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SELECTIVE ESTERIFICATION OF 1,6-ANHYDROHEXOPYRANOSES: THE POSSIBLE ROLE OF INTRAMOLECULAR HYDROGEN-BONDING

J. MARTIN MACLEOD, LELAND R. SCHROEDER,
The Institute of Paper Chemistry, Appleton, Wisconsin 54911 (U. S. A.)
AND PAUL A. SEIB
Department of Grain Science and Industry, Kansas State University, Manhattan, Kansas 66506 (U. S. A.)
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ABSTRACT

Selective esterification reactions of 1,6-anhydro-3-deoxy-β-D-*xylo*-hexopyranose (**1**), 1,6-anhydro-β-D-glucopyranose (**7**), and several derivatives of **7**, were conducted with an acid chloride or acid anhydride in pyridine. Reaction of **1** with *p*-toluenesulfonyl chloride and with benzoyl chloride gave 70 and 63%, respectively, of the 2-esters. The 2-methyl and 2-benzyl ethers of **7**, both having a strongly hydrogen-bonded C-4 hydroxyl group, reacted with *p*-toluenesulfonyl chloride to yield the 4-monosulfonates (71 and 74%, respectively). Esterification of the 2-methyl ether and 2-*p*-toluenesulfonate of **7** with *p*-toluenesulfonic anhydride instead of with *p*-toluenesulfonyl chloride led to increased yields of the 4-*p*-toluenesulfonates after a shorter reaction-time.

INTRODUCTION

Selective esterification has been useful in carbohydrate chemistry, even though factors controlling selectivity are not fully understood[1–8]. In the reactions of carbohydrates with acid chlorides in pyridine, intramolecular hydrogen-bonding (rather than steric effects) can often be used to explain selectivity. However, accurate prediction of products from partial esterification reactions are difficult at present, and more information is needed concerning how intramolecular hydrogen-bonding influences selectivity.

Here we describe selective esterification of 1,6-anhydro-3-deoxy-β-D-*xylo*-hexopyranose (**1**) and of several derivatives of 1,6-anhydro-β-D-glucopyranose (levoglucosan, **7**). The first compound was chosen because: (*a*) its pyranoid ring is conformationally rigid, having the two hydroxyl groups fixed in axial and equatorial orientations, (*b*) esterification of either hydroxyl group in **1** should not substantially affect the reactivity of the other, and (*c*) OH-2 in compound **1** can form an intramolecular hydrogen-bond (with O-5), whereas OH-4 cannot. We consider that the

results provide further insight into the factors governing relative reactivities of hydroxyl groups in 1,6-anhydrides, which should lead to improved yields of useful synthetic intermediates. In the past, for example, partially esterified 1,6-anhydrides have been used in preparing fluoro sugars[9,10], amino sugars[11,12], 2-deoxy-1,6-anhydrides[13], and disaccharides[14,15].

RESULTS AND DISCUSSION

1,6-Anhydro-3-deoxy-β-D-*xylo*-hexopyranose (**1**) was prepared crystalline by way of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-*xylo*-hexofuranose[16] (**8**). Treating **8** with warm, aqueous acid gave a mixture of 3-deoxy-D-*xylo*-hexose and the 1,6-anhydride **1**, which were separated by column chromatography on silica gel in 64 and 25% yields, respectively. Angyal and Dawes[17] previously reported 44.7% of **1** existing in equilibrium with the free sugar. Trnka and Černý[18] recently reported isolation of **1** having physical constants substantially in agreement with ours. The specific rotation of **1** in aqueous solution (−8°) also agrees well with the predicted value[19] (−5°) for **1** in the *1C*(D) conformation.

