Tetrahedron Vol. 49, No. 16, pp. 3359-3366, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00
Pergamon Press Ltd

SYNTHESIS FROM D-LYXONOLACTONE OF 1,4-DIDEOXY-1,4-IMINO-L-ARABINITOL, A GLUCOSIDASE INHIBITOR WITH *IN VITRO* ANTI-VIRAL ACTIVITY

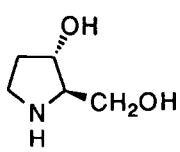
James R. Behling,[a] Arthur L. Campbell,[a] Kevin A. Babiak,[a]
John S. Ng,[a] John Medich,[a] Payman Farid[a] and George W. J. Fleet[b]

G D Searle, 4901, Searle Parkway, Skokie, Illinois, 60077, U S A
Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, U K

(*Received in UK* 7 *January* 1993)

Abstract: Benzylidenation is the only protection required in a 7 step synthesis of the hydrochloride of 1,4-dideoxy-1,4-imino-L-arabinitol from D-lxyonolactone in an overall yield of 21%.

Analogues of sugars, in which the ring oxygen has been replaced by nitrogen and the anomeric oxygen has been removed, usually[1] but not always[2] cause inhibition of the enzymic hydrolysis of the corresponding glycosidic bond. A number of naturally occurring analogues of hexoses containing six or more carbon atoms have been reported;[3] however, nitrogen analogues of only two pentoses, 2-deoxyribose and D-arabinose, have so far been isolated as natural products and these are pyrrolidine rather than piperidine derivatives. CYB3 (1), an analogue of 2-deoxyribose, was isolated from *Castanospermum australe*[4] although, as yet, no significant biological activity has been described. Nectrisine (2),[5] an imine nominally derived from dehydration of 4-amino-4-deoxy-D-arabinose, is an immunomodulator isolated from a fungus which shows potent inhibition of α-glucosidase and α-mannosidase activity.[6] DAB1 [1,4-Dideoxy-1,4-imino-D-arabinitol] (3), isolated from both *Angylocalyx boutiqueanus*[7] and *Arachniodes standishii*,[8] is a powerful inhibitor of yeast α-glucosidase[9] and also inhibits different mouse gut disacharidases to different degrees.[10] Some studies on the mechanism of insect antifeedant activity of DAB1 have been reported;[11] additionally, compounds such as DAB1 may be carcinogenic to rodents.[12] DAB1 inhibits the hydrolysis of sinigrin and progoitrin by thioglucosidases from mustard and the cabbage aphid, *Brevicoryne brassicae*.[13] DAB1 inhibits phloem unloading and/or utilisation of sucrose, resulting in insufficient sucrose transport from cotyledons to roots and hypocotyls.[14]



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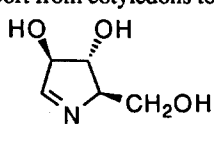

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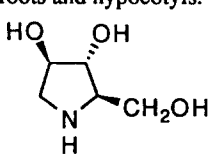

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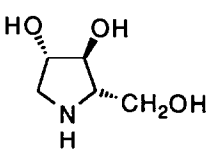

