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An Expeditious Synthesis of Iminosugars

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A short and expedient synthesis of the potent glycosidase inhibitors, 1-deoxynojirimycin, miglitol, miglustat, 1-deoxymannojirimycin, and 1-deoxygalactonojirimycin is presented.

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The iminosugars are a family of polyhydroxylated heterocycles containing an endocyclic nitrogen atom, which are well known, competitive glycosidase inhibitors.[1] The carbohydrate mimicry displayed by iminosugars has resulted in their use as tools in the investigation of enzymatic processes as well as in the study of various disease states. The best known member of this family, 1-deoxynojirimycin **1** is an example of a naturally occurring iminosugar that potently inhibits α-glucosidases,[2] and along with some of its *N*-alkylated derivatives, namely *N*-butyl-1-deoxynojirimycin **2** and *N*-(2-hydroxyethyl)-1-deoxynojirimycin **3**, has clinical applications.[3–6] Other members of this family, 1-deoxygalactonojirimycin **4**, and 1-deoxymannojirimycin **5**, have also been prepared and have been found to exhibit potent α-mannosidase[7] and α-galactosidase[8] inhibitory activity, respectively (Fig. 1).

As a result of their biological importance, there have been several syntheses of these and other iminosugars published to date.[1,9–13] The route that was of interest to us, due to its simplicity and efficiency, is the one employed by Stutz and coworkers in their synthesis of 2-acetamido-1,2-dideoxynojirimycin-lysine hybrids.[14] An intermediate ulososide **6**, which is prepared by the 3-chloroperbenzoic acid oxidation of the corresponding 5,6-alkene, in the presence of benzyl alcohol (followed by a subsequent Zemplen *O*-deacetylation), was employed. This method appealed to us as the ulososide **6** is not only quite stable but can be readily used to generate, under reducing conditions, the 1,5-dicarbonyl compound needed for the preparation of the desired iminosugar in situ. Furthermore, the subsequent reductive amination and intramolecular cyclization, results in the exclusive formation of the D-*gluco* configured iminosugar in excellent isolated yields (Fig. 2).

To date, this synthetic methodology presented by Stutz and coworkers has not been formally investigated for the preparation of **1**–**5**. It seemed to us, given the importance of access to significant amounts of these compounds for biological studies, coupled with what would be a short and inexpensive synthetic route for the preparation of them, as well as the literature precedent for the preparation of iminosugars using 1,5-dicarbonyl precursors,[15–17] that such an exploration was warranted.

Methyl β-D-glucopyranoside **7**, was converted into the corresponding iodide **8**, using the procedure of Garegg and Samuelsson,[18] then elimination of hydroiodic acid with DBU afforded the desired alkene **9** (Scheme 1).[19] Oxidation with 3-chloroperbenzoic acid, in the presence of benzyl alcohol, provided the presumed ulososide **10** as a mixture of stereoisomers. Deacetylation gave the tetrol **11** in good yield with this compound being shelf-stable for at least 2 weeks. Attention was then directed at the reductive amination in an attempt to prepare **1**. Treatment of **11** with ammonium acetate in the presence of palladium(II) hydroxide and hydrogen gratifyingly gave 1-deoxynojirimycin in 76% yield. The overall yield for the preparation of **1** from **7** is 42% over four steps, which compares very favourably with literature syntheses, including a chemoenzymatic method.[20]

With this result, we turned our attention to the preparation of some *N*-alkylated derivatives. Debenzylation/reductive amination of **11** with *n*-butylamine or 2-aminoethanol under the established conditions gave *N*-butyl-1-deoxynojirimycin **2** and *N*-(2-hydroxyethyl)-1-deoxynojirimycin **3**, respectively, in high yields.

These excellent results encouraged further investigations into the synthesis of other iminosugars; the analogous route for methyl β-D-galactopyranoside **12** was explored. The results were similarly satisfying; the iodide **13** was converted to the alkene **14**, followed by the ulososides **15**, and thence tetrol **16**. Reductive amination of **16** then provided the desired iminosugar, 1-deoxygalactonojirimycin **4** exclusively and in high yield (64%) not only for this reaction but for the overall synthesis (33%). Similarly, starting from methyl α-D-mannopyranoside **17** the preparation of 1-deoxymannojirimycin **5**, proceeded smoothly (through the iodide **18**, alkene **19**, ulososides **20**, and tetrols **21**) with an overall yield of 32%.