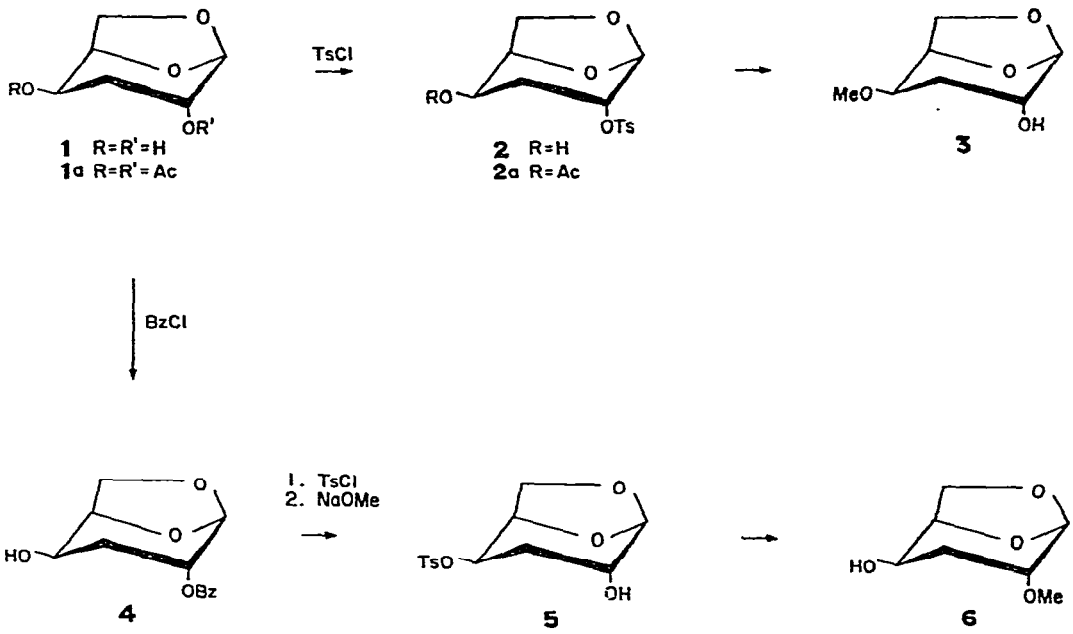
Reaction of **1** with three equiv. of *p*-toluenesulfonyl chloride in pyridine for 36 h at 25°, followed by column chromatography, gave syrupy monosulfonate (70%) and disulfonate (11%) fractions. The monoester fraction was shown to be pure 1,6-anhydro-3-deoxy-2-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexopyranose (**2**) by the following:

(*a*) Acetylation of syrupy **2** gave a crystalline product (in 75% yield) whose n.m.r. spectrum showed a single acetoxyl resonance (τ 8.01, Me_2SO–d_6).

(*b*) Methylation of **2**, followed by desulfonation, gave a monomethyl ether whose n.m.r. spectrum (Me_2SO–d_6) was consistent with the 4-methyl ether (**3**) structure. Compound **3** had a single OH resonance (τ 5.20, *J* 5.8 Hz). The chemical shift of the H-1 signal (τ 4.89) of **3** was almost identical to that of **1** (τ 4.90), whereas the H-5 signal (τ 5.48) was shifted 0.26 p.p.m. downfield from that of **1**. We previously had shown[20] that methylation of the 2-OH or 4-OH group in 1,6-anhydro-β-D-glucopyranose (**7**) shifts (downfield by 0.17 p.p.m.) the H-1 or H-5 signal, respectively, of the methylated 1,6-anhydride.

(*c*) The isomeric 2-methyl ether (**6**) was prepared by way of selective benzoylation of **1**, as shown in the accompanying formulas. The n.m.r. spectrum of **6** (Me_2SO–d_6) showed, as expected[19], that the anomeric-proton signal (τ 4.73) had been shifted down-field (by 0.17 p.p.m.) from the H-1 signal of the parent 1,6-anhydride (**1**), whereas the H-5 signal of **6** (τ 5.76) resonated at almost the same frequency as H-5 of **1** (τ 5.74).

It is clear that the axial hydroxyl group at C-2 of **1** reacts with acid chlorides in pyridine more rapidly than does the equatorial one at C-4. The preferential esterification of hydroxyl groups that are more sterically hindered, has been observed in the past for several compounds[1], and in each instance the more reactive hydroxyl group was capable of donating an intramolecular hydrogen-bond to an oxygen atom.



That generalization again holds true for compound **1**, where the more reactive 2-OH group is geometrically well situated for hydrogen-bonding to O-5.

Intramolecular hydrogen-bonding is generally detected[21] by measuring the i.r. hydroxyl-stretching frequencies of a compound in dilute solution (<5mM) in non-polar solvents (generally carbon tetrachloride). As **1** was insoluble in carbon tetrachloride, measurements were made in 1,2-dichloroethane at a concentration of 50mM, to observe the hydroxyl-stretching absorption above the solvent background. Under those conditions, compound **1** exhibited hydroxyl-stretching bands at 3590 and 3610 cm^{-1}, indicating an intramolecular hydrogen-bond (3590 cm^{-1}; 2-O-H···O-5) and a free hydroxyl group (3610 cm^{-1}). With five molar equivalents of pyridine added to the solution, no change in the two bands was observed. The same intramolecular hydrogen-bond was also detected in a solution of 1,6-anhydro-3-deoxy-4-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexopyranose (**5**) in carbon tetrachloride; the spectrum showed a band of medium intensity at 3590 cm^{-1} and a weak band at 3627 cm^{-1} (Table I).

