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Polyhydroxylated pyrrolizidine alkaloids from transannular iodoaminations: application to the asymmetric syntheses of (−)-hyacinthacine A1, (−)-7a-*epi*-hyacinthacine A1, (−)-hyacinthacine A2, and (−)-1-*epi*-alexine†‡

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The transannular iodoamination of substituted 1,2,3,4,7,8-hexahydroazocine scaffolds has been developed into a versatile, diastereodivergent route to enable the synthesis of a range of pyrrolizidine alkaloids, as demonstrated by the syntheses of (−)-hyacinthacine A1, (−)-7a-*epi*-hyacinthacine A1, (−)-hyacinthacine A2, and (−)-1-*epi*-alexine. The requisite 1,2,3,4,7,8-hexahydroazocines (bearing either an *N*-α-methyl-*p*-methoxybenzyl group or no *N*-substituent) were readily prepared *via* conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to either *tert*-butyl (4*S*,5*R*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2,7-dienoate (derived from D-ribose) or *tert*-butyl (*S*,*S*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2,7-dienoate (derived from L-tartaric acid) coupled with *in situ* enolate oxidation with (−)-camphorsulfonyloxaziridine, followed by ring-closing metathesis with Grubbs I catalyst. Subsequent reaction with I_2 resulted in transannular iodoamination (accompanied by concomitant loss of the *N*-α-methyl-*p*-methoxybenzyl group for tertiary amine substrates) to give the corresponding pyrrolizidine scaffolds.

Introduction

Polyhydroxylated pyrrolizidine (hexahydro-1*H*-pyrrolizine) alkaloids are characterized by an azabicyclic core bedecked with dense oxygen (hydroxyl) functionality,[1] as exemplified by the structures of (+)-hyacinthacine A1,[2] (+)-alexine[3] and (+)-casuarine[4] (Fig. 1). A considerable amount of effort has been put into the isolation, structural elucidation, and synthesis of polyhydroxylated pyrrolizidine alkaloids, with Fleet *et al.* being lead exponents within this field.[2–5] The burgeoning interest in this type of compound stems mainly from the often potent biological activities exhibited, in particular specific glycosidase inhibition.[1,6] The distribution and orientation of hydroxyl groups around the bicyclic core enables these alkaloids to act as specific sugar mimics, the nitrogen atom becoming protonated within the enzyme pocket thereby mimicking the postulated oxo-carbenium ion intermediate of glycosidic bond cleavage.[1,6]

We have recently developed efficient asymmetric syntheses of both pyrrolizidine[7] and tropane[8] molecular architectures which are reliant on transannular[9] iodoamination as a key step. For example, conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **1** (>99% ee)[10] to α,β,ε,ζ-diunsaturated ester **2** (derived from D-ribose) and *in situ* enolate oxidation with (−)-camphorsulfonyloxaziridine [(−)-CSO] gave α-hydroxy-β-amino-ε,ζ-unsaturated ester **3** in 50% yield and >99 : 1 dr. Subsequent treatment of **3** with Grubbs I catalyst gave hexahydroazocine[11] **4** in 73% yield.

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‡Electronic supplementary information (ESI) available: Full experimental details, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic data. CCDC 922276 and 922277. For ESI and crystallographic data in CIF format see DOI: 10.1039/c3ob40205c

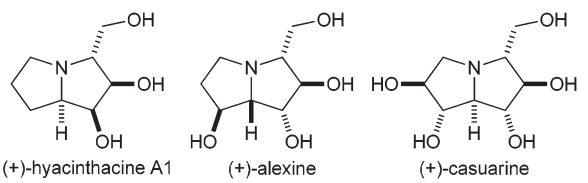
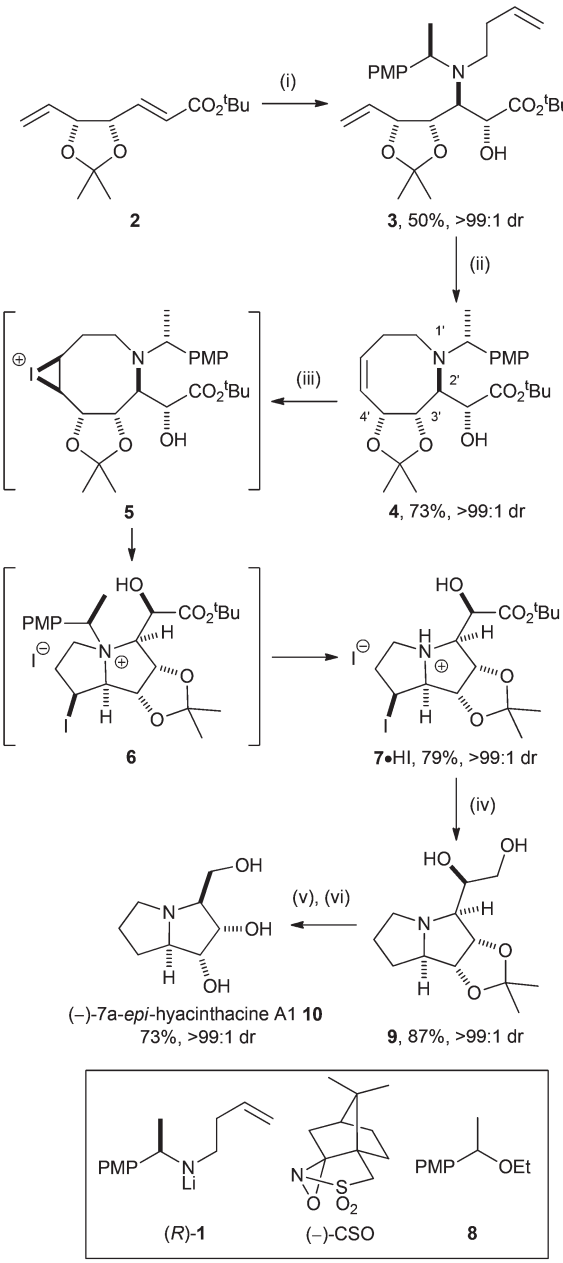


Fig. 1 Structures of (+)-hyacinthacine A1, (+)-alexine, and (+)-casuarine.

Under optimised conditions, transannular iodoamination of **4**[12] in CH_2Cl_2 (EtOH-stabilised) gave a 1 : 1 mixture of iodopyrrolizidine **7**·HI and α-methyl-*p*-methoxybenzyl ethyl ether **8**, from which **7**·HI could be isolated in 79% yield (>99 : 1 dr) by crystallisation from 30–40 °C petrol. Chromatographic purification of the residue from the mother liquors gave **8** in 95% yield and 3% ee.[13] The stereochemical outcome of this reaction is consistent with initial reversible iodonium ion formation being followed by preferential ring-opening of intermediate iodonium ion **5** upon transannular attack of the nitrogen atom to give **6**. Subsequent loss of the α-methyl-*p*-methoxybenzyl group as the corresponding cation (S_N1-type process) followed by salt formation with *in situ* generated HI gives iodopyrrolizidine **7**·HI, and trapping of the α-methyl-*p*-methoxybenzyl cation by the EtOH stabiliser present in the reaction solvent gives ether **8**; the isolation of essentially racemic ether **8** supports the intermediacy of a cation in this process. Elaboration of iodopyrrolizidine **7** to the corresponding 1,2-dihydroxy-3-hydroxymethyl pyrrolizidine scaffold [in this case (−)-7a-*epi*-hyacinthacine A1 **10**, a known (synthetic) diastereoisomer[14] of the pyrrolizidine alkaloid hyacinthacine A1] was next accomplished in four further steps and 64% yield, or 10% yield over nine steps from D-ribose (Scheme 1).[7]

In order to exploit this approach for the synthesis of polyhydroxylated pyrrolizidine alkaloids, several structural analogues of hexahydroazocine **4**, which encompass systematic removal of the *N*-substituent and *O*-isopropylidene group, presence of an α-branch within the C(2′)-substituent, and variation of the relative configuration of the C(4′)-stereogenic centre, were prepared. It was anticipated that subjection of these analogues to the previously optimised conditions for transannular iodoamination may give some insight into the origin of the diastereoselectivity of the process, as well as providing further iodopyrrolizidines for elaboration to polyhydroxylated pyrrolizidine alkaloids. Herein we report our investigations within this area, which culminate in the asymmetric syntheses of (−)-hyacinthacine A1, (−)-hyacinthacine A2, and (−)-1-*epi*-alexine, and an alternative synthesis of (−)-7a-*epi*-hyacinthacine A1.



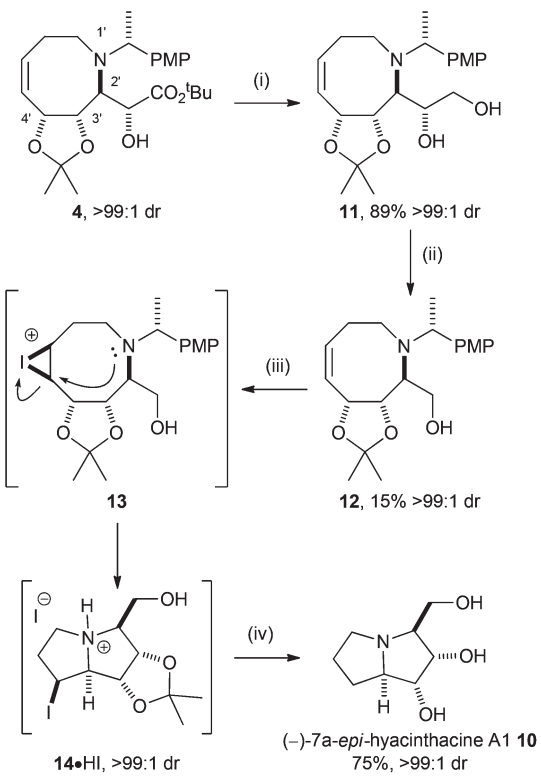
Scheme 1 *Reagents and conditions*: (i) (*R*)-**1**, THF, −78 °C, 2 h then (−)-CSO, −78 °C to rt, 12 h; (ii) Grubbs I, CH_2Cl_2, rt, 12 h then $P(CH_2OH)_3$, Et_3N, SiO_2, CH_2Cl_2, rt, 12 h; (iii) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h; (iv) $LiAlH_4$, THF, −78 °C to rt, 12 h; (v) $NaIO_4$, MeOH, H_2O, rt, 4 h then $NaBH_4$, rt, 12 h; (vi) HCl (3.0 M aq.), MeOH, reflux, 2 h. PMP = *p*-methoxyphenyl.

Results and discussion

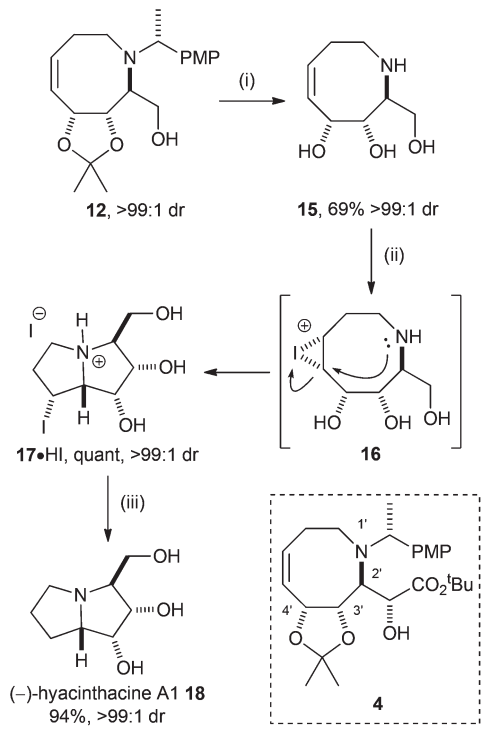
The significance of the α-branch within the C(2′)-substituent of **4** on the diastereoselectivity of the transannular iodoamination reaction was investigated first. Thus, treatment of **4** with $LiAlH_4$ resulted in the reduction of the ester to give diol **11** in 89% yield and >99 : 1 dr. Oxidative cleavage of this diol upon treatment with $NaIO_4$ and then reduction with $NaBH_4$ proved to be somewhat problematic, producing a white solid which gave an intractable ^1H NMR spectrum in an range of solvents. However, chromatographic purification allowed the isolation of **12** in >99 : 1 dr, albeit in only 15% yield. Transannular iodoamination of hexahydroazocine **12** under our optimised conditions[7] gave a single compound, subsequently assigned as iodopyrrolizidine **14**·HI. Immediate hydrogenolysis of **14**·HI under 1 atm H_2 in the presence of Et_3N and 10% Pd/C (to effect reduction of the C–I bond) was followed by acid-catalysed hydrolysis on treatment with 6.0 M aq. HCl. Purification *via* ion exchange chromatography gave (−)-7a-*epi*-hyacinthacine A1 **10** in 75% yield and >99 : 1 dr. In addition, given the known enantiomeric purity of the lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **1** (*i.e.*, >99% ee)[10] employed for the conjugate addition to α,β,ε,ζ-diunsaturated ester **2** (itself prepared from D-ribose), from which **10** is ultimately derived, the enantiomeric purity of **10** (as well as those of **4**

and **11–14**) can be confidently assigned as >99% ee. The identity of **10** as the product in this case was established by comparison of its ^{1}H and ^{13}C NMR spectra and specific rotation {[α]$_D^{20}$ −39.5 (*c* 0.3 in H_2O)} with our sample prepared previously {[α]$_D^{25}$ −45.9 (*c* 0.2 in H_2O)} from transannular iodoamination of hexahydroazocine **4**.[7] These data were in good agreement with those previously reported for (+)-7a-*epi*-hyacinthacine A1 **10** {[α]$_D^{27}$ +47.0 (*c* 0.65 in H_2O)} by Izquierdo *et al.*,[14a] (−)-7a-*epi*-hyacinthacine A1 **10** {[α]$_D^{22}$ −45.3 (*c* 1.5 in H_2O)} by Clapés *et al.*,[14c] and (±)-7a-*epi*-hyacinthacine A1 **10** by Affolter *et al.*[14d] The stereochemical outcome of this transannular iodoamination is therefore in accordance with that for **4**, and indicates that the presence of the α-branch within the C(2′)-substituent is not crucial for determining the diastereoselectivity of the reaction. Assuming, in both cases, that analogous mechanisms operate (*i.e.*, *via* reversible iodonium ion formation and subsequent attack by the nitrogen atom), the configuration within iodopyrrolizidine **14** was assigned from that of **10**. In turn, **14** would result from transannular cyclisation of iodonium ion **13** (Scheme 2).

