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# THE DISPLACEMENT OF SULFONATE GROUPS BY AZIDE IN CYCLITOLS. FULLY SUBSTITUTED 4-SULFONATES OF D-PINITOL AND 2-SULFONATES OF 1L-1-*O*-METHYL-*allo*-INOSITOL

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ABSTRACT

A series of *p*-toluenesulfonic and *p*-bromobenzenesulfonic esters was prepared from 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-*chiro*-inositol ("diisopropylidenepinitol", **1**). In these compounds, the arylsulfonyl group was at position 4(3), and the substituents at positions 1,2,5, and 6 were isopropylidene, acetyl, methyl, and cyclic carbonate, respectively. Inversion of configuration at C-4 in **1** gave 1D-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*allo*-inositol, from which a corresponding series of *allo*-inositol sulfonates was prepared. Rates of displacement of the sulfonate groups by azide ion (*N*,*N*-dimethylformamide, 110°) were measured in both series, and the azido products were isolated and characterized. All of the azides except the penta-*O*-methyl-*chiro* derivative were convertible to one of two inosamine pentaacetates, which were shown to be 1L-2-amino-2-deoxy-1-*O*-methyl-*allo*-inositol pentaacetate and 1D-3-amino-3-deoxy-4-*O*-methyl-*chiro*-inositol pentaacetate, respectively.

## INTRODUCTION

Derivatives of 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-*chiro*-inositol† (**1**, "diisopropylidenepinitol") were among the sulfonic esters used in a study in this laboratory of the parameters governing the rate of displacement of sulfonate groups by azide ion in the sugar series[2]. The *p*-tolylsulfonyl (**2a**), *p*-bromophenylsulfonyl ("brosyl") (**2b**), and *p*-chlorophenylsulfonyl compounds reacted straightforwardly

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†The cyclitol derivatives described here are named and numbered according to the IUPAC–IUB 1973 Recommendations for Cyclitols (Ref. 1). It will be noted that, in some cases, the methylated position of pinitol is assigned the number 3, and the sulfonylated position the number 4, whereas, in other cases, the opposite is true. Similar shifts of numbering occur with the *allo*-inositol derivatives, accompanied by a change in the designation of configurational series (D or L). These unfortunate variations result from the necessity of choosing between the two equivalent numberings inherent in the stereochemistry of each of the parent inositols. The choice is made, as stipulated in the Rules, by the principle of "lowest number to the substituent first in alphabetical order." Confusion is best avoided by constant reference to the formulas in Schemes I–III.

with azide, albeit at lower rates than the other secondary sulfonates examined. At the time these data were collected, the steric and electronic factors affecting sulfonate displacements were not understood, whence we were led to prepare and study a series of additional 1D-*chiro*-inositol esters in which the isopropylidene groups of **2a** and **b** were replaced by other substituents. We also prepared a companion series of 1L-1-*O*-methyl-*allo*-inositol sulfonates that are epimeric with the *chiro* compounds at the sulfonylated position. The synthesis of these cyclitol sulfonates, and the characterization of the azidocyclitols derived from them, are described in this paper. Kinetic data are recorded for the reaction of several of the sulfonates with azide ion, and the various results obtained are briefly discussed in relation to present knowledge of steric effects on sulfonate displacements.

## RESULTS

*Synthesis of the sulfonic esters.* — In the pinitol series, our aim was to prepare a derivative differing from **2a** and **b** but still carrying fused rings at positions 1, 2 and 5, 6, and also derivatives having individual substituents at these positions. The syntheses proceeded as shown in Scheme I. Removal of the isopropylidene groups from **2a** and **2b** gave the unprotected sulfonates **3a** and **3b**, which were readily acetylated to **6a** and **6b**. The brosyl derivative **3b** was also converted into the bis-(cyclic carbonate) **7** by the method of Doane *et al.*[3].

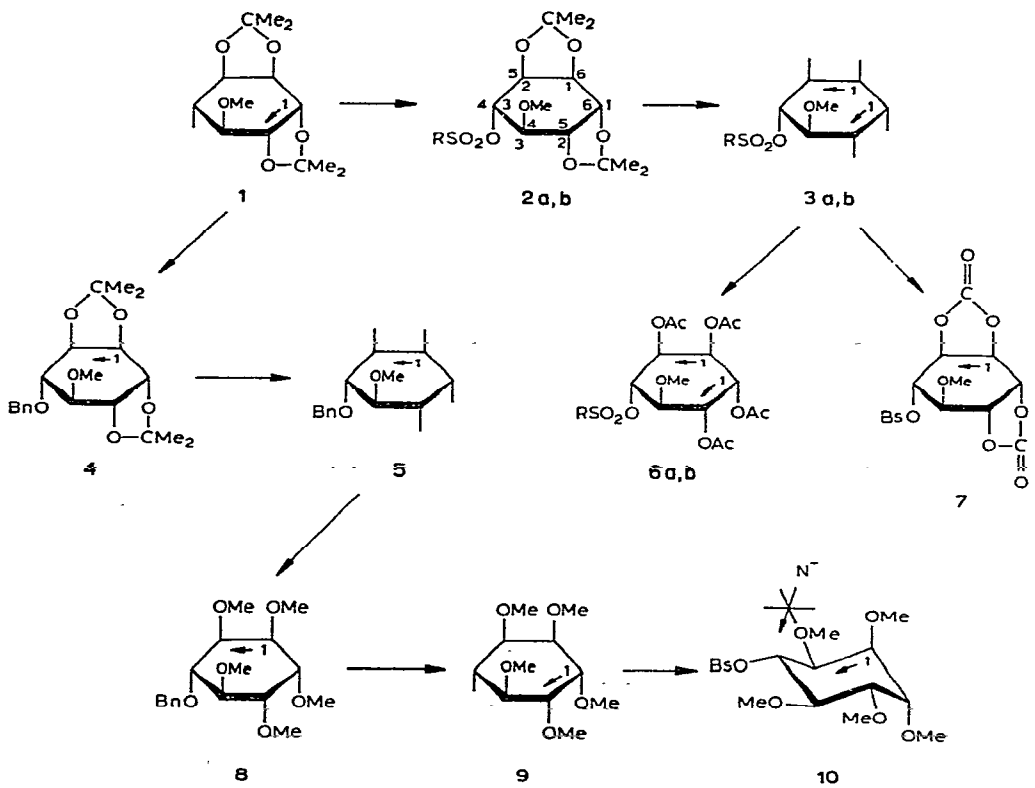
Attempted direct methylation of **3b** gave a complex mixture because of the alkali lability of the sulfonate group. Hence, an indirect route was chosen for the synthesis of the methylated brosyl ester **10**. The free hydroxyl group of diisopropylidenepinitol (**1**) was temporarily substituted by an *O*-benzyl group, and methylation was performed after removal of the isopropylidene groups (**4**→**5**→**8**). Removal of the *O*-benzyl group from **8** gave the pentamethyl ether **9**, which yielded **10** on treatment with brosyl chloride.

