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Asymmetric syntheses of the 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines (−)-macronecine, (−)-petasinecine, (−)-1-*epi*-macronecine, (+)-1-*epi*-petasinecine and (+)-2-*epi*-rosmarinecine

Marta Brambilla, Stephen G. Davies, Ai M. Fletcher, Paul M. Roberts, James E. Thomson

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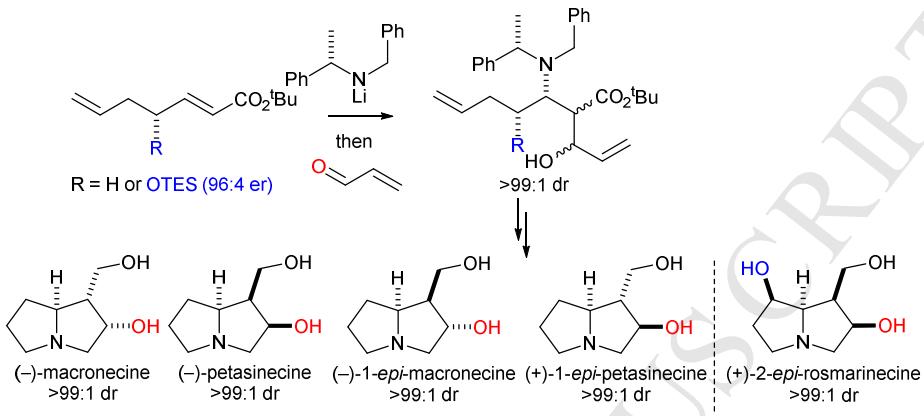
Marta Brambilla, Stephen G. Davies,* Ai M. Fletcher, Paul M. Roberts, James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K.

steve.davies@chem.ox.ac.uk



Asymmetric syntheses of the 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines (–)-macronecine, (–)-petasinecine, (–)-1-*epi*-macronecine, (+)-1-*epi*-petasinecine and (+)-2-*epi*-rosmarinecine

Marta Brambilla, Stephen G. Davies,* Ai M. Fletcher, Paul M. Roberts, James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road Oxford OX1 3TA, U.K.

Email: steve.davies@chem.ox.ac.uk

Abstract

The asymmetric syntheses of all four possible diastereoisomeric 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines, (–)-macronecine, (–)-petasinecine, (–)-1-*epi*-macronecine and (+)-1-*epi*-petasinecine, are reported. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl (*E*)-hepta-2,6-dienoate, followed by aldol reaction with acrolein under various conditions gave four possible diastereoisomeric β-amino esters with the required stereogenic centres installed. In each case, the pyrrolizidine scaffold was rapidly accessed by reduction of the ester moiety followed by a sequential two-step protocol involving ozonolysis and hydrogenolysis/double reductive cyclisation. Following this route, (–)-macronecine, (–)-petasinecine, (–)-1-*epi*-macronecine and (+)-1-*epi*-petasinecine were synthesised in 21, 14, 10 and 19% overall yield, respectively, in 6 steps or fewer from commercially available starting materials. An analogous strategy employing enantiopure *tert*-butyl (*R*,*E*)-4-(triethylsilyloxy)hepta-2,6-dienoate facilitated the asymmetric synthesis of (+)-2-*epi*-rosmarinecine in 21% overall yield and >99:1 dr, in 13 steps from commercially available starting materials.

Key words: (–)-macronecine, (–)-petasinecine, (–)-1-*epi*-macronecine, (+)-1-*epi*-petasinecine, (+)-2-*epi*-rosmarinecine, asymmetric synthesis, pyrrolizidines

Introduction

1-Hydroxymethyl-2-hydroxy substituted pyrrolizidines **1** and 1-hydroxymethyl-2,7-dihydroxy substituted pyrrolizidines **2** are sub-classes of the necine bases. To date, several alkaloids incorporating these pyrrolizidine motifs have been isolated and shown to display a range of different biological activities:[1] for example, (+)-petasinine **3**, which was isolated from the young flower stalks of *petasites japonicas Maxim.*,[2] has been shown to possess carcinogenicity;[2] its regioisomer hectorine **4** was isolated along with (+)-petasinine **3** from *Brachyglottis hectori*.[3] The related alkaloid (–)-petasinoside A **5** was isolated from the perennial plant *Senecio nemorensis L.*,[4] which has been used for treating influenza virus, enteritis and

pneumonia in Chinese medicine. The 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines, (–)-petasinecine **8** and (+)-macronecine **9** were obtained by hydrolysis of (–)-petasinine **3**[2,5] and macrophylline,[6] respectively. The 1-hydroxymethyl-2,7-dihydroxy substituted pyrrolizidines (–)-rosmarinecine **10** and (+)-croalbinecine (also known as helifolinecine)[7] **11** were obtained by hydrolysis of (–)-rosmarinine **6** (from *Senecio rosmarinifolius* and in *S. Hygrophilus*)[8] and (+)-croalbidine **7** (from *C. albida*),[9] respectively (Fig. 1). Total syntheses of these classes of 1-hydroxymethyl-2-hydroxy and 1-hydroxymethyl-2,7-dihydroxy substituted pyrrolizidines have attracted considerable interest from the synthetic community: the strategies employed include, for example, Ireland-Claisen type rearrangement of an L-proline derived precursor,[10] the zirconium-mediated ring-contraction of vinylmorpholine derivatives,[11] [4+2] cycloaddtion of nitroalkenes and enantiopure vinylethers,[12] and chiral pool manipulation from α-D-glucosamine.[13]

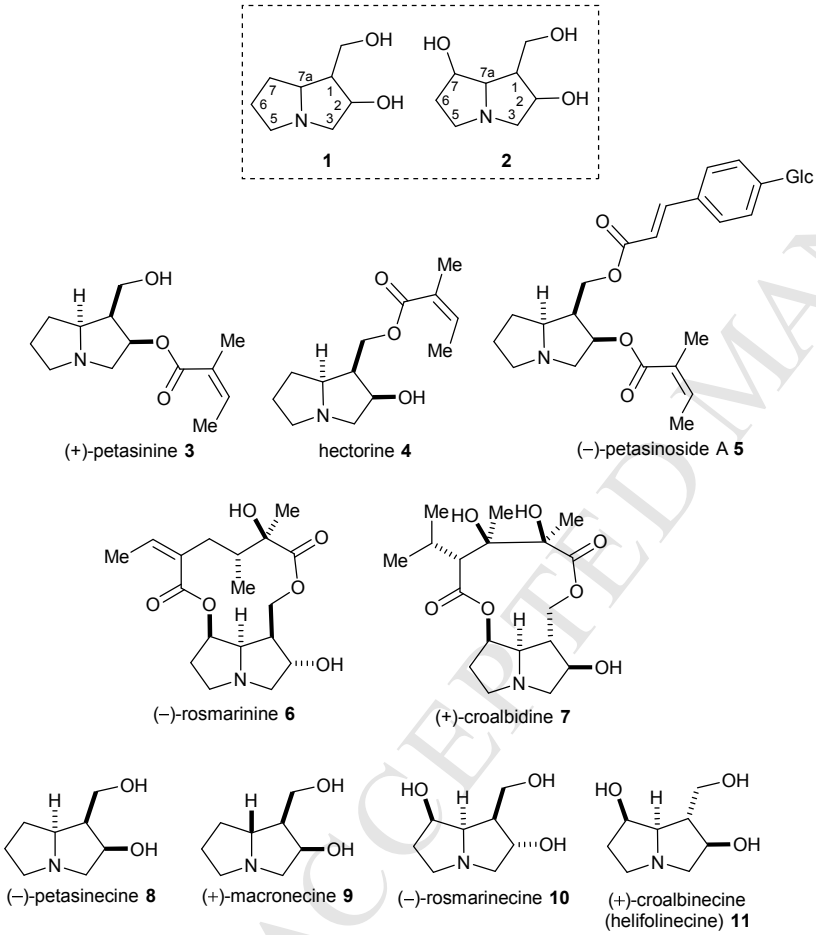
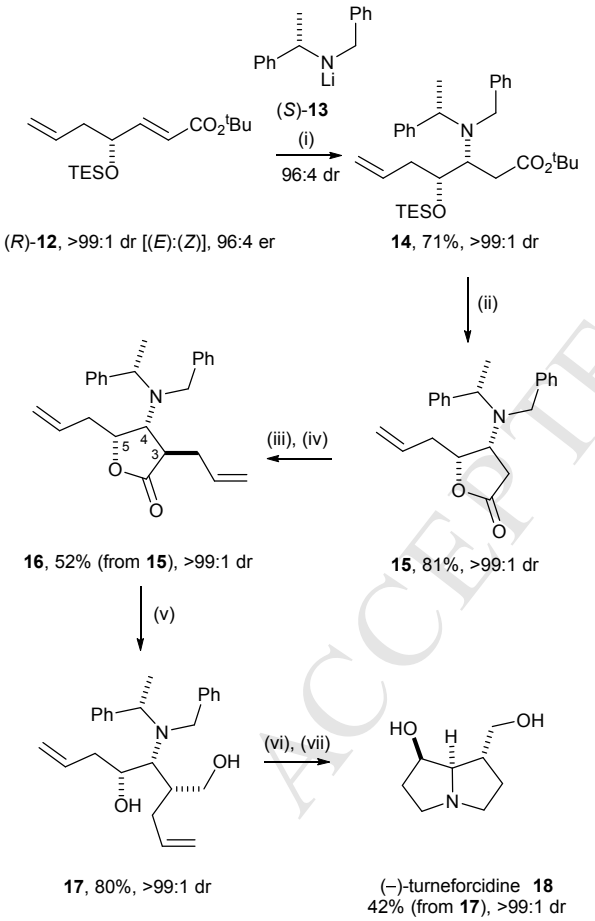


Fig. 1. 1-Hydroxymethyl-2-hydroxy substituted pyrrolizidines **3–11**. [Glc = β-D-glucopyranosyl].

As part of our ongoing research programme concerning the asymmetric synthesis of naturally occurring nitrogen containing compounds,[14] we became interested in developing methodology for the synthesis of 1-hydroxymethyl substituted pyrrolizidines. We have recently reported the asymmetric synthesis of three diastereomeric 1-hydroxymethyl-7-hydroxy substituted pyrrolizidines (–)-hastanecine, (–)-turneforcidine **18** and (–)-platynecine by employing the diastereoselective conjugate addition[15] of enantiopure lithium (*R*)- or (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **13** to α,β-unsaturated ester (*R*)-**12** (96:4 er) followed by enolate

allylation as the key steps.[16] For example, total asymmetric synthesis of (–)-turneforcidine **18** was achieved in 11 steps and 8% overall yield, in which the key steps were diastereoselecive conjugate addition of (*S*)-**13** to enanitopure (*R*)-**12** to give **14**, enolate alkylation of lactone **15** with LDA and allyl bromide, and ozonolysis of **17**·HCl followed by double reductive cyclisation to furnish (–)-turneforcidine **18** (Scheme 1). Having established efficient methodology to access 1-hydroxymethyl-7-hydroxy substituted pyrrolizidines,[16,17] we envisaged that 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines and even more densely functionalised 1-hydroxymethyl-2,7-dihydroxy substituted pyrrolizidines could also be accessed via the double reductive cyclisation of the corresponding bisaldehydes. These substrates would be prepared via our diastereoselective conjugate addition methodology[15] followed by diastereoselective aldol reaction with acrolein to install the required hydroxyl group followed by further functional group manipulation. Herein, we report the application of this strategy in asymmetric syntheses of the pyrrolizidines: (–)-macronecine *ent*-**9**, (–)-petasinecine **8**, (–)-1-*epi*-macronecine **28** [also known as (–)-7-deoxy-rosmarinecine],[13] (+)-1-*epi*-petasinecine **35** [also known as (+)-2-*epi*-macronecine][18] and (+)-2-*epi*-rosmarinecine **42**.

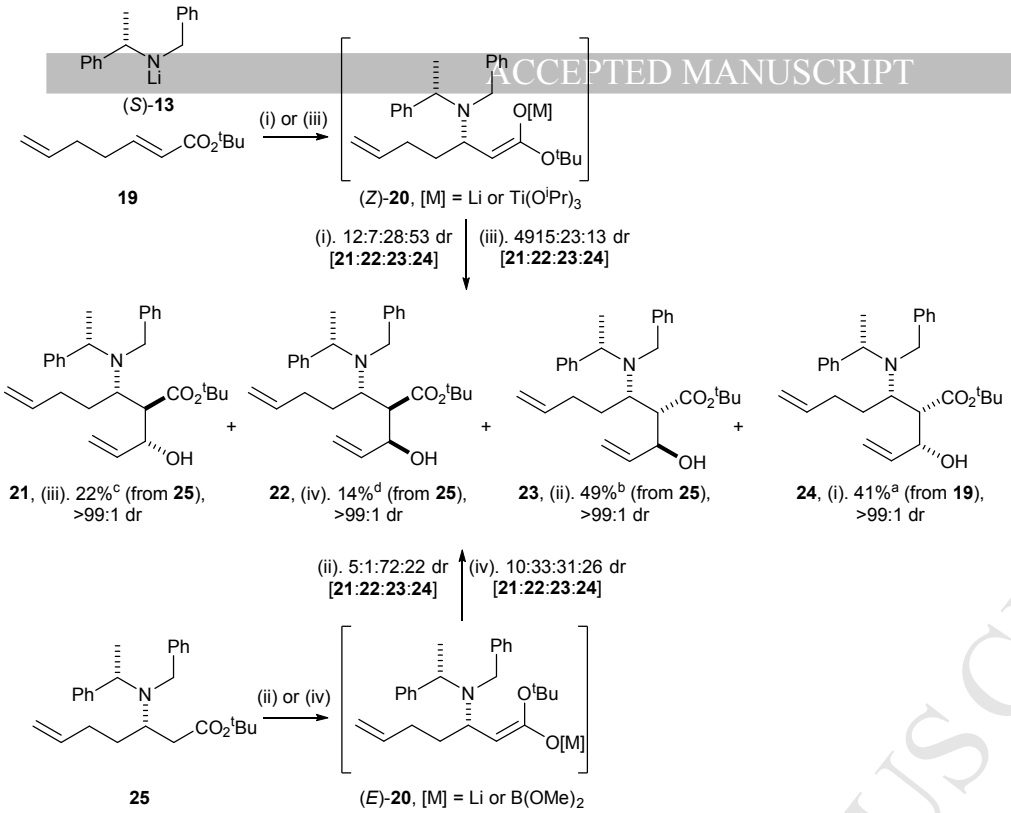


Scheme 1. *Reagents and Conditions*: (i) (*S*)-**13**, THF, –78 °C, 2 h; (ii) TBAF (1.0 M in THF), THF, rt, 48 h; (iii) LDA, THF, 0 °C, 1 h then allyl bromide, 0 °C to rt, 2 h; (iv) KO^{t}Bu, THF, rt, 18 h; (v) $LiAlH_4$, THF, 0 °C, 2 h; (vi) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 2 h; (vii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h.

