Synthesis of a 5-Hydroxypiperidine-2,3,4,6-tetramethanol, a New 2,6-Dideoxy-2,6-iminoheptitol Derivative

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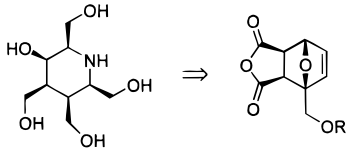
Polyhydroxylated piperidines (e.g., 1,5-dideoxy-1,5-iminohexitols) and pyrrolidines (e.g., 1,4-dideoxy-1,4-imino- and 2,5-dideoxy-2,5-iminohexitols) have attracted considerable attention due to their ability to inhibit glycohydrolases,[1,2] making these compounds potential antibacterial, antiviral, antimetastatic, antidiabetes, antihyperglycemic, antiadhesive, or immunostimulatory agents.[3,4] Higher analogues such as 2,6-dideoxy-2,6-iminoheptitols[2,5] and 2,6-dideoxy-2,6-iminooctitols[6] have also shown promising glycosidase inhibitory activities. We report here the synthesis of **1**, a new kind of hydroxymethylated piperidine, starting from *rac*-**2**, an inexpensive Diels−Alder adduct of maleic anhydride to furfuryl alcohol.



1 **2** R = H
(-)-**11** R = (1′*R*)-camphanoyl

Reduction of **2** with $LiAlH_4$ gave triol **3**[7−11] which was peracetylated into triacetate **4**.[12] Treatment of **4** with BBr_3 at −78 °C provided the allylic bromide **5** (95%) that could be displaced by tetramethylguanidinium azide to produce the corresponding azido derivative **6** (93% yield).[12] Double hydroxylation of **6** with $RuCl_3 \cdot H_2O/NaIO_4$ in H_2O led to a mixture of diols (89% yield) that could be cleaved on treatment with $Pb(OAc)_4$ in CH_2Cl_2 at room temperature. This generated the aldehydo-hemiacetal **7** in 95% yield. The ^1H NMR spectrum of **7** was consistent with a single hemiacetal, the relative configuration of which at C-2 was not established unambiguously. Reduction of **7** with $NaBH_4$ in $EtOH/CH_2Cl_2$ at −78 °C generated the corresponding primary alcohol **8** without affecting the hemiacetal, in an overall yield **6** → **8** of 80%. Attempts to reduce the azido moiety of **8** with catalytic hydrogenation (10% Pd/C, 10% $Pd(OH)_2/C$, PtO_2) led to complex mixtures indicating that elimination of acetic acid competes with the desired azide reduction and formation of imine with the carbonyl function at C-2.[13,14] Methanolysis of the triacetate **8** (MeOH, anhydrous K_2CO_3, neutralization with HCl) followed by hydrogenation in MeOH (10% Pd/C) generated imine **9** (85% yield) which could not be purified because of its instability. It was then directly reduced with $NaBH_4$ in MeOH giving the iminosugar **1** as a single product, thus demonstrating the high facial selectivity of the reduction, its less sterically hindered face being preferred for the hydride addition. A procedure was found that allowed one to convert azide **8** directly into **1** in 88% yield. When neutralization of the product of methanolysis of **8** with 1 N HCl was avoided, the crude azido-polyol obtained was hydrogenated directly into amine **1** in the presence of a catalytical amount of 10% Pd/C or of $Pd(OH)_2/C$. The iminosugar **1** was characterized as its peracetyl derivative **10** obtained in 91% yield on treatment with anhydrous pyridine and acetic anhydride.

