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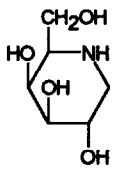
Synthesis of 1,5-Dideoxy-1,5-imino-D-galactitol from L-Sorbose

Richard H Furneaux, Peter C Tyler*, and Lynley A Whitehouse

Industrial Research Ltd., P O Box 31310, Lower Hutt, New Zealand

Abstract: A facile new synthesis of 1-deoxygalactonojirimycin (1) [1,5-dideoxy-1,5-imino-D-galactitol] is described. The L-sorbose derivative (15) is epimerised at C-3 and converted, *via* the L-tagatofuranose (18) into the deoxyazide (20). Reduction of azide (20) and deprotection affords 1-deoxygalactonojirimycin (1).

In connection with studies underway in our laboratories, we required several grams of 1,5-dideoxy-1,5-imino-D-galactitol (1-deoxygalactonojirimycin) (1). 1-Deoxygalactonojirimycin is a potent α-D-galactosidase inhibitor[1] and is a member of a family of polyhydroxy alkaloid glycosidase inhibitors that includes the natural products deoxynojirimycin (2), castanospermine (3) and swainsonine (4).[2] Compounds in this family display a diverse range of biological activity that has made them the subject of considerable recent interest.[3]



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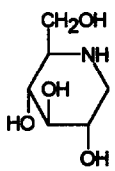

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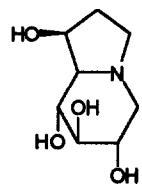

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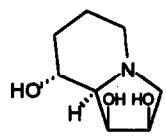

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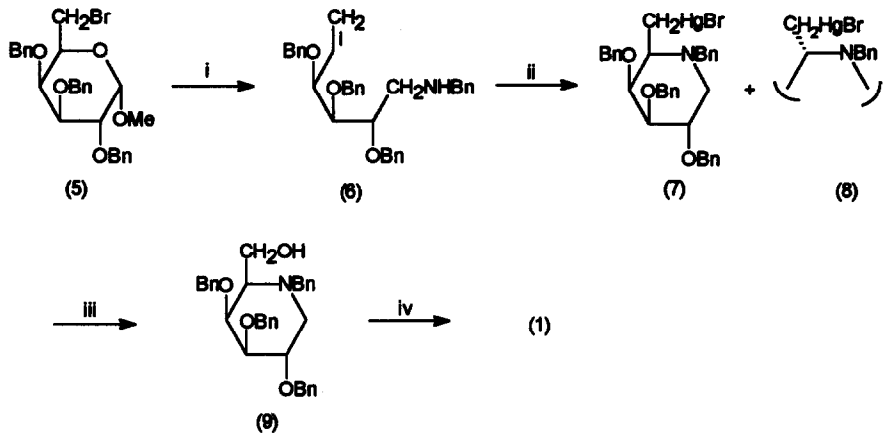
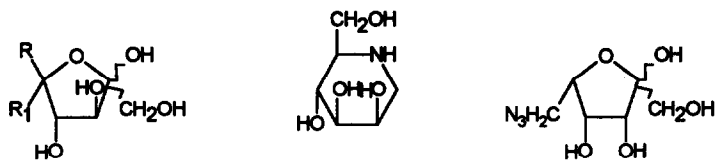
1-Deoxygalactonojirimycin was first synthesized by Paulsen *et al.*[4] in six steps from 1,6-anhydro-β-D-galactofuranose. It has also been synthesized in 13 steps from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[5], in 10 steps from deoxynojirimycin[6] (itself available by a variety of routes), and in nine steps from methyl α-D-galactopyranoside.[1] We initially chose to repeat this latter synthesis since it appeared to be relatively short, used a readily available starting material, and offered reasonable overall yield (25%). Following the reported method (Scheme 1), methyl 2,3,4-tri-*O*-benzyl-6-bromo-6-deoxy-α-D-galactopyranoside (5) was converted directly into the 1-benzylamino-hex-5-enitol derivative (6), and thence by amino-mercuration into a 7.5:1 mixture of organomercurials (7) and (8). Reductive oxygenation of this mixture (step iii) should then have provided the alcohol (9), from which 1-deoxygalactonojirimycin (1) would have been available by hydrogenolysis. Unfortunately, in our hands, this procedure would not yield the desired alcohol (9), despite many attempts.

The unexpectedly capricious nature of this reductive oxygenation step led us to develop the alternative approach to the target (1) set out in Scheme 2. Hydrogenation of 6-azido-6-deoxy-L-sorbose (10) and -D-fructose (11), is known to result in reduction of the azide group to a primary amine followed by *in situ* intramolecular reductive amination with the 2-keto-function to afford 1-deoxynojirimycin (2)[7] and 1-deoxymannojirimycin (12)[8], respectively. It seemed likely then that 1-deoxygalactonojirimycin (1) might similarly be obtained from 6-azido-6-deoxy-L-tagatose (13), the C-3 epimer of 10.