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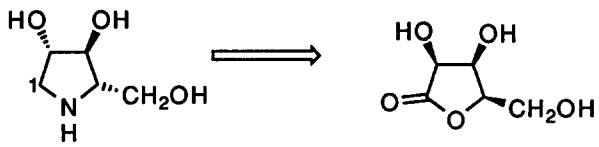
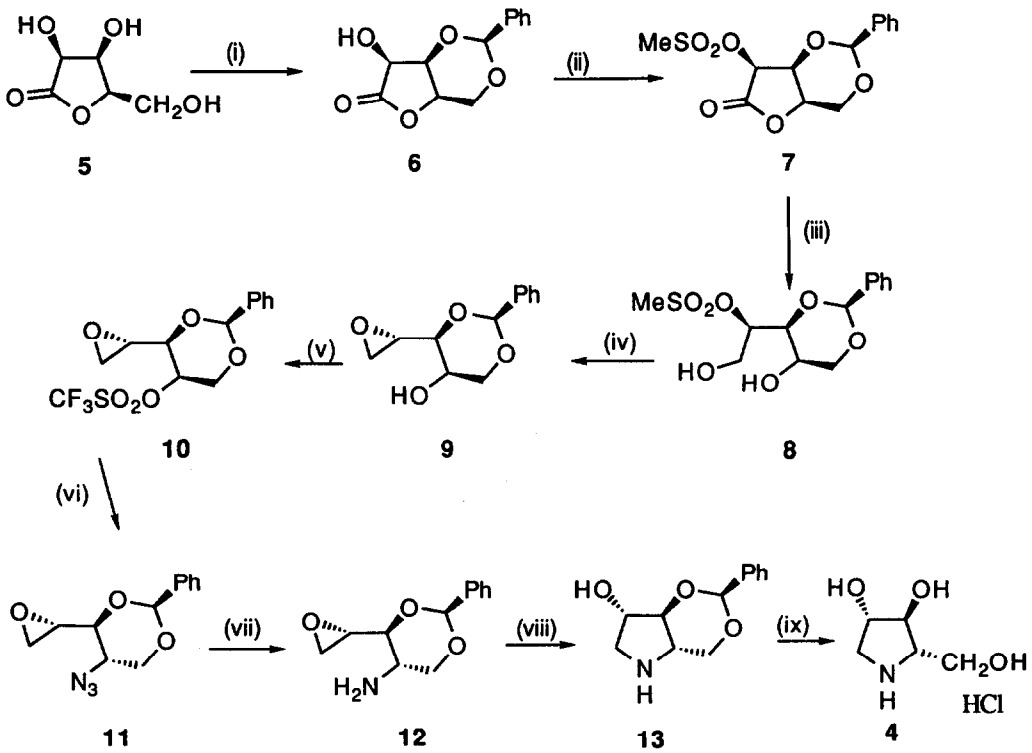
The structure of DAB1 (3) was established by synthesis of both DAB1 and its enantiomer LAB1 (4) from L-arabinose[15] and from D-xylose.[9,16] Other syntheses of DAB1 and its stereoisomers have been reported from carbohydrate[17] and other chiral pool starting materials,[18] by sequences involving the use of aldolases as the key step,[19] and by other methods.[20] LAB1 (4) was shown to be a potent inhibitor of the α-L-arabinofuranosidase III of *Monilinia fructigena*;[21] although LAB1 is a much weaker inhibitor of yeast α-glucosidase than is the natural

product DAB1, LAB1 is a much more powerful inhibitor of some mouse gut α-glucosidases than is DAB1;[22] molecular modelling studies have been used to account for the observation that LAB1 is about ten times more powerful an inhibitor of sucrase than DAB1.[23] A number of polyhydroxylated nitrogen heterocycles was screened as agents for the inhibition of HIV-induced syncthia formation.[24] of which LAB1 was among the most powerful antiviral agents.[25] In order to investigate further the value of LAB1 and its derivatives as potential antiviral agents,[26] a synthesis from D-lyxonolactone was investigated.



4 **5**

Although D-lyxonolactone (5) is readily available from oxygenation of an alkaline solution of D-galactose,[27] there are very few examples of its use as a constituent of the chiral pool. It has been used for efficient syntheses of the fucosidase inhibitor deoxyfuconojirimycin[28] and of the potent antiviral oxetane nucleoside epinoroxetanocin.[29]



5 **6** **7** **8** **9** **10** **11** **12** **13** **4**

(i) PhCHO, conc. HCl (ii) $MeSO_2Cl$, pyridine (iii) $LiBH_4$, THF (iv) K_2CO_3, MeOH (v) $(CF_3SO_2)_2$, pyridine, CH_2Cl_2 (vi) NaN_3, DMF (vii) H_2, 5% Pd/C, MeOH (viii) Bu_4NI, THF (ix) aq. H_2SO_4; then aq. HCl

