An Aza Analogue of *iso*-Levoglucosenone: Synthesis and Application of a New Building Block for Imino Sugars

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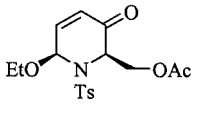
The aza analogue **3** of *iso*-levoglucosenone, which is easily accessible from furylglycine, was used as a flexible building block for the synthesis of various imino sugars. Enantiomerically pure products are available starting from optically active furylglycine derivatives.

Introduction

Glycosidases are crucial in many biochemical processes, so interest continues in applications of their potent and selective inhibitors to medicinal use or basic research.[1–3] Imino sugar ("azasugar") inhibitors are compounds that result from the exchange of the O-ring atom in carbohydrates by an NH group. This class of compound typically exhibits excellent inhibitory properties.[4,5] The natural product nojirimycin — a classic imino sugar — and its derivatives[6] have been studied extensively because of their high potential in anti-HIV, anticancer, and antidiabetic therapies.[7–11]

For this reason, many efforts have been made to develop simple syntheses of such systems. The common approach is based on transformations of naturally occurring D-hexoses. Polyhydroxypiperidines can be synthesized, however, also from non-carbohydrate precursors. Several routes have been described, and our group has developed previously the flexible chiral building blocks **1** and **2** as key compounds for the synthesis of polyhydroxylated piperidines.



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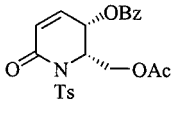

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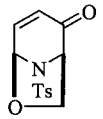
Dihydropyridone **1** has been obtained by an aza-Achmatowicz rearrangement[12] of a protected amino alcohol derived from furylglycine.[13] The unsaturated lactam **2** was prepared by a "chiral pool" approach from L-serine.[14]

Many publications in recent years have been testament to the continuing interest in the synthesis of synthetically useful building blocks. In this work, we present a new compound **3** that is applicable generally and is a flexible key intermediate for the preparation of imino sugars of various configurations and substitution patterns.[15]

The structure of **3** is reminiscent of another building block often used in the synthesis of natural products, the well-known *iso*-levoglucosenone **4**.[16]



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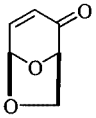

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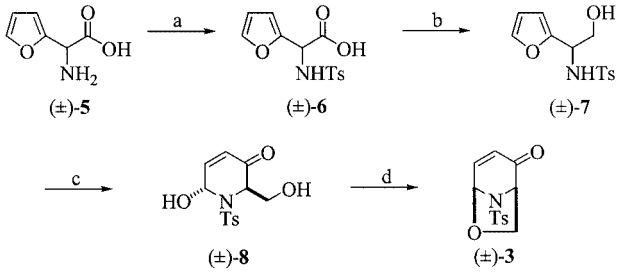
iso-Levoglucosenone **4** and its isomer levoglucosenone[17] have been chosen as starting compounds in many syntheses over the years because the functionality is confined in a structurally biased rigid bicyclic framework. Because of the 1,6-anhydro bridge, there is no need for protecting groups at the anomeric carbon atom or the primary hydroxy group at C-6. Furthermore, the β-D-face of the molecule is sterically more hindered than the α-face. This selectivity of *iso*-levoglucosenone also should be observed with compound **3**, and this feature would augment its great potential as a versatile building block.

Results and Discussion

Our efforts in the synthesis of the building block **3** followed a strategy, recently published by our group, starting

from the well-known furylglycine[18] (±)-**5** which was converted into the amino alcohol (±)-**7**, as depicted in Scheme 1. Oxidative ring expansion[12] occurred on reaction with NBS leading to the dihydropyridone (±)-**8** with complete control of diastereoselectivity in excellent yield. Intramolecular formation of the bicyclic acetal was carried out in benzene under reflux conditions in the presence of a catalytic amount of *p*TsOH to give the desired molecule (±)-**3**.



Scheme 1. Synthesis of building block **3**; reagents: (a) NEt(*i*Pr)$_2$, TsCl, 8 h, room temp. (61%). (b) 1. $LiAlH_4$, −5 °C, 4 h. 2. HCl, H_2O (62%). (c) NBS, 0 °C, 4 h (83%). (d) benzene, *p*-toluenesulfonic acid, 30 min, reflux (87%)

The structure of **3** as drawn is suggested by the close analogy of its NMR spectroscopic data to that of *iso*-levoglucosenone **4**, and has been confirmed by an X-ray structural study[19] (Figure 1).

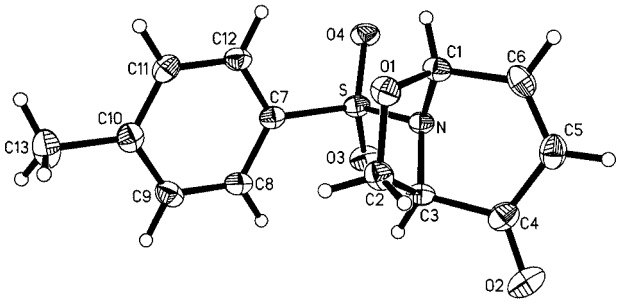
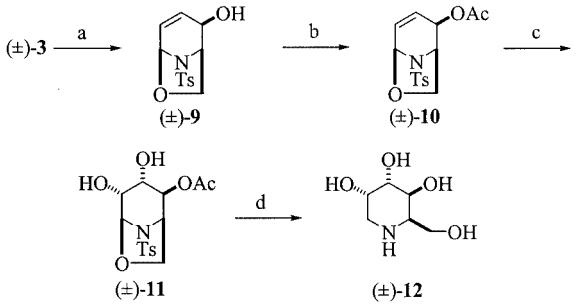


Figure 1. A perspective drawing of **3** with thermal ellipsoids (20% probability) for the non-hydrogen atoms

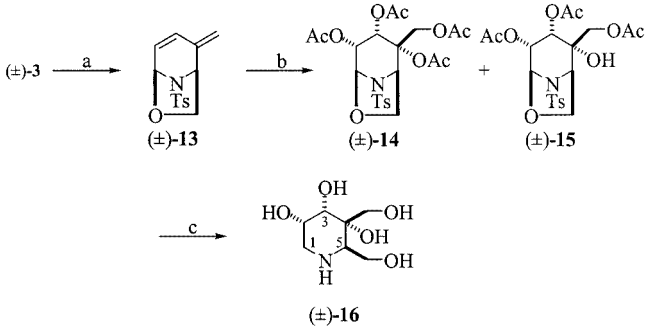
In order to probe its potential, the new key compound **3** was examined in de novo synthesis of known and unknown imino sugar systems. Some successful transformations involving stereospecific addition of reagents to the lower face of the building block have provided entry into a range of diastereoisomerically defined products, and these are reported in the following sections.