Next, the effect of removing both the (acid labile) *N*-α-methyl-*p*-methoxybenzyl and *O*-isopropylidene groups on the outcome of the transannular iodoamination reaction was investigated. Thus, treatment of hexahydroazocine **12** with 3.0 M aq. HCl in MeOH gave the fully deprotected hexahydroazocine triol **15** in 69% yield after purification by ion-exchange chromatography (Scheme 3). The structure and relative configuration of **15** were confirmed by single crystal X-ray diffraction analysis[15] (Fig. 2). Due to the inherent insolubility of hexahydroazocine triol **15** in CH_2Cl_2 the transannular iodoamination was performed in MeOH. In order to avoid partial dissolution of $NaHCO_3$ or $Na_2S_2O_3$ (used during work-up), a new procedure was designed whereby no $NaHCO_3$ was used and only 1.0 equiv. of I_2 was employed to ensure that there was no excess reagent left to quench at the end of the reaction. After stirring the reaction mixture for 12 h at rt the solvent was removed *in vacuo* to give a single product, subsequently assigned as iodopyrrolizidine **17**·HI. Hydrogenolysis of **17**·HI and purification of the resultant product by ion exchange chromatography gave a single polyhydroxylated pyrrolizidine, which was isolated in 94% yield and >99 : 1 dr, and identified as (−)-hyacinthacine A1 **18**[2,14b,16] by comparison of its ^{1}H and



Scheme 2 *Reagents and conditions*: (i) $LiAlH_4$, THF, −78 °C to rt, 12 h; (ii) $NaIO_4$, MeOH, rt, 4 h then $NaBH_4$, rt, 4 h; (iii) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h; (iv) H_2, Pd/C, Et_3N, MeOH, rt, 18 h then HCl (6.0 M aq.), MeOH. PMP = *p*-methoxyphenyl.



Scheme 3 *Reagents and conditions*: (i) HCl (3.0 M aq.), MeOH, reflux, 2 h; (ii) I_2, MeOH, rt, 12 h; (ii) H_2, Pd/C, Et_3N, MeOH, rt, 18 h.

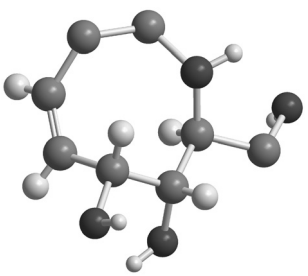
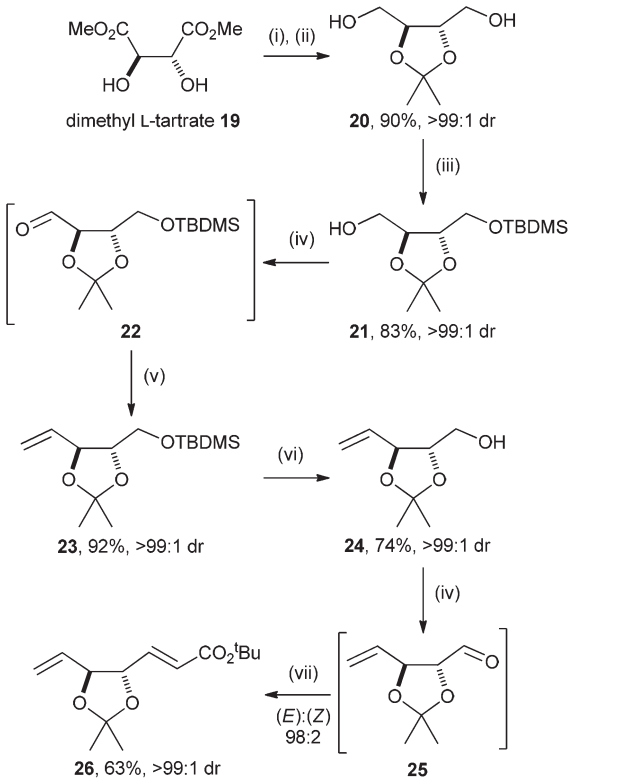


Fig. 2 Chem 3D representation of the single crystal X-ray diffraction structure of **15** (selected H atoms are omitted for clarity).

^{13}C NMR spectra and specific rotation {$[\alpha]_D^{20}$ −34.1 (*c* 0.4 in H_2O); $[\alpha]_D^{20}$ −32.0 (*c* 0.6 in MeOH)} with those previously reported by Asano *et al.* for a sample of (+)-hyacinthacine A1 **18** isolated from *Muscari armeniacum* {$[\alpha]_D^{20}$ +38.2 (*c* 0.23 in H_2O)},[2] and those reported for synthetic samples of (+)-hyacinthacine A1 **18** {$[\alpha]_D^{24}$ +35.6 (*c* 0.32 in H_2O);[14b] $[\alpha]_D^{20}$ +45.0 (*c* 0.23 in H_2O);[16a] $[\alpha]_D^{25}$ +33.5 (*c* 0.2 in MeOH);[16b] $[\alpha]_D^{21}$ +43.9 (*c* 0.29 in H_2O);[16c] $[\alpha]_D^{22}$ +43.5 (*c* 0.23 in H_2O)}[16d] and (−)-hyacinthacine A1 **18** {$[\alpha]_D^{20}$ −20.0 (*c* 1.0 in MeOH)}.[16e] As before, by invoking a mechanism which involves reversible iodonium ion formation and subsequent attack of the nitrogen atom, the isolation of **18** from this sequence of reactions suggested that the transannular cyclisation of hexahydroazocine triol **15** had occurred *via* iodonium ion **16** to give iodopyrrolizidine **17**, indicating that this reaction proceeds with complementary diastereocontrol to that observed for hexahydroazocines **4** and **12** (Scheme 3).

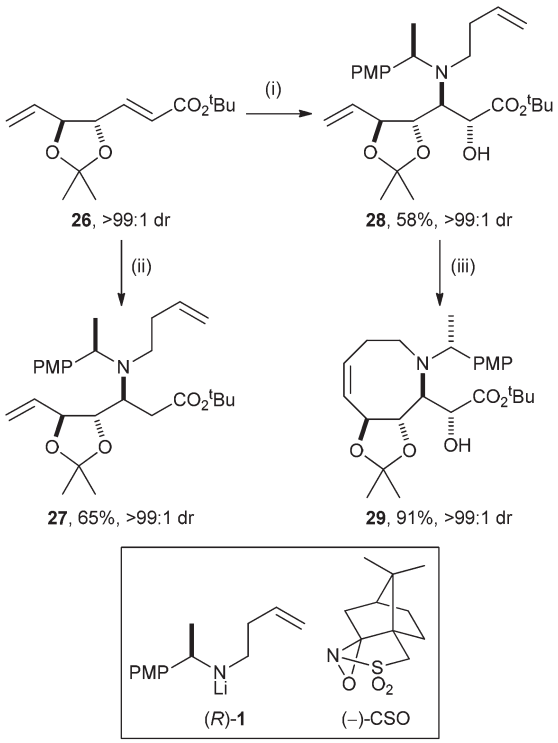
To increase further the synthetic value of the transannular iodoamination approach to polyhydroxylated pyrrolizidines, it was desirable to be able to access the corresponding 1,2-*anti*-configured pyrrolizidine diastereoisomers. Since these stereocentres are derived from the α,β,ε,ζ-diunsaturated ester, it was proposed that this could be achieved if α,β,ε,ζ-diunsaturated ester **26** was employed in the conjugate addition/ring-closing metathesis/transannular iodoamination approach[7] in the place of **2**. The optimum procedure for the preparation of **26** on scale involved initial acetonide protection of dimethyl L-tartrate **19** followed by treatment with $LiAlH_4$ to give diol **20**[17,18] in 90% yield. Selective mono-*O*-TBDMS protection of one of the hydroxyl groups within **20** on treatment with 1.0 equiv. TBDMSCl and 1.0 equiv. NaH gave **21**[18,19] in 83% yield. This was followed by Swern oxidation of the remaining (free) hydroxyl group within **21** to give the corresponding aldehyde **22**,[19] which was immediately subjected to Wittig reaction with the ylide derived from triphenylmethylphosphonium iodide and KO^{t}Bu to give alkene **23**[20] in 92% yield. Removal of the *O*-TBDMS group within **23** upon treatment with TBAF gave alcohol **24**[21] in 74% yield. Finally, 'one-pot' Swern/Wittig reaction[22] (which circumvented the need to isolate the volatile, intermediate aldehyde **25**)[21] gave **26**[23] (in 98 : 2 dr), which was isolated in 63% yield and >99 : 1 dr after chromatographic purification (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) $(MeO)_2CMe_2$, TsOH, PhMe, reflux, 16 h; (ii) $LiAlH_4$, THF, reflux, 16 h; (iii) NaH, THF, 0 °C to rt, 45 min then TBDMSCl, rt, 16 h; (iv) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h then Et_3N, −78 °C to rt, 30 min; (v) KO^{t}Bu, $[Ph_3PMe]^+[I]^-$, THF, rt, 1 h; (vi) TBAF, THF, 0 °C, 2.5 h; (vii) $Ph_3P{=}CHCO_2{}^tBu$, CH_2Cl_2, rt, 12 h.

Conjugate addition of (*R*)-**1** to **26**[24,25] resulted in formation of a single β-amino ester **27**, which was isolated in 65% yield. The synthesis of the corresponding α-hydroxy-β-amino ester **28** was next achieved upon conjugate addition of (*R*)-**1** to **26** in THF at −78 °C followed by the addition of (−)-CSO,[26] which gave **28** in 58% isolated yield and >99 : 1 dr (and **27** in 9% isolated yield and >99 : 1 dr). Subsequent ring-closing metathesis[27] of **28** required treatment with 10 mol% Grubbs I catalyst in CH_2Cl_2 at 30 °C to effect complete conversion to hexahydroazocine **29**, which was isolated in 91% yield and >99 : 1 dr (Scheme 5). The relative configuration within **29** was unambiguously established by single crystal X-ray diffraction analysis (Fig. 3),[15] with the absolute (2*R*,2′*S*,3′*S*,4′*S*,α*R*)-configuration being assigned from the known configurations of the C(3′) and C(4′)-stereocentres (derived from dimethyl L-tartrate), and the known (*R*)-configuration of the *N*-α-methyl-*p*-methoxybenzyl group. This analysis also allowed the absolute (3*S*,4*S*,5*S*,α*R*)-configuration within β-amino ester **27** and the absolute (2*R*,3*S*,4*S*,5*S*,α*R*)-configuration within α-hydroxy-β-amino ester **28** to be unambiguously assigned. These stereochemical outcomes are not only consistent with our previous observations in closely related systems,[25] but also with our transition state mnemonic for conjugate addition of this class of lithium amide to achiral α,β-unsaturated esters[28] and with the well-established *anti*-stereochemical outcome of our aminohydroxylation procedure.[26]

As transannular iodoamination of hexahydroazocine **29** would result in concomitant formation of a *trans*-5,5-fused bicyclic system it was envisaged that this would not be a feasible process. Indeed, treatment of **29** under the previously optimised conditions to effect transannular iodoamination of hexahydroazocine **4**[7] resulted in the formation of a 68 : 32 mixture of secondary amine **32** and tricyclic hemiaminal ether **33**, with no evidence of pyrrolizidine products. Chromatographic purification gave **32** in 40% yield and >99 : 1 dr, and **33** in 24% yield and >99 : 1 dr. The structure of **33** was established by extensive NMR spectroscopic analysis, including ^{1}H–^{1}H 2D COSY and HMBC; in particular the ^{1}H and ^{13}C NMR chemical shifts corresponding to C(7)H (δ_H 5.10 ppm and δ_C



Scheme 5 *Reagents and conditions*: (i) (*R*)-**1**, THF, −78 °C, 2 h then (–)-CSO, −78 °C to rt, 12 h; (ii) (*R*)-**1**, THF, −78 °C, 2 h; (iii) Grubbs I, CH_2Cl_2, 30 °C, 12 h then $P(CH_2OH)_3$, Et_3N, SiO_2, CH_2Cl_2, rt, 12 h. PMP = *p*-methoxyphenyl.

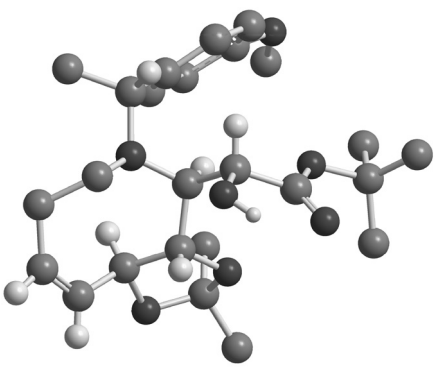
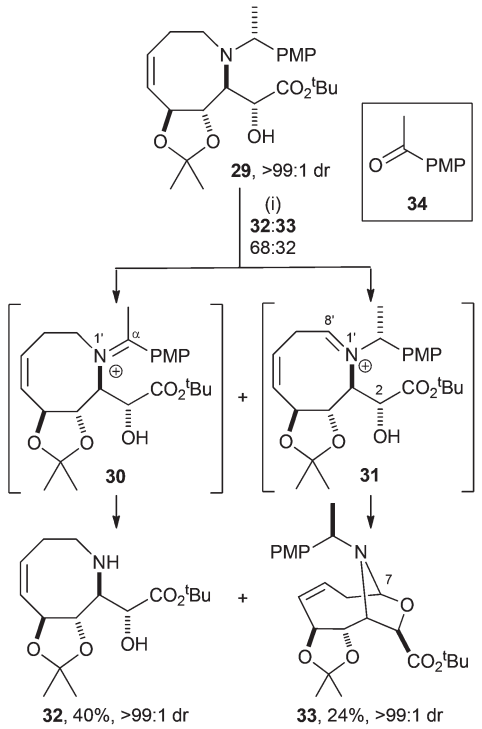


Fig. 3 Chem 3D representation of the single crystal X-ray diffraction structure of **29** (selected H atoms are omitted for clarity).

94.5 ppm) were characteristic of the formation of an N–O acetal (Scheme 6). The mechanism for halogen promoted *N*-dealkylation of tertiary amines has been proposed to involve initial *N*-oxidation followed by the formation of an iminium ion, which undergoes hydrolysis upon aqueous work-up to give a secondary amine and the corresponding aldehyde or ketone.[29] Iodine-promoted oxidation of hexahydroazocine **29** and subsequent formation of the most substituted/stable imine **30** followed by hydrolysis would result in the formation of secondary amine **32** and ketone **34**. Although **34** was not isolated, it was tentatively assigned as being present in the ^{1}H NMR spectrum of the crude reaction mixture. Meanwhile,

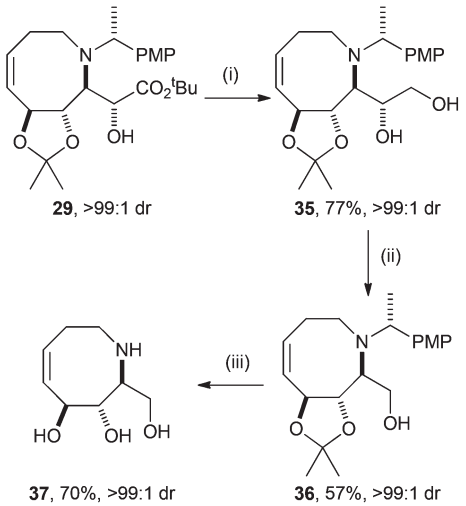


Scheme 6 *Reagents and conditions*: (i) I_2, $NaHCO_3$, CH_2Cl_2 (EtOH-stabilised), rt, 12 h. PMP = *p*-methoxyphenyl.