The synthesis of LAB1 (4) from lyxonolactone (5) requires the formation of the pyrrolidine ring by the joining by nitrogen between C-1 and C-4 and inversion of configuration at both C-2 and C-4; the C-3 and C-5 hydroxyl groups are protected throughout the sequence by benzylidenation. Treatment of D-lyxonolactone (5) with benzaldehyde and aqueous concentrated hydrochloric acid gave the benzylidene derivative (6) [96%] in which only the C-2 hydroxyl group remained free; the configuration of the benzylidene carbon has been established by an X-ray crystal structure of a benzylidene derivative of epinoroxetanocin formed from (6).[29] Esterification of (6) with mesyl chloride in pyridine afforded the mesylate (7) [83%] which was reduced to the diol (8) by lithium borohydride in tetrahydrofuran [90%]. Reaction of (8) with potassium carbonate in methanol gave the epoxide (9) [80%]; there was no competition from formation of the alternative oxetane derived by attack from the C-4 OH. Treatment of (9) with triflic anhydride gave the corresponding triflate (10) which was further reacted with sodium azide to give the azidoepoxide (11) [92%]. Hydrogenation of the azide (11) in the presence of palladium gave the amine (12) [62%]. Closure of (12) to the required pyrrolidine (13) would require a forbidden 6-endo-*tet* process;[30] accordingly, (12) was treated with tetrabutylammonium iodide to give an intermediate iodoalcohol which spontaneously closed to afford (13) [76%]. Finally, the benzylidene protecting group in (13) was removed by aqueous acid to give LAB1 (4), most conveniently isolated as the hydrochloride [84%]. The overall yield of LAB1 from lyxonolactone was 21%.

In summary this paper describes an efficient synthesis of the antiviral aminosugar LAB1 (4) and further demonstrates the value of D-lyxonolactone as a starting material from the chiral pool.

Experimental

General Procedures. Proton nuclear magnetic resonance (δ_H) spectra were recorded at 200MHz or 400MHz on Varian VXR200 or VXR400 spectrometers, respectively. All chemical shifts are quoted on the δ-scale. Infra-red spectra were recorded on Perkin Elmer 281 spectrophotometer Optical rotations were measured on a Perkin Elmer 241 polarimeter with a path length of 1 dm. Concentrations were given in g/100 ml. Microanalyses were performed by Searle physical methodology group on a CEC 240 automatic elemental analyser. Thin layer chromatography (t.l.c.) was carried out on aluminium sheets coated with $60F_{254}$ silica. Plates were developed using either 5% v/v concentrated sulphuric acid in methanol, 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric acid and 0.5% ninhydrin in methanol. Flash chromatography was carried out using Merck 60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures; dichloromethane was refluxed over and distilled from calcium hydride, *N,N*-dimethylformamide was distilled under reduced pressure from calcium hydride, methanol was distilled from magnesium methoxide, pyridine was distilled from, and stored over, potassium hydroxide and tetrahydrofuran was distilled from a purple solution of sodium benzophenone ketyl immediately before use. Hexane was distilled at 68 °C before use to remove involatile fractions. Lyxono-1,4-lactone (5) was prepared from D-galactose as previously described.[27]

3,5(S)-O-Benzylidene-D-lyxono-1,4-lactone (6). Lyxono-1,4-lactone (5) (75 g, 0.507 mole) was dissolved in benzaldehyde (750 ml) and cooled to 0 °C using an ice bath. Concentrated hydrochloric acid (75 ml, 12 N) was added over a one hour time period after which the reaction mixture was allowed to mix at this temperature for

