alcohol **96** in 85% yield over two steps (51:49 dr). Oxidation with MnO_2 proceeded to give α,β-unsaturated ketone **97** in 84% yield. Michael addition with KCN gave the nitrile adduct **98** in 99% yield and >90:10 dr. Interestingly, the relative configuration of the two substituents within the major component was found to be *cis*, which was attributed to kinetic protonation of the enolate after the Michael addition. A similar approach to that employed by Ma *et al*. was then used to construct the pyrrolidine ring:[25] hydrogenolysis of **98** gave alcohol **99** in quantitative yield. Triflation gave **100** in 72% yield, which was converted to the aryl ester **101** by a

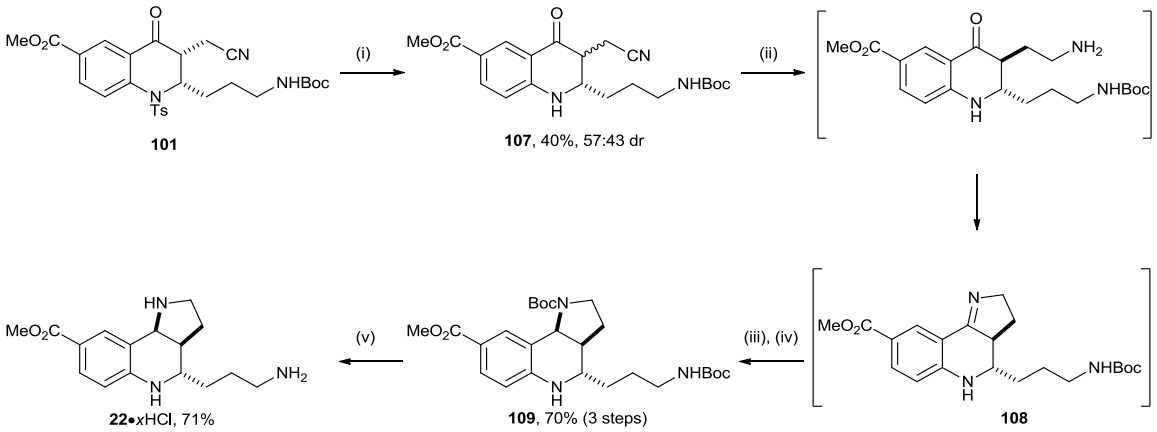
carbonylation reaction in 45% yield. Hydrogenation of the nitrile within **101** gave the corresponding amine, which underwent cyclisation *in situ* to give imine **102**, which was treated with $NaBH_3CN$ to give **103** in 85% yield. *N*(1)-Boc protection gave **104** in quantitative yield, which was deprotected at the *N*(5) position with Mg to give **105** in 97% yield. Global *N*-deprotection with methanolic HCl gave triamine **106**·*x*HCl, an analogue of "Ma's intermediate", in 94% yield (Scheme 12). Thus the synthesis of **106**·*x*HCl proceeded in 15 steps from aldehyde **92** in 14.5% overall yield. Including the synthesis of aldehyde **92**, the synthesis was completed in 20 steps (longest linear sequence) and 13.1% yield.



Scheme 12 *Reagents and Conditions*: (i) (*R*)-**91** (0.05 equiv), AcOH (0.05 equiv), MeCN, –20 °C, 24 h; (ii) $NaBH_4$, $CeCl_3·H_2O$, MeOH, rt, 18 h; (iii) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 45 h; (iv) PPh_3, I_2, imidazole, C_6H_6, rt, 20 min; (v) Zn, AcOH, MeOH, rt, 30 min; (vi) MnO_2, CH_2Cl_2, rt, 16 h; (vii) KCN, AcOH, H_2O, EtOH, 50 °C, 40 min; (viii) H_2, Pd/C, EtOAc, rt, 60 h, quant; (ix) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt, 2 h; (x) CO, $Pd(OAc)_2$, dppp, Et_3N, MeOH, DMF, 70 °C, 2 h; (xi) Raney Ni, EtOH, H_2 (1 atm), 50 °C, 24 h; (xii) $NaBH_3CN$, MeOH, AcOH (pH 5); (xiii) Boc_2O, Et_3N, rt, 1 h, quant; (xiv) Mg, MeOH, rt, 18 h, 97%; (xv) 2.0 M methanolic HCl, –15 °C, 23 h.

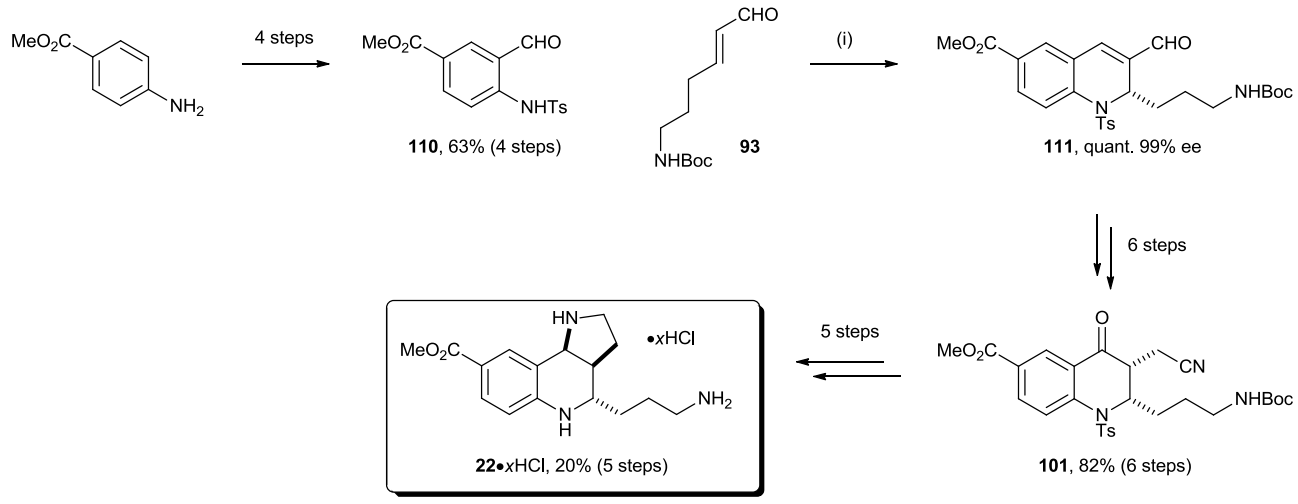
In order to complete the synthesis of (–)-martinellic acid **8**, it was necessary for Iwabuchi *et al.* to epimerise at an earlier stage in the synthesis to the desired 3a,4-*anti* diastereoisomer **109**. Thus, the tosyl group within **101** was deprotected with Na in naphthalene/DME to give **107** in 40% yield and 57:43 dr. Upon treatment with Raney Nickel, imine **108** was obtained almost exclusively. The authors proposed that, in the absence of the bulky *N*-tosyl group, epimerisation of the C(3) stereocentre occurs prior to cyclisation of the amine onto the ketone. Alternatively, it may be that a mixture of diastereoisomeric imines form during the reaction, which are subsequently epimerised to

the more stable product **108**. This is in contrast to the lack of epimerisation as described above. A series of analogous reactions completed an asymmetric synthesis of Ma's intermediate **22**·*x*HCl, which was obtained in 19.9% yield over five steps from **101** (Scheme 13).



Scheme 13. *Reagents and Conditions*: (i) Na, naphthalene, DME, −78 °C, 1.5 h; (ii) Raney Ni, H_2 (1 atm), EtOH, 50 °C, 29 h; (iii) $NaBH_3CN$, AcOH, MeOH, rt, 3 h; (iv) Boc_2O, $NaHCO_3$, dioxane/H_2O (1:2), 0 °C to rt, 42 h; (v) 2.0 M methanolic HCl, −15 °C to rt, 14 h.

Hamada *et al.* optimised the synthesis of nitrile **101** from methyl 4-aminobenzoate, negating the poor yield for the methoxycarbonylation reaction. Thus, methyl 4-aminobenzoate was converted in four steps to aldehyde **110** in 63% overall yield. A Michael-Aldol reaction of **110** and **93** with (*R*)-**91** catalyst gave **111** in quantitative yield and 99% ee (Scheme 14). An analogous series of transformations to those shown in Scheme 13 gave ketone **101** in 82% yield over six steps. Thus the optimised synthesis of **22**·*x*HCl proceeded in 10% yield over 16 steps.



Scheme 14. *Reagents and Conditions*: (i) (*R*)-**91** (0.2 equiv), MeCN, −20 °C, 24 h.

1.4. Summary

The previous sections have described the various formal and total asymmetric syntheses of (–)-martinellic acid **8**, which and are summarised below (Table 1). Two enantiospecific syntheses of (–)-martinellic acid **8** have been reported by Iwabuchi *et al.* and Naito *et al.*,[19,26] both starting from L-glutamic acid, in 0.4 and 7.0% overall yield, in 29 and 17 steps, respectively. However, to date, only one asymmetric synthesis has been reported, by Ma *et al.*, in 1.3% overall yield over 27 steps.[25] Since the publication of this work, "Ma's intermediate" has been identified as a convenient late stage

intermediate and has also been synthesised by a number of groups, constituting a formal synthesis of (–)-martinellic acid **8**, with the highest yielding synthesis of **22**·*x*HCl being that of Hamada *et al.*, in 13.1% over 20 steps.[53]

Product	Group	Classification	Number of steps	Overall yield
(–)-Martinellic acid **8**	Ma[25]	Asymmetric synthesis	27	1.3%
(–)-Martinellic acid **8**	Iwabuchi[19]	Enantiospecific from L-glutamic acid	29	0.4%
(–)-Martinellic acid **8**	Naito[26]	Enantiospecific from L-glutamic acid	17	7.0%
(–)-**22**•*x*HCl	Hamada[53]	Asymmetric synthesis	20	13.1%
(–)-**22**•*x*HCl	Lovely[36]	Enantiospecific from pyroglutamate	21	0.9%

Table 1. Comparison of formal and total asymmetric syntheses of (–)-martinellic acid **8**.

1.5. Project aims

The aims of this project were to develop a short and efficient asymmetric synthesis of the tricyclic core found within (–)-martinellic acid **8** and (+)-martinelline **9**, which would be amenable to the synthesis of either desired enantiomer. It was envisaged that the application of Davies' conjugate addition methodology,[29,55] followed by alkylation of the resultant β-amino ester, could be used to introduce the C(3a) and C(9b) stereocentres found within (–)-martinellic acid **8**. It was envisaged that further elaboration would allow access to (–)-martinellic acid **8** or (+)-martinelline **9**, or their enantiomers (Fig 5).

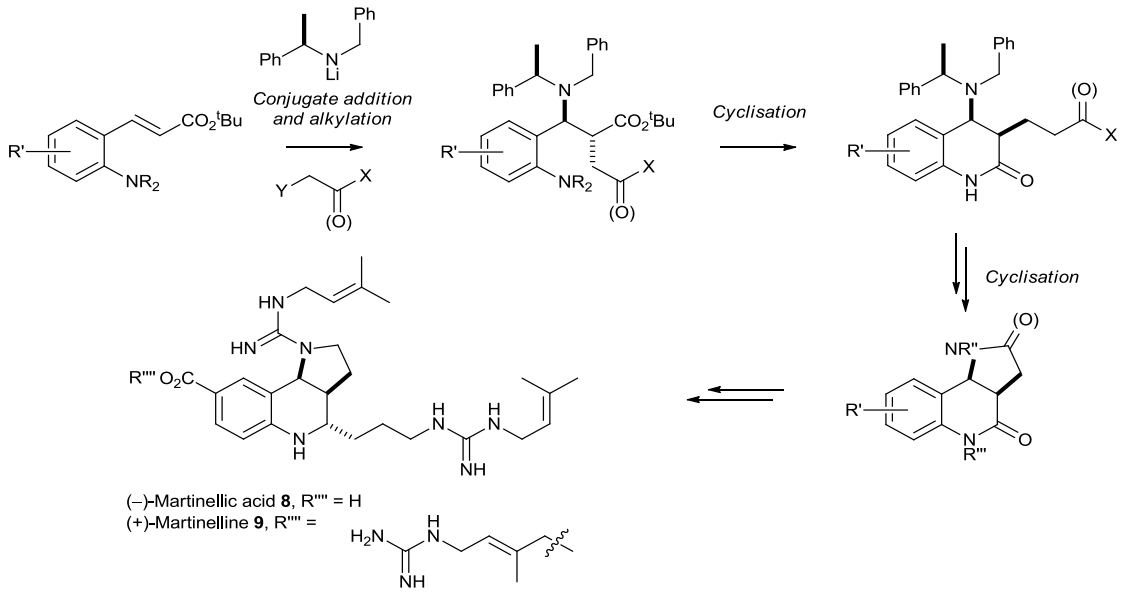


Fig 5. Lithium amide conjugate addition route to martinellic acid.

1.6. References and notes

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Chapter 2: Synthesis of 4-amino-tetrahydroquinoline derivatives

2.1. Introduction

This Chapter describes studies into the synthesis of functionalised α-alkyl-β-aminoester derivatives **115**, using the conjugate addition of an enantiopure lithium amide and *in situ* alkylation as the key steps. Cyclisation of **114** to the corresponding dihydroquinolin-2-one derivatives **115**, and preliminary efforts into their conversion towards "Ma's intermediate" **22**·*x*HCl are described (Fig 6).

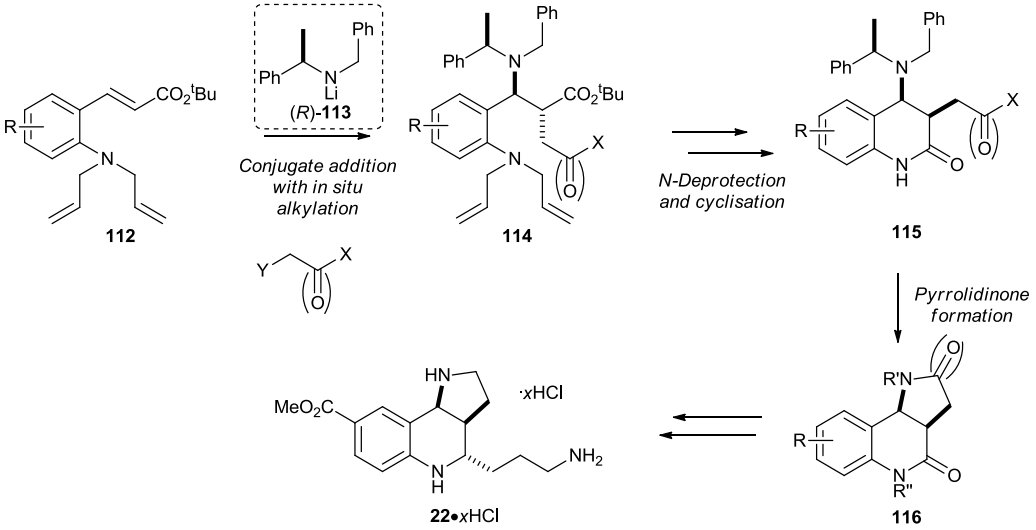


Fig 6. 4-Amino-tetrahydroquinolines as intermediates in a synthesis towards "Ma's intermediate" **22**·*x*HCl.

2.2. Synthesis of stereogenic centres bearing an α-nitrogen atom

The construction of molecules with complete control of relative and absolute stereochemistry has long been the goal of the synthetic chemist. In particular, the formation of stereogenic centres bearing an α-nitrogen atom has received considerable attention. Examples for their preparation include the asymmetric reduction of imines, as exemplified in the industrial synthesis of the herbicide (*S*)-metolachlor **120**.[1,2] In this process, a mixed Ir/ferrocene catalyst **118** allows the asymmetric hydrogenation of imine **117** with a turnover frequency of >1,800,000/h.[1] Other routes for the production of such stereogenic centres include the asymmetric hydrogenation of enamines,[3] S_N2 displacement of enantiopure alcohol derivatives with nitrogen nucleophiles, aza-Diels-Alder reactions,[4] allyl cyanate to isocyanate rearrangements,[5] and the conjugate addition of amines to unsaturated carbonyl systems.[6,7] For example, the asymmetric synthesis of (+)-Cisapride **123** was reported by Davies *et al.*,[8] using the conjugate addition of enantiopure lithium amide (*R*)-**113** and *in situ* enolate oxidation with (–)-CSO to install the C(3) and C(4) stereocentres within the target molecule (Fig 7).

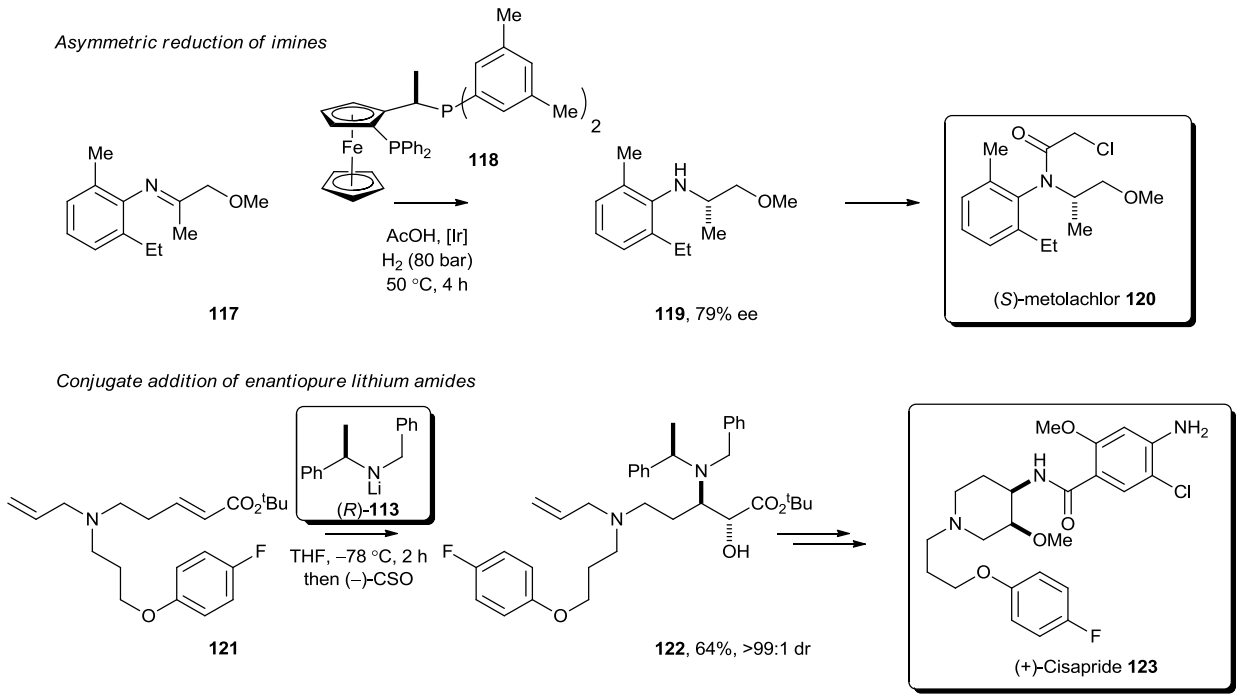
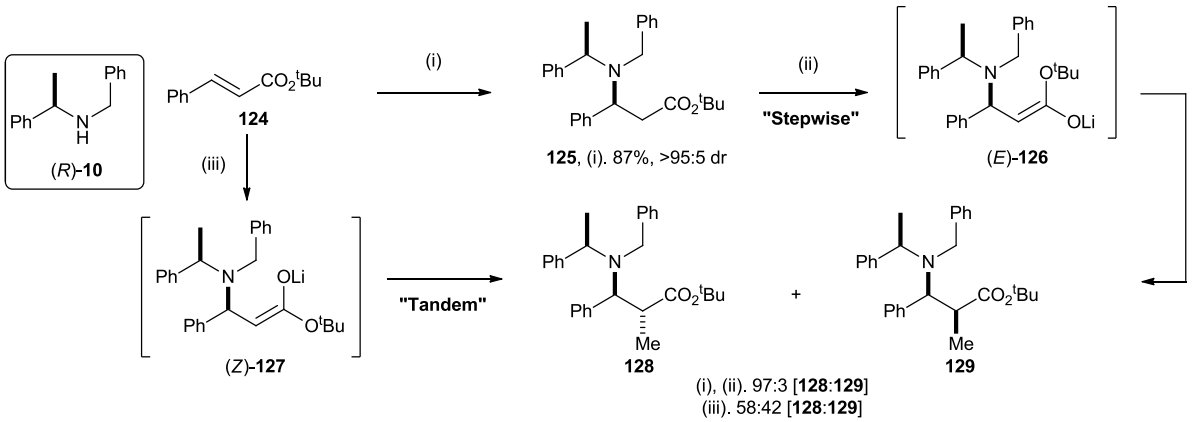


Fig 7. Drug molecules containing an α-nitrogen stereocentre.

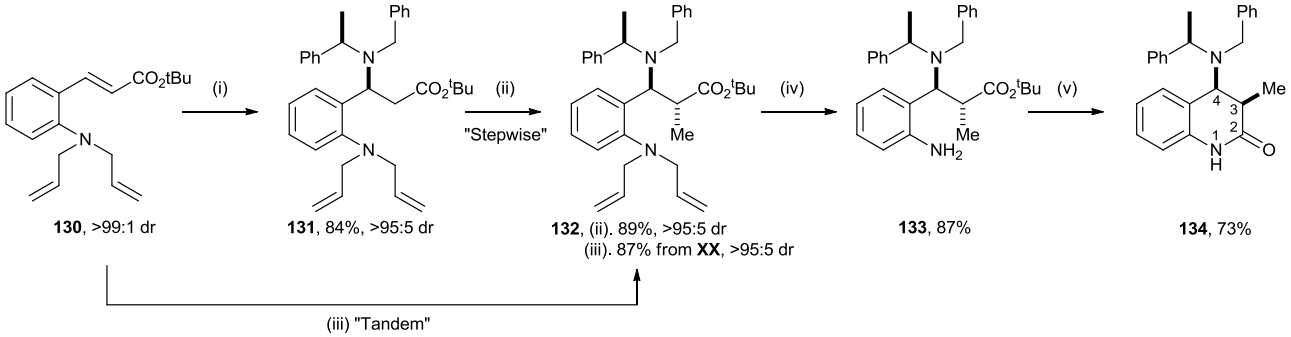
2.3. Conjugate addition of enantiopure lithium amides to α,β-unsaturated esters

Davies *et al*. have shown that the conjugate addition of lithium amides derived from commercially available α-methylbenzyl amine to α,β-unsaturated esters is an efficient method for the preparation of enantiopure β-amino esters and their derivatives, and the subject has been reviewed.[7,8] Typically, addition of 1.6 equivalents of a lithium amide such as **113** to the requisite substrate in THF at −78 °C proceeds within 2 h to give the corresponding β-amino ester [*via* the intermediate lithium (*Z*)-β-amino enolate **127**][9,10] in high yield with a high and predictable sense of diastereoselectivity.[6] For instance, conjugate addition of lithium amide (*R*)-**113** (derived from amine (*R*)-**10** upon deprotonation with BuLi) to α,β-unsaturated ester **124** gave β-amino ester **125** in 87% yield and >95:5 dr.[10] The intermediate enolate **127** can be functionalised further by treatment with an electrophile such as MeI (i.e., a "tandem" procedure). Thus, treatment of the intermediate lithium (*Z*)-β-amino enolate **127** with MeI proceeded to give a 58:42 mixture of 2,3-*anti* and 2,3-*syn* epimers **128** and **129**, respectively. Although alkylation of the lithium (*Z*)-β-amino enolate **127** with MeI shows a slight preference for formation of the 3,4-*anti*-diastereoisomer, alkylation of the lithium (*E*)-β-amino enolate **126** (derived from treatment of β-amino ester **125** with LDA) proved highly selective for formation of the *anti* diastereoisomer **128**, giving a 97:3 mixture of 2,3-*anti* and 2,3-*syn* epimers **128** and **129**, respectively (i.e., a "stepwise" procedure). This methodology provides a powerful tool for the production of α-alkyl-β-amino esters (Scheme 15).[10]



Scheme 15. *Reagents and Conditions*: (i) (*R*)-**10** (1.6 equiv), BuLi (1.6 equiv), THF, −78 °C, 2 h; (ii) LDA (1.5 equiv), THF, −78 °C, 1 h then MeI (3.0 equiv), −78 °C to rt; (iii) (*R*)-**10** (1.6 equiv), BuLi (1.6 equiv), THF, −78 °C, 2 h then MeI (3.0 equiv), −78 °C to rt.

Davies *et al*. have reported the synthesis of 3-methyl-4-amino-dihydroquinolin-2-one **134** from α,β-unsaturated ester **130** in an application of this approach. Conjugate addition of (*R*)-**113** to α,β-unsaturated ester **130** gave β-amino ester **131** in 84% yield and >95:5 dr.[11] A "stepwise" protocol involving deprotonation of **131** with LDA and treatment of the resulting lithium (*E*)-β-amino enolate with MeI (5.0 equiv.) gave **132** in 89% yield and >95:5 dr. Alternatively, the "tandem" approach gave equally good results, yielding **132** in 87% yield and >95:5 dr directly from **130**. *N*,*N*-Deallylation of **132** was achieved by treatment with $Pd(PPh_3)_4$ (0.04 equiv) and excess *N*,*N*-dimethylbarbituric acid (DMBA), following a procedure reported by Guibé *et al*.,[12] which gave aniline **133** in 87% isolated yield. Cyclisation of **133** proceeded cleanly upon treatment with $PhCO_2H$ (3.0 equiv) in CH_2Cl_2 at rt to give **134** in 73% yield after purification (Scheme 16).



Scheme 16. *Reagents and Conditions*: (i) (*R*)-**10** (1.6 equiv), BuLi (1.6 equiv) THF, −78 °C; (ii) LDA (1.5 equiv), THF, −78 °C, 1 h then MeI (3.0 equiv), −78 °C to rt; (iii) (*R*)-**10** (1.6 equiv), BuLi, THF, −78 °C, 2 h then MeI (3.0 equiv) −78 °C to rt, 16 h; (iv) $Pd(PPh_3)_4$ (0.04 equiv), DMBA (3.0 equiv), CH_2Cl_2, rt, 24 h; (v) $PhCO_2H$ (3.0 equiv), CH_2Cl_2, rt, 16 h.

It was previously reported by Davies *et al*. that application of either the "tandem" or "stepwise" alkylation protocol with α,β-unsaturated ester **130** was unsuccessful with electrophiles other than MeI.[11] It was hoped that alkylation could be achieved by screening a wider range of functionalised electrophiles, in particular those bearing an adjacent π-substituent such as a carbonyl, olefin or nitrile. The rate acceleration for displacement reactions of such compounds is well known,[13] and such electrophiles have previously been used by Davies *et al.* in the alkylation of enolates derived from *N*-acyl oxazinanones.[14] Furthermore, it was anticipated that the reactivity of the respective enolates

could be enhanced by the use of additives, such as crown ethers (*vide infra*).

2.4. Synthetic strategy towards (–)-martinellic acid

It was thought that the conversion of α,β-unsaturated ester **130** into (–)-martinellic acid **8** could proceed through 4 key intermediates **136-138** and **22**·*x*HCl. Firstly, conjugate addition of an enantiopure lithium amide **135** to α,β-unsaturated ester **130** followed by alkylation could be used to install the C(3a) and C(9b) stereocentres within the target molecule, to give α-alkyl-β-amino ester **136**. *N*-Deprotection followed by cyclisation to form both the 5- and 6- membered rings would give the tricyclic pyrroloquinoline core **137**. It was envisaged that manipulation of the C(4) carbonyl within **137** could be achieved to allow diastereoselective introduction of a C(4) substituent within **138**, with several groups having previously demonstrated the feasibility of this approach (*vide infra*).[15,16,17] A series of steps including bromination of the aromatic ring followed by Pd-catalysed methoxycarbonylation to introduce the aryl ester, and conversion of the C(4) substituent within **138** to the 3-aminopropyl moiety would give "Ma's intermediate" **22**·*x*HCl. (–)-Martinellic acid **8** could then be derived from **22**·*x*HCl by literature protocols (Fig 8).

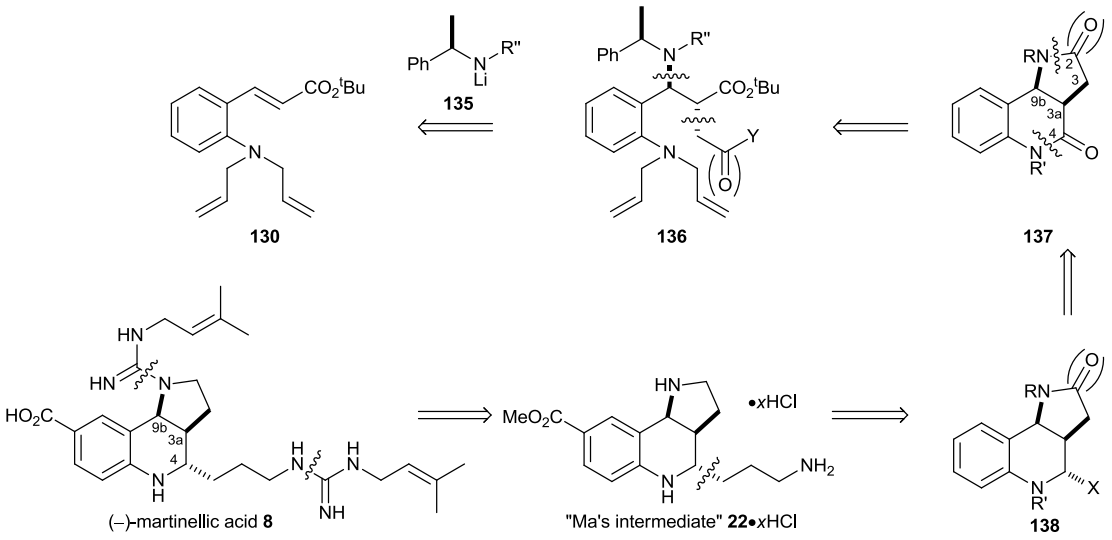
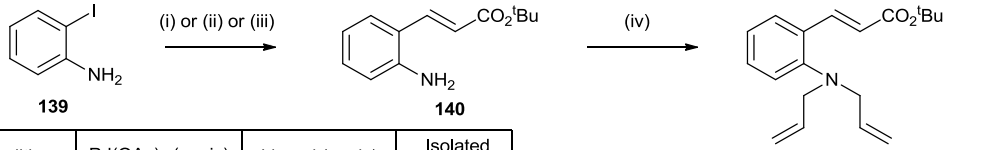


Fig 8. Retrosynthetic analysis of (–)-martinellic acid **8**.

2.5. Introduction of the C(3a) and C(9b) stereocentres within the pyrroloquinoline core

Initial efforts were first directed at the optimisation of the synthesis of α,β-unsaturated ester **130**, which was needed in large quantities. Davies and Mujtaba have reported the synthesis of aniline **140** through a Heck coupling of commercially available 2-iodoaniline **139** and *tert*-butyl acrylate: treatment of **139** with $Pd(OAc)_2$ (0.1 equiv), P(*o*-Tol)$_3$ (0.2 equiv) and *tert*-butyl acrylate (1.1 equiv) in MeCN at 70 °C for 16 h was reported to give **140** in 95% yield and >99:1 dr.[11] It was decided to first attempt lowering the amount of catalyst in order to make this process more scalable. Treatment of **139** with $Pd(OAc)_2$ (0.05 or 0.01 equiv) and P(*o*-Tol)$_3$ (0.1 or 0.02 equiv) under the same conditions proceeded to full conversion, to give **140** as a single geometric isomer [>99:1, (*E*):(*Z*)], in

85% yield. Bis-*N*-allylation of **140** was achieved by treatment with excess allyl iodide (3.0 equiv) and K_3PO_4 in acetone at reflux for 48 h to give **130** in 73% yield and >99:1 dr after purification. It was found that purification of the intermediate aniline **140** after the Heck coupling was unnecessary as **140** could be used directly in the next bis-*N*-allylation step without detriment to the yield; in this case **130** was isolated in 89% yield (over two steps) and >99:1 dr after chromatographic purification. This method was amenable to the synthesis of α,β-unsaturated ester **130** on a 25 g batch scale (Scheme 17).



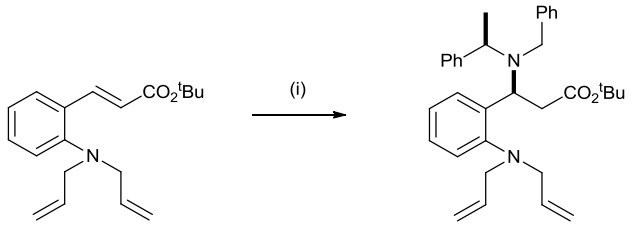
139 **140**

Conditions	$Pd(OAc)_2$ (equiv)	Ligand (equiv)	Isolated yield of **140**
(i)	0.1	P(*o*-Tol)$_3$ (0.2)	95%
(ii)	0.05	P(*o*-Tol)$_3$ (0.1)	85%
(iii)	0.01	P(*o*-Tol)$_3$ (0.02)	-

130, (iv). 73% [from **140**], >99:1 dr
(iii), (iv). 89% [from **139**], >99:1 dr

Scheme 17. *Reagents and Conditions*: (i)-(iii) $Pd(OAc)_2$, *tert*-butyl acrylate (1.1 equiv), ligand, Et_3N (2.0 equiv), MeCN, 70 °C, 16 h; (iv) allyl iodide (3.0 equiv), K_3PO_4, acetone, reflux, 48 h.

As the *in situ* alkylation of the lithium (*Z*)-β-aminoenolate derived from conjugate addition of lithium amide (*R*)-**113** ("tandem approach") provides the most rapid and elegant route to α-alkyl-β-amino esters, this route was investigated first. An authentic sample of β-amino ester **131** was prepared in 97% yield and in >99:1 dr by treatment of α,β-unsaturated ester **130** with (*R*)-**113** (1.6 equiv) in THF at −78 °C for 2 h (Scheme 18). The relative (3*S*,α*R*)-configuration within **131** was assigned in the first instance by analogy to the established and predictable diastereoselectivity exhibited by (*R*)-**113** in conjugate addition reactions and by reference to the transition state mnemonic developed for these conjugate addition reactions.[6,18] The formation of **131** with complete stereocontrol at C(3) showed that any mixtures of diastereoisomers obtained in subsequent alkylation reactions could therefore be assigned as being epimeric at the C(2)-position.

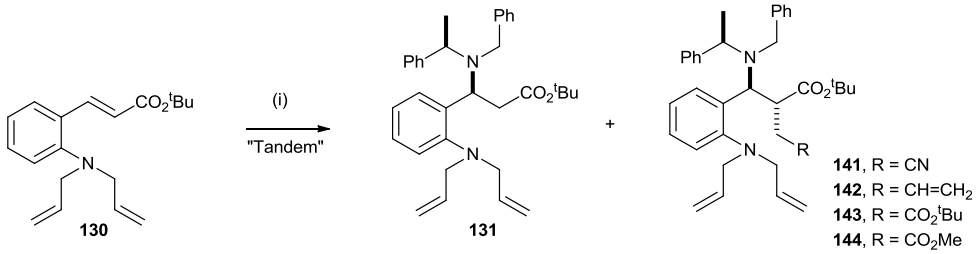


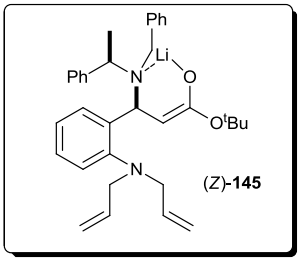
130 **131**, 97%, >99:1 dr

Scheme 18. *Reagents and Conditions*: (i) (*R*)-**10** (1.6 equiv), BuLi (1.6 equiv), THF, –78 °C, 2 h.

A range of electrophiles containing a functional handle such as a tosylate, halide, ester or C=C bond were screened initially in the "tandem protocol". Analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy indicated no alkylation occurred during the "tandem protocol" when 1,2-ethylene ditosylate, 1,2-dibromoethane, methyl bromoacetate or *tert*-butyl bromoacetate were employed as the

electrophile, instead **131** was observed as the sole product in all cases. However, in the case of allyl iodide a 32:68 mixture of **131** and **142**, respectively, was observed, with the diastereoisomeric purity of the alkylated product being assigned as >95:5 dr. However, separation of **131** and **142** could not be achieved chromatographically. In the case where bromoacetonitrile was employed as the electrophile, a 46:54 mixture of **131** and **141**, respectively, was observed, with the diastereoisomeric purity of the alkylated product again being assigned as >95:5 dr. It was thought that the proportion of alkylated product in some cases could be due to the low reactivity of the intermediate lithium (*Z*)-β-amino enolate **145**. It was hoped that the addition of a crown ether additive such as 12-crown-4, which is known to have a high affinity for the Li^+ cation,[19] would produce a more reactive "naked" enolate and hence lead to a greater reaction conversion. The "tandem" experiments were therefore repeated with activated electrophiles in the presence of 12-crown-4. In the case of bromoacetonitile, a 33:69 mixture of **131** and **141**, respectively, was obtained, with **141** being isolated in 64% yield and >99:1 dr after purification. In the case of allyl iodide, a 29:71 mixture of **131** and **142**, respectively, was observed, although **142** was isolated in only 19% yield and >99:1 dr due to difficulties encountered upon attempted separation from **131**. In the case of *tert*-butyl bromoacetate, a 30:70 mixture of **131** and **143**, respectively, was obtained, with recovered starting material **131** isolated in 30% yield and >99:1 dr, and **143** isolated in 64% yield and >99:1 dr. In the case of methyl bromoacetate, a 64:36 mixture of **131** and **144**, respectively, was obtained, with **131** being isolated in 51% yield and >99:1 dr, and **144** isolated in 36% yield and >99:1 dr (Scheme 19). In each case the 2,3-*anti* relative configurations within **141-144** were assigned by analogy to the known *anti* diastereoselectivity of this class of alkylation reaction,[11] and in the case of **141**, **143** and **144** were confirmed by single crystal X-ray diffraction analysis of derivatives (*vide infra*). The ^{1}H NMR chemical shifts and *J* coupling constants corresponding to the C(1') protons within **141**, **143** and **144** also proved diagnostic of the relative configurations within these substrates, while the relative 2,3-*anti*-configuration within **142** was assigned by analogy to those within **141**, **143** and **144**. The addition of 12-crown-4 resulted in a significant improvement in the reaction conversion in all cases. A stepwise procedure was investigated next in an attempt to increase the reaction conversion.

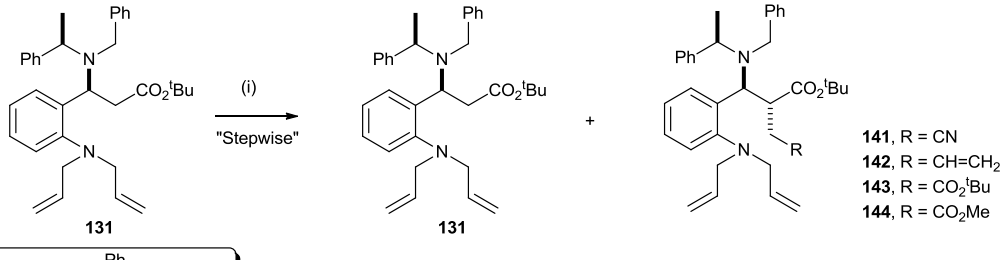


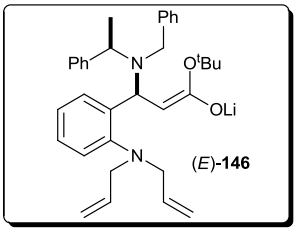


Electrophile	(i) Crude ratio (**131**:alkylated product)	(ii) Crude ratio (**131**:alkylated product)[a]	(ii) Isolated yield of alkylated product
$BrCH_2CN$	46:54	33:69	**141**, 64%, >99:1 dr
allyl iodide	32:68	29:71	**142**, 19%, >99:1 dr
$BrCH_2CO_2{}^tBu$	100:0	30:70	**143**, 64%, >99:1 dr
$BrCH_2CO_2Me$	100:0	64:36	**144**, 36%, >99:1 dr
$TsOCH_2CH_2OTs$	100:0		
$BrCH_2CH_2Br$	100:0		

Scheme 19. *Reagents and Conditions*: (i) (*R*)-**10** (1.6 equiv), BuLi (1.6 equiv), THF, −78 °C, 2 h then electrophile (3.0 equiv), −78 °C to rt, 16 h; (ii) (*R*)-**10** (1.6 equiv), BuLi (1.6 equiv), THF, −78 °C, 2 h, then 12-crown-4 (3.0 equiv), 1 h, then alkyl halide (3.0 equiv), −78 °C to rt, 16 h. [[a] In each case the dr of the alkylated product was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture]

Treatment of β-amino ester **131** with LDA (1.5 equiv), followed by addition of bromoacetonitrile at –78 °C, resulted in a 20:80 mixture of **131** and **141**, respectively, with **141** isolated in 67% yield and >99:1 dr after chromatographic purification. In the case of allyl iodide a 25:75 mixture of **131** and **142**, respectively, was obtained which was found to be inseparable by chromatography, and was therefore taken on to the next step. In the case of *tert*-butyl bromoacetate, full conversion to **143** was observed, with **143** being isolated in quantitative yield and >99:1 dr after chromatographic purification. In the case of methyl bromoacetate, only **144** was observed in the ^{1}H NMR spectrum of the crude reaction mixture; **144** was then isolated in 82% yield and >99:1 dr after chromatographic purification (Scheme 20). The "stepwise" procedure therefore proved to be superior to the "tandem" procedure with all electrophiles screened, and was also found to be amenable to scale-up. With a range of suitably functionalised substrates **141-144** in hand, attention was turned to their deprotection and cyclisation to give dihydroquinolin-2-ones.



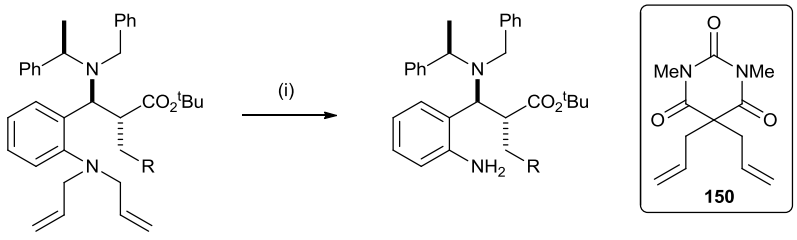


Electrophile	crude ratio (**131**:alkylated product)	Isolated yield of alkylated product
$BrCH_2CN$	20:80	**141**, 67%
$ICH_2CH{=}CH_2$	25:75[a]	-
$BrCH_2CO_2{}^tBu$	0:100	**143**, quant
$BrCH_2CO_2Me$	0:100	**144**, 82%

Scheme 20. *Reagents and Conditions*: (i) ^{i}Pr$_2$NH, (1.5 equiv), BuLi (1.5 equiv) THF, –78 °C, 1 h, then electrophile (3.0 equiv), −78 °C to rt, 16 h. [[a] **131** and **142** were obtained as an inseparable mixture]

2.6. *N*-Deallylation and cyclisation of α-alkyl-β-amino ester substrates

N-Deallylation of **141**, **143** and **144** was achieved using the conditions reported by Guibé *et al.*,[12] employing a Tsuji-Trost reaction with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (DMBA) as the allyl cation scavenger. DMBA is particularly effective for this purpose, as excess DMBA can be removed from the crude reaction mixture by extraction into aqueous solutions of K_2CO_3. Treatment of **141** with $Pd(PPh_3)_4$ (0.05 equiv) and DMBA in CH_2Cl_2 at 35 °C for 16 h gave **147** which was isolated in 54% yield and >99:1 dr after purification. Treatment of **143** with $Pd(PPh_3)_4$ (0.05 equiv) and DMBA in CH_2Cl_2 at 35 °C for 16 h gave **148** in 74% isolated yield and >99:1 dr after chromatographic purification. Analogous treatment of **144** proceeded to give **149** in 68% isolated yield and >99:1 dr (Scheme 21). In all cases barbiturate derivative **150** was observed as the sole by-product of the reaction, in accord with the observations by Guibé *et al.*[12] Aniline **149** proved to be crystalline, and the relative configuration within **149** was then unambiguously established by single crystal X-ray diffraction analysis (Fig 9),[20] with the absolute (2*R*,3*S*,α*R*)-configuration within **149** assigned relative to the known (*R*)-configuration of the α-methylbenzyl substituent. The similarities between the ^{1}H NMR chemical shifts and ^3J coupling constants for both the C(3)*H* and C(1')*H* protons within **147**-**149** allowed the configurations within **147** and **148** to be assigned by analogy. Drs J. E. Thomson, J. A. Lee and A. M. Fletcher are gratefully acknowledged for carrying out the X-Ray structure determination described throughout this thesis. With **147**-**149** in hand, attention was turned to their cyclisation to 3-alkyl-4-amino-dihydroquinolin-2-ones.



141, R = CN, >99:1 dr
143, R = $CO_2{}^t$Bu, >99:1 dr
144, R = CO_2Me, >99:1 dr

147, R = CN, 54%, >99:1 dr
148, R = $CO_2{}^t$Bu, 74%, >99:1 dr
149, R = CO_2Me, 68%, >99:1 dr

Scheme 21. *Reagents and Conditions*: (i) $Pd(PPh_3)_4$ (0.05 equiv), DMBA (3.0 equiv), CH_2Cl_2, 35 °C, 16 h.

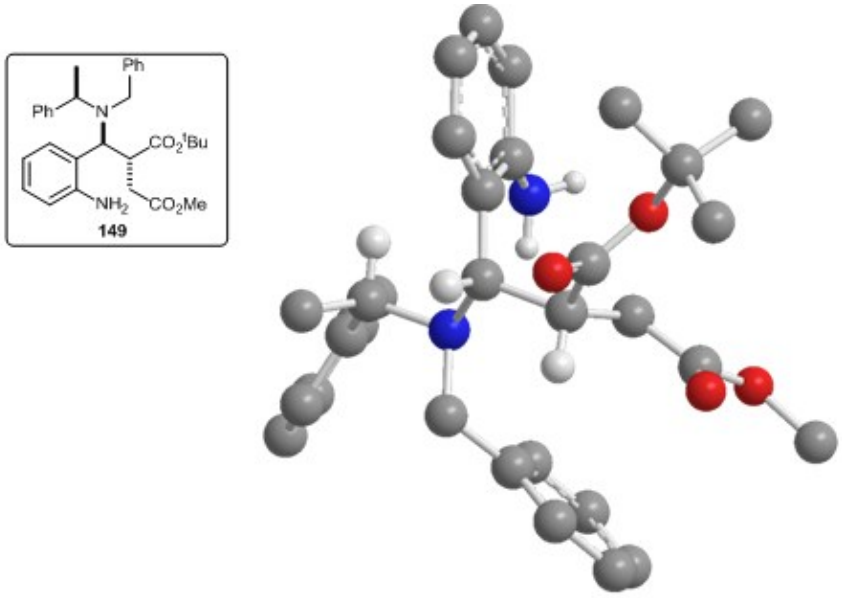
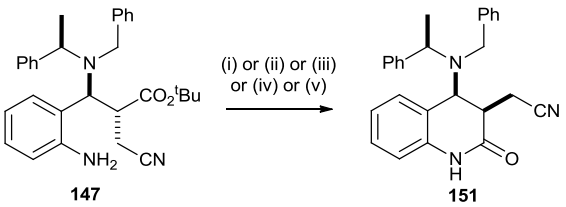


Fig 9. Chem 3D representation of the single crystal X-ray diffraction structure of **149** (selected H atoms are omitted for clarity).

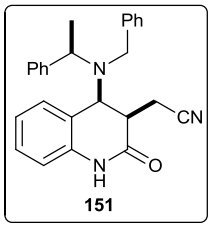
Following the conditions previously reported by Davies *et al.* in the cyclisation of **133** to give **134**,[5] treatment of **147** with $PhCO_2H$ (3.0 equiv) in CH_2Cl_2 at rt for 16 h gave an 87:13 mixture of **147** and **151**, respectively. Increasing the reaction temperature to 50 °C in THF gave a 65:35 mixture of **147** and **151**, which were isolated in 22 and 29% yield, respectively. An increase in the reaction time to 48 h at 50 °C gave an 18:82 mixture of **147** and **151**, respectively. Finally, after a further increase in the reaction time to 72 h full conversion to **151** was observed, and after purification **151** was isolated in quantitative yield. Cyclisation of **147** could also be achieved within 16 h by treatment with $PhCO_2H$ (0.1 equiv) at reflux in PhMe, with **151** being isolated in 80% yield, after purification, in this case (Table 2). The longer reaction time and higher temperatures required for the cyclisation of **147** presumably reflect the greater steric clash present within **151** (and the corresponding transition state leading to it) compared to **134**. The relative configuration within **151** was unambiguously established by single crystal X-ray diffraction analysis, with the absolute (3*R*,4*S*,α*R*)-configuration within **151** being assigned relative to the known (*R*)-configuration of the α-methylbenzyl group (Fig 10).[20]



147 151

Conditions	$PhCO_2H$ (equiv)	Solvent	Temperature (°C)	Time (h)	Ratio **147**:**151**	Isolated yield of **151**
(i)	3.0	CH_2Cl_2	rt	16	87:13	-
(ii)	3.0	THF	50	16	65:35	29%
(iii)	3.0	THF	50	48	18:82	-
(iv)	3.0	THF	50	72	0:100	quant
(v)	0.1	PhMe	110	16	0:100	80%

Table 2. *Reagents and Conditions*: see table.



151

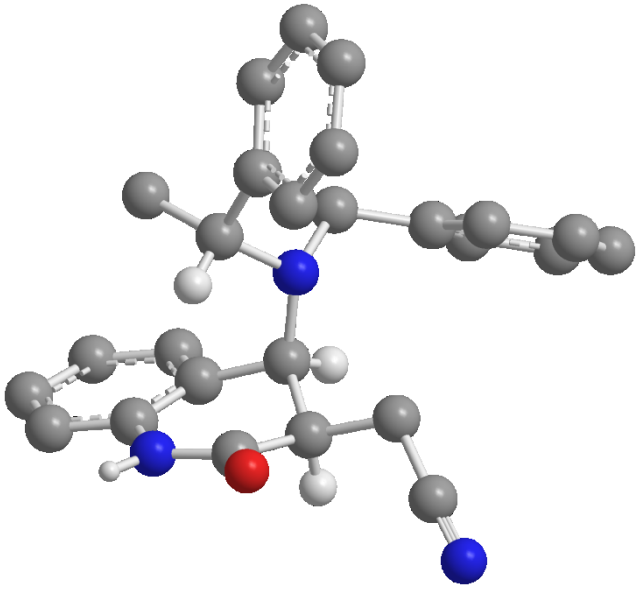
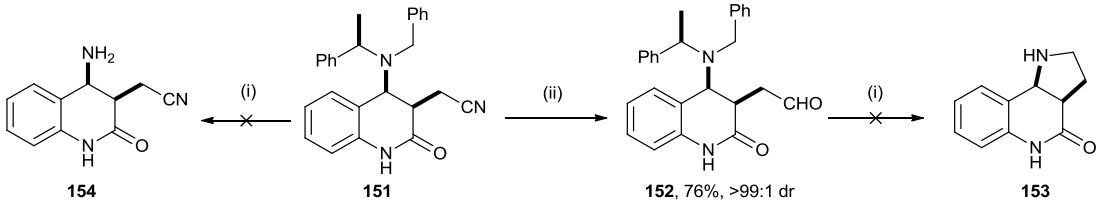


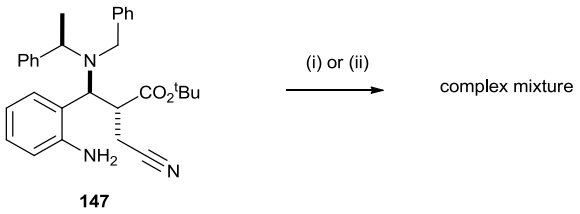
Fig 10. Chem 3D representation of the single crystal X-ray diffraction structure of **151** (selected H atoms are omitted for clarity).

With the synthesis of **151** proceeding in high yield, attention was turned to construction of the pyrrolidine ring. Reduction of the nitrile within **151** with DIBAL-H (3.0 equiv) in CH_2Cl_2 at −78 °C gave aldehyde **152** in 76% yield and >99:1 dr after purification. Attempted hydrogenolysis of **152** with $Pd(OH)_2/C$ in MeOH under H_2 (1 atm) gave returned starting material. When the reaction was repeated under a higher pressure of H_2 (2 atm) substantial decomposition was observed. Attempted hydrogenolysis with $Pd(OH)_2/C$ in MeOH/AcOH (95:5 v/v) under H_2 (1 atm) also gave returned starting material. Similarly, treatment of **151** with $Pd(OH)_2/C$ in MeOH under H_2 gave returned starting material after 16 h, in which neither the *N*-benzyl nor nitrile groups were affected (Scheme 22). This lack of reactivity is unusual, but may be a result of the bulky *N*-benzyl-*N*-(α-methylbenzyl)-amino group blocking the approach of the nitrile to the catalyst surface and *vice versa*.



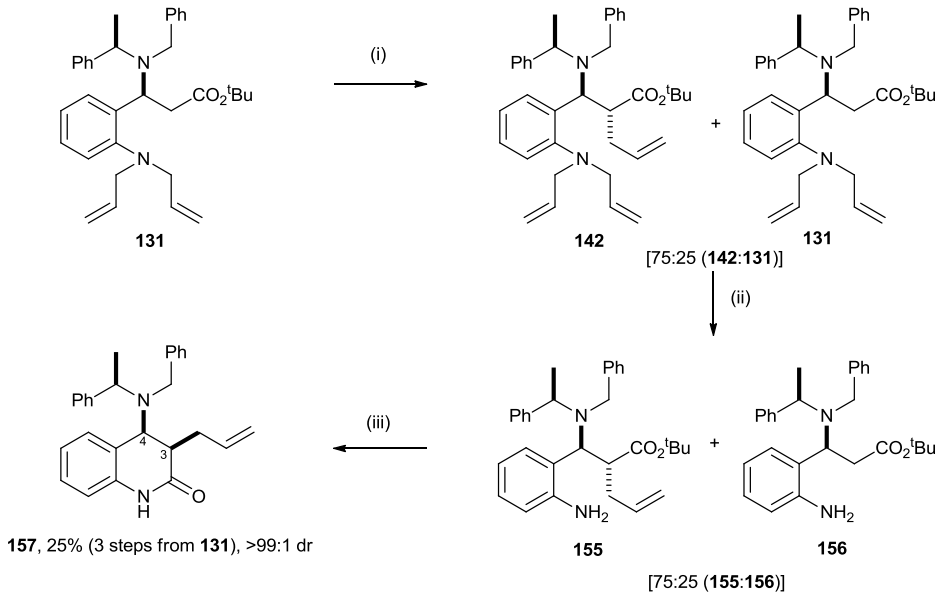
Scheme 22. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, MeOH, H_2 (2 atm), 16 h; (ii) DIBAL-H (3.0 equiv), CH_2Cl_2, −78 °C, 2 h.

It was hoped that hydrogenolysis of the *N*-benzyl-*N*-(α-methylbenzyl)amino moiety within aniline **147** prior to cyclisation would give a primary amine at the C(3) position, which it was thought may allow cyclisation of the aniline more readily. Attempted hydrogenolysis of **147** with $Pd(OH)_2/C$ (20% w/w) in MeOH under H_2 (1 atm) for 16 h gave predominantly returned starting material (Scheme 23). Resubjection of the crude reaction mixture to the reaction conditions with a higher catalyst loading (50% w/w) resulted in a complex mixture of products, and this route was therefore not pursued further.



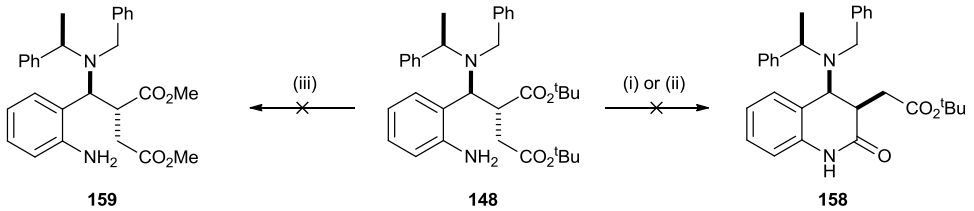
Scheme 23. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (20% w/w), H_2 (1 atm), MeOH, rt, 16 h; (ii) $Pd(OH)_2/C$ (50% w/w), H_2 (1 atm), MeOH, rt, 16 h.

Cyclisation of **142** was next attempted. Treatment of the (inseparable) 75:25 mixture of **142** and **131** with $Pd(PPh_3)_4$ and DMBA gave a 75:25 mixture of **155** and **156**, which was followed by treatment with $PhCO_2H$ (0.1 equiv) in PhMe at reflux for 16 h to give **157**, in 25% yield and >99:1 dr (over three steps from **131**) (Scheme 24). The configuration within **157** was assigned by analogy to **151**, with the ^3J coupling constants providing evidence for the relative 3,4-*syn* configuration in each case [For **151** $^3J_{3,4}$ = 6.6 Hz, for **157** $^3J_{3,4}$ = 6.3 Hz].



Scheme 24. *Reagents and Conditions*: (i) LDA (1.5 equiv), THF, −78 °C, 1 h, then allyl iodide (3.0 equiv), −78 °C to rt, 16 h, (ii) $Pd(PPh_3)_4$ (0.05 equiv), DMBA (3.0 equiv), CH_2Cl_2, 35 °C, 16 h; (iii) $PhCO_2H$ (0.1 equiv), PhMe, reflux, 16 h.

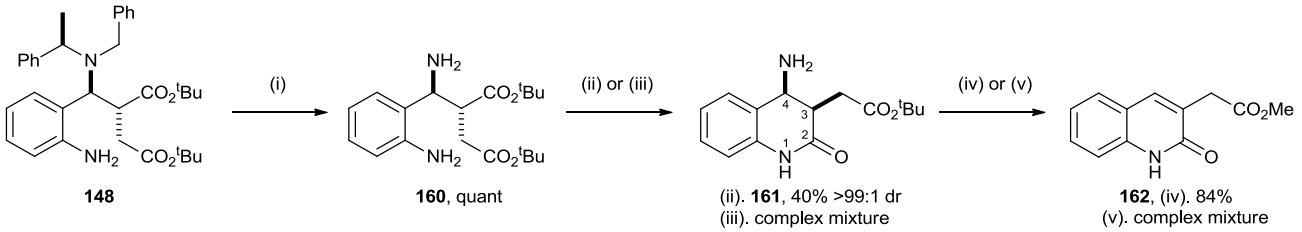
Attempted cyclisation of **148** by treatment with $PhCO_2H$ in either CH_2Cl_2 at rt or THF at 50 °C resulted in returned starting material, presumably due to the increased bulk of the C(3)-substituent within **148**. It was hoped that cyclisation of bis-*tert*-butyl ester **148** could be achieved after transesterification of **148** to the corresponding bis-methyl ester **159**. However, treatment of **148** with $SOCl_2$/MeOH resulted in a complex mixture of products (Scheme 25).



Scheme 25. *Reagents and Conditions*: (i) $PhCO_2H$ (3.0 equiv), CH_2Cl_2, rt, 16 h; (ii) $PhCO_2H$ (3.0 equiv), THF, 50 °C, 16 h; (iii) $SOCl_2$, MeOH, reflux, 16 h.

In order to probe the possibility of making the cyclisation process more facile by reducing the steric clash between the amino moiety and the C(2)-substituent during cyclisation, hydrogenolysis of the *N*-protecting groups was next investigated. Hydrogenolysis of **148** with $Pd(OH)_2$/C in MeOH under H_2 (4 atm) gave **160** in quantitative yield and >99:1 dr. However, attempted chromatographic purification of a portion of **160** resulted in partial cyclisation, with dihydroquinolin-2-one **161** being isolated in 41% yield after column chromatography (>99:1 dr). The relative (3*R*,4*S*)-configuration within **161** was unambiguously determined by single crystal X-ray diffraction analysis (Fig 11).[20,21] Amine **161** proved unstable to acidic conditions, and substantial decomposition was observed upon treatment of **161** with $PhCO_2H$ (3.0 equiv) in THF at 50 °C for 16 h. With **161** in hand, efforts were directed to formation of the γ-lactam, which would result in the tricyclic framework. However, treatment of **161** with DBU (5.0 equiv) in CH_2Cl_2 resulted in a complex mixture of unidentified products. Attempted transesterification of **161** to the corresponding methyl ester in an effort to affect ring-closure, gave **162** in 84% yield as the sole product (Scheme 26).[22] As the synthesis of **161** was

low yielding and attempts to convert **161** into the tricyclic martinelline core were unsuccessful, an alternative route starting from **149** was pursued.



Scheme 26: *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (50% w/w), MeOH, H_2 (4 atm), 16 h, no purification; (ii) attempted purification on SiO_2, EtOAc/Et_3N (100:1); (iii) $PhCO_2H$ (3.0 equiv), CH_2Cl_2, rt, 16 h; (iv) HCl (1.0 M in MeOH), reflux, 1 h; (v) DBU (5 equiv), CH_2Cl_2, rt, 16 h.

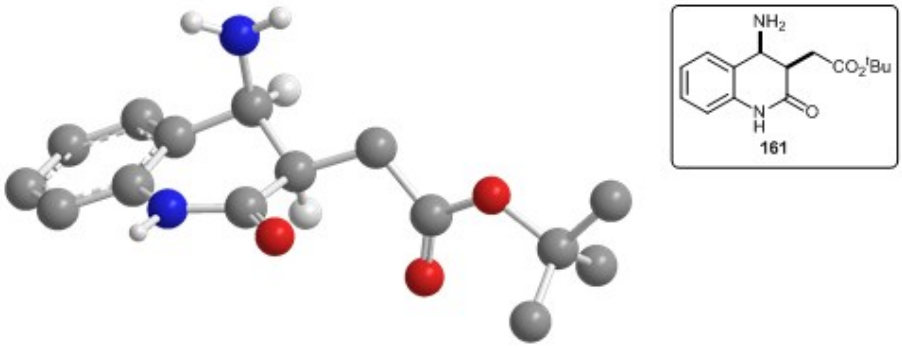
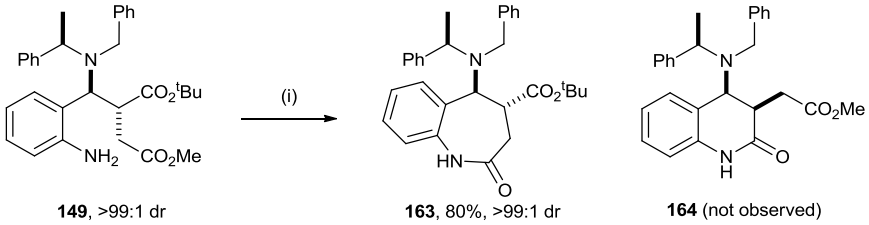


Fig 11. Chem 3D representation of the single crystal X-ray diffraction structure of **161** (selected H atoms are omitted for clarity).

Treatment of **149** with $PhCO_2H$ (0.1 equiv) in PhMe at relux for 16 h gave benzazipine **163** in 80% yield and >99:1 dr (Scheme 27). The relative configuration within **163** was unambiguously established by single crystal X-ray diffraction analysis,[20] with the absolute (4*R*,5*S*,α*R*)-configuration within **163** being assigned relative to the known (*R*)-configuration of the α-methylbenzyl group (Fig 12). Furthermore the determination of a Flack *x* parameter[23] of –0.01(15) for the crystal structure of **163** allowed this assignment to be confirmed unambiguously.[20]



Scheme 27. *Reagents and Conditions*: (i) $PhCO_2H$, PhMe, reflux, 16 h.

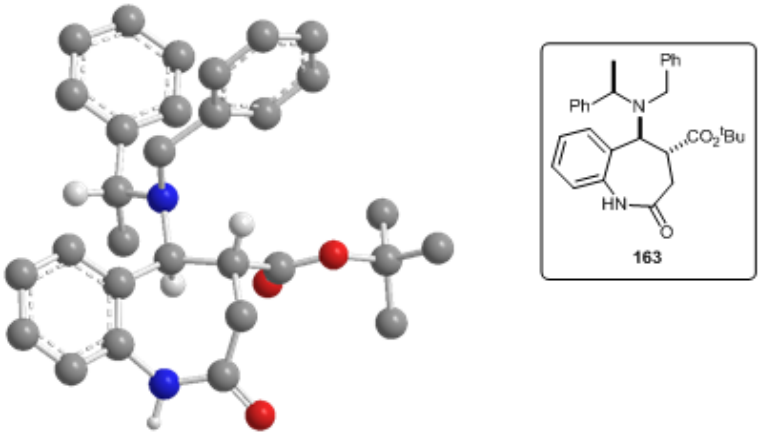
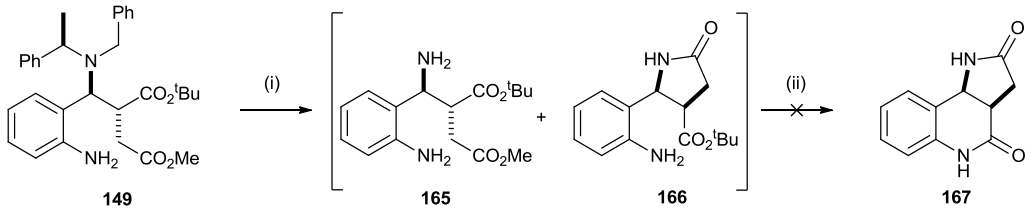


Fig 12. Chem 3D representation of the single crystal X-ray diffraction structure of **163** (selected H atoms are omitted for clarity).

Treatment of **149** with $Pd(OH)_2/C$ (20% w/w) in MeOH under H_2 (1 atm) gave an ~50:50 mixture of **165** and a product which was tentatively assigned as pyrrolidinone **166** from ^1H NMR, COSY and HSQC analyses of the crude reaction mixture, along with mass spectrometric evidence (Scheme 28). Additionally, products arising from incomplete hydrogenolysis of the *N*-benzyl-*N*-(α-methylbenzyl) moiety were observed under the reaction conditions. Resubjection of the crude reaction mixture gave a 39:61 mixture of **165** and **166**, respectively. Treatment of the crude mixture at reflux in PhMe in an effort to drive cyclisation to pyrroloquinolindione **167** resulted in substantial decomposition to an intractable mixture of products.



Scheme 28. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (20% w/w), MeOH, H_2 (1 atm), rt, 16 h; (ii) PhMe, reflux, 16 h.

2.7. Double cyclisation strategy

The observation of γ-lactam **166** during cyclisation of a substrate containing a methyl ester at the C(2') position suggested that this approach could be combined with acid promoted cyclisation to the quinolin-2-one to allow both rings to be formed in one step. It was thought that variation of the lithium amide to lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide (*R*)-**173** would give α-alkyl-β-amino ester **168** after conjugate addition with *in situ* enolate alkylation. Global deallylation would give **169**, which it was predicted may also undergo cyclisation to the γ-lactam **170**, rather than the benzazapine. Additionally, it was thought that this approach would allow cyclisation of the aniline onto the second ester moiety, allowing access to the tricyclic core **171**. If successful, this would constitute a rapid and novel approach to the construction of the tricyclic scaffold in enantiopure form (Fig 13).

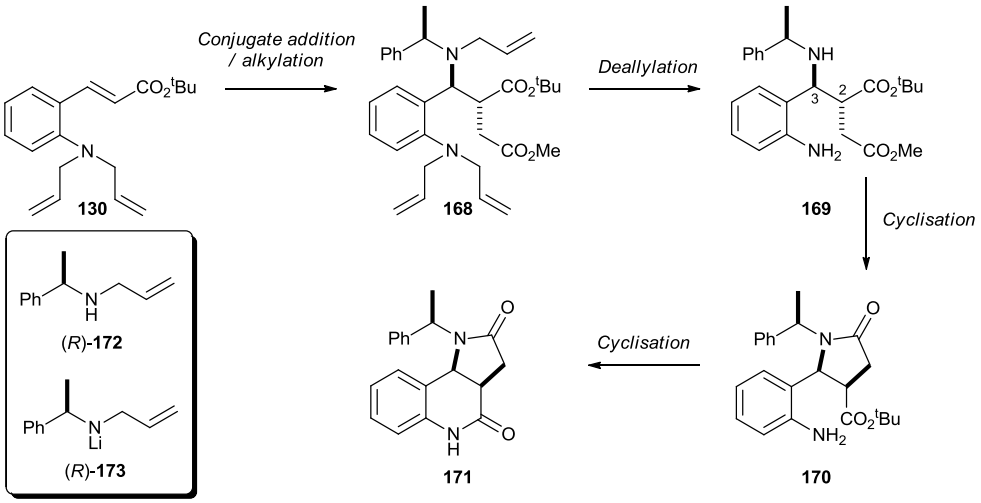
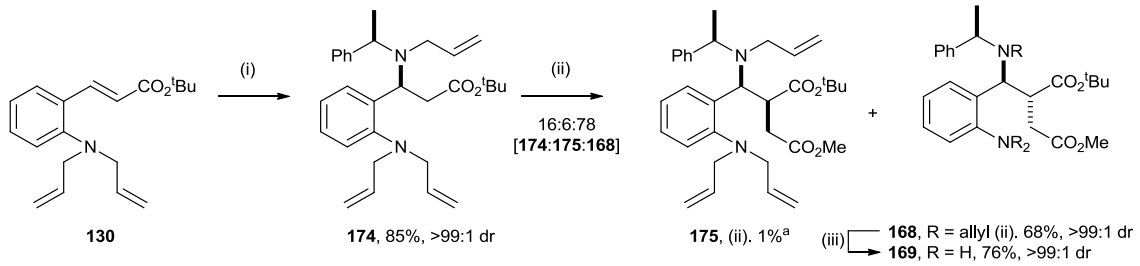


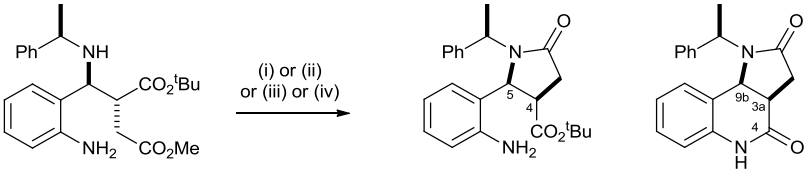
Fig 13. Synthetic route to the martinelline core using lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)-amide (*R*)-**173**.

Conjugate addition of lithium amide (*R*)-**173** (formed upon treatment of (*R*)-**172** with BuLi) to α,β-unsaturated ester **130** gave **174** in 85% yield and >99:1 dr.[24] Deprotonation of **174** with LDA followed by addition of methyl bromoacetate (3.0 equiv) gave a 16:6:78 mixture of **174**:**175**:**168**, respectively, of which the major product **168** was isolated in 68% yield and >99:1 dr. A sample of the minor 2,3-*syn* product **175** was also isolated in 1% yield and >90:10 dr. The observation of the 3,4-*syn* diastereoisomer in this case may indicate that the relative bulk of the amino substituent at C(3) plays an important role in the alkylation diastereoselectivity, as compared to the previous substrates containing the *N*-benzyl-*N*-α-methylbenzyl moiety, in addition to the nature of the electrophile.[25] Deallylation of **168** was achieved by treatment with $Pd(PPh_3)_4$ (0.15 equiv) and DMBA to give **169** in 76% yield and >99:1 dr after purification (Scheme 29). With **169** in hand, attention was turned to the double cyclisation reaction to give the tricyclic pyrroloquinoline core found within (–)-martinellic acid **8** and (+)-martinelline **9**.



Scheme 29. *Reagents and Conditions*: (i) (*R*)-**172**, BuLi, THF, −78 °C, 2 h; (ii) $^{i}Pr_2NH$, BuLi, THF, −78 °C, 1 h, then methyl bromoacetate, −78 °C to rt, 16 h; (iii) **168**, $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h. [[a] **175** was isolated as the major component of a >90:10 mixture of **175** and **168**]

The cyclisation of **169** was first attempted in the absence of an acid catalyst. Treatment of **169** in $CHCl_3$ at reflux for 16 h gave only returned starting material. Treatment of **169** in THF at reflux for 72 h gave a 78:22 mixture of **169** and **170**, respectively. The presence of **170** in the crude reaction mixture was tentatively assigned from the diagnostic ^{1}H NMR signals corresponding to the C(α) and C(5) protons within **170** [For **170** δ_H 5.54 (1H, q, *J* 7.2, C(α)*H*); 3.89 (1H, d, *J* 4.4, C(5)*H*)]. The downfield resonance corresponding to C(α)*H* suggested the formation of the pyrrolidinone. Increasing the reaction temperature further gave a 68:29:3 mixture of **169**, **170** and **171**, respectively upon treatment in PhMe at reflux. As no decomposition was observed, acid was added in an effort to promote cyclisation of both 5- and 6- membered rings. Thus, treatment of **169** with $PhCO_2H$ (0.1 equiv) in PhMe at reflux for 16 h proceeded to give **171** as the sole product, which was isolated in 80% yield and >99:1 dr (Table 3). This route therefore constituted a rapid and high yielding synthesis of the tricyclic core found within (–)-martinellic acid **8** and (+)-martinelline **9**.



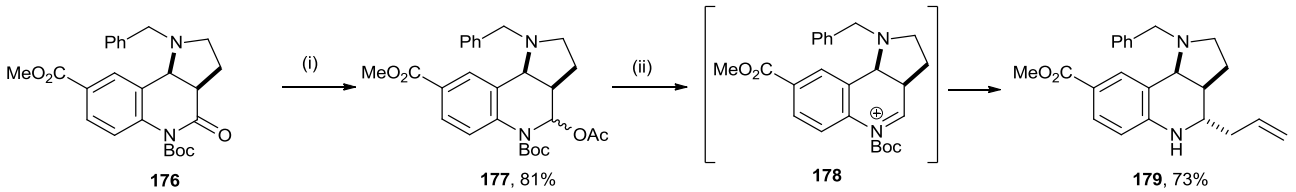
Conditions	Solvent	Temperature	Time (h)	$PhCO_2H$	**169:170:171**	Isolated yield of **171**
(i)	$CHCl_3$	rt	16 h	0 equiv	100:0:0	-
(ii)	THF	reflux	72 h	0 equiv	78:22:0	-
(iii)	PhMe	reflux	16 h	0 equiv	68:29:3	-
(iv)	PhMe	reflux	16 h	0.1 equiv	0:0:100	80%

Table 3. *Reagents and Conditions*: see table.

2.8. Introduction of the C(4) substituent within the pyrroloquinoline core

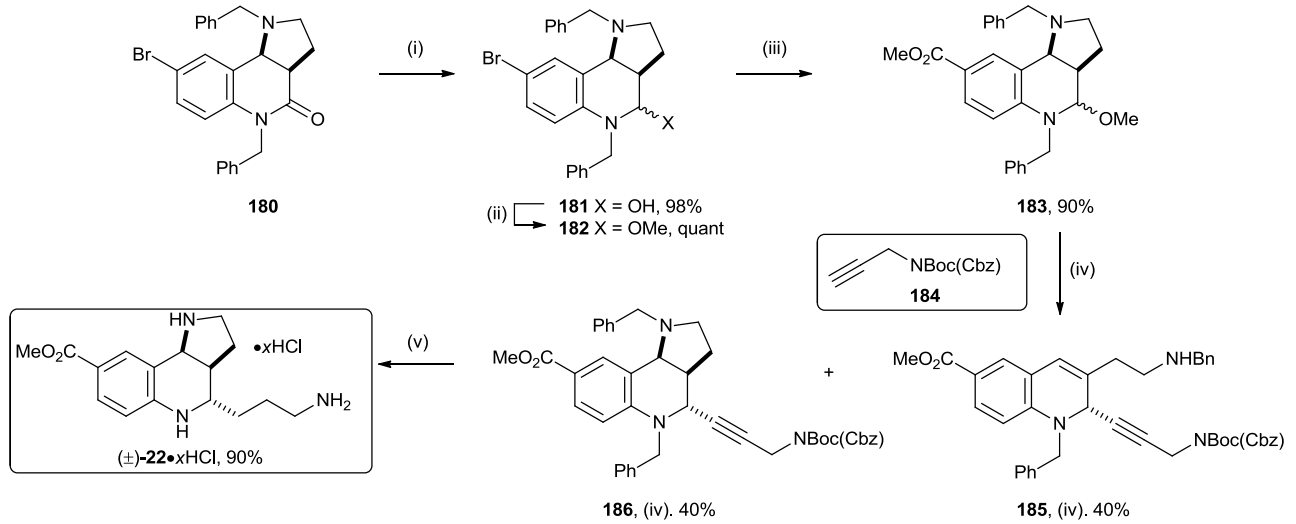
With tricyclic core **171** in hand, attention was turned to the introduction of the stereochemistry at C(4). There are various reports in the literature concerning the introduction the C(4) sidechain where either a carbonyl or methylene is present at the C(4) position within the martinelline core, although in no instance has the product been fully elaborated to (+)-martinellic acid **8** or (–)-martinelline **9**. For example, Shaw *et al*. reported that the stereochemistry at C(4) could be introduced *via* the trapping of an *N*-acyliminium ion with an allyl silane.[15] Treatment of **176** with $LiEt_3BH$ is reported to give the corresponding hemiaminal, which was trapped with Ac_2O to give **177** in 81% yield. Treatment of **177**

with $Sc(OTf)_3$ gave *N*-acyliminium ion **178**, which was trapped on the least hindered face with trimethylallylsilane; after concomitant *N*-deprotection **179** was isolated in 73% yield (Scheme 30).



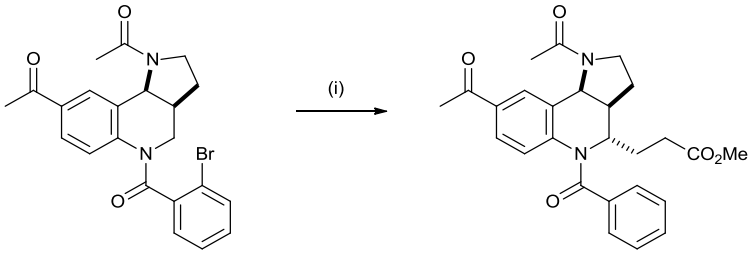
Scheme 30. *Reagents and Conditions*: (i) $LiEt_3BH$, CH_2Cl_2/THF, −78 °C, 2 h then Ac_2O, Et_3N, DMAP, CH_2Cl_2, 16 h; (ii) $Sc(OTf)_3$, allyltrimethylsilane, CH_2Cl_2, −40 °C, 3 h.

A similar method was adopted by Lovely *et al*. in a synthesis of (±)-**22**·*x*HCl. In this synthesis, tricyclic lactam **180** was reduced with DIBAL-H at −78 °C to give hemiaminal **181** in 98% yield.[16] Treatment of **181** with MeOH/$CHCl_3$ at reflux gave aminal **182** in quantitative yield. The ester at the C(8) position within **182** was introduced by lithium halogen exchange, followed by quenching the corresponding aryllithium with dimethyl carbonate to give **183** in 90% isolated yield. Coupling of **183** with acetylene **184** under Sonogashira-type conditions mediated by CuBr was reported to proceed *via* the corresponding iminium ion to give **186** in 40% isolated yield, and fragmentation product **185** in 40% yield. Treatment of **186** with $Pd(OH)_2$/C and H_2 in methanolic HCl gave "Ma's intermediate" (±)-**22**·*x*HCl in 90% yield (Scheme 31).



