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PREFERENTIAL SULFONYLATION OF METHYL 2,6-DI-*O*-MESYL-α-D-GLUCOPYRANOSIDE

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ABSTRACT

When equimolar ratios of mesyl chloride and methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside were allowed to react in pyridine and the product resolved by preparative t.l.c., the 2,6-di-, 2,3,6-tri-, 2,4,6-tri-, and 2,3,4,6-tetra-mesyl esters were obtained in (0.5–0.6):1:(4–5):(1.2–1.4) molar ratio. Benzoylation of either the isolated 2,4,6-tri-*O*-mesyl ester or, more conveniently, the mixture from monomesylation gave the crystalline methyl 3-*O*-benzoyl-2,4,6 -tri*O*-mesyl-α-D-glucopyranoside (**8**). As both of these trimesyl esters (**7** and **8**) are unreported, isolation of the benzoate established the 2,4,6-ester arrangement, and the 2,3,6-triester was prepared by standard methods. Treating methyl α-D-glucopyranoside with 3 molar equivalents of mesyl chloride and, subsequently, with 1 molar equivalent of benzoyl chloride, proved a convenient method for preparing the 3-*O*-benzoyl derivative in moderate yield. Monotosylation of methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside was not so definitive as mesylation, but a molar ratio of 1:2.8 for the 3-*O*-tosyl:4-*O*-tosyl product was derived from n.m.r. data. This work, when combined with literature reports, establishes that, in methyl α-D-glucopyranoside, the reactivity toward sulfonylation is 6-OH>2-OH>4-OH>3-OH.

INTRODUCTION

Several articles[1] review the preferential reactivity of the hydroxyl groups in carbohydrates. In general, a primary hydroxyl group is esterified and etherified in preference to a secondary hydroxyl group. Triphenylmethyl (trityl) ethers[1d], formed by the action of chlorotriphenylmethane in pyridine, are prepared readily with practically no reaction at a secondary hydroxyl group. Esterification does not present the specificity of trityl ether formation; nevertheless, many examples of selective esterification have been reported[1b,c;2].

The question of relative reactivity of the ring hydroxyl groups in carbohydrates remains unsettled. With methyl α-D-glucopyranoside, 2 molar equivalents of

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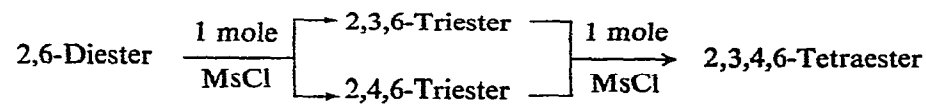
methanesulfonyl (mesyl) chloride in pyridine gives the 2,6-di-*O*-mesyl derivative in 51% yield, whereas the β-anomer under similar conditions gives five products, none in greater than 13% yield[3]. Dimesylation of methyl α-D-galactopyraoside gave a mixture of 2,3,6-tri-*O*-mesyl (10%), 2,6-di-*O*-mesyl (20%), and 3,6-di-*O*-mesyl (4%) derivatives and the β-anomer gave 26% of the 3,6-di-*O*-mesyl derivative[3b]. Several workers[4] have reported a difference in reactivity between the 2 and 3 hydroxyl groups on monosulfonylation of the α- and β-anomers of methyl 4,6-*O*-benzylidene-D-glucopyranoside with mesyl chloride or *p*-toluenesulfonyl (tosyl) chloride. Monosulfonylation of the β-anomer gave a mixture of the 2-, 3-, and 2,3-esters, whereas the α-anomer gave only the 2-ester[4a]. From competitive experiments using a 1:1:1 molar ratio of α-anomer:β-anomer:tosyl chloride, Guthrie and coworkers[4a] demonstrated that the 2-hydroxyl group of both anomers was the more reactive. On monotosylation, methyl 6-*O*-trityl-α-D-mannopyranoside gave mainly the 3-ester[5].

Using benzoyl chloride in pyridine on the methyl α-D-pyranosides of glucose, mannose, and galactose, Williams and Richardson[2b] concluded that the reactivity of the secondary hydroxyl groups was in the order: 2>3>4 for glucose, 3>2>4 for mannose, and 2≈3>4 for galactose. With methyl 6-deoxy-α-D-glucopyranoside, an order of reactivity of the secondary hydroxyl groups 2-OH>3-OH>4-OH was noted[2f]. Acyl migration[1a,2a] in carbohydrate esters, and variation in products on using different esterifying reagents and catalysts[4d,6] point out that factors contribute in ways not fully understood to the relative reactivity of ring-hydroxyl groups in carbohydrates.