three hours. The reaction mixture was allowed to come to room temperature and was stirred at this temperature overnight (14 h). The reaction mixture was again cooled to 5 °C using an ice bath and was diluted with cold ether (1.6 l). The resulting mixture was stirred rapidly, and a saturated solution of sodium bicarbonate (500 ml) was added slowly. The resulting mixture was filtered and the filter cake was washed with cold ether to provide the crude product. The residue was recrystallized from ethanol (2 l) to provide 3,5(S)-O-benzylidene-D-lyxono-1,4-lactone (6) as a white solid (114 g, 96%), m.p. 203-204 °C; ν_{max} (KBr): 3450, 1770, 1380, 1185, 1150, 1050, 1010, 700 cm^{-1}; ^1H NMR (DMSO d_6) ∂ 4.15 (d, 1 H), 4.25 (d, 1 H), 4.40 (d, 2 H), 4.70 (m, 2 H), 5.65 (s, 1 H), 6.05 (d, 1 H), 7.40 (m, 5 H); ^{13}C NMR (DMSO d_6) ∂ 65.80, 69.54, 70.86, 74.19, 97.60, 126.18, 127.89, 128.76, 137.70, 175.96; $[\alpha]_D^{25}$ +40.1° (c 1.0, DMSO). (Found: C, 60.64; H, 5.12%. $C_{12}H_{12}O_5$ requires C,61.01; H, 5.12%).

3,5(S)-O-Benzylidene-2-O-methanesulphonyl-D-lyxono-1,4-lactone (7). Methanesulfonyl chloride (62g, 42 ml, 0.542 mole) was added dropwise to a solution of 3,5(S)-O-benzylidene-D-lyxono-1,4-lactone (6) (113 g, 0.478 mole) in pyridine (500 ml) over a twenty minute time period at ambient temperature. The resulting reaction mixture was stirred at ambient temperature for three additional hours and was then poured into cold water (2 l) to complete the precipitation of the product. The resulting solids were isolated by filtration and the filter cake was washed with cold water (2 l). After pulling the filter cake dry, the crude product was dissolved in hot acetone (1 l) and filtered through a plug of glass wool. The resulting solution was heated to reflux, and hot isopropanol (500 ml) was added with agitation. The solution was cooled to room temperature and then to 5 °C using an ice bath. The product (104.4 g) was isolated by filtration and the resulting white crystalline material was dried in a vacuum oven; a second crop (19.5 g) of equal purity was obtained from the filtrate to afford *3,5(S)-O-benzylidene-2-O-methanesulphonyl-D-lyxono-1,4-lactone (7),* (123.9 g, 83%), m.p. 116.5-117 °C; ν_{max} (KBr): 3410, 2930, 1775, 1370, 1180, 1105, 1040, 1000, 965, 820, 700 cm^{-1}; ^1H NMR (DMSO d_6) ∂ 3.32 (s, 1H), 3.36 (s, 3 H), 4.32 (ABX, 2 H), 4.62 (d, 1H), 5.10 (m, 1 H), 5.71 (s, 1 H), 5.91 (d, 1 H), 7.40 (s, 5 H); ^{13}C NMR (DMSO d_6) ∂ 38.67, 65.48, 70.42, 72.55, 75.76, 97.55, 125.95, 128.06, 128.96, 137.14, 170.39; $[\alpha]_D^{25}$ +66.3° (c 0.95, DMSO). (Found: C, 49.63; H, 4.51; S, 10.18%. $C_{13}H_{14}O_7S$ requires C, 49.68; H, 4.49; S, 10.20%).

