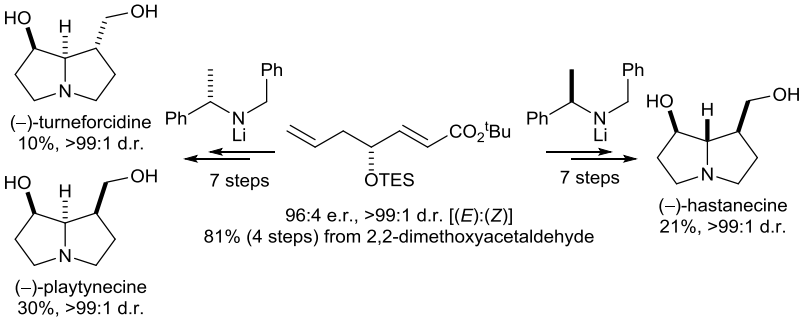
Asymmetric syntheses of (–)-hastanecine, (–)-turneforcidine and (–)-platynecine

Marta Brambilla, Stephen G. Davies,* Ai M. Fletcher, Paul M. Roberts, and 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 (–)-hastanecine, (–)-turneforcidine and (–)-platynecine

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

Abstract

Concise total asymmetric syntheses of three diastereoisomeric 1-hydroxymethyl-7-hydroxy substituted pyrrolizidines, (–)-hastanecine, (–)-turneforcidine and (–)-platynecine, are reported. The doubly diastereoselective conjugate additions of lithium (*R*)- or (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl (*R*,*E*)-4-(triethylsilyloxy)hepta-2,6-dienoate [which was prepared (in 96:4 e.r.) via Lewis acid mediated catalytic asymmetric allylation of *tert*-butyl (*E*)-4-oxobut-2-enoate] proceeded in both cases under the dominant control of the lithium amide reagent. Subsequent diastereoselective enolate allylations installed the required stereogenic centres, and the pyrrolizidine ring system was rapidly accessed by a two-step protocol (viz. ozonolysis and one-pot hydrogenolysis/double reductive cyclisation), to complete the asymmetric syntheses of (–)-hastanecine, (–)-turneforcidine and (–)-platynecine in 17, 8 and 24% overall yield, respectively, in 11 steps from commercially available 2,2-dimethoxyacetaldehyde in each case.

Key words: (–)-hastanecine, (–)-turneforcidine, (–)-platynecine, lithium amide, conjugate addition, asymmetric synthesis, pyrrolizidines

Introduction

Pyrrolizidines **1** are commonly occurring structural units within natural products that display an extensive range of biological activities.[1] Among them, 1-hydoxymethyl-7-hydroxy substituted pyrrolizidines **2** are a sub-class of the pyrrolizidine alkaloids. To date, several naturally occurring 1-hydroxymethyl-7-hydroxy substituted pyrrolizidines have been isolated,[2] such as (–)-hastanecine **3**[2i] (–)-turneforcidine **4**,[2l] and (–)-platynecine **5**.[2k] 1-Hydoxymethyl-2,7-dihydroxy substituted pyrrolizidines such as (–)-rosmarinecine **6**[2j] and (+)-croalbinecine (helifolinecine) **7**,[2m] and more recently (–)-hadinecine **8**[2p] have also been isolated. Retrohoustine **9** was isolated along with other two related 1-hydroxymethyl-7-hydroxyl pyrrolizidine alkaloids, heliohoustine **10** and isoretrohoustine **11**, from leaves of *Ageratum houstonianum*, which have been used in traditional medicine in Mexico for their antifungal and antimicrobial properties (Figure 1).[3]

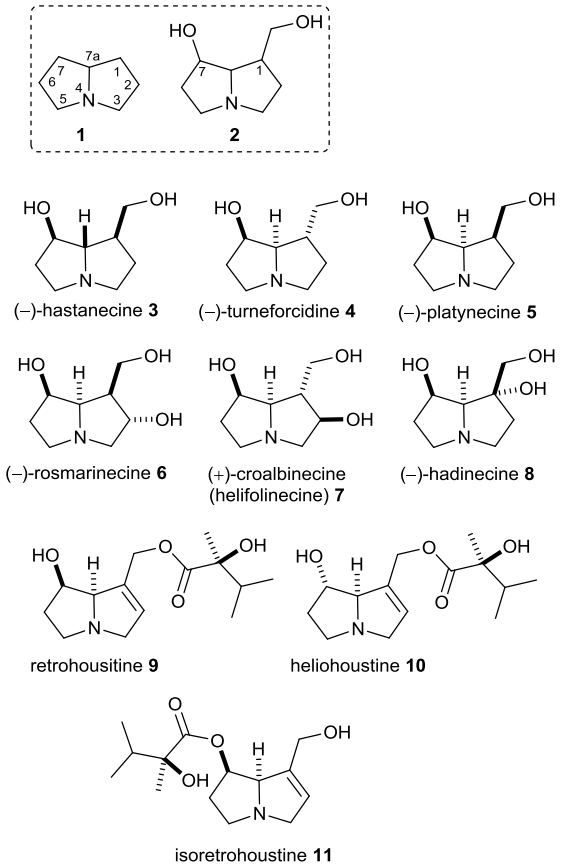


Fig. 1. 1-Hydroxymethyl-7-hydroxy substituted pyrrolizidines **3**–**5** and their more highly substituted analogues **6**–**11**.

Asymmetric and enantiospecific syntheses of 1-hydroxymethyl substituted pyrrolizidines have been actively pursued employing strategies such as chiral auxiliary approaches,[4] enantioselective catalysis,[5] diastereoselective reactions of enantiopure precursors derived from L-proline (e.g., hydrogenation of unsaturated azabicycles,[6] and radical[7] or transition metal[8] mediated cyclisations).[9] As part of our on-going research programme concerning the synthesis of azacyclic natural products,[10] we became interested in developing methodology for the synthesis of 1-hydroxymethyl pyrrolizidines. We have recently reported the asymmetric synthesis of (–)-isoretronecanol and (–)-trachelantamidine by employing the diastereoselective conjugate addition[11] of enantiopure lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to an α,β-unsaturated ester followed by enolate allylation as the key stereodefining steps. Olefinic oxidation[12,13] and reduction with $LiAlH_4$ allowed construction of the pyrrolizidine motif via a two-step protocol involving oxidative cleavage of the resultant 1,2-diol followed by one-pot hydrogenolysis and double reductive cyclisation of the corresponding aldehyde to give (–)-isoretronecanol and (–)-trachelantamidine as single diastereoisomers.[14,15] Following a related approach, we envisaged that 1-hydroxymethyl-7-hydroxy substituted pyrrolizidines **17** could be efficiently accessed via the double reductive cyclisation of bisaldehyde **16** (X = $CO_2{}^tBu$ or CH_2OH), which could be directly derived from olefinic oxidation (such as ozonoylsis) of diastereoisomerically pure dienyl β-amino ester **14** or the corresponding alcohol **15**. These substrates would be prepared via our diastereoselective conjugate addition methodology[11] upon reaction of the enantiopure

lithium amide reagents (*R*)-**13** or (*S*)-**13** with enantiopure α,β-unsaturated ester **12**, followed by enolate allylation (Figure 2). Herein, we report the application of this strategy in concise asymmetric syntheses of three diastereoisomeric 1-hydroxymethyl-7-hydroxy substituted pyrrolizidine alkaloids: (–)-hastanecine **3**, (–)-turneforcidine **4** and (–)-platynecine **5**.

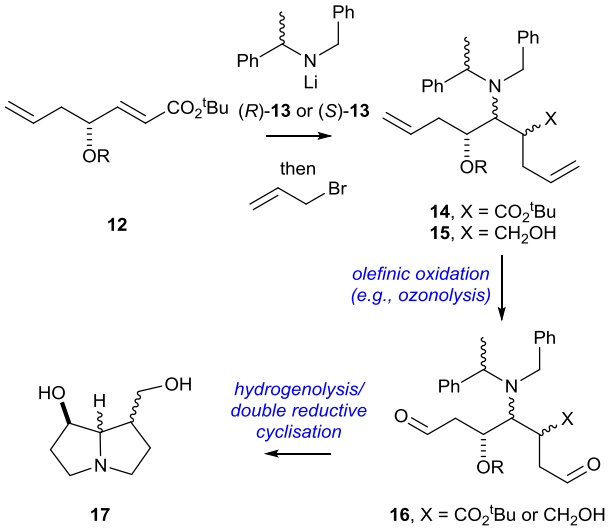
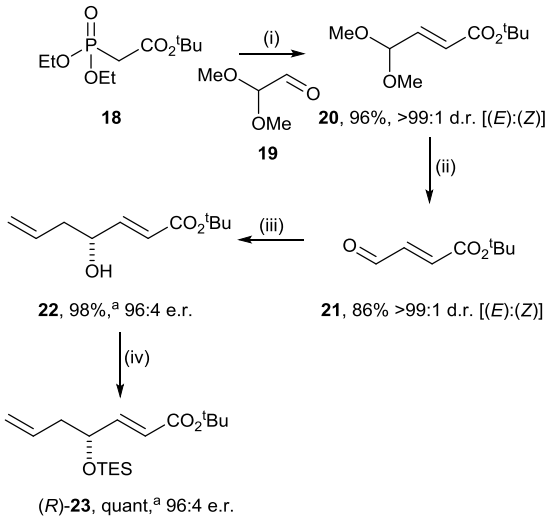


Fig. 2. Synthetic strategy towards 1-hydroxymethyl-7-hydroxy substituted pyrrolizidines **17**.

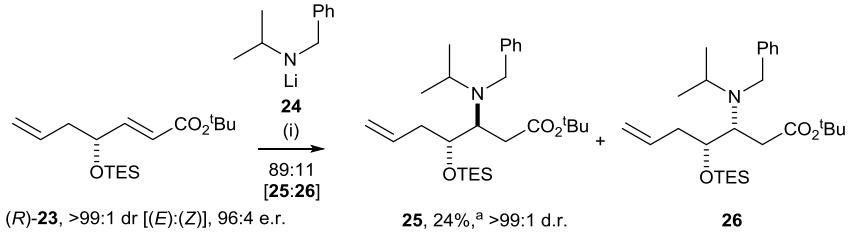
2. Results and Discussion

The enantiopure γ-hydroxy-α,β-unsaturated ester (*R*)-**22** was prepared via an analogous route to the corresponding known ethyl ester.[16,17] Aldehyde **21** was prepared by olefination of 2,2-dimethoxyacetaldehyde **19** with *tert*-butyl phosphonoacetate **18** followed by acetal hydrolysis in the presence of TsOH, which gave **21** in 83% yield (over 2 steps) and >99:1 d.r. Treatment of aldehyde **21** with allyltributyltin and a catalytic amount of $Ti(O^iPr)_4$, CF_3CO_2H and (+)-(*R*)-BINOL gave α,β-unsaturated ester (*R*)-**22** in 98% yield and 96:4 e.r.[18] The absolute configuration of **22** was first assigned by analogy to that of the corresponding ethyl ester,[16] and was later unambiguously established by single crystal X-ray diffraction analyses of several derivatives (*vide infra*). The *O*-silyl protected derivative (*R*)-**23**, the common precursor for (–)-hastanecine **3**, (–)-turnefocidine **4** and (–)-platynecine **5**, was prepared in quantitative yield upon treatment of (*R*)-**22** with TESCl and imidazole in the presence of a catalytic amount of DMAP (Scheme 1).



Scheme 1. *Reagents and Conditions*: (i) K_2CO_3, **19**, cyclohexane, 60 °C, 16 h; (ii) TsOH, acetone/H_2O (1:1), 70 °C, 1.5 h; (iii) $Ti(O^iPr)_4$, CF_3CO_2H, (+)-(*R*)-BINOL, 4 Å MS then allyltributyltin, CH_2Cl_2, –78 °C, 10 min then –20 °C, 72 h; (iv) TESCl, imidazole, DMAP, CH_2Cl_2, rt, 16 h. [[a] >99:1 d.r., (*E*):(*Z*)].

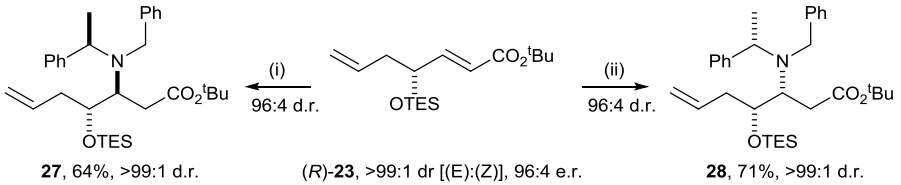
The inherent level of substrate control offered by the enantiopure α,β-unsaturated ester (*R*)-**23**[19] upon conjugate addition was evaluated upon reaction with achiral lithium *N*-benzyl-*N*-isopropylamide **24**: the conjugate addition of **24** to α,β-unsaturated ester (*R*)-**23**[20] gave an 89:11 mixture of 3,4-*anti*-**25** and 3,4-*syn*-**26**, respectively. Upon purification, the major product **25** was isolated in 24% yield as a single diastereoisomer (>99:1 d.r.), along with an 85:15 mixture of **25** and **26**, respectively, in 67% combined yield (Scheme 2). The configurations of **25** and **26** were determined by chemical correlation (*vide infra*). It was predicted that the reaction between lithium amide (*R*)-**13** and α,β-unsaturated ester (*R*)-**23** would be the doubly diastereoselective[21] "matched" pairing of chiral reagent and chiral substrate, and the reaction between (*S*)-**13** and (*R*)-**23** would be the doubly diastereoselective[21] "mismatched" pairing.



Scheme 2. *Reagents and Conditions*: (i) **24**, THF, –78 °C, 2 h. [[a] an 85:15 mixture of **25** and **26** was also isolated in 67% combined yield].

