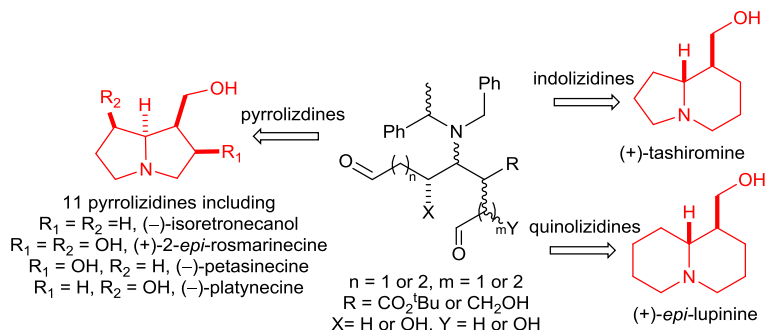


Asymmetric Synthesis of Pyrrolizidines, Indolizidines and Quinolizidines via a Double Reductive Cyclisation Protocol

Stephen G. Davies^{*a}Ai M. Fletcher^aPaul M. Roberts^aJames E. Thomson^a^a Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK.

steve.davies@chem.ox.ac.uk

Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday.

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Abstract This account describes an overview of the asymmetric syntheses of pyrrolizidines, indolizidines and quinolizidines via a common double reductive cyclisation protocol. The highly diastereoselective conjugate addition of an enantiopure lithium amide to an α,β -unsaturated ester incorporating a terminal C=C bond installed the nitrogen bearing stereogenic centre and was followed by alkenylation of the corresponding enolate to introduce the second olefinic functionality. Alternatively, conjugate addition to the corresponding α -alkenyl α,β -unsaturated ester followed by α -protonation of the intermediate enolate may also be used to access the cyclisation precursor. After oxidation of the two terminal olefinic units to give the corresponding dialdehyde, tandem hydrogenolysis/hydrogenation was employed to efficiently construct the azabicyclic core of each target molecule. This double reductive cyclisation strategy was successfully utilized in the syntheses of 13 azabicyclic alkaloids or closely related analogues.

Key words Asymmetric synthesis, pyrrolizidine, indolizidine, quinolizidine, conjugate addition, lithium amide, reductive cyclisation

1. Introduction

Azabicycles with two fused aliphatic rings, whose endocyclic nitrogen atom is placed in a bridgehead position, can be classified depending on the ring sizes; pyrrolizidines **1** (i.e., [3.3.0]-azabicycles), indolizidines **2** (i.e., [3.4.0]-azabicycles) and quinolizidines **3** (i.e., [4.4.0]-azabicycles) are the three most common classes. These structural motifs are commonly occurring within natural products, which display various biological activities. For example, (+)-pochonicine **4**¹ exhibits GlcAc-ase inhibitory activity, (-)-steviamine **5**² is known to display potent glycosidase inhibition, and (-)-swainsonine **6**³ shows *anti*- α -mannosidase activity.⁴ In 2003, (+)-epiquinamide **7** was first reported as an agonist for the acetylcholine receptor, thus has been of interest as a potential nicotinic receptor agonist (Figure 1).⁵

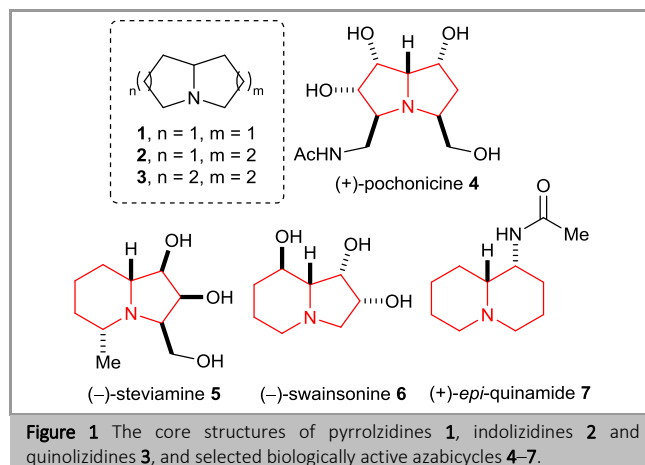


Figure 1 The core structures of pyrrolizidines **1**, indolizidines **2** and quinolizidines **3**, and selected biologically active azabicycles **4–7**.

1-Hydroxymethyl substituted pyrrolizidines, indolizidines and quinolizidines are sub-classes of the corresponding azabicyclic compounds, several of which are known in Nature. For example, all four stereoisomers of 1-hydroxymethylpyrrolizidines have been isolated from natural sources and named as (-)-trachelanthamidine **8**,⁶ (+)-laburnine *ent*-**8**,⁷ (-)-isoretronecanol **9**,⁸ and (+)-lindelofidine *ent*-**9**.⁹ Some plants containing 1-hydroxymethylpyrrolizidines are poisonous to livestock,¹⁰ and (-)-isoretronecanol **9** was reported to possess stimulant actions in the guinea-pig ileum preparation.¹¹ Numerous analogous alkaloids of the 1-hydroxymethylpyrrolizidines have been isolated and some of their biological activities have been evaluated: for example, (-)-madhumidine **A 10** displays weak cytotoxicity against cancer cell lines A549, PC-3 and MCF-7, and also inhibits NO production.¹² 1-Hydroxymethyl substituted azabicyclic natural products with other ring sizes (i.e., indolizidines or quinolizidines) have also been reported, for example (+)-tashiromine **11**,¹³ (-)-lupinine **12**¹⁴ and (+)-epi-lupinine **13**

display *in vitro* inhibitory activity against leukaemia.¹⁵ In addition, several polyhydroxylated 1-hydroxymethyl pyrrolizidines have been isolated from natural sources:¹⁶ for example, (–)-hastanecine **14**,¹⁷ (–)-turnefordine **15**,¹⁸ (–)-platynecine **16**,¹⁹ (–)-petasinecine **17**,²⁰ (–)-macronecine **18**²¹ and (–)-rosmarinecine **19**.²² However, limited data are known concerning their biological activity (Figure 2).