Scheme 31. *Reagents and Conditions*: (i) DIBAL-H, (ii) MeOH/$CHCl_3$ (4:1, v/v), reflux; (iii) BuLi, THF, $(MeO)_2CO$, −78 °C; (iv) **184**, CuBr, ultrasound; (v) $Pd(OH)_2$/C, H_2, methanolic HCl.

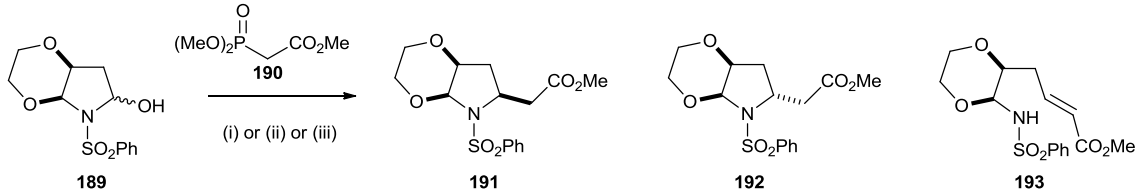
Another approach to the introduction of the C(4) stereochemistry was reported by Naito *et al*. In this synthesis, treatment of 2-bromobenzoyl derivative **187** with AIBN and Bu_3SnH led to bromine abstraction from **187** to generate the corresponding aryl radical.[17] Intramolecular 1,5-hydrogen abstraction was followed by *in situ* trapping with methyl acrylate to give **188** as a single diastereoisomer in 43% isolated yield (Scheme 32).



187 **188**, 43%

Scheme 32: *Reagents and Conditions*: (i) methyl acrylate, Bu_3SnH, AIBN, PhH, reflux.

A Wittig reaction of hemiaminal **189** with ensuing intramolecular Michael addition was reported by Rapoport *et al.* using the anion derived by treatment of phosphonate ester **190** with NaH.[26] Treatment of hemiaminal **189** with phosphonate **190** and NaH at −30 °C for 4 h was reported to give (*E*)-**193** as the sole product in 83% yield (Scheme 33). Extension of the reaction time to 40 h at −30 °C gave a 7:2:91 mixture of **191**, **192** and **193**, respectively, in 81% combined yield. At temperatures above −15 °C the subsequent Michael addition reaction occurred readily: treatment of hemiaminal **189** with **190** and NaH at 0 °C for 2 h gave a 67:33 mixture of 2,5-*syn*-**191** and 2,5-*anti*-**192**, respectively, in 86% combined yield. It was thought that this method would be suitable for the introduction of the C(4) stereocentre from a hemiaminal derived from **171**.



189 **191** **192** **193**

(i). 0:0:100 [**191**:**192**:**193**]; 83% combined yield
(ii). 7:2:91 [**191**:**192**:**193**]; 81% combined yield
(iii). 67:33:0 [**191**:**192**:**193**]; 86% combined yield

Scheme 33. *Reagents and Conditions*: (i) **190** (1.5 equiv), NaH (1.5 equiv), THF, –30 °C, 4 h; (ii) **190** (1.5 equiv), NaH (1.5 equiv), THF, –30 °C, 40 h; (iii) **190** (1.5 equiv), NaH (1.5 equiv), THF, 0 °C, 2 h.

It was envisaged that a different approach to those described previously in the literature could be adopted for the introduction of the C(4) stereochemistry, and it was desirable to develop a diastereodivergent approach that could also be applicable in syntheses of the epimers of (–)-martinellic acid **8** and (+)-martinelline **9**. Reduction of **194** would give the corresponding hemiaminal **195**. It was hoped that treatment of **195** with a suitable Wittig reagent would generate an electrophilic olefin which could be followed by *in situ* Michael addition of the amine to generate the C(4) stereocentre (Fig 14). Furthermore, the electron withdrawing group (e.g. ester) within **196** would then provide a functional handle for the introduction of the 3-aminopropyl moiety found within "Ma's intermediate" **22**·*x*HCl.

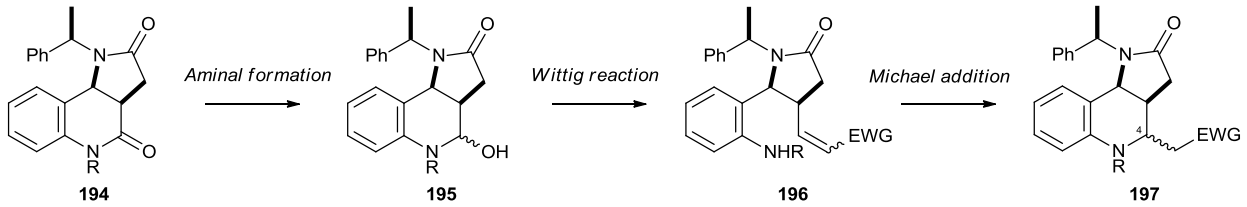
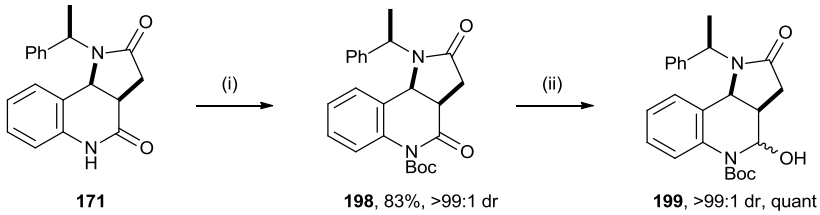


Fig 14. Proposed synthetic route for the introduction of the C(4) stereocentre.

It was anticipated that in order to achieve chemoselective reduction of the quinolinone, rather than the γ-lactam within **171**, the C(4) carbonyl would need activation by an electron withdrawing group on the *N*(5) atom. Treatment of **171** with $LiAl(O^tBu)_3H$ (2.0 equiv) in THF at 0 °C for 1 h returned clean starting material, indicating that both the γ-lactam and the quinolinone within **171** were stable under the reaction conditions. Treatment of **171** with Boc_2O, Et_3N and DMAP in CH_2Cl_2 gave **198** in 83% isolated yield. The relative (3a*R*,9b*S*,α*R*)-configuration within **198** was determined unambiguously by single crystal X-ray diffraction analysis, with the absolute configuration within **198** being assigned from the known (*R*)-configuration of the α-methylbenzyl stereocentre (Fig 15).[20] Treatment of **198** with $LiAl(O^tBu)_3H$ (1.5 equiv) in THF at 0 °C for 1 h gave complete conversion to hemiaminal **199** as a single diastereoisomer (>99:1 dr), of undetermined configuration at C(4), in quantitative yield (Scheme 34).



Scheme 34. *Reagents and Conditions*: (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (ii) $LiAl(O^tBu)_3H$ (1.5 equiv), THF, 0 °C, 1 h.

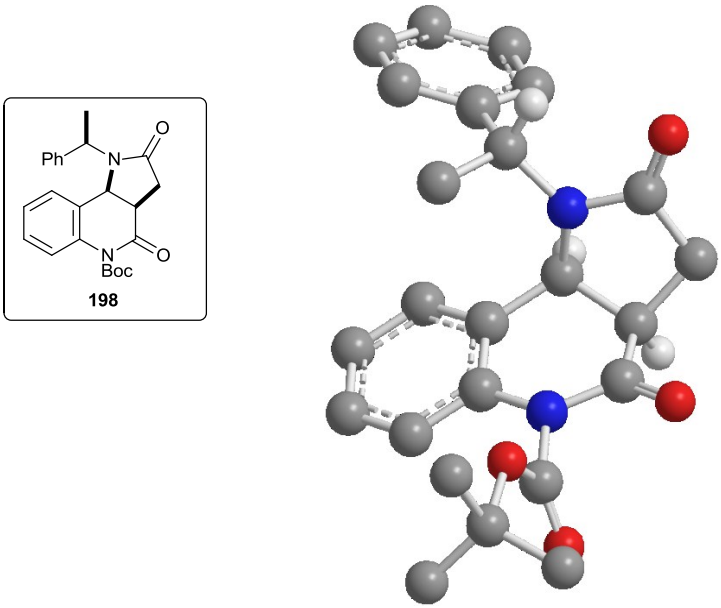
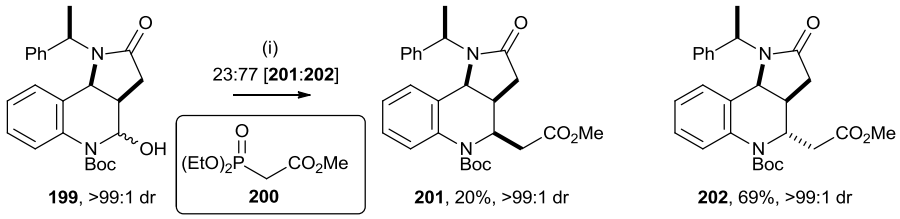


Fig 15. Chem 3D representation of the single crystal X-ray diffraction structure of **198** (selected H atoms are omitted for clarity).

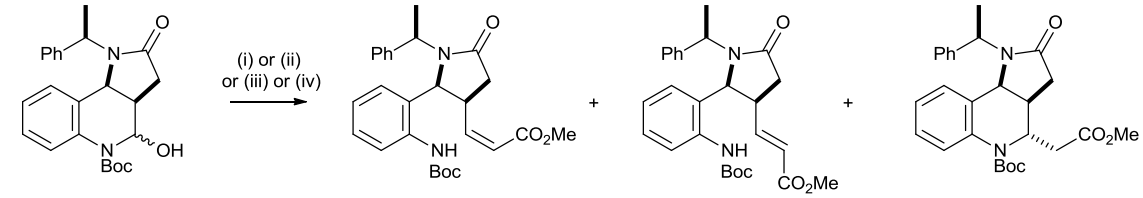
Treatment of aminal **199** with phosphonate **200** (1.2 equiv) and NaH (1.2 equiv) in THF at 0 °C for 2 h gave a 23:77 mixture of **201** and **202** which were isolated in 20 and 69% yield, respectively, and

>99:1 dr in each case (Scheme 35).[27] The relative configurations within both **201** and **202** were subsequently assigned in each case by X-ray diffraction analyses of derivatives (*vide infra*).



Scheme 35. *Reagents and Conditions*: (i) **200** (1.2 equiv), NaH (1.2 equiv), THF, 0 °C, 2 h.

It was thought that the diastereoselectivity of the reaction could be tuned by the use of a different Wittig reagent such as phosphorane **206**.[28] Thus, treatment of **199** with **206** (1.1 equiv) in CH_2Cl_2 at rt for 48 h gave a 47:29:13:11 mixture of **199**, **203**, **204** and **202**, respectively, along with small amounts of other unidentified products. Treatment of **199** with **206** (1.1 equiv) in dioxane at 100 °C for 16 h gave a 17:83 mixture of **203** and **202**, along with several other unidentified products. Treatment of **199** with **206** (1.1 equiv) in PhMe at 50 °C for 16 h gave a 22:5:73 mixture of **203**, **204** and **202**, respectively, along with small amounts of unidentified products. Under optimised conditions treatment of **199** with phosphorane **206** (2.0 equiv) in PhMe at 80 °C for 72 h gave **202** as the only product as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. In this case **202** was isolated in 80% yield after purification (Scheme 36). This provided a high yielding, efficient and diastereoselective route for the synthesis of the 3a,4-*anti*-3a,9b-*syn* configured tricyclic architecture, as found within (–)-martinellic acid **8** and (+)-martinelline **9**.[29] The origin of the diastereoselectivity of this reaction will be discussed further in Chapter 3.



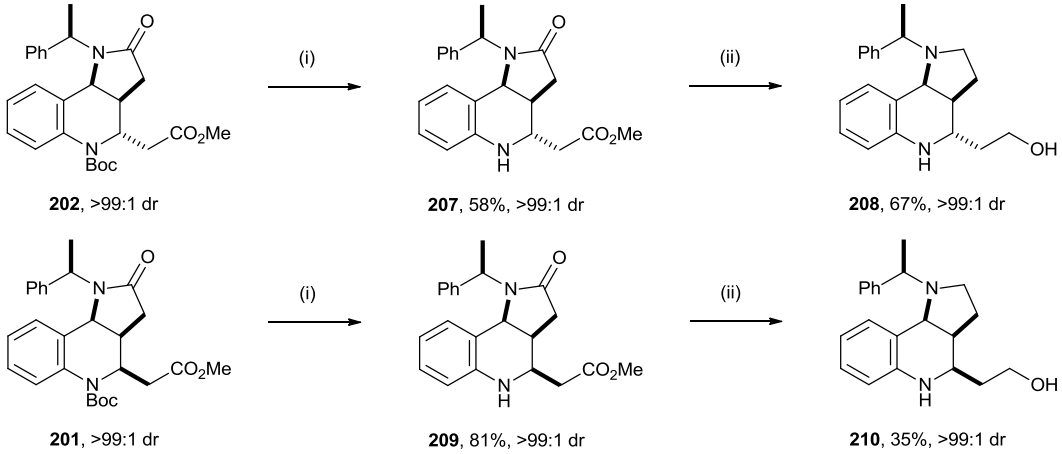
Conditions	Solvent	**206** (equiv)	Temperature (°C)	Time (h)	**199**:**203**:**204**:**202**	Isolated yield
(i)	CH_2Cl_2	1.1	rt	16	47:29:13:11	-
(ii)	1,4-dioxane	1.1	100	16	0:17:0:83	-
(iii)	PhMe	1.1	50	16	0:22:5:73	-
(iv)	PhMe	2.0	80	72	0:0:0:100	**202**, 80%

Scheme 36. *Reagents and Conditions*: (i)-(iv) see table; (v) 2.0 M aq NaOH.

2.9. Elaboration towards "Ma's intermediate"

Deprotection of the *N*-Boc protecting groups within both **202** and **201** was achieved by treatment with TFA in CH_2Cl_2 to give **207** and **209** in 58 and 81% yield, respectively, and >99:1 dr in each case. Subsequent reduction of both **207** and **209** upon treatment with $LiAlH_4$ (5.0 equiv) in THF at reflux for 16 h gave **208** and **210** in 67 and 35% yield, respectively, and in >99:1 dr in each case

(Scheme 37). The relative (3a*S*,4*S*,9b*S*,α*R*)- and (3a*S*,4*R*,9b*S*,α*R*)-configurations within **207** and **210**, respectively, were determined unambiguously by single crystal X-ray diffraction analyses, with the absolute configurations being assigned from the know (*R*)-configurations of the α-methylbenzyl fragments (Fig 16). Furthermore the determination of a Flack *x* parameter[23] of –0.07(17) for the crystal structure of **210** allowed the assignment to be confirmed unambiguously. These analyses therefore also confirmed the assigned configurations within **202**, **208**, **201** and **209**. Elaboration of **208** containing the "natural" 3a-4-*anti* configuration was first attempted to establish a route to "Ma's intermediate" **22**·*x*HCl. Efforts towards the synthesis of the corresponding C(4)-epimer will be discussed in chapter 4.



Scheme 37. *Reagents and Conditions*: (i) CH_2Cl_2/TFA (10:1 v/v), 35 °C, 4 h; (ii) $LiAlH_4$, THF, reflux, 16 h.

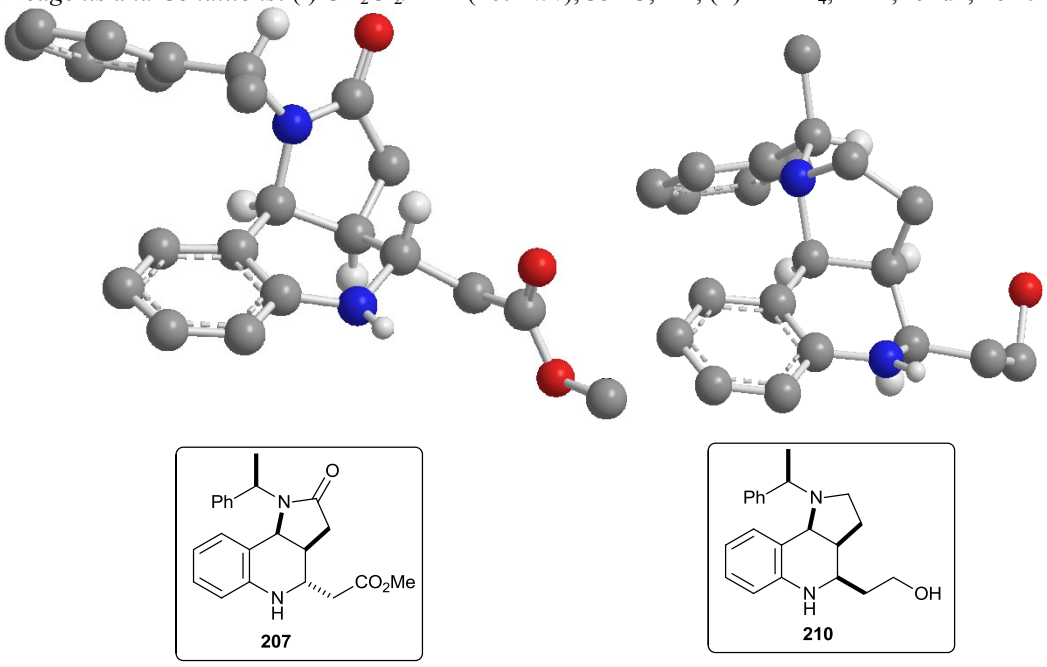
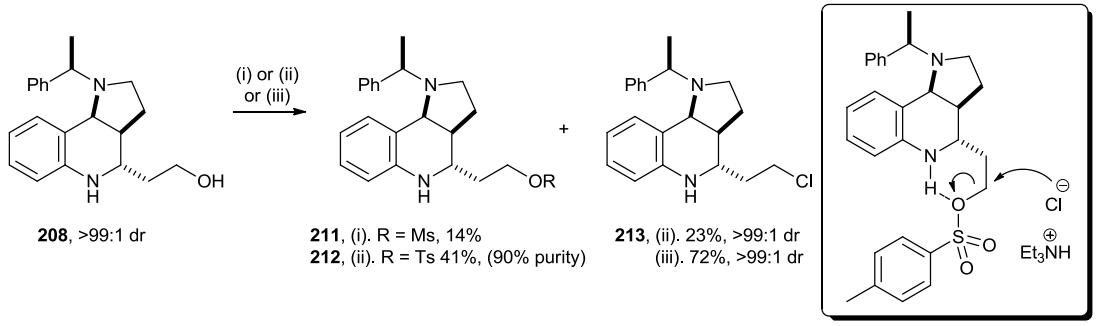


Fig 16. Chem 3D representation of the single crystal X-ray diffraction structures of **207** [*left*] and **210** [*right*] (selected H atoms are omitted for clarity).

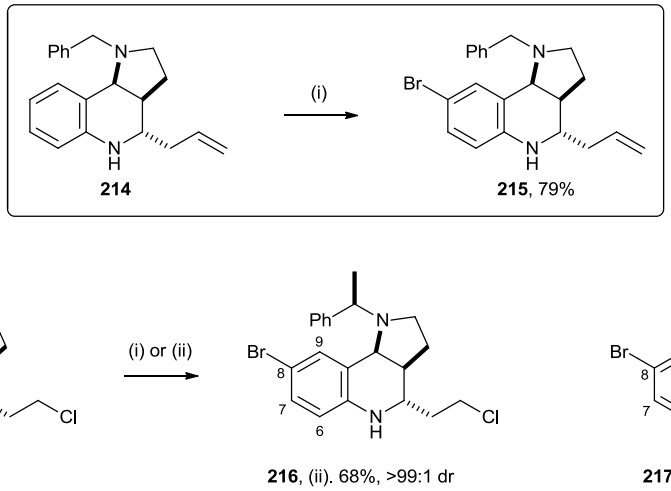
The carbon framework of the C(4) chain was expected to be introduced by suitable activation of the alcohol followed by displacement with NaCN (see Fig 8). Initial attempts to activate the alcohol within **208** as the mesylate by treatment with MsCl, Et_3N and DMAP in CH_2Cl_2 resulted in a complex mixture of products, of which an impure sample of mesylate **211** was isolated in 14% yield.

Activation as the tosylate was attempted next, as it was expected to exhibit greater stability towards side reactions. Treatment of **208** with TsCl, Et_3N, DMAP in CH_2Cl_2 gave a mixture of products including tosylate **212** and chloride **213**, which were isolated in 41 and 23% isolated yield, respectively. The observation of chloride **213** under tosylation conditions is unusual, although examples are known, for example in the tosylation of substituted benzylic alcohol derivatives.[30] Inspection of molecular models of **212** indicated a conformation in which the tosylate is able to hydrogen bond with the aniline N−H, which may activate it towards displacement by chloride. In order to avoid this mixture, Appel reaction of **208** gave chloride **213** as the sole product in 72% yield and >99:1 dr after purification (Scheme 38). With **213** in hand, introduction of the aryl ester functionality was explored next.



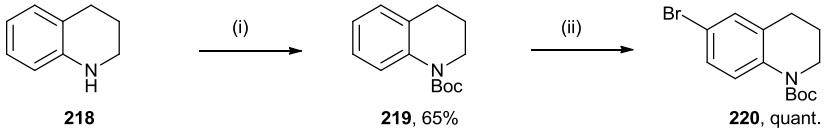
Scheme 38. *Reagents and Conditions*: (i) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 16 h; (iii) CCl_4, PPh_3, Et_3N, MeCN, rt, 16 h.

Miyata *et al.* reported the bromination of **214** with NBS in DMF to give **215** in 79% yield after purification.[31] Initial attempts at bromination of **213** under the conditions reported by Miyata *et al.* resulted in an extremely rapid and unselective bromination of **213** to give a complex mixture of products, including mono- and dibrominated products **216** and **217**.[32] Slow addition of a solution of NBS to a solution of **213**, followed by stirring for 1 h at rt gave **216** and **217** in 68 and 6% isolated yield, respectively, after purification (Scheme 39). The aromatic substitution pattern within **217** was assigned by ^{1}H NMR spectroscopic analysis, with the ^{1}H ^4J coupling constant (2.2 Hz) between the C(7)*H* and C(9)*H* protons suggesting a *meta* relationship between the protons on the aromatic ring, consistent with the strong *ortho* and *para* directing ability of anilines.



Scheme 39. *Reagents and Conditions*: (i) NBS, DMF, rt, 1 h; (ii) NBS (1.0 equiv), MeCN, 0 °C, 2 h to rt, 16 h.

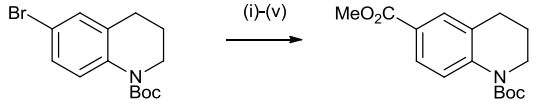
With **216** in hand, attention was turned to screening conditions for the conversion of **216** to the corresponding aryl ester. *N*(1)-Boc-6-bromo-2,3,4-tetrahydroquinoline **220** was chosen as a model substrate to optimise the carbonylation procedure, as it provided several practical advantages over the unprotected analogue. In particular, **220** was easy to handle and could be weighed and transferred accurately. Thus *N*-Boc protection of **218** gave **219** in 65% yield, and subsequent bromination with NBS (1.0 equiv) gave **220** in quantitative yield (Scheme 40).



Scheme 40. *Reagents and Conditions*: (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (ii) NBS, MeCN, 0 °C, 2 h, rt, 16 h.

Pd-catalysed carbonylation reactions have become a powerful tool in organic synthesis since their discovery in 1974 by Heck *et al.*,[33] and the subject has been reviewed.[34] A variety of nucleophiles have been utilised in this reaction as coupling partners. For example, the use of alcohols gives esters,[35] the use of amines gives amides,[36] the use of water gives carboxylic acids,[37] and the use of carboxylate salts gives anhydrides. Initially PPh_3 was chosen as the phosphine ligand, as previous studies by Davies *et al.* have shown this to be an efficient ligand in the carbonylation of morphine derivatives.[38,39] 1,3-Bis(diphenylphosphino)propane (dppp) was also screened as it is known to be an effective carbonylation catalyst.[40] Experimental conditions were initially optimised to exclude water and air from the reaction to avoid catalyst deactivation.[41] Thus, treatment of **220** with $Pd(OAc)_2$ (0.1 equiv) and dppp (0.2 equiv) in Et_3N/MeOH (5:1 v/v) under CO (1 atm) at 70 °C gave an ~95:5 mixture of **220** and **221**. Treatment of **220** with $Pd(OAc)_2$ (0.1 equiv) and PPh_3 (0.4 equiv) under the same conditions gave an ~95:5 mixture of **220** and **221**. An increase in reaction time had no effect on the reaction conversion: in both instances a deposit of palladium black was observed after several hours suggesting catalyst deactivation had occured even under the rigorously dry conditions. Following conditions reported by Davies *et al.* in the carbonylation of morphine derivatives,[39] **220** was treated with $PdCl_2$ (0.1 equiv) and PPh_3 (0.2 equiv) in MeOH/Et_3N (6:1 v/v) under CO (1 atm) at

70 °C. However, despite rigorously dry conditions no conversion to **221** was observed. An increase in CO pressure resulted in an 89:11 mixture of **220** and **221**, respectively, although this may be due to the difficulty in maintaining a completely air free environment when preparing the reaction in a Fisher-Porter Bottle.[42] Finally, the use of P(*o*-Tol)$_3$ (0.4 equiv) which proved to be a highly effective ligand for the Heck reaction of aryl iodides and therefore was known to form Pd^0 *in situ*, gave only an ~97:3 mixture of **220** and **221**, respectively, when applied to **220** (Table 4).

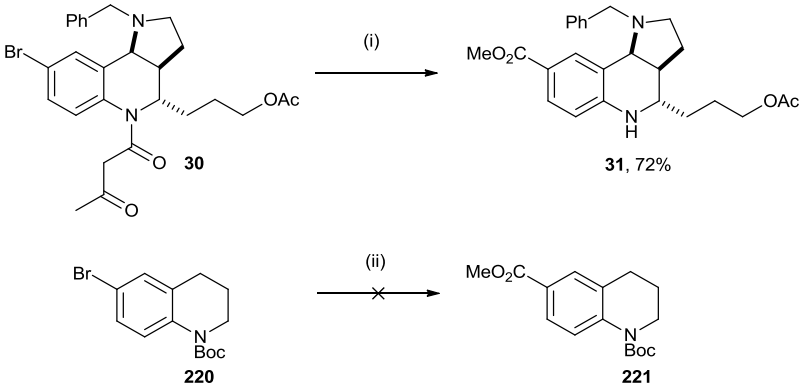


220 **221**

Conditions	[Pd] source	Solvent	Ligand (equiv)	**220**:**221**
(i)	$Pd(OAc)_2$	Et_3N/MeOH (5:1 v/v)	dppp (0.2 equiv)	95:5
(ii)	$Pd(OAc)_2$	Et_3N/MeOH (5:1 v/v)	PPh_3 (0.4 equiv)	95:5
(iii)	$PdCl_2$	Et_3N/MeOH (1:6 v/v)	PPh_3 (0.2 equiv)	100:0
(iv)	$PdCl_2$	Et_3N/MeOH (1:6 v/v)	PPh_3 (0.2 equiv)[a]	89:11
(v)	$Pd(OAc)_2$	Et_3N/MeOH (5:1 v/v)	P(*o*-Tol)$_3$ (0.4 equiv)	98:2

Table 4. *Reagents and Conditions*: (i) $Pd(OAc)_2$ or $PdCl_2$ (0.1 equiv), CO (1 atm), conditions (see table). [[a] A CO pressure of 3 bar was used]

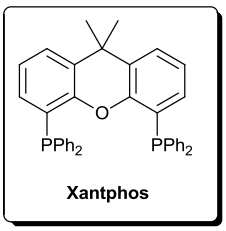
A key step in the synthesis (±)-martinellic acid **8** by Snider *et al*. was the methoxycarbonylation of **30** using $Pd(OAc)_2$ (0.1 equiv) and PPh_3 (0.4 equiv) in MeOH under CO (4 bar).[43] Methanolysis of the acetoacetamide also occured under the reaction conditions to give **31** in 72% yield. However, when these conditions were applied to **220** [1 atm CO at 70 °C] a 95:5 mixture of **220** and **221** was obtained, indicating this catalyst system may not be active at low CO pressures (Scheme 41).

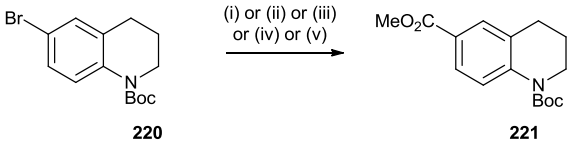


Scheme 41. *Reagents and Conditions*: (i) $Pd(OAc)_2$ (0.10 equiv), PPh_3 (0.40 equiv), MeOH, CO (4 bar), 120 °C, 3 days; (ii) $Pd(OAc)_2$ (0.10 equiv), PPh_3 (0.40 equiv), MeOH, CO (1 bar), 70 °C, 3 days.

Recent advances in Pd-catalysed alkoxycarbonylation have involved the development of more active Pd ligand systems such as $Pd(OAc)_2$/Xantphos,[44] and (BINAP)$PdCl_2$,[45] which perform alkoxycarbonylation at 1-5 atm CO pressure even with electron rich aryl bromides. It was found that methoxycarbonylation with $Pd(OAc)_2$ and the bidentate ligand Xantphos (0.1 and 0.2 equivalents, respectively); conditions which have previously been utilised by Buchwald *et al.* for the carbonylation of electron rich aryl bromides),[44] proceeded under 1 atm of CO to give an ~20:80 mixture of **220** and **221**, of which **221** was isolated in 27% yield. A decrease in the number of equivalents of $Pd(OAc)_2$ and Xantphos (to 0.02 and 0.04 respectively) resulted in a 75:25 mixture of

220 and **221**, respectively. An increase in catalyst loading (to 0.2 and 0.4 equiv) resulted in a 30:70 mixture of **220** and **221**, respectively. Treatment of **220** with an alternative Pd source ($PdCl_2$, 0.1 equiv) and Xantphos resulted in no reaction conversion. However, the optimised conditions were found to be treatment of **220** with $Pd(OAc)_2$ (0.1 equiv) and Xantphos (0.2 equiv) in Et_3N/MeOH (5:1, v/v) under CO (1 atm), followed by resubjection of the crude reaction mixture to the reaction conditions which proceeded to full conversion giving **221** in 49% isolated yield (Table 5).

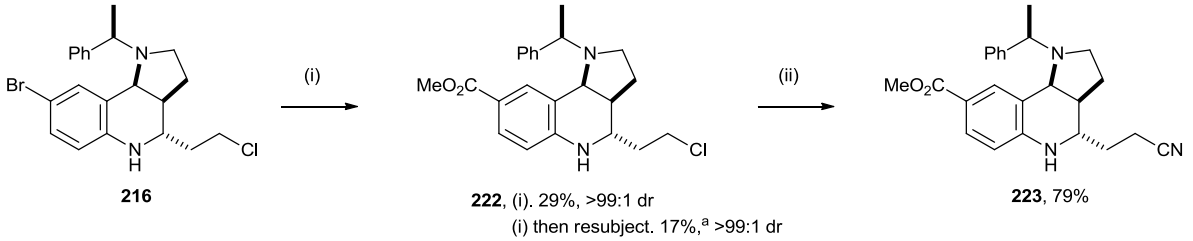




Conditions	Pd source (equiv)	Ligand (equiv)	Solvent	Temp (°C)	Time (h)	**220**:**221**	**221** (isolated yield)
(i)	$Pd(OAc)_2$ (0.1)	Xantphos (0.2)	Et_3N/MeOH	70	16 h	20:80	27%
(ii)	$Pd(OAc)_2$ (0.02)	Xantphos (0.04)	Et_3N/MeOH	70	16 h	75:25	-
(iii)	$Pd(OAc)_2$ (0.4)	Xantphos (0.8)	Et_3N/MeOH	70	16 h	30:70	-
(iv)	$PdCl_2$ (0.1)	Xantphos (0.2)	Et_3N/MeOH	70	16 h	100:0	-
(v)[a]	$Pd(OAc)_2$ (0.1)	Xantphos (0.2)	Et_3N/MeOH	70	16 h	0:100	49%

Table 5. *Reagents and Conditions*: (i)-(v) see table. [[a] The crude reaction mixture was resubjected once to the reaction conditions].

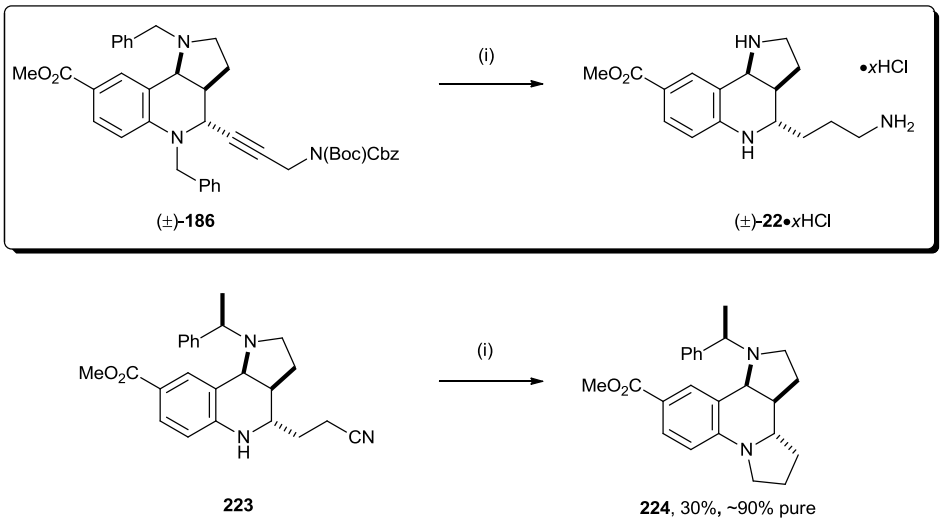
It was anticipated that "Ma's intermediate" **22**·*x*HCl could be obtained from **216** by (i) methoxycarbonylation to introduce the ester; (ii) displacement of the chloride by cyanide; and (iii) global hydrogenolysis under acidic conditions. Thus, treatment of **216** under the previously optimised conditions, using $Pd(OAc)_2$ (0.1 equiv) and Xanpthos (0.2 equiv) under CO (1 atm) at 70 °C for 16 h gave an ~50:50 mixture of **216** and **222**, respectively. Repeated purification gave **222** in 28% yield and >99:1 dr. As separation of **216** and **222** was proving troublesome, attempts were made to drive the reaction to completion. Although catalyst deactivation could not be avoided, resubjection of the crude reaction mixture to the optimised reaction conditions allowed full conversion to **222**. However, the presence of excess Xantphos ligand after multiple repetitions hindered the purification of **222**, with **222** being isolated in only 17% yield. Subsequent treatment of **222** with NaCN in DMSO at 90 °C gave **223** in 79% yield and >99:1 dr after purification (Scheme 42).



Scheme 42. *Reagents and Conditions*: (i) $Pd(OAc)_2$, Xantphos, Et_3N/MeOH, 70 °C, 16 h; (ii) NaCN, DMSO, 90 °C, 16 h. [[a] The poor yield reflects the difficulty in separation of **222** from the excess ligand residues].

Typical conditions for deprotection of the *N*-α-methylbenzyl group are treatment of the substrate with $Pd(OH)_2$/C in MeOH under H_2 (1 atm) for 16 h,[6] conditions which are also known to affect the

reduction of nitriles to the corresponding primary amines.[46] It was expected that hydrogenolysis of the *N*-α-methylbenzyl group within **223** would proceed smoothly given the precedent in a synthesis of (±)-**22**·*x*HCl by Lovely *et al.*, in which the *N*(1)-benzyl group within **186** was removed by hydrogenolysis with Pd/C.[16] It was also desired to trap the triamine product as the HCl salt, as the free amine is known to be unstable and difficult to handle.[43] However, treatment of **223** with $Pd(OH)_2/C$ in methanolic HCl under H_2 (1 atm) gave a mixture of products of which the major was identified as tetracycle **224**. Purification gave **224** in 30% yield and ~90% purity (Scheme 43). Tetracyclic products arising from intramolecular displacement of a C(3') substituent by the aniline in martinelline systems have previously been observed in the case of attempted displacement of a C(3') triflate,[47] and during attempted Mitsonobu reactions of C(3)-hydroxy substituted systems.[48] This route was therefore abandoned in favour of a strategy which incorporated *N*(5) protection.



Scheme 43. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, methanolic HCl, H_2 (1 atm), rt, 16 h.

2.10. Summary

In conclusion, the conjugate addition of an enantiopure lithium amide followed by alkylation of the resultant β-amino ester has been used to introduce the C(3a) and C(9b) stereocentres found within (–)-martinellic acid **8** and (+)-martinelline **9**. An efficient double cyclisation reaction was developed to form the tricyclic core within these molecules (Fig 17). Finally, a Wittig reaction combined with a stereoselective Michael addition allowed the introduction of the C(4) stereocentre with complete diastereoselectivity. However, the final hydrogenolysis/deprotection conditions did not lead to hydrogenolysis of the *N*-α-methylbenzyl group but instead gave tetracyclic product **224**. The next Chapter describes the optimisation of this strategy, using a differentially substituted *N*-α-methylbenzyl derivative to allow *N*(1)-deprotection at an alternative stage.

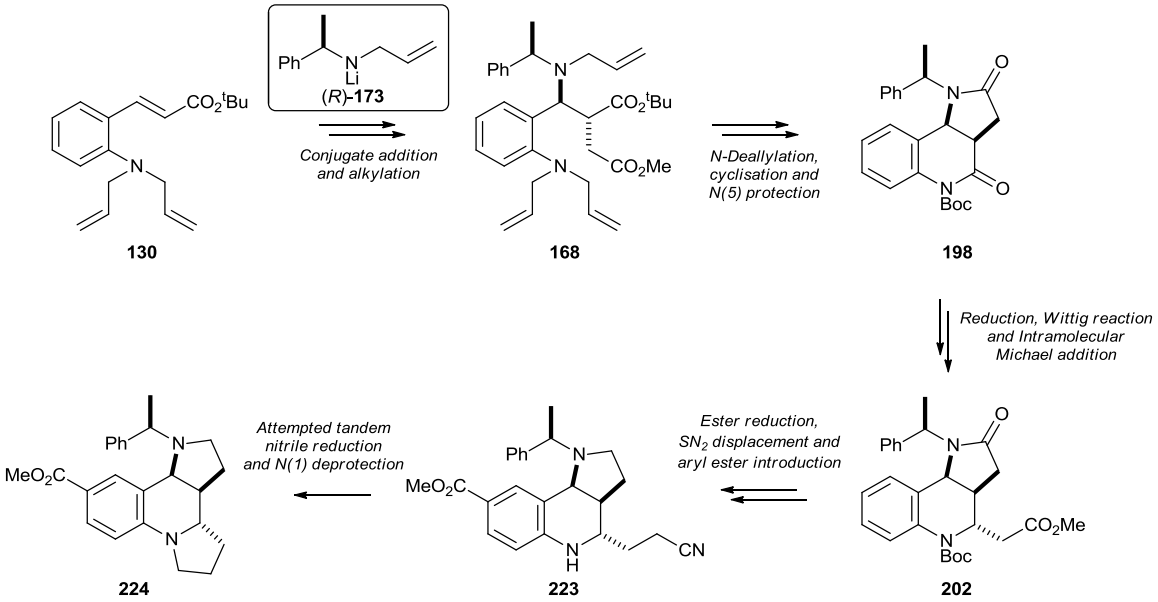


Fig 17. Key steps in the synthesis of the martinellic acid scaffold.

2.11. References and notes

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[28] Phosphonium salt **205** was prepared in quantitative yield by treatment of methylbromoacetate (1.0 equiv) and PPh_3 (1.0 eqiv) in EtOAc at rt for 16 h. Ylid **206** was prepared as required by treatment of **205** with 2.0 M aq NaOH.
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Chapter 3: A model system for the synthesis of (–)-Martinellic acid

3.1. Introduction

This Chapter describes a revised synthetic strategy towards (–)-martinellic acid **8** and reports the synthesis of **225**·*x*HCl, an analogue of "Ma's intermediate" **22**·*x*HCl lacking only the C(8) ester substituent (Fig 18).

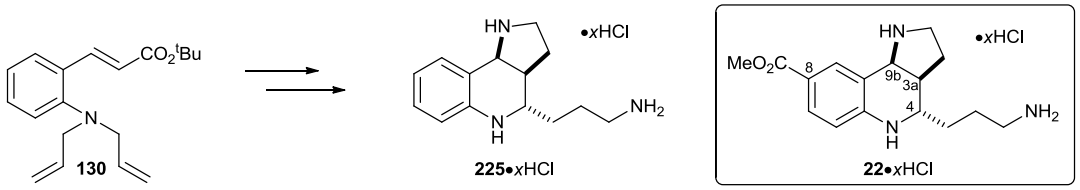
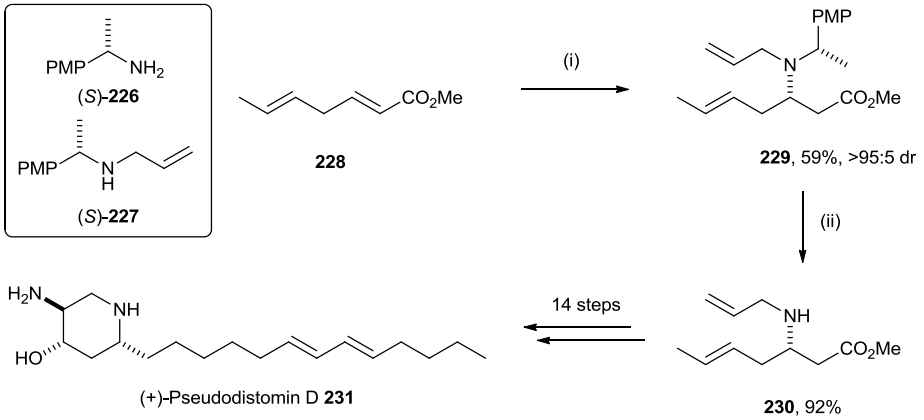


Fig 18. Synthesis of model triamine **225**·*x*HCl.

3.2. Revised synthetic route

The original synthetic route as outlined in Chapter 2 suffered a number of drawbacks: (i) bromination on the aromatic ring gave a substantial amount of dibrominated product, (ii) methoxycarbonylation of the aryl bromide was incomplete and the product was therefore isolated in low yield, (iii) the α-methylbenzyl group within **223** could not be deprotected by hydrogenolysis, and (iv) the *N*(5) atom participated in a cyclisation during attempted reduction of the nitrile group. It was hoped that issues (i), (ii) and (iv) could be addressed by maintaining the *N*(5)-Boc group until the end of the synthesis. It was thought that a differentially functionalised α-methylbenzyl group would allow deprotection without recourse to hydrogenolysis, ideally resulting in a global deprotection under acidic conditions (Fig 19). Numerous derivatives of α-methylbenzylamine are commercially available as either enantiomer and have the advantage of being deprotected under a variety of conditions.[1] In particular, derivatives of α-methyl-4-methoxybenzylamine (*S*)-**226** can be deprotected by treatment with acid,[2] CAN,[3] or DDQ.[4] This deprotection strategy has been used previously by Davies *et al.* in the synthesis of pseudodistomin D **231**.[2] β-Amino ester **229** was prepared by treatment of α,β-unsaturated ester **228** with the lithium amide derived from (*S*)-**227** in THF at –78 °C for 2 h, to give **229** in 59% yield and >95:5 dr. Deprotection of **229** was achieved on treatment with formic acid and Et_3SiH, to give **230** in 92% yield (Scheme 44).



Scheme 44. *Reagents and Conditions*: (i) (*S*)-**227** (1.6 equiv), BuLi (1.6 equiv), THF, –78 °C, 2 h; (ii) HCO_2H, Et_3SiH, 90 °C, 12 h.

As it was ultimately desired to isolate "Ma's intermediate" as the HCl salt (**22**·*x*HCl), following reports of the instability of the free base,[5] a strategy was adopted in which the final steps would be nitrile hydrogenolysis followed by global *N*-deprotection under acidic conditions.

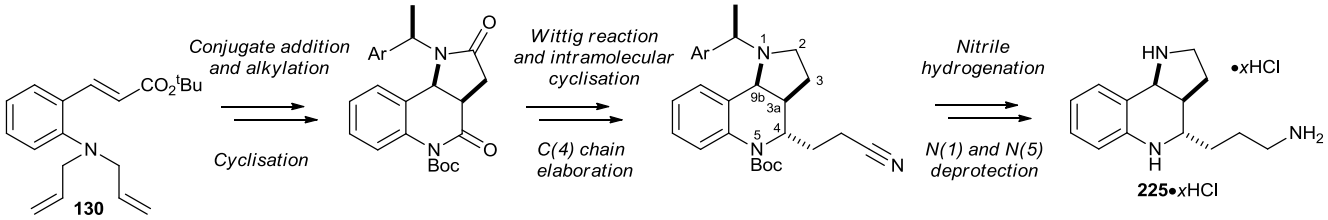
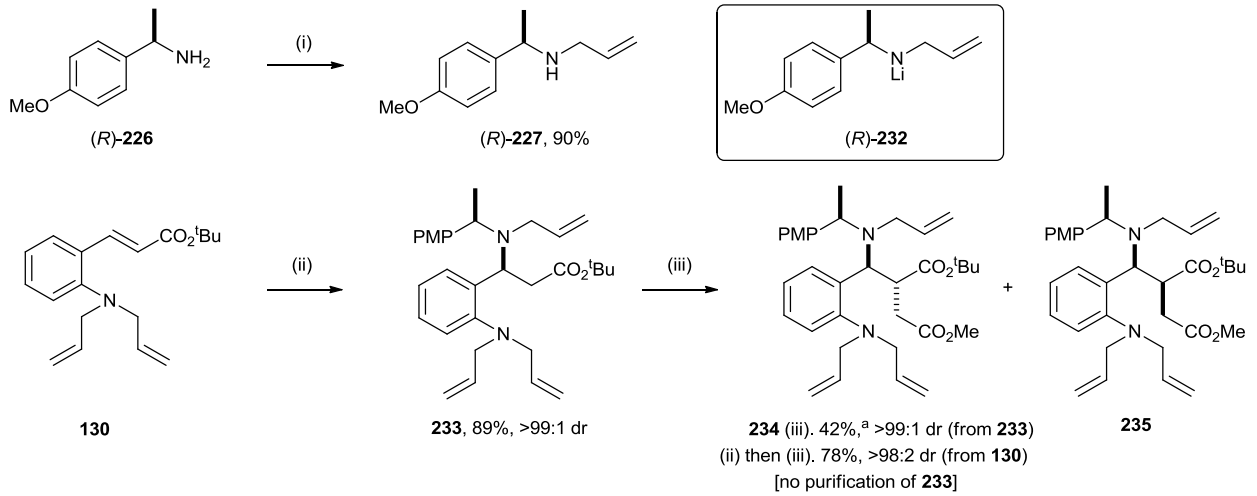


Fig 19. Synthesis of **22**·*x*HCl using an acid labile α-methylbenzyl analogue.

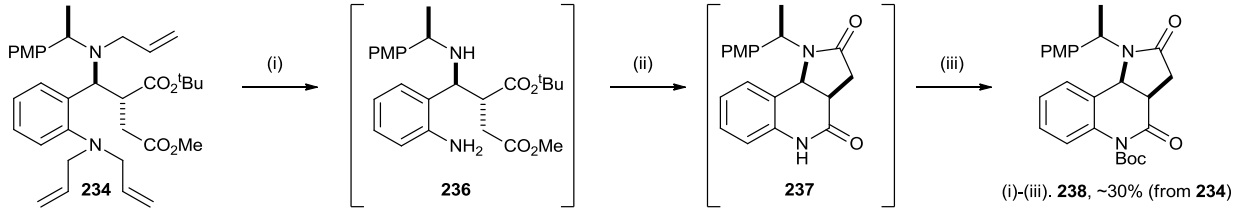
3.3. Synthesis of the tricyclic pyrroloquinoline core

Amine (*R*)-**227** was prepared in 90% yield by treatment of (*R*)-**226** with BuLi followed by addition of allyl bromide.[6] Treatment of α,β-unsaturated ester **130** with (*R*)-**232** in THF at –78 °C for 2 h gave **233** in 89% yield and >99:1 dr. Deprotonation of **233** with LDA followed by addition of methyl bromoacetate gave a >95:5 mixture of **234** and **235**, respectively, with **234** isolated in 42% yield (>99:1 dr) in addition to a 90:10 fraction of **234**:**235** in 48% yield.[7] Alternatively, the two steps could be run sequentially without purification of intermediate **233**, with no detriment to the reaction diastereoselectivity or conversion, which gave **234** in 78% isolated yield over 2 steps and >98:2 dr (Scheme 45). The stereochemistry within the major component **234** was assigned by analogy to **168** described in the previous Chapter, and was supported by single crystal X-ray diffraction analysis of a derivative (*vide infra*).



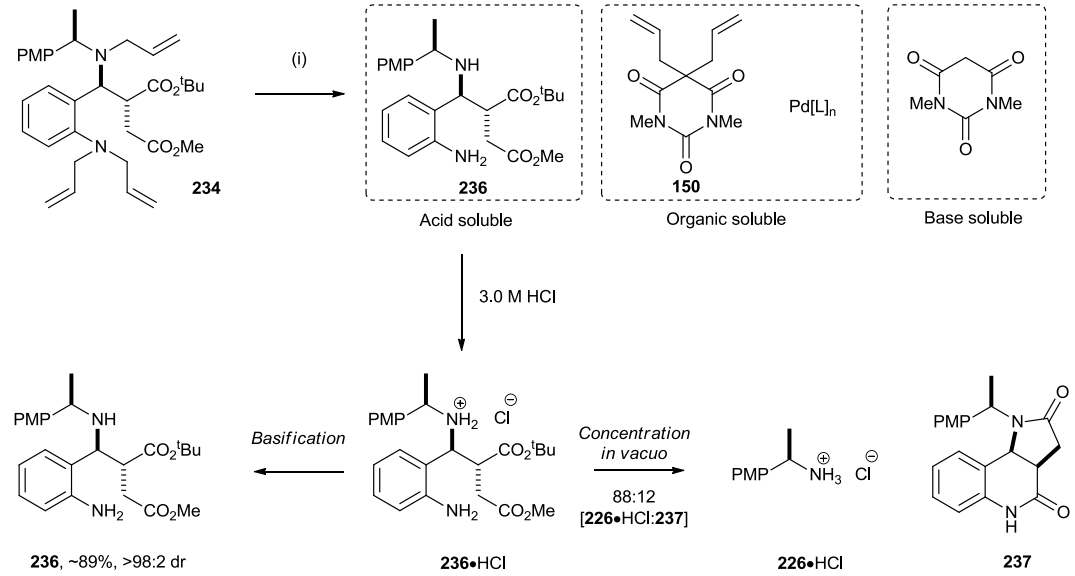
Scheme 45. *Reagents and Conditions*: (i) BuLi, allyl bromide, 0 °C to rt, 16 h; (ii) (*R*)-**227**, BuLi, THF, –78 °C, 2 h; (iii) $^{i}Pr_2NH$, BuLi, –78 °C, 1 h then methyl bromoacetate, –78 °C to rt, 16 h. [[a] A 90:10 mixture of **234** and **235**, respectively, was also isolated in 48% combined yield].

With **234** in hand, the optimised conditions for *N*-deallylation and cyclisation were employed, as described in Chapter 2. Thus, treatment of **234** with $Pd(PPh_3)_4$ (0.05 equiv) and DMBA in CH_2Cl_2 at 35 °C, with further addition of catalyst after 16 h, gave **236** in >98:2 crude dr. Treatment of the crude reaction mixture with $PhCO_2H$ (0.2 equiv) in PhMe at reflux for 16 h resulted in cyclisation to give **237**. Although chromatography allowed removal of scavenger **150**, low mass return of the tricyclic material **237** was encountered after chromatography, and this mixture contained a large amount of inseparable catalyst residues. Attempts at recrystallisation of **237** at this stage were unsuccessful and it was decided to proceed with *N*-Boc protection to facilitate the isolation of the tricyclic scaffold. *N*-Boc protection of the crude sample of **237** gave **238** which could be isolated by recrystallisation from THF, however the isolated yield of **238** over the 3 step sequence was generally less than 30% (Scheme 46).



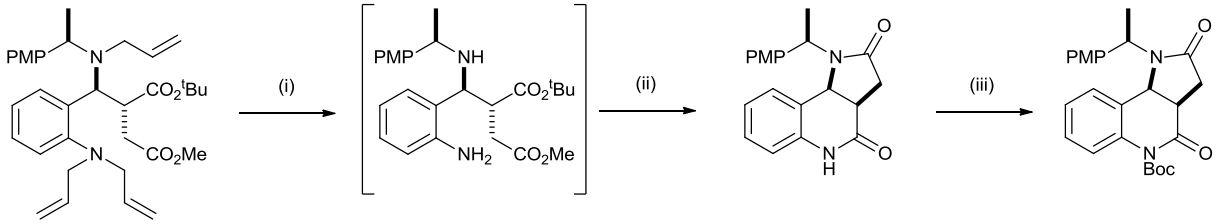
Scheme 46. *Reagents and Conditions*: (i) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h; (ii) $PhCO_2H$, PhMe, reflux, 16 h; (iii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h.

An alternative approach was to remove aniline **236** from the palladium residues by acid extraction. Thus, **234** was globally *N*-deallylated with $Pd(PPh_3)_4$ and DMBA then **236** was extracted with 3.0 M aq HCl. Attempts to isolate **236**·HCl resulted in an 88:12 mixture of **226**·HCl and **237**, suggesting that the retro-Michael addition and cyclisation were occurring. However, extraction of the crude product after the deallylation step with 3.0 M aq HCl followed by immediate basification gave **236** cleanly and >98:2 dr, with ~90% mass return. The material produced through this improved work-up procedure was essentially clean by ^1H NMR spectroscopic analysis, and contained <5% triphenylphosphine residues (Scheme 47).



Scheme 47. *Reagents and Conditions*: (i) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h.

Using this extraction procedure, cyclisation of **236** was next achieved upon immediate treatment of the crude sample with $PhCO_2H$ (0.1 equiv) in PhMe at reflux for 16 h. Chromatographic purification of the crude reaction mixture gave **237** in 52% isolated yield and >99:1 dr over 2 steps from **234**. *N*-Boc protection of **237** gave **238**, which was isolated in 78% yield and >99:1 dr after recrystallisation from PhMe. As the recrystallisation of **238** proved more efficient than that of **237**, the tricyclic material **237** formed after the cyclisation step was used without purification, giving **238** in an improved 57% overall yield after the final recrystallisation from PhMe, for the 3 step procedure (Scheme 48). The relative configuration within **238** was determined unambiguously by single crystal X-ray diffraction analysis, with the absolute (3a*R*,9b*S*,α*R*)-configuration within **238** being assigned by reference to the known (*R*)-configuration of the α-methyl-4-methoxybenzyl fragment (Fig 20). Under these optimised conditions, only two chromatographic purification steps are necessary over the 7 steps from 2-iodoaniline to **238**, facilitating the synthesis of **238** on a multigram scale.



Scheme 48. *Reagents and Conditions*: (i) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 16 h; (ii) $PhCO_2H$, PhMe, reflux, 16 h; (iii) Boc_2O, Et_2N, DMAP, CH_2Cl_2, 35 °C, 16 h.

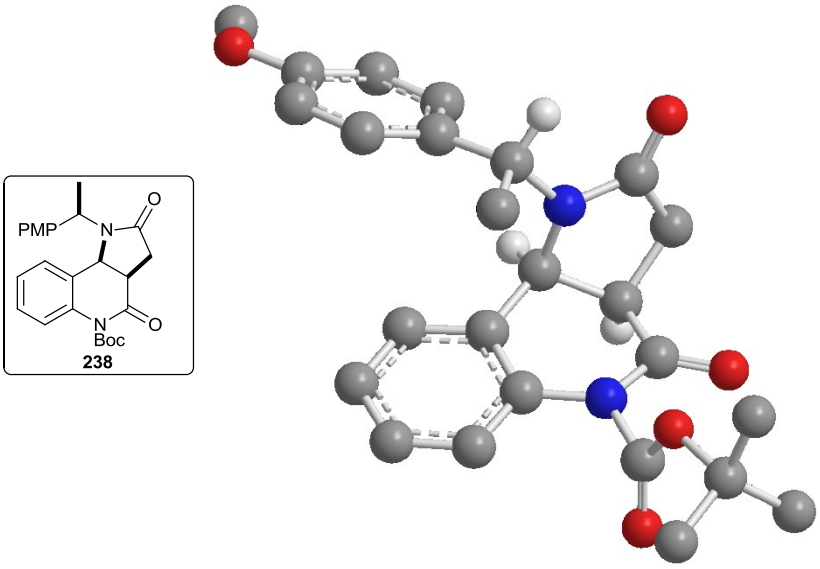
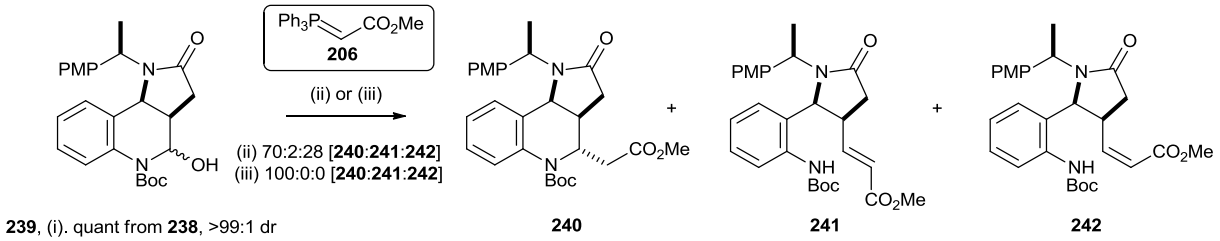


Fig 20. Chem 3D representation of the single crystal X-ray diffraction structure of **238** (selected H atoms are omitted for clarity).

3.4. Investigations of the Wittig-Michael reaction

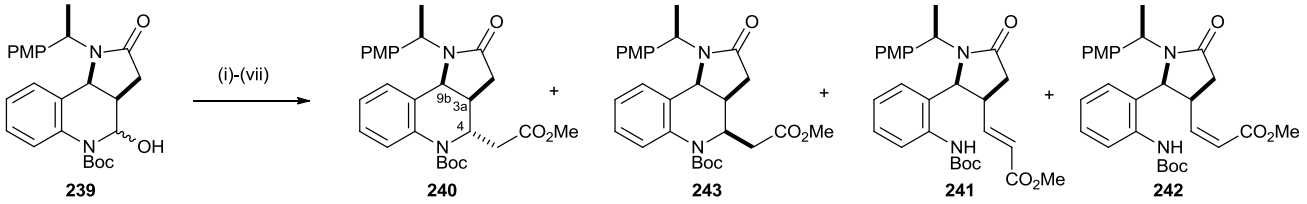
The introduction of the stereochemistry at C(4) in this system was anticipated to proceed in a similar fashion to that described for the *N*-benzyl-*N*-α-methylbenzyl substituted analogue in Chapter 2. Thus, treatment of **238** with LiAl(O^{t}Bu)$_3$H (1.5 equiv) in THF at 0 °C gave hemiaminal **239** in quantitative yield and >99:1 dr [of undetermined configuration at C(4)]. Attention was next turned to the Wittig-Michael reaction. Treatment of **239** with phosphorane **206** (1.05 equiv) in PhMe at 80 °C for 24 h gave a 70:2:28 mixture of **240**, **241** and **242**, respectively. Exposure of this mixture to the reaction conditions for 72 h did not result in any greater conversion to **240**. Treatment of **239** with excess phosphorane **206** (3.0 equiv) in PhMe at 80 °C, in an effort to improve the reaction conversion, proceeded within 72 h to give **240** as the sole product. However, separation of **240** from the remaining phosphorane **206** or Ph_3PO could not be achieved either by trituration or by flash column chromatography (Scheme 49).



Scheme 49. *Reagents and Conditions*: (i) LiAl(O^{t}Bu)$_3$H, THF, 0 °C, 1 h; (ii) **206** (1.05 equiv), PhMe, 80 °C, 16 h; (iii) **206** (3.0 equiv), PhMe, 80 °C, 72 h.

It was therefore decided to explore the Wittig-Michael protocol with phosphonate ester **200**, which it was hoped would be more readily separable from the reaction products. Initially the concentration, temperature and equivalents of base were screened. Thus, treatment of **239** with **200** (1.1 equiv) and NaH (1.1 equiv) at a concentration of 0.05 M in THF resulted in full conversion to a 59:41 mixture of **240** and **243**, respectively.[8] Treatment under the same conditions but at an overall concentration of 0.1 M in THF at 0 °C resulted in full conversion to a 71:29 mixture of **240** and **243**, respectively.

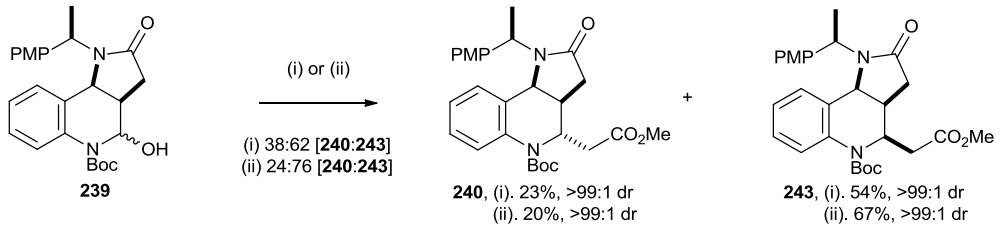
Treatment of **239** under the same conditions at the solubility limit ([**239**] = 0.35 M) resulted in a 62:11:22:5 mixture of **240**, **243**, **241** and **242**, respectively, corresponding to an 85:15 ratio of **240** and **243** and an 82:18 ratio of (*E*)-**241** and (*Z*)-**242**, respectively. A reduction in the number of equivalents of NaH (to 0.5 equivalents), with a concentration of **239** at 0.1 M, resulted in incomplete conversion, with a 39:7:1:46:8 mixture of **239**, **240**, **243**, **241** and **242** obtained, corresponding to an 87:13 ratio of **240** and **243** and an 85:15 ratio of (*E*)-**241** and (*Z*)-**242**, respectively. Addition of NaH (1.1 equiv) to a premixed solution of **239** and **200** in THF at 0 °C gave a 62:26:8:4 mixture of **240**, **243**, **241** and **242**, corresponding to a 70:30 ratio of **240** and **243** and a 69:31 ratio of (*E*)-**241** and (*Z*)-**242**, respectively. It was initially thought that the similarity in these product distributions was indicative of a stereoselective ring-closure of (*E*)-**241** to give 3a,4-*anti*-**240**, and (*Z*)-**242** to give 3a,4-*syn*-**243**. However, quenching of the reaction after 5 mins in an attempt to observe the initial product distribution gave a 12:21:28:34:5 mixture of **239**, **240**, **243**, **241** and **242**, respectively, which does not suggest a strong correlation between either (*E*)-**241** and **240** or (*Z*)-**242** and **243**. An increase in reaction temperature to 50 °C resulted in no significant difference in product distribution, complete conversion to an 80:20 mixture of **240** and **243**, respectively, was observed (Scheme 50).



Conditions	NaH (equiv)	Temperature (°C)	Time (min)	[**239**] (mol/L)	Product distribution **239**:**240**:**243**:**241**:**242**
(i)	1.1	0	120	0.05	0:59:41:0:0
(ii)	1.1	0	120	0.1	0:71:29:0:0
(iii)	1.1	0	120	0.34	0:62:11:22:5
(iv)	0.5	0	120	0.1	39:7:1:46:8
(v)	1.1	0	120	0.1 (premixed)	0:62:26:8:4
(vi)	1.1	0	5	0.1	12:21:28:34:5
(vii)	1.1	50	120	0.1	0:80:20:0:0

Scheme 50. *Reagents and Conditions*: (i)-(vii) **200** (1.1 equiv), see table.

It should be stated that although treatment of **239** with **200** (1.1 equiv) and NaH (1.1 equiv) in THF ([**239**] = 0.1 M) at 0 °C for 2 h [corresponding to conditions (ii) in Scheme 50] was reproducible on a small scale (~100 mg of **239**), repetition on a preparative scale (~1.0 g) resulted in substantially different ratios of products. For instance, on a 250 mg scale of **239**, a 38:62 mixture of **240** and **243**, was obtained, which were isolated in 23 and 54% yield, respectively. On a multi-gram scale, reaction of **239** with **200** (1.1 equiv), NaH at 0.1 M in THF gave a 24:76 mixture of **240** and **243**, which were isolated in 20 and 67% yield, respectively (Scheme 51).



Scheme 51. *Reagents and Conditions*: (i) **239** (240 mg scale), **200** (1.1 equiv), NaH (1.1 equiv), THF ([**239**] = 0.1 M), 0 °C, 2 h; (ii) **239** (4.70 g scale), **200** (1.1 equiv), NaH (1.1 equiv), THF ([**239**] = 0.1 M), 0 °C, 2 h.

The reason for this discrepancy upon scale-up is unclear, however it is possible that on a small scale quenching of the enolates corresponding to **241** and **242** by adventitious moisture is unavoidable, and the gradual equilibration between **240** and **243** is reduced. In contrast, on a large scale the enolates may survive for longer, allowing greater equilibration of the two epimers as reflected in the greater proportion of **243** in the mixture. These inconclusive results warranted further consideration of the reaction mechanism. The reaction between aldehyde **244** (derived from hemiaminal **239**) and the carbanion of **200** would be expected to proceed *via* a mixture of diasteroisomeric oxaphosphatanes **245** and **246**,[9] which collapse irreversibly to give **242** or **241**, respectively (Fig 21). The by-product of the initial formation of the olefin is most likely diethyl phosphate, in accordance with the reports of Wadsworth and Emmons.[10] The path of the diethyl phosphate has important consequences for this reaction. If the molecule releases ethoxide [pKa (EtOH) = 15.9 in H_2O][11] the Wittig reaction could be catalytic in base. If diethyl phosphate [pKa (diethylphosporic acid) = 1.29 in H_2O][12] does not decompose then no deprotonation of the lactams within **241** or **242**, or deprotonation of the remaining phosphonoacetate **200** can occur.[13] Further decomposition of the dialkylphosphonate is known, but generally requires electron withdrawing alkoxy groups on the phosphonate (Still-Gennari modification).[14] Deprotonation of the aniline within **241** or **242** and subsequent intramolecular Michael addition could give a mixture of enolates corresponding to the deprotonated forms of **240** and **243**. Under the reaction conditions it is possible that **240** and **243** could equilibrate during the course of the reaction *via* **241** or **242** and therefore an indication of the kinetic products of the reaction may be lost. In order to investigate the relative stereoselectivity of the Wittig and subsequent Michael reaction, efforts were directed at accessing **241** or **242** in pure form.

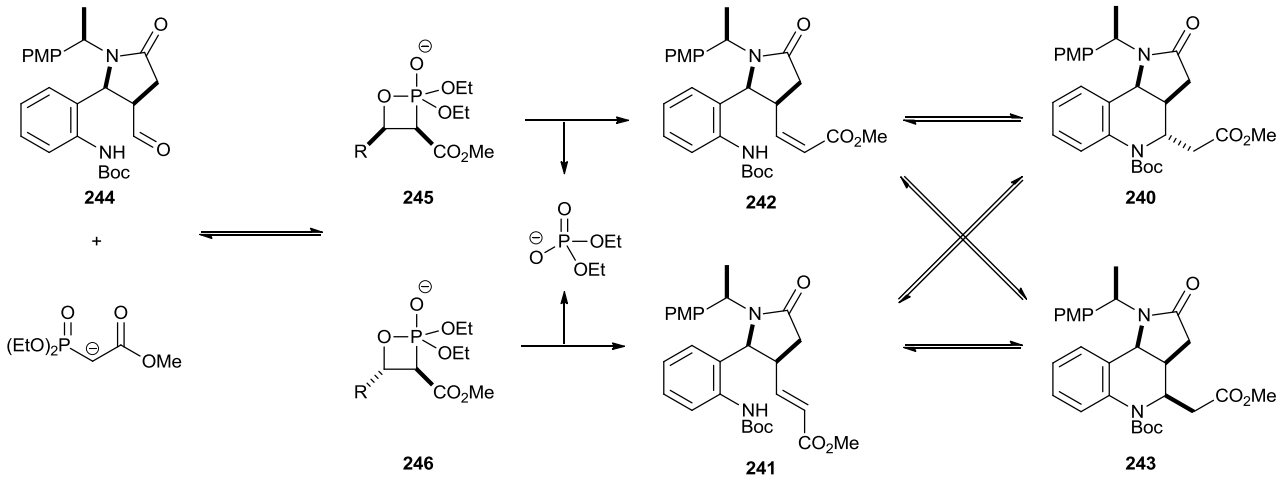
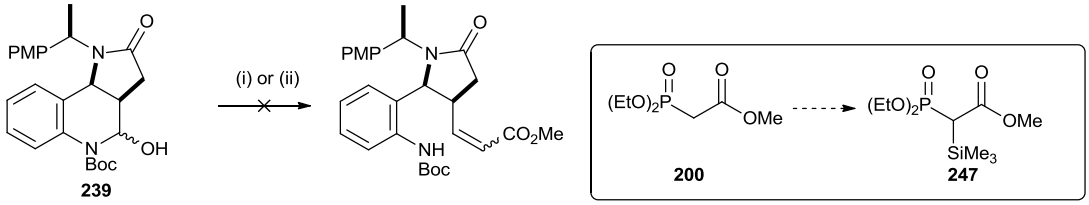


Fig 21. Key intermediates in the Wittig-Michael reaction of hemiaminal **239**.

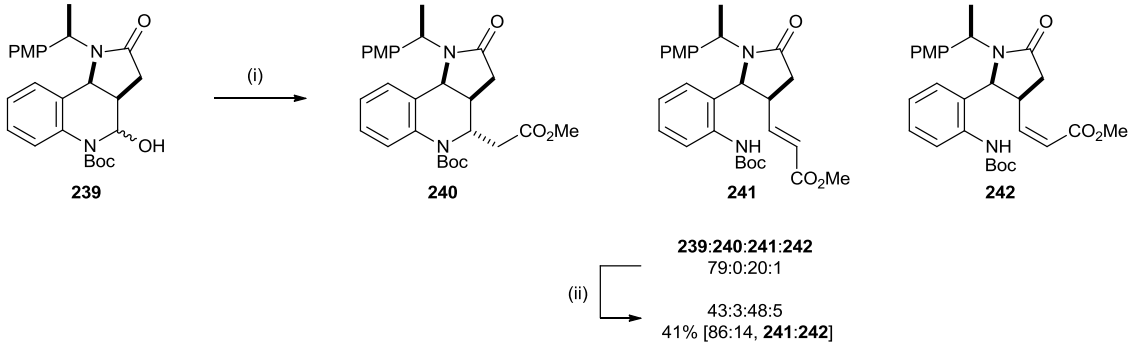
As the collapse of the oxaphosphetanes **245** and **246** results in the liberation of one equivalent of base (ethoxide or diethyl phosphate), in accordance with literature reports of the mechanism,[10] it was anticipated that trapping of the ethoxide with a suitable scavenger would suppress the subsequent base catalysed Michael addition. Trialkylsilylchlorides such as TMSCl are well known for their ability to scavenge alkoxide bases, and have found applicability in the Rühlmann modification of the acyloin reaction for this reason.[15] Treatment of **239** with phosphonate **200** (1.1 equiv) and NaH (0.1 equiv) in the presence of TMSCl (3.0 equiv) reproducibly gave returned starting material. It was initially thought that a low level of base may not be sufficient to initiate the reaction. However, repetition of the reaction with NaH (1.0 equiv) again gave predominantly starting material, along with only ~2% of (*E*)-**241**. The lack of reactivity in the presence of TMSCl is unclear. No evidence of *O*-silylation of hemiaminal **239** was observed by either ^{1}H NMR spectroscopic analysis of the reaction mixture or by mass spectrometric analysis. A possible explanation is that deprotonated form of **200** initially reacts with TMSCl in preference to aminal **239** to give **247**, which is desilylated upon aqueous work-up (Scheme 52).



Scheme 52. *Reagents and Conditions*: (i) **200** (1.1 equiv), NaH (0.1 equiv), TMSCl (3.0 equiv), THF, 0 °C, 2 h; (ii) **200** (1.1 equiv), NaH (1.0 equiv), TMSCl (3.0 equiv), THF, 0 °C, 2 h.

As attempts to drive the Wittig-Michael procedure to give only α,β-unsaturated esters **241** and **242** were proving unsuccessful, attempts were made to increase the proportion of **241** and **242** and allow their isolation. Previously, the reaction between **239** and **200** (1.1 equiv) in the presence of sub-stoichiometric NaH (0.5 equiv) led to a 39:7:1:46:8 mixture of **239**, **240**, **243**, **241** and **242**, respectively. It was hoped that portionwise addition of NaH would lead to a greater proportion of **241** and **242** by suppression of the Michael reaction. Treatment of **239** with phosphonate **200** and NaH

(0.2 equiv) gave a 79:20:1 mixture of **239**, (*E*)-**241** and (*Z*)-**242** [>93:7, (*E*)-**241**:(*Z*)-**242**]. Addition of more NaH (0.5 equiv) after 16 h gave a 44:3:48:5 mixture of **239**, **240**, **241** and **242**, from which the olefins were isolated in 41% combined yield after chromatography, as a mixture of isomers [>86:14, (*E*)-**241**:(*Z*)-**242**] (Scheme 53). Recrystallisation of this mixture allowed isolation of a single crystal of **241**, of which the (4*S*,5*S*,α*R*,*E*)-configuration within **241** was determined unambiguously by single crystal X-ray diffraction analysis, with the absolute configuration being assigned by reference to the known (*R*)-configuration of the α-methylbenzyl group (Fig 22).



Scheme 53. *Reagents and Conditions*: (i) **200** (1.1 equiv), NaH (0.2 equiv), THF, 0 ˚C to rt, 16 h; (ii) NaH (0.5 equiv), 0 °C to rt, 16 h.

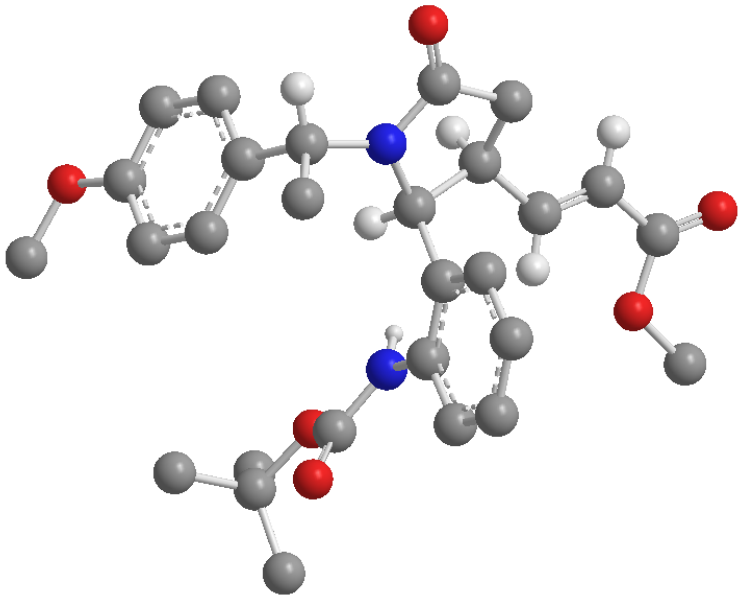
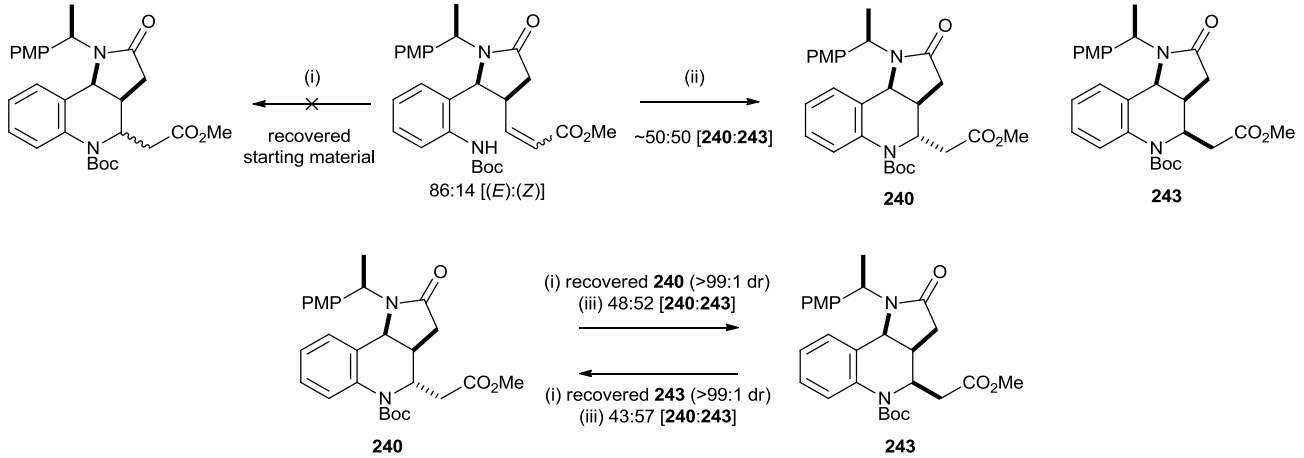


Fig 22. Chem 3D representation of the single crystal X-ray diffraction structure of **241** (selected H atoms are omitted for clarity).

With diasteroisomerically pure samples of **240** and **243**, and an enriched sample of **241**, the selectivity of ring-closure within **241** was investigated. Treatment of the 86:14 mixture of (*E*)-**241** and (*Z*)-**242** with NaH (1.0 equiv) in THF at 0 °C proceeded with complete consumption of starting material to give a ~50:50 mixture of **240** and **243**, along with other products which could not be identified. Treatment of the 84:14 mixture of **241** and **242** in MeOH at reflux for 16 h resulted in returned starting material with no equilibration observed. Treatment of either **240** or **243** in MeOH at reflux for 36 h also resulted in no loss of diasteroselectivity or decomposition, suggesting that the equilibration of either diastereoisomer requires the presence of a strong base. Treatment of **243** (>99:1 dr) with NaH (1.0 equiv) in THF at 0 °C to rt for 16 h gave a 43:57 mixture of **240** and **243**

which were isolated in 27 and 48% yield, respectively. Treatment of **240** (>99:1 dr) under the same conditions gave a 48:52 mixture of **240** and **243**. In neither case was there any evidence of olefinic products (*E*)-**241** nor (*Z*)-**242** in the ^{1}H NMR spectrum of the crude reaction mixture. Repetition of the reaction for either **240** or **243** with excess NaH (3.0 equiv) resulted in substantial decomposition to a mixture of unidentified products. (Scheme 54).



