Preparation of optically active 3-substituted piperidines *via* ring expansion: synthesis of 4-amino- and 4-fluoro-1,4,5-trideoxy-1,5-imino-D-ribitol and 1,5-dideoxy-1,5-imino-D-ribitol

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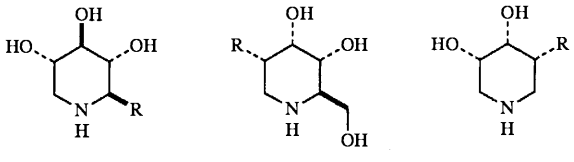
A new method for the preparation of optically active 3-substituted 1-benzylpiperidines based on the ring expansion of the 1-benzyl-2-(methylsulfonyloxymethyl)pyrrolidine 13 with various nucleophiles has been described. Synthesis of 4-amino-1,4,5-trideoxy-1,5-imino-D-ribitol 5, 1,4,5-trideoxy-4-fluoro-1,5-imino-D-ribitol 6 and 1,5-dideoxy-1,5-imino-D-ribitol 7 has also been achieved by a route which involves ring expansion of compound 13.

Introduction

Naturally occurring and designed polyhydroxylated piperidines have over recent years become synthetic targets of great interest.[1] Many of these compounds show specific and potent inhibitory activity against glycosidases due to their structural resemblance to sugars, and are therefore potentially useful for the treatment of diabetes,[2] viral infections including HIV,[2b,3] and cancer metastasis.[4] Deoxynojirimycin **1** is one of the most effective inhibitors of sweet almond β-glucosidase.[5] Bernotas *et al.*[1g] have recently reported that the inhibitory effect of de(hydroxymethyl)deoxynojirimycin **2** on sweet almond β-glucosidase was comparable to that of compound **1**, suggesting that the removal of the C-5 hydroxymethyl substituent of compound **1** has little effect on enzyme–substrate interaction. 1,2,5-Trideoxy-1,5-imino-D-*allo*-hexitol **3** which was recently isolated from *Morus alba*[6] showed a potent inhibitory activity against rat intestinal lactase and bovine liver β-galactosidase, and the D-*allo* isomer of compound **1** (compound **4**) retained a fair potency toward rat intestinal isomaltase and rat intestinal lactase.[1i] In the light of these observations we became interested in the synthesis of 1,5-dideoxy-1,5-imino-D-ribitols 5–7 having a substituent at C-4 that could function as a hydrogen-bond donor or acceptor with the enzyme.



1 R = CH_2OH
2 R = H

3 R = H
4 R = OH

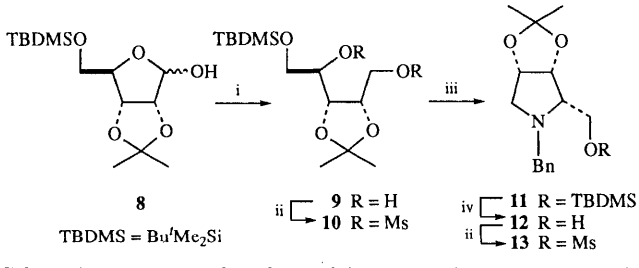
5 R = NH_2
6 R = F
7 R = OH

While the synthesis of compound **6** from 5-amino-5-deoxy-2,3-*O*-isopropylidene-D-ribonolactam has been described by Di *et al.*,[1h] their synthetic route is not applicable for the introduction of various substituents at C-4. Very recently, Cossy *et al.*[7] have reported that treatment of 1-alkyl-2-(hydroxymethyl)pyrrolidines with trifluoroacetic anhydride (TFAA) in tetrahydrofuran (THF), followed by addition of triethylamine and sodium hydroxide, led to the formation of 1-alkyl-3-hydroxypiperidines *via* ring expansion with a high enantiomeric excess. This method, however, is limited to the introduction of a hydroxy group only in the piperidine ring.

Results and discussion

In this report, we describe a new method for the preparation of optically active 3-substituted 1-benzylpiperidines based on the ring expansion of 1-benzyl-2-(methylsulfonyloxymethyl)-pyrrolidine and its application for the synthesis of compounds **5**–**7**.

First, 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribose **8**, prepared from D-ribose in two steps according to a published procedure,[8] was reduced with $NaBH_4$ in EtOH at room temperature for 2 h to give the diol **9** in 93% yield, which was subsequently treated with methanesulfonyl chloride in pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) at room temperature for 2 h to give the bis(methanesulfonate) **10** in 98% yield. Cyclisation of compound **10** with benzylamine (4 mol equiv.) in toluene at reflux temperature for 24 h afforded the 1-benzylpyrrolidine **11** with inversed stereochemistry at C-2 in 85% yield. Deprotection of the *tert*-butyldimethylsilyl group of compound **11** with tetrabutylammonium fluoride (TBAF) in THF at room temperature for 2 h gave the 1-benzyl-2-(hydroxymethyl)pyrrolidine **12** in 93% yield. Treatment of compound **12** with methanesulfonyl chloride in pyridine under the same reaction conditions for compound **10** produced the 1-benzyl-2-(methylsulfonyloxymethyl)pyrrolidine **13** in 98% yield (Scheme 1).



8
TBDMS = Bu^tMe_2Si

9 R = H
10 R = Ms

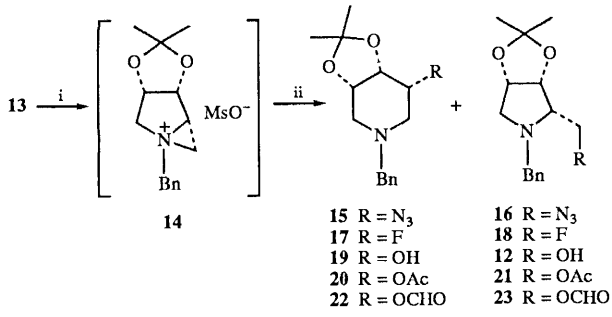
11 R = TBDMS
12 R = H
13 R = Ms

Scheme 1 *Reagents and conditions:* i, $NaBH_4$, EtOH, room temp., 2 h; ii, MsCl, pyridine, DMAP, room temp., 2 h; iii, $PhCH_2NH_2$ (4 mol equiv.), toluene, reflux, 24 h; iv, TBAF, THF, room temp., 2 h

We expected that compound **13** would form a reactive intermediate, aziridinium ion **14**, in solution upon heating, which could undergo ring expansion by an S_N2-type attack of various nucleophiles at the methine carbon of the aziridinium ring to give the 3-substituted piperidines. On the other hand, displacement of nitrogen from the methylene group of the aziridinium ring by nucleophiles would also give the 2-substituted pyrrolidines (Scheme 2). The reactions of mesyl

