An Expedient Asymmetric Synthesis of a Calystegine B_4 Analogue

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Abstract: A convenient, high-yielding synthetic route to polyhydroxylated 6-oxa-*nor*-tropanes that mimic the structural framework of calystegine B_4 is reported.

Key words: alkaloids, glycosidase inhibitors, piperidines, asymmetric synthesis, calystegines

The design and synthesis of compounds that selectively inhibit glycosidases have attracted considerable research interest during the last years.[1,2] Such inhibitors are not only useful for probing the biological functions of oligosaccharides but are also significant as potential drugs for the treatment of carbohydrate mediated diseases, such as diabetes,[3] cancer,[4] and viral infections (including AIDS).[5] For this purpose, numerous natural and synthetic polyhydroxy alkaloids have been extensively investigated, including compounds with the piperidine, pyrrolidine, indolizidine and pyrrolizidine azasugar skeletons.[6]

The recent discovery of calystegines has introduced an entirely new class of alkaloids to this group of biologically active compounds.[1] Calystegines constitute a novel class of plant secondary metabolites, which have been implicated in the establishment and maintenance of specific plant-bacterium relationships.[7] Their structure consists of a *nor*-tropane skeleton bearing two to four hydroxyl groups varying in position and stereochemistry.[8] Evaluation of their biological activities has indicated that *nor*-tropanes possess significant inhibitory activities against various glycosidase enzymes,[1,9] presumably because of their structural similarities with known powerful enzyme inhibitors. Thus, calystegine B_2 **1** is an efficient inhibitor of both β-glucosidase and α-galactosidase,[10] while calystegine B_4 **2** is a potent specific inhibitor of mammalian trehalases (Figure 1).[11] It is also noteworthy that both molecules have no inhibitory activity against other enzymes. Since there is a lack of convenient methods for their asymmetric preparation, no SAR studies have been reported to date.[12]

Recently, the synthesis of a polyhydroxylated 6-oxa-*nor*-tropane analogue of calystegine B_2 (Figure 1, **3**) from L-idofuranose derivatives was reported.[13] This novel compound, which contains the structural framework of a bridged 1,3-*O*,*N*-heterobicyclic system, was found to possess strong and highly specific inhibitory activity against bovine liver β-glucosidases. Accordingly, we were interested to develop a convenient route for the preparation of the corresponding glucomimetic analogue of calystegine B_4 **4** (Figure 1). As precursor (Scheme 1) we envisioned the structural framework of chiral 2*S*-hydroxymethyl-dihydropyridone **5**, which is easily accessible from D-glucal, according to our recently reported method.[14] Protection of substrate **6** followed by reduction, according to previously reported modified Luche conditions, resulted in the formation of alcohol **7** as a single diastereomer. Benzylation of the hydroxyl group and subsequent dihydroxylation of the double bond with OsO_4 in the presence of 4-methylmorpholine *N*-oxide afforded the dihydroxypiperidine derivative **9** as a single diastereomer. The diastereoselectivity of this reaction may be rationalized considering the effective steric shielding of the *re*-face of the double bond by the *pseudo* axially oriented 2,6-bulky substituents (Figure 2).

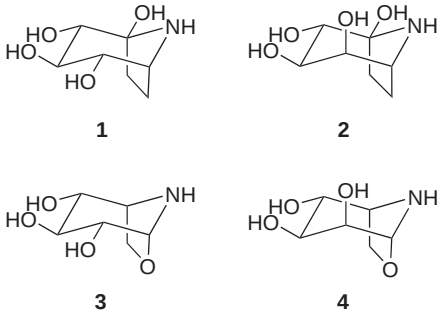

Figure 1

The diastereomeric purity of the product was revealed by HPLC and ^{1}H NMR spectroscopic analysis, since no trace of the other diastereomer was detected. The relative stereochemistry of compound **9** was deduced by 2D COSY and NOESY studies. Thus, the NOE correlation between H-5_{ax} and the hydroxyl proton on carbon atom C-3 and the small coupling constant between the β H-2 and H-3 are indicative of a $^4C_1$ conformation and the axial orientation of the hydroxy-group proton on carbon atom C-3. Furthermore, the interaction between the methylene-protons of the hydroxymethyl moiety and H-4_{ax}, is consistent with the equatorial orientation of the hydroxyl-group at carbon atom C-4 (Figure 2).

