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Asymmetric syntheses of (−)-isoretronecanol and (−)-trachelantamidine

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ABSTRACT

Short and concise total asymmetric syntheses of (−)-isoretronecanol and (−)-trachelantamidine are reported. Oxidative cleavage of *tert*-butyl (*S*,*S*,*S*,*Z*)-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cyclohept-3-ene-1-carboxylate, followed by hydrogenolysis promoted in situ cyclisation/reduction, which provided rapid access to the bicyclic core within (−)-isoretronecanol. Analogous treatment of the C(1)-epimer gave (−)-trachelantamidine. Overall, the syntheses of (−)-isoretronecanol and (−)-trachelantamidine were completed in eight and seven steps and 20 and 9.5% yield, respectively, from commercially available starting materials.

1. Introduction

Azabicyclic alkaloids with a nitrogen atom on the bridgehead (such as pyrrolizidines, indolizidines and quinolizidines) exhibit desirable and potent biological activity including glycosidase inhibition.[1] This class of alkaloids, exemplified by the structures of (−)-isoretronecanol **1**,[2] (−)-trachelantamidine **2**,[3] (−)-lentiginosine **3**,[4] (+)-pochonicine **4**[5] and (−)-lupinine **5**,[6,7] has therefore attracted considerable attention from the synthetic community (Fig. 1).

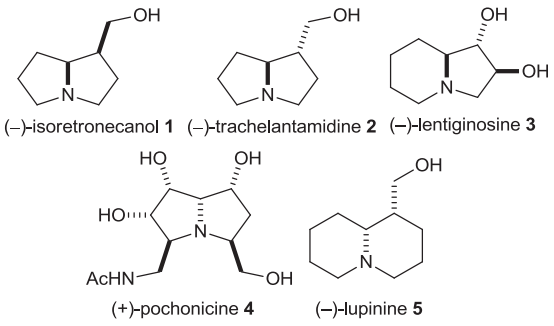

Fig. 1. Naturally occurring azabicyclic alkaloids **1**–**5**.

Recently we have developed efficient asymmetric syntheses of polyhydroxylated pyrrolizidines such as **8**[8] and its stereoisomers,[9] and the tropane alkaloid (+)-pseudococaine **11**,[10] utilising a transannular iodoamination as the key step. As part of our ongoing investigations in this area, we envisaged that the rapid construction of pyrrolizidine motifs could be achieved from *tert*-butyl 7-aminocyclohept-3-ene-1carboxylate **12**:[11] oxidative cleavage of the olefin within **12** followed by hydrogenolytic removal of the N-protecting groups would promote in situ cyclisation and reduction of the resultant imines to give azabicycles **15**, which can be readily elaborated to natural products **16** (Fig. 2). The key intermediate **12** could be readily prepared using our conjugate addition methodology,[12,13] followed by alkylation and ring-closing metathesis. Herein we report our preliminary investigations within this area, which culminate in the total asymmetric syntheses of (−)-isoretronecanol **1** and (−)-trachelantamidine **2**.[5]

2. Results and discussion

2.1. Asymmetric synthesis of (−)-isoretronecanol

Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)-amide (*S*)-**18** to α,β-unsaturated ester **17**[14] followed by alkylation of the resultant lithium (*Z*)-β-amino enolate[15] with allyl bromide gave β-amino ester **19** in 60% yield and 85:15 dr.[16] The stereochemical outcome of this reaction was later assigned unambiguously by single crystal X-ray diffraction analyses of several derivatives. Treatment of

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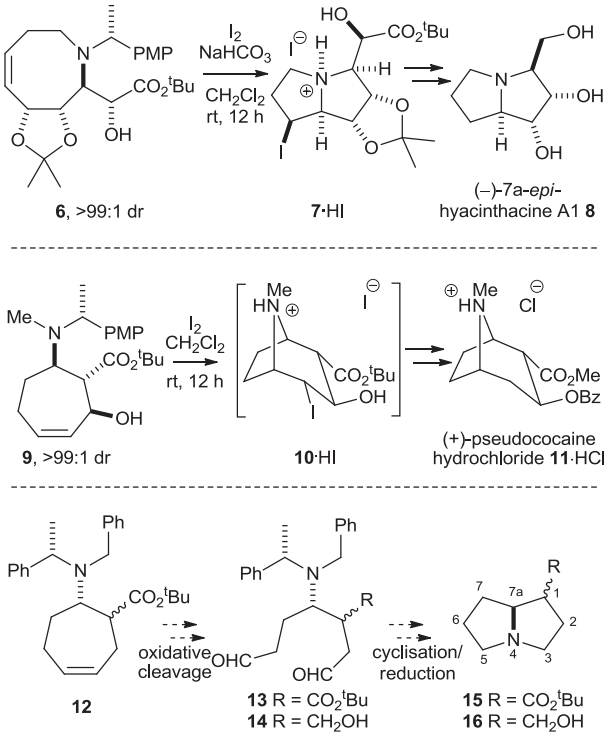
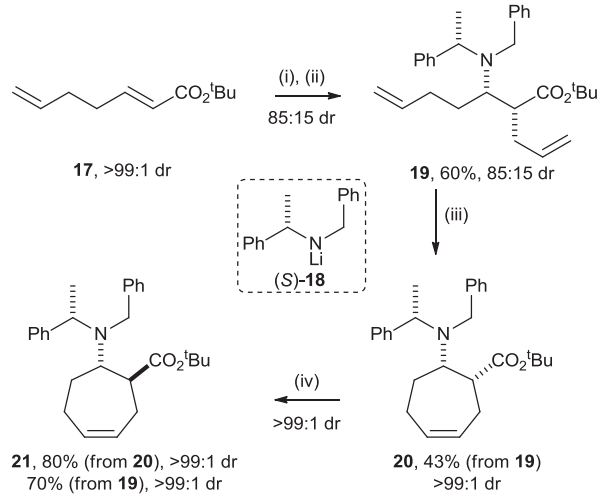


Fig. 2. Asymmetric syntheses of azabicyclic scaffolds.

19 with Grubbs I catalyst gave **20** in 85:15 dr, and in 43% isolated yield (~95% purity) from **19** and >99:1 dr after chromatographic purification. The C(1)-epimer **21** was obtained in 80% yield and >99:1 dr by treatment of **20** (>99:1 dr) with KHMDS in ^{t}BuOH/THF. Alternatively, **21** could be prepared in 70% yield and >99:1 dr directly from **19** (Scheme 1).[17]



Scheme 1. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)-amide (*S*)-**18**, THF, −78 °C, 2 h; (ii) allyl bromide, −78 °C to rt, 12 h; (iii) Grubbs I, CH_2Cl_2, 30 °C, 12 h; (iv) KHMDS, ^{t}BuOH, THF, rt, 16 h.