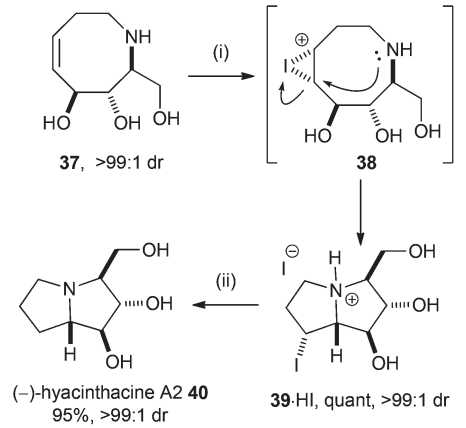
formation of the least substituted imine **31** followed by trapping upon attack of the C(2)-hydroxyl group gives tricyclic hemiaminal ether **33**. These results are entirely consistent with previous observations made by Deno and Fruit Jr., who studied the oxidative *N*-dealkylation of a range of acyclic, unsymmetrical amines with bromine.[29]

Given the expected difficulties encountered with effecting transannular iodoamination of **29**, preparation of a derivative which lacked the *O*-isopropylidene group and its subsequent transannular cyclisation was examined. Following the procedure developed for the synthesis of hexahydroazocine triol **15**, initial reduction of hexahydroazocine **29** with $LiAlH_4$ gave diol **35** in 77% yield. Subsequent oxidative cleavage of the 1,2-diol unit within **35** upon treatment with $NaIO_4$ and immediate reduction of the resultant aldehyde with $NaBH_4$ gave the required C(3)-hydroxymethyl substituted hexahydroazocine **36** in 57% yield. Acid-catalysed hydrolysis of the acetonide group within **36** proceeded with simultaneous *N*-debenzylation to give hexahydroazocine triol **37** in 70% yield after purification by ion exchange chromatography (Scheme 7).

Treatment of hexahydroazocine triol **37** with 1.0 equiv. of I_2 in MeOH for 12 h at rt followed by removal of the solvent *in vacuo* gave a single compound, which was subsequently assigned as iodopyrrolizidine **39**·HI, in >99 : 1 dr. As before, hydrogenolysis of **39**·HI and purification of the resultant product by ion exchange chromatography gave a single polyhydroxylated pyrrolizidine, which was isolated in 95% yield and >99 : 1 dr, and identified as (–)-hyacinthacine A2 **40** by comparison of its ^{1}H and ^{13}C NMR spectra with those



Scheme 7 *Reagents and conditions*: (i) $LiAlH_4$, THF, −78 °C to rt, 12 h; (ii) $NaIO_4$, MeOH, H_2O, rt, 4 h then $NaBH_4$, rt, 12 h; (iii) HCl (3.0 M aq.), MeOH, reflux, 2 h. PMP = *p*-methoxyphenyl.



Scheme 8 *Reagents and conditions*: (i) I_2, MeOH, rt, 12 h; (ii) H_2, Pd/C, Et_3N, MeOH, rt, 18 h.

previously reported by Asano *et al.* for a sample of (+)-hyacinthacine A2 **40** isolated from *Muscari armeniacum*,[2] and those reported for synthetic samples[16e,30] (Scheme 8).

It is noteworthy that although the sign of the specific rotation for our sample of (−)-hyacinthacine A2 **40** {$[\alpha]_D^{25}$ −11.0 (*c* 0.43 in H_2O); $[\alpha]_D^{25}$ −11.2 (*c* 0.83 in MeOH)} was, as expected, opposite to that reported for the sample of (+)-hyacinthacine A2 **40** isolated from the natural source {$[\alpha]_D^{25}$ +20.1 (*c* 0.44 in H_2O)},[2] their magnitudes differed significantly. However, comparison with data reported for other synthetic samples of (+)-hyacinthacine A2 **40** {$[\alpha]_D$ +12.5 (*c* 0.4 in H_2O);[30a] $[\alpha]_D^{24}$ +12.7 (*c* 0.13 in H_2O);[30b] $[\alpha]_D^{25}$ +10.5 (*c* 0.6 in H_2O);[30c] $[\alpha]_D^{20}$ +19.9 (*c* 0.97 in MeOH);[30d] $[\alpha]_D^{20}$ +11.2 (*c* 0.52 in H_2O);[30e] $[\alpha]_D$ +12.1 (*c* 0.3 in H_2O);[30f] $[\alpha]_D^{26}$ +12 (*c* 0.4 in H_2O);[30g] $[\alpha]_D^{20}$ +12.6 (*c* 1.64 in H_2O);[30h] $[\alpha]_D^{24}$ +12.4 (*c* 0.2 in H_2O);[30i] $[\alpha]_D^{20}$ +10.6 (*c* 1.2 in H_2O)};[30j] $[\alpha]_D$ +12 (*c* 0.4 in H_2O)}[30k] and (−)-hyacinthacine A2 **40** {$[\alpha]_D^{20}$ −11.0 (*c* 1.0 in MeOH)}[16e] revealed good agreement within a range of values ($10 < [\alpha]_D < 13$) in all but one case. In their synthesis of (+)-hyacinthacine A2 **40**, Martin *et al.*,[30a] reported $[\alpha]_D$ +12.5 (*c* 0.4 in H_2O) for their synthetic sample of (+)-**40** but noted that "a small sample purified by Professor Asano under the same conditions as the natural product gave $[\alpha]_D$ +23 (*c* 0.04 in H_2O)".

The configuration within iodopyrrolizidine **39** was assigned from that of **40** on the basis of a cyclisation mechanism involving attack of the nitrogen atom onto an iodonium ion, in this case **38**. The stereochemical outcomes of the highly diastereoselective and diastereodivergent transannular iodoaminations of hexahydroazocines **4**, **12**, **15** and **37** can, in all cases, be rationalised by invoking a mechanism involving the reversible formation of two diastereoisomeric iodonium ions. In the cases of hexahydroazocines **15** and **37**, transannular strain present in iodonium ions **43** and **44** may disfavour their cyclisation and hence the reaction proceeds *via* iodonium ions **16** and **38** to give pyrrolizidines **17** and **39**, respectively. In contrast, for the cases of **4** and **12**, cyclisation of iodonium ions **41** and **42** is presumably disfavoured due to the large 1,2-strain now present between the *N*-α-methyl-*p*-methoxybenzyl group and the C(2′)-substituent (rather than due to the presence of the *O*-isopropylidene group). The reaction thus preferentially proceeds *via* iodonium ions **5** and **13** (the transannular strain between the C(2′)-substituent and the distal ring hydrogen atoms being less significant than 1,2-strain in this case) to give pyrrolizidines **7** and **14**, respectively (Fig. 4).

The successful preparation of the 1,2-dihydroxy-3-(hydroxymethyl)pyrrolizidines (−)-7a-*epi*-hyacinthacine A1 **10**, (−)-hyacinthacine A1 **18** and (−)-hyacinthacine A2 **40** instigated a study into the synthesis of other, more densely hydroxylated pyrrolizidine scaffolds. As a representative example, it was envisaged that substitution of the C(7)-iodo functionality within pyrrolizidine **7** for a hydroxyl group would allow the synthesis of the 1,2,7-trihydroxy-3-hydroxymethyl substitution pattern to access diastereoisomers of the naturally occurring pyrrolizidine alkaloid alexine.[3] Using a range of conditions to attempt S_N2-type reaction delivered either returned starting material or a complex mixture of products. A radical-mediated substitution was therefore investigated.[31,32] Treatment of **7**·HI with Bu_3SnH in the presence of TEMPO gave a 75 : 25 mixture of diastereoisomeric pyrrolizidines **45** and **46**. Chromatographic purification on silica doped with 10% KF[33] gave **45** in 69% yield, and an impure sample of **46** in 19% yield, as single diastereoisomers in both cases. Given the known absolute configuration within pyrrolizidine **7**, pyrrolizidines **45** and **46** were assigned as being epimers at C(7). The absolute (1*R*,2*S*,3*S*,7*R*,7a*S*,1′*R*)-configuration within **45** was subsequently established unambiguously by chemical correlation (*vide infra*), and therefore the absolute (1*R*,2*S*,3*S*,7*S*,7a*S*,1′*R*)-configuration within **46** could also be assigned (Scheme 9).

Cleavage of the N–O bond within **45** was achieved by reaction with activated Zn in AcOH[32] to give the corresponding hydroxypyrrolizidine **47** in 61% yield and >99 : 1 dr. Reduction of **47** with $LiAlH_4$ gave **48** in 46% yield and >99 : 1 dr. Acid-catalysed hydrolysis of the acetonide group within **48** allowed the isolation of polyhydroxylated pyrrolizidine **49** in 84% yield as a

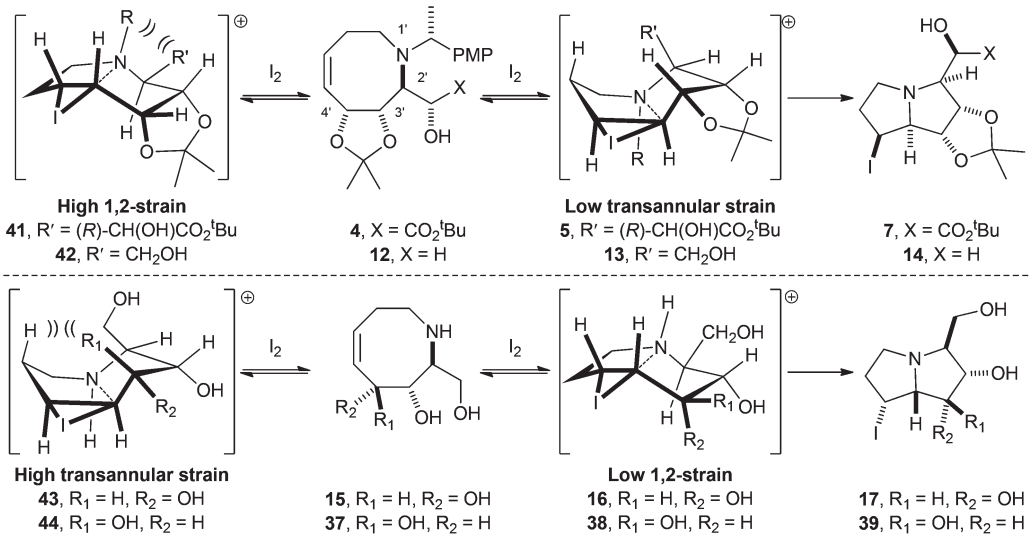
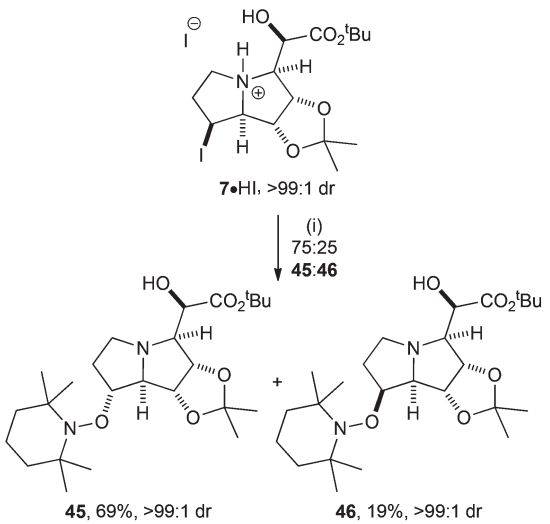


Fig. 4 Postulated mechanistic rationale for the observed stereochemical outcomes of transannular iodoamination of hexahydroazocines **4**, **12**, **15** and **37** [R = (*R*)-α-methyl-*p*-methoxybenzyl].

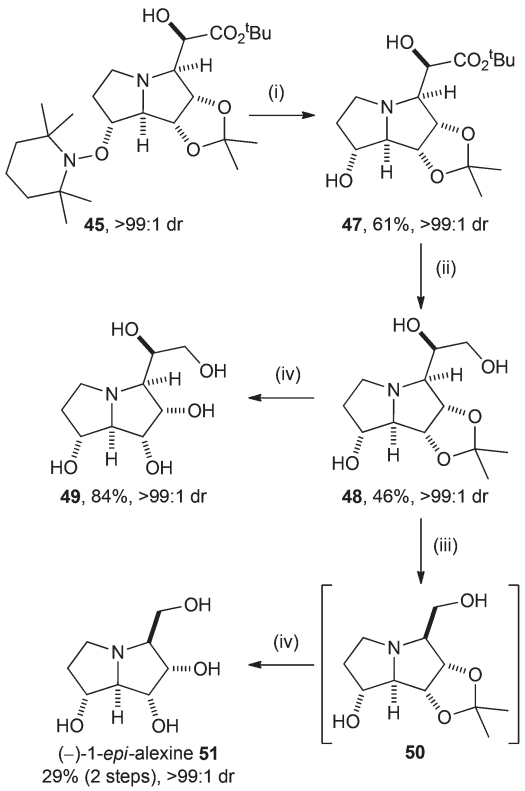


Scheme 9 *Reagents and conditions*: (i) Bu_3SnH, TEMPO, PhMe, 70 °C, 1.5 h.

single diastereoisomer. Treatment of pyrrolizidine **48** with $NaIO_4$ and immediate reduction of the resultant aldehyde with $NaBH_4$ proved problematic and resulted in a crude reaction mixture that produced a complex ^1H NMR spectrum. Attempted chromatographic purification did not allow the isolation of any identifiable species, although subjection of the crude reaction mixture to 3.0 M aq. HCl and subsequent ion-exchange chromatography, initially on DOWEX 1X8-200 (OH^- form) followed by DOWEX 50WX8 (H^+ form), allowed the isolation of (−)-1-*epi*-alexine **51** [also called (−)-2,3,7-tri-*epi*-australine][34,35] in 29% yield from **48**. A comparison of the ^1H and ^{13}C NMR spectroscopic data, and specific rotation, of our synthetic sample of (−)-1-*epi*-alexine **51** {$[\alpha]_D^{20}$ −48 (*c* 0.03 in H_2O); $[\alpha]_D^{20}$ −60 (*c* 0.03 in MeOH)} with those reported for (+)-1-*epi*-alexine **51** isolated from *Castanospermum australe* {$[\alpha]_D$ +59.7 (*c* 0.58 in H_2O);[34a] $[\alpha]_D^{25}$ +53.4 (*c* 0.43 in H_2O)},[34b] and those reported for a synthetic sample of (+)-1-*epi*-alexine **51** {$[\alpha]_D^{20}$ +34.8 (*c* 0.5 in H_2O)} by Ikota *et al.*[35a] and for a synthetic sample of (−)-1-*epi*-alexine **51** {$[\alpha]_D^{20}$ −51 (*c* 0.51 in H_2O)} by Donohoe *et al.*,[16d] showed good agreement and therefore allowed for its unambiguous structural and stereochemical assignment and, hence, those of **45–50** (Scheme 10).

