ChemComm

COMMUNICATION

View Article Online
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An efficient asymmetric synthesis of (−)-lupinine†‡

Cite this: *Chem. Commun.*, 2014, **50**, 8309

Received 22nd March 2014,
Accepted 8th June 2014

DOI: 10.1039/c4cc02135e

www.rsc.org/chemcomm

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The asymmetric synthesis of (−)-lupinine was achieved in 8 steps, 15% overall yield and >99 : 1 dr from commercially available starting materials. The strategy used for the construction of the quinolizidine scaffold involved reaction of an enantiopure tertiary dibenzylamine *via* two sequential ring-closures which both occurred with concomitant *N*-debenzylation.

Quinolizidine alkaloids,[1] such as (−)-lupinine **1**,[2,3] (+)-*epi*-lupinine **2**, (+)-*epi*-epiquinamide **3**, (+)-13β-hydroxymamanine **4**, and (−)-lasubine II **5** (Fig. 1), display a broad range of interesting biological activities.[4–6] Accordingly, strategies for the asymmetric synthesis of these azabicycles have received considerable attention from the synthetic community.[4]

We have recently described the application of a ring-closing iodoamination procedure in asymmetric syntheses of pyrrolidine,[7] piperidine,[8] pyrrolizidine[9] and tropane[10] ring systems from a range of enantiopure tertiary amines; in each case, concomitant *N*-debenzylation is also observed, effecting *in situ* deprotection of the nitrogen atom from the intermediate ammonium species. We envisaged that other azabicyclic scaffolds, including pyrrolizidines, indolizidines and quinolizidines, could be produced by a similar procedure involving two S_N2-type ring-closures which should also occur with concomitant *N*-debenzylation. Herein we report our preliminary results within this area (initially targeting the quinolizidine ring system), which culminates in the development of an efficient synthesis of (−)-lupinine **1**.

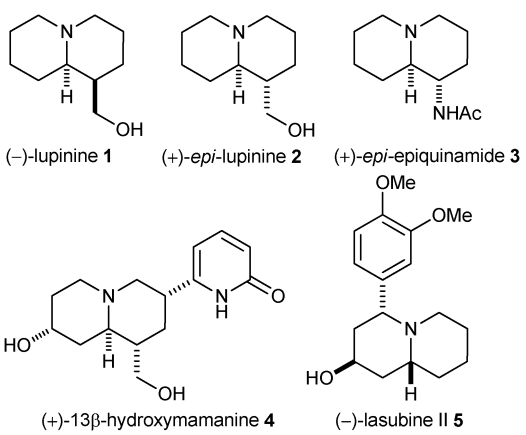

Fig. 1 The structures of quinolizidine alkaloids **1–5**.

Our strategy for the synthesis of the quinolizidine scaffold involved either (i) alkylation of an enantiopure β-amino ester such as **8** (which is readily available from our diastereoselective conjugate addition methodology upon reaction of the enantiopure lithium amide reagent **6** with a ζ-substituted α,β-unsaturated ester **7**),[11] followed by a double ring-closure of **9** in which both benzylic *N*-protecting groups are also lost during the one-pot tandem cyclisation process (*i.e.*, route A, Fig. 2);[12] or (ii) sequential ring-closure/concomitant *N*-debenzylation of **8** to give piperidine **11**, followed by alkylation of **11** to give **12**, and ring-closure/concomitant *N*-debenzylation of **12** to give quinolizidine **10** (*i.e.*, route B, Fig. 2); subsequent reduction of the ester moiety within **10** would then give (−)-lupinine **1** (Fig. 2). This methodology may then be adapted for the asymmetric synthesis of other azabicyclic alkaloids by changing the structure of either the α,β-unsaturated ester or electrophile used for enolate alkylation, which would then provide access to other ring systems such as pyrrolizidines and indolizidines.

ζ-Hydroxy-α,β-unsaturated ester **15** was prepared in a one-pot DIBAL-H/Wadsworth–Emmons reaction from δ-valerolactone **13** which gave the known ζ-hydroxy substituted α,β-unsaturated ester **15**[8c,13] in 71% yield as a single diastereoisomer (>99 : 1 dr). Treatment of **15** with CCl_4, PPh_3 and Et_3N in MeCN at reflux gave the known ζ-chloro substituted α,β-unsaturated ester **16**[8c,14] in 70% yield and >99 : 1 dr. Diagnostic ^{1}H NMR ^3J coupling constants of 15.7 Hz were observed between the C(2)*H* and C(3)*H* protons within both **15** and **16** which allowed the assigned (*E*)-configurations within these substrates to be confirmed. Conjugate addition of lithium (*R*)-*N*-(*p*-methoxybenzyl)-*N*-(α-methyl-*p*-methoxybenzyl)amide (*R*)-**17** to

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† This article is part of the Royal Society of Chemistry web theme issue commemorating the 65th birthday of Professor Richard J. K. Taylor.