Scheme II outlines the synthesis of the 1(4)-*O*-methyl-*allo*-inositol derivatives. The starting material was the known 1D-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*allo*-inositol (**11**), prepared from the diisopropylidenepinitol brosyl ester **2b** by benzoate displacement, as described for the tosyl derivative by Angyal and Stewart[4], and saponification of the intermediate benzoic ester. The use of the brosyl ester shortened the time required for the displacement step (compare Table I). Sulfonylation of **11** gave **12a** and **12b**, epimeric with **2a** and **2b**. Removal of the isopropylidene groups from **12a** and **12b**, and acetylation, gave **13a** and **13b**, epimeric with **6a** and **6b**. The brosylpenta-*O*-methyl derivative **18** was made by the same steps as used for the corresponding *chiro*-inositol derivative **10**.

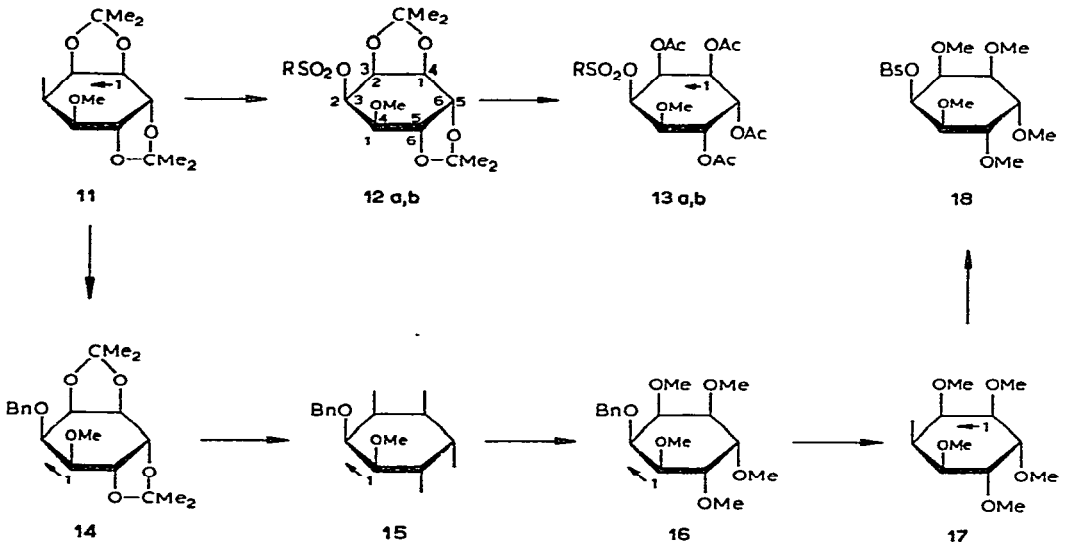
*Characterization of the azido products.* — The displacement of sulfonate groups from cyclitol derivatives in moist *N*,*N*-dimethylformamide, with or without added sodium benzoate, was investigated by Angyal and Stewart[4]. Displacement by azide ion (in aqueous 2-methoxyethanol) has been extensively studied by Suami and his collaborators[5]. In the examples described by these two sets of workers, it appears

that, when participation by a neighboring *trans* acetyl or hydroxyl group is possible, displacement usually proceeds by a participation mechanism. Direct displacement, or no reaction, results when neighboring groups cannot be involved. Among the compounds examined in the present study, if participation by methoxyl is regarded as unlikely, anchimerically assisted displacement appeared possible only in the acetylated pinitol sulfonates **6a** and **6b**. It was therefore provisionally assumed that, with the other pinitol derivatives **2a**, **2b**, and **7**, and the *allo*-inositol derivatives **12**, **13**, and **18**, the displacement would be direct, leading to inversion of configuration at the carbon atom affected. The observation that all of these latter displacements proceeded with second-order kinetics supported this expectation. Confirmatory evidence was obtained by p.m.r. spectroscopy, following a series of chemical interconversions of the initial azido products.

As shown in Scheme III, the products (**19** and **22**) from **2b** and **7** gave the same azidodeoxy-*O*-methylinositol tetraacetate **20**. An isomeric azido tetraacetate (**25**) was formed directly from the *allo*-inositol sulfonates **13** on reaction with azide. Inter-




Scheme I
a series $RSO_2$ = *p*-tolylsulfonyl (Ts)
b series, $RSO_2$ = *p*-bromophenylsulfonyl (Bs)
Bn = benzyl



