Asymmetric synthesis of 3,4-*anti*- and 3,4-*syn*-substituted aminopyrrolidines *via* lithium amide conjugate addition†

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Received 2nd April 2007, Accepted 8th May 2007
First published as an Advance Article on the web 17th May 2007
DOI: 10.1039/b704932c

The diastereoselective conjugate addition of homochiral lithium amides to methyl 4-(*N*-allyl-*N*-benzylamino)but-2-enoate has been used as the key step in a simple and efficient protocol for the preparation of 3,4-substituted aminopyrrolidines. This protocol provides a complementary and stereoselective route to both *anti*- and *syn*-3-amino-4-alkylpyrrolidines as well as *anti*- and *syn*-3-hydroxy-4-aminopyrrolidines, in high de and ee *via* β-amino enolate functionalisation. This methodology has been applied to the synthesis of *anti*-(3*S*,4*S*)- and *syn*-(3*R*,4*S*)-3-methoxy-4-(*N*-methylamino)pyrrolidine.

Introduction

Nitrogen-containing heterocyclic products are prevalent in a multitude of natural and unnatural products.[1] Pyrrolidines and piperidines are among the most common core heterocyclic structures included within these series, with a plethora of synthetic methodologies having been utilised for their synthesis or the preparation of their derivatives.[2] Aminopyrrolidines are particularly attractive synthetic targets within this arena. While polyhydroxylated aminopyrrolidines are of widespread interest due to their potential role as glycosidase inhibitors,[3] 3-aminopyrrolidines are a useful subset of this molecular class that have been used widely as chiral ligands[4] and as common building blocks in the preparation of bioactive compounds.[5,6] Typical routes to aminopyrrolidines employ resolution of racemates,[7] radical cyclisation,[8] or utilise the chiral pool with carbohydrates[9] or amino acid derivatives[10] as starting materials.

Previous investigations from this laboratory have shown that the conjugate addition of homochiral secondary lithium amides, derived from α-methylbenzylamine, to α,β-unsaturated esters may be used for the asymmetric synthesis of β-amino acids.[11] This methodology has been utilised in a number of synthetic applications, such as the kinetic and parallel kinetic resolution of racemates,[12] the asymmetric synthesis of natural products,[13] and rearrangement protocols,[14] and has recently been reviewed.[15] As part of our continuing synthetic applications of this versatile methodology we wished to use this attractive and operationally simple transformation for the stereodivergent asymmetric synthesis of enantiomerically pure 3,4-*anti*- and 3,4-*syn*-substituted aminopyrrolidines. We report herein our full investigations within this area, part of which has been communicated previously.[16]

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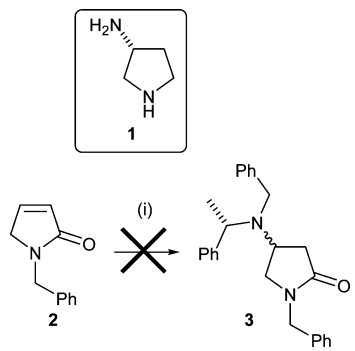
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b704932c

Results and discussion

Model studies: asymmetric synthesis of 3-aminopyrrolidines

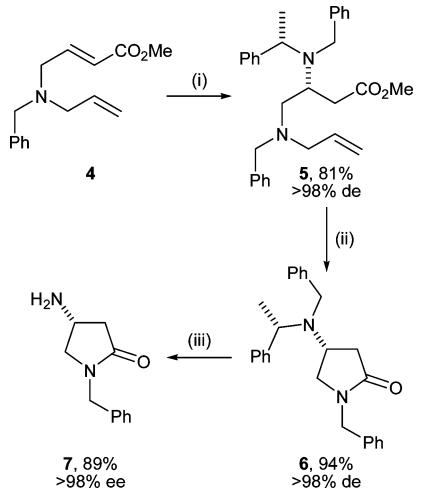
Germinal studies were directed towards the delineation of a simple and high yielding route to the 3-aminopyrrolidine scaffold **1** in homochiral form. The direct preparation of the 3-aminopyrrolidinone skeleton by conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *N*-benzyl-1,5-dihydropyrrol-2-one **2**[17] failed, returning only starting material. The lack of conjugate addition in this system is attributed to the enforced *s-trans* enone conformation, as it has previously been demonstrated that the *s-cis* conformation of an α,β-unsaturated system is necessary for lithium amide conjugate addition to occur (Scheme 1).[18]



Scheme 1 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h.

An alternative, stepwise process for the synthesis of the 3-aminopyrrolidinone skeleton was therefore envisaged *via* conjugate addition of a homochiral lithium amide to an *N*-protected 4-aminobutanoate, followed by selective *N*-deprotection and cyclisation. The ability to deprotect an *N*-allyl functionality in the presence of an *N*-benzyl tertiary amine was anticipated to fulfil the criteria necessary for this protocol to succeed.[19] Following

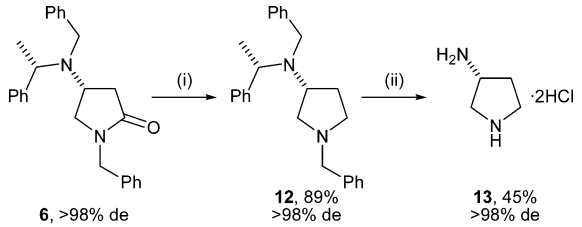
this rationale, conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to methyl 4-(*N*-allyl-*N*-benzylamino)but-2-enoate **4** (readily prepared on a multigram scale by addition of *N*-allyl-*N*-benzylamine to methyl 4-bromocrotonate) gave the corresponding β-amino ester (3*R*,α*S*)-**5** in >98% de, and 81% yield and >98% de after chromatographic purification.[20] Chemoselective *N*-deallylation of **5** could be achieved on a small (<1 g) scale using either $Pd(PPh_3)_4$ and 1,3-dimethyl barbituric acid (DMBA)[21] or Wilkinson's catalyst[22] with equal efficacy, with concomitant intramolecular cyclisation furnishing the desired aminopyrrolidinone **6**. However, upon scale-up, the use of $Pd(PPh_3)_4$ and DMBA proved optimal, allowing the preparation of **6** in 94% yield on a 20 g scale. Aminopyrrolidinone **6** was inferred as being of >98% ee by NMR studies on the corresponding Mosher's amide[23] of aminopyrrolidinone **7**, obtained *via* hydrogenolysis of **6** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (ii) $Pd(PPh_3)_4$, DMBA, DCM, rt, 16 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, rt, 40 h.

