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Ethambutol–sugar hybrids as potential inhibitors of mycobacterial cell-wall biosynthesis☆

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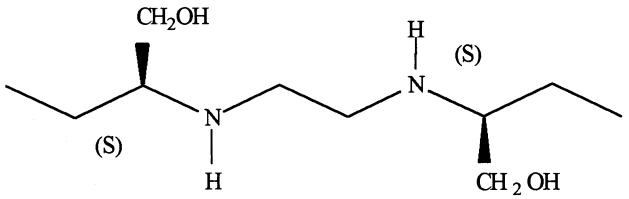
Abstract

Ethambutol is an established front-line agent for the treatment of tuberculosis, and is also active against *Mycobacterium avium* infection. However, this agent exhibits toxicity, and is considered to have low potency. The action of ethambutol on the mycobacterial cell wall, particularly the arabinan, and comparison of the structure of ethambutol with several of the cell-wall saccharides, suggested that ethambutol–saccharide hybrids might lead to agents with a more selective mechanism of action. To this end, eight ethambutol–saccharide hybrids were synthesized and screened against *M. tuberculosis* and several clinical isolates of *M. avium*.

Keywords: Glycosyltransferases; Tuberculosis; Ethambutol

1. Introduction

The emergence of multiple-drug-resistant strains of tuberculosis [1], and the debilitating infections caused by several mycobacteria in immunocompromised individuals [2], have fueled a resurgence of interest in developing novel drugs to combat these organisms [3–5]. One of the primary agents used for the treatment of tuberculosis, and one of the few drugs employed against *Mycobacterium avium* infection, is (*S*,*S*)-(+)-2,2′-(ethylenediimino)di-1-butanol, or ethambutol (**1**) [6].



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First reported over 30 years ago [7], extensive structure–activity studies by Wilkinson and coworkers established the parameters necessary for effective antimycobacterial activity [8]. Among these prerequisites are two basic nitrogen atoms optimally separated by a two-carbon bridge, hydroxyl groups on each distal nitrogen substituent, and, where substitution of these terminal substituents introduces chirality, the *S* stereochemistry at the carbon center. These requirements are consistent with a mechanism of action involving metal chelation, and indeed antituberculosis activity parallels the stability of certain metal–

☆ A preliminary account of this work has appeared: J.A. Maddry, W.J. Suling, R.C. Reynolds, Glycosyl transferases as targets for inhibition of cell-wall synthesis in *M. tuberculosis* and *M. avium*, *Res. Microbiol.*, 147 (1996) 106–112.

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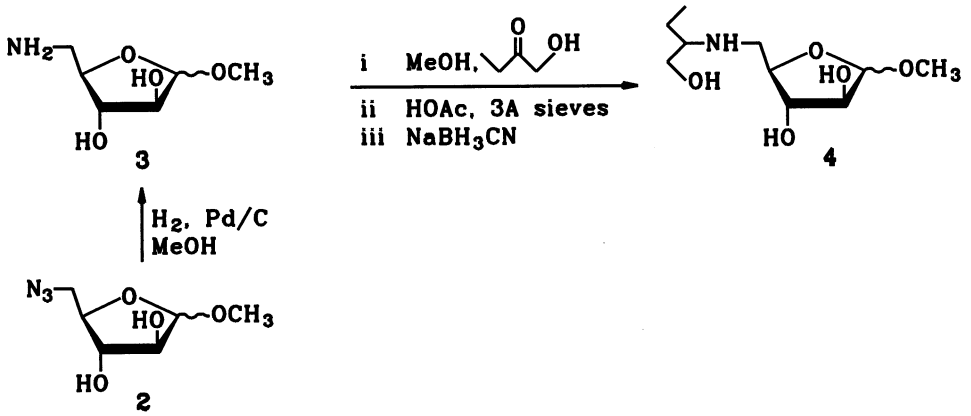


Scheme 1.

ethambutol derivative chelates [8]. Beyond the metal chelation hypothesis, however, the precise mechanism of action of **1** and its congeners remains unknown, although the strict stereochemical preference argues for a macromolecular site of action. Not until the pioneer-ing work of Takayama et al. was the cell wall recognized as the probable target of these compounds [9]. Subsequent investigations have shown that prevention of mycolylation discovered by Takayama resulted from inhibition of an earlier stage of wall biogenesis, in particular arabinan metabolism [10].

Interest in the design of inhibitors of cell-wall biosynthesis continues not only because of the unusual nature of this essential mycobacterial structure, which affords many opportunities for selective drug development, but also because some wall inhibitors potentiate the activity of otherwise inactive agents [11]. The possibility that **1** exerts its antimycobacterial effect by binding at the substrate site of a metal-utilizing, sugar-processing enzyme, such as an arabinosyl transferase, prompted us to examine several conformationally constrained arabinofuranose congeners that incorporate **1** as a substructure. As to be expected for a long-chain acyclic molecule, molecular modeling studies[2] show that ethambutol is very flexible, with many energetically readily accessible conformations likely to be populated. The modeling studies demonstrated that several of these minima superpose quite well upon the reference structure, α-D-arabinofuranosyl phosphate, supporting the plausibility of an arabinan site of action. Based on this association, we synthesized several arabinose and imino-arabinose analogues to test this conjecture. We also prepared several trehalose analogues bearing a related chelating side chain because of the reported link between **1** and glucose and mycolate biosynthesis [10], and since the mycolyl transferase might also contain an essential cation in the active site.

2. Results and discussion

Chemistry

An ethambutol D-*arabinose hybrid.* The 5-substituted ethambutol–arabinose hybrid **4** was prepared as a diastereomeric mixture by reductive amination of methyl 5-amino-5-deoxy-α-β-D-arabinofuranoside (**3**) with 1-hydroxy-2-butanone in the presence of $NaBH_3CN$ (Scheme 1). The amino saccharide was prepared by the catalytic reduction of the known 5-azido derivative **2** [12] of D-arabinose, using palladium on activated carbon.

Ethambutol pyrrolidine hybrids. The *N*-alkylated pyrrolidine **5** was prepared and deprotected to form **6** using the method of Baxter and Reitz (Scheme 2) [13], and was then reprotected by a benzyloxycarbonyl (Cbz) group to yield **7**.

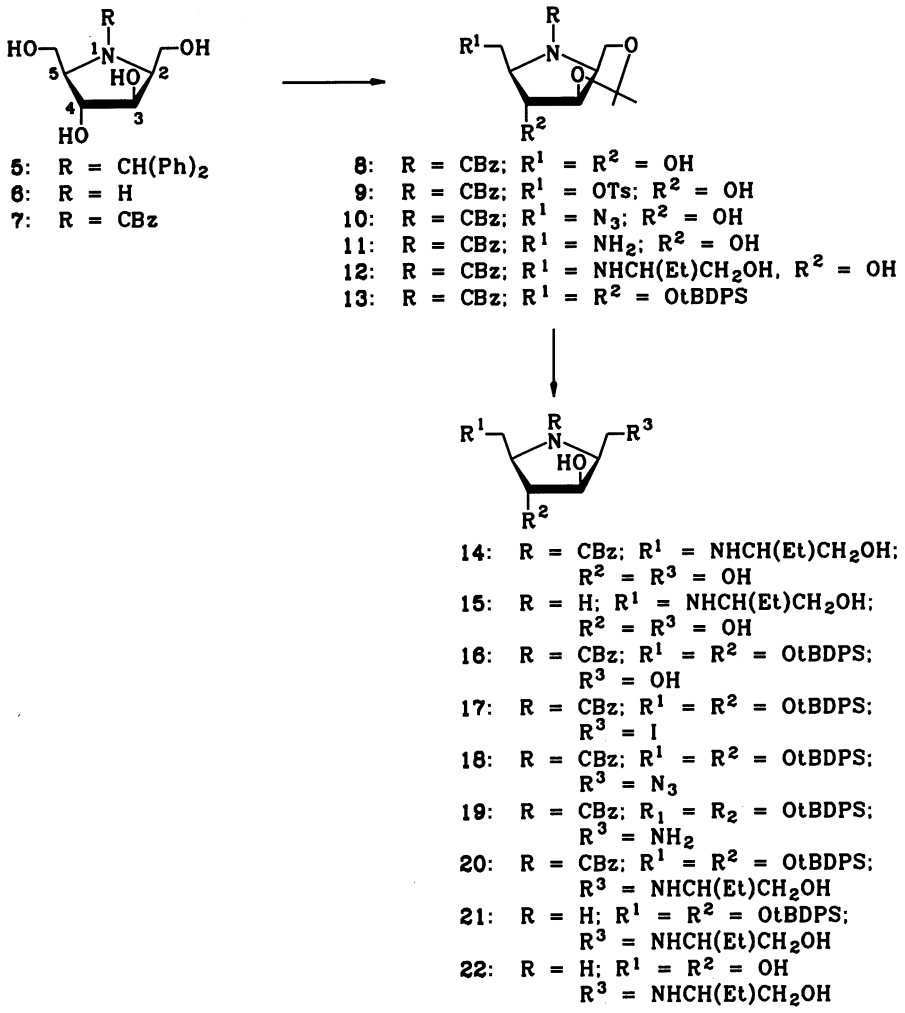
[2] Complete conformational searches for both **1** and α-D-arabinofuranosyl phosphate were performed using the torsional grid algorithm and the MACROMODEL V. 4.5 software suite (W.C. Still, et al. Columbia University, NY); for **1**, energy minimization to convergence was conducted with the MM2 molecular mechanics force field, while the AMBER force field provided in MACROMODEL was used for the arabinose derivative.

Subsequent treatment with acetone in the presence of 2,2-dimethoxypropane and an acid catalyst afforded the isopropylidene derivative **8**, the common intermediate for both **15** and **22**.

