Potential Glycosidase Inhibitors: Synthesis of 1,4-Dideoxy-1,4-imino Derivatives of D-Glucitol, D- and L-Xylitol, D- and L-Allitol, D- and L-Talitol, and D-Gulitol

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Conversion of 2,3,5,6-tetra-*O*-benzyl-D-galactofuranose (**19**) into its oxime and subsequent treatment with methanesulphonyl chloride gave 2,3,5,6-tetra-*O*-benzyl-4-*O*-methylsulphonyl-D-galactonitrile (**21**). Reductive cyclization by sodium borohydride/cobalt(II) chloride, followed by hydrogenolysis under acidic conditions yielded 1,4-dideoxy-1,4-imino-D-glucitol hydrochloride (**11**). A similar reaction sequence was used to convert 2,3,5-tri-*O*-benzyl L-arabinofuranose (**23**) *via* the nitrile (**25**) into 1,4-dideoxy-1,4-imino-D-xylitol hydrochloride (**12**), and the corresponding D-arabinose derivative (**27**) gave 1,4-dideoxy-1,4-imino-L-xylitol hydrochloride (**13**), using the same chemistry.

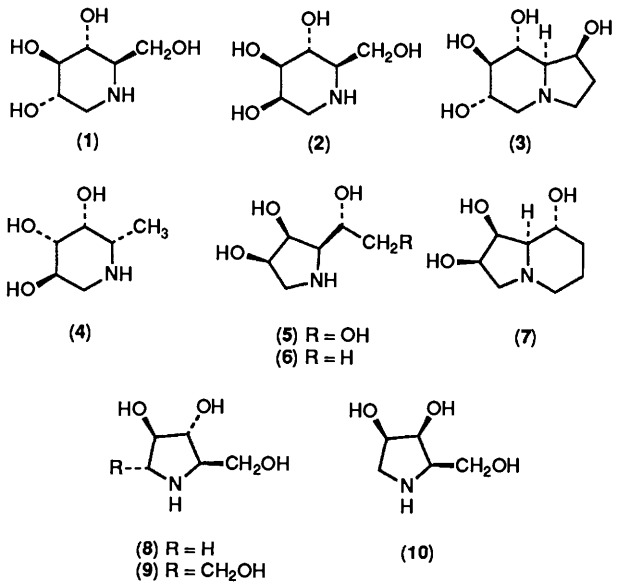
Treatment of 2,3:5,6-di-*O*-isopropylidene-β-D-gulofuranose (**31**) with hydroxylamine and then methanesulphonyl chloride in pyridine gave 4-*O*-methylsulphonyl-2,3:5,6-di-*O*-isopropylidene-D-gulononitrile (**32**), which was converted by treatment with lithium aluminium hydride and subsequent acid hydrolysis into 1,4-dideoxy-1,4-imino-D-allitol hydrochloride (**14**); similar chemistry in the enantiomeric series gave the L-allitol derivative (**15**). An analogous reaction sequence was used to convert 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose into 4-*O*-methylsulphonyl-2,3:5,6-di-*O*-isopropylidene D-mannononitrile (**38**) and thence into 1,4-dideoxy-1,4-imino-D-talitol hydrochloride (**16**); L-mannonolactone was converted *via* 2,3:5,6-di-*O*-isopropylidene-α-L-mannofuranose (**41**) into 1,4-dideoxy-1,4-imino-L-talitol hydrochloride (**17**).

2,3:5,6-Di-*O*-isopropylidene-β-D-allofuranose (**45**) was converted *via* its oxime (**46**) into 4-*O*-methylsulphonyl-2,3:5,6-di-*O*-isopropylidene-D-allononitrile (**47**), which on reductive cyclization with lithium aluminium hydride, and subsequent acid hydrolysis, gave 1,4-dideoxy-1,4-imino-D-gulitol hydrochloride (**18**).

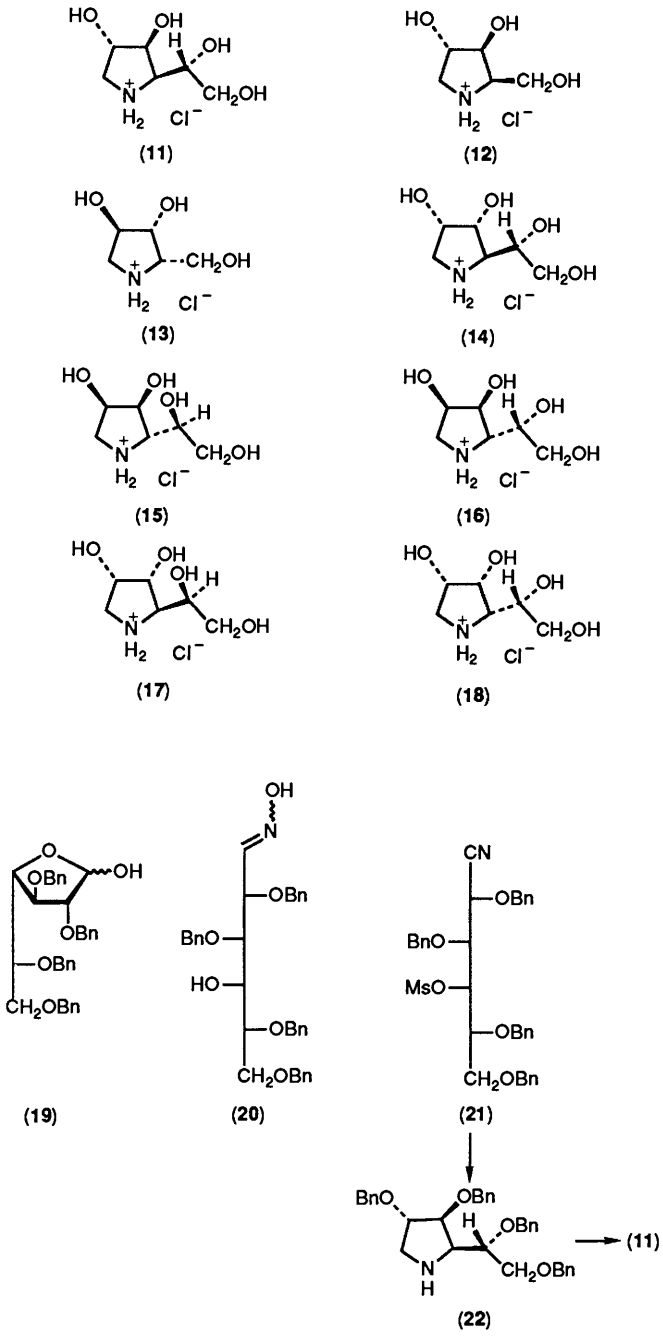
In recent years, a number of polyhydroxylated reduced nitrogen heterocycles, both natural and synthetic, have emerged, which have the property of inhibiting particular glycosidase enzymes. Amongst these compounds are piperidines such as deoxynojirimycin (**1**), synthesized some time ago[1] prior to its isolation as a natural product,[2] which inhibits a number of glucosidases,[3] and deoxymannojirimycin (**2**),[4] which is an inhibitor of various mannosidases.[5] The more complex indolizidine castanospermine (**3**)[6] has also been demonstrated to inhibit glucosidases.[7] In these cases, and in others such as that of the α-L-fucosidase inhibitor (**4**),[8] the stereochemical similarity between the inhibitor and the appropriate hexose sugar, or an enzyme-bound intermediate derived from it, is apparent.

However, there are also a number of pyrrolidines known which display powerful glycosidase activity. Examples include 1,4-dideoxy-1,4-imino-D-mannitol (**5**),[9] and its 6-deoxy analogue (**6**),[10] both of which are powerful mannosidase inhibitors, related to the naturally occurring mannosidase inhibitor swainsonine (**7**).[9,11] Similarly, 1,4-imino-1,4-dideoxy-D-arabinitol (**8**) is a strong α-glucosidase inhibitor,[12] and 2,5-imino-2,5-dideoxy-D-mannitol (**9**) inhibits both α- and β-glucosidases,[13] whilst 1,4-dideoxy-1,4-imino-D-lyxitol (**10**) is an α-galactosidase inhibitor.[13,14] In these cases, the structural similarity between the inhibitor and the appropriate hexopyranose sugar is much less apparent.

