Asymmetric Synthesis of Piperidines and Octahydroindolizines

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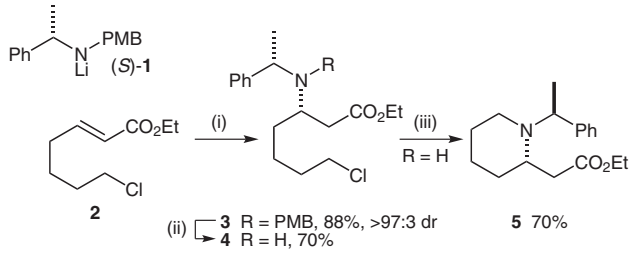
Dedicated to Professor Gerry Pattenden on the occasion of his 70th birthday in recognition of his efforts to ensure UK chemistry is where it is today.

Abstract: The conjugate addition of a homochiral lithium amide to a ξ-hydroxy-α,β-unsaturated ester, followed by a one-pot, ring-closure–N-debenzylation protocol has been used in the asymmetric syntheses of (*S*)-coniine and (*R*)-δ-coniceine (isolated as the corresponding hydrochloride salts) and the bicyclic core of stellettamide A.

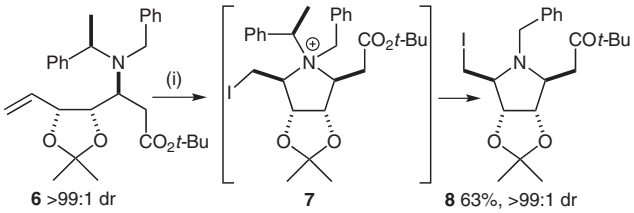
Key words: asymmetric synthesis, lithium amides, piperidines, coniine, δ-coniceine

Enantiopure piperidines are common structural motifs present in a range of natural products and biologically significant molecules,[1] and as such there has been a great deal of interest in their synthesis. These syntheses have employed a vast range of synthetic methods, including manipulation of the chiral pool,[2] chiral-auxiliary-based approaches,[3] asymmetric catalysis,[4] and the conjugate addition of homochiral lithium amides. For example, O'Brien et al. have shown that addition of lithium amide (*S*)-**1** to α,β-unsaturated ester **2** gives the corresponding ξ-chloro-β-amino ester **3** which may then be cyclised, after oxidative N-debenzylation, via an intramolecular S_N2-type displacement to give piperidine **5** (Scheme 1).[5]



Scheme 1 *Reagents and conditions*: (i) (*S*)-*N*-(α-methylbenzyl)-*N*-(*p*-methoxybenzyl)amine, BuLi, THF, –78 °C, 30 min; (ii) CAN, MeCN–H_2O (5:1), 0 °C, 30 min; (iii) K_2CO_3, NaI, EtOH, reflux, 16 h.

As part of our ongoing research program concerning the application of enantiopure lithium amides[6] as homochiral ammonia equivalents in total synthesis[7] we became interested in developing methodology for one-pot processes involving cyclisation with concomitant N-debenzylation of a β-amino ester. For example, we have recently reported that iodoamination of **6** upon treatment with I_2 occurs with in situ loss of the *N*-α-methylbenzyl protecting group. The reaction proceeds via quaternary ammonium ion **7** that undergoes preferential loss of the *N*-α-methylbenzyl cation, which is then trapped by acetonitrile in a Ritter reaction to give racemic *N*-α-methylbenzylacetamide in 72% yield in addition to pyrrolidine **8** which was isolated in 63% yield and >99:1 dr (Scheme 2).[8]



Scheme 2 *Reagents and conditions*: (i) I_2, $NaHCO_3$, MeCN, r.t., 20 h.

We envisaged that a similar one-pot procedure may be employed in the synthesis of homochiral piperidine scaffolds **9** from the corresponding ξ-halo-β-amino esters **10** via an intramolecular S_N2-type displacement of the halide by the amino substituent with concomitant loss of the *N*-α-methylbenzyl group. It was anticipated that the cyclisation precursors **10** could either be accessed directly from the conjugate addition of enantiopure lithium amides **11** to ξ-halo-α,β-unsaturated esters **12** or via the intermediacy of the known ξ-hydroxy-β-amino esters **14**[9] which can be readily produced via the addition of a lithium amide **11** to ξ-hydroxy-α,β-unsaturated ester **13**, which in turn is derived from commercially available δ-valerolactone (Scheme 3).