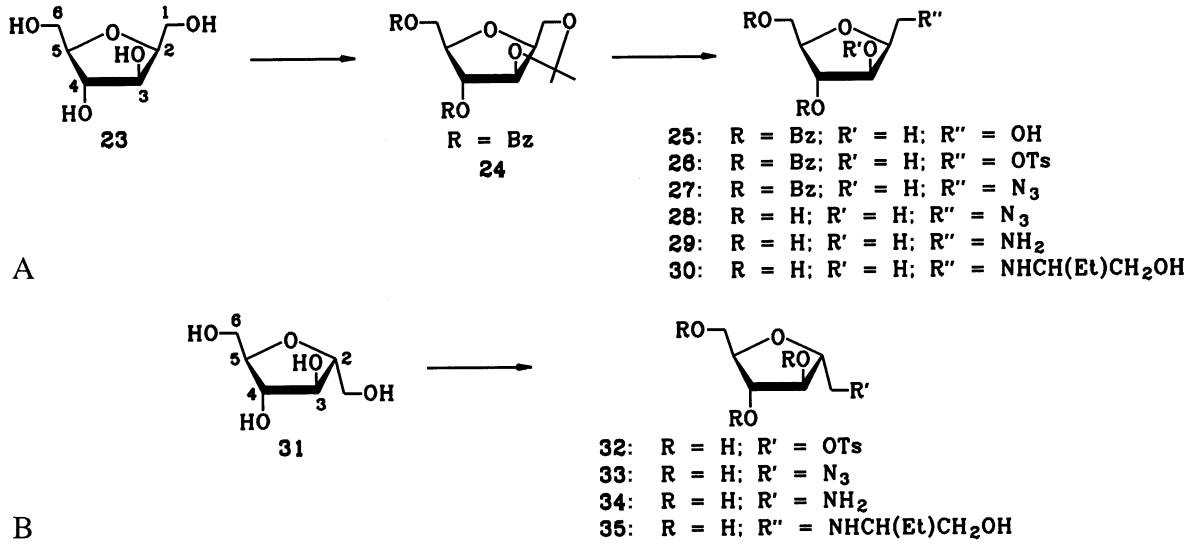
2,5-Anhydro-6-[[1-(hydroxymethyl)propyl]-amino]-2,5-imino-D-glucitol (**15**) was prepared by selective tosylation of **8** to form **9**, followed by displacement of the tosyl group with azide ion yielding **10**, catalytic hydrogenation over Raney nickel gave the amine **11**, reductive amination of **11** by the action of $NaBH_3CN$ and 2-hydroxybutanone to prepare **12**, and formation of **14** and **15** by the removal of the isopropylidene and Cbz protecting groups, respectively. The product (**15**) obtained was tested as a diastereomeric mixture.

The related derivative 2,5-anhydro-1-{[1-(hydroxymethyl)propyl]amino}-2,5-imino-D-glucitol (**22**) was prepared by first protecting the intermediate **8** as the 4,6-di-*t*-butyldiphenylsilyl derivative **13**. The isopropylidene protecting group was hydrolyzed in hot 80% acetic acid to form **16**, followed by iodination at the 5-position using I_2–Ph_3P–imidazole [14] to give **17**. Reaction with NaN_3 in anhydrous DMF gave **18**, followed by catalytic reduction over Raney nickel yielding **19**. Reductive amination with 1-hydroxy-2-butanone and deprotection gave the target **22** as a diastereomeric mixture.

*Ethambutol–anhydro-*D*-alditol hybrids*. 2,5-Anhydro-D-glucitol (**23**) was prepared by acid-catalyzed dehydration of D-mannitol using the method of Koerner et al. [15], but was isolated as the crystalline 4,6-di-*O*-benzoyl-1,3-*O*-isopropylidene derivative **24** (Scheme 3A). Mild acid treatment and monotosylation



Scheme 2.



Scheme 3.

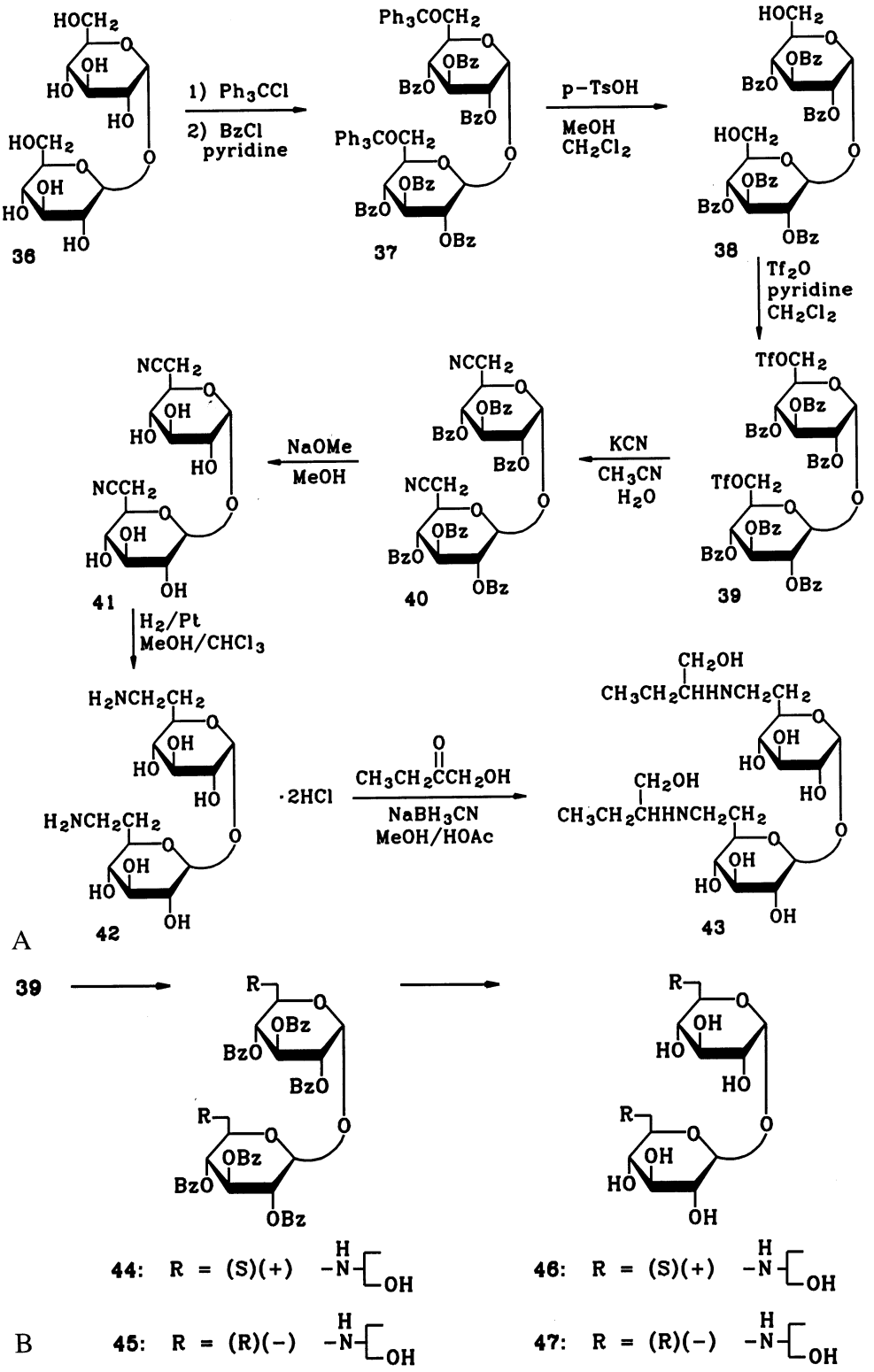
led to 2,5-anhydro-4,6-*O*-dibenzoyl-1-*O*-*p*-tolylsulfonyl-D-glucitol (**26**). Treatment with NaN_3 and debenzoylation followed by reduction with Raney nickel gave the desired 1-amino compound **29** as an oil. Treatment of the amine with 1-hydroxy-2-butanone in the presence of $NaBH_3CN$–HOAc afforded the desired ethambutol–arabinose hybrid **30**. This product appeared to be formed in a 1:1 ratio by TLC analysis, and each diastereomer could be isolated for screening.

2,5-Anhydro-D-mannitol (**31**) was prepared by ring contraction of D-glucosamine hydrochloride via diazotization, followed by reduction of the resulting aldehyde with sodium borohydride according to the procedure of Horton and Philips (Scheme 3B) [16]. The crude product was isolated as the tetraacetate, which was then deprotected and monotosylated at C-1 (a significant amount of the ditosyl compound is also formed) and treated with azide. The tetraacetate is easily chromatographed or distilled via Kugelrohr. This removes the need for large quantities of mixed-bed resin in the reported procedure. Reduction of the azide derivative followed by reductive amination of the amine product using $NaBH_3CN$–HOAc and 1-hydroxy-2-butanone led to the desired ethambutol–arabinose hybrid **35**.

Trehalose–ethambutol hybrids. As a result of the minimal nucleophilicity of 6,6′-diaminotrehalose (unpublished observations), it was necessary to use a different strategy to prepare the trehalose–ethambutol hybrids. Preparation of the 6,6′-dityrityl derivative followed by perbenzoylation and detritylation isolated the 6,6′-positions for reaction with triflic anhydride by the method of Baer et al. for preparation of the analogous hexa-*O*-acetyl compound (Scheme 4A) [17]. Treatment of the 6,6′-ditriflate **39** with either (*R*)(−)- or (*S*)(+)-2-amino-1-butanol in CH_2Cl_2 at room temperature (rt), afforded the diastereomers of **44** and **45**, that were deprotected with MeOH–NaOMe to yield the target trehalose–ethambutol hybrids **46** and **47** (Scheme 4B).

The 6,6′-ditriflate was also reacted with potassium cyanide, and reduced to give the homologated 6,6′-diaminomethyl trehalose analog **42** (Scheme 4A). Reductive amination with 1-hydroxy-2-butanone in the presence of $NaBH_3CN$–HOAc gave the trehalose–ethambutol hybrid **43**, a mixture of four diastereomers.

Antimycobacterial activity.—Compounds **4**, **15**, **22**, **30a** and **30b**, **35**, **43**, **46**, and **47** were evaluated for antimycobacterial activity against *M. tuberculosis* strain H37Ra and a panel of three to five clinical isolates of *M. avium* using a colorimetric microdilution broth assay to determine the minimum inhibitory concentration (MIC) [4]. All of the compounds had MICs of >128 μg/mL while the MICs of ethambutol for the same strains ranged from 8 to 32 μg/mL.



Scheme 4.

Experimental

General methods.—Melting points were determined by the capillary method on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Molecular Spectroscopy Section of the Southern Research Institute or by Atlantic Micro-

lab, Inc., Atlanta, GA. Where solvents like EtOH or water are included in the reported analysis, their presence was supported by the ^{1}H NMR spectrum. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Nicolet NT300NB spectrometer operating at 300.635 and 75.603 MHz, respectively. Chemical shifts are reported in parts per million (ppm) downfield from Me_4Si (^{1}H NMR) and acetone (^{13}C NMR), and chemical shifts for multiplets are measured from the approximate center of the multiplet. Coupling constants (*J* values) are reported in Hz. In all cases where ^{13}C NMR was recorded, final target compounds appeared to be formed in an equal ratio of diastereomers within the error of the peak height measurements. Optical rotations were measured on a Perkin–Elmer polarimeter, model 241 for solutions in water. Mass spectra were recorded on a Varian/MAT 311A double-focusing mass spectrometer in the fast atom bombardment (FAB) mode. Addition of a trace of LiCl to some samples gave an $[M + Li]^+$ cluster peak that was stronger than the $[M + H]^+$ peak. IR spectra were recorded on a Nicolet FT IR spectrometer, model 10DX, using KBr discs. Thin-layer chromatography was performed on Analtech precoated (250 μm) silica gel (GF) plates. Column chromatography in either the flash column or gravity mode was performed with 230–400 mesh Silica Gel 60 from E. Merck.

