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SELECTIVELY BLOCKED DERIVATIVES OF *muco*-INOSITOL AND THEIR CONVERSION INTO DERIVATIVES OF *epi*- AND *cis*-INOSITOL

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ABSTRACT

Benzylation, and then hydrolysis, of 1,2:4,5-di-*O*-isopropylidene-*muco*-inositol (**1**) gave 3,6-di-*O*-benzyl-*muco*-inositol (**3**). This was converted into a series of derivatives, including the 1,5-di-*O*-benzoyl-3,6-di-*O*-benzyl-2,4-di-*p*-toluenesulfonate **7**. The resistance to displacement of the sulfonate groups in **7** prevented conversion of **7** into an intermediate for the synthesis of aminoglycoside antibiotics. Monobenzylation of **1**, followed by an oxidation–reduction cycle, yielded 6-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*epi*-inositol (**10**). From this was synthesized a series of *epi*-inositol derivatives, analogous to the *muco* series but less complete. For derivatives of 1,2:5,6-di-*O*-isopropylidene-*epi*- and *muco*-inositol, the p.m.r. data indicate modified skew conformations. The reaction of the 3,6-di-*p*-bromobenzenesulfonate (**17**) of **1** with anhydrous hydrazine proceeded in part by S–O cleavage to regenerate **1**, and in part by displacement of both sulfonate groups by the same nitrogen atom. The resulting, novel 1,4-epimino-*cis*-inositol was converted into further derivatives.

INTRODUCTION

The hope of preparing diaminocyclitols, or precursors thereof, suitably blocked for use in the synthesis of aminoglycoside antibiotics, led us to explore the chemistry of *muco*-inositol. The configuration of *muco*-inositol is such that steric inversion at positions 1 and 5 (2 and 4)†, as might occur during the insertion of nitrogen functions, would give *myo*-inositol derivatives closely related to actinamine, streptamine, and deoxystreptamine[2]. Suami and his collaborators[3] have described syntheses of these amines from *myo*-inositol, but the products do not carry blocking groups, which are required for their further elaboration into aminoglycosides.

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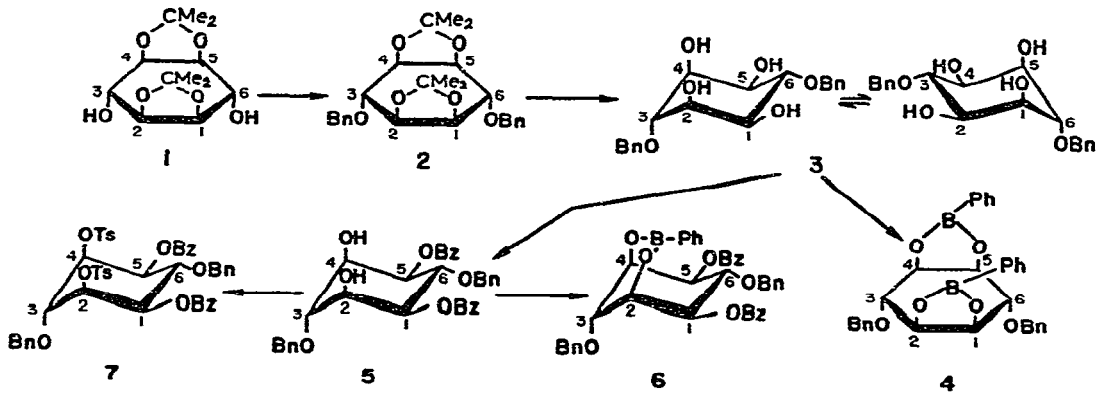
†The cyclitol derivatives described here are named and numbered according to the IUPAC–IUB 1973 Recommendations for Cyclitols (ref. 1). The apparent use of two different ways of numbering *muco*-inositol derivatives is a function of the symmetry of the parent inositol and the orientation of the formulas.

muco-Inositol is nowadays fairly readily obtainable from *myo*-inositol, and it is easily converted into the 1,2:4,5-di-*O*-isopropylidene acetal **1**. This compound served as the starting material for the three synthetic sequences described here. Although end-products of the desired type were not obtained, a variety of differentially blocked derivatives of *muco*- and *epi*-inositol resulted. Some of these are potentially useful as synthetic intermediates. A novel, nitrogen-bridged, bicyclic derivative of *cis*-inositol is described.

RESULTS AND DISCUSSION

In the first sequence, the proximate objective was to attach persistent* blocking groups at positions 3 and 6 of *muco*-inositol, temporary blocking groups at positions 1 and 5, and (hopefully displaceable) sulfonate groups at the other two positions. Toward this end, the di-*O*-isopropylidene acetal (**1**) was readily converted into 3,6-di-*O*-benzyl-*muco*-inositol (**3**). Compound **3** undergoes facile chair–chair interconversion, but the two conformers are identical, and each has a pair of *syn*-axial hydroxyl groups. An attempt to block these as the phenylboronate[5] was unsuccessful; treatment with triphenylboroxole yielded instead the bis ester **4**.



Bn = $PhCH_2$

Treatment of **3** with a 2.2-molar proportion of benzoyl chloride in pyridine gave a mixture of benzoates from which a pure dibenzoate could be isolated in 12% yield. A much improved yield (33%) was subsequently obtained by using *N*-benzoylimidazole[6,7] in toluene–dichloromethane as the acylating agent. Characterization of the crystalline dibenzoate as the desired 1,5-isomer (**5**) is based on its p.m.r. spectrum, and the spectrum of the derived phenylboronate **6**. In both spectra, the protons on the

*A persistent blocking group (ref. 4) is one that is attached early in a synthetic sequence and left in place during all intermediate steps, its removal being one of the final operations of the overall synthesis.

benzoylated carbon atoms gave a single signal, a doublet of doublets at low field displaying large (9.0 Hz) and small (2.5–3.5 Hz) spacings. Thus, the two protons are axial and each has one axial and one equatorial neighbor. In the spectrum of **6**, H-2 and H-4 resonate as a triplet at τ 5.15, having a spacing (3.5 Hz) indicative of $\sim 60°$ projection angles with both neighboring protons, as required by the assigned structure. Compound **5** was readily converted into the di-*p*-toluenesulfonate **7**, isolated in 19% overall yield from **1**. The p.m.r. spectrum of **7** closely resembles that of **6**, indicating that the preponderant conformation of **7** is the one illustrated, having the sulfonate groups axial.

