Synthesis of β-1-Homonojirimycin and β-1-Homomannojirimycin using the Enzyme Aldolase

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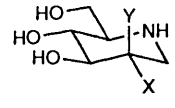
The four stereoisomers of the four-carbon azido sugar **11** have been stereoselectively synthesised by a route involving Sharpless epoxidation and all are found to be substrates for rabbit muscle fructose 1,6-bisphosphate aldolase, giving (after treatment with phosphatase) 6-azido-6-deoxyheptuloses **14**; hydrogenation of **14a** and **14b** gave β-1-homomannojirimycin **15a** and β-1-homonojirimycin **15b** with high selectivity.

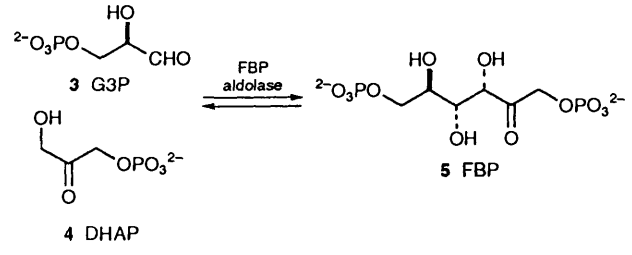
Deoxynojirimycin (DNJ) **1** is a potent inhibitor of exoglucosidases due to its close similarity to glucose and its positive charge when protonated, which resembles the positively charged transition state for glycoside hydrolysis.[1] DNJ, and more particularly its *N*-butyl derivative, show good activity against HIV as a result of inhibition of one of the glucosidases responsible for processing the glycoproteins that form the outer coat of the virus.[2] The epimer at C-2, deoxymannojirimycin (DMJ) **2**, is also a natural product and a potent inhibitor of mannosidases.[3] However, because DNJ and DMJ lack any substituents at C-1, they show little selectivity for inhibition of α- *vs.* β-glucosidases. Furthermore, they show little inhibition towards endoglycosidases, which generally only bind compounds with at least two sugar units.[4,5] We, therefore, set out to synthesise the α- and β-1-homonojirimycins **15c** and **15b**, as well as their C-2 epimers, α- and β-1-homomannojirimycins **15d** and **15a**. It was reasoned that the extra carbon substituent at C-1 would lead to selective inhibition of α- or β-glycosidases, as appropriate, and that the hydroxy group could provide a point of attachment for further binding groups, such as another sugar unit.

Our approach to the synthesis of compounds **15a–d** envisaged the use of fructose 1,6-bisphosphate (FBP) aldolase to make the linear C_7 ketones **14a–d**, having an amino function masked as an azide group. Hydrogenation of **14** would unmask the amine, which would condense with the ketone and the resulting imine would be further hydrogenated to give the saturated piperidine ring of **15**. The reaction catalysed *in vivo* by FBP aldolase is the reversible aldol reaction between dihydroxyacetone phosphate (DHAP) **4** and glyceraldehyde 3-phosphate (G3P) **3** to give FBP **5** (which exists predominantly in the cyclic furanose form) (Scheme 1). However, many studies have shown that the commercially available FBP aldolase from rabbit muscle (RAMA), although specific for DHAP, can accept a wide range of aldehydes in place of G3P.[6] In the past 5 years, several publications have appeared describing similar approaches using RAMA to synthesise imino sugars but only C_5 and C_6 sugar analogues have been made.[7,8]

