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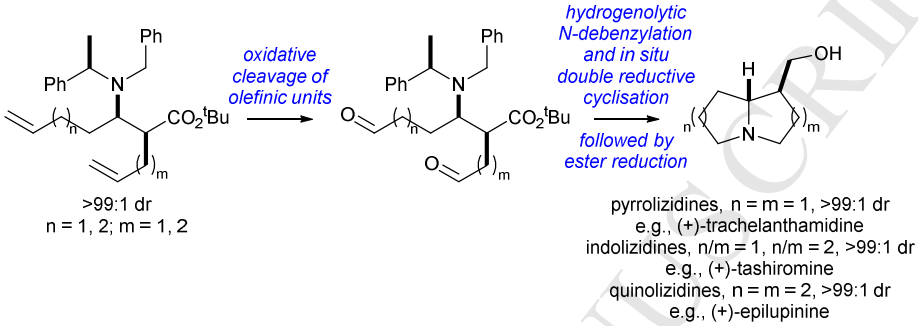

Pyrrolizidines, indolizidines and quinolizidines via a double reductive cyclisation protocol: concise asymmetric syntheses of (+)-trachelanthamidine, (+)-tashiromine and (+)-epilupinine

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Abstract

The asymmetric syntheses of pyrrolizidine, indolizidine and quinolizidine alkaloids have been achieved using the diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to α-alkenyl-α,β-unsaturated esters followed by diastereoselective protonation of the resultant enolates as the key stereodefining steps. The azabicyclic scaffolds were then efficiently constructed upon sequential oxidative cleavage of the olefinic units within the resultant β-amino esters and hydrogenolytic N-debenzylation of the corresponding dialdehydes, which occurs with concomitant double reductive cyclisation. Subsequent reduction of the ester moieties with $LiAlH_4$ gave (+)-trachelanthamidine, (+)-tashiromine, (1*S*,8a*R*)-1-(hydroxymethyl)octahydroindolizine and (+)-epilupinine in 4.9, 4.1, 3.0 and 5.9% overall yield, respectively, in only six steps from commercially available starting materials.

Key words: (+)-trachelanthamidine, (+)-tashiromine, (+)-epilupinine, azabicyclic alkaloids, asymmetric synthesis

1. Introduction

Azabicycles can be defined as systems exhibiting two fused aliphatic rings with an endocyclic nitrogen atom. Pyrrolizidines **1**, indolizidines **2** and quinolizidines **3** are sub-classes of [x.y.0]-azabicycles[1] which have the nitrogen atom located at a bridgehead position.[2] Azabicyclic alkaloids of this type are prevalent in Nature and display a broad array of different biological activity. For example, (+)-hyacinthacine A1 **4** is a potent glycosidase inhibitor,[3] (–)-swainsonine **5** exhibits anti-cancer activity,[4] and (–)-castanospermine **6** has been used to treat Dengue virus (Fig. 1).[5]

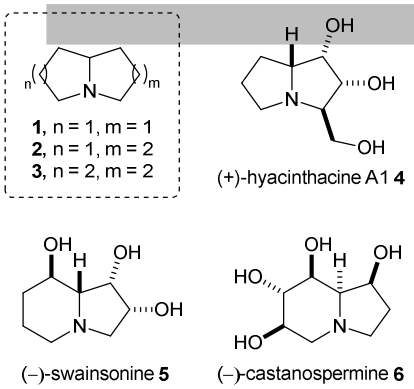
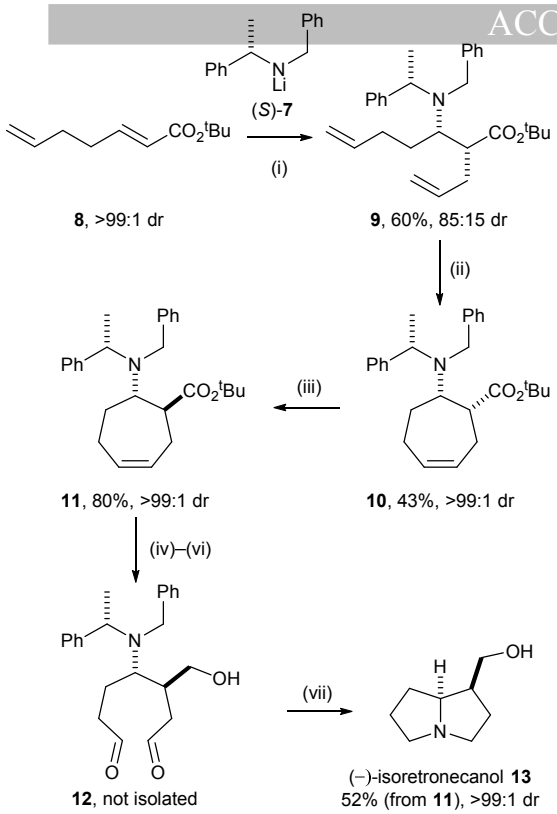


Fig. 1. The core structures of pyrrolizidines **1**, indolizidines **2** and quinolizidines **3**, and selected biologically active azabicyclic alkaloids **4**–**6**.

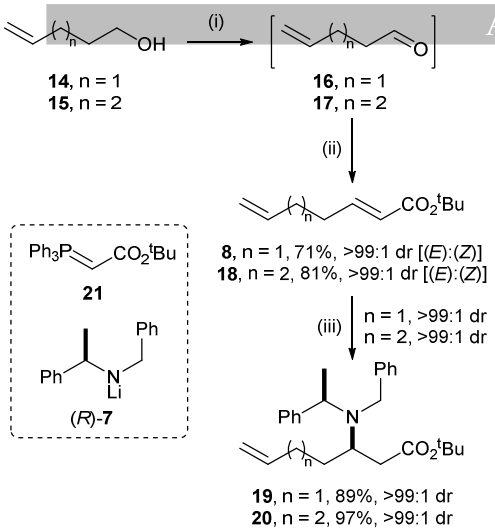
A fundamental step in the synthesis of these structures is the effective and stereoselective construction of the azabicyclic scaffold. We have recently developed highly efficient routes to several pyrrolizidine alkaloids employing a tandem hydrogenolytic N-debenzylation/double reductive cyclisation sequence to construct the [3.3.0]-azabicyclic ring system.[6] For example, conjugate addition[7,8] of lithium amide (*S*)-**7** to α,β-unsaturated ester **8** followed by allylation of the resultant lithium (*Z*)-β-amino enolate[9] gave **9** in 60% yield and 85:15 dr. Ring-closing metathesis of **9**, followed by treatment of **10** with KO^{t}Bu gave **11** in 34% yield (from **9**) and >99:1 dr. Olefinic oxidation[10,11] of **11**, reduction of the resultant lactone, and oxidative cleavage of the corresponding 1,2-diol gave dialdehyde **12**. Subsequent tandem hydrogenolytic N-debenzylation/double reductive cyclisation of **12** gave (–)-isoretronecanol **13** in 52% yield (from **11**) and >99:1 dr (Scheme 1). Herein, we report a modification to this methodology and also expand its scope to encompass the asymmetric syntheses of [4.3.0]- and [4.4.0]-azabicyclic targets (i.e., indolizidines and quinolizidines), which culminates in the syntheses of (+)-trachelanthamidine[12] (originally trachelantamidine[13]), (+)-tashiromine, (1*S*,8a*R*)-1-(hydroxymethyl)octahydroindolizine and (+)-epilupinine.[14]



Scheme 1. *Reagents and conditions*: (i) (*S*)-**7**, THF, –78 °C, 2 h then allyl bromide, –78 °C to rt, 12 h; (ii) Grubbs I, CH_2Cl_2, 35 °C, 16 h; (iii) KHMDS, ^{t}BuOH, THF, rt, 16 h; (iv) HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h; (v) $LiAlH_4$, THF, 0 °C, 2 h; (vi) $NaIO_4$, MeOH, rt, 1 h; (vii) H_2 (5 atm), MeOH/AcOH (20:1), rt, 24 h.

2. Results and discussion

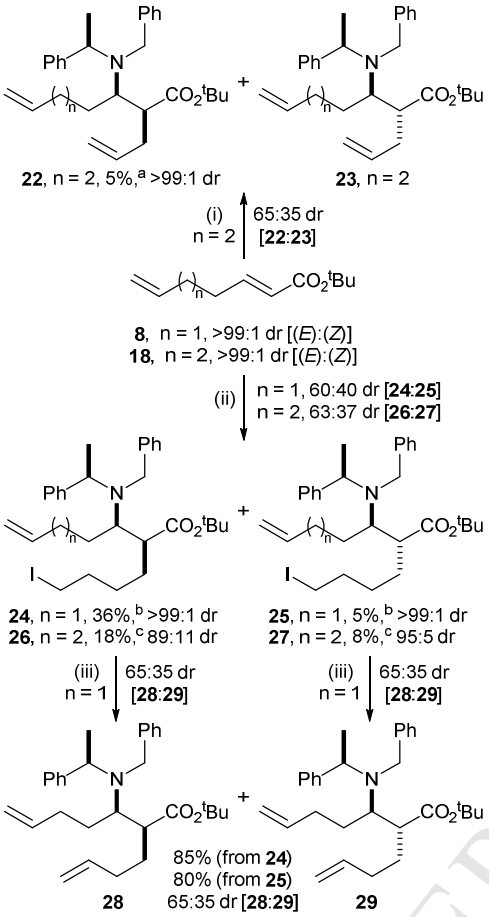
We initially set out to extend our existing methodology to the homologous substrates to access the target indolizidines and quinolizidines. The requisite α,β-unsaturated esters were prepared from commercially available alcohols **14** and **15** upon Swern oxidation and stereoselective Wittig reaction of the resultant aldehydes **16** and **17**, with *tert*-butyl 2-(triphenylphosphanylidene)acetate **21** (which was prepared in 68% yield from *tert*-butyl bromoacetate and PPh_3), which gave α,β-unsaturated esters **8** and **18** in 71 and 81% isolated yield, respectively, and >99:1 dr [(*E*):(*Z*)] in each case. Conjugate addition[7] of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**7** to α,β-unsaturated ester **8** (n = 1), followed by treatment of the resultant lithium (*Z*)-β-amino enolate[9] with satd aq NH_4Cl, gave the known[14l] β-amino ester **19** in 89% yield and >99:1 dr. Similarly, conjugate addition of lithium amide (*R*)-**7** to α,β-unsaturated ester **18** (n = 2), followed by protonation of the resultant lithium (*Z*)-β-amino enolate[9] with satd aq NH_4Cl, gave β-amino ester **20** as a single diastereoisomer (>99:1 dr) in 97% yield (Scheme 2). The relative configuration within **20** was assigned by reference to the transition state mnemonic[8] which has been developed to correctly predict the stereochemical outcome upon conjugate addition of lithium amide reagents to achiral α,β-unsaturated esters (>200 examples), including the conjugate addition of (*R*)-**7** to **8** (n = 1).



Scheme 2. *Reagents and conditions*: (i) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, then Et_3N, –78 °C to rt, 10 min; (ii) **21**, rt, 18 h; (iii) (*R*)-**7**, THF, –78 °C, 2 h, then NH_4Cl (satd aq).

By analogy to our established tandem conjugate addition/alkylation procedure, described above for **8** (n = 1),[6a] conjugate addition of lithium amide (*R*)-**7** to α,β-unsaturated ester **18** (n = 2) followed by treatment of the resultant lithium (*Z*)-β-amino enolate[9] with allyl bromide gave a 65:35 mixture of C(2)-epimers **22** and **23**, respectively. β-Amino esters **22** and **23** proved to be extremely difficult to separate, and the major product **22** was isolated in only 5% yield as a single diastereoisomer (>99:1 dr) after exhaustive chromatographic purification; a 65:35 mixed fraction of **22** and **23**, respectively, was also isolated in 64% combined yield. As complete diastereoselectivity was observed upon conjugate addition in the formation of β-amino ester **20**, compounds **22** and **23** were assigned as being C(2)-epimers. The 2,3-*syn*-relative configuration within the major diastereoisomer **22** was tentatively assigned by analogy to the stereochemical outcome observed upon tandem conjugate addition/alkylation of **8** (n = 1),[6a] and this assignment was later unambiguously confirmed by chemical correlation to the target indolizidine (*vide infra*). We have previously observed that the alkylation of lithium β-amino enolates with but-3-enyl bromide is a low yielding process; however, alkylation with 1,4-diiodobutane followed by elimination of HI from the resultant α-alkyl-β-amino ester can be an efficient method to introduce a but-3-enyl group at the C(2)-position. Indeed, conjugate addition of lithium amide (*R*)-**7** to α,β-unsaturated ester **8** (n = 1) followed by alkylation of the intermediate lithium (*Z*)-β-amino enolate[9] with 1,4-diiodobutane was found to yield a 60:40 partially separable mixture of C(2)-epimers **24** and **25**, which were isolated in 36 and 5% yield, respectively; a 50:50 mixed fraction of **24** and **25** was also obtained in 34% combined yield. Identical treatment of the homologous substrate **18** (n = 2) gave a 63:37 mixture of C(2)-epimers **26** and **27**, respectively. Although chromatographic purification of **26** and **27** proved difficult and various mixed fractions were obtained, **26** was isolated in 18% yield and 89:11

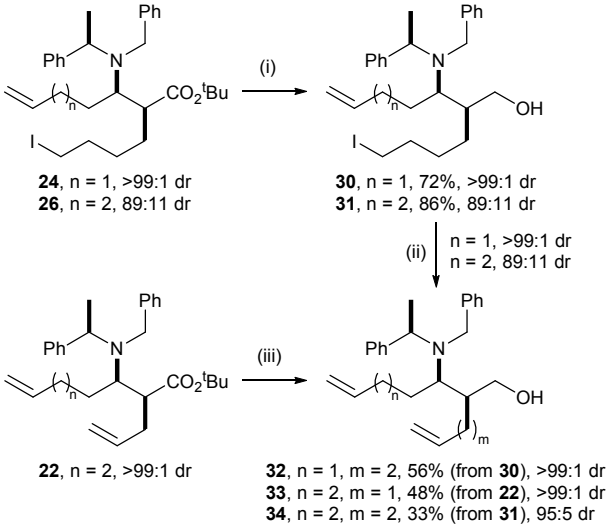
dr, and **27** was isolated in 8% yield and 95:5 dr. The relative configurations within **24**–**27** were again tentatively assigned by analogy to the outcome observed upon tandem conjugate addition/alkylation of **8** (n = 1).[6a] Elimination of HI from within both **24** (n = 1, >99:1 dr) and **25** (n = 1, >99:1 dr), upon treatment with KO^{t}Bu, yielded a 65:35 mixture of **28** and **29**, respectively, in both cases (Scheme 3). These results are consistent with C(2)-epimerisation occurring as well as elimination of HI under the basic reaction conditions.