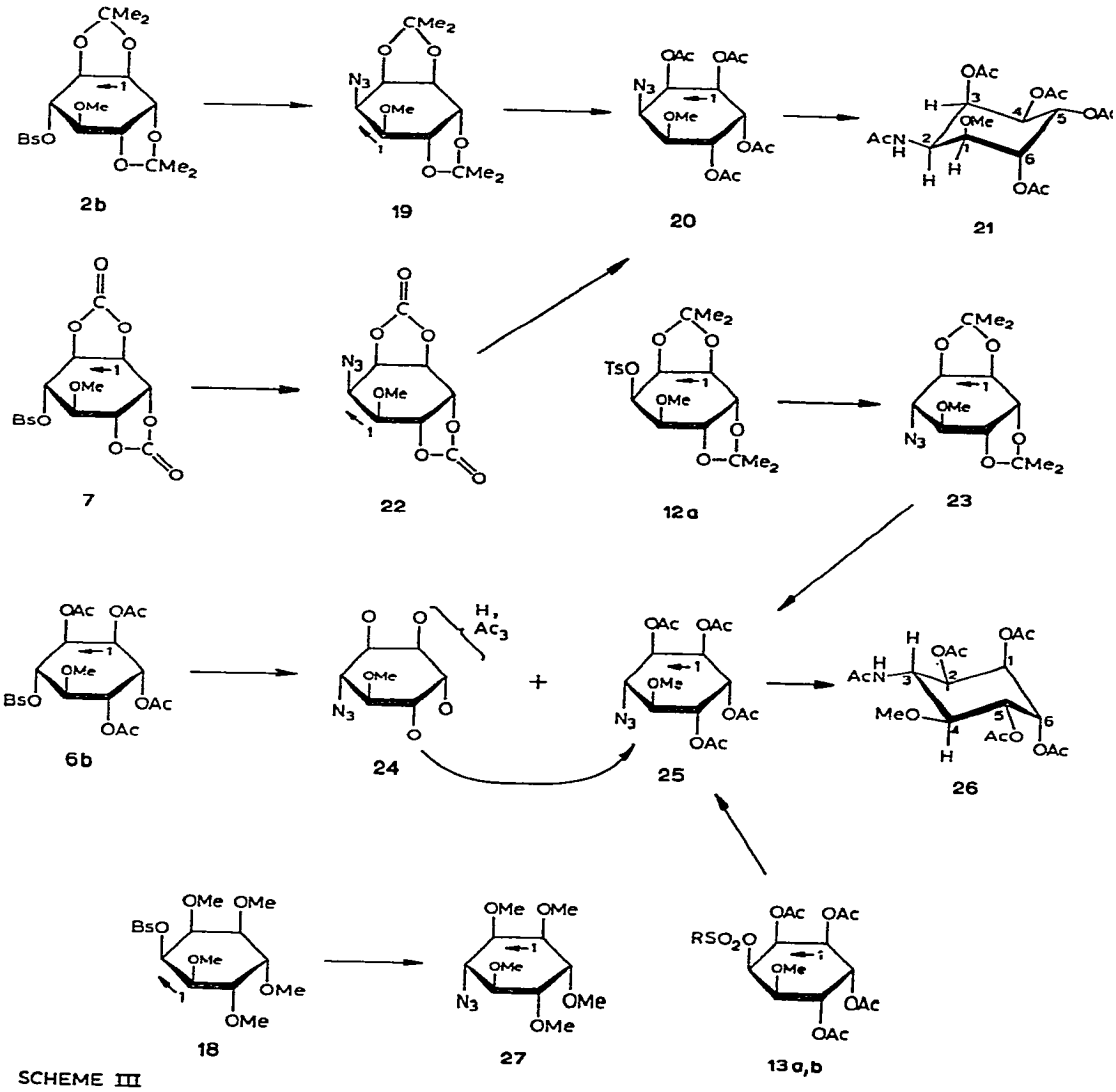

SCHEME II

TABLE I

SECOND-ORDER RATE-CONSTANTS FOR THE AZIDE DISPLACEMENT-REACTION OF CYCLITOL AND SUGAR SULFONATES IN *N,N*-DIMETHYLFORMAMIDE AT 110°

| *Series* | *Compound number (sufonate group)* | *Substituents at positions 1,2,5,6* (chiro) *or 3,4,5,6(1,2,5,6)* (allo) | $10^2 k_2$ $(M^{-1}.min^{-1})^a$ |
|---|---|---|---|
| Pinitol | **2a** (Ts) | Isopropylidene | 0.97 ±0.03[b] |
| | **2b** (Bs) | Isopropylidene | 3.0 ±0.1[b] |
| | **7** (Bs) | Cyclic C=O | 1710[c] |
| 1(4)-*O*-Methyl-*allo*-inositol | **12a** (Ts) | Isopropylidene | 8.2 ±0.6 |
| | **13a** (Ts) | Acetyl | 5.3 ±0.2[d] |
| | **18** (Bs) | Methyl | 5.0 ±0.2[d] |
| Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-brosyl-α-D-glucopyranoside | | | 44 ±2 |
| Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-brosyl-α-D-galactopyranoside | | | 100 ±14 |
| Methyl 2,4,6-tri-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranoside | | | 7.9 ±0.6[b] |
| Methyl 2,4,6-tri-*O*-acetyl-3-*O*-brosyl-β-D-glucopyranoside | | | 30.4 ±0.8[b] |

[a]Values are mean ± range or, where 3 or more runs were made, ± standard deviation. [b]From ref. 2. [c]Value calculated for 110° from value measured at 80° (1.61 ±0.09 $M^{-1}.min^{-1}$) under assumption that rate increases by a factor of 2.2 with each 10° increase in temperature (ref. 2). [d]See experimental. The errors in *k* due to slight impurities in these compounds are within the normal experimental error.




SCHEME III

mediate **23**, derived from **12a**, also gave **25**. The p.m.r. spectra of the azido tetra-acetates **20** and **25** did not provide clear evidence for the presumed configurations of the two compounds. Hence, they were reduced and acetylated to the inosamine derivatives **21** and **26**. In the spectra of these compounds, the multiplets for the protons on the carbon atoms bearing the acetamido groups, clearly separated from other signals, simplified to triplets on the addition of a little deuterium oxide and trifluoroacetic acid.

The spacings of the triplet in the spectrum of **21** indicated projection angles of $\sim 60°$ for the acetamido-C*H* and its neighboring protons ($J_{1,2} = J_{2,3} = 4$ Hz). By contrast, the spacings of the acetamido-C*H* signal of **26** indicated projection angles of

$\sim 180°$ ($J_{2,3} = J_{3,4} = 10$ Hz). These findings confirm the assignment of the *allo* configuration to compound **21** and the *chiro* configuration to compound **26**, by the following reasoning. For the derivative having the *allo* configuration, the chair conformation shown in formula **21** and the alternative chair conformation are about equally probable, as the two conformations are enantiomeric in the parent *allo*-inositol. In either conformation, the projection angles of H-2 with its neighbors are $\sim 60°$. Only in the *chiro* configuration, in the conformation shown in formula **26** (favored for *chiro* derivatives), can the acetamido-C*H* have projection angles of 180°. Hence the compound showing *J* values of 10 Hz must have the *chiro* configuration, and the isomer must be the *allo* compound.

It follows that the *allo* configuration must be assigned, as shown, to the azido precursors (**19**, **20**, and **22**) of **21**. Similarly, the azides **23** and **25** must have the *chiro* configuration, as postulated. No attempt was made to correlate the product (**27**) from the penta-*O*-methyl-*allo*-inositol brosyl ester **18** with the other azides but, in view of the foregoing, the assignment of the *chiro* configuration to **27** seems safe.

The acetyl-methyl signals in the spectra of **21** and **26** were examined, as the chemical shifts of these signals are regarded as indicators of conformation[6]. In the spectrum of the *allo* derivative **21**, there was a signal at $\tau$ 8.04, just below the range ($\tau$ 8.05–8.10) for equatorial *N*-acetyl groups. This suggests that the preponderant conformation of the compound might be the one shown in formula **21**. However, there was no high-field signal in the spectrum of **26**, which must also have an equatorial *N*-acetyl group.

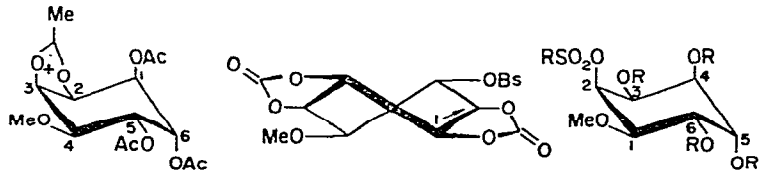
The reaction of the brosylpinitol tetraacetate **6b** with azide was shown by t.l.c. to give two products, which were separated on a preparative scale. One of the products was the azido tetraacetate **25**, now assigned the *chiro* configuration. The other was a triacetate (**24**) that gave **25** on acetylation. Thus, the displacement of the brosyl group from **6b** proceeded with retention of configuration and partial loss of an acetyl group.