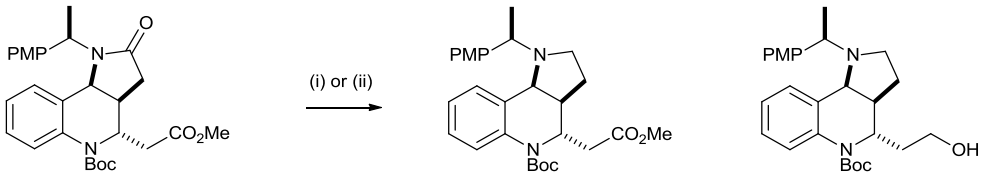
Scheme 54. *Reagents and Conditions*: (i) MeOH, reflux, 16 h; (ii) NaH (1.0 equiv), THF, 0 °C, 2 h; (iii) NaH (1.0 equiv), THF, 0 °C to rt, 16 h.

In summary, the reaction of **239** with phosphorane **206** proceeded to give the 3,4-*anti* diastereoisomer exclusively. In the case where the reaction with phosphorane **206** did not proceed to full completion, **242** was observed as the major olefinic product, suggesting that the Wittig reaction in this case is (*Z*)-selective. However, the synthetic utility of this reaction is diminished by the difficulty in separating **240** from the reaction by-products. In contrast, the reaction of **239** with phosphonate **200** proceeds to give a mixture of **240** and **243**. In all cases where the reaction did not proceed to full completion, **241** was observed as the major olefinic product, suggesting that the initial Wittig reaction in this case is (*E*)-selective, as would be expected from the known diastereoselectivity of the Wadsworth-Emmons reaction.[10] It has been shown that diastereoisomerically pure samples of both **240** and **243** equilibrate in the presence of NaH to give a ~50:50 mixture of **240** and **243**, but it is difficult to draw any firm conclusions about the diastereoselectivity of ring-closure with equilibration occurring in tandem. Nevertheless, the reaction between **239**, NaH and **200** at 0.05 M in THF allows access to both C(4)-epimers in synthetically useful yields.

3.5. Elaboration towards a model triamine

In this revised synthetic route the presence of an *N*(5)-Boc group was firstly desirable to improve the conversion of the methoxycarbonylation reaction, and secondly to prevent unwanted cyclisation through *N*(5) during reduction of the nitrile. The choice of reducing agent was therefore revised as the conditions previously used to reduce the ester and amide functionalities within **207** (refluxing $LiAlH_4$ in THF) were thought to be incompatible with the presence of an *N*-Boc protecting group.[16]

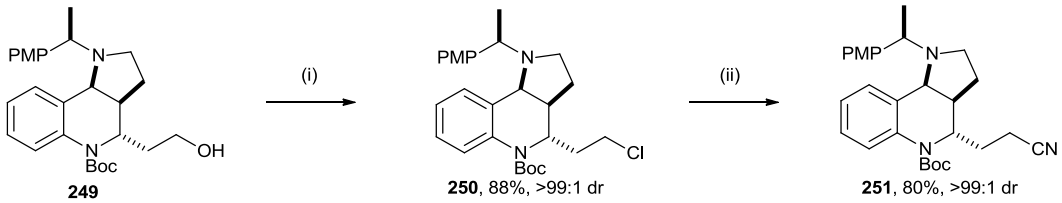
Thus, reduction of **240** with BH_3·THF (8 equiv) in THF at rt gave a 36:64 mixture of **248** and **249**, which were isolated in 29 and 33% yield, respectively. However, the reaction proceeded to completion with an increase in the equivalents of BH_3·THF solution (14 equiv), with **249** being isolated in 77% yield in this case (Scheme 55).



240, >99:1 dr **248**, (i). 29%, >99:1 dr **249**, (i). 33%, >99:1 dr (ii). 77%, >99:1 dr

Scheme 55. *Reagents and Conditions*: (i) BH_3·THF (8 equiv), THF, 0 °C to rt, 16 h; (ii) BH_3·THF (14 equiv), THF, 0 °C to rt, 16 h.

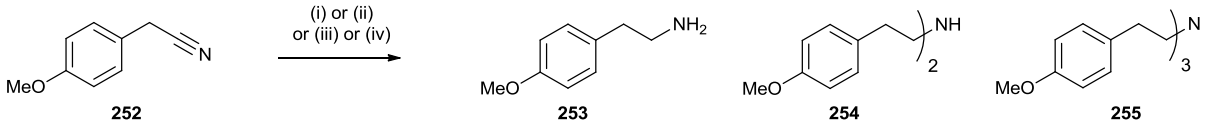
Alcohol **249** was converted to the corresponding chloride **250** *via* an Appel reaction with CCl_4, PPh_3 and Et_3N in MeCN to give **250** in 88% isolated yield. Subsequent displacement of the chloride functionality within **250** with NaCN in DMSO gave nitrile **251** in 80% yield (Scheme 56).



249 **250**, 88%, >99:1 dr **251**, 80%, >99:1 dr

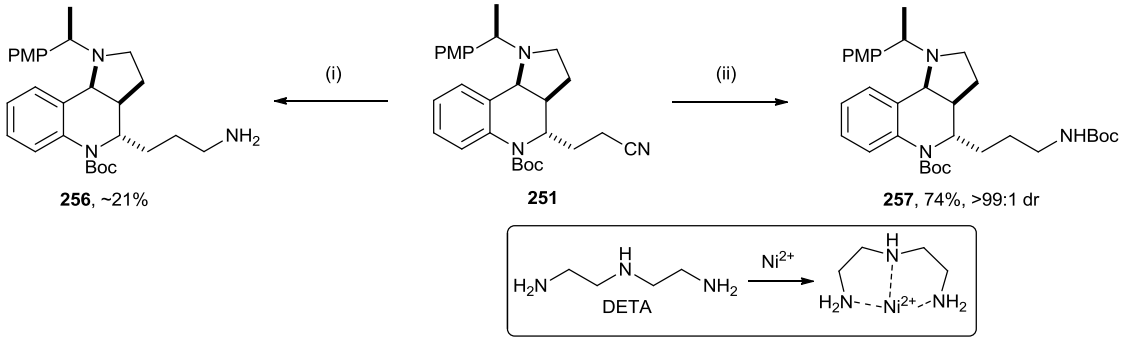
Scheme 56. *Reagents and Conditions*: (i) CCl_4, PPh_3, Et_3N, MeCN, 0 °C to rt, 16 h; (ii) NaCN, DMSO, 90 °C, 16 h.

A variety of methods are known for the selective reduction of nitriles to primary amines including hydrogenation in the presence a variety of metal catalysts, or reduction with hydridic reagents such as $LiAlH_4$ or BH_3·THF.[17] 4-Methoxybenzonitrile **252** was initially used to screen hydrogenation conditions: treatment of **252** with $Pd(OH)_2/C$ (50% w/w of substrate) in MeOH under H_2 (1 atm) gave full conversion to a mixture of **254** and **255** as judged by ^1H NMR spectrosopic and mass spectrometric analyses.[18] Other literature reports suggested that the primary amine can be trapped either through protonation or *N*-protection *in situ* to prevent dimerisation from occurring. However, treatment of **252** with $Pd(OH)_2/C$ in AcOH/MeOH (1:1 v/v) also resulted in a mixture of secondary and tertiary amine products. Treatment of **252** with $Pd(OH)_2/C$ under an elevated pressure of H_2 (5 atm) in the presence of HCl resulted in a mixture of **253**-**255**. Ni_2B and Co_2B are also reported as efficient catalysts for the reduction of nitriles to the corresponding primary amines, and can be readily prepared *in situ* by the reaction of either $NiCl_2·6H_2O$ or $CoCl_2·6H_2O$ with excess $NaBH_4$.[19] Following a procedure by Kokotos,[20] nitrile **252** was treated with $NiCl_2·6H_2O$ (5 equiv) and $NaBH_4$ (8 equiv) in MeOH to give predominantly primary amine **253** (Scheme 57).



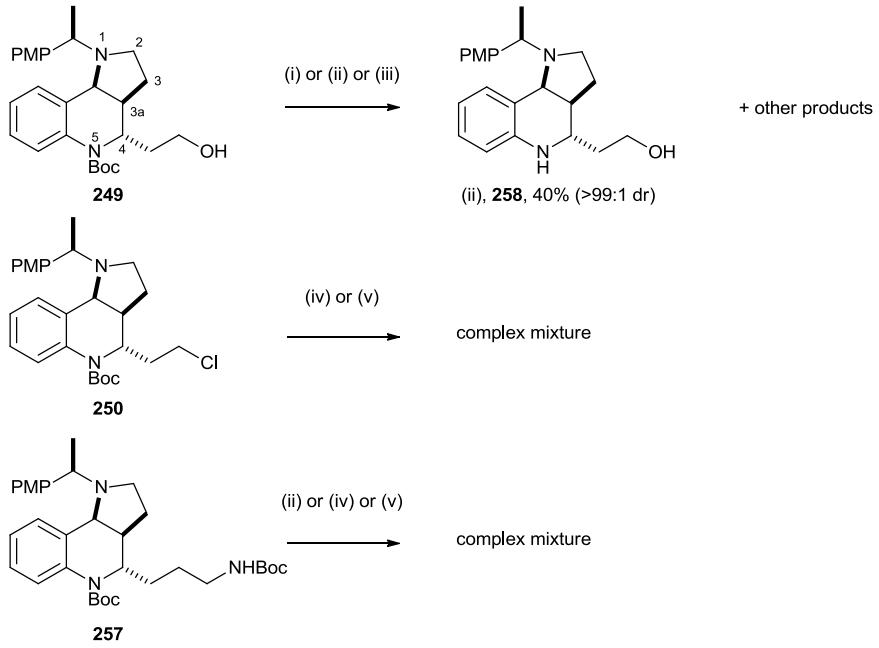
Scheme 57. *Reagents and Conditions*: (i) $Pd(OH)_2/C$, MeOH, H_2 (1 atm), rt, 16 h; (ii) MeOH/AcOH (1:1 v/v), $Pd(OH)_2/C$, H_2 (1 atm), rt, 16 h; (iii) $Pd(OH)_2/C$, methanolic HCl, H_2 (5 atm), rt, 16 h; (iv) $NiCl_2 \cdot 6H_2O$ (5.0 equiv), $NaBH_4$ (8.0 equiv), MeOH , 0 °C to rt, 1 h.

Application of the conditions reported by Kokotos to **251** gave primary amine **256** in 21% isolated yield. The work-up was complicated by the fine precipitate of Ni_2B formed during the reaction, which could not be separated despite repeated filtration through Celite, and additionally the high polarity of **256** hindered chromatographic purification. Caddick *et al.* have reported that a variety of nitrile containing substrates can be selectively reduced to the corresponding *N*-Boc derivatives with catalytic $NiCl_2 \cdot 6H_2O$ (0.1 equiv) and excess $NaBH_4$ in the presence of Boc_2O.[21] In their procedure, diethylenetriamine (DETA) was added to the work-up as a Ni scavenger to facilitate the removal of the fine precipitate of Ni_2B. Application of these conditions to nitrile **251** gave **257** in 74% yield and >99:1 dr (Scheme 58).



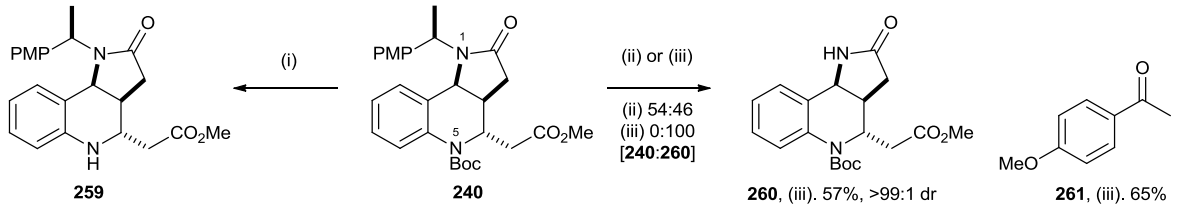
Scheme 58. *Reagents and Conditions*: (i) $NiCl_2 \cdot 6H_2O$ (7.0 equiv), $NaBH_4$ (21 equiv), MeOH/THF, 0 °C, 1 h; (ii) $NiCl_2 \cdot 6H_2O$ (0.2 equiv), Boc_2O (2.0 equiv), $NaBH_4$ (14 equiv), MeOH, 0 °C to rt, 16 h then DETA (1.0 equiv), rt, 30 mins.

Reagents for the deprotection of amines bearing an α-methyl-4-methoxybenzyl group include oxidants such as DDQ[22] or CAN,[3] or alternatively the use of protic acids.[2] Treatment of representative substrate **249** with Et_3SiH in HCO_2H resulted in a complex mixture of products, from which no determinable products could be isolated. Treatment of **249** in refluxing TFA gave a complex mixture of products, from which only **258** (resulting from *N*(5)-deprotection) could be isolated in 40% yield. Similarly, treatment of **249** with methanolic HCl resulted only in deprotection of the *N*-Boc group. Treatment of **250** with either CAN or DDQ resulted in a complex mixture of products. Similarly, treatment of **257** with either CAN, DDQ or refluxing TFA resulted in a complex mixture of products. Attempts at chromatographic purification resulted in low mass return of unidentified species in all cases (Scheme 59).



Scheme 59. *Reagents and Conditions*: (i) Et_3SiH (3.0 equiv), HCO_2H, 90 °C, 16 h; (ii) TFA, reflux, 16 h; (iii) methanolic HCl, rt, 2 h; (iv) CAN (2.0 equiv), $MeCN/H_2O$, rt, 16 h; (v) DDQ (1.2 equiv), CH_2Cl_2/H_2O, rt, 16 h.

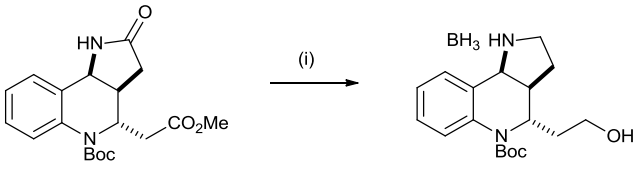
N(1)-Deprotection of γ-lactam **240** was next attempted. Treatment of **240** with CAN (2.2 equiv) in $MeCN/H_2O$ at rt for 1 h gave a 54:46 mixture of **240** and **260**, respectively. An increase in the number of equivalents of CAN (3.0 equiv) led to complete deprotection after 1 h, although the yield was low due to difficulties associated with the work-up.[23] Variation of the work-up procedure from those previously reported allowed a more facile work-up and higher mass recovery, principally by omitting the neutralisation step after the reaction, which otherwise led to an emulsion. *N*(5)-Deprotection was not observed, with **260** being isolated in 57% yield and >99:1 dr, and ketone **261** being isolated in 65% yield after purification. The mechanism of this reaction could be either through acidic deprotection, or *via* an oxidative process. In an attempt to gain insight into the mechanism, treatment of **240** with methanolic HCl at rt for 2 h gave **259** exclusively, in which the *N*(1) protecting group was unaffected. This suggests that the mechanism of deprotection by CAN is indeed an oxidative mechanism, rather than a facet of the acidic reaction conditions (Scheme 60).



Scheme 60. *Reagents and Conditions*: (i) methanolic HCl, rt, 16 h; (ii) CAN (2.2 equiv), $MeCN/H_2O$ (v/v, 1:1), rt, 1 h; (iii) CAN (3.0 equiv), $MeCN/H_2O$ (v/v 1:1), rt, 1 h.

Subsequent treatment of lactam **260** with excess $BH_3 \cdot THF$ in THF at rt for 16 h gave a mixture of products, from which borane complex **262**·BH_3 was isolated as the major product, after chromatographic purification, in 57% yield and >99:1 dr (Scheme 61). The identity of **262**·BH_3 was confirmed by the observation of a single resonance in the ^{11}B NMR spectrum (δ_B –14.9 ppm), a characteristic B–H stretch in the IR spectrum of **262**·BH_3 (ν_{max} = 2361, 2370 cm^{-1}), and by high

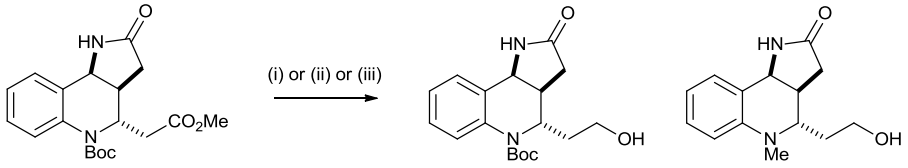
resolution mass spectrometry {*m*/*z* ([**262**·BH_3+Na]$^+$) requires 355.2163; found 355.2162}. Of note is the resistance of the *N*-Boc group within **260** to undergo reduction, even at reflux.



260, >99:1 dr **262**•BH_3, 57%, >99:1 dr

Scheme 61. *Reagents and Conditions*: (i) BH_3·THF (12 equiv), THF, reflux, 4 h.

Efforts were next directed towards tuning the reducing agent to give free amine **262** directly. However, treatment of **260** with $LiAlH_4$ (4.0 equiv) in THF at rt for 6 h gave **263** as the major product, in which the amide was unaffected. Treatment of **260** with $LiAlH_4$ in THF at 60 °C for 4 h gave a complex mixture of products, in which partial reduction of the carbamate had occurred to give the *N*-methyl tetrahydroquionoline derivative **264**. It is known that addition of $AlCl_3$ can reduce the reactivity of $LiAlH_4$ by virtue of the formation of alane, which in turn is a more selective reducing agent than $LiAlH_4$.[24] However, treatment of **260** with $AlCl_3$ (1.0 equiv) and $LiAlH_4$ (3.0 equiv) at 0 °C gave a complex mixture of products, from which **263** was isolated in 14% yield and >99:1 dr after purification, and **264** in 29% yield (~85% pure) (Scheme 62).

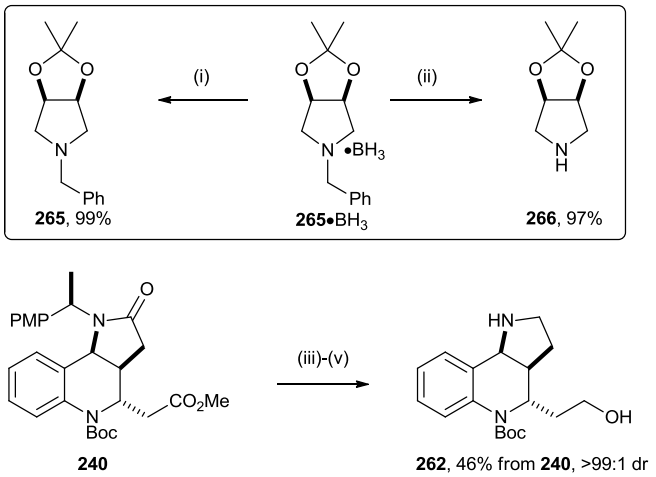


260, >99:1 dr **263**, (iii) 14%, >99:1 dr **264**, (iii) 29%, (~85% pure)

Scheme 62. *Reagents and Conditions*: (i) $LiAlH_4$ (4 equiv), THF, 0 °C, 6 h; (ii) $LiAlH_4$ (4 equiv), THF, 60 °C, 4 h; (iii) $AlCl_3$ (1.0 equiv), $LiAlH_4$ (3.0 equiv), 0 °C to rt, 16 h.

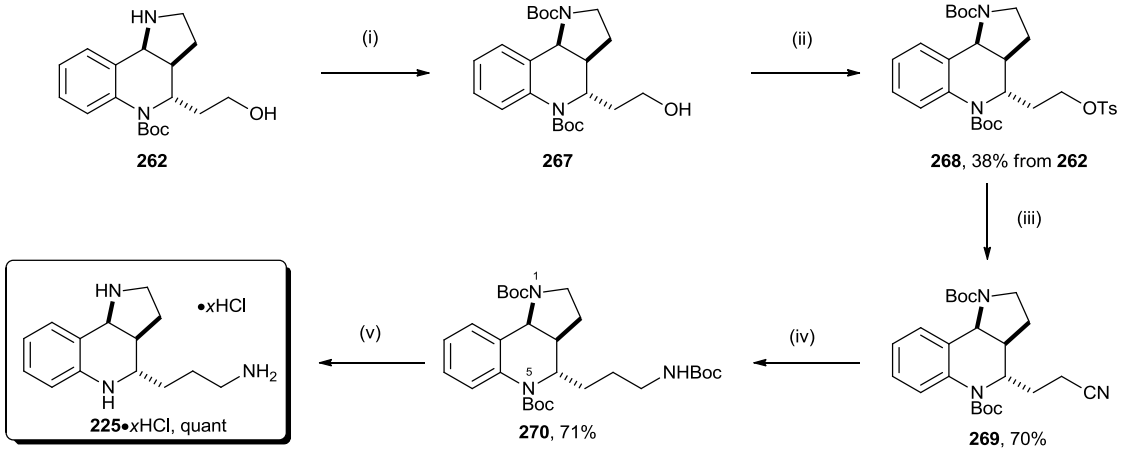
As modification of the hydride source did not result in reduction of the lactam, efforts were directed at the decomplexation of borane adduct **262**·BH_3. In contrast to the high reactivity of borane ether complexes, borane amine complexes are generally air stable crystalline compounds. Indeed, the formation of borane amine complexes can be a problem for the synthetic chemist due to the harsh conditions required for their decomplexation; typically refluxing HCl, which may not be compatible with other functional groups present within a molecule. Recently, chemists at Pfizer discovered that the rate of methanolysis of borane amine complexes is greatly enhanced by the addition of Pd/C.[25] For example, the background solvolysis of **265**·BH_3 was reported to proceeded to give **265** in 99% yield after 170 h at rt in MeOH. In contrast, decomplexation and hydrogenolysis of **265**·BH_3 in the presence of catalytic Pd/C was reported to give **266** in 97% yield after 12 h. Although no mechanism for the rate enhancement has been suggested, the reaction is proposed to proceed *via* the corresponding trimethoxyborate amine complex, from which the free amine can be obtained by

removal of $B(OMe)_3$ by co-evaporation with MeOH. The authors subsequently showed that H_2 generated *in situ* from decomplexation of the borane adduct can be used to effect other transformations such as reductive epoxide opening, alkene hydrogenation, *O*- or *N*-debenzylation and aryl triflate reduction.[26] Treatment of **262**·BH_3 with Pd/C in MeOH proceeded to full conversion to give amine **262**. This simple decomplexation procedure was applied to crude material from the borane reduction step, with **262** being isolated in 46% yield (over 3 steps) from **240** and >99:1 dr (Scheme 63).



Scheme 63. *Reagents and Conditions*: (i) MeOH, 170 h, rt; (ii) MeOH, Pd/C (10% w/w), 12 h; (iii) CAN (3.0 equiv), $MeCN/H_2O$, rt, 1 h; (iv) BH_3·THF, reflux, 4 h; (v) Pd/C (10% w/w of substrate), MeOH, rt, 16 h.

Efforts were now directed at the synthesis of **225**·*x*HCl. The most convenient *N*(1)-protecting group was *N*-Boc, as both the *N*(1) and *N*(5) atoms could be deprotected later in the synthesis by treatment with acid. *N*-Boc protection of **262** gave **267** in >99:1 dr. The crude product was tosylated to give **268** in 38% yield over 2 steps. Treatment of **268** with NaCN in NMP gave **269** in 70% yield after purification. Reduction of the nitrile within **269** and *in situ* protection by treatment with $NiCl_2·6H_2O$, $NaBH_4$ and Boc_2O in MeOH gave **270** in 71% isolated yield and >99:1 dr. Global *N*-deprotection with methanolic HCl gave triamine **225**·*x*HCl in quantitative yield (Scheme 64).[27]



Scheme 64. *Reagents and Conditions*: (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (iii) NaCN, NMP, 60 °C, 16 h; (iv) $NiCl_2·6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C to rt, 16 h; (v) methanolic HCl, rt, 16 h.

3.6. Summary

The synthesis of model triamine **225**·*x*HCl has been completed using three key steps: (i) conjugate addition and subsequent alkylation of α,β-unsaturated ester **130** to set the C(3a) and C(9b) stereocentres within the tricyclic scaffold, (ii) a double cyclisation reaction to generate the tricyclic core, and (iii) a Wittig olefination of hemiaminal **239** with *in situ* Michael addition to generate the C(4) stereocentre within **240** (Fig 23). The *N*-deprotection and elaboration of **240** to give triamine **225**·*x*HCl has been completed in good yield (Fig 25). With a proof of concept established for the conversion of α,β-unsaturated ester **130** to **225**·*x*HCl, the synthesis of "Ma's intermediate" **22**·*x*HCl was next investigated. Chapter 4 uses the synthetic route developed in this Chapter for the total asymmetric synthesis of (–)-martinellic acid **8** and for the first time, the corresponding C(4)-epimer.

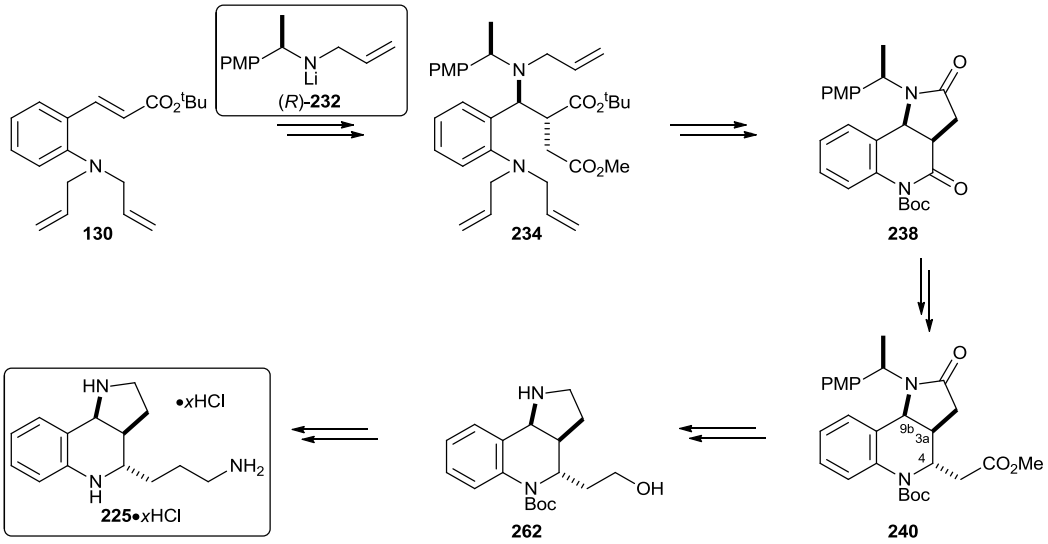


Fig 23. Synthesis of model triamine **225**·*x*HCl.

3.7. References and notes

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[6] (*R*)-α-Methyl-[4-methoxybenzyl]amine (*R*)-**226** was purchased from the AlfaAesar chemical company in >99% ee. The ee of (*R*)-**227** was determined to be >99% by ^{1}H NMR spectroscopic analysis in the presence of either antipode of the chiral solvating agent *O*-acetyl-mandelic acid and comparison with an authentic racemic sample.
[7]The diastereoisomeric purity was calculated by integration of diagnostic signals in the ^{1}H NMR of the crude reaction mixture.
[8] These reactions were performed by addition of a solution of **239** at twice the stated concentration to an equal volume solution of **200** and NaH.
[9] For clarity, the remaining two diastereoisomers of **245** and **246** are not shown.
[10] Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *81*, 1733.
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[13] The pKa value of **200** in H_2O has not been reported. For comparison, the pKa value of $(EtO)_2POCH_2CO_2Et$ is 18.6 in DMSO, and therefore would be expected to lie within the range 1.29 < pKa < 15.9 in H_2O. See: Bordwell, F. G. http://www.chem.wisc.edu/areas/reich/pkatable/ (unpublished results).
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[23] Satd aq $NaHCO_3$ is usually added at the end of the reaction to basify the amine products which become protonated during the course of the reaction.
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[26] For the use of this reaction as a hydrogen source, see: Couturier, M.; Andresen, B. M.; Tucker, J. L.; Dubé, P.; Brenek, S. J.; Negri, J. T. *Tetrahedron Lett.* **2001**, *42*, 2763.
[27] The free amine (±)-**225** has been reported previously, see: Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett.* **1999**, *40*, 3339.

Chapter 4: Total asymmetric synthesis of (–)-martinellic acid and (–)-4-*epi*-martinellic acid

4.1. Introduction

This Chapter describes the optimisation of a total asymmetric synthesis of (–)-martinellic acid **8** using methodology developed in the previous chapters, and reports the first total asymmetric synthesis of (–)-4-*epi*-martinellic acid **271** (Fig 24).

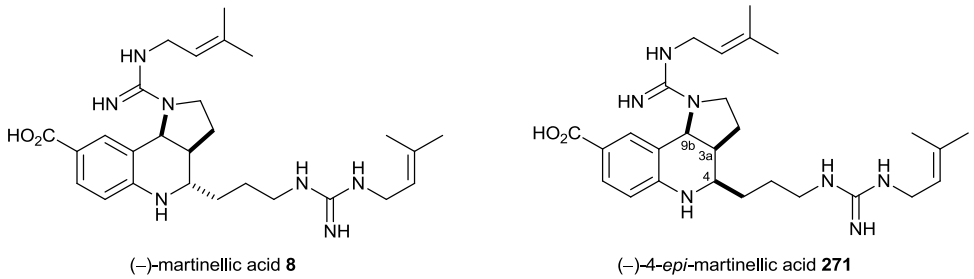
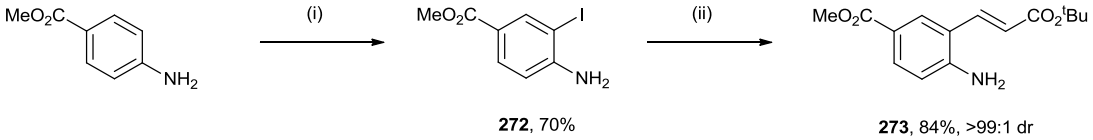


Fig 24. (–)-Martinellic acid **8** and (–)-4-*epi*-martinellic acid **271**.

4.2. Synthesis of *p*-substituted-2-iodoaniline substrates

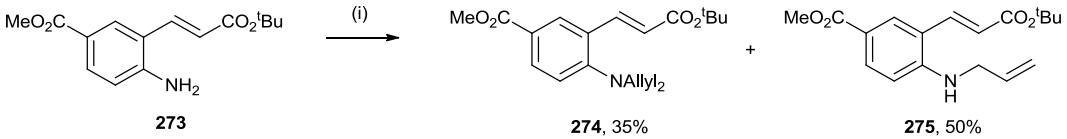
With conditions optimised for the synthesis of triamine **225**·*x*HCl, an analogue of "Ma's intermediate" **22**·*x*HCl lacking only the methyl ester substituent on the aromatic ring, it was planned that modification of the synthetic strategy to include the ester moiety from the outset would enable the synthesis of "Ma's intermediate" **22**·*x*HCl. Thus, methyl 3-iodo-4-aminobenzoate **272** was first prepared by a modified literature procedure.[1] Treatment of methyl 4-aminobenzoate with KI, KIO_3 and HCl in MeOH/H_2O gave **272** as a single regioisomer (>99% *ortho*), which was isolated in 70% yield after recrystallisation.[2] Heck coupling of **272** with *tert*-butyl acrylate in the presence of $Pd(OAc)_2$, P(*o*-Tol)$_3$ and Et_3N gave **273** in 84% yield and >99:1 dr (Scheme 65).



Scheme 65. *Reagents and Conditions*: (i) KI, KIO_3, MeOH/H_2O (1:5, v/v), HCl, rt, 6 h; (ii) $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, *tert*-butyl acrylate, MeCN, 70 °C, 16 h.

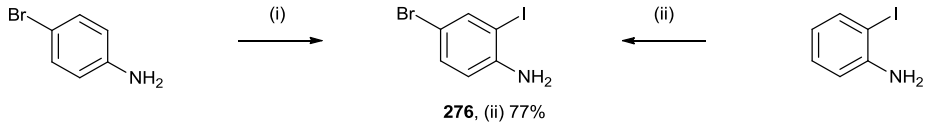
It was hoped that conjugate addition of lithium amide (*R*)-**232** to α,β-unsaturated ester **273** would proceed without protection of the aniline, thereby saving a protecting group step. Deprotonation of the aniline was expected to occur first, followed by Michael addition of the lithium amide. It is known in related systems that the conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide (*R*)-**173** proceeds with unprotected 2-aminocinnamate derivatives, although this can be accompanied by a loss in diastereoselectivity.[3] However, treatment of **273** with (*R*)-**232** (2.6 equiv) in THF at –78 °C for 2 h gave returned starting material **273** as the major product. Protection of the aniline within **273** against deprotection was therefore investigated. Treatment of **273** with allyl iodide and K_3PO_4 in acetone at reflux for 72 h gave a 42:58 mixture of **274** and **275**, which were isolated in 35 and 50%

yield, respectively (Scheme 66). The reduced reaction conversion may result from the decreased nucleophilicity of the conjugated aniline within **273** compared to that within **140** (see chapter 2). Treatment of **274** with (*R*)-**232** (1.6 equiv) in THF at –78 °C for 2 h gave a mixture of products, including predominantly starting material **274**. As the bis-*N*-allylation of **273** proceeded in low yield and the reaction conversion of the conjugate addition was poor, it was decided to modify this approach to a substrate containing an aryl bromide, which could be converted to an ester later in the synthesis. Additionally, it was anticipated that an aryl bromide would be also be less susceptible to reaction with the hydridic reagents needed later in the synthesis.



Scheme 66. *Reagents and Conditions*: (i) allyl iodide (2.5 equiv), K_3PO_4, acetone, reflux, 72 h.

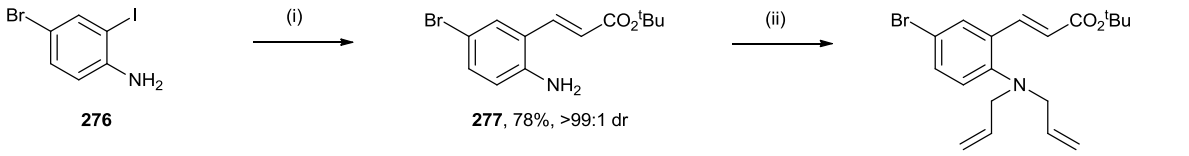
4-Bromo-2-iodoaniline **276** was chosen as a starting material for the revised synthetic route, which although commercially available, is prohibitively expensive.[4] Therefore, following a procedure reported by Kotha *et al*.,[1] commercially available and inexpensive 4-bromoaniline was iodinated with KI and KIO_3 to give **276** in quantitative yield. However, the reaction was found to be non-reproducible, and on subsequent repetition gave mixtures of 4-bromoaniline and **276**. The reason for the variability of this reaction is unclear, but may possibly be due to the insolubility of both 4-bromoaniline and **276** in the solvent system, which resulted in precipitation and thus ineffective stirring of the reaction mixture. As the reaction did not give repeatedly good conversion, an alternative method was sought. Following a procedure reported by Prasad *et. al.*,[5] 2-iodoaniline was brominated by treatment with KBr, $NaBO_3 \cdot 4H_2O$ and ammonium molybdate in AcOH which gave **276** in >90% conversion; **276** was isolated in 77% yield after purification (>99% *para*) (Scheme 67).



Scheme 67. *Reagents and Conditions*: (i) KI, KIO_3, HCl, MeOH/H_2O (1:5, v/v), rt, 16 h; (ii) KBr, $NaBO_3 \cdot 4H_2O$, $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, AcOH, rt, 2 h.

4.3. Elaboration towards the tricyclic pyrroloquinoline core

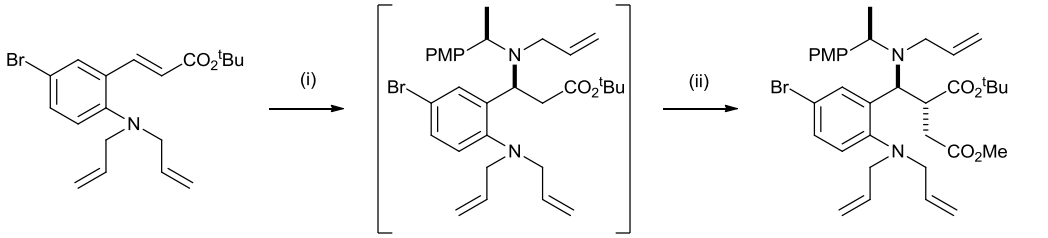
The synthesis of the pyrroloquinoline core was next achieved using a series of analogous reactions to those used for the synthesis of **238**, as described in Chapter 3. Heck coupling of **276** with *tert*-butyl acrylate in the presence of $Pd(OAc)_2$, P(*o*-Tol)$_3$ and Et_3N in MeCN gave **277** as the sole product in 78% yield and >99:1 dr. Bis-*N*-allyl protection of **277** by treatment with allyl iodide and K_3PO_4 in acetone at reflux for 3 days gave **278** in 89% yield and >99:1 dr after purification. This procedure could also be carried out without purification of intermediate **277**, after which **278** was isolated in 90% yield (from **276**) and >99:1 dr (Scheme 68).



276 **277**, 78%, >99:1 dr **278**, (ii). 89% (from **277**), >99:1 dr (i),(ii). 90% (from **276**), >99:1 dr

Scheme 68. *Reagents and Conditions*: (i) $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, *tert*-butyl acrylate, MeCN, 70 °C, 16 h; (ii) allyl iodide, K_3PO_4, acetone, reflux, 72 h.

Conjugate addition of (*R*)-**232** to α,β-unsaturated ester **278** gave β-amino ester **279** in >99:1 dr. Deprotonation of **279** with LDA followed by alkylation with methyl bromoacetate resulted in >95% conversion to give **280** in >98:2 dr. Purification of the crude reaction mixture gave **280** in 81% yield and >98:2 dr over the 2 step sequence (Scheme 69). The stereochemistry within **280** and **279** was assigned by analogy to substrates described in previous chapters, and is in accord with the well known *anti* selectivity exhibited in these alkylation reactions.[6] Additionally, both the chemical shifts and ^3J coupling constants of the C(1')H_2 and C(3)*H* protons were in accord with the analogues **144** and **234** reported in chapters 2 and 3, respectively.

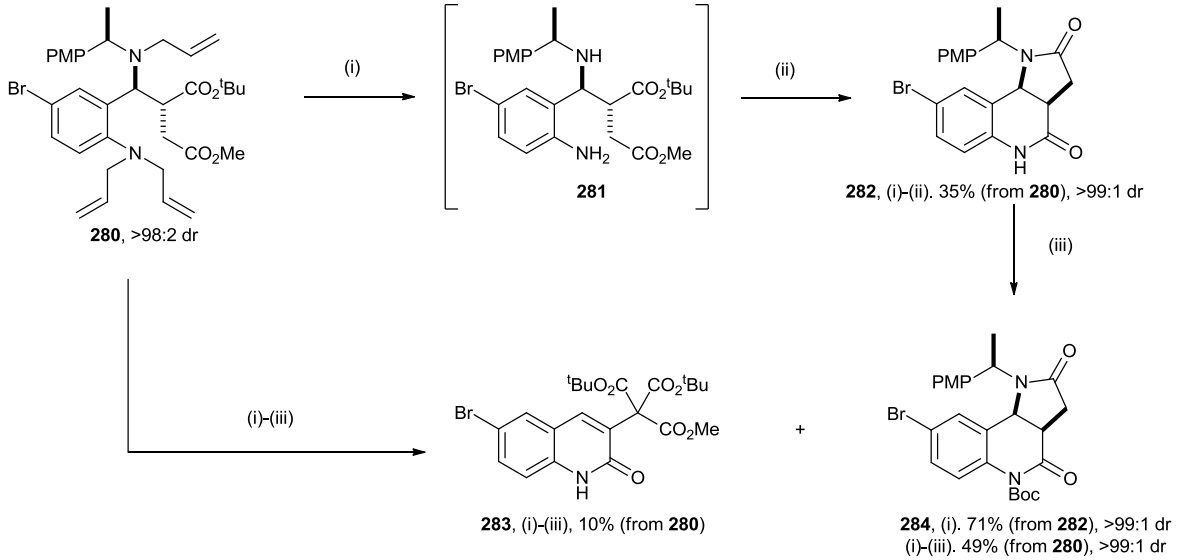


278 **279** **280**, (i)-(ii). 81% (from **278**), >98:2 dr

Scheme 69. *Reagents and Conditions*: (i) (*R*)-**227**, BuLi, THF, −78 °C, 2 h; (ii) LDA, methyl bromoacetate, −78 °C to rt, 16 h.

Treatment of **280** with $Pd(PPh_3)_4$ and DMBA in CH_2Cl_2 at 35 °C gave **281** in ~91% yield (based on mass return) and >99:1 dr, using the improved work-up procedure described in Chapter 3. As expected, the absence of the proto-demetallated product **236**, as determined by either ^{1}H NMR or mass spectrometric analysis confirmed that the addition of the active Pd(0) catalyst into the C−Br bond is a slow or negligible process under these reaction conditions. Cyclisation was achieved by treatment with $PhCO_2H$ in PhMe at reflux for 16 h to give **282**, which was highly crystalline and precipitated from solution during the course of the reaction. Filtration of the crude reaction mixture gave **282** in 35% isolated yield over 2 steps in >99:1 dr. Treatment of **282** with Boc_2O, Et_3N and DMAP in CH_2Cl_2 at 35 °C for 16 h gave **284** in 71% yield after recrystallisation. Rather than isolation of **282**, *N*-Boc protection of the crude material after the cyclisation step gave **284**, which was isolated in 49% yield (>99:1 dr) over 3 steps after recrystallisation (Scheme 74). The relative configuration within **284** was assigned by single crystal X-ray diffraction analysis, with the absolute (3a*R*,9b*S*,α*R*)-configuration assigned relative to the known (*R*)-configuration of the α-methyl-4-methoxybenzyl group. Furthermore, determination of a Flack *x* parameter[7] of 0.011(8) for the crystal structure of **284** allowed this assignment to be confirmed unambiguously (Fig 25).[12] This analysis

also allowed the configurations within both **282** and **281** to be confirmed. Additionally, chromatographic purification of the mother liquor allowed isolation of quionlin-2-one by-product **283** in 10% yield over 3 steps from **280**. The presence of **283** had not been previously identified due to the few diagnostic signals present in the ^{1}H NMR spectrum of **283**, which overlapped with those of the tricyclic product **284** and those of the catalyst, prior to recrystallisation. The structure of **283** was determined unambiguously by single crystal X-ray diffraction analysis (Fig 25).[12] Presumably, quionlin-2-one **283** is formed as a by-product of the cyclisation step after the elimination of (*R*)-**226**. Quinolin-2-one **283** was not observed during the *N*-Boc protection of **282**, supporting the suggestion that elimination of the amine occurs during the cyclisation step. Although *C*-acylation of an enolate by Boc_2O is known,[8] the *C*-acylation of an enol by Boc_2O is unprecedented.



Scheme 74. *Reagents and Conditions*: (i) $Pd(PPh_3)_4$ (0.15 equiv), DMBA, CH_2Cl_2, 35 °C, 16 h; (ii) $PhCO_2H$, PhMe, reflux, 16 h; (iii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 16 h.

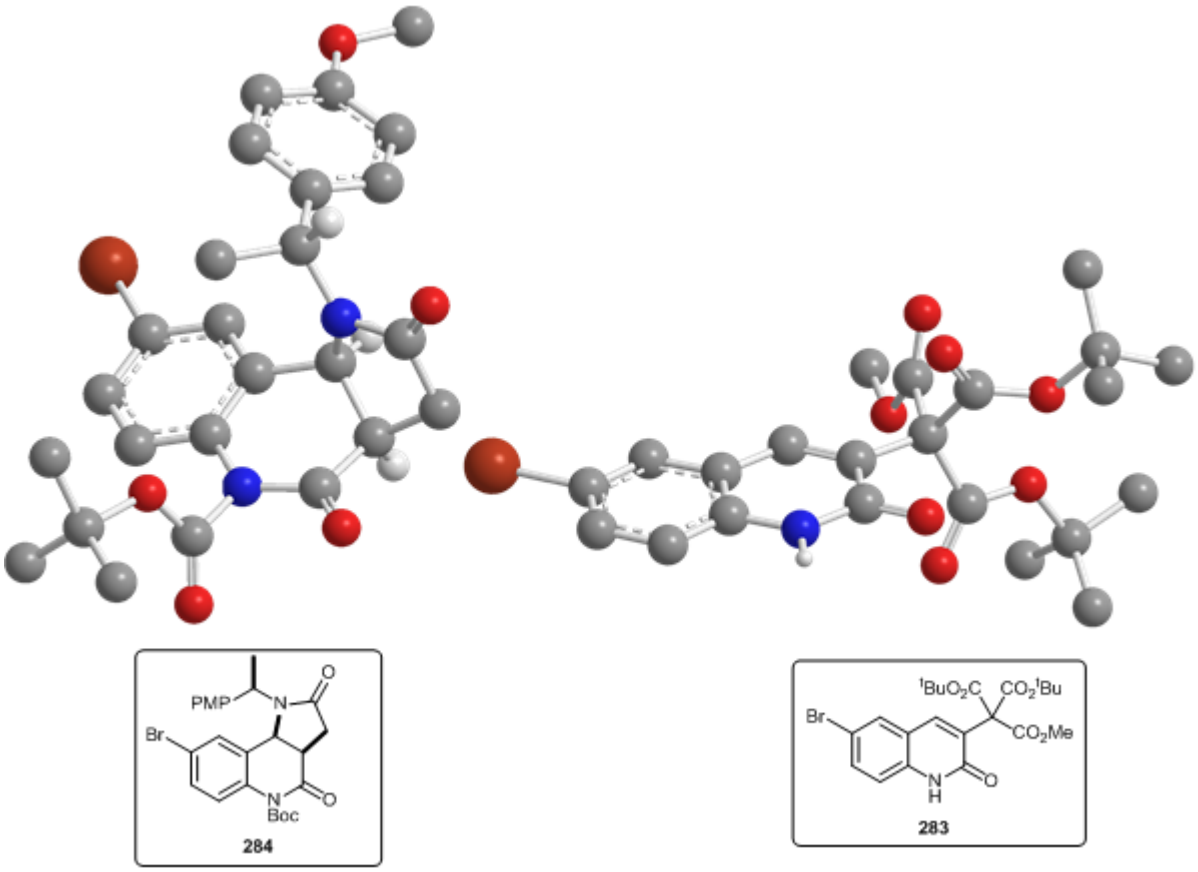
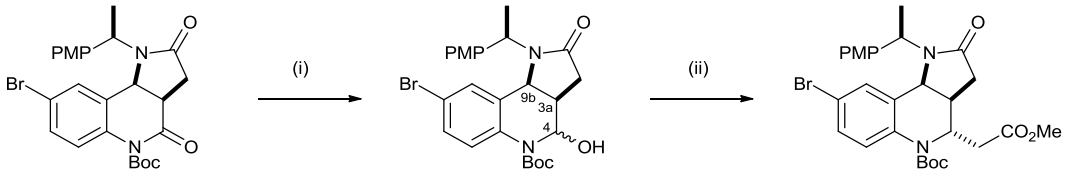


Fig 25. Chem 3D representations of the single crystal X-ray diffraction structures of **284** [*left*] and **283** [*right*] (selected H atoms are omitted for clarity).

4.4. Optimisation of the Wittig-Michael procedure

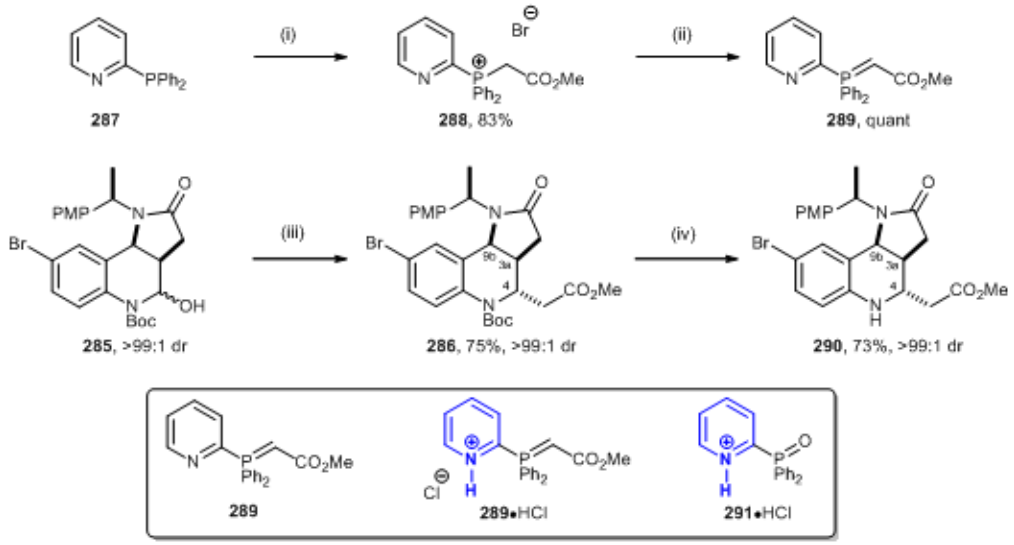
Chemoselective reduction of **284** was achieved by treatment with LiAl(O^{t}Bu)$_3$H in THF at 0 °C which gave hemiaminal **285** as a single diastereoisomer (>99:1 dr), of undetermined configuration at C(4), in quantitative yield. Treatment of **285** with phosphorane **206** in PhMe at 80 °C for 16 h gave **286** as the only detectable diastereoisomer (>99:1 dr). Chromatographic purification of **286** was again difficult as it co-eluted with the excess phosphorane **206** and the Ph$_3$PO by-product formed during the reaction. It was therefore necessary to develop an alternative work-up procedure. It was thought that, if the remaining phosphorane **206** could be consumed by the addition of a sacrificial aldehyde such as acetaldehyde, **286** could be separated from the Ph$_3$PO by trituration; as the methyl acrylate by-product is volatile and could then be removed *in vacuo*. Thus, treatment of **284** with phosphorane **206** (3.0 equiv) in PhMe at 80 °C proceeded to completion after 72 h. Once complete, acetaldehyde was added in excess to consume the remaining phosphorane, to give a mixture of **286** and Ph$_3$PO. However, attempted trituration of the remaining Ph$_3$PO residues from a variety of solvent systems gave **286** as a mixture with Ph$_3$PO in all cases (Scheme 71).



284 **285**, quant, >99:1 dr **286**, >99:1 dr

Scheme 71. *Reagents and Conditions*: (i) $LiAl(O^tBu)_3H$, THF, 0 °C, 1 h; (ii) **206** (3.0 equiv), PhMe, 80 °C, 16 h, then acetaldehyde.

Phosphines bearing solubilising groups are gaining popularity amongst medicinal chemistry and flow chemistry groups, due to their ease of removal from the desired reaction products.[9,10] For example, (2-pyridyl)diphenylphosphine **287** and the corresponding oxide **291** can be removed from a reaction mixture by extraction with 2.0 M aq HCl. This method was thought to be applicable to the purification of **286**. Phosphorane **289** was prepared in 2 steps from commercially available (2-pyridyl)diphenylphosphine **287**. Treatment of (2-pyridyl)diphenylphosphine **287** with methyl bromoacetate (1.0 equiv) in PhMe at rt gave the phosphonium bromide salt **288** in 83% yield. The phosphorane **289** was prepared as required by treatment of **288** with 2.0 M aq NaOH. Under the previously optimised conditions, treatment of hemiaminal **285** with **289** (3.0 equiv) at 80 °C for 72 h gave complete conversion to **286** as a single diastereoisomer (>99:1 dr). Removal of **289** and **291** from **286** was achieved by repeated washing with 2.0 M aq HCl, which gave **290** in 75% yield and >99:1 dr after chromatographic purification. Again, in this instance, the 3a,4-*anti*-diastereoisomer was the only detectable product of the Wittig-Michael reaction (Scheme 72).[11] Deprotection of the *N*-Boc protecting group within **286** was achieved by treatment with methanolic HCl for 16 h which gave **290** in 73% isolated yield. The absolute (3a*S*,4*S*,9b*S*,α*R*)-configuration within **290** was unambiguously established by single crystal X-ray diffraction analysis, with the absolute configuration assigned relative to the known (*R*)-configuration of the α-methyl-4-methoxybenzyl group (Fig 26).[12] Furthermore, the determination of a Flack *x* parameter[7] of 0.014(9) for the crystal structure of **290** allowed this assignment to be confirmed. This analysis also allowed the relative and absolute configuration within **286** to be assigned by analogy.



Scheme 72. *Reagents and Conditions*: (i) methyl bromoacetate, PhMe, rt, 16 h; (ii) $LiAl(O^tBu)_3H$, 0 °C, 1 h; (iii) **289**, PhMe, 80 °C, 72 h; (iv) HCl, MeOH, rt, 16 h.

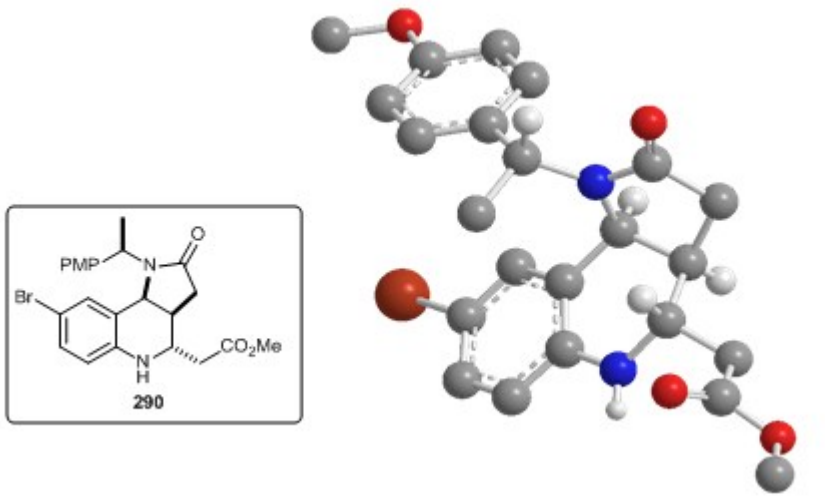
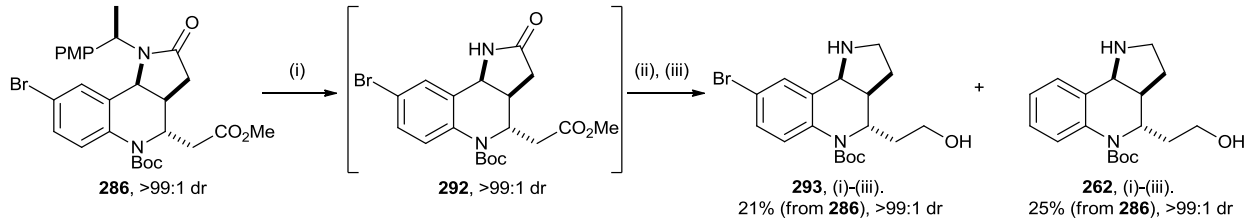


Fig 26. Chem 3D representation of the single crystal X-ray diffraction structure of **290** (selected H atoms are omitted for clarity).

4.5. Elaboration towards "Ma's intermediate"

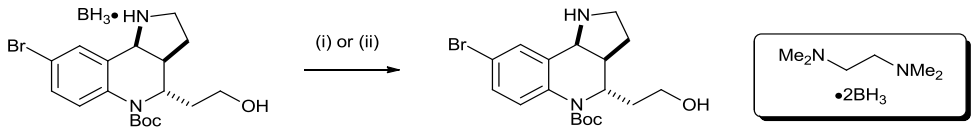
Deprotection of **286** by treatment with CAN in $MeCN/H_2O$ (1:1, v/v) gave **292** in >99:1 dr. No reduction of the aryl bromide or deprotection of either the *N*-Boc or *N*-PMP group was observed either by ^1H NMR spectroscopic analysis or mass spectrometric analysis. Reduction of **292** with $BH_3 \cdot THF$ gave a mixture of **293** and the corresponding borane complex **293**$\cdot BH_3$. However, attempted decomplexation by treatment of the crude mixture with Pd/C in MeOH/cyclohexene (4:1, v/v) resulted in partial reduction of the aryl bromide,[13] with **293** isolated in 21% yield over 3 steps (>99:1 dr) and **262** in 25% yield over 3 steps (Scheme 73).



286, >99:1 dr — **292**, >99:1 dr — **293**, (i)-(iii). 21% (from **286**), >99:1 dr — **262**, (i)-(iii). 25% (from **286**), >99:1 dr

Scheme 73. *Reagents and Conditions*: (i) CAN, MeCN/H_2O, rt, 1 h; (ii) BH_3·THF, THF, reflux, 4 h; (iii) Pd/C (10% w/w), MeOH/cyclohexene (4:1, v/v), rt, 16 h.

As decomplexation of **293**·BH_3 with Pd/C was proving problematic, other methods for the decomplexation of borane amine complexes were explored. A procedure reported by Brown *et al*. relies on the insolubility of the borane adduct TMEDA·2BH_3 in Et_2O or THF solutions to drive the precipitation of BH_3 from such solutions, allowing separation of the TMEDA·2BH_3 complex by centrifugation.[14,15] It was hoped that this method would also be applicable to the decomplexation of borane amine complexes. However, treatment of **293**·BH_3 with TMEDA (0.5 equiv) in Et_2O followed by centrifugation of the mixture, resulted in a mixture of **293**, **293**·BH_3 and TMEDA·*x*BH_3. Chromatograhpic purification allowed isolation of **293** in 24% yield, with an inseparable mixture of decomplexed material **293**·BH_3 and TMEDA·*x*BH_3 accounting for the remaining mass balance. An increase in the number of equivalents of TMEDA also did not achieve full decomplexation (Scheme 74). As decomplexation could not be driven to completion, and purification was proving difficult, an alternative approach was adopted.

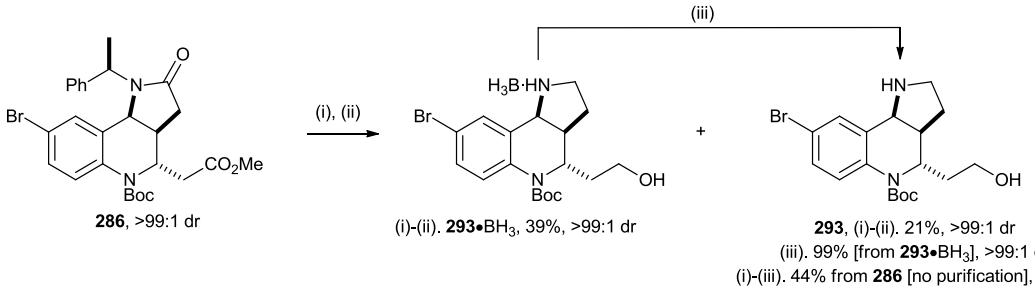


293·BH_3 — (i) **293**, 24%, >99:1 dr

Scheme 74. *Reagents and Conditions*: (i) TMEDA (0.5 equiv), Et_2O, rt, 2 h; (ii) TMEDA (excess), rt, 2 h.

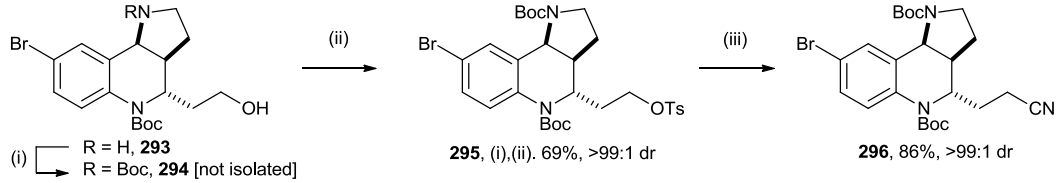
Decomplexation can be achieved through slow methanolysis in the absence of a catalyst such as acid or Pd/C. For example, in the methanolysis of **265**·BH_3 by chemists at Pfizer, the background methanolysis of **265**·BH_3 proceeded within 170 h (see Chapter 3).[16] As catalytic Pd/C had led to problems of reduction of the aryl bromide within **293**·BH_3, the background rate of decomplexation of **293**·BH_3 was monitored by ^{1}H NMR spectroscopic analysis in MeOH-d_4. There was no detectable change in the ^{1}H NMR spectrum even after 2 weeks at rt to indicate formation of the trimethoxyborate adduct, although interestingly slow deuterium incorporation (~8 days for full incorporation) was observed at the *N*(1) position. However, reaction under more forcing conditions (100 °C in MeOH for 48 h) resulted in full decomplexation, after which **293** was isolated in 99% yield and >99:1 dr after purification. Using this procedure, it was also possible to obtain **293** directly from **286** in 44% yield over 3 steps, without purification of the intermediates **292** or **293**·BH_3. It was found that it was more efficacious to purify the mixture after reduction with BH_3·THF, with **293** being isolated in 21% yield over 2 steps, and **293**·BH_3 in 39% yield over 2 steps in this case.

Decomplexation of **293**·BH_3 was then achieved by methanolysis to give **293** in 99% yield (Scheme 75).



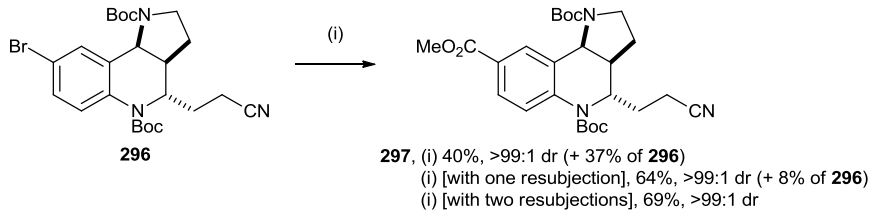
Scheme 75. *Reagents and Conditions*: (i) CAN, MeCN/H_2O, rt, 1 h; (ii) BH_3·THF, THF, reflux, 4 h; (iii) MeOH, reflux, 48 h.

By analogy to the results described in Chapter 3, it was anticipated that "Ma's intermediate" **22**·*x*HCl could be obtained from **293** via (i) appropriate *N*-protection and *O*-activation; (ii) displacement with NaCN; (iii) palladium catalysed methoxycarbonylation to introduce the ester functionality; (iv) reduction of the nitrile to an amine and finally global deprotection to yield **22**·*x*HCl. Thus, treatment of **293** with Boc_2O in the presence of Et_3N and catalytic DMAP gave alcohol **294**, which was *O*-tosylated to give **295** in 69% yield over 2 steps. Displacement of the tosylate within **295** was achieved by treatment with NaCN in NMP at 60 °C for 16 h which gave **296** in 86% yield and >99:1 dr (Scheme 76).



Scheme 76. *Reagents and Conditions*: (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 5 h; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (iii) NaCN, NMP, 60 °C, 16 h.

Attention was then turned to installing the ester functionality within **296**. Treatment of **296** with $Pd(OAc)_2$ (0.1 equiv), Xantphos (0.2 equiv) in Et_3N/MeOH (5:1 v/v) under a CO atmosphere (1 bar) at 70 °C for 16 h gave a 50:50 mixture of **296** and **297**. Chromatographic purification of this mixture gave returned starting material in 37% yield (>99:1 dr) and ester **297** in 40% yield (>99:1 dr). Although deactivation of the catalyst could not be avoided, resubjection of the mixture to the reaction conditions resulted in increased conversion, giving **297** and **296** in 64 and 8% yield, respectively, after purification. After two resubjections full conversion was achieved, with **297** being isolated in 69% yield after purification (Scheme 77). In all cases, no proto-demetallated product **269** or other side products were observed.

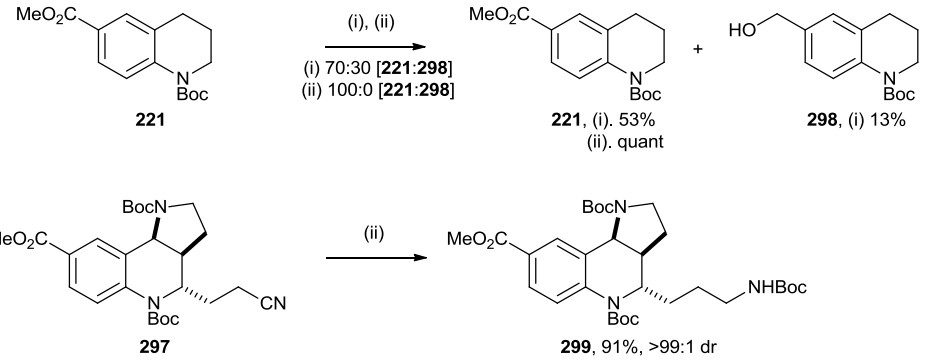


296

297, (i) 40%, >99:1 dr (+ 37% of **296**)
(i) [with one resubjection], 64%, >99:1 dr (+ 8% of **296**)
(i) [with two resubjections], 69%, >99:1 dr

Scheme 77. *Reagents and Conditions*: (i) $Pd(OAc)_2$, Xantphos, Et_3N/MeOH (5:1, v/v), CO (1 atm), 70 °C, 16 h.

With **297** in hand, the previously optimised conditions for nitrile hydrogenolysis and *in situ N*-Boc protection were anticipated to provide **299**. However, it was suspected that a possible side reaction could be hydridic reduction of the ester within **297** to yield the corresponding benzylic alcohol. Therefore, the conditions previously optimised in Chapter 3 were screened on model system **221** initially. Thus, **221** was treated with $NiCl_2 \cdot 6H_2O$ (0.2 equiv), $NaBH_4$ (14 equiv), Boc_2O (2.0 equiv) in MeOH at 0 °C to rt over 16 h, to give a 70:30 mixture of **221** and **298**, with chromatographic purification yielding **221** in 53% yield and **298** in 13% yield. These results suggested that a shorter reaction time would suppress the unwanted ester reduction pathway leading to benzylic alcohol **298**, whereas nitrile hydrogenation is generally rapid and has been achieved within 1 h on some substrates by Caddick *et al*.[17] Repetition of the reaction for 1 h at 0 °C resulted in no observed reduction of ester within **221**, with **221** returned quantitatively, confirming that the ester reduction pathway is relatively slow. With optimised conditions established, these conditions were applied to **297**: treatment of **297** with $NiCl_2 \cdot 6H_2O$ (0.2 equiv), $NaBH_4$ (14 equiv) and Boc_2O (2.0 equiv) in MeOH at 0 °C for 1 h gave full conversion to **299**, which was isolated in 91% yield and >99:1 dr (Scheme 78).



221

221, (i). 53%
(ii). quant

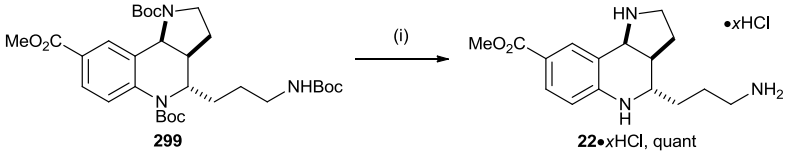
298, (i) 13%

297

299, 91%, >99:1 dr

Scheme 78. *Reagents and Conditions*: (i) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C to rt, 16 h; then DETA; (ii) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C, 1 h; then DETA.

Treatment of **299** with methanolic HCl at rt for 6 h gave "Ma's intermediate" **22**·*x*HCl in quantitative yield. The ^1H and ^{13}C NMR spectroscopic data and specific rotation for **22**·*x*HCl were consistent with those reported previously in the literature (Table 5). The synthesis of "Ma's intermediate" **22**·*x*HCl was thus completed in 6.0% yield over 17 linear steps from commercially available 2-bromo-4-iodoaniline **276**.[18] This compares favourably with other reported syntheses (Table 5).[19,20,21,22,18]



Group	Overall yield of (–)-**22**•*x*HCl	Number of steps	Specific rotation of (–)-**22**•*x*HCl
Ma[19]	2.1%	21	$[\alpha]_D^{20}$ –49.9 (c 1.25 in MeOH)
Lovely[20]	0.9%	21	not reported
Iwabuchi[21]	3.3%	25	$[\alpha]_D^{25}$ –57.7 (c 0.3 in MeOH).
Hamada[22]	10.2%	16	$[\alpha]_D^{18}$ –54.4 (c 0.29 in MeOH)
Davies[18]	6.0%	17	$[\alpha]_D^{20}$ –48.7 (*c* 0.3 in MeOH)

Table 5. *Reagents and Conditions* (i) methanolic HCl, rt, 6 h.

4.6. Stability studies of hexahydropyrroloquinoline systems

It has been previously reported by several groups that "Ma's intermediate" **22**·*x*HCl is best characterised as the hydrochloride salt as decomposition occurs on storage as the free amine, which has been attributed to polymerisation.[23] To test this hypothesis, a freshly prepared sample of **22**·*x*HCl was basified by addition of K_2CO_3 and the resultant solution was monitored by ^{1}H NMR in MeOH-d_4. It was observed that after ~72 h the peak corresponding to the methyl ester had disappeared, and was accompanied by a change in the apparent splitting patterns of the C(6)*H*, C(7)*H* and C(9)*H* protons, and the appearance of additional resonances in the aromatic region of the ^{1}H NMR spectrum, although the bulk of the aliphatic region was unaltered. Although mass spectrometric analysis was inconclusive, a peak at *m*/*z* = 318 [corresponding to $[M\text{-}d_6+Na]^+$, (M = 289)] suggested the incorporation of MeOH-d_4 into the aryl ester. On standing in MeOH a peak at 290 ($[M+H]^+$) was observed, corresponding to proton and methanol exchange. On standing for weeks several additional products were observed by ^{1}H NMR spectroscopic analysis, although their identity could not be fully elucidated. It was thought that a clearer picture could be obtained by recovering any signals lost due to deuterium incorporation, thus the sample was stirred for 72 h in MeOH, giving acid **300** as essentially the only product (>90% pure) (Fig 27). The presence of acid **300** was confirmed by both high resolution mass spectrometry ($[M+H]^+$ requires 276.1707; found 276.1712), and was supported by a broad stretch in the IR spectrum (ν_{max} = 3348 cm^{-1}). Treatment of **300** with methanolic HCl resulted in full recovery of "Ma's intermediate" **22**·*x*HCl after 48 h. In conclusion, "Ma's intermediate" **22**·*x*HCl quickly produces a complex ^{1}H NMR spectrum when basified, although this appears to be due to several factors such as hydrolysis or methanolysis. However, the "decomposition" reported by Snider *et al.* can easily be reversed by stirring in methanolic HCl to regenerate **22**·*x*HCl.[23]

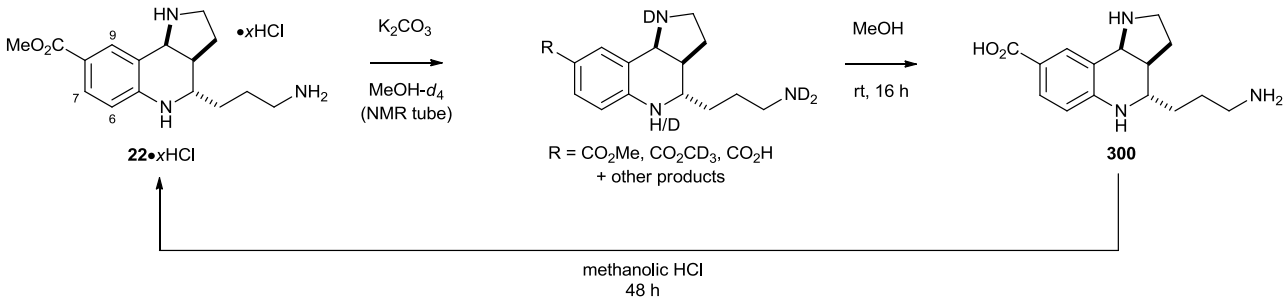
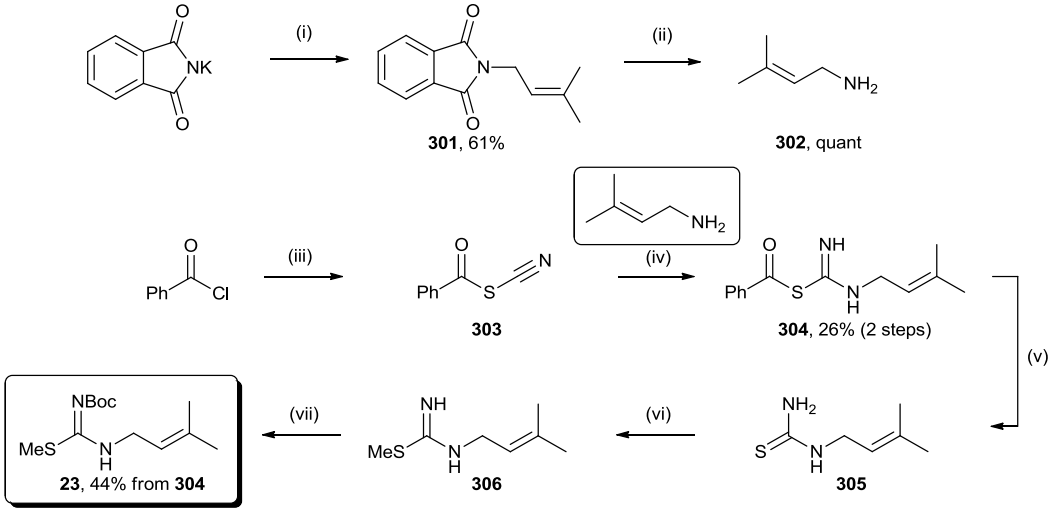


Fig 27. NMR Stability experiments on "Ma's intermediate" **22**·*x*HCl.

4.7. Introduction of the guanidine moieties

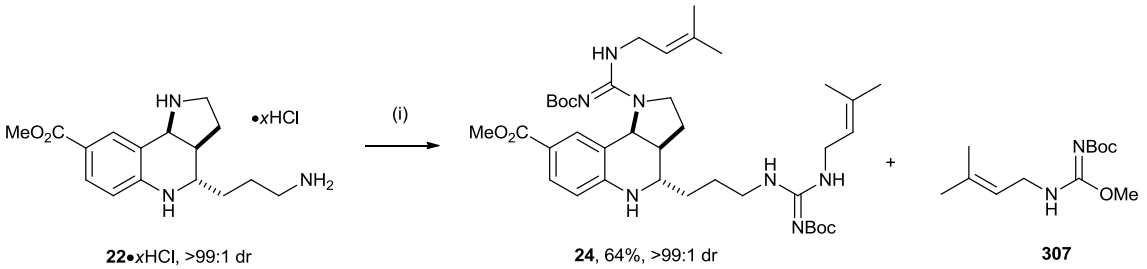
It was anticipated that the synthesis of (–)-martinellic acid **8** could be completed following the procedure reported by Ma *et al.*,[19] in which coupling of **22**·*x*HCl with isothiourea **23** would be followed by ester hydrolysis and global *N*-deprotection. The synthesis of isothiourea **23** was therefore carried out first. Prenylamine **302** was prepared *via* a procedure reported by Coxon.[24] A Gabriel reaction between potassium phthalimide and 3,3-dimethylallyl bromide in DMF gave **301** in 61% yield after recrystallisation. Treatment of **301** with $NH_2NH_2{\cdot}H_2O$ in EtOH at reflux for 1 h gave prenylamine **302**. Isothiourea **23** was prepared *via* a 5 step sequence reported by Ma *et al.*[25] Treatment of benzoyl chloride with KSCN in acetone at rt gave **303**. Subsequent treatment of **303** with prenylamine gave isothiourea **304** in 26% yield over 2 steps. Transesterification of **304** with K_2CO_3 in MeOH gave **305**, which was methylated with MeI in DMF to give **306**. Finally, *N*-Boc protection of **306** with Boc_2O, Et_3N and DMAP in CH_2Cl_2 gave **23** in 44% isolated yield from **304** (Scheme 79).



Scheme 79. *Reagents and Conditions*: (i) 3,3-dimethyl allyl bromide, DMF, 180 °C, 16 h; (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 1 h; (iii) KSCN, acetone, rt, 2 h; (iv) prenylamine, MeCN, rt, 16 h; (v) K_2CO_3, MeOH, rt, 6 h; (vi) MeI, DMF, rt, 16 h; (vii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h.

Following the procedure reported by Ma *et al.*, coupling of **22**·*x*HCl with isothiourea **23**, $AgNO_3$ and Et_3N in MeCN/MeOH at 40 °C for 16 h gave **24** in 64% yield and >99:1 dr.[19] By-product **307**, arising from trapping of the isothiourea with MeOH was also isolated from the reaction in 18% yield with respect to the isothiourea (Scheme 80). The spectroscopic properties of **24** were also consistent with those in the literature, including its specific rotation {for this sample $[\alpha]_D^{20}$ −142 (*c* 0.80 in

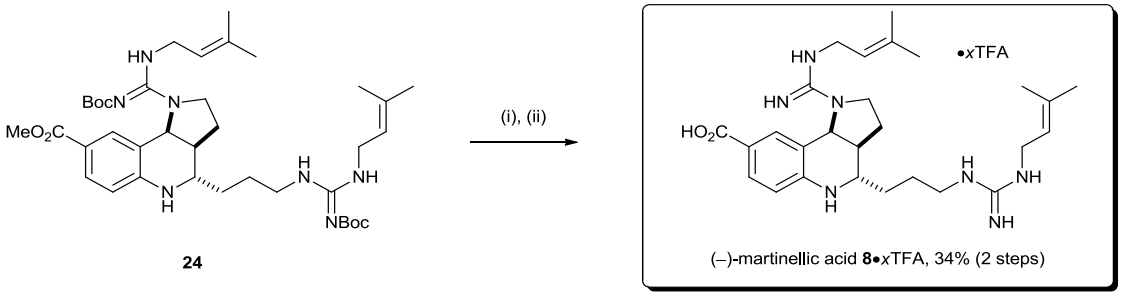
$CHCl_3$); lit.[19] $[\alpha]_D^{20}$−94.2 (*c* 0.28 in $CHCl_3$); lit.[21] $[\alpha]_D^{28}$−179.1 (*c* 0.80 in $CHCl_3$); lit.[20] $[\alpha]_D^{20}$−95.2 (*c* 0.58 in $CHCl_3$)}.



22•*x*HCl, >99:1 dr **24**, 64%, >99:1 dr **307**

Scheme 80. *Reagents and Conditions*: (i) **23**, Et_3N, $AgNO_3$, MeCN/MeOH (4:1, v/v), 40 °C, 16 h.

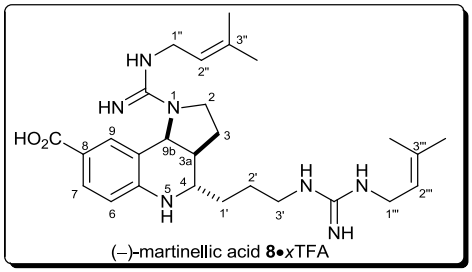
Hydrolysis of **24** with 0.2 M aq NaOH in MeOH gave the corresponding acid, which was immediately *N*,*N*-deprotected by treatment with TFA in the presence of anisole. Purification *via* preparative HPLC gave (–)-martinellic acid **8**·*x*TFA in 36% yield over 2 steps (Table 6).[18,26] The ^1H and ^{13}C NMR spectra were consistent with those reported for the sample isolated from the natural source by Witherup *et al.*[27], and were also in good agreement with those reported by Ma,[19] Iwabuchi,[21] Naito,[28] Snider[23] and Batey[29] (Table 7). The observation of a resonance in the ^{19}F NMR at δ_F –73.7 ppm confirmed the presence of the trifluoroacetate salt. The specific rotation of this sample {$[\alpha]_D^{20}$−118 (*c* 0.31 in MeOH} was also consistent with the values reported in the literature.