Interest in this area has been heightened by the finding that certain compounds of this type display activity against the human immunodeficiency virus; in particular, castanospermine



(**3**) and *N*-alkyl derivatives of deoxynojirimycin (**1**) have attracted attention,[15,16] and it is thought that the activity of such compounds may lie in their ability to inhibit α-glucosidase I, thus impairing the processing of viral glycoprotein. Additionally, swainsonine (**7**), and its monocyclic analogue (**5**) have immunostimulant activity,[17] which may well relate to their

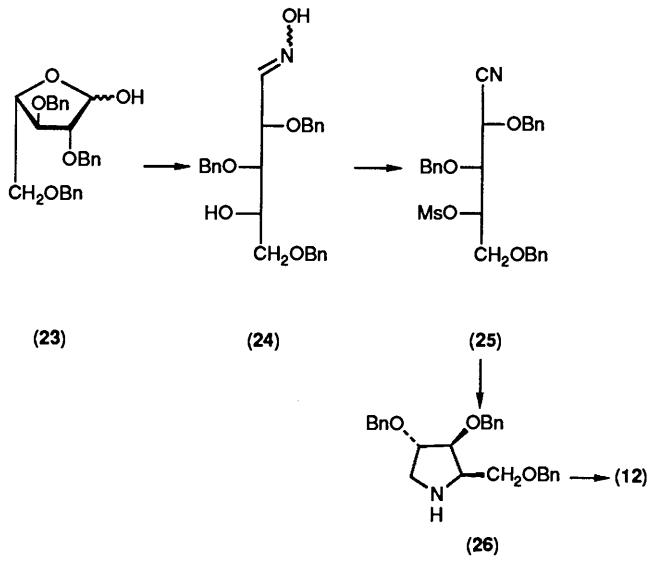


Scheme 1.

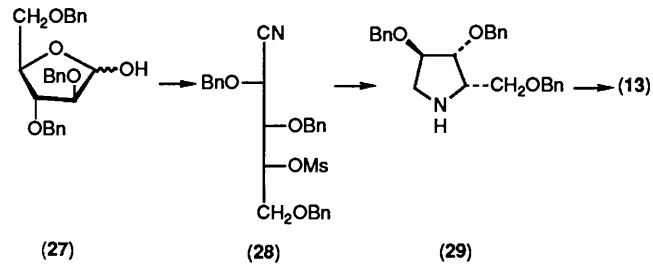
ability to inhibit mannosidases of glycoprotein processing.

Given the above considerations, we were interested in probing structure–activity relationships amongst pyrrolidines (1,4-dideoxy-1,4-iminoalditols) related to those mentioned above. In this paper we report syntheses of the hydrochlorides of the title compounds (**11**)–(**18**); during or since completion of our work, other workers have reported alternative routes to the hydrochlorides of 1,4-dideoxy-1;4-imino-D-glucitol (**11**),[18,19] 1,4-dideoxy-1,4-imino-D-xylitol (**12**),[20] 1,4-dideoxy-1,4-imino-D-allitol (**14**),[19] and 1,4-dideoxy-1,4-imino-D-talitol (**16**).[17,21]

Our route to 1,4-dideoxy-1,4-imino-D-glucitol hydrochloride (**11**) commenced from 2,3,5,6-tetra-*O*-benzyl-D-galactofuranose (**19**)[22] (Scheme 1). Conversion of (**19**) into its oxime (**20**) and subsequent treatment with methanesulphonyl chloride in pyridine gave the mesyloxy nitrile (**21**) [85% from (**19**)]. This was subjected to reductive cyclization using cobalt(II) chloride–sodium borohydride to give the pyrrolidine (**22**); this cyclization procedure is one which we have earlier applied in other work.[23] Conventional hydrogenolysis in acidic ethanol then led to the amine hydrochloride (**11**), with physical properties in excellent agreement with those reported by others.[18,19]



Scheme 2.

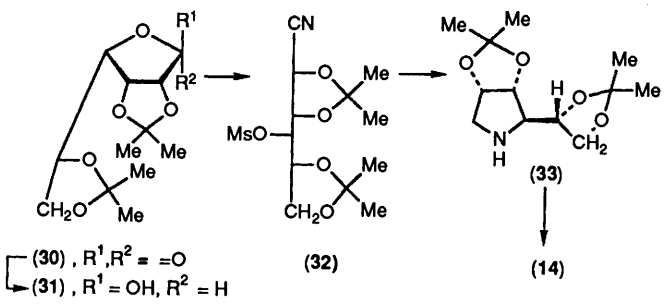


Scheme 3.

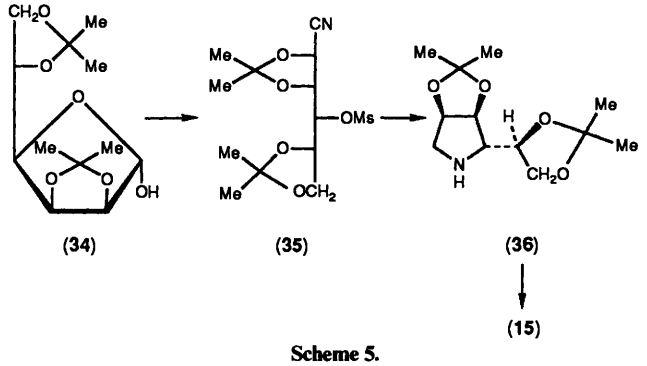
We had expected that (**11**) might well be a powerful glucosidase inhibitor, on the basis of molecular modelling studies. However, (**11**) had K_I = 1.33 mM for the hydrolysis of 4-nitrophenyl-β-D-glucoside by almond emulsin β-glucosidase, and also showed only weak inhibition of the β-glucosidase of *Helix pomatia*. The material also inhibited weakly the β-galactosidase of *H. pomatia*, and was a slight *activator* of the α-glucosidase from a *Bacillus* species. Other workers[18] have stated that (**11**) is 'a potent α-D-glucosidase inhibitor', but we feel that a critical evaluation of the data[18] does not support this claim.

We had also predicted that 1,4-dideoxy-1,4-imino-D-xylitol (**12**) might display glucosidase inhibition. This material was readily accessible by conversion of 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**23**)[24] into its oxime (**24**) (Scheme 2), and dehydration–sulphonylation to give the nitrile mesylate (**25**) [95% from (**23**)]; cyclization using either cobalt(II) chloride–sodium borohydride or lithium aluminium hydride gave the protected pyrrolidine (**26**) in the same (53%) yield, which was hydrogenolysed to yield (**12**).

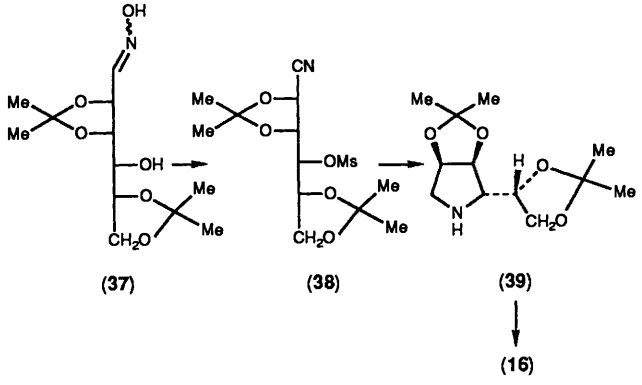
Concurrently we also prepared (**13**), the enantiomer of (**12**), from tri-*O*-benzyl-D-arabinofuranose (**27**), *via* intermediates (**28**) and (**29**) (Scheme 3). When (**12**) and (**13**) were evaluated as inhibitors of almond emulsin β-glucosidase, with *p*-nitrophenyl-β-D-glucoside as substrate, they displayed very similar, high K_I values [7.1 mM for (**12**), 7.3 mM for (**13**)], and, with various other glucosidases, low, non-specific inhibition was found for both enantiomers.



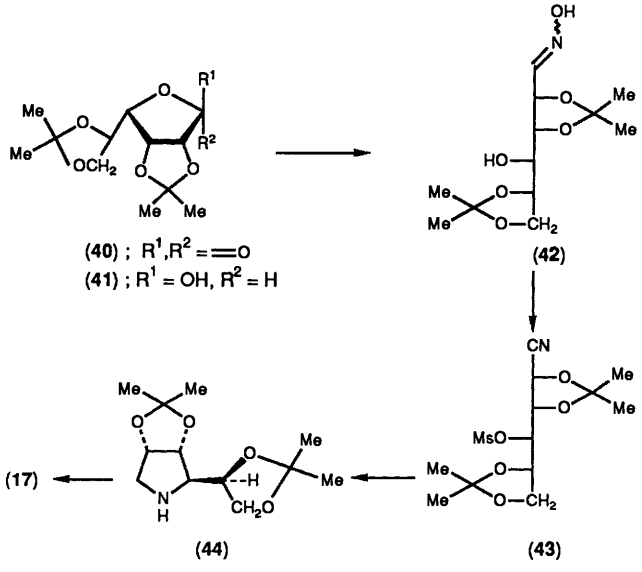
Scheme 4.



