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Synthesis of 3-oxagranatane-type alkaloid analogs from carbohydrates

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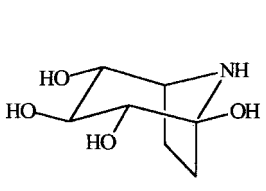
Abstract—3-Oxagranatane derivatives have been synthesized from dialdehydes obtained by the periodate oxidation of D-glucopyranosides. Reduction of the carbonyl group and removal of the substituents afforded bicyclic iminosugar analogs.

Iminosugars (i.e. polyhydroxypyrrolidines and piperidines), and structurally related saccharide-analog alkaloids carrying piperidine building blocks, are potent inhibitors of different glycosidase enzymes.[1] This property is manifested in various biological effects, such as inhibition of glycoprotein processing, antiviral (anti-HIV), antitumor, insecticide, and nematicide activities,[1] and thus the synthesis of these natural products and their structural analogs has become an intensively studied subject. Calystegines, a recently discovered family[2] of the iminosugars, contain a bridged tropane skeleton (Fig. 1). With this structure in mind, we decided to investigate the glycosidase enzyme inhibitory properties of certain carbohydrate analogs carrying an oxagranatane skeletone, which are readily available from simple saccharides in a few synthetic steps.

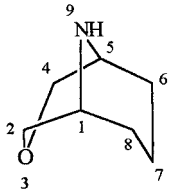
The synthesis of a few compounds with a 3-oxagranatane structure was reported by the groups of Guthrie[3] and Masamune.[4,5] The former authors[3] prepared the substituted derivatives of 3-oxagranatane using the Robinson–Schöpf reaction[6,7] of the dialdehydes derived from β-L-arabinopyranose or α-L-rhamnopyranose by means of periodate oxidation. Masamune et al.[4,5] employed a dioxo compound as the starting material, which was obtained upon ozonolysis of 2,5-dihydrofurane derivatives. At the same time, neither of the two groups investigated the enzyme inhibitory properties of the products prepared.

Our present methodology is based on the oxidation of methyl α-D-glucopyranoside (**1**) with sodium metaperiodate and subsequent Robinson–Schöpf reaction of the resulting, non-isolated chiral dialdehyde (**2**) with benzylamine and acetonedicarboxylic acid in aqueous medium (Scheme 1). In a diastereoselective reaction a single ketone isomer (**3**) with 3-oxagranatane skeleton was formed. Stereoselective reduction of the oxo function in **3** with lithium aluminium hydride furnished **4** carrying an *axially*-oriented hydroxyl group. Removal of the *N*-benzyl function by catalytic hydrogenation gave **5**, whose acetal function was hydrolyzed in acidic medium to obtain the target compound **6**.

In order to study the role of the configuration of the glycosidic center on the stereochemical outcome of the Robinson–Schöpf reaction, the transformations described above were also performed with the β-anomer (**7**, methyl β-D-glucopyranoside) of **1**. In this case the ketone **8** and (after reduction) the diol **9** were obtained, indicating that the 4-OCH_3 and the 2-CH_2OH are present in an energetically rather unfavorable *cis–diaxial* relationship at the double-chair oxagranatane skeletone of **8** and **9**. A similar, *diaxially*-substituted product was also observed by Masamune et al.[4,5] The development of such a stereochemistry can be explained by an attack of acetonedicarboxylic acid on the intermediary cyclic hemiaminal of the Robinson–Schöpf reaction from the side opposite to that on which the bulky hydroxyalkyl and methoxy substituents are located, and thus compound **8** is formed



Calystegine B_2



3-Oxagranatane skeleton

Figure 1.