Reduction of (±)-**3** under Luche[20] conditions with $NaBH_4$ and $CeCl_3$ led to allylic alcohol (±)-**9** as the main product in 74% yield (Scheme 2). As found[16,17] for *iso*-levoglucosenone **4**, the 1,6-anhydro bridge effectively blocks the top face of the enone and $NaBH_4$ attacks exclusively from the less-hindered face of the enone. 2D-NOESY Spectroscopic analysis of the derived acetate (±)-**10** suggests the *syn*-arrangement of the acetate group with respect to CH_2−O group, as the hydrogen atom at the CHOAc group shows a weak coupling to the aromatic hydrogen atoms, but not to the CH_2 group of the anhydro bridge. *cis*-Dihydroxylation employing the method of Shing et al.[21] gave diastereoisomer (±)-**11** exclusively. To confirm that the observed stereoselectivity is again a result of a reaction from the less-hindered side, the product depicted was transformed further to the known[22−24] (±)-1-deoxygulonojirimycin **12** in a straightforward manner. Presumably cleavage of the aminal is followed by reductive removal of the amino protecting group with Red-Al. Ion-exchange purification led to the product shown.



Scheme 2. Synthesis of (±)-1-deoxygulonojirimycin; reagents: (a) 1. MeOH, $CeCl_3$, $NaBH_4$; 2. H_2O (74%). (b) Ac_2O, DMAP, 2 h (89%). (c) 1. $RuCl_3$, $NaIO_4$, MeCN, 10 min; 2. $Na_2S_2O_3$ (74%). (d) 1. Red-Al, DME, 24 h, reflux; 2. HCl, H_2O; 3. Dowex 50X8 (29%).

To demonstrate the synthetic potential of the building block, (±)-**3** was first converted into (±)-**13** by Wittig olefination (Scheme 3). The resulting diene seemed to be a very promising precursor for the synthesis of imino sugars with more than one hydroxymethyl side chain.



Scheme 3. Synthesis of (±)-2-(hydroxymethyl)piperidine-3,5-diol; reagents: (a) 1. $Me(Ph)_3PBr$, *n*BuLi, −78 °C to room temp., 5 h. 2. H_2O (67%). (b) 1. OsO_4, NMO, 4 d; 2. $Na_2S_2O_3$; 3. Ac_2O, pyridine, 24 h (48%). (d) 1. Red-Al, DME, 24 h, reflux; 2. HCl, H_2O; 3. Dowex 50X8 (41%)

Because of the steric effect of the bridge unit, the two double bonds should undergo modifications only from the lower face of the molecule as mentioned before. On reaction with OsO_4/NMO in aqueous acetone, a clean double *cis*-dihydroxylation occurred leading to a product that was difficult to extract from water during workup. Therefore, after evaporation of the solvent the crude reaction product was

peracetylated with acetic anhydride and pyridine for 24 h, giving two products that were separated by flash chromatography and identified as tetraacetate (±)-**14** and triacetate (±)-**15** in a ratio of 1.2:1. A shorter reaction time gave more of the triacetate. This observation is in line with the notion that a diastereoselective reaction from the less-hindered side had occurred to form an axial hydroxy group that is difficult to acetylate. 2-D NOESY spectra exhibit crosspeaks from the methylene group of the anhydro bridge unit to the axial hydrogen atom at C-3 for both products, which is evidence for the expected diastereoselective character of the dihydroxylation of the ring. Deprotection and reduction of both of the compounds led to (±)-**16**. Again, evaluation of the 2-D NOESY spectroscopic data pointed to the depicted structure.

The CH_2 group attached at the quaternary carbon atom shows a small coupling to the adjacent equatorial hydrogen atom at C-3, but no coupling to those at the anomeric centre C-1 or to the neighbouring hydrogen atom at C-5. In order to substantiate the proposed structure further, we are still trying to grow suitable crystals of **16** for X-ray crystallography.

Since the enantiopure form of furylglycine also is well known,[25] clearly it is desirable to prepare and to use it for the synthesis of enantiomerically pure compounds. Starting with L-furylglycine, we synthesized (+)-**3** without any problems using the described route. In addition to the synthesis of deoxynojirimycins in enantiomerically pure forms, our main interest was the application of (+)-**3** to the preparation of 1,3-dideoxynojirimycins because up to now only a few approaches to such systems are known.[26,27] In this work, we demonstrate the application of the key compound to the de novo synthesis of this class of compounds by the preparation of (+)-1,3-dideoxygulonojirimycin as a representative example.

