1,5-Anhydro-D-fructose as Chiral Building Block: A Novel Approach to 1-Deoxymannojirimycin

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Received 2 August 2005; revised 6 October 2005

Dedicated to the memory of Professor Christian Pedersen, the excellent Danish carbohydrate chemist

Abstract: A novel six-step synthesis of 1-deoxymannojirimycin from 1,5-anhydro-D-fructose in 35% overall yield is reported. The key steps are nucleophilic piperidine ring formation and subsequent Lewis acid induced pyran ether cleavage.

Key words: chiral pool, azasugars, glycosidase inhibitors, ring opening

As part of our ongoing interest for using 1,5-anhydro-D-fructose (**1**, AF) as a chiral building block,[1,2] we present here the synthesis of the important glycosidase inhibitor 1-deoxymannojirimycin (**2**) from **1** through an efficient and highly stereoselective route via the bicyclic 2,6-anhydro-1-deoxymannojirimycin (**3**) (Figure 1). 1,5-Anhydro-D-fructose (**1**), which was first synthesized by a multistep synthesis from D-glucose in low yield,[3] is now available in larger amounts by enzymatic degradation of starch by α-1,4-glucan lyase.[4] AF (**1**) has already proven to be a valuable chiral building block, since it was used in the synthesis of the natural products polythazin[5] and bissetone.[6] Likewise, we previously reported the highly stereoselective formation of 2-amino-1,5-anhydro-2-deoxy-D-mannitol by Pd-catalysed hydrogenation of 1,5-anhydro-D-fructose oximes[2b] as well as the stereoselective reduction of the carbonyl group to give either 1,5-anhydro-D-glucitol or 1,5-anhydro-D-mannitol.[2b]

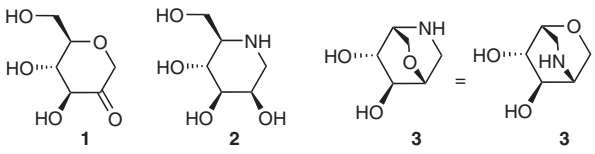


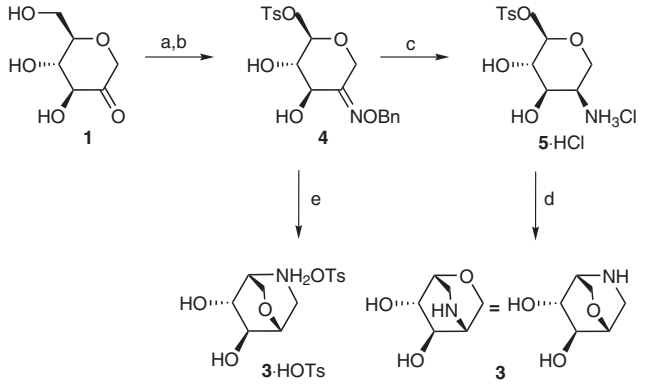
Figure 1 Compounds **1**–**3**

The naturally occurring 1-deoxymannojirimycin (1,5-dideoxy-1,5-imino-D-mannitol) represents a class of iminosugars that have attracted considerable attention in recent years. These compounds are among the most effective inhibitors of glycosidases[7] and glycosyltransferases[8] due to their ability to mimic charge and conformation of the cationic intermediates generated in the enzymatic process.[9] 1-Deoxymannojirimycin (**2**) and its derivatives are known to be potent inhibitors of α-L-fucosidase and α-D-mannosidase[10] and have potential therapeutic value.[11] As a result much effort has been undertaken in developing methodologies for the synthesis of **2**.[12]

The synthesis of the bicyclic iminosugar **3** is shown in Scheme 1. Thus, treatment of 1,5-anhydro-D-fructose (**1**) with *O*-benyzlhydroxylamine gave the crystalline oxime in excellent yield. Subsequent regioselective tosylation afforded the 6-*O*-tosylated oxime **4** in 77% yield after purification by column chromatography. Hydrogenation of **4**, in the presence of hydrochloric acid, afforded stereoselectively amine **5** as the crystalline hydrochloride (**5**·HCl). The Pd-catalysed hydrogenation thus followed the general trend to give selectively *manno*-configured product as we have shown for similar hydrogenations of AF-derivatives and their oximes.[2b] Deprotonation of **5**·HCl with triethylamine induced intramolecular nucleophilic displacement of the tosyloxy group by the amine giving 2,6-anhydro-1-deoxymannojirimycin (**3**). This procedure provided **3** in four steps from 1,5-anhydro-D-fructose (**1**) with an overall yield of 57%. Conducting the reduction of **4** in the absence of acid resulted in direct formation of the bicyclic iminosugar **3**, which was obtained together with uncyclised 2-amino intermediate **5**. A complete ring closure was achieved by treating the crude product with pyridine. The latter procedure seems, although lower yielding (43% from **1**), more suitable for larger scale preparations since **3** could simply be crystallised as toluenesulfonic acid salt without preceding column chromatographic purification. A synthesis of 2,6-anhydro-1,5-dideoxy-1,5-imino-D-mannitol (**3**) has been described as a nine-step procedure in an overall yield of 11% from 1,5-anhydro-D-glucitol.[13]