2. Results and Discussion

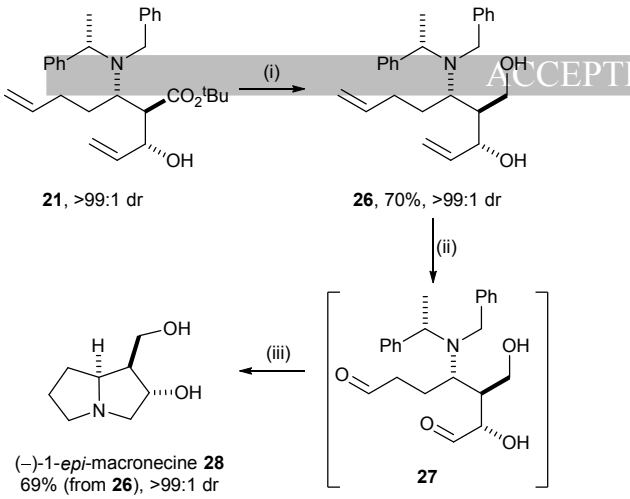
2.1. Asymmetric synthesis of 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines

The stereochemical outcomes of aldol reactions are known to be highly dependent on the geometry of the intermediate enolates and the reaction conditions, such as choice of metal counterion, solvent and temperature etc.[19,20] Thus, upon aldol reaction of β-amino enolates it was anticipated that selective formation of several of the possible diastereoisomers could be evaluated by tuning the reaction conditions via either (i) treatment of the intermediate lithium (*Z*)-β-amino enolate (*Z*)-**20**[21] arising from conjugate addition of the enantiopure lithium amide reagent (*S*)-**13** to α,β-unsaturated ester **19** with acrolein (i.e., a "tandem" approach), or (ii) deprotonation of the corresponding β-amino ester **25** [which can be readily accessed via conjugate addition of lithium amide (*S*)-**13** to α,β-unsaturated ester **19** and protonation of the intermediate enolate (*Z*)-**20**] followed by treatment of the resultant (*E*)-β-amino enolate (*E*)-**20**[21] with acrolein (i.e., a "stepwise" approach). The conjugate addition of (*S*)-**13** to α,β-unsaturated ester **19**[22] followed by the addition of acrolein to the corresponding lithium (*Z*)-β-amino enolate[21] (*Z*)-**20** gave a 12:7:28:53 mixture of **21**, **22**, **23** and **24**, respectively, from which **24** was isolated in 41% yield and >99:1 dr along with mixed fractions of **21**–**24** in an additional 38% total yield. The alternative "stepwise" protocol, whereby deprotonation of β-amino ester **25**[23] with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) followed by reaction of the resultant lithium (*E*)-β-amino enolate[21] (*E*)-**20** with acrolein gave a 5:1:72:22 mixture of **21**, **22**, **23** and **24**, respectively, from which **23** was isolated in 49% yield and >99:1 dr and along with mixed fractions of **21**–**24** in an additional 24% total yield. The relative and absolute configurations of **21**, **22**, **23** and **24** were established either by chemical correlation or single crystal X-ray diffraction analyses of their derivatives (*vide infra*). The selective formation of the remaining two diastereoisomers, **21** and **22** via transmetallation of the intermediate lithium enolates was also investigated. The optimised conditions for the isolation of **21** involved transmetallation of the corresponding lithium (*Z*)-β-amino enolate (*Z*)-**20** [which was derived from conjugate addition of (*S*)-**13** to α,β-unsaturated ester **19**] upon addition of $TiCl(O^iPr)_3$, followed by treatment with acrolein, which gave a 49:15:23:13 mixture of **21**, **22**, **23** and **24**, respectively, from which **21** was isolated in 22% yield and >99:1 dr and along with mixed fractions of **21**–**24** in an additional 48% total yield. Optimised conditions for the formation of **22** involved treatment of lithium (*E*)-β-amino enolate[24] (*E*)-**20** (which was generated from deprotonation of **25** with LDA) with $B(OMe)_3$,[25] followed by the addition of acrolein to give a 10:33:31:26 mixture of **21**, **22**, **23** and **24**, respectively, from which **22** was isolated as a single diastereoisomer (>99:1 dr) in 14% yield and along with mixed fractions of **21**–**24** in an additional 52% total yield (Scheme 2).



Scheme 2. *Reagents and Conditions*: (i) THF, −78 °C, 2 h then acrolein, −78 ° to 0 °C, 3 h; (ii) LiTMP, THF, 0 °C, 1 h then acrolein, −78 ° to 0 °C, 3 h; (iii) THF, −78 °C, 2 h then $TiCl(O^iPr)_3$, −78 °C, 1 h then acrolein, −78 to 0 °C, 3 h; (iv) LDA, THF, 0 °C, 2 h then $B(OMe)_3$, −78 °C, 1 h, then acrolein, −78 to 0 °C, 3 h. [[a] other fractions containing **21**–**24** were also isolated in 38% total yield; [b] other fractions containing **21**–**24** were also isolated in 24% total yield; [c] other fractions containing **21**–**24** were also isolated in 48% total yield; [d] other fractions containing **21**–**24** were also isolated in 52% total yield].

With four diastereoisomeric products **21**–**24** in hand, attention was turned to the syntheses of the corresponding 1-hydroxymethyl-2-hydroxypyrrolizidines. Reduction of β-amino ester **21** with $LiAlH_4$ gave aminodiol **26** in 70% yield and >99:1 dr. The relative configuration within **26** was confirmed by single crystal X-ray diffraction analysis[26] of the corresponding tetrafluoroboric acid salt **26**·HBF_4 and the absolute (1*S*,2*S*,1'*R*,α*S*)-configuration of **26** was assigned by reference to the known (*S*)-configuration of the α-methylbenzyl fragment (Fig. 2). This assignment also secured the configuration of the β-amino ester precursor **21**. To prevent *N*-oxidation in the subsequent ozonolysis step, **26** was converted into the corresponding hydrochloride salt **26**· HCl. Treatment of **26**· HCl with O_3 followed by the addition of polymer supported PPh_3 gave the corresponding dialdehyde **27**, and subsequent hydrogenolytic removal of the N-protecting groups facilitated in situ double reductive cyclisation onto both pendant aldehyde functionalities. Purification of the crude reaction mixture on DOWEX ion exchange resin gave (–)-1-*epi*-macronecine **28**[27] in 69% yield (from **26**) and >99:1 dr (Scheme 3). The melting point and specific rotation for this sample of **28** were in good agreement with literature data {mp 90–91 °C; lit.[28] mp 91–93 °C; $[\alpha]_D^{20}$ –96.0 (*c* 0.1 in EtOH); lit.[28] $[\alpha]_D^{25}$ –114 (*c* 0.9 in EtOH)}.



Scheme 3. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 16 h; (ii) HCl (2.0 M in Et_2O), rt then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 3 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h.

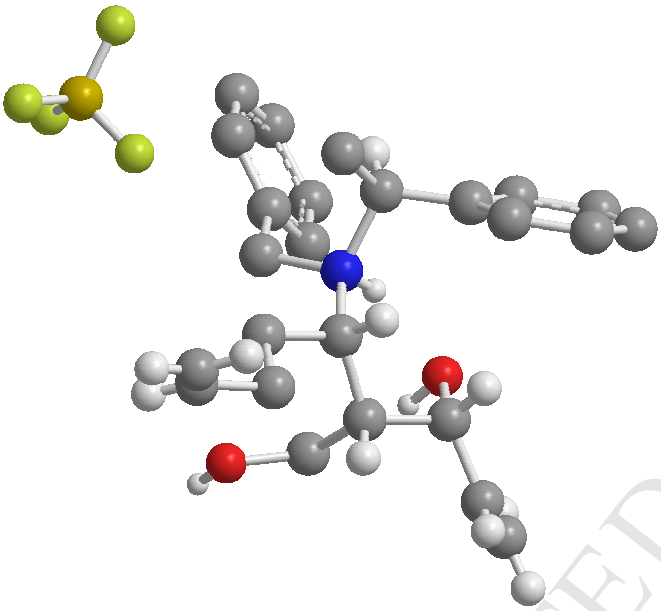
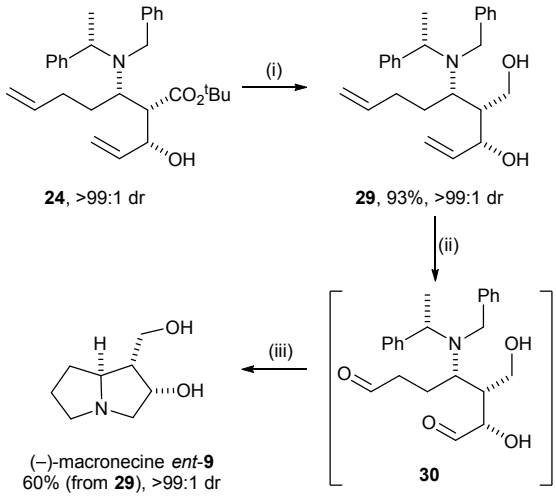


Fig. 2. X-Ray crystal structure of (1*S*,2*S*,1'*R*,α*S*)-**26**·HBF_4 (selected H atoms are omitted for clarity).

Similarly, the reduction of β-amino ester **24** with $LiAlH_4$ at –78 °C gave aminodiol **29** in 93% yield and >99:1 dr. Subsequent submission of **29**·HCl to the ozonolysis conditions gave dialdehyde **30**, and hydrogenolytic *N*-deprotection and in situ double reductive cyclisation gave (–)-macronecine *ent*-**9** in 60% yield and >99:1 dr after purification on DOWEX (50WX8) ion exchange resin (Scheme 4). The melting point and specific rotation for this sample of *ent*-**9** were in good agreement with literature data {mp 120–123 °C; lit.[11] mp 124–127 °C; lit.[29] mp 128–129 °C; lit.[6] mp 126–128 °C; $[\alpha]_D^{20}$ –40.0 (*c* 0.6 in EtOH); lit.[11] $[\alpha]_D^{20}$ –49.4 (*c* 1.0 in EtOH); lit.[30] $[\alpha]_D^{20}$ –42.1 (*c* 1.0 in EtOH); lit.[29] for **9**: $[\alpha]_D^{20}$ +42.7 (*c* 1.0 in EtOH); lit.[6] for **9** (from natural source): $[\alpha]_D^{20}$ +49.3 (*c* 0.5 in EtOH)}. Comparison of the ^1H and ^{13}C NMR spectroscopic data for this synthetic sample of (–)-macronecine *ent*-**9** also showed good agreement with data previously reported for both enantiomerically pure[29] and racemic[18,31] samples. Moreover, the relative configuration within **9** was confirmed by single crystal X-ray diffraction analysis[26] and the absolute (1*R*,2*S*,7a*S*)-configuration of *ent*-**9** was assigned by the reference to the known (*S*)-configuration of the C(7a) stereogenic

center generated upon conjugate addition of lithium amide (*S*)-**13** to unsaturated ester **19**[32] (Fig. 3). This assignment also unambiguously established the configurations of β-amino ester **24** and aminodiol **29**.



Scheme 4. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 16 h; (ii) HCl (2.0 M in Et_2O), rt then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 3 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 36 h.

