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REACTIONS OF PHENYL CHLOROSULFATE AT OH-1, -4, AND -6 OF ALDOHEXOPYRANOSE DERIVATIVES. FORMATION OF 1,2-OXAZOLINE AND 4,6-CYCLIC SULFATE RINGS

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ABSTRACT

In the reaction of phenyl chlorosulfate–sodium hydride with compounds having both OH-4 and OH-6 free, as in methyl 2,3-di-*O*-benzylaldohexopyranosides, either regioselective substitution of the primary hydroxyl group occurs, or a 4,6-cyclic sulfate is formed, depending on the experimental conditions. The addition of a 6-(phenylsulfate) substituent to the di-*O*-benzylglycosides appears to cause little or no interference with disaccharide synthesis at the nearby O-4 atom. Conformations of both *cis*- and *trans*-fused types of 4,6-cyclic sulfates are discussed. At an unsubstituted anomeric center, the course of reaction by phenyl chlorosulfate is determined by neighboring-group participation possibilities, and the strong leaving-group affinity of a phenylsulfate substituent. This is demonstrated by a 60% conversion of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose into the corresponding 1,2-oxazoline derivative, in contrast to the formation of a mixture of anomeric glycosides and (1↔1) disaccharide when the O-2 substituent is benzyl.

INTRODUCTION

Sulfate derivatives of sugars are usually synthesized[1] by a base-catalyzed reaction between the appropriately substituted sugar and chlorosulfonic acid or sulfur trioxide. In contrast to these syntheses of anionic sulfates, the use of phenyl chlorosulfate[2–4] provides access to protected organosulfate derivatives, which may offer specific advantages in some chemical applications. As shown[3] by the high-yield synthesis of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose 3-(phenylsulfate) and 1,2:3,5-di-*O*-methylene-α-D-glucofuranose 6-(phenylsulfate), an isolated secondary or primary hydroxyl group is readily substituted by phenyl chlorosulfate in the presence of sodium hydride. The present study is concerned with the application of this substitution reaction to some methyl 2,3-di-*O*-benzylaldohexopyranosides, as well as to two types of aldose derivatives allowing, respectively, for neighboring-group participation, and non-participation, at the anomeric center.

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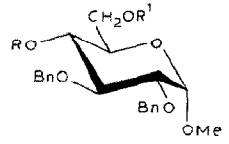
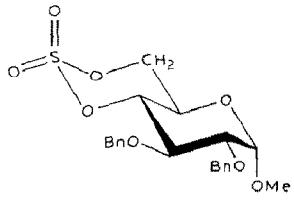
RESULTS AND DISCUSSION

Methyl 2,3-di-O-benzyl-α- and -β-D-glucopyranoside. — When phenyl chlorosulfate (1.4 equiv.) was added to a solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**1**) and sodium hydride (3 equiv.) in oxolane at −30°, a mixture of the 6-(phenylsulfate) (**2**; 77% yield) and the 4,6-di-(phenylsulfate) (**3**; 8%) was obtained. The location of the substituent at O-6 of product **2** was confirmed by its ^{1}H-n.m.r. spectrum, as well as by that of the corresponding 4-*O*-acetyl derivative (**4**). At room temperature, the corresponding reaction gave compound **3**, again as a minor product (11%), whereas none of the mono-substituted product (**2**) was found. Instead, the main product (60%) was the 4,6-cyclic sulfate (**5**).

Closely similar characteristics were observed in the reactions between methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside (**6**) and phenyl chlorosulfate. That is, at −30°, the 6-(phenylsulfate) (**7**); characterized as its 4-acetate (**8**), and the 4,6-di-(phenylsulfate) (**9**) were obtained in yields of 60 and 10%, respectively. At room





1 R = R^1 = H

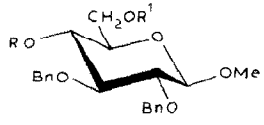
2 R = H, R^1 = PhOSO$_2$

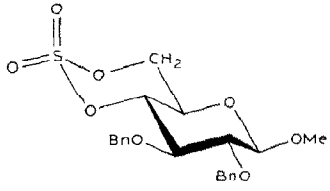
3 R = R^1 = PhOSO$_2$

4 R = Ac, R^1 = PhOSO$_2$

Bn = PhCH$_2$

5





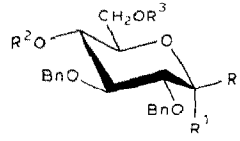
6 R = R^1 = H

7 R = H, R^1 = PhOSO$_2$

8 R = Ac, R^1 = PhOSO$_2$

9 R = R^1 = PhOSO$_2$

10



11 R = H, R^1 = OMe, R^2 = β-Glc(OAc)$_4$, R^3 = PhOSO$_2$

12 R = OMe, R^1 = H, R^2 = β-Glc(OAc)$_4$, R^3 = PhOSO$_2$

temperature, as previously, the 4,6-cyclic sulfate (**10**) was the major product (67%), and it was accompanied by 6% of **9**.