ξ-Iodo-, ξ-bromo-, and ξ-chloro-α,β-unsaturated esters **16**–**18** were synthesized from *tert*-butyl 7-hydroxyhept-2-enoate **13**[10] via standard procedures.[11] Addition of lithium amide (*R*)-**15** to ξ-iodo substituted **16** gave exclusively the known transhexacin derivative **19**,[12] resulting from in situ cyclisation of the intermediate lithium β-amino enolate onto the pendant ξ-iodo functionality,[13] in 58% isolated yield and >99:1 dr. Conjugate addition of (*R*)-**15** to ξ-bromo-substituted **17** resulted in an inseparable 56:44 mixture of **19** and ξ-bromo-β-amino ester **20**, respectively, both as single diastereomers (>99:1 dr), consistent with the decreased reactivity of the ξ-bromo group towards S_N2 displacement. However, addition of (*R*)-**15** to ξ-chloro-

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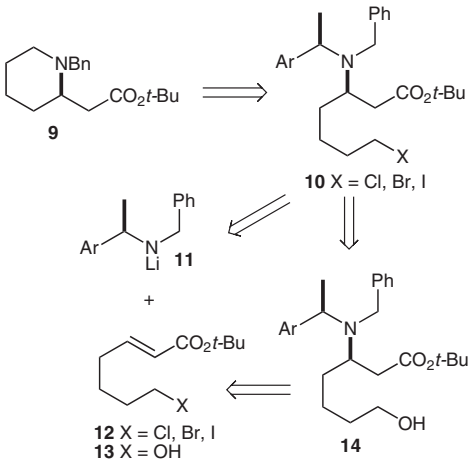
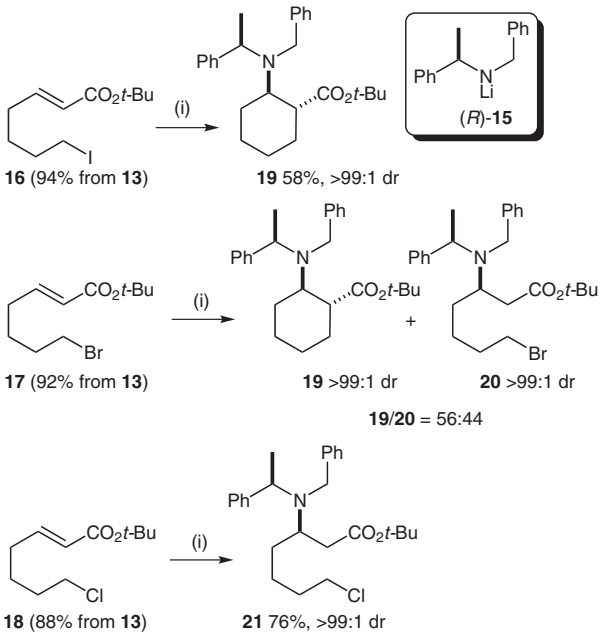


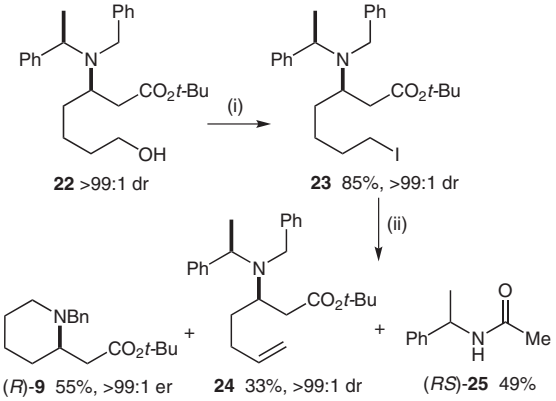
Scheme 3 Retrosynthetic analysis of enantiopure piperidine **9**

substituted **18** gave exclusively ξ-chloro-β-amino ester **21** in >99:1 dr, which was isolated in 76% yield and >99:1 dr after purification (Scheme 4). Attempted cyclisation and in situ N-debenzylation by heating **21** in MeCN at 80 °C for 16 hours unfortunately returned only starting material, even in the presence of 1.5 equivalents of $AgBF_4$.



Scheme 4 *Reagents and conditions*: (i) (*R*)-**15**, THF, –78 °C, 2 h.