Scheme 3. *Reagents and conditions*: (i) (*R*)-**7**, THF, –78 °C, 2 h, then allyl bromide, –78 °C to rt, 12 h; (ii) (*R*)-**7**, THF, –78 °C, 2 h, then 1,4-diiodobutane, –78 °C to rt, 12 h; (iii) KO^{t}Bu, THF, rt, 16 h. [[a] a 65:35 mixture of **22** and **23** was also isolated in 64% combined yield; [b] a 50:50 mixed fraction of **24** and **25** was also isolated in 34% combined yield; [c] further mixed fractions were also isolated in 20% total yield].

As C(2)-epimerisation was noted upon elimination of HI from within both **24** and **25**, it was proposed that reduction of the ester moiety should be performed first, removing the risk of epimerisation during the subsequent elimination step. Following a literature procedure for the chemoselective reduction of an ester in the presence of an ω-iodo substituent,[15] both **24** (n = 1, >99:1 dr) and **26** (n = 2, 89:11 dr) were treated with DIBAL-H in PhMe. After purification of the crude reaction mixtures, alcohols **30** (>99:1 dr) and **31** (89:11 dr) were isolated in 72 and 86% yield, respectively. Subsequent elimination of HI from within **30** and **31** upon treatment with KO^{t}Bu gave **32** in 56% yield and >99:1 dr, and **34** in 33% yield and 95:5 dr,

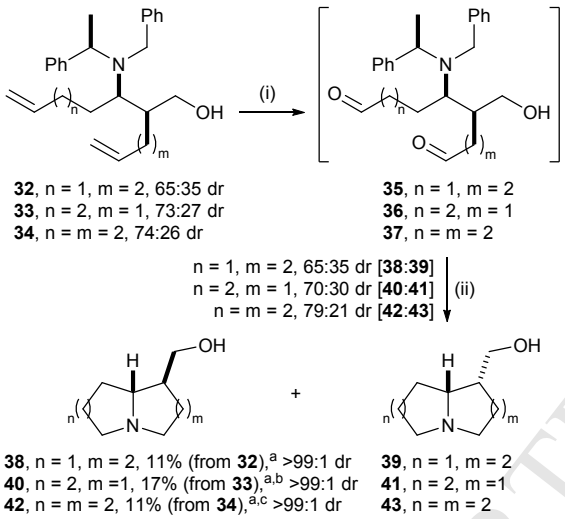
respectively. In addition, α-allyl-β-amino ester **22** (>99:1 dr) was reduced with $LiAlH_4$ to give the corresponding alcohol **33** in 48% yield and >99:1 dr (Scheme 4).



Scheme 4. *Reagents and conditions*: (i) DIBAL-H, PhMe, 0 °C, 4 h; (ii) KO^{t}Bu, THF, rt, 16 h; (iii) $LiAlH_4$, THF, –78 °C to rt, 18 h.

Attempts to optimise the overall yields of the requisite dienes via a strategy reliant on ring-closing metathesis [i.e., an analogous approach to that which we used previously[6a] for the truncated analogue **9** (n = 1)] were thwarted by both poor conversion and low isolated yields. Instead, it was envisaged that oxidative cleavage of the olefinic units within α-alkenyl-β-amino alcohols **32**–**34** would afford the requisite dialdehydes, and application of the tandem hydrogenolytic N-debenzylation/double reductive cyclisation protocol would then furnish the corresponding azabicycles. Initially, the efficacy of this route was evaluated using mixtures of C(2)-epimeric alcohols **32**–**34** as these samples could easily be prepared on multigram scales. Oxidative cleavage of the olefinic units within **32** (65:35 dr) via ozonolysis of the corresponding hydrochloride salt **32**·HCl (to circumvent N-oxidation) gave the corresponding dialdehyde **35**. Subsequent hydrogenolysis of **35** effected N-debenzylation and concomitant double reductive cyclisation, and following purification of the crude reaction mixture on Dowex 50WX8 ion-exchange resin, (+)-tashiromine **38** was isolated in 11% yield (from **32**) and >99:1 dr. Similarly, ozonolysis of **33** (73:27 dr) followed by tandem hydrogenolytic N-debenzylation/double reductive cyclisation of the resultant dialdehyde **36** gave, after purification on Dowex 50WX8 ion-exchange resin, (1*S*,8a*R*)-1-(hydroxymethyl)indolizidine **40** as a single diastereoisomer (>99:1 dr) in 17% isolated yield (from **33**). In the homologous series, ozonolysis of **34** (74:26 dr) and tandem hydrogenolytic N-debenzylation/double reductive cyclisation of dialdehyde **37** gave a 79:21 mixture of quinolizidines **42** and **43**, respectively. Sequential purification by ion-exchange chromatography on Dowex 50WX8 resin followed by flash column chromatography on neutral alumina

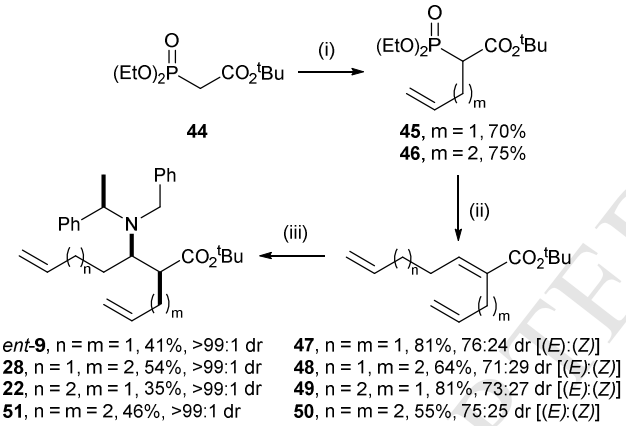
gave (+)-epilupinine **42** in 11% yield (from **34**) and >99:1 dr (Scheme 5). In each case, the samples of the azabicyclic targets **38**, **40** and **42** were found to be contaminated with ~5% unidentified impurities, although the specific rotations and spectroscopic data for these samples of (+)-tashiromine **38,** (1*S*,8a*R*)-1-(hydroxymethyl)indolizidine **40** and (+)-epilupinine **42** were all in reasonably good agreement with literature data {for **38**: $[\alpha]_D^{20}$ +30.0 (*c* 0.5 in $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ +43.4 (*c* 0.53 in $CHCl_3$); for **40**: $[\alpha]_D^{20}$ +30.1 (*c* 0.42 in EtOH); lit.[14l] $[\alpha]_D^{20}$ +27.4 (*c* 1.0 in EtOH); for **42**: $[\alpha]_D^{20}$ +20.1 (*c* 0.33 in EtOH); lit.[14j] $[\alpha]_D^{20}$ +31.8 (*c* 0.6 in EtOH)}. Despite the relatively low yields of **38**, **40** and **42** obtained, these results established that the tandem hydrogenolytic N-debenzylation/double reductive cyclisation protocol is indeed applicable to the synthesis of indolizidines and quinolizidines. An alternative, higher yielding synthesis of diastereoisomerically pure cyclisation precursors was therefore investigated via conjugate addition of lithium amide (*R*)-**7** to the corresponding α-alkenyl substituted α,β-unsaturated esters.



Scheme 5. *Reagents and conditions*: (i) HCl/Et_2O, rt, 5 min, then O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 1 h, then polymer supported PPh_3, –78 °C to rt, 2 h; (ii) H_2, $Pd(OH)_2/C$, MeOH/AcOH (25:1), 35 °C, 24 h. [[a] ~95% purity; [b] an 86:14 mixture of **40** and **41**, respectively, was also isolated in 14% combined yield and ~95% purity; [c] a 77:23 mixture of **42** and **43**, respectively, was also isolated in 8% combined yield and ~95% purity].

The requisite α-alkenyl substituted phosphonate reagents **45** and **46** were readily prepared from **44** upon deprotonation with NaH and alkylation of the resultant anion with either allyl bromide or but-3-enyl bromide, which gave **45** and **46** in 70 and 75% yield, respectively. Following a modified Wadsworth-Emmons protocol[17] deprotonation of the α-alkenyl phosphonate reagents **45** and **46** with MeMgBr and ensuing reaction with aldehydes **16** and **17** gave α-alkenyl-α,β-unsaturated esters **47**–**50** in good yield and moderately high [(*E*):(*Z*)] ratios (>70:30 dr); the presence of the (*Z*)-configured α,β-unsaturated esters was not deemed to be a problem as it is known that lithium amides only undergo conjugate addition to (*E*)-configured substrates.[7] In accordance with our previous observations concerning conjugate additions of

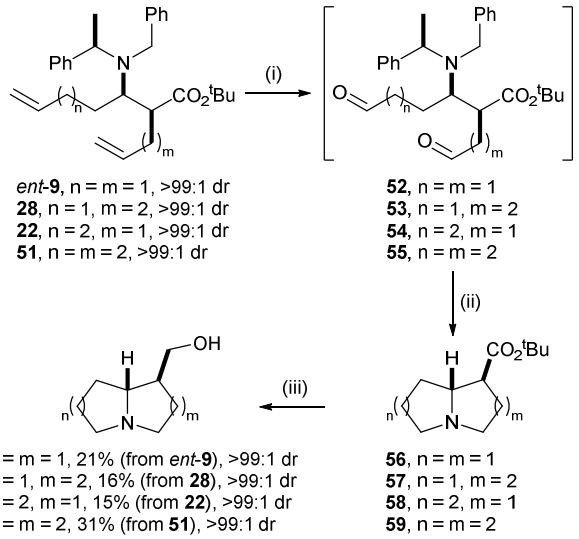
lithium amide (*R*)-**7** to α,β-unsaturated esters bearing either methyl or benzyl substituents at the α-position,[18] an alternative procedure was required for the conjugate addition of (*R*)-**7** to α-alkenyl-α,β-unsaturated esters **47**–**50** due to poor diastereoselectivity and the formation of various side products under the standard conditions for lithium amide conjugate addition (i.e., THF, –78 °C, 2 h). In order to overcome the issues associated with both reactivity and diastereoselectivity, the conjugate addition was performed in PhMe prior to dilution of the reaction medium with THF and subsequent addition of 2,6-di-*tert*-butyl phenol to the resultant solution of the intermediate enolate.[18] In each case, the α-alkenyl-β-amino esters *ent*-**9**, **28**, **22** and **51** were prepared as single diastereoisomers (>99:1 dr) in 35–54% yield (Scheme 6). The configurations of these β-amino ester products were assigned by analogy to the stereochemical outcome observed upon conjugate addition of (*R*)-**7** to the corresponding α-methyl- and α-benzyl-substituted α,β-unsaturated esters, which was followed by diastereoselective protonation of the intermediate β-amino enolates with 2,6-di-*tert*-butyl phenol;[18] these assignments were later confirmed unambiguously by chemical correlation to the target azabicycles (*vide infra*).



Scheme 6. *Reagents and conditions*: (i) NaH, THF, rt, 1 h then allyl bromide or but-3-enyl bromide, 70 °C, 36 h; (ii) MeMgBr, THF, rt, 15 min then **16** (n = 1) or **17** (n = 2), 70 °C, 3 h; (iii) (*R*)-**7**, PhMe, –78 °C, 1 h then –30 °C, 2 h then THF, –78 °C, 30 min then 2,6-di-*tert*-butylphenol, –78 °C to rt, 30 min.