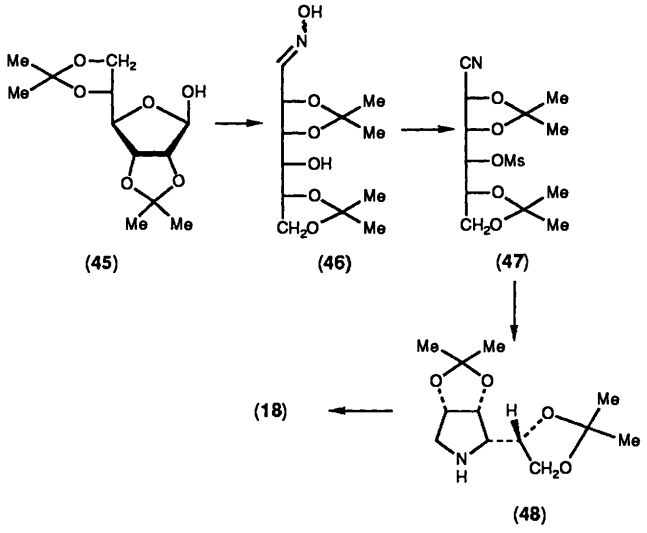
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

Similar chemistry was also employed for the synthesis of the enantiomeric pair 1,4-dideoxy-1,4-imino-D-allitol hydrochloride (**14**), and its L-isomer (**15**). Thus, conversion of D-gulonolactone into its di-*O*-isopropylidene derivative (**30**)[25,26] (Scheme 4), and reduction[26] to the lactol (**31**), was followed by the sequence of oximation, mesylation-dehydration to give (**32**), and reductive cyclization to yield (**33**). That cyclization had occurred with inversion of configuration at C-4 was clear from the ^{1}H NMR spectrum, which displayed $J_{3,4}$ *ca.* 0. Acidic hydrolysis then gave (**14**).

The same chemistry was also carried out in the enantiomeric series (Scheme 5) to convert L-gulonolactone[27] *via* the lactol (**34**), the nitrile (**35**), and the di-*O*-isopropylidene derivative (**36**) into 1,4-dideoxy-1,4-imino-L-allitol (**15**).

When 2,3:5,6-di-*O*-isopropylidene-α-D-mannose was converted into its oxime (**37**),[28] followed by treatment with methanesulphonyl chloride in pyridine, the crystalline nitrile mesylate (**38**) was produced (Scheme 6). Reductive cyclization of this using lithium aluminium hydride to give the pyrrolidine (**39**), and acidic deprotection gave the crystalline hydrochloride of 1,4-dideoxy-1,4-imino-D-talitol (**16**). This compound has also been prepared during our work by other groups, and shown to display immunostimulatory activity,[17] and to be a specific and competitive inhibitor of human liver α-mannosidase.[21]

Given the commercial availability of L-mannonolactone, the enantiomeric 1,4-dideoxy-1,4-imino-L-talitol (**17**) also became readily available as indicated in Scheme 7. Thus, conversion of L-mannonolactone into its di-*O*-isopropylidene derivative (**40**) using anhydrous copper(II) sulphate and concentrated sulphuric acid in dry acetone (94% yield) was followed by reduction to 2,3:5,6-di-*O*-isopropylidene-α-L-mannofuranose (**41**) using di-isobutyl aluminium hydride (88% yield).[29] Formation of the L-oxime (**42**) (94%) as described for the enantiomer[28] and treatment with mesyl chloride–pyridine gave the L-nitrile mesylate (**43**) in 63% crystalline yield. Reductive cyclization to (**44**) and acidic hydrolysis gave the hydrochloride of 1,4-dideoxy-1,4-imino-L-talitol (**17**).

As a final example of the use of this methodology, we report the synthesis of 1,4-dideoxy-1,4-imino-D-gulitol (**18**) (Scheme 8). Rearrangement of the readily available[30] 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose in acidic acetone is known to give the 2,3:5,6-di-*O*-isopropylidene isomer (**45**).[31] This material was converted using hydroxylamine hydrochloride and sodium hydrogen carbonate in aqueous ethanol into its oxime (**46**), obtained crystalline in 84% yield as a mixture (^{1}H NMR) of *E* and *Z* isomers in a ratio of 8:2. Conversion into the

nitrile mesylate (**47**) (66%) was carried out in the usual way with an excess of methanesulphonyl chloride in pyridine. Reductive cyclization then gave the crystalline pyrrolidine (**48**), but in somewhat poor yield, which may reflect the sterically congested nature of the transition state leading from (**47**) to (**48**). The product (**48**) was clearly different from the C-4 isomer (**33**), showing, in partiicular $J_{3,4}$ 4.3 Hz, thus confirming the expected inversion of configuration during the ring formation. Treatment of (**48**) with aqueous acid, and purification by ion-exchange chromatography, gave the hydrochloride of 1,4-imino-D-gulitol (**16**) in 77% yield.

Fuller biological data on compounds (**11**)–(**18**) will be published elsewhere.

Experimental

IR spectra were recorded on Perkin-Elmer 157G or 580 instruments. Mass spectrometery was performed using updated M.S.9, or VG 70-70 instruments. NMR spectra were recorded on Perkin-Elmer R12B, Bruker WP 80SY, WP 200SY and WH 360 spectrometers using deuteriochloroform as solvent unless otherwise stated. Specific rotations were measured at room temp. using a Bendix-NPL 143D automatic polarimeter (path length 1 cm). M.p.s were determined in capillaries and are uncorrected. Adsorption chromatography was carried out using Kieselgel H type 60 (Merck 7734); an external pressure was applied to the top of columns. For TLC, pre-coated aluminium-backed plates [Kieselgel HF_{254} type 60 (Merck)] were used. Light petroleum refers to material of b.p. 40–60 °C. Organic extracts were dried with anhydrous magnesium sulphate.

2,3,5,6-*Tetra*-O-*benzyl*-4-O-*methylsulphonyl*-D-*galactono*-*nitrile* (**21**).—Hydroxylamine hydrochloride (1.45 g) was added to a solution of sodium methoxide [from sodium (0.36 g)] in methanol (30 ml). To the resultant suspension was added, with stirring 2,3,5,6-tetra-*O*-benzyl-D-galactofuranose[22] (**19**) (5.0 g), and the mixture was maintained at room temperature with stirring overnight. The residue after evaporation was partitioned between water (50 ml) and dichloromethane (3 × 50 ml). The washed, dried organic extract was evaporated to give the oxime (**20**) (5.14 g, 100%) as a viscous oil. A solution of this material (5.14 g) in dry pyridine (23 ml) was added dropwise with stirring to methanesulphonyl chloride (9.0 ml) in pyridine (23 ml) at −20 °C. The mixture was allowed to warm to room temperature and stirred for 18 h. Water (5 ml) was added dropwise with cooling, after which solvents were evaporated. The residue was partitioned between ether and 5% aqueous citric acid solution. The washed, dried organic layers were evaporated to give a dark oil (7 g) which was chromatographed on silica, eluting with ether–light petroleum (1:1) to give the *nitrile* (**21**) (5.01 g, 88%) as an oil, $[\alpha]_D$ +15.2° (*c* 1.25 in $CHCl_3$); ν_{max}(film) 1 350 and 1 180 cm^{-1} (SO_2); δ_H(360 MHz) 2.99 (3 H, s, SO_2Me), 3.62 (2 H, d, *J* 4.6 Hz, 6-H_2), 4.00 (1 H, dt, 5-H), 4.06 (1 H, dd, $J_{3,2}$ 4.85 Hz, $J_{3,4}$ 4.0 Hz, 3-H), 4.4–4.85 (8 H, 4AB systems, PhCH_2), 4.53 (1 H, d, 2-H), 5.22 (1 H, dd, $J_{4,5}$ 5.5 Hz, 4-H), and 7.3 (20 H, m, Ph); *m*/*z* 615 (M^+) and 524 (M^+ − $PhCH_2$) (Found: C, 68.7; H, 6.2; N, 2.3; S, 5.2. $C_{35}H_{37}NO_7S$ requires C, 68.3; H, 6.1; N, 2.3; S, 5.2%).

2,3,5,6-*Tetra*-O-*benzyl*-1,4-*dideoxy*-1,4-*imino*-D-*glucitol* (**22**).—To a stirred solution of the nitrile (**21**) (0.5 g) and cobalt(II) chloride hexahydrate (0.39 g) in methanol (8 ml), was added in portions sodium borohydride (0.31 g). After 18 h, the mixture was evaporated and the residue was partitioned between water and dichloromethane. The dried organic extracts were evaporated, and the residue was chromatographed on silica, eluting with ether, to give the *pyrrolidine* (**22**) (0.214 g, 50%) as a syrup, $[\alpha]_D$ −21.1° (*c* 3.04 in $CHCl_3$); δ_H(200 MHz) 2.2 (1 H, br s, NH), 2.97 (1 H, dd, J_{gem} 12.2, $J_{1a,2}$ 2.3 Hz, 1_a-H), 3.37 (1 H, dd, $J_{1b,2}$ 5.4 Hz, 1_b-H), 3.53 (1 H, dd, $J_{4,3}$ 3.97, $J_{4,5}$ 9.46 Hz, 4-H), 3.73 (1 H, dd, J_{gem} 10.8, $J_{6a,5}$ 5.1 Hz, 6_a-H), 3.85–4.05 (3 H, m, 2, 5, 6_b-H), 4.15 (1 H, br d, *J* 3.95 Hz, 3-H), 4.4–4.6 (7 H, m, PhCH_2), 4.79 (1 H, d, *J* 11.5 Hz, PhCH_2), and 7.35 (20 H, m, Ph); *m*/*z* 524 (M^+ + H), 432 (M^+ − $PhCH_2$), 282 (M^+ − side chain) (Found: C, 77.8; H, 7.2; N, 3.0. $C_{34}H_{37}NO_4$ requires C, 78.0; H, 7.1; N, 2.7%).