Keywords: alkaloids; carbohydrate mimetics; aza compounds.
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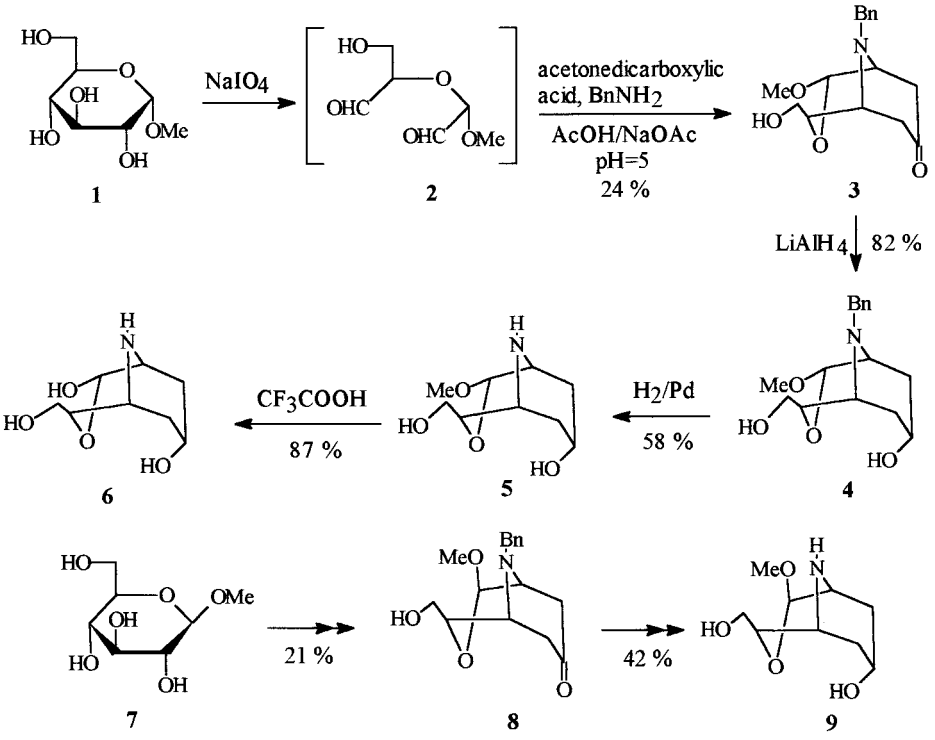
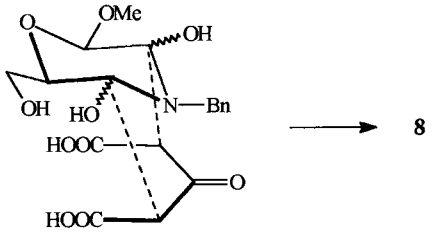


Scheme 1.

after decarboxylation (Scheme 2). The exclusive formation of **4** can also be similarly explained by the decisive directing effect of the bulky 2-CH_2OH function.

The structural properties of the 3-oxagranatane derivatives were readily substantiated by the NMR spectra. The structure of **3** was deduced from the results of 2D NOE experiments (Fig. 2). The configuration of the chiral centers of **8** was established according to the NOE data shown in Fig. 2, and all of these measurements unequivocally supported the *cis-diaxial* relationship between the 2-CH_2OH and the 4-OCH_3 groups. It is interesting to note that the chemical shift of the *axial* proton at the C-4 pseudo-anomeric center in compounds **4** and **5** is higher with 0.3–0.5 ppm than that of the respective, *equatorially*-oriented proton of **8** and **9**. This phenomenon is opposite to that observed for hexospyranose derivatives.[8] The configuration of the C-7 chiral center in **4** could be easily deduced from the coupling constants shown in Fig. 2.



Scheme 2.

As the acid hydrolysis of **5** was rather sluggish, the transformations described above were also performed starting with benzyl β-D-glucopyranoside (**10**) to result in the *N*,*O*-dibenzyl derivative **11** (Scheme 3). The crude **11** was subjected to catalytic hydrogenation, however, instead of the expected product **5**, only the piperidine derivative **12** could be isolated from the reaction mixture. The formation of **12** can be explained if the hydrogenolysis of the *O*-benzyl group is considerably faster than that of the *N*-benzyl function, and thus upon removal of this latter the hemiacetal-structure suffers reduction as well.