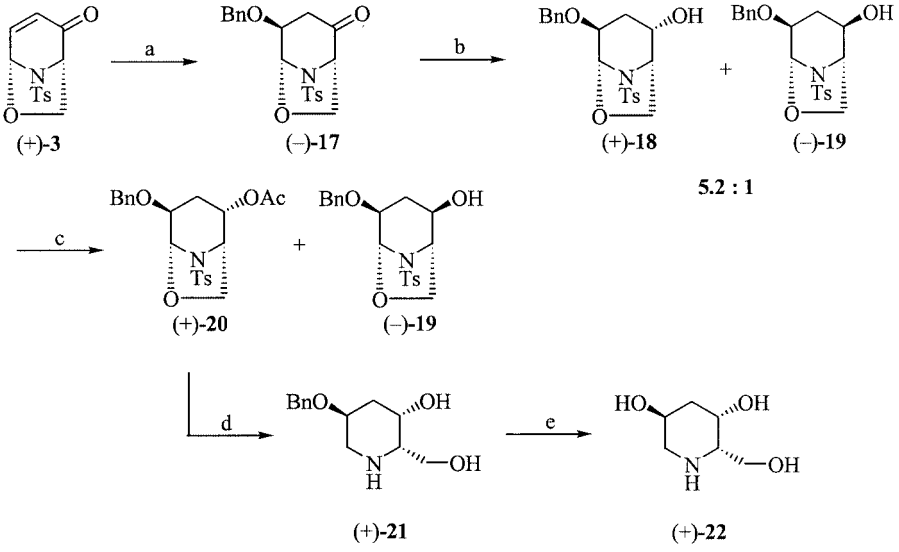
As depicted in Scheme 4, treatment of (+)-**3** with benzyl alcohol in the presence of triethylamine leads to a Michael addition at the enone, which yields (−)-**17** under complete stereocontrol. The addition occurs exclusively from the less-hindered side of the molecule. Reduction of (−)-**17** under Luche[21] conditions affords a mixture of the two possible diastereoisomers (+)-**18** and (−)-**19** in a 5.2:1 ratio. Without workup, reaction of the crude product with acetic anhydride and a catalytic amount of DMAP for one hour gives acetate (+)-**20** and alcohol (−)-**19**, which could be separated easily by flash chromatography. The configurations of both compounds are based on 2D-NOESY spectroscopic analyses that indicate that the main product is in the expected gulo form. Treatment of (+)-**20** with Red-Al, followed by chromatography on a column of Dowex-50 (H^+), gives monobenzylated (+)-**21**. Finally, deprotection using hydrogen gas in the presence of Pd/C leads to (+)-1,3-dideoxygulonojirimycin **22**.

Conclusion

In summary, a new, versatile building block **3** has been synthesized, as a racemate and in its optically pure form, and has been used for the preparation of (±)-deoxygulonojirimycin **12** and (+)-1,3-dideoxygulonojirimycin **22**. Moreover, we have demonstrated the application of **3** in the synthesis of (±)-**16**, the first member of a new class of imino sugars with an interesting substitution pattern in position C-4.

Experimental Section

General Remarks: All solvents were distilled and purified by standard procedures.[28] Products were purified by flash chromatography



Scheme 4. Synthesis of (+)-1,3-dideoxygulonojirimycin: reagents: (a) BnOH, NEt_3, 24 h (69%). (b) 1. MeOH, $CeCl_3 \cdot 7H_2O$, −5 °C; 2. HCl, H_2O (77%). (c) Ac_2O, DMAP, 2 h (93%). (d) 1. Red-Al, DME, 24 h, reflux; 2. HCl, H_2O; 3. Dowex 50X8 (54%). (e) H_2, Pd/C, 24 h (92%)

on Silica gel 60 (mesh 20−63, Merck) with various mixtures of ethyl acetate and cyclohexane. NMR spectroscopy was performed with an ARX 400 (Bruker) at room temperature. Chemical shifts are given in ppm (δ) relative to the solvent as internal standard. Mass spectra were recorded with MAT 311 A (Varian). High-resolution mass spectra (HRMS) were recorded at Bayer AG, Wuppertal (HR-EI: MAT95 Finnigan; HR-ESI: LCT Micro Mass). Infrared spectroscopy was performed with a Perkin−Elmer 1420 spectrometer. A VarioEL V2.6 (Elementar Analysensysteme GmbH) was used for elemental analyses.

***N*-[1-(2-Furyl)-2-(hydroxyethyl)]-4-methylbenzenesulfonamide (7): 5** (19.6 g, 0.14 mol) was dissolved in water (225 mL). A solution of *N*-ethyldiisopropylamine (47 mL, 0.28 mol) in ethyl acetate (450 mL) was added. At 0 °C the reaction mixture was treated with *p*-toluenesulfonyl chloride (29.19 g, 0.15 mol). The mixture was stirred vigorously for 8 h at room temperature. The phases were separated, the aqueous phase was extracted with ethyl acetate, and then the combined organic layers were washed with NaOH (1 M). The combined aqueous layers were treated at 0 °C with HCl (6 M). At pH 1, the aqueous layer was extracted with ethyl acetate and the organic phase was dried over $MgSO_4$. Removal of solvents and recrystallization from ethyl acetate/hexane gave **6** (25 g, 61%). Lithium aluminium hydride (6.4 g, 0.17 mol) was suspended in diethyl ether (500 mL) and cooled to −15 °C. A solution of **6** (23 g, 78 mmol) in THF was added dropwise. After stirring at room temperature for 3 h, the reaction mixture was treated at −10 °C with HCl (1 M, 300 mL) and then with ethyl acetate (200 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$. Removal of solvents and recrystallization from ethyl acetate/hexane gave the title compound (13.5 g, 62%). Using the same procedure, (+)-**7** was obtained from (+)-**6**. M.p. 72 °C. $[\alpha]_D^{20}$ = +29.7 (*c* = 1.0, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.78 (m, 2 H), 4.49 (s, 1 H), 6.02 (m, 1 H), 6.15 (m, 1 H), 7.13 (m, 1 H), 7.43 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.31, 53.33, 63.83, 107.75, 110.11, 126.93, 129.33, 137.34, 142.04, 143.11, 150.85 ppm. IR (neat): $\tilde{\nu}$ = 3400, 3280, 3120, 3080, 1595, 1320−1150, 800 cm^{-1}. MS: *m*/*z* (%) = 281 (2) [M$^+$], 250 (35), 155 (37), 91 (100), 65 (32). $C_{13}H_{15}NO_4S$ (281): calcd. C 56.66, H 7.14; found C 56.47, H 7.21.