The preparation of differentially *N*-Boc-protected 3-aminopyrrolidine **11** was achieved from aminopyrrolidinone **6** *via* a four-step procedure. Selective *N*-debenzylation using sodium in liquid ammonia gave **8** in 74% yield after recrystallisation, with sequential $LiAlH_4$ reduction, *N*-Boc protection and hydrogenolysis giving **11** in 50% yield over three steps, with spectroscopic properties consistent with those of the literature[24,25] {$[\alpha]_D^{22}$ −3.3 (*c* 0.2 in $CHCl_3$); lit.[25] $[\alpha]_D^{20}$ −2.0 (*c* 1.0 in $CHCl_3$)} (Scheme 3).

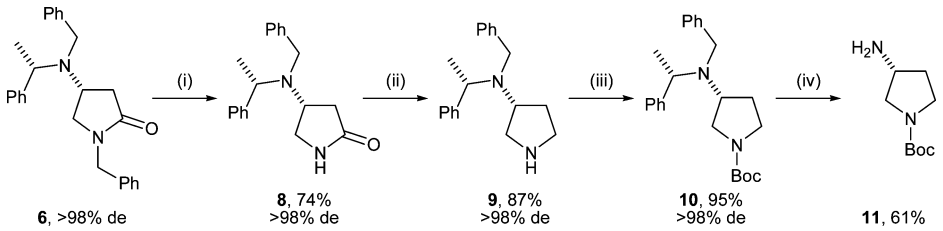
The global *N*-deprotection of aminopyrrolidinone **6** to the parent diamine dihydrochloride salt **13** was achieved following a two-step protocol, with $LiAlH_4$ reduction followed by hydrogenolysis and treatment with HCl giving the dihydrochloride salt **13** in 40% overall yield (Scheme 4). The spectroscopic properties of **13** {$[\alpha]_D^{24}$ −4.7 (*c* 0.9 in H_2O)} were consistent with those of an authentic sample {$[\alpha]_D^{23}$ −4.7 (*c* 1.3 in H_2O)} derived from commercially available (*R*)-(+)-3-aminopyrrolidine **1**.[26]



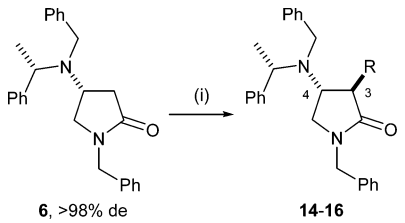
Scheme 4 *Reagents and conditions*: (i) $LiAlH_4$, THF, reflux, 12 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, rt, 40 h then HCl, Et_2O.

Asymmetric synthesis of 3,4-*anti*-substituted aminopyrrolidines

With a simple protocol in hand for the preparation of the desired 3-aminopyrrolidine motif, the extension of this methodology to allow the preparation of 3,4-*anti*-substituted aminopyrrolidines *via* enolate alkylation of aminopyrrolidinone **6** was investigated. A variety of bases have been used in the literature for the alkylation of pyrrolidinones, with NaH[27] or BuLi[28] commonly used. Application of these bases to the benzylation of **6** gave only low conversions to the desired product, so a range of lithium amide bases were screened for their ability to promote the desired alkylation. Treatment of **6** with LDA or LiHMDS and alkylation with benzyl bromide at −78 °C for 4 h gave 11 and 18% conversion, respectively, to the desired 3-benzyl pyrrolidinone **14**, while the use of LiTMP under identical conditions gave 76% conversion to **14**. Further optimization led to a convenient reaction protocol, whereby deprotonation at −78 °C with LiTMP and alkylation at −78 °C for 16 h gave complete conversion to *anti*-3-benzyl-4-aminopyrrolidinone **14** in >98% de, giving **14** in 94% yield and >98% de after purification (Scheme 5). The relative 3,4-*anti* configuration within **14** was confirmed unambiguously by X-ray crystallographic analysis.[29] Following the optimised protocol, alkylation of aminopyrrolidinone **6** with both methyl iodide and allyl bromide proceeded readily to give the corresponding *anti*-3-alkyl-4-aminopyrrolidinones **15** and **16** as single diastereoisomers (>98% de) which were isolated in 95 and 80% yield respectively (Scheme 5). The *anti* configurations within **15** and **16** were assigned by analogy to that established for **14**, and the *anti* preference upon enolate alkylation may simply be ascribed to preferential reaction



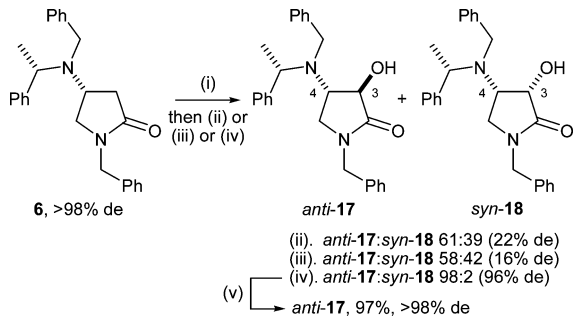
Scheme 3 *Reagents and conditions*: (i) Na, NH_3 (l), −78 °C, THF; (ii) $LiAlH_4$, THF, reflux, 12 h; (iii) Boc_2O, $NaHCO_3$, MeOH, •))), rt, 12 h; (iv) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, rt, 16 h.



Scheme 5 *Reagents and conditions*: (i) LiTMP, THF, −78 °C, 2 h, then RX, −78 °C to rt, 16 h.