In conclusion, we have demonstrated a new synthesis for commonly used iminosugars that is robust, efficient, and high yielding. The stability and ease of preparation of the tetrol precursors makes this route particularly attractive. Notably one gram of 1-deoxynojirimycin **1** can now be prepared from methyl β-D-glucopyranoside, in an overall yield of 42%, in approximately 4 days, with similar yields and time periods for analogous compounds.

Experimental

Standard workup refers to dilution with water, repeated extraction into an organic solvent, sequential washing of the

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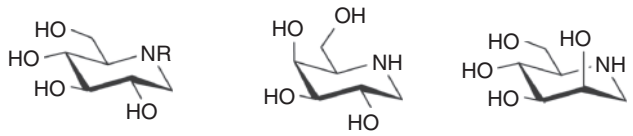
combined extracts with 1 M hydrochloric acid (where appropriate), saturated aqueous sodium bicarbonate and brine, followed by drying over anhydrous magnesium sulfate, filtration, and evaporation of the solvent by means of a rotary evaporator at reduced pressure. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV600 (600 MHz for ^{1}H and 150 MHz for ^{13}C) in $CDCl_3$ unless otherwise noted.



1 R = H
2 R = $(CH_2)_3CH_3$
3 R = $(CH_2)_2OH$

4 **5**

Fig. 1. Compounds synthesized in the present study.

General Procedure for the Preparation of Iodides

Triphenylphosphine (30 mmol), imidazole (60 mmol), and I_2 (29 mmol) were added to a suspension of the methyl glycoside (20 mmol) in PhMe (200 mL) with vigorous stirring at 70°C (2 h). The mixture was cooled, quenched with H_2O, and concentrated to give a yellow residue; pyridine (50 mL) and Ac_2O (50 mL) were added and the solution stirred (rt, 3 h). Concentration of the mixture, followed by a standard workup (EtOAc) and flash chromatography (EtOAc/petrol 1:4), furnished the desired iodides.

*Methyl Tri-O-acetyl-6-deoxy-6-iodo-β-D-glucopyranoside **8***

Obtained as a colourless oil (7.4 g, 86%). $[\alpha]_D$ +1.3° (in $CHCl_3$; lit.[19] +2.0° in $CHCl_3$). Gave ^{1}H and ^{13}C NMR spectra consistent with those found in the literature.[19]

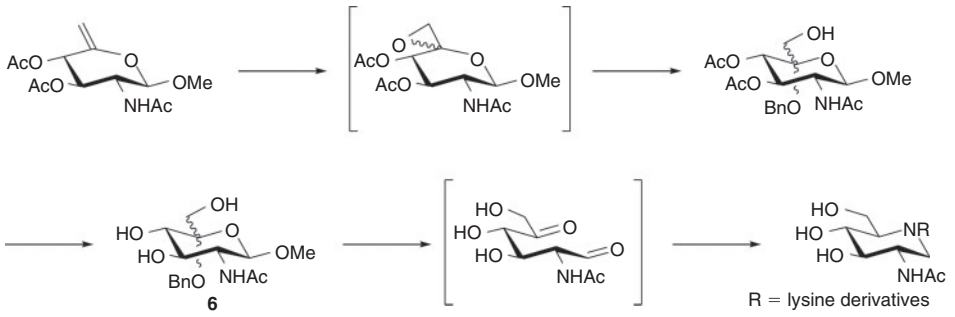
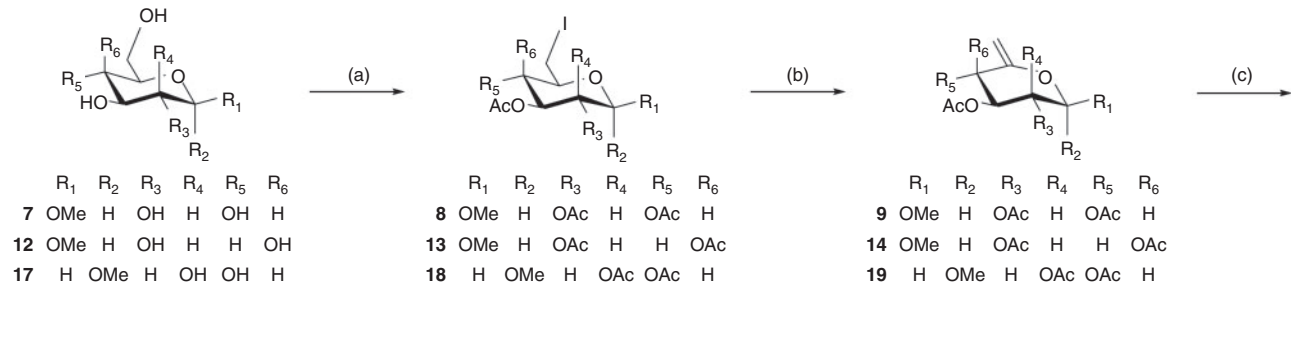


