Synthesis of Polyhydroxylated Pyrrolidines and Aziridinopyrrolidines from [4π+2π] Cycloadducts of Cyclopentadiene and Imines/2*H*-Azirines

José Enrique Rodriguez-Borges,*[a] Maria Luísa C. Vale,[a] Fabio Rizzo Aguiar,[a] Maria José Alves,*[b] Xerardo García-Mera*[c]

[a] CIQ, Departamento de Química, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre, 687, 4169-007 Porto, Portugal

[b] Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal

[c] Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Fax +34(981)594912; E-mail: qoxgmera@usc.es

Received 12 November 2007

Abstract: The synthesis of 2-functionalized 3,5-bis(hydroxymethyl)pyrrolidines from readily available polycyclic Diels–Alder adducts by a reaction sequence involving three steps is described. The same methodology has been applied to obtain the aziridine counterparts from the corresponding methyl 2-azatricyclo[3.2.1.0^{2,4}]oct-6-ene-4-carboxylates. The key steps in the synthetic strategy are dihydroxylation with osmium tetroxide/*N*-methylmorpholine *N*-oxide, oxidative cleavage with sodium periodate, and reduction using sodium borohydride or lithium aluminum hydride; overall yields ranged from 40–60%.

Keywords: asymmetric synthesis, cycloadditions, dihydroxylations, aziridinopyrrolidines, polyhydroxylated pyrrolidines

The synthesis of iminosugars is, at present, one of the most active fields in synthetic organic chemistry.[1] Due to the structural resemblance to sugars, these unique molecules have a tremendous potential in biological functions mediated by carbohydrates and have been postulated in the control of diabetes,[2,3] Gaucher's disease,[4,5] cancer,[3,6] HIV,[7] and viral infections like influenza.[3,5] In particular, DAB1 **1** and (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**2**), known pyrrolidinic 'glycomimetics', have been screened as potential inhibitors of HIV replication (Figure 1).[8] A survey of the recent literature reveals that the synthesis of 3,5-substituted prolines (or pyrrolidines) **3** is not a trivial task since there are only a few general routes to enantiomerically pure compounds and all of them are multistep procedures.[9]

1-Azabicyclo[3.1.0]hexanes are also important subunits found in a great variety of biologically active compounds.

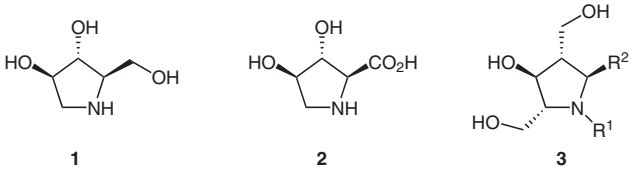
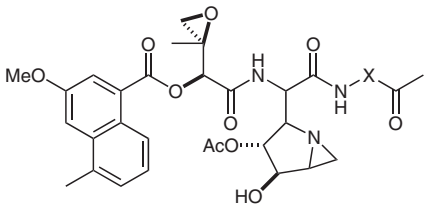


Figure 1

SYNTHESIS 2008, No. 6, pp 0971–0977
Advanced online publication: 28.02.2008
DOI: 10.1055/s-2008-1032196; Art ID: P13007SS



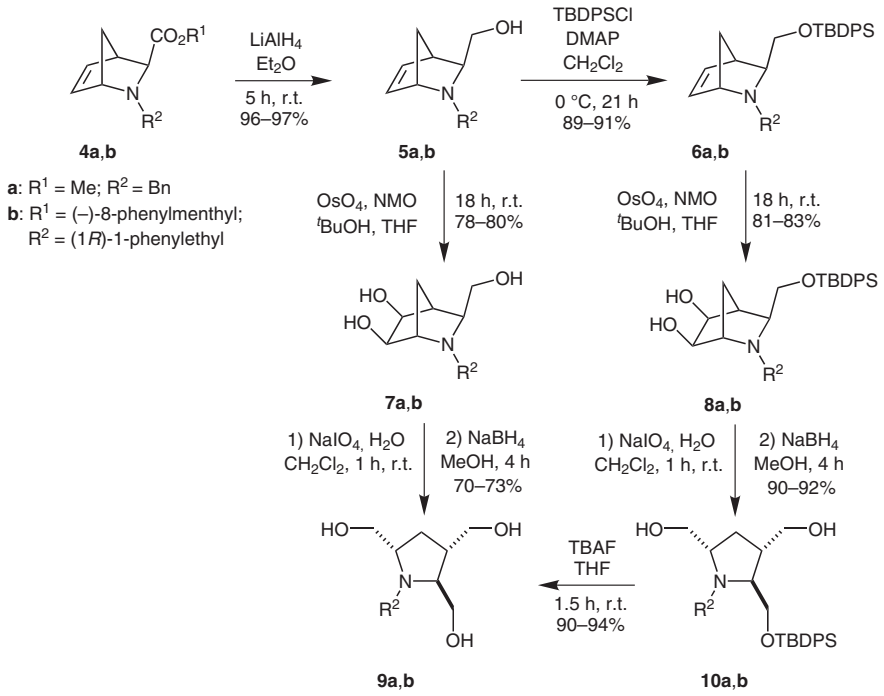
azinomycin A (X = CH_2)
azinomycin B (X = C=CHOH)

Figure 2

For example, azinomycins A and B, known for their potent *in vitro* cytotoxic activity, both possess the 1-azabicyclo[3.1.0]hexane unit (Figure 2), and it is thought that their action is related to the ability of the azirinopyrrolidine unit to promote covalent alkylation and cross-link formation of DNA.[10] Furthermore, aziridinopyrrolidines can be transformed into pyrrolidine or piperidine derivatives under different acidic conditions and so the usefulness of such compounds can be significantly improved.[11]

In this work we describe the synthesis of 2,3,5-tris(hydroxymethyl)pyrrolidines **9a**,**b**[12] and 5-functionalized 2,4-bis(hydroxymethyl)-1-azabicyclo[3.1.0]hexanes **14** and **15** from readily available polycyclic Diels–Alder adducts **4a**,[13] **4b**, **11a**, and **11b**[14] through dihydroxylation of the double bond followed by oxidative cleavage of the corresponding diols and reduction of the resulting intermediates. Although 3,6-bis(hydroxy)piperidinic compounds have been obtained previously from 2-azabicyclo[2.2.1]hept-5-enes by the same methodology,[15] as far as we know the synthesis of the corresponding pyrrolidinic analogues has not been described. The process can be applied to chiral materials with retention of configuration.

Racemic and chiral Diels–Alder cycloadducts **4a**,**b** obtained from imines and cyclopentadiene are known compounds,[13,16] used as starting materials for the synthesis of polyhydroxylated pyrrolidines. The absolute configuration of **4b** has now been established for the first time: the amino alcohol **5b**, obtained by reduction of **4b** with lithium aluminum hydride showed identical melting point and spectroscopic data (^{1}H and ^{13}C NMR), but opposite specific rotation to an authentic sample of (+)-**5b**. Compound



Scheme 1

(+)-**5b** was formed by reduction of one of the adducts obtained from the aza-Diels–Alder of (*S*)-phenylethyl imine of (–)-8-phenylmenthyl glyoxylate to cyclopentadiene,[16] and its configuration has been unambiguously assigned by X-ray crystallography (Figure 3).[17]

Scheme 1 encapsulates the reaction conditions used throughout the whole process. In the first step cycloadducts **4a**,**b** were reduced to the corresponding amino alcohols **5**, which were then, either directly or after protection of the hydroxy group with *tert*-butyldiphenylsilyl chloride, submitted to dihydroxylation using osmium tetroxide and *N*-methylmorpholine *N*-oxide. Oxidative cleavage of the resulting diols **7a**,**b** or **8a**,**b** and reduction of the intermediates was performed in one pot giving the final pyrrolidine compounds **9a**,**b** and **10a**,**b** in excellent yields.