In the context of a discussion of the stereochemistry of various blocked derivatives of *muco*-inositol, the starting material (di-*O*-isopropylidene-*muco*-inositol, **1**) is of interest. Angyal and Hoskinson[8], on the basis of an infrared study of internal hydrogen-bonding, considered that **1** adopts a skew conformation, or a conformation intermediate between a skew and a boat. The p.m.r. spectrum of **1** reveals little, but when the compound is converted into its diacetate[9] **18** the multiplet for H-3,6 is well separated from that for H-1,2,4,5 (Fig. 1)*. The spectrum, which has a high degree of degeneracy because of the high symmetry of the molecule of **18**, can be treated as an AA′A″A‴XX′ case. Values for the coupling constants obtained by analysis on this basis, and confirmed by computer simulation (Program SIM 8K, Varian), are $J_{1,2} = J_{4,5} = 7.36$ Hz and $J_{2,3} = J_{3,4} = J_{1,6} = J_{5,6} = 8.85$ Hz. These values show excellent fit (Karplus equations) to a conformation derived from the $^{3,6}B$ boat (dioxolane rings at the sides) by twisting it, first one way and then the other, until the boat-axial hydrogen pairs (H-1,2 and H-4,5) have projection angles of 16–18°. The projection angles of the "end" protons (H-3,6) with a given neighbor would then alternate between $\sim 163°$ and $\sim 180°$ (mean 171–172°). In view of the uncertainties involved in calculations with the Karplus equations, these estimates of the projection angles can only be regarded as approximate. Nevertheless the data support Angyal and Hoskinson's suggestion of a conformation between the boat and the ideal skew. The rapidly interconverting, enantiomeric skewed forms involved may be designated as modified $^1S_3$(1D) and $^3S_1$(1L)†.

Both chair forms of **7** have features tending to make the sulfonate groups resistant to displacement. The conformer having axial sulfonate groups suffers from the unfavorable polar effect[10] of the neighboring, axial benzyloxy group at position 3, and in the alternative conformer, the entering nucleophile would have *syn*-axial interference[10,11] from the (now axial) benzyloxy group on C-6. Favoring the possibility of displacement is the fact that both chair forms have a rather high confor-

*The preparation of **18** from starting material provided by the senior author, and the analysis and interpretation of the spectrum, were performed by Prof. N. V. Riggs, University of New England, Armidale, Australia.

†The boat form of **1** (and its derivatives) has planes of symmetry, but twisting this boat generates chirality. Hence the two skew forms are designated as belonging to the D and L series, respectively, by the conventions of cyclitol nomenclature (ref. 1). The same applies to the corresponding derivatives of *epi*-inositol.