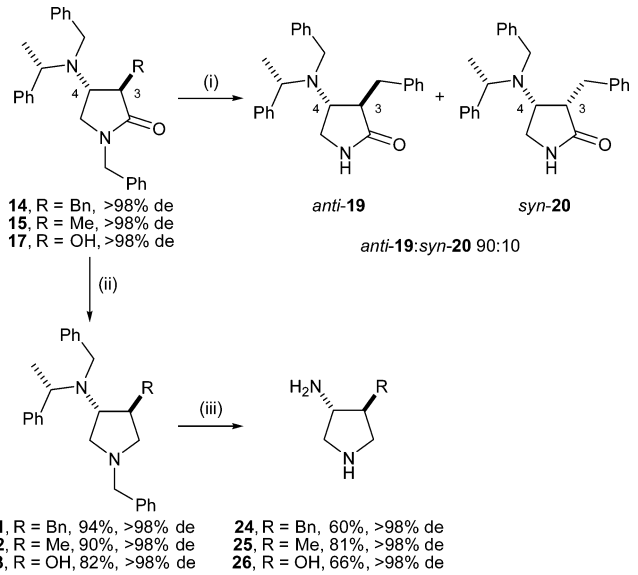
on the face of the enolate *anti* to the adjacent *N*-benzyl-*N*-(α-methylbenzyl)amino group.

Having established a route to *anti*-3-alkyl-4-amino-pyrrolidinones **14–16**, the further extension of this methodology to the preparation of the corresponding *anti*-3-hydroxy-4-aminopyrrolidinone **17** *via* enolate oxidation was investigated. Deprotonation of aminopyrrolidinone **6** with LiTMP followed by addition of 2-phenylsulfonyl-3-phenyloxaziridine proceeded to ~25% conversion to furnish an inseparable 61 : 39 mixture of *anti*-**17** : *syn*-**18**, isolated in 23% yield and 22% de (Scheme 6). The use of both antipodes of (camphorsulfonyl)oxaziridine (CSO) as enolate oxidants in this pyrrolidinone system was next probed.[30] Deprotonation of **6** with LiTMP followed by treatment with (−)-CSO gave an inseparable 58 : 42 mixture of alcohols *anti*-**17** : *syn*-**18**, which was isolated in 80% yield, while addition of (+)-CSO to the lithium enolate of **6** gave *anti*-**17** in 96% de, and in 97% isolated yield (>98% de) after chromatographic purification (Scheme 6). The *anti* configuration within **17** was assigned by analogy to that within **14–16**, and also on the basis of ^{1}H NMR NOE data.



Scheme 6 *Reagents and conditions*: (i) LiTMP, THF, −78 °C, 2 h; (ii) 2-phenylsulfonyl-3-phenyloxaziridine, THF, −78 °C to rt; (iii) (−)-CSO, THF, −78 °C to rt; (iv) (+)-CSO, THF, −78 °C to rt; (v) chromatographic purification.

Differential *N*-deprotection of aminopyrrolidines **14–17** was next investigated using 3-benzyl **14** as a model system. Following the protocol previously applied to **6**, attempted selective debenzylation of **14** furnished a 90 : 10 mixture of *anti*-**19** : *syn*-**20**, indicating that partial epimerisation of the C(3) centre had occurred under the reaction conditions (Scheme 7). Separation *via* column chromatography and recrystallisation allowed isolation of *anti*-**19** as a single diastereoisomer whose relative stereochemistry was proven unambiguously by single crystal X-ray analysis‡, with the absolute (3*R*,4*R*,α*S*) configuration being assigned from the known (*S*)-α-methylbenzyl stereocentre (Fig. 1). Due to this unwanted epimerisation, the global *N*-deprotection of **14** was probed *via* sequential $LiAlH_4$ reduction and hydrogenolysis, giving 3-amino-4-benzyl **24** in >98% de and 56% yield over 2 steps (Scheme 7). An analogous sequence of reactions applied to 3-methyl **15** and 3-hydroxy **17** gave the corresponding aminopyrrolidines **25** and **26** as single diastereoisomers in 73 and 54% yield, respectively, over 2 steps (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) Na, NH_3 (l), −78 °C, THF; (ii) $LiAlH_4$, THF, reflux, 12 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, 16 h.

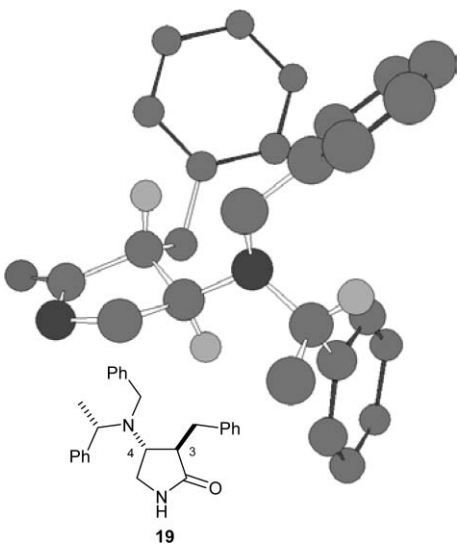


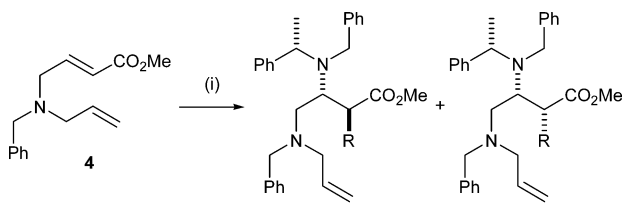
Fig. 1 Chem 3D representation of the X-ray crystal structure of **19** (some H atoms removed for clarity)‡.

Asymmetric synthesis of 3,4-*syn*-substituted aminopyrrolidines

Having established that enolate functionalisation of aminopyrrolidinone **6** proceeds with high levels of *anti*-stereoselectivity

‡ CCDC reference number 629877. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b704932c

and allows access to a range of 3,4-*anti*-substituted aminopyrrolidines, the development of methodology for the synthesis of the corresponding 3,4-*syn*-substituted aminopyrrolidines was established. Previous investigations from this laboratory have shown that either tandem lithium amide conjugate addition and enolate functionalisation, or stepwise deprotonation of a β-amino ester and subsequent enolate functionalisation can be used to access α-functionalised-β-amino esters with moderate to high levels of *anti*-stereoselectivity.[31] It was envisaged that the application of these methods to either methyl 4-(*N*-allyl-*N*-benzylamino)but-2-enoate **4** or β-amino ester **5** would give the corresponding *anti*-β-amino esters, which after selective *N*-allyl deprotection and cyclisation would give the corresponding 3,4-*syn*-substituted aminopyrrolidines. Using alkylation with benzyl bromide as a model, conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated ester **4**, followed by *in situ* alkylation of the resulting (*Z*)-β-amino enolate[18] with benzyl bromide gave *anti*-2-benzyl-3-amino **27** in 94% de, and in 94% yield and 94% de after purification. The generality of this approach was then established. The tandem conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated ester **4**, followed by alkylation with methyl iodide gave *anti*-2-methyl-3-amino **29** in 92% de, and in 83% yield and >98% de after purification, while using allyl bromide gave *anti*-2-allyl-3-amino **31** in 81% de, and in 82% yield and 81% de after purification. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide and enolate oxidation with (+)-CSO gave *anti*-2-hydroxy-3-amino **33** in >98% de, and in 88% yield and >98% de after purification (Scheme 8).