In methyl α-D-glucopyranoside, the hydroxyl groups show the reactivity order 6>2 (refs. 2c, 3a) toward sulfonylation. No report has been found on the relative reactivity of the 3 and 4 ring hydroxyl groups. As mesyl and tosyl chloride exhibit a reactivity in carbohydrates similar to that of benzoyl chloride, it seemed plausible to expect that the 3-OH group would be more reactive than the 4-OH group[2b]. To establish if, indeed, the sequence of reactivity is followed in methyl α-D-glucopyranoside, monomesylation was performed on the known methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside.

RESULTS AND DISCUSSION

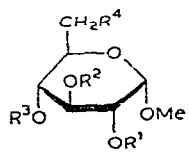
Monomesylation of methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside with mesyl chloride in pyridine gave a mixture showing four well-defined spots on t.l.c. The slowest-migrating one was identified as unchanged 2,6-dimesyl ester and the fastest as the 2,3,4,6-tetramesyl ester by comparing the R_F values with known compounds. That the two intermediate spots were trimesyl esters was confirmed when subsequent addition of 1.05 molar equivalents of mesyl chloride to the mixture gave only the 2,3,4,6-tetramesyl ester (>90% yield). The reaction scheme is as shown:



As both the 2,3,6- and 2,4,6-trimesyl esters of methyl α-D-glucopyranoside are unreported, no chromatographic standard was available. A synthesis of the 2,3,6-triester was conducted by standard methods: methyl 4,6-*O*-benzylidene-2,3-di-*O*-mesyl-α-D-glucopyranoside was debenzylidenated and the product monomesylated to give methyl 2,3,6-tri-*O*-mesyl-α-D-glucopyranoside.

A mixture resulting from the monomesylation of methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside was developed chromatographically with the known 2,3,6-trimesyl ester, and the minor, slower-moving intermediate spot was identified as this 2,3,6-triester. As a result, the predominant, faster-moving intermediate component was assigned as the 2,4,6-triester.

Preparative t.l.c. was used to resolve the mixture. Even with multiple ascents, overlap of the two triesters on 2-mm thick plates prevented clean separation. Plates of 0.25-mm thickness proved satisfactory for multiple ascents, but were restricted to a 10–15 mg load per plate. After development, the components were excised and isolated as syrups, which usually crystallized in the case of the 2,6-di-, 2,3,6-tri-, and 2,3,4,6-tetraesters. The 2,4,6-triester, on prolonged vacuum pumping, was obtained as a slightly hygroscopic foam. Recovery varied between 70 and 80% (molar basis) and afforded an individual ratio of (0.5–0.6):1:(4–5):(1.2–1.4) (molar basis), respectively, for the 2,6, 2,3,6-, 2,4,6-, and 2,3,4,6-esters. N.m.r. spectroscopy (Table I)



No.	R^1	R^2	R^3	R^4	*No.*	R^1	R^2	R^3	R^4
1	H	H	H	OH	9	Ms	Ms	Ms	OMs
2	H	H	—PhCHO—		10	Ms	Ms	Ac	OAc
3	Ms[a]	Ms	—PhCHO—		11	Ms	Bz	Ms	Cl
4	Ms	Ms	H	OH	12	Ms	Bz	Ts	OMs
5	Ms	Ms	H	OMs	13	Ms	Ts	Bz	OMs
6	Ms	H	H	OMs	14	Bz	Bz	Ms	OMs
7	Ms	H	Ms	OMs	15	Ms	Bz	Bz	OMs
8	Ms	Bz	Ms	OMs					

[a]Ms = methanesulfonyl, Ts = *p*-tolylsulfonyl, Bz = benzoyl, Ac = acetyl.

further confirmed the assignment of the 2,3,6- and 2,4,6-trimesyl esters. When differences in the H-3 and H-4 lines of the 2,6-di-, 2,3,6-tri-, and 2,4,6-tri-*O*-mesyl esters are compared, the data follow an expected pattern–the mesyl esters cause a downfield shift of the proton attached to the alcoholic carbon atom.