Steric considerations alone cannot always account for experimental results observed in esterification of 1,6-anhydro sugars. For example, Shapiro *et al.*[22] treated 2-*O*-acetyl-1,6-anhydro-β-D-galactopyranose with 1.1 molar equivalents of acetic anhydride in pyridine and obtained the 2,3-diacetate in 54% yield. The same authors reported a 41% yield of the 2,3-diester upon treatment of unsubstituted 1,6-anhydro-β-D-galactopyranose with 2.5 equivalents of acetic anhydride. In both instances the 3-hydroxyl group, although *syn*-axial to the anhydro bridge, was acetylated in preference to the sterically unhindered, equatorial 4-hydroxyl group.

TABLE I

HYDROXYL-STRETCHING FREQUENCIES OF 1,6-ANHYDROHEXOPYRANOSES AND RESULTS OF *p*-TOLUENESULFONYLATION REACTIONS

1,6-Anhydro-β-D-hexopyranoside	*Hydroxyl-stretching frequencies*[a] (cm^{-1})	*Frequency shifts*[b] (cm^{-1})	*Assigned hydroxyl*[c]	*Principal product of sulfonylation*	*Yield* (%)	
					p-*Toluenesulfonyl chloride (equiv.)*	p-*Toluenesulfonic anhydride (equiv.)*
gluco (7)				2,4-di-*p*-toluenesulfonate	69 (2.1 equiv.)[d]	79 (2.8 equiv.)
2-*O*-methyl-*gluco* (9)	3562 (s) 3608 (m)	67 21	4-OH 3-OH	4-*p*-toluenesulfonate-2-methyl ether	71 (1.3 equiv.)	84 (1.3 equiv.)
2-*O*-benzyl-*gluco* (10)	3562 (s) 3608 (w)	67 21	4-OH 3-OH	4-*p*-toluenesulfonate-2-benzyl ether	74 (1.3 equiv.)	
2-*O*-*p*-tolylsulfonyl-*gluco* (12)	3585 (m) 3608 (m)	44 21	4-OH 3-OH	2,4-di-*p*-toluenesulfonate	64 (1.3 equiv.)	88 (1.3 equiv.)
4-*O*-benzyl-*gluco* (11)	3562 (s) 3608 (m)	67 21	2-OH 3-OH	2-*p*-toluenesulfonate-4-benzyl ether	71 (1.3 equiv.) 77 (1.6 equiv.)[e]	
3-deoxy-*xylo* (1)	3590 (s)[f] 3610 (m)	39 19	2-OH 4-OH	2-*p*-toluenesulfonate	70 (3 equiv.)	
3-deoxy-4-*O*-*p*-tolylsulfonyl-*xylo* (5)	3590 (m) 3627 (w)	39 —	2-OH			
2-*O*-benzoyl-3-deoxy-*xylo* (4)	3625 (s)	—	4-OH			

[a]Determined in dilute carbon tetrachloride solution (≤5mM), s, strong; m, moderate; w, weak. [b]Difference between frequency of bonded hydroxyl group and standard free hydroxyl group at 3629 cm^{-1}, A. H. Cole and P. R. Jeffries, *J. Chem. Soc.*, (1956) 4391. [c]P. C. Wollwage and P. A. Seib[20]. [d]R. W. Jeanloz, A. M. C. Rapin, and S. Hakomori[25]. [e]P. A. Seib[13]. [f]Determined in 1,2-dichloroethane at 50mM.

In other work, Koenigs–Knorr condensation between 2-substituted 1,6-anhydro-β-D-galactopyranose and a monosaccharide glycosyl bromide[22], and between 1,6-anhydro-β-D-glucopyranose and a disaccharide glycosyl bromide[23], showed that OH-3 could be as reactive as OH-4, despite the unfavorable steric orientation of OH-3.

Internal hydrogen-bonding can be invoked as well as steric factors[24,25] to explain the products of partial esterification of 1,6-anhydro-β-D-glucopyranose (levoglucosan) (**7**) and its derivatives. The 2-methyl and 2-benzyl ethers of **7** (**9** and **10**, respectively) contain strongly hydrogen-bonded C-4 hydroxyl groups[20] ($\nu_{4\text{-OH}}$ = 3562 cm^{-1}, Table I), and both compounds reacted with 1.3 equivalents of *p*-toluenesulfonyl chloride to give a small proportion of disulfonate and 71–74% of 1,6-anhydro-2-*O*-methyl-4-*O*-*p*-tolylsulfonyl-β-D-glucopyranose or 1,6-anhydro-2-*O*-benzyl-4-*O*-*p*-tolylsulfonyl-β-D-glucopyranose. *p*-Toluenesulfonylation of the 4-benzyl ether (**11**) of **7** under identical conditions yielded 71% of 1,6-anhydro-4-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (Table I).