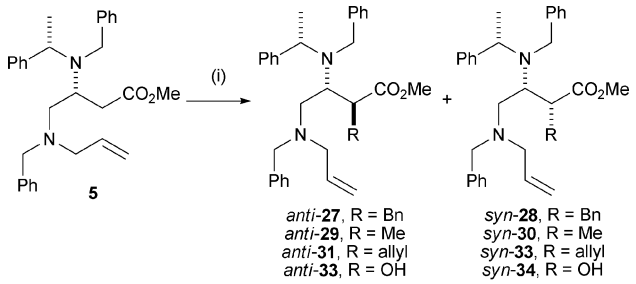


RX	Products	*anti*:*syn* ratio	Yield *anti* (de) %
BnBr	*anti*-**27**, *syn*-**28**	97:3	94 (94)
MeI	*anti*-**29**, *syn*-**30**	96:4	83 (>98)
allyl bromide	*anti*-**31**, *syn*-**32**	90.5:9.5	82 (81)
(+)-CSO	*anti*-**33**, *syn*-**34**	>99:<1	86 (>98)

Scheme 8 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then RX, −78 °C to rt, 16 h.

Alternatively, *via* a stepwise procedure, deprotonation of β-amino ester **5** with LDA and alkylation with benzyl bromide also gave *anti*-2-benzyl-3-amino **27** as the major diastereoisomeric product in 84% de, and in 89% yield and 84% de after purification. Application of the stepwise protocol to enolate methylation, allylation and oxidation was next probed. Deprotonation of β-amino ester **5** with LDA and functionalisation proceeded with comparable yields and stereoselectivities for enolate methylation and oxidation as the tandem procedure, but with a slightly decreased level of stereoselectivity for enolate allylation (Scheme 9).

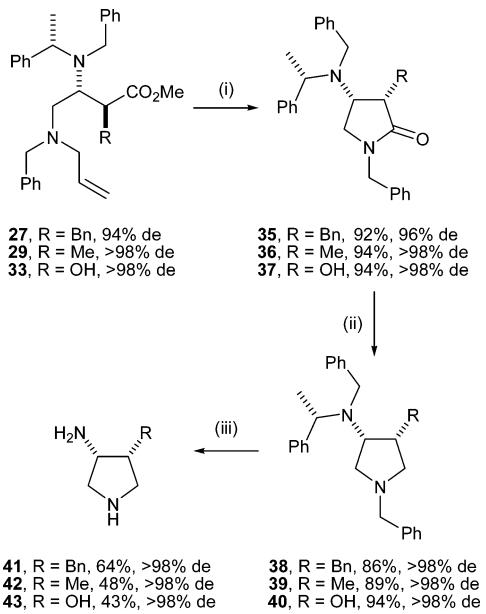
Cyclisation and deprotection of these α-functionalised-β-amino ester derivatives to the corresponding 3,4-*syn*-aminopyrrolidines



RX	Products	*anti*:*syn* ratio	Yield *anti* (de) %
BnBr	*anti*-**27**, *syn*-**28**	92:8	89 (84)
MeI	*anti*-**29**, *syn*-**30**	95:5	90 (>98)
allyl bromide	*anti*-**31**, *syn*-**32**	81.5:18.5	83 (63)
(+)-CSO	*anti*-**33**, *syn*-**34**	>99:<1	92 (>98)

Scheme 9 *Reagents and conditions*: (i) LDA, THF, −78 °C, 2 h, then RX, −78 °C to rt, 16 h.

was next studied. Deallylation of 2-benzyl **27** (94% de) and cyclisation promoted by SiO_2, followed by chromatographic purification, gave *syn*-3-benzyl-4-aminopyrrolidinone **35** 92% yield and 96% de. $LiAlH_4$ reduction of **35** and purification to homogeneity by chromatography gave **38** as a single diastereoisomer in 86% yield, with subsequent hydrogenolysis giving 4-benzyl pyrrolidine **41** in 64% yield and >98% de. Cyclisation and deprotection of 2-methyl **29** and 2-hydroxy **33** gave the corresponding pyrrolidines *syn*-3-amino-4-methyl **42** and *syn*-3-hydroxy-4-amino **43** as single diastereoisomers in 40 and 38% overall yield, respectively (Scheme 10).



Scheme 10 *Reagents and conditions*: (i) $Pd(PPh_3)_4$, 1,3-DMBA, DCM, rt, 16 h, then SiO_2, DCM; (ii) $LiAlH_4$, THF, reflux, 12 h; (iii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, 16 h.

Synthetic applications: asymmetric synthesis of *anti*-(3*S*,4*S*)- and *syn*-(3*R*,4*S*)-3-methoxy-4-(*N*-methylamino)pyrrolidine

With an efficient and general route to *anti*- and *syn*-3-hydroxy-4-aminopyrrolidine demonstrated, attention turned to the

application of this strategy to the synthesis of *anti*-(3*S*,4*S*)- and *syn*-(3*R*,4*S*)-3-methoxy-4-(*N*-methylamino)pyrrolidine, *anti*-**44** and *syn*-**45**, fragments of a series of recently reported quinolinone- and naphthyridinone-derived synthetic products, of which AG-7352 **46** and **47** are representative. These compounds have high *in vivo* and excellent *in vitro* antibacterial activity against Gram positive and Gram negative bacteria, and show potent cytotoxic activity against Murine P388 leukaemia cells (Fig. 2).[32]