Benzoylation of the 2,4,6-triester gave a syrup, resolved by preparative t.l.c. into a slow-moving, major component characterized as methyl 3-*O*-benzoyl-2,4,6-tri-*O*-mesyl-α-D-glucopyranoside (8) and a faster-moving, minor one identified as

TABLE I

N.M.R. DATA FOR VARIOUS MESYL DERIVATIVES OF METHYL α-D-GLUCOPYRANOSIDE

Compound No.	*Chemical shifts (δ units)*							*Solvent*
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6,6'*	*Methyl*	
4	5.37	5.08	5.52	~4.2	4.02	~4.2	3.31 3.46 3.48	P[a]
5	5.36	5.10	5.45	~4.15	~4.15	4.89	3.50 3.48 3.31 3.29	P
6	5.28	4.89	4.47	3.97	4.22	~4.9	3.43 3.34 3.27	P
7	4.92	~4.3	4.09	4.51	~4.0	~4.5	3.02 3.10 3.16 3.39	A+~30% B
8	~5.39	~5.35	6.28	5.43	~4.33	4.74 4.91	3.22 3.31 3.39(2)	P
9	~5.4	~5.15	~5.45	~5.3	~4.2	~4.7 ~4.9	3.25 3.34 3.47 3.48 3.50	P
11	5.04	4.73	5.82	4.83	~4.1	~3.8	3.50 2.82(2)	C
12[b]	4.84	4.57	5.96	4.91	~3.8	~4.3		B
14	~5.09	~5.06	5.87	4.73	~4.05	4.48 4.31	2.61 2.83 3.24	C+40% B
15	5.10	4.82	5.94	5.42	~4.2	~4.2	2.84 2.99	C

[a] P = pyridine-d_5, A = acetonitrile-d_3, B = benzene-d_6, C = chloroform-d. [b] Peaks selected from mixture (see text).

methyl 6-deoxy-3-*O*-benzoyl-6-chloro-2,4-di-*O*-mesyl-α-D-glucopyranoside (**11**). Displacement of the 6-*O*-mesyl group proved a serious side-reaction during benzoylation of the triester. If a large excess of benzoyl chloride was used, or if the mixture was kept for more than 24 h at room temperature, or the temperature was greater than 30°, a fast-migrating spot on t.l.c. invariably appeared.

Methyl 2,4,6-tri-*O*-mesyl-α-D-glucopyranoside was conveniently isolated as its 3-benzoate **8** when a mixture from monomesylation of the 2,6-dimesyl ester was treated directly with benzoyl chloride. On storage, the resulting syrup slowly solidified. After purification by crystallization, the benzoate **8** was characterized by analysis and

by u.v., i.r., and n.m.r. spectroscopy. The n.m.r. spectrum confirmed the location of the benzoyl group at C-3; the deshielding effect of the ester group[2b,7] causes the H-3 signal to lie at low field (δ 6.28). Data in Table I further demonstrate the low-field position of H-3 in several related 3-*O*-benzoyl derivatives (**12**, **14**, and **15**).

As dimesylation[3a] of methyl α-D-glucopyranoside gives the 2,6-diester **6** and as the present work demonstrates that monomesylation of **6** gives mainly the 2,4,6-triester, the question arose as to whether trimesylation would give the 2,4,6-triester in acceptable yield. On treatment of methyl α-D-glucopyranoside with 3 molar equivalents of mesyl chloride, followed by 1 molar equivalent of benzoyl chloride, a 28% yield of methyl 3-*O*-benzoyl-2,4,6-tri-*O*-mesyl-α-D-glucopyranoside was obtained after four crystallizations.

Monotosylation of methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside was not as straightforward as was monomesylation. With a 1:1 molar ratio of glucoside to tosyl chloride at 0°, only a trace of reaction occurred after 1 week. Although at room temperature, some reaction was discernible after 36 h, the mixture was complex (t.l.c.), and the R_F values[8] suggested that displacement of the 6-*O*-mesyl group by chloride had occurred.

By using a 1:10 molar ratio of glucoside to tosyl chloride for 24 h and benzoylating the resultant syrup directly, a low-melting solid (40–50% yield) was obtained by preparative t.l.c. (on 0.25-mm thick plates). Analysis, although unsatisfactory for analytical purity, fitted adequately for a methyl *O*-benzoyl-di-*O*-mesyl-*O*-tosylhexoside.