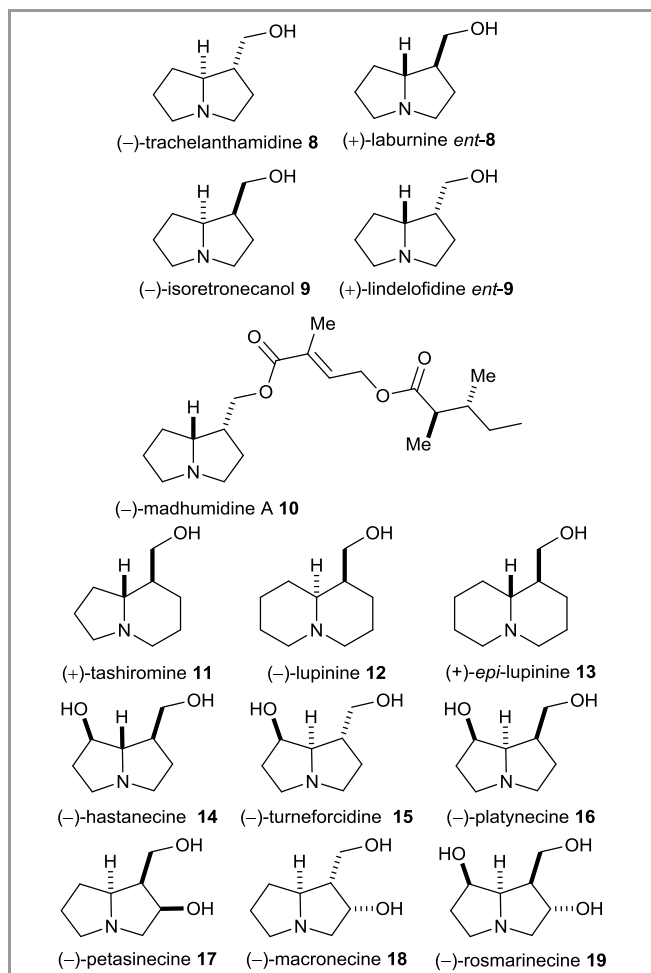


Figure 2 Naturally occurring 1-hydroxymethyl substituted pyrrolizidines, indolizidines and quinolizidines.

These classes of azabicyclic scaffolds have attracted considerable attention as synthetic targets in organic synthesis. The majority of the synthetic approaches involve stepwise formation of the two rings,²³ although some have constructed both rings in one synthetic operation.²⁴ We envisaged that the rapid construction of azabicyclic scaffolds, such as pyrrolizidines, indolizidines and quinolizidines, could be developed via a common double reductive cyclisation approach upon tandem hydrogenolysis/hydrogenation of a tertiary amino dialdehyde substrate such as **24**.²⁵ The aldehyde functionalities could be revealed upon olefinic oxidation of the corresponding dienes **23**, and these precursors can be prepared by diastereoselective lithium amide conjugate addition²⁶ of enantiopure lithium *N*-benzyl-*N*-(α -methylbenzyl)amide (*R*)-**21** or (*S*)-**21** to an α,β -unsaturated ester **20**, followed by enolate alkylation with an alkenyl halide **22**. This account will describe a summary of our asymmetric syntheses of pyrrolizidines, indolizidines and quinolizidines

using this double reductive cyclisation strategy as the key ring-forming step (Figure 3).

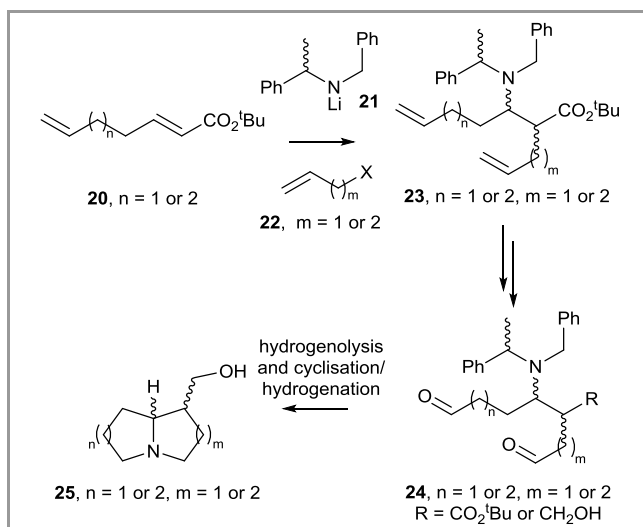
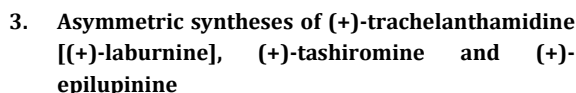


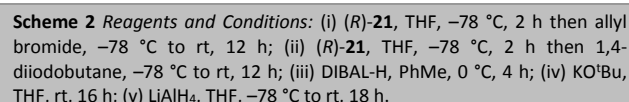
Figure 3 Formation of azabicyclic compounds via a double reductive cyclisation strategy.

2. Asymmetric syntheses of (–)-isoretronecanol and (–)-trachelanthamidine

Our first endeavours in this area culminated in methodology for the formation of pyrrolizidines via a double reductive cyclisation of the corresponding dialdehydes derived from *tert*-butyl 7-aminocyclohept-3-ene-1-carboxylates **28** and **29**.²⁷ The substrates were prepared via conjugate addition of (*S*)-**21** to α,β -unsaturated ester **26** followed by alkylation of the resultant lithium (*Z*)- β -amino enolate²⁸ with allyl bromide, which gave β -amino ester **27** in 60% yield and 85:15 dr. Diastereomerically pure **28** was subsequently isolated in 43% yield after ring-closing metathesis using Grubbs I catalyst. While epimerisation at the C(2)-position within **27** upon treatment with base was not possible, treatment of **28** (>99:1 dr) with KO^tBu gave C(1)-epimer **29** in 80% yield and >99:1 dr. A superior overall yield of **29** was obtained without purification of the intermediate **28**, after which **29** was isolated in 70% yield (from **27**). Using our chemoselective epoxidation methodology,²⁹ amine **29** was protonated first with HBF_4 to protect the nitrogen lone pair from oxidation, followed by treatment with *m*-CPBA. Hydrogen bond directed epoxidation of **29** occurred on the same face as the ammonium group followed by *in situ* acid-mediated ring-opening/lactonisation to give **30**. Treatment of **30** with LiAlH_4 gave triol **31** in 80% yield (from **29**) and >99:1 dr. Oxidative cleavage of the diol unit within **31** with NaIO_4 gave dialdehyde **32**, and subsequent hydrogenolysis and *in situ* cyclisation/reduction, followed by purification on DOWEX ion exchange resin, gave (–)-isoretronecanol **9** $\{[\alpha]_{\text{D}}^{20} -70.5$ (*c* 1.0 in EtOH)} in 65% yield and >99:1 dr. The epimeric cyclic β -amino ester **28** was reacted via the same sequence of reactions to give (–)-trachelanthamidine **8** $\{[\alpha]_{\text{D}}^{20} -13.0$ (*c* 0.2 in EtOH)} in 40% overall yield (from **28**) and >99:1 dr (Scheme 1).