6-Hydroxy-2-(hydroxymethyl)-1-[(4-methylphenyl)sulfonyl]-1,6-dihydropyridin-3(2*H*)-one (8): 7 (5 g, 17.8 mmol) and sodium acetate (1.86 g, 22.7 mmol) were dissolved in THF/H_2O (80 mL, 4:1), cooled to −5 °C, and then treated portionwise with *N*-bromosuccinimide (4.37 g, 24.6 mmol) such that the reaction temperature did not exceed 0 °C. The deep-orange solution was then stirred at 0 °C for 3 h. After the addition of ethyl acetate (200 mL), the mixture was treated subsequently with saturated aqueous KI (100 mL), saturated aqueous NaS_2O_3 (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) for workup. The organic layer was separated, washed with saturated aqueous NaCl (80 mL), and dried over $MgSO_4$. Removal of the solvent and flash chromatography gave the title compound (4.38 g, 83%). Using the same procedure, (+)-**8** was obtained from (+)-**7**. M.p. 132−136 °C (dec.). $[\alpha]_D^{20}$ = +40 (*c* = 1.0, acetone). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 2.41 (s, 3 H), 3.65 (d, *J* = 11.1 Hz, 1 H), 3.93 (m, 1 H), 4.39 (m, 1 H), 5.03 (s, 1 H), 5.92 (d, *J* = 9.4 Hz, 1 H), 6.01 (d, *J* = 10.2 Hz, 1 H), 6.06 (dd, *J* = 4.7, 8.6 Hz, 1 H), 7.05 (dd, *J* = 4.7, 10.2 Hz, 1 H), 7.42 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]acetone): δ = 22.06, 64.28, 64.91, 73.72, 128.70, 128.93, 131.39, 139.39, 145.54, 147.74, 194.33 ppm. IR (neat): $\tilde{\nu}$ = 3193, 3113, 3068, 2980−2887, 1691, 1597, 1453, 1388, 1340, 1310, 1230, 1153, 1060, 970, 917, 850, 811, 730 cm^{-1}. MS: *m*/*z* (%) = 279 (9) [M$^+$ − H_2O], 267 (15), 250 (24), 249 (23), 156 (15), 155 (82), 139 (18), 125 (12), 124 (76), 112 (11), 108 (11), 96 (39), 95 (21), 92 (46), 91 (100), 83 (20), 79 (14), 66 (12), 55 (93), 41 (28), 39 (77). $C_{13}H_{15}NO_5S$ (297): calcd. C 52.53, H 5.05, N 4.71; found C 52.25, H 5.11, N 4.69.

8-[(4-Methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]oct-3-en-2-one (3): 8 (3 g, 10.1 mmol) was dissolved in benzene (350 mL), a catalytic amount of *p*-TsOH was added, and the reaction mixture was heated under reflux for 30 min using a Dean−Stark trap. The hot solution was filtered and then washed with aqueous $NaHCO_3$ (5%, 50 mL). The organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent, flash chromatography of the crude product, followed by recrystallization from ethyl acetate/hexane, gave the title compound (2.45 g, 87%). Using the same procedure, (+)-**3** was obtained from (+)-**8**. M.p. 155−158 °C (dec.). $[\alpha]_D^{20}$ = +99 (*c* = 1.01, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.35 (dd, *J* = 8.9, 1.42 Hz, 1 H), 3.41 (dd, *J* = 8.8, 5.8 Hz, 1 H), 4.62 (m, 1 H), 6.05 (dd, *J* = 9.5, 1 Hz, 1 H), 6.11 (d, *J* = 4.9 Hz, 1 H), 7.18 (dd, *J* = 4.9, 9.6 Hz, 1 H), 7.53 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.57, 62.43, 65.49, 83.94, 127.5, 128.06, 129.92, 134.43, 145.13, 146.41, 192.43 ppm. IR (neat): $\tilde{\nu}$ = 3080−3060, 2995−2880, 1700, 1600, 1360−1330, 1180−1150 cm^{-1}. MS: *m*/*z* (%) = 279 (6) [M$^+$], 155 (15), 124 (69), 96 (60), 91 (76), 83 (19), 65 (31), 55 (100), 41 (18), 39 (32). $C_{13}H_{13}NO_4S$ (279.3): calcd. C 55.91, H 4.67, N 5.02; found C 56.17, H 4.66, N 5.13.

8-[(4-Methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]oct-3-en-2-ol (9): 3 (837 mg, 3 mmol) was dissolved in a methanolic solution of $CeCl_3 \cdot 7H_2O$ (0.4 M, 200 mL) and cooled to −10 °C. $NaBH_4$ (117 mg, 3.07 mmol) was dissolved in MeOH and added dropwise to the reaction mixture in such a way that the temperature did not rise higher than −5 °C. The solution was stirred for 2.5 h and then quenched with H_2O (130 mL). The MeOH was evaporated and the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$. The solvent was evaporated and the crude product purified by flash chromatography, followed by crystallization, to give the title compound (624 mg, 74%). M.p. 89−93 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 2.03 (s, OH), 2.47 (s, 3 H), 3.00 (dd, *J* = 8.3, 5.8 Hz, 1 H), 3.90 (dd, *J* = 8.5, 1.6 Hz, 1 H), 4.25 (m, 1 H), 4.90 (m, 1 H), 5.70 (d, *J* = 9.5 Hz, 1 H), 5.80 (d, *J* = 4.6 Hz, 1 H), 5.96 (ddd, *J* = 9.4, 1.5, 4.8 Hz, 1 H), 7.45 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, CD_2Cl_2): δ = 21.42, 60.06, 61.77, 83.82, 127.16, 128.22, 129.75, 130.31, 135.13, 144.83 ppm. IR (neat): $\tilde{\nu}$ = 3580−3500, 3050, 2980−2920, 1600, 1380, 1160, 1095 cm^{-1}. MS: *m*/*z* (%) = 281 (36) [M$^+$], 234 (21), 197 (55), 155 (96), 139 (19), 133 (84), 126 (100), 106 (33), 98 (17), 96 (30), 91 (100), 89 (15), 80 (22), 70 (100), 68 (37), 57 (33), 55 (17), 41 (73), 39 (54). $C_{13}H_{15}NO_4S$ (281.3): calcd. C 55.52, H 5.34, N 4.98; found C 55.85, H 5.34, N 4.72.