The main goal of the 'parallel' synthesis of the silylated derivatives was to obtain the pyrrolidinic derivatives **10**, which allow selective functionalization at positions 3 and 5 prior to deprotection.

Aziridinopyrrolidines were obtained from cycloadducts **11a**,**b** using the methodology employed above for the synthesis of pyrrolidines: dihydroxylation giving products **12a**,**b** followed by oxidative cleavage to produce **13a**,**b** as solids in 72% and 73% yield, respectively. Simultaneous reduction of the dialdehydes and the ester functions could be achieved with lithium aluminum hydride. The method was applied to **13a** giving **14** in 95% yield. On the other hand, **13b** was selectively reduced with sodium borohydride in tetrahydrofuran to give the 'proline-type' derivative **15** in 34% yield (Scheme 2).

In conclusion, an efficient and a straightforward method for the synthesis of 2-functionalized 3,5-bis(hydroxymethyl)pyrrolidines, 'prolinol mimetics' as well as their aziridine counterparts, has been achieved.

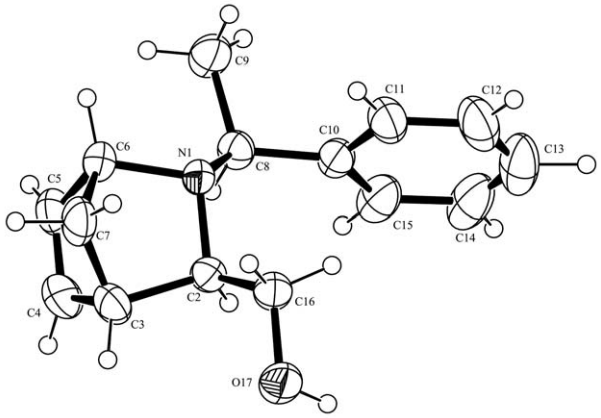
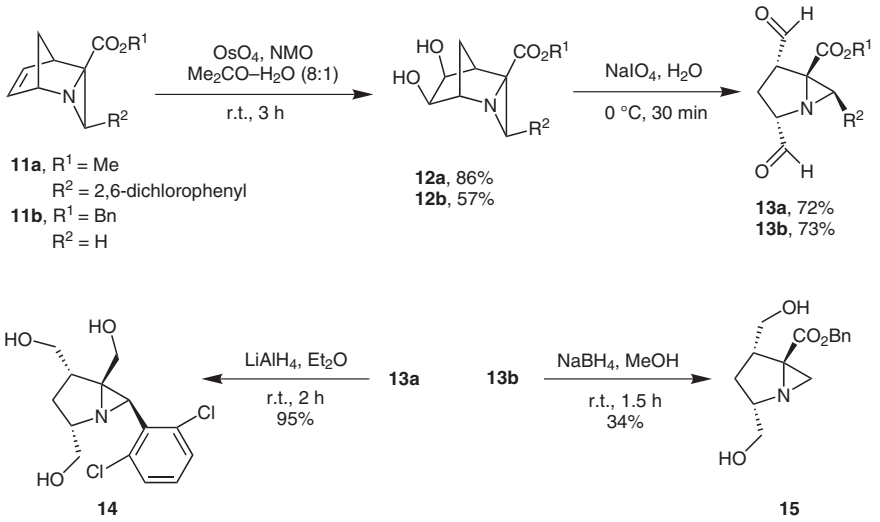


Figure 3 ORTEP projection of the molecular structure of compound (+)-**5b**

^{1}H NMR spectra and ^{13}C NMR spectra (75.47 MHz) were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer or on a Bruker WM AMX spectrometer using TMS as internal standard. IR spectra were recorded on a Bomem MB 104 or on a Perkin-Elmer 1640-FT spectrophotometer. Samples were run as Nujol mulls; oils were run as thin films. Melting points were determined on a Gallenkamp block and are uncorrected. Elemental analyses were obtained on a LECO-CHNS-932 analyzer (University of Minho) or on a Perkin-Elmer 240B microanalyzer (Microanalysis Service of the University of Santiago de Compostela). Optical rotations at the Na D-line were determined using a Perkin-Elmer 241 thermostated polarimeter. Flash column chromatography was performed on silica gel (Merck 60, 230–240 mesh) and analytical TLC on pre-coated silica gel plates (Merck 60 GF_{254}) using I_2 vapor and/or UV light for visualization. Dry column flash chromatography was carried out using Kieselgel 60 and a water-pump vacuum. Silica gel was purchased from Merck. All other chemicals used were of reagent grade and



Scheme 2

were obtained from Aldrich Chemical Co. Toluene was dried over Na followed by distillation. CH_2Cl_2 was dried over CaH_2 and distilled. Petroleum ether (bp 40–60 °C) (PE) was distilled before use. Compound **4a** was obtained by a literature procedure.[12] The syntheses of **4b**, **5a**, and **5b** were adapted from the literature.[18] Compounds **11a**[14b] and **11b**[19] are also known.

(–)-(1*R*,2*S*,5*R*)-8-Phenylmenthyl (1*S*,3*S*,4*R*)-2-[(1*R*)-1-Phenylethyl)]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (4b)

A soln of (*R*)-1-phenylethylamine (1.86 mL, 1.70 g, 14.0 mmol) in anhyd CH_2Cl_2 (10 mL) was added under argon to a stirred suspension of (–)-8-phenylmenthyl glyoxylate (4.04 g, 14.0 mmol) and 3 Å molecular sieves (10 g) in anhyd CH_2Cl_2 (50 mL) at 0 °C. When the addition was complete the mixture was cooled to –78 °C and treated successively with TFA (1.08 mL, 1.60 g, 14.0 mmol), $BF_3{\cdot}OEt_2$ (1.77 mL, 1.99 g, 14.0 mmol) and freshly distilled cyclopentadiene (2.3 mL, 28 mmol; ca. 2 equiv). After 6 h, sat. aq $NaHCO_3$ soln (28 mL) and then solid $NaHCO_3$ (3.3 g) were added. The mixture was allowed to reach r.t. and filtered through a pad of Celite and the organic layer of the resulting mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The pooled organic layers were washed with sat. aq $NaHCO_3$ (3 × 100 mL) and brine (3 × 100 mL) and dried (Na_2SO_4). Removal of the solvent on a rotary evaporator yielded a yellow oil that was purified by chromatography (silica gel, hexane–EtOAc, 3:1) to afford pure **4b** (5.09 g, 79%) as a yellow oil; R_f = 0.6.

$[\alpha]_D^{25}$ –66.5 (*c* 1, $CHCl_3$).