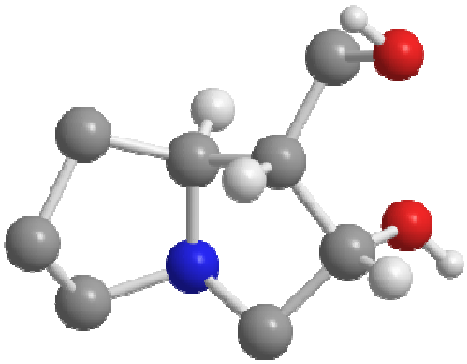
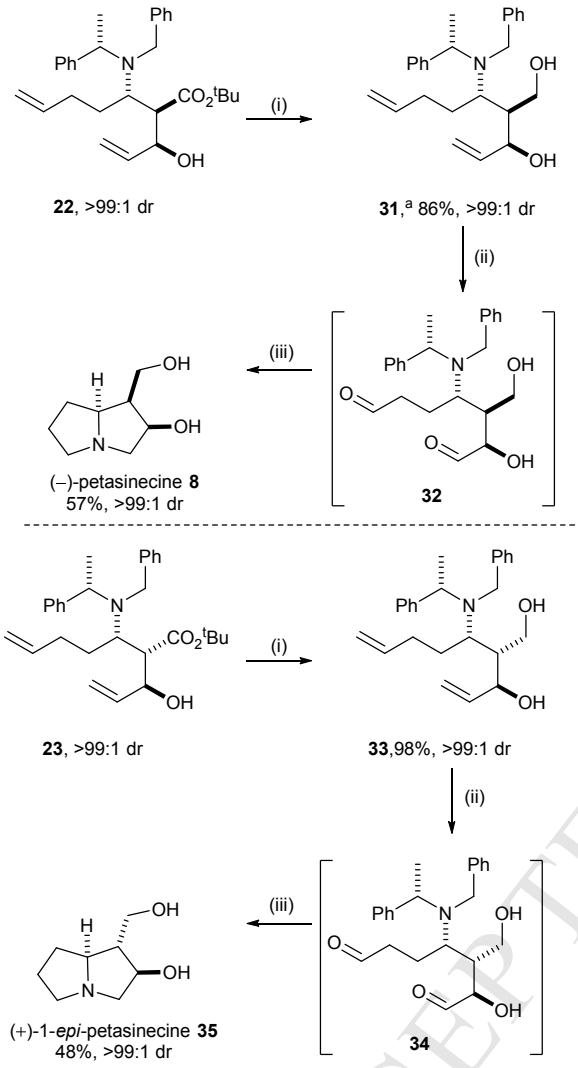


Fig. 3. X-Ray crystal structure of (1*R*,2*S*,7a*S*)-**9** [(–)-macronecine] (selected H atoms are omitted for clarity).

The same sequence of reactions was applied to both **22** and **23**: reduction of **22** with $LiAlH_4$ gave **31** in 86% yield as a single diastereoisomer (>99:1 dr). However, a superior yield of **31** was obtained from β-amino ester **25** following boron-mediated aldol reaction of **25** and acrolein, and reduction of the resultant 55:45 mixture of **22** and **23**, respectively, which gave **31** in 31% overall yield (from **25**) after chromatographic purification. Ozonolysis of **31**·HCl followed by hydrogenolytic *N*-deprotection and in situ double reductive cyclisation gave, after purification on DOWEX (50WX8) ion exchange resin, (–)-petasinecine **8** in 57% yield and >99:1 dr. The spectroscopic data,[10,29,33] melting point and specific rotation for this sample of **8** were in good agreement with literature data {mp 128–130 °C; lit.[29] mp 132–134 °C; lit.[34] mp 134–135 °C; lit.[10] mp 135 °C; lit.[2] mp 132–134 °C; $[\alpha]_D^{20}$ –26.0 (*c* 0.8 in EtOH); lit.[34] $[\alpha]_D^{25}$ –32.0 (*c* 1.3 in EtOH); lit.[10] $[\alpha]_D^{20}$ –21.0 (*c* 0.3 in EtOH); lit.[2] $[\alpha]_D^{20}$ –20 (*c* 0.3 in EtOH); lit.[33] $[\alpha]_D^{25}$ –27 (*c* 0.3 in EtOH); lit.[29] for *ent*-**8**: $[\alpha]_D^{20}$ +24.8 (*c* 0.25 in EtOH)}. Similarly, reduction of β-amino ester **23** with $LiAlH_4$ gave aminodiol **33** in 98% yield and >99:1 dr. Ozonolysis of **33**·HCl followed by hydrogenoytic *N*-deprotection and in situ double

reductive cyclisation gave, after purification on DOWEX ion exchange resin, (+)-1-*epi*-petasinecine **35** in 48% yield and >99:1 dr (Scheme 5). The spectroscopic data,[18,35] melting point and specific rotation for this sample of **35** were also in good agreement with literature data {mp 98–100 °C; lit.[18] mp 94–96 °C; lit.[35] mp 104–105 °C; lit.[34] mp 114–115 °C; $[\alpha]_D^{20}$ +30.0 (*c* 0.8 in EtOH); lit.[34] $[\alpha]_D^{25}$ +40.0 (*c* 1.0 in EtOH); lit.[35] for *ent*-**35**: $[\alpha]_D^{25}$ –29.4 (*c* 0.5 in EtOH)}.

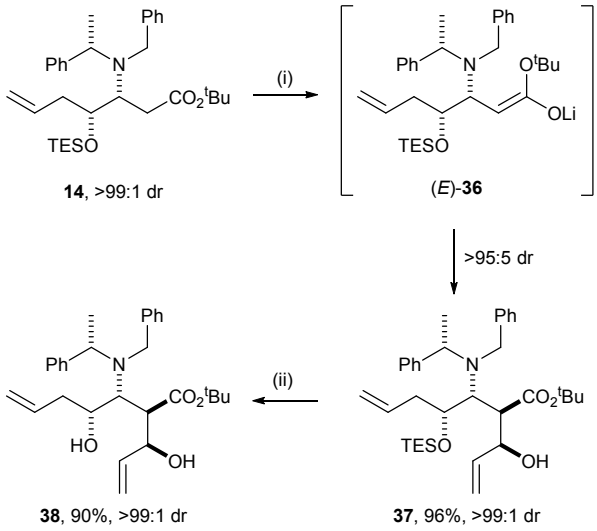


Scheme 5. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 16 h; (ii) HCl (2.0 M in Et_2O), rt then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 3 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h.

2.2. Asymmetric synthesis of (+)-2-*epi*-rosmarinecine

Four diastereoisomeric 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines (–)-petasinecine **8**, (–)-macronecine *ent*-**9**, (+)-1-*epi*-petasinecine **28** and (–)-1-*epi*-macronecine **35** were achieved via conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**13** to *α,β*-unsaturated ester **19** followed by aldol reaction with acrolein and subsequent reductive double cyclisation of the corresponding dialdehyde intermediates. An analogous strategy was employed in asymmetric total synthesis of 1-hydroxymethyl-2,7-dihydroxy subsisuted pyrrolizine. Treatment of the known enantiopure γ-silyloxy-β-amino ester **14**[16] with LiTMP in THF at 0 °C gave lithium (*E*)-β-amino enolate[36] **36**. Subsequent addition of acrolein gave only

one product out of the four possible diastereoisomers.[37] Chromatographic purification afforded **37** in 96% yield and >99:1 dr. Desilylation of **37** with HF in pyridine gave **38** in 90% yield as a single diastereoisomer (>99:1 dr) after chromatographic purification (Scheme 6). The relative configuration within **38** was confirmed by single crystal X-ray diffraction analysis and the absolute (2*R*,3*R*,4*R*,1'*S*,α*S*)-configuration of **38** was assigned by reference to the known (*S*)-configuration of the α-methylbenzyl fragment (Fig. 8). This analysis therefore also unambiguously established the configuration of **37**.



Scheme 6. *Reagents and Conditions*: (i) LiTMP, THF, 0 °C, 1 h then acrolein, −78 °C to 0 °C, 3 h; (ii) HF·py, THF, 0 °C to rt, 16 h.

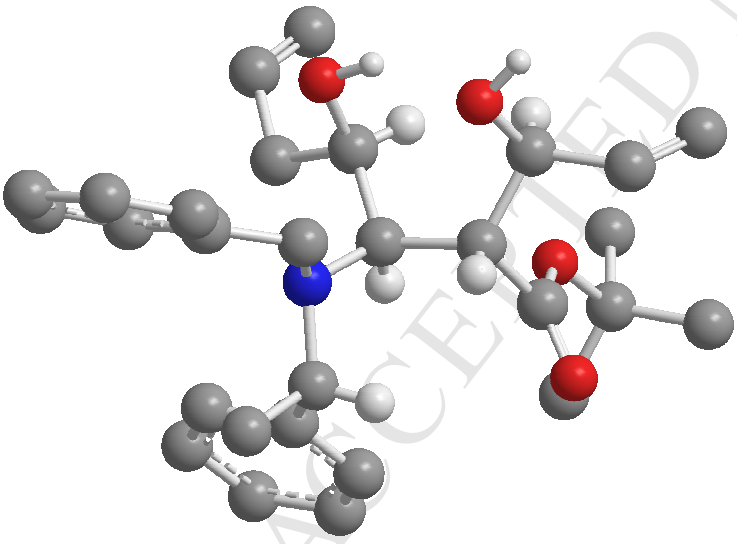
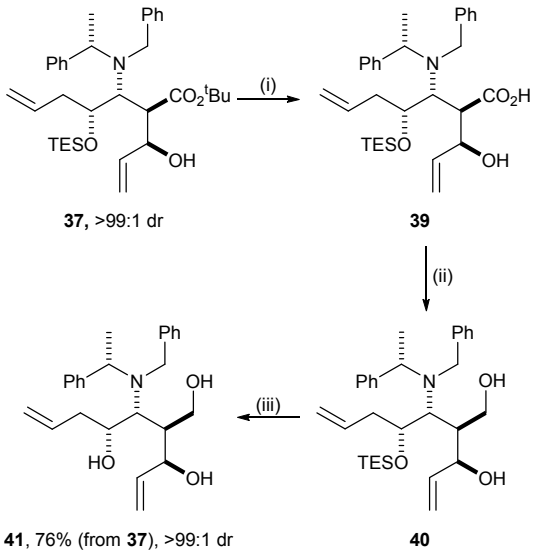


Fig. 3. X-Ray crystal structure of (2*R*,3*R*,4*R*,1'*S*,α*S*)-**38** (selected H atoms are omitted for clarity).

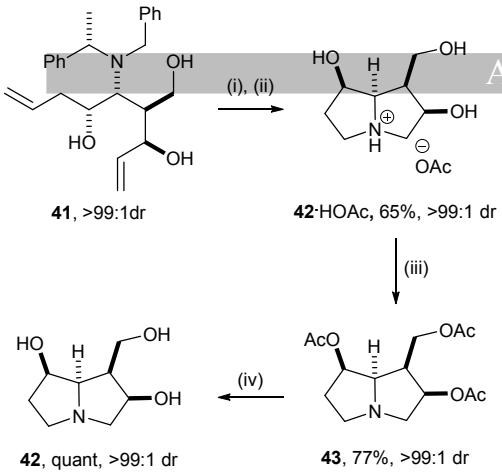
Reduction of β-amino ester **38** with $LiAlH_4$ gave an impure sample of **41** in 81% yield (~70% purity). Attempted reduction of either **37** or **38** with $LiAlH_4$ or DIBAL-H under various alternative conditions gave either poor conversion or complex mixtures of products. Therefore, **37** was hydrolysed under acidic conditions to give the corresponding carboxylic acid **39**, which was treated with $LiAlH_4$ under reflux

followed by HF in pyridine (to facilitate *O*-deprotection) to give triol **41** in 76% yield (from **37**) and >99:1 dr (Scheme 7).



Scheme 7. *Reagents and Conditions:* (i) CF_3CO_2H, CH_2Cl_2, 16 h, rt; (ii) $LiAlH_4$, THF, 0 °C then 70 °C, 16 h; (iii) HF·py, THF, rt, 18 h.

Ozonolysis of **41**·HCl followed by hydrogenolytic *N*-deprotection and in situ double reductive cyclisation gave **42**·HOAc which was isolated in 65% yield and >99:1 dr. In order to facilitate the purification of (+)-2-*epi*-rosmarinecine **42**,[38] **42**·HOAc was first treated with Ac_2O in pyridine to give **43** in 77% isolated yield and >99:1 dr. Subsequent global deprotection of the masked hydroxyl functionalities within **43** upon treatment with K_2CO_3 in MeOH gave (+)-2-*epi*-rosmarinecine **42** in quantitative yield and >99:1 dr after chromatographic purification (Scheme 8). The relative configuration within **42** was confirmed by single crystal X-ray diffraction analysis[26] and the assigned absolute (1*S*,2*R*,7*R*,7a*R*)-configuration of **42** was confirmed following the determination of a Flack *x* parameter[39] of 0.06(16) for the structure of **42** (Figure 4). This analysis therefore also established the configurations of **39**–**41** and **43**. Comparison of the ^{1}H and ^{13}C NMR spectroscopic data for this sample of (+)-2-*epi*-rosmarinecine **42** with those reported by Chakraborty[40] for a sample of (±)-2-*epi*-rosmarinecine **42** revealed several discrepancies.[41] Whilst the origin of these discrepancies is unclear, the stereochemical assignment of our sample of (+)-2-*epi*-rosmarinecine **42** remains secure. In summary, the asymmetric synthesis of (+)-2-*epi*-rosmarinecine **42** was accomplished in thirteen steps and 21% overall yield from the commercially available starting materials.



Scheme 8. *Reagents and Conditions*: (i) HCl (2.0 M in Et_2O), rt then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min then polymer supported PPh_3, rt, 3 h; (ii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h; (iii) Ac_2O, pyridine, DMAP, rt, 16 h; (iv) K_2CO_3, MeOH, rt, 16 h.

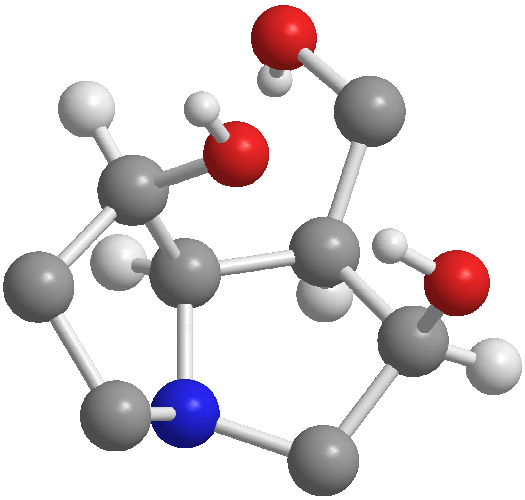


Fig. 4. X-Ray crystal structure of (1*S*,2*R*,7*R*,7a*R*)-**42** [(+)-2-*epi*-rosmarinecine] (selected H atoms are omitted for clarity).