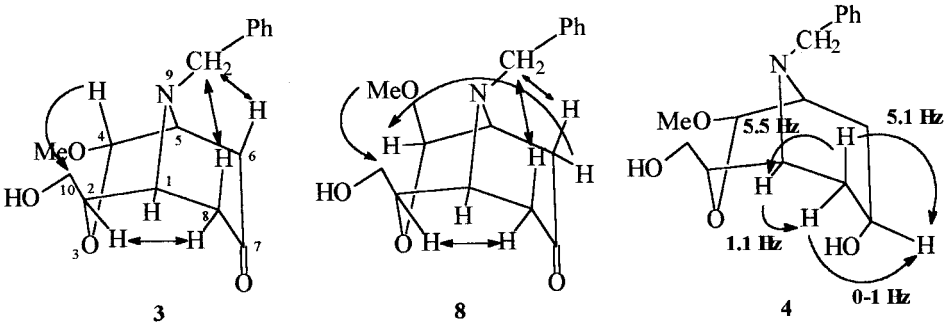
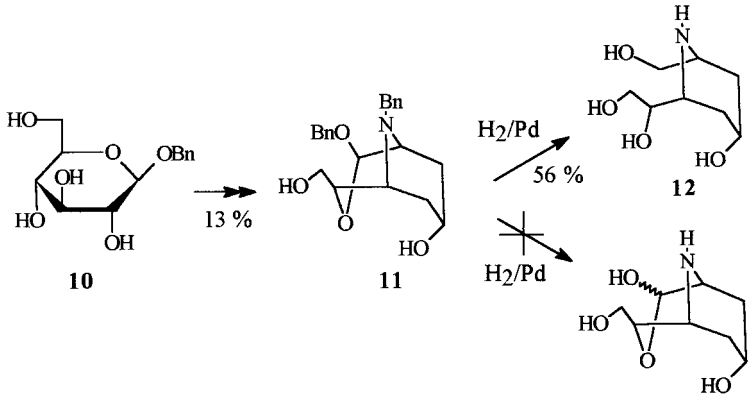


Figure 2.



Scheme 3.

The enzyme inhibitory studies revealed that the iminosugar analogs **5**, **6**, and **9** were not active towards eleven enzymes: β-glucosidases (from almonds (Sigma), *Aspergillus carbonarius*, *A. niger*, *A. phoenicis*), β-galactosidases (from testicles of bull, *A. carbonarius*, *A. niger*, *A. phoenicis*), α-glucosidase (from bakers yeast, Sigma), α-galactosidase (green coffee beans, Sigma) and the α-mannosidase (Jack beans, Sigma). At the same time, **12** was shown to possess a medium inhibitory effect ($K_i = 5 \times 10^{-4}$) on the almond β-glucosidase enzyme (crude, lyophilized powder).

1. Experimental

The organic extracts were dried over magnesium sulfate. and the solutions were concentrated at 35–40°C (bath) at ca. 17 mmHg. For TLC precoated aluminium-backed plates (Silica gel 60 F_{254}, Merck, layer thickness: 0.2 mm) were used. Compounds were visualized by charring with 5% sulfuric acid in ethanol or spraying with 7% ammonium molibdate in 5% sulfuric acid and heating. Column chromatography: Merck Silica gel 60 (0.062–0.200 mm). Specific rotations were measured on a Perkin–Elmer 141 MC polarimeter. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker WP 200 SY and Bruker AM 500 instruments in $CDCl_3$ with TMS as the internal standard. Plasmaspray (PSP) mass spectra were recorded on a VG TRIO-2 instrument connected with a Waters 501 HPLC pump in an isocratic mode; samples were dissolved in a 0.1 M ammonium acetate buffer/methanol mixture (1:1) and injected into the same solvent system at a flow rate of 1 mL/min; PSP tip interface temperature 210°C.

Glycosidase activities were measured in 0.2 M citrate-phophate buffer (pH 5.2) at 37°. The total volume was 5 mL. The reaction was initiated by addition of the substrate, and the hydrolysis was allowed to proceed for 20 min and stopped by the addition of 1 mL of the reaction mixture to 0.5 M borate buffer (2 mL, pH 10). The concentration of *p*-nitrophenolate ion was measured spectrophotomertically at 400 nm. Substrate concentration ranges for *p*-nitrophenyl glycopyranosides were 0.1–5 mM. Inhibition constants were determined from Lineweaver–Burk and Dixon plots, fitted by a least-squares treatment.