IR (NaCl): 3086, 3059, 2954, 2870, 1741 (C=O), 1600 (C=C), 1564 (Ar), 1494 (Ar), 1454, 1371, 1347, 1325, 1289, 1244, 1219, 1191, 1169, 1108, 1078, 1059, 1032, 1009, 982 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.67 [s, 3 H, 8′-C(CH_3)(CH_3)Ph], 0.70–0.88 (m, 3 H, menthyl), 0.81 (d, *J* = 6.3 Hz, 3 H, 5′-Me), 0.89 [s, 3 H, 8′-C(CH_3)(CH_3)Ph], 1.23 (dd, *J* = 10.1, 2.9 Hz, 1 H, H7$_{anti}$), 1.37 [d, *J* = 6.5 Hz, 3 H, NCH(CH_3)Ph], 1.48 (dd, *J* = 10.1, 2.5 Hz, 1 H, H7$_{syn}$), 1.30–1.40 (m, 1 H, menthyl), 1.70–1.79 (m, 2 H, menthyl), 1.80–1.93 (m, 2 H, menthyl), 1.99 (s, 1 H, H3$_{endo}$), 2.80 (br s, 1 H, H4), 3.03 [q, *J* = 6.5 Hz, 1 H, NC*H*(CH_3)Ph], 4.29 (br s, 1 H, H1), 4.50 (dt, *J* = 6.5, 2.3 Hz, 1 H, H1′), 6.28 (dd, *J* = 5.6, 1.4 Hz, 1 H, H5), 6.35 (dd, *J* = 5.6, 2.9 Hz, 1 H, H6), 6.98–7.38 (m, 10 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 22.2 (5′-CH_3), 23.7 [CH(*C*H_3)Ph], 24.8 (8′-CH_3), 27.3 (C3′), 28.3 (8′-CH_3), 31.5 (C5′), 35.0 (C7), 40.1 (C4′), 41.5 (C8′), 45.6 (C6′), 49.9 (C2′), 50.9 (C4), 63.6 [*C*H(CH_3)Ph], 64.4 (C1), 65.6 (C3), 75.1 (C1′), 125.2, 125.8, 127.5, 128.1, 128.3, 128.7 (arom CH), 133.9 (C5), 136.4 (C6), 145.4 (8′-C-*C*1$_{Ph}$), 151.9 [CH(CH_3)-*C*1$_{Ph}$], 172.9 [C(O)O].

Anal. Calcd for $C_{31}H_{39}NO_2$: C, 81.36; H, 8.59; N, 3.06. Found: C, 81.15; H, 8.62; N, 2.99.

{(1*S*,3*S*,4*R*)-2-[(1*R*)-1-Phenylethyl]-2-azabicyclo[2.2.1]hept-5-en-3-yl}methanol (5b); Typical Procedure

A soln of **4b** (1.70 g, 3.71 mmol) in anhyd Et_2O (10 mL) was added dropwise under argon to a suspension of $LiAlH_4$ (0.85 g, 22.3 mmol, ca. 6 equiv) in anhyd Et_2O (10 mL) at 0 °C. The mixture was stirred at r.t. for 12 h and MeOH (20 mL) and H_2O (100 mL) were added dropwise at 0 °C. The resulting mixture was extracted with EtOAc (4 × 100 mL) and the combined organic layers were washed with brine (100 mL) and dried (Na_2SO_4). Removal of solvent in a rotary evaporator left a yellow oil that was chromatographed (silica gel, hexane–EtOAc, 3:1) to afford the chiral auxiliary, (–)-8-phenylmenthol (0.84 g, 97%)[20] in the early fractions (R_f = 0.4) and **5b** (0.82 g, 96%) as a white solid, in the later fractions; mp 110–113 °C (hexane–Et_2O); R_f = 0.1.

$[\alpha]_D^{25}$ –41.8 (*c* 1, $CHCl_3$).

IR (KBr): 3272, 3214 (OH), 2988, 2863, 1454, 1375, 1323, 1181, 1034, 1011, 806 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.35 (dd, *J* = 8.5, 1.0 Hz, 1 H, H7$_{anti}$), 1.39 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.80 (d, *J* = 8.5 Hz, 1 H, H7$_{syn}$), 1.74–1.82 (m, 1 H, H3$_{endo}$), 2.02 (br s, 1 H, D_2O exch., OH), 2.70–2.77 (m, 2 H, C*H*HOH, H4), 3.05 (q, *J* = 6.5 Hz, 1 H, C*H*CH_3), 2.99–3.08 (m, 1 H, CH*H*OH), 4.15 (d, *J* = 1.4 Hz, 1 H, H1), 6.20 (dd, *J* = 5.6, 1.7 Hz, 1 H, H5), 6.46 (dd, *J* = 5.6, 3.3 Hz, 1 H, H6), 7.19–7.31 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 22.5 [CH(*C*H_3)], 45.3 (C7), 47.5 (C4), 63.3 [*C*H(CH_3)], 63.9 (C1), 64.3 (C3), 65.3 (CH_2OH), 127.8, 128.2, 128.8 (CH), 132.1 (C5), 138.1 (C6), 146.2 (C9).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.49; H, 8.41; N, 6.02.

(±)-{(3-*exo*)-2-Benzyl-2-azabicyclo[2.2.1]hept-5-en-3-yl}methanol (5a)

Following the typical procedure for **5b** using **7a**. Flash chromatography of the crude product (EtOAc–MeOH, 20:1) afforded pure **5a**[16] (97% yield); R_f = 0.1.

(–)-(1*S*,3*S*)-3-[(*tert*-Butyldiphenylsiloxy)methyl]-2-[(1*R*)-1-phenylethyl]-2-azabicyclo[2.2.1]hept-5-ene (6b); Typical Procedure

To a soln of **5b** (0.75 g, 3.27 mmol), DMAP (20 mg, 0.16 mmol, ca. 0.05 equiv), and Et_3N (0.91 mL, 0.66 g, 6.53 mmol) in anhyd CH_2Cl_2 (30 mL) was added dropwise TBDPSCl (1.69 mL, 1.79 g, 6.51 mmol) under argon at 0 °C. The mixture was stirred at r.t. for 21 h and EtOAc (50 mL) and H_2O (50 mL) were added. The aqueous layer was extracted with EtOAc (3 × 40 mL) and the combined organic layers were washed with brine (60 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a yellow oil, which was purified by chromatography (silica gel, hexane–EtOAc 6:1) to afford **6b** (1.39 g, 91%) as a yellow oil; R_f = 0.3.

$[\alpha]_D^{25}$ –4.1 (*c* 1, $CHCl_3$).

IR (NaCl): 2954, 2931, 2750, 1580, 1477, 1431, 1113, 818, 738 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.89 [s, 9 H, $C(CH_3)_3$], 1.19–1.26 (m, 1 H, $H7_{anti}$), 1.32 [d, *J* = 6.6 Hz, 3 H, $NCH(CH_3)Ph$], 1.60 (d, *J* = 8.3 Hz, 1 H, $H7_{syn}$), 1.87–1.92 (m, 1 H, H3), 2.98–3.09 [m, 4 H, $NCH(CH_3)Ph$, CH_2OSi, H4], 4.09 (br s, 1 H, H1), 6.16 (d, *J* = 5.4 Hz, 1 H, H5), 6.44–6.48 (m, 1 H, H6), 7.10–7.50 (m, 15 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 19.2 [$C(CH_3)_3$], 22.0 [$NCH(CH_3)Ph$], 26.8 [$C(CH_3)_3$], 44.1 (C7), 44.6 (C4), 63.1 [$NCH(CH_3)Ph$], 63.2 (C1), 64.3 (C3), 67.1 (CH_2OSi), 127.0, 127.4, 127.9, 128.1, 129.2, 129.3, 131.6, 135.3, 135.4, 135.5, 137.0 (C5, C6, arom CH), 129.5 and 133.9 (2 Si-$C1_{Ph}$), 135.2 (CHMe-$C1_{Ph}$).