3. Conclusion

In conclusion, the asymmetric syntheses of all four possible diastereoisomeric 1-hydroxymethyl-2-hydroxy substituted pyrrolizidines, (–)-macronecine, (–)-petasinecine, (–)-1-*epi*-macronecine and (+)-1-*epi*-petasinecine were achieved via conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl (*E*)-hepta-2,6-dienoate followed by aldol reaction with acrolein as the key stereodefining steps. By tuning the reaction conditions for the aldol step it was possible to isolate four diastereoisomeric products in >99:1 dr. Subsequent ester reduction followed by ozonolysis of the corresponding hydrochloride salts and one-pot hydrogenolysis/double reductive cyclisation provided rapid access to the corresponding pyrrolizidines (–)-macronecine, (–)-petasinecine, 1-*epi*-macronecine and (+)-1-*epi*-petasinecine in 21, 14, 10 and 19% overall yield, respectively, in six steps or fewer from commercially available starting materials. The analogous strategy employing *tert*-butyl (*R*,*E*)-4-(triethylsilyloxy)hepta-2,6-dienoate facilitated the first asymmetric synthesis of (+)-2-*epi*-rosmarinecine, which was completed in thirteen steps and 21% overall yield from commercially available starting materials.

4. Experimental Section

4.1. General Experimental

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 flame dried and cooled under nitrogen before use. BuLi was purchased from Sigma-Aldrich (as a solution in hexanes) and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[42] Water was purified by an Elix® UV-10 system. All other reagents 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.

Melting points were recorded on a Gallenkamp Hot Stage apparatus. 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/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. 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 internally calibrated with polyalanine, 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.

4.2. *tert*-Butyl (*S*,*S*)-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]hept-6-enoate 25[43]

BuLi (2.2 M in hexanes, 0.77 mL, 1.70 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (371 mg, 1.76 mmol, >99:1 er) in THF (5 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then solution of **19** (200 mg, 1.10 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (5 mL) at −78 °C was then added dropwise via cannula. The resultant reaction mixture was stirred at −78 °C for 2 h, then satd aq NH_4Cl (5 mL). The resultant mixture was allowed to warm to rt over 15 min, then concentrated *in vacuo*. The residue was then partitioned between Et_2O (10 mL) and 10% aq citric acid (10 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic

extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **25** in >95:5 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 50:1) gave **25** as a colourless oil (370 mg, 86%, >99:1 dr); $[\alpha]_D^{20}$ −9.2 (*c* 3.46 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.2, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.49−1.61 (2H, m, C(4)H_2), 1.84−1.90 (2H, m, C(2)H_2), 2.10−2.19 (1H, m, C(5)H_A), 2.36−2.44 (1H, m, C(5)H_B), 3.33−3.40 (1H, m, C(3)*H*), 3.50 (1H, app d, *J* 14.9, CH_AH$_B$Ph), 3.79−3.85 (2H, m, C(α)*H*, CH$_A$$H_B$Ph), 4.93−4.96 (1H, m, C(7)H_A), 4.99−5.05 (1H, m, C(7) H_B), 5.76−5.86 (1H, m, C(6)*H*), 7.24−7.46 (10H, m, *Ph*).

4.3. *tert*-Butyl (2*R*,3*S*,1'*R*,α*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 21

BuLi (2.2 M in hexanes, 390 μL, 0.85 mmol) was added dropwise via syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (185 μL, 0.88 mmol) in THF (3 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **19** (100 mg, 0.55 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (3 mL) at −78 °C was added dropwise via cannula. The resultant mixture was stirred at −78 °C for 2 h, before $TiCl(O^iPr)_3$ (395 μL, 1.65 mmol) was added. The resultant mixture was stirred at −78 °C for 1 h, then acrolein (515 μL, 7.75 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 2 h. Satd aq NH_4Cl (2 mL) was then added, the resultant mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 49:15:23:13 mixture of **21**, **22**, **23** and **24**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave **21** as a colourless oil (55 mg, 22%, >99:1 dr); $[\alpha]_D^{25}$ +14.3 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3522 (O−H), 2976 (C−H), 1701 (C=O), 1634 (C=C); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 1.45−1.55 (1H, m, C(4)H_A), 1.65−1.76 (1H, m, C(4)H_B), 2.03−2.15 (2H, m, C(5)H_2), 2.43 (1H, dd, *J* 8.5, 2.2, C(2)*H*), 3.25−3.32 (1H, m, C(3)*H*), 3.72 (1H, d, *J* 14.5, NCH_AH$_B$Ph), 3.87−3.93 (2H, m, C(α)*H*, C(1')*H*), 3.94 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 4.85−5.00 (3H, m, C(3')H_A, C(7)H_2), 5.10−5.15 (1H, m, C(3')H_B), 5.56−5.75 (2H, m, C(2')*H*, C(6)*H*), 7.10−7.40 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 28.3 (C*Me*$_3$), 29.9 (*C*(4)), 32.0 (*C*(5)), 50.8 (N*C*H$_2$Ph), 54.3 (*C*(2)), 57.3 (*C*(3)), 59.1 (*C*(α)), 70.8 (*C*(1')), 81.8 (*C*Me$_3$), 114.6, 114.7 (*C*(7), *C*(3')), 126.7, 126.9, 127.9, 128.1, 128.4, 128.9 (*o,m,p-Ph*), 138.5, 138.8 (*C*(6), *C*(2')), 141.3, 143.7 (*i-Ph*), 173.4 (*C*(1)); *m/z* $(ESI)^+$ 450 ($[M+H]^+$,100%); HRMS (ESI^+) $C_{29}H_{40}NO_3^+$ ($[M+H]^+$) requires 450.3003; found 450.3003. Further elution gave a 28:21:33:18 mixture of **21**, **22**, **23** and **24**, respectively (120 mg, 48%).

4.4. *tert*-Butyl (2*R*,3*S*,1'*S*,α*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 22

BuLi (2.2 M in hexanes, 4.5 mL, 9.90 mmol) was added to a stirred solution of $^{i}Pr_2NH$ (1.62 mL, 11.6 mmol) in THF (10 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **25** (1.30 g, 3.30 mmol, >99:1 dr) in THF (10 mL) at 0 °C was added dropwise. The reaction mixture was left to stir at 0 °C for 1 h then cooled to −78 °C and $B(OMe)_3$ (4.5 mL, 13.2 mmol) was added. The reaction mixture was left to stir at −78 °C for 1 h then acrolein (1.1 mL, 16.5 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 2 h. Satd aq NH_4Cl (5 mL) was then added, the resultant mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed sequentially with H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 10:33:31:26 mixture of **21**, **22**, **23** and **24**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave **21** (30 mg, 3%, >99:1 dr), an 80:20 mixture of **22** and **21**, respectively (100 mg, 10%, 80:20 dr) and **22** (210 mg, 14%, >99:1 dr) as a colourless oil; $[\alpha]_D^{25}$ −38.5 (*c* 1.4 in $CHCl_3$); ν_{max} (ATR) 3427 (O−H), 2976 (C−H), 1721 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.32 (3H, d, *J* 7.0, C(α)*Me*), 1.70−1.90 (2H, m, C(4)*H*$_2$), 1.90−2.02 (1H, m, C(5)*H*$_A$), 2.10−2.22 (1H, m, C(5)*H*$_B$), 2.24 (1H, dd, *J* 9.8, 4.4, C(2)*H*), 3.13 (1H, app dt, *J* 9.8, 3.9, C(3)*H*), 3.59 (1H, d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.90 (1H, d, *J* 13.7, NCH$_A$*H*$_B$Ph), 3.99 (1H, q, *J* 7.0, C(α)*H*), 4.15−4.27 (1H, m, C(1')*H*), 4.93−5.04 (3H, m, C(3')*H*$_A$, C(7)*H*$_2$), 5.12 (1H, app dt, *J* 17.0, 1.6, C(3')*H*$_B$), 5.69 (1H, ddd, *J* 17.0, 10.6, 5.6, C(2')*H*), 5.79 (1H, app ddt, *J* 17.0, 10.2, 6.7, C(6)*H*), 7.15−7.32 (8H, m, *Ph*), 7.40−7.46 (2H, d, *J* 7.3, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 29.3 (*C*(4)), 31.7 (*C*(5)), 51.2 (NCH_2Ph), 54.0 (*C*(2)), 54.7 (*C*(3)), 56.7 (*C*(α)), 70.1 (*C*(1')), 80.9 (*C*Me$_3$), 115.6, 115.1 (*C*(7), *C*(3')), 127.0, 127.3, 128.3, 128.3, 128.5, 129.4 (*o,m,p-Ph*), 138.2 (*C*(6)), 138.7 (*C*(2')), 140.9, 143.9 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI)$^+$ 450 ([M+H]$^+$,100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_3^+$ ([M+H]$^+$) requires 450.3003; found 450.2996. Further elution gave a 78:22 mixture of **23** and **22**, respectively (280 mg, 19%), a 91:9 mixture of **23** and **24**, respectively (200 mg, 20%).

4.5. *tert*-Butyl (*S*,*S*,*S*,*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 23

BuLi (2.2 M in hexanes, 1.67 mL, 3.67 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperridine (645 μL, 3.81 mmol) in THF (10 mL) at 0 °C. The resultant mixture was stirred at 0

°C for 30 min, then a solution of **25** (500 mg, 1.20 mmol, >99:1 dr) in THF (10 mL) at 0 °C was added dropwise. The reaction mixture was left to stir at 0 °C for 1 h then cooled to −78 °C and acrolein (470 μL, 6.35 mmol) was added. The reaction mixture was then allowed to warm to rt over 3 h. Satd aq NH_4Cl (5 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 mL) and satd aq NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a 5:1:72:22 mixture of **21**, **22**, **23** and **24**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave an 85:15 mixture of **21** and **22**, respectively (25 mg, 5%), a 14:86 mixture of **22** and **23**, respectively (37 mg, 7%) and **23** as a colourless oil (260 mg, 49%, >99:1 dr); $[\alpha]_D^{20}$ −16.4 (*c* 0.55 in $CHCl_3$); ν_{max} (ATR) 3484 (O−H), 2976, 2934 (C−H), 1697 (C=O), 1640 (C=C); δ_H (500 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.33−1.42 (1H, m, C(4)H_A), 1.60−1.70 (1H, m, C(4)H_B), 1.79−1.88 (1H, m, C(5)H_A), 2.04−2.15 (1H, m, C(5)H_B), 2.25 (1H, dd, *J* 8.5, 3.2, C(2)*H*), 3.14 (1H, app d, *J* 14.8, O*H*), 3.24 (1H, app dt, *J* 8.5, 4.4, C(3)*H*), 3.75 (1H, d, *J* 14.8, NCH_AH$_B$Ph),3.94 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 4.02 (1H, q, *J* 6.9, C(α)*H*), 4.15−4.23 (1H, m, C(1')*H*), 4.80−4.90 (2H, m, C(7)H_2) 4.92 (1H, app dt, *J* 10.8, 1.5, C(3')H_A), 5.05 (1H, app dt, *J* 17.3, 1.5, C(3')H_B), 5.42 (1H, app ddd, *J* 17.3, 10.8, 4.4, C(2')*H*), 5.63 (1H, ddt, *J* 17.0, 10.4, 6.6, C(6)*H*), 7.10−7.30 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.7 (C(α)*Me*), 28.0 (C*Me*$_3$), 30.4 (*C*(4)), 31.7 (*C*(5)), 50.6 (N*C*H$_2$Ph), 53.9 (*C*(2)), 57.4 (*C*(3)), 59.9 (*C*(α)), 71.2 (*C*(1')), 81.7 (*C*Me$_3$), 114.3, 114.3 (*C*(7), *C*(3')), 126.7, 126.9, 127.0, 127.8, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 139.1 (*C*(6)), 138.7 (*C*(2')), 142.0, 145.0 (*i*-*Ph*), 173.9 (*C*(1)); *m/z* (ESI)$^+$ 450 ([M+H]$^+$,100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_3^+$ ([M+H]$^+$) requires 450.3003; found 450.3005. Further elution gave an 20:80 mixture of **23** and **24**, respectively (60 mg, 12%).

4.6. *tert*-Butyl (2*S*,3*S*,1'*R*,α*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]hept-6-enoate 24

BuLi (2.2 M in hexanes, 260 μL, 0.57 mmol) was added dropwise via syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (125 μL, 0.54 mmol) in THF (2 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **19** (100 mg, 0.54 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (7 mL) at −78 °C was added dropwise via cannula. The resultant mixture was stirred at −78 °C for 2 h, then acrolein (75 μL, 1.08 mmol) was added and the reaction mixture was allowed to warm to rt over 3 h. Satd aq NH_4Cl (1 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (5 mL) and 10% aq citric acid (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL), H_2O (5 mL)

and brine (5 mL), then dried and concentrated *in vacuo* to give a 12:7:28:53 mixture of **21**, **22**, **23** and **24**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave a 29:24:40:7 mixture of **21**, **22**, **23** and **24**, respectively (85 mg, 38%). Further elution gave **24** as a pale yellow oil (100 mg, 41%, >99:1 dr); $[\alpha]_D^{20}$ +3.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O−H), 2976 (C−H), 1720 (C=O), 1640 (C=C); δ_H (500 MHz, $CDCl_3$) 1.30 (9H, s, C*Me*$_3$), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.45−1.54 (1H, m, C(4)H_A), 1.75−1.85 (1H, m, C(4)H_B), 2.05−2.25 (2H, m, C(5)H_2), 2.41 (1H, app t, *J* 8.2, C(2)*H*), 3.35 (1H, app dt, *J* 8.2, 4.4, C(3)*H*), 3.56 (1H, app t, *J* 8.2, C(1')*H*), 3.72 (1H, d, *J* 13.5, NCH_AH$_B$Ph), 3.84 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 7.0, C(α)*H*), 4.89−5.06 (4H, m, C(7)H_2, C(3')H_2), 5.57 (1H, ddd, *J* 17.3, 10.4, 8.2, C(2')*H*), 5.72 (1H, ddt, *J* 16.9, 10.2, 6.5, C(6)*H*), 6.34 (1H, br s, O*H*), 7.12−7.35 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 28.4 (C*Me*$_3$), 30.0 (*C*(4)), 32.3 (*C*(5)), 51.1 (N*C*H$_2$Ph), 54.7 (*C*(2)), 58.4 (*C*(α)), 58.7 (*C*(3)), 75.5 (*C*(1')), 81.2 (*C*Me$_3$), 114.8 (*C*(7)), 116.8 (*C*(3')), 127.3, 127.4, 128.3, 128.5, 128.6, 129.4 (*o,m,p-Ph*), 137.6 (*C*(2')), 138.3 (*C*(6)), 138.9, 142.3 (*i-Ph*), 171.4 (*C*(1)); *m/z* $(ESI)^+$ 450 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{40}NO_3^+$ ($[M+H]^+$) requires 450.3003; found 450.3000.