N.m.r. spectroscopy of the low-melting solid allowed assignment of one low-field proton as a H-3 of the 3-*O*-benzoyl-4-*O*-tosyl isomer. Decoupling permitted assignment of the other ring protons of this isomer (Table I).

N.m.r. spectroscopy also revealed one large peak in the methyl-singlet area that was assigned the aryl methyl (tosyl) group. This assignment is presumed to be correct on the basis of its chemical shift and previous experience[9], where observations have shown that aryl methyl groups in tosylated carbohydrate derivatives rarely differ appreciably in chemical shift. Six other peaks were noted in the methyl-singlet area (methoxyl and mesyl), confirming that the low-melting solid was a mixture of the 3-benzoyl-4-tosyl and 3-tosyl-4-benzoyl esters of methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside.

A ratio of 3-*O*-tosyl to 4-*O*-tosyl isomer may be derived by comparing the integrated values for the aryl methyl protons (11.0) with the H-3 signal of the 3-*O*-benzoyl-4-*O*-tosyl isomer (2.7). Thus, H-3 of the 4-*O*-tosyl isomer would equal $(2.7/11.0) \times 3.0 = 0.74$ proton; as a result, the H-3 proton of the 3-*O*-tosyl isomer would equal $(1.0 - 0.74) = 0.26$ proton, which results in a ratio of 3-*O*-tosyl to 4-*O*-tosyl isomer of 0.26:0.74 = 1:2.8.

Exploratory studies with 2,4,6-trimethylbenzenesulfonyl (mesitylenesulfonyl) chloride and methyl 2,6-di-*O*-mesyl-α-D-glucopyranoside disclosed a reaction too slow for study.

Although the relative reactivity of the ring hydroxyl groups in methyl α-D-

glucopyranoside towards benzoylation has been reported[2b] as 2-OH>3-OH>4-OH, the results here indicate a 2-OH>4-OH>3-OH order for reactivity toward sulfonylation.

Hydrogen bonding between the 2-OH group and the glycosidic oxygen atom at C-1 is suggested[1a,c;4a] to explain the high reactivity of the 2-OH group, but this generalization leaves unexplained the selectivity of benzoylation and sulfonylation observed in methyl α-D-mannopyranoside[2b,5] and does not account for the low selectivity of benzoylation[2b] and sulfonylation[3b] of methyl α-D-galactopyranoside. Steric hindrance is suggested[2b] as a reason for the greater reactivity of the 3-OH group over 4-OH toward benzoylation in the α-glucopyranoside.

Neither from this work nor from that reported in the literature[1–6] can the relative reactivity of the ring-hydroxyl groups in carbohydrates be generalized at present with regard to anomeric configuration, stereochemistry, or reactant.

EXPERIMENTAL

General methods. — T.l.c. was performed on precoated plates of Silica Gel F-254. Layers of 0.25 mm and 2 mm were used as specified; and the plates were air-equilibrated. Spots were rendered visible either by spraying with 5% ethanolic sulfuric acid and heating until charring occurred or by viewing with a short-wavelength u.v. lamp. U.v. spectra were recorded with a Cary Model 14 spectrophotometer. I.r. spectra were determined with a Perkin–Elmer 621 spectrophotometer. N.m.r. spectra were obtained with a Varian HA-100 spectrometer. Chemical shifts were compared against internal tetramethylsilane and reported as δ values. Melting points are uncorrected. Analytical samples were dried in the presence of sodium hydroxide and sulfuric acid for 24–48 h at room temperature and 10–20 torr. Solutions were evaporated *in vacuo*.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside (**2**). — This compound was prepared by the method of Richtmyer[10].

Methyl 4,6-O-benzylidene-2,3-di-O-mesyl-α-D-glucopyranoside (**3**). — The procedure of Honeyman and Morgan[11] was followed, except that the mixture was kept for 3 days at 0°.

Methyl 2,3,4,6-tetra-O-mesyl-α-D-glucopyranoside (**9**). — Compound **9** was prepared by the method of Helferich and Gnüchtel[12].

Methyl 2,6-di-O-mesyl-α-D-glucopyranoside (**6**). — Compound **6** was prepared by the method of Mitra *et al.*[3a] with the following modifications: the reaction was maintained at 0° throughout, during a 16 to 22-h period. Mesyl chloride was added through a Hershberg dropping funnel[13], and the mixture was kept for 24 h after completing the addition.