*Methyl 5-amino-5-deoxy-α,β-*D*-arabinofuranoside* (**3**).—Compound **3** was prepared according to the method for compound **11**. The crude material was chromatographed on silica gel successively with 9:1, 4:1, and 2.3:1 $CHCl_3$–MeOH, to afford a yellow solid in 32% yield. This material was rechromatographed using 3.77:1 $CHCl_3$–MeOH with 1.5% Et_3N to obtain an analytical sample. MS: *m*/*z* 164 $[M + H]^+$; ^{1}H NMR (Me_2SO-d_6): δ 2.60 (m, 1 H, H-5), 2.76 (m, 1 H, H-5′), 3.22 (s, 3 H, OCH_3), 3.62 (m, 1 H, H-3), 3.70 (m, 1 H, H-4), 3.75 (m, 1 H, H-2), 4.60 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1). Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.27; H, 8.05; N, 8.45.

*Methyl 5-deoxy-5-{[1-(hydroxymethyl)propyl]amino}-α,β-*D*-arabinofuranoside* (**4**).—Compound **4** was prepared according to the procedure given for compound **12**, and the crude material was chromatographed with 9:1 $CHCl_3$–MeOH containing 1% NH_4OH. A clear, colorless oil was obtained in 41% yield. This oil was further purified over a Bio-Bead column, dissolved in water, frozen over a dry ice–acetone bath, and lyophilized to obtain an analytical sample; MS: *m*/*z* 236 $[M + H]^+$; ^{1}H NMR ($CDCl_3$): 0.93, 0.95 (2 t, 3 H, $-CH_2CH_3$), 1.38–1.55 (m, 2 H, $-CH_2CH_3$), 2.58 (m, –NHC*H*–), 2.74, 2.82 (2 dd, 1 H, 5–CH_2), 3.08, 3.14 (2 dd, 1 H, 5-CH_2), 3.48 (m, 1 H, $-CH_2OH$), 3.62–3.76 (m, 1 H, $-CH_2OH$), 3.86, 3.89 (2 bs, 1 H, H-3), 3.96 (s, 1 H, H-2), 4.24 (m, 1 H, H-4), 4.90, 4.91 (2 bs, 1 H, H-1). Anal. Calcd for $C_{10}H_{21}NO_5$: C, 51.05; H, 9.00; N, 5.95. Found: C, 51.18; H, 9.05; N, 5.94.

*2,5-Anhydro-*N*-benzyloxycarbonyl-2,5-imino-*D*-glucitol* (**7**).—To **6** (2.3 g, 14.72 mmol) and $NaHCO_3$ (1.6 g, 19.14 mmol) taken in 1,4-dioxane–water (200 mL, 95:5 v/v), was added benzyl chloroformate (2.7 mL, 19.14 mmol) in 1,4-dioxane over a period of 25 min. The mixture was stirred for 18 h at 25 °C. The reaction mixture was then evaporated, diluted with water and extracted with EtOAc (4 × 200 mL). The combined organic layers were dried (Na_2SO_4), evaporated, and dried in vacuo over P_2O_5 to give 3.74 g of product **7** as a clear oil (89% yield); MS: *m*/*z* 298 $[M + 1]^+$; ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 3.40–3.76 (m, 5 H, 5-CH_2OH, 2-CH_2OH, H-5), 3.82 (m, 1 H, H-2), 4.0 (m, 2 H, H-3, H-4), 4.4, 4.93 (bs, 2 H, 2 and 5 CH_2OH), 5.08 (s, 2 H, CH_2Ph), 5.13, 5.24 (d, 2 H, 3-OH, 4-OH, $J_{H\text{-}3,HO\text{-}3}$ 4.4 Hz), 7.36 (m, 5 H, ArH).

*2,5-Anhydro-*N*-benzyloxycarbonyl-2,5-imino-1,3-*O*-isopropylidene-*D*-glucitol* (**8**).—To 200 mL of acetone (dried over $MgSO_4$) was added 2,2-dimethoxypropane (10.5 mL, 85.4 mmol). The solution was stirred for 2 min and 70% $HClO_4$ (9.1 mL) was added, and the resulting solution was stirred for 5 min. The clear solution was then added to **7** (6.37 g, 21.4 mmol). The solution was stirred for 30 min, after which $NaHCO_3$ was added slowly. Stirring was continued for an additional 20 min and the mixture was evaporated to remove the solvent. Water was added to the

residue, and the mixture was extracted with $CHCl_3$ (3×100 mL). The combined extracts were dried (Na_2SO_4), evaporated, and dried to give the product **8** as a clear oil (6.1 g). The aq layer was extracted with EtOAc to recover unreacted starting material. The yield was 96%, based on recovered starting material; MS: 338 $[M+H]^+$; ^1H NMR (300 MHz, Me_2SO-d_6): δ 1.24 (s, 3 H, Me), 1.34 (bs (s at 80 °C); 3 H, Me), 3.58 (m, 2 H, 5-CH_2OH), 3.6–3.9 (m, 3 H, H-2, H-5, and 1 H of 2-CH_2O), 4.03 (bs, 2 H, 1 H of 2-CH_2OH, H-4), 4.16 (bs, 1 H, H-3), 4.82 (t, 1 H, 5-CH_2 OH), 5.10 (bs, 2 H, CH_2Ph), 5.30 (d, 1 H, 4-OH), 7.36 (m, 5 H, ArH). Anal. Calcd for $C_{17}H_{23}NO_6 \cdot 0.05\ C_2H_5OH$: C, 60.10; H, 7.07, N, 4.06. Found: C, 60.47; H, 6.91; N, 4.12.

2,5-Anhydro-N-*benzyloxycarbonyl*-*2,5-imino*-*1,3*-O-*isopropylidene*-*6*-O-p-*tolylsulfonyl*-D-*glucitol* (**9**).—To a cold solution (−5 °C) of **8** (6.1 g, 18.1 mmol) in dry pyridine (50 mL) was added portionwise *p*-toluenesulfonyl chloride (3.5 g, 18.4 mmol). The solution was maintained for 18 h at −5 °C, after which it was filtered and washed with additional pyridine. The combined filtrate and wash was poured into an ice-cold solution of $NaHCO_3$ (18.4 mmol, 1.5 g). The aq layer was extracted with $CHCl_3$ (3×150 mL). The combined $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated, and immediately chromatographed on a silica gel column (98:2 $CHCl_3$–MeOH) to give 5.1 g (57% yield) of pure **9**. MS: m/z 492 $[M+H]^+$; ^1H NMR (300 MHz, Me_2SO-d_6): δ 1.04 (bs, 3 H, Me), 1.35 (bs, 3 H, Me), 2.40 (s, 3 H, $-SO_2C_6H_4CH_3$), 3.72 (bd, 1 H, 1 H of 2-CH_2O), 3.78–4.18 (m, 7 H, 1 H of 2-CH_2O, H-2, H-3, H-4, 5-CH_2O H-5), 5.05 (bs, 2 H, CH_2Ph), 5.57 (d, 1 H, 4-OH), 7.34 (m, 7 H, ArH, 2 H of $SO_2C_6H_4CH_3$), 7.70 (d, 2 H of $SO_2C_6H_4CH_3$).

2,5-Anhydro-*6-azido*-N-*benzyloxycarbonyl*-*6-deoxy*-*1,3*-O-*isopropylidene*-*2,5-imino*-D-*glucitol* (**10**).—To **9** (5.1 g, 10.37 mmol) in dry DMF (100 mL) was added NaN_3 (2.7 g, 41.5 mmol), and the mixture was heated for 24 h at 100 °C. TLC showed the reaction was complete (sprayed with NBP* to see the disappearance of the starting material). The solution was evaporated under diminished pressure and the residue was extracted with 2:1 acetone–ether. The extract was concentrated and purified by silica gel column chromatography (99:1 $CHCl_3$–MeOH) to give pure **10** (2.86 g, 76% yield); MS: m/z 363 $[M+H]^+$.

6-Amino-*2,5-anhydro*-*2,5-imino*-N-*benzyloxycarbonyl*-*1,3*-O-*isopropylidene*-D-*glucitol* (**11**).—To **10** (2.86 g, 7.89 mmol) dissolved in EtOH (100 mL) was added Raney nickel (8.6 g, wet wt). The mixture was hydrogenated at atmospheric pressure for 4 h at 25 °C. The resulting mixture was filtered though Celite and the catalyst washed with EtOH. The combined filtrate and wash were evaporated to dryness and chromatographed on silica gel (5:1 $CHCl_3$–CH_3OH + 1% NH_4OH) to give pure **11** as a white foam. MS: m/z 337 $[M+H]^+$; ^1H NMR (300 MHz, Me_2SO-d_6): δ 1.24 (s, 3 H, CH_3), 1.35 (bs, 3 H, CH_3), 1.56 (bs, 2 H, NH_2), 2.80 (bd, 2 H, 5-CH_2NH_2), 3.59 (t, 1 H, H-5), 3.70–4.08 (m, 4 H, H-2, 2-CH_2O, H-4), 4.13 (bs, 1 H, H-3), 5.08 (bs, 2 H, CH_2Ph), 5.24 (bs, 1 H, 4-OH), 7.36 (m, 5 H, ArH). Anal. Calcd for: $C_{17}H_{24}NO_5 \cdot 0.3\ H_2O$: C, 59.49; H, 7.25; N, 7.90. Found: C, 59.74, H, 7.25; N, 8.20.

2,5-Anhydro-N-*benzyloxycarbonyl*-*6-deoxy*-*6*-*{[1*-*(hydroxymethyl)propyl]amino}*-*2,5-imino*-*1,3*-O-*isopropylidene*-D-*glucitol* (**12**).—To a solution of **11** (500 mg, 1.49 mmol) in dry MeOH was added 1-hydroxy-2-butanone (0.13 mL, 1.5 mmol), followed by the addition of HOAc (0.09 mL, 1.5 mmol) and $NaCNBH_3$ (95 mg, 1.5 mmol). The solution was stirred for 24 h at 25 °C. The pH of the solution was adjusted to 2 with 2 M HCl; the resulting solution was stirred for 5 min, and the pH was then adjusted to ~8 with M NaOH. The solvent was evaporated, water was added, and the aq layer was extracted with $CHCl_3$ (5×100 mL). The combined $CHCl_3$ layers were dried ($MgSO_4$), evaporated, and dried in vacuo to give **12** (600 mg, 98% yield); MS: m/z 409 $[M+H]^+$.