3,5(S)-O-Benzylidene-2-O-methanesulphonyl-D-lyxitol (8). Lithium borohydride (198 ml, 2M in tetrahydrofuran, 0.398 mole) was added to a solution of 3,5(S)-O-benzylidene-2-O-methanesulphonyl-D-lyxono-1,4-lactone (7) (122 g, 0.388 mole) in tetrahydrofuran (1.5 l) at -68 °C over a fifteen minute time period under an atmosphere of argon. The resulting mixture was allowed to slowly warm to room temperature over a 25 min time period and then the reaction was stirred at ambient temperature for 16 hours. The reaction mixture was then cooled to 15 °C and quenched by the dropwise addition of saturated ammonium chloride solution (100 ml). The resulting mixture was partitioned between ethyl acetate (500 ml) and water (100 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 ml). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to dryness by rotary evaporation to provide the crude product as a crystalline residue. The product was recrystallized from 2:3 acetone:hexane (500 ml) to provide *3,5(S)-O-benzylidene-2-O-methanesulphonyl-D-lyxitol (8),* (111.23 g, 90%) as a white crystalline solid, m.p. 99-100 °C; ν_{max} (KBr): 3490, 3390, 2910, 1410, 1350, 1340, 1170, 1090, 1020, 925, 770 cm^{-1}; ^1H NMR (acetone d_6) ∂ 2.90 (bs, 1 H), 3.25 (s, 3 H), 3.65 (d, 1 H), 3.98 (ABX, 2 H), 4.22 (m, 3 H), 4.35 (t, 1 H), 4.85 (m, 1 H), 5.70 (s, 1 H), 7.38 (m, 3 H), 7.55 (m, 2 H); ^{13}C NMR (acetone d_6) ∂ 38.46, 61.35, 63.10, 72.99, 77.25,

81.66, 101.91, 127.15, 128.77, 129.52, 139.44; $[\alpha]_D^{25}$ -15.9° (c 1.03, acetone). (Found: C, 48.82; H, 5.85; S, 9.93%. $C_{13}H_{18}O_7S$ requires C, 49.05; H, 5.70; S, 10.07%).

1,2-Anhydro-3,5(S)-O-benzylidene-D-xylitol (9). Potassium carbonate (52.5 g, 0.380 mole) was added to a solution of 3,5(S)-O-benzylidene-2-O-methanesulphonyl-D-lyxitol (8) (110 g, 0.345 mole) in methanol (2 l). The resulting mixture was stirred for 24 hours at ambient temperature. The reaction mixture was concentrated to dryness by rotary evaporation leaving a white solid (170 g). This solid was digested with ether:acetone (1:1, 2 l) and the remaining solids were removed by filtration. The filtrate was concentrated to dryness by rotary evaporation leaving a off white solid (85 g). This solid was dissolved in hot acetone (300 ml) and then diluted with hot hexane (500 ml). After cooling to 5 °C the product was collected by filtration and rinsed with hexane. The product was dried in a vacuum oven leaving *1,2-anhydro-3,5(S)-O-benzylidene-D-xylitol (9),* (61.3 g, 80%) as a white solid, m.p. 119-120 °C; ν_{max} (KBr): 3470, 2910, 2860, 1400, 1290, 1140, 1090, 1020, 990, 960, 765, 705 cm^{-1}; ^1H NMR ($CDCl_3$) ∂ 2.75 (m, 1 H), 2.90 (t, 1 H), 2.99 (d, 1 H), 3.38 (m, 1 H) 3.65 (m, 2 H), 4.15 (ABq, 2 H), 5.60 (s, 1 H), 7.40 (m, 3 H), 7.55 (m, 2 H). ^{13}C NMR ($CDCl_3$) ∂ 43.47, 52.00, 65.14, 72.30, 81.37, 101.17, 125.92, 128.18, 129.05, 137.27; $[\alpha]_D^{25}$ +5.6° (c 0.952, $CHCl_3$). (Found: C, 64.45; H, 6.40%. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%).