In order to prepare 1-deoxymannojirimycin (**2**) from the 2,6-anhydro derivative **3** the pyran ether bond in **3** needed to be cleaved. Many reagents are capable of cleaving ethers as discussed in several earlier reviews.[14] We were especially inspired by some more recently published examples,[15] reporting the use of boron trifluoride and boron tribromide. Therefore our initial attempts were carried out using these boron containing Lewis acids and the acetyl protected derivative of **3**, but no ether cleavage was observed under these conditions. Vogel et al., who investigated the BBr_3-promoted ether cleavage of 7-oxabicyclo[2.2.1]heptane derivatives,[16] reported that a

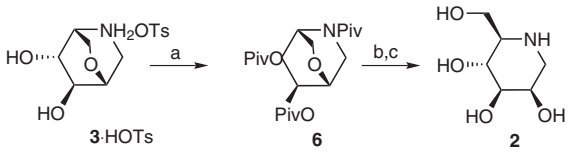
SYNTHESIS 2006, No. 5, pp 0827–0830
Advanced online publication: 08.02.2006
DOI: 10.1055/s-2006-926343; Art ID: T10405SS



Scheme 1 *Reagents and conditions*: a) $NH_2OBn{\cdot}HCl$, KOH, r.t., EtOH, 91%; b) TsCl (1.2 equiv), pyridine, –20 °C, 77%; c) H_2, Pd/C, MeOH/HCl, 30 bar, r.t., 81%; d) Et_3N, DMF, r.t., quant; e) H_2, Pd/C, MeOH, 30 bar, r.t., then pyridine, r.t., 62%.

successful ether cleavage was only achieved when the pivaloylated ether derivative was applied. The corresponding acetylated compound showed no reactivity. They assumed that this lack of reactivity was due to the favoured BBr_3 coordination of the acetyl group, whereas coordination of the bulky pivaloyl groups is sterically hindered, thus not preventing the formation of an intermediary Lewis acid ether complex. Encouraged by this report compound **3** was pivaloylated to give **6**. Reaction of **6** with BBr_3 followed by quenching with either H_2O/$NaHCO_3$ or with MeOH and neutralisation with ion-exchange resin, gave a mixture of differently pivaloylated derivatives of 1-deoxymannojirimycin (**2**), of which the 4,6-di-*O*-pivalate was the main compound. This crude mixture was then treated with NaOMe in MeOH to give **2** as sole reaction product. Purification by column chromatography afforded the desired crystalline iminosugar **2** in a yield of 67% (Scheme 2).

The remarkable result of this BBr_3 induced pyran ether cleavage led to further investigations of the reaction. Concerning the mechanism, it appears interesting to mention that the ether cleavage occurred, independently whether MeOH or $H_2O/NaHCO_3$ was used to hydrolyse the reaction mixture and that the presence of a large excess of

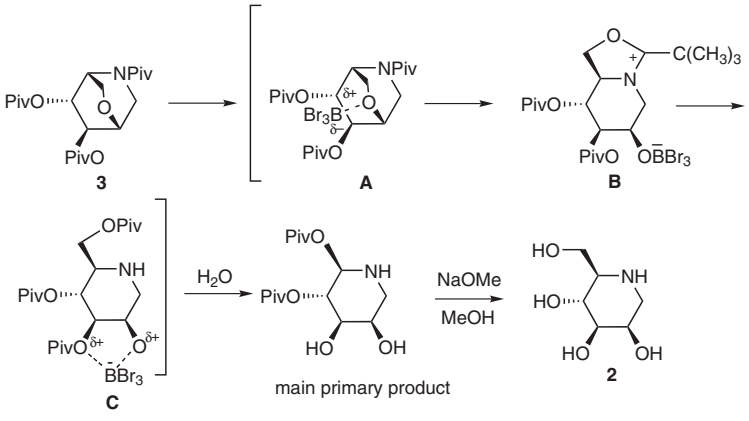


Scheme 2 *Reagents and conditions:* a) PivCl, DMAP, pyridine, r.t., 93%; b) BBr_3 (1.5 equiv), $CHCl_3$, then MeOH, r.t.; c) NaOMe, MeOH, r.t., 67% (2 steps).