Methyl 2,3-di-O-mesyl-α-D-glucopyranoside (**4**). — Compound **4** may be prepared by acid hydrolysis of **3**, but the following procedure avoiding isolation of **3** proved easier: A solution of **2** (30 g) in pyridine (500 ml) was cooled to 0° and mesyl

chloride (34 ml) was added dropwise. After storing for ~66 h at 0° water (10 ml + 5 ml) was added, and the mixture was briefly swirled (~15 min) before pouring it into a slush of ice–water (2 l). A solid deposited, that was filtered off and washed on the funnel with ice–water (1 liter). The solid was dissolved in warm chloroform (600 ml), and the solution was washed with water (two 250-ml portions), dried, and evaporated to an off-white solid. This solid was covered with 1,4-dioxane (300 ml) and 75mM sulfuric acid (160 ml), and the mixture was heated to boiling and maintained under reflux until t.l.c. [1:1 (v/v) benzene–ethyl acetate] indicated that hydrolysis was complete (about 2–3 h), whereupon the solution was cooled in an ice bath and 10% sodium hydrogencarbonate was added (50 ml). The filtrate was decolorized with Darco G-60 (~2 g) for 30 min and then evaporated to a semi-solid material, which was triturated with boiling ethanol (four 250-ml portions). Removal of the ethanol deposited a solid that was dissolved in boiling ethanol (200 ml) and the solution was filtered while near boiling to remove any trace of insoluble material. On cooling, crystalline **4**, m.p. 150.6°, 28.7 g (77%) separated from solution (lit.[14] m.p. 150–151°).

*Methyl 4,6-di-*O*-acetyl-2,3-di-*O*-mesyl-α-D-glucopyranoside* (**10**). — Compound **4** (5 g) was treated with acetic anhydride (25 ml) in pyridine (25 ml) for 3 h, and evaporated to a syrup that was covered with water (~300 ml), stirred well, and kept overnight at 5°. A viscous syrup settled out on storage; the upper (aqueous) layer was decanted, and the lower one dissolved in warm ethanol (~10 ml). On cooling to room temperature, crystals separated slowly. After storing overnight at 5°, the crystals were separated by filtration, washed with ice-cold ethanol (~5 ml), and air dried to give **10** (3.32 g, 53%); m.p. 87–89.9°. Additional **10** could be isolated by concentrating the filtrate and washings. (Fraser-Reid and Boctor[14] reported m.p. 79.5–80.5° for **10**, apparently a different crystalline form.)

Anal. Calc. for $C_{13}H_{22}O_{12}S_2$: C, 35.94; H, 5.10; S, 14.76. Found: C, 35.53; H, 5.16; S, 14.23.

*Methyl 2,3,6-tri-*O*-mesyl-α-D-glucopyranoside* (**5**). — A solution of **4** (3.00 g) in pyridine (20 ml) was cooled to −20°; after mesyl chloride (0.73 ml) had been added, the mixture was stored for 16 h at 5°. Pouring the mixture into ice–water gave a syrup that was extracted with chloroform (three 20-ml portions). After drying, the extract was evaporated to a thick syrup that slowly turned solid after 5 days. On dissolving the solid in ethanol (80 ml) and cooling the solution, fine, crystalline **5** (2.16 g, 59%), m.p. 138°, separated. One recrystallization from ethanol gave an analytical sample of **5**, m.p. 141–143°; R_F 0.37 (R_F of **4** is 0.15 and R_F of **9** is 0.58) 1:1 (v/v) in benzene–ethyl acetate.

Anal. Calc. for $C_{10}H_{20}O_{12}S_3$: C, 28.03; H, 4.70; S, 22.45. Found: C, 27.89; H, 5.08; S, 22.47.

*Methyl 2,4,6-tri-*O*-mesyl-α-D-glucopyranoside* (**7**). — A typical experiment is described. Compound **6** (383 mg) in pyridine (5 ml) was cooled to −15°; mesyl chloride (125 µl) was added in one portion, and the mixture was stored for 3 days at −15°. Pyridine was evaporated off (bath temperature <40°) to leave a syrup. Ethanol

(~25 ml) was added and evaporated off three times. The resulting syrup was transferred to a continuous extractor and extracted with ethyl acetate for 18 h. After removing most of the ethyl acetate by evaporation, the volume of ethyl acetate was adjusted to 30 ml.