Attempts at the oxidative cleavage of both **20** and **21** via ozonolysis gave only complex mixtures. However, treatment of **21** under Donohoe dihydroxylation conditions (OsO_4, TMEDA)[18] gave an 80:20 mixture of *syn*-diols **22** in 80% combined yield. An analytically pure sample of the major diastereoisomer **22** was isolated by column chromatography and the relative configuration within **22** was unambiguously established by single crystal X-ray

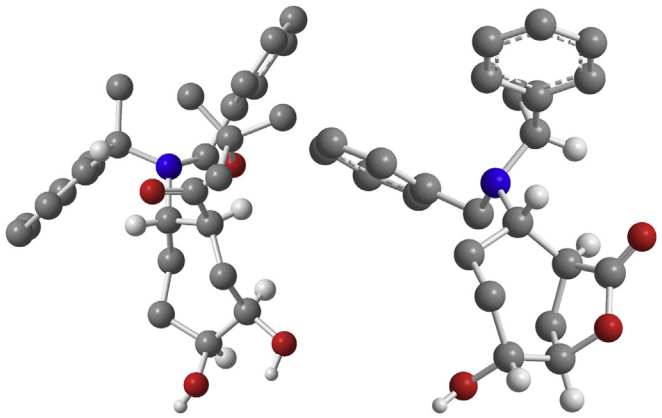
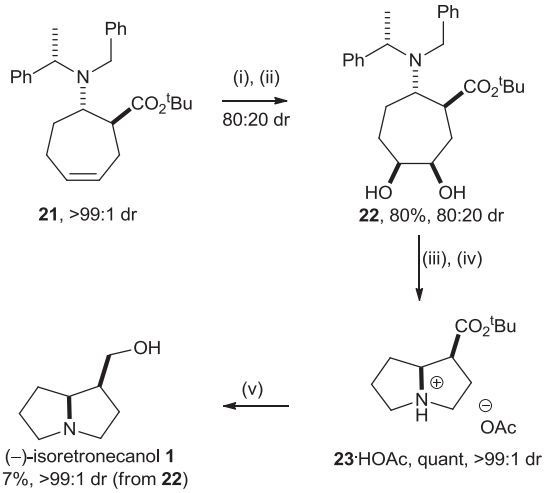


Fig. 3. X-ray crystal structures of **22** [*left*] and **24** [*right*] (selected H atoms are omitted for clarity).

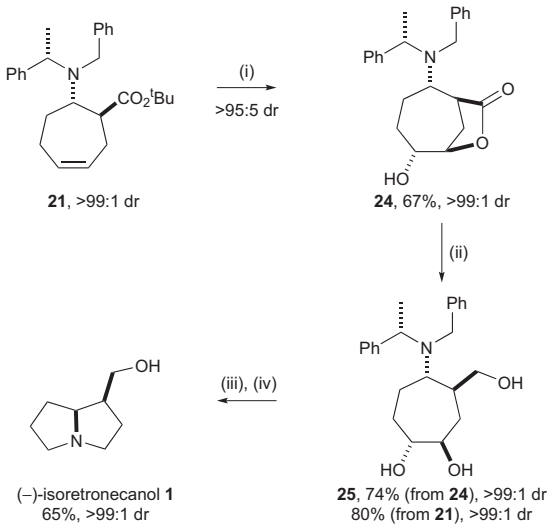
diffraction analysis (Fig. 3),[19] which also secured the assigned configurations within **19**–**21**. The stereochemical outcome of this reaction can be explained by the approach of OsO_4 on the face opposite the bulky amino group, consistent with previous observations in related systems.[18] Oxidative cleavage of the diol within **22** with $NaIO_4$ gave the corresponding bis-aldehyde intermediate, and subsequent treatment with $Pd(OH)_2/C$ under H_2 (5 atm) afforded **23**, which was isolated as the corresponding AcOH salt in quantitative yield and >99:1 dr. Subsequent reduction of **23** with DIBAL-H gave (−)-isoretronecanol **1** in 17% yield (~90% purity and >99:1 dr) from **22**. The low yield of **1** was due to the difficulties encountered upon isolation (Scheme 2).



Scheme 2. Reagents and conditions: (i) OsO_4, TMEDA, CH_2Cl_2, −78 °C, 1 h then rt, 15 min; (ii) $P(CH_2OH)_3$, Et_3N, SiO_2, rt, 48 h; (iii) $NaIO_4$, MeOH, rt, 1 h; (iv) H_2 (5 atm), $Pd(OH)_2/C$, MeOH/AcOH (20:1), rt, 24 h; (v) DIBAL-H, THF, 0 °C to rt, 18 h.

An improved synthetic route towards **1**, using our ammonium-directed oxidation conditions,[20] was developed. Amine **21** was protonated first with HBF_4 to protect the nitrogen lone pair from oxidation, followed by treatment with *m*-CPBA, which gave **24** in 67% yield and >99:1 dr. The relative configuration within **24** was unambiguously established by single crystal X-ray diffraction analysis (Fig. 3).[19] The high diastereoselectivity in this reaction could be rationalised by analogy to our previous observations: epoxidation of **21** occurs on the same face as ammonium group due to hydrogen bonding with the peracid, followed by in situ acid-mediated ring-opening/lactonisation to give **24** in >99:1 dr.

Reduction of **24** with $LiAlH_4$ gave triol **25** in 74% yield and >99:1 dr. Under optimised conditions, **25** was isolated in 80% yield and >99:1 dr from **21** without purification of **24**. Treatment of **25** with $NaIO_4$ for 1 h, subsequent hydrogenolysis and in situ cyclisation/reduction, followed by purification on DOWEX ion exchange resin gave **1** in 65% yield and >99:1 dr {$[\alpha]_D^{20}$ −70.5 (*c* 1.0, EtOH); lit.[21] $[\alpha]_D^{20}$ −65.7 (*c* 1.88, EtOH)} (Scheme 3). The spectroscopic data for both samples of (−)-isoretronecanol **1** were in excellent agreement with literature data[22] including a sample isolated from a natural source.[21]



Scheme 3. Reagents and conditions: (i) HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h; (ii) $LiAlH_4$, THF, 0 °C, 2 h; (iii) $NaIO_4$, MeOH, rt, 1 h; (iv) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (20:1), rt, 24 h.

2.2. Asymmetric synthesis of (−)-trachelantamidine

Next, the C(1)-epimeric substrate **20** was elaborated to (−)-trachelantamidine **2** employing the analogous tandem cyclisation approaches. Treatment of **20** under Donohoe dihydroxylation conditions gave *syn*-diol **26** in 52% yield and >99:1 dr.[23] The relative configuration within diol **26** was confirmed by single crystal X-ray diffraction analysis of the mono-*N*-debenzylated derivative **27** (Fig. 4),[19] which was obtained in 97% yield and >99:1 dr by treatment of **26** with CAN.[24] The diastereofacial selectivity for this dihydroxylation was consistent with the oxidation of **21** (i.e., OsO_4 approaches from the less hindered face of the C=C double bond). Oxidative cleavage of the diol within **26**, subsequent hydrogenolysis and in situ cyclisation/reduction gave **28**·AcOH in quantitative yield and >99:1 dr. (−)-Trachelantamidine **2** was then obtained in 62% yield and >99:1 dr after reduction of **28** with DIBAL-H (Scheme 4).