Bu_4NBr did not effect the reaction either. The observation that the products shared the fact, that the *N*-pivaloyl group in all cases was cleaved and a C-6-*O*-pivaloyl group was introduced, could be interpreted in terms of a neighbouring group participation of the *N*-acyl group in the mechanism of the ether cleavage between C-6 and the oxygen (Scheme 3). This is further supported by the fact that no *gluco*-isomer has been formed as a result of ether cleavage between C-2 and the oxygen. It should be mentioned that acyloxonium ions as intermediates in similar BBr_3 induced ether cleavages have been suggested.[16] Also in this case no external nucleophile could be introduced in the end product as a proof for such an intermediate species.

In summary the very potent glycosidase inhibitor 1-deoxymannojirimycin (**2**) was synthesized from 1,5-anhydro-D-fructose (**1**) via nucleophilic piperidine ring formation and BBr_3-induced pyran ether cleavage in a highly stereoselective manner and with an overall yield of 35% (7 steps) or 27% (6 steps), respectively.

The bicyclic iminosugar intermediate 2,6-anhydro-1-deoxymannojirimycin (**3**) was also assayed for inhibition of a selection of glycosidases. Bennet et al.[13] showed that the hydrochloride of **3** was inactive (K_i >1 mM) against α- and β-D-glucosidases and α-D-mannosidase. We have shown[17] that **3** was a weak inhibitor of α-L-fucosidase from bovine kidney (K_i 520 μM), while other tested glycosidases were not inhibited to any extent. Since 2,6-anhydro-1-deoxymannojirimycin (**3**) is a conformationally restricted azasugar, it is forced to adopt a boat-like conformation ($^{2,5}B$). This conformation is different from the conformation of the natural substrates and thus also from their intermediates in the active site of the glycosidases.



Scheme 3 Suggested reaction mechanism for the BBr_3-induced ether cleavage in **3**

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument. Chemical shifts were measured in deuterated solvents; the solvent peak was used as reference ($CDCl_3$: δ = 7.26 for ^{1}H, 77.20 for ^{13}C; MeOH-d_4: δ = 4.87 for ^{1}H, 49.10 for ^{13}C). NMR data were assigned using HH- and CH-correlated spectra. Melting points are uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Institute of Physical Chemistry, Vienna. HR-MS was performed by Bio Centrum, DTU. TLC was performed on Merck 60 F254 precoated silica plates and spots were generally detected by spraying with a solution of 1.5% $NH_4Mo_2O_2$, 1% Ce(IV)SO_4 and 10% H_2SO_4 or conc. HCl/MeOH (3:1) and 4-*N*,*N*-dimethylaminobenzaldehyde (10 g/L), followed by charring. Flash chromatography was performed on silica gel 60 (Merck, 40–63 μm). The solvents were concentrated on a rotary evaporator at a temperature below 45 °C. The solvents were dried according to standard procedures and distilled prior to use. Additions of chemicals were performed by using disposable plastic syringes. Celite refers to Filter Aid from Celite Corporation.

1,5-Anhydro-6-*O*-tosyl-D-fructose *O*-benzyloxime (4)