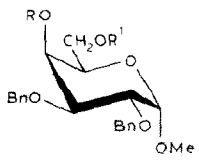
One objective of the study was to determine the influence of the phenylsulfate substituent on subsequent chemical modifications of such derivatives as **2** and **7**. Consequently, as a model of potential usage in the synthesis of sulfated oligosaccharides in the glycosaminoglycan series, compounds **2** and **7** were converted into the 4-substituted disaccharides **11** and **12**, respectively, both in 40% yield, *via* Koenigs–Knorr reactions with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide. As these yields are similar to those obtained under *comparable* conditions[5] in disaccharide syntheses with *O*-acetylglycosyl bromides, it appears that the 6-(phenylsulfate) group has neither a pronounced steric, nor electronic, deactivating influence on substitution reactions at the nearby 4-hydroxyl group.

As to the subsequent preparation of the ionic monosulfates corresponding, *e.g.*, to **2** and **7**, or to disaccharides **11** and **12**, the phenyl protecting group has been shown[3] to be removable by catalytic hydrogenolysis in the presence of platinum. In that reaction, the phenyl group is converted into a more-labile cyclohexyl group, which then appears as cyclohexanol in the reaction mixture.

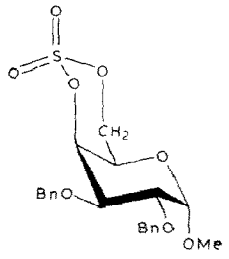
*Methyl 2,3-di-*O*-benzyl-α-*D*-galactopyranoside.* — High regioselectivity at O-6 was also found in the reaction of methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (**13**) with phenyl chlorosulfate (2 equiv.) at −30°; the 6-(phenylsulfate) (**14**) was isolated in 80% yield, compared with 15% of the 4,6-di-(phenylsulfate) (**15**). By analogy with the reactions in the *gluco* series, when the temperature was raised to 25°, **13** afforded the 4,6-cyclic sulfate **16** (52%), as well as **15** (30%). Presumably, relative to substitution at O-4, the *galacto* configuration is slightly less conducive to the cyclization process.

Formation of cyclic sulfates. — The formation of cyclic sulfates between vicinal, *secondary*, hydroxyl groups of sugar derivatives by base-catalyzed reactions of sulfuryl chloride is well known[6–8]. For example, methyl α-D-glucopyranoside was shown[8] to give methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,3-di(chlorosulfate), which was then converted with base into the 2,3-cyclic sulfate. Although a chlorosulfuric ester had formed readily at O-6, displacement of this primary chlorosulfate group by the chloride ion present in the medium was comparably facile. Hence, in this type of procedure, cyclization may be effected at secondary positions, whereas O-6 is prevented from participating, due to competing reactions.

In the present experiments, by contrast, through the selective synthesis of a *primary* phenylsulfate derivative, such as **2**, intramolecular attack by the O-4 anion on the sulfur atom, and displacement of the phenoxy group, promoted formation of a 4,6-cyclic sulfate (**5**). By analogy, the 6-substituted β anomer (**7**) and galactoside ester **14** are regarded as intermediates in the cyclization steps leading to products **10** and **16**, respectively. It should be noted that the comparable formation of 2,3-cyclic sulfates had been observed[4] in the reaction of phenyl chlorosulfate and sodium hydride with sugar derivatives in which OH-2 and -3 are unsubstituted.



13 R = R' = H
14 R = H, R' = $PhOSO_2$
15 R = R' = $PhOSO_2$



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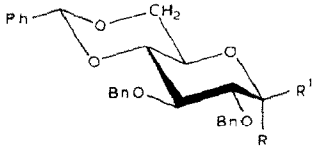
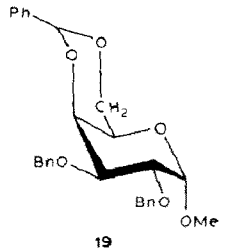


17 R = OMe, R' = H
18 R = H, R' = OMe



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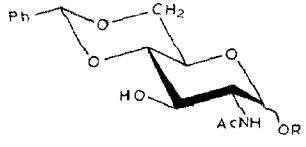
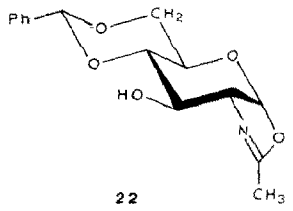


20 R = H
21 R = $PhOSO_2$



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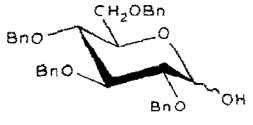

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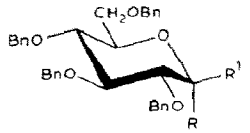