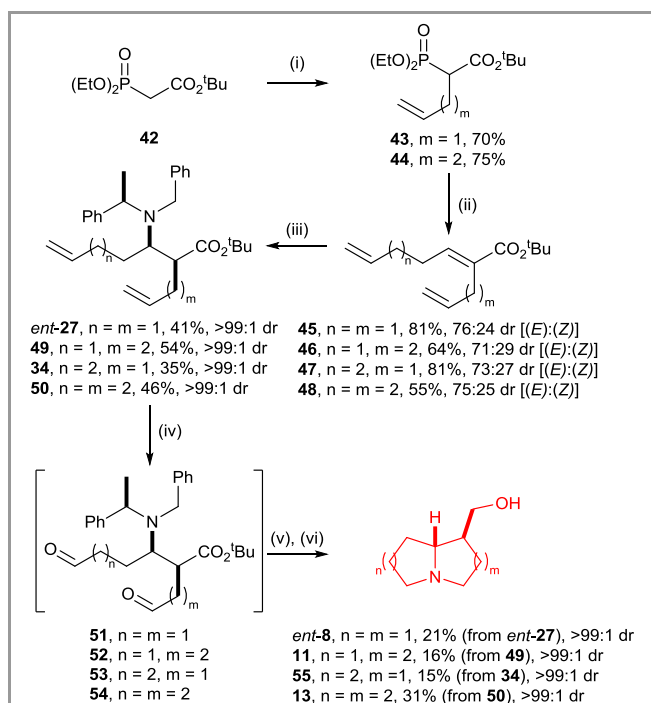


after exhaustive chromatographic purification. Analogous alkylation of the lithium (*Z*)- β -amino enolates resulting from conjugate addition of (*R*)-**21** to either **26** (*n* = 1) or **33** (*n* = 2) with but-3-enyl bromide failed. However, conjugate addition of lithium amide (*R*)-**21** to α,β -unsaturated ester **26** (*n* = 1) followed by alkylation of the intermediate enolate with 1,4-diiodobutane afforded a 60:40 partially separable mixture of C(2)-epimers, from which **35** was isolated in 36% yield and >99:1 dr. Similarly, conjugate addition of lithium amide (*R*)-**21** to **33** (*n* = 2) followed by alkylation with 1,4-diiodobutane gave a 63:37 mixture of C(2)-epimers from which **36** was isolated in 18% yield and 89:11 dr. Chemoselective reduction of both **35** (*n* = 1, >99:1 dr) and **36** (*n* = 2, 89:11 dr) with DIBAL-H in PhMe gave alcohols **37** (>99:1 dr) and **38** (89:11 dr) in 72 and 86% yield, respectively. Subsequent treatment of **37** and **38** with KO^tBu gave **39** in 56% yield and >99:1 dr, and **41** in 33% yield and 95:5 dr, respectively. In addition, α -allyl- β -amino ester **34** (>99:1 dr) was reduced with LiAlH₄ to give the corresponding alcohol **40** in 48% yield and >99:1 dr (Scheme 2).



Unfortunately, cyclisation precursors **39–41** were obtained in low overall yields after exhaustive chromatographic purification, and ring-closing metathesis to give the corresponding 8- and 9-membered rings (in order to enrich the diastereoisomeric purity upon epimerisation) was not possible for these substrates. Therefore, an alternative, more selective, and higher yielding synthetic approach was investigated via diastereoselective conjugate addition of (*R*)-**21** to α -alkenyl

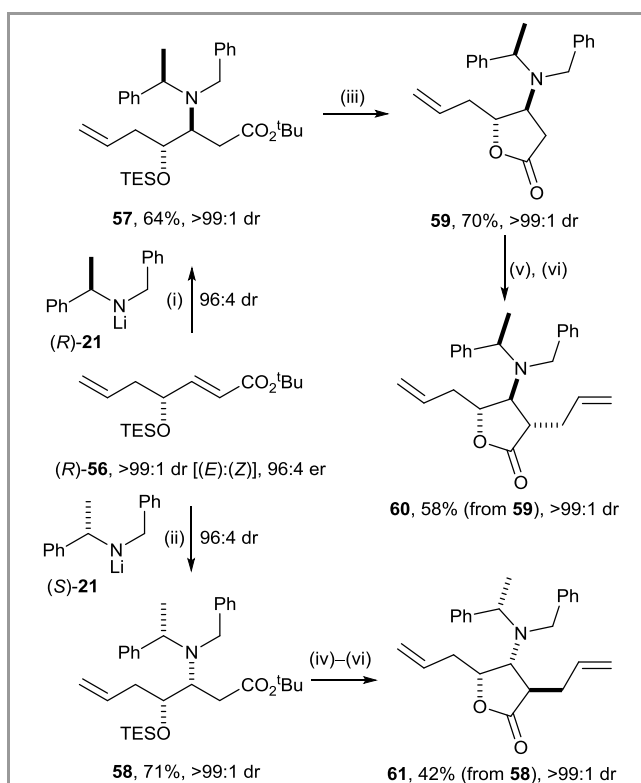
substituted α,β -unsaturated esters **45–48**, followed by diastereoselective protonation of the resultant enolates. Treatment of **42** with NaH followed by addition of either allyl bromide or but-3-enyl bromide gave **43** ($m = 1$) and **44** ($m = 2$) in 70 and 75% yield, respectively. Our modified Wadsworth-Emmons protocol³¹ was employed for olefination of either 4-pentenal ($n = 1$) or 5-hexenal ($n = 2$) upon treatment with either **43** or **44** and MeMgBr, which gave α -alkenyl- α,β -unsaturated esters **45–48** in good yield and moderately high (*E*):(*Z*) ratios (>70:30 dr). Under the optimised conditions,³² the conjugate addition of (*R*)-**21** to **45–48** and subsequent addition of 2,6-di-*tert*-butyl phenol gave α -alkenyl- β -amino esters *ent*-**27**, **49**, **34** and **50** as single diastereoisomers (>99:1 dr) in 35–54% yield. Various attempts at the ozonolysis of these substrates (as the corresponding hydrochloride salts) were found to be problematic. However, dialdehydes **51–54** were obtained upon treatment of *ent*-**27**, **49**, **34** and **50** with OsO₄ and NaIO₄ in the presence of 2,6-lutidine.³³ The tandem hydrogenolytic *N*-debenzylation/double reductive cyclisation of dialdehydes **51–54** was followed by reduction of the resultant azabicyclic esters with LiAlH₄ to give the corresponding hydroxymethyl substituted azabicyclic targets. Purification of the crude reaction mixtures gave (+)-trachelanthamidine [(+)-laburnine] *ent*-**8** {[α]_D²⁵ +15.9 (*c* 1.0 in EtOH)}, (+)-tashiromine **11** {[α]_D²⁵ +39.0 (*c* 0.2 in EtOH)}, (1*S*,8*aR*)-1-(hydroxymethyl)octahydroindolizine **55** {[α]_D²⁵ +39.8 (*c* 0.5 in EtOH)} and (+)-*epi*-lupinine **13** {[α]_D²⁵ +29.1 (*c* 0.3 in EtOH)} as single diastereoisomers (>99:1 dr) in each case (Scheme 3).



Scheme 3 Reagents and Conditions: (i) NaH, THF, rt, 1 h then allyl bromide or but-3-enyl bromide, 70 °C, 36 h; (ii) MeMgBr, THF, rt, 15 min then 4-pentenal ($n = 1$) or 5-hexenal ($n = 2$), 70 °C, 3 h; (iii) (*R*)-**21**, PhMe, –78 °C, 1 h then –30 °C, 2 h then THF, –78 °C, 30 min then 2,6-di-*tert*-butylphenol, –78 °C to rt, 30 min; (iv) OsO₄, NaIO₄, 2,6-lutidine, 1,4-dioxane/H₂O (3:1), rt, 40 min; (v) H₂ (5 atm), Pd(OH)₂/C, MeOH, rt, 120 h; (vi) LiAlH₄, THF, –78 °C to rt, 2 h.

