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Synthesis of (+)-3,7,8-trideoxy-3,7-imino-D-*threo*-L-*galacto*-octitol and its inhibition of β-glucosidases

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Abstract

The readily available 2,3:6,7-di-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone [(−)-**5**] was converted in four synthetic steps into the new iminooctitol (+)-3,7,8-trideoxy-3,7-imino-D-*threo*-L-*galacto*-octitol [(+)-**10**]. Although the piperidine unit of (+)-**10** has the absolute configuration of β-D-*galacto*-hexopyranosides, this iminoalditol does not inhibit five commercially available β-galactosidases. However, (+)-**10** was found to be a good competitive inhibitor of β-glucosidases from almond (K_i = 15 μM) and from *Caldocellum saccharolyticum* (K_i = 41 μM).

Keywords: Azasugars; Glycosidase inhibitors; Iminoalditols; 3,7-Iminooctitol

1. Introduction

Inhibition of glycohydrolases [1] may be useful for the treatment of several diseases such as diabetes, cancer, viral infections, bacterial infections and inflammation [2]. Among the most promising known inhibitors, one finds polyhydroxypiperidines and pyrrolidines (imino sugars [2,3]) and analogues such as *N*-alkyl iminoalditols [4], polyhydroxyindolizidines [5] and polyhydroxy-*nor*-tropane alkaloids [6]. The first example of a naturally occurring iminoheptitol, (+)-α-homonojirimycin, was isolated from leaves of *Omphalea diandra* [7]. It is a powerful α-glucosidase inhibitor [8] (for syntheses of (+)-homonojirimycin, and analogues, see for example, ref. [9]). Pyrrolidine analogues of *N*-acetylneuraminic acid such as {(2′*R*,3′*S*,4′*S*)-3′-acetamido-4′-hydroxy-

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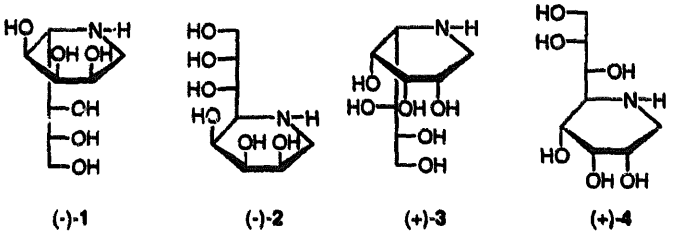
2′-[(1″*S*,2″*R*)-1″,2″,3″-trihydroxypropyl]pyrrolidin-1′-yl}methyl} phosphonic acid have been prepared as potential sialidase inhibitors [10]. Few syntheses of derivatives of 2,5-dideoxy-2,5-iminoheptitols [11] and 1,5-dideoxy-1,5-iminoheptitols [12] as well as of 7-carbonyl homologues of 1-deoxynojirimycin [13] have been reported. Iminooctitols are even rarer than iminoheptitols. The "elongated" nojirimycin (6*S*)-6-*C*-ethyl-1-deoxynojirimycin has inhibitory activity against α-glucosidases from yeast and rice superior to those of 1,6-dideoxy-6-fluoronojirimycin, 1-deoxynojirimycin and its bicyclic analogue (+)-castanospermine [14]. The first four 1,5-dideoxy-1,5-iminoctitols (−)-**1**, (−)-**2**, (+)-**3** and (+)-**4** were prepared by Chen and Vogel [15].