24 R = OSO_3Ph, R' = H
25 R = H, R' = OSO_3Ph
26 R = β-Glc(OBn)$_4$, R' = H

Cyclization is favored in both instances, because the mono-(phenylsulfate), formed initially, undergoes rapid intramolecular attack at sulfur by the alkoxide anion formed from the unsubstituted hydroxyl group with sodium hydride. As this proceeds in the presence of an excess of phenyl chlorosulfate, the extreme ease with which the anion engages in the neighboring-group participation step, rather than in forming a phenylsulfate, is emphasized[9] by the fact that phenoxide ion is a much *poorer* leaving-group than is chloride ion. Although the use of a weaker base may be expected to result in higher yields of mono- or di-(phenylsulfate)s by lessening cyclic sulfate formation, such reagents as pyridine or collidine do not[3] promote substitution by phenyl chlorosulfate. To a substantial degree, however,

TABLE I

A COMPARISON OF ^{1}H-N.M.R. PARAMETERS FOR 4,6-CYCLIC SULFATES (**5**, **10**, AND **16**) AND 4,6-BENZYLIDENE ACETALS (**17**–**19**)[a]

Compound	*Atom*	δ	*Atoms*	*J*[b]	*Compound*	*Atom*	δ	*Atoms*	*J*[b]
α-gluco (**5**)	H-4	4.47	4,5	9.6	**17**	H-4	3.14	4,5	9.8
	H-5	3.63	5,6[c]	11.4		H-5	3.64	5,6[d]	4.8
	H-6	4.14	6,6′	10.9		H-6	3.94	6,6′	10.2
	H-6′	3.61	5,6′[d]	5.0		H-6′	3.29	5,6′[c]	10.1
β-gluco (**10**)	H-4	4.47	4,5	10.1	**18**	H-4	3.78	4,5	8.7
	H-5	2.82	5,6[c]	10.7		H-5	3.69	5,6[d]	4.3
	H-6	4.12	6,6′	10.6		H-6	4.15	6,6′	10.0
	H-6′	3.62	5,6′[d]	5.1		H-6′	3.59	5,6′[c]	9.6
α-galacto (**16**)	H-4	5.14[e]	4,5	3.2	**19**	H-4	4.44	4,5	1.2
	H-5	3.15[e]	5,6	1.6		H-5	2.79	5,6	1.6
	H-6	4.50[e]	6,6′	12.5		H-6	3.86	6,6′	12.6
	H-6′	4.11[e]	5,6′	1.8		H-6′	3.10	5,6′	1.8

[a]Solvent, C_6D_6. [b]Observed spacing, in Hz. [c]H-6*ax*. [d]H-6*ef*. [e]Solvent, 19:1 C_6D_6–Me_2SO-d_6.

these alternative pathways have here been controlled by varying the reaction temperature.

Conformations of the 4,6-cyclic sulfates. — The cyclic sulfates bear obvious structural analogies to 4,6-cyclic phosphates. An example of the latter, prepared[10] by cyclization of D-glucose 6-phosphate with dicyclohexylcarbodiimide, has been depicted as a pyranose *trans*-fused bicyclic species in which both rings adopt a chair conformation. 4,6-Cyclic sulfates are also expected to be sterically related to 4,6-cyclic acetals of pyranosides, a supposition which is clearly borne out by a comparison of n.m.r. data. These show (see Table I) that cyclic sulfates **5**, **10**, and **16** give vicinal ^{1}H–^{1}H coupling parameters for the 4-, 5-, 6-, and 6′-protons contained within the 4,6-ring structures, that are closely similar to those of related 4,6-*O*-benzylidene derivatives (**17**–**19**). Accordingly, their conformations are analogous, for both the *trans*-fused *(gluco)* and *cis*-fused *(galacto)* bicyclic pairs of compounds.

As seen from the *gauche* and *anti* couplings of 4.8–4.9 Hz and 9.6–11.4 Hz, respectively, between H-5 and the two primary protons, the chemical shifts of the equatorial and axial 6-protons of **5** and **17**, and **10** and **18**, are reversed, reflecting differences in the magnetic anisotropy of the two six-membered substituent rings. It is not evident from the uniformly small couplings for the *galacto* isomers that the same difference holds for **16** and **19**.

Overall, the 4,6-cyclic sulfate group induces deshielding of the 4-, 6-, and 6′-protons relative to those of the *O*-benzylidene derivatives, an effect comparable in magnitude to that found for salts of sugar sulfates. Far more deshielding, however, is the phenylsulfate substituent, as seen (Table II) from a comparison of chemical shifts for the cyclic sulfates with those of the mono- and di-(phenylsulfate) derivatives.