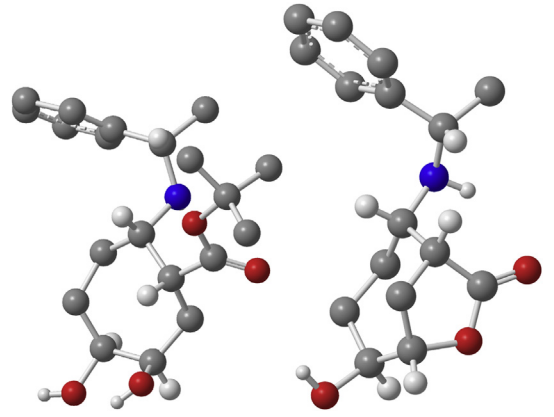
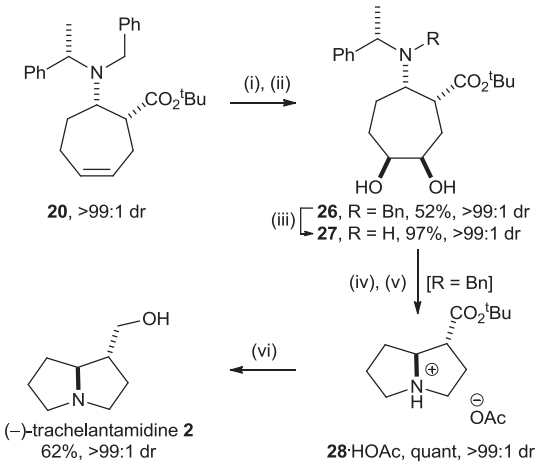
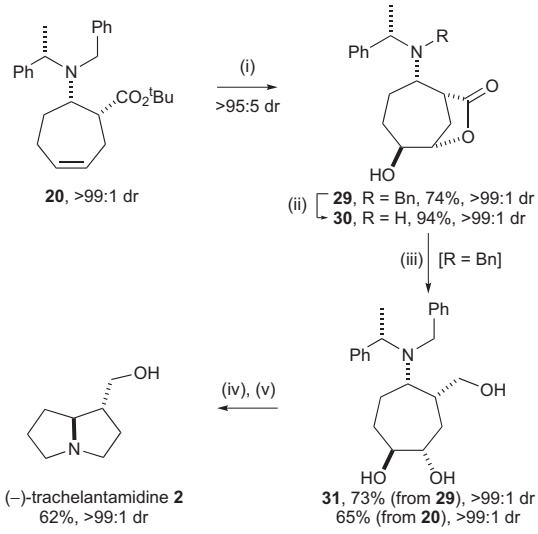


Fig. 4. X-ray crystal structures of **27** [*left*] and **30** [*right*] (selected H atoms are omitted for clarity).



Scheme 4. Reagents and conditions: (i) OsO_4, TMEDA, CH_2Cl_2, −78 °C, 1 h then rt, 15 min; (ii) $P(CH_2OH)_3$, NEt_3, SiO_2, rt, 48 h; (iii) CAN, MeCN/H_2O (5:1), rt, 2 h; (iv) $NaIO_4$, MeOH, rt, 1 h; (v) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (20:1), rt, 24 h.

Alternatively, treatment of **20** with HBF_4/*m*-CPBA gave lactone **29** in 74% yield and >99:1 dr. The relative configuration within **29** was confirmed by single crystal X-ray diffraction analysis of the mono-*N*-debenzylated derivative **30** (Fig. 4),[19] which was obtained in 94% yield and >99:1 dr by treatment of **29** with CAN. In this case, the stereochemical outcome could be rationalised by the epoxidation of **20** occurring under steric control on the opposite face to *both* the ammonium and *tert*-butyl ester groups. Reduction of **29** with $LiAlH_4$ gave **31** in 73% yield and >99:1 dr. Alternatively, **31** was isolated in 65% yield and >99:1 dr directly from **20** (without purification of **29**). Oxidative cleavage of the diol within **31** followed by hydrogenolysis and in situ cyclisation/reduction gave **2** in 62% yield and >99:1 dr {$[\alpha]_D^{20}$ −13.0 (*c* 0.2, EtOH); lit.[25] $[\alpha]_D^{20}$ −13.8 (*c* 1.28, EtOH)} after purification (Scheme 5). The spectroscopic data for both samples of (−)-trachelantamidine **2** were in excellent



Scheme 5. Reagents and conditions: (i) HBF_4, *m*-CPBA, CH_2Cl_2, rt, 48 h; (ii) CAN, MeCN/H_2O (5:1), rt, 2 h; (iii) $LiAlH_4$, THF, 0 °C, 2 h; (iv) $NaIO_4$, MeOH, rt, 1 h; (v) H_2 (5 atm), $Pd(OH)_2$/C, MeOH/AcOH (20:1), rt, 24 h.

agreement with literature data[26] including a sample isolated from a natural source.[25]

3. Conclusion

In conclusion, the rapid construction of an enantiopure pyrrolidizine scaffold was achieved by the oxidative cleavage of the C=C double bonds within two epimeric *tert*-butyl 7-aminocyclohept-3-ene-1-carboxylate substrates (by either Donohoe dihydroxylation or an ammonium-directed *m*-CPBA oxidation protocol, followed by oxidative cleavage of the resultant 1,2-diol) and hydrogenolysis to promote in situ cyclisation and reduction of the intermediate imines. The total asymmetric syntheses of (−)-isoretronecanol and (−)-trachelantamidine were completed in 20 and 9.5% overall yield, respectively, from commercially available starting materials.

4. Experimental

4.1. General experimental

All reactions involving organometallic or other moisture sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and coworkers.[27] Water was purified by an Elix® UV−10 system. BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied 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 are uncorrected. Optical rotations were recorded in 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 using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. In cases where methylene protons of cyclic ring systems could not be unambiguously assigned to a specific carbon atom, the descriptor 'CH_2' is employed throughout. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

4.2. *tert*-Butyl (2*R*,3*S*,α*S*)-2-allyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-6-enoate 19