Conjugate addition of (*R*)-**13** to α,β-unsaturated ester (*R*)-**23** (96:4 e.r.) gave a 96:4 mixture of β-amino esters **27** and *ent*-**28**, and **27** was isolated in 64% yield and >99:1 d.r. after purification, while conjugate addition of (*S*)-**13** to (*R*)-**23** (96:4 e.r.) gave a 96:4 mixture of β-amino esters **28** and *ent*-**27**, and **28** was isolated in 71% yield and >99:1 d.r. after purification (Scheme 3). The relative configurations within **27** and **28** were unambiguously established by single crystal X-ray diffraction analyses of their derivatives (*vide infra*). In each case the minor diastereoisomeric product must be derived from the minor enantiomeric component of the starting material (*S*)-**23** as the 96:4 d.r. observed upon conjugate addition indicates that

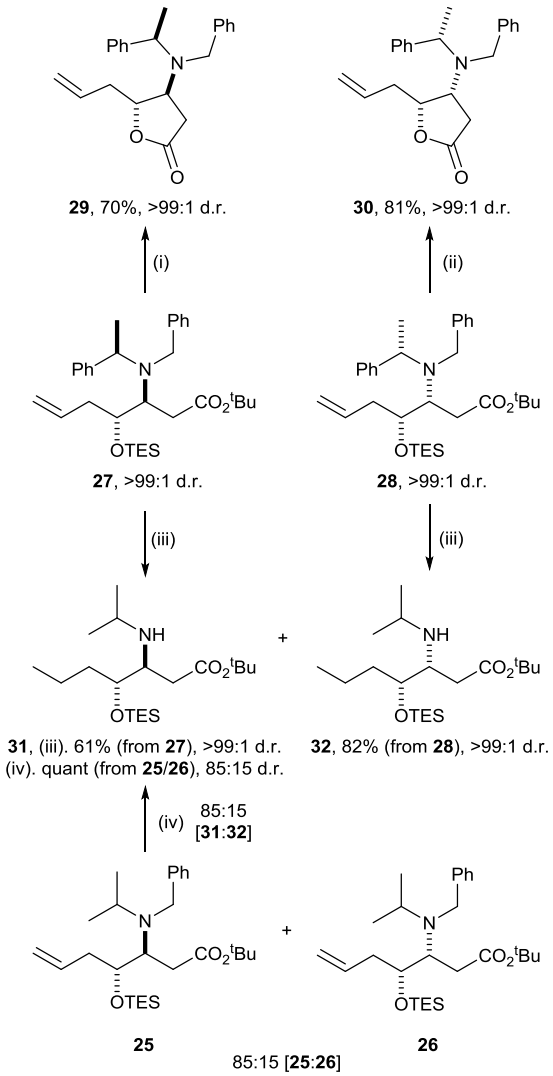
both reactions are completely diastereoselective under the (totally) dominant control of the lithium amide reagent, despite the reasonable levels of substrate control (89:11 d.r.) observed upon conjugate addition of achiral lithium *N*-benzyl-*N*-isopropylamide **24** to α,β-unsaturated ester (*R*)-**23**.



27, 64%, >99:1 d.r. (*R*)-**23**, >99:1 dr [(E):(Z)], 96:4 e.r. **28**, 71%, >99:1 d.r.

Scheme 3. *Reagents and Conditions*: (i) (*R*)-**13**, THF, –78 °C, 2 h; (ii) (*S*)-**13**, THF, –78 °C, 2 h.

Treatment of β-amino esters **27** and **28** with TBAF promoted *O*-desilylation and *in situ* lactonisation to give exclusively **29** and **30** in 70 and 81% yield, respectively, and >99:1 d.r. in each case (Scheme 4). The relative configurations within **29** and **31** were unambiguously established by single crystal X-ray diffraction analyses and the absolute (4*S*,5*R*,α*R*)-configuration of **29** and absolute (4*R*,5*R*,α*S*)-configuration of **30** were assigned by reference to the known (*R*)- and (*S*)-configurations of the α-methylbenzyl fragments, respectively (Fig. 3).[22] These analyses therefore also confirmed the assigned configurations of β-amino esters **27** and **28**, and α,β-unsaturated esters **22** and **23**. Hydrogenolysis of **27** and **28** mediated by Pearlman's catalyst, in a 10:1 mixture of MeOH/acetone promoted concomitant *N*-debenzylation and reductive alkylation to give **31** and **32** in 61 and 82% yield, respectively, and >99:1 d.r. in both cases. Similarly, hydrogenolysis of an 85:15 mixture of **25** and **26** [derived from the conjugate addition of achiral lithium amide **24** to α,β-unsaturated ester **23**], gave an 85:15 mixture of β-amino esters **31** and **32**, respectively, in quantitative yield (Scheme 4). The ^{1}H and ^{13}C NMR spectroscopic data of the major diastereisomer **31** obtained from the *N*-debenzylation of the 85:15 mixture of **25** and **26**, respectively were identical to those obtained from the authentic sample of **31** obtained by hydrogenolytic N-debenzylation and *in situ* reductive alkylation of **27**. Thus, the relative configurations within **25** and **26** and the sense of the substrate control offered by enantiopure α,β-unsaturated ester **23** upon conjugate addition, were unambiguously established by these correlation experiments.



Scheme 4. *Reagents and Conditions*: (i) TBAF (1.0 M in THF), THF, rt, 16 h; (ii) TBAF (1.0 M in THF), THF, rt, 48 h; (iii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH/acetone (10:1), rt, 24 h; (iv) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h.

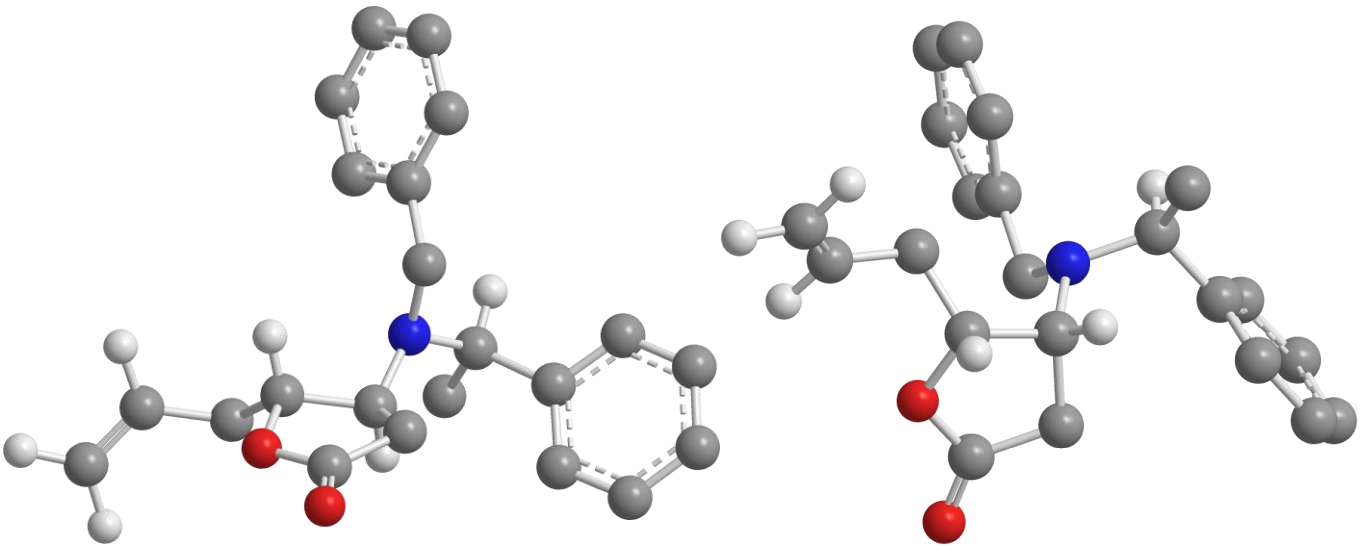
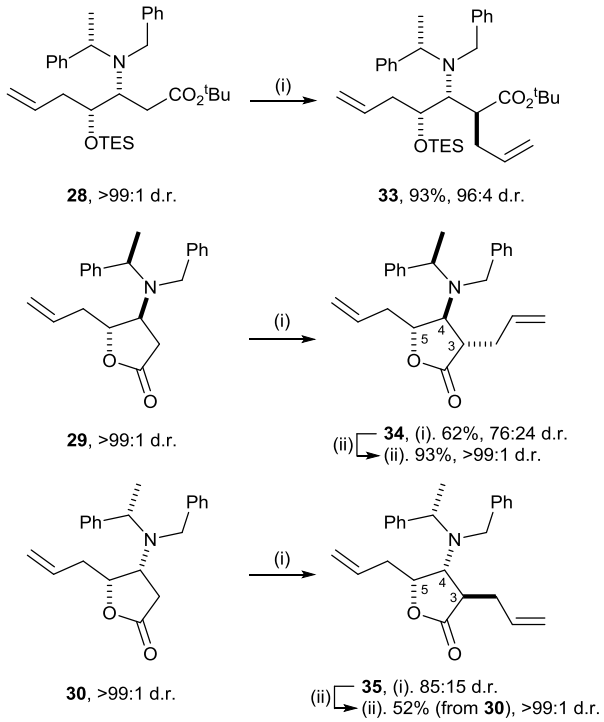


Fig. 3. X-ray crystal structures of (4*S*,5*R*,α*R*)-**29** [*left*] and (4*R*,5*R*,α*S*)-**30** [*right*] (selected H atoms are omitted for clarity).

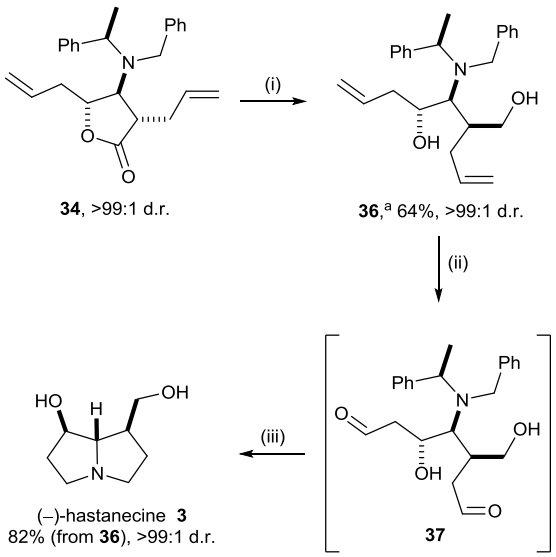
Efforts to install the second olefinic unit required for the oxidation then double reductive cyclisation protocol were next evaluated via either (i) treatment of the intermediate lithium (*Z*)-β-amino enolate[23] arising from conjugate addition of the enantiopure lithium amide reagent (*S*)-**13** or (*R*)-**13** to α,β-unsaturated ester **23** with

allyl bromide (i.e., a "tandem" approach), or (ii) deprotonation of the corresponding β-amino esters **27** or **28** followed by treatment of the corresponding lithium (*E*)-β-amino enolate[23] with allyl bromide (i.e., a "stepwise" approach). Attempts to obtain α-allyl-β-amino esters via a "tandem" approach were not successful, giving only β-amino esters **27** and **28**, respectively. Under the optimised "stepwise" conditions, allylation of the lithium (*E*)-amino enolate derived from deprotonation of β-amino ester **28** with LDA gave **33** in 93% yield and 96:4 d.r. The relative configuration of **33** was unambiguously established by single crystal X-ray diffraction analysis of a derivative (*vide infra*). In contrast to the successful "stepwise" enolate allylation of β-amino ester **28**, attempted allylation of **27** under identical conditions gave mainly starting material **27** (>50%). The somewhat substrate dependent nature of both "tandem" and "stepwise" enolate allylations of β-amino esters has been reported in similar systems.[15,23a,24] Instead, sequential treatment of lactone **29** with LDA and allyl bromide gave **34** in 62% yield and 76:24 d.r., as an inseparable mixture of C(3)-epimers. The diastereoisomeric purity of **34** (76:24 d.r.) was enriched upon treatment with KO^{t}Bu, which gave **34** in 93% yield and >99:1 d.r. Similarly, allylation of lactone **30** upon sequential treatment with LDA and allyl bromide gave **35** in 85:15 d.r. Subsequent treatment of **35** (85:15 d.r.) with KO^{t}Bu afforded **35** as a single diastereoisomer (>99:1 d.r.) in 52% isolated yield after chromatographic purification (Scheme 5). The relative 3,4-*anti* configurations within **34** and **35** were tentatively assigned by analogy to literature examples, where allylation of β-subsituted γ-butyrolactones is known to give the corresponding 3,4-*anti* diastereoisomers as the major products;[25] these assignments were supported by ^{1}H NMR nOe analyses of **34** and **35**, and subsequently confirmed by chemical correlation to known pyrrolizidine alkaloids (*vide infra*).



Scheme 5. *Reagents and Conditions*: (i) LDA, THF, 0 °C, 1 h then allyl bromide, 0 °C to rt, 2 h; (ii) KO^{t}Bu, THF, rt, 18 h.