TABLE II

CHEMICAL SHIFTS (δ) OF PROTONS ON 4,6-CYCLIC SULFATE RINGS, AND OF RELATED MONO- AND DI-(PHENYLSULFATES)[a]

Isomer	*H Atom*	*Parent compound*	*4,6-Cyclic sulfate*	*4,6-Di-(phenylsulfate)*	*6-(Phenylsulfate)*
α-gluco (**5**)	4	3.75	4.47	4.96[b]	3.76[b]
	5	3.76	3.63	4.01[b]	4.04[b]
	6	3.9	4.14	4.72[b]	4.94[b]
	6′	3.9	3.61	4.57[b]	4.76[b]
β-gluco (**10**)	4	3.60	4.47	4.72	3.55[b]
	5	3.11	2.82	3.23	3.56[b]
	6	3.8	4.12	4.62	4.92[b]
	6′	3.8	3.62	4.35	4.72[b]
α-galacto (**16**)	4	3.99	5.14[b]	5.49[b]	3.40
	5	3.63	3.15[b]	4.15[b]	3.70
	6	3.9	4.50[b]	4.80[b]	4.81
	6′	3.9	4.11[b]	4.80[b]	4.50

[a]Solvent, C_6D_6. [b]Solvent 19:1 C_6D_6–Me_2SO-d_6.

Reactions at the anomeric position. — The facility with which a phenylsulfate substituent may be displaced, as evident from the present findings, was also demonstrated in a reaction involving the anomeric position. In that instance, the reaction of 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranose (**20**) with phenyl chlorosulfate at room temperature, the acetamido function participated satisfactorily in a displacement at C-1 of the 1-(phenylsulfate) intermediate (**21**; inferred), to produce the 1,2-oxazoline* derivative (**22**) in 60% yield. This reaction is analogous to one[12] in which **20** reacted with trifluoromethanesulfonic anhydride–Cl^-, affording the 1,2-oxazoline, presumably, in the same manner.

Direct substitution at the anomeric center was effected in the *absence* of neighboring-group participation contributions. Thus, 2,3,4,6-tetra-*O*-benzyl-D-glucose (**23**) gave a 3:1 mixture of the anomeric 1-(phenyl sulfate)s **24** and **25** in an overall yield of 84%. A minor product (12%) was the (1↔1)-α,β-disaccharide (**26**).

EXPERIMENTAL

N.m.r. spectroscopy. — A Varian XL-300 spectrometer was used to record the ^1H-(300 MHz) and ^{13}C-(75 MHz) n.m.r. spectra, all at room temperature. The solvent was C_6D_6 or, where specified, C_6D_6 containing 5% of dimethyl sulfoxide-d_6, and chemical shifts (δ) are referenced with respect to tetramethylsilane. For ^1H-n.m.r. spectra, the acquisition time was 4 s, and the pulse width, 35°. For ^1H-decoupled, ^{13}C-n.m.r. spectra, the acquisition time was 1 s, and the pulse width, 18°.

*For a recent, alternative synthesis of 1,2-oxazolines, see ref. 11.

The HOMCOR pulse sequence was employed for the analysis of ^{1}H-n.m.r. spectra by homonuclear correlated 2D spectroscopy. The ^{1}H data for methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 4,6-disulfate (**5**), which were not available through first-order analysis, were obtained (see Table I) by spectral simulation, in which H-6′,-5,-6, and -4 were treated as an ABCX spin system.

Reaction of phenyl chlorosulfate with methyl 2,3-di-O-benzyl-α-D-glucopyranoside (**1**) *at room temperature.* — A mixture of sodium hydride (400 mg, 8.3 mmol) and oxolane (25 mL), contained in a flask fitted with a nitrogen inlet and a drying tube, was stirred for 10 min. Then, a solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[13] (1.0 g, 2.7 mmol) in oxolane (25 mL) was introduced dropwise, with stirring, during 1 h, followed by freshly prepared phenyl chlorosulfate[3] (0.5 mL, 3.6 mmol). After 24 h, the suspension was filtered, the filtrate was evaporated, and a solution of the residue in dichloromethane was washed successively with 0.5M hydrochloric acid and saturated sodium hydrogencarbonate, dried, and evaporated. When subjected to chromatography using 1:9 ethyl acetate–benzene, the syrupy product afforded (*a*) methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 4,6-di-(phenylsulfate) (**3**; 0.2 g, 11%); $[\alpha]_D$ +15.0° (*c* 4.7, $CHCl_3$), and (*b*) methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 4,6-cyclic sulfate (**5**; 0.7 g, 60%); after crystallization from ether–hexane, m.p. 109–110°, $[\alpha]_D$ +11.5° (*c* 3.3, $CHCl_3$).

The ^{1}H-n.m.r. data for **3** (19:1 C_6D_6–Me_2SO-d_6): δ 7.34–6.94 (m, 20 H, 4 Ph), 4.96 (dd, 1 H, $J_{4,5}$ 10.20 Hz, H-4), 4.87, 4.80 (2 d, 2 H, *J* 10.6 Hz, CH_2), 4.72 (dd, 1 H, $J_{5,6'}$ 2.2 Hz, H-6), 4.57 (dd, 1 H, $J_{6,6'}$ 11.1 Hz, H-6′), 4.54 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.49, 4.39 (2 d, 2 H, *J* 11.9 Hz, CH_2), 4.14 (t, 1 H, $J_{3,4}$ 9.10 Hz, H-3), 4.01 (m, 1 H, $J_{5,6'}$ 5.4 Hz, H-5), 3.42 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), and 3.08 (s, 3 H, OCH_3).