Various attempts at the ozonolysis of these substrates (as the corresponding hydrochloride salts) were found to be problematic. However, under optimised conditions, dialdehydes **52**–**55** were prepared upon treatment of α-alkenyl-β-amino esters *ent*-**9**, **28**, **22** and **51** with OsO_4 and $NaIO_4$ in the presence of 2,6-lutidine.[19] Immediate subjection of dialdehydes **52**–**55** to the tandem hydrogenolytic N-debenzylation/double reductive cyclisation conditions followed by reduction of the resultant azabicyclic esters **56**–**59** with $LiAlH_4$ gave the target hydroxymethyl bearing azabicycles **60**, **38**, **40** and **42** in >99:1 dr in each case. Purification of the crude reaction mixtures gave (+)-trachelanthamidine **60**, (+)-tashiromine **38**, (1*S*,8a*R*)-1-(hydroxymethyl)-octahydroindolizine **40** and (+)-epilupinine **42** as single diastereoisomers (>99:1 dr) in each case (Scheme 7).

The specific rotations and spectroscopic data for these samples of **60**, **38**, **40** and **42** were in good agreement with literature values {for (+)-trachelanthamidine **60**: $[\alpha]_D^{25}$ +15.9 (*c* 1.0 in EtOH); lit.[14g] $[\alpha]_D^{20}$ +15.4 (*c* 1.2 in EtOH); for (+)-tashiromine **38**: $[\alpha]_D^{25}$ +39.0 (*c* 0.2 in EtOH); lit.[20] $[\alpha]_D^{22}$ +41.9 (*c* 1.1 in EtOH); for (1*S*,8a*R*)-1-(hydroxymethyl)octahydroindolizine **40**: $[\alpha]_D^{25}$ +39.8 (*c* 0.5 in EtOH); lit.[14l] $[\alpha]_D^{23}$ +27.4 (*c* 1.0 in EtOH); for (+)-epilupinine **42**: $[\alpha]_D^{25}$ +29.1 (*c* 0.3 in EtOH); lit.[14k] for *ent*-**42** $[\alpha]_D^{26}$ −29.2 (*c* 1.0 in EtOH)}, thereby also confirming the assigned configurations within the synthetic precursors *ent*-**9**, **28**, **22**, **51** and **52**–**59**.



Scheme 7. *Reagents and conditions*: (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1), rt, 40 min; (ii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 120 h; (iii) $LiAlH_4$, THF, –78 °C to rt, 2 h.

3. Conclusion

In conclusion, concise asymmetric syntheses of pyrrolizidine, indolizidine and quinolizidine alkaloids have been achieved using the diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to α-alkenyl-α,β-unsaturated esters followed by diastereoselective protonation of the resultant enolates with 2,6-di-*tert*-butylphenol as the key stereodefining steps. The azabicyclic scaffolds were then efficiently constructed upon sequential oxidative cleavage of the olefinic units and hydrogenolytic N-debenzylation of the resultant dialdehydes, which occurs with concomitant double reductive cyclisation. Subsequent reduction of the ester moieties with $LiAlH_4$ gave the target hydroxymethyl bearing azabicycles. Following this route, enantiopure samples of (+)-trachelanthamidine, (+)-tashiromine, (1*S*,8a*R*)-1-(hydroxymethyl)octahydroindolizine and (+)-epilupinine were prepared as single diastereoisomers (>99:1 dr) in 4.9, 4.1, 3.0 and 5.9% overall yield, respectively, in only six steps from commercially available starting materials.

4. Experimental

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. ^{t}BuOH was distilled from activated magnesium turnings. Allyl bromide and but-3-enyl bromide were distilled from $MgSO_4$. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[21] 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. $^{1}H-^{1}H$ COSY, $^{1}H-^{13}C$ HMQC, and $^{1}H-^{13}C$ 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.

tert-Butyl (*E*)-hepta-2,6-dienoate 8

A solution of $(COCl)_2$ (2.38 mL, 28.4 mmol) in CH_2Cl_2 (40 mL) at –78 °C was treated with DMSO (2.20 mL, 31.0 mmol) in CH_2Cl_2 (40 mL). The resultant mixture was stirred at –78 °C for 10 min, then a solution of 4-penten-1-ol **14** (2.00 g, 23.2 mmol) in CH_2Cl_2 (40 mL) was added. The resultant mixture was stirred at –78 °C for 1 h, then Et_3N (6.39 mL, 45.9 mmol) was added. The reaction mixture was allowed to warm to rt, then **21** (8.74 g, 23.2 mmol) was added and the resultant mixture was stirred at rt for 18 h. Satd aq Na_2CO_3

(40 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (40 mL), then dried and concentrated in vacuo to give **8** in >99:1 dr [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **8** as a colourless oil (2.95 g, 71%, >99:1 dr [(*E*):(*Z*)]);[22] δ_H (200 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 2.14–2.36 (4H, m, C(4)*H*$_2$, C(5)*H*$_2$), 5.00–5.16 (2H, m, C(7)*H*$_2$), 5.77–5.95 (2H, m, C(2)*H*, C(6)*H*), 6.92 (1H, dt, *J* 15.7, 6.7, C(3)*H*).

***tert*-Butyl (*E*)-octa-2,7-dienoate 18**

A solution of $(COCl)_2$ (2.37 mL, 28.0 mmol) in CH_2Cl_2 (40 mL) at –78 °C was treated with DMSO (2.15 mL, 30.3 mmol) in CH_2Cl_2 (40 mL). The resultant mixture was stirred at –78 °C for 10 min, then a solution of 5-hexen-1-ol **15** (2.80 mL, 23.3 mmol) in CH_2Cl_2 (40 mL) was added. The resultant mixture was stirred at –78 °C for 1 h, then Et_3N (7.80 mL, 56.0 mmol) was then added. The reaction mixture was allowed to warm to rt, then **21** (8.76 g, 23.3 mmol) was added and the resultant mixture was stirred at rt for 18 h. Satd aq Na_2CO_3 (50 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated in vacuo to give **18** in >99:1 dr [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **18** as a colourless oil (3.72 g, 81%, >99:1 dr [(*E*):(*Z*)]); ν_{max} (ATR) 1719 (C=O), 1653 (C=C); δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 1.55–1.61 (2H, m, C(5)*H*$_2$), 2.07–2.24 (4H, m, C(4)*H*$_2$, C(6)*H*$_2$), 4.98–5.07 (2H, m, C(8)*H*$_2$), 5.74–5.68 (2H, m, C(2)*H*, C(7)*H*), 6.88 (1H, dt, *J* 15.6, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.2 (*C*(5)), 28.1 (C*Me*$_3$), 31.3 (*C*(4)), 33.1 (*C*(6)), 80.0 (*C*Me$_3$), 115.0 (*C*(8)), 123.2 (*C*(2)), 138.1 (*C*(7)), 147.6 (*C*(3)), 166.1 (*C*(1)); *m/z* (ESI$^+$) 219 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{20}NaO_2^+$ ([M+Na]$^+$) requires 219.1356; found 219.1356.

***tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 19**

BuLi (2.5 M in hexanes, 1.85 mL, 4.26 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.92 mL, 4.40 mmol, >99:1 er) in THF (10 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **8** (500 mg, 2.75 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (10 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 2 h, then satd aq NH_4Cl (10 mL) was added. The resultant mixture was allowed to warm to rt and stirred at rt for 15 min, then concentrated in vacuo. 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 (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 **19** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 100:1) gave **19** as a pale yellow oil (959 mg, 89%, >99:1 dr);[14l] $[\alpha]_D^{20}$ +8.7 (*c* 1.0 in $CHCl_3$); {lit.[14l] $[\alpha]_D^{26}$ +8.1 (*c* 0.9 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 7.0, C(α)*Me*), 1.28–1.39 (1H, m, C(4)H_A), 1.31 (9H, s, CMe_3), 1.46 (1H, app dtd, *J* 14.9, 9.3, 5.0, C(4)H_B), 1.74–1.82 (2H, m, C(2)H_2), 2.00–2.09 (1H, m, C(5)H_A), 2.26–2.34 (1H, m, C(5)H_B), 3.27 (1H, app tt, *J* 8.7, 4.4, C(3)*H*), 3.39 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.67–3.75 (2H, m, C(α)*H*, NCH$_A$$H_B$Ph), 4.83–4.94 (2H, m, C(7)H_2), 5.70 (1H, app ddt, *J* 17.1, 10.3, 6.5, C(6)*H*), 7.12–7.35 (10H, m, *Ph*).

***tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-enoate 20**

BuLi (2.5 M in hexanes, 1.23 mL, 3.08 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.67 mL, 3.18 mmol, >99:1 er) in THF (8 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **18** (390 mg, 1.99 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (8 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 2 h, then satd aq NH_4Cl (10 mL) was added. The resultant mixture was allowed to warm to rt and stirred at rt for 15 min, then concentrated in vacuo. 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 (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 **20** in >99:1 dr. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 20:1) gave **20** as a pale yellow oil (787 mg, 97%, >99:1 dr); $[\alpha]_D^{20}$ +6.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1726 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, CMe_3), 1.46–1.63 (4H, m, C(4)H_2, C(5)H_2), 1.87−2.06 (4H, m, C(2)H_2, C(6)H_2), 3.31−3.38 (1H, m, C(3)*H*), 3.52 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.81−3.87 (2H, m, C(α)*H*, NCH$_A$$H_B$Ph), 4.96−5.05 (2H, m, C(8)H_2), 5.79−5.89 (1H, m, C(7)*H*), 7.25−7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 26.3 (*C*(5)), 28.1 (CMe_3), 33.0 (*C*(4)), 33.7 (*C*(6)), 37.7 (*C*(2)), 50.1 (*C*(3)), 53.8 (N*C*H$_2$Ph), 58.3 (*C*(α)), 80.0 (*C*Me$_3$), 114.4 (*C*(8)), 126.6, 127.0, 128.0, 128.2, 128.3 (*o,m,p-Ph*), 139.1 (*C*(7)), 142.0, 140.7 (*i-Ph*), 172.2 (*C*(1)); *m/z* (ESI$^+$) 408 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{38}NO_2^+$ ([M+H]$^+$) requires 408.2897; found 408.2898.

***tert*-Butyl (2*S*,3*R*,*αR*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-enoate 22**

Method A: BuLi (2.3 M in hexanes, 15.5 mL, 35.7 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (7.63 mL, 36.5 mmol, >99:1 er) in PhMe (15 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **49** (2.39 g, 10.1 mmol, 73:27 dr [(*E*):(*Z*)]) in PhMe (8 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 1 h and then maintained at –30 °C for 2 h before being cooled to –78 °C. THF (80 mL) at –78 °C was added swiftly via cannula and the resultant mixture was then stirred at –78 °C for 30 min. A solution of 2,6-di-*tert*-butylphenol (8.26 g, 40.1 mmol) in THF (30 mL) was added dropwise via cannula and the resultant mixture was allowed to warm to rt over 30 min then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (60 mL) and 10% aq citric acid (60 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (180 mL), H_2O (180 mL) and brine (180 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **22** as a colourless oil (1.58 g, 35%, >99:1 dr); $[\alpha]_D^{25}$ +40.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1723 (C=O), 1641 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.46–1.70 (4H, m, C(4)H_2, C(5)H_2), 1.94–2.03 (3H, m, C(6)H_2, C(1')H_A), 2.18–2.24 (1H, m, C(1')H_B), 2.22–2.28 (1H, m, C(2)*H*), 2.69–2.74 (1H, m, C(3)*H*), 3.84 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.96 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.91–5.04 (4H, m, C(8)H_2, C(3')H_2), 5.49–5.63 (1H, m, C(7)*H*), 5.76–5.86 (1H, m, C(2')*H*), 7.24–7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 27.3 (*C*(5)), 28.1 (*C*(1')), 28.2 (C*Me*$_3$), 30.1 (*C*(4)), 34.0 (*C*(6)), 49.7 (*C*(2)), 51.2 (N*C*H$_2$Ph)), 59.3 (*C*(α)), 59.9 (*C*(3)), 80.3 (*C*Me$_3$), 114.5 (*C*(3')), 116.0 (*C*(8)), 126.5, 126.9, 127.9, 128.0, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 136.0 (*C*(2')), 138.9 (*i*-*Ph*), 142.3 (*C*(7)), 144.8 (*i*-*Ph*), 174.4 (*C*(1)); *m/z* (ESI^+) 448 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{42}NO_2^+$ ($[M+H]^+$) requires 448.3210; found 448.3212.

Method B: BuLi (2.5 M in hexanes, 6.87 mL, 15.8 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.40 mL, 16.3 mmol, >99:1 er) in THF (45 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **18** (2.00 g, 10.2 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (45 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 2 h, then freshly distilled allyl bromide (2.65 mL, 30.6 mmol) was added. The resultant mixture was allowed to warm to rt and stirred at rt for 12 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 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 a 65:35 mixture of **22** and **23**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave an inseparable 65:35 mixture of **22** and **23**, respectively, as a colourless oil (2.90 g, 64%). Data for mixture: ν_{max} (ATR) 1723 (C=O), 1641 (C=C); *m/z* (ESI^+) 448 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{42}NO_2^+$ ($[M+H]^+$) requires 448.3210; found 448.3212. Data for **23**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.20 (3H, d, *J* 7.0, C(α)*Me*), 1.33 (9H, s, CMe_3) 2.89–2.95 (1H, m, C(3)*H*), 3.68–3.72 (2H, m, NCH_2Ph), 4.91–5.04 (4H, m, C(8)H_2, C(3')H_2), 5.49–5.63 (1H, m, C(7)*H*), 5.76–5.86 (1H, m, C(2')*H*), 7.24–7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 28.1 (CMe_3), 79.8 (*C*Me_3), 114.6 (*C*(3')), 115.4 (*C*(8)), 135.0 (*C*(2')), 137.9 (*C*(7)), 142.1, 144.6 (*i-Ph*), 174.0 (*C*(1)). Further elution gave **22** as a colourless oil (232 mg, 5%, >99:1 dr); $[\alpha]_D^{20}$ +36.5 (*c* 1.0 in $CHCl_3$).