1,2-Anhydro-4-azido-3,5(S)-O-benzylidene-4-deoxy-L-arabinitol (11). Triflic anhydride (5.8 g, 3.5 ml, 20.6 mmol) was added dropwise to a -30 °C solution of 1,2-anhydro-3,5(S)-O-benzylidene-D-xylitol (9) (4.0 g, 18 mmol) and pyridine (2.8 g, 36.0 mmol) in dichloromethane (50 ml). The resulting mixture was stirred for 2 hours at ~-30 °C. The reaction mixture was then poured into water (60 ml) and the resulting mixture was stirred for 10 min. The layers were separated and the aqueous layer was extracted with two 25 ml portions of dichloromethane. The combined organic layers were washed once with brine (25 ml), dried over anhydrous sodium sulfate and filtered, The filtrate was concentrated to dryness by rotary evaporation leaving a yellow oil which was dried further under high vacuum for 2 hours affording the corresponding triflate (10) as a yellow solid (6.3 g, 100 %); the triflate (10) was used in the next stage without further purification. Sodium azide (1.4 g, 21.6 mmol) was added portionwise to a 0 °C solution of the triflate (10) in dimethylformamide (20 ml). The resulting mixture was stirred for 2 hours at 0 °C. The dimethylformamide was removed by rotary evaporation using high vacuum and the residue was dissolved in water (40 ml). The mixture was extracted with dichloromethane (4 x 25 ml) and the combined organic extracts were dried (sodium sulfate) and filtered. The filtrate was concentrated to dryness by rotary evaporation then under high vacuum to provide *1,2-anhydro-4-azido-3,5(S)-O-benzylidene-4-deoxy-L-arabinitol (11),* (4.1 g, 92%) as a yellow solid, m.p. 53-54 °C; ν_{max} (KBr): 4330, 3000, 2880, 2120, 1450, 1380, 1285, 1150, 1080, 1030, 755, 705 cm^{-1}; ^1H NMR ($CDCl_3$) ∂ 2.95 (d, 2 H), 3.26 (m, 1 H), 3.50 (m, 1 H), 3.70 (m, 2 H), 4.40 (ABX, 2 H), 5.46 (s, 1 H), 7.38 (m, 3 H), 7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$) ∂ 44.11, 51.29, 54.40, 68.67, 80.05, 100.80, 126.00, 128.14, 129.07, 136.37; $[\alpha]_D^{25}$ +29.3° (c 1.02, $CHCl_3$). (Found: C, 58.17; H, 5.35; N, 17.01%. $C_{12}H_{13}O_3N_3$ requires C, 58.29; H, 5.30; N, 16.99%).

1,2-Anhydro-4-amino-3,5(S)-O-benzylidene-4-deoxy-L-arabinitol (12). A solution of 1,2-anhydro-4-azido-3,5(S)-O-benzylidene-4-deoxy-L-arabinitol (11) (4.0 g, 16.0 mmol) in the presence of 5% palladium on carbon (50% wet, 10.4 g) in methanol (75 ml) was placed under 5 psi hydrogen pressure for 30 min. The mixture was filtered and the filtrate was concentrated to dryness by rotary evaporation leaving the crude product (4 g) as a

yellow solid. The product was purified by flash chromatography on a 60 mm column using 120 g of silica gel and 20/80 ethanol/$CHCl_3$ as the eluent. The appropriate fractions were combined and concentrated to dryness by rotary evaporation to provide *1,2-anhydro-4-amino-3,5(S)-O-benzylidene-4-deoxy-L-arabinitol (12)*, (2.2 g, 62%), m.p. 100-102 °C; ν_{max} (KBr): 3360, 3300, 2970, 2860, 1600, 1450, 1390, 1100, 1030, 865, 750, 700 cm^{-1}; ^1H NMR (CD_3OD) ∂ 2.90 (m, 2 H), 3.00 (m, 1 H), 3.22 (m, 1 H), 3.40 (dd, 1 H), 3.55 (t, 1 H), 4.20 (dd, 1 H), 4.60 (bs, 2 H), 5.50 (s, 1 H), 7.32 (m, 3 H), 7.45 (m, 2 H); ^{13}C NMR (CD_3OD) ∂ 45.23, 47.09, 52.75, 72.69, 84.29, 101.87, 127.28, 128.94, 129.79, 139.34; $[\alpha]_D^{25}$ +138.2° (c 0.997, CH_3OH). (Found: C, 64.99; H, 6.83; N, 6.15%. $C_{12}H_{15}O_3N$ requires C, 65.14; H, 6.83; N, 6.33%).