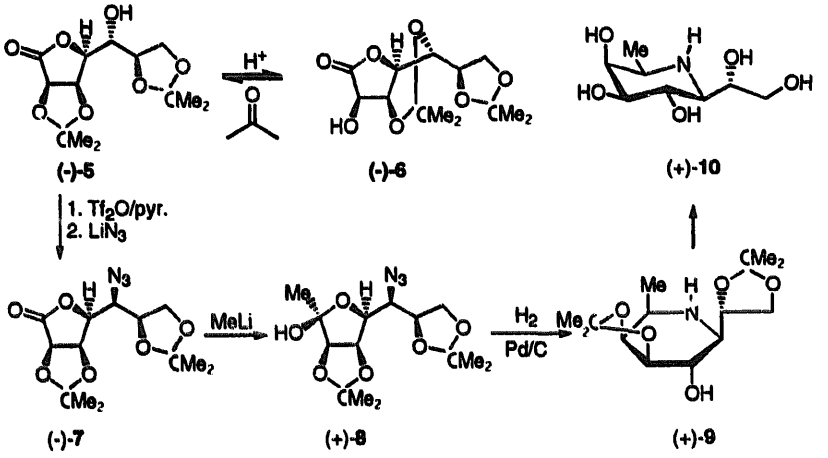


While (−)-**1** and (−)-**2** did not show any significant inhibition toward fifteen commercially available glycosidases, iminooctitols (+)-**3** and (+)-**4** were weak inhibitors of β-glucosidase from almond and of β-galactosidases from *Aspergillus niger*, *Aspergillus orizae* and from jack beans [5]c. Among the higher homologues of iminosugars 2,6-dideoxy-2,6-iminosialic acid, prepared the first time by Vasella and co-workers [16], and the first example of an imino-*C*-disaccharide made by Johnson and co-workers [17], that is, 1,5-dideoxy-1,5-imino-D-mannitol linked at C-6 of D-galactose through a methylene unit, must be mentioned. We report here the synthesis of (+)-3,7,8-trideoxy-3,7-imino-D-*threo*-L-*galacto*-octitol [(+)-**10**], an iminooctitol derivative that can be viewed as a β-*C*-6-deoxy-imino-D galactopyranoside. Contrary to our expectations, this imino-D-galactose derivative does not inhibit β-galactosidases but was found to be better than (+)-castanospermine as an inhibitor of β-glucosidases from almond and from *Caldocellum saccharolyticum*.

2. Results

The inexpensive D-*glycero*-D-*gluco*-heptono-(1,4)-lactone [18] was known to yield a mixture of the corresponding bis-acetonides (−)-**5** and (−)-**6** when treated with acetone and sulfuric acid [19]a or anhydrous zinc chloride and phosphoric acid [19]b. Under these conditions, the desired lactone (−)-**5** could never be isolated with a yield higher than 6%. We found that the treatment of D-*glycero*-D-*gluco*-heptono-(1,4)-lactone with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid led to a 1:7 mixture of (−)-**5** and (−)-**6** from which (−)-**5** could be isolated in 12% yield. The major isomer (−)-**6**, obtained in 74% yield, was readily equilibrated into a mixture of (−)-**5** and (−)-**6** on treatment with acetone and *p*-toluenesulfonic acid at 25 °C, allowing recovery

of (−)-**5** in 9% yield and (−)-**6** in 68% yield. Esterification of (−)-**5** with trifluoromethanesulfonic anhydride and pyridine in dichloromethane (−20 °C) gave the corresponding trifluoromethanesulfonate which, without purification, was treated with lithium azide in anhydrous *N*,*N*-dimethylformamide (20 °C, 15 h) to provide the corresponding azide (−)-**7** (68%, two steps). Addition of methyllithium in ether to a solution of (−)-**7** in tetrahydrofuran led to a single adduct (−)-**8** isolated in 94%. As expected for steric reasons, the addition was *anti* with respect to the acetonide moiety at C-2, C-3.



Hydrogenation of (+)-**8** reduced the azido group into a primary amine which equilibrated with the corresponding imine resulting from the intramolecular addition onto the ulose moiety. The latter was hydrogenated selectively to give (+)-**9**. Again, for steric reasons, the face *anti* with respect to the neighbouring acetonide was preferred for the hydrogenation of the intermediate imine, giving (+)-**9** in 92% yield. This compound and the corresponding iminooctitol (+)-**10**, obtained in 95% yield by acidic hydrolysis of the two acetonide moieties of (+)-**9**, were fully characterized from their elemental analyses and spectral data. The *β-galacto* relative configuration of these compounds was established from the coupling constants measured between their vicinal proton pairs and by NOE measurements in their ^{1}H NMR spectra.

Glycosidase inhibition measurements under standard conditions [5]c were performed for 24 commercially available enzymes. The iminooctitol (+)-**10** did not inhibit the following enzymes: bovine epididymis α-L-fucosidase (EC 3.2.1.51), *Aspergillus niger* and *Escherichia coli* α-galactosidases (EC 3.2.1.22), coffee beans, *Aspergillus niger*, *Escherichia coli*, bovine liver and *Aspergillus orizae* β-galactosidases (EC 3.2.1.23), yeast and rice maltases (EC 3.2.1.20), isomaltase from baker yeasts (EC 3.2.1.10), *Aspergillus niger* and *Rhizopus* mold amyloglucosidases (EC 3.2.1.3), jack beans and almond α-mannosidases (EC 3.2.1.24), *Helix pomatia* β-mannosidase (EC 3.2.1.25) and *Aspergillus niger* β-xylosidase (EC 3.2.1.37) and α-*N*-acetylhexosaminidases from chicken liver (EC 3.2.1.49), from jack beans and from bovine epididymis (EC 3.2.1.30). A weak activity was detected for the α-galactosidase from coffee bean (34% inhibition