In levoglucosan (**7**), the hydrogen-bond between O-2 and O-4 is decreased upon acylation at either OH-2 or OH-4; the 4-OH stretching frequencies of the 2,3-dibenzoate[20] and the 2-*p*-toluenesulfonate (**12**) of **7** occur near 3585 cm^{-1} (Table I). However, the hydrogen-bond involving the 2- or 4-OH group in a 4- or 2-*O*-acyl derivative of levoglucosan is still stronger than the bond involving the 3-OH group (*ca.* 3605 cm^{-1}); therefore, dimolar *p*-toluenesulfonylation of **7** with the acid chloride gives a high yield (69%) of the 2,4-diester.

Selectivity in esterification reactions employing acid anhydride–pyridine appears to be much less influenced by intramolecular hydrogen-bonding than in reactions conducted with acid chloride–pyridine[1,2,26–28]. For that reason, and because few investigators[6] have used sulfonic anhydrides as esterifying agents, we examined the reaction of *p*-toluenesulfonic anhydride with levoglucosan (**7**), its 2-methyl ether (**9**), and its 2-*p*-toluenesulfonate (**12**).

Treatment of **12** with 1.3 equivalents of *p*-toluenesulfonic anhydride for 0.5 h at 0°, followed by chromatographic separation of the mixture on silica gel, gave 88% of 1,6-anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose, together with a small proportion of trisulfonate (Table I). In contrast, use of *p*-toluenesulfonyl chloride for esterification of **12** gave decreased selectivity (64% of the 2,4-diester), and required 3–4 days at 25° for completion. Almost identical results were observed for the *p*-toluenesulfonylation of 1,6-anhydro-2-*O*-methyl-β-D-glucopyranose (**9**, Table I), except that its reaction with *p*-toluenesulfonyl chloride was faster (complete in <24 h). Thus, *p*-toluenesulfonic anhydride is a better reagent than *p*-toluenesulfonyl chloride for preferential esterification of levoglucosan, possibly[2,29] because the former reagent is used at a lower temperature.

EXPERIMENTAL

General methods. — Melting points were determined on a Thomas–Hoover capillary apparatus. Optical rotations were obtained with a Zeiss–Winkel visual

polarimeter. All evaporations were conducted under diminished pressure below 50°. T.l.c. was performed on plates coated with Silica Gel G (Brinkmann Instruments, Inc., Westbury, N.Y.); developing solvents (*v/v*) are quoted in parentheses. The components were located by spraying with 5% sulfuric acid in methanol followed by charring on a hot plate. Column chromatography was performed with silica gel (Davison, grade 950, 60–200 mesh, Fischer Scientific, Pittsburgh); fractions were collected at a flow rate of 1–2 ml min^{-1}, and were monitored by t.l.c. N.m.r. spectra were recorded for 10% (*w/v*) solutions with a Varian A-60A spectrometer at the normal probe temperature. Tetramethylsilane [in Me_2SO-d_6 and $CDCl_3$] and sodium 4,4-dimethyl-4-silapentane-1-sulfonate (in D_2O) were used as internal standards. Spin decoupling was accomplished by the "field-sweep" technique. I.r. spectra were recorded on a Perkin–Elmer 621 grating spectrophotometer for carbon tetrachloride solutions (10-mm cell) or 1,2-dichloroethane solutions (1-mm cell).

Materials. — The following sugar derivatives were prepared according to published procedures: 1,6-anhydro-β-D-glucopyranose[30] (**7**), m.p. 160–161°; 1,6-anhydro-2-*O*-methyl-β-D-glucopyranose[31] (**9**), m.p. 93–94°; and 1,6-anhydro-4-*O*-benzyl-β-D-glucopyranose[20] (**11**), m.p. 53–54°. 1,6-Anhydro-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**12**) was prepared by hydrogenation of 1,6-anhydro-4-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose[32] in ethyl acetate at 1 atm pressure over 5% palladium on charcoal. Compound **12** had m.p. 113–115°; reported[25] 116–119°.

p-Toluenesulfonic anhydride was prepared according to the procedure described by Field and McFarland[33]. The anhydride had m.p. 120–127° in a sealed tube.