3,5(S)-O-Benzylidene-1,4-dideoxy-1,4-imino-L-arabinitol (13). 1,2-Anhydro-4-amino-3,5(S)-O-benzylidene-4-deoxy-L-arabinitol (12) (1.0 g, 4.5 mmol), tetrabutylammonium iodide (1.6 g, 4.5 mmol) and tetrahydrofuran (50 ml) were combined and heated at reflux for 72 hours. The cooled reaction mixture was filtered to remove the precipitated tetrabutylammonium iodide and the filtrate was concentrated to dryness by rotary evaporation. The residue was dissolved in dichloromethane (60 ml) and concentrated to a volume of ~25 ml using a steam bath. After cooling to 5 °C the product was collected by filtration and rinsed with ice-cold dichloromethane. The solid was dried under vacuum to provide the product (0.58 g, 58%) as a white solid. The filtrate was concentrated by rotary evaporation leaving a yellow oil (0.89 g) which was flash chromatographed to provide an additional 0.18 g of *3,5(S)-O-benzylidene-1,4-dideoxy-1,4-imino-L-arabinitol (13)*, (76% combined yield), m.p. 165.5-166 °C; ν_{max} (KBr): 3400, 3300, 2860, 1620, 1450, 1375, 1150, 1045, 910, 690; ^1H NMR (CD_3OD) ∂ 2.75 (dd, 1 H), 2.90 (m, 1 H), 3.40 (m, 1 H), 3.60 (m, 1 H), 3.84 (t, 1 H), 4.32 (m, 2 H), 4.85 (bs, 2 H), 5.55 (s 1 H), 7.35 (m, 3 H), 7.50 (m, 2 H); ^{13}C NMR (CD_3OD) ∂ 51.19, 55.19, 72.81, 72.90, 88.34, 103.24, 127.44, 129.01, 129.86, 139.16; $[\alpha]_D^{25}$ +76.4° (c 0.725, CH_3OH). (Found: C,65.01; H, 6.86; N, 6.21%. $C_{12}H_{15}O_3N$ requires C, 65.14; H, 6.83; N, 6.33%).

1,4-Dideoxy-1,4-imino-L-arabinitol hydrochloride [L-AB1] (4). A solution of 3,5(S)-O-benzylidene-1,4-dideoxy-1,4-imino-L-arabinitol (13) (400 mg, 1.81 mmol) in aqueous sulfuric acid (0.1 N, 20 ml) was heated at 100 °C for 3 hours. The cooled reaction mixture was neutralized by the slow addition of 50% aqueous sodium hydroxide. The resulting mixture was concentrated by rotary evaporation, removing residual water by azeotroping with toluene. The residue was purified by flash chromatography using 2/98 NH_4OH/ethanol as the eluent. The appropriate fractions were combined and concentrated by rotary evaporation to provide the free amine (0.24 g, 90%) as a yellow oil. This oil was dissolved in methanol (6 ml) and aqueous hydrochloric acid (12 M, 0.15 ml) was slowly added. After 10 min. ether (5 ml) was slowly added. After cooling to 5 °C the solid was collected by filtration and dried in a vacuum oven to yield *1,4-dideoxy-1,4-imino-L-arabinitol hydrochloride [L-AB1] (4)*, (0.258 g, 84%) as a white solid, m.p. 165.5-166 °C; ν_{max} (KBr): 3410, 3360, 3010, 2960, 2740. 1570, 1390, 1370, 1255, 1070, 1000, 960; ^1H NMR (CD_3OD) ∂ 3.30 (t, 1 H), 3.50 (m, 2 H), 3.80 (m, 2 H), 3.95 (s 1 H), 4.20 (t, 1 H); ^{13}C NMR (CD_3OD) ∂ 51.71, 60.61, 60.66, 69.43, 75.96, 77.27; $[\alpha]_D^{25}$ -32.9° (c 0.319, H_2O).

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