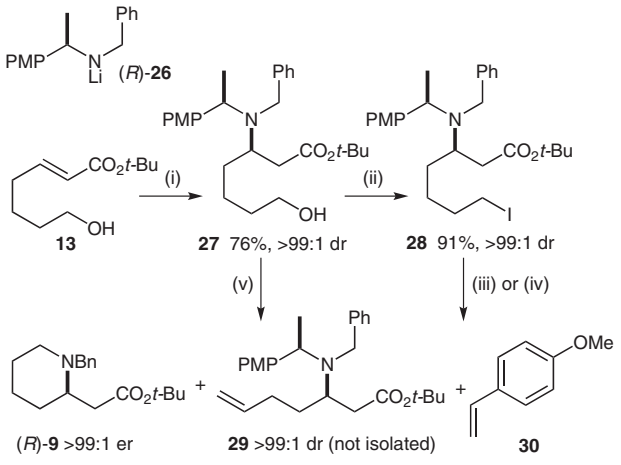
Attention next turned towards our second strategy involving the synthesis of ξ-iodo-β-amino ester **23** from the corresponding known ξ-hydroxy-β-amino ester **22**. Thus, iodination[11c] of **22**[9] (>99:1 dr) gave **23** in 85% isolated yield as a single diastereomer. Heating a solution of **23** in MeCN for 16 hours at reflux resulted in a 48:49:3 mixture of starting material **23**, the desired piperidine **9** and ω-unsaturated β-amino ester **24**, respectively, in addition to racemic *N*-α-methylbenzylacetamide **25** (resulting from Ritter reaction of the α-methylbenzyl cation). However, repetition of this reaction in the presence of 1.5 equivalents of $AgBF_4$ resulted in complete consumption of starting material, giving a 63:37 mixture of **9** and **24**, respectively, in addition to **25**. Purification of this mixture enabled isolation of **9** in 55% yield, **24** in 33% yield and >99:1 dr, and (*RS*)-**25** in 49% yield (Scheme 5). The formation of **24** in this case is consistent with silver-promoted elimination of HI from **23**.



Scheme 5 *Reagents and conditions*: (i) Ph_3P, imidazole, I_2, PhMe–MeCN (4:1), 65 °C, 2 h; (ii) $AgBF_4$, MeCN, 80 °C, 16 h.

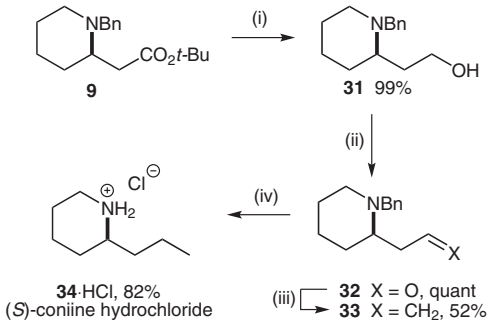
Since it was probable that loss of the benzylic cation could be rate-limiting, the corresponding *N*-(*p*-methoxy-α-methylbenzyl)-substituted analogue **27**, which was produced in 76% yield and >99:1 dr from the conjugate addition of (*R*)-**26** to **13**, was also investigated. Iodination[11c] of **27** gave ξ-iodo-β-amino ester **28** in 91% yield and >99:1 dr. Subsequent treatment of **28** under the $AgBF_4$-promoted cyclisation conditions gave an 86:14 mixture of **9** and a compound which was tentatively assigned as ω-unsaturated β-amino ester **29**, although only **9** was isolated in 84% yield after purification. Interestingly, heating a solution of **28** in MeCN at reflux for 16 hours (in the absence of $AgBF_4$) caused complete consumption of starting material, to give **9** and *p*-methoxystyrene **30** which were isolated in 94% and 65% yield, respectively. The one-pot conversion of ξ-hydroxy-β-amino ester **27** into **9** was next attempted by heating a solution of **27** in MeCN in the presence of I_2, Ph_3P, and imidazole. Under these conditions cyclisation and in situ N-debenzylation gave piperidine **9** in 75% isolated yield (in 3 steps and 31% overall yield from δ-valerolactone) and **30** in 33% isolated yield (Scheme 6).