2,5-Anhydro-N-*benzyloxycarbonyl*-*4,6-di*-O-tert-*butyldiphenylsilyl*-*2,5*-*imino*-*1,3*-O-*isopropylidene*-D-*glucitol* (**13**).—To **8** (11.5 g, 34.2 mmol) in dry DMF (150 mL) was added *t*-butylchlorodiphenylsilane (19.6 mL, 75.2 mmol), followed by the addition of imidazole

(10.2 g, 150.4 mmol). The solution was stirred for 24 h at rt, after which, the solvent was removed in vacuo at ~40 °C. The residue was partitioned between EtOAc and satd NaCl solution. The organic layer was removed and the aq layer was extracted (3 ×) with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on a silica gel column (95:5 cyclohexane–EtOAc) to give **13** (15.6 g, 56% yield); MS: m/z 814 $[M+H]^+$; ^1H NMR (300 MHz, Me_2SO-d_6): δ 0.82 (s, 9 H, ^{t}Bu), 0.88 (s, 3 H, Me), 1.02 (s, 9 H, ^{t}Bu), 1.20 (s, 3 H, Me), 3.73 (m, 2 H, 15-CH_2O), 3.86 (bs, 1 H, H-2), 3.91 (bs, 1 H, 2-CH_2O), 4.04 (m, 1 H, 2-CH_2O), 4.16 (m, 2 H, H-3, H-5), 4.45 (bs, 1 H, H-4), 4.96–5.18 (m, 2 H, –CH_2Ph), 7.22–7.60 (m, 25 H, ArH).

2,5-Anhydro-N-*benzyloxycarbonyl-6-deoxy-6-{[1-(hydroxymethyl)propyl]amino}-2,5-imino*-D-*glucitol* (**14**).—Compound **12** (600 mg, 1.47 mmol) was heated in 80% AcOH (100 mL) for 20 h at 64 °C. The solvent was evaporated, toluene added, and evaporated again to remove residual acetic acid. The residue was chromatographed on silica gel (9:1 $CHCl_3$–MeOH + 1% NH_4OH) to give pure **14** (336 mg, 62% yield); MS: m/z 369 $[M+H]^+$.

2,5-Anhydro-6-deoxy-6-{[1-(hydroxymethyl)-propyl]amino}-2,5-imino-D-*glucitol* (**15**).—A solution of **14** (0.34 g, 0.91 mmol) in 20 mL EtOH was catalytically reduced with 5% Pd on carbon (84 mg) at atmospheric pressure and rt for 24 h. The mixture was filtered though Celite and the filtrate evaporated to dryness. The free base was converted into the hydrochloride salt with EtOH–HCl to yield 90 mg of the product **15** (32% yield); $[\alpha]_D^{20}$ + 8.88° (*c* 1); MS: m/z 235 $[M+H]^+$; ^1H NMR (300 MHz, Me_2SO-d_6): δ 0.94 (s, 3 H, Me), 1.7 (m, 24, CH_2CH$_3$), 3.1 (s, 1 H, –CH–), 3.4–3.84 (m, 9 H, 2-CH_2OH, H-2, H-5, 5-CH_2NH, CH_2OH), 4.04 (s, 2 H, H-3, H-4). The OH signals were broad between 5 and 6; ^{13}C NMR (300 MHz, D_2O): δ 78.29 (C-4), 74.12 (C-3), 64.23 (C-2), 62.37, 62.26, 62.04, 61.93 (C-5, –NHCH(CH_2OH)CH_2CH$_3$), 58.32 (–NH-CH–(CH_2OH)CH_2CH$_3$), 57.35 (C-1), 45.15 (C-6), 20.71, 20.52 (–NHCH(CH_2OH)-CH_2CH$_3$), 9.27 (CH_3). Anal. Calcd for: $C_{10}H_{22}N_2O_4 \cdot 2HCl \cdot 0.1H_2O$). C, 38.87; H, 7.89; N, 9.07. Found: C, 38.67; H, 8.21; N, 8.84.

2,5-Anhydro-N-*benzyloxycarbonyl-4,6-di*-O-tert-*butyldiphenylsilyl-2,5-imino*-D-*glucitol* (**16**).—Compound **13** (13 g, 16 mmol) was heated in 1:20 MeOH–80% aq AcOH (400 mL) at 50 °C (under reflux conditions) for 24 h. The reaction mixture was processed as previously described (compound **14**). Column chromatography (3:1 cyclohexane–EtOAc) afforded 16 (8 g) (yield 82% based on recovered starting material); ^1H NMR (300 MHz, Me_2SO-d_6): δ 0.82 (s, 9 H, ^{t}Bu), 1.0 (s, 9 H, ^{t}Bu), 3.52 (m, 2 H, 1 H of 5-CH_2O, 1 H of 2-CH_2OH), 3.76 (m, 2 H, 1 H of 5-CH_2O, 1 H of 2-CH_2OH), 3.96 (m, 1 H, H-2), 4.10 (m, 1 H, H-5), 4.18 (t, 1 H, H-3), 4.28 (bs, 2 H, H-4, 2-CH_2OH), 4.92, 5.10 (d, 2 H –CH_2Ph), 5.36 (bs, 1 H, 3-OH), 7.2–7.62 (m, 25 H, ArH). Anal. Calcd for $C_{40}H_{55}NO_6Si \cdot 0.2H_2O$: C, 71.04; H, 7.18; N, 1.80. Found: C, 70.80; H, 7.37; N, 1.61.

2,5-Anhydro-N-*benzyloxycarbonyl-1-deoxy-4,6-di*-O-tert-*butyldiphenylsilyl-1-iodo-2,5-imino*-D-*glucitol* (**17**).—To a solution of **16** (5.0 g, 6.5 mmol) in toluene (100 mL) were added Ph_3P (6.9 g, 26.32 mmol), imidazole (1.8 g 26.32 mmol), and iodine (5.1 g, 19.74 mmol). The mixture was heated for 2.5 h at 108 °C. To the cooled reaction mixture was added an equal volume of a satd $NaHCO_3$ solution. The mixture was stirred for 5 min, followed by the portionwise addition of iodine. When the color of iodine persisted in the toluene layer, the mixture was stirred for an additional 10 min. Excess iodine was removed by the addition of aq $Na_2S_2O_3$. The organic layer was diluted with toluene, extracted with water, dried ($MgSO_4$) and concentrated. The residue was purified by passing though a silica gel pad (300 g of silica gel) with 95:5 cyclohexane–EtOAc to give pure **17** (4.1 g, 80% yield); MS: m/z 774 $[M+H]^+$; ^1H NMR (300 MHz, Me_2SO-d_6): δ 0.80 (s, 9 H, ^{t}Bu), 9.98 (s, 9 H, ^{t}Bu), 3.08 (m, 1 H, 1 H of 2-CH_2I), 3.58 (m, 2 H, 1 H of 2-CH_2I, 1 H of 5-CH_2O–), 3.74 (m, 1 H, 1 H of 5-CH_2O), 4.18 (m, 3 H, H-2, H-3, H-5), 4.48 (s, 1 H, H-4), 4.92, 5.12 (d, 2 H, CH_2Ph), 5.83 (d, 1 H, 3-OH), 7.16–7.60 (m, 25 H, ArH). Anal.

Calcd for $C_{46}H_{54}INO_5Si_2 \cdot 0.1\ H_2O$: C, 62.37; H, 6.17; N, 1.58. Found: C, 61.97; H, 6.33; N, 1.51.

2,5-Anhydro-1-azido-N-*benzyloxycarbonyl-1-deoxy-4,6-di*-O-tert-*butyl-diphenylsilyl-2,5-imino*-D-*glucitol* (**18**).—To **17** (2.1 g, 2.4 mmol) in dry DMF (20 mL) was added NaN_3 (630 mg, 9.7 mmol). The reaction mixture was heated for 24 h at 100 °C. The reaction was worked up as described for **10**. After column chromatography (95:5 cyclohexane–EtOAc), 1.5 g of pure **18** was obtained (79% yield); ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 0.82 (s, 94, ^{t}Bu), 1.0 (s, 9 H, ^{t}Bu), 3.4–3.8 (m, 4 H, 2-CH_2N_3 and 5-CH_2O), 4.06 (bs, 2 H, H-2, H-5), 4.18 (bs, 1 H, H-3), 4.5 (s, 1 H, H-4), 4.92, 5.10 (d, 2 H, CH_2Ph), 5.82 (bs, 1 H, 3-OH), 7.12–7.64 (m, 25 H, ArH). Anal. Calcd for $C_{46}H_{54}N_4O_5Si_2$: C, 69.14; H, 6.81; N, 7.01. Found: C, 69.18; H, 7.01; N, 6.66.

1-Amino-2,5-anhydro-N-*benzyloxycarbonyl-1-deoxy-4,6-di*-O-tert-*butyldiphenylsilyl-2,5-imino*-D-*glucitol* (**19**).—Compound **19** was made in a similar way to compound **11** except that 2 equiv of Raney nickel (wet wt) was used, and the reaction was stopped after 1 h (if let run for a longer time, the Cb group comes off). After the conventional work up and column chromatography (9:1 cyclohexane–EtOAc) 2.2 g of **19** was obtained (82% yield based on recovered starting material); ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 0.82 (s, 9 H, ^{t}Bu), 1.0 (s, 9 H, ^{t}Bu), 2.80, 2.96 (m, 2 H, 2-CH_2–), 3.60, 3.74 (m, 2 H, 5-CH_2O), 3.92 (m, 1 H, H-2), 4.10 (m, 1 H, H-5), 4.20 (d, 1 H, H-3), 4.46 (s, 1 H, H-4), 4.90, 5.11 (d, 2 H, CH_2Ph), 7.18–7.64 (m, 25 H, ArH). Anal. Calcd for $C_{46}H_{56}N_2O_5Si_2 \cdot 0.4H_2O$: C, 70.80; H, 7.34; N. 3.59. Found: C, 70.53; H, 7.49; N, 3.66.

2,5-Anhydro-N-*benzyloxycarbonyl-4,6-di*-O-tert-*butyldiphenylsilyl-1-deoxy-1-{[1-hydroxymethyl)propyl]amino}-2,5-imino*-D-*glucitol* (**20**).—The procedure for making **20** was similar to that for **12** except that a 20% excess of the reagents was added. The reaction was monitored by MS since the starting material and product have the same R_f value. Product **20** was obtained in 80% yield; MS: m/z 895 $[M + H]^+$.