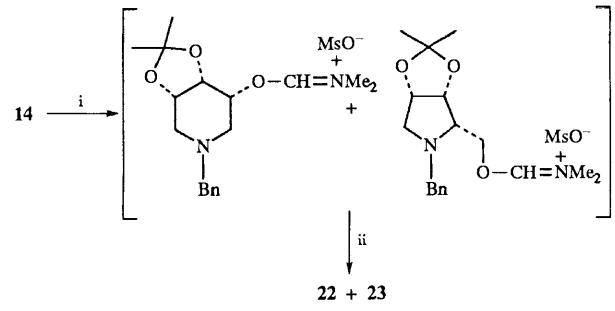
Table 1 Reaction of 1-benzyl-3,4-(isopropylidenedioxy)pyrrolidine-2-methyl methanesulfonate **13** with various nucleophiles (see Scheme 2)

Entry	R	Nucleophile (mol equiv.)	Solvent	Temp. (T/°C)	Time (t/h)	Products (% yield)
1	N_3	NaN_3 (1.1)	DMF	100	1	**15** (63), **16** (28)
2	N_3	LiN_3 (1.1)	DMF	100	1	**15** (61), **16** (29)
3	N_3	NaN_3 (1.1)	DMF	60	15	**15** (64), **16** (24)
4	N_3	LiN_3 (1.1)	DMF	60	15	**15** (65), **16** (25)
5	F	TBAF (3.0)	THF	reflux	5	**17** (54), **18** (26)
6	OH	NaOH (3.0)	Water–1,4-dioxane	reflux	0.5	**19** (55), **12** (40)
7	OAc	AcONa (2.0)	DMF	100	0.5	**20** (52), **21** (34)
8	OCHO	DMF	DMF	100	5	**22** (38), **23** (50)



Scheme 2 *Reagents and conditions:* i, reflux; ii, Nu:

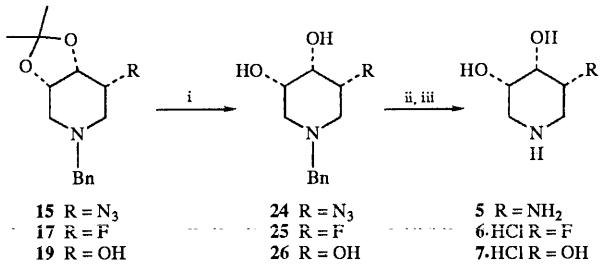
ester **13** with various nucleophiles were investigated, and the results are summarized in Table 1. Treatment of compound **13** with NaN_3 (1.1 mol equiv.) in *N*,*N*-dimethylformamide (DMF) at 100 °C for 1 h afforded diastereoisomerically pure compound **15** in 63% yield along with compound **16** in 28% yield (entry 1). Either replacement of NaN_3 with LiN_3 or changes of reaction temperature and reaction time in this reaction had little effect on the total yield and the product selectivity (**15**:**16** ratio) (entries 2–4). Similar reactions of compound **13** with TBAF (3.0 mol equiv.) in THF, NaOH (3.0 mol equiv.) in water–1,4-dioxane and AcONa (2.0 mol equiv.) in DMF, respectively, afforded diastereoisomerically pure compounds **17**, **19** and **20** in 52–55% yield along with isomers **18**, **12** and **21** in 26–40% yield (entries 5–7). It is especially noteworthy that DMF itself could serve as a nucleophile in this reaction (Scheme 3). When



Scheme 3 *Reagents and conditions:* i, DMF, 100 °C; ii, water

compound **13** was heated in DMF at 100 °C for 5 h, diastereoisomerically pure products **22** (38%) and **23** (50%) were obtained after standard work-up (entry 8). The formation of compounds **22** and **23** further indicates that this reaction must proceed *via* the highly reactive intermediate **14** since DMF is much less nucleophilic compared with other nucleophiles.

Treatment of compounds **15**, **17** and **19** with 80% trifluoroacetic acid (TFA) at room temperature for 2 h produced **24**–**26** in quantitative yield. As expected, the *meso* compound **26** was optically inactive, thus confirming that the absolute configuration at C-3 in the piperidine ring was (*R*). Reductive hydrogenation of compounds **24**–**26** in the presence of 10% Pd–C in MeOH afforded 4-amino-1,4,5-trideoxy-1,5-imino-D-ribitol **5** (98%), 1,4,5-trideoxy-4-fluoro-1,5-imino-D-ribitol **6** (95%) and 1,5-dideoxy-1,5-imino-D-ribitol **7** (99%), respectively (Scheme 4). Compounds **6** and **7** were converted into stable,



Scheme 4 *Reagents and conditions:* i, TFA–water (4:1), room temp., 2 h; ii, H_2 (3 atm), 10% Pd–C, MeOH, 40 °C, 1 h; iii, 1 mol dm^{-3} HCl (2 mol equiv.), MeOH (for **6**·HCl and **7**·HCl)

crystalline hydrochloride salts by treatment with 1 mol dm^{-3} HCl (2 mol equiv.) in MeOH.

Compounds **5**–**7** have been evaluated for their inhibitory effects on the replication of human immunodeficiency virus type 1 (HIV-1) in MT-4 cells in the National Institute of Health (Seoul, Korea) and were found to be inactive at concentrations up to 100 μg cm^{-3}.

In conclusion, we have shown that the 2-(methylsulfonyloxymethyl)pyrrolidine **13** undergoes ring expansion with a wide range of nucleophiles to give the various optically active 3-substituted piperidines. Application of this ring-expansion reaction to the synthesis of compounds **5**–**7** starting from D-ribose as the key-step reaction has also been accomplished.

Experimental

Mps were determined on an Electrothermal F500MA digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. ^1H NMR spectra were recorded on a Varian Unity 300 spectrometer. The chemical shifts are reported in parts per million (ppm) relative to internal tetramethylsilane in $CDCl_3$ or $(CD_3)_2SO$ ([$^2H_6$]DMSO) and to sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) in D_2O. ^{13}C NMR spectra were recorded on a Varian Unity 300 spectrometer at 75.4 MHz. When $CDCl_3$ or [$^2H_6$]DMSO was used as solvent, it served as the internal standard at δ_C 77.0 or 39.5, respectively. When D_2O was used, DSS (δ −1.6) was added as the internal standard. *J*-Values are given in Hz. Electron-impact mass spectra (EI-MS) were obtained on a VG Quattro mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Analytical TLC was performed on Merck silica gel 60F-254 glass plates. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh). Elemental analyses were performed on a Carlo Erba 1106 elemental analyser.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribitol 9