4.7. (*S,S,Z*)-1-*tert*-Butoxy-1-trimethylsiloxy-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]-hepta-1,6-diene (*Z*)-20

BuLi (2.2 M in hexanes, 125 μL, 0.27 mmol) was added dropwise to a stirred solution of (*S*)-**13** (55 μL, 0.27 mmol) in THF (0.5 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **19** (50 mg, 0.27 mmol) in THF (0.5 mL) at −78 °C was added. The resultant mixture was stirred at −78 °C for 2 h, then TMSCl (55 μL, 0.41 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give **20** [(*Z*)-**20**:(*E*)-**20** >95:5]. δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.01 (9H, s, OSi*Me*$_3$), 1.25 (9H, s, C*Me*$_3$), 1.28 (3H, d, *J* 6.7, C(α)*Me*), 3.30 (1H, dt, *J* 9.8, 7.2, C(3)*H*), 3.42 (1H, d, *J* 15.6, NCH_AH$_B$Ph), 3.77 (1H, d, *J* 9.8, C(2)*H*), 3.83 (1H, q, *J* 6.7, C(α)*H*), 3.87 (1H, d, *J* 15.6, NCH$_A$$H_B$Ph), 4.75 (1H, app ddt, *J* 10.2, 2.2, 1.5, C(7)H_A), 4.82 (1H, app dq, *J* 17.0, 1.5, C(7)H_B), 5.63 (1H, ddt, *J* 17.0, 10.2, 6.6, C(6)*H*), 7.05−7.43 (10H, m, *Ph*).

4.8. (*S,S,E*)-1-*tert*-Butoxy-1-trimethylsiloxy-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]-hepta-1,6-diene (*E*)-20

Method A: BuLi (2.2 M in hexanes, 125 μL, 0.28 mmol) was added dropwise to a stirred solution of TMP (50 μL, 0.28 mmol) in THF (0.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **25** (100 mg, 0.25 mmol) in THF (0.5 mL) at 0 °C was added. The resultant mixture was stirred at

0 °C for 1 h, then TMSCl (65 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give **20** [(*E*)-**20**:(*Z*)-**20** >95:5]. δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.18 (9H, s, OSi*Me*$_3$), 1.12 (9H, s, C*Me*$_3$), 1.11 (3H, d, *J* 7.1, C(α)*Me*), 3.37 (1H, dt, *J* 9.7, 7.3, C(3)*H*), 3.47 (1H, d, *J* 15.5, NC*H*$_A$H$_B$Ph), 3.73 (1H, d, *J* 9.7, C(2)*H*), 3.83−3.90 (2H, m, NCH$_A$*H*$_B$Ph, C(α)*H*), 4.75−4.90 (2H, m, C(7)*H*$_2$), 5.67 (1H, ddt, *J* 17.1, 10.3, 6.6, C(6)*H*), 7.10−7.49 (10H, m, *Ph*).

Method B: BuLi (2.2 M in hexanes, 125 μL, 0.28 mmol) was added dropwise to a stirred solution of iPr_2NH (40 μL, 0.28 mmol) in THF (0.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **25** (100 mg, 0.25 mmol) in THF (0.5 mL) at 0 °C was added. The resultant mixture was stirred at 0 °C for 1 h, then TMSCl (65 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give a mixture containing **20** [(*E*)-**20**:(*Z*)-**20** >95:5].

4.9. (2*S*,3*S*,1'*R*,α*S*)-2-(1'-Hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1-ol 26

$LiAlH_4$ (1.0 M in THF, 1.5 mL, 1.50 mmol) was added to a stirred solution of **21** (170 mg, 0.38 mmol, >99:1 dr) in THF (5 mL) at –78 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. 2.0 M aq NaOH (0.75 mL, 1.5 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **26** as a colourless oil (101 mg, 70%, >99:1 dr); $[\alpha]_D^{20}$ +14.4 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 3350 (O–H) 2972, 2933 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29–1.34 (1H, m, C(2)*H*), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 1.60–1.73 (1H, m, C(4)*H*$_A$), 1.82–1.92 (1H, m, C(4)*H*$_B$), 2.06–2.18 (1H, m, C(5)*H*$_A$), 2.21–2.34 (1H, m, C(5)*H*$_B$), 3.07 (1H, app dt, *J* 8.5, 2.0, C(3)*H*), 3.61 (1H, dd, *J* 11.8, 2.6, C(1)*H*$_A$), 3.65 (1H, d, *J* 13.6, NC*H*$_A$H$_B$Ph), 3.74 (1H, app s, C(1')*H*), 3.86–3.97 (3H, m, C(1)*H*$_B$, C(α)*H*, NCH$_A$*H*$_B$Ph), 4.95 (1H, app d, *J* 10.2, C(3')*H*$_A$), 4.98–5.05 (2H, m, C(7)*H*$_2$), 5.18 (1H, app d, *J* 17.2, C(3')*H*$_B$), 5.60 (1H, ddd, *J* 17.2, 10.2, 4.0, C(2')*H*), 5.81 (1H, ddt, *J* 16.9, 10.2, 6.7, C(6)*H*), 7.11–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.4 (C(α)*Me*), 29.7 (*C*(4)), 32.2 (*C*(5)), 46.6 (*C*(2)), 51.2 (N*C*H$_2$Ph), 54.6 (*C*(3)), 56.5 (*C*(α)), 60.2 (*C*(1)), 73.6 (*C*(1')), 113.8, 115.0 (*C*(7), (*C*(3')), 127.3, 127.4, 128.4, 128.5, 128.7, 129.3 (*o*,*m*,*p*-*Ph*), 138.5, 140.7 (*C*(6), *C*(2')), 140.1, 143.3 (*i*-*Ph*); *m/z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{33}NNaO_2^+$ ([M+Na]$^+$) requires 402.2404; found 402.2402.

4.10. (*S*,*S*,*S*)-1-(Hydroxymethyl)2-hydroxy-hexahydro-1*H*-pyrrolizidine [(–)-1-*epi*-macronecine] 28

Aminodiol **26** (790 mg, 2.08 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 4 mL), then the residue of **26**·HCl was dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant mixture was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 2.08 g, 6.24 mmol) was added and the reaction mixture was allowed to warm to rt and stirred at rt for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a total volume of 3 mL, then AcOH (0.15 mL) and $Pd(OH)_2$/C (200 mg, 25% w/w) were added. The resultant mixture was degassed with N_2 and saturated with H_2, then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **28** as a white solid (224 mg, 69%, >99:1 dr); mp 90−91 °C; lit.[28] mp 91–93 °C; $[\alpha]_D^{20}$ −96 (*c* 0.12 in EtOH); lit.[28] $[\alpha]_D^{25}$ –114 (*c* 0.9 in EtOH); ν_{max} (ATR) 3312 (O−H); δ_H (400 MHz, MeOH-d_4) 1.42−1.55 (1H, m, C(7)H_A), 1.55−1.69 (1H, m, C(6)H_A), 1.70−1.86 (2H, m, C(6)H_B, C(7)H_B), 2.19 (1H, app dq, *J* 7.6, 5.8, C(1)*H*), 2.45 (1H, app td, *J* 10.0, 6.3, C(5)H_A), 2.70−2.85 (2H, m, C(3)H_2), 3.02 (1H, ddd, *J* 10.0, 7.0, 3.6, C(5)H_B), 3.50−3.61 (2H, m, C(7a)*H*, C(1')H_A), 3.69 (1H, dd, *J* 10.9, 5.8, C(1')H_B), 3.94 (1H, app q, *J* 7.6, C(2)*H*); δ_H (400 MHz, $CDCl_3$) 1.33−1.48 (1H, m, C(6)H_A), 1.64−1.79 (2H, m, C(6)H_B, C(7)H_A), 1.81−1.94 (1H, m, C(7)H_B), 2.37 (1H, app q, *J* 7.0, C(1)*H*), 2.46−2.65 (1H, m, C(3)H_A), 2.84 (1H, app dd, *J* 11.4, 6.8, C(5)H_A), 2.93 (1H, app dd, *J* 11.4, 6.3, C(5)H_B), 3.10 (1H, ddd, *J* 10.8, 7.1, 3.9, C(3)H_B), 3.55−3.63 (1H, m, C(7a)*H*), 3.76 (2H, app d, *J* 7.3, C(1')H_2), 4.13 (1H, app q, *J* 7.0, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 25.9 (*C*(7)), 26.2 (*C*(6)), 50.7 (*C*(1)), 55.5 (*C*(5)), 60.4 (*C*(3)), 60.5 (*C*(1')), 65.5 (*C*(7a)), 71.2 (*C*(2)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1172.

4.11. (2*R*,3*S*,1'*R*,*αS*)- 2-(1'-Hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1-ol 29

$LiAlH_4$ (1.0 M in THF, 2.7 mL, 2.70 mmol) was added to a stirred solution of **24** (300 mg, 0.67 mmol, >99:1 dr) in THF (15 mL) at –78 °C. The resultant solution was allowed to warm to rt and stirred at rt for 6 h, 2.0 M aq NaOH (1.35 mL, 2.7 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **29** as a colourless oil

(235 mg, 93%, >99:1 dr); $[\alpha]_D^{20}$ +6.9 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3330 (O–H) 2966 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 6.9, C(α)*Me*), 1.37−1.49 (1H, m, C(4)H_A), 1.62−1.73 (1H, m, C(4)H_B), 1.81−1.90 (1H, m, C(2)*H*), 1.96−2.07 (1H, m, C(5)H_A), 2.07−2.18 (1H, m, C(5)H_B), 2.00−2.40 (2H, br s, O*H*), 2.77 (1H, app dt, *J* 7.0, 4.5, C(3)*H*), 3.44 (1H, dd, *J* 11.1, 7.0, C(1)H_A), 3.53 (1H, dd, *J* 11.1, 3.5, C(1)H_B), 3.73 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.87 (1H, d, *J* 14.2, NC$H_A$$H_B$Ph), 3.93 (1H, q, *J* 6.9, C(α)*H*), 4.09 (1H, app t, *J* 6.1, C(1')*H*), 4.88–5.02 (4H, m, C(7)H_2, C(3')H_2), 5.44 (1H, ddd, *J* 16.9, 10.4, 6.1, C(2')*H*), 5.71 (1H, ddt, *J* 16.9, 10.2, 6.7, C(6)*H*), 7.11−7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.9 (C(α)*Me*), 29.4 (*C*(4)), 32.5 (*C*(5)), 47.4 (*C*(2)), 50.9 (N*C*H_2Ph), 56.9 (*C*(3)), 58.5 (*C*(α)), 61.8 (*C*(1)), 75.3 (*C*(1')), 114.8, 115.8 (*C*(7), (*C*(3')), 127.0, 127.2, 128.2, 128.4, 128.4, 129.0 (*o*,*m*,*p*-*Ph*), 138.4, 138.5 (*C*(6), *C*(2')), 140.6, 143.6 (*i*-*Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{33}NNaO_2^+$ ($[M+Na]^+$) requires 402.2404; found 402.2407.