With methodology for the synthesis of piperidine **9** established, attention was turned towards the conversion of **9** into the Hemlock alkaloids (*S*)-coniine **34** and (*R*)-δ-coniceine **37**. Reduction of **9** with DIBAL-H gave the corresponding alcohol **31** in 99% yield. Subsequent oxidation of **31** under Swern conditions gave aldehyde **32** in quantitative yield.[14] Wittig reaction of β-amino aldehyde **32** gave olefin **33** in 52% yield which, when subjected to tandem hydrogenation–hydrogenolysis conditions gave **34**, which was isolated as the corresponding hydrochloride salt, in 82% yield (Scheme 7).[15]



Conditions	Ratio **9**/**29**	Yield of **9**	Yield of **30**
(iii) from **28**	86:14	84%	--
(iv) from **28**	100:0	94%	65%
(v) from **27**	100:0	75%	33%

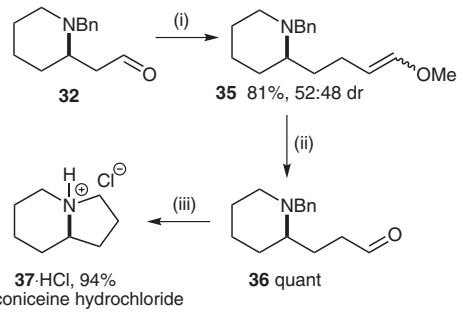
Scheme 6 *Reagents and conditions*: (i) THF, –78 °C, 2 h; (ii) Ph_3P, imidazole, I_2, PhMe–MeCN (4:1), 65 °C, 2 h; (iii) $AgBF_4$, MeCN, 80 °C, 16 h; (iv) MeCN, 80 °C, 16 h; (v) Ph_3P, imidazole, I_2, MeCN, 80 °C, 16 h.



Scheme 7 *Reagents and conditions*: (i) DIBAL-H, THF, 0 °C to r.t., 6 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to r.t.; (iii) $MePPh_3Br$, KO*t*-Bu, THF, 0 °C to r.t., 16 h; (iv) $Pd(OH)_2/C$ (20 wt%), H_2 (1 atm), MeOH, r.t., 48 h then HCl.

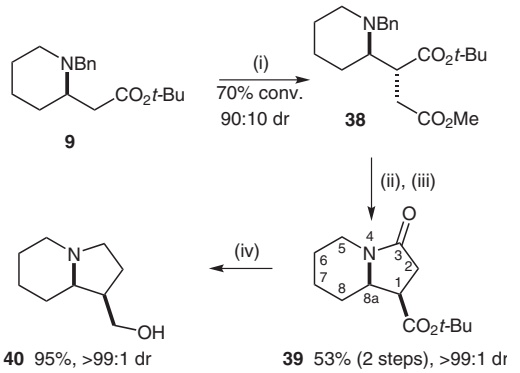
For the synthesis of (*R*)-δ-coniceine **37**, chain extension of aldehyde **32** gave enol ether **35** in 81% yield as a 52:48 mixture of geometric isomers. Hydrolysis of this mixture gave γ-amino aldehyde **36** in quantitative yield, which upon treatment with $Pd(OH)_2/C$ under 1 atm of H_2 underwent one-pot hydrogenolysis, imine formation, and in situ reduction to give (*R*)-δ-coniceine **37**, which was isolated as the corresponding hydrochloride salt, in 94% yield (Scheme 8).[17]

Further efforts focused upon the elaboration of **9** to give **40** (the bicyclic core of stellettamide A).[18] Thus, alkylation of **9** with 2.0 equivalents of LiTMP and 3.0 equivalents of methyl bromoacetate proceeded to 70% conversion giving **38** in 90:10 dr.[19,20] Attempted purification of the crude reaction mixture gave a 77:23 mixture of **38** (98:2 dr) and recovered starting material **9**, respectively. Treating this mixture under hydrogenolysis conditions led to successful N-debenzylation, although heating the crude reaction mixture at reflux in $CHCl_3$ for 16 hours was



Scheme 8 *Reagents and conditions*: (i) $MeOCH_2PPh_3Br$, KO*t*-Bu, THF, 0 °C to r.t., 16 h; (ii) HCO_2H, CH_2Cl_2, r.t., 16 h; (iii) $Pd(OH)_2/C$ (20 wt%), H_2 (1 atm), MeOH, r.t., 48 h then HCl.

required to promote cyclisation to give hexahydroindolizin-3-one **39**.[19] Subsequent purification enabled isolation of **39** in 53% yield and >99:1 dr. The relative configuration within **39** was confirmed by ^1H NMR NOE analysis which showed strong reciprocal enhancements between the C(1)*H* and C(8a)*H* protons. Subsequent treatment of **39** with $LiAlH_4$ gave (1*R*,8a*R*)-1-(hydroxymethyl)-octahydroindolizine **40** in 95% yield and >99:1 dr (Scheme 9).[21–23]



Scheme 9 *Reagents and conditions*: (i) LiTMP, THF, –78 °C then $BrCH_2CO_2Me$, –78 °C to r.t., 16 h; (ii) $Pd(OH)_2/C$ (20 wt%), H_2 (1 atm), MeOH, r.t., 48 h; (iii) $CHCl_3$, reflux, 16 h; (ix) $LiAlH_4$, THF, reflux, 16 h.