BuLi (2.2 M in hexanes, 1.7 mL, 4.26 mmol) was added dropwise via syringe to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)-amine (930 mg, 4.40 mmol, >98% ee) in THF (10 mL) at −78 °C. After stirring for 30 min, a solution of **17** (500 mg, 2.75 mmol, >99:1 dr) in THF (10 mL) at −78 °C was added dropwise via cannula. The reaction mixture was left to stir for 2 h at −78 °C, before freshly distilled allyl bromide (0.70 mL, 8.23 mmol) was added. The resultant mixture was allowed to warm to rt over 12 h, then concentrated in vacuo. The residue was partitioned between Et_2O (15 mL) and 10% aq citric acid solution (15 mL). The aqueous layer was extracted with Et_2O (2×20 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 100:1) gave **19** as a colourless oil (714 mg, 60%, 85:15 dr). Data for mixture: ν_{max} (ATR) 1721 (C=O); *m*/*z* (ESI$^+$) 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{39}NNaO_2^+$ ([M+Na]$^+$) requires 456.2873; found 456.2865. Data for **19**: δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)*Me*), 1.31 (9H, s, C*Me*$_3$), 1.41–1.43 (1H, m, C(4)H_A), 1.43–1.70 (1H, m, C(4)H_B), 1.81–2.00 (2H, m, C(5)H_A, C(1′)H_A), 2.01–2.10 (1H, m, C(1′)H_B), 2.14–2.28 (2H, m, C(2)*H*, C(5)H_B), 2.70–2.77 (1H, m, C(3)*H*), 3.74 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.85 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 3.92 (1H, q, *J* 6.9, C(α)*H*), 4.78–4.93 (4H, m, C(7)H_2, C(3′)H_2), 5.35–5.48 (1H, m, C(2′)*H*), 5.59–5.74 (1H, m, C(6)*H*), 7.06–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 28.1 (C*Me*$_3$), 29.8 (*C*(4)), 32.2 (*C*(5)), 36.3 (*C*(1′)), 49.5 (*C*(2)), 51.2 (NCH_2Ph), 59.1 (*C*(α)), 59.6 (*C*(3)), 80.3 (*C*Me$_3$), 114.4, 116.1 (*C*(7), *C*(3′)), 126.6, 127.9, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 135.9 (*C*(2′)), 138.9 (*C*(6)), 142.2, 144.6 (*i*-*Ph*), 174.3 (*C*(1)).

4.3. *tert*-Butyl (1*R*,7*S*,α*S*)-7-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]cyclohept-3-ene-1-carboxylate 20

Grubbs I catalyst (152 mg, 0.18 mmol) was added to a stirred solution of **19** (800 mg, 1.85 mmol, 85:15 dr) in degassed CH_2Cl_2 (60 mL) at 30 °C. The resultant mixture was stirred at 30 °C for 12 h then allowed to cool to rt and tris(hydroxymethyl)phosphine (4.10 g, 33.2 mmol), Et_3N (0.5 mL, 3.5 mmol) and excess silica gel were added sequentially. The resultant mixture was left to stir at rt for 12 h, then filtered and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 75:1) gave **20** as a white solid (320 mg, 43%, >99:1 dr, 95% purity); mp 30–32 °C; $[\alpha]_D^{25}$ −86.4 (*c* 0.25, $CHCl_3$); ν_{max} (ATR) 1723 (C=O); δ_H (500 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.6, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 1.70–1.84 (2H, m, C(2)H_A, C(6)H_A), 1.85–1.96 (1H, m, C(5)H_A), 2.18–2.34 (3H, m, C(2)H_B, C(5)H_B, C(6)H_B), 2.47–2.52 (1H, m, C(1)*H*), 2.81 (1H, app dt, *J* 12.0, 3.1, C(7)*H*), 3.82 (1H, d, *J* 14.5, NCH_AH$_B$Ph), 3.97 (1H, q, *J* 6.6, C(α)*H*), 4.18 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 5.48–5.58 (1H, m, C(3)*H*), 5.79–5.88 (1H, m, C(4)*H*), 7.10–7.50 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 26.5 (*C*(6)), 26.8 (*C*(5)), 28.1 (C*Me*$_3$), 29.6 (*C*(2)), 48.3 (*C*(1)), 51.3 (NCH_2Ph), 57.1 (*C*(α)), 62.5 (*C*(7)), 79.8 (*C*Me$_3$), 127.8 (*C*(3)), 126.4, 126.5, 127.9, 128.5 (*o*,*m*,*p*-*Ph*), 132.6 (*C*(4)), 142.5, 144.6 (*i*-*Ph*), 173.9 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2^+$ ([M+H]$^+$) requires 406.2741; found 406.2726. Further elution gave a mixture of **20** and **21** (250 mg, 33%, 55:45 dr) and **21** (18 mg, 3%, >99:1 dr).

4.4. *tert*-Butyl-(1*S*,7*S*,α*S*)-7-[*N*-benzyl-*N*-(α-methylbenzyl)-amino]cyclohept-3-ene-1-carboxylate 21

KHMDS (0.5 M in PhMe, 0.5 mL, 0.25 mmol) was added to a solution of freshly distilled ^{t}BuOH (25 μL, 0.25 mmol) in THF (5 mL) at rt. After 15 min a solution of **20** (100 mg, 0.25 mmol, >99:1 dr) in THF (5 mL) was added. The resultant solution was left to stir at rt for 16 h then concentrated in vacuo. The residue was then partitioned between satd aq NH_4Cl (5 mL) and Et_2O (5 mL), and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 75:1) gave **21** as a colourless oil (80 mg, 80%, >99:1 dr); $[\alpha]_D^{25}$ −54.3 (*c* 1.4, $CHCl_3$); ν_{max} (ATR) 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.51–1.61 (1H, m, C(6)H_A), 1.71–1.82 (1H, m, C(6)H_B), 1.94–2.06 (1H, m, C(5)H_A), 2.24–2.39 (3H, m, C(2)H_2, C(5)H_B), 2.50 (1H, td, *J* 8.3, 3.5, C(1)*H*), 3.50 (1H, td, *J* 10.3, 3.5, C(7)*H*), 3.72 (2H, app s, NCH_2Ph), 4.05 (1H, q, *J* 7.0, C(α)*H*), 5.50–5.65 (1H, m, C(3)*H*), 5.65–5.80 (1H, m, C(4)*H*), 7.05–7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.5 (C(α)*Me*), 26.0 (*C*(5)), 28.0 (*C*(6)), 28.1 (C*Me*$_3$), 28.9 (*C*(2)), 49.9 (*C*(1)), 50.0 (NCH_2Ph), 60.6 (*C*(α)), 62.5 (*C*(7)), 79.6 (*C*Me$_3$), 127.8 (*C*(3)), 126.4, 126.6, 127.8, 127.9, 128.9 (*o*,*m*,*p*-*Ph*) 133.1 (*C*(4)), 141.8, 144.2 (*i*-*Ph*), 174.6

($CO_2{}^t$Bu); *m*/*z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{36}NO_2{}^+$ ([M+H]$^+$) requires 406.2741; found 406.2724.

4.5. *tert*-Butyl (1*S*,3*R*,4*S*,7*S*,α*S*)-3,4-dihydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cycloheptane-1-carboxylate 22