To a stirred solution of 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribose **8** (7.21 g, 23.7 mmol) in EtOH (60 cm^3) at 0 °C was added $NaBH_4$ (0.90 g, 23.8 mmol) in portions and the mixture was allowed to warm to room temp. After 2 h, NH_4Cl (1.27 g, 23.8 mmol) was added to it and the reaction mixture was stirred for an additional 5 min. The inorganic salt was filtered off and the filtrate was evaporated to dryness to give an oily residue. The residue was passed through a short silica gel column with EtOAc as eluent to give the *title compound* **9** (6.77 g, 93%) as a solid, mp 80.2–80.8 °C (from EtOAc) (Found: C, 54.9; H, 9.8. $C_{14}H_{30}O_5Si$ requires C, 54.85; H, 9.85%); $[\alpha]_D^{25}$ −2.4 (*c* 2.7, MeOH); ν_{max}(KBr)/cm^{-1} 3279 (OH); δ_H($CDCl_3$) 0.10 [6 H, s, $Si(CH_3)_2$], 0.92 [9 H, s, $(CH_3)_3$], 1.34 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 3.09 (1 H, d, *J* 4.2, OH), 3.20 (1 H, br s, OH), 3.66 (1 H, dd, $J_{5,5'}$ 9.9, $J_{5,4}$ 5.7, 5-H), 3.73–3.93 (3 H, m, 2-H and CH_2OH), 3.86 (1 H, dd, $J_{5',5}$ 9.9, $J_{5',4}$ 3.0, 5'-H), 4.06 (1 H, dd, $J_{3,4}$ 9.6, $J_{3,2}$ 6.0, 3-H) and 4.36 (1 H, m, 4-H); δ_C($CDCl_3$) −5.43, −5.35, 18.33, 25.20, 25.88, 27.83, 60.92, 64.39, 69.49, 76.53, 77.65 and 108.48; *m*/*z* 291 (M^+ − CH_3, 3%) and 75 (100).

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribitol 1,4-bis(methanesulfonate) 10

To a stirred solution of the diol **9** (4.66 g, 15.2 mmol) and DMAP (0.75 g, 6.1 mmol) in anhydrous pyridine (30 cm^3) at 0 °C was added MsCl (3.8 cm^3, 48.7 mmol) dropwise and the mixture was allowed to warm to room temp. After 2 h, the reaction mixture was evaporated to dryness, coevaporated with toluene twice, and dissolved in CH_2Cl_2 (50 cm^3). The CH_2Cl_2 solution was washed successively with water (30 cm^3), 5% HCl (30 cm^3), saturated aq. $NaHCO_3$ (30 cm^3) and brine (30 cm^3). The organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was passed through a short silica gel column with EtOAc–hexane (1 : 1) as eluent to give the *title compound* **10** (6.91 g, 98%) as an oil (Found: C, 41.6; H, 7.35. $C_{16}H_{34}O_9S_2Si$ requires C, 41.55; H, 7.4%); $[\alpha]_D^{25}$ −34.4 (*c* 1.8, MeOH); ν_{max}(neat)/cm^{-1} 1177 and 1356 (SO_2); δ_H($CDCl_3$) 0.11 [6 H, s, $Si(CH_3)_2$], 0.91 [9 H, s, $(CH_3)_3$], 1.37 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 3.08 (3 H, s, SO_2CH_3), 3.14 (3 H, s, SO_2CH_3), 3.89 (1 H, dd, $J_{5,5'}$ 12.0, $J_{5,4}$ 4.2, 5-H), 4.07 (1 H, dd, $J_{5',5}$ 12.0, $J_{5',4}$ 2.7, 5'-H), 4.32–4.56 (4 H, m, 1-H_2, 2- and 3-H) and 4.81 (1 H, ddd, $J_{4,3}$ 6.9, $J_{4,5}$ 4.2, $J_{4,5'}$ 2.7, 4-H); δ_C($CDCl_3$) −5.59, −5.50, 18.31, 25.36, 25.79, 27.52, 37.56, 39.23, 62.61, 68.49, 74.08, 75.03, 79.64 and 109.42; *m*/*z* 447 (M^+ − 1 − CH_3, 2%) and 153 (100).

(2*S*,3*R*,4*S*)-1-Benzyl-2-(*tert*-butyldimethylsiloxymethyl)-3,4-(isopropylidenedioxy)pyrrolidine 11

To a stirred solution of the bis(methanesulfonate) **10** (5.75 g, 12.4 mmol) in anhydrous toluene (60 cm^3) was added benzylamine (5.4 cm^3, 49.7 mmol) and the mixture was heated at reflux temp. for 24 h under nitrogen. After cooling of the mixture to room temp., the precipitated salts were filtered off and the filtrate was evaporated to dryness. The residue was purified by flash column chromatography on silica gel with diethyl ether–hexane (1 : 9) as eluent to give the *title compound* **11** (4.00 g, 85%) as an oil (Found: C, 66.95; H, 9.2; N, 3.6. $C_{21}H_{35}NO_3Si$ requires C, 66.8; H, 9.35; N, 3.7%); $[\alpha]_D^{25}$ +82.0 (*c* 2.1, MeOH); δ_H($CDCl_3$) 0.07 (3 H, s, $SiCH_3$), 0.08 (3 H, s, $SiCH_3$), 0.90 [9 H, s, $(CH_3)_3$], 1.30 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 2.01 (1 H, dd, $J_{5\alpha.5\beta}$ 11.1, $J_{5\alpha.4}$ 4.5, 5-H^α), 2.40 (1 H, dd, *J* 5.7, $J_{2,3}$ 4.5, 2-H), 3.01 (1 H, d, $J_{5\beta.5\alpha}$ 11.1, 5-H^β), 3.21 (1 H, d, *J* 13.8, NCH), 3.84 (1 H, dd, *J* 10.5 and 5.7, CHOSi), 4.01 (1 H, dd, *J* 10.5 and 5.7, CHOSi), 4.25 (1 H, d, *J* 13.8, NCH), 4.55 (1 H, dd, $J_{4,3}$ 6.6, $J_{4.5\alpha}$ 4.5, 4-H), 4.64 (1 H, dd, $J_{3,4}$ 6.6, $J_{3,2}$ 4.5, 3-H) and 7.19–7.35 (5 H, m, ArH); δ_C($CDCl_3$) − 5.36, 18.33, 25.67, 25.96, 26.38, 58.07, 59.92, 62.31, 69.49, 78.00, 80.91, 111.12, 126.70, 128.12, 128.55 and 139.04; *m*/*z* 377 (M^+ − 1, 2%) and 91 (100).

(2*S*,3*R*,4*S*)-[1-Benzyl-3,4-(isopropylidenedioxy)pyrrolidin-2-yl]-methanol 12

To a stirred solution of the pyrrolidine **11** (4.55 g, 12.0 mmol) in THF (25 cm^3) at 0 °C was added TBAF (18.0 mmol, 18 cm^3 of a 1.0 mol dm^{-3} solution in THF) dropwise over a period of 5 min and the mixture was allowed to warm to room temp. After 2 h, the reaction mixture was evaporated to dryness and the residue was dissolved in CH_2Cl_2 (40 cm^3). The CH_2Cl_2 solution was washed with water (40 cm^3), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc–hexane (1 : 1) as eluent to give the *title compound* **12** (2.95 g, 93%) as an oil (Found: C, 68.25; H, 8.1; N, 5.25. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.05; N, 5.3%); $[\alpha]_D^{25}$ +101.8 (*c* 1.9, MeOH); ν_{max}(neat)/cm^{-1} 3440 (OH); δ_H($CDCl_3$) 1.32 (3 H, s, CH_3), 1.54 (3 H, s, CH_3), 2.13 (1 H, dd, $J_{5\alpha.5\beta}$ 10.8, $J_{5\alpha.4}$ 4.5, 5-H^α), 2.36 (1 H, td, *J* 4.5 and 4.5, 2-H), 3.08 (1 H, d, $J_{5\beta.5\alpha}$ 10.8, 5-H^β), 3.22 (1 H, d, *J* 13.5, NCH), 3.95 (2 H, m, CH_2OH), 4.05 (1 H, d, *J* 13.5, NCH), 4.59 (1 H, dd, $J_{4,3}$ 6.3, $J_{4.5\alpha}$ 4.5, 4-H), 4.71 (1 H, dd, $J_{3,4}$ 6.3, $J_{3,2}$ 4.5, 3-H) and 7.18–7.37 (5 H, m, ArH); δ_C($CDCl_3$) 25.02, 26.17, 56.73, 58.77, 59.72, 67.18, 77.87, 81.86, 111.39, 126.96, 128.20, 128.67 and 138.05; *m*/*z* 264 (M^+ + 1, 2%) and 91 (100).