Anal. Calc. for $C_{33}H_{34}O_{12}S_2$: C, 57.72; H, 4.99; S, 9.34. Found: C, 58.01; H, 5.21; S, 9.32.

The ^{1}H-n.m.r. data for **5** (C_6D_6): δ 7.30–7.07 (m, 10 H, 2 Ph), 4.69, 4.40 (2 d, 2 H, *J* 11.5 Hz, CH_2), 4.47 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.50, 4.29 (2 d, 2 H, *J* 12.1 Hz, CH_2), 4.23 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.14 (dd, 1 H, $J_{6,6'}$ 10.9 Hz, H-6), 3.92 (dd, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 3.63 (m, 1 H, $J_{5,6}$ 11.4 Hz, H-5), 3.61 (dd, 1 H, $J_{5,6'}$ 5.0 Hz, H-6′), 3.13 (dd, 1 H, $J_{2,3}$ 9.29 Hz, H-2), and 2.85 (s, 3 H, OCH_3).

Anal. Calc. for $C_{21}H_{24}O_8S$: C, 57.79; H, 5.54; S, 7.35. Found: C, 58.03; H, 5.39; S, 7.28.

Reaction of phenyl chlorosulfate with methyl 2,3-di-O-benzyl-α-D-glucopyranoside (**1**) *at −30°.* — This was carried out on the same scale as in the previous experiment. The reaction mixture consisting of **1** (ref. 13) and sodium hydride in oxolane was cooled to −30° prior to the introduction of phenyl chlorosulfate, which was added portionwise (4×) during 36 h. After an additional 60 h, workup and chromatography as before gave methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 4,6-di-(phenylsulfate) (**3**; 0.14 g, 8%), and methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 6-(phenylsulfate) (**2**; 1.1 g, 77%); $[\alpha]_D$ +14.5° (*c* 6.2, $CHCl_3$). The ^{1}H-n.m.r. data for **2** (19:1 C_6D_6–Me_2SO-d_6): δ 7.60–6.95 (m, 15 H, 3 Ph), 5.10, 4.99

(2 d, 2 H, *J* 12.8 Hz, CH_2), 4.94 (dd, 1 H, $J_{5,6}$ 5.6 Hz, H-6), 4.76 (dd, 1 H, $J_{6,6'}$ 10.6 Hz, H-6'), 4.68 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.61, 4.49 (2 d, 2 H, *J* 11.0 Hz, CH_2), 4.10 (t, 1 H, $J_{3,4}$ 8.9 Hz, H-3), 4.04 (m, 1 H, $J_{5,6}$ 1.8 Hz, H-5), 3.76 (dd, 1 H, $J_{4,5}$ 9.1 Hz, H-4), 3.48 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), and 3.12 (s, 3 H, OCH_3).

*Methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-α-*D*-glucopyranoside 6-(phenylsulfate)* (**4**). — Acetylation of syrupy **2** with acetic anhydride–pyridine afforded the crystalline 4-*O*-acetyl derivative **4**; after crystallization from ether–hexane, m.p. 70–71°, $[\alpha]_D$ +24.0° (*c* 3.7, $CHCl_3$); ^{1}H-n.m.r. data (19:1 C_6D_6–Me_2SO-d_6): δ 7.30–6.89 (m, 15 H, 3 Ph), 5.10 (dd, 1 H, $J_{4,5}$ 8.7 Hz, H-4), 4.82, 4.58 (2 d, 2 H, *J* 11.9 Hz, CH_2), 4.57 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.51 (dd, 1 H, $J_{6,6'}$ 11.2 Hz, H-6), 4.51, 4.41 (2 d, 2 H, *J* 11.8 Hz, CH_2), 4.42 (dd, 1 H, $J_{5,6'}$ 6.3 Hz, H-6'), 4.00 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.91 (m, 1 H, $J_{5,6}$ 2.6 Hz, H-5), 3.43 (dd, 1 H, $J_{2,3}$ 9.7 Hz, H-2), 3.07 (s, 3 H, OCH_3), and 1.63 (s, 3 H, COCH_3).

Anal. Calc. for $C_{29}H_{32}O_{10}S$: C, 60.83; H, 5.63; S, 5.60. Found: C, 60.72; H, 5.56; S, 5.49.