4. Asymmetric syntheses of (–)-hastanecine, (–)-turneforcidine and (–)-platynecine

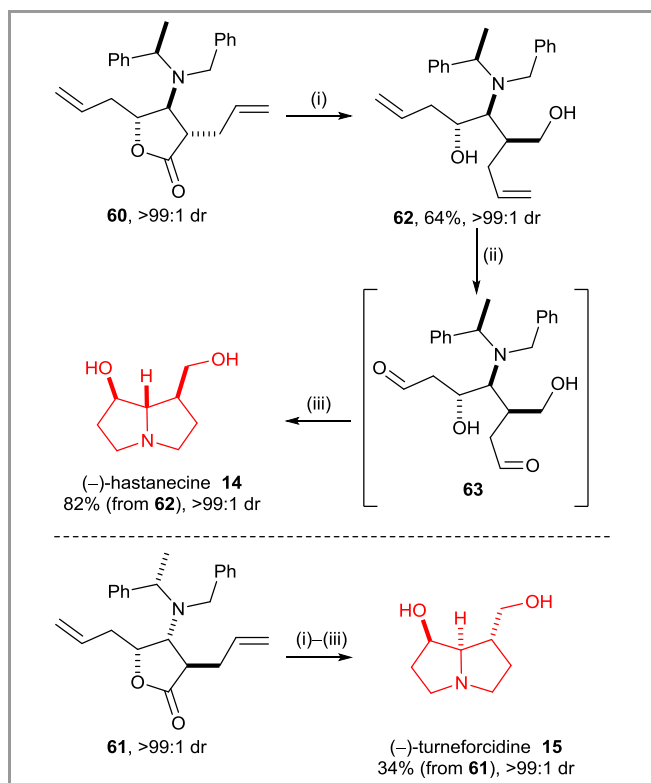
Double reductive cyclisation was next employed in the synthesis of hydroxylated pyrrolizidines starting from enantiopure (*R*)-**56** (96:4 er),³⁴ which was prepared from commercially available 2,2-dimethoxyacetaldehyde using known enantioselective allylation conditions.³⁵ Conjugate addition of (*R*)-**21** to α,β -unsaturated ester (*R*)-**56** (96:4 er) gave **57** in 64% yield and >99:1 dr, while conjugate addition of (*S*)-**21** to (*R*)-**56** (96:4 er) gave **58** in 71% yield and >99:1 dr after purification. In both cases, the reactions were completely diastereoselective under the (totally) dominant control of the lithium amide reagent. Treatment of β -amino ester **57** with TBAF promoted *O*-desilylation and *in situ* lactonisation to give exclusively **59** in 70% yield and >99:1 dr. Treatment of lactone **59** with LDA and allyl bromide gave **60** (76:24 dr) initially and subsequent treatment of **60** (76:24 dr) with KO^tBu gave **60** in 58% yield (from **59**) as a single diastereoisomer. Identical treatment of β -amino ester **58** gave **61** in 42% yield (from **58**) and >99:1 dr (Scheme 4).



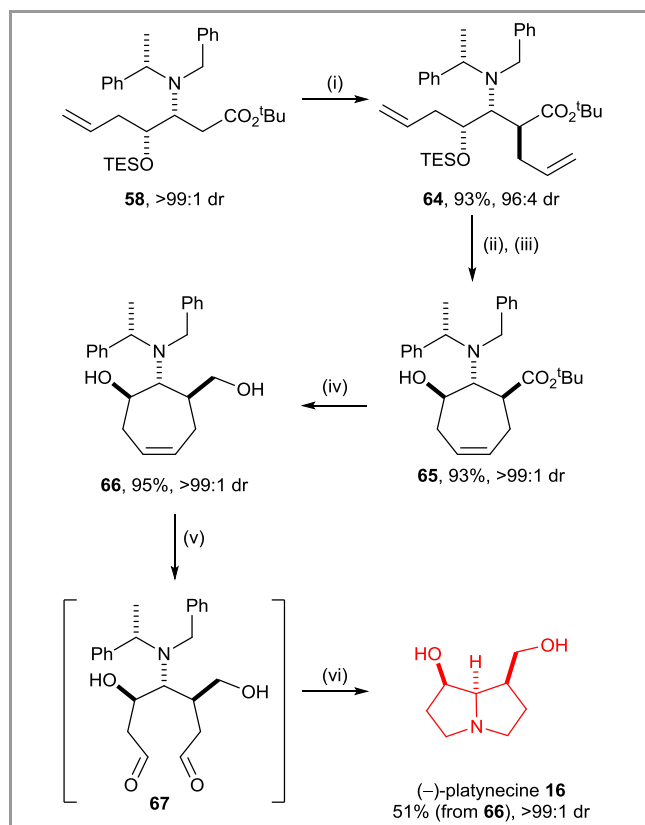
Scheme 4 Reagents and Conditions: (i) (*R*)-**21**, THF, –78 °C, 2 h; (ii) (*S*)-**21**, THF, –78 °C, 2 h; (iii) TBAF, THF, rt, 16 h; (iv) TBAF, THF, rt, 48 h; (v) LDA, THF, 0 °C, 1 h then allyl bromide, 0 °C to rt, 2 h; (vi) KO^tBu, THF, rt, 18 h.

Reduction of **60** with LiAlH₄ gave diol **62** in 64% yield and >99:1 dr. Treatment of **62**·HCl with ozone followed by addition of polymer-bound PPh₃ gave the corresponding dialdehyde **63**, and subsequent hydrogenolytic removal of the *N*-protecting groups facilitated *in situ* double reductive cyclisation. Purification of the crude reaction mixture on DOWEX ion exchange resin gave (–)-hastanecine **14** {[α]_D²⁰ –8.3 (*c* 0.9 in EtOH)} in 82% yield (from **62**) and >99:1 dr. Reaction of **61** via the same sequence of transformations gave (–)-turneforcidine

15 {[α]_D²⁰ -10.0 (*c* 0.8 in MeOH)} in 34% yield (from **61**) and >99:1 dr (Scheme 5).



Allylation of the lithium β-amino enolate derived from deprotonation of β-amino ester **58** with LDA gave **64** in 93% yield and 96:4 dr.³⁶ Ring-closing metathesis of **64** in the presence of Grubbs I catalyst followed by *O*-TES deprotection with HF·pyridine gave **65** in 93% yield and >99:1 dr. Subsequent reduction of **65** with LiAlH₄ gave diol **66** in 95% yield and >99:1 dr. Ozonolysis of the corresponding hydrochloride salt **66**·HCl followed by hydrogenolysis/double reductive cyclisation of the corresponding dialdehyde **67** gave (-)-platynecine **16** {[α]_D²⁰ -58.8 (*c* 0.9 in EtOH)} in 51% yield (from **66**) and >99:1 dr (Scheme 6).