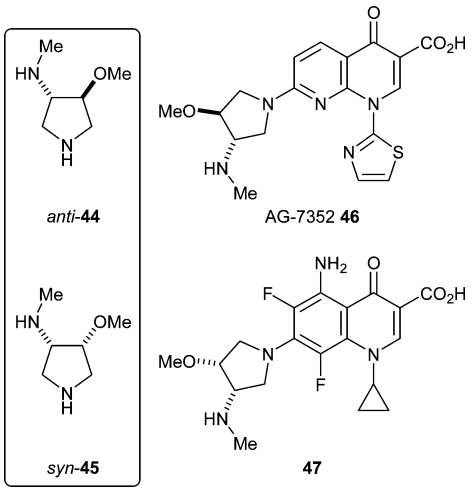
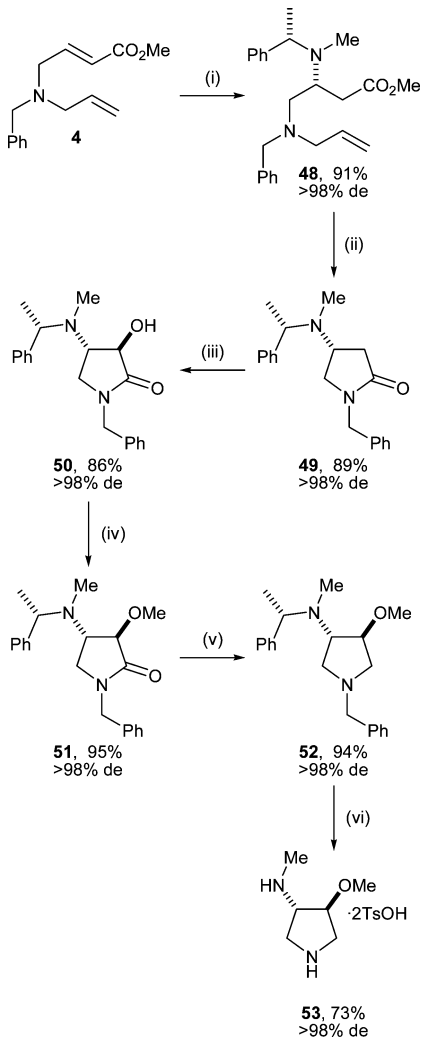


Fig. 2 Structures of *anti*-(3*S*,4*S*)- and *syn*-(3*R*,4*S*)-3-methoxy-4-(*N*-methylamino)pyrrolidine *anti*-**44** and *syn*-**45**, **46** and **47**.

Rather than use a deprotection and subsequent *N*-methylation strategy in this synthesis, it was envisaged that the *N*-methyl fragment within both **44** and **45** could be directly installed through the use of the lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide in the conjugate addition step, with the *anti* diastereoisomer **44** targeted initially. Thus, conjugate addition of lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide to α,β-unsaturated ester **4** gave the corresponding β-amino ester (3*R*,α*S*)-**48** in >98% de, and in 91% yield and >98% de after purification. *N*-Deallylation and cyclisation gave aminopyrrolidinone **49** in 89% yield, with deprotonation of **49** with LiTMP followed by enolate functionalisation with (+)-CSO giving **50** in 86% yield and >98% de after purification. Completion of the synthesis of *anti*-**44** was achieved by sequential *O*-methylation, $LiAlH_4$ reduction and hydrogenolysis, giving the target as its di-*p*-toluenesulfonic acid salt **53** in 65% over 3 steps (Scheme 11). The spectroscopic properties of **53** were in good agreement with those in the literature {$[\alpha]_D^{24}$ +10.1 (*c* 1.1 in MeOH); lit.[33] $[\alpha]_D^{29}$ +10.3 (*c* 1.0 in MeOH)}.

The synthesis of *syn*-(3*R*,4*S*)-3-methoxy-4-(*N*-methylamino)-pyrrolidine **45** was achieved using a complementary route. Conjugate addition of lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide to **4** and *in situ* enolate oxidation with (+)-CSO gave α-hydroxy-β-amino ester **54** in 92% yield and >98% de. Sequential *O*-methylation and cyclisation *via* selective *N*-deallylation gave pyrrolidinone **56** in 41% yield over 2 steps, with subsequent $LiAlH_4$ reduction and hydrogenolytic *N*-deprotection followed by acidification giving *syn*-(3*R*,4*S*)-3-methoxy-4-(*N*-methylammonio)pyrrolidinium dichloride **58** in 84% yield over 2 steps {$[\alpha]_D^{24}$ −52.4 (*c* 1.0 in MeOH); lit.[34] $[\alpha]_D^{25}$ −52.0 (*c* 0.75 in MeOH)} (Scheme 12).



Scheme 11 *Reagents and conditions*: (i) lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h; (ii) $Pd(PPh_3)_4$, 1,3-DMBA, DCM, rt, 16 h, then SiO_2, DCM; (iii) LiTMP, THF, −78 °C, 2 h, then (+)-CSO, THF, −78 °C to rt, 16 h; (iv) NaH, THF, 0 °C, 1 h, then MeI, 0 °C to rt, 12 h; (v) $LiAlH_4$, THF, reflux, 12 h; (vi) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, 48 h, then TsOH.

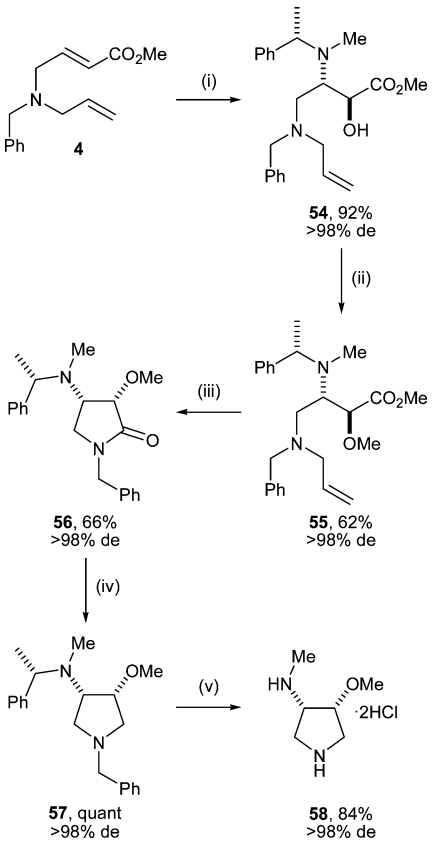
Conclusion

Lithium amide conjugate addition can be used as the key step in a simple and efficient protocol for the preparation of 3,4-substituted aminopyrrolidines. This methodology provides a route to both *anti*- and *syn*-3-amino-4-alkylpyrrolidines, as well as *anti*- and *syn*-3-hydroxy-4-aminopyrrolidines, in high de and ee *via* β-amino enolate functionalisation, and has furthermore been applied to the synthesis of *anti*-(3*S*,4*S*)- and *syn*-(3*R*,4*S*)-3-methoxy-4-(*N*-methylamino)pyrrolidine in >98% de.