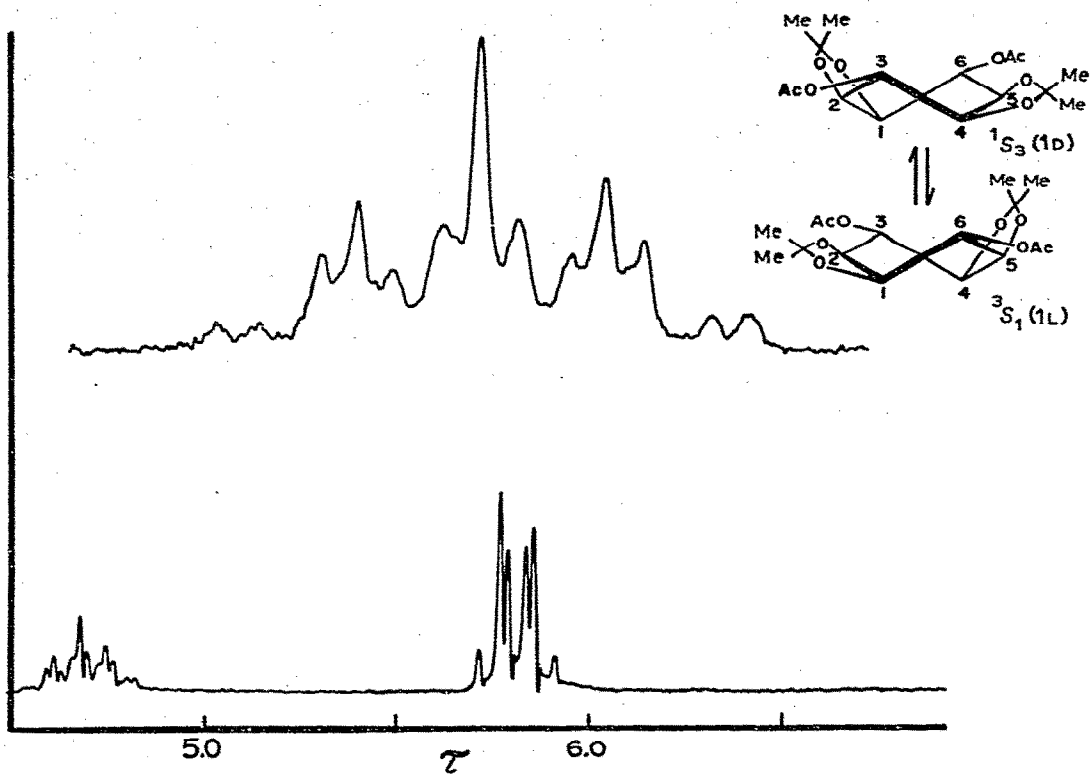


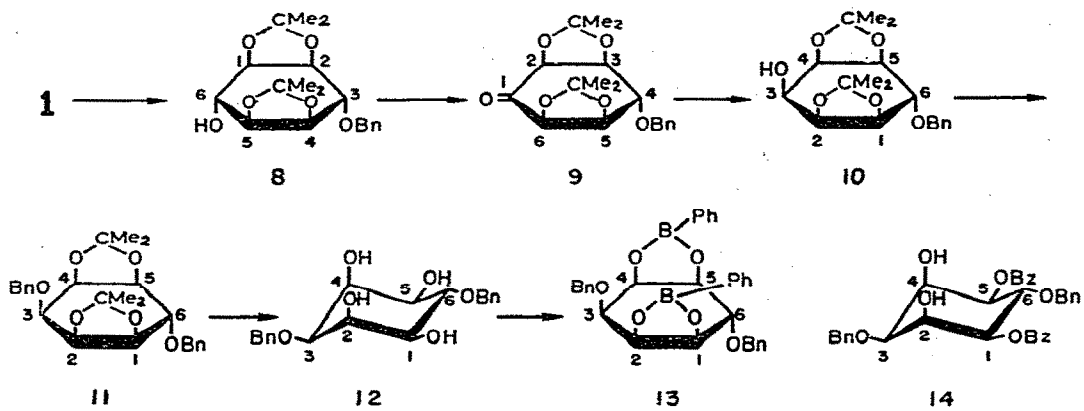
Fig. 1. The ring proton portion of the 100-MHz p.m.r. spectrum of 3,6-di-*O*-acetyl-1,2:4,5-di-*O*-isopropylidene-*muco*-inositol (**18**) in chloroform-*d*. The spectrum was recorded with a Varian HA-100 instrument, with tetramethylsilane as a reference.

mational energy (three axial substituents each), so that conversion into a boat or skew form for reaction might be energetically feasible. However, all attempts to displace the sulfonate groups were unsuccessful. When **7** was treated with sodium azide in *N*,*N*-dimethylformamide, methyl sulfoxide, or hexamethylphosphortriamide at moderate temperatures it was recovered unchanged. At higher temperatures, mixtures of decomposition products were formed. Similar results were obtained with anhydrous hydrazine.

In view of these results, the second synthetic sequence was designed to convert **1** into the *epi*-inositol analog of **7**. The benzyloxy group on C-3 would be equatorial in the analog, which should then be free of the hindrances to displacement found in **7**. The first phase of the sequence involved the monobenzylation of **1**, and epimerization at the remaining hydroxyl group.

By treatment of **1** with a 1.1-molar proportion of benzyl bromide and methylsulfinyl carbanion in methyl sulfoxide, a mixture was obtained from which the monobenzyl ether **8** and the dibenzyl ether **2** could be isolated chromatographically in yields of 41 and 23%, respectively. The oxidation of **8** with methyl sulfoxide-based

reagents[12,13] gave low yields of the ketone **9**, and preformed ruthenium tetraoxide[14] was likewise unsatisfactory, leading to a mixture of products. In some of these, the benzyl group on O-3 had been oxidized to benzoyl. Oxidation with ruthenium tetraoxide generated *in situ*[15] was more productive, giving a crude preparation of **9** (estimated yield 50%) that could be reduced with sodium borohydride. Chromatographic separation of the reduction products furnished mono-*O*-benzyl-di-*O*-isopropylidene-*epi*-inositol (**10**) in a yield of 49% (based on **8**), and a 16% recovery of **8**. The *epi* configuration of **10** was established by converting it into the known *epi*-inositol hexaacetate.



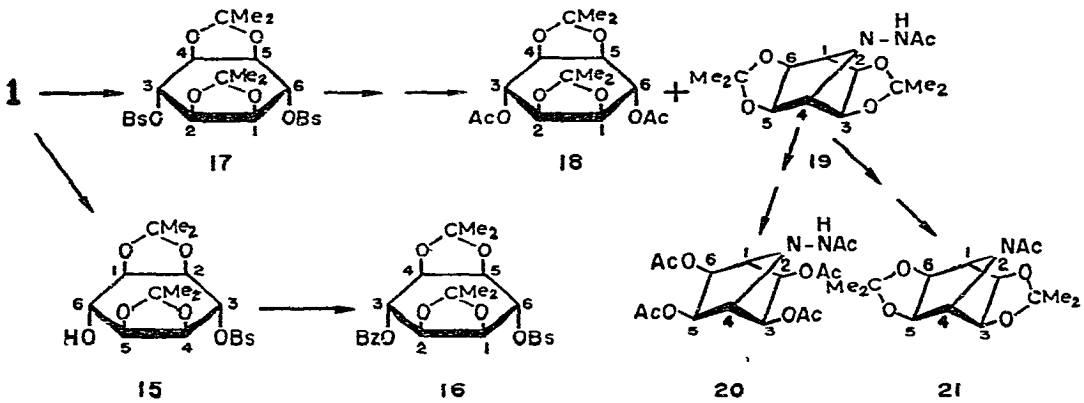
The conversion of **10** into **11** and **12**, epimers of compounds **2** and **3** in the *muco* series, was readily accomplished. The p.m.r. spectrum of **11** in benzene-d_6 was fully resolved, and should indicate whether derivatives of 1,2:4,5-di-*O*-isopropylidene-*epi*-inositol exist in skew or modified-skew conformations. The i.r. data of Angyal and Hoskinson[8] were equivocal on this point. The assignment of the lines in the spectrum of **11** (see Experimental) is based on correlations with the (less well resolved) spectrum of the 3-acetyl analog, in which the signal for H-3 could be definitely identified. The apparent coupling constants for the ring protons of **11** are $J_{1,6} = J_{5,6} = 8.0$ Hz, $J_{1,2} = J_{4,5} = 8.0$ Hz, and $J_{2,3} = J_{3,4} = 3.5$ Hz. These values are most compatible with modified-skew conformations [$^1S_3$(1D) and $^3S_1$(1L)] similar to those described earlier for di-*O*-isopropylidene-*muco*-inositol derivatives. Flattened-chair forms, which are the only reasonable alternatives, seem to be excluded. The same considerations apply to **10**, which gave a spectrum less well resolved than that of **11**, but with similar features.