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(7) Inhibitors of glycohydrolases do not have to be transition state mimetics of the enzyme-catalyzed hydrolysis of the glycosidic bond.[8] Compound that do not resemble sugars such as (−)-(3a*S*,5*S*,6*S*,6a*R*)-3a,5,6,6a-tetrahydro-5,6-isopropylidenedioxyfuro[2,3-*d*]isoxazole-3-methanol inhibits *β*-galactosidase from *Aspergillus niger* ($K_i = 18\ \mu M$) and that from *Aspergillus orizae* ($K_i = 72\ \mu M$) specifically (uncompetitive inhibition).[9] The neutral C-disaccharide α-C(1→3)-mannopyranoside of *N*-acetylgalactosamine is a inhibitor of *β*-galactosidase from jack bean ($K_i = 7.5\ \mu M$, mixed mode of inhibition).[10]

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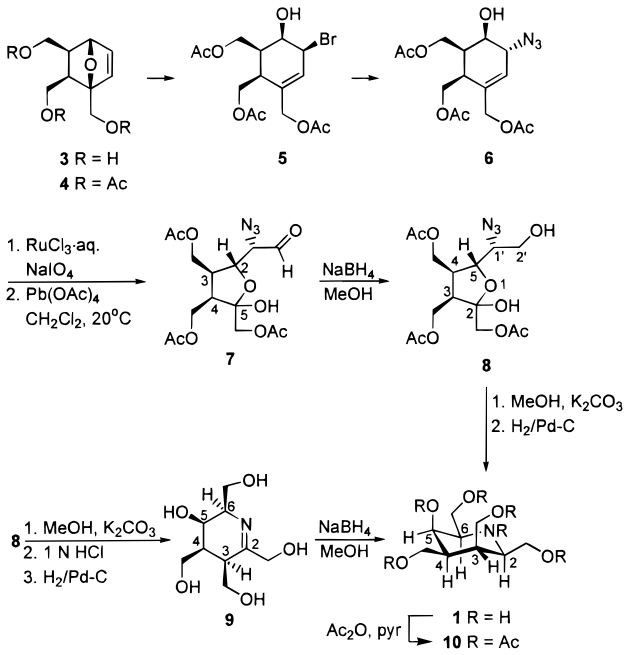
The structure and major conformation shown for **1** were confirmed by the ^{1}H NMR spectrum that displayed coupling constants between vicinal protons of the piperidine ring typical for axial/equatorial proton pairs (^3J(H-2,H-3) = 3.5 Hz, ^3J(H-3,H-4) = 3.0 Hz, ^3J(H-4,H-5) = 2.5 Hz, ^3J(H-5,H-6) = 2.0 Hz). The 2D-NOESY ^{1}H NMR spectrum of **1** showed cross-peaks for the signals at δ_H: 2.96, 2.75 and 1.94 ppm assigned to protons H-2, H-6, and H-4, respectively, in agreement with the relative configuration proposed for **1**. The known enantiopure Diels−Alder adduct (−)-**11** and its enantiomer (+)-**11**[15] will generate both enantiomers of **1** following our procedure. Preliminary enzymatic inhibition studies have shown **1** to be a weak inhibitor of β-galactosidase from bovine liver (30% inhibition at 1 mM concentration of **1**) and from jack beans (40% inhibition at 1 mM).[16]



Experimental Section

For general remarks, see ref 17.