24

Group	Overall yield of (–)-**8**•*x*TFA	Number of steps	Specific rotation of (–)-**8**•*x*TFA
Ma[19]	1.3%	27	$[\alpha]_D^{20}$ –122.7 (c 0.31 in MeOH)
Iwabuchi[21]	0.4%	29	$[\alpha]_D^{29}$ –164.3 (c 0.14 in MeOH)
Naito[28]	7.0%	17	$[\alpha]_D^{23}$ –164.8 (c 0.33 in MeOH)
Davies[18]	1.3%	20	$[\alpha]_D^{20}$ –118.0 (*c* 0.31 in MeOH)

Table 6. *Reagents and Conditions*: (i) 0.2 M aq NaOH, MeOH, reflux, 16 h; (ii) TFA, anisole, CH_2Cl_2, rt, 16 h; then reverse phase HPLC purification.



Resonance	"Natural" Martinellic acid δ_H (ppm)	"Synthetic" Martinellic acid δ_H (ppm)	"Natural" Martinellic acid δ_C (ppm)	"Synthetic" Martinellic acid δ_C (ppm)
1	-	-	-	-
2	3.39 (2H)	3.33-3.43 (2H, m)	45.7	45.8
3	1.69 (1H) 2.07 (1H)	1.51-1.76 (3H[a], m) 2.03-2.14 (1H, m)	26.2	26.3
3a	2.43 (1H)	2.37-2.48 (1H, m)	39.3	[b]
4	3.28 (1H)	3.27 (1H, m)	49.1	49.2
6a	-	-	146.3	146.3
6	6.58 (1H, d, *J* 8.6)	6.58 (1H, d, *J* 8.5)	113.2	113.3
7	7.54 (1H, dd, *J* 8.6, 1.7)	7.54 (1H, d, *J* 8.6, 1.7)	130.0	130.0
8	-	-	117.1	117.1
9	7.65 (1H)	7.66 (1H, s)	130.4	130.5
9a	-	-	115.6	115.7
9b	5.26 (1H, d, *J* 6.6)	5.25 (1H, d, *J* 6.4)	53.0	53.0
1'	1.43 (2H)	1.35-1.52 (2H, m)	33.3	33.4
2'	1.57 (1H) 1.63 (1H)	1.51-1.76 (3H[a], m)	25.2	25.3
3'	3.13 (2H)	3.04-3.20 (2H, m)	40.7	40.7
1"	3.84 (2H)	3.79-3.87 (1H, m) 3.88-3.89 (1H, m)	39.8	39.5[c]
2"	5.31 (2H)	5.27-5.34 (1H, m)	119.5	119.6
3"	-	-	135.5	135.6
3"Me_A	1.69 (3H)	1.68 (3H, s)	17.9	17.8
3"Me_B	1.74 (3H)	1.73 (3H, s)	25.3	25.2
1'''	3.74 (2H)	3.66-3.77 (2H, m)	38.9	39.8[c]
2'''	5.17 (1H)	5.13-5.20 (1H, m)	119.1	119.2
3'''	-	-	135.8	136.0
3'''Me_A	1.64 (3H)	1.63 (3H, s)	17.8	17.9
3'''Me_B	1.70 (3H)	1.69 (3H, s)	25.2	25.2
guanidine			155.4	155.5
guanidine			154.2	154.3
CO_2H			167.1	167.2
$F_3CCO_2^{\ominus}$			-	158.2 (q, *J* 33.4)

δ_F (470 MHz) –73.66

Table 7. Data comparison for synthetic (–)-martinellic acid **8**·*x*TFA and the natural sample. [[a] These resonances were observed as an overlapping multiplet in the ^{1}H NMR spectrum of the synthetic sample. [b] This resonance was obscured by DMSO-d_6 in both the ^{13}C NMR and HSQC spectra of the synthetic sample. [c] This resonance was determined from the HSQC spectrum of the synthetic sample.]

4.8. Synthesis of 4-*epi*-martinellic acid

The preceding sections have shown the efficient conversion of **276** to (–)-martinellic acid **8**. However, the biosynthesis of (–)-martinellic acid **8** and (+)-martinelline **9** remains a matter of speculation, with some proponents suggesting a Povarov reaction as the key step.[30] A proposed biosynthesis occurring *via* an imine such as (*E*)-**308** could reasonably also proceed *via* the isomer (*Z*)-**309**, which would give rise to the C(4)-epimer after cycloaddition (Fig 28).[31] Discovery of a C(4)-epimer in *Martinella iquitoensis* or related species would give credence to this proposed biosynthesis. Thus, it was proposed to demonstrate the utility of this synthetic route by establishing a synthesis of 4-*epi*-martinellic acid **271** for the first time.

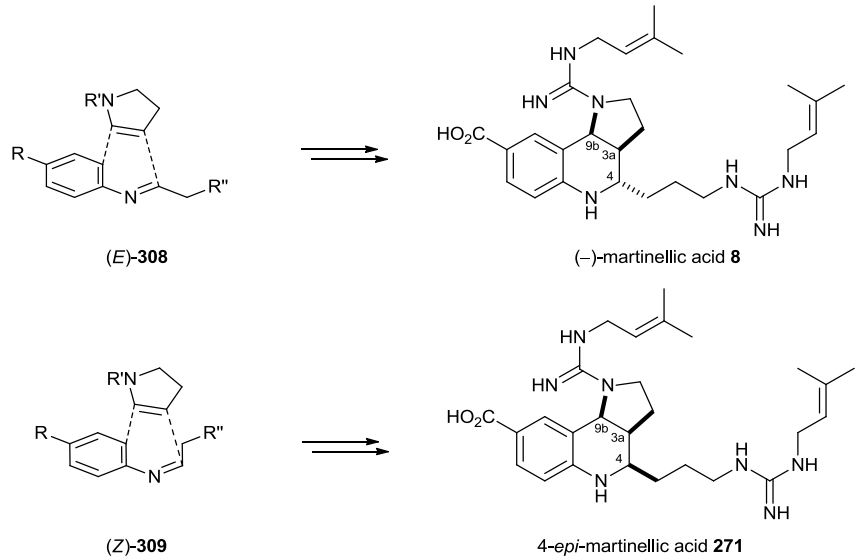
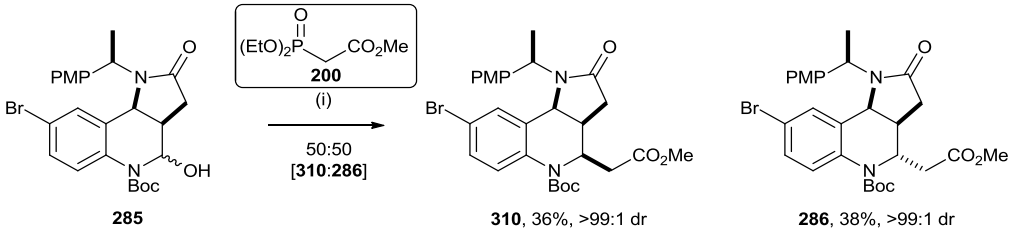


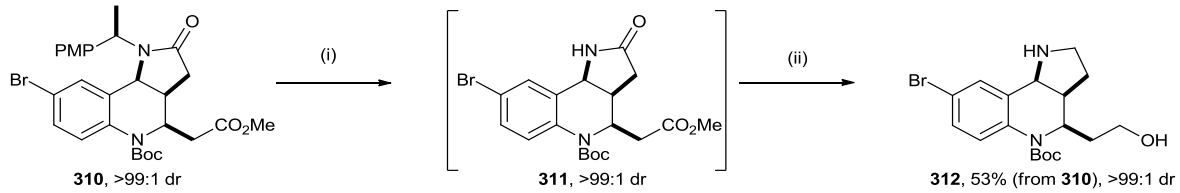
Fig 28. Proposed biosynthesis of the *Martinella* alkaloids *via* a Povarov approach.

Chapter 3 investigated the origins of the diastereoselectivity of the Wittig-Michael reaction of hemiaminal **239** which lacked substitution on the aromatic ring. In this system the highest proportion of the 3a,4-*syn* product **243** was obtained by treatment of aminal **239** with phosphonate **200** and NaH at 0.05 M in THF. It was hoped that similar diastereoselectivity would be observed for aminal **285** which contains a *p*-bromo substituent. Thus, treatment of **285** with phosphonate **200** and NaH in THF ([**285**] = 0.05 M) at 0 °C for 2 h gave a 50:50 mixture of **310** and **286**, which were isolated in 36 and 38% yield, respectively, and >99:1 dr in each case (Scheme 81). The reaction was reproducibly performed on a 2 g scale.



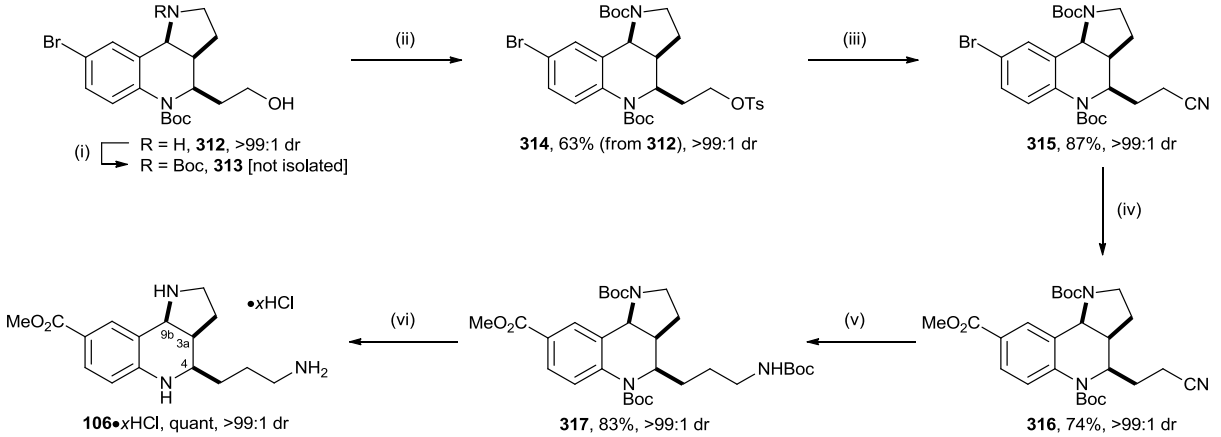
Scheme 81. *Reagents and Conditions*: (i) **200** (1.1 equiv), NaH (1.1 equiv), THF, 0 °C, 2 h.

With **310** in hand, an analogous series of steps as used for the synthesis of (–)-martinellic acid **8** were followed in an effort to access the C(4)-epimer of this natural product. Treatment of **310** with CAN in MeCN/H_2O (1:1, v/v) gave **311** in >99:1 dr. The crude reaction mixture was treated with BH_3·THF at reflux in THF which gave a mixture of **312** and **312**·BH_3, as evidenced by the presence of a B–H stretch in the IR spectrum of the crude reaction mixture (ν_{max} = 2362 and 2269 cm^{-1}), and by TLC analysis. The crude reaction mixture was then decomplexed by treatment with MeOH at reflux for 48 h; purification gave **312** in 53% yield over 2 steps from **310** (Scheme 82).



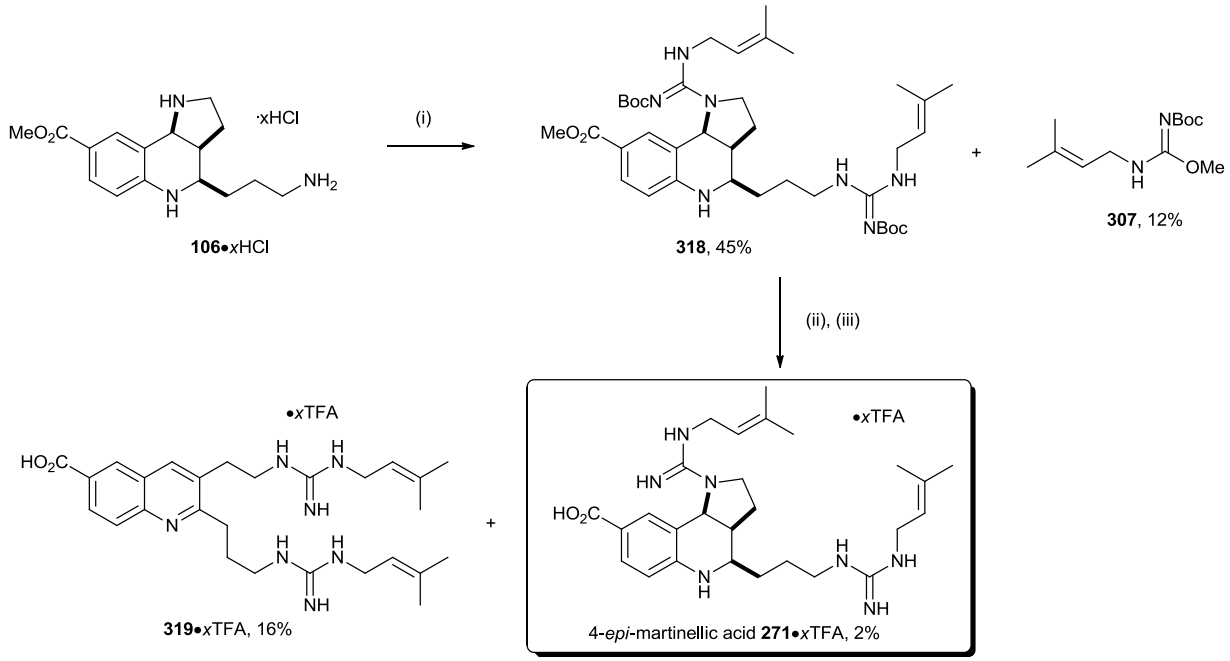
Scheme 82. *Reagents and Conditions*: (i) CAN, MeCN/H_2O (1:1, v/v), rt, 1 h; (ii) BH_3·THF, THF, reflux, 4 h, then MeOH, reflux, 48 h.

N-Boc protection of **312** gave alcohol **313**, which was tosylated to give **314** in 63% yield over 2 steps. Displacement of the tosylate within **314** with NaCN in NMP gave **315** in 87% yield. Pd catalysed methoxycarbonylation of **315** using the $Pd(OAc)_2$/Xantphos catalyst system gave **316** in 74% yield and >99:1 dr after two resubjections. Subsequent reduction of the nitrile within **316** by hydrogenation with Ni_2B and H_2 formed *in situ* from $NiCl_2·6H_2O$ and $NaBH_4$, and trapping of the primary amine with Boc_2O gave **317** in 83% yield. Global *N*-deprotection was then achieved by treatment of **317** with methanolic HCl for 6 h at rt which gave "4-*epi*-Ma's intermediate" (+)-**106**·*x*HCl in quantitative yield and >99:1 dr (Scheme 83). The spectroscopic properties of this sample of (+)-**106**·*x*HCl were in good agreement with those reported for the enantiomer by Hamada *et al.*[22] {$[\alpha]_D^{20}$+93.7 (*c* 0.35 in MeOH); lit.[22] for enantiomer $[\alpha]_D^{16}$−73.7 (*c* 0.34 in MeOH)}. The synthesis of **106**·*x*HCl therefore proceeded in 6.4% yield over 9 steps from hemiaminal **285**.



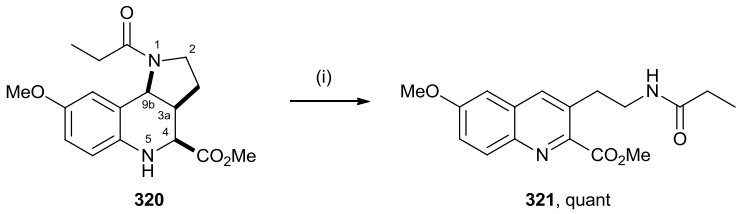
Scheme 83. *Reagents and Conditions*: (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, 35 °C, 16 h; (iii) NaCN, NMP, 60 °C, 16 h; (iv) $Pd(OAc)_2$, Xantphos, Et_3N/MeOH (5:1, v/v), CO (1 atm), 70 °C, 16 h (Resubject × 2); (v) $NiCl_2·6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C, 1 h; (vi) HCl, MeOH, rt, 6 h.

The synthesis of 4-*epi*-martinellic acid **271** was thought to proceed in an analogous manner to that of (–)-martinellic acid **8**. Coupling of **106**·*x*HCl with isothiourea **23** in the presence of Et_3N and $AgNO_3$ in MeCN/MeOH gave **318** in 45% yield and by-product **307** in 12% yield after chromatography. Hydrolysis of **318** with 0.2 M NaOH in MeOH, followed by global *N*-Boc deprotection with TFA and anisole in CH_2Cl_2 gave a mixture of 4-*epi*-martinellic acid **271**·*x*TFA and quinoline **319**·*x*TFA, which were isolated in 2 and 16% yield over 2 steps from **106**·*x*HCl, respectively, after repeated reverse phase HPLC purification (Scheme 84).



Scheme 84. *Reagents and Conditions*: (i) **23**, $AgNO_3$, Et_3N, MeOH/MeCN, 40 °C, 16 h; (ii) 0.2 M aq NaOH, MeOH, reflux, 16 h; (iii) TFA, anisole, CH_2Cl_2, rt, 16 h.

It was initially unclear why other substrates in the 3a-4-*syn* series had not also shown a propensity to oxidise to the corresponding quinolines. Quinoline product **319** could arise from either aerial oxidation of the *N*(5)-atom, followed by aromatisation, or elimination across the C(3a)–C(9b) bond, followed by aerial oxidation. Stevenson *et al*. have observed similar fragmentation pathways in related hexahydropyrroloquinoline systems,[32,33] where **320** was observed to be highly unstable with respect to quinoline **321**.[34] It was observed that **320** underwent quantitative conversion to quinoline **321** after 16 h, although the sequence of reaction steps was not determined (Scheme 85). A possible explanation for the instability of **271** compared to (–)-martinellic acid **8** is that the all *syn* configuration within **271** results in an unhindered convex face, which may allow the approach of O_2 to the *N*(1) or *N*(5) centres, with ensuing oxidation and elimination giving **319**. This may be postulated to occur to a lesser degree with (–)-martinellic acid **8**, as the C(4) substituent in this case is positioned to hinder the approach of an oxidant.

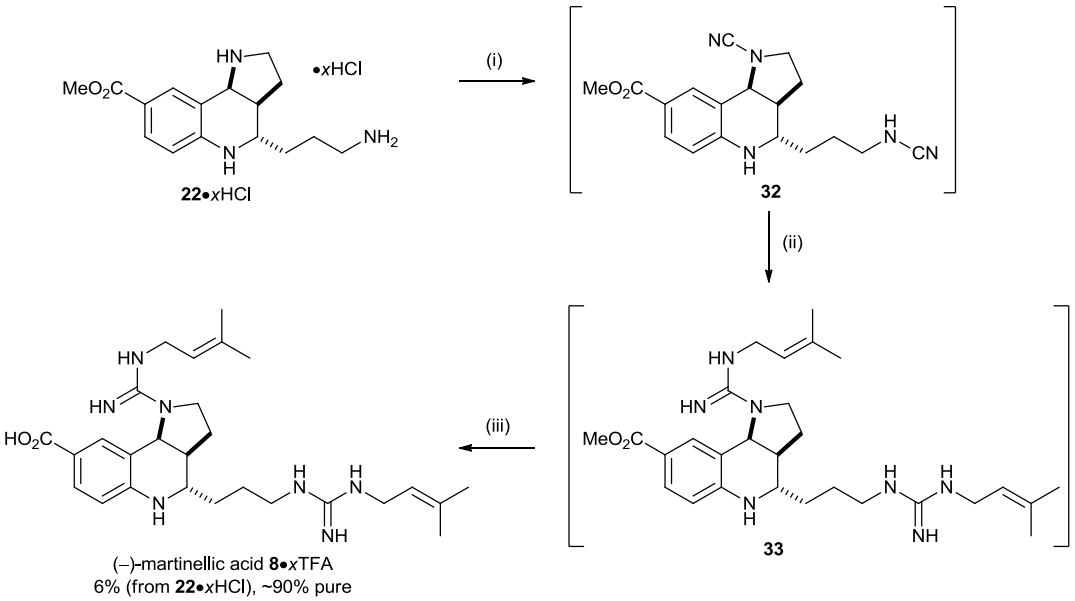


Scheme 85. *Reagents and Conditions*: (i) CD_2Cl_2, rt, 16 h.

4.9. Alternative guanylation procedure

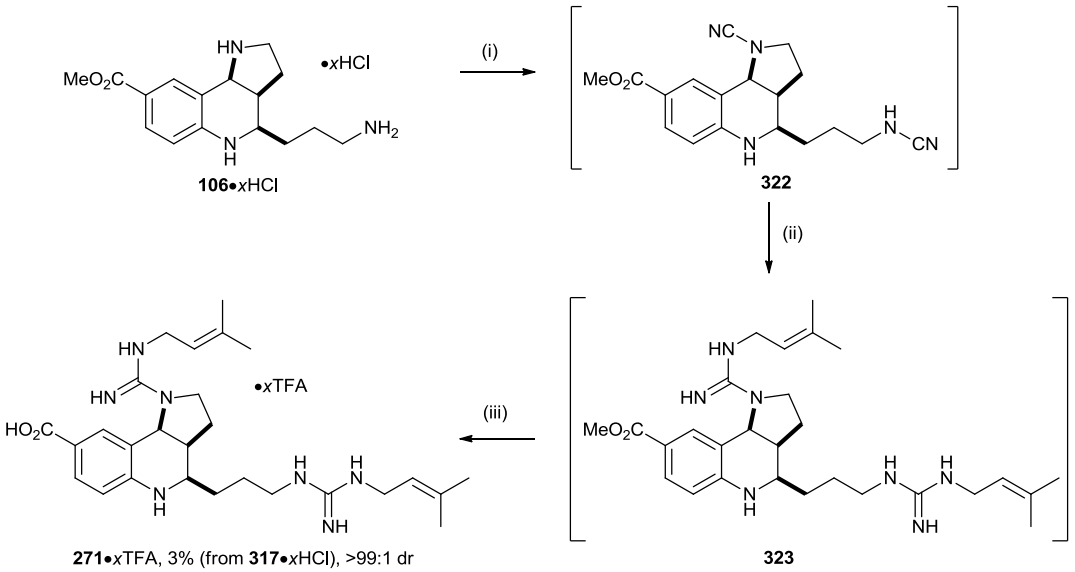
With the procedure used for the hydrolysis and *N*-Boc deprotection of **318** proving unsuccessful for the synthesis of 4-*epi*-martinellic acid **271**, an alternative guanylation and deprotection strategy was screened. Snider *et al*. reported a procedure to introduce the guanidine moieties by treatment of (±)-**22**·*x*HCl with BrCN to generate cyanamide (±)-**32**, followed by addition of prenylamine **302** to

give guanidine **33**,[35] with subsequent basic hydrolysis of the ester giving (±)-martinellic acid **8** (see Chapter 1).[23] Thus, treatment of **22**·*x*HCl with BrCN gave bis-cyanamide **32** cleanly. Treatment of **32** with prenylamine **302** in HFIP at 110 °C for 32 h according to the procedure of Snider *et al.* resulted in incomplete conversion to **33**,[36] with the mono-cyanamide remaining.[37] Extension of the reaction time to 5 days resulted in a mixture of products, including **33**.[37] Methanolysis of the crude reaction mixture was achieved upon treatment with 0.15 M NaOH at reflux in MeOH. However, purification *via* reverse phase HPLC gave (–)-martinellic acid **8** in only 6% yield and ~90% purity over 3 steps from **22**·*x*HCl (Scheme 86). Although this procedure was operationally simple and did not require the multi-step synthesis of isothiourea **23**, it proceeded in lower yield than the procedure reported by Ma *et al.*[19]



Scheme 86. *Reagents and Conditions*: (i) BrCN, $NaHCO_3$, MeOH, 0 °C, 1 h; (ii) prenylamine **302**, HFIP, 110 °C, 5 days; (iii) 0.15 M aq NaOH, MeOH, reflux, 16 h.

Under analogous conditions, treatment of (+)-**106**·*x*HCl with BrCN gave cyanamide **322** cleanly, then treatment of **322** with prenylamine **302** in HFIP at 110 °C for 5 days proceeded to give **323**, without the observation of quinoline by-products. Hydrolysis of **323** with 0.15 M aq NaOH at reflux in MeOH proceeded to give 4-*epi*-martinellic acid **271**, in this case without the formation of quinoline **319** as determined by inspection of the ^{1}H NMR spectrum of the crude reaction mixture. Purification *via* reverse phase HPLC gave 4-*epi*-martinellic acid **271**·*x*TFA, in superior yield to that obtained using the Ma procedure, in 3% yield over 3 steps from (+)-**106**·*x*HCl (Scheme 87).[38]



Scheme 87. *Reagents and Conditions*: (i) BrCN, $NaHCO_3$, MeOH, 0 °C, 1 h; (ii) prenylamine **302**, HFIP, 110 °C, 5 days; (iii) 0.15 M aq NaOH, MeOH, reflux, 16 h.

4.10. Summary

In summary, the key steps in the syntheses of (–)-martinellic acid **8** and (–)-4-*epi*-martinellic acid **271** include the conjugate addition of enantiopure lithium amide (*R*)-**232** to α,β-unsaturated ester **130**, followed by alkylation of the resultant β-amino ester. A double ring-closure then allowed access to the tricyclic scaffold in high yield. Subsequent *N*-Boc protection and reduction at C(4) to give hemiaminal **285**, followed by Wittig-Michael reaction with phosphorane **289** allowed the introduction of the C(4) substituent with total stereocontrol to give the "natural" 3a,4-*anti*-configuration within (–)-martinellic acid **8**. Alternatively, the use of phosphonate **200** gives access to the C(4)-epimer **310**. Subsequent elaboration of "Ma's intermediate" **22**·*x*HCl concluded the asymmetric synthesis of (–)-martinellic acid **8** in >99:1 dr and 1.3% overall yield in 20 steps from commercially available starting materials.[18] Elaboration of **106**·*x*HCl allowed (–)-4-*epi*-martinellic acid **271** to be synthesised for the first time in >99:1 dr and 0.07% overall yield over the 20 step procedure. This methodology should be amenable to the synthesis of analogues of (–)-martinellic acid **8** and (–)-4-*epi*-martinellic acid **271** for subsequent biological evaluation (Fig 29).

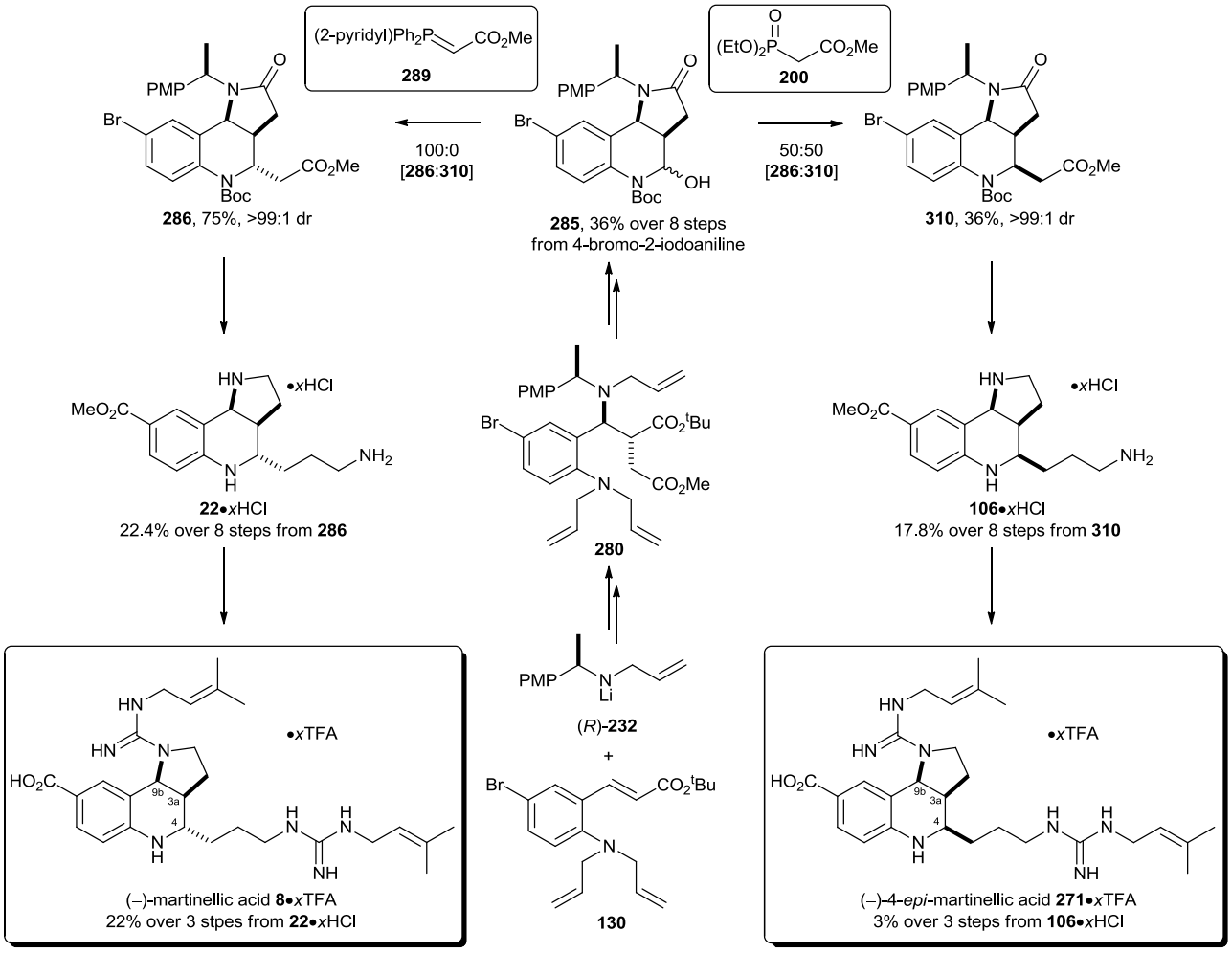


Fig 29. Diastereodivergent route to (–)-martinellic acid **8** and (–)-4-*epi*-martinellic acid **271**.

4.11. References and notes

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Chapter 5: Experimental

5.1. General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs *et al*.[1] Water was purified by an Elix® UV-10 system. BuLi was supplied as a solution in hexanes and titrated against Ph_2CHCO_2H before use. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over Na_2SO_4. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film), a KBr disc (KBr) or on a diamond ATR module (ATR), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Low-resolution mass spectra were recorded on either a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

5.2. General Procedures

General Procedure 1: Conjugate addition of lithium amides to α,β-unsaturated esters

BuLi was added dropwise to a solution of the requisite amine (1.6 equiv) in THF (0.2 M in THF) at −78 °C and the mixture was stirred at this temperature for 30 min. A solution of the requisite acceptor (0.2 M in THF) at −78 °C was added dropwise *via* cannula and the mixture was stirred at −78 °C for 2 h. The reaction was quenched by addition of satd aq NH_4Cl and was allowed to warm gradually to rt. The mixture was washed with 10% aq citric acid (× 2) and the combined aqueous layers were extracted with Et_2O. The combined organic layers were washed sequentially with satd aq $NaHCO_3$ and brine, then dried (Na_2SO_4) and concentrated *in vacuo*.

General Procedure 2: Tandem lithium amide conjugate addition with *in situ* alkylation

BuLi was added dropwise to a solution of the requisite amine (1.6 equiv) in THF (0.2 M in THF) at −78 °C and the mixture was stirred at this temperature for 30 min. A solution of the requisite acceptor (0.2 M in THF) at −78 °C was added dropwise *via* cannula and the mixture was stirred at −78 °C for 2 h. The requisite electrophile (3.0 equiv) was added slowly dropwise and the mixture was allowed to warm to rt over 16 h, then the reaction was quenched by addition of satd aq NH_4Cl. The mixture was washed with 10% aq citric acid (× 2) and the combined aqueous layers were extracted with Et_2O. The combined organic layers were washed sequentially with satd aq $NaHCO_3$ and brine, then dried (Na_2SO_4) and concentrated *in vacuo*.

General Procedure 3: Tandem lithium amide conjugate addition with *in situ* alkylation in the presence of 12-crown-4

BuLi was added dropwise to a solution of the requisite amine (1.6 equiv) in THF (0.2 M in THF) at −78 °C and the mixture was stirred at this temperature for 30 min. A solution of the requisite acceptor (0.2 M in THF) at −78 °C was added dropwise *via* cannula and the mixture was stirred at −78 °C for 2 h. 12-Crown-4 was added dropwise and the mixture was stirred for a further 30 min at −78 °C. The requisite electrophile (3.0 equiv) was added slowly dropwise and the mixture was allowed to warm to rt over 16 h, then the reaction was quenched by addition of satd aq NH_4Cl. The mixture was washed with 10% aq citric acid (× 2) and the combined aqueous layers were extracted with Et_2O. The combined organic layers were washed sequentially with satd aq $NaHCO_3$ and brine, then dried (Na_2SO_4) and concentrated *in vacuo*.

General Proceudre 4: Stepwise alkylation procedure

BuLi was added to a solution of $^{i}Pr_2NH$ (1.5 equiv) in THF (0.2 M in THF) at 0 °C. The mixture was stirred for 15 min at 0 °C then at −78 °C for 30 min. A solution of the requisite substrate (1.0 equivalent) in THF (0.2 M in THF) at −78 °C was added dropwise *via* cannula, and the resultant mixture was stirred at −78 °C for 1 h. The requisite electrophile (3.0 equiv) was added slowly dropwise and the mixture was allowed to warm to rt over 16 h, then the reaction was quenched by addition of satd aq NH_4Cl. The mixture was washed with 10% aq citric acid (× 2) and the combined aqueous layers were extracted with Et_2O. The combined organic layers were washed sequentially with satd aq $NaHCO_3$ and brine, then dried (Na_2SO_4) and concentrated *in vacuo*.

General Procedure 5: Deallylation of *N*-allyl groups

A solution of the requisite substrate [0.1 M in CH_2Cl_2] and DMBA (3.0 equivalents per allyl group) was thoroughly purged with argon *via* balloon for ~10 mins. $Pd(PPh_3)_4$ was added in one portion under a stream of argon. The resultant mixture was stirred at 35 °C in the dark for the time stated, then was concentrated *in vacuo*. The residue was dissolved in Et_2O and was washed with satd aq K_2CO_3 (× 2). The combined aqueous layers were extracted with Et_2O and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*.

General Procedure 6: Cyclisation of aniline derivatives

$PhCO_2H$ was added to a solution of the requisite aniline in the solvent stated. The resultant mixture was heated at the temperature stated for the time stated and then was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and was washed with satd aq K_2CO_3 (× 2). The combined aqueous layers were extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*.

General Procedure 7: Oxidative deprotection of amides with CAN

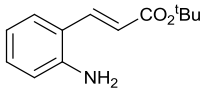
A solution of CAN (3.0 equiv) in H_2O (10 mL per mmol of substrate) was added dropwise to a solution of substrate in MeCN (10 mL per mmol of substrate) and the resultant mixture was stirred at rt for 1 h. The MeCN was then concentrated *in vacuo*. The mixture was partitioned between brine and $CHCl_3$/IPA (3:1 v/v). The mixture was washed with brine (× 2) and the combined aqueous layers were extracted with $CHCl_3$/IPA (3:1 v/v, × 5). The combined organic layers were dried ($NaSO_4$) and concentrated *in vacuo*.

General Procedure 8: Palladium catalysed methoxycarbonylation

A flask containing the requisite substrate was evacuated using a vacuum manifold and was backfilled with N_2 (× 3). The requisite phosphine ligand and palladium source were added sequentially. Degassed Et_3N then degassed MeOH were added *via* syringe. The resultant mixture was stirred and the apparatus was carefully evacuated using a vacuum manifold, then was backfilled with N_2. The process was repeated (× 2). The mixture was purged for 30 with CO *via* balloon. The apparatus was carefully evacuated using a vacuum manifold, then was backfilled with CO. The process was repeated (× 2). The resultant mixture was submerged in a preheated oil bath at 70 °C and was vigorously stirred under CO for the time stated. After this time the mixture was filtered through Celite® (eluent MeOH/Et_3N, 100:1) then was concentrated *in vacuo*.

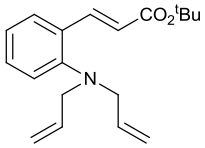
5.3. Experimental for chapter 2

tert-Butyl (*E*)-3-(2'-aminophenyl)propenoate 140



P(*o*-Tol)$_3$ (3.77 g, 12.4 mmol), Et_3N (32.0 mL), *tert*-butyl acrylate (18.4 mL, 125 mmol) and $Pd(OAc)_2$ (1.28 g, 5.70 mmol) were added sequentially to a solution of 2-iodoaniline **139** (25.0 g, 114 mmol) in degassed MeCN (250 mL) under an argon atmosphere, and the solution was stirred at 70 °C for 16 h. The mixture was allowed to cool to rt and then was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (300 mL) and was washed with H_2O (2 × 200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O 1:1) gave **140** as a yellow solid (21.5 g, 85%, >99:1 dr); mp 76-77 °C; {lit. mp 68-70 °C};[2] δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 3.97 (2H, br s, N*H*$_2$), 6.29 (1H, d, *J* 15.7, C(2)*H*), 6.70 (1H, dd, *J* 8.2, 1.0, *Ar*), 6.74-6.78 (1H, m, *Ar*), 7.14-7.18 (1H, m, *Ar*), 7.36-7.38 (1H, m, *Ar*), 7.74 (1H, d, *J* 15.7, C(3)*H*).

tert-Butyl (*E*)-3-(2'-*N*,*N*-diallylaminophenyl)propenoate 130



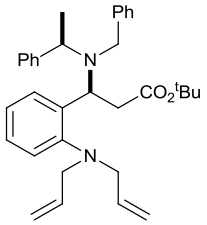
Method A: Allyl iodide (1.87 mL, 20.0 mmol) was added to a solution of K_3PO_4 (18.0 g, 84.6 mmol) and **140** (6.07 g, 27.7 mmol) in acetone (50 mL) and the mixture was heated at reflux for 48 h. The resultant solution was allowed to cool to rt then diluted with H_2O (50 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 ˚C petrol/Et_2O, 95:5) gave **130** as a yellow oil (2.00 g, 73%, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.55 (9H, s, C*Me*$_3$), 3.65 (4H, d, N(C*H*$_2$CH=CH$_2$)$_2$), 5.12-5.21 (4H, m, N(CH$_2$CH=C*H*$_2$)$_2$), 5.77-5.87 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 6.31 (1H, d, *J* 16.2, C(2)*H*), 7.00-7.05 (2H, m, *Ar*), 7.25-7.31 (1H, m, *Ar*), 7.51-7.55 (1H, m, *Ar*), 8.04 (1H, d, *J* 16.2, C(3)*H*).[2]

Method B: *Step 1*: P(*o*-Tol)$_3$ (725 mg, 2.38 mmol), Et_3N (33.1 mL, 238 mmol), *tert*-butyl acrylate (19.2 mL, 131 mmol) and $Pd(OAc)_2$ (267 mg, 1.19 mmol) were added sequentially to a solution of 2-iodoaniline (26.0 g, 119 mmol) in degassed MeCN (300 mL) under an argon atmosphere, and the solution was stirred at 70 °C for 16 h. The mixture was allowed to cool to rt and then concentrated *in*

vacuo. The residue was dissolved in CH_2Cl_2 (300 mL) and washed with H_2O (2 × 200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), and the combined organic layers were dried and concentrated *in vacuo* to give crude **140** (26.0 g) which was used without purification in the next step.

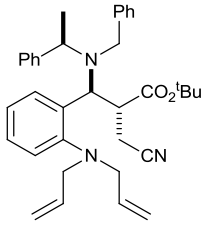
Step 2: Allyl iodide (27.0 mL, 298 mmol) was added to a solution of K_3PO_4 (76.0 g, 357 mmol) and **140** (26.0 g) in acetone (250 mL) and the mixture was heated at reflux for 48 h. The resultant solution was allowed to cool to rt then diluted with H_2O (100 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL). The combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 ˚C petrol/Et_2O, 92:8) gave **130** as a yellow oil with spectroscopic properties identical to those described above (31.6 g, 89% from **139**, >99:1 dr).

tert-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2'-*N*,*N*-diallylaminophenyl)propanoate 131



Following *General Procedure 1*, BuLi (2.25 M in hexanes, 16.9 mL, 38.0 mmol), (*R*)-**10** (8.57 g, 25.4 mmol) in THF (150 mL), **130** (7.61 g, 25.4 mmol) in THF (150 mL) at −78 °C were used according to General Procedure 1. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **131** as a yellow oil (12.6 g, 97%, >99:1 dr); $[\alpha]_D^{25}$−9.5 (*c* 1.1 in $CHCl_3$); {lit.[2] $[\alpha]_D^{23}$−8.0 (*c* 0.7 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.28 (9H, s, C*Me*$_3$), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 2.45 (1H, dd, *J* 15.5, 6.6, C(2)H_A), 2.68 (1H, dd, *J* 15.5, 7.6, C(2)H_B), 3.52 (2H, dd, *J* 14.2, 6.3, N(CH_AH$_B$CH=CH$_2$)$_2$), 3.61 (2H, dd, *J* 14.2, 6.7, N(CH$_A$$H_B$CH=CH$_2$)$_2$), 3.74 (1H, d, *J* 15.1, NCH_AH$_B$Ph), 3.86 (1H, d, *J* 15.1, NCH$_A$$H_B$Ph), 3.98 (1H, q, *J* 6.8, C(α)*H*), 5.08-5.24 (5H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$), 5.75-5.90 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 7.07-7.37 (13H, m, 2 × *Ph*, 3 × *Ar*), 7.56 (1H, d, *J* 7.3, *Ar*).

***tert*-Butyl (2*R*,3*S*,α*R*)-2-(cyanomethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2'-*N*,*N* diallylaminophenyl)propanoate 141**

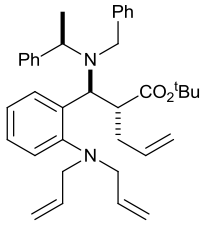


Method A: Following *General Procedure 2*, (*R*)-**10** (113 mg, 0.11 mL, 0.53 mmol) in THF (2 mL), BuLi (2.5 M in hexanes, 0.21 mL, 0.53 mmol), **130** (100 mg, 0.33 mmol) in THF (2 mL) and bromoacetonitrile (70 μL, 1 mmol) gave a 46:54 mixture of **131** and **141**, respectively.

Method B: Following *General Procedure 3*, (*R*)-**10** (660 mg, 3.13 mmol) in THF (30 mL), BuLi (2.5 M in hexanes, 1.25 mL, 3.13 mmol), **130** (1.00 g, 1.96 mmol) in THF (30 mL), 12-crown-4 (899 mg, 5.88 mmol) and bromoacetonitrile (0.50 mL, 5.88 mmol) gave a 33:69 mixture of **131** and **141**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 89:11:1) gave **141** as a yellow oil (689 mg, 64%, >99:1 dr); $[\alpha]_D^{25}$ −8.7 (*c* 1.9 in $CHCl_3$); ν_{max} (film) 2978, 2933, 2821 (C−H), 2249 (C≡N), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.6, C(α)*Me*), 1.60 (9H, s, C*Me*$_3$), 2.19 (1H, dd, *J* 16.4, 3.4, C(1′)H_A), 2.38 (1H, dd, *J* 16.4, 11.5, C(1′)H_B), 3.40 (1H, td, *J* 11.5, 3.4, C(2)*H*), 3.52-3.68 (5H, m, NCH_AH$_B$Ph, N(CH_2CH=CH$_2$)$_2$), 3.84 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.19 (1H, q, *J* 6.6, C(α)*H*), 5.13-5.25 (5H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$, 5.77-5.90 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 7.07-7.39 (14H, m, *Ph* × 2, *Ar* × 4); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 19.1 (*C*(1′)), 28.2 (C*Me*$_3$), 46.9 (*C*(2)), 51.6 (N*C*H$_2$Ph), 57.5 (N(*C*H$_2$CH=CH$_2$)$_2$), 57.7, 57.8 (*C*(3), *C*(α)), 82.4 (*C*Me$_3$), 117.7 (*C*(2′)), 118.8 (N(CH$_2$CH=*C*H$_2$)$_2$), 124.6, 125.2, 126.3, 126.5, 127.6, 128.3, 128.4, 128.8, 129.2, 133.6, 134.0, 140.9, 143.9, 151.5 (*Ar*, *Ph*, N(CH$_2$*C*H=CH$_2$)$_2$), 172.1 (*C*(1));[3] *m*/*z* (ESI$^+$) 572 ([M+Na]$^+$, 100%), 550 ([M+H]$^+$, 25%); HRMS (ESI$^+$) $C_{36}H_{43}N_3NaO_2^+$ ([M+Na]$^+$) requires 572.3247; found 572.3240.

Method C: Following *General Procdure 4*, ^{i}Pr$_2$NH (0.43 mL, 3.09 mmol) in THF (10 mL), BuLi (2.3 M in hexanes, 1.34 mL, 3.09 mmol), **131** (1.05 g, 2.06 mmol) in THF (10 mL) and bromoacetonitrile (0.43 mL, 6.18 mmol) gave a 23:77 mixture of **131** and **141**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 89:11:1) gave **131** as a colourless oil (238 mg, 23%, >99:1 dr) with spectroscopic properties identical to thos described above. Further elution gave **141** as a yellow oil (765 mg, 67%, >99:1 dr) with spectroscopic properties identical to those described above.

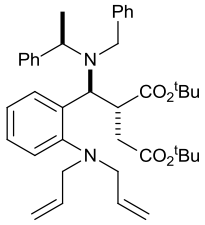
***tert*-Butyl (2*R*,3*S*,α*R*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2'-*N*,*N*-diallylaminophenyl)propanoate 142**



Method A: Following *General Procedure 2*, (*R*)-**10** (113 mg, 0.54 mmol) in THF (2.0 mL), BuLi (2.5 M in hexanes, 0.22 mL, 0.54 mmol), **130** (100 mg, 0.33 mmol) in THF (2.0 mL) and allyl iodide (90 μL, 1.00 mmol) gave a 32:68 mixture of **131** and **142**, respectively.

Method B: Following *General Procedure 3*, (*R*)-**10** (1.10 mL, 5.28 mmol) in THF (20 mL), BuLi (2.5 M in hexanes, 2.12 mL, 5.28 mmol), **130** (1.00 g, 3.30 mmol) in THF (20 mL), 12-crown-4 (1.60 mL, 10.0 mmol) and allyl iodide (0.91 mL, 10.0 mmol) gave a 29:71 mixture of **131** and **142**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 30:1) gave **142** as a colourless oil (342 mg, 19%, >99:1 dr); $C_{37}H_{46}N_2O_2$ requires C, 80.7; H, 8.4; N, 5.1%; found C, 80.7; H, 8.5; N, 5.0%; $[\alpha]_D^{21}$ −16.3 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 3063, 3026, 2977, 2932 (C−H), 1727 (C=O), 1641, 1595 (C=C); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.6, C(α)*Me*), 1.57 (9H, s, C*Me*$_3$), 1.99-2.08 (1H, m, C(1')*H*$_A$), 2.08-2.19 (1H, m, C(1')*H*$_B$), 3.20 (1H, td, *J* 11.6, 3.3, C(2)*H*), 3.42 (1H, d, *J* 14.4, NC*H*$_A$H$_B$Ph), 3.61 (2H, dd, *J* 14.3, 5.9, N(C*H*$_A$H$_B$CH=CH$_2$)$_2$), 3.75 (2H, dd, *J* 14.3, 7.5, N(CH$_A$*H*$_B$CH=CH$_2$)$_2$), 3.93 (1H, d, *J* 14.4, NCH$_A$*H*$_B$Ph), 4.24 (1H, q, *J* 6.6, C(α)*H*), 4.93-5.03 (1H, m, NCH$_2$C*H*=CH$_2$), 5.13-5.26 (5H, m, C(3)*H*, N(CH$_2$CH=C*H*$_2$)$_2$), 5.66-5.79 (1H, m, C(2)CH$_2$C*H*=CH$_2$), 5.80-5.93 (2H, m, C(2)CH$_2$CH=C*H*$_2$), 6.95-7.49 (14H, m, 2 × *Ph*, 4 × *Ar*); δ_C (100 MHz, $CDCl_3$) 18.1 (C(α)*Me*), 28.4 (C*Me*$_3$), 36.0 (C(1')), 50.0 (*C*(2)), 51.3 (N*C*H$_2$), 57.0 (2 × N*C*H$_2$CH=CH$_2$), 57.7 (C(α)), 58.4 (*C*(3)), 80.7 (*C*Me$_3$), 116.5, 118.3 (NCH$_2$CH=C*H*$_2$, N(CH$_2$CH=C*H*$_2$)$_2$), 123.9, 124.3, 125.8, 126.1, 127.2, 127.2, 127.4, 128.7, 128.9, 129.4, 134.3, 134.4, 135.6, 141.6, 144.0, 151.5 (NCH$_2$*C*H=CH$_2$, N(CH$_2$*C*H=CH$_2$)$_2$, *Ar*), 174.3 (*C*(1)); *m*/*z* (ESI$^+$) 573 ([M+Na]$^+$, 30%), 551 ([M+H]$^+$, 55%); HRMS (ESI$^+$) $C_{37}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 551.3632; found 551.3627. Further elution gave a 33:67 mixture of **131** and **142** (820 mg), respectively.

***tert*-Butyl (2*R*,3*S*,α*R*)-2-(2'-*tert*-butoxy-2'-oxoethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2''-*N*,*N*-diallylaminophenyl)propanoate 143**

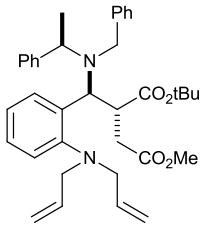


Method A: Following *General Procedure 2*, (*R*)-**10** (113 mg, 0.11 mL, 0.53 mmol) in THF (2 mL), BuLi (2.5 M in hexanes, 0.21 mL, 0.53 mmol), **130** (100 mg, 0.33 mmol) in THF (2 mL) and *tert*-butylbromoacetate (100 μL, 1.0 mmol) gave a 100:0 mixture of **131** and **143**, respectively.

Method B: Following *General Procedure 3*, (*R*)-**10** (1.13 g, 5.30 mmol) in THF (15 mL), BuLi (2.5 M in hexanes, 2.14 mL, 5.34 mmol), **130** (1.00 g, 3.34 mmol) in THF (15 mL), 12-Crown-4 (1.60 mL, 10.0 mmol) and *tert*-butylbromoacetate (1.95 g, 10.0 mmol) gave a 30:70 mixture of **131** and **143**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1) gave firstly **131** as a colourless oil (836 mg, 30% >99:1 dr). Further elution gave **143** as a colourless oil (1.54 g, 64%, >99:1 dr); $C_{40}H_{52}N_2O_4$ requires C, 76.9; H, 8.4; N, 4.5%; found C, 76.7; H, 8.4; N, 4.4%; $[\alpha]_D^{25}$ −9.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3004, 2977, 2933 (C−H), 1731 (C=O), 1642, 1596 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.6, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 2.13 (1H, dd, *J* 15.4, 2.8, C(1')H_A), 2.37 (1H, dd, *J* 15.4, 11.4, C(1')H_B), 3.44-3.69 (6H, m, C(2)*H*, N(CH_2CH=CH_2)$_2$, NC$H_A$$H_B$Ph), 3.92 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.23 (1H, q, *J* 6.6, C(α)*H*), 5.08-5.22 (5H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$), 5.71-5.86 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 6.95-7.42 (14H, m, 2 × *Ph,* 4 × *Ar*); δ_C (100 MHz, $CDCl_3$) 18.2 (C(α)*Me*), 28.0, 28.1 (2 × C*Me*$_3$), 37.4 (*C*(1')), 46.4 (*C*(2)), 51.2 (N*C*H$_2$Ph), 57.0 (N(*C*H$_2$CH=CH$_2$)$_2$), 57.6 (*C*(α)), 58.1 (*C*(3)), 80.8, 80.5 (2 × *C*Me$_3$), 118.3 (N(CH$_2$CH=*C*H$_2$)$_2$), 124.1, 124.4, 125.8, 126.1, 127.3, 127.3 127.6, 128.5, 128.7, 129.5 (*Ar*, N(CH$_2$*C*H=CH$_2$)$_2$), 134.2, 134.3, 141.5, 143.9, 151.4 (*Ph*, *Ar*), 171.0, 173.9 (*C*(1), *C*(2')); *m*/*z* (ESI$^+$) 647 ([M+Na]$^+$, 100%), 625 ([M+H]$^+$, 73%); HRMS (ESI$^+$) $C_{40}H_{53}N_2O_4^+$ ([M+H]$^+$) requires 625.4000; found 625.3999.

Method C: Following *General Procedure 4*, ^{i}Pr$_2$NH (4.25 g, 20.2 mmol) in THF (150 mL), BuLi (1.6 M in hexanes, 18.3 mL, 29.3 mmol), **131** (10.3 g, 20.2 mmol) in THF (150 mL) and *tert*-butylbromoactete (9.85 g, 50.5 mmol) gave **143**. The crude product was passed through a short pad of silica (eluent 30-40 °C petrol/Et_2O, 5:1) to give **143** as a yellow oil with spectroscopic properties identical to those reported above (16.3 g, >99:1 dr, quant).

***tert*-Butyl (2*R*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(2'-*N*,*N*-diallylaminophenyl)propanoate 144**

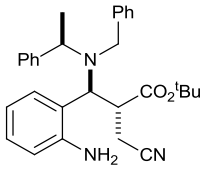


Method A: Following *General Procedure 2*, (*R*)-**10** (113 mg, 0.11 mL, 0.53 mmol) in THF (2.0 mL), BuLi (2.5 M in hexanes, 0.21 mL, 0.53 mmol), **130** (100 mg, 0.33 mmol) in THF (2.0 mL) and methyl bromoacetate (95 μL, 1 mmol) gave a 100:0 mixture of **131** and **144**, respectively.

Method B: Following *General Procedure 3*, (*R*)-**10** (1.03 g, 5.34 mmol) in THF (15 mL), BuLi (2.1 M in hexanes, 2.50 mL, 5.34 mmol), **130** (1.03 g, 3.34 mmol) in THF (15 mL), 12-crown-4 (1.76 g, 10.0 mmol) and methyl bromoacetate (1.53 g, 10.0 mmol) gave a 64:36 mixture of **131** and **144**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave **131** as a colourless oil (880 mg, 51%, >99:1 dr). Further elution gave **144** as a colourless oil (710 mg, 36%, >99:1 dr); $C_{37}H_{46}N_2O_4$ requires C, 76.3; H, 8.0; N, 4.8; found C, 76.3; H, 8.1; N, 4.8%; $[\alpha]_D^{25}$ −16.2 (*c* 2.0 in $CHCl_3$); ν_{max} (film) 3062, 3027, 2977 (C−H); 1741 (C=O); 1666, 1642, 1597, 1485 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.6, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 2.21 (1H, dd, *J* 15.4, 2.8, C(1')H_A), 2.46 (1H, dd, *J* 15.4, 11.5, C(1')H_B), 3.45-3.68 (9H, m, C(2)*H*, O*Me*, N(CH_2CH=CH_2)$_2$, NC$H_A$$H_B$Ph), 3.93 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.22 (1H, q, *J* 6.6, C(α)*H*), 5.10-5.20 (5H, m, C(3)*H*, N(CH_2CH=CH_2)$_2$), 5.72-5.85 (2H, m, N(CH_2C*H*=CH_2)$_2$), 6.96-7.41 (14H, m, *Ph* × 2, *Ar* × 4); δ_C (100 MHz, $CDCl_3$) 17.8 (C(α)*Me*), 28.1 (C*Me*$_3$), 36.0 (*C*(1')), 46.3 (*C*(2)), 51.3 (N*C*H_2Ph), 51.6 (O*Me*), 57.0 (N(*C*H_2CH=CH_2)$_2$), 57.4 (*C*(α)), 58.0 (*C*(3)), 80.9 (*C*Me$_3$), 118.4 (N(CH_2CH=*C*H_2)$_2$), 124.2, 124.5, 125.9, 126.2, 127.3, 127.4, 127.7, 128.5, 128.7, 129.4, 134.1, 134.2 (*Ar*, *Ph*, N(CH_2*C*H=CH_2)$_2$), 141.4, 143.8, 151.4 (*Ar*, *i-Ph*), 172.1, 173.5 (*C*(1), *C*(2')); *m*/*z* (ESI$^+$) 605 ([M+Na]$^+$, 100%), 583 ([M+H]$^+$, 99%); HRMS (ESI$^+$) $C_{37}H_{47}N_2O_4^+$ ([M+H]$^+$) requires 583.3530; found 583.3532.

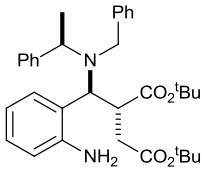
Method C: Following *General Procedure 4*, ^{i}Pr$_2$NH (0.44 mL, 3.14 mmol) in THF (10 mL), BuLi (2.3 M in hexanes, 1.37 mL, 3.14 mmol), **131** (1.07 g, 2.09 mmol) in THF (10 mL) and methyl bromoacetate (0.59 mL, 6.27 mmol) gave a 5:>95 mixture of **131** and **144**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 89:11:1) gave **144** as a yellow oil with spectroscopic properties identical to those reported above (1.00 g, 82%, >99:1 dr).

tert-Butyl (2*R*,3*S*,α*R*)-2-cyanomethyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2'-aminophenyl)propanoate 147



Following *General Procedure 5*, **141** (371 mg, 0.67 mmol) in CH_2Cl_2 (10 mL), DMBA (627 mg, 4.02 mmol) and $Pd(PPh_3)_4$ (23 mg, 20.2 μmol), with additional $Pd(PPh_3)_4$ (23 mg, 20.2 μmol) added after 16 h, gave **147** in >99:1 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 75:25:1→50:50:1) gave **147** as a white foam (169 mg, 54%, >99:1 dr); $[\alpha]_D^{25}$+21.7 (*c* 1.8 in $CHCl_3$); ν_{max} (film) 3443, 3374 (N−H), 2977, 2935 (C−H), 2248 (C≡N), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.8, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 2.14 (1H, dd, *J* 16.4, 3.3, C(1′)H_A), 2.26 (1H, dd, *J* 16.4, 11.1, C(1′)H_B), 3.31-3.38 (1H, m, C(2)*H*), 3.63 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 4.03-4.24 (4H, m, C(α)*H*, NCH$_A$$H_BPh, NH_2$), 4.40 (1H, d, *J* 6.8, C(3)*H*), 6.65 (1H, d, *J* 7.8, *Ar*), 6.76 (1H, t, *J* 7.5, *Ar*), 7.08-7.46 (12H, 2 × *Ph*, 2 × *Ar*); δ_C (100 MHz, $CDCl_3$) 11.3 (C(α)*Me*), 17.0 (*C*(1′)), 27.9 (C*Me*$_3$), 47.2 (*C*(2)), 51.6 (N*C*H$_2$), 57.0 (*C*(α)), 62.0 (*C*(3)), 82.8 (*C*Me$_3$), 117.1, 118.4 (*Ar*), 118.4 (*C*N), 121.8, 127.1, 127.2, 128.2, 128.3, 128.4, 128.6, 128.9, 129.8, 140.7, 143.5, 145.6 (*Ar*, *Ph*), 171.0 (*C*(1)); *m*/*z* (ESI$^+$) 961 ([2M+Na]$^+$, 53%), 492 ([M+Na]$^+$, 30%), 470 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}N_3NaO_2^+$ ([M+Na]$^+$) requires 492.2621; found 492.2622.

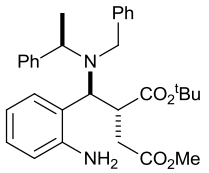
tert-Butyl (2*R*,3*S*,α*R*)-2-(2'-_tert_-butoxy-2'-oxoethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2''-aminophenyl)propanoate 148



Following *General Procedure 5*, **143** (1.59 g, 2.54 mmol), DMBA (1.23 g, 7.87 mmol) and $Pd(PPh_3)_4$ (147 mg, 0.13 mmol) in CH_2Cl_2 (50 mL) gave **148** in >99:1 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/ Et_2O, 5:1) gave **148** as a yellow oil (1.02 g, 74%, >99:1 dr); $[\alpha]_D^{25}$+11.7 (*c* 0.92 in $CHCl_3$); ν_{max} (film) 2977 (C−H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24-1.32 (12H, m, C(α)*Me*, C*Me*$_3$), 1.34 (9H, s, C*Me*$_3$), 2.03 (1H, dd, *J* 17.2, 2.8, C(1')H_A), 2.31 (1H, dd, *J* 17.2, 11.6, C(1')H_B), 3.37-3.47 (1H, m, C(2)*H*), 3.63 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 4.02-4.18 (2H, br s, NH_2), 4.15-4.23 (2H, m, NCH$_A$$H_B$Ph, C(α)*H*), 4.37 (1H, d, *J* 6.3, C(3)*H*), 6.62 (1H, d, *J* 7.8, *Ar*), 6.71 (1H, t, *J* 7.5, *Ar*), 7.06 (1H, t, *J* 7.5, *Ar*), 7.09-7.37 (9H, m, *Ph*, *Ar*), 7.47 (2H, d, *J* 7.6, *o*-*Ph*); δ_C (100 MHz, $CDCl_3$) 11.4 (C(α)*Me*), 27.8, 28.0 (2 × C*Me*$_3$), 33.5 (*C*(1')), 46.4 (*C*(2)), 51.9

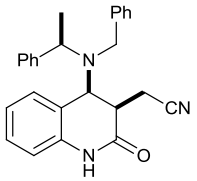
(N*C*H$_2$Ph), 57.0 (*C*(α), *C*(3)), 79.7, 80.9 (2 × *C*Me$_3$), 116.7, 118.0, 126.6, 126.9, 128.1, 128.1, 128.1, 128.2, 128.5, 130.1, 141.5, 141.5, 144.1, 145.5 (*Ar*), 171.1, 171.4 (*C*(1), *C*(2')); *m*/*z* (ESI$^+$) 567 ([M+Na]$^+$, 100%), 545 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{44}N_2NaO_4^+$ ([M+Na]$^+$) requires 567.3193; found 567.3187.

tert-Butyl (2*R*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl-)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(2''-aminophenyl)propanoate 149



Following General Procedure 5, **144** (528 mg, 0.91 mmol), DMBA (848 mg, 5.43 mmol), Pd(PPh$_3$)$_4$ (31 mg, 27.0 μmol) in CH$_2$Cl$_2$ (10 mL) gave **149** in >99:1 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et$_2$O/Et$_3$N, 66:34:1) gave firstly **150** as a white solid (98 mg, 92%); mp 45-48 °C; δ_H (400 MHz, CDCl$_3$) 2.65 (4H, d, *J* 7.3, CH$_2$CH=C*H*$_2$ × 2), 3.21 (6H, s, 2 × N*Me*), 4.95-5.09 (4H, m, CH$_2$CH=C*H*$_2$ × 2), 5.37-5.51 (2H, m, CH$_2$C*H*=CH$_2$ × 2). Further elution gave **149** as a white solid (310 mg, 68%, >99:1 dr); mp 147-150 °C; $[\alpha]_D^{25}$+11.7 (*c* 1.3 in CHCl$_3$); ν_{max} (film) 3061, 3027 (N–H), 2975, 2949 (C−H), 1736 (C=O); δ_H (400 MHz, CDCl$_3$) 1.30 (3H, d, *J* 6.8, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 2.18 (1H, dd, *J* 17.1, 2.7, *C*(1')*H*$_A$), 2.40 (1H, dd, *J* 17.1, 11.2, (*C*(1')*H*$_B$), 3.42 (3H, s, O*Me*), 3.41-3.50 (1H, m, C(2)*H*), 3.65 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 4.02-4.23 (2H, br s, N*H*$_2$), 4.14-4.25 (2H, m, C(α)*H*, NCH$_A$*H*$_B$Ph), 4.40 (1H, d, *J* 6.3, C(3)*H*), 6.62 (1H, d, *J* 8.1, *Ar*), 6.71 (1H, t, *J* 7.3, *Ar*), 7.06 (1H, t, *J* 7.3, *Ar*), 7.11-7.49 (11H, m, 2 × *Ph*, *Ar*); δ_C (100 MHz, CDCl$_3$) 11.5 (C(α)*Me*), 27.8, (C*Me*$_3$), 32.5 (*C*(1')), 46.4 (*C*(2)), 51.2 (O*Me*), 51.9 (N*C*H$_2$Ph), 57.0 (*C*(α)), 60.3 (*C*(3)), 81.2 (*C*Me$_3$), 116.8, 118.0, 123.1, 126.5, 126.9, 128.1, 128.1, 128.3, 128.3, 128.5, 129.9, 141.4, 144.0, 145.5 (*Ar*, *Ph*), 172.4, 172.8 (*C*(1), *C*(2')); *m*/*z* (ESI$^+$) 525 ([M+Na]$^+$, 100%), 503 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{38}N_2NaO_4^+$ ([M+Na]$^+$) requires 525.2724; found 525.2723.

(3*R*,4*S*,α*R*)-3-(Cyanomethyl)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,4-dihydro-1*H*-quinolin-2-one 151



Method A: Following *General Procedure 6*, **147** (1.60 g, 3.40 mmol) and $PhCO_2H$ (1.24 g, 10.2 mmol) in THF (30 mL) at 50 °C for 16 h gave a 65:35 mixture of **147** and **151**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 50:50:1→25:75:1) gave **147** as a colourless foam (580 mg, 36%, >99:1 dr). Further elution gave **151** as a white solid (387 mg, 29%, >99:1 dr); mp 158-163 °C; $[\alpha]_D^{25}$ −28.4 (*c* 2.5 in $CHCl_3$); ν_{max} (film) 3061, 3027, 2977, 2933 (C−H), 2247 (C≡N), 1680 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.8, C(α)*Me*), 2.35 (1H, dd, *J* 16.9, 6.8, C(1')H_A), 2.68-2.97 (1H, m, C(3)*H*), 3.14 (1H, dd, *J* 16.9, 6.8, C(1')H_B), 3.64 (1H, d, *J* 14.0, NCH_A), 3.71 (1H, d, *J* 14.0, NCH_B), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.20 (1H, d, *J* 6.6, C(4)*H*), 6.99 (1H, d, *J* 7.8, *Ar*), 7.10-7.43 (13H, m, 2 × *Ph*, 3 × *Ar*), 9.65 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*(1')), 14.8 (C(α)*Me*), 43.0 (*C*(3)), 50.2 (N*C*H_2), 55.6 (*C*(4)), 56.9 (*C*(α)), 116.8 (*Ar*), 119.5, 122.7, 123.5, 127.3, 127.5, 127.7, 128.6, 128.6, 129.2, 129.4, 129.5, 137.2, 139.2, 143.5 (*Ar*, *Ph*, *C*(2')), 170.2 (*C*(2)); *m*/*z* (ESI^+) 813 ($[2M+Na]^+$, 84%), 418 ($[M+Na]^+$, 49%), 396 ($[M+H]^+$, 10%); HRMS (ESI^+) $C_{26}H_{25}N_3NaO^+$ ($[M+Na]^+$) requires 418.1890; found 418.1887.

Method B: Following *General Procedure 6*, **147** (44.2 mg, 94.0 μmol) and $PhCO_2H$ (34 mg, 0.28 mmol) in CH_2Cl_2 (1.50 mL) at rt for 16 h gave an 87:13 mixture of **147** and **151**, respectively.

Method C: Following *General Procedure 6*, **147** (352 mg, 0.75 mmol) and $PhCO_2H$ (275 mg, 2.25 mmol) in THF (7.5 mL) at 50 °C for 16 h gave a 65:35 mixture of **147** and **151**, respectively.

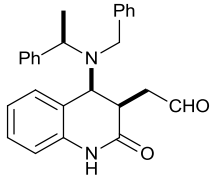
Method D: Following *General Procedure 6*, **147** (352 mg, 0.75 mmol) and $PhCO_2H$ (275 mg, 2.25 mmol) in THF (7.5 mL) at 50 °C for 48 h gave an 18:82 mixture of **147** and **151**, respectively.

Method E: Following *General Procedure 6*, **147** (580 mg, 1.23 mmol) and $PhCO_2H$ (452 mg, 3.70 mmol) in THF (7.5 mL) at 50 °C for 72 h gave a 0:100 mixture of **147** and **151**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 50:50:1→25:75:1) gave **151** as a white solid (488 mg, quant., >99:1 dr) with spectroscopic properties identical to those reported above.

Method F: $PhCO_2H$ (2 mg, 17 μmol) was added to a solution of **147** (82 mg, 0.17 mmol) in PhMe (10 mL). The mixture was heated at reflux for 16 h and then was concentrated *in vacuo*. Purification *via*

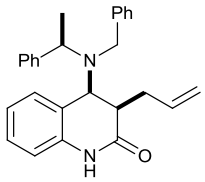
flash column chromatography (eluent 30-40 ˚C petrol/EtOAc/Et_3N, 66:34:1) gave **151** as a white solid with spectroscopic properties identical to those reported above (54 mg, 80%, >99:1 dr).

(3*R*,4*S*,α*R*)-3-(2'-Oxoethyl)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,4-dihydro-1*H*-quinolin-2-one 152



DIBAL-H (1.0 M in CH_2Cl_2, 0.62 mL, 0.62 mmol) was added to a stirred solution of **151** (81.4 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C and the mixture was stirred at this temperature for 2 h. Satd aq Rochelle′s salt (5 mL) was added and the mixture stirred vigorously at rt for 5 min. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic extracts dried and concentrated *in vacuo*. The crude product was passed through a short plug of silica (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:50:1) to give **152** as a yellow oil (63 mg, 76%, >99:1 dr); $[\alpha]_D^{25}$ −78.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3061 (C−H), 1721 [C=O (aldehyde)], 1673 [C=O (lactam)]; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.8, C(α)*Me*), 2.59-2.69 (1H, m, C(1')H_A), 3.26-3.37 (2H, m, C(1')H_B, C(3)*H*), 3.59 (1H, d, *J* 13.8 NCH_A), 3.73 (1H, d, *J* 13.8, NCH_B), 4.00-4.08 (2H, m, C(4)*H*, C(α)*H*), 6.93 (1H, d, *J* 8.1, *Ar*), 7.00-7.17 (3H, m, *Ar*), 7.18-7.40 (10H, m, 2 × *Ph*), 9.48 (1H, s, C*H*O), 9.52 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 39.5 (*C*(1')), 39.6 (*C*(3)), 50.3 (N*C*H_2), 55.5, 56.1 (*C*(α), *C*(4)), 116.5, 123.1, 123.7, 126.9, 127.2, 127.9, 128.3, 128.4, 129.0, 129.3, 129.5, 137.5, 139.6, 144.0 (*Ar*, *Ph*), 172.4 (*C*(2)), 200.2 (*C*(2')); *m*/*z* (ESI^+) 777 ($[2M+Na]^+$, 100%), 421 ($[M+Na]^+$, 40%), 399 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{26}N_2NaO_2^+$ ($[M+Na]^+$) requires 421.1886; found 421.1883.

(3*R*,4*S*,α*R*)-3-Allyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,4-dihydro-1*H*-quinolin-2-one 157

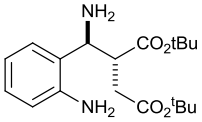


Step 1: Following *General Procedure 4*, $^iPr_2NH$ (0.55 mL, 3.94 mmol) in THF (13 mL), BuLi (2.5 M in hexanes, 1.58 mL, 3.94 mmol), **131** (1.21 g, 2.63 mmol) in THF (13 mL) and allyl iodide (0.72 mL, 7.89 mmol) gave a 25:75 mixture of **131** and **142**, respectively. The product was passed through a short pad of silica (eluent 30-40 °C petrol/Et_2O/Et_3N, 50:50:1) to give the mixture as a yellow oil (1.06 g) which was used without further purification.

Step 2: Following *General Procedure 5*, the crude material from the previous step (1.06 g), DMBA (900 mg, 5.76 mmol) and $Pd(PPh_3)_4$ (336 mg, 0.29 mmol) in CH_2Cl_2 (20 mL) gave a 75:25 mixture of **155** and **156** (915 mg), respectively, which was used in the next step without purification.

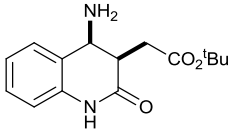
Step 3: Following *General Procedure 6*, the crude mixture from the previous step (915 mg) and $PhCO_2H$ (23.0 mg, 0.19 mmol) in PhMe (10 mL) at reflux for 16 h gave the crude product. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 50:50:1) gave **157** as a yellow oil (257 mg, 25% over 3 steps from **131**, >99:1 dr); $[\alpha]_D^{25}$ −51.0 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3062, 2979 (C−H), 1673 [C=O (δ lactam)]; δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.8, C(α)*Me*), 2.38-2.49 (1H, m, C(1')H_A), 2.57-2.67 (1H, m, C(3)*H*), 2.99-3.10 (1H, m, C(1')H_B), 3.68 (2H, s, NCH_2), 4.09 (1H, d, *J* 6.3, C(4)*H*), 4.21 (1H, q, *J* 6.8, C(α)*H*), 4.88-5.05 (2H, m, CH=CH_2), 5.68-5.80 (1H, m, C*H*=CH_2), 6.91 (1H, d, *J* 7.8, *Ar*), 7.07 (1H, t, *J* 7.8, *Ar*), 7.19-7.50 (12H, m, *Ar*, *Ph*), 9.18 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.5 (C(α)*Me*), 29.2 (*C*(1')), 45.8 (*C*(3)), 49.6 (N*C*H_2), 55.8 (*C*(4)), 56.2 (*C*(α)), 116.4 (CH=*C*H_2), 116.7, 118.1, 124.4, 126.7, 126.7, 127.9, 128.0, 128.0, 128.3, 128.6, 129.1, 135.4, 141.2, 144.1, 145.6 (*Ar*, *Ph*), 174.0 (*C*(2)); *m*/*z* (ESI^+) 815 ($[2M+Na]^+$, 100%), 419 ($[M+Na]^+$, 50%); HRMS (ESI^+) $C_{27}H_{28}N_2NaO^+$ ($[M+Na]^+$) requires 419.2094; found 419.2092.

tert-Butyl (2*R*,3*S*)-2-(2'-_tert_-butoxy-2'-oxoethyl)-3-amino-3-(2''-aminophenyl)propanoate 160



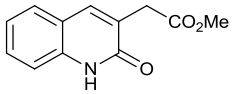
$Pd(OH)_2$/C (100 mg) was added to a solution of **148** (200 mg, 0.36 mmol) in MeOH (15 mL) and the resultant mixture was vigorously stirred under H_2 (4 atm) for 16 h. The resultant suspension was passed through a pad of Celite® (eluent MeOH/Et_3N, 100 mL) and the filtrate was concentrated *in vacuo* to give **160** as a colourless oil (120 mg, quant); $[\alpha]_D^{25}$+1.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3429, 3383, 3311 (N−H), 2978, 2932 (C−H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 1.48 (9H, s, C*Me*$_3$), 1.69-1.87 (2H, br s, NH_2), 2.25 (1H, dd, *J* 16.9, 5.3, C(1')H_A), 2.31 (1H, dd, *J* 16.9, 8.2, C(1')H_B), 3.27-3.35 (1H, m, C(2)*H*), 4.23 (1H, d, *J* 9.4, C(3)*H*), 4.76-4.86 (2H, m, ArNH_2), 4.76-4.86 (2H, m, *Ar*), 6.95-7.00 (1H, m, *Ar*), 7.04-7.09 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 28.0, 28.1 (2 × C*Me*$_3$), 35.9 (*C*(1')), 45.4 (*C*(2)), 57.4 (*C*(3)), 80.1, 80.5 (2 × *C*Me$_3$), 116.7, 117.5, 125.2, 128.5, 129.7, 146.3 (*Ar*), 171.1, 173.7 (*C*(1), *C*(2')); *m*/*z* (ESI^+) 351 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{31}N_2O_4^+$ ($[M+H]^+$) requires 351.2278; found 351.2277.

(3*R*,4*S*)-3-(2'-*tert*-Butoxy-2'-oxoethyl)-4-amino-3,4-dihydro-1*H*-quinolin-2-one 161



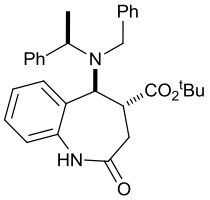
Attempted purification of a portion of **160** (231 mg, 0.66 mmol) on silica (eluent EtOAc:Et_3N, 100:1) gave firstly **160** along with other unknown contaminants (9 mg). Further elution gave **161** as a white solid (74 mg, 41%); mp 144-146 °C; $[\alpha]_D^{25}$ −16.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3029 (N−H), 2778, 2929 (C−H), 1725 [C=O (ester)], 1680 [C=O (δ lactam)]; δ_H (400 MHz, $CDCl_3$) 1.31 (2H, br s, NH_2), 1.49 (9H, s, CMe_3), 2.55 (1H, dd, *J* 16.4, 7.7, C(1')H_A), 3.06 (1H, dd, *J* 16.4, 6.5, C(1')H_B), 3.19-3.26 (1H, m, C(3)*H*), 4.09 (1H, d, *J* 4.1, C(4)*H*), 6.86 (1H, d, *J* 7.9, *Ar*), 7.02 (1H, t, *J* 7.5, *Ar*), 7.19-7.25 (2H, m, *Ar*), 9.22 (1H, d, N*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 32.0 (C(1')), 43.2 (*C*(3)), 51.3 (*C*(4)), 80.8 (*C*Me_3), 116.0, 123.4, 126.7, 128.1 , 128.7, 136.1 (*Ar*), 171.4, 171.7 (*C*(2), *C*(2')); *m/z* (ESI^+) 575 ($[2M+Na]^+$, 100%), 299 ($[M+Na]^+$, 62%), 277 ($[M+H]^+$, 84%); HRMS (ESI^+) $C_{15}H_{20}N_2NaO_3^+$ ($[M+Na]^+$) requires 299.1366; found 299.1366.