(2*S*,3*R*,4*S*)-[1-Benzyl-3,4-(isopropylidenedioxy)pyrrolidin-2-yl]-methyl methanesulfonate 13

Following the procedure outlined for compound **10**, the 2-(hydroxymethyl)pyrrolidine **12** (4.00 g, 15.2 mmol) was mesylated using MsCl and DMAP in pyridine to give the *title compound* **13** (5.07 g, 98%) as an oil (Found: C, 56.05; H, 6.9; N, 3.95. $C_{16}H_{23}NO_5S$ requires C, 56.3; H, 6.8; N, 4.1%); $[\alpha]_D^{25}$ +82.9 (*c* 2.2, MeOH); ν_{max}(neat)/cm^{-1} 1177 and 1360 (SO_2); δ_H($CDCl_3$) 1.32 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 2.18 (1 H, dd, $J_{5\alpha.5\beta}$ 11.1, $J_{5\alpha.4}$ 4.5, 5-H^α), 2.68 (1 H, ddd, *J* 7.5, 4.8 and 4.2, 2-H), 3.00 (3 H, s, SO_2CH_3), 3.10 (1 H, d, $J_{5\beta.5\alpha}$ 11.1, 5-H^β), 3.34 (1 H, d, *J* 13.8, NCH), 4.00 (1 H, d, *J* 13.8, NCH), 4.34 (1 H, dd, *J* 9.9 and 4.8, $CHOSO_2$), 4.50 (1 H, dd, *J* 9.9 and 7.5, $CHOSO_2$), 4.62 (1 H, dd, $J_{4,3}$ 6.3, $J_{4.5\alpha}$ 4.5, 4-H), 4.70 (1 H, dd, $J_{3,4}$ 6.3, $J_{3,2}$ 4.2, 3-H) and 7.20–7.37 (5 H, m, ArH); δ_C($CDCl_3$) 25.38, 26.25, 37.03, 57.74, 59.55, 65.95, 68.38, 77.96, 80.19, 111.64, 127.13, 128.33, 128.40 and 137.90; *m*/*z* 341 (M^+, 0.5%) and 91 (100).

(3*R*,4*R*,5*S*)-3-Azido-1-benzyl-4,5-(isopropylidenedioxy)piperidine 15 and (2*S*,3*R*,4*S*)-2-azidomethyl-1-benzyl-3,4-(isopropylidenedioxy)pyrrolidine 16

A mixture of the 2-(methylsulfonyloxymethyl)pyrrolidine **13** (1.00 g, 2.9 mmol) and NaN_3 (0.21 g, 3.2 mmol) in anhydrous DMF (15 cm^3) was heated at 100 °C for 1 h under nitrogen. The resulting suspension was cooled to room temp. and evaporated to dryness under reduced pressure. The residue was treated with water (25 cm^3) and the aqueous phase was extracted with EtOAc (3 × 40 cm^3). The organic phase was washed with brine (40 cm^3), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc–hexane (1 : 5) as eluent to give the two isomeric *title compounds* **15** and **16**.

Compound **15** was obtained as an oil (0.53 g, 63%) (Found: C, 62.3; H, 7.05; N, 19.2. $C_{15}H_{20}N_4O_2$ requires C, 62.5; H, 7.0; N, 19.45%); $[\alpha]_D^{25}$ +22.2 (*c* 2.4, MeOH); ν_{max}(neat)/cm^{-1} 2098 (N_3); δ_H($CDCl_3$) 1.38 (3 H, s, CH_3), 1.54 (3 H, s, CH_3), 2.12 (1 H, dd, $J_{6\alpha.6\beta}$ 11.1, $J_{6\alpha.5}$ 9.6, 6-H^α), 2.34 (1 H, dd, $J_{2\alpha.2\beta}$ 10.8, $J_{2\alpha.3}$ 5.4, 2-H^α), 2.81 (1 H, ddd, $J_{2\beta.2\alpha}$ 10.8, $J_{2\beta.3}$ 5.1, 2-H^β), 2.88 (1 H, ddd, $J_{6\beta.6\alpha}$ 11.1, $J_{6\beta.5}$ 7.8, $J_{6\beta.2\beta}$ 1.5, 6-H^β), 3.57 (2 H, s, NCH_2), 3.64 (1 H, ddd, $J_{3,2\alpha}$ 5.4, $J_{3,2\beta}$ 5.1, $J_{3,4}$ 3.0, 3-H), 4.21 (1 H, ddd, $J_{5,6\alpha}$ 9.6, $J_{5,6\beta}$ 7.8, $J_{5,4}$ 4.5, 5-H), 4.38 (1 H, dd, $J_{4,5}$ 4.5, $J_{4,3}$ 3.0, 4-H) and 7.20–7.37 (5 H, m, ArH); δ_C($CDCl_3$) 26.41, 28.09, 51.09, 54.98, 56.61, 62.03, 72.77, 73.55, 109.73, 127.31, 128.32, 128.80 and 137.49; *m*/*z* 273 (M^+ − CH_3, 2%) and 91 (100).

Compound **16** was obtained as an oil (0.24 g, 28%) (Found: C, 62.25; H, 7.1; N, 19.3. $C_{15}H_{20}N_4O_2$ requires C, 62.5; H, 7.0; N, 19.45%); $[\alpha]_D^{25}$ +110.3 (*c* 2.3, MeOH); ν_{max}(neat)/cm^{-1} 2101 (N_3); δ_H($CDCl_3$) 1.34 (3 H, s, CH_3), 1.54 (3 H, s, CH_3), 2.13 (1 H, dd, $J_{5\alpha.5\beta}$ 11.1, $J_{5\alpha.4}$ 4.5, 5-H$^{\alpha}$), 2.41 (1 H, ddd, *J* 8.7, 4.5 and 4.5, 2-H), 3.08 (1 H, d, $J_{5\beta.5\alpha}$ 11.1, 5-H$^{\beta}$), 3.28 (1 H, d, *J* 13.5, NCH), 3.43 (1 H, dd, *J* 12.0 and 4.5, CHN_3), 3.68 (1 H, dd, *J* 12.0 and 8.7, CHN_3), 3.98 (1 H, d, *J* 13.5, NCH), 4.61 (1 H, dd, $J_{4.3}$ 6.3, $J_{4.5\alpha}$ 4.5, 4-H), 4.68 (1 H, dd, $J_{3.4}$ 6.3, $J_{3.2}$ 4.5, 3-H) and 7.20–7.35 (5 H, m, ArH); δ_C($CDCl_3$) 25.47, 26.25, 49.68, 57.53, 59.64, 66.80, 77.82, 80.46, 111.56, 127.04, 128.29, 128.36 and 138.14; *m*/*z* 273 ($M^+ - CH_3$, 1.5%) and 91 (100).