Conclusion

In conclusion, a range of substituted 1,2,3,4,7,8-hexahydroazocines (bearing either an *N*-α-methyl-*p*-methoxybenzyl group or no *N*-substituent) were prepared *via* conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to either *tert*-butyl (4*S*,5*R*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2,7-dienoate (derived from D-ribose) or *tert*-butyl (*S*,*S*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2,7-dienoate (derived from L-tartaric acid) coupled with *in situ* enolate oxidation with (−)-camphorsulfonyloxaziridine, followed by ring-closing metathesis with Grubbs I catalyst as the key steps. Subsequent reaction with I_2 resulted in highly diastereoselective and diastereodivergent transannular iodoaminations (accompanied by concomitant loss of the *N*-α-methyl-*p*-methoxybenzyl group for tertiary amine substrates) to give the corresponding pyrrolizidine scaffolds. The stereochemical outcomes of these reactions can be rationalised by invoking reversible iodonium ion formation and subsequent cyclisation upon attack of the nitrogen atom, with the delicate interplay between 1,2-strain and transannular strain in the intermediate iodonium ions being responsible for the diastereoselectivity observed. The utility of this approach for pyrrolizidine alkaloid synthesis has been demonstrated by the preparation of (−)-hyacinthacine A1, (−)-7a-*epi*-hyacinthacine A1, (−)-hyacinthacine A2, and (−)-1-*epi*-alexine.



Scheme 10 *Reagents and conditions*: (i) Zn, AcOH, THF, H_2O, 70 °C, 2 h; (ii) $LiAlH_4$, THF, −78 °C to rt, 12 h; (iii) $NaIO_4$, MeOH, H_2O, rt, 4 h then $NaBH_4$, rt, 12 h; (iv) HCl (3.0 M aq.), MeOH, reflux, 2 h.

Experimental

General experimental details

Reactions involving moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[36] Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points are uncorrected. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL. IR spectra were recorded as a thin film on NaCl plates (film), or using an ATR module (ATR), as stated. 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.

(1*R*,2*S*,3*S*,7a*R*)-1,2-Dihydroxy-3-hydroxymethylhexahydro-1*H*-pyrrolizidine [(−)-7a-*epi*-hyacinthacine A1] 10. I_2 (77 mg, 0.30 mmol) was added to a stirred solution of **12** (35 mg, 0.10 mmol) in CH_2Cl_2 (EtOH-stabilised, 3 mL). The resultant mixture was left to stir at rt for 12 h then concentrated *in vacuo*. The residue was dissolved in degassed MeOH (3 mL) and 10% Pd/C (18 mg, 50% w/w) and Et_3N (0.03 mL, 0.20 mmol) were added. The reaction mixture was stirred at rt under 1 atm H_2 for 18 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in MeOH (2 mL) and co-evaporated with 6.0 M aq. HCl (2 mL), the process repeated, and the residue was dissolved in H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **10** as a colourless oil (13 mg, 75%, >99 : 1 dr);[7,14] $[\alpha]_D^{20}$ −39.5 (*c* 0.3 in H_2O) {lit. for (+)-**10** $[\alpha]_D^{27}$ +47.0 (*c* 0.65 in H_2O);[14a] lit. for (−)-**10** $[\alpha]_D^{25}$ −45.9 (*c* 0.2 in H_2O);[7] $[\alpha]_D^{22}$ −45.3 (*c* 1.5 in H_2O)};[14b] δ_H (500 MHz, MeOH-d_4) 1.50–1.58 (1H, m, C(7)H_A), 1.69–1.70 (1H, m, C(6)H_A), 1.89–1.95 (1H, m, C(6)H_B), 2.16–2.22 (1H, m, C(7)H_B), 2.86 (1H, td, *J* 10.1, 6.0, C(5)H_A), 2.97–3.01 (1H, m, C(5)H_B), 3.29 (1H, td, *J* 8.8, 4.1, C(3)*H*), 3.47 (1H, td, *J* 8.2, 2.3, C(7a)*H*), 3.81 (1H, dd, *J* 5.3, 2.3, C(1)*H*), 3.84–3.91 (2H, m, C(1′)H_2), 3.93 (1H, dd, *J* 8.8, 5.3, C(2)*H*); δ_H (500 MHz, D_2O) 1.39–1.47 (1H, m, C(7)-H_A), 1.53–1.62 (1H, m, C(6)H_A), 1.78–1.84 (1H, m, C(6)H_B), 2.07–2.13 (1H, m, C(7)H_B), 2.64 (1H, td, *J* 10.4, 5.7, C(5)H_A), 2.82–2.85 (1H, m, C(5)H_B), 3.14 (1H, dt, 6.3, 9.5, C(3)*H*), 3.31 (1H, td, 7.9, 2.2, C(7a)*H*), 3.79 (2H, d, *J* 6.3, C(1′)H_2), 3.82 (1H, dd, *J* 5.0, 2.2, C(1)*H*), 3.92 (1H, dd, *J* 9.5, 5.0, C(2)*H*); δ_H (500 MHz, D_2O [TSP])[37] 1.49–1.57 (1H, m, C(7)H_A), 1.63–1.73 (1H, m, C(6)H_A), 1.89–1.94 (1H, m, C(6)H_B), 2.17–2.23 (1H, m, C(7)H_B), 2.76 (1H, td, *J* 10.4, 5.7, C(5)H_A), 2.94–2.97 (1H, m, C(5)H_B), 3.25 (1H, app dd, 9.5, 6.6, C(3)*H*), 3.43 (1H, app dd, 8.2, 2.3, C(7a)*H*), 3.89 (2H, d, *J* 6.6, C(1′)H_2), 3.82 (1H, dd, *J* 5.0, 2.3, C(1)*H*), 3.92 (1H, dd, *J* 9.5, 5.0, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 27.3 (*C*(6)), 30.9 (*C*(7)), 46.5 (*C*(5)), 60.9 (*C*(1′)), 66.9 (*C*(3)), 71.7 (*C*(7a)), 72.4 (*C*(2)), 77.0 (*C*(1)); δ_C (125 MHz, D_2O) 25.7 (*C*(6)), 29.3 (*C*(7)), 47.2 (*C*(5)), 59.4 (*C*(1′), 64.4 (*C*(3)), 69.5 (*C*(7a)), 70.8 (*C*(2)), 75.4 (*C*(1)); δ_C (125 MHz, D_2O [TSP])[37] 28.6 (*C*(6)), 32.2 (*C*(7)), 50.1 (*C*(5)), 62.3 (*C*(1′), 67.3 (*C*(3)), 72.6 (*C*(7a)), 73.8 (*C*(2)), 78.2 (*C*(1)); *m*/*z* $(ESI)^+$ 174 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M + H]^+$) requires 174.1125; found 174.1129.

(2*S*,3*S*,4*R*,1′*R*,α*R*,*Z*)-*N*(1)-(α-Methyl-*p*-methoxybenzyl)-2-(1′,2′-dihydroxyethyl)-3,4-dihydroxy-3,4-*O*-isopropylidine-1,2,3,4,7,8-hexahydroazocine 11. $LiAlH_4$ (1.0 M in THF, 0.52 mL, 0.52 mmol) was added to a stirred solution of **4** (118 mg, 0.26 mmol) in THF (10 mL) at −78 °C. The resultant mixture was allowed to warm to rt over 12 h before 2.0 M aq. NaOH (1 mL) was added. The resultant mixture was stirred at rt for 1 h then filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2–MeOH, 20 : 1) gave **11** as a white oil (91 mg, 89%, >99 : 1 dr); $[\alpha]_D^{25}$ +44.9 (*c* 0.2 in MeOH); ν_{max} (film) 3356 (O–H), 2933 (C–H), 1609 (C=C); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, *Me*CMe), 1.49 (3H, d, *J* 6.8, C(α)*Me*), 1.53 (3H, s, *Me*CMe), 1.66 (1H, br s, O*H*), 2.01–2.08 (1H, m, C(7)H_A), 2.21–2.29 (1H, m, C(7)H_B), 2.33 (1H, br s, O*H*), 2.77 (1H, app dd, *J* 14.9, 11.1, C(8)H_A), 3.29–3.35 (2H, m, C(2)*H*, C(8)H_B), 3.49–3.54 (2H, m, C(2′)H_2), 3.80 (3H, s, O*Me*), 3.80–3.84 (1H,

m, C(1′)*H*), 4.33 (1H, q, *J* 6.8, C(α)*H*), 4.63 (1H, dd, *J* 10.4, 5.3, C(3)*H*), 5.24–5.27 (1H, m, C(4)*H*), 5.59–5.64 (1H, m, C(5)*H*), 5.89–5.96 (1H, m, C(6)*H*), 6.85 (2H, d, *J* 8.6, *Ar*), 7.20 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 23.0 (C(α)*Me*), 26.7, 28.1 (C*Me*$_2$), 31.1 (*C*(7)), 48.4 (*C*(8)), 55.0 (*C*(α)), 55.2 (O*Me*), 61.2 (*C*(2)), 64.8 (*C*(2′)), 73.9 (*C*(1′)), 77.8 (*C*(4)), 80.8 (*C*(3)), 110.2 (*C*Me$_2$), 113.7, 127.9 (*Ar*), 131.2 (*C*(6)), 132.7 (*C*(5)), 137.7, 158.2 (*Ar*); *m*/*z* (ESI$^+$) 777 ([2M + Na]$^+$, 100%), 400 ([M + Na]$^+$, 30%); HRMS (ESI$^+$) $C_{21}H_{31}NNaO_5^+$ ([M + Na]$^+$) requires 400.2094; found 400.2094.

(2*S*,3*S*,4*R*,α*R*,*Z*)-*N*(1)-(α-Methyl-*p*-methoxybenzyl)-2-(hydroxymethyl)-3,4-dihydroxy-3,4-*O*-isopropylidine-1,2,3,4,7,8-hexahydroazocine 12. $NaIO_4$ (2.63 g, 12.3 mmol) was added to a solution of **11** (464 mg, 1.23 mmol) in MeOH (10 mL). The resultant mixture was stirred at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (465 mg, 12.3 mmol) was then added to the filtrate and the reaction mixture was allowed to stir at rt for 4 h before satd aq. NH_4Cl (1 mL) was added. The resultant mixture was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography gave **12** as a colourless oil (66 mg, 15%, >99 : 1 dr); $[\alpha]_D^{25}$ +2.81 (*c* 0.96 in MeOH); ν_{max} (film) 3463 (O–H), 2970, 2937 (C–H), 1609 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 2.03–2.09 (1H, m, C(7)H_A), 2.22–2.30 (1H, m, C(7)H_B), 2.36 (1H, br s, O*H*), 2.73 (1H, app dd, *J* 14.4, 11.4, C(8)H_A), 3.31–3.45 (3H, m, C(1′)H_A, C(2)*H*, C(8)H_B), 3.65 (1H, dd, *J* 10.9, 5.1, C(1′)H_B), 3.80 (3H, s, O*Me*), 4.24 (1H, q, *J* 6.8, C(α)*H*), 4.34 (1H, dd, *J* 10.1, 5.6, C(3)*H*), 5.15–5.18 (1H, m, C(4)*H*), 5.64 (1H, dd, *J* 11.1, 5.8, C(5)*H*), 5.83–5.91 (1H, m, C(6)*H*), 6.87 (2H, d, *J* 8.7, *Ar*), 7.25 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.2 (C(α)*Me*), 26.4, 28.0 (C*Me*$_2$), 30.6 (*C*(7)), 48.9 (*C*(8)), 53.5 (*C*(α)), 55.2 (O*Me*), 62.0 (*C*(1′)), 62.1 (*C*(2)), 77.0 (*C*(4)), 80.9 (*C*(3)), 109.2 (*C*Me$_2$), 113.9, 127.6 (*Ar*), 130.6 (*C*(6)), 133.4 (*C*(5)), 137.9, 158.4 (*Ar*); *m*/*z* (ESI$^+$) 717 ([2M + Na]$^+$, 100%), 370 ([M + Na]$^+$, 80%), 348 ([M + H]$^+$, 30%); HRMS (ESI$^+$) $C_{20}H_{29}NNaO_4^+$ ([M + Na]$^+$) requires 370.1989; found 370.1983.

(2*S*,3*S*,4*R*,*Z*)-2-(Hydroxymethyl)-3,4-dihydroxy-1,2,3,4,7,8-hexahydroazocine 15. 3.0 M aq. HCl (0.5 mL) was added to a stirred solution of **12** (53 mg, 0.15 mmol) in MeOH (1 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (1.5 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **15** as a white solid (18 mg, 69%, >99 : 1 dr); mp 194–198 °C; $[\alpha]_D^{20}$ −8.1 (*c* 0.27 in H_2O); δ_H (500 MHz, D_2O) 2.09–2.22 (2H, m, C(7)H_2), 2.35–2.39 (1H, m, C(2)*H*), 2.46–2.52 (1H, m, C(8)H_A), 3.02 (1H, ddd, *J* 13.2, 4.4, 3.2, C(8)H_B), 3.38 (1H, dd, *J* 11.5, 7.9, C(1′)H_A), 3.54 (1H, dd, *J* 9.5, 3.2, C(3)*H*), 3.78 (1H, dd, *J* 11.5, 3.2, C(1′)H_B), 4.79 (1H, app ddd, *J* 8.2, 3.2, 1.3, C(4)*H*), 5.54–5.58 (1H, m, C*H*), 5.89–5.95 (1H, m, C*H*); δ_C (125 MHz, D_2O) 29.4, (*C*(7)), 50.4 (*C*(8)), 63.5 (*C*(1′)), 64.2, (*C*(2)), 69.2 (*C*(4)), 75.9 (*C*(3)), 131.2, 131.3 (*C*(5), *C*(6)); *m*/*z* (ESI$^+$) 196 ([M + Na]$^+$, 100%), 174 ([M + H]$^+$, 75%); HRMS (ESI$^+$) $C_8H_{15}NNaO_3^+$ ([M + Na]$^+$) requires 196.0944; found 196.0950.