For the synthesis of the required C_7 intermediates **14** we need C_4 aldehydes such as **10** (and its stereoisomers). Our synthesis of **10** started with *cis*-but-2-ene-1,4-diol **6**, which was mono-protected with *tert*-butyldiphenylsilyl chloride. This large protecting group gave good selectivity for mono- *vs.* di-protection. Sharpless epoxidation[9] of the resulting allylic alcohol, using L-(+)-diethyl tartrate, then produced the (2*S*,3*R*)-epoxide **7**. The enantiomeric excess of **7** was determined from the ^{19}F NMR spectrum of its Mosher's ester to be *ca.* 89%. Oxidation of the epoxy alcohol **7** to the corresponding aldehyde proceeded well with the mild oxidising agent tetrapropylammonium perruthenate (TPAP) and the aldehyde was protected as its dimethyl acetal **8** using Amberlyst-15 in trimethyl orthoformate.[10] Nucleophilic opening of the epoxide ring of **8** with sodium azide proceeded, as expected,[11] *via* attack at the end further from the acetal group to give almost exclusively the 3-azido acetal **9**. Finally, deprotection in aqueous trifluoroacetic acid gave our target aldehyde **10**.

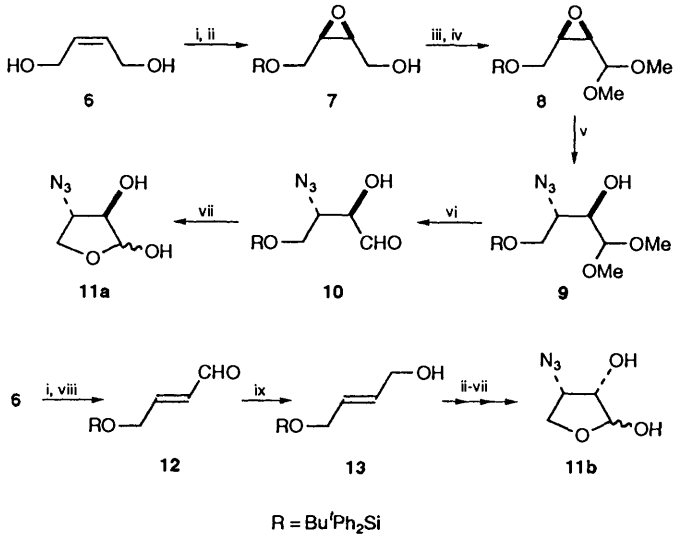


1 DNJ, X = OH, Y = H
2 DMJ, X = H, Y = OH



3 G3P **4** DHAP **5** FBP

Scheme 1



Scheme 2 *Reagents:* i, BuLi, BDPSiCl; ii, DET, $Ti(OPr^i)_4$, Bu^tOOH; iii, TPAP, NMMO; iv, Amberlyst-15, $CH(OMe)_3$; v, NaN_3, NH_4Cl; vi, CF_3CO_2H, $CHCl_3$, H_2O; vii, TBAF; viii, PCC; ix, DiBAl-H

Table 1 Inhibition constants (K_i mmol dm^{-3}) for the inhibition of four glycosidases by β-homomannojirimycin **15a** and β-homonojirimycin **15b**

Enzyme	15a	15b
α-Glucosidase[a]	N.I.[e]	0.90
β-Glucosidase[b]	3.0	0.43
α-Mannosidase[c]	N.I.[e]	26
β-Mannosidase[d]	0.08	3.3