(3*R*,4*S*,5*S*)-1-Benzyl-3-fluoro-4,5-(isopropylidenedioxy)-piperidine 17 and (2*R*,3*R*,4*S*)-1-benzyl-2-fluoromethyl-3,4-(isopropylidenedioxy)pyrrolidine 18

To a stirred solution of compound **13** (1.00 g, 2.9 mmol) in THF (15 cm^3) was added TBAF (8.7 mmol, 8.7 cm^3 of 1.0 mol dm^{-3} solution in THF) and the mixture was heated at reflux temp. for 5 h. The reaction mixture was cooled to room temp. and evaporated to dryness. The residue was treated with water (20 cm^3) and the aqueous phase was extracted with EtOAc (3 × 30 cm^3). The organic phase was washed with brine (30 cm^3), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc–hexane (1:8) as eluent to give the two isomeric *title compounds* **17** and **18**.

Compound **17** was obtained as an oil (0.42 g, 54%) (Found: C, 67.75; H, 7.7; N, 5.15. $C_{15}H_{20}FNO_2$ requires C, 67.9; H, 7.6; N, 5.3%); $[\alpha]_D^{25}$ −38.8 (*c* 1.6, MeOH); ν_{max}(neat)/cm^{-1} 1064 (C–F); δ_H($CDCl_3$) 1.39 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 2.26 (1 H, dd, $J_{6\alpha.6\beta}$ 11.4, $J_{6\alpha.5}$ 8.7, 6-H$^{\alpha}$), 2.51 (1 H, ddd, $J_{2\alpha.2\beta}$ 10.5, $J_{2\alpha.3}$ 8.7, 2-H$^{\alpha}$), 2.79–2.92 (2 H, m, 2- and 6-H$^{\beta}$), 3.59 (2 H, s, NCH_2), 4.28 (1 H, ddd, $J_{5.6\alpha}$ 8.0, $J_{5.4}$ 5.0, 5-H), 4.42 (1 H, ddd, $J_{4.5}$ 5.0, $J_{4.3}$ 3.9, 4-H), 4.77 (1 H, dddd, $J_{3.F}$ 45.9, $J_{3.2\alpha}$ 8.7, $J_{3.2\beta}$ 6.6, $J_{3.4}$ 3.9, 3-H) and 7.20–7.37 (5 H, m, ArH); δ_C($CDCl_3$) 26.40, 27.87, 51.33 (d, $^2J_{2.F}$ 25.6, C-2), 54.66 (C-6), 61.92 (d, ^4J 1.2, CH_2Ph), 72.95 (d, $^2J_{4.F}$ 14.9, C-4), 73.23 (d, $^3J_{5.F}$ 5.2, C-5), 86.60 (d, $^1J_{3.F}$ 181.0, C-3), 110.29, 127.32, 128.33, 128.86 and 137.48; *m*/*z* 265 (M^+, 3.5%), 232 (37) and 91 (100).

Compound **18** was obtained as an oil (0.20 g, 26%) (Found: C, 67.65; H, 7.8; N, 5.2. $C_{15}H_{20}FNO_2$ requires C, 67.9; H, 7.6; N, 5.3%); $[\alpha]_D^{25}$ +75.8 (*c* 2.7, MeOH); ν_{max}(neat)/cm^{-1} 1099 (C–F); δ_H($CDCl_3$) 1.31 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 2.12 (1 H, dd, $J_{5\alpha.5\beta}$ 11.4, $J_{5\alpha.4}$ 4.5, 5-H$^{\alpha}$), 2.65 (1 H, m, 2-H), 3.07 (1 H, d, $J_{5\beta.5\alpha}$ 11.4, 5-H$^{\beta}$), 3.34 (1 H, d, *J* 13.8, NCH), 4.11 (1 H, d, *J* 13.8, NCH), 4.60 (1 H, dd, $J_{4.3}$ 6.3, $J_{4.5\alpha}$ 4.5, 4-H), 4.61 (1 H, m, CHF), 4.68 (1 H, dd, $J_{3.4}$ 6.3, $J_{3.2}$ 4.5, 3-H), 4.82 (1 H, m, CHF) and 7.20–7.38 (5 H, m, ArH); δ_C($CDCl_3$) 25.44, 26.25, 57.76 (d, $^4J_{5.F}$ 2.5, C-5), 59.30 (CH_2Ph), 66.68 (d, $^2J_{2.F}$ 20.7, C-2), 78.19 (C-4), 80.53 (d, $^3J_{3.F}$ 6.7, C-3), 83.66 (d, ^1J 163.5, CH_2F), 111.62, 126.95, 128.22, 128.55 and 138.21; *m*/*z* 265 (M^+, 22%) and 91 (100).

(3*R*,4*R*,5*S*)-1-Benzyl-4,5-(isopropylidenedioxy)piperidin-3-ol 19 and (2*S*,3*R*,4*S*)-[1-benzyl-3,4-(isopropylidenedioxy)pyrrolidin-2-yl]methanol 12

A stirred solution of compound **13** (1.00 g, 2.9 mmol) in 1,4-dioxane (10 cm^3) was treated with aq. 1 mol dm^{-3} NaOH (9 cm^3) and the mixture was heated at reflux temp. for 30 min. After cooling to room temp., the reaction mixture was evaporated to dryness. The residue was treated with water (20 cm^3) and the aqueous phase was extracted with EtOAc (3 × 30 cm^3). The organic phase was washed with brine (30 cm^3), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with EtOAc–hexane (1:1) as eluent to give the two isomeric *title compounds* **19** and **12**.

Compound **19** was obtained as an oil (0.42 g, 55%), which solidified upon storage in a refrigerator for a few days, mp 67.2–68.8 °C (Found: C, 68.15; H, 8.2; N, 5.1. $C_{15}H_{21}NO_3$ requires C, 68.4; H, 8.05; N, 5.3%); $[\alpha]_D^{25}$ −31.5 (*c* 1.5, MeOH); ν_{max}(KBr)/cm^{-1} 3456 (OH); δ_H($CDCl_3$) 1.36 (3 H, s, CH_3), 1.55 (3 H, s, CH_3), 2.36 (1 H, dd, $J_{2\alpha.2\beta}$ 10.8, $J_{2\alpha.3}$ 8.4, 2-H$^{\alpha}$), 2.44 (2 H, dd, $J_{6\alpha.6\beta}$ 11.7, $J_{6\alpha.5}$ 5.7, 6-H$^{\alpha}$ and OH), 2.60 (1 H, dd, $J_{2\beta.2\alpha}$ 10.8, $J_{2\beta.3}$ 3.6, 2-H$^{\beta}$), 2.73 (1 H, dd, $J_{6\beta.6\alpha}$ 11.7, $J_{6\beta.5}$ 4.7, 6-H$^{\beta}$), 3.56 (2 H, s, NCH_2), 3.88 (1 H, ddd, $J_{3.2\alpha}$ 8.4, $J_{3.4}$ 3.9, $J_{3.2\beta}$ 3.6, 3-H), 4.18–4.28 (2 H, m, 4- and 5-H) and 7.20–7.37 (5 H, m, ArH); δ_C($CDCl_3$) 26.28, 27.46, 54.69, 55.02, 62.03, 66.62, 72.88, 74.60, 109.31, 127.24, 128.29, 128.92 and 137.54; *m*/*z* 263 (M^+, 12%) and 91 (100).