*Methyl 2,3-di-*O*-benzyl-β-*D*-glucopyranoside 4,6-di-(phenylsulfate)* (**9**). — The reaction of phenyl chlorosulfate with methyl 2,3-di-*O*-benzyl-β-D-glucopyranoside[14] (**6**) at room temperature, under the same conditions, and on the same scale, as for the α-anomer **1**, gave 0.1 g (6%) of **9**; after crystallization from ether–hexane, m.p. 65–67°, $[\alpha]_D$ +8.3° (*c* 3.9, $CHCl_3$); ^{1}H-n.m.r. data (C_6D_6): δ 7.48–6.82 (m, 20 H, 4 Ph), 4.85, 4.56 (2 d, 2 H, *J* 11.4 Hz, CH_2), 4.84 (s, 2 H, CH_2), 4.72 (dd, 1 H, $J_{4,5}$ 9.9 Hz, H-4), 4.62 (dd, 1 H, $J_{5,6'}$ 2.1 Hz, H-6'), 4.35 (dd, 1 H, $J_{6,6'}$ 11.5 Hz, H-6), 3.94 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.51 (t, 1 H, $J_{3,4}$ 8.9 Hz, H-3), 3.29 (dd, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 3.23 (m, 1 H, $J_{5,6}$ 6.1 Hz, H-5), and 3.19 (s, 3 H, OCH_3).

Anal. Calc. for $C_{33}H_{34}O_{12}S_2$: C, 57.72; H, 4.99; S, 9.34. Found: C, 58.02; H, 5.34; S, 9.48.

*Methyl 2,3-di-*O*-benzyl-β-*D*-glucopyranoside 4,6-cyclic sulfate* (**10**). — Compound **10**, isolated chromatographically as the major product (0.8 g, 67%) from the reaction of **6** at room temperature, had, after crystallization from ether–hexane, m.p. 85–86°, $[\alpha]_D$ −8.4° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. data (C_6D_6): δ 7.15–7.05 (m, 10 H, 2 Ph), 4.79, 4.60 (2 d, 2 H, *J* 11.4 Hz, CH_2), 4.71, 4.61 (2 d, 2 H, *J* 11.6 Hz, CH_2), 4.47 (dd, 1 H, $J_{4,5}$ 10.1 Hz, H-4), 4.12 (t, 1 H, $J_{6,6'}$ 10.7 Hz, H-6), 3.88 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 3.62 (dd, 1 H, $J_{5,6'}$ 10.3 Hz, H-6'), 3.43 (t, 1 H, $J_{3,4}$ 9.2 Hz, H-3), 3.24 (dd, 1 H, $J_{2,3}$ 8.7 Hz, H-2), 2.85 (s, 3 H, OCH_3), and 2.82 (m, 1 H, $J_{5,6}$ 5.1 Hz, H-5); ^{13}C-n.m.r. data (C_6D_6): δ 105.17 (C-1), 84.38 (C-4), 81.48 (C-2), 79.04 (C-3), 75.18, 75.03 (CH_2), 71.65 (C-6), 63.99 (C-5), and 56.88 (OCH_3).

Anal. Calc. for $C_{21}H_{24}O_8S$: C, 57.79; H, 5.54; S, 7.35. Found: C, 57.95; H, 5.41; S, 7.06.

*Methyl 2,3-di-*O*-benzyl-β-*D*-glucopyranoside 6-(phenylsulfate)* (**7**), *and its 4-*O*-acetyl derivative* (**8**). — At −30°, the major product of the reaction of β-D-glucoside **6** with phenyl chlorosulfate was **7** (0.84 g, 60%); $[\alpha]_D$ −16.2° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. data (19:1 C_6D_6–Me_2SO-d_6): δ 7.48–6.96 (m, 15 H, 3 Ph), 5.10, 5.00 (2 d, 2 H, *J* 11.5 Hz, CH_2), 4.92 (dd, 1 H, $J_{6,5}$ 1.6 Hz, H-6), 4.89 (dd, 2 H, CH_2), 4.72

(dd, 1 H, $J_{6,6'}$ 10.2 Hz, H-6'), 4.24 (d, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.68 (dd, 1 H, $J_{3,4}$ 9.8 Hz, H-3), 3.56 (m, 1 H, $J_{5,6'}$ 5.0 Hz, H-5), 3.55 (m, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 3.47 (t, 1 H, $J_{2,3}$ 8.7 Hz, H-2), and 3.29 (s, 3 H, OCH_3).

Acetylation of **7** afforded **8**; m.p. 88–90° (dec.), $[\alpha]_D$ −2.5° (*c* 0.9, $CHCl_3$); ^{1}H-n.m.r. data (19:1 C_6D_6–Me_2SO-d_6): δ 7.33–6.90 (m, 15 H, 3 Ph), 5.06 (t, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 4.88, 4.79 (2 d, 2 H, *J* 11.6 Hz, CH_2), 4.61, 4.57 (2 d, 2 H, *J* 6.9 Hz, CH_2), 4.51 (dd, 1 H, $J_{6,6'}$ 10.9 Hz, H-6), 4.44 (dd, 1 H, $J_{5,6'}$ 6.34 Hz, H-6'), 4.14 (dd, 1 H, $J_{1,2}$ 7.7 Hz, H-1), 3.56 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), 3.52 (m, 1 H, $J_{5,6}$ 2.1 Hz, H-5), 3.42 (dd, 1 H, $J_{2,3}$ 9.3 Hz, H-2), 3.25 (s, 3 H, OCH_3), and 1.64 (s, 3 H, $COCH_3$).