In contrast to **3**, compound **12** should exist predominantly in a single chair conformation having the hydroxyl groups at positions 2 and 4 axial, as shown. This feature, and the availability of the ether oxygen atom (O-3) for coordination, might be expected to favor the formation of a 2,4-phenylboronate. However, compound **12**, like **3**, gave a bis(phenylboronate), formulated as **13**. Analysis of the p.m.r. spectrum of **13** was not possible, because it has only one well-resolved ring-proton signal, which

could be due to either H-1,5 or H-2,4. The two splittings (2.0 and 4.5 Hz) present in this signal suggest that, conformationally, compound **13** differs substantially from **10** and **11**. However, as the remaining ring-protons are themselves strongly coupled, the true *J* values may differ considerably from the observed ones, and firm conformational conclusions cannot be drawn.

In view of the more-stable conformation of **12**, it was expected that selective benzoylation of the equatorial hydroxyl groups at positions 1 and 5 would be easier than with **3**. However, all attempts at partial benzoylation gave complex mixtures, suggesting that the axial hydroxyl groups were as reactive as the equatorial ones. From one mixture, a very small proportion (3%) of dibenzoate **14** was isolated. The high reactivity of the axial hydroxyl groups may be due to the availability for hydrogen bonding[16] of a neighboring (position 3) *cis*-disposed ether oxygen atom.

In the third reaction-sequence, the displacement of sulfonate groups from the "end" positions (3 and 6) of di-*O*-isopropylidene-*muco*-inositol was explored. Previous work with *muco*-inositol 3,6-disulfonates has involved the 1,2,4,5-tetra-acetate-3,6-dimethanesulfonate, which with azide gives the 3,6-diazido-*muco* derivative[9], and 3,6-di-*O*-*p*-tolylsulfonyl-*muco*-inositol, which with hydrazine gives 4,6-dideoxy-4,6-hydrazo-*myo*-inositol[17]. Neighboring-group participation is a feature of both these reactions, whence it was expected that different products would be obtained from sulfonates of **1**. The reaction of **1** with limited amounts of *p*-bromobenzenesulfonyl (brosyl) chloride gave a modest yield of the 3-monobrosylate **15**, and an excess of reagent gave good yields of the 3,6-dibrosylate **17**. Treatment of **17** with sodium azide in *N*,*N*-dimethylformamide resulted in a complex mixture. However, the reaction of **17** with anhydrous hydrazine at 90° gave two products, which could be



separated by chromatography after acetylation. The major product (60%) proved to be the diacetate (**18**) of 1,2:4,5-di-*O*-isopropylidene-*muco*-inositol (**1**), formed from **17** by S–O cleavage of the sulfonate groups[18].

From its elemental analysis, it was deduced that the second product (31%) was derived from **17** by displacement of both brosyl groups by a single hydrazine molecule.

In the p.m.r. spectrum of this compound, the six cyclitol ring-protons gave three singlets, which were assigned to H-1 and 4, H-2 and 3, and H-5 and 6. The lack of coupling suggested that the cyclitol ring must be in a rigid boat-form[19,20], so that the projection angles between H-1 and H-4 and their neighbors would be near 90°. These data, and the fact that only one *N*-acetyl group was present, led to the conclusion that the product was the *cis*-inositol derivative **19** in which positions 1 and 4 are bridged by a single nitrogen atom. The chemical-shift difference between H-2,3 and H-5,6 indicates that the molecule is unsymmetric about the plane through C-1, C-4, and the bridge nitrogen atom. The lack of symmetry must be due to hindered rotation about the N–N bond, which previously has been observed in a number of tetraacyl and *N,N'*-diacylhydrazines[21], but not, apparently, in monoacylhydrazines.

Confirmatory evidence for the structure was obtained by reducing **19** and acetylating the product. One nitrogen atom was lost in the reduction, and the p.m.r. spectrum of the product showed a change in symmetry in that H-2,3,5 and 6 now gave a 4-proton singlet, whereas H-1 and H-4 gave separate signals. The assignment of structure **21** to the reduction product is based on these findings: H-1 and H-4 are heterotopic because the acetyl group is in the C-1–C-4–N plane, and there is hindered rotation about the N–CO bond[19]. The mass spectra of **19** and **21** are consistent with the assigned structures.

Compound **19** arises because neighboring-group participation in the displacement of the sulfonate groups from **17** is not possible, and the boat conformation required for formation of the nitrogen bridge is energetically readily accessible. Many derivatives of 7-azabicyclo[2.2.1]heptane, the parent ring-system of **19**, have been synthesized in recent years[19,20,22], but the 1,4-epiminoinositols **19**, **20**, and **21** are, to the best of our knowledge, the first cyclitols of this class. Several of the corresponding oxygen analogs (1,4-anhydroinositols) are known[23,24].

EXPERIMENTAL

General methods. — Melting points, which are uncorrected, were determined on a Glas–Treibel melting-point apparatus. P.m.r. spectra, except that of compound **18**, were recorded on a Varian T-60 spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded with an AEI MS-902 instrument, using direct sample introduction. T.l.c. was conducted on glass plates (5 × 20 cm) coated with Silica Gel G (E. Merck). Ethyl ether–ethanol–hexane (Skellysolve B), 1:1:8 (v/v/v) (system A), and 1:1 (v/v) ethyl ether–chloroform (system B) were used as developing solvents, and spots were detected by charring with sulfuric acid. Evaporations were performed *in vacuo*. All compounds reported as pure were recrystallized to constant melting point, at which stage they gave single spots on t.l.c. Elemental analyses were performed by Galbraith Laboratories.

Starting material. — The 1,2:4,5-di-*O*-isopropylidene-*muco*-inositol (**1**) used in this work was made by the isomerization of *myo*-inositol hexaacetate in liquid hydrogen fluoride, with deacetylation and acetonation incorporated into the

processing of the reaction mixture. The procedure (K. A. Brackmann, D. B. Finkelstein, and L. Anderson, unpublished) was based on Hedgley and Fletcher's original description of the isomerization[25]. Alternatively, the synthesis of Suami, Lichtenthaler and Ogawa[9] could be used to make crude *muco*-inositol from *myo*-inositol. The product was then acetonated with 2,2-dimethoxypropane by the procedure of Angyal and Hoskinson[26]. Acetylation of **1** by a standard procedure gave the diacetate **18**, m.p. (after recrystallization from ethanol) 212° (see under **19**).