8-[(4-Methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]oct-3-en-2-yl Acetate (10): Acetic anhydride (0.7 mL, 6.4 mmol) and a catalytic amount of 4-dimethylaminopyridine were added to a solution of **9** (1.8 g, 6.4 mmol) in dichloromethane (50 mL) and then the reaction mixture was stirred for 5 h at room temperature. The solution was quenched with 5% aqueous $NaHCO_3$ (20 mL) and the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography and crystallization to give the title compound (1.85 g, 89%). M.p. 84−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 2.44 (s, 3 H), 3.11 (m, 1 H), 3.86 (d, *J* = 8.5 Hz, 1 H), 4.42 (m, 1 H), 5.66 (d, *J* = 9.6 Hz, 1 H), 5.73 (m, 1 H), 5.83 (d, 1 H, *J* = 4.6 Hz, 1 H), 6.04 (ddd, *J* = 4.7, 7.9, 1.5 Hz, 1 H), 7.55 (m, 4 H) ppm. ^{13}C NMR

(100.6 MHz, $CDCl_3$): δ = 20.75, 21.47, 57.43, 62.50, 72.45, 83.65, 126.35, 128.04, 128.96, 129.59, 134.80, 144.46, 169.62 ppm. IR (neat): ṽ = 3071, 2983−2951, 1792, 1598, 1475, 1370, 1346, 1306, 1287, 1232, 1158, 1118, 1092, 1036, 1009, 934, 878, 813, 751, 690 cm^{-1}. MS: *m*/*z* (%) = 323 (33) [M^+], 234 (16), 197 (37), 168 (28), 155 (34), 133 (24), 126 (40), 106 (16), 91 (83), 80 (12), 70 (11), 65 (14),43 (100), 41 (15), 39 (10). $C_{15}H_{17}NO_5S$ (323.4): calcd. C 55.73, H 5.26, N 4.33; found C 55.44, H 5.31, N 4.16.

3,4-Dihydroxy-8-[(4-methylphenyl)sulfonyl]-6-oxa-8-azabicyclo-[3.2.1]oct-2-yl Acetate (11): Acetate **10** (670 mg, 2.02 mmol) was dissolved in acetonitrile (50 mL) and cooled to −5 °C. A mixture of $NaIO_4$ (651 mg, 3.05 mmol), $RuCl_3$ (23 mg, 0.10 mmol) and H_2O (5 mL) was added and the solution was stirred for 13 min. The reaction was then quenched with aqueous $Na_2S_2O_3$ (15%, 50 mL). After separation the aqueous layer was extracted several times with ethyl acetate. The combined organic phases were dried over $MgSO_4$. The solvent was evaporated and the residue was recrystallized from ethyl acetate/hexane to give the title compound (546 mg, 73%). M.p. 170−175 °C (dec.). ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.97 (s, 3 H), 2.37 (s, 3 H), 2.60 (dd, *J* = 4.9, 8.3 Hz, 1 H), 3.50−3.55 (m, 2 H), 3.69 (m, 1 H), 4.27 (t, *J* = 4.1 Hz, 1 H), 4.72 (dd, *J* = 3.4, 9.2 Hz, 1 H), 4.81 (d, *J* = 6.7 Hz, 1 H), 5.10 (d, *J* = 4.5 Hz, 1 H), 5.44 (d, *J* = 3.7 Hz, 1 H), 7.36−7.7 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, [D_6]DMSO): δ = 20.09, 21.0, 55.7, 63.5, 66.8, 69.7, 73.1, 88.8, 127.5, 129.8, 135.6, 144.2, 169.8 ppm. IR (neat): ṽ = 3561, 3394, 3070−3024, 2975−2914, 1731, 1595, 1356, 1249, 1187, 1167, 1066, 984, 935, 908, 923, 678, 609, 550 cm^{-1}. MS: *m*/*z* (%) = 355 (2) [M^+ − 2H], 202 (63), 200 (27), 160 (32), 155 (80), 140 (44), 142 (66), 124 (12), 115 (32), 108 (49), 100 (67), 97 (53), 91 (93), 84 (20), 69 (65), 60 (16), 57 (14), 55 (16), 46 (79), 43 (100), 39 (24). $C_{15}H_{19}NO_7S$ (357): calcd. C 50.37, H 5.32, N 3.92; found C 50.07, H 5.18, N 3.85.

1-Deoxygulonojirimycin (12): Red-Al® (3.5 M solution in toluene, 2.8 mL) was added to a solution of diol **11** (357 mg, 1 mmol) in dry dimethoxyethane (40 mL) and then the reaction mixture was heated under reflux for 24 h. The deeply yellow solution then was quenched with HCl (0.75 N, 10 mL). The mixture was filtered, the volatile solvents were evaporated, the aqueous layer was lyophilized, and the residue was purified over Dowex 50 eluting with NH_4OH, to give of the title compound (47 mg, 29%) as a hygroscopic syrup. The analytical data are consistent with those reported in the literature.[23−25]