Fig. 2. Method used by Stutz and coworkers in the preparation of 2-acetamido-1,2-dideoxynojirimycin-lysine hybrids.[14]



	R_1	R_2	R_3	R_4	R_5	R_6
7	OMe	H	OH	H	OH	H
12	OMe	H	OH	H	H	OH
17	H	OMe	H	OH	OH	H

	R_1	R_2	R_3	R_4	R_5	R_6
8	OMe	H	OAc	H	OAc	H
13	OMe	H	OAc	H	H	OAc
18	H	OMe	H	OAc	OAc	H

	R_1	R_2	R_3	R_4	R_5	R_6
9	OMe	H	OAc	H	OAc	H
14	OMe	H	OAc	H	H	OAc
19	H	OMe	H	OAc	OAc	H

	R_1	R_2	R_3	R_4	R_5	R_6
10	OMe	H	OAc	H	OAc	H
15	OMe	H	OAc	H	H	OAc
20	H	OMe	H	OAc	OAc	H

	R_1	R_2	R_3	R_4	R_5	R_6
11	OMe	H	OH	H	OH	H
16	OMe	H	OH	H	H	OH
21	H	OMe	H	OH	OH	H

	R_1	R_2	R_3	R_4	R_5
1	OH	H	OH	H	H
2	OH	H	OH	H	$(CH_2)_2CH_3$
3	H	OH	OH	H	$(CH_2)_2OH$
4	OH	H	H	OH	H
5	H	OH	OH	H	H

Scheme 1. (a) i. I_2, Ph_3P, imidazole, PhMe, ii. Ac_2O, pyridine. (b) DBU, THF. (c) 3-Chloroperbenzoic acid, CH_2Cl_2, BnOH. (d) NaOMe, MeOH. (e) NH_4OAc (for **1**, **4**, **5**) or *n*-$BuNH_2$ (for **2**) or 2-aminoethanol (for **3**), $Pd(OH)_2/C$, H_2, MeOH:H_2O (15:1).

Methyl Tri-O-acetyl-6-deoxy-6-iodo-β-D-galactopyranoside **13**

Obtained as a colourless oil (7.0 g, 81%). $[\alpha]_D$ −3.6° (in $CHCl_3$; lit.[21] −4.3° in $CHCl_3$). δ_H (500 MHz, $CDCl_3$) 1.96 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.15 (dd, $J_{5,6}$ 6.1, $J_{6,6}$ 10.4, 1H, H6), 3.24 (dd, $J_{5,6}$ 7.8, $J_{6,6}$ 10.4, 1H, H6), 3.55 (s, 3H, OCH_3), 3.82 (ddd, $J_{4,5}$ 1.0, $J_{5,6}$ 6.1, $J_{5,6}$ 7.8, 1H, H5), 4.39 (d, $J_{1,2}$ 7.7, 1H, H1), 5.02 (dd, $J_{2,3}$ 10.4, $J_{3,4}$ 3.3, 1H, H3), 5.16 (dd, $J_{1,2}$ 7.7, $J_{2,3}$ 10.4, 1H, H2), 5.54 (dd, $J_{3,4}$ 3.3, $J_{4,5}$ 1.0, 1H, H4). δ_C (125.8 MHz, $CDCl_3$) 0.1 (C6), 20.5 (CH_3), 20.6 (CH_3), 20.8 (CH_3), 57.2 (OCH_3), 68.4, 68.6, 71.0, 73.4 (C2,3,4,5), 101.9 (C1), 169.5 (C=O), 170.1 (C=O), 170.2 (C=O). *m/z* 431.0219; $[M+H]^+$ requires 431.0203. Anal. Calc. for $C_{13}H_{19}IO_8$: C 36.30, H 4.45. Found: C 36.29, H 4.40%.