Included in the kinetic study were the 4-brosyl esters of methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside and α-D-galactopyranoside. As it was known that the corresponding tosyl esters react with azide ion with inversion on configuration at C-4, it was expected that the azido products from the brosyl esters would be the *galacto* and *gluco* derivatives, respectively. This was in fact what was found.

*Rates of displacement by azide ion.* — Reaction rates were measured in nominally dry *N*,*N*-dimethylformamide and, with one exception, at 110°. The second-order rate-constants are listed in Table I, together with selected values obtained under the same conditions in the previous work[2]. Most noteworthy is the high reaction rate shown by the brosylpinitol bis(cyclic carbonate) **7**. The reaction could not be monitored at the standard temperature of 110°, but the $k_2$ value for 110° estimated from measurements made at 80° is nearly 600 times that for the structurally similar brosyldiisopropylidenepinitol **2b**. No value is quoted for brosylpinitol tetraacetate (**6b**) because the reaction of this compound with azide ion is not a simple bimolecular displacement.

## DISCUSSION

The pinitol sulfonates examined in this study showed a wide range of behavior in their reaction with azide ion. Considering first those having individual substituents at positions 1, 2, 5, and 6, the pentamethyl brosyl ester **10** did not react, even on prolonged heating. The reason for the lack of reactivity is readily apparent upon examination of the conformation of the compound: the methoxyl group at position 1 is *syn*-axial to the attacking nucleophile. Richardson[7] has summarized the evidence that this arrangement effectively hinders displacement. *syn*-Axial interference also prevents direct displacement of the sulfonate group from brosylpinitol tetraacetate (**6b**). In this compound, however, displacement can be effected by the carbonyl oxygen atom of the acetyl group at position 2, giving the intermediate acetoxonium ion **28**. The acetoxyl group at position 6 shields position 2 of the ion by the *syn*-axial effect, hence attack by azide is at position 3, giving overall retention of configuration.




28 29 30

Compounds **2** differ from **10** and **6** in that in **2** the oxygen atoms at positions 1, 2, 5, and 6 are involved in dioxolane ring-structures. Evidence pointing to a change in the conformation of a 6-membered ring when two 5-membered rings are fused to it was adduced by Angyal[8], and compounds related to **2** have recently been studied in detail in his laboratory[9]. It was shown that, in the most pertinent example, (1L-3-*O*-acetyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-*p*-tolylsulfonyl-*chiro*-inositol), the cyclohexane ring is flattened at carbon atoms 1, 2, 5, and 6. As a result, O-1 and O-6 (which are axial in the parent compound) are moved outward. Existence in this flattened conformation would explain the behavior of compounds **2a** and **2b**, namely, normal bimolecular reaction with nucleophiles, but at low rates, as if the *syn*-axial effect were moderated but not entirely eliminated.

The nearly 600-fold increase in rate observed when the isopropylidene groups of **2b** are replaced by cyclic carbonate groups (**7**) seems rather startling. However, if the dioxolanone rings of **7** have a requirement for being nearly planar, this would probably force the cyclohexane ring into the $^1S_3$ conformation **29**. In this form, the *syn*-axial effect, and the polar effect as well[7], appear to be completely absent. This may suffice to explain why the reaction rate of **7** is in the range for unhindered primary sulfonates[2], or an electronic effect of the cyclic carbonate group at positions 1 and 2 may contribute to the elevated rate.

The *O*-methyl-*allo*-inositol derivatives, including those (**13a** and **18**) having individual substituents on each oxygen atom all reacted at modest rates. Whichever

chair form is the favored ground-state conformation of these compounds, it may be assumed that the form shown in **30** is the reactive one. In the alternative chair conformation, the substituent at position 6 would offer *syn*-axial interference to the incoming azide ion.

The inosamines obtained (as the pentaacetates **21** and **26**) from the azidocyclitols described here may be of interest in relation to the chemistry of aminoglycoside antibiotics. The racemic parent inosamine related to **26** has been described by Nakajima *et al.*[10] under the name *rac*-inosamine-5, but the parent inosamine related to **21** has apparently not been made.

## EXPERIMENTAL

*General methods.* — Thin layer chromatography plates were prepared from Silica Gel G (Merck) and developed with 1:9 (v/v) ethanol–Skellysolve B. Column chromatography was performed on silica gel (Merck), with 1:5:5 (v/v/v) acetone–benzene–Skellysolve B as the developing solvent, unless otherwise specified. Melting points were determined in Pyrex glass capillaries immersed in a heated oil bath equipped with a calibrated thermometer. P.m.r. spectra were recorded with Varian A-60 or T-60 spectrometers, with tetramethylsilane as internal reference ($\tau = 10.0$). Infrared spectra were recorded on a Beckman IR-5 spectrometer. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter. The procedure for the measurement of reaction rates was given in the previous paper[2].

*Known compounds.* — 1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-*p*-tolylsulfonyl-*chiro*-inositol[11] (**2a**) and 1D-3-*O*-*p*-bromophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol[2] (**2b**) were prepared from 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-*chiro*-inositol (**1**, "diisopropylidenepinitol")[12]. Compound **1** was made by the procedure of Angyal and Hoskinson[13], with 2,2-dimethoxypropane as the acetonating agent. The tosyl ester **2a** was converted successively into 1D-3-*O*-methyl-4-*O*-*p*-tolylsulfonyl-*chiro*-inositol[11] (**3a**) and 1D-1,2,5,6-tetra-*O*-acetyl-3-*O*-methyl-4-*O*-*p*-tolylsulfonyl-*chiro*-inositol[11] (**6a**).

*Hydrolysis of O-isopropylidene derivatives.* — To a solution of 1 to 2 g of the isopropylidene acetal in 1,4-dioxane (50 ml), concentrated hydrochloric acid (1 ml) was added. The solution was refluxed for 2 h, cooled to room temperature, and neutralized with solid sodium hydrogen carbonate. The solid material was filtered off and the filtrate was deionized with Amberlite MB-3 mixed-bed ion-exchange resin, and then evaporated to dryness.

*Acetylation.* — The hydroxyl compound was treated with 5–10 times the calculated amount of acetic anhydride in 5–10 volumes (based on hydroxyl compound) of pyridine for 4 h at room temperature, and then the mixture was stirred into ice and water to precipitate the product.

Sulfonylations were preformed by treating the respective hydroxyl compounds with an excess of *p*-toluenesulfonyl or *p*-bromobenzenesulfonyl chloride in 2–10 volumes (based on hydroxyl compound) of pyridine at room temperature.

*Azides from sulfonates.* — Sufficient sodium azide to leave an excess undissolved at the end of the reaction[2] was added to a solution of the sulfonate in 2–10 vols. of *N,N*-dimethylformamide. The mixture was heated at 110° with magnetic stirring until t.l.c. showed completion of the reaction. The solvent was removed by means of a rotary evaporator (50°, 20 torr) and the residue was extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate and evaporated to yield the crude product.