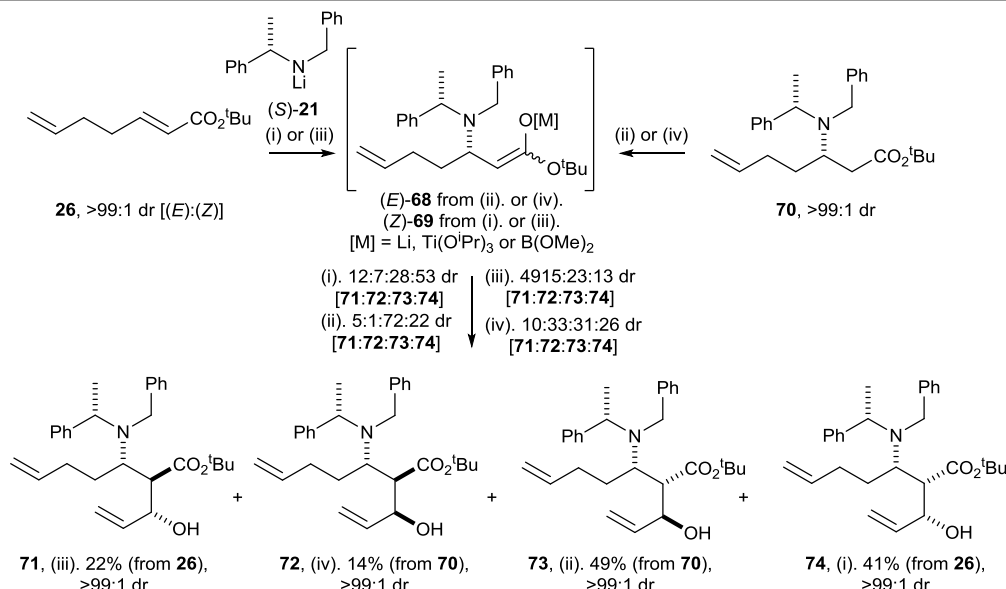


5. Asymmetric syntheses of (-)-macronecine, (-)-petasinecine, (-)-1-*epi*-macronecine, (+)-1-*epi*-petasinecine and (+)-2-*epi*-rosmarinecine

This double reductive cyclisation approach has also been employed in the synthesis of 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines. Conjugate addition of (*S*)-**21** to α,β-unsaturated ester **26** followed by reaction with acrolein, either following a one-pot or stepwise approach,³⁷ introduces the extra hydroxyl group at the C(2)-position of the pyrrolizidine scaffold. Reaction of a diastereoisomerically pure enolate [either derived from conjugate addition of (*S*)-**21** to α,β-unsaturated ester **26**, or from deprotonation of β-amino ester **70**] with acrolein creates two further stereogenic centres, and therefore four diastereoisomeric products are possible. By tuning the reaction conditions, we have managed to produce all four possible diastereoisomeric products **71–74** in moderate yields. For example, conjugate addition of (*S*)-**21** to α,β-unsaturated ester **26** followed by addition of acrolein to the corresponding lithium (*Z*)-β-amino enolate (*Z*)-**69** gave a 12:7:28:53 mixture of **71**, **72**, **73** and **74**, respectively, from which **74** was isolated in 41% yield and >99:1 dr. The alternative 'stepwise' protocol, whereby deprotonation of β-amino ester **70** with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) followed by reaction of the resultant lithium (*E*)-β-amino enolate²⁸ (*E*)-**68** with acrolein gave a 5:1:72:22 mixture of **71**, **72**, **73** and **74**, respectively, from which **73** was isolated in 49% yield and >99:1 dr. The optimised conditions for the isolation of **71** involved transmetalation of the corresponding lithium (*Z*)-β-amino enolate (*Z*)-**69** [which was derived from

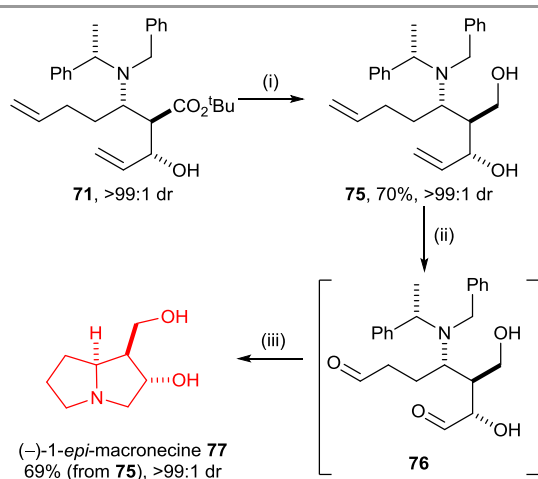
conjugate addition of (*S*)-**21** to α,β -unsaturated ester **26**] upon addition of $\text{TiCl}(\text{O}^i\text{Pr})_3$, followed by treatment with acrolein, which gave a 49:15:23:13 mixture of **71**, **72**, **73** and **74**, respectively, from which **71** was isolated in 22% yield and >99:1 dr. The optimised conditions for the formation of **72** involved treatment of lithium (*E*)- β -amino enolate (*E*)-**68**

(which was generated upon deprotonation of β -amino ester **70** with LDA) with $\text{B}(\text{OMe})_3$, followed by the addition of acrolein to give a 10:33:31:26 mixture of **71**, **72**, **73** and **74**, respectively, from which **72** was isolated as a single diastereoisomer (>99:1 dr) in 14% yield (Scheme 7).



Scheme 7 Reagents and Conditions: (i) THF, -78°C , 2 h then acrolein, -78°C to 0°C , 3 h; (ii) LiTMP, THF, 0°C , 1 h then acrolein, -78°C to 0°C , 3 h; (iii) THF, -78°C , 2 h then $\text{TiCl}(\text{O}^i\text{Pr})_3$, -78°C , 1 h then acrolein, -78°C to 0°C , 3 h; (iv) LDA, THF, 0°C , 2 h then $\text{B}(\text{OMe})_3$, -78°C , 1 h then acrolein, -78°C to 0°C , 3 h.