(2*RS*,3*SR*,4*SR*,5*SR*,6*RS*)-5-Hydroxypiperidine-2,3,4,6-tetramethanol ((±)-1). A mixture of (±)-**8** (100 mg, 0.256 mmol), anhydrous MeOH (1 mL), and anhydrous K_2CO_3 (11 mg, 0.8 mmol) was stirred at 20 °C for 12 h. The solvent was evaporated to dryness and the residue taken in MeOH (0.5 mL). A suspension of 10% $Pd(OH)_2$ on charcoal (20 mg) or of 10% Pd on charcoal (20 mg) in MeOH previously degassed (vacuum line) and saturated with H_2 was added, and the mixture was degassed (vacuum line), pressurized with H_2 (1 atm), and shaken for 30 min under H_2 atmosphere. The catalyst was filtered off on Celite and the solvent evaporated to dryness giving a colorless oil (49.7 mg, 88%); R_f (MeOH/NH_3/H_2O 20:0.2:1) = 0.61; ^{1}H NMR (400 MHz, CD_3OD): δ 3.83 (dd, J = 2.5, 2.0, 1 H), 3.80 (dd, J = 11.0, 7.1, 1 H), 3.78 (dd, J = 11.5, 7.0, 1 H), 3.74 (dd, J = 11.5, 6.0, 1 H), 3.73 (dd, J = 11.0, 7.0, 1 H), 3.72 (dd, J = 11.5, 6.0, 1 H), 3.71 (dd, J = 11.0, 7.0, 1 H), 3.70 (dd, J = 11.0, 6.0, 1 H), 3.64 (dd, J = 11.5, 7.0, 1 H), 2.96 (td, J = 7.0, 3.5, 1 H), 2.75 (ddt, J = 7.0, 6.0, 2.0, 1 H), 1.99 (dddd, J = 7.0, 6.0, 3.5, 3.0, 1 H), 1.94 (dddd, J = 7.1, 6.0, 3.0, 2.5, 1 H); ^{13}C NMR (100.6 MHz, CD_3OD): δ 65.4 (d), 63.9, 63.5, 62.3, 58.4 (4t), 63.7, 62.6 (2d), 47.3, 37.9 (2d).

(α*RS*,2*SR*,3*SR*,4*RS*,5*RS* or 5*SR*)-3,4,5-Tris[(acetoxy)-methyl)-α-azido-tetrahydro-5-hydroxy-2-furanethanal ((±)-7). A solution of $RuCl_3$ hydrate (41% Ru, 0.028 mmol) and $NaIO_4$ (127 mg, 0.595 mmol) in H_2O (1 mL) was added dropwise to a stirred solution of (±)-**6**[12,13] (140 mg, 0.394 mmol) in 1:1 EtOAc/MeCN (7 mL) cooled to 0−5 °C (ice−water bath). After the mixture was stirred vigorously for 1 min, a saturated aqueous solution of $Na_2S_2O_3$ (14 mL) was added under vigorous stirring and the mixture immediately extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated to dryness in vacuo. The residue was taken with anhydrous CH_2Cl_2 (2 mL) and Ac_2O (20 μL). 85% $Pb(OAc)_4$ (200 mg, 0.384 mmol) was added and the mixture was stirred vigorously at 20 °C for 1 min. It was then poured into H_2O and extracted with EtOAc. The organic extract was washed with H_2O and dried ($MgSO_4$). Solvent evaporation afforded a colorless oil (128 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1 H), 4.63 (dd, J = 4.0, 3.3, 1 H), 4.35 (dd, J = 11.0, 5.2, 1 H), 4.26 (dd, J = 11.0, 9.3, 1 H), 4.25 (dd, J = 12.2, 7.5, 1 H), 4.20 (dd, J = 12.2, 7.4, 1 H), 4.22, 4.14 (2 d, J = 11.7, 2 H), 3.87 (d, J = 3.3, 1 H), 3.74 (s, 1 H), 2.79 (dddd, J = 9.7, 9.3, 5.2, 4.0, 1 H), 2.69 (ddd, J = 9.7, 7.5, 7.4, 1 H), 2.09, 2.06, 2.05 (3 s, 9 H).

(1′*RS*,2*RS* or 2*SR*,3*RS*,4*SR*,5*SR*)-5-(1-Azido-2-hydroxymethyl)-tetrahydro-2-hydroxyfuran-2,3,4-trimethanol α^2,α^3,α^4-triacetate ((±)-8). $NaBH_4$ (17 mg, 0.44 mmol) was added in one portion to a stirred solution of (±)-**7** (154 mg, 0.397 mmol) in anhydrous CH_2Cl_2 (2.8 mL) and EtOH (1.2 mL) cooled to −78 °C. After the mixture was stirred at −78 °C for 10 min, an excess of acetaldehyde was added and the solution was allowed to warm to room temperature under stirring. It was diluted with EtOAc, washed with saturated aqueous solution of NH_4Cl, then with H_2O and dried ($MgSO_4$). Solvent evaporation and filtration through a pad of Florisil (EtOAc for rinsing) afforded a colorless oil (145 mg, 94%), R_f (EtOAc/light petroleum 2:1): 0.81; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (dd, J = 10.9, 4.9, 1 H), 4.28−4.23 (m, 4 H), 4.27, 4.19 (2 d, J = 11.7, 2 H), 3.88 (dd, J = 11.6, 5.1, 1 H), 3.84 (dd, J = 11.6, 6.0, 1 H), 3.51 (br. s, 1 H), 3.44 (ddd, J = 6.0, 6.0, 5.1, 1 H), 2.74−2.67 (m, 2 H), 2.12, 2.08, 2.07 (3 s, 9 H).