Anal. Calcd for $C_{31}H_{37}NOSi$: C, 79.61; H, 7.97; N, 2.99. Found: C, 79.83; H, 8.09; N, 2.77.

(±)-(3-*exo*)-2-Benzyl-3-[(*tert*-butyldiphenylsiloxy)methyl]-2-azabicyclo[2.2.1]hept-5-ene (6a)

Following the typical procedure for **6b** using **5a**. Flash chromatography of the crude product (hexane–EtOAc, 1:1) afforded pure **6a** (89%) as an oil; R_f = 0.6.

IR (NaCl): 2956, 2936, 2748, 1583, 1479, 1436, 1118, 816, 737 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.04 [s, 9 H, $C(CH_3)_3$], 1.27 (d, *J* = 8.4 Hz, 1 H, $H7_{anti}$), 1.57 (d, *J* = 8.4 Hz, 1 H, $H7_{syn}$), 1.87–1.92 (m, 1 H, H3), 2.97 (br s, 1 H, H4), 3.37 (s, 2 H, NCH_2Ph), 3.39–3.47 (m, 1 H, H1), 3.60–3.65 (m, 2 H, OCH_2), 6.14 (dd, *J* = 5.4, 1.8 Hz, 1 H, H5), 6.48–6.44 (m, 1 H, H6), 7.10–7.80 (m, 15 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 19.0 [$C(CH_3)_3$], 26.5 [$C(CH_3)_3$], 45.0 (C7), 45.2 (C4), 58.6 (NCH_2Ph), 63.7 (C1), 65.0 (C3), 67.2 (CH_2OSi), 127.3, 128.0, 128.6, 129.5, 129.8, 129.9 (Si-$C1_{Ph}$), 132.4, 135.2, 136.0 (C5, C6, arom CH), 134.3 (NCH_2-$C1_{Ph}$).

Anal. Calcd for $C_{30}H_{35}NOSi$: C, 79.42; H, 7.78; N, 3.09. Found C 79.33; H, 7.65; N, 3.21.

(+)-(1*S*,3*S*,4*S*,5*S*,6*R*)-3-(Hydroxymethyl)-2-[(1*R*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane-5,6-diol (7b); Typical Procedure

To a soln of **5b** (0.39 g, 1.71 mmol) in *t*-BuOH (5 mL), THF (5 mL), and H_2O (1 mL), kept under magnetic stirring for 30 min, was slowly added NMO (0.27 g, 2.30 mmol) and OsO_4 (5 mM in dioxane–H_2O (3:1); 5.4 mL, 0.015 equiv). After stirring the mixture at r.t. for 18 h, EtOAc (20 mL) and H_2O (20 mL) were added and the resulting mixture was filtered through a pad of Celite and silica gel. The aqueous layer was extracted with EtOAc (2 × 20 mL); the combined organic phases were washed with H_2O (50 mL) and brine (60 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure yielded a brown oil, that was subjected to column chromatography (silica gel, CH_2Cl_2–MeOH, 9:2) affording **7b** (0.35 g, 78%) as a yellow oil; R_f = 0.5.

$[\alpha]_D^{25}$ +6.5 (*c* 1, $CHCl_3$).

IR (NaCl): 3386, 3181, 2977, 1454, 1386, 1034, 761 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.46 (d, *J* = 6.5 Hz, 3 H, $CHCH_3$), 1.72 (br s, 2 H, $H7_{syn}$, $H7_{anti}$), 2.03 (d, *J* = 5.1 Hz, 1 H, H4), 2.18 (br s, 1 H, H3), 2.43 (dd, *J* = 10.4, 6.5 Hz, 1 H, CH_aHOH), 2.75 (d, *J* = 10.4 Hz, 1 H, CH_bHOH), 2.80 (br s, 3 H, D_2O exch., 3 OH), 3.50 (br s, 1 H, H1), 3.57 (q, *J* = 6.5 Hz, 1 H, $CHCH_3$), 3.82 (d, *J* = 4.5 Hz, 1 H, H5), 4.29 (d, *J* = 4.5 Hz, 1 H, H6), 7.20–7.35 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 22.1 ($CHCH_3$), 29.5 (C7), 48.0 (C4), 60.2 (C3), 62.6 ($CHCH_3$), 63.5 (CH_2OH), 65.2 (C1), 67.7 (C5), 73.3 (C6), 127.9 ($C4_{Ph}$), 127.5 ($C3_{Ph}$, $C5_{Ph}$), 128.6 ($C2_{Ph}$, $C6_{Ph}$), 127.3 ($C1_{Ph}$).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.33; H, 8.24; N, 5.45.

(±)-(3-*exo*,5-*exo*,6-*exo*)-2-Benzyl-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane-5,6-diol (7a)

Following the typical procedure for **7b** using **5a**. Flash chromatography of the crude product (CH_2Cl_2–MeOH, 9:1) afforded pure **7a** (80%) as an oil; R_f = 0.2.

IR (NaCl): 3385 (OH), 3179, 2970, 1450, 1381, 1030 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.65 (d, *J* = 11.3 Hz, 1 H, $H7_{syn}$), 1.70 (d, *J* = 11.3 Hz, 1 H, $H7_{anti}$), 2.16 (d, *J* = 4.5 Hz, 1 H, H4), 2.23 (br s, 1 H, H3), 2.63 (br s, 3 H, D_2O exch., 3 OH), 3.11 (br s, 1 H, H1), 3.31 (br s, 2 H, CH_2OH), 3.73 (d, *J* = 13.3 Hz, 1 H, NCH_aHPh), 3.80 (d, *J* = 13.3 Hz, 1 H, $NCH H_bPh$), 3.87 (d, *J* = 5.7 Hz, 1 H, H5), 4.31 (d, *J* = 5.7 Hz, 1 H, H6), 7.20–7.35 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 30.4 (C7), 47.6 (C4), 55.1 (CH_2Ph), 64.0 (C3), 64.6 (CH_2OH), 66.2 (C1), 68.0 (C5), 73.6 (C6), 127.8 ($C4_{Ph}$), 129.1 ($C3_{Ph}$, $C5_{Ph}$), 129.4 ($C2_{Ph}$, $C6_{Ph}$), 140.6 ($C1_{Ph}$).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.62; H,, 7.55; N, 5.54.

(±)-(3-*exo*,5-*exo*,6-*exo*)-2-Benzyl-3-[(*tert*-butyldiphenylsiloxy)methyl]-2-azabicyclo[2.2.1]heptane-5,6-diol (8a)

Following the typical procedure for **7b** using **6a**. Flash chromatography of the crude product (hexane–EtOAc, 1:1) afforded pure **8a** (83%); R_f = 0.3.