at 1 mM concentration of (+)-**10**). However, for the hydrolysis of *p*-nitrophenyl β-D-glucopyranoside catalyzed by β-glucosidase (EC 3.2.1.21) from almond (pH 4.5, 37 °C) $IC_{50} = 98$ μM and $K_i = 15$ μM were measured. Under similar conditions, the β-glucosidase from *Caldocellum saccharolyticum* was inhibited with $IC_{50} = 107$ μM and $K_i = 41$ μM. The two latter glycosidases accepted (+)-**10** as a reversible inhibitor. For a comparison, (+)-castanospermine was a weaker inhibitor of β-glucosidase from almond than (+)-**10** since its inhibitory activity (IC_{50}) toward this enzyme was 250 μM.

3. Discussion

Although the piperidine unit of (+)-**10** has the same absolute configuration as β-D-*galacto*-hexopyranosides, it was a surprise to find that it does not inhibit the five β-galactosidases tested above. This suggests that these enzymes are quite restricted in terms of the type of β-galactosides they can accommodate as substrates. The two β-glucosidases that were found to be inhibited by (+)-**10** are certainly more tolerant concerning the structure of the substrates they can accommodate at their active sites. As a matter of fact, several β-glucosidases are known to catalyze the hydrolysis of a variety of β-D-glycosides [23,24]. Furthermore, β-D-glucosidase from almond can be inhibited efficiently by compounds such as 4-phenylimidazole ($K_i = 6.2$ μM [20]), D-gluconolactone ($K_i = 15$ μM [21]), D-fuconolactone ($K_i = 4$ μM [21]) and 7-azacyclophellitol ($IC_{50} = 220$ mg/mL [22]).

4. Experimental

Solvents were either reagent or technical grade (Fluka, Kodak, Aldrich, or E. Merck) and when necessary were purified and dried by distillation from an appropriate desiccant under an atmosphere of N_2. Concentration of solutions after reactions and extractions was achieved using a rotatory evaporator operating at reduced pressure. Liquid/solid flash chromatography (FC) employed silica gel (0.040–0.63 μm, E. Merck).

Melting points (uncorrected) were determined on a Tottoli (SMP-20) apparatus. Control thin layer chromatography was carried out with silica plates (Kieselgel 60, F_{254}, E. Merck), developed with UV light or with Pancaldi solution [5% aq H_2SO_4 with 4% $(NH_4)_6Mo_4O_7 \cdot 4H_2O$ and 0.2% $Ce(SO_4)_2$]. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. IR spectra were obtained on a Perkin–Elmer 1420 CW or a Perkin–Elmer Paragon 1000 FT-IR spectrometer. ^1H NMR spectra were recorded on a Bruker DPX-400 FT or Bruker ARX-400 FT (400 MHz) spectrometer. ^{13}C NMR spectra were obtained on the same instruments (100.61 MHz). Chemical shifts are reported in parts per million downfield from tetramethylsilane (Me_4Si), using the solvent's residual proton or carbon signal ($CHCl_3$, δ_H 7.27 ppm, δ_C 77.0; CD_2HCN, δ_H 2.05, $\delta_C = 1.3$) as internal reference. Also reported are the apparent multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons (when appropriate), coupling constants (hertz), and signal assignments. Mass

spectra were obtained on a Nermag R 10-10C spectrometer under chemical ionization. Elemental analyses were performed in the laboratory of Ilse Beetz, Kronach, Germany.

Enzymatic measurements followed the method described in [5c].

