Lithium amide conjugate addition for the asymmetric synthesis of 3-aminopyrrolidines

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Conjugate addition of homochiral lithium amides to methyl 4-(*N*-benzyl-*N*-allylamino)but-2-enoate, chemoselective *N*-deprotection and concomitant cyclisation, followed by enolate functionalisation and deprotection allows access to *syn*- and *anti*-3,4-disubstituted aminopyrrolidines in > 98% d.e. and > 98% e.e.

Substituted homochiral aminopyrrolidines are common subunits found in a plethora of natural products. A variety of molecular classes are encompassed by this structural motif, which have become attractive synthetic targets due to their increasing demand as building blocks in bioactive compounds.[1] For example, hydroxylated aminopyrrolidines constitute one of the main classes of naturally occurring sugar mimics,[2] with much attention focused upon their potential therapeutic applications due to their role as glycosidase inhibitors.[3] Within this structural family, (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidine **1** is an important fragment of the quinolone antitumour agent AG-7352 **2** which shows high *in vivo* and excellent *in vitro* antibacterial activity against both Gram positive and Gram negative bacteria, as well as potent cytotoxic activity against Murine P388 leukaemia cells (Fig. 1).[4] Typical synthetic routes to enantiomerically enriched pyrrolidine derivatives include the enantioselective cycloaddition of azomethine ylides[5] or the diastereoselective cycloaddition of ynoates to chiral nitrones,[6] with hydroxylated aminopyrrolidines usually prepared using carbohydrates as starting materials,[7] or resolution of the racemates.[8] Previous investigations from this laboratory have shown that conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters may be used for the asymmetric synthesis of β-amino acid derivatives.[9] We wished to apply this versatile methodology to the stereodivergent asymmetric synthesis of enantiomerically pure aminopyrrolidines and report herein our preliminary investigations within this area.

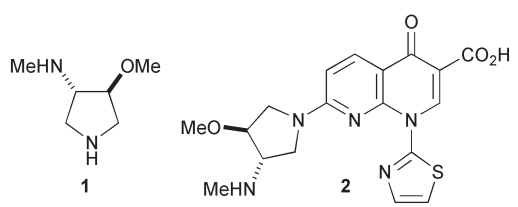

Fig. 1 Structure of (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidine **1** and AG-7352 **2**.

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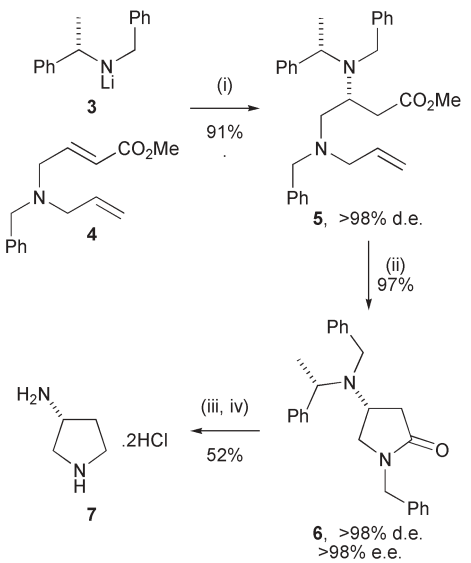
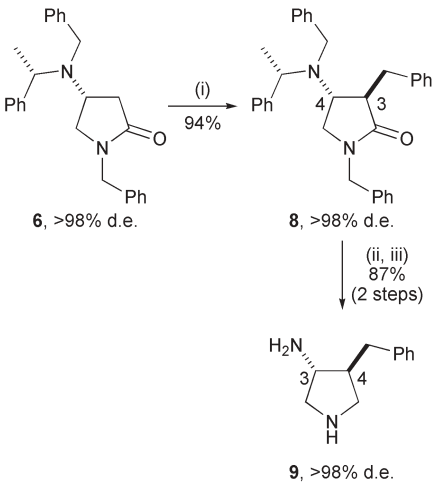
Initial studies were directed toward the delineation of a simple, high yielding and scaleable route to homochiral aminopyrrolidines, with the preparation of (*R*)-3-aminopyrrolidine dihydrochloride **7** chosen as a model for optimization of this methodology. Conjugate addition of homochiral lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **3** to methyl 4-(*N*-benzyl-*N*-allylamino)but-2-enoate **4**[10] gave β-amino ester (3*R*,α*S*)-**5** in > 98% d.e.,[11] and in 91% yield (> 98% d.e.) after chromatographic purification.[12] Chemoselective *N*-allyl deprotection upon treatment with $Pd(PPh_3)_4$ and 1,3-dimethylbarbituric acid (DMBA)[13] and concomitant intramolecular cyclisation furnished aminopyrrolidinone **6** (> 98% d.e., > 98% e.e.)[14] in 97% yield on a > 30 gram scale. Global *N*-deprotection of aminopyrrolidinone **6** was achieved following an efficient two-step protocol, with $LiAlH_4$ reduction followed by hydrogenolysis and treatment with HCl (6 M, aq) giving the homochiral dihydrochloride salt (*R*)-**7** in 52% overall yield, with spectroscopic properties consistent with those of a commercially available sample[15] {$[\alpha]_D^{23}$ −1.7 (*c* 0.9 in H_2O); lit.[15] $[\alpha]_D^{23}$ −1.7 (*c* 1.3 in H_2O)} (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **3**, THF, −78 °C, 2 h; (ii) $Pd(PPh_3)_4$, 1,3-DMBA, DCM, rt, 16 h; (iii) $LiAlH_4$, THF, reflux, 12 h; (iv) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, rt, 40 h, then HCl (6 M, aq).