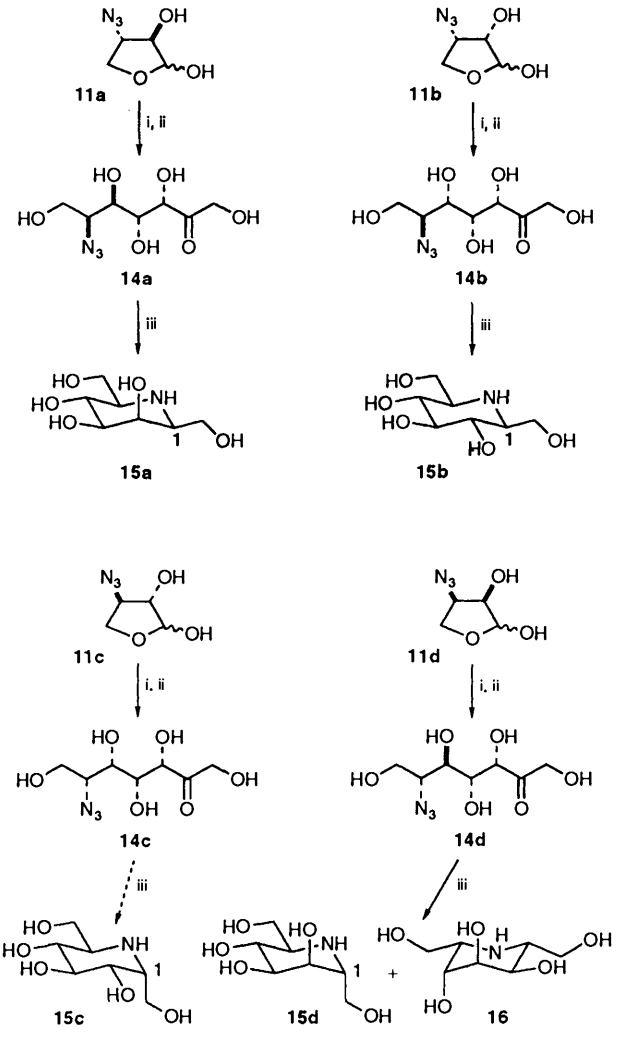
[a] From yeast. [b] From almonds. [c] From jack beans. [d] From snail. [e] N.I.—No detectable inhibition at 1 mmol, *i.e.* K_i > *ca.* 25 mmol dm^{-3}.

We had hoped to use the aldehyde **10**, having the 4-hydroxy protected, in the enzymic aldol reaction but preliminary tests showed that, though it was a substrate, it reacted very slowly (compared with a good substrate such as propionaldehyde) and the reaction never proceeded beyond about 25% completion, possibly because of the poor solubility of **10**. Therefore, the silyl protecting group was removed using tetrabutylammonium fluoride (TBAF). The resulting hydroxy aldehyde cyclised spontaneously to give the lactol **11a** as a mixture of epimers at the hemiacetal centre. We wondered whether this lactol formation might prevent the enzymic aldol reaction, which presumably requires the open-chain aldehyde; in fact, it is reported that the four-carbon sugar D-erythrose is not a substrate.[6] However, when assayed with RAMA and DHAP **11a** was found to be a good substrate, reacting with an initial rate about one fifth as fast as propionaldehyde, and the reaction proceeded to completion.

In order to synthesise the diastereoisomer **11b**, the *trans*-allylic alcohol **13** was required. As *trans*-but-2-ene-1,4-diol is not commercially available, **13** was made by monoprotecting the *cis*-diol **6**, as before, and then oxidising to the aldehyde using pyridinium chlorochromate (PCC). These (acidic) conditions also caused isomerisation of the *cis*- to the *trans*-aldehyde **12** and subsequent reduction with DiBAL yielded the desired *trans*-alcohol **13**. Sharpless epoxidation of this allylic alcohol, using D-(−)-diethyl tartrate, gave an enantiomeric excess of >98% (only one set of signals could be seen in the ^{1}H and ^{19}F NMR spectra of its Mosher's ester) and the other reactions proceeded as before to give the lactol **11b**. Finally, repetition of the same two syntheses using the opposite enantiomers of diethyl tartrate in the epoxidation reactions yielded the enantiomeric lactols **11c** and **11d**.

In assays with RAMA and DHAP, all four lactols **11a–d** reacted at similar rates and the reactions all proceeded to completion. Preparative runs typically used about 600 mg (4 mmol) of lactol and 2.7 mmol of DHAP[12] with 11 mg (150 units) of RAMA. The resulting product was immediately dephosphorylated at pH 4.8 with acid phosphatase to give, in yields of up to 80%, the 6-azido-6-deoxyheptuloses **14a–d**, which existed predominantly in their furanose forms.