4.12. (1*R*,2*S*,7a*S*)-1-(Hydroxymethyl)-2-hydroxy-hexahydro-1*H*-pyrrolizidine [(–)-macronecine] *ent*-9

Aminodiol **29** (330 mg, 0.87 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3 mL), then the residue of **29**·HCl was dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant mixture was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 870 mg, 2.6 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a total volume of 3 mL. AcOH (0.25 mL) and $Pd(OH)_2$/C (50 mg, 0.36 mmol) were added and the resultant mixture was degassed with N_2 and saturated with H_2, then stirred under an atmosphere of H_2 (5 atm) at rt for 36 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave *ent*-**9** as a white solid (82 mg, 60%, >99:1 dr); mp 120−123 °C; {lit.[11] mp 124–127 °C; lit.[29] mp 128–129 °C; lit.[6] mp 126–128 °C}; $[\alpha]_D^{20}$ –40.0 (*c* 0.6 in EtOH); {lit.[11] $[\alpha]_D^{20}$ –49.4 (*c* 1.0 in EtOH); lit.[30] $[\alpha]_D^{20}$ –42.1 (*c* 1.0 in EtOH); lit.[29] for **9**: $[\alpha]_D^{20}$ +42.7 (*c* 1.0 in EtOH); lit.[6] for **9** (from natural source): $[\alpha]_D^{20}$ +49.3 (*c* 0.5 in EtOH)}; ν_{max} (ATR) 3302 (O−H); δ_H (400 MHz, MeOH-d_4) 1.64−1.73 (1H, m, C(7)H_A), 1.78−2.07 (4H, m, C(1)*H*, C(6)H_2, C(7)H_B), 2.63 (1H, app dt, *J* 10.8, 6.2, C(5)H_A), 2.77 (1H, dd, *J* 11.1, 3.6, C(3)H_A), 2.98 (1H, dt, *J* 10.8, 6.2, C(5)H_B), 3.19 (1H, app d, *J* 11.1, C(3)H_B), 3.47 (1H, ddd, *J* 9.3, 7.6, 5.0, C(7a)*H*), 3.67 (1H, dd, *J* 10.8, 6.2, C(1')H_A), 3.85 (1H, dd, *J* 10.8, 7.4, C(1')H_B), 4.46 (1H, t, *J* 3.6, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 25.1 (*C*(7)), 30.9 (*C*(6)), 52.5 (*C*(1)), 54.6 (*C*(5)), 59.8 (*C*(1')), 62.8 (*C*(3)),

65.6 (*C*(7a)), 73.7 (*C*(2)); δ_H (400 MHz, $CDCl_3$) 1.55 (1H, app dq, *J* 11.9, 6.1, C(7)H_A), 1.78−1.90 (3H, m, C(6)H_2, C(7)H_B), 1.92−2.05 (1H, m, C(1)*H*), 2.56−2.65 (1H, m, C(5)H_A), 2.71 (1H, dd, *J* 11.0, 3.7, C(3)H_A), 3.01 (1H, dt, *J* 11.0, 6.6, C(5)H_B), 3.23 (1H, app d, *J* 11.0, C(3)H_B), 3.56−3.65 (1H, m, C(7a)*H*), 3.80−3.92 (2H, m, C(1')H_2), 4.51 (1H, app t, *J* 3.7, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 25.5 (*C*(6)), 31.2 (*C*(7)), 52.4 (*C*(1)), 54.9 (*C*(5)), 60.9 (*C*(1')), 62.9 (*C*(3)), 64.2 (*C*(7a)), 75.6 (*C*(2)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1173.

4.13. (*S*,*S*,*S*,*S*)- 2-(1'-Hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1-ol 31

Method A: $LiAlH_4$ (2.4 M in THF, 100 μL, 0.24 mmol) was added to a stirred solution of **22** (26 mg, 58 μmol, >99:1 dr) in THF (0.5 mL) at −78 °C. The resultant solution was allowed to warm to rt and stirred at rt for 16 h. 2.0 M aq NaOH (115 μL, 0.23 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **31** as a colourless oil (19 mg, 86%, >99:1 dr); $[\alpha]_D^{20}$ +12.2 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3351 (O–H) 3063, 3028, 2974 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26 (1H, d, *J* 7.0, C(α)*Me*), 1.48–1.68 (3H, m, C(2)*H*, C(4)H_2), 1.90–2.11 (2H, m, C(5)H_2), 3.14 (1H, app dt, *J* 9.3, 3.8, C(3)*H*), 3.66−3.72 (2H, m, C(1)H_A, NC$H_A$$H_B$Ph), 3.82 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.85 (1H, dd, *J* 10.8, 6.9, C(1)H_B), 3.92 (1H, q, *J* 7.0, C(α)*H*), 3.98 (1H, t, *J* 4.9, C(1')*H*), 4.90–4.99 (3H, m, C(7)H_2, C(3')H_A), 5.06 (1H, app d, *J* 16.8, C(3')H_B), 5.43 (1H, ddd, *J* 16.8, 10.5, 5.5, C(2')*H*), 5.70 (1H, app ddt, *J* 17.0, 10.1, 6.7, C(6)*H*), 7.12–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 28.8 (*C*(4)), 32.0 (*C*(5)), 47.7 (*C*(2)), 51.6 (N*C*H_2Ph), 56.6 (*C*(3)), 59.0 (*C*(α)), 60.9 (*C*(1)), 73.1 (*C*(1')), 115.0, 115.3 (*C*(7), (*C*(3')), 127.3, 127.5, 128.2, 128.6, 128.7, 129.0 (*o,m,p-Ph*), 138.0, 140.1 (*C*(6), *C*(2')), 139.8, 142.4 (*i-Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%), 402 ($[M+Na]^+$, 4%); HRMS (ESI^+) $C_{25}H_{34}NO_2^+$ ($[M+H]^+$) requires 380.2584; found 380.2583.

Method B-step 1: BuLi (2.2 M in hexanes, 3.5 mL, 7.65 mmol) was added to a stirred solution of $^iPr_2NH$ (1.25 mL, 9.0 mmol) in THF (10 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **25** (1.00 g, 2.55 mmol, >99:1 dr) in THF (10 mL) at 0 °C was added dropwise. The reaction mixture was left to stir at 0 °C for 1 h then cooled to −78 °C and $B(OMe)_3$ (3.5 mL, 10.2 mmol) was added. The reaction mixture was left to stir at −78 °C for 1 h then acrolein (0.85 mL, 12.8 mmol) was added and the reaction mixture was allowed to warm to 0 °C over 2 h. Satd aq NH_4Cl (5 mL) was then added, the resultant mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 mL) and satd aq $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic

extracts were washed sequentially with H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1 increased to 10:1) gave a 55:45 mixture of **22** and **23** (700 mg) as a colourless oil.

Method B-step 2: $LiAlH_4$ (1.0 M in THF, 6.3 mL, 6.30 mmol) was added to a stirred solution of the residue of a **22** and **23** (700 mg, 55:45 dr) in THF (10 mL) at –78 °C. The resultant solution was allowed to warm to rt and stirred at rt for 16 h. 2.0 M aq NaOH (3.1 mL, 6.24 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **31** as a colourless oil (300 mg, 31% from **25**, >99:1 dr). Further elution gave **33** as a colourless oil (280 mg, 29% from **25**, >99:1 dr).

4.14. (1*S*,2*R*,7a*S*)-1-(Hydroxymethyl)-2-hydroxyhexahydro-1H-pyrrolizidine [(–)-petasinecine] 8

Aminodiol **31** (380 mg, 1.00 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3 mL), then the residue of **31**·HCl was dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant mixture was cooled to –78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 1.00 g, 3.00 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a total volume of 3 mL. AcOH (0.10 mL) and $Pd(OH)_2$/C (100 mg, 25% w/w) were added and the resultant mixture was degassed with N_2 and saturated with H_2 and then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) to give **8** as a white solid (89 mg, 57%, >99:1 dr); mp 128–130 °C; {lit.[29] mp 132–134 °C; lit.[34] mp 134–135 °C; lit.[10] mp 135 °C; lit.[2] mp 132–134 °C}; $[\alpha]_D^{20}$ –26.0 (*c* 0.8 in EtOH); {lit.[34] $[\alpha]_D^{25}$ –32.0 (*c* 1.3 in EtOH); lit.[10] $[\alpha]_D^{20}$ –21.0 (*c* 0.3 in EtOH); lit.[2] $[\alpha]_D^{20}$ –20 (*c* 0.3 in EtOH); lit.[33] $[\alpha]_D^{25}$ –27 (*c* 0.3 in EtOH); lit.[29] for *ent*-**8**: $[\alpha]_D^{20}$ +24.8 (*c* 0.25 in EtOH)}; ν_{max} (ATR) 3341 (O–H); δ_H (400 MHz, MeOH-d_4) 1.61–1.73 (1H, m, C(6)H_A), 1.75–1.83 (1H, m, C(7)H_A), 1.93–2.08 (2H, m, C(6)H_B, C(7)H_B), 2.25–2.35 (1H, m, C(1)*H*), 2.90 (1H, app d, *J* 12.7, C(3)H_A), 2.90–3.00 (1H, m, C(5)H_A), 3.19 (1H, dd, *J* 12.7, 3.7, C(3)H_B), 3.32 (1H, app t, *J* 7.9, C(5)H_B), 3.68 (1H, dd, *J* 11.0, 7.5, C(1')H_A), 3.75–3.90 (1H, m, C(7a)*H*), 3.83 (1H, dd, *J* 11.0, 7.3, C(1')H_B), 4.27 (1H, app t, *J* 3.7, C(2)*H*); δ_H (400 MHz, $CDCl_3$) 1.62–1.89 (3H, m, C(6)H_2, C(7)H_A), 1.93–2.02 (1H, m, C(7)H_B), 2.34–2.43 (1H, m, C(1)*H*), 2.69–2.82 (2H, m, C(3)H_A, C(5)H_A),

3.09−3.17 (1H, m, C(3)H_B), 3.24 (1H, app dd, *J* 11.7, 5.0, C(5)H_B), 3.45−3.53 (1H, m, C(7a)*H*), 3.82 (1H, dd, *J* 10.8, 5.0, C(1')H_A), 3.94 (1H, dd, *J* 10.8, 9.3, C(1')H_B), 4.47−4.54 (1H, m, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 26.3 (*C*(6)), 27.1 (*C*(7)), 49.1 (*C*(1)), 56.6 (*C*(5)), 57.8 (*C*(1')), 61.4 (*C*(3)), 67.4 (*C*(7a)), 72.5 (*C*(2)); *m/z* (ESI$^+$) 158 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_2^+$ ([M+H]$^+$) requires 158.1176; found 158.1179.

4.15. (2*R*,3*S*,1'*S*,α*S*)-2-(1'-Hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1-ol 33

$LiAlH_4$ (1.0 M in THF, 2.8 mL, 2.80 mmol) was added to a stirred solution of **23** (310 mg, 0.69 mmol, >99:1 dr) in THF (10 mL) at –78 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 16 h. 2.0 M aq NaOH (1.4 mL, 2.8 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **33** as a colourless oil (255 mg, 98%, >99:1 dr); $[\alpha]_D^{20}$ –23.2 (*c* 0.35 in $CHCl_3$); ν_{max} (ATR) 3342 (O–H) 2973, 2933 (C−H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.25 (1H, app dd, *J* 9.5, 2.4, C(2)*H*), 1.38 (1H, d, *J* 7.0, C(α)*Me*), 1.48–1.61 (1H, m, C(4)H_A), 1.81−1.92 (1H, m, C(4)H_B), 2.11–2.36 (2H, m, C(5)H_2), 3.03 (1H, ddd, *J* 9.5, 7.7, 3.1, C(3)*H*), 3.30 (1H, dd, *J* 11.9, 2.4, C(1)H_A), 3.70–3.75 (1H, m, C(1)H_B), 3.72 (1H, d, *J* 13.5, NC$H_A$$H_B$Ph), 3.84 (1H, d, *J* 13.5, NCH$_A$$H_B$Ph), 3.93 (1H, q, *J* 7.0, C(α)*H*), 4.66 (1H, app s, C(1')*H*), 4.90–5.06 (3H, m, C(7)H_2, C(3')H_A), 5.14 (1H, app dt, *J* 17.2, 1.8, C(3')H_B), 5.60 (1H, ddd, *J* 18.3, 11.9, 4.3, C(2')*H*), 5.82 (1H, app ddt, *J* 17.0, 10.2, 6.6, C(6)*H*), 7.13–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 30.3 (*C*(4)), 32.3 (*C*(5)), 47.3 (*C*(2)), 51.2 (N*C*H$_2$Ph), 52.9 (*C*(3)), 56.7 (*C*(α)), 60.5 (*C*(1)), 72.5 (*C*(1')), 114.2, 114.7 (*C*(7), (*C*(3')), 127.2, 127.2, 128.3, 128.4, 128.6, 129.2 (*o*,*m*,*p*-*Ph*), 138.9, 140.0 (*C*(6), *C*(2')), 140.7, 144.3 (*i*-*Ph*); *m/z* (ESI$^+$) 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}NO_2^+$ ([M+H]$^+$) requires 380.2584; found 380.2581.

4.16. (1*R*,2*R*,7a*S*)-1-(Hydroxymethyl)-2-hydroxy-hexahydro-1*H*-pyrrolizidine [(+)-1-*epi*-petasinecine] 35

Aminodiol **33** (310 mg, 0.82 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3 mL), the residue of **33**·HCl was then dissolved in CH_2Cl_2 (20 mL) and MeOH (20 mL). The resultant mixture was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 820 mg, 2.4 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for

3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a total volume of 3 mL. AcOH (0.3 mL) and $Pd(OH)_2/C$ (63 mg, 25% w/w) were added and the resultant mixture was degassed with N_2 and saturated with H_2, then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was coevaporated with HCl (2.0 M in Et_2O, 3 mL) and purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **35** as a white solid (62 mg, 48%, >99:1 dr); mp 98−100 °C; {lit.[18] mp 94–96 °C; lit.[35] mp 104–105 °C; lit.[34] mp 114–115 °C}; $[\alpha]_D^{20}$ +30.0 (*c* 0.8 in EtOH); {lit.[34] $[\alpha]_D^{25}$ +40.0 (*c* 1.0 in EtOH); lit.[35] for *ent*-**35**: $[\alpha]_D^{25}$ −29.4 (*c* 0.5 in EtOH)}; ν_{max} (ATR) 3311 (O−H); δ_H (400 MHz, MeOH-d_4) 1.60−1.75 (3H, m, C(1)*H*, C(6)H_A, C(7)H_A), 1.85−1.97 (2H, m, C(6)H_B, C(7)H_B), 2.42 (1H, dd, *J* 9.8, 8.1, C(3)H_A), 2.61−2.70 (1H, m, C(5)H_A), 2.81−2.89 (1H, m, C(5)H_B), 3.14 (1H, dd, *J* 9.8, 6.1, C(3)H_B), 3.16−3.20 (1H, m, C(7a)*H*), 3.47 (1H, dd, *J* 11.1, 7.1, C(1')H_A), 3.64 (1H, dd, *J* 11.1, 4.7, C(1')H_B), 3.96 (1H, app dt, *J* 8.1, 6.1, C(2)*H*); δ_H (400 MHz, $CDCl_3$) 1.58−1.71 (1H, m, C(6)H_A), 1.72−1.89 (2H, m, C(6)H_B, C(7)H_A), 1.89−2.03 (2H, m, C(1)*H*, C(7)H_B), 2.54 (1H, app t, *J* 9.1, C(3)H_A), 2.69−2.77 (1H, m, C(5)H_A), 2.97−3.05 (1H, m, C(3)H_B), 3.26−3.34 (1H, m, C(5)H_B), 3.42 (1H, dd, *J* 9.8, 5.6, C(7a)*H*), 3.72 (1H, dd, *J* 10.7, 6.9, C(1')H_A), 3.87 (1H, dd, *J* 10.7, 4.5, C(1')H_B), 4.30−4.38 (1H, m, C(2)*H*); δ_C (100 MHz, MeOH-d_4) 24.9, 31.9 (*C*(6), *C*(7)), 54.7 (*C*(5)), 55.0 (*C*(1)), 60.5 (*C*(3)), 61.6 (*C*(1')), 66.1 (*C*(7a)), 73.2 (*C*(2)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1174.