Reagents: i, Zn, $NaBH_3CN$, $BnNH_2$; ii, $Hg(OCOCF_3)_2$, then KBr; iii, O_2, $NaBH_4$; iv, Pd/C, EtOH, HCl, H_2.

SCHEME 1

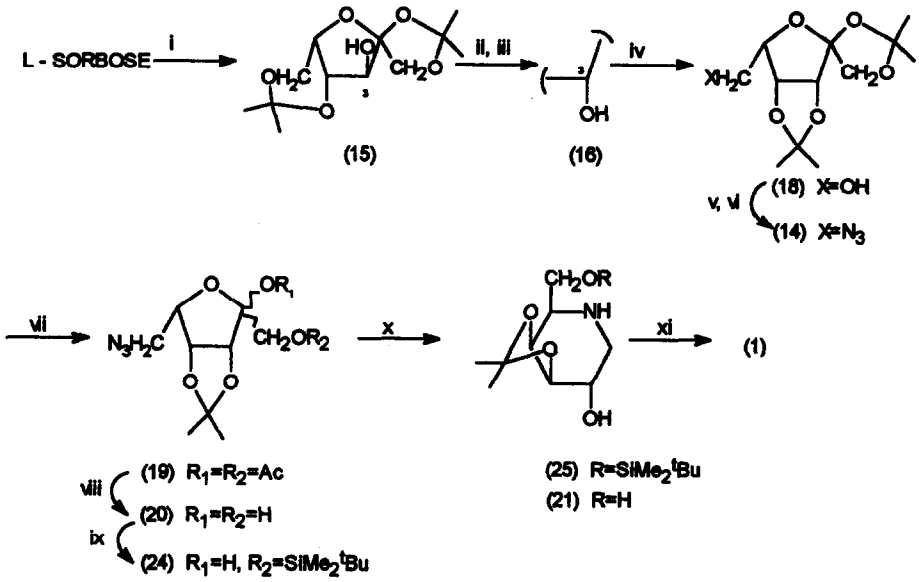


In order to investigate this, 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-L-tagatose (**14**) was synthesised in six steps from L-sorbose. Acetonation with 2,2-dimethoxypropane and catalytic amounts of tin (II) chloride in 1,2-dimethoxyethane gave crystalline 1,2:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**15**), in good yield as reported.[9,10] Because the lower face of **15** is sterically crowded, it was predicted that an oxidation-reduction sequence appplied to **15** would predominantly result in inversion at C-3. Swern oxidation using trifluoroacetic anhydride as activating agent[11] and *in situ* reduction of the resulting ketone by the addition of an ethanolic solution of sodium borohydride, gave exclusively 1,2:3,4-di-*O*-isopropylidene-α-L-tagatofuranose (**16**)[12] isolated crystalline in 70% yield. The alternative use of oxalyl chloride as activating agent for the Swern oxidation, produced substantial amounts of the methylthiomethyl vinyl ether (**17**)[12], along with the desired alcohol (**16**) following borohydride reduction. Acid catalysed isomerization of the 1,2:4,6-diacetonide (**16**) was expected to yield 1,2:3,4-di-*O*-isopropylidene-α-L-tagatofuranose (**18**) containing two five membered ring ketals and thereby being thermodynamically favoured. It was indeed the sole product at equilibrium, and was isolated in 85% yield. The primary alcohol (**18**) was then converted to the 6-azido-6-deoxy-derivative (**14**)[12] by conventional mesylation followed by nucleophilic displacement with azide, the product being isolated as a syrup in 82% yield following flash chromatography.

It was envisaged that 1-deoxygalactonojirimycin (**1**) would be available in two further steps, involving hydrolytic removal of the acetonide groups of (**14**) to yield 6-azido-6-deoxy-L-tagatose (**13**) and hydrogenation. Our plans were initially frustrated when it became apparent that conditions of acid hydrolysis sufficient to

cleave both acetonide groups resulted in considerable concomitant decomposition. Acetolysis on the other hand cleanly generated the diacetate (**19**) as a mixture of anomers, from which the syrupy anomeric mixture of diols (**20**)[12] were obtained on Zémplen deacetylation, in 90% overall yield from (**14**).

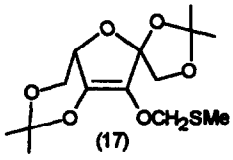
Attempted direct conversion of the diol mixture (**20**) to 3,4-*O*-isopropylidene-deoxygalactonojirimycin (**21**) by hydrogenation (H_2-1 atm-Pd/C-EtOH) resulted mainly in degradation, only traces of the desired product being isolated. This was surprising because hydrogenation of the enantiomeric 1-deoxygenated azide (**22**) in our hands gave the 1,5-dideoxy-1,5-imino-L-fucitol derivative (**23**) in high yield exactly as reported.[13]



Reagents: i, $Me_2C(OMe)_2$, $SnCl_2$, $MeOCH_2CH_2OMe$; ii, Me_2SO, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; iii, $NaBH_4$, EtOH; iv, camphorsulfonic acid, Me_2CO; v, MsCl, Et_3N, CH_2Cl_2; vi, NaN_3, Me_2SO, 80°C; vii, 0.5%$BF_3.OEt_2$ in Ac_2O, 0°C; viii, MeONa, MeOH; ix, $^tBuMe_2SiCl$, imidazole, DMF; x, H_2, Pd/C, EtOH; xi, CF_3CO_2H, H_2O (3:7 v/v), RT.