3-(2'-Methoxy-2'-oxoethyl)-1*H*-quinolin-2-one 162



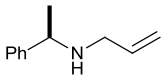
A solution of **161** (84 mg, 0.30 mmol) in MeOH (4 mL) and HCl (2.0 M in Et_2O, 4 mL) was heated at reflux for 1 h. The mixture was cooled to rt and concentrated *in vacuo*. The product was dissolved in CH_2Cl_2 (5 mL) and washed with satd aq $NaHCO_3$ (5 mL). The organic layer was dried and concentrated *in vacuo* to give **162** as a white solid (56 mg, 84%); mp 176-178 °C; ν_{max} (film) 2952, 2857 (C−H), 1736 [C=O (ester)], 1665 [C=O (quinolinone)]; δ_H (400 MHz, $CDCl_3$) 3.73 (2H, s, *C*(1')H_2), 3.75 (3H, s, O*Me*), 7.17-7.22 (1H, m, *Ar*), 7.38-7.57 (3H, m, *Ar*), 7.78 (1H, s, *Ar*), 12.52 (1H, br s, N*H*); δ_C (400 MHz, $CDCl_3$) 35.7 (*C*(1')), 52.2 (O*Me*), 116.0, 119.9, 122.6, 126.5, 127.5, 130.2, 138.1, 139.4 (*Ar*), 163.9 (*C*(2)), 171.5 (*C*(2')); *m/z* (ESI^+) 457 ($[2M+Na]^+$, 100%), 240 ($[M+Na]^+$, 75%); HRMS (ESI^+) $C_{12}H_{11}NNaO_3^+$ ($[M+Na]^+$) requires 240.0631; found 240.0630.

tert-Butyl (4*R*,5*S*,α*R*)-2-Oxo-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-2,3,4,5-tetrahydro-1*H*-benzo[b]azepine-4-carboxylate 163



$PhCO_2H$ (2 mg, 18.0 μmol) was added to a solution of **149** (90.4 mg, 0.18 mmol) in PhMe (2 mL) and the resultant solution was heated at reflux for 16 h. After this time the mixture was allowed to cool to rt and was diluted with Et_2O (10 mL). The mixture was washed with satd aq K_2CO_3 (2 × 5 mL) and the aqueous layer was extracted with Et_2O (5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **163** as a colourless oil (68 mg, 80%, >99:1 dr); mp 129-132 °C; $[\alpha]_D^{25}$ −1.50 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3207 (N−H), 3028, 2976, 2932 (C−H), 1729 [C=O (ester)], 1677 [C=O (lactam)]; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (9H, s, C*Me*$_3$), 2.48 (1H, dd, *J* 14.4, 5.6, C(3)H_A), 2.71 (1H, dd, *J* 14.4, 8.1, C(3)H_B), 3.28-3.35 (1H, m, C(4)*H*), 3.68 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.78 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.12 (1H, q, *J* 6.8, C(α)*H*), 4.56 (1H, d, *J* 5.8, C(5)*H*), 6.86 (1H, d, *J* 7.6, *Ar*), 7.09-7.32 (11H, m, 2 × *Ph, Ar*), 7.41-7.47 (2H, m, *Ar*), 8.14 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.9 (C*Me*$_3$), 34.6 (*C*(3)), 48.4 (*C*(4)), 52.7 (N*C*H$_2$Ph), 57.5 (*C*(α)), 66.1 (*C*(5)), 81.3 (*C*Me$_3$), 121.9, 124.5, 126.5, 126.9, 128.0, 128.0, 128.0, 128.2, 128.8, 130.9, 132.2, 137.4, 141.1, 143.2 (*Ar*), 171.9, 173.2 (*C*(2), *C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 963 ([2M+Na]$^+$, 40%), 493 ([M+Na]$^+$, 25%), 471 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{34}N_2NaO_3^+$ requires 493.2462; found 493.2465.

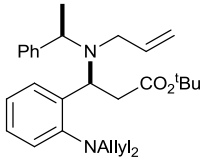
(*R*)-*N*-Allyl-*N*-[α-methylbenzyl]amine 172



BuLi (2.1 M in hexanes, 39.0 mL, 82.3 mmol) was added dropwise to a solution of (*R*)-α-methylbenzylamine (9.50 g, 78.4 mmol) in THF (150 mL) at 0 ˚C. The mixture was stirred at 0 ˚C for 1 h then allyl bromide (7.46 mL, 86.2 mmol) was added dropwise. The mixture was allowed to warm gradually to rt over 16 h, then was quenched by addition of satd aq NH_4Cl (10 mL). The mixture was washed with 10% aq citric acid (3 × 50 mL) and the combined aqueous layers were extracted with Et_2O (50 mL). The combined aqueous layers were neturalised with 2.0 M NaOH and were extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo* to give (*R*)-**172** as a yellow oil (11.5 g, 91%);[4] $[\alpha]_D^{25}$ +50.4 (*c* 1.4 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38

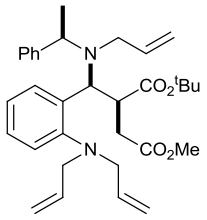
(3H, d, *J* 6.8, C(α)*Me*), 3.09-3.13 (2H, m, N(CH_2CH=CH_2)$_2$), 3.81 (1H, q, *J* 6.8, C(α)*H*), 5.04-5.18 (2H, m, NCH$_2$CH=CH_2), 5.84-5.96 (1H, m, NCH$_2$C*H*=CH$_2$), 7.22-7.37 (5H, m, *Ph*).

tert-Butyl (3*S*,α*R*)-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(2'-*N*,*N*-diallylaminophenyl)propanoate 174

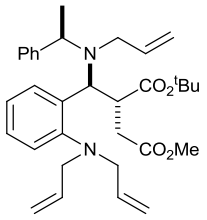


Following *General Procedure 1*, BuLi (2.1 M in hexanes, (*R*)-**172** (1.20 g, 7.42 mmol) in THF (25 mL) and **130** (1.39 g, 4.64 mmol) in THF (25 mL) gave **174** in >99:1 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 5:1) gave **174** as a yellow oil (1.80 g, 85%, >99:1 dr); $[\alpha]_D^{25}$+8.71 (*c* 2.1 in CHCl$_3$); ν_{max} (film) 3073, 3025, 3004, 2877, 2931, 2816, 2349 (C−H), 1728 (C=O), 1640, 1596 (C=C); δ_H (400 MHz, CDCl$_3$) 1.23 (3H, d, *J* 6.8, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 2.57 (1H, dd, *J* 15.3, 6.2, C(2)H_A), 2.92 (1H, dd, *J* 15.3, 8.5, C(2)H_B), 3.20 (1H, dd, *J* 15.7, 4.7, N(CH_AH$_B$CH=CH$_2$)), 3.39 (1H, dd, *J* 15.7, 6.7, N(CH$_A$$H_B$CH=CH$_2$)), 3.49-3.76 (4H, m, N(CH_2CH=CH$_2$)$_2$), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.90-5.26 (7H, m, C(3)*H*, N(CH$_2$CH=CH_2)$_2$, N(CH$_2$CH=CH_2)), 5.73-5.96 (3H, m, N(CH$_2$C*H*=CH$_2$), N(CH$_2$C*H*=CH$_2$)$_2$), 7.07-7.31 (6H, m, *Ar*, *Ph*), 7.38 (2H, d, *J* 7.6, *o-Ph*), 7.55 (1H, d, *J* 7.6, *Ar*); δ_C (100 MHz, CDCl$_3$) 15.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 40.4 (*C*(2)), 49.2 (N(*C*H$_2$CH=CH$_2$)), 53.6 (*C*(3)), 56.3 (*C*(α)), 57.0 (N(*C*H$_2$CH=CH$_2$)$_2$), 80.1 (*C*Me$_3$), 114.5 (N(CH$_2$CH=*C*H$_2$)), 117.7 (N(CH$_2$CH=*C*H$_2$)$_2$), 123.7, 124.1, 126.3, 127.1, 127.8, 127.8, 238.9, 135.0, 139.2, 140.0, 145.2, 150.0 (*Ar*, *Ph*), 171.6 (*C*(1)); *m*/*z* (ESI$^+$) 483 ([M+Na]$^+$, 98%), 461 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{41}N_2O_2^+$ ([M+H]$^+$) requires 461.3163; found 461.3163.

tert-Butyl (2*S*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl)-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(2''-*N*,*N*-diallylaminophenyl)propanoate 175 and _tert_-Butyl (2*R*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl)-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-(2''-*N*,*N*-diallylaminophenyl)propanoate 168



175

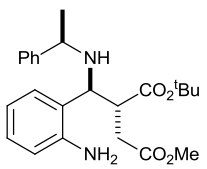


168

Following *General Procedure 4*, ^{i}Pr$_2$NH (11.5 mL, 82.0 mmol) in THF (250 mL), BuLi (2.5 M in hexanes, 31.7 mL, 79.3 mmol), **175** (25.2 g, 54.7 mmol) in THF (250 mL) and methylbromoacetate

(15.5 mL, 164 mmol) gave a >95:5 mixture of **168** and **175**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 86:14:1) gave **175** as a yellow oil (397 mg, 1%, >90:10 **175**:**168**); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, *J* 6.6, C(α)*Me*), 1.12 (9H, s, C*Me*$_3$), 2.73 (1H, dd, *J* 16.0, 11.2, C(1′)H_A), 3.07 (1H, dd, *J* 14.5, 5.9, NCH_AH$_B$CH=CH$_2$), 3.28-3.52 (3H, m, C(2)*H*, C(1')H_B, NCH$_A$$H_B$CH=CH$_2$), 3.57-3.74 (7H, m, N(C$H_2$CH=CH$_2$)$_2$, CO_2*Me*), 4.19 (1H, q, *J* 6.6, C(α)*H*), 4.69 (1H, d, *J* 11.4, C(3)*H*), 4.95-5.04 (2H, m, NCH$_2$CH=CH_2), 5.09-5.24 (4H, m, N(CH$_2$CH=CH_2)$_2$), 5.48-5.62 (1H, m, NCH$_2$C*H*=CH$_2$), 5.75-5.92 (2H, m, N(CH$_2$C*H*=CH$_2$), 7.06-7.13 (2H, t, *J* 7.0, *Ph*), 7.15-7.32 (6H, *Ph*, 3 × *Ar*), 7.61 (1H, dd, *J* 8.1, 1.3, *Ar*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 17.0 (C(α)*Me*), 27.5 (C*Me*$_3$), 37.2 (*C*(1')), 45.5 (*C*(2)), 49.1 (N*C*H$_2$CH=CH$_2$), 51.5 (CO_2*Me*), 55.5 (*C*(α)), 56.5 (*C*(3)), 80.4 (*C*Me$_3$), 116.4 (NCH$_2$CH=*C*H$_2$), 118.2 (N(CH$_2$CH=*C*H$_2$)$_2$), 123.3, 123.4, 126.2, 127.5, 128.0, 130.5 (*Ar*, *Ph*), 134.8 (N(CH$_2$*C*H=CH$_2$)$_2$), 138.0 (NCH$_2$*C*H=CH$_2$), 145.5, 150.6 (*Ar*), 173.3, 173.5 (*C*O_2Me, *C*O_2^{t}Bu); *m*/*z* (ESI$^+$) 555 ([M+Na]$^+$, 100%), 533 ([M+H]$^+$, 50%); HRMS (ESI$^+$) $C_{33}H_{45}N_2O_4^+$ ([M+H]$^+$) requires 533.3374; found 555.3193. Further elution gave **168** as a yellow oil (20.0 g, 68%, >99:1 dr); $[\alpha]_D^{20}$+5.76 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3073, 2978, 2820 (C–H), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 1.04 (3H, app dd, *J* 6.6, 1.3, C(α)*H*), 1.50 (9H, s, C*Me*$_3$), 2.20 (1H, dd, *J* 15.7, 3.0, C(1′)H_A), 2.50 (1H, dd, *J* 15.7, 11.5, C(1′)H_B), 3.10-3.19 (1H, m, N(CH_AH$_B$CH=CH$_2$)), 3.21-3.30 (1H, m, N(CH$_A$$H_B$CH=CH$_2$)), 3.45-3.67 (8H, m, C(2)*H*, CO_2*Me*, N(CH_2CH=CH_2)$_2$), 4.16 (1H, q, *J* 6.6, C(α)*H*), 4.77-4.89 (2H, m, NCH$_2$CH=CH_2), 5.03 (1H, d, *J* 11.6, C(3)*H*), 5.12-5.22 (4H, m, N(CH$_2$CH=CH_2)$_2$), 5.61-5.73 (1H, m, NCH$_2$C*H*=CH$_2$), 5.81-5.94 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 7.10-7.31 (8H, m, *Ar*, *Ph*), 7.35-7.40 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 35.9 (*C*(1′)), 46.6 (O*Me*), 49.9 (N(*C*H$_2$CH=CH$_2$)), 51.6 (*C*(2)), 56.5 (*C*(α)), 57.3 (*C*(4)), 57.4 (N(*C*H$_2$CH=CH$_2$)), 80.7 (*C*Me$_3$), 114.8 (N(CH$_2$CH=*C*H$_2$)), 118.4 (N(CH$_2$CH=*C*H$_2$)$_2$), 124.4, 124.5, 126.0, 127.6, 127.7, 127.9, 129.1, 134.3, 134.6, 138.7, 145.4, 151.4 (*Ph*, *Ar*, N(CH$_2$*C*H=CH$_2$)$_2$, NCH$_2$*C*H=CH$_2$), 172.1, 173.7 (*C*(1), *C*(2')); *m*/*z* (ESI$^+$) 555 ([M+Na]$^+$, 35%), 533 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{45}N_2O_4^+$ ([M+H]$^+$) requires 533.3374; found 533.3377.

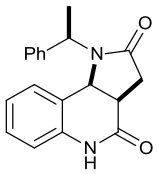
tert-Butyl (2*R*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-(2''-aminophenyl)propanoate 169



Following *General Procedure 5*, **168** (1.07 g, 2.02 mmol), DMBA (1.42 g, 9.09 mmol) and

$Pd(PPh_3)_4$ (350 mg, 0.30 mmol) and CH_2Cl_2 (20 mL) gave **169** in >99:1 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 66:34:1) gave **169** as a yellow oil (631 mg, 76%, >99:1 dr); $[\alpha]_D^{20}$–1.6 (*c* 1.15 in $CHCl_3$); ν_{max} (film) 3428, 3298 (N–H), 3027, 2974, 2930 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 2.21 (1H, dd, *J* 16.9, 4.6, C(1')H_A), 2.45 (1H, dd, *J* 16.9, 9.8, C(1')H_B), 3.43 (1H, td, *J* 9.8, 4.6, C(2)*H*), 3.58 (3H, s, O*Me*), 3.62 (1H, q, *J* 6.6, C(α)*H*), 4.08 (1H, d, *J* 9.6, C(3)*H*), 4.76 (2H, br s, NH_2), 6.51 (1H, d, *J* 7.8, *Ar*), 6.62 (1H, t, *J* 7.3, *Ar*), 6.92 (1H, d, *J* 6.8, *Ar*), 7.03 (1H, td, *J* 7.6, 1.5, *Ar*), 7.15-7.29 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (C(α)*Me*), 28.1 (C*Me*$_3$), 34.7 (*C*(1')), 44.5 (*C*(2)), 51.5 (O*Me*), 54.5 (*C*(α)), 62.7 (*C*(3)), 81.4 (*C*Me$_3$), 116.5, 117.4, 122.4, 126.3, 126.6, 128.2, 128.5, 130.8, 145.8, 146.6 (*Ar*, *Ph*), 172.3, 173.6 (*C*(1), *C*(2')); *m*/*z* (ESI^+) 413 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{33}N_2O_4^+$ ($[M+H]^+$) requires 413.2435; found 413.2443.

(3a*R*,9b*S*,α*R*)-1-(α-Methylbenzyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline-2,4-dione 171



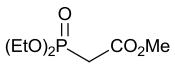
Method A: Following *General Procedure 6*, **169** (280 mg, 0.68 mmol) and $PhCO_2H$ (9 mg, 68 μmol) in PhMe (5 mL) at reflux for 16 h gave **171**. Purification *via* flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **171** as a white solid (166 mg, 80%, >99:1 dr); mp 174-177 °C; $[\alpha]_D^{20}$+86.8 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 3216 (N–H), 3061, 2988, 2924 (C–H); 1682 [C=O (γ-lactam)], 1616 [C=O (δ-lactam)]; δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 7.1, C(α)*Me*), 2.81 (1H, dd, *J* 16.7, 8.1, C(3)H_A), 3.06-3.14 (1H, m, C(3a)*H*), 3.31 (1H, d, *J* 16.7, C(3)H_B), 4.72 (1H, d, *J* 5.6, C(9b)*H*), 5.49 (1H, q, *J* 7.1, C(α)*H*), 6.29 (1H, d, *J* 7.3, *Ar*), 6.85 (1H, t, *J* 7.4, *Ar*), 6.93 (2H, d, *J* 7.8, *o-Ph*), 7.26-7.40 (5H, m, *m-Ph*, *p-Ph*, 2 × *Ar*), 10.04 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 34.3 (*C*(3)), 38.6 (*C*(3a)), 49.1 (*C*(α)), 57.7 (*C*(9b)), 116.0 (*Ar*), 117.3 (*i-Ar*), 122.7, 127.3, 127.5, 128.5, 130.7, 131.6, 137.3, 139.0, 171.0, 173.6 (*C*(2), *C*(4)); *m*/*z* (ESI^+) 941 ($[3M+Na]^+$, 70%), 635 ($[2M+Na]^+$, 100%), 613 ($[2M+H]^+$, 30%), 329 ($[M+Na]^+$, 55%); HRMS (ESI^+) $C_{19}H_{18}N_2NaO_2^+$ ($[M+Na]^+$) requires 329.1260; found 329.1261.

Method B: A solution of **169** (100 mg, 0.24 mmol) and THF (5 mL) was heated at reflux for 72 h and then was concentrated *in vacuo* to give a 78:22 mixture of **169** and **170**, respectively; δ_H (400 MHz, $CDCl_3$) [selected peaks for **170**] 4.80 (1H, d, *J* 9.1, C(5)*H*), 5.54 (1H, q, *J* 7.2, C(α)*H*).

Method C: A solution of **169** (44 mg, 0.11 mmol) and PhMe (2 mL) was heated at reflux for 16 h and

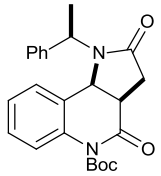
then was concentrated *in vacuo* to give a 68:29:3 mixture of **169**, **170** and **171**, respectively.

Methyl-2-(diethoxyphosphoryl)acetate 200



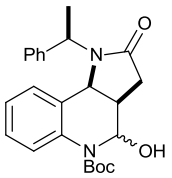
Methyl bromoacetate (2.18 mL, 23.0 mmol) was added to $P(OEt)_3$ (4.00 mL, 23.0 mmol) and the mixture was stirred (neat) at rt for 12 h, then at 50 ° C for 24 h, then concentrated to give **200** as a colourless oil (4.83 g, quant); δ_H (400 MHz, $CDCl_3$)[5] 1.34 (6H, t, *J* 7.2, $OCH_2CH_3 \times 2$), 2.97 (2H, d, *J* 21.5, PCH_2), 3.74 (3H, s, O*Me*), 4.17 (4H, m, $2 \times OCH_2CH_3$).

(3a*R*,9b*S*,α*R*)-*N*(1)-[α-Methylbenzyl]-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 198



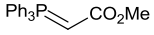
Boc_2O (6.68 g, 30.6 mmol), Et_3N (6.40 mL, 45.9 mmol) and DMAP (93 mg, 0.78 mmol) were added sequentially to a stirred solution of **171** (4.69 g, 15.3 mmol) in CH_2Cl_2 (150 mL) and the resultant mixture was stirred at 35 ˚C for 16 h. The mixture was washed with 1.0 M HCl (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:50:1 → 0:100:1) gave **198** as a yellow solid (5.14 g, 83%, >99:1 dr); $C_{24}H_{26}N_2O_4$ requires C, 70.9; H, 6.45; N, 6.9%; found C, 70.8; H, 6.6; N, 7.0%; mp 155-168 °C; $[\alpha]_D^{20}$+53.3 (*c* 2.1 in $CHCl_3$); ν_{max} (film) 2981, 2936 (C–H), 1766, 1694 [C=O (δ lactam)], 1608 [C=O (carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, d, *J* 7.3, C(α)*Me*), 1.61 (9H, s, CMe_3), 2.73 (1H, dd, *J* 16.4, 7.5, C(3)H_A), 3.08-3.14 (1H, m, C(3a)*H*), 3.28 (1H, d, *J* 16.4, C(3)H_B), 4.63 (1H, d, *J* 5.3, C(9b)*H*), 5.48 (1H, q, *J* 7.3, C(α)*H*), 6.26 (1H, d, *J* 7.6, *Ar*), 6.87-6.95 (2H, m, *Ar*), 7.04-7.10 (2H, d, *J* 7.8, *o-Ph*), 7.28-7.39 (4H, m, *m-Ph*, *p-Ph*, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.7 (C(α)*Me*), 27.6 (CMe_3), 34.5 (*C*(3)), 39.5 (*C*(3a)), 48.9 (*C*(α)), 57.4 (*C*(9b)), 85.8 (*C*Me_3), 116.1, 118.6, 123.7, 127.4, 127.4, 128.5, 130.6, 131.9, 137.1, 138.9 (*Ar*, *Ph*), 150.8 (N*C*O), 167.7, 173.2 (*C*(2), *C*(4)); *m*/*z* (ESI^+) 429 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{24}H_{26}N_2NaO_4^+$ ($[M+Na]^+$) requires 429.1785; found 429.1782.

(3a*R*,4*R*,9b*S*,α*R*)- or (3a*R*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methylbenzyl]-4-hydroxy-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 199[6]



$LiAl(O^tBu)_3H$ (5.44 g, 21.4 mmol) was added portionwise to a stirred solution of **198** (4.35 g, 10.7 mmol) in THF (100 mL) at 0 °C and the solution was stirred at this temperature for 1 h and H_2O (1 mL) was added dropwise. EtOAc (20 mL) was added and the mixture was allowed to stir at rt for 10 min. The mixture was filtered through a pad of Celite® (eluent EtOAc), then dried and concentrated *in vacuo* to give **199** as a white foam which was used without further purification in subsequent steps (4.40 g, quant, >99:1 dr). A small portion of this material was purified *via* flash column chromatography (eluent EtOAc/Et_3N, 100:1) to give an authentic sample of **199** as a white foam (>99:1 dr); $[\alpha]_D^{20}$+68.6 (*c* 1.6 in $CHCl_3$); ν_{max} (film) 3429 (O–H), 3032, 2951 (C–H), 1695 [C=O (carbamate)], 1664 [C=O (γ lactam)]; δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 7.3, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 2.54 (1H, dd, *J* 16.8, 1.9, C(3)H_A), 2.76-2.92 (2H, m, C(3)H_B, C(3a)*H*), 3.74 (1H, br s, O*H*), 4.48 (1H, d, *J* 7.3, C(9b)*H*), 5.38 (1H, s, C(4)*H*), 6.38 (1H, dd, *J* 7.6, 1.0, *Ar*), 6.93 (1H, td, *J* 7.5, 1.3, *Ar*), 7.05 (2H, d, *J* 7.8, *Ph*), 7.24-7.38 (5H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 28.3 (C*Me*$_3$), 36.1 (*C*(3)), 42.2 (*C*(3a)), 49.8 (*C*(α)), 56.9 (*C*(9b)), 81.9, 81.9 (*C*(4), *C*Me$_3$), 124.3, 126.0, 127.3, 127.8, 128.2, 129.1, 130.4, 137.4, 138.6 (*Ar*), 152.7 (N*C*O), 173.5 (*C*(2)); *m*/*z* (ESI^+) 839 ($[2M+Na]^+$, 100%), 431 ($[M+Na]^+$, 76%); HRMS (ESI^+) $C_{24}H_{28}N_2NaO_4^+$ ($[M+Na]^+$) requires 431.1941; found 431.1937.

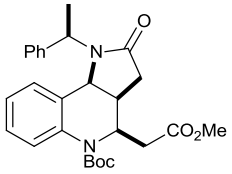
Methyl 2-[triphenylphosphoranylidene]acetate 206



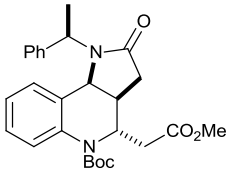
Step 1: Methyl bromoacetate (3.95 mL, 41.7 mmol) was added dropwise to a solution of triphenylphosphine (11.0 g, 41.7 mmol) in EtOAc (100 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered to collect the white precipitate, which was then washed with cold EtOAc (50 mL). The solid was then dried under vacuum to give **205** as a white crystalline solid (17.2 g, quant);[7] δ_H (400 MHz, $CDCl_3$) 3.61 (3H, s, O*Me*), 5.62 (2H, d, *J* 15.5, C(2)H_2), 7.35-7.83 (15H, m, *Ar*).

Step 2: Phosphorane **206** was prepared, as required, by treatment of a solution of **205** in CH_2Cl_2 with 2.0 M aq NaOH. The aqueous layer was then extracted with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo* to give **206** as a white solid.

(3*aS*,4*R*,9*bS*,α*R*)-*N*(1)-[α-Methylbenzyl]-4-[2'-methoxy-2'-oxoethyl]-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3*a*,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 201 and (3*aS*,4*S*,9*bS*,α*R*)-*N*(1)-[α-Methylbenzyl]-4-[2'-methoxy-2'-oxoethyl]-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3*a*,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 202



201



202

Method A: NaH (60% in mineral oil, 89 mg, 2.23 mmol) was added to a stirred solution of **200** (469 mg, 2.23 mmol) in THF (20 mL) at 0 °C and the mixture was stirred at 0 °C for 30 min. A solution of **199** (759 mg, 1.86 mmol) in THF (20 mL) was added *via* cannula and the mixture was stirred at 0 °C for 2 h. The mixture was quenched by addition of H_2O (10 mL) and was diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O and the combined organic extracts were dried and concentrated *in vacuo* to give a 23:77 mixture of **201**:**202**. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 66:34) gave **201** as a colourless oil (171 mg, 20%, >99:1 dr); $[\alpha]_D^{20}$–40.3 (*c* 1.4 in $CHCl_3$); ν_{max} (film) 2978, 2934 (C–H), 1739 [C=O (ester)], 1697 [C=O (carbamate, lactam)]; δ_H (400 MHz, C_6D_6) 1.09 (3H, d, *J* 7.2, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 1.94 (1H, dd, *J* 16.4, 8.9, C(3)H_A), 2.02-2.19 (2H, m, C(3)H_B, C(1')H_A), 2.44 (1H, br, C(1')H_B), 2.52-2.64 (1H, m, C(3a)*H*), 3.32 (3H, s, O*Me*), 4.13 (1H, d, *J* 7.9, C(9b)*H*), 4.57 (1H, br, C(4)*H*), 5.48 (1H, q, *J* 7.2, C(α)*H*), 6.85 (2H, d, *J* 4.8, *o-Ph*), 7.02-7.18 (6H, m, *m-Ph*, *p-Ph*, 3 × *Ar*), 7.50 (1H, d, *J* 8.2, *Ar*); δ_C (400 MHz, C_6D_6) 18.0 (C(α)*Me*), 28.2 (C*Me*$_3$), 32.4 (*C*(3)), 36.1 (*C*(1')), 40.6 (*C*(3a)), 51.3 (O*Me*), 51.5 (*C*(α)), 57.0 (*C*(9b)), 80.9 (*C*Me$_3$), 124.8, 126.9, 127.4, 127.6, 128.3, 128.6, 131.5, 141.8 (*Ph*, *Ar*), 153.3 (N*C*O), 170.9, 173.6 (*C*(2), *C*(2'));[8] *m*/*z* (ESI$^+$) 951 ([2M+Na]$^+$, 99%), 487 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}N_2NaO_5^+$ ([M+Na]$^+$) requires 487.2203; found 487.2190. Further elution gave **202** as a colourless oil (593 mg, 69%, >99:1 dr); $[\alpha]_D^{20}$+96.8 (*c* 0.7 in $CHCl_3$); ν_{max} (film) 2976, 2934 (C–H), 1739 [C=O (ester)], 1695 [C=O (carbamate, lactam)]; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 7.1, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 2.04-2.17 (2H, m, C(1')H_2), 2.65-2.78 (2H, m, C(3)H_A, C(3a)*H*), 2.88-2.99 (1H, m, O*Me*), 4.44 (1H, d, *J* 7.8, C(9a)*H*), 4.80-4.93 (1H, br m, C(4)*H*), 5.46 (1H, q, *J* 7.1, C(α)*H*), 6.38 (1H, d, *J* 7.3, *Ar*), 6.92-6.99 (1H, m, *Ar*), 7.07 (2H, d, *J* 7.8, *Ph*), 7.25-7.40 (5H, m, *Ph*, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 28.3 (C*Me*$_3$), 38.4, 39.1 (*C*(3), *C*(1')), 39.8 (*C*(3a)), 49.7(*C*(α)), 51.7 (O*Me*), 56.0 (broad, *C*(4)), 56.7 (*C*(9a)), 81.5 (*C*Me$_3$), 124.5, 126.7, 127.3, 127.8, 128.3, 129.0, 129.2, 130.3, 138.6, 138.7 (*Ph*, *Ar*), 152.8 (weak, N*C*O), 170.8, 173.7 (*C*(2), *C*(2')); *m*/*z* (ESI$^+$) 951 ([2M+Na]$^+$, 99%), 487 ([M+Na]$^+$, 100%); HRMS (ESI$^+$)

$C_{27}H_{32}N_2NaO_5^+$ ([M+Na]$^+$) requires 487.2203; found 487.2199.

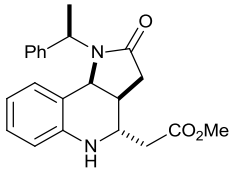
Method B: Phosphorane **206** (18 mg, 54 μmol) was added to a solution of **199** (20 mg, 49 μmol) in CH_2Cl_2 (2 mL) and the mixture was stirred at rt for 48 h. The mixture was concentrated *in vacuo* to give a 47:29:13:11 mixture of **199**, **203**, **204** and **202**, respectively.

Method C: Phosphorane **206** (44 mg, 0.13 mmol) was added to a solution of **199** (49 mg, 0.12 mmol) in 1,4-dioxane (1.2 mL) and the mixture was heated at reflux for 16 h. The mixture was concentrated *in vacuo* to give a 17:83 mixture of **203** and **202** respectively, along with other unidentified products.

Method D: Phosphorane **206** (43 mg, 0.13 mmol) was added to a solution of **199** (48 mg, 0.12 mmol) in PhMe (1.2 mL) and the mixture was stirred at 50 ˚C for 16 h. The mixture was concentrated *in vacuo* to give a 22:5:73 mixture of **203**, **204** and **202**, respectively.

Method E: Phosphorane **206** (7.15 g, 21.4 mmol) was added to a solution of **199** (4.40 g, 10.7 mmol) in PhMe (100 mL) and the resultant mixture was stirred at 80 °C for 72 h then was concentrated *in vacuo* to give **202** in >99:1 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 75:25:1) gave an inseparable mixture of **202**, **206** and $OPPh_3$. The fractions were combined and the mixture was triturated repeatedly with Et_2O to give **202** as a yellow oil (3.97 g, 80% over 2 steps, >99:1 dr) with spectroscopic properties identical to those described previously.

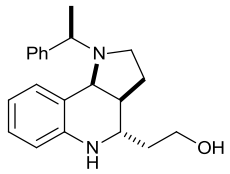
(3a*S*,4*S*,9b*S*,α*R*)-1-[α-methylbenzyl]-4-(2'-methoxy-2'-oxoethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 207



TFA (6.0 mL) was added to a stirred solution of **202** (3.97 g, 8.54 mmol) in CH_2Cl_2 (70 mL) at rt and the resultant mixture was stirred at 35 °C for 4 h. The mixture was allowed to cool to rt and was neutralized carefully with satd aq K_2CO_3. The resultant solution was washed with satd aq K_2CO_3 (2 × 50 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **207** as a pale yellow solid which was ~95% pure. Recrystallisation (CH_2Cl_2/pentane) gave **207** as a white solid (1.61 g, 58%, >99:1 dr); mp 150-155 °C; $[\alpha]_D^{20}$–31.7 (*c* 1.01 in $CHCl_3$); ν_{max} (neat) 3392, 3338 (N–H), 3029, 2973, 2847 (C–H), 1731 [C=O (ester)], 1678 [C=O (γ lactam)]; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 7.3, C(α)*Me*), 2.17-2.25 (1H, m, C(3a)*H*), 2.32 (1H, dd, *J* 16.7, 1.5, C(1')H_A), 2.39 (1H, dd, *J* 16.2, 10.1, C(3)H_A), 2.65 (1H, dd, *J* 16.2, 2.5, C(3)H_B), 2.73 (1H, dd, *J* 16.7, 7.0, C(1')H_B), 3.47 (1H, br t, C(4)*H*), 3.72 (3H, s, O*Me*), 4.63 (1H, d, *J* 5.1, C(9b)*H*), 4.91 (1H, s, N*H*), 5.38 (1H, q, *J* 7.3, C(α)*H*), 6.40 (1H, dd, *J* 7.8,

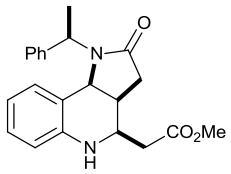
1.1, *Ar*), 6.51 (1H, td, *J* 7.3, 1.0, *Ar*), 6.56 (1H, dd, *J* 8.1, 0.8, *Ar*), 7.08 (1H, td, *J* 7.6, 1.5, *Ar*), 7.12-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 35.9 (*C*(1')), 36.0 (*C*(3a)), 38.2 (*C*(3)), 48.1 (*C*(4)), 49.3 (*C*(α)), 52.0 (O*Me*), 56.7 (*C*(9b)), 115.0, 115.6, 117.0, 126.9, 127.3, 128.3, 129.9, 132.4, 140.1, 144.3 (*Ph*, *Ar*), 172.5, 173.5 (*C*(2), *C*(2')); *m*/*z* (ESI^+) 751 ($[2M+Na]^+$, 100%), 387 ($[M+Na]^+$, 90%); HRMS (ESI^+) $C_{22}H_{24}N_2NaO_3^+$ ($[M+Na]^+$) requires 387.1679; found 387.1665.

(3a*S*,4*S*,9b*S*,α*R*)-1-[α-Methylbenzyl]-4-(2'-hydroxyethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 208



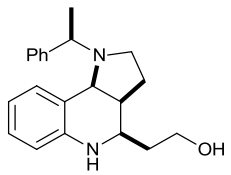
$LiAlH_4$ (2.0 M in Et_2O, 8.40 mL, 16.8 mmol) was added dropwise to a solution of **207** (1.53 g, 4.20 mmol) in THF (60 mL) at 0 °C. The resultant mixture was heated at reflux for 16 h and then was cooled to 0 °C. The reaction was quenched by careful dropwise addition of 2.0 M NaOH (5.0 mL) and EtOAc (20 mL) and stirred at rt for 20 min. The mixture was diluted with EtOAc (50 mL) and filtered through a pad of Celite® (eluent EtOAc/Et_3N, 100:1, 150 mL) then dried and concentrated *in vacuo*. Purifiaction *via* flash column chromatography (eluent 90:10, $CHCl_3$/MeOH) gave **208** as a yellow oil (898 mg, 67%, >99:1 dr); $[\alpha]_D^{20}$ −99.1 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3390 (O–H), 3025, 2965, 2934, 2876 (C–H); δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, *J* 6.6, C(α)*Me*), 1.55-1.73 (2H, m, C(3)H_A, C(1')H_A), 1.79-1.91 (1H, m, C(1')H_B), 1.92-2.10 (2H, m, C(3)H_B, C(3a)*H*), 2.58-2.72 (2H, m, C(2)H_2), 3.41 (1H, dt, *J* 8.6, 2.2, C(4)*H*), 3.71 (1H, d, *J* 5.3, C(9b)*H*), 3.73-3.82 (1H, m, C(2')H_A), 3.85-3.93 (1H, m, C(2')H_B), 4.34 (1H, q, *J* 6.6, C(α)*H*), 6.62 (1H, d, *J* 7.8, *Ar*), 6.67-6.72 (1H, m, *Ar*), 7.06-7.12 (1H, m, *Ar*), 7.17-7.34 (4H, m, *Ar*, *m*-*Ph*, *p*-*Ph*), 7.41 (2H, d, *J* 7.3, *o*-*Ph*); δ_C (100 MHz, $CDCl_3$) 11.2 (C(α)*Me*), 26.1 (*C*(3)), 35.6 (*C*(1')), 39.6 (*C*(3a)), 42.9 (*C*(2)), 52.3 (*C*(4)), 53.7 (*C*(α)), 58.7 (*C*(9b)), 61.5 (*C*(2')), 114.6, 116.6, 120.6, 126.4, 127.5, 127.9, 128.1, 131.1, 144.7, 144.9 (*Ph*, *Ar*); *m*/*z* (ESI^+) 323 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{27}N_2O^+$ ($[M+H]^+$) requires 323.2118; found 322.2108.

(3a*S*,4*R*,9b*S*,α*R*)-1-[α-methylbenzyl]-4-(2'-methoxy-2'-oxoethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 209



TFA (3.0 mL) was added to a solution of **201** (1.33 g, 2.87 mmol) in CH_2Cl_2 (30 mL) at rt and the resultant mixture was stirred at 35 ˚C for 4 h. The mixture was allowed to cool to rt and was neutralized carefully with satd aq K_2CO_3 The mixture was washed with satd aq K_2CO_3 (2 × 50 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (50 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc, 100%) gave **209** as a yellow oil (851 mg, 81%, >99:1 dr); $[\alpha]_D^{20}$ –15.2 (*c* 0.8 in $CHCl_3$); ν_{max} (film) 3368, 3323 (N–H), 2918, 2849 (C–H), 1734 [C=O (ester)], 1676 [C=O (lactam)]; δ_H (400 MHz, $CDCl_3$) 1.55 (3H, d, *J* 7.3, C(α)*Me*), 2.33 (1H, dd, *J* 15.5, 7.8, C(3)H_A), 2.50 (2H, d, *J* 6.8, C(1')H_2), 2.81-2.88 (1H, m, C(3a)*H*), 2.93 (1H, dd, *J* 15.5, 10.1, C(3)H_B), 3.52 (1H, td, *J* 6.8, 2.5, C(4)*H*), 3.72 (3H, s, O*Me*), 4.24 (1H, s, N*H*), 4.68 (1H, d, *J* 8.3, C(9b)*H*), 5.41 (1H, q, *J* 7.3, C(α)*H*), 6.61-6.68 (2H, m, *Ar*), 6.92-6.96 (1H, m, *Ar*), 7.05 (1H, td, *J* 7.7, 1.4, *Ar*), 7.24-7.31 (3H, m, *Ph*), 7.34-7.40 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 30.2 (*C*(3)), 37.3 (*C*(1')), 39.2 (*C*(3a)), 51.1, 52.0, 52.1 (*C*(4), *C*(α), O*Me*), 57.4 (*C*(9b)), 116.3, 118.9, 121.9, 127.2, 127.5, 128.5, 128.6, 130.9, 139.6, 146.6 (*Ph*, *Ar*), 172.2, 174.4 (*C*(2), *C*(2')); *m*/*z* (ESI^+) 751 ($[2M+Na]^+$, 100%), 387 ($[M+Na]^+$, 10%); HRMS (ESI^+) $C_{22}H_{24}N_2NaO_3^+$ ($[M+Na]^+$) requires 387.1679; found 387.1671.

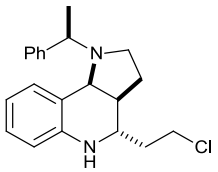
(3a*S*,4*R*,9b*S*,α*R*)-1-[α-Methylbenzyl]-4-(2'-hydroxyethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 210



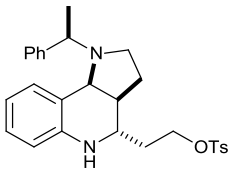
$LiAlH_4$ (2.0 M in Et_2O, 3.90 mL, 7.83 mmol) was added dropwise to a stirred solution of **209** (714 mg, 1.96 mmol) in THF (60 mL) at 0 °C. The mixture was heated at reflux for 16 h and then was cooled to 0 °C. The reaction was quenched by careful dropwise addition of 2.0 M NaOH (3.0 mL) and EtOAc (20 mL) and stirred at rt for 20 min. The mixture was diluted with EtOAc (50 mL) and filtered through a pad of Celite® (eluent EtOAc/Et_3N, 100:1, 150 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 85:15) gave **210** as a yellow oil (252 mg, 35% >99:1 dr). A small portion of this material was recrystallised (EtOH) to give

an analytical sample; mp 125-128 °C; $[\alpha]_D^{20}$+5.4 (*c* 0.89 in $CHCl_3$); ν_{max} (film) 3370 (O–H), 2874, 2962 (C–H); δ_H (500 MHz, $CDCl_3$) 1.51 (3H, d, *J* 6.6, C(α)*Me*), 1.62-1.70 (1H, m, C(1')H_A), 1.73-1.98 (3H, m, C(3)H_2, C(1')H_B), 2.43-2.56 (1H, br s, C(3a)*H*), 2.67-2.77 (1H, m, C(2)H_A), 2.83-2.92 (1H, m, C(2)H_B), 3.39-3.46 (1H, m, C(4)*H*), 3.69-3.77 (1H, m, C(2')H_A), 3.80-3.87 (1H, m, C(2')H_B), 3.93 (1H, q, *J* 6.6, C(α)*H*), 4.12 (1H, br s, C(9b)*H*), 6.50 (1H, d, *J* 7.3, *Ar*), 6.71 (1H, td, *J* 7.7, 1.3, *Ar*), 6.95-7.02 (1H, m, *Ar*), 7.17-7.35 (2H, m, *Ar*, *p*- *Ph*), 7.36 (2H, app t, *J* 7.6, *m*-*Ph*), 7.43-7.49 (2H, d, *J* 6.9, *o*-*Ph*); δ_C (125 MHz, $CDCl_3$) 19.3 (C(α)*Me*), 23.0 (*C*(3)), 36.8 (*C*(1')), 41.3 (*C*(3a)), 47.2 (*C*(2)), 52.8 (*C*(4)), 60.4 (*C*(α)), 60.9 (*C*(9b)), 61.6 (*C*(2')), 114.8, 118.4, 125.3, 127.0, 127.2, 127.8, 128.3, 128.4, 129.0, 129.8 (*Ph*, *Ar*); *m*/*z* (ESI^+) 323 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{27}N_2O^+$ ($[M+H]^+$) requires 323.2118; found 323.2107.

(3a*S*,4*S*,9b*S*,α*R*)-1-[α-Methylbenzyl]-4-(2'-chloroethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 213 and (3a*S*,4*S*,9b*S*,α*R*)-1-[α-methylbenzyl]-4-[2'-(4''-toluenesulfonyloxy)ethyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 212



213



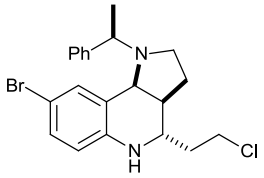
212

Method A: CCl_4 (0.78 mL, 7.80 mmol) was added dropwise to a solution of **208** (257 mg, 0.80 mL), PPh_3 (523 mg, 2.00 mmol) and Et_3N (1.11 mL, 7.80 mmol) in MeCN (10 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 5 h and then was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 75:25) gave **213** as a yellow oil (196 mg, 72%, >99:1 dr); ν_{max} (film) 3410 (N−H), 2965, 2931, 2875 (C–H); $[\alpha]_D^{20}$−64.9 (*c* 1.3 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$); 1.50 (3H, d, *J* 6.6, C(α)*Me*), 1.62-1.72 (1H, m, C(3)H_A), 1.90-2.14 (4H, m, C(3)H_B, C(3a)*H*, C(1')H_2), 2.59-2.72 (2H, m, C(2)H_2), 3.48 (1H, td, *J* 7.9, 3.2, C(4)*H*), 3.65-3.74 (3H, m, C(9b)*H*, C(2')H_2), 4.08 (1H, br s, N*H*), 4.20 (1H, q, *J* 6.6, C(α)*H*), 6.57 (1H, d, *J* 7.9, *Ar*), 7.05 (1H, td, *J* 7.6, 1.3, *Ar*), 7.17-7.22 (2H, m, *Ar*, *p*- *Ph*), 7.26-7.31 (2H, m, *m*-*Ph*), 7.38 (2H, d, *J* 7.6, *o*- *Ph*); δ_C (125 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 26.5 (*C*(3)), 36.6 (*C*(1')), 39.3 (*C*(3a)), 42.2 (*C*(2')), 43.6 (*C*(2)), 50.8 (*C*(4)), 54.9 (*C*(α)), 58.3 (*C*(9b)), 114.4, 117.1, 121.3, 126.4, 127.4, 128.0, 128.0, 130.8, 144.0, 145.0 (*Ph*, *Ar*); *m*/*z* 341 ($[M(^{35}Cl)+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}{}^{35}ClN_2^+$ ($[M(^{35}Cl)+H]^+$) requires 341.1779; found 341.1778.

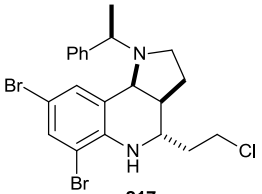
Method B: DMAP (11 mg, 91 μmol), Et_3N (0.19 mL, 1.36 mmol) and TsCl (208 mg, 1.09 mmol) were added sequentially to a stirred solution of **208** (293 mg, 0.91 mmol) in CH_2Cl_2 (20 mL) and the

resultant mixture was stirred at rt for 16 h. The mixture was washed with 1.0 M HCl (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were was sequentially with satd aq $NaHCO_3$ (10 mL), brine (10 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 66:34:1) gave firstly **213** as a yellow oil (72 mg, 23%, >99:1 dr) with spectroscopic properties identical to those reported above. Further elution gave **212** as a yellow oil (180 mg, 41%, ~90% pure); $[\alpha]_D^{20}$ –82.2 (*c* 1.2 in $CHCl_3$); ν_{max} (film) 3401 (N–H), 3055, 3026, 2966, 2931, 2876 (C–H); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.6, C(α)*Me*), 1.52-1.64 (1H, m, C(3)H_A), 1.70-1.81 (1H, m, C(1')H_A), 1.86-2.06 (3H, m, C(3)H_B, C(3a)*H*, C(1')H_B), 2.45 (3H, s, C(4")*Me*), 2.52-2.71 (2H, m, C(2)H_2), 3.36 (1H, td, *J* 8.0, 2.8, C(4)*H*), 3.66 (1H, d, *J* 5.3, C(9b)*H*), 4.12-4.29 (3H, m, C(α)*H*, C(2')H_2), 6.46 (1H, d, *J* 7.3, *Ar*), 6.66 (1H, td, *J* 7.3, 1.0, *Ar*), 7.03 (1H, td, *J* 7.6, 1.4, *Ar*), 7.16 (1H, d, *J* 6.6, *Ar*), 7.20 (1H, t, *J* 6.5, *p-Ph*), 7.28 (2H, app t, *J* 7.5, *m-Ph*), 7.32-7.40 (4H, m, *o-Ph*, C(3")*H*, C(5")*H*), 7.83 (2H, d, *J* 8.3, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 12.8 (C(α)*Me*), 21.7 (C(4")*Me*), 26.3 (*C*(3)), 32.9 (*C*(1')), 39.3 (*C*(3a)), 43.5 (*C*(2)), 49.9 (*C*(4)), 54.8 (*C*(α)), 58.2 (*C*(9b)), 68.1 (*C*(2'), 114.4, 117.0, 121.0 (*Ar*), 126.4 (*p-Ph*), 127.4, 127.9, 128.0, 130.0, 130.8 (*C*(2″), *C*(3″), *C*(5″), *C*(6″), *m-Ph*, *o-Ph*, 2 × *Ar*), 132.9, 143.8, 145.0 (*Ar*);[9] *m/z* (ESI$^+$) 477 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}N_2O_3S^+$ ([M+H]$^+$) requires 477.2206; found 477.2206.

(3a*S*,4*S*,9b*S*,α*R*)-1-[α-Methylbenzyl]-4-(2'-chloroethyl)-8-bromo–2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 216 and (3a*S*,4*S*,9b*S*,α*R*)-1-[α-Methylbenzyl]-4-(2'-chloroethyl)-6,8-dibromo–2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 217



216

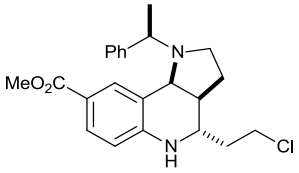


217

A solution of NBS (39.0 mg, 0.22 mmol) in DMF (0.6 mL) was added dropwise *via* syringe over a period of 10 mins to a solution of **213** (71 mg, 0.21 mmol) in DMF (1 mL) at rt. Once addition was complete the resultant mixture was stirred at rt for 1 h. The mixture was diluted with $CHCl_3$ (50 mL) and washed with H_2O (2 × 10 mL). The aqueous layer was extracted with $CHCl_3$ (20 mL) and the combined organic extracts were washed with brine (2 × 20 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 60:40) gave firstly **217** as a colourless oil (6.2 mg, 6%, ~90% purity); $[\alpha]_D^{20}$ –47.8 (*c* 0.37 in $CHCl_3$); ν_{max} (film) 3396 (N–H), 2962, 2928 (C–H); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.54-1.66 (1H, m, C(3)H_A),

1.75-2.06 (4H, m, C(3)H_B, C(3a)*H*, C(1')H_2), 2.59-2.69 (2H, m, C(2)H_2), 3.43-3.51 (1H, m, C(4)*H*), 3.54-3.65 (3H, m, C(9b)*H*, C(2')H_2), 3.93 (1H, q, *J* 6.6, C(α)*H*), 4.68 (1H, br s, N*H*), 7.10-7.17 (2H, *p-Ph*, *Ar*), 7.18-7.29 (4H, m, *o-*,*m-Ph*), 7.32 (1H, d, *J* 2.2, *Ar*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 15.1 (C(α)*Me*), 26.8 (*C*(3)), 28.0 (*C*(3a)), 36.6 (*C*(1')), 39.1 (*C*(4)), 42.0 (*C*(2')), 44.7 (*C*(2)), 50.8 (*C*(4)), 56.9 (*C*(α)), 58.6 (*C*(9b)), 126.8 (*p-Ph*), 127.3, 128.2 (*o-Ph*, *m-Ph*), 132.4, 132.9, 144.6 (*Ph*, *Ar*); *m*/*z* (ESI^+) 499 ([M($^{79}Br^{81}Br^{35}Cl$)+H]$^+$, 100%); HRMS (ESI^+) $C_{21}H_{24}{}^{79}Br^{81}Br^{35}ClN_2{}^+$ ([M($^{79}Br^{81}Br^{35}Cl$)+H]$^+$) requires 498.9968; found 498.9957. Further elution gave **216** as a yellow oil (60 mg, 68%, >99:1 dr); $[\alpha]_D^{20}$−65.2 (*c* 1.55 in $CHCl_3$); ν_{max} (film) 3416 (N–H), 3058, 3025, 2964, 2932, 2874 (C–H); δ_H (300 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.7, C(α)*Me*), 1.47-1.64 (1H, m, C(3)H_A), 1.70-2.02 (4H, m, C(3)H_B, C(3a)*H*, C(1')H_2), 2.52-2.64 (2H, m, C(2)H_2), 3.29-3.40 (1H, m, C(4)*H*), 3.49-3.59 (3H, m, C(9b)*H*, C(2')H_2), 3.96 (1H, q, *J* 6.7, C(α)*H*), 6.31 (1H, d, *J* 8.5, C(6)*H*), 6.99 (1H, dd, *J* 8.5, 2.3, C(7)*H*), 7.06-7.32 (6H, m, C(9)*H*, *Ph*); δ_C (75 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 26.8 (*C*(3)), 36.6 (*C*(1')), 39.2 (*C*(3a)), 42.1 (*C*(2')), 44.5 (*C*(2)), 50.7 (*C*(4)), 56.4 (*C*(α)), 58.2 (*C*(9b)), 108.7, 116.0, 123.8, 126.7, 127.4, 128.2, 130.6, 133.1, 142.8, 144.9 (*Ph*, *Ar*); *m*/*z* (ESI^+) 421 ([M($^{81}Br^{35}Cl$)+H]$^+$, 100%); HRMS (ESI^+) $C_{21}H_{25}{}^{81}Br^{35}ClN_2{}^+$ ([M($^{81}Br^{35}Cl$)+H]$^+$) requires 421.0863; found 421.0849.

(3a*S*,4*S*,9b*S*,α*R*)-1-[α-Methylbenzyl]-4-(2'-chloroethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 222

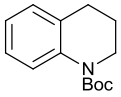


Method A: Following *General Procedure 8*, $Pd(OAc)_2$ (4.0 mg), Xantphos (20.8 mg), **216** (76 mg, 0.18 mmol), (2.0 mL) and MeOH (1.0 mL) at 70 °C for 16 h gave a 50:50 mixture of **216** and **222**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 66:34→50:50) gave firstly **216** as a colourless oil (9.5 mg, 22.6 μmol, 13%). Further elution gave a 79:21 mixture of **212** and **216** (39 mg), respectively. Repeated column chromatography of this fraction gave **222** as a colourless oil (20 mg, 28%, >99:1 dr); $[\alpha]_D^{20}$−73.5 (*c* 1.06 in $CHCl_3$); ν_{max} (neat) 3371 (N–H), 2950, 2876, 2839 (C–H), 1689 (C=O); δ_H (400 MHz, $CDCl_3$) 1.50 (3H, d, *J* 6.8, C(α)*Me*), 1.57-1.68 (1H, m, C(3)H_A), 1.87-2.14 (4H, m, C(3)H_B, C(3a)*H*, C(1')H_2), 2.61-2.70 (2H, m, C(2)H_2), 3.45-3.58 (1H, m, C(4)*H*), 3.63-3.74 (3H, m, C(2')H_2, C(9b)*H*), 3.85 (3H, s, O*Me*), 4.13 (1H, q, *J* 6.8, C(α)*H*), 4.64 (1H, s, N*H*), 6.51 (1H, d, *J* 8.2, C(6)*H*), 7.13-7.20 (1H, m, *p-Ph*), 7.22-7.29 (2H, m, *m-Ph*), 7.32 (2H, d, *J* 7.5, *o-Ph*), 7.71 (1H, dd, *J* 8.2, 1.7, C(7)*H*), 7.84 (1H, d, *J* 1.7,

C(9)*H*); δ_C (125 MHz, $CDCl_3$) 13.0 (*C*(α)*Me*), 26.4 (*C*(3)), 36.6 (*C*(1')), 38.8 (*C*(3a)), 42.1 (*C*(2')), 43.6 (*C*(2)), 50.8 (*C*(4)), 51.6 (O*Me*), 55.0 (*C*(α)), 58.5 (*C*(9b)), 113.4, 118.0, 119.5, 126.5, 127.4, 128.0, 130.1, 133.4, 144.9, 148.0 (*Ph*, *Ar*), 167.4 (*C*O_2Me); *m*/*z* (ESI^+) 399 ($[M(^{35}Cl)+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{28}{}^{35}ClN_2O_2^+$ ($[M(^{35}Cl)+H]^+$) requires 399.1834; found 399.1820.

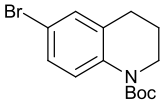
Method B: Following *General Procedure 8*, $Pd(OAc)_2$ (11.4 mg, 51 μmol), Xantphos (59 mg, 0.10 mmol), **216** (213 mg, 0.51 mmol), Et_3N (3.4 mL) and MeOH (0.6 mL) at 70 °C for 16 h gave the crude product. The crude product was resubjected to the reaction conditions once more. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 75:25) gave **222** as a colourless oil (35 mg, 17%, >99:1 dr).

N-(*tert*-Butoxycarbonyl)-2,3,4-trihydroquinoline 219



Boc_2O (4.78 g, 21.9 mmol), Et_3N (5.60 mL, 40.2 mmol) and DMAP (127 mg, 1.04 mmol) were added sequentially to a solution of tetrahydroquinoline **218** (2.78 g, 20.8 mmol) in CH_2Cl_2 (50 mL) at rt and the mixture was stirred at 35 °C for 16 h. The mixture was washed with 1.0 M HCl (2 × 50 mL) and the combined aqueous washings were extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed sequentially with sat. ap. $NaHCO_3$ (50 mL), brine (50 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 ˚C petrol/EtOAc, 83:17) gave **219** as a colourless oil (3.13 g, 65%);[10] δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, C*Me*$_3$), 1.93 (2H app quin, *J* 6.6, C(3)*H*$_2$), 2.77 (2H, t, *J* 6.6, C(4)*H*$_2$), 3.72 (2H, t, *J* 6.0, C(2)*H*$_2$), 6.99 (1H, td, *J* 7.3, 1.1, *Ar*), 7.08 (1H, d, *J* 7.5, *Ar*), 7.11-7.18 (1H, m, *Ar*), 7.65 (1H, d, *J* 8.4, *Ar*).

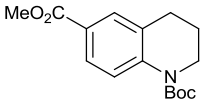
N-(*tert*-Butoxycarbonyl)-6-bromo-1,2,3,4-tetrahydroquinoline 220



NBS (294 mg, 1.65 mmol) was added portionwise over 5 mins to a solution of **219** (385 mg, 1.65 mmol) in MeCN (15 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, then was allowed to warm to rt over 16 h and was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and was washed with brine (2 × 10 mL), then dried and concentrated *in vacuo* to give **220** as a yellow solid which was >99% *para* and was used without further purification; mp 85-87 °C; ν_{max} (ATR) 2948, 2893 (C−H), 1698 (C=O); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, C*Me*$_3$), 1.85-1.94 (2H, m, C(3)*H*$_2$), 2.69-2.77 (2H, app t, *J* 6.5, C(4)*H*$_2$), 3.68 (2H, app t, *J* 6.1, C(2)*H*$_2$), 7.18-7.28 (2H, m, C(5)*H*,

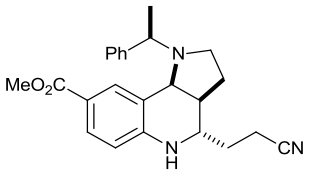
C(7)*H*), 7.56 (1H, d, *J* 8.6, C(8)*H*); δ_C (100 MHz, $CDCl_3$) 23.2 (*C*(3)), 27.4 (*C*(4)), 28.4 (C*Me*$_3$), 44.6 (*C*(2)), 81.1 (*C*Me$_3$), 115.9 (*Ar*), 125.7 (*C*(8)), 128.7, 131.1 (*C*(5), *C*(7)), 132.0, 137.7 (*Ar*), 153.7 (N*C*O); *m*/*z* (ESI$^+$) 334 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{18}{}^{79}BrNNaO_2{}^+$ ([M(^{79}Br)+Na]$^+$) requires 334.0413; found 334.0407.

_N_-(*tert*-Butoxycarbonyl)-6-(methoxycarbonyl)-1,2,3,4-tetrahydroquinoline 221



Following *General Procedure 8*, $Pd(OAc)_2$ (7.2 mg, 32 μmol), Xantphos (37 mg, 64 μmol), **220** (100 mg, 0.32 mmol), Et_3N (2.1 mL) and MeOH (0.4 mL) gave a >80:20 mixture of **221** and **220**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 83:17) gave **221** as a yellow solid (54 mg, 27%); mp 107-109 °C; ν_{max} (ATR) 2965, 2898, 2847 (C−H), 1720 [C=O (ester)], 1692 [C=O (carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, C*Me*$_3$), 1.92 (2H, m, C(3)*H*$_2$), 2.79 (2H, t, *J* 6.3, C(4)*H*$_2$), 3.72 (2H, t, *J* 6.1, C(2)*H*$_2$), 7.74-7.82 (3H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 23.1 (*C*(3)), 27.7 (*C*(4)), 28.3 (C*Me*$_3$), 45.1 (*C*(2)), 51.9 (O*Me*), 81.4 (*C*Me$_3$), 123.3, 124.3, 127.3, 129.4, 130.1, 142.9 (*Ar*), 153.6 (N*C*O), 166.9 (CO_2Me); *m*/*z* (ESI$^+$) 314 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{21}NNaO_4{}^+$ ([M+Na]$^+$) requires 314.1363; found 314.1355.

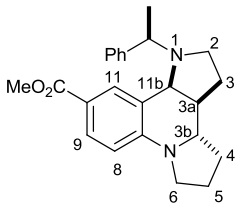
(3a*S*,4*S*,9b*S*,α*R*)-1-[α-Methylbenzyl]-4-(2'-cyanoethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 223



NaCN (10 mg, 0.19 mmol) was added to a solution of **222** (50 mg, 0.13 mmol) in DMSO (1.0 mL) and the resultant mixture was heated for 16 h at 90 °C. The mixture was allowed to cool to rt and was partitioned between H_2O (10 mL) and EtOAc (20 mL). The mixture was washed with H_2O (3 × 10 mL) and the combined aqueous layers were extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 50:50) gave **223** as a pale brown oil (38 mg, 79%, >99:1 dr); $[\alpha]_D^{20}$–70.0 (*c* 0.96 in $CHCl_3$); ν_{max} (film) 3374 (N–H), 2949, 2876, 2849 (C–H), 2247 (C≡N), 1703 (C=O); δ_H (500 MHz, $CDCl_3$) 1.50 (3H, d, *J* 6.6, C(α)*Me*), 1.57-1.66 (1H, m, C(3)*H*$_A$), 1.87-2.07 (4H, m, C(3)*H*$_B$, C(3a)*H*, C(1')*H*$_2$), 2.44 (1H, dd, *J* 17.0, 7.3, C(2')*H*$_A$), 2.51 (1H, dd, *J* 17.0, 7.6, C(2')*H*$_B$), 2.62-2.72 (2H, m, C(2)*H*$_2$), 3.47-3.56 (1H, br m, C(4)*H*), 3.70 (1H, d,

J 4.1, C(9b)*H*), 3.86 (3H, s, O*Me*), 4.13 (1H, q, *J* 6.6, C(α)*H*), 4.49 (1H, br s, N*H*), 6.54 (1H, d, *J* 8.5, C(6)*H*), 7.13-7.19 (1H, m, *p-Ph*), 7.21-7.34 (4H, m, *o-Ph*, *m-Ph*), 7.72 (1H, d, *J* 8.5, C(7)*H*), 7.84 (1H, s, C(9)*H*); δ_C (125 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 13.2 (*C*(2')), 26.1 (*C*(3)), 29.3 (*C*(1')), 37.8 (*C*(3a)), 43.4 (*C*(2)), 51.2 (*C*(4)), 51.7 (O*Me*), 54.8 (*C*(α)), 58.5 (*C*(9b)), 113.7 (*C*(6)), 118.4, 119.5 (*Ar*), 119.7 (*C*(3')), 126.5, 127.3, 128.0 (*o-*, *m-*, *p- Ph*), 130.2 (*C*(7)), 133.4 (*C*(9)), 144.7, 147.9 (*Ar*), 167.3 (*C*O_2Me); *m*/*z* (ESI^+) 412 ($[M+Na]^+$, 25%), 390 ($[M+H]^+$, 100%); HMRS (ESI^+) $C_{24}H_{28}N_3O_2^+$ ($[M+H]^+$) requires 390.2176; found 390.2164.

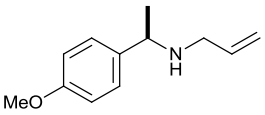
(3a*S*,3b*S*,11b*S*,α*R*)-1-(α-Methylbenzyl)-10-(1'-oxo-1'-methoxy)-2,3,3a,3b,4,5,6,11b-octahydro-1*H*-dipyrrolo[1,2-a:3′,2′-c]quinoline 224



$Pd(OH)_2$/C (5 mg) was added to a stirred, degassed solution of **223** (10 mg, 0.1 mmol) in methanolic HCl (0.4 M in MeOH, 2 mL). The mixture was purged with H_2 and the mixture was vigorously stirred under H_2 (1 atm) at rt for 16 h. After this time the mixture was purged with N_2, filtered through a short pad of Celite® (eleuent MeOH/Et_3N, 100:1, 10 mL) and concentrated *in vacuo*. The residue was redissolved in EtOAc (10 mL) and was washed with 2.0 M NaOH (2 × 10 mL). The organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **224** as a colourless oil (3 mg, 30%, ~90% pure); ν_{max} (ATR) 2360, 2341 (C−H), 1703 (C=O); δ_H (400 MHz, C_6D_6) 1.00-1.14 (1H, m, C(4)H_A), 1.23-1.34 (1H, m, C(5)H_A), 1.36-1.53 (5H, m, C(3)H_A, C(3a)*H*, C(α)*Me*), 1.57-1.65 (1H, m, C(3)H_B), 1.65-1.74 (1H, m, C(5)H_B), 1.77-1.85 (1H, m, C(4)H_B), 2.42-2.51 (1H, m, C(6)H_A), 2.60 (1H, td, *J* 8.9, 4.7, C(6)H_B), 2.87-2.95 (1H, m, C(2)H_A), 3.06 (1H, td, *J* 9.5, 1.6, C(2)H_B), 3.40 (1H, td, *J* 10.4, 5.0, C(3b)*H*), 3.58 (1H, d, *J* 4.4, C(11b)*H*), 3.78 (3H, s, O*Me*), 4.60 (1H, q, *J* 6.6, C(α)*H*), 6.42 (1H, d, *J* 8.5, C(8)*H*), 7.09-7.15 (1H, m, *p-Ph*), 7.20 (2H, app t, *J* 7.6, *m-Ph*), 7.36 (2H, d, *J* 7.6, *o-Ph*), 8.36 (1H, d, *J* 1.9, C(11)*H*), 8.41 (1H, dd, *J* 8.5, 1.9, C(9)*H*); δ_C (125 MHz, C_6D_6) 9.1 (C(α)*Me*), 23.5 (*C*(3)), 25.8 (*C*(5)), 31.9 (*C*(4)), 39.4 (*C*(3a)), 41.7 (*C*(6)), 47.2 (*C*(2)), 51.1 (O*Me*), 52.5 (*C*(α)), 58.7 (*C*(3b)), 60.4 (*C*(11b)), 110.2 (*C*(8)), 116.3, 119.3, 126.4 (*Ar*), 131.5 (*C*(9)), 133.9 (*C*(11)), 145.0, 148.2 (*C*(8a), *Ar*), 167.4 (*C*O_2Me);[11] *m*/*z* (ESI^+) 377 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{29}N_2O_2^+$ ($[M+H]^+$) requires 377.2224; found 377.2210.

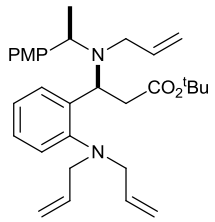
5.4. Experimental for chapter 3

(*R*)-*N*-Allyl-*N*-(α-methyl-4-methoxybenzyl)amine 227



BuLi (2.17 M in hexanes, 71.0 mL, 154 mmol) was added dropwise to a solution of (*R*)-**226** (22.1 g, 147 mmol, >99% ee) in THF (250 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C then allyl bromide (13.9 mL, 161 mmol) was added slowly dropwise. The mixture was allowed to warm to rt over 16 h and then was quenched by addition of satd aq NH_4Cl (5 mL). The mixture was washed with 10% aq citric acid (3 × 100 mL) and the combined aqueous washings were extracted with Et_2O (2 × 100 mL). The aqueous extracts were neutralised by addition of 2.0 M NaOH to pH > 9, then were extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **227** as a pale yellow oil (25.1 g, 90%, >99% ee);[12] $[\alpha]_D^{20}$+63.9 (*c* 0.96 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.7, C(α)*Me*), 1.57 (1H, br s, N*H*), 3.10 (2H, dd, *J* 6.0, 1.4, NC*H*$_2$CH=CH$_2$), 3.77 (1H, q, *J* 6.7, C(α)*H*), 3.81 (3H, s, O*Me*), 5.03-5.22 (2H, m, NCH$_2$CH=C*H*$_2$), 5.83-5.97 (1H, m, NCH$_2$C*H*=CH$_2$), 6.88 (2H, d, *J* 8.5, C(3)*H*, C(5)*H*), 7.24 (2H, d, *J* 8.5, C(2)*H*, C(6)*H*).

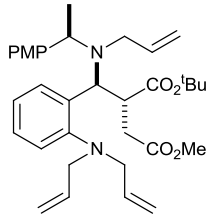
tert-Butyl (3*S*,α*R*)-3-[*N*-allyl-*N*-(α-methyl-4''-methoxybenzyl)amino]-3-(2'-*N*,*N*-diallylaminophenyl)propanoate 233



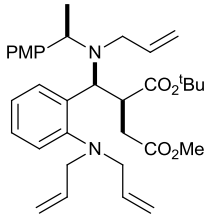
Following *General Procedure 1*, (*R*)-**227** (4.86 g, 25.4 mmol) in THF (75 mL), BuLi (2.5 M in hexanes, 10.2 mL, 25.4 mmol) and **130** (4.75 g, 15.9 mmol) in THF (75 mL) gave **233** in >99:1 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 83:17) gave **233** as a yellow oil (6.90 g, 89%, >99:1 dr); $[\alpha]_D^{20}$+19.9 (*c* 1.3 in $CHCl_3$); ν_{max} (film) 3074, 2977, 2932, 2834 (C–H), 1727 (C=O), 1640, 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.8, C(α)*Me*), 1.34 (9H, s, C*Me*$_3$), 2.54 (1H, dd, *J* 15.4, 6.1, C(2)*H*$_A$), 2.88 (1H, dd, *J* 15.4, 8.2, C(2)*H*$_B$), 3.11-3.20 (1H, m, NC*H*$_A$H$_B$CH=CH$_2$), 3.29-3.37 (1H, m, NCH$_A$*H*$_B$CH=CH$_2$), 3.49-3.67 (4H, m, N(C*H*$_2$CH=CH$_2$)$_2$), 3.79 (3H, s, O*Me*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.89-5.19 (7H, m, C(3)*H*, NCH$_2$CH=C*H*$_2$, N(CH$_2$CH=C*H*$_2$)$_2$), 5.70-5.91 (3H, m, NCH$_2$C*H*=CH$_2$, N(CH$_2$C*H*=CH$_2$)$_2$), 6.81 (2H, d, *J* 8.9, C(3''), C(5'')), 7.06-7.14 (2H, m, *Ar*), 7.16-7.24 (1H, t, *J* 7.6, *Ar*), 7.27 (2H, d, *J* 8.9, C(2''), C(6'')), 7.53 (1H,

dd, *J* 7.9, 1.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 40.4 (*C*(2)), 49.0 (N*C*H$_2$CH=CH$_2$), 54.5 (*C*(3)), 55.2 (O*Me*), 55.7 (*C*(α)), 57.0 (N(*C*H$_2$CH=CH$_2$)$_2$), 80.0 (*C*Me$_3$), 113.1 (*C*(3"), *C*(5")), 114.3 (NCH$_2$CH=*C*H$_2$), 117.6 (N(CH$_2$CH=*C*H$_2$)$_2$), 123.7, 124.1, 127.0 (*Ar*), 128.8 (*C*(2"), *C*(6")), 128.9 (*Ar*), 135.0 (NCH$_2$*C*H=CH$_2$), 137.2, 139.9 (*Ar*), 140.1 ((NCH$_2$*C*H=CH$_2$)$_2$), 150.0 (*Ar*), 158.1 (*C*(4')), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 513 ([M+Na]$^+$, 55%), 491 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{43}N_2O_3^+$ ([M+H]$^+$) requires 491.3268; found 491.3253.

tert-Butyl (2*R*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl)-3-[*N*-allyl-*N*-(α-methyl-4'''-methoxybenzyl)amino]-3-(2''-*N*,*N*-diallylaminophenyl)propanoate 234 and _tert_-Butyl (2*S*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl)-3-[*N*-allyl-*N*-(α-methyl-4'''-methoxybenzyl)amino]-3-(2''-*N*,*N*-diallylaminophenyl)propanoate 235



234



235

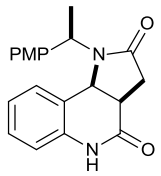
Method A: Following *General Procedure 4*, $^iPr_2NH$ (7.72 mL, 55.1 mmol) in THF (250 mL), BuLi (2.5 M in hexanes, 22.0 mL, 55.1 mmol), **233** (18.0 g, 36.7 mmol, >99:1 dr) in THF (250 mL) and methyl bromoacetate (10.4 mL, 110 mmol) gave a >95:5 mixture of **234** and **235**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 5:1) gave a 90:10 mixture of **234** and **235** (9.93 g, 48%); δ_H (400 MHz, $CDCl_3$) [selected peaks for **235**] 2.71 (1H, dd, *J* 16.0, 11.3, C(1')*H*$_A$), 4.66 (1H, d, *J* 11.4, C(3)*H*). Further elution gave **234** as a yellow oil (8.63 g, 42%, >99:1 dr); $[\alpha]_D^{20}$+12.3 (*c* 1.4 in $CHCl_3$); ν_{max} (film) 3074, 2977, 2835 (C–H), 1728 (C=O), 1640, 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.6, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 2.20 (1H, dd, *J* 15.5, 3.2, C(1')*H*$_A$), 2.50 (1H, dd, *J* 15.5, 11.5, C(1')*H*$_B$), 3.10-3.26 (2H, m, NC*H*$_2$CH=CH$_2$), 3.48-3.58 (3H, m, C(2)*H*, N(C*H*$_A$H$_B$CH=CH$_2$)$_2$), 3.60 (3H, s, CO$_2$*Me*), 3.58-3.68 (2H, m, N(CH$_A$*H*$_B$CH=CH$_2$)$_2$), 3.78 (3H, s, O*Me*), 4.11 (1H, q, *J* 6.6, C(α)*H*), 4.76-4.89 (2H, m, NCH$_2$CH=C*H*$_2$), 5.02 (1H, d, *J* 11.9, C(3)*H*), 5.11-5.22 (4H, m, N(CH$_2$CH=C*H*$_2$)$_2$), 5.60-5.73 (1H, m, NCH$_2$C*H*=CH$_2$), 5.81-5.95 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 6.66 (2H, d, *J* 8.8, C(3''')*H*, C(5''')*H*), 7.10-7.21 (4H, m, C(2''')*H*, C(6''')*H*, *Ar*), 7.24-7.30 (1H, m, *Ar*), 7.37 (1H, dd, *J* 7.8, 1.5, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(α)*Me*), 28.1 (C*Me*$_3$), 35.9 (*C*(1')), 46.6 (CO$_2$*Me*), 49.8 (N*C*H$_2$CH=CH$_2$), 51.6 (*C*(2)), 55.2 (O*Me*), 55.9 (*C*(α)), 57.3 (N(*C*H$_2$CH=CH$_2$)$_2$), 57.4 (*C*(3)), 80.7 (*C*Me$_3$), 112.9 (*C*(3"), *C*(5")), 114.6 (NCH$_2$CH=*C*H$_2$), 118.4 (N(CH$_2$CH=*C*H$_2$)$_2$), 124.4, 124.5, 127.6 (*Ar*), 129.0 (*C*(2"),

C(6")), 134.3 (N(CH_2*C*H=CH_2)$_2$), 134.7, 137.4 (*Ar*), 138.9 (NCH_2*C*H=CH_2), 151.4 (*Ar*), 158.0 (*C*(4')), 172.1, 173.7 (*C*(1), *C*(2'));[13] *m*/*z* (ESI$^+$) 585 ([M+Na]$^+$, 40%), 563 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{47}N_2O_5^+$ ([M+H]$^+$) requires 563.3479; found 563.3458.

Method B: *Step 1*: Following *General Procedure 1*, (*R*)-**227** (10.0 g, 52.5 mmol) in THF (150 mL), BuLi (2.17 M in hexanes, 24.0 mL, 52.2 mmol) and **130** (9.79 g, 32.7 mmol, >99:1 dr) in THF (150 mL) gave **233** in >99:1 crude dr which was used in the next step without purification.

Step 2: Following *General Procedure 4*, **233** from the previous reaction in THF (150 mL), ^{i}Pr$_2$NH (6.90 mL, 49.1 mmol) in THF (150 mL), BuLi (2.17 M in hexanes, 22.6 mL, 49.1 mmol), methyl bromoacetate (9.30 mL, 98.1 mmol) and THF (300 mL) gave **235** in >95:5 crude dr. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 83:17) gave **235** as a yellow oil (14.4 g, 78% over 2 steps from **130**, >98:2 dr).

(3a*R*,9b*S*,α*R*)-1-[α-Methyl-4'-methoxybenzyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 237

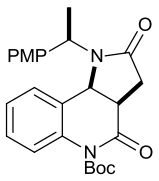


Step 1: $Pd(PPh_3)_4$ (112 mg, 98 μmol) was added to a stirred, degassed solution of **234** (1.10 g, 1.95 mmol, >98:2 dr) and DMBA (2.74 g, 17.6 mmol) in degassed CH_2Cl_2 (30 mL) under Ar and the resultant mixture was stirred at 35 °C for 16 h. Additional $Pd(PPh_3)_4$ (112 mg, 98 μmol) was then added and the mixture was stirred at 35 °C for a further 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in Et_2O (50 mL). The resultant solution was washed with satd aq K_2CO_3 solution (2 × 20 mL) and the combined aqueous layers were extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with 3.0 M aq HCl (3 × 20 mL), and 2.0 M aq NaOH was added to the combined aqueous layers until pH >10 was achieved. The aqueous layer was then extracted with $CHCl_3$/IPA (3:1, 3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **236** as a yellow oil (755 mg, >98:2 dr) which was used without further purification in the next step; δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.19 (1H, dd, *J* 16.9, 4.6, C(1')H_A), 2.43 (1H, dd, *J* 16.9, 4.4, C(1')H_B), 3.40 (1H, td, *J* 9.7, 4.4, C(2)*H*), 6.51 (1H, dd, *J* 7.9, 1.0, *Ar*), 6.62 (1H, td, *J* 7.4, 1.0, *Ar*), 6.78 (2H, d, *J* 8.6, C(3''')*H*, C(5''')*H*), 6.90 (1H, dd, *J* 7.5, 1.4, *Ar*), 7.03 (1H, td, *J* 7.6, 1.5, *Ar*), 7.11 (2H, d, *J* 8.6, C(2''')*H*, C(6''')*H*).

Step 2: Following *General Procedure 6*, $PhCO_2H$ (47 mg, 0.39 mmol) and **236** (755 mg, >98:2 dr) in PhMe (10 mL) at reflux for 16 h gave the crude product **237**. Purification *via* flash column

chromatography (eluent CH_2Cl_2/MeOH, 95:5) gave **237** as a pale yellow solid (341 mg, 52% from **234**, >99:1 dr); mp 108-112 °C; $[\alpha]_D^{20}$+61.8 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3216, 3063, 2922, 2933 (C–H), 1682 [C=O (γ-lactam)], 1615 [C=O (δ-lactam)]; δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 7.3, C(α)*Me*), 2.78 (1H, dd, *J* 16.4, 8.1, C(3)H_A), 3.05-3.13 (1H, m, C(3a)*H*), 3.28 (1H, d, *J* 16.4, C(3)H_B), 3.81 (3H, s, O*Me*), 4.69 (1H, d, *J* 5.6, C(9b)*H*), 5.43 (1H, q, *J* 7.3, C(α)*H*), 6.36 (1H, d, *J* 7.6, *Ar*), 6.83-7.04 (6H, m, C(2')*H*, C(3')*H*, C(5')*H*, C(6')*H*, *Ar*), 7.26-7.33 (1H, m, *Ar*), 10.06 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 34.3 (*C*(3)), 38.5 (*C*(3a)), 48.5 (*C*(α)), 55.3 (O*Me*), 57.6 (*C*(9b)), 113.8 (*C*(3'), *C*(5')), 116.0, 117.4, 122.6 (*Ar*), 128.7 (*C*(2'), *C*(6')), 130.7, 131.0, 131.6, 137.7 (*Ar*), 158.7 (*C*(4')), 171.0, 173.6 (*C*(2), *C*(4)); *m*/*z* (ESI^+) 695 ($[2M+Na]^+$, 100%), 359 ($[M+Na]^+$, 20%); HRMS (ESI^+) $C_{20}H_{20}N_2NaO_3^+$ ($[M+Na]^+$) requires 359.1366; found 359.1362.