1.1. (1*R*,2*R*,4*S*,5*S*)-9-Aza-9-benzyl-2-hydroxymethyl-4-methoxy-3-oxabicyclo[3.3.1]nonane-7-one (3)

Methyl α-D-glucopyranoside (3.88 g, 20 mmol) was dissolved in water (100 mL) and sodium periodate (8.56 g, 40 mmol) was added in portions at 0°C. The solution was left in the dark for 3 h at room temperature after the pH was adjusted to 5–6 with a 1 M $NaHCO_3$ solution (18 mL). ethanol was (250 mL) added, the precipitate was filtered off and the solution was evaporated. The syrupy dialdehyde was directly subjected to further transformations. Sodium acetate (8 g) and acetic acid (10 mL) were dissolved water (50 mL), and then benzylamine (4.6 mL, 43 mmol) and acetonedicaboxylic acid (6.1 g, 42 mmol) were added. To the stirred solution the dialdehyde (in 30 mL water) was poured. The solution was left stirred overnight and the solution with some brown precipitate was neutralized with the slow addition of potassium carbonate. The slurry was washed with ethyl acetate (2×100 mL), and the organic phase was dried and evaporated. Column chromatography in hexane: acetone=6:4 resulted in 1.35 g (24%) of a dark brown syrup. MS 292 (M+1, PSP), $[\alpha]_D^{23}=+22.0$ (*c*0.72, CH_2Cl_2), ν_{max}(KBr) 3444, 3028, 2932, 1738, 1422, 1214, 1046 cm^{-1}. ^{1}H NMR (500 MHz): δ=2.34 (1H, dt, $J_{8a,8e}$=15.7 Hz, $J_{1,8e}$=1.6 Hz, $J_{6e,8e}$=1.6 Hz, H8e), 2.44 (1H, dd, $J_{6a,6e}$=15.8 Hz, $J_{5,6a}$=5.9 Hz, H6a), 2.52 (1H, dt, $J_{5,6e}$=1.6 Hz, $J_{6e,8e}$=1.6 Hz, $J_{6a,6e}$=15.8 Hz, H6e), 2.8 (1H, dd, $J_{8a,8e}$=15.7 Hz, $J_{1,8a}$=6.0 Hz, H8a), 3.14 (2H, m, H5 and H1), 3.45 (3H, s, OMe), 3.8 (1H, t, $J_{2,10a}=J_{2,10b}$=5.8 Hz, $J_{1,2}$=0 Hz, H2), 3.88 (1H, dd, $J_{10a,10b}$=11.3 Hz, $J_{2,10a}$= 5.8 Hz, H10a), 3.92 (2H, s, N–CH_2), 4.08 (1H, dd, $J_{2,10b}$= 5.8 Hz, $J_{10a,10b}$=11.3 Hz, H10b), 4.9 (1H, d, $J_{4,5}$=2.4 Hz, H4), 7.4 (5H, m, aromatic). ^{13}C NMR: δ=33.7; 40.2 (C6, C8); 55.0 (C5); 56.2 (OMe); 56.4 (C1) 58.7 (N–*C*H_2); 62.9 (C10); 78.4 (C2); 97.9 (C4); 127.8–128.6; 137.0 (6C, aromatic); 206.5 (C=O). Anal. calcd for $C_{16}H_{21}NO_4$: C 65.96%, H 7.27%, N 4.81%. Found: C 66.05%, H 7.20%, N 4.93%.