OsO_4 (141 mg, 0.55 mmol) was added to a stirred solution of **21** (202 mg, 0.50 mmol, >99:1 dr) and TMEDA (100 μL, 0.70 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to rt over 15 min. The residue was then diluted in CH_2Cl_2 (40 mL) and tris(hydroxymethyl)phosphine (6.20 g, 50 mmol), Et_3N (1.4 mL, 10 mmol) and excess silica gel were added sequentially. The resultant mixture was left to stir at rt for 48 h, then filtered and concentrated in vacuo to give **22** in 80:20 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **22** as a white solid (175 mg, 80%, 80:20 dr). Data for mixture: mp 115–116 °C; ν_{max} (ATR) 3412 (O–H), 1723 (C=O). Data for **22**: δ_H (400 MHz, $CDCl_3$) 1.17–1.19 (1H, m, C(6)H_A), 1.25 (3H, d, *J* 6.9, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.45–1.60 (2H, m, C(2)H_A, C(5)H_A), 1.56–1.70 (1H, m, C(6)H_B), 1.79–1.94 (2H, m, C(2)H_B, C(5)H_B), 2.25–2.57 (2H, m, 2×O*H*), 2.44–2.53 (1H, app q, *J* 5.9, C(1)*H*), 3.38 (1H, td, *J* 10.0, 2.5, C(7)*H*), 3.50–3.58 (3H, m, C(3)*H*, NCH_2Ph), 3.71 (1H, app dd, *J* 9.1, 2.0, C(4)*H*), 3.89 (1H, q, *J* 6.9, C(α)*H*), 7.06–7.23 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.5 (C(α)*Me*), 22.0 (*C*(6)), 28.1 (CMe_3), 30.5, 30.6 (*C*(2), *C*(5)), 49.1 (*C*(1)), 49.6 (NCH_2Ph), 60.7 (*C*(α)), 62.4 (*C*(7)), 80.8 (*C*Me$_3$), 72.7 (*C*(4)), 73.3 (*C*(3)), 126.4, 126.6, 127.8, 128.1, 128.8 (*o*,*m*,*p*-*Ph*), 141.5, 143.7 (*i*-*Ph*), 176.7 ($CO_2{}^t$Bu); *m*/*z* (ESI$^+$) 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{38}NO_4{}^+$ ([M+H]$^+$) requires 440.2795; found 440.2774.

4.6. (1*S*,7a*S*)-1-(*tert*-Butoxycarbonyl)octahydropyrrolizin-4-ium acetate 23·HOAc

Step 1: $NaIO_4$ (690 mg, 3.20 mmol) was added to a solution of **22** (470 mg, 1.07 mmol, 80:20 dr) in MeOH (30 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) then concentrated in vacuo. The residue was dissolved in Et_2O (30 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) then concentrated in vacuo.

Step 2: Pd(OH)$_2$/C (75 mg) was added to a stirred solution of the residue in degassed MeOH (10 mL) and AcOH (0.5 mL) and the resultant suspension was stirred at rt for 24 h under an atmosphere of H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give **23**·HOAc as pale yellow oil (350 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ −14.1 (*c* 0.78, $CHCl_3$); ν_{max} (ATR) 3381 (N–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25–1.45 (10H, m, CMe_3, CH_2), 1.51–1.64 (1H, m, CH_2), 1.80–1.95 (4H, m, CH_2, *Me*C$O_2{}^-$), 2.00–2.02 (3H, m, CH_2), 2.60–2.80 (1H, m, C(5)H_A), 2.95–3.01 (1H, m, C(3)H_A), 3.21 (1H, q, *J* 8.2, C(1)*H*), 3.47–3.58 (1H, m, C(3)H_B), 3.70–3.78 (1H, m, C(5)H_B), 4.35 (1H, q, *J* 8.2, C(7a)*H*); δ_C (100 MHz, $CDCl_3$) 22.0 (*Me*C$O_2{}^-$), 25.9, 26.7, 27.8 (*C*(2), *C*(6), *C*(7)), 27.8 (CMe_3), 46.4 (*C*(1)), 52.6, 55.0 (*C*(3), *C*(5)), 66.5 (*C*(7a)), 82.1 (*C*Me$_3$), 169.9 ($CO_2{}^t$Bu), 176.3 (MeC$O_2{}^-$); *m*/*z* (ESI$^+$) 212 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_2{}^+$ ([M+H]$^+$) requires 212.1645; found 212.1637.

4.7. (1*S*,2*S*,5*R*,6*R*,α*S*)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-hydroxy-7-oxabicyclo[4.2.1]nonan-8-one 24

HBF_4 (48% in H_2O, 160 μL, 1.25 mmol) was added to a stirred solution of **21** (100 mg, 0.25 mmol, >99:1 dr) in CH_2Cl_2 (0.7 mL). After 5 min *m*-CPBA (70% in H_2O, 120 mg, 0.50 mmol) was added and the resultant mixture was left to stir at rt for 48 h. CH_2Cl_2 (10 mL), satd aq Na_2SO_3 (5 mL) and satd aq $NaHCO_3$ (5 mL) were added sequentially and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were then dried and concentrated in vacuo to give **24** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **24** as a white solid (60 mg, 67%, >99:1 dr); mp 191–193 °C; $[\alpha]_D^{25}$ +20.8 (*c* 0.9, $CHCl_3$); ν_{max} (ATR) 3463 (O–H), 1750 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 7.1, C(α)*Me*), 1.34–1.48 (1H, m, C(4)H_A), 1.49–1.63 (1H, m, C(3)H_A), 1.63–1.83 (1H, m, C(4)H_B), 1.49–1.83 (1H, m, O*H*), 1.82–2.34 (1H, m, C(9)H_A), 2.00–2.18 (1H, app q, *J* 12.3, C(3)H_B), 2.31 (1H, app d, *J* 13.7, C(9)H_B), 2.41 (1H, app d, *J* 9.3, C(1)*H*), 3.39 (1H, app dd, *J* 12.0, 4.9, C(2)*H*), 3.43 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.82 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.83 (1H, q, *J* 7.1, C(α)*H*), 3.97 (1H, app q, *J* 4.0, C(5)*H*), 4.46 (1H, app dd, *J* 7.8, 4.7, C(6)*H*), 7.15–7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.1 (C(α)*Me*), 24.4 (*C*(4)), 24.8 (*C*(9)), 27.9 (*C*(3)), 39.5 (*C*(1)), 50.0 (NCH_2Ph), 59.2 (*C*(α)), 59.6 (*C*(2)), 68.4 (*C*(5)), 79.4 (*C*(6)), 126.7, 127.1, 127.8, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 141.6, 142.6 (*i*-*Ph*), 180.8 (*C*(8)); *m*/*z* (ESI$^+$) 366 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{38}NO_3{}^+$ ([M+H]$^+$) requires 366.2064; found 366.2053.

4.8. (1*S*,3*R*,4*R*,7*S*,α*S*)-1-Hydroxymethyl-3,4-dihydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cycloheptane 25