*2,3:6,7-Di-*O*-isopropylidene-*D-glycero-D-gulo-*heptono-1,4-lactone [(−)-5] and 3,5:6,7-di-*O*-isopropylidene-*D-glycero-D-gulo-*heptono-1,4-lactone [(−)-6].*—2,2-Dimethoxypropane (20 mL) and *p*-toluenesulfonic acid (375 mg, 1.97 mmol) were added to a stirred solution of D-*glycero*-D-*gulo*-heptono-1,4-lactone (10 g, 48.04 mmol, Aldrich) in dry acetone (125 mL). After stirring at 20 °C for 18 h, the solution was neutralized with Na_2CO_3 and then filtered. After the addition of silica gel (40 g), the solvent was evaporated under reduced pressure. FC (silica gel, 400 g, 3:2 EtOAc/light petroleum) afforded 9.68 g (70%) of (−)-**6** and 1.66 g (12%) of (−)-**5**.

*Recycling of (−)-***6***.*—*p*-Toluenesulfonic acid (300 mg, 1.58 mmol) was added to a stirred suspension of (−)-**6** (10 g, 37.7 mmol) in dry acetone (120 mL). After stirring at 20 °C for 3 days, the solution was neutralized with Na_2CO_3, filtered and separated by FC as above, giving 7.4 g (68%) of (−)-**6** and 1.06 g (9%) of (−)-**5**. Data for (−)-**5** and (−)-**6** were identical to those reported for these compounds [19].

*(−)-5-Azido-5-deoxy-2,3:6,7-di-*O*-isopropylidene-*D-glycero-L-manno-*heptono-1,4-lactone [(−)-7].*—Trifluoromethanesulfonic anhydride solution (4.14 mL, 24.7 mmol) in anhyd CH_2Cl_2 (18 mL) was added dropwise to a stirred solution of pyridine (2.4 mL, 29.4 mmol) in anhyd CH_2Cl_2 (25 mL) cooled to −20 °C under Ar. After stirring at −20 °C for 0.5 h, a solution of **5** (3.7 g, 12.8 mmol) in anhyd CH_2Cl_2 (30 mL) was added and the stirring continued for an additional hour. The mixture was poured into ice-cold 2 M HCl in H_2O (100 mL) and separated. The aq layer was extracted with CH_2Cl_2 (50 mL, 4 times), the combined organic extract washed successively with saturated aq $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated in vacuo at 20 °C. LiN_3 (0.8 g, 16.7 mmol) was added to a stirred solution of the crude product in anhyd DMF (10 mL) under an Ar atmosphere. After stirring at 20 °C for 15 h, the solvent was evaporated and the residue purified by FC (silica gel, 140 g, 1:4 EtOAc/light petroleum) yielding after recrystallization from EtOAc/light petroleum, 2.72 g (68%) of colourless crystals; mp 108.5–109.5 °C. $[\alpha]_D^{25}$ −7.1, $[\alpha]_{577}^{25}$ −7.2, $[\alpha]_{546}^{25}$ −8.0, $[\alpha]_{435}^{25}$ −13.8, $[\alpha]_{405}^{25}$ −16.7° (*c* 1.3, $CHCl_3$); IR (KBr): ν 2995, 2110, 1790, 1375, 1265, 1185, 1100, 1060, 1020, 910, 850 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.94 (dd, ^3J 5.1, 3.5 Hz, H-3), 4.86 (d, ^3J 5.1 Hz, H-2), 4.53 (dd, ^3J 10.1, 3.4 Hz, H-4), 4.43 (ddd, ^3J 6.7, 6.5, 4.1 Hz, H-6), 4.16 (dd, ^2J 8.6, ^3J 6.7 Hz, H-7), 3.98 (dd, ^2J 8.6, ^3J 6.5 Hz, H′-7), 3.66 (dd, ^3J 10.1, 4.1 Hz, H-5), 1.50 (6 H, Me_2C), 1.45, 1.38 (2 s, Me_2C); ^{13}C NMR ($CDCl_3$): δ 172.2 (s, C-1), 114.5, 109.9 (2 s, $(Me_2C)_2$), 76.3, 75.8 (2 C), 75.2 (4 d, ^1J(C,H) 150, 164, 158, 150 Hz, C-2, C-3, C-4, C-6), 66.2 (t, ^1J(C,H) 149 Hz, C-7), 60.1 (d, ^1J(C,H) 145 Hz, C-5), 26.8, 25.9 (2 C), 25.0 (4 q, ^1J(C,H) 127 Hz, $(Me_2C)_2$); CI-MS (NH_3): *m/z* 314 (1), 299 (10), 298 (72), 286 (14), 270 (10), 212 (5), 102 (10), 101 (100), 85 (9), 83 (10), 73 (14). Anal. Calcd for $C_{13}H_{19}O_6N_3$ (313.12): C 49.84; H 6.11; N 13.41. Found: C 49.78; H 6.02; N 13.32.