O-Benzylhydroxylamine hydrochloride (5.7 g, 35.9 mmol) and KOH pellets (85%, 2.35 g, 35.6 mmol) in EtOH (80 mL) were stirred for 1 h at r.t. and filtered. The filtrate was cooled to 0 °C and 1,5-anhydro-D-fructose (**1**; 5.8 g, 35.9 mmol) was added as a solid under argon. The mixture was stirred at r.t. overnight. Concentration gave 1,5-anhydro-D-fructose *O*-benzyloxime as a crude residue, which crystallised on addition of Et_2O (8.7 g, 91%).[2b] The obtained 1,5-anhydro-D-fructose *O*-benzyloxime (7.0 g, 26.2 mmol) was dissolved in pyridine (130 mL) and cooled to –20 °C. TsCl (4.5 g, 23.6 mmol) was added as a solid and the mixture was stirred under argon at this temperature. Further portions of TsCl (each 0.5 g, 2.6 mmol) were added after a reaction time of 17, 24 and 43 h. After 48 h, the reaction was quenched by addition of 6 M HCl (80 mL) at –20 °C, EtOAc (200 mL) was added and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (40 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (SiO_2, heptane–EtOAc, 2:1) afforded **4** as a syrup; yield: 8.5 g (77%); R_f 0.45 (EtOAc); $[\alpha]_D^{20}$ +2.7 (*c* 1.6, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 2.42 (s, 3 H, ArCH_3), 3.38 (dd, ^3J = 7.6, 8.8 Hz, 1 H, H-4), 3.45 (ddd, ^3J = 1.7, 6.2, 8.8 Hz, 1 H, H-5), 3.77 (d, ^2J = 15.0 Hz, 1 H, H-1a), 4.09 (d, ^3J = 7.6 Hz, 1 H, H-3), 4.13 (dd, ^3J = 6.2 Hz, ^2J = 10.9 Hz, 1 H, H-6a), 4.28 (dd, ^3J = 1.7 Hz, ^2J = 10.9 Hz, 1 H, H-6a), 4.89 (d, ^2J = 15.0 Hz, 1 H, H-1b), 5.09 (s, 2 H, PhCH_2Bn), 7.24–7.47, 7.74–7.82 (m, 9 H, CH_{arom}).

^{13}C NMR (75 MHz, CD_3OD): δ = 21.7 (Ar*C*H_3Ts), 62.3 (C-1), 71.0 (C-6), 73.2 (C-4), 74.4 (C-3), 77.4 (Ph*C*H_2), 78.9 (C-5), 129.0, 129.2, 129.3, 129.5, 131.1 (CH_{arom}), 134.3, 139.0, 146.6 (C_{arom}), 156.3 (C-2).

HRMS: *m*/*z* calcd for $C_{20}H_{24}NO_7S$: 422.1273 (M + H^+); found: 422.1290.

2-Amino-1,5-anhydro-2-deoxy-6-*O*-tosyl-D-mannitol (5·HCl)

Compound **4** (740 mg, 1.8 mmol) was dissolved in MeOH (40 mL) and a suspension of 5% Pd/C (76 mg) and AcCl (0.25 mL, 3.5 mmol) in MeOH (10 mL) was added. The mixture was hydrogenated at 30 bar for 30 h. Filtration and concentration gave a foam, which upon addition of Et_2O crystallised to give **5** as its hydrochloride; yield: 507 mg (82%); mp 156–158 °C; $[\alpha]_D^{20}$ –11.6 (*c* 1.2, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 2.43 (s, 3 H, ArCH_3), 3.32–3.50 (m, 3 H, H-2, H-4, H-5), 3.66 (dd, ^3J = 1.5 Hz, ^2J = 13.3 Hz, 1 H, H-1a), 3.72 (dd, ^3J = 4.8, 8.8 Hz, 1 H, H-3), 3.92 (dd, ^3J = 1.5 Hz, ^2J = 13.3 Hz, 1 H, H-1b), 4.09 (dd, ^3J = 6.6, 11.0 Hz, 1 H, H-6a), 4.32 (dd, ^3J = 1.0 Hz, ^2J = 11.0 Hz, 1 H, H-6b), 7.39–7.46, 7.73–7.82 (m, 4 H, CH_{arom}).

^{13}C NMR (75 MHz, CD_3OD): δ = 21.7 (Ar*C*H_3), 53.8 (C-2), 67.3 (C-1), 68.4 (C-4), 71.0 (C-6), 71.7 (C-3), 80.2 (C-5), 129.2, 131.2 (CH_{arom}), 134.2, 146.7 (C_{arom}).

Anal. Calcd for $C_{13}H_{20}ClNO_6S$: C, 44.13; H, 5.70; N, 3.96; Cl, 10.02. Found: C, 44.26; H, 5.75; N, 3.96; Cl, 9.92.