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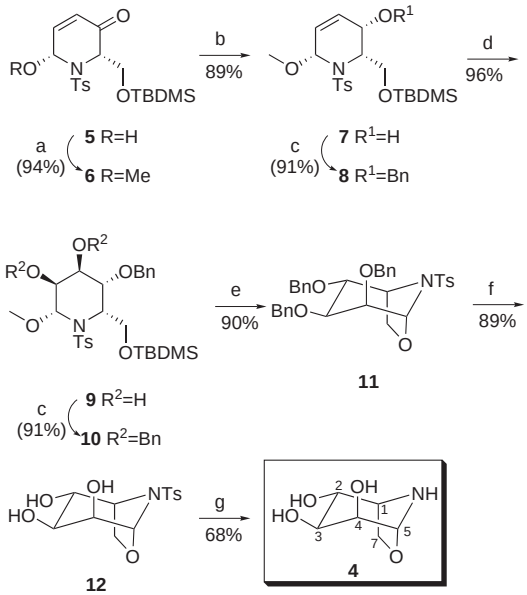

Scheme 1 a) $HC(OMe)_3$, $BF_3{\cdot}OEt_2$, 4Å molecular sieves, THF, 0 °C (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -30 °C (c) NaH, BnBr, Bu_4NI, THF (d) OsO_4, NMO, *t*-BuOH−acetone, 1:1 (e) $LiAlH_4$, $AlCl_3$, THF (f) H_2, Pd/C, MeOH (g) Na, naphthalene, THF.

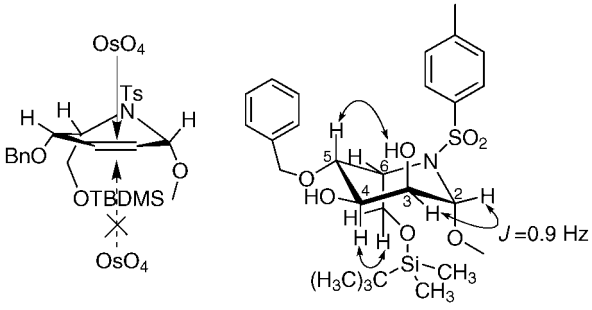

Figure 2

Diol **9** was protected and then treated with aluminum trichloride and lithium aluminum hydride in tetrahydrofuran. The analytical and spectroscopic data of the reaction product were consistent with the structure of bicyclic oxazolidone **11**. Apparently, under the reaction conditions cleavage of the TBDMS ether takes place, while the intramolecular nucleophilic attack of the unmasked alcohol to the corresponding imminium ion leads to the observed product. These results are in accordance with previous observations made by Fleet on corresponding polyhydroxylated δ-lactam derivatives.[15] Use of alternative reaction conditions such as sodium borohydride, formic acid or $BF_3{\cdot}Et_2O$, lithium aluminum hydride resulted in the formation of the same product. Finally, hydrogenolysis of the benzyl ethers and cleavage of the tosyl group provided the target calystegine B_4 glucomimetic **4** in 8 steps and 36% overall yield (from **5**).