*1D-3-O-p-Bromophenylsulfonyl-4-O-methyl-chiro-inositol* (**3b**). — Hydrolysis of the isopropylidene acetal **2b** by the general procedure already given gave **3b** in 85% yield. It was recrystallized from water–ethanol; m.p. 188° (dec.), $[\alpha]_{589}$ +27.3° (*c* 2, $HCONMe_2$); p.m.r. ($CDCl_3$): $\tau$ 2.16 (s, 4, Ph-*H*) and 6.90 (s, 3, $OCH_3$).

*Anal.* Calc. for $C_{13}H_{17}BrO_8S$ (413.25): C, 37.78; H, 4.15. Found: C, 37.93; H, 4.23.

*1D-1,2,5,6-Tetra-O-acetyl-3-O-p-bromophenylsulfonyl-4-O-methyl-chiro-inositol* (**6b**). — This compound was obtained by acetylation (general procedure already given) of **3b**. Recrystallization from ethanol gave pure **6b**; m.p. 174–176°, $[\alpha]_{589}$ −23.8° (*c* 4, chloroform); $\nu_{max}^{KBr}$ 1780 $cm^{-1}$ (C=O); p.m.r. ($CDCl_3$): $\tau$ 2.22, 2.34 ($q_{AB}$, 4, *J* 9 Hz, Ph-*H*), 6.85 (s, 3, $OCH_3$), 7.82 (s, 3), 7.86 (s, 3), 7.99 (s, 3), and 8.02 (s, 3) ($CH_3CO$).

*Anal.* Calc. for $C_{21}H_{25}BrO_{12}S$ (581.38): C, 43.39; H, 4.33. Found: C, 43.45; H, 4.45.

*1D-3-O-p-Bromophenylsulfonyl-1,2:5,6-di-O-carbonyl-4-O-methyl-chiro-inositol* (**7**). — Application of the procedure of Doane *et al.*[3] to 4.1 g (10 mmole) of **3b** gave the crude title compound in 89% yield. After recrystallization from benzene, the compound had m.p. 151–154°, $[\alpha]_{589}$ +52.6° (*c* 1, chloroform); $\nu_{max}^{KBr}$ 1820 $cm^{-1}$ (cyclic C=O); p.m.r. ($CDCl_3$): $\tau$ 2.22 (s, 4, Ph-*H*) and 6.53 (s, 3, $OCH_3$).

*Anal.* Calc. for $C_{15}H_{13}BrO_{10}S$ (465.24): C, 38.72; H, 2.82. Found: C, 39.16; H, 3.11.

*1D-3-O-Benzyl-1,2,4,5,6-penta-O-methyl-chiro-inositol* (**8**) *and its debenzylation.* — A mixture of diisopropylidenepinitol (**1**, 7.5 g, 27.3 mmole), powdered potassium hydroxide (20 g), and 1,4-dioxane (35 ml) was efficiently stirred and slowly warmed to the boiling point while α-chlorotoluene (12.5 ml) was added dropwise. Heating and stirring were continued for 2 h after the addition had been completed. The mixture was cooled to ~70°, and then steam-distilled to remove 1,4-dioxane, α-chlorotoluene and benzyl alcohol. The distilland was extracted with chloroform (3 × 50 ml) and the chloroform extract was washed with water, 10% sulfuric acid, and water. After drying over anhydrous sodium sulfate, the chloroform was evaporated off to give 8.0 g (80%) of syrupy 1D-3-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol (**4**); p.m.r. ($CDCl_3$): $\tau$ 2.66 (ps, 5, Ph-*H*), 5.19 (s, 2, $PhCH_2$), 6.40 (s, 3, $OCH_3$), 8.50, 8.53, and 8.67 (3 s, total 12, C–$CH_3$).

Compound **4** (3.6 g, 9.9 mmole) was hydrolyzed according to the general procedure already given. Evaporation of the deionized hydrolyzate gave 2.5 g (89%) of 1D-3-*O*-benzyl-4-*O*-methyl-*chiro*-inositol (**5**). The compound was a syrup at first, but it crystallized on being kept overnight. It was not further purified; p.m.r. [$D_2O$,

sodium 4,4-dimethyl-4-silapentane-1-sulfonate (DSS) as internal standard]: $\tau$ 2.57 (ps, 5, Ph-*H*), 5.20 (s, 2, PhC$H_2$), and 6.40 (s, 3, OC$H_3$).

For methylation, a solution of 1 g (3.5 mmoles) of **5** in 20 ml of *N,N*-dimethylformamide was cooled (ice bath) and stirred with barium oxide (5 g) and barium hydroxide (2 g) while iodomethane (5 ml) was added dropwise. The reaction was continued for 5 h, at 0°, and then overnight at room temperature. The mixture was poured into ice–water (50 ml) and extracted with chloroform. The extract was washed with water, 10% sulfuric acid, saturated sodium hydrogen carbonate, and water. After drying over sodium sulfate, the solvent was evaporated off to give 1.0 g (83%) of the title compound (**8**) as a thick syrup. This syrup was further purified by column chromatography; $[\alpha]_{589}$ +27.9° (*c* 3, chloroform); p.m.r. ($CDCl_3$): $\tau$ 2.67 (m, 5, Ph-*H*), 5.20 (s, 2, PhC$H_2$), 6.31, 6.42, and 6.55 (3 s+m, 21, OC$H_3$ and ring *H*).

*Anal.* Calc. for $C_{18}H_{28}O_6$ (340.40): C, 63.51; H, 8.29. Found: C, 62.90; H, 8.00.

The purified compound **8**, less samples for analysis, was dissolved in 20 ml of chloroform in a beaker, and the solution was cooled in an ice bath. Bromine (0.2 ml) was added and the solution was irradiated with a 60-watt incandescent bulb for 3 h. The solvent and bromine were removed, and then the residue was extracted with chloroform. After drying over sodium sulfate, the chloroform was evaporated, leaving syrupy 1D-1,2,3,5,6-penta-*O*-methyl-*chiro*-inositol (**9**); $\nu_{max}^{film}$ 3500 $cm^{-1}$ (OH); p.m.r. ($D_2O$, DSS as internal standard): $\tau$ 6.46 (s), 6.55 (s), and 6.64 (s) (OC$H_3$), no Ph-*H*.

*1*D-*3*-O-p-*Bromophenylsulfonyl-1,2,4,5,6-penta*-O-*methyl*-chiro-*inositol* (**10**). — This product was prepared from compound **9** by the general procedure for sulfonylation already given, The crude syrupy product was purified on a column of silica gel, with 1:5:5, (v/v/v) acetone–benzene–Skellysolve B as eluant. Recrystallized from ethanol, it had m.p. 78–80°, $[\alpha]_{589}$ +33.2° (*c* 1, chloroform); i.r., no OH; m.p.r. ($CDCl_3$): $\tau$ 2.22, 2.36 ($q_{AB}$, 4, *J* 9 Hz, Ph-*H*), 5.42–5.50 (m, 1, H-4), and 6.43–6.90 (m, 20, OC$H_3$ and ring-*H*).