IR (NaCl): 3240 (OH), 2920, 2850, 1470, 1380, 1080, 690 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.02 [s, 9 H, $C(CH_3)_3$], 1.48 (d, *J* = 10.5 Hz, 1 H, $H7_{anti}$), 1.61 (d, *J* = 10.5 Hz, 1 H, $H7_{syn}$), 2.14 (t, *J* = 6.3 Hz, 1 H, H4), 2.38 (br s, 1 H, H3), 2.51, 2.75 (2 br s, 2 H, D_2O exch., 2 OH), 2.93 (br s, 1 H, H1), 3.28, 3.31 (2 br s, 2 H, NCH_2Ph), 3.58–3.63 (m, 2 H, CH_2OSi), 3.84 (d, *J* = 6.0 Hz, 1 H, H5), 4.23 (d, *J* = 6.0 Hz, 1 H, H6), 7.18–7.69 (m, 15 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 19.6 [$C(CH_3)_3$], 27.3 [$C(CH_3)_3$], 29.6 (C7), 46.5 (C4), 54.7 (CH_2Ph), 63.3 (C3), 66.0 (C1), 66.1 (CH_2OSi), 68.3 (C5), 73.6 (C6), 127.7, 128.7, 128.6, 128.7, 129.3, 130.6, 130.7, 136.4, 136.5 (arom CH), 133.9, 133.7 (2 Si-$C1_{Ph}$), 140.0 ($C1_{Bn}$).

Anal. Calcd for $C_{30}H_{37}NO_3Si$: C, 73.88; H, 7.65; N, 2.87. Found: C, 74.03; H, 7.44; N, 2.99.

(–)-(1*S*,3*S*,4*S*,5*S*,6*R*)-3-[(*tert*-Butyldiphenylsiloxy)methyl]-2-[(1*R*)-1-phenylethyl]-2-azabicyclo[2.2.1]heptane-5,6-diol (8b)

Following the typical procedure for **7b** using **6b**. Flash chromatography of the crude product (hexane–EtOAc, 1:1) afforded pure **8b** (81%); R_f = 0.5.

$[\alpha]_D^{25}$ –1.1 (*c* 1, $CHCl_3$).

IR (NaCl): 3363 (OH), 2932, 2750, 1460, 1420, 1369, 1102, 750 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.88 [s, 9 H, $C(CH_3)_3$], 1.34 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.49 (d, *J* = 10.1 Hz, 1 H, $H7_{syn}$), 1.69 (d, *J* = 10.1 Hz, 1 H, $H7_{anti}$), 2.14 (dd, *J* = 9.9, 4.2 Hz, 1 H, CH_aHOSi), 2.47 (s, 1 H,

H4), 2.53 (dd, J = 9.9, 3.1 Hz, 1 H, CH_bHOSi), 2.90–3.30 (br s, 2 H, D_2O exch., 2 OH), 2.84 (t, J = 9.9 Hz, 1 H, H3), 3.38 (s, 1 H, H1), 3.46 (q, J = 6.6 Hz, 1 H, CHCH$_3$), 3.87 (d, J = 6.0 Hz, 1 H, H5), 4.27 (d, J = 6.0 Hz, 1 H, H6), 7.09–7.45 (m, 15 H, Ar).

^{13}C NMR ($CDCl_3$): δ = 19.5 (CH_3), 22.8 (CHCH_3), 27.0 [C(CH_3)$_3$], 29.0 (C7), 46.1 (C4), 60.4 (CHCH$_3$), 62.9 (C1), 65.5 (CH$_2$OSi), 66.1 (C3), 68.3 (C5), 73.9 (C6), 127.7, 127.8, 128.0, 128.4, 128.5, 129.6, 129.7, 135.7, 135.8, 134.1, 134.2 (arom CH, Si-C1$_{Ph}$), 146.0 (CHC1$_{Ph}$).

Anal. Calcd for $C_{31}H_{39}NO_3Si$: C, 74.21; H, 7.83; N, 2.79. Found: C, 74.42; H, 7.97; N, 2.92.

(–)-(2*S*,3*S*,5*S*)-2,3,5-Tris(hydroxymethyl)-1-[(1*R*)-1-phenylethyl]pyrrolidine (9b); Typical Procedures

Method A: To a suspension of silica gel (10 g) in CH_2Cl_2 (50 mL) was added a soln of $NaIO_4$ (2.54 g, 11.87 mmol) in H_2O (5 mL) under vigorous magnetic stirring. Then **7b** (3.12 g, 11.87 mmol) was added as a soln in CH_2Cl_2 (50 mL), keeping the reaction protected from light. After 1 h, solid Na_2SO_4 was added and the suspension was filtered and washed with CH_2Cl_2 (ca. 200 mL). The solvent was removed under vacuum, MeOH was added to the residue followed by $NaBH_4$ (1.38 g, 36.5 mmol) in small portions. After 4 h, the solvent was removed, EtOAc (50 mL) was added and the organic soln was washed with brine (100 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), and the solvent removed under reduced pressure to give an oil that was purified by flash chromatography (CH_2Cl_2–MeOH, 9:2) to afford pure **9b** (2.35 g, 73%) as a transparent oil; R_f = 0.3.

Method B. To a soln of **10b** (0.14 g, 0.28 mmol) in THF (5 mL), was added a 75 wt% soln of TBAF in H_2O (5 mL, 0.14 g, 0.40 mmol). The mixture was kept stirring at r.t. for 90 min. Hexane (50 mL) was added and the soln was dried (Na_2SO_4) and filtered. The solvent was removed under vacuum to give an oil that was purified by column chromatography (CH_2Cl_2–MeOH, 9:2) to afford pure **9b** (0.07 g, 94%) as a transparent oil.

$[\alpha]_D^{25}$ –11.3 (*c* 1, $CHCl_3$).

IR (NaCl): 3340 (OH), 2931, 1465, 1420, 1034, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.47 (d, J = 6.7 Hz, 3 H, CHCH_3), 1.49–1.57 (m, 1 H, H4$_{syn}$), 2.05–2.23 (m, 2 H, H4$_{anti}$, H3), 2.93 (br s, 3 H, D_2O exch., 3 OH), 3.10–3.69 (m, 8 H, 3 CH_2OH, H2, H5), 4.03 (q, J = 6.7 Hz, 1 H, CHCH$_3$), 7.21–7.38 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 20.2 (CHCH$_3$), 30.4 (C4), 41.9 (C3), 56.6 (CHCH$_3$), 61.1 (C5), 61.6 (C2), 63.3 (3-CH$_2$OH), 65.3 (2-CH$_2$OH), 66.3 (5-CH$_2$OH), 127.7 (C4$_{Ph}$), 127.9 (C3$_{Ph}$, C5$_{Ph}$), 129.0 (C2$_{Ph}$, C4$_{Ph}$), 144.3 (C1$_{Ph}$).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 68.16; H, 8.61; N, 5.13.

(±)-1-Benzyl-2,3,5-tris(hydroxymethyl)pyrrolidine (9a)

Following the typical procedures for **9b** (method A or method B) using either **7a** or **10a**. Flash chromatography of the crude product (hexane–EtOAc, 1:1) afforded pure **9a** (method A: 70% yield, method B: 90% yield) as a thick oil; R_f = 0.3.