1,4-*Dideoxy*-1,4-*imino*-D-*glucitol Hydrochloride* (**11**).—A solution of (**22**) (0.38 g) in ethanol (7 ml) and aqueous HCl (2M; 3 ml) was hydrogenated using palladium-on-charcoal (5%; 80 mg) as catalyst. The mixture was filtered, and the catalyst washed well with ethanol–dilute HCl. The solid residue after evaporation was recrystallized from ethanol–acetone to give the iminoglucitol hydrochloride (**11**) (0.137 g, 94%) as white crystals, m.p. 142–144 °C (lit.,[18] 140–142 °C), $[\alpha]_D$ −25.0° (*c* 0.34 in water) [lit.,[18] −27 °C (water)]; $\nu_{max.}$ 3 500–3 100br cm^{-1} (NH, OH); δ_H(360 MHz, D_2O) 3.37 (1 H, dd, J_{gem} 13.05, $J_{1\alpha,2}$ 0.65, 1_α-H), 3.8 (4 H, m, 1_β-H, 4-H, 6-H_2), 4.18 (1 H, dt, *J* 8.8, 5.0 Hz, 5-H), and 4.45 (2 H, m, 2-, 3-H); *m*/*z* (FAB) 164 (MH^+) (Found: C, 35.8; H, 7.0; N, 7.0. Calc. for $C_6H_{14}ClNO_4$: C, 36.1; H, 7.0; N, 7.0%).

2,3,5-*Tri*-O-*benzyl*-4-O-*methylsulphonyl*-L-*arabinono*-*nitrile* (**25**).—Hydroxylamine hydrochloride (1.66 g), and 2,3,5-tri-*O*-benzyl-L-arabinose (**23**) (4.92 g) were added to a stirred solution of sodium methoxide [from sodium (0.46 g)] in methanol (30 ml). After 16 h, solvent was evaporated and the residue was partitioned between water (50 ml) and dichloromethane (3 × 50 ml). The washed, dried organic layers were evaporated to give the oxime (**24**) (5.10 g, 100%) as a 7:3 mixture of (*E*)-and (*Z*)-isomers; δ_H(200 MHz) 7.0 (0.3 H, d, *J* 5 Hz, 1-H, *Z*-isomer) and 7.5 (0.7 H, d, *J* 7 Hz, 1-H, *E*-isomer).

The oxime (5.0 g) in pyridine (25 ml) was added dropwise over 1 h to a stirred solution of methanesulphonyl chloride (11 ml) in pyridine (30 ml) at −20 °C. After a further 1 h, the mixture was allowed to warm to room temperature and stirred overnight. Water (3 ml) was added dropwise with cooling in ice, the solvents were evaporated, and the residue was partitioned between aqueous HCl (2M) and ether. The organic layers were dried and evaporated to give a dark oil which was chromatographed on silica, eluting with ether–light petroleum (initially 2:3, increasing to 2:1) to give the *nitrile mesylate* (**25**) (5.42 g, 95%), as an oil, $[\alpha]_D$ +24.0° (*c* 1.45 in $CHCl_3$); ν_{max}(film) 1 360 and 1 180 cm^{-1} (SO_2); δ_H(200 MHz) 2.95 (3 H, s, SO_2Me), 3.76 (1 H, dd, J_{gem} 11.2, $J_{5a.4}$ 6.1 Hz, 5a-H), 3.89 (1 H, dd, $J_{5b.4}$ 3.3 Hz, 5_b-H), 4.08 (1 H, dd, $J_{3,2}$ 4.1, $J_{3,4}$ 5.65 Hz, 3-H), 4.40 (1 H, d, 2-H), 4.52 (2 H, s, PhCH_2), 4.59, 4.63, 4.72, and 4.73 (each 1 H, d, *J* 11 Hz, PhCH_2), 5.04 (1 H, dt, 4-H), and 7.3 (15 H, m, Ph); *m*/*z* 495 (M^+), 404 (M^+ − C_7H_7) (Found: C, 65.3; H, 5.9; N, 2.8; S, 6.8. $C_{27}H_{29}NO_6S$ requires C, 65.4; H, 5.9; N, 2.8; S, 6.5%).

2,3,5-*Tri*-O-*benzyl*-1,4-*dideoxy*-1,4-*imino*-D-*xylitol* (**26**).—(*a*) Sodium borohydride (1.53 g) was added in small portions to a stirred mixture of the nitrile (**25**) (2.0 g) and cobalt(II) chloride hexahydrate (1.92 g) in methanol (40 ml), the temperature being maintained < 30 °C. After 16 h, the solvent was evaporated and the residue was partitioned between dilute HCl (2M) and dichloromethane. The aqueous layer was made basic with aqueous $NaHCO_3$, and extracted repeatedly with dichloromethane. The dried extracts were evaporated to give a residue (1.7 g) which was chromatographed on silica, eluting with ether–light petroleum (1:1, then to 9:1) to give the *pyrrolidine* (**26**) (0.87 g, 53%) as an oil, $[\alpha]_D$ −2.5° (*c* 0.79 in $CHCl_3$); δ_H(200 MHz) 2.2 (1 H, br s, NH), 2.91 (1 H, dd, J_{gem} 11.5, $J_{1a,2}$ 3.5 Hz, 1_a-H), 3.36 (1 H, dd, $J_{1b,2}$ 5.5 Hz, 1_b-H), 3.51 (1 H, m, 4-H), 3.63 (1 H, dd, J_{gem} 9.0, $J_{5a.4}$ 6.5 Hz, 5a-H), 3.72 (1 H, dd, $J_{5b.4}$ 6.5 Hz,

5_b-H), 4.0 (2 H, m, 2-, 3-H), 4.5 (6 H, m, PhCH_2) and 7.3 (15 H, m, Ph); *m/z* 404 (M^+ + H), 312 (M^+ − C_7H_7), 282 (M^+ − CH_2OCH_2Ph) (Found: C, 77.2; H, 7.6; N, 3.7. $C_{26}H_{29}NO_3$ requires C, 77.4; H, 7.2; N, 3.5%).

(*b*) A solution of the nitrile (**25**) (0.5 g) in ether (5 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (96 mg) in ether (10 ml) at 0 °C. After being stirred overnight at room temperature the mixture was poured into ethyl acetate (25 ml) and saturated aqueous NH_4Cl (10 ml). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (3 × 25 ml). Evaporation gave a residue which was chromatographed as in (*a*) to give the *pyrrolidine* (**26**) (0.218 g, 53%), with properties as above.

1,4-*Dideoxy*-1,4-*imino*-D-*xylitol Hydrochloride* (**12**).—A solution of (**26**) (0.73 g) in ethanol (18 ml) and dilute HCl (2M; 8 ml) was hydrogenated at 1 atm using palladium-on-charcoal (5%; 0.15 g) as catalyst, until no further hydrogen uptake occurred (113 ml uptake). The mixture was filtered and the catalyst washed with ethanol–dilute HCl. Evaporation gave a solid which was recrystallized from ethanol–acetone to give the iminoxylitol hydrochloride (**12**) (0.19 g, 62%), m.p. 127–129 °C, $[\alpha]_D$ +7.4° (*c* 0.68 in water) [lit.,[20] $[\alpha]_D$ +12.0° (in water)]; δ_H(360 MHz, D_2O) 3.35 (1 H, br d, J_{gem} 13.0 Hz, 1_a-H), 3.71 (1 H, dd, $J_{1b,2}$ 4.3 Hz, 1_b-H), 3.9–4.0 (2 H, m, 4-, 5_a-H), 4.07 (1 H, dd, J_{gem} 15.5, $J_{5b,4}$ 8.55 Hz, 5_b-H), 4.37 (m, becomes d, *J* 2.5 Hz, on decoupling at δ 4.44, 3-H), and 4.44 (1 H, dt, *J* ~4.6, ~1.3 Hz, 2-H); *m/z* (FAB) 134 (MH^+) (Found: C, 35.3; H, 7.1; N, 8.1. Calc. for $C_5H_{12}ClNO_3$: C, 35.4; H, 7.1; N, 8.3%).

2,3,5-*Tri*-O-*benzyl*-4-O-*methylsulphonyl*-D-*arabinononitrile* (**28**).—Treatment of 2,3,5-tri-*O*-benzyl-D-arabinose (**27**) (4.85 g) as described above for the enantiomer gave the D-*nitrile* (**28**) (4.43 g, 78%) as an oil, $[\alpha]_D$ −25.0° (*c* 1.0 in $CHCl_3$), with spectra as for the enantiomer (Found: C, 65.7; H, 6.0; N, 2.9. $C_{27}H_{29}NO_6S$ requires C, 65.4; H, 5.9; N, 2.8%).