Hydrogenation of the azido heptuloses **14a–d** is, as explained above, expected to proceed with cyclisation and further reduction of the imine formed. This reduction of the imine introduces the fifth asymmetric centre and the hydrogen could, in principle, be added from below to give imino sugars of D-configuration **15** or from above to give the L-configuration, *e.g.* **16**. Hydrogenation of similar compounds to **14** (lacking the terminal hydroxymethyl group) has been reported by Wong's group and others[7,8,13,14] to give only the compounds of D-configuration (DNJ and DMJ) but in our case the extra substituent (CH_2OH) on the carbon adjacent to the nitrogen atom would be expected to have some directing influence. This is indeed what has been observed in a published synthesis of β-L-homofuconojirimycin.[15] In our case also, the influence of the CH_2OH group was marked: the hydrogenations of **14a** and **14b**



Scheme 3 *Reagents:* i, RAMA, DHAP; ii, acid phosphatase; iii, 10% Pd/C, H_2, 40 psi.

were both stereospecific giving β-1-homomannojirimycin **15a** and β-1-homonojirimycin **15b**, respectively, in 90% yield. The latter product is symmetrical and so has very much simplified ^{1}H and ^{13}C NMR spectra. In both these cases the CH_2OH group at C-1 of the product is up and in the equatorial position thus presenting no hindrance to addition of hydrogen to the imine from below, which results in the CH_2OH group at C-5 also being in the more favourable equatorial position. Hydrogenation of **14d**, however, was not stereospecific and yielded a mixture of **15d** and **16** in a 1 : 1 ratio and 73% combined yield. Clearly when the CH_2OH group at C-1 is pointing down (*i.e.* α) it does interfere with the hydrogenation process. Hydrogenation of the fourth isomer **14c** has not, as yet, yielded any well characterised product. It is not certain whether this is because the reduction does not proceed as expected or the product(s) are unstable; further investigation of this reaction is needed.

The two α-isomers **15c** and **15d** are both known compounds: **15c** is a natural product[16,17] and both isomers have been synthesised by lengthy synthetic procedures involving much use of protecting groups.[18–22] The two β-isomers **15a** and **15b** are, to our knowledge, both new compounds. The relatively short and efficient syntheses described here illustrate well the advantages of using enzymes for key reactions in synthesis.

The two β-imino sugars synthesised here, β-1-homomannojirimycin **15a** and β-1-homonojirimycin **15b**, have been tested as inhibitors of four representative glycosidases, α- and

β-glucosidases and α- and β-mannosidases. Compound **15a**, which has the β-mannose stereochemistry, showed excellent selectivity, inhibiting β-mannosidase strongly but the other three enzymes much less, see Table 1. Compound **15b**, with the β-glucose stereochemistry, does inhibit β-glucosidase more than the other three enzymes but the difference is less marked than for **15a**. In comparison, it is reported that α-homonojirimycin **15c** has a much greater effect on α- than β-glucosidase activity[16] and α-mannosidases are inhibited by **15d** but β-mannosidases are not.[20] The specificity of inhibition of glycosidases shown by the 1-homonojirimycin and 1-homomannojirimycin isomers, and especially by compound **15a** described here, may be of considerable value in studying the pathways of oligosaccharide biosynthesis.[23]

Experimental

Experimental details are given here for the synthesis of β-1-homomannojirimycin **15a**. The other compounds described in the text were synthesised in a similar way. Asymmetric epoxidation[9] of the monosilylated butenediol and oxidation of the resulting epoxy alcohol **7** using TPAP[24] followed published general procedures.