IR (NaCl): 3386 (OH), 3180, 2975, 1458, 1390, 1037 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.55–1.64 (m, 1 H, H4$_{syn}$), 2.10–2.17 (m, 1 H, H4$_{anti}$), 2.21–2.33 (m, 1 H, H3), 3.05–3.11 (m, 1 H, H5), 3.17–3.20 (m, 1 H, H2), 3.28–3.72 (m, 9 H, 3 CH_2OH, 3 CH$_2$OH), 3.81 (d, J = 14.2 Hz, 1 H, CH_aHPh), 3.88 (d, J = 14.2 Hz, 1 H, CH_bHPh), 7.19–7.34 (m, 5 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 29.86 (C14), 42.3 (C3), 51.6 (CH$_2$Ph), 61.5 (2-CH$_2$OH), 62.5 (C2), 62.9 (3-CH$_2$OH), 65.6 (5-CH$_2$OH), 66.0 (C5), 127.5 (C4$_{Ph}$), 128.4 (C3$_{Ph}$, C5$_{Ph}$), 128.9 (C2$_{Ph}$, C6$_{Ph}$), 139.6 (C1$_{Ph}$).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.08; H, 8.21; N, 5.72.

(±)-1-Benzyl-2-[(*tert*-butyldiphenylsiloxy)methyl]-3,5-bis(hydroxymethyl)pyrrolidine (10a)

Following the typical procedure for **9b** (method A) using **8a**. Flash chromatography of the crude product (CH_2Cl_2–MeOH, 9:1) afforded pure **10a** (90% yield) as a transparent oil; R_f = 0.5.

IR (NaCl): 3454 (OH), 2931, 1291, 1109, 1077 cm^{-1} (OSi).

^{1}H NMR ($CDCl_3$): δ = 1.06 [s, 9 H, C(CH_3)$_3$], 1.68–1.74 (m, 1 H, H4$_{syn}$), 2.28–2.35 (m, 2 H, H3, H4$_{anti}$), 2.81 (br s, 2 H, D_2O exch., 2 OH), 3.08 (m, 1 H, H5), 3.33 (m, 1 H, H2), 3.43–3.80 (m, 7 H, 3-CH_2OH, 5-CH_2OH, 2-CH$_2$OSi, N-CH_aHPh), 3.88 (d, J = 14.1 Hz, 1 H, N-CHH_bPh), 7.11–7.70 (m, 15 H, Ar).

^{13}C NMR ($CDCl_3$): δ = 19.5 [C(CH_3)$_3$], 27.4 [C(CH$_3$)$_3$], 30.6 (C4), 42.0 (C3), 51.9 (CH$_2$Ph), 62.0 (3-CH$_2$OH), 63.6 (5-CH$_2$OH), 64.0 (C5), 65.1 (C2), 67.1 (CH$_2$OSi), 127.3 and 130.2 (Si-C4$_{Ph}$), 130.3 (Bn-C1$_{Ph}$), 128.1, 128.2 (Si-C3$_{Ph}$, Si-C5$_{Ph}$), 136.1 (Bn-C3$_{Ph}$, Bn-C5$_{Ph}$), 128.9, 128.3 (Si-C2$_{Ph}$, Si-C6$_{Ph}$), 136.2 (Bn-C2$_{Ph}$, Bn-C6$_{Ph}$), 133.5, 133.3 (Si-C1$_{Ph}$), 139.2 C$_q$ (Bn-C1$_{Ph}$).

Anal. Calcd for $C_{30}H_{39}NO_3Si$: C, 73.58; H, 8.03; N, 2.86. Found: C, 73.73; H, 7.86; N, 2.73.

(+)-(2*S*,3*S*,5*S*)-2-[(*tert*-Butyldiphenylsiloxy)methyl]-3,5-bis(hydroxymethyl)-1-[(1*R*)-1-phenylethyl]pyrrolidine (10b)

Following the typical procedure for **9b** (method A) using **8b**. Flash chromatography of the crude product (hexane–EtOAc, 1:6) afforded pure **10b** (92%) as a transparent oil; R_f = 0.4.

$[\alpha]_D^{25}$ +18.4 (*c* 1, $CHCl_3$).

IR (NaCl): 3386 (OH), 2931, 2863, 1465, 1426, 1386, 1284, 1107, 1084 cm^{-1} (OSi).

^{1}H NMR ($CDCl_3$): δ = 1.06 [s, 9 H, C(CH_3)$_3$], 1.25 (d, J = 6.6 Hz, 3 H, CHCH_3), 1.61–1.67 (m, 1 H, H4$_{syn}$), 2.20–2.40 (m, 2 H, H3, H4$_{anti}$), 2.45 (br s, 2 H, D_2O exch., 2 OH), 2.83 (dd, J = 11.1, 4.2 Hz, 1 H, 3-CH_aHOH), 3.01 (dd, J = 11.4, 2.1 Hz, 1 H, 3-CHH_bOH), 3.12 (br s, 1 H, H5), 3.30 (dd, J = 7.0, 3.2 Hz, 1 H, H2), 3.57–3.71 (m, 4 H, 5-CH_2OH, 2-CH_2OSi), 3.84 (q, J = 6.6 Hz, 1 H, CHCH$_3$), 7.10–7.69 (m, 15 H, ArH).

^{13}C NMR ($CDCl_3$): δ = 19.1 [C(CH_3)$_3$], 20.6 (CHCH$_3$), 26.9 [C(CH$_3$)$_3$], 30.7 (C4), 40.3 (C3), 57.1 (CHCH$_3$), 61.4 (C5), 62.5, 62.4 [5-CH$_2$OH, 3-CH$_2$OH], 65.5 (C2), 67.2 (CH$_2$OSi), 127.1, 127.4, 127.8, 128.5, 129.8 (Si-CH$_{Ph}$, CH-C3$_{Ph}$, CH-C5$_{Ph}$, CH-C4$_{Ph}$), 135.6 (CH-C2$_{Ph}$, CH-C6$_{Ph}$), 133.1 and 133.2 (Si-C1$_{Ph}$), 144.3 (CH-C1$_{Ph}$).

Anal. Calcd for $C_{31}H_{41}NO_3Si$: C, 73.91; H, 8.20; N, 2.78. Found: C, 74.15; H, 8.01; N, 2.66.

(±)-Methyl 7-(2,6-Dichlorophenyl)-5,6-dihydroxy-3-azatricyclo[3.2.1.0]octane-6-carboxylate (12a); Typical Procedure

Cycloadduct **11a** (1.0 g, 3.22 mmol) was dissolved in a mixture of acetone–H_2O (8:1, 50 mL), treated with NMO (0.76 g, 3.23 mmol) and a soln of OsO_4 in toluene (39 mM; 3.12 mL, 0.122 mmol). After 3 h at r.t., the reaction was quenched with 5% aq Na_2SO_3 (20 mL) and stirred for a further 20 min. The mixture was concentrated and extracted with EtOAc (4 × 100 mL); the combined organic extracts were dried ($MgSO_4$) and evaporated to give pure **12a** (0.95 g, 86%) as a transparent oil.

IR (Nujol): 3068, 1737, 1328, 1257, 1239, 1126, 1066, 758 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 1.96 (dm, J = 10.8 Hz, 1 H, H8), 2.28 (d, J = 10.8 Hz, 1 H, H8), 3.21 (s, 1 H, H3), 3.56 (s, 3 H, OMe), 3.62

(s, 1 H, H1), 3.82 (s, 1 H, H5), 3.94–3.98 (m, 1H), 3.98–4.03 (m, 1 H), 7.27 (t, *J* = 8.1 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 44.7 (C8), 46.5 (C3), 52.8 (OMe), 53.9 (C5), 57.1 (C_q), 66.0 (C1), 71.3 (C6), 71.4 (C7), 129.4 (CH), 130.3 (CH), 133.8 (C_q), 136.4 (C_q), 171.7 (CO).