*Anal.* Calc. for $C_{17}H_{25}BrO_8S$ (469.35): C, 43.50; H, 5.37. Found: C, 43.38; H, 5.45.

*1*D-*1,2:5,6-Di*-O-*isopropylidene-4*-O-*methyl-3*-O-p-*tolylsulfonyl*-allo-*inositol* (**12a**). — Prepared from compound **11** (see under **15**, later) and recrystallized from ethanol, it had m.p. 136–139°, $[\alpha]_{589}$ +34.7° (*c* 2, chloroform); p.m.r. ($CDCl_3$): $\tau$ 2.08, 2.58 ($q_{AB}$, 4, *J* 9 Hz, Ph-*H*), 6.60 (s, 3, OC$H_3$), 7.54 (s, 3, Ph-C$H_3$), 8.55 (s, 3), 8.65 (s, 3), and 8.68 (s, 6) (C–C$H_3$).

*Anal.* Calc. for $C_{20}H_{28}O_8S$ (428.48): C, 56.06; H, 6.59. Found: C, 55.94; H, 6.53.

*1*L-*2*-O-p-*Bromophenylsulfonyl-3,4:5,6-di*-O-*isopropylidene-1*-O-*methyl*-allo-*inositol* (**12b**). — Prepared from compound **11** (see under **15**, later) as a syrup, purified by column chromatography on silica gel, it had $[\alpha]_{589}$ +22.7° (*c* 2, chloroform); p.m.r. ($CDCl_3$): $\tau$ 2.22, 2.37 ($q_{AB}$, 4, *J* 9 Hz, Ph-*H*), 6.70 (s, 3, OC$H_3$), 8.60 (s, 3), 8.70 (s, 3), and 8.74 (s, 6) (C–C$H_3$).

*Anal.* Calc. for $C_{19}H_{25}BrO_8S$ (493.37): C, 46.25; H, 5.11. Found: C, 46.77; H, 5.69.

*1L-2-O-p-Bromophenylsulfonyl-1-O-methyl-allo-inositol.* — On storage for some months a sample of compound **12b** was converted into a crystalline brei. This was dissolved in hot ethyl acetate, and on the addition of Skellysolve B the solution deposited crystals of the title compound. After two recrystallizations, the second from abs. ethanol, the compound had m.p. 157–158° (dec.), $[\alpha]_{589}$ +21.4°, $[\alpha]_{436}$ +42.6° (*c* 1.6, acetone); p.m.r. [$(CD_3)_2CO$]: $\tau$ 2.03 (s, 4, Ph-*H*), 4.87 (m, 1, H-2), 5.70–6.57 (m, 8, 5 ring *H*+3 O*H*), 6.58 (s, 3, $OCH_3$), and 7.15 (bs, $H_2O$+1 O*H*?).

*Anal.* Calc. for $C_{13}H_{17}BrO_8S$ (413.25): C, 37.78; H, 4.15; S, 7.76. Found: 37.65; H, 4.16; S, 7.46.

*1D-1,2,5,6-Tetra-O-acetyl-4-O-methyl-3-O-p-tolylsulfonyl-allo-inositol* (**13a**). — This compound was prepared from **12a** as already described for the sequence **2b** → **3b** → **6b**. The intermediate 1L-1-*O*-methyl-2-*O*-*p*-tolylsulfonyl-*allo*-inositol was not purified. When recrystallized from ethanol, the compound gave a single spot on t.l.c., m.p. 167–169°, $[\alpha]_{589}$ −18.8° (*c* 2, chloroform); p.m.r. ($CDCl_3$): $\tau$ 2.08, 2.57 ($q_{AB}$, 4, *J* 9 Hz, Ph-*H*), 6.65 (s, 3, $OCH_3$), 7.53 (s, 3, Ph-$CH_3$), 7.91 (s, 6), 7.94 (s, 3), and 7.97 (s, 3) ($CH_3CO$).

*Anal.* Calc. for $C_{22}H_{28}O_{12}S$ (516.50): C, 51.16; H, 5.46. Found: C, 52.03, 51.68; H, 5.47, 5.58. (The analytical samples were possibly contaminated with decolorizing carbon).

*1D-1,2,5,6-Tetra-O-acetyl-3-O-p-bromophenylsulfonyl-4-O-methyl-allo-inositol* (**13b**). — Crude *O*-brosyl-*O*-methyl-*allo*-inositol was obtained by the hydrolysis of **12b**. It was acetylated (general procedure) and recrystallized from ethanol; m.p. 193–194°, $[\alpha]_{589}$ −20.1°, $[\alpha]_{436}$ −51.5° (*c* 1, chloroform); p.m.r. ($CDCl_3$): $\tau$ 2.28, 2.37 ($q_{AB}$, 4, *J* 9 Hz, Ph-*H*), 6.78 (s, 3, $OCH_3$), 7.92 (s, 6), 7.95 (s, 3), and 8.00 (s, 3) ($COCH_3$).

*Anal.* Calc. for $C_{21}H_{25}BrO_{12}S$ (581.39): C, 43.38; H, 4.33. Found: C, 43.69; H, 4.46.

*1L-2-O-benzyl-1-O-methyl-allo-inositol* (**15**) *and its methylation and debenzylation.* — The known 1L-2-*O*-benzoyl-3,4:5,6-di-*O*-isopropylidene-1-*O*-methyl-*allo*-inositol was prepared[4] by refluxing compound **2b** in *N*,*N*-dimethylformamide with sodium benzoate for 12 h. The benzoate (5.7 g, 1.5 mmole) was kept overnight at room temperature in 40 ml of methanol containing the methoxide from 0.4 g of sodium. The solution was neutralized with Amberlite IRC-120 ($H^+$), and then evaporated *in vacuo* to give 1D-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*allo*-inositol (**11**) as a colorless syrup; yield 3.8 g (93%); $\nu_{max}^{film}$ 3500 $cm^{-1}$ (OH); p.m.r. ($CDCl_3$): $\tau$ 6.50 (s, 3, $OCH_3$), 8.46 (s, 3), 8.50 (s, 3), and 8.62 (s, 6) (C–$CH_3$).

Treatment of **11** with $\alpha$-chlorotoluene and potassium hydroxide (compare compound **8**) gave syrupy 1L-2-*O*-benzyl-3,4:5,6-di-*O*-isopropylidene-1-*O*-methyl-*allo*-inositol (**14**); $[\alpha]_{589}$ +11.6° (*c* 8, chloroform); p.m.r. ($CDCl_3$): $\tau$ 2.66 (s, 5, Ph-*H*), 5.30 (s, 2, $PhCH_2$), 6.62 (s, 3, $OCH_3$), 8.50, and 8.63 (2 s, 6 ea., C–$CH_3$).