2,5-Anhydro-4,6-di-O-tert-*butyldiphenylsilyl-1-deoxy-1-{[1-(hydroxymethyl)propyl]amino}-2,5-imino*-D-*glucitol* (**21**).—To a solution of **20** (0.45 g, 0.54 mmol) in EtOH (20 mL) was added 5% Pd on carbon (0.11 g). The mixture was stirred under atmospheric hydrogen for 18 h at rt. The mixture was then filtered though Celite and washed with more EtOH. The combined filtrate was evaporated and dried in vacuo over P_2O_5 to give 0.37 g of **21** (95% yield); MS: m/z 711 $[M + H]^+$; ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 0.88 (m, 3 H, Me), 0.9, 1.02 (s, 18 H, ^{t}Bu), 1.45 (q, 2 H, –CH_2–), 2.65 (bs, 1 H, –CH–), 2.80 and 2.96 (m, 2 H, 2-CH_2), 3.02–3.42 (bm, 6 H, CH_2OH, 5-CH_2O, H-5), 3.49 (m, 1 H, H-2), 3.99 (m, 2 H, H-3, H-4), 7.26–7.62 (m, 20 H, ArH). Anal. Calcd for $C_{42}H_{58}N_2O_4Si_2 \cdot 0.9\ H_2O$: C, 69.36; H, 8.29; N, 3.85. Found: C, 68.99; H, 8.12; N, 3.63.

2,5-Anhydro-1-deoxy-1-{[1-(hydroxymethyl)-propyl]amino}-2,5-imino-D-*glucitol* (**22**).—To a solution of **21** (0.37 g, 0.52 mmol) in acetonitrile (5 mL) was added Et_4NF (0.22 g, 1.5 mmol) and the solution was stirred for 24 h at rt and then evaporated to dryness. To the residue, THF was added and the mixture kept in a freezer for 2 h. The THF layer was removed and evaporated to dryness. The residue was converted to the hydrochloride salt with EtOH–HCl and recrystallized from MeOH–$CHCl_3$ to give pure **22** (33% yield); $[\alpha]_D^{20} + 27.4°$ (c 0.76); MS: m/z 235 $[M + H]^+$; ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 0.92 (t, 3 H, Me), 1.6 (m, 2 H, –CH_2CH$_3$), 2.96 (s, 1 H –CH–), 3.1–3.86 (m, 9 H, 2-CH_2–NH, H-2, H-5, 5-CH_2OH, –CH_2OH), 4.02 (s, 2 H, H-3, H-4). The OH signals were broad between 5 and 6; ^{13}C NMR (300 MHz, D_2O): δ 76.49 (C-4), 75.68 (C-3), 67.17 (C-5), 62.16 (C-2), 60.28 (C-6), 58.54, 58.46 (–NHCH(CH_2-OH)CH_2CH_3), 57.52, 57.48 (–NHCH(CH_2-OH)CH_2CH_3), 42.12, 41.95 (C-1), 20.58, 20.52 (–NHCH(CH_2OH)CH_2CH_3), 9.29 (CH_3). Anal. Calcd for $C_{10}H_{22}N_2O_4 \cdot 2$ HCl·0.2 C_2H_5OH. C, 39.48; H, 8.03; N, 8.85. Found: C, 39.15; H, 8.31; N, 8.56.

All of the compounds in Scheme 3 were made from starting materials **22** and **30** by the same standard procedures as reported in this paper. The analytical data on the intermediate compounds are as follows.

2,5-Anhydro-4,5-di-O-benzoyl-1,3-O-isopropylidene-D-glucitol (**24**).—The 1,3-*O*-isopropylidene derivative, prepared by a slight modification of the known method [15], was isolated as the crystalline 4,6-dibenzoyl compound. Impure 2,5-anhydro-D-glucitol [15] (22.4 g, 0.14 mol) was dissolved in 500 mL dry acetone, and dimethoxypropane (50 mL) and conc H_2SO_4 (5 mL) were added with warming to dissolve the oil. The reaction was stirred overnight at rt, and TLC (9:1 $CHCl_3$–MeOH) showed complete conversion into a less polar material. Next, the reaction was neutralized by adding 50 mL of satd $NaHCO_3$, and the volatile solvents were removed by rotary evaporation. Solid was filtered from the remaining solution, which was then extracted with EtOAc (3 × 500 mL). Removal of the solvent yielded 13.6 g of a colorless oil (48%) that was carried on to the next step. The crude oil from the previous reaction was dissolved in dry pyridine (500 mL) and cooled on an MeOH–ice bath to −10 °C. To this solution was added BzCl (50 mL) dropwise with stirring. The mixture was stirred overnight and the reaction was stopped by pouring into ice-water, stirring for 3 h to decompose excess BzCl, and extracting with EtOAc (3 × 500 mL). The organic layer was evaporated to remove excess pyridine. The crude oil was dissolved in EtOAc (500 mL), extracted with ice-cold 10% HCl (3 × 100 mL) to remove excess pyridine, followed by $NaHCO_3$ (100 mL), and deionized water (100 mL). The separated organic layer was dried (Na_2SO_4), and evaporated to yield a clear, colorless oil that was further purified by column chromatography on silica gel using $CHCl_3$ as the elution solvent. Evaporation of the appropriate fractions gave 25.8 g of a clear, colorless oil (92.4%). A sample crystallized readily from MeOH for spectral analysis; MS: m/z 413 $[M+H]^+$; ^{1}H NMR (Me_2SO-d_6): δ 1.30 (s, 3 H, Me), 1.44 (s, 3 H, Me), 3.90 (m, 1 H, 1-CH_2OH), 4.0 (bs, 1 H, H-2), 4.1 (m, 1 H, 1-CH_2OH), 4.38 (m, 1 H, 5-H), 4.55 (m, 3 H, H-3, 6-CH_2O–), 5.22 (d, 1 H, H-4), 7.45–8.0 (m, 10 H, ArH).

2,5-Anhydro-4,5-di-O-benzoyl-D-glucitol (**25**).—Compound **25** was prepared by the same procedure used for compound **14**. Crude material was chromatographed on silica gel with 99:1 $CHCl_3$–MeOH to afford the pure product in 93% yield; MS: m/z 372 $[M+H]^+$; ^{1}H NMR (Me_2SO-d_6): δ 3.60 (m, 1 H, 1-CH_2OH), 3.90 (m, 1 H, 1-CH_2OH), 4.05 (m, 1 H, H-2), 4.28 (m, 2 H, H-3, 5-H), 4.48 (m, 2 H, 6-CH_2O–), 4.68 (t, 1 H, 1-CH_2OH), 5.22 (d, 1 H, H-4), 5.55 (d, 1 H, 3-OH), 7.45, 8.0 (m, 10 H, ArH).

2,5-Anhydro-4,5-di-O-benzoyl-1-O-p-tolylsulfonyl-D-glucitol (**26**).—Compound **26** was prepared by the same procedure used for compound **9**. Compound **25** (0.835 g, 2.24 mmol) was dissolved in dry pyridine (25 mL) and cooled to −15 °C in an ice–MeOH bath. *p*-Toluenesulfonylchloride (0.45 g, 1.05 equiv) was added, and the solution was placed in a freezer for 2 days, and then poured into ice-water (250 mL), extracted with EtOAc (3 × 50 mL), 10% HCl (3 × 100 mL), and water (2 × 100 mL) and dried (Na_2SO_4). After evaporation, the crude material was chromatographed on silica gel with hexanes to hexanes–EtOAc (1:1), yielding 1.017 g (86%) as crystals from MeOH; MS: m/z 527 $[M+H]^+$; ^{1}H NMR (Me_2SO-d_6): δ 2.38 (s, 3 H, Ar–CH_3), 4.08 (m, 1 H, 1-CH_2OH), 4.20 (m, 4 H, 1-CH_2–, H-2,3,5), 4.40 (m, 2 H, 6 CH_2), 5.22 (m, 1 H, H-4), 5.88 (d, 1 H, 3-OH), 7.42–8.0 (m, 34 H, ArH).

2,5-Anhydro-1-azido-4,5-di-O-benzoyl-1-deoxy-D-glucitol (**27**).—Compound **27** was prepared by the same procedure as compound **10**. After column chromatography of the crude material in 3:1 cyclohexane–EtOAc, **27** was obtained in 72% yield; MS: m/z 398 $[M+H]^+$; ^{1}H NMR (Me_2SO-d_6): δ 3.52 (m, 2 H, 1-CH_2OH), 4.25 (m, 1 H, H-2), 4.34 (m, 2 H, H-3, 5-H), 4.52 (m, 2 H, 6-CH_2O–), 5.24 (m, 1 H, H-4), 5.88 (d, 1 H, 3-OH), 7.2–8.02 (m, 30 H, ArH).

2,5-Anhydro-1-azido-1-deoxy-D-glucitol (**28**).—Compound **28** was prepared by the same procedure used for compound **46**. Column chromatography on crude material in 9:1 $CHCl_2$–MeOH gave **28** in 89% yield; MS m/z 190 $[M+H]^+$; ^{1}H NMR (Me_2SO-d_6): δ 3.35 (m, 2 H, 1-CH_2–), 3.45 (m, 2 H, 6-CH_2OH), 3.64 (m, 1 H, H-2), 3.82 (m, 2 H, H-3, H-4), 3.88 (m, 1 H, 5-H), 4.90 (t, 1 H, 6-OH), 5.14 (d, 1 H, 3-OH), 5.20 (d, 1 H, 4-OH). Anal. Calcd for $C_6H_{11}N_3O_4$: C, 38.10;

H, 5.86; N, 22.21. Found: C, 38.34; H, 5.92; N, 22.10.

1-Amino-2,5-anhydro-1-deoxy-D-*glucitol* (**29**).—Compound **29** was prepared by the same procedure used for compound **11**. After evaporation of the filtrate, the residue was triturated with ether, dissolved in water, frozen, and lyophilized, to obtain the product in 70% yield; MS: m/z 164 $[M+H]^+$; ^1H NMR (Me_2SO-d_6): δ 2.70 (dd, 1 H, 1-CH_2–), 2.80 (dd, 1 H, 1-CH_2–), 3.45 (m, 2 H, 6-CH_2OH), 3.60 (m, 1 H, 5-H), 3.82 (m, 1 H, H-4), 3.84 (m, 1 H, H-2), 3.88 (m, 1 H, H-3), –OH and NH_2 were broad. Anal. Calcd for $C_6H_{13}NO_4 \cdot 0.6\ H_2O$: C, 41.42; H, 8.23; N, 8.05. Found: C, 41.07; H, 8.39; N, 7.71.