Compound **12** was obtained as an oil (0.31 g, 40%), which was identical with that mentioned above in all aspects.

(3*R*,4*S*,5*S*)-1-Benzyl-4,5-(isopropylidenedioxy)piperidin-3-yl acetate 20 and (2*S*,3*R*,4*S*)-[1-benzyl-3,4-(isopropylidenedioxy)pyrrolidin-2-yl]methyl acetate 21

A mixture of compound **13** (1.00 g, 2.9 mmol) and AcONa (0.48 g, 5.8 mmol) in anhydrous DMF (15 cm^3) was heated at 100 °C for 30 min under nitrogen. The reaction mixture was cooled to room temp. and evaporated to dryness under reduced pressure. The residue was treated with water (20 cm^3) and the aqueous phase was extracted with EtOAc (3 × 30 cm^3). The organic phase was washed with brine (30 cm^3), dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel with diethyl ether–hexane (1:2) as eluent to give the two isomeric *title compounds* **20** and **21**.

Compound **20** was obtained as an oil (0.46 g, 52%) (Found: C, 66.9; H, 7.8; N, 4.45. $C_{17}H_{23}NO_4$ requires C, 66.85; H, 7.6; N, 4.6%); $[\alpha]_D^{25}$ −9.8 (*c* 0.7, MeOH); ν_{max}(neat)/cm^{-1} 1746 (CO); δ_H($CDCl_3$) 1.35 (3 H, s, CH_3), 1.55 (3 H, s, CH_3), 2.10 (3 H, s, Ac), 2.14 (1 H, dd, $J_{6\alpha.6\beta}$ 10.5, $J_{6\alpha.5}$ 4.2, 6-H$^{\alpha}$), 2.32 (1 H, dd, $J_{2\alpha.2\beta}$ 9.8, $J_{2\alpha.3}$ 5.4, 2-H$^{\alpha}$), 2.76 (1 H, dd, $J_{2\beta.2\alpha}$ 9.8, $J_{2\beta.3}$ 5.4, 2-H$^{\beta}$), 2.86 (1 H, dd, $J_{6\beta.6\alpha}$ 10.5, $J_{6\beta.5}$ 6.9, 6-H$^{\beta}$), 3.56 (2 H, s, NCH_2), 4.25 (1 H, ddd, $J_{5.6\beta}$ 6.9, $J_{5.4}$ 4.5, $J_{5.6\alpha}$ 4.2, 5-H), 4.41 (1 H, dd, $J_{4.5}$ 4.5, $J_{4.3}$ 4.2, 4-H), 5.13 (1 H, ddd, $J_{3.2\alpha} = J_{3.2\beta}$ = 5.4, $J_{3.4}$ 4.2, 3-H) and 7.20–7.38 (5 H, m, ArH); δ_C($CDCl_3$) 21.15, 26.47, 28.26, 50.80, 54.89, 62.00, 68.56, 72.77, 73.09, 109.87, 127.25, 128.31, 128.79, 137.64 and 170.32; *m*/*z* 306 (M^+ + 1, 2.5%) and 91 (100).

Compound **21** was obtained as an oil (0.30 g, 34%) (Found: C, 66.7; H, 7.65; N, 4.5. $C_{17}H_{23}NO_4$ requires C, 66.85; H, 7.6; N, 4.6%); $[\alpha]_D^{25}$ +92.7 (*c* 1.4, MeOH); ν_{max}(neat)/cm^{-1} 1741 (CO); δ_H($CDCl_3$) 1.32 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 2.07 (3 H, s, Ac), 2.07 (1 H, dd, $J_{5\alpha.5\beta}$ 11.1, $J_{5\alpha.4}$ 4.2, 5-H$^{\alpha}$), 2.48 (1 H, td, *J* 5.6, 4.2, 2-H), 3.05 (1 H, d, $J_{5\beta.5\alpha}$ 11.1, 5-H$^{\beta}$), 3.25 (1 H, d, *J* 13.5, NCH), 4.11 (1 H, d, *J* 13.5, NCH), 4.38 (2 H, d, *J* 6.0, CH_2O), 4.60 (1 H, dd, $J_{4.3}$ 6.6, $J_{4.5\alpha}$ 4.2, 4-H), 4.66 (1 H, dd, $J_{3.4}$ 6.6, $J_{3.2}$ 4.2, 3-H) and 7.20–7.38 (5 H, m, ArH); δ_C($CDCl_3$) 21.00, 25.63, 26.31, 57.61, 59.51, 62.76, 66.01, 78.01, 80.57, 111.55, 126.92, 128.21, 128.32, 138.26 and 170.81; *m*/*z* 290 ($M^+ - CH_3$, 3%), 91 (92) and 43 (100).

(3*R*,4*S*,5*S*)-1-Benzyl-4,5-isopropylidenedioxy)piperidin-3-yl formate 22 and (2*S*,3*R*,4*S*)-[1-benzyl-3,4-(isopropylidenedioxy)-pyrrolidin-2-yl]methyl formate 23

A solution of compound **13** (1.00 g, 2.9 mmol) in anhydrous DMF (15 cm^3) was heated at 100 °C for 5 h. The reaction mixture was diluted with water (15 cm^3) and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography on silica gel with EtOAc–hexane (1:6) as eluent to give the two isomeric *title compounds* **22** and **23**.