4.17. *tert*-Butyl (2*R*,3*R*,4*R*,1'*S*,*αS*)-2-(1'-Hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triethylsilyloxy)hept-6-enoate 37

BuLi (2.2 M in hexanes, 2.60 mL, 5.64 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperridine (970 μL, 5.74 mmol) in THF (9 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min then a solution of **14** (600 mg, 1.15 mmol, >99:1 dr) in THF (9 mL) at 0 °C was added dropwise via cannula. The resultant mixture was stirred at 0 °C for 1 h then cooled to −78 °C. Acrolein (385 μL, 5.74 mmol) was then added and the reaction mixture was allowed to warm to 0 °C and stirred at 0 °C for 3 h. Satd aq NH_4Cl (5 mL) was then added, the reaction mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (20 mL) and satd aq NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography gave **37** as a colourless oil (666 mg, 96%, >99:1 dr); $[\alpha]_D^{25}$ +40.0 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3373 (O−H), 2877, 2956 (C−H), 1721 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 0.29 (6H, q, *J* 8.0,

Si(CH_2CH_3)$_3$), 0.77 (9H, t, *J* 8.0, Si(CH_2CH_3)$_3$), 0.97 (3H, d, *J* 7.0, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 2.24−2.38 (2H, m, C(5)H_2), 2.87 (1H, dd, *J* 9.3, 8.1, C(2)*H*), 3.28 (1H, dd, *J* 9.3, 3.8, C(3)*H*), 2.80−2.86 (1H, m, C(4)*H*), 4.00 (1H, d, *J* 16.7, NCH_AH$_B$Ph), 4.10−4.21 (3H, m, C(1')*H*, C(α)*H*, NCH$_A$$H_B$Ph), 4.71 (1H, br s, O*H*), 4.81−4.91 (2H, m, C(7)H_2), 5.08 (1H, m, C(3')H_A), 5.22 (1H, app d, *J* 17.0, C(3')H_B), 5.40−5.57 (1H, m, C(6)*H*), 5.82 (1H, ddd, *J* 17.0, 10.2, 7.0, C(2')*H*), 7.10−7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 4.5 (Si(CH_2CH_3)$_3$), 6.9 (Si(CH_2CH_3)$_3$), 22.7 (C(α)*Me*), 28.3 (C*Me*$_3$), 37.1 (*C*(5)), 52.1 (NCH_2Ph), 53.7 (*C*(2)), 63.2 (*C*(α)), 63.5 (*C*(3)), 73.6 (*C*Me$_3$), 76.8 (*C*(1')), 81.4 (*C*(4)), 117.3, 117.4 (*C*(7), *C*(3')), 126.3, 126.9, 127.3, 128.1, 128.2, 128.5 (*o,m,p-Ph*), 135.3 (*C*(6)), 137.6 (*C*(2')), 144.1, 146.5 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI)$^+$ 580 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{54}NO_4Si^+$ ([M+H]$^+$) requires 580.3817; found 580.3814.

4.18. (3*R*,4*R*,α*S*,*E*)-1-*tert*-Butoxy-1-triethylsiloxy-3-[*N*-benzyl-*N*-(α-methyl-benzyl)amino]-3-[1′-(triethylsilyloxy)]but-3′-enylpropene (*E*)-36

BuLi (2.2 M in hexanes, 70 μL, 0.15 mmol) was added dropwise to a stirred solution of TMP (30 μL, 0.15 mmol) in THF (0.2 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min, then a solution of **14** (70 mg, 0.13 mmol) in THF (0.2 mL) at 0 °C was added. The resultant mixture was stirred at 0 °C for 1 h, then TESCl (50 μL, 0.50 mmol) was added dropwise and the resultant mixture was allowed to warm to rt over 1 h before being concentrated *in vacuo* to give **36** [(*E*)-**36**:(*Z*)-**36** >95:5]. δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.54 (6H, q, *J* 8.0, C(4)OSi(CH_2CH_3)$_3$), 0.73 (6H, q, *J* 8.1, OSi(CH_2CH_3)$_3$), 0.89 (9H, t, *J* 8.0, C(4)OSi(CH_2CH_3)$_3$), 1.05 (9H, t, *J* 8.0, OSi(CH_2CH_3)$_3$), 1.16 (3H, C(α)*Me*), 1.26 (9H, s, C*Me*$_3$), 2.17 (1H, ddd, *J* 13.3, 8.2, 5.1, C(5)H_A), 2.74 (1H, quin, *J* 6.9, C(5)H_B), 3.39 (1H, dd, *J* 10.0, 2.7, C(3)*H*), 3.46 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.59 (1H, ddd, *J* 7.7, 5.1, 2.7, C(4)*H*), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, d, *J* 10.0, C(2)*H*), 4.77−4.86 (2H, m, C(7)H_2), 4.53 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 5.13−5.25 (1H, m, C(6)*H*), 7.15−7.55 (10H, m, *Ph*).

4.19. *tert*-Butyl (2*R*,3*R*,4*R*,1'*S*,α*S*)-2-(1'-hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-hydroxyhept-6-enoate 38

HF (70% in py, 1.5 mL, 52.8 mmol) was added to a stirred solution of **37** (1.02 g, 1.76 mmol) in THF (10 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ was added until pH > 7 was achieved and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **38** as a white solid (740 mg, 90%, >99:1 dr); mp 90−92 °C; $[\alpha]_D^{25}$ +14.1 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 3360 (O−H), 3064, 2918, 2978

(C−H), 1722 (C=O), 1640 (C=C); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.9, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 2.15−2.31 (2H, m, C(5)*H*$_2$), 2.67 (1H, dd, *J* 7.3, 4.8, C(2)*H*), 2.85 (2H, br s, 2 × O*H*), 3.26 (1H, app t, *J* 4.8, C(3)*H*), 3.90 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.85−3.92 (1H, m, C(4)*H*), 4.15 (1H, q, *J* 6.9, C(α)*H*), 4.21 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.29 (1H, app t, *J* 7.3, C(1')*H*), 4.99–5.03 (1H, m, C(7)*H*$_A$), 5.02–5.06 (1H, m, C(7)*H*$_B$), 5.07 (1H, app d, *J* 10.5, C(3')*H*$_A$), 5.20 (1H, app d, *J* 17.2, C(3')*H*$_B$), 5.60−5.72 (1H, m, C(6)*H*), 5.80 (1H, ddd, *J* 17.2, 10.5, 7.3, C(2')*H*), 7.10−7.36 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 28.1 (C*Me*$_3$), 39.9 (*C*(5)), 52.2 (N*C*H$_2$Ph), 53.4 (*C*(2)), 60.7 (*C*(4)), 61.8 (*C*(3)), 70.9 (*C*(α)), 72.1 (*C*(1')), 81.5 (*C*Me$_3$), 117.1 (*C*(3')), 117.9 (*C*(7)), 126.6, 127.0, 128.2, 128.2, 128.3, 128.4 (*o,m,p-Ph*), 135.3 (*C*(6)), 138.1 (*C*(2')), 142.1, 144.7 (*i-Ph*), 172.3 (*C*(1)); *m/z* (ESI$^+$) 466 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_4^+$ ([M+H]$^+$) requires 466.2952; found 466.2947.

4.20. (2*S*,3*R*,4*R* 1'*S*,α*S*)-2-(1'-Hydroxyprop-2'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-en-1,4-diol 41

Step 1: CF_3CO_2H (3 mL) was added dropwise to a stirred solution of **37** (600 mg, 0.86 mmol, >99:1 dr) in CH_2Cl_2 (3 mL) at 0 °C. The resultant solution was allowed to warm to rt and stirred at rt for 16 h then satd aq $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **39** as a pale yellow oil (600 mg, >95:5 dr); δ_H (400 MHz, $CDCl_3$) 0.65 (6H, q, *J* 8.0, Si(C*H*$_2$CH$_3$)$_3$), 0.94 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 1.48 (3H, d, *J* 6.9, C(α)*Me*), 2.49−2.66 (2H, m, C(5)*H*$_2$), 2.94 (1H, dd, *J* 10.4, 4.3, C(2)*H*), 3.48 (1H, dd, *J* 10.4, 2.2, C(3)*H*), 3.83 (1H, d, *J* 13.9, NC*H*$_A$H$_B$Ph), 4.18−4.24 (1H, m, C(4)*H*), 4.24−4.36 (2H, m, C(1')*H*, C(α)*H*), 4.45 (1H, d, *J* 13.9, NCH$_A$*H*$_B$Ph), 5.05 (1H, d, *J* 10.4, C(3')*H*$_A$), 5.17 (3H, m, C(7)*H*$_2$, C(3')*H*$_B$), 5.62−5.85 (2H, m, C(6)*H*, C(2')*H*), 7.05−7.25 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.5 (Si(*C*H$_2$CH$_3$)$_3$), 7.1 (Si(CH$_2$*C*H$_3$)$_3$), 18.3 (C(α)*Me*), 39.4 (*C*(5)), 46.6 (*C*(2)), 52.8 (N*C*H$_2$Ph), 61.4 (*C*(3)), 62.3 (*C*(α)), 72.4 (*C*(4)), 73.1 (*C*(1')), 118.1 *C*(3')), 119.1 (*C*(7)), 128.1, 128.6, 128.7, 128.7, 128.8, 129.4 (*o,m,p-Ph*), 133.6 (*C*(2')), 134.9 (*i-Ph*), 137.1 (*C*(6)), 139.2 (*i-Ph*), 175.9 (*C*(1)); *m/z* (ESI)$^+$ 524 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{46}NO_4Si^+$ ([M+H]$^+$) requires 524.3190; found 524.3187.

Step 2: $LiAlH_4$ (2.4 M in THF, 1.7 mL, 4.16 mmol) was added to a stirred solution of the residue of **39** (600 mg, >95:5 dr) in THF (5 mL) at 0 °C. The resultant solution was allowed to warm to rt and heated at 70 °C for 16 h. The reaction mixture was allowed to cool to rt, then 2.0 M aq NaOH (2.1 mL, 4.20 mmol) was then added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was filtered through Celite® (eluent THF), then dried and concentrated *in vacuo* to give **40** (460 mg, >95:5 dr).

Step 3: HF (70% in py, 760 μL, 27.0 mmol) was added to a stirred solution of residue of **40** (460 mg, >95:5 dr) in THF (8 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 16 h. Satd aq $NaHCO_3$ was added until pH > 7 was achieved and the resultant mixture was stirred at rt for 30 min, then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **41** as a colourless oil (260 mg, 76% from **37**, >99:1 dr); $[\alpha]_D^{25}$ –9.9 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3359 (O−H), 2974 (C−H), 1701 (C=O), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.9, C(α)*Me*), 1.80−2.00 (1H, m, C(2)*H*), 2.30−2.40 (2H, m, C(5)H_2), 3.00 (1H, dd, *J* 6.6, 4.9, C(3)*H*), 3.44 (1H, dd, *J* 11.1, 3.9, C(1)H_A), 3.55 (1H, dd, *J* 11.1, 6.6, C(1)H_B), 3.93–3.98 (1H, m, C(4)*H*), 4.00 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.05 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.16 (1H, app t, *J* 5.7, C(1')*H*), 4.22 (1H, q, *J* 6.9, C(α)*H*), 5.08−5.16 (3H, m, C(3')H_A, C(7)H_2), 5.19−5.25 (1H, m, C(3')H_B), 5.74−5.90 (2H, m, C(6)*H*, C(2')*H*), 7.17−7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.2 (C(α)*Me*), 39.8 (*C*(5)), 46.0 (*C*(2)), 52.2 (N*C*H$_2$Ph), 58.5 (*C*(α)), 59.9 (*C*(3)), 62.1(*C*(1)), 71.0 (*C*(4)), 73.5 (*C*(1')), 116.1, 117.9 (*C*(7), *C*(3')), 127.0, 127.1, 128.0, 128.3, 128.4, 129.0 (*o,m,p-Ph*), 135.3 (*C*(2')), 139.1 (*C*(6)), 140.3, 144.0 (*i-Ph*); *m/z* $(ESI)^+$ 396 ($[M+H]^+$,100%); HRMS (ESI^+) $C_{25}H_{34}NO_3^+$ ($[M+H]^+$) requires 396.2533; found 396.2525.