(3a*R*,9b*S*,α*R*)-1-[α-Methyl-4'-methoxybenzyl]-5-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 238



Method A: Boc_2O (243 mg, 1.12 mmol) was added to a solution of **237** (341 mg, 1.01 mmol), Et_3N (0.28 mL, 2.02 mmol) and DMAP (12 mg, 0.10 mmol) in CH_2Cl_2 (20 mL) and the resultant mixture was heated at 35 °C for 16 h. The mixture was then washed with 1.0 M aq HCl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* recrystallisation (PhMe) gave **238** as a white solid (345 mg, 78%, >99:1 dr); $C_{25}H_{28}N_2O_5$ requires C, 68.8; H, 6.5; N, 6.4%; found C, 68.8; H, 6.6; N, 6.5%; mp 162-167 °C; $[\alpha]_D^{20}$+49.0 (*c* 1.04 in $CHCl_3$) ν_{max} (ATR) 2980, 2936, 2837 (C–H), 1767 [C=O (carbamate)], 1691 (C=O [γ lactam]); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 7.1, C(α)*Me*), 1.59 (9H, s, CMe_3), 2.69 (1H, dd, *J* 16.4, 7.5, C(3)H_A), 3.04-3.12 (1H, app t, *J* 6.1, C(3a)*H*), 3.25 (1H, d, *J* 16.4, C(3)H_B), 3.81 (3H, s, O*Me*), 4.59 (1H, d, *J* 5.1, C(9b)*H*), 5.42 (1H, q, *J* 7.1, C(α)*H*), 6.34 (1H, d, *J* 6.8, *Ar*), 6.82-7.00 (6H, m, C(2')*H*, C(3')*H*, C(5')*H*, C(6')*H*, *Ar*), 7.33 (1H, td, *J* 7.8, 1.3, *Ar*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 27.6 (CMe_3), 34.6 (*C*(3)), 39.5 (*C*(3a)), 48.4 (*C*(α)), 55.3 (O*Me*), 57.4 (*C*(9b)), 85.8 (*C*Me_3), 113.8 (*C*(3'), *C*(5')), 116.1, 118.7, 123.7 (*Ar*), 128.6 (*C*(2'), *C*(6')), 130.5, 130.9, 132.0, 137.0 (*Ar*), 156.8 (N*C*O), 158.8 (*C*(4')), 167.7, 173.2 (*C*(2), *C*(4)); *m*/*z* (ESI^+) 895 ($[2M+Na]^+$, 100%), 459 ($[M+Na]^+$, 30%); HRMS (ESI^+) $C_{25}H_{28}N_2NaO_5^+$ ($[M+Na]^+$) requires 459.1890; found 459.1885.

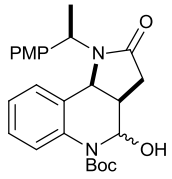
Method B: *Step 1*: $Pd(PPh_3)_4$ (488 mg, 0.42 mmol) was added to a stirred, degassed solution of **234**

(4.75 g, 8.44 mmol, >98:2 dr) and DMBA (11.8 g, 76 mmol) in CH_2Cl_2 (100 mL), and the resultant mixture was stirred at 35 °C for 16 h. Additional $Pd(PPh_3)_4$ (488 mg, 0.42 mmol) was then added and the mixture was stirred at 35 °C for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in Et_2O (100 mL). The resultant solution was washed with satd aq K_2CO_3 solution (2 × 50 mL) and the combined aqueous layers were extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with 3.0 M HCl (3 × 40 mL) and 2.0 M aq NaOH was added to the combined aqueous layers until pH >10 was achieved. The aqueous layer was then extracted with $CHCl_3$/IPA (3:1, 3 × 40 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **236** as a yellow oil (3.70 g, >99:1 dr) which was used without further purification in the next step.

Step 2: Following *General Procedure 5*, **236** (3.70 g, >99:1 dr) and $PhCO_2H$ (206 mg, 1.60 mmol) in PhMe (100 mL) at reflux for 16 h gave **237** which was used in the next step without purification.

Step 3: Boc_2O (2.02 g, 9.28 mmol), Et_3N (3.50 mL, 25.0 mmol) and DMAP (103 mg, 0.84 mmol) were added sequentially to a solution of **237** (3.70 g, >99:1 dr) in CH_2Cl_2 (80 mL) and the resultant solution was stirred at 35 °C for 16 h. The solution was washed with 1.0 M HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were then washed sequentially with satd aq $NaHCO_3$ (50 mL), brine (50 mL) then dried and concentrated *in vacuo*. Recrystallisation (PhMe) gave **238** as a pale yellow solid (2.09 g, 57% over 3 steps from **234**, >99:1 dr).

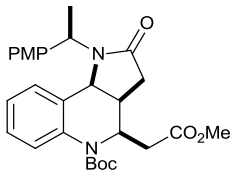
(3a*R*,4*R*,9b*S*,α*R*)- or (3a*R*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4'-methoxybenzyl]-4-hydroxy-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 239[14]



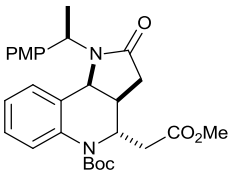
$LiAl(O^tBu)_3H$ (5.97 g, 23.4 mmol) was added portionwise to a stirred solution of **238** (6.83 g, 15.6 mmol) in THF (150 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. H_2O (2.0 mL) was then added dropwise and the mixture was diluted with EtOAc (50 mL) and stirred at rt for 30 min, then filtered through Celite® (eluent EtOAc/Et_3N, 100:1, 300 mL). The filtrate was then dried and concentrated *in vacuo* to give **239** as a colourless foam which was used without further purification (6.86 g, quant, >99:1 dr); $[\alpha]_D^{20}$+45.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3299 (O–H), 2976, 2934, 2837 (C–H), 1695 [C=O (γ-lactam, carbamate)]; δ_H (500 MHz, $CDCl_3$) 0.93 (3H, d, *J* 7.3, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 2.60 (1H, d, *J* 15.1, C(3)H_A), 2.82-2.94 (2H, m, C(3)H_B, C(3a)*H*), 3.84

(3H, s, O*Me*), 4.48 (1H, d, *J* 6.9, C(9b)*H*), 5.39 (1H, q, *J* 7.3, C(α)*H*), 5.84 (1H, s, C(4)*H*), 6.47 (1H, d, *J* 7.3, *Ar*), 6.88 (2H, d, *J* 8.5, C(3')*H*, C(5')*H*), 6.96-7.02 (3H, m, C(2')*H*, C(6')*H*, *Ar*), 7.29-7.69 (2H, m, *Ar*); δ_C (125 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 28.4 (C*Me*$_3$), 36.5 (*C*(3)), 42.4 (*C*(3a)), 49.3 (*C*(α)), 55.4 (O*Me*), 56.8 (*C*(9b)), 82.1, 82.2 (*C*(4), *C*Me$_3$), 113.6 (*C*(3'), *C*(5')), 124.3, 125.9, 128.3 (*Ar*), 129.0 (*C*(2'), *C*(6')), 129.3, 130.6, 130.7, 137.3 (*Ar*), 152.8 (N*C*O), 158.8 (*C*(4')), 173.4 (*C*(2)); *m*/*z* (ESI$^+$) 461 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{30}N_2NaO_5^+$ ([M+Na]$^+$) requires 461.2047; found 461.2037.

(3a*S*,4*R*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-methoxy-2'-oxoethyl)-N(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinolin-2-one 243 and (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-methoxy-2'-oxoethyl)-N(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinolin-2-one 240



243



240

Method A: NaH (60% w/w in mineral oil, 636 mg, 15.9 mmol) was added to a stirred solution of **200** (3.34 g, 15.9 mmol) in THF (50 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 10 min. A solution of **239** (4.65 g, 10.6 mmol) in THF (50 mL) at 0 °C was added dropwise *via* cannula and the resultant mixture was stirred at 0 °C for 2 h, then was quenched by addition of H_2O (1 mL). The solution was diluted with brine (50 mL) and the aqueous layer was extracted with EtOAc (50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 24:76 mixture of **240** and **243**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **243** as a colourless oil (3.54 g, 67%, >99:1 dr); $[\alpha]_D^{20}$–38.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2979, 2935, 2838 (C–H), 1738 [C=O (ester)], 1696 [C=O (γ-lactam, carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 7.1, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 2.31 (2H, app d, *J* 8.6, C(3)H_2), 2.39 (1H, dd, *J* 15.2, 7.1, C(1')H_A), 2.53-2.69 (1H, m, C(1')H_B), 3.04-3.16 (1H, m, C(3a)*H*), 3.65 (3H, s, CO_2Me), 3.82 (3H, s, ArO*Me*), 4.36 (1H, d, *J* 7.8, C(9b)*H*), 4.60 (1H, br s, C(4)*H*), 5.54 (1H, q, *J* 7.1, C(α)*H*), 6.88 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.05 (1H, d, *J* 7.3, *Ar*), 7.11 (1H, td, *J* 7.3, 1.3, *Ar*), 7.17 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*), 7.30 (1H, td, *J* 7.6, 1.4, *Ar*), 7.37 (1H, d, *J* 7.8, *Ar*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 28.2 (C*Me*$_3$), 32.5 (*C*(3)), 36.2 (*C*(1')), 40.8 (*C*(3a)), 50.3 (*C*(α)), 51.9 (CO_2Me), 52.3 (broad, *C*(4)), 55.2 (ArO*Me*), 56.5 (*C*(9b)), 81.4 (*C*Me$_3$), 113.9 (*C*(3"), *C*(5")), 124.9, 126.3, 128.0, 128.1 (*Ar*), 128.4 (*C*(2"), *C*(6")), 130.7, 132.5, 153.2 (*Ar*, N*C*O),

158.9 (*C*(4")), 171.2, 174.5 (*C*(2), *C*(2'));[15] *m/z* (ESI$^+$) 517 ([M+Na]$^+$, 100%), 495 ([M+H]$^+$, 50%); HRMS (ESI$^+$) $C_{28}H_{34}N_2NaO_6^+$ ([M+Na]$^+$) requires 517.2309; found 517.2310. Further elution gave **240** as a colourless oil (1.03 g, 20%, >99:1 dr); $[\alpha]_D^{20}$+70.5 (*c* 1.45 in $CHCl_3$); ν_{max} (ATR) 2975, 2936, 2838 (C–H), 1738 (C=O, [ester]), 1695 [C=O (γ-lactam, carbamate)], 1609 [C=O (carbamate)]; δ_H (400 MHz, C_6D_6) 1.02 (3H, d, *J* 7.3, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 1.89 (1H, dd, *J* 15.4, 7.3, C(1')*H*$_A$), 1.97 (1H, dd, *J* 15.4, 8.1, C(1')*H*$_B$), 2.14-2.25 (1H, m, C(3a)*H*), 2.67 (1H, dd, *J* 17.2, 9.6, C(3)*H*$_A$), 2.72-2.82 (1H, m, C(3)*H*$_B$), 3.38 (3H, s, CO_2*Me*), 3.52 (3H, s, ArO*Me*), 4.17 (1H, *J* 7.8, C(9b)*H*), 5.04 (1H, br s, C(4)*H*), 5.70 (1H, q, *J* 7.3, C(α)*H*), 6.50 (1H, dd, *J* 7.6, 1.3, C(9)*H*), 6.87 (1H, dd, *J* 7.6, 1.0, C(8)*H*), 6.91 (2H, d, *J* 8.8, C(3")*H*, C(5")*H*), 7.05 (2H, d, *J* 8.8, C(2")*H*, C(6")*H*), 7.19 (1H, app td, *J* 7.8, 1.5, C(7)*H*), 7.53 (1H, br s, C(6)*H*); δ_C (100 MHz, C_6D_6) 17.0 (C(α)*Me*), 28.2 (C*Me*$_3$), 38.7 (*C*(3)), 39.2 (*C*(1′)), 40.3 (*C*(3a)), 49.4, 51.1 (O*Me*, *C*(α)), 53.5, 54.9, 56.6 (*C*(4), *C*(9b), O*Me*), 80.9 (*C*Me$_3$), 113.9 (*C*(3"), *C*(5")), 124.3 (*C*(8)), 127.5 (*C*(6)), 129.0 (*C*(7)), 129.3, (*C*(2"), (*C*(6")), 130.2 (*C*(9)), 130.4, 131.7, 139.3, 152.9 (*Ar*, N*C*O), 159.2 (*C*(4")), 170.3, 173.1 (*C*(2), *C*(2')); *m/z* (ESI$^+$) 989 ([2M+H]$^+$, 100%), 517 ([M+Na]$^+$, 100%), 495 ([M+H]$^+$, 35%); HRMS (ESI$^+$) $C_{28}H_{34}NaN_2O_6^+$ ([M+Na]$^+$) requires 517.2309; found 517.2307.

The conditions (i)-(iv) reported in Scheme 54 and conditions (i) reported in Scheme 55 were performed according to the above procedure, differing only in concentration or equivalents of NaH.

Method B: NaH (60% w/w in mineral oil, 8.3 mg, 0.21 mmol) was added to a solution of **200** (44 mg, 0.21 mmol) and **239** (83 mg, 0.19 mmol) in THF (1.90 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 2 h, then was quenched by addition of H_2O (1 mL). The solution was diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 62:26:8:4 mixture of **240**, **243**, (*E*)-**241** and (*Z*)-**242**, respectively.

Method C: NaH (60% w/w in mineral oil, 13 mg, 0.32 mmol) was added to a solution of **200** (68 mg, 0.32 mmol) in THF (1.50 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 10 min. A solution of **239** (129 mg, 0.29 mmol) in THF (1.50 mL) at 0 °C was added dropwise *via* cannula and the mixture was stirred at 0 °C for 5 min, then was quenched by addition of H_2O (1 mL). The solution was diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 12:21:28:34:5 mixture of **239**, **240**, **243**, (*E*)-**241** and (*Z*)-**242**, respectively.

Method D: NaH (60% w/w in mineral oil, 12 mg, 0.31 mmol) was added to a solution of **200** (64 mg, 0.31 mmol) in THF (1.4 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 10 min. A solution of **239** (122 mg, 0.28 mmol) in THF (1.4 mL) at 0 °C was added dropwise *via* cannula and the resultant mixture was stirred at 0 °C for 5 min, then at 50 °C for 2 h, then was quenched by addition of H_2O (1 mL). The solution was diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give an 80:20 mixture of **240** and **243**, respectively.

Method E: NaH (60% w/w in mineral oil, 0.8 mg, 20 μmol) was added to a solution of **200** (46 mg, 0.22 mmol) in THF (1.0 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 10 min. A solution of **239** (89 mg, 0.20 mmol) and TMSCl (76 μL, 0.60 mmol) in THF (1.0 mL) at 0 °C was added dropwise *via* cannula and the resultant mixture was stirred at 0 °C for 2 h, then was quenched by addition of H_2O (1 mL). The solution was diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give returned starting material.

Method F: NaH (60% w/w in mineral oil, 5.8 mg, 0.15 mmol) was added to a solution of **200** (31 mg, 0.15 mmol) in THF (0.6 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 10 min. A solution of **239** (58 mg, 0.13 mmol) and TMSCl (51 μL, 0.40 mmol) in THF (0.70 mL) at 0 °C was added dropwise *via* cannula and the resultant mixture was stirred at 0 °C for 2 h, then was quenched by addition of H_2O (1 mL). The solution was diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 98:2 mixture of **239** and (*E*)-**241**, respectively.

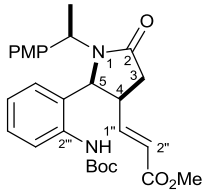
Method G: NaH (60% w/w in mineral oil, 2.8 mg, 70 μmol) was added to an 86:14 mixture of (*E*)-**241** and (*Z*)-**242** (35 mg, 70 μmol) in THF (0.7 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 2 h, then was quenched by addition of H_2O (1 mL). The mixture was diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a ~50:50 mixture of **240** and **243**, respectively.

Method H: NaH (60% w/w in mineral oil, 168 mg, 4.19 mmol) was added to a solution of **243** (2.07 g, 4.19 mmol) in THF (40 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h, then was quenched by addition of H_2O (10 mL). The solution was diluted with EtOAc (2 × 10 mL) and was washed with brine (20 mL), then dried and concentrated *in vacuo* to give a 43:57 mixture of **240** and **243**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **243** as a colourless oil (1.00 g, 48%, >99:1 dr). Further elution

gave **240** as a colourless oil (552 mg, 27%, >99:1 dr).

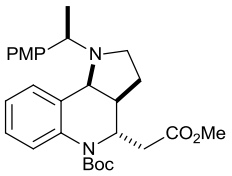
Method I: NaH (60% w/w in mineral oil, 2 mg, 51 μmol) was added portionwise to a solution of **240** (25 mg, 51 μmol) in THF (0.50 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h, then was quenched by addition of H_2O (1 mL). The solution was diluted with EtOAc (5 mL) and was washed with (5 mL), then dried and concentrated *in vacuo* to give a 48:52 mixture of **243** and **240**, respectively.

(4*S*,5*S*,α*R*,*E*)-*N*(1)-(α-Methyl-4''-methoxybenzyl)-4-(3''-methoxy-3''-oxopropenyl)-5-(2'''-*N*-(*tert*-butoxycarbonylamino)phenyl)pyrrolidin-2-one 241

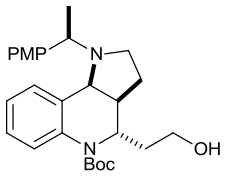


NaH (60% w/w in mineral oil, 7.7 mg, 0.19 mmol) was added to a stirred solution of **239** (421 mg, 0.96 mmol) and **200** (222 mg, 0.19 mmol) in THF (9.6 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h. After this time the mixture was cooled to 0 °C and additional NaH (60% w/w in mineral oil, 19 mg, 0.48 mmol) was added. The mixture was allowed to warm to rt over 16 h, then was quenched by addition of H_2O (1 mL). The solution was diluted with brine (10 mL) and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 44:3:48:5 mixture of **239**, **240**, (*E*)-**241** and (*Z*)-**242**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 33:67→0:100) gave an 86:14 mixture of (*E*)-**241** and (*Z*)-**242**, respectively, as a white foam which crystallised on standing to a white solid (195 mg, 41%); mp 186-194 °C; δ_H (400 MHz, $CDCl_3$) [selected peaks for (*E*)-**241**] 1.16 (3H, d, *J* 7.3, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 2.46 (1H, dd, *J* 16.1, 8.5, C(3)*H*$_A$), 2.65 (1H, dd, *J* 16.1, 11.9, C(3)*H*$_B$), 3.15-3.28 (1H, m, C(4)*H*), 3.60 (3H, s, CO_2*Me*), 3.80 (3H, s, ArO*Me*), 4.73 (1H, d, *J* 8.3, C(5)*H*), 5.55 (1H, q, *J* 7.3, C(α)*H*), 5.60 (1H, br s, N*H*), 5.76 (1H, d, *J* 15.7, C(2'')*H*), 6.16 (1H, dd, *J* 15.7, 8.8, C(1'')*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks for (*E*)-**241**] 17.7 (C(α)*Me*), 28.3 (C*Me*$_3$), 35.3 (*C*(3)), 41.7 (*C*(4)), 50.4 (*C*(α)), 51.6 (CO_2*Me*), 55.2 (ArO*Me*), 56.7 (*C*(5)), 80.7 (*C*Me$_3$), 123.2 (*C*(2'')), 145.2 (*C*(1'')).

(3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-methoxy-2'-oxoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 248 and (3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 249



248



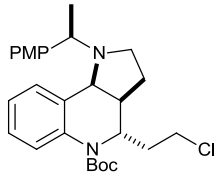
249

Method A: BH_3·THF (1.0 M in THF, 4.0 mL, 4.0 mmol) was added dropwise to a stirred solution of **240** (252 mg, 0.51 mmol) in THF (15 mL) at 0 °C and the mixture was allowed to warm to rt over 16 h. The mixture was cooled to 0 °C and satd aq K_2CO_3 (4 mL) was added carefully. The resultant mixture was heated at reflux for 1 h and then was concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and brine (20 mL), and the aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 36:64 mixture of **248** and **249**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 66:34→0:100) gave **248** as a colourless oil (70 mg, 29%, >99:1 dr); $[\alpha]_D^{20}$+14.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2970, 2934, 2835 (C–H), 1739 (C=O [ester]), 1696 (C=O [carbamate]); δ_H (400 MHz, C_6D_6) 1.30 (3H, d, *J* 6.6, C(α)*Me*), 1.59 (9H, s, C*Me*$_3$), 1.91-2.05 (2H, m, C(3)H_2), 2.13 (1H, dd, *J* 14.9, 7.3, C(1')H_A), 2.21-2.42 (3H, m, C(3a)*H*, C(2)H_A, C(1')H_B), 2.60-2.69 (1H, m, C(2)H_B), 3.41 (3H, s, O*Me*), 3.44 (3H, s, O*Me*), 3.54 (1H, d, *J* 8.6, C(9b)*H*), 3.92 (1H, q, *J* 6.6, C(α)*H*), 5.27 (1H, br s, C(4)*H*), 6.90 (2H, d, *J* 8.7, *C*(3")*H*, *C*(5")*H*), 6.94-7.02 (1H, m, C(8)*H*), 7.08 (1H, d, *J* 7.3, C(9)*H*), 7.22 (1H, td, *J* 7.7, 1.8, C(7)*H*), 7.30 (2H, d, *J* 8.7, *C*(2")*H*, *C*(6")*H*), 7.71 (1H, br s, C(6)*H*); δ_C (100 MHz, C_6D_6) 11.5 (C(α)*Me*), 28.4 (C*Me*$_3$), 30.4 (*C*(3)), 38.9 (*C*(1')), 44.9 (*C*(2)), 45.6 (*C*(3a)), 51.0 (O*Me*), 53.9 (*C*(α)), 54.7 (O*Me*), 55.5 (*C*(4)), 59.2 (*C*(9b)), 80.0 (C*Me*$_3$), 113.6 (*C*(3"), *C*(5")), 124.2 (*C*(8)), 127.3 (*C*(6)), 127.5 (*C*(7)), 128.7 (*C*(2"), *C*(6")), 129.8 (*C*(9)), 132.5, 137.1, 128.4 (*Ar*), 153.9 (N*C*O), 158.8 (*C*(4")), 170.9 (*C*(2')); *m*/*z* (ESI$^+$) 983 ([2M+Na]$^+$, 100%), 503 ([M+Na]$^+$, 15%), 481 ([M+H]$^+$, 75%); HRMS (ESI$^+$) $C_{28}H_{37}N_2O_5^+$ ([M+H]$^+$) requires 481.2697; found 481.2690. Further elution gave **249** as a colourless oil (76 mg, 33%, >99:1 dr); $[\alpha]_D^{20}$+23.8 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3467 (O–H), 2968, 2933, 2875 (C–H), 1692 (C=O [carbamate]); δ_H (400 MHz, $CDCl_3$) 1.19-1.33 (1H, m, C(1')H_A), 1.37 (3H, d, *J* 6.6, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 1.54-1.64 (1H, m, C(1')H_B), 1.67-1.79 (1H, m, C(3)H_A), 2.09-2.19 (1H, m, C(3)H_B), 2.44-2.64 (3H, m, C(2)H_2, C(3a)*H*), 3.18 (1H, br s, O*H*), 3.42-3.55 (2H, m, C(2')H_2), 3.74 (1H, d, *J* 8.3, C(9b)*H*), 3.77 (3H, s, O*Me*), 3.80 (1H, q, *J* 6.6, C(α)*H*), 4.58 (1H, dd, *J* 12.3, 2.7, C(4)*H*), 6.76 (2H, d, *J* 8.8, C(3"), C(5")),

7.01 (1H td, *J* 7.3, 1.0, C(7)*H*), 7.09 (1H, d, *J* 6.8, C(6)*H*), 7.15-7.22 (3H, m, C(2")*H*, C(6″)*H*, *Ar*), 7.24-7.33 (1H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 12.6 (C(α)*Me*), 28.4 (C*Me*$_3$), 30.7 (*C*(3)), 35.7 (*C*(1′)), 44.9 (*C*(2)), 45.2 (*C*(3a)), 54.5, 55.1, 55.2 (*C*(4), *C*(α), O*Me*), 58.9 (*C*(2′)), 59.5 (*C*(9b)), 81.1 (*C*Me$_3$), 113.2 (*C*(3"), *C*(5")), 124.1, 125.5, 127.2 (*Ar*), 128.3 (*C*(2"), *C*(6")), 129.7, 132.1, 137.1, 137.2 (*Ar*), 158.1 (C(4"));[16] *m*/*z* (ESI^+) 927 ($[2M+Na]^+$, 100%), 475 ($[M+Na]^+$, 15%), 453 ($[M+H]^+$, 95%); HRMS (ESI^+) $C_{27}H_{37}N_2O_4^+$ ($[M+H]^+$) requires 453.2748; found 453.2742.

Method B: BH_3·THF (1.0 M in THF, 14.7 mL, 14.7 mmol) was added dropwise *via* syringe to a solution of **240** (609 mg, 1.23 mmol) in THF (15 mL) at 0 °C and the mixture was allowed to warm to rt over 16 h. The mixture was cooled to 0 °C and satd aq K_2CO_3 (8 mL) was added cautiously. The resultant mixture was heated at reflux for 4 h and then was concentrated *in vacuo*. The residue was partitioned between EtOAc (20 mL) and brine (20 mL), and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc, 100%) gave **249** as a colourless oil (429 mg, 77%, >99:1 dr).

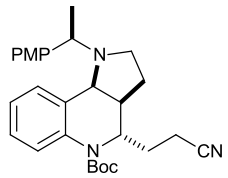
(3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-chloroethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 250



CCl_4 (0.50 mL, 5.23 mmol) was added dropwise *via* syringe to a stirred solution of **249** (237 mg, 0.52 mmol), PPh_3 (343 mg, 1.31 mmol) and Et_3N (0.73 mL, 5.23 mmol) in MeCN (20 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h and then was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 50:50) gave **250** as a colourless oil (217 mg, 88%, >99:1 dr); $[\alpha]_D^{20}$+30.6 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 2933, 2875 (C–H), 1692 (C=O); δ_H (400 MHz, C_6D_6) 1.32 (3H, d, *J* 6.6, C(α)*Me*), 1.34-1.44 (1H, m, C(1')H_A), 1.48-1.63 (1H, m, C(1')H_B), 1.58 (9H, s, C*Me*$_3$), 1.83-2.00 (2H, m, C(3)H_2), 2.07-2.17 (1H, m, C(3a)*H*), 2.30-2.40 (1H, m, C(2)H_A), 2.61-2.70 (1H, m, C(2)H_B), 3.18-3.29 (1H, m, C(2')H_A), 3.33-3.42 (1H, m, C(2')H_B), 3.44 (3H, s, O*Me*), 3.54 (1H, d, *J* 8.6, C(9b)*H*), 3.90 (1H, q, *J* 6.6, C(α)*H*), 4.82 (1H, dd, *J* 10.9, 4.0, C(4)*H*), 6.90 (1H, d, *J* 8.7, C(3")*H*, C(5")*H*), 6.97 (1H, td, *J* 7.5, 1.0, C(8)*H*), 7.10 (1H, d, *J* 7.5, C(9)*H*), 7.17 (1H, td, *J* 7.7, 1.5, C(7)*H*), 7.31 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*), 7.59 (1H, br s, C(6)*H*); δ_C (100 MHz, C_6D_6) 11.9 (C(α)*Me*), 28.3 (C*Me*$_3$), 30.1 (*C*(3)), 36.5 (*C*(1')), 41.7 (*C*(2')), 45.0 (*C*(2)), 45.5 (*C*(3a)), 54.2, 54.7, 55.8 (*C*(4), *C*(α), O*Me*), 59.2 (*C*(9b)), 80.0 (*C*Me$_3$), 113.6 (*C*(3"),

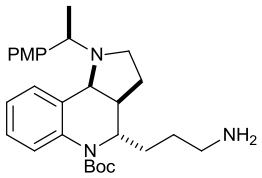
C(5")), 124.2, 126.9, 127.5 (*Ar*), 128.7 (*C*(2"), *C*(6")), 129.8, 132.7, 137.1, 138.1 (*Ar*), 154.3 (N*C*O), 158.9 (*C*(4")); *m*/*z* (ESI$^+$) 473 ([M(^{37}Cl)+H]$^+$, 60%), 471 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}{}^{35}ClN_2O_3^+$ ([M(^{35}Cl)+H]$^+$) requires 471.2409; found 471.2404.

(3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-cyanoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 251



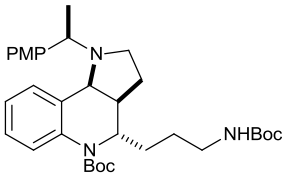
NaCN (57 mg, 1.17 mmol) was added to a solution of **250** (367 mg, 0.78 mmol) in DMSO (3.0 mL) at rt and the resultant mixture was stirred at 90 °C for 16 h. The mixture was allowed to cool to rt, then was partitioned between H_2O (5 mL) and EtOAc (20 mL). The solution was washed with H_2O (3 × 20 mL) and the combined aqueous washings were extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 75:25:1) gave **251** as a colourless oil (289 mg, 80%, >99:1 dr); $[\alpha]_D^{20}$+8.74 (*c* 1.06 in $CHCl_3$); ν_{max} (ATR) 2970, 2933, 2874 (C–H), 2246 (C≡N), 1694 (C=O); δ_H (400 MHz, C_6D_6) 0.89-0.99 (1H, m, C(1')H_A), 1.01-1.14 (1H, m, C(1')H_B), 1.31 (3H, d, *J* 6.6, C(α)*Me*), 1.60 (9H, s, C*Me*$_3$), 1.65-1.92 (4H, m, C(3)H_2, C(2')H_2), 1.95-2.04 (1H, m, C(3a)*H*), 2.29-2.38 (1H, m, C(2)H_A), 2.59-2.68 (1H, m, C(2)H_B), 3.45 (3H, s, O*Me*), 3.49 (1H, d, *J* 8.3, C(9b)*H*), 3.86 (1H, q, *J* 6.6, C(α)*H*), 4.49 (1H, dd, *J* 11.6, 3.5, C(4)*H*), 6.90 (2H, d, *J* 8.8, C(3")*H*, C(5")*H*), 6.97 (1H, td, *J* 7.3, 1.3, C(8)*H*), 7.08 (1H, d, *J* 7.1, C(9)*H*), 7.18 (1H, td, *J* 7.7, 1.5, C(7)*H*), 7.30 (2H, d, *J* 8.8, C(2")*H*, C(6")*H*),7.59 (1H, br s, C(6)*H*); δ_C (100 MHz, C_6D_6) 12.0 (C(α)*Me*), 14.0 (*C*(2')), 28.3 (C*Me*$_3$), 29.0 (*C*(1')), 30.1 (*C*(3)), 44.9 (*C*(2)), 45.6 (*C*(3a)), 54.3, 54.7 (*C*(α), O*Me*), 57.4 (*C*(4)), 59.2 (*C*(9b)), 80.4 (*C*Me$_3$), 113.6 (*C*(3"), *C*(5")), 119.0 (*C*(3')), 124.3 (*C*(8)), 127.0, 127.5 (*Ar*), 128.7 (*C*(2"), *C*(6")), 129.8 132.5, 137.1, 137.5 (*Ar*), 154.4 (N*C*O) 158.9 (*C*(4")); *m*/*z* (ESI$^+$) 484 ([M+Na]$^+$, 15%), 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{36}N_3O_3^+$ ([M+H]$^+$) requires 462.2751; found 462.2744.

(3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(3'-aminopropyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 256



$NiCl_2 \cdot 6H_2O$ (420 mg, 1.77 mmol) was added to a stirred solution of **251** (117 mg, 0.25 mmol) in MeOH/THF (3:1 v/v, 8 mL) and the resultant mixture was cooled to 0 °C.[17] $NaBH_4$ (201 mg, 5.31 mmol) was added portionwise over 20 mins and the resultant mixture was allowed to warm to rt over 16 h, then was concentrated *in vacuo*. The mixture was filtered through Celite® (eluent EtOAc/Et_3N, 100:1) and was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH, 90:10) gave **256** as a colourless oil (25 mg, 21%, ~80% pure); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.36 (3H, d, *J* 6.7, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 2.72 (2H, t, *J* 7.2, C(3)*H*$_2$), 3.64-3.86 (2H, m, C(9b)*H*, C(α)*H*), 3.76 (3H, s, O*Me*), 4.34-4.53 (1H, br m, C(4)*H*), 4.95 (2H, br s, N*H*$_2$), 6.75 (2H, d, *J* 8.8, C(3")*H*, C(5")*H*), 7.16 (2H, d, *J* 8.8, C(2")*H*, C(6")*H*).

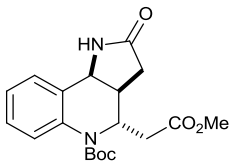
(3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-[3'-*N*-(*tert*-butoxycarbonylamino)propyl]-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 257



$NiCl_2 \cdot 6H_2O$ (19 mg, 81 μmol) was added to a solution of **251** (186 mg, 0.40 mmol) and Boc_2O (176 mg, 0.81 mmol) in dry MeOH (4 mL) and the mixture was cooled to 0 °C.[17] $NaBH_4$ (213 mg, 5.64 mmol) was added portionwise over 1 h and the mixture was allowed to warm to rt over 16 h. Diethylenetriamine (44 μL) was added and the mixture was stirred at rt for 30 min, then was concentrated *in vacuo*. The residue was partitioned between EtOAc (30 mL) and was washed with satd aq $NaHCO_3$ (2 × 20 mL). The combined aqueous layers were extracted with EtOAc, and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **257** as a colourless oil (170 mg, 74%, >99:1 dr); $[\alpha]_D^{20}$+17.2 (*c* 0.86 in $CHCl_3$); ν_{max} (ATR) 3366 (N–H), 2972, 2933, 2872 (C–H), 1692 (C=O); δ_H (400 MHz, C_6D_6) 0.93-1.19 (2H, m, C(1')*H*$_2$), 1.34 (3H, d, *J* 6.7, C(α)*Me*), 1.29-1.56 (2H, m, C(2')*H*$_2$), 1.53 (9H, s, C*Me*$_3$), 1.58 (9H, s, C*Me*$_3$), 1.86-2.02 (2H, m, C(3)*H*$_2$), 2.19-2.31 (1H, m, C(3a)*H*), 2.31-2.45 (1H, m, C(2)*H*$_A$), 2.59-2.72 (1H, m, C(2)*H*$_B$), 2.91-3.07 (2H, m, C(3')*H*$_2$), 3.46

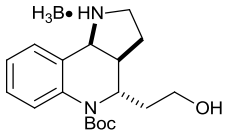
(3H, s, O*Me*), 3.61 (1H, d, *J* 8.3, C(9b)*H*), 3.94 (1H, q, *J* 6.7, C(α)*H*), 4.29 (1H, br s, N*H*), 4.60 (1H, br s, C(4)*H*), 6.89 (2H, m, d, *J* 8.7, C(3")*H*, C(5")*H*), 6.99 (1H, t, *J* 7.3, C(8)*H*), 7.12 (1H, d, *J* 7.3, C(9)*H*), 7.21 (1H, t, *J* 7.7, C(7)*H*), 7.32 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*), 7.61 (1H, br s, C(6)*H*); δ_C (100 MHz, C_6D_6) 11.8 (C(α)*Me*), 27.0 (*C*(2')), 28.4, 28.5 (2 × C*Me*$_3$), 30.3, 30.7 (*C*(1'), *C*(3)), 40.2 (*C*(3')), 45.0 (*C*(2)), 46.0 (*C*(3a)), 54.1 (*C*(α)), 54.7 (O*Me*), 57.9 (*C*(4)), 59.4 (*C*(9b)), 77.8, 78.2 (2 × *C*Me$_3$), 113.6 (*C*(3"), *C*(5")), 124.0 (*C*(8)), 126.9, 127.3 (*C*(6), *C*(7)), 128.7 (*C*(2"), *C*(6")), 129.8 (*C*(9)), 133.0, 137.3, 138.3 (*Ar*), 154.6, 155.8 (2 × N*C*O), 158.8 (*C*(4")); *m*/*z* (ESI$^+$) 566 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{48}N_3O_5^+$ ([M+H]$^+$) requires 566.3588; found 566.3585.

(3a*R*,4*S*,9b*S*)-4-(2'-Methoxy-2'-oxoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 260



Following *General Procedure 7*, CAN (1.55 g, 2.84 mmol) in H_2O (10 mL) and **240** (467 mg, 0.95 mmol) in MeCN (10 mL) gave **260** in >99:1 crude dr. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave 4-methoxy acetophenone **261** as a yellow oil (92 mg, 65%); δ_H (400 MHz, $CDCl_3$) 2.54 (3H, s, *Me*), 3.85 (3H, s, O*Me*), 6.92 (2H, d, *J* 8.9, C(3)*H*, C(5)*H*), 7.92 (2H, d, *J* 8.9, C(2)*H*, C(6)*H*). Further elution gave **260** as a yellow oil (195 mg, 57%, >99:1 dr); $[\alpha]_D^{20}$+32.1 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3227 (N–H), 2977 (C–H), 1738 [C=O (ester)], 1696 [C=O (γ-lactam, carbamate)]; δ_H (400 MHz, C_6D_6) 1.45 (9H, s, C*Me*$_3$), 2.10 (1H, dd, *J* 15.2, 6.3, C(1')H_A), 2.28 (1H, dd, *J* 15.2, 8.6, C(1')H_B), 2.41-2.57 (3H, m, C(3)H_2, C(3a)*H*), 3.40 (3H, s, CO_2*Me*), 4.38 (1H, d, *J* 7.6, C(9b)*H*), 5.18 (1H, app br t, *J* 7.2, C(4)*H*), 6.94 (1H, td, *J* 7.6, 1.0, C(8)*H*), 7.10 (1H, td, *J* 7.6, 1.4, C(7)*H*), 7.28 (1H, dd, *J* 7.7, 1.1, C(9)*H*), 7.74 (1H, br s, C(6)*H*), 8.73 (1H, s, N*H*); δ_C (100 MHz, C_6D_6) 28.1 (C*Me*$_3$), 34.1 (*C*(3)), 36.8 (*C*(1')), 38.8 (*C*(3a)), 51.3 (O*Me*), 52.1, 52.1 (*C*(4), *C*(9b)), 81.1 (*C*Me$_3$), 125.1 (*C*(8)), 126.2 (*C*(6)), 127.9 (*C*(7)), 129.4 (*Ar*), 129.6 (*C*(9)), 135.5 (*Ar*), 153.7 (N*C*O), 170.6, 176.7 (*C*(2), *C*(2')); *m*/*z* (ESI$^+$) 383 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{24}N_2NaO_5^+$ ([M+Na]$^+$) requires 383.1577; found 383.1574.

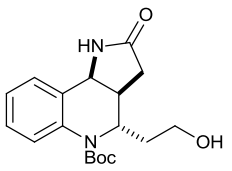
(3a*R*,4*S*,9b*S*)-4-(2'-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline borane complex 262·BH_3



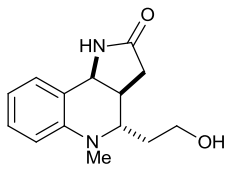
BH_3·THF (1.0 M in THF, 5.70 mL, 5.70 mmol) was added dropwise to a solution of **260** (172 mg, 0.47 mmol) in THF (10 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h and then was quenched by dropwise addition of satd aq K_2CO_3 (5 mL) at 0 °C. The mixture was heated at 70 °C for 1 h then allowed to cool to rt. The mixture was washed with brine (2 × 20 mL) and the combined aqueous washings were extracted EtOAc (2 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **262**·BH_3 as a colourless foam (86 mg, 57%, >99:1 dr); $[\alpha]_D^{20}$+55.2 (*c* 1.4 in $CHCl_3$); ν_{max} (ATR) 3465 (N–H), 3193 (O–H), 2975, 2936, 2880 (C–H), 2361, 2270 (B–H), 1684 [C=O (carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.30-1.42 (1H, m, C(1')H_A), 1.52 (9H, s, CMe_3), 1.45-1.63 (1H, m, C(1')H_B), 1.77 (1H, app tt, *J* 10.1, 2.8, C(3)H_A), 2.26-2.39 (1H, m, C(3)H_B), 2.81 (1H, dd, *J* 17.8, 16.1, C(2)H_A), 2.86-2.95 (1H, m, C(3a)*H*), 3.22-3.34 (1H, m, C(2)H_B), 3.36-3.51 (2H, m, C(2')H_2), 4.04 (1H, br s, N*H*), 4.25 (1H, dd, *J* 9.6, 5.8, C(9b)*H*), 4.63 (1H, dd, *J* 11.7, 2.9, C(4)*H*), 7.13 (1H, td, *J* 7.5, 0.9, C(8)*H*), 7.28 (1H, td, *J* 7.8, 1.5, C(7)*H*), 7.39 (1H, br s, C(6)*H*), 7.61 (1H, dd, *J* 7.7, 0.9, C(9)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 30.4 (*C*(3)), 34.3 (*C*(1')), 43.6 (*C*(3a)), 52.8 (*C*(4)), 54.0 (*C*(2)), 58.6 (*C*(2')), 63.6 (*C*(9b)), 82.4 (*C*Me$_3$), 124.9, 125.0 (*C*(6), *C*(8)), 126.3 (*Ar*), 129.2 (*C*(7)), 130.4 (*C*(9)), 135.8 (*Ar*) 155.0 (weak, N*C*O); δ_B (^{11}B, 160 MHz, $CDCl_3$) −14.9; *m*/*z* (ESI^+) 687 ($[2M+Na]^+$, 100%), 319 ($[M–BH_3+H]^+$, 50%); HRMS (ESI^+) $C_{18}H_{29}BN_2NaO_3^+$ ($[M+Na]^+$) requires 355.2163; found 355.2162.

(3a*R*,4*S*,9b*S*)-4-(2'-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 263 and

(3a*R*,4*S*,9b*S*)-4-(2'-Hydroxyethyl)-*N*(5)-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 264



263

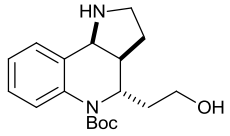


264

A solution of $AlCl_3$ (36 mg, 0.27 mmol) in Et_2O (2 mL) was added dropwise *via* cannula to a stirred solution of $LiAlH_4$ (1.0 M in THF, 0.80 mL, 0.80 mmol) in Et_2O (10 mL) at 0 °C. The cooling bath

was removed and the mixture was allowed to warm to rt, stirred for 1 h at rt and then was cooled to 0 °C. A solution of **260** (96 mg, 0.27 mmol) in Et_2O (5 mL) was added dropwise *via* cannula, during which time a white suspension formed. The mixture was allowed to warm to rt over 16 h and then was quenched by cautious addition of H_2O (0.5 mL) followed by 2.0 M NaOH (0.5 mL). The mixture was diluted with EtOAc (10 mL) and was stirred at rt for 1 h. The mixture was filtered through Celite® (eluent EtOAc/Et_3N, 100:1, 100 mL), then dried and concentrated *in vacuo*. Purification *via* column chromatography (eluent $CHCl_3$/MeOH, 90:10) gave **263** as a colourless oil (13 mg, 14%, >99:1 dr); $[\alpha]_D^{20}$+25.9 (*c* 0.63 in $CHCl_3$); ν_{max} (ATR); 3287 (O–H), 2978, 2931 (C–H), 1696 [C=O (γ-lactam, carbamate)]; δ_H (400 MHz, $CDCl_3$) 1.47-1.58 (1H, m, C(1')H_A), 1.53 (9H, s, CMe_3), 1.59-1.87 (2H, m, C(1')H_B, O*H*), 2.36 (1H, dd, *J* 17.0, 9.8, C(3)H_A), 2.59 (1H, dd, *J* 17.0, 9.5, C(3)H_B), 2.96-3.01 (1H, m, C(3a)*H*), 3.47-3.59 (2H, m, C(2')H_2), 4.71-4.78 (2H, m, C(4)*H*, C(9b)*H*), 6.74 (1H, br s, N*H*), 7.09 (1H, td, *J* 7.6, 1.0, C(8)*H*), 7.16 (1H, dd, *J* 7.6, 1.6, C(9)*H*), 7.23 (1H, td, *J* 7.7, 1.6, C(7)*H*), 7.44 (1H, br s, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 33.6, 33.9 (*C*(3), *C*(1')), 39.0 (*C*(3a)), 51.7, 52.0 (*C*(4), *C*(9b)), 58.7 (*C*(2')), 82.6 (*C*Me_3), 124.8, 124.8, 128.2, 128.3, 128.9, 134.8 (*Ar*), 155.2 (N*C*O), 176.6 (*C*(2)); *m*/*z* (ESI^+) 687 ($[2M+Na]^+$, 85%), 665 ($[2M+H]^+$, 100%), 355 ($[M+Na]^+$, 95%); HRMS (ESI^+) $C_{18}H_{24}N_2NaO_4^+$ ($[M+Na]^+$) requires 355.1628; found 355.1625. Further elution gave **264** as a white foam (17 mg, 29%, ~85% pure); δ_H (400 MHz, $CDCl_3$) 1.58-1.67 (1H, m, C(1')H_A), 1.77-1.87 (1H, m, C(1')H_B), 2.13 (1H, br s, O*H*), 2.37 (1H, dd, *J* 16.7, 8.8, C(3)H_A), 2.61 (1H, dd, *J* 16.7, 10.7, C(3)H_B), 2.94 (3H, s, N*Me*), 2.96-3.05 (1H, m, C(3a)*H*), 3.29-3.36 (1H, m, C(4)*H*), 3.63-3.74 (2H, m, C(2')H_2), 4.73 (1H, d, *J* 8.8, C(9b)*H*), 6.56 (1H, d, *J* 7.8, *Ar*), 6.69 (1H, td, *J* 7.6, 1.0, *Ar*), 6.84 (1H, s, N*H*), 6.99 (1H, d, *J* 6.6, *Ar*), 7.14 (1H, td, *J* 7.8, 1.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 32.0 (*C*(1')), 33.8 (*C*(3)), 38.4, 38.8 (*C*(3a), N*Me*), 51.3 (*C*(9b)), 58.7 (*C*(4)), 59.8 (*C*(2')), 112.4, 117.6, 123.4, 128.9, 128.9, 143.8 (*Ar*), 178.1 (*C*(2)); *m*/*z* (ESI^+) 761 ($[3M+Na]^+$, 80%), 515 ($[2M+Na]^+$, 100%), 269 ($[M+Na]^+$, 35%); HRMS (ESI^+) $C_{14}H_{18}N_2NaO_2^+$ ($[M+Na]^+$) requires 269.1260; found 269.1261.

(3a*R*,4*S*,9b*S*)-4-(2'-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 262



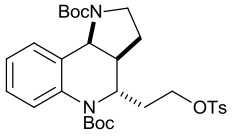
Step 1: Following *General Procedure 7*, CAN (2.22 g, 4.06 mmol) in H_2O (13 mL) and **240** (669 mg, 1.35 mmol) in MeCN (13 mL) gave **260** as a yellow oil (589 mg, >99:1 crude dr), which was used

without purification in the next step.

Step 2: BH_3·THF (1.0 M in THF, 16.0 mL, 16.0 mmol) was added dropwise to a solution of **260** (589 mg, >99:1 dr) in THF (50 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h then allowed to cool to rt before being cooled further to 0 °C. Satd aq K_2CO_3 (20 mL) and EtOAc (20 mL) were then carefully added and the resultant mixture was heated at 60 °C for 1 h. The mixture was then allowed to cool to rt and washed with satd aq K_2CO_3 (2 × 10 mL). The combined aqueous layers were extracted with EtOAc (20 mL) then the organic extract was dried and concentrated *in vacuo* to give a mixture of **262** and **262**·BH_3 (831 mg) which was used without purification in the next step

Step 3: Pd/C (10% w/w, 60 mg) was added portionwise to a solution of the crude product from the previous reaction (584 mg) in MeOH (15 mL) and the mixture was stirred at rt for 16 h. The mixture was filtered through a pad of Celite® (eluent MeOH/Et_3N, 100:1) and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2:MeOH:Et_3N, 95:5:1) gave **262** as a colourless oil (197 mg, 46% over 3 steps from **240**, >99:1 dr); $[\alpha]_D^{20}$+50.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3377 (O–H, N–H), 2974, 2934, 2878, 2730 (C–H), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40-1.52 (1H, m, C(1')H_A), 1.48 (9H, s, CMe_3) 1.54-1.63 (1H, m, C(1')H_B), 1.66-1.79 (1H, m, C(3)H_A), 2.18-2.28 (1H, m, C(3)H_B), 2.68 (1H, app q, *J* 8.8, C(3a)*H*), 2.87-2.98 (1H, m, C(2)H_A), 2.97-3.07 (1H, m, C(2)H_B), 3.40-3.50 (2H, m, C(2')H_2), 4.57 (1H, d, *J* 9.4, C(9b)*H*), 4.66 (1H, dd, *J* 11.5, 3.4, C(4)*H*), 7.08 (1H, t, *J* 7.5, C(8)*H*), 7.21 (1H, td, *J* 7.8, 1.3, C(7)*H*), 7.38 (1H, br d, *J* 6.8, C(6)*H*), 7.43 (1H, d, *J* 7.6, C(9)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (CMe_3), 30.6 (*C*(3)), 34.6 (*C*(1′)), 43.2 (*C*(3a)), 44.9 (*C*(2)), 52.6 (*C*(4)), 55.9 (*C*(9b)), 58.7 (*C*(2')), 82.1 (*C*Me_3), 125.0, 127.1, 128.5, 130.0, 136.1 (*Ar*) 155.0 (broad, N*C*O);[18] *m*/*z* (ESI^+) 341 ($[M+Na]^+$, 95%), 319 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{18}H_{26}N_2NaO_3^+$ ($[M+Na]^+$) requires 341.1836; found 341.1837.

(*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-[2'-(4''-toluenesulfonyloxy)ethyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 268

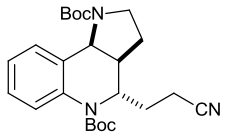


Step 1: Boc_2O (147 mg, 0.67 mmol), DMAP (8 mg, 61 μmol) and Et_3N (0.26 mL, 1.83 mmol) were added sequentially to a stirred solution of **262** (195 mg, 0.61 mmol) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred at 35 °C for 16 h. The mixture was diluted with CH_2Cl_2 (20 mL) and was washed with 1.0 M aq HCl (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3:1 v/v, 2 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10

mL) and brine (10 mL), then dried and concentrated *in vacuo* to give crude **267** (178 mg) which was used in the next step without purification.

Step 2: TsCl (140 mg, 0.73 mmol), DMAP (8 mg, 61 μmol) and Et_3N (0.26 mL, 1.83 mmol) were added sequentially to a stirred solution of **267** (178 mg) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred at 35 °C for 16 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with 1.0 M HCl (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3:1 v/v, 2 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 80:20:1) gave **268** as a colourless oil (134 mg, 38% over 2 steps from **262**, >99:1 dr); $[\alpha]_D^{20}$ −104 (*c* 0.97 in $CHCl_3$); ν_{max} (ATR) 2976, 2932 (C–H), 1691 (C=O); δ_H (400 MHz, PhMe-d_8, 363K) 1.33-1.55 (2H, C(1')H_2), 1.47 (9H, s, CMe_3), 1.49 (9H, s, CMe_3), 1.58-1.74 (2H, m, C(3)H_2), 1.86-1.95 (1H, m, C(3a)*H*), 2.02 (3H, s, C(4")*Me*), 3.05-3.15 (1H, m, C(2)H_A), 3.23-3.41 (1H, m, C(2)H_B), 3.82-3.91 (1H, m, C(2')H_A), 3.92-4.03 (1H, m, C(2')H_B), 4.57-4.64 (1H, m, C(4)*H*), 5.01 (1H, d, *J* 7.6, C(9b)*H*), 6.87 (2H, d, *J* 8.0, C(3"), C(5")), 6.94 (1H, t, *J* 7.4, *Ar*), 6.97-7.06 (1H, m, *Ar*), 7.56 (1H, d, *J* 8.2, *Ar*), 7.69 (2H, d, *J* 8.0, C(2")*H*, C(6")*H*), 8.08 (1H, br s, *Ar*); δ_C (100 MHz, PhMe-d_8, 363K) 21.0 (C(4")*Me*), 28.1 (*C*(3)), 28.3, 28.6 (2 × CMe_3), 32.2 (*C*(1')), 42.7 (broad, *C*(3a)), 45.6 (*C*(2)), 52.3 (*C*(4)), 54.6 (*C*(9b)), 67.2 (*C*(2)), 79.2, 80.9 (2 × *C*Me_3), 124.5, 125.5, 127.4 (*Ar*), 128.1 (*C*(2"), *C*(6")), 129.6 (*C*(3"), *C*(5")), 130.1, 131.0, 135.2, 135.6, 143.9 (*Ar*), 154.2, 155.5 (2 × N*C*O); *m*/*z* (ESI$^+$) 595 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{40}N_2NaO_7S^+$ ([M+Na]$^+$) requires 595.2448; found 595.2445.

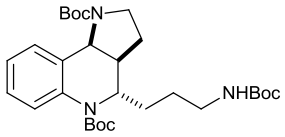
(*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-(2'-cyanoethyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 269



NaCN (12 mg, 0.23 mmol) was added to a stirred solution of **268** (85 mg, 0.15 mmol) in NMP (2 mL) and the resultant mixture was stirred at 60 °C for 16 h.[19] The mixture was then diluted with EtOAc (20 mL) and washed with H_2O (2 × 10 mL). The organic layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **269** as a white foam (45 mg, 70%, >99:1 dr); $[\alpha]_D^{20}$ −127 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 2976, 2933 (C–H), 2247 (C≡N), 1691 (C=O); δ_H (500 MHz, PhMe-d_8, 363K) 1.02-1.13 (1H, m, C(1')H_A), 1.23-1.38 (1H, m,

C(1')H_B), 1.47 (9H, s, CMe_3), 1.50 (9H, s, CMe_3), 1.61-1.90 (5H, m, C(3)H_2, C(3a)*H*), C(2')H_2), 3.05-3.15 (1H, m, C(2)H_A), 3.27-3.40 (1H, m, C(2)H_B), 4.42 (1H, d, *J* 11.0, C(4)*H*), 4.99 (1H, d, *J* 7.3, C(9b)*H*), 6.95 (1H, t, *J* 7.6, C(8)*H*), 7.05 (1H, t, *J* 7.6, C(7)*H*), 7.59 (1H, d, *J* 8.2, *C*(6)*H*), 8.08 (1H, br s, C(9)*H*); δ_C (125 MHz, PhMe-d_8, 363K) 14.1 (*C*(2')), 28.2, 28.3, 28.5, 28.6 (*C*(3), *C*(1'), 2 × CMe_3), 42.8 (*C*(3a)), 45.5 (*C*(2)), 54.6, 54.6 (*C*(4), *C*(9b)), 79.3, 81.2 (2 × *C*Me$_3$), 118.3 (*C*(3')), 124.7 (*C*(8)), 125.6 (*C*(6)), 127.5 (*C*(7)), 129.9 (*C*(9)), 131.0, 135.2 (*Ar*), 154.3, 155.5 (2 × N*C*O); *m*/*z* (ESI$^+$) 450 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{33}N_3NaO_4^+$ ([M+Na]$^+$) requires 450.2363; found 450.2368.

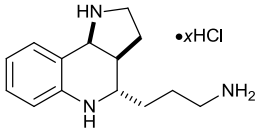
(*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-[3'-(*N*-*tert*-butoxycarbonylamino)propyl]-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 270



Boc_2O (45 mg, 0.21 mmol) was added to a stirred solution of $NiCl_2 \cdot 6H_2O$ (5 mg, 21 μmol) and **269** (45 mg, 0.10 mmol) in dry MeOH (3 mL) and the resultant mixture was stirred at 0 °C for 5 min. $NaBH_4$ (55 mg, 1.45 mmol) was then added portionwise, during which time a fine black precipitate of Ni_2B formed and a gas was evolved. The mixture was allowed to warm to rt over 16 h then DETA (11 μL, 0.10 mmol) was added and the mixture was allowed to stir for 30 min at rt before being concentrated *in vacuo*. The mixture was dissolved in EtOAc (10 mL) and was washed with satd aq $NaHCO_3$ (2 × 10 mL). The aqueous washings were extracted with EtOAc (10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 50:50:1) gave **270** as a colourless oil (40 mg, 71%, >99:1 dr); $[\alpha]_D^{20}$−67.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3361 (N−H), 2976, 2932 (C−H), 1693 (C=O); δ_H (500 MHz, PhMe-d_8, 363K) 1.20-1.62 (4H, m, C(1')H_2, C(2')H_2), 1.63-1.84 (2H, m, C(3)H_2), 1.44 (9H, s, CMe_3), 1.46 (9H, s, CMe_3), 1.50 (9H, s, CMe_3), 1.99-2.09 (1H, br m, C(3a)*H*), 2.99-3.22 (1H, br m, C(2)H_A), 3.26-3.45 (1H, br m, C(2)H_B), 3.87-4.03 (1H, br m, C(3')H_A), 4.12-4.22 (1H, br m, C(3')H_B), 4.37-4.77 (2H, br m, C(4)*H*, N*H*), 4.99-5.22 (1H, br m, C(9b)*H*), 6.85-7.17 (2H, br m, *Ar*),[20] 7.51-7.73 (1H, br m, *Ar*), 7.99-8.23 (1H, br m, *Ar*); δ_C (125 MHz, PhMe-d_8) 26.8, 31.6 (*C*(1'), *C*(2')), 27.9, 28.1, 28.2 (3 × CMe_3), 45.2 (*C*(2)), 47.7 (*C*(4)), 52.1 (*C*(9b)), 64.4 (*C*(3')), 78.2, 78.7, 80.2 (3 × *C*Me$_3$), 129.8, 130.1, 130.7 (*Ar*), 153.8, 155.4, 155.7 (3 × N*C*O);[21] *m*/*z* (ESI$^+$) 554 ([M+Na]$^+$, 100%), 532 ([M+H]$^+$, 40%); HRMS (ESI$^+$) $C_{29}H_{45}N_3NaO_6^+$ ([M+Na]$^+$) requires 554.3201; found 554.3203.

(*S*,*S*,*S*)-4-(3'-Aminopropyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*HCl

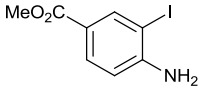
225·*x*HCl



A solution of **270** (35 mg, 65 μmol) in methanolic HCl (1.25 M in MeOH, 4 mL) was stirred at rt for 16 h and then was concentrated *in vacuo*. Methanolic HCl (1.25 M, 2 mL) was added and the resultant mixture was concentrated *in vacuo* to give **225**·*x*HCl as an amorphous white solid (19 mg, quant);[22] $[\alpha]_D^{20}$ −58.0 (*c* 0.2 in MeOH); ν_{max} (ATR) 3376 (N−H), 2904, 2745 (C−H); δ_H (500 MHz, MeOD-d_4) 1.84-2.09 (4H, m, C(1')H_2, C(2')H_2), 2.15-2.25 (1H, m, C(3)H_A), 2.51-2.62 (1H, m, C(3)H_B), 2.82-2.91 (1H, m, C(3a)*H*), 3.00-3.13 (2H, m, C(3')H_2), 3.31-3.35 (1H, m, C(4)*H*), 3.40-3.57 (2H, m, C(2)H_2), 4.85 (1H, d, *J* 7.3, C(9b)*H*), 7.22-7.28 (1H, m, *Ar*), 7.32 (1H, d, *J* 7.9, *Ar*), 7.40-7.46 (1H, m, *Ar*), 7.57 (1H, d, *J* 6.3, *Ar*); δ_C (125 MHz, MeOD-d_4) 24.1 (*C*(1')), 28.3 (*C*(3)), 29.6 (*C*(2')), 39.5 (*C*(3a)), 40.6 (*C*(3')), 44.7 (*C*(2)), 54.0 (*C*(4)), 58.4 (*C*(9b)), 120.6, 121.0, 125.6, 131.5, 131.8, 139.5 (*Ar*); *m*/*z* (ESI$^+$) 232 ($[M+H]^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{22}N_3^+$ ($[M+H]^+$) requires 232.1808; found 232.1815.

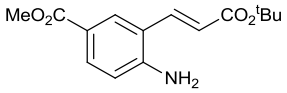
5.5. Experimental for chapter 4

Methyl-3-iodo-4-aminobenzoate 272



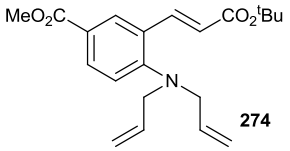
KIO_3 (2.66 g, 12.4 mmol) was added portionwise to a vigorously stirred solution of methyl-4-amino benzoate (5.00 g, 33.1 mmol) and KI (4.12 g, 24.8 mmol) in H_2O/MeOH (5:1 v/v, 180 mL). Aqueous 1.0 M HCl (33 mL) was added dropwise over 30 min and the resultant mixture was stirred at rt for 16 h. The mixture was diluted with Et_2O (100 mL) and was washed with H_2O (50 mL). The organic layer was washed with dil. aq. $Na_2S_2O_3$ (50 mL) then dried and concentrated *in vacuo*. Recrystallisation (CH_2Cl_2/30-40 °C petrol) gave **272** as a black solid (6.46 g, 70%); mp 87.3-89.0 °C {lit.[23] mp 89-90 °C); δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, O*Me*), 4.55 (2H, br s, NH_2), 6.70 (1H, d *J* 8.4, C(6)*H*), 7.81 (1H, dd, *J* 8.4, 1.9, C(5)*H*), 8.33 (1H, d, *J* 1.9, C(3)*H*).

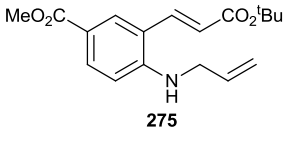
tert-Butyl (*E*)-3-(2'-amino-5'-(methoxycarbonyl)phenyl)acrylate 273



$Pd(OAc)_2$ (8 mg, 33 μmol) was added to a stirred solution of P(*o*-Tol)$_3$ (20 mg, 66 μmol), **272** (909 mg, 3.28 mmol), Et_3N (0.91 mL, 6.56 mmol) and *tert*-butyl acrylate (0.53 mL, 3.61 mmol) in MeCN (20 mL) and the resultant mixture was stirred at 70 °C for 16 h. The mixture was allowed to cool to rt then was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and was washed with H_2O (2 × 10 mL). The combined aqueous layers were extracted with CH_2Cl_2 (10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:50) gave **273** as a yellow solid (766 mg, 85%, >99:1 dr); mp 111-113 °C; ν_{max}(ATR) 3541, 3464, 3356, 3240 (N−H), 2983, 2952 (C−H), 1709, 1684 (C=O), 1626, 1601 (C=C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, CMe_3), 3.85 (3H, s, O*Me*), 4.45 (2H, s, NH_2), 6.35 (1H, d, *J* 15.7, C(2)*H*), 6.66 (1H, d, *J* 8.3, C(3')*H*), 7.64 (1H, d, *J* 15.7, C(3)*H*), 7.80 (1H, dd, *J* 8.3, 1.8, C(4')*H*), 8.06 (1H, d, *J* 1.8, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 51.7 (O*Me*), 80.7 (*C*Me$_3$), 115.6 (*C*(3')), 118.9, 120.2 (*Ar*), 121.4 (*C*(2)), 130.3 (*C*(6')), 132.3 (*C*(4')), 137.8 (*C*(3)), 149.3 (*Ar*), 166.3, 166.7 (*C*O_2Me, *C*O_2^{t}Bu); *m/z* (ESI$^+$) 854 ([3M+Na]$^+$, 100%), 577 ([2M+Na]$^+$, 60%), 300 ([M+Na]$^+$, 15%); HRMS (ESI$^+$) $C_{15}H_{19}NNaO_4^+$ ([M+Na]$^+$) requires 300.1206; found 300.1204.

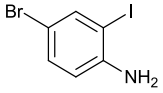
tert-Butyl (_E_)-3-[2'-(_N_,_N_-diallylamino)-5'-(methoxycarbonyl)-phenyl]acrylate 274 and _tert_-Butyl (_E_)-3-[2'-(_N_-allylamino)-5'-(methoxycarbonyl)-phenyl]acrylate 275





Allyl iodide (4.04 mL, 44.3 mmol) was added dropwise to a stirred solution of K_3PO_4 (7.52 g, 35.5 mmol) and **273** (4.91 g, 17.7 mmol) in acetone (150 mL) and the resultant mixture was stirred at reflux for 3 days. The mixture was diluted with H_2O (100 mL) and was extracted with Et_2O (2 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 42:58 mixture of **274**:**275**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 80:20) gave **274** as a yellow oil (2.23 g, 35%, >99:1 dr); ν_{max} (ATR) 3080, 2979, 2951 (C−H), 1710 (C=O), 1632, 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 3.75 (4H, d, *J* 5.8, (N(C*H*$_2$CH=CH$_2$)$_2$), 3.89 (3H, s, O*Me*), 5.15-5.25 (4H, m, N(CH$_2$CH=C*H*$_2$)$_2$), 5.75-5.85 (2H, m, (N(CH$_2$C*H*=CH$_2$)$_2$), 6.38 (1H, d, *J* 15.9, C(2)*H*), 6.99 (1H, d, *J* 8.6, C(3')*H*), 7.87 (1H, d, *J* 15.9, C(3)*H*), 7.92 (1H, dd, *J* 8.6, 2.0, C(4')*H*), 8.17 (1H, d, *J* 2.0, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 51.9 (O*Me*), 55.4 ((NCH$_2$CH=CH$_2$)$_2$), 80.4 (*C*Me$_3$), 118.1 ((NCH$_2$CH=*C*H$_2$)$_2$), 119.9 (*C*(3')), 120.4 (*C*(2)), 123.1, 127.9 (*Ar*), 130.1 (*C*(6')), 131.0 (*C*(4')), 133.9 ((NCH$_2$*C*H=CH$_2$)$_2$), 141.0 (*C*(3)), 154.6 (*Ar*), 166.4, 166.7 (*C*O$_2$Me, *C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 737 ([2M+Na]$^+$, 100%), 380 ([M+Na]$^+$, 50%); HRMS (ESI$^+$) $C_{21}H_{27}NNaO_4^+$ ([M+Na]$^+$) requires 380.1832; found 380.1826. Further elution gave **275** as a yellow oil (2.81 g, 50%, >99:1 dr); ν_{max} (ATR) 3368 (N−H), 2979, 2952 (C−H), 1708 (C=O), 1660, 1606, 1589 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 3.84-3.95 (5H, m, O*Me*, NC*H*$_2$CH=CH$_2$), 4.63 (1H, t, *J* 5.3, N*H*), 5.20-5.33 (2H, m, NCH$_2$CH=C*H*$_2$), 5.88-5.99 (1H, m, NCH$_2$C*H*=CH$_2$), 6.37 (1H, d, *J* 15.7, C(2)*H*), 6.62 (1H, d, *J* 8.6, C(3')*H*), 7.68 (1H, d, *J* 15.7, C(3)*H*), 7.90 (1H, dd, *J* 8.6, 2.0, C(4')*H*), 8.06 (1H, d, *J* 2.0, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 46.0 (N*C*H$_2$CH=CH$_2$), 51.7 (O*Me*), 80.7 (*C*Me$_3$), 110.5 (*C*(3')), 117.2 (NCH$_2$CH=*C*H$_2$), 118.6, 119.3 (*Ar*), 122.0 (*C*(2)), 130.1 (*C*(6')), 132.7 (*C*(4')), 133.7 (NCH$_2$*C*H=CH$_2$), 137.8 (*C*(3)), 149.5 (*Ar*), 166.3, 166.9 (*C*O$_2$Me, *C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 657 ([2M+Na]$^+$, 100%), 340 ([M+Na]$^+$, 50%); HRMS (ESI$^+$) $C_{18}H_{23}NNaO_4^+$ ([M+Na]$^+$) requires 340.1519; found 340.1516.

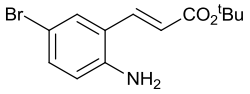
4-Bromo-2-iodoaniline 276



$NaBO_3 \cdot 4H_2O$ (4.78 g, 31.1 mmol) was added portionwise to a solution of 2-iodoaniline (6.48 g, 29.6

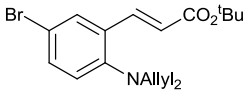
mmol), KBr (4.22 g, 35.5 mmol) and $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (366 mg, 0.30 mmol) in AcOH (35 mL) and the resultant mixture was stirred at rt for 3 h, then was diluted with EtOAc (50 mL). The mixture was quenched by dropwise addition of satd aq K_2CO_3. The organic layer was washed with satd aq K_2CO_3 (2 × 50 mL) and the combined aqueous washings were extracted with EtOAc (50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (eluent 30-40 °C petrol/Et_2O, 83:17) gave **276** as a deep red solid (8.82 g, 77%, >99:1 *para*); mp 64-69 °C {lit.[24] mp 69-72 °C}; δ_H (400 MHz, $CDCl_3$) 4.11 (2H, br s, N*H*$_2$), 6.63 (1H, d, *J* 8.6, C(6)*H*), 7.24 (1H, dd, *J* 8.6, 2.3, C(5)*H*), 7.74 (1H, d, *J* 2.3, C(3)*H*).

tert-Butyl (*E*)-3-(2'-*N*,*N*-diallylamino-5'-bromophenyl)propenoate 277



$Pd(OAc)_2$ (163 mg, 0.72 mmol) was added to a stirred, degassed solution of **276** (21.7 g, 72.7 mmol), P(*o*-Tol)$_3$ (442 mg, 1.45 mmol), *tert*-butyl acrylate (10.6 g, 80.1 mmol) and Et_3N (20 mL, 145 mmol) in MeCN (400 mL) and the mixture was heated at 70 °C for 16 h and then was concentrated *in vacuo*. The mixture was dissolved in CH_2Cl_2 (400 mL) and was washed with H_2O (2 × 200 mL). The combined aqueous layers were extracted with CH_2Cl_2 (400 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* column chromatography (eluent 30-40 °C petrol/Et_2O, 50:50) gave **277** as a dark brown oil (16.8 g, 78%, >99:1 dr);[25] δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, C*Me*$_3$), 3.95 (2H, s, N*H*$_2$), 6.28 (1H, d, *J* 15.7, C(2)*H*), 6.58 (1H, d, *J* 8.7, C(3')*H*), 7.23 (1H, dd, *J* 8.7, 2.3, C(4')*H*), 7.48 (1H, d, *J* 2.3, C(6')*H*), 7.61 (1H, d, *J* 15.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 80.6 (*C*Me$_3$), 110.6 (*Ar*), 118.1 (*C*(3')), 121.5 (*C*(2)), 121.9 (*Ar*), 130.3 (*C*(6')), 133.4 (*C*(4')), 137.4 (*C*(3)), 144.2 (*Ar*), 166.1 (*C*(1)).

tert-Butyl (*E*)-3-(2'-*N*,*N*-diallylamino-5'-bromophenyl)-acrylate 278



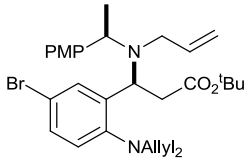
Method A: Allyl iodide (14.5 mL,159 mmol) was added to a solution of **277** (15.9 g, 53 mmol) and K_3PO_4 (28.0 g, 133 mmol) in acetone (250 mL) and the mixture was heated at reflux for 5 days, then was allowed to cool to rt. The mixture was diluted with Et_2O (300 mL) and washed with H_2O (2 × 200 mL). The combined aqueous washings were extracted with Et_2O (200 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The crude product was passed through a short

plug of silica (eluent 30-40 °C petrol/Et_2O, 86:14) to give **278** as a yellow oil (17.8 g, 89%, >99:1 dr); $C_{19}H_{24}BrNO_2$ requires C, 60.3; H, 6.4; N, 3.7%; found C, 60.4; H, 6.4; N, 3.8%; ν_{max} (ATR) 3078, 2978, 2931, 2822 (C−H), 1705 (C=O), 1631, 1585 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 3.61 (4H, d, *J* 6.3, N(C*H*$_2$CH=CH$_2$)$_2$), 5.10-5.21 (4H, m, N(CH$_2$CH=C*H*$_2$)$_2$), 5.72-5.84 (2H, m, N(CH$_2$C*H*=CH$_2$)$_2$), 6.30 (1H, d, *J* 15.9, C(2)*H*), 6.89 (1H, d, *J* 8.6, C(3')*H*), 7.36 (1H, dd, *J* 8.6, 2.3, C(4')*H*), 7.63 (1H, d, *J* 2.3, C(6')*H*), 7.92 (1H, d, *J* 15.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 56.0 (N(*C*H$_2$CH=CH$_2$)), 80.5 (*C*Me$_3$), 115.5 (*C*(5')), 118.0 (N(CH$_2$CH=*C*H$_2$)$_2$), 120.8 (*C*(2)), 123.2 (*C*(3')), 130.4 (*C*(6')), 131.7 (*C*(1')), 132.4 (*C*(4')), 134.2 (N(CH$_2$*C*H=CH$_2$)$_2$), 139.9 (*C*(3)), 149.6 (*C*(2')), 166.2 (*C*(1)); *m*/*z* (ESI$^+$) 779 ([M(^{81}Br)+M(^{79}Br)+Na]$^+$, 100%), 400 ([M(^{79}Br)+Na]$^+$, 85%), 380 ([M(^{81}Br)+H]$^+$, 60%); HRMS (ESI$^+$) $C_{19}H_{24}{}^{81}BrNNaO_2{}^+$ ([M(^{81}Br)+Na]$^+$) requires 402.0862; found 402.0867.

Method B: *Step 1*: $Pd(OAc)_2$ (80 mg, 0.36 mmol) was added to a stirred, degassed solution of **276** (10.6 g, 35.5 mmol), P(*o*-Tol)$_3$ (216 mg, 0.71 mmol), *tert*-butyl acrylate (5.72 mL, 39.1 mmol) and Et_3N (9.89 mL, 71.0 mmol) in MeCN (200 mL). The resultant mixture was heated at 70 °C for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 mL) and the resultant solution was washed with H_2O (2 × 200 mL). The combined aqueous layers were extracted with CH_2Cl_2 (200 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **277** as a brown oil (10.7 g, >99:1 dr).

Step 2: Allyl iodide (9.80 mL, 107 mmol) was added to a solution of **277** (10.7 g, >99:1 dr) and K_3PO_4 (18.8 g, 88.7 mmol) in acetone (200 mL), and the resultant mixture was heated at reflux for 48 h. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (300 mL), and washed with H_2O (2 × 200 mL). The combined aqueous layers were extracted with Et_2O (200 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was passed through a short plug of silica (eluent 30-40 °C petrol/Et_2O, 20:1) and the filtrate was concentrated *in vacuo* to give **278** as a yellow oil (12.1 g, 90% from **276**, >99:1 dr).

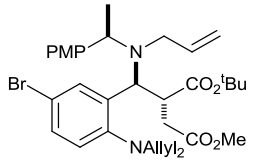
tert-Butyl (3*S*,α*R*)-3-[*N*-allyl-*N*-(α-methyl-4''-methoxybenzyl)amino]-3-(2'-*N*,*N*-diallylamino-5'-bromophenyl)propanoate 279



Following *General Procedure 1*, (*R*)-**227** (13.1 g, 68.7 mmol, >99% ee) in THF (200 mL), BuLi (2.3 M in hexanes, 29.2 mL, 68.7 mmol) and **278** (16.3 g, 42.9 mmol, >99:1 dr) in THF (200 mL) gave

279 (25.0 g, quant, >99:1 dr crude). Purification of an aliquot via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave an analytical sample of **279** as a pale yellow oil (>99:1 dr); $C_{31}H_{41}BrN_2O_3$ requires C, 65.4; H, 7.3; N, 4.9%; found C, 65.45; H, 7.3; N, 4.9%; $[\alpha]_D^{20}$ –5.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3075, 2977, 2931, 2834 (C–H), 1727 (C=O), 1641, 1610, 1584 (C=C); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.6, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 2.54 (1H, dd, *J* 15.2, 6.3, C(2)H_A), 2.86 (1H, dd, *J* 15.2, 8.3, C(2)H_B), 3.13-3.23 (1H, m, NCH_AH$_B$CH=CH$_2$), 3.30-3.39 (1H, m, NCH$_A$$H_B$CH=CH$_2$), 3.47-3.64 (4H, m, N(C$H_2$CH=CH$_2$)$_2$), 3.80 (3H, s, O*Me*), 3.89 (1H, q, *J* 6.6, C(α)*H*), 4.92-5.20 (7H, m, C(3)*H*, NCH$_2$CH=CH_2, N(CH$_2$CH=CH_2)$_2$), 5.72-5.88 (3H, m, NCH$_2$C*H*=CH$_2$, N(CH$_2$C*H*=CH$_2$)$_2$), 6.84 (1H, d, *J* 8.7, C(2")*H*, C(6")*H*), 6.96 (1H, d, *J* 8.6, C(3')*H*), 7.28 (2H, d, *J* 8.7, C(3")*H*, C(5")*H*), 7.31 (1H, dd, *J* 8.6, 2.5, C(4')*H*), 7.67 (1H, d, *J* 2.5, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 15.8 (C(α)*Me*), 28.0 (C*Me*$_3$), 39.9 (*C*(2)), 48.8 (N*C*H$_2$CH=CH$_2$), 53.6 (*C*(3)), 55.2 (O*Me*), 56.0 (*C*(α)), 56.9 (N(*C*H$_2$CH=CH$_2$)$_2$), 80.2 (*C*Me$_3$), 113.2 (*C*(3"), *C*(5")), 114.6 (NCH$_2$CH=*C*H$_2$), 117.4 (*Ar*), 118.1 (N(CH$_2$CH=*C*H$_2$)$_2$), 125.6 (*C*(3')), 128.7 (*C*(2"), *C*(6")), 130.0 (*C*(4')), 132.1 (*C*(6')), 134.5 (N(CH$_2$*C*H=CH$_2$)$_2$), 136.7 (*Ar*), 139.8 (NCH$_2$*C*H=CH$_2$), 141.9, 148.9 (*Ar*), 158.2 (*C*(4")), 171.2 (*C*(1)); *m/z* (ESI$^+$) 571 ([M(^{81}Br)+H]$^+$, 100%), 569 ([M(^{79}Br)+H]$^+$, 95%); HRMS (ESI$^+$) $C_{31}H_{42}{}^{79}BrN_2O_3{}^+$ ([M(^{79}Br)+H]$^+$) requires 569.2373; found 569.2367.