All reactions were carried out under an argon atm unless otherwise noted. Solvents were dried by distillation prior to use. THF was distilled from sodium-benzophenone, and CH_2Cl_2 over CaH_2 immediately prior to use. Starting materials and reagents were purchased from Aldrich (analytical reagent grades) and used without further purification. Chiral 2*S*-hydroxymethyl-dihydropyridone (**5**) {$[\alpha]^{22}_D = -26.7$ (*c* 0.84, EtOAc), mp 101−103 °C} was prepared according to literature procedure.[14] Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Nicolet Magna 750, series II spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker AM-250 or DRX-400 spectrometers (250 MHz and 400 MHz, respectively) using TMS as internal standard. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at ambient temperature. Elemental analyses were provided by the University of Illinois microanalytical service laboratory. HPLC separations were performed using a Hewlett Packard 1100 series instrument with a variable wavelength UV detector and coupled to HP Chem-Station utilizing the manufacturer's 5.01 software package. TLC was conducted on Merck glass plates coated with silica gel 60 F_{254}. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh ASTM).

(2*S*,6*R*)-2-(*tert*-Butyl-dimethyl-silyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (6)

To an ice-cold soln of azapyranone **5** (1.53 g, 3.72 mmol), trimethyl orthoformate (0.8 mL, 7.44 mmol) and 4Å molecular sieves (0.35 g) in anhyd THF (25 mL), $BF_3{\cdot}Et_2O$ (0.7 mL) was added. The reaction mixture was stirred for 3 h at 0 °C, quenched with H_2O and extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to give a yellowish solid which was chromatographed (EtOAc−hexane, 1:4, R_f 0.35) to furnish the desired product **6** as colorless fine needles; yield: 1.49 g (94%).

Mp 68–70 °C (Et_2O−hexane).

$[\alpha]_D^{22}$ +106 (*c* 0.51, EtOAc).

IR (neat): 1695 (C=O), 1637 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, CH_3), 0.89 (s, 9 H, C−CH_3), 2.40 (s, 3 H, ArCH_3), 3.58 (s, 3 H, OCH_3), 3.94 (dd, *J* = 10.1, 7.3 Hz, 1 H, C*H*HOTBDMS), 4.00 (dd, *J* = 10.1, 7.5 Hz, 1 H, CH*H*OTBDMS), 4.39 (t, *J* = 7.3 Hz, 1 H, H-2), 5.55 (dd, *J* = 4.4, 0.9 Hz, 1 H, H-6), 5.78 (d, *J* = 10.1 Hz, 1 H, H-4), 6.74 (dd, *J* = 10.1, 4.4 Hz, 1 H, H-5), 7.25 (d, *J* = 8.3 Hz, 2 H, Ar-H), 7.59 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{20}H_{30}NO_5SSi$ (425.6): C, 56.44; H, 7.34; N, 3.29. Found: C, 56.55; H, 7.11; N, 3.34.

(2*S*,6*R*)-2-(*tert*-Butyl-dimethyl-silyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridin-3-ol (7)

To a stirred soln of compound **6** (0.76 g, 1.79 mmol) and $CeCl_3{\cdot}7H_2O$ (0.33 g, 0.89 mmol) in MeOH (20 mL) at -30 °C, $NaBH_4$ (0.24 g, 6.23 mmol) was added in portions. After 40 min of stirring at that temperature, the reaction was quenched with sat. aq NH_4Cl (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and chromatographed (EtOAc–hexane, 1:4, R_f 0.3) to afford **7** as a colorless oil; yield: 0.681 g (89%).

$[\alpha]_D^{22}$ +60 (*c* 0.9, EtOAc).

IR (neat): 3445 (OH), 1650 (C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, CH_3), 0.84 (s, 9 H, C−CH_3), 2.40 (s, 3 H, ArCH_3), 3.45 (s, 3 H, OCH_3), 3.66 (dd, *J* = 10.5, 3.9 Hz, C*H*HOTBDMS), 3.82 (m, 1 H, CH*H*OTBDMS), 4.04 (dt, *J* = 10.1, 5.3 Hz, 1 H, H-3), 4.3 (m, 2 H, OH, H-2), 5.24 (s, 1 H, H-6), 5.66 (dt, *J* = 10.3, 2.2 Hz, 1 H, H-4), 5.77 (d, *J* = 10.3 Hz, 1 H, H-5), 7.25 (d, *J* = 8.3 Hz, 2 H, ArH), 7.66 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{20}H_{33}NO_5SSi$ (427.6): C, 65.17; H, 7.78; N, 3.28. Found: C, 56.35; H, 7.89; N, 3.11.