3,6-Di-O-benzyl-1,2:4,5-di-O-isopropylidene-muco-inositol (**2**). — Compound **1** (10.2 g, 39.2 mmol) was stirred with benzyl chloride (70 ml) and potassium hydroxide (10 g) for 6 h at 150°. The cooled mixture was evaporated to a syrup, and then steam distilled. The distilland was extracted with chloroform (50 ml), the extract was evaporated, and the product was crystallized and recrystallized from ethanol–water; yield 16.6 g (96%); m.p. 170–171°; p.m.r. ($CDCl_3$): τ 2.65 (m, 10, Ph-*H*) and 5.20 (s, 4, PhCH_2).

Anal. Calc. for $C_{26}H_{32}O_6$ (440.52): C, 70.89; H, 7.32. Found: C, 71.02; H, 7.25.

3,6-Di-O-benzyl-muco-inositol (**3**). — Compound **2** (12.2 g, 27.7 mmol) was refluxed in 90% acetic acid (300 ml) for 4 h. After evaporating the solution to a syrup, a hot ethanolic solution of the product was decolorized with carbon, filtered, and evaporated. The resultant syrup was dissolved in a hot mixture of benzene and Skellysolve B. Slow cooling gave crystals of **3** (9.1 g, 91%) having m.p. 147–148°; p.m.r. ($CDCl_3$): τ 2.64 (m, 10, Ph-*H*), and 5.25 (s, 4, PhCH_2), no C–CH_3.

Anal. Calc. for $C_{20}H_{24}O_6$ (360.39): C, 66.65; H, 6.71. Found: C, 66.46; H, 6.91.

3,6-Di-O-benzyl-muco-inositol 1,2:4,5-bis(phenylboronate) (**4**). — Compound **3** (0.3 g, 0.83 mmol) and triphenylboroxole (90 mg, 0.29 mmol) were refluxed in benzene (20 ml) for 3 h while water was removed by a Dean–Stark trap. After evaporation, crystals of **3** (0.125 g, 42% recovery) were obtained from benzene–Skellysolve B. The mother liquor slowly deposited crystals of **4** (0.14 g, 60% based on triphenylboroxole) having m.p. 170–171°; p.m.r. ($CDCl_3$): τ 2.15, 2.60 (m, 4 and m, 16, Ph-*H*), and 4.98 (s, 4, PhCH_2).

Anal. Calc. for $C_{32}H_{30}B_2O_6$ (532.18): C, 72.22; H, 5.68; B, 4.06. Found: C, 72.29; H, 5.76; B, 4.20.

1,5-Di-O-benzoyl-3,6-di-O-benzyl-muco-inositol (**5**). — Imidazole (0.18 g, 2.6 mmol) was dissolved in dichloromethane (10 ml) and the solution cooled to 0°. Benzoyl chloride (0.2 g, 1.4 mmol) was added, and the mixture was stirred for 10 min and then filtered into a flask containing **3** (0.23 g, 0.64 mmole) and toluene (30 ml). The entire mixture was refluxed for 9 h and then evaporated. A solution of the resultant syrup in chloroform (250 ml) was washed with saturated aqueous sodium hydrogen carbonate (2 × 100 ml), saturated aqueous sodium chloride (2 × 100 ml), and water (2 × 100 ml). The chloroform layer was then evaporated to a syrup, which was dissolved in hot ethanol–water and cooled slowly to yield crystals of **5** (0.12 g, 33%) having m.p. 208–210°; p.m.r. ($CDCl_3$): τ 4.40 (dd, 2, $J_{1,6} = J_{5,6}$ 9.0 Hz, $J_{1,2} = J_{4,5}$ 2.5 Hz, H-1,5), 4.75 and 5.20 (2 s, 2 each, PhCH_2).

Anal. Calc. for $C_{34}H_{32}O_8$ (568.60): C, 71.82; H, 5.67. Found: C, 72.19; H, 5.76.

1,5-Di-O-benzoyl-3,6-di-O-benzyl-muco-*inositol 2,4-phenylboronate* (**6**). — Compound **5** (85 mg, 0.15 mmol) and triphenylboroxole (16 mg, 50 μmol) were refluxed in benzene (15 ml) for 4 h while water was removed with a Dean–Stark trap. The mixture was evaporated and the residue dissolved in hot benzene–Skellysolve B. Slow cooling yielded crystals of **6** (84 mg, 86%) having m.p. 140–141°; p.m.r. (C_6D_6): τ 3.83 (dd, 2, $J_{1,6} = J_{5,6}$ 9.0 Hz, $J_{1,2} = J_{4,5}$ 3.5 Hz, H-1,5), 5.15 (t, 2, *J* 3.5 Hz, H-2,4), 5.40 and 5.66 (2 s, 2 each, PhCH_2), 5.43 (m, 1, H-6), and 6.38 (t, 1, *J* 3.5 Hz, H-3).

Anal. Calc. for $C_{40}H_{35}BO_8$ (654.49): C, 73.40; H, 5.39; B, 1.65. Found: C, 73.32; H, 5.27; B, 1.66.

1,5-Di-O-benzoyl-3,6-di-O-benzyl-2,4-di-O-p-tolylsulfonyl-muco-*inositol* (**7**). — Compound **5** (85 mg, 0.15 mmol) and *p*-toluenesulfonyl chloride (0.12 g, 0.63 mmole) were stirred in anhydrous pyridine (3 ml) for 20 h at 40°. The mixture was poured into water (100 ml) and extracted with chloroform (2 × 50 ml). The chloroform layers were combined and washed with 0.1M hydrochloric acid (2 × 100 ml) and water (2 × 100 ml). Evaporation of the chloroform layer gave a syrup, which was dissolved in hot ethanol–water. Slow cooling gave crystals of **7** (88 mg, 67%), m.p. 157–159°; p.m.r. (C_6D_6); τ 4.16 (dd, 2, $J_{1,6} = J_{5,6}$ 8.0 Hz, $J_{1,2} = J_{4,5}$ 2.5 Hz, H-1,5), 4.61 (t, 2, *J* 2.5 Hz, H-2,4), 5.40 (t, 1, *J* 8.0 Hz, H-6), 5.49 and 5.62 (2 s, 2 each, PhCH_2), 5.67 (t, 1, *J* 2.5 Hz, H-3), and 8.26 (s, 6, PhCH_3).