2-Methylene-8-[(4-methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]-oct-3-ene (13): *n*-BuLi (5.4 mmol) was added to a suspension of methyltriphenylphosphonium bromide (1.92 g, 5.4 mmol) in dry THF (50 mL) at −78 °C and then the mixture was stirred for 15 min. A solution of **3** (1 g, 3.58 mmol) in dry THF (50 mL) then was added dropwise. The reaction mixture was warmed to room temperature, stirred for 3 h, and then quenched with H_2O (50 mL). The aqueous layer was separated, extracted with ethyl acetate, and then the combined organic phases were dried over $MgSO_4$. The solvent was evaporated and the residue purified by flash chromatography, and recrystallization from ethyl acetate/hexane, to give of a colorless solid (669 mg, 67%). M.p. 140−145 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.24 (m, 1 H), 3.34 (m, 1 H), 4.61 (d, *J* = 5.6 Hz, 1 H), 4.89 (s, 1 H), 5.00 (s, 1 H), 5.81 (d, *J* = 4.6 Hz, 1 H), 6.05 (dd, *J* = 4.5, 9.3 Hz, 1 H), 6.10 (d, *J* = 9.2 Hz, 1 H), 7.51 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.51, 61.12, 68.76, 83.82, 112.25, 127.99, 128.64, 129.09, 129.56, 135.40, 144.20, 144.24 ppm. IR (neat): ṽ = 3090−3040, 2960−2890, 1735, 1640, 1590, 1345−1325, 1185−1156, 1100−1080, 1050, 1030−1010, 890, 870, 815−800, 773, 692, 678, 661 cm^{-1}. MS: *m*/*z* (%) = 277 (2) [M^+], 248 (44), 247 (76), 155 (18), 93 (32), 92 (100), 91 (93), 70 (17), 67 (16), 66 (12), 65 (97), 63 (12), 53 (11), 43 (24), 42 (10), 41 (35), 39 (86). $C_{14}H_{15}NO_3S$ (277.3): calcd. C 60.65, H 5.42, N 5.05; found C 60.65, H 5.82, N 4.58.

2,3,4-Triacetoxy-8-[(4-methylphenyl)sulfonyl]-6-oxa-8-azabicyclo-[3.2.1]oct-2-ylmethyl Acetate (14) and 4-Acetoxy-2-acetoxymethyl-2-hydroxy-8-[(4-methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]oct-3-yl Acetate (15): NMO (1.26 g, 9.32 mmol) and an aqueous solution of OsO_4 (2 g/L, 12.03 mL, 0.10 mmol) were added to diene **13** (1.06 g, 3.82 mmol) dissolved in acetone (80 mL), and then the mixture was stirred for 4 d at room temperature. $Na_2S_2O_3$ (10 equiv.) dissolved in water (30 mL) was added, the mixture stirred for 1 h, then all the solvents were evaporated. Acetic anhydride (20 mL) and pyridine (20 mL) were added to the crude product, the mixture was stirred for 3 d, and then all the volatile compounds were evaporated. The resulting solid was suspended in a mixture of brine (150 mL) and ethyl acetate (150 mL). After stirring for 1 h, the phases were separated and the aqueous layer was extracted several times with ethyl acetate. The combined organic phases were dried over $MgSO_4$. The solvents were evaporated and the residue purified by flash chromatography to give the tetraacetate **14** (416 mg) and the triacetate **15** (484 mg) (48% yield of the tetrole).

14: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.98 (s, 3 H), 2.01 (s, 3 H), 2.06 (s, 3 H), 2.08 (s, 3 H), 2.44 (s, 3 H), 3.19−3.23 (dd, *J* = 5.3, 8.9 Hz, 1 H), 3.96 (d, *J* = 8.9 Hz, 1 H), 4.50 (d, *J* = 12.5 Hz, 1 H), 5.01 (d, *J* = 5.1 Hz, 1 H), 5.07 (d, *J* = 12.5 Hz, 1 H), 5.13−5.15 (dd, *J* = 3.7 Hz; 5.4 Hz, 1 H), 5.37 (d, *J* = 5.3 Hz, 1 H), 5.61 (d, *J* = 3.6 Hz, 1 H), 7.33−7.78 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.52, 20.56, 20.68, 21.60, 21.72, 57.52, 61.14, 65.22, 68.75, 69.20, 82.30, 86.01, 127.72, 130.00, 135.11, 145.00, 169.02, 169.32, 169.60, 169.95 ppm. IR (film): ṽ = 3063, 2972−2922, 1752, 1597, 1493, 1433, 1369, 1228, 1168, 1106, 1041, 954, 908, 881, 861, 817, 737, 684, 613 cm^{-1}. MS: *m*/*z* (%) = 513 (2) [M^+], 454 (18), 358 (80), 352 (31), 326 (13), 316 (40), 292 (31), 242 (24), 238 (81), 224 (69), 210 (81), 196 (77), 168 (39), 155 (97), 138 (63), 126 (67), 108 (81), 91 (100), 84 (15), 70 (59), 55 (22), 43 (98). HRMS: 514.1406; calcd. for $C_{22}H_{28}NO_{11}S$ [M + H]: 514.1383.

15: ^1H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 6 H), 2.13 (s, 3 H), 2.45 (s, 3 H), 3.10−3.14 (dd, *J* = 5.2, 8.6 Hz, 1 H), 4.06 (d, *J* = 8.7 Hz, 1 H), 4.31 (d, *J* = 12.1 Hz, 1 H), 4.38 (d, *J* = 5.0 Hz, 1 H), 4.50 (d, *J* = 12.1 Hz, 1 H), 5.10 (d, *J* = 5.1 Hz, 1 H), 5.16−5.19 (dd, *J* = 3.7 Hz; 5.1 Hz, 1 H), 5.62 (d, *J* = 3.6 Hz, 1 H), 7.32−7.77 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.57, 20.61, 20.78, 21.60, 58.74, 64.81, 64.86, 68.47, 71.83, 74.47, 85.90, 127.54, 129.95, 135.50, 144.85, 169.48, 170.47, 170.51 ppm. IR (film): ṽ = 3476, 3083, 2973−2906, 1751, 1597, 1372, 1231, 1167, 1128, 1090, 1044, 947, 910, 855, 817, 728, 685, 615 cm^{-1}. MS: *m*/*z* (%) = 412 (16) [M^+ − OAc], 316 (88), 274 (43), 224 (10), 214 (12), 196 (23), 172 (15), 155 (68), 138 (58), 130 (14), 124 (13), 111 (13), 108 (17), 103 (12), 96 (11), 91 (100), 84 (16), 71 (43), 65 (30), 55 (36), 43 (74), 39 (16). HRMS: 516.116; calcd. for $C_{21}H_{26}NO_{12}S$ [M + HCOOH]: 516.1176.