(2*S*,3*S*,6*R*)-3-Benzyloxy-2-(*tert*-butyl-dimethyl-silyloxymethyl)-6-methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine (8)

To an ice-cold stirred soln of compound **7** (0.941 g, 2.2 mmol) in anhyd THF (3.5 mL), NaH (63 mg, 2.64 mmol) was added in portions. The reaction mixture was allowed to reach r.t. and stirred for 30 min. Then, a catalytic amount of Bu_4NI (40 mg, 0.11 mmol) was added followed by addition of BnBr (0.37 mL, 3.31 mmol). After 2 h of stirring, the reaction was quenched with sat. aq NH_4Cl (8 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to a yellowish slurry which was purified by chromatography (EtOAc–hexane, 1:4, R_f 0.55) yielding **8** as a colorless oil; yield: 1.036 g (91%).

$[\alpha]_D^{22}$ +82 (*c* 0.4, EtOAc).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, CH_3), 1.04 (s, 9 H, C−CH_3), 2.41 (s, 3 H, $ArCH_3$), 3.48 (s, 3 H, $ArCH_3$), 3.97 (dd, *J* = 11.1, 3.2 Hz, 1 H, C*H*HOTBDMS), 4.01 (m, 1 H, CH*H*OTBDMS), 4.15 (m, 2 H, H-3, H-2), 4.53 (d, *J* = 11.5 Hz, 1 H, CH_2Ar), 4.60 (d, *J* = 11.5 Hz, 1 H, CH_2Ar), 5.24 (s, 1 H, H-6), 5.66 (dt, *J* = 10.2, 2.4 Hz, 1 H, H-4), 5.75 (d, *J* = 10.2 Hz, 1 H, H-4), 7,21 (d, *J* = 7.9 Hz, 2 H, ArH), 7.25 (d, *J* = 8.3 Hz, 2 H, ArH), 7,34 (m, 3 H, ArH), 7,67 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{27}H_{39}NO_5SSi$ (517.8): C, 62.63; H, 7.59; N, 2.71. Found: C, 62.85; H, 7.77; N, 2.51.

***(2R,3S,4R,5R,6S)*-5-Benzyloxy-6-(*tert*-butyl-dimethyl-silyl-oxymethyl)-2-methoxy-1-(toluene-4-sulfonyl)-piperidin-3,4-diol (9)**

To a stirred soln of alkene **8** (0.46 g 1.08 mmol), in *t*-BuOH–acetone, 1:1 (5 mL), NMO (0.234 g, 2 mmol) and catalytic amount of soln OsO_4 (1% w/v, 1 mL) were added. The mixture was stirred for 6 h, then quenched with Na_2SO_3 (0.284 g, 2 mmol) and stirred for 30 min. The mixture was extracted with EtOAc (2 × 30 mL), the combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated to a yellowish slurry which was purified by chromatography (EtOAc–hexane, 1:1, R_f 0.3) yielding **9** as a colorless oil; yield: 0.530 g (96%).

$[\alpha]_D^{22}$ +39 (*c* 0.65, EtOAc).