2,6-Anhydro-1,5-dideoxy-1,5-imino-D-mannitol (3)

*Method a, from **5***: The tosylated amine **5**·HCl (165 mg, 0.47 mmol) was dissolved in DMF (2 mL) and Et_3N (0.07 mL, 0.50 mmol) was added. The mixture was stirred for 16 h at r.t. and concentrated to give a crude residue. Purification by flash chromatography [SiO_2, CH_2Cl_2–MeOH (5% NH_3), 3:1] afforded **3** as a syrup (73 mg, quant), which upon addition of a small amount of EtOH crystallised; yield: 40 mg (59%); R_f 0.13 [CH_2Cl_2–MeOH (5% NH_3), 2:1]; mp 176–184 °C; $[\alpha]_D^{20}$ –64.3 (*c* 1.2, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 3.02 (m, 1 H, H-5), 3.07 (dd, ^3J = 1.5 Hz, ^2J = 12.5 Hz, 1 H, H-1a), 3.33 (dd, ^3J = 3.5 Hz, ^2J = 12.5 Hz, 1 H, H-1b), 3.65 (dd, ^3J = 1.5, 3.0 Hz, 1 H, H-3), 3.72 (ddd, ^3J = 1.5, 1.5, 3.5 Hz, 1 H, H-2), 3.83 (m, 1 H, H-4), 3.90 (dd, ^3J = 1.5 Hz, ^2J = 10.0 Hz, 1 H, H-6a), 4.10 (dd, ^3J = 2.5 Hz, ^2J = 10.0 Hz, 1 H, H-6b).

^{13}C NMR (75 MHz, CD_3OD): δ = 45.6 (C-1), 51.9 (C-5), 66.3 (C-6), 70.6 (C-2), 75.7 (C-4), 77.3 (C-3).

HRMS: *m*/*z* calcd for $C_6H_{11}NO_3$: 145.0739 (M^+); found: 145.0739.

*Method b, from **4***: The tosylated oxime **4** (2.1 g, 5.1 mmol) was dissolved in MeOH (120 mL) and a suspension of 10% Pd/C (255 mg) in MeOH (40 mL) was added. The mixture was hydrogenated at 30 bar for 27 h. Filtration through Celite and concentration in vacuo gave a crude residue, which was dissolved in pyridine and stirred at r.t. overnight. The mixture was then concentrated in vacuo and co-concentrated three times in vacuo with toluene to give a solid residue, which upon addition of MeOH crystallised to give **3** as toluenesulfonic acid salt; yield: yield: 1.0 g (62%). Purification of the mother liquor by flash chromatography [SiO_2, CH_2Cl_2–MeOH (5% NH_3), 4:1] afforded an additional amount of **3** (amine) as a syrup; yield: 82 mg (11%).

3·TsOH

Mp 210–212 °C; $[\alpha]_D^{20}$ –32.0 (*c* 1.2, MeOH).

^{1}H NMR (300 MHz, CD_3OD): δ = 2.32 (s, 3 H, ArCH_3), 3.19 (br d, ^2J = 12.5 Hz, 1 H, H-1a), 3.26 (m, 1 H, H-5), 3.51 (dd, ^3J = 3.8 Hz, ^2J = 12.8 Hz, 1 H, H-1b), 3.53, 3.65, 3.86 (m, 3 H, H-2,3,4), 3.87 (br d, ^2J = 11.2 Hz, 1 H, H-6a), 4.08 (dd, ^3J = 2.8 Hz, ^2J = 11.2 Hz, 1 H, H-6b) 7.18–7.21, 7.65–7.67 (m, 4 H, CH_{arom}).

^{13}C NMR (75 MHz, CD_3OD): δ = 21.4 (Ar*C*H_3), 44.5 (C-1), 51.9 (C-5), 62.5 (C-6), 68.1 (C-2), 72.5 (C-4), 75.8 (C-3), 127.0, 129.9 (CH_{arom}), 141.9, 143.5 (C_{arom}).

Anal. Calcd for $C_{13}H_{19}NO_6S$: C, 49.20; H, 6.03; N, 4.41. Found: C, 48.97; H, 5.95; N, 4.27.

3,4-Di-*O*-pivaloyl-*N*-pivaloyl-2,6-anhydro-1,5-dideoxy-1,5-imino-D-mannitol (6)

The toluenesulfonic acid salt of **3** (1.1 g, 3.5 mmol) was neutralised with Amberlite IRA 400 (OH^-) ion-exchange resin, the resin was filtered off and the filtrate was concentrated in vacuo. The crystalline residue was dissolved in pyridine (20 mL), and DMAP (27 mg, cat.) and pivaloyl chloride (5.0 mL, 40.6 mmol) were added. The mixture was stirred at r.t. under argon overnight. The reaction was quenched by the addition of ice, CH_2Cl_2 (100 mL) was added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered,

evaporated in vacuo and co-evaporated three times in vacuo with toluene. Crystallization from Et_2O gave **6**; yield: 1.3 g (93%); R_f 0.36 (heptane–EtOAc, 1:1); mp 118–121 °C; $[\alpha]_D^{20}$ –43.0 (*c* 1.1, MeOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15, 1.20, 1.23 [s, 27 H, 3 $C(CH_3)_3$], 3.90–4.80 (m, 6 H, H-1a, H-1b, H-2, H-5, H-6a, H-6b), 4.75 (br m, 1 H, H-4], 4.97 (m, 1 H, H-3).