Compound **22** was obtained as an oil (0.32 g, 38%) (Found: C, 65.7; H, 7.25; N, 4.7. $C_{16}H_{21}NO_4$ requires C, 65.95; H, 7.25; N, 4.8%); $[\alpha]_D^{25}$ −10.0 (*c* 0.2, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1727 (CO); δ_H($CDCl_3$) 1.36 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 2.15 (1 H, dd, $J_{6\alpha.6\beta}$ 10.8, $J_{6\alpha.5}$ 4.2, 6-H$^{\alpha}$), 2.37 (1 H, dd, $J_{2\alpha.2\beta}$ 9.9, $J_{2\alpha.3}$ 5.3, 2-H$^{\alpha}$), 2.81 (1 H, dd, $J_{2\beta.2\alpha}$ 9.9, $J_{2\beta.3}$ 5.3, 2-H$^{\beta}$), 2.88 (1 H, dd, $J_{6\beta.6\alpha}$ 10.8, $J_{6\beta.5}$ 6.9, 6-H$^{\beta}$), 3.56 (1 H, d, *J* 12.0, NCH), 3.58 (1

H, d, J 12.0, NCH), 4.27 (1 H, ddd, $J_{5,6\beta}$ 6.9, $J_{5,4}$ 4.5, $J_{5,6\alpha}$ 4.2, 5-H), 4.42 (1 H, dd, $J_{4,5}$ 4.5, $J_{4,3}$ 4.2, 4-H), 5.27 (1 H, ddd, $J_{3,2\alpha} = J_{3,2\beta}$ = 5.3, $J_{3,4}$ 4.2, 3-H), 7.20–7.38 (5 H, m, ArH) and 8.08 (1 H, s, OCHO); δ_C($CDCl_3$) 26.44, 28.14, 50.69, 54.78, 61.93, 68.11, 72.48, 73.10, 109.99, 127.30, 128.25, 128.76, 137.43 and 159.96; m/z 291 (M^+, 4%) and 91 (100).

Compound **23** was obtained as an oil (0.43 g, 50%) (Found: C, 65.85; H, 7.35; N, 4.65. $C_{16}H_{21}NO_4$ requires C, 65.95; H, 7.25; N, 4.8%); $[\alpha]_D^{25}$ +112.2 (*c* 1.6, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1727 (CO); δ_H($CDCl_3$) 1.33 (3 H, s, CH_3), 1.54 (3 H, s, CH_3), 2.12 (1 H, dd, $J_{5\alpha,5\beta}$ 11.1, $J_{5\alpha,4}$ 4.2, 5-H$^\alpha$), 2.54 (1 H, ddd, J 6.0, 5.4 and 4.2, 2-H), 3.08 (1 H, d, $J_{5\beta,5\alpha}$ 11.1, 5-H$^\beta$), 3.28 (1 H, d, J 13.5, NCH), 4.07 (1 H, d, J 13.5, NCH), 4.44 (1 H, dd, J 11.1 and 6.0, CHO), 4.48 (1 H, dd, J 11.1 and 5.4, CHO), 4.62 (1 H, dd, $J_{4,3}$ 6.3, $J_{4,5\alpha}$ 4.2, 4-H), 4.68 (1 H, dd, $J_{3,4}$ 6.3, $J_{3,2}$ 4.2, 3-H), 7.20–7.38 (5 H, m, ArH) and 8.08 (1 H, s, OCHO); δ_C($CDCl_3$) 25.53, 26.26, 57.64, 59.47, 62.18, 65.76, 78.02, 80.44, 111.64, 127.02, 128.26, 128.44, 138.05 and 160.74; m/z 292 (M^+ + 1, 1.5%) and 91 (100).

General procedure for the preparation of the 1-benzylpiperidines 24–26

A solution of 1-benzyl-4,5-(isopropylidenedioxy)piperidine (2.5 mmol) in 80% TFA (10 cm^3) was stirred at room temp. for 2 h. The reaction mixture was diluted with MeOH (20 cm^3), neutalized with Amberlite® IRA-400 (OH^-) ion-exchange resin, and filtered. The filtrate was evaporated to dryness and the residue was purified by flash column chromatography on silica gel with MeOH–$CHCl_3$ (1 : 19 for **24** and **25**; 1 : 4 for **26**) as eluent.

(3*S*,4*R*,5*R*)-5-Azido-1-benzylpiperidine-3,4-diol 24. Following the general procedure, the 1-benzyl-4,5-(isopropylidenedioxy)piperidine **15** gave the *title compound* **24** in quantitative yield as an oil (Found: C, 57.9; H, 6.7; N, 22.4. $C_{12}H_{16}N_4O_2$ requires C, 58.05; H, 6.5; N, 22.55%); $[\alpha]_D^{20}$ +25.0 (*c* 2.2, MeOH); ν_{max}(neat)/cm^{-1} 2099 (N_3) and 3404 (OH); δ_H([$^2H_6$]DMSO) 2.16 (1 H, dd, $J_{2\alpha,2\beta} = J_{2\alpha,3}$ = 10.2, 2-H$^\alpha$), 2.36 (1 H, dd, $J_{6\alpha,5}$ 10.8, $J_{6\alpha,6\beta}$ 10.2, 6-H$^\alpha$), 2.46 (1 H, dd, $J_{2\beta,2\alpha}$ 10.2, $J_{2\beta,3}$ 4.5, 2-H$^\beta$), 2.59 (1 H, dd, $J_{6\beta,6\alpha}$ 10.2, $J_{6\beta,5}$ 4.5, 6-H$^\beta$), 3.25 (1 H, ddd, $J_{5,6\alpha}$ 10.8, $J_{5,6\beta}$ 4.5, $J_{5,4}$ 2.1, 5-H), 3.47 (1 H, dddd, $J_{3,2\alpha}$ 10.2, $J_{3,OH}$ 6.3, $J_{3,2\beta}$ 4.5, $J_{3,4}$ 2.1, 3-H), 3.52 (1 H, d, J 13.2, NCH), 3.57 (1 H, d, J 13.2, NCH), 3.91 (1 H, ddd, $J_{4,OH}$ 4.2, $J_{4,3}$ 2.1, $J_{4,5}$ 2.1, 4-H), 4.67 (1 H, d, J 6.3, 3-OH), 5.01 (1 H, d, J 4.2, 4-OH) and 7.20–7.38 (5 H, m, ArH); δ_C([$^2H_6$]DMSO) 49.55, 52.75, 58.18, 61.54, 67.91, 69.71, 127.55, 128.64, 129.42 and 137.93; m/z 249 (M^+ + 1, 3%) and 91 (100).

(3*S*,4*S*,5*R*)-1-Benzyl-5-fluoropiperidin-3,4-diol 25. Following the general procedure, the 1-benzyl-4,5-(isopropylidenedioxy)piperidine **17** gave the *title compound* **25** in quantitative yield as an oil (Found: C, 63.8; H, 7.1; N, 6.1. $C_{12}H_{16}FNO_2$ requires C, 64.0; H, 7.15; N, 6.2%); $[\alpha]_D^{20}$ −11.4 (*c* 2.5, MeOH); ν_{max}(neat)/cm^{-1} 3422 (OH); δ_H([$^2H_6$]DMSO) 2.15 (1 H, dd, $J_{6\alpha,6\beta}$ 10.2, $J_{6\alpha,5}$ 9.6, 6-H$^\alpha$), 2.34–2.47 (1 H, m, 6-H$^\alpha$ overlapped with 6-H$^\beta$), 2.42 (1 H, dd, $J_{6\beta,6\alpha}$ 10.2, $J_{6\beta,5}$ 3.6, 6-H$^\beta$), 2.62 (1 H, ddd, $J_{2\beta,3}$ 4.8, 2-H$^\beta$), 3.47 (1 H, dddd, $J_{5,4}$ 10.5, $J_{5,6\alpha}$ 9.6, $J_{5,OH}$ 7.2, $J_{5,6\beta}$ 3.6, 5-H), 3.53 (1 H, d, J 10.5, NCH), 3.56 (1 H, d, J 10.5, NCH), 3.93 (1 H, dddd, $J_{4,5}$ 10.5, $J_{4,OH}$ 3.9, $J_{4,3}$ 2.4, 4-H), 4.52 (1 H, dddd, $J_{3,F}$ 47.1, $J_{3,2\alpha}$ 9.9, $J_{3,2\beta}$ 4.8, $J_{3,4}$ 2.4, 3-H), 4.54 (1 H, d, J 7.2, 3-OH), 4.83 (1 H, d, J 3.9, 4-OH) and 7.20–7.38 (5 H, m, ArH); δ_C([$^2H_6$]DMSO) 49.69 (d, $^2J_{2,F}$ 26.2, C-2), 52.56, 61.07, 66.91 (d, $^3J_{5,F}$ 8.6, C-5), 68.47 (d, $^2J_{4,F}$ 15.2, C-4), 88.78 (d, $^1J_{3,F}$ 177.0, C-3), 127.03, 128.17, 128.87 and 137.88; m/z 225 (M^+, 12%) and 91 (100).