Reduction of **34** with $LiAlH_4$ gave diol **36** in 64% yield and >99:1 d.r. However, superior overall yield of **36** was obtained directly from **29** without purification of the intermediates. To prevent *N*-oxidation in the subsequent ozonolysis step, **36** was converted into the corresponding hydrochloride salt **36**·HCl. Treatment of **36**·HCl with O_3 followed by addition of polymer-bound PPh_3 gave the corresponding dialdehyde **37**, and subsequent hydrogenolytic removal of the *N*-protecting groups facilitated *in situ* reductive cyclisation onto both pendant aldehyde functionalities to give pyrrolizidine **3**. Purification of the crude reaction mixture on DOWEX ion exchange resin gave (–)-hastanecine **3** in 82% yield (from **36**) and >99:1 d.r. (Scheme 6). The spectroscopic data, melting point and specific rotation for this sample of (–)-hastanecine **3** were in good agreement with literature data[26] {mp 109–110 °C; lit.[26g] mp 112.5–113.5 °C; lit.[26e] mp 113–114 °C; lit.[26d] mp 111–112 °C; $[\alpha]_D^{20}$ –8.3 (*c* 0.9 in EtOH); lit.[26g] $[\alpha]_D^{25}$ –10.0 (*c* 0.7 in EtOH); lit.[26d] $[\alpha]_D^{23}$ –10.4 (*c* 0.4 in EtOH)} and distinct from those for the known C(1)-epimer.[26e,27] Thus, this also confirmed the configurations of **34**, **36** and **37**. The total asymmetric synthesis of (–)-hastanecine **3** was therefore achieved in 11 steps and 17% overall yield from commercially available aldehyde **19**.



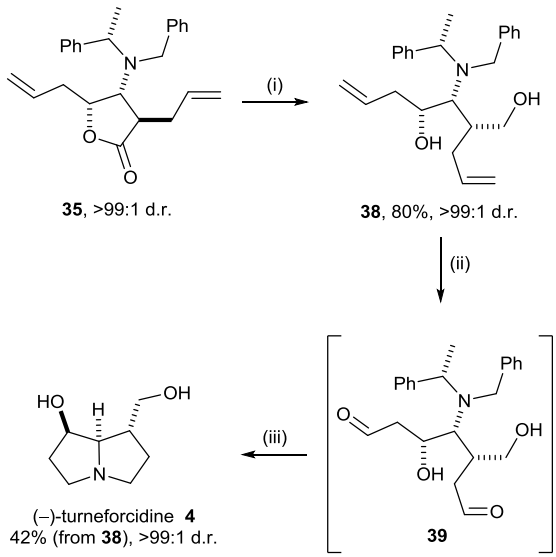
34, >99:1 d.r.

36,[a] 64%, >99:1 d.r.

(–)-hastanecine **3**
82% (from **36**), >99:1 d.r.

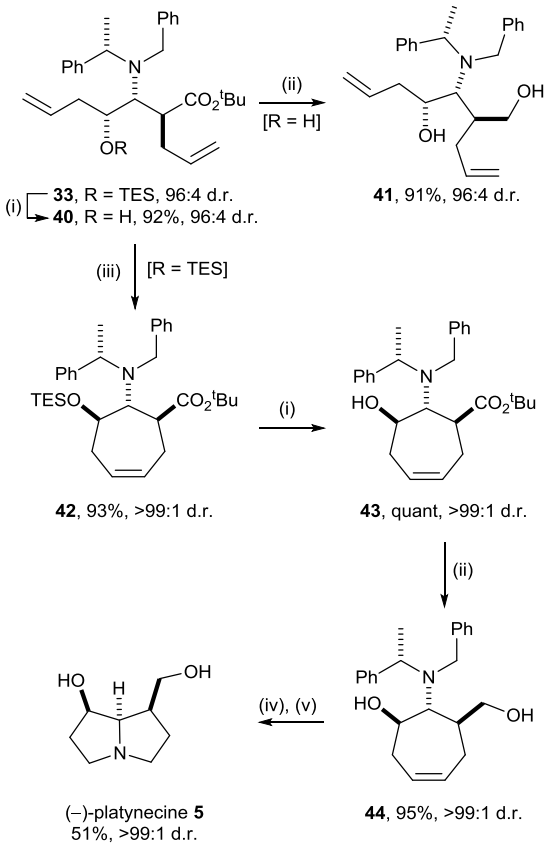
Scheme 6. *Reagents and Conditions*: (i) $LiAlH_4$, THF, 0 °C, 2 h; (ii) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C then polymer-bound PPh_3, rt, 2 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h. [[a] **36** was also isolated in 57% yield and >99:1 d.r. (from **29**) over 3 steps without purification of the intermediates].

Reduction of **35** with $LiAlH_4$ gave diol **38** in 80% yield and >99:1 d.r. Ozonolysis of the corresponding hydrochloride salt **38**·HCl, followed by hydrogenolysis/double reductive cyclisation gave (–)-turneforcidine **4** in 42% yield and >99:1 d.r. after purification (Scheme 7). The spectroscopic data, melting point and specific rotation for this sample of (–)-turneforcidine **4** were in good agreement with literature data[26a,26b,26i,28] {mp 109–110 °C; lit.[26i] mp 118–120 °C; $[\alpha]_D^{20}$ –10.0 (*c* 0.8 in MeOH); lit.[26i] $[\alpha]_D^{24}$ –11.4 (*c* 1.2 in MeOH); lit.[28a,28d] $[\alpha]_D^{26}$ –13.9 (*c* 0.4 in MeOH); lit.[26j] $[\alpha]_D^{23}$ –12.5 (*c* 1.3 in MeOH)}. The total asymmetric synthesis of (–)-turneforcidine **4** was therefore achieved in 11 steps and 8% overall yield from commercially available aldehyde **19**.



Scheme 7. *Reagents and Conditions*: (i) $LiAlH_4$, THF, 0 °C, 2 h; (ii) HCl (2.0 M in Et_2O) then O_3, CH_2Cl_2/MeOH (1:1), –78 °C then polymer-bound PPh_3, rt, 2 h; (iii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h then 50 °C, 72 h.

Treatment of **33** (96:4 d.r.) with TBAF for 24 h gave only partial deprotection of the *O*-TES group, however, complete removal of the *O*-TES group was achieved by using HF·pyridine within 18 h, which gave **40** in 92% yield and 96:4 d.r. Reduction of **40** with $LiAlH_4$ gave diol **41** in 91% yield and 96:4 d.r. The attempted formation of the corresponding pyrrolizidine was performed under identical conditions to those employed in the syntheses of (–)-hastanecine **3** and (–)-turneforcidine **4** (i.e., ozonolysis of the corresponding hydrochloride salt **41**·HCl followed by hydrogenolysis/double reductive cyclisation), but unfortunately this gave a complex mixture of products, containing some *N*-methylated species (which are presumably derived from the competitive reductive *N*-methylation upon reaction with the formaldehyde formed in the ozonolysis step). Alternatively, **33** was treated with Grubbs I catalyst to give **42** in 93% yield and >99:1 d.r. Subsequent *O*-TES deprotection with HF·pyridine afforded **43** in quantitative yield and >99:1 d.r. (Scheme 8). The relative configuration within **43** was unambiguously established by single crystal X-ray diffraction analysis and the absolute (1*S*,6*R*,7*R*,α*S*)-configuration of **43** was assigned by reference to the known (*S*)-configuration of the α-methylbenzyl fragment (Figure 4).[22] This analysis therefore also confirmed the assigned configurations within β-amino esters **33**, **40** and **42**, and diol **41**. Reduction of **43** with $LiAlH_4$ gave diol **44** in 95% yield and >99:1 d.r. Ozonolysis of the corresponding hydrochloride salt **44**·HCl followed by hydrogenolysis/double reductive cyclisation gave (–)-platynecine **5** in 51% yield and >99:1 d.r. (Scheme 8). The spectroscopic data, melting point and specific rotation for this sample of (–)-platynecine **5** were in good agreement with literature data[26a,26b,26i,26j,27a,28a–e,29] {mp 140–142 °C; lit.[30] mp 145–146 °C; lit.[29g] mp 149–151 °C; lit.[29e] mp 147–148 °C; lit.[26i] mp 151–152 °C; lit.[29f] mp 147.5–149 °C; $[\alpha]_D^{20}$ –58.8 (*c* 0.9 in EtOH); lit.[26a] $[\alpha]_D^{20}$ –51 (*c* 0.9 in EtOH); lit.[29g] $[\alpha]_D^{20}$ –58 (*c* 1 in EtOH)}. The total asymmetric synthesis of (–)-platynecine **5** was therefore achieved in 11 steps and 24% overall yield from commercially available aldehyde **19**.



Scheme 8. *Reagents and Conditions*: (i) HF·pyridine, THF, rt, 18 h; (ii) $LiAlH_4$, THF, –78 °C to rt, 18 h; (iii) Grubbs I, CH_2Cl_2, 35 °C, 18 h; (iv) HCl (2.0 M in Et_2O), rt then O_3, CH_2Cl_2/MeOH, –78 °C then polymer-bound PPh_3, rt, 2 h; (v) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (10:1), rt, 48 h.

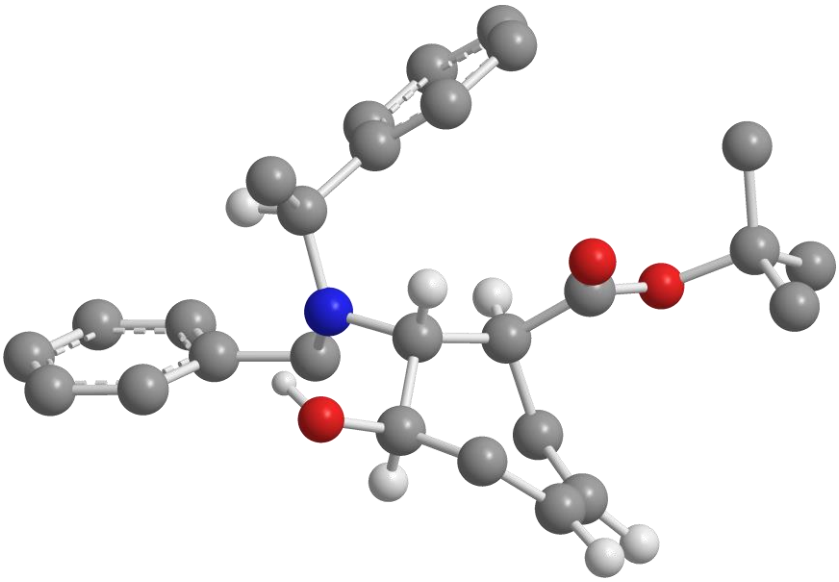


Fig. 4. X-ray crystal structure of (1*S*,6*R*,7*R*,α*S*)-**43** (selected H atoms are omitted for clarity).

3. Conclusion

Asymmetric syntheses of pyrrolizidine alkaloids (–)-hastanecine, (–)-turneforcidine and (–)-platynecine were achieved via conjugate addition of the requisite antipode of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl (*R*,*E*)-4-(triethylsilyloxy)hepta-2,6-dienoate followed by diastereoselective allylations of either the resultant β-amino esters or the corresponding γ-butyrolactones as the key steps. Subsequent ester/lactone reduction followed by ozonolysis of the corresponding hydrochloride salts and one-

pot hydrogenolysis/double reductive cyclisation provided rapid access to the corresponding pyrrolizidine alkaloids (–)-hastanecine, (–)-turneforcidine and (–)-platynecine, which were isolated as single diastereoisomers (>99:1 d.r.) in 17, 8 and 24% overall yield, respectively, in 11 steps from commercially available 2,2-dimethoxyacetaldehyde. Further applications of this methodology in the asymmetric synthesis of more densely substituted azabicyclic alkaloids are under investigation within our laboratory.

4. Experimental Section

4.1. General Experimental All 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. *n*-BuLi was purchased (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.[31] Water was purified by an Elix® UV-10 system. Organic solvents 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) or 1% aq $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. ^1H–^1H COSY and ^1H–^{13}C HMQC analyses were used to establish atom connectivity. Accurate mass measurements were run on a MicroTOF instrument internally calibrated with polyalanine.

4.2. *tert*-Butyl (*E*)-3-formyl-2-propenoate 21

Step 1: K_2CO_3 (7.90 g, 57.1 mmol) was added to a stirred solution of **18** (8.00 g, 31.7 mmol) in cyclohexane (50 mL) and the resultant suspension was stirred at 60 °C for 2 h. 2,2-Dimethoxyacetaldehyde **19** (60% in H_2O, 12 mL, 69.3 mmol) was added, and the resultant mixture was stirred at 60 °C for 16 h, then allowed to cool to rt before satd aq NH_4Cl (50 mL) was added. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give **20** in >99:1 d.r. [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **20** as a colourless oil (7.00 g, 96%, >99:1 d.r. [(*E*):(*Z*)]);[32] δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 3.34 (6H, s, CH(O*Me*)$_2$), 4.92 (1H, dd, *J* 4.3, 1.3, C(4)*H*), 6.06 (1H, dd, *J* 15.9, 1.3, C(2)*H*), 6.67 (1H, dd, *J* 15.9, 4.3, C(3)*H*).

Step 2: *p*-Toluensulfonic acid monohydrate (1.98 g, 10.4 mmol) was added to a stirred solution of **20** (18.1 g, 89.6 mmol, >99:1 d.r. [(*E*):(*Z*)]) in a 1:1 mixture of H_2O and acetone (400 mL). The resultant mixture was heated at reflux for 1.5 h, then satd aq $NaHCO_3$ (100 mL) was added. The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo* to give **21** in >99:1 d.r. [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **21** as a colourless oil (14.0 g, 86%, >99:1 d.r. [(*E*):(*Z*)]);[32] δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 6.65 (1H, d, *J* 15.9, C(2)*H*), 6.88 (1H, dd, *J* 15.9, 7.8, C(3)*H*), 9.73 (1H, d, *J* 7.8, C(4)*H*).