2,3,5-*Tri*-O-*benzyl*-1,4-*dideoxy*-1,4-*imino*-L-*xylitol* (**29**).—Treatment of the nitrile (**28**) (0.5 g) as described above for the enantiomer [procedure (*b*)] gave the *imino*-L-xylitol (**29**) (0.256 g, 63%) as a syrup, $[\alpha]_D$ +2.0° (*c* 1.0 in $CHCl_3$), with spectra as for the enantiomer (Found: C, 77.4; H, 7.5; N, 3.8. $C_{26}H_{29}NO_3$ requires C, 77.4; H, 7.2; N, 3.5%).

1,4-*Dideoxy*-1,4-*imino*-L-*xylitol Hydrochloride* (**13**).—Hydrogenolysis of (**29**) (0.64 g) as described above for the enantiomer gave, after recrystallization from ethanol–acetone, the *imino*-L-*xylitol hydrochloride* (**13**) (0.166 g, 62%), m.p. 128–129 °C, $[\alpha]_D$ −9.9° (*c* 0.71 in water), with spectroscopic data as for the enantiomer (Found: C, 35.1; H, 7.2; Cl, 22.3; N, 8.0. $C_5H_{12}ClNO_3$ requires C, 35.4; H, 7.1; Cl, 20.9; N, 8.3%).

2,3:5,6-*Di*-O-*isopropylidene*-D-*gulonolactone* (**30**).—Sulphuric acid (conc.; 3 ml) was added dropwise to a stirred suspension of D-gulonolactone (30 g) and anhydrous copper(II) sulphate (135 g) in dry acetone (1.5 l). After 3 days, the mixture was neutralized with anhydrous sodium carbonate and filtered. The residue after evaporation was partitioned between water and dichloromethane. The washed, dried organic layer was evaporated, and the residue was crystallized from toluene–light petroleum (b.p. 60–80 °C) to give the di-isopropylidene derivative (**30**) (38.9 g, 90%), as colourless crystals, m.p. 152–154 °C, $[\alpha]_D$ −68.7° (*c* 0.66 in $CHCl_3$) {lit.,[25,26] m.p. 153–153.5 °C, $[\alpha]_D$ −67.8° (*c* 4.16 in $CHCl_3$)}, with spectroscopic properties as reported.[19]

2,3:5,6-*Di*-O-*isopropylidene*-β-D-*gulose* (**31**).—Reduction of the lactone (**30**) (20 g) as reported [26] gave the lactol (**31**) (14.0 g, 70%), m.p. 113–115 °C, $[\alpha]_D$ −6.1° (*c* 1.3 in $CHCl_3$) {lit.,[26] m.p. 114–115 °C, $[\alpha]_D$ −2.6° (*c* 4.12 in $CHCl_3$)}; δ_H(200 MHz) 1.28, 1.38 (each 3 H, s, CMe_2), 1.45 (6 H, s, CMe_2), 3.3 (1 H, br s, OH), 3.71 (1 H, dd, J_{gem} 8.3, $J_{6a,5}$ 7.05 Hz, 6_a-H), 4.11 (1 H, dd, $J_{4,5}$ 8.4, $J_{4,3}$ 3.6 Hz, 4-H), 4.19 (1 H, dd, $J_{6b,5}$ 6.5 Hz, 6_b-H), 4.34 (1 H, dt, 5-H), 4.61 (1 H, d, $J_{2,3}$ 5.9 Hz, 2-H), 4.67 (1 H, dd, 3-H), and 5.44 (1 H, s, 1-H).

4-O-*Methylsulphonyl*-2,3:5,6-*di*-O-*isopropylidene*-D-*gulononitrile* (**32**).—To a stirred solution of sodium methoxide (1.10 g) in methanol (40 ml) was added hydroxylamine hydrochloride (1.89 g), followed by (**31**) (3.15 g). After 16 h, the solvent was evaporated and the residue was partitioned between dichloromethane (3 × 40 ml) and water (50 ml). The washed, dried organic extracts were evaporated to give the oxime (3.0 g) as a syrup containing *ca.* equal amounts of *E*- and *Z*-isomers; δ_H(200 MHz) 7.1 (0.5 H, d, *J* 3 Hz, 1-H, *Z*-isomer) and 7.55 (0.5 H, d, *J* 7 Hz, 1-H, *E*-isomer). This material in pyridine (20 ml) was added dropwise with stirring to methanesulphonyl chloride (10.5 ml) in pyridine (20 ml) at −20 °C. After 0.5 h, the mixture was allowed to warm to room temperature, and then stirred for 16 h. Water (3 ml) was added dropwise with stirring at 0 °C, after which solvents were evaporated, and the residue was partitioned between water and ether. The ether extracts were washed with aqueous citric acid solution (11M), dried, and evaporated to give a residue which was chromatographed on silica, eluting with ether–light petroleum (1:1); the resultant solid was recrystallized from ether–light petroleum to give the *nitrile mesylate* (**32**) (2.01 g, 50%), m.p. 105–107 °C; ν_{max}(KBr) 1 350 and 1 170 cm^{-1} (SO_2); δ_H(200 MHz) 1.37, 1.42, 1.45, and 1.60 (each 3 H, s, CMe_2), 3.15 (3 H, s, SO_2Me), 4.13 (2 H, m, 6-H_2), 4.32 (1 H, dt, $J_{5.6a}$ ~$J_{5.6b}$ 6.5, $J_{5,4}$ 2.8 Hz, 5-H), 4.49 (1 H, dd, $J_{3,4}$ 8.8, $J_{3,2}$ 5.0 Hz, 3-H), 4.88 (1 H, d, 2-H), and 4.91 (1 H, dd, 4-H); *m/z* 320 (M^+ − CH_3) (Found: C, 46.6; H, 6.3; N, 4.1; S, 9.2. $C_{13}H_{21}NO_7S$ requires C, 46.6; H, 6.3; N, 4.2; S, 9.6%).

1,4-*Dideoxy*-2,3:5,6-*di*-O-*isopropylidene*-1,4-*imino*-D-*allitol* (**33**).—Lithium aluminium hydride (0.142 g) was added to a stirred solution of the nitrile (**32**) (0.5 g) in ether (15 ml) at 0 °C. The mixture was stirred at room temperature overnight and then cooled to 0 °C. It was then diluted at 10 min intervals with water (0.15 ml), aqueous sodium hydroxide (15% w/v; 0.15 ml), and water (0.45 ml) and then filtered. The dried filtrate was evaporated to dryness to give a residue that was chromatographed on silica, eluting with ether–methanol (97:3) to give the pyrrolidine (**33**) (0.17 g, 47%) as a colourless oil, $[\alpha]_D$ +40.9° (*c*, 1.44 in $CHCl_3$) [lit.,[19] +34.1° (*c* 0.41 in $CHCl_3$)]; ν_{max}(film) 3 330 cm^{-1} (NH); δ_H(360 MHz) 1.28 (6 H, s, CMe_2), 1.39 and 1.43 (each 3 H, s, CMe_2), 2.5 (1 H, br s, NH), 2.84 (1 H, dd, J_{gem} 13.6, $J_{1\beta,2}$ 3.9 Hz, 1_β-H), 2.99 (1 H, d, $J_{1\alpha,2}$ ~NO, 1_α-H), 3.08 (1 H, d, $J_{4,5}$ 7–8, $J_{4,3}$ ~0 Hz, 4-H), 3.79 (1 H, dd, J_{gem} 8.3, $J_{6a,5}$ 5.85 Hz, 6_a-H), 3.90 (1 H, dt, 5-H), 4.06 (1 H, dd, $J_{6b,5}$ 6.35 Hz, 6_b-H), 4.67 (1 H, dd, $J_{2,3}$ 5.6 Hz, 2-H), and 4.72 (1 H, d, 3-H); *m/z* 243 (M^+), 228 (M − Me)$^+$, 142 (M^+ − side chain) (Found: C, 58.8; H, 8.7; N, 6.1. Calc. for $C_{12}H_{21}NO_4$: C, 59.2; H, 8.7; N, 5.8%).

1,4-*Dideoxy*-1,4-*imino*-D-*allitol Hydrochloride* (**14**).—The isopropylidene derivative (**33**) (0.243 g) was stirred in aqueous HCl (2M; 10 ml) for 24 h. The mixture was lyophilized and the solid residue recrystallized from 95% ethanol to give 1,4-dideoxy-1,4-imino-D-allitol hydrochloride (**14**) (0.19 g, 95%), m.p. 112–113 °C, $[\alpha]_D$ +25.6° (*c* 0.9 in water) {lit.,[19] m.p. 110–111 °C, $[\alpha]_D$ +29.4° (*c* 0.53 in water)}; ν_{max}(KBr) 3 600–3 200br cm^{-1} (NH, OH); δ_H(360 MHz, D_2O) 3.41 (1 H, dd, J_{gem} 12.8, $J_{1a,2}$ 2.1 Hz, 1_a-H), 3.50 (1 H, dd, $J_{1b,2}$ 3.8 Hz, 1_b-H), 3.73 (1 H, dd, $J_{4,3}$ 8.2, $J_{4,5}$ 3.5 Hz, 4-H), 3.79 (2 H, m, 6-H_2), 4.18 (1 H, m, 5-H), 4.41 (1 H, dt, 2-H), and 4.47 (1 H, dd, $J_{3,2}$ 4.2 Hz, 3-H); *m/z* (FAB) 164 (MH^+) (Found: C, 35.8; H, 7.4; Cl, 17.7; N, 7.1. Calc. for $C_6H_{14}ClNO_4$: C, 36.1; H, 7.0; Cl, 17.8; N, 7.0%).