Anal. Calc. for $C_{29}H_{32}O_{10}S$: C, 60.83; H, 5.63; S, 5.60. Found: C, 61.02; H, 5.44; S, 5.40.

*Methyl 2,3-di-O-benzyl-α-*D*-galactopyranoside 6-(phenylsulfate)* (**14**). — The reaction of methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (**13**; 0.51 g, 1.4 mmol) with phenyl chlorosulfate (0.51 mL, 3.7 mmol) at −30° afforded **14** as the major product (0.57 g, 80%); after crystallization from ether–hexane, m.p. 67–68°, $[\alpha]_D$ +47.9° (*c* 1.3, $CHCl_3$); ^{1}H-n.m.r. data (C_6D_6): δ 7.33–6.81 (m, 15 H, 3 Ph), 4.81 (dd, 1 H, $J_{6,6'}$ 10.4 Hz, H-6), 4.63 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.56, 4.48 (2 d, 2 H, *J* 11.6 Hz, CH_2), 4.41, 4.35 (2 d, 2 H, *J* 6.7 Hz CH_2), 4.50 (dd, 1 H, $J_{5,6'}$ 8.0 Hz, H-6'), 3.86 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2), 3.74–3.68 (b, 1 H, H-5), 3.71 (dd, 1 H, $J_{3,4}$ 3.3 Hz, H-3), 3.44–3.42 (b, 1 H, H-4), 3.04 (s, 3 H, OCH_3), and 2.33 (d, 1 H, OH-4, exchanged with D_2O).

Anal. Calc. for $C_{27}H_{30}O_9S$: C, 61.12; H, 5.70; S, 6.04. Found: C, 60.92; H, 5.68; S, 6.16.

*Methyl 2,3-di-O-benzyl-α-*D*-galactopyranoside 4,6-di-(phenylsulfate)* (**15**). — Compound **15** was isolated chromatographically in a yield of 15% (0.14 g) from the reaction of **13** with phenyl chlorosulfate at −30°, and also in a yield of 30% from the reaction at room temperature; after crystallization from ether–hexane, m.p. 78–80°, $[\alpha]_D$ +189.0° (*c* 0.2, $CHCl_3$); ^{1}H-n.m.r. data (19:1 C_6D_6–Me_2SO-d_6): δ 7.45–6.88 (m, 20 H, 4 Ph), 5.49 (d, 1 H, $J_{4,5}$ 2.5 Hz, H-4), 4.80 (m, 2 H, H-6,6'), 4.86, 4.72 (2 d, 2 H, *J* 11.7 Hz, CH_2), 4.71 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 4.44, 4.30 (2 d, 2 H, *J* 11.9 Hz, CH_2), 4.15 (t, 1 H, $J_{5,6'}$ 3.4 Hz, H-5), 4.09 (dd, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 3.85 (dd, 1 H, $J_{2,3}$ 10.2 Hz, H-2), and 3.06 (s, 3 H, OCH_3).

Anal. Calc. for $C_{33}H_{34}O_{12}S_2$: C, 57.72; H, 4.99; S, 9.34. Found: C, 57.86; H, 5.04; S, 9.54.

*Methyl 2,3-di-O-benzyl-α-*D*-galactopyranoside 4,6-cyclic sulfate* (**16**). — In the reaction of α-galactoside **13** with 2 equiv. of phenyl chlorosulfate at room temperature, the cyclic sulfate **16** was the main product (0.6 g, 52%); after crystallization from chloroform–hexane, m.p. 156–157°, $[\alpha]_D$ +51.3° (*c* 1.7, $CHCl_3$); ^{1}H-n.m.r. data (19:1 C_6D_6–Me_2SO-d_6): δ 7.36–7.12 (m, 10 H, 2 Ph), 5.14 (dd, 1 H, $J_{4,5}$ 3.2 Hz, H-4), 4.66 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.64–4.34 (4 H, 2 CH_2), 4.50 (dd, 1 H, $J_{6,6'}$ 12.5 Hz, H-6), 4.11 (dd, 1 H, $J_{5,6'}$ 1.8 Hz, H-6'), 4.00 (dd, 1 H, $J_{3,4}$ 3.1 Hz, H-3), 3.91 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 3.15 (dd, 1 H, $J_{5,6}$ 1.6 Hz, H-5), and 3.01

(s, 3 H, OCH_3); ^{13}C-n.m.r. data (19:1 C_6D_6–Me_2SO-d_6): δ 99.23 (C-1), 82.67 (C-4), 75.91 (C-2), 75.02 (CH_2), 73.90 (C-3), 73.70, 72.34 (CH_2 or C-6), 60.36 (C-5), and 55.61 (OCH_3).