1.2. (1*R*,2*R*,4*S*,5*S*,7*R*)-9-Aza-9-benzyl-7-hydroxy-2-hydroxymethyl-4-methoxy-3-oxabicyclo[3.3.1] nonane (4)

Compound **3** (1 g, 3.4 mM) was dissolved in abs. THF (30 mL) and $LiAlH_4$ (180 mg, 5.1 mM) was slowly added

to the stirred solution. One hour later the suspension was diluted with ethyl acetate (100 mL) and sat. $NaHCO_3$ solution was added. The organic phase was washed with sat. $NaHCO_3$ solution (100 mL), dried and evaporated. Chromatography in hexane/acetone=6:4 resulted in 820 mg (82%) of a brown syrup. MS 294 (M+1, PSP), $[\alpha]_D^{23}=+16.3$ (c0.96, CH_2Cl_2), ν_{max}(KBr) 3390, 2930, 1650, 1494, 1190, 1040 cm^{-1}. ^1H NMR: δ=1.55 (1H, dd, $J_{6a,6e}$=15.6 Hz, $J_{5,6e}$=1.1 Hz, H6e), 1.85 (1H, dd, $J_{8a,8e}$=15.7 Hz, $J_{1,8e}$= 1.1 Hz, H8e), 2.0 (1H, dt, $J_{7,6a}$=5.2 Hz, $J_{5,6a}$=5.7 Hz, $J_{6a,6e}$=15.6 Hz, H6a), 2.3 (1H, dt, $J_{7,8a}$=5.1 Hz, $J_{1,8a}$=5.5 Hz, $J_{8a,8e}$=15.7 Hz, H8a), 2.8 (2H, m, H5 and H1), 3.45 (3H, s, OMe), 3.73 (2H, s, N–CH_2), 3.9 (4H, m, H2, H7 and H10a,b), 5.0 (1H, d, $J_{4,5}$=2.6 Hz, H4), 7.35 (5H, m, benzyl).^{13}C NMR: δ=22.5; 29.6 (C6,C8); 50.9 (C5); 52.5 (C1); 55.6 (N–CH_2); 56.6 (OMe); 62.0 (C7); 65.7 (C10); 77.4 (C2); 99.2 (C4); 126.9–128.8; 137.2 (6C, aromatic). Anal. calcd for $C_{16}H_{23}NO_4$: C 65.51%, H 7.90%, N 4.77%. Found: C 65.62%, H 7.81%, N 4.86%.

1.3. (1*R*,2*R*,4*S*,5*S*,7*R*)-9-Aza-7-hydroxy-2-hydroxymethyl-4-methoxy-3-oxabicyclo[3.3.1]nonane (5)

Compound **4** (1.1 g) was dissolved in acetic acid (30 mL) and hydrogenated overnight over Pd/C catalyst (200 mg). After filtration and evaporation the syrup was dissolved in water and stirred 10–20 min with some *Serdolit Blue* (OH^- form resin). Chromatography in dichloromethane/methanol 8:2 and freeze-drying resulted in 455 mg (58%) of a brownish yellow syrup. MS 204 (M+1, PSP), $[\alpha]_D^{23}=+24.7$ (c0.8, methanol), ν_{max}(KBr) 3442, 2930, 1620, 1450, 1098, 1017 cm^{-1}. ^1H NMR (D_2O): δ=1.83 and 2.03 (3H, 2m, H6a,e, H8e) 2.21 (1H, dt, $J_{7,8a}$=5.0 Hz, $J_{1,8a}$=5.3 Hz, $J_{8a,8e}$=15.7 Hz, H8a), 3.24 (2H, m, H5, H1), 3.5 (3H, s, OMe), 3.7 (1H, dd, $J_{10a,10b}$=11.1 Hz, $J_{2,10a}$=5.6 Hz, H10a), 4.05 (3H, m, H2, H7, H10b), 5.1 (1H, d, $J_{4,5}$=2.7 Hz, H4). ^{13}C NMR: δ=24.0; 29.2 (C6, C8); 45.0 (C5); 48.1 (C1); 57.4 (OMe); 62.0 (C7); 62.4 (C10); 77.8 (C2); 97.1 (C4). Anal. calcd for $C_9H_{17}NO_4$: C 53.19%, H 8.43%, N 6.89%. Found: C 53.11%, H 8.49%, N 6.78%.