^{13}C NMR (75 MHz, CD_3OD): δ = 27.1, 27.2, 28.1 [C(*C*H_3)], 38.8, 38.9, 39.1 [*C*(CH_3)], 47.1, 49.0 (C-1, C-5), 67.7 (C-6), 68.0 (C-2), 74.5, 75.7 (C-3, C-4), 177.3, 177.7, 177.9 (C=O).

Anal. Calcd for $C_{21}H_{35}NO_6$: C, 63.45; H, 8.87; N, 3.52. Found: C, 63.39; H, 8.76; N, 3.42.

1-Deoxymannojirimycin (2, 1,5-Dideoxy-1,5-imino-D-mannitol)
Compound **6** (364 mg, 0.915 mmol) was dissolved in anhyd $CHCl_3$ (13 mL) and BBr_3 (0.15 mL, 1.59 mmol) was added at r.t. under argon and the mixture was stirred for 3 d. The resulting suspension was quenched by addition of MeOH (10 mL) at r.t., and the solution was neutralised with Amberlite IRA 400 (OH^-) ion-exchange resin. The resin was filtered off and washed with MeOH. The filtrate was concentrated in vacuo, giving a crude product mainly consisting of 4,6-di-*O*-pivaloyl-1,5-dideoxy-1,5-imino-D-mannitol.

4,6-Di-*O*-pivaloyl-1,5-dideoxy-1,5-imino-D-mannitol
^{1}H NMR (300 MHz, CD_3OD): δ = 1.18, 1.19 [s, 18 H, 2 $C(CH_3)_3$], 2.79 (dd, ^3J = 1.5 Hz, ^2J = 14.2 Hz, 1 H, H-1a), 2.84 (m, 1 H, H-5), 3.01 (dd, ^3J = 2.8 Hz, ^2J = 14.2 Hz, 1 H, H-1b), 3.59 (dd, ^3J = 3.0, 9.7 Hz, 1 H, H-3), 3.89 (m, 1 H, H-2), 3.91 (dd, ^3J = 2.2 Hz, ^2J = 11.8 Hz, 1 H, H-6a), 4.15 (dd, ^3J = 3.4 Hz, ^2J = 11.8 Hz, 1 H, H-6b), 5.13 (dd, ^3J = 9.7, 10.0 Hz, 1 H, H-4).

^{13}C NMR (75 MHz, CD_3OD): δ = 27.6, 27.7 [C(*C*H_3)$_3$], 38.8, 39.9, 40.1 [*C*(CH_3)$_3$], 50.4 (C-1), 58.7 (C-5), 63.7 (C-6), 70.9, 71.0 (C-2, C-3), 74.5 (C-4), 179.3, 179.5 (C=O).

HRMS: *m*/*z* calcd for $C_{16}H_{29}NO_6$: 332.207 (M + H^+); found: 332.2050.

The residue was dissolved in MeOH (4 mL) and a solution of Na (42 mg, 1.83 mmol) in MeOH (2 mL) was added. The mixture was stirred at r.t. overnight. It was then loaded on a column of Amberlite IRA 120 (H^+) ion-exchange resin. The column was first eluted with MeOH and then with 24% aq NH_3. The alkaline phase was evaporated in vacuo and co-evaporated three times in vacuo with toluene to give 1-deoxymannojirimycin (**2**) as the sole reaction product. Purification by flash chromatography [SiO_2, CH_2Cl_2–MeOH (5% NH_3), 3:1] afforded **2** as a white foam (100 mg, 67%), which was crystallised from MeOH–Et_2O; mp 181–183 °C (Lit. mp 183–185 °C;[18] mp 185–187 °C[19]). The NMR data agreed with those reported previously.[20]

Acknowledgment

This work was partially supported by the European Union under the Cell Factory of 5th Framework Program, QLK3-2001-02400.

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