4.3. *tert*-Butyl (*R*,*E*)-hepta-4-hydroxy-2,6-dienoate 22

(*R*)-(+)-BINOL (733 mg, 2.56 mmol), Ti(O^{i}Pr)$_4$ (1.0 M in CH_2Cl_2, 1.28 mL, 1.28 mmol) and CF_3CO_2H (0.5 M in CH_2Cl_2, 0.18 mL, 0.098 mmol) were added to a stirred mixture of 4 Å molecular sieves (2.00 g) in CH_2Cl_2 (40 mL). The resultant mixture was heated at reflux for 1 h, then allowed to cool to rt. **21** (2.00 g, 12.8 mmol) was added and the resultant mixture was stirred at rt for 30 min, then cooled to –78 °C and allyltributyltin (6.00 mL, 1.93 mmol) was added. The reaction mixture was stirred for 10 min at –78 °C, then transferred to a –20 °C freezer. After 72 h, satd aq $NaHCO_3$ (5 mL) was added and the resultant mixture was purified via flash column chromatography (10% KF in SiO_2,[16b] eluent 30–40 °C petrol/acetone, 95:5 increased to 90:10) to give **22** as a colourless oil (2.50 g, 98%, >99:1 d.r. [(*E*):(*Z*)], 96:4 e.r.);[16b,18] $[\alpha]_D^{20}$ +1.4 (*c* 1.6 in $CHCl_3$); ν_{max} (ATR) 3433 (O–H), 2983 (C–H), 1718 (C=O) 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 2.23–2.36 (1H, m, C(5)H_A), 2.37–2.48 (1H, m, C(5)H_B), 4.31–4.38 (1H, m, C(4)*H*), 5.14–5.24 (2H, m, C(7)H_2), 5.74–5.87 (1H, m, C(6)*H*), 5.98 (1H, dd, *J* 15.7, 1.5, C(2)*H*), 6.84 (1H, dd, *J* 15.7, 4.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 41.1 (*C*(5)), 69.9 (*C*(4)), 80.6 (*C*Me$_3$), 119.4 (*C*(7)), 122.5 (*C*(2)), 133.2 (*C*(6)), 147.8 (*C*(3)), 165.8 (*C*(1)); *m/z* (CI$^+$) 199 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{11}H_{19}O_3^+$ ([M+H]$^+$) requires 199.1329; found 199.1333.

4.4. *tert*-Butyl (*R*,*E*)-4-(triethylsilyloxy)hepta-2,6-dienoate 23

TESCl (4.4 mL, 26.1 mmol), imidazole (3.0 g, 43.4 mmol) and DMAP (530 mg, 4.34 mmol) were added to a stirred solution of **22** (4.20 g, 21.7 mmol, >99:1 d.r. [(*E*):(*Z*)], 96:4 e.r.[18]) in CH_2Cl_2 (70 mL). The reaction mixture was stirred at rt for 16 h, then washed with 1.0 M aq HCl (3 × 20 mL). The organic layer was dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **23** as a colourless oil (6.75 g, quant, >99:1 d.r. [(*E*):(*Z*)], 96:4 e.r.); $[\alpha]_D^{20}$ −3.8 (*c* 1.5 in $CHCl_3$); ν_{max} (ATR) 2878, 2957 (C–H), 1715 (C=O), 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 0.53 (6H, q, *J* 8.0, Si(CH_2CH$_3$)$_3$), 0.88 (9H, t, *J* 8.0, Si(CH$_2$CH_3)$_3$), 1.41 (9H, s, C*Me*$_3$), 2.20–2.28 (2H, m, C(5)H_2), 4.24 (1H,

tdd, *J* 6.3, 4.9, 1.6, C(4)*H*), 4.99–5.04 (2H, m, C(7)H_2), 5.65–5.77 (1H, m, C(6)*H*), 5.82 (1H, dd, *J* 15.5, 1.6, C(2)*H*), 6.74 (1H, dd, *J* 15.5, 4.9, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 4.8 (Si(*C*H_2CH$_3$)$_3$), 6.8 (Si(CH$_2$*C*H$_3$)$_3$), 28.1 (C*Me*$_3$), 42.1 (*C*(5)), 71.4 (*C*(4)), 80.2 (*C*Me$_3$), 117.7 (*C*(7)), 121.9 (*C*(2)), 133.8 (*C*(6)), 148.9 (*C*(3)), 166.0 (*C*(1)); *m/z* (CI^+) 313 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{17}H_{32}O_3Si^+$ ($[M+H]^+$) requires 313.2193; found 313.2196.

4.5. *tert*-Butyl (3*S*,4*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4-(triethylsilyloxy)hept-6-enoate 25 and *tert*-butyl (*R*,*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4-(triethylsilyloxy)hept-6-enoate 26

n-BuLi (2.2 M in hexanes, 0.43 mL, 0.99 mmol) was added dropwise to a stirred solution of *N*-benzyl-*N*-isopropylamine (0.17 mL, 1.02 mmol) in THF (1.5 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **23** (200 mg, 0.64 mmol, >99:1 d.r. [(*E*):(*Z*)], 96:4 e.r.) in THF (1.5 mL) at −78 °C was added dropwise via cannula. The resultant mixture was stirred at −78 °C for 2 h, then satd aq NH_4Cl (15 mL) was added. The resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was then 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 an 89:11 mixture of **25** and **26**, respectively. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave an 85:15 mixture of **25** and **26**, respectively, as a colourless oil (200 mg, 67%). Data for mixture: ν_{max} (ATR) 2960, 2877 (C–H), 1730 (C=O) 1640 (C=C); *m/z* (ESI^+) 462 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{48}NO_3Si^+$ ($[M+H]^+$) requires 462.3398; found 462.3393. Data for **26**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.39 (9H, s, C*Me*$_3$), 2.98 (1H, app septet, *J* 6.7, NC*H*Me$_2$), 3.04 (1H, ddd, *J* 8.9, 4.0, 2.4, C(3)*H*), 4.00 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 4.85–4.93 (1H, m, C(7)H_A), 5.53 (1H, ddt, *J* 17.2, 10.2, 6.9, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 5.1 (Si(*C*H_2CH$_3$)$_3$), 6.9 (Si(CH$_2$*C*H$_3$)$_3$), 17.2 (NCH*Me*$_A$Me$_B$), 22.6 (NCHMe$_A$*Me*$_B$), 28.1 (C*Me*$_3$), 34.7, 38.5 (*C*(2), *C*(5)), 49.5 (*C*HMe$_2$), 51.7 (N*C*H$_2$Ph), 80.2 (*C*Me$_3$), 116.4 (*C*(7)), 136.0 (*C*(6)). Further elution gave **25** as a colourless oil (70 mg, 24%, >99:1 d.r.). $[\alpha]_D^{20}$ −4.0 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 2960, 2878 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.52 (6H, q, *J* 8.0, Si(C*H*$_2$CH$_3$)$_3$), 0.91 (9H, t, *J* 8.0, Si(CH$_2$C*H*$_3$)$_3$), 0.97 (6H, t, *J* 6.7, NCH*Me*$_2$), 1.45 (9H, s, C*Me*$_3$), 2.20–2.33 (1H, m, C(5)H_A), 2.40–2.42 (2H, m, C(2)H_2), 2.33−2.47 (1H, m, C(5)H_B), 2.83 (1H, septet, *J* 6.7, NC*H*Me$_2$), 3.43 (1H, q, *J* 5.9, C(3)*H*), 3.61 (1H, d, *J* 14.8, NCH_AH$_B$Ph), 3.78 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.72–3.78 (1H, m, C(4)*H*), 5.00–5.05 (2H, m, C(7)H_2), 5.79 (1H, app ddt, *J* 17.2, 9.5, 7.0, C(6)*H*), 7.14−7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.2 (Si(*C*H_2CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 19.2 (NCH*Me*$_A$Me$_B$), 20.9 (NCHMe$_A$*Me*$_B$), 28.1 (C*Me*$_3$), 35.2 (*C*(2)), 39.8 (*C*(5)), 49.6 (N*C*HMe$_2$), 50.3 (N*C*H$_2$Ph), 56.0 (*C*(3)), 74.2

(*C*(4)), 79.8 (*C*Me$_3$), 117.4 (*C*(7)), 126.4, 128.0, 128.2 (*o,m,p-Ph*), 134.6 (*C*(6)), 141.9 (*i-Ph*), 172.6 (*C*(1)); *m/z* (ESI$^+$) 462 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{48}NO_3Si^+$ ([M+H]$^+$) requires 462.3398; found 462.3395.

4.6. *tert*-Butyl (3*S*,4*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triethylsilyloxy)hept-6-enoate 27

n-BuLi (2.2 M in hexanes, 2.95 mL, 6.48 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.4 mL, 6.69 mmol, >99:1 e.r.[33]) in THF (15 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **23** (1.30 g, 4.18 mmol, >99:1 d.r. [(*E*):(*Z*)], 96:4 e.r.[18]) in THF (15 mL) at −78 °C was added dropwise via cannula. The resultant reaction mixture was stirred at −78 °C for 2 h, then satd aq NH_4Cl (5 mL) was added. The resultant mixture was allowed to warm to rt then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (15 mL) and 10% aq citric acid (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 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 **27** in 96:4 d.r. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **27** as a colourless oil (1.40 g, 64%, >99:1 d.r.); $[\alpha]_D^{20}$ −27.4 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 2956, 2877 (C–H), 1727 (C=O), 1636 (C=C); δ_H (400 MHz, $CDCl_3$) 0.48 (6H, q, *J* 8.0, Si(CH_2CH$_3$)$_3$), 0.83 (9H, t, *J* 8.0, Si(CH$_2$CH_3)$_3$), 1.29 (3H, d, *J* 7.0, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 1.65 (1H, dd, *J* 15.9, 2.3, C(2)H_A), 1.99−2.05 (1H, dd, *J* 15.9, 8.7, C(2)H_B), 2.30−2.40 (1H, m, C(5)H_A), 2.58 (1H, app dd, *J* 14.4, 7.7, C(5)H_B), 3.51 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.59−3.65 (3H, m, C(3)*H*, C(4)*H*, NCH$_A$$H_B$Ph), 3.69 (1H, q, *J* 7.0, C(α)*H*), 4.99−5.08 (2H, m, C(7)H_2), 5.78−5.91 (1H, m, C(6)*H*), 7.15−7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.0 (Si(*C*H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 19.6 (C(α)*Me*), 29.2 (C*Me*$_3$), 34.7 (*C*(2)), 38.8 (*C*(5)), 51.0 (N*C*H$_2$Ph), 55.6 (*C*(3)), 58.2 (*C*(α)), 73.5 (*C*(4)), 79.6 (*C*Me$_3$), 117.3 (*C*(7)), 126.7, 127.0, 128.0, 128.1, 128.3, 128.4 (*o,m,p-Ph*), 134.7 (*C*(6)), 141.5, 141.7 (*i-Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 524 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{50}NO_3Si^+$ ([M+H]$^+$) requires 524.3554; found 524.3541.

4.7. *tert*-Butyl (3*R*,4*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(triethylsilyloxy)hept-6-enoate 28

n-BuLi (2.2 M in hexanes, 19.9 mL, 43.7 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (9.4 mL, 44.8 mmol, >99:1 e.r.[34]) in THF (35 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **23** (7.00 g, 22.4 mmol, >99:1 d.r., 96:4 e.r.[18]) in THF (35 mL) at −78 °C was added dropwise via cannula. The resultant mixture was stirred at −78 °C for 2 h, then satd aq NH_4Cl (50 mL) was added. The resultant mixture was allowed to warm to rt, then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were washed

sequentially with satd aq $NaHCO_3$ (100 mL), H_2O (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give **28** in 96:4 d.r. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **28** as a colourless oil (8.30 g, 71%, >99:1 d.r.); $[\alpha]_D^{25}$ −7.2 (*c* 2.0 in $CHCl_3$); ν_{max} (ATR) 2956, 2877 (C–H), 1725 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 0.45 (6H, q, *J* 7.8, $Si(CH_2CH_3)_3$), 0.79 (9H, t, *J* 7.8, $Si(CH_2CH_3)_3$), 1.25 (3H, d, *J* 7.1, C(α)*Me*), 1.33 (9H, s, CMe_3), 1.45–1.55 (1H, m, C(2)H_A) 2.33 (1H, dd, *J* 15.2, 10.2, C(5)H_A), 2.25−2.35 (1H, m, C(2)H_B), 2.80 (1H, app dt, *J* 15.2, 7.0, C(5)H_B), 3.28–3.30 (1H, m, C(3)*H*), 3.35 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 3.69 (1H, q, *J* 7.1, C(α)*H*), 3.60−3.69 (1H, m, C(4)*H*), 4.23 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 4.99 (1H, d, *J* 10.2, C(7)H_A), 5.04 (1H, d, *J* 17.2, C(7)H_B), 5.67 (1H, app ddt, *J* 17.2, 10.2, 7.0, C(6)*H*), 7.10−7.27 (8H, m, *Ph*), 7.43 (2H, d, *J* 7.5, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.1 ($Si(CH_2CH_3)_3$), 6.9 ($Si(CH_2CH_3)_3$), 20.3 (C(α)*Me*), 28.1 (CMe_3), 33.4 (*C*(2)), 39.1 (*C*(5)), 52.9 (NCH_2Ph), 53.7 (*C*(3)), 58.0 (*C*(α)), 76.1 (*C*(4)), 79.9 (CMe_3), 116.6 (*C*(7)), 126.3, 127.0, 128.0, 128.1, 128.2, 128.6 (*o,m,p-Ph*), 136.0 (*C*(6)), 141.7, 142.3 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI^+) 524 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{49}NNaO_3Si^+$ ($[M+Na]^+$) requires 546.3374; found 546.3377.