1.4. (1*R*,2*R*,4*S*,5*S*,7*R*)-9-Aza-4,7-dihydroxy-2-hydroxymethyl-3-oxabicyclo[3.3.1]nonane (6)

Compound **5** (100 mg) was dissolved in a mixture of trifluoracetic acid (5 mL) and water (0.5 mL) and left at 60°C for 6 h. The solution was evaporated and purified with dichloromethane: methanol= 9:1 to give 81 mg (87%) of a colorless oil. MS 190 (M+1, PSP), 172 (M−H_2O+1), $[\alpha]_D^{23}=+3.3$ (c1.25, methanol), ν_{max}(KBr) 3400, 2956, 1440, 1206, 1138, 1020 cm^{-1}. ^1H NMR (D_2O): δ=1.80 (3H, 2m, H6a,e and H8e) 2.15 (1H, m, H8a), 3.3 (2H, m, H5 and H1), 3.7 (3H, m, H2, H7, H10a), 3.95 (1H, m, H10b), 5.55 (1H, d, $J_{4,5}$=4.0 Hz, H4). ^{13}C NMR: δ=38.4; 39.0 (C6, C8); 50.9 (C5); 56.3 (C1); 65.8 (C7); 77.0 (C10); 78.1 (C2); 101.9 (C4). Anal. calcd for $C_8H_{15}NO_4$: C 50.78%, H 7.99%, N 7.40%. Found: C 50.70%, H 8.11%, N 7.45%

1.5. (1*R*,2*R*,4*R*,5*S*)-9-Aza-9-benzyl-2-hydroxymethyl-4-methoxy-3-oxabicyclo[3.3.1]nonane-7-one (8)

Starting from methyl β-D-glucopyranoside (1.95 g, 10 mmol) and applying the procedure described for **3** 0.61 g (21%) of **8** was obtained. MS 292 (M+1, PSP), $[\alpha]_D^{23}=-62.8$ (c0.95, CH_2Cl_2), ν_{max}(KBr) 3444, 3025, 2932, 1738, 1420, 1204, 1026 cm^{-1}. ^1H NMR (500 MHz): δ=2.2 (1H, d, $J_{6a,6e}$= 15.4 Hz, $J_{5,6e}$=0 Hz, H6e), 2.26 (1H, dd, $J_{8a,8e}$=15.2 Hz, $J_{1,8e}$=1.2 Hz, H8e), 2.74 (1H, dd, $J_{6a,6e}$=15.4 Hz, $J_{5.6a}$= 6.3 Hz, H6a), 2.83 (1H, dd, $J_{1,8a}$=6.1 Hz, $J_{8a,8e}$=15.2 Hz, H8a), 3.3 (1H, dd, $J_{1,2}$=0 Hz, $J_{1,8a}$=6.1 Hz, $J_{1,8e}$=1.2 Hz, H1), 3.41 (1H, d, $J_{4,5}$=0 Hz, $J_{5.6a}$=6.3 Hz, H5), 3.45 (3H, s, OMe), 3.68 (1H, t, $J_{2,10a}$=$J_{2,10b}$=5.3 Hz, H2), 3.89 (1H, dd, $J_{10a,10b}$=11.4 Hz, $J_{2,10a}$=5.3 Hz, H10a), 3.94 (2H, s, N–CH_2), 4.06 (1H, dd, $J_{10a,10b}$=11.4 Hz, $J_{2,10b}$=5.3 Hz, H10b), 4.4 (1H, s, H4), 7.45 (5H, m, aromatic). ^{13}C NMR: δ=38.6; 41.0 (C6, C8); 55.1 (C1); 55.8 (OMe); 56.6 (C5); 57.8 (N–CH_2); 77.8 (C2); 100.6 (C4); 127.6–128.6; 137.2 (6C, aromatic); 206.7 (C=O). Anal. calcd for $C_{16}H_{21}NO_4$: C 65.96%, H 7.27%, N 4.81%. Found: C 66.01%, H 7.30%, N 4.85%.