*1,6-Anhydro-3-deoxy-β-*D-xylo-*hexopyranose* (**1**). — A mixture of 1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-*xylo*-hexopyranose[16] (11.4 g) and 0.25M aqueous sulfuric acid (1000 ml) was heated for 40 h on a steam bath, cooled, and neutralized with barium carbonate. Filtration, and concentration of the filtrate, gave a syrup (7.3 g) that was chromatographed on silica gel (200 g). Successive elution with 9:1 ethyl acetate–methanol and methanol gave 1.01 g (25%) of 1,6-anhydro-3-deoxy-β-D-*xylo*-hexopyranose (**1**) and 2.92 g (64%) of 3-deoxy-D-*xylo*-hexose. The 1,6-anhydride (**1**) crystallized from a mixture of ethyl acetate–petroleum ether (b.p. 60–110°); m.p. 138–139°, $[\alpha]_D^{22}$ −8° (*c* 1.0, H_2O). [lit.[18] m.p. 131–137°, $[\alpha]_D^{25}$ −9.5° (*c* 0.8, H_2O) (erroneously given as +)]. N.m.r. data (Me_2SO-d_6): τ 4.90 (1H doublet, $J_{1,2}$ 2.0 Hz, H-1), 5.15 (1H doublet, $J_{OH-4,H-4}$ 4.5 Hz, OH-4) (see n.m.r. data for **6**), 5.28 (1H doublet, $J_{OH-2,H-2}$ 6.0 Hz, OH-2) (see n.m.r. data for **3**), 5.74 (1H multiplet, H-5), and 8.1–8.8 (2H multiplet, H-3,3′).

Anal. Calc. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.41; H, 6.74.

Compound **1** gave a crystalline diacetate (**1a**), m.p. 73–75°, and a crystalline dibenzoate, m.p. 118–120°, $[\alpha]_D^{28}$ +11° (*c* 1.0, chloroform). Both compounds displayed the anticipated distribution of protons in their n.m.r. spectra. The diacetate **1a** has been reported[18]: m.p. 74–75°, $[\alpha]_D$ −13.5° (*c* 0.7, chloroform) (erroneously given as +).

*1,6-Anhydro-2-*O*-benzyl-β-*D*-glucopyranose* (**10**). — The starting material for preparation of **10** was 1,6:3,4-dianhydro-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose

(**13**), which was readily prepared[34] in >50% yield from 1,6-anhydro-β-D-glucopyranose. Hook and Lindberg[35] reported desulfonation of **13** with sodium amalgam, whereas Foster and his colleagues[9] were unsuccessful in attempts to produce 1,6:3,4-dianhydro-β-D-galactopyranose (**14**) by reducing **13** with sodium amalgam. The latter investigators, however, removed the *p*-tolylsulfonyl group from **13** by photolysis in methanol containing sodium methoxide. We have routinely used sodium amalgam to prepare **14** from **13** by using very rapid reduction conditions, during which time a minimum of the desired product (**14**) is converted in the alkaline medium to the more thermodynamically favored[36] 1,6:2,3-dianhydro-β-D-gulopyranose.

A mixture of 1,6:3,4-dianhydro-2-*O*-*p*-tolylsulfonyl-β-D-galactopyranose (**13**, 6 g) and 4:1 methanol–water was heated at reflux until **13** dissolved completely. The source of heat was removed, and then finely divided, 4% sodium amalgam was added with rapid stirring. After 20 min, t.l.c. analysis using 10:3 isopropyl ether–ethyl acetate showed that all starting material (R_F 0.6) had been consumed with the formation of a major and a minor component (R_F 0.2 and 0.3, respectively). The aqueous-alcoholic solution, decanted from the unreacted amalgam and mercury, was neutralized with carbon dioxide. The neutralized solutions from four separate reductions were combined, evaporated to dryness, and the residue extracted with hot chloroform. The chloroform extract was dried over sodium sulfate, and evaporated to a clear syrup (12.4 g) that crystallized from ethyl acetate (7 ml) at −10°; yield 6.67 g, m.p. 69–70°. Recrystallization gave 4.79 g of pure 1,6:3,4-dianhydro-β-D-galactopyranose (**14**); m.p. 70–71°, $[\alpha]_D^{25}$ −74° (*c* 2.3, water) [lit.[36] m.p. 67–69°, $[\alpha]_D^{20}$ −80° (*c* 1.05, water)]. Second (3.01 g) and third (1.20 g) crops were obtained by adding petroleum ether (b.p. 30–60°) to the initial ethyl acetate solution. Combination and recrystallization yielded 2.24 g of additional pure **14**; total yield of **14**, 7.03 g (60%).