Methyl Tri-O-acetyl-6-deoxy-6-iodo-α-D-mannopyranoside **18**

Obtained as a colourless oil (7.0 g, 82%). $[\alpha]_D$ +35.9° (in $CHCl_3$; lit.[21] +37.0° in $CHCl_3$). δ_H 1.97 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.17 (dd, $J_{5,6}$ 9.6, $J_{6,6}$ 10.8, 1H, H6), 3.29 (dd, $J_{5,6}$ 2.4, $J_{6,6}$ 10.8, 1H, H6), 3.46 (s, 3H, OCH_3), 3.78 (ddd, $J_{4,5}$ 9.6, $J_{5,6}$ 2.4, $J_{5,6}$ 9.6, 1H, H5), 4.71 (d, $J_{1,2}$ 1.8, 1H, H1), 5.09 (dd, $J_{3,4}$ 9.6, $J_{4,5}$ 9.6, 1H, H4), 5.20 (dd, $J_{1,2}$ 1.8, $J_{2,3}$ 3.6, 1H, H2), 5.29 (dd, $J_{2,3}$ 3.6, $J_{3,4}$ 9.6, 1H, H3). δ_C 3.8 (C6), 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 55.4 (OCH_3), 68.6, 69.5, 70.0, 70.1 (C2,3,4,5), 98.5 (C1), 169.7 (C=O), 169.8 (C=O), 170.0 (C=O). *m/z* 431.0214; $[M+H]^+$ requires 431.0203. Anal. Calc. for $C_{13}H_{19}IO_8$: C 36.30, H 4.45. Found: C 36.22, H 4.43%.

General Procedure for the Preparation of the 5,6-Alkenes

1,8-Diazabicyclo[5.4.0]undec-7-ene (40 mmol) was added to the iodide (10 mmol) in THF (60 mL) and the mixture refluxed until no starting material was observed (t.l.c.). Concentration of the mixture, followed by a standard workup (EtOAc) and flash chromatography (EtOAc/petrol 2:3), gave the desired hex-5-enopyranosides.

*Methyl Tri-O-acetyl-6-deoxy-β-D-*xylo*-hex-5-enopyranoside* **9**

The title compound was obtained as a colourless oil (2.7 g, 89%) after a reaction time of 2 h. $[\alpha]_D$ −32.9° (in $CHCl_3$; lit.[19] −34.6° in $CHCl_3$). Gave ^1H and ^{13}C NMR spectra consistent with that found in the literature.[19]

*Methyl Tri-O-acetyl-6-deoxy-α-L-*arabino*-hex-5-enopyranoside* **14**

The title compound was obtained as a colourless oil (2.5 g, 83%) after a reaction time of 2 h. $[\alpha]_D$ −48.1° (in $CHCl_3$; lit.[22] −46.2° in $CHCl_3$). δ_H 2.03 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 4.52 (d, $J_{1,2}$ 5.9, 1H, H1), 4.55 (s, 1H, H6), 4.78 (s, 1H, H6), 5.06 (dd, $J_{2,3}$ 8.7, $J_{3,4}$ 3.7, 1H, H3), 5.28 (dd, $J_{1,2}$ 5.9, $J_{2,3}$ 8.7, 1H, H2), 5.70 (d, $J_{3,4}$ 3.7, 1H, H4). δ_C 20.6 (CH_3), 20.7 (CH_3), 20.9 (CH_3), 56.7 (OCH_3), 67.9, 68.8, 69.3 (C2,3,4), 101.5, 102.2 (C1,6), 150.0 (C5), 169.4 (C=O), 169.8 (C=O), 170.0 (C=O). *m/z* 300.1086; $[M+H]^+$ requires 300.1080. Anal. Calc. for $C_{13}H_{18}O_8$: C 51.65, H 6.00. Found: C 51.61, H 6.12%.