(2R,3R)-4-(tert-*Butyldiphenylsilyloxy*)-2,3-*epoxybutanal Dimethyl Acetal* **8**.—Amberlyst-15 (2.2 g) was added portionwise to a solution of (2*R*,3*R*)-4-(*tert*-butyldiphenylsilyloxy)-2,3-epoxybutanal (13.0 g, 38.2 mmol) in anhydrous trimethyl orthoformate (25.1 cm^3, 230 mmol) at 0 °C to 4 °C.[10] The mixture was stirred at this temperature for 2 h and then filtered to remove the Amberlyst-15 resin. Excess of trimethyl orthoformate was removed under reduced pressure and the residue was purified by flash chromatography on a column of SiO_2 (first treated with a solution of 1% Et_3N in methanol, then washed with dichloromethane), eluting with dichloromethane, to yield the *epoxy acetal* **8** (13.1 g, 89%) as a colourless oil (Found: $M + NH_4^+$, 404.2303. $C_{22}H_{30}O_4Si$ requires $M + NH_4$, 404.2257); R_F (CH_2Cl_2) 0.37; ν_{max}($CHCl_3$)/cm^{-1} 3065 (m, Ph-H), 3040 (w, Ph-H), 1255 (m, CH–O–CH), 1108 (s, C–O), 914 (m, CH–O–CH) and 855 (m, CH–O–CH); δ_H(300 MHz, $CDCl_3$) 1.08 (9 H, s, Bu^t), 3.11 (1 H, dd, *J* 4.2 and 6.0, 2-CH), 3.24 (1 H, ddd, *J* 3.9, 4.2 and 6.3, 3-CH), 3.31 and 3.38 (each 3 H, s, OCH_3), 3.78 (1 H, dd, *J* 6.3 and 11.7, 4-CH_AH_B), 3.93 (1 H, dd, *J* 3.9 and 11.7, 4-CH_AH_B), 4.14 (1 H, d, *J* 6.0, 1-CH), 7.37–7.48 (6 H, m, Ph-H) and 7.70–7.73 (4 H, m, Ph-H); δ_C(75 MHz, $CDCl_3$) 19.1 (CMe_3), 26.7 (CMe_3), 53.6, 53.76 (2 × OCH_3), 55.5 and 56.0 (2 and 3-CH), 62.2 (4-CH_2), 101.6 (1-CH) and 127.6, 129.7, 133.0, 133.2 and 135.5 (Ph); *m*/*z* (CI, NH_3) 404 (100%, $M + NH_4^+$) and 340 (7, $M + NH_4 - 2 \times CH_3OH$); $[\alpha]_D^{20}$ +2.5 ° (*c* 6 in $CHCl_3$).

(2R,3S)-3-*Azido*-4-(tert-*butyldiphenylsilyloxy*)-2-*hydroxybutanal Dimethyl Acetal* **9**.—Sodium azide (10.95 g, 168.5 mmol) and ammonium chloride (3.96 g, 74.0 mmol) were added to a solution of the epoxy acetal **8** (13.0 g, 33.7 mmol) in MeOH–H_2O 8:1 (300 cm^3) and the mixture was heated at reflux with stirring for 44 h.[11] The mixture was cooled, diluted with water (100 cm^3) and extracted with diethyl ether (3 × 200 cm^3). The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was chromatographed on a column of silica (first treated with 1% Et_3N in methanol and then washed with 10% EtOAc in hexane), eluting with 10% to 20% ethyl acetate in hexane, to give the starting epoxy acetal **8** (2.8 g) and the *azido alcohol* **9** (8.0 g, 71% based on unrecovered starting material) as an oil (Found: C, 61.6; H, 7.2; N, 9.8% $M + NH_4^+$, 447.2499. $C_{22}H_{31}N_3O_4Si$ requires C, 61.5; H, 7.25; N, 9.8%; $M + NH_4$, 447.2428); R_F (20% EtOAc in hexane) 0.24; ν_{max}($CHCl_3$)/cm^{-1} 3600–3260 (m, br, OH), 3065 (m, Ph-H), 3040 (w, Ph-H), 2100 (s, N_3) and 1110 (s, CH-O-CH_3); δ_H(300 MHz, $CDCl_3$) 1.10 (9 H, s, Bu^t), 2.43 (1 H, d, *J* 3.6, OH), 3.44 and 3.45 (each 3 H, s, OCH_3), 3.73–3.65 (2 H, m, 2,3-CH), 3.90 (1 H, dd, *J* 5.1 and 10.5, 4-CH_AH_B), 3.97 (1 H, dd, *J* 7.5 and 10.5, 4-CH_AH_B), 4.42 (1 H, d, *J* 6.9, 1-CH), 7.38–7.48 (6 H, m, Ph-H) and 7.72–7.68 (4 H, m, Ph-H); δ_C(75 MHz, $CDCl_3$) 19.0 (CMe_3), 26.6 (CMe_3), 54.7 and 55.5 (2 × OCH_3), 62.7 (3-CH), 64.4 (4-CH_2), 70.4 (2-CH), 104.4 (1-CH) and 127.7, 129.8, 132.8 and 135.5 (Ph); *m*/*z* (CI, NH_3) 447 (100%, $M + NH_4^+$) and 383 (15, $M + NH_4 - 2 \times CH_3OH$); $[\alpha]_D^{20}$ +15.8° (*c* 1.6 in $CHCl_3$).