2,5-Anhydro-1-deoxy-1-{[1-(hydroxymethyl)-propyl]amino}-D-*glucitol hydrate* (**30**).—Compound **30** was prepared by the same procedure used for compound **12**. Chromatography of the mixture (3:1 $CHCl_9$–MeOH + 2% NH_4OH) showed two closely running products in ~1:1 ratio, assumed to be the diastereomers formed in the reductive amination. Column chromatography of the mixture with the same solvent system gave two products **30a** (35 mg) and **30b** (28 mg) in overall 44% yield. The isolated ratio is an artifact of the column because the first spot trailed into the second making isolation of the second material more difficult.

Compound **30a**: $[\alpha]_D^{20} + 9.11°$ (c 0.96); MS: m/z 236 $[M+H]^+$; ^1H NMR (Me_2SO-d_6): δ 0.82 (t, 3 H, –CH_2CH_3), 1.36 (m, 2 H, –CH_2CH$_3$), 2.42 (m, 1 H, –NHCH), 2.74, 2.90 (m, 2 H, –CH_2NH), 3.25 (m, 2 H, –CH_2OH), 3.46 (m, 2 H, 5-CH_2OH), 3.58 (m, 1 H, H-5), 3.74 (t, 1 H, H-4), 3.84 (m, 1 H, H-3), 3.90 (m, 1 H, H-2), 5.10 (d, 1 H, 3-OH); ^{13}C NMR (300 MHz, D_2O): δ 85.10 (C-5), 78.94, 78.54, 78.03 (C-2, C-3, C-4), 62.09, 62.01 (C-6, –NHCH(CH_2OH)CH_2CH_3), 60.18 (–NHCH-(CH_2OH)CH_2CH_3), 45.15 (C-1), 22.72 (–NH-CH(CH_2OH)CH_2CH_3), 9.63 (CH_3). Anal. Calcd for $C_{10}H_{21}NO_5 \cdot 0.8\ H_2O$: C, 48.10; H, 9.12; N, 5.61. Found: C, 47.84; H, 9.38; N, 5.65.

Compound **30b**: $[\alpha]_D^{20} + 23.6°$ (c 0.70); MS: m/z 236 $[M+H]^+$; ^1H NMR (Me_2SO-d_6): δ 0.83 (t, 3 H, –CH_2CH_3), 1.36 (m, 2 H, –CH_2CH$_3$), 2.48 (m, 1 H, –NHCH), 2.72, 2.85 (m, 2 H, –CH_2NH), 3.34 (m, 2 H, –CH_2OH), 3.48 (m, 2 H, 5-CH_2OH), 3.58 (m, 1 H, H-5), 3.78 (t, 1 H, H-4), 3.84 (m, 1 H, H-3), 3.90 (m, 1 H, H-2), 5.10 (d, 1 H, 3-OH); ^{13}C NMR (300 MHz, D_2O): δ 85.00 (C-5), 79.13, 78.50, 77.91 (C-2, C-3, C-4), 62.10 (C-6, –NHCH-(CH$_2$OH)CH$_2$CH$_3$), 60.28 (–NHCH(CH$_2$-OH)CH$_2$CH$_3$), 45.40 (C-1), 22.69 (–NHCH-(CH$_2$OH)CH$_2$CH$_3$), 9.55 (CH$_3$). Anal. Calcd for $C_{10}H_{21}NO_5 \cdot 1.4\ H_2O$: C, 46.10; H, 9.21; N, 5.38. Found: C, 45.95; H, 9.21; N, 5.61.

2,5-Anhydro-1-O-p-*tolyl-sulfonyl*-D-*mannitol* (**32**).—Compound **32** was prepared by the same procedure used for compound **9**. MS: m/z 319 $[M+H]^+$; ^1H NMR (Me_2SO-d_6): δ 2.22 (m, 3 H, tosyl-CH_3), 3.38, 3.34 (m, 2 H, 6-CH_2OH), 3.55 (m, 1 H, 5-H), 3.70 (t, 1 H, H-3), 3.78 (m, 2 H, H-2, H-4), 4.04 (m, 2 H, 1-CH_2O–), 4.74 (t, 1 H, 6-CH$_2$OH), 5.20 (d, 1 H, 4-OH), 5.31 (d, 1 H, 3-OH), 7.50, 7.78 (d, 4 H, ArH). Anal. Calcd for $C_{13}H_{17}O_7 \cdot 0.5H_2O$: C, 47.84; H, 5.56. Found: C, 48.21; H, 5.94.

2,5-Anhydro-1-azido-1-deoxy-D-*mannitol* (**33**).—Compound **33** was prepared by the same procedure as compound **10**. MS: m/z 190 $[M+H]^+$; ^1H NMR (Me_2SO-d_6): δ 3.32 (m, 1 H, 1-CH_2–), 3.42 (m, 2 H, 1-CH_2–, 6-CH_2OH), 3.50 (m, 1 H, 6-CH_2OH), 3.65 (m, 1 H, 5-H), 3.78 (m, 3 H, H-2, H-3, H-4), 4.72 (t, 1 H, 6-CH$_2$OH), 5.20 (d, 1 H, 4-OH), 5.28 (d, 1 H, 3-OH). Anal. Calcd for $C_6H_{11}N_3O_4 \cdot 0.1H_2O$: C, 37.74; H, 5.91; N, 22.00. Found: C, 37.47; H, 6.03; N, 22.17.

1-Amino-2,5-anhydro-1-deoxy-D-*mannitol* (**34**).—Compound **34** was prepared by the same procedure used for compound **11**; MS: m/z 164 $[M+H]^+$; ^1H NMR (Me_2SO-d_6): δ 2.60 (dd, 1 H, 1-CH_2–), 2.70 (dd, 1 H, 1-CH_2–), 3.45 (m, 2 H, 6-CH_2OH), 3.62 (m, 2 H, H-2, 5-H), 3.74 (m, 2 H, H-3, H-4); OH and NH_2 signals were broad. Anal. Calcd for $C_6H_{13}NO_4 \cdot 0.1H_2O$: C, 40.73; H, 8.35; N, 7.79. Found: C, 41.05; H, 8.07; N, 7.53.

2,5-Anhydro-1-deoxy-1-{[1-(hydroxymethyl)-propyl]amino}-D-*mannitol hydrate* (**35**).—Compound **35** was prepared by the same procedure as compound **12**. Column chromatography using 3:1 $CHCl_3$–MeOH + 5% NH_4OH gave pure product in 50% yield; $[\alpha]_D^{20} + 46.6°$ (c 1.98); MS: m/z 236 $[M+H]^+$;

^{1}H NMR (Me_2SO-d_6): δ 0.84 (t, 3 H, –CH_2CH_3), 1.40 (m, 2 H, –CH_2CH_3), 2.58 (m, 1 H, –NHCH–), 2.80 (m, 2 H, –CH_2NH–), 3.30 (m, 2 H, –CH_2OH), 3.42 (m, 2 H, 5-CH_2OH), 3.70 (m, 2 H, H-4, H-5), 3.78 (m, 2 H, H-2, H-3); ^{13}C NMR (300 MHz, D_2O): δ 83.40, 83.36, 83.30, 81.79, 81.64 (C-2, C-3), 79.39, 77.21 (C-4, C-5), 62.25, 62.18, 61.65 (C-6, –NHCH(CH_2OH)CH_2CH_3), 60.27, 60.08 (–NHCH(CH_2OH)CH_2CH_3), 48.17, 47.97 (C-1), 22.84, 22.73 (–NHCH–(CH_2OH)CH_2CH_3), 9.61 (CH_3). Anal. Calcd for $C_{10}H_{21}NO_5 \cdot 0.8\ H_2O$: C, 48.10; H, 9.12; N, 5.61. Found: C, 47.81; H, 9.02; N, 5.92.

2,3,4,2′,3′,4′-Hexa-O-*benzoyl-6,6′-di*-O-*triphenylmethyl-α,α-trehalose* (**37**).—A solution of α,α-trehalose dihydrate (26.95 g, 71.23 mmol) in pyridine (1500 mL) was distilled slowly until the vapor temperature rose to 115 °C and the poorly soluble anhydrous trehalose began to separate. The slurry was cooled to 10 °C, and chlorotriphenylmethane (41.33 g, 148 mmol) was added. The stirred mixture was allowed to warm slowly to rt. After 4 days, the bright yellow solution was again chilled to near 0 °C; BzCl (90.1 g, 641 mmol) was added rapidly dropwise, and the solution was stirred for 2 days at rt and then poured with vigorous stirring into ice-water (8 L). A solution of the solid precipitate in CH_2Cl_2 (1 L) was washed by shaking with water, satd $NaHCO_3$, and water (500 mL of each). Evaporation of the dried (Na_2SO_4) organic layer gave a brittle foam that was recrystallized from EtOH (6 L) to give an off-white waxy solid that was dried in vacuo over P_2O_5 at rt; yield 66.2 g (64%). Concentration of the filtrate gave additional product suitable for use as an intermediate; yield 28.32 g (27%). Both crops contained a mixture of **2** with a small amount of 2,3,4,6,2′,3′,4′-hepta-*O*-benzoyl-6-*O*-trityl-α,α-trehalose (estimated $< 20\%$ by TLC). To obtain a sample of **2** for analysis, a small portion of the main crop was recrystallized twice from EtOH and dried in vacuo over P_2O_5 for 4 h at 65 °C; mp 136–137 °C with prior sintering; MS: m/z 1351 $(M+H)^+$, 1191 $[M-Ph_3CO]^+$, 717 $(1/2[M-16])^+$, 243 $[Ph_3C]^+$, 105 $[Bz]^+$; with LiCl, 1457 $[M+Li]^+$; ^{1}H NMR (Me_2SO-d_6): δ 2.58 (dd, 2 H, $J_{5,6}$ 2.0, $J_{6,6}$ 11.0 Hz, H-6), 2.86 (d, 2 H, J 11.0 Hz H-6′), 4.14 [app. d (poorly resolved; may be dt), 2 H, $J_{4,5}$ 9.8 Hz, H-4], 5.68 (m, 4 H, H-2 overlapped by H-4), 5.82 (d, 2 H, $J_{1,2}$ 3.9 Hz, H-1), 6.07 (dd, 2 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.9 Hz, H-3), 7.16–7.84 (4 m, 60 H, Bz and trityl C*H*). Anal. Calcd for $C_{92}H_{74}O_{17}$: C, 76.12; H, 5.14. Found: C, 76.40; H, 5.16.