***tert*-Butyl (2*S*,3*R*,α*R*) 2-(4-iodobut-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 24 and *tert*-butyl (*R*,*R*,*R*) 2-(4-iodobut-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 25**

BuLi (2.5 M in hexanes, 6.84 mL, 17.1 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.68 mL, 17.6 mmol, >99:1 er) in THF (40 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **8** (2.00 g, 11.0 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (40 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 2 h, then 1,4-diiodobutane (7.26 mL, 55.0 mmol) was added. The resultant mixture was allowed to warm to rt and stirred at rt for 12 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (50 mL) and 10% aq citric acid (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 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 a 60:40 mixture of **24** and **25**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **24** as a pale yellow oil (2.30 g, 36%, >99:1 dr); $[\alpha]_D^{20}$ +12.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1721 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 0.95–1.04 (1H, m, C(2')H_A), 1.06–1.21 (3H, m, C(1')H_2, C(2')H_B), 1.24 (3H, d, *J* 6.8, C(α)*Me*), 1.35 (9H, s, CMe_3), 1.41–1.49 (1H, m, C(4)H_A), 1.54–1.63 (3H, m, C(4)H_B, C(3')H_2), 1.91–1.98 (1H, m, C(5)H_A), 2.12–2.17 (1H, m, C(2)*H*), 2.19–2.26 (1H, m, C(5)H_B), 2.68–2.72 (1H, m, C(3)*H*), 3.00 (2H, t, *J* 6.9, C(4')H_2), 3.74 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 3.84 (1H, d, *J* 14.9, NC$H_A$$H_B$Ph), 3.91 (1H, q, *J* 6.8, C(α)*H*), 4.84–4.91 (2H, m, C(7)H_2), 5.63–5.71 (1H, m, C(6)*H*), 7.15–7.29 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 6.9 (*C*(4')), 19.4 (C(α)*Me*), 28.1 (CMe_3), 28.2 (*C*(2')), 29.8 (*C*(4)), 30.7 (*C*(1')), 32.1 (*C*(5)), 33.2 (*C*(3')), 49.8 (*C*(2)), 51.3 (NCH_2Ph), 58.7

(*C*(α)), 59.8 (*C*(3)), 80.3 (*C*Me$_3$), 114.4 (*C*(7)), 138.9 (*C*(6)), 126.6, 126.7, 127.9, 128.2, 128.3 (*o,m,p-Ph*), 142.1, 144.6 (*i-Ph*), 174.9 (*C*(1)); *m/z* (ESI$^+$) 576 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{43}INO_2^+$ ([M+H]$^+$) requires 576.2333; found 576.2333. Further elution gave an inseparable 50:50 mixture of **24** and **25** as a colourless oil (2.13 g, 34%). Further elution gave **25** as a pale yellow oil (289 mg, 5%, >99:1 dr); $[\alpha]_D^{20}$ +17.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1721 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 0.79–0.86 (1H, m, C(2')*H*$_A$), 0.90–0.99 (1H, m, C(2')*H*$_B$), 1.10–1.19 (2H, m, C(1')*H*$_2$), 1.23 (3H, d, *J* 6.9, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 1.53–1.63 (4H, m, C(4)*H*$_2$, C(3')*H*$_2$), 1.99–2.10 (2H, m, C(5)*H*$_2$), 2.19–2.23 (1H, m, C(2)*H*), 2.88–2.23 (1H, m, C(3)*H*), 2.98 (2H, t, *J* 7.0, C(4')*H*$_2$), 3.70 (1H, d, *J* 14.3 NC*H*$_A$H$_B$Ph), 3.76 (1H, d, *J* 14.3 NCH$_A$*H*$_B$Ph), 3.88 (1H, q, *J* 6.9, C(α)*H*), 4.86–4.98 (2H, m, C(7)*H*$_2$), 5.65–5.80 (1H, m, C(6)*H*), 7.11–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 6.9 (*C*(4')), 16.8 (C(α)*Me*), 28.1 (C*Me*$_3$), 28.2 (*C*(2')), 28.7 (*C*(4)), 29.1 (*C*(1')), 32.1 (*C*(5)), 33.4 (*C*(3')), 48.6 (*C*(2)), 50.9 (N*C*H$_2$Ph), 58.4 (*C*(α)), 58.6 (*C*(3)), 80.3 (*C*Me$_3$), 114.7 (*C*(7)), 138.6 (*C*(6)), 126.6, 126.9, 127.9, 128.2, 128.3 (*o,m,p-Ph*), 142.0, 144.4 (*i-Ph*), 174.4 (*C*(1)); *m/z* (ESI$^+$) 576 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{43}INO_2^+$ ([M+H]$^+$) requires 576.2333; found 576.2333.

***tert*-Butyl (2*S*,3*R*,α*R*)-2-(4'-iodobut-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-enoate 26 and *tert*-butyl (*R*,*R*,*R*)-2-(4'-iodobut-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-enoate 27**

BuLi (2.5 M in hexanes, 6.09 mL, 14.0 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.01 mL, 14.4 mmol, >99:1 er) in THF (40 mL) at –78 °C. After stirring at –78 °C for 30 min a solution of **18** (1.77 g, 9.00 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (40 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 2 h, then 1,4-diiodobutane (5.94 mL, 45.0 mmol) was added. The resultant mixture was allowed to warm to rt and stirred at rt for 12 h, then concentrated in vacuo. The residue was partitioned between Et_2O (60 mL) and 10% aq citric acid (60 mL). The aqueous layer was extracted with Et_2O (2 × 80 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (80 mL), H_2O (80 mL) and brine (80 mL), then dried and concentrated in vacuo to give a 63:37 mixture of **26** and **27**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **27** as a colourless oil (425 mg, 8%, 95:5 dr); $[\alpha]_D^{20}$ +15.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1722 (C=O), 1634 (C=C); δ_H (400 MHz, $CDCl_3$) 0.87−0.90 (1H, m, C(1')*H*$_A$), 1.00−1.09 (1H, m, C(1')*H*$_B$), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.46−1.69 (8H, m, C(4)*H*$_2$, C(5)*H*$_2$, C(2')*H*$_2$, C(3')*H*$_2$), 1.97−2.02 (2H, m, C(6)*H*$_2$), 2.27−2.32 (1H, m, C(2)*H*), 2.92−2.95 (1H, m, C(3)*H*), 3.07 (2H, t, *J* 7.0, C(4')*H*$_2$), 3.77 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.83 (1H, d, *J* 14.3,

NCH$_A$*H*$_B$Ph), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.97−5.04 (2H, m, C(8)*H*$_2$), 5.76−5.86 (1H, m, C(7)*H*), 7.18−7.48 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 6.9 (*C*(4')), 16.8 (C(α)*Me*), 27.3 (*C*(1')), 28.2 (C*Me*$_3$), 28.8 (*C*(2')), 29.7 (*C*(5)), 33.4 (*C*(4)), 34.0 (*C*(3')), 35.6 (*C*(6)), 48.9 (*C*(2)), 52.5 (N*C*H$_2$Ph), 58.5 (*C*(α)), 59.2 (*C*(3)), 80.2 (*C*Me$_3$), 114.5 (*C*(8)), 126.5, 126.7, 127.8, 128.0, 128.4, 128.7 (*o,m,p-Ph*), 138.7 (*C*(7)), 143.7, 144.4 (*i-Ph*), 174.5 (*C*(1)); *m/z* (ESI$^+$) 590 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{45}INO_2^+$ ([M+H]$^+$) requires 590.2489; found 590.2473. Further elution gave various mixed fractions of **26** and **27** as colourless oils (1.08 g, 20%). Further elution gave **26** as a colourless oil (962 mg, 18%, 89:11 dr); $[\alpha]_D^{20}$ +23.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1722 (C=O), 1636 (C=C); δ_H (400 MHz, $CDCl_3$) 1.04−1.29 (2H, m, C(1')*H*$_2$), 1.32 (3H, d, *J* 6.9, C(α)*Me*), 1.35−1.41 (1H, m, C(5)*H*$_A$), 1.43 (9H, s, C*Me*$_3$), 1.55−1.70 (7H, m, C(4)*H*$_2$, C(5)*H*$_B$, C(2')*H*$_2$, C(3')*H*$_2$), 1.94−2.00 (2H, m, C(6)*H*$_2$), 2.23 (1H, ddd, *J* 10.6, 7.0, 3.7, C(2)*H*), 2.76 (1H, td, *J* 7.0, 3.7, C(3)*H*), 3.09 (2H, t, *J* 6.9, C(4')*H*$_2$), 3.81 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.92 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 3.99 (1H, q, *J* 6.9, C(α)*H*), 4.94−5.02 (1H, m, C(8)*H*$_2$), 5.74−5.84 (1H, m, C(7)*H*), 7.23−7.37 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 6.9 (*C*(4')), 19.4 (C(α)*Me*), 27.3 (*C*(5)), 28.0 (C*Me*$_3$), 28.2 (*C*(1')), 30.2 (*C*(2')), 30.6 (*C*(3')), 33.2 (*C*(4)), 34.1 (*C*(6)), 50.0 (*C*(2)), 51.3 (N*C*H$_2$Ph), 58.8 (*C*(α)), 60.1 (*C*(3)), 80.2 (*C*Me$_3$), 114.5 (*C*(8)), 126.5, 126.9, 127.8, 128.1, 128.2, 128.3 (*o,m,p-Ph*), 138.8 (*C*(7)), 142.2, 144.7 (*i-Ph*), 174.9 (*C*(1)); *m/z* (ESI$^+$) 590 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{45}INO_2^+$ ([M+H]$^+$) requires 590.2489; found 590.2474.

***tert*-Butyl (2*S*,3*R*,*αR*)-2-(but-3'-en-1'-yl)-3-[*N*-benzyl-*N*-(*α*-methylbenzyl)amino]hept-6-enoate 28**

Method A: BuLi (2.3 M in hexanes, 21.5 mL, 49.5 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (10.6 mL, 50.5 mmol, >99:1 er) in PhMe (21 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **48** (3.40 g, 14.4 mmol, 71:29 dr [(*E*):(*Z*)]) in PhMe (11 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 1 h and then maintained at –30 °C for 2 h before being cooled to –78 °C. THF (110 mL) at –78 °C was added swiftly via cannula and the reaction mixture was then stirred at –78 °C for 30 min. A solution of 2,6-di-*tert*-butylphenol (11.5 g, 55.6 mmol) in THF (40 mL) was added dropwise via cannula and the resultant mixture was allowed to warm to rt and stirred at rt for 30 min, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (80 mL) and 10% aq citric acid (80 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (240 mL), H_2O (240 mL) and brine (240 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **28** as a colourless oil (3.48 g, 54%, >99:1 dr);

$[\alpha]_D^{25}$ +43.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1721 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.8, C(α)*Me*), 1.30–1.38 (2H, m, C(1')H_2), 1.40 (9H, s, CMe_3), 1.48–1.55 (1H, m, C(4)H_A), 1.58–1.65 (1H, m, C(4)H_B), 1.66–1.73 (1H, m, C(2')H_A), 1.83–1.89 (1H, m, C(2')H_B), 1.95–2.01 (1H, m, C(5)H_A), 2.24–2.31 (2H, m, C(2)*H*, C(5)H_B), 2.76 (1H, ddd, *J* 8.5, 6.0, 3.9, C(3)*H*), 3.78 (1H, d, *J* 15.1, NCH_AH_BPh), 3.90 (1H, d, *J* 15.1, NCH$_A$$H_B$Ph), 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.87–4.94 (4H, m, C(7)H_2, C(4')H_2), 5.61–5.74 (2H, m, C(6)*H*, C(3')*H*), 7.18–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 28.0 (C*Me*$_3$), 29.7 (*C*(4)), 31.3 (*C*(1')), 31.6 (*C*(2')), 32.1 (*C*(5)), 49.0 (*C*(2)), 51.2 (N*C*H$_2$Ph), 59.2 (*C*(α)), 60.2 (*C*(3)), 80.2 (*C*Me$_3$), 114.3 (*C*(4')), 114.8 (*C*(7)), 126.5, 126.9, 127.9, 128.2 (*o,m,p-Ph*), 138.1 (*C*(3')), 138.9 (*C*(6)), 142.4, 144.6 (*i-Ph*), 174.9 (*C*(1)); *m/z* (ESI^+) 448 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{42}NO_2^+$ ($[M+H]^+$) requires 448.3210; found 448.3205.