Compound **14** was converted into syrupy 1,6:3,4-dianhydro-2-*O*-benzyl-β-D-galactopyranose by established procedures[37] (see also Prystaš and Šorm[38]) with silver oxide and benzyl bromide in *N*,*N*-dimethylformamide. The benzylated dianhydride (2.52 g) was dissolved in 1,4-dioxane (80 ml), and the solution was added to 1.2M aqueous potassium hydroxide (140 ml) in a Teflon-lined, bomb calorimeter (Parr Instrument Co., Moline, Ill.). The bomb was heated for 24 h at 105°. The reaction mixture was cooled, adjusted to pH 8.0 by adding M aqueous sulfuric acid, and evaporated to dryness. The residue was extracted twice with hot abs. ethanol. An equal volume of water was added to the ethanol extract and the resulting solution was passed through Amberlite MB-3 (H^+, OH^-) resin (100 ml). The effluent was evaporated to a syrup (2.15 g) that crystallized at 0° from a mixture of acetone (5 ml) and ethyl ether (60 ml). Two crops of pure 1,6-anhydro-2-*O*-benzyl-β-D-glucopyranose (**10**) were obtained; 1.78 g (71%), m.p. 73–74°, $[\alpha]_D^{22}$ −64° (*c* 1.0, ethanol).

Anal. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.05; H, 6.28.

The structure of **10** was confirmed by methylation and reductive debenzylation, which gave 1,6-anhydro-3,4-di-*O*-methyl-β-D-glucopyranose[20]; m.p. and mixed m.p. with an authentic sample, 41–43°.

*Esterification of 1,6-anhydro-3-deoxy-β-*D*-xylo-hexopyranose* (**1**). — A solution of *p*-toluenesulfonyl chloride (220 mg, 3 equivs.) in pyridine (5 ml) was added dropwise, with stirring, to a mixture of **1** (55 mg) and pyridine at 25°. After 36 h at 25°, t.l.c. showed no starting material remaining. The reaction was stopped by adding water, and the products were dissolved in benzene. The organic layer was successively washed with 5% aqueous hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and water. The benzene solution was dried over sodium sulfate and evaporated to a syrup, which was chromatographed on a column of silica gel. Elution with 4:1 chloroform–ethyl acetate gave two fractions as syrups. The faster-moving component (20 mg, 11%) proved to be the disulfonate of **1** (n.m.r. showed two *p*-toluenesulfonate substituents, τ 2.0–2.7), and was not investigated further. The slower-moving component, 1,6-anhydro-3-deoxy-2-*O*-*p*-tolylsulfonyl-β-D-*xylo*-hexopyranose (**2**, 80 mg, 70%), yielded 75% of a crystalline monoacetate monosulfonate (**2a**) upon treatment with acetic anhydride–pyridine; m.p. 114–116°, $[\alpha]_D^{24}$ −27° (*c* 1.0, chloroform).

Anal. Calc. for $C_{15}H_{18}O_7S$: C, 52.62; H, 5.30; S, 9.37. Found: C, 52.10; H, 5.44; S, 9.13.

Compound **2** was characterized largely through its conversion in two steps into 1,6-anhydro-3-deoxy-4-*O*-methyl-β-D-*xylo*-hexopyranose (**3**), a compound whose n.m.r. spectrum was consistent with its assigned structure. Methylation of **2** was accomplished in 67% yield by using methyl iodide and silver oxide in *N*,*N*-dimethylformamide[39]. The product was reduced in 4:1 methanol–water with 4% sodium amalgam (see foregoing preparation of **14**) to give **3** in 90% yield as a chromatographically pure syrup; n.m.r. data (Me_2SO–d_6): τ 4.89 (1H, narrow multiplet, H-1), 5.19 (1H, doublet, $J_{OH-2,H-2}$ 5.8 Hz, OH-2), 5.48 (1H, triplet with major splittings of $J_{4,5} \simeq J_{5,6} \simeq 4.2$ Hz and many small, long-range couplings, H-5), 6.15 (1H, quartet, $J_{6,6'}$ 7.0, $J_{5,6'}$ 0.8 Hz, H-6′ *exo*), 5.6–6.6 (3H, multiplets, H-6 *endo*, H-2, and H-4), 6.75 (3H, singlet, methoxyl), and 8.08–8.80 (2H, multiplet, two protons on C-3).