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c4cc02135e

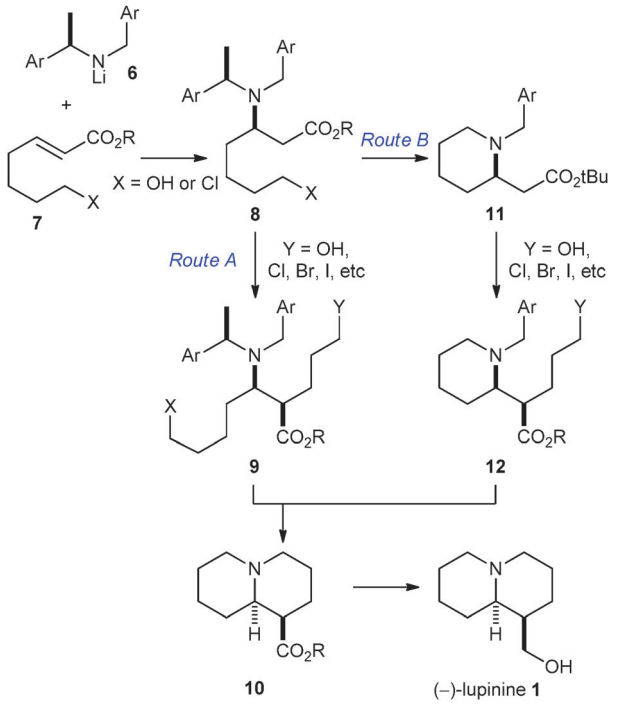
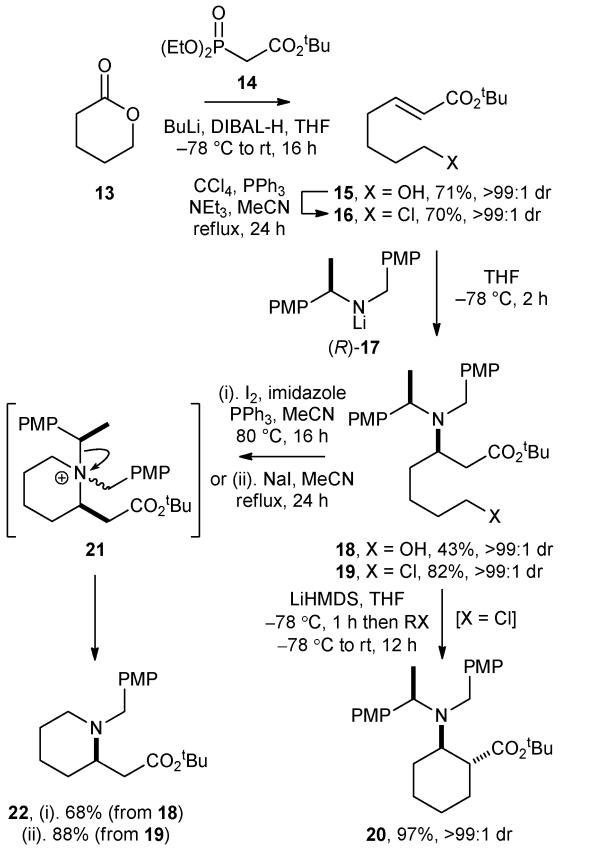


Fig. 2 Synthetic strategy towards (–)-lupinine **1**. [Ar = Ph, *p*-methoxyphenyl, *etc.*]

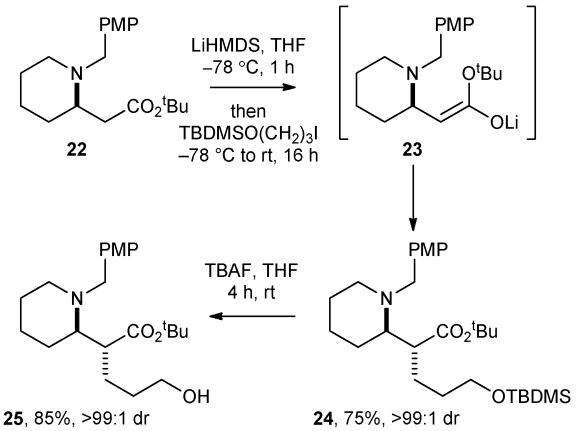


Scheme 1 [PMP = *p*-methoxyphenyl].