IR (neat): 3475 (OH) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, CH_3), 0.90 (s, 9 H, C-CH_3), 2.30 (d, *J* = 2.2 Hz, 1 H, OH), 2.43 (s, 3 H, $ArCH_3$), 2.48 (d, *J* = 2.2 Hz, 1 H, OH), 3.39 (s, 3 H, OCH_3), 3.40 (m, 1 H, H-5), 3.82 (dd, *J* = 10.5, 5.7 Hz, 1 H, C*H*HOTBDMS), 3.95 (dt, *J* = 10.5, 5.7 Hz, 1 H, H-4), 4.01 (dd, *J* = 10.5, 6.1 Hz, 1 H, CH*H*OTBDMS), 4.08 (br s, 1 H, H-3), 4.16 (dt, *J* = 10.7, 5.7 Hz, 1 H, H-6), 4.23 (d, *J* = 11.4 Hz, 1 H, C*H*HAr), 4.65 (d, *J* = 11.4 Hz, 1 H, CH*H*Ar), 5.22 (d, *J* = 0.9 Hz, 1 H, H-2), 7.16 (dd, *J* = 5.7, 3.5 Hz, 2 H, ArH), 7.25 (d, *J* = 8.3 Hz, 2 H, ArH), 7.31 (m, 3 H, ArH), 7.82 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{27}H_{41}NO_7SSi$ (551.8): C, 58.77; H, 7.49; N, 2.54. Found: C, 58.50; H, 7.61; N, 2.39.

***(2S,3R,4S,5S,6R)*-3,4,5-Tris-benzyloxy-2-(*tert*-butyl-dimethyl-silyloxy methyl)-6-methoxy-1-(toluene-4-sulfonyl)-6-piperidine (10)**

To an ice-cold stirred soln of compound **9** (1.46 g 2.64 mmol) in anhyd THF (7 mL), sodium hydride was added in portions (126 mg, 5.28 mmol). The reaction mixture was allowed to warm to 15 °C and stirred for additional 30 min. Then a catalytic amount of Bu_4NI (80 mg, 0.22 mmol) and BnBr (0.74 mL, 6.61 mmol) were added. After 2 h of stirring, the reaction was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to a yellowish slurry which was purified by chromatography (EtOAc–hexane, 1:4, R_f 0.67) yielding **10** as a colorless oil; 1.76 g (91%).

$[\alpha]_D^{22}$ +21 (*c* 1.2, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6 H, CH_3), 0.88 (s, 9 H, C-CH_3), 2.23 (s, 3 H, $ArCH_3$), 3.37 (s, 3 H, OCH_3), 3.69 (m, 1 H, C*H*HOTBDMS), 3.82 (m, 3 H, CH*H*OTBDMS, H-5, H-4), 4.01 (m, 2 H, H-3, H-2), 4.36-4.60 (m, 5 H, CH_2Ar), 4.69 (d, *J* = 11.8 Hz, 1 H, CH_2Ar), 5.17 (d, *J* = 1.8 Hz, 1 H, H-6), 6.84 (d, *J* = 7.9 Hz, 2 H, ArH), 7.21 (m, 15 H, ArH), 7.58 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{41}H_{53}NO_7SSi$ (732.0): C, 67.27; H, 7.30; N, 1.91. Found: C, 67.41; H, 7.49; N, 1.82.

(1*S*,2*R*,3*S*,4*S*,5*R*)-2,3,4-Tris-benzyloxy-8-(toluene-4-sulfonyl)-6-oxa-8-aza-bicyclo[3.2.1]octane (11)

To a soln of **10** (1.10 g, 1.5 mmol) in anhyd THF (30 mL), $LiAlH_4$ (0.114 g, 3 mmol) and $AlCl_3$ (0.4 g, 3 mmol) were added. The reaction mixture was stirred for 3 h, then quenched with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to a yellowish slurry which was purified by chromatography (hexane–EtOAc, 4:1, R_f 0.65) to afford product **11** as colorless oil; yield: 0.8 g (90%).

$[\alpha]_D^{22}$ +35 (*c* 1.02, EtOAc).

IR (neat): 1700 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, $ArCH_3$), 3.10 (dd, *J* = 7.5, 4.4 Hz, 1 H, H-7), 3.57 (dd, *J* = 8.8, 4.9 Hz, 1 H, H-3), 3.75 (t, *J* = 4.9 Hz, 1 H, H-2), 3.79 (d, *J* = 7.5 Hz, 1 H, H-7), 3.85 (dd, *J* = 8.8, 3.5 Hz, 1 H, H-4), 4.14 (t, *J* = 4.9 Hz, 1 H, H-1), 4.51-4.61 (m, 5 H, $CH_{2a}Ar$), 4.66 (d, *J* = 11.4 Hz, 1 H, $CH_{2a}Ar$), 5.61 (d, *J* = 3.5 Hz, 1 H, H-5), 7.15-7.32 (m, 17 H, ArH), 7.73 (d, *J* = 8.8 Hz, 2 H, ArH).