*(+)-6-Azido-1,6-dideoxy-3,4:7,8-di-*O*-isopropylidene-β-*D-glycero-L-manno-*oct-2-ulofuranose [(+)-8].*—1.6 M MeLi in Et_2O (2.08 mL, 3.33 mmol) was added dropwise to a stirred solution of (−)-**7** (946 mg, 3.02 mmol) in anhyd THF (26 mL) cooled to −78 °C under an Ar atmosphere. After stirring at −78 °C for 1.5 h, acetic acid (2 mL)

was added and the mixture was poured into aq saturated solution of $NaHCO_3$ (100 mL). The aq layer was extracted with EtOAc (75 mL, 4 times), the combined organic extract dried ($MgSO_4$), the solvent was evaporated, and the residue purified by FC (silica gel, 20 g, 1:1 EtOAc/light petroleum) giving 932 mg (94%) of colourless crystals; mp 79.5–81 °C. $[\alpha]_D^{25}$ 0.0, $[\alpha]_{577}^{25}$ +0.1, $[\alpha]_{546}^{25}$ +0.8, $[\alpha]_{435}^{25}$ +3.5, $[\alpha]_{405}^{25}$ +5.6° (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2): ν 3670, 3570, 2940, 2100, 1600, 1370, 1200, 1140, 1065, 970, 915, 875, 860 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.87 (dd, ^3J 5.8, 3.7 Hz, H-3), 4.44 (d, ^3J 5.8 Hz, H-2), 4.35 (ddd, ^3J 7.0, 6.6, 4.8 Hz, H-6), 4.13 (dd, ^3J 10.0, 3.7 Hz, H-4), 4.08 (dd, ^2J 8.4, ^3J 7.0 Hz, H-7), 3.93 (dd, ^2J 8.4, ^3J 6.6 Hz, H′-7), 3.66 (dd, ^3J 10.0, 4.8 Hz, H-5), 2.72 (s, -OH), 1.49, 1.47, 1.38, 1.35 (4 s, $(Me_2C)_2$), 1.49 (s, H_3-1); ^{13}C NMR ($CDCl_3$): δ 112.8, 109.6 (2 s, $(Me_2C)_2$), 105.6 (s, C-2), 84.9, 80.5, 77.2, 76.3 (4 d, ^1J(C,H) 159, 161, 182, 155 Hz, C-3, C-4, C-5, C-7), 66.6 (t, ^1J(C,H) 149 Hz, C-8), 60.5 (d, ^1J(C,H) 145 Hz, C-6), 26.1 (2 C), 25.2, 24.7 (4 q, ^1J(C,H) 127 Hz, $(Me_2C)_2$), 22.4 (*q*, ^1J(C,H) 128 Hz, C-1); CI-MS (NH_3): *m/z* 315 (3), 314 (16), 302 (5), 284 (5), 126 (3), 102 (6), 101 (100), 83 (5), 73 (10). Anal. Calcd for $C_{14}H_{23}O_6N_3$ (329.35): C 51.04; H 7.04; N 12.76. Found: C 51.10; H 7.09; N 12.68.