4.8. (4*S*,5*R*,α*R*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-allyl-dihydrofuran-2-one 29

TBAF (1.0 M in THF, 2.68 mL, 2.68 mmol) was added to a stirred solution of **27** (1.40 g, 2.68 mmol, >99:1 d.r.) at rt. The reaction mixture was stirred at rt for 16 h, satd aq $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred at rt for 10 min. The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 5:1) gave **29** as a white solid (380 mg, 70%, >99:1 d.r.); mp 128−130 °C; $[\alpha]_D^{20}$ +160.5 (*c* 1.2 in $CHCl_3$); ν_{max} (ATR) 2960, 2912 (C–H), 1777 (C=O) 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 7.0, C(α)*Me*), 1.37 (1H, dd, *J* 18.3, 8.7, C(3)H_A), 2.08 (1H, dd, *J* 18.3, 7.7, C(3)H_B), 2.29−2.39 (1H, m, C(1')H_A), 2.51−2.60 (1H, m, C(1')H_B), 3.53−3.69 (3H, m, C(4)*H*, NCH_2Ph), 3.73 (1H, q, *J* 7.0, C(α)*H*), 4.26 (1H, app q, *J* 6.4, C(5)*H*), 5.06−5.15 (2H, m, C(3')H_2), 5.68−5.80 (1H, m, C(2')*H*), 7.14−7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.0 (C(α)*Me*), 29.5 (*C*(3)), 37.6 (*C*(1')), 50.6 (NCH_2Ph), 57.4 (*C*(4)), 58.0 (*C*(α)), 82.6 (*C*(5)), 119.1 (*C*(3')), 127.3, 127.6, 127.7, 128.0, 128.7, 128.7 (*o,m,p-Ph*), 132.4 (*C*(2')), 139.6, 141.3 (*i-Ph*), 175.8 (*C*(2)). *m/z* (ESI^+) 336 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{26}NO_2^+$ ($[M+H]^+$) requires 336.1958; found 336.1952.

4.9. (4*R*,5*R*,α*S*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-allyl-dihydrofuran-2-one 30

TBAF (1.0 M in THF, 4.88 mL, 4.88 mmol) was added to a stirred solution of **28** (1.70 g, 3.25 mmol, >99:1 d.r.) at rt. The reaction mixture was stirred at rt for 48 h, then satd aq $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred at rt for 10 min. The reaction mixture was extracted with EtOAc (3 × 20 mL)

and the combined organic extracts were washed with brine (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 5:1) gave **30** as a white solid (880 mg, 81%, >99:1 d.r.); mp 153−155 °C; $[\alpha]_D^{25}$ +219 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 3020, 2966 (C–H), 1781 (C=O), 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 7.1, C(α)*Me*), 1.66 (1H, dd, *J* 18.2, 3.8, C(3)H_A), 2.05 (1H, dd, *J* 18.2, 8.0, C(3)H_B), 2.47−2.55 (1H, m, C(1')H_A), 2.64−2.71 (1H, m, C(1')H_B), 3.59 (1H, d, *J* 17.4, NC$H_A$$H_B$Ph), 3.63 (1H, d, *J* 17.4, NCH$_A$$H_B$Ph), 3.79 (1H, q, *J* 7.1, C(α)*H*), 3.90 (1H, ddd, *J* 8.0, 6.4, 3.8, C(4)*H*), 4.50 (1H, app dt, *J* 9.0, 5.6, C(5)*H*), 5.10 (1H, dd, *J* 10.2, 1.5, C(3')H_A), 5.16 (1H, dd, *J* 17.2, 1.5, C(3')H_B), 5.90 (1H, ddt, *J* 17.2, 10.2, 6.8, C(2')*H*), 7.13−7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1 (C(α)*Me*), 32.1 (*C*(3)), 33.9 (*C*(1')), 51.9 (N*C*H$_2$Ph), 55.0 (*C*(4)), 56.3 (*C*(α)), 84.4 (*C*(5)), 118.1 (*C*(3')), 127.3, 127.7, 127.7, 127.9, 128.5, 128.8 (*o,m,p-Ph*), 133.8 (*C*(2')), 138.9, 140.4 (*i-Ph*), 176.4 (*C*(2)); *m/z* (ESI^+) 336 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{25}NNaO_2^+$ ($[M+Na]^+$) requires 358.1778; found 358.1780.

4.10. *tert*-Butyl (3*S*,4*R*)-3-(*N*-isopropylamino)-4-(triethylsilyloxy)heptanoate 31

Method A: $Pd(OH)_2$/C (50 mg, 50% w/w) was added to a stirred solution of **27** (100 mg, 0.19 mmol, >99:1 d.r.) in degassed MeOH (2 mL) and acetone (0.2 mL) at rt under nitrogen. The resultant solution was stirred under an atmosphere of H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **31** as a pale yellow oil (43 mg, 61%, >99:1 d.r.); $[\alpha]_D^{20}$ −3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2876, 2935, 2958 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 0.60 (6H, q, *J* 8.0, Si(CH_2CH$_3$)$_3$), 0.90 (3H, t, *J* 6.9, C(7)H_3), 0.95 (9H, t, *J* 8.0, Si(CH$_2$CH_3)$_3$), 1.0 (3H, d, *J* 6.2, NCH*Me*$_A$Me$_B$), 1.01 (3H, d, *J* 6.2, NCHMe$_A$*Me*$_B$), 1.21−1.50 (4H, m, C(5)H_2, C(6)H_2), 1.44 (9H, s, C*Me*$_3$), 2.19 (1H, dd, *J* 15.0, 7.8, C(2)H_A), 2.33 (1H, dd, *J* 15.0, 5.2, C(2)H_B), 2.85 (1H, septet, *J* 6.2, NC*H*Me$_2$), 3.05 (1H, ddd, *J* 7.8, 5.2, 2.7, C(3)*H*), 3.75 (1H, td, *J* 6.0, 2.7, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 5.2 (Si(*C*H$_2$CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 14.2 (*C*(7)), 19.1 (*C*(6)), 23.2, 23.4 (NCH*Me*$_2$), 28.1 (C*Me*$_3$), 36.0 (*C*(5)), 37.1 (*C*(2)), 45.4 (N*C*HMe$_2$), 55.8 (*C*(3)), 73.5 (*C*(4)), 80.0 (*C*Me$_3$), 172.5 (*C*(1)); *m/z* (ESI^+) 374 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{44}NO_3Si^+$ ($[M+H]^+$) requires 374.3085; found 374.3085.

Method B: $Pd(OH)_2$/C (40 mg, 40% w/w) was added to a stirred solution of an 85:15 mixture of **25** and **26** (100 mg, 0.21 mmol) in degassed MeOH (1.5 mL) at rt under nitrogen. The resultant solution was stirred under an atmosphere of H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give an 85:15 mixture of **31** and **32** as a pale yellow oil (80 mg, quant).

4.11. *tert*-Butyl (*R*,*R*)-3-(*N*-isopropylamino)-4-(triethylsilyloxy)heptanoate 32

$Pd(OH)_2/C$ (33 mg, 50% w/w) was added to a stirred solution of **28** (66 mg, 0.13 mmol, >99:1 d.r.) in degassed MeOH (1.5 mL) and acetone (0.15 mL) at rt under nitrogen. The resultant solution was stirred under an atmosphere of H_2 (1 atm). After 24 h, the reaction mixture was filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **32** as a pale yellow oil (40 mg, 82%, >99:1 d.r.); $[\alpha]_D^{20}$ +6.1 (*c* 0.9 in $CHCl_3$); ν_{max} (ATR) 2876, 2957 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.61 (6H, q, *J* 8.0, $Si(CH_2CH_3)_3$), 0.90 (3H, t, *J* 7.1, C(7)H_3), 0.96 (9H, t, *J* 8.0, $Si(CH_2CH_3)_3$), 1.00 (3H, d, *J* 6.2, $NCHMe_AMe_B$), 1.03 (3H, d, *J* 6.2, $NCHMe_AMe_B$), 1.17−1.36 (2H, m, C(5)H_A, C(6)H_A), 1.45 (9H, s, CMe_3), 1.35−1.46 (1H, m, C(6)H_B), 1.53−1.64 (1H, m, C(5)H_B), 2.15 (1H, dd, *J* 14.8, 7.9, C(2)H_A), 2.50 (1H, dd, *J* 14.8, 5.0, C(2)H_B), 2.84 (1H, septet, *J* 6.2, $NCHMe_2$), 3.05 (1H, ddd, *J* 7.9, 5.0, 3.4, C(3)*H*), 3.65−3.70 (1H, m, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 5.1 ($Si(CH_2CH_3)_3$), 6.9 ($Si(CH_2CH_3)_3$), 14.2 (*C*(7)), 19.4 (*C*(6)), 23.4, 23.5 ($NCHMe_2$), 28.0 (CMe_3), 34.3 (*C*(5)), 37.5 (*C*(2)), 46.0 ($NCHMe_2$), 55.9 (*C*(3)), 73.6 (*C*(4)), 80.1 (CMe_3), 172.7 (*C*(1)); *m/z* (ESI^+) 374 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{44}NO_3Si^+$ ($[M+H]^+$) requires 374.3085; found 374.3079.

4.12. *tert*-Butyl (2*S*,3*R*,4*R*,α*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]4-(triethylsilyloxy)hept-6-enoate 33

n-BuLi (2.2 M in hexanes, 2.60 mL, 5.74 mmol) was added dropwise to a stirred solution of $^iPr_2NH$ (0.94 mL, 6.70 mmol) in THF (15 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. A solution of **28** (1.00 g, 1.91 mmol, >99:1 d.r.) in THF (15 mL) at 0 °C was then added. The resultant mixture was stirred at 0 °C for 1 h, then allyl bromide (0.50 mL, 5.74 mmol) was added and the resultant mixture was allowed to warm to rt over 2 h. Satd aq NH_4Cl (15 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (15 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **33** in 96:4 d.r. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 40:1) gave **33** as a colourless oil (1.00 g, 93%, 96:4 d.r.); $[\alpha]_D^{25}$ −31.3 (*c* 2.2 in $CHCl_3$); ν_{max} (ATR) 2977, 2955, 2912, 2876 (C−H), 1723 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 0.40 (6H, q, *J* 8.0, $Si(CH_2CH_3)_3$), 0.78 (9H, t, *J* 8.0, $Si(CH_2CH_3)_3$), 1.07 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (9H, s, CMe_3), 2.06 (1H, ddd, *J* 12.7, 7.5, 5.0, C(5)H_A), 2.15−2.33 (2H, m, C(1')H_2), 2.49 (1H, app dt, *J* 7.5, 6.3, C(5)H_B), 2.75−2.85 (1H, m, C(2)*H*), 2.88 (1H, dd, *J* 7.9, 2.1, C(3)*H*), 3.76 (1H, ddd, *J* 7.5, 5.0, 2.1, C(4)*H*), 3.86 (1H, d, *J* 15.4, NCH_AH_BPh), 4.12 (1H, q, *J* 6.9, C(α)*H*), 4.45 (1H, d, *J* 15.4, NCH_AH_BPh), 4.65−4.74 (2H, m, C(3')H_2), 4.84−4.99 (3H, m, C(6)*H*, C(7)H_2), 5.63 (1H, ddt, *J* 17.2, 7.9, 6.3, C(2')*H*), 7.07−7.53 (10H, m, *Ph*); δ_C (100

MHz, $CDCl_3$) 5.3 (Si(*C*H_2CH$_3$)$_3$), 7.0 (Si(CH$_2$*C*H$_3$)$_3$), 22.1 (C(α)*Me*), 28.2 (C*Me*$_3$), 35.6 (*C*(1')), 39.2 (*C*(5)), 46.6 (*C*(2)), 52.8 (N*C*H$_2$Ph), 61.3 (*C*(α)), 61.9 (*C*(3)), 75.0 (*C*(4)), 80.7 (*C*Me$_3$), 116.5, 116.5 (*C*(7), *C*(3')), 125.8, 126.7, 127.7, 128.0, 128.1, 128.5 (*o,m,p-Ph*), 135.4, 135.6 (*C*(6), *C*(2')), 144.4, 146.2 (*i-Ph*), 174.8 (*C*(1)); *m/z* (ESI)$^+$ 564 ([M+H]$^+$,100%); HRMS (ESI$^+$) $C_{35}H_{54}NO_3Si^+$ ([M+H]$^+$) requires 564.3867; found 564.3858.

4.13. (3*S*,4*S*,5*R*,α*R*)-3,5-Diallyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2-one 34

Step 1: n-BuLi (2.2 M in hexanes, 0.39 mL, 0.87 mmol) was added dropwise to a stirred solution of ^{i}Pr$_2$NH (0.125 mL, 0.90 mmol) in THF (3 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. A solution of **29** (100 mg, 0.30 mmol, >99:1 d.r.) in THF (2 mL) was then added at 0 °C. The resultant mixture was stirred at 0 °C for 1 h, then allyl bromide (51 μL, 0.60 mmol) was added and the resultant mixture was then allowed to warm to rt over 2 h. Satd aq NH_4Cl (3 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **34** in 76:24 d.r. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc, 20:1) gave **34** as a colourless oil (70 mg, 62%, 76:24 d.r.).