Anal. Calcd for $C_{34}H_{35}NO_6S$ (585.7): C, 69.72; H, 6.02; N, 2.39. Found: C, 70.03; H, 6.17; N, 2.21.

(1*S*,2*R*,3*S*,4*S*,5*R*)-8-(Toluene-4-sulfonyl)-6-oxa-8-aza-bicyclo-[3.2.1]octane-2,3,4-triol (12)

Tris-benzyloxy piperidine **11** (0.3 g, 0.49 mmol) was dissolved in MeOH (2 mL) and hydrogenated over 10% Pd/C (30 mg) under 1 bar pressure for 20 h. The mixture was filtered through celite and concentrated under reduced pressure to give a yellowish oil which was purified by chromatography ($CHCl_3$–MeOH, 9:1, R_f 0.41) furnishing **12** as a white amorphous solid; yield: 137 mg (89%).

Mp 80–82 °C; $[\alpha]_D^{22}$ +67 (*c* 0.3, MeOH).

IR (neat): 3400–3340 (OH) cm^{-1}.

^{1}H NMR (250 MHz, DMSO): δ = 2.42 (s, 3 H, $ArCH_3$), 3.22 (dd, *J* = 7.4, 4.2 Hz, 1 H, H-7), 3.70 (m, 1 H, H-3), 3.78-3.82 (m, 2 H, H-7, H-4), 4.02 (m, 1 H, H-2), 4.55 (t, *J* = 4.9 Hz, 1 H, H-1), 5.73 (d, *J* = 3.2 Hz, 1 H, H-5), 7.25 (d, *J* = 8.3 Hz, 2 H, ArH), 7.70 (d, *J* = 8.3 Hz, 2 H, ArH).

Anal. Calcd for $C_{13}H_{17}NO_6S$ (315.3): C, 49.51; H, 5.43; N, 4.44. Found: C, 49.77; H, 5.27; N, 4.36.

(1*S*,2*R*,3*S*,4*S*,5*R*)-6-Oxa-8-aza-bicyclo[3.2.1]octane-2,3,4-triol (4)

To a soln of naphthalene (300 mg, 2.34 mmol) in freshly distilled THF (10 mL) sodium (54 mg, 2.28 mmol) was added. The mixture was stirred at ambient temperature for 45 min (dark-green color), then cooled to –78 °C and a soln of compound **12** (130 mg, 0.376 mmol) in THF (3 mL) was added. The reaction mixture was stirred at that temperature for 30 min, quenched with brine (2 mL) and con-

centrated under reduced pressure to give a slurry which was purified by chromatography ($CHCl_3$–MeOH, 4:1, R_f 0.33) to furnish the desired product as an off white solid; yield: 41 mg (68%).

Mp 61–62 °C; $[\alpha]_D^{22}$ +81.4 (*c* 0.7, H_2O).

IR (neat): 3440-3390 (OH), 3324 (NH) cm^{-1}.

^1H NMR (250 MHz, D_2O): δ = 3.43 (t, *J* = 4.9 Hz, 1 H, H-2), 3.47 (m, 1 H, H-4), 3.50 (dd, *J* = 8.8, 4.9 Hz, 1 H, H-3), 3.65-3.71 (m, 2 H, H-1, H-7), 3.91 (d, *J* = 7.2 Hz, 1 H, H-7), 4.90 (d, *J* = 2.9 Hz, 1 H, H-5).

Anal. Calcd for $C_6H_{11}NO_4$ (161.2): C, 44.72; H, 6.88; N, 8.69. Found: C, 44.56; H, 6.70; N, 8.48.

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