Selective benzoylation of **1** was performed as follows: benzoyl chloride (355 mg, 1.5 equivs.) was added dropwise, with stirring, to a solution of **1** (260 mg) in pyridine (10 ml) maintained at 5–10°. After 1 h, t.l.c. showed no starting material, but two new components had appeared. The reaction mixture was processed in benzene solution, and the isolated syrup was chromatographed on silica gel. Elution with 3:1 benzene–ethyl acetate gave a dibenzoate fraction (195 mg, 31%) and a monobenzoate fraction (280 mg, 63%). The dibenzoate crystallized from ethyl acetate–petroleum ether (b.p. 60–110°); m.p. 118–120°, $[\alpha]_D^{28}$ +11° (*c* 1.0, chloroform).

The syrupy monobenzoate fraction was shown to contain preponderantly 1,6-anhydro-2-*O*-benzoyl-3-deoxy-β-D-*xylo*-hexopyranose (**4**) by the following evidence. *p*-Toluenesulfonylation of **4**, followed by debenzoylation with sodium methoxide in methanol, gave a syrupy monosulfonate **5**, which showed an i.r. band at 3590 cm^{-1} of moderate intensity, indicating an intramolecularly hydrogen-bonded, hydroxyl-stretching absorption; this is possible only between the axial OH-2 and O-5. Acetylation of **5** yielded a monoacetate monosulfonate whose n.m.r. spectrum

($CDCl_3$) exhibited a single acetoxyl methyl resonance at τ 7.93, downfield by 0.05 p.p.m. from the acetoxyl resonance of **2a**. Furthermore, compound **5** was converted into 1,6-anhydro-3-deoxy-2-*O*-methyl-β-D-*xylo*-hexopyranose (**6**) by Kuhn methylation and reductive desulfonation with sodium amalgam. N.m.r. data for **6** (Me_2SO-d_6) τ 4.73 (1H, narrow multiplet, H-1), 5.12 (1H, doublet, $J_{OH-4,H-4}$ 4.8 Hz, OH-4), 5.76 (1H, triplet with major splittings of $J_{5,6} \simeq J_{4,5} \simeq 4.5$ Hz and many small, long-range couplings, H-5), 6.04 (1H, quartet, $J_{6,6'}$ 7.0, $J_{5,6'}$ 1.0 Hz, H-6′ *exo*), 6.76 (3H, singlet, methoxyl), and 8.0–8.8 (2H, multiplet, two protons at C-3).

Reaction of levoglucosan derivatives with p-*toluenesulfonyl chloride.* — Esterification reactions of levoglucosan 2-methyl ether (**9**), 2-benzyl ether (**10**), 4-benzyl ether (**11**), and 2-*p*-toluenesulfonate (**12**) were conducted as follows: the substituted 1,6-anhydride (5 mmoles) was dissolved in pyridine (8 ml) at 25°, and 1.3 equivs. of *p*-toluenesulfonyl chloride (1.24 g) was added. The mixture was maintained at 25°, and t.l.c. with 3:2 benzene–ethyl acetate showed that esterification of **9**, **10**, or **12** was complete in less than 24 h, whereas **11** required 3–4 days. Each reaction was quenched by adding a small amount of water, and the products were isolated in chloroform solution. Separation of the products of a reaction was achieved by column chromatography on silica gel (80 g) with 7:3 benzene–ethyl acetate as the developing solvent. The yield of trisubstituted levoglucosan derivative from the column was always less than 4%. No attempt was made to recover the trace of starting compound in the reaction mixture. The principal product of esterification, its yield, and method of identification are now discussed.

Compound **9** gave 1.17 g (71%) of 1,6-anhydro-2-*O*-methyl-4-*O*-*p*-tolylsulfonyl-β-D-glucopyranose as a crystalline solid; m.p. 111–112°, $[\alpha]_D^{22}$ −53° (*c* 0.8, chloroform).

Anal. Calc. $C_{14}H_{18}O_7S$: C, 50.90; H, 5.49; S, 9.70. Found: C, 50.75; H, 5.64; S, 9.57.

The monosulfonate derived from **9** was identified by its reaction with sodium methoxide to give (65% yield) the known[36] 1,6:3,4-dianhydro-2-*O*-methyl-β-D-galactopyranose; m.p. 91–92°, $[\alpha]_D^{22}$ −74° (*c* 1.0, chloroform). [Lit.[36] m.p. 91–92°, $[\alpha]_D^{20}$ −77° (*c* 1.35, chloroform)].