X-Ray crystal structure determination for 15‡

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]

X-ray crystal structure data for **15** [$C_8H_{15}NO_3$]: M = 173.21, orthorhombic, space group $P2_12_12_1$, a = 6.9174(2) Å, b = 9.4363(3) Å, c = 14.0634(4) Å, V = 917.99(5) Å^3, Z = 4, μ = 0.790 mm^{-1}, colourless plate, crystal dimensions = 0.03 × 0.13 × 0.20 mm. A total of 1119 unique reflections were measured for $6 < \theta < 76$ and 2676 reflections were used in the refinement. The final parameters were wR_2 = 0.086 and R_1 = 0.038 [$I > 0.0\sigma(I)$], with Flack enantiopole = 0.1(2).[39] CCDC 922276.

(1*R*,2*S*,3*S*,4*R*,7*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-7-iodohexahydropyrrolizidinium iodide 17·HI. I_2 (21 mg, 0.08 mmol) was added to a stirred solution of **15** (14 mg, 0.08 mmol) in MeOH (1.5 mL). The resultant mixture was stirred at rt for 12 h then concentrated *in vacuo* to give **17**·HI as a brown oil (35 mg, quant, >99 : 1 dr); δ_H (500 MHz, MeOH-d_4) 2.44–2.49 (1H, m, C(6)H_A), 2.76–2.85 (1H, m, C(6)H_B), 3.44–3.48 (1H, m, C(5)H_A), 3.54 (1H, td, *J* 12.0, 6.9, C(5)H_B), 3.63–3.67 (1H, m, C(3)*H*), 3.85 (1H, dd, *J* 12.1, 5.0, C(1′)H_A), 4.01 (1H, dd, *J* 12.1, 2.8, C(1′)H_B), 4.18 (1H, dd, *J* 10.4, 3.3, C(2)*H*), 4.26–4.32 (2H, m, C(7)*H*, C(7a)*H*), 4.41 (1H, app t, *J* 2.8, C(1)*H*); δ_C (125 MHz, MeOH-d_4) 9.3 (*C*(7)), 36.8 (*C*(6)), 57.5 (*C*(5)), 58.5 (*C*(1′)), 71.8 (*C*(7a)), 73.3 (*C*(2)), 74.7, 74.8 (*C*(1), *C*(3)); *m*/*z* (ESI$^+$) 322 ([M + Na]$^+$, 10%), 300 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{15}INO_3^+$ ([M + H]$^+$) requires 300.0091; found 300.0086.

(1*R*,2*S*,3*S*,7a*R*)-1,2-Dihydroxy-3-hydroxymethylhexahydro-1*H*-pyrrolizidine [(−)-hyacinthacine A1] 18. 10% Pd/C (17 mg, 50% w/w) was added to a solution of **17**·HI (35 mg, 0.08 mmol) and Et_3N (0.08 mL, 0.58 mmol) in degassed MeOH (2 mL). The resultant mixture was stirred at rt under 1 atm H_2 for 18 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in HCl (1.25 M in MeOH, 2 mL). The resultant solution was stirred at rt for 5 min then concentrated *in vacuo*. This process was repeated and the residue was dissolved in H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **18** as a colourless oil (13 mg, 94%, >99 : 1 dr);[2,14b,16] $[\alpha]_D^{20}$ −34.1 (*c* 0.4 in H_2O); $[\alpha]_D^{20}$ −32.0 (*c* 0.64 in MeOH); {lit. for (+)-**18** $[\alpha]_D^{20}$ +38.2 (*c* 0.23 in H_2O);[2] $[\alpha]_D^{24}$ +35.6 (*c* 0.32 in H_2O);[14b] $[\alpha]_D^{20}$ +45.0 (*c* 0.23 in H_2O);[16a] $[\alpha]_D^{25}$ +33.5 (*c* 0.2 in MeOH);[16b] $[\alpha]_D^{21}$ +43.9 (*c* 0.29 in H_2O);[16c] $[\alpha]_D^{22}$ +43.5 (*c* 0.23 in H_2O);[16d] lit. for (−)-**18** $[\alpha]_D^{20}$ −20.0 (*c* 1.0 in MeOH)};[16e] δ_H (500 MHz, MeOH-d_4) 1.66–1.72 (1H, m, C(7)H_A), 1.75–1.82 (1H, m, C(6)H_A), 1.92–1.99 (1H, m, C(6)H_B), 2.06–2.13 (1H, m, C(7)H_B), 2.63–2.68 (1H, m, C(5)H_A), 2.75–2.79 (1H, m, C(3)*H*), 3.05–3.09 (1H, m, C(5)H_B), 3.46 (1H, td, *J* 7.6, 3.8, C(7a)*H*), 3.60 (1H, dd, *J* 11.0, 6.6, C(1′)H_A), 3.81 (1H, dd, *J* 11.0, 3.5, C(1′)H_B), 3.87–3.90 (2H, m, C(1)*H*, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 25.2 (*C*(7)), 28.1 (*C*(6)), 56.8 (*C*(5)), 64.7 (*C*(1′)), 66.9 (*C*(7a)), 71.1 (*C*(3)), 72.9 (*C*(1)), 76.8 (*C*(2)); *m*/*z* (ESI$^+$) 196 ([M + Na]$^+$, 15%),

174 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_3^+$ ([M + H]$^+$) requires 174.1125; found 174.1123.

(*S*,*S*)-2,2-Dimethyl-4,5-dihydroxymethyl-1,3-dioxolane 20. *Step* 1: $(MeO)_2CMe_2$ (12.0 mL, 96.9 mmol) and TsOH (128 mg, 0.65 mmol) were added to a solution of dimethyl L-tartrate **19** (11.5 g, 64.6 mmol) in PhMe (75 mL). The reaction mixture was fitted with a Dean-Stark apparatus and heated at reflux for 16 h, then allowed to cool to rt before satd aq. $NaHCO_3$ (50 mL) was added. The resultant mixture was stirred at rt for 15 min then the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with H_2O (40 mL) and brine (40 mL), then dried and concentrated *in vacuo* to give a yellow oil (13.5 g).

Step 2: $LiAlH_4$ (1.0 M in THF, 100 mL, 100 mmol) was added dropwise to a stirred solution of the residue (10.0 g) in THF (160 mL) at 0 °C. The reaction mixture was heated at reflux for 16 h then allowed to cool to rt before 10% aq. NaOH (150 mL), H_2O (70 mL) and EtOAc (150 mL) were added sequentially. The resultant mixture was stirred at rt for 1 h then filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **20** as a pale yellow oil (7.00 g, 90% from **19**, >99 : 1 dr);[17,18] δ_H (400 MHz, $CDCl_3$) 1.44 (6H, s, CMe_2), 2.52 (2H, br s, O*H*), 3.67–3.74 (2H, m, 2 × CH_AH_BOH), 3.81–3.87 (2H, m, 2 × CH_AH_BOH), 4.02–4.05 (2H, m, C(4)*H*, C(5)*H*).

(*S*,*S*)-2,2-Dimethyl-4-(*tert*-butyldimethylsilyloxy)methyl-5-hydroxymethyl-1,3-dioxolane 21. A solution of **20** (10.7 g, 66.0 mmol) in THF (50 mL) was added dropwise to a stirred slurry of NaH (60% dispersion in mineral oil, 2.61 g, 66.0 mmol) in THF (50 mL) at 0 °C. The reaction mixture was allowed to warm to for 45 min before TBDMSCl (9.84 g, 66.0 mmol) was added. The resultant mixture was stirred at rt for 16 h then diluted with Et_2O (50 mL) and satd aq. $NaHCO_3$ (2 × 50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 5 : 1) gave **21** as a pale yellow oil (15.3 g, 83%, >99 : 1 dr);[18,19] $[\alpha]_D^{24}$ +14.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, SiMe_2), 0.91 (9H, s, SiCMe_3), 1.41 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 2.38 (1H, dd, *J* 8.3, 4.4, O*H*), 3.64–3.81 (3H, m, CH_2OH, CH_AH_BOSi), 3.86–3.92 (2H, m, C*H*, CH_AH_BOSi), 4.00 (1H, dt, *J* 7.5, 4.6, C*H*).

(*S*,*S*)-2,2-Dimethyl-4-(*tert*-butyldimethylsilyloxy)methyl-5-hydroxymethyl-1,3-dioxolane 23. DMSO (14.8 mL, 208 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (8.92 mL, 104 mmol) in CH_2Cl_2 (100 mL) at −78 °C. The reaction mixture was left to stir for 15 min before a solution of **21** (14.4 g, 51.9 mmol) in CH_2Cl_2 (50 mL) was added. The resultant mixture was stirred at −78 °C for 1 h, then Et_3N (43.4 mL, 312 mmol) was added and the reaction mixture was allowed to warm to rt over 30 min. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and the resultant solution washed sequentially with H_2O (100 mL) and brine (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts dried and concentrated *in vacuo*. The residue was dissolved in THF (50 mL) and the resultant solution was added dropwise to a solution of $[Ph_3PMe]^+[I]^-$ (63.3 g, 156 mmol) and KO^{t}Bu (17.5 g, 156 mmol) in THF (100 mL) that had been stirring at rt for 2 h. The resultant mixture was stirred at rt for 1 h before H_2O (100 mL) was added. The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were washed sequentially with H_2O (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. The residue was passed through a plug of silica (eluent 30–40 °C petrol–EtOAc, 50 : 1) to give **23** as a colourless oil (13.0 g, 92%, >99 : 1 dr);[20] $[\alpha]_D^{20}$ −6.1 (*c* 0.2 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.07 (3H, s, *Me*SiMe), 0.08 (3H, s, *Me*SiMe), 0.90 (9H, s, SiCMe_3), 1.43 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 3.74–3.78 (3H, m, C*H*, CH_2OSi), 4.32–4.37 (1H, m, C*H*), 5.24 (1H, app dt, *J* 10.2, 1.4, CH=CH_AH_B), 5.37 (1H, app dt, *J* 17.2, 1.4, CH=CH_AH_B), 5.82–5.91 (1H, m, C*H*=CH_2).

(*S*,*S*)-2,2-Dimethyl-4-[(*tert*-butyldimethylsilyloxy)methyl]-5-vinyl-1,3-dioxolane 24. TBAF (1.0 M in THF, 57.3 mL, 57.3 mmol) was added to a stirred solution of **23** (13.0 g, 47.7 mmol) in THF (500 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 2.5 h before satd aq. NH_4Cl (15 mL) was added. The resultant mixture was partitioned between Et_2O (200 mL) and H_2O (300 mL) and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic extracts were washed with brine (500 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography gave **24** as a colourless oil (5.57 g, 74%, >99 : 1 dr);[21] $[\alpha]_D^{20}$ −3.6 (*c* 1.1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45 (6H, s, CMe_2), 1.99 (1H, br s, O*H*), 3.58–3.64 (1H, m, CH_AH_BOH), 3.79–3.87 (2H, m, CH_AH_BOH, C*H*), 4.33 (1H, app t, *J* 7.5, C*H*), 5.28 (1H, app dt, *J* 10.2, 1.0, CH=CH_AH_B), 5.40 (1H, app dt, *J* 17.1, 1.0, CH=CH_AH_B), 5.80–5.89 (1H, m, C*H*=CH_2).

***tert*-Butyl (*S*,*S*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylideneheptа-2,6-dienoate 26.** DMSO (3.25 mL, 45.7 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (3.63 mL, 42.3 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The resultant mixture was left to stir at −78 °C for 15 min before **24** (5.57 g, 35.2 mmol) in CH_2Cl_2 (50 mL) was added. The reaction was stirred for 1 h at −78 °C then Et_3N (9.82 mL, 70.4 mmol) was added and the reaction mixture was allowed to warm to rt over 30 min. After this time Ph_3P=$CHCO_2{}^tBu$ (13.3 g, 35.2 mmol) was added and the resultant mixture was left to stir for 12 h at rt then concentrated *in vacuo* to give (*S*,*S*,*E*)-**26** in 98 : 2 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol–Et_2O, 25 : 1) gave (*S*,*S*,*E*)-**26** as a colourless oil (5.64 g, 63%, >99 : 1 dr);[23] $[\alpha]_D^{25}$ +7.1 (*c* 0.4 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, *Me*CMe), 1.47 (3H, s, *Me*CMe), 1.49 (9H, s, CMe_3), 4.14 (1H, app t, *J* 7.7, C(5)*H*), 4.21–4.25 (1H, m, C(4)*H*), 5.31 (1H, app d, *J* 9.6, C(7)H_A), 5.41 (1H, app d, *J* 17.1, C(7)H_B), 5.78–5.88 (1H, m, C(6)*H*), 6.04 (1H, app dd, *J* 15.7, 1.5, C(2)*H*), 6.76 (1H, dd, *J* 15.7, 5.5, C(3)*H*).

***tert*-Butyl (3*S*,4*S*,5S,α*R*)-3-[*N*-but-3′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylideneheptа-6-enoate 27.** BuLi (2.5 M in hexanes, 0.47 mL, 1.18 mmol) was added dropwise to a stirred solution of (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amine[10] (258 mg, 1.26 mmol) in THF (5 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of (*S*,*S*,*E*)-**26** (200 mg, 0.79 mmol) in THF (5 mL) at

−78 °C was added dropwise *via* cannula. The reaction mixture was left to stir for 2 h, before satd aq. NH_4Cl (2 mL) was added. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (10 mL) and 10% aq. citric acid solution (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. $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **27** in >99 : 1 dr. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 10 : 1) gave **27** as a yellow oil (230 mg, 65%, >99 : 1 dr); $[\alpha]_D^{25}$ −23.6 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 2979, 2933, 2835 (C–H), 1726 (C=O), 1640, 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.38 (9H, app d, *J* 7.3, C(α)*Me*, C*Me*$_2$), 1.44 (9H, s, C*Me*$_3$), 2.10–2.17 (2H, m, C(2′)H_2), 2.20 (1H, dd, *J* 15.7, 5.8, C(2)H_A), 2.31 (1H, dd, *J* 15.7, 6.3, C(2)H_B), 2.48–2.61 (2H, m, C(1′)H_2), 3.54 (1H, app q, *J* 5.8, C(3)*H*), 3.79 (3H, s, O*Me*), 3.84 (1H, dd, *J* 8.3, 4.3, C(4)*H*), 3.93 (1H, q, *J* 6.8, C(α)*H*), 4.09 (1H, app t, *J* 7.8, C(5)*H*), 4.91–5.00 (2H, m, C(4′)H_2), 5.24 (1H, app d, *J* 10.6, C(7)H_A), 5.39 (1H, app d, *J* 17.2, C(7)H_B), 5.64–5.75 (1H, m, C(3′)*H*), 5.83–5.93 (1H, m, C(6)*H*), 6.82 (2H, d, *J* 8.7, *Ar*), 7.25 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 27.0 (*Me*CMe), 28.1 (*Me*CMe, C*Me*$_3$), 34.3, 34.5 (*C*(2), *C*(2′)), 46.3 (*C*(1′)), 55.2 (*C*(3), O*Me*), 57.0 (*C*(α)), 80.0 (*C*Me$_3$), 81.0 (*C*(5)), 82.1 (*C*(4)), 109.0 (*C*Me$_2$), 113.3 (*Ar*), 115.2 (*C*(4′)), 118.0 (*C*(7)), 128.8 (*Ar*), 136.1 (*C*(6)), 136.2 (*Ar*), 137.0 (*C*(3′), 158.4 (*Ar*), 172.0 (*C*(1)); *m*/*z* (ESI)$^+$ 482 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{42}NO_5^+$ ([M + H]$^+$) requires 460.3057; found 460.3041.