2,3-Bis(hydroxymethyl)piperidine-3,4,5-triol (16): Red-Al® (3.5 M solution in toluene, 2.1 mL) was added of a solution of trisacetate **15** (365 mg, 0.71 mmol) in dry dimethoxyethane (40 mL), and then the reaction mixture was heated under reflux for 24 h. The light-green solution then was quenched with HCl (0.75 N, 10 mL), filtered, and the volatile solvents were evaporated. The aqueous layer was lyophilized and the residue was purified over Dowex 50 eluting with NH_4OH to give the title compound (56 mg, 41%). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.70−2.76 (t, *J* = 11.8 Hz; 12.0 Hz, 1 H),

2.86−2.88 (dd, J = 4.1 Hz; 6.5 Hz, 1 H), 2.93−2.98 (m, 1 H), 3.63−3.80 (m, 4 H), 3.90 (d, J = 2.7 Hz, 1 H), 4.00−4.05 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 46.15, 57.37, 62.69, 66.29, 67.85, 72.21, 77.33 ppm. IR (neat): ṽ = 3382, 2928, 1284, 1050, 1005. MS: *m*/*z* (%) = 193 (11) [M^+], 162 (74), 144 (12), 114 (12), 102 (21), 84 (15), 73 (52), 60 (100), 56 (19), 43 (37) cm^{-1}. HRMS: 194.1021; calcd. for $C_7H_{16}NO_5$ [M + H]: 194.1028.

4-Benzyloxy-8-[(4-methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]-octan-2-one [(−)-17]: Triethylamine (0.2 mL) was added to a solution of (+)-**3** (800 mg, 2.86 mmol) in benzyl alcohol (30 mL) and the mixture was stirred for 24 h at room temperature. The benzyl alcohol was evaporated in vacuo and the resulted yellow oil was crystallized from ethanol to give the title compound (764 mg, 69%). M.p. 144−145 °C. $[\alpha]_D^{20}$ = −32.4 (c = 1.19, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 2.52 (dd, J = 17.7, 2.5 Hz, 1 H), 2.63 (dd, J = 17.7, 6.6 Hz, 1 H), 3.46 (dd, J = 8.6, 5.2 Hz, 1 H), 3.70 (d, J = 8.6 Hz, 1 H), 3.87 (m, 1 H), 4.47 (d, J = 5.1 Hz, 1 H), 4.51 (d, J = 11.7 Hz, 1 H), 4.57 (d, J = 11.7 Hz, 1 H), 5.89 (d, J = 2.0 Hz, 1 H), 7.23−7.79 (m, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.56, 39.84, 64.88, 67.14, 71.32, 74.96, 87.86, 127.68, 127.78, 127.93, 128.45, 129.87, 135.70, 137.16, 144.74, 199.71 ppm. IR (neat): ṽ = 3071−3023, 2978−2870, 1730, 1593, 1490, 1452, 1394, 1347, 1170, 1138, 1080, 1000, 931, 889, 818, 747, 693, 682, 620 cm^{-1}. MS: *m*/*z* (%) = 296 (11) [M^+], 250 (13), 232 (74), 156 (13), 155 (76), 124 (12), 108 (13), 107 (12), 96 (11), 92 (62), 91 (100), 90 (11), 89 (12), 79 (17), 77 (20), 70 (46), 65 (65), 55 (23), 51 (16), 43 (24), 42 (32), 41 (17), 39 (32). $C_{20}H_{21}NO_5S$ (387.5): calcd. C 62.02, H 5.43, N 3.62; found C 61.94, H 5.43, N 3.61.

4-Benzyloxy-8-[(4-methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]-oct-2-yl Acetate [(+)-20] and 4-Benzyloxy-8-[(4-methylphenyl)sulfonyl]-6-oxa-8-azabicyclo[3.2.1]octan-2-ol [(−)-19]: The Michael adduct (−)-**17** (348 mg, 0.9 mmol) was dissolved in a methanolic solution of $CeCl_3{\cdot}7H_2O$ (0.4 M, 140 mL) and cooled to −10 °C. $NaBH_4$ (75 mg, 1.27 mmol) was dissolved in MeOH and added dropwise to the reaction mixture in a way such that the temperature did not rise above −5 °C. The solution was stirred for 2.5 h and then quenched with H_2O (100 mL). The MeOH was evaporated, the aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent yielded a mixture of diastereoisomers of **18** and **19** (5.2:1; 271 mg, 77%). The crude product (200 mg, 0.51 mmol) was dissolved in dichloromethane (20 mL), acetic anhydride (0.52 mmol) and a catalytic amount of 4-dimethylaminopyridine were added, and then the reaction mixture was stirred for 2 h at room temperature. The solution then was quenched with aqueous $NaHCO_3$ (5%, 10 mL), and the organic layer was separated and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography, followed by recrystallization from ethyl acetate/hexane, to give acetate (+)-**20** (127 mg) and alcohol (−)-**19** (71 mg) (93%; alcohols after separation).

(+)-20: M.p. 107−109 °C. $[\alpha]_D^{20}$ = +12.8 (c = 0.96, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62−1.69 (ddd, J = 14.6, 10.8 Hz, 1 H), 2.00 (s, 3 H), 2.15−2.20 (dd, J = 14.2, 6.2 Hz, 1 H), 2.40 (s, 3 H), 3.30 (dd, J = 8.1, 4.8 Hz, 1 H), 3.67 (m, 1 H), 3.90 (d, J = 8.2 Hz, 1 H), 4.35 (m,1 H), 4.49−4.58 (2 × d, J = 11.7 Hz, 2 H), 5.07−5.13 (m, 1 H), 5.73 (d, J = 3.3 Hz, 1 H), 7.22−7.82 (m, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.78, 21.40, 28.83, 57.24, 64.24, 68.26, 70.97, 86.34, 127.51, 127.55, 127.59, 128.22, 129.58, 136.15, 137.65, 144.10, 169.41 ppm. IR (neat): ṽ = 3039, 2977−2931, 1741, 1598, 1496, 1455, 1349, 1239, 1141, 1064, 980, 900, 858, 813, 737, 688 cm^{-1}. MS: *m*/*z* (%) = 340 (4) [M^+ − benzyl], 277 (14), 276 (91), 155 (29), 108 (9), 92 (26), 91 (100), 65 (16), 59 (22), 43 (78), 41 (17), 39 (12). HRMS: 432.1447; calcd. for $C_{22}H_{22}NO_6S$ [M + H]: 432.1481.