Step 2: KO^{t}Bu (18 mg, 0.16 mmol) was added to a stirred solution of **34** (54 mg, 0.16 mmol, 74:26 d.r.) in THF (3 mL). The resultant solution was stirred at rt for 16 h then satd aq NH_4Cl (3 mL) was added. The reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (5 mL) and brine (5 mL), then dried and concentrated *in vacuo* to give **34** in >95:5 d.r. Purification via flash column chromatography (eluent 30−40 °C petrol/EtOAc 10:1) gave **34** as a colourless oil (50 mg, 93%, >99:1 d.r.); $[\alpha]_D^{20}$ +24.4 (*c* 1.6 in $CHCl_3$); ν_{max} (ATR) 3063, 3029, 2977, 2933 (C−H), 1770 (C=O), 1642 (C=C); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)*Me*), 2.06−2.30 (3H, m, C(1')*H*$_2$, C(1")*H*$_A$), 2.38−2.46 (1H, m, C(1")*H*$_B$), 2.67 (1H, app q, *J* 6.0, C(3)*H*), 3.21 (1H, app t, *J* 6.3, C(4)*H*), 3.71−3.82 (2H, m, NC*H*$_2$Ph), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, ddd, *J* 7.4, 6.0, 4.6, C(5)*H*), 4.76 (1H, dd, *J* 17.0, 1.2, C(3')*H*$_A$), 4.88 (1H, dd, *J* 10.5, 1.2, C(3')*H*$_B$), 4.98 (1H, dd, *J* 17.1, 1.5, C(3")*H*$_A$), 5.08 (1H, app d, *J* 10.3 C(3")*H*$_B$), 5.45 (1H, ddt, *J* 17.0, 10.5, 0.9, C(2')*H*), 5.66 (1H, ddt, *J* 17.1, 10.3, 6.9, C(2")*H*), 7.16−7.29 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 33.8 (*C*(1')), 38.4 (*C*(1")), 42.9 (*C*(3)), 51.1 (N*C*H$_2$Ph), 59.3 (*C*(α)), 62.8 (*C*(4)), 81.0 (*C*(5)), 118.5 (*C*(3')), 118.8 (*C*(3")), 127.2, 127.4, 127.7, 127.9, 128.5, 128.5 (*o,m,p-Ph*), 132.7 (*C*(2")), 133.9 (*C*(2')), 140.7, 144.0 (*i-Ph*), 177.4 (*C*(2)); *m/z* (ESI$^+$) 376 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{30}NO_2^+$ ([M+H]$^+$) requires 376.2271; found 376.2264.

4.14. (3*R*,4*R*,5*R*,α*S*)-3,5-Diallyl-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]dihydrofuran-2-one 35

Step 1: n-BuLi (2.2 M in hexanes, 1.75 mL, 3.84 mmol) was added dropwise to a stirred solution of $^{i}Pr_2NH$ (0.63 mL, 4.48 mmol) in THF (4.5 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. A solution of **30** (430 mg, 1.28 mmol, >99:1 d.r.) in THF (9 mL) was then added at 0 °C. The resultant mixture was stirred at 0 °C for 1 h, then allyl bromide (0.22 mL, 2.56 mmol) and the resultant mixture was allowed to warm to rt over 2 h. Satd aq NH_4Cl (5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **35** (400 mg, 85:15 d.r.).

Step 2: KHMDS (0.7 M in PhMe, 0.76 mL, 0.53 mmol) was added to $^{t}BuOH$ (0.20 mL, 2.14 mmol) in THF (10 mL) and the resultant mixture was stirred at rt for 15 min, then added to a stirred solution of **35** (400 mg, 1.28 mmol, 85:15 d.r.) in THF (10 mL). The resultant mixture was stirred at rt for 24 h then satd aq NH_4Cl (5 mL) was added and the reation mixture was concentrated *in vacuo*. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give **35** in >95:5 d.r. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc 20:1) gave **35** as a colourless oil (250 mg, 52% from **30**, >99:1 d.r.); $[\alpha]_D^{25}$ +42.6 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3062, 2979 (C−H), 1764 (C=O), 1642 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, *J* 7.1, C(α)*Me*), 1.92−2.00 (1H, m, C(1')H_A), 2.04−2.12 (1H, m, C(3)*H*, C(1')H_B), 2.48−2.65 (2H, m, C(1")H_2), 3.50 (1H, dd, *J* 6.0, 1.5, C(4)*H*), 3.78 (2H, s, NCH_2Ph), 3.81 (1H, q, *J* 7.1, C(α)*H*), 4.45 (1H, td, *J* 8.8, 6.0, C(5)*H*), 4.90 (1H, d, *J* 17.1, C(3')H_A), 4.94 (1H, d, *J* 10.2, C(3')H_B), 5.09 (1H, d, *J* 10.2, C(3")H_A), 5.14 (1H, d, *J* 17.1, C(3")H_B), 5.47 (1H, app ddt, *J* 17.1, 10.2, 7.0, C(2')*H*), 5.88 (1H, app ddt, *J* 17.1, 10.2, 6.8, C(2")*H*), 7.15−7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3 (C(α)*Me*), 34.2 (*C*(1')), 34.4 (*C*(1")), 42.6 (*C*(3)), 52.2 (NCH_2Ph), 56.9 (*C*(α)), 59.9 (*C*(4)), 83.4 (*C*(5)), 117.9 (*C*(3")), 118.4 (*C*(3')), 127.3, 127.7, 127.8, 127.8, 127.6, 128.8 (*o*,*m*,*p*-*Ph*), 133.6 (*C*(2')), 134.1 (*C*(2")), 139.2, 141.4 (*i*-*Ph*), 178.1 (*C*(2)); *m/z* (ESI^+) 376 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{30}NO_2^+$ ($[M+H]^+$) requires 376.2271; found 376.2271.

4.15. (2*S*,3*S*,4*R*,α*R*)-2-Allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1,4-diol 36

$LiAlH_4$ (1.0 M in THF, 1.5 mL, 1.5 mmol) was added to a stirred solution of **34** (140 mg, 0.37 mmol, >99:1 d.r.) in THF (3 mL) at 0 °C. The resultant solution was allowed to warm to rt for 2 h, 2.0 M aq NaOH (0.75 mL, 1.5 mmol) was then added and the resultant mixture was stirred 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 **36** as a colourless oil (90 mg, 64%, >99:1 d.r.); $[\alpha]_D^{20}$ +34.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3268 (O–H) 2973 (C−H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (1H, d, *J* 6.9, C(α)*Me*), 1.56–1.68 (1H, m, C(2)*H*), 1.76–1.88 (1H, m, C(1')H_A), 2.13–2.28 (2H, m, C(1')H_B, C(5)H_A), 2.53–2.63 (1H, m, C(5)H_B), 2.61 (1H, app t, *J* 5.0, C(3)*H*), 2.79 (1H, br s, O*H*), 3.34 (1H, dd, *J* 11.4, 6.5, C(1)H_A), 3.62 (1H, app d, *J* 11.4, C(1)H_B), 3.82 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.88–4.01 (2H, m, C(4)*H*, C(α)*H*), 3.95 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.82 (2H, d, *J* 14.0, C(3')H_2), 5.02–5.05 (1H, m, C(7)H_A), 5.06–5.10 (1H, m, C(7)H_B), 5.36 (1H, dddd, *J* 17.7, 14.2, 8.5, 5.6, C(2')*H*), 5.71–5.87 (1H, m, C(6)*H*), 7.12–7.33 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.4 (C(α)*Me*), 35.5 (*C*(1')), 40.6 (*C*(2)), 41.2 (*C*(5)), 51.7 (N*C*H_2Ph), 58.0 (*C*(α)), 62.3 (*C*(1)), 63.0 (*C*(3)), 71.5 (*C*(4)), 115.9, 118.0 (*C*(7), *C*(3')), 126.8, 127.0, 128.1, 128.2 128.4, 128.6 (*o*,*m*,*p*-*Ph*), 136.0, 137.8 (*C*(6), *C*(2')), 141.4, 143.9 (*i*-*Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{34}NO_2^+$ ($[M+H]^+$) requires 380.2584; found 380.2574.

4.16. (1*S*,7*R*,7a*S*)-1-Hydroxymethyl-7-hydroxyhexahydro-1*H*-pyrrolizine 3 [(–)-hastanecine]

Amino diol **36** (380 mg, 1.00 mmol, >99:1 d.r.) was coevaporated with HCl (3 × 3 mL, 2.0 M in Et_2O), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution 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 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 volume of 3 mL, then AcOH (0.3 mL) and $Pd(OH)_2$/C (100 mg, 25% w/w) were added. The resultant solution was degassed and 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 and coevaporated with HCl (2.0 M in Et_2O, 3 mL). Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **3** as a white solid (129 mg, 82% from **36**, >99:1 d.r.); {mp 108–109 °C; lit.[2i] 113–114 °C; lit.[35] 113–114 °C; lit.[26j] 113–114 °C; lit.[26g] mp 112.5–113.5 °C; lit.[26e] mp 113–114 °C; lit.[26d] mp 111–112 °C; lit.[26i] mp 113–114 °C; lit.[26c] mp 110 °C; $[\alpha]_D^{20}$ −8.3 (*c* 0.9 in EtOH); lit.[2i] $[\alpha]_D^{20}$ –9.1 (in EtOH); lit.[35] $[\alpha]_D^{25}$ –10.0 (*c* 0.4 in EtOH); lit.[26g] $[\alpha]_D^{25}$ –10.0 (*c* 0.7 in EtOH); lit.[26e] $[\alpha]_D^{20}$ –9.7 (*c* 0.9 in EtOH); lit.[26d] $[\alpha]_D^{23}$ –10.4 (c 0.4 in EtOH); lit.[26c] for *ent*-**3**: $[\alpha]_D^{25}$ +8.5 (*c* 0.6 in EtOH); lit.[26e] for *ent*-**3**: $[\alpha]_D^{20}$ +9.0 (*c* 0.5 in EtOH); lit.[26i] for *ent*-**3**: $[\alpha]_D^{20}$ +8.2 (*c* 1.43 in EtOH); lit.[26j] for *ent*-**3**: $[\alpha]_D^{18}$ +8.5 (*c* 2.2 in EtOH)}; ν_{max} (ATR) 3290 (O−H); δ_H (400 MHz, MeOH-d_4) 1.40−1.55 (1H, m, C(2)H_A), 1.58−1.68 (1H, m, C(6)H_A), 1.75−2.00 (3H, m, C(1)*H*, C(2)H_B, C(6)H_B), 2.46 (1H, dt, *J* 10.1, 5.6, C(3)H_A), 2.63 (1H, ddd, *J*

11.2, 6.9, 4.1, C(5)H_A), 2.90 (1H, dd, *J* 7.5, 2.0, C(7a)*H*), 2.98−3.10 (2H, m, C(3)H_B, C(5)H_B), 3.45−3.55 (2H, m, C(1')H_2), 3.96−4.01(1H, m, C(7)*H*); δ_C (100 MHz, $CDCl_3$) 30.8 (*C*(2)), 33.5 (*C*(6)), 47.6 (*C*(1)), 53.3 (*C*(5)), 55.6 (*C*(3)), 65.0 (*C*(1')), 77.3 (*C*(7a)), 77.5 (*C*(7)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1176.

4.17. (2*R*,3*R*,4*R*,α*S*)-2-Allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-ene-1,4-diol 38

$LiAlH_4$ (2.4 M in THF, 3.2 mL, 7.68 mmol) was added to a stirred solution of **35** (700 mg, 1.92 mmol, >99:1 d.r.) in THF (10 mL) at 0 °C. The resultant solution was allowed to warm to rt for 2 h, 2.0 M aq NaOH (3.8 mL, 7.6 mmol) was then added at 0 °C and the resultant mixture was stirred 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 **38** as a colourless oil (570 mg, 80%, >99:1 d.r.); $[\alpha]_D^{20}$ −31.2 (*c* 0.8 in $CHCl_3$); ν_{max} (ATR) 3327 (O−H), 3063, 2974, 2930 (C−H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.0, C(α)*Me*), 1.47 (1H, app tt, *J* 9.1, 4.4, C(2)*H*), 1.87−2.00 (2H, m, C(5)H_2), 2.26−2.36 (2H, m, C(1')H_2), 2.73 (1H, m, C(3)*H*), 3.35 (1H, br s O*H*), 3.35 (1H, dd, *J* 11.7, 4.4, C(1)H_A), 3.59 (1H, dd, *J* 11.7, 4.4, C(1)H_B), 3.78 (1H, app q, *J* 5.8, C(4)*H*), 3.86 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 4.02 (1H, q, *J* 7.0, C(α)*H*), 4.20 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 4.84–4.88 (2H, m, C(7)H_2), 5.07 (1H, m, C(3')H_A), 5.08−5.13 (1H, m, C(3')H_B), 5.30−5.43 (1H, m, C(6)*H*), 5.08−5.13 (1H, m, C(2')*H*), 7.15−7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(α)*Me*), 36.3 (*C*(5)), 39.8 (*C*(1')), 40.8 (*C*(2)), 52.6 (N*C*H_2Ph), 58.4 (*C*(α)), 62.7 (*C*(1)), 62.8 (*C*(3)), 69.7 (*C*(4)), 116.3 (*C*(7)), 117.7 *C*(3')), 126.9, 127.2, 128.0, 128.2, 128.4, 128.5, 128.6 (*o,m,p-Ph*), 135.7 (*C*(2')), 137.6 (*C*(6)), 141.1, 143.6 (*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.