$LiAlH_4$ (1.0 M in THF, 0.88 mL, 0.88 mmol) was added to a stirred solution of **24** (80 mg, 0.22 mmol, >99:1 dr) in THF (6 mL) at 0 °C. The resultant solution was left to stir at 0 °C for 2 h, then 2.0 M aq NaOH (0.44 mL, 0.88 mmol) was added and the reaction mixture was left to stir at rt for 1 h. The resultant mixture was then filtered through Celite® (eluent THF), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **25** as a white solid (60 mg, 74%, >99:1 dr); mp 56–57 °C; $[\alpha]_D^{25}$ +32.7 (*c* 0.67, $CHCl_3$); ν_{max} (ATR) 3362 (O–H); δ_H (400 MHz, $CDCl_3$) 1.26–1.31 (1H, m, C(2)H_A), 1.41 (3H, d, *J* 7.0, C(α)*Me*), 1.55 (1H, dt, *J* 14.4, 2.2, C(2)H_B), 1.69–1.90 (4H, m, C(1)*H*, C(5)H_2, C(6)H_A), 1.93–2.04 (1H, m, C(6)H_B), 2.83 (1H, dt, *J* 10.1, 5.0, C(7)*H*), 3.04 (1H, dd, *J* 10.6, 6.3, CH_AH$_B$OH), 3.20 (3H, br s, 3×O*H*), 3.36–3.42 (2H, m, C(4)*H*, CH$_A$$H_B$OH), 3.47 (1H, m, C(3)*H*), 3.61 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.99 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 3.97 (1H, q, *J* 7.0, C(α)*H*), 7.10–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (C(α)*Me*), 24.0 (*C*(6)), 29.6 (*C*(5)), 33.8 (*C*(2)), 39.3 (*C*(1)), 50.3 (NCH_2Ph), 56.3 (*C*(α)), 57.8 (*C*(7)), 67.9 (*C*H$_2$OH), 76.9 (*C*(3)), 77.6 (*C*(4)), 127.2, 127.3, 128.1, 128.3, 128.5, 129.4 (*o*,*m*,*p*-*Ph*), 139.5, 143.1 (*i*-*Ph*); *m*/*z* (ESI$^+$) 370 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{32}NO_3{}^+$ ([M+H]$^+$) requires 370.2377; found 370.2370.

4.9. (1*S*,7a*S*)-1-Hydroxymethylhexahydro-1*H*-pyrrolizine [(−)-isoretronecanol] 1

Method A – step 1: $NaIO_4$ (174 mg, 0.81 mmol) was added to a solution of **25** (100 mg, 0.27 mmol, >99:1 dr) in MeOH (10 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the resultant solution was concentrated in vacuo. The residue was dissolved in Et_2O (30 mL) and filtered through a short plug of Celite® (eluent Et_2O) and concentrated in vacuo.

Method A – step 2: Pd(OH)$_2$/C (19 mg) was added to a stirred solution of the residue in degassed MeOH (5 mL) and AcOH (0.25 mL) and the resultant suspension was stirred at rt for 24 h under an atmosphere of H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **1** as a colourless oil (23 mg, 65%, >99:1 dr); $[\alpha]_D^{20}$ −70.1 (*c* 1.0, EtOH); {lit.[21] $[\alpha]_D^{20}$ −65.7 (*c* 1.88, EtOH); lit.[22a] $[\alpha]_D^{21}$ −76.4 (*c* 1.14, EtOH); lit.[22b] $[\alpha]_D^{20}$ −74.0 (*c* 0.2, EtOH)}; ν_{max} (film) 3331 (O–H), 2871 (C–H); δ_H (400 MHz,

$CDCl_3$) 1.30–1.60 (2H, m, CH_2), 1.63–1.95 (4H, m, CH_2), 2.36–2.54 (2H, m, C(1)*H*, C(3)H_A), 2.58–2.72 (1H, m, C(5)H_A), 2.90–3.01 (1H, m, C(5)H_B), 3.12–3.27 (1H, m, C(3)H_B), 3.36 (1H, br s, O*H*), 3.40–3.55 (1H, m, C(7a)*H*), 3.60–3.71 (2H, m, CH_2OH); δ_C (100 MHz, $CDCl_3$) 25.9, 26.6, 27.3 (*C*(2), *C*(6), *C*(7)), 43.8 (*C*(1)), 53.9, 55.5 (*C*(3), *C*(5)), 63.6 (*C*H_2OH), 66.5 (*C*(7a)); *m*/*z* (ESI$^+$) 142 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_8H_{16}NO^+$ ([M+H]$^+$) requires 142.1226; found 142.1229.

Method B: DIBAL-H (1.0 M in THF, 7.0 mL, 7.0 mmol) was added to a stirred solution of **23**·HOAc (150 mg, 0.7 mmol) in THF (15 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 18 h. 2.0 M aq NaOH (3.5 mL, 7.00 mmol) was then added and the resultant mixture was heated at reflux for 1 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 M aq NH_4OH) gave **1** as a pale yellow oil (11 mg, 17%, >99:1 dr, ~90% purity).

4.10. *tert*-Butyl (1*R*,3*R*,4*S*,7*S*,α*S*)-3,4-dihydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cycloheptanecarboxylate 26

OsO_4 (125 mg, 0.49 mmol) was added to a stirred solution of **20** (150 mg, 0.44 mmol) and TMEDA (95 μL, 0.62 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to rt over 15 min. The residue was then diluted with CH_2Cl_2 (40 mL) and tris(hydroxymethyl)phosphine (5.5 g, 45 mmol), Et_3N (1.2 mL, 8.8 mmol) and excess silica gel were added sequentially. The resultant mixture was left to stir at rt for 48 h, then filtered through a short plug of silica gel (eluent CH_2Cl_2) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **26** as a white solid (100 mg, 52%, >99:1 dr); mp: 102–104 °C; $[\alpha]_D^{25}$ −56.3 (*c* 1.00, $CHCl_3$); ν_{max} (ATR) 3401 (O–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(α)*Me*), 1.43 (9H, s, CMe_3), 1.55–1.70 (2H, m, C(2)H_A, C(5)H_A), 1.70–1.85 (2H, m, C(2)H_B, C(5)H_B), 1.82 (1H, app dt, *J* 9.8, 1.2, C(6)H_A), 2.06–2.23 (1H, m, C(6)H_B), 2.56 (1H, app dt, *J* 7.6, 4.3, C(1)*H*), 3.13 (1H, app dt, *J* 11.1, 4.3, C(7)*H*), 3.84 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.83–3.96 (3H, m, C(3)*H*, C(4)*H*, C(α)*H*), 4.05 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 7.18–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.5 (C(α)*Me*), 24.5 (*C*(6)), 28.1 (CMe_3), 29.7 (*C*(5)), 32.2 (*C*(2)), 46.4 (*C*(1)), 51.1 (NCH_2Ph), 57.5 (*C*(α)), 58.7 (*C*(7)), 71.3 (*C*(3)), 74.1 (*C*(4)), 80.4 (*C*Me$_3$), 126.4, 126.6, 127.8, 127.9, 128.0, 128.4 (*o*,*m*,*p*-*Ph*), 142.2, 144.3 (*i*-*Ph*), 174.7 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{37}NNaO_4^+$ ([M+Na]$^+$) requires 462.2615; found 462.2592.