The title compound **15** was obtained from **14** by the general procedure for the

hydrolysis of isopropylidene acetals. After recrystallization from ethanol, compound **15** had m.p. 131–133°; $[\alpha]_{589}$ +35.3° (*c* 1, $HCONMe_2$); p.m.r. [$(CD_3)_2SO$, DSS as standard]: $\tau$ 2.60 (s, 5, Ph-*H*), 5.33 (s, 2, $PhCH_2$), and 6.60 (s, 3, $OCH_3$).

*Anal.* Calc. for $C_{14}H_{20}O_6$ (284.30): C, 59.14; H, 7.09. Found: C, 59.66; H, 7.31.

Methylation of **15** was performed as described for the preparation of **8**. The product, 1L-2-*O*-benzyl-1,3,4,5,6-penta-*O*-methyl-*allo*-inositol (**16**) was a syrup; p.m.r. ($CDCl_3$): $\tau$ 2.65 (m, 5, Ph-*H*), 5.30 (s, 2, $PhCH_2$), and 6.20–6.50 (m, 21, $OCH_3$ and ring-*H*).

Compound **16** was debenzylated in the same way as its *chiro* analog (compare **8**). The product, 1D-1,2,4,5,6-penta-*O*-methyl-*allo*-inositol (**17**) was again a syrup. The absence from the p.m.r. spectrum of signals for aromatic and benzyl-methylene protons verified the loss of the *O*-benzyl group.

*1L-2-*O*-p-Bromophenylsulfonyl-1,3,4,5,6-penta-*O*-methyl-*allo*-inositol* (**18**). — Prepared from compound **17** by the standard procedure for sulfonylation, compound **18** was obtained as a syrup; one spot on t.l.c. after purification by column chromatography; $[\alpha]_{589}$ +17.1° (*c* 1, chloroform); p.m.r. ($CDCl_3$): $\tau$ 2.22, 2.36 ($q_{AB}$, 4, *J* 9 Hz, Ph-*H*), and 6.43–6.66 (m, 21, $OCH_3$ and ring *H*).

*Anal.* Calc. for $C_{17}H_{25}BrO_8S$ (469.35): C, 43.50; H, 5.37. Found: C, 44.70; H, 5.32. (Possible contamination by the chromatographic solvent; 3% would give the observed carbon value.)

*1L-2-Azido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-1-*O*-methyl-*allo*-inositol* (**19**). — This compound was obtained from **2b** by the general procedure given for azides. Purification by vacuum distillation (b.p. 115–120°, 0.5 torr) gave the compound as a yellowish syrup in 84% yield; $[\alpha]_{589}$ +90.3° (*c* 2, $HCONMe_2$); $\nu_{max}^{film}$ 2100 $cm^{-1}$ ($N_3$); p.m.r. ($CDCl_3$): $\tau$ 6.55 (s, 3, $OCH_3$), 8.46 (s, 3), 8.55 (s, 3), and 8.67 (s, 6) ($C-CH_3$), no Ph-*H*.

*Anal.* Calc. for $C_{13}H_{21}N_3O_5$ (299.32): C, 52.16; H, 7.07. Found: C, 51.94; H, 7.38.

*1D-1,2,5,6-Tetra-*O*-acetyl-3-azido-3-deoxy-4-*O*-methyl-*allo*-inositol* (**20**). — *A. From* **19**. Compound **19** was treated according to the general procedure for the hydrolysis of isopropylidene acetals, and the syrupy product was acetylated. The title compound precipitated when the acetylation mixture was poured into ice–water and was recrystallized from ethanol, yield 83%; m.p. 153–155°, $[\alpha]_{589}$ −41.5° (*c* 2, chloroform); $\nu_{max}^{KBr}$ 2100 ($N_3$) and 1750 $cm^{-1}$ (C=O); p.m.r. ($CDCl_3$): $\tau$ 6.47 (s, 3, $OCH_3$), 7.90 (s, 3), 7.92 (s, 3), and 7.97 (s, 6) ($CH_3CO$), no Ph-*H*.

*Anal.* Calc. for $C_{15}H_{21}N_3O_9$ (387.34): C, 46.51; H, 5.47. Found: C, 46.95; H, 5.80.

*B. From* **22**. A sample of **22** was saponified with methanolic sodium methoxide, and the residue was acetylated. After recrystallization, the product had m.p. 153–155°, undepressed on admixture with the product from **19**. The i.r. and p.m.r. spectra were identical with those of the product from **19**.

*1L-2-Acetamido-3,4,5,6-tetra-*O*-acetyl-2-deoxy-1-*O*-methyl-*allo*-inositol* (**21**). — Compound **20** (0.5 g) was dissolved in acetic acid (20 ml) and acetic anhydride (5 ml)

The solution was stirred with palladium on charcoal (0.5 g, 5% Pd) under hydrogen gas at atmospheric pressure. After 5 h of reaction, the catalyst was filtered off and the solvent was evaporated. The residue was dissolved in chloroform and the solution washed with sodium hydrogencarbonate. The residue obtained after evaporation of the chloroform was recrystallized from ethanol; yield 0.5 g (96%); m.p. 210°, $[\alpha]_{589}$ −13.1° (*c* 2, chloroform); $\nu_{max}^{KBr}$ 3350 (NH) and 1700 $cm^{-1}$ (C=O); p.m.r. ($CDCl_3$): $\tau$ 3.95 (d, 1, *J* 10 Hz, NH), 5.27–5.63 (m, 1, H-2), 7.87 (s, 3), 7.89 (s, 3), 8.00 (s, 3), and 8.04 (s, 6) ($CH_3CO$); after addition of a few drops of $CF_3CO_2H$ and $D_2O$: $\tau$ 5.42 (t, 1, *J* 4 Hz, H-2), no signal at $\tau$ 3.95.

*Anal.* Calc. for $C_{17}H_{25}NO_{10}$ (403.38): C, 50.62; H, 6.25. Found: C, 51.04; H, 6.35.

*1L-2-Azido-3,4:5,6-di-*O*-carbonyl-2-deoxy-1-*O*-methyl-*allo*-inositol* (**22**). — From compound **7**. Purification by column chromatography gave a syrup that crystallized after storage for several months. Recrystallization was from ethyl acetate–Skellysolve B; m.p. 120–121°; $[\alpha]_{589}$ +87° (*c* 4, acetone); $\nu_{max}^{KBr}$ 2130 ($N_3$), and 1800 $cm^{-1}$ (cyclic C=O); p.m.r. ($CDCl_3$): $\tau$ 6.47 (s, 3, $OCH_3$), no Ph-*H*.

*Anal.* Calc. for $C_9H_9N_3O_7$ (271.18): C, 39.85; H, 3.34. Found: C, 39.60; H, 3.21.