Method B: KHMDS (0.7 M in PhMe, 24.9 mL, 17.4 mmol) was added to a solution of freshly distilled ^{t}BuOH (1.66 mL, 17.4 mmol) in THF (75 mL) at rt. The resultant mixture was stirred at rt for 15 min, then a solution of **24** (2.00 g, 3.48 mmol, >99:1 dr) in THF (75 mL) was added. The resultant mixture was left to stir at rt for 16 h, then concentrated in vacuo. The residue was partitioned between satd aq NH_4Cl (40 mL) and Et_2O (40 mL), and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (40 mL) and brine (40 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave an inseparable 65:35 mixture of **28** and **29**, respectively, as a colourless oil (1.32 g, 85%). Data for mixture: ν_{max}(ATR) 1721 (C=O), 1639 (C=C); *m/z* (ESI^+) 448 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{42}NO_2^+$ ($[M+H]^+$) requires 448.3210; found 448.3211. Data for **29**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.21 (3H, d, *J* 7.0, C(α)*Me*), 1.35 (9H, s, C*Me*$_3$), 2.90–2.94 (1H, m, C(3)*H*), 3.64 (1H, d, *J* 14.4, NCH_AH_BPh), 3.78 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.81–4.94 (4H, m, C(7)H_2, C(4')H_2), 5.33–5.72 (2H, m, C(6)*H*, C(3')*H*), 7.11–7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 28.1 (C*Me*$_3$), 59.2 (*C*(3)), 80.1 (*C*Me$_3$), 114.1 (*C*(4')), 114.6 (*C*(7)), 138.2 (*C*(3')), 138.7 (*C*(6)), 141.7, 144.0 (*i-Ph*), 174.7 (*C*(1)).

Method C: KHMDS (0.7 M in PhMe, 3.23 mL, 2.26 mmol) was added to a solution of freshly distilled ^{t}BuOH (0.22 mL, 2.26 mmol) in THF (9 mL) at rt. The resultant mixture was stirred at rt for 15 min, then a solution of **25** (260 mg, 0.45 mmol, >99:1 dr) in THF (9 mL) was added. The resultant mixture was left to stir at rt for 16 h, then concentrated in vacuo. The residue was partitioned between satd aq NH_4Cl (10 mL) and Et_2O (10 mL), and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL), then dried and concentrated in

vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave an inseparable 65:35 mixture of **28** and **29**, respectively, as a colourless oil (162 mg, 80%).

(2*S*,3*R*,α*R*)-2-(4'-Iodobut-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-en-1-ol 30

DIBAL-H (1.0 M in PhMe, 2.08 mL, 2.08 mmol) was added to a stirred solution of **24** (600 mg, 1.04 mmol, >99:1 dr) in PhMe (18 mL) at 0 °C. The resultant mixture was allowed to stir at 0 °C for 4 h, then 2.0 M aq NaOH (1.04 mL, 2.08 mmol) was added and the resultant mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction mixture was then filtered through Celite® (eluent THF), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **30** as a pale yellow oil (295 mg, 72%, >99:1 dr); $[\alpha]_D^{20}$ –13.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3416 (O–H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.17−1.37 (2H, m, C(2')H_2), 1.41 (3H, d, 7.0, C(α)*Me*), 1.44−1.60 (2H, m, C(1')H_2), 1.75−1.85 (5H, m, C(4)H_A, C(5)H_2, C(3')H_2), 2.00−2.18 (2H, m, C(2)*H*, C(4)H_B), 2.80 (1H, br s, O*H*), 2.92−2.94 (1H, m, C(3)*H*), 3.02−3.06 (1H, m, C(1)H_A), 3.10−3.20 (2H, m, C(4')H_2), 3.39−3.42 (1H, m, C(1)H_B), 3.76 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 3.89−3.95 (1H, m, C(α)*H*), 3.94 (1H, d, *J* 13.6, NC$H_A$$H_B$Ph), 5.04−5.11 (2H, m, C(7)H_2), 5.83−5.94 (1H, m, C(6)*H*), 7.23−7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 6.9 (*C*(4')), 12.7 (*C*(1')), 23.9 (C(α)*Me*), 28.0 (*C*(2')), 29.2 (*C*(5)), 31.9 (*C*(4)), 33.7 (*C*(3')), 41.9 (*C*(2)), 52.5 (N*C*H_2Ph), 57.0 (*C*(3)), 57.4 (*C*(α)), 63.4 (*C*(1)), 115.2 (*C*(7)), 127.2, 128.1, 128.5, 128.6, 128.9 (*o,m,p-Ph*), 138.2 (*C*(6)), 140.4, 143.1 (*i-Ph*); *m/z* (ESI^+) 506 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{37}INO^+$ ($[M+H]^+$) requires 506.1914; found 506.1914.

(2*S*,3*R*,α*R*)-2-(4'-Iodobut-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-en-1-ol 31

DIBAL-H (1.0 M in PhMe, 4.66 mL, 4.66 mmol) was added to a stirred solution of **26** (920 mg, 1.55 mmol, 89:11 dr) in PhMe (30 mL) at 0 °C. The resultant mixture was allowed to stir at 0 °C for 4 h, then 2.0 M aq NaOH (2.33 mL, 4.66 mmol) was added and the resultant mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction mixture was then filtered through Celite® (eluent THF), dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **31** as a pale yellow oil (694 mg, 86%, 89:11 dr); $[\alpha]_D^{20}$ –28.0 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3412 (O–H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.16–1.23 (1H, m, C(2')H_A), 1.34–1.38 (1H, m, C(2)*H*), 1.40 (3H, d, *J* 7.0, C(α)*Me*), 1.43–1.59 (5H, m, C(1')H_2, C(5)H_2, C(2')H_B), 1.64–1.73 (2H, m, C(4)H_2), 1.74–1.85 (2H, m, C(3')H_2), 2.13 (2H, app q, *J* 7.1, C(6)H_2), 2.94–3.00 (1H, m, C(3)*H*), 3.12–3.17 (2H, m, C(4')H_2), 3.76 (1H,

d, *J* 13.7, NC*H*$_A$H$_B$Ph), 3.88–3.98 (2H, m, C(α)*H*, NCH$_A$*H*$_B$Ph), 4.11–4.16 (2H, m, C(1)*H*$_2$), 5.03–5.12 (2H, m, C(8)*H*$_2$), 5.87 (1H, app ddt, *J* 17.0, 10.2, 6.6, C(7)*H*), 7.24–7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 7.00 (*C*(4')), 14.2 (C(α)*Me*), 21.1 (*C*(5)), 24.1 (*C*(1')), 28.1 (*C*(4)), 29.3 (*C*(2')), 33.8 (*C*(3')), 34.0 (*C*(6)), 42.2 (*C*(2)), 52.5 (N*C*H$_2$Ph), 57.4 (*C*(α)), 57.8 (*C*(3)), 60.4 (*C*(1)), 114.9 (*C*(8)), 127.2, 127.3, 128.1, 128.5, 128.6, 129.0 (*o,m,p-Ph*), 138.6 (*C*(7)), 140.7, 143.3 (*i-Ph*); *m/z* (ESI$^+$) 520 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{39}INO^+$ ([M+H]$^+$) requires 520.2071; found 520.2054.

(2*S*,3*R*,α*R*)-2-(But-3'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-en-1-ol 32

KHMDS (0.7 M PhMe, 3.54 mL, 2.48 mmol) was added to a stirred solution of freshly distilled ^{t}BuOH (0.24 mL, 2.48 mmol) in THF (12 mL) at rt. The resultant mixture was stirred at rt for 15 min, then a solution of **30** (250 mg, 0.50 mmol, >99:1 dr) in THF (12 mL) was added. The resultant mixture was left to stir at rt for 16 h, then concentrated in vacuo. The residue was partitioned between satd aq NH_4Cl (20 mL) and Et_2O (20 mL), and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **32** as a pale yellow oil (101 mg, 56%, >99:1 dr); $[\alpha]_D^{20}$ –17.2 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3420 (O–H), 1639 (C=C); δ_H (400 MHz, $CDCl_3$) 1.18−1.27 (1H, m, C(2)*H*), 1.41 (3H, d, *J* 6.8, C(α)*Me*), 1.52−1.61 (2H, m, C(4)*H*$_2$), 1.66−1.78 (1H, m, C(1')*H*$_A$), 1.79−1.91 (2H, m, C(1')*H*$_B$, C(2')*H*$_A$), 1.97−2.06 (1H, m, C(5)*H*$_A$), 2.09−2.23 (2H, m, C(5)*H*$_B$, C(2')*H*$_B$), 2.88–2.93 (1H, m, C(3)*H*), 3.05−3.13 (1H, m, C(1)*H*$_A$), 3.40−3.51 (1H, m, C(1)*H*$_B$), 3.71−3.98 (3H, m, C(α)*H*, NC*H*$_2$Ph), 4.84−5.15 (4H, m, C(7)*H*$_2$, C(4')*H*$_2$), 5.53−6.01 (2H, m, C(6)*H*, C(3')*H*), 7.23−7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 24.0 (*C*(4)), 27.3 (*C*(1')), 31.8 (*C*(5)), 32.3 (*C*(2')), 40.9 (*C*(2)), 52.5 (N*C*H$_2$Ph), 57.1 (*C*(α)), 57.3 (*C*(3)), 63.9 (*C*(1)), 114.9 (*C*(4')), 115.1 (*C*(7)), 127.2, 128.1, 128.4, 128.6, 129.0, 129.2 (*o,m,p-Ph*), 138.3 (*C*(3')), 138.7 (*C*(6)), 140.5, 143.2 (*i-Ph*); *m/z* (ESI$^+$) 378 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO^+$ ([M+H]$^+$) requires 378.2791; found 378.2794.

(2*S*,3*R*,α*R*)-2-Allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-en-1-ol 33

$LiAlH_4$ (1.0 M in THF, 2.57 mL, 2.57 mmol) was added to a stirred solution of **22** (230 mg, 0.51 mmol, >99:1 dr) in THF (7 mL) at –78 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 18 h. 2.0 M aq NaOH (1.29 mL, 2.57 mmol) was then added and the resultant mixture was stirred at rt for 2 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/EtOAc, 20:1) gave **33** as a pale yellow oil (93 mg, 48%, >99:1 dr); $[\alpha]_D^{20}$ –23.0 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3443, (O–H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30–1.33 (3H, m, C(α)*Me*), 1.36–1.55 (2H, m, C(4)H_2), 1.59–1.77 (2H, m, C(5)H_2), 1.89–2.26 (5H, m, C(2)*H*, C(6)H_2, C(1')H_2), 2.40 (1H, br s, O*H*), 2.86–2.94 (1H, m, C(1)H_A), 3.25–3.37 (1H, m, C(1)H_B), 3.49–3.52 (1H, m, C(3)*H*), 3.66–3.70 (1H, m, NC$H_A$$H_B$Ph), 3.81–3.85 (1H, m, NC$H_A$$H_B$Ph), 3.90 (1H, q, *J* 6.9, C(α)*H*), 4.83–5.04 (4H, C(8)H_2, C(3')H_2), 5.48–5.61 (1H, m, C(7)*H*), 5.66–5.84 (1H, m, C(2')*H*), 7.13–7.51 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.2 (C(α)*Me*), 28.3 (*C*(5)), 34.0 (*C*(1')), 34.4 (*C*(4)), 38.7 (*C*(6)), 42.4 (*C*(2)), 51.0 (*C*(1)), 52.3 (N*C*H_2Ph), 56.8 (*C*(3)), 63.4 (*C*(α)), 114.9 (*C*(3')), 117.6 (*C*(8)), 127.1, 128.1, 128.4, 128.5, 128.8, 129.3 (*o,m,p-Ph*), 134.4 (*C*(2')), 137.9 (*C*(7)), 138.4, 138.5 (*i-Ph*); *m/z* (ESI^+) 378 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{36}NO^+$ ($[M+H]^+$) requires 378.2791; found 378.2791.