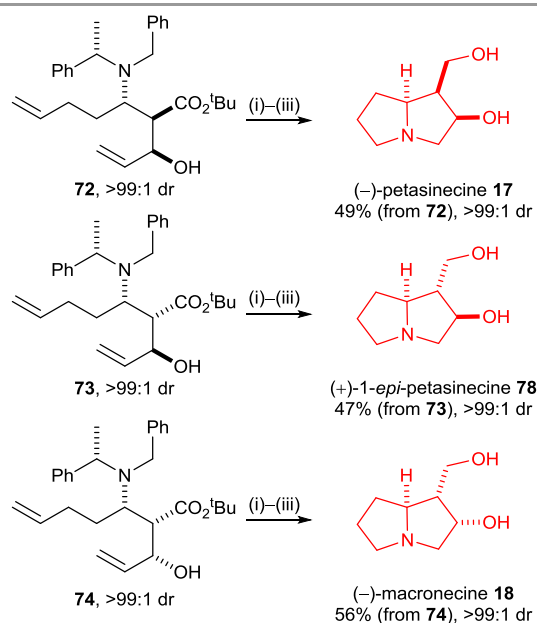
Reduction of β -amino ester **71** with LiAlH_4 gave aminodiol **75** in 70% yield and >99:1 dr. Treatment of **75**·HCl with O_3 followed by the addition of polymer supported PPh_3 gave the corresponding dialdehyde **76**, and subsequent hydrogenolytic removal of the *N*-protecting groups facilitated *in situ* double reductive cyclisation to give (–)-1-*epi*-macronecine **77** $\{[\alpha]_{\text{D}}^{20} -96.0$ (*c* 0.1 in EtOH) $\}$ in 69% isolated yield (from **75**) and >99:1 dr after purification (Scheme 8).



Scheme 8 Reagents and Conditions: (i) LiAlH_4 , THF, -78°C to rt, 16 h; (ii) HCl (2.0 M in Et₂O), rt then O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1), -78°C , 10 min then polymer supported PPh_3 , rt, 3 h; (iii) H_2 (5 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH/AcOH (10:1), rt, 48 h.

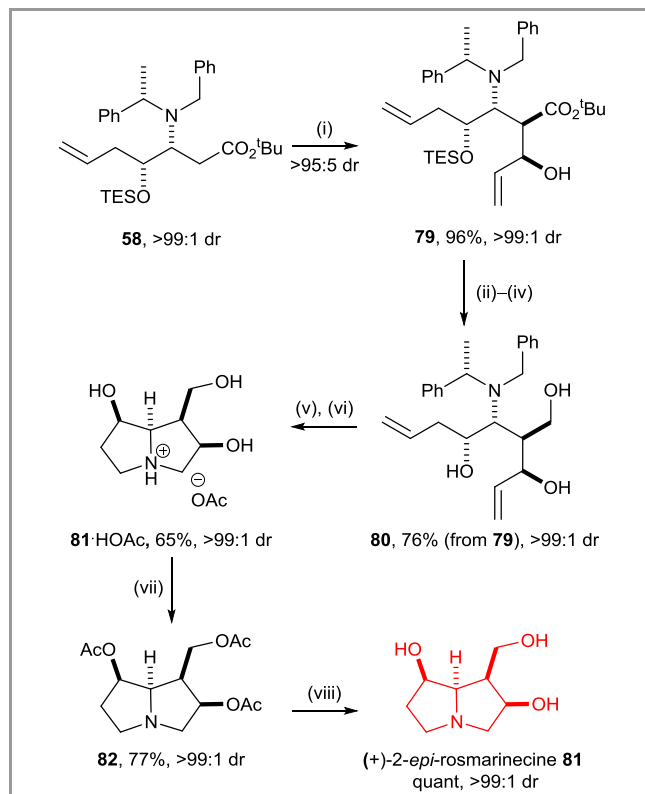
This three step protocol was also applied to β -amino esters **72–74**, which gave, after purification on DOWEX ion exchange

resin, (–)-petasinecine **17** $\{[\alpha]_{\text{D}}^{20} -26.0$ (*c* 0.8 in EtOH) $\}$, (+)-1-*epi*-petasinecine **78** $\{[\alpha]_{\text{D}}^{20} +30.0$ (*c* 0.8 in EtOH) $\}$, and (–)-macronecine **18** $\{[\alpha]_{\text{D}}^{20} -40.0$ (*c* 0.6 in EtOH) $\}$, respectively, as a single diastereoisomer (>99:1 dr) in 47–56% yield over 3 steps (Scheme 9).



Scheme 9 Reagents and Conditions: (i) LiAlH_4 , THF, -78°C to rt, 16 h; (ii) HCl (2.0 M in Et₂O), rt then O_3 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:1), -78°C , 10 min then polymer supported PPh_3 , rt, 3 h; (iii) H_2 (5 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH/AcOH (10:1), rt, 48 h.

Finally, the more densely hydroxylated pyrrolizidine (+)-2-*epi*-rosmarinecine **81** was prepared from enantiopure γ -silyloxy- β -amino ester **58**. Treatment of **58** with LiTMP followed by the addition of acrolein gave only one diastereoisomeric product in this case. Chromatographic purification of the crude reaction mixture afforded **79** in 96% yield and >99:1 dr. Hydrolysis of **79** under acidic conditions gave the corresponding carboxylic acid, which was sequentially treated with LiAlH₄ and HF in pyridine to give triol **80** in 76% yield (from **79**) and >99:1 dr. Ozonolysis of **80**·HCl followed by hydrogenolytic *N*-deprotection and *in situ* double reductive cyclisation gave **81**·HOAc which was isolated in 65% yield and >99:1 dr. In order to facilitate the purification of (+)-2-*epi*-rosmarinecine **81**, the crude sample of **81**·HOAc was first treated with Ac₂O in pyridine to give **82** in 77% isolated yield, and subsequent global deprotection of all three acetyl groups within **82** upon treatment with K₂CO₃ in MeOH gave (+)-2-*epi*-rosmarinecine **81** {[α]_D²⁰ +18.3 (*c* 0.37 in EtOH)} in quantitative yield and >99:1 dr (Scheme 10).



Scheme 10 Reagents and Conditions: (i) LiTMP, THF, 0 °C, 1 h then acrolein, –78 °C to 0 °C, 3 h; (ii) CF₃CO₂H, CH₂Cl₂, 16 h, rt; (iii) LiAlH₄, THF, 0 °C then 70 °C, 16 h; (iv) HF·pyridine, THF, rt, 18 h; (v) HCl (2.0 M in Et₂O), rt then O₃, CH₂Cl₂/MeOH (1:1), –78 °C, 10 min then polymer supported PPh₃, rt, 3 h; (vi) H₂ (5 atm), Pd(OH)₂/C, MeOH/AcOH (10:1), rt, 48 h; (vii) Ac₂O, pyridine, DMAP, rt, 16 h; (viii) K₂CO₃, MeOH, rt, 16 h.

6. Conclusion

In conclusion, a protocol for the double reductive cyclisation of enantiopure amines bearing two pendant aldehyde functionalities proved to be an efficient and general method for the rapid construction of pyrrolizines, indolizidines and quinolizidines, including polyhydroxylated analogues. The key cyclisation precursors **85** were prepared via the diastereoselective conjugate addition of the requisite antipode of enantiopure lithium amide reagent **21** to either an α,β -unsaturated ester **83** (*n* = 1 or 2, X = H or TES) or an α -alkenyl α,β -unsaturated ester **84** (*n* = 1 or 2, *m* = 1 or 2) as the stereodefining step. Following oxidative cleavage of the olefinic units, the double reductive cyclisation was achieved in a single operation upon hydrogenolysis of the *N*-benzyl groups followed by *in situ* cyclisation and hydrogenation to form both rings within the pyrrolizidine, indolizidine or quinolizidine target scaffolds. This protocol was successfully applied in the asymmetric syntheses of 13 naturally occurring azabicyclic alkaloids and their analogues in good yield (Figure 4).