The ethyl acetate solution was applied to thirty 0.25-mm plates of Silica Gel F-254. Each plate was developed 4 times to 15 cm from the spotting line with 1:1 (v/v) toluene–ethyl acetate, with 1 h of drying in an air stream between each development. When each plate was exposed briefly to iodine vapor, four areas (centered at ~2.5, 6.5, 8.0, and 10.5 cm from the spotting line) were revealed and marked. To remove iodine, each plate was kept in an air stream for no less than 4 h and then each area from the plates was removed. The combined adsorbent from each area was triturated with acetone (four 25-ml portions) and the extracts evaporated to afford **5**, **6**, **7**, and **9** (in order of increasing R_t value).

The identities of **5**, **6**, and **9** were established readily by comparing them with known compounds, thus establishing the identity of **7** by elimination, although the structure of **7** was further confirmed as its 3-*O*-benzoyl derivative (see later). From four experiments, the range of molar ratios of **6**:**5**:**7**:**9** was (0.5–0.6):1:(4–5):(1.2–1.4), with a 70–80% recovery. Compound **7** was not crystallized; it formed a slightly hygroscopic foam.

*Methyl 3-*O*-benzoyl-2,4,6-tri-*O*-mesyl-α-*D*-glucopyranoside* (**8**). — *A. From methyl 2,6-di-*O*-mesyl-α-*D*-glucopyranoside* (**6**). Compound **6** (3.404 g) was dissolved in pyridine (100 ml) and the solution cooled to 5°. Mesyl chloride (1.2 ml) was then added in one portion and the mixture was stored for 3 days at 5°, whereupon benzoyl chloride (2.5 ml) was mixed in and the mixture was kept again for 3 days at 5°. Water (5 ml) was added in small portions, and the solution was transferred to a separatory funnel with toluene (150 ml) and washed with 600 ml each of: water (twice), 4M hydrochloric acid, water, 10% sodium hydrogencarbonate, and water (twice). After drying the organic layer, evaporation left a syrup that was dissolved in 1:1 (v/v) toluene–ethyl acetate (10 ml) by warming. On cooling, a granular solid separated from solution. Two recrystallizations from 95% ethanol (170 ml) gave crystalline plates of **8** yield 1.094 g (21%); m.p. 194.5° (decomp.), $[\alpha]_D^{24}$ +96° (*c* 0.031, 95% ethanol); $\lambda_{max}^{95\%\ EtOH}$ 274 nm (ε 900); $\lambda_{max}^{CHCl_3}$ 1740 cm^{-1} (ester); n.m.r. in Table I.

Anal. Calc. for $C_{17}H_{24}O_{13}S_3$: C, 38.34; H, 4.54; S, 18.06. Found: C, 38.25; H, 4.65; S, 17.45.

*B. From methyl α-*D*-glucopyranoside* (**1**). Mesyl chloride (90 ml, 1.11 moles) was added from a Hershberg dropping funnel[12] over 16–18 h to a solution of **1** (68 g, 0.35 mole) in pyridine (600 ml) maintained at 0°. After stirring for an additional 24 h, benzoyl chloride (50 ml, 0.43 mol) was added in one portion and the mixture kept for 2 days at 0°. Water (10 ml) was added in small portions, and the mixture was transferred to a separatory funnel with chloroform (200 ml) and diluted with water (1.2 liters). The organic layer was separated and the aqueous layer extracted with two 200-ml portions of chloroform. The combined chloroform extracts were washed with 500 ml of: 2M hydrochloric acid (three times), water, 5% sodium hydrogencarbonate

(twice), and water (twice). The chloroform solution was dried (magnesium sulfate) and kept overnight, whereupon pure **8** (14.2 g) separated.

After separating **8** by filtration, the filtrate was concentrated (aspirator) to a thick syrup, which was dissolved by warming in ethanol (400 ml) and reconcentrating (aspirator) four times; progressively the syrup deposited a granular solid and its solubility in ethanol decreased as the amount of granular solid increased. Finally, the solid was covered with ethanol (500 ml). The mixture was heated to boiling with stirring, cooled to room temperature, and kept for 2 days. After separating and air drying, 152.6 g solid was isolated. A 100-g portion was recrystallized four times by dissolving it in boiling acetone (160 ml), adding boiling ethanol (1.6 l), and allowing the solution to cool and stand 1 day before separating the crystals by filtration. This procedure afforded 25.5 g of **8**, m.p. 193.5° (decomp.). Extrapolation of the recovery to the entire solid, plus the earlier isolated **8**, would have yielded 53 g (28%).