*1D-3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol* (**23**) — *From* **12a**. The product was recrystallized from ethanol; m.p. 68–70°, $[\alpha]_{589}$ +71.2° (*c* 2, chloroform); $\nu_{max}^{KBr}$ 2100 $cm^{-1}$ ($N_3$); p.m.r. ($CDCl_3$): $\tau$ 6.33 (s, 3, $OCH_3$), 8.47 and 8.63 (2 s, 6 ea., $C{-}CH_3$), no Ph-*H*.

*Anal.* Calc. for $C_{13}H_{21}N_3O_5$ (299.32): C, 52.16; H, 7.07. Found: C, 52.38; H, 7.65.

*1D-1,2,5,6-Tetra-*O*-acetyl-3-azido-3-deoxy-4-*O*-methyl-*chiro*-inositol* (**25**). — *A. From* **6b**. When treated by the general procedure for preparing azides, the brosyl ester **6b** gave a thick syrup. According to t.l.c., two major products and some minor ones were present. On column chromatography the first eluted of the major products was **25**, which could be crystallized from ethanol; m.p. 110–111°, $[\alpha]_{589}$ −9.6° (*c* 2, chloroform); $\nu_{max}^{KBr}$ 2100 ($N_3$) and 1750 $cm^{-1}$ (C=O); p.m.r. ($CDCl_3$): $\tau$ 6.22 (t, 1, *J* 9 Hz, H-3), 6.43 (s, 3, $OCH_3$), 6.58 (t, 1, *J* 9 Hz, H-4), 7.87, and 7.97 (2 s, 6 ea., $CH_3CO$), no Ph-*H*; p.m.r. ($C_6D_6$): $\tau$ 6.10 (t, 1, *J* 10 Hz, H-3), 6.47 (t, 1, *J* 10 Hz, H-4), and 6.57 (s, 3, $OCH_3$).

*Anal.* Calc. for $C_{15}H_{21}N_3O_9$ (387.33): C, 46.51; H, 5.47. Found: C, 46.31; H, 5.62.

The second major product, eluted later from the column, failed to crystallize. The i.r. spectrum showed strong absorptions at 3300 (OH), 2100 ($N_3$), and 1750 $cm^{-1}$ (C=O). In the p.m.r. spectrum there were signals for only three acetate groups ($\tau$ 7.83, 7.88, and 7.95), and no signals for aromatic protons. The compound was, therefore, an azido-triacetate (**24**). Acetylation of this product gave **25**.

*B. From* **13a** *and* **13b**. These two sulfonates, on conversion into azides by the standard procedure, gave products melting at 110–111°. The i.r. and p.m.r. spectra were identical with those just described for **25** made from **6b**.

*C. From* **23.** Hydrolysis of **23** and acetylation of the hydrolyzed product gave a product having m.p. 110–111°; i.r. and p.m.r. spectra identical with those just described.

*1D-3-Acetamido-1,2,5,6-tetra-*O*-acetyl-3-deoxy-4-*O*-methyl-*chiro*-inositol* (**26**).— This compound was obtained from **25** by the procedure described for compound **21.** It was recrystallized from ethanol; m.p. 78–80°, $[\alpha]_{589}$ −20.0° (*c* 1, chloroform); $\nu_{max}^{KBr}$ 3350 (NH) and 1720 $cm^{-1}$ (C=O); p.m.r. ($CDCl_3$): $\tau$ 4.11 (d, 1, *J* 10 Hz, N*H*), 5.70 (m, 1, H-3), 6.35 (t, 1, *J* 10 Hz, H-4), 6.55 (s, 3, OC$H_3$), 7.84 (s, 3), 7.96 (s, 3), 7.98 (s, 6), and 8.00 (s, 3) (C$H_3$CO); after the addition of a few drops of $CF_3CO_2H$ and $D_2O$: $\tau$ 5.70 (t, 1, *J* 10 Hz, H-3), no signal at 4.11.

*Anal.* Calc. for $C_{17}H_{25}NO_{10}$ (403.38): C, 50.62; H, 6.25. Found C, 50.23; H, 6.27.

*1D-3-Azido-3-deoxy-1,2,4,5,6-penta-*O*-methyl-*chiro*-inositol* (**27**). — This compound was obtained from **18** by the general procedure for the preparation of azides, and it was purified by column chromatography; $[\alpha]_{589}$ +28.3° (*c* 0.3, chloroform); $\nu_{max}^{film}$ 2100 $cm^{-1}$ ($N_3$); p.m.r. ($CDCl_3$): $\tau$ 6.10–6.70 (m), no other signals.

*Anal.* Calc. for $C_{11}H_{21}N_3O_5$ (275.30): C, 47.99; H, 7.69. Found: C, 48.44; H, 7.75.

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-p-bromophenylsulfonyl-α-*D*-glucopyranoside.* — Obtained by the sulfonylation of methyl 2,3,6-tri-*O*-benzoyl-α-D-glucopyranoside (prepared by the selective benzoylation of methyl α-D-glucopyranoside[14]) and recrystallized from ethanol–chloroform, this compound had m.p. 161–162°, $[\alpha]_{589}$ +81.3° (*c* 2, chloroform); p.m.r. ($CDCl_3$): $\tau$ 1.80–2.87 (m, 19, Ph-*H*), and 6.60 (s, 3, OC$H_3$).

*Anal.* Calc. for $C_{34}H_{29}BrO_{11}S$ (725.55): C, 56.28; H, 4.03. Found: C, 56.87; H, 4.32.

The syrupy azide from methyl 2,3,6-tri-*O*-benzoyl-4-*O*-brosyl-α-D-glucopyranoside was purified by column chromatography and then debenzoylated in methanol–sodium methoxide to give the known methyl 4-azido-4-deoxy-α-D-galactopyranoside, m.p. 152–154° (lit.[15] 153–155°).

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-p-bromophenylsulfonyl-α-*D*-galactopyranoside.* — Obtained by sulfonylation of methyl 2,3,6-tri-*O*-benzoyl-α-D-galactopyranoside (prepared by the selective benzoylation of methyl α-D-galactopyranoside[14]) and recrystallized from ethanol, this product had $[\alpha]_{589}$ +101° (*c* 2, chloroform); p.m.r. ($CDCl_3$): $\tau$ 1.80–2.80 (m, 19, Ph-*H*), 4.77 (d, 1, *J* 4 Hz, H-1), and 6.57 (s, 3, OC$H_3$).

*Anal.* Calc. for $C_{34}H_{29}BrO_{11}S$ (725.55): C, 56.28; H, 4.03. Found: C, 55.80; H, 3.96.

The syrupy azide from methyl 2,3,6-tri-*O*-benzoyl-4-*O*-brosyl-α-D-galactopyranoside was purified by column chromatography and then debenzoylated in methanol–sodium methoxide to give the known methyl 4-azido-4-deoxy-α-D-glucopyranoside, m.p. 108–110° (lit.[16] 108–109°).

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