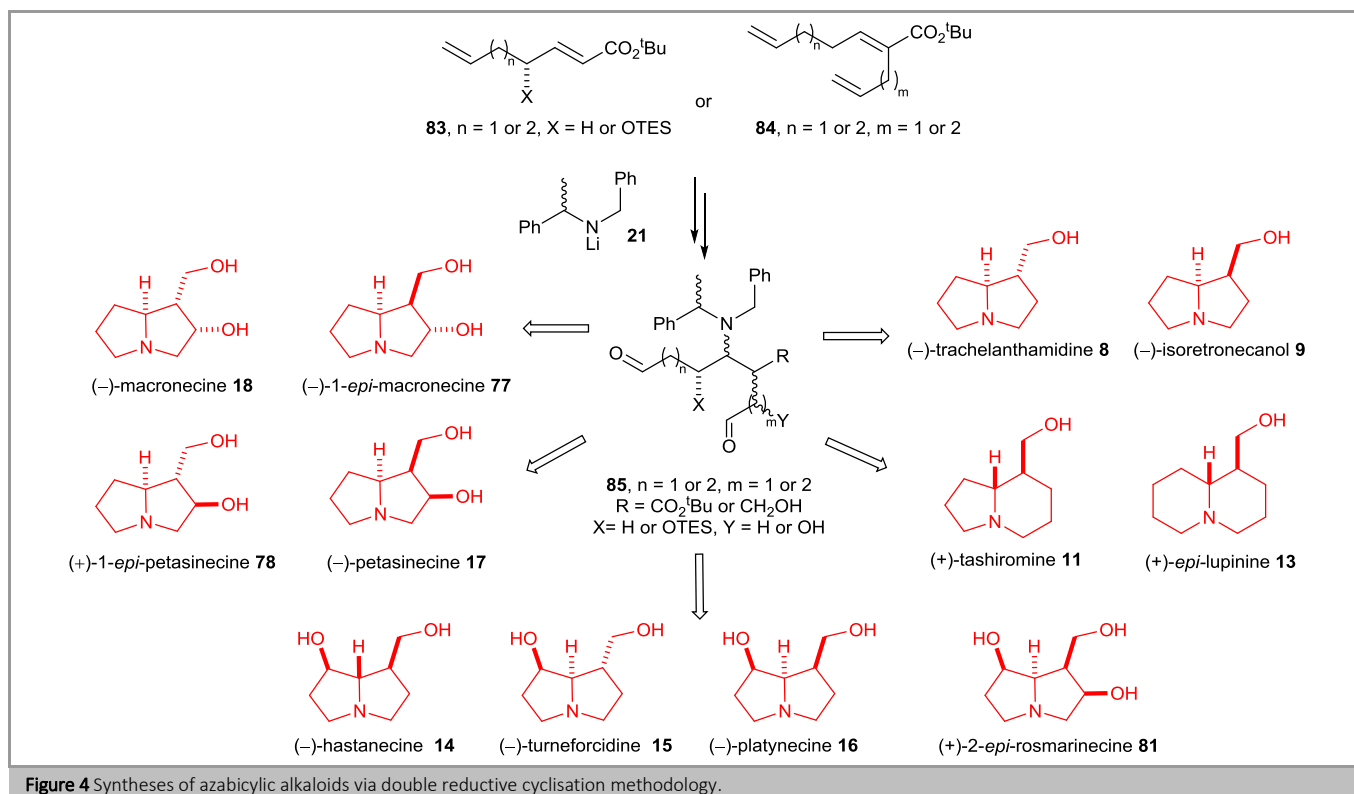



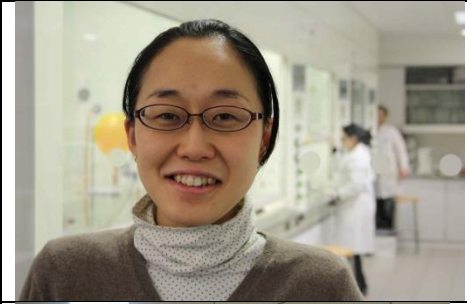

Figure 4 Syntheses of azabicyclic alkaloids via double reductive cyclisation methodology.