SCHEME 2

Evidently the C-1 hydroxyl groups in the diols (**20**) play some role in the degradation process. When the primary hydroxy groups in the diol mixture (**20**) were selectively silylated the resulting syrupy silyl ethers (**24**)[12] were successfully converted to the crystalline 1,5-imino-galactitol derivative (**25**)[12] on hydrogenation, in 75% overall yield from the anomeric diols (**20**). Acid hydrolysis then afforded deoxygalactonojirimycin (**1**) in near quantitative yield, isolated as its crystalline hydrochloride salt, mp 244-246°C, $[\alpha]_D$ + 55° (*c*1, H_2O); Lit.,[1] mp 240-241.5°C, $[\alpha]_D$ + 44° (*c*0.5, 9:1 MeOH-H_2O). The ^1H- and ^{13}C-NMR spectra correlated exactly with the literature.[1]



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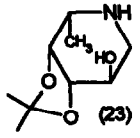

(23)

The procedure presented here has provided ready access to gram scale quantities of deoxygalactonojirimycin in *ca* 20-25% overall yield from L-sorbose.

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10 1,2:4,6-Di-*O*-isopropylidene-α-L-sorbofuranose[15] is now available commercially (Aldrich®).

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12 For (**14**): $[\alpha]_D$ - 46° (*c*2,$CHCl_3$), ^{13}C NMR ($CDCl_3$) 112.9 and 111.8, C-2 and $(CH_3)_2\underline{C}$; 85.0, 79.7 and 77.6, C-3,4,5; 69.1, C-1; 49.4, C-6; 26.4, 26.2, 25.9 and 24.7, $(\underline{C}H_3)_2C$; MH^+ Calc. for $C_{12}H_{20}N_3O_5$ requires 286.1403; Obs. 286.1411.
For (**16**): m.p. 56-58°C, $[\alpha]_D$ -57°C (*c*l, $CHCl_3$), ^{13}C NMR ($CDCl_3$) 112.9, 110.2 and 98.9, C-2 and $(CH_3)_2\underline{C}$; 77.5, 70.0 and 68.8, C-3,4,5; 70.0, C-1; 60.8, C-6; 28.5, 26.3, 26.1 and 19.7, $(\underline{C}H_3)_2C$. MH^+ Calc. for $C_{12}H_{21}O_6$ requires 261.1338; Obs. 261.1343.
For (**18**): m.p. 65-66°C, $[\alpha]_D$ - 63° (cl,$CHCl_3$), ^{13}C NMR ($CDCl_3$) 112.9, 111.8 and 111.7, C-2 and $(CH_3)_2\underline{C}$; 85.3, 80.4 and 78.9, C-3,4,5; 69.2, C-1; 60.9, C-6; 26.4, 25.9 and 24.7, $(\underline{C}H_3)_2C$. MH^+ Calc. for $C_{12}H_{21}O_6$ requires 261.1338; Obs. 261.1327.
For (**20**): ^{13}C NMR ($CDCl_3$) Major anomer 113.2, $(CH_3)_2\underline{C}$; 104.8, C-2; 84.9, 80.3 and 77.8, C-3,4 and 5; 64.2, C-1; 49.7, C-6; 25.8 and 24.5, $(\underline{C}H_3)_2C$. Minor anomer 113.8, 103.1, 79.8, 79.4, 76.2, 64.0, 50.1, 25.8 and 24.5.
For (**24**): $[\alpha]_D$ - 6.3° (*c*1, $CHCl_3$), ^{13}C NMR ($CDCl_3$) 112.9, $(CH_3)_2\underline{C}$; 104.0, C-2; 85.4, 80.3 and 77.7, C-3,4 and 5; 64.4, C-1; 49.8, C-6; 26.0 and 24.7, $(\underline{C}H_3)_2C$; 25.9, $(\underline{C}H_3)_3C$; 18.4, $(CH_3)_3\underline{C}$. MNH_4^+ Calc. for $C_{15}H_{33}N_4O_5Si$ requires 377.2220; Obs. 377.2207.
For (**25**): m.p. 198-203°C, $[\alpha]_D$ + 21° (*c*2, $CHCl_3$), ^{13}C NMR ($CDCl_3$) 109.7, $(CH_3)_2\underline{C}$; 78.3, 72.4 and 69.6, C-2,3 and 4; 62.8, C-6; 56.0, C-5; 46.6, C-1; 27.8 and 25.7, $(\underline{C}H_3)_2C$; 25.9, $(\underline{C}H_3)_3C$; 18.3, $(CH_3)_3\underline{C}$; -5.3 and -5.4, $Si(CH_3)_2$. MH^+ Calc. for $C_{15}H_{32}NO_4Si$ requires 318.2101; Obs. 318.2116.

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