Anal. Calcd for $C_{15}H_{15}Cl_2NO_4$: C, 52.33; H, 4.36; N, 4.07. Found: C, 52.13; H, 4.47; N, 4.08.

(±)-Benzyl 5,6-Dihydroxy-3-azatricyclo[3.2.1.0]octane-6-carboxylate (12b)

Following the typical procedure for **12a** using **11b** gave **12b** (57% yield) as a white solid; mp 156.3–157.3 °C.

IR (Nujol): 3410, 3090, 2990, 2980, 2850, 2748, 1733, 1502, 1460, 1340, 1245, 1168, 1145, 1118, 1061, 1015, 987, 964, 740, 690, 599 cm^{-1}.

^{1}H NMR (CD_3Cl): δ = 2.13 (br d, *J* = 10.5 Hz, 1 H, H8), 2.18 (br d, *J* = 10.5, 1 H, H8), 2.44 (d, *J* = 2.1 Hz, 1 H, H3), 2.62 (t, *J* = 2.1 Hz, 1 H, H3), 2.96 (s, 1 H, H5), 3.35 (s, 1 H, H1), 3.62 (d, *J* = 6.0 Hz, 1 H), 3.68 (d, *J* = 6.0 Hz, 1 H), 5.06 (d, *J* = 12.0 Hz, 1 H), 5.19 (d, *J* = 12.0 Hz, 1 H), 7.31 (s, 5 H, Ph).

^{13}C NMR (CD_3Cl) 42.9 (C5), 43.3 (C3), 45.6 (C8), 49.1 (Cq), 63.6 (C1), 67.1 (OCH_2), 69.5 (C6 or C7), 70.0 (C6 or C7), 128.1 (CH, Ph), 128.3 (CH, Ph), 128.5 (CH, Ph), 135.3 (Cq, Ph), 171.4 (CO).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18; N, 5.09. Found: C, 65.29; H, 6.22; N, 5.21.

(±)-Methyl 6-(2,6-Dichlorophenyl)-2,4-diformyl-1-azabicyclo[3.1.0]hexane-5-carboxylate (13a); Typical Procedure

A soln of $NaIO_4$ (0.59 g, 2.76 mmol) in H_2O (5.5 mL) was cooled in an ice-water bath and the diol **12a** (0.95 g, 2.76 mmol) was added in small portions over 10 min. The suspension was stirred at 0 °C for 20 min, then H_2O (10 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give pure **13a** (0.68 g, 72%) as a white solid; mp 128.3–132.3 °C (dec).

IR (Nujol): 3322, 1722, 1560, 1347, 1278, 1245, 1195, 1169, 1136, 1093, 1076, 1064, 1038, 988, 784, 769 cm^{-1}.

^{1}H NMR (CD_3Cl): δ = 2.04 (m, 1 H, H3), 2.50 (dt, *J* = 10.8, 14.4 Hz, 1 H, H3), 3.32 (s, 1 H, H6), 3.56 (s, 3 H), 3.95 (t, *J* = 9.6 Hz, 1 H, H4), 4.37 (dd, *J* = 7.5, 10.8, 1 H, H2), 7.16 (t, *J* = 7.2 Hz, 1 H, Ph), 7.29 (d, *J* = 7.2 Hz, 2 H, Ph), 10.21 (d, *J* = 1.2 Hz, 1 H, CHO), 10.23 (d, *J* = 1.8 Hz, 1 H, CHO).

^{13}C NMR (CD_3Cl): δ = 22.6 (C3), 40.8 (C6), 52.4 (C4), 53.0 (OMe), 55.2 (Cq), 71.4 (C2), 128.6 (CH, Ph), 129.4 (CH, Ph), 129.8 (Cq, Ph), 135.6 (Cq, Ph), 168.9 (CO), 197.5 (CHO), 197.9 (CHO).

Anal. Calcd for $C_{15}H_{13}Cl_2NO_4 \cdot H_2O$: C, 50.00; H, 4.17; N, 3.89. Found: C, 50.04; H, 4.18; N, 3.90.

(±)-Benzyl 2,4-Diformyl-1-azabicyclo[3.1.0]hexane-5-carboxylate (13b)

Following the typical procedure for **13a** using **12b** gave **13b** (73% yield) as a brownish solid; does not melt till 350 °C (dec).

IR (Nujol): 3409, 1733, 1339, 1243, 1144, 1060, 677 cm^{-1}.

^{1}H NMR (CD_3Cl): δ = 1.99 (s, 1 H, H6), 2.02–2.11 (m, 2 H, H3), 2.43 (s, 1 H, H6), 2.82 (dd, *J* = 9.0, 10.5 Hz, 1 H, H4), 4.17 (dd, *J* = 8.1, 10.8 Hz, 1 H, H2), 5.17 (d, *J* = 12.3, 1 H, OCH_2Ph), 5.29 (d, *J* = 12.3, 1 H, OCH_2Ph), 7.22–7.42 (m, 5 H, Ar), 9.85 (s, 1 H, CHO), 9.91 (s, 1 H, CHO).

^{13}C NMR (CD_3Cl): δ = 22.9 (C3), 30.7 (C6), 48.2 (C5), 50.8 (C4), 67.8 (OCH_2), 70.4 (C2), 128.4 (CH, Ph), 129.6 (CH, Ph), 128.7 (CH, Ph), 134.8 (Cq, Ph), 169.6 (CO), 197.9 (CHO), 198.0 (CHO).

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}NO_4$: 274.107933; found: 274.107819.

(±)-6-(2,6-Dichlorophenyl)-2,4,5-tris(hydroxymethyl)-1-azabicyclo[3.1.0]hexane (14)

Compound **13a** (0.42 g, 1.17 mmol) was solubilized in THF (20 mL) and cooled in an ice-water bath for 10 min. 1 M $LiAlH_4$ in Et_2O (10 mL, 10 mmol, 12.6 equiv) was slowly added. The mixture was allowed to reach r.t. and stirred for 2 h. Then the reaction was quenched by successive addition of H_2O (0.1 mL), 15% NaOH (0.1 mL), and H_2O (0.3 mL) and extracted with EtOAc (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give an oil that eventually crystallized ($CHCl_3$) to give **14** (0.35 g, 95%) as a white solid; mp 167–168 °C (dec).

IR (Nujol): 3308, 2900, 2854, 1461, 1429, 1377, 1039, 1025, 783 cm^{-1}.

^{1}H NMR (CD_3OD): δ = 1.25–1.45 (m, 1 H), 2.05–2.20 (m, 1 H), 3.02 (d, *J* = 12.0 Hz, 1 H), 3.26 (s, 1 H, H6), 3.60–3.70 (m, 2 H), 3.72–3.85 (m, 2 H), 3.89 (d, *J* = 12.0 Hz, 1 H), 4.02–4.15 (m, 2 H), 7.24 (t, *J* = 7.8 Hz, 1 H), 7.36 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (CD_3OD): δ = 30.5 (C3), 39.3 (C6), 43.7 (C4), 57.8 (Cq), 62.1 (CH_2), 63.9 (CH_2), 64.4 (CH_2), 66.7 (C2), 130.2 (CH, Ph), 133.3 (CH, Ph), 137.5 (Cq, Ph).

Anal. Calcd for $C_{14}H_{17}Cl_2NO_3$: C, 53.12; H, 5.08; N, 4.26. Found: C, 52.80; H, 5.34; N, 4.40.