4-O-*Methylsulphonyl*-2,3:5,6-*di*-O-*isopropylidene*-L-*gulononitrile* (**35**).—2,3:5,6-Di-*O*-isopropylidene-β-L-gulose (**34**), m.p. 113–115 °C, $[\alpha]_D$ +4.3° (*c* 1.4 in $CHCl_3$), was prepared (62% overall) from L-gulonolactone[27] as described above in the D-series. This material (8.0 g) was treated as described above for the enantiomer to give the L-*nitrile mesylate* (**35**) (6.23 g, 61%), m.p. 103–105 °C, with spectroscopic properties as for the enantiomer (Found: C, 46.8; H, 6.5; N, 4.1; S, 9.6. $C_{13}H_{21}NO_7S$ requires C, 46.6; H, 6.3; N, 4.2; S, 9.6%).

1,4-*Dideoxy*-2,3:5,6-*di*-O-*isopropylidene*-1,4-*imino*-L-*allitol* (**36**).—Treatment of nitrile (**35**) (5.5 g) as described above for the enantiomer gave 1,4-*dideoxy*-2,3:5,6-*di*-O-*isopropylidene*-1,4-*imino*-L-*allitol* (**36**) (2.0 g, 50%), as a syrup, $[\alpha]_D$ −33.1° (*c* 4.27 in $CHCl_3$), with spectroscopic properties as for the enantiomer (Found: C, 58.4; H, 9.0; N, 5.7. $C_{12}H_{21}NO_4$ requires C, 59.2; H, 8.7; N, 5.8%).

1,4-*Dideoxy*-1,4-*imino*-L-*allitol Hydrochloride* (**15**).—Treatment of the isopropylidene derivative (**36**) (1.83 g) as for the enantiomer gave the *hydrochloride* (**15**) (1.4 g, 93%), m.p. 110–112 °C, $[\alpha]_D$ −24.0° (*c* 2.1 in water) with spectra as for the enantiomer (Found: C, 35.8; H, 7.1; Cl, 18.0; N, 6.9. $C_6H_{14}ClNO_4$ requires C, 36.1; H, 7.0; Cl, 17.8; N, 7.0%).

2,3:5,6-*Di*-O-*isopropylidene*-4-O-*methylsulphonyl*-D-*mannononitrile* (**38**).—To a solution of 2,3:5,6-di-*O*-isopropylidene-D-mannose oxime (**37**)[28] (1.1 g) in pyridine (10 ml) at 0 °C, was added a solution of methanesulphonyl chloride (0.93 ml) in pyridine (10 ml) over 1 h. After the mixture had been heated at 60 °C for 2 h the pyridine was removed under reduced pressure. The residue was partitioned between chloroform (20 ml) and water (20 ml). The washed, dried organic layer was evaporated under reduced pressure to give an orange oil which when chromatographed on silica with ether–toluene (1:7) as eluant gave 2,3:5,6-*di*-O-*isopropylidene*-4-O-*methylsulphonyl*-D-*mannononitrile* (**38**) (630 mg, 47%), m.p. 82–83 °C, $[\alpha]_D$ +52° (*c* 1.0 in $CHCl_3$); ν_{max}(KBr) 1 370 and 1 175 cm^{-1} (OSO_2Me); δ_H(360 MHz) 1.348, 1.349, 1.406, and 1.407 (each 3 H, s, CMe_2), 3.14 (3 H, s, SO_2Me), 4.07–4.12 (2 H, m, 5-, 6_b-H), 4.24–4.26 (2 H, m, 3-, 6-H), 4.81 (1 H, dd, $J_{4,3}$ 9.4, $J_{4,5}$ 8.7 Hz, 4-H), and 4.91 (1 H, d, $J_{2,3}$ 4.7 Hz, 2-H); δ_C(50 MHz) 25.3, 25.5, 26.1, and 26.9 (CMe_2), 38.8 (S-CH_3), 66.6, 67.7 (6-C), 74.1, 77.8, 80.7, 111.5 and 112.0 (*C*Me_2), and 116.5 (CN); *m/z* (CI, NH_3), 353 (*M* + NH_4^+, 100%), 336 (*M* + H^+, 67%), 320 ($M^+ - CH_3^{\bullet}$, 46%), and 262 ($M^+ - CH_3^{\bullet}$, $-Me_2CO$, 19%) (Found: C, 46.5; H, 6.5; N, 4.2; S, 9.8. $C_{13}H_{21}NO_7S$ requires C, 46.6; H, 6.3; N, 4.2; S, 9.6%).

1,4-*Dideoxy*-2,3:5,6-*di*-O-*isopropylidene*-1,4-*imino*-D-*talitol* (**39**).—To a solution of nitrile mesylate (**38**) (1.59 g) in ether (16 ml) at 0 °C was added, over 1 h, a suspension of lithium aluminium hydride (0.45 g) in ether (16 ml). The mixture was maintained at room temperature for 18 h, after which were added sequentially at 0 °C at intervals of 10 min, water (0.45 ml), 15% aqueous sodium hydroxide (0.45 ml), and water (1.5 ml). The solution was filtered, dried, and evaporated under reduced pressure to give an oil which was chromatographed on silica with ether–methanol (98:2) as eluant to afford the pyrrolidine (**39**) (495 mg, 43%), m.p. 59–60 °C, $[\alpha]_D$ −40.4 (*c*, 1.0 in $CHCl_3$) {lit.,[21] m.p. 60 °C, $[\alpha]_D$ −44.1° (*c* 0.37 in $CHCl_3$)}; ν_{max}(KBr) 3 320 cm^{-1} (NH); δ_H(360 MHz) 1.30, 1.32, 1.40, and 1.46 (each 3 H, s, CMe_2), 2.27 (1 H, br s, NH), 3.02 (1 H, dd, J_{gem} 13.0, $J_{1\beta,2}$ 1.70 Hz, 1_β-H), 3.06 (1 H, dd, $J_{1\alpha,2}$ 4.0 Hz, 1_α-H), 3.14 (1 H, dd, $J_{4,3}$ 1.6, $J_{4,5}$ 5.7 Hz, 4-H), 3.83 (1 H, t, $J_{6a,5} \approx J_{gem}$ 7.4 Hz, 6_a-H), 4.01 (1 H, dd, $J_{6b,5}$ 6.3 Hz, 6_b-H), 4.10 (1 H, ddd, 5-H), 4.46 (1 H, dd, $J_{3,2}$ 5.8 Hz, 3-H), and 4.70 (1 H, ddd, 2-H); δ_C(50 MHz) 24.2, 25.3, 26.4, and 26.5 (*C*Me_2), 53.2 (1-C), 66.8 (4- and 6-C), 76.1 (5-C), 82.2 (2-C), 84.0 (3-C), and 109.3 and 111.5 (*C*Me_2); *m/z* 243 (M^+, 1.6%), 228 ($M^+ - CH_3$, 7.9%), and 142 (M^+ − side chain, 100%) (Found: C, 59.3; H, 9.0; N, 5.8. Calc. for $C_{12}H_{21}NO_4$; C, 59.2; H, 8.7; N, 5.8%).

1,4-*Dideoxy*-1,4-*imino*-D-*talitol Hydrochloride* (**16**).—1,4-Dideoxy-2,3:5,6-di-*O*-isopropylidene-1,4-imino-D-talitol (**39**) (279 mg) was dissolved in hydrochloric acid (1M; 12 ml) and stirred at room temperature for 18 h. Neutralization, at 0 °C, with aqueous sodium hydroxide (1M) was followed by purification using ion exchange chromatography (Dowex 50 × 2 100, H^+ form, eluting with 0.5M aqueous ammonium hydroxide). Acidification, to pH 4, of the free base in water with dilute hydrochloric acid afforded, after freeze drying, 1,4-dideoxy-1,4-imino-D-talitol hydrochloride (**16**) (133 mg, 58%), m.p. 152–154 °C, $[\alpha]_D$ −50.5° (*c* 1.01 in water) {lit.,[21] m.p. 144–145 °C, $[\alpha]_D$ −56.3° (*c* 0.41 in water)}; ν_{max}(KBr) 3 600–2 850br cm^{-1} (NH and OH); δ_H(200 MHz, D_2O) 3.32 (1 H, dd, J_{gem} 13.0, $J_{1\beta,2}$ 1.74 Hz, 1_β-H), 3.45 (1 H, dd, $J_{1\alpha,2}$ 3.7 Hz, 1_α-H), 3.54 (1 H, dd, $J_{3,4}$ 8.8, $J_{4,5}$ 4.4 Hz, 4-H), 3.62 (1 H, dd, J_{gem} 12.1, $J_{5,6a}$ 5.0 Hz, 6_a-H), 3.75 (1 H, dd, $J_{5,6b}$ 3.74 Hz, 6_b-H), 3.98 (1 H, m, 5-H), 4.24 (1 H, dd, $J_{2,3}$ 3.90 Hz, 3-H), and 4.33 (1 H, dt, 2-H); δ_C(50 MHz, D_2O with DEPT) 49.71 (1-C), 61.72 (4-C), 63.16 (6-C), 67.62 (5-C), 69.02 (3-C), and 71.87 (2-C); *m/z* (FAB); 164 (*M*H^+, 100%) [Found (*M*H), 164.0923. Calc. for $C_6H_{14}NO_4$; *m/z* 164.0922).