In conclusion, a one-pot ring closure with concomitant N-debenzylation protocol for the synthesis of *tert*-butyl (*R*)-(*N*-benzylpiperidin-2′-yl)acetate has been developed and subsequently employed in the total asymmetric syntheses of (*S*)-coniine and (*R*)-δ-coniceine (as the corresponding hydrochloride salts), and the bicyclic core of stellettamide A.

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(10) ξ-Hydroxy-α,β-unsaturated ester **13** was prepared in 55% yield [96:4 *E*/*Z* ratio] via the one-pot treatment of δ-valerolactone with DIBAL-H, *tert*-butyl 2-(diethoxyphosphoryl)acetate and BuLi at –78 °C. See ref. 9 for details.

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(15) **Data for (*S*)-Coniine Hydrochloride (34·HCl)**
Mp 208 °C (lit.[16] mp 214 °C); $[\alpha]_D^{23}$ +9.2 (*c* 0.33 in EtOH) {lit.[16] $[\alpha]_D^{23}$ +9.4 (*c* 0.3 in EtOH)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 [3 H, t, *J* = 7.3 Hz, C(3′)H_3], 1.36–2.04 [10 H, m, C(3)H_2, C(4)H_2, C(5)H_2, C(1′)H_2, C(2′)H_2], 2.75–2.86 [1 H, m, C(6)H_A], 2.87–3.00 [1 H, m, C(6)H_B], 3.40–3.53 [1 H, br m, C(2)*H*], 9.19 [1 H, br s, NH_A], 9.49 (1 H, br s, NH_B].

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(17) **Data for (*R*)-δ-Coniceine Hydrochloride (37·HCl)**
Mp 175 °C; $[\alpha]_D^{23}$ –1.5 (*c* 1.0 in EtOH). IR (KBr): ν_{max} = 3477 (NH) cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.56–2.35 [10 H, m, C(1)H_2, C(2)H_2, C(6)H_2, C(7)H_2, C(8)H_2], 2.92–3.22 [3 H, m, C(3)H_A, C(5)H_A, C(8a)*H*], 3.55–3.68 [2 H, m, C(3)H_B, C(5)H_B]. ^{13}C NMR (125 MHz, CD_3OD): δ = 20.5, 23.5, 24.4, 29.2, 29.5 [C(1), C(2), C(6), C(7), C(8)], 52.8, 53.6 [C(3), C(5)], 68.0 [C(8a)]. HRMS (ESI$^+$): *m/z* (%) = 126 (100) [M + H]$^+$. HRMS (ESI$^+$): *m/z* calcd for $C_8H_{16}N^+$ [M + H]$^+$: 126.1283; found: 126.1278.

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(21) **Data for (1*R*,8a*R*)-1-(Hydroxymethyl)octahydroindolizine (40)**
$[\alpha]_D^{23}$ –35.8 (*c* 0.50 in EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.37 (2 H, m), 1.40–1.69 (3 H, m), 1.74–1.87 (4 H, m), 1.90–2.13 (3 H, m), 3.05–3.40 [2 H, m, C(3)H_A, C(5)H_A], 3.46 [1 H, dd, *J* = 10.2, 2.4 Hz, C(1′)H_A], 3.86 [1 H, dd, *J* = 10.2, 2.8 Hz, C(1′)H_B], 3.95 (1 H, br s, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 25.3, 25.4, 26.7 [C(2), C(6), C(7), C(8)], 41.0 [C(1)], 53.6, 53.9 [C(3), C(5)], 64.6 [*C*(1′)], 66.2 [C(8a)]. HRMS (ESI$^+$): *m/z* (%) = 156 [M + H]$^+$.

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(23) Some discrepancies exist between the reported characterisation data for **40** and its epimer; these will be highlighted in a forthcoming publication from this laboratory. However, our synthesis unambiguously confirms the relative and absolute configuration of **40**.