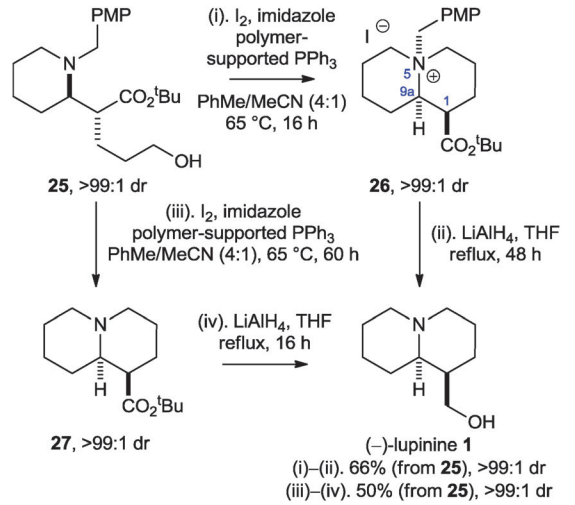
15 and **16** [using either 2.6 or 1.6 equiv. of lithium amide (*R*)-**17**, respectively], proceeded to give the corresponding β-amino esters **18** and **19** as single diastereoisomers (>99:1 dr) which were isolated in 43 and 82% yield after purification by flash column chromatography. The stereochemical outcomes of these reactions were assigned by reference to our transition state mnemonic[15] and by analogy to the well-established outcome of this diastereoselective conjugate addition protocol.[11] Unfortunately, treatment of the intermediate lithium (*Z*)-β-amino enolates[16] derived from conjugate addition of (*R*)-**17** to both **15** and **16** with a range of electrophiles (*i.e.*, a tandem conjugate addition/alkylation process) resulted in either poor reaction conversion or the formation of complex mixtures of unidentifiable products. In addition, attempted alkylation of **19** (X = Cl) upon treatment with LiHMDS and a range of electrophiles (*i.e.*, following a stepwise conjugate addition/alkylation process) was found to promote cyclisation of the intermediate lithium (*E*)-β-amino enolate[16] onto the pendant ζ-chloro functionality to give *tert*-butyl 2-amino-cyclohexane-1-carboxylate **20** in 97% yield and >99:1 dr. Since both the tandem and stepwise alkylation procedures were not successful, it was resolved to explore the conversion of β-amino esters **18** and **19** to the corresponding piperidine **22** and subsequently examine its diastereoselective alkylations. Appel reaction of ζ-hydroxy substituted β-amino ester **18** upon treatment with I_2, imidazole and PPh_3 in MeCN at 80 °C for 16 h gave piperidine **22** in 68% yield. However, **22** was obtained in a superior yield *via* treatment of ζ-chloro substituted β-amino ester **19** with NaI in MeCN (*i.e.*, under Finkelstein conditions) at reflux for 24 h which gave **22** in 88% yield; in both cases, 4-methoxystyrene was also isolated in 40–53% yield as a result of *in situ* E1-type deprotection of the *N*-(α-methyl-*p*-methoxybenzyl) group from the intermediate quaternary ammonium species **21**, which results from cyclisation of the amino group onto the *in situ* formed ζ-iodo moiety (Scheme 1).

Piperidine **22** was then alkylated (under optimised conditions) upon deprotonation with 5.0 equiv. of LiHMDS followed by reaction of the resultant lithium (*E*)-β-amino enolate[16] **23** with 7.0 equiv. of 1-iodo-3-(*tert*-butyldimethylsilyloxy)propane, which gave **24** as a single diastereoisomer (>99:1 dr) in 75% isolated yield after chromatographic purification. The relative configuration within **24** was initially assigned by analogy to the stereochemical outcomes observed upon alkylation of analogous substrates,[8c,17] and was later confirmed by chemical correlation. *O*-Deprotection of **24** upon treatment with TBAF gave alcohol **25** in 85% yield and >99:1 dr (Scheme 2).