2,3,4,2′,3′,4′-Hexa-O-*benzoyl-α,α-trehalose* (**38**).—The mixture of **37** and the monotrityl-hepta-*O*-benzoyltrehalose (93.7 g, 64.5 mmol as **37**) just referred to, was dissolved in a mixture of MeOH (2 L) and CH_2Cl_2 (1 L), and solid *p*-toluenesulfonic acid was added in portions with stirring until a few drops shaken with a few drops of water gave a reading of $\sim$pH 4 on Hydrion paper. The solution was heated to reflux and then cooled slowly and stirred for 3 days at rt. Triethylamine (5 mL) was added; solvents were evaporated, and a solution of the residue in $CHCl_3$ (500 mL) was washed by shaking with water (500 mL) to which was added 10 mL of 1 M HCl, satd $NaHCO_3$ solution (500 mL), and water (500 mL). The dried (Na_2SO_4) organic layer was evaporated to give 112.6 g of a pale amber gum. Column chromatography on silica gel with elution by $CHCl_3$–MeOH (99:1) gave Ph_3COCH_3 (33.9 g) and Ph_3COH (1.0 g). Further elution with 98:2 gave, in order, the hepta-*O*-benzoyltrehalose (11.0 g, $\sim$16%), the desired hexa-*O*-benzoyltrehalose 3 (7.31 g, $\sim$12%) slightly contaminated with trailings from the heptabenzoyl band, and homogeneous **3** (40.31 g, 64%) as a white solid. After drying in vacuo over P_2O_5 at rt the solid had mp $\sim$120 °C with prior sintering; MS: m/z 967 $[M+H]^+$, 845 $[M-Obz]^+$, 475 $(1/2[M-16])^+$, with LiCl, 973 $[M+Li]^+$; ^{1}H NMR ($CDCl_3$): δ 2.45 (dd, 2 H, 6-O*H*), 2.92, 3.14 (2m, 4 H, H-6,6), 3.90 [d (poorly resolved; may be dt), 2 H, J 10.0 Hz, H-5], 5.40 (dd, 2 H, $J_{1,2}$ 3.9, $J_{2,3}$ 10.1 Hz, H-2), 5.48 (dd, 2 H, $J_{3,4} = J_{4,5} = 9.9$ Hz, H-4), 5.71 (d, 2 H, $J_{1,2}$ 3.9 Hz, H-1), 6.31 (dd, 2 H, H-3), 7.32–8.05 (4m, 30, Bz). Anal. Calcd for $C_{54}H_{46}O_{17} \cdot 0.5\ H_2O$: C, 66.46; H, 4.85. Found: C, 66.55; H, 4.84.

2,3,4,2′,3′,4′-Hexa-O-benzoyl-6,6′-di-O-trifluoromethylsulfonyl-α,α-trehalose (**39**).—Under a nitrogen atmosphere, a solution of trifluoromethanesulfonic anhydride (17.35 g, 61.48 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to a solution of dry pyridine (9.73 g, 123 mmol) in CH_2Cl_2 (100 mL) that had been precooled to −10 °C. The white slurry was stirred for 15 min at −10 °C after addition was complete, and a solution of **38** (15.00 g, 15.37 mmol) in CH_2Cl_2 (100 mL) was added rapidly dropwise, while the temperature was kept below 0 °C. The pale yellow solution was stirred in the cooling bath for 30 min and then transferred to a separating funnel and washed with ice-cold dilute HCl (250 mL, 0.5 M), cold satd $NaHCO_3$ (2 × 250 mL), and cold water (2 × 250 mL). The dried (Na_2SO_4) organic layer was evaporated to give a porous brittle foam that was used without further treatment; yield 18.68 g (99%); MS (with LiCl): *m/z* 1237 $[M+Li]^+$, 1160 $[M-CHF_3]^+$, 1109 $[M-OBz]^+$, 607 $(1/2[M-16])^+$; ^1H NMR ($CDCl_3$): δ 3.76 (dd, 2 H, $J_{5,6}$ 2.0 Hz, H-6), 3.95 (dd, 2 H, $J_{5,6}$ 4.0, $J_{6,6}$ 11.0 Hz, H-6′), 4.25 (double m, 2 H, H-5), 5.43 (dd, 2 H, $J_{1,2}$ 3.9, $J_{2,3}$ 10.0 Hz, H-2), 5.56 (dd, 2 H, $J_{3,4} = J_{4,5} = 10$ Hz, H-4), 5.71 (d, 2 H, $J_{1,2}$ 3.9 Hz, H-1), 6.26 (dd, 2 H, H-3), 7.35–8.08 (4 m, 30 H, Bz).

2,3,4,2′,3′,4′-Hexa-O-benzoyl-6,6′-dicyano-6,6′-dideoxy-α,α-trehalose (**40**).—Solid KCN (1.06 g, 16.24 mmol) was added to a solution of the ditriflate **39** (5.00 g, 4.06 mmol) in a mixture of MeCN (90 mL) and water (10 mL), and the resulting yellow solution was stirred for 24 h at rt. Solvents were evaporated, and the residue was stirred with CH_2Cl_2 (200 mL). The mixture was filtered, and the filtrate was washed by shaking gently (to prevent emulsion formation) with water (100 mL). The dried (Na_2SO_4) organic layer was evaporated to give a gummy yellow residue; yield 3.50 g (87%). Column chromatography on silica gel with 2:1 cyclohexane–EtOAc as eluent gave the desired product as a viscous gum. Evaporation with CH_2Cl_2 (2 × 50 mL) and drying under high vacuum gave a tractable brittle white foam that was dried further in vacuo over P_2O_5 for 20 h at 65 °C; yield 2.66 g (66%); mp (softens gradually) ~116–120 °C; MS: *m/z* 985 $[M+H]^+$, 863 $[M-OBz]^+$, 484 $(1/2[M-16])^+$, with LiCl, 991 $[M+Li]^+$; IR: ν_{max} 2258 cm^{-1} (CN, weak), 1734 (Bz C=O); ^1H NMR ($CDCl_3$): δ 2.00, 2.06 (dd, 2 H, H-6), 2.09, 2.15 (dd, 2, H-6′), 4.18 (dt, 2, $J_{5,6} = J_{5,6'} = 5.1$, $J_{4,5}$ 10.0 Hz, H-5), 5.47 (m, 4 H, H-4 and H-2), 5.73 (d, 2 H, $J_{1,2}$ 3.9 Hz, H-1), 6.24 (dd, 2 H, $J_{2,3} = J_{3,4} = 10.0$ Hz, H-3) 7.34–8.10 (m, 30, Bz). Anal. Calcd for $C_{56}H_{44}N_2O_{15}$: C, 68.29; H, 4.50; N, 2.84. Found: C, 68.27; H, 4.44; N, 2.84.

6,6′-Dicyano-6,6′-dideoxy-α,α-trehalose (**41**).—A solution of $NaOCH_3$ in MeOH (3 mL of 1.2 *N*) was added to a suspension of **40** (2.58 g, 2.62 mmol) in dry MeOH (75 mL). The mixture was stirred for 1 h at rt; then the solution was diluted with an equal volume of water and adjusted to pH 3.5 by portionwise addition of Dowex 50W-X8 (H^+) cation-exchange resin. After filtration and evaporation of the filtrate, the residue was evaporated with EtOH (3 ×) to aid removal of water. The residue was triturated with Et_2O and washed liberally on a filter funnel with Et_2O to remove MeOBz. A solution of the solid in abs EtOH (50 mL) was diluted slowly dropwise with Et_2O (400 mL) and the off-white solid was collected by filtration and dried briefly in vacuo; yield 683 mg. Evaporation of the filtrate and reprecipitation with EtOH–Et_2O (10 and 250 mL) gave a second crop of a white solid identical by TLC with the main crop; yield 144 mg. The crops were combined and redried in vacuo over P_2O_5 for 48 h at 82 °C; total yield 804 mg (81% as $C_{14}H_{20}N_2O_9 \cdot 0.25EtOH \cdot 0.4H_2O$); mp ~125 °C with prior sintering. Solvation was confirmed by ^1H NMR; $[\alpha]_D^{20} + 140.7°$ (*c* 0.56); MS: *m/z* 361 $[M+H]^+$, 343 $[M-OH]^+$; IR: ν_{max} 2259 cm^{-1} (CN); ^1H NMR (Me_2SO-d_6): δ 2.76 (m, 4 H, 6-CH_2), 3.04 (m, 2 H, H-4), 3.30 (m, 2 H, H-2), 3.53 (m, 2 H, H-3), 3.92 (dt, 2 H, H-5), 4.88 (d, 2 H, $J_{1,2}$ 3.9 Hz, H-1), 5.00 (m, 4 H, O*H*-2 and O*H*-3), 5.35 (d, 2 H, *J* 5.2 Hz, OH-4); ^{13}C NMR (300 MHz, D_2O): δ 118.91 (2 × *C*N), (C-2, C-3, C-4, C-2′, C-3′, C-4′), 67.94 (C-5, C-5′), 20.41 (C-6, C-6′). Anal. Calcd for $C_{14}H_{20}N_2O_9 \cdot 0.25$ EtOH·0.4 H_2O: C, 45,95; H, 5.93; N, 7.39. Found: C, 46.01; H, 5.88; N, 7.42.

6,6′-Bis(aminomethyl)-6,6′-dideoxy-α,α-trehalose dihydrochloride (**42**).—A mixture of the dinitrile **41** (735 mg, 1.94 mmol), PtO_2 (200 mg), $CHCl_3$ (2 mL), and MeOH (100 mL) was hydrogenated by shaking in a Parr apparatus at an initial H_2 pressure of 50 lb/in^2. After 20 h, the mixture was filtered though a Celite pad under N_2 pressure, and the catalyst was washed with MeOH. The colorless filtrate was evaporated; the residue was dissolved in dry MeOH (20 mL), and the solution was diluted dropwise with Et_2O (350 mL). The dense solid deposit was filtered under N_2 pressure, washed with Et_2O, and dried in vacuo over P_2O_5 at rt, and then for 20 h at 82 °C; yield 797 mg (89%); mp dec above 160 °C with prior charring; MS: *m/z* 369 $[M+H]^+$, 176 $(1/2[M-16])^+$; ^{1}H NMR-(Me_2SO-d_6): δ 1.59, 2.05 (complex m, 4 H, 6-CH_2), 2.82 (complex m, 4 H, H_2NCH_2–), 2.92 (dd, 2 H, *J* 9.5 Hz, H-4), 3.30 (dd, 2 H, *J* 3.9 Hz, H-2), 3.48 (m, 2 H, H-3), 3.84 (dd, 2 H, *J* 3.2 Hz; H-5), 4.81 (d, 2 H, $J_{1,2}$ 3.9 Hz, H-1), 5.01 (d, 2 H, *J* 4.8 Hz, 3-OH), 5.18 (br, 4 H, 2-OH and 4-OH), 7.87 (br, 6 H, $-NH_3^+$). Anal. Calcd for $C_{14}H_{28}N_2O_9 \cdot 2HCl \cdot H_2O$: C, 36.61; H, 7.02; N, 6.10; Cl, 15.44. Found: C, 36.64; H, 7.00; N, 6.02; Cl, 15.30.