Experimental

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



Scheme 12 *Reagents and conditions*: (i) lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to rt, 12 h; (ii) NaH, THF, 0 °C, 1 h; then MeI, rt, 12 h; (iii) $Pd(PPh_3)_4$, 1,3-DMBA, DCM, rt, 16 h, then SiO_2, DCM; (iv) $LiAlH_4$, THF, reflux, 12 h; (v) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), MeOH, 48 h, then HCl.

flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[35] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq. $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of Oxford, UK. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film) or a KBr disc (KBr), as stated. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF and were internally calibrated with polyanaline in positive and negative modes, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General procedure 1 for pyrrolidinone alkylation. BuLi was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine in THF at −78 °C. After 1 h, a solution of the requisite pyrrolidinone in THF was added dropwise *via* cannula, and the reaction mixture stirred at −78 °C for 2 h, after which a solution of the requisite electrophile in THF was added *via* cannula. The reaction mixture was allowed to warm slowly to rt over 16 h before being quenched with saturated aq. NH_4Cl. The mixture was then partitioned between DCM and brine, dried and concentrated *in vacuo*.

General procedure 2 for tandem lithium amide conjugate addition and enolate alkylation. BuLi (2.5 M in hexanes, 1.55 eq.) was added dropwise *via* syringe to a stirred solution of the requisite amine (1.6 eq.) in THF at −78 °C. After stirring for 30 min, a solution of **4** (1.0 eq.) in THF at −78 °C was added dropwise *via* cannula. After stirring for a further 2 h at −78 °C, the reaction mixture was quenched with the requisite alkyl halide and allowed to warm to rt over 12 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between DCM and 10% aq. citric acid. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were washed sequentially with saturated aq. $NaHCO_3$ and brine, dried and concentrated *in vacuo*.

General procedure 3 for *N*-deallylation and concomitant cyclisation. $Pd(PPh_3)_4$ (10 mol%) was added to a stirred solution of the requisite substrate (1 eq.) and 1,3-DMBA (3 eq.) in DCM at rt. After stirring for 12 h, SiO_2 was added to the reaction mixture and stirring continued for a further 6 h before the reaction mixture was concentrated *in vacuo*.

General procedure 4 for reduction of pyrrolidinones with $LiAlH_4$. $LiAlH_4$ (1.0 M in hexanes) was added to a solution of the requisite substrate in THF at 0 °C, and then heated under reflux. After 16 h, the reaction was cooled to rt and quenched with 'wet' Et_2O. Saturated aq. sodium potassium tartrate solution and DCM were added, the organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were dried and concentrated *in vacuo*.

General procedure 5 for hydrogenolysis. $Pd(OH)_2/C$ (50% w/w) was added to a stirred solution of the requisite substrate in degassed MeOH, and placed under a hydrogen atmosphere. After 16 h, the reaction mixture was filtered through Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*.

(3*R*,4*R*,α*S*)-*N*(1)-Benzyl-3-benzyl-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)amino]pyrrolid-2-one 14. BuLi (1.6 M in hexanes, 0.60 mL, 0.94 mmol), 2,2,6,6-tetramethylpiperidine (0.17 mL, 0.96 mmol) in THF (5 mL), **6** (300 mg, 0.78 mmol) in THF (5 mL), and benzyl bromide (0.18 mL, 1.56 mmol) in THF (5 mL) were reacted according to *general procedure 1* to give **14** in >98% de. Chromatography (silica, eluent 30–40° petrol–Et_2O 3 : 2) gave **14** as a white crystalline solid (348 mg, 94%, >98% de); $C_{12}H_{20}O_4$ requires C, 83.5; H, 7.2; N, 5.9%; found C, 83.3; H, 7.1; N, 5.9%; mp 164–165 °C (DCM); $[\alpha]_D^{25}$ +61.1 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr)

3085, 3061, 3029, 2921, 2851, 1952, 1811, 1683, 1603, 1584, 1494, 1452, 1373; δ_H (400 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5 Hz, C(α)*Me*), 2.60 (1H, dd, *J* 11.0, 5.0 Hz, C(3)CH_A), 2.69 (1H, app t, *J* 8.9 Hz, C(5)H_A), 2.86 (1H, q, *J* 5.2 Hz, C(3)*H*), 3.05 (1H, dd, *J* 11.0, 5.2 Hz, C(3)CH_B), 3.14 (1H, dd, *J* 8.9, 4.7 Hz, C(5)H_B), 3.29–3.32 (1H, m, C(4)*H*), 3.63 (1H, d, *J* 8.3 Hz, NCH_A), 3.75 (1H, d, *J* 8.3 Hz, NCH_B), 3.81 (1H, q, *J* 6.5 Hz, C(α)*H*), 4.19 (1H, d, *J* 9.9 Hz, NCH_A), 4.51 (1H, d, *J* 9.9 Hz, NCH_B), 6.60–7.40 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6, 34.5, 46.4, 47.5, 48.1, 50.0, 52.9, 56.9, 126.2, 126.7, 127.1, 127.4, 128.0. 128.2, 128.3, 128.6, 128.9, 129.6, 129.9, 136.0, 138.0, 140.3, 143.9, 174.6; *m/z* (CI^+) 475 ($[M + H]^+$, 100%); HRMS (CI^+) $C_{33}H_{35}N_2O^+$ ($[M + H]^+$) requires 475.2745; found 475.2749.