The extension of this protocol to the preparation of 3,4-disubstituted pyrrolidines was next investigated, with functionalisation of pyrrolidinone **6** *via* enolate alkylation expected to lead to the corresponding 3,4-*anti*-aminopyrrolidine. Treatment of pyrrolidinone **6** with LiTMP at −78 °C, followed by addition of benzyl bromide at −78 °C gave complete conversion to *anti*-3-benzyl-4-aminopyrrolidinone (3*R*,4*R*,α*S*)-**8** in > 98% d.e.,[11] giving **8** in > 98% d.e. and 94% isolated yield after purification. The relative 3,4-*anti*-configuration within **8** was confirmed unambiguously by X-ray crystallographic analysis, with the absolute (3*R*,4*R*,α*S*)-configuration known relative to the (*S*)-*N*-α-methylbenzyl stereocentre (Fig. 2).†[16,17] $LiAlH_4$ reduction of pyrrolidinone **8**, followed by hydrogenolysis gave (3*R*,4*R*)-**9** in > 98% d.e. and 87% yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) LiTMP, THF, −78 °C, 2 h, then BnBr (2 eq), −78 °C, 16 h; (ii) $LiAlH_4$, THF, reflux, 12 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 40 h.

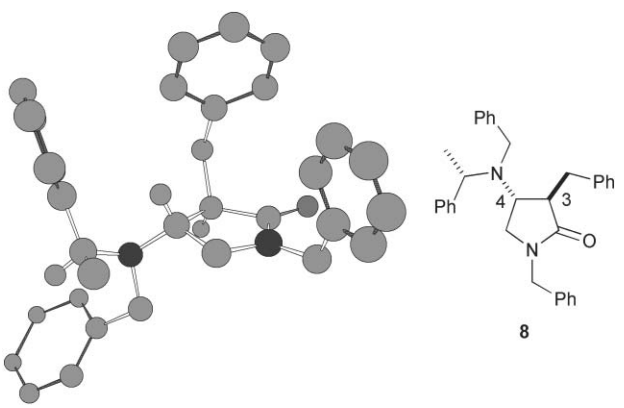
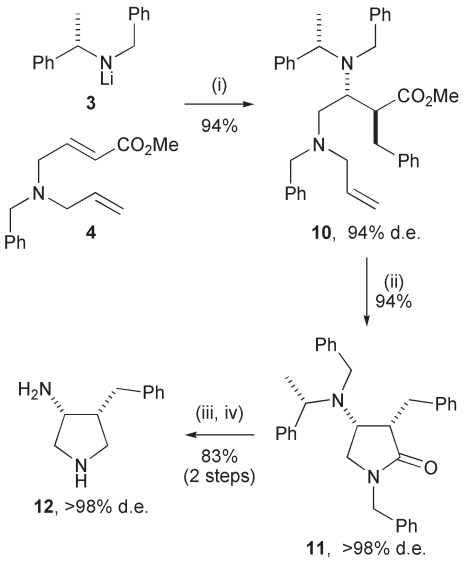
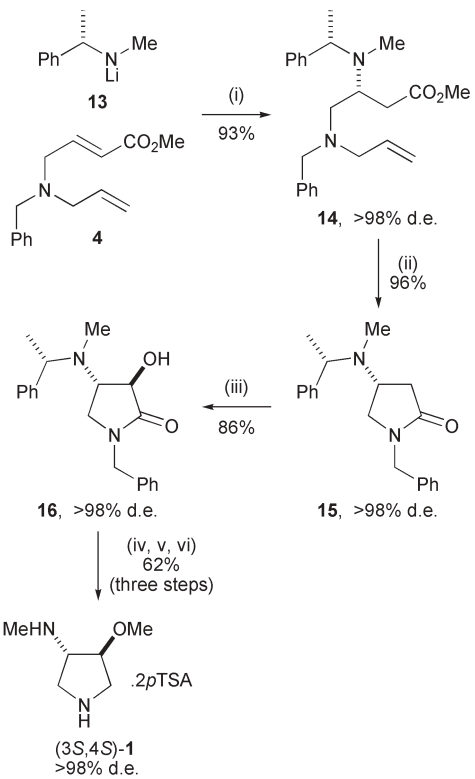


Fig. 2 Chem 3D representation of the X-ray crystal structure of (3*R*,4*R*,α*S*)-**8** (some H atoms omitted for clarity).