***tert*-Butyl (2*R*,3*S*,4*S*,5*S*,α*R*)-2,4,5-trihydroxy-3-[*N*-but-3′-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-4,5-*O*-isopropylideneheptenoate 28.** BuLi (2.3 M in hexanes, 8.35 mL, 19.4 mmol) was added dropwise to a stirred solution of (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amine[10] (4.12 g, 20.0 mmol) in THF (10 mL) at −78 °C. After stirring at −78 °C for 30 min a solution of (*S*,*S*,*E*)-**26** (3.19 g, 12.5 mmol) in THF (5 mL) at −78 °C was added dropwise *via* cannula. The reaction mixture was left to stir for 2 h, before (−)-CSO (5.75 g, 25.0 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 30 : 1) gave **27** as a colourless oil (520 mg, 9%, >99 : 1 dr). Further elution gave **28** as a yellow oil (3.47 g, 58%, >99 : 1 dr); $[\alpha]_D^{25}$ −57.8 (*c* 0.6 in $CHCl_3$); ν_{max} (film) 3491 (O–H), 2980, 2934, 2836 (C–H), 1726 (C=O), 1640, 1610 (C=C); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 2.21–2.31 (1H, m, C(2′)H_A), 2.33–2.42 (1H, m, C(2′)H_B), 2.60–2.67 (1H, m, C(1′)H_A), 2.98–3.06 (1H, m, C(1′)H_B) overlapping 3.04 (1H, d, *J* 6.2, O*H*), 3.50 (1H, app d, *J* 9.4, C(3)*H*), 3.74 (1H, app d, *J* 6.2, C(2)*H*), 3.80 (3H, s, O*Me*), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.06 (1H, app t, *J* 9.4, C(4)*H*), 4.22 (1H, app t, *J* 7.8, C(5)*H*), 4.98–5.01 (1H, m, C(4′)H_A), 5.07–5.09 (1H, m, C(4′)H_B), 5.21–5.24 (1H, m, C(7)H_A), 5.40–5.45 (1H, m, C(7)H_B), 5.74–5.85 (1H, m, C(3′)*H*), 5.98–6.06 (1H, m, C(6)*H*), 6.83 (2H, d, *J* 8.4, *Ar*), 7.26 (2H, d, *J* 8.4, *Ar*); δ_C (100 MHz, $CDCl_3$) 20.4 (C(α)*Me*), 26.7, 27.1 (C*Me*$_2$), 28.1 (C*Me*$_3$), 33.6 (*C*(2′)), 46.5 (*C*(1′)), 55.2 (O*Me*), 57.4 (*C*(α)), 61.9 (*C*(3)), 70.4 (*C*(2)), 78.1 (*C*(4)), 81.4 (*C*(5)), 82.2 (*C*Me$_3$), 108.4 (*C*Me$_2$), 113.4 (*Ar*), 115.4 (*C*(4′)), 116.3 (*C*(7)), 129.2, 134.4 (*Ar*), 136.9, 137.3 (*C*(6), *C*(3′)), 158.7 (*Ar*), 173.3 (*C*(1)); *m*/*z* (ESI$^+$) 498 ([M + Na]$^+$, 95%), 476 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{41}NNaO_6^+$ ([M + Na]$^+$) requires 498.2826; found 498.2824.

***tert*-Butyl (2*R*,2′*S*,3′*S*,4′*S*,α*R*,*Z*)-2-hydroxy-2-[*N*(1′)-(α-methyl-*p*-methoxybenzyl)-3′,4′-dihydroxy-3′,4′-*O*-isopropylidine-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 29.** Grubbs I (625 mg, 0.76 mmol) was added to a stirred solution of **28** (3.40 g, 7.15 mmol) in CH_2Cl_2 (300 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and tris(hydroxymethyl)phosphine (17.7 g, 143 mmol), Et_3N (2.0 mL, 14.3 mmol) and excess silica were added sequentially. The resultant mixture was left to stir at rt for 12 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 5 : 1) gave **29** as a yellow crystalline solid (2.91 g, 91%, >99 : 1 dr); mp 60–63 °C; $[\alpha]_D^{25}$ +17.9 (*c* 1.6 in $CHCl_3$); ν_{max} (ATR) 3482 (O–H), 2980, 2934, 2836 (C–H), 1723 (C=O), 1611 (C=C); δ_H (400 MHz, $CDCl_3$) 1.11 (3H, s, *Me*CMe), 1.29 (3H, s, *Me*CMe), 1.35 (9H, s, C*Me*$_3$), 1.40 (3H, d, *J* 6.7, C(α)*Me*), 2.02–2.12 (1H, m, C(7′)H_A), 2.34–2.45 (1H, m, C(7′)H_B), 2.83–2.91 (1H, m, C(8′)H_A), 3.11–3.16 (1H, m, C(8′)H_B), 3.17 (1H, app d, *J* 8.8, C(2′)*H*), 3.21 (1H, d, *J* 4.6, O*H*), 3.77 (3H, s, O*Me*), 3.94 (1H, q, *J* 6.7, C(α)*H*), 4.27–4.33 (2H, m, C(2)*H*, C(3′)*H*), 4.66–4.70 (1H, m, C(4′)*H*), 5.65–5.73 (1H, m, C(6′)*H*), 5.79–5.84 (1H, m, C(5′)*H*), 6.84 (2H, d, *J* 8.7, *Ar*), 7.25 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.3 (C(α)*Me*), 26.1, 27.0 (C*Me*$_2$), 27.9 (C*Me*$_3$), 30.5 (*C*(7′)), 46.5 (*C*(8′)), 55.2 (O*Me*), 61.3 (*C*(α)), 63.3 (*C*(2′)), 68.6, 78.0, 78.4 (*C*(2), *C*(3′), *C*(4′)), 82.3 (*C*Me$_3$), 108.1 (*C*Me$_2$), 113.8 (*Ar*), 128.5, 128.6 (*C*(6′), *Ar*), 130.6 (*C*(5′)), 137.1, 158.5 (*Ar*), 173.6 (*C*(1)); *m*/*z* (ESI$^+$) 917 ([2M + Na]$^+$, 100%), 470 ([M + Na]$^+$, 65%), 448 ([M + H]$^+$, 90%); HRMS (ESI$^+$) $C_{25}H_{37}NNaO_6^+$ ([M + Na]$^+$) requires 470.2513; found 470.2500.

X-Ray crystal structure determination for 29‡

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[38]

X-ray crystal structure data for **29** [$C_{25}H_{37}NO_6$]: M = 447.57, orthorhombic, space group $P2_12_12_1$, a = 9.0523(1) Å, b = 11.9795(2) Å, c = 22.5183(4) Å, V = 2441.93(7) Å^3, Z = 4, μ = 0.086 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.29 × 0.34 mm. A total of 3145 unique reflections were measured for $5 < \theta < 27$ and 2332 reflections were used in the refinement. The final parameters were wR_2 = 0.068 and R_1 = 0.032 [$I > -3.0\sigma(I)$]. CCDC 922277.

***tert*-Butyl (2*R*,2′*S*,3′*S*,4′*S*,*Z*)-2-hydroxy-2-[3′,4′-dihydroxy-3′,4′-*O*-isopropylidine-1′,2′,3′,4′,7′,8′-hexahydroazocin-2′-yl]ethanoate 32 and (1*R*,2*S*,3*S*,7*S*,9*R*,α*R*,*Z*)-2,3-dihydroxy-2,3-*O*-isopropylidene-9-(*tert*-butoxycarbonyl)-*N*(10)-(α-methyl-*p*-methoxybenzyl)-8-oxa-10-azabicyclo[5.2.1]dec-4-ene 33.** I_2 (340 mg, 1.34 mmol) and $NaHCO_3$ (113 mg, 1.34 mmol) were added sequentially to

a stirred solution of **29** (200 mg, 0.45 mmol) in CH_2Cl_2 (EtOH-stabilised, 20 mL). The reaction mixture was stirred at rt for 12 h before $Na_2S_2O_3$ (excess) was added. After stirring for 1 h the reaction mixture was filtered and concentrated *in vacuo* to give a 68 : 32 mixture of **32** and **33**. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 5 : 1) gave **33** as a colourless oil (48 mg, 24%, >99 : 1 dr); $[\alpha]_D^{25}$ −26.0 (*c* 0.52 in $CHCl_3$); ν_{max} (ATR) 2980, 2932 (C–H), 1731 (C═O), 1611 (C═C); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.43–1.45 (12H, m, C*Me*$_3$, C(α)*Me*), 2.26–2.31 (1H, m, C(6)H_A), 2.64–2.71 (1H, m, C(6)H_B), 3.44 (1H, dd, *J* 8.6, 1.15, C(2)*H*), 3.69 (1H, dd, 6.3, 1.15, C(1)*H*), 3.81 (3H, s, O*Me*), 3.95 (1H, q, *J* 6.6, C(α)*H*), 3.99 (1H, d, *J* 6.3, C(9)*H*), 4.81–4.85 (1H, m, C(3)*H*), 5.10 (1H, d, *J* 4.3, C(7)*H*), 5.59–5.65 (1H, m, C(5)*H*), 5.77–5.82 (1H, m, C(4)*H*), 6.87 (2H, d, *J* 8.6, *Ar*), 7.28 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 21.5 (C(α)*Me*), 27.0, 27.1 (C*Me*$_2$), 28.0 (C*Me*$_3$), 34.8 (*C*(6)), 55.2 (O*Me*), 61.3, 61.6 (*C*(1), *C*(α)), 77.5, 77.8 (*C*(9), *C*(3)), 81.5 (*C*(2)), 82.0 (*C*Me$_3$), 94.5 (*C*(7)), 108.1 (*C*Me$_2$), 113.9 (*Ar*), 125.4 (*C*(5)), 128.8 (*Ar*), 129.6 (*C*(4)), 134.9, 159.0 (*Ar*), 168.0 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 913 ([2M + Na]$^+$, 100%), 446 ([M + H]$^+$, 80%); HRMS (ESI$^+$) $C_{25}H_{36}NO_6^+$ ([M + H]$^+$) requires 446.2573; found 446.2542. Further elution gave **32** as a colourless oil (57 mg, 40%, >99 : 1 dr); $[\alpha]_D^{25}$ −1.65 (*c* 1.03 in $CHCl_3$); ν_{max} (ATR) 3493 (O–H), 2982, 2933, 2867 (C–H), 1727 (C═O), 1611 (C═C); δ_H (400 MHz, $CDCl_3$) 1.40 (6H, s, C*Me*$_2$), 1.48 (C*Me*$_3$), 2.03–2.09 (1H, m, C(7′)H_A), 2.29–2.40 (1H, m, C(7′)H_B), 2.79 (1H, ddd, *J* 14.4, 12.6, 4.6, C(8′)H_A), 2.85 (1H, dd, *J* 9.8, 3.5, C(2′)*H*), 2.93–2.98 (1H, m, C(8′)H_B), 3.38 (1H, app t, *J* 9.8, C(3′)*H*), 4.19 (1H, app d, *J* 3.5, C(2)*H*), 4.49 (1H, br t, *J* 7.3, C(4′)*H*), 5.55–5.62 (1H, m, C(6′)*H*), 5.86–5.90 (1H, m, C(5′)*H*); δ_C (100 MHz, $CDCl_3$) 26.9, 27.0 (C*Me*$_2$), 28.1 (C*Me*$_3$), 28.7 (*C*(7′)), 46.8 (*C*(8′)), 59.9 (*C*(2′)), 72.8 (*C*(2)), 78.5 (*C*(4′)), 81.2 (*C*(3′)), 81.9 (*C*Me$_3$), 109.1 (*C*Me$_2$), 127.4 (*C*(6′)), 130.4 (*C*(5′)), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 649 ([2M + Na]$^+$, 100%), 336 ([M + Na]$^+$, 85%), 314 ([M + H]$^+$, 90%); HRMS (ESI$^+$) $C_{16}H_{27}NNaO_5^+$ ([M + Na]$^+$) requires 336.1781; found 336.1787.

(2*S*,3*S*,4*S*,1′*R*,α*R*,*Z*)-*N*(1)-(α-Methyl-*p*-methoxybenzyl)-2-(dihydroxyethyl)-3,4-dihydroxy-3,4-*O*-isopropylidine-1,2,3,4,7,8-hexahydroazocine 35. $LiAlH_4$ (1.0 M in THF, 11.4 mL, 11.4 mmol) was added to a stirred solution of **29** (2.56 g, 5.72 mmol) in THF (100 mL) at −78 °C. The reaction mixture was allowed to warm to rt over 12 h before 2.0 M aq. NaOH (10 mL) was added. The resultant mixture was stirred for 1 h then filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 10 : 1 increased to 2 : 1) gave **35** as a pale brown oil (1.65 g, 77%, >99 : 1 dr); $[\alpha]_D^{25}$ +53.3 (*c* 0.29 in $CHCl_3$); ν_{max} (ATR) 3425 (O–H), 2982, 2934, 2836 (C–H), 1610 (C═C); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, s, *Me*CMe), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.31 (3H, s, *Me*CMe), 2.08–2.18 (1H, m, C(7)H_A), 2.32–2.42 (1H, m, C(7)H_B), 2.71 (1H, dd, *J* 8.6, 3.0, C(2)*H*), 2.81–3.05 (2H, m, 2 × O*H*) overlapping 2.87–2.91 (1H, m, C(8)H_A), 3.05–3.13 (1H, m, C(8)H_B), 3.39 (1H, dd, *J* 11.6, 3.5, C(2′)H_A), 3.51 (1H, dd, *J* 11.6, 4.3, C(2′)H_B), 3.80 (3H, s, O*Me*), 3.92 (1H, q, *J* 6.8, C(α)*H*), 3.94–3.98 (1H, m, C(1′)*H*), 4.28 (1H, app t, *J* 8.6, C(3)*H*), 4.68–4.72 (1H, m, C(4)*H*), 5.69–5.76 (1H, m, C(6)*H*), 5.80–5.86 (1H, m, C(5)*H*), 6.85 (2H, d, *J* 8.7, *Ar*), 7.19 (2H, d, *J* 8.7, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.5 (C(α)*Me*), 26.4, 27.0 (C*Me*$_2$), 29.9 (*C*(7)), 46.3 (*C*(8)), 55.3 (O*Me*), 60.9 (*C*(α)), 63.0 (*C*(2)), 65.1 (*C*(2′)), 69.7 (*C*(1′)), 79.1, 79.2 (*C*(3), *C*(4)), 108.6 (*C*Me$_2$), 113.9, 128.3 (*Ar*), 128.7 (*C*(6)), 129.9 (*C*(5)), 137.4, 158.6 (*Ar*); *m*/*z* (ESI$^+$) 400 ([M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{31}NNaO_5^+$ ([M + Na]$^+$) requires 400.2094; found 400.2082.