(3*R*,4*S*,α*S*)-*N*(1)-Benzyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)-amino]-4-benzylpyrrolidine 21. $LiAlH_4$ (1.0 M in THF, 1.3 mL, 1.3 mmol) and **14** (200 mg, 0.42 mmol) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **21** as a yellow, viscous oil (183 mg, 94%); $[\alpha]_D^{25}$ +11.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3061, 3027, 2930, 1602, 1494, 1452; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8 Hz, C(α)*Me*), 1.88–1.92 (1H, m, C(5)H_A), 2.09 (1H, dd, *J* 13.6, 10.7 Hz, C(4)CH_A), 2.33 (1H, app t, *J* 4.5 Hz, C(2)H_A), 2.39–2.45 (1H, m, C(4)*H*), 2.77 (1H, app t, *J* 9.1 Hz, C(5)H_B), 2.74 (1H, dd, *J* 13.6, 10.1 Hz, C(4)CH_B), 2.93 (1H, dd, *J* 9.8, 4.3 Hz, C(2)H_B), 2.96–3.02 (1H, m, C(3)*H*), 3.43 (1H, d, *J* 13.3 Hz, NCH_A), 3.64 (1H, d, *J* 14.8 Hz, NCH_B), 3.80 (1H, d, *J* 14.8 Hz, NCH_A), 3.93 (1H, q, *J* 6.7 Hz, C(α)*H*), 4.19 (1H, d, *J* 14.7 Hz, NCH_B), 7.20–7.51 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.3, 38.6, 46.0, 50.4, 55.8, 56.6, 58.4, 60.6, 61.8, 126.7, 126.8, 128.6, 128.8, 127.8, 128.1, 128.3, 128.4, 128.7, 139.3, 141.6, 141.9, 144.7; *m/z* (CI^+) 461 ($[M + H]^+$, 100%); HRMS (CI^+) $C_{33}H_{37}N_2^+$ ($[M + H]^+$) requires 461.2957; found 461.2965.

(3*R*,4*S*)-3-Amino-4-benzylpyrrolidine 24. $Pd(OH)_2/C$ (50 mg, 25% w/w), **21** (200 mg, 0.43 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **24** as a colourless crystalline solid (70 mg, 60%); mp 65–67 °C; $[\alpha]_D^{24}$ +35.0 (*c* 1.6 in MeOH); ν_{max} (film) 3406, 1604, 1495; δ_H (400 MHz, d_4-MeOH) 2.23–2.33 (1H, m, C(4)*H*), 2.60 (1H, dd, *J* 11.4, 6.1 Hz, C(5)H_A), 2.83–2.93 (2H, m, C(2)H_A, C(4)CH_A), 3.01 (1H, dd, *J* 11.1, 5.4 Hz, C(5)H_B), 3.20–3.32 (2H, m, C(3)*H*, C(4)CH_B), 3.39 (1H, dd, *J* 10.4, 5.7 Hz, C(2)H_B), 7.11–7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 37.3, 48.7, 50.3, 55.5, 56.1, 126.5, 128.6, 128.7, 128.9, 140.4; *m/z* (ESI^+) 177 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{11}H_{17}N_2^+$ ($[M + H]^+$) requires 177.1392; found 177.1395.

Methyl (2*S*,3*R*,α*S*)-2-benzyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]-4-(*N*′-benzyl-*N*′-allylamino)butanoate *anti*-27. *Tandem procedure*: BuLi (2.5 M in hexanes, 0.63 mL, 1.58 mmol), (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.34 mL, 1.63 mmol) in THF (5 mL), **4** (0.25 g, 1.02 mmol) in THF (5 mL), and BnBr (0.6 mL, 5.10 mmol) were reacted according to *general procedure 2* and gave a 97 : 3 mixture of *anti*-**27**:*syn*-**28**. Chromatography (silica, eluent 30–40° petrol–Et_2O 20 : 1) gave *anti*-**27** as a yellow oil (522 mg, 94%, 90% de); $[\alpha]_D^{22}$ −4.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1644, 1733, 2834, 3441; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.8 Hz, C(α)*Me*), 2.37 (1H, dd, *J* 17.0, 2.9 Hz, C(4)H_A), 2.72 (1H, dd, *J* 10.8, 3.2 Hz, C(2)CH_A), 2.78 (1H, dd, *J* 17.0, 2.4 Hz, C(4)H_B), 2.91–3.01 (2H, m, C(2)CH_B, CH_AH$_B$CH=CH$_2$), 3.03–3.12 (1H, m, C(2)*H*), 3.17 (1H, dd, *J* 14.2, 5.8 Hz, CH$_A$$H_B$CH=CH$_2$), 3.21–3.26 (1H, m, C(3)*H*), 3.32 (3H, s, O*Me*), 3.48 (1H, d, *J* 12.8 Hz, NCH_A), 3.73 (1H, d, *J* 12.8 Hz, NCH_B), 3.77 (2H, s, NCH_2), 3.98 (1H, q, *J* 6.8 Hz, C(α)*H*), 5.10–5.19 (2H, m, CH=CH_2), 5.71–5.92 (1H, m, C*H*=CH$_2$), 6.85–7.42 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8, 35.6, 50.3, 50.8, 50.9, 55.4, 56.7, 57.0, 57.2, 58.9, 117.7, 125.7, 126.7, 126.9, 127.8, 128.0, 128.1, 128.2, 128.4, 128.7, 128.9, 129.1, 135.5, 138.8, 140.7, 141.0, 144.1, 173.3; *m/z* (CI^+) 547 ($[M + H]^+$, 100); HRMS (EI^+) $C_{37}H_{43}N_2O_2^+$ ($[M + H]^+$) requires 547.3325; found 547.3328.

Data for syn-***28***. δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.42 (3H, d, *J* 6.7 Hz, C(α)*Me*), 2.30 (1H, d, *J* 14.0 Hz, C(4)H_A), 2.55–2.62 (2H, m, C(2)CH_A, C(4)H_B), 2.82–3.01 (3H, m, C(2)*H*, C(2)CH_B, CH_AH$_B$CH=CH$_2$), 3.25 (3H, s, O*Me*), 3.36–3.52 (3H, m, C(3)*H*, CH$_A$$H_B$CH=CH$_2$, NC$H_A$), 3.68 (1H, d, *J* 12.6 Hz, NCH_B), 3.80 (1H, d, *J* 12.7 Hz, NCH_A), 3.91 (1H, d, *J* 12.7 Hz, NCH_B), 4.07 (1H, q, *J* 6.7 Hz, C(α)*H*).