1.6. (1*R*,2*R*,4*R*,5*S*,7*R*)-9-Aza-7-hydroxy-2-hydroxymethyl-4-methoxy-3-oxabicyclo[3.3.1]nonane (9)

Starting from **8** (460 mg, 1.56 mmol) and using the procedures described for **4** and **5**, 133 mg (42%) of **9** was obtained after freeze-drying. MS 204 (M+1, PSP), $[\alpha]_D^{23}=-46.2$ (c1.1, methanol), ν_{max}(KBr) 3412, 2930, 1444, 1104, 1030 cm^{-1}. ^1H NMR (D_2O): δ=1.8 (2H, m, H6e, H8e) 2.2 (2H, m, H6a, H8a), 2.95 (2H, 2m, H5, H1), 3.5 (3H, s, OMe), 3.9 (4H, m, H2, H7, H10a,b), 4.63 (1H, s, H4). ^{13}C NMR: δ=33.9; 36.8 (C6, C8); 44.0 (C5); 48.3 (C1); 56.0 (OMe); 63.4 (C7); 65.6 (C10); 75.6 (C2); 99.4 (C4). Anal. calcd for $C_9H_{17}NO_4$: C 53.19%, H 8.43%, N 6.89%. Found: C 53.05%, H 8.54%, N 6.92%.

1.7. (1*R*,2*R*,4*S*,5*S*)-9-Aza-9-benzyl-2-hydroxymethyl-4-benzyloxy-3-oxabicyclo[3.3.1]nonane-7-one (11)

Starting from benzyl β-D-glucopyranoside **10** (2 g, 7.5 mmol) and employing the procedure described for **3**, 295 mg (13%) of a dark brown syrup was obtained. MS 368 (M+1, PSP), $[\alpha]_D^{23}=-54.4$ (c0.5, CH_2Cl_2), ν_{max}(KBr) 3370, 3110, 3030, 1698, 1454, 1246, 1102 cm^{-1}. ^1H NMR (aceton-d_6): δ=2.3 (2H, m, H6e and H8e), 2.7 (2H, m, H6a, H8a), 3.2 and 3.4 (2H, 2m, H1 and H5), 3.75 (1H, dd, $J_{2,10a}$=5.4 Hz, $J_{2,10b}$=5.0 Hz, H2), 3.6 (1H, dd, $J_{10a,10b}$=11.0 Hz, $J_{2,10a}$=5.4 Hz, H10a), 3.9 (2H, d, O–CH_2), 4.07 (1H, dd, $J_{10a,10b}$=11.0 Hz, $J_{2,10b}$=5.0 Hz, H10b), 4.7 (1H, d, $J_{4,5}$=0.5 Hz, H4) 7.45 (10H, m, aromatic). ^{13}C NMR: δ=37.8; 40.5 (C6, C8); 54.3 (C1); 55.7 (OMe); 56.8 (C5); 62.3 (N–CH_2); 68.8 (O–CH_2); 78.2 (C2); 98.2 (C4); 126.5–127.8; 137.7 (12C, aromatic); 199.6 (C=O). Anal. calcd for $C_{22}H_{25}NO_4$: C 71.91%, H 6.86%, N 3.81%. Found: C 71.82%, H 6.97%, N 3.85%.

1.8. (2*R*,4*S*,6*S*)-2-(1*R*)-1,2-Dihydroxyethyl-4-hydroxy-6-hydroxymethylpiperidine (12)

Compound **11** (350 mg, 0.95 mmol) was reduced and hydrogenated as described for **4** and **5**. The polar product was purified in dichloromethane:methanol=3:7 and freeze-dried to give 102 mg (56%) of a brownish yellow syrup. MS 192 (M+1, PSP), $[\alpha]_D^{23}=+3.7$ (c0.45, methanol), ν_{max}(KBr)

3430, 2920, 1422, 1122, 1068 cm^{-1}. ^1H NMR (D_2O) δ=1.7 and 2.0 (4H, 2m, 4H, H3a,b, H5a,b), 3.4–4.2 (8H, 3m, other protons). ^{13}C NMR: δ=25.5; 29.3 (C3, C5); 57.9 (C6); 58.4 (C2); 65.6 (CH_2–OH); 67.8 (C2′); 70.7 (C4); 77.0 (C1′). Anal. calcd for $C_8H_{17}NO_4$: C 50.25%, H 8.96%, N 7.32%. Found: C 50.21%, H 9.04%, N 7.44%.

Acknowledgements

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