Anal. Calc. for $C_{48}H_{44}O_{12}S_2$ (876.96): C, 65.74; H, 5.06. Found: C, 65.49; H, 5.33.

3-O-Benzyl-1,2:4,5-di-O-isopropylidene-muco-*inositol* (**8**). — Sodium hydride (4 g of a 50% dispersion in oil) was washed with Skellysolve B (2 × 20 ml) and then added to methyl sulfoxide (180 ml) which had been dried over Linde 4A molecular sieves and distilled. This mixture was stirred under nitrogen for 30 min and then **1** (10.2 g, 39 mmol) was added. After an additional 30 min of stirring, benzyl bromide (7.3 g, 43 mmol) was added dropwise to the solution during 50 min at room temperature. The mixture was stirred for an additional 18 h, poured into water (1000 ml), and extracted with chloroform (4 × 50 ml). The combined chloroform extracts were washed with water (6 × 200 ml) and concentrated to a syrup, which was applied to a column (7.0 cm diameter, 1400 g) of silica gel. Elution with 1:50 (v/v) ethyl acetate–chloroform gave first **2** (3.9 g, 23%) and then **8** (5.6 g, 41%). Compound **8** gave crystals from hot ethanol–water which melted at 121–122°; p.m.r. (C_6D_6): τ 5.09 (s, 2, PhCH_2) and 7.20 (s, 1, exchangeable, O*H*).

Anal. Calc. for $C_{19}H_{26}O_6$ (350.40): C, 65.12; H, 7.48. Found: C, 65.14; H, 7.37.

6-O-Benzyl-1,2:4,5-di-O-isopropylidene-epi-*inositol* (**10**). — The monobenzyl ether **8** (0.135 g) was oxidized with methyl sulfoxide and acetic anhydride[13] for 30 h, and the solution was evaporated. A solution of the resultant syrup in chloroform, was washed with aqueous sodium hydrogen carbonate and water, and then evaporated. The product, dissolved in ethanol, was decolorized (carbon), and the solution again evaporated. A solution of the final syrup in hot carbon tetrachloride–Skellysolve B, on slow cooling, deposited 30 mg (22%) of crystals melting at 140–146°. Recrystal-

lization raised the m.p. to 144–146°; ν_{max}^{KBr} 1754 cm^{-1} (C=O); p.m.r. ($CDCl_3$): τ 2.67 (m, 5, Ph-*H*); (C_6D_6): τ 5.02 (s, 2, PhC*H*$_2$), 5.57–5.80 (m, 4, H-2,3,5,6), 6.56 (t, 1, *J* 8.0 Hz, H-4), 8.54 and 8.77 (2 s, 6 each, C–C*H*$_3$). The spectral data identified the compound as 4-*O*-benzyl-2,3:5,6-di-*O*-isopropylidene-2,3,5,6/4-pentahydroxycyclohexanone (**9**). The reduction of this ketone with sodium borohydride (see next paragraph) gave the *epi*-inositol product **10** and the *muco*-inositol precursor **8** in a ratio of about 10:1 (t.l.c.).

For a better preparation of **10**, compound **8** (1.05 g, 3.0 mmol) was dissolved in dichloromethane (25 ml). Water (3 ml), sodium hydrogen carbonate (0.3 g), and ruthenium dioxide (35 mg) were added, and the mixture was stirred vigorously. A solution of sodium metaperiodate (1.48 g) in water (30 ml) was added dropwise during a 2-h period. The vigorous stirring was continued for 4 h and then 2-propanol (5 ml), water (500 ml), and chloroform (100 ml) were added. The mixture was filtered and the organic layer was separated and evaporated to a syrup, which was dissolved in 2-propanol (150 ml). Sodium borohydride (1.2 g) was added and the mixture was refluxed for 6 h. After the addition of water (300 ml), the solution was concentrated to a syrup, which was applied to a column of silica gel (2.5 cm diameter, 180 g). Elution with 1:50 (v/v) ethyl acetate–chloroform gave at first compound **10** (0.51 g, 49%), and then **8** (0.17 g, 16%). Compound **10** was recrystallized from ethanol–water; m.p. 151–152°; p.m.r. (C_6D_6): τ 5.04 (s, 2, PhC*H*$_2$), 5.48 (t, 1, *J* 7.0 Hz, H-6), 6.00 (m, 3, H-1,3,5), 6.47 (dd, 2, *J* 7.0 and 2.5 Hz, H-2,4), and 7.71 (s, 1, exchangeable, O*H*).

Anal. Calc. for $C_{19}H_{26}O_6$ (350.40): C, 65.12; H, 7.48. Found: C, 64.87; H, 7.31.

Acetylation of **10** gave a sample of the 3-acetate, which was not purified; p.m.r. ($CDCl_3$): τ 4.33 (t, 1, *J* 3.2 Hz, becoming s on irradiation at τ 6.33, H-3 because of low field position), 5.60–6.15 (m, 3, H-1,5,6), and 6.33 (dd, 2, *J* 3.2 and 8.0 Hz, becoming d, *J* 8.0 Hz on irradiation at τ 4.33, H-2,4).

A sample of **10** that was sequentially debenzylated (H_2, Pd/C), hydrolyzed (aqueous acetic acid), and acetylated gave *epi*-inositol hexaacetate, m.p. 188–189° (lit.[27] 188°), mixture m.p. with an authentic sample 188–190°, with *muco*-inositol hexaacetate 110–114°.