Stepwise procedure. BuLi (2.5 M in hexanes, 1.72 mL, 4.30 mmol) was added dropwise to a solution of di-*iso*-propylamine (0.62 mL, 4.40 mmol) in THF (5 mL) at 0 °C. After 1 h, the LDA solution was added to a solution of **5** (1.00 g, 2.20 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 2 h before being quenched with BnBr (1.60 mL, 13.2 mmol), and allowed to warm slowly to rt overnight. Saturated aq. NH_4Cl (25 mL) was added, the reaction mixture was extracted with $CHCl_3$ (3 × 25 mL) and the combined organic extracts were washed sequentially with saturated aq. $NaHCO_3$ (25 mL) and brine (25 mL), dried and concentrated *in vacuo* to give a 92 : 8 mixture of *anti*-**27** : *syn*-**28**. Chromatography (silica, eluent 30–40° petrol–Et_2O 20 : 1) gave a mixture of *anti*-**27** and *syn*-**28** as a yellow oil (1.07 g, 89%, 84% de).

(3*S*,4*R*,α*S*)-*N*(1),3-Dibenzyl-4-[*N*′-benzyl-*N*′-(α-methylbenzyl)-amino]pyrrolid-2-one 35. $Pd(PPh_3)_4$ (451 mg, 0.39 mmol) was added to a rapidly stirred solution of *anti*-**27** (2.0 g, 3.7 mmol, 94% de) and 1,3-DMBA (2.01 g, 13.0 mmol) were reacted according to *general procedure 3*. Chromatography (silica, eluent 30–40° petrol–Et_2O 30 : 1) gave **35** as a clear oil (1.60 g, 92%, 96% de); $[\alpha]_D^{21}$ +5.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2968, 1733, 1687, 1603, 1494; δ_H (400 MHz, d_4-MeOH) 1.22 (3H, d, *J* 7.0 Hz, C(α)*Me*), 2.66–2.74 (1H, m, C(4)*H*), 2.95 (1H, dd, *J* 14.7, 5.3 Hz, C(5)H_A), 3.11 (1H, dd, *J* 14.7, 7.4 Hz, C(5)H_B), 3.29 (2H, s, NCH_2Ph), 3.32–3.41 (2H, m, C(3)CH_2), 3.60–3.67 (1H, m, C(3)*H*), 3.80 (1H, q, *J* 7.0 Hz, C(α)*H*), 4.24 (1H, d, *J* 14.3 Hz, NCH_AH$_B$Ph), 4.59 (1H, d, *J* 14.3 Hz, NCH$_A$$H_B$Ph), 6.90–7.41 (15H, m, *Ph*); δ_C (100 MHz, d_4-MeOH) 12.8, 29.4, 46.4, 47.6, 48.0, 50.3, 53.5, 56.1, 125.7, 127.0, 127.3, 128.1, 128.2, 128.3, 128.5, 128.8, 136.6, 139.7, 141.4, 142.7, 176.8; *m/z* (CI^+) 475 ($[M + H]^+$, 100%); HRMS (CI^+) $C_{33}H_{35}N_2O^+$ ($[M + H]^+$) requires 475.2749; found 475.2757.

(3*R*,4*R*,α*S*)-*N*(1),4-Dibenzyl-3-[*N*′-benzyl-*N*′-(α-methylbenzyl)-amino]pyrrolidine 38. $LiAlH_4$ (1.0 M in THF, 3.16 mL, 3.16 mmol) and **35** (500 mg, 1.05 mmol, 96% de) in THF (10 mL) were reacted according to *general procedure 4*. Chromatography (silica, eluent Et_2O) gave **38** as a colourless oil (418 mg, 86%, >98% de); $[\alpha]_D^{22}$ −53.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3084, 3061, 3026, 2965, 2795; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.8 Hz, C(α)*Me*), 2.32–2.43 (2H, m, C(4)*H*, C(5)H_A), 2.54–2.62 (1H, m, C(4)CH_A), 2.66 (1H, dd, *J* 9.1, 7.2 Hz, C(5)H_B), 2.74 (1H, dd, *J*

9.4, 7.6 Hz, C(2)H_A), 2.83 (1H, dd, *J* 9.4, 7.3 Hz, C(2)H_B), 3.32 (1H, dd, *J* 11.8, 1.7 Hz, C(4)CH_B), 3.54 (1H, q, *J* 7.5 Hz, C(3)*H*), 3.61 (2H, s, NCH_2Ph), 3.99 (2H, s, NCH_2Ph), 4.08 (1H, q, *J* 6.8 Hz, C(α)*H*), 7.10–7.62 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6, 36.2, 44.4, 53.1, 56.0, 56.6, 58.7, 59.3, 60.8, 125.7, 126.7, 126.9, 128.0, 128.1, 128.3, 128.4, 128.6, 128.9, 139.4, 141.3, 142.5, 143.8; *m*/*z* (CI^+) 461 ([M + H]$^+$, 100%); HRMS (CI^+) $C_{33}H_{37}N_2^+$ ([M + H]$^+$) requires 461.2957; found 461.2957.

(3*R*,4*R*)-3-Amino-4-benzylpyrrolidine 41. $Pd(OH)_2$/C (140 mg, 50% w/w), **38** (280 mg, 0.61 mmol) in MeOH (5 mL) and H_2 (5 atm) were reacted according to *general procedure 5*. Chromatography (basic alumina, eluent MeOH) gave **41** as a colourless oil (103 mg, 64%); $[\alpha]_D^{22}$ −39.1 (*c* 1.1 in $CHCl_3$); ν_{max} (film) 3358, 2928, 1495; δ_H (400 MHz, d_4-MeOH) 2.53–2.66 (1H, m, C(4)*H*), 2.69 (1H, dd, *J* 11.5, 3.8 Hz, C(4)CH_A), 2.93 (1H, dd, *J* 11.5, 7.6 Hz, C(4)CH_B), 3.16–3.23 (3H, m, C(2)H_A, C(5)H_2), 3.40 (1H, dd, *J* 12.1, 6.8 Hz, C(2)H_B), 3.62–3.65 (1H, m, C(3)*H*), 4.89 (1H, br s, NH_2), 7.16–7.34 (5H, m, *Ph*); δ_C (100 MHz, d_4-MeOH) 33.6, 44.9, 48.9, 52.3, 52.7, 126.6, 128.7, 128.8, 139.8; *m*/*z* (CI^+) 177 ([M + H]$^+$, 100%); HRMS (CI^+) $C_{11}H_{17}N_2^+$ ([M + H]$^+$) requires 177.1392; found 177.1393.

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