Subsequent Appel reaction of alcohol **25** upon treatment with I_2, imidazole and polymer-supported PPh_3 in a mixture of PhMe/MeCN (4:1) at 65 °C promoted cyclisation to give quaternary ammonium salt **26** as a single diastereoisomer (>99:1 dr); the configuration at the N(5) atom was tentatively assigned from the diagnostic values of the ^{1}H NMR ^3J coupling constants for the C(1)*H* proton ($^3J_{1,2}$ = 12.9, 3.8 Hz; $^3J_{1,9a}$ = 3.8 Hz). Subsequent treatment of ammonium species **26** with $LiAlH_4$ effected both reduction of the ester moiety and removal of the *N*-(*p*-methoxybenzyl) group to give (–)-lupinine **1** which was isolated in 66% yield (from **25**) and >99:1 dr after chromatographic purification. However, it was found that Appel reaction of **25** under identical conditions, but for an increased reaction time (60 h), gave quantitative conversion to quinolizidine



Scheme 2 [PMP = *p*-methoxyphenyl].



Scheme 3 [PMP = *p*-methoxyphenyl].

27 which was immediately treated with $LiAlH_4$ to give (−)-lupinine **1** in 50% yield (from **25**) and >99 : 1 dr (Scheme 3). The spectroscopic data,[18] and specific rotation, for our samples of (−)-lupinine **1** were in excellent agreement with literature values[12,19] $[\alpha]_D^{20}$ − 12.0 (*c* 0.4 in EtOH); lit.[12] for *ent*-**1** $[\alpha]_D^{30}$ + 12.7 (*c* 0.35 in EtOH), thereby confirming the assigned configurations within intermediates **24–27**.

In conclusion, a concise and efficient asymmetric synthesis of (−)-lupinine has been developed. The key steps in this synthesis involved the preparation of an enantiopure β-amino ester, upon conjugate addition of a lithium amide reagent to a ζ-substituted α,β-unsaturated ester, followed by ring-closure. Concomitant *N*-debenzylation, *via* an E1-type deprotection step, was also observed during the cyclisation which gave the corresponding piperidine in good yield. Subsequent alkylation of this enantiopure piperidine scaffold, followed by a second ring-closure/concomitant *N*-debenzylation step formed the quinolizidine motif. Finally, reduction with $LiAlH_4$ then gave (−)-lupinine in 8 steps from commercially available starting materials. The application of this methodology in the synthesis of other azabicyclic ring systems is currently under investigation within our laboratories.

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18 Spectroscopic data for (−)-lupinine **1**: ν_{max} (ATR) 3323 (O–H), 2933, 2857, 2807, 2763 (C–H); δ_H (400 MHz, C_6D_6) 0.94–1.06 (1H, m, C(8)H_A), 1.15–1.25 (2H, m, C(1)*H*, C(9)H_A), 1.25–1.44 (4H, m, C(2)H_A, C(3)H_A, C(7)H_2), 1.49–1.58 (2H, m, C(6)H_A, C(8)H_B), 1.63–1.80 (4H, m, C(2)H_B, C(4)H_A, C(9)H_B, C(9a)*H*), 2.23–2.37 (1H, m, C(3)H_B), 2.44–2.56 (2H, m, C(4)H_B, C(6)H_B), 3.75 (1H, app d, *J* 10.7, CH_AH$_B$OH), 4.18 (1H, dd, *J* 10.7, 4.8, CH$_A$$H_B$OH); δ_H (400 MHz, $CDCl_3$) 1.21–1.34 (1H, m, CH_2), 1.49–1.64 (6H, m, C(1)*H*, CH_2), 1.71–1.91 (4H, m, CH_2), 1.98–2.08 (1H, m, CH_2), 2.10–2.23 (2H, m, C(9a)*H*, CH_2), 2.79–2.88 (2H, m, C(4)H_A, C(6)H_A), 3.70 (1H, d, *J* 10.8, CH_AH$_B$OH), 4.17 (1H, ddd, *J* 10.8, 4.6, 1.2, CH$_A$$H_B$OH); δ_C (100 MHz, C_6D_6) 23.3 (*C*(3)), 25.0 (*C*(8)), 25.9 (*C*(7)), 29.9 (*C*(9)), 31.6 (*C*(2)), 38.9 (*C*(1)), 57.3 (*C*(6)), 57.4 (*C*(4)), 65.2 (*C*(9a)), 65.7 (*C*H$_2$OH); *m*/*z* (ESI$^+$) 170 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{20}NO^+$ ([M+H]$^+$) requires 170.1539; found 170.1541.
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