*3,6-Di-*O*-benzyl-1,2:4,5-di-*O*-isopropylidene-*epi*-inositol* (**11**). — Compound **10** (80 mg, 0.23 mmol) was benzylated as described for the preparation of **2**. The residue obtained after steam distillation failed to crystallize. Chromatography on a column of silica gel (2.5 cm diameter, 160 g, elution with 1:20 ethyl acetate–chloroform) gave 80 mg (79%) of pure, syrupy **11**; p.m.r. (C_6D_6): τ 4.86, 5.00 (2 s, 2 each, PhC*H*$_2$), 5.37 (t, 1, *J* 8.0 Hz, attributable to H-6 if τ 6.18 is H-3), 5.87 (t, 2, *J* 8.0 Hz, H-1,5 because of common *J* with H-6), 6.18 (t, 1, *J* 3.5 Hz, H-3 by analogy with τ 4.33 of acetylated **10**), and 6.40 (dd, 2, H-2,4 because *J* 8.0 Hz is common with H-1,5, and *J* 3.5 Hz is common with H-3).

Anal. Calc. for $C_{26}H_{32}O_6$ (440.52): C, 70.89; H, 7.32. Found: C, 70.98; H, 6.92.

*3,6-Di-*O*-benzyl-*epi*-inositol* (**12**). — Compound **11** (75 mg, 0.17 mmol) was refluxed in 80% acetic acid (25 ml) for 5 h. After evaporation to a syrup, the product

was crystallized from hot ethanol; yield 44 mg (72%), m.p. 166–167°; p.m.r. ($CDCl_3$): τ 5.21, 5.34 (2 s, 2 each, PhCH_2), 5.74 (m, 2,H-2,4), 6.54 (m, 6, H-1,3,5,6, and 2 OH), and 7.18 (m, 2, OH).

Anal. Calc. for $C_{20}H_{24}O_6$ (360.39): C, 66.65; H, 6.71. Found: C, 66.57; H, 6.61.

In one of several attempts at the selective, partial benzoylation of **12**, 0.12 g of the compound was treated with *N*-benzoylimidazole (compare the foregoing preparation of **5**) in chloroform. Chromatography of the crude reaction mixture on a column of silica gel with 1:1:18 ether–ethanol–Skellysolve B, as the eluting solvent gave a fraction evincing two components, R_F 0.52 and 0.55 on t.l.c. in system A. This fraction was not further resolved by column chromatography with 20:1 chloroform–methanol as the eluant. A small amount (5 mg, 3%) of the component having R_F 0.52 was eventually obtained by fractional crystallization from ethanol–water. The spectrum and analysis of this product characterized it as *1,5-di*-O-*benzoyl-3,6-di*-O-*benzyl*-epi-*inositol* (**14**); m.p. 289–293°; p.m.r. (C_6D_5): τ 4.70 (dd, 2, $J_{1,6} = J_{5,6}$ 9.0 Hz, $J_{1,2} = J_{4,5}$ 2.5 Hz, H-1,5), 5.24 (s+m, 3, PhCH_2 and H-6), 5.53 (m, 2, H-2,4), 5.80 (s, 2, PhCH_2), 6.16 (m, 2, exchangeable, OH), and 7.08 (t, 1, $J_{2,3} = J_{2,4}$ 2.5 Hz, H-3).

Anal. Calc. for $C_{34}H_{32}O_8$ (568.60): C, 71.82; H, 5.67. Found: C, 71.79; H, 6.16.

3,6-Di-O-*benzyl*-epi-*inositol 1,2:4,5 bis*(*phenylboronate*) (**13**). — Compound **12** (60 mg, 0.17 mmol) and triphenylboroxole (17 mg, 0.055 mmol) were refluxed in toluene (15 ml) for 20 h while water was collected in a Dean–Stark trap. The mixture was concentrated and then diluted with hot chloroform–Skellysolve B. Slow cooling yielded two successive crops of crystals of **12** (total recovery 27 mg, 45%). The mother liquor was evaporated to a syrup which was dissolved in hot benzene–Skellysolve B. Slow cooling gave crystals of **13** (25 mg, 57% based on triphenylboroxole) having m.p. 107–109°; p.m.r. ($CDCl_3$): τ 2.16, 2.60, 2.98 (3 m, 20, Ph-H), 5.00 and 5.20 (2 s, 2 protons each, PhCH_2); (C_6D_6): τ 5.55, 5.72, 5.87 (3 m, 4, H-1,3,5,6?), and 6.13 (dd, 2, J 2.0 and 4.5 Hz, H-2,4?).

Anal. Calc. for $C_{32}H_{30}B_2O_6$ (532.18): C, 72.22; H, 5.68. Found: C, 71.99; H, 5.73.

3-O-*Benzoyl-6*-O-p-*bromophenylsulfonyl-1,2:4,5-di*-O-*isopropylidene*-muco-*inositol* (**16**). — Compound **1** (1.60 g, 6.15 mmol) was dissolved in anhydrous pyridine (5 ml) and *p*-bromobenzenesulfonyl chloride (1.73 g, 6.77 mmol) was added. The mixture was stirred for 2 days at room temperature, poured into water (100 ml), and then extracted with chloroform (3 × 50 ml). The chloroform layers were combined and washed with 0.1M hydrochloric acid (2 × 100 ml) and water (2 × 100 ml). The chloroform layer was evaporated to a syrup, toluene (20 ml) was added, and the solution was again evaporated. The resultant syrup was dissolved in hot ethanol. Slow cooling yielded a crystalline product (yield 32%), m.p. 114–115°, having the p.m.r. spectrum expected for *3*-O-p-*bromophenylsulfonyl-1,2:4,5-di*-O-*isopropylidene*-muco-*inositol*(**15**).

An amount of 1.12 g (2.34 mmole) of **15** was treated with benzoyl chloride (0.50 ml, 4.4 mmol) in pyridine (5 ml) for 4 h at room temperature. The solution was poured into ice–water (300 ml) and extracted with chloroform (3 × 50 ml). The

chloroform extracts were combined and evaporated to a syrup, which was dissolved in a hot mixture of benzene–Skellysolve B. Slow cooling gave crystals of **16** (1.22 g, 89%), m.p. 213–215°. Recrystallization from ethanol–water gave fine needles melting at 216–218°; p.m.r. (CD_3COCD_3): τ 4.55 (m, 1, H-3) and 5.18 (m, 1, H-6).