*(*R,S*)-6,6′-Dideoxy-6,6′-bis{[[1-(hydroxymethyl)propyl]amino]methyl}-α,α-trehalose* (**43**).—Solid anhydrous $NaHCO_3$ (71 mg, 0.84 mmol) was added to a stirred solution of the diamine dihydrochloride **42** (203 mg, 0.413 mmol) in MeOH (12 mL), followed after 10 min by 1-hydroxy-2-butanone (87 mg, 0.99 mmol, 20% excess) and glacial HOAc (60 mg, 0.99 mmol). After 30 min, solid $NaBH_3CN$ (62 mg, 0.99 mmol) was added, and the resulting colorless mixture was stirred for 4 days at rt. Volatiles were evaporated; a solution of the residue in water (10 mL) was allowed to stand for 30 min, evaporated and reevaporated with MeOH (2 × 20 mL). A solution of the residue in 1:1 $CHCl_3$–MeOH was filtered and applied to a silica gel flash column. Elution with $CHCl_3$–MeOH–conc NH_4OH (10:10:1) gave homogeneous fractions (TLC) of the desired product that were pooled, evaporated, and reevaporated with EtOH (2 × 25 mL) and with CH_2Cl_2 (2 × 25 mL). A smaller crop (44 mg, 20%) with only a trace contaminant (TLC) was also collected using the same workup. The homogeneous crop was dried in vacuo over P_2O_5 for 18 h at 65 °C; yield 96 mg (43%); mp softens gradually above ~80 °C; $[\alpha]_D^{20}$ +116.3° (*c* 1.15); MS: *m/z* 513 $[M+H]^+$, 248 $(1/2[M-16])^+$, 102 $[EtCH(CH_2OH)NHCH_2]^+$; ^{1}H NMR (Me_2SO-d_6): δ 0.84 (t, 6 H, CH_3CH_2), 1.39 (m, 4 H, CH_3CH_2), 1.44 (m, 2 H, H-6), 1.88 (m, 2 H, H-6′), 2.45 (m, 2 H, EtC*H*NH–), 2.65 (m, 4 H, –NHCH_2CH_2), 2.90 (dd, 2 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 3.29 and 3.39 (2m, H_2O superimposed on H-2 and –CH_2OH), 3.47 (m, 2 H, H-3), 3.78 (m, 2 H, H-5), 4.79 (m, 2 H, H-1), 4.2–5.6 (very broad, best seen in integral, NH, OH); ^{13}C NMR (300 MHz, D_2O): δ 93.98 (C-1, C-1′), 73.79, 72.89, 71.45 (C-2, C-3, C-5, C-2′, C-3′, C-5′), 71.14, 70.89 (C-4, C-4′), 61.96, 61.85 (–NHCH(*C*H_2OH)CH_2CH_3), 60.12 (–NH*C*H–(CH_2OH)CH_2CH_3), 42.93, 42.83 (–*C*H_2NHCH(CH_2OH)CH_2CH_3), 30.46 (C-6, C-6′), 22.73, 22.51 (–NHCH(CH_2OH)*C*H_2-CH_3), 9.63 (CH_3). Anal. Calcd for $C_{22}H_{44}N_2O_{11} \cdot 0.1$ EtOH$\cdot H_2O$: C, 49.82; H, 8.78; N, 5.23. Found: C, 49.79; H, 8.82; N, 5.21.

(S)(+)-2,3,4,2′,3′,4′-Hexa-O-benzoyl-6,6′-bis[1-(hydroxymethyl)propylamino]-α,α-trehalose (**44**).—To a solution of **39** (1.14 mmol, 1.4 g) in 5 mL of dry CH_2Cl_2 was added (*S*)(+)-2-amino-1-butanol (5.7 mmol, 0.54 mL). The resulting solution was stirred for 18 h at rt. The reaction mixture was directly separated on a silica gel column with 99:1 $CHCl_3$–MeOH as eluent to obtain 867 mg of product (68% yield); mp 93–95 °C; MS: *m/z* 1109 $[M+H]^+$; ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 6 H, CH_3CH_2–), 1.35 (m, 4 H, CH_3CH_2), 2.25 (dd, 2 H, H-6, H-6′), 2.35 (m, 2 H, EtC*H*NH–), 2.62 (m, 2 H, H-6, H-6′), 3.18 (m, 2 H, CH_2OH), 3.48 (m, 2 H, CH_2OH), 3.90 (m, 2 H, H-5), 5.38 (m, 2 H, H-2), 5.45 (m, 2 H, H-4), 5.98 (d, 2 H, H-1), 6.20 (t, 2 H, H-3), 7.28–8.2 (m, 30 H, Bz). Anal. Calcd For $C_{62}H_{62}N_2O_{17} \cdot 0.2$ H_2O: C, 66.92; H, 5.83; N, 2.52. Found: C, 66.52; H, 5.91; N, 2.69.

(R)(−)-2,3,4,2′,3′,4′-Hexa-O*-benzoyl-6,6′-dideoxy - 6,6′ - bis[1 - (hydroxymethyl)propylamino]-α,α-trehalose* (**45**).—Compound **45** was prepared by the same procedure as **44** with (*R*)(−)-2-amino-1-butanol. Pure product was obtained after silica gel chromatography in 65% yield; mp 146–148 °C; MS: *m/z* 1109 $[M+H]^+$; ^{1}H NMR ($CDCl_3$): δ 0.82 (t, 6 H, C*H*$_3$CH$_2$), 1.30 (m, 4 H, CH$_3$C*H*$_2$), 2.0 (dd, 2 H, H-6, H-6′), 2.18 (m, 2 H, EtC*H*NH–), 2.35 (dd, 2 H, H-6, H-6), 3.14 (m, 1 H, CH$_2$OH), 3.36 (m, 1 H, C*H*$_2$OH), 4.0 (m, 2 H, H-5), 5.34 (dd, 2 H, H-2), 5.68 (d, 2 H, H-1), 5.85 (t, 2 H, H-4), 6.22 (t, 2 H, H-3), 7.26–8.12 (m, 30 H, Bz). Anal. Calcd for $C_{62}H_{64}N_2O_{17}\cdot 0.2H_2O$: C, 66.92; H, 5.83; N, 2.52. Found: C, 66.51; H, 5.85; N, 2.52.

(S)(+)6,6′ - Dideoxy - 6,6′ - bis[1 - (hydroxymethyl)propylamino]-α,α-trehalose (**46**).—A solution of sodium metal (20 mg) in dry MeOH (8 mL) was added to **44** (832 mg, 0.75 mmol). After stirring the resulting solution for 1 h, more MeOH (10 mL) was added and the pH was adjusted to 8 with Dowex 50W-X8 (H^+) cation-exchange resin. After filtration and evaporation of the filtrate, the residue was separated by column chromatography (3:1 $CHCl_3$–MeOH + 5% NH_4OH) to give pure 296 mg of product (82% yield); mp 104–107 °C. $[\alpha]_D^{20}$ + 138.3° (*c* 0.5); MS: *m/z* 485 $[M+H]^+$; ^{1}H NMR (Me_2SO-d_6,): δ 0.80 (t, 6 H, C*H*$_3$CH$_2$–), 1.30 (m, 4 H, CH$_3$C*H*$_2$–), 2.42 (m, 2 H, EtC*H*NH–), 2.62 (dd, 2 H, H-6, H-6′), 2.76 (dd, 2 H, H-6, H-6′), 3.12 (t, 2 H, H-4), 3.24 (m, 4 H, H-2, –CH$_2$OH), 3.36 (m, 2 H, –C*H*$_2$OH), 3.54 (m, 2 H, H-3), 3.78 (m, 2 H, H-5), 4.52 (bs, 2 H, –CH$_2$O*H*), 4.68 (d, 2 H, OH-2), 4.76 (d, 2 H, OH-3), 4.88 (d, 2 H, H-1), 4.94 (bs, 2 H, OH-4). Anal. Calcd for $C_{20}H_{40}N_2O_{11}\cdot H_2O$: C, 49.03; H, 8.35; N, 5.72. Found: C, 48.82; H, 8.74; N, 5.55.

(R)(−)- 6,6′ - Dideoxy - 6,6′ - bis[1 - (hydroxymethyl)propylamino]-α,α-trehalose (**47**).—This compound was prepared by the same procedure as **46**. After column chromatography, pure product was obtained in 78% yield; mp 96–98 °C with glass formation; $[\alpha]_D^{20}$ + 115.7° (*c* 0.5); MS: *m/z* 485 $[M+H]^+$; ^{1}H NMR (Me_2SO-d_6): δ 0.81 (t, 6 H, C*H*$_3$CH$_2$–), 1.31 (m, 4 H, CH$_3$C*H*$_2$–), 2.36 (m, 2 H, EtC*H*NH–), 2.52 (dd, 2 H, H-6, H-6′), 2.63 (dd, 2 H, H-6, H-6′), 3.04 (t, 2 H, H-4), 3.20 (m, 4 H, H-2, –C*H*$_2$OH), 3.36 (m, 2 H, –C*H*$_2$OH), 3.54 (m, 2 H, H-3), 3.70 (m, 2 H, H-5), 4.42 (bs, 2 H, –CH$_2$O*H*), 4.60 (bs, 2 H, OH-2), 4.78 (d, 2 H, OH-3), 4.86 (d, 2 H, H-1), 5.0 (bs, 2 H, OH-4); ^{13}C NMR (300 MHz, D_2O): δ 93.38 (C-1, C-1′), 72.63, 72.51, 71.31, 70.40 (C-2, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 62.79 (–NHCH(*C*H$_2$OH)-CH$_2$CH$_3$), 59.31 (–NH*C*H(CH$_2$OH)CH$_2$CH$_3$), 47.04 (C-6, C-6′), 22.66 (–NHCH(CH$_2$OH)-*C*H$_2$CH$_3$), 9.63 (CH$_3$). Anal. Calcd for $C_{20}H_{40}N_2O_{11}\cdot 1.5H_2O$: C, 46.96; H, 8.47; N, 5.48. Found: C, 46.58; H, 8.51; N, 5.41.

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