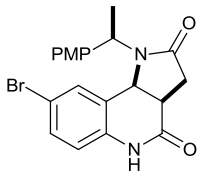
***tert*-Butyl (2*R*,3*S*,α*R*)-2-(2'-methoxy-2'-oxoethyl)-3-[*N*-allyl-*N*-(α-methyl-4'''-methoxybenzyl)amino]-3-(2''-*N*,*N*-diallylamino-5''-bromophenyl)propanoate 280**



Following *General Procedure 4*, $^iPr_2NH$ (9.02 mL, 64.5 mmol) in THF (200 mL), BuLi (2.3 M in hexanes, 27.4 mL, 64.4 mmol) and **279** (24.5 g, 42.9 mmol, >99:1 dr) in THF (150 mL) gave **280** in >98:2 crude dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 83:17) gave **280** as a yellow oil (27.5 g, 81%, >98:2 dr); $[\alpha]_D^{20}$ –47.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3076, 2977, 2951, 2835 (C–H), 1741 (C=O), 1641, 1610, 1585 (C=C); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.6, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 2.17 (1H, dd, *J* 15.7, 3.5, C(1')H_A), 2.52 (1H, dd, *J* 15.7, 11.1, C(1')H_B), 3.09-3.25 (2H, m, NCH_2CH=CH$_2$), 3.43-3.64 (5H, m, C(2)*H*, N(CH_2CH=CH$_2$)$_2$), 3.61 (3H, s, CO$_2$*Me*), 3.77 (3H, s, ArO*Me*), 4.05 (1H, q, *J* 6.6, C(α)*H*), 4.82-4.97 (3H, m, C(3)*H*, NCH$_2$CH=CH_2), 5.10-5.21 (4H, m, N(CH$_2$CH=CH_2)$_2$), 5.64-5.89 (3H, m, NCH$_2$C*H*=CH$_2$, N(CH$_2$C*H*=CH$_2$)$_2$), 6.76 (2H, d, *J* 8.8, *C*(3''')*H*, *C*(5''')*H*), 7.03 (1H, d, *J* 8.6, C(3")*H*), 7.13 (2H, d, *J* 8.8, *C*(2''')*H*, *C*(6''')*H*), 7.36 (1H, dd, *J* 8.6, 2.5, C(4")*H*), 7.49 (1H, d, *J* 2.5, C(6")*H*); δ_C (100 MHz,

$CDCl_3$) 18.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 35.7 (*C*(1')), 46.3 (*C*(2)), 49.9 (N*C*H_2CH=CH_2), 51.7 (CO_2*Me*), 55.2 (O*Me*), 56.3 (*C*(α)), 57.1 (N(*C*H_2CH=CH_2)$_2$), 57.4 (*C*(3)), 80.8 (*C*Me$_3$), 113.1 (*C*(3'''), *C*(5''')), 114.9 (NCH$_2$CH=*C*H_2), 117.7 (*Ar*), 118.8 (N(CH$_2$CH=*C*H$_2$)$_2$), 126.3 (*C*(3")), 128.9 (*C*(2'''), *C*(6''')), 130.5 (*Ar*), 132.1 (*C*(6")), 133.7 (N(CH$_2$*C*H=CH$_2$)$_2$), 137.0, 137.4 (*Ar*), 138.6 (NCH$_2$*C*H=CH_2), 150.1 (*Ar*), 158.1 (*C*(4")), 171.8, 173.4 (*C*(1), *C*(2')); *m*/*z* (ESI$^+$) 643 ([M(^{81}Br)+H]$^+$, 100%), 641 ([M(^{79}Br)+H]$^+$, 95%); HRMS (ESI$^+$) $C_{34}H_{46}{}^{79}BrN_2O_5^+$ ([M(^{79}Br)+H]$^+$) requires 641.2585; found 641.2590.

(3a*R*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4'-methoxybenzyl]-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 282

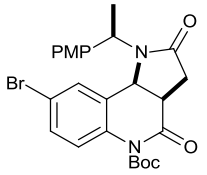


Step 1: Pd(PPh$_3$)$_4$ (283 mg, 0.24 mmol) was added to a stirred, degassed solution of **280** (3.14 g, 4.89) and DMBA (6.87 g, 44.0 mmol) in degassed CH_2Cl_2 (40 mL) under argon, and the mixture was stirred at 35 °C for 16 h. Additional Pd(PPh$_3$)$_4$ (283 mg, 0.24 mmol) was added and the mixture was stirred at 35 °C for a further 16 h, and then was concentrated *in vacuo*. The mixture was dissolved in Et_2O (100 mL) and was washed with satd aq K_2CO_3 solution (2 × 50 mL). The aqueous washings were extracted with Et_2O (50 mL). The combined organic extracts were washed with 1M HCl (3 × 40 mL) and the combined aqueous extracts were washed with Et_2O (20 mL). The HCl layer was basified to pH >10 by addition of 2M NaOH and the mixture was extacted with $CHCl_3$/IPA (3:1 v/v, 3 × 30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **281** as a pale yellow oil (2.49 g, >98:2 dr) which was used in the next step without further purification; δ_H (400 MHz, $CDCl_3$) [selected peaks] 2.23 (1H, dd, *J* 16.9, 4.6, C(1')H_A), 2.42 (1H, dd, *J* 16.9, 4.4, C(1')H_B), 3.34 (1H, td, *J* 9.5, 4.7, C(2)*H*), 3.96 (1H, d, *J* 9.5, C(3)*H*), 6.37 (1H, d, *J* 8.5, *Ar*), 6.96 (1H, d, *J* 2.4, *Ar*).

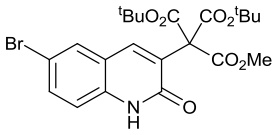
Step 2: $PhCO_2H$ (54 mg, 0.49 mmol) was added to a solution of **281** (2.49 g, >98:2 dr) in PhMe (100 mL) and the mixture was heated at reflux for 16 h, during which time a white solid precipitated. The mixture was allowed to cool slowly to rt, then was filtered and washed with cold petrol to give **282** as a white solid (646 mg, 35%, >99:1 dr); $C_{20}H_{19}BrN_2O_3$ requires C, 57.8; H, 4.6; N, 6.75%; found C, 57.8; H, 4.7; N, 6.7%; mp 258-262 °C; $[\alpha]_D^{20}$+155 (*c* 0.7 in $CHCl_3$); ν_{max} (ATR) 3228 (N–H), 3076, 2935 (C–H), 1687 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 7.3, C(α)*Me*), 2.79 (1H, dd, *J* 16.7, 8.1, C(3)H_A), 3.02-3.09 (1H, m, C(3a)*H*), 3.28 (1H, app d, *J* 16.7, C(3)H_B), 3.87 (3H, s, O*Me*), 4.62

(1H, d, *J* 5.3, C(9b)*H*), 5.53 (1H, q, *J* 7.3, C(α)*H*), 6.24 (1H, d, *J* 2.3, C(9)*H*), 6.80 (1H, d, *J* 8.3, C(6)*H*), 6.97 (2H, d, *J* 9.0, C(3')*H*), C(5')*H*), 7.02 (2H, d, *J* 8.7, C(2')*H*), C(6')*H*), 7.42 (1H, dd, *J* 8.7, 2.3, C(7)*H*), 9.97 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 34.0 (*C*(3)), 38.3 (*C*(3a)), 48.5 (*C*(α)), 55.4 (O*Me*), 57.1 (*C*(9b)), 114.1 (*C*(3'), *C*(5')), 114.8 (*Ar*), 117.3 (*C*(6)), 119.2 (*Ar*), 128.8 (*C*(2'), *C*(6')), 130.2 (*Ar*), 133.4 (*C*(7)), 134.6 (*C*(9)), 136.6 (*Ar*), 158.9 (*C*(4')), 170.8, 173.3 (*C*(2), *C*(4)); *m/z* (ESI^+) 439 ($[M(^{81}Br)+Na]^+$, 95%), 437 ($[M(^{79}Br)+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{19}{}^{79}BrN_2NaO_3{}^+$ ($[M(^{79}Br)+Na]^+$) requires 437.0471; found 437.0473.

(3a*R*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4'-methoxybenzyl]-5-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2,4-dione 284 and 2-(1'-(Bis-*tert*-butoxycarbonyl)-1'-(methoxycarbonyl)-methyl)-6-bromo-1*H*-quinolin-2-one 283



284



283

Method A: Boc_2O (607 mg, 2.78 mmol) was added portionwise to a solution of **282** (1.05 g, 2.53 mmol), Et_3N (0.71 mL, 5.06 mmol) and DMAP (31 mg, 0.25 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at rt for 16 h. The mixture was washed with 1.0 M HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (50 mL), brine (50 mL) then dried and concentrated *in vacuo*. Recrystallisation (PhMe) gave **284** as a white solid (928 mg, 71%, >99:1 dr); mp 178–182 °C; $[\alpha]_D^{20}$+97.7 (*c* 1.2 in $CHCl_3$); ν_{max} (ATR) 2976 (C–H), 1737 (C=O), 1749 (C=O); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 7.3, C(α)*Me*), 1.58 (9H, s, C*Me*$_3$), 2.70 (1H, dd, *J* 16.4, 7.3, C(3)H_A), 3.01-3.12 (1H, m, C(3a)*H*), 3.24 (1H, app d, *J* 16.4, C(3)H_B), 3.84 (3H, s, O*Me*), 4.50 (1H, d, *J* 5.1, C(9b)*H*), 5.50 (1H, q, *J* 7.3, C(α)*H*), 6.18 (1H, d, *J* 2.0, C(9)*H*), 6.77 (1H, d, *J* 8.7, C(6)*H*), 6.93 (2H, d, *J* 8.8, C(3')*H*, C(5')*H*), 6.98 (2H, d, *J* 8.8, C(2')*H*, C(6')*H*), 7.42 (1H, dd, *J* 8.7, 2.0, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 27.5 (C*Me*$_3$), 34.4 (*C*(3)), 39.4 (*C*(3a)), 48.3 (*C*(α)), 55.4 (O*Me*), 56.9 (*C*(9b)), 86.1 (*C*Me$_3$), 114.1 (*C*(3'), *C*(5')), 116.1 (*Ar*), 117.7 (*C*(6)), 120.6 (*Ar*), 128.7 (*C*(2'), *C*(6')), 130.1 (*Ar*), 133.2 (*C*(7)), 134.8 (*C*(9)), 136.1 (*Ar*), 150.4 (N*C*O), 159.0 (*C*(4')), 167.4, 172.9 (*C*(2), *C*(4)); *m/z* (ESI^+) 539 ($[M(^{81}Br)+Na]^+$, 95%), 537 ($[M(^{79}Br)+Na]^+$, 100%); HRMS (ESI^+) $C_{25}H_{27}{}^{79}BrN_2NaO_5{}^+$ ($[M(^{79}Br)+Na]^+$) requires 537.0996; found 537.0998.

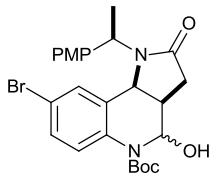
Method B: *Step 1*: $Pd(PPh_3)_4$ (357 mg, 0.31 mmol) was added to a stirred, degassed solution of **280** (3.97 g, 6.19 mmol, >98:2 dr) and DMBA (8.68 g, 55.7 mmol) in CH_2Cl_2 (80 mL) under argon and

the resultant mixture was stirred at 35 °C for 16 h. Additional $Pd(PPh_3)_4$ (357 mg, 0.31 mmol) was then added and the resultant mixture was stirred at 35 °C for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in Et_2O (200 mL). The resultant solution was washed with satd aq K_2CO_3 (2 × 100 mL) and the combined aqueous layers were extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with 3.0 M aq HCl (5 × 50 mL) and 2.0 M aq NaOH was added to the combined aqueous layers until pH >10 was achieved. The aqueous layer was then extracted with $CHCl_3$/IPA (3:1, 3 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **281** as a yellow oil (3.97 g, >98:2 dr).

Step 2: $PhCO_2H$ (76 mg, 0.62 mmol) was added to a solution of **281** (3.97 g, >98:2 dr) in PhMe (50 mL). The resultant solution was heated at reflux for 16 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and the resultant solution was washed with satd aq K_2CO_3 (2 × 50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (50 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **282** as a brown solid (1.72 g, >99:1 dr).

Step 3: Boc_2O (1.13 g, 5.16 mmol) was added to a solution of **282** (1.72 g, >99:1 dr), Et_3N (1.31 mL, 9.38 mmol) and DMAP (57 mg, 0.50 mmol) in CH_2Cl_2 (50 mL) and the resultant mixture was stirred at 35 °C for 16 h. The reaction mixture was then washed with 1.0 M aq HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification via recrystallisation (PhMe) gave **284** as a white solid (1.19 g, 49% from **280**, >99:1 dr) with spectroscopic properties identical to those described above. Purification of the mother liquor by flash column chromatography (eluent 30-40 °C petrol/EtOAc, 66:34) gave **283** as a yellow solid (236 mg, 10% from **280**); mp 203-208 °C, ν_{max} (ATR) 2980, 2931 (C−H), 1737 [C=O (ester)], 1659 [C=O (quinolinone)]; δ_H (400 MHz, $CDCl_3$) 3.79 (18H, s, 2 × C*Me*$_3$), 5.29 (3H, s, O*Me*), 7.23 (1H, d, *J* 8.8, C(8)*H*), 7.54 (1H, dd, *J* 8.8, 1.8, C(7)*H*), 7.68 (1H, d, *J* 1.8, C(5)*H*), 7.93 (1H, s, C(4)*H*), 12.94 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (2 × C*Me*$_3$), 53.1 (O*Me*), 69.1 (*C*(1')), 83.7 (2 × *C*Me$_3$), 115.1 (*Ar*), 117.5 (*C*(8)), 120.7, 129.3 (*Ar*), 130.4 (*C*(5)), 133.4 (*C*(7)), 136.4 (*C*(4)), 136.9 (*Ar*), 163.0, 164.1, 166.1 (*C*(2), *C*O_2Me, 2 × *C*$O_2{}^t$Bu); *m*/*z* (ESI$^+$) 520 ([M(^{81}Br)+Na]$^+$, 95%), 518 ([M(^{79}Br)+Na]$^+$, 100%), 498 ([M(^{81}Br)+H]$^+$, 40%), 496 ([M(^{79}Br)+H]$^+$, 40%); HRMS (ESI$^+$) $C_{22}H_{26}{}^{79}BrNNaO_7{}^+$ ([M(^{79}Br)+Na]$^+$) requires 518.0785; found 518.0769.

(3a*R*,4*R*,9b*S*,α*R*)- or (3a*R*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4'-methoxybenzyl]-4-hydroxy-*N*(5)-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 285[26]



$LiAl(O^tBu)_3H$ (659 mg, 2.59 mmol) was added portionwise to a solution of **284** (891 mg, 1.72 mmol, >99:1 dr) in THF (20 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. H_2O (1 mL) was then added and the reaction mixture was diluted with EtOAc (20 mL) and stirred at rt for 30 min, then filtered through Celite® (eluent EtOAc/Et_3N, 100:1, 100 mL). The filtrate was then concentrated *in vacuo* to give **285** as a white foam (900 mg, quant, >99:1 dr); $[\alpha]_D^{20}$+67.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3311 (O–H), 2976, 2933, 2838 (C–H), 1699, 1665 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 2.51 (1H, d, *J* 15.4, C(3)H_A), 2.75-2.90 (2H, m, C(3)H_B, C(3a)*H*), 3.83 (3H, s, O*Me*), 4.39 (1H, d, *J* 7.3, C(9b)*H*), 5.78 (1H, s, C(4)*H*), 6.35 (1H, d, *J* 2.2, C(9)*H*), 6.91 (2H, d, *J* 8.8, C(3")*H*, C(5")*H*), 6.97 (2H, d, *J* 8.8, C(2")*H*, C(6")*H*), 7.21 (1H, d, *J* 8.5, C(6)*H*), 7.36 (1H, dd, *J* 8.5, 2.2, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 25.3 (C(α)*Me*), 28.2 (C*Me*$_3$), 36.0 (*C*(3)), 42.1 (*C*(3a)), 49.4 (*C*(α)), 55.4 (O*Me*), 56.4 (*C*(9b)), 81.8 (*C*(4)), 82.3 (*C*Me$_3$), 113.9 (*C*(3′), *C*(5′)), 116.9 (*Ar*), 127.3 (*C*(6)), 129.1 (*C*(2′), *C*(6′)), 129.9, 130.4 (*Ar*), 131.9 (*C*(7)), 133.5 (*C*(9)), 136.6 (*Ar*), 152.5 (N*C*O), 158.9 (*C*(4′)), 173.3 (*C*(2)); *m*/*z* (ESI$^+$) 541 ([M(^{81}Br)+Na]$^+$, 100%), 539 ([M(^{79}Br)+Na]$^+$, 95%); HRMS $C_{25}H_{29}{}^{79}BrN_2NaO_5^+$ ([M(^{79}Br)+Na]$^+$) requires 539.1152; found 539.1158.

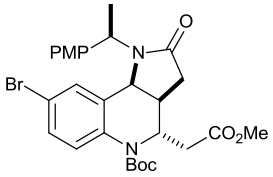
Methyl 2-[diphenyl(pyridin-2-yl)phosphoranylidene]acetate 289

Step 1: Methyl bromoacetate (1.89 mL, 19.9 mmol) was added dropwise to a solution of diphenyl-2-pyridylphosphine **287** (5.26 g, 19.9 mmol) in PhMe (50 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered to collect the white precipitate, which was then washed with cold PhMe (20 mL). The filtrate was allowed to stand at rt for 16 h during which time a second crop of crystals formed. Both crops of crystals were then combined to give (2-methoxy-2-oxoethyl)diphenyl-2-pyridylphosphonium bromide **288** as a white crystalline solid (6.87 g, 83%); mp 168–162 °C; ν_{max} (ATR) 2802, 2738 (C−H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 3.62 (3H, s, O*Me*), 5.62 (2H, d, *J* 13.5, C(2)H_2), 7.61-7.72 (5H, m, *Ar*), 7.73-7.82 (2H, m, *Ar*), 7.87-7.98 (4H, m, *Ar*), 8.05-8.13 (1H, m, *Ar*), 8.41-8.48 (1H, m, *Ar*), 8.87 (1H, d, *J* 4.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 31.8 (d, *J* 59.1, *C*(2)), 53.5 (O*Me*), 117.1 (d, *J* 88.7, *Ar*), 128.2 (d, *J* 3.2, *Ar*), 130.1 (d, *J* 12.8, *Ar*), 131.9 (d, *J* 24.8, *Ar*), 134.3 (d, *J* 10.4, *Ar*), 135.2, (d, *J* 3.2, *Ar*), 138.3 (d, *J* 10.4, *Ar*), 144.1 (d, *J* 121.4, *Ar*),

151.7 (d, *J* 20.0, *Ar*), 165.3 (d, *J* 3.2, *C*(1)); δ_P (162 MHz, $CDCl_3$) 16.0.

Step 2: Phosphorane **289** was prepared, as required, by treatment of a solution of **288** in CH_2Cl_2 with 2.0 M aq NaOH. The aqueous layer was then extracted with CH_2Cl_2 and the combined organic extracts were dried and concentrated *in vacuo* to give **289** as a pink solid.

(3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-methoxy-2'-oxoethyl)-*N*(5)-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 286



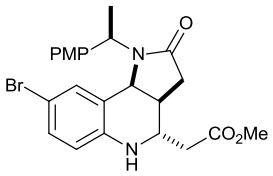
Method A: Phosphorane **289** (2.36 g, 7.05 mmol) was added to a solution of **285** (1.03 g, 2.35 mmol, >99:1 dr) in PhMe (50 mL) and the resultant mixture was heated at 80 °C for 72 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL) and the resultant solution was washed with 3.0 M aq HCl (6 × 10 mL). The combined aqueous layers were extracted with EtOAc (10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 50:50) gave **286** as a colourless oil (1.01 g, 75%, >99:1 dr); $[\alpha]_D^{20}$ +109.8 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 2978, 2935, 2838 (C–H), 1739, 1696 (C=O); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, d, *J* 7.3, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 2.11 (2H, d, *J* 7.6, C(1')*H*$_2$), 2.60-2.76 (2H, m, C(3)*H*$_A$, C(3a)*H*), 2.85-2.97 (1H, m, C(3)*H*$_B$), 3.59 (3H, s, CO_2*Me*), 3.84 (3H, s, ArO*Me*), 4.36 (1H, d, *J* 7.8, C(9b)*H*), 4.78-4.91 (1H, m, C(4)*H*), 5.42 (1H, q, *J* 7.3, C(α)*H*), 6.40 (1H, d, *J* 2.3, C(9)*H*), 6.93 (2H, d, *J* 8.8, C(3")*H*, C(5")*H*), 7.00 (2H, d, *J* 8.8, C(2")*H*, C(6")*H*), 7.25 (1H, br s, C(6)*H*), 7.41 (1H, dd, *J* 8.6, 2.3, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 17.1 (C(α)*Me*), 28.2 (C*Me*$_3$), 38.2 (*C*(3)), 38.9 (*C*(1')), 39.7 (*C*(3a)), 49.4 (*C*(α)), 51.8 (CO_2*Me*), 55.3 (ArO*Me*), 55.8, 56.2 (*C*(4), *C*(9b)), 81.9 (*C*Me$_3$), 113.8 (*C*(3"), *C*(5")), 117.1 (*C*(8)), 128.1 (*C*(6)), 129.1 (*C*(2"), *C*(6")), 130.0, 131.0 (*Ar*), 132.0 (*C*(7)), 133.4 (*C*(9)), 137.6 (*Ar*), 152.5 (N*C*O), 158.9 (*C*(4")), 170.5, 173.5 (*C*(2), *C*(2')); *m*/*z* (ESI$^+$) 597 ([M(^{81}Br)+Na]$^+$, 95%), 595 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}{}^{79}BrN_2NaO_6^+$ ([M(^{79}Br)+Na]$^+$) requires 595.1414; found 595.1412.

Method B: Phosphorane **206** (6.16 g, 18.4 mmol) was added to a solution of **285** (3.18 g, 6.14 mmol) in PhMe (60 mL) and the resultant mixture was heated at 80 °C for 72 h, after which time the solvent was concentrated *in vacuo*. The insoluble residues were precipitated by addition of cold Et_2O (50 mL). Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 34:66) gave **286** as a colourless oil which contained phosphorane impurities (2.17 g, ~62%, >99:1 dr).

Method C: Phosphorane **206** (1.72 g, 5.16 mmol) was added to a solution of **285** (891 mg, 1.72

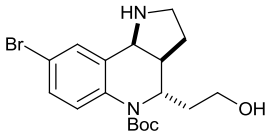
mmol) in PhMe (50 mL) and the resultant mixture was heated at 80 °C for 72 h. The mixture was cooled to 0 °C and acetaldehyde (0.48 mL, 8.6 mmol) was added. The mixture was allowed to warm to rt over 4 h and then additional acetaldehyde (0.2 mL, 3.6 mmol) was added and the mixture was stirred for a further 4 h at rt, then was concentrated *in vacuo*. Repeated trituration with Et_2O was unsuccessful at removing the remaining PPh_3O residues from **286**.

(3a*S*,4*S*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-methoxy-2'-oxoethyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinolin-2-one 290



A solution of **286** (162 mg, 0.28 mmol, >99:1 dr) in methanolic HCl (1.25 M, 4 mL) was stirred at rt for 16 h and then was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant solution was washed with 2.0 M aq NaOH (2 × 10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via recrystallisation ($CHCl_3$/hexane) gave **290** as a yellow solid (98 mg, 73%, >99:1 dr); mp 206–209 °C; $[\alpha]_D^{20}$ +16.3 (*c* 0.7 in $CHCl_3$); ν_{max} (ATR) 3392, 3318 (N–H), 2952, 2935, 2938 (C–H), 1735, 1680 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 7.1, C(α)*Me*), 2.09-2.18 (1H, m, C(3a)*H*), 2.26-2.42 (2H, m, C(3)H_A, C(1')H_A), 2.63 (1H, dd, *J* 16.3, 2.4, C(1')H_B), 2.71 (1H, dd, *J* 16.7, 6.8, C(3)H_B), 3.71 (3H, s, CO_2Me), 3.82 (3H, s, ArO*Me*), 4.50 (1H, d, *J* 5.1, C(9b)*H*), 4.96 (1H, br s, C(4)*H*), 5.46 (1H, q, *J* 7.1, C(α)*H*), 6.28 (1H, d, *J* 2.0, C(9)*H*), 6.21 (1H, d, *J* 2.2, N*H*), 6.42 (1H, d, *J* 8.6, C(6)*H*), 6.92 (2H, d, *J* 8.7, C(3")*H*, C(5")*H*), 7.06 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*), 7.12 (1H, dd, *J* 8.6, 2.0, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 35.6 (*C*(3a)), 35.7 (*C*(3)), 38.0 (*C*(1')), 48.0 (*C*(4)), 48.7 (*C*(α)), 52.1 (CO_2Me), 55.3 (ArO*Me*), 56.1 (*C*(9b)), 108.0 (*Ar*), 114.0 (*C*(3"), *C*(5")), 116.4 (*C*(6)), 117.4 (*C*(8)), 128.5 (*C*(2"), *C*(6")), 131.4 (*Ar*), 132.5 (*C*(7)), 134.9 (*C*(9)), 143.2 (*Ar*), 158.7 (*C*(4")), 172.4, 173.3 (*C*(2), *C*(2')); *m*/*z* (ESI^+) 497 ($[M(^{81}Br)+Na]^+$, 95%), 495 ($[M(^{79}Br)+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{25}{}^{79}BrN_2NaO_4^+$ ($[M(^{79}Br)+Na]^+$) requires 495.0890; found 495.0889.

(3a*R*,4*S*,9b*S*)-4-(2'-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 293



Method A: *Step 1*: Following *General Procedure 7*, CAN (5.64 g, 10.3 mmol) in H_2O (30 mL) and **286** (1.97 g, 3.44 mmol, >99:1 dr) in MeCN (30 mL) gave the crude product **292** as a pale yellow oil (1.95 g, >99:1 dr); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.50 (9H, s, C*Me*$_3$), 3.05 (1H, app ddd, *J* 18.3, 9.4, 1.4, C(3a)*H*), 3.65 (3H, s, CO_2*Me*), 4.70 (1H, d, *J* 8.9, C(9b)*H*), 5.05 (1H, app t, *J* 7.5, C(4)*H*), 6.73 (1H, s, N*H*), 7.32 (1H, d, *J* 2.2, C(9)*H*), 7.36 (1H, dd, *J* 8.9, 2.2, C(7)*H*), 7.47 (1H, br d, *J* 8.9, C(6)*H*).

Step 2: BH_3·THF (1.0 M in THF, 34.0 mL, 34.0 mmol) was added dropwise to a solution of **292** (1.95 g, >99:1 dr) in THF (35 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h then allowed to cool to rt before being cooled further to 0 °C. Satd aq K_2CO_3 (20 mL) and EtOAc (20 mL) were then carefully added and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt and washed with satd aq K_2CO_3 (2 × 30 mL). The combined aqueous layers were extracted with EtOAc (50 mL) then the organic extract was dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **293**·BH_3 as a white foam (554 mg, 39% from **286**, >99:1 dr); $[\alpha]_D^{20}$+102.6 (*c* 1.03 in $CHCl_3$); ν_{max} (ATR) 3416 (N–H), 3197 (O–H), 2973, 2933, 2874 (C–H), 2362, 2269 (B–H), 1687 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32-1.44 (1H, m, C(1')H_A), 1.44-1.65 (10H, m, C(1')H_B, C*Me*$_3$), 1.67-1.81 (1H, m, C(3)H_A), 2.28-2.39 (1H, m, C(3)H_B), 2.77-2.97 (2H, m, C(2)H_A, C(3a)*H*), 3.24-3.34 (1H, m, C(2)H_B), 3.36-3.53 (2H, m, C (2')H_2), 4.04 (1H, br s, O*H*), 4.21 (1H, dd, *J* 9.6, 5.8, C(9b)*H*), 4.65 (1H, dd, *J* 11.7, 3.0, C(4)*H*), 7.32 (1H, br s, C(6)*H*), 7.41 (1H, dd, *J* 8.6, 2.3, C(7)*H*), 7.78 (1H, d, *J* 2.3, C(9)*H*);[27] δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 30.3 (*C*(3)), 34.3 (*C*(1')), 43.5 (*C*(3a)), 52.7 (*C*(4)), 54.1 (*C*(2)), 58.6 (*C*(2')), 63.1 (*C*(9b)), 82.8 (*C*Me$_3$), 117.7 (*Ar*), 126.5 (*C*(6)), 128.2 (*Ar*), 132.3 (*C*(7)), 133.0 (*C*(9)), 135.0 (*Ar*);[28] *m*/*z* (ESI$^+$) 845 ([2M+Na]$^+$, 100%), 435 ([M(^{81}Br)+Na]$^+$, 68%), 433 ([M(^{79}Br)+Na]$^+$, 70%); HRMS (ESI$^+$) $C_{18}H_{28}B^{79}BrN_2NaO_3^+$ ([M(^{79}Br)+Na]$^+$) requires 433.1269; found 433.1266. Further elution ($CHCl_3$/MeOH/Et_3N, 95:5:1) gave **293** as a pale yellow oil (288 mg, 21% from **286**, >99:1 dr); $C_{18}H_{25}BrN_2O_3$ requires C, 54.4; H, 6.3; N, 7.05%; found C, 54.4; H, 6.3; N, 6.9%; $[\alpha]_D^{20}$+125 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3310 (O–H, N–H), 2974, 2934, 2878, 2730 (C–H), 1694 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40-1.56 (1H, m, C(1')H_A), 1.45 (9H, s, C*Me*$_3$),1.56-1.70 (2H, m, C(3)H_A, C(1')H_B), 2.00-2.10 (1H, m, C(3)H_B), 2.52 (1H, app q, *J* 8.8, C(3a)*H*), 2.76-2.86 (1H, m,

C(2)H_A), 2.86-2.95 (1H, m, C(2)H_B), 3.23 (1H, br s, O*H*), 3.43-3.54 (2H, m, C(2')H_2), 4.24 (1H, d, *J* 8.8, C(9b)*H*), 4.65-4.74 (1H, m, C(4)*H*), 7.24-7.34 (2H, m, C(6)*H*, C(7)*H*), 7.42 (1H, s, C(9)*H*); δ_C (100 MHz, $CDCl_3$) 28.3 (CMe_3), 31.6 (*C*(3)), 34.8 (*C*(1')), 43.7 (*C*(3a)), 45.6 (*C*(2)), 52.9 (*C*(4)), 55.7 (*C*(9b)), 58.8 (*C*(2')), 82.0 (*C*Me_3), 117.3, 126.5, 130.5, 132.1, 133.2, 134.8 (*Ar*), 154.9 (N*C*O); *m*/*z* (FI^+) 398 ([M(^{81}Br)]$^+$, 95%), 396 ([M(^{79}Br)]$^+$, 100%); HRMS (FI^+) $C_{18}H_{25}{}^{79}BrN_2O_3{}^+$ ([M(^{79}Br)]$^+$) requires 396.1043; found 396.1049. A solution of **293**·BH_3 (554 mg, 1.34 mmol) in MeOH (30 mL) was heated at reflux for 48 h then allowed to cool to rt and concentrated *in vacuo* to give **293** as a colourless oil (525 mg, 39% from **286**, >99:1 dr).

Method B: A solution of **293**·BH_3 (393 mg, 0.96 mmol, >99:1 dr) in MeOH (20 mL) was heated at reflux for 48 h and then was concentrated *in vacuo*. Excess $B(OMe)_3$ was removed by co-evaporation with MeOH (2 × 20 mL). Purification *via* flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **293** as a colourless oil (379 mg, quant, >99:1 dr).

Method C: *Step 1*: Following *General Procedure 7*, CAN (6.83 g, 12.4 mmol) in H_2O (40 mL) and **286** (2.38 g, 4.15 mmol, >99:1 dr) in MeCN (40 mL) gave the crude product **292** as a pale yellow oil (2.08 g, >99:1 dr) which was used in the next step without purification.

Step 2: BH_3·THF (1.0 M in THF, 42.0 mL, 42.0 mmol) was added dropwise to a solution of **292** (2.08 g, >99:1 dr) in THF (40 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h then allowed to cool to rt before being cooled further to 0 °C. Satd aq K_2CO_3 (20 mL) and EtOAc (20 mL) were then carefully added and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt and washed with satd aq K_2CO_3 (2 × 30 mL). The combined aqueous layers were extracted with EtOAc (50 mL) then the organic extract was dried and concentrated *in vacuo*. Purification via flash column chromatography gave a mixture of **293** and **293**·BH_3 (1.90 g) which was used without purification. The residue was dissolved in MeOH (100 mL) and was heated at reflux for 48 h then concentrated *in vacuo*. Excess $B(OMe)_3$ was removed by repeated coevaporation with MeOH. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 50:50:1 → MeOH/Et_3N, 100:1) gave **293** as a colourless oil (720 mg, 44% over 3 steps from **286**, >99:1 dr).

Method D: *Step 1*: Following *General Procedure 7*, CAN (4.36 g, 2.65 mmol) in H_2O (25 mL) and **286** (1.52 g, 2.65 mmol, >99:1 dr) in MeCN (25 mL) gave the crude product **292** (1.60 g, >99:1 dr) which was used in the next step without purification.

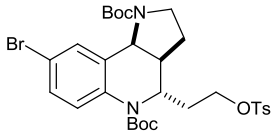
Step 2: A solution of BH_3·THF (1.0 M in THF, 37 mL, 37 mmol) was added dropwise to a solution of **292** (1.32 g) in THF (50 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h and then

was cooled to 0 °C. The reaction was quenched by addition of satd aq K_2CO_3 (20 mL) and EtOAc (20 mL) then heated at reflux for 1 h. The mixture was cooled to rt and then was partitioned between satd aq K_2CO_3 (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (20 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give the crude product mixture containing **293**·BH_3 and **293** (1.32 g).

Step 3: Pd/C (10% w/w on C, 150 mg) was added to a stirred, degassed solution of the above reaction mixture (1.32 g) in MeOH/cyclohexene (4:1, 25 mL) and the resultant mixture was stirred at rt for 16 h. The mixture was filtered through Celite® (eluent MeOH/Et_3N, 100:1) and was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/Et_3N, 90:10:1) gave **293** (217 mg, 21% over 3 steps from **286**, >99:1 dr). Further elution gave **262** as a colourless oil (200 mg, 25% over 3 steps from **286**, >99:1 dr).

Method E: TMEDA (12 μL, 80 μmol) was added to a solution of **293**·BH_3 (66 mg, 0.16 mmol) in Et_2O (1 mL) and the resultant mixture was stirred for 30 mins, during which time a precipitate of TMEDA·$2BH_3$ formed.[29] The suspension was centrifuged at 1000 rpm for 5 mins, and the supernatant was collected and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/Et_3N, 95:5:1) gave firstly a mixture of **293** and **293**·BH_3 (48 mg). Further elution gave **293** as a colourless oil (15 mg, 24%, >99:1 dr).

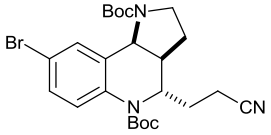
(*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-[2'-(4''-toluenesulfonyloxy)ethyl]-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 295



Step 1: Boc_2O (148 mg, 0.68 mmol), DMAP (8 mg, 62 μmol) and Et_3N (0.26 mL, 1.85 mmol) were added sequentially to a solution of **293** (245 mg, 0.62 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred at 35 °C for 5 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and the resultant solution was washed with 1.0 M aq HCl (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3:1, 2 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **294** (300 mg, >99:1 dr); δ_H (400 MHz, $CDCl_3$) 1.27-1.89 (3H, m, C(3a)*H*, C(1')H_2), 1.52 (18H, s, 2 × CMe_3), 2.00-2.15 (1H, br m, C(3)H_A), 2.40-2.58 (1H, m, C(3)H_B), 3.27-3.49 (2H, br m, C(2)H_2), 3.50-3.69 (2H, br m, C(2')H_2), 4.62-5.17 (2H, br m, C(4)*H*, C(9b)*H*), 7.21-7.43 (2H, br m, C(6)*H*, C(7)*H*), 8.09 (1H, s, C(9)*H*).

Step 2: TsCl (141 mg, 0.74 mmol), DMAP (8 mg, 62 μmol) and Et_3N (0.26 mL, 1.85 mmol) were added sequentially to a solution of **294** (300 mg, >99:1 dr) in CH_2Cl_2 (10 mL) and the resultant mixture was stirred at 35 °C for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and was washed with 1.0 M aq HCl (10 mL). The aqueous layer was extracted with $CHCl_3$/IPA (3:1, 2 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 50:50:1) gave **295** as a colourless oil (275 mg, 69% from **293**, >99:1 dr); $[\alpha]_D^{20}$ –57.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976, 2933 (C−H), 1693 (C=O); δ_H (500 MHz, PhMe-d_8, 363K) 1.29-1.30 (2H, m, C(1')H_2), 1.45 (9H, s, CMe_3), 1.50 (9H, s, CMe_3), 1.54-1.66 (2H, m, C(3)H_2), 1.79-1.89 (1H, m, C(3a)*H*), 2.04 (3H, s, C(4")*Me*), 2.99-3.13 (1H, m, C(2)H_A), 3.18-3.34 (1H, m, C(2)H_B), 3.80-3.90 (1H, m, C(2')H_A), 3.90-3.99 (1H, m, C(2')H_B), 4.47-4.60 (1H, m, C(4)*H*), 4.86 (1H, br d, *J* 6.9, C(9b)*H*), 6.88 (2H, d, *J* 8.4, C(3")*H*, C(5")*H*), 7.15 (1H, dd, *J* 8.8, 2.2, C(7)*H*), 7.39 (1H, d, *J* 8.8, C(6)*H*), 7.68 (2H, d, *J* 8.4, C(2")*H*, C(6")*H*), 8.32 (1H, br s, C(9)*H*); δ_C (125 MHz, PhMe-d_8, 363K) 21.0 (C(4")*Me*), 27.9 (*C*(3)), 28.2, 28.5 (2 × CMe_3), 32.1 (*C*(1')), 42.6 (*C*(3a)), 45.6 (*C*(2)), 52.3 (*C*(4)), 54.3 (*C*(9b)), 67.0 (*C*(2')), 79.8, 81.4 (2 × *C*Me_3), 117.7 (*Ar*), 127.1 (*C*(6)), 129.7 (*C*(3"), *C*(5")), 130.6 (*C*(7)), 132.2 (*Ar*), 133.9 (*C*(9)), 134.7, 135.1, 144.1 (*Ar*), 153.8, 155.2 (2 × N*C*O);[30] *m*/*z* (ESI^+) 675 ([M(^{81}Br)+Na]$^+$, 100%), 673 ([M(^{79}Br)+Na]$^+$, 95%); HRMS (ESI^+) $C_{30}H_{39}{}^{79}BrN_2NaO_7S^+$ ([M(^{79}Br)+Na]$^+$) requires 673.1554; found 673.1559.

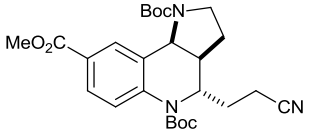
(*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-(2'-cyanoethyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 296



NaCN (28 mg, 0.58 mmol) was added to a solution of **295** (252 mg, 0.39 mmol, >99:1 dr) in NMP (4 mL) and the resultant mixture was stirred at 60 °C for 16 h.[19] The reaction mixture was then diluted with EtOAc (20 mL) and washed with H_2O (2 × 10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 83:17:1) gave **296** as a colourless oil (167 mg, 86%, >99:1 dr); $C_{24}H_{32}BrN_3O_4$ requires C, 56.9; H, 6.4; N, 8.3%; found C, 57.1; H, 6.5; N, 8.3%; $[\alpha]_D^{20}$ –61.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2976, 2933 (C–H), 2247 (C≡N), 1693 (C=O); δ_H (500 MHz, PhMe-d_8, 363K) 0.81-0.90 (1H, m, C(1')H_A), 0.98-1.09 (1H, m, C(1')H_B), 1.29 (9H, s, CMe_3), 1.34 (9H, s, CMe_3), 1.38-1.68 (5H, m, C(3)H_2, C(3a)*H*), C(2')H_2), 1.51-

1.68 (1H, m, C(2)H_A), 2.86-2.95 (1H, m, C(2)H_B), 4.21 (1H, app d, *J* 10.7, C(4)*H*), 4.68 (1H, d, *J* 6.3, C(9b)*H*), 7.03 (1H, dd, *J* 8.8, 1.9, C(7)*H*), 7.25 (1H, d, *J* 8.8, C(6)*H*), 8.15 (1H, br s, C(9)*H*); δ_C (125 MHz, PhMe-d_8, 363K) 9.3 (*C*(2')), 23.1 (*C*(3)), 23.3, 23.6 (2 × C*Me*$_3$), 40.5 (*C*(3a)), 49.3, 49.6 (*C*(4), *C*(9b)), 72.6, 74.9 (2 × *C*Me$_3$), 113.0, 113.3, 122.3, 125.8, 127.1, 128.9, 129.3 (*Ar*, *C*(3')), 149.1 (2 × N*C*O);[31] *m*/*z* (ESI$^+$) 530 ([M(^{81}Br)+Na]$^+$, 95%), 528 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}{}^{79}BrN_3NaO_4^+$ ([M(^{79}Br)+Na]$^+$) requires 528.1468; found 528.1475.

(*S*,*S*,*S*)-*N*(1),*N*(5)-(Bis-*tert*-Butoxycarbonyl)-4-(2'-cyanoethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 297

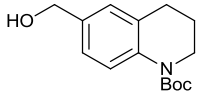


Method A: Following *General Procedure 8*, Pd(OAc)$_2$ (1.8 mg, 8 μmol), Xantphos (9 mg, 16 μmol), **296** (39 mg, 78 μmol), Et$_3$N (1.0 mL) and MeOH (0.20 mL) gave a 50:50 mixture of **296** and **297**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 75:25) gave **296** as a colourless foam (14.5 mg, 37%, >99:1 dr) with spectroscopic properties identical to those described above. Further elution gave **297** as a white foam (15 mg, 40%, >99:1 dr); $[\alpha]_D^{20}$ –39.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977, 2953, 2933 (C–H), 2247 (C≡N), 1717, 1693 (C=O); δ_H (500 MHz, PhMe-d_8, 363K) 1.07-1.17 (1H, m, C(1')H_A), 1.23-1.35 (1H, m, C(1')H_B), 1.45 (9H, s, C*Me*$_3$), 1.50 (9H, s, C*Me*$_3$), 1.52-1.71 (2H, m, C(3)H_2), 1.74-1.96 (3H, m, C(3a)*H*, C(2')H_2), 3.11 (1H, br td, *J* 9.6, 3.5, C(2)H_A), 3.31-3.42 (1H, br m, C(2)H_B), 3.63 (3H, s, O*Me*), 4.39-4.45 (1H, br m, C(4)*H*), 4.97 (1H, d, *J* 7.6, C(9b)*H*), 7.64 (1H, d, *J* 8.8, C(6)*H*), 7.91 (1H, dd, *J* 8.8, 1.6, C(7)*H*), 8.80 (1H, m, C(9)*H*); δ_C (125 MHz, PhMe-d_8, 363 K) 13.8 (*C*(2')), 27.4, 27.5, 27.8, 28.1, 28.2 (*C*(3), *C*(3a), *C*(1'), 2 × C*Me*$_3$), 45.0 (*C*(2)), 50.8 (O*Me*), 53.9 (*C*(9b)), 54.5 (*C*(4)), 79.6, 81.6 (2 × *C*Me$_3$), 118.0 (*C*(3')), 126.7 (*C*(6)), 127.8 (*Ar*), 128.7 (*C*(7)), 129.2 (*Ar*), 132.4 (*C*(9)), 138.8 (*Ar*), 153.7, 165.7 (2 × N*C*O), 175.3 (*C*O$_2$Me); *m*/*z* (ESI$^+$) 508 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{35}N_3NaO_6^+$ ([M+Na]$^+$) requires 508.2418; found 508.2414.

Method B: Following *General Procedure 8*, Pd(OAc)$_2$ (15 mg, 68 μmol), Xantphos (79 mg, 0.14 mmol), **296** (344 mg, 0.68 mmol, >99:1 dr), (5 mL) and MeOH (1 mL) gave the crude reaction mixture. Resubjection of the crude reaction mixture to the reaction conditions once more gave a >75:25 mixture of **296** and **297**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et$_3$N, 75:25:1) gave **296** as a colourless oil (43 mg, 12%, >99:1 dr). Further elution gave **297** as a white foam (210 mg, 64%, >99:1 dr).

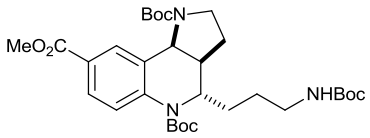
Method C: Following *General Procedure 8*, $Pd(OAc)_2$ (15 mg, 68 μmol), Xantphos (79 mg, 0.14 mmol), **296** (342 mg, 0.68 mmol, >99:1 dr), Et_3N (5 mL) and MeOH (1 mL) gave the crude reaction mixture. Resubjection of the crude reaction mixture to the reaction conditions twice more gave **297** as the sole product. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 75:25:1) gave **297** as a white foam (228 mg, 69%, >99:1 dr)

_N_-(_tert_-Butoxycarbonyl)-6-(1'-hydroxymethyl)-1,2,3,4-tetrahydroquinoline 298



$NaBH_4$ (76 mg, 2.02 mmol) was added portionwise over 15 mins to a solution of **221** (42 mg, 0.14 mmol) and $NiCl_2 \cdot 6H_2O$ (7 mg, 29 μmol) in MeOH (4 mL) at 0 °C. The resultant mixture was allowed to warm gradually to rt over 16 h. DETA (16 μL, 0.14 mmol) was added and the resultant mixture was stirred for 30 min at rt, then was concentrated *in vacuo*. The residue was dissolved in EtOAc (10 mL) and was washed with satd aq $NaHCO_3$ (10 mL). The organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O, 80:20) gave **221** as a white solid (22 mg, 53%). Further elution gave **298** as a colourless oil (5 mg, 13%); δ_H (400 MHz, $CDCl_3$)[32] 1.53 (9H, s, C*Me*$_3$), 1.87-1.98 (2H, m, C(3)*H*$_2$), 2.77 (2H, t, *J* 6.4, C(2)*H*$_2$), 3.68-3.75 (2H, m, C(2)*H*$_2$), 4.62 (2H, s, C*H*$_2$OH), 7.08-7.18 (2H, m, *Ar*), 7.65 (1H, d, *J* 8.2, *Ar*).

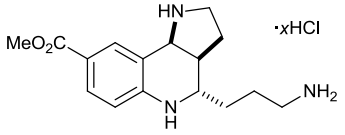
(_S_,_S_,_S_)-_N_(1),_N_(5)-(Di-_tert_-butoxycarbonyl)-4-[3'-(_N-tert_-butoxycarbonylamino)propyl]-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1_H_-pyrrolo[3,2-_c_]quinoline 299



Boc_2O (199 mg, 0.91 mmol) was added to a solution of $NiCl_2 \cdot 6H_2O$ (21.7 mg, 91 μmol) and **297** (222 mg, 0.45 mmol, >99:1 dr) in dry MeOH (5 mL) and the resultant mixture was stirred at 0 °C for 5 min. $NaBH_4$ (241 mg, 6.38 mmol) was then added portionwise over a period of 15 min, during which time a fine black precipitate formed and a gas was evolved. The reaction mixture was stirred at 0 °C for 1 h then diethylenetriamine (49 μL, 0.46 mmol) was added and the resultant mixture was allowed to stir for 30 min at 0 °C before being concentrated *in vacuo*. The residue was dissolved in EtOAc (30 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2 × 10 mL). The combined aqueous layers were extracted with EtOAc (30 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–

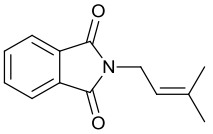
40 °C petrol/Et_2O/Et_3N, 75:25:1) gave **299** as a colourless oil (244 mg, 91%, >99:1 dr); $[\alpha]_D^{20}$ –9.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3362 (N–H), 2977, 2933 (C–H), 1695 (C=O); δ_H (400 MHz, C_6D_6) 0.87-1.05 (1H, br s, C(2')H_A), 1.05-1.18 (1H, br s, C(2')H_B), 1.71 (2H, app s, C(3)H_2), 1.39 (9H, s, CMe_3), 1.41 (9H, s, CMe_3), 1.42 (9H, s, CMe_3), 1.77-1.91 (1H, br s, C(3a)*H*), 2.69-3.32 (4H, br m, C(2)H_2, C(1')H_2), 3.51 (3H, s, O*Me*), 4.26-4.56 (2H, br m, C(3')H_2), 4.86-5.32 (2H, br m, C(4)*H*, C(9b)*H*), 7.72 (1H, d, *J* 8.6, C(6)*H*), 7.93-8.13 (1H, br m, C(7)*H*), 8.91 (1H, br s, C(9)*H*); δ_C (100 MHz, C_6D_6) [selected peaks] 26.8 (*C*(3)), 29.2 (*C*(2')), 27.8, 28.2, 28.2 (3 × CMe_3), 42.5 (*C*(3a)), 45.3 (*C*(2)), 51.1 (O*Me*), 53.9, 54.3 (*C*(4), *C*(9b)), 125.0 (*C*(6)), 125.9 (*Ar*), 128.3 (*C*(7)), 129.5 (*Ar*), 132.3 (*C*(9)), 139.6 (*Ar*), 153.8, 155.6, 155.9 (3 × N*C*O), 166.0 (*C*O_2Me);[33] *m*/*z* (ESI^+) 590 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{47}N_3NaO_8^+$ ($[M+Na]^+$) requires 612.3255; found 612.3258.

(*S*,*S*,*S*)-4-(3'-Aminopropyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]-quinoline·*x*HCl ["Ma's intermediate"] 22·*x*HCl



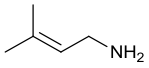
A solution of **299** (37 mg, 62 μmol, >99:1 dr) in methanolic HCl (1.25 M, 4 mL) was stirred at rt for 6 h then concentrated *in vacuo*. Methanolic HCl (1.25 M, 2 mL) was then added and the resultant mixture was concentrated *in vacuo* again to give **22**·*x*HCl as a white amorphous solid (24 mg, quant, >99:1 dr); $[\alpha]_D^{20}$ –48.7 (*c* 0.3 in MeOH);[34] {lit.[35] $[\alpha]_D^{20}$ –49.9 (*c* 1.25 in MeOH); lit.[36] $[\alpha]_D^{18}$ –54.4 (*c* 0.29 in MeOH); lit.[37] $[\alpha]_D^{29}$ –57.7 (*c* 0.3 in MeOH)}; ν_{max} (ATR) 2950, 2892 (N–H), 2748, 2576 (C–H), 1704 (C=O); δ_H (500 MHz, MeOD-d_4) 1.67-1.79 (1H, br m, C(1')H_A), 1.81-2.01 (3H, br m, C(1')H_B, C(2')H_2), 2.12-2.23 (1H, br m, C(3)H_A), 2.39-2.54 (2H, br m, C(3)H_B, C(3a)*H*), 2.96-3.09 (2H, br m, C(3')H_2), 3.09-3.17 (1H, br m, C(4)*H*), 3.38-3.45 (2H, br m, C(2)H_2), 3.86 (3H, s, O*Me*), 4.66-4.73 (1H, br d, C(9b)*H*), 6.86 (1H, d, *J* 8.5, C(6)*H*), 7.76-7.82 (1H, br m, C(7)*H*), 8.02 (1H, d, *J* 1.3, C(9)*H*); δ_C (125 MHz, MeOD-d_4) 23.9 (*C*(2')), 28.0 (*C*(3)), 30.5 (*C*(1')), 39.4 (*C*(3a)), 40.9 (*C*(3')), 43.6 (*C*(2)), 50.9 (*C*(4)), 52.3 (O*Me*), 59.3 (*C*(9b)), 113.4 (*Ar*), 115.8 (*C*(6)), 119.3 (*Ar*), 132.8 (*C*(7)), 134.0 (*C*(9)), 151.1 (*Ar*), 168.5 (*C*O_2Me); *m*/*z* (ESI^+) 290 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{24}N_3O_2^+$ ($[M+H]^+$) requires 290.1863; found 290.1864.

2-(3-Methylbut-2-enyl)-isoindiline-1,3-dione 301



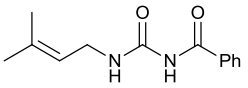
4-Bromo-2-methyl-2-butene (4.19 mL, 36 mmol) was added dropwise to a solution of potassium phthalimide (8.00 g, 43.2 mmol) in DMF (50 mL) and the mixture was heated at 160 °C for 1 h and then 180 °C for 16 h. The mixture was allowed to cool to rt and partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were washed sequentially with 1.0 M aq NaOH (50 mL), H_2O (50 mL) then dried and concentrated *in vacuo*. Recrystallisation (EtOH) gave **301** as a white solid (4.04 g, 61%);[38] mp 96-99 °C {lit.[38] mp 100-101 °C}; δ_H (400 MHz, $CDCl_3$) 1.70 (3H, s, CH=*Me*$_A$Me), 1.83 (3H, s, NCH_2CH=Me*Me*$_B$), 4.26 (2H, d, *J* 7.2, N*C*H_2), 5.23-5.34 (1H, m, NCH_2C*H*=CMe_2), 7.70 (1H, dd, *J* 5.5, 3.1, C(4)*H*, C(7)*H*), 7.83 (1H, dd, *J* 5.5, 3.1, C(5)*H*, C(6)*H*).

Prenylamine 302



$N_2H_4 \cdot H_2O$ (1.00 mL, 20.8 mmol) was added to a solution of **301** (3.73 g, 17.3 mmol) in EtOH and the resultant mixture was heated at reflux for 1 h.[38] The mixture was cooled to 0 °C and 1.0 M HCl (26 mL) was added dropwise. The resultant mixture was heated at reflux for 1 h and then was allowed to cool to rt. The mixture was filtered and washed with cold H_2O (20 mL). The filtrate was concentrated *in vacuo* to give **302**·HCl as a white solid.[39] The solid was dissolved in CH_2Cl_2 (50 mL) and was washed with 2M NaOH (2 × 20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **302** as a yellow oil (650 mg, quant)[40] which was used in the next step without further purification; δ_H (400 MHz, $CDCl_3$) 1.37 (2H, br s, N*H*$_2$), 1.64 (3H, s, C*Me*$_A$Me$_B$), 1.71 (3H, s, CMe$_A$*Me*$_B$), 3.27 (2H, d, *J* 6.1, N*C*H_2), 5.21-5.29 (1H, m, C*H*=CMe_2).

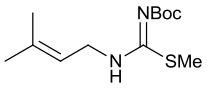
1-Benzoyl-3-(3'-methyl-but-2-enyl)thiourea 304



Benzoyl chloride (2.00 mL, 17.3 mmol) was added dropwise to a solution of KSCN (1.68 g, 17.3 mmol) in acetone (20 mL) and the resultant mixture was stirred for 1 h at rt. The mixture was filtered through a pad of Celite® (eluent acetone, 100 mL) and the filtrate was concentrated *in vacuo*. The residue was dissolved in dry MeCN (20 mL) and a solution of **302** (1.47 g, 17.3 mmol) in MeCN (15 mL) was added dropwise *via* cannula. The mixture was stirred at rt for 16 h and then was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/Et_2O/Et_3N, 87:13:1) gave **304** as a white solid (543 mg, 26%);[41] mp 107-109 °C; δ_H (400

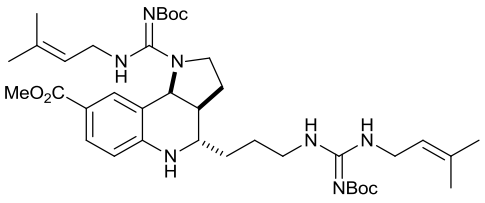
MHz, $CDCl_3$) 1.74 (3H, d, CH=C*Me*$_A$Me$_B$), 1.77 (3H, d, CH=CMe$_A$*Me*$_B$), 5.27 (2H, app t *J* 6.1, NC*H*$_2$), 5.32-5.40 (1H, m, C*H*=CMe$_2$), 7.51 (2H, app t, *J* 7.7, *m-Ph*), 7.59-7.65 (1H, m, *p-Ph*), 7.83 (2H, d, *J* 7.2, *o-Ph*), 9.02 (1H, br s, N*H*), 10.57 (1H, br s, N*H*).

tert-Butyl (3-methylbut-2-enylamino)methylthiomethlenecarbamate 23



K_2CO_3 (724 mg, 5.24 mmol) was added to a solution of **304** (1.74 g, 7.01 mmol) in MeOH (20 mL) and the resultant mixture was stirred at rt for 6 h, after which time the solvent was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (10 mL) and was washed with H_2O (10 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL) and the combined organic extracts were washed with brine (10 mL) then dried and concentrated *in vacuo*. The residue was dissolved in DMF (5 mL) and MeI (0.79 mL, 12.6 mmol) was added dropwise. The mixture was stirred at rt for 16 h and then was diluted with CH_2Cl_2 (40 mL). Et_3N (1.95 mL, 14.0 mmol), DMAP (43 mg, 0.35 mmol) and Boc_2O (1.61 mL, 7.01 mmol) were added sequentially, and the resultant mixture was stirred at 35 °C for 16 h. The solution was washed with H_2O (2 × 10 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (10 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc, 25:1) gave **23** as a colourless oil (801 mg, 44% from **304**); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 1.69 (3H, s, CH=C*Me*$_A$Me$_B$), 1.75 (3H, s, CH=CMe$_A$*Me*$_B$), 2.49 (3H, s, S*Me*), 3.84-3.94 (2H, m, N*C*H$_2$), 5.20-5.28 (1H, m, C*H*=CMe$_2$), 9.69 (1H, br s, N*H*).

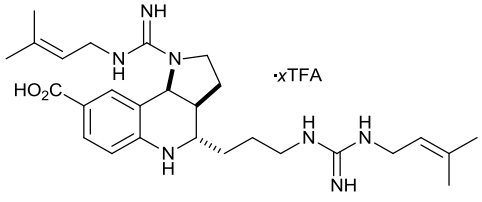
(*S*,*S*,*S*)-*N*(1)-[*N*'-(*tert*-Butoxycarbonyl)-*N*''-prenylcarbamimidoyl]-4-{3'-[*N*'-(*tert*-butoxycarbonyl)-*N*''-prenylguanidino]propyl}-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 24



Et_3N (0.38 mL, 2.75 mmol) was added to a solution of **22**·*x*HCl (92 mg, 0.23 mmol, >99:1 dr) and **23** (296 mg, 1.14 mmol) in MeCN/MeOH (2:1, 7 mL) at 40 °C. A solution of $AgNO_3$ (272 mg, 1.60 mmol) in MeCN (2 mL) was added dropwise via syringe (in the dark) over a period of 30 min. The resultant mixture was stirred at 40 °C (in the dark) for 16 h. The reaction mixture was then filtered through a short pad of Celite® (eluent $CHCl_3$/Et_3N, 100:1) and the filtrate was concentrated *in vacuo*.

The residue was dissolved in $CHCl_3$ (20 mL) and the resultant solution was washed with H_2O (10 mL). The aqueous layer was extracted with $CHCl_3$ (20 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 30:1) gave alkoxyurea **307** as a yellow solid (51 mg, 18% with respect to thiourea **23**); mp 57-65 °C; ν_{max} (ATR) 3282 (N−H), 3010, 2977, 2930 (C−H), 1617 (C=N, C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.59 (3H, s, CH=C*Me*$_A$Me$_B$), 1.65 (3H, s, CH=CMe$_A$*Me*$_B$), 3.74 (2H, t, *J* 6.2, NC*H*$_2$), 3.79 (3H, s, O*Me*), 5.09-5.18 (1H, m, C*H*=CMe$_2$), 8.55 (1H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 17.8 (CH=C*Me*$_A$Me$_B$), 25.6 (CH=CMe$_A$*Me*$_B$), 28.3 (C*Me*$_3$), 39.0 (N*C*H$_2$CH=CMe$_2$), 54.5 (O*Me*), 78.9 (*C*Me$_3$), 119.8 (*C*H=CMe$_2$), 136.3 (CH=*C*Me$_2$), 163.4, 163.5 (*C*=NBoc, *C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 243 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}N_2NaO_3^+$ ([M+Na]$^+$) requires 265.1523; found 265.1519. Further elution gave **24** as a colourless oil (104 mg, 64%, >99:1 dr); $[\alpha]_D^{20}$ –142.5 (*c* 0.8 in $CHCl_3$); {lit.[35] $[\alpha]_D^{20}$ –94.2 (*c* 0.28 in $CHCl_3$); lit.[37] $[\alpha]_D^{28}$ –179.1 (*c* 0.80 in $CHCl_3$); lit.[42] $[\alpha]_D$ –95.2 (*c* 0.58 in $CHCl_3$)}; ν_{max} (ATR) 3281 (N−H), 2974 (C−H), 1708, 1606 (C=O); δ_H (500 MHz, $CDCl_3$) 1.12-1.35 (2H, m, C(1')*H*$_2$), 1.49 (9H, s, C*Me*$_3$), 1.52 (9H, s, C*Me*$_3$), 1.54-1.68 (2H, m, C(2')*H*$_2$), 1.65 (6H, s, 2 × NCH$_2$CH=C*Me*$_A$Me$_B$), 1.68 (6H, s, 2 × NCH$_2$CH=CMe$_A$*Me*$_B$), 1.89-2.21 (2H, m, C(3)*H*$_2$), 2.31-2.42 (1H, m, C(3a)*H*), 3.10-3.20 (1H, m, C(3')*H*$_A$), 3.27-3.50 (4H, m, C(2)*H*$_2$, C(4)*H*, C(3')*H*$_B$), 3.67-3.93 (4H, m, 2 × NC*H*$_2$CH=CMe$_2$), 3.81 (3H, s, O*Me*), 5.16-5.33 (2H, m, 2 × NCH$_2$C*H*=CMe$_2$), 5.75 (1H, d, *J* 6.9, C(9b)*H*), 6.60 (1H, d, *J* 8.3, C(6)*H*), 7.10 (1H, br s, N*H*), 7.67 (1H, dd, *J* 8.3, 1.9, C(7)*H*), 7.97 (1H, br s, C(9)*H*), 8.95 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 18.0, 18.0 (2 × NCH$_2$CH=C*Me*$_A$Me$_B$), 25.6, 25.6 (2 × NCH$_2$CH=CMe$_A$*Me*$_B$), 27.9 (*C*(3)), 28.3 (*C*(2')), 28.4, 28.5 (2 × C*Me*$_3$), 29.7 (*C*(1')), 39.4, 39.4 (*C*(3a), N*C*H$_2$CH=CMe$_2$), 42.5 (N*C*H$_2$CH=CMe$_2$), 46.8, 46.8 (*C*(2), *C*(3')), 50.5 (*C*(4)), 51.4 (O*Me*), 53.4 (*C*(9b)), 77.8, 78.3 (2 × *C*Me$_3$), 113.8 (*C*(6)), 118.1 (*Ar*), 119.5, 120.2 (2 × NCH$_2$*C*H=CMe$_2$), 127.8, 128.8 (*Ar*), 130.0 (*C*(7)), 131.7 (*C*(9)), 137.2, 137.3 (2 × NCH$_2$CH=*C*Me$_2$), 146.3, 159.9, 163.7 (2 × N*C*O, 2 × N*C*N), 167.4 (*C*O$_2$Me);[43] *m*/*z* (ESI$^+$) 710 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{60}N_7O_6^+$ ([M+H]$^+$) requires 710.4600; found 710.4601.

(*S*,*S*,*S*)-*N*(1)-[*N*''-Prenylcarbamimidoyl]-4-{3'-[*N*''-prenylguanidino]propyl}-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(–)-martinellic acid] 8·*x*TFA



Method A: Step 1: A solution of 0.2 M aq NaOH (2 mL) was added to a solution of **24** (39 mg, 55

μmol, >99:1 dr) in MeOH (6 mL) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then partially concentrated *in vacuo* to approximately 25% of its original volume and the residue was poured onto satd aq NH_4Cl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*.

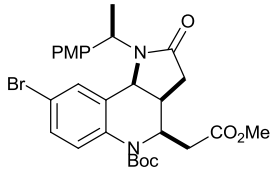
Step 2: Anisole (60 μL, 0.55 mmol) and TFA (0.12 mL, 1.62 mmol) were added sequentially to a solution of the residue in CH_2Cl_2 (3.5 mL) and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by preparative HPLC[44,45,46] to give **8**·*x*TFA as a pale yellow oil (13.3 mg, 34% from **24**, >99:1 dr); $[\alpha]_D^{20}$ –118 (*c* 0.3 in MeOH); {lit.[47] for sample isolated from natural source $[\alpha]_D$ –8.5 (*c* 0.01 in MeOH); lit.[35] $[\alpha]_D^{20}$ –122.7 (*c* 0.31 in MeOH); lit.[37] $[\alpha]_D^{29}$ –164.3 (*c* 0.14 in MeOH); lit.[48] $[\alpha]_D^{23}$ –164.8 (*c* 0.33 in MeOH)}; ν_{max}(ATR) 3338, 3207 (N–H, O–H) 2980, 2932 (C–H), 1673 (C=O), 1611, 1526, 1452; δ_H (500 MHz, DMSO-d_6) 1.35-1.52 (2H, m, C(1')H_2), 1.51-1.76 (3H, m, C(3)H_A, C(2')H_2), 1.63 (3H, s, NCH_2CH=C*Me*Me), 1.68 (3H, s, NCH_2CH=C*Me*Me), 1.69 (3H, s, NCH_2CH=C*Me*Me), 1.73 (3H, s, NCH_2CH=C*Me*Me), 2.03-2.14 (1H, m, C(3)H_B), 2.37-2.48 (1H, m, C(3a)*H*), 3.04-3.20 (2H, m, C(3')H_2), 3.27 (1H, br s, C(4)*H*), 3.33-3.43 (2H, m, C(2)H_2), 3.66-3.77 (2H, m, NCH_2CH=CMe_2), 3.79-3.87 (1H, m, NCH_AH_BCH=CMe_2), 3.88-3.89 (1H, m, NCH_AH_BCH=CMe_2), 5.13-5.20 (1H, m, NCH_2CH=CMe_2), 5.25 (1H, d, *J* 6.4, C(9b)*H*), 5.27-5.34 (1H, m, NCH_2CH=CMe_2), 6.58 (1H, d, *J* 8.5, C(6)*H*), 7.07 (1H, br s, N*H*), 7.43 (2H, br s, 2 × N*H*), 7.54 (1H, dd, *J* 8.5, 1.5, C(7)*H*), 7.51-7.62 (2H, br m, 2 × N*H*), 7.66 (1H, br s, C(9)*H*), 7.70 (1H, br s, N*H*), 7.78 (1H, br s, N*H*); δ_C (125 MHz, DMSO-d_6) 17.8, 17.9, 25.2, 25.2 (2 × NCH_2CH=CMe_2), 25.3 (*C*(2')), 26.3 (*C*(3)), 33.4 (*C*(1')), 39.5, 39.8 (2 × N*C*H_2CH=CMe_2), 40.7 (*C*(3')), 45.8 (*C*(2)), 49.2 (*C*(4)), 53.0 (*C*(9b)), 113.3 (*C*(6)), 115.7 (*C*(9a)), 116.6 (br q, *J* 299, *C*F_3), 117.1 (*C*(8)), 119.2, 119.6 (2 × NCH_2CH=CMe_2), 130.0 (*C*(7)), 130.5 (*C*(9)), 135.6, 136.0 (2 × NCH_2CH=*C*Me_2), 146.3 (*C*(5a)), 154.3, 155.5 (2 × N*C*N), 158.2 (q, *J* 33.4, $CF_3CO_2^-$), 167.2 (*C*O_2H);[49] δ_F (470 MHz, DMSO-d_6) –73.7 (CF_3); *m*/*z* (ESI^+) 496 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{42}N_7O_2^+$ ($[M+H]^+$) requires 496.3395; found 496.3377.

Method B: *Step 1*: $NaHCO_3$ (289 mg, 3.45 mmol) was added to a stirred solution of BrCN (32 mg, 0.30 mmol) and **22**·*x*HCl (40 mg, 0.14 mmol) in MeOH (1.5 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 1 h. H_2O (1 mL) was added and the resultant mixture was stirred at rt for 15 min. The solution was diluted with CH_2Cl_2 (10 mL) and was washed with H_2O (2 × 5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **32** (15 mg, >99:1 dr) as a yellow oil which was used without

purification in the next step; δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.85 (3H, s, O*Me*) 4.25 (1H, t, *J* 5.1, C(4)*H*), 4.45 (1H, d, *J* 5.1, C(9b)*H*), 4.76 (1H, br s, N*H*), 6.60 (1H, d, *J* 8.6, C(6)*H*), 7.78 (1H, dd, *J* 8.6, 2.0, C(7)*H*), 8.00 (1H, d, *J* 2.0, C(9)*H*).[50]

Step 2: A solution of prenylamine (35 mg, 0.41 mmol) and **32** (15 mg, >99:1 dr) in HFIP (1.5 mL) was heated in a sealed vial at 110 °C for 5 days, then was concentrated *in vacuo*. The residue was dissolved in MeOH (4 mL) and 0.15 M aq NaOH (1.0 mL) was added. The resultant mixture was heated at reflux for 16 h, then was allowed to cool to rt. The mixture was neutralised by addition of 1% TFA in MeOH, and the resultant mixture was concentrated *in vacuo*. Purification *via* preparative HPLC[45] gave (–)-martinellic acid **8**·*x*TFA as a yellow oil (6 mg, 6% over 3 steps from **22**·*x*HCl, ~90% pure).

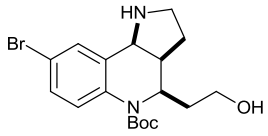
(3a*S*,4*R*,9b*S*,α*R*)-*N*(1)-[α-Methyl-4''-methoxybenzyl]-4-(2'-methoxy-2'-oxoethyl)-5-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]quinolin-2-one 310



NaH (60% w/w in mineral oil, 236 mg, 5.90 mmol) was added portionwise to a solution of **285** (1.24 g, 5.90 mmol) in THF (59 mL) at 0 °C and the mixture was stirred for 5 mins 0 °C. A solution of **200** (2.78 g, 5.36 mmol) in THF (59 mL) at 0 °C was added dropwise *via* cannula. The mixture was stirred at 0 °C for 2 h, then was quenched by addition of H_2O (2 mL). The mixture was diluted with EtOAc (50 mL) and was washed with brine (2 × 50 mL). The combined aqueous layers were extracted with EtOAc (50 mL) and the combined organic layers were dried and concentrated *in vacuo* to give a ~50:50 mixture of **286** and **310**, respectively. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 66:34:1) gave firstly **310** as a colourless oil (1.09 g, 35%, >99:1 dr); $[\alpha]_D^{20}$ −19.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977, 2935, 2837 (C−H), 1738 (C=O, [ester]), 1698 (C=O, [carbamate]); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.1, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 2.16-2.46 (3H, m, C(3)H_A, C(1′)H_2), 2.49-2.70 (1H, br s, C(3)H_B), 2.91-3.06 (1H, m, C(3a)*H*), 3.56 (3H, s, CO_2Me), 3.72 (3H, s, ArO*Me*), 4.26 (1H, d, *J* 8.1, C(9b)*H*), 4.39 (1H, br s, C(4)*H*), 5.43 (1H, q, *J* 7.1, C(α)*H*), 6.82 (2H, d, *J* 8.7, C(3")*H*, C(5")*H*), 6.93 (1H, br s, C(9)*H*), 7.07 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*), 7.19 (1H, d, *J* 8.6, C(6)*H*), 7.32 (1H, dd, *J* 8.6, 2.2, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 28.1 (C*Me*$_3$), 32.3 (*C*(1')), 35.9 (*C*(3)), 40.1 (*C*(3a)), 50.3 (*C*(α)), 51.9 (CO_2Me), 53.0 (*C*(4)), 55.2 (ArO*Me*), 56.5 (*C*(9b)), 81.8 (*C*Me$_3$), 114.0 (*C*(3"), *C*(5")), 117.8 (*C*(6)), 127.8 (*Ar*), 128.5 (*C*(2"), *C*(6")), 131.1 (*C*(7)), 131.4 (*C*(9)), 131.7, 132.5, 139.0 (*Ar*), 152.8, 158.9 (*C*(4"),

N*C*O$_2$^{t}Bu), 171.0, 174.2 (*C*(2), *C*(2')); *m*/*z* (ESI$^+$) 595 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{33}{}^{79}BrN_2NaO_6^+$ ([M(^{79}Br)+Na]$^+$) requires 595.1414; found 595.1414. Further elution gave **286** as a colourless oil (1.15 g, 38%, >99:1 dr).

(3a*R*,4*R*,9b*S*)-4-(2'-Hydroxyethyl)-*N*(5)-(*tert*-butoxycarbonyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 312

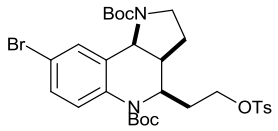


Step 1: Following *General Procedure 5*, CAN (6.05 g, 11.1 mmol) in H_2O (35 mL) and **310** (2.11 g, 3.68 mmol) in MeCN (35 mL) gave **311** as a yellow oil (2.11 g), which was used without purification in the next step; δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.51 (9H, s, C*Me*$_3$), 2.20-2.31 (2H, m, C(2)*H*$_A$, C(2')*H*$_A$), 3.05-3.15 (1H, m, C(3a)*H*), 4.72 (1H, d, *J* 7.1, C(9b)*H*), 5.04-5.17 (1H, m, C(4)*H*), 6.86 (1H, br s, N*H*), 7.36-7.51 (3H, m, C(6)*H*, C(7)*H*, C(9)*H*).

Step 2: BH_3·THF (1.0 M in THF, 37.0 mL, 37.0 mmol) was added dropwise to a solution of **311** (2.11 g) in THF (50 mL) at 0 °C. The resultant mixture was heated at reflux for 4 h then allowed to cool to rt before being cooled further to 0 °C. Satd aq K_2CO_3 (30 mL) and EtOAc (30 mL) were then carefully added and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt and washed with satd aq K_2CO_3 (2 × 30 mL). The combined aqueous layers were extracted with EtOAc (50 mL) then the organic extract was dried and concentrated *in vacuo* to give a mixture of **312** and **312**·BH_3 (831 mg) which was used without purification in the next step.[51]

Step 3: The residue from the previous reaction (831 mg) was dissolved in MeOH (100 mL) and the resultant mixture was heated at reflux for 48 h, then was allowed to cool to rt and was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **312** as a white foam (770 mg, 53% from **310**, >99:1 dr); $[\alpha]_D^{20}$ −11.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3315 (O−H, N−H), 2975, 2931, 2879 (C−H), 1692 (C=O); δ_H (400 MHz, $CDCl_3$) 1.11 (1H, m, C(1')*H*$_A$), 1.52 (9H, s, C*Me*$_3$), 1.64-1.82 (2H, m, C(3)*H*$_A$, C(1')*H*$_B$), 2.02-2.15 (1H, m, C(3)*H*$_B$), 2.77-2.88 (1H, m, C(3a)*H*), 2.90-3.00 (1H, m, C(2)*H*$_A$), 3.03-3.12 (1H, m, C(2)*H*$_B$), 3.40-3.54 (2H, m, C(2')*H*$_2$), 3.97 (1H, d, *J* 8.1, C(9b)*H*), 4.68-4.82 (1H, m, C(4)*H*), 7.23-7.33 (2H, m, C(6)*H*, C(7)*H*), 7.62 (1H, d, *J* 1.3, C(9)*H*);[52] δ_C (100 MHz, $CDCl_3$) 28.3 (C*Me*$_3$), 28.6 (*C*(3)), 29.9 (*C*(1')), 41.2 (*C*(3a)), 45.7 (*C*(2)), 49.3 (*C*(4)) 56.6 (*C*(9b)), 58.7 (*C*(2')), 82.1 (*C*Me$_3$), 117.4 (*Ar*), 126.4, 129.9 (*C*(6), *C*(7)), 131.4 (*C*(9)), 133.7, 133.8 (*Ar*);[53] *m*/*z* (ESI$^+$) 397 ([M(^{79}Br)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{26}{}^{79}BrN_2O_3^+$ ([M(^{79}Br)+H]$^+$) requires 397.1121; found 397.1114.

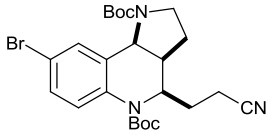
(3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-[2'-(4''-toluenesulfonyloxy)ethyl]-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 314



Step 1: Boc_2O (447 mg, 2.05 mmol), DMAP (23 mg, 0.19 mmol) and Et_3N (0.78 mL, 5.58 mmol) were added sequentially to a solution of **312** (739 mg, 1.86 mmol) in CH_2Cl_2 (50 mL) and the resultant mixture was stirred at 35 °C for 16 h. The mixture was diluted with CH_2Cl_2 (20 mL) and was washed with 1.0 M aq HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL), and brine (10 mL), then dried and concentrated *in vacuo* to give **313** (900 mg) which was used in the next step without purification; δ_H (400 MHz, $CDCl_3$) [selected peaks] 4.66 (rotameric, d, *J* 6.3, C(9b)*H*), 4.77 (rotameric, d, *J* 7.3, C(9b)*H*), 4.95 (1H, t, *J* 11.2, C(4)*H*).

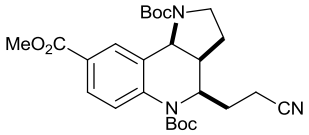
Step 2: TsCl (390 mg, 2.05 mmol), DMAP (23 mg, 0.19 mmol) and Et_3N (0.78 mL, 5.58 mmol) were added sequentially to a solution of **313** (900 mg) in CH_2Cl_2 (20 mL) and the mixture was stirred at 35 °C for 16 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and was washed with 1.0 M aq HCl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **314** as a colourless foam (760 mg, 63% over 2 steps from **312**, >99:1 dr); $[\alpha]_D^{20}$−91.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977, 2932 (C−H), 1694, 1598 (C=O); δ_H (400 MHz, C_6D_6) 0.57-0.92 (2H, br m, C(3)H_2), 0.94-1.16 (2H, br m, C(1')H_2), 1.38 (18H, s, 2 × CMe_3), 1.86 (3H, s, C(4'')*Me*), 2.20-2.46 (1H, br s, C(3a)*H*), 2.83-3.34 (2H, br m, C(2)H_2), 3.90-4.11 (2H, br m, C(2')H_2), 4.37-4.55 (1H, br m, C(9b)*H*), 4.62 (1H, td, *J* 10.7, 3.5, C(4)*H*), 6.76 (2H, d, *J* 8.2, C(3'')*H*, C(5'')*H*), 6.91-7.12 (1H, br s, *Ar*), 7.18 (1H, br d, *J* 8.3, *Ar*), 7.65 (1H, br s, *Ar*), 7.81 (2H, d, *J* 8.2, C(2'')*H*, C(6'')*H*); δ_C (100 MHz, C_6D_6)[54] 20.8 (C(4'')*Me*), 27.8, 28.0 (2 × CMe_3), 30.4 (*C*(1')), 45.8 (*C*(2)), 48.0 (*C*(4)), 55.7 (*C*(9b)), 67.3 (*C*(2')) 79.4, 80.7 (2 × *C*Me$_3$), 118.5, 128.2, 129.3 (*Ar*), 129.6 (*C*(2''), *C*(6'')), 129.9, 133.9, 134.7, 135.5 (*Ar*), 144.1, 152.9 (2 × N*C*O);[55] *m*/*z* (ESI^+) 675 ([M(^{81}Br)+Na]$^+$, 95%), 673 ([M(^{79}Br)+Na]$^+$, 100%); HRMS (ESI^+) $C_{30}H_{39}{}^{79}BrN_2NaO_7S^+$ ([M(^{79}Br)+Na]$^+$) requires 673.1554; found 673.1562.