4.11. *tert*-Butyl (1*R*,3*R*,4*S*,7*S*,α*S*)-3,4-dihydroxy-7-[*N*-(α-methylbenzyl)amino]cycloheptanecarboxylate 27

CAN (150 mg, 0.22 mmol) was added to a stirred solution of **26** (60 mg, 0.13 mmol, >99:1 dr) in MeCN/H_2O (5:1, 2.7 mL) and the resultant mixture was stirred at rt for 2 h. Then satd aq $NaHCO_3$ (5 mL) was added and the reaction mixture was left to stir at rt for 10 min. The resultant mixture was then extracted with EtOAc (3×10 mL) and the combined organic extracts were dried and concentrated in vacuo to give **27** as a white solid (42 mg, 97%, >99:1 dr); mp: 106–108 °C; $[\alpha]_D^{25}$ −26.8 (*c* 1.2, $CHCl_3$); ν_{max} (ATR) 3397 (O–H), 1715 (C=O); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.6, C(α)*Me*), 1.30–1.38 (1H, m, C(6)H_A), 1.58 (9H, s, CMe_3), 1.52–1.57 (1H, m, C(5)H_A), 1.56–1.66 (1H, m, C(5)H_B), 1.83–1.92 (2H, m, C(2)H_A, C(6)H_B), 1.93–2.00 (1H, m, C(2)H_B), 3.04–3.10 (2H, m, C(1)*H*, C(7)*H*), 3.70 (1H, app td, *J* 9.8, 3.5, C(4)*H*), 3.83 (1H, q, *J* 6.6, C(α)*H*), 4.06 (1H, app td, *J* 7.3, 3.5, C(3)*H*), 7.20–7.33 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 24.0 (C(α)*Me*), 27.9 (*C*(5)), 28.2 (CMe_3), 28.9 (*C*(2)), 29.4 (*C*(6)), 42.2 (*C*(1)), 55.4 (*C*(α)), 55.8 (*C*(7)), 70.4 (*C*(3)), 74.6 (*C*(4)), 80.5 (*C*Me$_3$), 126.5, 126.6, 128.3 (*o*,*m*,*p*-*Ph*), 146.4 (*i*-*Ph*), 174.1 (*C*O$_2$^{t}Bu); *m*/*z* (ESI$^+$) 350 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{32}NO_4^+$ ([M+H]$^+$) requires 350.2326; found 350.2321.

4.12. (1*R*,7a*S*)-1-(*tert*-Butoxycarbonyl)octahydropyrrolizin-4-ium acetate 28·HOAc

Step 1: $NaIO_4$ (220 mg, 1.03 mmol) was added to a solution of **26** (150 mg, 0.34 mmol, >99:1 dr) in MeOH (10 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) then concentrated in vacuo. The residue was dissolved in Et_2O (20 mL) and the resultant solution was filtered through a short plug of Celite® (eluent Et_2O) and then concentrated in vacuo.

Step 2: $Pd(OH)_2$/C (24 mg) was added to a stirred solution of the residue in degassed MeOH (5 mL) and AcOH (0.25 mL) and the resultant suspension was stirred at rt for 24 h under an atmosphere of H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo to give **28**·HOAc as pale yellow oil (350 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ −11.9 (*c* 0.7, $CHCl_3$); ν_{max} (ATR) 3401 (N–H), 1719 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, CMe_3), 1.72–1.85 (1H, m, CH_2), 1.88–1.96 (4H, m, CH_2, *Me*CO_2^-), 1.99–2.08 (1H, m, CH_2), 2.15–2.28 (3H, m, CH_2), 2.65 (1H, app q, *J* 8.1, C(1)*H*), 2.69–2.86 (2H, m, C(3)H_A, C(5)H_A), 3.52–3.64 (1H, m, C(3)H_B), 3.81–3.90 (1H, m, C(5)H_B), 4.25–4.34 (1H, m, C(7a)*H*); δ_C (100 MHz, $CDCl_3$) 21.9 (*Me*CO_2^-), 24.6, 29.2, 30.3 (*C*(2), *C*(6), *C*(7)), 27.9 (CMe_3), 50.1 (*C*(1)), 53.9, 54.5 (*C*(3), *C*(5)), 67.9 (*C*(7a)), 82.3 (*C*Me$_3$), 169.7 (*C*O$_2$^{t}Bu), 176.6 (*Me*CO_2^-); *m*/*z* (ESI$^+$) 212 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_2^+$ ([M+H]$^+$) requires 212.1645; found 212.1646.

4.13. (1*R*,2*S*,5*S*,6*S*,α*S*)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)-amino]-5-hydroxy-7-oxabicyclo[4.2.1]nonan-8-one 29

HBF_4 (48% in H_2O, 320 μL, 2.50 mmol) was added to a stirred solution of **20** (200 mg, 0.50 mmol, >99:1 dr) in CH_2Cl_2 (1.3 mL). After 5 min *m*-CPBA (70% in H_2O, 240 mg, 1.00 mmol) was added and the resultant mixture was left to stir at rt for 48 h. CH_2Cl_2 (20 mL), satd aq Na_2SO_3 (10 mL) and satd aq $NaHCO_3$ (10 mL) were added sequentially and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were then dried and concentrated in vacuo to give **29** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 4:1) gave **29** as a white solid (120 mg, 74%, >99:1 dr); mp 39–40 °C; $[\alpha]_D^{25}$ −30.2 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3433 (O–H), 1772 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.7, C(α)*Me*), 1.31–1.45 (1H, m, C(9)H_A), 1.60–1.80 (3H, m, C(4)H_A, C(3)H_A, O*H*), 1.93–2.02 (1H, m, C(3)H_B), 2.10–2.25 (2H, m, C(4)H_B, C(9)H_B), 2.00–2.62 (1H, app d, *J* 8.8, C(1)*H*), 2.86 (1H, app dt, *J* 10.3, 2.8, C(2)*H*), 3.83 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 4.01 (1H, d, *J* 14.6, NCH$_A$$H_B$Ph), 3.94–4.00 (1H, m, C(5)*H*), 4.04 (1H, q, *J* 6.7, C(α)*H*), 4.49 (1H, app q, *J* 8.1, C(6)*H*), 7.20–7.60 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.4 (C(α)*Me*), 25.7 (*C*(3)), 28.0 (*C*(4)), 31.5 (*C*(9)), 43.6 (*C*(1)), 51.0 (NCH_2Ph), 57.4 (*C*(α)), 62.1 (*C*(2)), 71.8 (*C*(5)), 81.9 (*C*(6)), 126.6, 126.8, 127.6, 128.2, 128.4 (*o*,*m*,*p*-*Ph*), 142.0, 144.0 (*i*-*Ph*), 178.5 (*C*(8)); *m*/*z* (ESI$^+$) 366 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{27}NNaO_3^+$ ([M+Na]$^+$) requires 388.1883; found 388.1871.