4.18. (1*R*,7*R*,7a*R*)-1-Hydroxymethyl-7-hydroxyhexahydro-1*H*-pyrrolizine 4 [(–)-turneforcidine]

Amino diol **38** (230 mg, 0.60 mmol, >99:1 d.r.) was coevaporated with HCl (3 × 3 mL, 2.0 M in Et_2O), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution 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, 600 mg, 1.80 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 volume of 3 mL, then AcOH (0.15 mL) and $Pd(OH)_2$/C (92 mg, 40% w/w) were added. The resultant solution was degassed and stirred under an atmosphere of H_2 (5 atm) at rt for 48 h, and then heated at 50 °C for 72 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/18 M aq NH_4OH, 6:4:1) gave **4** as a

white solid (40 mg, 42% from **38**, >99:1 d.r.); {mp 109–110 °C; lit.[26i] mp 118–120 °C; lit.[36] mp 119–120 °C; $[\alpha]_D^{20}$ –10.0 (*c* 0.8 in MeOH); lit.[26i] $[\alpha]_D^{24}$ –11.4 (*c* 1.2 in MeOH); lit.[28b] $[\alpha]_D^{24}$ –13.9 (*c* 0.4 in MeOH); lit.[26j] $[\alpha]_D^{24}$ –12.5 (*c* 1.3 in MeOH); lit.[36] $[\alpha]_D^{24}$ –12.0 (*c* 0.8 in MeOH)}; ν_{max} (ATR) 3391 (O−H), 2967, 2934 (C−H); δ_H (400 MHz, MeOH-d_4) 1.66 (1H, dtd, *J* 12.4, 9.3, 6.8, C(2)H_A), 1.93−1.99 (2H, m, C(6)H_2), 2.07 (1H, dtd, *J* 12.4, 6.8, 3.0, C(2)H_B), 2.46−2.60 (2H, m, C(1)*H*, C(3)H_A), 2.68 (1H, q, *J* 8.9, C(5)H_A), 2.97−3.08 (2H, m, C(3)H_B, C(5)H_B), 3.14 (1H, dd, *J* 6.9, 4.6, C(7a)*H*), 3.49 (1H, dd, *J* 10.6, 7.1, C(1')H_A), 3.54 (1H, dd, *J* 10.6, 6.6, C(1')H_B), 4.14 (1H, app q, *J* 3.7, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 32.6 (*C*(2)), 37.6 (*C*(6)), 40.9 (*C*(1)), 52.9 (*C*(3)), 56.4 (*C*(5)), 65.8 (*C*(1')), 72.1 (*C*(7)), 73.8 (*C*(7a)); *m/z* (ESI$^+$) 158 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_2^+$ ([M+H]$^+$) requires 158.1176; found 158.1176.

4.19. *tert*-Butyl (2*R*,3*R*,4*R*,α*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-hydroxyhept-6-enoate 40

HF (70% in pyridine, 1.45 mL, 53.3 mmol) was added to a stirred solution of **33** (1.00 g, 1.78 mmol, 96:4 d.r.) in THF (10 mL) at 0 °C and the resultant solution was allowed to warm to rt for 18 h. Satd aq $NaHCO_3$ was added until pH >7 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 **40** as a colourless oil (760 mg, 92%, 96:4 d.r.); $[\alpha]_D^{25}$ −13.3 (*c* 1.3 in $CHCl_3$); ν_{max} (ATR) 3375 (O−H), 2977 (C−H), 1722 (C=O), 1641 (C=C); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.50 (9H, s, C*Me*$_3$), 2.00−2.11 (1H, m, C(5)H_A), 2.22−2.33 (2H, m, C(5)H_B, C(1')H_A), 2.39 (1H, ddd, *J* 14.3, 10.9, 6.9, C(1')H_B), 2.52 (1H, dt, *J* 10.9, 2.6, C(2)*H*), 3.36 (1H, dd, *J* 8.0, 2.6, C(3)*H*), 3.67 (1H, app t, *J* 7.8, C(4)*H*), 3.74 (1H, d, *J* 14.3, NCH_AH$_B$Ph), 3.94 (1H, br s, O*H*), 4.10 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 4.13 (1H, q, *J* 6.9, C(α)*H*), 4.95 (1H, app d, *J* 7.1, C(3')H_A), 4.98 (1H, app s, C(3')H_B), 5.05 (1H, d, *J* 10.2, C(7)H_A), 5.09 (1H, dd, *J* 17.0, 1.6, C(7)H_B), 5.67 (1H, ddt, *J* 16.8, 10.5, 6.5, C(2')*H*), 5.83 (1H, app ddt, *J* 17.0, 10.2, 7.0, C(6)*H*), 7.24−7.42 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 27.1 (C*Me*$_3$), 31.5 (*C*(1')), 38.1 (*C*(5)), 44.2 (*C*(2)), 50.2 (NCH_2Ph), 58.7 (*C*(α)), 61.6 (*C*(3)), 67.0 (*C*(4)), 80.1 (*C*Me$_3$), 115.0 (*C*(3')), 115.8 (*C*(7)), 125.9, 126.3, 127.1, 127.3, 127.5, 127.8 (*o*,*m*,*p*-*Ph*), 134.5 (*C*(6)), 135.2 (*C*(2')), 139.5, 141.9 (*i*-*Ph*), 172.7 (*C*(1)); *m/z* (ESI)$^+$ 450 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_3^+$ ([M+H]$^+$) requires 450.3003; found 450.2999.

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

$LiAlH_4$ (2.4 M in THF, 2.6 mL, 6.24 mmol) was added to a stirred solution of **40** (700 mg, 1.56 mmol, 96:4 d.r.) in THF (7 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 (3.15 mL, 6.3 mmol) was then added at 0 °C and the resultant mixture was stirred 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 **41** as a colourless oil (530 mg, 91%, 96:4 d.r.); $[\alpha]_D^{25}$ −49.2 (*c* 1.3 in $CHCl_3$); ν_{max} (ATR) 3405 (O–H), 3062, 2975, 2934 (C−H) 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.0, C(α)*Me*), 1.55−1.66 (1H, m, C(2)*H*), 1.75−1.86 (1H, m, C(1')H_A), 1.97−2.09 (1H, m, C(5)H_A), 2.21−2.36 (2H, m, C(5)H_B, C(1')H_B), 2.81 (1H, dd, *J* 7.5, 3.4, C(3)*H*), 3.12−3.23 (1H, m, C(1)H_A), 3.23 (1H, dd, *J* 10.5, 5.0, C(1)H_B), 3.69 (1H, app td, *J* 8.0, 2.5, C(4)*H*), 3.75 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 3.80 (1H, br s, O*H*), 3.98 (1H, d, *J* 13.9, NC$H_A$$H_B$Ph), 4.01 (1H, q, *J* 7.0, C(α)*H*), 4.86−4.95 (2H, m, C(3')H_2), 5.00−5.09 (2H, m, C(7)H_2), 5.55−5.66 (1H, m, C(2')*H*), 5.76−5.88 (1H, m, C(6)*H*), 7.17−7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.9 (C(α)*Me*), 33.3 (*C*(1')), 39.2 (*C*(5)), 40.0 (*C*(2)), 51.4 (N*C*H_2Ph), 58.0 (*C*(α)), 61.5 (*C*(3)), 65.8 (*C*(1)), 67.8 (*C*(4)), 115.9 (*C*(3')), 117.2 (*C*(7)), 127.1, 127.3, 128.0, 128.4, 128.6, 128.7 (*o,m,p-Ph*), 135.6 (*C*(2')), 137.4 (*C*(6)), 140.1, 143.2 (*i-Ph*); *m/z* (ESI^+) 380 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{34}NO_2^+$ ($[M+H]^+$) requires 380.2584; found 380.2580.

4.21. *tert*-Butyl (1*S*,6*R*,7*R*,α*S*)-6-(triethylsilyloxy)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclohept-3-ene-1-carboxylate 42

Grubbs I catalyst (102 mg, 0.12 mmol) was added to a stirred solution of **33** (350 mg, 0.62 mmol, 96:4 d.r.) in degassed CH_2Cl_2 (35 mL) at 35 °C. The resultant mixture was stirred at 35 °C for 18 h then allowed to cool to rt and concentrated *in vacuo*. Purification via column chromatography (eluent 30–40 °C petrol/Et_2O, 40:1) gave **42** as a colourless oil (310 mg, 93%, >99:1 d.r.); $[\alpha]_D^{25}$ –8.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2955, 2876 (C–H), 1726 (C=O), 1656 (C=C); δ_H (400 MHz, $CDCl_3$) 0.72 (6H, q, *J* 8.0, Si(C$H_2$$CH_3$)$_3$), 1.05 (9H, t, *J* 8.0, Si(CH_2CH_3)$_3$), 1.48 (9H, s, C*Me*$_3$), 1.46 (3H, m, C(α)*Me*), 2.09 (1H, dd, *J* 15.0, 6.6, C(2)H_A), 2.37–2.55 (4H, m, C(1)*H*, C(2)H_B, C(5)H_2), 3.72 (1H, d, *J* 14.5, NC$H_A$$H_B$Ph), 3.80 (1H, dd, *J* 8.2, 6.6, C(7)*H*), 3.88 (1H, d, *J* 14.5, NC$H_A$$H_B$Ph), 4.05 (1H, q, *J* 6.9, C(α)*H*), 4.17–4.25 (1H, m, C(6)*H*), 5.50–5.58 (1H, m, C(4)*H*), 5.63–5.71 (1H, m, C(3)*H*), 7.07–7.29 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.6 (Si(*C*$H_2$$CH_3$)$_3$), 7.1 (Si($CH_2$*C*$H_3$)$_3$), 20.1 (C(α)*Me*), 28.1 (C*Me*$_3$), 28.9 (*C*(2)), 35.3 (*C*(5)), 48.9 (*C*(1)), 52.3 (N*C*H_2Ph), 61.5 (*C*(α)), 64.8 (*C*(7)), 71.9 (*C*(6)), 79.7 (*C*Me$_3$), 126.8 (*C*(4)), 126.2, 126.2, 127.5, 127.6, 128.0, 128.9 (*o,m,p-Ph*), 129.6 (*C*(3)), 141.5, 145.9 (*i-Ph*), 174.1 (*C*O_2^{t}Bu); *m/z* (ESI^+) 536 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{50}NO_3Si^+$ ($[M+H]^+$) requires 536.3554; found 536.3551.

4.22. *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 43

HF (70% in pyridine, 0.33 mL, 11.4 mmol) was added to a stirred solution of **42** (200 mg, 0.38 mmol) in THF (3 mL) at 0 °C and the resultant solution was allowed to warm to rt for 18 h. Satd aq $NaHCO_3$ was

added until pH > 7 and the resultant mixture was stirred at rt the 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 **43** as a white solid (167 mg, quant, >99:1 d.r.); $[\alpha]_D^{25}$ −55.7 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3443 (O−H), 2930, 2974, 3026 (C−H), 1724 (C=O), 1656 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 7.2, C(α)*Me*), 2.08−2.15 (1H, m, C(1)*H*), 2.23−2.58 (4H, m, C(2)H_2, C(5)H_2), 3.53 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.88 (1H, q, *J* 7.2, C(α)*H*), 3.84−3.95 (2H, m, C(6)*H*, C(7)*H*), 3.95 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.01 (1H, br s, O*H*), 5.37 (1H, m, C(3)*H*), 5.55 (1H, app ddt, *J* 11.1, 6.5, 2.0, C(4)*H*), 7.20−7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 28.0 (C*Me*$_3$), 27.8 (*C*(2)), 34.4 (*C*(5)), 43.5 (*C*(1)), 49.5 (N*C*H$_2$Ph), 56.7 (*C*(α)), 59.7 (*C*(7)), 66.9 (*C*(6)), 80.3 (*C*Me$_3$), 126.4 (*C*(3)), 128.6 (*C*(4)), 127.2, 127.3, 128.0, 128.4, 128.7, 128.7 (*o,m,p-Ph*), 139.6, 140.7 (*i-Ph*), 173.2 (*C*O$_2$^{t}Bu); *m/z* (ESI)$^+$ 422 ([M+H]$^+$,100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_3^+$ ([M+H]$^+$) requires 422.2690; found 422.2687.

4.23. (1*S*,6*R*,7*R*,α*S*)-1-hydroxymethyl-6-hydroxy-7-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-cyclohept-3-ene 44

$LiAlH_4$ (2.4 M in THF, 0.67 mL, 1.6 mmol) was added to a stirred solution of **43** (165 mg, 0.39 mmol, >99:1 d.r.) in THF (2 mL) at –78 °C. The reaction solution was allowed to warm to rt then stirred at rt for 18 h. 2.0 M aq NaOH (0.8 mL, 1.6 mmol) was then added at 0 °C and the resultant mixture was stirred 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/EtOAc, 4:1) gave **44** as a colourless oil (140 mg, 95%, >99:1 d.r.); $[\alpha]_D^{25}$ −68.5 (*c* 1.1 in $CHCl_3$); ν_{max} (ATR) 3415 (O−H), 3025, 2969, 2915 (C–H), 1660 (C=C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.0, C(α)*Me*), 1.63 (1H, br s, O*H*), 1.77–1.86 (1H, m, C(1)*H*), 1.77–1.86 (1H, m, C(5)H_A), 2.08–2.28 (2H, m, C(2)H_2), 2.43 (1H, dd, *J* 9.0, 2.6, C(7)*H*), 2.48 (1H, dd, *J* 17.6, 6.3, C(5)H_B), 3.16 (1H, dd, *J* 10.5, 5.5, C(1')H_A), 3.30 (1H, m, C(1')H_B), 3.72 (1H, d, *J* 14.3, NCH_AH$_B$Ph), 3.77 (1H, br s, O*H*), 3.81–3.89 (1H, m, C(6)*H*), 3.96 (1H, q, *J* 7.0, C(α)*H*), 3.99 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 5.39–5.47 (1H, m, C(3)*H*), 5.47–5.55 (1H, m, C(4)*H*), 7.18–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (C(α)*Me*), 26.9 (*C*(2)), 34.9 (*C*(5)), 38.5 (*C*(1)), 50.2 (N*C*H$_2$Ph), 60.0 (*C*(α)), 65.3 (*C*(1')), 65.6 (*C*(7)), 67.7 (*C*(6)), 127.0 (*C*(3)), 127.4 (*C*(4)), 126.8, 127.1, 127.9, 128.4, 128.5, 128.6 (*o,m,p-Ph*), 140.6, 143.3 (*i-Ph*); *m/z* (ESI$^+$) 352 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NO_2^+$ ([M+H]$^+$) requires 352.2271; found 352.2268.