2,3:5,6-*Di*-O-*isopropylidene*-L-*mannono*-1,4-*lactone* (**40**).—L-Mannono-1,4-lactone (10 g), copper(II) sulphate (45 g) and concentrated sulphuric acid (1 ml) were stirred in dry acetone (500 ml) for 22 h. After neutralization with sodium carbonate, the mixture was filtered, evaporated, and partitioned between chloroform (150 ml) and water (150 ml). The washed, dried organic layer was evaporated to give a yellow solid. Crystallization from toluene–hexane (1:20) gave 2,3:5,6-*di*-O-*isopropylidene*-L-*mannono*-1,4-*lactone* (**40**) (13.64 g, 94%), m.p. 123–125 °C, $[\alpha]_D$ −48.6° (*c* 1.0 in $CHCl_3$) {lit.,[32] for D-isomer, m.p. 125 °C, $[\alpha]_D$ +50.6° (*c* 1.0 in $CHCl_3$)}; ν_{max}(KBr) 1 770 cm^{-1} (CO); δ_H(200 MHz) 1.31, 1.32, 1.35, and 1.39 (each 3 H, s, CMe_2), 3.95–4.11 (2 H, m, 6-H_2), 4.30–4.41 (2 H, m, 4-, 5-H), and 4.78–4.85 (2 H, m, 2-, 3-H); δ_C(50 MHz) 24.3, 25.7, 26.6, and 26.8 (*C*Me_2), 72.5, 75.8, 77.6, 78.1, 109.7 and 114.2 (*C*Me_2), and 173.4 (1-C); *m/z* (CI), NH_3), 276 (*M* + NH_4^+, 20%), 259 (*M* + H^+, 100%), and 243 ($M^+ - CH_3$, 64%) (Found: C, 55.8; H, 7.3. $C_{12}H_{18}O_6$ requires C, 55.8; H, 7.0%).

2,3:5,6-*Di*-O-*isopropylidene*-α-L-*mannofuranose* (**41**).—Di-isobutylaluminium hydride (1.2M in toluene; 87 ml) was added over 30 min to a solution of 2,3:5,6-di-*O*-isopropylidene-L-mannono-1,4-lactone (**40**) (9 g) in dichloromethane (250 ml) at −78 °C. After 1 h, slow, careful addition of dry methanol (36 ml) quenched any unchanged DIBAL-H. The solution was allowed to warm to room temperature and dichloromethane (500 ml) was added. The organic layer was washed with 2M aqueous potassium sodium tartrate (150 ml), water (3 × 180 ml), and brine (180 ml), and dried. Evaporation under reduced pressure and recrystallization of the residue from ether–light petroleum (1:8) gave 2,3:5,6-*di*-O-*isopropylidene*-α-L-*mannofuranose* (**41**) (7.98 g, 88%), m.p. 123–124 °C, $[\alpha]_D$ −8.25° (*c* 1.45 in $CHCl_3$) {lit.,[33] for D-isomer m.p. 122 °C, $[\alpha]_D$ +16.6° (*c*, 2.5 in EtOH)} (Found: C, 55.5; H, 8.0. $C_{12}H_{20}O_6$ requires C, 55.4; H, 7.7%).

2,3:5,6-*Di*-O-*isopropylidene*-L-*mannose Oxime* (**42**).—2,3:5,6-Di-*O*-isopropylidene-L-*mannofuranose* (**41**) (7.48 g) was treated as described for the enantiomer to give the L-oxime (**42**) (7.4 g, 94%) as a 3:7 mixture of *Z*- and *E*-isomers, m.p. 135–137 °C, $[\alpha]_D$ +161.2° (*c*, 1.1 in $CHCl_3$) {lit.,[28] for the

enantiomer, m.p. 139–141 °C, $[\alpha]_D$ −163.7° (*c* 1.14 in $CHCl_3$)} with spectroscopic properties as for the enantiomer.[28]* (Found: C, 52.8; H, 7.8; N, 5.3. $C_{12}H_{21}NO_6$ requires C, 52.4; H, 7.8; N, 5.1%).

2,3:5,6-*Di*-O-*isopropylidene*-4-O-*methylsulphonyl*-L-*mannononitrile* (**43**).—Methanesulphonyl chloride (10.3 ml) was dissolved in pyridine (50 ml) and the solution cooled to 0 °C. A solution of the oxime (**42**) (1 g) in pyridine (77 ml) was added over 1 h and the resulting mixture heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and water (1 ml) carefully added. After 15 min the reaction mixture was poured into ice–water which was extracted with ether (6 × 50 ml). The combined extracts were dried and evaporated. The residue was chromatographed on silica eluting with ether–toluene (1:7) to give 2,3:5,6-*di*-O-*isopropylidene*-4-O-*methylsulphonyl*-L-*mannonitrile* (**43**) (773 mg, 63%), m.p. 82–83 °C, $[\alpha]_D$ −55.1° (*c* 1.76 in $CHCl_3$), with spectroscopic data as for the enantiomer (Found: C, 46.8; H, 6.8; N, 4.3; S, 9.7. $C_{13}H_{21}NO_7S$ requires C, 46.6; H, 6.3; N, 4.2; S, 9.6%).

1,4-*Dideoxy*-2,3:5,6-*di*-O-*isopropylidene*-1,4-*imino*-L-*talitol* (**44**).—Treatment of the nitrile (**43**) (0.985 g) as described above for the enantiomer gave the *pyrrolidine* (**44**) (0.322 g, 45%), m.p. 57–59 °C, $[\alpha]_D$ +41.1° (*c* 1.24 in $CHCl_3$), with spectroscopic properties as for the enantiomer (Found: C, 59.5; H, 9.0; N, 5.6. $C_{12}H_{21}NO_4$ requires C, 59.2; H, 8.7; N, 5.8%).

1,4-*Dideoxy*-1,4-*imino*-L-*talitol Hydrochloride* (**17**).—A solution of 1,4-dideoxy-2,3:5,6-di-*O*-isopropylidene-1,4-imino-L-talitol (**44**) (113 mg) in 50% trifluoroacetic acid (10 ml) was stirred at room temperature for 18 h. After removal of the trifluoroacetic acid, by evaporation under reduced pressure, the mixture was processed as described for the enantiomer above to give 1,4-*dideoxy*-1,4-*imino*-L-*talitol hydrochloride* (**17**) (46 mg, 49%), m.p. 148–152 °C, $[\alpha]_D$ +46.7° (*c* 1.05 in water), with spectroscopic properties as for the enantiomer [Found: $(M\,H)^+$, 164.0923. $C_6H_{14}NO_4$ requires *m/z* 164.0922].