(2*S*,3*R*,α*R*)-2-(But-3'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-en-1-ol 34

KHMDS (0.5 M in PhMe, 12.9 mL, 6.45 mmol) was added to a stirred solution of freshly distilled ^{t}BuOH (0.62 mL, 6.5 mmol) in THF (25 mL) at rt. The resultant mixture was stirred at rt for 15 min, then a solution of **31** (670 mg, 1.29 mmol, 89:11 dr) in THF (25 mL) was added. The resultant solution was left to stir at rt for 16 h, then concentrated in vacuo. The residue was partitioned between satd aq NH_4Cl (30 mL) and Et_2O (30 mL), and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **34** in 95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 20:1) gave **34** as a colourless oil (167 mg, 33%, 95:5 dr); $[\alpha]_D^{20}$ –30.6 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3420 (O–H), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.39–1.45 (3H, m, C(2)*H*, C(5)H_2), 1.47–1.54 (1H, m, C(1')H_A), 1.57–1.75 (3H, m, C(4)H_2, C(1')H_B), 1.83 (1H, app dq, *J* 14.7, 7.5, C(2')H_A), 2.05–2.10 (2H, m, C(6)H_2), 2.12–2.19 (1H, m, C(2')H_B), 2.85–2.88 (1H, m, C(1)H_A), 2.94–2.97 (1H, m, C(3)*H*), 3.34–3.38 (1H, m, C(1)H_B), 3.67–3.71 (1H, d, *J* 13.7, NC$H_A$$H_B$Ph), 3.87–3.92 (2H, m, C(α)*H*, NC$H_A$$H_B$Ph), 4.88–5.06 (4H, m, C(8)H_2, C(4')H_2), 5.66–5.86 (2H, m, C(7)*H*, C(3')*H*), 7.19–7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.5 (C(α)*Me*), 24.0 (*C*(1')), 27.0 (*C*(5)), 27.9 (*C*(4)), 32.2 (*C*(2')), 33.4 (*C*(6)), 41.1 (*C*(2)), 52.4 (N*C*H_2Ph), 57.1 (*C*(α)), 57.8 (*C*(3)), 63.3 (*C*(1)), 114.7 (*C*(8)), 114.8 (*C*(4')), 127.0, 127.2, 128.0, 128.5, 128.9 (*o,m,p-Ph*), 138.5 (*C*(7)), 138.7 (*C*(3')), 140.5, 143.1 (*i-Ph*); *m/z* (ESI^+) 392 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{38}NO^+$ ($[M+H]^+$) requires 392.2948; found 392.2936.

***tert*-Butyl 2-(diethoxyphosphoryl)pent-4-enoate 45**

A solution of **44** (20.0 g, 79.4 mmol) in THF (60 mL) was added dropwise via cannula to a stirred solution of NaH (60% in mineral oil, 3.49 g, 87.3 mmol) in THF (530 mL) at rt. The resultant mixture was stirred at rt for 1 h, then a solution of freshly distilled allyl bromide (3.40 mL, 39.7 mmol) in THF (60 mL) at rt was added dropwise via cannula. The resultant mixture was heated at reflux for 36 h then allowed to cool to rt before H_2O (250 mL) was added. The aqueous layer was extracted with Et_2O (2 × 350 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:1) gave **45** as a colourless oil (8.08 g, 70%); ν_{max} (ATR) 1728 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28–1.32 (6H, m, P(OCH$_2$*Me*)$_2$), 1.42 (9H, s, C*Me*$_3$), 2.48–2.66 (2H, m, C(3)*H*$_2$), 2.85–2.92 (1H, m, C(2)*H*), 4.08–4.15 (4H, m, P(OC*H*$_2$Me)$_2$), 4.99–5.09 (2H, m, C(5)*H*$_2$), 5.73 (1H, ddt, *J* 16.9, 10.2, 6.7, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 16.2 (d, *J* 1.9, P(OCH$_2$*Me*)), 16.3 (d, *J* 2.9, P(OCH$_2$*Me*)), 27.8 (C*Me*$_3$), 30.9 (d, *J* 4.8, *C*(3)), 46.1 (d, *J* 129.7, *C*(2)), 62.4 (d, *J* 7.6, P(O*C*H$_2$Me)), 62.5 (d, *J* 5.7, P(O*C*H$_2$Me)), 81.7 (*C*Me$_3$), 116.8 (*C*(5)), 134.7 (d, *J* 17.2, *C*(4)), 167.5 (d, *J* 4.8, *C*(1)); *m/z* (ESI$^+$) 315 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{25}NaO_5P^+$ ([M+Na]$^+$) requires 315.1332; found 315.1331.

***tert*-Butyl 2-(diethoxyphosphoryl)hex-5-enoate 46**

A solution of **44** (20.0 g, 79.4 mmol) in THF (60 mL) was added dropwise via cannula to a stirred solution of NaH (60% in mineral oil, 3.49 g, 87.3 mmol) in THF (530 mL) at rt. The resultant mixture was stirred at rt for 1 h, then a solution of freshly distilled but-3-enyl bromide (4.03 mL, 39.7 mmol) in THF (60 mL) at rt was added dropwise via cannula. The resultant mixture was heated at reflux for 36 h then allowed to cool to rt before H_2O (250 mL) was added. The aqueous layer was extracted with Et_2O (2 × 350 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 1:1) gave **46** as a colourless oil (9.12 g, 75%); ν_{max} (ATR) 1728 (C=O), 1642 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30–1.34 (6H, m, P(OCH$_2$*Me*)$_2$), 1.47 (9H, s, C*Me*$_3$), 1.83–1.92 (1H, m, C(3)*H*$_A$), 2.00–2.08 (2H, m, C(3)*H*$_B$, C(4)*H*$_A$), 2.14–2.19 (1H, m, C(4)*H*$_B$), 2.83–2.90 (1H, m, C(2)*H*), 4.10–4.17 (4H, m, P(OC*H*$_2$Me)$_2$), 4.99–5.05 (2H, m, C(6)*H*$_2$), 5.75 (1H, ddt, *J* 17.0, 10.3, 6.6, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 16.3 (d, *J* 2.9, P(OCH$_2$*Me*)), 16.4 (d, *J* 2.9, P(OCH$_2$*Me*)), 26.1 (d, *J* 4.8, *C*(3)), 27.9 (C*Me*$_3$), 32.2 (d, *J* 16.2, *C*(4)), 45.7 (d, *J* 130.7, *C*(2)), 62.4 (d, *J* 3.8, P(O*C*H$_2$Me)), 62.5 (d, *J* 3.8, P(O*C*H$_2$Me)), 81.7 (*C*Me$_3$), 116.0 (*C*(6)), 136.8 (*C*(5)), 168.1 (d, *J* 4.8, *C*(1)); *m/z* (ESI$^+$) 329 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{27}NaO_5P^+$ ([M+Na]$^+$) requires 329.1488; found 329.1487.

***tert*-Butyl (*E*)-2-allyl-hepta-2,6-dienoate 47**

MeMgBr (2.9 M in Et_2O, 3.33 mL, 9.66 mmol) was added dropwise to a stirred solution of **45** (2.92 g, 10.0 mmol) in THF (130 mL) at rt. The resultant mixture was stirred at rt for 15 min, then **16** (1.10 mL, 11.2 mmol) was added. The resultant mixture was heated at reflux for 3 h, then the reaction mixture was allowed to cool to rt and partitioned between satd aq NH_4Cl (150 mL) and Et_2O (150 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL), and the combined organic extracts were washed with brine, then dried and concentrated in vacuo to give **47** in 76:24 dr [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **47** as a yellow oil (1.80 g, 81%, 76:24 dr [(*E*):(*Z*)]). Data for mixture: ν_{max} (ATR) 1710 (C=O), 1640 (C=C); *m/z* (ESI^+) 245 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{22}NaO_2^+$ ($[M+Na]^+$) requires 245.1512; found 245.1513. Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, C*Me*$_3$), 2.13–2.18 (2H, m, C(5)*H*$_2$), 2.21–2.26 (2H, m, C(4)*H*$_2$), 3.00 (2H, d, *J* 5.9, C(1')*H*$_2$), 4.93–5.04 (4H, m, C(7)*H*$_2$, C(3')*H*$_2$), 5.72–5.83 (2H, m, C(6)*H*, C(2')*H*), 6.71 (1H, t, *J* 7.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (*C*(4)), 28.0 (C*Me*$_3$), 30.9 (*C*(1')), 32.6 (*C*(5)), 80.0 (*C*Me$_3$), 114.7 (*C*(3')), 115.2 (*C*(7)), 131.6 (*C*(2)), 135.6 (*C*(2')), 137.4 (*C*(6)), 141.4 (*C*(3)), 166.6 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 2.17 (2H, app q, *J* 7.0, C(5)*H*$_2$), 2.52 (2H, app q, *J* 7.3, C(4)*H*$_2$), 2.96 (2H, d, *J* 6.6, C(1')*H*$_2$), 4.97–5.07 (4H, m, C(7)*H*$_2$, C(3')*H*$_2$), 5.77–5.87 (3H, m, C(3)*H*, C(6)*H*, C(2')*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 28.7 (*C*(4)), 33.4 (*C*(5)), 38.9 (*C*(1')), 80.6 (*C*Me$_3$), 114.9 (*C*(7)), 115.9 (*C*(3')), 132.1 (*C*(2)), 136.2 (*C*(2')), 137.9 (*C*(6)), 139.9 (*C*(3)), 167.1 (*C*(1)).

***tert*-Butyl (*E*)-2-(but-3'-en-1'-yl)hepta-2,6-dienoate 48**

MeMgBr (2.9 M in Et_2O, 3.33 mL, 9.66 mmol) was added dropwise to a stirred solution of **46** (2.92 g, 10.0 mmol) in THF (130 mL) at rt. The resultant mixture was stirred at rt for 15 min, then **16** (1.10 mL, 11.2 mmol) was added. The resultant mixture was heated at reflux for 3 h, then the reaction mixture was allowed to cool to rt and partitioned between satd aq NH_4Cl (150 mL) and Et_2O (150 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL), and the combined organic extracts were washed with brine, then dried and concentrated in vacuo to give **48** in 71:29 dr [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **48** as a pale yellow oil (1.51 g, 64%, 71:29 dr [(*E*):(*Z*)]). Data for mixture: ν_{max} (ATR) 1709 (C=O), 1641 (C=C); *m/z* (ESI^+) 259 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{24}NaO_2^+$ ($[M+Na]^+$) requires 259.1669; found 259.1670. Data for major diastereoisomer: δ_H (400 MHz,

$CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 2.12–2.21 (4H, m, C(4)*H*$_2$, C(1')*H*$_2$), 2.23–2.28 (2H, m, C(2')*H*$_2$), 2.33–2.37 (2H, m, C(5)*H*$_2$), 4.94–5.08 (4H, m, C(7)*H*$_2$, C(4')*H*$_2$), 5.77–5.86 (2H, m, C(6)*H*, C(3')*H*), 6.67 (1H, t, *J* 7.3, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 26.5 (*C*(5)), 28.0 (*C*(2')), 28.1 (C*Me*$_3$), 32.9 (*C*(4)), 33.5 (*C*(1')), 80.0 (*C*Me$_3$), 114.8 (*C*(7)), 115.3 (*C*(4')), 133.4 (*C*(2)), 137.6 (*C*(3')), 138.1 (*C*(6)), 140.8 (*C*(3)), 167.1 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C*Me*$_3$), 2.14–2.20 (4H, m, C(1')*H*$_2$, C(2')*H*$_2$), 2.28–2.31 (2H, m, C(5)*H*$_2$), 2.48 (2H, app q, *J* 7.4, C(4)*H*$_2$), 4.95–5.06 (4H, m, C(7)*H*$_2$, C(4')*H*$_2$), 5.75–5.86 (3H, m, C(3)*H*, C(6)*H*, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 28.6 (*C*(5)), 33.4 (*C*(1')), 33.5 (*C*(2')), 34.3 (*C*(4)), 80.5 (*C*Me$_3$), 114.8 (*C*(4')), 114.9 (*C*(7)), 133.4 (*C*(2)), 138.0 (*C*(6)), 138.0 (*C*(3')), 139.0 (*C*(3)), 167.5 (*C*(1)).

***tert*-Butyl (*E*)-2-allyl-octa-2,7-dienoate 49**

MeMgBr (2.9 M in Et_2O, 1.34 mL, 3.84 mmol) was added dropwise to a stirred solution of **45** (1.18 g, 3.84 mmol) in THF (50 mL) at rt. The resultant mixture was stirred at rt for 15 min, then **17** (0.51 mL, 4.27 mmol) was added. The resultant mixture was heated at reflux for 3 h, then the reaction mixture was allowed to cool to rt and partitioned between satd aq NH_4Cl (60 mL) and Et_2O (60 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, then dried and concentrated in vacuo to give **49** in 73:27 dr [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **49** as a pale yellow oil (737 mg, 81%, 73:27 dr [(*E*):(*Z*)]). Data for mixture: ν_{max} (ATR) 1712 (C=O), 1641 (C=C); *m/z* (ESI$^+$) 259 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{24}NaO_2^+$ ([M+Na]$^+$) requires 259.1669; found 259.1669. Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, C*Me*$_3$), 1.50–1.58 (2H, m, C(5)*H*$_2$), 2.08–2.11 (2H, m, C(6)*H*$_2$), 2.15–2.20 (2H, m, C(4)*H*$_2$), 3.02 (2H, d, *J* 6.1, C(1')*H*$_2$), 4.95–5.05 (4H, m, C(8)*H*$_2$, C(3')*H*$_2$), 5.75–5.85 (2H, m, C(7)*H*, C(2')*H*), 6.74 (1H, t, *J* 7.5, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 27.8 (*C*(4)), 27.9 (*C*(5)), 28.1 (C*Me*$_3$), 31.0 (*C*(1')), 33.4 (*C*(6)), 80.1 (*C*Me$_3$), 114.8 (*C*(3')), 114.9 (*C*(8)), 131.5 (*C*(2)), 135.8 (*C*(2')), 138.2 (*C*(7)), 142.1 (*C*(3)), 166.9 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 1.51–1.55 (2H, m, C(5)*H*$_2$), 2.06–2.11 (2H, m, C(6)*H*$_2$), 2.40–2.45 (2H, m, C(4)*H*$_2$), 2.96 (2H, d, *J* 6.6, C(1')*H*$_2$), 4.94–5.08 (4H, m, C(8)*H*$_2$, C(3')*H*$_2$), 5.77–5.87 (3H, m, C(3)*H*, C(7)*H*, C(2')*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 28.7 (*C*(5)), 29.0 (*C*(4)), 33.4 (*C*(6)), 38.7 (*C*(1')), 80.5 (*C*Me$_3$), 114.6 (*C*(8)), 115.9 (*C*(3')), 132.0 (*C*(2)), 136.3 (*C*(7)), 138.5 (*C*(2')), 140.4 (*C*(3)), 167.2 (*C*(1)).