[(3*R*)-(3α,4α,5α)]-1-Benzylpiperidine-3,4,5-triol 26. Following the general procedure, the 1-benzyl-4,5-(isopropylidenedioxy)-piperidine **19** gave the *title compound* **26** in quantitative yield as crystals, mp 133.8–134.8 °C (from EtOAc) (Found: C, 64.7; H, 7.75; N, 6.0. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.65; N, 6.25%); $[\alpha]_D^{20}$ 0.0; ν_{max}(KBr)/cm^{-1} 3300 and 3373 (OH); δ_H([$^2H_6$]DMSO) 2.14 (2 H, dd, $J_{6\alpha,6\beta} = J_{2\alpha,2\beta}$ = 10.2, $J_{6\alpha,5} = J_{2\alpha,3}$ = 9.6, 2- and 6-H$^\alpha$), 2.39 (2 H, dd, $J_{6\beta,6\alpha} = J_{2\beta,2\alpha}$ = 10.2, $J_{6\beta,5} = J_{2\beta,3}$ = 4.2, 2- and 6-H$^\beta$), 3.40–3.55 (2 H, m, 3- and 5-H), 3.48 (2 H, s, NCH_2), 4.30 (1 H, d, J 3.6, 4-OH), 4.41 (2 H, d, J 6.6, 3- and 5-OH) and 7.20–7.38 (5 H, m, ArH); δ_C([$^2H_6$]DMSO) 53.33, 61.53, 67.97, 70.56, 126.93, 128.17, 128.90 and 138.40; m/z 223 (M^+, 12%) and 91 (100).

General procedure for the preparation of the piperidines 5–7

A solution of 1-benzylpiperidine (1.0 mmol) in MeOH (20 cm^3) was hydrogenated in the presence of 10% Pd–C (0.05 g) at 3 atm at 40 °C for 1 h. The reaction mixture was filtered through a pad of Celite and evaporated to dryness to give the analytically pure product. For **6**·HCl and **7**·HCl, the product was dissolved in MeOH (10 cm^3) and to the solution was added 1 mol dm^{-3} HCl (2.0 mmol). The mixture was evaporated to dryness and the resulting solid was crystallized from a suitable solvent.

(3*S*,4*R*,5*R*)-5-Aminopiperidine-3,4-diol (4-amino-1,4,5-trideoxy-1,5-imino-D-ribitol) 5. Following the general procedure, the 1-benzylpiperidine **24** gave the *title compound* **5** in 98% yield as crystals, mp 171.6–172.4 °C (decomp.; from EtOAc–EtOH) (Found: C, 45.20; H, 9.0; N, 21.1. $C_5H_{12}N_2O_2$ requires C, 45.45; H, 9.15; N, 21.2%); $[\alpha]_D^{20}$ +4.5 (*c* 1.0, MeOH); ν_{max}(KBr)/cm^{-1} 3046, 3272 and 3364 (OH and NH_2); δ_H(D_2O) 2.43 (1 H, dd, $J_{6\alpha,6\beta}$ 12.6, $J_{6\alpha,5}$ 11.1, 6-H$^\alpha$), 2.58 (1 H, dd, $J_{2\alpha,2\beta}$ 13.2, $J_{2\alpha,3}$ 9.9, 2-H$^\alpha$), 2.69 (1 H, dd, $J_{6\beta,6\alpha}$ 12.6, $J_{6\beta,5}$ 4.5, 6-H$^\beta$), 2.69–2.82 (1 H, m, 5-H, overlapped with 2- and 6-H$^\beta$), 2.76 (1 H, dd, $J_{2\beta,2\alpha}$ 13.2, $J_{2\beta,3}$ 4.5, 2-H$^\beta$), 3.66 (1 H, ddd, $J_{3,2\alpha}$ 9.9, $J_{3,2\beta}$ 4.5, 3-H) and 3.93 (1 H, br s, 4-H); δ_C(D_2O) 45.17, 46.38, 51.23, 69.93 and 72.29; m/z 133 (M^+ + 1, 19%) and 72 (100).

(3*S*,4*S*,5*R*)-5-Fluoropiperidine-3,4-diol (1,4,5-trideoxy-4-fluoro-1,5-imino-D-ribitol) hydrochloride 6·HCl. Following the general procedure, the 1-benzylpiperidine **25** gave the title compound **6**·HCl in 95% yield as crystals, mp >250 °C (decomp.; from DMF–EtOH) {lit.,[1h] >250 °C (decomp.)}; $[\alpha]_D^{20}$ +2.0 (*c* 1.0, water) {lit.,[1h] $[\alpha]_D^{25}$ +1.9 (*c* 0.21, water)}; δ_C(D_2O) 46.00 (d, $^2J_{6,F}$ 22.8, C-6), 48.18 (C-2), 65.82 (d, $^3J_{3,F}$ 1.5, C-3), 67.38 (d, $^2J_{4,F}$ 16.4, C-4) and 87.86 (d, $^1J_{5,F}$ 179.4, C-5).

[(3*R*)-(3α,4α,5α)]-Piperidine-3,4,5-triol (1,5-dideoxy-1,5-imino-D-ribitol) hydrochloride 7·HCl. Following the general procedure, the 1-benzylpiperidine **26** gave the *title compound* **7**·HCl in 99% yield as crystals, mp 161.0–163.0 °C (decomp.; from DMF–EtOH) (Found: C, 35.2; H, 7.2; N, 7.95. $C_5H_{12}ClNO_3$ requires C, 35.4; H, 7.15; N, 8.25%); ν_{max}(KBr)/cm^{-1} 3300 (OH); δ_H(D_2O) 3.16–3.32 (4 H, m, 2- and 6-H_2) and 4.02–4.14 (3 H, m, 3-, 4- and 5-H); δ_C(D_2O) 45.18, 66.42 and 69.21; m/z 133 (M^+, 18%) and 43 (100).

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