(3R,4S)-4-*Azidotetrahydrofuran*-2,3-*diol* **11a**.—To a solution of the azido acetal **9** (100 mg, 0.23 mmol) in chloroform (1 cm^3) and water (*ca.* 20 mm^3) at 0 °C was added dropwise trifluoroacetic acid (1 cm^3). The mixture was stirred at 0 °C for 2.5 h and then concentrated under reduced pressure. The residue was dissolved in THF (0.5 cm^3) and stirred with a solution of tetrabutylammonium fluoride in THF (1.1 mol dm^{-3}; 0.63 cm^3, 0.69 mmol) at 20 °C for 0.75 h. The mixture was concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (first treated with 1% Et_3N in methanol, then washed with 40% EtOAc in hexane), eluting with 40 to 80% ethyl acetate in hexane, to yield the unstable *hemiacetal* **11a** (27 mg, 81%) as an oil; R_F (80% EtOAc in hexane) 0.38, (0.5% MeOH in CH_2Cl_2) 0.25; ν_{max}(liquid film)/cm^{-1} 3500–3160 (s br, OH), 2100 (s, N_3) and 1040 (m, C–O); δ_C(100 MHz, CD_3OD) 63.2, 63.4 (4-CH, two anomers), 65.3, 65.5 (5-CH_2, two anomers), 74.1, 74.2 (3-CH, two anomers) and 99.2, 104.1 (2-CH, two anomers).