(3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Bis-*tert*-butoxycarbonyl)-4-(2'-cyanoethyl)-8-bromo-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]-quinoline 315



NaCN (72 mg, 1.47 mmol) was added to a solution of **314** (639 mg, 0.98 mmol) in NMP (4 mL) and the resultant mixture was stirred at 60 °C for 16 h.[19] The mixture was diluted with EtOAc (30 mL) and was washed with H_2O (3 × 10 mL). The organic layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **315** as a white foam (430 mg, 87%, >99:1 dr); $[\alpha]_D^{20}$ −119 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2977, 2932 (C−H), 2247 (C≡N), 1693 (C=O); δ_H (400 MHz, C_6D_6) 0.53-0.88 (4H, br m, C(3)H_2, C(1')H_2), 1.38 (18H, s, 2 × CMe_3), 1.61-1.74 (1H, m, C(2')H_A), 1.74-1.89 (1H, m, C(2')H_B), 2.16-2.42 (1H, br s, C(3a)*H*), 2.87-3.34 (2H, br m, C(2)H_2), 4.46 (1H, td, *J* 11.0, 3.4, C(4)*H*), 4.53-4.74 (1H, br s, C(9b)*H*), 7.10-7.29 (2H, br m, 2 × *Ar*), 7.64 (1H, br s, *Ar*); δ_C (100 MHz, C_6D_6) 14.1 (*C*(2')), 24.6, 26.7 (*C*(3), *C*(1')), 27.8, 28.0 (2 × *C*Me_3), 43.9 (br, *C*(3a)), 45.7 (*C*(2)), 50.3 (*C*(4)), 55.7 (*C*(9b)), 79.5, 81.0 (2 × *C*Me_3), 118.7, 119.1 (*C*(3'), *Ar*), 128.4, 129.2, 130.0, 134.4, 135.4 (*Ar*), 153.2, 154.5 (2 × N*C*O); *m*/*z* (ESI^+) 528 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{24}H_{32}{}^{79}BrN_3NaO_4^+$ ($[M(^{79}Br)+Na]^+$) requires 528.1468; found 528.1469.

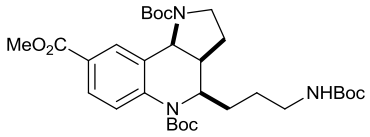
(3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Bis-*tert*-Butoxycarbonyl)-4-(2'-cyanoethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 316



Following *General Procedure 8*, $Pd(OAc)_2$ (16 mg, 73 μmol), Xantphos (85 mg, 0.15 mmol), **315** (372 mg, 0.73 mmol), Et_3N (5 mL) and MeOH (1 mL) gave the crude reaction mixture. Resubjection of the crude reaction mixture to the reaction conditions twice more gave **316** as the sole product. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 75:25:1) gave **316** as a colourless oil (263 mg, 74%, >99:1 dr); $[\alpha]_D^{20}$ −172 (*c* 1.0 in $CHCl_3$);[56] ν_{max} (ATR) 2977, 2934 (C−H), 2247 (C≡N), 1694, 1611 (C=O); δ_H (400 MHz, C_6D_6) 0.51-0.80 (4H, m, C(3)H_2, C(1')H_2), 1.16 (9H, s, CMe_3), 1.24 (9H, s, CMe_3), 1.52-1.74 (2H, m, C(2')H_2), 2.23 (1H, br s, C(3a)*H*), 2.71-3.16 (2H, br m, C(2)H_2), 3.29 (3H, s, O*Me*), 4.24-4.38 (1H, m, C(4)*H*), 4.36-4.56 (1H, br s, C(9b)*H*), 7.21 (1H, br s, C(6)*H*), 7.78 (1H, d, *J* 7.8, C(7)*H*), 7.99 (1H, s, C(9)*H*); δ_C (100 MHz,

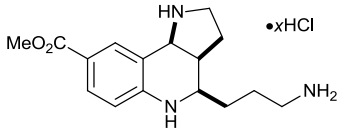
C_6D_6) 14.1 (*C*(2')), 25.0, 26.9 (*C*(3), *C*(1')), 27.8, 28.0 (2 × C*Me*$_3$), 43.9 (br, *C*(3a)), 45.8 (*C*(2)), 50.6 (*C*(4)), 51.3 (O*Me*), 55.6 (*C*(9b)), 79.5, 81.2 (2 × *C*Me$_3$), 119.1 (*C*(3')), 126.5 (*C*(6)), 127.0 (*C*(9)), 128.2 (*C*(7)), 133.0, 139.6 (*Ar*), 153.0, 154.6 (2 × N*C*O), 166.1 (*C*O$_2$Me);[57] *m*/*z* (ESI$^+$) 508 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{35}N_3NaO_6^+$ ([M+Na]$^+$) requires 508.2418; found 508.2408.

(3a*S*,4*R*,9b*S*)-*N*(1),*N*(5)-(Di-*tert*-butoxycarbonyl)-4-[3'-(*N*-*tert*-butoxycarbonylamino)propyl]-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 317



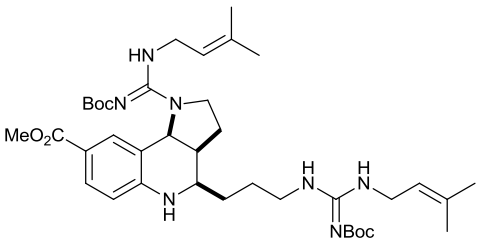
Boc_2O (195 mg, 0.89 mmol) was added to a solution of $NiCl_2 \cdot 6H_2O$ (21 mg, 89 μmol) and **316** (217 mg, 0.45 mmol) in dry MeOH (5 mL) and the mixture was stirred at 0 °C for 5 min. $NaBH_4$ (237 mg, 6.26 mmol) was then added portionwise over a period of 15 min, during which time a fine black precipitate formed and a gas was evolved. The reaction mixture was stirred at 0 °C for 1 h then diethylenetriamine (48 μL, 0.45 mmol) was added and the resultant mixture was allowed to stir for 30 min at 0 °C before being concentrated *in vacuo*. The mixture was dissolved in EtOAc (20 mL) and was washed with satd aq $NaHCO_3$ (2 × 10 mL). The aqueous washings were extracted with EtOAc (10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **317** as a colourless oil (218 mg, 83%, >99:1 dr); $[\alpha]_D^{20}$ −151 (*c* 0.98 in $CHCl_3$); ν_{max} (ATR) 3368 (N−H), 2977, 2933 (C−H), 1692, 1611 (C=O); δ_H (400 MHz, C_6D_6) 0.79-1.14 (4H, m, C(3)*H*$_2$, C(1')*H*$_2$), 1.25-1.70 (2H, br m, C(2')*H*$_2$), 1.37 (9H, s, C*Me*$_3$), 1.43 (18H, s, 2 × C*Me*$_3$), 2.41-2.65 (1H, br s, C(3a)*H*), 2.83-3.43 (4H, br m, C(2)*H*$_2$, C(3')*H*$_2$), 3.50 (3H, s, O*Me*), 4.38 (1H br m, N*H*Boc), 4.49-4.89 (2H, br m, C(4)*H*, C(9b)*H*), 7.42 (1H, br s, C(6)*H*), 8.09 (1H, d, *J* 7.8, C(7)*H*), 8.35 (1H, s, C(9)*H*); δ_C (100 MHz, C_6D_6) 25.1 (br, *C*(3)), 26.7 (*C*(2')), 27.9 (C*Me*$_3$), 28.0 (*C*(1')), 28.1, 28.2 (2 × C*Me*$_3$), 39.9 (*C*(3')), 46.0 (*C*(2)), 50.9, 51.2 (*C*(4), O*Me*), 55.8 (*C*(9b), 78.1, 79.4, 80.5 (3 × *C*Me$_3$), 126.0 (*C*(6)), 126.6 (*Ar*), 128.1, 128.1 (*C*(7), *C*(9)), 133.3, 140.4 (*Ar*), 153.0, 154.7, 155.6 (3 × N*C*O), 166.1 (*C*O$_2$Me);[58] *m*/*z* (ESI$^+$) 612 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{47}N_3NaO_8^+$ ([M+Na]$^+$) requires 612.3255; found 612.3247.

(3a*S*,4*R*,9b*S*)-4-(3'-Aminoethyl)-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-pyrrolo[3,2-*c*]-1*H*-quinoline·*x*HCl [4-*epi*-"Ma's intermediate"] 106·*x*HCl



A solution of **317** (158 mg, 0.27 mmol) in methanolic HCl (1.25 M, 4 mL) was stirred at rt for 6 h then was concentrated *in vacuo*. Methanolic HCl (1.25 M, 2 mL) was then added and the resultant mixture was concentrated *in vacuo* again to give **106**·*x*HCl as an amorphous white solid (105 mg, quant., >99:1 dr); $[\alpha]_D^{20}$+93.7 (*c* 0.35 in MeOH) {lit.[36] for enantiomer $[\alpha]_D^{20}$−73.7 (*c* 0.34 in MeOH)}; ν_{max} (ATR) 2361, 2948 (N−H), 2361, 2342 (C−H), 1699 (C=O); δ_H (400 MHz, MeOD-d_4) 1.64-1.99 (4H, br m, C(1')H_2, C(2')H_2), 1.99-2.13 (1H, m, C(3)H_A), 2.14-2.27 (1H, br m, C(3)H_B), 2.92-3.03 (1H, m, C(3a)*H*), 3.06 (2H, t, *J* 7.1, C(3')H_2), 3.26-3.39 (2H, br m, C(2)H_2), 3.47-3.58 (1H, br m, C(4)*H*), 3.86 (3H, s, O*Me*), 5.07-5.16 (1H, C(9b)*H*),[59] 6.90 (1H, d, *J* 8.6, C(6)*H*), 7.77 (1H, dd, *J* 8.6, 1.5, C(7)*H*), 8.01 (1H, d, *J* 1.5, C(9)*H*); δ_C (100 MHz, MeOD-d_4) 22.3 (*C*(3)), 23.4 (*C*(2')), 29.4 (*C*(1')), 39.2 (*C*(3')), 40.9 (*C*(3a)), 44.1 (*C*(2)), 50.9, 50.9 (*C*(4), O*Me*), 57.4 (*C*(9b)), 115.1 (*Ar*), 115.2 (*C*(6)), 119.6 (*Ar*), 130.8 (*C*(7)), 131.4 (*C*(9)), 150.4 (*Ar*), 166.9 (*C*O_2Me); *m*/*z* (ESI^+) 290 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{24}N_3O_2^+$ ($[M+H]^+$) requires 290.1863; found 290.1862.

(3a*S*,4*R*,9b*S*)-*N*(1)-[*N*'-(*tert*-Butoxycarbonyl)-*N*''-prenylcarbamimidoyl]-4-{3'-[N'-(*tert*-butoxycarbonyl)-*N*''-prenylguanidino]propyl}-8-(methoxycarbonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline 318

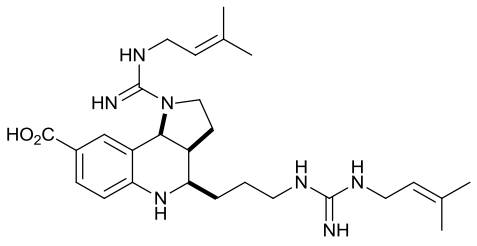


Et_3N (0.45 mL, 3.22 mmol) was added to a solution of **106**·*x*HCl (88 mg, 0.27 mmol) and thiourea **23** (346 mg, 1.34 mmol) in MeCN/MeOH (2:1, 9 mL) at 40 °C. A solution of $AgNO_3$ (252 mg, 1.48 mmol) in MeCN (2 mL) was added dropwise *via* syringe (in the dark) over a period of 30 min. The resultant mixture was stirred at 40 °C (in the dark) for 16 h. The mixture was filtered through a short pad of Celite® (eluent $CHCl_3$/Et_3N, 100:1) and the filtrate was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (30 mL) and the resultant solution was washed with H_2O (30 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* column chromatography (eluent $CHCl_3$/MeOH, 97:3) gave

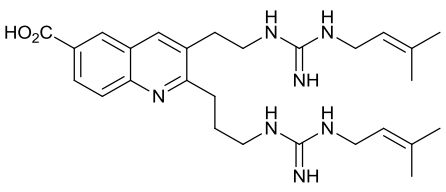
307 as a white solid (40 mg, 12% with respect to thiourea **23**). Further elution gave **318** as a pale yellow oil which crystallised slowly on standing to a yellow solid (86 mg, 45%, >99:1 dr); mp 130-136 °C; $[\alpha]_D^{20}$ −52.0 (*c* 0.25 in $CHCl_3$); ν_{max} (ATR) 3271 (N−H), 2974, 2931 (C−H), 1715 [C=O (ester)], 1639, 1609 [C=O (carbamate), C=N]; δ_H (400 MHz, $CDCl_3$) 1.44-1.57 (2H, C(2')H_2), 1.48 (9H, s, CMe_3), 1.51 (3H, s, CMe_3), 1.57-1.66 (2H, m, C(1')H_2), 1.66 (3H, s, NCH_2CH=C$Me_A$$Me_B$), 1.69 (3H, s, NCH_2CH=C$Me_A$$Me_B$), 1.72 (3H, s, NCH_2CH=C$Me_A$$Me_B$), 1.74 (3H, s, CH_2CH=C$Me_A$$Me_B$), 1.85 (3H, app t, *J* 9.7, C(3)H_2), 2.28-2.40 (1H, m, C(3a)*H*), 3.21-3.51 (5H, m, C(2)H_2, C(4)*H*, C(3')H_2), 3.71-3.91 (7H, O*Me*, 2 × NCH_2CH=CMe_2), 4.58 (1H br s, N(5)*H*), 5.19-5.27 (1H, m, NCH_2CH=CMe_2), 5.27-5.35 (1H, m, NCH_2CH=CMe_2), 5.85 (1H, d, *J* 6.9, C(9b)*H*), 6.52 (1H, d, *J* 8.4, C(6)*H*), 7.65 (1H, dd, *J* 8.4, 1.8, C(7)*H*), 7.87 (1H, br s, C(9)*H*), 7.29-7.76 (6H, br m, 6 × N*H*); δ_C (100 MHz, $CDCl_3$) 18.0, 18.0 (2 × NCH_2CH=CMe_2), 22.6 (*C*(3)), 25.6, 25.7 (2 × NCH_2CH=CMe_2), 28.5, 28.5 (2 × CMe_3), 31.0 (*C*(2'), 39.0 (*C*(3a)), 39.5 (NCH_2CH=CMe_2), 40.8 (*C*(2)), 42.7 (NCH_2CH=CMe_2), 47.3 (*C*(3')), 50.4 (*C*(4)), 51.5 (O*Me*), 56.0 (*C*(9b)), 77.9, 78.1 (2 × *C*Me_3), 113.6 (*C*(6)), 119.2, 119.6 (*Ar*), 119.8, 120.2 (2 × NCH_2CH=CMe_2), 129.8 (*C*(7)), 131.5 (*C*(9)), 136.9, 137.1 (2 × NCH_2CH=*C*Me_2), 147.7 (*Ar*), 160.1, 162.0, 162.8, 164.0 (2 × N*C*O, 2 × N*C*N), 167.3 (*C*O_2Me);[60] *m*/*z* (ESI^+) 710 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{38}H_{60}N_7O_6^+$ ($[M+H]^+$) requires 710.4600; found 710.4594.

(3a*S*,4*R*,9b*S*)-*N*(1)-[*N*''-Prenylcarbamimidoyl]-4-{3'-[*N*''-prenylguanidino]propyl}-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(–)-4-*epi*-martinellic acid] 271·*x*TFA

and 3-(2-(3-(3-Methylbut-2-en-1-yl)guanidino)ethyl)-2-(3-(3-(3-methylbut-2-en-1-yl)guanidino)propyl)-6-carboxy-quinoline·*x*TFA 319·*x*TFA



271•*x*TFA



319•*x*TFA

Method A: *Step 1*: A solution of 0.2 M aq NaOH (2 mL) was added to a solution of **318** (35 mg, 49 μmol, >99:1 dr) in MeOH (6 mL) and the resultant mixture was heated at reflux for 16 h. The reaction mixture was then partially concentrated *in vacuo* to approximately 25% of its original volume and the residue was poured onto satd aq NH_4Cl (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL), then

dried and concentrated *in vacuo*.

Step 2: Anisole (60 μL, 0.55 mmol) and TFA (0.1 2 mL, 1.62 mmol) were added sequentially to a solution of the crude acid in CH_2Cl_2 (3.5 mL) and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by preparative HPLC[44,61] to give **271**·*x*TFA as a brown oil (0.8 mg, 2% from **318**, ~90% pure); $[\alpha]_D^{20}$ –7.1 (*c* 0.31 in MeOH); ν_{max} (ATR) 3304, 3177 (O–H, N–H), 2879, 2854 (C–H), 1695 (C=O); δ_H (500 MHz, DMSO-d_6) 1.40-1.78 (5H, m, C(3)H_A, C(1')H_2, C(2')H_2), 1.66 (3H, s, NCH_2CH=C*Me*Me), 1.70 (3H, s, NCH_2CH=C*Me*Me), 1.72 (3H, s, NCH_2CH=C*Me*Me), 1.74 (3H, s, NCH_2CH=C*Me*Me), 1.97-2.05 (1H, m, C(3)H_B), 3.14-3.24 (2H, m, C(3')H_2), 3.75 (2H, app t, *J* 5.5, N*C*H_2CH=CMe_2), 3.80-4.05 (2H, m, N*C*H_2CH=CMe_2), 5.20 (1H, t, *J* 6.6, NCH_2C*H*=CMe_2), 5.31 (1H, d, *J* 6.3, C(9b)*H*), 5.25-5.40 (1H, m, NCH_2C*H*=CMe_2), 6.57 (1H, br s, N*H*), 6.64 (1H, d, *J* 8.5, C(6)*H*), 7.56 (1H, dd, *J* 8.5, 1.6, C(7)*H*), 7.67 (1H, br s, C(9)*H*), 12.20 (1H, br s, CO_2H); δ_C (125 MHz, DMSO-d_6) 17.8, 17.9 (2 × NCH_2CH=C*Me*$_2$), 21.3 (*C*(3)), 24.6 (*C*(2')), 25.3, 25.4 (2 × NCH_2CH=C*Me*$_2$), 30.1 (*C*(1')), 40.9 (*C*(3')), 49.1 (*C*(4)), 113.4 (*C*(6)), 116.9, 117.8 (*Ar*), 119.2, 119.6 (2 × NCH_2*C*H=CMe_2), 128.4 (*Ar*), 129.9 (*C*(7)), 130.5 (*C*(9)), 147.9 (*Ar*), 154.2, 155.5 (2 × N*C*N), 157.8 (q, *J* 32.0, $CF_3CO_2^-$), 147.9 (CO_2H);[62] *m*/*z* (ESI^+) 496 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{42}N_7O_2^+$ ($[M+H]^+$) requires 496.3395; found 496.3390. Further elution gave **319**·*x*TFA as a pale yellow oil (6 mg, 16% from **318**); UV λ_{max} (MeOH) 243 nm (ε 27,453); ν_{max} (ATR) 3327, 3205 (N–H), 2979, 2922 (C–H), 1670, 1636 (C=O, C=N); δ_H (500 MHz, DMSO-d_6) 1.60 (3H, s, NCH_2CH=C*Me*Me), 1.65 (3H, s, NCH_2CH=C*Me*Me), 1.67 (3H, s, NCH_2CH=C*Me*Me), 1.71 (3H, s, NCH_2CH=C*Me*Me), 2.04-2.13 (2H, m, C(2')H_2), 3.05 (4H, app q, *J* 7.4, C(1')H_2, C(1")H_2), 3.31 (2H, app q, *J* 6.6, C(3')H_2), 3.57 (2H, app q, *J* 6.5, C(2")H_2), 3.69 (2H, app t, *J* 5.7), 3.75 (2H, app t, *J* 5.7), 5.07-5.13 (1H, m, NCH_2C*H*=CMe_2), 5.16-5.23 (1H, m, NCH_2C*H*=CMe_2), 7.41-7.72 (8H, m, 8 × N*H*), 8.02 (1H, d, *J* 8.8, C(8)*H*), 8.17 (1H, dd, *J* 8.8, 1.9, C(7)*H*), 8.30 (1H, s, C(4)*H*), 8.56 (1H, d, *J* 1.9, C(5)*H*); δ_C (125 MHz, DMSO-d_6) 17.7, 17.8 (2 × (CH=C*Me*$_A$Me$_B$)), 25.2, 25.3 (2 × (CH=CMe$_A$*Me*$_B$)), 26.6 (*C*(2')), 30.6 (*C*(1")), 31.3 (*C*(1')), 40.5 (*C*(2")), 40.6 (*C*(3')), 119.1, 119.2 (2 × (NCH_2*C*H=CMe_2)), 125.9 (*C*(8a)), 128.2 (*C*(8)), 128.4 (*C*(7)), 130.1 (*C*(5)), 131.3 (*C*(3)), 136.0, 136.0 (2 × (CH=*C*Me$_2$)), 137.1 (*C*(4)), 147.3 (*C*(5a)), 155.5 (*C*(2")N*C*=NH_2), 155.6 (*C*(3')N*C*=NH_2), 158.3 (q, *J* 34.3, $CF_3CO_2^-$), 162.7 (*C*(2)), 167.0 (*C*(6)), 173.1 (CO_2H);[63] δ_F (470 MHz, DMSO-d_6) –74.2 ($CF_3CO_2^-$); *m*/*z* (ESI^+) 494 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{40}N_7O_2^+$ ($[M+H]^+$) requires 494.3238; found 494.3230.

Method B: *Step 1*: $NaHCO_3$ (71 mg, 0.84 mmol) was added to a stirred solution of BrCN (8 mg, 74 μmol) and **106**·*x*HCl (20 mg, 34 μmol) in MeOH (1.5 mL) at 0 °C, and the resultant mixture was

stirred at 0 °C for 1 h. H_2O (1 mL) was added and the resultant mixture was stirred at rt for 15 min. The solution was diluted with CH_2Cl_2 (10 mL) and was washed with H_2O (2 × 5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **322** (9 mg, >99:1 dr) as a yellow oil which was used without purification in the next step; δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.87 (3H, s, O*Me*), 4.82 (1H, d, *J* 7.8, C(9b)*H*), 6.55 (1H, d, *J* 8.6, C(6)*H*), 7.76 (1H, dd, *J* 8.6, 1.9, C(7)*H*), 8.13 (1H, d, *J* 1.9, C(9)*H*).

Step 2: A solution of prenylamine **302** (5.7 mg, 67 μmol) and **322** (9 mg, >99:1 dr) in HFIP (1.5 mL) was stirred in a sealed vial at 110 °C for 5 days, then was concentrated *in vacuo*. The residue was dissolved in MeOH (4 mL) and 0.15 M aq NaOH (1.0 mL) was added. The resultant mixture was heated at reflux for 16 h, then was allowed to cool to rt. The mixture was neutralised by addition of 1% TFA in MeOH, and the resultant mixture was concentrated *in vacuo*. Purification *via* preparative HPLC[64] gave 4-*epi*-martinellic acid **271**·*x*TFA as a yellow oil (0.7 mg, 3% over 3 steps from **106**·*x*HCl, >95% pure); $[\alpha]_D^{20}$ –12.6 (*c* 0.31 in MeOH).

5.6. References and notes

[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
[2] All spectroscopic data for **140** (IR, ^{1}H NMR, ^{13}C NMR) was otherwise in accord with that reported in: Mujtaba, N. *D.Phil. Thesis*, University of Oxford, **2005**.
[3] One resonance corresponding to *Ar* in the ^{13}C NMR spectrum of **141** could not be unambiguously determined, as it lay underneath other reported peaks.
[4] S. G. Davies, D. R. Fenwick, *Chem. Commun.* **1995**, 1109.
[5] Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.
[6] Compound **199** was isolated as a single diastereoisomer of unknown configuration at C(4).
[7] Boers, R. B.; Randulfe, Y. P.; van der Haas, H. N. S.; van Rossum-Baan, M.; Lugtenburg, J. *Eur. J. Org. Chem.* **2002**, *13*, 2094.
[8] The resonance corresponding to *C*(4) within the ^{13}C NMR spectrum of **201** was not observed. One resonance corresponding to *Ar* was not observed as it lay underneath the residual solvent peak.
[9] Two resonances corresponding to *Ar* in the ^{13}C NMR spectrum of **212** could not be unambiguously determined, as they lay underneath other reported peaks.
[10] Padwa, A.; Brodney, M.A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595.
[11] Two resonances corresponding to *Ar* were not observed in the ^{13}C NMR spectrum of **224** as they lay underneath the resonance of C_6D_6.
[12] A value has not previously been reported for the specific rotation of (*R*)-**227**.
[13] One resonance corresponding to *Ar* was not observed in the ^{13}C NMR spectrum of **234** as it lay underneath other reported peaks.
[14] Compound **239** was isolated as a single diastereoisomer of unknown configuration at C(4).
[15] One ^{13}C resonance corresponding to *Ar* was not observed in the ^{13}C NMR of **243**.
[16] One ^{13}C resonance corresponding to N*C*O was not observed in the ^{13}C NMR of **249**.
[17] For the reduction of nitrile containing substrates by this method see: Caddick, S.; Judd, D. B.; Lewise, A. K. de K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417.
[18] One ^{13}C resonance corresponding to a quaternary *Ar* was not observed in the ^{13}C NMR of **262**.
[19] For the use of NMP as a solvent in cyanide displacements of allyl bromides, see: Davies, S. G.; Whitham, G. *J. Chem. Soc. Perkin Trans. 1*, **1976**, 2279.
[20] These resonances within **262** overlapped with the residual solvent resonance of PhMe-d_8.
[21] Four resonances corresponding to *C*(3) and 3 × *Ar* could not be observed in the ^{13}C NMR spectrum of **270** as they lay underneath the residual solvent resonance. The resonance corresponding to *C*(3a) was not observed in the ^{13}C spectrum, but could be observed in the HSQC spectrum, at 42.3 ppm. The resonance corresponding to *C*(3) was also observed in the HSQC spectrum at 27.8 ppm.
[22] For ^{1}H and ^{13}C NMR data of (±)-**225** see: Snider, B.B.; Ahn, Y.; Foxman, B.M. *Tetrahedron Lett.* **1999**, *40*, 3339.
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[25] Slavish, P. J.; Jiang, Q.; Xiaoli. C.; Morris, S. W.; Webb, T. R. *Bioorg. Med. Chem. Lett*. **2009**, *17*, 3308.
[26] Compound **285** was isolated as a single diastereoisomer of unknown configuration at C(4).
[27] The resonances corresponding to N*H* and BH_3 were not observed in the ^{1}H NMR spectrum of **293**·BH_3.
[28] The ^{13}C resonance corresponding to N*C*O was not observed in the ^{13}C NMR spectrum of **293**·BH_3.
[29] Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem*. **1982**, *47*, 3153.
[30] The remaining peak in the ^{13}C NMR spectrum, corresponding to *C*(2") and *C*(6") within **295**, was obscured by the resonances corresponding to PhMe-d_8.
[31] The remaining peaks in the ^{13}C NMR spectrum, corresponding to *C*(2), *C*(1') and one of the *Ar* carbons within **296**, were obscured by the resonances corresponding to PhMe-d_8.
[32] A synthesis of **298** has been reported previously, see: Guzi, T.; Rane, D. F.; Mallams, A. K.; Cooper, A. B.; Doll, R. J.; Girijavallabhan, V. M.; Taveras, A. G.; Strickland, C.; Kelly, J. M.; Chao, J. WO 2000/037458.
[33] Some of the peaks in the ^{13}C NMR spectrum of **299** in C_6D_6 at rt are broad, and the peaks corresponding to the *C*(1'), *C*(3') and 3 × *C*Me_3 carbons were not observed in this spectrum.
[34] Triamine **22**·*x*HCl was found to be insoluble at concentrations of >3 mg/mL.
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[37] Ikeda, S.; Shibuya, M.; Iwabuchi, Y. *Chem. Commun.* **2007**, 504.
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[39] Prenylamine is best stored as the hydrochloride salt **300**·HCl.
[40] A vacuum pressure of ~600mbar was used.
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[42] Badarinarayana, V.; Lovely, C.J. *Tetrahedron Lett.* **2007**, *48*, 2607.
[43] Some of the peaks in the ^{13}C NMR spectrum of **24** in $CDCl_3$ at rt are broad.
[44] Prof. Véronique Gouverneur and Stefan Verhoog are gratefully acknowledged for their assistance with HPLC purification.

[45] Purification of **8**·*x*TFA was conducted using a SunFire™ preparative column (C_{18}, 10 μm, 10 × 250 mm) eluting with H_2O/MeOH/CF_3CO_2H (80:20:0.1 → 20:80:0.1, gradient elution) 40 mins with a flow rate of 2.50 mL/min. The detector was set to 330 nm and the major component had a rentention time of 19.1 min.

[46] Although several literature reports begin the solvent gradient in 80:20 H_2O/MeOH, this is not a suitable solvent system to load the crude material. After optimisation, it was found best to dissolve the crude sample in ~500μL of MeOH and perform purification with several ~125 μL injections.

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[49] The remaining peak in the ^{13}C NMR spectrum, corresponding to *C*(3a) within **8**·*x*TFA, was obscured by the resonance corresponding to DMSO-d_6.

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[51] The presence of **312**·BH_3 could be distinguished by TLC analysis and by the observation of a characteristic B−H stretch in the IR spectrum of the crude reaction mixture; ν_{max} (ATR) 2368, 2273 (B–H).

[52] The resonances corresponding to N*H* and O*H* were not observed in the ^{1}H NMR spectrum of **312**.

[53] The ^{13}C resonance corresponding to N*C*O was not observed in the ^{13}C NMR spectrum of **312**.

[54] The resonances corresponding to *C*(3), *C*(3"), *C*(5") and one *Ar* were not observed in the ^{13}C NMR spectrum of **314**, as they lay underneath the residual solvent peak.

[55] The resonances corresponding to *C*(3), *C*(3a), *C*(2") and *C*(6") and one *Ar* were not observed in the ^{13}C NMR spectrum of **314**, as they lay underneath the residual solvent peak. The ^{13}C resonances corresponding to *C*(3), *C*(3a), *C*(2") and *C*(6") could however be observed in the HSQC, at 24.7, 43.4 and 127.7, respectively.

[56] Measurement of the specific rotation of a more dilute sample of **316** gave a consistent value for the specific rotation ($[\alpha]_D^{20}$ −184 (*c* 0.5 in $CHCl_3$).

[57] One resonance corresponding to *Ar* was not observed in the ^{13}C NMR spectrum of **316**, as it lay underneath the residual solvent peak.

[58] The resonance corresponding to *C*(3a) was not observed in the ^{13}C NMR spectrum of **317**. The resonance was however observed in the HSQC spectrum, at 43.8 ppm.

[59] The ^3J coupling constant could not be determined as the peak was partially obscured by the residual solvent peak.

[60] A resonance corresponding to *C*(1') was not observed in the ^{13}C spectrum of **318**. The resonance was however observed in the HSQC spectrum at 25.8 ppm.

[61] Purification of **271**·*x*TFA and **319**·*x*TFA was conducted using a SunFire™ preparative column (C_{18}, 10 μm, 10 × 250 mm) eluting with H_2O/MeOH/CF_3CO_2H (80:20:0.1 → 20:80:0.1, gradient elution) 40 mins with a flow rate of 2.50 mL/min. The detector was set to 330 nm; **271**·*x*TFA and **319**·*x*TFA had retention times of 20.4 and 21.9 min, respectively.

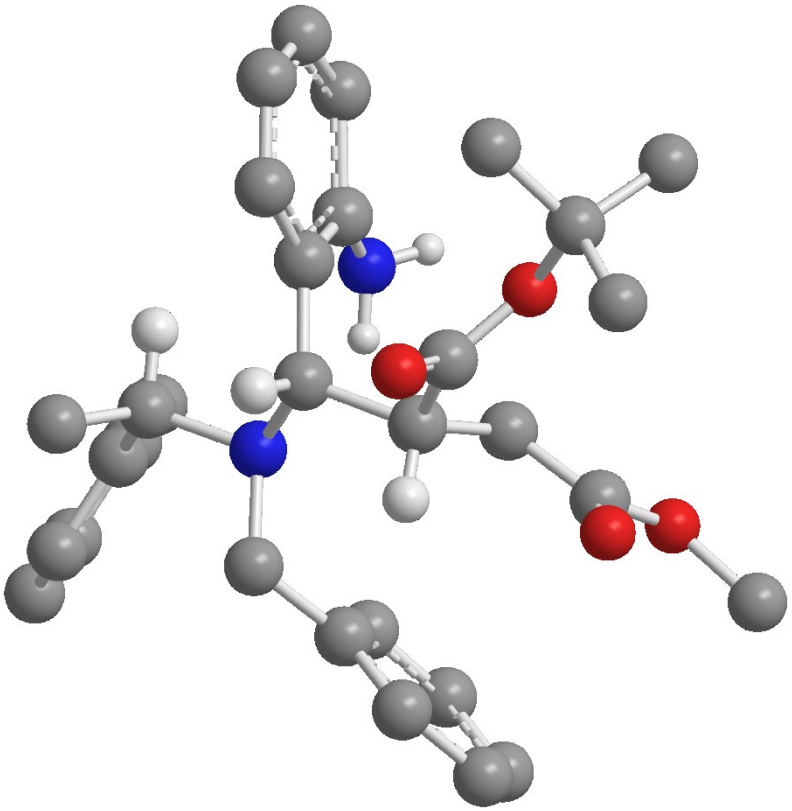
[62] The resonances corresponding to *C*(9b), *C*F_3, one *Ar* and both NCH_2CH=*C*Me_2 were not observed in the ^{13}C NMR spectrum of **271**·*x*TFA. The resonance corresponding to *C*(9b) could however be observed in the HSQC spectrum at 56.1 ppm. The resonances corresponding to *C*(2), *C*(3a) and both N*C*H_2CH=CMe_2 were also not observed in the ^{13}C NMR spectrum of **271**·*x*TFA as they lay underneath the residual solvent peak.

[63] The resonances corresponding to both N*C*H_2CH=CMe_2 were not observed in the ^{13}C NMR spectrum of **319**·*x*TFA.

[64] Purification of **271**·*x*TFA was conducted using a SunFire™ preparative column (C_{18}, 10 μm, 10 × 250 mm) eluting with H_2O/MeOH/CF_3CO_2H (80:20:0.1 → 20:80:0.1, gradient elution) 40 mins with a flow rate of 2.50 mL/min. The detector was set to 330 nm and the major component had a rentention time of 19.1 min.

X-Ray crystal structure data for (2*R*,3*S*,α*R*)-149

(selected H atoms are omitted for clarity)



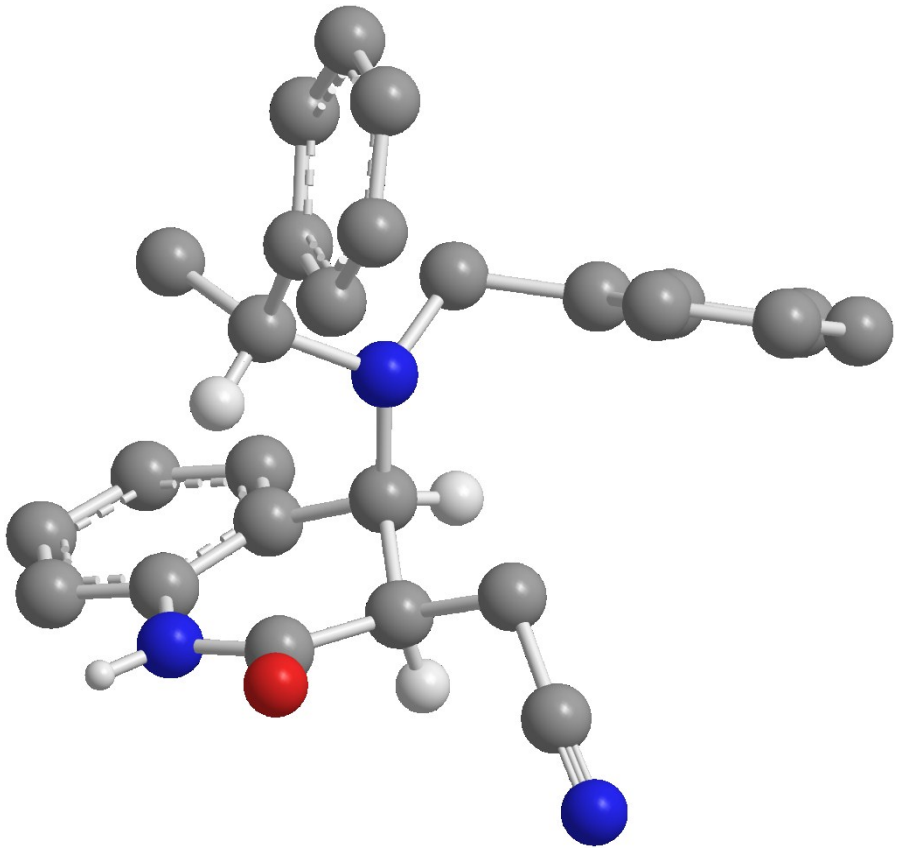
X-ray crystal structure determination for 149

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **149** [$C_{31}H_{38}N_2O_4$]: M = 502.65, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 11.6741(5) Å, b = 14.7667(6) Å, c = 15.9529(9) Å, V = 2750.1(2) Å^3, Z = 4, μ = 0.080 mm^{-1}, colourless block, crystal dimensions = 0.15 × 0.16 × 0.17 mm^3. A total of 3429 unique reflections were measured for $5 < \theta < 27$ and 1906 reflections were used in the refinement. The final parameters were wR_2 = 0.096 and R_1 = 0.074 [I>3.0σ(I)].[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*R*,4*S*,α*R*)-151

(selected H atoms are omitted for clarity)



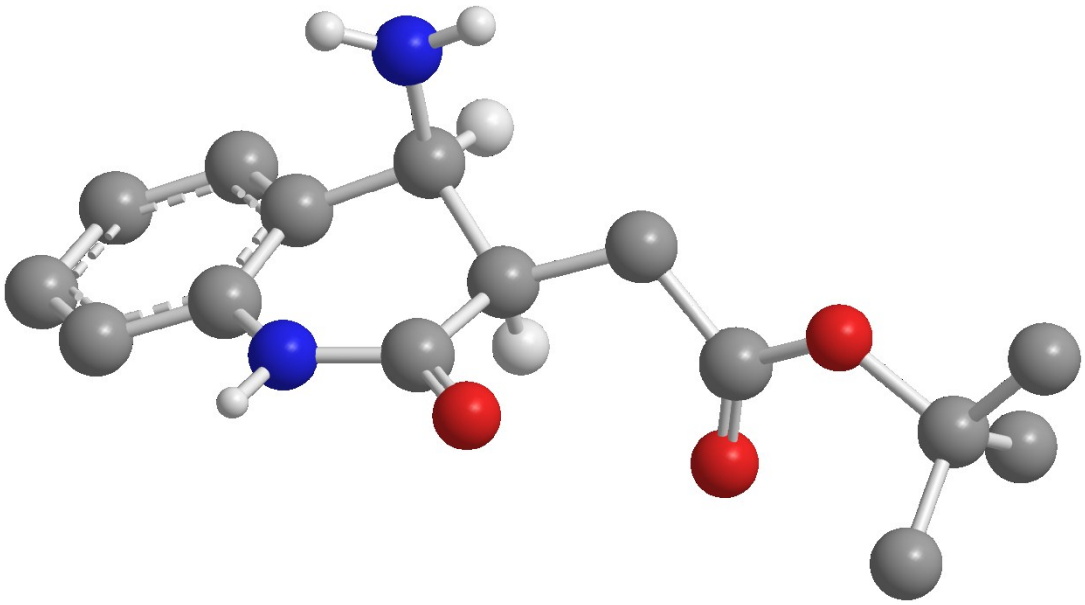
X-ray crystal structure determination for 151

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **151** [$C_{26}H_{25}N_3O$]: M = 791.01, monoclinic, space group $P\ 2_1$, a = 8.9877(6) Å, b = 25.027(2) Å, c = 9.5610(9) Å, β = 97.034(4)º, V = 2134.4(3) Å^3, Z = 4, μ = 0.076 mm^{-1}, colourless block, crystal dimensions = 0.04 × 0.05 × 0.06 mm^3. A total of 1806 unique reflections were measured for 5 < θ < 21 and 1806 reflections were used in the refinement. The final parameters were wR_2 = 0.086 and R_1 = 0.039 [I>–3.0σ(I)].[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*R*,4*S*)-161

(selected H atoms are omitted for clarity)



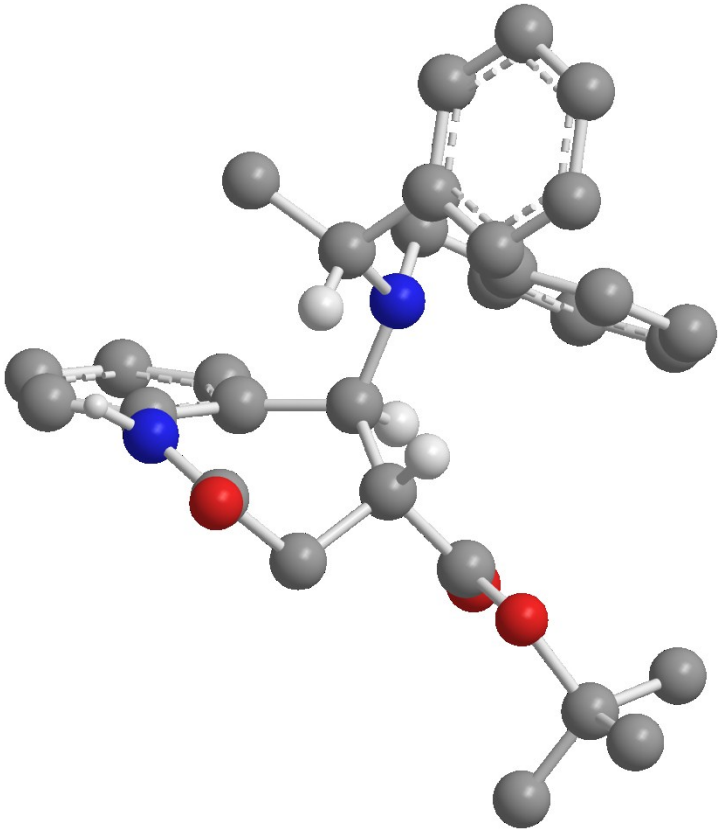
X-ray crystal structure determination for 161

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **161** [$C_{15}H_{20}N_2O_3$]: M = 276.34, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.08990(10) Å, b = 10.5533(3) Å, c = 22.9435(7) Å, V = 1474.55(7) Å^3, Z = 4, μ = 0.087 mm^{-1}, colourless plate, crystal dimensions = 0.13 × 0.16 × 0.25 mm^3. A total of 1910 unique reflections were measured for $5 < \theta < 27$ and 1540 reflections were used in the refinement. The final parameters were wR_2 = 0.102 and R_1 = 0.057 [I>–3.0σ(I)].[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (4*R*,5*S*,α*R*)-163

(selected H atoms are omitted for clarity)



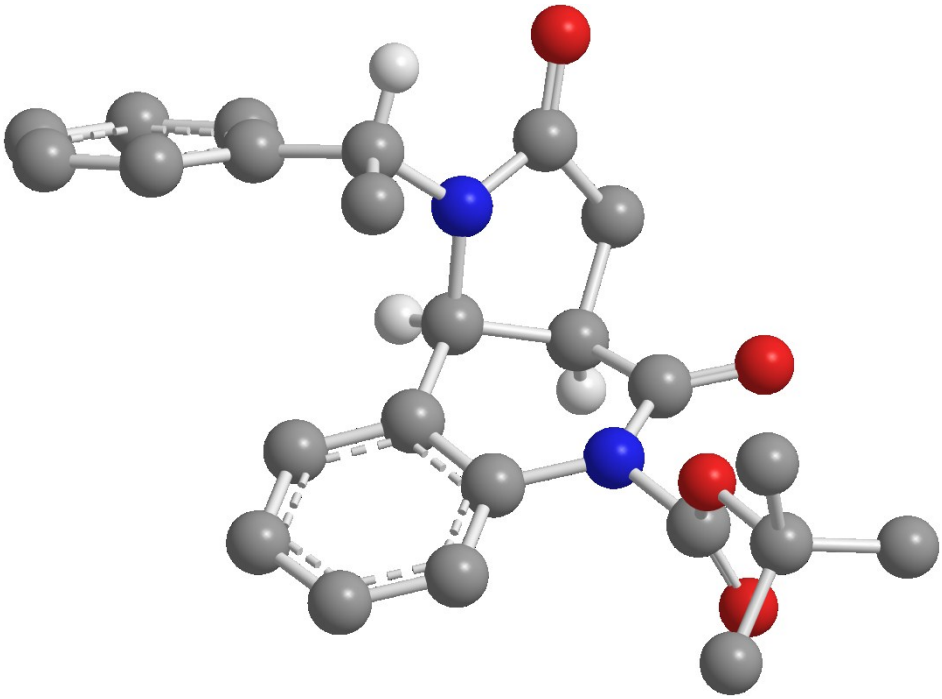
X-ray crystal structure determination for 163

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **163** [$C_{33.5}H_{42}N_2O_3$]: M = 1041.43, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.2540(1) Å, b = 16.3050(2) Å, c = 39.2418(4) Å, V = 5921.06(11) Å^3, Z = 8, μ = 0.581 mm^{-1}, colourless block, crystal dimensions = 0.19 × 0.23 × 0.26 mm^3. A total of 12226 unique reflections were measured for 4 < θ < 76 and 9767 reflections were used in the refinement. The final parameters were wR_2 = 0.092 and R_1 = 0.038 [I>–3.0σ(I)], with Flack enantiopole = –0.01(15).[2,3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3a*R*,9b*S*,α*R*)-198

(selected H atoms are omitted for clarity)



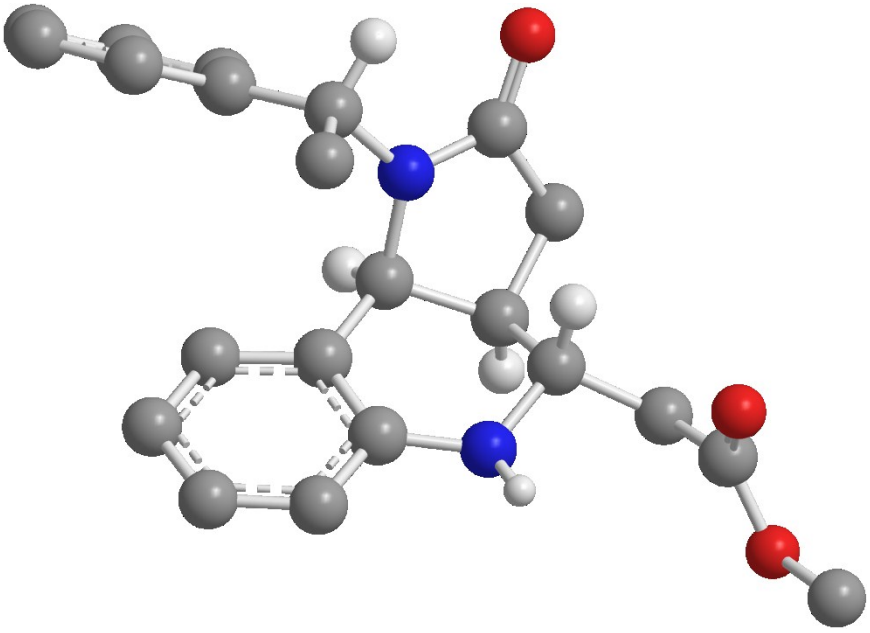
X-ray crystal structure determination for 198

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **198** [$C_{24}H_{26}N_2O_4$]: M = 406.48, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.5494(2) Å, b = 11.5467(3) Å, c = 19.9204(5) Å, V = 2086.24(9) Å^3, Z = 4, μ = 0.08 mm^{-1}, colourless block, crystal dimensions = 0.12 × 0.15 × 0.27 mm^3. A total of 2678 unique reflections were measured for $5 < \theta < 27$ and 2276 reflections were used in the refinement. The final parameters were wR_2 = 0.087 and R_1 = 0.045 [I>–3.0σ(I)].[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3a*S*,4*S*,9b*S*,α*R*)-207

(selected H atoms are omitted for clarity)



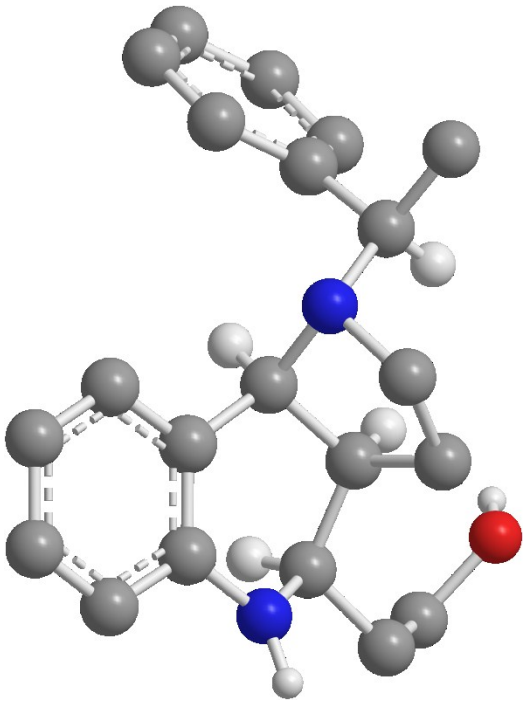
X-ray crystal structure determination for 207

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **207** [$C_{22}H_{24}N_2O_3$]: M = 364.44, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 7.4086(1) Å, b = 11.2254(2) Å, c = 23.2167(5) Å, V = 1930.81(6) Å^3, Z = 4, μ = 0.084 mm^{-1}, colourless plate, crystal dimensions = 0.08 × 0.16 × 0.28 mm^3. A total of 2516 unique reflections were measured for $5 < \theta < 27$ and 2516 reflections were used in the refinement. The final parameters were wR_2 = 0.113 and R_1 = 0.072 [I>–3.0σ(I)].[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3a*S*,4*R*,9b*S*,α*R*)-210

(selected H atoms are omitted for clarity)



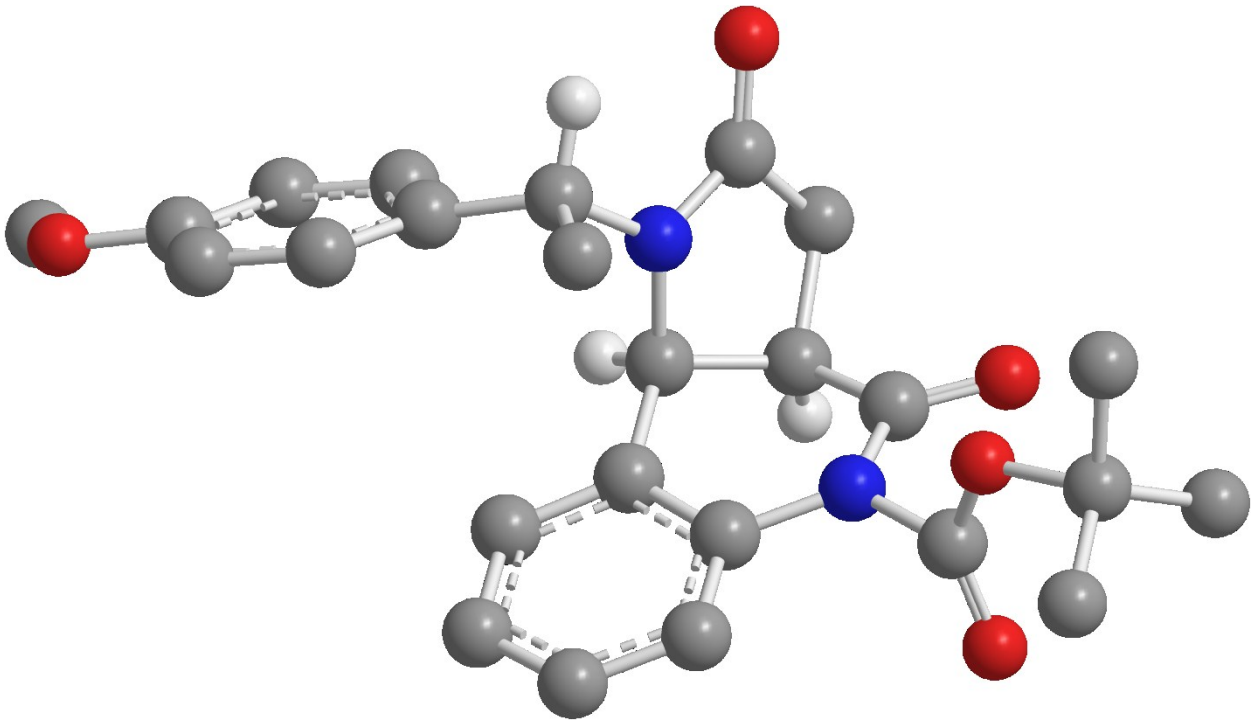
X-ray crystal structure determination for 210

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **210** [$C_{21}H_{26}N_2O$]: M = 322.45, monoclinic, space group $P\ 2_1$, a = 7.1828(1) Å, b = 12.9653(2) Å, c = 9.6676(2) Å, β = 106.193(2)°, V = 864.60(3) Å^3, Z = 2, μ = 0.591 mm^{-1}, colourless block, crystal dimensions = 0.20 × 0.21 × 0.39 mm^3. A total of 7453 unique reflections were measured for $5 < \theta < 76$ and 7333 reflections were used in the refinement. The final parameters were wR_2 = 0.055 and R_1 = 0.042 [I>3.0σ(I)], with Flack enantiopole = –0.07(17).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3a*R*,9b*S*,α*R*)-238

(selected H atoms are omitted for clarity)



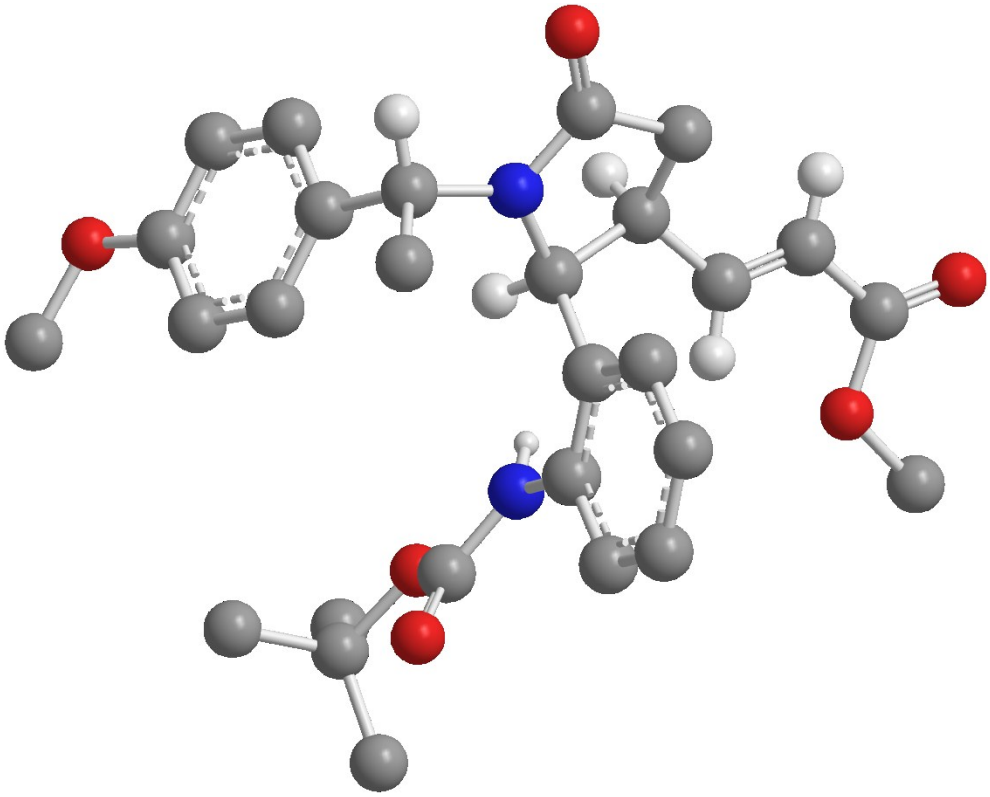
X-ray crystal structure determination for 238

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **238** [$C_{25}H_{28}N_2O_5$]: M = 436.51, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.4521(2) Å, b = 12.1847(3) Å, c = 17.5985(4) Å, V = 2241.27(9) Å^3, Z = 4, μ = 0.090 mm^{-1}, colourless block, crystal dimensions = 0.12 × 0.22 × 0.25 mm^3. A total of 2873 unique reflections were measured for 5 < θ < 27 and 2873 reflections were used in the refinement. The final parameters were wR_2 = 0.090 and R_1 = 0.044 [I>–3.0(I)].[3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (4*S*,5*S*,α*R*,*E*)-241

(selected H atoms are omitted for clarity)



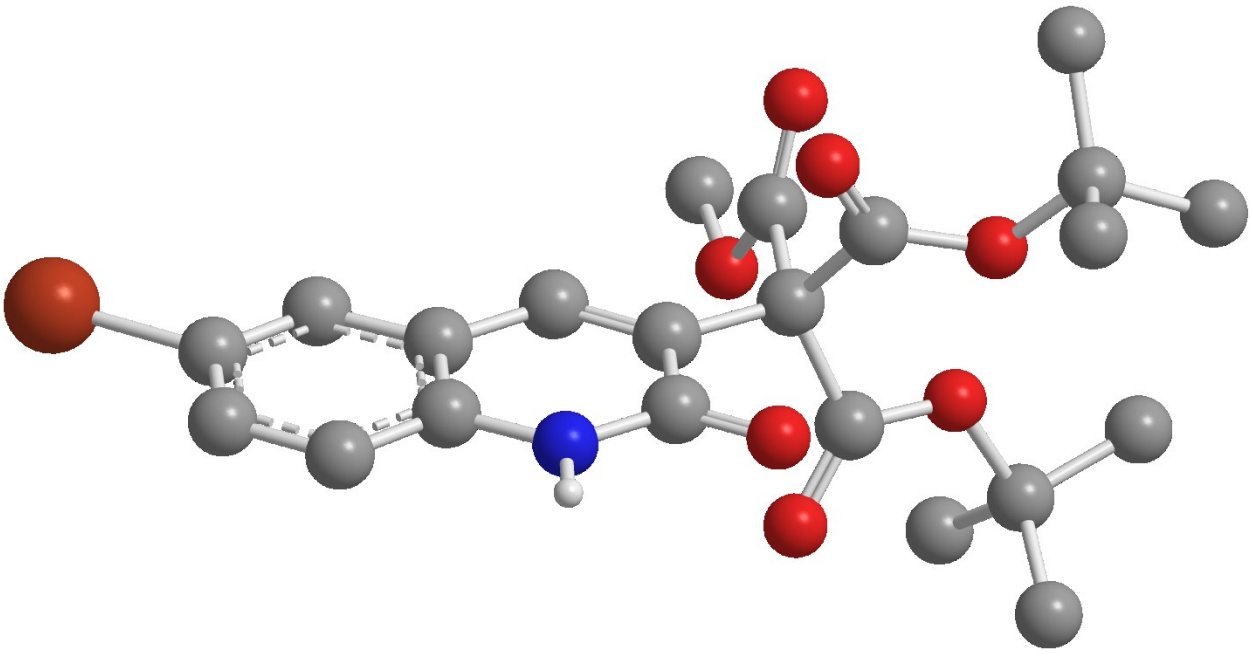
X-ray crystal structure determination for 241

Data were collected using a an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **241** [$C_{28}H_{34}N_2O_6$]: M = 494.59, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.0909(3) Å, b = 11.6409(4) Å, c = 22.0994(7) Å, V = 2595.96(14) Å^3, Z = 4, μ = 0.726 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.22 × 0.24 mm^3. A total of 3882 unique reflections were measured for 4 < θ < 77 and 3880 reflections were used in the refinement. The final parameters were wR_2 = 0.126 and R_1 = 0.071 [I>–3.0σ(I)], with Flack enantiopole = 0.4(3).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for 283

(selected H atoms are omitted for clarity)



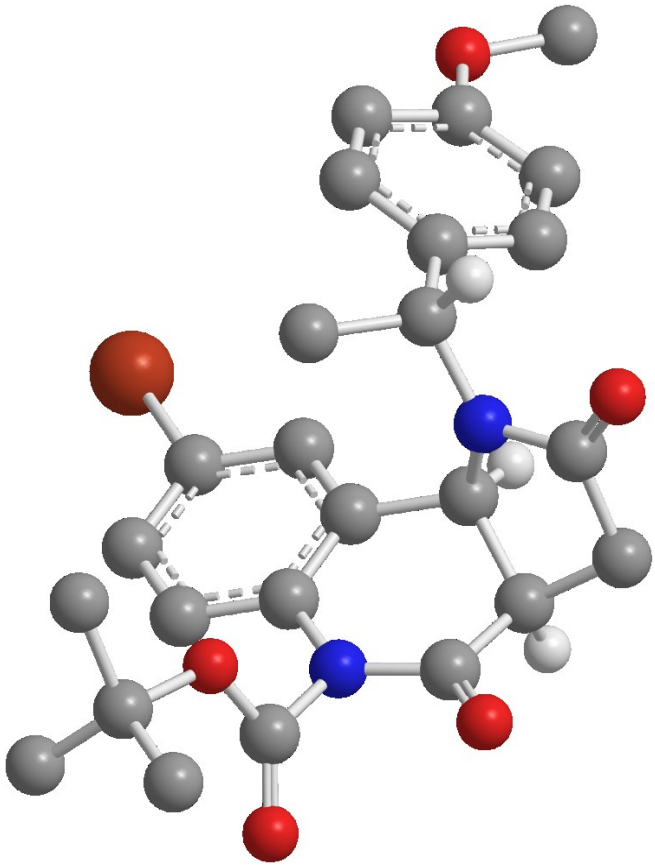
X-ray crystal structure determination for 283

Data were collected using a an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **283** [$C_{22}H_{26}BrNO_7$]: M = 992.71, triclinic, space group P –1, a = 13.1008(7) Å, b = 13.6263(8) Å, c = 15.7692(9) Å, α = 105.703(5)°, β = 111.028(5)°, γ = 103.689(5)°, V = 2348.5(3) Å^3, Z = 4, μ = 2.741 mm^{-1}, colourless block, crystal dimensions = 0.07 × 0.08 × 0.32 mm^3. A total of 9736 unique reflections were measured for 4 < θ < 77 and 8471 reflections were used in the refinement. The final parameters were wR_2 = 0.195 and R_1 = 0.114 [I>3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3a*R*,9b*S*,α*R*)-284

(selected H atoms are omitted for clarity)



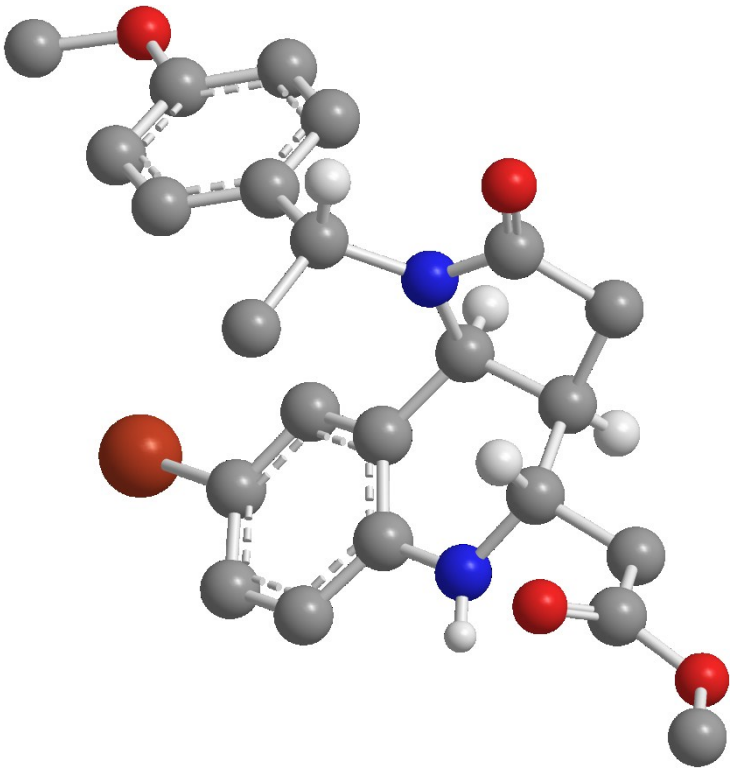
X-ray crystal structure determination for 284

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **284** [$C_{25}H_{27}BrN_2O_5$]: M = 515.40, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 9.6810(2) Å, b = 12.7183(2) Å, c = 19.2223(4) Å, V = 2366.76(8) Å^3, Z = 4, μ = 1.446 mm^{-1}, colourless prism, crystal dimensions = 0.14 × 0.17 × 0.36 mm^3. A total of 3028 unique reflections were measured for $5 < \theta < 27$ and 5258 reflections were used in the refinement. The final parameters were wR_2 = 0.076 and R_1 = 0.047 [I>–3.0σ(I)], with Flack enantiopole = 0.011(8).[2,3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3a*S*,4*S*,9b*S*,α*R*)-290

(selected H atoms are omitted for clarity)



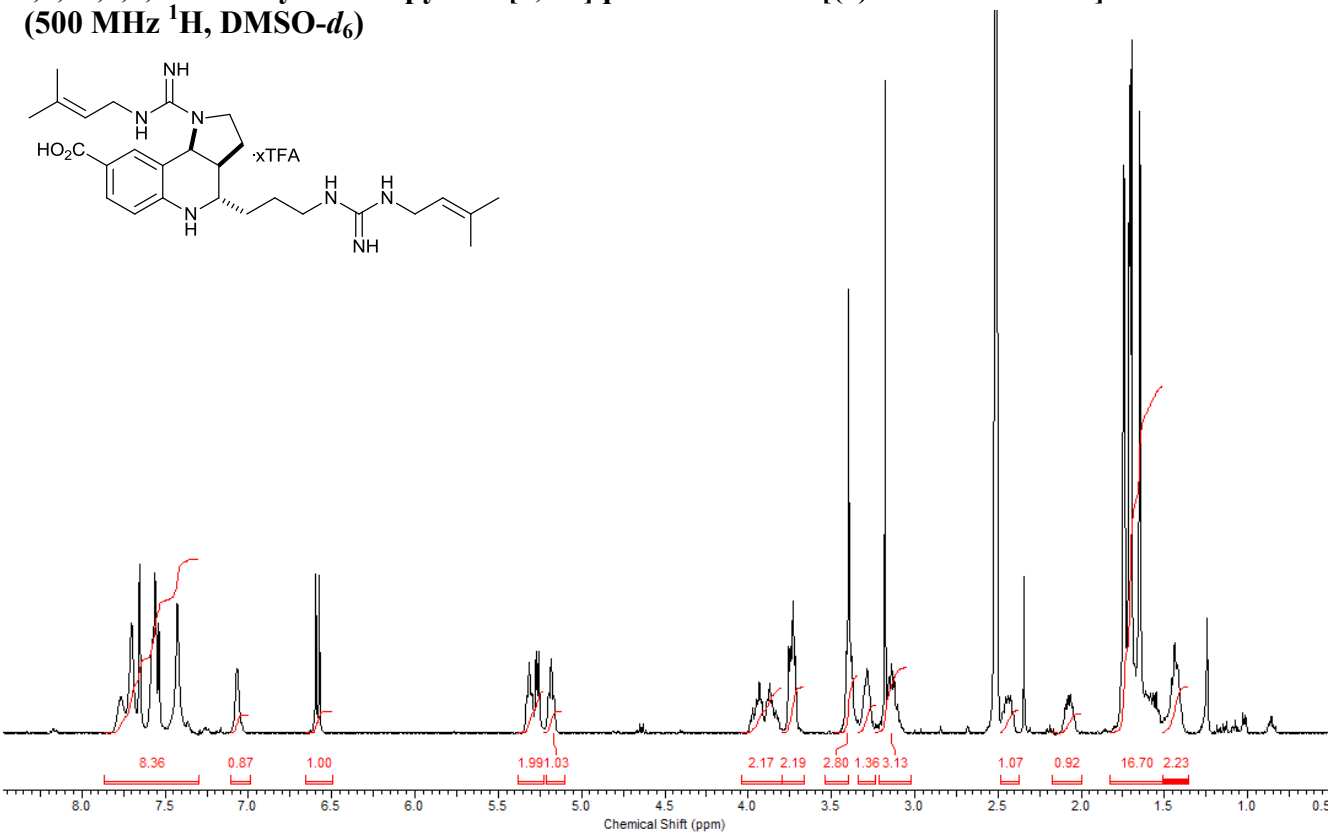
X-ray crystal structure determination for 290

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

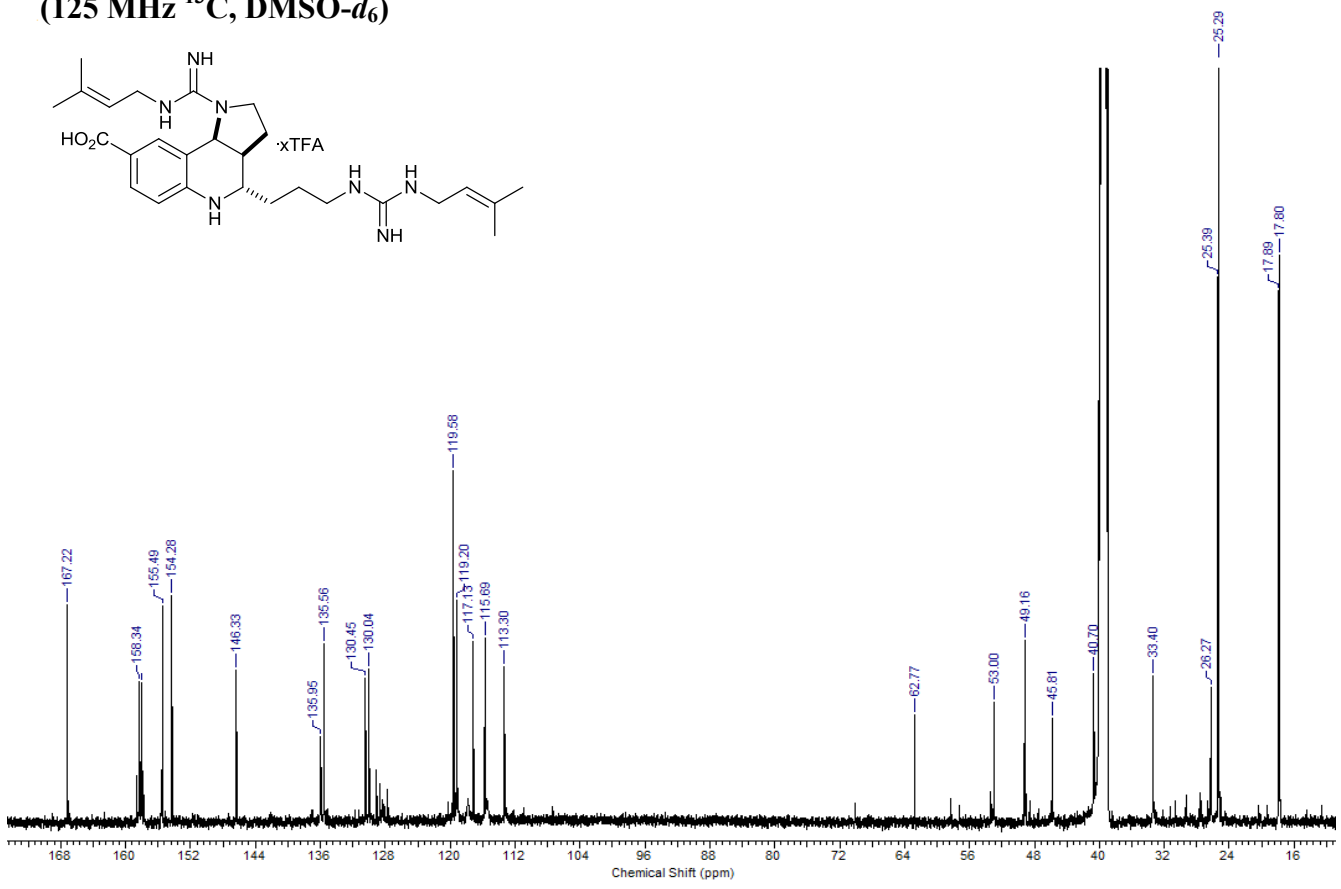
X-ray crystal structure data for **290** [$C_{23}H_{25}N_2O_4$]: M = 473.37, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.8274(1) Å, b = 11.2253(2) Å, c = 27.9028(5) Å, V = 2138.46(6) Å^3, Z = 4, μ = 1.955 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.21 × 0.30 mm^3. A total of 2774 unique reflections were measured for $5 < \theta < 27$ and 4675 reflections were used in the refinement. The final parameters were wR_2 = 0.082 and R_1 = 0.047 [I>–3.0σ(I)], with Flack enantiopole = 0.014(9).[2,3] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[2] Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.
[3] Crystallographic data (excluding structure factors) for the structures of **149**, **151**, **161**, **163**, **198**, **207**, **238**, **284** and **290** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 951639-951645, 926034 and 926035, respectively.

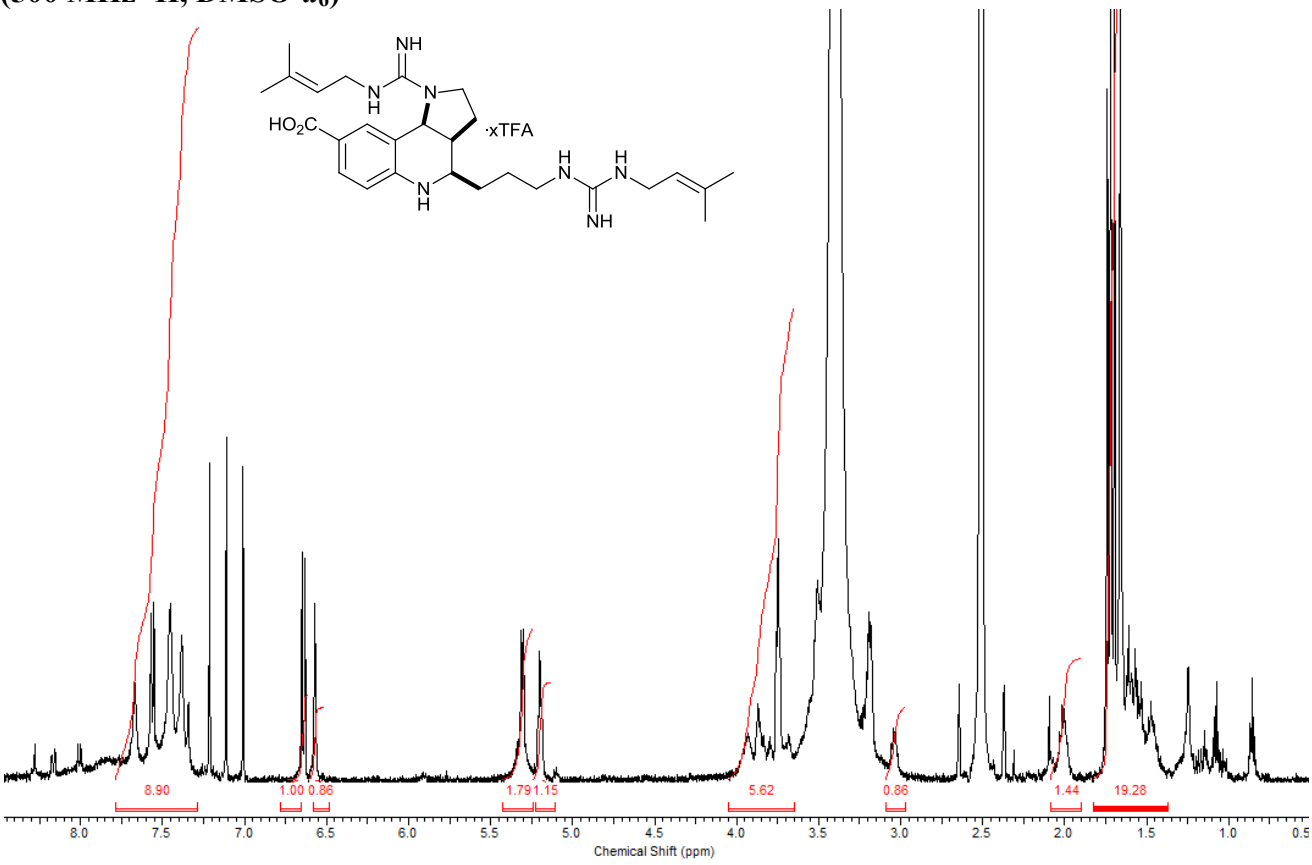
(*S*,*S*,*S*)-*N*(1)-[*N*''-Prenylcarbamimidoyl]-4-{3'-[*N*''-prenylguanidino]propyl}-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(–)-martinellic acid] 8·*x*TFA (500 MHz ^{1}H, DMSO-d_6)



(*S*,*S*,*S*)-*N*(1)-[*N*''-Prenylcarbamimidoyl]-4-{3'-[*N*''-prenylguanidino]propyl}-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(–)-martinellic acid] 8·*x*TFA (125 MHz ^{13}C, DMSO-d_6)



(3a*S*,4*R*,9b*S*)-*N*(1)-[*N*''-Prenylcarbamimidoyl]-4-{3'-[*N*''-prenylguanidino]propyl}-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(–)-4-*epi*-martinellic acid]
271·*x*TFA
(500 MHz ^{1}H, DMSO-d_6)



(3a*S*,4*R*,9b*S*)-*N*(1)-[*N*''-Prenylcarbamimidoyl]-4-{3'-[*N*''-prenylguanidino]propyl}-8-carboxy-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline·*x*TFA [(–)-4-*epi*-martinellic acid]
271·*x*TFA
(125 MHz ^{13}C DEPTQ, DMSO-d_6)