*Methyl 3-*O*-benzoyl-2,4,6-tri-*O*-mesyl-α-*D*-glucopyranoside* (**8**) *and methyl 6-deoxy-3-*O*-benzoyl-6-chloro-2,4-di-*O*-mesyl-α-*D*-glucopyranoside* (**11**). — To 356 mg of **7** in pyridine (5 ml) was added benzoyl chloride (0.7 ml), and the mixture was kept for 3 days at room temperature. Water (1 ml) was added, and the mixture was transferred to a separatory funnel with chloroform (50 ml). The organic layer was washed with 50 ml of water (twice), 5% sodium hydrogencarbonate, and water. After drying, the chloroform was evaporated and the resultant syrup was dissolved in dichloromethane and spread on eight 2-mm plates of Silica Gel F-254. Each plate was developed to 15 cm from the spotting line with 2:1 (v/v) toluene–ethyl acetate and dried in an air stream for 16 h. A short-wavelength u.v. lamp revealed two areas on each plate, one centered about 4 cm and the other 8 cm from the spotting line. These areas were marked, excised and the adsorbent extracted with acetone (four 50-ml portions) to yield crystaline solids. From the 4-cm area, after recrystallization from boiling ethanol (150 ml), 353 mg (79.7%) of **8** (m.p. 192–193°) was isolated. From the 8-cm area, after recrystallization from ethanol (2 ml), 46.6 mg (11.8%) of **11**, m.p. 169–170° (n.m.r. in Table I), was isolated.

Anal. Calc. for $C_{16}H_{21}ClO_{10}S_2$: C, 40.63; H, 4.47; Cl, 7.50; S, 13.56. Found: C, 40.77; H, 4.74; Cl, 7.91; S, 13.52.

*Methyl 3-*O*-benzoyl-2,6-di-*O*-mesyl-4-*O*-tosyl-α-*D*-glucopyranoside* (**12**) *and methyl 4-*O*-benzoyl-2,6-di-*O*-mesyl-3-*O*-tosyl-α-*D*-glucopyranoside* (**13**) *mixture.* — A typical experiment is described. To a solution of **6** (366 mg) in pyridine (15 ml) was added tosyl chloride (2.1 g), and the solution was swirled by hand until the tosyl chloride disssolved. The mixture was kept at room temperature. After 24 h,ice–water (~50 ml) was added, the mixture was transferred to a separatory funnel with dichloromethane (20 ml), and the organic layer separated. After four additional extractions with dichloromethane (20-ml portions), the extracts were combined, washed with 20 ml each of water, 5% sodium hydrogencarbonate, and water, dried, and evaporated to a syrup. Benzoyl chloride (0.5 ml) was added to a solution of this syrup in pyridine (5 ml). After keeping for 24 h at room temperature, the solution was processed as for the initial tosylation. Removal of the organic extract left a syrup

(in a few experiments this syrup slowly turned solid, m.p. ~35–80°) that was dissolved in dichloromethane and distributed equally on 30 t.l.c. plates (20 cm × 20 cm) of 0.25-mm thickness.

The plates were developed with 4:1 (v/v) toluene–ethyl acetate and were thoroughly air-dried between each of two ascents. When the plates were viewed by short-wavelength u.v. light, one major area appeared, about 4.5–6.5 cm from the origin, together with many minor spots (varying between 7 to 11 with different preparations). The major area was removed from the plates; the fractions were combined, triturated with acetone (eight 50-ml portions), and evaporated to a syrup that was dissolved in ethanol by warming. On cooling, a syrup separated that was slowly converted into a granular solid (265 mg), m.p. ~75–81° (the narrowest melting-range of all experiments). The n.m.r. spectrum is discussed in the text.

Anal. Calc. for $C_{23}H_{28}O_{13}S_3$: C, 45.39; H, 4.64; S, 15.80. Found: C, 43–47; H, 3.6–4.6; S, 14.8–16.2.

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