(2*S*,3*S*,4*S*,α*R*,*Z*)-*N*(1)-(α-Methyl-*p*-methoxybenzyl)-2-(hydroxymethyl)-3,4-dihydroxy-3,4-*O*-isopropylidine-1,2,3,4,7,8-hexahydroazocine 36. $NaIO_4$ (9.41 g, 44.0 mmol) was added to a solution of **35** (1.66 g, 4.40 mmol) in MeOH–H_2O (v/v 5 : 1, 40 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (1.66 g, 44.0 mmol) was then added to the filtrate and the reaction mixture was allowed to stir at rt for 12 h before satd aq. NH_4Cl (2 mL) was added. The resultant mixture was filtered through Celite® (eluent $CHCl_3$–MeOH, 3 : 1) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol–EtOAc, 5 : 1) gave **36** as a yellow oil (877 mg, 57%, >99 : 1 dr); $[\alpha]_D^{25}$ +38.7 (*c* 0.38 in $CHCl_3$); ν_{max} (ATR) 3469 (O–H), 2980, 2933 (C–H), 1610 (C═C); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (3H, s, *Me*CMe), 2.05–2.24 (3H, m, C(7)H_2, O*H*), 2.88–3.01 (3H, m, C(2)*H*, C(8)H_2), 3.65 (1H, dd, *J* 11.1, 6.3, C(1′)H_A), 3.72 (1H, dd, *J* 11.1, 6.6, C(1′)H_B), 3.77 (3H, s, O*Me*), 3.84 (1H, app t, *J* 8.6, C(3)*H*), 4.06 (1H, q, *J* 6.8, C(α)*H*), 4.61–4.66 (1H, m, C(4)*H*), 5.64–5.71 (1H, m, C(6)*H*), 5.84 (1H, dd, *J* 11.6, 3.8, C(5)*H*), 6.84 (2H, d, *J* 8.6, *Ar*), 7.22 (2H, d, *J* 8.6, *Ar*); δ_C (100 MHz, $CDCl_3$) 22.4 (C(α)*Me*), 26.6, 27.0 (C*Me*$_2$), 29.9 (*C*(7)), 46.0 (*C*(8)), 55.2 (O*Me*), 58.9 (*C*(α)), 61.8, 62.0 (*C*(2), *C*(1′)), 79.1 (*C*(4)), 82.3 (*C*(3)), 108.8 (*C*Me$_2$), 113.9, 127.8 (*Ar*), 128.5 (*C*(6)), 130.3 (*C*(5)), 138.2, 158.4 (*Ar*); *m*/*z* (ESI$^+$) 717 ([2M + Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{29}NNaO_4^+$ ([M + Na]$^+$) requires 370.1989; found 370.1983.

(*S*,*S*,*S*,*Z*)-2-(Hydroxymethyl)-3,4-dihydroxy-1,2,3,4,7,8-hexahydroazocine 37. 3.0 M aq. HCl (2 mL) was added to a stirred solution of **36** (656 mg, 1.89 mmol) in MeOH (6 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (2 mL) and purified on DOWEX 1X8–200 (OH^- form) ion exchange resin to give **37** as a colourless oil (229 mg, 70%, >99 : 1 dr); $[\alpha]_D^{25}$ −1.23 (*c* 1.06 in MeOH); ν_{max} (ATR) 3340 (O–H), 2939 (C–H), 1648 (C═C); δ_H (500 MHz, MeOH-d_4) 2.13–2.18 (1H, m, C(7)H_A), 2.26–2.35 (1H, m, C(7)H_B), 2.42–2.47 (1H, m, C(2)*H*), 2.64 (1H, ddd, *J* 13.6, 12.3, 4.7, C(8)H_A), 2.82 (1H, ddd, *J* 13.6, 6.0, 1.9, C(8)H_B), 3.13 (1H, app t, *J* 9.5, C(3)*H*), 3.41 (1H, dd, *J* 10.6, 7.3, C(1′)H_A), 3.81 (1H, dd, *J* 10.6, 4.7, C(1′)H_B), 4.16–4.19 (1H, m, C(4)*H*), 5.51–5.57 (1H, m, C(6)*H*), 5.74–5.77 (1H, m, C(5)*H*); δ_C (125 MHz, MeOH-d_4) 28.8 (*C*(7)), 46.1 (*C*(8)), 61.4 (*C*(2)), 65.5 (*C*(1′)), 74.0 (*C*(4)), 76.2 (*C*(3)), 127.0 (*C*(6)), 136.0 (*C*(5)); *m*/*z* (ESI$^+$) 196 ([M + Na]$^+$, 30%), 174 ([M + H]$^+$, 55%); HRMS (ESI$^+$) $C_8H_{15}NNaO_3^+$ ([M + Na]$^+$) requires 196.0944; found 196.0945.

(1*S*,2*S*,3*S*,4*R*,7*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-7-iodohexahydropyrrolizidinium iodide 39·HI. I_2 (74 mg, 0.29 mmol) was added to a stirred solution of **37** (50 mg, 0.29 mmol) in MeOH (5 mL). The resultant mixture was stirred at rt for 12 h

then concentrated *in vacuo* to give **39**·HI as a brown oil (124 mg, quant, >99 : 1 dr); δ_H (400 MHz, MeOH-d_4) 2.52–2.61 (1H, m, C(6)H_A), 2.64–2.74 (1H, m, C(6)H_B), 3.39–3.43 (1H, m, C(3)*H*), 3.50–3.61 (2H, m, C(5)H_2), 3.68 (1H, app t, *J* 7.3, C(7a)*H*), 3.87 (1H, dd, *J* 12.4, 4.55, C(1′)H_A), 3.97 (1H, dd, *J* 12.4, 3.0, C(1′)H_B), 4.06 (1H, dd, *J* 10.1, 7.3, C(2)*H*), 4.19 (1H, app t, *J* 7.3, C(1)*H*), 4.73 (1H, app q, *J* 5.8, C(7)*H*); δ_C (100 MHz, MeOH-d_4) 19.0 (*C*(7)), 37.5 (*C*(6)), 54.1 (*C*(5)), 56.5 (*C*(1′)), 71.0, 71.1 (*C*(3), *C*(7a)), 75.0 (*C*(2)), 81.1 (*C*(1)); *m*/*z* (ESI^+) 300 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_8H_{15}INO_3^+$ ($[M + H]^+$) requires 300.0091; found 300.0087.

(*S*,*S*,*S*,*S*)-1,2-Dihydroxy-3-hydroxymethylhexahydro-1*H*-pyrrolizidine [(−)-hyacinthacine A2] 40. 10% Pd/C (43 mg, 50% w/w) was added to a solution of **39**·HI (86 mg, 0.20 mmol) and Et_3N (0.08 mL, 0.58 mmol) in degassed MeOH (2 mL). The resultant mixture was stirred at rt under 1 atm H_2 for 18 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. The residue was dissolved in MeOH (2 mL) and co-evaporated with 6.0 M aq. HCl (2 mL), the process repeated, and the residue was dissolved in H_2O (2 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **40** as a colourless oil (33 mg, 95%, >99 : 1 dr);[2,16e,30] $[\alpha]_D^{25}$ −11.0 (*c* 0.43 in H_2O); $[\alpha]_D^{25}$ −11.2 (*c* 0.83 in MeOH); lit. for (+)-**40** $[\alpha]_D^{25}$ +20.1 (*c* 0.44 in H_2O);[2] $[\alpha]_D^{24}$ +12.5 (*c* 0.4 in H_2O);[30a] $[\alpha]_D^{24}$ +12.7 (*c* 0.13 in H_2O);[30b] $[\alpha]_D^{25}$ +10.5 (*c* 0.6 in H_2O);[30c] $[\alpha]_D^{20}$ +19.9 (*c* 0.97 in MeOH);[30d] $[\alpha]_D^{20}$ +11.2 (*c* 0.52 in H_2O);[30e] $[\alpha]_D$ +12.1 (*c* 0.3 in H_2O);[30f] $[\alpha]_D^{26}$ +12 (*c* 0.4 in H_2O);[30g] $[\alpha]_D^{20}$ +12.6 (*c* 1.64 in H_2O);[30h] $[\alpha]_D^{24}$ +12.4 (*c* 0.2 in H_2O);[30i] $[\alpha]_D^{20}$ +10.6 (*c* 1.2 in H_2O);[30j] lit. for (−)-**40** $[\alpha]_D^{20}$ −11.0 (*c* 1.0 in MeOH)};[16e] δ_H (400 MHz, MeOH-d_4); 1.71–1.80 (2H, m, C(6)H_A, C(7)H_A), 1.81–1.88 (1H, m, C(6)H_B), 1.92–1.99 (1H, m, C(7)H_B), 2.58–2.62 (1H, m, C(3)*H*), 2.76–2.82 (1H, m, C(5)H_A), 2.90–2.96 (1H, m, C(5)H_B), 3.15–3.20 (1H, m, C(7a)*H*), 3.56–3.61 (2H, m, C(1)*H*, C(1′)H_A), 3.71–3.77 (2H, m, C(2)*H*, C(1′)H_B); δ_H (500 MHz, D_2O) 1.61–1.70 (2H, m, C(6)H_A, C(7)H_A), 1.73–1.80 (1H, m, C(6)H_B), 1.81–1.88 (1H, m, C(7)H_B), 2.59–2.62 (1H, m, C(3)*H*), 2.62–2.67 (1H, m, C(5)H_A), 2.77–2.82 (1H, m, C(5)H_B), 3.05 (1H, app td, *J* 7.6, 4.4, C(7a)*H*), 3.54 (1H, dd, *J* 11.7, 6.6, C(1′)H_A), 3.63–3.70 (3H, m, C(1)*H*, C(2)*H*, C(1′)H_B); δ_H (500 MHz, D_2O [TSP])[37] 1.73–1.81 (2H, m, C(6)H_A, C(7)H_A), 1.84–1.91 (1H, m, C(6)H_B), 1.93–1.99 (1H, m, C(7)H_B), 2.71–2.74 (1H, m, C(3)*H*), 2.75–2.79 (1H, m, C(5)H_A), 2.89–2.94 (1H, m, C(5)H_B), 3.17 (1H, app td, *J* 7.9, 4.7, C(7a)*H*), 3.65 (1H, dd, *J* 12.0, 6.6, C(1′)H_A), 3.72–3.81 (3H, m, C(1)*H*, C(2)*H*, C(1′)H_B); δ_C (100 MHz, MeOH-d_4) 24.8 (*C*(6)), 30.6 (*C*(7)), 55.2 (*C*(5)), 63.4 (*C*(1′)), 67.5 (*C*(7a)), 70.9 (*C*(3)), 77.9 (*C*(2)), 81.6 (*C*(1)); δ_C (125 MHz, D_2O) 24.5 (*C*(6)), 29.8 (*C*(7)), 54.8 (*C*(5)), 63.1 (*C*(1′)), 66.0 (*C*(7a)), 69.1 (*C*(3)), 77.2 (*C*(2)), 80.2 (*C*(1)); δ_C (125 MHz, D_2O [TSP])[37] 27.4 (*C*(6)), 32.6 (*C*(7)), 57.7 (*C*(5)), 65.7 (*C*(1′)), 69.0 (*C*(7a)), 72.1 (*C*(3)), 80.0 (*C*(2)), 83.0 (*C*(1)); *m*/*z* (ESI^+) 174 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO_3^+$ ($[M + H]^+$) requires 174.1125; found 174.1131.