Compound **10** gave 1.5 g (74%) of crystalline 1,6-anhydro-2-*O*-benzyl-4-*O*-*p*-tolylsulfonyl-β-D-glucopyranose; m.p. 101–102°, $[\alpha]_D^{23}$ −51° (*c* 0.8, chloroform).

Anal. Calc. $C_{20}H_{22}O_7S$: C, 59.10; H, 5.45; S, 7.90. Found: C, 59.47; H, 5.45; S, 7.99.

The structure of the monoester derived from **10** was established by its reaction with sodium methoxide, followed by catalytic debenzylation with hydrogen over palladium-on-charcoal catalyst, to give (65% yield) 1,6:3,4-dianhydro-β-D-galactopyranose (**14**), identical in all respects with **14** prepared by the method described in this paper.

p-Toluenesulfonylation of compound **12** yielded 1.51 g (64%) of 1,6-anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose. The disulfonate was difficult to crystallize[24], but was readily identified by its conversion (81% yield) into 3-*O*-acetyl-1,6-

anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose; m.p. 157–158°, $[\alpha]_D^{26}$ −39.6° (*c* 1.2, chloroform). [(Lit.[24] m.p. 162–163°, $[\alpha]_D^{20}$ −39.5° (*c* 1.01, chloroform)].

Compound **11** gave 1.44 g (71%) of 1,6-anhydro-4-*O*-benzyl-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose as a crystalline solid; m.p. 124–126°, $[\alpha]_D^{27}$ −18.3° (*c* 5.0, chloroform). [Lit.[32] m.p. 126–127°, $[\alpha]_D^{22}$ −18° (*c* 1.75, chloroform)].

Reaction of levoglucosan derivatives with p-*toluenesulfonic anhydride.* — Freshly prepared *p*-toluenesulfonic anhydride[33] (0.27 g, 1.3 equivs.) was added to 1,6-anhydro-2-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (**12**, 0.200 g) dissolved in pyridine (5.0 ml) and maintained at 0°. Analysis of the stirred reaction mixture, by t.l.c. with 3:2 benzene–ethyl acetate, showed the reaction to be complete after approximately 30 min. Water was added and stirring was continued for 30 min at 25°. The reaction products were isolated in chloroform. The chloroform solution was dried over sodium sulfate and concentrated to a syrup (0.314 g) that was chromatographed on silica gel (15 g). Elution with 7:3 benzene–ethyl acetate gave 1,6-anhydro-2,3,4-tri-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (14 mg, 3.6%), m.p. 105–106° (reported[25], m.p. 102–105°), and 1,6-anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (260 mg, 88%) as a syrup, $[\alpha]_D^{27}$ −41° (*c* 1.0, chloroform). Černý *et al.*[24], reported this compound to have m.p. 116–118°, $[\alpha]_D^{20}$ −43° (*c* 0.96, chloroform). The disulfonate (0.149 g) was acetylated to give 0.131 g (81%) of crystalline 1,6-anhydro-3-*O*-acetyl-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose[24], m.p. 157–158°.

1,6-Anhydro-2-*O*-methyl-β-D-glucopyranose (**9**, 0.252 g) was treated with *p*-toluenesulfonic anhydride (0.61 g, 1.3 equivs.) by the foregoing procedure to produce syrupy 1,6-anhydro-2-*O*-methyl-3,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (27 mg, 3.9%) and 1,6-anhydro-2-*O*-methyl-4-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (398 mg, 84%), m.p. 111–112°. Treatment of the latter with sodium methoxide in chloroform gave the known[36] 1,6:3,4-dianhydro-2-*O*-methyl-β-D-galactopyranose, m.p. 91–92°.

1,6-Anhydro-β-D-glucopyranose (**7**, 2 g) was sulfonylated at 0° in pyridine (80 ml) by six additions of *p*-toluenesulfonic anhydride (11.4 g total) during 2.0 h. The reaction mixture was stirred for a total of 4 h at 0°, and then a small amount of water was added, and the mixture was allowed to warm to 25°. After 30 min, the mixture was concentrated at <1 mm Hg to remove most of the pyridine. The products (4.1 g) were obtained in the normal manner, and chromatographed on silica gel (200 g). The first fraction was the trisulfonate of levoglucosan (0.54 g, 7.2%), and the second fraction was 1,6-anhydro-2,4-di-*O*-*p*-tolylsulfonyl-β-D-glucopyranose (4.57 g, 79%). No attempt was made to recover the monosulfonate fraction, as t.l.c. showed only a trace amount.

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