4.21. (1*S*,2*R*,7*R*,7a*R*)-1-Hydroxymethyl-2,7-dihydroxy-hexahydro-1*H*-pyrrolizinium acetate 42·HOAc

Aminotriol **41** (250 mg, 0.63 mmol, >99:1 dr) was coevaporated with HCl (2.0 M in Et_2O, 3 × 3 mL), then the residue of **41**·HCl was dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant mixture was cooled to −78 °C and degassed with N_2 and O_2 before O_3 was purged through the solution until it turned blue. The reaction mixture was then purged with O_2, until it turned colourless, then polymer supported Ph_3P (3 mmol/g, 630 mg, 1.90 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo* to a total volume of 3 mL. AcOH (0.3 mL) and $Pd(OH)_2$/C (100 mg, 40% w/w) were added and the resultant mixture was degassed with N_2 and saturated with H_2, then stirred under an atmosphere of H_2 (5 atm) at rt for 48 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 6:4:1) gave **42**·HOAc as a white solid (90 mg, 65%, >99:1 dr); mp 212–214 °C; $[\alpha]_D^{20}$ +112.0 (*c* 0.2 in MeOH); ν_{max} (ATR) 3274 (O−H), 1572 (C=O); δ_H (400 MHz, D_2O) 1.84 (1H, s, CO*Me*), 1.07−2.14 (2H, m, C(6)H_2), 2.71−2.83 (1H, m, C(1)*H*), 3.30−3.40 (2H, m, C(3)H_A, C(5)H_A), 3.73 (1H, dd, *J* 13.7, 4.9, C(3)H_B), 3.89 (1H, dd, *J* 11.4, 6.7, C(1')H_A), 3.92 (1H, app dd, *J* 11.9, 6.4, C(5)H_B), 4.01 (1H, dd, *J* 11.4, 8.2, C(1')H_B), 4.33 (1H, dd, *J* 9.8, 3.5, C(7a)*H*), 4.48 (1H, app t, *J* 4.7, C(2)*H*), 4.53

(1H, app t, *J* 3.5, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 23.2 (CO*Me*), 35.8 (*C*(6)), 46.8 (*C*(1)), 55.1 (*C*(5)), 55.9 (*C*(1')), 62.2 (*C*(3)), 69.6 (*C*(7a)), 70.4, 72.9 (*C*(2), *C*(7)), 185 (*C*OMe); *m/z* (ESI^+) 174 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M+H]^+$) requires 174.1125; found 174.1124.

4.22. (1*S*,2*R*,7*R*,7a*R*)-1-(Acetoxymethyl)2,7-diacetoxyhexahydro-1*H*-pyrrolizidine 43

Ac_2O (375 μL, 4.00 mmol) and DMAP (10 mg, 0.08 mmol) were added to a stirred solution of **42**·HOAc (70 mg) in py (0.6 mL) and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with H_2O (3 × 5 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 2:1) gave **43** as a colourless oil (92 mg, 77%, >99:1 dr); $[\alpha]_D^{20}$ −22.0 (*c* 0.6 in $CHCl_3$); ν_{max} (ATR) 1734 (C=O); δ_H (400 MHz, $CDCl_3$) 2.03 (3H, s, CO*Me*$_A$), 2.07 (3H, s, CO*Me*$_B$), 2.10 (3H, s, CO*Me*$_C$), 2.01−2.16 (2H, m, C(6)H_2), 2.80−2.95 (3H, m, C(1)*H*, C(3)H_A, C(5)H_A), 3.12−3.19 (1H, m, C(5)H_B), 3.44 (1H, dd, *J* 12.0, 6.0, C(3)H_B), 3.63 (1H, dd, *J* 9.2, 4.0, C(7a)*H*), 4.20 (1H, dd, *J* 11.0, 7.3, C(1')H_A), 4.38 (1H, dd, *J* 11.0, 8.5, C(1')H_B), 5.22 (1H, app t, *J* 4.0, C(7)*H*), 5.36 (1H, app td, *J* 6.0, 3.4, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 20.8 (CO*Me*$_A$), 21.1 (CO*Me*$_B$), 21.6 (CO*Me*$_C$), 34.9 (*C*(6)), 42.1 (*C*(1)), 52.4 (*C*(5)), 60.1 (*C*(1')), 60.6 (*C*(3)), 68.6 (*C*(7a)), 74.7 (*C*(2)), 75.0 (*C*(7)), 169.9, 170.4, 170.9 (*C*OMe$_A$, *C*OMe$_B$, *C*OMe$_C$); *m/z* (ESI^+) 300 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{22}NO_6^+$ ($[M+H]^+$) requires 300.1442; found 300.1442.

4.23. (1*S*,2*R*,7*R*,7a*R*)-1-Hydroxymethyl-7,2-dihydroxy-hexahydro-1*H*-pyrrolizine [(+)-2-*epi*-rosmarinecine] 42

K_2CO_3 (70 mg, 0.51 mmol) was added to a solution of **43** (50 mg, 0.17 mmol, >99:1 dr) in MeOH (1 mL). The resultant mixture was stirred at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification via column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 6:4:1) gave **42** as a white solid (30 mg, quant, >99:1 dr); mp 187–189 °C; $[\alpha]_D^{20}$ +18.3 (*c* 0.37 in EtOH); for **42**·HCl: $[\alpha]_D^{20}$ −27.0 (*c* 0.3 in EtOH); {lit.[44] for **42**·HCl: $[\alpha]_D^{20}$ −31.2 (*c* 1.3 in EtOH)}; ν_{max} (ATR) 3243 (O–H); δ_H (400 MHz, D_2O) 1.71−1.92 (2H, m, C(6)H_2), 2.40−2.50 (1H, m, C(1)*H*), 2.70−2.83 (2H, m, C(3)H_A, C(5)H_A), 3.08 (1H, dd, *J* 13.4, 4.0, C(3)H_B), 3.14−3.23 (1H, m, C(5)H_B), 3.49 (1H, dd, *J* 9.1, 3.6, C(7a)*H*), 3.81 (1H, dd, *J* 11.0, 6.3, C(1')H_A), 3.95 (1H, dd, *J* 11.0, 8.5, C(1')H_B), 4.13−4.21 (2H, m, C(2)*H*, C(7)*H*); δ_C (100 MHz, D_2O) 36.1 (*C*(6)), 47.1 (*C*(1)), 53.4 (*C*(5)), 57.0 (*C*(1')), 62.0 (*C*(3)), 69.8 (*C*(7a)), 70.6, 71.5 (*C*(2), *C*(7)); *m/z* (ESI^+) 174 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M+H]^+$) requires 174.1125; found 174.1125.

References and Notes

[1] (a) Searle, P. A.; Molinski, T. F. *J. Org. Chem.* **1993**, *58*, 7578; (b) Rich, D. H. In *Peptidase Inhibitors in Comprehensive Medicinal Chemistry*, Ed. Sammes, P. G. Pergamon Press, Oxford, 1990, Vol. 2, pp. 391; (c) Woo, P. W. K. *Tetrahedron Lett.* **1985**, *26*, 2973; (d) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Lett.* **1987**, *16*, 1531; (e) Maibaum, J.; Rich, D. H. *J. Org. Chem.* **1988**, *53*, 869; (f) Devant, R. M.; Radunz, H. E. *Tetrahedron Lett.* **1988**, *29*, 2307; (f) Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014**, *31*, 1721.

[2] Yamada, K.; Tatematsu, H.; Unno, R.; Hirata, Y. *Tetrahedron Lett.* **1978**, *46*, 4543.

[3] Bai, Y.; Duke, N.; Gul, W.; Huang, Y. Y.; Rueger, H. *Arkivoc* **2006**, *iii*, 34.

[4] Shi, B.-J.; Xiong, A.-Z.; Zheng, S.-S.; Chou, G.-X.; Wang, Z.-T. *Nat. Prod. Rep.* **2010**, *24*, 1897.

[5] Haberer, W.; Dobler, S. *Chemoecology* **1999**, *9*, 169.

[6] Danilova, A.; Utkin, L.; Massagetov, P. *Zh. Obshch. Khim.* **1955**, *25*, 831.

[7] Mohanraj, S.; Kulanthaivel, P.; Subramanian, P.; Herz, W. *Phytochemistry* **1981**, *20*, 1991.

[8] (a) De Waal, H. L. *Nature* **1940**, *146*, 777; (b) Richardson, M. F.; Warren, F. L. *J. Chem. Soc.* **1943**, 452.

[9] Sawhney, R. S.; Atal, C. K.; Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1974**, *27*, 1805.

[10] Mulzer, J.; Scharp, M. *Synthesis* **1993**, 615.

[11] Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y.; Shiro, M. *J. Am. Chem. Soc.* **1994**, *116*, 5469.

[12] (a) Denmark, S. E.; Parker, D. L. Jr.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 435; (b) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Org. Chem.* **1995**, *60*, 3574; (c) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266.

[13] Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096.

[14] For example, see: (a) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2012**, *14*, 4278; (b) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron* **2012**, *68*, 4302; (c) 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; (d) Davies, S. G.; Fletcher, A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 9779; (e) Brock, E. A.; Davies, S. G.; Lee, J. A; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2013**, *11*, 3187; (f) Davies, S. G.; Fletcher A. M.; Lee, J. A.; Lorkin, T. J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2013**, *15*, 2050; (g) Davies, S. G.; Fletcher, A. M.; Lebée, C.; Roberts, P. M.; Thomson, J. E.; Yin, J. *Tetrahedron* **2013**, *69*, 1369; (h) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 2544; (i) Buchman, M.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Houlsby, I. T. T.; Roberts, P. M.; Rowe, S.; Thomson, J. E. *J. Org. Chem.* **2016**, *81*, 4907; (j) Davies, S. G.; Goddard, E, C.; Roberts, P. M.; Russell, A. J.; Smith, A. D.;

Thomson, J. E.; Withey, J. M. *Tetrahedron: Asymmetry* **2016**, *27*, 274; (k) Davies, S. G.; Fletcher, A. M.; Shah, R. S.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2015**, *80*, 4017; (l) Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Ford, J. G.; Klauber, D. J.; Roberts, P. M. Thomson, J. E. *Tetrahedron* **2015**, *71*, 7170; (m) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Shah, R. S.; Thompson, A. L.; Thomson, J. E. *Org. Lett.* **2014**, *16*, 1354.

[15] 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.

[16] Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2016**, *72*, 4523.

[17] Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 204.

[18] Sengoku, T.;Suzuki, T.; Kakimoto, T.; Takahashi, M.; Yoda, H. *Tetrahedron* **2009**, *65*, 2415.

[19] For selected reviews, see: (a) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917; (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352; (c) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65; (d) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506; (e) Kan, S. B. J.; Ng, K. K.-H.; Paterson, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 9097.

[20] For example, see: (a) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, 20, 131; (b) Ariza, X.; Garcia, J.; Romea, P.; Urpí, F. *Synthesis* **2011**, 2175.

[21] (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1129; (b) Davies, S. G.; Fletcher, A. M.; Hermann, G. J.; Poce, G.; Roberts, P. M.; Smith, A. D.; Sweet, M. J.; Thomson, J. E. *Tetrahedron: Asymmetry* **2010**, *21*, 6135; (c) 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.

[22] Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron*, **2009**, *65*, 10192.

[23] β-Amino ester was prepared in 86% yield and >99:1 dr upon conjugate addition of (*S*)-**13** to α,β-unsaturated ester **19**.

[24] The geometries of lithium enolates (*E*)-**20** and (*Z*)-**20** were confirmed by trapping with TMSCl and analysing the resultant silyl ketene acetals by ^{1}H NMR and NOESY spectroscopic analyses.

[25] Davies, S. G.; Fenwick, D. R. *Chem. Commun*. **1997**, 565.

[26] Crystallographic data (excluding structure factors) for the structures of **26**·HBF_4, **9**, **38** and **42** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1497139–1497142, respectively.

[27] NMR spectroscopic data for (−)-1-*epi*-macronecine **28** have not been previously reported.

[28] Aasen, A. J.; Culvenor, C. C. J. *J. Org. Chem.* **1969**, *34*, 4143.

[29] Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045.

[30] Aasen, A. J.; Culvenor, C. C. J. *Chem. Commun.* **1969**, 34.

[31] Sarkar, T. S.; Hazra, A.; Gangopadhyay, P.; Panda, N.; Slanina, Z.; Lin, C.-C.; Chem, H.-T. *Tetrahedron*, **2005**, 1155.

[32] The absolute configuration of the C(7a) stereogenic center was unambiguously established by single crystal X-ray diffraction analyses of **26**·HBF_4 and also *tert*-butyl (2*S*,3*R*,4*R*,α*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]4-(triethylsilyloxy)hept-6-enoate and *tert*-butyl (1*S*,6*R*,7*R*,α*S*)-6-hydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-hydroxylcyclohept-3-en-1-carboxylate which all derive from the common lithium (*Z*)-β-amino enolate precursor; see ref 16.

[33] Ma, D.; Zhang, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1703.

[34] Rüeger, H.; Benn, M. *Heterocycles* **1983**, *20*, 235.

[35] Ahn, J.-B.; Yun, C.-S.; Kim, K. H.; Ha, D.-C. *J. Org. Chem.* **2000**, *65*, 9249.

[36] The geometry of lithium enolate (*E*)-**36** was confirmed by trapping with TESCl and analysing the resultant silyl ketene acetal by ^{1}H NMR and NOESY spectroscopic analyses.

[37] Various other attempts to selectively form the diastereoisomeric products, including the addition of acrolein to the corresponding (*Z*)-β-amino enolate [derived from conjugate addition of (*S*)-**13** to γ-silyloxy-β-amino ester **12**], gave only complex mixtures of products; in all cases **37** was present as the major component.

[38] Difficulties in the purification in a related system have been previously reported in literature; see: ref 12(c).

[39] Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876; (b) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143.

[40] Basu, S.; Kandiyal, S. P.; Ampapathi, R. A.; Chakraborty, T. K. *RSC Adv.* **2013**, *3*, 13630.

[41] It is noteworthy that the ^{1}H and ^{13}C NMR spectroscopic data for the corresponding AcOH salt **42**·HOAc also did not match with those reported by Chakraborty et al.

[42] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[43] 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.

[44] Rüger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331.