The utility of this methodology for the synthesis of the corresponding 3,4-*syn*-aminopyrrolidine was next established, with conjugate addition of lithium amide (*S*)-**3** to α,β-unsaturated ester **4**, followed by alkylation of the resulting (*Z*)-β-amino enolate with benzyl bromide giving *anti*-3-amino-2-benzyl **10** in 94% d.e., and in 94% yield (94% d.e.) after purification.[18] Deallylation of **10** (94% d.e.) and concomitant cyclisation, followed by purification to homogeneity by chromatography, gave *syn*-3-benzyl-4-aminopyrrolidinone **11** as a single diastereoisomer in 94% yield. Subsequent $LiAlH_4$ reduction and hydrogenolysis gave (3*R*,4*S*)-**12** in 83% yield over two steps (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **3**, THF, −78 °C, 2 h, then BnBr (2 eq), −78 °C, 16 h; (ii) $Pd(PPh_3)_4$, 1,3-DMBA, DCM, rt, 16 h; (iii) $LiAlH_4$, THF, reflux, 12 h; (iv) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 24 h.



Scheme 4 *Reagents and conditions*: (i) lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide **13**, THF, −78 °C, 2 h; (ii) $Pd(PPh_3)_4$, 1,3-DMBA, DCM, rt, 16 h; (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, rt, 12 h; (v) $LiAlH_4$, THF, reflux, 12 h; (vi) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 48 h, then *p*TSA.

With an efficient stereodivergent route to functionalised *syn*- and *anti*-3-amino-4-benzylpyrrolidines **9** and **12** in hand, the application of this strategy to the synthesis of (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidine **1** was investigated, with incorporation of the desired *N*-methyl fragment within **1** deriving from conjugate addition of lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide **13**. Conjugate addition of lithium amide (*S*)-**13** to butenoate **4** gave β-amino ester (3*R*,α*S*)-**14** in > 98% d.e., and in 93% yield and > 98% d.e. after purification. *N*-Deallylation and cyclisation gave pyrrolidinone **15** in 96% yield, with deprotonation of **15** with LiTMP followed by enolate oxygenation with (+)-camphorsulfonyloxaziridine (CSO) giving exclusively 3,4-*anti*-(3*R*,4*S*,α*S*)-**16**, furnishing **16** in 86% yield and > 98% d.e. after purification. *O*-Methylation, $LiAlH_4$ reduction and hydrogenolysis furnished the desired (3*S*,4*S*)-pyrrolidine **1** in 62% overall yield (3 steps) as its di-*p*-toluenesulfonic acid salt with comparable spectroscopic properties to the literature {$[\alpha]_D^{24}$ 10.1 (*c* 1.1 in MeOH); lit.[19] $[\alpha]_D^{29}$ +10.4 (*c* 1.0 in MeOH)} (Scheme 4).

In conclusion, lithium amide conjugate addition has been used as the key step for the development of a simple and efficient protocol for the preparation of polysubstituted aminopyrrolidines in high d.e. and e.e. This protocol provides a stereodivergent route to both *anti*- and *syn*-3-alkyl-4-aminopyrrolidines, and has been applied to the synthesis of (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidine **1** in > 98% d.e. The further application of this methodology to the synthesis of a variety of natural product targets is currently under investigation in this laboratory.

Notes and references

† CCDC 602326. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604835h

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10 Methyl 4-(*N*-benzyl-*N*-allylamino)but-2-enoate **4** can be prepared readily on a multigram scale by addition of *N*-benzyl-*N*-allylamine to methyl 4-bromocrotonate.

11 As indicated by 400 MHz ^{1}H NMR spectroscopic analysis of the crude reaction product.

12 The absolute configuration of **5** was assigned as (3*R*,α*S*) by analogy with previous models developed to explain the stereoselectivity observed during addition of lithium amide **3** to α,β-unsaturated acceptors; see J. F. Costello, S. G. Davies and O. Ichihara, *Tetrahedron: Asymmetry*, 1994, **5**, 3919.

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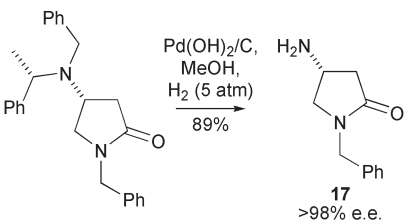
14 The e.e. of aminopyrrolidinone **6** was inferred by ^{1}H NMR studies of the corresponding Mosher's amides of pyrrolidinone **17**, obtained in 89% yield *via* hydrogenolysis of **6**, and comparison with an authentic racemic standard.



15 (*R*)-(+)-3-Aminopyrrolidine (> 98% e.e.) is commercially available from Aldrich.

16 X-ray crystal structure determination for **8**. Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 190 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.[17] X-ray crystal structure data for **8**: $[C_{33}H_{34}N_2O]$: M = 474.65, monoclinic, space group *C* 1 2 1, a = 17.1297(3) Å, b = 8.2098(2) Å, c = 19.4751(4) Å, β = 100.0736(8)°, V = 2696.6(1) Å^3, Z = 4, μ = 0.070 mm^{-1}, colourless block, crystal dimensions = 0.2 × 0.2 × 0.2 mm. A total of 3244 unique reflections were measured for $5 < \theta < 27$ and 2894 reflections were used in the refinement. The final parameters were wR_2 = 0.032 and R_1 = 0.032 [$I > 3\sigma(I)$].

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