***tert*-Butyl (*E*)-2-(but-3'-en-1'-yl)octa-2,7-dienoate 50**

MeMgBr (2.9 M in Et_2O, 4.62 mL, 13.2 mmol) was added dropwise to a stirred solution of **46** (4.04 g, 13.2 mmol) in THF (50 mL) at rt. The resultant mixture was stirred at rt for 15 min, then **17** (1.76 mL, 14.7 mmol) was added. The resultant mixture was heated at reflux for 3 h, then the reaction mixture was allowed to cool to rt and partitioned between satd aq NH_4Cl (200 mL) and Et_2O (200 mL). The aqueous layer was extracted with EtOAc (2 × 200 mL), and the combined organic extracts were washed with brine, then dried and concentrated in vacuo to give **50** in 75:25 dr [(*E*):(*Z*)]. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **50** as a pale yellow oil (1.81 g, 55%, 75:25 dr [(*E*):(*Z*)]). Data for mixture: ν_{max} (ATR) 1711 (C=O), 1641 (C=C); *m/z* (ESI^+) 273 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{26}NaO_2^+$ ($[M+Na]^+$) requires 273.1825; found 273.1825. Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, C*Me*$_3$), 1.50–1.57 (2H, m, C(5)*H*$_2$), 2.06–2.19 (6H, m, C(4)*H*$_2$, C(6)*H*$_2$, C(2')*H*$_2$), 2.31–2.42 (2H, m, C(1')*H*$_2$), 4.93–5.05 (4H, m, C(8)*H*$_2$, C(4')*H*$_2$), 5.73–5.86 (2H, m, C(7)*H*, C(3')*H*), 6.67 (1H, t, *J* 7.5, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 26.4 (*C*(1')), 27.9 (*C*(4)), 28.0 (*C*(5)), 28.1 (C*Me*$_3$), 33.4 (*C*(2')), 33.5 (*C*(6)), 80.0 (*C*Me$_3$), 114.7 (*C*(4')), 114.9 (*C*(8)), 133.2 (*C*(2)), 138.2 (*C*(3')), 138.2 (*C*(7)), 141.4 (*C*(3)), 167.1 (*C*(1)). Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 1.51–1.54 (2H, m, C(5)*H*$_2$), 2.05–2.11 (2H, m, C(6)*H*$_2$), 2.15–2.21 (2H, m, C(2')*H*$_2$), 2.28–2.32 (2H, m, C(1')*H*$_2$), 2.36–2.42 (2H, m, C(4)*H*$_2$), 4.95–5.04 (4H, m, C(8)*H*$_2$, C(4')*H*$_2$), 5.73–5.87 (3H, m, C(3)*H*, C(7)*H*, C(3')*H*); δ_C (100 MHz, $CDCl_3$) 28.2 (C*Me*$_3$), 28.8 (*C*(4)), 28.9 (*C*(5)), 33.4 (*C*(6)), 33.4 (*C*(2')), 34.4 (*C*(1')), 80.4 (*C*Me$_3$), 114.6 (*C*(8)), 114.8 (*C*(4')), 133.2 (*C*(2)), 138.0 (*C*(7)), 138.6 (*C*(3')), 139.6 (*C*(3)), 167.6 (*C*(1)).

***tert*-Butyl (2*S*,3*R*,α*R*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate *ent*-9**

Method A: BuLi (2.3 M in hexanes, 26.8 mL, 61.7 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (13.2 mL, 63.0 mmol, >99:1 er) in PhMe (27 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **47** (4.00 g, 18.0 mmol, 76:24 dr [(*E*):(*Z*)]) in PhMe (13 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 1 h and then maintained at –30 °C for 2 h before being cooled to –78 °C. THF (140 mL) at –78 °C was added swiftly via cannula and the resultant mixture was then stirred at –78 °C for 30 min. A solution of 2,6-di-*tert*-butylphenol (14.3 g, 69.3 mmol) in THF (50 mL) was added dropwise via cannula and the resultant mixture was allowed to warm to rt over 30 min, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100

mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (300 mL), H_2O (300 mL) and brine (300 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave *ent*-**9** as a colourless oil (3.20 g, 41%, >99:1 dr); $[\alpha]_D^{25}$ +47.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1722 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.9, C(α)*Me*), 1.36 (9H, s, C*Me*$_3$), 1.49–1.56 (1H, m, C(4)H_A), 1.61–1.69 (1H, m, C(4)H_B), 1.90–2.03 (2H, m, C(5)H_A, C(1')H_A), 2.08–2.13 (1H, m, C(1')H_B), 2.23–2.32 (2H, m, C(2)*H*, C(5)H_B), 2.79 (1H, ddd, *J* 8.1, 6.5, 4.0, C(3)*H*), 3.79 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.90 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.97 (1H, q, *J* 6.9, C(α)*H*), 4.85–4.96 (4H, m, C(7)H_2, C(3')H_2), 5.43–5.51 (1H, m, C(2')*H*), 5.71 (1H, ddt, *J* 17.0, 10.3, 6.6, C(6)*H*), 7.18–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 28.0 (C*Me*$_3$), 29.7 (*C*(4)), 32.1 (*C*(5)), 36.2 (*C*(1')), 49.4 (*C*(2)), 51.2 (N*C*H$_2$Ph), 59.1 (*C*(α)), 59.6 (*C*(3)), 80.3 (*C*Me$_3$), 114.4 (*C*(7)), 116.0 (*C*(3')), 126.5, 126.9, 127.9, 128.2 (*o,m,p-Ph*), 135.9 (*C*(2')), 138.8 (*C*(6)), 142.2, 144.6 (*i-Ph*), 174.3 (*C*(1)); *m/z* (ESI$^+$) 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_2^+$ ([M+H]$^+$) requires 434.3054; found 434.3049.

***tert*-Butyl (2*S*,3*R*,α*R*)-2-(but-3'-en-1'-yl)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]oct-7-enoate 51**

BuLi (2.3 M in hexanes, 7.10 mL, 16.3 mmol) was added dropwise via syringe to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (3.47 mL, 16.6 mmol, >99:1 er) in PhMe (8 mL) at –78 °C. After stirring at –78 °C for 30 min, a solution of **50** (1.17 g, 4.68 mmol, 75:25 dr [(*E*):(*Z*)]) in PhMe (4 mL) at –78 °C was added dropwise via cannula. The reaction mixture was left to stir at –78 °C for 1 h and then maintained at –30 °C for 2 h before being cooled to –78 °C. THF (36 mL) at –78 °C was added swiftly via cannula and the resultant mixture was then stirred at –78 °C for 30 min. A solution of 2,6-di-*tert*-butylphenol (3.76 g, 18.3 mmol) in THF (15 mL) was added dropwise via cannula and the resultant mixture was allowed to warm to rt over 30 min then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (30 mL) and 10% aq citric acid (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (90 mL), H_2O (90 mL) and brine (90 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **51** as a colourless oil (992 mg, 46%, >99:1 dr); $[\alpha]_D^{25}$ +39.4 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 1722 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.8, C(α)*Me*), 1.34–1.38 (3H, m, C(5)H_A, C(1')H_2), 1.39 (9H, s, C*Me*$_3$), 1.40–1.42 (1H, m, C(4)H_A), 1.50–1.63 (2H, m, C(4)H_B, C(5)H_B), 1.65–1.73 (1H, m, C(2')H_A), 1.82–1.94 (3H, m, C(6)H_2, C(2')H_B), 2.24–2.30 (1H, m, C(2)*H*), 2.73 (1H, ddd, *J* 8.2, 6.3, 3.9, C(3)*H*), 3.76 (1H, d, *J* 15.1, NCH_AH$_B$Ph), 3.89 (1H, d, *J* 15.1, NCH$_A$$H_B$Ph), 3.96 (1H, q, *J*

6.8, C(α)*H*), 4.89–4.96 (4H, m, C(8)H_2, C(4')H_2), 5.60–5.68 (1H, m, C(3')*H*), 5.73 (1H, ddt, *J* 17.0, 10.3, 6.7, C(7)*H*), 7.17–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 27.3 (*C*(5)), 28.0 (CMe_3), 30.1 (*C*(4)), 31.2 (*C*(1')), 31.6 (*C*(2')), 34.1 (*C*(6)), 49.2 (*C*(2)), 51.2 (N*C*H_2Ph), 59.4 (*C*(α)), 60.5 (*C*(3)), 80.2 (*C*Me_3), 114.4 (*C*(4')), 114.8 (*C*(8)), 126.4, 126.8, 127.9, 128.1, 128.2 (*o,m,p-Ph*), 138.2 (*C*(3')), 138.9 (*C*(7)), 142.5, 144.8 (*i-Ph*), 174.9 (*C*(1)); *m/z* (ESI^+) 462 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{44}NO_2^+$ ($[M+H]^+$) requires 462.3367; found 462.3360.

(1*S*,7a*R*)-1-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine [(+)-trachelanthamidine] 60

Step 1: 2,6-Lutidine (0.28 mL, 2.40 mmol), OsO_4 (6.1 mg, 24.0 μmol) and $NaIO_4$ (1.03 g, 4.82 mmol) were sequentially added to a stirred solution of *ent*-**9** (260 mg, 0.60 mmol, >99:1 dr) in 1,4-dioxane/H_2O (3:1, 24 mL) at rt. The resultant mixture was stirred at rt for 40 min, then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **52**.

Step 2: $Pd(OH)_2$/C (260 mg, 100% w/w) was added to a stirred solution of the residue of **52** in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 120 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give **56**.

Step 3: $LiAlH_4$ (2.4 M in THF, 1.50 mL, 3.60 mmol) was added to a stirred solution of the residue of **56** in THF (5 mL) at –78 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 2 h. 2.0 M aq NaOH (1.8 mL, 3.6 mmol) was then added and the resultant mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite® (eluent THF), then dried and concentrated in vacuo. Purification via ion exchange chromatography on Dowex 50WX8 resin (hydrogen form, 100–200 mesh, eluent 18.0 M aq NH_4OH) gave **60** as a pale yellow oil (18 mg, 21% from *ent*-**9**, >99:1 dr);[14g] $[\alpha]_D^{25}$ +15.9 (*c* 1.0 in EtOH); {lit.[14g] $[\alpha]_D^{20}$ +15.4 (*c* 1.2 in EtOH)}; ν_{max} (ATR) 3347 (O–H), 2932 (C–H);δ_H (400 MHz, $CDCl_3$) 1.48–1.56 (1H, m, C(7)H_A), 1.56–1.68 (1H, m, C(2)H_A), 1.69–1.77 (1H, m, C(6)H_A), 1.78–1.86 (1H, m, C(6)H_B), 1.88–2.01 (3H, m, C(1)*H*, C(2)H_B, C(7)H_B), 2.51 (1H, app td, *J* 9.9, 6.8, C(3)H_A), 2.58 (1H, app dt, *J* 10.7, 6.6, C(5)H_A), 2.94 (1H, dt, *J* 10.7, 6.3, C(5)H_B), 3.11 (1H, ddd, *J* 9.9, 6.8, 3.2, C(3)H_B), 3.20 (1H, app q, *J* 6.5, C(7a)*H*), 3.55–3.62 (2H, m, CH_2OH), 3.72 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 25.7 (*C*(6)), 30.0

(*C*(2)), 31.9 (*C*(7)), 48.4 (*C*(1)), 54.5 (*C*(3)), 54.7 (*C*(5)), 65.3 (*C*H_2OH), 67.7 (*C*(7a)); *m/z* (ESI$^+$) 142 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO^+$ ([M+H]$^+$) requires 142.1226; found 142.1229.

(8*S*,8a*R*)-8-(Hydroxymethyl)octahydro-8*H*-indolizine [(+)-tashiromine] 38

Method A – Step 1: 2,6-Lutidine (0.31 mL, 2.7 mmol), OsO_4 (6.8 mg, 27 μmol) and $NaIO_4$ (1.15 g, 5.37 mmol) were sequentially added to a stirred solution of **28** (300 mg, 0.67 mmol, >99:1 dr) in 1,4-dioxane/H_2O (3:1, 24 mL) at rt. The resultant mixture was stirred at rt for 40 min, then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **53**.

Method A – Step 2: $Pd(OH)_2$/C (300 mg, 100% w/w) was added to a stirred solution of the residue of **53** in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 120 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give **57**.