Anal. Calc. for $C_{25}H_{27}BrO_9S$ (583.45): C, 51.46; H, 4.67; Br, 13.70; S, 5.50. Found: C, 51.08; H, 4.64; Br, 13.52; S, 5.59.

3,6-Di-O-p-*bromophenylsulfonyl-1,2:4,5-di*-O-*isopropylidene*-muco-*inositol* (**17**). — Compound **1** (1.16 g, 4.46 mmol) and *p*-bromobenzenesulfonyl chloride (3.36 g, 13.1 mmol) were stirred in pyridine (10 ml) for 20 h at 50°. The mixture was then poured into water (300 ml) and extracted with chloroform (2 × 100 ml). The combined chloroform layers were washed with water (2 × 200 ml) and evaporated to dryness. The resultant syrup gave crystals of **17** from hot ethanol; yield 2.9 g (93%); m.p. 233°; p.m.r. ($CDCl_3$): τ 2.25 (q_{AB}, 8, J 7.5 Hz) and 5.33 (m, 2, H-3,6).

Anal. Calc. for $C_{24}H_{26}Br_2O_{10}S_2$ (698.41): C, 41.27; H, 3.75; Br, 22.89. Found: C, 41.30; H, 3.93; Br, 22.90.

(N-*Acetamido*)-*1,4-epimino-1,4-dideoxy-2,3:5,6-di*-O-*isopropylidene*-cis-*inositol* (**19**). — Compound **17** (0.17 g, 0.24 mmol) and anhydrous hydrazine (5 ml) were heated under nitrogen for 36 h at 90°. After cooling, the hydrazine was removed by distillation and the resulting residue was acetylated with acetic anhydride (2 ml) in pyridine (2 ml). T.l.c. (solvent B) indicated the presence of two major components. The mixture was applied to a column of silica gel (15 g, 1.5 cm diameter) which was eluted with 1:4 (v/v) ethyl ether–chloroform. The first product eluted (50 mg, 60%) was identified as **18** by its m.p. of 207–208° (lit.[9] 202.5–203.5°), its elemental analysis, and its p.m.r. and mass spectra. The second component was **19** (22 mg, 31%), m.p. 245–247° when crystallized from benzene–Skellysolve B; p.m.r. ($CDCl_3$): τ 2.23 (s, 1, exchangeable, N*H*), 5.70 and 6.06 (2 s, 2 each, H-2,3 and H-5,6 or vice versa), 6.33 (s, 2, H-1 and H-4), and 8.18 (s, 3, $NCOCH_3$); *m/e* (relative intensity) 298 (2) (M^+), 283 (1), 255 (0.3), 240 (0.2), 198 (0.3), 140 (6), 85 (70), and 43 (100).

Anal. Calc. for $C_{14}H_{22}N_2O_5$ (298.33): C, 56.36; H, 7.43; N, 9.39. Found: C, 56.56; H, 7.40; N, 9.08.

(N-*Acetamido*)-*1,4-epimino-2,3,5,6-tetra*-O-*acetyl-1,4-dideoxy*-cis-*inositol* (**20**).— Compound **19** (15 mg, 50 μmol), acetic acid (9 ml), and water (2 ml) were refluxed for 4 h. The solution was evaporated to a syrup, water was added, and the solution was again evaporated. The syrup was dried at 50° and then acetylated with acetic anhydride (2 ml) and pyridine (2 ml) for 6 h at room temperature. The mixture was evaporated to a syrup, which was dissolved in chloroform (5 ml) and washed with water (2 × 15 ml). Skellysolve B was added to the chloroform layer until it became cloudy. Warming, and then slowly cooling the solution yielded crystals of **20** (12 mg, 62%), m.p. 228–230°; p.m.r. ($CDCl_3$): τ 2.80 (s, 1, exchangeable, N*H*), 4.78, 5.18 (2 s, 2 each, H-2,3 and H-5,6 or vice versa), 6.38 (s, 2, H-1 and H-4), 7.78 and 7.86 (2 s, 15, $COCH_3$); *m/e* (rel. intensity) 386 (23) (M^+), 342 (7), 326 (60), 284 (46), 267 (9), 225 (19), 183 (32), 140 (23), 60 (49), and 43 (100).

Anal. Calc. for $C_{16}H_{22}N_2O_9$ (386.35): C, 49.74; H, 5.74; N, 7.25. Found: C, 49.71; H, 6.03; N, 7.01.

(N-*Acetyl*)-*1,4-epimino-1,4-dideoxy-2,3:5,6-di*-O-*isopropylidene*-cis-*inositol* (**21**). — Compound **19** (20 mg, 67 μmol) was dissolved in anhydrous tetrahydrofuran (1 ml) in a flask fitted with a condenser cooled by a slurry of Dry Ice. Dried ammonia gas was passed in until 2 ml had condensed. Sodium (40 mg) was added and the mixture was boiled for 90 min at reflux before the ammonia was allowed to evaporate. Methanol (2 ml) was added to the residue and the solution was evaporated to dryness. Water was added, carbon dioxide was bubbled in for 10 min, and the solution was again evaporated to dryness. The residue was acetylated with acetic anhydride (2 ml) in pyridine (2 ml). After the acetylated product had been treated with decolorizing carbon in hot ethanol, crystals of **21** (11 mg, 58%) were obtained from benzene–Skellysolve B, m.p. 204–205°; p.m.r. (C_6D_6): τ 5.24, 6.21 (2 d, 1 each, $J_{1,4}$ 1.0 Hz, H-1 and H-4 or vice versa), 6.43 (s, 4, H-2,3,5,6), and 8.03 (s, 3, $NCOCH_3$); *m/e* (rel. intensity) 283 (28) (M^+), 268 (19), 254 (11), 241 (3), 224 (18), 210 (14), 196 (9), 183 (16), 142 (27), 125 (94), 96 (63), 59 (17), and 43 (100).

Anal. Calc. for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.17; H, 7.60; N, 4.87.

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