4.24. (1*S*,7*R*,7a*R*)-1-Hydroxymethyl-7-hydroxyhexahydro-1*H*-pyrrolizine 5 [(–)-platynecine]

Amino diol **44** (170 mg, 0.48 mmol, >99:1 d.r.) was coevaporated with HCl (3 × 2 mL, 2.0 M in Et_2O), then dissolved in CH_2Cl_2 (10 mL) and MeOH (10 mL). The resultant solution 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, 540 mg, 1.62 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 volume of 3 mL. AcOH (0.15 mL) and $Pd(OH)_2/C$ (76 mg, 40% w/w) were added. The resultant solution was degassed and 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 and coevaporated with HCl (2.0 M in Et_2O, 3 mL). Purification via column chromatography (eluent $CHCl_3$/MeOH/18 M aq NH_4OH, 6:4:1) gave **5** as a white solid (39 mg, 51%, >99:1 d.r.); {mp 140–142 °C; lit.[30] mp 145–146 °C; lit.[29h] mp 146–147 °C; lit.[26i] mp 151–153 °C; lit.[29e] mp 147–148 °C; lit.[29g] mp 149–151 °C; lit.[29a] mp 147–148 °C; lit.[29f] mp 147.5–149 °C; $[\alpha]_D^{20}$ –58.8 (*c* 0.9 in EtOH) ; $[\alpha]_D^{20}$ –55.0 (*c* 0.2 in $CHCl_3$); lit.[26i] $[\alpha]_D^{20}$ –55.1 (*c* 2.1 in $CHCl_3$); lit.[29h] $[\alpha]_D^{20}$ –63.4 (*c* 0.2 in $CHCl_3$); lit.[30] $[\alpha]_D^{20}$ –61.5 (*c* 1.0 in $CHCl_3$); lit.[26a] $[\alpha]_D^{20}$ –51 (*c* 0.9 in EtOH); lit.[29e] $[\alpha]_D^{20}$ –60.3 (*c* 0.3 in $CHCl_3$); lit.[29g] $[\alpha]_D^{20}$ –58.0 (*c* 1.0 in EtOH); lit.[29f] $[\alpha]_D^{20}$ –65.5 (*c* 0.8 in $CHCl_3$)}; ν_{max} (ATR) 3334 (O−H); δ_H (400 MHz, MeOH-d_4) 1.78 (1H, app dtd, *J* 11.8, 7.2, 2.3, C(2)H_A), 1.89−1.96 (2H, m, C(6)H_2), 1.99−2.11 (1H, m, C(2)H_B), 2.42−2.57 (1H, m, C(1)*H*), 2.85−3.00 (2H, m, C(3)H_A, C(5)H_A), 3.20 (1H, app td, *J* 10.5, 7.2, C(3)H_B), 3.33−3.38 (1H, m, C(5)H_B), 3.43 (1H, dd, *J* 8.1, 3.2, C(7a)*H*), 3.90−4.00 (2H, m, C(1')H_2), 4.30 (1H, app q, *J* 2.7, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 29.0 (*C*(2)), 37.4 (*C*(6)), 45.0 (*C*(1)), 55.1 (*C*(5)), 56.7 (*C*(3)), 61.6 (*C*(1')), 73.0 (*C*(7)), 73.2 (*C*(7a)); *m/z* (ESI^+) 158 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_2^+$ ($[M+H]^+$) requires 158.1176; found 158.1175.

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] (a) Adams, R.; Rogers, E. F. *J. Am. Chem. Soc.* **1942**, *61*, 2815; (b) Adams, R.; Hamlin, K. E. Jr. *J. Am. Chem. Soc.* **1942**, *64*, 2597; (c) Labenskii, A. S.; Men'shikov, G. P. *Zh. Obshch. Khim.* **1948**, *18*, 1836; (d) Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1967**, *20*, 2499; (e) Men'shikov, G. P.; Borodina, G. M. *Zh. Obshch. Khim.* **1941**, *11*, 209; (f) Tsuda, Y.; Marion, L. *Can. J. Chem.* **1963**, *41*, 1919; (g) Galinovsky, F.;

Goldberger, H.; Pohm, M. *Monatsh. Chem.* **1949**, *80*, 550; (h) Hartmann, T.; Witte, L. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, **1995**; vol 9, p 155; (i) Konovalov, V. S.; Men'shikov, G. P. *Zh. Obshch. Khim.* **1945**, *15*, 328; (j) De Waal, H. L. *Nature* **1940**, *146*, 777; (k) Orekhov, A. P.; Konovalova, R.; Tiedebel, V. *Chem. Ber.* **1935**, *68B*, 1886; (l) Men'shikov, G. P.; Denisova, S. O.; Massagetov, P. S. *Zh. Obcshch. Khim.* **1952**, *22*, 1509; (m) Sawhney, R. S.; Atal, C. K.; Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1974**, *27*, 1805; (n) Yamada, K.; Tatematsu, H.; Unno, R.; Hirata, Y.; Hirono, I. *Tetrahedron. Lett.* **1978**, *46*, 4543; (o) Danilova, A.; Utkin, L.; Massagetov, P. *Zh. Obshch. Khim.* **1955**, *25*, 831; (p) Were, O.; Benn, M.; Munavu, R. M. *J. Nat. Prod.* **1991**, *54*, 491; (q) Medina, J. C. M.; Gauze, G. F.; Vidotti, G. J.; Sarragiotto, M. H.; Basso, E. A.; Peixoto, J. L. B. *Tetrahedron Lett.* **2009**, *50*, 2640.

[3] Wiedenfeld, H.; Andrade-Cetto, A. *Phytochemistry* **2001**, *57*, 1269.

[4] For example, see: (a) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289; (b) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148; (c) Pereira, E.; Alves, C. de F.; Böckelmann, M. A.; Pilli, R. A. *Tetrahedron Lett.* **2005**, *46*, 2691; (d) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3173; (e) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Eur. J. Org. Chem.* **2000**, 2227.

[5] For example, see: (a) Konno, H.; Kishi, M.; Hiroya, K.; Ogasawara, K. *Heterocycles* **1998**, *49*, 33; (b) Han, X.; Zhong, F.; Wang, Y.; Lu. Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767.

[6] For example, see: (a) Rüeger, H.; Benn, M. *Heterocycles* **1982**, *19*, 1677; (b) Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 909.

[7] For example, see: (a) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536; (b) Ikeda, M.; Teranishi, H.; Iwamura, N.; Ishibashi, H. *Heterocycles* **1997**, *45*, 863; (c) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R. J.; Ónega, M. G.; Ruiz, M. *Tetrahedron* **1992**, *48*, 1637; (d) Ishibashi, H.; Sasaki, M.; Taniguchi, T. *Tetrahedron* **2008**, *64*, 7771.

[8] For example, see: (a) Le Coz, S.; Mann, A.; Thareau, F.; Taddei, M. *Heterocycles* **1993**, *36*, 2073; (b) Craig, D.; Hyland, C. J. T.; Ward, S. E. *Synlett* **2006**, 2142; (c) Knight, J. G.; Ley, S. V. *Tetrahedron Lett.* **1991**, *32*, 7119; (d) Ley, S. V. *Pure Appl. Chem.* **1994**, *66*, 1415.

[9] For a recent review, see: Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2014**, *25*, 387.

[10] 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.

[11] 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.

[12] (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.* **2014**, *68*, 610; (f) Brennan, M. B.; 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.

[13] For a review, see: Davies, S. G.; Fletcher, A. M.; Thomson, J. E. *Org. Biomol. Chem.* **2014**, *12*, 4544.

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

[15] We have also reported the asymmetric synthesis of (+)-isoretronecanol using a tandem ring-closure/N-debenzylation process; see: 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.

[16] (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.

[17] Stambouli, A.; Amouroux, M.; Chastrette, M. *Tetrahedron Lett.* **1987**, *28*, 5301.

[18] The enantiomeric excess of (*R*)-**22** was determined by chiral HPLC analysis on an Agilent 1200 Series instrument; HPLC Chiralpack AD-H [hexane/iso-propanol 95:5, λ 210, 1 mL/min] t_R [(*R*)-**22**] = 8.82 min, t_R [(*S*)-**22**] = 9.55 min, and comparison with an authentic racemic sample.

[19] We have previously investigated the effects of double asymmetric induction upon conjugate addition of enantiopure lithium amides to several enantiopure α,β-unsaturated esters; see: (a) Cailleau, T.; Cooke, J. W. B.; Davies, S. G.; Ling, K. B.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.;

Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 3922; (b) Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761; (c) 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*, 1635; (d) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Yin, J. *Tetrahedron* **2011**, *67*, 6382; (e) Beddow, J. E.; Davies, S. G.; Smith, A. D.; Russell, A. J. *Chem. Commun.* **2004**, 2778; (f) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812; (g) Davies, S. G.; Foster, E. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Biomol. Chem.* **2012**, *10*, 6186; (h) Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8680; (i) Davies, S. G.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2014**, *25*, 534; (j) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; Waul, M. A. *Tetrahedron* **2014**, *70*, 7106.

[20] Conjugate addition of both antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**13** and (*S*)-**13** (3.0 equiv) to α,β-unsaturated ester **22** returned only starting material.

[21] Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

[22] Crystallographic data (excluding structure factors) for the structures of **29**, **30** and **43** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1470439–1470441, respectively.

[23] (a) Davies, S. G.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, *9*, 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.

[24] (a) Abraham, E.; Cooke, J. W. B.; Davies, S. G.; Naylor, A.; Nicholson, R. L.; Price, P. D.; Smith, A. D. *Tetrahedron* **2007**, *63*, 5855; (b) Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Smith, A. D.; Rodríguez-Solla, H.; Thomson, J. E.; Toms, S. M. *Org. Biomol. Chem.* **2007**, *5*, 1961; (c) Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodríguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.

[25] For example, see: (a) Miyaoka, H.; Hara, Y.; Shinohara, I.; Kurokawa, T.; Yamada, Y. *Tetrahedron Lett.* **2005**, *46*, 7945; (b) Hickmann, V.; Kondoh, A.; Gabor, B.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2011**, *133*, 13471.

[26] (a) Marín-Loaiza, J. C.; Ernst, L.; Beuerle, T.; Theuring, C.; Céspedes, C. L.; Hartmann, T. *Phytochemistry* **2008**, *69*, 154; (b) Niwa, H.; Kuroda, A.; Sakata, T.; Yamada, K. *Bull. Chem. Soc. Jpn.*

1997, *70*, 2541; (c) Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187; (d) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672; (e) Mulzer, J.; Scharp, M. *Synthesis* **1993**, 615; (f) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959; (g) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235; (h) Hart, D. J.; Yang, T.-K. *J. Chem. Soc., Chem. Commun.* **1983**, 135; (i) Camberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425; (j) Aasen, A. J.; Culvenor, C. C. J.; Smith, L. W. *J. Org. Chem.* **1969**, *34*, 4137.

[27] (a) Hashimura, K.; Tomita, S.; Hiroya, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1995**, 2291; (b) Adams, R.; Van Duuren, B. L. *J. Am. Chem. Soc.* **1954**, *76*, 6379; (c) Dener, J.; Hart, D. J. *Tetrahedron* **1988**, *44*, 7037; (d) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345.

[28] (a) Vanecko, J.; West, F. G. *Org. Lett.* **2005**, *7*, 2949; (b) Wee, A. G. H. *J. Org. Chem.* **2001**, *66*, 8513; (c) An, D. K.; Duncan, D.; Livinghouse, T.; Reid, P. *Org. Lett.* **2001**, *3*, 2961; (d) Wee, A. G. H. *Tetrahedron Lett.* **2000**, *41*, 9025; (e) Knight, D. W.; Share, A. C.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans 1* **1997**, 2089; (f) Aasen, A. J.; Culvenor, C. C. J.; Smith, L. W. *J. Org. Chem.* **1969**, *34*, 2949.

[29] (a) Martinez, S. T.; Pinto, A. C.; Glasnov, T.; Kappe, C. O. *Tetrahedron Lett.* **2014**, *55*, 4181; (b) Zhou, C.-Y.; Yu, W.-Y.; Chan, P. W. H.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 7072; (c) Donohoe, T. J.; Guillermin, J.-B.; Walter, D. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1269; (d) de Faira, A. R.; Salvador, E. L.; Correia, C. R. D. *J. Org. Chem.* **2002**, *67*, 3651; (e) Kang, S. H.; Kim, G. T.; Yoo, Y. S. *Tetrahedron Lett.* **1997**, *38*, 603; (f) Fleet, G. W. J.; Seijas, J. A.; Vázquez-Tato, M. P. *Tetrahedron* **1991**, *47*, 525; (g) Rodgers, M.; Robins, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2437; (h) Asada, Y.; Furuya, T. *Chem. Pharm. Bull.* **1984**, *32*, 475; (i) Jenett-Siems, K.; Schimming, T.; Kaloga, M.; Eich, E.; Siems, K.; Gupta, M. P.; Witte, L.; Hartmann, T. *Phytochemistry* **1998**, *47*, 1551; (j) Mody, N. V.; Sawhney, R. S.; Pelletier, S. W. *J. Nat. Prod.* **1979**, *42*, 417.

[30] Denmark, S. E.; Parker, D. L., Jr.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 435.

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

[32] Kano, T.; Maruyama, H.; Sakamotoa, R.; Maruoka, J. *Chem. Commun.* **2015**, *51*, 10062.

[33] (*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine was assessed to be >99:1 e.r. by 400 MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acetylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic sample.

[34] (*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine was assessed to be >99:1 e.r. by 400 MHz ^{1}H NMR spectroscopic analysis in the presence of (*R*)-*O*-acetylmandelic acid in $CDCl_3$, and in comparison with that of an authentic racemic sample.

[35] Culvenor, C. C. J.; Koretskaya, N. I.; Smith, L. W.; Utkin, L. M. *Aust. J. Chem.* **1968**, *21*, 1671.

[36] Niwa, H.; Ishiwata, H.; Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 789.