Benzyl 2,4-Bis(hydroxymethyl)-1-azabicyclo[3.1.0]hexane-5-carboxylate (15)

A soln of **13b** in THF (20 mL) was cooled in an ice-water bath for 10 min. Solid $NaBH_4$ (0.48 g, 12.6 mmol, 8 equiv) was slowly added and the mixture was stirred at r.t. for 1.5 h. The mixture was concentrated and EtOAc (30 mL) was added. The mixture was then extracted with 10% aq citric acid (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and evaporated to give an oil that was subjected to dry flash chromatography (silica gel, EtOAc–EtOH, 1:1) to give **15** (0.034 g, 34%) as a transparent oil.

IR (film): 3363, 3045, 2929, 1729, 1455, 1393, 1268, 1215, 1174, 1134, 1089, 1043, 992, 911, 733, 699, 647 cm^{-1}.

^{1}H NMR (CD_3Cl): δ = 1.05 (dt, *J* = 13.5, 10.8 Hz, 1 H, H3), 1.76–1.85 (m, 1 H, H3), 2.04 (s, 1 H, H6), 2.12 (s, 1 H, H6), 2.80–3.10 (br s, 2 H, OH), 2.90–3.05 (m, 1 H, H4), 3.50–3.80 (m, 5 H, H2, 2 × CH_2OH), 5.08 (d, *J* = 12.0 Hz, 1 H, OCH_2), 5.24 (d, *J* = 12.0 Hz, 1 H, OCH_2), 7.34 (s, 5 H, Ph).

^{13}C NMR (CD_3Cl): δ = 27.0 (C4), 28.6 (C6), 41.6 (C3), 49.5 (C5), 63.1 (CH_2), 63.7 (CH_2), 63.9 (CH_2), 67.4 (CH_2), 128.3 (CH, Ph), 128.4 (CH, Ph), 128.6 (CH, Ph), 135.2 (C_q), 172.3 (CO).

Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.57; H, 6.88; N, 5.14. Found: C, 64.91; H, 6.91; N, 5.05.

Acknowledgment

The authors thank the Xunta de Galicia for financial support of this work under project PGIDIT05PXIB20301PR and Fundação para a Ciência e Tecnologia.

References and Notes

(1) (a) *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P.; Martin, O. R., Eds.; Wiley: Chichester, **2007**. (b) Cipolla, L.; Fernandes, M. R.; Gregori, M.; Airoldi, C.; Nicotra, F. *Carbohydr. Res.* **2007**, *342*, 1813. (c) Liao, W.; Ibrahem, I.; Cordova, A. *Chem. Commun.* **2006**, 674. (d) McDonnell, C.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *J. Org. Chem.* **2004**, *69*, 3565. (e) Cipolla, L.; LFerla, B.; Nicotra, F. *Curr. Top. Med. Chem.* **2003**, *3*, 485.

(2) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

(3) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

(4) (a) Cox, T.; Lachmann, R.; Hollack, C.; Aerts, J.; van Welly, S.; Hrebicek, M.; Platt, F.; Butters, T.; Dwek, R.; Moyses, C.; Gow, I.; Elstein, D.; Zimran, A. *Lancet* **2000**, *355*, 1481. (b) Kolter, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 1955.

(5) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N. *Nat. Rev. Drug Disc.* **2002**, *1*, 65.

(6) (a) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546. (b) Pearson, W. H.; Guo, L. *Tetrahedron Lett.* **2001**, *42*, 8267. (c) Fleet, G. W. J.; Nash, R. J.; Fellows, L. E.; Parekh, R. J.; Rademacher, T. W. *Chem. Lett.* **1986**, 1051.

(7) Greimel, P.; Spreitz, J.; Stutz, A. E.; Wrodniggm, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513.

(8) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F. X.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128.

(9) (a) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599. (b) Merino, I.; Laxmi, S. Y. R.; Flórez, J.; Barluenga, J. *J. Org. Chem.* **2002**, *67*, 648. (c) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862.

(10) (a) Coleman, R. S.; Kong, J.-She. *J. Am. Chem. Soc.* **1998**, *120*, 3538. (b) Coleman, R. S.; Richardson, T. E.; Carpenter, A. J. *J. Org. Chem.* **1998**, *63*, 5738.

(11) Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, *111*, 7500.

(12) Alves, M. J.; García-Mera, X.; Vale, M. L. C.; Santos, T. P.; Aguiar, F. R.; Rodríguez-Borges, J. E. *Tetrahedron Lett.* **2006**, *47*, 7595.

(13) Rodríguez-Borges, J. E.; García-Mera, X.; Fernández, F.; Lopes, V. H. C.; Magalhães, A. L.; Cordeiro, M. N. D. S. *Tetrahedron* **2005**, *61*, 10951.

(14) (a) Bhullar, P.; Gilchrist, T. L.; Maddocks, P. *Synthesis* **1997**, 271. (b) Alves, M. J.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 299. (c) Gilchrist, T. L.; Mendonça, R. *Synlett* **2000**, 1843. (d) Alves, M. J.; Bickeley, J. F.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1399. (e) Gilchrist, T. L. *Aldrichimica Acta* **2001**, *34*, 51. (f) Álvares, S. P.; Alves, M. J.; Azoia, N. G.; Bickeley, J. F.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1911. (g) Alves, M. J.; Gilchrist, T. L.; Fortes, A. G.; Lemos, A.; Martins, C. *Synthesis* **2005**, 5555. (h) Timen, A. S.; Fischer, A.; Somfai, P. *Chem Commun.* **2003**, 1150. (i) Timen, A. S.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958.

(15) (a) García, M. D.; Caamaño, O.; Fernández, F.; Abeijon, P.; Blanco, J. M. *Synthesis* **2006**, 73. (b) Bickley, J. F.; Gilchrist, T. L.; Mendonça, R. *ARKIVOC* **2002**, *(vi)*, 192; http://www.arkat-usa.org/home.

(16) Bailey, P. D.; Londesbrough, D. J.; Hancox, T. C.; Heffernan, J. D.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2543.

(17) The crystallographic data (excluding structure factors) for structure of **5b** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 240700. Empirical formula: $C_{30}H_{38}N_2O_2$. Formula weight: 458.62. Crystal size: $0.38 \times 0.37 \times 0.28$ mm^3. Crystal system: orthorhombic. Space group: $P2_12_12_1$. Unit cell dimensions: a = 10.912 (3) Å, b = 12.029 (3) Å, c = 19.685 (3) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$. D_{calc} = 1.179 mg/m^3. $F(000)$ = 992. $R1$ = 0.0710, $wR2$ 0 0.0772. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

(18) (a) Vale, M. L. C.; Rodríguez-Borges, J. E.; Caamaño, O.; Fernández, F.; García-Mera, X. *Tetrahedron* **2006**, *62*, 9475; and references cited therein. (b) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263.

(19) Alves, M. J.; Gilchrist, T. L. *Tetrahedron Lett.* **1998**, *39*, 7579.

(20) The recovered alcohol {$[\alpha]_D^{25}$ –25.2 (*c* 0.5, $CHCl_3$)}, was identified as (–)-8-phenylmenthol by comparison of its spectroscopic and specific rotation data with those reported in literature: Fernández, F.; García-Mera, X.; López, C.; Rodríguez, G.; Rodríguez-Borges, J. E. *Tetrahedron: Asymmetry* **2000**, *11*, 4805.