(3*RS*,4*RS*,5*SR*,6*SR*)-3,4,5,6-Tetrahydro-5-hydroxypyridine-2,3,4,6-tetramethanol ((±)-9). A mixture of (±)-**8** (100 mg, 0.256 mmol), anhydrous MeOH (1 mL) and anhydrous K_2CO_3 (11 mg, 0.8 mmol) was stirred at 20 °C for 12 h and then neutralized by addition of aqueous 1 N HCl. The solvent was evaporated to dryness and the residue taken in MeOH (0.5 mL). After the addition of 10% Pd on charcoal (10 mg) suspended in MeOH (0.5 mL) previously degassed (vacuum line) and saturated with H_2, the mixture was degassed and then pressurized with H_2 (1 atm). After shaking at 20 °C for 10 min the mixture was filtered though Celite and the solvent evaporated affording a colorless oil (48 mg, 85%) that rapidly becomes yellow (decomposition). ^{13}C NMR (100.6 MHz, CD_3OD): δ 172.0 (s), 63.6 (t, J = 151), 62.5 (d, J = 140), 61.9, 60.3 (2t, J = 145, 142), 57.8 (d, J = 145), 54.0 (t, J = 179), 45.1 (d, J = 128), 33.0 (d, J = 133).

(2*RS*,3*SR*,4*SR*,5*RS*,6*RS*)-*N*-Acetyl-5-acetoxypiperidine-2,3,4,6-tetramethyl Tetraacetate ((±)-10). A mixture of (±)-**1** (30 mg, 0.136 mmol), anhydrous pyridine (0.5 mL), and acetic anhydride (0.5 mL) was stirred at 20 °C for 18 h. The solvent was evaporated to dryness in vacuo, the residue was taken up in toluene (5 mL) and the solvent was evaporated to dryness. The latter operation was repeated twice. The residue was taken in EtOAc and filtered through a pad of silica gel. The solvent was evaporated to dryness in vacuo affording a yellowish oil (52.3 mg, 91%), R_f (EtOAc) = 0.57. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (t, J = 2.0, 1 H), 4.31 (dd, J = 12.0, 8.0, 1 H), 4.28 (dd, J = 11.4, 4.2, 1 H), 4.22 (dd, J = 12.0, 3.0, 1 H), 4.17 (dd, J = 11.0, 5.0, 1 H), 4.14 (dd, J = 11.5, 8.5, 1 H), 4.03 (dd, J = 11.6, 6.0, 1 H), 4.01 (dd, J = 11.4, 8.6, 1 H), 3.85 (dd, J = 11.0, 8.0, 1 H), 3.08 (ddd, J = 8.0, 5.0, 2.0, 1 H), 3.06 (ddd, J = 8.6, 4.2, 3.0, 1 H), 2.18 (ddt, J = 8.5, 6.0, 2.0, 1 H), 2.12 (dtd, J = 8.0, 3.0, 2.0, 1 H), 2.10, 2.09, 2.07, 2.04 (4s, 18 H). Anal. Calcd for $C_{21}H_{31}O_{11}N$ (473.49): C, 53.27; H, 6.60; O, 37.17. Found: C, 53.00; H, 6.72; O, 37.30.

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Supporting Information Available: Detailed ^{1}H and ^{13}C NMR spectra and signal assignments, UV, IR, MS spectra, and elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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