*Methyl Tri-O-acetyl-6-deoxy-α-D-*lyxo*-hex-5-enopyranoside* **19**

The title compound was obtained as a colourless oil (2.7 g, 91%) after a reaction time of 6 h. $[\alpha]_D$ +15.8° (in $CHCl_3$; lit.[23] +14.6° in $CHCl_3$). δ_H 2.00 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 3.44 (s, 3H, OCH_3), 4.55 (dd, $J_{4,6} \approx J_{6,6}$ 1.8, 1H, H6), 4.76 (d, $J_{1,2}$ 2.4, 1H, H1), 4.78 (dd, $J_{4,6} = J_{6,6}$ 1.8, 1H, H6), 5.30–5.34 (m, 2H, H2,3), 5.70 (ddd, $J_{3,4}$ 10.2, $J_{4,6}$ 1.8, $J_{4,6}$ 1.8, 1H, H4). δ_C 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 55.5 (OCH_3), 67.2, 68.6, 69.4 (C2,3,4), 97.1, 99.3 (C1,6), 151.0 (C5), 169.6 (C=O), 169.7 (C=O), 169.9 (C=O). *m/z* 300.1099; $[M+H]^+$ requires 300.1080. Anal. Calc. for $C_{13}H_{18}O_8$: C 51.65, H 6.00. Found: C 51.78, H 6.05%.

General Procedure for the Preparation of the Ulososides

To a 1% solution of the alkene (10 mmol) in a mixure of dichloromethane/benzyl alcohol (1:1 v/v), 3-chloroperbenzoic acid (20 mmol) was added, and the mixture was stirred at ambient temperature overnight. The mixture was partitioned between dichloromethane (120 mL) and aqueous sodium bicarbonate (5%), the organic layer was dried (Na_2SO_4), the solvent removed under reduced pressure, and the resulting residue was chromatographed (EtOAc/hexane 2:3) on silica gel providing a presumed diastereomeric mixture of ulososides. The residue was then dissolved in MeOH and treated with sodium methoxide and then stirred at ambient temperature (30 min). The mixture was quenched with resin (Amberlite IR-120, H^+), filtered, and concentrated. The residue obtained was sufficiently pure for the next step of the synthesis. Purification of the major epimer by flash chromatography (MeOH/EtOAc 1:9) gave the desired tetrols.

*Methyl (5R/S)-5-C-Benzyloxy-β-D-*xylo*-hexopyranoside* **11**

Obtained as a colourless oil (2.4 g, 81% over two steps). $[\alpha]_D$ −26.6° (in CH_3OH). δ_H 5*S* epimer (600 MHz, CD_3OD) 3.50 (s, 3H, OCH_3), 3.58–3.64 (m, 2H, H2,3), 3.78 (d, $J_{3,4}$ 7.3, 1H, H4), 3.83–3.87 (m, 2H, H6,6), 4.59 (d, $J_{1,2}$ 6.8, 1H, H1), 4.66 (A part of ABq, *J* 10.9, 1H, CH_2Ph), 4.72 (B part of ABq, *J* 10.9, 1H, CH_2Ph), 7.21–7.41 (m, 5H, Ph). δ_C 5*S* epimer (125.8 MHz, CD_3OD) 56.9 (OCH_3), 62.2, 64.5 (C6,*C*H_2Ph), 74.5, 75.6, 76.0 (C2,3,4), 102.9, 103.6 (C1,5), 128.2, 128.9, 129.1, 140.0 (Ph). *m/z* 301.1299; $[M+H]^+$ requires 301.1287. Anal. Calc. for $C_{14}H_{20}O_7$: C 55.99, H 6.71. Found: C 55.82, H 6.79%.