References

- Usaki, H.; Toyo-oka, M.; Kanzaki, H.; Okuda, T.; Nitoda, T. *Bioorg. Med. Chem.* **2009**, *17*, 7248.
- Hu, X.-G.; Bartholomew, B.; Nash, R. J.; Wilson, F. X.; Fleet, G. W. J.; Nakagawa, S.; Kato, A.; Jia, Y.-M.; van Well, R.; Yu, C.-Y. *Org. Lett.* **2010**, *12*, 2562.
- Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257.
- Dorling, P. R.; Colegate, S. M.; Huxtable, C. R. *Toxicon* **1983**, *21*, 93.
- Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345.
- Trachelanthamidine was originally named trachelantamidine; see: Men'shikov, G. P.; Borodina, G. M. *Zh. Obshch. Khim.* **1945**, *15*, 225.
- Galinovsky, F.; Goldberger, H.; Pohm, M. *Monatsh. Chem.* **1949**, *80*, 550.
- Men'shikov, G. P.; Kuzovkov, A. D. *Zh. Obshch. Khim.* **1949**, *19*, 1702.
- Labenskii, A. S.; Men'shikov, G. P. *Zh. Obshch. Khim.* **1948**, *18*, 1836.
- For example, see: Belakhdar, G.; Benjouad, A.; Kessabi, M.; Abdennebi, E. H. *J. Mater. Environ. Sci.* **2014**, *3*, 811.
- Pomeroy, A. R.; Paper, C. *Eur. J. Pharm.* **1971**, *14*, 374.
- Hoang, L. S.; Tran, M. H.; Lee, J. S.; To, D. C.; Nguyen, V. T.; Kim, J. A.; Lee, J. H.; Woo, M. H.; Min, B. S. *Chem. Pharm. Bull.* **2015**, *63*, 481.
- Ohimiya, S.; Kubo, H.; Otomasu, H.; Saito, K.; Murakoshi, I. *Heterocycles* **1990**, *30*, 537.
- Sadykov, A.; Lazur'evskii, G. *Zh. Obshch. Khim.* **1943**, *13*, 319.
- (a) Winterfeld, K.; Holschneider, F. W. *Chem. Ber.* **1931**, *64*, 137. (b) Beck, A. B.; Goldspink, B. H.; Knox, J. R. *J. Nat. Prod.* **1979**, *42*, 385.
- For a review, see: Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2014**, *25*, 387.
- Konovalov, V. S.; Men'shikov, G. P. *Zh. Obshch. Khim.* **1945**, *15*, 328.
- Men'shikov, G. P.; Denisova, S. O.; Massagetov, P. S. *Zh. Obshch. Khim.* **1952**, *22*, 1465.
- For example, see: (a) Konovalova, R. A.; Orekhov, A. P. *Bull. Soc. Chim. Fr.* **1937**, *4*, 2037. (b) Culvenor, C. C. J.; Kobetskaya, N. O.; Smith, L. W.; Utkin, L. M. *Aust. J. Chem.* **1968**, *21*, 1671. (c) Asada, Y.; Furuya, T. *Chem. Pharm. Bull.* **1984**, *32*, 475.
- Yamada, K.; Tatamatsu, H.; Unno, R.; Hirata, Y. *Tetrahedron Lett.* **1978**, *46*, 4543. (b) Haberer, W.; Dobler, S. *Chemoecology* **1999**, *9*, 169.
- Danilova, A.; Utkin, L.; Massagetov, P. *Zh. Obshch. Khim.* **1955**, *25*, 831.
- De Waal, H. L. *Nature* **1940**, *140*, 777.
- We have recently reported asymmetric syntheses of azabicyclic targets via stepwise ring-forming protocols; see: (a) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T. T.; Roberts, P. M.; Schofield, T. M.; Thomson, J. E. *Chem. Commun.* **2014**, *50*, 8309. (b) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Houlsby, I. T. T.; Roberts, P. M.; Schofield, T. M.; Thomson, J. E. *Org. Biomol. Chem.* **2014**, *12*, 9223. (c) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975. (d) Davies, S. G.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567.
- For representative examples, see: (a) Cutter, A. C.; Miller, I. R.; Keily, J. F.; Bellingham, R. K.; Light, M. E.; Brown, R. C. D. *Org. Lett.* **2011**, *13*, 3988. (b) Janowitz, A.; Vavrecka, M.; Hesse, M. *Helv. Chim. Acta* **1991**, *74*, 1352. (c) Vavrecka, M.; Janowitz, A.; Hesse, M. *Tetrahedron Lett.* **1991**, *32*, 5543. (d) O'Connell, K. M.; Diaz-Gavilan, M.; Galloway, W. R. J. D.; Spring, D. R. *Beilstein J. Org. Chem.* **2012**, *8*, 850. (e) Airiau, E.; Spangenberg, T.; Girard, N.; Breit, B.; Mann, A. *Org. Lett.* **2010**, *12*, 528. (f) Gradnig, G.; Grassberger, B. V.; Stütz, A. E. *Tetrahedron Lett.* **1991**, *32*, 4889. (g) Kiss, L.; Forró, E.; Fülöp, F. *Beilstein J. Org. Chem.* **2015**, *11*, 596. (h) Barthelme, A.; Richards, D.; Mellor, I. R.; Stockman, R. A. *Chem. Commun.* **2013**, *49*, 10507. (i) Jones, T. H.; Hight, R. J.; Don, A. W.; Blum, M. S. *J. Org. Chem.* **1986**, *51*, 2712. (j) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, *65*, 3222.

- (25) We have previously reported the asymmetric synthesis of some 3,4-dihydroxyhomoproline from the corresponding D-pentoses using *N*-debenzylation followed by *in situ* reductive cyclisation to form the pyrrolidine scaffold; see: Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8680.
- (26) For reviews, see: (a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833. (b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.
- (27) Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 204.
- (28) (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129. (b) Davies, S. G.; Foster, E. M.; McIntosh, C. R.; Roberts, P. M.; Rosser, T. E.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2011**, *22*, 1035.
- (29) (a) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751. (b) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762. (c) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Kurosawa, W.; Lee, J. A.; Fletcher, A. M.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, *74*, 6735. (d) Brennan, M. B.; Claridge, T. D. W.; Compton, R. G.; Davies, S. G.; Fletcher, A. M.; Henstridge, M. C.; Hewings, D. S.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Schoonen, A. K.; Thomson, J. E. *J. Org. Chem.* **2012**, *77*, 7241. (e) Brennan, M. B.; Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Aust. J. Chem.* **2015**, *68*, 610. (f) Brennan, M.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Green, W. D.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *J. Org. Chem.* **2015**, *80*, 6609.
- (30) Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2016**, *72*, 7417.
- (31) Claridge, T. D. W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.
- (32) Davies, S. G.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1141.
- (33) Wensheng, Y.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.
- (34) Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2016**, *72*, 4523.
- (35) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (b) Keck, G. E.; Welch, D. S.; Vivian, P. K. *Org. Lett.* **2006**, *8*, 3667. (c) Stambouli, A.; Amouroux, M.; Chastrette, M. *Tetrahedron Lett.* **1987**, *28*, 5301.
- (36) The analogous treatment of β -amino ester **57** with LDA followed by allyl bromide gave only returned **57**.
- (37) Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2016**, *72*, 7449.

Biosketches

	<p>Steve Davies is the fifth Waynflete Professor of Chemistry at the University of Oxford. He has been the recipient of numerous prizes, including the following Royal Society of Chemistry awards: Hickinbottom Fellowship, Corday Morgan Medal and Prize, Award for Organometallic Chemistry, Bader Award, Tilden Lectureship, Award for Stereochemistry, and Perkin Prize for Organic Chemistry. He has published more than 500 papers and has research interests ranging from organometallic chemistry, asymmetric synthesis and natural product chemistry to medicinal chemistry and drug discovery. In 2014, he was elected Dr Honoris Causa, University of Salamanca (Spain).</p>
	<p>Ai Fletcher obtained a B. En. from Keio University, Japan, then moved to the U.K. where she pursued a Ph.D. at Imperial College London under supervision of Professor Chris Braddock. Since completing her Ph.D. in 2004, she has explored a range of chemistry as a post-doctoral researcher at the University of Regensburg (Professor Oliver Reiser), and at the University of Bath (Professor Michael Willis), she joined the group of Professor Steve Davies in Oxford in 2007, where she has been involved with the development of asymmetric synthetic methodology and its application to the total synthesis of natural products.</p>
	<p>Paul Roberts graduated with an M.Chem. from Jesus College, Oxford, in 2000, which was followed by a D.Phil. with Professor Steve Davies in the area of the asymmetric synthesis of piperidine alkaloids employing a ring closing metathesis approach. In 2005, he took up a post-doctoral position with Professor Davies at Oxford, where his research interests centre upon natural product synthesis and the development of new stereoselective methodologies, for example to effect the chemo- and stereoselective functionalisation of allylic amines with a range of electrophilic reagents.</p>



Jim Thomson studied chemistry at the University of Oxford where he gained an M.Chem. (2003) and then D.Phil. (2007), working with Professor Steve Davies in the area of β -amino acid organocatalysis. He then took up a post-doctoral position with Professor Davies, as a Junior Research Fellow, and in 2010 was appointed to a Research Fellowship in association with St. Catherine's College, Oxford. His research interests centre upon the development of novel asymmetric transformations and the total synthesis of natural products.