2,3:5,6-*Di*-O-*isopropylidene*-D-*allose Oxime* (**46**).—2,3:5,6-Di-*O*-isopropylidene-β-D-allofuranose (**45**) (6 g), hydroxylamine hydrochloride (7.7 g), and sodium hydrogen carbonate (7.7 g) were dissolved in ethanol–water (1:1; 60 ml) and the mixture was stirred at 60 °C for 2.5 h. After cooling to room temperature the reaction mixture was extracted with ethyl acetate (3 × 50 ml) and the combined extracts were dried and evaporated. Recrystallization of the residue from ether–light petroleum (2:5) gave 2,3:5,6-di-*O*-isopropylidene-D-allose oxime (**46**) (5.3 g, 84%) (*E*:*Z*-isomers, 8:2), m.p. 102.5–103.5 °C, $[\alpha]_D$ +99.0° (*c* 1.0 in CHCl); ν_{max}(KBr) 3 400 and 3 220 (OH, hydrogen bonding), 1 660 (CN), and 1 165–1 065 cm^{-1} (CO); δ_H(360 MHz) signals for *E*-isomer: 1.33, 1.37, 1.42, and 1.46 (each 3 H, s, CMe_2), 3.68 (1 H, br s, 4-OH), 7.44 (1 H, d, *J* 7.8 Hz, 1-H), 9.18 (1 H, br s, N-OH); signals for *Z*-isomer: 1.35, 1.44, 1.48, and 1.50 (each 3 H, s, CMe_2), 3.30 (1 H, br s, 4-OH), 5.37 (1 H, t, *J* 6.18 Hz, 2-H), 6.93 (1 H, d, *J* 6 Hz, 1-H), and 9.46 (1 H, br s, NOH); δ_C(50 MHz) signals for *E*-isomer: 25.4 (2 × CMe_2), 26.1 and 27.8 (CMe_2), 63.6 (6-C), 67.3, 75.6, 76.5, 77.6, 109.2 and 110.1 (CMe_2), and 148.2 (1-C); signals for *Z*-isomer: 24.9 (2 × CMe_2), 26.2 and 27.4 (CMe_2), 64.0 (6-C), 68.9, 70.9, 76.4, 78.3, 108.9 and 109.7 (CMe_2), and 150.1 (1-C); *m/z* (CI, NH_3): 276 ($M + H^+$, 67%), 274 ($M + H^+$, $-H_2$, 11%), 260 ($M^+ - CH_3^\bullet$, 100%), 258 ($M^+ - CH_3^\bullet$, $-H_2$, and $M^+ - OH^\bullet$, 97%), 243 ($M^+ - HNOH^\bullet$, 25%), 242 ($M^+ - H_2NOH$, 25%), 218 ($M + H^+$, $-Me_2CO$, 25%), and 200 ($M^+ - Me_2C(OH)O^\bullet$, 14%) (Found: C, 51.8; H, 7.9; N, 5.0. $C_{12}H_{21}NO_6$ requires C, 52.4; H, 7.8; N, 5.1%).

2,3:5,6-*Di*-O-*isopropylidene*-4-O-*methylsulphonyl*-D-*allononitrile* (**47**).—To a solution of 2,3:5,6-di-*O*-isopropylidene-D-allose oxime (**46**) (2.2 g) in pyridine (20 ml) at 0 °C was slowly added a solution of methanesulphonyl chloride (6.4 ml) in pyridine (20 ml). The reaction mixture was stirred at room temperature for 18 h, after which it was cooled to 0 °C and water (40 ml) carefully added. The mixture was extracted with ether (4 × 40 ml). The combined extracts were washed with brine (3 × 20 ml), treated with decolourizing charcoal, dried, and evaporated to give a residue which was chromatographed on silica eluting with ether–toluene (1:7) to give 2,3:5,6-*di*-O-*isopropylidene*-4-O-*methylsulphonyl*-D-*allononitrile* (**47**) (1.78 g, 66%), oil, $[\alpha]_D$ −37.6° (*c* 1.0 in $CHCl_3$); ν_{max}(film) 1 370 and 1 170 (OSO_2Me) and 1 075 cm^{-1} (CO); δ_H(200 MHz) 1.34, 1.36, 1.41, and 1.56 (each 3 H, s, CMe_2), 3.13 (3 H, s, SO_2Me), 4.02 (1 H, dd, $J_{5.6a}$ 6.49, J_{gem} 8.73 Hz, 6_a-H), 4.13 (1 H, dd, $J_{5.6b}$ 6.59 Hz, 6_b-H), 4.36 (1 H, t, $J_{2.3} = J_{3.4}$ 5.17 Hz, 3-H), 4.47 (1 H, dt, $J_{4.5}$ 4.66 Hz, 5-H), 4.95 (1 H, d, 2-H), and 5.07 (1 H, t, 4-H); δ_C(50 MHz) 24.9, 25.7, 26.2, and 26.6 (CMe_2), 38.6 (SCH_3), 65.3 (6-C), 65.7, 74.2, 76.5, 76.8, 110.2 and 112.6 (CMe_2), and 116.4 (CN); *m/z* (CI, NH_3): 353 ($M + NH_4^+$, 41%), 336 ($M + H^+$, 36%), 320 ($M^+ - CH_3^\bullet$, 10%), and 276 [$M^+ - CH_3)_2COH^\bullet$, 100%] [Found: $(M^+ - CH_3)$, 320.078 ± 0.003. $C_{12}H_{18}NO_7S$ requires *m/z* 320.0803].

1,4-*Dideoxy*-2,3:5,6-*di*-O-*isopropylidene*-1,4-*imino*-D-*gulitol* (**48**).—To a solution of the nitrile mesylate (**47**) (788 mg) in ether (8 ml) at 0 °C was added, over 1 h, a suspension of lithium aluminium hydride (0.22 g) in ether (8 ml). The mixture was maintained at room temperature for 18 h, after which were added sequentially at 0 °C at intervals of 10 min, water (0.22 ml), 15% aqueous sodium hydroxide (0.22 ml) and water (0.66 ml). The solution was filtered, dried, and evaporated under reduced pressure to give an oil which was chromatographed on silica, eluting with ether–methanol (98:2) to give the *pyrrolidine* (**48**) (180 mg, 31%), m.p. 56–57 °C, $[\alpha]_D$ +56° (*c* 1.0 in $CHCl_3$); ν_{max}(KBr) 3 290 cm^{-1} (NH); δ_H(360 MHz) 1.25, 1.34, 1.40, and 1.41 (each 3 H, s, CMe_2), 2.11 (1 H, br s, NH), 2.63 (1 H, dd, J_{gem} 13, $J_{1\beta.2}$ 3.90 Hz, 1_β-H), 2.66 (1 H, dd, $J_{3.4}$ 4.30, $J_{4.5}$ 7.70 Hz, 4-H), 3.12 (1 H, d, 1_α-H), 3.72 (1 H, m, 5-H), 4.17 (2 H, m, 6-H_2), 4.46 (1 H, dd, $J_{2.3}$ 5.66 Hz, 3-H), and 4.65 (1 H, dd, 2-H); δ_C(50 MHz) 23.9, 25.4, 25.6, and 26.7 (CMe_2), 52.6 (1-C), 66.3 (4-C), 67.2 (6-C), 75.8 (5-C), 81.0 (2-C), 81.6 (3-C), and 109.2 and 111.0 (CMe_2); *m/z* 243 (M^+, 4%), 228 ($M^+ - CH_3^\bullet$, 9%), and 142 (M^+ − side chain, 100%) (Found: C, 57.1; H, 8.6; N, 5.5. $C_{12}H_{21}NO_4$ requires C, 59.2; H, 8.7; N, 5.8%).

1,4-*Dideoxy*-1,4-*imino*-D-*gulitol Hydrochloride* (**18**).—A solution of the acetonide (**48**) (281 mg) in hydrochloric acid (2M; 6 ml) was stirred at room temperature for 18 h. Neutralization of the solution at 0 °C with aqueous sodium hydroxide (1M) was followed by purification using ion exchange chromatography (Dowex 50 × 2-100, H^+ form, eluting with 0.5M aqueous ammonium hydroxide). Acidification of the free base in water to pH 4 with dilute hydrochloric acid afforded, after freeze drying, 1,4-*dideoxy*-1,4-*imino*-D-*gulitol hydrochloride* (**18**) (177 mg, 77%), m.p. 180–182 °C, $[\alpha]_D$ −4.9° (*c* 1.0 in water) {lit.,[14] for L-isomer, m.p. 170–173 °C, $[\alpha]_D$ +7.1° (*c* 0.48 in water)}; ν_{max}(KBr) 3 500–2 900 cm^{-1} (br, NH and OH); δ_H(360 MHz, D_2O) 3.22 (1 H, dd, $J_{1a.2}$ 8.36, J_{gem} 11.97 Hz, 1_a-H), 3.60 (1 H, dd, $J_{1b.2}$ 8.06 Hz, 1_b-H), 3.68 (1 H, dd, $J_{5.6a}$ 5.13, J_{gem} 12.21 Hz, 6_a-H), 3.69 (1 H, m, 4-H), 3.81 (1 H, dd, $J_{5.6b}$ 3.24 Hz, 6_b-H), 4.18 (1 H, ddd, $J_{4.5}$ 8.64 Hz, 5-H), 4.34 (1 H, t, $J_{2.3} = J_{3.4}$ 3.74 Hz, 3-H), and 4.55 (1 H, dt, 2-H); δ_C(50 MHz, D_2O with DEPT) 46.3 (1-C), 62.7 (4-C), 62.7 (6-C), 67.8 (5-C), 69.5 (3-C), and

* The ^1H chemical shift of 2-H (*Z*-isomer) should read δ 5.26.

70.1 (2-C); *m/z* (FAB) 164 (*M*H, 100%) (Found: C, 35.7; H, 7.3; Cl, 17.7 N, 7.0. $C_6H_{13}NO_4$·HCl requires C, 36.1; H, 7.0; Cl, 17.8; N, 7.0%).

Acknowledgements

We thank the SERC for financial support and for access to high-field NMR facilities at the University of Edinburgh, directed by Dr. I. H. Sadler.

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Paper 9/03454D
Received 11*th August* 1989
Accepted 28*th September* 1989