*Methyl (5R/S)-5-C-Benzyloxy-α-L-*arabino*-hexopyranoside* **16**

Obtained as a colourless oil (2.3 g, 78% over two steps). $[\alpha]_D$ −37.9° (in CH_3OH). δ_H 5*S* epimer (600 MHz, CD_3OD) 3.46 (s, 3H, OCH_3), 3.59 (dd, $J_{1,2}$ 7.9, $J_{2,3}$ 9.8, 1H, H2), 3.79 (d, $J_{6,6}$ 12.1, 1H, H6), 3.87 (d, $J_{6,6}$ 12.1, 1H, H6), 3.88 (dd, $J_{2,3}$ 9.8, $J_{3,4}$ 3.4, 1H, H3), 3.96 (d, $J_{3,4}$ 3.4, 1H, H4), 4.41 (d, $J_{1,2}$ 7.9, 1H, H1), 4.66 (A part of ABq, *J* 11.4, 1H, CH_2Ph), 4.70 (B part of ABq, *J* 11.4, 1H, CH_2Ph), 7.25–7.40 (m, 5H, Ph). δ_C 5*S* epimer (125.8 MHz, CD_3OD) 57.2 (OCH_3), 59.7, 63.6 (C6, *C*H_2Ph), 70.6, 71.7, 72.0 (C2,3,4), 102.3, 102.8 (C1,5), 127.9, 128.5, 129.3, 139.3 (Ph). *m/z* 301.1276; $[M+H]^+$ requires 301.1287. Anal. Calc. for $C_{14}H_{20}O_7$: C 55.99, H 6.71. Found: C 56.07, H 6.76%.

*Methyl (5R/S)-5-C-Benzyloxy-α-D-*lyxo*-hexopyranoside* **21**

Obtained as a colourless oil (2.2 g, 74% over two steps). $[\alpha]_D$ +27.1° (in CH_3OH). δ_H 5*R* epimer (600 MHz, CD_3OD) 3.50 (s, 3H, OCH_3), 3.70 (dd, $J_{1,2}$ 7.5, $J_{2,3}$ 3.6, 1H, H2), 3.77 (d, $J_{6,6}$ 12.1, 1H, H6), 3.86 (d, $J_{6,6}$ 12.1, 1H, H6), 3.94 (dd, $J_{2,3}$ 3.6, $J_{3,4}$ 3.9, 1H, H3), 4.02 (d, $J_{3,4}$ 3.9, 1H, H4), 4.73–4.75 (m, 3H, H1, CH_2Ph), 7.25–7.45 (m, 5H, Ph). δ_C 5*S* epimer (125.8 MHz,

CD_3OD) 57.1 (OCH_3), 60.8, 64.2 (C6, CH_2Ph), 69.2, 69.7, 73.7 (C2,3,4), 100.0, 104.6 (C1,5), 127.9, 128.8, 129.5, 139.1 (Ph). *m/z* 301.1283; $[M+H]^+$ requires 301.1287. Anal. Calc. for $C_{14}H_{20}O_7$: C 55.99, H 6.71. Found: C 56.10, H 6.79%.

General Procedure for the Intramolecular Reductive Amination

To a 0.03 M solution of the ulososide in MeOH/H_2O (20 mL, 15:1v/v), one equivalent of the amine component as well as Pd$(OH)_2$/C (20%, 0.1 equiv.) was added, and the heterogeneous reaction mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature for 24 h. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/concd NH_3, 10:10:1 v/v/v), yielding the target compounds. The formation of L-*ido* configured products was not observed in any of the reported cases.

1-Deoxynojirimycin ***1***

Obtained as a colourless oil (70 mg, 68%). $[\alpha]_D$ +34.0° (in H_2O; lit.[24] +34.4° in H_2O). Gave ^1H and ^{13}C NMR spectra consistent with that found in the literature.[24]

N-*Butyl-1-deoxynojirimycin* ***2***

Obtained as a colourless oil (80 mg, 61%). $[\alpha]_D$ −16.2° (in H_2O; lit.[24] −15.9° in H_2O). Gave ^1H and ^{13}C NMR spectra consistent with that found in the literature.[24]

N-*(2-Hydroxyethyl)-1-deoxynojirimycin* ***3***

Obtained as a colourless oil (72 mg, 58%). $[\alpha]_D$ −7.2° (in H_2O; lit.[24] −7.7° in H_2O). Gave ^1H and ^{13}C NMR spectra consistent with that found in the literature.[24]

1-Deoxygalactonojirimycin ***4***

Obtained as a colourless oil (63 mg, 64%). $[\alpha]_D$ +50.5° (in H_2O; lit.[25] +50.2° in H_2O). Gave ^1H and ^{13}C NMR spectra consistent with that found in the literature.[25]

1-Deoxymannojirimycin ***5***

Obtained as a colourless oil (62 mg, 61%). $[\alpha]_D$ −35.5° (in H_2O; lit.[24] −36.1° in H_2O). Gave ^1H and ^{13}C NMR spectra consistent with that found in the literature.[24]

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