*(+)-3,7,8-Trideoxy-1,2:5,6-di-*O*-isopropylidene-3,7-imino-*D-threo-L-galacto-*octitol [(+)-9].*—A solution of (+)-**8** (95 mg, 0.29 mmol) and 10% Pd on charcoal (5 mg) in AcOEt (10 mL) was stirred at 20 °C under H_2 atmosphere for 12 h. Filtration through Celite, evaporation and FC (silica gel, 5 g, 2:1 EtOAc/light petroleum) yielded 76 mg (92%) of a colourless oil. $[\alpha]_D^{25}$ +40.3, $[\alpha]_{577}^{25}$ +41.8, $[\alpha]_{546}^{25}$ +47.5, $[\alpha]_{435}^{25}$ +79.0, $[\alpha]_{405}^{25}$ +94.0° (*c* 1.1, $CHCl_3$); IR (film): ν 3445, 2985, 1380, 1220, 1150, 1055, 865, 755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.25 (ddd, ^3J 8.1, 6.5, 5.3 Hz, H-2), 4.04 (dd, ^2J 8.1, ^3J 6.5 Hz, H-1), 4.00 (dd, ^3J 5.3, 2.7 Hz, H-6), 3.90 (dd, ^2J 8.1, ^3J 8.1 Hz, H′-1), 3.87 (dd, ^3J 7.4, 5.3 Hz, H-3), 3.48 (dd, ^3J 10.2, 7.4 Hz, H-4), 3.05 (dq, ^3J 6.6, 2.7 Hz, H-7), 2.37 (dd, ^3J 10.2, 5.3 Hz, H-5), 1.51, 1.38, 1.35 (6 H) (4 s, $(Me_2C)_2$), 1.24 (d, ^3J 6.6 Hz, H_3-8); ^{13}C NMR ($CDCl_3$): δ 109.3, 108.3 (2 s, $(Me_2C)_2$), 81.5, 77.2, 75.7, 72.7 (4 d, ^1J(C,H) 148, 149, 150, 145 Hz, C-3, C-4, C-5, C-7), 67.0 (t, ^1J(C,H) 150 Hz, C-1), 59.4, 50.9 (2 d, ^1J(C,H) 132, 132 Hz, C-7, C-3), 28.3, 26.4 (2 C), 25.4 (4 q, ^1J(C,H) 127–128 Hz, $(Me_2C)_2$), 17.6 (q, ^1J(C,H) 127 Hz, C-8); CI-MS (NH_3): *m/z* 290 (20), 289 (73), 288 (100), 230 (3), 230 (33), 212 (6), 186 (28), 172 (17), 154 (3), 128 (7), 100 (5), 86 (19), 83 (11). Anal. Calcd for $C_{14}H_{25}O_5N$ (287.17): C 58.52; H 8.77; N 4.87. Found: C 58.48; H 8.74; N 4.95.

*(+)-3,7,8-Trideoxy-3,7-imino-*D-threo-L-galacto-*octitol [(+)-**10**].*—A solution of (+)-**9** (80 mg, 0.28 mmol) in 50% aq trifluoroacetic acid (2 mL) was stirred at 20 °C for 12 h. Evaporation and purification over Dowex 50 W × 8 (H^+ form, 5 g, 200–400 mesh), eluting first with H_2O (8 mL) then with MeOH (5 mL) and finally with 5% aq NH_3 (5 mL) provided a solution of (+)-**10**. Lyophilization afforded 55 mg (95%) of a very hygroscopic white powder; mp 178 °C (dec.). $[\alpha]_D^{25}$ +17.3, $[\alpha]_{577}^{25}$ +18.6, $[\alpha]_{546}^{25}$ +20.1, $[\alpha]_{435}^{25}$ +32.7, $[\alpha]_{405}^{25}$ +37.4° (*c* 0.76, H_2O); IR (film): ν 3385, 2970, 2925, 1650, 1435, 1110, 1065, 840, 145 cm^{-1}; ^1H NMR (D_2O, CH_3CN as internal standard): δ 3.93 (ddd, ^3J 7.5, 4.7, 1.7 Hz, H-2), 3.68 (d, ^3J 3.0 Hz, H-6), 3.60 (dd, ^2J 11.5, ^3J 7.5 Hz, H-1), 3.54 (dd, ^2J 11.5, ^3J 4.7 Hz, H′-1), 3.53 (dd, ^3J 9.8, 9.8 Hz, H-4), 3.43 (dd, ^3J 9.8, 3.0 Hz, H-5), 2.78 (q, br, ^3J 6.7 Hz, H-7), 2.45 (d, br, ^3J 9.8 Hz, H-3), 1.00 (d, ^3J 6.7 Hz, H_3-8); ^{13}C NMR (D_2O, CH_3CN as internal standard): δ 73.4, 70.8, 67.4,

66.1 (2 d, ^1J(C,H) 143–146 Hz, C-6, C-5, C-4, C-2), 62.7 (t, ^1J(C,H) 144 Hz, C-1), 58.4 (d, ^1J(C,H) 135 Hz, C-3), 50.8 (d, ^1J(C,H) 137 Hz, C-7), 14.7 (q, ^1J(C,H) 127 Hz, C-8); CI-MS (NH_3): *m/z* 222 (1), 208 (5), 207 (4), 196 (3), 178 (3), 164 (9), 131 (13), 115 (28), 91 (100), 86 (91). Anal. Calcd for $C_8H_{17}O_5N$ (207.23): C 46.35; H 8.27; N 6.76. Found: C 46.24; H 8.34.

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