(3S,4R,5R,6S)-6-*Azido*-1,3,4,5,7-*pentahydroxyheptan*-2-*one* **14a**.—A solution of rabbit muscle aldolase (0.536 cm^3, 202 U) in TRIS-maleate buffer (50 mmol dm^{-3}; pH 6.6; 2.29 cm^3) was treated with a solution of the triose phosphate isomerase inhibitor 3-bromo-1-hydroxyacetone phosphate in the same buffer (190 mg dm^{-3}; 1.01 cm^3) for 10 min and then added to a mixture of solutions of the hemiacetal **11a** (650 mg, 4.5 mmol) in DMSO (4.5 cm^3) and DHAP[12] (0.1 mol dm^{-3}; 28 cm^3, 2.8 mmol) in triethanolamine buffer (0.2 mol dm^{-3}; pH 7; 8.05 cm^3). The solution was stirred slowly at room temperature and 50 mm^3 aliquots were assayed for DHAP at various time intervals. A control reaction containing no hemiacetal was run and assayed at the same time. When no significant DHAP remained (24 h), the mixture was adjusted to pH 1.5 and left for 2 min. The pH of the mixture was adjusted to 4.8 using aqueous sodium hydroxide (2 mol dm^{-3}), after which argon was bubbled through it for 15 min and then acid phosphatase (250 mg, 100 U) added to it. After the mixture had been stirred slowly at 37 °C overnight, the test for inorganic phosphate indicated complete reaction. The mixture was then stirred at 75 °C for 5 min, filtered, its pH adjusted to 7 and water removed from it under reduced pressure. The residue was extracted with hot methanol (2 × 100 cm^3) and the extracts were evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with 0 to 10% MeOH in EtOAc, to yield the *heptanone* **14a** (371 mg, 56%) as an oil. The compound exists as a mixture of furanose anomers (Found: $M + NH_4^+$, 253.1148. $C_7H_{13}N_3O_6$ requires $M + NH_4$, 253.1148); R_F (10% MeOH in EtOAc) 0.23; ν_{max}(liquid film)/cm^{-1} 3500–3200s, br (OH) and 2110s (N_3); δ_H(400 MHz, CD_3OD) major anomer: 3.34 (1 H, ddd, *J* 3.9, 4.2 and 7.8, 6-CH), 3.40–3.51 (3 H, m, 7-CH_AH_B and 1-CH_2), 3.61 (1 H, dd, *J* 3.9 and 7.8, 5-CH), 3.63 (1 H, dd, *J* 4.2 and 11.6, 7-CH_AH_B), 3.86 (1 H, d, *J* 8.0, 3-CH) and 3.98 (1 H, dd, *J* 7.8 and 7.9, 4-CH); δ_C(100 MHz, CD_3OD) major anomer: 62.6 (C-7), 64.2 (C-1), 67.0 (C-6), 77.5 and 76.8 (C-4 and 5), 81.3 (C-3) and 103.3 (C-2); minor anomer: 63.1 (C-7), 65.1 (C-1), 65.7 (C-6), 79.3 and 81.6

(C-4 and 5), 84.4 (C-3) and 105.8 (C-2); *m/z* (CI, NH_3) 253 (50%, $M + NH_4^+$), 235 (92, $M + NH_4 - H_2O$), 192 (75, $M + NH_4 - HOCH_2CHOH$) and 60 [100, $(CHOH)_2$]; $[\alpha]_D^{20}$ +17.4° (*c* 1.2 in CH_3OH).

β-1-*Homomannojirimycin* **15a**.—A solution of the heptanone **14a** (330 mg, 1.40 mmol) in methanol (100 cm^3) was degassed with nitrogen for 20 min and then 10% palladium-on-carbon (150 mg) was added to it. The mixture was hydrogenated at 40 psi overnight and then filtered through Celite. The filtrate was evaporated under reduced pressure and the residue purified using a column of Dowex-50X8 (100 mesh) H^+ resin, eluting with water then aqueous ammonia (0.1 mol dm^{-3}), to yield β-1-*homomannojirimycin* **15a** (240 mg, 89%) as a solid (Found: MH^+, 194.1028; $C_7H_{15}NO_5$ requires *M*H, 194.1028); R_F (EtOAc–MeOH–H_2O, 12:6:3) 0.58; ν_{max}(Nujol)/cm^{-1} 3540–3440s, br (OH) and 3420–3200s, br (NH); δ_H(400 MHz, CD_3OD) 2.46 (1 H, ddd, *J* 2.6, 5.6 and 9.5, 5-CH), 2.72 (1 H, dd, *J* 6.2 and 6.5, 1-CH), 3.29 (1 H, dd, *J* 2.6 and 9.5, 3-CH), 3.48 (1 H, t, *J* 9.5 4-CH), 3.58–3.63 (3 H, m, 5′-CH_AH_B and 1′-CH_2), 3.78 (1 H, dd, *J* 2.6 and 11.0, 5′-CH_AH_B) and 3.81 (1 H, d, *J* 2.6, 2-CH); δ_C(100 MHz, CD_3OD) 60.5 and 62.6 (C-1 and 5), 63.5 and 62.9 (C-1′ and 5′) and 70.5, 70.8 and 77.4 (C-2, 3 and 4); *m/z* (CI, NH_3) 194 (100%, MH^+); $[\alpha]_D^{20}$ −4.3 (*c* 1.3 in MeOH).

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