Method A – Step 3: $LiAlH_4$ (2.4 M in THF, 1.68 mL, 4.03 mmol) was added to a stirred solution of the residue of **57** in THF (5 mL) at –78 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 2 h. 2.0 M aq NaOH (2.02 mL, 4.03 mmol) was then added and the resultant mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite® (eluent THF) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/NH_4OH, 30:1:1) gave **38** as a pale yellow oil (17 mg, 16% from **28**, >99:1 dr);[20] $[\alpha]_D^{25}$ +39.0 (*c* 0.23 in EtOH); {lit.[15] $[\alpha]_D^{22}$ +41.9 (*c* 1.1 in EtOH)}; ν_{max} (ATR) 3341 (O−H), 2930 (C−H), 2794 (C−H); δ_H (400 MHz, $CDCl_3$) 1.04 (1H, app qd, *J* 12.6, 4.4, C(7)H_A), 1.44–1.98 (10H, m, C(1)H_2, C(2)H_2, C(5)H_A, C(6)H_2, C(7)H_B, C(8)*H*, C(8a)*H*), 2.06 (1H, app q, *J* 9.0, C(3)H_A), 3.03–3.10 (2H, m, C(3)H_B, C(5)H_B), 3.46 (1H, dd, *J* 10.7, 6.7, C$H_A$$H_B$OH), 3.63 (1H, dd, *J* 10.7, 4.6, CH$_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) 20.7 (*C*(2)), 25.1 (*C*(6)), 27.6 (*C*(7)), 29.1 (*C*(1)), 44.6 (*C*(8)), 52.7 (*C*(5)), 54.1 (*C*(3)), 65.6 (*C*H_2OH), 66.3 (*C*(8a)); *m/z* (ESI$^+$) 156 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO^+$ ([M+H]$^+$) requires 156.1383; found 156.1383.

Method B – Step 1: A sample of **32** (370 mg, 1.10 mmol, 65:35 dr) was co-evaporated with HCl (3 × 2.0 mL, 2.0 M in Et_2O), then the residue was dissolved in CH_2Cl_2/MeOH (1:1, 20 mL). The resultant mixture was cooled to –78 °C and degassed with N_2 and O_2 before O_3 was bubbled through the solution until a persistent blue colour appeared. O_2 was then bubbled through the solution until it became colourless. Polymer

supported PPh_3 (1.52 g, 3.30 mmol) was then added and the reaction mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction mixture was filtered through Celite® (eluent MeOH) then concentrated in vacuo to give **35** (65:35 dr).

Method B – Step 2: $Pd(OH)_2/C$ (77 mg, 20% w/w) was then added to a stirred solution of the residue of **35** in MeOH (5 mL), H_2O (0.5 mL) and AcOH (0.2 mL) at 35 °C. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 24 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give a 65:35 mixture of **38**·HOAc and **39**·HOAc, respectively, as a pale yellow oil. Purification via ion exchange chromatography on Dowex 50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **38** as a pale yellow oil (16 mg, 11%, >99:1 dr, ~95% purity);[16] $[\alpha]_D^{20}$ +30.0 (*c* 0.5 in $CHCl_3$); {lit.[16] $[\alpha]_D^{20}$ +43.4 (*c* 0.53 in $CHCl_3$)}.

(1*S*,8a*R*)-1-(Hydroxymethyl)octahydro-1*H*-indolizine 40

Method A – Step 1: 2,6-Lutidine (0.31 mL, 2.68 mmol), OsO_4 (6.8 mg, 26.8 μmol) and $NaIO_4$ (1.15 g, 5.37 mmol) were sequentially added to a stirred solution of **22** (300 mg, 0.67 mmol, >99:1 dr) in 1,4-dioxane/H_2O (3:1, 24 mL) at rt. The resultant mixture was stirred at rt for 40 min, then partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **54**.

Method A – Step 2: $Pd(OH)_2/C$ (300 mg, 100% w/w) was added to a stirred solution of the residue of **54** in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 120 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give **58**.

Method A – Step 3: $LiAlH_4$ (2.4 M in THF, 1.68 mL, 4.03 mmol) was added to a stirred solution of the residue of **58** in THF (5 mL) at –78 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 2 h. 2.0 M aq NaOH (2.02 mL, 4.03 mmol) was then added and the resultant mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite® (eluent THF) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 30:1:1) gave **40** as a pale yellow oil (15 mg, 15% from **22**, >99:1 dr);[14l] $[\alpha]_D^{25}$ +39.8 (*c* 0.5 in EtOH); {lit.[16] $[\alpha]_D^{23}$ +27.4 (*c* 1.0 in EtOH)}; ν_{max} (ATR) 3353 (O−H), 2931 (C−H); δ_H (400 MHz, $CDCl_3$) 1.18–1.31 (2H, m, C(7)H_A, C(8)H_A),

1.43–1.48 (1H, m, C(6)H_A), 1.51–1.64 (3H, m, C(2)H_2, C(8a)*H*), 1.77–1.80 (1H, m, C(7)H_B), 1.88–2.01 (5H, m, C(1)*H*, C(3)H_A, C(6)H_B, C(8)H_B, O*H*), 2.10–2.15 (1H, m, C(5)H_A), 3.00–3.07 (2H, m, C(3)H_B, C(5)H_B), 3.59 (1H, dd, *J* 10.6, 6.0, CH_AH$_B$OH), 3.65 (1H, dd, *J* 10.6, 5.7, CH$_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) 24.3 (*C*(7)), 25.2 (*C*(2)), 25.3 (*C*(6)), 30.5 (*C*(8)), 46.1 (*C*(1)), 53.1 (*C*(3)), 53.4 (*C*(5)), 65.0 (*C*H$_2$OH), 67.2 (*C*(8a)); *m/z* (ESI$^+$) 156 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO^+$ ([M+H]$^+$) requires 156.1383; found 156.1381.

Method B – Step 1: A sample of **33** (200 mg, 0.531 mmol, 73:27 dr) was co-evaporated with HCl (3 × 2.0 mL, 2.0 M in Et_2O), then the residue was dissolved in CH_2Cl_2/MeOH (1:1, 20 mL). The resultant mixture was cooled to –78 °C and degassed with N_2 and O_2 before O_3 was bubbled through the solution until a persistent blue colour appeared. O_2 was then bubbled through the solution until it became colourless. Polymer supported PPh_3 (530 mg, 1.59 mmol) was then added and the reaction mixture was allowed to warm to rt then stirred at rt for 2 h. The reaction mixture was filtered through Celite® (eluent MeOH) then concentrated in vacuo to give **36** (73:27 dr).

Method B – Step 2: $Pd(OH)_2$/C (189 mg, 100% w/w) was added to a stirred solution of **36** in MeOH (2.66 mL), H_2O (0.27 mL) and AcOH (60 µL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) at 35 °C for 24 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give a 70:30 mixture of **40**·HOAc and **41**·HOAc, respectively, as a pale yellow oil. Purification via ion exchange chromatography on Dowex 50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **40** as a pale yellow oil (14 mg, 17%, >99:1 dr, ~95% purity);[14l] $[\alpha]_D^{20}$ +30.1 (*c* 0.4 in EtOH); {lit.[14l] $[\alpha]_D^{20}$ +27.4 (*c* 1.0 in EtOH)}. Further elution gave an 86:14 mixture of **40** and **41**, respectively, as a pale yellow oil (11 mg, 14%, ~95% purity). Data for mixture: ν_{max} (ATR) 3347 (O–H), 2931 (C–H); *m/z* (ESI$^+$) 156 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO^+$ ([M+H]$^+$) requires 156.1383; found 156.1381. Data for **41**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 3.39 (1H, app dd, *J* 10.1, 2.3, CH_AH$_B$OH), 3.85 (1H, app dt, *J* 10.1, 3.0, CH$_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) [selected peaks] 40.2 (*C*(1)), 64.2 (*C*H$_2$OH).

(1*S*,9a*R*)-1-(Hydroxymethyl)-octahydro-1*H*-quinolizine [(+)-epilupinine] 42

Method A – Step 1: 2,6-Lutidine (0.30 mL, 2.60 mmol), OsO_4 (6.6 mg, 26.0 µmol) and $NaIO_4$ (1.11 g, 5.21 mmol) were sequentially added to a stirred solution of **51** (300 mg, 0.65 mmol, >99:1 dr) in 1,4-dioxane/H_2O (3:1, 24 mL) at rt. The resultant mixture was stirred at rt for 40 min, then partitioned between CH_2Cl_2 (10

mL) and 10% aq citric acid (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated in vacuo to give **55**.

Method A – Step 2: $Pd(OH)_2/C$ (300 mg, 100% w/w) was added to a stirred solution of the residue of **55** in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 120 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give **59**.

Method A – Step 3: $LiAlH_4$ (2.4 M in THF, 1.63 mL, 3.91 mmol) was added to a stirred solution of the residue of **59** in THF (5 mL) at –78 °C. The resultant mixture was allowed to warm to rt and stirred for 2 h. 2.0 M aq NaOH (1.95 mL, 3.91 mmol) was then added and the resultant mixture was stirred at rt for 2 h. The reaction mixture was filtered through Celite® (eluent THF) then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH/NH_4OH, 30:1:1) gave **42** as a pale yellow oil (34 mg, 31% from **51**, >99:1 dr);[14k] $[\alpha]_D^{25}$ +29.1 (*c* 0.3 in EtOH); {lit.[23] for *ent*-**42**: $[\alpha]_D^{26}$ −29.2 (*c* 1.0 in EtOH)}; ν_{max} (ATR) 3352 (O–H), 2929 (C–H), 2858 (C–H); δ_H (400 MHz, $CDCl_3$) 1.13–1.26 (3H, m, C(2)H_A, C(8)H_A, C(9)H_A), 1.36–1.43 (1H, m, C(1)*H*), 1.56–1.61 (2H, m, C(7)H_2), 1.63–1.70 (3H, m, C(9a)*H*, C(3)H_2), 1.73–1.77 (1H, m, C(8)H_B), 1.81–1.91 (2H, m, C(2)H_B, C(9)H_B), 1.98–2.04 (2H, m, C(4)H_A, C(6)H_A), 2.28 (1H, br s, O*H*), 2.74–2.83 (2H, m, C(4)H_B, C(6)H_B), 3.53 (1H, dd, *J* 10.8, 6.0, CH_AH$_B$OH), 3.63 (1H, dd, *J* 10.8, 3.6, CH$_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) 24.5 (*C*(8)), 25.0 (*C*(3)), 25.5 (*C*(7)), 28.2 (*C*(2)), 29.7 (*C*(9)), 43.9 (*C*(1)), 56.6 (*C*(4)), 56.8 (*C*(6)), 64.3 (*C*(9a)), 64.4 (*C*H$_2$OH); *m/z* (ESI$^+$) 170 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{10}H_{20}NO^+$ ([M+H]$^+$) requires 170.1539; found 170.1536.

Method B – Step 1: A sample of **34** (220 mg, 0.56 mmol, 74:26 dr) was co-evaporated with HCl (3 × 2.0 mL, 2.0 M in Et_2O), then the residue was dissolved in CH_2Cl_2/MeOH (1:1, 20 mL). The resultant mixture was cooled to –78 °C and degassed with N_2 and O_2 before O_3 was bubbled through the solution until a persistent blue colour appeared. O_2 was then bubbled through the solution until it became colourless. Polymer supported PPh_3 (563 mg, 1.69 mmol) was then added and the reaction mixture was allowed to warm to rt then stirred at rt for 2 h. The reaction mixture was filtered through Celite® (eluent MeOH) then concentrated in vacuo to give **37**.

Method B – Step 2: $Pd(OH)_2/C$ (196 mg, 100% w/w) was then added to a stirred solution of the residue of **37** in MeOH (2.67 mL), H_2O (0.27 mL) and AcOH (60 μL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 24 h. The reaction mixture

was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give a 79:21 mixture of **42**·HOAc and **43**·HOAc, respectively as a pale yellow oil. Purification via ion exchange chromatography on Dowex 50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) and flash column chromatography on neutral alumina (eluent CH_2Cl_2/MeOH, 20:1) gave a 77:23 mixture of **42** and **43**, respectively, as a pale yellow oil (7 mg, 8%, ~95% purity). Data for mixture: ν_{max} (ATR) 3368 (O–H), 2930 (C–H), 2857 (C–H); *m/z* (ESI^+) 170 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{10}H_{20}NO^+$ ($[M+H]^+$) requires 170.1539; found 170.1536. Data for **43**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.42–1.51 (C(1)*H*), 1.53–1.65 (2H, m, C(3)H_2), 3.73–3.77 (1H, m, CH_AH$_B$OH), 4.15–4.19 (1H, m, CH$_A$$H_B$OH); δ_C (100 MHz, $CDCl_3$) [selected peaks] 22.9 (*C*(3)), 38.0 (*C*(1)), 66.0 (*C*H_2OH). Further elution gave **42** as a pale yellow oil (10 mg, 11%, >99:1 dr, ~95% purity).

References and notes

[1] Pyrrolizidines, indolizidines and quinolizidines are also known as 2,3,5,6,7,8-hexahydro-1*H*-pyrrolizines, octahydroindolizines and 2,3,4,6,7,8,9,9a-octahydro-1*H*-quinolizines, respectively.

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