4.14. (1*R*,2*S*,5*S*,6*S*,α*S*)-2-[*N*-(α-Methylbenzyl)amino]-5-hydroxy-7-oxabicyclo[4.2.1]nonan-8-one 30

CAN (620 mg, 1.13 mmol) was added to a stirred solution of **29** (200 mg, 0.54 mmol, >99:1 dr) in MeCN/H_2O (5:1, 9 mL) and the resultant mixture was stirred at rt for 2 h. Satd aq $NaHCO_3$ (10 mL) was then added and the reaction mixture was left to stir at rt for 10 min. The resultant mixture was extracted with EtOAc (3×20 mL) and the combined organic extracts were dried and concentrated in

vacuo to give **30** in >95:5 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 3:1) gave **30** as a white solid (140 mg, 94%, >99:1 dr); mp 107–109 °C; $[\alpha]_D^{25}$ −64.2 (*c* 1.0, $CHCl_3$); ν_{max} (ATR) 3403 (O–H), 1756 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.6, C(α)*Me*), 1.20–1.30 (1H, m, C(3)H_A), 1.34–1.43 (1H, m, C(4)H_A), 1.89–2.05 (3H, m, C(3)H_B, C(4)H_B, C(9)H_A), 2.17 (2H, br s, N*H*, O*H*), 2.36 (1H, app dt, *J* 13.7, 8.6, C(9)H_B), 2.60 (1H, app dt, *J* 10.3, 3.8, C(2)*H*), 2.99 (1H, app dd, *J* 8.6, 3.8, C(1)*H*), 3.91–3.97 (1H, m, C(5)*H*), 4.02 (1H, q, *J* 6.6, C(α)*H*), 4.61 (1H, app d, *J* 8.1, C(6)*H*), 7.22–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.5 (*C*(9)), 26.0 (C(α)*Me*), 28.5 (*C*(3)), 28.7 (*C*(4)), 39.5 (*C*(1)), 54.7 (*C*(α)), 57.3 (*C*(2)), 70.6 (*C*(5)), 82.7 (*C*(6)), 126.7, 127.1, 128.6 (*o*,*m*,*p*-*Ph*), 145.4 (*i*-*Ph*), 177.8 (*C*(8)); *m*/*z* (ESI^+) 276 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{22}NO_3^+$ ($[M+H]^+$) requires 276.1594; found 276.1596.

4.15. (1*R*,3*S*,4*S*,7*S*,α*S*)-1-Hydroxymethyl-3,4-hydroxy-7-[*N*-benzyl-*N*-(α-methylbenzyl)amino]cycloheptane 31

$LiAlH_4$ (1.0 M in THF, 2.2 mL, 2.20 mmol) was added to a stirred solution of **29** (200 mg, 0.55 mmol, >99:1 dr) in THF (20 mL) at 0 °C. The resultant mixture was left stirring at 0 °C for 2 h, then 2.0 M aq NaOH (1.1 mL, 2.20 mmol) was added and the resultant mixture was left to stir at rt for 1 h. The resultant mixture was then filtered through Celite® (eluent THF), dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 95:5) gave **31** as a white solid (150 mg, 73%, >99:1 dr); mp 52–54 °C; $[\alpha]_D^{25}$+14.2 (*c* 1.03, $CHCl_3$); ν_{max} (ATR) 3356 (O–H); δ_H (400 MHz, $CDCl_3$) 1.23–1.43 (1H, m, C(5)H_A), 1.36 (3H, d, *J* 7.1, C(α)*Me*), 1.49–1.59 (1H, m, C(2)H_A), 1.59–1.71 (2H, m, C(1)*H*, C(2)H_B), 1.71–1.84 (1H, m, C(6)H_A), 1.83–1.94 (1H, m, C(5)H_B), 1.94–2.05 (1H, m, C(6)H_B), 3.00–3.11 (1H, m, C(7)*H*), 3.13–3.26 (2H, m, C(3)*H*, CH_AH_BOH), 3.27–3.38 (1H, m, C(4)*H*), 3.46–3.56 (1H, m, CH_AH_BOH), 3.38–4.00 (3H, br s, 3×O*H*), 3.80 (1H, d, *J* 13.6, NCH_AH_BPh), 3.89 (1H, d, *J* 13.6, NCH_AH_BPh), 3.95 (1H, q, *J* 7.1, C(α)*H*), 7.17–7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.1 (C(α)*Me*), 23.3 (*C*(6)), 30.4 (*C*(5)), 32.6 (*C*(2)), 39.6 (*C*(1)), 52.6 (NCH_2Ph), 55.7 (*C*(7)), 56.4 (*C*(α)), 65.3 (CH_2OH), 77.5 (*C*(3)), 79.0 (*C*(4)), 127.2, 127.4, 128.1, 128.3, 128.7, 129.0 (*o*,*m*,*p*-*Ph*), 139.6, 143.0 (*i*-*Ph*); *m*/*z* (ESI^+) 370 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{32}NO_3^+$ ($[M+H]^+$) requires 370.2377; found 370.2375.

4.16. (1*R*,7a*S*)-1-Hydroxymethylhexahydro-1*H*-pyrrolizine [(−)-trachelantamidine] 2

Method A – step 1: $NaIO_4$ (260 mg, 1.23 mmol) was added to a solution of **31** (150 mg, 0.41 mmol, >99:1 dr) in MeOH (15 mL) and the resultant suspension was stirred at rt for 1 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the resultant solution was concentrated in vacuo. The residue was dissolved in Et_2O (30 mL) and filtered through a short plug of Celite® (eluent Et_2O) and concentrated in vacuo.

Method A – step 2: $Pd(OH)_2$/C (28 mg) was added to a stirred solution of the resultant residue in degassed MeOH (5 mL) and AcOH (0.25 mL) and the resultant suspension was stirred at rt for 24 h under an atmosphere of H_2 (5 atm). The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 18 M aq NH_4OH) gave **2** as a colourless oil (35 mg, 62%, >99:1 dr); $[\alpha]_D^{20}$ −13.0 (*c* 0.2, EtOH); lit.[25] $[\alpha]_D^{20}$ −13.8 (*c* 1.28, EtOH); lit.[26a] $[\alpha]_D^{20}$ −10.3 (*c* 0.65, EtOH); lit.[26b] $[\alpha]_D^{25}$ −13.5 (*c* 2.0, EtOH); ν_{max} (ATR) 3349 (O–H), 2869 (C–H); δ_H (400 MHz, $CDCl_3$) 1.50–1.61 (1H, m, CH_2), 1.63–1.73 (1H, m, CH_2), 1.74–1.92 (2H, m, CH_2), 1.93–2.08 (3H, m, CH_2, C(1)*H*), 2.57 (1H, app td, *J* 9.8, 6.3, C(5)H_A), 2.63 (1H, app td, *J* 10.8, 6.6, C(3)H_A), 3.04 (1H, dt, *J* 10.8, 6.3, C(3)H_B), 3.22 (1H, ddd, *J* 9.8, 6.8, 3.2, C(5)H_B), 3.31 (1H, q, *J* 6.3, C(7a)*H*), 3.55–3.75 (2H, m, CH_2OH); δ_C (100 MHz, $CDCl_3$) 25.7 29.9 31.9 (*C*(2), *C*(6), *C*(7)), 48.3 (*C*(1)), 54.5, 54.7 (*C*(3), *C*(5)), 65.0 (CH_2OH), 67.7 (*C*(7a)); *m*/*z* (ESI^+) 142 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_8H_{16}NO^+$ ($[M+H]^+$) requires 142.1226; found 142.1226.

Method B: DIBAL-H (1.0 M in THF, 4.0 mL, 4.0 mmol) was added to a stirred solution of **28**·HOAc (80 mg, 0.40 mmol) in THF (8 mL) at 0 °C. The solution was allowed to warm to rt and stirred at rt for 18 h. 2.0 M aq NaOH (2.0 mL, 4.0 mmol) was then added and the resultant mixture was heated at reflux for 1 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 M NH_4OH) gave **2** as a pale yellow oil (35 mg, 62%, >99:1 dr).

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