(−)-19: M.p. 125−128 °C. $[\alpha]_D^{20}$ = −19.2 (c = 1.10, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 1 H), 1.88 (d, J = 3.1 Hz, 1 H), 2.41 (s, 3 H), 3.26−3.29 (dd, J = 5.2, 8.2 Hz, 1 H), 3.57 (d, J = 8.2 Hz, 1 H), 3.67−3.69 (dd, J = 2.9, 6.1 Hz, 1 H), 3.73 (d, J = 3.1 Hz, 1 H), 4.32−4.34 (t, J = 4.5 Hz, 1 H), 4.53−4.67 (2 × d, J = 11.6 Hz, 2 H), 5.86 (d, J = 4.5 Hz, 1 H), 7.24−7.80 (m, 9 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.53, 29.43, 61.92, 66.19, 67.46, 71.14, 73.94, 87.03, 127.67, 127.82, 128.42, 129.75, 135.96, 137.41, 144.28 ppm. IR (neat): ṽ = 3557, 3414, 2972−2874, 1596, 1492, 1454, 1399, 1385, 1354, 1335, 1308, 1289, 1258, 1188, 1168, 1138, 1138, 1097, 1044, 1021, 993, 915, 873, 818, 751, 688, 577 cm^{-1}. MS: *m*/*z* (%) = 298 (11) [M^+ − benzyl], 281 (10), 250 (16), 234 (79), 155 (53), 126 (59), 108 (35), 98 (20), 96 (12), 91 (100), 84 (76), 79 (25), 70 (47), 65 (54), 57 (33), 55 (20), 51 (16), 47 (35), 43 (31), 39 (30). HRMS: 434.1298; calcd. for $C_{21}H_{24}NO_7S$ [M^+ − H + HCOOH]: 434.1273.

5-Benzyloxy-2-(hydroxymethyl)piperidin-3-ol [(+)-21]: Red-Al® (3.5 M solution in toluene, 3.0 mL) was added to a solution of acetate (+)-**20** (430 mg, 1 mmol) in dry dimethoxyethane (40 mL), and then the reaction mixture was heated under reflux for 24 h. The deeply yellow solution then was quenched with HCl (0.75 N, 12 mL), filtered, and the volatile solvents were evaporated. The aqueous layer was lyophilized and purified over Dowex 50 eluting with NH_4OH to give the title compound (123 mg, 53%). $[\alpha]_D^{20}$ = +7.8 (c = 0.45, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 1.60−1.67 (q, J = 2.2, 11.3 Hz, 1 H), 2.32−2.36 (m, 1 H), 2.62−2.67 (t, J = 11.7 Hz, 1 H), 3.00−3.03 (t, J = 6.8 Hz, 1 H), 3.43−3.47 (dd, J = 12.2 Hz, 1 H), 3.63−3.68 (dd, J = 8.1, 11.8 Hz, 1 H), 3.71−3.76 (dd, J = 5.5, 11.7 Hz, 1 H), 3.97−4.03 (m, 1 H), 4.20 (s, 1 H), 4.63 (s, 2 H), 7.42 (s, 5 H) ppm. ^{13}C NMR (100.6 MHz, D_2O): δ = 38.93, 50.44, 61.34, 63.66, 67.88, 72.98, 73.16, 130.59, 130.77, 131.01, 139.05 ppm. IR (neat): ṽ = 3373, 3062−3031, 2931, 1675, 1605, 1496, 1454, 1399−1371, 1092, 1077, 1028, 911, 876, 741, 699, 616 cm^{-1}. MS: *m*/*z* (%) = 206 (56) [M^+ − CH_2OH], 115 (9), 100 (6), 91 (100), 74 (7), 65 (8), 56 (9), 43 (5),36 (15). HRMS: 238.1465; calcd. for $C_{13}H_{20}NO_3$ [M + H]: 238.1443.

2-(Hydroxymethyl)piperidin-3,5-diol [(+)-22]: Benzyl ether (+)-**21** (70 mg, 0.30 mmol) was dissolved in H_2O (30 mL) and then stirred for 24 h under an atmosphere of hydrogen gas in the presence of Pd/C. Filtration and evaporation of the solvent gave the title compound (40 mg, 92%). $[\alpha]_D^{20}$ = +7.2 (c = 0.91, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 1.63−1.70 (q, J = 2.5, 11.3 Hz, 1 H), 2.23−2.27 (d, J = 13.6 Hz, 1 H), 2.78−2.84 (t, J =1.6 Hz, 1 H), 3.28−3.32 (dd, J = 4.8, 8.6 Hz, 1 H), 3.46−3.50 (dd, J = 4.0, 12.2 Hz, 1 H), 3.70−3.76 (dd, J = 8.9, 12.3 Hz, 1 H), 3.83−3.87 (dd, J = 4.6, 12.2 Hz, 1 H), 4.20−4.25 (m, 1 H), 4.28 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, D_2O): δ = 39.60, 50.10, 61.38, 62.13, 62.51, 65.71 ppm. IR (neat): ṽ = 3355, 2956−2819, 1407, 1299, 1115, 1073, 1044, 1011 cm^{-1}. MS: *m*/*z* (%) = 147 (2) [M^+], 116 (100), 100 (8), 98 (19), 74 (17), 70 (169, 60 (46), 56 (39), 43 (30), 36 (96). HRMS: 148.0976; calcd. for $C_6H_{14}NO_3$ [M + H]: 148.0974.

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