Anal. Calc. for $C_{21}H_{24}O_8S$: C, 57.79; H, 5.54; S, 7.35. Found: C, 58.04; H, 5.46; S, 7.54.

Synthesis of disaccharides **11** *and* **12**. — Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside 6-(phenylsulfate) (**2**) (or its β anomer **7**) was condensed with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2 mol/mol) in the presence of mercuric cyanide (2 mol/mol) in 1:1 nitromethane–benzene. After 48 h at r.t., the crude product was subjected to column chromatography on silica gel (eluant, 1:3 ethyl acetate–benzene), affording syrupy **11** (or **12**) in 40% yield. In addition to the chromatographic evidence as to their purity, their ^{1}H-n.m.r. spectra were consistent with the structures proposed; the measured ^{1}H-integrals for phenyl:sugar:acetoxyl were 1:1.47:0.88 (theoretical 1:1.4:0.8) for **11**, and 1:1.46:0.82 for **12**.

*Reaction of phenyl chlorosulfate with 2,3,4,6-tetra-*O*-benzyl-*D*-glucopyranose*. — A suspension of sodium hydride (132 mg, 2.8 mmol) in oxolane (50 mL) was stirred for 15 min at r.t. under nitrogen. The sugar derivative (1.0 g, 1.9 mmol) was introduced, stirring was continued for 1 h, and phenyl chlorosulfate (0.3 mL, 2.2 mmol) was added under anhydrous conditions. After 12 h, the mixture was worked up as described earlier, and the oily residue obtained was subjected to column chromatography (eluant, 1:5 ethyl acetate–hexane), to afford the following: (*a*) 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl (phenylsulfate), an oil (474 mg, 63%) $[\alpha]_D$ −5° (*c* 2.0, $CHCl_3$); ^{1}H-n.m.r. data (C_6D_6): δ 7.50–6.75 (m, 25 H, 5 Ph), 4.83 (d, 1 H, $J_{1,2}$ 4.76 Hz, H-1), 3.82 (dd, 1 H, $J_{2,3}$ 9.01 Hz, H-2), 3.71 (m, 2 H, H-3,6), 3.62 (m, 2 H, H-5,6′), and 3.35 (m, 1 H, H-4); ^{13}C-n.m.r. data ($CDCl_3$): δ 100.95, 83.91, 81.26, 77.70, 77.00, 76.24, 74.80, 74.41, 74.19, 68.15, and 67.61. (*b*) 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl (phenylsulfate), an oil (133 mg, 21.0%), $[\alpha]_D$ +8° (*c* 3.8, $CHCl_3$); ^{1}H-n.m.r. data (C_6D_6): δ 7.52–6.58 (m, 25 H, 5 Ph), 5.11 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), and 3.77–3.66 (m, 5 H); ^{13}C-n.m.r. data ($CDCl_3$): δ 103.60, 83.90, 81.20, 77.70, 76.20, 74.90, 74.40, 74.20, 68.20, and 67.60. (*c*) 2,3,4,6,2′,3′,4′,6′-octa-*O*-benzyl-α,β-trehalose, isolated as an oil (120 mg, 12%); $[\alpha]_D$ +29.0° (*c* 2.2, $CHCl_3$) (lit.[15] +43°); ^{13}C-n.m.r. data ($CDCl_3$): δ 104.33, 99.59, 84.85, 81.94, 79.57, 78.55, 77.70, 77.14, 75.74, 75.09, 74.60, 73.53, 72.83, 71.37, 69.16, and 68.24.

*Reaction of phenyl chlorosulfate with 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranose* (**20**). — A suspension of sodium hydride (100 mg, 2.1 mmol) in 1,4-dioxane (50 mL) was stirred for 30 min at r.t. under nitrogen. The sugar derivative **20** (500 mg, 1.7 mmol) was added, the mixture was stirred for 1 h, phenyl chlorosulfate (0.25 mL, 1.8 mmol) was introduced, and stirring was continued for 3 h, after which the mixture was worked up as described earlier. The crystalline product (350 mg, 73%) was recrystallized from acetone, affording 2-methyl-(4,6-*O*-benzylidene-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-Δ^2-oxazoline (**22**), m.p. 163–165°; ^{1}H-n.m.r. data ($CDCl_3$): δ 7.46–7.26 (m, 5 H, Ph), 6.22 (br, 1 H), 5.97 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 5.60 (s, 1 H, PhC*H*), 4.37 (m, 1 H), 3.93 (m, 1 H), 3.68 (m, 4 H), and 1.83 (s, 3 H, OCH_3).

Anal. Calc. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.77; H, 5.97; N, 5.01.

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