(1*R*,2*S*,3*S*,7*R*,7a*S*,1′*R*)- and (1*R*,2*S*,3*S*,7*S*,7a*S*,1′*R*)-1,2-Dihydroxy-1,2-*O*-isopropylidene-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)-7-{[2″,2″,6″,6″-tetramethylpiperidin-*N*(1″)-yl]oxy}hexahydro-1*H*-pyrrolizidine 45 and 46. Bu_3SnH (0.15 mL, 0.53 mmol) was added in three portions to a stirred solution of **7**·HI (100 mg, 0.18 mmol) and TEMPO (140 mg, 0.88 mmol) in PhMe (5 mL) at 70 °C. The reaction mixture was heated at 70 °C for 1.5 h then cooled to rt and concentrated *in vacuo* to give a 75 : 25 mixture of **45** and **46**. Purification *via* flash column chromatography (silica doped with 10% KF,[33] eluent 30–40 °C petrol–acetone, 50 : 1 increased to 10 : 1) gave **45** as a yellow oil (57 mg, 69%, >99 : 1 dr); $[\alpha]_D^{20}$ −6.3 (*c* 2.4 in $CHCl_3$); ν_{max} (ATR) 3484 (O–H), 2977, 2833, 2871 (C–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.07 (3H, s, *Me*CMe), 1.09 (3H, s, *Me*CMe), 1.16 (3H, s, *Me*CMe), 1.22–1.27 (1H, m, CH_A) overlapping 1.22 (3H, s, *Me*CMe) and 1.26 (3H, s, *Me*CMe), 1.28–1.34 (1H, m, CH_B), 1.40–1.47 (4H, m, 2 × CH_2) 1.47 (3H, s, *Me*CMe), 1.49 (9H, s, CMe_3), 1.88–1.97 (1H, m, C(6)H_A), 2.26–2.33 (1H, m, C(6)H_B), 2.67 (1H, td, *J* 10.1, 6.3, C(5)H_A), 2.92–2.95 (1H, m, C(5)H_B), 3.22 (1H, d, *J* 4.3, O*H*), 3.40 (1H, app d, *J* 5.8, C(3)*H*), 3.55–3.58 (1H, m, C(7a)*H*), 4.36 (1H, td, *J* 7.6, 4.3, C(7)*H*), 4.41–4.43 (1H, m, C(1′)*H*), 4.54 (1H, dd, *J* 6.8, 3.5, C(1)*H*), 4.73 (1H, app t, *J* 6.8, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 17.2 (*C*H_2), 20.2 (2 × *Me*CMe), 25.4 (*Me*CMe), 27.7 (*Me*CMe), 27.9 (C*Me*$_3$), 34.2, 34.3 (*Me*CMe), 34.8 (*C*(6)), 40.2 (2 × *C*H_2), 47.7 (*C*(5)), 59.4, 59.8 (*C*Me_2), 68.8 (*C*(3), *C*(1′)), 75.6 (*C*(7a)), 78.9 (*C*(2)), 83.4 (*C*Me_3), 85.4 (*C*(1)), 89.7 (*C*(7)), 113.5 (*C*Me_2), 172.9 (*C*(2′)); *m*/*z* (ESI^+) 469 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{45}N_2O_6^+$ ($[M + H]^+$) requires 469.3272; found 469.3275. Further elution gave an impure sample of **46** as a brown oil (16 mg, 19%, >99 : 1 dr); δ_H (400 MHz, $CDCl_3$) 1.16 (6H, s, 2 × *Me*CMe), 1.24–1.33 (2H, m, CH_2) overlapping 1.26 (6H, s, 2 × *Me*CMe) and 1.32 (3H, s, *Me*CMe), 1.43–1.49 (4H, m, 2 × CH_2), 1.49 (3H, s, *Me*CMe), 1.50 (9H, s, CMe_3), 2.08 (2H, app q, *J* 7.1, C(6)H_2), 2.63–2.69 (1H, m, C(5)H_A), 3.00–3.06 (1H, m, C(5)H_B), 3.27 (1H, d, *J* 3.8, O*H*), 3.38 (1H, dd, *J* 6.1, 1.5, C(3)*H*), 3.53–3.58 (1H, m, C(7a)*H*), 4.39–4.42 (1H, m, C(1′)*H*), 4.56 (1H, app q, *J* 6.1, C(7)*H*), 4.76 (1H, app t, *J* 6.6, C(2)*H*), 4.91 (1H, dd, *J* 6.8, 4.3, C(1)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 17.2 (*C*H_2), 25.4, 27.7 (C*Me*$_2$), 28.0 (C*Me*$_3$), 29.7 (CH_2), 33.2 (*C*(6)), 40.4 (*C*H_2), 45.5 (*C*(5)), 69.1 (*C*(3), *C*(1′)), 73.3 (*C*(7a)), 78.8 (*C*(1)), 80.1 (*C*(2)), 83.1 (*C*Me_3), 83.6 (*C*(7)), 113.4 (*C*Me_2), 172.5 (*C*(2′)); *m*/*z* (ESI^+) 469 ($[M + H]^+$, 100%); HRMS (ESI^+) $C_{25}H_{45}N_2O_6^+$ ($[M + H]^+$) requires 469.3272; found 469.3263.

(1*R*,2*S*,3*S*,7*R*,7a*S*,1′*R*)-1,2,7-Trihydroxy-1,2-*O*-isopropylidene-3-(1′-hydroxy-2′-*tert*-butoxy-2′-oxoethyl)hexahydro-1*H*-pyrrolizidine 47. Activated Zn dust (1.12 g, 17.1 mmol) was added to a stirred solution of **45** (200 mg, 0.43 mmol) in AcOH–THF–H_2O (v/v 3 : 1 : 1, 35 mL). The reaction mixture was heated at 70 °C for 2 h then cooled to rt and filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo*. The residue was redissolved in EtOAc (20 mL) and filtered through Celite® (eluent EtOAc). Purification *via* flash column chromatography (eluent 30–40 °C petrol–acetone, 2 : 1) gave **47** as a yellow oil (86 mg, 61%, >99 : 1 dr); $[\alpha]_D^{20}$ +3.4 (*c* 1.3 in MeOH); ν_{max} (ATR) 3313 (O–H), 2981 (C–H), 1732 (C=O); δ_H (300 MHz, MeOH-d_4) 1.30 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 1.51 (9H, s, CMe_3), 1.68–1.79 (1H, m, C(6)H_A), 2.17–2.26 (1H, m, C(6)H_B), 2.90–2.97 (1H, m, C(5)H_A), 3.03–3.11 (1H, m, C(5)H_B), 3.27 (1H, dd, *J* 5.1, 3.1, C(7a)*H*), 3.47–3.49 (1H, m, C(3)*H*), 4.19 (1H, app q,

J 6.9, C(7)*H*), 4.39 (1H, d, *J* 2.1, C(1′)*H*), 4.54 (1H, dd, *J* 6.3, 3.1, C(1)*H*), 4.77–4.81 (1H, m, C(2)*H*); δ_C (75 MHz, MeOH-d_4) 25.6, 27.9 (C*Me*$_2$), 28.3 (C*Me*$_3$), 36.4 (*C*(6)), 47.1 (*C*(5)), 69.6 (*C*(1′)), 70.1 (*C*(3)), 75.4 (*C*(7)), 79.7 (*C*(7a)), 82.4 (*C*(2)), 83.5 (*C*Me$_3$), 84.2 (*C*(1)), 114.0 (*C*Me$_2$), 173.7 (*C*(2′)); *m*/*z* (ESI$^+$) 330 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{28}NO_6^+$ ([M + H]$^+$) requires 330.1911; found 330.1907.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2,7-Trihydroxy-1,2-*O*-isopropylidene-3-(1′,2′-dihydroxyethyl)hexahydro-1*H*-pyrrolizidine 48. $LiAlH_4$ (1.0 M in THF, 0.91 mL, 0.91 mmol) was added to a stirred solution of **47** (75 mg, 0.23 mmol) in THF (5 mL) at −78 °C. The resultant mixture was allowed to warm to rt over 12 h before 2.0 M aq. NaOH (1 mL) was added. The resultant mixture was left to stir at rt for a further 1 h, then filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2–MeOH–Et_3N, 10 : 1 : 0.1) gave **48** as a pale yellow oil (27 mg, 46%, >99 : 1 dr); $[\alpha]_D^{20}$ −19.1 (*c* 1.1 in MeOH); ν_{max} (ATR) 3367 (O–H), 2983, 2933 (C–H); δ_H (300 MHz, MeOH-d_4) 1.22 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.57–1.68 (1H, m, C(6)H_A), 2.05–2.15 (1H, m, C(6)H_B), 2.79–2.84 (2H, m, C(5)H_2), 2.96–3.00 (1H, m, C(3)*H*), 3.17 (1H, app t, *J* 3.8, C(7a)*H*), 3.39–3.54 (2H, m, C(2′)H_2), 3.76–3.82 (1H, m, C(1′)*H*), 4.13–4.18 (1H, m, C(7)*H*), 4.42 (1H, dd, *J* 6.6, 3.8, C(1)*H*), 4.73–4.77 (1H, m, C(2)*H*); δ_C (75 MHz, MeOH-d_4) 25.5, 27.8 (C*Me*$_2$), 36.0 (*C*(6)), 47.6 (*C*(5)), 65.9 (*C*(2′)), 69.4 (*C*(3)), 71.3 (*C*(1′)), 75.5 (*C*(7)), 79.2 (*C*(7a)), 82.3 (*C*(2)), 85.1 (*C*(1)); *m*/*z* (ESI$^+$) 282 ([M + Na]$^+$, 30%), 260 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_5^+$ ([M + H]$^+$) requires 260.1492; found 260.1489.

(1*R*,2*S*,3*S*,7*R*,7a*R*,1′*R*)-1,2,7-Trihydroxy-3-(1′,2′-dihydroxyethyl)-hexahydro-1*H*-pyrrolizidine 49. 3.0 M aq. HCl (0.5 mL) was added to a stirred solution of **48** (7 mg, 0.03 mmol) in MeOH (1 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (0.5 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin to give **49** as a colourless oil (5 mg, 84%, >99 : 1 dr); $[\alpha]_D^{20}$ −22.0 (*c* 0.3 in MeOH); δ_H (500 MHz, MeOH-d_4) 1.71–1.78 (1H, m, C(6)H_A), 2.07–2.13 (1H, m, C(6)H_B), 2.92 (1H, ddd, *J* 10.4, 6.9, 3.5, C(5)H_A), 3.06–3.11 (2H, m, C(3)*H*, C(5)H_B), 3.17 (1H, dd, *J* 5.4, 3.0, C(7a)*H*), 3.63 (1H, dd, *J* 11.4, 6.6, C(2′)H_A), 3.69 (1H, dd, *J* 11.4, 6.6, C(2′)H_B), 3.91 (1H, dd, *J* 5.6, 3.0, C(1)*H*), 4.00–4.07 (2H, m, C(7)*H*, C(1′)*H*), 4.17 (1H, dd, *J* 8.5, 5.6, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 35.7 (*C*(6)), 47.0 (*C*(5)), 66.1 (*C*(3)), 66.5 (*C*(2′)), 71.4 (*C*(1′)), 71.9 (*C*(2)), 75.3 (*C*(1)), 75.9 (*C*(7)), 78.4 (*C*(7a)); *m*/*z* (ESI$^+$) 220 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_9H_{18}NO_5^+$ ([M + H]$^+$) requires 220.1179; found 220.1188.

(1*R*,2*S*,3*S*,7*R*,7a*R*)-1,2,7-Trihydroxy-3-hydroxymethylhexahydro-1*H*-pyrrolizidine [(−)-1-*epi*-alexine] 51. $NaIO_4$ (165 mg, 0.77 mmol) was added to a solution of **49** (19 mg, 0.08 mmol) in MeOH–H_2O (v/v 2 : 1, 1.5 mL). The resultant mixture was left to stir at rt for 4 h then filtered through Celite® (eluent MeOH). $NaBH_4$ (29 mg, 0.77 mmol) was then added to the filtrate and the resultant mixture was allowed to stir at rt for 12 h before satd aq. NH_4Cl (0.5 mL) was added. The resultant mixture was filtered through Celite® (eluent EtOAc–MeOH, 3 : 1) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CH_2Cl_2–MeOH, 10 : 1) gave **50**. 3.0 M aq. HCl (0.5 mL) was added to a stirred solution of **50** in MeOH (1 mL). The reaction mixture was heated at reflux for 2 h then concentrated *in vacuo*. The residue was dissolved in H_2O (0.5 mL) and purified on DOWEX 1X8-200 (OH^- form) ion exchange resin, and then on DOWEX 50WX8 (H^+ form) to give **51** as a colourless oil (4 mg, 29%, >99 : 1 dr);[34,35] $[\alpha]_D^{20}$ −48 (*c* 0.03 in H_2O); $[\alpha]_D^{20}$ −60 (*c* 0.03 in MeOH); {lit. for (+)-**51** $[\alpha]_D$ +59.7 (*c* 0.58 in H_2O);[34a] $[\alpha]_D^{25}$ +53.4 (*c* 0.43 in H_2O);[34b] $[\alpha]_D^{20}$ +34.8 (*c* 0.5 in H_2O);[35a] lit. for (−)-**51** $[\alpha]_D^{20}$ −51.0 (*c* 0.51 in H_2O)};[16d] δ_H (500 MHz, D_2O) 1.62–1.70 (1H, m, C(6)H_A), 2.02–2.07 (1H, m, C(6)H_B), 2.80 (1H, td, *J* 10.5, 5.8, C(5)H_A), 2.88–2.91 (1H, m, C(5)H_B), 3.07–3.12 (2H, m, C(3)*H*, C(7a)*H*), 3.76 (1H, s, C(1′)H_A), 3.78 (1H, d, *J* 1.9, C(1′)H_B), 3.85 (1H, dd, *J* 9.8, 5.2, C(2)*H*), 3.96 (1H, dd, *J* 5.2, 2.2, C(1)*H*), 4.02–4.06 (1H, m, C(7)*H*); δ_H (500 MHz, D_2O [TSP])[37] 1.71–1.78 (1H, m, C(6)H_A), 2.09–2.16 (1H, m, C(6)H_B), 2.85 (1H, td, *J* 10.4, 5.7, C(5)H_A), 2.96 (1H, ddd, *J* 10.1, 6.9, 3.2, C(5)H_B), 3.13 (1H, dd, J 5.7, 2.4, C(7a)*H*), 3.15–3.18 (1H, m, C(3)*H*), 3.86 (1H, d, *J* 1.6, C(1′)H_A), 3.87 (1H, d, *J* 4.1, C(1′)H_B), 3.93 (1H, dd, *J* 9.5, 5.4, C(2)*H*), 4.05 (1H, dd, *J* 5.4, 2.4, C(1)*H*), 4.12 (1H, ddd, *J* 8.2, 6.3, 6.0, C(7)*H*); δ_C (125 MHz, D_2O) 33.4 (*C*(6)), 44.7 (*C*(5)), 58.9 (*C*(1′)), 64.4 (*C*(3)), 70.9 (*C*(2)), 73.6 (*C*(1)), 74.2 (*C*(7)), 75.7 (*C*(7a); δ_C (125 MHz, D_2O [TSP])[37] 36.4 (*C*(6)), 47.5 (*C*(5)), 62.0 (*C*(1′)), 67.3 (*C*(3)), 73.9 (*C*(2)), 76.7 (*C*(1)), 77.2 (*C*(7)), 78.5 (*C*(7a); *m*/*z* (ESI$^+$) 190 ([M + H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO_4^+$ ([M + H]$^+$) requires 190.1074; found 190.1076.

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9 The phrase "*a transannulation effect*" was coined by Cope in 1952; see: A. C. Cope, S. W. Fenton and C. F. Spencer, *J. Am. Chem. Soc.*, 1952, **74**, 5884. Prelog also reported a similar "*chemical transannular effect*"; see: V. Prelog and K. Schenker, *Helv. Chim. Acta*, 1952, 2044. Prior to 1952, reactions had been reported which occurred in a transannular manner but which were not referenced as such; for example, see: R. Willstätter, *Liebigs Ann. Chem.*, 1903, **326**, 23.

10 Enantiopure (*R*)-α-methyl-*p*-methoxybenzylamine (>99% ee) is commercially available. Alkylation of (*R*)-α-methyl-*p*-methoxybenzylamine upon treatment with 4-bromobut-1-ene in the presence of K_2CO_3 gave (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amine; subsequent deprotonation with BuLi in THF generated a yellow solution of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)-amide **1**.

11 Throughout this manuscript, "hexahydroazocine" specifically refers to 1,2,3,4,7,8-hexahydroazocine.

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